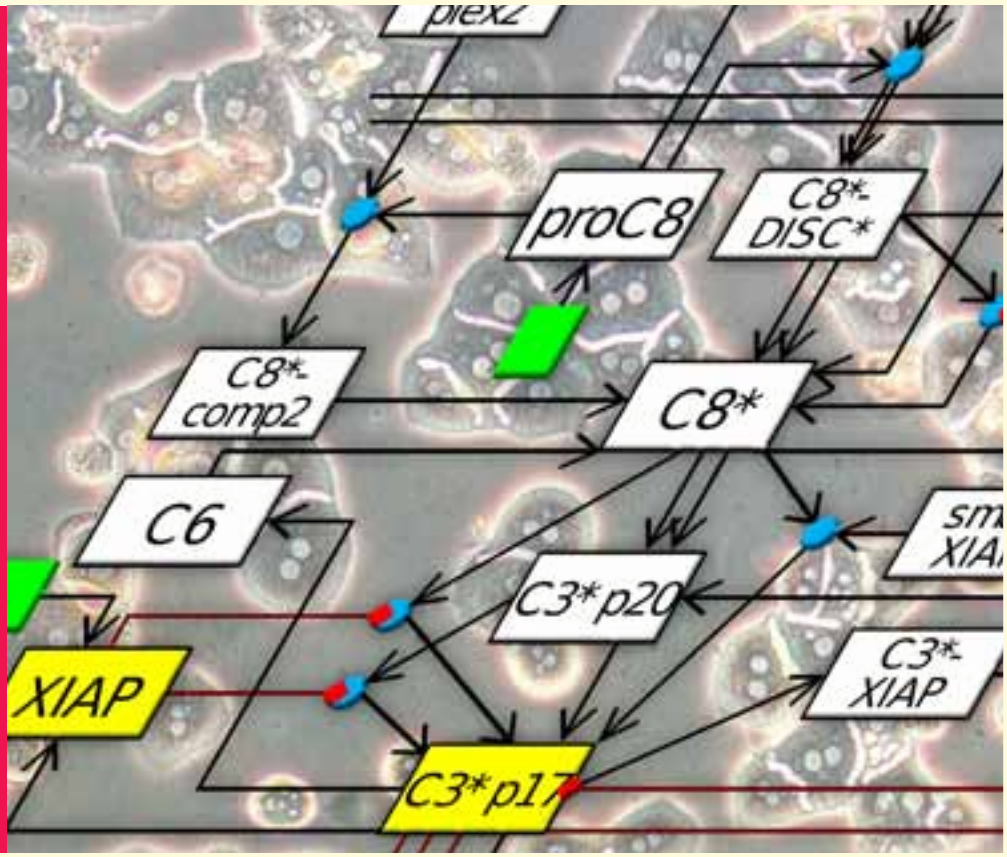
Systems Biology in Baden-Württemberg



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Baden-Württemberg

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Prof. Peter Frankenberg

Baden-Württemberg Minister of Science, Research and the Arts from 2001 to 2011

Dear readers,

"A New Biology for the 21st Century – Ensuring the United States Leads the Coming Biology Revolution" is the name of a strategic paper published by the US National Research Council (NRC) in 2009. The NRC report highlights the future challenges facing modern biology and makes recommendations on how these challenges can be addressed.

The report concludes that the nature of "New Biology" requires integration, both a re-integration of the numerous biology disciplines as well as an integration of these biology disciplines with other sciences, including physics, chemistry, mathematics, computer and engineering sciences. Systems biology is able to provide this integration through the pursuit of a holistic, systemic approach.

In Baden-Württemberg, systems biology has been receiving funding since the late 1990s. With the financial support of the Baden-Württemberg government, new systems biology research buildings were constructed at the Universities of Freiburg and Heidelberg. Funding was provided through the Competition for the Establishment of Life Sciences Centers as part of the Baden-Württemberg "Zukunftsoffensive III" funding program and also by the German federal government. The Freiburg Center for Biosystems Analysis (ZBSA) and the Heidelberg Center for the Quantitative Analysis of Molecular and Cellular Biosystems (BIOQUANT) provide effective infrastructure for systems biologists. The University of Stuttgart, which is rightly proud to be known as the cradle of systems biology in Germany, received financial support for the establishment of the Center Systems Biology (CSB). With the establishment of these three centers, Baden-Württemberg has created a systems biology landscape that has the best infrastructure of all the German states.

In the future, Baden-Württemberg will continue to make every effort to support systems biology research with its version of the NRC motto: "A New Biology for the 21st Century – Ensuring Baden-Württemberg Is Part of the Coming Biology Revolution".

Dr. Ralf Kindervater

CEO
BIOPRO Baden-Württemberg GmbH

Modern biotechnology is defined by its numerous groundbreaking innovations. In no other scientific discipline is so much intensive research carried out at such top-quality international levels. In 2010, only a few years after the first human genome was sequenced, another breakthrough hit the headlines: A group of researchers led by Craig Venter brought a bacterium "to synthetic life" with the first synthetic genome. The first journalists to write about Venter's work were divided in their views as to whether the work was a world-first in "the creation of artificial life" or whether it was a more moderate step towards the establishment of the emerging field of synthetic biology. All observers agreed that the group of scientists working with Venter did not - with the exception of a small genetic watermark - code any relevant additional information or additional functions into their synthetic genome. Before researchers can create real synthetic life, said Venter, we need to know more about the respective functional mechanisms and the tools to control these functions.

A true bioscientific revolution is however occurring from an entirely different angle without the interference of the sensationalist press: the worldwide research activities in the field of systems biology. Biologists, mathematicians and computer scientists are working together in a unique interdisciplinary way to investigate and model biological systems, deduce function-related knowledge from these models and compare them with real systems. Step by step, the building blocks of metabolic cycles, synthesis and degradation processes in living organisms are being represented.

Thanks to its forward-looking experts in the Baden-Württemberg Ministry of Science, Research and the Arts, the state of Baden-Württemberg very quickly recognized the opportunities that systems biology had to offer and the state established an infrastructure for carrying out research in this sector. When, in May 2010, the flood of information on synthetic life out of the USA became a matter for wider public discussion, one thing became clear: Baden-Württemberg has timed its investments in future-oriented systems biology research perfectly. In this brochure, BIOPRO Baden-Württemberg presents the activities of the three systems biology centers in Baden-Württemberg.

In the field of systems biology, Baden-Württemberg research is already a step ahead of mainstream research. In cooperation with scientists and industrial companies in the Biopolymers/Biomaterials Cluster, BIOPRO is already addressing a field Craig Venter saw as the next step in his quest to create synthetic life: The use of systems biology technologies to optimize the synthesis ability of bacteria to an extent that biobased plastics will not only become technically but also economically feasible.

Several cluster projects have shown that the latest systems biology findings and tools are entering industrial applications in modern biotechnology with breathtaking speed. Systems biology is a powerful tool in our fight against climate change and in our effort to replace fossil resources with renewable resources. Please make the most of the current 7th BIOPRO Edition.

Prof. Hans Westerhoff

AstraZeneca Professor of Systems Biology
Director of the MCISB
University of Manchester

Professor of Microbial Physiology
Netherlands Institute for Systems Biology
VU University Amsterdam

Systems Biology has reached adulthood ..... in some places

Looking for understanding

It seems so easy to understand a Porsche. Just take it apart and describe each of its parts. Photograph each part at 1 nanometer resolution. Most parts differ from those of a Mercedes Benz. But would those photographs satisfy your friends, who all drive Porsche or Mercedes Benz? Most probably not. They are after something more than the sum of the parts. If you happen to own two Porsches, please take a few moments to take one of them apart and drop the components into a box in front of your house. Tomorrow, please take this Porsche to work. If you only appreciate parts, you may still be disappointed. The box contains all of the Porsche, but cannot be driven. In fact it will not be able to perform any Porsche functionality at all; not even impress the neighbors...

Recently Baden-Württemberg has become known for more than fast cars and that is what this special issue is about. Living organisms also consist of many components, and their functions also depend on the interactions between these components. We can maybe overexpress and crystallize all human genes and determine their structures. We can put the structures of the proteins together in a folder on a computer and would obtain some kind of picture of the structure of a human. But will that human function *in silico*? Of course not; it will not even come close to functioning. For living organisms, the function is maintenance if not proliferation. And for humans, it is the enjoyment of reading, listening and thinking. It never is the structure of their ATPases. An organism can only function when all its components make up a whole. And how a system as a whole functions cannot be described directly from the functions of its individual components.

The holistic point of view is that whenever one breaks open a living organism to isolate and then characterize its molecules, one destroys life (e.g. by dissipating the membrane potential and hence ATP free energy) and that therefore molecular biology cannot study the latter. Without pistons, a Porsche cannot function as a Porsche and therefore one can only study the Porsche as a whole, e.g. by observing how turning the steering wheel correlates with taking corners. Accordingly, physiology's understanding remains at the system level; the blood flow from the heart equals the number of heartbeats per second multiplied by the volume of the ventricle, for instance. A limitation to physiology is that it has no way of understanding the effects of drugs and genetic differences between individuals. The potential of (functional) genomics, chemistry and physics has not yet been harvested.

"When the first combustion process engine simulations and laser diagnostics were developed, nobody could foresee that this would accelerate engine development in the way it did. The issues currently being worked on in systems biology will perhaps become important for the pharmaceutical industry in about 20 years' time. However, the example of the automotive industry shows that issues that were worked on 20 years ago with future development in mind have now become reality."

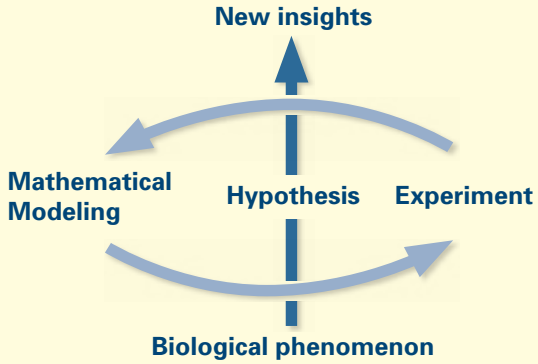
Prof. Jürgen Wolfrum, Director BioQuant Center, Universität Heidelberg

The reductionist view is that living systems are too complex to be analyzed with scientific rigor and that one should therefore break down the system to the smallest possible units that can be studied in a completely defined *in vitro* setting. In biochemistry and molecular biology this has led to the isolation and then characterization of enzymes (the smallest units of chemical reactions) and genes (the smallest units of information). The approach has been tremendously successful in its own right, to the extent that now the genes of many living organisms have been sequenced and the catalytic function of many enzymes identified. However, as with the Porsche, the sum of the understandings of the components is not even close to the understanding of function.

What is systems biology?

Systems biology is meant to fill the gap. It is the science that aims at understanding which functions are important for living systems based on an analysis of the interactions between individual components which give rise to these funtions. This definition has a number of implications. First, it focuses on 'the' specific vital functions of the entire organism, not on any odd, perhaps molecular function. Second, it refers to 'the' complete set of interactions that are involved in the emergence of 'the' functions. Since molecules in organisms are connected to almost all other molecules, this involves functional genomics. Third, it implies that most functions are not present in the components. For new properties to arise in interactions, the interactions need to be nonlinear. To understand nonlinear interactions, one needs mathematical modeling and analysis. Emergence of new functionalities such as robustness and cycling depend on the strengths of the interactions, which again depend on the operating point of the system. Hence these strengths need to be determined rather precisely for *in vivo* conditions. Consequently, systems biology requires precise experimentation under *in vivo*-like conditions. And clearly, to produce the desired understanding, modeling, analysis, precise experimentation and genomics all need to be integrated.

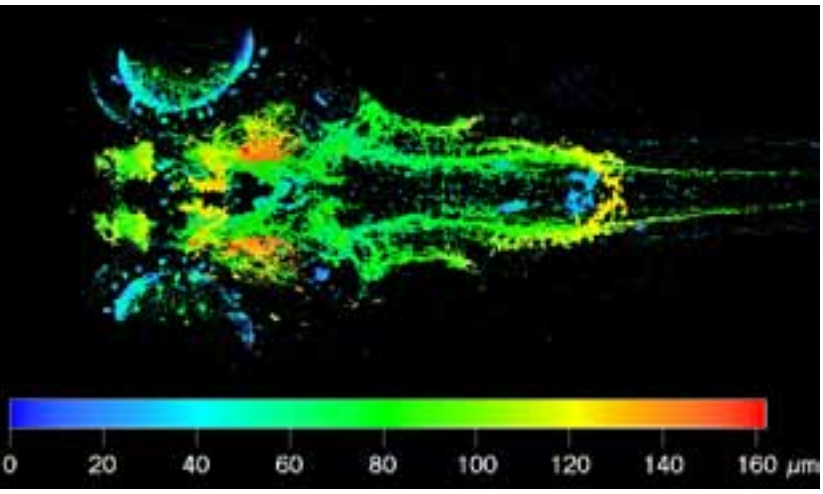
Definition systems biology



The objective of systems biology is to describe the interplay between all components of a biological system to gain a holistic picture of the system under consideration. To this end biological processes are described by mathematical models. Iterative cycles of model-based experimental investigations and data-based modeling help researchers to achieve a validated mathematical model of a given system. This is only possible through interdisciplinary cooperation between different sciences.

Hurdles

For a long time, any comprehensive form of systems biology research has been impossible. For no living organisms were all components known or accessible. In every experimental setting falsifying a hypothesis, the hypothesis could still be right because an unidentified component was involved *in vivo*; biology was soft. Genomics and then functional genomics put this to an end. Slowly but steadily these approaches now also begin to enable the more precise measurement of concentrations. When the amount of information required became prohibitive, bioinformatics and advances in computation came to the rescue. Software has become suitable for the modeling of biochemical reaction networks. And theoretical frameworks such as flux, flux-balance, control and regulation analysis have been developed and implemented. Also the microscopic methods looking at macromolecules and their spatial and temporal distributions have been improved greatly. If all methodology seems to be available, what is limiting further progress? Why isn't every department interested in Life Sciences engaging in systems biology and contributing to the good course?



Overview of a zebrafish larva stained for catecholaminergic neurons depth-coded in color

I see four major hurdles, which can be summarized as 'people, people, people, and people', or 'personalities, pupils, peers and prophets'. The first hurdle is that of personalities. The thing is that systems biology is way too big. For any research topic in systems biology, one needs to understand the smallest details of experimental molecular biology, the many factors involved in cells or tissue in culture, the physics of molecules moving through the cell, and the mathematics of the models describing all of this. Understanding genetics, epidemiology, anatomy, bioinformatics, biochemistry and microscopy is another prerequisite. In other words, for PhD students and principal investigators alike, it is just too much for any human brain. The only way to carry out systems biology at a professional level is for multiple scientists to collaborate intensively with extreme respect for each other's expertise and opinions. However, this is not the way today's scientists work. In my eyes, this is one reason why the North American Alliance for Cellular Signaling failed; apart from a massive underappreciation of the modeling component, it was not composed of scientists who were willing to forget competition. The BMBF-supported HepatoSys and Virtual Liver are trying to be different by strongly enforcing collaboration.

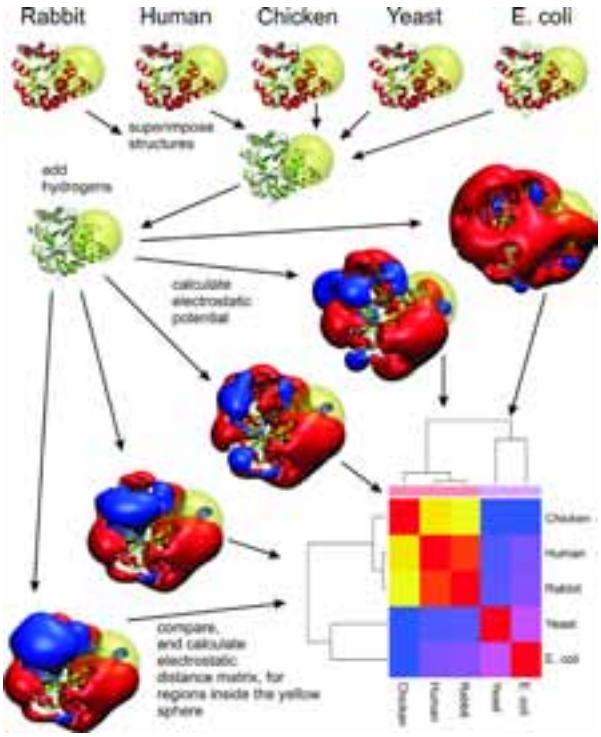
The second hurdle is that of 'pupils'. I have estimated that for the United Kingdom alone one would have to produce

"Systems biology has for the first time ever made it possible to work towards an understanding of all the processes in an organism (although this goal is still a distant one). As part of what is referred to as synthetic biology, the iterative combination of experiments and modeling in systems biology will also enable the construction of made-to-measure microorganisms for use in white biotechnology."

Prof. Peter Dürre, University of Ulm

more than 60 PhDs in systems biology per year in order to satisfy the needs of human capital for government-funded research only. UK industry suffers greatly from the lack of biologists who understand even a bit of mathematics, not to speak of mathematicians who have even heard of biology. By the end of this academic year, the UK will produce its first 15 PhDs and the number will not go up to more than 30/year in the near future. The situation in Germany is not much better; there continues to be a lack of MSc and PhD courses in systems biology. Here one should not forget that systems biology requires much more inter- and transdisciplinary skills than traditional sciences. More training centers, such as the one we run in Manchester, are needed urgently.

The third hurdle is that of 'peers'. Science is one of the most quality-controlled activities of humans. Before publication, results are scrutinized by peer reviewers. Research proposals are decimated before being funded by panels of peers. Top systems biology research depends on the progress achieved in a multitude of various disciplines. No single expert in a panel will be able to understand all aspects of any, let alone of all proposals (s)he has to evaluate. In practice, one panel member not understanding a proposal suffices to have it rejected. In addition, many scientific experts are chauvinistic about their disciplines. Molecular biologists may not tolerate equations, whereas physicists find any biology worse than stamp collecting. Counterproductive for integrative systems biology is also the tradition prevalent in many disciplines to jugde a person's success in terms of the number of sole author papers he has produced. This hurdle has been overcome by



Comparative analysis of the electrostatic characteristics of protein molecules using the webPIPSA web server (pipsa.h-its.org). (Richter et al, Nucl. Acids Res. 36, 276-280, 2008)

the physicists jointly searching for the elementary particle called Higgs boson.

It is this Higgs boson and the Hadron Particle collider near Grenoble that brings me to the fourth 'p' for 'prophet'. The Hadron Particle collider was built at a cost of 6 billion euro, which I estimate to be more than 3 times what it takes to make a first 'silicon human' (a realistic molecule-based computer model of the human) through systems biology. The contribution to human well-being of the hefty instrument in Grenoble is likely to be negative.

Proper systems biology, however, would almost certainly lead to the discovery of new drugs against the many multifactorial diseases that plague mankind today. One extra drug per year would produce a revenue for the pharmaceutical industry well over 0.5 billion euro per year and reduce the worldwide economic cost of diseases such as cancer by more than 30 billion euro per year. In particular, it could also create a renewed basis for the European pharmaceutical industry around Stuttgart, Heidelberg, Freiburg and Mannheim. A public-private partnership could result in an economic dimension that would dwarf Porsche and approach that of Daimler-Benz.

Most of all, we need visionary prophets to define, and creative scientists to pursue and achieve ambitious goals in systems biology, for the benefit of science and society.

From the present to the future

Many eminent examples of systems biology have been treating the organism as a single bag of enzymes, with metabolites in between. An exception is the systems biology of *Trypanosoma brucei*, the causative agent of sleeping sickness, where systems biology pinpointed a, and perhaps even "the", biological function of an extra compartment this organism is host to. Other systems biology studies have been addressing information networks, i.e. transcription factors or signal transduction cascades. Comparatively few studies have examined the interactions between these two 'worlds' of systems biology, leading to the virtually complete plasticity of the biochemical reaction networks, comparable to the Porsche convertible with sunshine-triggered electric roof. Another omission from much of present-day systems biology is the spatial and structural aspects. Regulation of activity sometimes involves moving proteins around. And many functional activities of living organisms, such as cell division and chemotaxis, are inherently structural. Another important part of biology has been missing from most systems biology, i.e. the evolutionary aspect. In recent years however, this aspect has been given more attention, e.g. in the field of comparative systems biology.

Because of these limitations, one should perhaps call much of the systems biology until now, excellent as it is, 'systems biochemistry'. The highly exciting aspects where biology goes beyond systems biochemistry have been underrepresented, in part for good reasons: Chemical reaction networks in unicellular organisms are simpler than in multicellular organisms, yet complex enough to offer an almost insurmountable challenge. We should start with the simple and proceed to the complex. Then systems biology should also be the science that aims at understanding how the functions of the human arise from the interactions of its components, all the way up from (or down to) its molecules. All the different kinds of networks, ie. metabolic, gene expression, structural and spatial, together with their interactions, should be taken into account without neglecting dynamic cell compartmentation and adaption. Systems biology should also deal with malfunction, dysfunction, disease, recovery and aging.

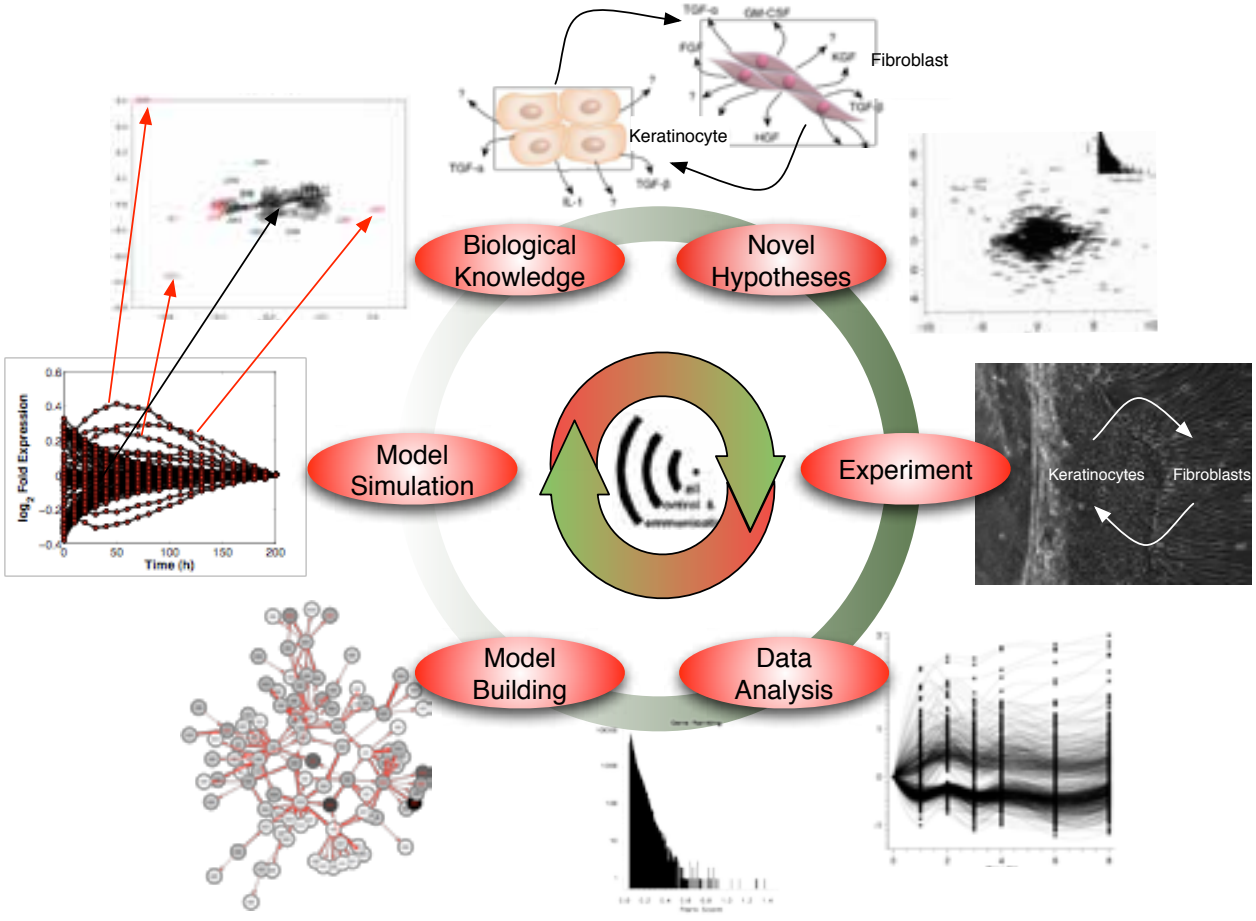
Beauties, in the eye of the beholder

All too often, after an exposé of systems biology, I am asked politely 'and what new molecule have you now discovered?' Systems biology is an entirely new discipline and cannot therefore be measured by the old metrics, be they

"The technical influences on biological production systems in industrial bioreactors are complex and dominant. Systems biology methods can be used to clarify the underlying mechanisms, thus facilitating the sensitive step from laboratory to production scale."

Prof. Ralf Takors, CSB, University of Stuttgart

molecular or physiological. When I discuss the success stories of systems biology therefore, they will typically not be recognized as such by molecular biologists or by physiologists. I consider the sequencing of the first genome of any organism, and than the sequencing of the human genome, to be great milestones in human history, much cheaper (costing < 1 % of) but 100 times more valuable than putting a man on the moon. That was genomics, not systems biology. I view it as a great success for systems biology that virtually the complete chemical capability of living organisms such as yeast and soon the human, has been mapped, in terms of reactions and fluxes. Another great success is



Systems biology approach used to clarify how human keratinocytes and fibroblasts communicate with each other by analyzing the gene regulatory response to stimulation. The combination of dynamic gene responses with thetopology of the gene network enables the identification of important effector genes and network nodes.

that we can now calculate the concentrations of fluxes and drug targets in important metabolic pathways.

I was also enchanted by seeing the contraction wave spread across the myocardium of the virtual heart produced by the consortium around Denis Noble, predicting the effect of drugs on the heart rate (QT interval). This method has now been accepted by the FDA for animal-free pretesting of drugs. Major stories of academic success are the ones that have revealed fundamental principles that rule living organisms. Akin to laws of non-equilibrium thermodynamics, they address control, regulation, robustness and fragility. In terms of applications, I have heard of at least one case where the *in silico* testing of a drug candidate by a pharmaceutical company led to its early elimination, possibly saving the company 100 million euro. Systems biology has also led to the much enhanced production of amino acids in metabolic engineering environments on three continents.

As an enthusiastic scientist, I ultimately enjoy the observation and resolution of paradoxes. A good example is the finding – using systems biology – that the nuclear export of a transcription factor does not suppress transcription as presumed but – on the contrary – enhances transcription as confirmed in models. Where was this found out? In Baden-Württemberg.

The author of this text, Professor Hans V. Westerhoff, is Director of the Manchester Centre for Integrative Systems Biology and of the Manchester Doctoral Training Centre on Systems Biology at the University of Manchester. He also holds the AstraZeneca Chair for Systems Biology at the University of Manchester, as well as the Chair for Microbial Physiology at the VU University Amsterdam.

Hans Westerhoff has been involved in many emerging systems biology programs, including the German HepatoSys, UKs Integrative Systems Biology, Luxembourgs BIOLUXMP, Europe's BioSim, NucSys and EC-MOAN, as well as the transnational SysMO and ERA-SysBio research programs.

He is now engaged with the Future and Emerging Technologies (FET) Flagship ITFoM (IT Future of Medicine) and with the research infrastructure proposal ISBE (Infrastructure for Systems Biology).

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Systems Biology in Baden-Württemberg

BioQuant in Heidelberg

On Heidelberg campus, biomedical research is combined with mathematical and physical approaches in order to elucidate how complex cellular systems function. The BioQuant Center established in April 2007 is the first center for Systems Biology in Germany where experimental and theoretical researchers work together under one roof.

The basis for the successful systems biology research community on Heidelberg campus was laid in 2001. At that time, the state of Baden Württemberg launched a competition aiming at the establishment of new interdisciplinary research centers for the life sciences.
This led to the formation of the interdisciplinary research network Quantitative Analysis of Molecular and Celluar Biosystems (BioQuant) designed to join forces across traditional research boundaries to obtain a quantitative and system-oriented understanding of complex biological processes.

Thanks to its success in this competition, Heidelberg University was able to establish a core structure for the research network where scientists from different disciplines e.g. biology/biomedicine, mathematics, computer sciences, physics, and chemistry work together under one roof. The construction of the building and its basic scientific equipment were financed in equal parts by the federal government and the state of Baden-Württemberg.

The BioQuant Center at Heidelberg University was inaugurated in spring 2007 and offers around 5000 m^2 space for research and education in the field of systems biology.

With several central communication areas, the BioQuant Center ideally promotes scientific communication and interdisciplinary research at the interface between mathematics and experimental life sciences. It has received several prizes for its remarkable architecture. Most recently, the center was awarded with the prestigious Hugo Häring Prize for exemplary buildings in the state of Baden-Württemberg by the Association of German Architects (BDA).
BioQuant currently brings together more than 30 theoretical and experimental research groups who aim at the quantitative and comprehensive description of complex biological systems. The research activities focus on cellular processes with an emphasis on medically relevant topics e.g. virus host cell interactions, regulatory networks and cancer biology.

"There is no doubt that the computer-assisted modeling of biological processes will become indispensable for biomedical research in the future."

Prof. Roland Eils, Director BioQuant Center

Technology platforms

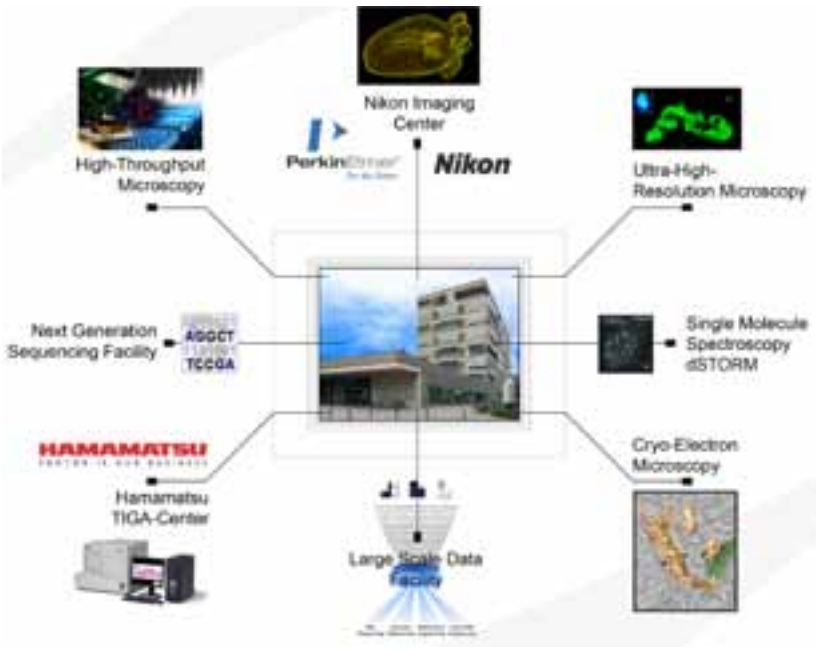
A reliable mathematical description of biological systems depends on the availability of quantitative and spatio-temporal resolved data. In order to accomplish this, BioQuant has been equipped with powerful IT infrastructure as well as a comprehensive technology platform for systematic functional and quantitative live cell imaging.

The imaging systems available range from high and ultra-high resolution microscopy (dSTORM, 4PI-STED), high-content and high-throughput methods to electron microscopy (conventional and cryo EM). BioQuant's technology platform is complemented by a RNAi Screening Facility and a recently established Deep Sequencing Facility. Furthermore, the NIKON Imaging Center and the Hamamatsu TIGA (Tissue Imaging and Analysis) Center are both integral parts of BioQuant's technology platform.

To manage and store the huge amounts of data generated by these technologies, a Large Scale Data Facility for the Life Sciences (LSDF) is being established at the BioQuant Center with financial support from both the federal Government and the state of Baden-Württemberg. In 2012, the LSDF at BioQuant will have a data storage capacity of around 6 petabyte exclusively available for life science research.

Major research focus: cellular processes

With significant support from the state of Baden-Württemberg and the Klaus Tschira Foundation, Heidelberg University pioneered together with several non-university research partners (German Cancer Research Center, European Molecular Biology Laboratory, and the Max Planck Institute for Medical Research) in setting up the first local systems biology initiative (Center for Modeling and Simulation in the Biosciences, BioMS) in Germany in the year 2004.



BioQuant's technology platform

BioMS (coordinated by Prof. Kummer/Prof. Jäger) is one of the main research programs at the BioQuant Center. It focuses particularly on the support and training of young investigators in systems biology.

BioQuant is also home to the BMBF-funded FORSYS ViroQuant Center (coordinated by Prof. Eils/Prof. Wolfrum). FORSYS ViroQuant was established in 2007 and deals with the systems biology of virus host-cell interactions. The interdisciplinary research program is mainly concerned with the viruses that are known to cause AIDS (HIV), chronic hepatitis (HCV) and cervical cancer (HPV). With remarkable support by FORSYS-ViroQuant, a sustainable and internationally recognized research and teaching infrastructure for systems biology was established at the BioQuant Center during recent years.

In addition, numerous projects of the Helmholtz Alliance on Systems Biology, e.g. SBCancer (coordinated by Prof. Eils/PD Dr. Klingmüller), are carried out at the BioQuant Center. This initiative is funded by the German Helmholtz Association. The CellNetworks excellence cluster (coordinated by Prof. Kräusslich) funded under the German Excellence Initiative is to some extent also affiliated with the BioQuant Center.

The BioQuant Center has also been successfully involved in several new systems biology research initiatives, for instance the BMBF-funded programs Virtual Liver, SysMo, MedSys, SysTec, GerontoSys, and EraSysBio, as well as several EU FP7 integrated projects.

Besides its research goals, BioQuant is committed to implementing sustainable education and training infrastructure to provide research-oriented interdisciplinary education in systems biology.
Representative examples are the establishment of an interdisciplinary systems biology curriculum in the international master's program on Molecular Biosciences at Heidelberg University and the Heidelberg iGEM team initiative on the bachelor and master's degree level.

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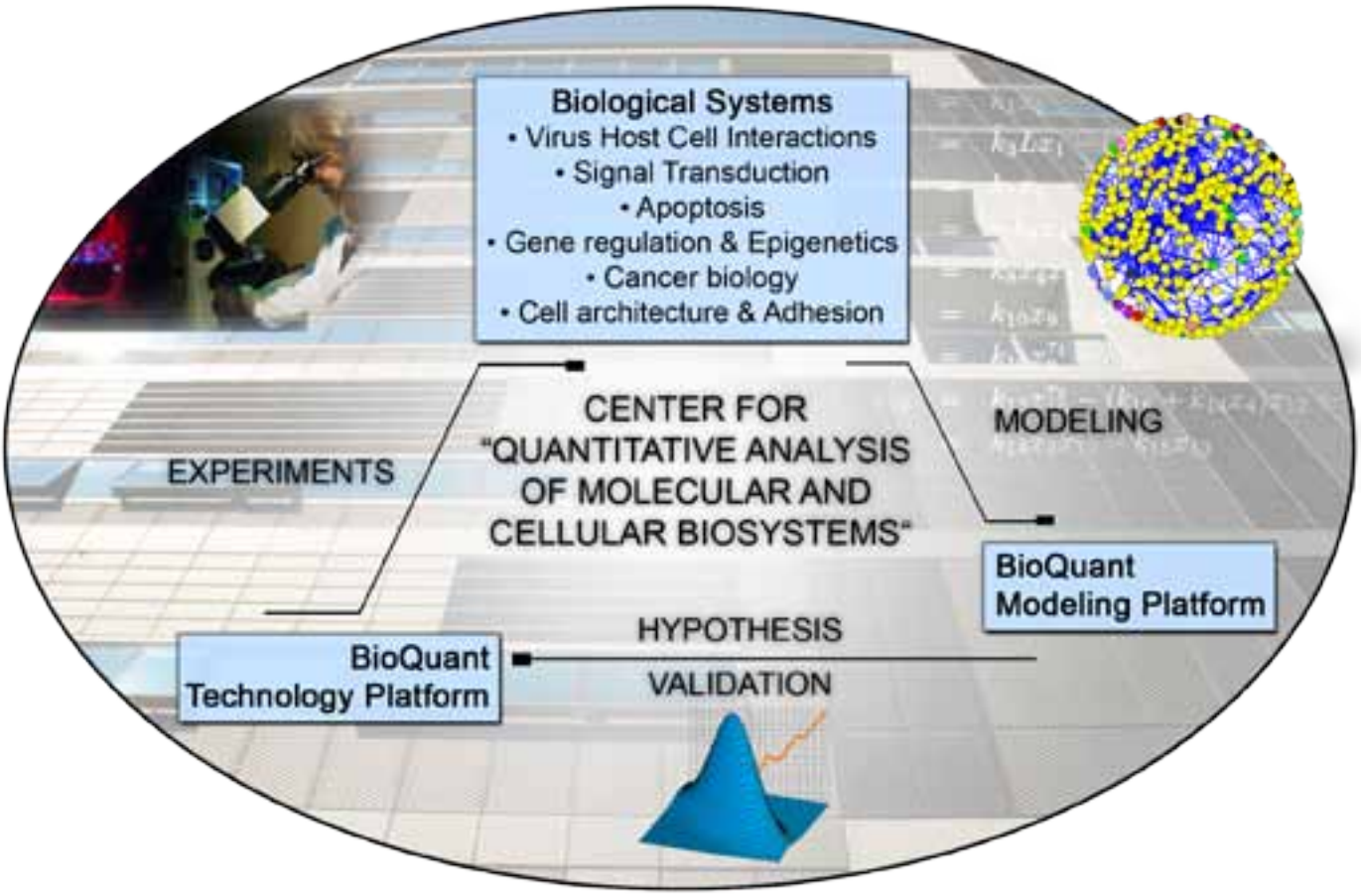
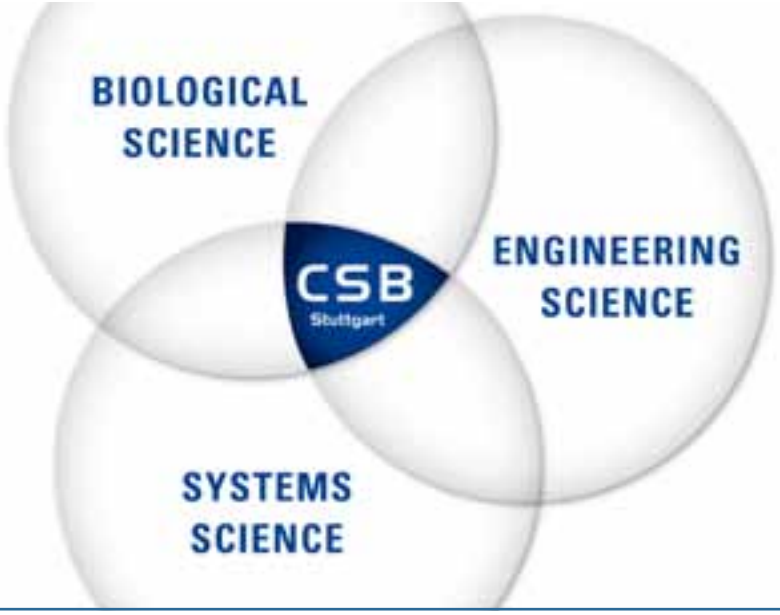
BioQuant
MODEL base of LIFE



BioQuant's interdisciplinary research structure



Center Systems Biology (CSB) in Stuttgart

The Center Systems Biology (CSB) at the University of Stuttgart was set up in 2005, making it to one of the first interfaculty systems biology center in Germany. Systems biology research at the University of Stuttgart stands out for its close networking between systems, engineering and biological sciences and it also has a strong profile that crosses university boundaries.

The systemic treatment of biology at the University of Stuttgart dates back to the early 1990s with the establishment of the new Metabolic Engineering research discipline, followed in the mid-1990s by the Biosystems Engineering priority, which combines systems and engineering sciences approaches. The further development of this concept on the initiative of the Baden-Württemberg government in 2005 led to the establishment of the virtual Center for Systems Biology at the University of Stuttgart.

Work at the Center started in 2006 with the CSB Research Program, twelve projects that brought together research groups from six faculties at the University of Stuttgart and the Proteome Center at the University of Tübingen. The projects were financed for the first three years by the Baden-Württemberg Zukunftsoffensive III program.

Tasks and structure of the CSB

The faculty-independent Center is responsible for the coordination of interfaculty research projects in the field of systems biology and the establishment of a platform for participating institutes and faculties. The necessary infrastructure is provided by the University of Stuttgart. A central coordination office submits joint funding proposals and oversees the planning and administration of projects.

The Central Facility for Advanced Microscopy at the Institute of Cell Biology and Immunology is part of the Center's infrastructure, providing all CSB members with access to state-of-the-art microscopic equipment and services.

"The huge demands on systems biology and the resultant expectations mean that boundaries need to be crossed and bridges need to be established between all the natural sciences and engineering disciplines involved in systems biology. Equally important is the integration of experiments and mathematical modeling as well as the ability to control interactions between the broad spatial and temporal scales of biological systems."

Prof. Matthias Reuss, Director CSB

Research areas

The Center's systems biology research activities concentrate on three areas: the development of methods and tools as well as research in the fields of red and white biotechnology.

Due to its very special combination of research areas - basic principles and applications in the field of white and red biotechnology - the CSB at the University Stuttgart provides an interactive platform for successful integration of the different networks such as metabolism, gene regulation and signal transduction.

Development of methods and tools

Basic principles, fundamentals
- Multi-scale modeling
- Modeling concepts
- Metabolic, regulatory and signaling networks
- New quantitative data
- Systems theoretical investigations

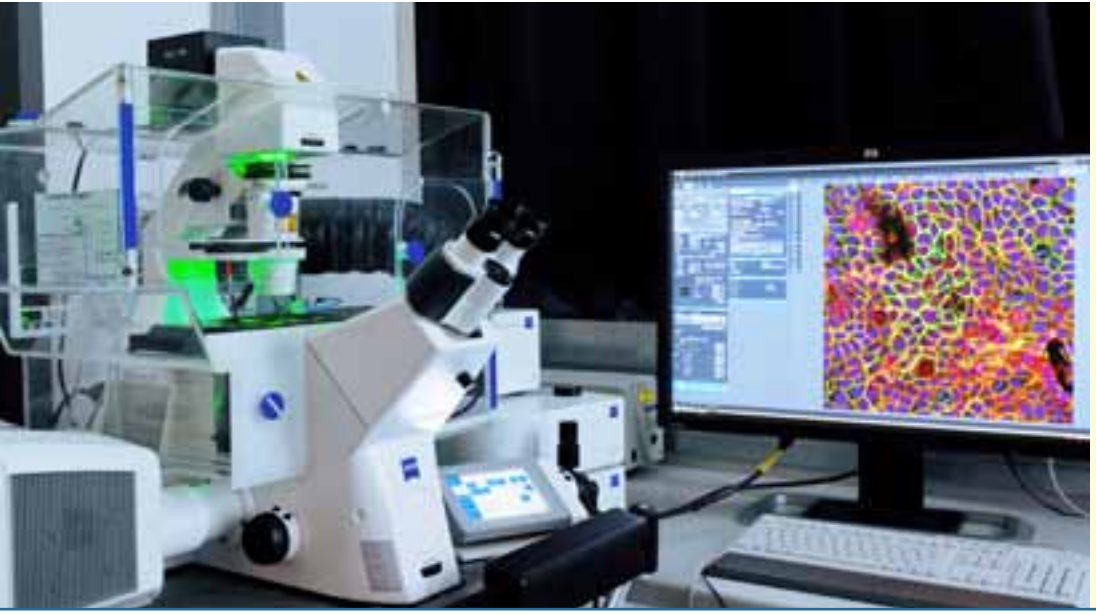
Red Biotechnology

Application to medical and pharmaceutical issues

White Biotechnology

Application to industrial biotechnology
- Metabolic engineering
- Synthetic biology

The three research areas of the CSB are the development of methods and tools and the application of systems biology findings in the fields of red and white biotechnology.



Another major focus of research activities is related to multi scale modeling. The implications of the interactions between the various levels (molecules, cellular networks, cells, tissue, organ and whole organisms for biomedical applications or, in case of biotechnological production, molecules, cellular networks, population, bioreactor and large scale production plant) are quite striking and manifold and demand new modeling and simulation strategies.

"FORSYS Partner: A Systems Biology Approach towards Predictive Cancer Therapy" is one example of many research projects being carried out at the CSB in the field of red biotechnology. This research project uses systems biology and model-based approaches to develop new drugs and methods for the treatment of cancer with special focus on the transport of drugs to targets. The CSB deals with further medical and pharmaceutical issues for example within the BMBF funding initiatives: "New Methods in Systems Biology – SysTec" and "Medical Systems Biology – MedSys."

The background of engineering and systems sciences at the University of Stuttgart has shaped the CSB's life science research activities largely. This, in turn, has led to another distinctive characteristic, namely the CSB's focus on white biotechnology and recently also on synthetic biology where findings gained in systems biology research are used e.g. to create microorganisms for technical production processes. Stuttgart researchers are investigating, amongst other things, the metabolic processes in *Pseudomonas* in order to optimize industrial processes in the long term and develop new biotechnological processes involving the bacterium.

At present, six University of Stuttgart faculties are involved in the CSB's research projects, along with partners from the University of Tübingen, the University of Hohenheim and the University of Magdeburg. External partners include non-university institutions as well as industrial research partners.

More projects are already in the planning stage and it is envisaged that in the long term, the CSB will become a partner in other regional, national and international networks. When the CSB was established in 2005, the founders expected the Center to become self-financed once initial funding came to an end. The CSB was positively evaluated in 2009 and its research activities are currently secured through third-party financing until 2012.

Center Systems Biology (CSB)

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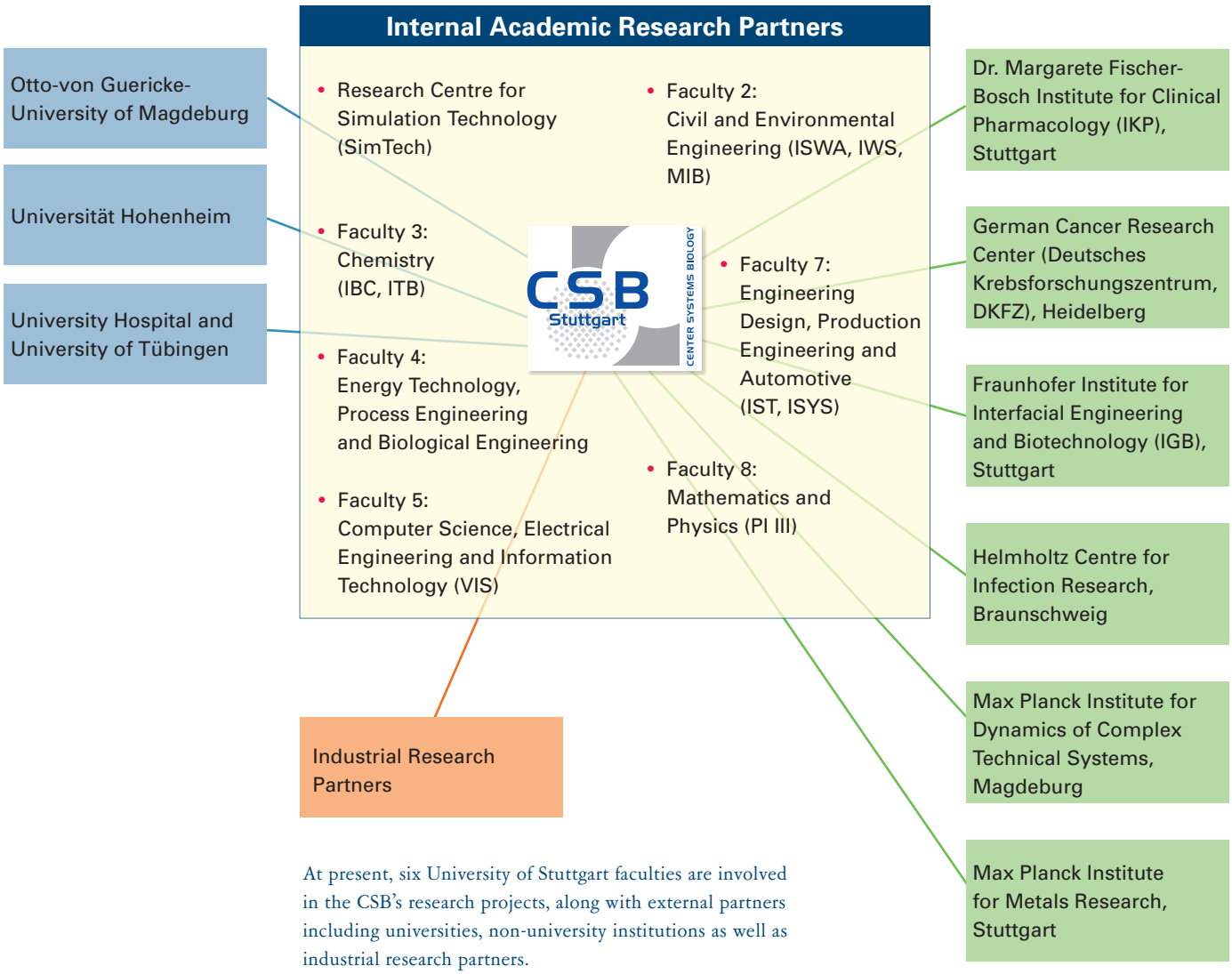

At present, six University of Stuttgart faculties are involved in the CSB's research projects, along with external partners including universities, non-university institutions as well as industrial research partners.

The Center for Biological Systems Analysis (ZBSA) in Freiburg

At the Center for Biological Systems Analysis (ZBSA) in Freiburg, scientists from all the university's natural science faculties and the medical faculty work together on systems biological aspects in an interdisciplinary way. In close cooperation, modellers and laboratory-based scientists focus on the development, verification and optimization of models of biological systems. The four Core Facilities of the ZBSA provide state-of-the-art platform technologies that generate data in the fields of genomics, proteomics, metabolomics and life imaging.

The concept of an interfaculty systems biology center at the University of Freiburg was first mooted back in 2001. Research groups from the university's life sciences and medical faculties submitted a joint application for financial support from the Baden-Württemberg government's "Zukunftsoffensive III" program entitled "Call for the Establishment of Life Science Centers". The Freiburg researchers' application was successful, and the construction and equipping of the ZBSA were carried out with 22.6 million euro in funding from the German and Baden-Württemberg governments. Research began in June 2008 in the building that was specifically created for systems biological research.

As a central institution of the University of Freiburg, the ZBSA comes under the auspices of the university rectorate. The interdisciplinarity of systems biology is reflected in the large number of faculties that contribute to the ZBSA's research activities, including the faculties of biology, chemistry, pharmacy, geosciences, forestry and environmental sciences, mathematics, physics, medicine and engineering.

The ZBSA is divided into three complementary subunits:

- Project groups focusing on different scientific questions
- 4 "Core Facilities" – Genomics, Proteomics, Metabolomics and Life Imaging Center
- Data analysis and modelling

Project groups

In early 2011, twelve project groups were working on different systems biology issues. Some of the project groups contributing to the ZBSA are groups from faculties at the University of Freiburg based in the ZBSA project laboratories alongside third-party funded ZBSA research groups.

The FRISYS (Freiburg Initiative for Systems Biology) research groups deal predominantly with the elucidation of cellular signalling processes during cell growth and differentiation using different model prokaryotic and eukaryotic

"The development of organs from stem cells is governed by complex regulatory networks. Only the quantitative and dynamic understanding of these networks using systems biology approaches will make it possible to explain cell differentiation and open up strategies in the field of regenerative medicine to control the networks."

Prof. Wolfgang Driever, Executive Director ZBSA

organisms. FRISYS was one of only four research projects selected by the German Ministry of Education and Research (BMBF) under the FORSYS initiative in 2006 and is receiving funding of 12.5 million euros between 2007 and 2011.

Researchers at the Centre for Biological Signalling Studies (bioss) combine synthetic biology methods with biological signalling studies in which synthetic biology and systems biology are seen as complementary approaches in the investigation of complex biological systems. The interfaculty bioss excellence cluster is funded under the German federal and state governments' Excellence Initiative. Research at the ZBSA is being carried out by the five junior scientists of the "bioss incubator" funding program as well as by bioss principal investigators.

The ZBSA is also home to research groups from the School of Life Sciences – LifeNet, which is one of the four schools of the Freiburg Institute for Advanced Studies (FRIAS) funded under the German federal and state governments' Excellence Initiative. FRIAS LifeNet works on numerous research topics, including the organization of cells, regulatory networks, the composition of tissue, the study of metabolic processes and products (metabolomics) as well as the analysis of pathological alterations of these processes. A major focus is the development of methods for the investigation of gene and protein regulation. In addition to five faculties of the University of Freiburg, LifeNet also brings together the Max Planck Institute of Immunobiology and the Fraunhofer Institutes for Physical Measurement Techniques (IPM) and Applied Solid State Physics (IAF).

The "Regulatory Networks" research group investigates the functional relationships of Parkinson's disease using the *Caenorhabditis elegans* model organism with the aim of establishing principle methodological approaches that are suitable for modelling cellular interactions.

The Core Facilities

The Core Facilities in which data are acquired and analyzed from the fields of genomics, proteomics, metabolomics and life imaging constitute the ZBSA's second major area of research. The combination of state-of-the-art high-throughput technology and analysis tools is unique in Germany, and is made possible thanks to the cooperation of companies that provide cutting-edge technologies to the Core Facilities, and in turn benefit from working closely with the users.

As they are central institutions of the University of Freiburg, the Core Facilities can also be used by researchers that are not directly part of the ZBSA.

Data analysis: data management and modeling

The fundamental goal of the third ZBSA area is data analysis, with particular focus on data management and modelling. Primary data acquired by the Core Facilities are organized and prepared for subsequent model engineering. The modelers, including mathematicians, physicists and computer scientists, use the data to develop models that are later tested in the project group laboratories.

The new building offers excellent conditions for scientists from a broad range of disciplines to work together. Central communication rooms link the different areas of the building and give researchers from different disciplines the opportunity to exchange information and knowledge. This provides an ideal environment for fulfilling the ZBSA's goal of characterizing complex biological systems through the combination of experimental research, the generation of data using high-throughput methods and the theoretical analysis of primary data.

The first steps have already been taken. The structures that were envisaged in the original funding application are already in place and around 120 people are using the facilities in the search for new insights into biological systems using systems biology approaches.

The Center for Biological Systems Analysis (ZBSA)

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Head Administrator

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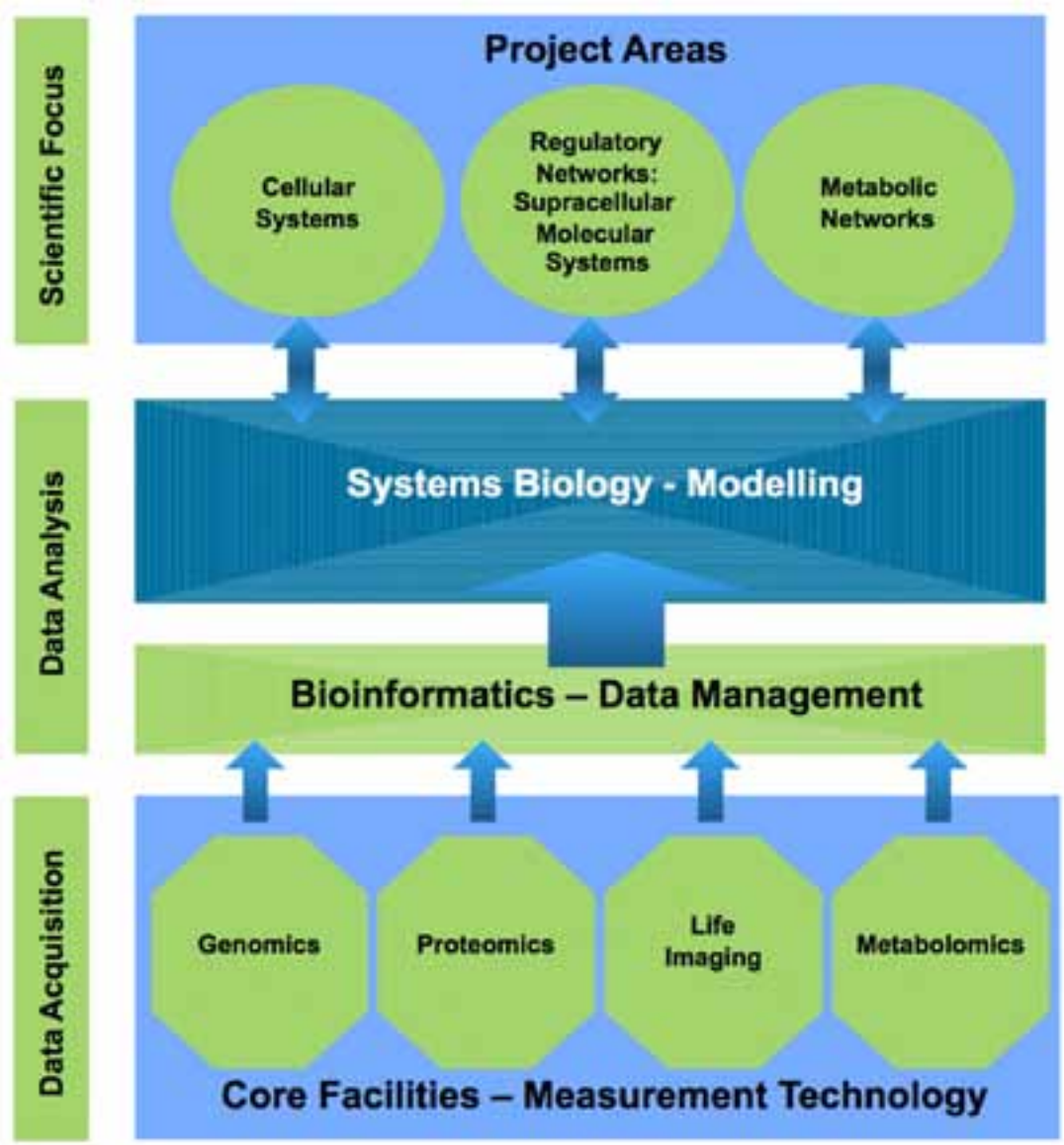
zbsa
zentrum für
biosystemanalyse

Concept of the scientific organisation at the ZBSA



The main activities are data analysis and the resulting engineering models. The data analysts and modeling engineers are supplied with data by the four Core Facilities: (Genomics, Proteomics, Metabolomics and the Life Imaging Center) and by the project groups (FRIAS, FRISYS, bioss and Regulatory Networks). In iterative cycles of model-based experimental investigations and data-based modeling, the researchers achieve validated mathematical models of biological systems.

A scientific discipline with great innovation potential is looking for young talents

Over the last ten years, systems biology has been established as a new research approach with the potential to revolutionize the life sciences. Let us use cells as an example to explain why: In order to understand a cell as a holistic system, it needs to be looked at in a way that does not simply focus on molecular details or the qualitative analysis of cellular processes, but that also enables the quantitative analysis of interactions between the individual components of a cell and the interactions with their environment. The combination of laboratory experiments and the modeling of a particular system enables predictions to be made on the complex behavior of the system under investigation which can then be tested and improved.

In order to undertake such a systems biology research approach, interdisciplinary qualifications are needed. Collaboration between scientists from the fields of biology, mathematics, (bio-)informatics, chemistry, physics and the engineering sciences is indispensable. However, scientific exchange between researchers from different disciplines and with different background knowledge is highly demanding and time-consuming as every discipline has its own terminology, rules and dogmas.

The current scarcity of up-and-coming scientists capable of handling these issues poses a huge challenge for systems biology research. Whether systems biology will gain in importance in the future and prove its value with innovative applications depends decisively on the extent to which the interest of up-and-coming researchers can be directed to this emerging science.

It is therefore important for students to become acquainted with interdisciplinary competences and interdisciplinary work during their studies. The universities and institutes of the three systems biology centers in Baden-Württemberg have already started running courses in the field of systems biology and this will continue in the future. Moreover, other Baden-Württemberg universities have also integrated systems biology into their curricula. The following study and doctoral program are all designed to give insights into systems biology courses that are currently on offer.

"Interdisciplinary training is essential for successful research in systems biology. However, traditional cell and molecular biology curricula often do not cover required mathematics and physics knowledge. In Heidelberg, we have therefore chosen to combine all the relevant areas from different disciplines in one highly interdisciplinary teaching program."

Prof. Ursula Kummer, BioQuant Center and coordinator of BIOMS, Universität Heidelberg

Freiburg: Bioinformatics and Systems Biology

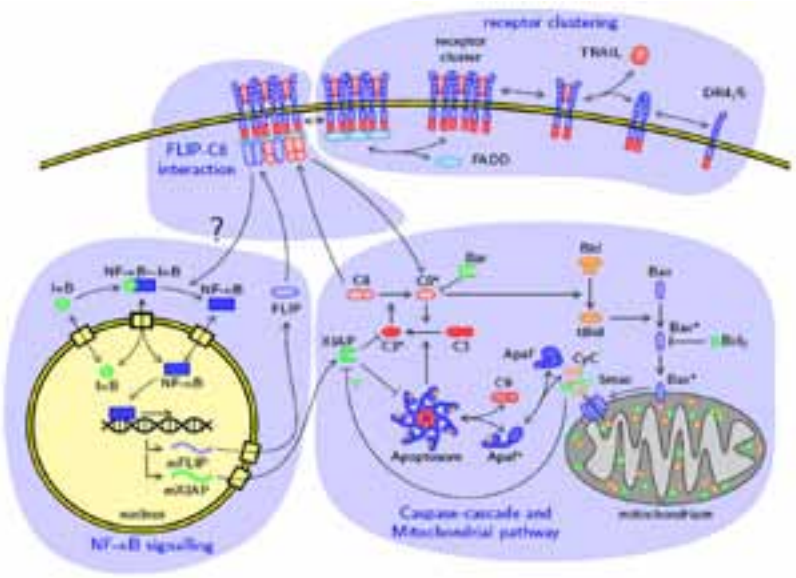
The University of Freiburg offers a two-year, interdisciplinary Bioinformatics and Systems Biology master's degree course (Master of Science/MSc) for German and foreign students. The students deal with topics from the disciplines of bioinformatics, systems biology, mathematics, computer science and biology in small international groups where discussions are held in both English and German. Students participate in compulsory modules but may also opt for certain lectures, seminars and lab courses according to their background, language proficiency and areas of interest.

In order to be eligible for the Bioinformatics and Systems Biology master's degree course, BSc students studying Biology or Computer Science at Freiburg University are advised to opt for specific modules. Students holding a BSc in biology, computer science or another scientific discipline from another university need to present equivalent qualifications. The study program was initiated by the Freiburg Initiative for Systems Biology (FRISYS) in the 2008 winter semester with the goal of integrating top systems biology research in Freiburg into university education. The master's degree course is jointly run by the Freiburg Faculties of Biology and Technology.

Heidelberg: Major Systems Biology and teaching activities at bachelor level

Supported by the BMBF-funded FORSYS ViroQuant consortium and the Helmholtz Alliance on Systems Biology, an interdisciplinary teaching program for systems biology has been established at Heidelberg University during the recent years.

Systems Biology is an integral part of the curriculum offered by the Faculty of Biosciences at Heidelberg University. Bachelor level students can already opt for seminars, lectures and practical courses on systems biology. Further specialization is offered by the international master's program entitled Molecular Biosciences. Since 2008 a major program on systems biology has been offered as one of eight major master's subjects. This program combines theoretical and experimental lectures and courses and thereby promotes familiarity with interdisciplinary research approaches. The four-semester curriculum covers fundamental topics in bioinformatics, computational analysis, network reconstruction, and dynamic pathway analysis as well as multi-scale modeling. The biological systems to be presented focus on cellular systems with emphasis on



Death-receptor-mediated intracellular signalling pathways.

infectious diseases, cellular signaling, and cancer biology. Master students follow a training course run by BioQuant in cooperation with several others University institutes (e. g. the Institute of Pharmacy and Molecular Biology, the Institute of Theoretical Physics, and the Interdisciplinary Center for Scientific Computing) as well as the German Cancer Research Center. Practical courses and the master's thesis are performed within the framework of the research activities of the teaching faculty. Thus, from an early stage on students are integrated into cutting-edge research projects. In January 2009, an international exchange program was initiated with the universities of Amsterdam, Luxembourg, Goteborg, and Manchester. This offers students the opportunity to carry out internships at the participating Systems Biology centers for up to one semester.

Stuttgart: Systems biology combined with systems and engineering sciences

Systems biology is taught at the University of Stuttgart in the Technical Biology and Technical Cybernetics programs. Major contributors to the curriculum are the Institute of Systems Dynamics, the Institute of Bioprocess Engineering, the Institute of Systems Theory and Automatic Control and the Center Systems Biology.

The Technical Biology (BSc and MSc) course differs from classical biology studies in that fundamental mathematical and bioscientific topics are combined with issues from the fields of engineering and systems science. Systems biology is an integral part of the BSc program, which leads to admission to the Technical Biology master's degree program due to be introduced in the 2012/2013 winter semester.

The Technical Cybernetics bachelor's program deals with fundamental topics related to dynamic systems. Biological Systems may be chosen as an optional subject to broaden fundamental knowledge and know-how in the field of modeling and analysis of biological systems. The University of Stuttgart plans to offer a Technical Cybernetics master's degree course from the 2011/2012 winter semester onwards.

The Process Engineering BSc degree program focuses on fundamental issues in technical biology and bioprocess engineering. The subsequent master's program offers systems biology lectures, seminars etc. and courses in metabolic engineering (specialization in bioprocess engineering) which is important for systems biology applications in industrial biotechnology.

At present, the University of Stuttgart is planning to establish a Systems Biology master's degree program, which will admit students from the three programs mentioned above.

In addition, the Stuttgart Research Centre for Simulation Technology and the SimTech (Simulation Technology) cluster of excellence introduced the Simulation Technology BSc degree program at the beginning of the 2010/2011 winter semester. A master's degree program is due to start in the 2013/2014 winter semester. From their third year onwards, BSc students can select modules from all the bachelor courses offered by the University of Stuttgart in

"Systems biology offers students with a theoretical background in the field of either physics, mathematics or computer sciences an exciting field of work where they can put their knowledge and skills to good use in a previously unknown but highly interesting area. The experience they can gain from systems biology opens up a broad range of career options at the boundary between the theoretical and the life sciences."

Prof. Jens Timmer, Delegate Executive Director ZBSA, directorate FRIAS, University of Freiburg

mathematics, biosciences, engineering sciences and computer science. The students are also trained in simulation technology and interdisciplinary principles and can chose systems biology as their major subject. Simulations are used to answer questions such as: How do molecules bind to each other? or How does a drug spread in the body of a person suffering from lung cancer?

Further study programs focusing on systems biology

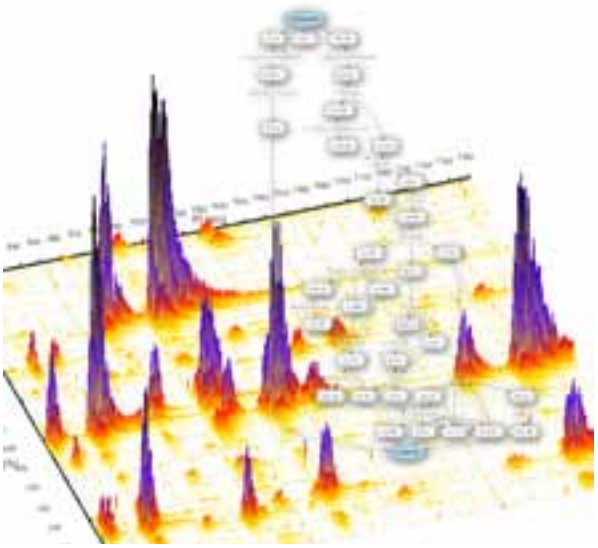
At the University of Tübingen, systems biology is closely connected with the Center for Bioinformatics (which is part of the Department of Computer Sciences). Systems biology is an integral part of MSc and BSc degree programs, which also offer students the possibility to chose systems bioinformatics as a subject.

Seminars, lectures and practical training in systems biology are also available for computer science and molecular medicine students at the Ulm-based Institute of Neuroinformatics. At the Karlsruhe Institute of Technology, systems biology is dealt with in lectures and practical training as part of the Biology BSc study program. This emerging field of science is slowly but steadily becoming part of university curricula. For example, systems biology is taught at the Furtwangen University of Applied Sciences as part of the Biomedicine priority of the Biomedical Engineering master's degree course.

Doctoral programs

Graduate schools (also referred to as 'research training groups') offer doctoral students a training program that goes beyond their own research priority, and is therefore an ideal platform for interdisciplinary scientific exchange and for establishing networks among up-and-coming scientists. First-class supervision in an excellent scientific environment in graduate schools enables students to obtain excellent qualifications.

The Freiburg Initiative for Systems Biology supports doctoral students by offering courses and meetings designed to impart knowledge and skills in specific systems biology methods. Doctoral students can also attend seminars, courses, meetings and practical training from the Bioinformatics and Systems Biology master's degree course. The Spemann Graduate School of Biology and Medicine was established in Freiburg as a result of the University's



Modern mass spectrometry techniques generate very comprehensive and complex data. The automatic analysis of the data provides detailed insights into the dynamics of biological networks.

outstanding achievements in the German government's excellence initiative. The Graduate School works closely with the BIOSS excellence cluster, the ZBSA and FRISYS with the aim of involving their PhD candidates in current research projects while setting up courses and seminars in the field of systems biology.

The BioQuant-PhD program on Systems Biology is integrated into the curricula of both the Hartmut Hoffmann-Berling International Graduate School of Molecular & Cellular Biology and the Heidelberg Graduate School of Mathematical and Computational Methods for the Sciences. Within this framework, topic-based workshops, lab rotations and a spring school on modeling are mandatory. BioQuant also hosts a seminar series introducing special topics of current systems biology research by invited guest speakers.

The Graduate School of the SimTech excellence cluster at the University of Stuttgart also offers advanced training in systems biology. These courses are provided in cooperation with the Institute of Systems Theory and Automatic Control and the Institute of Applied and Experimental Mechanics.

The MTZ® Awards for Systems Biology

But not only research institutions have recognized the huge potential of systems biology by integrating the subject into their curricula. Since 2006, the MTZ®stiftung foundation has been committed to biomedical cell biology, genetic and stem cell research. The foundation's MTZ®-BioQuant Award for Systems Biology is awarded to outstanding young scientists at the Heidelberg-based BioQuant research network who have made a considerable contribution to the interdisciplinary field of systems biology. The MTZ®-Award for Medical Systems Biology jointly offered by MTZ®stiftung and the German Ministry of Education and Research is awarded on a national level for outstanding achievements by young scientists in the field of medical systems biology. It is worth noting that a comparatively high number of young Baden-Württemberg scientists has been awarded this prize.

Service facilities in Baden-Württemberg

Dr. Holger Erfle S. 32

Dr. Niels Grabe S. 34

Prof. Armin Huber S. 36

Dr. Thorsten Kurz S. 38

Dr. Yong Li S. 39

Prof. Boris Maček S. 40

Dr. Roland Nitschke S. 42

Dr. Andreas Schlosser S. 44

Andrea Weber S. 46

Dr. Holger Erfle

Universität Heidelberg
BioQuant Center
ViroQuant-CellNetworks RNAi Screening Facility

4 members of staff

The ViroQuant-CellNetworks RNAi Screening Facility provides an RNAi screening platform including assay automation and advanced automated microscopy techniques. Moreover, in collaboration with various internal and external groups the Core Facility develops new and enhances existing technologies in terms of fully automation towards high content information acquisition. Furthermore it implements data management tools using novel standards for controlling, monitoring and storing of the data highly efficiently. The aim is to collect maximum information for a biological question in the cellular context.

In systems biology knowledge of the function and interactions of all elements describing the system of interest is indispensable. By knocking-down genes in a systematic manner and by examining phenotypic changes with automated high resolution microscopy the RNAi Screening Facility contributes to an extremely high degree to systems biology.

The RNAi Screening Facility provides a fully automated high-throughput and high-content microscopy-based screening platform in BioQuant. It could as the first lab automate solid phase transfection on cell arrays and in 384 well plates. Its portfolio includes manufacturing of human genome-wide siRNA microarrays and multiwell plates, automated time-lapse microscopy of human cells transfected on those arrays or multiwell plates and computerized analysis of the phenotypes by digital image processing.

The ViroQuant-CellNetworks RNAi Screening Facility assists in assay development for high throughput screening and performs in the frame of VIROQUANT with the corresponding groups genome wide RNAi screens with the aim to identify cellular genes involved in viral replication of HIV, HCV, DV. The general idea is to systematically knock down host cell genes, to quantify changes in the level of viral protein expression, and to detect genes whose knock down leads to significant changes in virus replication.

For first genome wide screens a druggable siRNA library (9102 genes, 27306 siRNAs, 2418 control siRNAs) has been used and was extended recently to genome-wide (20203 genes, 60609 siRNAs, 5366 controls). The first big screens of 9102 “druggable” human target genes resulted in a broad set of genes potentially involved in replication of HIV-1, HCV and DV and the “hits” revealed are under statistical and bioinformatical evaluation.

Besides those screens around 10 screens are ongoing in collaboration with diverse groups at DKFZ and the University of Heidelberg. The unit is capable to fabricate substrates and perform nearly 15 genome-wide screens per year.

Moreover, the Facility enhances existing technologies in terms of fully automation and implements data management tools using novel standards for monitoring, controlling and storing of the data in a highly efficient manner.

Developments and grants:

The group coordinates the BMBF funded "SysTec"project "Functional analysis of non-coding RNAs in living cells" and the Baden-Württemberg Stiftung funded "Neue Methoden in den Lebenswissenschaften" project "An integrated high-throughput and super high-resolution platform for fluorescence microscopic analysis of miRNA-targets in living cells".

Special equipment and techniques

- RNAi Library for genome wide screens
- automated liquid handler "Star" from Hamilton
- automated microarrayer („Pro", BioRad)
- 3 automated wide-field scanning microscopes "ScanR" from Olympus Biosystems, 2 equipped with incubation chambers for live cell imaging.
- 2 automated SP5 CLSM from Leica, equipped with incubation chambers for live cell imaging.

Joint research projects

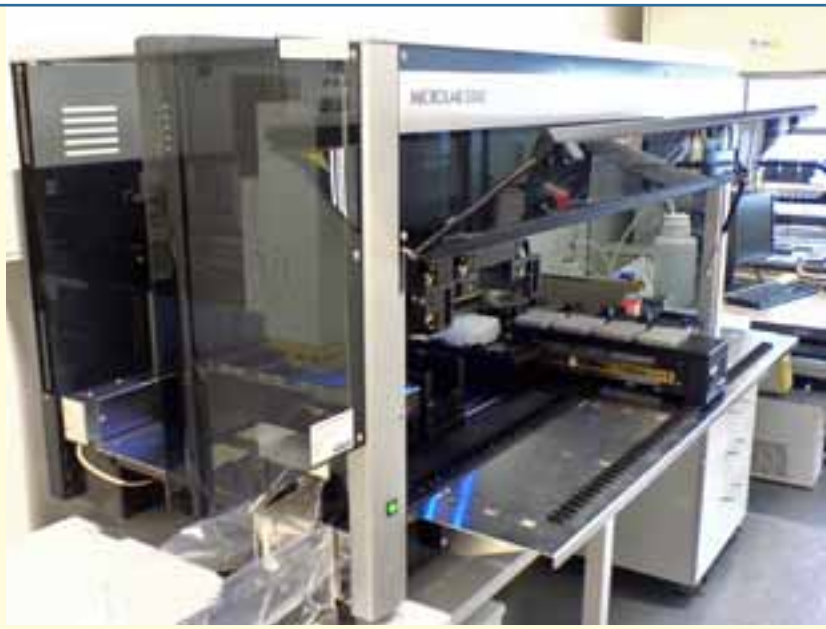
- FORSYS/ ViroQuant (BMBF)
- CellNetworks

Cooperations

- The facility is at the moment used from or collaborates with more than 100 users of the scientific community in Heidelberg.

Selected publications

- From experimental setup to bioinformatics: an RNAi screening platform to identify host factors involved in HIV-1 replication. Börner K, Hermle J, Sommer C, Brown, N, Knapp B, Glass B, Kunkel J, Torralba G, Reymann J, Beil N, Beneke J, Pepperkok R, Schneider R, Ludwig T, Hausmann M, Hamprecht F, Erfle H, Kaderali L, Kräusslich HG and Lehmann M. Biotechnol J. 2010 Jan;5(1):39-49.
- Next generation 9216 microwell cell array for high content screening microscopy. Reymann J, Beil N, Beneke J, Kaletta PP, Burkert K and Erfle H., Biotechniques, 2009 Oct;47(4):877-8.
- Identification of cholesterol-regulating genes by targeted RNAi screening. Bartz F, Kern L, Erz D, Zhu M, Gilbert D, Meinhof T, Wirkner U, Erfle H, Muckenthaler M, Pepperkok R and Runz H. Cell Metab. 2009 Jul;10(1):63-75.



Automated liquid handler "Star" from Hamilton

Dr. Niels Grabe

Universität Heidelberg
BioQuant Center
Hamamatsu Tissue Imaging and Analysis Center

18 members of staff (biologists, bioinformaticians)

The Hamamatsu Tissue Imaging and Analysis (TIGA) Center at the University of Heidelberg is a unique cooperative project in Germany that was established in 2007 with the goal of integrating virtual microscopy into clinical and research applications. The TIGA-Center plays a pioneering role in Europe in the introduction of virtual microscopy into clinical and research applications (Grabe N., 2009).

