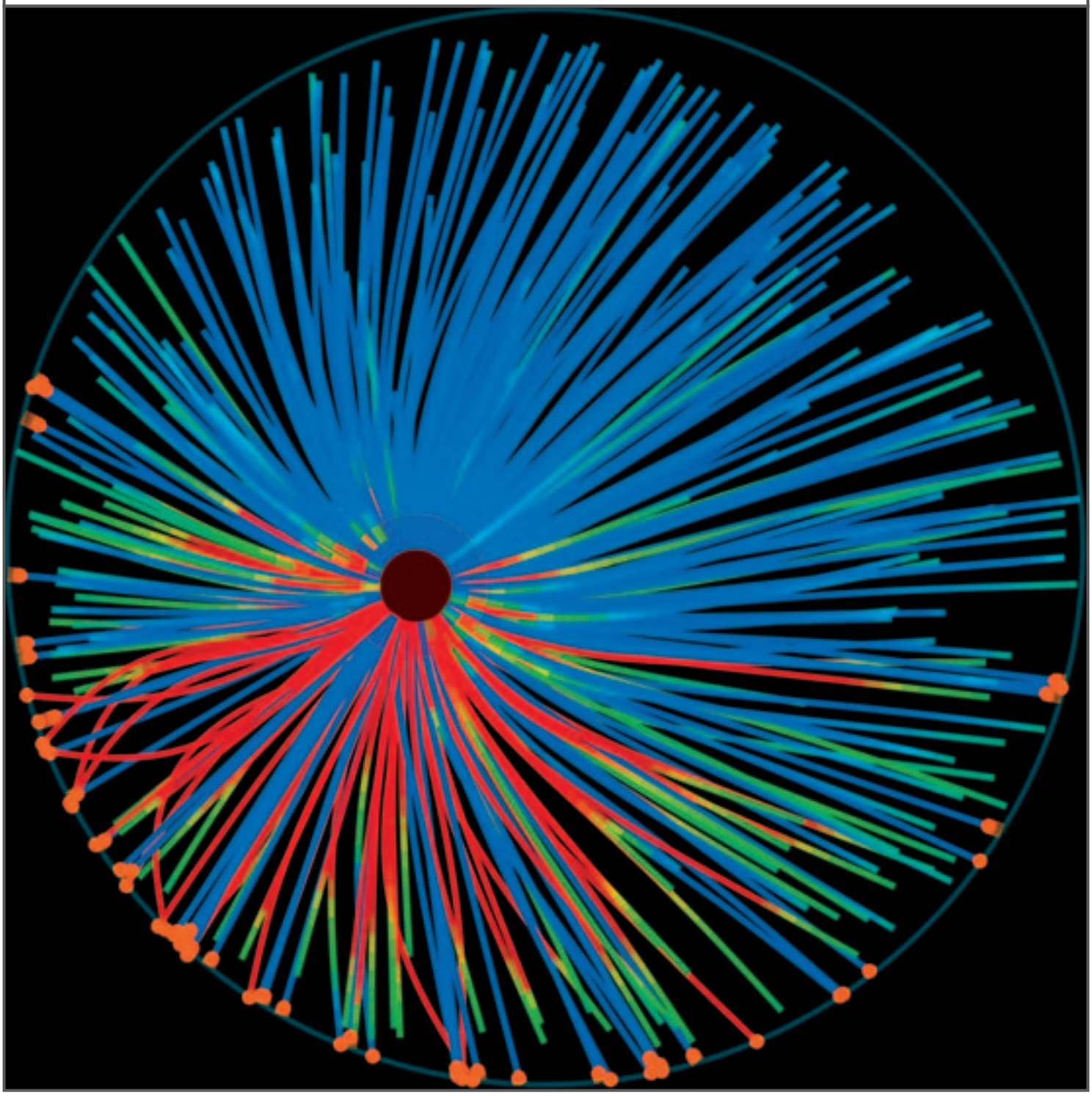
BioQuant.

Center for quantitative Analysis of molecular and cellular Biosystems

University of Heidelberg

BioQuant
MODEL base of LIFE



The Optical Connection

The current English brochure for BioQuant, the innovative research center for systems biology at the University of Heidelberg, makes use of the newly designed image for the first time.

The new BioQuant logo provides a simplified representation of the merging of life sciences and scientific computing. The focal point of the logo is a graphic portrayal of the Fibonacci sequence. Fibonacci (Leonardo von Pisa, abbreviated to "Filius Bonacci") identified this sequence of numbers, which is defined by a recurrence relation, at the start of the 13th century. It assumes that the numbers zero and one are the first two numbers. The numbers which follow derive from the respective sum of their two predecessors.

A number of natural additive growth processes can be described using the Fibonacci numbers. This characteristic geometry can be observed in, for example, the growth of the nautilus' shell or the pattern created by of the arrangement florets in the head of a sunflower. The golden angle emerges naturally. The golden angle is a geometric representation of the Fibonacci sequence and creates a visualisation of the laws that govern the growth of every living organism.

This is also the method which was used to create the BioQuant logo. Two segments of a circle, equal in size, form the logo's central origin, representing the two sciences of equal status at BioQuant.

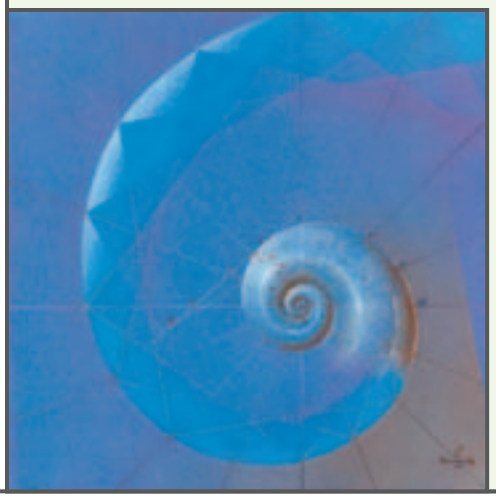
The spiral structure of a biological shape, continually opening and expanding outwards in accordance with the Fibonacci sequence, develops from the starting elements in the new BioQuant colours, light blue and light green. This symbolises the wide spectrum of uses and the diverse future applications for BioQuant's research.

The Fibonacci graphic is then framed by squares symbolising BioQuant's own custom-built premises with spaces for communication and interaction which serve as the new home of the internationally-oriented research teams.

The motto, "MODEL base of LIFE", further emphasizes the message of merging life sciences and scientific computing.

Further reading

Lutz, Franz Xaver. 2007. Ein mathematisches Kunstbuch – ein künstlerisches Mathematikbuch.
Exhibition catalogue, First Publication of the Klaus Tschira Foundation gGmbH series.



"Spiralenuhr",
© Franz Xaver Lutz

Frontpage: A computer model of spindle motions during anaphase in *C. elegans* embryos. Accurate spindle positioning is a key prerequisite of asymmetric cell division.

Index

A new research design and a unique opportunity

Dear reader,

With BioQuant Heidelberg University founded a new research design aiming at a comprehensive understanding of the complex biological factors that make life possible. The BioQuant network supports interdisciplinary collaborations between research groups from the biological/biomedical sciences and researchers in the fields of chemistry, physics, mathematics, and computer sciences to obtain a quantitative and system-oriented understanding of biological processes.

This project can fairly claim to be all but unique in Europe and it represents a major advance in the experimental life sciences. With the funding provided by the state government for the construction of a central BioQuant location in Heidelberg the University has been given a unique opportunity to intertwine an innovative research design with a building specially conceived for the purpose and thus to forge a functional unit out of these two components. Accordingly, BioQuant represents a major advance not only for interdisciplinary research within the University itself but also for the numerous connections with non-university research institutions in the area of Heidelberg and the cooperation between the University and industry. Within the framework of the BioQuant project industrial partners have already embarked on collaboration with University research groups. This gives them a unique opportunity to test their products and develop them further in an ongoing exchange of experience with research scientists. The scientists of Heidelberg University have ideal

"A new research design aiming at a comprehensive understanding of the complex biological factors that make life possible."

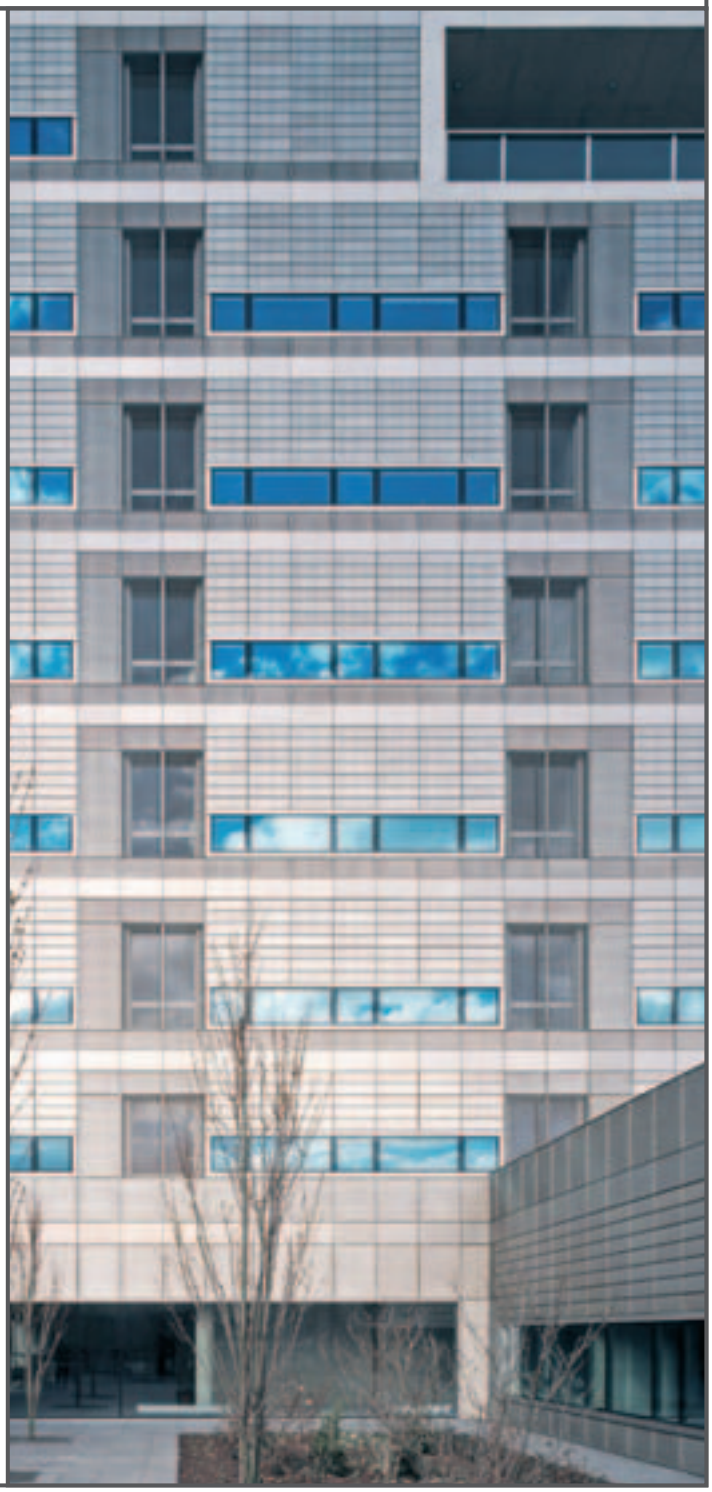
Bernhard Eitel

conditions in which to teach and pursue their research and with these conditions it is not surprising that a cluster of excellence and a graduate school which draw on this concept were successful in the excellence initiative by the German Federal and State Governments but could also be successfully integrated into the BioQuant network.

The BioQuant network is indeed fortunate in having Professor Roland Eils, Professor Hans-Georg Kräusslich and Professor Jürgen Wolfrum as its founding directors. These three scientists are a far reaching visible sign that BioQuant puts a world wide unique collaboration between different disciplines into effect.

Last but not least, Heidelberg University wishes to express its gratitude to the state of Baden-Württemberg, to all the scientists involved in the BioQuant project and to the University Planning Department for their visions and their outstanding commitment to the undertaking. We expectantly look forward to the first scientific and practical fruits of this ambitious interdisciplinary venture.

Bernhard Eitel
Rector of University of Heidelberg



BioQuant. A New Research Network in Heidelberg

Dear reader,

Understanding the amazing diversity and the equally astounding efficiency of living structures is one of the great scientific challenges of the 21st century. Animate systems display an extraordinary degree of interaction between chemical reactions and the different physical processes regulating the transport of matter, energy and information. The sheer abundance of the phenomena involved is entirely beyond the scope of the trial-and-error methods prevalent in traditional scientific inquiry. What we need now is a strategic approach capable of measuring up to the extreme complexity of life in all its forms. Accordingly, mathematical models and the latest imaging techniques, to name only two examples, will be integral resources in the testing of scientific hypotheses both now and in future.

Heidelberg is an ideal location for such an approach. The University's Interdisciplinary Center for Scientific Computing (IWR) is internationally acknowledged as a leading research institution for the development and application of mathematical models. In addition, Heidelberg can look back on a long and eminent tradition in chemical kinetics and molecular biology. In the early 20th century the chemist Max Bodenstein laid the foundations for the mathematical description of elementary chemical reactions. And it was here that the Nobel Prize laureates Albrecht Kossel and Otto Meyerhof discovered the components of molecular machines and important energy-generating cycles in biological reaction sequences. In the aftermath of these and many other discoveries the University of Heidelberg has developed into an internationally respected center for modern research in molecular biology, with renowned institutions like the Center for Molecular Biology (ZMBH), the Center for Biochemistry (BZH) and

"Scientists from different disciplines will be working together to find a common language capable of adequately describing the complexity of life."

Jürgen Wolfrum

the Interdisciplinary Center for Neurosciences (IZN). Leading non-university institutions have also established themselves in the city, including the European Molecular Biology Laboratory (EMBL), the German Cancer Research Center (DKFZ) and the Max Planck Institute for Medical Research.

The BioQuant network, Europe's first center for quantitative biology, intends to make the most of this enormous potential. Mathematicians, computer scientists, chemists, biochemists, physicists and medical researchers will be working together to find a "common language" capable of adequately describing complex life processes. The creativity required for such a purpose cannot be "organized." It needs a communicative setting and an atmosphere in which new developments can materialize and thrive undisturbed.

With its extensive foyer areas and green inner courtyards the BioQuant research building conceived by Berlin architect Volker Staab is a superb location for close cooperation between basic biological/medical research and mathematical modeling. More importantly still, it is an ideal setting for collaborative exchange, thought and action, facilitating communication across traditional research boundaries and the kind of interdisciplinary cooperation that can engender highly productive "role switches": a mathematician may suggest a biological experiment, a chemist will come up with the solution of a mathematical problem, physicists and medical researchers work hand in hand. Common to all is the enthusiasm for the tasks they are involved in.
Key features in experimental work will be high-resolution and high-throughput microscopic diagnostics combined with digital image processing. Classical microscopy will be exploring new avenues for the direct observation of biomolecules. Proceeding from individual molecules the subsequent task will be to achieve the quantitative description of larger molecular complexes, cells, tissues, organs and populations.

With the help of joint funding from the state of Baden-Württemberg, the Klaus Tschira Foundation, the University of Heidelberg, EMBL, DKFZ , the EML Research gGmbH and the Max Planck Institute for Medical Research, several junior research groups started in the Center for Modelling and Simulation in Biosciences(BIOMS). With the VIROQUANT project supported by the Federal Ministry of Education and Research and the Cluster of Excellence "Cellular Networks" two major research collaborations could be established in BioQuant with a number of new junior research groups and professorships.

This brochure is designed to acquaint you with the vision that BioQuant stands for and with some selected examples of ongoing research work.

I hope you will find it interesting reading.

Jürgen Wolfrum
Founding Director of BioQuant

A Puzzle with Thousands of Pieces: Understanding the Complexity of Life

The mass of data produced by the biosciences over the last few years is immense. Systems biology is a new, interdisciplinary research field that attempts to integrate these data into mathematical models. Roland Eils, founding director of BioQuant, explains why systems biology is necessary and outlines the formidable mission it has set out to fulfil: assembling thousands of different puzzle pieces to form a unified picture of life.

The Human Genome Project's ambitious programme has been to identify all the genes present in the human organism. The immense amount of data and the progress achieved by this programme and various other high-throughput projects have given biomedical research an entirely new definition. The challenge now is to incorporate these gigantic masses of information into meaningful models and to integrate our molecular and cellular insights at a higher level - the level of tissues, organs and organisms. It is for this purpose that the University of Heidelberg has established BioQuant, Europe's first center for quantitative biology. BioQuant is the German counterpart to other centers of excellence for quantitative biology taking shape in the United States and Japan.

More than the sum of its parts

The terms "quantitative biology" and "systems biology" are only a few years old. They reflect a paradigmatic shift in the life sciences based on heightened awareness of the fact that living systems are more than the sum of their parts. They can only be truly understood as complex wholes. The reductionist approach hitherto prevalent in the natural sciences concentrated on investigating individual parts of these systems, intentionally refraining from adopting an overall perspective on biological processes. One reason for this is the immensity of the tasks involved in taking a holistic view of complex systems. Another is the scientific

"The term systems biology reflects a paradigm shift in the life sciences."

Roland Eils

precept, upheld above all in physics, that investigation should be largely restricted to well-defined systems manageable enough to be described in terms of physical laws.

It has taken quite some time to realise that the crucial task is in fact to describe dynamic, spatially and temporally resolved, non-linear systems far removed from thermodynamic equilibrium. We need to understand them because they are the systems that make life possible in the first place. The reductionist approach was essential in identifying the key factors of crucially important biological processes. But all life processes are the result of interaction between very different units and modules. Accordingly, modern bioscience must take a holistic view. If we restrict ourselves to the study of local events or isolated parts, we will never achieve an accurate description and understanding of complex life processes.

At present, systems biologists are working on highly developed, computer-assisted models for the analysis of the plethora of data the new technologies have generated. In this way they can decode complex, intricately connected biological processes and devise realistic models of what actually goes on in cells, tissues and organisms. Ultra-modern computers, the latest developments in information technology, global data networks and gigantic databases make mathematical simulation increasingly important - and an increasingly feasible proposition. There is no doubt whatever that computer-assisted modeling will be an indispensable factor in future life science research.

BioQuant is the ideal setting for this highly up-to-date and hugely promising research strategy. It unites experimental scientists and theoreticians, and its objective is to represent a platform for the constant refinement of models and the swift validation of scientific hypotheses via experimental data. A further crucial aim of BioQuant is to achieve the greatest possible speed in transferring the scientific knowledge obtained with these methods to clinical application for the benefit of patients.

Central Terms in Systems Biology

in vitro "in the test tube". Ideally all parameters are controlled, one variable is changed and the effect on the system measured.

in vivo "in the living system", normally in cell cultures or animal experiments. Here one variable is changed and the impact on the system measured with reference to a limited number of parameters. The reaction studied takes place in its "natural" environment. This process may also involve events that cannot be controlled, although they may have an influence on the reaction under investigation. In vivo investigation is used to substantiate results obtained in vitro.

in silico "in the computer". The data and the regularities derived from in vitro and in vivo experimentation are translated into mathematical models forming the basis for computer-assisted simulations of biological processes. These simulations predict the results of experimental modifications of individual parameters. The predictions are then tested in "real-life" experiments. If the experimental results agree with the model predictions, then they validate the model. If they deviate from the predictions, the mathematical model has to be adjusted accordingly.

systems biology In systems biology large amounts of data obtained in vitro and in vivo are combined in silico and go through many experimental refinement cycles up to final validation. The approach aims at achieving a holistic picture of biological processes as they actually take place in organisms.

Integrating huge amount of data into reasonable mathematic models – one of the major goals of Roland Eils' research group.

Pioneering Approaches

Soon computers will be an absolutely indispensable factor in experimental biology. Without their assistance life processes cannot be described in all their complexity. Hans-Georg Kräusslich, founding director of BioQuant, tells us why research networks are more important than ever for the understanding of dynamic systems and why BioQuant is ideal for the purpose.

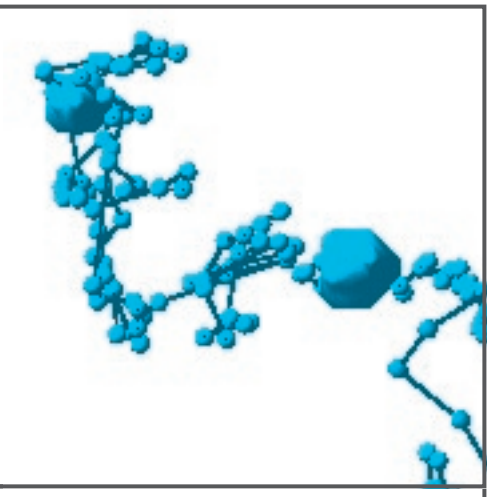
An "investment of key significance for the future of Baden-Württemberg as a research and education location" - these were the words used by then state premier Erwin Teufel and higher-education minister Professor Peter Frankenberg to refer to the BioQuant research network. The Council of Ministers of the state of Baden-Württemberg decided to establish this network in early 2002. This decision was based on a proposal by the University of Heidelberg made on behalf of all the science Faculties (including medicine) and the central institutions of the University. Thus the University of Heidelberg paved the way for the establishment of the emerging research field known as "systems biology" or "quantitative biology" at a very early stage in its development.

Three major research projects

In the meantime we have succeeded in obtaining substantial funding for three collaborative projects. At the systems biology research center VIROQUANT (Systems Biology of Virus-Cell Interaction) supported by the Federal Ministry of Education and Research (BMBF) we will systematically develop model-based approaches for investigating the complex processes involved in virus-cell interaction. This project is unique in the world and combines the expertise of research groups from the following

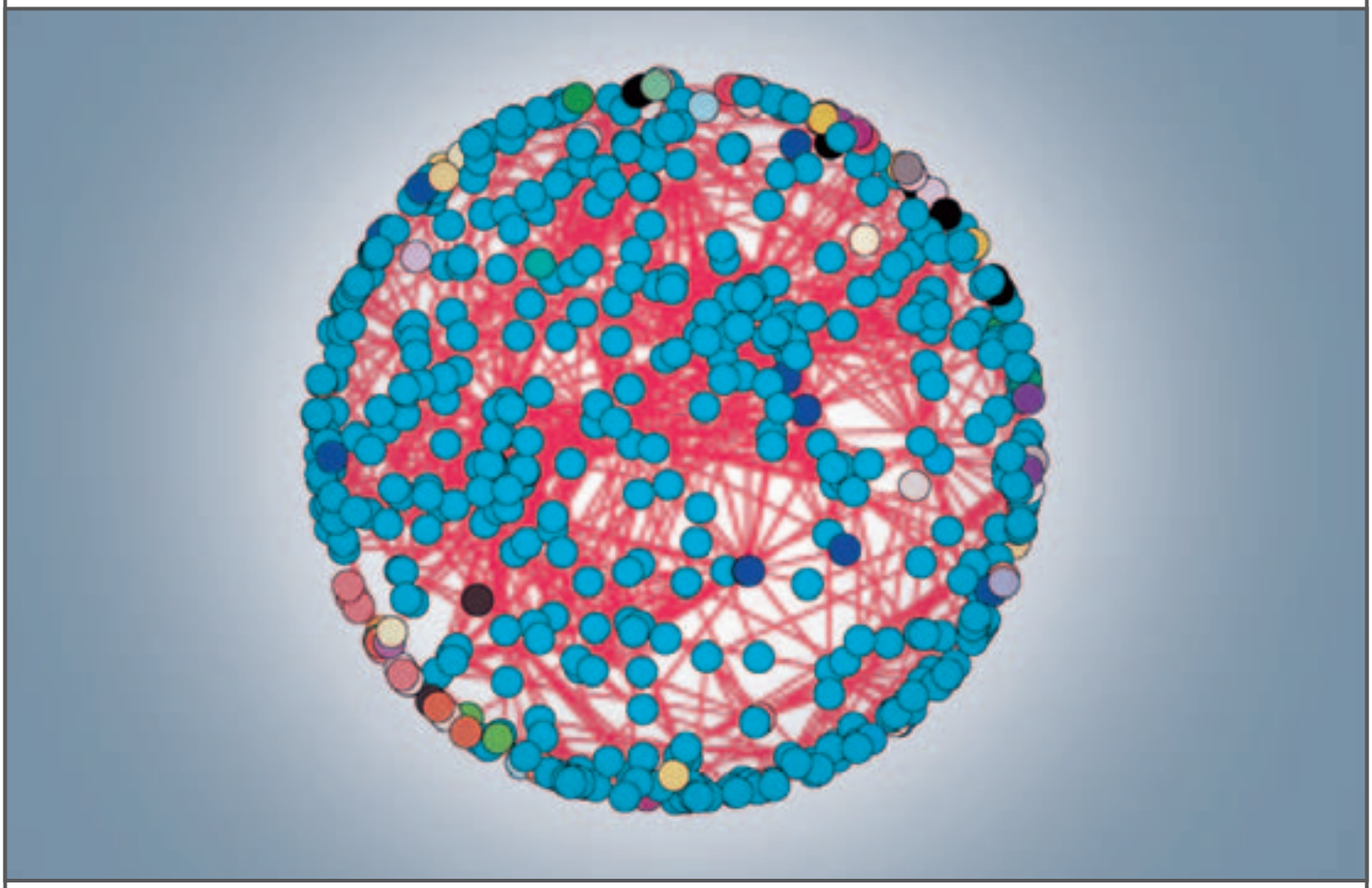
"New angles of vision open up prospects for improving the treatment of infections and diseases like cancer."

