Federal Ministry
of Education
and Research

Systems Biology – Understanding the Networks of Life

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Foreword

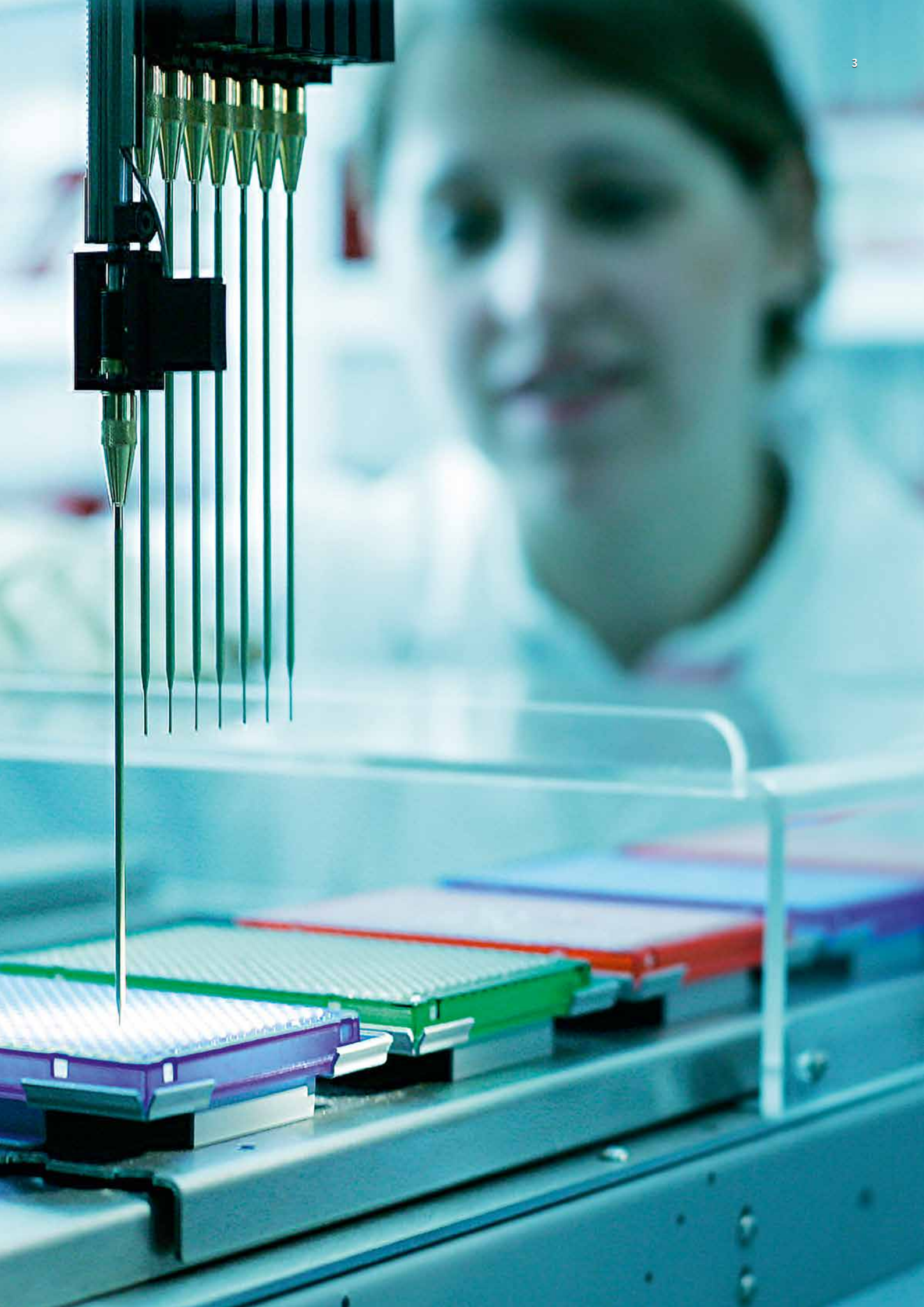
A sticky layer of dental plaque forms on teeth that are not brushed properly. This so-called biofilm can cause dental caries. To date, there have been very few ways of tackling this problem. A research team at the Helmholtz Centre for Infection Research in Braunschweig now intends to harness the inhibiting effect of bacteria. Using a combination of biological and mathematical methods, the researchers are studying the potential application of these bacteria in preventing caries.

Today we are seeing increasing instances of interdisciplinary cooperation in more and more fields of the life sciences. The emerging discipline of systems biology is a shining example of this approach. It strives to find answers and viable solutions for tomorrow's world by combining the traditional subjects of biology and medicine with the fields of mathematics, physics and computer science at the interface between practical laboratory experiments and mathematical modelling. Hypotheses are tested and subsequently revised or rejected on the basis of experiments and model predictions; this leads to a greater understanding of complex life processes in both basic and applied research and helps to predict mechanisms and their effects.

The Federal Ministry of Education and Research (BMBF) was quick to recognise the future potential of systems biology: it has been fostering interdisciplinary cooperation among research groups and supporting the creation of systems biology centres since the beginning of the millennium. Other funding priorities have included international networking and the provision of further training for young researchers. Thus, Germany took the international lead in the development of systems biology from an early stage.

This brochure describes the beginnings of systems biology funding in Germany and presents the innovative results of the funding measures to date. It portrays successful projects from the entire spectrum of systems biology – from medicine to plant research, right through to biotechnology. It makes for fascinating reading, coupled with new insights.

Prof. Dr. Johanna Wanka
Federal Minister of Education and Research



What is systems biology?

If we want to decode the mysteries of life, it is futile to simply examine individual components thereof. Instead, we need an understanding of how and in what context biomolecules function and an awareness of what networks they affect. Systems biology takes a holistic view in order to decipher, and thus understand, the complex correlations involved.

To some extent, the processes of life may be compared to a railway network: it is widely ramified and an error at one juncture may cause problems at remote points of the network. In other words, a malfunction at the control centre in Augsburg may lead to massive delays, causing travellers all over Germany to miss their connections. Only by keeping track of all the junctions on the entire rail network is it possible to predict what repercussions the fault in Augsburg may have in Frankfurt, Cologne or Berlin. It is imperative to know which essential arteries are affected by the malfunction and how it interferes with trains, junctions and branch lines alike. Only with this overview can the railway company make decisions regarding detours and timetable changes to ensure that passengers get to their destinations.

Complex interaction of molecules

This image also helps to illustrate the workings and processes of living systems. Metabolic pathways, cells, organs or entire organisms are composed of countless units, each with their own specific function: DNA, proteins, lipids or carbohydrates. Many of these components have been exhaustively researched. Nevertheless, if we do not know how the individual components interact, we cannot understand what is really going on in a living system like a cell or an organism.

The complex, spatiotemporal interaction of different biomolecules causes a cell to grow, die or, in a

worst-case scenario in humans, mutate into tumour cells. When under attack, this interaction determines whether the host's immune system or the pathogen prevails, whether a drug is able to beat the infection or whether the side effects predominate.

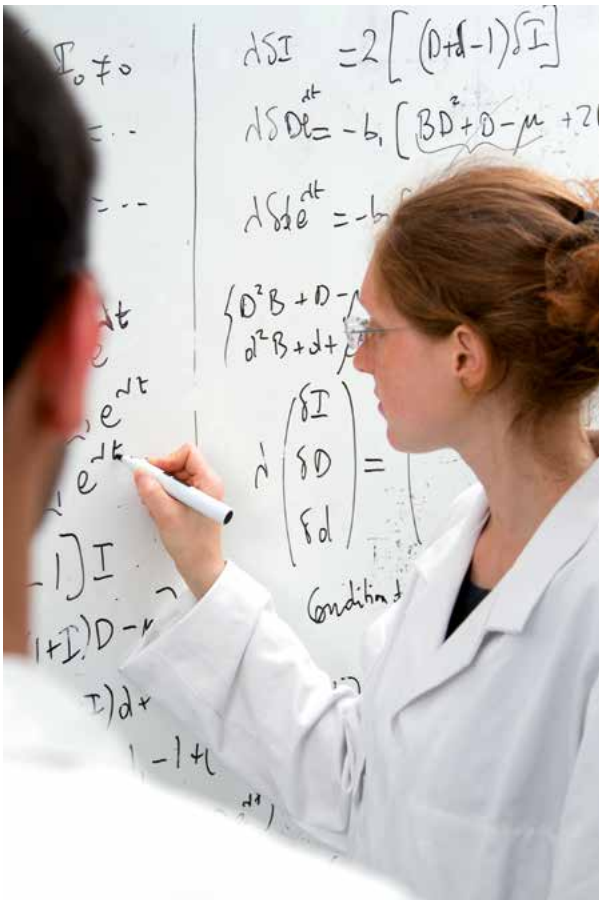
Systems biology explores the overall picture of the dynamic networks of life. This calls for all molecular biological and biochemical data to be linked, from the genome to the active genes and the available proteins, right through to the metabolic processes of a system: which biomolecules are present at a specific point in time? In what concentrations do they occur? What functions do they carry out and with which other elements do they interact?

Combining laboratory experiments and computational models

Systems biology provides answers to complex issues such as these; it combines the cutting-edge experimental methods of the life sciences, like molecular biology, biochemistry and medicine, with knowledge and technologies in the fields of mathematics, computer science, physics and engineering. Mathematical concepts are applied to biological systems so that an iterative process takes place between laboratory experiments and computational modelling. This facilitates predictions about the complex biological processes that occur among cells, organs or entire organisms.

The systems biology research approach leads to an in-depth understanding of the processes of life itself, thereby opening up new strategies for the treatment of various diseases. Systems biology models clearly show why certain medicines are able to heal the body, while others are ineffective or even harmful. Pharmaceutical development will thus become more effective and safer. Elsewhere, systems biology enhances biotechnological processes – for example, in the production of biofuels – or paves the way for environmentally sound and sustainable agriculture.

Its enormous potential for development and diverse range of applications have placed systems biology on the centre stage of modern life sciences. Around the turn of the millennium, the first working groups to use systems biology methods sprang up in the United States and Japan, with Europe following suit shortly thereafter. Having recognised the advantages of systems biology at an early stage, the Federal Ministry of Education and Research (BMBF) subsequently invested in fundamental research and in establishing and developing the necessary infrastructure. In 2004, it funded *HepatoSys,* a pilot project that shed light on important metabolic pathways in liver cells (hepatocytes). Following on from this successful pilot project, the Virtual Liver Network (VLN) was launched, to date the world's largest systems biology research initiative. Since then, the BMBF has initiated and sponsored a variety of national and transnational research projects, placing Germany in the international vanguard in the field of systems biology.



In systems biology, theoretical and experimental research teams work hand in hand.

Germany paves the way for systems biology

Overview of the funding

From processes in individual cells or entire organs to questions regarding medicine, biotechnology, the food industry or the energy supply, from individual junior research groups to major international consortia, the BMBF supports systems biology research with numerous funding measures.

In 2001, the BMBF gave the go-ahead for a new funding priority, "Living Systems – Systems Biology". Thereafter, the pilot project "Systems Biology of the Liver Cell – *HepatoSys*" was launched in 2004 (see page 11 *ff*), the largest interdisciplinary competence network in the world. While focusing on the processes in the liver cells (hepatocytes), the initiative also created structures for working with systems biology in Germany. Launched in 2010, the Virtual Liver Network is based on this successful pilot project. Research no longer focuses on individual cells but on the entire organ of the liver.

In early 2007, the BMBF introduced the "Research Units for Systems Biology – *FORSYS*" funding measure, which aimed to establish a functioning systems biology infrastructure. In order to embed systems biology in Germany's science landscape in the long term, four interdisciplinary research centres have been set up at different locations (see page 16 *ff*). From 2008 onwards, the *FORSYS* Partner measure extended this initiative. One of two main components, the *FORSYS* cooperations encouraged the transfer of know-how among the *FORSYS* centres and partners from academia and industry in order to pool expertise and capacities. At the same time, the *FORSYS* Young Investigators Groups offered the next generation of scientists the opportunity to develop their creative potential and contribute to systems biology research in Germany (see page 18 *ff*).

Focus on biomedicine

Developing the right tools is crucial to the success of a research discipline that is still in its infancy. In 2009, as part of the "New Methods in Systems Biology – *SysTec*" programme, scientists developed methods and technologies that enable quantitative data to be generated and analysed. Announced in 2006, the funding priority on "Quantitative analysis for the description of dynamic processes in living systems – *QuantPro*" pursued similar objectives.

Even at an early stage, biomedicine emerged as a priority for systems biology research in Germany. In 2008, by introducing the "Medical Systems Biology – *MedSys*" funding measure, the BMBF began to address the potential applications of systems biology in medicine and pharmaceutical research. Since 2009, the "Systems Biology for Health in Old Age – *GerontoSys*" project has focused on the mechanisms of the natural ageing process and age-related diseases. 2010 saw the launch of "Systems Biology in Cancer Research – *CancerSys*", which seeks to develop new cancer drugs and individualised therapy.

With its interdisciplinary research and funding concept *"e:Med"*, introduced in 2012, the BMBF is now also embracing systems medicine, which combines the methods and insights of systems biology with medical research topics. In addition to individualised medicine, the programme is dedicated to research into widespread diseases and all aspects of prevention and nutrition.

By virtue of its diverse fields of application, systems biology opens up new solutions in biotechnology and may provide answers to the urgent questions of global food security and nutrition, as well as the supply of raw materials and energy. For instance, the "Systems Biology for Bioenergy" funding activity (2009 – 2012) included a separate module for systems biology research projects that contributed to the cultivation of optimised energy crops.

Cross-border funding

As of 2007, the "Systems Biology of Microorganisms – *SysMO*", programme focused on the systems biology study of microorganisms that are of significance for biotechnology, health, nutrition and environmental protection. This programme was a first for the BMBF as it involved the funding of systems biology research across national borders: the project was aimed at interdisciplinary consortia with partners from at least three European countries. *SysMO* was an integral part of the European *ERASysBio* initiative, a milestone on the way to establishing an international network (see page 44).

Since 2013, the "Innovative Toxicology for the Reduction of Animal Experimentation – *e:ToP*" initiative has been striking out in new directions. It aims to use the

SYSTEMS BIOLOGY NEWS

Systems biology fascinates researchers and non-specialists alike. This was the bright idea that led the BMBF and the Helmholtz Alliance on Systems Biology to join forces in launching the journal *systembiologie.de* in 2010. Published in German as well as English to attract an international audience, the journal reports at regular intervals on new projects and findings and presents the scientists behind the groundbreaking research field. "When I am abroad, people compliment me all the time on this fantastic showcase for systems biology in Germany", says editor-in-chief Prof. Dr. Roland Eils from the German Cancer Research Center in Heidelberg.