The TIGA-Center is a joint initiative of the Institute of Pathology and the Institute for Medical Biometry and Informatics at the Heidelberg University Hospital, the National Center for Tumour Diseases (NCT Heidelberg) and the Japanese company Hamamatsu Photonics. TIGA is an integral part of the technology platforms of BioQuant, the interdisciplinary center for systems biology at the University of Heidelberg. In technological terms, the TIGA-Center is dedicated to the fully automated microscopic analysis of tissue slices. At the heart of TIGA's technology platform is the "NanoZoomer" scanning robot developed by Hamamatsu Photonics which enables the automated microscopic imaging of whole slides (Fig. 1).

Quantum leap in tissue research: The digitalised tissue slices are used in routine clinical investigations of histological preparations, and also form the basis for the application of systems biology in the field of medicine. The NanoZoomer provided by Hamamatsu Photonics for automated tissue slide scanning at the TIGA-Center is a unique technology that will continue to be of fundamental importance for pathological investigations in the future. Automated whole-slide imaging (virtual microscopy) enables a completely new, quantitative approach for the analysis of tissue morphology and cell conglomerates. Information about tissue (e.g., different protein expression patterns inside a cell conglomerate) obtained with automated image processing forms the basis for the mathematical modelling of the underlying cellular networks. Therefore, this allows for a systems biology approach to analysing the processes that underlie cell-cell interactions and forms the basis for the spatial understanding of dysfunctional tissues and entire organs.

Systems pathology in cancer research: Located and embedded in the structures of BIOQUANT, the TIGA-Center is part of BMBF-funded systems biology research programmes such as FORSYS-Partner and MedSys. The main focus of these projects is the mathematical modelling of pathological alterations of epithelial tissue homoeostasis like those that occur during wound healing (see special article on this topic in this brochure).

This work forms the basis for the application of systems biology in tissue-related clinically relevant biomedical applications. Through its connection with the NCT's tumour and tissue bank, virtual microscopy is also used for the comprehensive analysis of the biomedical processes involved in tumour development and metastasis. The combination of data obtained from expression analyses using microarrays with the quantitative spatial microscopic imaging of whole tissue slides forms the basis of mathematical models that can be used for the development of new diagnosis and therapy methods. The models developed in this new systems pathology area take into

account information on the molecular, gene-regulatory and morphological tissue level, thereby enabling realistic models of complex diseases to be developed. These models can be of direct benefit for clinical applications in terms of diagnosis, prognosis and therapy.

In cooperation with the NCT Heidelberg, the systems pathology approach is currently used to investigate metastasing colorectal cancer. Using virtual microscopy, researchers are investigating the impact of immune cells on the long-term progression of this tumour disease. Preliminary results suggest a close connection between the success of chemotherapies and the immune response of individual patients (Halama N. et al., 2009, 2010), in which the density and distribution of immune cells in the tumour tissue plays an important role in the analysis of individual patients.

Joint research projects

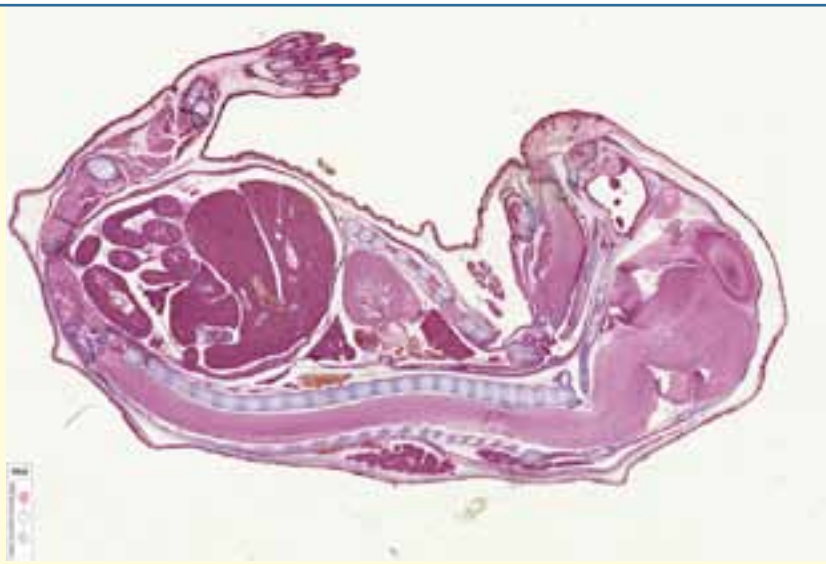
- Gerontosys (BMBF): Stromal ageing
- MedSys (BMBF): Medical systems biology of chronic wounds
- Virtual Liver (BMBF): Virtual microscopy in the "Virtual Liver" competence network
- FORSYS Partner (BMBF): Reconstructing networks of epithelial tissue homoeostasis

Cooperations

- The TIGA Center is exclusively financed through third-party-funded projects undertaken in cooperation with external partners.

Selected publications

- Pommerencke T, Westphal K, Ernst C, Safferling K, Dickhaus H, Steinberg T, Tomakidi P, Grabe N. Spatial quantification and classification of skin response following perturbation using organotypic skin cultures. Bioinformatics, accepted; in press
- Halama N, Zoernig I, Michel S, Kloor M, Grauling-Halama S, Schirmacher P, Jäger D, Grabe N. Tumor Maps: Quantification of Prognostic Immune Cell Markers in Colorectal Cancer Using Whole Slide Imaging. Analytical and Quantitative Cytology and Histology, in press
- Grabe N, Pommerencke T, Steinberg T, Dickhaus H, Tomakidi P. Reconstructing protein networks of epithelial differentiation from histological sections. Bioinformatics. 2007 Dec 1;23(23):3200-3208. PMID: 18042556



Prof. Armin Huber

Universität Hohenheim
Life Science Center
Proteomics Core Facility

5 members of staff (2 chemists, 2 biologists and 1 biomedical researcher)

The Proteomics Core Facility of the Life Science Center (LSC) is part of the University of Hohenheim and it focuses on genome and proteome analyses. It is equipped with state-of-the-art devices for carrying out differential gene and protein expression analyses as well as mass spectrometric analyses of proteins, peptides and other biomolecules.

In addition to contract research, the Proteomics Core Facility also undertakes own research projects in the field of proteomics. Major priorities are differential protein expression analyses and the analysis of posttranslational protein modifications (e.g., phosphorylation and glycosylation). Differential protein expression analyses are carried out using 2D-DIGE or nano-LC-ESI-MS. Posttranslational modifications are identified and, if applicable, also quantified using mass spectrometric methods such as nano-LC-MALDI-TOF or nano-LC-ESI-MS/MS following the specific enrichment of modified peptides.

Since September 2009, the Proteomics Core Facility has been involved in the BMBF-funded project "Systems Biology in *Pseudomonas* for Industrial Biocatalysis" whose objective is to establish an efficient biocatalyst platform for application in the field of white biotechnology based on systems biology analysis of established and newly generated *Pseudomonas* strains. The systems biology analysis of *Pseudomonas strains* is based on experimental data on the proteome, transcriptome and metabolome of the bacteria acquired under variable, process-related conditions. The acquired data will be used to develop dynamic, computer-based models of metabolic processes in *Pseudomonas*, which will in turn be used for the rational development of bacteria using biotechnological procedures. The project is carried out in collaboration with BASF SE and Insilico as well as with a number of academic partners at the University of Stuttgart. The subproject being worked on by the Proteomics Core Facility relates to the quantitative analysis of the *Pseudomonas* proteome under conditions relevant for industrial processes. State-of-the-art methods, including quantitative protein analysis (2D-DIGE, MALDI-TOF, LC-ESI-MS/MS), are used to obtain an analysis of the regulatory mechanisms at the cellular level. Researchers will initially investigate alterations in the proteome of a reference strain in the presence of solvents used in biotechnological production (e.g., butanol or glyoxylic acid). In a next step, investigations will be carried out with recombinant *Pseudomonas* strains and the data will be compared with reference strain data. The results are aimed at obtaining a better understanding of the mechanisms of solvent tolerance in *Pseudomonas* bacteria, that will help to optimize the biotechnological syntheses of relevant chemicals.

In addition to his post as head of the LSC's Proteomics Core Facility, Prof. Huber is also chair of the Department of Biosensorics at the Institute of Physiology.

Special equipment and techniques

- MALDI-TOF, nano-LC-MALDI coupling
- ESI-MS
- Nano-HPLC, HPLC
- 2D-electrophoresis, 2D-DIGE
- Identification and quantitative analysis of posttranslational protein modifications
- Equipment for DNA array hybridisation
- DNA array scanners

Joint research projects

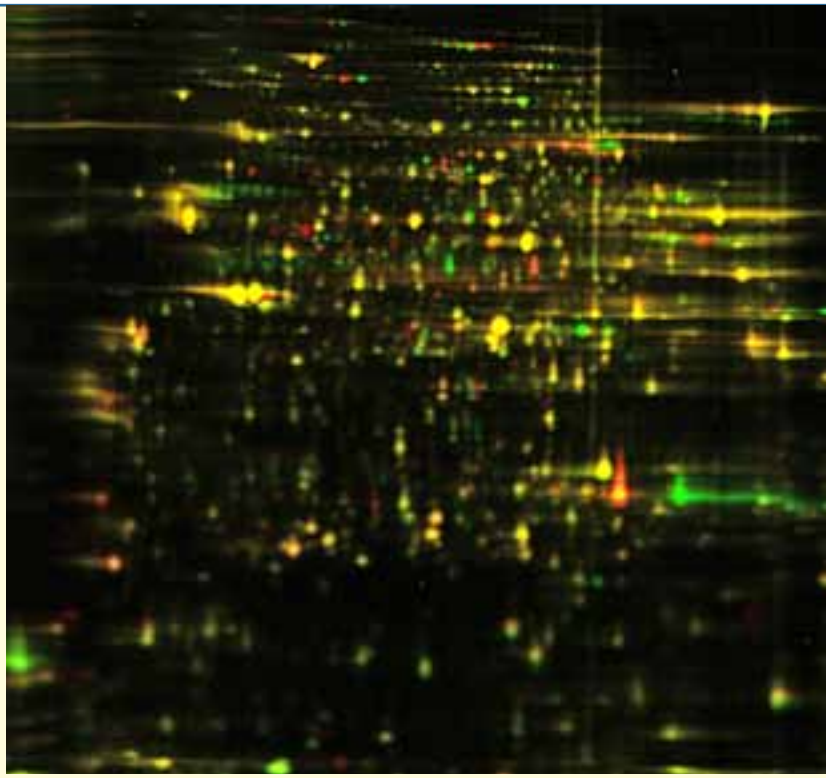
- Systems Biology in *Pseudomonas* for Industrial Biocatalysis (BMBF)

Cooperations

- The services of the Proteomics Core Facility are available to staff at the University of Hohenheim as well as external cooperation partners. The Proteomics Core Facility works closely with the mass spectrometry core facilities of the ZMBH and DKFZ in Heidelberg in the field of method development for mass spectrometric protein analytics. At present, 14 research groups of the University of Hohenheim and 9 external cooperation partners use the Core Facility's services.

Selected publications

- Voolstra, O., Oberhauser, V., Sumser, E., Meyer, N.E., Maguire, M.E., Huber, A., and von, Lintig, J. (2010). NinaB is essential for *Drosophila* vision but induces retinal degeneration in opsin-deficient photoreceptors. J. Biol. Chem. 285, 2130-2139.
- Cedzich, A., Huttenlocher, F., Kuhn, B.M., Pfannstiel, J., Gabler, L., Stintzi, A., Schaller, A. (2009) The protease-associated (pa) domain and C-terminal extension are required for zymogen processing, sorting within the secretory pathway, and activity of tomato subtilase 3 (SLSBT3). J. Biol. Chem. 284; 14068-14078.
- Voolstra, O., Beck, K., Oberegelsbacher, C., Pfannstiel, J., Huber, A. (2010) Identification and functional characterization of light-dependent phosphorylation sites of the *Drosophila* TRP ion channel. J. Biol. Chem. 285, 14275-14284.



The figure shows a photograph of a differential two-dimensional gel electrophoresis (2D-DIGE) involving fluorescence-labelled proteins. The photo shows a comparison of protein extracts of the heads of wild-type Drosophila (Cy3-labelled, green) and those of an eyeless mutant (Cy5-labelled, red). The objective of the experiment is to identify proteins that are specifically expressed in the eyes. Identical quantities of a certain protein in both wild-type and mutant flies result in yellow spots; differentially expressed spots are green or red. The latter can be excised from the gel and subsequently identified using MALDI-TOF or ESI mass spectrometry.

Dr. Thorsten Kurz

University of Freiburg
ZBSA
Core Facility Genomics

3 members of staff (lab technicians, bioinformaticians)

The basic purpose of the Core Facility Genomics is the establishment of state-of-the-art technologies and the provision of scientific and metrological services for all projects carried out by the faculties of the University of Freiburg and the Freiburg University Medical Centre.
The "Core Facility Genomics" assures the acquisition of primary data, which, on the one hand will generate similar data on the international level, and on the other hand guarantees the diversity of analyses that are needed to acquire quantitative data from numerous system components.
In the post-genomic era, the focus of the life sciences has shifted from the identification and functional analysis of individual genes to the investigation of functional networks of many genes and gene products, with the overall goal of gaining a molecular understanding of entire biological systems. In order to achieve this, it is necessary to acquire quantitative data of excellent temporal and spatial resolution from many system components. Bioinformatics and modelling are used to process the data and develop systems models, which not only provide explanations but are also of predictive value.

The Core Facility Genomics aims to acquire quantitative data from many system components and subsequently integrate the data into predictive models. The researchers have the following technology and application spectrum at their disposal:

Special equipment and techniques

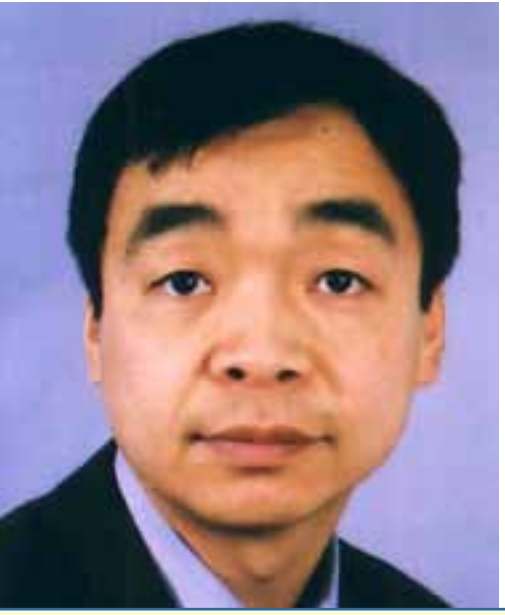
- Illumina GAIIx (Solexa) (Deep sequencing): Library Type, Fragment, Paired-End, Mate Pair
- Chip-Sequencing for: Reduced representation sequencing, Targeted genomic resequencing, Paired end sequencing, Metagenomic sequencing, Transcriptome sequencing, Small RNA sequencing, Sequencing of bisulfite-treated DNA, Chromatin immunoprecipitation-sequencing (ChIP-Seq), Nuclease fragmentation and sequencing, Molecular barcoding
- Agilent Technologie / Microarrays for: Gene Expression, Oligo aCGH / CNV Analysis, microRNA, ChIP-on-chip DNA methylation, SpliceArray, custom
- Illumina iSCan / Microarrays for: SNP Genotyping (Whole Genome + custom), Gene Expression, Oligo aCGH / CNV Analysis, microRNA, ChIP- on-chip, DNA methylation, SpliceArray, custom

Cooperations

- The Core Facility Genomics works in close cooperation with the Institute of Medical Biometry and Medical Informatics and with numerous departments at the University of Freiburg and the University Medical Centre Freiburg as well as with other university facilities.

Selected publications

- Klingmüller, U. et al. Primary mouse hepatocytes for systems biology approaches: a standardized in vitro system for modelling of signal transduction pathways. IEE Proc Syst Biol 153, 433-447 (2006).
- Mohr R., Voss B., Schliep M., Kurz T., Maldener I., Adams D.G., Larkum A.D.W., Chen M., Hess W.R. (2010) A new chlorophyll d-containing cyanobacterium: Evidence for niche adaptation in the genus Acaryochloris. ISME J.



Dr. Yong Li

University of Freiburg
ZBSA
Core Facility Data Management

2 members of staff (biologist, computer scientist)

Modern high-throughput technologies such as microarray and mass spectrometry generate a huge amount of experimental data, and it becomes challenging to manage and integrate these data for further analysis.

The FRISYS Core Facility Data Management manages and supports a number of bioinformatics software to fulfill the "omics" data management and integration requirements of FRISYS groups working with various model organisms. These software are dedicated to transcriptomics and proteomics data processing, analysis and visualization, as well as literature mining. The experimental data are processed in a standardized and integrated manner. All the processing steps along with the experimental data are stored in a central server. The Core Facility not only supports the users using existing software by e-mail helpdesk and regular on-site user trainings, but also provides customized data analysis solutions to address specific needs of users using open source software such as R/Bioconductor.

The Core Facility Data Management serves as a bridging step between raw experimental data and mathematical modeling.

Special equipment and techniques

- "Omics" data analysis using Expressionist and R/Bioconductor

Joint research projects

- FORSYS/ FRISYS (BMBF)

Cooperations

- The service of the Core Facility is used by many research groups at the University of Freiburg and the University Medical Centre Freiburg.

Selected publications

- B. Ulker, Y. Li, M.G. Rosso, E. Logemann, I.E. Somssich, B. Weisshaar. (2008) T-DNA-mediated transfer of Agrobacterium chromosomal DNA sequences into plants. Nat Biotechnol 26(9): 1015-7.
- Y. Li, M.G. Rosso, P. Viehoever, B. Weisshaar. (2007) GABI-Kat SimpleSearch: an Arabidopsis thaliana T-DNA mutant database with detailed information for confirmed insertions. Nucleic Acids Res. 35(Database issue): D874-8.
- Y. Li, M.G. Rosso, B. Ulker, B. Weisshaar (2006) Analysis of T-DNA insertion site distribution patterns in Arabidopsis thaliana reveals special features of genes without insertions. Genomics 87(5): 645-52.

Prof. Boris Maček

University of Tübingen
Interdepartmental Institute for Cell Biology, Proteome Center Tuebingen

8 members of staff (3 biologists, 1 biochemist, 1 biotechnologist, 1 information scientist and 1 lab technician)

Systems biology relies on global analytical methodologies such as genomics, transcriptomics and proteomics to provide a quantitative description of the living cell. It is widely accepted that system complexity grows in the direction genome - transcriptome - proteome, and that studying proteins, as well as their modifications and interactions provides the best measure of the gene function.

The PCT develops and applies state-of-the-art methodologies in quantitative mass spectrometry-based proteomics. It currently employs a staff of 10 scientists and support personnel and operates on ca. 500 m^2 of laboratory and office space. The laboratory is equipped with several LC-MS/MS systems, including a high accuracy mass spectrometer (LTQ-Orbitrap), and posesses elaborate infrastructure for protein biochemistry, tissue culture, molecular biology and bioinformatics.

The major research area of the PCT is the investigation of the structure and evolution of signal transduction networks in prokaryotes and eukaryotes, with an emphasis on phosphoproteomics and identification of kinase substrates. Other research areas include clinical proteomics and proteogenomics (refinement of genomic data using MS-based proteomics).

As a core facility of the University of Tübingen, the PCT offers proteomic analyses against a fee. Qualitative analyses of proteins, proteomes and subproteomes (e.g. phosphoproteome, interactome) are routinely performed and other posttranslational modifications can also be analyzed upon request. Quantitative workflows are mainly based on stable isotope labeling of cells and tissues (SILAC). Inquiries and requests should be made by e-mail to pct@ifiz.uni-tuebingen.de.

Special equipment and techniques

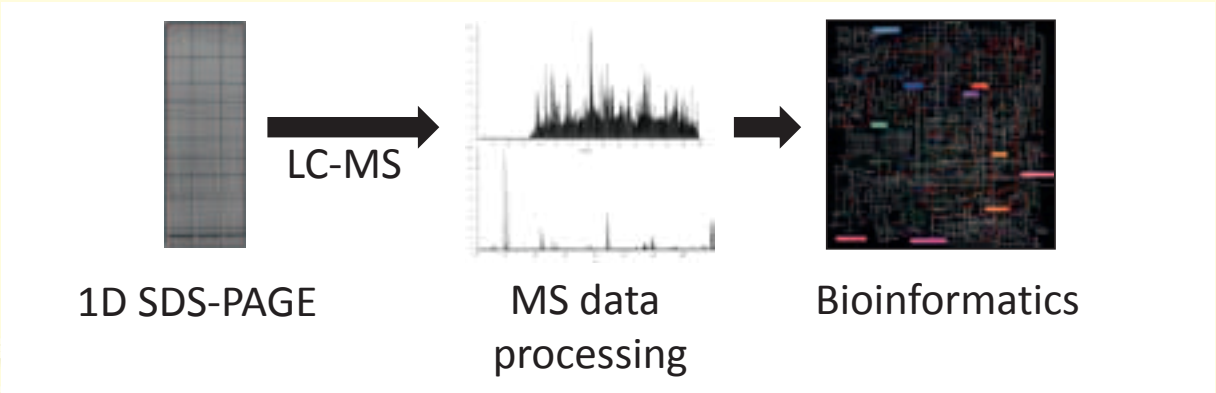
- Offgel and SCX peptide separation
- Phosphopeptide enrichment
- Stage-tip peptide purification
- Filter-aided sample preparation (FASP)
- Pipeline for Orbitrap data analysis (based on Mascot and MaxQuant)
- Pipeline for Q-TRAP data analysis (based on Mascot and OpenMS)
- Downstream analysis of shotgun proteomics data
- Liquid chromatography - Mass spectrometry (NanoHPLC column packing, 2D HPLC (SCX+RP), nanoHPLC-MS/MS (LTQ-Orbitrap XL and Q-TRAP 4000))

Cooperations

- As a core facility of the University of Tübingen, the Proteome Center Tuebingen currently collaborates with over 20 groups, mainly from Tübingen and Stuttgart area. The PCT offers services to research groups from the academia, as well as the industry.

Selected publications

- Soufi, B., Kumar, C., Gnad, F., Mann, M., Mijakovic, I., Maček, B. 2010. Stable Isotope Labeling by Amino Acids in Cell Culture (SILAC) applied to quantitative proteomics of *Bacillus subtilis.* J Prot Res 9(7):3638-46
- Borchert, N., Dieterich, C., Krug, K., Schütz, W., Jung, S., Nordheim, A., Sommer, R., Maček, B. 2010. Proteogenomics of *Pristionchus pacificus* reveals distinct proteome structure of nematode models. Genome Res 20(6):837-46
- Maček, B., Mann, M., Olsen, J.V. 2009. Global and site-specific quantitative phosphoproteomics: principles and applications. Ann Rev Pharmacol 49: 199-221



A typical "Shot-gun" proteomics workflow.

Dr. Roland Nitschke

University of Freiburg
ZBSA
Life Imaging Center

5 members of staff (computer scientists, physicists, lab technicians)

The Life Imaging Center (LIC) was founded by R. Nitschke and W. Driever in 2001 as a central project Z2 of a Collaborative Research Centre (SFB 592 - Signaling mechanisms in embryogenesis and organogenesis) funded by the German research Foundation (DFG). The LIC moved in April 2008 into the Centre for Biological Systems Analysis (ZBSA). Beside the LIC three other core facilities for Genomics, Proteomics and Metabolomics are located in the ZBSA with the aim to simplify interactive projects between these areas. The LIC is a central research unit of the University, not dedicated to any special faculty, but jointly supported by the 4 Faculties of Biology, Medicine, Mathematics and Physics, and Engineering.

The LIC has a major focus on live cell imaging of all kind of organisms and culture systems used in developmental biology, cell signaling research and systems biology. Samples are:

- Embryos (zebrafish, *Drosophila*, mouse, *Xenopus*)
- Model organism or cell clusters (*C.elegans*, sphere, cyst)
- Plants (root, leave, growth cone)
- Neuronal cultures (primary neurones, brain slices)
  Explants and biopsies from ....
- Tissue slices
- Spheroids
- Flow cultures

The LIC is specialized in long time observation and experiments on these objects, high resolution large area and/or multiple location recordings with 2P and VIS excitation. A further specialty is culturing and permanent microscopic observation of cells and spheroids over periods of up to 10 days (also under flow conditions in special chambers). All types of fluorescent proteins including photo-activatable and photo-convertible are used. The LIC has a large library of proteins (more than 150) available for LIC users and does pilot experiments with these before giving them out.

In the cluster of excellence "Centre for biological signaling studies (BIOSS)" the LIC is currently extending its expertise beyond imaging in several joint projects with the Faculty of Engineering. Projects with Division of Pattern Recognition, Image Processing and Laboratory for Bio- and Nano-Photonics aim for a new microscopic tool named 4D analyzer. The LIC is also working within the systems biology network HEPATOSYS and with groups of the Comprehensive Cancer Center Freiburg (CCCF) both funded by the BMBF.

Currently LIC has 200 active users from the faculties of biology, chemistry, earth sciences, engineering, material science, forest science, medicine, pharmacology, and physics. Approximately 10% of the users are externals via joint projects of university research groups. Equipment is booked app. 75 % of the time (14 h usage per day def. as 100%).

The LIC is member of the European Light Microscopy Initiative (ELMI) and the Euro-BioImaging initiative.
The LIC has longstanding partnerships with companies in the imaging field:
Zeiss – confocal and widefield microscope hard- and software (> 15 year)

Major projects: AOTF, LSM 510, AxioObserver, SPIMicroscopy, Stitching and HDR imaging, InTune Laser IBIDI – microscope chambers for long term culture and perfusion (> 4 years)
Nikon – Biostation development (> 2 years)

LIC has a partnership with the FMI Imaging facility in Basel in exchange of knowhow, software, test platforms and evaluation of equipment.
LIC has collaborations in Freiburg with the 11. Faculty (development of microfluidic devices) and many laboratories in the Biological and Medical Faculty.
It has developed and patented together with the Bundesanstalt für Materialforschung (BAM), and the companies Fluka and Schott probes for the calibration of fluorescence microscopes to allow easy quantification of signals.

LIC infrastructure:
The LIC has lab and office space of app. 400 m^2 in 16 rooms. All lab space has biosafety level S2. Maintaining of the infrastructure of the LIC is currently financed through three major sources: University, CRC 592 (DFG) cluster of excellence – Centre for biological signaling studies (BIOSS). New equipment can only be realized via joint or individual grant applications, which dedicate the equipment then to the LIC.

The LIC works tightly together and shares equipment and software licenses with the Imaging facility of Max Planck Institute for Immunbiology (MPI-IB) in Freiburg.

Special equipment and techniques

- 9 confocal microscopes
- 6 widefield-Live-cell imaging microscopes
- all kinds of fluorescence techniques like cell or organelle tracking, FRET, FRAP, FLIP, 2-P, spectral unmixing, medium throughput image screening and large area tile image recording and stitching

Joint research projects

- BIOSS
- HepatoSys (BMBF)

Cooperations

- Currently the LIC has 285 active users.

Selected publications

- Boehlke,C., Kotsis,F., Patel,V., Voelker,H., Bredt,S., Beyer,T., Müller,K., Herbst,M., Hornung,M., Doerken,M., Köttgen,M., Nitschke,R., Igarashi,P., Walz,G. Kuehn,E.W. Primary cilia regulate mTORC1 activity and cell size through Lkb1, Nat.Cell.Bio., 11 (2010), 1115-1122.
- Emmenlauer,M., Ronneberger,O., Ponti,A., Schwarb,P., Griffa,A., Filippi,A., Nitschke,R., Driever,D., Burkhardt,H. XuvTools: Free, fast and reliable stitching of large 3D datasets. J.Microsc., 233 (2009), 42-60.
- Resch-Genger,U., Grabolle,M., Cavaliere-Jaricot,S., Nitschke,R., Nann,T. Quantum dots versus organic dyes as fluorescent labels. Nat.Methods, 5 (2008), 763-775.

Dr. Andreas Schlosser

University of Freiburg
ZBSA
Core Facility Proteomics

5 members of staff (biologists, pharmacists, engineers)

The Core Facility (CF) Proteomics at the ZBSA offers a broad range of methods and techniques for the global analysis of proteomes as well as for the detailed analysis of individual proteins. Typical projects focus on comparative quantitative proteome analyses (e.g., using SILAC or 15N labelling), the characterisation of organelle proteomes, the identification of protein interaction partners and the analysis of covalent protein modifications. A broad range of model organisms are used for the analyses, including simple bacteria (e.g. *Sinorhizobium meliloti*), animals (*C. elegans*) and plants (*Arabidopsis thaliana, Physcomitrella patens*). In addition to these model organisms, the researchers also use clinical human tissue samples for their analyses. In addition to using established methods, the Core Facility develops new mass spectrometry-based methods in order to address biologically and medically relevant issues. These methods are developed in close cooperation with other research groups at the University of Freiburg.

The CF Proteomics carries out analyses of covalent (posttranslational) protein modifications such as phosphorylation, ubiquitination, hydroxylation, deamidation, methylation and ADP ribosylation. These analyses involve methods for the selective enrichment of modified peptides, advanced tandem mass-spectrometric methods (e.g. electron transfer dissociation or multiple reaction monitoring) and the development of algorithms for the analysis of data.

Currently, the CF Proteomics is mainly focused on developing new quantitative methods for the analysis of protein phosphorylation. This work is part of the BMBF-funded Virtual Liver project, which is carried out in cooperation with biologists who generate the protein samples required and theoreticians who use the generated quantitative data to develop mathematical models.

In line with the character of a core facility, the Proteomics Core Facility has numerous collaboration partners at the ZBSA and the University of Freiburg (Biology, Medicine, Chemistry) as well as outside Freiburg, for example the Charité in Berlin and the DKFZ (German Cancer Research Centre) in Heidelberg.

Special equipment and techniques

- ESI mass spectrometers (Q-TOF, triple quadrupole, ion trap) with chip-HPLC
- Orbitrap with nano-HPLC
- ETD fragmentation
- Multiple Reaction Monitoring (MRM)
- Automated phosphopeptide enrichment with TiO2
- Off-gel fractionation
- Horizontal gel electrophoresis
- Fluorescence scanner
- Quantification using ^{15}N-labelling

Joint Research Projects

- FORSYS/ FRISYS (BMBF)
- Virtual Liver (BMBF)

Cooperation partners

- The service of the facility is currently used by approximately 30 cooperation partners (mainly from the faculty of biology and the medical faculty of the University of Freiburg).

Selected publications

- Lang, AE, Schmidt, G, Schlosser, A, Hey, TD, Larrinua, IM, Sheets, JJ, Mannherz, HG, Aktories, K (2010) Photorhabdus luminescens Toxins ADP-Ribosylate Actin and RhoA to Force Actin Clustering. Science 327: 1139-1142.
- Orth JHC, Preuß I, Fester I, Schlosser A, Wilson BA, Aktories K (2009) Molecular mode of action of *Pasteurella multocida* toxin - Activation of heterotrimeric G proteins by deamidation. Proc Natl Acad Sci 106: 7179-7184.
- Schlosser A, Vanselow JT, Kramer A (2005) Mapping of phosphorylation sites by a multi-protease approach with specific phosphopeptide enrichment and nanoLC-MS/MS analysis. Anal Chem 77: 5243-5250.

Mass spectrometry laboratory of the Core Facility Proteomics at the ZBSA.

Andrea Weber

University of Freiburg
Centre of Biological Signalling Studies / ZBSA
BIOSS Toolbox

3 members of staff (lab technicians)

The BIOSS Toolbox is a central part of the Centre of Biological Signalling Studies (BIOSS) in Freiburg. BIOSS, the Cluster of Excellence EXC294 will investigate biological signalling in a new, highly interdisciplinary and cross-systems approach.
As a resource and information centre for biological materials with focus on signalling science, the BIOSS Toolbox will facilitate and accelerate the exchange of material between scientists and laboratories.

As the scientific community gets more complex, sharing of data and materials is becoming a critical factor. For this reason the BIOSS Toolbox is collecting, annotating and archiving material (mainly plasmids and expression vectors, cell lines, chemicals etc.) from the scientists, and grants its accessibility to the scientific community inside and outside Freiburg, providing a high level of quality control.
An implemented database will handle all materials and related information and an online portal (under construction) will publish all relevant information and functional description of the materials.

Due to the signalling research approach of BIOSS the Toolbox plasmid repository specializes on the collection of materials that are specific for signalling research studies. In particular this refers to plasmids that allow control and examination of dynamic processes in cells like induction of signals and changes in morphology, or can be used for switchable interactions. The collection includes many proteins which play a role in various signalling pathways, e.g. receptor and adaptor proteins, kinases and phosphatases, and functional subunits and domains usable for localization and interaction studies.

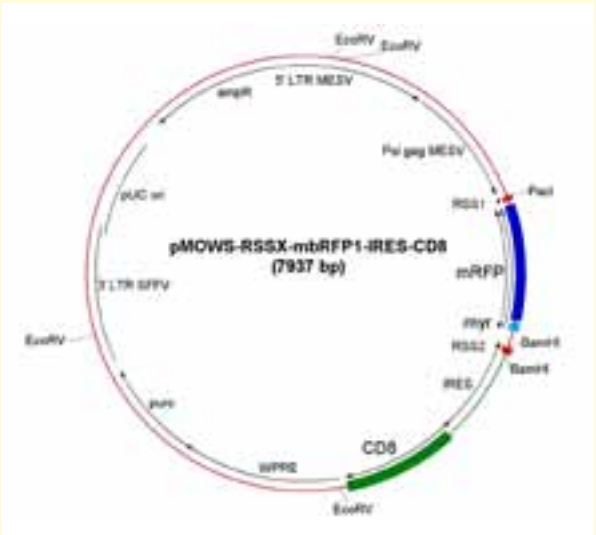
Furthermore the BIOSS Toolbox manages the storage and distribution of other materials for scientists at their own university, like a human cDNA library, a small hairpin RNA kinase library, and it will established a collection of cell lines in the near future.

Joint research projects

- BIOSS

Cooperations

- The BIOSS Toolbox services are currently used by research groups at the University of Freiburg and the University Medical Center Freiburg. Access will also be provided to any research institution and non-profit organisation once the establishment of Toolbox has been completed.



Research groups in Heidelberg


Prof. Peter Angel S. 48


Prof. Ralf Barten-schlager S. 50


Prof. Michael Boutros S. 52


Dr. Nathan Brady S. 54


Prof. Karl-Heinz Brenner S. 56


Prof. Steven Dooley S. 58


Prof. Roland Eils S. 60


Dr. Elfriede Friedmann S. 62


Dr. Anne-Claude Gavin S. 64


Dr. Frauke Gräter S. 66


Prof. Fred A. Hamprecht S. 67


Prof. Michael Hausmann S. 68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Dr. Lars Kaderali S. 72


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Prof. Peter Angel

German Cancer Research Center, Heidelberg
Division of Signal Transduction and Growth Control

20 members of staff (biologists, biochemists)

Dysregulated gene expression and its effect on cellular properties have been shown to be a major cause of cancer. Numerous cellular functions contribute to tumour development and progression: unrestricted proliferation of cancer cells, defective apoptosis programmes (programmed cell death), induction of the growth of new blood vessels to supply the tumour with nutrients, or the ability of tumours to form metastases at secondary locations. These highly complicated and finely tuned processes represent "normal" abilities of the body that are required for regenerative processes (e.g., wound healing) and which are "reactivated" in uncontrolled ways in malignant cancer cells.

Intrinsic, "cell-autonomous" control mechanisms and cell-cell communication play a crucial role in the modulation of genetic programmes: for example, wound healing in which the decision of whether epidermal cells (keratinocytes) initiate the genetic programme of migration, proliferation or differentiation is decisively influenced by soluble paracrine factors of neighbouring cells (fibroblasts, endothelial cells and immune cells). Similar cell-cell communication principles also underlie the process of tumorigenesis where the interaction of different cell types in what is known as the microenvironment of the tumours affects the properties of tumour cells. In addition, factor-mediated systemic interactions play a key role in this process: for example, epidemiological and experimental studies have revealed a strong correlation between metabolic disorders (e.g., adiposity, diabetes) and chronic inflammation associated with the development of cancer.

The research group led by Prof. Angel deals with the question of how physiological and pathological signals, which act on the cell from the outside, affect the activity of genes by way of intracellular signalling pathways and transcription factors such as AP-1 and NF-κB. Based on global expression studies involving samples from cell culture models and genetically modified mouse models, the research group is working on the determination of quantitative and dynamic gene expression changes during regenerative processes (wound healing) and in key processes that lead to the development of cancer (proliferation, invasion, tumour angiogenesis, chronic inflammation). This work is carried out in close cooperation with the Departments of Molecular Genetics (Prof. Dr. Lichter), of Medical Informatics (Dr. Niels Grabe) and Theoretical Bioinformatics (Prof. Dr. Eils) at the DKFZ in Heidelberg.

In addition, the group is carrying out research into the enrichment of transcription factor binding sites in the promoter sequences of genes that are differently expressed. This enables the scientists i) to calculate the topology of relevant signalling cascades and metabolic and gene-regulatory networks under pathological conditions, ii) to develop theoretical models on the regulation of transcription factors involved in these processes and on their modular interactions, iii) to confirm these calculations with functional analyses in cell cultures and with genetically modified mouse models, and iv) to verify the clinical significance of these findings by analysing patient samples, thus identifying new target structures for translational research projects. In cooperation with partners from the University Hospital Heidelberg

(Pathology: Prof. Dr. Schirmacher PD Dr. Breuhahn; Endocrinology: Prof. Dr. Nawroth, PD Dr. Bierhaus; Department of Otolaryngology: Prof. Dr. Plinkert, PD Dr. Heß), Dr. Angel's group is also working on the identification of diagnostic properties of cancer cells and the development of innovative cancer therapies.

Special equipment and techniques

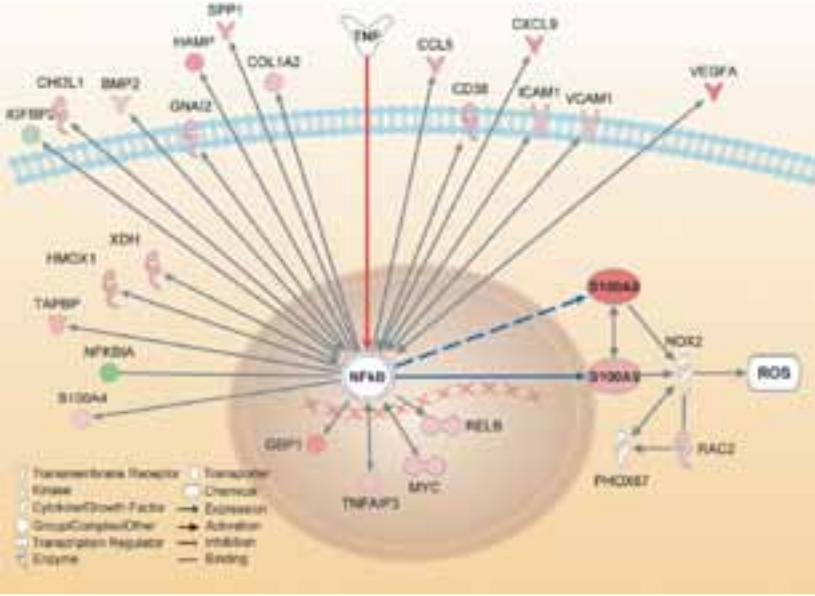
- Live cell imaging; FACS analysis
- Generation of genetically modified mice (transgenic and conditional knock-out mice), isolation and cultivation of primary and immortalized cells
- Development of in vitro organ cultures (e.g., blood vessels, skin)
- Functional analyses (proliferation, apoptosis, differentiation, migration, invasion)
- Gene expression analyses (mRNA, miRNA)
- Molecular analysis of signalling cascades and transcription factors (protein-protein interactions, reporter gene analyses, chromatin immunoprecipitation)

Joint research projects

- Medical Systems Biology (BMBF)
- NGFN Plus
- Systems Biology of Cancer (Helmholtz Association)

Selected cooperation partners

- Prof. Peter Lichter, Molecular Genetics, and Prof. Roland Eils, Theoretical Bioinformatics, German Cancer Research Center, Heidelberg, Germany
- Prof. Peter Plinkert und Dr. Jochen Heß, Department of Otolaryngology, University Hospital Heidelberg, Germany



Model of the NF-kB-dependent genetic network during the development of hepatocellular carcinomas (HCC) (Nemeth et al., Hepatology 2009)

- Prof. Erwin F. Wagner, Cancer Cell Biology, Spanish National Cancer Research Center, Madrid, Spain
- Dr. Eli Pikarsky und Prof. Yinin Ben-Neriah, Hadassah Medical School, Hebrew University, Jerusalem, Israel

Selected Publications

- Németh J, Stein I, Haag D, Riehl A, Longerich T, Horwitz E, Breuhahn K, Gebhardt C, Schirmacher P, Hahn M, Ben-Neriah Y, Pikarsky E, Angel P, Hess J. S100A8 and S100A9 are novel nuclear factor kappa B target genes during malignant progression of murine and human liver carcinogenesis. Hepatology, 50(4): 1251-62, 2009
- Busch H, Camacho-Trullio D, Rogon Z, Breuhahn K, Angel P, Eils R, Szabowski A. Gene network dynamics controlling keratinocyte migration. Mol Syst Biol, 4:199, 2008

Prof. Ralf Bartenschlager

University Hospital Heidelberg
Department of Infectious Diseases
Molecular Virology

44 members of staff (biologists, biochemists, veterinarians and physicians)

The Department of Infectious Diseases, Molecular Virology which is a part of the Heidelberg University Hospital is headed by Ralf Bartenschlager. His division concentrates on 5 main research areas:

(1) understanding the molecular and cellular mechanisms which orchestrate the flaviviral replication cycle with a specific focus on the hepatitis C virus (HCV) and dengue virus (DENV);

(2) studying the host-pathogen interaction through RNAi-based high-throughput screening in combination with bioinformatical and systems biology approaches to reveal relevant cellular networks;

(3) analysing the replication cycle of an acute lytic (DENV) and a chronic persistent virus (HCV) to understand how these viruses interfere with the immune response, especially innate immunity to achieve maximal virus production (DENV) or chronic infection (HCV);

(4) development of dynamic models for cellular networks responsible for HCV and DENV replication, spread and counteracting innate immune response;

(5) studying the molecular and structural biology of the hepatitis B virus (HBV) to develop novel antiviral concepts.

The division of Ralf Bartenschlager consists of three independent working groups (AG Bartenschlager, AG Lohmann, and AG Urban) and has a long lasting experience in HCV, DENV and HBV research and major contributions to this field were made, most notably the development of efficient and reliable HCV cell culture systems. Only by using these novel systems detailed molecular studies of the HCV replication cycle could be conducted leading to groundbreaking insights into both, viral replication and HCV-host interaction. A further major contribution was made in the field of HBV therapy by the development of HBV envelope protein-derived lipopeptides. These lipopeptides are currently tested in a preclinical trial. Recently, for the first time a 3D model of DENV replication and assembly sites was generated. Furthermore, the group has substantially contributed to the development and implementation of an RNAi screening platform within the FORSYS-ViroQuant consortium.

The overall aim of the systems biology branch of research in the Bartenschlager laboratory is the application of high-throughput approaches as well as mathematical models to study interactions of HCV, DENV and HBV with the host cell at the systems level to identify cellular networks required for productive replication of these medically highly relevant viruses. To this end siRNA-based high-throughput screens in combination with cell culture systems that support production of infectious virus particles are being applied. The group has access via the FORSYS-ViroQuant initiative to 3 different siRNA sub-libraries corresponding to the complete human kinome (predicted 719 human kinases), human druggable genes (9103 humane genes of potential therapeutic value) and all human genes involved in cytoskeleton related processes. So far, systematic screening approaches were initiated to identify cellular factors involved in the complete HCV and DENV replication cycle as well as regulatory factors implicated in innate antiviral defense.

In a follow-up study bioinformatics approaches will be used to integrate the generated data sets (phenotypes from

knock-down, genome-wide interactome and proteome studies, transcriptome profiling) with results from literature in order to identify cellular pathways perturbed by viral infection. Spatio-temporal analysis primarily by using time-lapse microscopy of targeted host cell components will generate required data-sets to establish mathematical models of distinct virus-host interactions and will identify steps within the viral replication cycle where intervention is suitable.

Special techniques

- RNAi based screening
- Electron microscopy
- Electron Tomography

Joint research projects

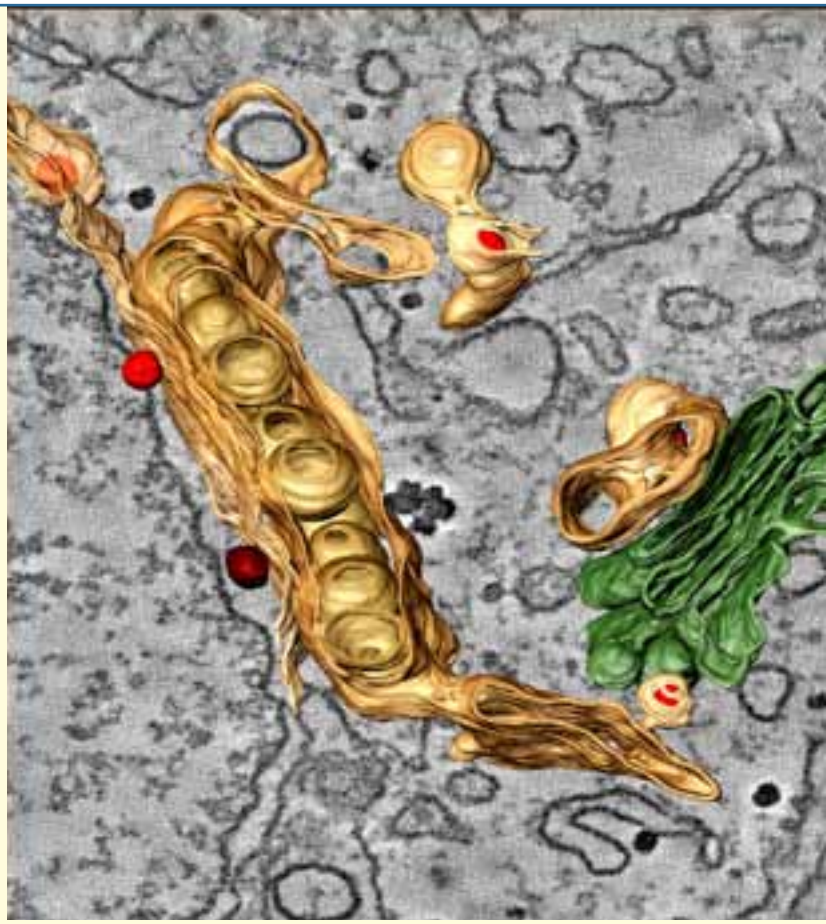
- ViroQuant / FORSYS (BMBF)

Selected cooperation partners

- M. Albrecht, Max-Planck-Institut for Informatics, Saarbrücken, Germany
- R. Eils, DKFZ / BioQuant, Universität Heidelberg, Germany
- U. Klingmüller, DKFZ / BioQuant, Universität Heidelberg, Germany
- H.G. Kräusslich, Department of Infectious Diseases, Virology; University Hospital, Heidelberg, Germany
- L. Kaderali, ViroQuant, Universität Heidelberg, Germany

Selected publications

- Welsch S, Miller S, Romero-Brey I, Merz A, Bleck CK, Walther P, Fuller SD, Antony C, Krijnse-Locker J, Bartenschlager R. 2009. Composition and three-dimensional architecture of the dengue virus replication and assembly sites. Cell Host Microbe. 5:365-75
- Matula P, Kumar A, Wörz I, Erfle H, Bartenschlager R, Eils R, Rohr K. 2009. Single-cell-based image analysis of high-throughput cell array screens for quantification of viral infection. Cytometry A. 75:309-18.
- Kaderali L, Dazert E, Zeuge U, Frese M, Bartenschlager R. 2009. Reconstructing Signaling Pathways from RNAi Data using Probabilistic Boolean Threshold Networks. Bioinformatics. 25:2229-35.



3D reconstruction of flaviviral replication and assembly sites.

Prof. Michael Boutros

German Cancer Research Center, Heidelberg
Division of Signaling and Functional Genomics

Universität Heidelberg
Department Cell and Molecular Biology

30 members of staff (biologists, physicians, chemists, bioengineers and bioinformaticians)

The research group focuses on the systematic analysis of signaling networks that control key decisions during development of organisms and are often mutated in human diseases. The group uses modern genomic, genetic and computational approaches to dissect signaling processes. By applying high-throughput screening methods they identify novel candidate genes that are further analyzed in model organisms and human cells. The group develops high-throughput methods to discover novel signaling pathway components and for systematic functional analysis. Research is carried out in a joint Department at the University of Heidelberg and the German Cancer Research Center in Heidelberg.

Systems level understanding of complex biological pathways and networks requires knowledge of its units, structures and temporal processes. The building of cellular network models involves the identification of their elementary building blocks from their quantitative properties. RNA interference (RNAi) allows the silencing of genes through introduction of short double-stranded RNAs and has enabled comprehensive studies which were previously not feasible.

RNAi libraries that target most genes in worms, flies and humans have been created and are of use in genome-wide screens. Genome-wide RNAi approaches have become a powerful genetic approach to systematically identify pathway-specific genes, dissect their role in pathway topologies and to identify the respective biological building blocks.

One example of the research program is an ERASysBio+ consortium with Prof. Rainer Spang (University of Regensburg, Germany) and Prof. Henning Walczak (Imperial College London, UK). The aim of this project is to systematically analyze death receptor signaling networks in development of hepatocellular carcinoma, which are one of the most common forms of cancers worldwide. Therapeutic options are limited due to chemo-resistance to current therapies, mostly caused by failure to undergo cell death (apoptosis). To understand how the apoptosis signaling networks are regulated in normal cells and dysregulated in cancer is of key importance for the design of effective cancer therapies.

The project aims to understand and predict the basic biological system that governs pro- and anti-apoptotic signaling in normal versus transformed cells. Based on the experimental data generated in the group of Prof. Michael Boutros and Prof. Walczak's group, the group of Prof. Spang will build Dynamic Nested Effects Models to identify critical points for pathway regulation. These statistical models will be used to reconstruct pathway activity. In addition to providing specific insight into apoptosis signaling on a systems level in normal versus transformed cells, it is expected that the study will also lead to new insights on principal mechanisms of tumorigenesis and therapy of resistant tumors.

Special equipment and techniques

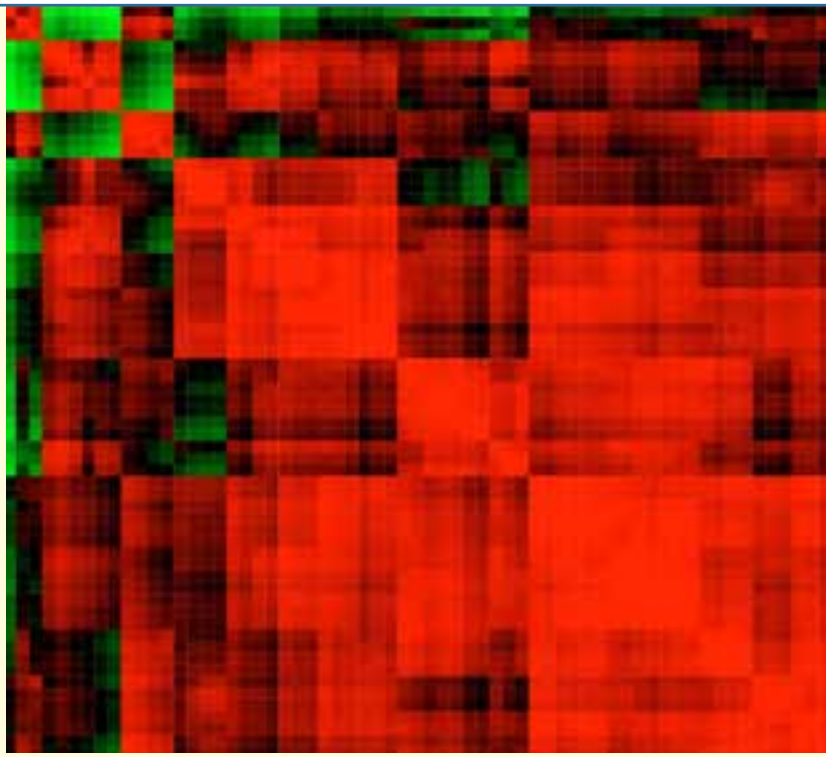
- High-throughput RNAi and compound screening
- Next generation sequencing and transcriptome analysis
- Automated high-content microscopy
- Databases and computational tools

Joint research projects

- CancerPathways
- EraSysBio+ (BMBF)
- NGFN Plus (BMBF)

Selected publications

- Boutros M, Ahringer J. 2008. The art and design of genetic screens: RNA interference. Nat Rev Genet. 9(7):554-66.
- Boutros M, Brás LP, Huber W. 2006. Analysis of cell-based RNAi screens. Genome Biol. 7(7):R66.
- Muller, P., D. Kuttenkeuler, V. Gesellchen, M. Zeidler, and M. Boutros. 2005. Identification of JAK/STAT signaling components by genome-wide RNAi. Nature, 436:871-5.



Computational analysis of high-content RNAi screens. Phenotypic profiles of RNAi-treated cells are identified by multi-parameter image analyses and subsequently used for cluster analysis.

Dr. Nathan Brady

German Cancer Research Center / BioQuant Center
Systems Biology of Cell Death Mechanisms

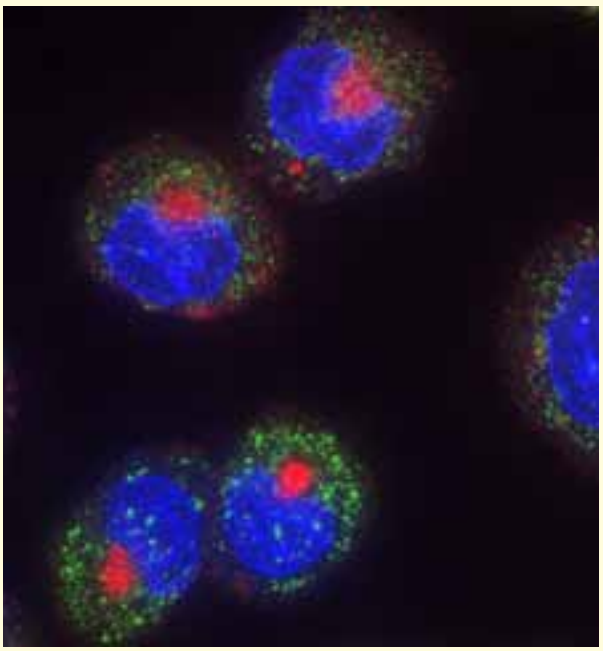
6 members of staff (molecular and cellular biologists, systems biologists, computer scientists)

The research group investigates the control and crosstalk between programmed cell death (PCD) mechanisms of apoptosis, autophagy and necrosis in pancreactic cancer, a leading cause of cancer death due to lack of effective treatments. Apoptosis, the most studied PCD mode (Type I), is activated by either the death receptor or the mitochondrial pathway, and both modes are executed by caspases which proteolytically disassemble the cell. Autophagy is a process by which intracellular components are sequestered by autophagosomes, which then fuse with and are degraded by lysosomes.

In the cancer cell autophagy can paradoxically act as either an alternative cell death pathway (Type II PCD) or as a potent survival response to stress (e.g. hypoxia, chemotherapies). Although considered a passive cell death, many pathways are common to necrosis and PCD modes, including calpains, cytosolic proteases which are activated as a result of disruption to calcium homeostasis, and cytosolic cathepsins, proteases normally sequestered into the lysosomal compartment.

In contrast to apoptosis, necrosis is inflammatory due to the rupture of the plasma membrane and the release of specific cytosolic components. Moreover autophagy can stimulate the release of key immunogenic cytosolic factors from tumors cells, as well as mediate antigen presentation in dendritic cells. As apoptosis does not generate an immune response, the strict focus on apoptosis-inducing therapies may not be fully productive. Rather, the interactions between the cancer cell and immune system offer a powerful means to amplify cell death enough to improve treatment outcome. The research of the group aims at revealing how individual pathway activities and crosstalk between PCD pathways can be tuned to optimize intrinsic and extrinsic pancreatic cancer cell death.

The initial goal of the research group is to quantitatively map activities and interdependencies of PCD modes within cell types, and between cell types in an in vitro tumor model consisting of pancreatic cancer cells, stroma and immune cells. To do so the group quantifies single-cell level PCD signaling events within large population of cells using high-resolution imaging of high-content biosensors, combined with rich feature extraction and statistical



The pancreatic cancer cells shown are in a novel mode of cell death, where lysosomes are activating mitochondrial apoptosis. Stained are lysosomes (red), mitochondria (green) and nuclei (blue).

analysis. This approach achieves superior information content than commonly reported population-averaged and representative responses.

Measured activities and dependencies, ranging from protein-protein interactions, intra-organellar crosstalk, and bi-directional cell-to-cell signaling are combined using a fuzzy logic modeling platform which is capable of integrating qualitative and quantitative multi-parametric, multivariate datasets. The overall goal is to predict and test chemotherapies which will optimize both initial PCD responses, as well as promote an immunogenic response to induce secondary killing of cancer cells by the immune system.

The group "Systems Biology of Cell Death Mechanisms (B170)" is part of the SBCancer network within the Helmholtz Alliance on Systems Biology and is located in BioQuant, Heidelberg University's center for quantitative biology. Furthermore the group is closely cooperating with the European Pancreas Center at Heidelberg University Hospital headed by Prof. Dr. Markus Wolfgang Büchler.

Special equipment and techniques

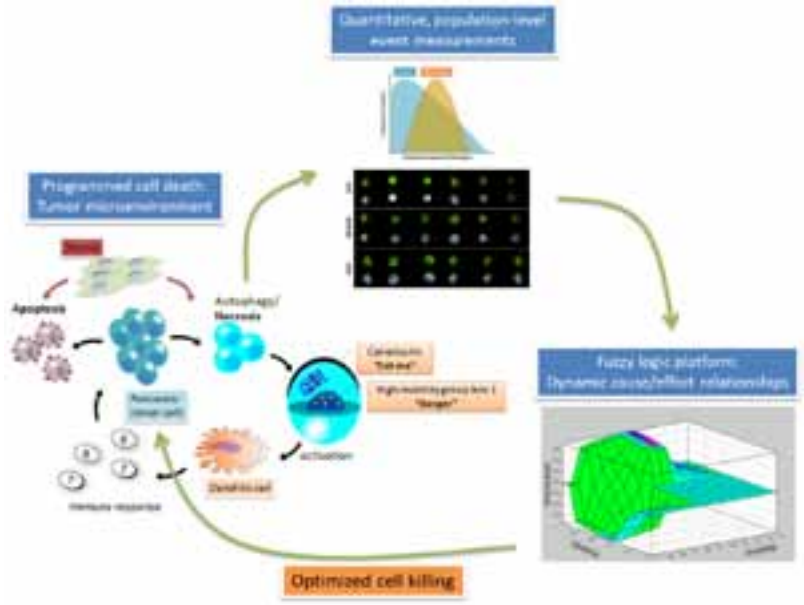
- ImagestreamX

Joint research projects

- Systems Biology of Cancer (Helmholtz Association)

Selected cooperation partners

- Dr. Anne Hamacher-Brady, Prof. Roland Eils, Division of Theoretical Bioinformatics (AG Prof. Roland Eils), The German Cancer Research Center/ BioQuant, Heidelberg, Germany



Workflow for integrative quantitative experimental and computational optimization of PCD.

- Nathalia Giese, Department of Surgery, Medical Faculty, Universität Heidelberg, Germany

Selected publications:

- Systems biological analysis of epidermal growth factor receptor internalization dynamics for altered receptor levels. Schmidt-Glenewinkel H, Reinz E, Eils R, Brady NR. J Biol Chem. 2009
- The autophagic response to nutrient deprivation in the hl-1 cardiac myocyte is modulated by Bcl-2 and sarco/endoplasmic reticulum calcium stores. Brady NR, Hamacher-Brady A, Yuan H, Gottlieb RA. FEBS J. 2007
- The interplay between pro-death and pro-survival signaling pathways in myocardial ischemia/ reperfusion injury: apoptosis meets autophagy. Hamacher-Brady A, Brady NR, Gottlieb RA. Cardiovasc Drugs Ther. 2006

Prof. Karl-Heinz Brenner

Universität Heidelberg
ziti-Institute of Computer Engineering / BioQuant Center
Chair for Optoelectronics / ViroQuant Technology Platform (ViroQuant C)

Approximately 25 members of staff (physicists, computer scientists)

The ViroQuant project is seeking to speed up the acquisition and processing of data on all levels, including microscope image acquisition, pre-processing, image analysis and data storage. With regard to genome-wide scans and image sequences, an accelerated acquisition of data means that the time required for the experiments can be reduced from months down to a few hours. On hand, this enables researchers to perform more experiments resulting in less statistical variations and thus higher reliability.

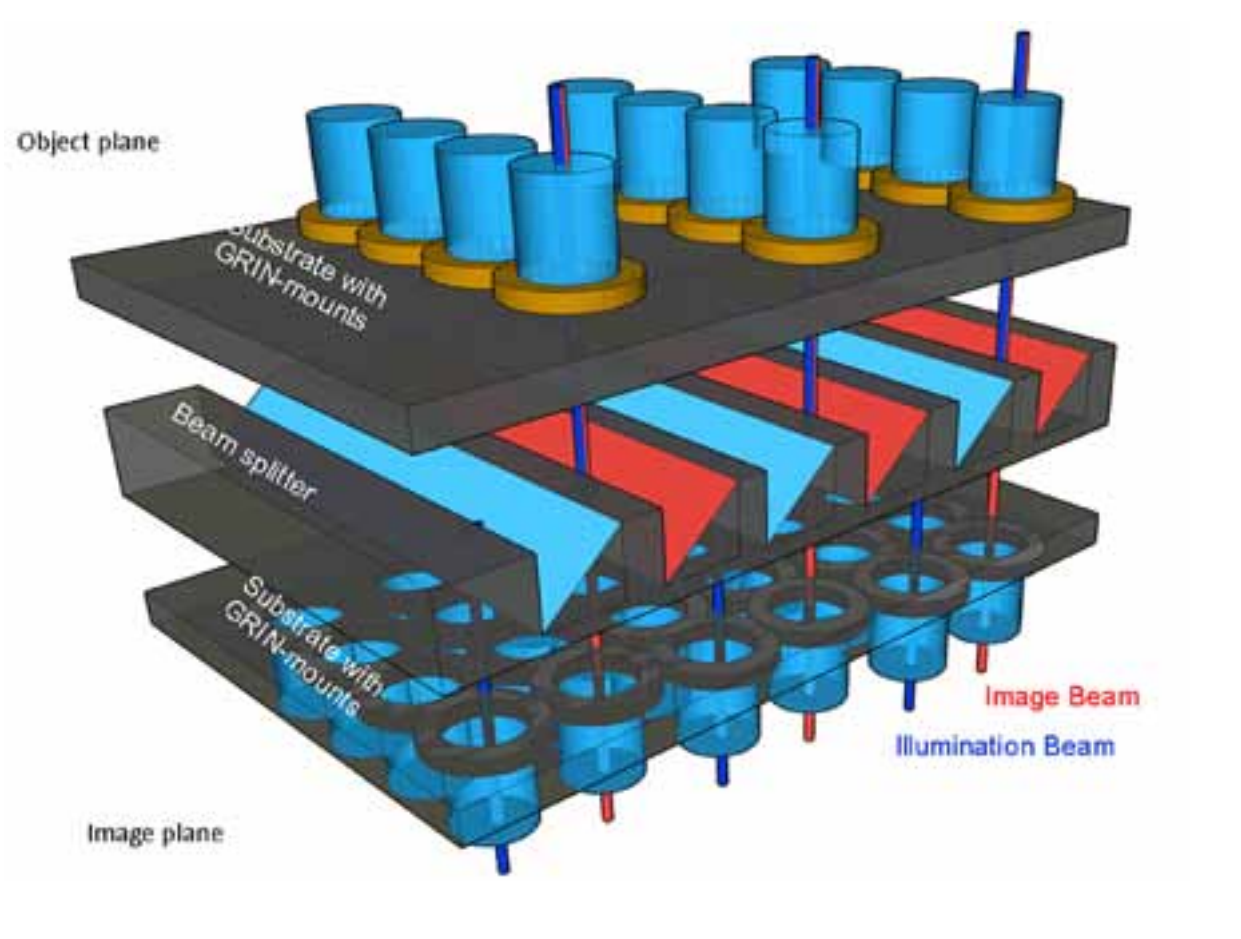
On the other hand, temporal image series can be produced from a large number of individual experiments. The scan rate can be shifted into the second range as a result of faster image acquisition. One pre-project focused on the analysis of the limits of image acquisition speed, and the results of this investigation led to an implementation of an accelerated single-microscope system. At present, researchers are focusing on the development of an optical system for a miniaturised parallel microscope consisting of three layers: A beam-splitting layer, mounted between two layers of GRIN-rod lenses for image formation directs the excitation light to the fluorescent probe (see figure). Parallel to this, the researchers have also developed methods that enable them to speed up image analysis, both on the software- and hardware level. A dedicated prototype cluster for carrying out accelerated processing algorithms was developed for the processing of data in one pipeline, i.e. in a set of data processing elements connected in series. A parallel file system based on open source code is used to speed up the storage of data. In cooperation with work groups A and B (Biology and Modelling), Prof. Brenner's team is working specifically on issues related to the interaction between virus and cell wall as well as the signalling in cells.

Joint research projects

- FORSYS/ ViroQuant (BMBF)

Selected publications

- E. Slogsnat, K.-H. Brenner, DGaO-Proceedings 2008, ISSN: 1614-8436
- S. Remmele, J. Ritzerfeld, W. Nickel, J. Hesser: „Automated Cell Analysis Tool for a Genome-Wide RNAi Screen". MIAAB 2008
- Kuhn M, Kunkel J, Ludwig T. Euro-Par 2008—Parallel Processing, Lecture Notes in Computer Science, vol. 5168



Schematic representation of a miniaturised, parallel set-up consisting of 12 microscopes. The set-up consists of three layers, where beam splitters are mounted between gradient index (GRIN) lenses.

Prof. Steven Dooley

Medical Faculty Mannheim at the University of Heidelberg
II. Medical Clinic
Molecular Hepatology – Alcohol-dependent Diseases

20 members of staff (biologists, biochemists, physicians)

Since the morphology, cellular composition and biochemistry of the liver is very complex, the "Molecular Hepatology – Alcohol-dependent Diseases" department uses a systems biology approach to investigate the physiology and function of the liver. The investigations are part of the BMBF-funded "Virtual Liver" programme. The goal of the project is to investigate the liver on different levels (cellular, intercellular, lobular and organ) and to subsequently integrate the levels in order to construct a "virtual liver". The programme intends to establish a model that is as complete as possible to represent the central processes in a healthy liver and of selected pathological states. These processes include key metabolic processes, detoxification, signal processing, hepatocyte proliferation and endocytosis. The pathological states are represented by hepatotoxic treatment, inflammation and regeneration. The group will focus particularly on molecular and cellular mechanisms in order to describe the function of polarised and differentiated liver cells.

The research group generates quantitative data on the following topics:

1) Crosstalk between signalling pathways and endocytosis in hepatocytes:

- Effect of cell polarity and expression of transporters
- Crosstalk between signalling pathways
- Receptor sorting
- Hepatocyte polarity

2) Hepatic stellate cells as source and target for hepatocellular growth factors:

- Activation of hepatic stellate cells
- Effect of hepatic stellate cells on hepatocyte polarity and transdifferentiation
- TGF-β signal transduction on the activation of hepatic stellate cells
- Effect of activated hepatic stellate cells on hepatocyte functions and (de)differentiation/polarity

3) Structural changes and functional consequences for the hepatic lobular/sinusoidal system during inflammation and fibrogenesis.

- Animal models for chronic liver damage and inflammation
- Quantitative in vivo IHC/IF staining
- Gene expression in tissues
- Cytokine profiling

4) Organisation and function of the sinusoidal system and the hepatic lobe during regeneration following partial hepatectomy:

The data generated contribute to the development of mathematical models that are integrated into the virtual liver model. By interfering with the liver's stable state, the integrative comprehensive model enables the researchers to gain a better understanding of liver function and to forecast key target molecules and time windows for molecular therapies and their side effects. A better understanding of aetiology, pathology and disease progression helps to refine existing treatment protocols and enables individual patient predictions, which in turn will provide improved early diagnosis and personalised prognosis strategies. The research group also intends to establish a new platform for screening and toxicological studies, which will facilitate industrial application and improved therapeutic strategies for the treatment of chronic liver diseases. These are important prerequisites for patient-specific therapies.

Special equipment and techniques

- Animal models
- Cell isolation and cultivation
- Affymetrix GeneChip microarrays for gene expression profiling
- Confocal fluorescence microscopy and live cell imaging
- Quantitative Western blotting

Joint research projects

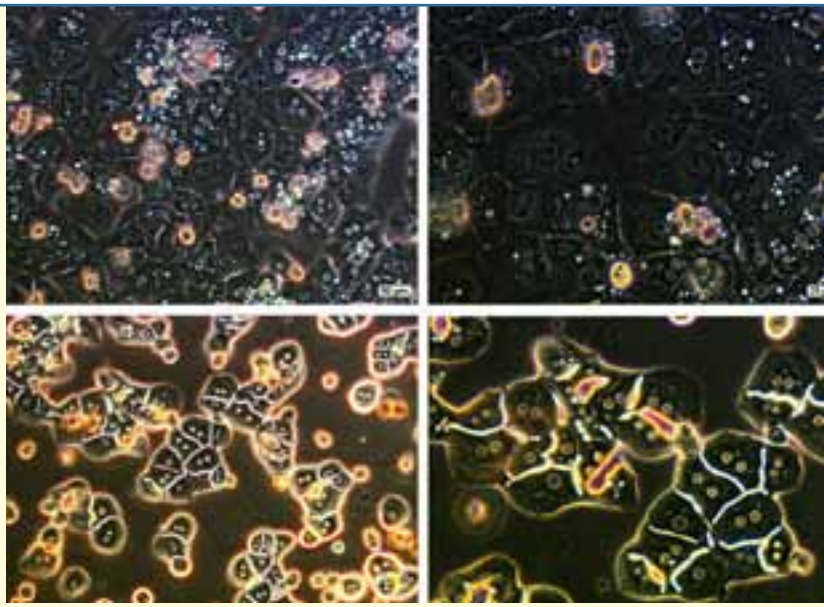
- HepatoSys (BMBF)
- Virtual Liver (BMBF)
- Stem cell therapy of chronic liver diseases (BMBF)
- TRR-SFB Hepatocellular Cancer (DFG)

Selected cooperation partners

- Prof. Zerial, Max Planck Institute of Molecular Cell Biology and Genetics, Dresden, Germany
- Prof. Deutsch, Center for Information Services and High Performance Computing, Technical University Dresden, Germany
- Prof. Hengstler, Department of Toxicology, IfADo Leibniz Research Center, Dortmund, Germany
- Prof. Kummer, Modelling of Biological Processes Dept., Institute of Zoology/BIOQUANT, Heidelberg, Germany
- PD Dr. Klingmüller, Systems Biology of Signal Transduction Division, DKFZ, Heidelberg, Germany

Selected publications

- Klingmüller U, Bauer A, Bohl S, Nickel PJ, Breitkopf K, Dooley S, Zellmer S, Kern C, Merfort I, Sparna T, et. al. (2006) Primary mouse hepatocytes for systems biology approaches: a standardized in vitro system for modelling of signal transduction pathways Syst Biol (Stevenage) 153:433447.



Morphology of hepatocytes in different culture conditions:
Two culture conditions representing two majour states of hepatocytes, with and without cell polarity. Primary murine hepatocytes were isolated and seeded either on collagen monolayer or in collagen sandwich. Upper pannel - images were acquired on day 1 for collagen monolayer culture, where hepatocyte have a lost cell polarity (x20 objective, left; x40 objective, right). Lower pannel - images were acquired on day 3 for collagen sandwich, where hepatocyte regain cell polarity, cell-cell contacts and „trabelucar“ structures, which were lost during isolation procedure (x20 objective, left; x40 objective, right).

- Godoy P, Hengstler JG, Ilkavets I, Meyer C, Bachmann A, Müller A, Tuschl G, Mueller SO, Dooley S. Extracellular matrix modulates sensitivity of hepatocytes to fibroblastoid dedifferentiation and transforming growth factor beta-induced apoptosis. Hepatology (2009) 49(6):203143.
- Dooley S, Hamzavi J, Ciuclan L, Godoy P, Ilkavets I, Ehnert S, Ueberham E, Gebhardt R, Kanzler S, Geier A, Breitkopf K, Weng H, Mertens PR. Hepatocyte-specific Smad7 expression attenuates TGF-beta-mediated fibrogenesis and protects against liver damage. Gastroenterology (2008) 135(2):64259.

Prof. Roland Eils

Director BioQuant Center

Universität Heidelberg & German Cancer Research Center / BioQuant Center
Integrative Bioinformatics and Systems Biology (iBioS)

Approx. 90 members of staff (mathematicians, (bio) informaticians, physicists, molecular biologists, engineers, technicians)

The last decade of Bioinformatics was dominated by challenges brought about by the massive production of functional genomics data in combination with disease specific information. More recently, we have witnessed the birth of the era of systems biology. In this field, genome-wide or large-scale functional genomics data and bioinformatics for quantitative data analysis are complemented by theoretical or computational modelling to gain a systems level insight into complex biochemical and pathological processes.

Roland Eils' research group "integrative Bioinformatics and Systems Biology (iBioS)" develops computer-assisted methods and procedures for analyzing, modelling and simulation of complex processes in molecular cell biology. The research group covers the entire spectrum of methodology in systems biology. While it remains to have a strong theoretical and computational focus with external experimental collaboration partners, Roland Eils' research group have also ventured into applied systems biology several years ago. Currently, six post docs supported by more than 12 students and two technicians tackle complex biological problems with an emphasis on cell death and signal transduction pathways in the context of cancer in the Eils' lab. Exploiting their expertise in live cell imaging and analysis of spatio-temporal processes Roland Eils' lab studies these pathways in the context of (living) cells. The combination of this newly generated knowledge with functional genomics data analyzed in a disease context will finally deepen our understanding of the relevance of pathways in the context of diseases studied in collaboration with biomedical partners.

The Eils' lab is affiliated with both Heidelberg University and the German Cancer Research Center and structured into four major research projects:

- Systems Biology (Dr. Joel Beaudouin, Dr. Anne Hamacher-Brady): Experimental study of cell death mechanisms; mathematical modeling and simulation of pathways and spatially resolved kinetic processes in cellular biology
- Biomedical Computer Vision (Prof. Dr. Karl Rohr): Image analysis and visualization of high-dimensional image data in biomedical applications
- Network Modeling (Dr. Rainer König): Mapping functional genomics data onto biochemical networks
- Computational Oncology (Dr. Benedikt Brors) and Databases (Jürgen Eils and Chris Lawerenz): Analysis, statistical modeling, and management of functional genomics and clinical data for deciphering complex pathomechanisms in genetic diseases.

Almost all systems biology activities of the division are located at the BioQuant center where the computational and applied systems biology activities are pursued under one roof. Besides his position as Chair of Bioinformatics, Roland Eils was also appointed as one of three founding directors of BioQuant, the interdisciplinary center for research and education in systems biology at Heidelberg University.
Furthermore, Roland Eils was instrumental for the initiation of most of the funding initiatives in systems biology in Germany. He is presently coordinating the two largest national initiatives (BMBF funded ForSys and the Helmholtz alliance on Systems Biology) with a total funding volume of 100 million euros over five years.

Special equipment and techniques

- Bioinformatic methods for the analysis of high-dimensional data in molecular cell biology
- Modeling of biochemical networks
- Automated quantitative image analysis
- Databases for Life Science Research
- Large Scale Data Facility for the Life Sciences
- Next Generation Sequencing

Joint research projects

- Helmholtz Alliance on Systems Biology/SB Cancer
- International Cancer Genome Consortium
- FORSYS/ViroQuant (BMBF)
- Center for Modeling and Simulation in the Biosciences (BioMS)
- SysTec (BMBF)
- MedSys (BMBF)
- NGFN Plus (BMBF)
- EU FP7 Pathosys (Coordination)

Selected publications

- Neumann L, Pforr C, Beaudouin J, Pappa A, Fricker N, Krammer PH, Lavrik IN &Eils R. (2010) Dynamics within the CD95 death-inducing signaling complex decide life and death of cells. Mol Syst Biol. 6:352. Epub 2010 Mar 9.
- Bacher CP, Guggiari M, Brors B, Augui S, Clerc P, Avner P, Eils R* & Heard E* (2006) Transient colocalization of X-inactivation centres accompanies the initiation of X inactivation. Nat Cell Biol 8:293-9. *corresponding author

A mathematical model of receptor induced programmed cell death (Bentele et al. 2004)

- Gerlich D, Kalbfuss B, Beaudouin J, Daigle N, Eils R* & Ellenberg J (2003) Inheritance of chromosome topology throughout mitosis. Cell 112:751-764. *corresponding author

Dr. Elfriede Friedmann

Universität Heidelberg
Department of Applied Mathematics
Analytical and Numerical Methods in Systems Biology

3 members of staff

The cooperation between biologists and mathematicians is nowadays necessary to achieve successes in systems biology. The model construction, its solvability, the simulations and visualization of the obtained results help to describe, decode and understand biological processes, here the functionality of signaling pathways. On the other hand the mathematical models can not be formulated precisely without knowing details about the experiments. Signaling pathways are very important for all development stages of a cell. Concerning cancer diseases some of the perturbed signal transduction mechanisms can play an important role in the development of the disease so that the understanding of the functionality of these pathways is one goal of cancer researchers.

