Life Sciences –
the source of inspiration for research into future innovations
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Life Sciences – the source of inspiration for research into future innovations

Ensuring the competitiveness of research and the economy’s capability for innovation, securing and restoring the health of its citizens and improving their quality of life into old age – these are the key challenges for our society. The Federal Government has been quick to recognise the potential of molecular life sciences to address these tasks.

The ’High-Tech Strategy for Germany’ describes this area of research as the leading discipline, in particular, for three important fields of the future: it unleashes a growth market in pharmaceutical and healthcare research and medical technology, promises numerous applications in biotechnology and is breaking new ground in agriculture and industry. Thanks to the concerted efforts of academic and industrial healthcare research, life expectancy in industrial nations has increased significantly in the last 50 years. Nevertheless, many diseases – particularly multifactorial diseases such as diabetes, arthritis and cardiovascular disease – are still difficult or impossible to treat. Molecular biological research has already identified several key factors and control points for the severity of these common diseases and has determined promising target areas for new drugs or treatment strategies. To develop more effective drugs and therapies, there is now a need to reveal the complex interaction of molecular components in the affected tissue or organ.

Mathematical methods must be combined with experimental approaches

This ambitious goal can only be achieved through the consistent application of mathematical methods in life sciences and linking them to experimental approaches. Since it is only the collection of quantitative data and their mathematical description that allows us to record the diverse interactions in computer models and to predict and to understand the roles of individual components in the interactive structure of living cells. Three life sciences topics are characterised in particular through the integration of computer-based and experimental research approaches: systems biology, computational neuroscience and medical genome research. In addition, all three areas require a high degree of interdisciplinary and international cooperation and a coordinated effort by science and industry to devise application potentials. Due to significant support from the Federal Government, Germany is now part of an international elite group in these areas of research.

Systems biology, especially in combination with medical genome research, offers additional opportunities for far-reaching progress in application-
oriented biomedical research. Systems biology approaches in drug screening could shorten development periods for new drugs and reduce the costs involved. Systems biology approaches are becoming increasingly important in gerontology due to increasing life expectancy in industrial nations.

**The beneficiaries are biotechnology and health care.**

By linking neuroscientific knowledge with computer technologies, this gives computational neuroscience an impetus both for medical as well as technical developments. It promotes the development of neuronal implants and prostheses, and contributes to improving the efficiency of mechanical manufacturing processes with adaptive robots. A deeper understanding of neuronal processes will revolutionise information and communication technologies – and, not least, alter people’s self-conception.

Thanks to the swift progress of sequencing technologies, medical genome research has made an increasingly rapid and effective contribution to identifying the ‘building blocks of life’, their structure and function. So it opens up unique opportunities to increase our understanding of the genetic factors of health and illness, and to more precisely determine the influence of environmental factors in pathogenesis.

Furthermore, biotechnology, which includes a wide range of products from diagnostics, drugs and fine chemicals to waste-water processing and generating energy from biomass, benefits from the results of molecular life sciences. Today there are around 500 biotechnology companies located in Germany, more than in any other European country. This positive development should be further supported by expanding molecular life sciences. In particular, the use of microorganisms for the production of nutrients, drugs, biopolymers and energy sources can be made significantly more efficient with a systems biology approach and can be extended to include entirely new products.

However, public research funding is essential in freeing up this enormous potential for innovation since the system-oriented, interdisciplinary approach of molecular life sciences requires considerable financial resources and extensive technological, contextual and structural changes that neither academic nor industrial research can organise alone.

In particular, due to the infrastructure it requires, genome research is increasingly developing into internationally organised, large-scale research in which powerful players from all over the world work together to significantly shape scientific progress. In order to ensure that the Federal Republic remains competitive, it is crucial that German research groups participate in major projects and have access to the required technologies and personnel resources. Due to the size and cost intensity of this task, the Federal Government has a key role in establishing and strengthening molecular life sciences, one that cannot be performed by any other player in Germany.
Overview of BMBF funding schemes

**BMBF funding programmes for systems biology, computational neuroscience and medical genome research**

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*Beginning in mid 1995

**Project Descriptions**

- **SysTec**: New methods in systems biology
- **GerontoSys**: Systems biology for health in old age
- **MedSys**: Medical systems biology
- **SysMO**: Systems biology in microorganisms
- **QuantPro**: Quantitative analysis for describing dynamic processes in living systems
- **INREMOS**: Industry-related systems biology
- **EraSysBioPlus**: ERA-NETplus scheme for systems biology
- **HepatoSys**: Systems biology of the liver cell
- **The virtual liver**: A virtual model of the liver
- **BCCN-2**: Bernstein Centres for Computational Neuroscience
- **BFNL**: Bernstein Focus: Neuronal basics of learning
- **BFNT**: Bernstein Focus: Neurotechnology
- **G-Node**: National INCF node
- **BPCN**: Bernstein Award for Computational Neuroscience
- **BCOL**: Bernstein Collaborations for Computational Neuroscience
- **BGCN**: Bernstein Groups for Computational Neuroscience
- **BCOS**: Bernstein Coordination Office
- **BCCN-1**: Bernstein Centres for Computational Neuroscience
- **NGFN-Int.Coll**: International collaborations (1000 Genomes Project, International Cancer Genome Consortium)
- **NGFN-Transfer**: Innovation alliances for medical genome research
- **NGFN-Plus**: Integrated alliances in medical genome research
- **NGFN-2**: National genome research network
- **NGFN-1**: National genome research network
- **dHGP**: German human genome project
Systems biology
Systems biology: A new discipline with a holistic perspective

To understand how a cell grows, divides and specialises in performing certain tasks, communicates with other cells, responds to environmental stimuli, grows old and dies – or degenerates into a tumour cell – you must first understand its molecular components: proteins, fats, carbohydrates and the nucleic acids DNA and RNA. But, by themselves, all these molecules are not ‘alive’. Living systems only arise through their complex temporal-spatial interactions, that is, functional units which are self-sufficient and isolated from the environment.

The realisation that its whole design is more than and fundamentally different from the sum of its parts has produced a new research approach: systems biology. It links methods of molecular biology with mathematical concepts of data analysis to understand biological systems – be they metabolic pathways, cell organelles, whole cells, organs or organisms – and their functional properties and allow us to make predictions about their behaviour. Systems biology as an integrative scientific discipline: it combines approaches from established disciplines in life sciences – including biochemistry, molecular biology, genetics, physiology, medicine and neuroscience – with methods from engineering, mathematics, physics and chemistry.

What is the relationship between the system components?

A key aspect of the approach of systems biology research is the integration of experimental and theoretical research results. In order to understand the functioning of biological systems, one must first understand the crucial system components and their interaction with one another. Here, molecular biologists, biochemists, and genome researchers need to clarify the following questions with laboratory experiments: Which genes are expressed, which RNA molecules and enzymes play a role, which end products result from the source materials? This qualitative ‘inventory’ must be preceded by a quantitative compilation of spatial-temporal material flows: How many molecules of a protein are present in the cell at a given point in time, in what concentration are they present in various cell compartments, how quickly do they diffuse from one compartment to another?

Such precise data can currently only be obtained with lots of time and effort; accordingly, new technologies are in great demand.

Nowadays, high-resolution measuring methods such as real-time PCR, protein chips and mass spectrometry allow systems to detect systems with a few dozen components in terms of quantity. But their degree of networking using feedback and regulation mechanisms lacks an intuitive understanding. This is where the theorists step in: they capture the interactions observed in experiments between molecular components in mathematical formulae – preferably in differential equations borrowed from physical chemistry, statistical physics and control engineering. From this they can develop computer models that map the relationships of the entire system.
Laboratory experiments improve the computer models – and vice versa

A key feature of systems biology is the use of computer-based technologies for data processing. These serve to quantitatively analyse the immense amounts of data provided by molecular research, and allow hypotheses to be formulated about the significant functional properties of the examined systems. They also allow them to be mathematically modelled and, thereby, for these hypotheses to be verified through computer simulations. Such simulations allow assumptions about the behaviour of systems in silico (by computer) to be tested and modified, if necessary, before being examined in vitro (in test tubes) or in vivo (in living beings).

The results of the laboratory experiments help to improve the computer model and vice versa. This iterative process between empirical and theoretical data mining often leads to unexpected insights into cellular processes that are beyond the intuitive approach. At the same time, it opens up the possibility of predicting and specifically influencing the behaviour of the system being examined, e.g. for therapeutic purposes. Therefore, the drug development process can now be made more effective and safer, while keeping animal testing to a minimum. Furthermore, biological processes, such as developing new kinds of synthesis methods for fine and industrial chemicals, can also be optimised. Due to the enormous application potentials of systems biology, this new discipline is growing consistently in industrial nations. The first systems biology initiatives began at the turn of the century in the US and Japan, followed a little later by Europe. The majority of American systems biologists adopted a ‘top-down’ approach: It is a high throughput method of searching for interactions of individual genes and proteins, in order to gain a broad overview of the organisation of the system being examined. In contrast, most European systems biologists use a ‘bottom-up’ design: Here they concentrate on manageable subsystems whose limited number of components can be com-
Plants – in this case single-celled algae – not only have the genome in their nuclei (large blue dots) but also have DNA (small blue dots) in their chloroplasts (red). The complex interplay of these different genetic elements controls the basic processes of photosynthesis.

Completely and quantitatively captured. The aim of both approaches is to understand molecular network interactions in an iterative process between laboratory experiments and computer modelling.

**International standards to facilitate the exchange of results**

In order to facilitate the global flow of knowledge within systems biology, work is being carried out to specify mandatory standards for generating, documenting, storing and managing data and models. The International Conference on Systems Biology (ICSB) has taken place annually since 2000; a team of experts meets regularly at the conference to develop a binding markup language (SBML = Systems Biology Markup Language) for modelling biological systems. Notes on interaction partners are increasingly being added to publicly available and often interactive databases on genetic elements, proteins and other biomolecules. They are designed to meet generally recognised minimum requirements for information content (MIR = minimal information requests).

Germany started the world’s largest (then and now) research network back in 2004 with its HepatoSys pilot project and, since then, has consistently invested in developing national and international research projects. The following pages describe current BMBF funding programmes for systems biology and introduce some selected projects.

“Given the current process of climate change, responsible use of resources is becoming increasingly important. We support systems biological research with the aim of developing new technologies in the field of renewable energy and hence reducing global CO₂ emissions.”

Gerrit Holz, CEO of Biogas Nord AG
Systems biology research – BMBF funding measures

At the same time the National Genome Research Network was established in 2001, the BMBF began funding this new research field in Germany, calling it ‘Systems of life – systems biology’. From 2004, the pilot project, ‘Systems biology of the liver cell – HepatoSys’, implemented a competence network of six research groups in which 40 working groups came together from all over the Federal Republic (p. 13). In early 2007, by setting up four ‘Systems biology research units – FORSYS’ the necessary infrastructure was created to bundle specialist disciplines relevant to systems biology under one roof to treat a wide range of systems biology issues and, at the same time, to secure qualified training for young scientists (p. 16). This initiative continued from 2008 with the FORSYS Partner funding initiative. These FORSYS Collaborations help to transfer knowledge between existing FORSYS Centres.

The coordination offices for systems biology projects are divided by subject area
and partners from academia and industry and to encourage additional competence centres to be established for systems biology (p. 18). By funding up-and-coming FORSYS groups, young scientists are given the chance to develop their creative energy within systems-biological research and to introduce innovative ideas to this new discipline (p. 20).

The BMBF programme, ‘Medical systems biology – MedSys’, focuses on the potential applications of systems biology for medicine and pharmaceutical development; from 2009 the BMBF will look at understanding the mechanisms of the natural ageing process in a programme entitled, ‘Systems biology for health in old age – GerontoSys’ (p. 15). Also in 2009, the BMBF will fund ‘New methods in systems biology – SysTec’ (p. 24). These measures complement the ‘Quantitative analysis to describe dynamic processes in living systems – QuantPro’ programme, started in 2006, which was aimed at expanding the methodical and technological basis of molecular life sciences. QuantPro was aimed at developing quantitative methods for analysing dynamic processes to link bioinformatics, genome, proteome and metabolome research with the future fields of systems biology.

The need for interdisciplinary partnerships and the complexity of the new life sciences pose challenges that cannot solely be sustained at the national level. As early as 2006, the BMBF participated in the ERA networks, ERASysBio and Pathogenomics, at the bi-national ‘Industry-relevant molecular life sciences – INREMOS’ project with Slovenia. The ‘Systems biology in microorganisms – SysMO’ programme, also part of ERASysBio, was the first trans-national funding programme for systems biology (p. 22). In September 2008, after the publication of ‘Application of systems biology research approaches in biomedicine and other fields of innovation’, came the second call for a trans-national partnership to thematically complement the national funding programmes HepatoSys, MedSys and GerontoSys.

Developments processes can be observed in the transparent larval stages of the zebrafish. Systems biologists are studying them to find out how each cell differs and how they specialise.

Nematodes, Caenorhabditis elegans, serve as a model organism for systems biology research.
Liver cells as a model

The liver is the major metabolic organ in vertebrates: more than 10,000 biological molecules are broken down, converted or renewed by it every day. The liver supports the digestion of food, regulates iron levels, stores sugar and vitamins and produces numerous essential proteins. It also detoxifies the body by breaking down alcohol and other pollutants, as well as drugs. It owes its diverse capabilities to a cell type that accounts for 90 percent of its mass: the hepatocytes.

In order to understand what it is these extraordinary cells actually do and make them available for medical applications, the BMBF launched HepatoSys in 2004. This national competence network now has 43 research groups and is the world’s largest consortium of systems biology.

HepatoSys is divided into four regional networks and two national platforms that were established in the first funding phase (see interview on p. 14). Since then, the focus has been on results-oriented research and is supported by a growing number of industry partners. The regional networks are researching various aspects of liver performance, including detoxification, endocytosis, iron metabolism and regeneration.