The associated website *www.systembiologie.de* serves as the information portal for systems biology in Germany. In addition to articles on day-to-day research work, there is also a detailed overview of BMBF funding activities and up-to-date information on events and training opportunities. Moreover, the portal also invites readers to give feedback and submit proposals for topics.

www.systembiologie.de

systems biology approach to test chemicals for potential harmful effects – in cell cultures and without using live animals. Thus, systems biology is helping to develop alternative methods to animal testing. In late 2014, in order to continue this work, the BMBF announced the joint funding measure "*InnoSysTox* – Innovative Systems Toxicology for Alternatives to Animal Testing" with the Netherlands Organisation for Health Research and Development.

Wide thematic range

The BMBF currently covers a wide range of topics in its "*e:Bio* – Innovation Competition Systems Biology" funding activity. The largest programme in terms of funding focuses specifically on identifying innovative systems biology solutions for the most pressing problems facing society: from health research to global food security and nutrition, right through to the energy supply. At the same time, *e:Bio* promotes junior research groups. It places particular emphasis on the continued development of basic research findings for practical application.

Meanwhile, day-to-day research generates enormous quantities of data that need to be compiled, standardised and analysed. In order to optimise data management and processing, the BMBF has instituted several funding measures. One of which, the German Network for Bioinformatics Infrastructure *(de.NBI)*, creates tools that enable large quantities of data to be processed for systems biology applications. The "*i:DSem* – Integrative Data Semantics in Systems Medicine" initiative develops new methods of utilising the enormous amount of available but unstructured data from scientific literature.

Pilot project liver – the cornerstone of systems biology funding

It detoxifies the blood, produces vital proteins and stores vitamins: the liver is the most important metabolic organ in the human body. The BMBF has put the spotlight on the liver in its systems biology research funding mechanisms in Germany. This led to the creation of the world's largest interdisciplinary network that pools its efforts in researching a single organ.

In the late 1990s, the first systems biology initiatives materialised in the United States and Japan. By contrast, at the time, this emerging research discipline was still regarded with scepticism in Europe. However, the BMBF made a stand against these reservations by initiating *HepatoSys,* Europe's first funding measure in the field of systems biology. The *HepatoSys* research network was launched in 2004 with the goal of using a systems biology approach to study the processes in the liver cells (hepatocytes).

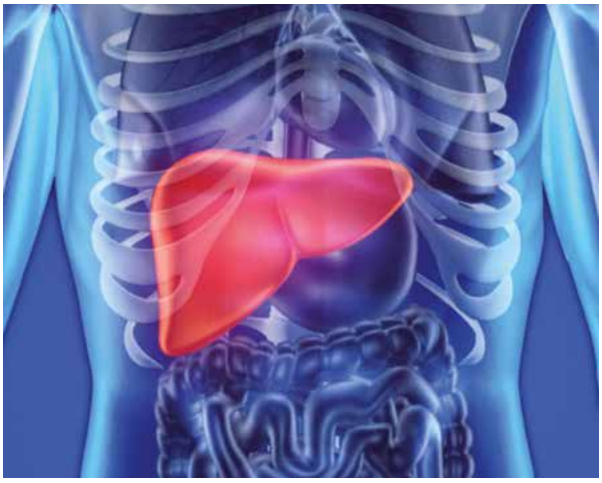
The liver produces bile acid that emulsifies the lipids in food to aid digestion. It stores glucose and vitamins. Furthermore, it breaks down and excretes toxins like alcohol and other harmful substances. As it also plays a key role in the effectiveness of numerous drugs, it is of enormous import for medical and pharmaceutical research. When developing new therapeutics, it is important to know how quickly substances are broken down in the liver and via what intermediate products they are excreted. This is the only way of evaluating how a drug works and avoiding undesirable side effects.

Moreover, in some cases, liver cells may exhibit crucial genetic differences between one person and the next. "There are such a large number of variables that one individual research group would never be able to decipher the complex processes that take place in the organ", says Prof. Dr. Siegfried Neumann, a pharmacologist from Darmstadt. Having advocated the systems biology approach in researching hepatocytes, he was involved in the BMBF's first systems biology project from the outset. "This endeavour is positively crying out for a large research consortium".

Establishing a functioning research network

In setting up the *HepatoSys* research network, the BMBF and its cooperation partners were entering uncharted territory. The objective was to study key processes in the liver at the cellular level. The first step was to create a network structure. This included developing a central data management system to ensure that all members had easy access to the network's comprehensive research findings.

Support was provided by two technology platforms. The Cell Biology platform was tasked with developing suitable cell cultures from freshly isolated hepatocytes. Furthermore, working procedures were standardised to enable comparisons between the results produced in the different laboratories. The Modeling platform facilitated the development of suitable mathematical models to enable the simulation of hepatocyte processes on the computer. A total of 40 research teams from all over Germany collaborated in the research network.



The next step was based on the findings and insights achieved by *HepatoSys:* in 2010, the BMBF gave the go-ahead for the follow-up project, the Virtual Liver Network, which takes systems biology liver research to the next biological level. Drawing on the findings at cellular level, the processes are now being examined for the whole organ.

Nevertheless, Prof. Dr. Ursula Kummer from the Faculty of Biosciences of Heidelberg University emphasises that "It should not be assumed from the name 'Virtual Liver' that, in a few years' time, the entire organ and all its biological processes will be replicated in a computational model". As she was instrumental in developing

the concept for the Virtual Liver Network, she is aware of just how protracted the research process is. "Instead, our first priority must be to focus on several central processes that are crucial for medical research, about which we actually have a great deal more information today than a few years ago".

> "Our goal is to provide a strong impetus to the entire area of systems biological research".
>
> Dr. Adriano Henney,
> Programme Director of the Virtual Liver Network

A holistic understanding of the liver

The researchers of the Virtual Liver Network map the results of the *HepatoSys* project and use them to develop a new mathematical model. At the same time, they generate new data sets. In so doing, they study the different physiological processes taking place in the liver, like adiposis, regeneration and inflammation. The ultimate goal is to develop a multi-scale mathematical model of the liver, in other words, a model that spans multiple levels of organisational complexity; in this case, from a single liver cell to tissue aggregates, right up to the whole organ.

This model will prove conducive to a holistic understanding of the liver, thereby fostering the development of new approaches to benefit both biomedicine and biotechnology. For example, the virtual liver can be used to search systematically for toxic substances or new 'biomarkers'; these characteristic attributes may indicate whether a patient has an increased risk of certain liver diseases.

Like *HepatoSys,* the Virtual Liver Network is also breaking new ground: it is the first systems biology network to focus on an entire organ. A total of 70 research groups are involved in subprojects, including industry partners and international teams.

Enhanced diagnostics and therapy

Efficient organisation is a prerequisite for such a large-scale project. Therefore, in addition to the research consortium, the BMBF has instituted a management team specifically for the VLN. "Our goal is to provide a strong impetus to the entire area of systems biological research and to give evidence of a genuine impact on healthcare", says the programme director, Dr. Adriano Henney.

The BMBF intends to follow this course: the new "Research Network Systems Medicine of the Liver – *LiSyM*" funding measure continues to build on the results produced by *HepatoSys* and the Virtual Liver Network. *LiSyM* aims to transfer the computational models thus developed into clinical application for use as diagnostic tools to assist doctors in choosing the most appropriate therapy. Its primary objective is to identify and model the common key processes that lead to liver diseases. The understanding of these processes forms the basis for novel treatment and prevention approaches that enable liver diseases to be detected and treated at an early stage, which may prevent them from becoming severe.

INDUSTRY PARTNERS FOR SYSTEMS BIOLOGY

Bayer Technology Services

In close cooperation with Bayer subgroups, Bayer Technology Services (BTS) is developing a number of technology platforms, including some for systems biology, to support the research, development and production of new products and applications. The Joint Research Center for Computational Biomedicine (JRC) at RWTH Aachen University is exploring the use of computer-aided models and methods to research fundamental biological mechanisms and is developing these for clinical application in cooperation with the University Hospital Aachen.

BTS is involved in several projects that receive BMBF funding. Since 2004, the company has been collaborating with the *HepatoSys* network in order to create a metabolic model of the liver; today, the Virtual Liver Network is continuing this work, which will be extended for practical application. Under the *e:Bio* project *PREDICT* (see page 30), scientists are working on a mathematical model to illustrate tumour growth. Their objective is to enhance the effectiveness and tolerability of cancer drugs and foster the development of new active substances.

"As a company, we benefit enormously from the exchange with other scientists in the research networks", says Prof. Dr. Andreas Schuppert, systems biologist at Bayer and founding director of JRC. "Only by joining forces can we ensure that the research projects dovetail with the needs of practical applications".

Insilico Biotechnology AG

Scientists at the University of Stuttgart and the ETH Zurich founded Insilico Biotechnology in 2001. The company develops software that analyses experimental data and predicts processes in living cells, based on computational models. It has been granted BMBF funding several times in the past; in 2004, the company was a key partner in the *HepatoSys* network, the pilot project in the field of systems biology. Insilico Biotechnology was responsible for developing mathematical models to simulate the behaviour of substances in hepatocytes, thereby enabling conclusions to be drawn regarding the correlations between genes and metabolic processes. This work is being continued in the Virtual Liver Network.

"The research cooperations have enabled us to get innovations off the ground that we would not have been able to implement single-handedly", says co-founder and CEO Klaus Mauch. "Not only did this help to transfer fundamental research findings into applications, the BMBF-funded initiatives also made a valuable contribution by increasing the number of highly qualified jobs in our company".

“A prototype of a successful research network”

The *HepatoSys* research programme brought scientists together to form the largest interdisciplinary consortium to date, thereby combining theoretical and experimental research. For almost 30 years, the pharmacologist Prof. Dr. Siegfried Neumann was active in various areas of research for the pharmaceutical company Merck and served on the *HepatoSys* Steering Committee. Prof. Dr. Ursula Kummer’s research represented the theoretical aspect of the network. Moreover, the biochemist played a significant role in the conception of the follow-on programme, the Virtual Liver Network. In an interview, they talk about beginnings, successes and visions.

Prof. Dr. Ursula Kummer and Prof. Dr. Siegfried Neumann are among the pioneers of systems biology in Germany.

Approval for systems biology funding in Germany was given in 2001. How did this come about?

Siegfried Neumann: The BMBF appointed a panel of nine experts, of which I was one, and commissioned them to plan a new, long-term funding priority. Our task was to focus on systems biology as the interface between the fields of computer science and biology or medicine. After lengthy discussion, the committee agreed on a model of the liver cell.

To a certain extent, it was a real gamble as its sophisticated functions make this cell a highly complex system; one that has not yet been researched in depth, to boot. Nonetheless, it also offered the German research landscape the opportunity to raise its profile by adopting a systems biology research approach and to play a leading role on the international stage.

Looking back, has the gamble paid off?

Siegfried Neumann: Let me compare it to a birth. The baby has now been born and is thriving. But it took a whole team of obstetricians. We had to create structures, bring certain groups together and set up a nationwide network. It hasn't always been easy. Put it this way: it was a birth with plenty of labour pains..

What difficulties did you encounter?

Ursula Kummer: The systems biology approach called for a shift in our conceptual thinking. Lab researchers and modellers had to find a common language. The experimenters had to learn not only to describe things in qualitative terms but to generate quantitative data that modellers can work with. By the same token, quite a few theorists had difficulty with the rather vague terminology of the life sciences, where a single protein may well have several names ...

In specific terms, how did this affect the collaboration?

Ursula Kummer: Experimenters cannot simply pass on the data to the modellers, who take it from there. Vice versa, the modellers have to get a feel for what is technically feasible in the lab. Various disciplines have to learn to dovetail their scientific mindsets. The only solution is to meet as often as possible in order to plan and interpret the data together.

To this end, researchers have to be open about sharing their data – not always a given in the world of science ...

Ursula Kummer: There is always the fear that somebody might not be honoured personally for their work. If data is made available within a large network prior to its publication, is there not a certain risk of it being misappropriated? For example, what if somebody else suddenly claims the credit for themselves?

Siegfried Neumann: Added to which, the network brought together researchers from Max Planck Societies, Helmholtz Centres and universities. To some extent, the participants had very different opinions on when findings should be published. Moreover, collaboration across all hierarchy levels comes with its own set of problems. Who is authorised to pass on data from their own group to other cooperation partners? Finding solutions to all these concerns made *HepatoSys* a prototype of the successful organisation of national research networks.

***HepatoSys* was also designed to pave the way for similar networks. Did it achieve this goal?**

Siegfried Neumann: A great deal was invested in developing *HepatoSys*' central data management. We keep getting enquiries from abroad, asking for advice on how to set it up in similar networks. In this respect, Germany is leading the way internationally.

Ursula Kummer: However, the lessons learned by the individual groups during the interdisciplinary collaboration should also not be underestimated. They were extremely valuable for subsequent systems biology programmes.

How do you see the future of systems biology?

Ursula Kummer: I foresee a similar development to that of bioinformatics, which was the subject of much heated debate in the 1990s – today, bioinformatic research has become the norm. I can see the same thing happening in systems biology: more and more research consortia are demanding, encouraging and implementing interdisciplinarity. Quite simply, it will be standard practice.

Siegfried Neumann: Systems biology complements and modernises the established research disciplines of biology and medicine. Simulations have become indispensable in engineering, where they reduce costs and minimise risks. In the same way, they will serve as a tool that provides solutions in the life sciences. For example, they facilitate the development of active substances to ensure the effectiveness of therapeutics, enabling them to be combined successfully while keeping side effects to a minimum. Thus, systems biology is now being truly put into practice.

One-stop research – establishing a systems biology infrastructure

The internet has made it possible for data to be exchanged, even over long distances. Nonetheless, interdisciplinary collaboration also calls for direct contact. Therefore, the BMBF is underpinning the research infrastructure by establishing systems biology centres.

A buzz of conversation floats down from the sixth floor of the BioQuant Center in Heidelberg. There is a rattling of cups, a scraping of chairs and the aroma of freshly brewed coffee drifts through the open stairwell into the adjacent floors; a group of scientists are taking a break in the bright, inviting kitchenette on the extended landing. As it connects the two wings of the interdisciplinary research centre, it thus also forms an architectural bridge between theoretical research on the one side and experimental research on the other. The researchers from different disciplines congregate here every day in their coffee break to compare notes on their work.

The biophysicist Thomas Höfer now joins the group. The professor of theoretical systems biology develops mathematical models that aim to provide a clearer understanding of the complex processes of cancer. Thomas Höfer sets great store by these informal gatherings. "We come up with the best ideas when striking up a conversation in chance encounters", he says. "This building is an absolute godsend".

Room for exchange and cooperation

Bringing various disciplines together under one roof and thereby sowing the seeds for scientific exchange and cooperation – such was the fundamental concept behind the centre, which was financed by the Federal State of Baden-Württemberg. In terms of content, BioQuant was closely associated with *ViroQuant* from the outset, the Heidelberg consortium dedicated to the systems biology analysis of interactions between viruses and host cells.

ViroQuant was an integral part of the *FORSYS* – Research Units for Systems Biology funding measure. Between 2007 and 2011, the BMBF earmarked a total of 45 million euros to fund four *FORSYS* centres in Freiburg, Heidelberg, Magdeburg and Potsdam. The primary objective was to improve the systems biology research infrastructure at universities and non-university research institutes.