An important matter in systems biology is how the activated signaling molecules reach their destination. Is it free diffusion, anisotropic diffusion, active transport or even a combination of both transport mechanisms. The research group develops models, analyzes their solvability and performs numerical simulations of the different transport possibilities. The biological and systems biological questions are addressed by cooperation partners (here U. Klingmüller).

In addition to the way of transport the group wants to identify for which cells and pathways the diffusion plays a role or whether the processes are well described by systems of ordinary differential equations. By addressing these questions the researchers consider systems of partial differential equations and coupled systems of mixed type which are solved with the software Gascoigne developped in the Numerical Methods group of Prof. Dr. Dr. h.c. Rolf Rannacher since several years. Its main feature is a combination of error control, adaptive mesh refinement and a fast solution algorithm based on multigrid methods. The discretization is performed via finite elements on locally refined grids, including grids for complex geometries with curved boundaries.

Systems biological questions and experiments (in cooperation with the Klingmüller research group):
The group considers a fragment of the JAK2/STAT5 signaling pathway which is known to control the cell development and to be responsible for the production of the red blood cells. The signaling molecules bind to the receptors on the membrane. Thereby the JAK-proteins which are bound to the receptors are activated and trigger the phosphorylation of receptor bounded tyrosines. These STAT molecules are activated, dimerize and are transported into the nucleus where the DNA transcription takes place. Thereafter the STAT molecules are deactivated in the nucleus and exported back to the cytoplasm.
For the monitoring of the spatial and temporal distribution of protein concentrations so called marker proteins are used (GFP). For that purpose genetically modified DNA is used which produces GFP-marked STAT. Quantitative measurements of activation, localization and transport dynamics of several components of the JAK2/STAT5 pathway by immunoblotting and fluorescence microscopy (timelapse imaging, FRAP, FCS) in a NIH-3T3 fibroblast model system as well as CFU-E cells are performed by cooperation partners.
There are still a few open questions concerning the

functionality of this pathway. One of them is how the activated and inactivated STAT molecules move through the cytoplasm. The developed model will be explored in two different cell lines, to elucidate the influence of the geometry. The results of the simulations are then compared with measurements to conclude if diffusion is a major transport way for the STAT molecules or if other possibilities have to be reconsidered.

Special equipment and techniques

- Realistic geometry generation from microscopy data
- Finite elements
- Adaptivity
- Multigrid methods
- Scientific 3D visualisation of the simulation results in an VR-Environment

Joint research projects

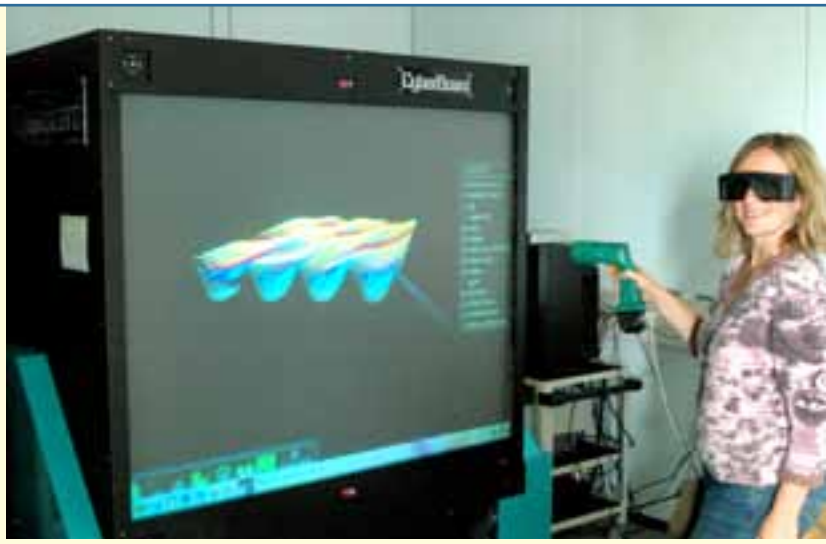
- Systems Biology of Cancer (Helmholtz Association)

Selected cooperation partners

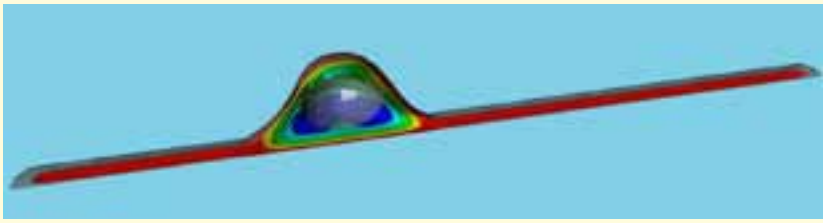
- Dr. Ursula Klingmüller, Systems Biology of Signal Transduction, German Cancer Research Center, Heidelberg, Germany
- Prof. Dr. Thomas Höfer, Modeling of biological systems, German Cancer Research Center, Heidelberg, Germany
- Dr. Dirk-Peter Herten, Single Molecule Spectroscopy, BioQuant, Universität Heidelberg, Germany

Selected publications

- R. Rannacher, E. Friedmann, Spatial Aspects in Signal Transduction – Modeling and Numerical Solution, German Symposium on Systems Biology, 2009
- E. Friedmann, A. C. Pfeifer, R. Neumann, U. Klingmüller and R. Rannacher, Interaction between experiment, modeling and simulation of spatial aspects in the JAK2/STAT5 Signaling pathway, Model based parameter estimation: theory and applications, Springer Series Contributions in Mathematical and Computational Sciences, to appear 2011.
- E. Friedmann, R. Neumann, R. Rannacher, Well-posedness for a spatio-temporal model of the JAK2/STAT5 Signaling Pathway, PMC Biophysics, Diffusion and Association Processes in Biological Systems: Theory, Computation and Experiments, to appear 2011.



Scientific 3D visualisation of the simulation results is realized in a Virtual Reality Environment at the Interdisciplinary Center for Scientific Computing.



3D isosurfaces of STAT5 molecules diffusing freely from the outer membraine to the nucleus in a fibroblast cell using COVISE.

Dr. Anne-Claude Gavin

EMBL, Heidelberg
Structural and Computational Biology Unit
Biochemical and chemical approaches to biomolecular networks

11 members of staff (biochemists, biologists and research technicians)

How is biological matter organised? Can the protein and chemical worlds be matched to understand the cell's inner works? We can now access an unprecedented level of knowledge on the basic components of living systems; an ever-growing number of molecular players and functions are being characterised and localised. Despite this spectacular progress we still don't understand how cellular components work collectively and achieve biological function.

The group's research focuses on three main areas in the detailed and systematic charting of cellular networks and circuitry at molecular levels, both spatially and temporally.

The charting of biological networks:
Biological function at cellular levels is achieved by groups of interacting proteins or protein complexes that represent the basic functional and structural units of proteome organisation. The systematic charting of their dynamics has been one of the group's main focuses, for which they use biochemical and quantitative mass spectrometry (MS) approaches in the eukaryote *S. cerevisiae*, the human pathogen *M. pneumoniae* and, in the future, thermophiles or other extremophiles.

The datasets produced allow an unbiased overview of important biological principles. Protein complexes often form larger assemblies, suggesting that sequential steps in biological processes have been captured, and they also often share components, implying protein multifunctionality or pleiotropy. Collaborations with structural groups at EMBL and incorporation of structural models, single-particle EM and cellular electron tomograms provides supporting structural details for this proteome organisation.
The group is also part of a network of EMBL groups tackling a range of biological networks in *M. pneumoniae*, for which they generated large-scale quantitative datasets on *Mycoplasma* transcription, metabolome and proteome organisation.

Development of new methods for charting new types of biological networks:
While current protein–protein or protein–DNA (regulatory) networks give spectacular results, huge uncharted areas still need to be tackled. For example, many metabolites have signalling functions and many proteins are allosterically modulated by metabolites. These bindings are sometimes mediated by a variety of specialised domains; to date, though, large-scale, unbiased analyses are still largely missing. The group developed interests in new methods for the systematic charting of interactions between cellular proteomes, small molecules or metabolites. For example, in S. cerevisiae they developed a generic biochemical assay based on miniaturised lipid arrays for the systematic study of protein-lipid interactions. New avenues such as affinity chromatography methods using immobilised metabolites as affinity probes are being explored. The research group is also interested in multiplexing the assays through miniaturisation using integrated microfluidic devices.

Bridging biological networks to phenotypes:
Because biological function arises from extensively interacting biomolecules, it is in the context of biological

networks that information encoded in genomes must be decrypted. The research group uses networks as a molecular frame for the interpretation of phenotypic data recorded after systematic cell perturbations; these include small molecule inhibitors, gene knock-outs and mutations. They also use network analyses to design models, predictions and perturbations that can be challenged experimentally.

Joint research projects

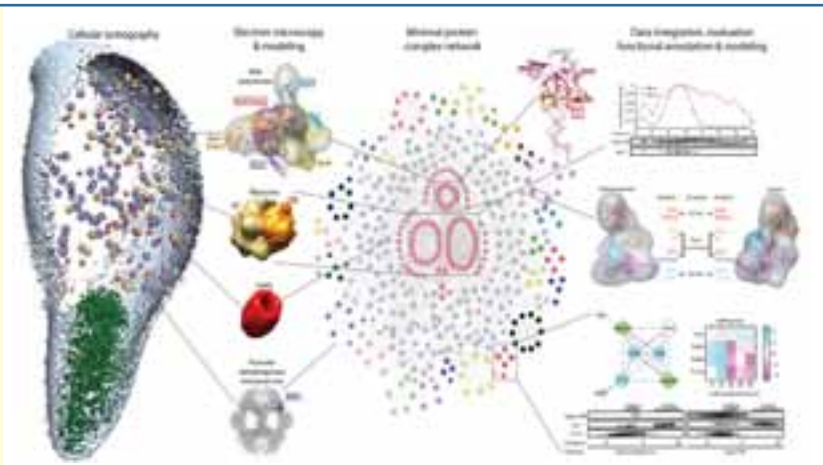
- NGFN-Plus/IG-Cellular Systems Genomics (BMBF)

Selected cooperation partners

- Peer Bork, EMBL, Heidelberg, Germany
- Rob B. Russell, BioQuant Center, Universität Heidelberg, Germany
- Marko Kaksonen, EMBL, Heidelberg, Germany
- Luis Serrano, Center for Genomic Regulation, Barcelona, Spain
- Stefan Wiemann, Faculty of Biosciences, Universität Heidelberg / German Cancer Research Center, Heidelberg, Germany

Selected publications

- Kühner S., van Noort V., Betts M.J., Leo-Macias A., Batisse C., Rode M., Yamada T., Maier T., Bader S., Beltran-Alvarez P., Castaño-Diez D., Chen W.H., Devos D., Güell Cargol M., Norambuena T., Racke I., Rybin V., Schmidt A., Yus E., Aebersold R., Herrmann R., Böttcher B., Frangakis A.S., Russell R.B., Serrano L., Bork P. and Gavin A.C. Proteome organization in a genome-reduced bacterium. 2009, Science 326, 1235-1240.
- Yus E., Maier T., Michalodimitrakis K., van Noort V., Yamada T., Chen W.-H., Wodke J.A.H., Güell M., Martínez S., Bourgeois R., Kühner S., Raineri E., Letunic I., Kalinina O.V., Rode M., Herrmann R., Gutiérrez-Gallego R., Russell R.B., Gavin A.C., Bork P. and Serrano L. Impact of genome reduction on bacterial metabolism and its regulation. 2009, Science 326, 1263-1268.
- Güell M., van Noort V., Yus E., Chen W.-H., Leigh-Bell J., Michalodimitrakis K., Yamada T., Arumugam M., Doerks T., Kühner S., Rode M., Suyama M., Gavin A.C., Bork P. and Serrano L. Transcriptome complexity in a genome-reduced bacterium. 2009, Science 326, 1268-1271.



From Kühner et al. (2009) Proteome organization in a genome-reduced bacterium. Science 326, 1235-1240. Reprinted with permission from AAAS.

Dr. Frauke Gräter

HITS, Heidelberg
Molecular Biomechanics

10 members of staff (biologists, biochemists, chemists, computer scientists, physicists and biophysicists)

All living organisms adapt to mechanical forces by sophisticated mechanisms that convert mechanical stimuli into biochemical responses and vice versa. The Molecular Biomechanics (MBM) group at the HITS aims at understanding the design principles that enable the major players in this game – proteins – to respond to mechanical forces such as those present in tensed muscle, stretched silk fibers, or flowing blood. High-performance simulation techniques and continuum mechanics models are developed to reveal and engineer the force-carrying and force-sensing building blocks in these biological systems and materials.

Most importantly, the group has developed a new technique, force distribution analysis (FDA), based on Molecular Dynamics simulations, to reveal the propagation of mechanial stress through complex biomolecules and biomaterials. FDA has already proven useful to reveal allosteric mechanisms in gene expression factors, as a step towards understanding the molecular basis of signaling networks.

Selected cooperation partners

- Dave Thirumalai, Institute for Physical Sciences and Technology, University of Maryland, USA
- Jianping Ding, Shanghai Institutes for Biological Sciences, China
- Matthias Wilmanns, European Molecular Biology Laboratory, Hamburg, Germany
- Gerrit Groenhof, Max-Planck-Institute for Biophysical Chemistry, Goettingen, Germany
- Jasna Brujic, Center for Soft Matter Research, New York University, USA

Selected publications

- C. Baldauf, R. Schneppenheim, T. Obser, A. Pieconka, S. Schneppenheim, Ulrich Budde, and Frauke Gräter. Mechanism of force-induced von Willebrand factor A2 domain unfolding as a pre-requisite for ADAMTS13 cleavage, Journal of Thrombosis and Haemostasis, in print.
- W. Stacklies, F. Xia, F. Gräter (2009) Dynamic Allostery in the Methionine Repressor Revealed by Force Distribution Analysis. PLoS Comput Biol 5(11): e1000574
- A. Witta, R. Perez-Jimenez, K. A. Walther, F. Gräter, B. J. Berne, J. M. Sanchez-Ruiz und J. Fernandez. Probing the chemistry of enzymatic catalysis with force. Nature, 450, 124-7, 2007.

Prof. Fred A. Hamprecht

Universität Heidelberg
Interdisciplinary Center for Scientific Computing
Multidimensional Image Processing

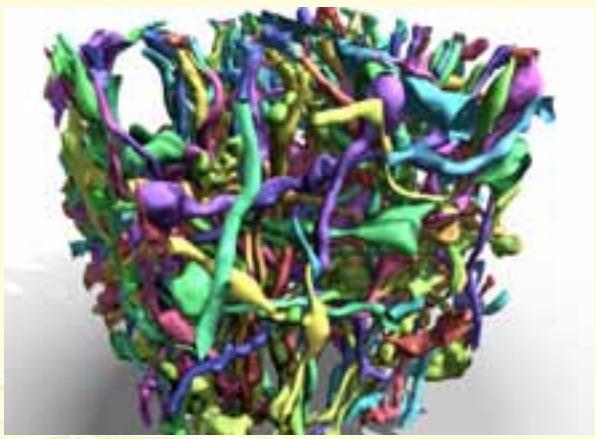
12 members of staff (physicists, computer scientists, mathematicians and engineers)

Systems biology is a data-hungry science that thrives on ultra-high throughput experiments. Often, these experiments yield images, e.g. from wide field, confocal, or even electron microscopy. The specialty of the group is the automated, objective, quantitative analysis of such experiments. Recurring specific tasks include automated quality control and segmentation (i.e., the decomposition of an image into meaningful entities such as cell nuclei or organelles).

On one hand the research group works on grand challenges such as connectomics, where the aim is to establish the wiring diagram of the brain; in these settings, they develop dedicated algorithms to solve just these problems.

On the other hand, the group develops the "ilastik" program with inbuilt machine learning capabilities that allows the biologist to train the procedure with a minimum of human effort.

Overall, the expertise of the group lies at the interface of image processing and machine learning.



Connectomics: segmentation in the neurosciences

Selected cooperation partners

- Jochen Wittbrodt, Institute for Zoology, Universität Heidelberg, Germany
- Ron Heeren, FOM Institute AMOLF, Amsterdam, The Netherlands
- Hanno Steen, Harvard Medical School, Boston, USA
- Winfried Denk, Max Planck Institute for Medical Research, Heidelberg, Germany
- Hans-Georg Kräusslich, Department for Infectiology, University Hospital Heidelberg, Germany

Selected publications

- From experimental setup to bioinformatics: An RNAi screening platform to identify host factors involved in HIV-1 replication. K. Börner, J. Hermle, C. Sommer, N. P. Brown, B. Knapp, B. Glass, G. Torralba, J. Reymann, N. Beil, J. Beneke, R. Pepperkok, R. Schneider, T. Ludwig, M. Hausmann, F. A. Hamprecht, H. Erfle, L. Kaderali, H.-G. Kräusslich, M. J. Lehmann Biotechnology Journal, (2010) 5, 39-49
- Computational Protein Profile Similarity Screening for Quantitative Mass Spectrometry Experiments. M. Kirchner, B. Y. Renard, U. Köthe, D. J. Pappin, F. A. Hamprecht, J. A. J. Steen, H. Steen Bioinformatics, (2009)
- Different Phosphorylation States of the Anaphase Promoting Complex in Response to Anti-Mitotic Drugs: A Quantitative Proteomic Analysis. J. Steen, H. Steen, A. Georgi, K. Parker, M. Springer, M. Kirchner, F. A. Hamprecht, M. W. Kirschner Proceedings of the National Academy of Sciences, (2008) 105, 6069-6074

Prof. Michael Hausmann

Universität Heidelberg
Kirchhoff Institute for Physics
Peptide Chips and Nucleotide FISH

11 members off staff (physicists, biologists, mathematicians, pharmacologists, computer scientists)

Life sciences elucidate the complex functional machinery in cells by systematic studies of bio-molecular interactions. Computer designed DNA probes and high density arrays with combinatorially designed peptides are tools developed and applied in Professor Hausmann's group.

In living systems the main data storage for cellular functions is the cell nucleus containing chromatin that is hierarchically organized in supra-molecular domains and sub-domains that follow functionally controlled arrangements. Cellular data are processed by complex cascades and regulatory cycles of proteins. In order to communicate this data processing to other cells, a cell, like in a showcase, displays complex patterns of specifically selected peptides on its membrane surface.

The research of the group addresses both levels of data presentation (nucleus and membrane) in order to better understand how cellular systems are functioning or, in cases of diseases, dysfunctioning.
For systematic investigations of peptide interactions with antibodies or other cells, arrays are required on which ten thousands of peptides are arranged with amino acid sequences permuting all different 20 amino acids in a combinatorial manner. The group designed and built high-voltage Complementary Metal Oxide Semiconductor (CMOS, Fig. 1) chips on which 10,000 different peptides per cm^2 can be synthesized simultaneously. The present generation of this peptide chip has 16,384 metal pixel electrodes (100 x 100 μm^2) on its surface. Each pixel can be computer controlled so that arbitrary electrical field patterns are generated, such that electrically charged micro-particles loaded with a given type of amino acids can be addressed on distinct pixel electrodes. The chip attracts the particles from aerosols. Peptide synthesis is initiated at once by melting a whole layer of particles. Chemical reaction and washing steps finish the cycle. Several cycles result in combinatorial synthesis of a complete peptide array. Peptides relevant for the detection of virus infections, bacterial infections, or cancer diseases can be searched for. Once having found these peptides, the chip may be a tool to investigate drugs that should interact with the peptides on the cell membrane and finally influence cellular dysfunction.
Moreover, the chip can be used as a tool to manipulate cellular function by electric field patterns and presentation of appropriate peptides to living cells which may incorporate them. For this purpose, a new surface technology has been developed allowing cell growth and movement on the CMOS chip.

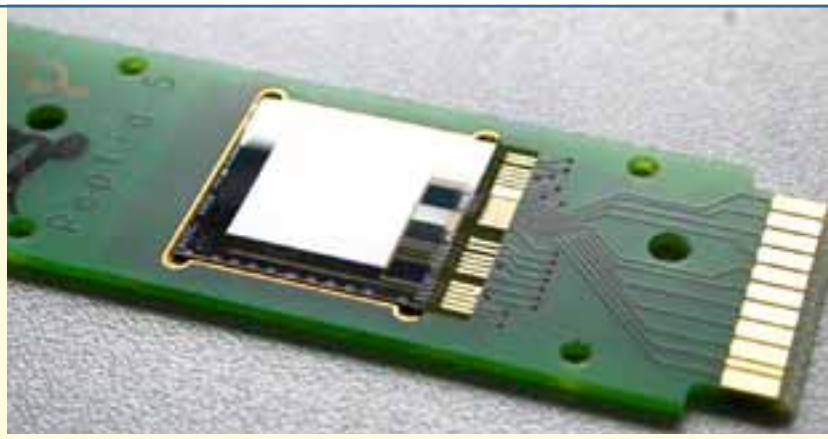
Since peptide presentation on cell surfaces can be triggered by gene activation, methods for specific probing of functionally correlated gene structures and organization are required. The research group developed a patented technique using computer designed oligo-nucleotides as probes that specifically bind to complementary DNA sequences. This technique called COMBO-FISH (COMBinatorial Oligo-nucleotide Fluorescence In Situ Hybridization) is based on screening genome data bases for combinations of short nucleotide sequences that uniquely colocalize at a given gene locus. Such probe sets can be designed and tested against the whole genome by computer search and analysis without time consuming

biological experiments. Once having found an optimum set of probes, the nucleotides are synthesized and labeled by fluorescent dyes so that the respective genome targets can be further analyzed by high resolution fluorescence microscopy. Techniques of molecular localization microscopy are applied which allow measurements with nanometer precision.

COMBO-FISH probe sets are available for many marker genes in tumor diagnostics. Due to the design strategy, the probe sets improve diagnostics by means of exact counting of gene copy numbers or analysis of structural modifications. The group investigates gene positions in nuclei of different cell and tumor precursor states. Since these positions appear to be functionally correlated, changes of the positions during tumor genesis are studied in order to obtain additional topologic parameters for diagnostics and tumor treatment control. Besides these diagnostic approaches, COMBO-FISH is also used as a tool for analyses of DNA breaks and their repair after exposure of cells to ionizing radiation.

Selected cooperation partners

- PD Dr. Ralf Bischoff, German Cancer Research Center, Heidelberg, Germany
- Prof. Dr. Christoph Cremer, Kirchhoff-Institut, Universität Heidelberg, Germany
- Prof. Dr. Martin Werner, Institute of Pathology, University Hospital Freiburg, Germany
- Dr. Luba Trakhtenbrot, Institute for Hematology, Chaim Sheba Medical Center, Tel Hashomer, Israel
- Dr. Tobias Knoch, Erasmus Medical Center, Rotterdam, The Netherlands



Peptidchip 5 mounted on its PCB support with dimensions of a standard microscope glass slide (75.8 mm x 25.9 mm x 1.0 mm).

Selected publications

- Hausmann M, Winkler R, Hildenbrand G, Finsterle J, Weisel A, Rapp A, Schmitt E, Janz S, Cremer C (2003) COMBO-FISH: specific labelling of nondenatured chromatin targets by computer-selected DNA oligonucleotide probe combinations. Biotechniques 35: 564 – 577
- Beyer M, Nesterov A, Block I, König K, Felgenhauer T, Fernandez S, Leibe K, Torralba G, Hausmann M, Trunk U, Lindenstruth V, Bischoff FR, Stadler V, Breitling F (2007) Combinatorial synthesis of peptide arrays onto a microchip. Science 318: 1888
- Börner K, Hermle J, Sommer C, Brown NP, Knapp B, Glass B, Kunkel J, Torralba G, Reymann J, Beil N, Beneke J, Pepperkok R, Schneider R, Ludwig T, Hausmann M, Hamprecht F, Erfle H, Kaderali L, Kräusslich H-G, Lehmann MJ (2010) From experimental setup to bioinformatics: a RNAi screening platform to identify host factors involved in HIV-1 replication. Biotechnology J. 5: 39-49

Prof. Thomas Höfer

German Cancer Research Center, Heidelberg/BioQuant Center
Modeling of Biological Systems

14 members of staff (mathematicians, physicists, biophysicists and biochemists)

How do multiple and noisy cell stimuli cause coordinated changes in gene expression? How are differentiation signals memorized by genetic and epigenetic networks? Can we rationalize how a limited number of signaling pathways regulate a great variety of cell behaviors? What are promising molecular targets to interfere with the complex cellular networks for therapeutic purposes? To address these questions, the research in Thomas Höfer's group aims at elucidating the dynamics of regulatory networks in eukaryotic cells, employing iterative cycles of theoretical and experimental work.

The research group has had long-standing expertise in developing experimentally-based mathematical models of regulatory networks in eukaryotic cells. Previous work on biological pattern formation and cellular calcium signaling has been well-recognized. The current research focuses on the regulation of cell proliferation and differentiation decisions in mammalian cells. The group has discovered a novel switch for T-cell proliferation mediated by a cytokine network. Here autocrine feedback causes a bistable response of T cells to their antigen stimulus that is sensitive to cellular context and defines whether a cell proliferates.

Again using iteration between theoretical and experimental work, the research group has defined the core gene-regulatory network that governs the differentiation of naïve, antigen-inexperienced T cells into pro-inflammatory type-1 T cells that mediate immune responses against viruses and tumors. Mathematical modeling has been instrumental in experimentally uncovering previously unknown interactions in this network. Focusing on the level of a single gene, the research group has elucidated the mechanistic basis for the stochastic expression of a prototypical inducible gene in mammalian cells. Interestingly, this model explains how a gene can be regulated both in a graded and binary manner, with graded regulation acting at the level of transcription initiation and binary control being associated with upstream changes of chromatin structure. These and other predictions of the model have been verified experimentally. Building on these advances in basic research, current work focuses on dissecting the molecular mechanisms that underlie the aberrant cell proliferation and differentiation decisions in cancer.

This work is based on a multi-scale modeling approach that aims at a mechanistic understanding of elementary modules of gene regulation, dynamic protein complex formation and posttranslational modification and their integration into predictive models of interacting signal-transduction and gene-regulatory networks. These cell-biological problems are addressed with a common modeling and simulation methodology, drawing on biochemical systems theory, nonlinear dynamics, stochastic processes, reaction-transport theory, and statistical concepts for parameter estimation and model identification. The group consists of experienced postdocs and PhD students from biophysics, biochemistry, physics and mathematics as well as technical support staff. It provides an interdisciplinary environment that fosters close collaborations between theoreticians and experimentalists.

Joint research projects

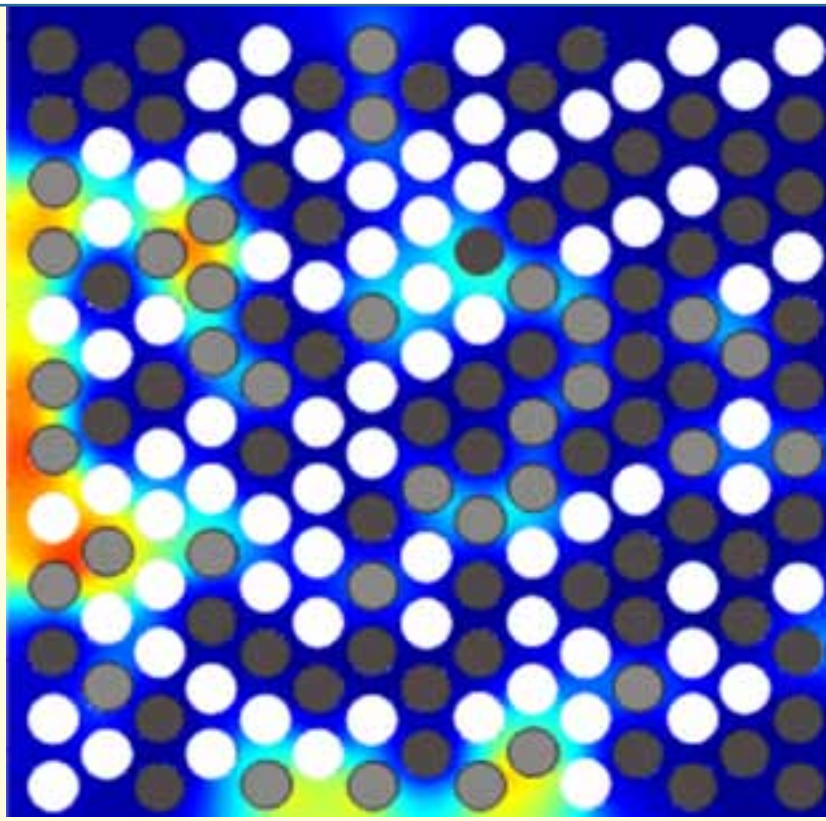
- ASSET (EU-FP-7)
- FORSYS-Partner (BMBF)
- FORSYS/ ViroQuant (BMBF)
- Helmholtz-Alliance on Systems Biology
- HepatoSys (BMBF)
- MedSys (BMBF)
- SYBILLA (EU-FP7)
- SysTec-EpiSys (BMBF)

Selected cooperation partners

- Oreste Acuto, University of Oxford, UK
- Roel van Driel, University of Amsterdam, The Netherlands
- Andreas Radbruch, Deutsches Rheumaforschungszentrum Berlin, Germany
- Wolfgang Schamel, University of Freiburg, Germany
- Max Löhning, Charité - Universitätsmedizin Berlin, Germany

Selected publications

- Mariani, L., Schulz, E. G., Lexberg, M., Radbruch, A., Löhning, M. and Höfer, T. (2010). Short-term Memory in Gene Induction Reveals the Regulatory Principle behind Stochastic IL-4 Expression. Mol. Syst. Biol. 6:359.
- Busse, D., de la Rosa, M., Hobiger, K., Thurley, K., Floßdorf, M., Scheffold, A. and Höfer, T. (2010). Competing feedback loops shape IL-2 signaling between helper and regulatory T cells in cellular microenvironments. Proc. Natl. Acad. Sci. USA, 107, 3058 - 3063.



Computer simulation of growth-factor signaling between T cells.

- Schulz, E., Mariani, L., Radbruch, A., and Höfer, T. (2009). Sequential polarization and imprinting of T-helper type 1 differentiation by interferon-γ and interleukin-12. Immunity 30, 678-688.

Dr. Lars Kaderali

Universität Heidelberg
BioQuant Center
ViroQuant Research Group Modeling

9 members of staff (mathematicians, bioinformaticians, chemical engineers and computer scientists)

The independent junior research group of Dr. Kaderali is working in theoretical systems biology, they analyze and model cellular processes using computational and mathematical methods. A special focus of the group is on modeling virus host interactions, based on high throughput experimental data. For this purpose, the group is combining statistical modeling and machine learning with direct bottom-up modeling approaches using differential equations. The goal is to map the two complementary approaches onto the same, minimal model, and thus obtain a systems-level description of the biological system under consideration. By applying these methods to virus host interactions, the research group aims at analyzing resulting models using control theory, and thus at ultimately identifying new target molecules for anti-viral drug development.

To achieve these objective, the research group concentrates on three main research areas:

(1) Statistical processing of data: The statistical processing of experimental measurements is the basis for further modeling. With the development of an automated pipeline for the analysis and bioinformatics annotation of high-content, high-throughput RNAi screening data, the research group has developed a core component for the analysis of virus host interactions within the BMBF-funded project „ViroQuant“ (Rieber et al, 2009). This pipeline imports and normalizes the experimental data, annotates genes and pathways, and uses statistical criteria to identify significant genes and pathways. The application of this method in screens regarding Hepatitis C virus and HIV has already led to the identification of several interesting candidate genes, which are currently being characterized further experimentally.

(2) Modeling viral replication and host signaling: Mathematical modeling of intracellular virus replication delivers a quantitiative, dynamic description of virus host interactions. The research group of Dr. Kaderali has developed, in close collaboration with the department of molecular virology of the University Hospital (Department Prof. Bartenschlager), a mathematical model of Hepatitis C Virus (HCV) replication. This model provides an accurate description of the dynamics of HCV replication in Huh-7 cells, and in particular points to an important role of the dynamics of replication vesicle formation and dissociation. Accurate modeling of these processes is indispensible to capture the full replication dynamics, pointing to the importance of these processes in the viral lifecycle. Ongoing work enhances the developed model regarding infection and virus assembly, and we are furthermore working on integrating the host immune response into the model. A particular focus in this context is on the Rig-I and the Jak/Stat pathways, two central pathways in the innate immune system. Two further projects concern the secretory pathway, and interaction between human papilloma virus (HPV) and EGFR signaling.

(3) Network reconstruction: While bottom-up approaches are fundamentally knowledge based, data driven approaches attempt to infer models directly from experimental data using machine learning. For this purpose, the research group of Dr. Kaderali has developed new methods to reconstruct

signal transduction and genetic regulatory networks from RNAi knockdown and gene expression time series data, respectively (Kaderali et al., Bioinformatics, 2009; Mazur et al., BMC Bioinformatics, 2009). In colleboration with the department of molecular virology, we have successfully applied these approaches to reconstruct the Jak/Stat pathway from RNAi data (Kaderali et al., Bioinformatics, 2009).

Joint research projects

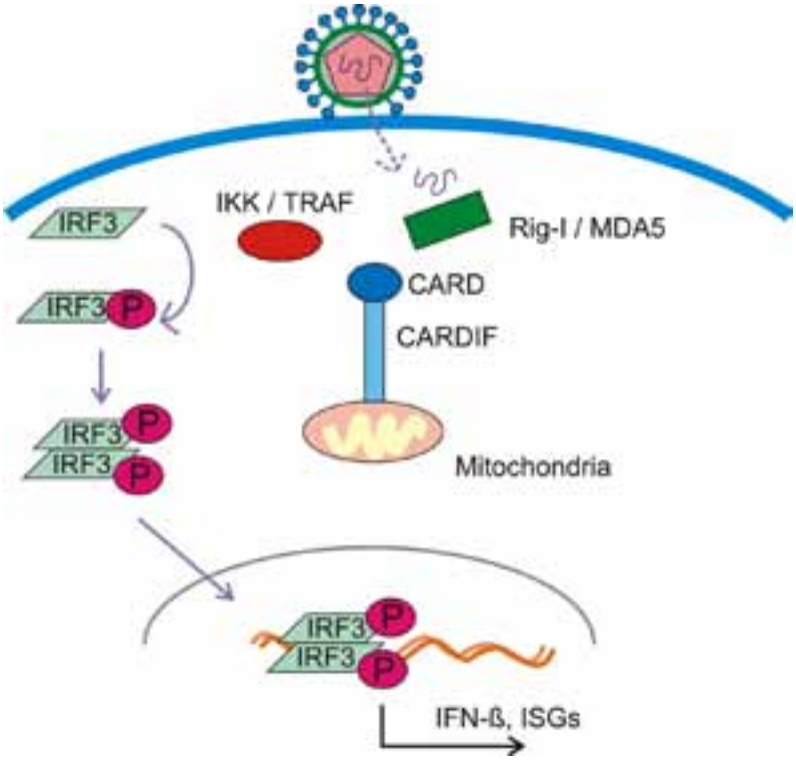
- FORSYS/ ViroQuant (BMBF)
- SysTec (BMBF)

Selected cooperation partners

- Prof. Bartenschlager / Prof. Kräusslich, University Hospital of Heidelberg, Germany
- Prof. Ogishima, Tokyo Dental and Medical University, Japan
- Prof. Berthold, University Hospital Cologne, Germany
- Prof. Kolchanov, Russian Academy of Sciences, Novosibirsk, Russia
- Prof. Eils, German Cancer Research Center, Heidelberg, Germany

Selected publications

- L. Kaderali, E. Dazert, U. Zeuge, M. Frese, R. Bartenschlager (2009). Recontructing Signaling Pathways from RNAi Data using Probabilistic Boolean Threshold Networks. Bioinformatics, 25(17), 2229-2235, doi:10.1093/bioinformatic/btp375.
- J. Mazur, D. Ritter, G. Reinelt, L. Kaderali (2009). Reconstructing Nonlinear Dynamic Models of Gene Regulation using Stochastic Sampling. BMC Bioinformatics, 10:448.



Schematic of the Rig-I signal transduction pathway. Rig-I recognizes viral RNA, and activates a cascade of signaling steps via several kinases, ultimately leading to the translocation of phosphorilated IRF3 dimers to the cell nucleus. This initiates the transcription of interferon beta and other anti-viral genes, in turn activating the Jak/Stat pathway and initiating the cellular immune response to the infection.

- N. Rieber, B. Knapp, R. Eils, L. Kaderali (2009). RNAither, an automated pipeline for the statistical analysis of high-throughput RNAi screens. Bioinformatics, 25, 678-679, doi:10.1093/bioinformatics/btp014.

Dr. Ursula Klingmüller

German Cancer Research Center, Heidelberg / BioQuant Center
Division "Systems Biology of Signal Transduction"

17 members of staff (16 biologists and 1 biophysicist)

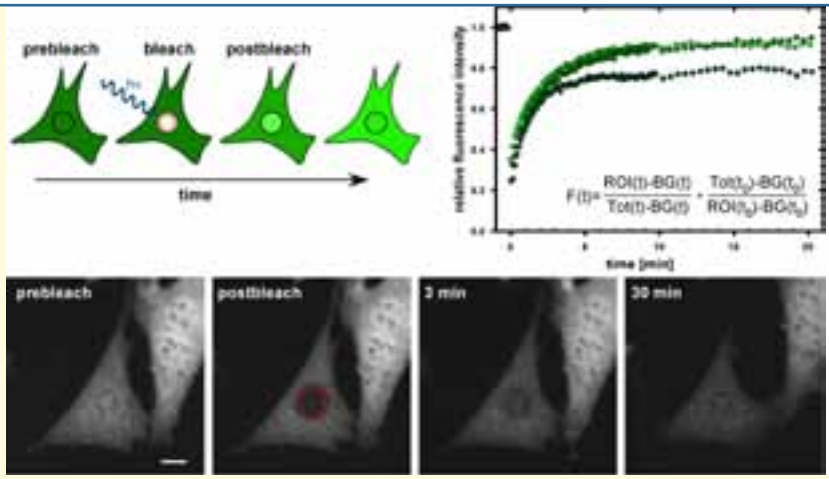
Dysregulation of communication in mammalian cells promotes tumor progression. Cell growth and differentiation is regulated by the coordinated activation of multiple signaling pathways. The components of many signaling cascades have been identified, yet it is largely unknown how information is processed and how decisions are made. To elucidate principal mechanisms regulating cellular decisions, it is important to analyze timing, extent and duration of signal activation. By combining quantitative experimental data with mathematical modeling, systems biology offers the advantage to identify key regulatory mechanisms in signaling networks and predict most sensitive targets for efficient intervention.

To establish meaningful mathematical models, it is essential that these models are based on high-quality quantitative data acquired under standardized conditions. Therefore, in the frame of HepatoSysII, the research group "Systems Biology of Signal Transduction" of Dr. Ursula Klingmüller established a standardized cell system for primary hepatocytes, established strategies for error reduction and automated data processing to reliably apply quantitative immunoblotting for acquiring time-course data sets and determining the stoichiometry of signaling pathway components. To extend the possibilities to simultaneously detect alterations in signaling components in small sample volumes, we developed quantitative protein arrays based on the detection in the near infrared range.

Hepatocyte regeneration is a highly controlled growth and differentiation process that is characterized by three consecutive phases: priming, proliferation and termination. In HepatoSysI and II we have established data-based mathematical models for signaling pathways critical during the priming and termination phase and could show that switch-like properties prepare hepatocytes for proliferation and that negative feedback regulation prevents excessive damaging responses during the termination phase. These models will be extended from the cell to the organ level within the frame of the virtual liver network. Within the EU-project CancerSys the group examines alterations in proliferative responses in hepatocellular carcinoma. In the frame of the FORSYS Network ViroQuant a mathematical model for interferon α signaling was established showing that the pathway is tightly controlled by the intricate interplay of positive and negative feedback loops. Currently, there is searched for steps in the signaling cascade that are targeted by the Hepatitis C Virus.

In the hematopoietic system the hormone erythropoietin (Epo) is a key regulator of erythropoiesis that leads from lineage commitment to mature erythrocytes. Since Epo-dependent proliferation and differentiation of erythroid progenitor cells can be monitored in vitro, this provides an ideal model to study general systems properties controlling unidirectional growth and maturation processes. In the frame of the Helmholtz Alliance on Systems in the Network SBCancer this model system is used to understand regulatory mechanisms determining cellular decisions. Within the MedSys consortium LungSys the group is employing this knowledge to unravel how the Epo-receptor can enhance lung cancer progression and will use the modeling approach to predict strategies for prevention.

In summary, the research group is employing a systems biology approach to elucidate mechanisms for information processing and regulation of cellular decisions, in order to unravel alterations that promote cancer progression or facilitate viral persistence. The long-term goal is to establish data-based multi-level multi-scale mathematical models facilitating the in silico prediction of strategies to fight infectious diseases and combat cancer.



Protein dynamics in living cells can be studied by fluorescence recovery after photobleaching (FRAP). In a typical FRAP experiment fluorophores in a region of interest (ROI) are photobleached with strong laser light and exchange of bleached and unbleached molecules is followed over time. Fluorescence recovery can be plotted by normalizing the fluoresence intensity in the ROI by that of the total cell (Tot) and additionally normalizing by the prebleach intensities at t0. Below data of a FRAP experiment investigating the nucleocytoplasmic shuttling of STAT5-GFP in NIH3T3-EpoR cells is shown. Nuclear STAT5-GFP was photobleached and recovery of nuclear fluorescence was observed. Scale bar, 10 µm.

Joint research projects

- "CancerSys" EU-STREP
- FORSYS/ ViroQuant (BMBF)
- HepatoSys (BMBF)
- Medical Systems Biology (BMBF)
- Systems Biology of Cancer (Helmholtz Association)
- Virtual Liver (BMBF)

Selected cooperation partners

- Prof. Jens Timmer, University of Freiburg, Germany
- Prof. Roland Eils / Dr. Stefan Legewie, German Cancer Research Center /Universität Heidelberg, Germany
- Prof. Thomas Höfer, German Cancer Research Center, Heidelberg, Germany
- Prof. Fabian Theis, Helmholtz Zentrum München, Germany
- Prof. Ursula Kummer, Universität Heidelberg, Germany

Selected publications

- Becker, V., Schilling, M., Bachmann, J., Baumann, U., Raue, A., Maiwald, T., Timmer, J., and Klingmüller, U., Covering a Broad Dynamic Range - Information Processing at the Erythropoietin Receptor. Science (2010), 328(5984):1404-8.
- Schilling, M., Maiwald, T., Hengl, S., Winter, D., Kolch, W., Lehmann, W. D., Timmer, J., and Klingmüller, U., Combined Theoretical and Experimental Analysis Links Isoform-specific MAP-kinase Signaling to Cellular Decisions. Molecular Systems Biology (2009), 5:334.
- Swameye, T. G. Müller, J. Timmer, O. Sandra, and U. Klingmüller. Identification of nucleocytoplasmic cycling as a remote sensor in cellular signaling by data-based dynamic modeling. PNAS (2003), 100:1028-33.

Dr. Michael Knop

EMBL, Heidelberg
Cell Biology and Biophysics Unit
Knop research group

9 members of staff (physicists, biologists, bioinformaticians and bioengineers)

Dr. Knop's research group is interested in questions that relate to cellular signal transduction, cell morphogenesis and genome recombination. For its work the group mainly uses bakers' yeast *Saccharomyces cerevisiae* as a convenient model organism and it focuses on the deciphering of molecular mechanisms that govern the various processes. Initially, the group pursued strategies that aimed to identify new components of the investigated processes. This important part of the work has mostly been completed.

Now the group concentrates on systematic descriptions of the molecular processes. Thereby it tries to complement its detailed qualitative knowledge with data retrieved from the application of new and quantitative methods, such as high content microscopy. Thereby the reserch group seeks to develop mathematical models that describe the corresponding processes. The goal is to solidify the fundamental understanding of the processes and to use the models to derive quantitative predictions about the behavior of cells under non-trivial conditions such as genetic disturbances.

The methods that are used for this type of systemic research are currently in the focus of intense research. This is connected to the hope that one day highly effective instruments will be available that allow precise predictions about the effect of medication and cures related to e.g. cancer or neurodegenerative diseases.
One of the specialties of Dr. Knop's group consists in the application of advanced microscopic methods, for example a technique called fluorescence cross correlation spectroscopy (FCCS). With the help of this and other methods it is for example possible to visualize and measure the interactions and activity of proteins directly within living cells. To further improve the available methods the group currently develops, in collaboration with physicists, a new microscope to allow FCCS measurements in two dimensions, instead of the currently common one-dimensional confocal setup. This will solve in the future a series of problems associated with single cell FCCS measurements, such as the high measurement error that is caused by cellular heterogeneities and changes of contrast. This microscope will also allow researchers to study the spatial organization of protein interaction and function.

Further the lab conducts research on questions that relate to the evolutionary process. Here the researchers seek to decipher the correlation between genome recombination associated with sexual reproduction (meiosis) and the design of molecular cellular systems. So far they have investigated the influence of population genetic parameters on genome organization. These studies were conducted in collaboration with the computing center at the Karlsruher Institut für Technologie (KIT), which allowed the group to conduct computation-intense computer simulations of the dynamics of evolving genomes. In the future Dr. Knop's group will expand these studies to investigate several aspects of the structure of functional protein networks.

Special equipment and techniques

- Access to the ALMF (advanced light microscopy facility) and other Core Facilities at EMBL
- Fluorescence cross correlation spectroscopy (FCCS)

Joint research projects

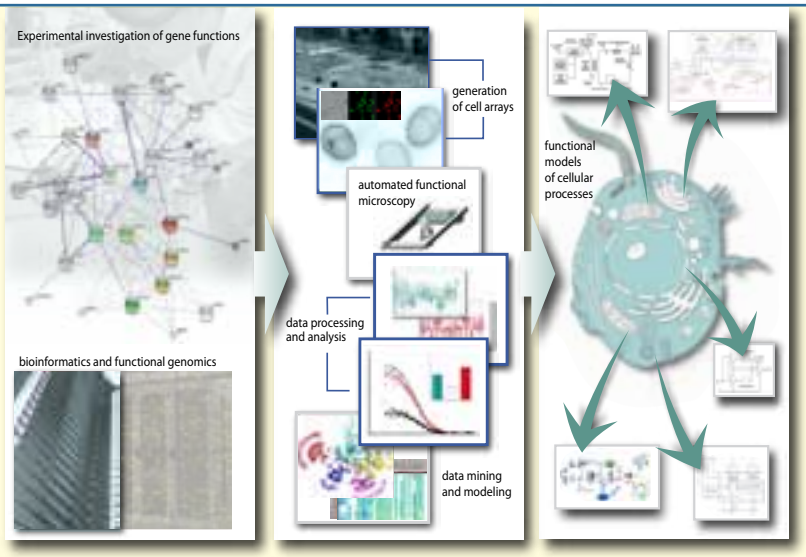
- CellNetworks

Selected cooperation partners

- Prof. Ph. I. Bastiaens, MPI Dortmund, Germany
- Prof. E. Schiebel, ZMBH Heidelberg, Germany

Selected publications

- Khmelinskii A, Keller PJ, Lorenz H, Schiebel E, Knop M. (2010) Segregation of yeast nuclear pores. Nature, in press
- Keller PJ, Knop M (2009) Evolution of Mutational Robustness in the Yeast Genome: A Link to Essential Genes and Meiotic Recombination Hotspots. PLoS Genetics 5(6): e1000533
- Maeder CI, Hink MA, Kinkhabwala A, Mayr R, Bastiaens PIH, Knop M (2007) Spatial regulation of Fus3 MAP kinase activity through a reaction-diffusion mechanism in yeast pheromone signalling. Nat Cell Biol 9(11): 1319-1326



Workflow for systemic functional studies: A combination of data mining and bioinformatics is used to define the components of a protein network. High content microscopy is used to probe the behavior and properties of the system components. Based on this data, functional models of the processes under investigation are generated.

Dr. Ulrike Korf

German Cancer Research Center, Heidelberg
Quantitative Proteomics

9 members of staff (biologists, biotechnologists and technicians)

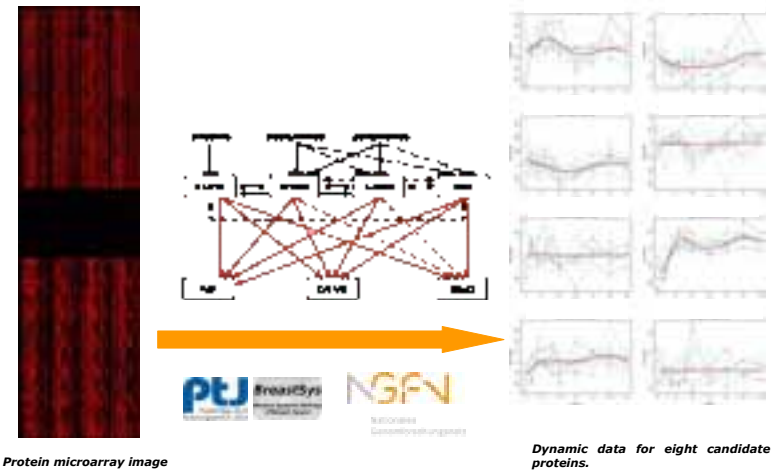
The Quantitative Proteomics group at the DKFZ Heidelberg started in 2004, with the optimization of protein microarray applications to develop experimental tools suitable for the quantitative analysis of signal transduction dynamics. As of now, two technically different approaches are routinely applied for the quantification of protein abundance, and both rely on highly specific antibodies to recognize specifically the protein of interest.

The microspot immunoassay (MIA) principle follows a strategy similar to that used by the well-known, and widely employed, enzyme-linked immunosorbent assay (ELISA); it relies on two different antibodies that recognize spatially-separated epitopes of a certain target protein. However, microspot immunoassays are carried out in a multiplexed and miniaturized format, so that several proteins or phosphoproteins can be monitored in parallel, and less sample material is required. Recently, the MIA format was also adapted to the quantification of human plasma proteins: the group developed protocols for multiplexed measurements of biomarkers, as well as tools for statistic data analysis, and protein microarray data presentation (http://code.google.com/p/quantproreloaded/).

Biological or clinical samples can also be printed directly on a solid-phase carrier (slide), which exploits the high-sample capacity of the microarray format. Using specialized robotics, 50-200 identical slides can be printed in a single print run, and each slide can be probed with a different, highly-specific antibody. The Quantitative Proteomics group at the DFKZ Heidelberg adapted an approach, which was introduced as reverse phase protein array (RPPA) by Lance Liotta and Emanuel Petricoin in the early 2000s, to fluorescence detection in the near infrared (NIR) range, to carry out protein profiling from as little as only 20,000 cells with sensitivity in the fg-range; this way, up to 4,000 different samples can be analyzed in parallel. The extremely high sample capacity makes this approach to generating high-quality data for systems biology very attractive. Standard RPPA applications include the analysis of signaling networks in response to drugs, RNAi-based silencing experiments, as well as protein-profiling of tumor biopsy samples. Additionally, the group developed a comprehensive software program, which was named RPPanalyzer; the program covers all steps of RPPA data analysis and data presentation, and is publicly available for download (http://cran.r-project.org).

Both protein microarray technologies described above are currently used to elucidate signaling through the ERBB receptor family, as well as mechanisms of their feedback control. Members of the ERBB family of receptor-tyrosine kinases are known to be over-expressed, or mutated in various human cancers, such as the HER2/ERBB2 gene in human breast cancer. Thus, systematic studies are currently carried out to quantify ligand- and dose-dependent signaling downstream of ERBB receptors in different human breast cancer cell lines, which express distinct subsets of ERBB family members. The resulting information will be used to identify key players in the control of apoptosis, proliferation, and migration. The data will feed into quantitative data-driven modeling of ERBB receptor network dynamics, and will aid the identification of new target points for clinical intervention.

In collaboration with the Max-Planck Institute for Molecular Genetics, a drug screen was initiated to identify the optimal combinatorial anti-cancer treatment strategy. Genomic alterations of a primary melanoma cell line were identified by next-generation sequencing, and the resulting information was used to predict suitable drug combinations. In silico, identified drug combinations are currently tested in cell culture experiments, and the resulting samples are analyzed by RPPA-based protein profiling, which will elucidate the impact of the drugs on the signaling networks of malignant cells for the eventual identification of tumor-tailored treatment strategies.



Protein microarray image

Dynamic data for eight candidate proteins.

Using reverse phase protein microarrays (RPPA) to elucidate the impact of the drugs on the signaling networks of cancer cell lines.

Special equipment and techniques

- Proteinmikroarray-Technology
- Sprint (Arrayjet), 2470 Arrayer (Aushon)

Joint research projects

- NGFNplus (BMBF)
- MedSys (BMBF): MOGLI, BreastSys
- EraSysBio+ (BMBF): iPS/Steatohepatitis
- Systems Biology of Cancer (Helmholtz Association)

Selected cooperation partners

- Tim Beissbarth, University of Freiburg, Germany
- Andreas Schneeweiss, National Center for Tumour Diseases (NCT) Heidelberg, Germany
- Holger Sültmann, German Cancer Research Center, Heidelberg, Germany
- Jens Timmer, University of Freiburg, Germany
- Stefan Wiemann, German Cancer Research Center, Heidelberg, Germany

Selected publications

- Korf U, Derdak S, Tresch A, Henjes F, Poustka A, Beissbarth T, Klingmueller U. Quantitative protein microarrays for time-resolved measurements of protein phosphorylation. Proteomics 2008, 8, 4603-12.
- Loebke C, Sueltmann H, Schmidt C, Henjes F, Wiemann S, Poustka A, Korf U. Infrared-based protein detection arrays for quantitative proteomics. Proteomics 2007, 7, 558-564.
- Sahin O, Loebke C, Korf U, Appelhans H, Sueltmann H, Poustka A, Wiemann S, Arlt D. Combinatorial RNAi for quantitative protein network analysis. Proc. Natl. Acad. Sci. USA 2007, 104, 6579-8.

Prof. Hans-Georg Kräusslich

Director BioQuant Center

University Hospitals Heidelberg
Department of Infectious Diseases / BioQuant Center
Research Group Virology

16 members of staff

HIV is an enveloped virus that enters host cells carrying appropriate receptors (CD4 and a coreceptor which can be either CXCR4 or CCR5) by fusion at the plasma membrane, but also from the endosome. The virus can non-specifically attach to cell surface glycosaminoglycans, but requires surface protein (gp120) receptor/coreceptor interactions for cytosolic entry. Fusion is mediated by the viral trans-membrane glycoprotein gp41 and leads to cytosolic release of the viral capsid containing the RNA genome and replication proteins. Following replication and gene expression, new virions are produced at and released from the plasma membrane of the infected cells. These virions initially consist of an immature shell of the main structural protein Gag underneath the membrane, which is subsequently cleaved by a virus encoded protease leading to morphological maturation, which is required for infectivity.

All research projects in Professor Kräusslich's research group address different aspects of human immunodeficiency virus (HIV) biology. A major focus in the lab is the formation and architecture of the infectious HIV particle. The group has developed *in vitro* assembly systems to analyze the molecular architecture of capsid assemblies, to study the effect of mutations on mature and immature particle formation and to identify inhibitors of HIV assembly. These studies are complemented by analyses of HIV particle formation in tissue culture.

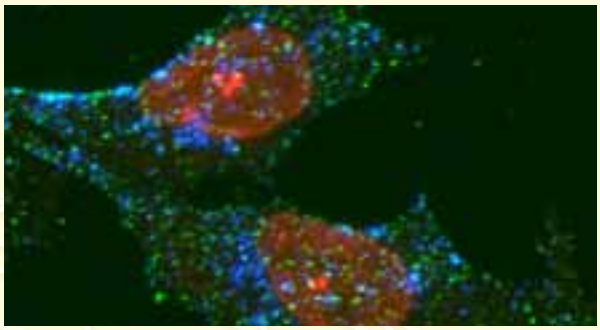
The research group employs structural analyses including transmission EM, cryo-EM and tomography to obtain detailed three-dimensional images of mature and immature virions, as well as viral budding sites, of wild-type and mutant HIV. These studies provide a better understanding of the mechanism and protein interface governing assembly as well as maturation and include the development of assembly inhibitors as a potential new antiviral strategy. Furthermore the group is developing and using *in vitro* screening systems for the identification of novel virus encoded protease inhibitors. Related studies are aimed at understanding the role of individual cleavage sites within Gag and the molecular mechanisms of resistance development against HIV PR inhibitors.

Further projects address the role of host factors for HIV entry and release. While numerous studies have yielded information on the interactions between viral proteins and cellular plasma membrane factors involved in viral entry, the dynamics of this process as well as the role of the host cell cytoskeleton are still not well understood. The group has recently generated infectious fluorescent HIV derivatives, which allow the direct observation of virus-cell interactions in real time at high temporal and spatial resolution. So far, the group has concentrated on virus attachment to the membrane and fusion, applying doubly fluorescent HIV-like particles carrying different envelope glycoproteins. Using automated tracking programs, more than 20,000 individual tracks have been analyzed identifying bona fide fusion events. Analyses involve direct fusion at the plasma membrane as well as endosomal uptake and fusion from the endosome in a pH independent manner. These virus derivatives are also used to study dynamics of HIV particle formation. Furthermore, Professor Kräusslich's group has begun to explore high

resolution fluorescence microscopy (STED, STORM) for the detailed analysis of HIV-cell interactions.

To identify cellular host factors with functional roles in HIV infection and release the group uses a sub-genomic siRNA-based screening approach in combination with high throughput fluorescence microscopy and automated imaging analysis. Knocked-down genes enhancing or reducing viral replication are used to assemble relevant cellular signalling networks and analyzed by graph based and machine learning techniques to shape out interactions that are functionally relevant. In this regard, assays have been established to quantify virus attachment, fusion, and initiation of reverse transcription, completion of reverse transcription, nuclear import, and virus production in a time-resolved manner. These projects are being pursued in cooperation with the ViroQuant CellNetworks RNAi Screening Facility at the BioQuant center Heidelberg.

Furthermore the group has determined the lipidome of a prototype HIV using mass spectroscopy and biochemical approaches. The group is currently analyzing the influence of host cells and viral proteins on the lipid composition of the envelope and study the influence of lipid composition on the properties of the virus.



Joint research projects

- Excellence Cluster CellNetworks
- FORSYS/ ViroQuant (BMBF)

Selected cooperation partners

- Barbara Müller, Department of Virology University Hospital Heidelberg, Germany
- Don Lamb and Christoph Bräuchle, Department of Chemistry and Biochemistry, LMU Munich, Germany
- Karl Rohr, Lars Kaderali, Fred Hamprecht and Roland Eils, BioQuant Center, Universität Heidelberg and German Cancer Research Center, Heidelberg, Germany
- Stefan Hell, BioQuant Center, Universität Heidelberg, Germany
- Mike Heilemann, Department of Physics, Bielefeld University, Germany

Selected publications

- Briggs JA, Riches JD, Glass B, Bartonova V, Zanetti G, Kräusslich HG. (2009) Structure and assembly of immature HIV. Proc Natl Acad Sci U S A. 106(27):11090-5.
- Brügger, B., Glass, B., Haberkant, P., Leibrecht, I., Wieland, F. T., Kräusslich, HG (2006). The HIV lipidome: a raft with an unusual composition. Proc Natl Acad Sci U S A 103, 2641-2646.
- von Schwedler UK, Stuchell M, Müller B, Ward DM, Chung HY, Morita E, Wang HE, Davis T, He GP, Cimbora DM, Scott A, Kräusslich HG, Kaplan J, Morham SG, Sundquist WI. (2003) The protein network of HIV budding. Cell 114, 701-713.

Prof. Ursula Kummer

Universität Heidelberg
Institute of Zoology / BioQuant Center
Modelling of Biological Processes

17 members of staff (biochemists, physicists, computer scientists, biologists, mathematicians and bioinformaticians)

The department "Modeling of Biological Processes" at the Universität Heidelberg was founded in 2007 and is headed by Prof. Dr. Ursula Kummer. The research focus of the department is on the development of methods for the simulation, modelling and analysis of biochemical networks as well as on the application of these methods to tackle specific biochemical questions. The software Copasi (Complex Pathway Simulator) developed together with the group of Pedro Mendes which allows the simulation, modelling and the analysis of biochemical networks is internationally widely used (annually about 4000 downloads). In addition, a web-based environment, Sycamore, which is developed together with Rebecca Wade's group at the HITS gGmbH is used for the database aided modeling of biochemical networks. Constantly, new algorithms and methods are developed which are then integrated in the above platforms. Examples for application studies within the department include the study of signal transduction pathways and information processing therein. Among these, calcium, TGF-ß and IFN signalling are prominent examples. Thus, encoding and decoding mechanisms of calcium oscillations have been postulated of which encoding mechanisms have been experimentally verified recently.

The activation of human neutrophilic leukocytes (with Lars Folke Olsen, Odense, Denmark, Gertrud Hänsch, Medical Faculty, Universität Heidelberg) is another central topic. Similar to the signal transduction projects, it is of interest here, how information is conveyed and how dynamics can carry different qualitative functions in biochemical systems.

The department is organizing bi-annual workshops on the computation of biochemical pathways and genetic networks.

Prof. Dr. Ursula Kummer has been one of the organisers of the ICSB2004 (International Conference on Systems Biology 2004) in Heidelberg and of the FEBS Advanced Course on Systems Biology 2009 in Alpbach, Austria. Furthermore, Ursula Kummer's group is member of the EU NoE BioSim which targets at the pharmaceutical use of modeling and simulation in the biosciences.
With respect to teaching, the department is very active in teaching courses and practicals on bioinformatics and computational systems biology. Prof. Dr. Ursula Kummer is one of the coordinators of the major program in systems biology at the faculty of biosciences and of the Center for Modeling and Simulation in the Biosciences (BIOMS).

Special equipment

- Software Copasi (Complex Pathway Simulator)

Joint research projects

- FORSYS/ViroQuant (BMBF)
- NoE BioSim
- SysMO (BMBF)
- Virtual Liver (BMBF)

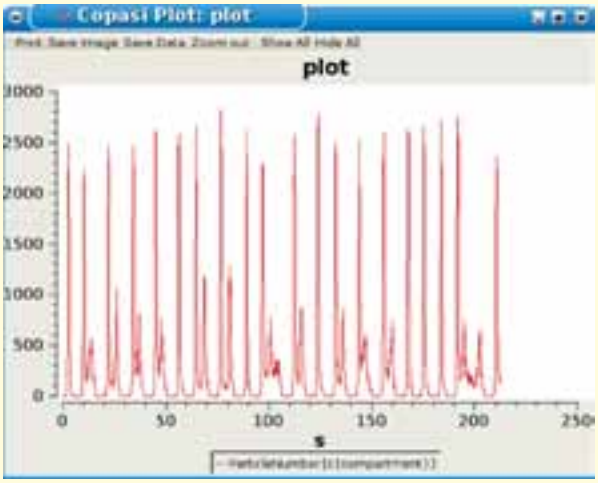
Selected cooperation partners

- Prof. Pedro Mendes, University of Manchester, UK and VBI, USA
- Prof. Lars Folke Olsen, SDU Odense, Denmark
- Prof. Bas Teusink, Vrije Universitet Amsterdam, The Netherlands
- Prof. Jeroen Hugenholtz, University of Amsterdam, The Netherlands
- PD Dr. Ursula Klingmüller, German Cancer Research Center, Heidelberg, Germany

Selected publications

- A new strategy for assessing sensitivities in biochemical models S. Sahle, P. Mendes, S. Hoops, U. Kummer, Phil. Trans. R. Soc. A, 366, 3619-3631, 2008
- COPASI – a Complex Pathway Simulator S. Hoops, S. Sahle, R. Gauges, C. Lee, J. Pahle, N. Simus, M. Singhal, L. Xu, P. Mendes and U. Kummer, Bioinformatics, 22, 3067-3074, 2006
- No music without melody: How to understand biochemical systems by understanding their dynamics U. Kummer and L.F. Olsen, Topics in Current Genetics, 13, 81-93, 2005

Screenshot of the Copasi GUI with the simulation window open.



Result of a stochastic simulation of calcium signalling in hepatocytes using Copasi.

Dr. Inna N. Lavrik

German Cancer Research Center, Heidelberg / BioQuant Center

Understanding life / death decisions in apoptosis using systems biology

5 members of staff (biologists, mathematician and technician)

Relevance / State of the art:

Apoptosis is common to all multicellular organisms. There are two main ways of apoptosis: intrinsic and extrinsic (Krammer et al., 2007, Nat Rev Imm). The intrinsic pathway is triggered via chemotherapeutic drugs, irradiation and growth factor withdrawal. These stimuli lead to changes in mitochondrial potential, which results in cytochrome C release and caspase activation. In the extrinsic apoptotic pathway, the caspase cascade is triggered by signals emanating from the cell-surface death receptors (DR) triggered by death ligands (L), (TNF, CD95L/FasL, TRAIL). Triggering of DR by death ligands results in the formation of a DISC, death-inducing signaling complex, where caspase-8 is activated leading to induction of the caspase cascade, which is followed by the demolition of the cell. Deregulation of apoptosis leads to a number of serious diseases such as cancer, autoimmune diseases and many others. Apoptotic pathways are very complex and a systemic view on apoptosis is still missing.

The goal of the group "Understanding life/death decisions in apoptosis using systems biology" is to understand the complexity of apoptotic signaling using systems biology approaches. From the apoptotic signaling the group focuses on CD95/Fas signaling pathway. CD95/Fas is a member of death receptor family. CD95 has been discovered more than 20 years ago by Prof. Peter H. Krammer, who is the head of the Division of Immunogenetics to which the group belongs.

There are several directions in the investigations:

First direction involves the regulation of apoptosis induction in the CD95/Fas system. The group has published the first-ever comprehensive model of apoptosis in collaboration with Prof. Eils (Bentele, Lavrik et al., 2004, J Cell Biol). The first model of the apoptotic CD95/Fas signaling has been built on series of experimental data and predicted the threshold behaviour of CD95 signaling. The mechanism of the threshold behaviour in CD95 apoptotic signaling predicted by the model has been recently investigated by the group in more detail (Lavrik et al., 2007, J Biol Chem).

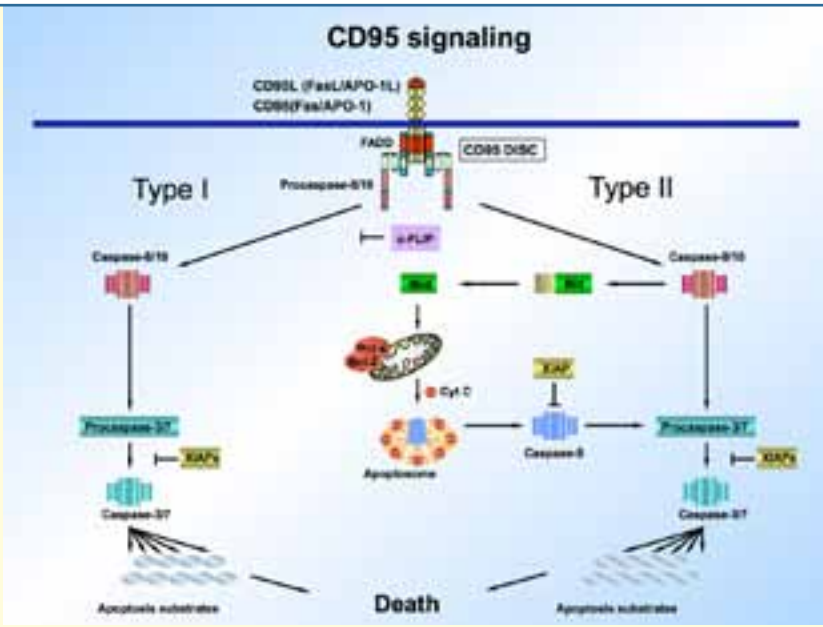
To further investigate the role of the inhibitors of the CD95 signaling the group has created the quantitative model of caspase-8 activation at the CD95 DISC considering c-FLIP$_{S/R/L}$-the central inhibitors of caspase-8 activation at the DISC and, thereby, of the CD95-induced apoptosis. The model has shown how different c-FLIP isoforms contribute to the apoptotic inhibition (Fricker et al., JCB, in press). Currently, approaches for quantitative proteomics to unravel stochiometry of the CD95 DISC are being developed together with the group of Dr. Schnölzer.

Second direction involves the study of the induction of non–apoptotic pathways via CD95/Fas. The group has created in collaboration with Roland Eils the first model of CD95-mediated apoptosis and NF-κB pathway, which has demonstrated that life/death decisions are taken at the CD95 DISC in a non-linear way (Neumann et al., 2010, Mol Syst Biol). Interestingly, the group has revealed the new link between CD95 stimulation and the induction of NF-κB pathway, which turned out to be the cleavage product of c-FLIP, p43-FLIP. It continues to study the crosstalk between CD95 apoptotic and non-apoptotic

pathways using systems biology.

Third direction deals with the development of new targets for sensitisation of cancer cells towards apoptosis. The research group collaborates with Dr. Natalia Giese on investigating CD95 signaling in pancreatic cancers using systems biology. This approach should provide the optimal ways of sensitization of pancreatic cancer cells towards apoptosis and the basis for developing novel treatments for anti-cancer therapy.

In addition, the researchers are interested in the role of new modulators in regulating sensitivity and resistance of cancer cells towards CD95-induced apoptosis. To achieve this goal they perform siRNA screens in collaboration with Prof. Boutros as well as proteomics screen together with Dr. Schnölzer. The role of new molecules, which were found by these screens, is currently under investigation.



Joint research projects

- Systems Biology of Cancer (Helmholtz Association)

Selected cooperation partners

- Prof. Roland Eils, Division of Theoretical Bioinformatics, German Cancer Research Center, Heidelberg
- Dr. Natalia Giese, Department of General, Visceral and Transplantation Surgery, University Hospital Heidelberg, Germany
- Dr. Martina Schnoelzer, Group of protein analysis, German Cancer Research Center, Heidelberg
- Prof. Michael Boutros Division of siRNA screening, German Cancer Research Center, Heidelberg
- Prof. Fabian Theis, Institute of Bioinformatics and Systems Biology at the Helmholtz Zentrum München, Germany

Selected publications

- Neumann L, Pforr C, Beaudouin J, Pappa A, Fricker N, Krammer PH, Lavrik IN, Eils R. Dynamics within the CD95 death-inducing signaling complex decide life and death of cells. Mol Syst Biol. 2010;6:352.
- Lavrik IN, Eils R, Fricker N, Pforr C, Krammer PH. Understanding apoptosis by systems biology approaches. Mol Biosyst. 2009 Oct 5; (10):1105-11.
- Bentele M, Lavrik I, Ulrich M, Stösser S, Heermann DW, Kalthoff H, Krammer PH, Eils R. Mathematical modeling reveals threshold mechanism in CD95-induced apoptosis. J Cell Biol. 2004 Sep 13;166(6):839-51.

Prof. Wolf-Dieter Lehmann

German Cancer Research Center, Heidelberg
Molecular Structure Analysis

9 members of staff

Kinase-catalysed reversible phosphorylation is the most important principle of covalent protein modification. Phosphorylation/dephosphorylation effectively changes and controls the activity, interaction and localisation of many proteins. Reversible protein phosphorylation plays a significant role in a wide range of cellular processes, including cellular stress response, signal transduction and growth control. Many cancers are characterised and caused by a dysregulated balance of protein phosphorylation underlining the potential of this phenomenon for the classification and functional characterization of healthy and malignant cells.

Prof. Lehmann's research group focuses on the qualitative and quantitative analysis of protein phosphorylation using mass spectrometry. Qualitative analyses involve the identification of protein phosphorylation sites using in-gel protein digestion, phosphopeptide enrichment, LC-MS/MS and data analysis. The team has expertise in the automatic and manual analysis of fragment ion spectra of modified peptides, in particular of phosphopeptides.

Quantitative analyses focus on the determination of the site-specific degree of phosphorylation. Procedures with and without internal standards are being developed further, evaluated and applied. The highest accuracy is achieved with synthetic, stable isotope-labelled internal standards. The biological or clinical samples are prepared by collaborating research groups. The results are discussed and interpreted with the cooperation partners and serve as basis for the advancement of functional models of biological systems and model calculations.

Special equipment and techniques

- nanoUPLC-MS/MS
- Element mass spectrometry
- Phosphopeptide enrichment

Joint research projects

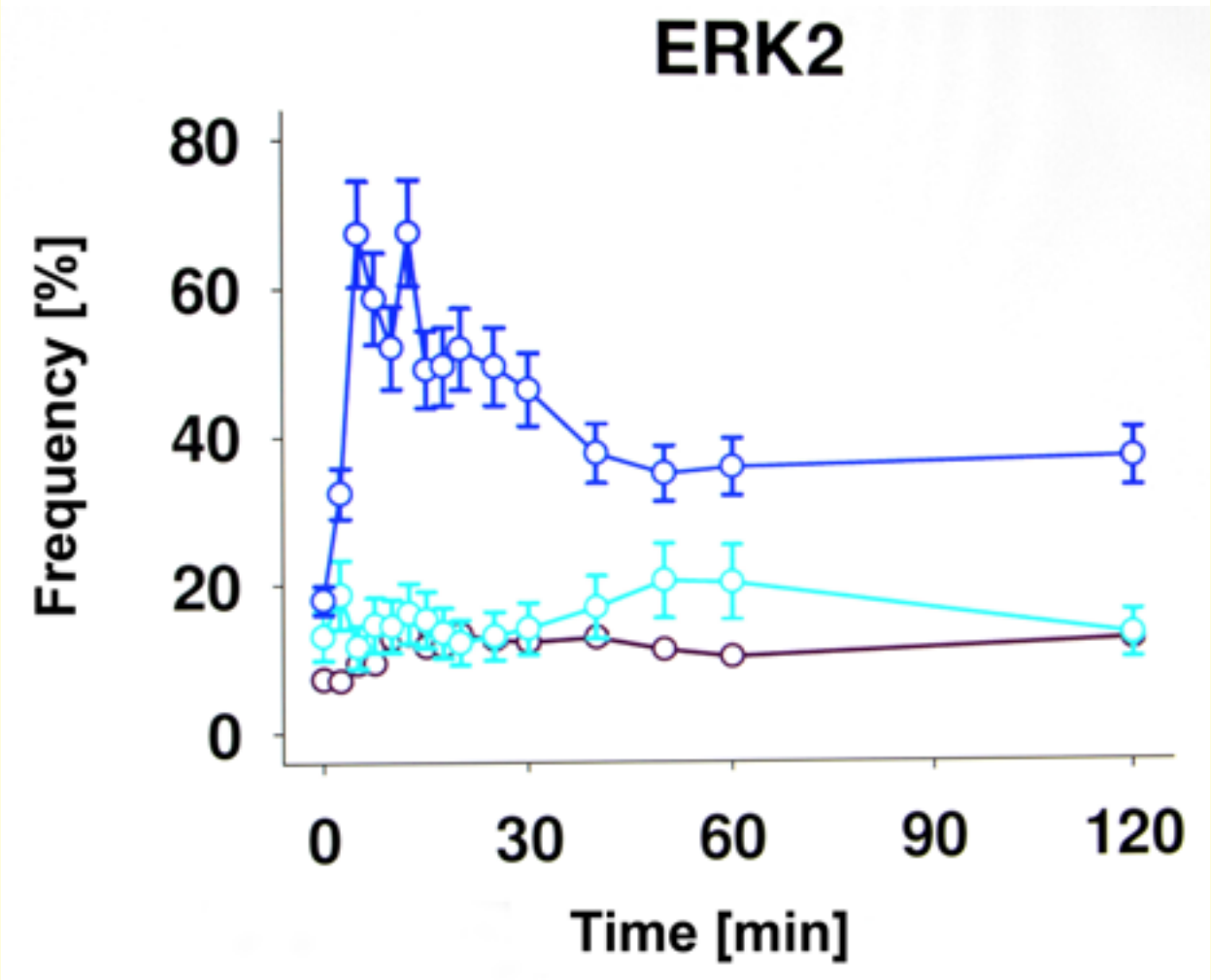
- SB Cancer (Helmholtz Alliance on Systems Biology)
- LungSys (BMBF)

Selected cooperation partners

- Dr. U. Klingmüller, German Cancer Research Center, Heidelberg, Germany
- Dr. D. Bossemeyer, German Cancer Research Center, Heidelberg, Germany
- Dr. M. Müller, German Cancer Research Center, Heidelberg, Germany
- Prof. Dr. F. Hamprecht, Interdisciplinary Center for Scientific Computing, Universität Heidelberg, Germany
- Dr. A. Schlosser, ZBSA, University of Freiburg, Germany

Selected publications

- Winter D, Seidler J, Ziv Y, Shiloh Y, Lehmann WD. J Proteome Res 2009, 8, 418-424. Citrate boosts the performance of phosphopeptide analysis by UPLC-ESI-MS/MS.
- Schilling M, Maiwald T, Hengl S, Winter D, Kreutz C, Kolch W, Lehmann WD, Timmer J, Klingmüller U. Mol Syst Biol 2009, 5, 334. Theoretical and experimental analysis links isoform-specific ERK signalling to cell fate decisions.
- Lehmann WD. Protein Phosphorylation Analysis by Electrospray Mass Spectrometry, Royal Society of Chemistry, London, 2010, ISBN: 978-0-85404-185-5.



Activation kinetics of the signaling protein ERK2 generated by stimulation of primary mouse hepatocytes with a growth factor. The blue data represent thev relative amount of doubly phosphorylated, fully activated ERK2. The green and brown data show the relative amount of the two singly phosphorylated, transient forms of the signaling protein. The cells react with a fast phosphorylation reaction at ERK2 in response to the growth factor stimulation.