Hans-Georg Kräusslich



fields: cell-based high-throughput screening, high-resolution microscopy, biosensorics, parallel data banks, mathematical modeling and virology. These groups are affiliated to various Heidelberg research institutions and will all be working under one roof on the BioQuant premises. Unlike traditional antiviral strategies which are targeted at the viral system itself, approaches developed by VIROQUANT will focus on the interplay between viruses and host cells. This will give us opportunities to develop completely new strategies for combating viral diseases for which there are no effective therapies available at the moment.

The SBCANCER network (Systems Biology of Signaling in Cancer) is devoted to achieving a systematic understanding of the role played by disorders of cellular signal transmission paths

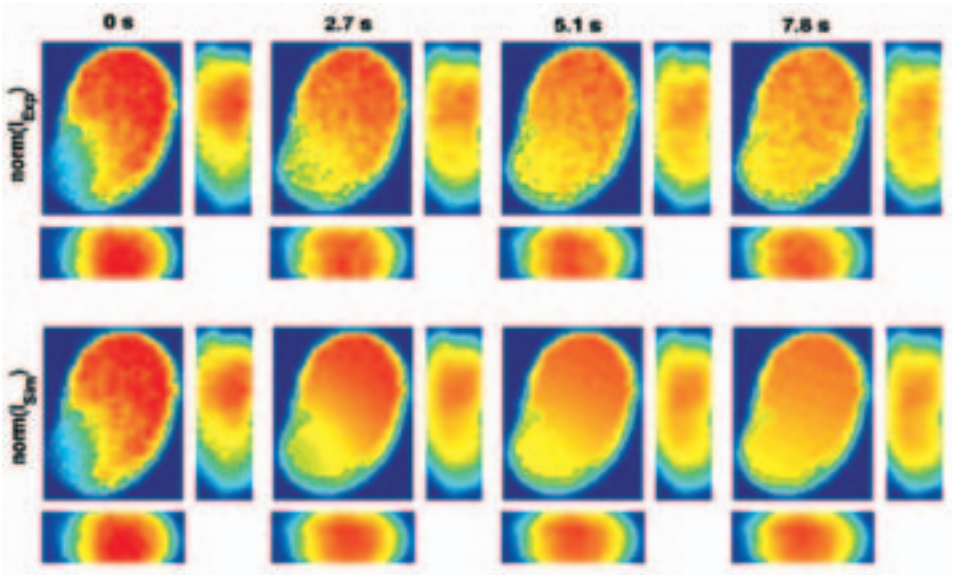


Metabolic network: Model of the *Escherichia coli (E.coli)* metabolism. The bacteria *E.coli* is a habitant of the human colon.

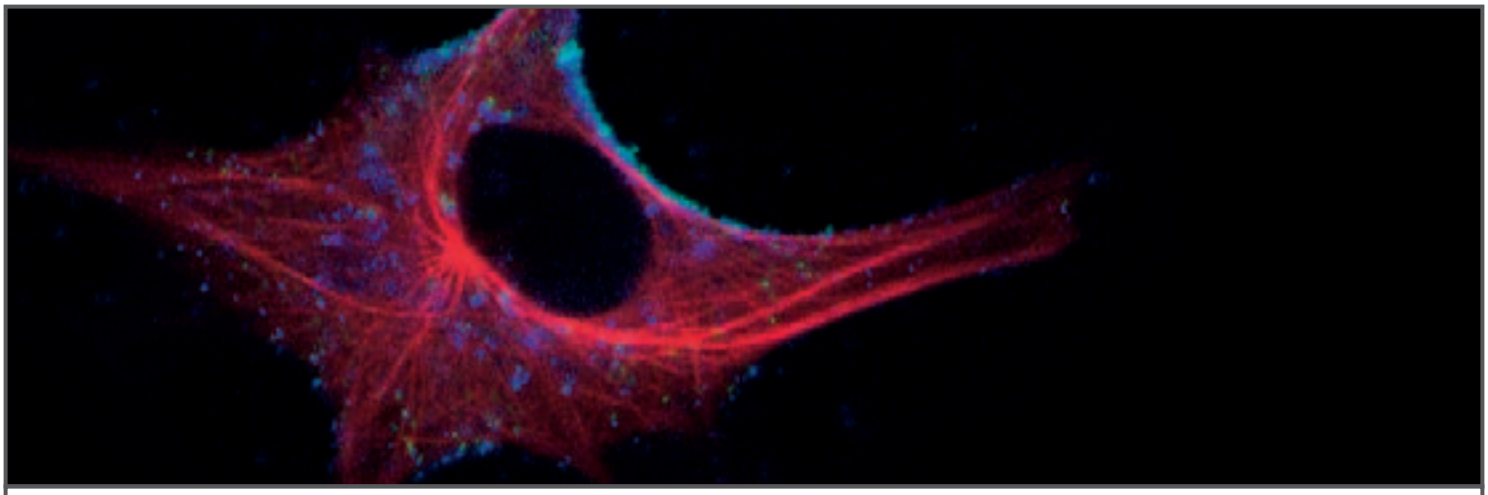
in the genesis of cancer. The consortium operates under the aegis of the German Cancer Research Center (DKFZ), consists of 50 research groups belonging to the DKFZ, the University of Heidelberg and other renowned institutions, and is funded by the Helmholtz Association of German Research Centers. In this network, research groups from the University of Heidelberg working in the field of scientific computing contribute their knowledge and experience in an attempt to understand cancer as "a disease affecting cellular networks". Here again, the essential objective is to achieve a new understanding of cancer from a systems-based perspective.

The Cluster of Excellence "Cellular Networks" receiving funding in the framework of the Initiative for Excellence will also be closely associated with BioQuant. Two new chairs and a number of young research groups investigating such matters as modern methods in cryo-electron microscopy and the evolution of proteins will be based at the BioQuant location. Central objectives of the Cluster of Excellence are to describe complex intra- and inter-cellular networks, understand the dynamics inherent in them, and achieve a systems-based understanding of their regulation.

Protein kinetics in living cells



Experiment (top) and simulation (bottom).



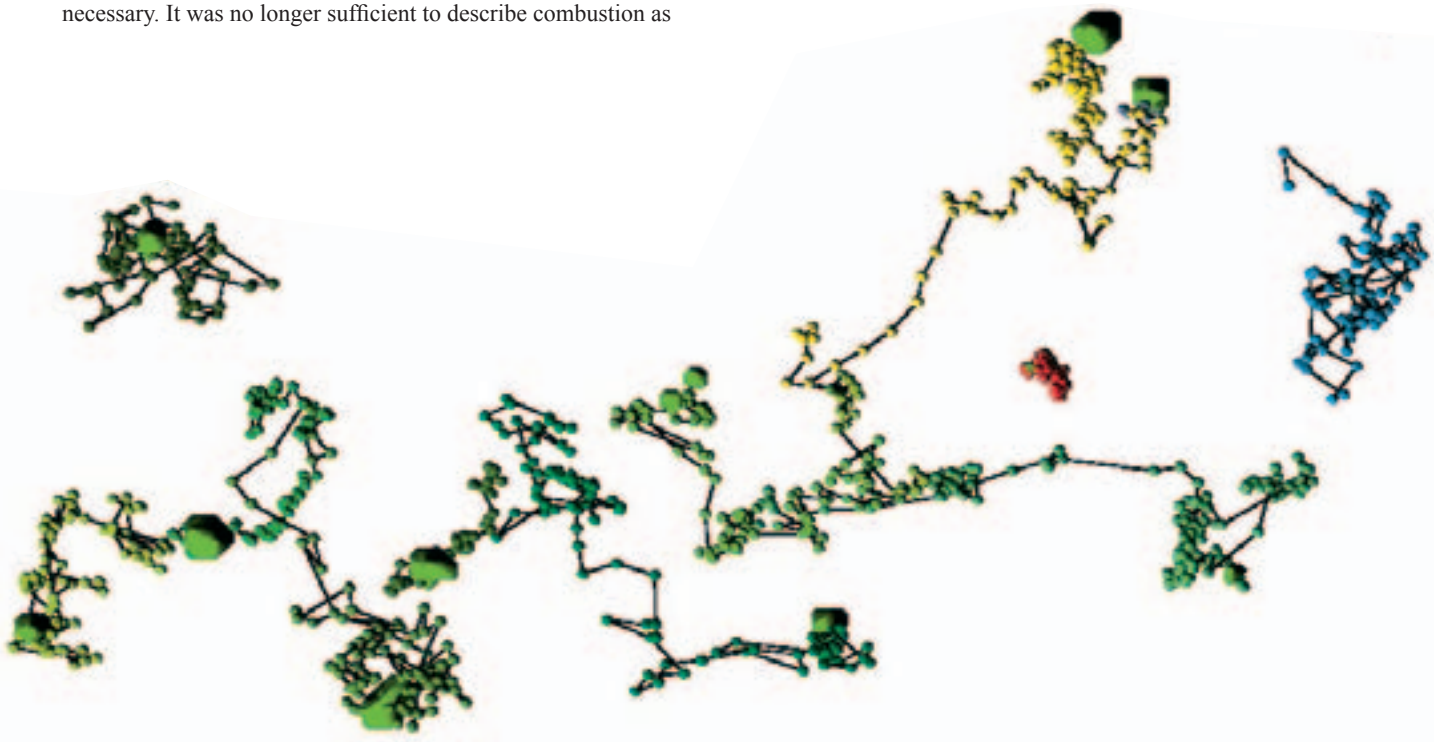
Studying the dynamics of virus-cell interactions: Virus particles (green and blue spots) are utilizing the cytoskeleton of a cell (in red) to move through the host cell.

Dynamic interaction

One example of the kind of goals aimed at by the BioQuant project and the way experimental and theoretical research can be dovetailed is the TECFLAM integrated research project. It has been operating in Heidelberg for some 20 years and its aim is to optimise technical combustion processes with the aid of mathematical simulation and non-invasive laser-spectroscopic analysis. The motivation for the research project was the realisation that environment-friendly, efficient and innovative combustion techniques could not be advanced quickly enough with the empirical approaches customary up to that point.

In this research field, as in the life sciences today, it became obvious back in the early 1980s that a radically new approach was necessary. It was no longer sufficient to describe combustion as the sum of the events going on within it. Rather, it was essential to reconstruct those events from the microscopic, chemical and physical processes involved and to derive the visible effects from this in a "holistic" way. This alone made it possible to identify the causes triggering the formation of pollutants or incomplete combustion and to devise optimal solutions based on mathematical models.

The Heidelberg BioQuant network intends to achieve something very similar in the life sciences. The objective is to identify all the biochemical components involved in complex processes, to attain a detailed understanding of their dynamic interaction with different transport and information processes, and to represent that interaction in computer models.



With the aim to develop novel antiviral therapeutic, researchers at BioQuant track the interactions of viruses with the protein machinery of their host cells.

Architecture for Collaborative Research

Heidelberg's BioQuant location is Europe's very first quantitative biology center. Superbly equipped labs, offices and lecture halls centrally situated on the University of Heidelberg's life science campus provide unbeatable conditions for interdisciplinary research at the interface between mathematics and the life sciences. Angret Joester, facility manager of the BioQuant building, presents the special features of the BioQuant network's new homebase.

The BioQuant building is the heart of the BioQuant scientific network. Here life scientists and theorists find ideal conditions for their collaborative projects. The laboratories and offices at the disposal of researchers from different Faculties and non-university research institutions are all within close reach of one another, thus creating the spatial prerequisites for the establishment of an entirely new culture of interdisciplinary interaction.

The history of BioQuant

In 2001 the government of Baden-Württemberg invited the universities of the state to participate in a competition for the establishment of innovative research centers in the life sciences. The University of Heidelberg's proposal for the "establishment of a central location for a cross-center network of competence in the quantitative analysis of molecular and cellular biosystems (BioQuant)" found favour and in January 2002 the Council of Ministers approved the funding for the new BioQuant research building (26.9 million euros).

Distinguished architecture at a pivotal location

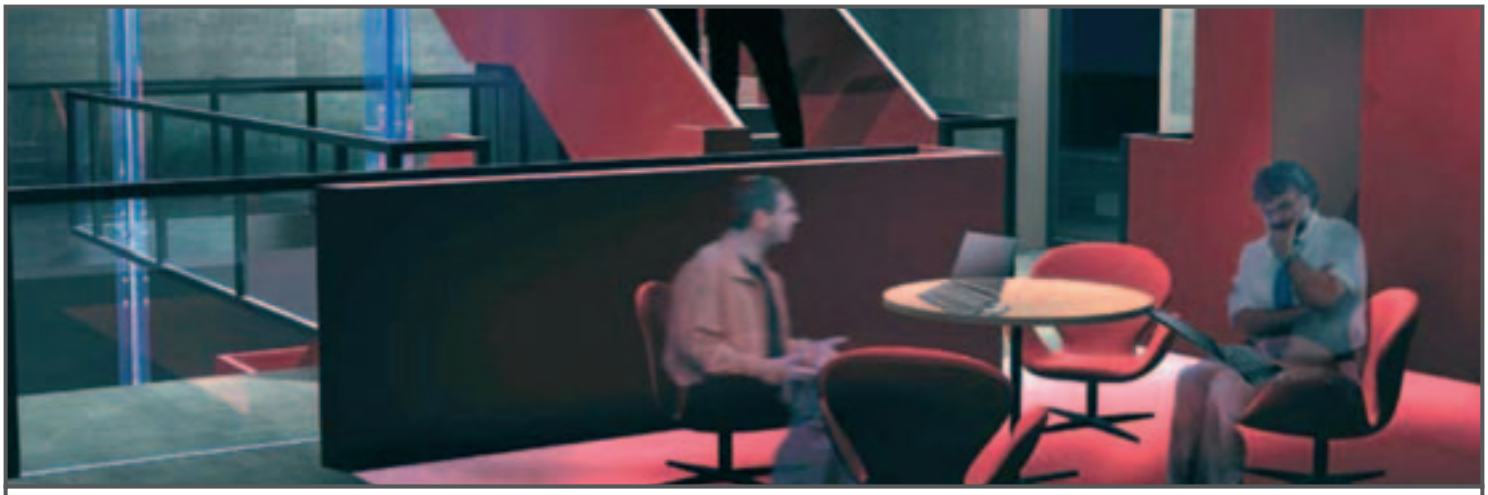
The BioQuant building is situated at the very center of the Heidelberg life science campus "Im Neuenheimer Feld". It is surrounded by the University's institutes for the biosciences, medicine, chemistry, physics, and scientific computing. The German Cancer Research Center and the Max Planck Institute for Medical Research are within easy walking distance.

The plans for the new BioQuant building were devised by Staab Architekten, Berlin. The clinching features of the architectural concept are the optimal translation of the underlying research and communication concept into a structural design and the harmonious integration of the new building into the existing architectural landscape.

The three functional sectors of BioQuant, research, method development and teaching are located on different levels of the building.

The structure of the high-rise building (first to sixth floor) is an architectural reflection of the interdisciplinary collaboration between experimental biological and medical research, on the one hand, and the mathematical disciplines on the other. On each storey, the north side of the building houses laboratories and auxiliary rooms for the life sciences, while the south side contains offices equipped with the infrastructure required for scientific computing.

The laboratories in the basement of the BioQuant building provide superbly equipped working areas for groups dedicating their activities to the further development of modern microscopy methods extending to maximum-resolution optical and cryo-electron microscopy.



Next to the stairway connecting the different levels, a light object by swiss artist Christopher Hunziker is providing an additional transparent and almost free-floating link through the entire building. The dynamic processes involved in research are reflected by the changing light fluxes within the sculpture.

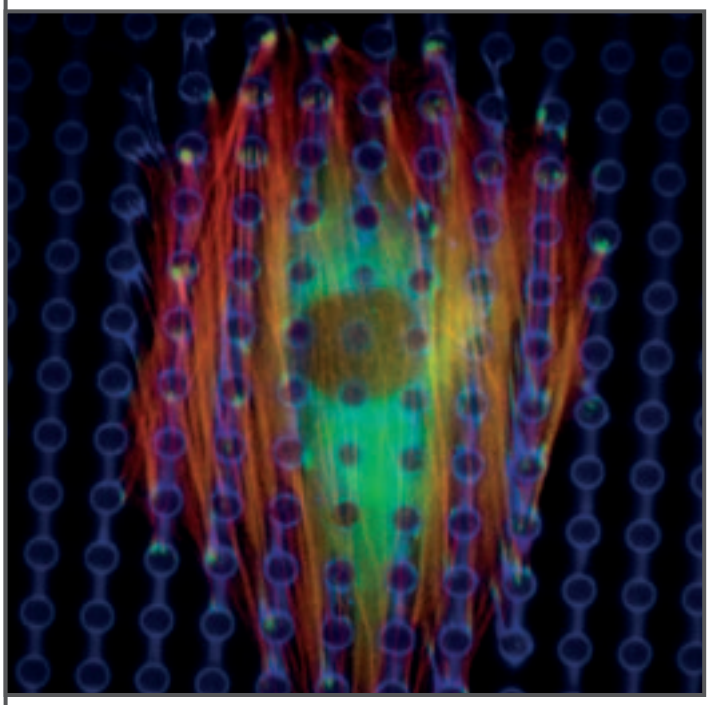
The ground floor houses a lecture hall, severeal seminar rooms and laboratories for theoretical and practical scientific instruction. The teaching rooms serve not only for the cross-faculty instruction of budding researchers in the fundamentals and methods of quantitative biology but also for the continuing education of the scientists involved in the BioQuant network. An additional conference hall is situated on the seventh storey.

The different functional areas of the BioQuant building converge in the central hall that connects all parts of the building by an almost free standing stairway construction extending from the basement to the top storey. This open-plan design with integrated meeting areas establishes a communicative axis throughout the entire building. It is complemented by two green inner courtyards and extensive foyer areas that prove to be ideal for informal communication.

Connections Are Crucial

To function properly cells need contacts. Those contacts are provided by proteins connecting cells either with other cells or with the surrounding "matrix". Ulrich Schwarz and Joachim Spatz describe what can happen when things go wrong and outline the methods that promise a better understanding of cell relations.

The human body consists of 10^{13} cells belonging to over 200 different cell types. To function properly cells have to satisfy two conditions that at first glance appear to be contradictory. They have to stick to one another, otherwise our bodies would fall apart. At the same time they have to be able to separate and reorganize themselves, otherwise our bodies could not grow, respond to injury or deal with illnesses.



Novel tools from materials science allow us to investigate cell behaviour in controlled environments. Here the organization of the actin cytoskeleton (red) is determined by the underlying microstructure covered with adhesion molecules (blue).

Like children on a climbing frame

Nature resolves this apparent contradiction with a variety of dynamic connections between cells. Some enable them to establish new contacts, others ensure the structural identity of tissues and organs. In many parts of our bodies there also exists a structural element called the "extracellular matrix", a polymer network secreted by the cells that allows them to move around like children on a climbing frame.

The extracellular matrix can be regarded as a counterpart to the cytoskeleton. The cytoskeleton is another polymer network, this time in the interior of cells, giving them support and shape, just like an ordinary skeleton. In multicellular organisms most cell types only work properly if they have contact with other cells or the extracellular matrix. These contacts are especially important when cells replicate or differentiate, that is when they mature into "adult" cells with specific functions. If cells lose contact with other cells or the extracellular matrix, they either die or proliferate in an uncontrolled manner.

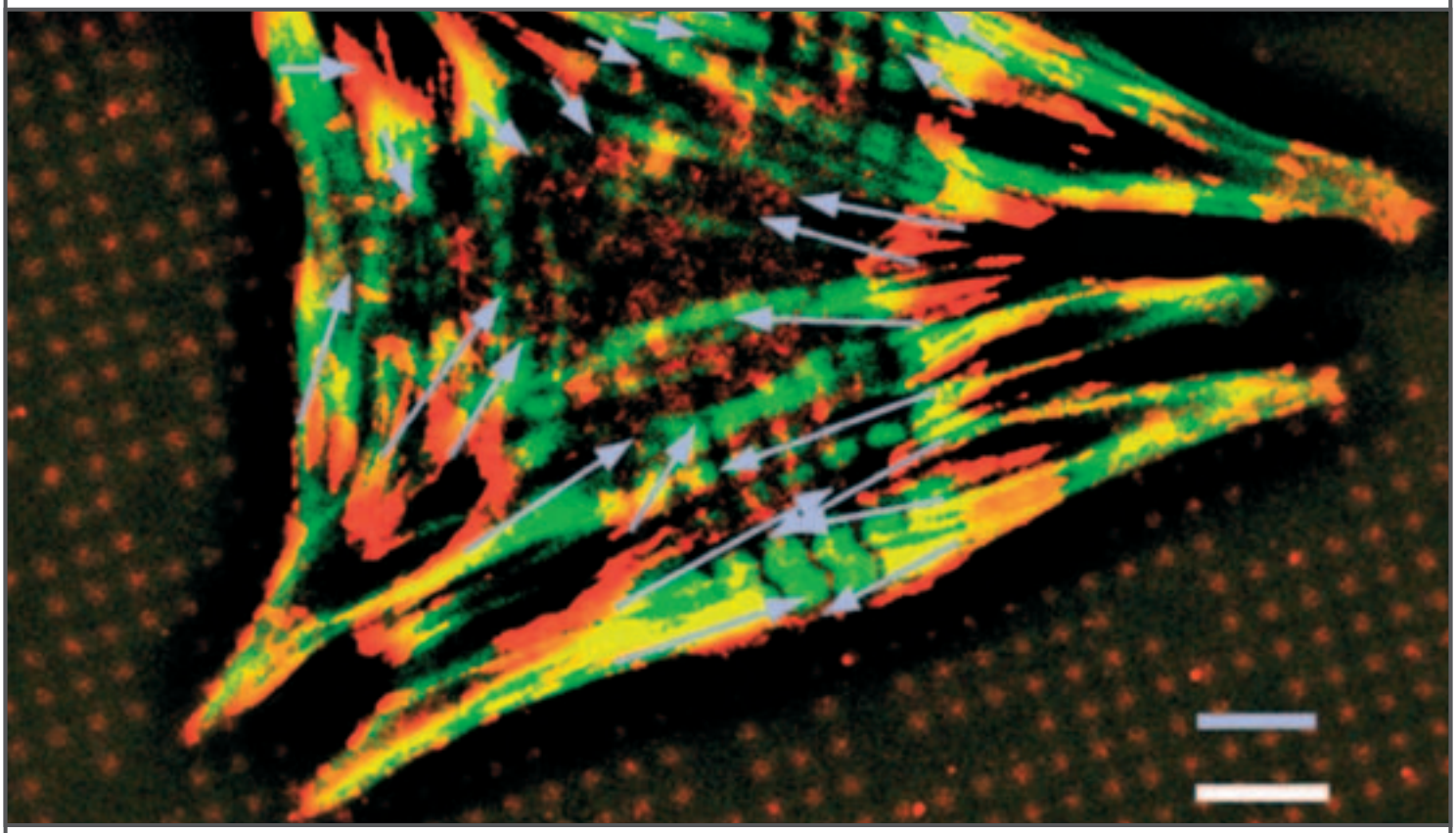
The dynamics of these cell contacts are controlled by many different signals impinging on the cell from the outside. Most of these signals are identified by receptors or "antennas" that are located on the surface of the cells, in their outer envelope or membrane. These receptors pass on information to the interior of the cell. Contact between the cells and the surrounding matrix - so-called cell-matrix adhesion - is largely ensured by transmembrane receptors of the integrin family. They span the cell membrane and thus link the interior of the cell to the outside. On the exterior, integrins bind with many different partners (ligands), for example the proteins fibronectin and collagen.

Knowledge of the way in which cells make contacts can help us achieve a better understanding of how cancer cells are able to leave their original site, move through the body and establish themselves elsewhere as dangerous metastases.