The Detoxification network is studying how liver cells break down contaminants. The systems biology analysis should make the metabolism of drugs predictable, identify key factors for their implementation, and help determine optimal dosages much faster and cheaper than with conventional studies.

Defects in the transport system of cells are associated with Alzheimer’s disease, asthma and viral infections, such as HIV and influenza, and endocytosis becomes of significant interest to medical and pharmacological research. The same-named network sheds light on mechanisms of uptake and transport within cells and their influence on signal transduction through hormones.

One network, initiated in 2007, is aimed at examining iron metabolism in which the liver plays a pivotal role. Iron ions are indispensable for energy and oxygen supply to the body as well as for detoxification; iron deficiency is just as harmful to health as too much of the trace element.

Another network examines the liver’s ability to regenerate. It is made possible by the interplay of various signal substances that stimulate hepatocyte proliferation and stop this process again once liver mass has been sufficiently restored. An excess of growth factors may lead to inflammatory processes, scarring and fibrosis and facilitate the development of liver cancer. A mathematical model of the signaling pathways involved should make the process of cell degeneration to tumour formation more transparent and allow the testing of molecular drugs on the effect of disease progression.

The new funding programme, ‘The virtual liver’, will take the systems biological approach to the next level of complexity based on the findings of HepatoSys and, thus, forming a bridge from the cell level to organs via the tissue. The first step is to merge the computer models of the various processes of liver metabolism, devised during both funding phases, in an integrated mathematical model which will be relevant for numerous medical and biotechnological applications, such as a screening platform for toxic substances or to identify new biomarkers for liver disease.

The aim is to adapt this model to new organisational levels. Furthermore, physiological and pathophysiological processes will be encoded with the aid of ‘virtual tissue’ and ultimately with the ‘virtual liver’, allowing predictions to be made about liver functions.
HepatoSys: the pilot project of systems biology in Germany
An interview with Prof. Jens Timmer, spokesman for the HepatoSys project committee

Why did you choose liver cells?

After the human genome project was completed, it became a matter of understanding the functional networks of gene products. If you wanted to pursue fundamental research you could have chosen E. coli or yeast cells as model systems for which there is an enormous amount of knowledge already and they can easily be manipulated. However, results obtained from micro-organisms are only of limited medical use. The BMBF intends to create targeted conditions for innovations. As a result, it was proposed in a discussion process involving research and industry that the complex system of primary liver cells be examined.

What challenges need to be overcome?

Liver tissue from patients must be used immediately so that scientists are always working with new and different, individual cells. But this high variability also characterises the patients who will ultimately benefit from our research. Consequently, we will examine how different certain enzymes in human livers can be and then use this knowledge for future therapies. It is somewhat easier with hepatocytes in mice. All the working groups in HepatoSys work with mice of the same stock whose liver cells are obtained using standardised procedures. Another challenge is to use molecular biological tools, which have long been available for bacteria, for mammalian cells.

How will the flow of knowledge be ensured within the consortium?

We have set up a platform which integrates all data from the four regional networks. We have discussed this central data management system at length to decide if we should set it up ourselves at university level and accept the usual change of personnel – or do it in collaboration with a company. In the end we opted for continuity and are now working with the GeneData company.

How important is HepatoSys in an international context?

The first international spin-off of HepatoSys is CancerSys, which achieved third place in a EU systems biology tender with 350 applications. CancerSys investigates how the defective regeneration of hepatocytes leads to liver cancer and has partners in England, France, Sweden and the US. Apart from specific projects, HepatoSys has developed some far more important things, namely a new working culture. The attitude ‘My lab is my castle’ is obsolete and the future is cooperation not competition. Life scientists must now emulate what physicists at CERN have been doing successfully for 50 years: having systems biologists from all over the world reading from the same page. This is my vision. HepatoSys is a first step in this direction.
Research for a healthy life

Gaining a better understanding of complex diseases and identifying new treatments – these are the goals of the 'Medical systems biology – MedSys' programme, started in 2008. The initiative aims to benefit patients with different diseases and, at the same time, to establish Germany as an attractive pharmaceutical location and lead market for medical technology. As a result, BMBF subsidises partnerships between scientists from academic and clinical research and research companies in the pharmaceutical and biotech industries.

Experimenter and theorists from different disciplines are working hand in hand on 18 selected joint projects to find biomarkers for the diagnosis and progression of diseases, to identify new targets for therapies, to assess the main and side effects of potential drugs and to use genetic differences between patients for individual therapy options. Studied diseases range from tooth decay and severe infections caused by hospital germs to AIDS and breast, lung, stomach and colon cancer. Other research groups are dealing with specific issues related to pain sensation, chronic wound formation or generating human stem cells from body tissue.

All the MedSys projects largely depend on currently available data from molecular life sciences and, in particular, rely on findings from other BMBF genomics research groups (p. 43 to 60). In order for fundamental research findings to be examined in clinical studies as quickly as possible, clinical working groups are assigned to all joint projects. The involvement of industry partners – especially small and medium-sized software, bioinformatics, and diagnostics companies, as well as major pharmaceutical companies such as Bayer Schering Pharma and Roche Diagnostics should ensure that research approaches lead to therapy or drug development in the medium term. A bi-national cooperation was established as part of the MedSys initiative through simultaneous tender in Austria. Two of the 18 joint projects have partners from Austria, one group is coordinated by the Austrians.

From 2009, the 'Systems biology for health in old age – GerontoSys' programme has been revealing the mechanisms that underlie the natural ageing process. Building on this, the factors that contribute to age-related diseases are to be identified and included in the development of new diagnostic and therapeutic applications or preventative measures. GerontoSys uses the enormous potential of the systems biological approach to gerontology, thereby making an important contribution to the BMBF’s funding priority, ‘Research for healthy ageing’.

The research results should lead to the development of new therapies and drugs. To this end, researchers are working closely with industry in the MedSys projects.
Beacons of systems biology

An interview with Prof. Roland Eils, spokesman for the FORSYS project committee

Since early 2007, the BMBF has funded ‘Systems biology research units’ (FORSYS). What are the objectives of this initiative?

Firstly, lighthouses of systems biology were set up in the form of regional centres unifying experimental and theoretical research under one roof. This point is crucial: they should not be virtual centres, but actual existing ones. As an inherently interdisciplinary science, systems biology thrives on the interaction between subjects whose communities have different approaches and languages. Consequently, one needs to create the prerequisites for daily exchange – side by side, hand in hand. This has been achieved at the four FORSYS Centres in Freiburg, Heidelberg, Magdeburg and Golm/Potsdam.

Why does systems biology research need state funding in Germany?

Some institutions had the necessary systems biology expertise early on, and local and central government funds were set aside for the buildings. What was missing was a well-defined research programme to pool the available resources for infrastructure, personnel and expertise. This is where the BMBF stepped in with FORSYS to take over the initial funding of the research cores. After five years, the universities will have to maintain the centres themselves – an outstanding concept as there is already significant interest in continuing these activities.

What is the purpose of the FORSYS Partner initiative?

Since the FORSYS Centres were not to be virtual but real, all the expertise had to be available in the region. This left excellent resources at other

With the help of an automation platform which coordinates the complex individual experiments, Freiburg biologists are working on the complex interactions of proteins with a high level of throughput.
locations unused. Using FORSYS Partners we have been able to disseminate expertise: now decentralised partners with their own projects can be incorporated into the centres, which in turn benefit from external expertise.

**What is the Heidelberg FORSYS Centre all about?**

We are studying viruses and their host cells using the AIDS pathogen HIV and the hepatitis C virus as examples. Which of 24,000 human genes do we need to deactivate to prevent or block the virus from being integrated into the genome of the host cell? To answer this we need a high degree of parallelisation and automation – from the experiments to data analysis and imaging. We are also developing mathematical models to describe the interactions between virus and host and to test these models against experimental data.

**What about the next generation of young scientists?**

Our present personnel did not have any comprehensive training in experiments, theory or technology. They had to learn everything on the job. As a result, the central part of the FORSYS programme was to create new master’s courses for bachelor graduates who received the classic education for biologists, computer scientists and mathematicians. More recently, systems biology courses have been offered either as a separate master’s course, as in Manchester or Göteborg, or – as here in Heidelberg – as a major subject as part of existing master’s courses.

**In order to strengthen the training of young scientists, new systems biology study courses and doctoral programmes are being set up at all four FORSYS Centres.**

**Freiburg:**
- Masters in Bioinformatics and Systems Biology (since 2008/2009)
- Programme for doctoral students with theoretical and practical orientation
- Courses in modern technology to collect data for systems biology
- Doctoral student retreats on modelling and sequence analysis

**Magdeburg:**
- Degree course in Biosystems Technology (since 2004)
- Bachelor’s degree course (since 2007/2008)
- Master’s degree course (from 2011)
- Doctoral programme with seminars by visiting scientists, workshops and a summer school
- Collaboration with the International Max Planck Research School for Analysis, Design and Optimization

**Potsdam:**
- Masters in Bioinformatics focusing on Systems Biology (since 2008/2009)
- Doctoral programme in collaboration with the International Max Planck Research School for Primary Metabolism and Plant Growth
- Support for postgraduate doctoral students by the Potsdam Graduate School and the Potsdam Welcome Center

**Heidelberg:**
- Major Systems Biology master’s degree in ‘Molecular Biosciences’ with an international exchange programme (since 2008/2009)
- Teaching activities in the systems biology section of the Life Sciences bachelor’s degree.
- Doctoral programme with workshops, summer schools and seminars; the doctoral programme is embedded in graduate programmes that are funded by the Excellence Initiative
- Award of PhD scholarships in conjunction with the graduate schools
- Support for doctoral programmes through the graduate academy of the University of Heidelberg (since 2005)
Hydrogen from the bioreactor

The fuel of the future must come from renewable sources — the warning signs are dwindling energy resources and global climate change. Solar energy and hydrogen are particularly promising alternatives to fossil fuels. A FORSYS Partner project combines these two power sources: it relies on a single-celled freshwater algae called Chlamydomonas reinhardtii, which produces hydrogen using sunlight.

Scientists and engineers at the Universities of Bielefeld, Münster and Karlsruhe, the MPI Golm and the energy company, Biogas Nord AG, want to better understand the metabolic activities of microalgae in order to utilise them for economical hydrogen production.

“The algae generate gas as a waste product of photosynthesis but with a very low level of efficiency and only under certain conditions”, explained project coordinator Olaf Kruse from the University of Bielefeld. Measured using the photon conversion efficiency (PCE), a commonly used measurement in photovoltaics, the level of efficiency of naturally occurring algae is just 0.1%. By comparison, modern PV systems have a PCE of up to 16%, but supply electricity instead of hydrogen. “If you want to turn it into a storable fuel — and that is what two-thirds of the global energy market wants — then the PCE goes through the floor and is close to that of Chlamydomonas”, said Kruse. In terms of efficiency, the protozoans are also on a par with classic energy crops: corn and rapeseed generate a maximum PCE of 0.4% when converting solar energy into biogas or biodiesel through photosynthesis. In addition, there are environmental concerns about their large-scale cultivation in monocultures as it deprives agriculture of fertile crop land.

Olaf Kruse works with a particularly efficient variant of C. reinhardtii which he tracked down in 2004 together with Australian Ben Hankamer from more than 20,000 artificially generated mutants. The now patented strain produces much more hydrogen than the naturally occurring type and thereby achieves an astoundingly high PCE of around 1.5%. Nevertheless, using algae to produce hydrogen is currently far too expensive. “In order to make it profitable, we need to overcome the bottlenecks in the system”, said Olaf Kruse, “both on the biological as well as on the technical side”. According to the concept of biorefinery, the same algae can be exploited in several ways: initially they produce hydrogen then later they are fermented into biogas. “We not only have to increase hydrogen production, but we also need to maximise the biomass structure itself”, said the researcher.

To achieve this, it is important to understand the complex process of photosynthesis. The FORSYS Centre Golm/Potsdam (GoFORSYS), one of the four systems biology research units, has dedicated itself to this task. With the participation of the University of Potsdam, the Max Planck Institute of Molecular Plant Physiology and the Max Planck Institute of Colloids and Interfaces, also in Potsdam, and the Metanomics GmbH, GoFORSYS unifies 18 working groups and two groups for up-and-coming scientists with excellent systems biology expertise. The joint research goal is a better understanding of photosynthesis, its regulation depending on various environmental factors and the resulting influences on plant growth. The common model organism is c. reinhardtii, since this protozoa is significantly easier to handle than wheat or potatoes. At the same time, it has largely the same photosynthetic apparatus

Under certain conditions, single-celled algae of the species Chlamydomonas reinhardtii produce hydrogen.
as the higher plants. Therefore, new findings from it can be transferred to multicellular model organisms, such as tomatoes or Arabidopsis thaliana and be used to optimise the use of crop plants.

“The common interest of GoFORSYS and our project partners is to convert sunlight into biomass as efficiently as possibly, in as short a time as possible”, explained Olaf Kruse. In order for the working groups in Golm, Münster and Bielefeld to be able to exchange their findings, all the genome, transcriptome and proteome studies are implemented with the same algae strains and under the exact same culture conditions. The systems biologists create models of material flows within the algae cells from the collected data. “We want to identify the metabolic components, which represent the bottlenecks for photosynthetic performance and hydrogen production”, said Kruse.