Dr. Ana Martin-Villalba

German Cancer Research Center, Heidelberg
Molecular Neurobiology

16 members of staff (biologists, chemical engineers, biochemists, bioinformaticians, physicians)

The Molecular Neurobiology research group joined the Systems Biology of Cancer network in order to understand in a greater detail the role of the CD95 (Fas, Apo-1) cell surface receptor and the outcomes of its stimulation in different cell systems.

CD95 has been originally discovered as a trigger of apoptosis, programmed cell death, and it is still known as the so-called death receptor. There is, however, accumulating evidence that many novel non-apoptotic pathways exist downstream of CD95. Therefore, the question appears what makes one system undergo apoptosis and another one respond in a totally different manner. And this is where the group seeks the help of systems biology approach. The researchers would like to explore the molecular stoichiometry that may lead to different responses. Their interest extends also to the possibility of cancer-related mutations having influence on the alternations in cellular behaviour.

The group led by Dr. Martin-Villalba already described several novel CD95-induced pathways and identified key molecules for those processes. The interaction with CD95 cognate ligand, CD95 ligand (CD95L), may lead to a plethora of outcomes depending on the cellular system studied. Coming back to the question of death vs. survival in the context of CD95, the group observed different outcomes of receptor stimulation in several glioblastoma multiforme (GBM, brain tumour) cell lines. Intriguingly, lack of apoptosis in malignant GBM does not mean a lack of response to CD95, but CD95 rather facilitates T98G malignant behaviour by promoting migration and invasion into brain parenchyma. Finding the link between molecular environment in GBM and their degree of malignancy could bring the researchers closer to developing curative therapy.

Migration is also a response of immune cells towards CD95L and the group is trying to exploit this finding in the context of spinal cord injury. The group has also elucidated the importance of CD95 system in neural stem cell's biology exhibited in propagation of neural stem cells (NSCs) differentiation as well as neuronal branching.

The group has not only described different phenotypical outcomes of CD95 involvement but has also characterized formation of phosphatidylinositol 3-kinase (PI3K) activating complex (PAC) in those cell types. Interestingly, the components of PAC are different from system to system. In glioma, neural stem cells (NSCs) and immune cells, non-receptor tyrosine kinases from the Src family (SFKs) are activated in order to transduce the signals emanating from CD95. Additionally, the group identified different SFKs involved in those two systems, namely c-Src in NSCs and Yes in glioma. In immune cells, on the other hand, the group described a cooperative system in which SFKs work together with the non-receptor tyrosine kinase Syk in order to activate PI3K.

Therefore, CD95 is able to transduce its signal by formation of different protein complexes depending on the cellular context. Indeed data suggest that inducing apoptosis does not necessarily have to be a default role of CD95. Another interesting problem is a variety of molecules binding to the complex formed by the receptor as well as activation of different signalling pathways like PI3K and extracellular

regulated kinase (ERK) pathways.

The research group cooperates with Joel Beaudouin within SBCancer network, who is investigating the clusterization of CD95 on the cell surface that is believed by many researchers to be pre-requisite for death-inducing-signaling-complex (DISC) formation and apoptotic signaling. The aim is to learn whether there is a difference in that process between the systems of interest. The group also establishes collaboration with Carsten Schulz on developing tools for detection and activation of mTOR and ERK pathways. In addition, there is a close cooperation with a biotech company called Apogenix. Thanks to this collaboration the group has access to commercially not available tools like recombinant CD95L or new antibodies, shares results and gets know-how of the biotech industry. The common goal is to develop therapeutic agents modulating CD95-related signals.

The group mostly utilizes basic molecular biology techniques but has additionally developed a robust protocol for translation state array analysis. This procedure involves isolation of actively translated mRNA by separating polysome-bound RNA via sucrose gradient. However, for the equipment the group relies on the courtesy of Ed Hurt at "Biochemie Zentrum der Universität Heidelberg". Similarly, the technical part of Affymetrix microchip analysis (RNA hybridization and readout) is performed at the "Universtitätsklinikum Mannheim". Apart from that the group successfully carries out several migration assays, e.g. two-chamber assay and soft agar colony formation to manipulate cells of interest *ex vivo*.

Joint research projects

- Systems Biology of Cancer (Helmholtz Association)

Selected cooperation partners

- Prof. Bassem Hassan, K.U.Leuven, Belgium
- Apogenix GmbH, Heidelberg, Germany
- Prof. Norbert Gretz, Medical Center, University Hospital Mannheim, Germany
- Dr. Carsten Schultz, EMBL, Heidelberg, Germany
- Dr. Matthias Weiss, BIOMS, Heidelberg, Germany

Selected publications

- Letellier E., Kumar S., Krauth S., Sancho-Martinez, I., Konecki K., Drost N., Klussmann S., Neumann A., Schreglmann N., Kleber S., Karray S., Levi-Strauss M., Brors B., Gretz N., Gieffers C., Hill O., Thiemann M., Martin-Villalba A. (2010) CD95-Ligand on myeloid cells triggers their recruitment via Syk to the inflammatory site. Immunity, 32, 240-52.
- Corsini, N., Sancho-Martinez, I., Laudenklos, S., Glagow, D., Kumar, S., Letellier, E., Koch, P., Teodorczyk, M., Kleber, S., Klussmann, S., Wiestler, B., Brüstle, O., Gieffers, C., Hill, O., Thiemann, M., Seedorf, M., Gretz, N., Sprengel, R., Celikel, T., Martin-Villalba, A. (2009). The death receptor CD95 activates adult neural stem cells for working memory formation and brain repair. Cell Stem Cell, 5, 128-30.
- Kleber S, Sancho-Martinez I, Wiestler B, Beisel A, Gieffers C, Hill O, Thiemann M, Mueller W, Sykora J, Kuhn A, Schreglmann N, Letellier E, Zuliani C, Klussmann S, Teodorczyk M, Grone HJ, Ganten TM, Sultmann H, Tuttenberg J, von DA, Regnier-Vigouroux A, Herold-Mende C, and Martin-Villalba A (2008) Yes and PI3K bind CD95 to signal invasion of glioblastoma. Cancer Cell, 13, 235-248.

Prof. Martina Muckenthaler

University Hospital Heidelberg
Molecular Medicine Partnership Unit
Iron Homeostasis in health and disease

10 members of staff (biologists, medical doctors)

As an essential nutrient and a potential toxin, iron poses an exquisite regulatory problem in biology and medicine. Disturbances of the delicate balancing systems for systemic and/or local iron homeostasis are emerging as underlying causes of common hematological, metabolic and neurodegenerative diseases. The group's research aims to understand the physiological regulation of genes involved in iron metabolism and its disturbances in human disease.

One major research focus of the lab is to understand molecular mechanisms involved in hereditary hemochromatosis (HH), the most prevalent genetic disorder in the western world. The disease is mainly caused by mutations in the *HFE* gene, which codes for a MHC class I–like molecule. Work from the lab and others demonstrated that HFE is required for appropriate hepatic expression of the iron hormone and anti-microbial peptide hepcidin: expression of this negative regulator of duodenal iron absorption is decreased and cannot be adjusted in response to elevated hepatic iron levels in *Hfe*-deficient mice and HH patients. These findings further our understanding of the molecular mechanism of Hfe function and suggest that the primary locus of Hfe function is the liver and not the duodenum, as was previously hypothesized. Indeed, analysis of tissue specific *Hfe* knock-out mice has recently unambiguously demonstrated that local *Hfe* expression in hepatocytes serves to maintain physiological iron homeostasis, answering this longstanding question in medicine. Additionally, HFE controls hepcidin expression in response to inflammatory stimuli. This links HFE to the immune system and to the anemia of chronic diseases (ACD), which results in iron redistribution in response to inflammation, infection and malignancy.

An important challenge is now to understand how signalling pathways in general and the hemochromatosis-associated proteins, specifically, regulate hepcidin expression.
The group is employing network/systems-based analysis of iron metabolism by integrating DNA microarray approaches, mouse models and high through-put siRNA screens. The overall aim is a more detailed understanding of regulatory mechanisms involved in iron homeostasis and the identification of novel regulators of iron metabolism.

Joint research projects

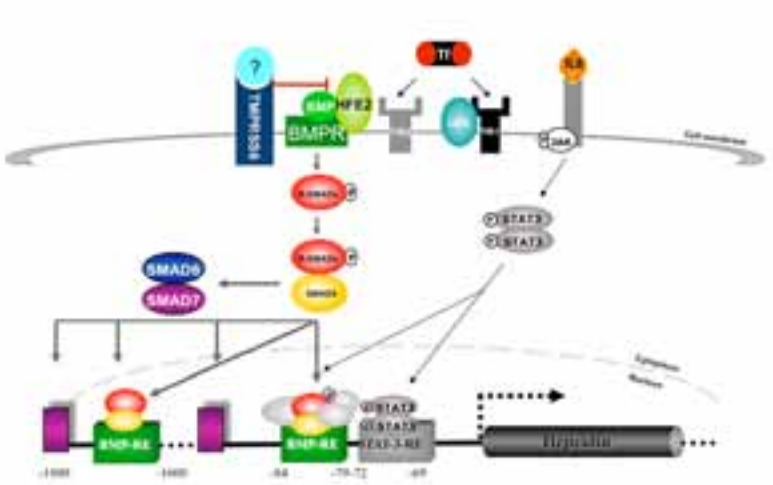
- Virtual Liver (BMBF)

Selected cooperation partners

- Klingmüller, German Cancer Research Center, Heidelberg, Germany
- Legewie, German Cancer Research Center / BioQuant, Heidelberg, Germany
- Schwab/Zanger, Dr. Margarete Fischer-Bosch Institute of Clinical Pharmacology, Stuttgart, Germany

Selected publications

- Hentze MW, Muckenthaler MU, Galy B, Camaschella C. Two to tango: regulation of Mammalian iron metabolism. Cell 142(1):24-38 (2010).
- Mleczko-Sanecka, K., Casanovas, G., Ragab, A., Breitkopf, K., Müller, A., Boutros, M., Dooley, S., Hentze, M.W. and Muckenthaler, M.U. SMAD7 controls iron metabolism as a potent inhibitor of hepcidin expression. Blood 115(13):2657-65 (2010).
- Maja Vujić Spasić, Judit Kiss, Thomas Herrmann, Bruno Galy, Stefanie Martinache, Jens Stolte, Hermann-Josef Gröne, Wolfgang Stremmel, Matthias W. Hentze and Martina U. Muckenthaler. Hfe acts in hepatocytes to prevent hemochromatosis. Cell Metabolism 7(2):173-8 (2008).



Signalling pathways involved in the regulation of the iron-hormone hepcidin.

Dr. Wolfgang Müller

HITS, Heidelberg
Scientific Databases and Visualization

10 members of staff (biologists and computer scientists)

The Scientific Databases and Visualization (SDBV)-group at HITS (Heidelberg Institute for Theoretical Studies, previously EML Research) both provides services and does research. The SDBV group works on tools and data collections for systems biology support.

When looking at the systems biology cycle of model-hypothesis-experiment-model, then SDBV's contributions target the communication within the systems biology process. This can be best seen in a short overview of current and finished projects of SDBV.

SABIO-RK and related projects:
The core activity of the SDBV group is the reaction kinetic database SABIO-RK. SABIO-RK contains data about metabolic and signalling reactions, experimental conditions and the resulting kinetics.
Developing and maintaining SABIO-RK involves two sets of tasks: (1) Developing and maintaining the software, e.g. the user interface, the data model or by doing computer linguistic matching of molecule names. (2) Maintaining the data collection is a full time job for several scientists.
The SDBV group sees its own software in the roles of both developer and user, which helps development.

SABIO-RK is currently funded via two BMBF-financed projects, one as part of the transnational SysMO funding initiative (http://www.sysmo.net) and another one as part of the Virtual Liver Network (VLN, http://www.virtuelle-leber.de). A DFG project with participation of SABIO-RK recently got approved. The long-term base funding for SABIO-RK is given by the Klaus Tschira Foundation.

SysMO-DB and related projects:
The goal of the transnational SysMO-DB project is to provide a common, federated data management for the SysMO projects. The goal is to collect data and models in the data management systems of the SysMO projects, to enrich them with meta data and thus to prepare them for interactive search and dissemination of data into other systems.

In the center of SysMO-DB is the user and an agile software engineering approach. SysMO-DB's hallmark is strong requirements engineering via a focus group, the SysMO-DB PALS and via visits and interviews. In addition, as part of VLN, SDBV will extend the SysMO-DB software and adapt to new groups of users.

What has SDBV to offer, what is SDBV interested in?
As described above, the SDBV group consists of computer scientists, computer linguists and scientists with experiences from the border area between computer science and biology. The SDBV group is interested in research cooperations, as well as consulting contracts or product development. Important fields of expertise are data modelling, biocuration, systems biology standards, explorative search, as well as concrete experiences on how to lower the entry barrier for systems biology data management software.

About the institute:
HITS (Heidelberg Institute for Theoretical Studies) is a private, non-for-profit research institute. It was established in 2010 as a successor to the EML Research gGmbH. It gets

its base funding from the Klaus Tschira Foundation, which was established in 1995. HITS gGmbH is jointly managed by Dr. h.c. Klaus Tschira and Prof. Dr.-Ing. Andreas Reuter.

Special equipment and techniques

- Data management for systems biology (data bases, information retrieval, natural language processing, biocuration)

Joint research projects

- SysMO (ERASysBio, BMBF)
- Virtual Liver (BMBF)

Selected cooperation partners

- Prof. U. Kummer, BioQuant Center, Universität Heidelberg, Germany
- Prof. C. Goble, Prof. P. Mendes, Manchester Centre for Integrated Systems Biology, University of Universität Manchester, UK
- Prof. H.-G. Holzhütter, Charité, Berlin, Germany
- Prof. A. Funahashi, Dept. of Biosciences and Informatics, Keio University, Japan

Selected publications

- Doug Howe, Maria Costanzo, Petra Fey, Takashi Gojobori, Linda Hannick, Winston Hide, David P. Hill, Renate Kania, Mary Schaeer, Susan St. Pierre, Simon Twigger, Owen White, and Seung Yon Rhee Yon. Big data: The future of biocuration. Nature, (455):477-50, 2008.
- Andreas Weidemann, Stefan Richter, Matthias Stein, Sven Sahle, Ralph Gauges, Razif Gabdoulline, Irina Surovtsova, Nils Semmelrock, Bruno Besson, Isabel Rojas, Rebecca Wade, and Ursula Kummer. SYCAMORE - A SYstems biology Computational and Analysis MOdeling Research Environment. Bioinformatics, 24(12):1463-1464, 2008.
- Ulrike Wittig, Renate Kania, Martin Golebiewski, Olga Krebs, Saqib Mir, Andreas Weidemann, Henriette Engelken, und Isabel Rojas. Integration and Annotation of Kinetic Data of Biochemical Reactions in SABIO-RK. In Proceedings of the 3rd International Beilstein Workshop on "Experimental Standard Conditions of Enzyme Characterizations", Rüdesheim am Rhein, Germany, 2008.

Dr. François Nédélec

EMBL, Heidelberg
Cell Biology and Biophysics Unit
Cellular Architecture Group

11 members of staff (biochemists, physicists, biologists and a biophysicist)

Modern microscopy has demonstrated the dynamic nature of biological organization. The mitotic spindle, for example, is a stable and solid cellular structure: in a given cell type, it has a precise symmetry and very reproducible dimensions. Yet, its main components - polar filaments called microtubules - are in rapid turnover. They grow, shrink and disappear in a matter of minutes, within a spindle that may remain steady for hours. Chromosomes and microtubules are connected by proteins which continuously and stochastically bind and unbind. The resulting assembly is highly dynamic and yet stable and remarkably precise: it applies the balanced forces necessary to position and segregate the chromosomes exactly.

The spindle is thus a fascinating structure, which illustrates a central question in biology: how can the uncoordinated and inevitably imperfect actions of proteins and molecules result in a structure able to fulfill its biological function with the utmost accuracy?

Obviously, understanding the collective behavior is the challenge here, but it cannot be deduced from a simple statistical average. It is a challenging problem for many reasons:

1] the diversity of molecular players is often enormous;
2] their interactions are often dynamic and out-of-equilibrium.
3] the properties of the proteins have been selected for the biological task by natural evolution

Understanding biological phenomena from their multiple biological components - systems biology - is a cutting-edge research topic.

The research group addresses this problem in practical terms by developing in vitro experiments and modeling tools. The *in vitro* approach allows the researchers of the group to reduce the number of components in the system: they can either remove a specific protein, or start from scratch by mixing purified components. Modeling allows them to recapitulate the process of protein organization in a framework in which all the interactions are known exactly and can even be specified at will.

In the past, they developed innovative numerical methods to simulate the collective behavior of multiple polar fibers and of their associated proteins. They are implemented in a simulation engine called *cytosim*, which is also made available to the community. Simulations are often used to validate or refute existing ideas, but the group tries to use them in a more creative way: one can generate systematically various properties for the molecules, and automatically test their ability to form stable structures. The analysis of successful scenarios leads to the formulation of new hypotheses.

Special equipment and techniques

- Computational modelling
- Modern high-performance computing infrastructure

Joint research projects

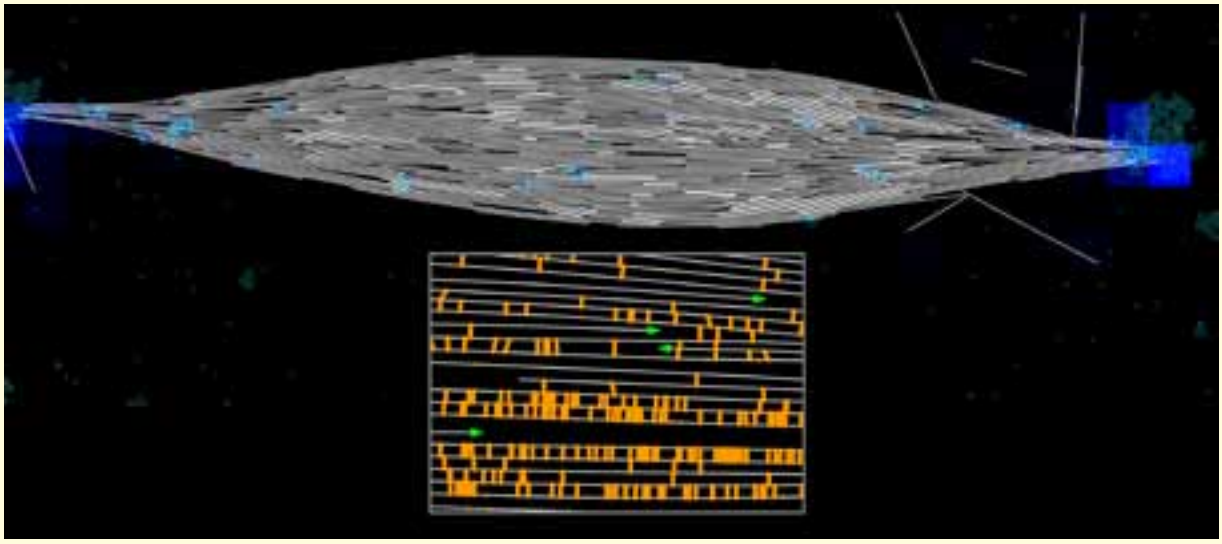
- BIOMS

Selected cooperation partners

- Phong Tran, Institut Curie, Paris, France
- Detlev Arendt, EMBL, Heidelberg, Germany
- Eric Karsenti, EMBL, Heidelberg, Germany
- Zoher Gueroui, Ecole normale superieure, Paris, France
- Joachim Spatz, MPI for Metals Research, Stuttgart, Germany

Selected publications

- Brun L, Rupp B, Ward J, Nedelec F; A theory of microtubule catastrophes and their regulation. PNAS 106 (50) 21173-21178; Dec 2009.
- Dinarina A, Pugieux C, Mora Corral M, Loose M, Spatz J, Karsenti E, Nedelec F; Chromatin shapes the mitotic spindle. Cell 138 (3), 502-513, Aug 2009.
- Jekely G, Colombelli J, Hausen H, Guy K, Stelzer E, Nedelec F, Arendt D; Mechanism of phototaxis in marine zooplankton. Nature 456, 395-399, Nov 2008.



Snapshot of a simulated mitotic spindle. Overlapping mitotic fibers are defining here a horizontal axis along which chromosomes will be segregated. A detailed view of the central region of the spindle is shown below, with plus-ends of fibers depicted in green, and molecular motors shown as orange links between adjacent fibers. The motors by moving along the fibers towards their plus-ends, push these fibers apart.

Dr. Karsten Rippe

German Cancer Research Center, Heidelberg / BioQuant Center
Genome Organization & Function

15 members of staff (biologist, physicist and chemists)

The Genome Organization & Function group at the BioQuant and the German Cancer Research Center is an interdisciplinary research team that combines molecular/cell biology and physics to develop quantitative descriptions that relate the dynamic organization of the (epi)genome with gene expression programs and functional cell states.

A special focus is put on the conformation and dynamic properties of the complex of DNA with histones and other chromosomal proteins referred to as chromatin. Both the DNA and the protein component of chromatin are subject to various post-translational modifications that include DNA/histone methylation, as well as acetylation and phosphorylation of histones. These so called epigenetic modifications define the cell's gene expression program and can be transmitted through cell division.

Understanding epigenetic regulation becomes increasingly important for medical diagnosis and therapy of cancer, developmental diseases and other pathologies. It is tightly related to chromatin (re)organization, which in turn is a key determinant of access to DNA sequence information for proteins involved in transcriptions as well as DNA replication and repair. The goal of the group is to provide an integrated view on how the dynamic balance between multiple activatory and inhibitory processes determines the stability and plasticity of epigenetic states.

To this end the group applies biophysical methods like fluorescence spectroscopy/microscopy-based techniques in living cells. This work is complemented with in vitro studies for example by analytical ultracentrifugation to elucidate how chromatin assembly, conformation, dynamics and accessibility are controlled. Furthermore, various modeling based projects with respect to the quantitative analysis of chromatin assembly, the chromatin fiber organization and the dynamic properties of nuclear subcompartments are conducted. The results from these studies are integrated into a systems biology approach to dissect epigenetic networks. The work has a number of implications for translational medical research with respect to understanding the complex effects of epigenetic drugs like histone deacetylase or DNA methylase inhibitors in treatments of cancer.

Special equipment and techniques

- Analysis of DNA/RNA and protein dynamics in living cells
- Fluorescence microscopy/spectroscopy
- Fluorescent labeling of proteins and nucleic acids in mammalian cell lines
- Genome-wide protein and nucleic acid interaction analysis
- Synthetic biology of chromatin
- Analytical ultracentrifugation
- Molecular dynamics simulation of protein-DNA complexes
- Monte-Carlo simulations of chromatin fibers
- Lattice models of DNA-protein interactions

Joint research projects

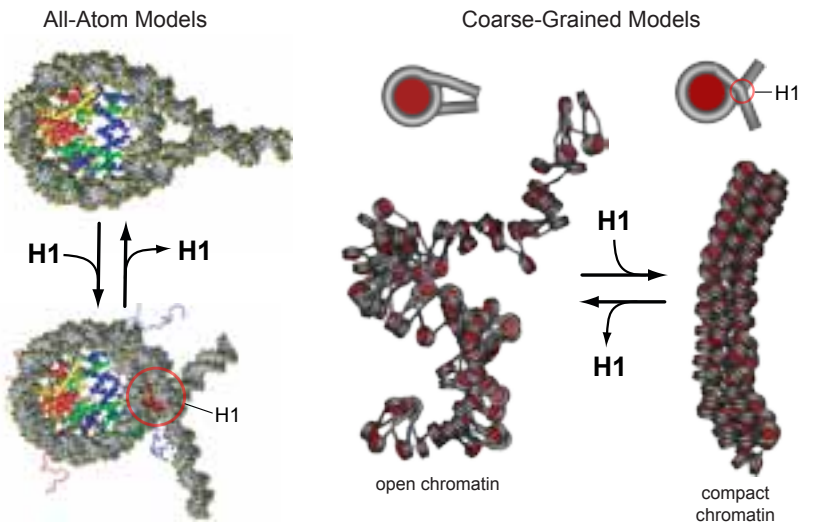
- EraSysBio Plus (EU)
- SysTec (BMBF)
- Systems Biology of Cancer (Helmholtz Association)

Selected cooperation partners

- Prof. Dr. Peter Lichter, German Cancer Research Center, Heidelberg, Germany
- Prof. Dr. Thomas Höfer, German Cancer Research Center & BioQuant, Universität Heidelberg, Germany
- Dr. Malte Wachsmuth, European Molecular Biology Laboratory, Heidelberg, Germany
- Prof. Dr. Gernot Längst, University of Regensburg, Germany
- Dr. Katalin Fejes Tóth, California Institute of Technology, Pasadena, USA

Selected publications

- Müller, K. P., Erdel, F., Caudron, M., Marth, C., Fodor, B. D., Richter, M., Scaranaro, M., Beoudoin, J., Wachsmuth, M. & Rippe, K. (2009). A multi-scale analysis of dynamics and interactions of heterochromatin protein 1 in the nucleus by fluorescence fluctuation microscopy, Biophys. J. 97, 2876-2885.
- Wachsmuth, M., Caudron-Herger, M. & Rippe, K. (2008). Genome organization: balancing stability and plasticity. Biochim. Biophys. Acta 1783, 2061-2079.
- Rippe, K., Schrader, A., Riede, P., Strohner, R., Lehmann, E. & Längst, G. (2007). DNA sequence- and conformation-directed positioning of nucleosomes by chromatin-remodeling complexes. Proc. Natl. Acad. Sci. USA 104, 15635-15640.



Model for chromatin fiber compaction induced by binding of linker histone H1. All-atom models of a nucleosome with and without linker histone H1 (left panel) were used to built coarse-grained models of this structure to evaluate the conformation of a DNA chain of 100 nucleosomes (right panel) in computer simulations. The change of the DNA geometry due to binding of linker histone H1 at the DNA entry-exit site of the nucleosome leads to a compaction of the chain into a condensed fiber structure with a diameter of about 30 nm. (Kepper, N., Foethke, D., Stehr, R., Wedemann, G. & Rippe, K. 2008, Nucleosome geometry and internucleosomal interactions control the chromatin fiber conformation, Biophys. J. 95, 3692–3705.)

Prof. Frank Rösl

German Cancer Research Center, Heidelberg
Viral Transformation Mechanisms

10 members of staff (molecular biologists, biochemists)

Type I Interferons (IFN) represents an integral part of the natural host defence system against most viral infections. Rapidly released following infection, they bind to ubiquitously expressed specific receptors on neighbouring cells to initiate the establishment of an antiviral state, prior to release of progeny virions from the infected cells. The IFN-receptor chains mediate activation of IFN-stimulated genes (ISG) via the JAK/STAT pathway. ISGs harbour a highly conserved sequence in their proximal promoter called IFN-Stimulated-Response-Element (ISRE) which is activated by ISGF3, the ternary transcription factor complex translocated to the cell nucleus after signalling from the IFN-receptor. ISGF3 is composed of STAT1 and STAT2 – activated by phosphorylation – and IRF-9 which constitutes the DNA-binding element of ISGF3. High-risk Human Papillomaviruses (e.g. HPV16) have developed several strategies during evolution to block the IFN signalling pathway, enabling these viruses to persistently infect basal keratinocytes of the cervix uteri. In particular, the oncogenes E6 and E7 are considered to repress IFN signalling and to be etiologically involved in the development of cervical cancer.

In contrast to these published data, the Rösl research group observed in HPV16-positive HPK1A keratinocytes a rapid and dynamic behaviour of IFN-α activated IRF-9 by quantitative Western Blotting. A first peak of activation was observed after 10 min of IFN-α treatment. In cooperation with T. Maiwald (AG U. Kummer) an in *silico* model was established based on the generated data, incorporating also data from A. Schneider (AG Klingmüller) on liver Huh7 cells, which show slower activation dynamics. Utilizing this model, IRF-9 could be identified as a limiting factor of IFN-signal transduction.

In consistence with this model prediction, HPK1A cells, as well as primary keratinocytes, showed higher steady state levels of IRF-9 molecules than Huh-7 cells. The enhanced levels of IRF-9 in the keratinocytes might be explained by the constitutive secretion of and autocrine stimulation by the keratinocyte-specific IFN-κ, which was only recently shown by the group to enhance endogenous IRF-9 levels. Recent data from members of the research group have revealed that IFN-κ is suppressed in a number of established HPV16 positive cervical carcinoma lines. Since constitutive low IFN-κ expression in an autocrine manner sensitizes keratinocytes to stimulation with additional IFN-α IFN-"priming" they will put a focus on analysing the dynamics of phospho-STAT1 and IRF-9 signalling molecules following modulation of IFN-κ expression by RNA interference.

Selected cooperation partners

- Dr. Ursula Klingmüller, German Cancer Research Center, Heidelberg, Germany
- Prof. Ursula Kummer, Universität Heidelberg, Germany

Selected publications

- Rincon-Orozco et al.2009. Epigenetic silencing of interferon-kappa in human papillomavirus type 16-positive cells. Cancer Research, 69(22):8718-25.

Dr. Reinhard Schneider

EMBL, Heidelberg
Structural and Computational Biology Unit
Data Integration and Knowledge Management

5 members of staff (pharmacologist, physicist, biologist and computer scientist)

The principal aim of the group is to capture and centralize the knowledge generated in the life sciences, and to organize the data in such a way that it is easily mined, browsed and navigated. The goal is to provide software systems, which enable the user to mine the data and support him in a hypothesis driven research effort. The group is involved in the following areas:

- Data schema design and technical implementation
- Metadata annotation with respect to experimental data
- Design and implementation of scientific data portal
- Providing access to data-mining tools (e.g. text-mining)
- Large scale data analysis pipelines
- Visualization tools for system biology

Special equipment and techniques

- High Performance Computers and large scale database mangement

Selected cooperation partners

- Dr. H. Erfle, Universität Heidelberg, Germany
- Prof. K. Djabali, TU Munich, Germany
- Prof. B. Rost, TU Munich, Germany
- Dr. P. Bergsten, Upsalla University, Sweden
- Dr. G. Terstappen, Siena biotech, Italy (EU Project: TAMAHUD)

Selected publications

- Gehlenborg, Nils; O'Donoghue, Sean; Baliga,Nitin S.; Goesmann, Alexander ; Hibbs, Matthew A; Kitano, Hiroaki; Kohlbacher, Oliver; Neuweger, Heiko ; Schneider,Reinhard; Tenenbaum,Dan; Gavin, Anne-Claude, Visualization of omics data for systems biology, Nature Methods, 2010, Nature Methods, 7, S56-68, 2010
- Bromberg, Y;Yachdav, G.; Ofran, Y; Schneider,R.; Rost, B., New in protein structure and function annotation: Hotspots, single nucleotide polymorphisms and the 'Deep Web', Current Opinion in Drug Discovery and Development, 2009, 12, 408-419
- Pafilis, E.; O'Donoghue, S.;Jensen, L.; Horn, H.; Kuhn, M.; Brown, N.P.; Schneider, R., Reflect: Augmented Browsing for the Life Scientist, Nature Biotechnology, 2009, 27, 508-510

Dr. Sven Sahle

Universität Heidelberg
BioQuant Center
Methods in computational systems biology

2 members of staff (physicist and mathematician)

The research group is active in the development of numerical methods for the simulation and analysis of biochemical reaction networks, software tool development, and standardisation of data exchange in systems biology.

Software development:
For the progress of systems biology it is important that powerful modeling tools are available that are comparatively easy to use for users that are not experts in the mathematical methods involved. The main software project the group is involved with is COPASI [2], a tool for modeling, simulation and analysis of biochemical reaction networks that is developed in an international cooperation.
COPASI is widely used (regularly several 1000s of downloads) for research and teaching. It contains state of the art algorithms for both deterministic and stochastic simulation, structural analysis, stability analysis, metabolic control analysis, etc.
An important focus for COPASI is a powerful and flexible implementation of parameter estimation. COPASI is free software and available for all major operating systems at www.copasi.org.

Methods development:
One of the problems in modeling is that commonly the modeler has to deal with models where many or even most of the parameters are unknown. One approach to deal with this situation is to analyze sensitivities of model properties, which indicate how sensitive a model property depends on some parameter. Using those you can estimate which of the unknown parameters are really important for the behaviour of the model. A severe restriction of this approach is that sensitivity analysis as it is commonly used in systems biology only yields local information; i.e. Information that is only valid for a specific value of the parameter whose value is actually unknown.
The group has investigated approaches based on global optimization to overcome this restriction applying a range of global optimization algorithms to calculate upper and lower limits on sensitivities.

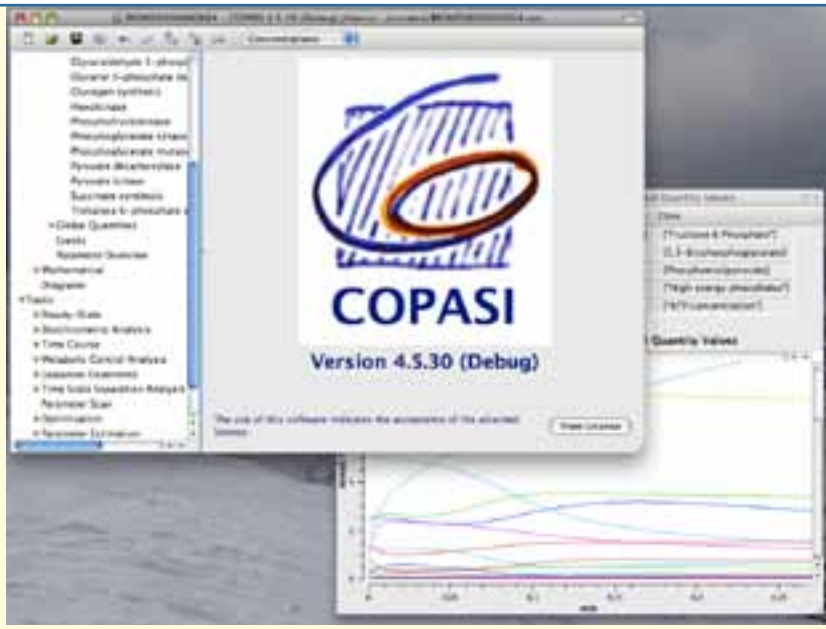
Data exchange standardisation:
The group is involved in several international projects for the standardisation of the exchange and storage of biochemical models and data. The most prominent one is SBML (systems biology markup language), which is by now the established standard for the exchange of models of reaction networks. The Sahle group developed an extension to SBML that describes the graphical representation of a model, in addition to its mathematical description [3].
Another standard the group is involved with is MIASE (minimal information about simulation experiments).
Sven Sahle is currently an elected editor for SBML.

Selected cooperation partners

- Pedro Mendes, Centre for Integrative Systems Biology, University of Manchester, UK
- Stefan Hoops, VBI, Virginia Tech, Blacksburg, VA, USA
- Akira Funahashi, Department of Biosciences and Informatics, Keio University, Yokohama, Japan

Selected publications

- [1] Sahle, S., P. Mendes, S. Hoops, and U. Kummer (2008): „A new strategy for assessing sensitivities in biochemical models"; Phil. Trans. R. Soc. A 366, 3619–3631
- [2] Hoops, S., S. Sahle, R. Gauges, C. Lee, J. Pahle, N. Simus, M. Singhal, L. Xu, P. Mendes, and U. Kummer (2006): „COPASI -- a Complex Pathway Editor"; Bioinformatics 22(24), 3067–3074
- [3] Gauges, R., U. Rost, S. Sahle, and K. Wegner (2006): „A model diagram layout extension for SBML"; Bioinformatics 22(15), 1879--1885



Screenshot of the Software COPASI, a tool for modeling, simulation and analysis of biochemical reaction networks.

Dr. Carsten Schultz

EMBL, Heidelberg
Cell Biology & Biophysics Unit
Schultz research group

13 members of staff (biologists and chemists)

The research interest of the Schultz group is to unravel basic signaling network underlying epithelial secretion as well as receptor endocytosis and recycling. For this purpose, the group developed a wide range of fluorescent reporter molecules, either genetically encoded or as small molecule fluorescent probes (Figure). The function of the probes is based on FRET or translocation and is suitable for imaging with spatial and temporal resolution.
Currently, the group uses the approaches in Multiparameter Imaging, where 5-6 cellular events are monitored simultaneously (Piljić & Schultz, 2008a). In addition, the group introduced a novel method to monitor the protein complex hierarchy in living cells (Piljić & Schultz, ACS Chem. Biol. 2008b). With these sensors, the group hopes to provide a more complete picture of signalling networks and to help finding compounds that might be beneficial for unraveling basic principles in signal transduction and ultimately for Cystic Fibrosis (CF) patients.

Currently, the group uses its prodrug approaches to dissect signaling networks by increasing the concentration of single lipids such as phosphoinositides in a non-invasive manner (Laketa et al., 2009). In 2009, the Schultz group introduced a novel method to fluorescently label lipids inside fixed and living cells (Neef & Schultz, Angew. Chem. 2009). These efforts to specifically manipulate and detect small molecules and proteins in cells are supported by novels ways to model intracellular signaling networks. The imaging expertise within the group is essential to validate these models and to support the emerging efforts towards Systems Biology at EMBL and within the collaborative networks SBCancer, TraPPS and the new Transregio 83.

As a member of the Molecular Medicine Partnership Unit [MMPU] of EMBL and the University of Heidelberg, the group is joining forces with Marcus Mall at the Medical School to test compounds in CF mice. Small molecule fluorescent FRET probes are prepared to study intra- and extracellular enzyme activities with a focus on phospholipases and proteases, such as a probe to monitor matrix metallo proteinase 12 (MMP12) activity on the surface of macrophages, an enzyme crucial for the development of lung emphysema (Cobos-Correa et al., Nat. Chem. Biol. 2009).

In 2010, the research group focuses predominantly on lipid signaling and lipid-controlled cell biology related to CF, endocytosis and cell migration. To examine the effect of phospholipids, i.e. phosphoinositides, on endocytosis, the researchers are preparing membrane-permeant phospholipids to specifically increase cellular phosphoinositide levels in a non-disruptive way. Very recently, they succeeded in synthesizing membrane-permeant, photoactivatable derivatives to provide an even more controlled way for manipulating lipid levels in living cells (Subramanian et al., 2010). Vesicle trafficking and endocytosis is investigated in collaboration with the group of Rainer Pepperkok.
Finally, researchers are interested in how the plasma membrane is repaired after physical impact, for which they combine fluorescence microcopy of tagged proteins with electron microscopy [correlative microscopy], the latter in collaboration with Claude Antony.

Special equipment and techniques

- Confocal fluorescence microscoopy
- Chemical biology and molecular biology,
- Preparative organic synthesis
- Real time imaging in living cells

Joint research projects

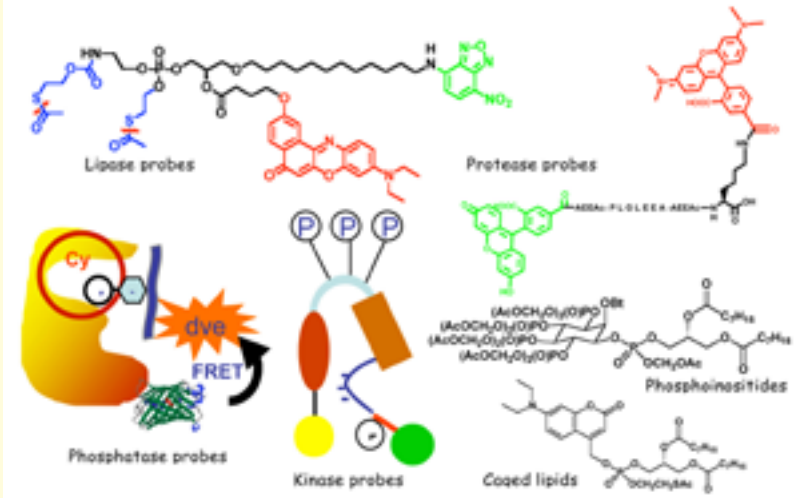
- LIVIMODE
  Light-based functional in vivo monitoring of diseases related enzymes (EU)
- Systems Biology of Cancer (Helmholtz Association)
- Transregio83
  Architecture of Lipid-Protein Assemblies (DFG)
- TraPPS
  Tracking phospholipid signaling (ESF/DFG)

Selected cooperation partners

- Prof. Dorus Gadella, Swammerdam-Institut University of Amsterdam, The Netherlands
- Prof. Marcus Mall, IIIrd Department of Pediatrics Universität Heidelberg, Germany
- Prof. Philippe Bastiaens, MPI of Molecular Physiology, Dortmund, Germany
- Dr. Rainer Pepperkok, EMBL Heidelberg, Germany
- Dr. Ana Martin-Villalba, German Cancer Research Center, Heidelberg, Germany

Selected publications

- Piljic, A., Schultz, C. Simultaneous recording of multiple cellular events by FRET. ACS Chem. Biol. 3, 156-160 (2008a).
- Laketa, V., Zarbakhsh, S., Mortier, E., Subramanian, D., Brumbaugh, J., Dinkel, C., Zimmermann, P., Pepperkok, R., Schultz, C. Membrane-permeant phosphoinositide derivatives as modulators of growth factor signaling and neurite outgrowth. Chem. Biol. 16, 1190-1196 (2009).
- Subramanian, D., Laketa, V., Müller, R., Tischer, C., Zarbakhsh, S., Pepperkok, R., Schultz, C. Activation of membrane-permeant caged PtdIns(3)P induces endosomal fusion in cells. Nat. Chem. Biol. 6, 324-326 (2010).



Several reporter and modulator molecules developed in the Schultz lab, including small molecule sensors for lipases and proteases, genetically encoded reporters for kinase and phosphatase activities, membrane-permeant and photoactivatable lipid molecules.

Prof. Ulrich Schwarz

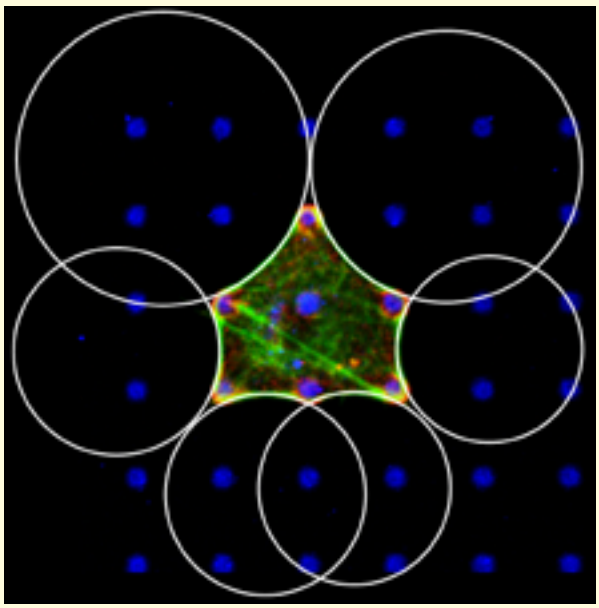
Universität Heidelberg
Institute for Theoretical Physics / BioQuant Center
Physics of complex biosystems / theoretical biophysics

10 members of staff

The long-term goal of the group of Physics of complex biosystems / theoretical biophysics is a systems level understanding of cell adhesion. During recent years, it has become clear that cells use actomyosin-generated forces to probe the stiffness and adhesive geometry of their environment. Combining cell experiments on elastic and micro-patterned substrates with modeling of cell shape and mechanics, the group investigates how the interplay between force generation by myosin motors, force propagation through the actin cytoskeleton, mechanotransduction at cell-matrix adhesions, and signal transduction by the GTPases from the Rho-family leads to the cellular response to extracellular physical cues. Such a comprehensive approach has to combine concepts and methods from many different fields, including reaction-diffusion models for signal transduction, viscoelastic models for the cytoskeleton and extracellular matrix, and non-linear dynamics models for motor activity.

Motivated by the work on the cellular level, the research group uses a middle-out approach to also address tissue and molecular levels. In order to model structure formation in tissues, the single cell response to mechanical cues is incorporated into a statistical framework of many contractile agents interacting through the extracellular matrix. In order to study the stochastic dynamics of supramolecular complexes, Langevin equations are used, which in contrast to all-atom molecular dynamics allows addressing large systems and long time scales. For example, stochastic models are applied to simulate how actin networks grow or how molecular motors transport cargo along cytoskeletal filaments.

The theory group works in close collaboration with experimental groups. Combining cell experiments on soft elastic substrates, image processing and elasticity theory, we reconstruct traction pattern of adherent cells, for example of migrating malaria parasites. Image processing is also used to detect changes to the actin cytoskeleton in high-throughput microscopy, for example after virus infection. Using a dynamical systems analysis, data were evaluated on the relaxation of the actin cytoskeleton after laser surgery. Recently it was found that cell shape on micropatterned substrates can be used to reveal its cell mechanical properties.



Quantitative analysis of cell shape on micro-patterned substrates reveals their cell mechanical properties. (Bischofs et al., Biophysical Journal 2008)

Joint research projects

- FORSYS / ViroQuant (BMBF)
- SysTec (BMBF)

Selected cooperation partners

- Frischknecht, The Department for Infectious Diseases, University Hospital, Heidelberg, Germany
- Bastmeyer, Department for Zoology, Karlsruhe Institute of Technology, Germany
- Gardel, Cellular Biophysics Lab, University of Chicago, USA
- Kräusslich, Department of Infectious Diseases, Virology, University Hospital Heidelberg, Germany
- Merkel, Institute for Bio- and Nanosystems, Research Center Jülich, Germany

Selected publications

- Sylvia Münter, Benedikt Sabass, Christine Selhuber-Unkel, Mikhail Kudryashev, Stephan Hegge, Ulrike Engel, Joachim P. Spatz, Kai Matuschewski, Ulrich S. Schwarz and Friedrich Frischknecht. *Plasmodium sporozoite* motility is modulated by the turnover of discrete adhesion sites. Cell Host Microbe, 551-562, 2009.
- Julian Weichsel, Nikolas Herold, Maik J. Lehmann, Hans-Georg Kräusslich and Ulrich S. Schwarz. A quantitative measure for alterations in the actin cytoskeleton investigated with automated high-throughput microscopy. Cytometry A, 52-63, 2010.
- J. Colombelli, A. Besser, H. Kress, E.G. Reynaud, P. Girard, E. Caussinus, U. Haselmann, J.V. Small, U. S. Schwarz, and E.H.K. Stelzer. Mechanosensing in actin stress fibers revealed by a close correlation between force and protein localization. J. Cell Sci., 122:1665-79, 2009.

Traction force microscopy of malaria parasites: cell on soft elastic substrate with two differently colored fluorescent marker beads, reconstructed force vector field, reconstructed force magnitude. Our analysis revealed that the parasites frequently get stuck due to adhesions at their ends. (Münter et al., Cell Host Microbe 2009)

Dr. Vytaute Starkuviene

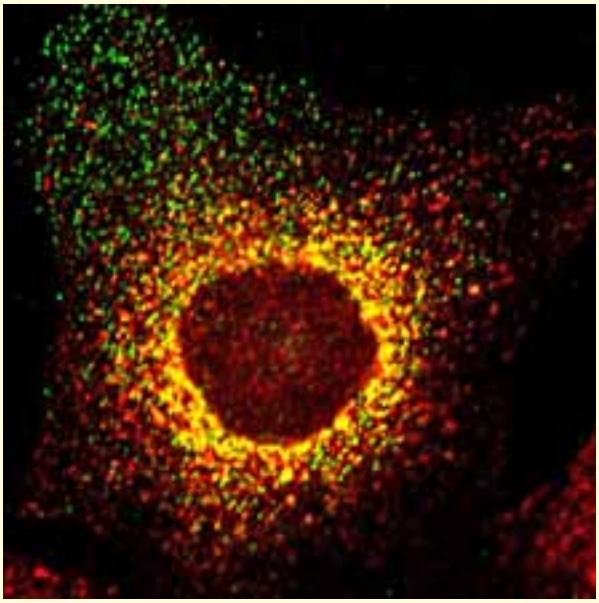
Universität Heidelberg
BioQuant Center
Screening of Cellular Networks

8 members of staff (7 biologists and 1 physicist)

Secretory membrane transport ensures the delivery of proteins, lipids and carbohydrates to their proper cellular destinations, and, with this, it is responsible for cellular homeostasis and growth. Elaborate molecular machinery is involved to secure a tight spatial and temporal regulation of the secretory steps. The basic principles as well as the core protein machinery have been under investigation over the last decades. However, this knowledge turned to be insufficient to explain the pathology of numerous human diseases associated with trafficking defects and to develop an effective pharmacological remedy.

Therefore, the research group focuses on regulation of secretory membrane trafficking of a selected set of disease-related proteins. Along these lines they harness RNAi and cDNA over-expression assays to analyze molecular machineries regulating trafficking of procollagen, integrins and GPI anchored proteins; and to identify mechanisms, which sort these proteins into specific trafficking pathways. Particular interest lies in understanding regulatory networks of Rab GTPases and kinesins.

Another branch of the group's activities focuses on understanding the secretory membrane trafficking as a crucial part of adaptive cellular response. Besides transcription factors, non-coding RNA molecules (ncRNA) are currently gaining an appreciated role of potent adaptive regulators of numerous cellular functions. One of these are microRNAs (miRNAs), which are capable of targeting hundreds of mRNAs simultaneously and, as a result, are capable of inducing well-tuned alterations in the synthesis of numerous proteins according rapidly changing cellular needs. Currently the group is analysing miRNAs as potential regulators of the secretory membrane trafficking by a large-scale and high-content screening microscopy. In a close perspective they are going to extend their work to other classes of ncRNAs, and to harness a high-resolution microscopy to dissect their biological roles directly in their natural environment – cells.



Variety of the secretory membrane trafficking pathways is demonstrated by the two internalised cargo proteins: integrin (in green) and transferrin (in red). Scale bar represents 20μm.

Special equipment and techniques:

- RNA interference of coding and non-coding RNAs
- Automated high-content microscopy

Joint research projects:

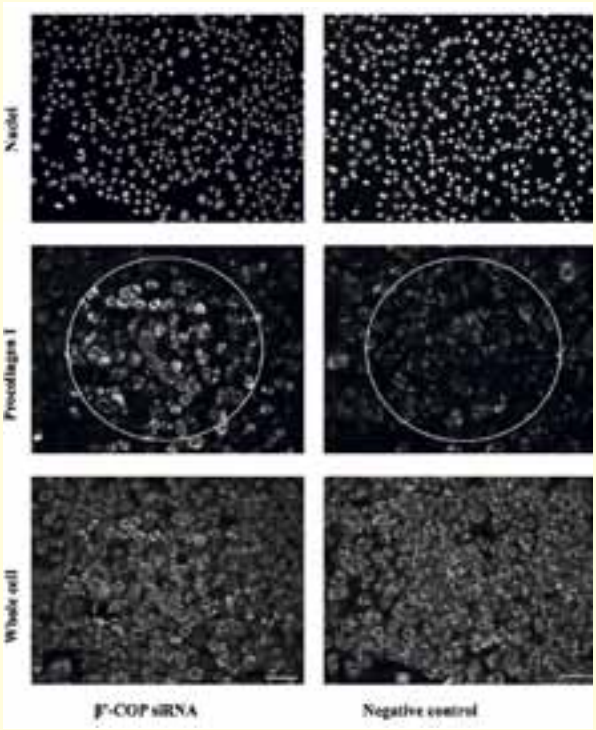
- FORSYS / ViroQuant
- SysTec (BMBF)

Selected cooperation partners

- Prof. U. Kummer, BioQuant / Institute of Zoology, University of Heidelberg, Germany
- Prof. K. Rohr, Institute of Pharmacy and Molecular Biotechnology, University of Heidelberg and German Cancer Research Center, Heidelberg, Germany
- Dr. A. Mokhir, Institute of Inorganic Chemistry, University of Heidelberg, Germany
- Prof. B. Goud, Institute Curie, Paris, France
- Prof. B. Storie, University of Arkansas for Medical Sciences, USA

Selected publications

- Erfle H, Lisauskas T, Reymann J and Starkuviene V. Cell arrays for the measurements of organelle dynamics in living cells, 2010 Methods in Molecular Biology, in press.
- Starkuviene V. and Pepperkok R. Differential requirements of the ts-O45-G and procollagen biosynthetic transport. 2007 Traffic, August 8, 1035-1051.
- Starkuviene V, Liebel U, Simpson JC, Erfle H, Poustka A, Wiemann S, Pepperkok R. High content screening microscopy identifies novel proteins with a putative role in secretory membrane traffic. 2004 Genome Research. October 14: 1948-1956.



NIH3T3 fibroblasts were incubated with siRNA and transfection reagent that had been spotted onto the bottom of a Labtek for 48 h (the spot area is marked in the middle row of the figure). Shown are cells that have been exposed to a negative control siRNA (right column) or a siRNA targeting the β'- subunit of the COP I coatomer (left column). The cells were then fixed, permeabilized and stained successively with a polyclonal antibody directed against collagen I and a secondary anti-rabbit antibody coupled to AlexaFluor 488 (middle row). Moreover, cell boundaries were visualized by staining of the plasma membrane with a concanavalin-AlexaFluor 647 conjugate (lower row), and nuclei were stained by incubation with Hoechst 33342 (upper row). Images were taken at 10x magnification on a Olympus IX81 inverted microscope. The size bars correspond to 100 µm.

Dr. Lars Steinmetz

EMBL, Heidelberg
Genome Biology Unit
Systems genetics of complex traits

15 members of staff (molecular and cell biologists, computer scientists)

Individuals differ at thousands of positions in the genome. These differences interact with each other and with the environment in complex ways to give rise to heritable phenotypic variation. This is the basis of quantitative phenotypes such as body height, cancer, diabetes, crop yield and fungal virulence. Naturally occurring genetic variants also influence the onset and intensity of diseases, as well as their treatment susceptibility, thus providing an incentive for personalised medicine.
The overall aim of the research of the Steinmetz group is to elucidate how genetic variation conditions complex phenotypes. To this end, the researchers integrate experimental and computational biology approaches at multiple layers along the molecular processes linking genotype to phenotype. In particular they investigate the level of the genome, transcriptome and proteome.

The group is following a systems approach to characterize the mitochondrial organelle. It has constructed a comprehensive functional network of mitochondrial proteins in yeast (Perocchi et al., PLoS Genetics, 2006), which brings together annotated and predicted functions into a single framework, and allowed a survey of mutant phenotypes, gene regulation, evolution, and disease susceptibility. Several instances of novel mitochondrial localization predicted by the model were validated. The network provides contextual information for genes underlying human mitochondrial disorders.

The research group has built a strong expertise in transcriptome profiling. A few years ago it designed jointly with Affymetrix a high-density oligonucleotide tiling array, which has allowed mapping transcription in yeast genome-wide in a strand-specific manner (David et al., PNAS, 2006, Perocchi et al., NAR, 2007). The group mapped the positions of 3' and 5' UTRs of coding genes and identified hundreds of RNA transcripts distinct from annotated genes. Apart from expected transcripts, the researchers found transcripts spanning several genes in an operon-like fashion, transcripts overlapping known genes in antisense orientation, novel transcripts arising in intergenic regions, and genes with complex transcriptional architecture. These data revealed an unexpected transcriptional complexity for a well-studied genome such as yeast. In collaboration with the group of Dr. Wolfgang Huber, the Steinmetz group has developed computational tools to identify transcript boundaries (Huber et al., Bioinformatics, 2006) and quantify allele-specific expression (Gagneur et al., Mol. Sys. Bio, 2009). This technology is the basis of several collaborations (Neil et al., Nature, 2009, for example), for which the contribution of the group usually consists in genome-wide data generation, data analysis and interpretation.

Selected projects of the last few years include elucidating the genetic basis of resistance to malaria parasites in mosquitoes to the level of single alleles (Blandin et al., Science, 2009); studying the function of pervasive transcription of non-coding RNAs and the mechanisms of how they are generated (Xu et al., Nature, 2009); and genotyping single-nucleotide polymorphisms across entire yeast genomes to infer meiotic recombination-activity distributions that define trait inheritance (Mancera et al., Nature, 2008).

The group is now developing technologies to determine the phenotypic contribution for all sequence variants between two genomes in a single step. Ultimately, by integrating genetics, genomics, systems biology and computational modeling with high-throughput sequencing and microarrays, the group aims to develop approaches that will enable personalised and preventative medicine across the world.

Special equipment and techniques

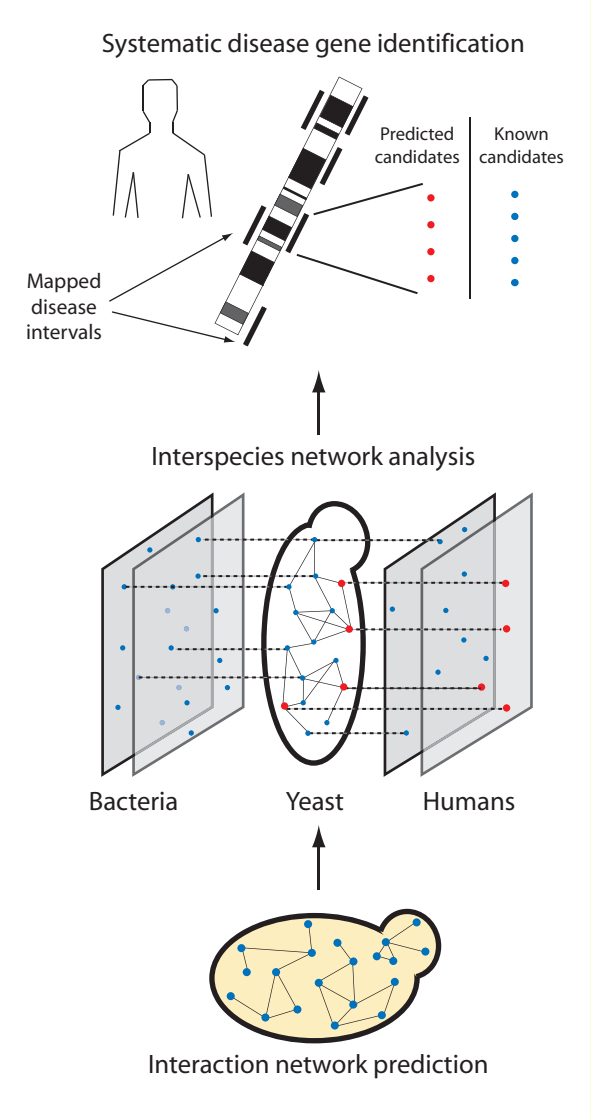
- Tiling arrays
- High-throughput sequencing (Illumina)

Selected cooperation partners

- Wolfgang Huber, EMBL, Heidelberg, Germany
- Leroy Hood, Institute for Systems Biology, Seattle, USA
- Ronald Davis, Stanford Genome Technology Center, Palo Alto, USA
- Mike Snyder, Stanford University, Stanford, USA
- Elena Levashina, CNRS, Strasbourg, France

Selected publications

- Dissecting the genetic basis of resistance to malaria parasites in Anopheles gambiae. Blandin, S.A., Wang-Sattler, R., Lamacchia, M., Gagneur, J., Lycett, G., Ning, Y., Levashina, E.A. & Steinmetz, L.M. Science. 2009 Oct 2;326(5949):147-50.
- Bidirectional promoters generate pervasive transcription in yeast. Xu, Z., Wei, W., Gagneur, J., Perocchi, F., Clauder-Munster, S., Camblong, J., Guffanti, E., Stutz, F., Huber, W. & Steinmetz, L.M. Nature. 2009 Feb 19;457(7232):1033-7. Epub 2009 Jan 25.
- High-resolution mapping of meiotic crossovers and non-crossovers in yeast. Mancera, E., Bourgon, R., Brozzi, A., Huber, W. & Steinmetz, L.M. Nature. 2008 Jul 24;454(7203):479-85. Epub 2008 Jul 9



Perocchi et al., Mol. Biosyst. 2008

Prof. Angela Stevens

Universität Heidelberg
Applied Mathematics
Mathematics in the Life-Sciences

10 members of staff

The research group is interested in understanding structure formation and function in developmental cellular systems by means of mathematical modeling, mathematical analysis and simulations.

Pattern formation and emergence of structures in interacting cellular systems are not only of principle interest, but are important means to reveal information on underlying functional mechanisms, especially when mutant populations show defined changes in structure in comparison to non-mutated populations. The same is true for cell populations which show variations with respect to a certain cellular function.

A major aim is to try to detect robust mechanisms of cellular interaction and to understand which of the biological information on the various involved small scales is needed to describe macroscopic quantities of interest correctly and to avoid the explicit resolution of microscopic structures and processes where not necessary.

Biological phenomena the group analyzes are, among others, self-organization of microorganisms as observed in populations of *Dictyostelium discoideum*, *Myxococcus xanthus*, and *Escherichia coli*. In this context the group deals with micro-, meso- and macroscopic models for chemotaxis and pattern formation due to cell surface bound signals.

Further the research group is interested in structure formation in neural tissues and the dynamics and restructuring of the cellular cytoskeleton. Recently projects were started on neuronal network oscillations in the hippocampus and on diffusion and transport of nuclear calcium.

Another recent focus is the development of suitable models for cell differentiation. A major question is, how variability of cells with respect to a certain cellular function can enhance processes of pre-differentiation.

Mathematically the group is dealing with non-linear partial- and integro-differential equations, interacting stochastic many particle systems, and related limiting procedures to connect models on different scales.

Selected cooperation partners

- BBZ, University of Leipzig, Germany
- MPI for Mathematics in the Sciences, Leipzig, Germany
- Department of Physiology, Universität Heidelberg, Germany
- Department of Neurobiology, Universität Heidelberg, Germany
- BIOMS, Universität Heidelberg, Germany

Selected publications

- E.E. Espejo, A. Stevens, J.J.L. Velàzquez: Simultaneous finite time blow-up in a two-species model for chemotaxis. Analysis (2009), Vol. 29, Issue 3, 317--338.
- J. Fuhrmann, J. Käs, A. Stevens: Initiation of cytoskeletal asymmetry for cell polarization and movement. J. of Theoretical Biology (2007), Vol. 249, 278--288.
- A. Stevens, L. Søgaard-Andersen: Making waves: pattern formation by a cell-surface-associated signal. Trends Microbiol. (2005), Vol. 13, No. 6, 249--252.

Dr. Rebecca Wade

HITS, Heidelberg
Molecular and Cellular Modeling Group

14 members of staff (physicists, chemists, bioinformaticians, biochemists, biologists, pharmacists, biotechnologists)

How do biological molecules recognize and distinguish their binding partners?
In what spatial arrangement and how tightly do they bind? How do molecules function together in complex networks in the cell? How do the dynamic motions of protein molecules affect their function? These are only a few of the questions investigated by the researchers in the Molecular and Cellular Modeling (MCM) group at HITS with computer-aided methods. In the process they develop software ranging from interactive, web-based visualization tools to programs for performing complex molecular simulations.

In the field of systems biology, the group has worked together with the Scientific Databases and Visualization (SDBV) group at HITS and the Modeling of Biological Processes group headed by Ursula Kummer at the University of Heidelberg, to develop SYCAMORE, a SYstems biology Computational Analysis and MOdeling Research Environment (http://sycamore.eml.org). SYCAMORE is a web browser-based application that facilitates construction, simulation and analysis of kinetic models in systems biology. Functions include database supported modeling, basic model checking, model simulation and the estimation of unknown kinetic parameters based on protein structures. The latter functionality is based on the group's PIPSA (Protein Interaction Property Similiarity Analysis) method, which is also available as a webserver, webPIPSA (http://pipsa.eml.org).

HITS (Heidelberg Institute for Theoretical Studies) is a private, non-for-profit research institute. It was established in 2010 as a successor to the EML Research gGmbH. Its base funding is from the Klaus Tschira Foundation, which was established in 1995.
HITS gGmbH is jointly managed by Dr. h.c. Klaus Tschira and Prof. Dr.-Ing. Andreas Reuter.

Joint research projects

- Virtual Liver (BMBF)
- SysMO (BMBF)

Selected cooperation partners

- Ursula Kummer, BioQuant Center, Universität Heidelberg, Germany
- Wolfgang Müller, Scientific Databases and Visualization group, HITS, Heidelberg, Germany

Selected publications

- Stein,M., Gabdoulline, R.R. and Wade, R.C. Cross-Species Analysis of the Glycolytic Pathway by Comparison of Molecular Interaction Fields, Mol. BioSyst., (2010), 6, 162–174; doi:10.1039 /b912398a
- Gabdoulline, R.R., Stein,M. and Wade, R.C. qPIPSA: Relating enzymatic kinetic parameters and interaction fields. BMC Bioinformatics (2007) 8, 373.
- Stein,M., Gabdoulline, R.R. and Wade, R.C. Bridging from molecular simulation to biochemical networks. Curr. Op. Struct. Biol. (2007) 17, 166-172.

Prof. Jürgen Wolfrum

Director BioQuant Center

Universität Heidelberg
BioQuant Center

Prof. Dr. Jürgen Wolfrum is one of the founding directors and currently executive director of the systems biology center BioQuant.

The frontiers between scientific disciplines have always interested Prof. Jürgen Wolfrum, a physicist who has been awarded many national and international prizes. Wolfrum is a pioneer in applied laser spectroscopy, which he uses successfully in a variety of fields. For example, in the automotive industry, he uses laser spectroscopy to investigate elementary chemical reactions and combustion processes. In the field of biosciences he uses the same basic technique to investigate cellular processes.

Wolfrum is by now emeritus professor of physical chemistry at the University of Heidelberg. The physicist habilitated in physical chemistry and in 1982 became the chair of physical chemistry at the University of Heidelberg where he would research and teach for now nearly 30 years physical chemistry. He was especially excited about mathematical modelling and laser-assisted investigations of combustion processes. Working together with his students, Wolfrum started to develop processes for the automotive industry that enabled the analysis of combustion processes in running engines. At the beginning, the engineers just smiled at them. At that time, the reduction of CO_2 gas was not yet an issue that had to be tackled. Many years later, the former Volkswagen boss Ferdinand Piëch said that without laser diagnostics, modern direct injection combustion engines cannot be constructed.

Wolfrum regards the work on the combustion engines as one of his and his students' most exciting projects. These were true pioneering activities, which also involved Wolfgang Ketterle, who did his postdoctoral period in Wolfrum's laboratory and was later awarded the Nobel Prize for Physics in 2001 for the construction of the first atom laser.

Following the success of laser technology in combustion processes, Wolfrum looked for additional fields where he could apply laser technology. Biology seemed to be an excellent area: Countless interactions occur in the restricted area of small cells and suitable methods were required to investigate the various reactions. 15 years ago, Wolfrum succeeded in detecting individual cellular molecules using diode lasers. The technique involved labelling DNA and other biomolecules with dyes that could then be detected with laser beams. Nowadays, the use of diode lasers has become a standard technique in molecular biology, for example in the sequencing of DNA.

Shortly before he retired from the chair of Physical Chemistry in 2005, Professor Wolfrum accepted the offer from the University of Heidelberg to become one of the three founding directors of BioQuant, one of the first interdisciplinary research centers for Systems Biology in Europe.

At BioQuant Wolfrum is responsible for the establishment of a comprehensive technology platform that covers a broad range of imaging methods. In order to develop

mathematical models further it is necessary to test and validate them with the in vivo situation. Thus, there is a scientific need for the development of new quantitative, non-invasive optical methods that can be exploited to study cellular processes in vivo. These methods developed in BioQuant are used to study complex cellular processes on the level of individual molecules. They are used to count individual molecules in cells and analyze their spatio-temporal behavior. Professor Wolfrum's particular interest is the further development of high-resolution and ultra high-throughput microscopy methods, in order to enable the investigation of cellular processes and their genetic origin in the nanometer range. A current project combines light microscopy with electron microscopy systems. This so called "correlative microscopy" focuses on the simultaneous application of these two optical methods in order to compensate for the "blind spots", a flaw the two methods have, and to obtain completely new insights in living systems.

Joint research projects

- FORSYS/ ViroQuant (BMBF)
- Excellence Cluster CellNetworks

Selected publications

- J. Wolfrum. Lasers in Combustion: From Basic Theory to Practical Devices. Proc. Comb. Inst. 27,1-42 (1998)
- Nicole Marmé, Jens-Peter Knemeyer, Jürgen Wolfrum, Markus Sauer. Highly Sensitive Protease Assay Using Fluorescence Quenching of Peptide Probes Based on Photoinduced Electron Transfer. Angew Chem Int Ed 43:3798-3801 (2004)
- Thomas Heinlein, Andreas Biebricher, Pia Schlüter, Christian Michael Roth, Dirk-Peter Herten, JürgenWolfrum, Mike Heilemann, Christian Müller, Philip Tinnefeld and Markus Sauer. High-Resolution Colocalization of Single Molecules within the Resolution Gap of Far-Field Microscopy. ChemPhysChem 6, 949-955 (2005)

Prof. Carsten Watzl

Universität Heidelberg
Institute for Immunology
Watzl research group

7 members of staff (biologists and biochemists)

Natural Killer (NK) cells, a special type of white blood cells, are an import part of the human immune system and once activated effectively kill tumor or virus-infected cells. The activation of NK cells is controlled by a balance of positive (figure, green symbols) and negative signals (figure, red symbols) that are transmitted by different surface receptors. With the help of mathematical modeling, the Watzl group aims to understand how NK cells first integrate these opposing signals and then compute a reliable killing decision. A two compartment model consisting of the contact area between NK and target cell and the rest of the NK cell was constructed containing distinct key signaling events described to be important for the activation.

Besides others, the model predicted a key function of the intracellular protein Vav1 for the activation of the NK cell, which was then experimentally confirmed. The current model of the group is consistent with a central role of Vav1 in the decision making process of NK cells and enables a novel insight into the integration of positive and negative signals during lymphocyte activation.

Joint research projects

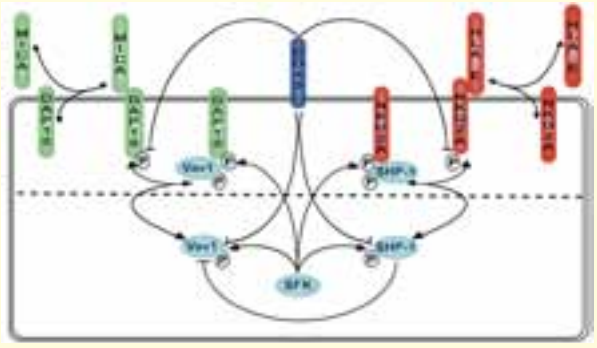
- Systems Biology of Cancer (Helmholtz Association)

Selected cooperation partners

- Prof. Dr. Roland Eils, German Cancer Research Center, Heidelberg, Germany

Selected publications

- Raemer, P., Kohl, K., and Watzl, C. (2009) Statins inhibit NK cell cytotoxicity by interfering with LFA-1-mediated conjugate formation. Eur. J. Immunol., 39, 1456–1465.
- Jacobi, C., Claus, M., Wildemann, B., Wingert, S., Korporal, M., Römisch, J., Meuer, S.,Watzl, C., Giese, T. (2009) Exposure of NK cells to intravenous immunoglobulin induces IFN release and degranulation but inhibits their cytotoxic activity. Clin. Immunol.,133, 393-401.



Research groups in Stuttgart


Dr. Christoph Albermann S. 116


Prof. Frank Allgöwer S. 118


Prof. Wolfgang Ehlers S. 120


Prof. K.-H. Engesser S. 122


Prof. Thomas Ertl S. 124


Dr. Jan Hansmann S. 126


Prof. Bernhard Hauer S. 128


Dr. Angelika Hausser S. 129


Prof. Rainer Helmig S. 130


Dr. Wolfgang Hilt S. 132


Prof. Dieter Jendrossek S. 133


Prof. Roland Kontermann S. 134


Prof. Ralf Mattes S. 136


Dr. Monilola Olayioye S. 138


Prof. Klaus Pfizenmaier S. 140


Prof. Jürgen Pleiss S. 142


Prof. Matthias Reuss S. 143


Jun.-Prof. Nicole Radde S.144


Jun.-Prof. Oliver Röhrle S. 146


Dr. Steffen Rupp S. 148


Prof. Oliver Sawodny S. 150


Prof. Peter Scheurich S. 152


Prof. Georg Sprenger S. 154


Prof. Christina Surulescu S. 156


Prof. Ralf Takors S. 158


Prof. Dieter H. Wolf S. 160


Prof. Jörg Wrachtrup S. 162


Prof. Ulrich M. Zanger S. 164

Dr. Christoph Albermann

University of Stuttgart
Institute of Microbiology / CSB
Synthesis of fine chemicals with *E.coli*

4 members of staff (biologists)

The research group "Synthesis of fine chemicals with *E. coli*" is primarily focused on establishing new metabolic pathways in bacteria (synthetic biology). *Escherichia coli*, which is one of the best-studied bacteria, is used as the preferred host organism. The scientists engineer recombinant bacterial strains to synthesise certain chemicals or active substances in whole-cell assays. The use of recombinant bacterial strains for the synthesis of new substances is of great interest in cases when the chemical or enzymatic formation of the substance is difficult or even impossible.

The researchers preferentially use regenerative materials such as glucose as a basic substrate and as energy source. In order to achieve the efficient formation of products by recombinant organisms, it is necessary to introduce new metabolic processes into the bacteria as well as to adapt the heterologous biosynthesis pathways specifically to the bacterial metabolism: substance flows of the central metabolism must be directed to the product and adverse effects that are caused by the recombinant metabolic pathway must be minimised.

Current research focuses on the synthesis of derivatives of isoprenoids, aromatic compounds and carbohydrates. The bacterial strains are mainly engineered and characterised using molecular biology and analytical techniques (isolation and quantification of educts, intermediary metabolites and products). The use of metabolic models allows the more detailed characterisation of the engineered strains and the identification of control points that can be modified to achieve higher productivity and selectivity.

Selected cooperation partners

- Prof. U. Beifuß, Universität Hohenheim, Germany
- Dr. W. Armbruster, Universität Hohenheim, Germany
- Dr. K. Lemuth, Fraunhofer Institute for Interfacial Engineering and Biotechnology IGB, Stuttgart, Germany

Selected publications

- Albermann C, Trachtmann N, Sprenger GA. (2010). A fast and reliable methode to conduct and monitor expression-cassettes integration into the *Escherichia coli* chromosome. Biotech. J., 5, 32-38.
- Vallon T, Ghanegaonkar S, Vielhauer O, Müller A, Sprenger GA, Reuss M, Albermann C, Lemuth K. (2008). Quantification of the isoprenoid precursors geranyl-, farnesyl- and geranylgeranyl pyrophosphate in recombinant *Escherichia coli* strains. Appl. Micro. Biotechnol., 81, 175-182.
- Albermann C, Ghanegaonkar S, Lemuth K, Vallon T, Reuss M, Armbruster W, Sprenger GA. (2008). Biosynthesis of the Vitamin E Compound delta-Tocotrienol in Recombinant *Escherichia coli* Cells, ChemBioChem, 9, 2524-2533.

Escherichia coli colonies

Prof. Frank Allgöwer

University of Stuttgart
Institute for Systems Theory and Automatic Control / CSB

25 members of staff (7 systems biologists: engineers, systems scientists, mathematicians and physicists)

The research focus of the Institute for Systems Theory and Automatic Control (IST) within systems biology is on the development of methods for modelling and analysis of biological networks on the cellular level. The applied approaches stem mainly from the areas of mathematical systems theory and control engineering. With the goal of an exemplary application of the developed methods, the IST is also active in modeling selected networks for important cellular processes such as cell death or differentiation, in collaboration with experimentally focussed research groups.

The strong foundations of the IST in mathematical systems theory enable the group to quickly pick up new research results in this area, and to refine them for an application to biological questions. The abstract consideration of dynamical processes which is common in control engineering is thereby made specific for the special properties of biological regulatory systems. The methods developed at the IST comprise approaches for parameter identification for biological network models, with a focus on cell-cell heterogeneity in large cell populations. In addition, the IST focusses on the development of methods that allow to gain further insight into the functionality of a biological network, going beyond a numerical simulation. This concerns for example methods for sensitivity analysis of uncertain models, or for robustness analysis of the biological function with respect to diverse perturbations, which is an important principle of biological regulatory networks. In the last few years, the IST has specifically contributed to work on the properties of switching behaviour in biological networks, where in particular the systems theoretic concept of bistability form an adequate methodological approach. To enable a straightforward construction of dynamical models for regulatory networks, researchers at the IST have developped a modelling approach to translate a qualitative description of such a network directly into a mathematical model. Several algorithmic procedures have been developped to infer possible states of the network from an analysis of such a qualitative model.

The mathematical analysis methods developped at the IST are applicable to a wide range of biological systems. This includes for example intracellular processes such as biochemical signal transduction in programmed cell death or cell differentiation, but also cell-cell interactions in specific tissues like a tumor. Moreover, researchers at the IST construct models on a physiological level comprising processes in individual cells, for example to describe the influence of hormone levels on bone remodelling. While biological expertise is mainly brought into these projects from the individual experimental cooperation partners, the models for the considered systems are mostly developped at the IST.

The wide range of considered biological systems is reflected by the range of modelling approaches which are applied in these projects. For a first qualitative analysis, it is often sufficient to rely on purely structural models, where only information about the structure of the biological network is used. Further analyses are often conducted with models based on ordinary differential equations, and for specific problems it may even become necessary

to formulate stochastic models. Furthermore, researchers at the IST study new modelling concepts on the level of cell populations, which allow to capture the cellular heterogeneity adequately.

To strengthen systems biology as a research field, the IST values a comprehensive offer of courses in this area. To achieve this goal, a specialised program in systems biology has been created for students of Engineering Cybernetics several years ago. Thereby, emphasis is put on imparting competences which are relevant for basic research. The courses offered in this area are also regularly visited by students from other engineering programs, as well as students from bioengineering. In addition, the IST is active in systems biology education on the PhD level, for example by offering specialised seminars in the scope of the graduate school in the cluster of excellence Simulation Technology.