A large family of proteins

The integrin system is very complex. Mammal cells have no fewer than 24 different integrin variants recruiting over 100 different proteins of the cytoplasm in the interior of the cell, notably the actin filaments of the cytoskeleton. Thus integrins connect the extracellular matrix with the cytoskeleton in the interior of the cell and thereby assure the structural identity of the tissue. Integrins are also involved in the way cells interpret biochemical messages such as the signals instructing them to grow.

All these properties make integrins a crucial factor in many natural processes, including the development of an organism, the maintenance of tissue and organ structure, or wound repair. Integrins are equally important for the migration of cells, for example when white blood cells set out to deal with pathogens. The role they play is just as essential when malaria parasites pervade the human body or when cancer cells leave their original site to establish themselves in a different part of the body as metastases (secondary tumors).



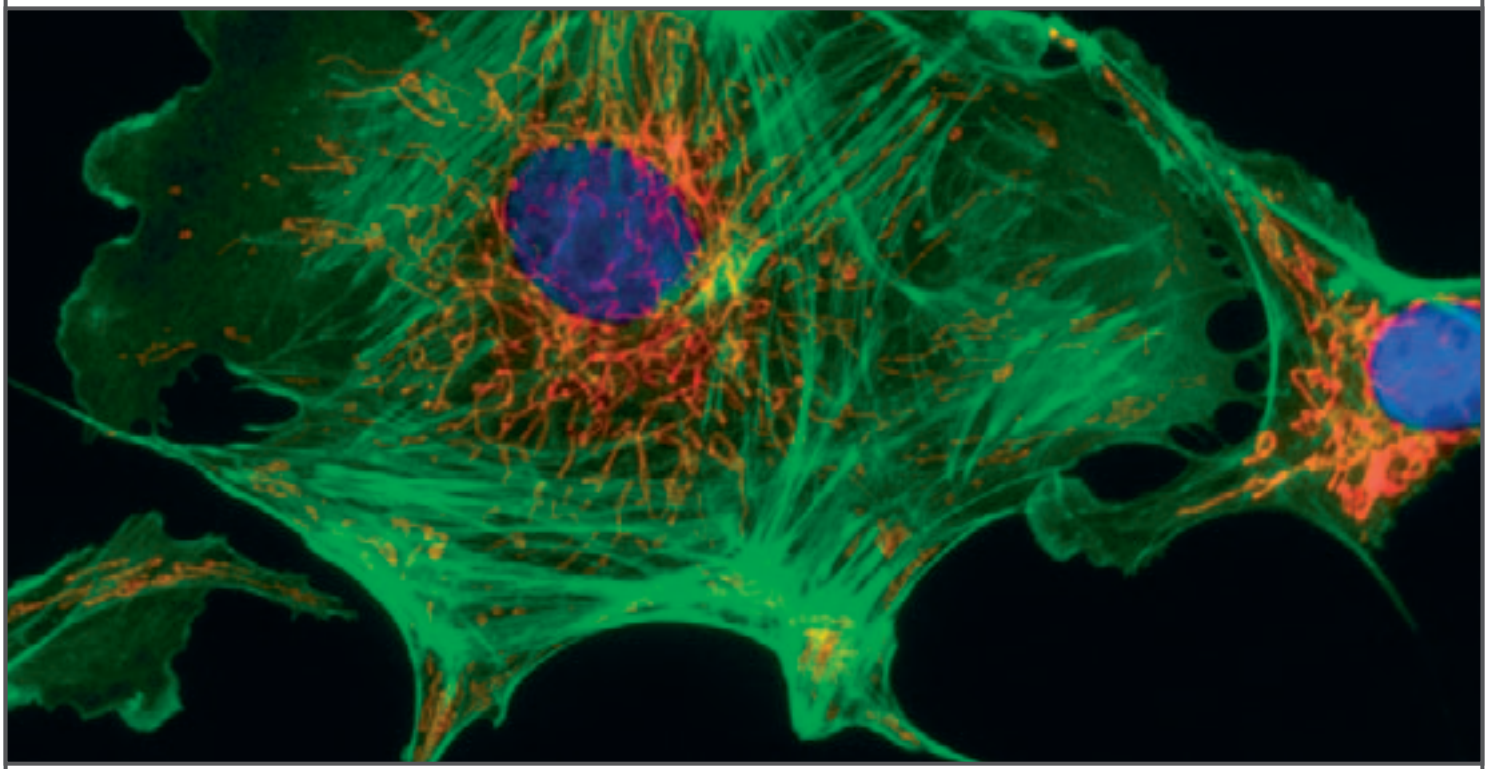
The forces generated by cardiac muscle cells can be measured by monitoring the deformations of a soft elastic substrate that has been patterned by microfabrication. Scale bars: forces (blue) 70 nN, distances (white) 6 microns.

In the last few years it has become evident that cell-matrix adhesion is regulated not only by biochemical but also by mechanical signals. It has long been known that the physiological function of many cells, e.g. those in bones, lungs and blood capillaries, is also dependent on the physical force exerted on them from their environment.

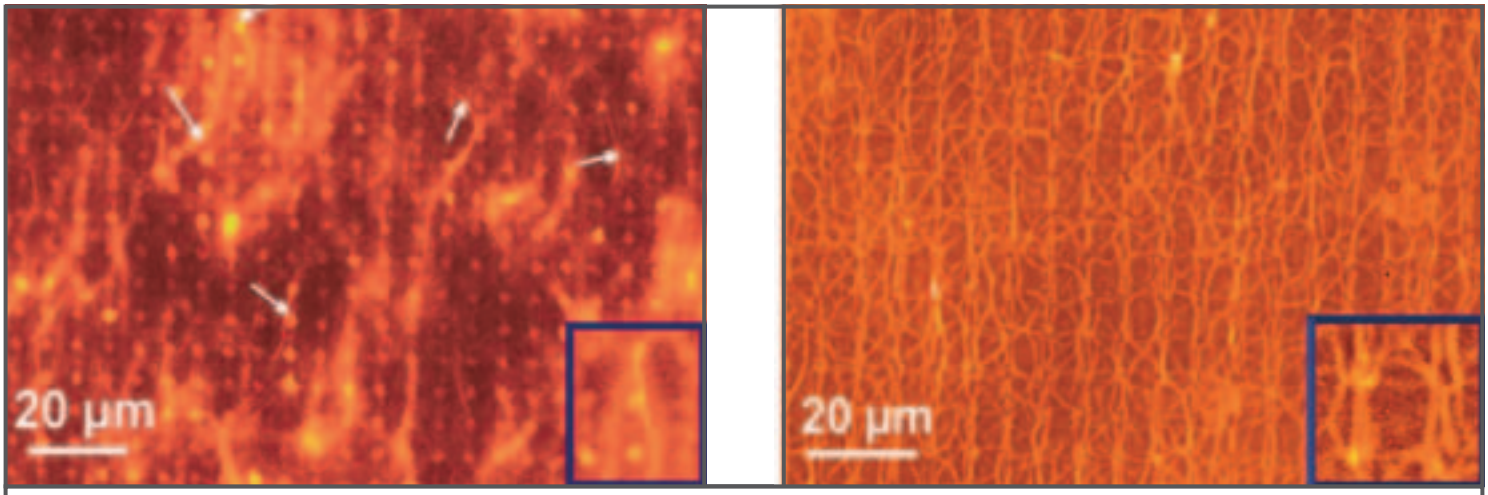
Only recently, however, has it become evident that mechanical transduction processes are closely connected with the integrin-mediated contacts between cells and the extracellular matrix. In particular, the forces cells generate by their own and channel through the integrin-based contacts seem to play an essential role in this context.

We now know that many cell types react very sensitively to the mechanical properties of their environment. For example, it has been possible to show that the differentiation of muscle and stem cells is dependent on the mechanical conditions (e.g. the rigidity) of their environment. These findings indicate that biochemical and structural processes are closely interconnected, an insight that opens up entirely new perspectives for regenerative medicine and its work on the design of artificial tissues and organs for transplantation purposes.

As cellular contacts are controlled both by biological and material determinants, the investigation of cell contacts must necessarily be interdisciplinary and quantitative. Interdisciplinarity is essential because it takes a combination of methods from cell biology, molecular biology, materials science and biophysics to



Cells adhering to flat rigid surfaces are usually under large mechanical tension, as evidenced by the tensed appearance of the actin cytoskeleton (green).



The cytoskeleton of a cell can be reconstituted in the test tube. However, only be adding crosslinkers (right hand side) does the kind of regular structure result which is typical for cells.

characterize all the aspects relevant for such systems. A quantitative approach is crucial because the exceedingly large number of potential combinations of cells and materials can only be dealt with by systematic characterisation and classification. In addition, this approach facilitates the rational design of new environments for cells, such as artificial tissues or biochips.

A better understanding of cancer

BioQuant assembles the activities of different research groups that have been investigating these matters in Heidelberg for a number of years. This offers a unique opportunity to actually achieve a quantitative systemic understanding of cell adhesion. For example, the group of Joachim Spatz is a world leader in the investigation of the behaviour of cells on nanostructured surfaces. This group applies knowledge from the material sciences to utilize structure formation in diblock copolymer systems for cell adhesion. It recently demonstrated that cell-matrix adhesion becomes unstable as soon as the distance between integrins exceeds 65 nanometres. New procedures such as arrays of elastic pillars or cell stretchers make it possible to investigate cell mechanics during adhesion. For example, work with the cell stretcher established that, in mechanical terms, tumor cells from the pancreas actually go “soggy”, a change associated with the dramatic reorganization of certain elements (keratins) of the cytoskeleton. This may be what enables the tumor cells to penetrate border layers and immigrate to other regions of the body. The forces involved in this process can be measured by “traction force microscopy”, which is at present being developed further by the group of Ulrich Schwarz. In collaboration with the group of Friedrich Frischknecht from the medical faculty, this method is now used to study the migration of malaria parasites.

The reaction of cells to signals from their environment is best investigated with high-resolution microscopes. The high-resolution fluorescence microscopy (4Pi-STED microscopy) set up at the BioQuant building by the group of Stefan Hell makes it possible to observe protein dynamics with a resolution of a few nanometres, for example for cell-matrix contacts. Many synergy effects can also be expected to result from cooperation between experimental BioQuant groups and research groups at Heidelberg’s Interdisciplinary Center for Scientific Computing (IWR), notably in image processing or the modeling and simulation of cellular decision processes. There are also medical research groups collaborating with the scientists involved in the BioQuant Cell Adhesion Project with expertise in the fields of regenerative medicine and cancer biology. This opens up the perspective that scientific results obtained within BioQuant can quickly be used for medical applications.

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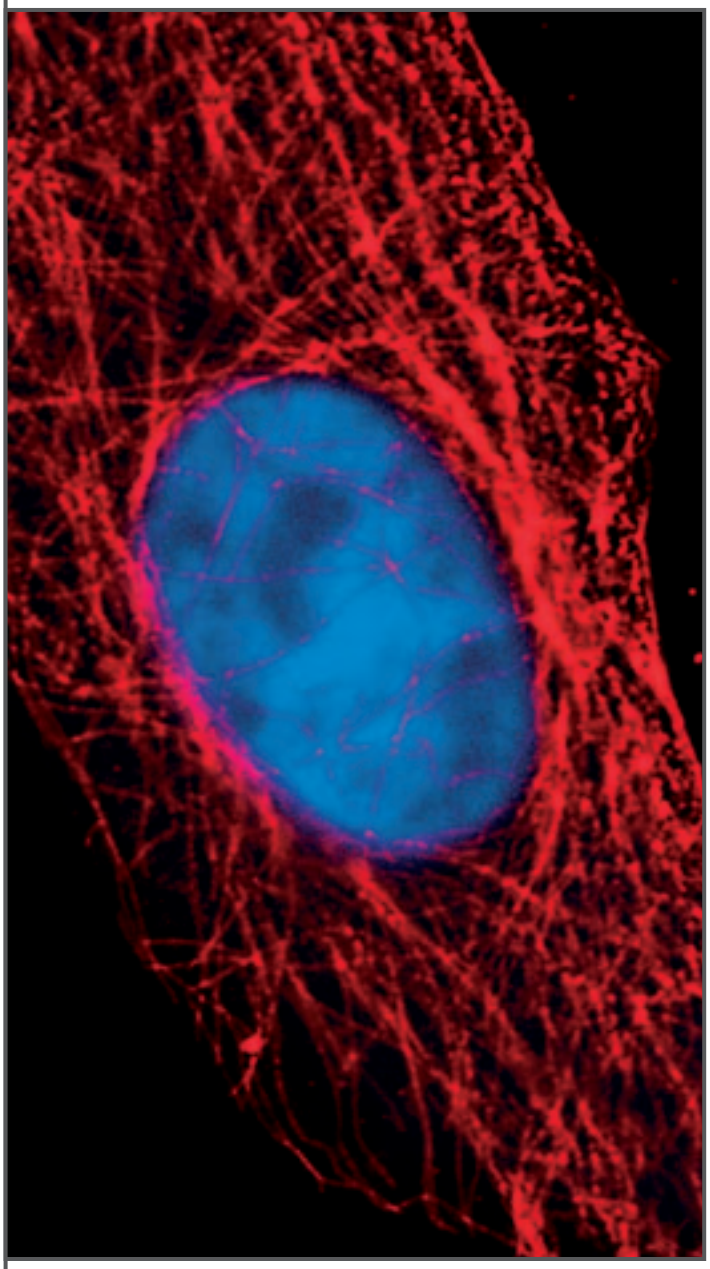
Cell Logistics



Typical picture of a mammalian cell. The cytoskeleton is highlighted in red while the DNA in the nucleus is stained in blue.

Traffic is busy in the cell, with powerful little locomotives pulling containers full of precious cargo along tiny rail-tracks. Diffusion is another cellular transport method, less energy-dependent and more random. Whatever option is selected, no cell can exist without transport. Matthias Weiss, head of the BIOMS Cellular Biophysics research group, explains the logistics of the cell and the research efforts required to understand the details of the vital processes involved.

In every cell there is always something being transported from one place to another. No cell can organize or sustain itself without transport processes. They ensure that cells can pass on their products to the exterior and communicate with other cells. Restrictions on transport can seriously impair a cell's viability and even set off the programmed cell death (called apoptosis).

The time-spans and distances involved in cellular transport processes are extremely variable. Some are over in a matter of milliseconds, while others last for hours or even days. The distances covered range from a few nanometres to several millimetres. In other words, transport processes in living cells are a "multiscale problem" in space and time.

In functional terms cellular transport processes can be divided into four groups. First of all we have the transport of material between the different compartments or organelles, the "reaction containers" of the cell. This takes place via channels or pores and is supported by specialized proteins. A different kind of transport also takes place between the organelles. It depends on structures derived from cellular membranes that take on the form of small bubbles (vesicles) or tubular structures (tubules). Active transport is powered by so-called molecular motors that move along filaments within the cell (the cytoskeleton). And finally we have

“To achieve a better understanding of transport processes in living cells we use a variety of approaches, ranging from molecular biology and biochemistry to single-molecule spectroscopy and computer simulations.”

Matthias Weiss

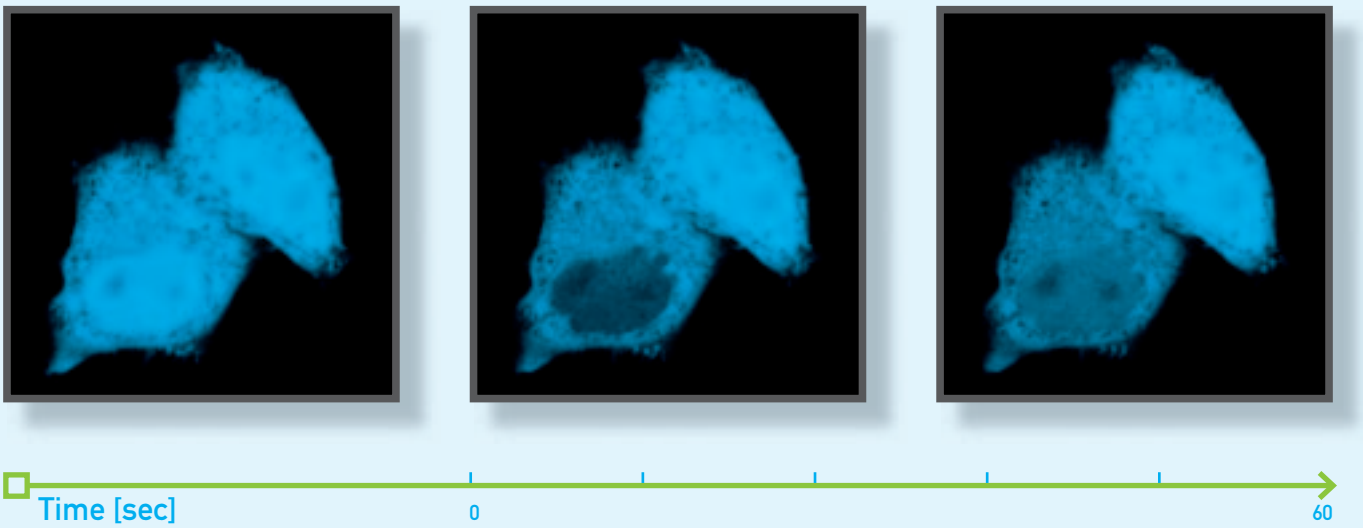
diffusion, i.e. the primary, random movement of all molecules that leads to the homogeneous distribution of soluble substances.

Dividing the kinds of transport operating in the interior of a cell is somewhat arbitrary. It is also a major simplification of the actual state of affairs, as there are many transport processes that would have to be assigned to more than one of these groups. But it will suffice for an initial overview. Within BioQuant all four categories are the subject of interdisciplinary research. A wide range of approaches is used to achieve a better understanding of cell logistics, ranging from molecular biology and biochemistry to single-molecule spectroscopy and computer simulations. The following is a brief summary of some ongoing projects.

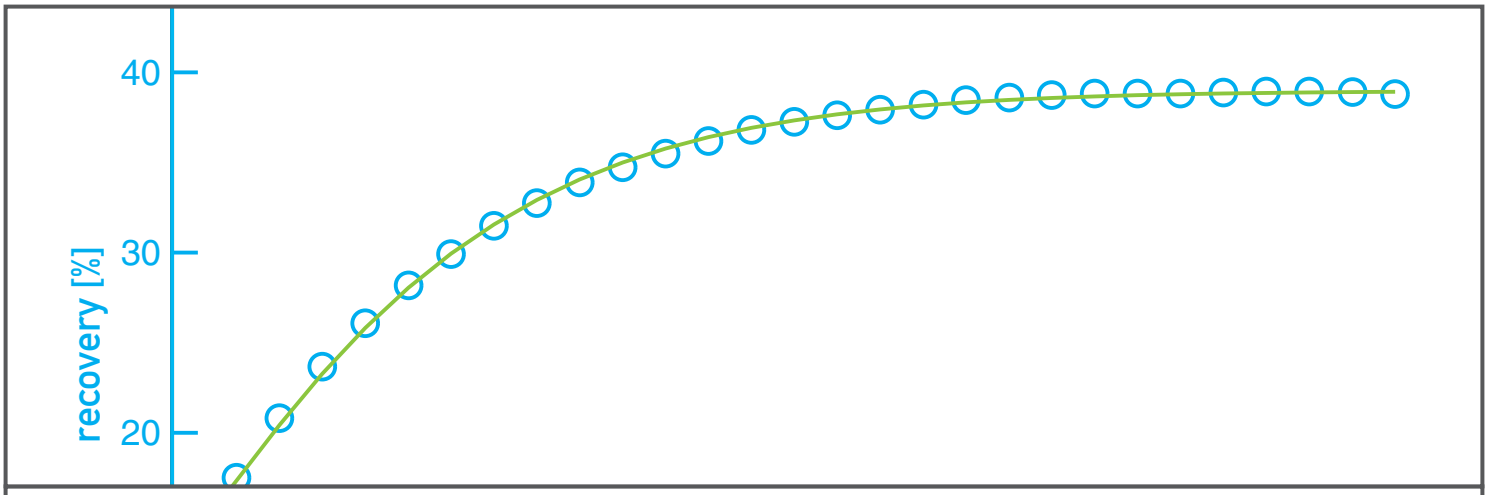
Strict import and export controls

When the cell is “at rest” and not in the process of division, the genetic code (the DNA) is packed in the cell nucleus and the nuclear membrane separates the cytoplasm from the nucleoplasm. But the exchange of molecules between the two compartments (cytoplasm and nucleoplasm) is of vital importance for the cell. This is where the “nuclear pore complex” comes in, a kind of channel in the nuclear membrane. It is formed by a large group of proteins that span the nuclear membrane and thus connect the cytoplasm with the nucleoplasm. But it is not merely a conduit system. The nuclear pore complex also acts as a “guard” controlling the import and export of substances. Very small

Transport of proteins into the nucleus



How do proteins enter the nucleus? The transport kinetics can be studied easily with fluorescently labeled proteins. After bleaching, i.e. irreversibly destroying, all dyes in the nucleus (picture in the middle), a recovery of the fluorescence in the nucleus is observed (picture on the right) over time. The shown transport happens on the time scale of about one minute.

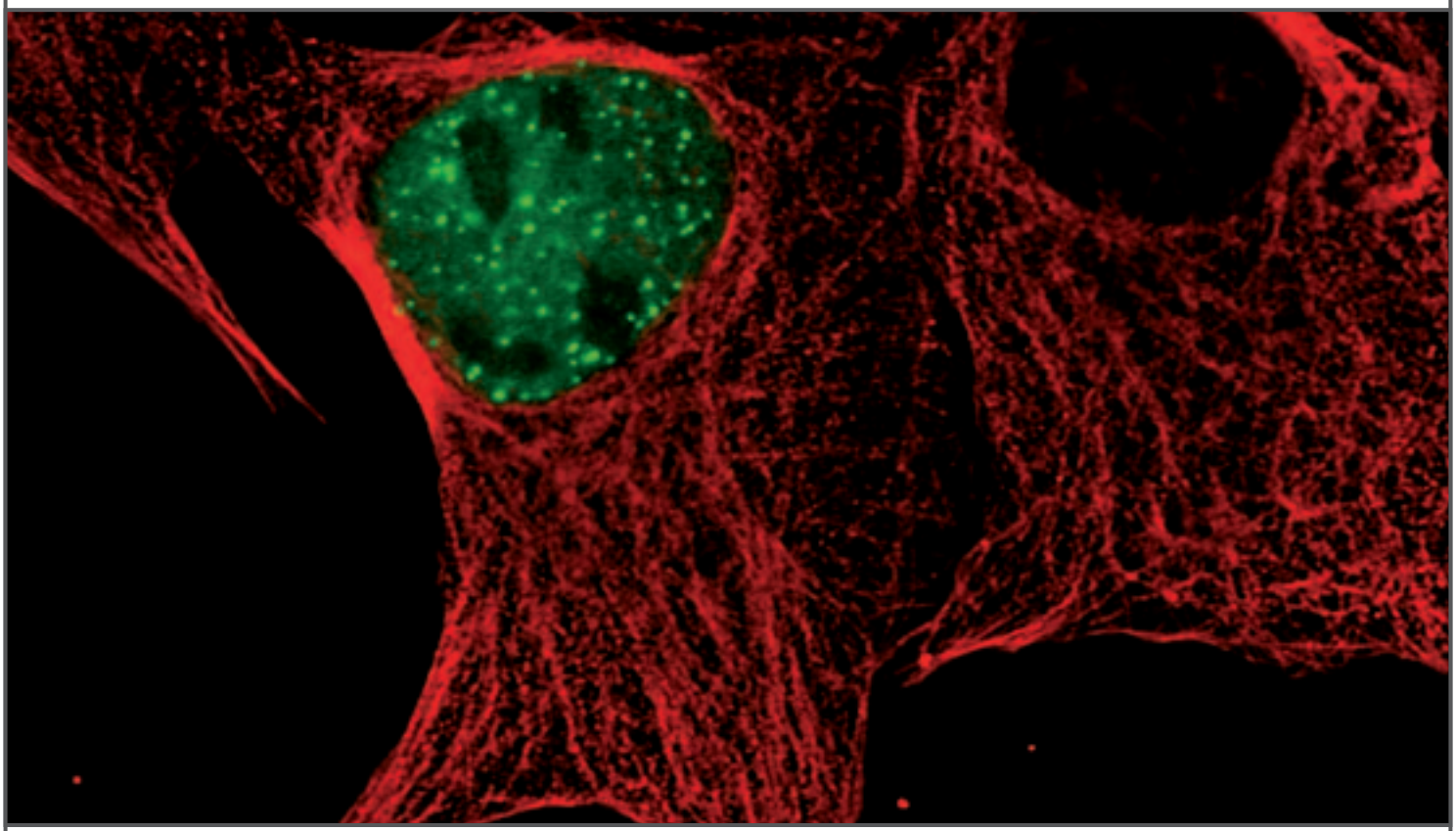


Recovery of the fluorescence in the nucleus after bleaching highlighting the import of proteins into the nucleus (c. f. page 19).