Scientific institutions were set up and extended in a joint venture with the regional centres. In the process, particular emphasis was placed on promoting young researchers and training the next generation of scientists (see page 18). In Heidelberg, for example, a Master's programme was introduced in molecular biosciences with a systems biology focus.

Modern technologies for improved research

The centres enable researchers from a variety of disciplines to collaborate more closely. Joint technology platforms make cutting-edge, costly procedures available to all the scientific teams in the centre. For instance, Dr. Höfer's team mainly benefits from the excellent microscopy facilities offered by the BioQuant Center. The researchers are studying the behaviour of individual cancer cells to discover the reason for some patients' resistance to certain therapies (see page 26).

The funding for the *FORSYS* centres has since expired; however, it has left its mark on all four locations. "Here in Heidelberg a vibrant centre has sprung up, in which active discussion and intensive interdisciplinary collaboration are an everyday event", says Dr. Angela Mauer-Oberthür, Managing Director of BioQuant. She takes great pride in the structures that have developed here: the training opportunities and diverse technology platforms. "Not only is the Center fully integrated in the scientific landscape of Heidelberg, it has also attracted international attention".

Other systems biology centres

Moreover, the BMBF supports the creation of further infrastructure for systems biology research, including the Berlin Institute for Medical Systems Biology (BIMSB) and the Center for Systems Biology in Dresden (CSBD).

The BIMSB was initiated in 2008 by the Max Delbrück Center for Molecular Medicine (MDC) in Berlin-Buch. It underpins the disease-oriented research conducted at the MDC by analysing gene regulatory networks from a systems biology standpoint and offers an international and interdisciplinary training programme, in addition to innovative technology applications. The BIMSB is thus also an important partner for the Berlin Institute of Health, in which the Charité and the MDC have joined forces to step up translational research. In 2018, the BIMSB is moving to its new building in the centre of Berlin, which will house up to 25 research groups, approximately half experimental and half computational.

Founded in 2010 as an initiative of the Max Planck Society in collaboration with the Technische Universität Dresden, the CSBD consolidates the joint interdisciplinary research programme at the site. The scientific focus is on the research theme "From cells to tissues". The groundbreaking ceremony for the new building, financed by the Federal State of Saxony, took place in autumn 2014.

OVERVIEW OF THE *FORSYS* CENTRES

***FRISYS*, Freiburg**

- Freiburg Initiative for Systems Biology at the University of Freiburg
- Focus on signalling pathways and networks in the growth and differentiation of cells
- Newly implemented international M.Sc. in Bioinformatics and Systems Biology
- Continuation of the *FRISYS* groups at the Center for Biological Systems Analysis (ZBSA), University of Freiburg

***GoFORSYS*, Potsdam**

- Cooperation between the University of Potsdam and the Max Planck Institutes of Molecular Plant Physiology and of Colloids and Interfaces
- Focus on the systems biology study of photosynthesis to increase plant productivity
- Introduction of a Master's in bioinformatics with a focus on systems biology
- Establishing a systems biology research approach in working groups at the Max Planck Institute of Molecular Plant Physiology

***MaCS*, Magdeburg**

- Magdeburg Centre for Systems Biology: a cooperation between Magdeburg University and the Max Planck Institute for Dynamics of Complex Technical Systems, which is integrated in the Research Centre for Dynamic Systems in Biomedicine and Process Engineering
- Focus on the regulation of dynamic networks and signal transmission
- Development of a Bachelor and Master's programme on biosystems technology
- A new building is currently under construction for systems biology research, which is now an integral part of Magdeburg's research landscape.

***ViroQuant*, Heidelberg**

- Collaboration between several institutes under the aegis of the University of Heidelberg
- Focus on virus-cell interactions
- Master's programme of molecular biosciences with a major on systems biology
- Extension of the *ViroQuant* working groups as an integral part of the BioQuant Center

CORE CENTRES FOR SYSTEMS BIOLOGY RESEARCH ON AGEING

Three core centres were established as part of the BMBF's "*GerontoSys* – Systems Biology for Health in Old Age" funding initiative: by providing pooled expertise, training programmes and technology platforms, they reinforce systems biology research on ageing, which is just starting to gain momentum in Germany.

***Sybacol*, Cologne:**
- Systems Biology of Ageing Cologne at the University of Cologne
- Focus on the metabolic aspect of ageing and signalling pathways that lead to longevity

***SyStaR*, Ulm**
- Systems biology analysis of impaired stem cell function and regeneration during ageing at Ulm University
- Focus on the ageing process of stem cells; enhanced stem cell and organ function in old age
- A chair is being established for medical systems biology

***JenAge*, Jena**
- Jena Centre for Systems Biology of Ageing at the University of Jena
- Focus on the impact of mild stress on the ageing process

Promoting young researchers – new momentum for an emerging research discipline

Systems biology research needs fresh young minds to advance developments with innovative ideas. Only those who are willing to look beyond their own discipline, to compare notes with scientists from other faculties and find a common language will be able to help decipher the networks of life. Therefore, the BMBF places particular emphasis on training and promoting up-and-coming researchers who work in systems biology.

"As a research discipline, systems biology is still in its infancy and therefore does not yet have recourse to numerous, specially trained experts", says Prof. Dr. Walter Kolch, Director of "Systems Biology Ireland" at University College Dublin. Originally trained as a medical doctor, his own career led first to biochemical laboratory research and bioinformatics, before focusing on systems biology. He knows from personal experience that "Systems biology merges experimental biological and medical research with mathematics and computer science – academic disciplines that are poles apart by tradition in terms of their mentality and way of thinking". According to Dr. Kolch, we need a new generation of scientists who will create and utilise these new synergies to the full.

He is not alone in this assessment. The BMBF came to the same conclusion many years ago: systems biology requires well-trained young researchers who, accustomed to an interdisciplinary approach from day one, go on to implement and maintain this way of working. Therefore, training and supporting young scientists is an important mainstay of systems biology funding in Germany. Many universities have appointed chairs and introduced special study programmes, with the BMBF repeatedly assuming the role of initiator.

Freedom of research for young scientists

As a researcher, developing and implementing your own creative ideas is a prerequisite for a successful academic career. For this reason, the BMBF has been supporting junior systems biology research groups in its *FORSYS* Partner funding measure since 2008. This gave twelve young researchers the opportunity to realise their full potential and develop their own scientific profile. Over a period of five years, they were able to set up their own working group in order to establish contacts and networks for interdisciplinary collaboration.

The BMBF is continuing this policy in its "*GerontoSys* – Systems Biology for Health in Old Age" initiative: it supports three junior research groups who are pursuing new approaches in systems biology research into the causes of ageing. Moreover, the "*e:Bio* – Innovation Competition Systems Biology" funding initiative has been financing young research groups since 2012: to date, 20 groups have received funding, with others planned in 2016.

The research and funding concept "*e:Med* – Paving the Way for Systems Medicine" also sponsors junior research groups in the field of systems-oriented medical research. Moreover, it supports junior consortia in which young researchers from different disciplines work together on a joint project.

Fellowships broaden individual horizons

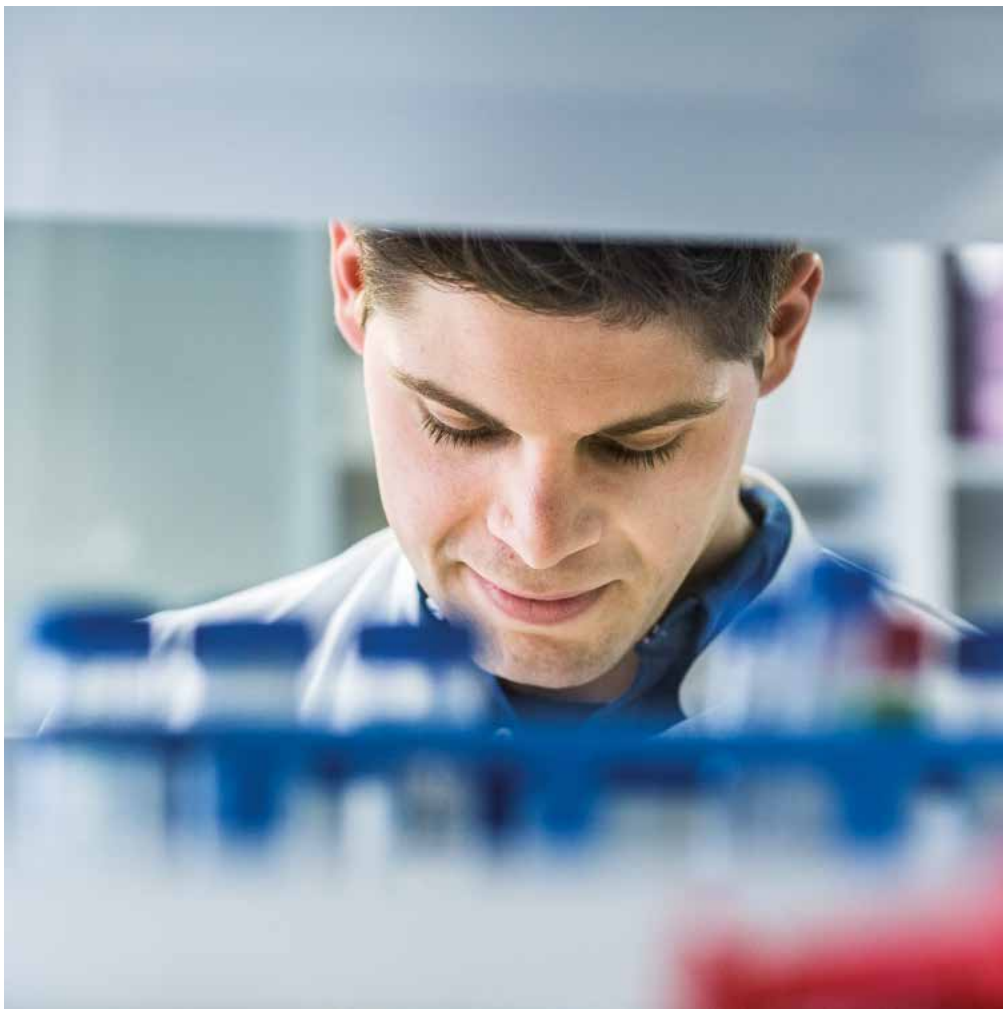
Furthermore, over the course of 2013, the BMBF granted a total of eleven fellowships to enable young scientists who were preparing their doctoral theses or who had obtained their doctorate within the previous three years to conduct research abroad over several months. In one fell swoop, the academic fellows were able to gain further qualifications and use the opportunity to initiate research collaborations or extend existing partnerships.

Bernhard Steiert, a physicist from Freiburg, spent six months at the prestigious Harvard University as part of the team headed by Dr. Peter Sorger, known for his pioneering work in the mathematical modelling of biological systems. "Apart from the fact that living in a foreign country means you are totally immersed in the language while broadening your personal horizons, the time I spent in the USA was the perfect opportunity for me to learn data analysis techniques that I would probably not have studied otherwise", says Dr. Steiert.

Outstanding young research talent

Even a private foundation is committed to funding young systems biologists. The MTZ Award for Medical Systems Biology honours outstanding dissertations in the field of medically oriented systems biology, which were produced as part of the BMBF's funding measures. The award promotes young research talent and is conferred every two years by the MTZ-Foundation in cooperation with the BMBF and the Project Management Jülich during the internationally renowned Conference on Systems Biology of Mammalian Cells (SBMC).

Meanwhile, the success of the training schemes is further underlined by the sophisticated new funding applications for research projects being submitted by young scientists. "I am extremely impressed by the quality of the research projects and the innovative ideas of Germany's young scientists", says Walter Kolch, the systems biologist who appraises the applications on behalf of the BMBF. He declared himself particularly inspired by the smooth interdisciplinary collaboration, which is going from strength to strength. This shows that the new systems biology mindset is firmly entrenched in Germany's scientific community.



"I have been fascinated by models for as long as I can remember"

The flyer on Dr. Jana Wolf's notice board is entitled "The Future of the Wolf"; it refers to the wolf population that is slowly but surely becoming re-established in Germany. "They are amazing animals", says the scientist, an outdoor enthusiast. Nevertheless, "The Future of the Wolf" is also a fitting motto for her as she has often been just that one step ahead. For example, even while writing her thesis, Jana Wolf began moulding biological processes as mathematical models. That was back in 1994 – a long time before systems biology came to the fore here in Germany.

Dr. Wolf finds it logical to approach biology in this way: "I have been fascinated by models for as long as I can remember. They open up new perspectives on biological processes". Many parameters are very difficult to determine experimentally. Mathematics is able to address this problem and reveal the connections. While still at school, Jana Wolf first encountered biomathematics during an internship at the Max Delbrück Center for Molecular Medicine in Berlin, the same institute in which she has her own group today. She went on to study biophysics with an emphasis on theory.

Dr. Jana Wolf heads a working group at the Max Delbrück Center in Berlin.

"Looking back, my career pretty much follows a straight path", says Dr. Wolf. "But I also made forays into various other fields". In other words, following her theoretically oriented course of study, she also tried out experimental research. She subsequently worked for a pharmaceutical company in England where she engaged in research on mathematical models of the signalling pathways in mammalian cells. "This is essential for drug development because many active substances interfere with cellular signalling", the researcher explains.

Her own niche

However, there finally came a time when she decided to pursue her own line of scientific questioning. "The only way is to set up your own group", she says. Dr. Wolf returned to Berlin and applied for funding for a junior *FORSYS* research group that was to focus on signalling pathways once again. According to Jana Wolf, "Five years is an ideal length of time to get things up and running – your own group, contacts and cooperation". The scientist made good use of her time: she is now an established member of Germany's systems biology community.

And what lies ahead for the "Future of the Wolf"? "Due to the cooperation with the Charité, my work is becoming increasingly application-oriented", she says. She is fascinated by research on clinical issues and developing specific solutions for cancer therapy, for example. And maybe her findings will help in developing a new drug in the future.

"My research needs systems biology"

A doctor as well as a researcher, Prof. Dr. Bernd Schmeck wears both hats with gusto. "The personal contact with patients is just as important to me as science", he says. Even as a student, both professions were close to his heart: therefore, he took part in research internships in addition to his medical training. Today, aged 40, he works in the laboratory and as an internist at the University Hospital of Marburg.

As a teenager, Bernd Schmeck was far more interested in information technology. "Back in the 1980s, while others were playing computer games, I was writing programs on my first computer", he recalls. Maybe that helped to spark his interest in systems biology. "At least this environment can accommodate my fascination with computers", the doctor smiles.

Finding common ground

Dr. Schmeck was more than a little sceptical of systems biology at first: is the vision of using computers to model organ systems or even entire organisms not too ambitious by far? Can biologists and medical professionals find any common ground at all with mathematicians and computer scientists? "As many mathematicians consider a combustion engine too chaotic to come up with a reasonable calculation of the details, how can they be expected to work with a living system?"