Selected cooperation partners

- Peter Scheurich, Institute of Cell Biology and Immunology, University of Stuttgart, Germany
- Klaus Pfizenmaier, Institute of Cell Biology and Immunology, University of Stuttgart, Germany
- Angelika Hausser, Institute of Cell Biology and Immunology, University of Stuttgart, Germany
- Fabian Theis, Computational Modeling in Biology, Helmholtz Zentrum München, Germany
- Alfred Nordheim, Interfaculty Institute for Cell Biology, University of Tübingen, Germany

Selected publications

- T. Eissing, S. Waldherr, F. Allgöwer, P. Scheurich and E. Bullinger. Steady state and (bi-) stability evaluation of simple protease signalling networks. BioSystems, 90:591–601, 2007.
- M. Chaves, T. Eissing and F. Allgöwer. Bistable biological systems: A characterization through local compact input-to-state stability. IEEE Trans. Automat. Control, 53:87–100, 2008.
- S. Waldherr and F. Allgöwer. Searching bifurcations in high-dimensional parameter space via a feedback loop breaking approach. Int. J. Syst. Sci., 40:769–782, 2009.

Prof. Wolfgang Ehlers

University of Stuttgart
Institute of Applied Mechanics / CSB

17 members of staff (predominantly engineers)

The research group has a long tradition in modelling continuum mechanical systems within the framework of Computational Mechanics. The research is specifically focused on multi-component and multi-physical models ranging from the description of coupled phenomena in soil mechanics (solid-fluid interaction) up to the investigation of biomechanical systems (solid-fluid interaction with electro-chemical effects).

In biomechanics, the group's expertise is concentrated on the development of mathematical and computational models for soft biological tissue such as cartilage or the intervertebral disc. This includes the description of local inhomogeneities and possible anisotropies as they occur, for example, as a result of the distribution of collagen fibres. Recent and future investigations include modelling and remodelling effects as well as the phenomenon of growth. Numerical results are obtained within the Finite Element Method (FEM) applied to initial boundary-value problems (IBVP) under geometrically two-dimensional (2-d) and three-dimensional circumstances. These computations are carried out by the finite element (FE) solver PANDAS, which has been designed and permanently improved by the group during the last 15 years. In case of the solution of large problems, PANDAS can be coupled to the parallel solver M++ to obtain the powerful FE solver M++/PANDAS.

Wolfgang Ehlers is the Executive Director of the Stuttgart Research Centre for Simulation Technology (SRC SimTech) and the coordinator of the Cluster of Excellence in Simulation Technology (SimTech) at the University of Stuttgart. Based upon the motto "From Isolated Numerical Approaches to an Integrative Systems Science", the cluster covers a broad variety of future-oriented scientific fields involving all core Research Areas (RA) of the University of Stuttgart concerning natural and engineering sciences as well as computer science. Additionally, an Integrative Platform of Reflexion and Evaluation is included. In particular, the cluster covers the following Research Areas:

A. Molecular and Particle Dynamics serving for nano and micro simulations and bridging scales by coupling particle dynamics with continuum mechanical approaches.
B. Advanced Mechanics of Multi-scale and Multi-field Problems exhibiting the basic scientific key for the description of complex problems in almost all branches of engineering simulation and design by bridging scales, coupling physics and linking domains.
C. Systems Analysis and Inverse Problems focusing on model validation, parameter identification and model reduction, as well as dynamical system analysis, control, aspects of autonomy, automation and hierarchical or networked structures of systems.
D. Numerical and Computational Mathematics guaranteeing advances towards multi-scale and multi-physics numerical models including the quantification of uncertainty and a self-adaptive choice of scales and physics in order to simulate dynamic and coupled processes in complex real-world problems.
E. Integrated Data Management and Interactive Visualisation mastering the explosion of information

in simulation technology through human-system interfaces for model setup, real-time simulation, control and interactive visualisation and through design of sensor networks for real-time control simulations.

F. Hybrid High-Performance Computing Systems and Simulation Software Engineering with the basic idea of harnessing the power of large-scale systems through advanced simulation software technology to solve grand challenge problems.

G. An Integrative Platform of Reflexion and Evaluation that contributes to the above Research Areas regarding Theory of Science, Philosophy of Technology, Sociology of Technology and Ethics.

Special equipment and techniques

- Beowolf Linux Compute Cluster, 102 CPU (440 GFlops peak performance)
- Simulation Software PANDAS

Joint research projects

- Cluster of Excellence in SimTech (DFG)
- SysTec / MSC (BMBF)

Selected cooperation partners

- Prof. Klaus Pfizenmaier, Institute of Cell Biology and Immunology / Central Microscopy Facility, University of Stuttgart, Germany
- Prof. Heike Walles, Department Cell and Tissue Engineering, Fraunhofer Institute for Interfacial Engineering and Biotechnology, Stuttgart, Germany
- Prof. Rolf Findeisen, Institute for Automation Engineering, Otto-von-Guericke University Magdeburg, Germany
- Prof. Frank Allgöwer, Institute for Systems Theory and Automatic Control, University of Stuttgart, Germany
- Prof. Joachim Spatz, Department of New Materials and Biosystems, Max Planck Institute for Metals Research, Stuttgart, Germany

Selected publications

- W. Ehlers, N. Karajan, B. Markert: An extended biphasic model for charged hydrated tissues with application to the intervertebral disc. Biomechanics and Modeling in Mechanobiology 8 (2009), 233 – 251.
- W. Ehlers: Challenges of porous media models in geo- and biomechanical engineering including electro-chemically active polymers and gels. International Journal of Advances in Engineering Sciences and Applied Mathematics 1 (2009), 1 – 24.
- W. Ehlers, A. Acartürk, N. Karajan: Advances in modelling saturated biological soft tissues and chemically active gels. Archive of Applied Mechanics 80 (2010), 467 – 478.

Prof. Karl-Heinrich Engesser

University of Stuttgart
Institute for Sanitary Engineering, Water Quality and Solid Waste Management / associated with the CSB
Biological Air Purification

4 members of staff (biologists, technical biologists and environmental protection chemist)

The Department of "Biological Air Purification" (ALR) at the Institute for Sanitary Engineering, Water Quality and Solid Waste Management focuses principally on the following areas:

Biological degradation of pollutants:
The search for and the use of degradative potentials of xenobiotic substances in nature is one of the team's major competences. Examples of enrichments and the investigation of degradation pathways:

- Enrichment, investigation and environmental use of *Burkholderia fungorum* FLU 100 bacteria that are able to live on fluorobenzene and toluene
- Enrichment, investigation and environmental use of bacterial strains that utilise butanone
- Research on the bacterial degradation of isophorone, 2-chlorotoluene, pharmaceuticals and other aromatic compounds
- Enrichment and investigation of bacterial strains that are able to utilise cyclohexane, n-butane and 1,1-dimethylpropylamine as sole carbon- and energy source
- Comprehensive investigation of the bacterial degradation of a range of aromatic and aliphatic ethers
- Research on the bacterial degradation of acetone and propanol in slightly contaminated wastewater.

Biotransformation:
Another major research focus of the group is the use of biotransformatory potentials for the production of specific compounds. The researchers identify key enzymes in enriched bacterial strains and clone them in a degradation-free context. These enzymes are used for the production of metabolites. Plans exist to use genetic methods to improve enzymes with regard to their substrate- and product specificity as well as their kinetics.

Biological air purification:
The department is specialised in the optimisation of the degradation performance of biological air purification methods. Microorganisms adapted to the particular air pollution problem under investigation are used and high-performance filters are developed and tested. Membrane filters, trickling and biofilters as well as bioscrubber systems are used for the biological treatment of polluted air. Besides focusing on selecting suitable methods and on filter biocoenosis, the researchers also carry out investigations on packaging, long-term stability, olfactometry and dimensionalisation.

Examples of recent investigations:

- Modelling of a laboratory-scale biofilter system for the purification of air polluted with benzyl alcohol. Regeneration and subsequent optimisation of an industrially operated air purification plant based on the results obtained.
- Investigation of the biological treatment of air polluted with chlorobenzene, fluorobenzene or toluene and mixtures thereof
- Investigation of special biotrickling filter systems with mechanical biomass discharge to prevent clogging phenomena when treating waste air polluted with toluene

- Investigation of the stripping behaviour of chlorobenzene and toluene mixtures and the subsequent purification of air polluted with such mixtures
- Degradation of butanone in biotrickling filters
- Degradation of cyclohexane in biotrickling filters.

Education and training:
The department offers numerous lectures, seminars and practical training on "Environmental technology", "Technical Biology", "Mechanical Engineering", "WAREM" and "WASTE". The institute organises practical training in companies and supervises seminar papers, bachelor's, master's, diploma and doctoral theses.

Systems biology:
The department is part of the BMBF-funded "Systems Biology in *Pseudomonas* for Industrial Biocatalysis" consortium and focuses on the subproject "Bacterial-enzymatic production of 1,4-butandiol, caprolactone and 3-amino-3,3-dimethylpropanol as key chemicals" which deals with the enrichment of bacterial strains that are able to utilise substrates specifically adapted to the biotransformation under investigation as sole carbon and energy source. These bacterial strains are investigated in detail and the key enzymes (mainly oxygenases) of the degradation pathways are identified. The genes encoding these enzymes are cloned to make the new biocatalysts available for optimisations in degradation-free contexts. Major focus will in the future be put on modifying and improving the enzymes' substrate and product specificities and on reaction kinetics.

Special equipment and techniques

- Planning, construction, establishment and operation of laboratory-scale biological air purification plants
- Substrate and metabolite analytics using IC, HPLC, GC and GCMS
- Established techniques for the enrichment of xenobiotics-degrading bacterial strains
- Microbiological, biochemical and genetic methods to elucidate the xenobiotics degradation pathways in bacteria

Joint research projects

- Systems Biology in *Pseudomonas* for Industrial Biocatalysis (BMBF)

Selected cooperation partners

- Dr. D. Pieper, Helmholtz Centre for Infection Research, Braunschweig, Germany

Selected publications

- Kim YH, Cha CJ, Engesser KH, et al. Degradation of various alkyl ethers by alkyl ether-degrading Actinobacteria isolated from activated sludge of a mixed wastewater treatment. Chemosphere 2008, 73(9), 1442-1447.
- Onaca C, Kieninger M, Engesser KH, Altenbuchner J. Degradation of alkyl methyl ketones by *Pseudomonas veronii* MEK700. Journal of Bacteriology 2007, 189(10), 3759-3767.
- Kim YH, Engesser KH, Kim SJ. Physiological, numerical and molecular characterization of alkyl ether-utilizing rhodococci. Environmental Microbiology 2007, 9(6), 1497-1510.

Prof. Thomas Ertl

University of Stuttgart
Visualization Research Center / associated with the CSB

40 members of staff (informaticians, mathematicians, engineers and natural scientists)

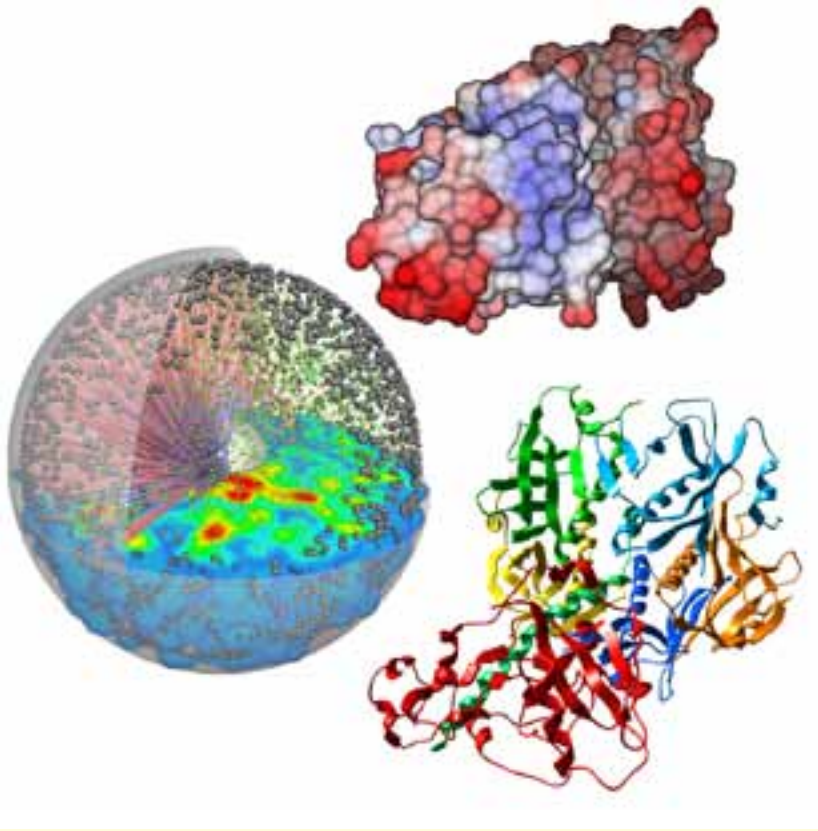
Thomas Ertl is the head of the Visualization Research Center of the University of Stuttgart (VISUS) and the Visualization and Interactive Systems Institute (VIS). In this function, he supervises research activities in the fields of medical visualization, flow visualization, visual analytics and interactive systems. Since life sciences became more and more prominent in recent years, the workgroup Visualization in Systems Biology was established.

In systems biology, correlations play an important role and visualizations are a great way to make these visible. Hence, the research focus of the workgroup lies in the visualization and the interactive exploration of data from this environment. Special emphasis is placed on the development of methods, which are carried out on graphic processing units (GPUs). The utilization of current consumer graphic hardware, for example, allows to render hundreds of thousands of atoms interactively in high quality. Additionally, high speedups of computations are possible because of the parallel architecture of GPUs.

A compute cluster consisting of 36 nodes is used to carry out simulations. All nodes are identical and both CPUs and GPUs can be employed for the computations. The graphics generated by the cluster are stereoscopically displayed with four projectors in high resolution. Projects exist in collaboration with the Center Systems Biology (CSB) and the Collaborative Research Centre (SFB) 716 “Dynamic Simulation of Systems with Large Amounts of Particles”.

The CSB project covers signal transduction processes on the cellular level. Here, effects of molecular crowding, hindered diffusion and transport with motor proteins along filaments of the cytoskeleton are subject to research. A simplified cellular model was established together with project partners from biology. This particle-based model allows to examine stochastic simulations. In contrast to classical approaches with differential equations, the stochastic modeling allows to consider asymmetries in the architecture of the cellular model. The visualization of the cell allows the validation of the simulation and the gain of new insights. For the near future it is planned to make the cellular model adjustable regarding the cellular shape and the cytoskeleton to fit experimental data. Furthermore, the visualization is to be merged with the simulation into an interactive exploration toolkit.

The subproject D4 of SFB 716 is concerned with visualizations and methods of analysis for dynamic protein-solvent systems. This project analyzes the characteristics of solvents because of their important effects on protein functions. The main focus lies on investigating the paths of solvent molecules and the clustering within the solvent. For the visualization of the protein structure, several techniques are employed. These include atom-based molecular representations, representations of the secondary structures and surface representations (solvent excluded surface). The utilization of GPUs leads again to insightful visualizations.



Special equipment and techniques

- 64-node GPU-cluster
- 100 megapixels stereo back-projection wall

Joint research projects

- Cluster of Excellence in SimTech (DFG)
- SFB 716: Dynamic simulation of systems with large particle numbers (DFG)

Selected cooperation partners

- Prof. Matthias Reuss, CSB, University of Stuttgart, Germany
- Prof. Jürgen Pleiss, Institute of Technical Biochemistry, University of Stuttgart, Germany
- Prof. Ralf Takors, Institute of Biochemical Engineering, University of Stuttgart, Germany
- Dr. Marc Baaden, IBPC, Paris, France
- Dr. Pablo Chacon, CSIC, Madrid, Spain

Selected publications

- M. Krone, K. Bidmon and T. Ertl. Interactive Visualization of Molecular Surface Dynamics. IEEE Transactions on Visualization and Computer Graphics (Proceedings Visualization / Information Visualization 2009), 15(6), 1391-1398, 2009.
- M. Falk, M. Klann, M. Reuss and T. Ertl. Visualization of Signal Transduction Processes in the Crowded Environment of the Cell. Proceedings of IEEE Pacific Visualization Symposium 2009 (PacificVis '09), 169-176, 2009.
- M. Falk, M. Klann, M. Reuss and T. Ertl. 3D Visualization of Concentrations from Stochastic Agent-based Signal Transduction Simulations. To appear in Proceedings of IEEE International Symposium on Biomedical Imaging: From Nano to Macro (ISBI '10), 2010.

Dr. Jan Hansmann

Fraunhofer Institute for Interfacial Engineering and Biotechnology, Stuttgart / associated with the CSB
Cell and Tissue Engineering

4 members of staff (engineers, biologists and lab technicians)

The research group led by Dr. Hansmann focuses primarily on two topics: the model-based investigation of angiogenic processes and the non-invasive characterisation of cells using Raman spectroscopy.

Angiogenesis is a process involving the growth of new blood vessels from pre-existing vessels. This process is of great interest in the field of regenerative medicine and tumour research as it is an important factor in the uncontrolled growth and spread of tumours (metastasis). The angiogenic processes are modelled using experimental data such as migration trajectories, marker expression and the release of second messengers. The models can subsequently be used to identify methods and strategies that enable the controlled induction and prevention of the growth of vessels.

In addition, bioreactors are being developed to deal with systems biology issues. These bioreactors allow the evaluation of biochemical influences as well as the defined mechanical stimulation of cells. The controlled stimulation of cells is a prerequisite for the identification of intracellular processes based on the cell's response to a certain stimulus.

Raman spectroscopy is a spectroscopic technique that relies on light from a laser and that is used to detect and analyse chemical information. The comparison of spectral data yielded by Raman spectroscopy can be used to investigate and differentiate individual prokaryotic and eukaryotic cells. The technique also enables the investigation of processes inside cells, for example those related to vitality and differentiation. These investigations are of great interest in the field of tissue engineering as they enable the rapid investigation of biological contaminations of transplants and the assessment of the quality of autologous transplants. At present, the group is investigating differentiation processes of mesenchymal stem cells that can turn either into adipogenic, chondrogenic or osteogenic cells. It is the goal of the researchers to investigate cellular differentiation processes without the use of markers and without destroying the sample. The experimental data can subsequently be used to develop models to predict the differentiation state of unknown samples and classify unknown samples. This classification can also be used for the characterisation of unknown microorganisms and different mammalian cells.

Special equipment and techniques

- Live cell imaging
- Bioreactor technology
- Micro-Raman spectroscopy
- Multiphoton microscopy

Selected cooperation partners

- Prof. Klaus Pfizenmaier, Institute of Cell Biology and Immunology, University of Stuttgart, Germany
- Prof. Joachim Spatz, Department of New Materials and Biosystems, Max Planck Institute for Metals Research, Stuttgart, Germany
- Prof. Rolf Findeisen, Institute for Automation Engineering, Otto-von-Guericke University Magdeburg, Germany
- Dr. Carsten Bolwien, Bioanalytics, Fraunhofer Institute for Physical Measurement Techniques, Freiburg, Germany
- CellTech Services, Seligenstadt, Germany

Selected publications

- Mertsching H, Hansmann J. Bioreactor Technology in Cardiovascular Tissue Engineering. Adv Biochem Eng Biotechnol. 2008 Oct 1. [Epub ahead of print].
- Koch S, Dreiling M, Gutekunst M, Bolwien C, Thielecke H, Mertsching H. Discrimination of microorganisms and cells in Tissue Engineering by Raman spectroscopy. Proceedings of SPIE, 7368-46, 2009.
- Schanz J, Pusch J, Hansmann J, Walles H, Vascularised human tissue models: A new approach for the refinement of biomedical research. J Biotechnology 2010, 148:56-63.

Bioreactors that enable the cultivation of endothelial cells under dynamic conditions and the investigation of the biochemical characteristics of the angiogenic process through the addition of messenger substances. The knowledge obtained with these systems can be used in models to simulate angiogenic processes.

Prof. Bernhard Hauer

University of Stuttgart
Institute of Technical Biochemistry / CSB

30 members of staff (technical biologists and chemists)

The research group led by Prof. Hauer focuses on the provision of innovative enzymes that broaden the spectrum of amenable reactions. This opens up innovative, selective synthesis routes that can be used to create products through the efficient use of available resources.

The research group develops protein sequence and structure databases as well as modelling enzyme properties using molecular dynamic simulations with the aim of designing new biocatalysts. The researchers are endeavouring to improve the biochemical properties of the proteins using protein engineering involving directed mutagenesis, gene synthesis or random libraries.

The group's knowledge of the molecular basis of protein properties is used in the area of white biotechnology in order to improve recombinant enzymes by way of protein design. Moreover, this knowledge is also required in systems biology and metabolic engineering in order to predict kinetic parameters and remove bottlenecks in the substance flow. In addition, the knowledge is used in synthetic biotechnology to gain access to new reactions. This requires the establishment of high-throughput analysis systems. With regard to synthesis applications, the research group led by Prof. Hauer provides recombinant proteins or develops whole-cell catalysts in which several enzymes are combined in new metabolic pathways.

Special equipment and techniques

- 2 computer clusters
- Graphical workstations
- GC/MS
- HPLC/MS
- Automated screening systems
- Array technology

Selected cooperation partners

- Prof. Pleiss, Institute of Technical Biochemistry, University of Stuttgart, Germany

Dr. Angelika Hausser

University of Stuttgart
Institute of Cell Biology and Immunology / CSB
Molecular characterisation and *in vivo* function of protein kinase D

8 members of staff (biologists)

The goal of this project is to elucidate the multifunctional role of serine-/threonine-specific protein kinases of the PKD family (PKD1, 2, and 3) using a new, interdisciplinary approach. PKDs play a key role in basic, though very different cellular processes, including vesicular substance transport to the plasma membrane, cell migration and the regulation of gene expression. However, the underlying mechanisms of action are not yet understood in detail.

In order to achieve in-depth insights into these highly complex processes, the innovative approach involves the combination of the know-how of different experimental and theoretical disciplines: Molecular biology methods are used to establish genetically defined cell systems, which however differ in terms of PKDs. The Proteome Center in Tübingen will investigate these cell systems by analysing the entire phosphoproteome in order to obtain insights into PKD-governed signalling pathways and networks. The target proteins that are identified and the different PKD variants will be analysed in living cells, and their spatial distribution (e.g. Golgi apparatus, nucleus, plasma membrane) will be described using a broad range of different quantitative microscopy methods. The researchers will also focus on dynamic compartment-specific interactions. The data acquired will be used to develop mathematical models that describe PKD function and contribute to an in-depth understanding of the role of this kinase family in the aforementioned basic biological processes. These models are being developed in cooperation with the Institute for Systems Theory and Automatic Control (IST) at the University of Stuttgart.

Joint research projects

- Biomimetic matrices (University of Stuttgart / Ministry of Science, Research and the Art Baden-Württemberg)
- SysTec / MSC (BMBF)

Selected cooperation partners

- Prof. Boris Maček, Interdepartmental Institute for Cell Biology / Proteome Center Tübingen, University of Tübingen, Germany
- Prof. Alfred Nordheim, Interfaculty Institute for Cell Biology, University of Tübingen, Germany
- Prof. Frank Allgöwer, Institute for Systems Theory and Automatic Control, University of Stuttgart, Germany
- Junior professor Nicole Radde, Institute for Systems Theory and Automatic Control, University of Stuttgart, Germany

Selected publications

- Breindl C, Waldherr S, Hausser A, Allgöwer F. (2009) Modelling cofilin mediated regulation of cell migration as a biochemical two-input switch. Proc. of the 3rd Foundations of Systems Biology in Engineering (FOSBE), pp. 60-63, Denver, Colorado.
- Peterburs P, Heering J, Link G, Pfizenmaier K, Olayioye MA, Hausser A. (2009) Protein Kinase D Regulates Cell Migration by Direct Phosphorylation of the Cofilin Phosphatase Slingshot 1 Like. Cancer Res 69(14):5634-8.
- Fuchs YF, Eisler SA, Link G, Schlicker O, Bunt G, Pfizenmaier K, Hausser A. (2009) A Golgi PKD activity reporter reveals a crucial role of PKD in nocodazole-induced Golgi dispersal. Traffic 10(7):858-67.

Prof. Rainer Helmig

University of Stuttgart
Institute of Hydraulic Engineering / CSB
Modeling of flow and transport processes in biological systems

2 members of staff (engineers)

The aim of the workgroup is the development of mathematical and numerical models that describe the distribution of targeted protein therapeutics in a human organ diseased with a tumor (lung, brain, etc.). To model the delivery of the therapeutic agent to the tumor cells, the transport of the drug molecules within the blood vessels, the flow across the vascular walls into the surrounding tissue and the transport through the interstitial space towards the tumor have to be described. If tumor-induced angiogenesis occurs, a direct transport of the therapeutic from the blood vessels to the tumor cells is possible. Currently, the group works on the following projects:

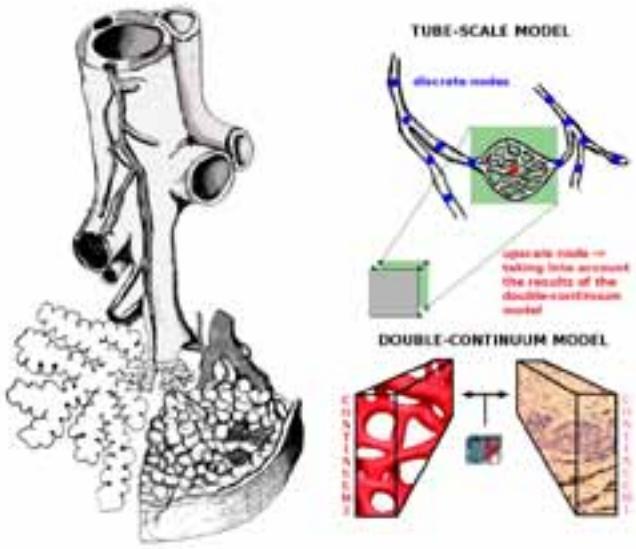
- Project 1: Joint research project / FORSYS cooperation: A systems biology approach towards predictive cancer therapy; subproject: Modeling the spatial and temporal distribution of therapeutics in the tumor, a continuum approach. (K. Erbertseder)
- Project 2: Within the framework of the project network "Coupled problems in biomechanics and systems biology" of the cluster of excellence "Simulation Technology": Coupling of micro- and macro-models for complex flow and transport processes in biological tissue. (K. Baber)

In project 1, the temporal and spatial evolution of the targeting agent within the capillary bed of the lung, the exchange processes between the pulmonary capillaries and the surrounding tissue and the flow and transport processes in the tissue are numerically modeled by a double-continuum approach valid on the macro-scale. This approach is based on two separate continua that are coupled by transfer functions. The first continuum represents the flow, transport and reaction processes in the pulmonary tissue. The second continuum represents the pulmonary capillary bed as an averaged quantity. The transfer functions reflect the exchange of drug molecules between the pulmonary tissue (continuum one) and the capillary bed (continuum two).
For the representation of the temporal and spatial distribution of the targeted protein therapeutic in the whole lung, the double-continuum approach is coupled with a tube-scale model. The tube-scale model expresses the blood flow from the right heart ventricle to the capillaries and the backflow from the capillaries to the heart.
The implementation of a tumor-growth model is one of the last steps of this project. The resultant deformations of the healthy tissue by the growing tumor are to be described by a linear elastic model.

Project 2 investigates the flow and transport processes between blood vessels and surrounding tissue, with the main focus on a detailed description of the structure and the influence of the microvascular wall. To model the interaction with and the transfer across the capillary wall, a coupled micro-/macro-model is developed. A computationally expensive but physically more appropriate micro-model is used in regions that are highly active with respect to transfer processes at interfaces, like the capillary-interstitium interface. Much faster macro-models are employed in less active parts such as the interstitial space and the interior of the vessels. This coupling of micro- and macro-models with the help of appropriate coupling conditions allows the description of processes on different time and length scales. The model is based on

the assumption, that tissue can be described as a porous medium using Darcy's law and that blood flow can be considered as free flow of a Newtonian fluid using the Stokes equation.

Furthermore, project 2 aims at applying an analytical upscaling to the three-dimensional PDEs that describe the capillary wall on the micro-scale, in order to obtain a two-dimensional interface with the respective equations and properties. If possible, further simplifications will be carried out to derive coupling conditions that can be implemented in project 1. For the validation of the model concept and the planned model reduction, the simulation results will be compared with the experimental results of the cooperation partners.



Description of flow and transport processes in the lung by coupling of tube-scale and double-continuum model.

Special equipment and techniques

- DUMUX (multi-scale multi-physics toolbox for the simulation of flow and transport processes in porous media; developed at the University Stuttgart)
- BW-Grid Cluster (cluster of parallel computing)

Joint research projects

- Cluster of Excellence in SimTech (DFG)
- FORSYS (BMBF)

Selected cooperation partners

- Prof. Matthias Reuss, Institute of Biochemical Engineering, University of Stuttgart, Germany
- Prof. Bernd Pichler, Laboratory for Preclinical Imaging and Imaging Technology of the Werner Siemens-Foundation, Department of Radiology, University of Tübingen, Germany
- Prof. Matthias Schwab, Dr. Margarete Fischer-Bosch - Institute of Clinical Pharmacology, Stuttgart, Germany
- Prof. Patrick Jenny, Institute of Fluid Dynamics, ETH Zürich, Switzerland
- Prof. Frank Allgöwer, Institute for Systems Theory and Automatic Control, University of Stuttgart, Germany

Selected publications

- Darcis M. Implementation of a numerical model for the convection-enhanced delivery of therapeutic agents into brain tumors. Master thesis, 2007.
- Niessner J. and Helmig R. Multi-physics modeling of flow and transport in porous media using a downscaling approach. Advances in Water Resources, S. 845-850, 2009.
- Flemisch B., Fritz J., Helmig R., Niessner J. and Wohlmuth B. DUMUX: a multi-scale multi-physics toolbox for flow and transport processes in porous media. ECCOMAS Thematic Conference on Multi-scale Computational Methods for Solids and Fluids, S. 82-87, 2007.

Dr. Wolfgang Hilt

University of Stuttgart
Institute of Biochemistry / associated with the CSB
Cellular Networks

4 members of staff (1 biochemist, 1 engineer aerospace technologies and 2 biologists)

The yeast protein network is the to date most comprehensively resolved network in eukaryotic biology. At present it contains more than 200 000 interactions (physical and genetic). The interaction data are hosted in a permanently updated database, the BioGrid. The aim of the research group's project is to analyze functional relationships in the yeast protein network following an exhaustive bottom-up approach. Based on the comparison of genetic interaction profiles the group has developed a strategy, called "conjunction" analysis. With this strategy functional relationships for any target gene ranging beyond the level of direct interaction can be explored.

Dr. Hilt's research group developed a JAVA based plugin for the systems biology program Cytoscape, which allows retrieval of BioGrid data and automated visualization of conjunction relationships. The concept of conjunction analysis is experimentally proven by application to defined complexes (ubiquitin ligases, regulators, transport systems) or components of established pathways or cellular programs (RAS1/2 pathway, metabolic adaptation, cell cycle, programmed cell death). As gold-standard also paralog pairs, which due to their common evolutionary origin are expected to share similar functions, are inspected. Results obtained so far underline the power of conjunction analysis. Further refinement of the conjunction strategy is in work. Future applications will include correlation of conjunction relationships with physical linkage, analysis of sets of targets operating in defined fields of cell function and generation of a refined conjunction network of the entire yeast genome.

Special equipment and techniques

- Special computer techniques (multiscale graphs and network analysis)

Selected cooperation partners

- Dr. Stephan Rudolph, Institute for Statics and Dynamics of Aerospace Structures, University of Stuttgart, Germany

Representation of the genetic interaction network of RAS proteins using a visualization method developed by Dr. Hilt's research group. The network graph portrays the degree of the relationship between yeast cell proteins that functionally interact with Ras2. RAS proteins play a key role in the development of tumours in mammals.

Prof. Dieter Jendrossek

University of Stuttgart
Institute of Microbiology
Microbial Biopolymers

Approximately 9 members of staff (biologists)

Prof. Jendrossek's research group focuses on the investigation of the metabolism of biopolymers (e.g., polyhydroxyalkanoates, caoutchouc compounds) in microorganisms. They also study the bacterial metabolism of low-molecular cyclic and acyclic terpene compounds using biochemical, molecular biology and systems biology methods. The researchers determine the concentration and activities of enzymes, nucleic acids and cell metabolites using state-of-the-art, bioanalytical methods. The comparison of results obtained with wild-type strains and specific mutant strains provides the researchers with information about qualitative and quantitative substance flows. The determination of the structure of selected enzymes and the specific alteration of amino acid sequences using molecular biology methods enables the researchers to modify and optimise the enzymes' catalytic properties.

Special equipment and techniques

- S2 genetic engineering laboratory and equipment
- PH-Stat device for the measurement of small, enzymatically-released amounts of acid
- Fluoroscence microscopy
- Traditional enzyme purification techniques

Selected cooperation partners

- Prof. Hauer, Institute of Technical Biochemistry, University of Stuttgart, Germany
- Prof. Saito, Institute of Microbiology, Kanagawa University, Japan
- Dr. Papageorgiou, Turku Centre for Biotechnology, University of Turku and Åbo Akademi University, Finland

Biological degradation of poly-3-hydroxybutyric acid (PHB) by sewage sludge microorganisms after 0, 2, 4, 6, 8 and 10 weeks.

- Prof. Einsle, Institute of Organic Chemistry and Biochemistry, University of Freiburg, Germany
- Dr. Breuer, BASF-SE, Ludwigshafen, Germany

Selected publications

- Schmitt G., Seiffert G., Kroneck P.M., Braaz R., Jendrossek D. 2010. Spectroscopic properties of rubber oxygenase RoxA from *Xanthomonas* sp., a new type of diheme dioxygenase. Microbiology 156:2537-2548
- Förster-Fromme K., Höschle B., Mack C., Bott M., Armbruster W., Jendrossek D. 2006. Identification of genes and proteins necessary for catabolism of acyclic terpenes and leucine/isovalerate in *Pseudomonas aeruginosa*. Appl Environ Microbiol. 72:4819-28.
- Uchino K., Saito B., Gebauer B., Jendrossek D. 2007. Isolated poly(3-hydroxybutyrate) (PHB) granules are complex bacterial organelles catalyzin formation of PHB from acetyl-CoA and degradation of PHB to acetyl-CoA. J. Bacteriol. 189:8250-8256.

Prof. Roland Kontermann

University of Stuttgart
Institute of Cell Biology and Immunology / CSB

Approximately 20 members of staff (biologists, biotechnologists and pharmaceutical engineers)

Immunotherapeutic approaches involving recombinant protein drugs are regarded as very promising strategies for the effective treatment of diseases that can currently only be treated insufficiently or not at all. The protein drugs market is therefore growing at an exponential rate and accounts for annual revenues of several billions of euros.

Dozens of new protein-based pharmaceuticals are currently undergoing preclinical and clinical testing. However, predictions about the drugs' general effectiveness and optimal treatment methods cannot yet be made. The long-term goal of the "systems biological approach towards predictive cancer therapy" cooperative project is to resolve this bottleneck using a predictive mathematical model and contribute to improving and accelerating the clinical investigation of new, potentially tumour-selective protein drugs.

Besides cardiovascular diseases, tumour diseases are the major cause of death in Western industrialised countries. The standard therapy of tumour patients still involves surgical resection and/or chemotherapy and radiotherapy. Antibody therapies, typically used in combination with chemotherapy, have been shown to be particularly effective in the treatment of certain malignant diseases, in particular some types of blood cancer. These immunotherapeutic approaches involving tumour-specific recombinant antibodies are complemented by therapeutic concepts involving cytokines and recently also by the use of substances derived from cytokines and recombinant antibodies and synthetic bi- or multifunctional molecules. However, the majority of these derivatives are still in preclinical development.

The new therapeutic approaches are mainly focused on using drugs with a targeted effect at the same time as trying as much as possible to limit the use of conventional therapeutic methods, which are often toxic and lead to a limited treatment outcome. An attractive principle is the application of growth-inhibiting and/or apoptosis (programmed cell death) -inducing agents that have a direct effect on the tumour cells, the stroma or the vascular system that supplies a solid tumour with oxygen and nutrients. In general, these innovative, targeted drugs raise hopes for a broader and greater success in the therapy of tumours. It is expected that a maximal anti-tumour effect, at the same time as being associated with as few as possible undesired side effects, can be achieved with an agent that meets all the requirements in a favourable combination. These requirements take into account quantitative parameters such as the drugs' circulation time in the blood, degradation, tissue distribution, distribution of the target structures in tumour and normal tissues, etc., whose comprehensive investigation in clinical studies and experimental models has been shown to be very time-consuming and costly, particularly as far as new immunotherapeutic drugs are concerned. Parameters obtained from individual findings only allow limited statements to be made on a drug's optimal spectrum of activity.

The goal of the collaborative project is to develop a comprehensive mathematical model that describes the behaviour of a certain drug in the body, starting from its application up to its molecular mechanism of action, and allows predictions to be made. Such a model can thus contribute to specifically improving a drug or treatment

strategy, which is the goal of the project. A predictive model will be developed on the basis of experimental and theoretical findings using new genetically engineered bifunctional protein drugs or protein-functionalised nanoparticles with a targeted effect.

As part of the collaborative project, the teams of Prof. Kontermann and Prof. Pfizenmaier are focusing on the development and characterisation of bifunctional protein drugs and protein-functionalised nanoparticles. This involves the genetic engineering and production of the protein components (antibody fragments, TRAIL derivatives, fusion proteins) and the functionalisation of the particles (polystyrene nanoparticles, liposomes, composite core-shell nanoparticles). Besides the physicochemical and biochemical characterisation of the particles, the researchers also focus on the *in vitro* analysis of targeting, the cytotoxic effects and the *in vivo* evaluation of pharmacokinetic and pharmacodynamic (anti-tumour activity) properties.

Special equipment and techniques

- Devices used for the production of particles (e.g. liposomes)
- Devices for the physicochemical characterisation (e.g. Zetasizer Nano for dynamic light scattering measurements)
- Confocal microscopy

Joint research projects

- FORSYS Partner (BMBF)

Selected cooperation partners

- Prof. Peter Scheurich, Institute of Cell Biology and Immunology, University of Stuttgart, Germany
- Prof. Matthias Reuss, Institute of Biochemical Engineering, University of Stuttgart, Germany
- Prof. Manfred Schwab, Dr. Margarete Fischer-Bosch - Institute of Clinical Pharmacology, Stuttgart, Germany
- Prof. Pichler, Laboratory for Preclinical Imaging and Imaging Technology of the Werner Siemens-Foundation, Department of Radiology, University of Tübingen, Germany
- Dr. Lippert, Bayer Technology Services GmbH, Leverkusen, Germany

Selected publications

- Gerspach, J., Pfizenmaier, K. und Wajant H. (2009) Improving TNF as a cancer therapeutic: tailor-maide TNF fusion protiens with conserved antitumor activity and reduced systemic side effects. Biofactors 35, 364- 372.
- Messerschmidt, S.K.E., Musyanovich A., Altvater, M., Scheurich, P., Pfizenmaier, K., Landfester, K. und Kontermann, R.E. (2009) Targeted lipid-coated nanoparticles: delivery of tumor necrosis factor-functionlized particles to tumor cells. J. Control. Release 137, 69-77.
- Stork, R., Campigna E., Robert, B., Müller, D. und Kontermann, R.E. (2009) Biodistribution of a bispecific single-chain diabody and its half-life extended derivatives. J. Biol. Chem. 284, 25612-25619.

Prof. Ralf Mattes

University of Stuttgart
Institute of Industrial Genetics / CSB

25 members of staff (biologists and chemists)

Its state-of-the-art equipment enables the Institute of Industrial Genetics to deal with biotechnological issues involving microorganisms and animal cells and to use molecular genetic and biochemical methods.

The priority of the projects is basic science but some practical applications may result thanks to the researchers' cooperation with academia and industry. Prof. Mattes' group primarily focuses on the specific improvement of biocatalysts, including enzymes and cells. Therefore, the methods used to genetically modify microorganisms are not specifically tailored to the laboratory organism *Escherichia coli*, but are targeted at applying existing knowledge to industrially important organisms, such as Streptomyces, Bacillus and Pseudomonas. The specific deletion and insertion of genes allows for the optimisation of microorganisms for cultivation purposes. As a result, defined metabolic interfaces can be defined and modified for the investigation of metabolic networks in complex biological systems.

Other research priorities include the analysis and construction of genetic modules for the regulated expression of genes in microorganisms that are used in industrial processes. The resolution of industry-related problems requires the use of instruments that are suitable to analyse enzymatic reactions and carbohydrates. Working in cooperation with researchers at the CNRS in Lyon (France), Prof. Mattes' group is investigating the structural basis that underlies the product specificity of sucrose isomerase and will then use this knowledge to modify the enzymes. The group has a lot of experience in producing highly pure enzymes in microbial cultures, the validation of nucleic acid contaminations in industrial processes and the diagnostic application of a broad range of reporter genes.

Selected cooperation partners

- Prof. R. Takors, Institute of Biochemical Engineering, University of Stuttgart, Germany
- Prof. B. Hauer, Institute of Technical Biochemistry, University of Stuttgart, Germany

Selected publications

- A. Wegerer, T. Sun, J. Altenbuchner. Optimization of an *E. coli* L-rhamnose-inducible expression vector: test of various genetic module combinations. BMC Biotechnol. 8:2, 2008.

E. coli expressing GFP

Dr. Monilola Olayioye

University of Stuttgart
Institute of Cell Biology and Immunology / CSB
Physiological functions of START domain proteins: From lipid transfer to tumor suppression

8 members of staff (biologists and biochemists)

Breast cancer is one of the most common causes of cancer deaths in women. Research in the lab focuses on signaling pathways underlying normal epithelial differentiation and their contribution to cell transformation when deregulated. The particular focus is on the ErbB family of receptor tyrosine kinases and the DLC family of RhoGAP proteins. The lab is furthermore interested in understanding how lipid metabolic pathways and the local composition of cellular membranes influence protein activities, signaling pathways and organelle function.

Members of the ErbB receptors are overexpressed and/or amplified in various tumor types, correlating with poor prognosis. It is now known that these receptors do not transmit signals in isolation but extensively 'cross-talk' with other classes of receptors, for example integrins. In collaboration with Prof. Joachim Spatz, Dr. Olayioye's group is investigating how the topology of the extracellular matrix cooperates with growth factors to activate integrin and ErbB receptors in a coordinated fashion. Here the researchers are using a novel nanolithographic technique that allows positioning of adhesive ligands at the nanometer scale and thus spatially controlled integrin clustering within the plasma membrane.

The DLC (Deleted in Liver Cancer) proteins are Rho GTPase-activating proteins (GAP) that have recently emerged as important tumor suppressors. In cooperation with other research groups, Dr. Olayioye's group has shown that DLC proteins play an important role in the regulation of cell motility through modulation of Rho GTPase signalling. Now the contribution of DLC loss to cellular transformation in three-dimensional cell culture systems that recapitulate aspects of epithelial differentiation is studied. Due to their multi-domain structure, it appears that DLC proteins fulfil additional GAP-independent functions that are being explored in ongoing studies. Protein profiling by antibody array has revealed that the cellular loss of the different DLC proteins leads to a unique fingerprint, reflected by the aberrant activation of distinct sets of cellular signaling pathways.

In collaboration with the group of Dr. Angelika Hausser, the group has recently shown that the ceramide transfer protein CERT is crucial for the secretory function of the Golgi complex. These findings were successfully translated to biotechnological processes to increase yields of secreted therapeutic proteins such as IgGs from mammalian cell cultures. Current projects aim to further optimize the productivity of host cells for production of biopharmaceuticals via a broad genetic engineering approach and by modelling the molecular network of key Golgi regulators (in collaboration with Prof. Nicole Radde).

Finally, the lipid composition and physical properties of cellular membranes are critical not only for organelle structure and function but also have pleiotropic effects on membrane-proximal signalling events, emanating from - for example - receptor tyrosine kinases, integrins and small GTPases. The goal of the research group is thus to understand the global effects of lipid homeostasis on signal transduction and processes related to cellular transformation such as actin cytoskeletal rearrangements, cell migration and invasion.

Special equipment and techniques

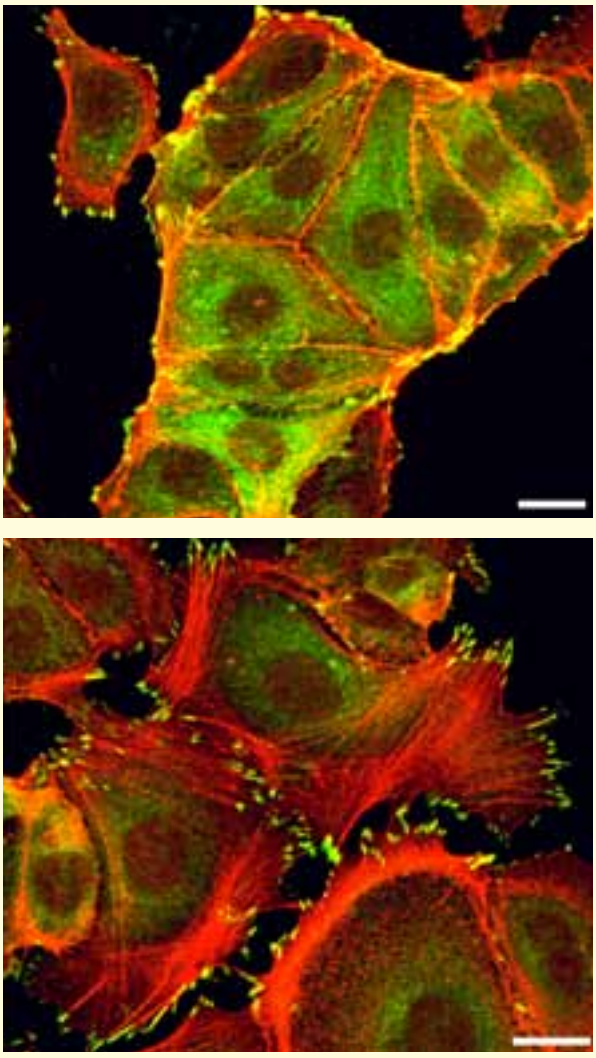
- Phosphorylation
- Protein-protein and protein-lipid interactions
- Cell migration
- 3D cell culture models

Selected cooperation partners

- Dr. Angelika Hausser, Institute of Cell Biology and Immunology, University of Stuttgart, Germany
- Dr. Tilman Brummer, ZBSA and Institute of Biology III, University of Freiburg, Germany
- Prof. Nicole Radde, Institute for Systems Theory and Automatic Control, University of Stuttgart, Germany
- Prof. Joachim Spatz, New Materials and Biosystems, Max Planck Institute for Metals Research, Stuttgart, Germany

Selected publications

- Erlmann P, Schmid S, Horenkamp FA, Geyer M, Pomorski TG, Olayioye MA. DLC1 activation requires lipid interaction through a polybasic region preceding the RhoGAP domain. Mol Biol Cell. 2009 Oct;20(20):4400-11. Epub 2009 Aug 26.
- Fugmann T, Hausser A, Schöffler P, Schmid S, Pfizenmaier K, Olayioye MA. Regulation of secretory transport by protein kinase D-mediated phosphorylation of the ceramide transfer protein. J Cell Biol. 2007 Jul 2;178(1):15-22. Epub 2007 Jun 25.
- Holeiter G, Heering J, Erlmann P, Schmid S, Jähne R, Olayioye MA. Deleted in liver cancer 1 controls cell migration through a Dia1-dependent signaling pathway. Cancer Res. 2008 Nov 1;68(21):8743-51.



Morphological changes of MCF7 breast epithelial cells lacking the tumor suppressor protein DLC1 (bottom) in comparison to control cells (top). Immunofluorescence stainings of the focal adhesion protein paxillin (green) and filamentous actin (red).

Holeiter et al., Cancer Research 2008, 68: 8743-8751.

Prof. Klaus Pfizenmaier

University of Stuttgart
Institute of Cell Biology and Immunology / CSB

Approximately 25 members of staff (biologists, chemists, physicists, mechanics engineers, systems theorists, cyberneticists and mathematicians)

The project "Systems Biology for Tissue Engineering of Mesenchymal Stem Cells: Integrating Novel Experimental Methods and Mathematical Models" is coordinated by Prof. Klaus Pfizenmaier and co-coordinated by Prof. Joachim Spatz, who is an associated member of the CSB. It addresses the development and integration of new experimental and theoretical tools to elucidate and consequently predict quantitatively mechanisms of adult stem cell differentiation subject to mechanical, biochemical and physical stimuli of the matrix. The ultimate aim is to apply the generated knowledge and established tools for tissue engineering of human mesenchymal stem cells (MSC) as a source for cartilage and bone replacement in regenerative medicine.

The project will combine High Throughput Screen (HTS) quantitative experimental methods, advanced material science technologies and high end tissue engineering with systems theory, mathematical modeling, continuum biomechanics and molecular simulation. The mathematical models of the signal pathways and the advanced continuum models that render the anisotropic mechanical force distributions impacting on the differentiating cells during tissue formation will provide a basis to guide and complement the experimental strategies.

For this purpose new experimental methods will be developed for delivering the large data sets which will correlate defined extracellular biochemical and mechanical signals presented to MSC with responses of MSC in a quantitative manner. Therefore, a particular focus will be on the design of an extracellular environment which mimics the physiological context of stem cell renewal and differentiation systematically on the basis of cell biochips. The biochips will be combined with optical microscopy for automated High-Throughput-Screens (HTS) of cell responses to systematical variation in presentation of biochemical and mechanical signals to cells. The obtained data sets will be the bases for identifying and finally predicting cell signaling pathways for MSC differentiation with the help of systems theory. Altogether, with the techniques developed, methods to determine optimum conditions for MSC proliferation and differentiation, respectively, should become available.

In a more general perspective, the HTS quantitative experimental tools and mathematical models established will be of broad applicability for basic cell biology research and systems biology approaches on questions relating to, but not only, cell adhesion and differentiation. Moreover, as a further innovation, the project will provide both experimental and mathematical tools to assess the impact of mechanical forces on cell differentiation and their integration into models describing conventional, ligand-induced signaling cascades. In this regard, systems biology acts as a key player in bridging the gap between the subcellular scale and the continuum approaches on cell/tissue level. As a long term goal, the project plans to exploit the results for large scale osteogenic and chondrogenic precursor cell production suited for clinical application.

Special equipment and techniques

- HTS microscopy
- Live Imaging
- GMP laboratories for stem cell culture

Joint research projects

- SysTec / MSC (BMBF)

Selected cooperation partners

- Prof. Joachim Spatz and Dr. Ralf Kemkemer, Department of New Materials and Biosystems, Max Planck Institute for Metals Research, Stuttgart, Germany
- Prof. Heike Walles and Dipl. Ing. Jan Hansmann, Department Cell and Tissue Engineering, Fraunhofer Institute for Interfacial Engineering and Biotechnology, Stuttgart, Germany
- Prof. Frank Allgöwer, Institute for Systems Theory and Automatic Control, University of Stuttgart, Germany
- Prof. Wolfgang Ehlers and Dr.-Ing. Bernd Markert, Institute of Applied Mechanics, University of Stuttgart, Germany
- Prof. Rolf Findeisen, Institute for Automation Engineering, Otto-von-Guericke University Magdeburg, Germany

Selected publications

- S. Bryde, I. Grunwald, A. Hammer, A. Krippner-Heidenreich, T. Schiestel, H. Brunner, G.E. Tovar, K. Pfizenmaier, P. Scheurich. Tumor necrosis factor (TNF)-functionalized nanostructured particles for the stimulation of membrane TNF-specific cell responses. Bioconjug Chem 16(6):1459-67 (Nov-Dec 2005)
- M. Arnold, V.C. Jakubick, T. Lohmüller, P. Heil, J. Blümmel, E.A. Cavalcanti-Adam, M. López-García, P. Walther, H. Kessler, B. Geiger, J.P. Spatz. Induction of Cell Polarization and Migration by a Gradient of Nanoscale Variations in Adhesive Ligand Spacing. Nano Lett 8, 2063-2069 (2008)
- W. Ehlers, B. Markert. A linear viscoelastic biphasic model for soft tissues based on the Theory of Porous Media. ASME Journal of Biomechanical Engineering 123, 418 – 424 (2001)

Prof. Jürgen Pleiss

University of Stuttgart
Institute of Technical Biochemistry / CSB
Bioinformatics

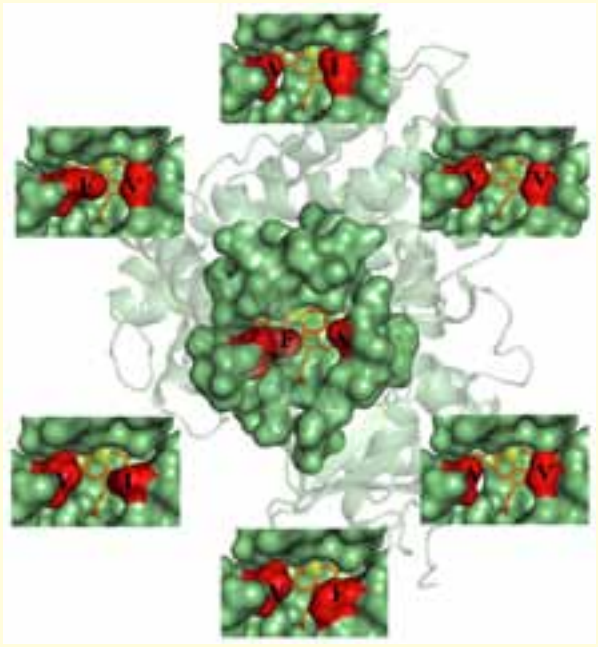
12 members of staff (technical biologists, chemists and bioinformaticians)

The research group led by Prof. Pleiss mainly focuses on investigating the molecular basis of protein properties using bioinformatics methods and molecular modelling. How can an enzyme's catalytic activity be predicted from its sequence? How does the structure of an enzyme determine its substrate specificity, chemo-, regio- and stereoselectivity? How can the effect of solvents on the properties of proteins in solution be explained?

In order to answer these questions, Prof. Pleiss' team combines two different approaches: the systematic analysis of sequences and structures of large protein families by establishing family-specific databases, and the molecular modelling of proteins and protein complexes using molecular dynamics simulations. The understanding of the molecular basis of protein properties is used in the field of white biotechnology to improve recombinant enzymes by protein design. It is also used in systems biology and metabolic engineering to predict kinetic parameters and remove bottlenecks in the metabolic flux, and in synthetic biotechnology to introduce new reactions. The research group is part of the experiment-oriented environment of the Institute of Technical Biochemistry and the Centre of Bioprocess Engineering at the University of Stuttgart. The group also works in close collaboration with research groups focused on biochemical, biotechnological and systems biology research in Germany and abroad.

Special equipment and techniques

- Perform molecular dynamics simulations using two computer clusters
- Develop protein family databases and make them available on a database server



Design of a minimal enzyme library: Modification of the access to the catalytically active haem (yellow) in a bacterial monooxygenase by modifying two hotspots (red) leads to highly selective enzyme variants.
Seifert A, Vomund S, Grohmann K, Kriening S, Urlacher VB, Laschat S, Pleiss J: Rational design of a minimal and highly enriched CYP102A1 mutant library with improved regio-, stereo- and chemoselectivity. ChemBioChem. 2009. 10: 853-861.

Prof. Matthias Reuss

Director CSB

University of Stuttgart
CSB
Metabolic Engineering & Computational Biomedicine

7 members of staff (mathematicians, physicists, process engineers and chemical engineers)

Additionally to the coordination of the Center Systems Biology (CSB) Stuttgart, the acting director is leader of the small research group "Metabolic engineering & Computational Biomedicine". This group is tightly linked with the Institute of Biochemical Engineering (IBVT).

The emphasis of the ongoing research lies at stochastic modelling and spatio-temporal diffusion processes in biosystems. The agent based modelling tools developed within the group consider the cellular and supracellular architecture for analysis of reaction coupled diffusion processes. In the analysis of hindered diffusion different obstacles are taken into account. The cytoskeleton is considered as a rigid net, whereas moving protein molecules are modelled as mobile particles. Application of this modelling concepts covers diffusion coupled signal transduction processes (MAP kinases and steroid signal transduction) and endocytosis (modelling the formation of vesicles, random and ordered movement of vesicles via motor proteins between cellular membrane and compartments).

In the FORSYS partner project "Predictive Cancer therapy" the modelling approach is being applied to the simulation of trajectories of drug molecules in the vascular system, the transvascular transport, the random walk in the interstitium and eventually the stochastic reaction between the drug and the receptors at the surface of the tumour cell. An additional modelling task aims at a quantitative description and simulation of the angiogenesis in the tumour. The group is also engaged in the modelling and simulation of the interaction between the pathogenic organism *Candida albicans* and host cells within the BMBF-funding initiative MedSys.

Joint research projects

- FORSYS-Partner (BMBF)
- MedSys (BMBF)

Selected cooperation partners

- Prof. Pfizenmaier, Institute of Cell Biology and Immunology, University of Stuttgart, Germany
- Prof. Findeisen, Institute for Automation Engineering, Otto-von-Guericke University Magdeburg, Germany
- Prof. Pichler, Laboratory for Preclinical Imaging and Imaging Technology of the Werner Siemens-Foundation, Department of Radiology, University of Tübingen, Germany
- Dr. Lippert, Bayer Technology Services GmbH, Leverkusen, Germany
- Dr. Kel, BIOBASE GmbH, Wolfenbuettel, Germany

Selected publications

- Hardiman T, Meinhold H, Hofmann J, Ewald JC, Siemann-Herzberg M, Reuss M. Prediction of kinetic parameters from DNA-binding site sequence for modeling global transcription dynamics in *Escherichia coli.* Metab Eng. 2009 Nov 4.
- Klann M, Lapin A, Reuss M. Stochastic simulation of signal transduction: impact of cellular architecture on diffusion. Biophys J. 2009 Jun 17;96(12):5122-9.
- Lapin A, Klann M, Reuss M. Multi-scale spatio-temporal modelling- lifelines of microorganisms in bioreactors and tracking molecules in cells. Adv Biochem Eng Biotechnol. 2010 Feb 6.

Junior professor Nicole Radde

University of Stuttgart
Institute for Systems Theory and Automatic Control / CSB
Systems Theory in Systems Biology

4 members of staff (physicist, microsystems engineer, technical biologist and technical cyberneticist)

The young research group 'Systems theory in systems biology' was founded in October 2008 in connection with the DFG funded Cluster of Excellence in Simulation Technology (EXC310). The group investigates analysis methods for intracellular networks and uses quantitative dynamic modeling approaches to describe regulatory mechanisms at the molecular level. A particular focus is on the development of analysis methods for feedback mechanisms and statistical approaches for network identification with sparse data. These methods are applied to biological networks.

Feedback mechanisms play an important role for the complexity of cellular processes, the ability of living organisms to adapt to various environmental changes, and their robustness against external perturbations. They regulate intracellular decision processes, can cause periodic behavior or maintain a physiological equilibrium. When two or more components mutually influence their activities, the system cannot be analyzed via separation of single parts any more, but has to be investigated as a whole. Systems Biology aims at such a holistic view, where the biological system is considered as a network of interacting cell components. Simple single-feedback mechanisms and related dynamic phenomena are already well-established, while only few methods are available for more complex networks with interlinked feedback structure. So far, these networks are mainly analyzed via heuristic approaches, which prohibits generalization of the results.

The Radde group develops such methods for model classes based on chemical reaction kinetics, which have become a standard modeling approach in systems biology in recent years. The overall goal is to get a mechanistic understanding about the functioning and robustness of intracellular processes and their role for living organisms.

The group has several cooperation projects together with experimental partners, where the focus is on modeling specific intracellular subsystems. Here, the inverse problem of parameter estimation from experimental data plays a crucial role. For quantitative models such as differential equations, which are used in the group, the available data do not contain the information to uniquely identify parameter values. This leads to ill-posed problems, for which standard methods such as least-squares or maximum-likelihood estimators fail. The group uses statistical Bayesian regularization approaches to stabilize the solution. These methods are particularly well suited for biological networks because they can handle hidden variables or allow to include uncertainties and measurement errors. On the downside, they are computationally very expensive, which soon becomes a limiting factor for applications to larger networks. This is particularly the case for nonlinear models for which the likelihood function has to be approximated by stochastic simulations and that induce conditions under which the standard sampling algorithms have poor convergence properties.

The goal is to improve the efficiency and accuracy of these statistical approaches in this respect, and to develop new methods that are particularly suited for biological settings. Here the researchers cooperate with the group of Prof. Kaltenbacher (Industrial Mathematics Institute, Johannes Kepler University Linz, Austria), who is an expert in

the field of regularization methods for ill-posed inverse problems.

The methodology is evaluated on specific biological subsystems such as for example the regulation of the secretory pathway at the trans-Golgi network in mammalian cells and the role of the protein kinase D for lipid homeostasis and vesicle formation (in cooperation with Dr. Angelika Hausser and Dr. Monilola Olayioye, Institue for Cell Biology and Immunology, University of Stuttgart), cross-talk between SRF-mediated signaling pathways in vascular smooth muscle cells (together with Prof. Alfred Nordheim, Interfaculty Institute for Cell Biology, University of Tübingen), or regulation of the spindle-assembly checkpoint at the kinetochor in yeast cells (collaboration with Dr. Silke Hauf, Friedrich-Miescher Laboratory, Max Planck Campus, Tübingen).

Joint research projects

- Cluster of Excellence in SimTech (DFG)

Selected cooperation partners

- Dr. Angelika Hausser, Institute of Cell Biology and Immunology, University of Stuttgart, Germany
- Dr. Monilola Olayioye, Institute of Cell Biology and Immunology, University of Stuttgart, Germany
- Prof. Alfred Nordheim, Interfaculty Institute for Cell Biology, University of Tübingen, Germany
- Prof. Barbara Kaltenbacher, Institute for Mathematics and Scientific Computing, University of Graz, Austria
- Dr. Silke Hauf, Friedrich Miescher Laboratory, Max Planck Campus Tübingen, Germany

Selected publications

- Kramer A., Radde N., 2010. Optimal experimental design using a Bayesian framework for parameter identification in dynamic intracellular network models. Proc. of the International Conference on Computational Science (ICCS2010), to appear.
- Radde N., 2008. The impact of time-delays on the robustness of biological oscillators and the effect of bifurcations on the inverse problem. Eurasip Journal on Bioinformatics and Systems Biology, vol. 2009, article ID 327503, doi:10.1155/2009/327503.
- Radde N., Bar N.S., Banaji M., 2009. Graphical methods for analysing feedback in biological networks - A survey. Int. J. Syst. Sci., vol. 41, issue 1, 35.

Junior professor Oliver Röhrle

University of Stuttgart
Institute of Applied Mechanics / associated with the CSB
Continuum Biomechanics and Mechanobiology

3 members of staff (mathematicians, environmental and biomedical engineers)

The expertise and the focus of the Junior Research Group „Continuum Biomechanics and Mechanobiology" at the Cluster of Excellence in Simulation Technology (SimTech) is on multi-scale modelling of biological soft tissue. The grand challenge, like in many other biomedical applications, is the fact that physiological and anatomically realistic simulations need to consider effects stemming from different temporal and spatial scales. For example, in the case of modelling the mechanical behaviour of a skeletal muscle, an action potential along a skeletal muscle fibre determines the contractile sate of a single sarcomere (a contractile unit within a skeletal muscle fibre and therefore can produce force) and, hence, influences the overall mechanical behaviour of an entire muscle. A sarcomere has a length of about 2.4 μm while the length of skeletal muscle fibre or a muscle typically ranges in the centimetre scale. A computational model that would require a spatial resolution equivalent to that of a single sarcomere would exceed the computational limits and resources even on modern high-performance computers. Homogenisation and multi-scale techniques need to be developed to realistically describe small scale phenomena on larger scales.

The electromechanical skeletal muscle model developed by Junior professor Oliver Röhrle is one example how different scales can be coupled. On the cellular scale, a model describing the electrophysiological properties of a single sarcomere has been coupled to the biomechanical behaviour of an entire muscle. The complex interactions in the biological system of a single sarcomere have been modelled using tools developed in the field of systems biology. In this example, the coupling was achieved by including homogenised cellular parameters, which are associated with contractile states on the cellular level, into the constitutive law that describes the mechanical properties of skeletal muscle tissue on the larger scale, the so-called organ scale. Within this framework, the great advantage of using system biology and its tools to describe phenomena on the cellular level is the fact that the cellular models can be exchanged and adopted to different cases without changing much or any of the existing biomechanical framework. For example, if the influence of a particular drug or of a particular disease should be tested with respect to the exerted muscle force, one can 'simply' adapt in collaboration with system biologists the respective biological interactions within the cellular model. Hence, system biology allows for much more flexibility, greater areas of application, and more accurate simulations and predictions.

To improve existing multi-scale models for biological (soft) tissue, future research has to focus on the interface between systems biology and biomechanical applications by carefully investigating the interactions between large-scale and small-scale phenomena, for example the interactions of mechanical stimuli stemming from a network of cells or a whole organ with the effects of signal transduction.

Special equipment and techniques

- Multiscale Modelling
- Finite Element software engineering
- Markup languages

Joint research projects

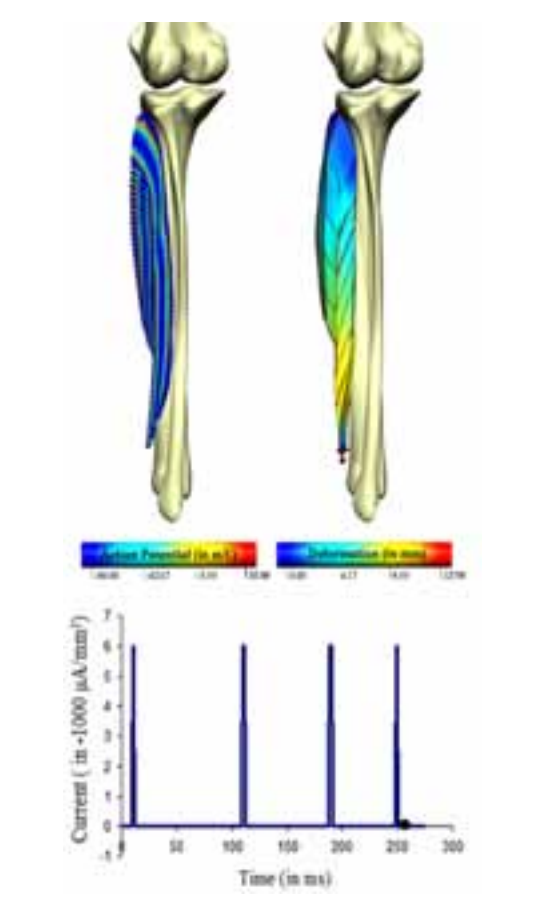
- Cluster of Excellence in SimTech (DFG)

Selected cooperation partners

- Junior professor Nicole Radde, Institute for Systems Theory and Automatic Control, University of Stuttgart, Germany
- Dr. Syn Schmitt, Institute for Sports and Movement Science, University of Stuttgart, Germany
- Prof. Peter Hunter, Auckland Bioengineering Institute, The University of Auckland, New Zealand
- Prof. Richard Hall, Institute of Medical and Biological Engineering, University of Leeds, UK
- Prof. Clayton Adam, Institute of Health and Biomedical Engineering, Queensland University of Technology, Australia

Selected publications

- Röhrle O. Simulating the Electro-Mechanical Behavior of Skeletal Muscles. IEEE Computing in Science and Engineering, DOI 10.1109/MCSE. 2010.30.
- Röhrle O, Davidson JB and Pullan AJ. Bridging Scales: A Three-dimensional Electromechanical Finite Element Model of Skeletal Muscle. SIAM Journal on Scientific Computing, Volume 30 (6), 2008.



Above (left): Distribution of the action potential as a solution of the cellular model within a computational model of the Tibialis Anterior. The current depicted in the bottom picture has been injected at each computational fibre point closest to the location of the neuromuscular junction. This mimics the simultaneous stimulation of each muscle fibre within the muscle. Above (right): Resulting deformation based on calculations on the cellular level (e.g. the action potential distribution) and computed resulting muscle force (red arrow).

Dr. Steffen Rupp

Fraunhofer Institute for Interfacial Engineering and Biotechnology, Stuttgart / associated with the CSB
Molecular Biotechnology

Approximately 45 members of staff (biologists, chemists and bioinformaticians)

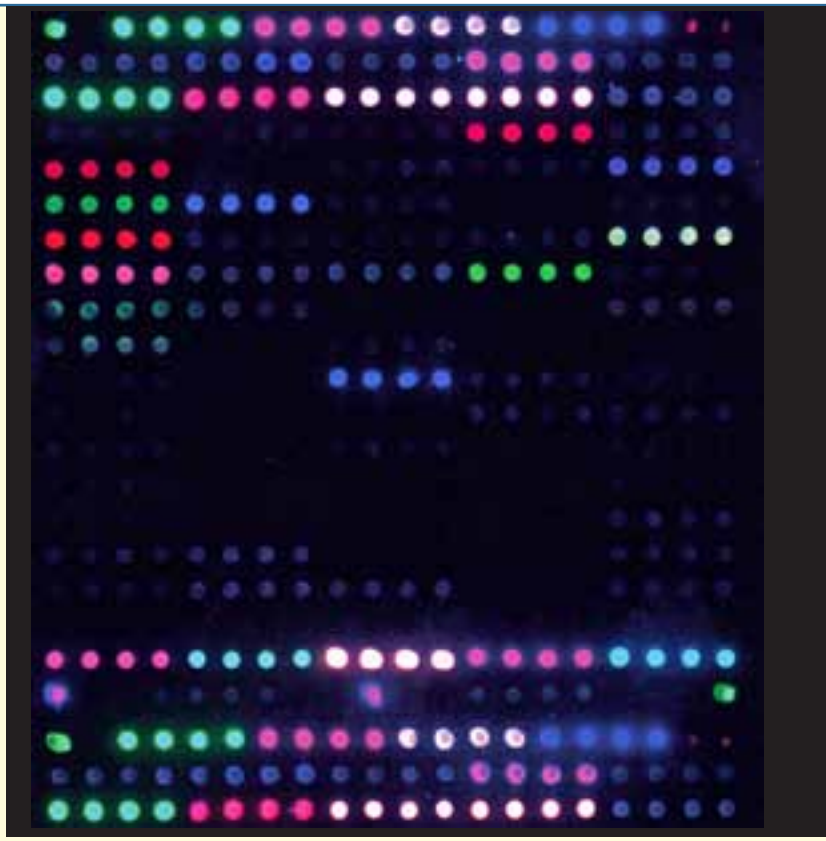
One of the key competences of the Department of Molecular Biotechnology at the Fraunhofer IGB is comprehensive expertise in the virulence mechanisms of human pathogenic fungi. The major research focus is the interaction between host and pathogen related to *Candida spp. (C. albicans and C. glabrata)* infections.

Using *in vitro* adhesion and invasion models, the research group has investigated the adaptation of the fungus to different host niches (Sohn et al, 2006). Using genome-wide transcription and proteome analyses to investigate host-pathogen interactions, the researchers found that *C. albicans* is able to specifically adapt to different conditions, for example when grown on different epithelia. The DNA microarrays used for the analysis of *C. albicans* and *C. glabrata* gene expression were developed and manufactured at the Fraunhofer IGB (Hauser et al, 2009). This work is an important basis for carrying out and analysing infection studies involving immune cells.

Another major research focus of the Fraunhofer IGB is the comprehensive identification and quantitative analysis of all cell surface proteins expressed and factors secreted by human pathogenic fungi. Using a specific protocol for preparing mass spectrometry samples from fungi and yeasts, the group was able to determine the secretome and the cell wall proteome of *C. albicans* under different physiological conditions (Hiller et al, 2007). The method is also well suited to the analysis of the secretome of infected epithelia.

In addition, the research group is developing universal methods for genome-wide gene expression analyses of any type of eukaryotic organism. These methods are based on an open architecture and enable the analysis of complex cDNA samples using two-dimensional DNA gel electrophoreses and "next generation" sequencing (Lindemann et al, 2010). Using these methods, the researchers now are enabled to simultaneously analysing, with high sensitivity, transcription profiles of human pathogenic fungi and infected host cells. These methods thus form the basis for global parallel transcriptome studies focusing on host-pathogen interactions (meta-transcriptome).

The Department of Molecular Biotechnology at the Fraunhofer IGB is involved in national and international projects dealing with host-pathogen interactions of human pathogenic yeasts and fungi. These projects are supported by the EU (in particular under FP6), ERA-NET Pathogenomics and the BMBF ("Basic innovations in genome-based infectious research" and "Medical systems biology"). In addition, the department is working on two subprojects under the SPP1160 DFG priority programme entitled "Colonisation and infection with human pathogenic fungi". The department also receives funds from the Baden-Württemberg Biotechnology funding programme to establish new technology platforms for the universal gene expression analysis using next-generation sequencing. Based on this know-how, the researchers have for the last few years been focusing on metabolic engineering, in particular the metabolic engineering of fungi used in industrial biotechnology. The department participates in cooperative projects focusing on the production of biosurfactants and of basic polymer components.



Special equipment and techniques

- Cell culture and microarray facilities: arrayers (Microgrid II, Biorobotics, GSM417), array scanners (GenePix 4300A, GSM 418, ArrayWorx)
- LC-ESI-MS/MS
- MALDI-TOF/TOF
- Accredited analytics for metabolome analyses
- GMP facilities for the controlled production of human cell systems and tissues

Joint research projects

- ERA-NET PathoGEnoMics: FunPath/Glycoshield (BMBF)
- MedSys (BMBF)

Selected cooperation partners

- Prof. Matthias Reuss, CSB, University of Stuttgart, Germany
- Prof. Klaus Schröppel, Institute of Microbiology and Infection Medicine, University of Tübingen, Germany
- Prof. Ursula Bilitewski, Target Identification, Helmholtz Centre for Infection Research, Braunschweig, Germany
- Dr. Peter Pohl, GATC Biotech AG, Konstanz, Germany
- Prof. Karl Kuchler, Abteilung für Molekulare Genetik, Medical University Vienna, Austria

Selected publications

- Sohn K, Senyürek I, Fertey J, Königsdoefer A, Joffroy C, Hausser N, Zelt G, Brunner H, Rupp S. (2006). An *in vitro*-assay to study the transcriptional response during adherence of *Candida albicans* to different human epithelia. FEMS Yeast Research, 6:1085-93.
- Hauser NC, Dukalska M, Fellenberg K, Rupp S. (2009). From experimental setup to data analysis in transcriptomics: copper metabolism in the human pathogen *Candida albicans.* J Biophotonics. 2(4):262-8.
- Hiller E, Heine S, Brunner H, Rupp S. (2007). *Candida albicans* Sun41p, a putative glycosidase, is involved in morphogenesis, cell wall biogenesis, and biofilm formation. Eukaryot Cell 6: 2056-2065.

Prof. Oliver Sawodny

University of Stuttgart
Institute for System Dynamics / CSB

35 members of staff
(7 systems biologists: engineers, biologist, bioengineer, biomathematician and systems scientist)

The Institute for System Dynamics (ISYS) is an engineering institute of the University of Stuttgart. Head of the systems biology group is Dr. Michael Ederer. The ISYS focuses on the analysis of the dynamics of systems originating from such different fields like mechatronics, process technology and biology, as well as on the possibilities of intervention in such systems. Thus the interdisciplinary team integrates sciences of many kinds. The unifying element is the mathematical modelling of the studied systems that allows one to abstract from the physics of the system and to apply the methods of mathematical system and control theory.

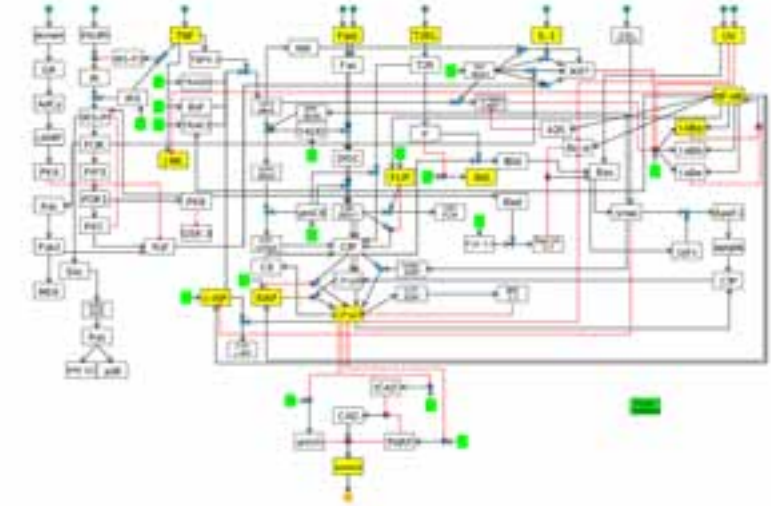
The Institute defines systems biology as the application and development of systems theoretic methods in biology. The focus is on mathematical modelling, model reduction and model analysis of intracellular metabolic and signal transducing networks. For this purpose theoretical and experimental studies are conducted. In all projects, the systems biology group closely cooperates with partners from the biological sciences.

One goal of the systems biology group of the ISYS is to explore the design principles that underlie complex biochemical networks. Mathematical models are especially suited for this task because they allow integrating existing knowledge of the system and measurement data. On the basis of the models one can plan new experiments that promise a maximum amount of additional information. Computational simulations can predict the results of the new experiments. The comparison of the predicted and the experimental results gives hints to erroneous or incomplete aspects of the model. In the next step one corrects the model and plans and conducts new experiments. The iterative cycle of experimental and modelling work reveals unknown aspects of the system, as e.g. unknown regulatory interactions. In this way, the project partners are supported by the biological sciences in the exploration of biological regulation.