At the same time, the production kinetics of various algae strains is also tested. To this end, a 250-litre model reactor was developed by Olaf Kruse’s working groups at the Faculty of Biology and by Clemens Posten at the Institute of Process Engineering in Life Sciences at the University of Karlsruhe, as well as the Bielefeld energy company, Biogas Nord AG. Olaf Kruse uses an example to explain how fruitful the interdisciplinary configuration of the FORSYS Partner is. “The engineers have pointed out that these dark-green algae shade each other in a dense cell culture. We needed an alga with little chlorophyll, i.e. with smaller light antennas, which would still highly efficiently transfer the light to the photosystems”. Using molecular genetic incisions, the biologists created such an algae strain with smaller light antennas whose light-green cultures would generate even more biomass per unit of time. “By the end of the project, we hope not only to have a working photobioreactor, but also a systems biology model of the material flows and production processes in the reactor”, said Kruse. “The systems biology should seamlessly merge into systems biotechnology”.

Karlsruhe engineers want to optimise the light yield and therefore the increase in biomass of the algae suspension contained in this 25-litre model reactor. To achieve this, they vary the materials and surface structure of the plates and their distance apart, and therefore the thickness of the layer of algae.
Networked signals determine growth and decay

In cancer cells, the genetic regulation of certain signalling molecules that control cell growth is disturbed. Nils Blüthgen wants to understand the complex structure of relationships within this signalling system and to find the optimum targets for corrective action.

How do cells decide whether to grow, specialise or initiate their own deaths? The answer to one of the most fascinating questions in biology is not only of scientific interest, but also opens up significant opportunities for medicine. Nils Blüthgen studied the complex signalling networks that regulate cell growth with the aid of systems biology approaches. In the future, this knowledge could help to predict the best therapy for every cancer patient.

Physics or biology? Even in his choice of subject, Nils Blüthgen had difficulty choosing between the two disciplines. In the end, the native of Bremen registered to study physics in Heidelberg and after his intermediate diploma, moved to the Humboldt University in Berlin. In addition to his regular studies, he also attended courses at the Institute for Theoretical Biology. Under the guidance of Hanspeter Herzel, he developed in his thesis a mathematical model of a cellular chain of signals responsible for controlling elementary processes in mammalian cells. "All of a sudden I was a systems biologist, even before I realised that this new field existed", recalls Blüthgen.

His dissertation – which the then 30-year-old graduated with summa cum laude also under Herzel – contributed to discovering how a signalling pathway called the MAPK cascade works. To explain its operational principle, the physicist uses an example from his own field. "You can think of it as a central heating system with a thermostat. It always keeps the room at the desired temperature – even when cold air flows in through the window. The thermostat makes the system robust against interferences". Body cells also have to be robust against changing environmental conditions in order to maintain vital processes. However, they have much more complex regulatory mechanisms than a heating thermostat. In the case of the MAPK signalling pathway, they include more than a dozen specific enzymes and transcription factors, which influence the regulation of over 300 genes.

The system is stimulated externally by various hormones. They start off a chain of enzyme reactions whose last link – the MAP kinase – determines the further fate of the cell. "If this kinase is active at all times then the cell will grow uninhibited and turn into a tumour cell", explained Blüthgen. In
fact, in one third of all known cancers the regulation of MAP kinase has gone off the rails. So, what could be more natural than to seek an agent that takes corrective action in this system? Consequently, many large pharmaceutical companies have since developed drugs that inhibit the signalling cascade here or there. In the laboratory, these inhibitors dramatically reduce the activity of the MAP kinase. But in many clinical studies, many of them do not work at all and others only work on some patients. “Obviously the system is robust enough to defend itself against such substances”, says Nils Blüthgen. So, to go back to our thermostat analogy, “these inhibitors only open a window. But then the heating system heats up again and offsets the heat loss. That is why I want to find out where to attack to disrupt the robustness of a cancer cell – and in such a way that healthy cells survive”.

**Negative feedback processes**

Nils Blüthgen explains at the beginning of his thesis how helpful a systems biology approach is in achieving this. “A bioinformatics analysis of various transcription factors leads to the prediction that the MAP kinases also stimulate production of precisely those enzymes that are inhibited themselves in their activity. Therefore, they induce their own inhibitors”. In order to more precisely understand this negative feedback process, Blüthgen has put together an interdisciplinary research group of up-and-coming scientists as part of the BMBF funding programme, FORSYS Partner. The molecular biologist Raphaela Günther is following the temporal dynamics of human embryonic kidney cells, with which various MAPK-dependent target genes are expressed. Parallel to this work, Blüthgen, assisted by biophysicist Stefan Legewie, wants to find out in silico how these target genes provide feedback to the MAPK cascade.

The MAPK cascade is associated with a further signalling pathway which plays a crucial role in the development of liver cancer. Blüthgen’s team studied this ‘cross-talk’ between two regulatory systems as part of a European research network called CancerSys. A total of nine partners from Germany, France, Sweden and the US are involved in the EU-financed consortium – including a working group lead by Jens Timmer at the FORSYS Centre in Freiburg (see interview on p. 14), with whom the Berlin group of up-and-coming scientists maintains an intensive exchange of knowledge and methods. The ultimate goal of CancerSys is to find those molecular switches that induce uncontrolled growth in healthy liver cells. The ColoNet research network, which Nils Blüthgen is involved with as part of the MedSys BMBF programme, is focussed on colon cancer (see p. 15). “My dream is a computer model that can predict the optimum therapy for every individual cancer patient. That will probably be possible in 10 or 20 years”, says Blüthgen, “but we are on the right path”.

In May 2008, Nils Blüthgen was awarded for his research, becoming the first recipient of the MTZ Award. The prize is offered by the Monika and Thomas Zimmermann Foundation in conjunction with the BMBF and Project Management Jülich, and is awarded every two years for outstanding achievements by young scientists in the field of medical-oriented systems biology. Blüthgen earned his doctorate at the Humboldt University in Berlin and then worked at the Freie Universität Berlin and at the Manchester Centre for Integrated Systems Biology in the UK. From there he moved back to Berlin, where he has been in charge of a young scientists research group as part of the BMBF’s FORSYS Partner initiative.
Useful and dangerous: microbes

Microorganisms are the oldest and most diverse creatures on Earth. Without them, life would stand still: they break down mineral and organic compounds into their raw materials and create a myriad of complex biomolecules. Microbes not only colonise every habitat from the ocean floor to the clouds, but also the human body – some as helpful symbionts, others as deadly pathogens. Their medical importance and their potential in biochemical activity bring bacteria and other microbes to the attention of systems biology research.

Already, microbes are used as aids in soil remediation and in purifying drinking water, industrial water and wastewater. Genetically modified bacteria produce a wide range of food additives and fine chemicals as well as vaccines, antibiotics, hormones, cancer therapeutics and other pharmaceutically active substances. A systems biological understanding could contribute to more effective microorganisms being used to fight or prevent environmental damage, to optimise well-established production processes and to develop entirely new therapeutics to combat bacterial pathogens.

Due to the immense economic importance of protozoa, in 2005 the BMBF set up the European initiative, “Systems biology in microorganisms – SysMO”, as part of the ERASysBio funding programme. This funding programme has 28 million euros at its disposal and is supported by government bodies in Great Britain, the Netherlands, Norway, Austria, Spain and Germany. France, Switzerland and the Czech Republic are also involved as external partners. The aim of this transnational effort is to bundle capacities in the European Research Area (ERA) in the field of systems biology microbial research, to make use of them later for new approaches in medicine, biotechnology and environmental protection. This should ensure the competitiveness of Europe ahead of North America and Asia.

The eleven SysMO joint projects with 85 working groups, including 32 teams from Germany, have been funded since March 2007. The central coordination of funding is the responsibility of the SysMO Office at Project Management Jülich. Since 2008, a dedicated data management group has been developing a system that cleverly manages the research results from all the SysMO groups and makes them available to the entire consortium. The focus here is on microbial groups heavily used in industry such as coliform bacteria and yeasts, and lactic acid or solvent producing species and intestinal bacteria, streptococcus and other pathogens. Three of the eleven joint projects are coordinated from Germany. They focus on the biotechnologically important bacteria, Clostridium acetobutylicum, Pseudomonas putida and Bacillus subtilis.

As the name of the species suggests, Clostridium acetobutylicum produces the solvents acetone and butanol. One is a coveted raw material in the chemical industry and the other is a renewable biofuel. Seven German, two Dutch and three British research groups headed by Peter Dürre from the University of Ulm are studying the conditions under which the bacteria makes these metabolites and how butanol yield can be increased.

Bacillus subtilis produces a wide range of valuable substances – from enzymes to vitamins and antibiotics. If this soil bacteria is starved, it can also exploit exceptional food sources using special enzymes and make industrially exploitable products. A transnational network of German, British and Dutch working groups together with colleagues
from the SysMO associated countries of Switzerland and France, headed by Uwe Völver from the University of Greifswald are researching which genes are active here and what physiological processes they trigger.

Biotechnological processes represent unnatural living conditions for the affected microorganisms and are often associated with nutrient deprivation, extreme heat, strong acids or toxins. A network of 18 German, Spanish and British working groups headed by Vitor Martins dos Santos at the Helmholtz Centre for Infection Research in Braunschweig is studying how microbes can adapt to these stress factors, using Pseudomonas putida as an example.

The common factor in all SysMO projects is the mutual optimisation process between experimental and theoretical data generation which characterises systems biology. Firstly, genes and gene products involved in the metabolic processes of interest are analysed. Then, the critical signalling and switching points are identified by computer models using this data, leading to the formation and further optimisation of the desired properties. Due to the successful cooperation of partner countries, a second funding period has been agreed for SysMO in which all partner countries are participating except Austria.

Systems biology approaches allow the reactions of microorganisms in biotechnological processes to be better predicted and managed more efficiently than to date. That makes them interesting for the chemical and pharmaceutical industries. In a joint project on systems biology research into Pseudomonas for industrial biocatalysis, the BMBF has been funding the interaction between academic and industrial partners since 2009. Six institutes of the Universities of Stuttgart and Hohenheim and Insilico Biotechnology AG Stuttgart are participating in the joint project, under the direction of BASF SE in Ludwigshafen. Researchers are looking closely at Pseudomonas stems which are characterised by increased tolerance to organic solvents and can turn the dissolved substrates within them into various odours and aromas.

Staphylococci may spread rapidly in hospitals and often become deadly because of their resistance to antibiotics.
New tools for describing life

Biological processes are inherently dynamic. To understand these dynamics, systems biologists are investigating the molecular components of the system and analysing their temporal and spatial interaction. Crucial to the success of research are suitable methods of isolating the essential biomolecules that influence the system and representing them in mathematical models.

Fourteen selected QuantPro alliances that open up a variety of application fields are to be funded. They focus primarily on medically important tasks, such as understanding disease mechanisms, drug development and improved preparation of biological samples. Furthermore, new medical approaches will optimise the use of enzymes, cells or microorganisms for the industrial production of biomolecules, help increase crop yields for potatoes and barley and find new targets for potential pesticides.

To ensure the rapid transfer of developed methods and technologies, an industrial partner participates in each joint project – some are major corporations and some are small or medium-sized enterprises. The close cooperation between industry and science is also reflected in a substantial co-financing of research projects by industry partners: They account for 25 percent of all funds.

Building on the success of QuantPro, a new programme, ‘New methods in systems biology – SysTec’, began in 2009. It also promotes the development of new experimental and theoretical approaches, with whose help complex biological networks can be better described and quantitatively recorded. Ten interdisciplinary joint projects are being funded, which experimental and theoretical research groups with largely medical prospects will work on. The aim is a better understanding of basic cell functions – such as dynamic membrane-resistant protein complexes, mechanical aspects of cell structure, cell-cell contact or signalling between cell and nucleus, as well as epigenetic effects to silence genes. The methods range from the refinement of classical microscopy techniques and their link to mass spectrometric technologies and the production of RNAi libraries to the adaptation of mathematical methods to solve systems biology problems.

The BMBF is supporting the steps from qualitative to quantitative analyses of the dynamics of cellular processes with its ‘Quantitative analysis to describe dynamic processes in living systems – QuantPro’ programme which began in 2006. The focus is on developing and further developing methods and technologies that link the systems biology approach more closely with molecular life sciences – in particular genome, proteome and metabolome research – and bioinformatics.
Computational Neuroscience
Computational Neuroscience: Key to understanding the brain

How does the human brain work? How do the 100 billion nerve cells in our heads allow us to pour a glass of wine in the evening, let us review the events of the day to the sound of Mozart’s Magic Flute, and make holiday plans? How are sounds, scents, memories, desires encrypted in the spatial and temporal patterns of neuronal activity, and then translated into matching sensory impressions, feelings and thoughts? What strategies are used for this behaviour, on which neuronal structures are they based?

Understanding our thoughts, feelings and actions and uncovering the relevant neuronal processes is one of the biggest challenges of this century. In recent decades, the study of brain functions has made significant progress in understanding the cellular and molecular basics of complex lifelong performances. New kinds of methods for studying individual nerve cells provide more accurate insights into their operation, the function of messenger molecules, the process of intracellular signalling procedures and the formation and propagation of neuronal stimulation. Modern techniques can capture the energy requirement of certain regions of the brain, visualise changes in magnetic fields around electrically active nerve cell clusters measured in milliseconds or measure their electrical activity almost in real time.

The rules that govern the way the brain works are still largely unknown

Nevertheless, the brain’s performance – for example spatial orientation, coordination and control of movements, pattern recognition, speech and image analysis, and also thinking, feeling, remembering and planning of actions – has not been sufficiently understood to date. How the brain works and how it views the world in such a way that new perceptions merge with previous experiences is still unclear. A breakthrough in understanding can only be reached through the mathematical description and modelling of cellular neuronal processes and defined performances of the nervous system. As a result, computer-based models are increasingly being used to study the human brain. The research field of computational neuroscience is pursuing this conceptual research approach.