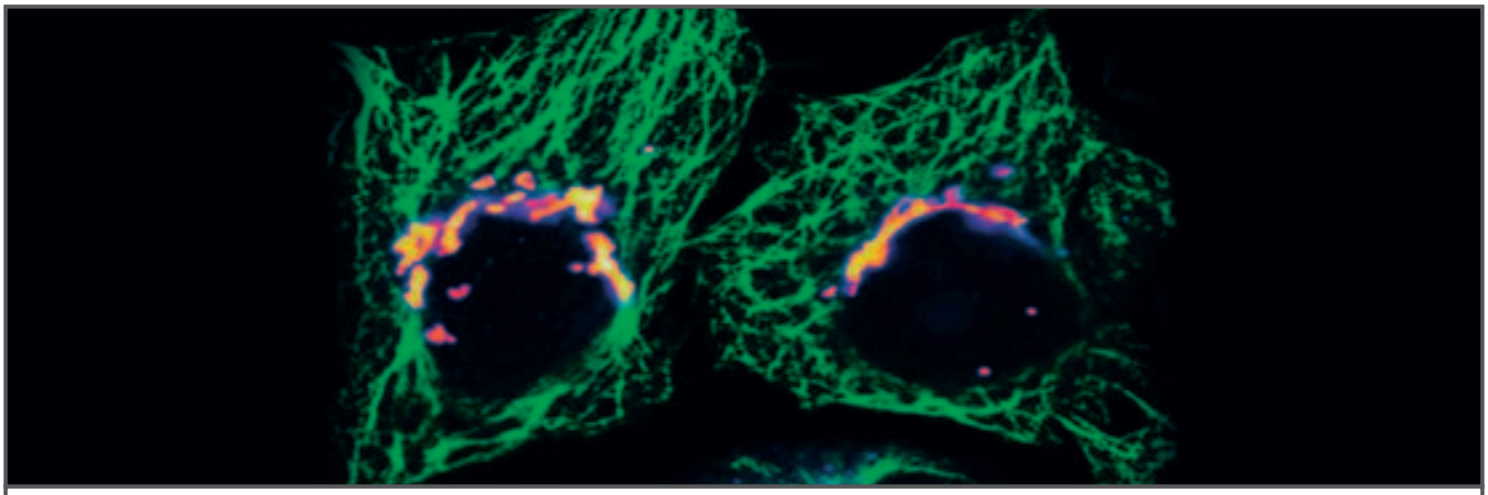
molecules (e.g. sugar) can pass freely through this gateway in both directions. But medium- to large-sized molecules will be impeded unless they have certain characteristics (motives) or are attached to proteins that normally faciliate their passage through the nuclear pores. So far we have very little knowledge of the filtering function of the nuclear pore complex. All we know for certain is that it is dependent on the size and the structure of the molecules transported. This is the key issue being investigated by one of our interdisciplinary research groups.

Tiny containers with precious cargo

In the cell, proteins and lipids are frequently transported by vesicles smaller than 100 nanometres. These vesicles are formed by budding off from intracellular membranes, an event that is supported by specialized protein families. These proteins coat the membrane at the point where the vesicle is meant to bud and in doing so they deform the membrane which is accompanied by the uptake of molecular cargo into the interior of the emerging vesicle. The protein coat appears to stabilize and protect



Fascinating details: Fluorescent dyes highlight the cell's railroad systems – the microtubules (page: 21 green, above: red), an important part of the cytoskeleton. Microtubules provide the main track along which newly synthesized proteins travel towards the Golgi apparatus (page 21: yellow) for subsequent modification. The green spots in the picture above are specialized nuclear bodies, i. e. functional domains in the cell's nucleus. Dark spots in the nucleus are due to the (not stained) nucleoli, another important kind of nuclear bodies.



vesicle formation and cargo selection. As soon as the vesicle has pinched off, the protein coat dissociates from the vesicle's membrane thus making it competent for later fusion with an acceptor membrane. If anything interferes with vesicle formation or vesicle transport, severe illnesses like diabetes or cystic fibrosis may result. In the last 10 years scientists have learned a lot about vesicular transport. But we still know very little about the precise timing and the dynamics of vesicle budding and the selection of molecular cargo. These issues are the central concern of another of our research groups.

A filigree network of vital significance

The cytoskeleton, a network of different proteins that assemble into filamentous structures spans the cell to give it shape and support. Microtubules, a major part of the cytoskeleton, are stiff protein rods, a few micrometres long, that play an important role in cell division. Together with so-called motor proteins they form a filigree structure resembling a spindle. The task of the spindle is the correct distribution of the chromosomes (which encode the hereditary information) to the developing daughter cells. One of our research groups is investigating the details of this process (see also the report by Nédélec, p. 44). Another research group has set out to establish, right down to the atomic level, exactly how motor proteins assist in this process. Besides microtubules there is another class of proteins operating in the cytoskeleton, the actin filaments. With their associated motor proteins they are involved in the movements of the cell and its adhesion to other cells. This aspect is of major significance for medical applications. For example, loss of cellular adhesion is a decisive factor in the ability of cancer cells to migrate through the body and form metastases (secondary tumors) (see also the report by Schwarz, p. 48).

Spreading things out evenly?

Diffusion is the simplest mechanism involved in cellular transport. At the single-molecule level it is no more than a random movement serving to offset differences in concentration. But diffusion is ubiquitous and its status has been underestimated. For example, diffusion enables small proteins to search the entire cytoplasm for suitable reaction partners in a matter of seconds. At the same time, the diffusion conditions for large molecules in the interior of the cell may be very different as intracellular fluids are very crowded. Indeed, up to 30 percent of the interior of the cell consists of proteins, which obstructs diffusion of proteins in a size and confirmation dependant manner. Learning more about diffusion, its due to crowding obstruction and the consequences of that is the objective of an interdisciplinary research group quantifying and characterizing the properties of diffusion processes.

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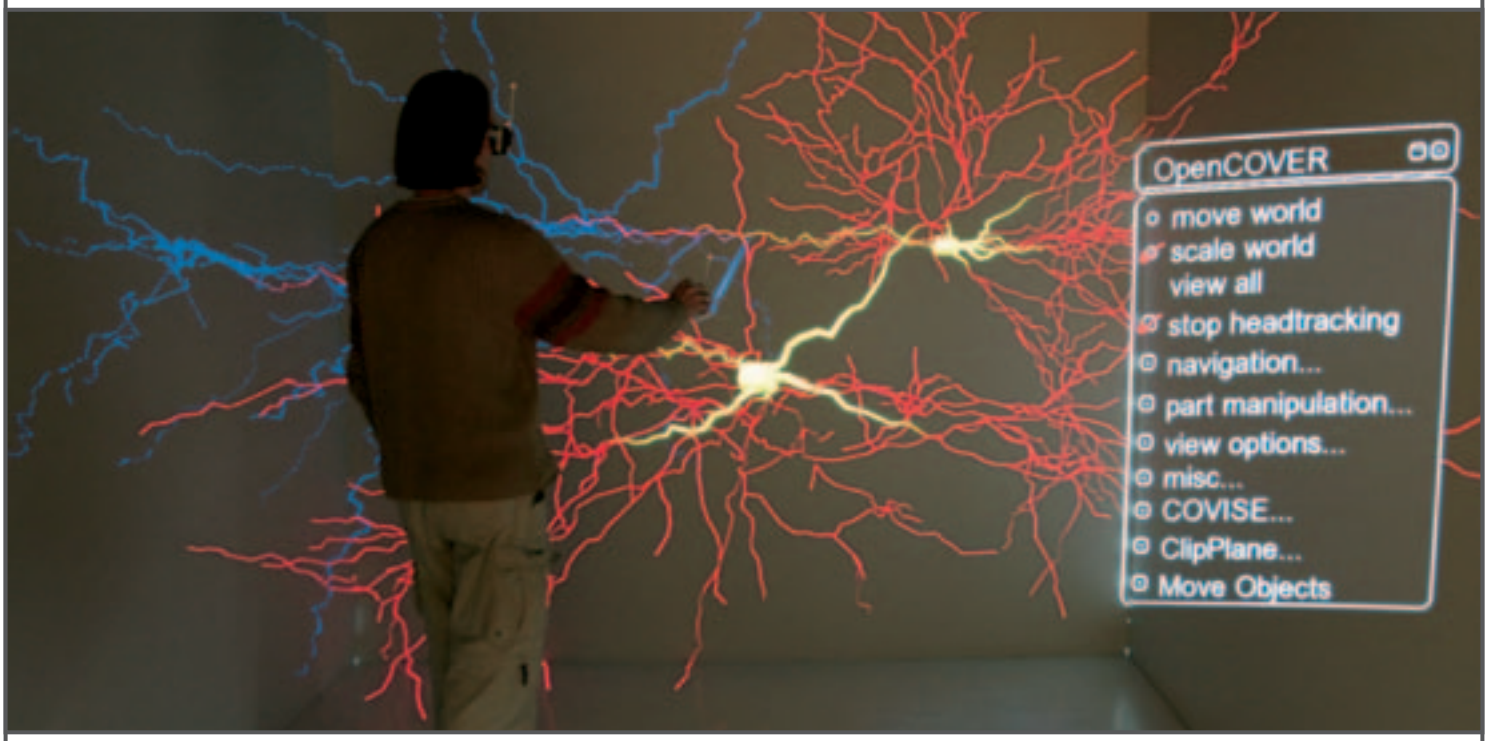
Networks in the Brain

No other organ in the human body is as complex as the brain or as difficult to see into. To find out more about the way nerve cells form networks and cooperate at a higher level, scientists have to develop some very ingenious methods. Gabriel Wittum reports on the sophisticated approaches devised to unravel some of the mysteries of the brain.

For all the research that has been done on the subject, our understanding of the way the brain processes signals is far from complete. Among the things we know nothing about are how sensory stimuli are encoded in the brain, what the structure of the cortex looks like on the subcellular plane, and what mechanisms underlie the plasticity of neurons (nerve cells). Despite the immense progress made in experimental techniques these processes can only be understood by means of modeling. So far the models used have greatly simplified the geometry of neurons, but today there are models available that get a lot closer to the highly complex nature of the brain.

The smallest functional unit in the brain

The paradigm used by our research group is the so-called cortical column, the smallest functional unit in the brain. We begin with three-dimensional volume models of individual neurons describing the most important physiochemical processes in mathematical detail. The next stage in the hierarchy is represented by local circuits, simple modules that take shape when a small number of



Three dimensional visualization of a network of 100 neurons generated by NeuGen and visualized by means of immersion in the CAVE of the HLRS (University of Stuttgart). Immersion allows a realistic insight into the three-dimensional structure of the network. (U. Wössner, HLRS)

"Today there are models available that get a lot closer to the complex nature of the brain."

Gabriel Wittum

neurons interconnect. The local circuits in their turn are the basic elements for assembling larger ensembles. The top end of the hierarchy is the entire cortical column.

The volume of the cortical column cannot be modeled with the resources available at present. The model required for the purpose would exceed the capacity of the world's biggest computer by three orders of magnitude. Accordingly, we use reduced models to describe the column. Suitable for this purpose are the so-called compartment models implemented in the "Neuron" simulation programme and developed on the basis of experimental data.

We anticipate that detailed mathematical simulations and simulations based on physical principles will provide new insights into the functioning of the brain. Mathematical models enable us to simulate the behaviour of large interconnected neuron ensembles by using new and sophisticated methods. The results of the various approaches are compared with one another and with the data produced by specific validation experiments.

"In silico" reconstruction

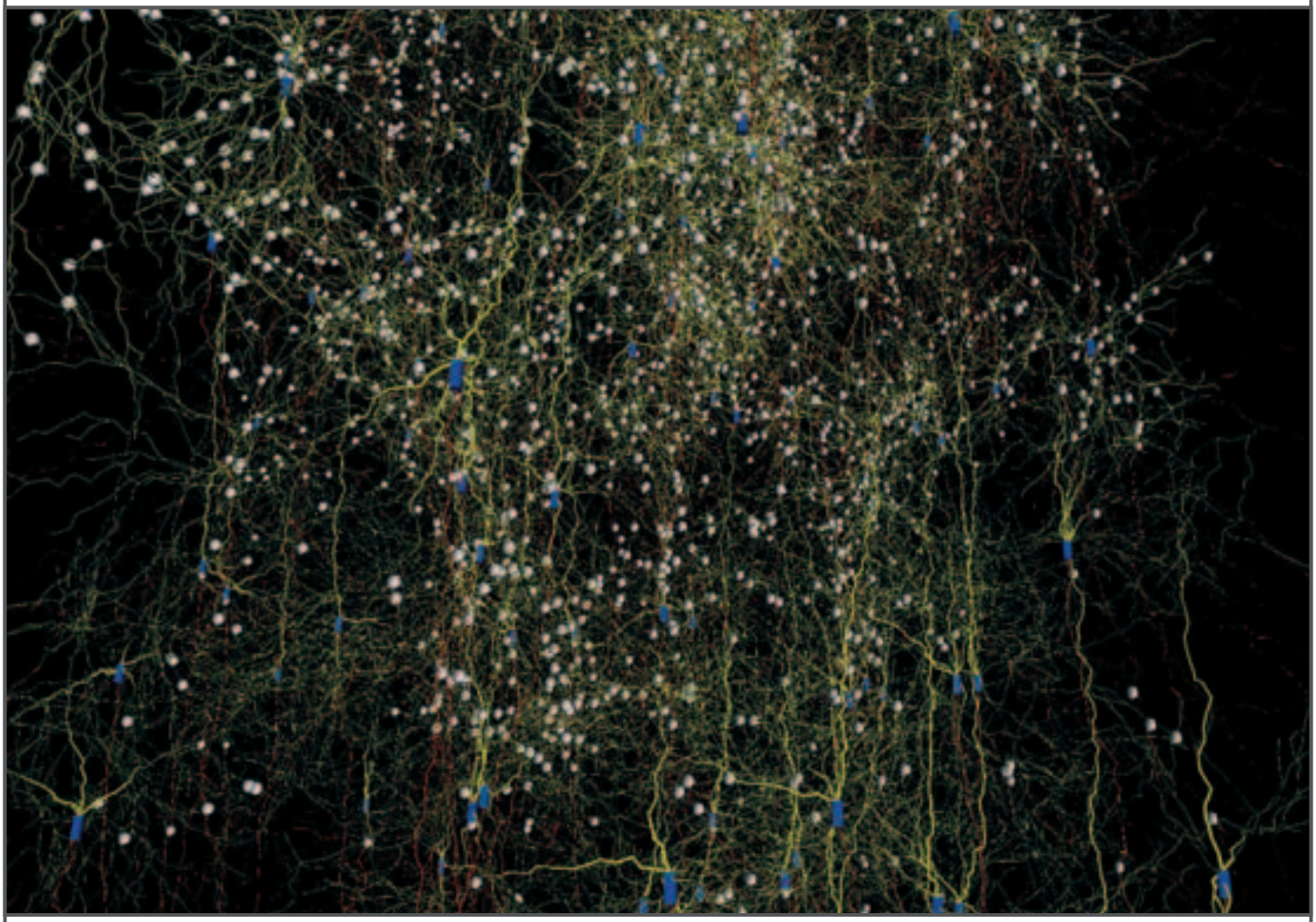
In concrete terms, the "in silico reconstruction" of the cortical column takes place in various stages. First we need to obtain the geometry and the connective structure of the neurons from raw data. This is done with so-called two-photon microscopes enabling us to acquire images of the living brain. For the reconstruction of the geometries we have developed special software ("NeuRA") enabling us to extract the neuron geometries automatically from the raw data. The heart of this software is a filter that prepares the data for reconstruction. This filter can identify one-dimensional substructures (e. g. dendrite branches, the short, highly ramified outgrowths of the nerve cell) and it can also be adapted to identify two-dimensional structures, e. g. the cell nuclei of neurons. At present we are working on a procedure for the localization of synapses, the junctions between nerve cells.

In a second stage we classify the cell geometries and the network topologies. The objective is to identify basic types of neuron and their statistical distribution. For this purpose we have established the "CortexDB" neuron database, containing raw data, processed geometric and topological data, and physiological data. So far this has largely been based on morphology, but the highly detailed data made available by new microscopy techniques require automatic algorithms. At present we are testing graph-based algorithms for the comparison of discrete trees. The identification of similarities on the basis of physiology (e. g. by comparing simulations) is also conceivable. The first thing we need to do is to determine elementary local circuits consisting of a small number of cells interconnected in typical ways. For this purpose we identify and compare local circuits from the basic cell types previously extracted. Structures identified as typical then serve as the basic elements in the structural plan of the column. The subsequent stage is the comparative classification of the network topologies. Proceeding from the local circuits, this leads to increasingly complex interconnections.

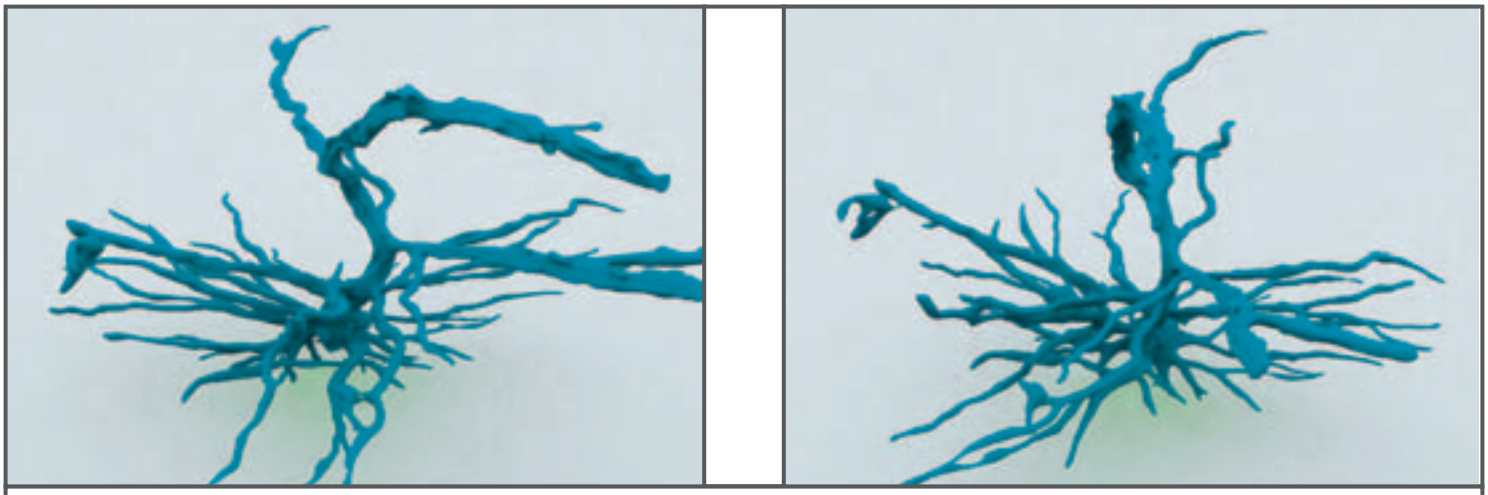
Computer simulations

Once the basic structure of a cortical column has been identified in this way, we can then enter it in "NeuGen". "NeuGen" enables us to produce artificial neurons and neuron networks that correspond to the structure and are realistically shaped and distributed. The data thus generated are then transferred to a simulation programme such as "NeuSim". With "NeuGen" and "NeuSim" we have already conducted a first study for a column with 5,000 neurons.

The actual modeling of all the processes involved takes place at different levels. In the detailed modeling approaches customary at present, individual cells are only subjected to piecewise cylindrical approximation. So far, no full three-dimensional mathematical approximation has been attempted. We have just set up a first three-dimensional volume-oriented model for signal conduction in the dendrite and have produced initial computations. The "UG" simulation system we have developed is used for the implementation.



Simple visualization of the same network from Page 22 including synapses connecting the cells. (U. Wössner, HLRS)



Three dimensional reconstruction of the geometry of a dendrite of a spiny stellate from layer four of a rat's cortex. The cell has been reconstructed by A. Heusel (SiT) by means of NeuRA. The data have been recorded by Dr. J. Waters (Northwestern University, formerly MPI Heidelberg)

This model can be generalized to model and simulate signal processing in typical local circuits. Just like individual cells, local circuits are susceptible of complete geometric representation. Parallelisation is crucial for the representation of a complete circuit. In addition, the simulation is to be drawn upon in the sense of an inverse problem for the identification of typical local circuits.

In conjunction with "NeuGen" we intend to compute major compartment-based models of a whole column. To this end we set up a column made up of 3,000 neurons of the cortex and 100 neurons of the thalamus (part of the subcortex) and calculate it with "NeuSim". The model for this purpose is the multi-compartment model implemented in "NeuGen". The description of the cell-specific ion channels in it encompasses active channels in the interior of the cell and in the axon, the long outgrowth of the nerve cell. Slow, active ion channels in the dendrite tree can also be captured. At present we are elaborating further process models with leading experts in this field. Ultimately we intend to extend the proto-column to a realistic configuration in which 300 thalamic neurons project to about 5,000 cortical neurons.

Such simulations require a great deal more computer power than desk top computers can furnish at present. Accordingly, a parallel simulation tool is indispensable. As no such parallel tool with the requisite flexibility, efficiency and robustness exists at the moment, we intend to develop a programme of our own. To this end we can draw upon our long years of experience in the development of simulation strategies for large-scale systems.

Once the geometry and topology of the cells have been parameterized, mathematical methods can be used to produce effective equations. They correctly describe the overall behaviour of the column without having to represent all the detail involved. For this purpose, the column is divided into sections predetermined by the stratification of the cortex. In each section the dendrites of the cells belonging to the given stratum are concentrated. Their parameterized description leads to the derivation of effective equations that can be numerically solved using multiscale/multigrid methods.

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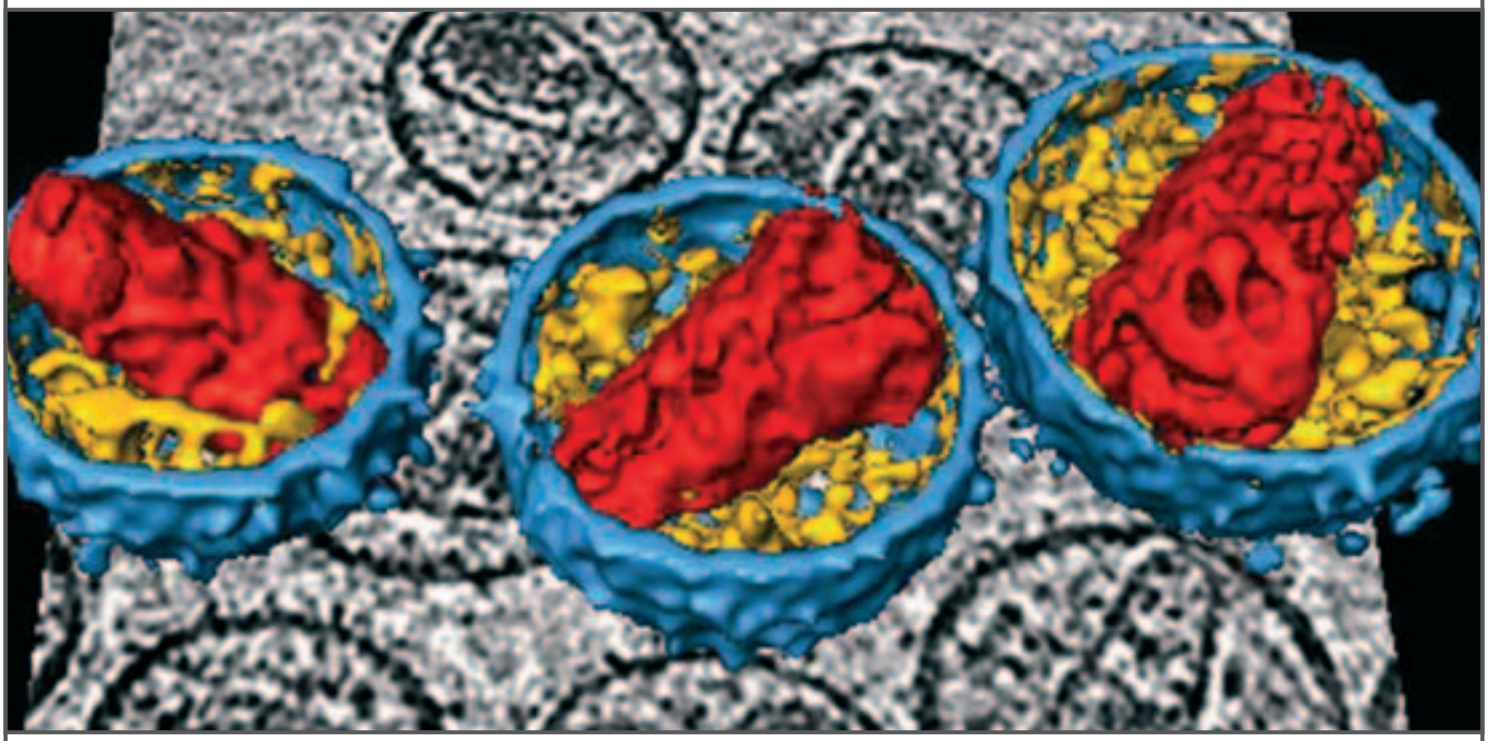
The tricks of viruses

Viruses are peculiar organisms that prey on cells to assure their own replication. Among them are some of the deadliest pathogens known to medical science, like the human immunodeficiency virus that causes Aids and claims over three million victims annually worldwide. Hans-Georg Kräusslich tells us how scientists set about identifying the malicious tricks used by these cell pirates and thus pave the way for new drugs that can foil their depredations.