The analysis problem is complemented by a respective design problem: How one needs to change a biochemical network such that its behaviour changes in a wanted fashion. Such problems occur in bioengineering, which e.g. optimizes microorganisms for the production of fine chemicals, but also in medicine that studies the targeted invention into diseased systems. Based on a mathematical model, one can study and design intervention, as e.g. genetic modifications or the addition of drugs. In this way, one can minimize the experimental effort and optimize the intervention into the biological system.

In cooperation with all research partners, the group works in the above mentioned fields by means of several example systems. Because of their relative simplicity, bacterial systems are especially suited for the development of systems biological methods. Parts of the metabolism of the bacteria *Rhodospirillum rubrum* and *Escherichia coli* are studied and methods are explored for the modelling of metabolic networks and their regulation, as well as their redesign into production strains. Further the sugar metabolism of the plant *Arabidopsis thaliana* is studied with the goal to reveal mechanisms of cold tolerance. A further focus is the modelling of signal transduction in human cells. Here, the

group is especially interested in the regulation of apoptosis, the programmed cell death. Apoptosis is an important process that removes diseased or not needed cells from the body in a controlled way. The decision if a certain cell goes to apoptosis is made by a complex intracellular network and is influenced by several other signalling pathways. Defects in the regulation of apoptosis are responsible for several diseases. The group addresses the specific problems that occur in the above mentioned example systems by developing novel system biological methods.



Boolean Model of Apoptosis. (Schlatter R. et al. (2009) ON/OFF and Beyond - A Boolean Model of Apoptosis. PLoS Comput Biol 5(12): e1000595. doi:10.1371/journal.pcbi.1000595)

Special equipment and techniques

- Bioreactors and programmable control system
- HPLC, IC and MS
- Dedicated computers for computationally expensive tasks

Joint research projects

- DYNAMO (BMBF)
- FORSYS-Partner (BMBF)
- InKoMBio (DFG)
- SysMO (BMBF)
- Virtual Liver (BMBF)

Selected cooperation partners

- Prof. Sprenger, Institute of Microbiology, University of Stuttgart, Germany
- Prof. Merfort, Institute for Pharmaceutical Sciences, University of Freiburg, Germany
- Prof. Gilles, Dr. Bettenbrock and Dr. Grammel, Max Planck Institute for Dynamics of Complex Technical Systems, Magdeburg, Germany
- Prof. Poole and Prof. Green, Molecular Biology and Biotechnology, University of Sheffield, UK
- Prof. Teixeira de Mattos, Swammerdam Institute for Life Sciences, University of Amsterdam, The Netherlands

Selected publications

- Witt J, Barisic S, Schumann E, Allgöwer F, Sawodny O, Sauter T, Kulms D. Mechanism of PP2A-mediated IKK beta dephosphorylation: a systems biological approach. BMC Syst Biol. 2009 Jul 16;3:71.
- Schlatter R, Conzelmann H, Gilles ED, Sawodny O, Sauter T. Analysis of an apoptotic core model focused on experimental design using artificial data. IET Syst Biol. 2009 Jul;3(4):255-65.
- Schlatter R, Schmich K, Avalos Vizcarra I, Scheurich P, Sauter T, Borner C, Ederer M, Merfort I, Sawodny O. ON/OFF and beyond - a boolean model of apoptosis. PLoS Comput Biol. 2009 Dec;5(12):e1000595. Epub 2009 Dec 11.

Prof. Peter Scheurich

University of Stuttgart
Institute of Cell Biology and Immunology / CSB
Molecular Immunology

8 members of staff (biologists)

The major focus of Prof. Scheurich's research group is to gain a quantitative understanding of death-receptor-mediated cell death, i.e. the cellular programme of apoptosis. All projects focusing on aspects related to systems biology are carried out in cooperation with systems scientists. However, some of the modelling work is done by Prof. Scheurich's research group.

One project focuses on the development and the analysis of a minimised mathematical model of the apoptotic activation of the caspase cascade. Another project has been set up to gain a quantitative understanding of the formation of large TNF/TNF receptor complexes on the cell membrane. Other research projects deal with intracellular signal transduction networks such as that induced by the joint stimulation of the two different TNF membrane receptors, TNFR1 und TNFR2. In this project, the major focus is on the cytoplasmic adapter protein TRAF2 that plays a key role in the regulation of the apoptotic TNFR1/TNFR2 crosstalk. The research group has also developed mathematical models of TNF-mediated activation of NF-κB (nuclear factor kappa B) transcription factor as well as models of the so-called intrinsic apoptotic signalling pathway in which the mitochondria play a key role.

Another major research focus of Prof. Scheurich's group is the understanding of the behaviour of cell populations. In typical cell biological assays, not all cells react identically. Such a heterogeneity can be also observed in the treatment of tumour patients. In patients undergoing anti-cancer therapy, some tumour cells will survive, which can be subsequently eliminated by the patient's immune response. The behaviour of cell populations is investigated in different models. One of the approaches focuses on the establishment of a cell-ensemble model to simulate a virtual cell population of 1000 cells, for example. Care must be taken that the individual cells differ from each other. Stochastic gene expression, typically leading to a log-normal distribution of the protein amounts in individual cells of the population, leads to cell-to-cell variations, even between cells of a clonal population. The log-normal distribution of protein concentrations can, for example, be directly monitored in a cytofluorograph using fluorophore-labelled antibodies. Based on such data, and supported by sensitivity analyses, some key proteins involved in the modelled signalling pathways were given a log-normal distribution. Initial evaluations of the resulting population model demonstrated its capability to describe programmed cell death of some, but not all, cells of a clonal cell population observed in experiments after application of small doses of the apoptosis inducing cytokines TNF or TRAIL (TNF-related apoptosis inducing ligand).

Special equipment and techniques

- Live Cell Imaging
- Microinjection

Joint research projects

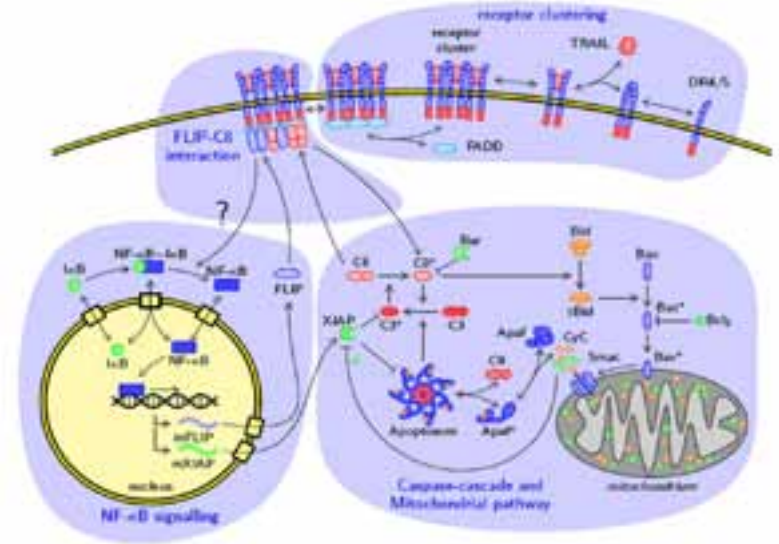
- Cluster of Excellence in SimTech (DFG)
- FORSYS Partner (BMBF)

Selected cooperation partners

- Prof. Frank Allgöwer, Institute for Systems Theory and Automatic Control, University of Stuttgart, Germany
- Prof. Christian Rhode and Dr. Christina Surulescu, Institute for Applied Analysis and Numerical Simulation, University of Stuttgart, Germany
- Prof. Eric Bullinger, Institute Montefiore, University of Liège, Belgium
- Prof. Rolf Findeisen, Institute for Automation Engineering, Otto-von-Guericke University Magdeburg, Germany
- Prof. Oliver Sawodny, Institute for System Dynamics, University of Stuttgart, Germany

Selected publications

- Eißing T, Conzelmann H, Gilles ED, Allgöwer F, Bullinger E, Scheurich P. Bistability analyses of a caspase activation model for receptor-induced apoptosis. J Biol Chem. 279 (2004) 36892-36897.
- Schliemann M, Eißing T, Scheurich P, Bullinger E. Mathematical modelling of TNF- induced apoptotic and anti-apoptotic signalling pathways in mammalian cells based on dynamic and quantitative experiments. 2nd Foundations of Systems Biology in Engineering FOSBE 2007, Stuttgart, Germany, 9-12 September 2007, pp. 213-218.



Death-receptor-mediated intracellular signalling pathways.

- Schlatter R, Schmich K, Avalos Vizcarra I, Scheurich P, Sauter T, Borner C, Ederer M, Merfort I, Sawodny O. ON/OFF and beyond - a boolean model of apoptosis. PLoS Comput Biol. 5 (2009): e1000595. Epub.

Prof. Georg Sprenger

University of Stuttgart
Institute of Microbiology / CSB

22 members of staff (biologists, microbiologists and chemists)

The major focus of the Institute of Microbiology at the University of Stuttgart is the investigation of the metabolic activities of microorganisms, in particular those of bacteria (*Escherichia coli, Pseudomonas species, Sphingomonas, Xanthomonas*). The institute is also investigating the bacterial enzymes involved in peripheral and central metabolic pathways by using biochemical and molecular biology (directed evolution) methods.

In addition to the degradation of substances such as caoutchouc, geraniol and PHB (research group led by Prof. Jendrossek), the group is highly interested in the production of substances such as amino acids, vitamins or fine chemicals using recombinant *Escherichia coli* cells.

As there are no modellers at the Institute of Microbiology, the institute works in cooperation with systems biology groups, such as those of Prof. Dr.-Ing. Matthias Reuss and his successor at the IBVT, Prof. Dr.-Ing. Ralf Takors, to model metabolic pathways in recombinant *Escherichia coli* cells.

As part of a CSB project, the group is studying evolutionary adaptation of the pyruvate auxotrophs of *E. coli* using microbiological, genetic and systems biology methods (in cooperation with Prof. Dr.-Ing. Oliver Sawodny, ISYS, University of Stuttgart). At a later date, Prof. Dr.-Ing. Bossert's research group (University of Ulm) will join the project and will focus on the regulation of metabolic pathways in *E. coli* (new DFG priority programme on Information and Communication Theory in Molecular Biology, InKomBio). In a BMBF-funded project (Systems Biology in *Pseudomonas* for Industrial Biocatalysis), the researchers will focus on the systems biology of *Pseudomonas putida* to investigate whether the bacteria can be used for the production of useful substances.

In general, systems biology contributes to a better understanding of microbial metabolic pathways and production organisms. Following their research, the researchers at the Institute of Microbiology will use the experimental data to feed them into systems biology models.

The institute is equipped with standard equipment for microbiological and molecular biological investigations as well as with HPLCs, GCs, small fermenters and UV/VIS spectrophotometers that are used for the acquisition and analysis of data.

Special equipment and techniques

- HPLC
- GC
- Small fermenters
- UV/VIS spectrophotometers

Joint research projects

- InKoMBio (DFG)
- Systems Biology in *Pseudomonas* for Industrial Biocatalysis (BMBF)

Selected cooperation partners

- Prof. Sawodny, Institute for System Dynamics, University of Stuttgart, Germany

Selected Publications

- Vallon, T., Ghanegaonkar, S., Vielhauer, O., Müller, A., Albermann, C., Sprenger, G., Reuss, M., Lemuth, K. (2008) Quantitative analysis of isoprenoid diphosphate intermediates in recombinant and wild-type *Escherichia coli* strains. Applied Microbiology and Biotechnology, 81: 175-182.

Prof. Christina Surulescu

University of Stuttgart
Institute for Applied Analysis and Numerical Simulation / associated with the CSB Biomathematics

4 members of staff (mathematicians)

The Biomathematics group at the Institute for Applied Analysis and Numerical Simulation investigates various issues in connection with pattern formation, cell migration and intracellular signaling pathways.

The aim of one of the research projects is to develop, analyze, implement and test mathematical models for biological processes which are conditioned by cellular signaling pathways. Thereby the focus is on chemotactic phenomena and on cell migration, both for the simpler case of bacteria and for tumor cells. The migration process of the latter is more complicated, due to the interaction with the surrounding tissue, leading to different moving regimes: amoeboid and mesenchymal. Intracellular factors like the production and activity of HSP heat shock proteins also play a crucial role in cancer cell invasion, which can also be acid mediated and dependent on the normal cell density.

Unlike most of the existing models Dr. Surulescu's group aims for a multiscale approach, since cell migration is a process occuring at the subcellular level (signaling pathways), but also as mutual cell interactions and at the level of populations. The main issue is to provide answers to a difficult question: how to mathematically convey the outcome of intracellular dynamics (microscopic level) to the behavior of the entire cell population (macroscopic level).

At the subcellular level the Biomathematics group develops mathematical models with the aid of (stochastic) differential equations and applies/improves various parameter estimation techniques which should enable making data based predictions about the corresponding biochemical processes.

A further research project aims to investigate the first steps in TNF (tumor necrosis factor) induced signal transduction. Thereby the focus is on the onset of the ligand/receptor interaction and subsequent formation of signal clusters which initiate intracellular signals eventually leading to cell death (apoptosis). Mathematical models are developed in order to describe the relevant mechanisms involved in this process. Enhanced knowledge is expected to be aquired from the mathematical analysis and numerical simulations of these models, leading to a better understanding of the constraints regulating the differential behavior of the two identified TNF receptors when binding the ligand TNF. The project is located at the interface between applied mathematics and cell biology and is pursued in tight collaboration with the group of Prof. Peter Scheurich (Institute of Cell Biology and Immunology, University of Stuttgart). The expertise of the partners from Biology provides the Biomathematics group with invaluable suggestions on adequately choosing the parameters: eventually the mathematical models are to be validated by comparing the predictions with experimental data.

Joint research projects

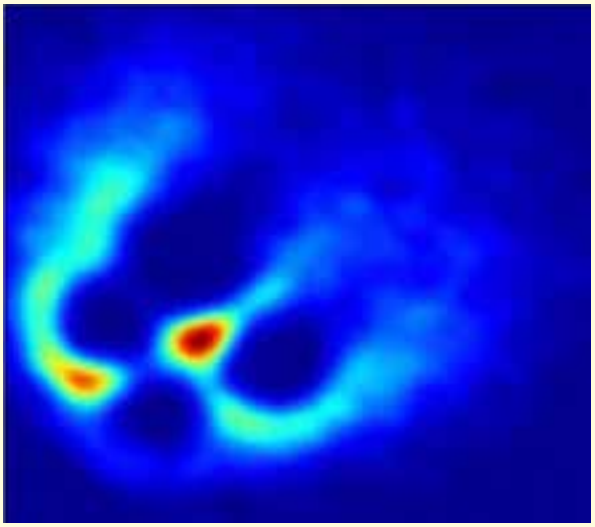
- Cluster of Excellence in SimTech (DFG)

Selected cooperation partners

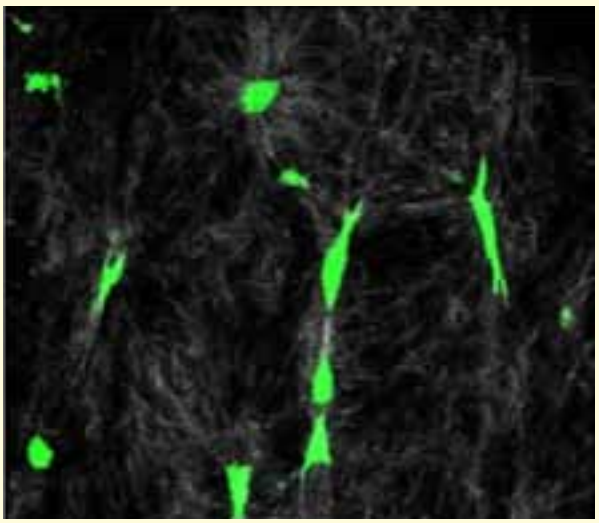
- Prof. Ing. Frank Allgöwer, Institute for Systems Theory and Automatic Control, University of Stuttgart, Germany
- Prof. Thomas Hillen, Department of Mathematical and Statistical Sciences, University of Alberta, Edmonton, Canada
- Prof. Miroslaw Lachowicz, Institute of Applied Mathematics and Mechanics, University of Warsaw, Poland
- Prof. Peter Scheurich, Institute of Cell Biology and Immunology, University of Stuttgart, Germany
- Prof. Guido Schneider, Institute for Analysis Dynamics and Modeling, University of Stuttgart, Germany

Selected publications

- C. Surulescu, N. Surulescu. A nonparametric approach to cell dispersal. International J. of Biomathematics and Biostatistics 1 (2010) 109 128.
- J. Kelkel, C. Surulescu. On a stochastic reaction diffusion system modeling pattern formation on seashells. Journal of Mathematical Biology 60 (2010) 765-796.
- J. Kelkel, C. Surulescu. A multiscale approach to cell migration in tissue networks. IANS preprint 3 (2010), submitted to Math. Models and Methods in the Applied Sciences.



Numerical simulation of the density of a bacterial population moving around four obstacles.



Tumor cells moving through a tissue.

Prof. Ralf Takors

University of Stuttgart
Institute of Biochemical Engineering / CSB

25 members of staff (technical biologists, environmental (process) engineers, process engineers, bioinformaticians and mathematicians)

The Institute of Biochemical Engineering (IBVT) at the University of Stuttgart develops new bioprocesses for application in "white" (industrial) and "red" (pharmaceutical) biotechnology. The bioprocesses are based on the quantitative understanding of biological systems. In the development process, the scientists use either isolated enzymes, bacterial cell systems or mammalian cells for the biotechnological production of fine or bulk chemicals and pharmaceutically active substances. The process involves the optimisation of already existing processes, the development of alternative methods and/or the development of completely new approaches, for example through the application of synthetic biology.

A detailed understanding of the cellular metabolism and the regulation and interaction with closely connected environmental conditions is the basis for the efficient development of bioprocesses. Achieving a quantitative understanding of cells is part of systems biology research, which is implemented in genome-scale models, for example. One major focus is the model-assisted coupling of metabolic and transcriptional networks in order to achieve a cell model that is as comprehensive as possible.

Systems biology investigations of microbial systems have traditionally played a pioneering role, as the cells, which are less complex than those of higher organisms, have often been the object of initial studies. However, the IBVT has been able to successfully use important systems biology tools for the quantitative investigation of complex liver cells. As a result, the simultaneous investigation of microbial and mammalian cell systems in systems biology studies will also become a big part of the IBVT's activities in future.

In order to be able to use a data basis for modelling that is as broad as possible, the IBVT carries out fermentations on the scale of 100 mL to 300 L. The Institute specialises in assessing intracellular metabolites in a comprehensive analytical way that is as quantitative as possible. For this purpose, the Institute has at its disposal numerous mass spectrometric devices such as GC-MS and LC-MS/MS, for which the respective methods are constantly being further developed. These tools are also used for the analysis of ^{13}C-labelled metabolites. For example, the IBVT scientists have successfully developed an innovative approach for the analysis of instationary, i.e. temporally transient ^{13}C labelling patterns for substance flow analysis. This approach enables intracellular substance flow distributions in biological systems to be determined in relatively short labelling periods. This represents a valuable basis for systems biology investigations.

Besides the aforementioned activities, the IBVT also focuses on dynamic systems analyses. Cell systems are boosted so that the dynamic cell response provides information about metabolic and transcriptional regulation. These data will of course also be used for dynamic modelling activities.

The IBVT also continuously develops new modelling methods for the description of biological systems. Current examples include the successful simulation of the

control of key metabolic genes through the cra-modulon in *E. coli* through the use of genome sequence analyses and the establishment of innovative approaches for the reverse engineering of regulatory networks on the basis of temporally transient transcription datasets.

Special equipment and techniques

- Fermenters (100 ml – 300 l)
- Mass spectrometric devices such as GC-MS and LC-MS/MS
- Analysis of ^{13}C-labelled metabolites

Joint research projects

- BaCell (BMBF)
- FORSYS-Partner (BMBF)
- MedSys (BMBF)
- SYSINBIO (EU)
- SysMO (BMBF): BaCell-SysMO, COSMIC, PSYSMO

Selected publications

- Hardiman T, Meinhold H, Hofmann J, Ewald J, Siemann-Herzberg M, Reuss M. (2009): Prediction of kinetic parameters from DNA-binding site sequences for modeling global transcription dynamics in *Escherichia coli.* Metab. Eng. Doi:10.1016/j.ymben.2009.10.006
- Schuhmacher T, Lemuth K, Vacun G, Hardiman T, Reuss M, Siemann-Herzberg M. (2009): Quantifying cytosolic mRNA concentrations in *Escherichia coli* using real-time PCR for a systems biology approach. Anal. Biochem. Doi: 10.1016/j.ab.2009.11.025
- Maier K, Hofmann U, Bauer A, Niebel A, Vacun G, Reuss M, Mauch K. (2009): Quantification of statin effects on hepatic cholesterol synthesis by transient ^{13}C-flux analysis. Metabolic Engineering 11 292-309.

One of the 300-l fermenters in the laboratory of the Institute of Biochemical Engineering.

Prof. Dieter H. Wolf

University of Stuttgart
Institute of Biochemistry
Ubiquitin Proteasome System

10 members of staff (biologists and chemists)

Selective protein degradation triggered by the ubiquitin-proteasome-system (UPS) is a central regulatory mechanism in higher eukaryotic cells. Two such UPS regulated processes are of special interest to Prof. Wolfs research group: (i) regulation of carbohydrate metabolism (Santt et al., 2008) and (ii) regulation of protein homeostasis, protein quality control and elimination of misfolded proteins (protein waste) (Park et al., 2007; Stolz and Wolf, 2010). Dysregulation of any of these two processes causes severe diseases in humans. Dysregulation of the carbohydrate metabolism causes diabetes, a mistaken protein homeostasis and protein quality control, among other diseases, leads to cancer and neurodegenerative diseases as for instance Alzeimer-, Parkinson- or Creutzfeld-Jakob disease.

For the study of the molecular basis of UPS-triggered carbohydrate regulation and cellular protein quality control, the yeast *Saccharomyces cerevisiae* is used. This eukaryotic model organism is easily amenable to a multitude of biological, biochemical and physical methods. Furthermore, the best studied biological network of higher cells is the yeast network.

The data of the database „BioGrid“, available for the studied processes, are significantly refined in cooperation with Dr. Wolfgang Hilt and the results are transfered into practical cell based research to get a detailed understanding of the processes. Among others, a novel analytical method, AquaSpec™ technology, based on mid infrased spectroscopy, will be applied to unravel the cellular proteome patterns. Understanding of the regulatory networks may finally lead to the development of pharmaceuticals to treat the human diseases connected to these networks.

Special equipment and techniques

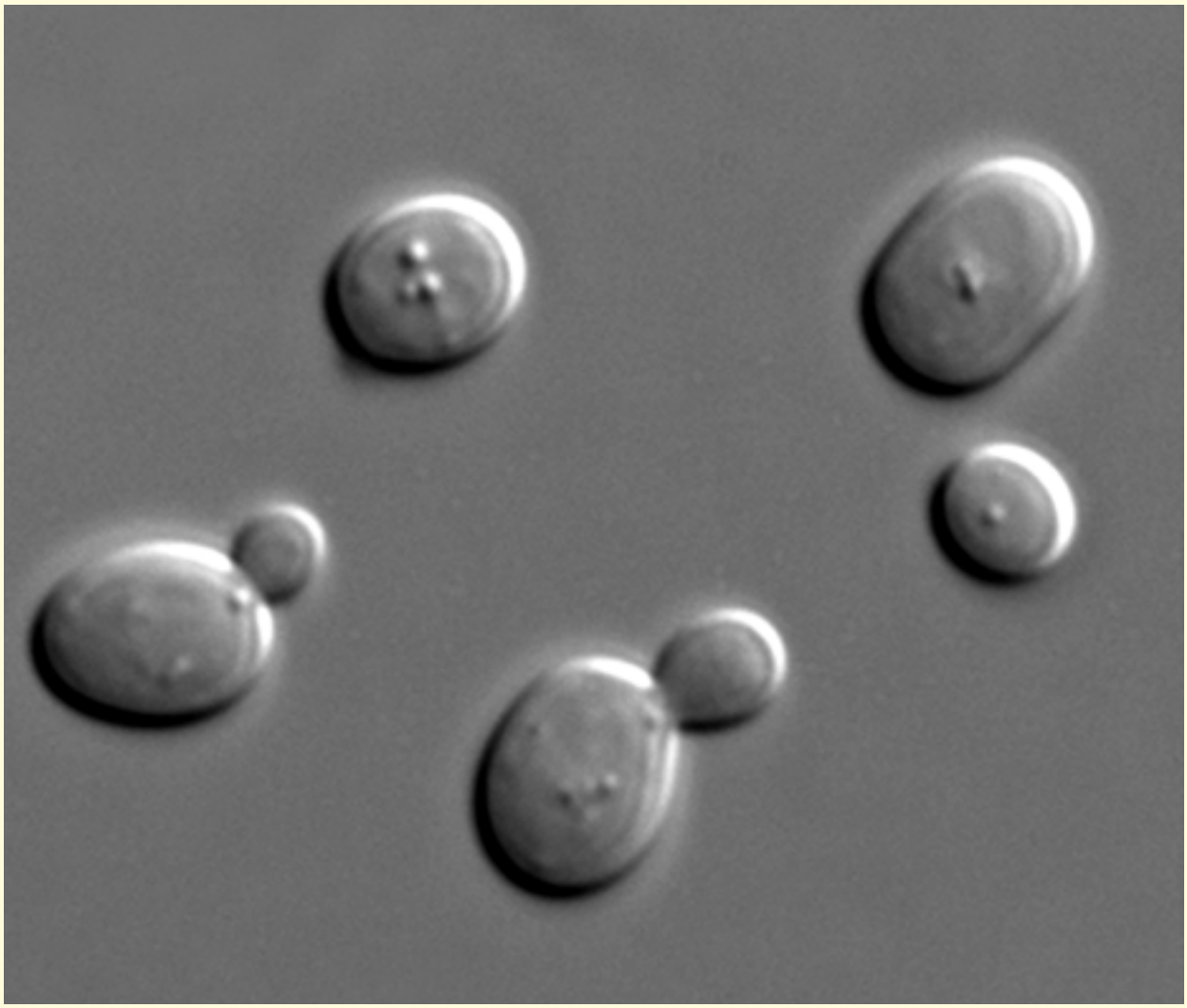
- Liquid-FTIR spectroscopy
- Computer-based analysis (AquaSpec ™ Technology; Micro-Biolytics)

Selected cooperation partners

- Dr. Wolfgang Hilt, Institute of Biochemistry, University of Stuttgart, Germany
- Micro-Biolytics GmbH, Esslingen am Neckar, Germany

Selected publications

- Santt O, Pfirrmann T, Braun B, Juretschke J, Kimmig P, Scheel H, Hofmann K, Thumm M, Wolf DH. (2008) The yeast GID complex, a novel ubiquitin ligase (E3) involved in the regulation of carbohydrate metabolism. Mol. Biol. Cell, 19, 3323-3333.
- Stolz A, Wolf DH. (2010) Endoplasmic reticulum associated protein degradation: a chaperone assisted journey to hell. Biochim. Biophys. Acta Mol. Cell Res., 1803, 694-705.
- Park SH, Bolender N, Eisele F, Kostova Z, Takeuchi J, Coffino P and Wolf DH. (2007) The cytoplasmic Hsp70 chaperone machinery subjects misfolded and ER import incompetent proteins to degradation via the ubiquitin-proteasome system. Mol. Biol. Cell 18, 153-165.



Saccharomyces cerevisiae, a model organism

Prof. Jörg Wrachtrup

University of Stuttgart
3rd physics institute / associated with the CSB
Biophysics group

3 members of staff (1 physicist, 1 biologist and 1 biochemist)

The biophysics group at the 3rd physics institute investigates biomolecules with single molecule methods *in vivo, in vitro* and *in silico*. Areas of interest are for example the investigation of the interaction of membrane proteins with their lipid environment, the identification of steps in the reaction cycle of enzymes and the study of the structure function relationship of proteins and protein complexes. This includes measurements of colocalization of single proteins in membrane embedded complexes or the association of cytoplasmic messengers to membrane bound proteins. The aim is to acquire quantitative information about the dynamics of the processes under investigation. Of particular interest are the stoichiometry, diffusion constants, association/dissociation rates and the identification of steps in the reaction cycle of proteins and protein complexes.

The extracted information can then be used to build up mathematical models of reaction networks inside a cell. The experimental studies provide quantitative information about specific steps of cellular processes and represent one important prerequisite for building up a detailed understanding of complex biological reaction pathways.

In order to provide quantitative data from living cells without major perturbation Prof. Wrachtrup's research group is using non-invasive optical techniques. Current biochemical methods allow the specific labeling of a protein of interest with a fluorescent marker. The optical setups offer ultra sensitive detection with single-molecule sensitivity and high spatio-temporal resolution. Thus, the researchers have access to the internal dynamics within a cell by following the pathway of the protein or its interaction with other species. The confocal and widefield setups enable particle tracking, FRET-analysis as well as lifetime measurements (FLIM) and fluorescence correlation spectroscopy (FCS/FCCS). Subsequent analysis yields important information about the processes in living cells, for example diffusion constants or distance and stoichiometry of protein complexes.

Another promising area of the research group relies in diamonds containing fluorescent NV centers. Because NV centers are very bright and photostable, the researchers use them for long-lasting particle tracking in live cells. By applying magnetic resonance imaging techniques it is possible to locate the nanodiamonds with sub-nanometer resolution which is a substantial improvement to traditional microscopy techniques. In addition, intracellular dynamics using molecular dynamics simulation can be modeled.

The link of well-known and novel experimental as well as computational approaches provides an excellent opportunity to further promote advances in systems biology.

Special equipment and techniques

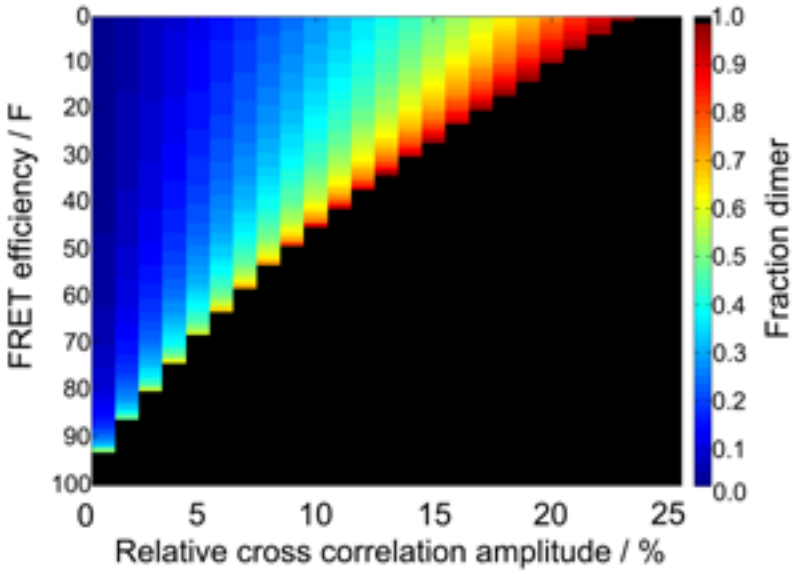
- FCS
- FCCS
- FRET
- FLIM
- Single Particle Tracking
- Magnetic Resonance Imaging

Selected cooperation partners

- Prof. Peter Scheurich, Institute of Cell Biology and Immunology, University of Stuttgart, Germany
- Prof. Frank Allgöwer, Institute for Systems Theory and Automatic Control, University of Stuttgart, Germnay
- Prof. Oliver Sawodny, Institute for System Dynamics, University of Stuttgart, Germany
- Dr. Birgit Singer-Krüger, Department of Biochemistry, Max Planck Institute for Developmental Biology, Tübingen, Germany
- Prof. Matthias Reuss, Institute of Biochemical Engineering, University of Stuttgart, Germany

Selected publications

- M. Branschädel, A. Aird, A. Zappe, C. Tietz, A. Krippner-Heidenreich and P. Scheurich. Dual function of cysteine rich domain (CRD) 1 of TNF receptor type 1: Conformational stabilization of CRD2 and control of receptor responsiveness. Cellular Signalling, 22(3), 2010.
- F. Neugart, A. Zappe, D. M. Buka, I. Ziegler, S. Steinert, M. Schumacher, E. Schopf, R. Bessey, K. Wurster, C. Tietz, M. Börsch, J. Wrachtrup and L. Graeve. Detection of ligand-induced CNTF receptor dimers in living cells by fluorescence cross correlation spectroscopy. Biochimica et Biophysica Acta-Biomembranes, 1788(9), 2009.
- M. Gerken, A. Krippner-Heidenreich, S. Steinert, S. Willi, F. Neugart, A. Zappe, J. Wrachtrup, C. Tietz and P. Scheurich. Fluorescence correlation spectroscopy reveals topological segregation of the two tumor necrosis factor membrane receptors. Biochimica et Biophysica Acta-Biomembranes, 1798(6), 2010.



Fraction of CNTFR or CNTF molecules which are part of a signaling complex as a function of FRET efficiency (Dissertation: Single molecule spectroscopy in living cells: development and application of alternative fluorescent labels with enhanced photo-physical properties).

Prof. Ulrich M. Zanger

Dr. Margarete Fischer-Bosch - Institute of Clinical Pharmacology, Stuttgart
Cellular and Molecular Biology
Pharmacogenetics and -genomics

11 members of staff (biologists, biochemists, pharmacists, physician and lab technicians)

The primary interests of Prof. Zanger's group are in the fields of drug metabolism, especially the cytochromes P450, and pharmacogenetics. The goal of the translational research concept is to bring basic research to the clinic in order to improve drug therapy. Of particular interest are the factors that contribute to inter- and intra-individual differences in the biotransformation of drugs and to identify biomarkers such as genetic signatures, that will allow the identification of patients at risk to develop adverse drug reactions or therapeutic failure. Recombinant enzymes, tissue fractions, human hepatocytes, as well as human volunteers and patients are being studied for this purpose.

In interdisciplinary collaborations the group has established biological tissue collections including archived and fresh frozen liver and other tissue, serum, blood and patient DNA, accompanied by comprehensive clinical data. Molecular analyses of these clinical samples concern expression and function of enzymes, population variability, genotype-phenotype relationships, mechanisms of drug-drug interactions, as well as role of nuclear receptors and microRNAs in gene regulation. Collaborative systems biology projects include both top-down and bottom-up approaches. Finally, diagnostic assays are developed to assess the clinical value of basic discoveries and to advance the idea of personalized medicine.

Special equipment and techniques

- Quantitative real-time PCR, Sequencer
- Denaturing HPLC
- Maldi-tof genotyping system, Protein Maldi-tof
- Analytical LC-MSMS
- Laser-capture microdissection
- Several cell culture rooms and S2 laboratory

Selected cooperation partners

- Dr. J. Lippert, Bayer Technology Services GmbH, Leverkusen, Germany
- K. Mauch, Insilico Biotechnology AG, Stuttgart, Germany
- Prof. J. Pleiss, Institute of Technical Biochemistry, University of Stuttgart, Germany
- Prof. D. Waxman, Department of Biochemistry, Boston University School of Medicine, USA
- Prof. A. Zell, Center for Bioinformatics Tübingen, University of Tübingen, Germany

Selected publications

- Klein K, Winter S, Turpeinen M, Schwab M, Zanger UM (2010): Pathway-targeted pharmacogenomics of CYP1A2 in human liver. Frontiers in Pharmacology 1:129. doi: 10.3389/fphar.2010.00129.
- Schwab M, Zanger UM, Marx C, Schaeffeler E, Klein K, Dippon J, Kerb R, Blievernicht J, Fischer J, Hofmann U, Bokemeyer C, Eichelbaum M; German 5-FU Toxicity Study Group (2008): Role of genetic and nongenetic factors for fluorouracil treatment-related severe toxicity: a prospective clinical trial by the German 5-FU Toxicity Study Group. J Clin Oncol 26:2131-2138.
- Saussele T, Burk O, Blievernicht JK, Klein K, Nussler AK, Nussler N, Hengstler JG, Eichelbaum M, Schwab M, Zanger UM (2007): Selective Induction of Human Hepatic Cytochromes P450 2B6 and 3A4 by Metamizole. Clin Pharmacol Ther 82:265-274.

Research groups in Freiburg

Prof. Rolf Backofen

University of Freiburg
Department of Computer Sciences / ZBSA
Bioinformatics Lab

14 members of staff

A wide range of recent findings show that RNAs perform many regulatory functions. Examples are regulatory small RNAs in bacteria and microRNAs (miRNAs) in eukaryotes. Similarly to proteins, these functions are often associated with evolutionary conserved motifs that contain specific sequence and structure properties. The group of Prof. Dr. Rolf Backofen investigates various aspects related to the systems biology of RNA in close collaboration with experimental groups.

The first aspect is the detection of regulatory or functional RNA motifs, which is important for the identification of key players in RNA-mediated regulation. Identification of functional RNA motifs is based on sequence-structure alignment. Current approaches were not applicable on a system-wide scale due to their high computational complexity. The group developed several efficient tools, which are currently amongst the leading approaches for the genome-wide applicable comparative analysis of RNA sequences.

The second aspect is the determination of RNA interaction networks, for which several methods for the prediction of RNA:RNA base-pair interactions have been introduced. This is computationally a very complex problem, and currently the most advanced tools for the estimation of RNA:RNA binding affinities can be found in that research group. All tools are used by various experimental groups for the prediction of RNA targets. For example, they are the standard tool in the context of the SPP„Sensory and regulatory RNAs in prokaryotes“.

Finally, the workgroup has a huge experience with the analysis of alternative splice forms, which is another form of translational control. In this area methods for the feature-based prediction of alternative spliceforms using different context information have been developed. These tools were successfully tested by different experimental groups.

Joint research projects

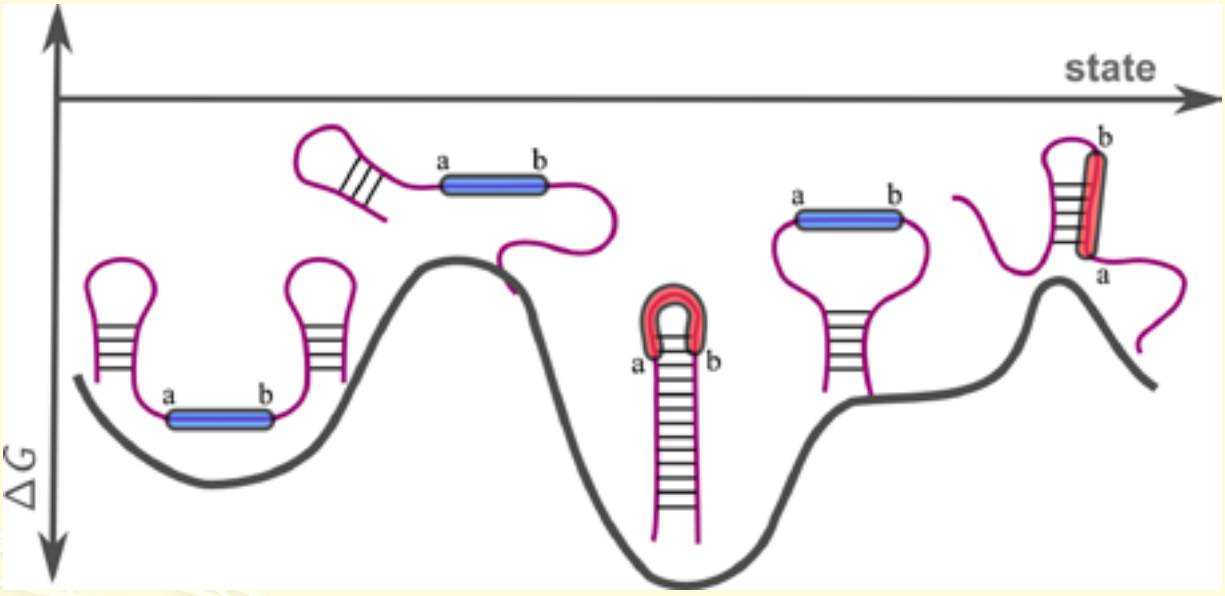
- BIOSS
- FORSYS / FRISYS (BMBF)
- InkoMBio (DFG)

Selected cooperation partners

- Prof. Bonny Berger, Massachusetts Institute of Technology (MIT), Cambridge, USA
- Prof. Cenk Sahinalp, Simon Fraser University, Vancouver, Canada
- Prof. Gad Landau, University of Haifa, Israel
- Prof. Wolfgang Hess, University of Freiburg, Germany
- Prof. Peter Stadler, University of Leipzig, Germany

Selected publications

- Hamidreza Chitsaz, Raheleh Salari, S. Cenk Sahinalp, and Rolf Backofen. A partition function algorithm for interacting nucleic acid strands. Bioinformatics, 25 no. 12 pp. i365-73, 2009.
- Matthias Platzer, Michael Hiller, Karol Szafranski, Niels Jahn, Jochen Hampe, Stefan Schreiber, Rolf Backofen, and Klaus Huse. Sequencing errors or SNPs at splice-acceptor guanines in dbSNP?. Nat Biotechnol, 24 no. 9 pp. 1068-70, 2006.
- Sebastian Will, Kristin Reiche, Ivo L. Hofacker, Peter F. Stadler, and Rolf Backofen. Inferring non-coding RNA families and classes by means of genome-scale structure-based clustering. PLOS Computational Biology, 3 no. 4 pp. e65, 2007.



RNA Biol. 2010 Jan 13;7(1). [Epub ahead of print] Computational prediction of sRNAs and their targets in bacteria. Backofen R, Hess WR.

Dr. María Matilde Bartolomé Rodríguez

University Hospital Freiburg
Department of Internal Medicine II
Insulin Mediated Signal Transduction in Hepatocytes

6 members of staff (biologists, physicians, physicists, lab technicians)

Due to its capacity to induce metabolic, proliferative and anti-apoptotic processes, insulin plays an essential role in the regeneration of the liver. The involvement of insulin in these processes is easy to see in patients suffering from insulin resistance or diabetes. The liver of such patients is only able to regenerate to a limited degree after damage.

Detailed insights into the interactions between insulin and other signalling molecules helps researchers to better understand processes such as insulin resistance, hyperglycaemia and adiposity, and to contribute to developing targeted therapies for patients suffering from steatohepatitis, NAFLD (non-alcoholic fatty liver disease), liver cirrhosis, diseases that can progress into hepatocellular carcinoma.

The complexity of these processes not only requires detailed knowledge about the molecular properties of the individual components, but also the determination of the dynamics between individual components of the system and their interactions. Whether this task is successful or not depends less on the size of a particular research team than on the close and complex networking with groups from a broad range of different disciplines.

Dr. M. Bartolomé's group of researchers is investigating how the metabolic functions of the liver can be maintained in situations such as induced hyperplasia, which means the regeneration of the organ after surgical removal of upto two thirds of the liver. This work is based on a mathematical model derived from experimental data.

Experimental data must be suitable for developing mathematical models. Important aspects of the acquisition of data are their quality and reproducibility. This requires adequate standards to be put in place that relate to the methods used and the quality of data. Another major aspect is the use of freshly isolated cells. Although the heterogeneity of cell preparations is much higher than that of cell lines, freshly prepared cells nevertheless mirror much better the actual *in vivo* situation.

Dr. Bartolomé's team of researchers focuses particularly on the aforementioned topics. Standards on the isolation and cultivation of human and mouse hepatocytes are available, which can also be applied to other research groups. Dr. Bartolomé's team is especially focused on important features such as the randomisation of samples used for statistical evaluation. The researchers are also working on the analysis of the heterogeneity of the isolated cells. Based on the experimental data obtained on phosphorylation processes following the addition of insulin to freshly isolated hepatocyte cultures using immunoblotting, the researchers have developed a statistical model for the analysis and correction of errors in cooperation with Clemens Kreutz from J. Timmer's group. The model can be used to assess the quality of data in hepatocyte cultures whilst taking into account the heterogeneity of different cultures (produced from other animals). At present, the researchers are developing and expanding error models that enable the acquisition of data on the single cell level (flow cytometry, confocal microscopy).

Experimental evaluation of the initial mathematical

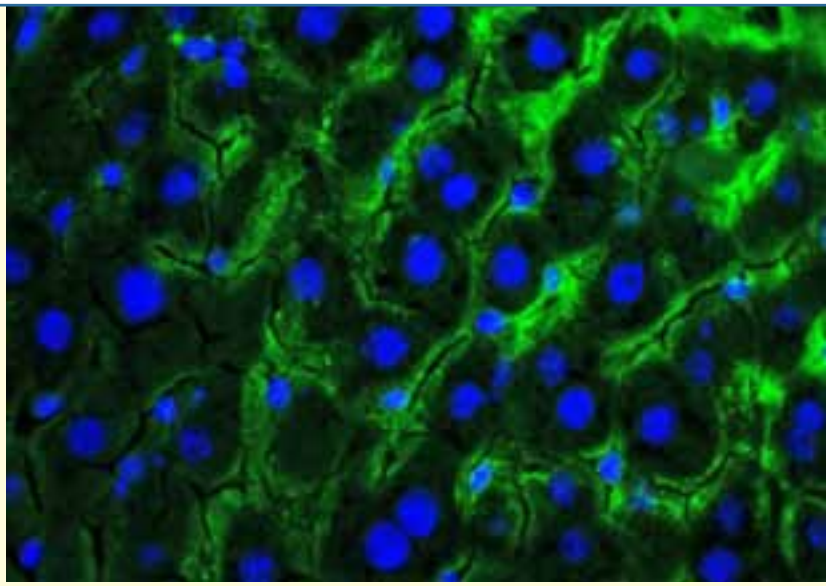
models has shown that it is necessary to investigate certain key processes in greater detail. Over the next few years, the researchers therefore plan to quantitatively investigate the complex interactions between insulin and its receptor on the single cell level. Major focus will be put on the endocytosis of the insulin receptor resulting in the removal of insulin from the blood, as well as the investigation of crosstalks with regard to the proliferative and metabolic characteristics of insulin. The researchers will integrate crosslinks with inflammatory signalling pathways, in particular the Wnt/ß signalling pathway. In addition, the group also intends to decipher the complex interactions of insulin in and between important target organs (fatty tissue, muscles, liver) in order to gain further insights into the development of diabetes. This objective is being pursued in collaboration with numerous European research groups.

Joint research projects

- Virtual Liver (BMBF)

Selected cooperation partners

- Jens Timmer, Institute of Physics, University of Freiburg, Germany
- Holger Conzelmann, Max Planck Institute, Magdeburg, Germany
- Rolf Gebhardt, Biochemical Institute, Medical faculty of the University of Leipzig, Germany
- Ursula Klingmüller, Systems Biology of Signal Transduction Division, German Cancer Research Center, Heidelberg, Germany
- Gunnar Cedersund, Department of Clinical & Experimental Medicine, Linköping University, Sweden



Distribution of insulin in the liver: liver slice after the in vivo addition of insulin-FITC (labelled with fluorescein molecules, green). The nuclei of the hepatocytes are stained blue.

Selected Publications

- Mohr L., Banerjee K., Tanaka S., Kleinschmidt M., Bartolomé Rodríguez M. M., Wands J. R.: Transgenic overexpression of Insulin Receptor Substrate 1 in hepatocytes enhances hepatocellular proliferation in young mice only. Hepatology Research. 2008. 38(12):1233.
- Bartolomé Rodríguez M. M., Ryu SM., Qian C., Geissler M., Grimm C., Prieto J., Blum H. E., Mohr L.: Immunotherapy of murine hepatocellular carcinoma by alpha Fetoprotein DNA vaccination combined with adenovirusmediated chemokine and cytokine expression. Human Gene Therapy. 2008.19:753.
- Bartolomé Rodríguez M. M., Kreutz C., Maiwald T., Seidl M., Blum H. E., Mohr L., Timmer J.: An error model for protein quantification. Bioinformatics. 2007. 2320: 2747.

Prof. Ralf Baumeister

University of Freiburg
FRIAS LIFENET / ZBSA
Bioinformatics and Molecular Genetics

28 members of staff (biologists, molecular medical scientists, bioinformaticians and bioengineers)

Professor Baumeister's research group investigates the functional networks of human diseases genes and their encoded proteins. The scientists are using the nematode *Caenorhabditis elegans (C. elegans)* as a model system. This animal is ideally suited for genome-wide and proteome-wide studies using a wide range of quantitative methods (genome-wide RNA interference, compound screens, genotype-phenotype maps, proteomic and metabolomic studies, pathway dissections). *C. elegans* was the first animal of which the genome has been sequenced completely. About 65% of all human disease genes have homologues in the worm.

Phenotyping the mutant morphology and behaviour is greatly facilitated by a complete cell lineage map and the existence of a wiring diagram of all 302 neurons. Despite its obvious simplicity, organogenesis and even complex neuronally controlled behaviours (e.g. associative learning and the response to noxious stimuli) can be studied and dysfunctions can be attributed to defects in individual cells. In addition, the animals are amenable to molecular, genetic and biochemical analyses allowing the identification of protein interactions and suppressor mutants and, thus, to the dissection of entire regulatory pathways.

The researchers are focusing in particular on the following projects:

Systems biology of aging and stress response. The insulin/IGF pathway is central to a complex functional network interconnecting with kinase signalling cascades and transcription factor networks. This involves the relay of phosphorylation signals from the membrane (activated through extracellular ligands) to the forkhead transcription factor FOXO to prevent its nuclear translocation. FOXO is a central regulator of diverse developmental and cellular responses, including resistance to pathogen intrusion, a variety of cellular stress signals, apoptosis, metabolic responses, and developmental functions. Moreover, the pathway controls cellular aging in all animal models in which it was studied so far. The pathway, but also the interconnecting signals, are strongly conserved in evolution and have a similar composition in invertebrate and vertebrate organisms. The key role of the insulin/IGF pathway is exemplified by the many crosstalks with other signalling mechanisms, including JNK, MAPK, ras/RAF, TGFß, and cell death pathways. The interplay between the transcriptional outputs of these pathways is crucial for the cellular response to stress, heat, and innate immunity after pathogen attack, and affects the onset of cancer, coronary heart diseases, and neurogeneration, (most notably Alzheimer's and Parkinson's Disease).

Functional networks of genes/proteins associated with hereditary human neurodegeneration. The researchers have established a platform for reiterative model building and experimental testing of pathways and functional networks involved in disease. This includes a protein interaction screening platform, validation tools for the high-throughput validation of genetic and protein interactions, as well as several highly parallel genetic screening technologies. Starting from a human disease gene, a reiterative process involving experimental network analysis, combined with modelling of interactions and candidate partners, was

established, which takes advantage of the high degree of homology between C. elegans genes and pathways and their human counterparts, and the simplicity of modulating them in the animal model by transgenesis, mutants, and RNA interference. Highly parallel metabolomics and proteomics studies, together with the development of PDMS-based manipulation devices and optical methods, add to a multidisciplinary research platform that also allows studying complex responses, including behavioural analyses, of permutations in the organism.

The goal of these studies is a holistic approach to understand the consequences of environment, genetic and protein perturbations on the response of an entire organism.

Special equipment and techniques

- High-throughput genetic and pharmacological screenings
- Protein interaction screening platform
- Confocal Nikon A1 CLEM
- COPAS particle sorter
- High-throughput automation platform
- Genome-wide RNA interference studies

Joint research projects

- BIOSS
- FRIAS LIFENET
- FRISYS / FORSYS (BMBF)
- LIFENET (EU)
- MEMOSAD (EU)
- SFB592 (DFG)
- SFB746 (DFG)
- SFB780 (DFG)
- SFB850 (DFG)

Selected cooperation partners

- Prof. T. Keith Blackwell, Joslin Diabetes Center, Harvard Medical School, Boston, USA
- Prof. Gerd Walz, Internal Medicine IV, University Hospital Freiburg, Germany
- Prof. Stig Omholt, CiGene, Norwegian University of Life Sciences, Aas, Norway
- Prof. Tom Kirkwood, CISBAN, Newcastle University, Newcastle upon Tyne, UK
- Prof. Anke Becker, Institute of Biology III, University of Freiburg, Germany

Selected publications

- Sämann J., Hegermann J., Gromoff E.V.,Eimer S., Baumeister R.*, Schmidt E. (2009) Caenorhabditis elegans LRK-1 and PINK-1 act antagonistically in stress response and neurite outgrowth. J Biol Chem. 284(24): 16482-91. *corresp. author
- Neumann-Haefelin E., Qi W., Finkbeiner E., Walz G., Baumeister R.*, Hertweck M. (2008) SHC-1/p52Shc targets the insulin/IGF-1 and JNK signaling pathways to modulate life span and stress response in C. elegans. Genes Dev. 22(19):2721-35, *corresp. author
- Tullet J.M.A., Hertweck M.T., An J.H., Baker J., Hwang J.Y., Liu S., Oliveira R.P., Baumeister R., and Blackwell T.K. (2008) Direct Inhibition of the Longevity-Promoting Factor SKN-1 by Insulin-like Signaling in C. elegans. Cell, 132, 1025-1038.

Prof. Anke Becker

University of Freiburg
Institute of Biology III / ZBSA
Molecular Genetics and Systems Biology of Procaryotes

12 members of staff (biologists and biotechnologists)

The group of Prof. Becker is interested in a systems-based understanding of regulatory networks in procaryotes. These include processing and integration of external and internal stimuli. The combination of molecular biology approaches to study defined components with high-throughput techniques leads to quantitative and dynamic data. Such data sets are essential for the development of a systems perspective of prokaryotic cells. Apart from standard molecular genetics and biochemical methods the approaches are largely based on omics techniques of genome research (transcriptomics, proteomics and metabolomics), biophysical methods and bioinformatics approaches.

Research focuses on the molecular aspects of symbiotic plant-microbe interactions and in particular on signalling and cell differentiation processes involved in establishment of symbiosis. The group is also interested in interactions between bacterial phytopathogens and their host plants. A major approach is the development of predictive mathematical models for regulation modules in these systems in collaboration with AG Paffelhuber and AG Fleck at the ZBSA.

Special equipment and techniques

- Automation platform

Joint research projects

- FORSYS/ FRISYS (BMBF)

Selected cooperation partners

- Prof. Dr. Peter Pfaffelhuber, Dr. Christian Fleck, ZBSA, University of Freiburg, Germany
- Dr. Enrico Schmidt, ZBSA, University of Freiburg, Germany
- Prof. Dr. Wolfgang Hess, Institute of Biology III, University of Freiburg, Germany
- Prof. Dr. Rolf Backofen, Department of Computer Science, University of Freiburg, Germany
- Dr. Eva Kondorosi, Dr. Peter Mergaert, CNRS, Gif-sur-Yvette, France

Selected publications

- M. McIntosh, S. Meyer, A. Becker (2009) Novel *Sinorhizobium meliloti* quorum sensing positive and negative regulatory feedback mechanisms respond to phosphate availability. Mol Microbiol 74(5): 1238-1256
- A. Becker, M. J. Barnett, D. Capela, M. Dondrup, P. B. Kamp, E. Krol, B. Linke, S. Rüberg, K. J. Runte, B. K. Schroeder, S. Weidner, S. N. Yurgel, J. Batut, S. R. Long, A. Pühler, A. Goesmann (2009) A portal for rhizobial genomes: RhizoGATE integrates a *Sinorhizobium meliloti* genome annotation update with postgenome data. J Biotechnol 140(1-2): 45-50

Laboratory automation system at the Center for Biological Systems Analysis (University of Freiburg). This robotic platform is used for high-throughput molecular biology screening and combinatorial experiments.

Prof. Christoph Borner

University of Freiburg
Institute of Molecular Medicine
Borner research group

2 members of staff (biologists)

Research topic and systems biology approach: acute and chronic liver damage is often caused by the death of large numbers of hepatocytes. The death of the cells is induced by the interaction of cytokines of the TNF family (e.g., TNF and FasL). Prof. Borner's team has been able to show that FasL can induce both the apoptosis and proliferation of hepatocytes. The decision as to whether the apoptotic or proliferative signalling pathway is chosen depends on the costimulation of FasL by extracellular matrix- and other growth factors.

In contrast to in vivo, the FasL-induced signalling behaviour of freshly isolated mouse hepatocytes changes when plated on collagen: they switch to the type I signalling pathway. In vivo (i.e. in the liver), hepatocytes use the mitochondrial signalling pathway (so-called type II pathway) which leads to the activation of death proteases (caspases) and death of the cells. It is interesting to note that the signalling does not switch but remains type II exactly as it does in vivo when cells are kept in suspension immediately after isolation. However, when the hepatocytes are plated onto a collagen matrix, thereby establishing extracellular matrix-integrin connections, they switch to type I signalling, which means that FasL directly activates the caspases, bypassing the mitochondrial components. The researchers therefore assume that the collagen-integrin signalling pathway interferes with the FasL pathway. The researchers use Boolean and ODE mathematical models to identify the interaction nodes of the two signalling pathways. They have already been able to show that caspase activation along the direct type I pathway is not governed by a positive feedback mechanism, and therefore is not bistable.

In addition, Prof. Borner's team is developing a literature-based Boolean model of the type I and II signalling pathways and the signalling pathways that interact with them (e.g., UV irradiation, IL-1, insulin). The coherence of the model was experimentally validated and revealed for the first time ever a UV-B dose effect on isolated mouse hepatocytes. The researchers found that the signalling pathways were strongly interconnected and involved numerous feedback loops, one of which turned out to be previously unknown.

The group also used a broad range of bioinformatic methods to gain a better understanding of the interaction between cell death and survival pathways, such as the interaction between FasL and integrin. These findings were again turned into a Boolean network.

Numerous signal interaction possibilities were tested with the SQUAD software. The researchers found that the complete network comprises four stable system states: two states of cell survival and two states of apoptosis (type I and type II signalling pathways). The model was validated with experimental data. In a next step, the Boolean models will be used to further elucidate the mechanisms that lead the cells to switch to type I signalling when the cells come into contact with collagen. In addition, the researchers hope to find out why exactly the opposite happens at low FasL levels, namely that the hepatocytes start to divide (proliferate). Prof. Borner's group hopes that a better understanding of the signalling processes on the molecular level will enable them to develop targeted therapies to counteract liver damage (hepatitis, liver cancer) and promote the regeneration of the liver when it is damaged.

Special equipment and techniques

- Culture of primary hepatocytes
- FACS analysis
- Transfection of cDNA and siRNA (lipofection and nucleofection)
- Quantification of Western blot lanes using chemiluminescence (LumiImager)
- Immunofluorescence
- Caspase activity assays
- Apoptosis assays (morphology, MTT survival assay, nuclear fragmentation, etc.)
- Phase contrast and fluorescence microscopy

Joint research projects

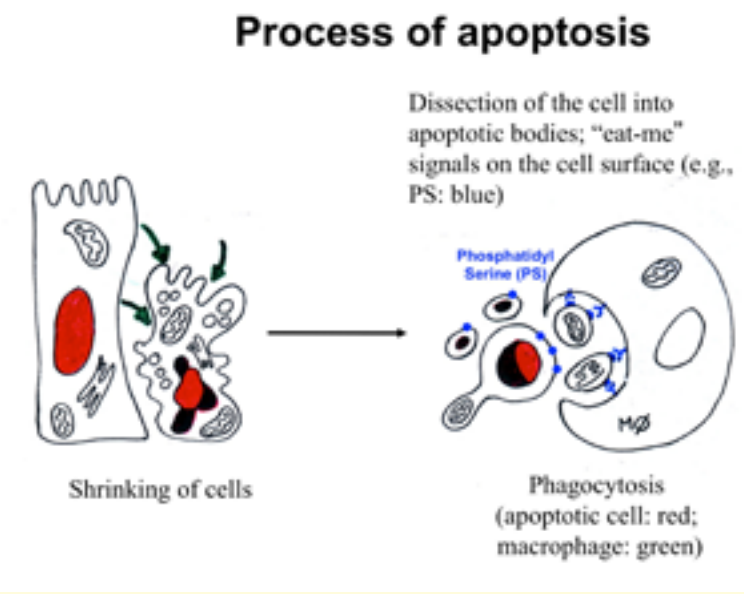
- HepatoSys (BMBF)

Selected cooperation partners

- Prof. Dr. Irmgard Merfort, Institute for Pharmaceutical Sciences, University of Freiburg, Germany
- Prof. Dr. Oliver Sawodny, Institute for System Dynamics, University of Stuttgart, Germany
- Prof. Dr. Thomas Dandkar, Biocenter, University of Würzburg, Germany

Selected publications

- Walter D, Schmich K, Vogel S, Pick R, Kaufmann T, Hochmuth FC, Haber A, Neubert K, McNelly S, von Weizsäcker F, Merfort I, Maurer U, Strasser A, Borner C. Switch from type II to Fas/CD95 death signaling on in vitro culturing of primary hepatocytes. Hepatology 2008; 48:1042-1953.
- Schlatter R, Walter D, Bury L, Bogyo M, Sawodny O, Sauter T, Borner C. Apoptosis does not need bistability. Manuscript in preparation



Morphological, cellular and biochemical alterations of an apoptotic cell

- Schlatter, R., Schmich, K., Avalos Vizcarra, I., Scheurich, P., Sauter, T., Borner C., Ederer, M., Merfort, I. & Sawodny O. (2009). ON/OFF and beyond – a Boolean model of apoptosis. PLoS Comp. Biol. 5(12), e1000595. Epub.

Dr. Tilman Brummer

University of Freiburg
ZBSA
Brummer research group / MAPK modulation

9 members of staff (biologists, molecular medicine specialists)

The Brummer research group tries to understand the mechanisms by which cells convert the information of extra- into intracellular signals and how these events steer cellular processes. In particular, the group is interested in the mechanisms underlying the fine-tuning of the mitogen-activated protein kinase (MAPK) and phosphatidyl-Inositol-3 Kinase (PI-3K) pathways. These pathways play a pivotal role in growth control and differentiation and are often dys-regulated in various human diseases.

Although the core components of these pathways have been identified by now, we are still far away from a thorough understanding as to how these signalling elements are fine-tuned. Indeed, recent Systems Biology approaches have revealed that, at the post-translational level, these core components are regulated by a plethora of ill-defined protein-protein interactions, feedback loops and crosstalk events. Consequently, a major challenge for Systems Biology will be the identification of these events, their quantitative, spatio-temporal description and ultimately their modelling.

For example, the list of phosphorylation sites grows rapidly with the improvement of mass spectrometry (MS) techniques. However, as technologies for the identification of the kinases and phosphatases controlling these events are still under-developed, MS data cannot be easily translated into networks yet. Consequently, the group is establishing screening platforms for the identification of substrate/kinase relationships. This is conducted in close collaboration with Enrico Schmidt and Anke Becker (both at ZBSA).

In its projects, the research group employs a bottom-up approach in that sense that it maps and functionally characterises phosphorylation and protein-protein interaction events in space and time for critical signalling elements of these pathways. The group is particularly interested in the proteins communicating between receptors and the apex of signaling cascades such as docking proteins and kinases.

The researchers expect that these studies will provide them with a deeper insight into the regulation of these pathways and will impact life sciences in two major ways: Firstly, this knowledge will eventually allow for a more accurate modelling of signalling pathways that are already used for paradigm development in Systems Biology.
Secondly, the knowledge of the spatio-temporal regulation of signaling networks is of growing importance for various clinical disciplines, e.g. to understand the mechanisms of disease and the success or failure of drugs, to identify novel drug targets and proteins of prognostic value and to steer cellular behaviour in regenerative medicine.

Special equipment and techniques

- Analysis of signal transduction events in three-dimensional tissue culture
- Inducible gene expression and knock-out/in systems
- Identification of novel substrate/kinase interactions by high-throughput systems (Cooperation with Prof. Anke Becker and Dr. Enrico Schmidt, both ZBSA)

Joint research projects

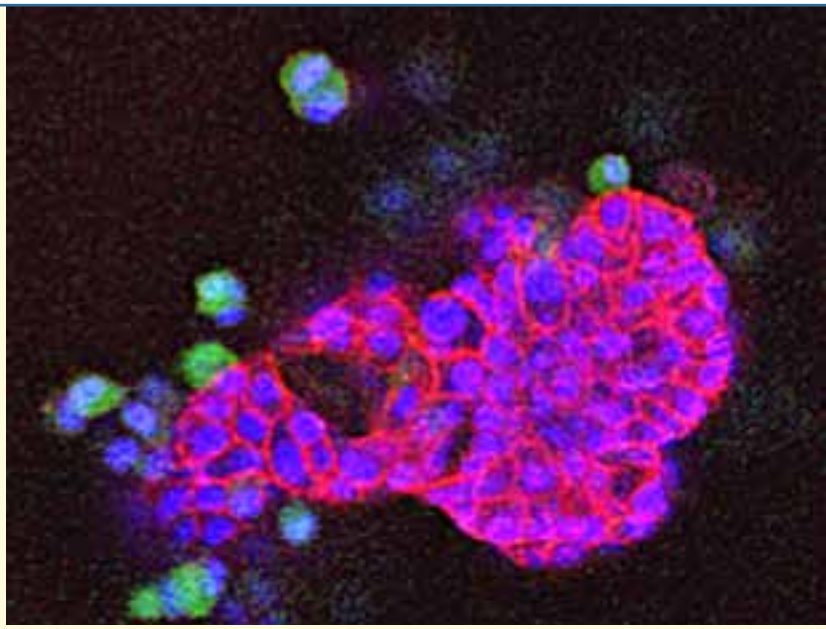
- EXC 294 BIOSS (DFG)
- SFB 850 (DFG)

Selected cooperation partners

- Dr. E. Schmidt, ZBSA, University of Freiburg, Germany
- Dr. J. Dengjel, ZBSA, University of Freiburg, Germany
- Dr. A. Schlosser, Core Facility Proteomics, ZBSA, Freiburg, Germany
- Prof. R. Daly, Garvan Institute of Medical Research, Sydney, Australia

Selected publications

- Brummer T, Larance M, Herrera Abreu MT, Lyons RJ, Timpson P, Emmerich CH, Fleuren ED, Lehrbach GM, Schramek D, Guilhaus M, James DE, Daly RJ. (2008). Phosphorylation-dependent binding of 14-3-3 terminates signalling by the Gab2 docking protein. EMBO Journal. 3;27(17):2305-16.
- Jeffrey KL, Brummer T, Rolph MS, Liu SM, Callejas NA, Grumont RJ, Gillieron C, Mackay F, Grey S, Camps M, Rommel C, Gerondakis SD, Mackay CR. (2006). Positive regulation of immune cell function and inflammatory responses by phosphatase PAC-1. Nature Immunology. 7:274-83.



- Brummer T, Martin P, Herzog S, Misawa Y, Daly RJ, Reth M.(2006). Functional analysis of the regulatory requirements of B-Raf and the B-Raf(V600E) oncoprotein. Oncogene. 25:6262-76.

Dr. Hauke Busch

University of Freiburg
Freiburg Institute for Advanced Studies / ZBSA
Group of Cell Control and Communication

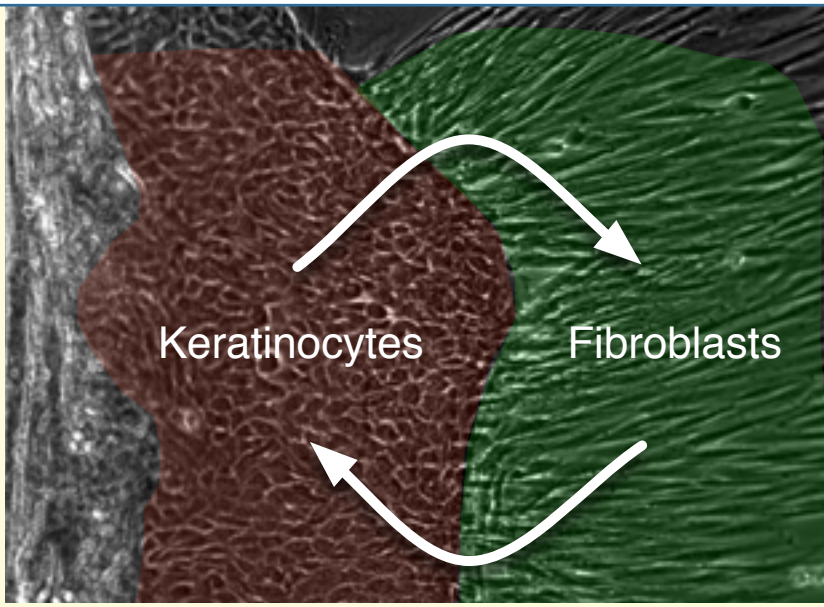
7 members of staff (physicist, physician, chemist and biologists)

The group of Dr. Hauke Busch focuses on the development and verification of mathematical models for cellular behavior from an initial stimulus to the final phenotype. In a systems biology approach they combine experimental research on cell-cell communication with the development of appropriate multi-scale dynamic models to investigate the necessary and sufficient control points that lead to cell proliferation, differentiation, migration or death.

The working group adapts concepts from non-linear dynamics and complex systems to develop appropriate dynamic models unraveling self-organizing properties in cellular behavior. Such behavior in a multicellular environment is most likely the results of time-sequential events, involving protein signaling and gene regulation in feedback-entangled processes lasting several hours.

Systems theory suggests that the slowest evolving variables determine the long term outcome of a system. In a biological context, it is thus the change in gene expression that reflects the macroscopic decision of a cell.
Formalizing these ideas in a dynamic modeling approach, the group will use abstract neural network approaches to reconstruct the dynamic control logic of cellular decision processes based on gene expression kinetics. Time-resolved experimental data is recorded in this lab under well defined cell culture and context-dependent conditions.
Data will be collected on the cell population level using DNA microarrays and RT-PCR (Biorad CFX-96 & Agilent Biolanalyzer for RNA Quality) as well as on the single cell level by time-lapse microscopy (Nikon TI-E Microscope with IBIDI climate chamber).

In the meantime the group also applies experimental design approach and modeling workflow to elucidate the effect of phenotype-causing stimuli on cell proliferation, differentiation, apoptosis and cell communication in various cell types and model organisms with the collaboration partners throughout Germany, looking not only for cell fate specific control points, but also for generic cell decision processes in general.



Joint research projects

- Gerontosys (BMBF)
- MedSys (BMBF)

Selected cooperation partners

- Prof. Leena Bruckner Tuderman, Department of Dermatology and Venerology, University of Freiburg, Germany
- Stefan Rensing, Institute of Biology, University of Freiburg, Germany
- Margareta Müller, German Cancer Research Center, Heidelberg, Germany
- Ursula Klingmüller, German Cancer Research Center, Heidelberg, Germany
- Fabian Theis, Helmholtz Center Munich, Germany

Selected publications

- H. Busch, D. Camacho, Z. Rogon, K. Breuhahn, P. Angel, R. Eils and A. Szabowski, Gene Network Dynamics controlling Keratinocyte Migration, Mol Syst Biol, 4, 199 (2008).
- H. Busch, W. Sandmann and V. Wolf, A numerical aggregation algorithm for the enzyme-catalyzed substrate conversion, in Lecture Notes in Computer Science 4210, 298 (2006).
- H. Busch and R. Eils, Systems Biology, in Encyclopedia of Molecular Cell Biology and Molecular Medicine, 14, 123, (2005).

Dr. Joern Dengjel

University of Freiburg
Freiburg Institute for Advanced Studies / ZBSA
Protein Dynamcis Group

6 members of staff (biologists, biochemists, chemists)

Cells possess two major degradation pathways: the ubiquitin/proteasome system and the autophagosomal/lysosomal system. Autophagy is an evolutionary conserved process wherein catabolism of cytoplasm generates energy which allows cell survival under conditions of reduced nutrient availability. Autophagy is initiated by a flat membrane cistern enwrapping parts of the cytoplasm, thus, forming an autophagosome with a characteristic double membraned organization. The autophagosome matures in a stepwise process which may involve fusion with endosomal vesicles, before it finally fuses with the lysosome leading to degradation of the autophagosomal material.

Autophagy is thought to be important for the turn-over of whole organelles and long-lived proteins. However, prolonged autophagy can lead to type II programmed cell death. Many aspects of autophagy regulation are still not fully understood. The best-characterized inhibitory pathway includes a class I PI3K and mTOR. On the other hand, a class III PI3K is needed for autophagy activation. Autophagy has been linked to several diseases amongst others cancer and neurodegenerative diseases.

Furthermore, autophagy is regarded as an unspecific bulk degradation pathway. However, in a recent study we analyzed protein dynamics during amino acid starvation and found that the subcellular localization of proteins had an influence on their degradation dynamics. Proteins were degraded in an ordered fashion, where cytosolic proteins and proteins involved in translation were degraded initially, followed by multiprotein complexes and proteins situated in organelles. Looking at proteasomal and lysosomal degradation ample cross-talk between the two degradation pathways became evident. The group's data implies that protein degradation during starvation-induced autophagy is far from being unspecific, and is rather tightly regulated.

Protein Dynamcis Group is following several projects concerning the characterization of autophagy using a combination of techniques including quantitative mass spectrometry (MS)-based proteomics, confocal-imaging, and RNA interference (RNAi)-based screens. Currently, the group is characterizing the autophagosome, the double-membrane bound vacuole containing cytoplasmic material destined for degradation, with the aim to identify human proteins related to autophagy. Further interest is situated in global protein dynamics during long-term starvation to characterize the influence of different types of autophagy, macroautophagy and chaperone-mediated autophagy (CMA), on the cellular proteome. Last but not least, Dengjel's group is using a quantitative phosphoproteomics approach to compare signaling events involved in autophagy and in type I programmed cell death pathways (apoptosis). Although the two processes are morphologically distinct, they are both characterized by lack of tissue inflammatory responses and may share signaling pathways. Ultimately, spatio-temporal resolved proteomics data will be used for modeling cellular decisions regarding organellar composition and signaling events. Models will be experimentally verified and critical nodes will be investigated in detail.

To reveal new components in the analyzed organelle and signaling networks MS-based proteomics in combination with stable isotope labelling by amino acids in cell culture (SILAC) is used. SILAC is a quantitative proteomic strategy that metabolically labels the entire proteome, thus, making it distinguishable by MS analysis. Different populations of cells can be grown in medium containing distinct forms of arginine (Arg) and lysine (Lys). Subsequently, cell populations can be mixed and analyzed in one MS experiment. This allows the quantitation of proteins from different cellular states. Depending on the setup it is able to describe an organellar proteome or to follow site-specific phosphorylation changes in signaling pathways over a certain timeframe. The newest mass spectrometers allow specific screening for phosphopeptides on a routine basis. As sensitivity is down to the subfemtomolar range it is now possible to perform systemic analyses on as few as 10^7 cells.

Special equipment and techniques

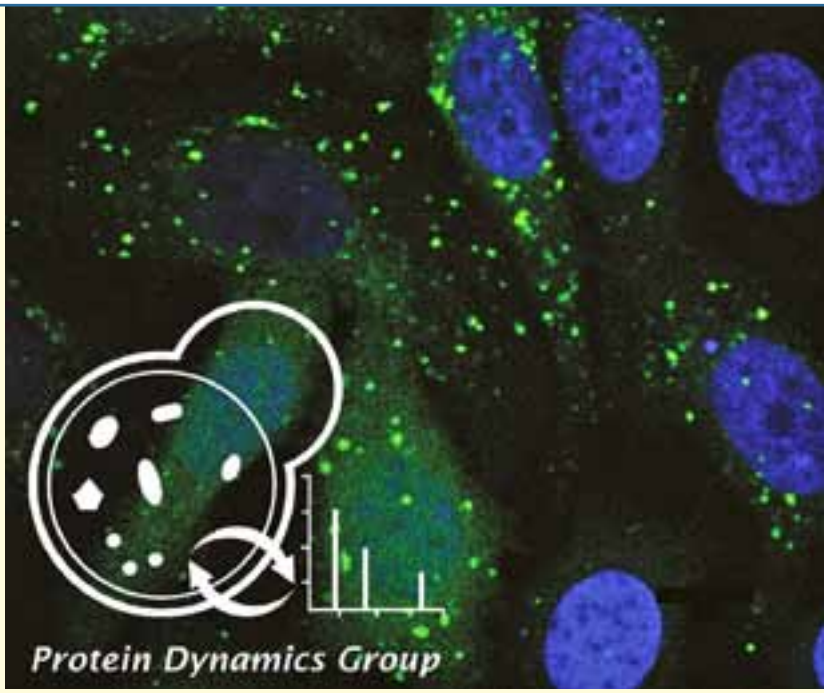
- MS-based proteomics in combination with stable isotope labelling by amino acids in cell culture (SILAC)

Joint research projects

- BIOSS
- FRIAS

Selected cooperation partners

- Leena Bruckner-Tuderman, University Hospital, University of Freiburg, Germany
- Hauke Busch, University of Freiburg, Germany
- Jens Andersen, University of Southern Denmark, Odense, Denmark



Autophagosomes during rapamycin treatment marked by eGFP-LC3-II.

- Marja Jäättelä, Danish Cancer Society, Copenhagen, Denmark
- Christian Münz, University of Zurich, Swizerland

Selected publications

- Dengjel, J., Kratchmarova, I., Blagoev, B., Receptor tyrosine kinase signaling: a view from quantitative proteomics. Mol. Biosystems, 2009, 5:1112-21.
- Kristensen, A.R., Gade, S., Hoyer-Hansen, M., Jaattela, M., Dengjel, J.*, Andersen, J.S.*, Ordered organelle degradation during starvation-induced autophagy. Mol Cell Proteomics, 2008, 7:2419-28.
- Dengjel,J.*, Akimov,V.*, Olsen,J.V., Bunkenborg,J., Mann,M., Blagoev,B., and Andersen,J.S., Quantitative proteomic assessment of very early cellular signaling events. Nat Biotechnol. 2007, 25:566-8.