Nonetheless, the interdisciplinary approach appealed to Bernd Schmeck and he realised: "That is precisely what my research needs". The doctor is studying the complex processes associated with pneumonia. Besides the actual infection, it is above all the body's own defence mechanisms that affect the progression of the illness. The immune system has to respond harshly to gain control of the pathogens. If it fights back too fiercely, a fatal sepsis could result. This occurs more often than you might expect, as Dr. Schmeck explains, "For many years, the mortality rate in severe cases of pneumonia has remained unchanged at around 12 to 13 percent". Conventional research methods are unable to make any further progress. However, the mathematical models of systems biology are able to simulate the

Prof. Dr. Bernd Schmeck is a professor of clinical pulmonology and the director of iLung, the Institute for Lung Research in Marburg.

complex interaction between the pathogens and the body's immune response, thereby leading to a better understanding of it. Dr. Schmeck and his cooperation partners are hopeful that their findings will be used to develop new therapies in the future.

"A ruthless method of testing our hypotheses"

Starting in 2007, Dr. Schmeck's junior research group received support under the *FORSYS* funding programme. "For five years", he says, "this gave me the freedom to base my research work on a systems biology approach and create the necessary infrastructure and network". Today, not only is Bernd Schmeck a professor of clinical pulmonology, but also director of the newly founded Institute for Lung Research in Marburg.

He is now firmly convinced of the success of the systems biology research approach; "Computational modelling is a ruthless method of testing our own hypotheses", says Dr. Schmeck. "It shows us exactly the points where we have been insufficiently critical of our own conjectures and where to go back to the drawing board".

Successful systems biology research projects

Medicine

Biotechnology

Plant research

Medicine

Dental fillings with built-in caries protection

Biofilms cause caries, block catheters and encourage centres of infection on hip prostheses. To date, there have been very few methods of inhibiting them. Across Germany, the scientists of the *e:biofilm* research consortium intend to change that by using carolacton, the metabolic product of a bacterium.

Cleaning your teeth helps remove plaque. If you don't brush regularly, you can feel a biofilm forming on your teeth. The sticky layer of slime is made of carbohydrates and proteins produced by the bacterial and fungal cells that are embedded in it. The main culprits are streptococci – those bacteria said to be the primary cause of caries.

Biofilms can accumulate in any moist environment but particularly on the boundary layers of different materials: in water pipes, on the rim of the dishwasher but also on the surface of medical implants like stents, catheters, hip prostheses and artificial heart valves. This makes them an almost insurmountable medical problem. Conventional antibiotics are just as powerless as disinfectants against the sticky biofilms.

How bacteria communicate

During the Roman Empire, a quorum was the minimum number of members required to hold a ballot in the Senate. Derived from this meaning, microbiologists now talk about 'quorum sensing'. This term refers to the ability of microorganisms to measure population density and communicate it to one another, thereby enabling them to coordinate processes that require a certain bacterial density.

But help is at hand. Just a few years ago, a research group headed by the microbiologist Prof. Dr. Irene Wagner-Döbler at the Helmholtz Centre for Infection Research identified a substance that destroys biofilms: carolacton, a secondary metabolite produced by a bacterium that occurs naturally in soil. The researchers have patented this new weapon in the fight against biofilms. The *e:biofilm* project, which receives BMBF funding, is focusing on how it works and how the effect can be utilised for medical purposes.

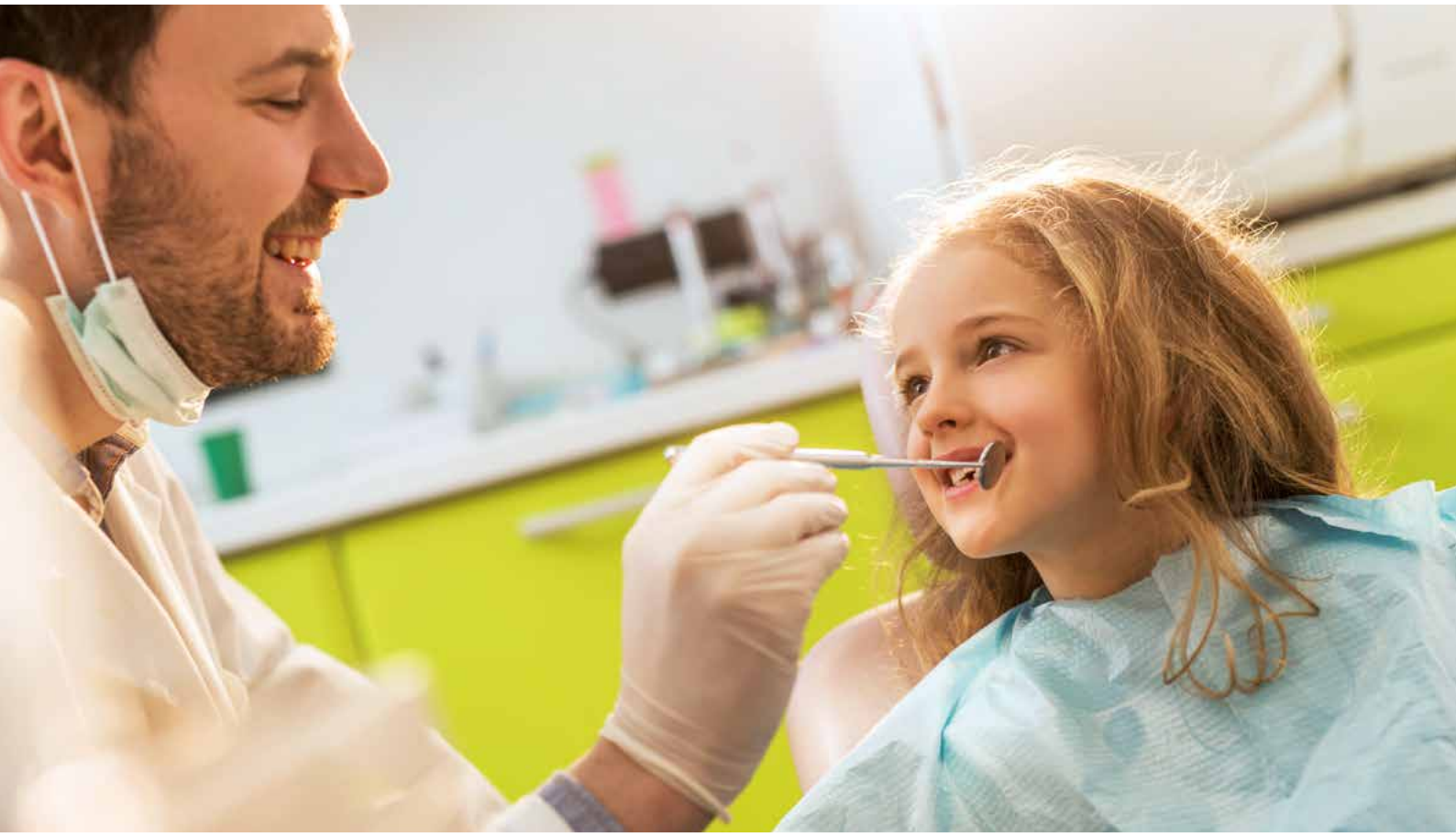
First preclinical trial

There are numerous applications for carolacton; "One obvious possibility would be to incorporate it in dental filling material", says Dr. Wagner-Döbler, project coordinator. This could prevent the accumulation of biofilms and thus further damage due to caries at the boundary layer between tooth and filling. Even in low concentrations, carolacton is biologically active and thus, in principle, eminently suitable as an additive in dental filling materials.

In preliminary preclinical trials, the project partners at RWTH Aachen University are testing the effect of carolacton on biofilms made up of bacteria from natural oral plaque. If the results are promising, a clinical study will follow: for a short period of time, subjects will be fitted with a type of brace, to which a panel with carolacton is attached.

Besides its effectiveness, the research group is also addressing the issue of producing carolacton. The soil-dwelling bacterium does not produce enough of the substance under laboratory conditions to enable its widespread use against biofilms. Therefore, the scientists are looking for a more appropriate method of manufacturing carolacton in larger quantities using biotechnology.

Streptococcus mutans is considered to be the main cause of caries.



Disrupting bacterial communication

As a microbiologist, Irene Wagner-Döbler is particularly interested in the cohabitation of the bacterial community in the mouth and how carolacton inhibits oral biofilms. She explains, "Microorganisms are involved in a constant exchange of information". They send out signalling molecules that determine the behaviour of the bacterial population. This enables them to detect when a certain cell density is attained, in other words further growth would be detrimental or whether it is advisable for the population to adopt alternative life strategies. Known as 'quorum sensing', this ability regulates a whole range of mechanisms that increase the bacteria's chances of survival.

"Quorum sensing is the key mechanism in the formation of biofilms", says Dr. Wagner-Döbler. "We are therefore interested in how carolacton affects this ability". Carolacton incapacitates a central signalling pathway in the bacterial cell. In turn, this impairs various processes in the bacterium, including quorum sensing, but also cell division.

The researchers of the *e:biofilm* consortium use systems biology methods to create mathematical models of the bacterial signal networks in order to better understand how carolacton works. "The findings obtained by our consortium are not just ammunition in the fight against caries", says Dr. Wagner-Döbler. The scientists are also hoping to gain new insights into the bacteria that cause pneumonia.

The project – facts and figures

Project title: *e:biofilm* – Fighting biofilms of Streptococci by a novel biofilm inhibitor: from bench to dental products
Project partners: Helmholtz Centre for Infection Research, Technische Universität Carolo-Wilhelmina zu Braunschweig, Hamburg University of Technology, Technische Universität München, University Hospital Aachen, VOCO GmbH

Funding initiative
Title: *e:Bio* – Innovation Competition Systems Biology
Funding period: 2012 to 2021
Funding volume: approximately 120 million euros

Medicine

New approaches to cancer therapy resistance

If tumours start growing again after treatment was initially successful, medical science is often powerless to help. In most cases, the re-growing cancerous cells resist treatment. This also applies to the neuroblastoma, or cancer of the nervous system, that occurs predominantly in infants and small children. Researchers at the German Cancer Research Center (DKFZ) in Heidelberg are investigating why some neuroblastoma cells evade destruction by chemotherapy.

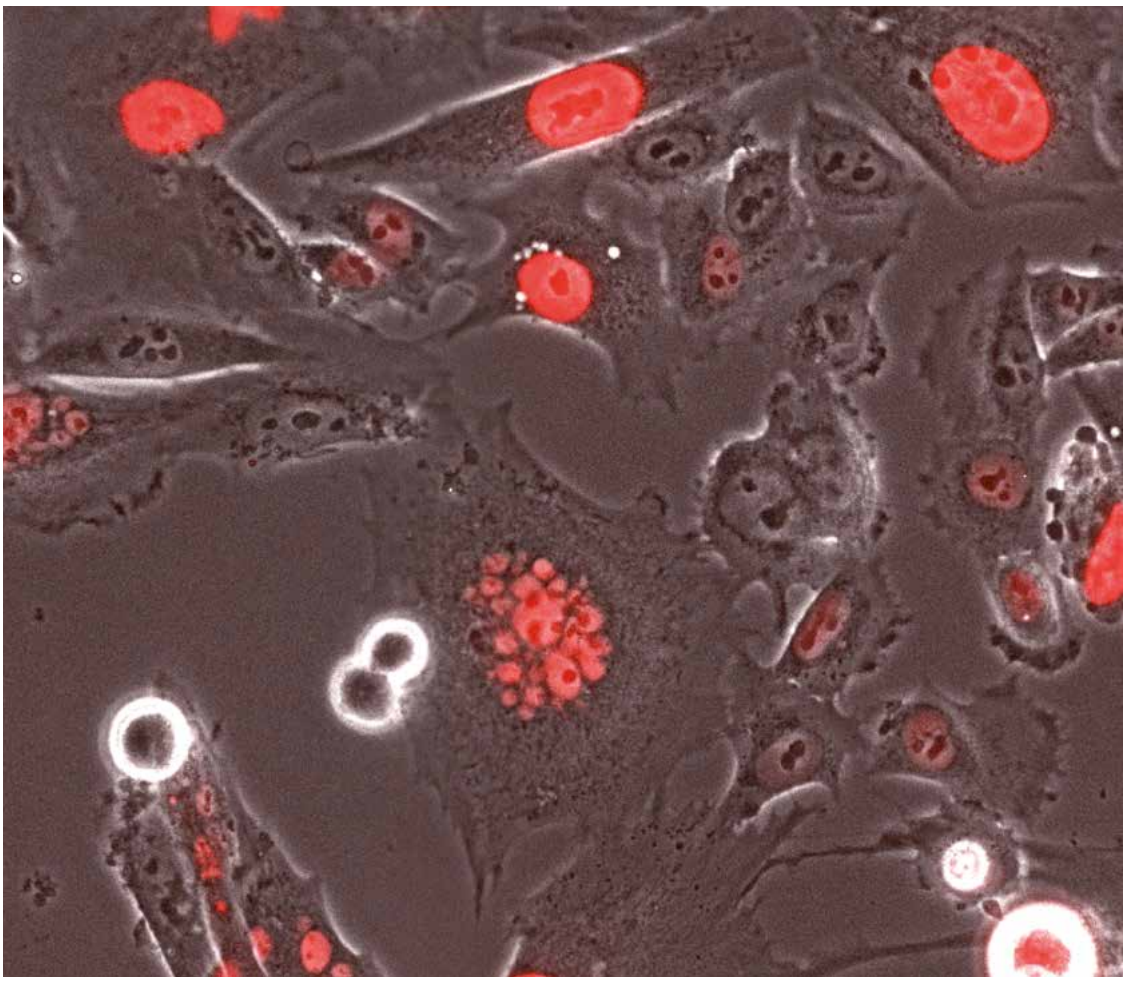
In most cases, the initial symptoms are relatively harmless: stomach ache and diarrhoea. Sometimes the young patients also start to vomit or develop a fever. It comes as a huge shock, then, when parents discover that their child has cancer. In Germany, approximately 150 children are diagnosed with neuroblastoma, a cancer of the nervous system, every year. At the time of diagnosis, most children are around two years old; in approximately one third of all cases, the disease is discovered before they are twelve months old.

There are extreme variations in how the disease advances: while some neuroblastomas regress spontaneously, others develop into fatal tumours that fail to respond to chemotherapy. In this aggressive form, a remarkable number of copies – up to a hundred – of a gene known as MYCN are often present in the genetic material of the cancerous cells. This was observed some years ago by the medical doctor and tumour geneticist, Dr. Frank Westermann, director of DKFZ's Neuroblastoma Reference Laboratory.

Unexplained resistance development

The MYCN gene is associated with the incidence of disease in a variety of tumours. "However, its precise function is still unknown", says Prof. Dr. Thomas Höfer, head of the interdisciplinary project *MYC-NET*. MYCN is probably involved in numerous different processes of cancer development and its further progression.