"A virus is a piece of bad news wrapped in protein." This is the definition proposed by the immunologist and Nobel Prize laureate Sir Peter Medawar for the tiny assailants. It is a matter of definition whether they are considered merely clusters of complex chemical compounds or actually forms of life on their own. Viruses carry only a few genes and the information contained in them is inadequate to perform complex life processes like metabolism, movement or replication. Thus, viruses are obligatory cell parasites. They use the synthetic apparatus of cells to replicate and they exploit cellular signal and transport pathways for their own purposes, frequently causing the death of their victims in the process. The properties of viruses make them an interesting subject for scientific research. For example, detailed knowledge of the relationship that a virus enters with its host cell will hopefully provide the molecular basis for new drugs capable of combating the worst pathogens among these diminutive marauders, including the human immunodeficiency virus (HIV) that causes Aids.



Three-dimensional structure of mature HIV particles: using cryo-electron microscopy, the structure of the tiny virus particles can be analyzed in detail.

“Detailed knowledge of the relationship that a virus enters with its host cell will hopefully provide the molecular basis for new drugs.”

Hans-Georg Kräusslich

Containers of genetic information

What does a virus look like? Effectively, viruses are no more than containers carrying genetic information in a stable envelope and capable of infecting a cell in a given target organism and using it for its own purposes - just as Medawar defined it. The virus’s stable shell is called the capsid and consists of proteins. In some classes of viruses the capsid is enveloped by a lipid membrane. This membrane is not a product of the virus itself but is derived from the plasma membrane surrounding the host cell or from one of the inner membranes of the cell.

The lipid membrane filched from the host cell gives the virus an essential advantage. With its aid the virus particles can penetrate the membrane of their host cell without destroying it in the process. The virus simply “fuses” with the membrane of the cell. But this advantage comes at a cost. The genetically sparsely equipped virus needs to develop a mechanism to envelop itself with the alien membrane.

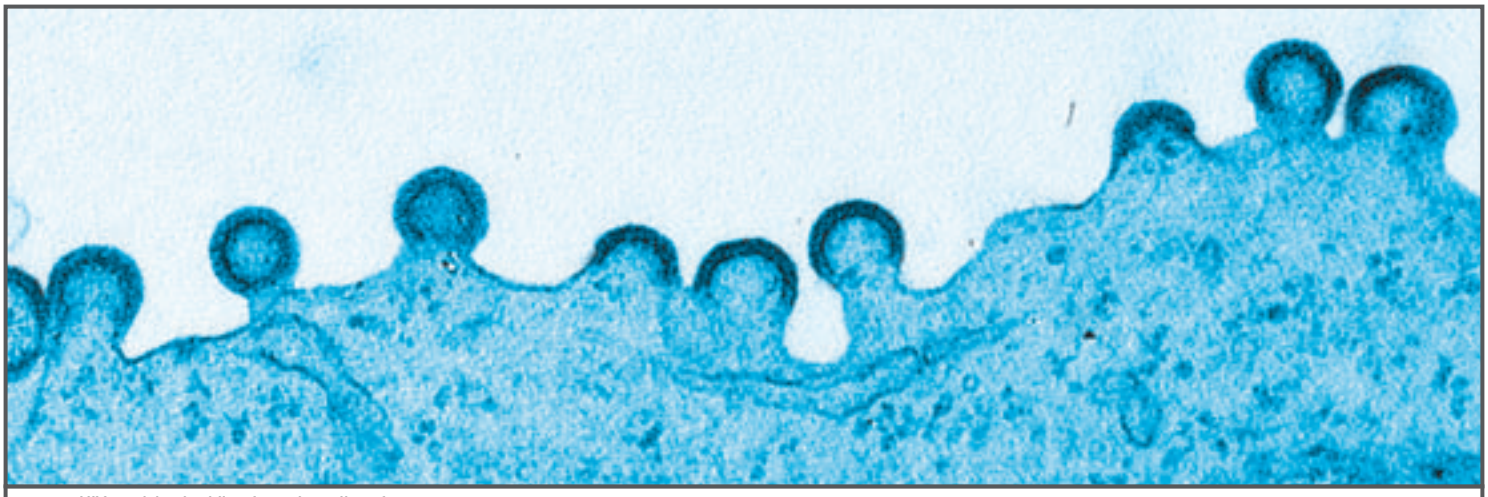
Many of the viral and cellular factors involved in this process have recently been identified. They are part of a network whose complexity has not yet been fathomed. One of the things we do know is that protein complexes play a major role in the process. We have also identified many of the proteins these complexes consist of. But we know next to nothing about the amounts in which they figure, the affinities between the individual proteins, or the individual stages this process goes through.

Viruses on their way through the human cell

One of the viruses that have been most thoroughly investigated - including its interactions with the human cell - is the HI virus that causes Aids. Recent developments in molecular biology, chemistry and physics have enabled scientists to trace the path of the virus through the human cell. For this purpose components of the viruses are tagged with fluorescent dyes so that the route they take can be determined with the help of a fluorescence microscope. If, for example, various parts of the virus are stained with different fluorescent dyes, we can directly observe how the virus docks on to the cell and how its membrane fuses with the cellular membrane. With a time resolution of 10 milliseconds per frame and high spatial resolution we can then see how viruses penetrate the cell and which subsequent routes they take.

The new techniques not only enable us to observe the viruses’ course through the cell in “real time”, they also yield data that can be integrated into mathematical models. Models of this kind would, for example, help us to simulate the extent to which the infection potential of a virus depends on the number of receptors on the surface of a human cell, or the effect produced when the surface proteins of different virus variants have differing affini-

Single virus particles and their interactions with their host cell can be observed in real time with the help of modern fluorescence microscopy.



HIV particles budding from the cell surface

ties to the cellular receptors. Based on this, it would also be possible to simulate the impact of drugs designed to target proteins involved in the fusion of the virus with the cell.

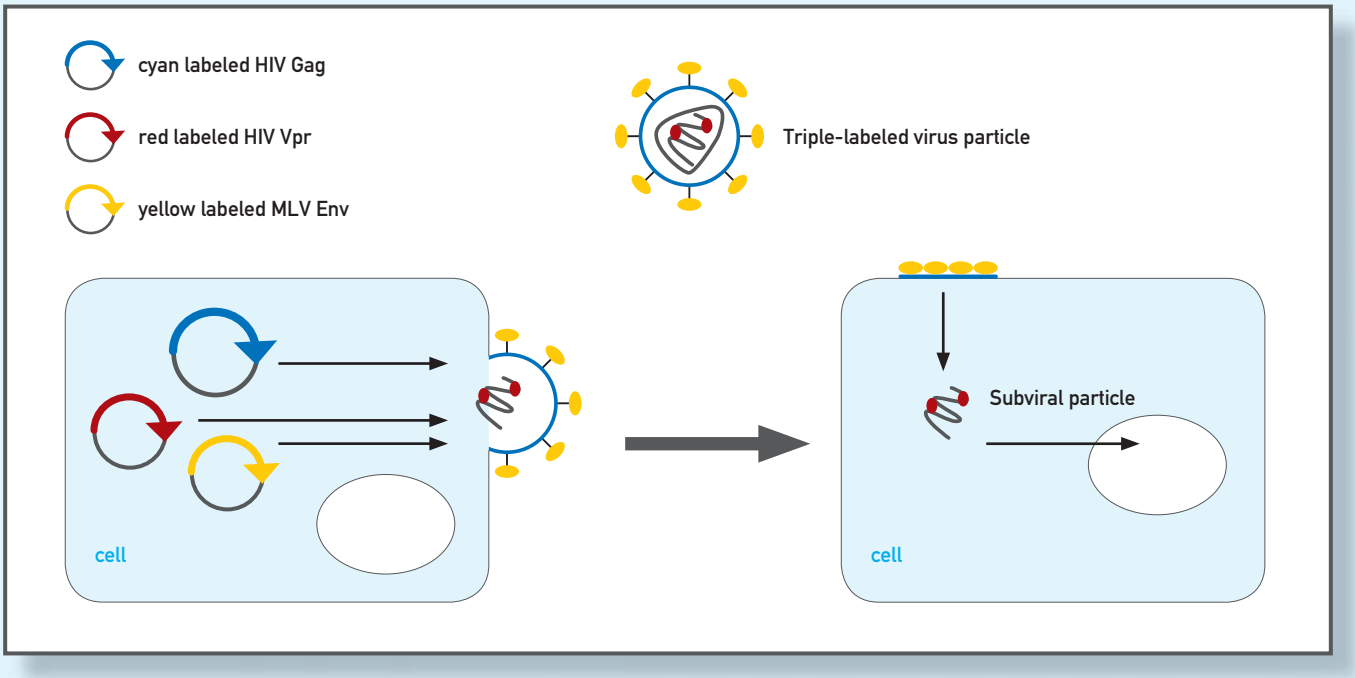
How viruses leave the cell

An equally important object of study is the mechanism by which new virus particles are released from the cell after making their way through it. This complex process known as "budding" could provide a whole range of targets for new antiviral drugs. So far, we know that budding is controlled by a viral structural protein.

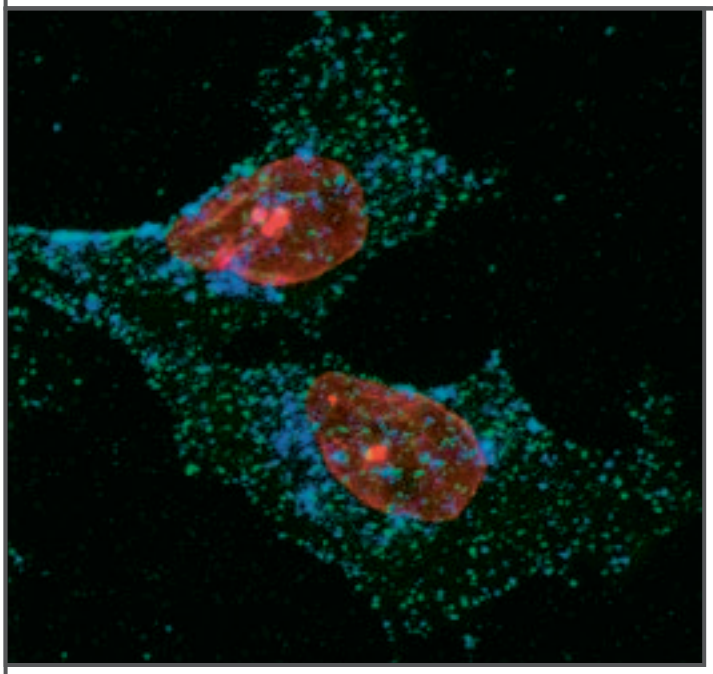
The components of the virus progeny are assembled at the cell membrane. Subsequently new virus particles bud out of the cell, thus acquiring the lipid membrane that allows them to invade further cells.

If the relatively flat lipid membrane of the cell is to fit the spherical surface of the tiny virus particles, it has to be bent accordingly. But how is this done? Theoretically, this bending might correspond to the coating of colloidal particles. This is a process that can be simulated mathematically. The resulting model allows predictions about virus budding that can subsequently be verified by experiments. It may however be that the virus recruits

Generation of triple labeled virus particles for fluorescence microscopy



Fluorescent proteins can be incorporated into virus particles by molecular cloning techniques. Differently colored fluorescent labels allow us to follow the interaction of virus and host cell in detail.



Using fluorescence microscopy, we can follow the path of the virus particles (bright dots) through the host cell.

cellular proteins able to bend the membrane. This alternative can also be simulated by means of mathematical models.

Further experimental information is supplied by new imaging techniques, for instance high-resolution fluorescent microscopy (STED microscopy) in conjunction with so-called cryo-electron tomography. Both methods will be available in the BioQuant network. These techniques provide detailed two- and three-dimensional images of the way viruses enter the cell and how they bud. Stepwise observation of these complex processes will enable us to characterize the structures in detail and to include them in existing models of viral penetration and release. These insights will be supplemented by precise quantitative analysis of the composition of the virus particles.

New drugs against viruses

The results of these complementary studies will furnish information required for the experimental verification of an integrative model of the individual stages of HIV infection and its implications. The methods described can be used not only to investigate the virus causing Aids but also other viral pathogens. These research projects are of major medical significance, as precise knowledge of the "tricks" resorted to by viruses is the prerequisite for developing novel drugs capable of thwarting these cell parasites.

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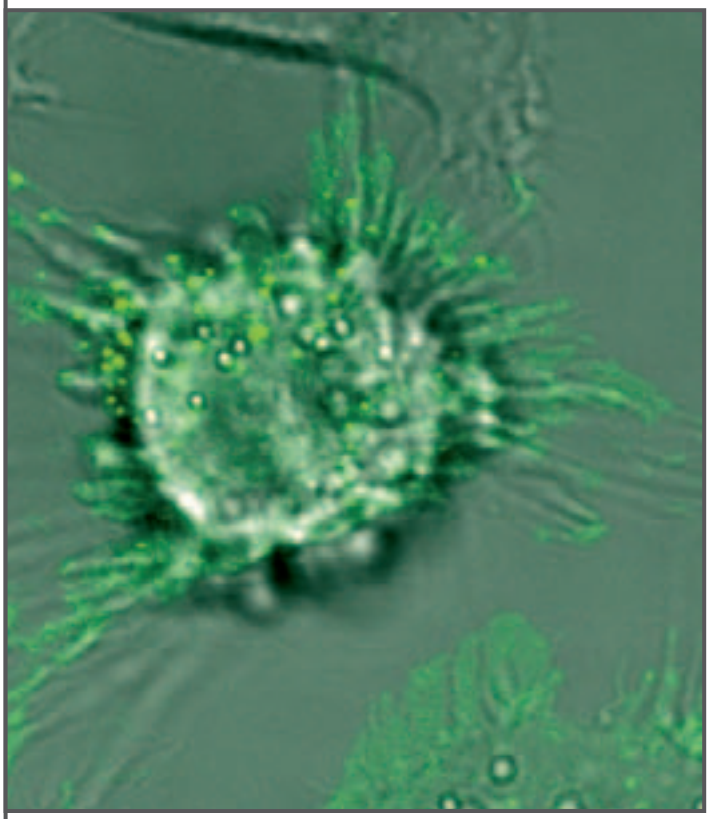
The Suicide Programme of the Cell: Apoptosis and Its Contribution to Life

Though apoptosis causes the death of cells, it is in fact one of the crucial programmes without which life would be impossible. Much is already known about how apoptosis functions and what triggers it. But it is far from being understood in its entirety. Roland Eils explains how mathematical models can help to supply a complete picture of the cellular suicide programme.

Modern molecular research has produced a hitherto unprecedented amount of data on the causes, the progress and the course of severe and complex illnesses like cancer or neurodegenerative disorders. The molecular roots of many other diseases have also been identified. Data material obtained at the level of genes and proteins is constantly accruing.



Photograph of an apoptotic cell

But data alone do not tell us enough about illnesses like these. The challenge is to integrate the data so as to achieve a holistic understanding of such disorders. An approach of this kind will center on mathematical models based on the strictly quantitative collection of molecular data. These models incorporate information about metabolic and signal transmission pathways as well as the regularities governing cellular communication. The general aim is to change the focus in the investigation of complex illnesses to the systems biology level. This is the only approach that can capture the dynamic nature of the processes going on in the entire cell.

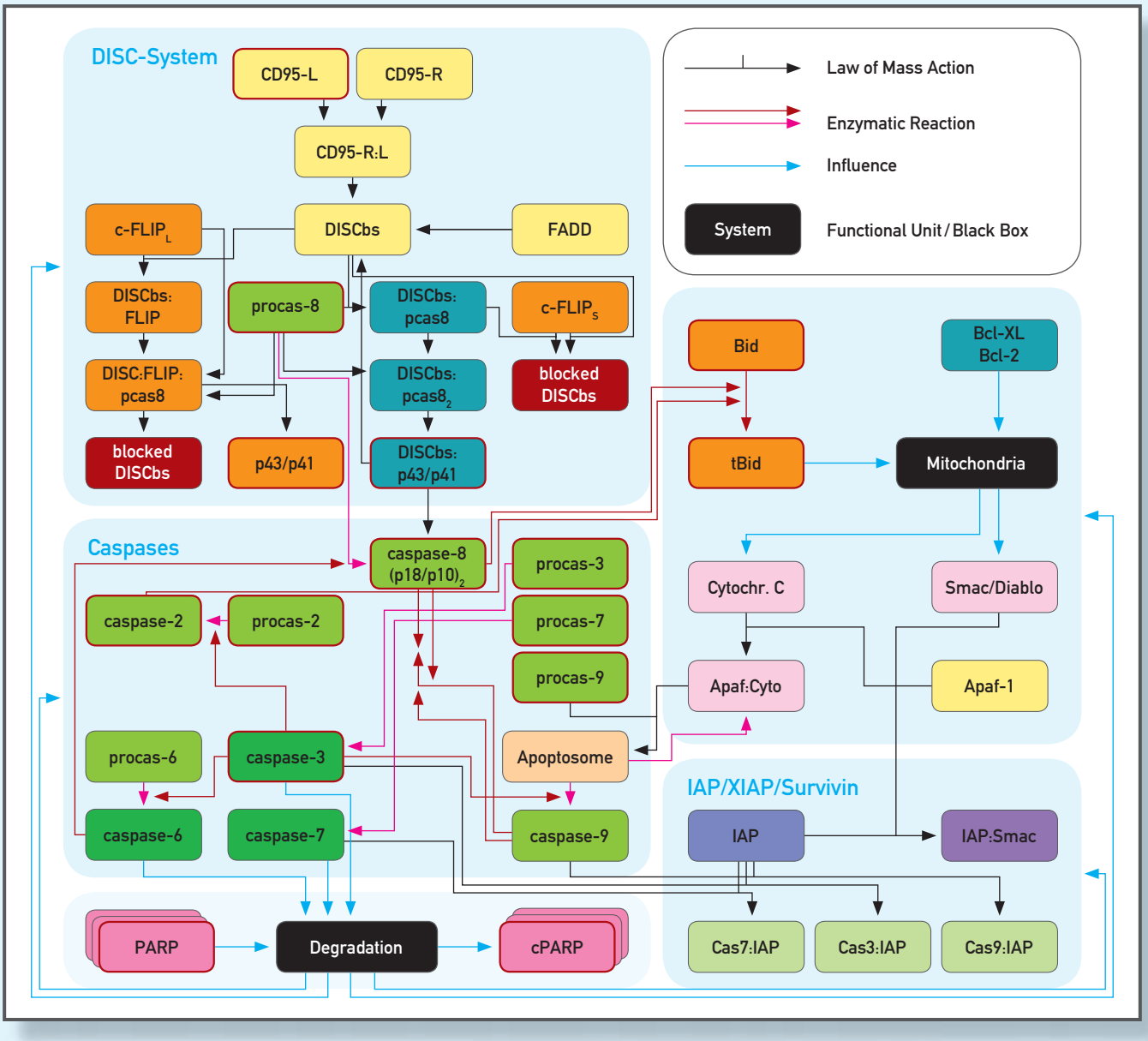
A key element of life

Our group's research emphasis is on cell death, one of the key elements of life. Biologists distinguish at least two forms of cell death, apoptosis and necrosis. Apoptosis is a tightly regulated process of elementary significance for the development of organisms, tissue homeostasis or the correct functioning of the immune system. Apoptosis makes it possible to rid the organism of superfluous, old or damaged cells. Cells dying as a result of apoptosis are disposed of "quietly". Usually, specialized immune cells called phagocytes take up the dying cells and "dispose of" them. Necrosis takes a more "dramatic" course and is invariably accompanied by signs of inflammation. One example of such inflammation is jaundice, which is caused by the sudden and massive death of liver cells as a result of necrosis.

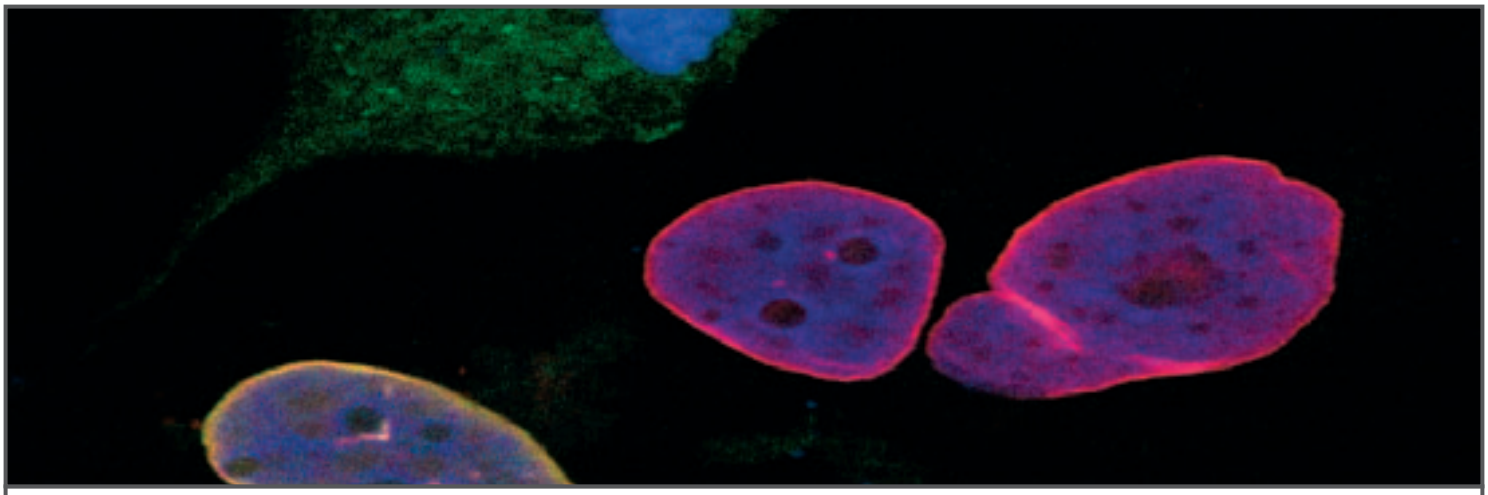
“If apoptosis does not function as it should, severe illnesses may be the result.”

Roland Eils

Model for CD95-induced Apoptosis



A simplified yet complex mathematical model of receptor induced programmed cell death.



MCF-7 cell expressing the nuclear lamin protein lamin B2.

Accordingly, apoptosis is at first glance less "spectacular" than necrosis. More importantly, it follows a predictable pattern, which is why it is also referred to as "programmed cell death". For example, studies of *Caenorhabditis* elegans, the thread worm, have indicated that during its embryonic development exactly the same 131 cells always die in a controlled manner. In human development, cells also die in a "pre-programmed" way. Every second, millions of cells in the adult body die an apoptotic death and are replaced by new cells. Essentially, all the cells in the human body are subject to apoptosis, which implies that all the elements required for an apoptotic reaction are part of the basic equipment of every cell.