Prof. Wolfgang Driever

University of Freiburg
Institute of Biology I / ZBSA
AG Prof. Wolfgang Driever

11 members of staff (biologists)

Professor Driever's research group is investigating basic developmental control mechanisms in vertebrates. The scientists are using zebrafish *(Danio rerio)* as model system. *Danio rerio* is an ideal model for acquiring a broad range of quantitative data (transcriptome, proteome, phenotype, cell behaviour – 3D and 4D life imaging) since the fish embryos develop synchronously and their transparency enables in vivo investigations at single cell resolution.

The researchers are focusing in particular on the following projects:
Pou5f1/Oct4-dependent control mechanisms of embryonic pluripotency, differentiation and pattern formation. Pou5f1/Oct4 is one of the most important stem cell factors of pluripotent cells in mammals. The objective of the researchers in Driever's laboratory is to analyse Pou5f1/Oct4 function in the embryo and to obtain in-depth insights into the structure and regulatory properties of the transcription networks "downstream" of Pou5f1/Oct4.

The group is investigating four major aspects:

(1) Identification and functional analysis of downstream transcription nodal points – the researchers are currently concentrating on the detailed investigation of KLFs, FOXD3 and Her3.
(2) Role of the SOXB protein family in the control of Pou5f1 activity and the activation of target genes.
(3) Mechanisms of the temporal control of zebrafish development based on the regulatory properties of the Pou5f1 downstream network.
(4) Pou5f1-dependent regulation of cell behaviour (adhesion, motility).

Transcription data with high temporal and spatial resolution are acquired with several different methods, including microarray series, quantitative RT-PCR and deep sequencing. Interactions at gene control regions are identified using interaction assays (ChIP-Seq, EMSA). The data are then used to develop network models and investigate their properties in dynamic simulations. The zebrafish model is excellently suited for the targeted and systematic disturbance of the control systems in gain-of-function and loss-of-function experiments, thereby enabling the verification and expansion of the dynamic network models.

The goal of systems biology modelling is to develop predictive models for the regulation of the differentiation of embryonic stem cells into neural, mesodermal and endodermal lineages. It is envisaged that this knowledge will in the long term provide new impulses in the field of regenerative medicine.

Another research area involves an investigation of the network of signalling and transcription factors, that governs the differentiation of dopaminergic neurons in the nervous system. The rapid development of zebrafish makes it possible to observe in vivo the differentiation of precursor cells into neurons as well as the axonal connection into neural networks. The systematic investigation of the transcriptome has led to the identification of transcriptional codes for the majority of dopaminergic subtypes.

Newly developed multicistronic vectors are used to express a combination of transcription factors in neural precursor

cells. The goal of this project is to develop a rational concept for the controlled differentiation of dopaminergic neurons.

Special equipment and techniques

- Genetics and genomics in the zebrafish model organism
- Quantitative microscopy and 3D/4D visualisation
- Transcriptome analysis

Joint research projects

- DOPAMINET (EU)
- FRISYS / FORSYS (BMBF)
- mdNEURODEV(EU)
- SFB592 (DFG)
- SFB 850 (DFG)
- ZF-HEALTH (EU)

Selected cooperation partners

- Prof. Jens Timmer, ZBSA and Institute of Physics, University of Freiburg, Germany
- Dr. Elias Stupka, Cancer Institute, University College London, Germany
- Dr. Verdon Taylor, Biomedical Sciences, University of Sheffield, UK
- Prof. Harold Bugess, National Institute of Child Health and Human Development, NIH, Bethesda, USA
- Dr. Tom Michoel, Freiburg Institute for Advanced Studies, University of Freiburg, Germany

Selected publications

- Lunde, K., Belting, H.-G., and Driever, W. (2004). Zebrafish pou5f1/pou2, homolog of mammalian Oct4, functions in the endoderm specification cascade. Current Biology: 14, 48-55.

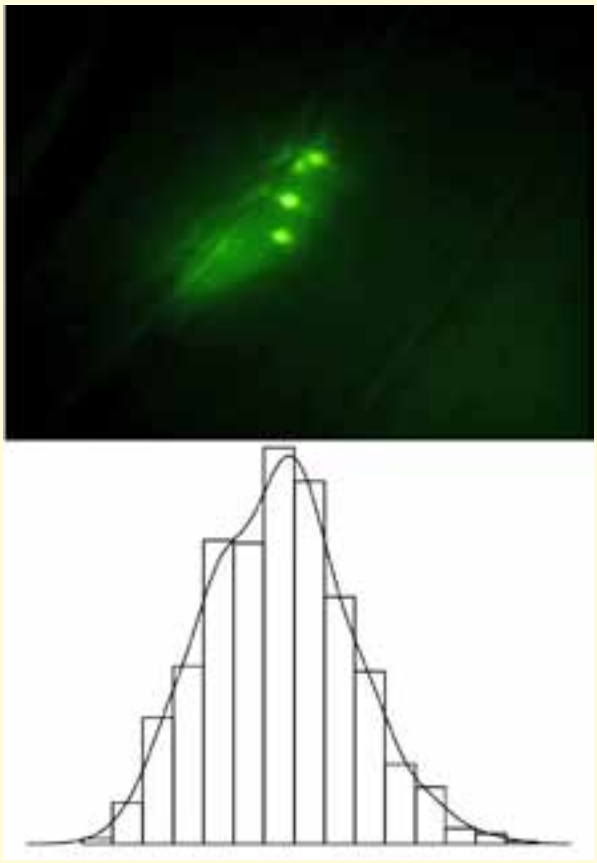
- Daria Onichtchouk, Florian Geier, Bozena Polok, Daniel M. Messerschmidt, Rebecca Mössner, Björn Wendik, Sungmin Song, Verdon Taylor, Jens Timmer, and Wolfgang Driever (2010). Zebrafish Pou5f1-dependent transcriptional networks in temporal control of early development. Molecular Systems Biology 6,354 (pp 1-18).
- Heiko Löhr, Soojin Ryu, and Wolfgang Driever (2009). Zebrafish diencephalic A11 related dopaminergic neurons share a conserved transcriptional network with neuroendocrine cell lineages. Development 136, 1007-1017.

Dr. Christian Fleck

University of Freiburg
ZBSA
Developmental Systems Biology

7 members of staff (physicists, biologists, mathematicians)

The research group deals mainly with aspects of the developmental biology of plants in which it strives to work in close cooperation with its various partners on experimental issues. In addition to the aforementioned, the group focuses on issues that are more theoretical and biophysical, where it uses a broad range of methods, including analytical mathematical methods, statistical methods and computer simulations. Although individual projects often require a detailed understanding and the expansion/modification of the methods used, the researchers always focus on the biological question.



Joint research projects

- FORSYS / FRISYS (BMBF)

Selected cooperation partners

- Kircher, Institute of Biology II, University of Freiburg, Germany
- Palme, Institute of Biology II, University of Freiburg, Germany
- Hiltbrunner, Center for Plant Molecular Biology, University of Tübingen, Germany
- Millar, Institute of Molecular Plant Sciences, University of Edinburgh, UK
- Hülskamp, Botanical Institute, University of Cologne, Germany

Selected publications

- Rausenberger, J.; Fleck, C.; Timmer, J.; Kollmann, M. (2009) Induction Level Determines Signature of Gene Expression Noise in Cellular Systems. Progress in Biophysics and Molecular Biology 100, 57–66
- Digiuni, S., Schellmann, S., Geier, F., Greese, B., Pesch, M., Wester, K., Dartan, B., Mach, V., Srinivas, B. P., Timmer, J., Fleck, C., Hulskamp, M. (2008) A competitive complex formation mechanism underlies trichome patterning on *Arabidopsis* leaves. Molecular Systems Biology 4, 217(1-11).
- Geier, F., Lohmann, J., Gerstung, M., Maier, A. Timmer, J., Fleck, C. (2008) A quantitative and dynamic model for plant stem cell regulation. PLoS ONE 3, 10, e3553(1-10).

Arabidopsis thaliana, a typical model organism.

Dr. Wolfgang Frank

University of Freiburg
Institute of Biology II
Plant Biotechnology-Abiotic Stress and RNA interference

10 members of staff (biologists)

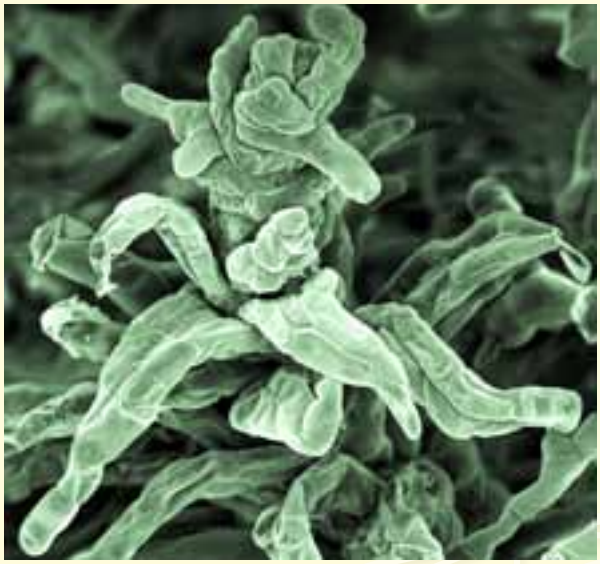
Small, non-coding RNAs (sRNAs) are important regulators of both post-transcriptional and transcriptional gene regulation. In principle, sRNAs bind to complementary RNA targets thereby mediating cleavage or translational inhibition of the cognate target RNA. Furthermore, sRNAs mediate epigenetic DNA modifications either by interacting with DNA with the help of accessory proteins or by forming sRNA-RNA duplexes that are targeted to the cognate DNA locus.
The fine balance between switched-on and switched-off genes differs between organs and changes during development and under varying environmental conditions. When this balance is disturbed disfiguration and illnesses such as cancer occur. Compared to animals plants have a surprising complex network of various sRNA pathways.

The group is particularly interested in understanding this complexity by dissecting sRNA pathways in the moss *Physcomitrella patens*. The important biological role of a specific class of sRNAs, so called microRNAs, is reflected by the fact that they predominantly control the expression level of mRNAs encoding transcription factors.

Why are these regulators controlled by miRNAs?
It is assumed that sRNAs have several advantages over "common" regulatory principles such as the activation of gene transcription.

Which regulatory principles can be identified involving sRNA regulation?
Using genome-wide expression analysis of protein-coding genes and non-coding RNAs in *Physcomitrella patens* the group unravelled regulatory networks which are controlled by different classes of small, non-coding RNAs. The research is focused on regulatory circuits involving sRNAs and transcription factors which are activated by different phytohormones and adverse environmental conditions.

Besides their ability to control gene expression at the post-transcriptional level, the group studies the role of sRNAs in the establishment and maintenance of epigenetic modifications to regulate gene expression at the transcriptional level. The dynamics of sRNA-mediated regulation at these different levels is addressed by the generation of particular *P. patens* mutant lines which cause specific perturbations of the networks. These mutant lines are currently used for the acquirement of molecular



Electron micrograph of a *Physcomitrella patens* mutant with a defective small RNA pathway.

data and subsequent mathematical modelling of miRNA-controlled regulatory networks.

Special equipment and techniques

- Generation of targeted gene knockout lines in *Physcomitrella patens*
- Design and expression of artificial microRNAs for medium to large-scale gene function analyses
- Methods for the analysis of small, non-coding RNA
- DNA methylation analysis, Epigenetics

Joint research projects

- Signal Systems in Plant Model Organisms (GRK1305 International Graduate School, DFG)
- FORSYS/FRISYS (BMBF)

Selected cooperation partners

- Prof. Dr. Ralf Reski, Plant Biotechnology, University of Freiburg, Germany
- Prof. Dr. Wolfgang R. Hess, Genetics and Experimental Bioinformatics, University of Freiburg, Germany
- Dr. Michael J. Axtell, Biology Department, Pennsylvania State University, USA
- Prof. Dr. Jens Timmer, Institute of Physics, University of Freiburg, Germany
- Prof. Dr. D. Weigel, Max-Planck-Institute for Developmental Biology, Tübingen, Germany

Selected publications

- Khraiwesh, B., Arif, M.A., Seumel, G.I., Ossowski, S., Weigel, D., Reski, R., Frank, W. (2010) Transcriptional control of gene expression by microRNAs. Cell 140, 111-122.
- Qudeimat, E., Faltusz, A.M.C., Wheeler, G., Lang, D., Brownlee, C., Reski, R., Frank, W. (2008) A PIIB-type Ca2+-ATPase is essential for stress adaptation in Physcomitrella patens. Proc. Natl. Acad. Sci. USA 105, 19555-19560.
- Khraiwesh, B., Ossowski, S., Weigel, D., Reski, R., Frank, W. (2008) Specific gene silencing by artificial microRNAs in *Physcomitrella patens*: An alternative for targeted gene knockouts. Plant Physiology 148, 684-693.

Electron micrograph of *Physcomitrella patens* wild type.

Dr. Britta Hartmann

University of Freiburg
Center of Biological Signalling Studies / ZBSA
Regulation of alternative splicing by cellular networks

1 member of staff

Alternative splicing affects more than 95% of the human genes and on average every gene has more than 7 different splice-variants generating a complex transcriptome. Deregulation of alternative splicing is being linked to an increasing number of diseases, giving additional significance to this new field of research (Wang et al. Science 2008; Pan et al. Nature Genetics 2008). Therefore it is crucial to explore the role of alternative splicing in different cellular programs. Splicing-sensitive microarrays enable the research group to uncover alternative splicing events regulated in different cellular context. The biological role of these alternative isoforms can subsequently be studied using *Drosophila* as a model organism.

Intercellular signalling pathways are essential for the development and life of organism and their role on transcriptional regulation has been intensively studied. Surprisingly, virtually nothing is known on how signalling pathways impact on post-transcriptional processes such as alternative splicing. Using genome-wide custom designed splicing sensitive microarray, Dr. Hartmann's group uncovered that two very different signalling pathways (wingless and insulin) regulate a large number of alternative splicing events (Hartmann et al. 2009). Currently the molecular mechanisms by which these signalling pathways control alternative splicing decisions and the biological function of some signal-regulated alternative splicing events are investigated in vivo.

Sex determination has served as a prime example for AS regulation, where sex-specific expression of a handful of genes triggers somatic differentiation and behavior. Using splicing microarrays the group identified hundreds of genes exhibiting vast differences in isoform levels between sexes in adult flies. Analysis of AS pattern of over 40 candidates in the adult body, head and in embryonic cell-lines uncovered interesting examples of tissue-specific and sex-specific AS. Further analysis revealed ubiquitously but also tissue-restricted alternative splicing regulation implying that posttransciptional programs, distinct from the classical pathways controlled by SXL and TRA, exist. Indeed, extensive sex-specific differences were observed in genes encoding for RNA binding proteins and splicing factors, a concept currently further explored by the research group.

Special equipment and techniques

- Alternative splicing microarrays
- Deep sequencing
- Real-time PCR

Joint research projects

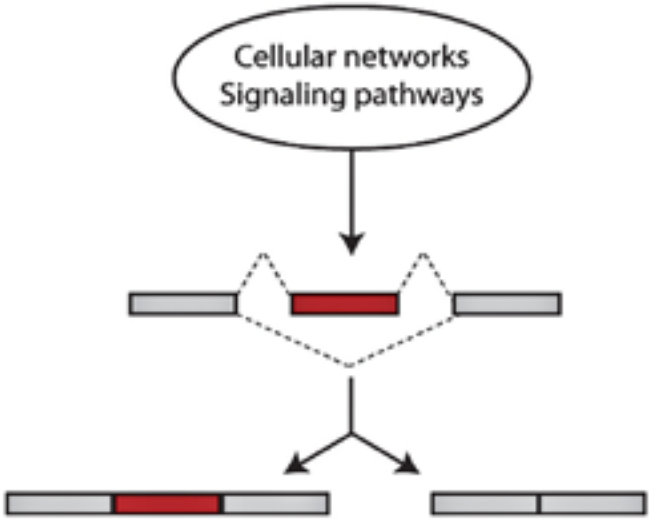
- BIOSS

Selected cooperation partners

- Dr. Pyrowolakis, Institute for Biology I, University of Freiburg, Germany
- M. Blanchette, PhD; Stowers Institute for Medical Research, Kansas City, USA

Selected publications

- Global analysis of alternative splicing regulation by insulin and wingless signaling in *Drosophila* cells. Hartmann B, Castelo R, Blanchette M, Boue S, Rio DC, Valcárcel J.Genome Biol. 2009;10(1):R11. Epub 2009 Jan 29.



Regulation of alternative splicing

Prof. Wolfgang R. Hess

University of Freiburg
Institute of Biology III
Genetics & Experimental Bioinformatics

20 members of staff (biologists, bioinformaticians, biochemists)

The "Genetics and Experimental Bioinformatics" research group deals with the functional and comparative analysis of microbial genomes, in particular those of cyanobacteria. Cyanobacteria are the only group of bacteria that are able to directly convert solar energy into organic compounds (oxygenic photosynthesis). This process is of particular interest because it binds the harmful greenhouse gas CO_2 and because some of the resulting compounds can be directly used as third-generation biofuels. The team led by Prof. Hess has special expertise in the identification of suitable organisms, their systematic analysis and optimisation using systems biology tools. This expertise is brought to good use in numerous collaborative projects (FORSYS-Partner project, EU-FP/ DirectFuel).

A special research focus centres on the systems biology of regulatory RNA molecules which are important regulators of stress responses, cell differentiation and development processes as well as biological signal processing. Due to their huge heterogeneity, this class of molecules has not yet been investigated in great detail and only a few basic mechanisms of action are known. Prof. Hess' team has developed methods that enable the prediction of genes of regulatory RNA molecules based on comparative genome analyses. Moreover, the group uses a broad range of transcriptome analysis techniques to characterise the functions of regulatory RNAs.

Joint research projects

- FORSYS / FRISYS (BMBF)
- FORSYS-Partner (BMBF)
- DirectFuel (EU FP7)

Selected cooperation partners

- Prof. Rolf Backofen, Department of Computer Sciences / ZBSA, University of Freiburg, Germany
- Prof. Anke Becker, Institute of Biology III / ZBSA, University of Freiburg, Germany
- Prof. Peter Pfaffelhuber, ZBSA, University of Freiburg, Germany
- Prof. Sallie W. Chisholm, Department of Civil and Environmental Engineering, MIT , Cambridge, USA
- Dr. Debbie Lindell, Technion - Israel Institute of Technology, Haifa, Israel

Selected publications

- Backofen R., Hess W.R. (2010) Computational prediction of sRNAs and their targets in bacteria. RNA Biology 7, 1-10. (Special Focus Review).
- Georg J., Voss B., Scholz I., Mitschke J., Wilde A., Hess W.R. (2009): Evidence for a major role of antisense RNAs in cyanobacterial gene regulation. Mol. Sys. Biol. 5, 305. (Faculty of 1000 selected).
- Steglich C., Futschik M., Lindell D., Voss B., Chisholm S.W., Hess W.R. (2008): The challenge of regulation in a minimal phototroph: Non-coding RNAs in *Prochlorococcus*. PLoS Genet. 4, e1000173.

Dr. Dirk Lebiedz

University of Freiburg
ZBSA
Lebiedz research group: Modelling and Scientific Computing

8 members of staff (mathematicians, physicists)

The research group led by Dr. Dirk Lebiedz deals with the development and application of scientific computing and numerical mathematics methods to scientific issues. These methods are used in different systems biology applications including:

- Optimisation and optimal control of dynamic systems
- Optimal experimental planning and model discrimination
- Multi-scale modelling and simulation
- Model- and complexity reduction of high-dimensional reaction networks
- Reaction-transport systems and reactive flows
- High-performance computing and parallelisation

Special equipment and techniques

- Numerical methods of scientific computing

Joint research projects

- FORSYS / FRISYS (BMBF)
- Helmholtz Alliance on Systems Biology

Selected cooperation partners

- Jens Timmer, Institute of Physics, University of Freiburg, Germany
- Ursula Klingmüller, German Cancer Research Center, Heidelberg, Germany
- Peter Beyer, Faculty of Biology, University of Freiburg, Germany
- Gerald Illerhaus, Internal Medicine I, Freiburg University Medical Center, Germany
- Sebastian Sager, Interdisciplinary Center for Scientific Computing, Universität Heidelberg, Germany

Selected publications

- Shaik, O. S., Sager, S., Slaby, O., Lebiedz, D. Phase tracking and restoration of circadian rhythms by model-based optimal control. IET Syst. Biol. 2, 16 (2008)
- Skanda, D., Lebiedz, D. An optimal experimental design approach to model discrimination in dynamic biochemical systems. Bioinformatics 26, 939 (2010)
- Engelhart, M., Lebiedz, D., Sager, S. Optimal control of selected chemotherapy ODE models: A View on the potential of optimal schedules and choice of objective function. Math. Biosci. 2011 (accepted)

Dr. Gerhard Leubner

University of Freiburg
Institute of Biology II
Seed Biology Group Leubner

8 members of staff (biologists, biomechanics, biotechnologists)

What happens to plant seeds during germination? Researchers led by Dr. Gerhard Leubner from the University of Freiburg ("The Seed Biology Place" - www.seedbiology.de) in collaboration with six international groups of researchers will be jointly looking into these processes. What makes the scientists' project so special is that they are planning to explain the molecular, physiological and mechanical processes of plant seeds in their entirety and bring these three levels together using mathematical models.

Over the next three years, the consortium „virtual Seed (vSEED)", which consists of four European partners, will take on the task of creating a mathematical description of the dynamic processes involved in the germination of seeds of the closely related plant species *Arabidopsis thaliana* (thale cress) and *Lepidium sativum* (garden cress). The researchers' concept won the European Research Area-Net Plant Genomics (ERA-Net PG) competition, outpacing 53 other contestants. The research consortium, led by Prof. Dr. Michael Holdsworth from the University of Nottingham (Great Britain), will receive 1.7 million euros in funding for the next three years for four laboratories and several postdoctoral positions.

The starting point for the researchers' interdisciplinary research is biomechanics. In cooperation with the Technical Workshop of the Institute of Biology II in Freiburg, Leubner's team has developed an apparatus that enables the measurement of mechanical changes in the seed coat as the seeds germinate. The researchers prepare the coats, clamp them into a rack, and press a metal rod with a controlled amount of force against the coats in order to discern the force required for the root tip to break through the coat.

Leubner's group is also investigating the molecular conditions underlying this process. They have already found that the germination process is initiated by the softening of the coat tissues, a process triggered by enzymes that degrade the cell walls of the seed coats. Another important aspect of germination is the interactions between plant hormones. In addition to projects funded under vSEED, there are postdocs and PhD students in Leubner's team, who are investigating the roles of hormones and cell wall changes during germination. These projects are funded by the German Research Foundation (Deutsche Forschungsgemeinschaft, DFG), the Alexander-von-Humbold Foundation and seed industry.

Leubner and his team also know from previous experiments that environmental influences such as temperature play a decisive role during germination. Molecular signalling networks need to integrate information about the environment. In order to identify and understand these networks, the scientists will use transcriptome analyses and modern imaging methods to obtain a comprehensive picture of the genes that are activated in the different tissues of germinating plant seeds and that mediate the germination process. Besides the Freiburg researcher groups, teams from the University of Nottingham, the University of Leeds (Great Britain) and the Universities of Wageningen and Utrecht (Netherlands) are contributing their molecular genetic, biochemical and material scientific know-how.

In order to cope with the flood of data, complex mathematical methods and suitable software programmes are required. Two other teams from Nottingham are in charge of the statistical analyses. The recently opened Centre for Biosystems Analysis at the University of Freiburg, with whom Leubner's team will work closely, also has similar know-how. The vSEED project is the first attempt to understand the biology of germinating plant seeds in its entirety.

Special equipment and techniques

- tissue-specific transcriptome analyses of seeds
- biomechanic analysis of endosperm weakening during seed germination

Joint research projects

- ERA-NET Plant Genomics vSEED ('virtual seed') project

Selected cooperation partners

- Thomas Speck, Botanical garden, University of Freiburg, Germany
- Mike Holdsworth, Division of Plant and Crop Sciences, The University of Nottingham, UK
- John King, Andy Wood, School of Mathematical Sciences, The University of Nottingham, UK
- Leonie Bentsink, Plant Sciences , Utrecht and Wageningen University, The Netherlands
- Paul Knox, Institute of Integrative and Comparative Biology, University of Leeds, UK

Selected publications

- Linkies A, Müller K, Morris K, Turecková V, Wenk M, Cadman CSC, Corbineau F, Strnad M, Lynn JR, Finch-Savage WE, Leubner-Metzger G Ethylene interacts with abscisic acid to regulate endosperm rupture during germination: a comparative approach using Lepidium sativum and Arabidopsis thaliana Plant Cell 21:3803-3822 (2009)
- Müller K, Tintelnot S, Leubner-Metzger G (2006). Endosperm-limited Brassicaceae seed germination: Abscisic acid inhibits embryo-induced endosperm weakening of Lepidium sativum (cress) and endosperm rupture of cress and Arabidopsis thaliana. Plant and Cell Physiology 47:864-877
- Finch-Savage WE, Leubner-Metzger G (2006). Seed dormancy and the control of germination. Tansley review: New Phytologist 171:01-523

Prof. Irmgard Merfort

University of Freiburg
Institute for Pharmaceutical Sciences
Merfort Research Group

10 members of staff (pharmacists, chemists, biologists)

In the „Virtual Liver Project“ financially supported by the BMBF the physiology and functionality of the liver will be explored in a systems biology approach. The aim is to provide a model which includes cellular metabolic functions and their regulation, the processing of extracellular signals, hepatocyte proliferation and endocytos. The project will open the route to answer complex questions in the context of liver function and liver diseases.

In cooperation with the Borner and the Timmer group, both in Freiburg, the Bode group in Düsseldorf and the Sawodny group in Stuttgart the Merfort group is involved in the subproject “Regulation of pro-apoptotic and anti-apoptotic responses in primary murine hepatocytes”. Here, the Merfort group explores in a close connectionship between mathematic modelling and experimental studies the mechanism why the tumornecrosis factor (TNF-alpha) is such a potent factor in sensitizing FasL-induced apoptosis in primary murine hepatocytes and whether further cytokines may have similar properties.

Furthermore, the role of JNK in TNFalpha/Actinomycin D induced apoptosis will be investigated combining again modelling and experimental studies. The obtained model will be integrated in other models of the project. TNF-alpha and FasL are cytokines of the TNF family and are involved in processes of acute and chronic liver damage induced by enhanced cell death. A better understanding of the molecular interrelation of these processes is suggested to finally lead to the development of a more target-oriented therapy and consequently to an improved control of liver diseases, such as hepatitis and liver cancer.

Joint research projects

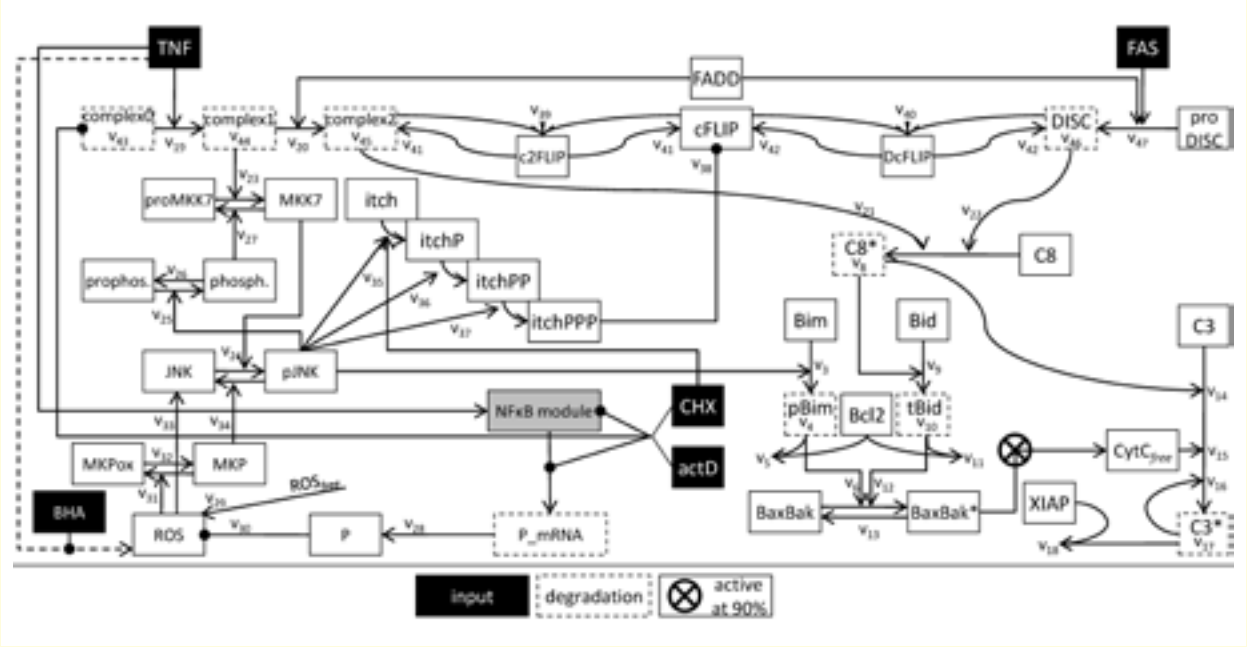
- HEPATOSYS (BMBF)
- Virtual Liver (BMBF)

Selected cooperation partners

- Prof. Christoph Borner, Institute of Molecular Medicine and Cell Research, University of Freiburg, Germany
- Dr. Johannes Bode, Department of Gastroenterology, Hepatology and Infectiology, University Hospital, Düsseldorf, Germany
- Prof. Oliver Sawodny, Institute for System Dynamics, University of Stuttgart, Germany
- Prof. Jens Timmer, Institute of Physics, Albert-Ludwigs University of Freiburg, Germany

Selected publications

- Sparna, T., Rétey, J., Schmich, K., Albrecht, U., Naumann, K., Gretz, N., Fischer, H.P, Bode, J.G., Merfort, I. (2010) Genome-wide comparison between IL-17 and combinedTNF-alpha/ IL-17 induced genes in primary murine hepatocytes, BMC Genomics 11:226
- Schlatter, R., Schmich, K., Avalos Vizcarra, I., Scheurich P., Sauter, T., Borner, C., Ederer, M., Merfort, I., Sawodny O. (2009) On/off and beyond – a Boolean model of apoptosis, PloS Computational Biology 5, e1000595



Modeling the TNFα-induced Apoptosis Pathway in Hepatocytes. Rebekka Schlatter, Kathrin Schmich, Anna Lutz, Judith Trefzger, Oliver Sawodny, Michael Ederer, Irmgard Merfort PloS ONE accepted 2011

Prof. Peter Pfaffelhuber

University of Freiburg
ZBSA
Stochastic Models in Systems Biology

4 members of staff (mathematicians)

Systems biology focuses predominantly on cellular processes. The "Stochastic Models in Systems Biology" research group focuses on the modelling of biochemical and biophysical processes. Special attention is paid to natural fluctuations and hence the probabilistic description of biological systems. The research group is currently working on the following projects:

Cellular chemical reaction networks: The mathematical theory of reaction networks is nowadays attracting attention through cellular processes studied in the field of systems biology. It is worth noting that cells might have only a few copies of some chemical substances, for example RNA. This can lead to stochastic fluctuations of the substances involved. The research group investigates generic situations of such networks, for example the influence of conformational changes of enzymes that underlie Michaelis-Menten kinetics.

Quorum sensing modelling: "Quorum sensing" refers to the phenomenon by which bacterial cells are able to sense the number of bacteria (cell density). The molecular causes of this phenomenon are autoinducer molecules that are exchanged between the cells. The researchers describe this system using a space-time multiscale model, in which the cells and the medium used represent two of these scales. Reaction mechanisms that occur in the cells involve a positive feedback that triggers the production of autoinducers when only a few bacteria are present in a certain environment and a negative feedback when high numbers of cells are present. Prof. Pfaffelhuber's team is studying this system in cooperation with a group working on *Sinrhyzobium meliloti* led by Prof. Anke Becker. This bacterial system lends itself well to manipulation and allows the validation of the mathematical approach.

Evolutionary aspects of systems biology: The influence of evolutionary forces such as mutation and selection on biological systems is also of great importance in systems biology research. Prof. Pfaffelhuber's research group uses classical probabilistic models from the field of population biology to study the effect of evolutionary forces. "Genetic hitchhiking" refers to the reduction of natural diversity as a result of strong selection. The resulting fluctuations in a population also play a major role in the reliable description of signalling pathways and metabolic networks. The researchers are investigating the neutral diversity of bacterial genomes from the presence and absence of genes. This provides them with information about the evolutionary importance of certain genes.

Joint research projects

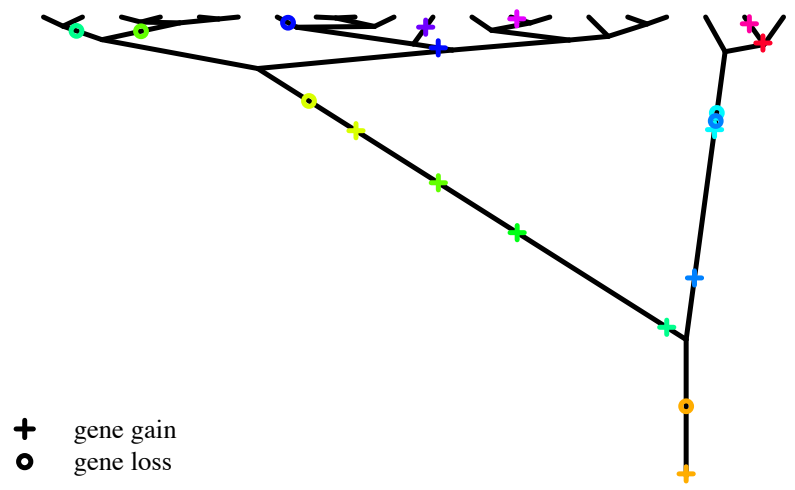
- FORSYS / FRISYS (BMBF)

Selected cooperation partners

- Wolfgang Hess, Institute of Biology III, University of Freiburg, Germany
- Anke Becker, Institute of Biology III / ZBSA, University of Freiburg, Germany
- Wolfgang Stephan, Department Evolutionary Biology, LMU Munich, Germany

Selected publications

- Baumdicker, F., W. R. Hess and P. Pfaffelhuber. The diversity of a distributed genome in bacterial populations, Annals of Applied Probability, 20(5), 1567-1606, 2010
- Depperschmidt, A. and P. Pfaffelhuber. Asymptotics of a Brownian ratchet for Protein Translocation, Stochastic Processes and their Applications, 120, 901-925, 2010
- Hermisson, J. and P. Pfaffelhuber. The pattern of genetic hitchhiking under recurrent mutation, Electronic Journal of Probability, 13(68), 2069-2106, 2008



The "infinitely many genes" model of bacterial population genomics assumes that a particular population has a common genealogy. The model assumes that genes that have never been present in a population before can be introduced from the environment, but that they can also be damaged and hence lost along ancestral lines.

Prof. (apl.) Stefan A. Rensing

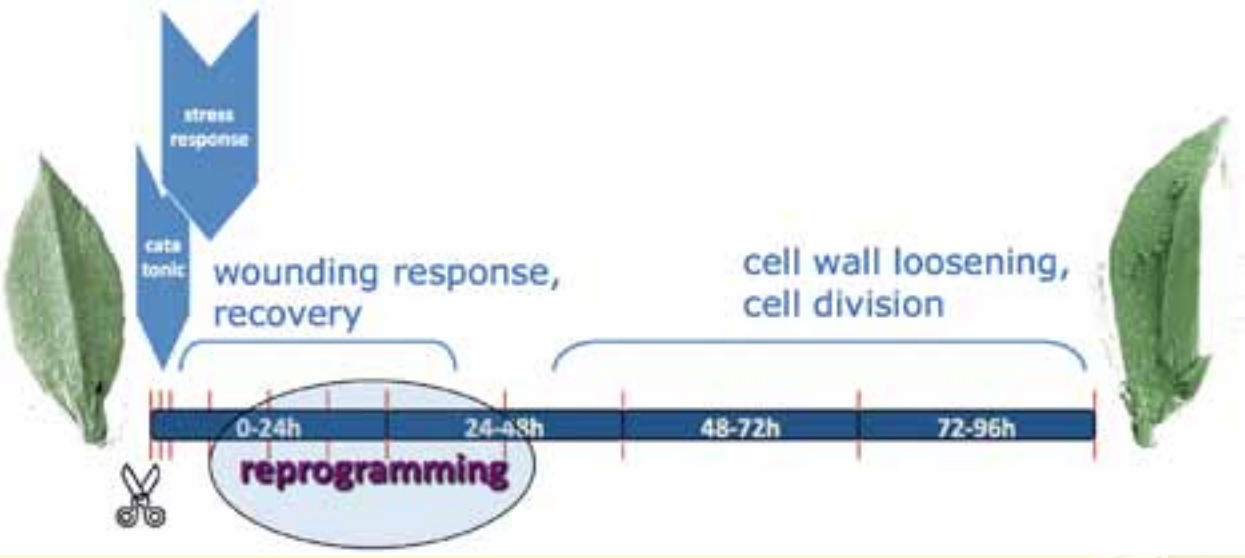
University of Freiburg
Faculty of Biology
Rensing research group

12 members of staff (biologists, bioinformaticians)

The Rensing group is working on the evolution of plants in the wide sense, encompassing land plants and algae. In terms of systems biology, the group is mainly interested in the determination of gene regulatory networks that have been evolutionary conserved. To achieve this goal, the group utilizes state-of-the-art, high-throughput wet lab methdology, like microarray expression profiling and next generation sequencing.

The resulting data are evaluated using phylogenetic and bioinformatic methods. In terms of mathematical modelling there is a collaboration with Peter Pfaffelhuber (ZBSA, Freiburg) on the evolutionary fixation of detrimental organellar mutations and their compensation by nuclear mutations.

Together with Hauke Busch (FRIAS, Freiburg) they are using time-resolved microarray data to determine network hubs of transcriptional regulation. The main model organism is the moss *Physcomitrella patens*, due to its interesting phylogenetic position and reverse-genetics capabilities. This lab is one of the main contributors to the international effort to further develop this model plant reference genome. In this regard the group of Dr. Rensing is closely collaborating with Ralf Reski (Biology, Freiburg). In terms of genome sequencing and analysis the group is also involved in the genome projects of other photosynthetic eukaryotes, like the club moss *Selaginella moellendorffii,* the moss *Ceratodon purpureus*, the multicellular brown alga *Ectocarpus siliculosus* or the algae *Volvox carteri* and *Emiliania huxleyi.*



Cartoon of the response timeframe after leaflet detachment in *P. patens*, ultimately resulting in several pluripotent apical stem cells.

Special equipment and techniques

- High throughput transcriptomics using next generation sequencing and microarray expression profiling
- Molecular phylogeny, phylogenomics and comparative genomics

Joint research projects

- BIOSS cluster of excellence
- FORSYS/ FRISYS (BMBF)

Selected cooperation partners

- R. Backofen, Department of Computer Sciences, University of Freiburg, Germany
- H. Busch, ZBSA, University of Freiburg, Germany
- P. Pfaffelhuber, ZBSA, University of Freiburg, Germany
- R. Reski, Institute of Biology II, University of Freiburg, Germany
- Joint Genome Institute, Physcomitrella genome consortium, USA

Selected publications

- Rensing et al., (2008) The genome of the moss *Physcomitrella patens* reveals evolutionary insights into the conquest of land by plants. Science 319:64-69
- Wolf L., Rizzini L., Stracke R., Ulm R., Rensing S.A. (2010) The molecular and physiological response of *Physcomitrella patens* to UV-B. Plant Physiology 153:1123
- Lang D., Weiche B., Timmerhaus G., Richardt S., Riano-Pachon D.M., Correa L.G.G., Reski R., Mueller-Roeber B., Rensing S.A. (2010) Genome-wide phylogenetic comparative analysis of plant transcriptional regulation: a timeline of loss, gain, expansion and correlation with complexity. Genome Biology and Evolution 2:488

Prof. Ralf Reski

University of Freiburg
Institute of Biology II
Plant Biotechnology

35 members of staff (biologists)

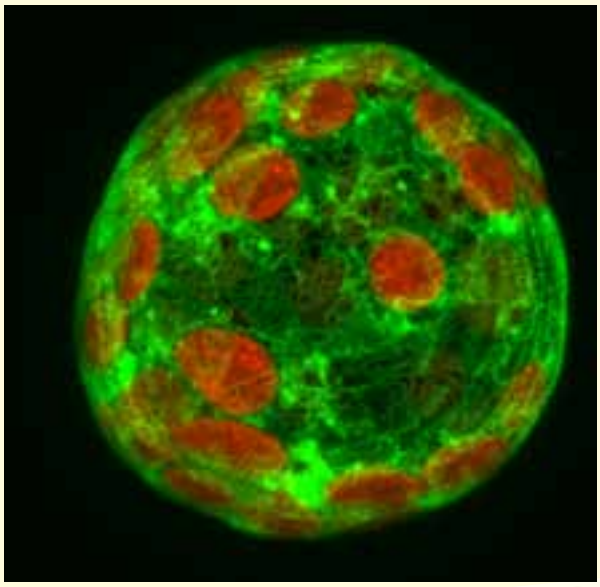
The Plant Biotechnology research group led by Prof. Reski has developed the moss *Physcomitrella patens* into a model system for use in systems biology and synthetic biology.

The moss is characterised by its simple morphology and ability to grow in pure mineral media under highly standardised conditions. Prof. Reski's team has deciphered the entire *Physcomitrella patens* genome in cooperation with the Joint Genome Institute (JGI) of the US Department of Energy and an international consortium.

In common with yeast and embryonic mouse stem cells, *Physcomitrella* genes can be modified by efficient gene targeting. This leads to knock-out mosses, whose gene functions can subsequently be deciphered using a method known as reverse genetics. Working in cooperation with BASF AG, Reski's group has optimised the gene targeting method, thereby making the moss amenable to functional genome analysis using high-throughput methods, a practice that is known as functional genomics.

The Plant Biotechnology research group is particularly interested in the control circuits that give the moss its high tolerance to stress factors such as salt and drought, as well as in genes encoding polyunsaturated fatty acids (PUFAs). The researchers are also investigating why, in contrast to higher plants, the *Physcomitrella* genome is characterised by a high rate of homologous recombination. If it were possible to clarify and transfer this mechanism to seed plants, this would be a very positive development for the field of green biotechnology as a whole.

In cooperation with the company greenovation Biotech GmbH, the Plant Biotechnology research group uses transgenic mosses with humanised glycosylation patterns in photobioreactors in order to produce complex biopharmaceuticals such as antibodies for therapy and diagnostics. This process, which is known as molecular farming, is facilitated by the fact that *Physcomitrella* genes do not exhibit a special codon bias, which, for example, enables them to express human genes relatively easily. In addition, numerous genetic control elements from animal cells or viruses can be used in the expression of the genes. Downstream processing is made easy as the proteins produced are secreted by the moss into the low-complexity medium.



Confocal Laser Scanning Microscope (CLSM) image of a single moss cell (protoplast). Chloroplasts are marked red and the Endoplasmic Reticulum (ER) is marked green.

The Plant Biotechnology research group also works with the BMBF-funded Freiburg Initiative for Systems Biology (FRISYS), the Centre for Biological Signalling Studies (BIOSS) and the Spemann Graduate School of Biology and Medicine (SGBM) funded by the German Excellence Initiative. The group is a member of the BMBF-funded GABI-PRECISE consortium and is associated with the trinational École supérieur de biotechnologie Strasbourg (ESBS).

Special equipment and techniques

- Bioreactors
- Microarrays
- Proteomics
- Life cell imaging
- Bioinformatics
- Gene targeting, functional genomics

Joint research projects

- FRISYS
- BIOSS

Selected publications

- Khraiwesh, B., M.A. Arif, G.I. Seumel, S. Ossowski, D. Weigel, R. Reski, W. Frank (2010): Transcriptional control of gene expression by microRNAs. Cell 140, 111-122.
- Martin, A., D. Lang, S.T. Hanke, S.J.X. Mueller, E. Sarnighausen, M. Vervliet-Scheebaum, R. Reski (2009): Targeted gene knockouts reveal overlapping functions of the five *Physcomitrella patens* FtsZ isoforms in chloroplast division, chloroplast shaping, cell patterning, plant development, and gravity sensing. Molecular Plant 2, 1359-1372.

Photobioreactors with moss cultures for the production of complex biopharmaceuticals (molecular farming).

- Rensing et al., (2008): The *Physcomitrella* genome reveals insights into the conquest of land by plants. Science 319, 64-69.

Prof. Wolfgang Schamel

University of Freiburg
Institute of Biology III
Systems Immunology

11 members of staff (biologists, chemists, biochemists)

The human immune system protects against disease by killing pathogens such as influenza viruses or HI viruses, and tumour cells such as breast and prostate cancer. On the other hand, overactive immune responses can lead to autoimmune diseases such as diabetes or rheumatism, or they may trigger allergies. Therefore, the immune system plays a key role in human health. The proper function of the immune system depends on the activation of immune cells, in particular T- and B-cells.

The activation of immune cells is a rather complicated process and depends on the strict regulation of signalling proteins. These molecules form a complex and dynamic intracellular network that controls the cells' reactions to stimuli such as tumour-specific molecules, antigens of pathogens or autoantigens. The impaired function of this protein-protein interaction network can lead to the aforementioned disorders. A better understanding of the network's characteristics is likely to be a crucial step in the search for improved treatments.

Huge amounts of money were put into the sequencing of the human and mouse genomes. The deciphering of DNA sequences is an important prerequisite for the identification of the transcriptomes and proteomes of immune cells, a process that is currently being done using high-throughput methods. It is also assumed that the signalling networks of these cells involve at least 150 different proteins that communicate with each other in a highly diverse way.

Traditionally, signalling events are investigated using immunoprecipitation and Western blotting. Such signalling events include reversible and dynamic posttranslational modifications (phosphorylation) as well as constitutive and stimulus-induced protein-protein interactions. Since the 1990s, these methods have led to the discovery of many activating and inhibitory interactions within the network. Hard work by many scientists led to the discovery of a large number of signalling events in the immune cells and the function of the first proteins was determined.

The data were acquired with non-standardised methods and most of them were neither quantitative nor multidimensional. It is therefore difficult to use these methods to accurately describe the interaction of signalling proteins. Instead, innovative and effective technologies are required that allow the researchers to study and understand this network as an entire whole, and not only individual parts thereof. Only an understanding of complex systems as a whole will enable researchers to make predictions on how the systems can be modulated to either enhance or suppress certain characteristics. Obtaining a detailed understanding of immune cell networks is crucial in our endeavour to interfere with disease development and progression.

The group of researchers led by Prof. Schamel is focused on the development and improvement of biochemical methods to study signalling networks. The group's methods have contributed to important insights into the function of the T-cell antigen receptor and the T-cell signal transduction network (Minguet und Schamel, Trends Biochem Sci 2008, 33: 51-57; Minguet et al., Immunity

2007, 26:43-54; Siegers et al., J Exp Med 2007, 204: 2537-2544; Gil et al., Cell 2002, 109:901-912).

Currently, the research group is generating quantitative data in order to gain an understanding of the early modules of the T-cell network. The modelling is done in cooperation with Thomas Höfer, Heidelberg. In addition, Wolfgang Schamel is the coordinator of SYBILLA (Systems biology of T-cell activation, www.sybilla-t-cell.de), a large EU-funded network.

Special equipment and techniques

- IP-FCM (immunoprecipitation by flow cytometry) for the generation of accurate protein data

Joint research projects

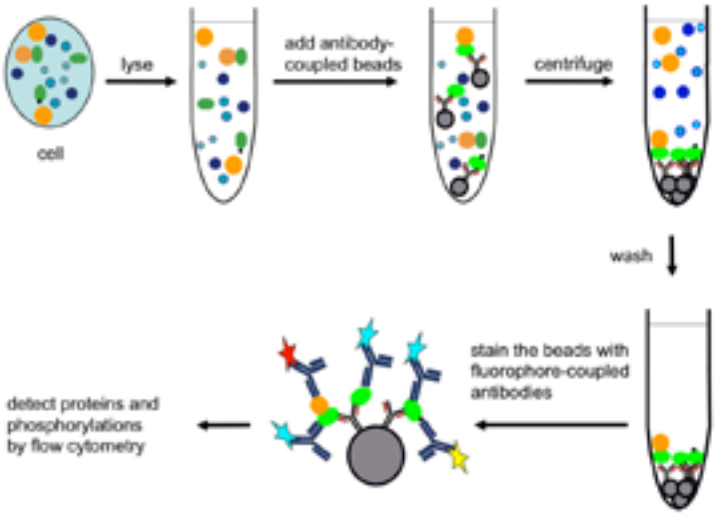
- BIOSS
- CCI
- FORSYS/FRISYS (BMBF)
- SYBILLA (EU FP7)

Selected cooperation partners

- Prof. Thomas Höfer, German Cancer Research Center / BioQuant, Universität Heidelberg, Germany
- Prof. Burkhart Schraven, Institute of Molecular and Clinical Immunology, University of Magdeburg, Germany
- Prof. Jens Timmer, Institute of Physics, University of Freiburg, Germany
- Dr. Matthias Gstaiger, Institute of Molecular Systems Biology, ETH Zurich, Switzerland

Selected publications

- A conformation- and avidity-based proofreading mechanism for the TCR-CD3 complex. Schamel WW, Risueño RM, Minguet S, Ortíz AR, Alarcón B. Trends Immunol. 2006, 176-82.
- High-sensitivity detection and quantitative analysis of native protein-protein interactions and multiprotein complexes by flow cytometry. Schrum AG, Gil D, Dopfer EP, Wiest DL, Turka LA, Schamel WW, Palmer E. Sci STKE. 2007, pl2.



Immunoprecipitation measured by flow cytometry (IP-FCM). This highly quantitative method starts with traditional immunoprecipitation, followed by the staining of the bead-bound proteins with fluorescence-labelled antibodies instead of separating the proteins in an SDS gel and detecting them in a Western blot. Fluorescence intensity can be determined with flow cytometry, also in a high-throughput manner. This enables the accurate determination of protein quantities, protein-protein interactions and posttranslational modifications. The use of calibration beads leads to absolute values instead of relative values.

Dr. Enrico Schmidt

University of Freiburg
Institute of Biology III / ZBSA
Regulatory Networks

10-12 members of staff (biologists, physicians and bioinformaticians)

To understand complex physiological or pathological mechanisms, it is important to gather information about the functional states of cells and the spatio-temporal environment of proteins which are involved in regulating these processes. The main task of systems biology is to identify biologically relevant functional states using both experimental and theoretical methods.
Important functional states of a cell under certain conditions are mainly defined by specific interplay of different proteins that is strictly regulated in time and space. To predict the most relevant cellular states a comprehensive and robust map of both genetical and physical interactions is required. To establish a generally applicable procedure as proof-of-principle the research group focused on the investigation of the functional connection between Parkinson's Disease-related genes.

The understanding of how genes functionally interact with a variety of molecular pathways in common networks is far from being complete. Mutations in Parkinson's Disease (PD) associated genes have been linked to multiple cellular processes including mitochondrial function, oxidative and endoplasmic reticulum stress responses as well as intracellular sorting. However, their physiological function and mechanistic contribution to pathological processes remain elusive. To target this specific question the group investigated the homologues of PD-related genes in *C. elegans* that represents an excellent model system. Based on the assumption that genes involved in the pathology of a certain disease are supposed to act in the same physiological pathway(s), the group started with genetical pilot experiments to test this hypothesis. Upon induction of both ER and oxidative stress they were able to show that the two PD-related kinases PINK-1 and LRK-1 are antagonistically connected (Sämann et al., 2009a).

In order to identify protein partners linking these two proteins the group performed protein-protein interaction studies using the Split-Ubiquitin system. The major limitation of the classical Y2H system is, that the detection of the interaction requires nuclear translocation of the interacting proteins. These are fused to the DNA-binding domain of a transcription factor on the one hand and to the transactivating domain on the other hand in a way that enables the reconstitution of a functional transcription factor. This readout excludes all proteins located in subcellular compartments or at the plasma membrane and also transcription factors that are already transactivating in yeast on their own. The yeast-split-ubiquitin system was developed to overcome these limitations. The major advantage of this approach is that no nuclear translocation is required for the interaction read-out. Consequently protein interactions can be detected at their native sites e.g. the plasma membrane, subcellular organelles and transcription factors can be used as baits.

Using the split-ubiquitin system the research group was able to identify in a non-saturating screen around 70 potential interaction partners for the two kinases. In order to identify cross-connecting pathway the group performed a systematic search for common targets and regulators of the interaction partners instead of using the classical intuition-based approach. Pathways were scored according to their relevance connecting PINK-1 and LRK-

1. Using this approach the group was able to postulate a potential connection between the two kinases through the Rho signaling pathway. In order to prove the postulated connection they genetically combined mutants of key members of the Rho signaling pathway with mutants lacking functional PINK-1 and LRK-1. As postulated by their network analysis approach the group was able to confirm the connection between PINK-1 and LRK-1 through the Rho signaling pathway using genetic epistasis analyses.

This approach represents a powerful tool to discover functional connection between different proteins of interest. However, the analysis is limited to a low number of proteins in a genetical network. To overcome this limitation the research group initiated collaborations with theoretical groups from the University of Freiburg (P. Pfaffelhuber) and the University of Magdeburg (U. Haus) to apply mathematical methods to model and understand large genetic networks based on genetic epistasis data.

In the project described above the group has demonstrated that a combination of physical and genetic interaction maps with theoretical modeling represents a powerful tool to investigate the crosstalk between proteins which defines the functional state of a cell under certain conditions. In order to get more robust interaction data the research group is currently establishing an automated platform to generate data of saturating screens validated by biochemical approaches in collaboration with A. Becker (Freiburg) and apply their platform for the investigation of other disease-related functional networks.

Joint research projects

- BIOSS
- FRIAS
- SFB 850

Selected cooperation partners

- Prof. Pfaffelhuber, ZBSA, University of Freiburg, Germany
- Dr. Brummer, ZBSA, University of Freiburg, Germany
- Prof. Anke Becker, Institute of Biology III, University of Freiburg, Germany
- Core Facilities ZBSA, University of Freiburg, Germany

Selected publications

- Springer, W., Hoppe, T., Schmidt, E., Baumeister, R. A *Caenorhabditis elegans* Parkin mutant with altered solubility couples alpha-synuclein aggregation to neurotoxicity. Hum. Mol. Genet. 2005 Oct 4
- Raphael Bluem#, Enrico Schmidt#, Carsten Corvey, Michael Karas, Andrea Schlicksupp, Joachim Kirsch and Jochen Kuhse. Components of the translational machinery are associated with juvenile glycine receptors and are redistributed to the cytoskeleton upon aging and synaptic activity (# these authors contributed equally to this work) J. Biol. Chem. 2007 Oct 26.
- *Caenorhabditits elegans* LRK-1 and PINK-1 Act Antagonistically in Stress Response and Neurite Outgrowth. Sämann J, Hegermann J, von Gromoff E, Eimer S, Baumeister R, Schmidt E. J Biol Chem. 2009 Jun 12;284(24):16482-91.

Prof. Matias Simons

University of Freiburg and University Hospital Freiburg
ZBSA
Simons research group

6 members of staff (biologists and physicians)

Cellular polarization is an important feature of development and critical for organ function. The well-known apical-basal polarity pathway allows organs/tissues to perform vectorial functions, including transport of fluid or directed secretion of specialized components. In addition, most epithelial tissues require a second axis of polarity, commonly referred to as planar cell polarity (PCP), which is within the plane of an epithelium. The PCP pathway contributes to the formation and maintenance of epithelia during development but also in adulthood. Recent discoveries have linked PCP factors to diseases, particularly genetic syndromes associated with ciliary functions.

In each tissue PCP generation can be subdivided into three steps:

1) definition of the source of a polarizing signal
2) reception and interpretation of the signal in single cells or groups of cells
3) organization of the cells in response to the signal

Although virtually nothing is known about the first step, a model of the Fz/PCP pathway and its regulation by some of the other PCP genes has emerged. This novel signaling pathway has been identified mainly through a genetic dissection in *Drosophila*. Based on the initial observation that the direction of PCP signaling depends on a Frizzled (Fz) gradient, the model suggests that Fz levels are sensed by Strabismus (Stbm or Vang). This leads to the formation of a complex of Stbm and Pk at the cell surface. Together, they act negatively on Dishevelled (Dsh) and Frizzled (Fz) possibly by interfering with the recruitment of Dsh to the membrane. The mutually exclusive interactions lead to an asymmetric distribution of the PCP core factors at the plasma membrane.

Using a genome-wide RNAi screen Professor Simons' research group could recently uncover a surprising connection between local pH and charge conditions and the subcellular localization of PCP core components. The group has since then focused on the role of electrochemical cues in the assembly of PCP signaling complexes at the plasma membrane. The group found that a PCP core protein, Dsh, requires the activity of a sodium-proton exchanger (Nhe2) at the plasma membrane in order to assume its subcellular distribution (Simons et al, Nature Cell Biology, 2009). This distribution is facilitated by the binding of Dsh to negatively charged lipids in an electrostatic manner. In addition, Dsh binds directly to its activating receptor, the G-protein coupled receptor (GPCR)-like Fz. Apart from Nhe2, the group also found other ion transporters such as the proton-pumping V-ATPase to be involved in *in vivo*-PCP signaling in *Drosophila* suggesting that ion fluxes, particularly those that involve protons, play a fundamental role in setting up PCP (Hermle et al, Current Biology 2010).

The group now aims to understand this relationship between ion transport and PCP at the systems level by studying cell behavior in an electrical field (EF). It has been known for quite some time that several *in vitro*-cell lines display oriented cell migration and cell division in EFs. Based on previous findings, the research group hypothesize that PCP core proteins are responsive to

electrical signals and therefore wants to study the role of PCP core proteins in EF-induced cell migration using RNAi and GFP-based live imaging technologies.
The group is also using *Drosophila* wing development and epidermal wound healing as *in-vivo* experimental models. The systems biology-based approach includes a mathematical description of cell behaviors in an electrical field as well as a multi-parametric analysis of the temporal and spatial distribution of PCP proteins during EF-induced polarization. For this, the group is collaborating with Hauke Busch from the ZBSA and FRISYS.

Special equipment and techniques

- Drosophila genetics, electrotaxis

Joint research projects

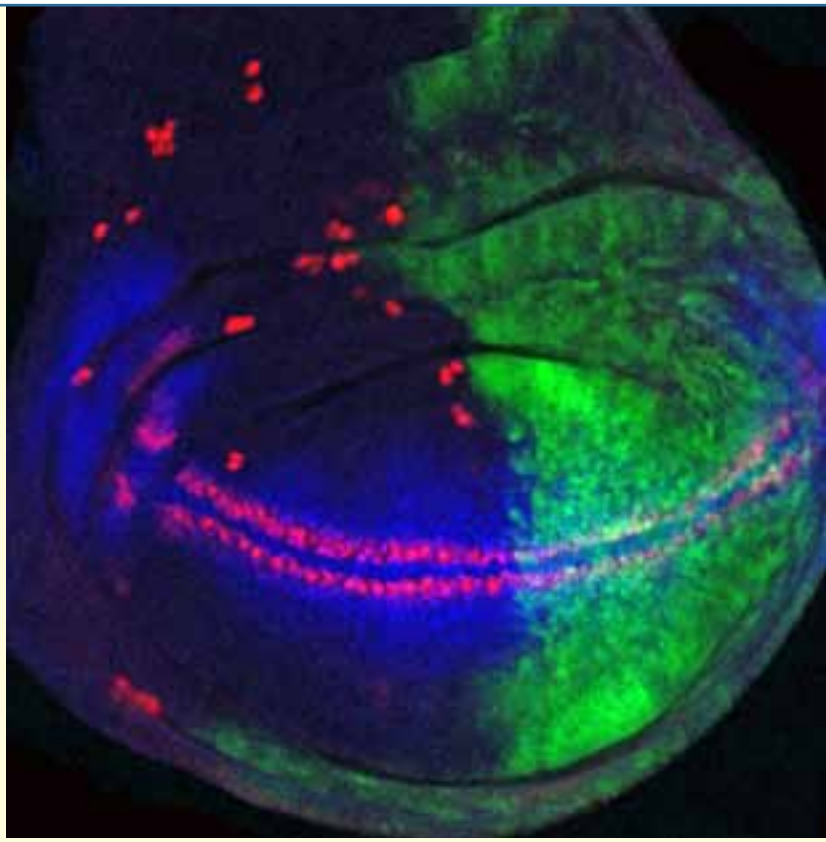
- FORSYS / FRISYS (BMBF)

Selected cooperation partners

- Dengjel, Busch, ZBSA, University of Freiburg, Germany
- Walz, Department of Internal Medicine IV, Renal Division, University Hospital Freiburg, Germany
- Boutros, German Cancer Research Center and University Heidelberg, Germany

Selected publications

- Hermle T, Saltukoglu D, Grünewald J, Walz G, Simons M (2010): Regulation of Frizzled-dependent planar polarity signaling by a V-ATPase subunit, Current Biology 20:1269-76.
- Simons M et al (2009): Electrochemical cues regulate the assembly of the Fz/Dsh complex at the plasma membrane during planar epithelial polarization, Nature Cell Biology 11:286-94.



Spatial expression of the Wingless target genes Senseless (red) and Distalless (blue) in the Drosophila imaginal wing disc. The posterior half of the wing disc is marked by GFP (green).

- Simons M et al (2005): Inversin, the nephronophthisis type II gene product, functions as a switch molecule between Wnt signaling pathways, Nature Genetics 37:537-43.

Prof. Jens Timmer

Delegate Executive Director

University of Freiburg
Institute of Physics / ZBSA
Data Analysis and Modelling of Dynamic Processes in the Life Sciences

35 members of staff (physicists, biologists, mathematicians, computer scientists)

The research group led by Prof. Timmer is developing mathematical methods for the modelling and systems analysis of dynamic models for use in cell biology. These methods are used in interdisciplinary projects, especially for biological applications, such as gaining deeper insights into signal transduction, gene regulation and pattern formation.

The group's systems biology approach involves the development of mathematical models of biological processes in order to gain an in-depth understanding of biological systems. This work is carried out in cooperation with biological partners. These studies then enable the researchers to gain insights into the design principles of systems and opens up possibilities of targeted intervention.
The group has developed numerous methods enabling the data-based modelling of biological systems, including methods used for experimental planning, parameter estimation, identifiability analyses and systems analysis.

At the beginning of any new project, the theoreticians of Timmer's group have to acquaint themselves with the underlying biological principles in order to share their mathematical modelling skills with their biological cooperation partners. Subsequently, the partners are able to plan the experiments jointly. Based on the experimental data, Timmer's group can then develop mathematical models in cooperation with their biological partners. Initially, the models provide the researchers with an idea on which additional data need to be acquired in order to develop valid mathematical models.

Iterative cycles of model-based experimental investigations and data-based modelling assist the researchers in obtaining a validated mathematical model of a system under consideration. The model's biological implications can subsequently be determined in cooperation with the experimental partners.

Joint research projects

- FRIAS
- Graduate College 1305 "Signalling systems in plant model organisms" (DFG)
- HepatoSys (BMBF)
- MedSysBio projects: LungSys, BreastSys, SARA (BMBF)
- SBCancer (Helmholtz Alliance)
- STREP CancerSys (EU: FP 7)
- Virtual Liver (BMBF)

Selected cooperation partners

- PD Dr. Ursula Klingmüller, German Cancer Research Center, Heidelberg, Germany
- Prof. Dr. Wolfgang Driever, Institute of Biology, University of Freiburg, Germany
- Dr. Maria Bartholome, Internal Medicine, Freiburg University Medical Center, Germany
- Prof. Dr Ralf Reski, Institute of Biology, University of Freiburg, Germany
- Prof. Dr. Wolfgang Hess, Institute of Biology, University of Freiburg, Germany

Selected publications

- D. Onichtchouk, F. Geier, B. Polok, D. Messerschmidt, R. Mössner, B. Wendik, S. Song, V. Taylor, J. Timmer, W. Driever. Zebrafish Oct4/Pou5f1-dependent transcriptional networks in temporal control of early development. Molecular Systems Biology 6, 2010, 354
- V. Becker, M. Schilling, J. Bachmann, U. Baumann, A. Raue, T. Maiwald, J. Timmer, U. Klingmüller. Covering a broad dynamic range: Information processing at the erythropoietin receptor. Science 328, 2010, 1404-1408
- A. Raue, C. Kreutz, T. Maiwald, J. Bachmann, M. Schilling, U. Klingmüller, J. Timmer. Structural and practical identifiability analysis of partially observed dynamical models by exploiting the profile likelihood. Bioinformatics 25, 2009, 1923-1929

Prof. Wilfried Weber

University of Freiburg
Institute of Biology II
„Synthetic Biology“

12 members of staff (biologists, chemists, engineers and biochemists)

The work of the research group is concentrating on signal-sensitive DNA-protein and protein-protein interactions that the researchers apply for the construction of synthetic genetic networks in mammalian cells, for the discovery of potential drugs against antibiotic-resistant bacteria, and for the synthesis of signal-sensing and signal-transducing biomaterials. Their systems approach is therefore rather synthetic than analytic: by the design, the mathematical modeling and the construction of biologic systems they aim at elucidating design principles and general strategies of how a biologic system with custom-tailored features can predictably be implemented.
The group has exemplified this approach by the construction of synthetic ecosystems in order to study interactions between multiple species and to gain insight into molecular tools and design principles that enable the synthetic communication between cells from different kingdoms. Based on this work the researchers were able to implement a synthetic ecosystem that emulated the interactions between a predator and a prey in order to investigate critical parameters that impact on the population density of both players.

Capitalizing on the molecular tools and implementation strategies for synthetic biologic systems that were developed in the above-described studies the group designed and constructed *Mycobacterium tuberculosis*-derived genetic networks in human cells in order to discover small molecule compounds that interfere with antibiotic resistance pathways. The molecules discovered in this study efficiently repressed the antibiotic resistance in tubercle bacteria and therefore enabled to eliminate the causative agent of tuberculosis by approved antibiotics at a very low dose.

In an interdisciplinary approach the Weber group transfers the signal-sensing and signal-transducing proteins from biology into materials science in order to synthesize hydrogels that perceive an external signal and respond to it, for example by the inducible release of a therapeutic growth factor. The overall goal of this study is to design smart implantable materials that perceive a pathologic signal in the body (e.g. pathologic metabolite concentration) and autonomously trigger a corrective response for example by the release of a therapeutic agent.

In order to perform this work, the lab is equipped for molecular and cell biology as well as for the chemical synthesis and characterization of polymers. The group has various collaborations with partners from biology, engineering, physics and materials science in order to jointly address the multidisciplinary challenges in the ongoing and future research work.

Special equipment and techniques

- Equipment for molecular and cell biology and organic chemistry.

Joint research projects

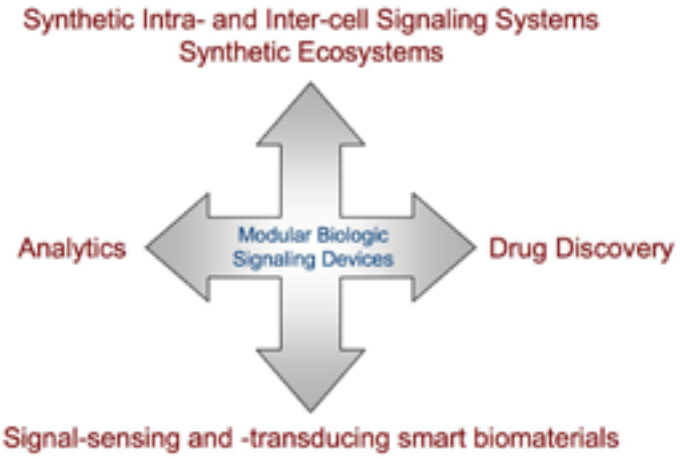
- BIOSS

Selected cooperation partners

- Prof. Martin Fussenegger, Molecular Biotechnology, ETH Zurich, Switzerland
- Prof. Dr. Matthias Lütolf, Laboratory of Stem Cell Bioengineering, EPFL Lausanne, Switzerland
- Prof. Dr. Andreas Herrmann, Polymer Chemistry and Bioengineering, University of Groningen, The Netherlands
- Dr. Martin Ehrbar, Department of Obstetrics, University Hospital Zurich, Switzerland
- Dr. Nediljko Budisa, Molecular Biotechnology, Max Planck Institute of Biochemistry, Munich, Germany

Selected publications

- Ehrbar M, Schoenmakers R, Christen EH, Fussenegger M, Weber W (2008). Drug-sensing hydrogels for the inducible release of biopharmaceuticals. Nature Materials 7, 800-804
- Weber W, Schoenmakers R, Keller B, Gitzinger M, Grau T, Daoud-El Baba M, Sander P, Fussenegger M (2008). A synthetic mammalian gene circuit reveals anti-tuberculosis compounds. PNAS 105, 9994-9998
- Weber W, Daoud-El Baba M, Fussenegger M (2007). Synthetic ecosystems based on airborne inter- and intrakingdom communication. PNAS 104, 10435-10440



Research areas in the group of Prof. Weber: The research group is developing new signaling systems in mammalian cells for drugdiscovery, analytics, ecology and materials science.

Other research groups in Baden-Württemberg


Dr. Michael Bonin S. 214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Dr. Michael Bonin

University Hospital Tübingen
Institute for Human Genetics
Transcriptomics

13 members of staff (5 biologists, 2 physicians, 2 bioinformaticians and 4 lab technicians)

The Working Group Transcriptomics of the Institute for Human Genetics, has a long experience in the systems biology analysis of transcription profiles, as well as neurotranscriptional characterization of animal and cell culture models of neurodegenerative diseases. Michael Bonin has also in recent years very successfully worked in the framework of European projects on neurodegenerative diseases (EUROSCA, GENEPARK).

GENEPARK, one project, has set itself the goal of defining biomarkers on the basis of the blood for the Parkinson's disease and its genetic forms. The world's largest blood bank samples (PAXgene tubes, BD) in Tübingen, with more than 1,000 Parkinson's patients is being established and will be brought together with its partners in the consortium under standardized conditions of expression profiles. Because of his long experience of microarray-based analysis of systems processes, he has a dense network of cooperation partners (Ulrich Zanger, Matthias Schwab, Marius Ueffing, Andreas Zell), which allows an optimized processing of holistic systems biology cases.

Special equipment and techniques

- Microarray applications involving three independent microarray platforms: Affymetrix, Illumina, Agilent
- Expression analyses, genotyping analyses, SNP arrays, copy number analyses

Joint research projects

- SysMO (BMBF)
- Clinical Research Group: Hereditary retinal disorders: clinical aspects, genetic and animal models (DFG)
- MEFOPA (EU)
- Individual Liver (BMBF)

Selected cooperation partners

- Dr. Kay Nieselt, Center for Bioinformatics Tübingen, University of Tübingen, Germany
- Prof. Andreas Zell, Wilhelm-Schickard-Institute for Computer Science, University of Tübingen, Germany
- Prof. Ulrich Zanger and Prof. Matthias Schwab, Dr. Margarete Fischer-Bosch-Institute of Clinical Pharmacology, Stuttgart, Germany

Selected publications

- Nieselt K, et al. The dynamic architecture of the metabolic switch in *Streptomyces coelicolor*. BMC Genomics. 2010 Jan 6; 11(1):10.
- Simón-Sánchez J, et al. Genome-wide association study reveals genetic risk underlying Parkinson's disease. Nat Genet. 2009 Dec; 41(12):1308-12.
- Berkel S, Marshall CR, Weiss B, Howe J, Roeth R, Moog U, Endris V, Roberts W, Szatmari P, Pinto D, Bonin M, Riess A, Engels H, Sprengel R, Scherer SW, Rappold GA. Mutations in the SHANK2 synaptic scaffolding gene in autism spectrum disorder and mental retardation. Nat Genet. 2010 Jun;42(6):489-91.

Dr. Karsten Borgwardt

Max Planck Campus Tübingen
MPI for Biological Cybernetics and MPI for Developmental Biology
Machine Learning & Computational Biology

8 members of staff (4 bioinformaticians, 2 computer scientists, 1 physicist and 1 mathematician)

The focus of the "Machine Learning & Computational Biology" research group is algorithmic systems biology. The research reaches deep into systems biology, bioinformatics and statistical genetics, but also into machine learning, data mining and scientific computing. The group develops algorithms and statistical tests to examine the effect of single genes on a biological system. The methods are part of the field of "Machine Learning". Machine Learning is concerned with the development of computer-based statistical procedures for finding patterns and dependencies in large volumes of data.

The Machine Learning & Computational Biology group develops such techniques in order to predict the function of a gene or a chemical compound. For this purpose, graph-based techniques are of utmost importance. This is due to the fact that graphs can be used to model the interactions of genes and proteins, or to describe the structure of a molecule. For this reason, machine learning on graphs and networks is a central research topic of the group.

Furthermore, Dr. Borgwardt's group works on Machine Learning methods for genome-wide association studies. Here the group studies whether sequence variation in the genomes of individuals leads to phenotypic variation. In collaboration with Prof. Dr. Detlef Weigel's department at the Max Planck Institute for Developmental Biology in Tübingen, Dr. Borgwardt's team analyzes the role of genetic factors in the variation in flowering time in *Arabidopsis thaliana*. With the Max Planck Institute for Psychiatry in Munich, the research group explores the question whether one can predict the response of a depressive patient to treatment with antidepressants.

Special equipment and techniques

- Machine Learning in Systems Biology

Joint research projects

- Microsoft Research Cambridge

Selected cooperation partners

- Prof. Bertram Müller-Myhsok, Max Planck Institute of Psychiatry, Munich, Germany
- Prof. Alexander Smola, Yahoo! Research, Santa Clara, USA
- Prof. Zoubin Ghahramani, University of Cambridge, UK

Selected publications

- Shervashidze, N. and Borgwardt, K. M.: Fast subtree kernels on graphs. Advances in Neural Information Processing Systems 22: Proceedings of the 2009 Conference (NIPS 2009), 1660-1668. (Eds.) Bengio, Y., Schuurmans, D., Lafferty, J., Williams, C., Culotta, A. (01 2010).
- Stegle, O., Denby, K., Wild, D.L., McHattie, S., Mead, A., Ghahramani, Z. and Borgwardt, K.M.: A robust Bayesian two-sample test for detecting intervals of differential gene expression in microarray time series. Journal of Computational Biology, 2010, 17(3):355-367.
- Lippert, C., Ghahramani, Z. and Borgwardt, K.M.: Gene function prediction from synthetic lethality networks via ranking on demand. Bioinformatics, 2010, 26(7):912-918.

Dr. Gary Davidson

Karlsruhe Institute of Technology
Institute of Toxicology and Genetics
Systems biochemistry of signal transduction

3 members of staff (biologists)

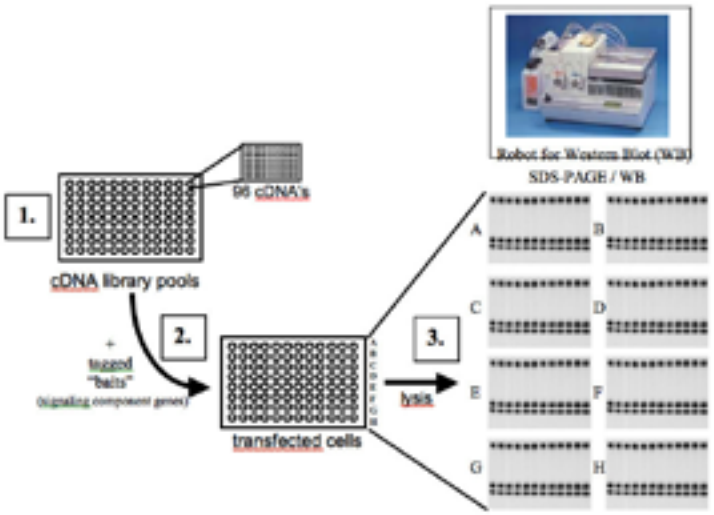
Signal transduction is mediated via intricate networks of proteins that transfer information within and between cells and is a fundamental mechanism that controls their function and behaviour. In multicellular organisms signaling pathways have evolved to co-ordinate multiple cell-cell communications and embryonic development is a remarkable example of how cells faithfully integrate signals from a complex and dynamic environment. Surprisingly few signaling pathways have been identified that are critical for embryonic development but the complexity within and between pathways is high.

Generally, development signaling pathways are activated when extracellular signaling molecules, called ligands, bind to trans-membrane receptors proteins on the cell surface. Receptor activation then initiates a cascade of molecular events that relays and transduces information within the cell. Such signal propagation is achieved mainly through regulatory modification of the individual signaling components. Most of the so-called "core components" of developmental signaling pathways are known and a major challenge now is to identify the modifiers that regulate these components through post-translational modifications (PTM).

Expression screening principle for detection of signaling pathway component modifications:
Mammalian cell based expression screening is used to detect PTM of signaling components. Dr. Davidson's research group simultaneously overexpresses signaling components with cDNA library clones and then screens for the ability of library products to modify the chosen signaling proteins, using SDS-PAGE / Immunoblot as a read out (see figure). The researchers can transfect pools of cDNA clones without loss of sensitivity in such screening experiments. Indeed the up-shift (a common modification seen by SDS-PAGE/WB) of the Wnt receptor LRP6, caused by CK1γ, was easily visualized upon its overexpression in a pool of 96 cDNA library clones. The pooling feature significantly reduces overall screening time and associated costs. The simple design and reductionist approach of the screening strategy allows not only identification of novel regulatory modifiers of signaling, but also the signaling component(s) they effect. This simplifies the process of critical evaluation of potential candidates and is an important aspect considering overexpression-based artefacts can be detected. A major advantage of working with developmental signaling pathways is their evolutionarily conserved nature, which allows libraries from one species to be used with signaling components from another, without compromising function. Indeed, the research group has identified modifiers from both *Xenopus* and *Drosophila* libraries, after overexpression with human signaling components. The group therefore takes full advantage of this conservation and swap libraries and species to best suit screening needs.