This new discipline of computational neuroscience combines methods from mathematics, physics and computer science with traditional approaches from neurobiology. The entire spectrum of modern experimental procedures comes into play: Here, molecular processes in individual nerve cells and their connecting points, the synapses, are studied; electrophysiological efferences record the stimulation patterns of individual or several neurones linked together; using electroencepha-
lography (EEG) or magnetoencephalography (MEG) and functional magnetic resonance imaging, patterns of activity in the brains of laboratory animals, volunteers and patients can be measured while they solve certain tasks.

Each of these methods contributes in its own way towards revealing the structure and function of the brain – from molecular level to behaviour level. But it was the mathematical formulation of the observed phenomena that allowed hypotheses about the principles of brain organisation and function to be tested quantitatively, and refined step by step. Computer simulations can make fast and precise predictions about the behaviour of the structures and systems being monitored, which can then be checked in experiments. Through this interplay of measurements, data analysis and computer simulation, experts are trying to reveal the fundamental principles of neuronal information processing and understand the brain as a whole using empirically oriented disciplines, such as neurobiology, psychology, cognitive and behavioural research and theory-oriented disciplines such as mathematics, physics and computer science. This interdisciplinary collaboration of experimenters and theorists and the consequent transfer of observed phenomena into mathematical models are the main characteristics of computational neuroscience.

"Modelling and experiments are the main pillars of computational neuroscience. The mathematical models should be simple and use parameters that can be reliably estimated with the help of experimental data. This is the only way to decode the functioning of the brain".
Andreas Herz, coordinator of the Bernstein Centre Munich.

Models describe the stimulus conduction in nerve cells

A major contribution to the inclusion of mathematics in neuroscience was made in 1952 by Britons Alan Lloyd Hodgkin and Andrew Fielding Huxley. They designed a model that describes with high accuracy the stimulus conduction in nerve cells.

Around the same time, the Canadian Donald Olding Hebb studied information processing in neuronal networks. The Hebbian theory, named after him, states that the more frequently signals are transferred via the contact points (synapses) between two nerve cells, the more effective this transfer becomes. This phenomenon – now known as ‘synaptic plasticity’ – is the neurophysiological basis of learning and memory and plays a crucial role in the mathematical formulation of artificial neuronal networks. The American Wilfrid Rall set another milestone in the history of neuroscience: In 1959 he created the ‘cable theory’, a mathematical framework linking the morphological and electrical structures of nerve cells with their functions. It takes into account the complex shape of nerve cells and their branching offshoots, called dendritic trees, through whose numerous synapses temporally and spatially offset signals are transmitted. Since then it has been possible to precisely describe the spread of voltage changes and the associated electrical power in dendrites.

Rall’s theory paved the way for the quantitative description of neuronal processes and accelerated their modelling on computers. In the end they became the foundation of the GENESIS and NEURON software programs, which are the most frequently used tools in computational neuroscience. The name of this new discipline came in the mid-1980s from the US, where a little later, the first study and research programmes began. An important pioneer of computational neuroscience in Germany was Valentino Braitenberg, a former director of the Max Planck Institute for Biological Cybernetics in Tübingen. In 1992, in his celebrated ‘Manifesto of
Brain Science’ he expressed the conviction that “a satisfactory explanation of thinking and behaviour will eventually be formulated in one of the physics-related languages, i.e. in mathematical terms”.

**In 1902, Julius Bernstein discovered the ‘action potentials’ in nerve cells.**

The pioneering work of another German scientist dates even further back: As early as 1902, the physician and physiologist Julius Bernstein, who was born in Halle, proposed a mechanism which explained the propagation of electrical impulses in nerve cells. Today this is referred to as ‘action potential’. With his ‘membrane theory’, Bernstein first proposed a physico-chemical explanation of the electrical events in neurobiology and established a quantitative theory of electrophysiology. The National Bernstein Network for Computational Neuroscience established by the BMBF is named after the discoverer of the action potential. It is presented on the following pages, using selected examples.

By linking neuroscientific knowledge with computer technologies, computational neuroscience is the driving force both for medical as well as technical developments. Neuronal implants and prostheses, helping the deaf hear and the blind see, and allowing paralysed patients to carry out complex grasping movements with the ‘power of thought’ are already on the market or are being tested in clinical trials. A better understanding of the sensory and motor performance of humans and animals improves the development of intelligent machines: A new generation of seeing and hearing robots could significantly simplify the future lives of the sick and healthy. Adaptive industrial robots that autonomously adapt complex movements to complete changing tasks will increase the efficiency of mechanical manufacturing processes. And a deeper understanding of neuronal processes will revolutionise information and communication technologies.
The National Bernstein Network – BMBF funding programme

Since 2004, the ‘National Network for Computational Neuroscience – NNCN’ has funded a series of initiatives that bring together and network German expertise in theoretical and experimental neurosciences. The creation of ‘Bernstein Centres for Computational Neuroscience’ concentrated specific expertise into four targeted regions. A total of 80 research groups from different university faculties, the local Max Planck Institutes, the German Primate Centre, and various industry partners at the centre all work together on application-oriented fundamental research. To further strengthen the substantive priorities of the four centres long-term, a total of nine new professors and working groups were set up and a separate master’s degree course was established in computational neuroscience (p. 38).

It is essential to produce excellent young scientific talent in order to establish this relatively young field of research. Consequently, The Bernstein Network has presented the Bernstein Award for Computational Neuroscience every year since 2006. The

The National Bernstein Network
The necessity for international collaborations was recognised early in computational neuroscience. In 1996, preparations began to establish a global structure under the auspices of the OECD, which resulted in the formation of the International Neuroinformatics Coordination Facility (INCF). The 15 member states from North America, Asia and Europe – with Germany as a founding member – have agreed to coordinate their programmes and initiatives on computational neuroscience/neuroinformatics. The INCF catalyses the global flow of information and scientific interaction for developing programmes, standards, guidelines and infrastructure in computational neuroscience and neuroinformatics. Like all participating countries, Germany set up a national focal point as part of its membership (p. 42). It acts as a link between the national structure of the Bernstein Network for Computational Neuroscience and the international research community.

Various dyeing methods are used to track the wiring of nerve cells in petri dishes. Neurons marked in red can be discerned from the surrounding tissue cells which are identifiable by their violet nuclei.
Four brain research centres

In the National Network for Computational Neuroscience (NCCN), the BMBF has created a highly efficient structure for fruitful and long-term cooperation between theorists and experimenters from all areas of neuroscience. The four Bernstein Centres in Berlin, Freiburg, Göttingen and Munich form the core of this network. They combine the expertise of universities and other research institutions in the particular region.

The Bernstein Centres are closely associated to the research groups of the Bernstein Foci and Bernstein Partner, in terms of personnel and content. Numerous collaborations with industry partners also promote the transfer of research results into the value chain. In addition to application-oriented fundamental research, the main tasks of the centres are to integrate computational neuroscience into university education and training young researchers according to international standards.

Bernstein Centre Berlin: Precision and variance

“When it comes to recognising faces or locating sources of noise, our brains work more accurately and reliably than any computer”, says the coordinator of the Bernstein Centre Berlin, Michael Brecht. "But if we measure brain activity when a person repeats the same task, then there is a significant variance in neuronal processes”. This apparent contradiction between the reliability and variability of neuronal processes can be observed in all levels of the brain – in major as well as in local neuronal networks, in individual neurons and the synapses between them.

The Bernstein Centre Berlin has focussed on determining to what extent this variability influences the performance of the brain. Michael Brecht is interested in finding out what influence the activity of individual brain cells may have on the behaviour of rats. The rodents are trained to display the electrical stimulation of a particular brain region by a special pattern of behaviour. “They change this behaviour if we only stimulate an individual neuron instead of numerous nerve cells. Our work shows that the cerebral cortex works very precisely despite its enormous variability and that just a few electrical impulses in a single cell of the animal may be significant”, said Brecht.

How does a nerve cell react to a flood of incoming signals? To resolve this question, a new method, dynamic photo stimulation, has been developed in Freiburg.

Taking account of neuronal variability is also of specific importance to medical and technological applications. For example, they are included in the development of modern analysis methods to more reliably interpret the brain waves of patients with neuronal diseases measured by EEG. Other research projects focus on brain-machine interfaces, lie detectors and aspects of machine learning.

Bernstein Centre Freiburg: Dynamics

The brain is constantly interacting with the outside world and develops its own dynamic in all levels of activity. “We want to characterise this dynamic using measurements and learn to understand it in computer models”, says Ad Aertsen about the overall research interests of the Bernstein Centre Freiburg, of which he is the coordinator. The development of suitable multi-channel measuring devices in cooperation with industrial partners is, therefore, just as advanced as the measurements themselves and the mathematical description of the data obtained. The experimental work of the Freiburg neuroscientists ranges from deriving individual nerve cells in tissue sections from rat brains to measuring brain waves using electrodes implant-
Berlin-based scientists are researching the neuronal wiring of the visual cortex. Its nerve cells have different response properties. Each colour symbolises the direction of an edge in the field of vision to which this cell reacts more strongly.

Mathematical models complement the analysis of neuronal networks – including the simulation of several 100,000 neurons, which are each linked to one other by 10,000 synaptic contacts. “All this will be used to find out what one cell says to another cell and how, together, they influence other groups of neurons up to larger parts of the brain”, said Aertsen.

A better understanding of these multiple dynamics opens up a variety of applications in biomedicine, robotics and new technologies. “We want to develop a more intelligent form of deep brain stimulation for patients with epilepsy and other neurological disorders”, said Ad Aertsen. “We are also working on developing methods to detect impending seizures early using EEG. In principle, it should also be possible to counteract spasms through targeted interventions”. Neuronal prostheses for paralysed people and other forms of ‘brain-machine interfaces’ are more remote targets that are increasingly likely to become reality through the research work being carried out at the Bernstein Centre Freiburg.

Bernstein Centre Göttingen: Adaptivity

One of the most outstanding characteristics of our brain is its tremendous ability to adapt to constantly changing requirements. This adaptability is the focus of research at the Bernstein Centre Göttingen, coordinated by Theo Geisel from the Max Planck Institute for Dynamics and Self-Organisation. It shows itself, as does the variance and dynamics of neuronal processes, on all levels of the organisation: Even individual nerve cells adapt their susceptibility and reaction to the type and frequency of incoming signals. Cognitive abilities such as attention, creativity, memory, orientation or learning also reflect the strong adaptive performances of our brain. What mechanisms underlie this adaptability? What role does it play in the encoding of sensory stimuli and in specific cognitive tasks? And how can we use it for medical and technical applications?

Scientists from four faculties at the University of Göttingen, two Max Planck Institutes, the German Primate Centre and the Research Department of Otto Bock HealthCare GmbH, are currently working on the answers to these questions. “In addition, there are joint projects with partners in France, England and Israel”, said Florentin Wörgötter, professor of computational neuroscience at the Bernstein Centre Göttingen. “Together with Israeli colleagues, the Bernstein Centre Göttingen has developed a method to magnetically stimulate cell cultures”, said Wörgötter. In this way, researchers want to better understand how so-called transcranial magnetic stimulation works in order to make it increasingly useful for the diagnosis and treatment of neurologi-
Muscle diseases. However, Wörgötter’s main research interest is developing robots that can adapt their movements to changing tasks through adaptive neuronal networks. One prime example is the RunBot, for a long time one of the fastest walking robots in the world. The algorithms responsible for its performances are now also being applied in the production of adaptive prostheses for patients with movement disorders.

Bernstein Centre Munich: Space and time

“Sensory perceptions always link space and time, the same applies to movements. This, then, poses the question of how this space-time is represented and processed in the brain”, says Andreas Herz on the thematic orientation of the Bernstein Centre Munich which he coordinates. Members of the Centre are involved in various aspects of space-time relationships in numerous projects. The Großhadern Clinic studies, among other things, the control of eye movements to better understand specific neurological defects; one key focus at the Max Planck Institute of Neurobiology is the question of how house flies process constantly changing impressions to control their course. Researchers at the Technical University of Munich are using this knowledge to develop algorithms for driver assistance systems in cars. “We want to reveal generally valid principles relevant for biological and technical systems. As a result, we at the Bernstein Centre Munich are consciously looking for the connection between fundamental research and application”, said Andreas Herz. Several working groups are involved, for example, with the spatial-temporal processing of sound signals; Their findings are used in developing speech-processing systems or by industrial partners to produce improved cochlea implants for hearing-impaired patients. “Many Bernstein projects are embedded in the Munich Centre for Neurosciences and the research cluster, CoTeSys – Cognition in technical systems”, said Andreas Herz. “The critical mass at the Bernstein Centre has contributed to this cluster and the Graduate School of Systemic Neurosciences being successfully set up as part of the Excellence Initiative in Munich”.

Munich-based scientists are researching how the brain of a fly analyses visual movements. The cells marked with fluorescent dyes react strongly to image shifts, such as those that arise when a fly turns around a certain body axis.
Neurotechnology in everyday life

Neuroscientific research findings form the basis for a variety of medical and technological products. In order to promote the forging of bridges between research and application, in 2008 the BMBF established the Bernstein Focus: Neurotechnology – BFNT. A key element of this funding initiative is the close collaboration of academic institutions and industry partners, including the exchange of scientists and the interdisciplinary and application-oriented training of young scientists.

"Behind this is the desire to use the expertise of the Bernstein Centres as efficiently as possible to develop marketable products in the long term", said the coordinator of the BFNT Göttingen, Florentin Wörgötter. The main topic of this BFNT is neurobiologic control systems in which biological and technical components are linked to one another. They form the basis for innovative medical products, such as neuroprostheses, but also to adaptively control machines. Six industry partners and eight scientific institutions are involved in the ten joint projects at the BFNT Göttingen, the German Primate Centre, the University of Göttingen, the DFG Research Centre Molecular Physiology of the Brain, three Max-Planck-Institutes in Göttingen, as well as the Medical University in Hanover and the Max Planck Institute for Biophysics in Frankfurt.