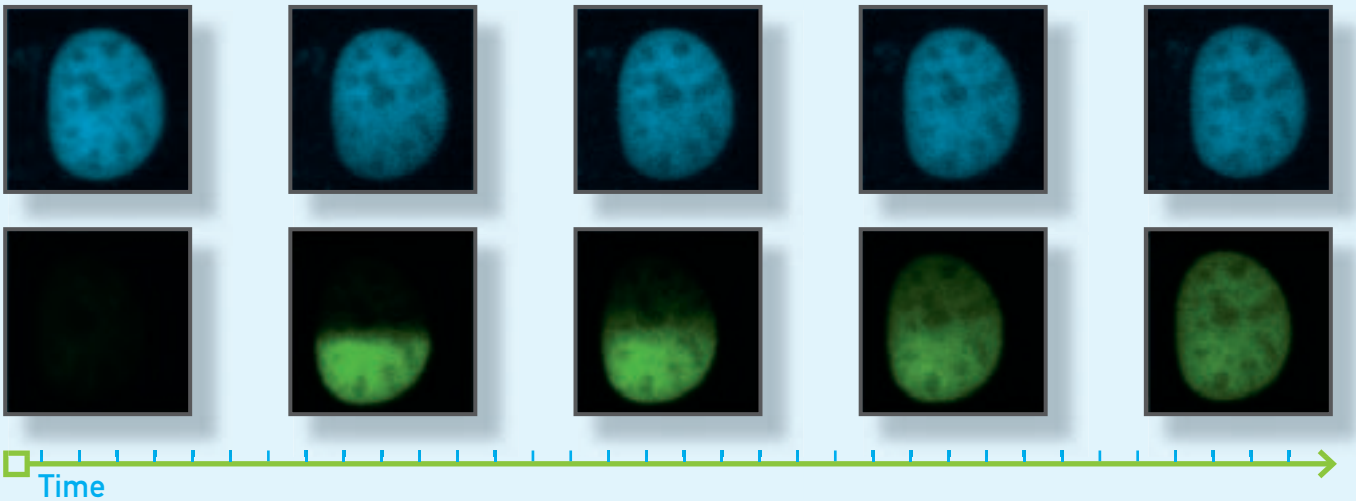
Defects in apoptosis result in severe illnesses. "Too little" apoptosis frequently leads to cancer or autoimmune diseases (in which the immune system attacks the body's own tissue). "Too much" apoptosis contributes to the development of the immune deficiency disorder AIDS, a number of infectious diseases as well as heart attacks and strokes.

Death Receptors

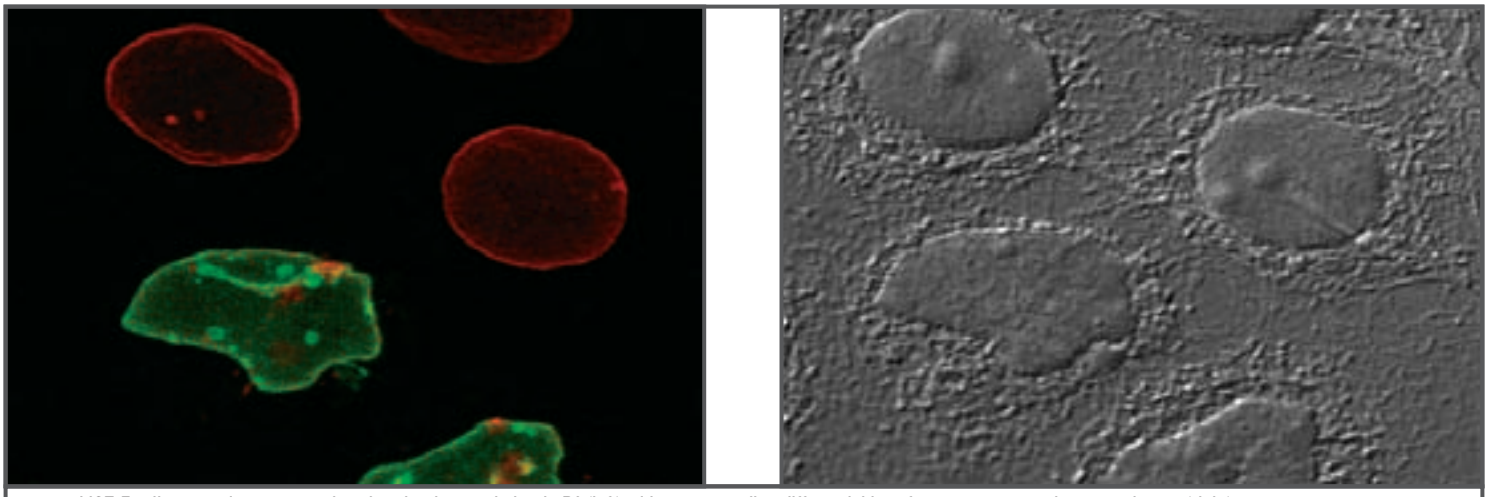
What triggers apoptosis in a cell? Potential factors include UV- or γ-irradiation, chemotherapeutic agents (*i.e.* drugs used to fight cancer), pathogens, the withdrawal of growth factors ("death by neglect") and the activation of receptors or "antennae" on the surface of the cell known as "death receptors".

In the interior of the cell there are two signaling pathways that end in apoptosis. The so-called extrinsic signaling pathway begins with the death receptors on the membranes of cells. The

Estimation of protein kinetics



Photoactivation can be used to perturb fluorescence distribution and characterize its redistribution over time.



MCF-7 cell expressing a mutated nuclear lamin protein lamin B1 (left) with corresponding differential interference contrast microscopy image (right).

intrinsic signaling pathway runs through the mitochondria, the "power plants" in the cell interior. In both signaling pathways the operative molecules are enzymes called caspases. Apoptosis triggered via the death receptors is one of the best-studied signal transmission pathways of the cell that we know most about. However, what we do not have yet is a systemic understanding of this complex signaling pathway and its regulation by a large variety of factors operating at once.

At present we have no experimental approach capable of observing the short- and long-term changes in all the molecules involved in apoptosis. It would thus be of major benefit to have a mathematical model of apoptosis bringing together the currently heterogeneous state of our knowledge on the subject. Such a model could for example enable us to identify sensitive signaling molecules or to predict an apoptotic effect sequence such as the reaction of the cell to the effects of chemotherapeutic agents. A mathematical model would also greatly benefit the rational design of new experiments.

A comprehensive model of apoptosis

Mathematical modeling can look back on a long tradition in biomedical research. By contrast, theoretical models describing the complex signal transmission pathways at a systemic level are a recent development. They are based either on discrete models describing signal transduction as information processing or on continuous models modeling information flux as a biochemical reaction network.

Recently, members of the BioQuant network developed an approach that circumvents the present obstacles to the modeling of signal transmission networks. The result was the first-ever comprehensive model of apoptosis. In addition, this approach brought a new apoptotic regulation mechanism to light, as well as identifying new key molecules regulating apoptosis.

This model of apoptosis is to be expanded in future to include signal transduction networks and processes affecting cellular metabolism, for example those involved in cell response to a stressor. Essential for this purpose is the advanced expertise in the field of high-resolution microscopy of the smallest structures of the living cell and in quantitative image analysis that BioQuant can draw upon. In this way we will be able to identify the individual responses of cells to apoptotic stimulation. In conjunction with biochemical experiments, mathematical modeling will do a great deal to enhance our still limited understanding of apoptosis.

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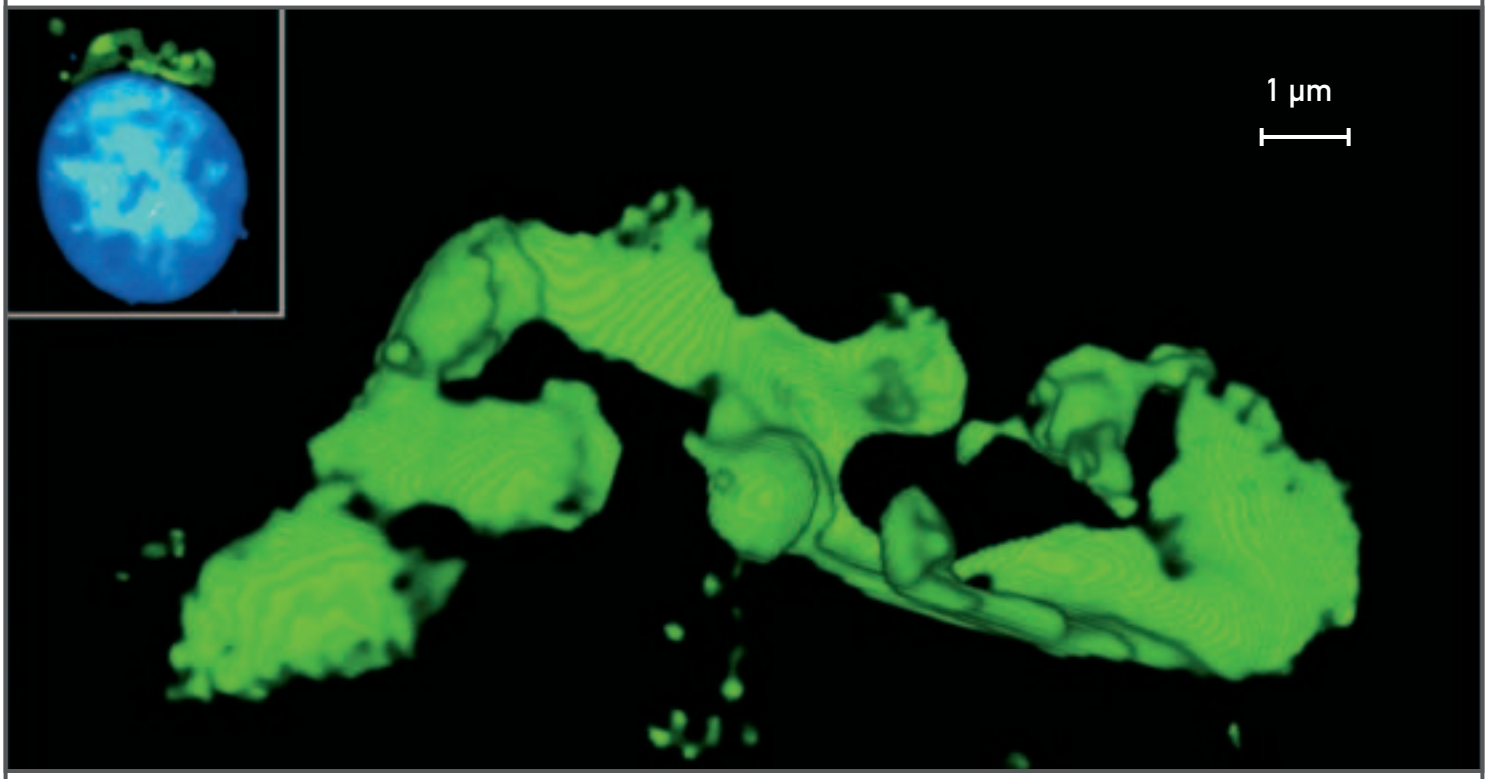
Inspecting the Nanocosmos

How do proteins interact and function in living cells? To study proteins at work, we need new microscopes with a resolution power greatly exceeding traditional optical microscopes. Stefan Hell and Dirk-Peter Herten describe new types of microscopes enabling us to inspect the nanocosmos of each individual cell.

Microscopy is the method of choice for observing living cells. With fluorescent dyes we can label proteins and nucleic acids and observe their distribution in the cell at a resolution of one thousandth of a millimetre. At this resolution we can actually visualize the individual compartments (the "reaction spaces") of the cell, for example its command center (the nucleus), its "power plants" (the mitochondria), or the Golgi apparatus, one of its distribution systems. Cell compartments like these are the locations of crucial biochemical processes such as the replication of DNA, the biosynthesis of proteins, or the formation and fusion of the tiny transport bubbles called vesicles.

Molecular machines in molecular factories

New research findings in cellular and molecular biology strongly suggest that these processes are organized and synchronized by



3D reconstruction of the Golgi apparatus in a live Vero cell at 100 nm spatial resolution. The data was obtained by 4Pi-confocal imaging of GalT-EGFP which primarily resides in the medial and trans part of the Golgi apparatus. The inset shows an Epifluorescence image simultaneously recorded in order to correlate the Golgi with the nucleus.

"We develop high-resolution microscopes with the aim to investigate the nanocosmos of living cells."

Stefan Hell

large assemblies of proteins known as "molecular machines" and even bigger structures called "molecular factories". One of the prime objectives of present-day biophysical research is to make molecular machines and molecular factories visible. The problem is that the protein assemblies in question are too small for standard optical microscopes to deal with.

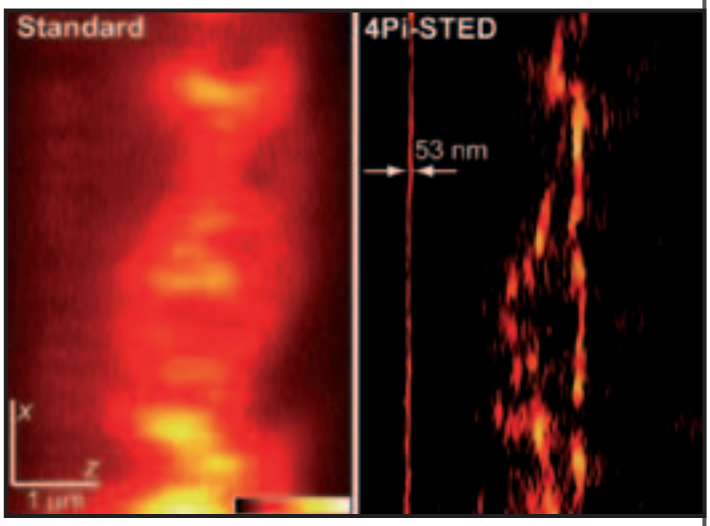
The Optical Nanoscopy research group headed by Stefan Hell sets out to solve this problem by developing novel microscopes with the nano-scale resolution (1 millionth of a millimetre) required to make the finest details inside a living cell visible and watch the proteins at work. Potentially, microscopes of this kind can help us to get to the bottom of biological puzzles that have so far resisted investigation. This challenging interdisciplinary endeavour requires the joint efforts of physicists, chemists and biologists alike.

The new techniques have one thing in common. They draw upon various optical or photophysical processes to limit the intensity profile of a spot-shaped light source (the so-called "point spread function" or PSF for short) of a single fluorescent dye molecule. Narrowing intensity distributions (so-called PSF engineering) reduces the overlap between neighbouring points of light and improves resolution accordingly. The effect is similar to a blurred light spot seen through a dirty windscreen at night. Turn the windscreen wipers on and the blurred spot turns out to be the two headlights of an oncoming car.

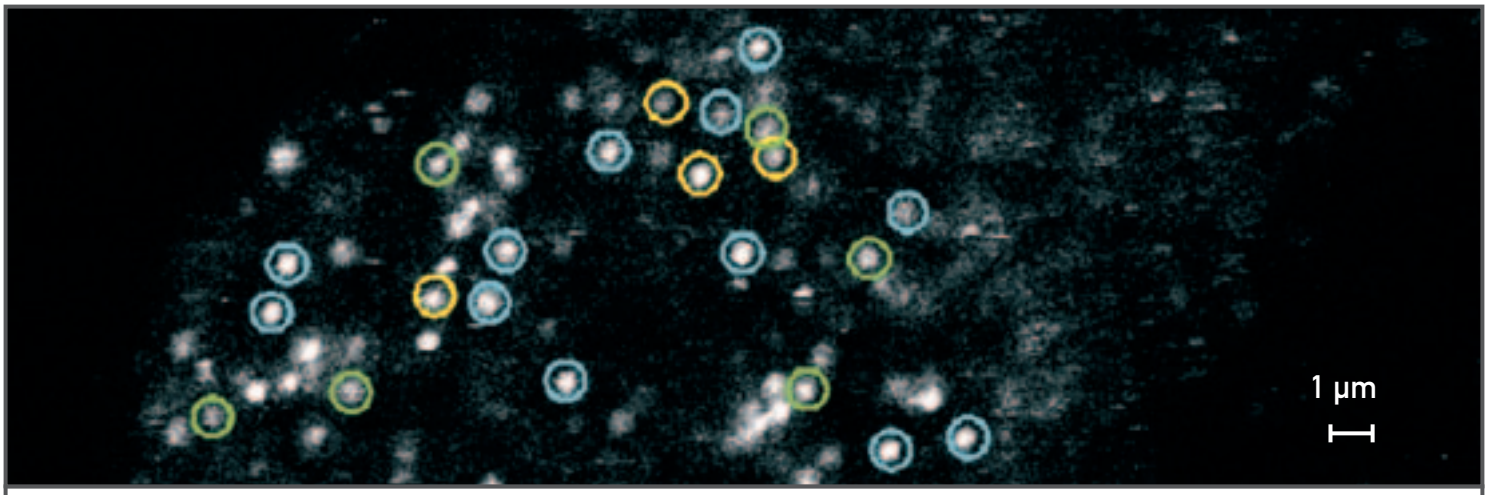
Cutting-edge microscopy

We have recently demonstrated that PSF engineering opens up entirely realistic prospects for breaking the diffraction barrier and substantially improving the resolution potential of optical microscopes (at present 200 nanometers). In biological samples we have achieved a resolution of <20 nanometres. This impressive enhancement of resolution is based on the saturation effects of the sample's optical response to the incident light. This is why we refer to our approach as "reversible saturable optical fluorescence transitions" (RESOLFT) between two states A and B.

"Stimulated emission depletion miocroscopy" (STED microscopy) breaks through the diffraction barrier of optical microscopy and uses photophysical processes for PSF engineering. As in confocal fluorescence microscopy, all fluorescent dye molecules within the diffraction-limited focal volume of the microscope are stimulated by a laser pulse. The "trick" behind the STED method is to selectively inhibit fluorescence at the periphery of the focal spot. This is done by "stimulated emission" a physical phenomenon by which an excited molecule is de-excited by light. Technically, the Stimulated Emission Depletion (STED-) microscope relies on pairs of synchronized laser pulses. The primary excitation pulse produces a three-dimensional spot of excited molecules



Simultaneously recorded standard confocal and STED-4Pi x-z images showing a section across the fluorescently labeled microtubular network of a HEK cell. The straight line is a fluorescent monomolecular layer attached to the coverslip, which demonstrates the superior resolution attained by the STED-4Pi-microscope.



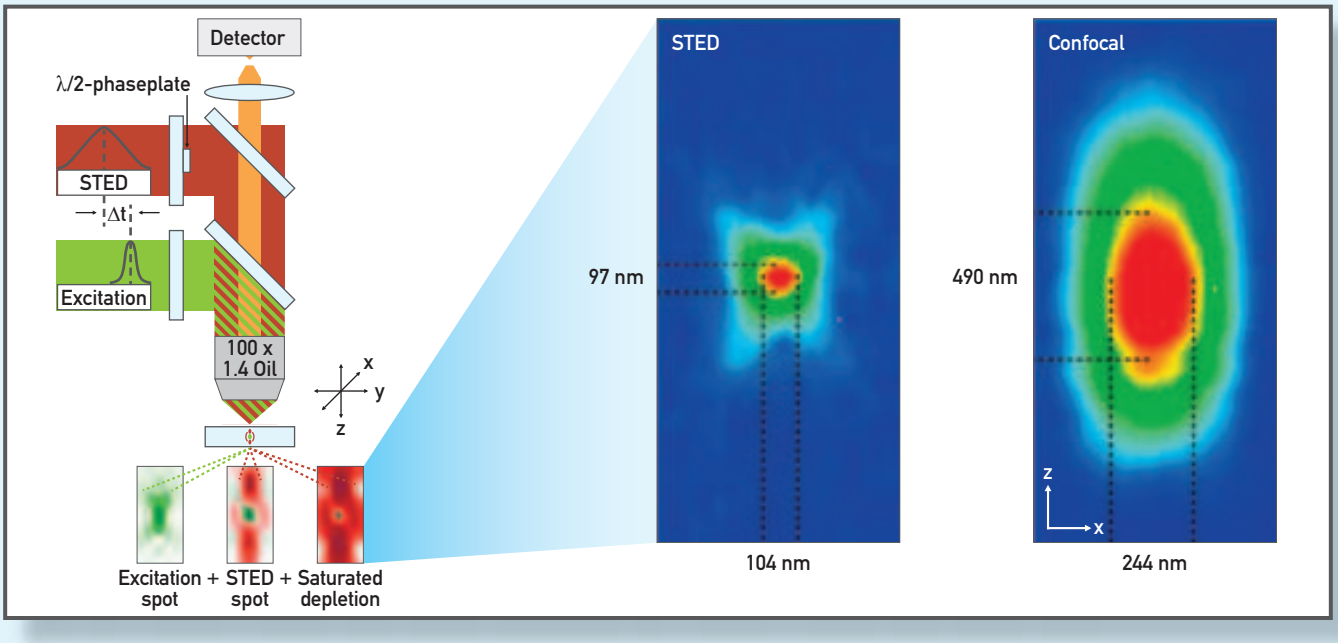
Cutting-edge methods in fluoresence microscopy allow us to count single molecules located in the cell nucleus; blue ring: 1 molecule, yellow ring: 2 molecules, green ring: more than 2 molecules

of regular diffraction size. A subsequent red-shifted STED pulse quenches the excited molecules back down to their ground state.

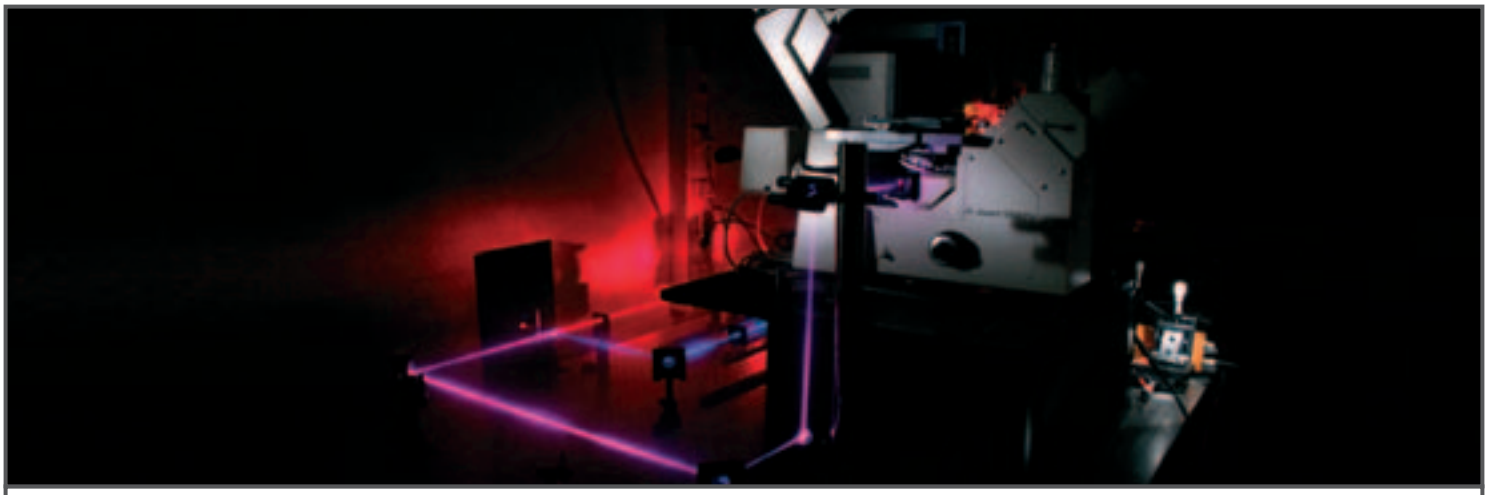
The STED pulse is arranged in a mode that only fluorescence at the periphery of the spot is inhibited, ideally leaving the center unaffected. Accordingly, the detectible fluorescence then stems from a spot that is smaller by a factor of 5 to 10 than the one defined by the diffraction limit of the excitation light. The picture below demonstrates an improvement of factor 3 in the transverse direction and up to 6 along the optical axis in a homogeneous fluorescent layer.

Another approach of PSF-engineering is the coherent superposition of focal wave fronts. This idea has been realized in our so called 4Pi-microscope that is already commercially available. By shaping the focal volume between two opposing objective lenses it is possible to achieve a 3- to 7-fold improvement in optical resolution along the optical axis. The superior 3D resolution of a 4Pi-confocal microscope is illustrated on page 34 showing a 3D rendered image of the Golgi apparatus in a live Vero cell. The number of image points in a three-dimensional image increases by the power of 3. Such a high-resolution image dramatically increases not only the amount of imaging data but also the time

Stimulated emission depletion microscopy (STED microscopy)



Concept of STimulated Emission Depletion and principle of the STED-microscope. Molecules in the excited state are forced to the ground state by a doughnut-shaped depletion pulse. The saturation ratio determines the degree of constriction of the resulting STED PSF, which in comparison with the confocal PSF shows resolution enhancement factors, which in the shown measurement amounts to ~ 5 in the z direction. Arranging the doughnut differently leaves enhancement factors of 3–5 in the xy-direction, as well.



Single-molecule fluorescence microscopy

necessary for image acquisition. Accordingly, parallelized data acquisition using multiple spots is an important approach for investigating fast biological processes in living samples which has been realized in the 4Pi-MMM-microscope.