By itself, the accumulation of MYCN copies does not provide sufficient explanation for the resistance development of cancerous cells. Although all tumour cells in an aggressive neuroblastoma have this genetic anomaly, only very few survive chemotherapy. The tumour subsequently grows back from these cells. First of all, the scientists of the *MYC-NET* research



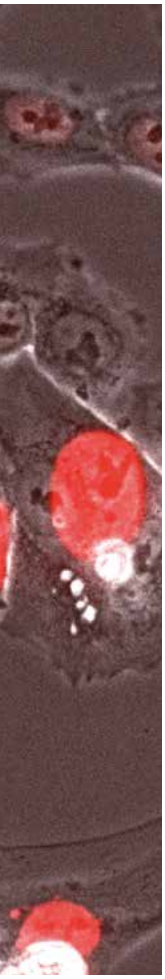
Under laboratory conditions, researchers observe which cancerous cells survive chemotherapy and which succumb.

group observed how neuroblastoma cells react to a chemotherapeutic agent in the culture medium in a cell culture dish. To do so, they utilise the technical possibilities offered by live cell imaging, which studies living cells using microscopy. The accurate documentation of their development enables scientists to track which cells survive the treatment and how they differed from the others at the beginning of the experiment.

Prof. Dr. Thomas Höfer values the collaboration between experimental and theoretical research in his working group.

The danger lies dormant

"In the past, scientists studied the entire cell population at once", says Dr. Höfer and goes on to explain, "but, as a general rule, the special features of a few individual cells get overlooked". However, in terms of developing resistance, it appears that these are particularly important. It therefore makes sense to take a look at the details.



Paradoxically, it appeared that the cell cultures with numerous MYCN copies responded particularly well to the chemotherapeutic agent. What at first may seem contradictory is actually no great surprise: the treatment attacks cells that are in the process of reproducing. Aggressive tumour cells are particularly fast growing and thus easily fall prey to the drug. However, a small percentage of cells – perhaps one in a hundred – manages to survive and eventually begins to divide and multiply all over again.

Upon closer investigation, it emerged that, unlike the tumour cells that were destroyed, the surviving cells were at a specific phase of the cell cycle. When the drug was administered, they were in the dormant phase, in other words, no cell division was taking place. "Some cells always appear more relaxed and reproduce more slowly – and it is precisely these cells that appear to be resistant", Thomas Höfer explains this observation. This opens up a whole new perspective on the therapy.

Combining chemotherapy with new active substances

But what role does the MYCN gene play? The Heidelberg team surmises that, after chemotherapy, MYCN stimulates cell division in the surviving cells, thereby causing the tumour to grow back. The scientists are now in the process of verifying this theory and researching the underlying mechanisms.

They are able to illustrate the interactions between MYCN and other genes in mathematical models. Based on these models, further systematic experiments can be planned in order to better understand the development of resistance and the effect of drugs on neuroblastoma or other forms of cancer. In cooperation with Bayer HealthCare and on this basis, the research team is currently searching for new active substances that are able to combat aggressive tumours more effectively in combination with chemotherapy. The idea is that the additional drugs interfere with the growth of the tumour cells to such an extent that as few as possible are in the resting phase of the cell cycle during chemotherapy.

Yet, according to Dr. Höfer, their vision goes even further. "We want to refine our mathematical models to ensure that they will be able to help doctors in selecting the right therapy and the optimal treatment plan for their patients". Therefore, the new insights gained in the role of MYCN could one day save the lives of numerous children.

The project – facts and figures

Project title: *MYC-NET* – Targeting MYC-Driven Therapy Resistance in Neuroectodermal Tumors
Project partners: German Cancer Research Center, Heidelberg University, Jena University Hospital

Funding initiative
Title: *CancerSys* – Systems Biology in Cancer Research
Funding period: 2010 to 2015
Funding volume: approximately 16.5 million euros

Blueprint for green energy – cyanobacterial biofuel

Biotechnology

Cyanobacteria could become the energy source of the future. With his team, Dan Kramer, a scientist living in Berlin, is researching bacterial strains that are extremely efficient at producing ethanol without using valuable resources like farmland and fresh water. The first pilot plants for fuel production are already in operation.

"The food vs. fuel debate does not apply to energy from cyanobacteria", says Dr. Dan Kramer, managing director of Algenol Biofuels Germany GmbH in Berlin. The biochemist is referring to the fundamental problem of many biofuels. In order to obtain fuel from plants, like sugar cane or maize, vast areas of farmland are required, which then cannot be used to grow food. In other cases, forests, natural areas or fallow fields are having to make way. Moreover, energy crops require vast quantities of fresh water.

"None of which is needed to generate energy from cyanobacteria: it is one hundred percent sustainable", Dr. Kramer emphasises. The unicellular organisms also grow in seawater and require nothing but sunlight and CO_2 from the atmosphere. The bioreactors that obtain ethanol from cyanobacteria are clear plastic mats, filled with seawater, which look like air mattresses. They work even under the most unfavourable environmental conditions.

Versatile bioreactors

"Cyanobacteria are incredibly fascinating", enthuses the biochemist, who first studied the microorganisms in his thesis. "They produce all manner of natural substances that are of enormous interest to pharmacology, yet can also be used in cosmetics and food supplements". All in all, the tiny bacteria offer exciting opportunities for biotechnology. While writing his thesis, Dan Kramer got together with colleagues to found his first company, which specialised in the manufacture of these natural substances. "At some point, Algenol, the American company, contacted us and asked whether we would also be interested in producing biofuel", he recalls.

Cyanobacteria produce ethanol in these clear plastic mats, which are filled with salt water.

Algenol has established itself as a global, industrial biotechnology company specialising in renewable transportation fuels. The economic focus is increasingly shifting onto these sources in light of the impending depletion of fossil fuels. Dr. Kramer explains that the Americans specifically approached a company in Germany because there are numerous cyanobacteria specialists in the Berlin-Potsdam region. "It has emerged as a real competence centre".

Increasing production using biochemical tricks

Some cyanobacteria produce ethanol naturally, although in much smaller quantities than those required for fuel production. The biochemical process only takes place under anaerobic conditions, in other words, in the absence of oxygen. However, oxygen is an inevitable byproduct when the single-celled organisms use sunlight and carbon dioxide to drive photosynthesis, thereby forming energy-rich carbon compounds.

This can be remedied by a gene that scientists have smuggled into the bacteria, which enables the production of ethanol even in an oxygenated environment. What is more, a biochemical trick allows the gene to be switched on or off as required. "Thus, we can multiply the bacteria to begin with until the population is large enough for production to be worthwhile", adds Dr. Kramer. Then you simply switch over to ethanol production, which would impede growth at an earlier stage. The biochemist goes on to allay any fears that genetically modified bacteria could escape into the environment. "Our cyanobacteria can only survive in the bioreactor".

Cyanobacteria or 'blue-green algae'

They can be seen as floating mats on bodies of water: a rapid increase in the population of cyanobacteria causes the so-called algal bloom. However, owing to their special ability, they can also be used in biotechnological processes. Thought to have been in existence for 2.5 billion years, cyanobacteria played a crucial role in facilitating the development of Earth's oxygenated atmosphere. They occur in various habitats, from freshwater and salt water through to deserts and on rock surfaces. Approximately 2,000 species have been documented. The misleading name 'blue-green algae' is attributed to the bluish-green colour of some bacteria species.

Ten times as efficient as sugar cane

Dan Kramer's cyanobacteria are highly efficient ethanol producers. Converting maize or sugar cane into fuel is considerably more time-consuming: first, crops have to be cultivated and then shredded, before yeast is added to the bioreactor to produce alcohol, which subsequently has to be distilled. Besides arable land, this requires an enormous quantity of energy. With cyanobacteria, the process runs from photosynthesis to producing alcohol without any further steps or additional energy input. The end product ethanol is extracted from the reactor via an elaborate system.

"With cyanobacteria, the yield is ten times greater than that of sugar cane, for example", Dr. Kramer points out. The bacteria convert approximately 80 percent of the CO_2 that they assimilate during photosynthesis into ethanol. Moreover, small amounts of petrol, diesel and kerosene are obtained from the residual biomass. Plants simply do not compare.

Sustainable biofuels are just around the corner

Nevertheless, Dan Kramer and his colleagues aim to improve production still further. The efficiency of the alcoholic fermentation process itself has probably been fully exploited. However, tests should be carried out to see whether the ethanol inhibits photosynthesis, thereby reducing production, or whether any other interactions in the system affect the yield. Researchers are exploring these questions as part of the BMBF's systems biology funding initiatives. Using mathematical models, they are searching for ways of maximising ethanol production.

At the same time, initial production trials are being carried out in pilot plants in America. It remains to be seen whether the Berlin cyanobacteria are also able to fulfil the promising laboratory results under economic conditions. "If all goes well, by the end of 2016 we will start with the construction of our first US production plant over an area of almost one thousand hectares", says Dr. Kramer. Then sustainable biofuel will be just around the corner.

The project – facts and figures

Project title: *CYANOSYSII* – Systems biology of cyanobacterial biofuel production
Project partners: Algenol Biofuels Germany GmbH, University of Freiburg, Humboldt-Universität zu Berlin, Max Planck Institute for Dynamics of Complex Technical Systems, Max Planck Institute of Molecular Plant Physiology, University of Rostock

Funding initiative
Title: *e:Bio* – Innovation Competition Systems Biology
Funding period: 2012 to 2021
Funding volume: approximately 120 million euros

Searching for the best anti-tumour drug

Used to treat cancer, chemotherapies usually have significant side effects, the reason being that they also attack healthy cells. Therefore, scientists in the *PREDICT* research consortium are investigating active substances that target the tumour cells only. To do so, they need detailed knowledge about the processes in the body, in the individual cancer cells, the tumour and the entire organism.

Cancer drugs tend to be developed as a lengthy process of 'trial and error', which does not always end in success. Many promising drug candidates fail to produce the desired result or come with the risk of serious side effects. Prof. Dr. Klaus Pfizenmaier, Director of the Institute of Cell Biology and Immunology at the University of Stuttgart, and his colleagues in the *PREDICT* team intend to change all that. They are working on complex mathematical models that enable a more accurate prediction of the effectiveness of new therapeutics.

At the same time, the consortium is developing new substances, which are being tested using the models. The Stuttgart team is focusing on so-called fusion proteins made up of two building blocks that are joined together. The actual drug is a protein molecule that docks onto diseased cells, triggering biochemical processes that lead to cell death. The second building block is an antibody that attaches itself to molecules existing mainly on the surface of cancer cells. Thus, it guides the active substance towards the tumour. These fusion proteins target cancer cells directly; healthy cells are not affected.

Predicting drugs' effectiveness

Whether or not the newly developed substances are suitable for treating cancer depends on a large number of different factors: how do the drug and cancer cell interact? How does the substance spread through the body and how quickly does it reach the cancer foci? Does the drug also reach the interior of the tumour or

> “At the cellular level, processes are relatively straightforward; things get more complicated at the level of the tumour”.
>
> Prof. Dr. Klaus Pfizenmaier,
> Director of the Institute of Cell Biology
> and Immunology at the University of Stuttgart

does it only affect the outer edges? “Numerous factors are relevant for the effectiveness of a therapeutic; however, it is extremely time-consuming to test each factor individually for every drug”, says Dr. Pfizenmaier. A suitable model aims to provide assistance in identifying promising drug candidates.

In order to achieve this goal, the scientists have to incorporate processes that take place in completely different orders of magnitude. “The active substances are only a few nanometres across, while the patient may be 1.80 metres tall”, Klaus Pfizenmaier points out. The timing also varies considerably. The drugs’ retention time in the human body ranges from a number of hours to several days, while molecular interactions with target cells take place in a matter of minutes. A mathematical model that takes account of the processes that extend over these enormous spatial and temporal dimensions is known as a multi-scale model.

From the cellular level to the entire body

Using the example of colon cancer, the *PREDICT* research group is developing a multi-scale model that is divided into three sub-models: the interaction between the active substance and the tumour cells, processes in the tumour and the mechanism of action in the body.

Dr. Pfizenmaier underlined the significance of the three model levels for tumour cells, “They are not all the same and thus respond very differently to the drug”. Therefore, it is imperative to study both the reaction of individual cells and the cell populations as a whole. Although the majority of the cells are destroyed, it is very likely that a few will survive. This is precisely where the danger lies, and with it, the risk of relapse and subsequent therapy resistance.

“At the cellular level, the processes are relatively straightforward; things get much more complicated at the level of the tumour or the body”, Klaus Pfizenmaier adds. For example, at the second model level, the research team observes the growth of blood vessels in the tumour, its supply of nutrients and the interactions with healthy cells. This allows them to calculate the correct drug dosage, ensuring that the active substances also reach the interior of the tumour.

Models assist in developing active substances

Research using sub-models is already so far advanced that it enables sophisticated simulations and reliable predictions at all three levels, thereby facilitating the development of new pharmaceuticals.

Now the great challenge is to piece the sub-models together. “This complete model will then be reviewed as part of a clinical trial of an initial therapeutic product”, says Dr. Andreas Herrmann, CEO of Baliopharm, one of the companies involved in the project. “This model would constitute a breakthrough in terms of predicting the retention time and particularly the distribution of a drug in the body and thus be highly informative as regards the efficiency of new active pharmaceutical ingredients”, emphasises Dr. Herrmann.

Several years’ work still lie ahead before these findings can be put into practice. But then research would have a valuable analytical tool to fall back on for developing drugs, stresses Dr. Pfizenmaier; “Many important biological principles are very similar for malignant tumours, meaning that, with some modifications, our models can also be applied to other forms of cancer”.

The project – facts and figures

Project title: *PREDICT* – Holistic Multi-Scale Modeling of Targeted Protein Therapeutics Action: Towards Predicting Effective Treatment of Cancer
Project partners: Baliopharm GmbH; Bayer Technology Services GmbH; University of Tübingen, Robert Bosch Gesellschaft für medizinische Forschung mbH, University of Stuttgart

Funding initiative
Title: *e:Bio* – Innovation Competition Systems Biology
Funding period: 2012 to 2021
Funding volume: approximately 120 million euros

Plant research

Research refines the selective breeding of maize

Slowly but surely, the supply of fossil fuels like crude oil and coal is dwindling. Therefore, it is becoming increasingly crucial to utilise – and optimise – sources of renewable energy. Since good forage maize is by no means good energy maize, the *OPTIMAS* project is developing methods of breeding better maize plants for energy purposes.

Maize is one of the most important plants for generating energy. Approximately 90 percent of Germany's biogas plants utilise the huge Poaceae or sweet grass. There are numerous disadvantages: the development of monocultures, the loss of arable land for food crops, increased fertiliser use and the considerable quantities of groundwater required to generate energy. Specially bred varieties could lessen the impact of these problems, rendering energy production from maize more resource-effective and efficient.

"An ideal solution would be a maize variety that results in the highest possible yield, in other words carbon-rich biomass, on the smallest possible area of land and using a minimum of resources", says Prof. Dr. Uwe Sonnewald, Head of Biochemistry at Universität Erlangen-Nürnberg. "At best, this would prevent excessive quantities of valuable drinking water, arable land and natural areas from being sacrificed for energy purposes". Furthermore, breeders have different requirements for energy maize than for forage maize. For example, forage crops with a high level of nitrogen fixation are preferred for the development of essential nutrients. By the same token, nitrogen is a disruptive element in energy maize due to the pollution caused when it is released into the atmosphere during energy production. Instead, it should contain plenty of carbon, the actual energy source.