For several years, Wörgötter’s working group has been developing improved prosthetic legs with the medical company Otto Bock HealthCare from Duderstadt. Here, signals are picked up directly by the leg or the prosthesis. "We use advanced control mechanisms based on adaptive neuronal networks", said Wörgötter. "They should not make autonomous rigid motions, instead they should use the natural momentum of the body when walking and absorb the weight of the body with each footfall or when climbing stairs". The BFNT develops control and regulation mechanisms for hand prostheses (see picture) and orthoses. The latter can give restricted limbs back a modicum of mobility.

In a cooperative project with the Starnberg company MED-EL, Tobias Moser and colleagues from the BFNT Göttingen are working on a new kind of hearing prosthesis which could significantly extend the frequency range of currently available devices – called cochlea implants. In contrast to the current principle, acoustic signals should not be converted...
into electrical signals, but into light stimuli. The idea is that if we can inject light-sensitive molecules into the nerve cells of the inner ear, then we could stimulate them with targeted light impulses and convey the impression of hearing in the brain.

Alexander Egner from the Göttingen Max Planck Institute for Biophysical Chemistry is looking for a method to better register and document the activity of nerve cells in cell cultures and tissue sections. Here, a new type of microscope from the Wetzlar-based Leica company is used: It shows structures marked with fluorescent dyes in up to ten times higher resolution than the better light microscopes, allowing images of living cells with unprecedented definition. Other projects deal with the deep stimulation of the midbrain in order to study the auditory system or the improvement of magnetic resonance tomography. The enormous potential of neurobi- onic control systems for commercial applications is shown in the commitment of the industry for the BFNT Göttingen: The BMBF will fund two new professorships in the fields of biosignal analysis, neuro rehabilitation and developing neurobiology with financial support from the firm Otto Bock Healthcare to the tune of 500,000 euros. After the end of the financing term, the University of Göttingen will continue funding the initiative.

In the context of ‘Bernstein Focus: Neurotechnology’, three further regions receive funding in addition to the Göttingen site.

Scientists at the Bernstein Focus Berlin want to improve direct dialogue between brain and computer. This is achieved by non-invasive brain computer interfaces (BCIs), which can measure specific activities in the brain without surgery, using methods such as electroencephalography or magnetic resonance tomography. Berlin scientists want use these BCIs to systematically further develop existing techniques of ‘brain reading’ into applications suitable for everyday use – for example, in driver assistance systems that recognise and take into account the state of alertness of drivers or pilots. Coordinator: Klaus-Robert Müller

The BFNT Freiburg/Tübingen also uses BCIs to pick up brain waves and chemical signals and use them to control prostheses or computers. Both invasive and non-invasive methods are being tested. Among other things, the ultimate aim is to develop medical-technical devices, for example, with which paralysed people can move artificial limbs solely with the power of thought or compensate for brain malfunctions and failures in epilepsy and stroke patients. This also addresses ethical issues, such as the question of how a neuroprosthesis changes the self-image of the people affected or society’s perception of them. Coordinator: Ulrich Egert

Bernstein Focus Frankfurt is working on a new generation of artificial vision systems. Based on the process of vision development in infants, such systems will learn, largely autonomously, the multifaceted aspects of vision, such as estimating distances, recognising objects from different perspectives or tracking objects, through interaction with the environment. The systems could be used for robots, security monitoring systems in buildings or traffic control. Coordinators: Christoph von der Malsburg, Jochen Triesch, Rudolph Mester

www.nncn.de/MitgliederNCCN/Neurotechnologie/BFNT
Controlling machines via brain signals

Whether we brush our teeth or tie our laces, all intentional movements start in the brain. The brain creates control signals and sends them via the spinal cord to the muscles to make them move. It is the aim of a Bernstein Collaboration between Tübingen University Hospital and the Bernstein Centre Freiburg to decode these signals and use them to control appliances.

“We want to be able to predict where the hand of a test subject will move – in real time at the very second the brain initiates the move”, says project coordinator Christoph Braun of the MEG Centre at Tübingen University Hospital. MEG is short for magnetoencephalography – a method used to record the brain’s magnetic activity. The test subject wears a type of helmet equipped with highly receptive sensors that record the magnetic signals and forward them to a computer for evaluation and storage. This device can localise the sources of brain activity more exactly than electroencephalography (EEG). Says Christoph Braun: “Our strength lies in accurately tapping brain signals with a high spatial and temporal resolution. Carsten Mehring of the Bernstein Centre Freiburg is engaged in developing suitable algorithms to gain the maximum amount of information from the brain signals and convert them into control signals for appliances”. The long-term aim of this joint project is a brain/computer interface that can be used for medical purposes, for example for patients whose limbs are temporarily or permanently paralysed.

"With the help of the signals measured, we can predict in which direction healthy test subjects will move their hands", emphasises Mr. Braun. This knowledge is now being incorporated in rehabilitation training for stroke patients with one-sided paralysis: “During the training, patients are required to imagine performing a certain movement with the paralysed hand. We measure their brain signals and use the signals to passively perform the exact movement at the same moment. The brain thus receives feedback that its instructions have arrived. We assume that the functionality of the patient’s motor cortex will be regained and its motivity restored”. Just three weeks after commencing this training, one patient already managed to seize small objects with a hand that had been paralysed for more than a year.

In the context of the 'Bernstein Focus: Neurotechnology’ initiative, paraplegic patients are now set to benefit from the new findings. Says Mr. Braun: “We intend to record their brain signals with the help of implanted EEG electrodes and use the signals to control computer-assisted systems”.

The hallmark of all eleven Bernstein Collaborations is close cooperation between experimenters and theorists as well as application-oriented research projects.

www.nncn.de/MitgliederNCCN/Bernstein%20Kooperationen
Focusing on the essential

Consider this common road traffic scene: A driver accelerates to cross a yellow traffic light, narrowly swerves around a cyclist, overtakes the school bus with a quick glance at rushing children and swiftly changes lanes to avoid getting stuck at the next building site. How does the driver manage to quickly and accurately deal with this surge of impulses which, moreover, are constantly changing?

Every day, we constantly coordinate a multitude of cognitive and motor skills. Bremen-based scientists are carrying out experiments and setting up computer models to find out how the brain adapts to constantly changing tasks.

“To filter the relevant aspects from the multitude of information and shut out what is not important is one of the brain’s great achievements”, says Klaus Pawelzik of the Institute of Theoretical Physics at the University of Bremen. As coordinator of the local Bernstein Group, he concentrates on the visual cortex, the part of the brain that processes visual impulses. “Vision is a dynamic process. The nervous system adjusts to changing tasks within a timeframe that may take anything from fractions of a second to many years. We want to find out how this adaptation works on different timescales”, says the physicist.

For this purpose, he is developing a mathematical model that recognises natural pictures swiftly and accurately with the help of few neuronal connections. He compares the results of model calculations with the experimental findings of his colleagues Manfred Fahle and Andreas Kreiter who work at the Centre for Cognitive Sciences right next door to Mr. Pawelzik. In Manfred Fahle’s experiments, healthy test subjects pick up objects while wearing prism glasses that shift their line of vision. “While the subjects are off the mark at the beginning, they eventually learn to adjust to the new conditions. These experiments give us an insight into the adaptability of the vision system”, explains Mr. Fahle. Andreas Kreiter researches the neuronal processes on which this adaptability is based. With the help of microelectrodes, he measures the activity and wiring of certain nerve cells in the brains of macaque monkeys while they are solving simple learning tasks on-screen. It appears that time coordination between nerve cells, their synchronisation, plays an important role in the vision process.

“Once we understand how vision functions, we can use this knowledge for technical applications”, emphasises Klaus Pawelzik, “for example for mechanical image recognition in robots, or for improved interpretation of x-ray and MRI images”.

In 2007, Bernstein groups were integrated to boost the National Network for Computational Neuroscience at five different sites. Their research focuses on the following areas:

- **Bochum**: Dynamic systems as a foundation of higher brain functions
  Coordinator: Gregor Schöner
  (info@computational-neuroscience.bochum.de)

- **Bremen**: Functional adaptation of the visual cortex
  (see adjacent article)
  Coordinator: Klaus Pawelzik
  (pawelzik@neuro.uni-bremen.de)

- **Heidelberg**: Detailed modelling of signal processing in neurons
  Coordinator: Gabriel Wittum
  (wittum@gcsc.uni-frankfurt.de)

- **Jena**: Model-based, spatial-temporal system analysis of the pain neuromatrix
  Coordinator: Herbert Witte
  (Herbert.Witte@mti.uni-jena.de)

- **Magdeburg**: Components of cognition – from small networks to flexible rules
  Coordinator: Jochen Braun
  (jochen.braun@ovgu.de)
Studying computational neuroscience

An interview with Prof. Klaus Obermayer, coordinator of the first German master's programme in CNS

Who is involved in designing the new master's programme?

The course programme is organised by the three Berlin-based universities, the Technische Universität, Freie Universität and Humboldt-Universität, in conjunction with the Charité hospital. The contents of the programme were developed by Professor Laurenz Wiskott and myself together with our colleagues at the Berlin Bernstein Centre, who will also take over some of the teaching responsibilities.

Who are your target students?

A wide range of bachelor graduates, people with technical or scientific qualifications, such as physics or mathematics, who would like to apply their discipline’s formal methods to the field of brain research. Conversely, we would like to offer neurobiologists or health professionals the necessary formal knowledge. This is a research-oriented course programme; after graduation, our students would work in research and development at universities, or hospitals and companies.

What distinguishes your programme from existing courses of study?

Our programme is the first in Germany to teach the theoretical methods that complement experiments. To understand the brain, we must use both approaches in conjunction with each other. Hence, we combine neurobiological issues with IT approaches used in artificial intelligence research and machine learning. We also merge experimental work with techniques used to analyse data that have been gained via very different methods. In contrast, neurobiology courses comprise very few theoretical components while neuroinformatics courses usually concentrate on technical aspects.

What is the structure of the programme?

Students require sound mathematical skills, everything else is taught during the first year: the modelling of neuronal systems and higher brain functions, analysis of neuronal data and machine learning. The second year is research-based and includes three scientific projects in the fields of ‘experiment and theory’ as well as the master’s thesis.
What feedback have you had so far?

In winter 2006, we started a course with eight students, some of which had to withdraw due to insufficient mathematical skills. This year, we had close to 50 applications for our 10 places, including many from abroad; at least half of the applicants are highly qualified. If this positive trend continues, we intend to raise the number of places to 15, or 20 at the most.

Where can students attend comparable course programmes?

The USA, Israel and various European countries have been offering combined Master/PhD programmes in computational neuroscience for some years now. Due to the BMBF’s Bernstein initiative, Germany has caught up swiftly in this field and is now playing a pioneering role. Our new course programme in Berlin is geared towards international students and is taught entirely in English. We are now in a position to compete with programmes abroad and aim to attract top students from all over the world.

Challenging research depends on well-qualified scientists. This is why the Bernstein Network supports a multitude of master’s, PhD and post-doctoral programmes.

**Berlin**
- MSc/PhD Programme in Computational Neuroscience
- International Graduate Programme in Medical Neuroscience
- Integrated Graduate Program in Human-Centric Communication
- Berlin School of Mind and Brain

**Bochum**
- International Graduate School of Neuroscience

**Bremen**
- Masters in Neurosciences

**Frankfurt**
- MSc Computational Science
- MSc Interdisciplinary Neuroscience

**Freiburg**
- Tri-national Joint Masters in Neuroscience
- PhD Programme in Computational Neuroscience
- Spemann Graduate School of Biology and Medicine
- Postdoctoral Training Programme in Computational Neuroscience

**Göttingen**
- MSc/PhD Programme in Neuroscience
- PhD Programme in Theoretical and Computational Neuroscience
- PhD Programme in Systems Neuroscience
- PhD Programme in Sensory and Motor Neuroscience
- Neuroscience Early Stage Research Training NEUREST

**Heidelberg**
- MSc Programme in Scientific Calculation

**Magdeburg**
- MSc/PhD in Integrative Neuroscience

**Munich**
- ENB Master’s Programme in Neurosciences
- ENB Master’s Programme in Neuro-Cognitive Psychology
- Graduate School of Systemic Neurosciences
- PhD Programme in Orientation and Motion in Space
- IMPRS Molecular and Cellular Life Sciences

**Rostock**
- MSc Programme in Medical Biotechnology

**Tübingen**
- MSc/PhD Program Neural & Behavioural Sciences
When nerve cells move in sync with each other

“Mathematics and neurobiology were my favourite subjects at school”, remembers Susanne Schreiber. Combining her favourite subjects opened up a fascinating field of research for the young academic: computational neuroscience. For the consistency of her research and analysis of neuronal processes using mathematical models, she received the BMBF’s international Bernstein Award in 2008.

In Germany, the new discipline of computational neuroscience was almost unknown when Susanne Schreiber passed her A-Levels and started looking at university courses in 1995. She settled on biophysics at Berlin’s Humboldt-Universität – the only university in Germany to offer this course programme at the time. She soon found out that she had made an excellent choice when the DFG, the German Research Foundation, founded an Innovation Research School for Theoretical Biology at Humboldt-Universität that also included a Theoretical Neurobiology group. “This was an even better place for me to follow my inclination”, says Ms. Schreiber.

Susanne Schreiber is interested in the molecular properties of individual nerve cells. The question whether or how a neuron becomes active, i.e. passes on signals in the form of electrical impulses, depends on how easily electrically charged particles get into or out of a cell. Their passage is controlled by complex molecules, so-called ion channels, that are positioned in the cell membrane and control its permeability. “While these channels are open, nerve cells require a lot of energy. They have to work highly efficiently”, explains Ms. Schreiber. In her thesis, which she researched in Simon Laughlin’s laboratory at Cambridge, she was asking the following question: How many ion channels should a nerve cell have if it dispenses of a limited amount of energy – and what are the probabilities of it opening these channels?