The combination of both types of microscopes, namely the STED-4Pi-microscope, was the first to demonstrate a spatial resolution down to 30-50 nanometres with visible light and regular objective lenses. The resolution is further enhanced by applying (non-linear) image restoration techniques (page 35) which require powerful algorithms and computational resources, especially for 3D image restoration.

Stefan Hell has already received several national and international distinctions for his work, most recently, he was awarded with the 2008 Gottfried Wilhelm Leibniz Prize, Germany's most prestigious research prize.

The aim of the CellNetwork research group "Single Molecule Microscopy" headed by Dirk-Peter Herten is the quantitative investigation of sub cellular structures and their dynamics in living cells. With methods recently developed on the basis of single-molecule fluorescence microscopy (SMFS) we can obtain fundamental structural information on molecular assemblies within cells. By detecting and counting the photons emitted by single fluorescent-labeled proteins we can determine the number of protein copies present in a given molecular assembly. By sorting the photons in accordance with characteristic properties of the fluorescent labels (say, the lifetime of the excited state or colour) we can distinguish individual molecules and determine the distance between two labeled proteins down to an accuracy of 7 nanometres. SMFS also enables us to observe the dynamics of individual molecular complexes on a microsecond time scale, using for this purpose distance-dependent photophysical processes like fluorescent resonance energy transfer (FRET) between individual dye molecules.

How do proteins move?

Another method under development at present is designed to supply quantitative information on the way in which metabolic products and signaling proteins are transported between different cellular reaction spaces (compartments). This kind of knowledge is crucial for the modeling and simulation of cellular processes.

The combination of fluorescence correlation spectroscopy (FCS) and raster scanning microscopy can make the movements of fluorescence-marked proteins visible. The objective here is to detect the way in which differences in protein mobility depend on location and the kind of proteins involved.

The experimental approaches outlined above are designed to furnish quantitative data for mathematical modeling and simulation and to thus enhance our understanding of the complex network of biochemical and molecular biological processes taking place in living cells.

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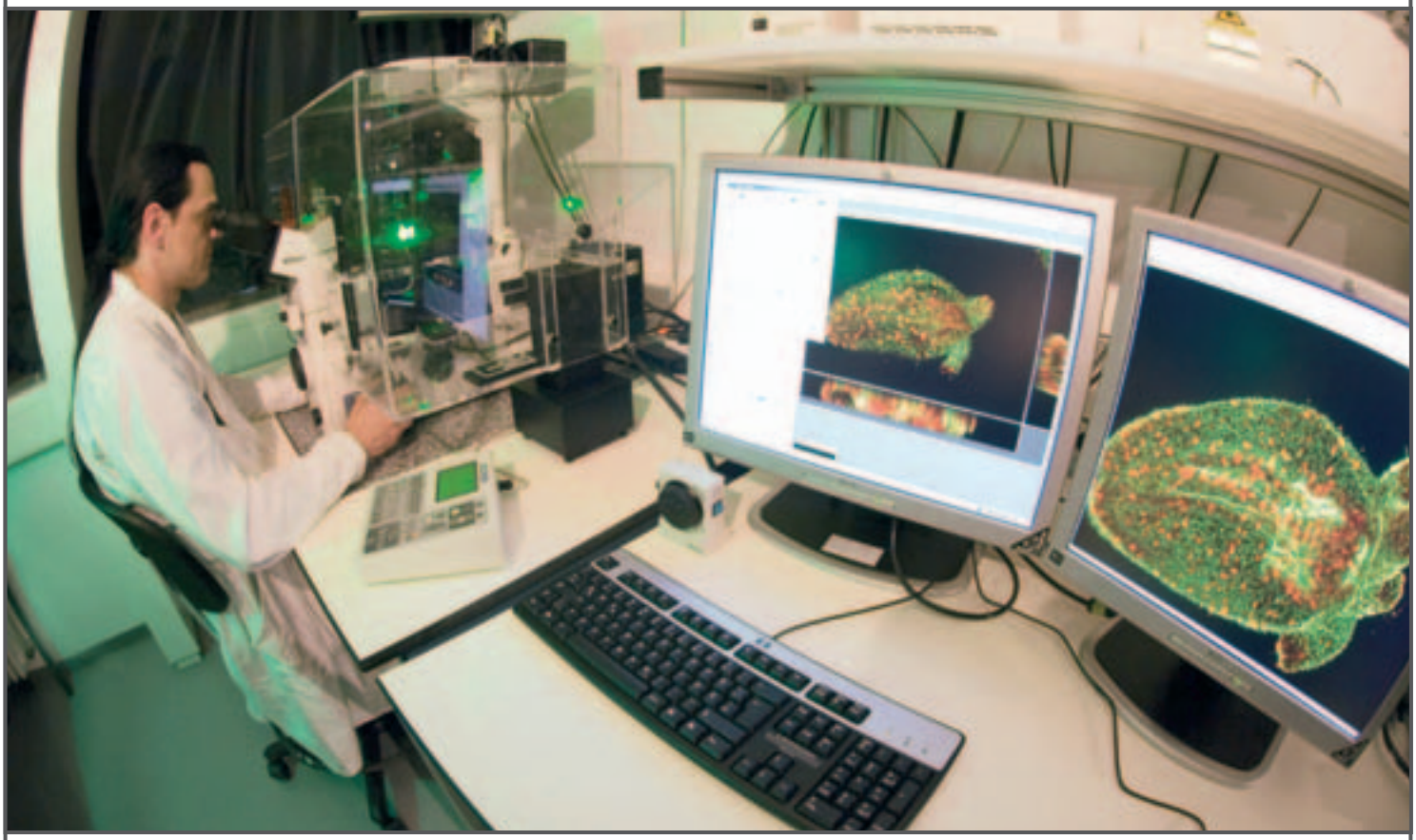
Unique Access to the Latest Microscopic Techniques

Modern cell biology research requires microscopes with the ultimate degree of sophistication. The collaboration between the University of Heidelberg, Nikon Instruments GmbH and other industrial partners has engendered a unique core facility offering the very latest in imaging technology, an essential prerequisite for research excellence. Ulrike Engel, the director of the NIC@Uni-Heidelberg, and Thomas Holstein of Heidelberg University's Institute of Zoology describe the new center and its exclusive resources.

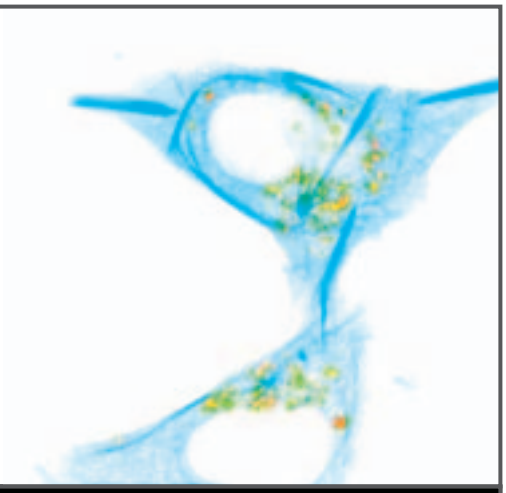
The Nikon Imaging Center (NIC) uses modern, high-performance microscopes to observe processes going on in vivo, i.e. in living cells. The NIC@Uni-Heidelberg has been established in cooperation with Nikon Instruments GmbH and other industrial partners. As the first center at the University of Heidelberg to implement the "industry on campus" concept, it provides scientists with access to highly sophisticated instrumentation required for modern cell biology. The NIC@Uni-Heidelberg was inspired by the Nikon Imaging Center established in 2001 at Harvard Medical School in Boston.



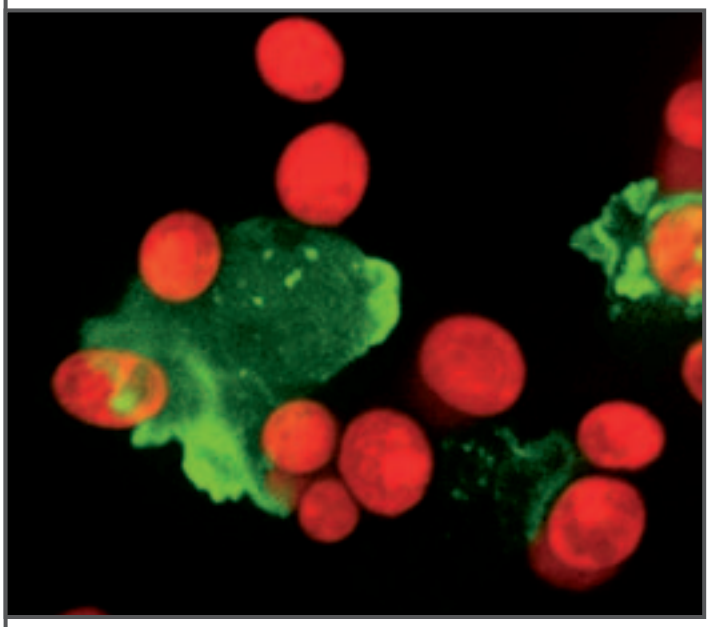
Laser Scanning Confocal Microscopy at the NIC, Dr. Christian Ackermann

“Research excellence in the biosciences requires the very latest in microscope technology.”

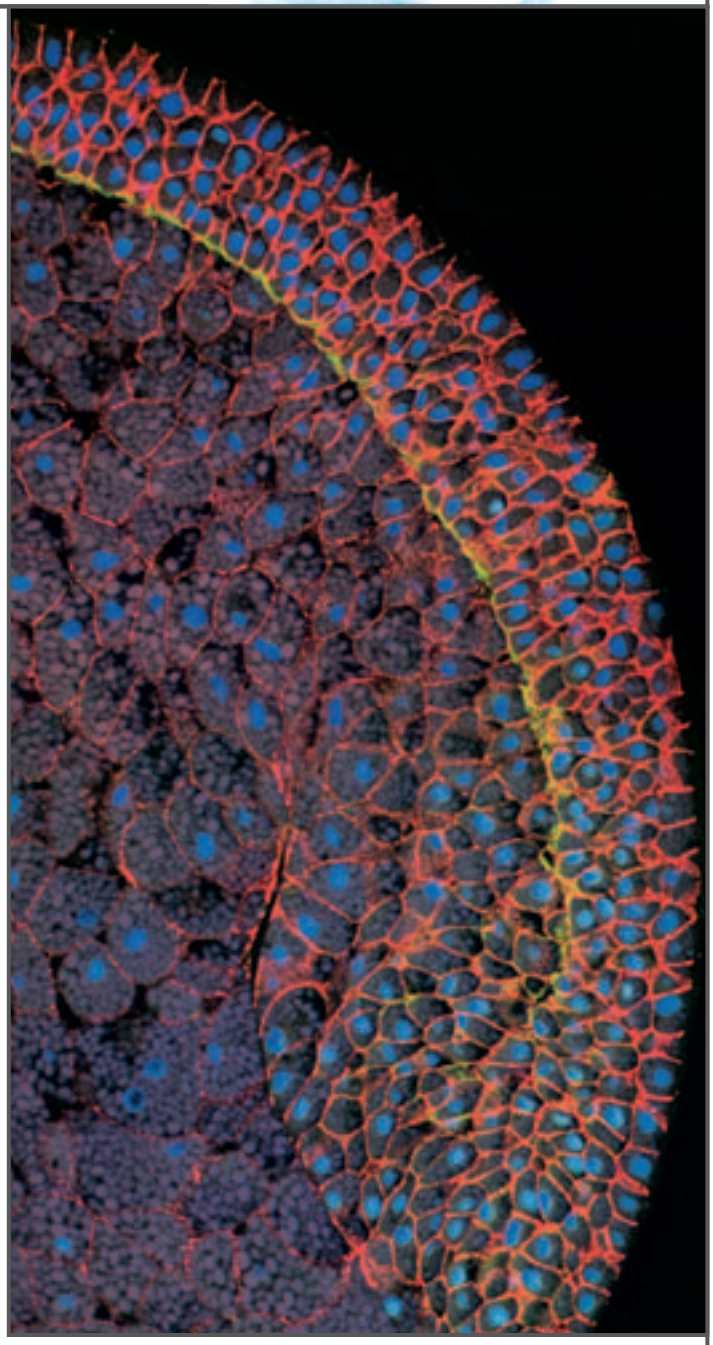
Thomas Holstein



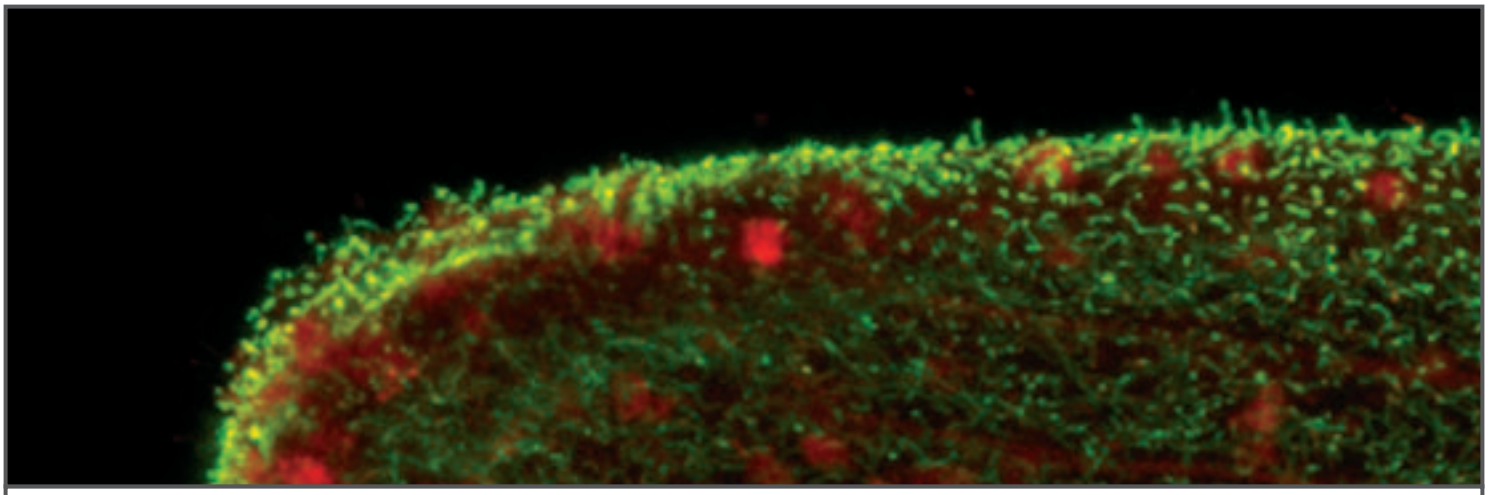
The center in Heidelberg has been serving Heidelberg’s research scientists since it opened its doors in 2005. The University provides space and infrastructure at the BioQuant as well as the scientific support. Nikon Instruments GmbH contributes the high-performance microscopes and other imaging equipment, which is regularly exchanged and adapted to Nikon’s newest innovations. In addition to the cooperate partner Nikon, additional cooperate contributors are involved (PerkinElmer, Hamamatsu, LIM, SVI, AHF and others). They provide real time confocal microscopes, highly sensitive cameras and specialized imaging equipment and analysis software. This gives research scientists on the Heidelberg campus access to state of the art microscope resources that in view of the headlong technical progress and the diversity of instrumentation, could hardly be financed by the University alone. The users of NIC@Uni-Heidelberg merely cover the running costs. Members of the institutions and research centers supporting



Microscopic snapshot at the site of crime: The unicellar amoeba Dictyostelium (green) in the process of devouring a yeast (red).



Gastrulation in the frog embryo. The clear demarkation line (yellow) between endoderm ant ectoderm is blurred at the site where ectodermal cells move into the embryo to form the future mesoderm.

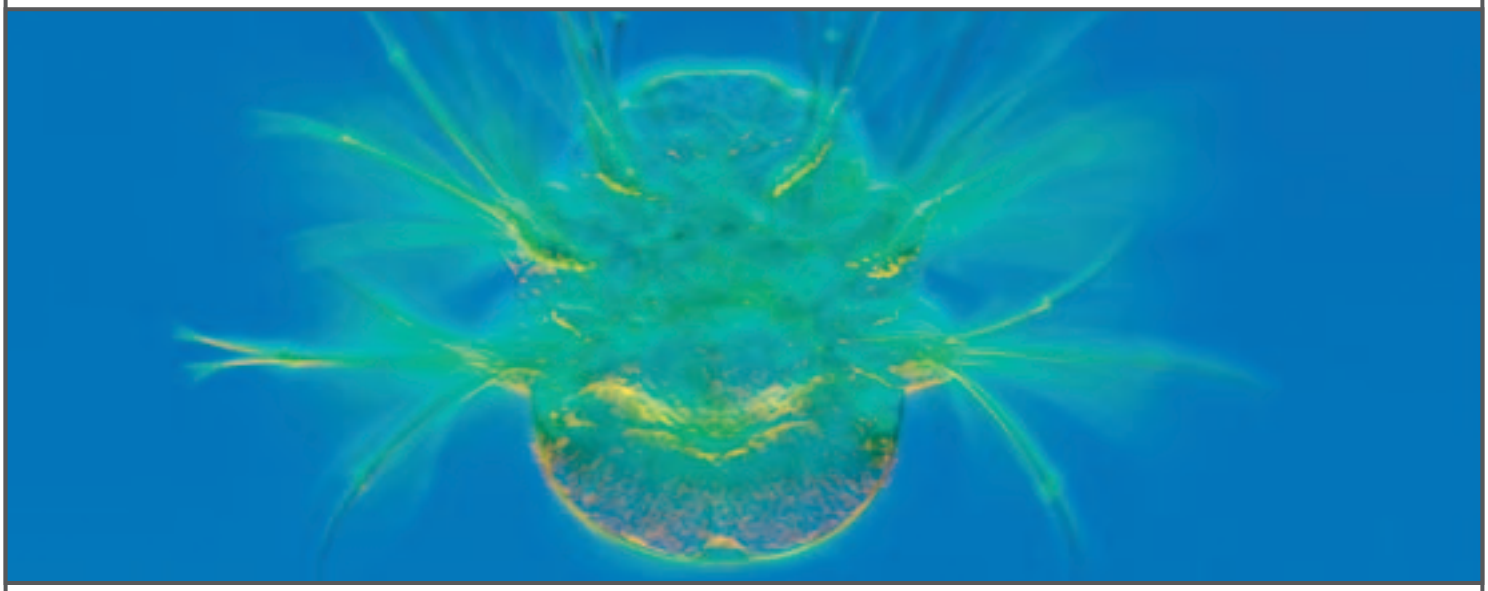


the NIC@Uni-Heidelberg (e.g. the German Research Foundation's SFB 488 and the excellence cluster "Cellular Networks") can use the center without incurring any further costs.

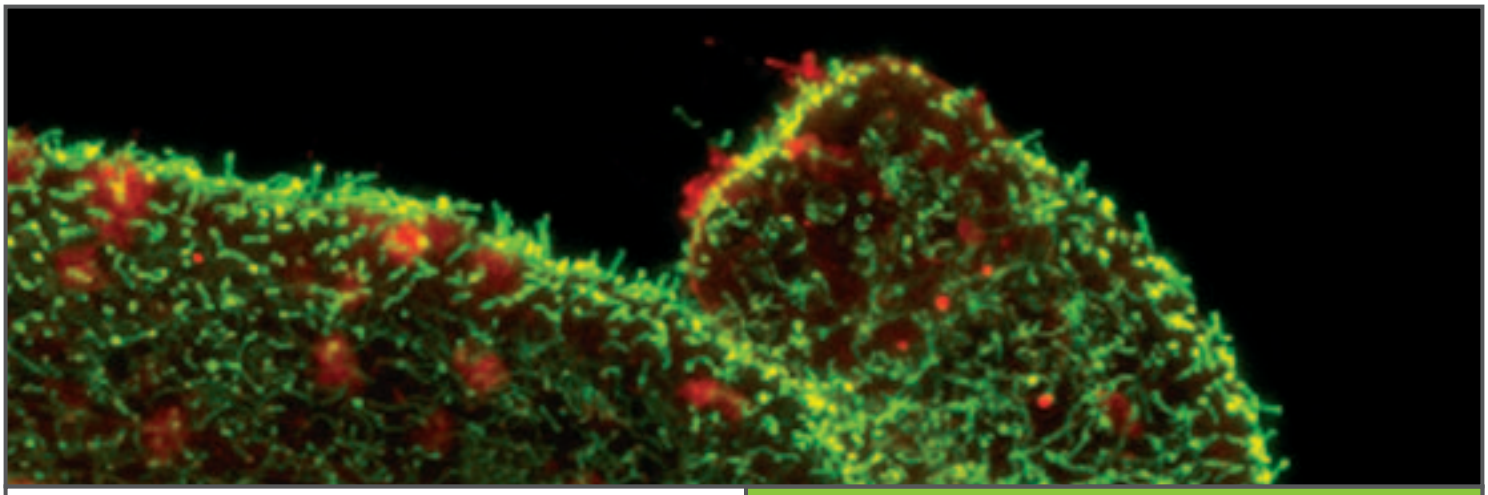
The imaging systems (on page 41) at NIC@Uni-Heidelberg enable scientists to engage in microscopic analysis of dynamic cellular and sub cellular processes in vitro and in vivo. For example, they make it possible to localize proteins, molecular interactions and signaling processes inside single cells. Or, on a different scale of magnification, detailed studies of pattern formation processes in the nervous system or in the course of embryonic development can be performed. The high temporal and spatial resolution of the microscopic systems generates vast amounts of data requiring storage capacities running to hundreds of terabytes.

The computing potential of the latest multi-processor systems can be drawn upon for the image deconvolution, analysis, and visualisation of cellular and molecular processes within cells and organisms. The imaging systems available at NIC@Uni-Heidelberg have already been used to explore a wide variety of topics, ranging from the description of cell dynamics within organisms to the observation of protein interactions in the cell interior.

In addition to the imaging techniques now available to Heidelberg scientists, another major asset for users of the NIC@Uni-Heidelberg is the competent scientific support provided by Ulrike Engel and Christian Ackermann. They advice scientists on the potential of the instrumentation with regard to the specimen and experimental approach. Typically, training consists of an assessment what equipment should be used, followed by a practical training session on the imaging setup. The supporting scientists can be consulted by the users until they are fully conversant with the imaging equipment and software. Experienced users work on the microscopes without supervision and may



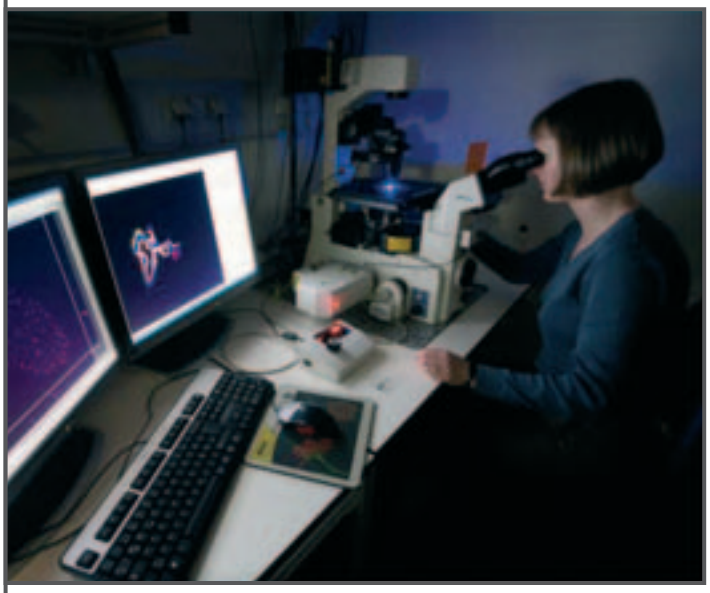
The making of a marine worm: The young polychaete (Platynereis) starts out as just head and tail armed with long bristles.



book microscope setups online. The NIC@Uni-Heidelberg also offers regular live cell imaging courses for PhD students and post-docs.

Current research projects include analysis of cell movement during gastrulation of amphibians, motility of the unicellular malaria agent (Plasmodium), actin dynamics in outgrowing mouse neurons, protein mobility inside the endoplasmic reticulum (ER) by photo-activation and FRAP. FRET applications cover redox state measurements inside mammalian cells, protein interaction at the immunological synapse during antigen presentation and assay of RNA doublex stability (RNAi method).

For more information go to http://www.nic.uni-hd.de or contact U. Engel and C. Ackermann (nic@uni-hd.de) or T.W. Holstein (holstein@uni-hd.de).