Comparing selected varieties of maize

The scientists involved in the *OPTIMAS* initiative are researching maize plants with corresponding genetic characteristics. The skilful cross-breeding of suitable maize plants results in improved varieties for energy purposes. "To achieve this, we have to examine numerous different aspects, which is only possible if we have an efficient network with partners from industry and academia", says Uwe Sonnewald.

One key task for this project was to compare different types of maize under various environmental conditions. What impact do low temperatures, arid conditions or a lack of nutrients like nitrogen and phosphate have on growth?

"There are thousands of different varieties of maize", says Dr. Sonnewald, indicating one of the great challenges facing the project. "It would be impossible to study them all individually". Therefore, the researchers work with core collections, compilations of archetypes of different maize lines that have already been thoroughly researched. The samples reflect the variety of existing maize lines and provide an overview of their particular attributes. Thus, the genetic diversity of maize can be mapped with a manageable number of plants.

Identifying the genes for growth characteristics

The researchers determined the growth capacities and characteristic attributes of the metabolic activity, including any metabolites, of each test plant in the greenhouse. Moreover, they studied the plants' transcriptomes, in other words, the set of genes that were being actively expressed under certain conditions at the time of examination. This enabled them to establish which genes are crucial for ensuring that the plant continues to thrive, even under difficult conditions.

Experiments such as these result in vast quantities of data, which are almost impossible to keep track of. This is where the theoretical work starts, using appropriate bioinformatic methods and mathematical models to organise the flood of data and extract its informative value.

Discovery of selection criteria for optimised breeding

Using these tools, the research team identified 16 genes that are always switched on in good growth phases under difficult conditions, even if the plant has to contend with low temperatures or a deficiency of nitrogen or phosphate. Further research is required to obtain detailed information on each gene's individual role in the plant's growth. Even today, these genes are

The researchers set great store by genetic analysis and mathematical models, which sift through the thousands of types of maize and identify the right plants for breeding.

giving valuable pointers as to which hybrids yield particularly fertile and robust varieties of maize.

The research group has identified the genes that are particularly active in the plant in the case of phosphate deficiency. Dr. Sonnewald explains that, for the time being, this finding is of interest for fundamental research. "However, the Earth's phosphate deposits are also finite, therefore this discovery could also prove to be of economic importance in the long term". In fact, the scientists are already focusing on certain features that may serve as suitable selection criteria for systematically breeding maize plants that only require small amounts of this valuable commodity.

The project – facts and figures

Project title: *OPTIMAS* – Systems Biology of Maize Plants
Project partners: Friedrich-Alexander-Universität Erlangen-Nürnberg, Heinrich Heine University Düsseldorf, Leibniz Institute of Plant Genetics and Crop Plant Research (IPK), Max Planck Institute of Molecular Plant Physiology, metanomics GmbH, Universität Regensburg, University of Cologne

Funding initiative
Title: *BioEnergieSys* – Systems Biology for Bioenergy
Funding period: 2009 to 2012
Funding volume: approximately 5 million euros

Improved microscopy opens up new therapy options

Medicine

Fluorescence microscopy is a widely used method of observing processes in living cells. This form of light microscopy uses fluorescent dyes to illuminate the individual cellular structures. Nevertheless, these images often only show that certain cell structures are present but not in what quantities and at what exact position. Prof. Dr. Mike Heilemann aims to visualise these details and is working with his team on improved microscopy techniques to achieve this goal.

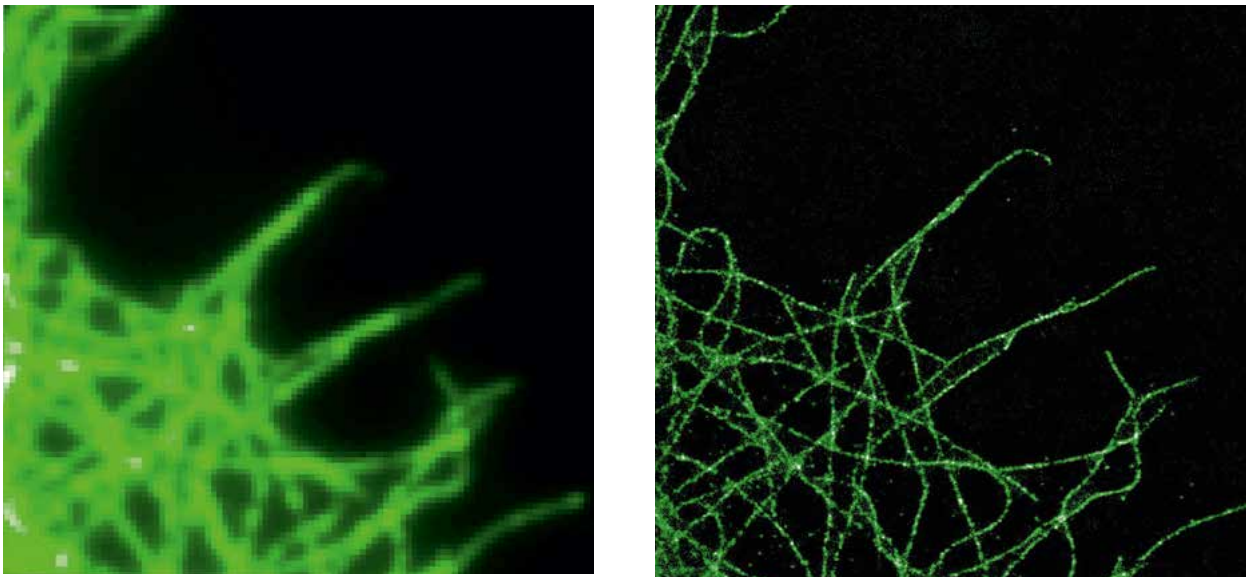
Satellite images taken at night show the world's megacities as dazzlingly bright spots of light on a black canvas. The urban complexes of Cairo, New York or Berlin are clearly identifiable among the patterns of light. However, details of the metropolises, like buildings, streets and squares, are impossible to distinguish as the numerous sources of light outshine the contours.

"A similar problem arises with the images captured from within the cell using conventional microscopy methods", says Mike Heilemann, who is developing new microscopy techniques with his team at Goethe University Frankfurt. Although structures like proteins can be identified using antibodies labelled with a fluorescent dye, the resolution is limited. Anything smaller than 200 to 300 nanometres, like most viruses, cannot be visualised in detail. Ultimately, like the satellite images, the details are lost in the general glow.

Observing dynamic processes in living cells

Furthermore, electron microscopy is not suitable for many research topics. Admittedly, it offers a higher resolution; yet this method requires the destruction and laborious processing of cells, which modifies the tissues. Thus, it is not possible to study dynamic processes in living cells. However, these processes are of particular interest in attempting to understand a biological system. "At the same time, we require a high resolution to capture the details", Dr. Heilemann emphasises. How many of the relevant molecules are present? How do the individual components form a cluster?

The chemist's goal is to visualise details on the nanoscale in microscopy images – initially with a BMBF-funded junior *FORSYS* research group in Bielefeld and Würzburg. Today, Mike Heilemann is involved in research with his team at Goethe University Frankfurt. He illustrates the method using the satellite images as an analogy, "If you turned off all the lights in a city and asked the inhabitants to illuminate one building at a time, you could capture each pinprick of light individually from space and thus reproduce the street map perfectly".



The new microscopy technique shows cellular structures in super-resolution imaging (right-hand image).

Using tricks to capture individual pinpricks of light

In order to transfer this concept to fluorescence microscopy, Dr. Heilemann deploys a physics trick: fluorescent dyes that can be switched on and off by light pulses. When light of a given wavelength is shone onto these molecules, only very few light up. The microscope then captures these as single points of light, enabling their position to be determined accurately. All illuminated molecules are then switched off. In a further step, other fluorescent molecules are irradiated, using light of a different wavelength. The research team repeats these steps several thousand times until all marked points have been captured and the individual measurements form a complete picture.

Working with cooperation partners in Heidelberg and Bielefeld, their studies look at cell signalling chains, among other topics. The research team are focusing on receptors and signalling molecules; these also provide starting points for new therapies, like blocking the signalling pathways that induce cancer cells to multiply or specifically targeting the tumour cells in order to activate these signalling chains.

More detailed images open up new therapy options

As Mike Heilemann explains, "To this end, we need detailed knowledge on how the receptors are spatially organised and how the interaction partners congregate".

Armed with this knowledge, researchers can then search systematically for active substances that are able to attach effectively to the corresponding binding site and trigger the desired reaction.

In a virology project with the University of Heidelberg, Dr. Heilemann is researching the interaction between the HIV pathogen and its host cells. Among other things, the new microscopy techniques showed that the viral envelope has a different structure than that previously assumed. This finding leads to a better understanding of the viruses and processes involved in HIV infection. Dr. Heilemann's research is thus laying the foundation for new therapy options in this field. This microscopy method may also be able to identify new vantage points for treating other infectious diseases.

The project – facts and figures

Name of the junior research group: Fluorescence techniques for quantitative studies of virus-cell interactions, integrated in the *ViroQuant* Center in Heidelberg

Funding initiative
Title: *FORSYS* partner (partner of the Research Units for Systems Biology)
Funding period: 2008 to 2014
Funding volume: approximately 32 million euros

Miniature masters of survival and biotechnology

They live in hot springs, bubbling mud holes and saltwater lakes, often in combination with highly acidic or alkaline environments: single-celled organisms that thrive in extreme conditions are known as extremophile archaeons. Owing to their exceptional adaptability and metabolic capacities, the *SulfoSYS-Biotec* research consortium aims to make use of these organisms in biotechnological processes.

To the west of Naples, jets of steam issue from fissures in the earth. Volcanic activity releases gases, including hydrogen sulphide, which reacts with the oxygen in the atmosphere. Microorganisms in the environment compound the situation, giving rise to sulphur and acids, with high temperatures to boot: an extremely inhospitable milieu. In 1980, scientists made an interesting discovery: a unicellular organism, *Sulfolobus solfataricus*, thrives in temperatures of 75 to 80 degrees Celsius and in alkaline environments with a pH level between 2.5 and 3.5 – conditions that would prove deadly for numerous other organisms.

Surviving under extreme conditions

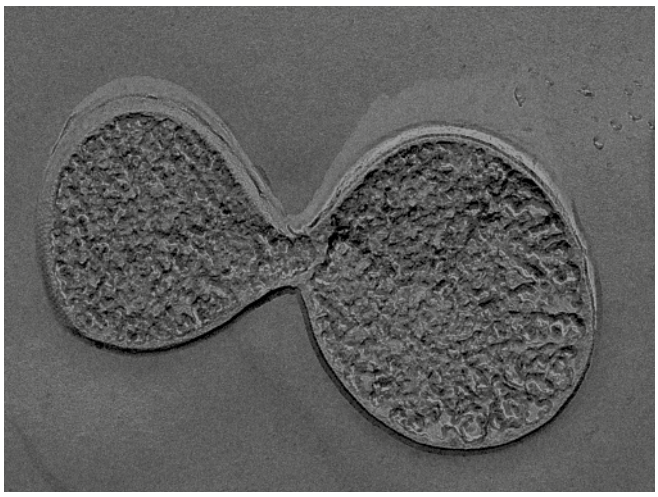
A species of hyperthermophilic Archaea, the single-celled *Sulfolobus solfataricus* can be clearly differentiated from bacteria. They form one of the three domains of life designated by biologists. Many of these Archaea, which evolutionary biology considers to be extremely old, prefer exceptional living conditions: temperatures up to and above the boiling point of water, high pressure, environments that are extremely salty, acidic or alkaline. These organisms are termed extremophile, i.e. they thrive under extreme conditions.

"We are interested in how Archaea adapt to such extreme environments, how they are able to maintain metabolism at all at high temperatures and what form their metabolic pathways take", says Bettina Siebers, Professor for Molecular Enzyme Technology and Biochemistry at the University of Duisburg-Essen and coordinator of the *SulfoSYS-Biotec* project. "Archaea are an incredibly exciting concept for biotechnology". They could be used to produce new substances or make processes more cost-effective and more environmentally friendly.

Applications in biotechnology

The extremophile organisms' special enzymes often have a high degree of stability and remain active in organic solvents, for example, where other enzymes break down. They would even make it possible to use resources that are difficult to process, like lignocellulosic biomass, i.e. cellulose obtained from wood pulp. As a renewable resource, it is used in industry to generate energy; however, it can only be utilised in biotechnology at high temperatures and under alkaline conditions: an environment in which Archaea feel very much at home.

Using Archaea as production strains leads to numerous advantages for the biotechnological production process; not only can the energy-intensive cooling of the bioreactors be dispensed with, the high temperatures at which metabolism takes place actually accelerate many reactions, thereby increasing the yield. Moreover, the high temperature prevents contamination with other bacteria and yeasts that would interfere with the production process. "Thus, there is no need to add antibiotics", says Dr. Siebers, the project coordinator. One other advantage is that alcohol, which often impedes the biotechnological production process, evaporates at these temperatures.



Electron microscopic image of the extremophile archaeon *Sulfolobus solfataricus*.

Hot springs are the typical habitat of *Sulfolobus solfataricus*. The species thrives in optimal temperatures of around 80° C.

Exploring extreme metabolic pathways

Further research is required into Archaea's metabolism and special enzymes before they can be used in biotechnological applications. The research consortium is actively pursuing this task. By researching interesting enzymes and developing systems biology models, the scientists hope to gain a greater understanding of the special metabolic pathways of *Sulfolobus solfataricus*. Their findings will lead to ideas for biotechnological applications in which the archaeal enzymes can be put to good use.

As Bettina Siebers reports, the consortium has also established cooperations with various companies, "In collaboration with industry partners, we have developed a biotechnological technique that enables the large-scale production of special intermediates of the sugar metabolism using *Sulfolobus solfataricus*". These are required to examine metabolic processes in other organisms, like bacteria, in the laboratory. Thus, the consortium's first commercial product is benefiting other scientists' research work.

The project – facts and figures

Project title: *SulfoSys-Biotec*: Applied Sulfolobus Systems Biology: Exploiting the hot archaeal metabolic potential for Biotechnology Project partners: University of Freiburg, enzymeta GmbH, Otto von Guericke University Magdeburg, Sigma-Aldrich, Technische Universität Carolo-Wilhelmina zu Braunschweig, Bielefeld University, University of Duisburg-Essen, University of Amsterdam, University of Sheffield

Funding initiative
Title: *e:Bio* – Innovation Competition Systems Biology
Funding period: 2012 to 2021
Funding volume: approximately 120 million euros

Computer-aided profiling for HIV therapy resistance

Medicine

The biggest problem in HIV therapy is the high mutation rate of viral DNA and the associated development of resistance to the drugs used as treatment. Therefore, several active substances are administered simultaneously. However, the right combination is crucial to the success of the treatment. Researchers from Heidelberg, Cologne and Saarbrücken are developing mathematical models to help select the optimal combination of drugs using a computer.