The mathematical model which she used to find the answer is based on very simple fundamental assumptions. The structure of living nerve cells is much more complex, and they do not pass on impulses unless their initially negative membrane voltage is raised to a positive threshold value via respective ion flows. How this happens depends on the properties of their ion channels. “I wanted to find out how they affect timing and the reliability of excitation”, explains Susanne Schreiber in describing the subject of her doctoral thesis. She did part of the work with Terrence Sejnowski, one of the pioneers of computational neuroscience, at the Sloan-Swartz Center of the Salk Institute for Biological Studies in California. In 2004, the 28-year-old received her doctoral title from Andreas Herz of the Institute for Theoretical Biology at Berlin’s Humboldt-Universität.

Nerve cells differ with regard to their excitation properties: Some discharge irregular excitation pulses (left picture, top) while others discharge in almost regular intervals (bottom). Each neuron has a type of favourite frequency at which it works particularly accurately (red area in right picture).
“I was lucky that the Bernstein Network was being established at the time and that I was allowed to work on a network project at the Bernstein Centre Berlin”, says the researcher. Once again, she designed computer models to study the behaviour of ion channels. The type and number of these molecular locks determine how individual neurons react to the signals of neighbouring cells: Some nerve cells fire entire volleys of impulses in quick succession while others transmit at regular intervals. Furthermore, each neuron has a type of favourite frequency at which it works particularly accurately, as Susanne Schreiber’s model calculations show. The scientist is convinced that the properties of the individual neurons also dominate the function of neuronal networks and the brain. “For the network to react accurately, the individual cell needs to react accurately”.

"Synchronicity depends on the interconnection of the nerve cells"

In fact, for us to store memories or use our short-term memory to explore a new environment, larger groups of neurons must coordinate their rhythmic behaviour and oscillate collectively. How do such synchronous oscillations arise? “It is known that synchronicity depends on the wiring of the nerve cells”, says Ms. Schreiber, “however, we assume that individual properties of the cells also have a decisive impact. I want to find out how they do this”.

To achieve this aim, the Bernstein Award winner, now mother of two daughters, is setting up her own research team in Berlin. Close cooperation with experimenters is of great importance to her. “My work constitutes pure fundamental research which, however, has strong links with application-relevant issues”, emphasises Susanne Schreiber, “some drugs, for example, affect specific ion channels and thus stop pathological synchronisation states in epileptics”. The young scientist is looking forward to a further research project that will be funded by BMBF as of summer 2009 in the context of the “Bernstein Focus: Neuronal basics of learning” initiative. “In the context of this project, I want to find out how ion channels are affected by learning processes”.

As part of the National Network for Computational Neuroscience, the Bernstein Award allows outstanding young scientists to establish an independent group of junior researchers. The international prize, which is worth 1.25 million euros, is awarded every year. In 2008, Susanne Schreiber received the coveted award (see portrait). Previous prize winners include Matthias Bethge and Jan Benda. At the Max-Planck Institute for Biological Cybernetics in Tübingen, Mr. Bethge is investigating the neuronal processes that underlie the processing of visual stimuli, thereby contributing to the development of technical image processing systems. At the Bio Centre at Munich University, Jan Benda is taking communication between weakly electric fish (see picture) as an example to investigate how complex sensory information is decoded in spatial and temporal patterns of neuronal activity and processed in the nerve system.
Transparency and standardisation

An interview with Prof. Andreas Herz, coordinator of the Bernstein Centre Munich and of the German Neuroinformatics Node (G-Node)

What is the aim of G-Node?

Neuroscientists are researching all levels of the brain using a wide variety of measuring devices, methods and models. It is the central aim of G-Node to make the collection, storage and analysis of data as well as mathematical modelling within computational neuroscience more transparent. Furthermore, the node is about the development of data formats and software programs that are not restricted to one particular study group but can be used by many groups and, in the long term, also at the global level.

A formidable undertaking!

Yes, it has long been recognised as a major problem which should be resolved at the international level. This is why the International Neuroinformatics Coordinating Facility INCF was established in Stockholm on the OECD’s initiative. Germany is one of the 14 member countries and has established a national node, the G-Node, in Munich. We primarily concentrate on one relevant sub-area of neurosciences, electrophysiology. It is our aim to promote the exchange of data and methods in this field.

Why electrophysiology?

Other INCF countries, for example the USA, work in the imaging field and Japan is developing a platform in the visual systems field. In contrast, Germany has traditionally had great expertise in the field of electrophysiology. Furthermore, the lack of transparency and standardisation is particularly serious in this area. We have intracellular and extracellular excitation discharges, individual and collective signals, in vitro and in vivo experiments – all this makes for a deluge of data in different formats and different description levels. No single laboratory is in a position to sort out this jumble. A national centre, such as G-Node, can do the job.

How do you intend to reach your aim?

Aside from the development of specific software, we plan to groom a new generation of scientists who collect, manage and analyse data with maximum transparency without a second thought. For this purpose, we offer doctoral students, for example, the possibility to revise their research data and all analyses and modelling programmes according to INCF standards, archive them at the G-Node and make them available to other groups. This initiative is financed by BMFB. Furthermore, we plan to introduce an electronic laboratory book. Scientists are obliged to report each experiment they carry out every day. With current technology, such laboratory books could be maintained electronically, introducing certain data collection standards at the same time. Finally, every year G-Node offers courses to students and doctoral students with the aim of inspiring young scientists to do research in the field of computational neuroscience. The students carry the knowledge they gained on our courses to their home universities, in Germany and abroad, leading to the gradual establishment of a new science culture.
Medical genome research
Medical genome research
Getting down to the roots of diseases

Aside from various environmental factors, it is our genetic makeup that crucially impacts our health. It is the aim of medical genome research to understand the molecular basis of disease and health processes. This field of research is making a major contribution towards the development of new strategies to prevent, diagnose and treat diseases. Knowledge of the molecular changes involved in the appearance and progress of diseases allows their specific manipulation via tailor-made drugs.

It took approx. 1,000 scientists, 13 years and 300 million dollars to decode a complete human genome, a feat that was achieved for the first time in 2003. Today, the same can be done in eight weeks at a cost of 100,000 dollars. These figures are clear evidence of the rapid progress made in the field of molecular biology. Fully automated sequencing devices swiftly and accurately provide crucial information on human, animal, plant and micro-organism genomes, giving the scientists entirely new insights into elementary life processes.

Uncovering the secret of interaction

Just a few years ago, biologists were convinced that organisms had to have at least as many genes as it had different proteins. Thanks to the trail-blazing results delivered by genome researchers, we now know that human cells have less than 23,000 genes and are nevertheless capable of producing a multiple quantity of proteins. Our genes have multiple uses due to a sophisticated machinery of specialised bio-molecules that can use a copy of a genome to produce several, in some cases even several hundreds of, different masters to produce proteins. Together with numerous other gene regulation possibilities, this process decides whether and when which types and quantities of proteins develop in which cells, in other words, which proteome is present in the cell.

The methodological and technological developments in molecular biology give scientists increasingly detailed insights into these fundamental life processes. Applying the key technology of medical genome research (the efficient determination of the basic sequence of the two nucleic acids DNA and RNA), the sequencing of genomes is becoming faster, more accurate and less costly. Furthermore, it has led to the discovery of previously unknown classes of RNA molecules which, in themselves, do not serve as masters for proteins but have a regulatory impact on the production of proteins and other RNAs at various levels. Highly integrated chip arrays also allow scientists to identify more than 500,000 variations of individual basic pairs, so-called single nucleotide polymorphisms, SNPs, in the genome of individual persons in the context of one single experiment. An international research project entitled HapMap has recorded over 3.9 million SNPs of healthy and sick persons from four different ethnic groups, which can be compared to further individually collected data. Such whole genome association studies (WGAS) present a promising tool for researching the causes of complex genetic diseases. With their help,
previously unknown risk genes were identified for various complex clinical pictures, such as asthma, adiposity and cardiovascular diseases. Some of this work was carried out by German research groups working in the context of NGFN, the German National Genome Research Network.

The massive volume of data gained with the help of state-of-the-art high-throughput technology illustrates the immense complexity and dynamics of the human genome. Due to the surprisingly low number of genes, scientists suspect that the interaction between genes and gene products is far more complex than originally assumed. Hence, the regulation of genes and their functions plays a central role in determining health or illness. The correct ratio between cell growth and cell death is particularly important in maintaining a healthy state. As we know today, malfunctions of these central processors can lead to the development of cancer in just one, or a few, of our several thousand million body cells.

**Networking proteins**

Various functional assays, based for example on specific activation or knocking-out of genes, show how cells react to such malfunctions. A new method, which was honoured with a Nobel Prize in 2006, consists of so-called RNA interference. The method is used to silence specific genes, thereby suppressing the production of their respective gene product with the aim of identifying its function. It has been shown that proteins do not work in linear processes but in networks, triggering different effects at different destinations. Regulatory feedback mechanisms and cross-links between various signal paths as well as the non-linear nature of enzymatic processes complicate our understanding of the cellular processes associated with the development of cancer, making it more difficult to predict therapeutic effects.

Similar complexity applies in the case of numerous infectious diseases. Viruses behave similarly to living systems, adapting constantly to fight the natural or medical defence strategies of their host. Hence, our search for suitable therapeutic agents must consider not only viruses, bacteria and other pathogenic agents themselves but also their interaction with the affected organs of the patients and their immune systems. Computer simulation is essential to model these many-layered webs of relationships and reduce them down to their essential determining factors. A system-biological approach that combines laboratory experiments with computer simulation is indispensable.
It is one of the long-term aims of medical genome research to envisage the optimum treatment for each individual patient.

To understand the impact of the genome on multi-factor diseases, scientists must combine genetic and molecular-biological data with information regarding the emergence and progress of the diseases. Mouse, fruit fly or zebra fish models involving clearly defined gene defects provide significant insights into the function of the respective genes and their influence on complex clinical pictures. Furthermore, they give scientists an opportunity to assess the effectiveness of potential remedies.

These complex experiments researching the function and relevance to diseases of genetic elements must be complemented with studies of very large groups of patients. This requires a close integration of clinical study groups. Joint efforts in the context of interdisciplinary associations between doctors, biologists, engineers and mathematicians are crucial to carry out an efficient search for links between gene or protein variants and certain clinical pictures as well as analysis of the identified candidates as to their function in healthy and diseased tissue using high-throughput procedures. In particular, bioinformaticians are needed to tap the multitude of generated data and derive the relevant information that will contribute towards an optimisation of system-oriented computer models.

Close cooperation with industrial partners is necessary, if nothing else, to allow for swift commercial use of the research results and practical application for the patients’ benefit. With the aim of promoting this close connection between academia and industry, bioscientists from various disciplines and clinicians, theorists and experimenters, BMBF has created a number of funding programmes in the field of medical genome research. These programmes will be described on the following pages and introduced with the help of selected research projects.
Research for the patient’s benefit – BMBF’s funding concept

It is the aim of BMBF’s medical genome research funding programme to boost Germany’s leading position in the field of human genome research. The programme builds on the NGFN, the National Genome Research Network, which was established in 2001 and has continued its work in the form of the NGFN-2 programme since 2004. In the context of the programme, nine disease-related genome networks were established for the purpose of researching the diseases with the largest impact on the country’s economy. A further twelve systematic-methodological platforms served to develop effective high-throughput technologies and 19 projects focused on the identification of new tools and applications in the field of human genome research. In the context of NGFN-2, German scientists took part

NGFN-Plus and NGFN-Transfer sites

www.ngfn.de
in over 60 EU projects and contributed to the discovery of numerous risk genes associated with the emergence of Alzheimer’s, Parkinson’s, epilepsy, chronic inflammatory bowel diseases and cardiovascular diseases; over 2,000 publications and 70 invention disclosures are evidence of the success of the NGFN-2 programme.

Now, basic genome research is to be integrated more closely into disease-related subjects in order to initiate the development of improved diagnosis and treatment processes for the diseases with the biggest national impact. In line with its High-Tech Strategy, BMBF has redirected its efforts towards applied research in order to turn innovative products, processes and services into integral components of medical genome research.

Supporting research and transferring results for practical application

The new funding programme has two sub-areas: NGFN-Plus and NGFN-Transfer. Through NGFN-Plus, the BMBF funds 26 ‘Integrated alliances in medical genome research’ for an initial period of three years. The alliances, which are committed to over 300 projects, apply methods used in human genome research and adjacent disciplines to gain comprehensive understanding of disease processes at the molecular level. The main focus is on cancer research (p. 55) and research of neural degenerative diseases (p. 52, 54) as well as cardiovascular and infectious diseases (p. 50 and 57). The scientific results will be used to develop new diagnosis and treatment processes for the diseases with the biggest national impact.

The BMBF has been funding link-ups between German and French research groups in the field of major national diseases in the context of the ‘Genomics and Pathophysiology of Cardiovascular and Metabolic Disorders’ bulletin. Numerous genome researchers participating in NGFN projects are working on other research questions in joint binational and multinational projects, especially in Europe. Since summer 2008, for example, the Berlin-based Max Planck Institute for Molecular Genetics has taken part in the ‘1,000 genomes project’ in the context of the NGFN funding programme. This consortium, consisting of a total of nine nations, is comparing a thousand human genomes from various ethnicities using state-of-the-art high-throughput sequencing devices to gain a detailed insight of the genetic diversity among humans.