High throughput detection of post-translational modification in cell signaling pathways using a microfluidics based biosensor platform:
The research team's primary method of polyacrylamide gel electrophoresis and Western Blot (SDS-PAGE/WB) analysis, although robust, lacks the key ability to be scaled up to very high throughput levels. Through collaboration

with the group of Bastian Rapp at the institute for microstructure technology (IMT), the researchers are developing an integrated detection platform consisting of Surface Acoustic Wave (SAW) biosensor chips harbouring antibodies that recognize signaling components or their specific modification. These biosensors can detect proteins in complex aqueous samples, such as cellular lysates and the researchers are adapting this technology for high throughput (HT) protein modification analysis. In order to achieve this the team is developing automated sample delivery to multiple SAW sensor arrays via a microfluidic system.



Schematic example of screening platform to identify novel modifiers.

Special equipment and techniques

- Automated robots for high throughput Western Blot screening (16 miniblots siultaneously)

Joint research projects

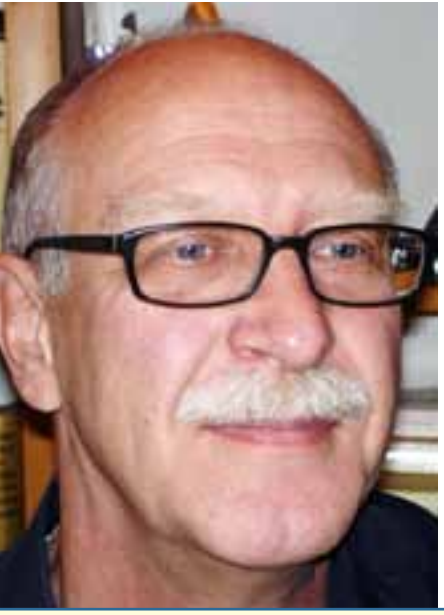
- BioInterfaces Twinning Project (Helmholtz Association)

Selected cooperation partners

- Dr. Bastian Rapp, Institute for Microstructure Technology, Karlsruhe Institute of Technology, Germany

Selected publications

- Davidson G., Shen J., Huang Y.L., Yi S., Karaluanov E., Bartscherer K., Hassler C., Boutros M., Niehrs C. (2009) Cell cycle control of Wnt receptor activation. Dev Cell. Dec 17(6):788-99.
- Davidson G., Wu W., Shen J., Bilic J., Fenger U., Stannek P., Glinka A., Niehrs C. (2005) Casein kinase 1 gamma couples Wnt receptor activation to cytoplasmic signal transduction. Nature 438, 867-72.
- Bilic J., Huang Y.L., Davidson G., Zimmermann T., Cruciat C.M., Bienz M., Niehrs C. (2007) Wnt induces LRP6 signalosomes and promotes dishevelled-dependent LRP6 phosphorylation. Science. Jun 15;316(5831).



Prof. Gerd Döring

University of Tübingen
Institute of Medical Microbiology and Hygiene
Mucoviscidosis

Approximately 8 members of staff (biologists, physicians and pharmacists)

Cystic fibrosis is the most common autosomal recessive lethal hereditary disorder in Caucasians. The causative gene, named CF transmembrane conductance regulator (CFTR), encodes a chloride channel in epithelial cells. Abnormal transport of chloride and sodium ions affects water movement across epithelia leading to pathophysiological consequences in various organs including the respiratory, gastrointestinal and reproductive tract, the pancreas and liver. The prognosis of the disease is substantially dependent on chronic respiratory infection and inflammation, a hallmark of CF. *Pseudomonas aeruginosa* is the dominating pathogen today in CF patients.

Prof. Döring's research group pursues several topics in the field of CF:

1. Mechanisms of colonization, adaptation and virulence of CF-related pathogens in CF airways
2. Mechanisms of inflammation and tissue remodelling in chronically infected CF airways
3. Antibiotic therapy strategies against CF-related pathogens
4. Vaccine and immunotherapy against *P. aeruginosa*
5. Tyrosine nitration in eosinophils

1. Mechanisms of colonization, adaptation and virulence of CF-related pathogens in CF airways:
The research group has demonstrated that bacteria invading the CF lung are trapped in this viscous mucus layer on top of respiratory epithelial cells, where they encounter microaerophilic or anaerobic growth conditions. The group demonstrated that these conditions in the CF mucus trigger a switch of *P. aeruginosa* and *S. aureus* from non-mucoid to mucoid cell types. In a cooperation with Erich Gulbins, University of Essen-Duisburg, the group described the accumulation of ceramide in the lungs of *cftr*-deficient mice and in epithelial cells from CF patients. As a consequence, the rate of cell death increased in respiratory epithelial cells of uninfected CF mice, resulting in the formation of DNA deposits on the respiratory epithelium, which facilitated bacterial infection. Several animal models have been developed to study the virulence of CF-related bacterial pathogens. Recently the virulence of strict anaerobic bacteria in CF airways has been investigated.

2. Mechanisms of inflammation and tissue remodelling in chronically infected CF airways:
Prof. Döring's group has investigated the role of neutrophil elastase as a regulatory enzyme in chronic inflammation, for example, its effects on opsonophagocytosis, immunoglobulins and cell receptors on neutrophils and T cells. Ongoing work concerns the role of NKT cells in CF.

3. Antibiotic therapy strategies:
The research group has demonstrated that early antibiotic therapy leads to eradication of *P. aeruginosa*. Currently the researchers of the group tested the *in vitro* activity of various antibiotics and other antimicrobial compounds against CF-specific pathogens, grown as biofilms *in vitro* and in animal models.

4. Vaccine and immunotherapy against *P. aeruginosa:*
Prof. Döring's group has carried out a placebo-controlled, randomized and double-blind multi-centre study, involving

483 CF patients without *P. aeruginosa* lung infection, using a bivalent flagella vaccine. The degree of protection against *P. aeruginosa* infection, calculated from the relative risk was 34%.

5. Tyrosine nitration in eosinophils:
The group has shown that eosinophils contain nitrotyrosine-positive proteins in specific granules, has identified the nitrosylated tyrosine residues in these proteins and unravelled the mechanism leading to tyrosine nitrosylation.

Special equipment and techniques

- Animal models
- Cell culture
- Serology

Selected cooperation partners

- Prof. Burkhard Tümmler, Hannover Medical School, Germany
- Prof. Soeren Molin, Technical University of Denmark, Lyngby, Denmark
- Dr. Thomas Eiwegger, Swiss Institute of Allergy and Asthma Research, Davos Platz, Switzerland
- Stephen Lory, Harvard Medical School, Boston, USA
- Dr. Mark L. Barr, University of Southern California, Los Angeles, USA

Selected publications

- Bragonzi A, Paroni M, Nonis A, Cramer N, Montanari A, Rejman J, Di Serio C, Döring G, Tümmler B. *Pseudomonas aeruginosa* microevolution during cystic fibrosis lung infection establishes clones with adapted virulence. Am J Respir Crit Care Dis, 2009;180:138-45.
- Ulrich M, Petre A, Youhnovski N, Prömm F, Schirle M, Schumm M, Pero RS, Doyle A, Checkel J, Kita H, Thiyagarajan N, Acharya KR, Schmid-Grendelmeier P, Simon H-U, Schwarz H, Tsutsui M, Shimokawa H, Bellon G, Lee JJ, Przybylski M, Döring G. Post-translational tyrosine nitration of eosinophil granule toxins mediated by eosinophil peroxidase. J Biol Chem 2008;243:28629-40.
- Teichgräber V, Ulrich M, Riethmüller J, Grassme H, Wilker B, De Oliveira-Munding CC, van Heeckeren AM, Barr M, von Kürthy G, Schmid KW, Weller M, Tümmler B, Lang F, Döring G, Gulbins E. Ceramide accumulation mediates inflammation, cell death and infection susceptibility in cystic fibrosis. Nat Med 2008;14:382-91.

Prof. Peter Dürre

University of Ulm
Institute of Microbiology and Biotechnology

25 members of staff

Clostridium acetobutylicum is an anaerobic bacterium that grows exclusively in the absence of oxygen. It has a fermentative metabolism which enables it to convert sugars such as glucose into butyric and acetic acid. However, the accumulation of the excreted acids in the environment puts *C. acetobutylicum* in life-threatening danger. To counteract this threat, the bacterium starts to take up the acids again and converts them into acetone and butanol, thereby securing its survival for further reproduction cycles and for the generation of endospores. However, this particular metabolic pathway is a dead end since higher butanol concentrations are also toxic for the bacteria.

C. acetobutylicum, and particularly its ability to produce acetone and butanol, is of great interest for industry. The two solvents are used in the chemical industry. Moreover, butanol is also of major interest for its ability to be used as biofuel (extender). It can be mixed with petrol in any concentration without having any negative effect on engine capacity. Butanol is less corrosive than ethanol, is easier to handle and, in addition, has better consumption values.
Until the middle of the last century, acetone and butanol were biotechnologically produced on a large scale. In fact, this is the most important and largest-scale industrial fermentation process that has been applied anywhere in the world to date. From 1950 onwards, crude oil was seen as a considerably cheaper starting material for producing acetone and butanol, which led to biotechnological production being stopped.
The dramatic increase in the price of oil and dwindling crude oil reserves have once again put the fermentative production of acetone and butanol with the aid of *C. acetobutylicum* under the spotlight. New methodological developments in molecular biology – generally known as "omics" technologies and also systems biology approaches – can be used for the development of tailor-made production strains. This makes it possible to more economically produce acetone and butanol as bulk materials for chemical synthesis and, moreover, in a CO2-neutral manner.

The objective of the project is to model and understand on the molecular and cellular level the mechanisms that enable *C. acetobutylicum* to switch its metabolism from producing acids to producing solvents. The individual processes in the cell, i. e. the metabolic pathways leading from the sugar substrate to acetic and butyric acid or butanol and acetone, are well known. This knowledge is used to establish computer models to make predictions on metabolic processes under certain conditions. The models also take into account the influence of other cells in the environment, i. e. the communication between bacteria (quorum sensing), the glycosylation of proteins in the cells, the substrates of different oxidation states and external stress factors such as heat or butanol.

The investigations are based on transcription analyses involving DNA microarrays, which, in addition to other methods used in functional genomics, are especially well suited for identifying the relevant components of a system and simultaneously analysing as many individual components as possible. DNA microarrays enable the quantitative determination of the transcription of all genes of a genome. Proteomics and metabolomics techniques provide information on which transcripts are converted into functional proteins and on their activity.

In order to investigate the two extreme points in the *C. acetobutylicum* metabolism, the bacteria are initially grown under defined conditions in continuous culture in which the final products are constantly withdrawn. On the one hand, this leads to sustained acid formation and, on the other hand, to the permanent production of solvents. After the identification of the genes that are differently expressed in these two extreme states, i. e. genes that belong to either the acid or the solvent metabolism, it is necessary to look for mechanisms that underlie this switch. In order to do this, the pH value of the cultures is modified and samples are removed for transcriptome analyses. In this way, it is possible to monitor the expression of the genes that are involved in switching between the two metabolic pathways.

The experimental data are subsequently used to develop a quantitative model containing all the information about the transcriptome, proteome and metabolome as well as about the different conditions and metabolic situations.
The model is used to simulate the processes that occur when the bacteria switch from the production of acids to the production of solvents. This should help to identify the key sensors and switches between the two alternative metabolic pathways. In addition, a suitable model generates predictions relating to production under modified conditions, thereby increasing the options for large-scale application of the bacteria, in which either alternative substrates are used or the final products are permanently withdrawn during the fermentation process. These insights will help to improve the biotechnological production of acetone and butanol, for example by creating ideal culture conditions, and potentially also by manipulating the key proteins involved.

Special equipment and techniques

- Anaerobic methods

Joint research projects

- SysMO (Systems biology of microorganisms)/ SysMO2 (BMBF)

Selected cooperation partners

- Hubert Bahl/Ralf-Jörg Fischer/Olaf Wolkenhauer/ Thomas Millat, University of Rostock, Germany
- Willem de Vos/Servé Kengen, Wageningen University, The Netherlands
- Armin Ehrenreich, TU München, Germany
- Matthias Reuss/Peter Götz, University of Stuttgart/ Beuth Hochschule Berlin, Germany
- Nigel Minton/Klaus Winzer/John King/Sara Jabbari, University of Nottingham, UK

Selected publications

- Dürre P, Ehrenreich A (2008) *Clostridium acetobutylicum* - a response to dwindling crude oil reserves. In: Reinberger S (ed) Systems Biology. Results, Progress and Innovations from BMBF Funding, Forschungszentrum Jülich GmbH, Jülich, pp. 56-57.
- Dürre P (2009) Metabolic networks in *Clostridium acetobutylicum*: interaction of sporulation, solventogenesis and toxin formation. In: Brüggemann H, Gottschalk G (eds) Clostridia. Molecular Biology in the Post-genomic Era, Caister Academic Press, Norfolk, UK, pp. 215-227.
- Dürre P (2009) Biotech Genomics - Genome-based Analysis of Biotechnologically Relevant Prokaryotes (ed) J Mol Microbiol Biotechnol 16: issue 1-2.

Dr. Hans A. Kestler

University of Ulm
Institute of Neural Information Processing
Bioinformatics and Systems Biology group

6 members of staff (computer scientists and biologists)

Research in biology will increasingly focus not only on local interactions of DNA, RNA, and proteins but rather on biological systems. The fundamental concept of the systems approach is that biology is basically an informational science. We believe that this approach, which includes quantitative measurements, global measurements, the integration of these measurements, and the accounting for dynamics, will revolutionize biology and medicine. This is already evident nowadays as misregulation of certain signaling pathways lead to various diseases such as cancer.

The Kestler research group builds models for signal transduction and gene regulation based on current knowledge of different granularity in order to generate new hypothesis that can be verified by experimentally oriented research groups.

The systems approach in molecular biology requires the generation and formalization of knowledge on different levels; this includes establishing links between genes and cell status, characterization of co-regulated genes or associating gene changes to pathways or networks. The methods used for these investigations largely stem from the field of machine learning. The group recently was able to find generalization error bounds, which can be used for model selection, for conjunctions of Boolean variables for classification. The group is currently further investigating this topic with particle swarm algorithms. How to arrive at these Boolean variables, i.e. how to binarize data from gene expression values in a well-defined way is another topic of current research. This is also directly linked to modeling signal transduction and gene regulation with Boolean functions from data via reverse engineering.

Other approaches that are investigated are models based on differential equations, which consist of many parameters that cannot all be estimated from data, but rather call for the inclusion of more global knowledge. In this regard the group was able to extend a model of the Wnt/β-catenin pathway via time-delay differential equations and substantiate the models principal behavior via an extended robustness analysis. Currently it is extending this model by integrating the receptor complex formation and by building a more abstract rule-based model integrating the canonical Wnt/b-catenin-, the Wnt/calcium and the Wnt/JNK pathways.

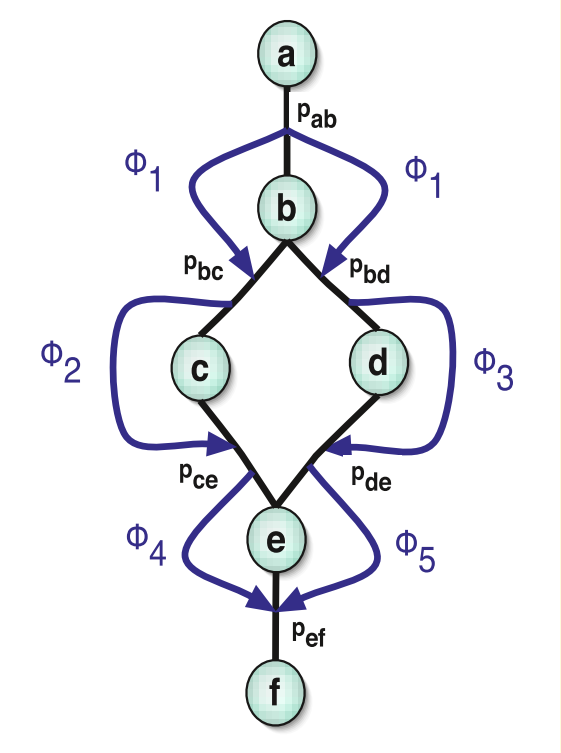
Associating genes to functional categories and ultimately to pathways is a step in identifying interaction partners. The research group recently was able to devise a method that facilitates this complex task by recognizing the important functional categories related to a gene expression microarray experiment via Euler/Venn diagrams.

Selected cooperation partners

- Michael Kühl, Institute for Biochemistry and Molecular Biology, University of Ulm, Germany
- K. Lenhard Rudolph, Institute of Molecular Medicine, University of Ulm, Germany
- Luc de Raedt, Department of Computer Science, Katholieke Universiteit Leuven, Belgium
- Thomas M. Gress, Department of Internal Medicine, University Hospital Giessen and Marburg, Germany

Selected publications

- Meyer LH*, Eckhoff SM*, Queudeville M, Kraus JM, Giordan M, Stursberg J, Zangrando A, Vendramini E, Moericke A, Zimmermann M, Schrauder A, Lahr G, Holzmann K, Schrappe M, Basso G, Stahnke K*, Kestler HA*, te Kronnie G*, Debatin KM. Early Relapse in Pediatric ALL is identified by Time To Leukemia in NOD/SCID mice and is characterized by a gene signature in- volving survival pathways. Cancer Cell, 19(2):206-17, 2011. * equal contribution
- Kestler HA, Müller A, Kraus JM, Buchholz M, Gress TM, Liu H, Kane DW, Zeeberg BR, Weinstein JN. VennMaster: Area-proportional Euler diagrams for functional GO analysis of microarrays. BMC Bioinformatics, 9(1):67, 2008.
- Wawra C, Kühl M, Kestler HA. Extended analyses of the Wnt/beta-catenin pathway: Robustness and oscillatory behaviour. FEBS Lett, 581/21:4043–4048, 2007.



Rule based random graph model for modeling qualitative interactions in signaling networks. Edge probabilities p_t are represent interaction probabilities (in its broadest sense) and then apply rules Φ that modify p_t based on the current edge state of the graph (interaction present or not) and the current probability distribution.

Prof. Oliver Kohlbacher

University of Tübingen
Center for Bioinformatics Tübingen
Simulation of Biological Systems

Approximately 20 members of staff (bioinformaticians, informaticians, chemists, biochemists and biotechnologists)

The group of Oliver Kohlbacher is concerned with the analysis of omics data (in particular proteomics and metabolomics), the integration of these data in a data warehouse and the interpretation of omics data in the context of biological networks. The group is one of the leading groups in the analysis of mass spectrometry-based data from proteomics and metabolomics and has developed a large open-source software package (OpenMS/TOPP) for data analysis that is being widely used in Academia.

The integration of omics data in the context of biological networks allows the identification of the underlying biological processes as well as deregulated or modified subnetworks. For the integration Prof. Kohlbacher's research group has developed together with several other groups a large software package for data integration, BN++, and used it to implement an integrative data warehouse providing full semantic integration of large data sets. For the interactive visual exploration of these data the research group uses network visualization techniques and automated analysis techniques. These help with the identification of the relevant parts of the networks and forming hypothese on the underlying biological processes. These techniques are applied to numerous problems in biomedicine and biochemical engineering. The group has a strong focus on the analysis of cancer-related data, general immunological data and data related to diabetes. Other work concerns simpler model systems such as *E. coli*, corynebacteria, or yeast.

Special equipment and techniques

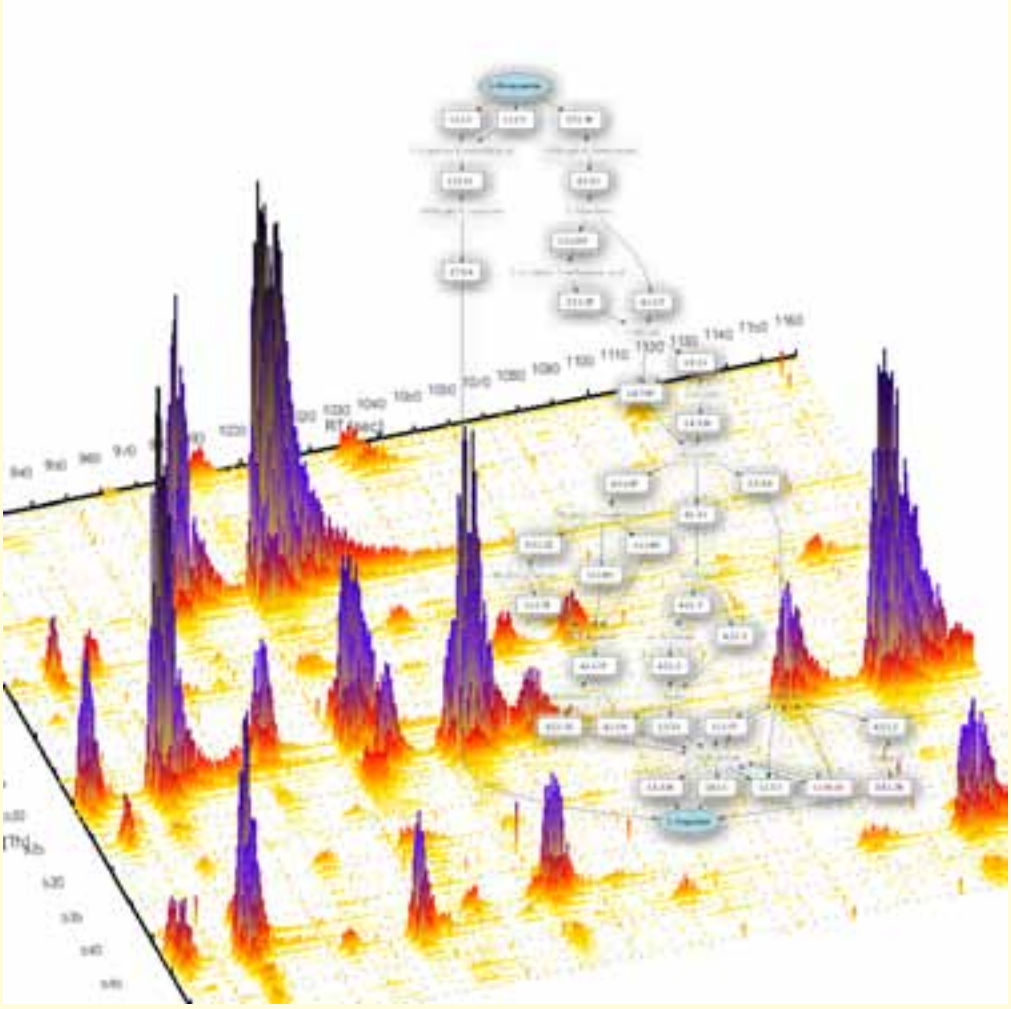
- Several large computer clusters
- Analysis and interpretation of high-throughput transcriptomics, metabolomics and proteomics data
- Modelling of biological networks
- Computational immunomics
- Structural bioinformatics

Selected cooperation partners

- Prof. Knut Reinert, Freie Universität Berlin, Germany
- Prof. Albert Sickmann, Leibniz-Institut für Analytische Wissenschaften, Dortmund, Germany
- Prof. Christian Huber, Paris Lodron University of Salzburg, Austria
- Prof. Hans-Peter Lenhof, Saarland University, Saarbrücken, Germany
- Prof. Jens Timmer, FRIAS, Freiburg, Germany

Selected publications

- Gehlenborg, N, O'Donoghue, SI, Baliga, NS, Goesmann, A, Hibbs, MA, Kitano, H, Kohlbacher, O, Neuweger, H, Schneider, R, Tenenbaum, D, and Gavin, A (2010). Visualization of omics data for systems biology. Nat. Methods, Mar; 7(3 Suppl):s56-58.
- Blum, T, and Kohlbacher, O (2008). MetaRoute - fast search for relevant metabolic routes for interactive network navigation and visualization. Bioinformatics, 24(18):2108-2109.
- Kohlbacher, O, Reinert, K, Gröpl, C, Lange, E, Pfeifer, N, Schulz-Trieglaff, O, and Sturm, M (2007). TOPP - The OpenMS Proteomics Pipeline. Bioinformatics, 23(2):e191-e197.



Modern mass spectrometry techniques generate very comprehensive and complex data. The automatic analysis of the data provides detailed insights into the dynamics of biological networks."

Dr. Urban Liebel

Karlsruhe Institute of Technology
Institute of Toxicology and Genetics
High content screening, image processing and bioinformatic information harvesting

9 members of staff (biologists, engineers, bioinformaticians, informaticians and software developers)

Dr. Liebel's group develops novel High Content Screening platforms. Every platform requires five core technologies.

a) Assay development and adaptation to automated assays (in cooperation with Dr. Grabher, Prof. Strähle and Prof. Wittbrodt)
b) Robotic sample handling systems for sample transport storage and image acquisition (in cooperation with Dr. Schulz)
c) Development of novel high throughput microscopes (in cooperation with Leica microsystems, Olympus Europe and Dr. Schulz)
d) Development of efficient storage methods and ultra fast image processing algorithms (in cooperation with Jos van Wezel, Dr. Reischl and Dr. Mikut)
e) Development of novel Search engine technologies, which integrate millions of documents from various research institutes (e.g. Bioinformatic Harvester and Sciencenet)

High Content Screening Platforms can acquire and analyze up to 200.000 biological samples per day. Samples can be subcellular structures in the 500nm range up to entire zebrafish (cm range). The research group develops its control software modules in the graphical programming language LabView. This allows even non software developers to easily use the developments of Dr. Liebel's researchers. The commercially available Scan^R Screening microscope software (Olympus Europa) which was co-developed by the researchers and which is used in over 70 labs worldwide, is such an example.

Only efficient automation technologies allow entire genome investigations. Sometimes millions of images are acquired to identify a novel gene or to investigate the effects of chemical compounds.

In close collaboration with the Large Scale Data Facility (Steinbuch Centre for Computing, KIT) the research group develops efficient storage and image processing methods.

The group's search engine research and development projects integrate large scale data sources. For example the Bioinformatic Harvester integrates the top 50 bioinformatic databases in a google like search interface. It is used by 10.000 scientists every day. The Sciencenet integrates some 1.000.000.000 scientific documents in a peer-to-peer search engine environment, which will ultimately allow to integrate all scientific data of all types.

Special equipment and techniques

- High-speed microscopes
- Intelligent microscopes that can autonomously identify structures of interest
- Rapid image processing and image processing clusters
- Distributed scientific search engine for 1.000.000.000 documents
- Bioinformatics search engine for real-time searches of over 50 databases

Joint research projects

- BioInterfaces (Helmholtz Association)

Selected cooperation partners

- Uwe Strähle and Clemens Grabher, Institute of Toxicology and Genetics, Karlsruhe Institute of Technology, Germany
- Markus Reischl, Stefan Schulz and Ralf Mikut, Institute for Applied Computer Science, Karlsruhe Institute of Technology, Germany
- Stefan Bräse, Institute of Organic Chemistry, Karlsruhe Institute of Technology, Germany
- Jos van Wezel, Steinbuch Centre for Computing, Karlsruhe Institute of Technology, Germany
- Joachim Wittbrodt, Institute of Zoology, Universität Heidelberg, Germany

Selected publications

- Gehrig J, Reischl M, Kalmar E, Ferg M, Hadzhiev Y, Zaucker A, Song C, Schindler S, Liebel U, Müller F. Automated High Throughput Mapping of Promoter-Enhancer Interactions in Zebrafish Embryos. Nature Methods, 6, S. 911-916; 2009.
- Neumann B, Walter T, Hériché JK, Bulkescher J, Erfle H, Conrad C, Rogers P, Poser I, Held M, Liebel U, Cetin C, Sieckmann F, Pau G, Kabbe R, Wünsche A, Satagopam V, Schmitz MH, Chapuis C, Gerlich DW, Schneider R, Eils R, Huber W, Peters JM, Hyman AA, Durbin R, Pepperkok R, Ellenberg J. Phenotypic profiling of the human genome by time-lapse microscopy reveals cell division genes. Nature. 2010 Apr 1;464(7289):684-5.
- Neumann B et al. Phenotypic profiling of the human genome by time-lapse microscopy reveals cell division genes. Nature 464, 721-727 (1 April 2010).

Dr. Daniel Mertens

University Hospital Ulm
Department of Internal Medicine III
DKFZ Cooperation Unit „Mechanisms of Leukemogenesis“

7 members of staff

In leukemogenesis, genetic and epigenetic lesions are complemented by leukemia-specific interactions with the non-malignant microenvironment. Chronic lymphocytic leukemia (CLL) is an excellent model system to investigate the synergy of intracellular pathomechanisms with the leukemogenic microenvironment. Although CLL is the most common leukemia in the western world, the underlying pathomechanism remains mostly unclear. In addition to intracellular defects, the microenvironmental niche is important as a functional unit required for proliferation and survival of tumor cells. The interaction between malignant and non-malignant cells is bidirectional, and the CLL cells induce niche formation as an essential part of leukemogenesis. The dependence of the CLL cells on pro-survival support from the microenvironment is apparent from the induction of apoptosis in primary CLL cells when they are cultured without support.

The Mertens group characterizes this microenvironmental stimulation by a candidate gene approach, in which the interaction of pro-survival ligand-receptor pairs and their dose-response curves in primary CLL cells and non-malignant B-cells are quantified. Dose-response curves of ligand-receptor pairs are evaluated in terms of their effect on the survival in primary CLL cells. In addition, combinations of ligand pairs are tested for highest synergy in promoting survival of primary CLL cells. The effector dependence display different saturation curves, pointing towards distinct differences in ligand-receptor interactions. These are quantified in terms of apparent equilibrium binding constants and cooperativity parameters. In addition, a high-resolution fluorescence microscopy analysis of the spatial organization of receptors in tumor and control B-cells is carried out.

In order to identify the changes to the transcriptional networks that are induced by pro-survival micro environmental stimuli of CLL cells, whole transcriptome analyses coupled to systems-biology modelling approaches are conducted. First results indicate that a large number of transcriptional changes are induced in CLL cells on the minute time scale upon co-culturing. In contrast, in non-stimulated CLL cells a change in transcriptional profiles can only be observed several hours later and directly before apoptosis occurs. Using gene-ranking, filtering and kinetic classification, genes are currently being identified that are deregulated upon micro environmental stimulation.

Via inverse modelling of the expression of these genes with continuous time recurrent neural networks, an abstract dynamic model of a regulatory gene network can be developed. In these networks, central signaling nodes can be identified that represent genes crucial for survival of primary CLL cells but not in sorted B-cells from healthy donors. After functional validation of the central role of these genes in a cohort of patients and healthy probands using knockdown and overexpression, these anti-apoptotic genes are interesting therapeutic targets in interrupting the interaction of CLL cells with their microenvironment.

Selected cooperation partners

- Prof. Peter Lichter, German Cancer Research Center, Heidelberg, Germany
- Prof. Christoph Plass, German Cancer Research Center, Heidelberg, Germany
- Hauke Busch, Freiburg Institute of Advanced Studies, Germany
- Karsten Rippe, BioQuant Center, Heidelberg, Germany

Selected publications

- Nupur Bhattacharya, Antonio Sarno, Irina Idler, Maria Nothing, Thorsten Zenz, Hartmut Döhner, Stephan Stilgenbauer, Daniel Mertens, "High-throughput detection of NF- B activity using a robust and sensitive oligo-based chemiluminescent ELISA", International Journal of Cancer, 127, 404-411
- Zenz, T., D. Mertens, R. Kuppers, H. Dohner and S. Stilgenbauer (2010). From pathogenesis to treatment of chronic lymphocytic leukaemia. Nat Rev Cancer 10(1): 37-50.
- Mertens, D., S. Wolf, C. Tschuch, C. Mund, D. Kienle, S. Ohl, P. Schroeter, F. Lyko, H. Dohner, S. Stilgenbauer and P. Lichter (2006). Allelic silencing at the tumor-suppressor locus 13q14.3 suggests an epigenetic tumor-suppressor mechanism Proc Natl Acad Sci U S A 103(20): 7741-6.

Self-organized map analysis: assessment of GO terms shows e.g. a gene cluster associated with anti-apoptotic signaling (arrows) to be induced upon co-culture (bottom rows, first 4 timepoints) but not in culture without stimulation (top rows, first 4 timepoints).

Dr. Ralf Mikut

Karlsruhe Institute of Technology
Institute for Applied Computer Science
Biosignal Analysis

6 members of staff (engineers and computer scientists)

Dr. Mikut's research team deals with computer-supported analysis of biosignals for biological, biochemical and clinical applications in the new research field BioInterfaces of the Helmholtz Association of National Research Centres. The main focuses are High-Throughput Image Analysis and Antibacterial Peptides. The group leaders are Dr. Ralf Mikut and Dr. Markus Reischl.

For the program BioInterfaces, the research group is cooperating with the Liebel Lab and the Rudolf Lab of the Institute for Toxicology and Genetics (ITG). The main application is the analysis of image data from high throughput experiments. Zebrafish larvae provide a unique combination of high throughput capabilities and the organismal complexity of the vertebrate animal for a variety of phenotype screening applications. Modern high content screening microscopes allow rapid image acquisition from thousands of zebrafish larvae daily. However, the automation of imaging technologies is required to exploit the throughput of the transparent larvae. Dr. Mikut's research group develops methods for detecting and quantifying domain specificities in zebrafish larvae suitable for the quantitative analysis for genetic, pharmaceutical or toxicological high throughput screens. The researchers evaluate domain specificity by reconstructing reporter activity in a two dimensional virtual reference larvae. Quantification methods have been developed to describe imaged larvae adequately and classification routines are applied to define the condition of larvae automatically. All computer vision and data mining methods are implemented in a graphical user interface and can be easily transferred to similar problems. This was proved by the automatic processing of neurological structures in the mouse model.

Antimicrobial peptides are a promising class of substances for overcoming multidrug resistant bacteria. Data from high-throughput screening of short peptides (Hilpert lab, Institute for Functional Interfaces) was analyzed using quantitative structure-activity relationship models (QSAR). The data are based on luminescence values indicating bacterial activities after treatment with different peptides with different concentrations. To avoid non-interpretable black-box behavior of the QSAR models, new features based on fuzzy logic and molecular descriptors were introduced. These features were used for comprehensive analysis and visualization. The new features provide good interpretability and are able to differentiate between active and inactive peptides. A feature selection and visualization of few features enables an in-depth understanding of regions with active and inactive peptides and the identification of outliers. In addition, the research group generated rules to explain typical amino acid distributions in active peptides. These rules can be used to increase the probability of finding active peptides in new peptide libraries, which can improve the speed of finding leading substances for drug development against resistant bacteria.

Dr. Mikut's team uses the Large Scale Data Storage Facility (LSDF) at the Steinbuch Centre for Computing of the KIT and together with the Institute for Data Processing and Electronics the team is developing innovative algorithms and concepts for data storage and distributed computing. Another aim is the development of open source software for data mining using biomedical and

technical data sets (MATLAB toolbox Gait-CAD). In this project, the researchers cooperate with the Department of Orthopaedics, University of Heidelberg, on the analysis of movement analysis data for patients with neurological dysfunctions.

In addition the research group transfers human skills for planning, controlling and supervising movements to technical systems (Collaborative Research Center "Humanoid Robots").

Special equipment and techniques

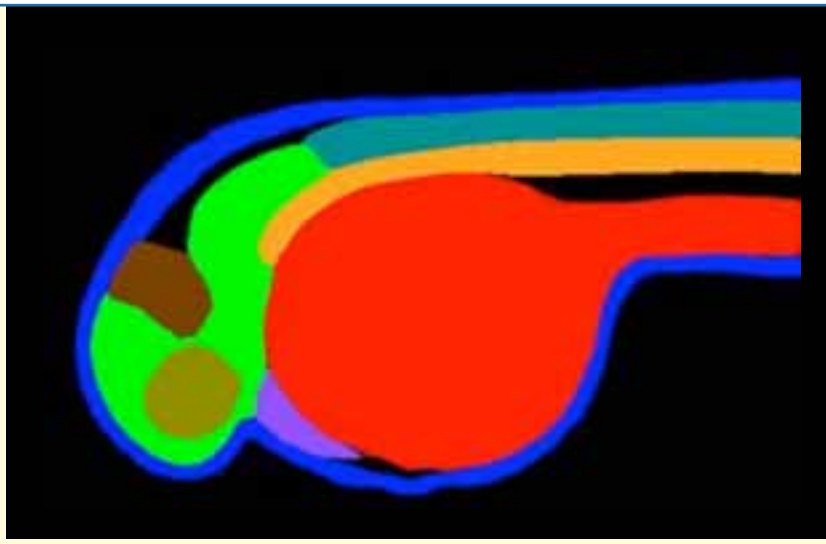
- Data Mining
- Image Analysis

Joint research projects

- BioInterfaces (Helmholtz Association)

Selected cooperation partners

- Uwe Strähle, Urban Liebel and Rüdiger Rudolf, Institute of Toxicology and Genetics, Karlsruhe Institute of Technology, Germany
- Kai Hilpert, Institute of Functional Interfaces, Karlsruhe Institute of Technology, Germany
- Jos van Wezel and Wilfried Juling, Steinbuch Centre for Computing, Karlsruhe Institute of Technology, Germany
- Rainer Stotzka and Marc Weber, Institute for Data Processing and Electronics, Karlsruhe Institute of Technology, Germany
- Rüdiger Rupp and Sebastian Wolf, Department of Orthopedics, University Hospital Heidelberg, Germany



Domain definitions from manually segmented embryos matched onto a reference embryo shape.

Selected publications

- Gehrig J, Reischl M, Kalmar E, Ferg M, Hadzhiev Y, Zaucker A, Song C, Schindler S, Liebel U and Müller F. Automated High Throughput Mapping of Promoter-Enhancer Interactions in Zebrafish Embryos. Nature Methods, 6, S. 911-916; 2009.
- Mikut R, Hilpert K. Interpretable Features for the Activity Prediction of Short Antimicrobial Peptides using Fuzzy Logic. International Journal of Peptide Research and Therapeutics. Springer, 15(2), pp. 129-137; 2009.
- Yang L, Ho NY, Alshut R, Legradi J, Weiss C, Reischl M, Mikut R, Liebel U, Müller F, Strähle U. Zebrafish embryos as models for embryotoxic and teratological effects of chemicals. Reproductive Toxicology, Elsevier, 28, S. 245-253; 2009.

Dr. Kay Nieselt

University of Tübingen
Center for Bioinformatics Tübingen
Proteomics Algorithms and Simulation

4 members of staff (bioinformaticians, computer scientists and mathematicians)

Thanks to the development of new technologies in the field of molecular biology, which enable entire genomes to be deciphered, as well as transcriptomes (all RNA molecules produced in a cell at a specific point in time), metabolomes (all metabolic products in a cell), and proteomes (all proteins present in a cell at a specific point in time) to be determined, it is now possible to systematically investigate cells, organs and entire organisms.

The objective of the European research initiative SysMO is to dissect and describe dynamic molecular processes in unicellular microorganisms, and to present these processes using computer-based mathematical models. Integrative approaches will be used to analyse and model "omics" data in a consistent manner in order to obtain new and more in-depth insights into complex biological systems. Dr. Nieselt's research team is a partner of STREAM, an international consortium that receives funding as part of SysMO. STREAM's goal is to study the soil bacterium *Streptomyces coelicolor* using a systems biology approach.

Streptomyces bacteria are the major producers of antibiotics used in biotechnology and clinical practice. During the lifetime of a fermenter culture, the soil bacterium *Streptomyces coelicolor* undergoes a major metabolic switch from exponential growth to antibiotics production. The regulation of antibiotics synthesis is fairly complex. One of the key issues Dr. Nieselt's team is seeking to answer using a systems biology approach, is the identification of the gene regulators that play an important part in the bacteria's ability to switch their metabolism from growth to antibiotics production. If the researchers succeed in understanding the role and importance of these metabolic switches, they will potentially be able to produce new bacterial strains that are able to produce modified or novel antibiotics.

In order to do this, Nieselt's team is investigating the transcriptomes of time-series samples removed from fermenter cultures. In cooperation with the US company Affymetrix, the researchers have developed a new microarray (GeneChip® for transcriptome profiling) which is specifically suited to the systems biological analysis of *Streptomyces coelicolor*. In addition to capturing the expression profiles of protein-encoding genes, the microarray also comprises the expression profiles of around 3,500 putative non-coding RNAs. These RNAs are of general importance as regulators in bacteria and also need to be taken into account in a systems biology model.

Over the last two years, Dr. Nieselt's team, in cooperation with the Microarray Facility in Tübingen, has produced and analysed more than 300 transcriptomes using a customised Affymetrix GeneChip®. The analysis of transcriptome data depends, like other "omics" technologies, on the visualisation of all individual steps involved in this process. This starts with the visual inspection of the raw data, which provides information on the quality of the experiments, and also involves the detailed manual inspection of the final results. The objective of visual inspection is to detect interesting phenomena and generate new hypotheses. The combination of visualisation with statistical and analytical methods will provide insights into the high-dimensional and highly complex data. This is the field of

visual analytics which is closely connected with the field of systems biology.

Highly complex data, such as those produced in systems biology, require effective analysis and visualisation platforms. Dr. Nieselt's team has created the "Mayday" platform for the analysis of transcriptomes. Mayday is a platform-independent visual analysis software for computer-based transcriptome analyses, which is designed for use by both biologists and bioinformaticians.

With regard to the modelling of the regulatory role of non-coding RNAs, the research group is particularly focused on developing methods that enable predictions to be made on non-coding RNA genes and on the construction of RNA-RNA interaction networks of entire prokaryotic genomes.

Special equipment and techniques

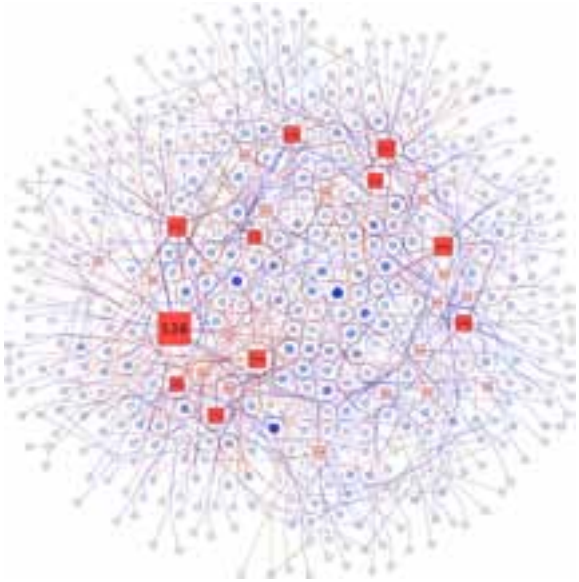
- In cooperation with Affymetrix: microarray for the systems biological analysis of *Streptomyces coelicolor*
- Interactive visual analytics
- Computer-based transcriptomics and statistics

Joint research projects

- SysMO – STREAM Consortium

Selected cooperation partners

- Prof. Wohlleben, Department of Microbiology / Biotechnology, University of Tübingen, Germany
- Prof. T. Ellingsen, Department of Biotechnology, Sintef Materials and Chemistry, Trondheim, Norway
- Prof. C. Müller-Tidow, Department of Medicine A, University Hospital of Münster, Germany
- Dr. M. Bonin, Microarray-Facility Tübingen, Germany



RNA-RNA interaction network.

- Prof. F. Goetz, Department of Microbial Genetics, University of Tübingen, Germany

Selected publications

- Nieselt K, Battke F, Herbig A, et al. The dynamic architecture of the metabolic switch in *Streptomyces coelicolor*. BMC Genomics 2010, 11:10.
- Battke F, Symons S, Nieselt K. Mayday - Integrative Analytics for Expression Data. BMC Bioinformatics 2010, 11:121.
- Symons S, Zipplies C, Battke F, Nieselt K. Integrative Systems Biology Visualization with MAYDAY. Journal of Integrative Bioinformatics 2010, 7:115.

Prof. Bernd Pichler

University of Tübingen
Department of Radiology / associated with the CSB
Laboratory for Preclinical Imaging and Imaging Technology of the Werner Siemens-Foundation

Approximately 35 members of staff

The Laboratory for Preclinical Imaging and Imaging Technology of the Werner Siemens-Foundation is broadly positioned and offers expertise in many areas of biomedical science. In the field of neurology Prof. Pichler's research group has a focus on Parkinson's (PD) and Alzheimer's disease (AD). While the researchers quantify the Dopamine receptor and -transporter binding potential in a α-synuclein transgenic mouse model of PD using in-vivo PET imaging, the focus of the AD research lies in the non-invasive detection of amyloid plaques by combined multi-functional and morphological PET and MR imaging.

One objective of the oncological research is the PET and MR-based detection of pancreas tumours in RIP1-Tag2 mice, so as to determine the minimum tumour-size that can be detected and distinguished from normal pancreatic tissue and to monitor tumour development using different tracers such as [^{18}F]FDG, [^{18}F]FLT, [^{64}Cu]RGD, [^{68}Ga]RGD and [^{64}Cu] labelled Th1-cells. In addition it is the goal of a related project to evaluate [^{11}C]Cholin and [^{18}F]FECh as early clinical diagnostic marker for prostate tumours, since [^{18}F]FDG is not perfectly suitable for the initial diagnosis, because these tumours lie in the very proximity of the bladder through which [^{18}F]FDG is excreted. In this context the research group also investigates the *in-vivo* behaviour and tumour uptake of radiolabeled anti-PSMA specific monoclonal antibodies and their evaluation as potential diagnostic tracers for the detection of prostate tumours.

A novel and very promising approach in the staging of important tumour parameters (for example glucose metabolism, cell proliferation, hypoxia, necrosis and angiogenesis) is the combination of PET/MR imaging modalities which is done in another oncological project of the lab using a U87MG mouse glioma model. Combined PET/MR imaging has several advantages compared to sequential PET and MR imaging like reduction of scan and anaesthesia time, accurate co-registration and quantification of PET images based on MR morphology as well as complimentary information generated from PET and MRI about treatment response and efficacy.

The analysis of the basic mechanisms of cellular immune therapies of cancer and the dynamics of T-cell trafficking in mouse models of inflammation is another topic pursued via non-invasive small animal PET imaging in the Pichler group. Furthermore, Prof. Pichler's research group is interested in the role of mast cells and in the *in-vivo* detection of hypoxia and angiogenesis during early stages of rheumatoid arthritis before incidence of clinical symptoms and histological visible joint inflammation.

Next to the direct biomedical research, the development of novel imaging detector technologies is another main topic of the laboratory. The world-wide first PET/MRI clinical brain scanner, located in Tübingen, is being evaluated and the issue of MR-based PET attenuation correction is being investigated. Also, simultaneous PET/MR imaging is being conducted in the fields of oncology, cardiology and neurology.

The group is also focussing its research on the development of new PET imaging compounds. Therefore the close proximity to the radiopharmacy group is of vital importance. Currently the Pichler group is working on PET tracer for angiogenesis, Alzheimer's disease and inflammation.

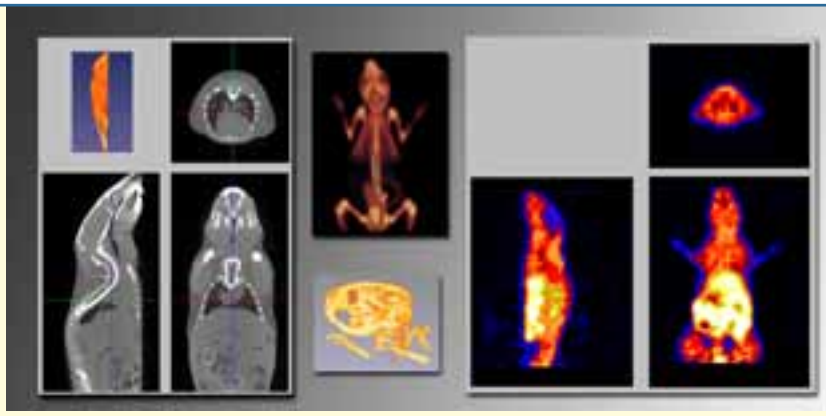
Beside these projects the continuous advancement of the already existing imaging modalities is pursued through the evaluation of performance parameters of small animal PET scanners.

Special equipment and techniques

- Two Inveon microPETs, Inveon microCT, combined SPECT/CT system, 7 T MRI, clinical as well as preclinical PET/MRI
- Optical imaging
- 16 MeV cyclotron
- Radiochemistry laboratories, Autoradiography
- GMP laboratory for tracer production
- RT-PCR and ELISA
- Fully equipped cell culture laboratory

Selected cooperation partners

- Prof. Autenrieth, Institute of Medical Microbiology and Hygiene, University Hospital Tübingen, Germany
- Prof. Nordheim, Interfaculty Institute for Cell Biology, University of Tübingen, Germany
- Prof. Rammensee, Interfaculty Institute for Cell Biology, University of Tübingen, Germany
- Prof. Pfizenmaier, Institute of Cell Biology and Immunology, University of Stuttgart, Germany
- Prof. Röcken, University Department of Dermatolgy, University Hospital Tübingen, Germany



CT (left) and PET (right) imaging of a mouse, also displayed in 3D (center).

Selected Publications

- M.S. Judenhofer, H.F. Wehrl, D.F. Newport, C. Catana, S.B. Siegel, M. Becker, A. Thielscher, M. Kneilling, M. Lichy, M. Eichner, K. Klingel, G. Reischl, S. Widmaier, M. Röcken, R.E. Nutt, H.-J. Machulla, K. Uludag, S.R. Cherry, C.D. Claussen, B.J. Pichler. Simultaneous PET/MRI: A new approach for functional and morphological imaging. Nat Med. 14(4):459-65, 2008.
- H-P. W. Schlemmer, B.J. Pichler, M. Schmand, Z. Burbar, C. Michel, R. Ladebeck, K. Jattke, D. Townsend, C. Nahmias, P.K. Jacob, W.-D. Heiss, C.D. Claussen. Simultaneous MR/PET Imaging of the Human Brain: Feasibility Study. Radiology 248(3):1028-1035, 2008.
- H.F. Wehrl, M.S. Judenhofer, S. Wiehr, B.J. Pichler. Pre-clinical PET/MR: technological advances and new perspectives in biomedical research. Eur J Nucl Med Mol Imaging. 36 Suppl 1:S56-68, 2009.

Dr. Klaus Schröppel

University of Tübingen
Institute of Microbiology and Infection Medicine
Molecular Mycology Lab

3 members of staff (2 biologists and 1 lab technician)

The fungus *Candida albicans* resides asymptomatically on the skin and mucosa of healthy people but causes serious invasive diseases in immunocompromised patients. Dr. Schröppel's group is focused on the molecular mechanisms of morphogenetic development that lead to hyphal formation and filamentous growth of *C. albicans*. The researchers are interested in the downstream signalling components which are involved in the transcriptional activation of virulence genes.

In collaboration with the Fraunhofer IGB, Stuttgart (Dr. Steffen Rupp), the research group identified the TEA transcription factor Tec1p as the terminal component of the signalling cascade that leads to filamentous growth. Additionally, components of the signalling cascade that activates morphogenetic development as well as the transcriptional activation of virulence factors alike secreted aspartic protease SAP genes were described. For the *in vivo* analyses of putative virulence factor genes by targeted deletion and construction of *C. albicans* mutants, animal models for superficial and invasive *C. albicans* infections as well as bioinformatics and computer-based data analysis were applied. With these tools the researchers could demonstrate the role of putative virulence factor genes during infection.

In a multidisciplinary, integrated approach, the cooperative projects focus on the Systems Biology of host-pathogen interactions by assessing, from a Systems Biology perspective, both the immune response of the host to the presence of the opportunistic pathogen and of the pathogen to the host under commensal and pathogenic conditions. The research of the team in Tübingen is focused on the signal transduction and transcriptional regulation of pathways which are relevant for *C. albicans* virulence gene regulation in response to the contact with the host surface or host defence mechanisms.

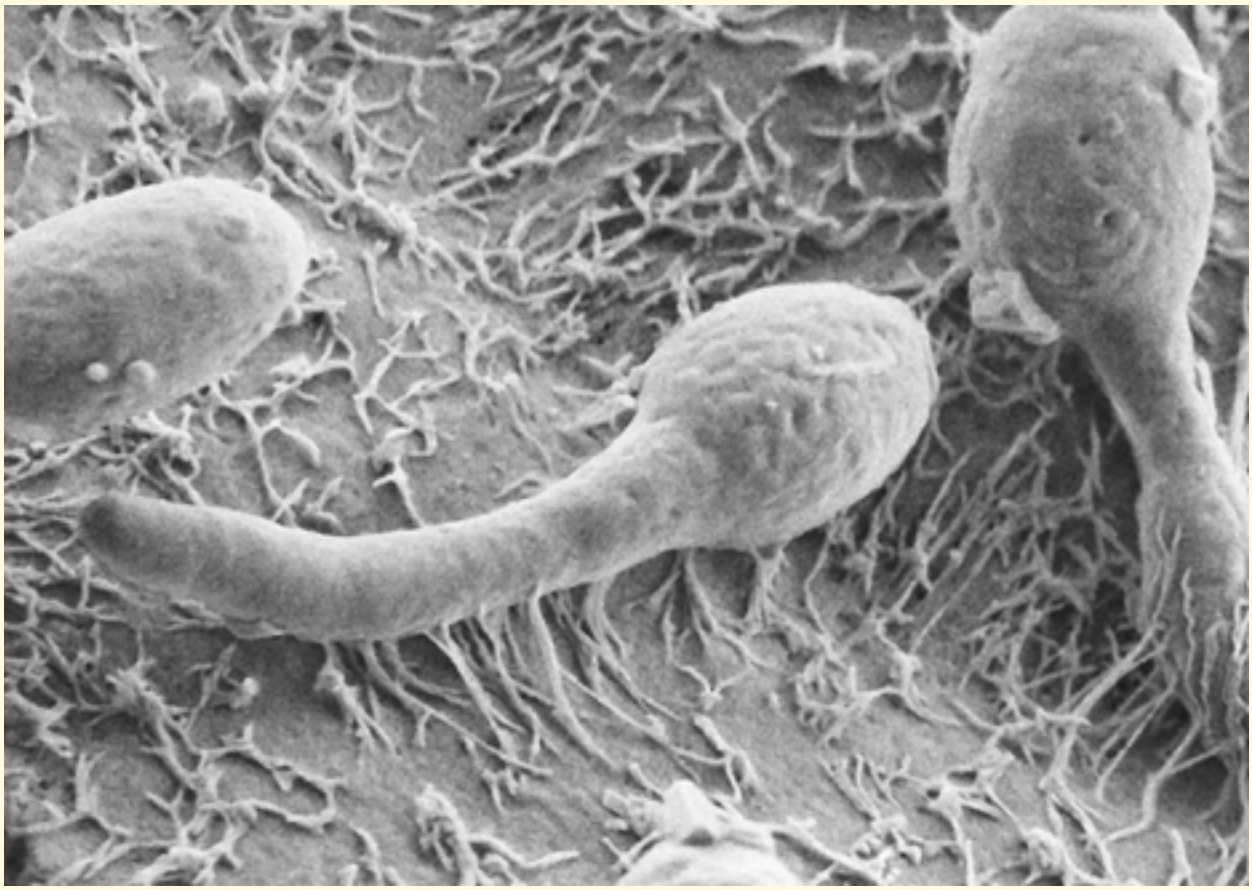
In cooperation with the team of Prof. Martin Schaller (Dermatology), the researchers target on the identification of novel biomarkers indicating the predisposition to acquire *C. albicans* infections from the correlation between the secretome (for example cytokines and secreted peptides profile) of the host and the transcriptome of the pathogen. The researchers will develop new therapeutic strategies to protect the host from *C. albicans* infections by the identification of the endogeneous protecting mechanisms.

Joint research projects

- MedSys (BMBF)
- PathoGenoMics (BMBF)

Selected cooperation partners

- Prof. Martin Schaller, Department of Dermatology, University Hospital Tübingen, Germany
- Prof. Karl-Heinz Wiesmüller, EMC microcollections, Tübingen, Germany
- Dr. Steffen Rupp, Department of Molecular Biotechnology, Fraunhofer IGB, Stuttgart, Germany
- Prof. Ursula Bilitewski, Prevention and Therapy, Helmholtz Centre for Infection Research, Braunschweig, Germany



Candida albicans (© Fraunhofer IGB)

Prof. Mathias Seeliger

University of Tübingen
Institute for Ophthalmic Research
Division of Ocular Neurodegeneration

7 members of staff (4 biologists, 1 physician, 1 pharmacologist and 1 lab technician)

The mission of Prof. Seeliger and his team is to uncover the pathophysiology of ocular neurodegenerative processes, to develop and test therapeutic strategies and to understand and model normal retinal function. The basis of the work is in-depth functional and morphological phenotyping of genetic models of blinding human neurodegenerative disorders with electroretinography (ERG), scanning-laser ophthalmoscopy (SLO) and opticalcoherence tomography (OCT), the same non-invasivetechniques used in affected patients.

Neurodegeneration research: Focus in this area of investigation is on the causes of and the disease mechanisms in retinal degenerations, which includes relating the findings in human patients to those in animal models with homologous genetic defects. This research is integral part of a worldwide network of national and international cooperation partners.

Systems biology: Even today, many aspects of normal retinal function are still unclear. Here, Dr. Seeliger's approach is to assess functional pathways, particularly in the outer retina, by means of mouse lines with specific genetic defects in photo-receptor function or connectivity. Cross-breeding of such lines enables his group to investigate isolated pathways,to obtain new insights about their nature, and to model their behavior mathematically.

Molecular therapy: Recent advances in therapeutic research (particularly gene and stem cell therapy) have led to collaborations with many leading groups on the evaluation of therapy in affected models. Main fields are the development of optimal application procedures,the evaluation of the therapeutic success by short- and long-term follow-up *in vivo*, and the translation to human patients.

Methodological innovation and refinement: Since more than a decade Prof. Seeliger's group is involved in the development and refinement of innovative diagnostic strategies in human patients and animal models. In addition, the researchers regularly contribute to ERG standards/guidelines issued by the International Society for Clinical Electrophysiology of Vision (ISCEV).

Special equipment and techniques

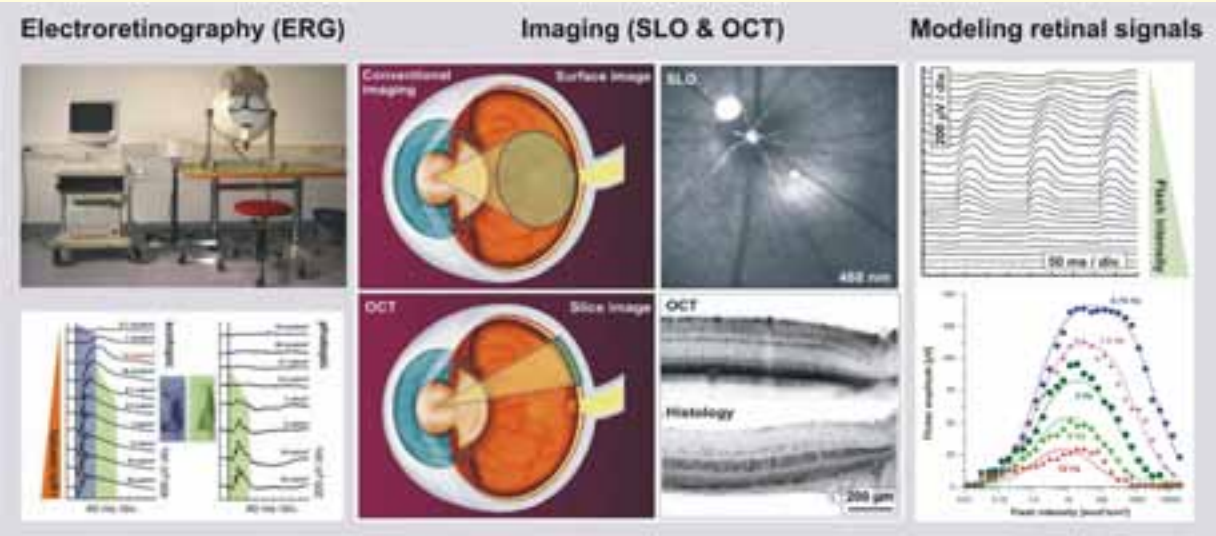
- Electroretinography (ERG)
- Scanning-laser ophthalmoscopy (SLO)
- Optical coherence tomography (OCT)

Selected cooperation partners

- Prof. Martin Biel, Center for Drug Research - Department of Pharmacy, LMU Munich, Germany
- Prof. Frank Müller, Institute of Structural Biology and Biophysics, Forschungszentrum Jülich, Germany
- Prof. Pete Humphries, Smurfit Institute of Genetics, Trinity College, Dublin, Ireland
- Prof. Reto Weiler, Department of Biology and Environmental Sciences, University of Oldenburg, Germany
- Prof. Laura Frishman, School of Optometry, University of Texas, USA

Selected Publications

- Seeliger MW, Grimm C, Ståhlberg F, Friedburg C, Jaissle G, Zrenner E, Guo H, Remé ChE, Humphries P, Hofmann F, Biel M, Fariss RN, Redmond TM, Wenzel A. New views on RPE65 deficiency: the rod system is the source of vision in a mouse model of Leber congenital amaurosis. Nat Genet 2001; 29: 70-74.
- Knop G, Seeliger M, Thiel F, Mataruga A, Kaupp UB, Friedburg C, Tanimoto N, Müller F. Light responses in the mouse retina are prolonged upon targeted deletion of the HCN1 channel gene. Eur J Neurosci 2008; 28: 2221-2230.
- Paquet-Durand F, Beck SC, Michalakis S, Goldmann T, Huber G, Mühlfriedel R, Trifunovic D, Fischer MD, Fahl E, Duetsch G, Becirovic E, Wolfrum U, van Veen T, Biel M, Tanimoto N, Seeliger MW. A key role for cyclic-nucleotide gated (CNG) channels in cGMP-related retinitis pigmentosa. Hum Mol Genet 2011; 20: 941-947.



Prof. Uwe Strähle

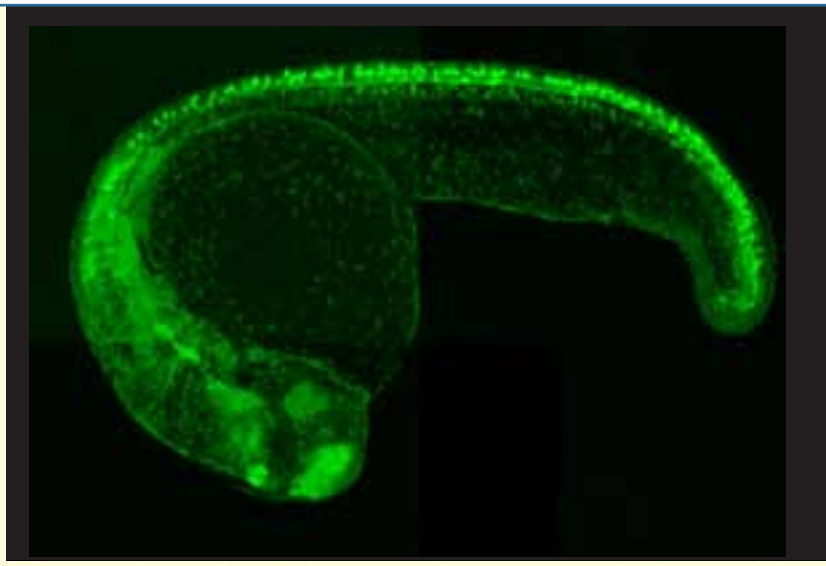
Karlsruhe Institute of Technology
Institute of Toxicology and Genetics
Molecular genetics and environmental toxicology of vertebrate nervous system development

14 members of staff (12 biologists and 2 informaticians)

Prof. Strähle's research group studies the development and regeneration of the vertebrate nervous system and the musculature. The main goals are to understand the gene networks controlling differentiation and function of the nervous system and musculature. The researchers use genetics and systems biology to model and thereby unravel the underlying regulatory processes. As experimental system they employ mostly the zebrafish.

A key challenge in the post-genome sequencing era is the comprehensive elucidation of the function of the genes and their regulation. The retrieval of genetic information (i.e. expression) is differently regulated depending on cell type and state of the cell. Cross-talk between cells by secretion of signaling molecules is essential for development and body homeostasis. Disturbance of these processes leads to malformations and disease including cancer. In particular, differential transcription into mRNA is a major mechanism controlling the expression of individual genes in development and body homeostasis. Transcription of genes is controlled by specific DNA elements (cis-regulatory elements) that either regulate the access to the DNA via modulating the chromatin structure and/or mediate the recruitment of sequence-specific transcription factors. Prof. Strähle's team refers to all of these genes as transcription regulators (TRs).

The cis-regulatory elements of genes are integration points, at which different signals converge to coordinately regulate gene programs characteristic of the cell states from a pluripotent stem cell to a particular differentiated cell state. A major emphasis of the work is the elucidation and functional characterization of the cis-regulatory architecture of the zebrafish genome. The researchers have undertaken a systematic screen for TRs in the zebrafish genome and determined their expression patterns in the 24 hour old embryo. So far they have mapped the expression pattern of more than 1000 TRs. These patterns will be matched to the temporal and spatial activity of cis regulatory elements to derive rules of the regulatory code. In selected structures of the developing central nervous system such as the ventral spinal cord, TRs are systematically knocked-down and protein/protein and protein/DNA interaction studies are carried out in comparison to the wild-type to assess the regulatory networks by functional means. The long-term plan is to derive quantitative models of these regulatory processes that integrate all available data in comprehensive and illustrative models that will also be useful to inform and educate the broader public. The modelling of the networks and establishment of virtual tissue models is carried out in close collaboration with groups at the Steinbuch Centre for Computing (SCC), the Institute for Applied Computer Science (IAI) and the Institute for Data Processing and Electronics (IPE) at KIT.



Transgenic zebrafish embryo expressing GFP in the central nervous system.

Special equipment and techniques

- Large fish facility
- Euopean Zebrafish Screening and Stock Facility
- Large scale testing of gene function and enhancer analysis
- Establishment of transgenics in the zebrafish
- Modern microscopes including automated high throughput microscopes
- In cooperation with the Large Scale Data Storage Facility at Steinbuch Centre for Computing (SCC) development of innovative concepts for data storage, organization and access

Joint research projects

- BioInterfaces (Helmholtz Association)
- EraSysBio (BMBF)
- EuTRACC (EU)
- NeuroXSys (EU)

Selected cooperation partners

- Urban Liebel, Institute of Toxicology and Genetics, Karlsruhe Institute of Technology, Germany
- Georg Bretthauer, Markus Reischl and Ralf Mikut, Institute for Applied Computer Science, Karlsruhe Institute of Technology, Germany
- Wilfried Juling and Jos van Wezel, Steinbuch Centre for Computing, Karlsruhe Institute of Technology, Germany
- Rainer Stotzka and Marc Weber, Institute for Data Processing and Electronics, Karlsruhe Institute of Technology, Germany

Selected publications

- Dickmeis T, Plessy C, Rastegar S, Aanstad P, Herwig R, Chalmel F, Fischer N and Strähle U. (2004). Expression profiling and comparative genomics identify a conserved regulatory region controlling midline expression in the zebrafish embryo. Genome Res 14, 228-38.
- Yang L, Kemadjou JR, Zinsmeister C, Bauer M, Legradi J, Müller F, Pankratz M, Jakel J and Strähle U. (2007). Transcriptional profiling reveals barcode-like toxicogenomic responses in the zebrafish embryo. Genome Biol 8, R227.
- Yang L, Rastegar S and Strähle U. (2010). Regulatory networks specifying Kolmer-Agduhr interneurons. Development 137, 2713-22.

Prof. Katja Wegner

Cooperative State University Karlsruhe
Computational and Systems Biology

2 members of staff (a bioinformatician and a computer scientist)

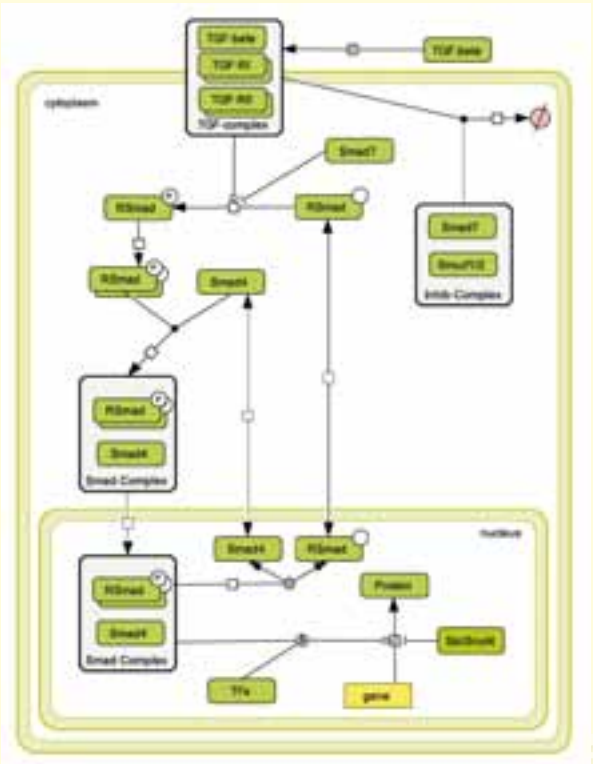
The research group led by Dr. Wegner deals with the mathematical modelling and dynamic analysis of signalling pathways and genetic networks as well as with the development of new algorithms and programmes for the modelling of these biological systems.

In cooperation with the group of researchers led by Prof. Dr. Ursula Kummer, BioQuant Center, Heidelberg, Dr. Wegner's team has developed a complex model of the TGF signalling pathway in order to study the influence of positive and negative regulators. This signalling pathway has a broad range of functions, in particular in regeneration, immune reactions and tumourigenesis. For this reason, the elucidation of the transduction of signals by TGF is an important step in the search for drugs for the treatment of behavioural disorders, cancer and other diseases.

Future projects will focus on the expansion of this model and provide information about how the TGF signalling pathway communicates with other signalling pathways. The experimental data used to validate the model are provided by a group of researchers led by Prof. Dr. Steven Dooley at the Mannheim University Hospital and a group of researchers led by PD Dr. Ursula Klingmüller at the German Cancer Research Center in Heidelberg.

The group also works with Dr. Maria Schilstra at the University of Hertfordshire, UK with the aim of further developing the NetBuilder' software (http://sourceforge.net/projects/apostrophe/) that enables the construction, modelling and analysis of genetic networks. The programme is based on the Petri net formalism and makes it possible to mathematically describe genetic networks with differential equations and logical terms.

The group is part of the international SBGN (Systems Biology Graphical Notation) project which has the mission to develop high-quality, standard graphical languages for representing biological processes and interactions. It is also part of the international Systems Biology Markup Language (SBML) project that deals with the development of an XML-based representation format for communicating and storing computational models of biological processes.



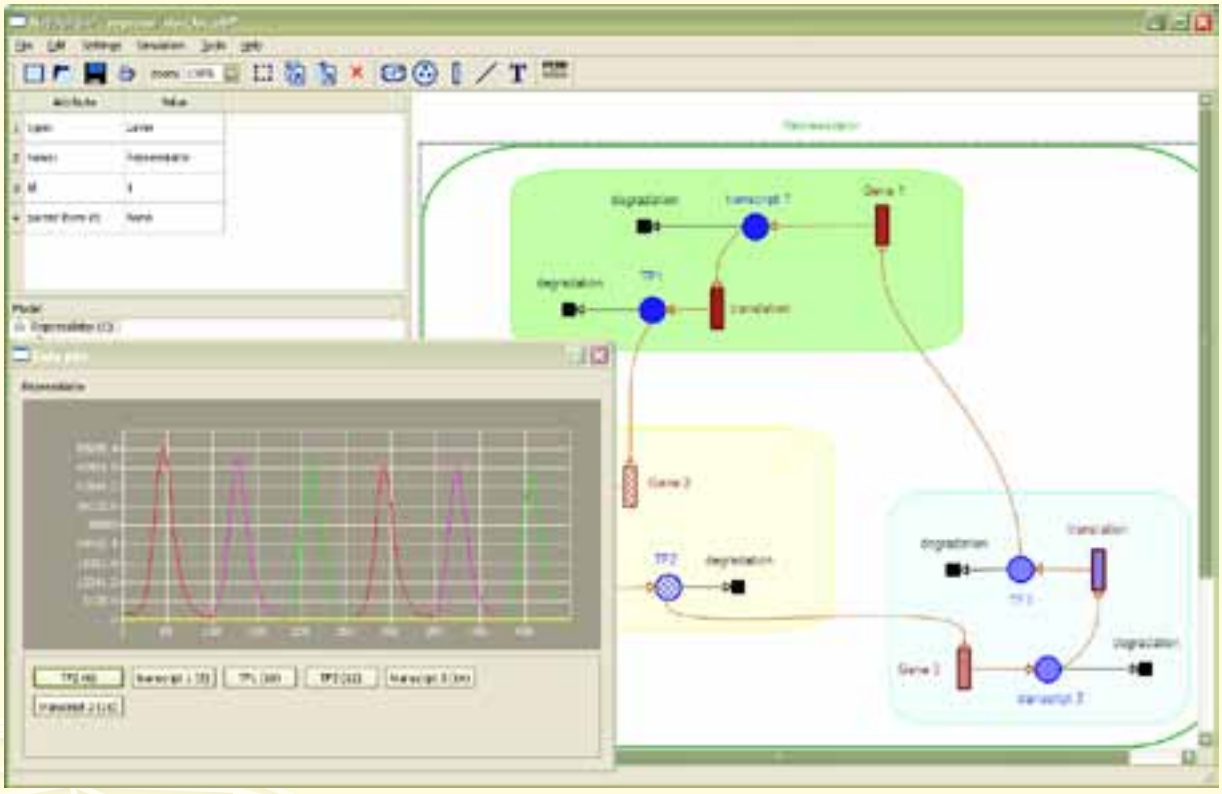
Simplified network of the TGF-ß signalling pathway, represented in SBGN.

Selected cooperation partners

- Prof. Ursula Kummer, BioQuant Center, Universität Heidelberg, Germany
- Prof. Steven Dooley, Medical Faculty Mannheim at the University of Heidelberg, Germany
- PD. Dr. Ursula Klingmüller, German Cancer Research Center, Heidelberg, Germany
- Dr. Maria Schilstra, STRI, University of Hertfordshire, Hatfield, UK

Selected publications

- Katja Wegner, Anastasia Bachmann, Jan-Ulrich Schad, Peter Nickel, Christoph Meyer, Sven Sahle, Ursula Klingmüller, Steven Dooley and Ursula Kummer, Dynamics and Feedback Loops in the Transforming Growth Factor β signaling pathway, submitted.
- Nicolas Le Neverè et al.,The Systems Biology Graphical Notation, Nature Biotechnology 27, 735 – 741, 2009.
- Ralph Gauges, Ursula Rost, Sven Sahle and Katja Wegner, A Model Diagram Layout Extension for SBML, Bioinformatics 22:15, 1879-1885, 2006.



Screenshot of the Netbuilder' programme used for the simulation of genetic networks.

Dr. Carsten Weiss

Karlsruhe Institute of Technology
Institute of Toxicology and Genetics
Molecular toxicology of genotoxins and nanomaterials

13 members of staff (biologists, chemists, biotechnologists, lab technicians)

The use of *in vitro* methods is indispensable for assessing the toxic potential of new materials that are produced in a broad range of variations. One project of the research group led by Dr. Weiss focuses on the establishment of a microscopy-based high-throughput method for testing nanomaterials and chemicals. The use of fluorescence dyes enables the detection of end points such as proliferation, cytotoxicity, activation of stress kinases and transcription factors, the expression of biomarker proteins and genotoxic markers, also in one and the same experimental approach. It is expected that nanomaterials and chemicals can be toxicologically assessed more quickly and more reliably with the microscopy-based high-throughput method than with traditional methods. This will most likely contribute to reducing the number of *in vivo* experiments.

In contrast to non-microscopic screening, fluorescence microscopy provides much more information, i.e. data on the single cell level or on the subcellular level. Traditional methods usually determine different parameters from the entire cell population. For example, the activation of kinases and the induction of target proteins can be determined in a whole cell lysate. However, this method does not capture all information since it is possible to activate a kinase enzyme in some of the cells while a certain target protein can be induced in others. Only the analysis on the single cell level provides information as to whether different effects occur in one or a number of cells.

The group is establishing genetic screening methods (siRNA screens) to gain an understanding of the mechanism of toxicity of different substances. Such methods enable the identification of individual relevant proteins that mediate toxicity.

Dr. Weiss' team is supported by the team of Urban Liebel (Institute of Toxicology and Genetics, KIT) and by the team of Ralf Mikut (Institute of Applied Informatics, KIT) in the operation of the group's robot system and its screening microscope as well as the use of software for data storage, image processing and bioinformatics. The team of Michael Boutros and Daniel Gilbert at the DKFZ in Heidelberg provides advice for establishing the siRNA screening platform.

Special equipment and techniques

- Olympus ScanR screening microscope
- Caliper robotic platform

Joint research projects

- BioInterfaces (Helmholtz Association)

Selected cooperation partners

- Urban Liebel, Institute of Toxicology and Genetics, Karlsruhe Institute of Technology, Germany
- Ralf Mikut, Institute for Applied Computer Science, Karlsruhe Institute of Technology, Germany
- Michael Boutros und Daniel Gilbert, Division of Signaling and Functional Genomics, German Cancer Research Center, Heidelberg, Germany

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