As a mathematician and computer scientist, Prof. Dr. Dr. Thomas Lengauer primarily comes into contact with viruses via his computer – an unusual yet effective weapon in the fight against HIV. "Using mathematical models, we aim to detect resistance mechanisms and predict which virus mutations are to be expected in order to offer patients optimal personalised treatment", says Dr. Lengauer, a researcher at the Max Planck Institute for Informatics in Saarbrücken.

In the past, doctors determined the composition of the drug cocktail using mutation tables. These contain the accumulated knowledge of many years of HIV therapy, including information on genetic modifications in viruses that cause resistance to certain medications. In practice, the patients' blood samples are analysed for resistance mutations in the virus gene. A comparison with the data indicates which antiviral drugs are a suitable match.

Mathematics opens the door to successful therapies

"Some time ago, in collaboration with our colleagues at the University of Cologne, we developed a mathematical model that is superior to the previous selection procedure", says Thomas Lengauer. Although this method is also based on the analysis of the viral genome, it is a great deal more accurate as it additionally factors in the combined effect of the genetic modifications. Thus, mutations can interact and, in the process, increase, reduce or even suppress a resistance.

"Our colleagues once had a patient, for whom they were no longer able to identify a suitable combination using the conventional procedure", Dr. Lengauer reports. "However, based on the in-depth analysis

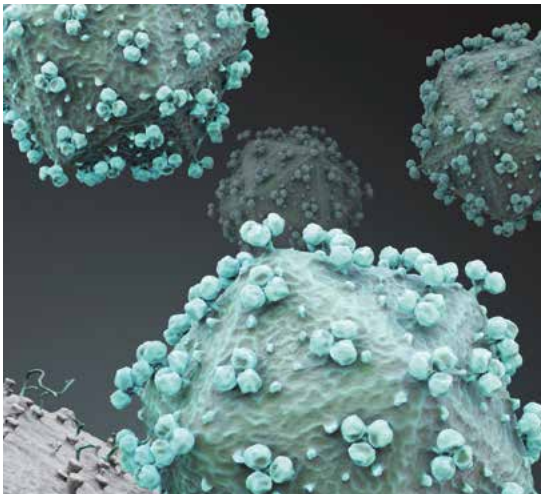
Computer programmes enable the researchers to identify the optimal combination of active substances.

offered by the model, the doctors were able to compile a treatment programme that proved effective for many years".

The model represents a major step forward; nevertheless, selecting the appropriate therapy simply from the mutation pattern is not always successful. Although the resistance response of a virus is generally encrypted in its genome, a number of other factors affect the interaction between the infection, the patient and the drug.

Enhanced models using the example of a modern drug

The countless variations of the human immunodeficiency virus in the body react differently to antiviral drugs, which may lead to unexpected resistance developments. The effectiveness of a therapeutic depends on the subtle differences in the three-dimensional structure of the viral proteins and the protein molecules of the body's cells.



The effectiveness of a drug depends on the subtle distinctions in the virus' three-dimensional structure.

"The mathematical models must be refined to include these aspects and enhance their accuracy", Thomas Lengauer explains. By studying Maraviroc, a relatively new drug that prevents the virus from entering the host cell, the researchers are compiling more detailed information on the interactions between antiviral drugs, HIV and the body's cells.

In order to infect a cell, HIV has to dock onto two different molecules on the cell surface. The virus first attaches to a receptor, thereby triggering structural changes in the envelope, which expose a second binding site, known as the co-receptor. Now the virus can make its way into the cell.

Maraviroc inhibits the entry of the virus in the cell by blocking a frequently used co-receptor. However, it is not effective for all types of HIV as some viruses target alternative co-receptors. Therefore, before initiating treatment, laboratory tests must be carried out to determine which receptor the virus uses. Its genome does not provide enough information on this.

More details increase the accuracy of predictions

In order to improve predictions on the resistance response of the virus, the researchers are refining their mathematical model by adding further parameters. These include the minute variations in the three-dimensional structure of HIV, which are a crucial factor in selecting the co-receptor. Although these nuances are not evident in the gene sequence, they have an impact on the effectiveness of the drug.

Another important aspect is that conventional blood tests only detect the commonest types of HIV. Owing to the high mutation rate, however, people infected with HIV have a large number of slightly genetically distinct variants, including resistant forms that prevent successful treatment. Modern technologies visualise the different virus variants and thus increase the risk of new resistances emerging.

This and other important findings discovered by the scientists of the research group as a result of their experiments are now being gradually incorporated into new resistance models. It will be some years yet before the refined models can be used in practice. But then they will serve as a valuable instrument, enabling doctors to select the optimal combination of drugs for each and every HIV patient and ensuring the success of the treatment for as long as possible.

The project – facts and figures

Project title: Patient- and Drug-Specific Models of HIV Cell Entry
Project partners: Max Planck Institute for Informatics Saarbrücken, Heidelberg University, University of Cologne

Funding initiative
Titel: *MedSys* – Medical Systems Biology
Funding period: 2008 to 2013
Funding volume: approximately 44 million euros

Four-dimensional microscopy improves plant breeding

Simply studying snapshots is not enough to gain an in-depth understanding of the biological processes in an organism. The research team of the *MICROSYSTEMS* project are therefore developing four-dimensional microscopy techniques that extend three-dimensional images to include the factor of time. Their mission is to better understand plant growth and development, while streamlining the work processes involved in breeding.

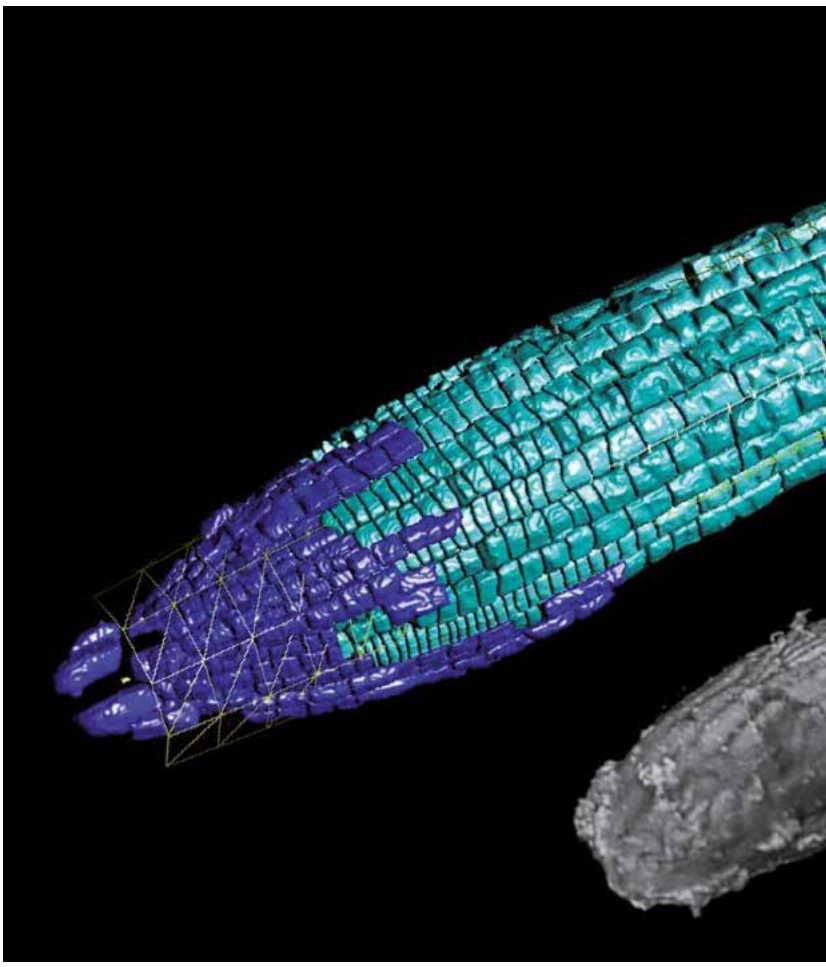
The world's population is growing at a tremendous pace. More than seven billion people live on the Earth today. UNO experts estimate that this figure will rise to well over nine billion by the year 2050. The demand for raw materials and food is increasing accordingly. At the same time, the amount of arable land is diminishing, while in many places erosion and intensive cultivation have depleted the nutrients from the soil. Climate change and the resulting aridity only serve to compound the situation.

Worldwide demand for robust, drought-resistant plants is rising. Yet conventional breeding has various limiting factors: crossing two varieties with the desired characteristics produces a promising first filial generation to begin with. However, the subsequent generations develop undesirable properties, which would have to be patiently eradicated over many years. Rapid results are simply not possible using this method.

Shortcuts in breeding

This is due to the fact that male and female gametes each carry a haploid, or half a set of chromosomes, which then merge when fertilised to form a doubled or diploid set. Therefore, the filial hybrids carry chromosomes from both parent plants. However, this mixed diploid set divides again in the next generation and with it also the traits. Only some of the progeny now come up to expectations – an effect observed by Gregor Mendel back in 1866.

"In exceptionally rare cases, this may lead to so-called doubled haploids", explains Prof. Dr. Klaus Palme, a plant researcher in Freiburg. This occurs when unripe pollen grains – known as microspores – unexpectedly form embryos.

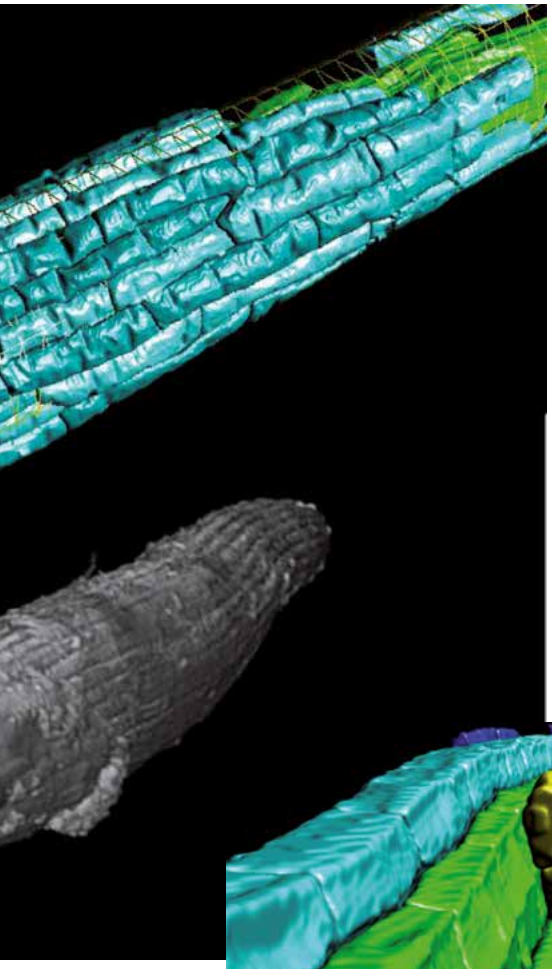


Modern 4D microscopy techniques enable the Freiburg research team to observe plants' root growth in real time.

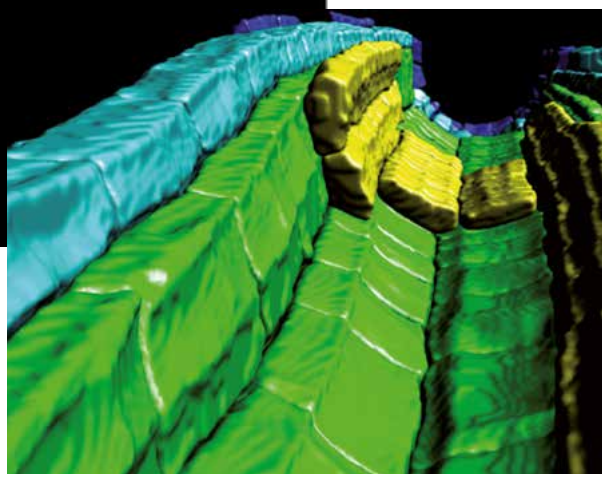
In the process, the microspores undergo spontaneous chromosome doubling, thereby producing a doubled haploid cell, a new plant, whose genome does not contain mixed but two identical sets of chromosomes. "Further reproduction does not change the characteristics of doubled haploid plants", Dr. Palme points out. Not only does this produce genetically stable plants, it is much quicker than the traditional method.

Facilitating modern plant breeding

Although working with doubled haploid plants has been common practice in modern breeding for some time, they are rarely bred in the laboratory. This unusual propagation method does not occur at all in some species. The reason for this is not clear; thus, in principle, breeding programmes are forced to rely on random occurrences. The *MICROSYSTEMS* research group is hoping to change that.



"Using a systems biology approach, we are studying how doubled haploidy develops", says Klaus Palme, the head of the project team. "We want to understand the mechanisms and are looking for the molecular biological switches that allow this process to be stimulated systematically for breeding purposes".



The cutting-edge 4D microscopy techniques developed by the team play a key role. Apart from a high, three-dimensional spatial resolution, this technology adds a fourth dimension: time. This enables the team to capture exactly wherever and whenever something happens in the cell, thereby providing further insight into the processes that take place in cells and organisms.

Deciphering unknown processes

The researchers map the microscopy results with molecular biological data, together with various external factors, like the pH level of the environment or a change in the food supply. Mathematical models are then used to predict which key components and cellular mechanisms decide whether doubled haploid plants sprout from ripe pollen grains.

The team's preliminary findings indicate that chemical attachments to the DNA play a role in this context by determining which sections of the genome are active and which are dormant. These are referred to as epigenetic mechanisms: regulation mechanisms that control the actual genome itself. The researchers aim to create a type of map that shows which epigenetic attachments change – and how – during the development of the pollen. To do so, they compare the different stages of development of normal pollen and those grains that go on to form doubled haploids. The scientists hope that this map will provide information on the specific epigenetic modifications that are responsible for this remarkable method of propagation.

The idea is not just to use the special microscopy technique to unlock the secret of the haploid cells. "In essence, these methods are ideally suited for visualising changes in the cells in detail", adds Dr. Palme. For example, in Freiburg, the scientist and his team observed plants' root growth in real time in order to study the interaction between environmental signals, like light and temperature, with signals emitted by the organism in the formation of plant organs.

The project – facts and figures

Project title: *MICROSYSTEMS* – BioSystems analysis of microspores to improve industrial plant embryo production
Project partners: University of Freiburg, Saaten-Union Biotec GmbH, TILL I. D. GmbH

Funding initiative
Title: *e:Bio* – **I**nnovation Competition Systems Biology
Funding period: 2012 to 2021
Funding volume: approximately 120 million euros

Metastases – what makes cancer cells migrate?