The NGFN-Transfer programme funds eight “innovation alliances in medical genome research” to promote the efficient transfer of genome research results to clinical and industrial applications (p. 59). It is the aim of the programme to advance close collaboration between research enterprises and academic institutions. On a joint leadership basis, both partners are involved in equal measure in the formulation and implementation of research activities and the development of marketable innovations. Consequently, the results of disease-orientated NGFN genome and proteom research, which have met with hesitant reactions from industrial suppliers due to lack of maturity, will be transferred to the commercial sector and thus used for the treatment of patients at an earlier stage.
"What we need is integrated fundamental research and clinical research"

Interview with Prof. Martin Hrabé de Angelis, spokesman of the NGFN project committee

What does medical genome research accomplish?

To improve the diagnosis, prevention and treatment of diseases, more, and to some degree different, knowledge is required than we have today. This is where medical genome research comes in which focuses on the impact of genomic elements in multi-factor diseases. Our NGFN projects go far beyond the mere analysis of genes. They research all important molecular elements, including RNAs, proteins, metabolic and signal paths as well as the impact of environmental factors.

What are your aims for the coming decade?

We intend to generate evidence-based strategies. Accordingly, we need to understand the molecular processes that cause a certain disease and look for treatment options on the basis of this evidence. At the same time we concentrate on individualised medication, focusing on the individual patient and asking whether a certain drug can be effective given the patient’s specific molecular constitution.

How will you achieve these aims?

On the one hand, the system-biological approach must gain ground in medical genome research, i.e. the interaction between experiment and modelling. Furthermore, an integrative approach is required in that clinical diseases must be researched with all available means and data interpreted on a comprehensive basis. Epidemiological studies, studies among healthy and sick persons, animal models, research of cell systems and analysis of molecular elements all play their part. This requires high-end analytics, which means platforms specialising in certain methods, something the NGFN provides. The result is added value that is difficult to generate in individual laboratories. It is crucial to apply a systemic approach that focuses on the whole body as opposed to individual organs. Let’s assume we discover a key molecule in the cardiovascular field. This leads to the question where else in the body the molecule appears and what happens in that area if the molecule is manipulated with the help of an active pharmaceutical agent. Cross-indication work in the consortia must be intensified in the context of NGFN in order to promote this systemic approach. The project committee, which has the task of identifying interconnections, plays an important role in this context.

Why do we need government funding for medical genome research?

To a large degree, this type of health research is not, or no longer, performed by the pharmaceutical industry in Germany. Support instruments directed at pure fundamental research, such as the DFG, are crucial; however, they exclude the NGFN project structures. The BMBF promotes crucial integration between specific fundamental research and clinical research. Furthermore, it shores up the German contribution to international consortia, such as the ‘1,000 genomes project’ or international disease modelling initiatives.
Helping weak hearts

In Germany, cardiac insufficiency causes more deaths than any other disease. With rising life expectancy, the number of cardiac patients is set to increase. All the currently available drugs can do is slow down the progress of the disease. Hence, BMBF supports the development of effective treatment approaches with the aim of benefiting the patients and easing the strain on the community.

Genetic makeup determines whether we will develop cardiac insufficiency in the course of our lives and which form and severity this insufficiency will take. “We know that individual gene mutations may lead to alterations of certain proteins in the heart muscle and thus to cardiac insufficiency. The course of this disease depends on our genetic background”, says Hugo Katus from the Heidelberg University Hospital. The cardiologist has been treating patients with various forms of cardiac insufficiency for 30 years. In the context of the NGFN, the National Genome Research Network, he has also done successful research into the molecular causes of this national disease.

“We follow a three-tiered research approach: Firstly, we identify gene mutations that are related to cardiac insufficiency. Secondly, we strive to understand the signal paths on which these gene mutations have a negative impact. And thirdly, we are interested in the role of the genetic environment, i.e. which modifying genes alleviate or reinforce the impact of the gene that leads to the disease”, declares Hugo Katus. “We” in this context refers to the NGFN-Plus network, the study groups at the universities of Heidelberg, Göttingen, Münster and Munich, at the DKFZ Heidelberg, the Max-Delbrück-Centrum and at the Charité in Berlin. “Furthermore, we benefit from the entire infrastructure and expertise of the genome research network, its methodological platforms and their gene sequenc-

“When the heart is under stress, it changes its metabolism. We measure the outcome”. Hugo Katus, NGFN-Plus

ers and bioinformaticians and not least from the mouse clinic that makes its animal models available to us. This is where doctors like me, who are driven by clinical problems, meet theorists and fundamental researchers. These meetings release formidable synergies”, emphasises Mr. Katus.

Researching cardiac insufficiency at all three levels crucially depends on the interdisciplinary collaboration within the NGFN. Heart-specific proteins

Everyday care of patients complements genetic studies: Prof. Hugo Katus (right) is performing a heart catheterization.
are identified in cell cultures and their impact on the main signal paths is studied. In parallel, thousands of mutated zebra fish are screened. Due to the fact that the animals are transparent, any pathological changes of the heart are visible from the outside. Interesting candidates are bred to form large fish families and become subject to more detailed studies. Transgenic mouse strains with precisely known gene defects complement these experiments. The identification of the modified genes is a highly complex process. “In the context of a whole genome associative study, we are researching four groups of a thousand patients each that suffer from four different forms of cardiac insufficiency. The results gained from this research, which is carried out in Munich, Berlin, Göttingen and Heidelberg, is subsequently compared to healthy subjects. We have already identified several genetic regions that impact the progress of cardiac insufficiency”, says Mr. Katus.

In parallel to causal research within the NGFN-Plus association, the cardiologist is looking for effective biomarkers in the context of an NGFN-Transfer project to help doctors detect early signs of cardiac insufficiency and make predictions as to the course of the disease. “When the heart is under stress, it changes its metabolism as a result of all genetic processes. We simply measure the outcome”, states Mr. Katus in describing the idea behind the project. For this purpose, the metabolic products of diseased and healthy heart cells are compared and the characteristic differences identified. In parallel, the scientists look for conspicuous metabolites in the blood of patients suffering from different forms of cardiac insufficiency. The equipment used to record the complex metabolic profiles and the biostatistical processes used to identify the decisive components were contributed by Metanomics, a Berlin-based biotech company.

**Decoy ODN treating cardiac insufficiency**

A further NGFN-Transfer project, headed by Markus Hecker at Heidelberg University, is pursuing a new cause-related approach to the prevention, or even healing, of cardiac insufficiency. It is based on the cellular signal paths that may lead to the characteristic symptoms when certain genes are expressed in excess. Three transcription factors that cause this overexpression have been characterised within NGFN’s cardiovascular genome network and the binding sites they use to bind themselves to the target genes have been identified.

The sequence of these binding sites comprises approximately 10 to 20 nucleotides and can be synthetically copied in the laboratory. If these synthetic oligodesoxynucleotides (ODNs) are brought in contact with a body cell, they autonomously move into the cytoplasm, where they bond with the compatible transcription factors before the latter can migrate into the cell nucleus and attach themselves to the DNA binding sites. Since they act as decoys, the synthetic DNA molecules are called decoy ODNs. “We use these ODNs to intercept surplus transcription factors”, explains Helga Grupe, managing director of the Munich-based Avontex GmbH, “and thus specifically inhibit the expression of the genes that represent important factors in the emergence of a disease”. Avontec has several decoy ODNs against transcription factors which are involved in the emergence of asthma, psoriasis and neurodermatitis. These pharmaceutical products are being tested on several hundreds of patients, both for safety and, to some extent, also for effectiveness. As an industrial partner, the company is contributing this globally unique know-how to the NGFN-Transfer project with the aim of making decoy ODNs available for the treatment of cardiac insufficiency in the future.
Parkinson’s research: in search of the fatal difference

“I have always been interested in the brain and its malfunctions”, remembers Birgit Liss. Today, the young professor is researching the causes of Parkinson’s disease. Why do individual nerve cells die in the brain of Parkinson’s sufferers while others do not? Birgit Liss is convinced that molecular properties decide the fate of each nerve cell.

Birgit Liss, the youngest of three children, grew up in Schafflund in Schleswig-Holstein where she attended science grammar school in nearby Flensburg. Her A-Level subjects, mathematics and biology, provided her with the perfect foundation for the course programme in biochemistry/molecular biology that was set up at the University of Hamburg in 1990. “It was all new not only for us but also for the professors”, remembers Ms. Liss. Ten semesters later, at age 24, she left university with her degree, having majored in genetic technology and minored in neurobiology.

She then transferred to Jochen Roeper at the Centre for Molecular Neurobiology in Hamburg where she researched the nerve cells of mice with neurodegeneration similar to Parkinson’s disease and compared them with the cells of healthy mice. The questions she posed in her doctoral thesis, which she graduated with summa cum laude, are still relevant to her today: Why do certain nerve cells die in the course of Parkinson’s disease while others survive; and how can these differences help us develop new treatments?

According to Birgit Liss, one key to understanding neurodegenerative diseases can be found in the molecular make-up of nerve cells. In the course of the disease, up to 90 percent of cells that produce the neurotransmitter dopamine die in the brain of Parkinson’s sufferers, more precisely in the substantia nigra of the midbrain. The resulting dopamine deficiency causes typical symptoms – muscle tremors, posture impairment and akinesia. “In contrast, the dopamine neurons adjacent to the substantia nigra, the VTA area, are much more resistant. So far, it is not clear why”, says Ms. Liss. To resolve this mystery, the neuroscientist compared the molecular properties of individual nerve cells from both brain areas. She acquired the complex technique of single cell gene expression analysis while writing her doctoral thesis. Cell liquid is suctioned from a single nerve cell and analysed as to its mRNA content (messenger RNA), which is the direct genetic product. The ingenious thing about this approach: Before the extraction, the electrophysiological properties of the cell are measured with the help of the suction pipette. “Consequently, the excitation patterns of nerve cells can be compared to their gene expression profiles to uncover potential correlations”, says Ms. Liss.

After receiving her doctorate, Birgit Liss went to England on the strength of a scholarship at Oxford University and a post-doc offer from Frances Ashcroft who was researching the same ion channels that Ms. Liss had identified as significant.
in dopamine neurons. In 2001, she received the renowned Royal Society Dorothy Hodgkin Research Fellowship and established her own group of young researchers. After close to four years in England, Birgit Liss was ready to return home. At the time, junior professorships, a topic of heated discussion, were being set up. To form her own opinion on the matter, Birgit Liss applied in Berlin and Marburg – and was accepted by both universities. She decided in favour of Marburg "because I was offered better equipment and the prospect of a C2 position with tenure track". The junior professor set about establishing her own research team and pursued her question regarding the individual differences in dopamine-discharging nerve cells. She established UV laser micro-dissection technology for gene expression analysis of individual cells. "This technology allows for contact-free excision of cells from fixed tissue, thereby minimising the contamination risk”. It also permits analysis of nerve cells of deceased Parkinson’s sufferers.

**In 2007, Birgit Liss received the Alfried Krupp Research Award.**

In April 2007, aged 35, Birgit Liss assumed the position of full professor for general physiology at the University of Ulm. In the same year, she received the Alfried-Krupp Award for Young Researchers, which is worth one million euros. She achieved further success in the context of 'Neuronetz', an NGFN-2 research association. In close cooperation with Jochen Roeper, who is now at Frankfurt University, she made the following discoveries: "We were able to show that the highly sensitive dopamine neurons in Parkinson mouse models have a certain ion channel in their cell membrane whose activity represents a decisive factor in the death of these cells. In healthy brains, we have also been able to define an alternative type of dopamine cells that differs from the classic highly vulnerable type with respect to essential functional and gene expression characteristics", says Ms. Liss. A sub-group of the alternative dopamine neurons, which are far more resistant in the course of Parkinson’s disease, is particularly interesting: "As these nerve cells have no autoreceptors for dopamine, the latter does not directly control their activities. This means that even some of the main Parkinson drugs are ineffective in this area”.

The NGFN-Plus project builds on these spectacular findings. "It is our long-term aim to selectively manipulate the activities of the various dopamine-discharging cell types with pharmaceuticals in order to slow down or even arrest the progress of the neurodegenerative disease. Using mouse models and dopamine neurons from Parkinson’s patients, we want to find out what distinguishes the nerve cells in terms of function and molecules – both in healthy brains and in various stages of the disease”.

In Germany alone, more than 300,000 Parkinson’s sufferers are hoping for new active substances that may treat their condition.
What Alzheimer’s and Parkinson’s have in common

Alzheimer’s and Parkinson’s, as well as less well-known conditions such as spinocerebellar ataxia, Charcot-Marie-Tooth disease and Huntington’s disease, all have one thing in common: They are neurodegenerative diseases triggered by the death of nerve cells in the brain. To date, there is still no cure for these conditions; all the drugs can do is alleviate the suffering or slow down the progress of the disease. Six working groups from Berlin, Heidelberg and Notre Dame, USA, have joined forces to form the NGFN-Plus NeuroNet project.

Project coordinator Erich Wanker of the Max-Delbrück-Centre for Molecular Medicine in Berlin describes the research concept as follows: “We are investigating the common factors in these five conditions, the differences and the fundamental molecular mechanisms involved”.

Some clues as to the causes of the diseases have already been identified, for example aberrant folding and aggregation of certain proteins. “We know of approx. one hundred proteins that affect the disease process”, explains Mr. Wanker, “but very little is known about their interaction”. The NeuroNet group systematically researches these interactions – with the help of cleverly modified yeast cells that can only grow if two previously selected proteins bond. “We will test 1,000 disease proteins against a library of approx. 20,000 proteins, that makes 20 million combinations”, says Mr. Wanker.

More needs to be known about the interaction between the proteins

Aside from combinations of two proteins, the team will also research three-protein complexes. “We have recently developed a new technology that allows us to analyse phosphorylation-independent protein interaction in yeast cells”, explains Mr. Wanker. The genome researcher is studying fruit flies which develop symptoms of Huntington’s disease due to a gene defect to investigate the question whether and how such interaction affects neurodegenerative processes. “During this process, the photo receptors in the eye also die off. We can make the flies produce more or less of a specific protein and see instantly whether this has a beneficial or harmful effect on the photo receptors”, explains Mr. Wanker.