Medicine

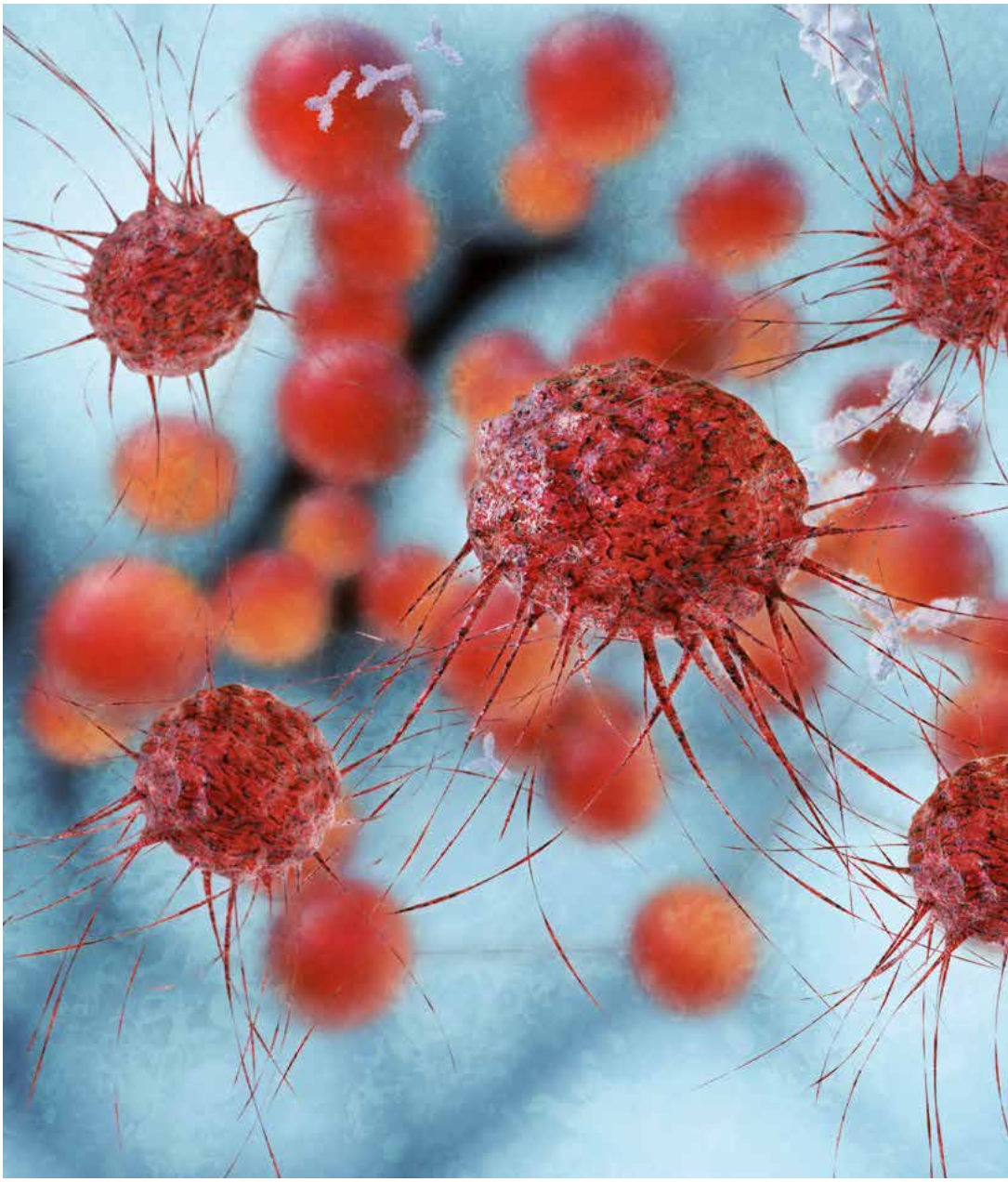
In most cases in which cancer proves fatal, it is not due to the primary tumour: it is the metastases that pose the greatest risk. They cause the disease to spiral out of control, often many years after the original tumour was treated successfully. The *SysMet* project is researching why individual cancer cells migrate and form secondary tumours.

Metastases: feared by doctors and patients alike, they severely jeopardise the patient's chances of recovery from a tumour as, in most cases, they cannot be surgically removed nor treated with radiation therapy. Often, they are also resistant to chemotherapy.

The term metastasis is derived from the Greek word for displacement. In fact, it occurs when cells break away from the primary tumour to settle in other parts of the body and form new tumours. Nonetheless, the cause of these migrations remains largely unclear. When do cells start migrating and what signal are they following when they settle in another part of the body? What then happens in the tumour cells? And what role does the environment play? The members of the *Sys-Met* research group (Systems Biology of *E2F1* Signaling in Tumor Progression and Metastasis), which is based in Rostock, are exploring these and similar questions. Once the scientific community has a greater appreciation of the mechanisms of metastasis, it will be possible to develop better therapies that will eventually help cancer sufferers with metastasising tumours.

The two-faced molecule

For some time now, Prof. Dr. Dr. Brigitte Pützer, a cancer researcher in Rostock, has been setting her sights on a biomolecule named *E2F1*. The so-called transcription factor plays a crucial role in decoding DNA and jointly controls which genes are active. Dr. Pützer's group at the Institute of Experimental Gene



It remains unclear why cancer cells spread. The Rostock research team aims to investigate what signals they follow.

Therapy and Cancer Research has discovered that *E2F1* is also involved in metastasis.

However, the molecule is literally two-faced. "*E2F1* can act as a tumour suppressor, but then again it may also turn out to be the bad guy and favour the formation of metastases", explains Prof. Dr. Olaf Wolkenhauer, Professor of Systems Biology at the University of Rostock and coordinator of the *SysMet* project. The scientists are hoping to follow up on this inconsistency.

Map of the molecules' interaction network

First, the project team scoured the available scientific literature – over 500 specialist publications – to compile a list of all the factors that interact with the *E2F1* molecule and the cascading signalling pathways. They then entered this data and their own analyses into the computer, merging them into a network. "Although this might sound fairly straightforward, the enormous quantity of available data meant that the task took over a year", says Dr. Wolkenhauer, who works with mathematical modelling and data analysis. The result was a huge map, documenting well over 3,000 interactions among approximately 750 molecules and molecular complexes.

In order to unravel this vast network, it was broken down into smaller, more manageable units. Using these individual modules, the scientists are now able to search systematically for the network components that accelerate the formation of secondary tumours. They are also looking for patterns in the system. "These could be feedback loops, in which a certain factor determines whether a signalling pathway continues or is inhibited", Olaf Wolkenhauer explains. These findings form the basis for mathematical models that allow the research team to predict the behaviour of the entire network.

Models for new therapy approaches

Even single tumour cells are crucial for the success of the treatment. "We can see from our simulations that just a few resistant cells are enough for a tumour to grow and metastasise at a later date", says Dr. Wolkenhauer. Therefore, in order to adopt new approaches to therapy, it is important to have in-depth knowledge of what makes tumour cells resistant. The research consortium has already discovered a mechanism that controls whether the *E2F1* biomolecule becomes the 'good guy' or the 'bad guy'.

Together with other interaction partners, known as microRNAs, the biomolecule can activate one that destroys cancer cells and thus suppresses tumorigenesis. In the absence of sufficient interaction partners, this cell death programme comes to a halt. The cells become resistant to chemotherapy. Thus, the biomolecule can no longer suppress the tumour and begins to favour metastases. "Based on our models, the medical professionals in the laboratory are carrying out experiments in order to study this connection more closely", Olaf Wolkenhauer explains. The results are ultimately re-entered into the mathematical model. The interdisciplinary team is hoping to use their findings to develop new therapy approaches in the future.

> "We can see from our simulations that just a few resistant cells are enough for a tumour to grow and metastasise at a later date".
>
> Prof. Dr. Olaf Wolkenhauer,
> Professor of Systems Biology
> at the University of Rostock

The project – facts and figures

Project title: *SysMet* – Systems Biology of *E2F1* Signaling in Tumor Progression and Metastasis
Project partners: University of Rostock, University Medicine Rostock

Funding initiative
Title: *e:Bio* – Innovation Competition Systems Biology
Funding period: 2012 to 2021
Funding volume: approximately 120 million euros

Cross-border systems biology research

Systems biology research benefits from excellent networks – even more so if they have an international reach. For this reason, the BMBF also initiates and coordinates European funding programmes. By pooling international expertise, they are empowering European systems biology and its diverse range of applications.

Good ideas transcend boundaries. There are creative scientists in numerous countries around the world. "We have been trained in different environments; as a result, we all have individual perspectives, from which everybody benefits as part of the collaboration", says Damjana Rozman, Associate Professor of Biochemistry and Molecular Biology at the University of Ljubljana. She represents Slovenia in European systems biology and systems medicine consortia.

Multifaceted ideas and perspectives, technical know-how, experience in different systems biology fields: all these resources can only be brought together by collaborating on an international scale. "It is imperative that we work as efficiently as possible and pool the available international expertise. It is the only way to fast-track development. International networks avoid any unnecessary duplication of effort", says Peter Sorger, Professor of Systems Biology at Harvard Medical School in Boston. Together with Prof. Dr. Roland Eils, a mathematician in Heidelberg, Dr. Sorger has been a pioneer of international networking for some years.

At a very early stage, the BMBF began pooling systems biology research resources and has been actively engaged for many years in European research and funding programmes in this field. In 2005, the ministry launched the pan-European "Systems Biology of Microorganisms – *SysMO*" funding initiative, which

was coordinated centrally by the Project Management Jülich. From 2007 until 2013, *SysMO* and later "Systems Biology of Microorganisms 2 (*SysMO2*)" sponsored systems biology research into microorganisms. The funding initiatives were aimed at interdisciplinary teams that included partners from at least three European countries.

ERASysBio – A milestone on the way to establishing an international network

SysMO was the first of three funding initiatives launched under *ERASysBio* (European Research Area for Systems Biology), a consortium of funding bodies, ministries and project management agencies from 13 countries, which was coordinated by Germany. The members – which included Israel as well as various European countries – developed a joint strategy in order to encourage systems biology endeavours in Europe and, in so doing, boost Europe's scientific potential. Building on the success of *SysMO,* two spin-offs, *ERASysBio+* and *SysMO2,* were published over the next few years.

ERASysBio led to the subsequent launch of further activities. A total of 16 partners from 13 European countries have joined forces in the *ERASysAPP* Europe-wide network with the goal of raising systems biology to the application-oriented and/or industry-relevant level. Therefore, at least one company is involved in each of the consortium's funded projects, including projects that aim to increase the biomass yield of barley, the application of biotechnological processes for efficient metal extraction and the development of antiviral drugs. Moreover, the initiative also promotes the further training of young systems biology researchers, seeks to improve data management and fosters networking between academia and industry. Germany is tasked with the central coordination of the network.

International strategy helps address medical challenges

Once again, Germany has agreed to coordinate and manage the most recent European systems biology initiative: the current *ERACoSysMed* consortium is made up of 14 European funding bodies from 13 countries. The objective is to encourage systems medicine research endeavours and position Europe at the forefront of this future-oriented discipline. Systems medicine combines the methods and insights of systems biology with medical research topics. This strategy has been designed to lead to completely new approaches to the prevention and treatment of disease. The consortium is sponsoring interdisciplinary projects in systems medicine research with a high degree of clinical applicability.

ERACoSysMed builds on the Coordinating Action Systems Medicine (CASyM), in which 22 partners from eleven European countries have joined forces to formulate a Europe-wide implementation strategy (road map) for systems medicine. One important step on the road to success was the founding of the European Association for Systems Medicine (EASyM).

> "International networks avoid any unnecessary duplication of effort".
>
> Prof. Dr. Peter Sorger,
> Professor of Systems Pharmacology
> at Harvard Medical School, Boston

Peter Sorger hopes that this will lead to further cooperation in the future, thereby forging closer links between Europe and the United States. "Personally, I believe that science can derive enormous benefit from international collaboration", he says. "Even in difficult political environments, science has continually brought like-minded people together in their common search for truth".

Systems biology – a life science success story

Since 2001, the BMBF has been focusing its attention on systems biology. The emerging research field is now firmly established in today's science landscape. Our task now is to tap its enormous potential in medical and biotechnological applications as well as in plant research.

During the early days of systems biology funding, the idea developed of revolutionising the life sciences by embracing computational modelling. The goal was to introduce new perspectives and create added value, as has been common engineering practice for years: no aeroplane is designed today without first being simulated on the computer. This speeds up the development process, reduces costs and mitigates risks. Computational models can benefit biology and medical research in the same way: creating a model of living systems enables predictions to be made regarding their behaviour and achieves better results, regardless of whether researchers are developing new pharmaceuticals, higher-yield crops or new biotechnological processes.

A sound basis is a prerequisite for tapping this scientific and economic potential. Therefore, the BMBF initially invested in fundamental research and the development of appropriate structures. At the same time, a functioning infrastructure came into being, along with research centres and technology platforms that offer the scientists access to cost-intensive equipment, thereby facilitating efficient research. Moreover, universities throughout Germany have created a number of chairs and introduced over 30 study programmes aimed at young systems biologists.

A wave of innovation for medical research

Following the initial period of establishment, the BMBF is now paving the way for systems biology to move onto applied research. Mathematical models are already being used in the development of new pharmaceuticals. Based on their systems biology research, scientists are developing new therapy approaches and preparing clinical trials. Furthermore, biotechnological innovations for use in energy generation, for example, are almost ready for the market.

The BMBF sees a great deal of potential, particularly in the medical field, for systems biology approaches and methods. Systems medicine draws on systems biology to map the body's complex physiological and pathological processes in their entirety. This includes the interaction between pathogens and the immune system, as well as environmental factors, personal lifestyle and genes. It is thus laying the foundation for new diagnostic methods, innovative therapies and customised prevention approaches – an important step towards individualised medicine and improved patient care. Nevertheless, the enormous quantities of medical data have to be coordinated and analysed in a meaningful way. To this end, the BMBF is investing in new funding measures that are dedicated to the constructive use and processing of data.

Science and industry in tandem

From the outset, the BMBF succeeded in getting industry partners on board by firing their enthusiasm for the research field. It is essential that academia and industry work in tandem in order to encourage new developments that are of social and economic interest. It was some twelve years ago, in 2004, that the first companies – pioneers of systems biology – became involved in the research consortia.

Today, for many companies, the systems biology approach has long been a mainstay of their business. "Pharmaceutical research attaches increasing importance to the simulation and analysis of system-wide aspects using mathematical models to better predict the effectiveness of drugs in the body", says Martin Ebeling, head of the bioinformatics group at Roche Innovation Center Basel. "This plays a key role for patient safety, where the watchword is understanding, and above all avoiding, unwanted side effects".

Worldwide recognition for Germany's systems biology

By virtue of its scientific and commercial strengths, German systems biology enjoys worldwide recognition. "Every systems biologist in the international research landscape is familiar with and respects the systems biology research being carried out in Germany", says Walter Kolch, Director of Systems Biology Ireland at University College Dublin. Peter Sorger, Professor of Systems Pharmacology at Harvard Medical School in Boston agrees, "Without a doubt, Germany has established its position in the systems biology vanguard".

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> Prof. Dr. Walter Kolch,
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In order to continue the transfer into application, it is imperative that the stakeholders from research, clinical practice and industry work together even more closely, using their expertise to provide mutual support. Successful product development requires more than a creative idea: the product must be guided directly towards market maturity. In funding systems biology initiatives, the BMBF is creating new instruments to facilitate the enhanced national and international networking of partners from academia and industry.

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