Searching for clues in the blood of healthy and sick subjects

In parallel to these functional tests, therapeutic substances are being tested on mice that have Parkinson’s or Alzheimer’s disease caused by known gene defects. Finally, the genome researchers are also searching for proteins in human blood cells that could be connected with one of the five neurodegenerative diseases; for this purpose, they are comparing the genetic fingerprints of cells from the blood of both sick and healthy subjects.

What happens to all the data? “As the name NeuroNet says”, explains Mr. Wanker, “ultimately, all data will be interconnected by our bioinformaticians and examined using a system-biological approach. We thus develop a comprehensive concept which may allow us for the first time to understand the molecular mechanisms that trigger neurodegenerative diseases”.
From genome research to cancer treatment

After nine semesters of biology at the University of Kaiserslautern and a thesis in plant physiology, Stefan Wiemann was convinced: “I wanted to know more about the molecular basis of life, especially about our genes”. Combining experiments with modelling, he is now searching for new molecular approaches to the diagnosis and treatment of breast cancer.

Stefan Wiemann’s career in science began at the German Cancer Research Centre (DKFZ) in Heidelberg where the scientist from North Rhine-Westphalia, the only molecular biologist in a group of protein chemists, cloned the various gene forms of a certain enzyme. In the course of his research he made a discovery that led to a doctorate with summa cum laude: a new isoform of the gene that is longer than those previously known and might have different functions. “It was not until years later when he saw the protein with his own eyes that my thesis supervisor really believed in my discovery”, says Mr. Wiemann. From this point onwards, his career shadowed the progress of genome research, from the beginnings of the human genome project to functional genome analysis and disease-oriented research using systems biology.

How do the cells react to an excess of these proteins? Do they have an impact on the cell dividing, diversifying, initiating its own death or continuing to grow unchecked?

In 1992, the young scientist moved from the DKFZ to Wilhlem Ansorge, one of the first scientists worldwide to develop DNA sequencing machines, at the European Molecular Biology Laboratory (EMBL) in Heidelberg. “At the EMBL, I worked predominantly as a biochemist optimising enzyme reactions for the sequencing”. He went on to take part in the European yeast genome project and sequenced not only the DNA of several yeast chromosomes but also, for the first time, cDNAs, a new class of synthetically produced nucleic acids. “When the German human genome project kicked off in 1996, I received a call from Annemarie Poustka’s laboratory at the DKFZ asking me to set up and systematically analyse
cDNA libraries”. In the same year, the German cDNA consortium formed to identify new genes; Stefan Wiemann was appointed coordinator in 1997 and remained in this position until the consortium’s dissolution in summer 2008.

“As early as the end of the 1990s, when we were still doing real fundamental research in the human genome project, my former colleague Rainer Peperkok from the EMBL had an idea: Why don’t we express all these cDNAs into proteins and see where they can be located within the cell. And that’s what we did, initially for several hundred of proteins, with Rainer doing the fluorescence microscopy. For the first time we collected functional information”, says Mr. Wiemann. The next questions arose naturally: How do the cells react to an excess of these proteins?

The function of selected proteins (red) is visible under the fluorescence microscope: In this case, it predominantly resides at the cytoskeleton (green) and leads to a reduction of various cell organelles (yellow) in the case of overexpression. The nucleus is blue.
Do they have an influence on the cell dividing, diversifying, initiating its own death or continuing to grow unchecked? “To find the answers we developed a multitude of assays that allowed us to examine human cell lines for apoptosis, cell proliferation, cell cycle, DNA replication and migration – all of which are cancer-relevant properties”.

Suddenly, Stefan Wiemann was involved in medical issues. Now, he no longer examines yeast cells but tumour tissue of breast cancer patients made available to him by Andreas Schneeweiss from Heidelberg’s Gynaecological University Hospital. Since 2001, he has systematically collected functional data of thousands of proteins and makes this valuable archive available to the public on the Internet. “We are constantly updating this database and are about to include the next screening generation”, says the researcher. He is referring to RNAi screening, a new gene suppression method that allows scientists to reduce the production of proteins in the cell and investigate their function (see p. 58).

One protein can assume several functions

At the beginning, Stefan Wiemann analysed each protein individually. Soon, he realised that this would not get him very far. “In many cases, the suppression of individual genes does not lead to any visible changes. However, the inclusion of a second or third gene may have fatal consequences. Cells are complex systems; one single protein often has several functions and many signal paths are linked. This means that several genes have to be analysed in parallel, leading us inevitably to systems biology”. The system-biological approach therefore dominates an NGFN-Plus project coordinated by Mr. Wiemann that involves not only the DKFZ and the EMBL but also Heidelberg’s Gynaecological University Hospital and the Berlin MPI for Molecular Genetics. In this context, the scientists are researching cancer-relevant signal networks – with the help of whole genome screening, function assays and cell microscopy as well as mathematical models.

The interaction between experiment and modelling is to allow the scientists to make predictions regarding the quality of new markers for the diagnosis and prognosis of breast cancer and to find new molecular treatment approaches.

On the basis of Wiemann’s NGFN-Plus project, a further system-biological research association has formed in the context of the BMBF Med-Sys support initiative (see p. 15). Aside from the DKFZ and Heidelberg’s Gynaecological University Hospital, the University of Göttingen, the Freiburg FOR-SYS Centre (see p. 16 to 18) and the pharmaceutical company Roche are involved. The latter is engaged in the development of breast cancer therapeutic agents, including one antibody named Herceptin that has already been licensed. “We are looking for mechanisms that play a role in the formation of resistance against Herceptin as well as further antibodies against breast tumours”, says Stefan Wiemann in describing the aim of the MedSys project. The right combination of different antibodies might overcome such resistances and subdue the cancer. The genome researcher, who has been acting head of the molecular genome analysis department since the death of Annemarie Poustka in May 2008, is convinced. “The promising combinations can best be determined using systems biological approaches”.

There are many different molecular causes of breast cancer. The study group headed by Stefan Wiemann is working to identify the crucial molecules that make breast cancer cells therapy-resistant.
A new point of application for antibiotics

Every year, over 3 million people die of malaria, more than 2 million of AIDS and approximately 600,000 of typhoid. This makes infectious diseases the biggest cause of death worldwide. The diseases are caused by viruses, bacteria or eukaryote parasites. An NGFN-Plus project is researching a little-known group of nucleic acids in the eight most important pathogens: so-called riboregulators which affect the regulation of gene expression and may thus provide a potential target for new drugs.

“Increasing numbers of bacterial pathogens are resistant to available antibiotics. To get a grip on these bacteria we need new weapons in our armoury”, says project coordinator Jürgen Brosius from the Centre for Molecular Inflammation Biology at Münster University. Effective therapies are also needed for non-bacterial pathogens, such as viruses and single cell parasites. “We need to understand the pathogen’s metabolism in each individual case and know how it distinguishes itself from that of the patient”, says Mr. Brosius. The genome researcher is of the opinion that research may not exclusively focus on proteins: “Today we know that RNA molecules are also involved in important metabolic processes in the cell”. Mr. Brosius himself has made a crucial contribution to this knowledge: For two decades, he has been studying non-protein coded RNA molecules, so-called ncRNAs, which in contrast to well-known messenger RNA, for example, do not serve as masters for protein molecules. “In the past, these ncRNAs were routinely thrown out. We have collected them and have discovered a multitude of new molecules, among them one that is predominantly expressed in nerve cells”, explains Mr. Brosius. In the context of an NGFN-2 project, he found evidence that the absence of this molecule is partly responsible for a form of mental disability, the Prader-Willi syndrome.

When antibiotics are no longer effective

The NGFN-Plus project focuses on eight serious infectious diseases: AIDS, typhoid, meningitis, pneumonia, stomach ulcers, toxoplasmosis, diarrhoea and malaria. The pathogens of these diseases differ significantly in their molecular structure, life cycle and infectious properties. Nevertheless, their genetic makeup consists of the same DNA and RNA nucleic acids. The consortium, consisting of Brosius’ group as well as scientists from the German Primate Centre at Göttingen, the Bio-Centre Würzburg and the two Berlin-based MPIs for Infection Biology and for Molecular Genetics, is working to identify riboregulators and further ncRNAs in all eight pathogens that affect the disease process. In parallel, they are investigating the question of how infections change the RNA profiles of the host cells. “Single-stranded areas of ncRNAs can easily be blocked with complimentary strands”, explains Mr. Brosius. However, according to the scientists, specific ncRNAs, which are essential for the pathogen, had to be identified first. “These are candidates for the future development of new drugs”. Several toxoplasmosis pathogens, marked in red with the help of fluorescent antibodies, have encapsulated themselves in a skin cell.
Silencing specific genes

The importance of the accelerator and the brake in a car becomes evident when one of the two fails. Function analysis of genes works on the same principle: One gene is taken out of operation and the resultant effects or defects are analysed. The property of a naturally occurring class of smaller RNA molecules, the small interfering RNA or siRNA, is exploited by one of the main gene silencing methods.

When siRNA interacts with the primary copy of a gene, it prevents the production of the final gene product. In living cells, many short siRNAs arise via the enzymatic dismantling of a longer RNA precursor. Today, individual siRNAs can be synthesised in the laboratory and used in functional genome research. However, synthetic siRNAs have significant disadvantages. “They are expensive and, even worse, often unspecific”, says Frank Buchholz from the MPI for Molecular Cell Biology and Genetics in Dresden, who made this discovery in the context of the NGFN-2 project. In conjunction with the industrial partners Cenix Bioscience (see adjacent interview) and the German Resource Centre for Genome Research (RZPD), the MPI Dresden developed a new class of gene blockers. Similar to living organisms, they are generated via the enzymatic dismantling of a long precursor.

“This presents us with a pool of large numbers of different esiRNAs. In combination, they silence the selected gene far more effectively and selectively than individual synthetic siRNAs”, explains Buchholz. The NHFN-2 team used the high-throughput process to generate esiRNAs against close to 16,000 human and mouse genes. This extensive library is a valuable tool in the functional analysis of mammal genes. “Our laboratory can no longer deal with the numerous enquiries we receive”, says Buchholz. Consequently, a follow-up BMBF project is preparing to set up a separate company to outsource the commercial production of esiRNAs.
A new active pharmaceutical ingredient against malaria

Interview with Dr. Birte Sönnichsen, Cenix Bioscience

How long has Cenix Bioscience been doing research in conjunction with academic institutions?

As early as 1999, the year our company was established, we were involved in a sub-project of the German Human Genome Project. In the context of NGFN-2, we focused on esi-RNA technology (see adjacent article). Eventually, we set up a high-throughput service platform that provided other working groups with efficient access to this technology.

What is the objective of the current NGFN-Transfer project?

We are working to identify an active pharmaceutical ingredient against malaria that is effective at an early stage of the infection when the parasite is settling in the liver and has not yet multiplied in the blood. We are focusing on host factors that are essential for the parasite but not for liver function. In conjunction with Maria Mota from the University of Lisbon we have analysed over 800 liver cell genes using RNAi. This is how we found the receptor molecule needed by the parasite to get into the host cell. We are now looking for agents that block the receptor. In parallel, we are improving the screening platform to allow us to search for targets for potential anti-malaria agents on the whole human genome.

How well do you work with your academic partners?

Collaboration between us is very smooth and efficient! We identify molecules in the host cell that are important for the parasite. Subsequently, Kai Matuschewski from the MPI for Infection Biology in Berlin identifies the equivalent in the parasite’s genome. And Friedrich Frischknecht from the University of Heidelberg develops imaging assays on the fluorescence microscope for a detailed view of the functions of specific molecules and the substances we need to manipulate them.

Are the research results made available for commercial use?

We are in contact with the ‘Medicines for Malaria Venture’ (MMV), a public-private partnership promoting the development of affordable anti-malaria drugs. Furthermore, we are talking to pharmaceutical companies that also work together with MMV and other support organisations.

The mobility of the crescent-shaped sporozoites of the malaria pathogen determines whether they can actually enter the liver cells. Layered and coloured film recordings show the paths (red) taken by individual cells between the start (green) and end positions (violet).
Risk to heart and kidneys

Patients with progressive chronic kidney failure need to undergo dialysis to prevent death from acute poisoning. However, even regular blood purification does not prevent patients from having a short life expectancy. "Most dialysis patients die after 10 to 15 years, almost exclusively as a consequence of cardiovascular diseases", says Joachim Jankowski from Berlin’s Charité. An NGFN-Transfer project focuses on the little researched association between renal failure and cardiovascular diseases.

The research association consists of Essen University Hospital, the Berlin MPI for Genetics and the industrial partners Schering Pharma und ExcorLab. It is the aim of the consortium to develop new measures to diagnose, prevent and treat cardiovascular diseases.

"Cardiovascular diseases are indirectly determined by our genes"

Vera Jankowski, the project’s bioanalysis coordinator, is working on the isolation and identification of trigger substances. "We are screening close to a hundred known mediators with toxic effects that accumulate in the plasma of dialysis patients", says the biochemist. "In addition, we are screening tissue and bodily fluids of patients with different degrees of renal insufficiency for previously unknown substances with cardiovascular effects. If we find any substances, we may be able to disarm them, either through selective dialysis or novel therapies". The consortium has already detected several candidates in the form of peptides, which are direct gene products. That is why Joachim Jankowski is convinced that "cardiovascular diseases are, at least indirectly, genetically determined".

To date, it is not yet known which substances trigger the cardiovascular damage. "Apparently, it is not severed through dialysis and accumulates in patients with kidney diseases", explains Joachim Jankowski, "which is why the patients inevitably get heart problems. Presumably, the same substances also lead to cardiovascular diseases in healthy persons, albeit at a significantly slower rate".
## Register of persons

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