Ulrike Engel, director of the NIC@Uni-Heidelberg, at the microscope

Excellent Science with Excellent Instruments: Imaging Equipment at the NIC@Uni-Heidelberg

The equipment available allows for the analysis of processes ranging from cell migration in entire organisms to protein interaction in solution. The following techniques are available:

Laser scanning confocal microscopy in combination with FRAP (Fluorescence Recovery after Photo bleaching) and spectral analysis. Overlapping fluorescence spectra can be unmixed by simultaneous acquisition onto a 32-photomultiplier array. This allows for multiplex fluorescence and FRET (Fluorescence Resonance Energy Transfer) measurements.

Total internal reflection microscopy (TIRFM) to visualize processes at the cell membrane. The perfect focus system actively measures and readjusts the focus. Multi-fluorescence time-lapse sequences acquisition uses automated fast filter wheels and highly sensitive EM-CCD cameras.

High-speed 3-D acquisition on spinning disc confocal systems. Fast z-stack recording (piezo-stepper) and laser switching (AOTF) of 6 laser lines allow for multiplex fluorescence imaging at high temporal and spatial resolutions.

Upright automated fluorescence microscopes for multi-channel, multipoint and z-stack acquisition. Detail images acquired at high resolution can be aligned to cover the whole specimen (stitching software).

For imaging at physiological temperature the microscopes are equipped with heated chambers and objective heating.

Image Deconvolution and high-resolution 3-D reconstruction of multichannel data to visualize morphology and morphological changes over time.

BIOMS. Top-Level Research and Unprecedented Support for Junior Scientists

BIOMS is the first German center for modelling and simulation in the Biosciences. It started its work in Heidelberg in early 2004. The programme is unique in various ways, even internationally, not least for the unprecedented support it provides for upcoming junior scientists. Its aim is to develop models of complex biological processes that build on theoretical and experimental insights and are susceptible both for mathematical formulation and for computer simulation. As such, BIOMS is a significant part of the BioQuant idea. Willi Jäger and Ursula Kummer, coordinators of the new center, outline the BIOMS programme.

In the last few decades bioscientists have made great progress in the investigation of the molecular structures and processes involved in living systems. Their findings are already being extensively drawn upon both in biotechnology and in medical diagnostics and therapy. Recent advances in biophysics, biochemistry and information processing make it possible to amass a host of data that can only be dealt with by developing and implementing quantitative methods of the kind that already play such an important role in physics and chemistry.

This requires the elaboration, mathematical formulation and computer simulation of models of biological processes based on experimental data. Systematic progress in research thus revolves around the constant interplay between real-life experimentation, model analysis and "virtual" experiments on the computer. This brings about major improvements not only in the theoretical and quantitative understanding of complex biological systems but also in the efficiency of quantitative analyzes, biotechnological processes and medical procedures.

Many of the technological achievements we use today without giving them a second thought – cars, aeroplanes, satellites – could never have been designed or produced without modeling and simulation. In biomedical research, however, modeling and simulation are still in their infancy. Accordingly, the BIOMS programme is a significant contribution to the enhancement of the quantitative biosciences.

BIOMS unites research scientists from the University of Heidelberg, the German Cancer Research Center (DKFZ), the Max Planck Institute for Medical Research, the European Molecular Biology Laboratory (EMBL) and EML Research gGmbH, the research institute of the Klaus Tschira Foundation. The annual

"Without modeling and simulation, cars, aeroplanes or satellites would be unthinkable. In biomedical research modeling and simulation are still in their infancy."

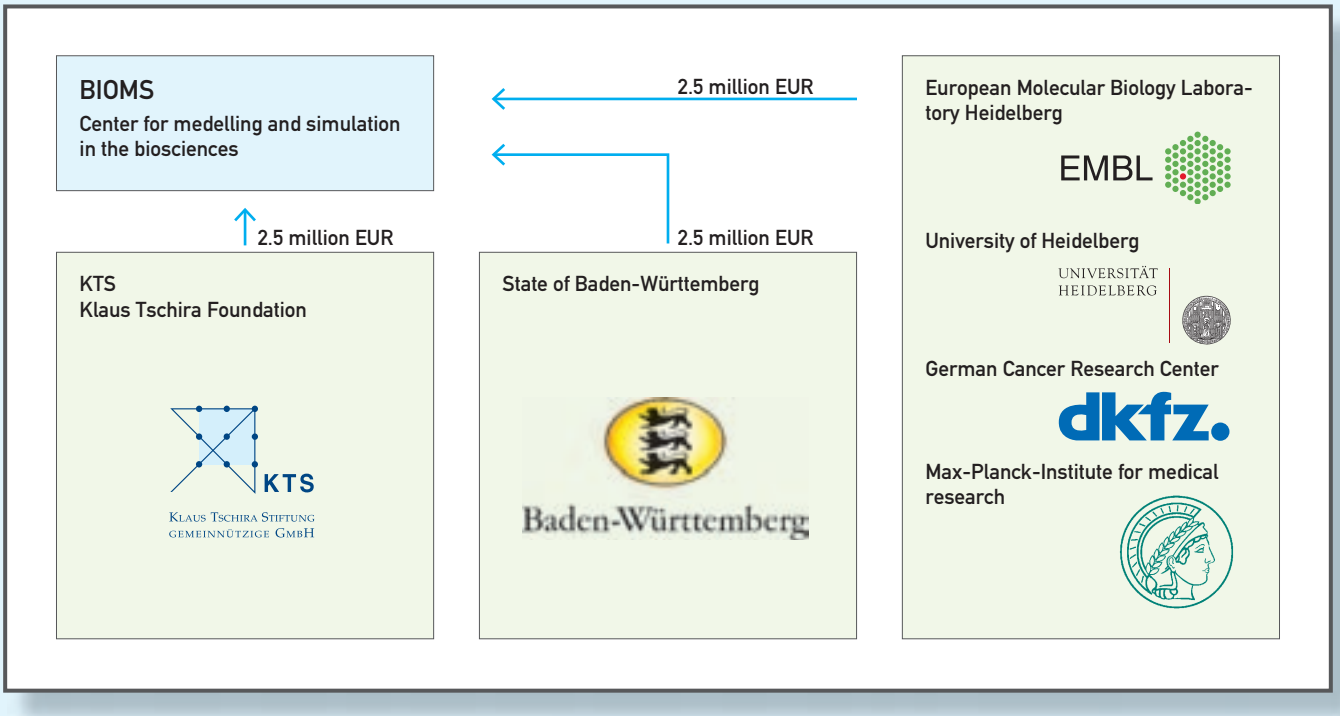
Willi Jäger

budget amounts to 1.5 million euros and is guaranteed for five years. It is funded equally by the state of Baden-Württemberg, the Klaus Tschira Foundation and the institutions involved. Such cooperation in the funding of cutting-edge research is in itself remarkable.

The resources placed at the disposal of the network are dedicated exclusively to the support and encouragement of junior scientists. Three junior research groups headed by outstanding young scientists have already been established. In the following pages these young scientists provide the reader with outlines of the work they are engaged in. In addition, the financial resources are used to support young post-docs applying for a research sojourn at one of the institutions involved in the programme. The posts are advertised internationally and to qualify for selection the candidates have to satisfy the exacting criteria applied by the center's scientific committee to assure the high standards of the BIOMS research projects. The scientists of the BIOMS center have been among the first to move into the central building of BioQuant which opened in early 2007.

www.bioms.de

BIOMS Partner



The Internal Architecture of the Cell

What is it that enables uncoordinated proteins to form into structures capable of performing biological tasks with astounding accuracy? This is a central issue in biology and no one has come up with an answer yet. With reference to a fascinating cellular structure called the spindle, BIOMS research group leader François Nédélec of the European Molecular Biology Laboratory explains how scientists set about solving this riddle.

The human genome project has been a major achievement, providing the DNA sequence determining all genes in our bodies (www.ensembl.org). Over the last few years, other powerful experimental techniques have increased the amount of available data even further. At present, scientists all over the world are in the process of characterizing the approximately 24,000 proteins encoded by the human genome.

One central issue is the identification of the proteins involved in vital cellular processes such as cell division. Today, a molecular-biological method known as RNA interference makes it possible to "silence" selected genes and compile a systematic catalogue of all the genes and proteins involved in cell division (www.mitocheck.org). Ultimately, these and other high-throughput techniques will enable us to make a complete list of all cell components, their functions and interactions.

The vast amount of data and the new methods for analyzing them swiftly are changing the face of research, shifting the emphasis from identifying components to studying how they interact collectively in order to produce cellular functions. The new archetype is not only to discover the proteins involved in a process, but also to understand how they function together.

Proteins are not passive components

However, even assuming that knowledge at the protein level is complete and devoid of artifacts, the task of putting it together is formidable. One notable difficulty is that cells operate far from thermodynamic equilibrium. For example, proteins can actively change conformations, e. g. when they bind together. So they are not passive components but something more like tiny, highly complex molecular machines. Moreover the same protein can be

"How can uncoordinated and inevitably imperfect movement of proteins and other molecules result in a structure like the mitotic spindle that is capable of performing a biological task with such incredible accuracy?"

François Nédélec

implicated in multiple cellular functions in different cell types. To piece together all the experimental data obtained on proteins so far we need a prediction model for the living cell. Creating this model will require constant interplay between theory and experiments, and careful quantitative analysis to test and re-test its validity. Our group is pursuing this objective in the research field of internal cellular architecture.

Remarkable versatility

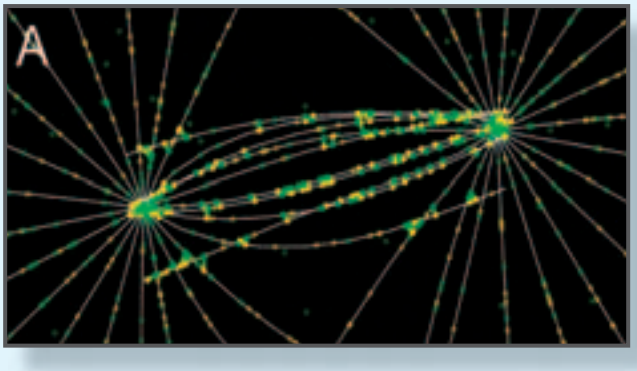
All multicellular organisms on earth, whether humans, animals or plants, consist of so called eukaryotic cells. These cells have a nucleus and organelles (characteristic cellular components performing specific functions) enveloped by membranes. Eukaryotic cells are able to specialize, i. e. to differentiate to form muscles, brain, skin, etc.

Eukaryotic cells largely owe their remarkable versatility to the plasticity of a structure that defines and determines their internal architecture: the cytoskeleton. It enables the cell to change its form, exert force or move around. All these processes are vital for the survival of multicellular organisms. Nerve cells, for example, extend their long outgrowths (axons) to establish precise connections with muscle cells; white blood cells migrate precisely to the place where the body has been invaded by pathogens; muscle cells contract.

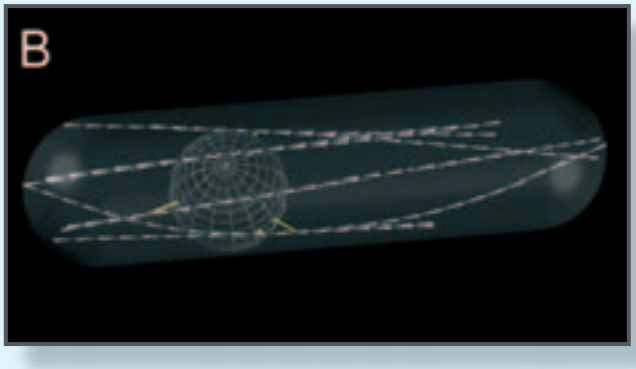
Miniature bones in the interior of the cell

The major components of the cytoskeleton are protein fibers, such as microtubules and actin filaments, which assemble spontaneously from protein-monomers. These filaments have an intrinsic polarity, thus resembling arrows rather than simple

Stochastic computer modeling of microtubules using Cytosim



(A) Snapshot from a simulation in 2D with two microtubule-asters and multimeric motor complexes. Yellow and green dots represent the Microtubule-associated motors. Two such motors are linked by a stretchable element to model the multimeric BimC family spindle Kinesins.



(B) Snapshot from a simulation in 3D of the microtubule organization during interphase in the yeast S. pombe. The microtubules are modeled with segments of appr. 0.75 µm, which are depicted here in a gradient of gray-level, to show the overall polarity of the microtubules. On a single processor, these two situations can be calculated in real time.

A computer model of spindle motions during anaphase in C. elegans embryos. Accurate spindle positioning is a key prerequisite of asymmetric cell division.

straight lines in space. Their mechanical properties are considerable. Microtubules are so firm and rigid that they can legitimately be compared to miniature bones. By contrast, actin filaments are more flexible and frequently function like contracting cables. Actin and microtubules often cover the entire cell, supporting it mechanically. A sophisticated system of auxiliary proteins supports the two types of fibre. Some of the auxiliary proteins connect up microtubules to actin filaments, others function as miniature locomotives moving along the fibres. Some of these locomotives transport vesicles bearing valuable cargo from the interior of the cell to the periphery, others convey their loads in the opposite direction.

Creating spontaneous order

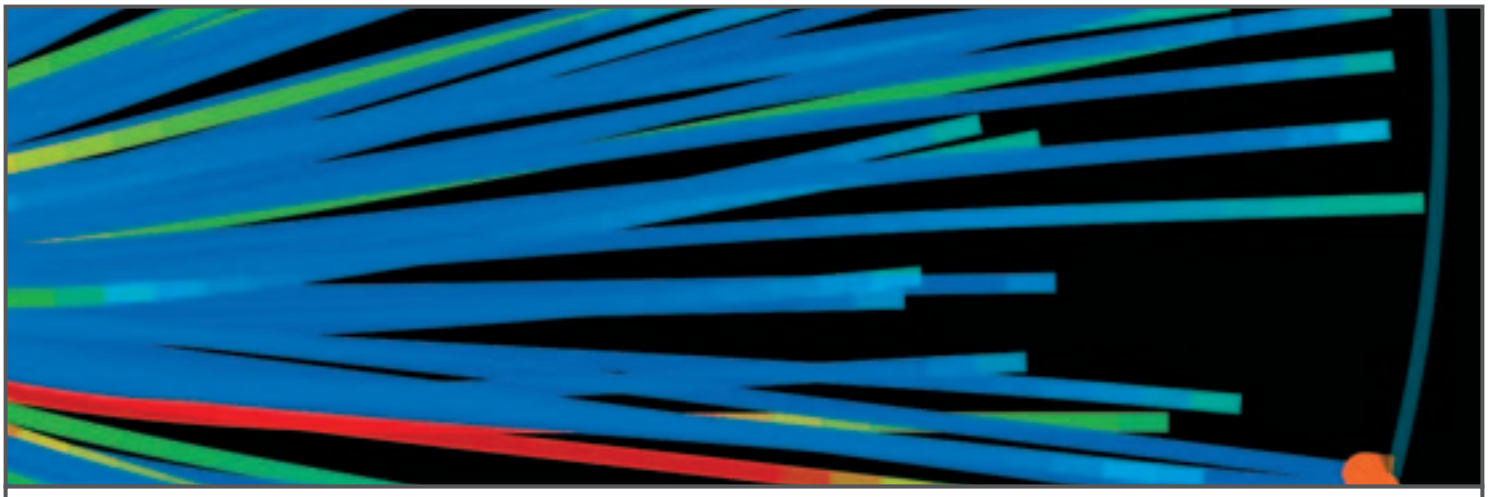
The cytoskeleton is able to create the order needed by cells to function properly. Interestingly, this ability is intrinsic to the fiber and associated proteins, rather than being driven by an upstream process, such as regulated expression of genes. It was shown, experimentally, that an initially uniform mixture of fibers and molecular motors could spontaneously organize in space and create spatial order. The presence of consumable energy in this system is essential, to fuel motor motion along the fibers, which drives the entire organization.

The same is true in vivo. For example, during cell division, segregation of the chromosomes is accomplished by a structure made of microtubules called the mitotic spindle. In this structure, the chromosomes, microtubules and numerous associated proteins (motors and crosslinkers) are all physically connected, forming a mechanical device that will eventually pull on the chromosomes and segregate them. Recent observations have shown that the structure is not in equilibrium, but rather highly dynamic: within the spindle, microtubules grow, shrink and disappear in a matter of minutes. New microtubules are also continuously created. The spindle itself, however, can subsist for hours. Actually, none of the proteins forming the spindle remain for long, yet their permanent interactions result in a stable overall structure: a spindle conserves its shape and size and applies the balanced forces necessary to position and segregate the chromosomes very precisely, as needed for the cells to duplicate and survive.

Random protein collisions

This is doubly astonishing in view of the micrometric scale on which these processes take place. At micrometric level, Brownian motion has a very dominant influence. All motions are stochastic and occur with unpredictable timing. The proteins are endlessly shaken and mixed by thermal forces. This results in random collisions, leading to protein interactions that at best obey the laws of probability. The spindle is thus a fascinating structure, which illustrates a central question in biology. How can uncoordinated and inevitably imperfect movement of proteins and other molecules result in a structure capable of performing a biological task with such incredible accuracy?

Somehow, the properties of the proteins enable them to cooperate constructively to form the structures that are crucial for cell survival. Deciphering this process is not at all straightforward for two main reasons: one is the huge diversity of proteins involved in most of the structures. For example, the spindle is made up of more than 200 components, some of them with millions of copies. The other is the enormous complexity and the dynamic of the interactions between these components.



Staggering complexity

Our research group's objective is to study cytoskeletal structures, such as the mitotic spindle. Our investigations are designed to enhance the understanding of severe illnesses like cancer, which arise when malignant cells divide and proliferate in an uncontrolled manner. The biological complexity we are faced with is staggering, yet a lot can already be done by applying quantification and modeling methods in biology the way they are used in physics.

To approach the problem of how the cytoskeleton generates cellular order, we first develop in vitro experiments and modeling tools. These in vitro assays are used to remove some of the unknown factors present in live cells. To complement this approach, computer simulations allow us to reconstitute the systems in a framework in which all the properties are specified exactly by the model. Using simulations, we can easily test the consistency of the models built from experimental observations. In practice, we develop innovative numerical methods to simulate the collective behavior of the various multiple polar fibers and the proteins associated with them (www.cytosim.org).

Simulations are often used to validate or refute existing theories, but they can also be used more creatively. We scan systematically through various properties of molecules, and automatically identify combinations able to produce a certain structure. This leads to new verifiable hypotheses on how proteins may be combined to form the observed cellular organization. Our group works experimentally and theoretically on mitotic spindle formation, using preparations made from the eggs of the African clawed frog *(Xenopus laevis)*. We also study cellular morphogenesis in the yeast *Schizosaccharomyces pombe* and the generation of asymmetry in the first division of the thread worm *Caenorhabditis elegans* embryo.

Successful ensembles

We can compare the future of biology to a puzzle. High-throughput experiments will give us a list of all the proteins and other molecular components of a given cell. These are the pieces of the puzzle. Microscopy will enable us to observe cells in increasing detail. We will then not only have all the pieces of the puzzles in our hands, we will also know what the complete puzzle should look like. The challenge is to reconstitute the image from the set of known pieces. This task requires careful quantification, theory formation alongside computer-assisted simulation.

In the biological context this is an especially fascinating task. After all, the individual parts are not random. They have developed over millions of years by natural selection. Evolution has favored the successful animals, and in the process has selected groups of proteins and other molecules that fit in with one another particularly well. Accordingly, we not only have to explain how a group of proteins collaborates. Rather, we need to explain why the properties of the proteins are what they are, i. e. reveal which combinations of properties, in a given set of proteins, make them a successful ensemble in evolutionary terms.

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Cell Power

What role do mechanical forces play in the adhesion of cells to surfaces? This issue is being investigated by the scientists of the BIOMS research group on "Cell Adhesion Forces". Ulrich Schwarz, the head of the group, describes what is known about cellular forces and how they can be predicted. He also explains why this knowledge is important for a complete understanding of multicellular organisms.

When we move our limbs, when blood flows through our veins, or when individual cells migrate from one place to another, all these processes have one thing in common: they would not be possible without mechanical force. However, only recently has it become clear that these mechanical forces are directly linked to many important biochemical decision making processes inside the cells. In the short term, these processes alter the structural organization of the cytoskeleton and in the long term they change gene expression, i.e. the "reading" of genetic information and the translation of that information into proteins.

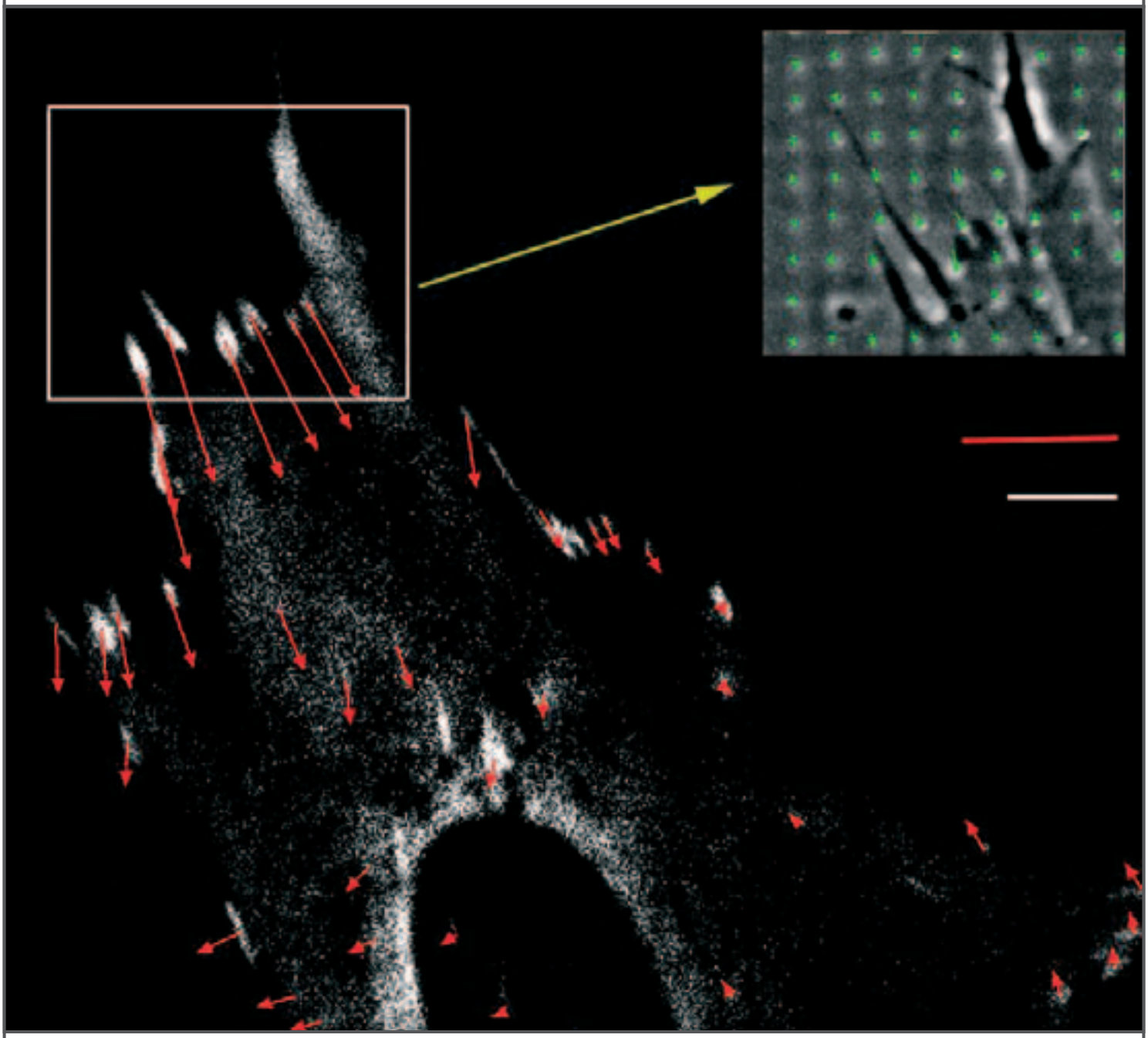
Interfaces with the outside world

Especially important for the mechanical force developed by cells are their contacts with the matrix, a polymer network surrounding the cells. These "cell-matrix contacts" form the interface between the "outside world" of the cell and what goes on in its interior. Accordingly, they are crucial for many physiological events such as development, wound healing, or the migration of white blood cells (leukocytes) to places where pathogens have invaded the body. These contacts are equally central to potentially lethal pathogenic processes such as the formation of metastases from cancer cells.

Our BIOMS research group on Cell Adhesion Forces aims to develop new theoretical concepts enabling us to understand these processes in quantitative detail. To ensure that we are investigating biologically relevant issues we collaborate closely with experimental groups, including scientists at the Weizmann Institute in Israel. Together we were recently able to show that there exists a linear correlation between the size of cell-matrix contacts and the force generated in the interior of the cell: a force of 5.5 nanonewton corresponds to a square micrometre of contact area.

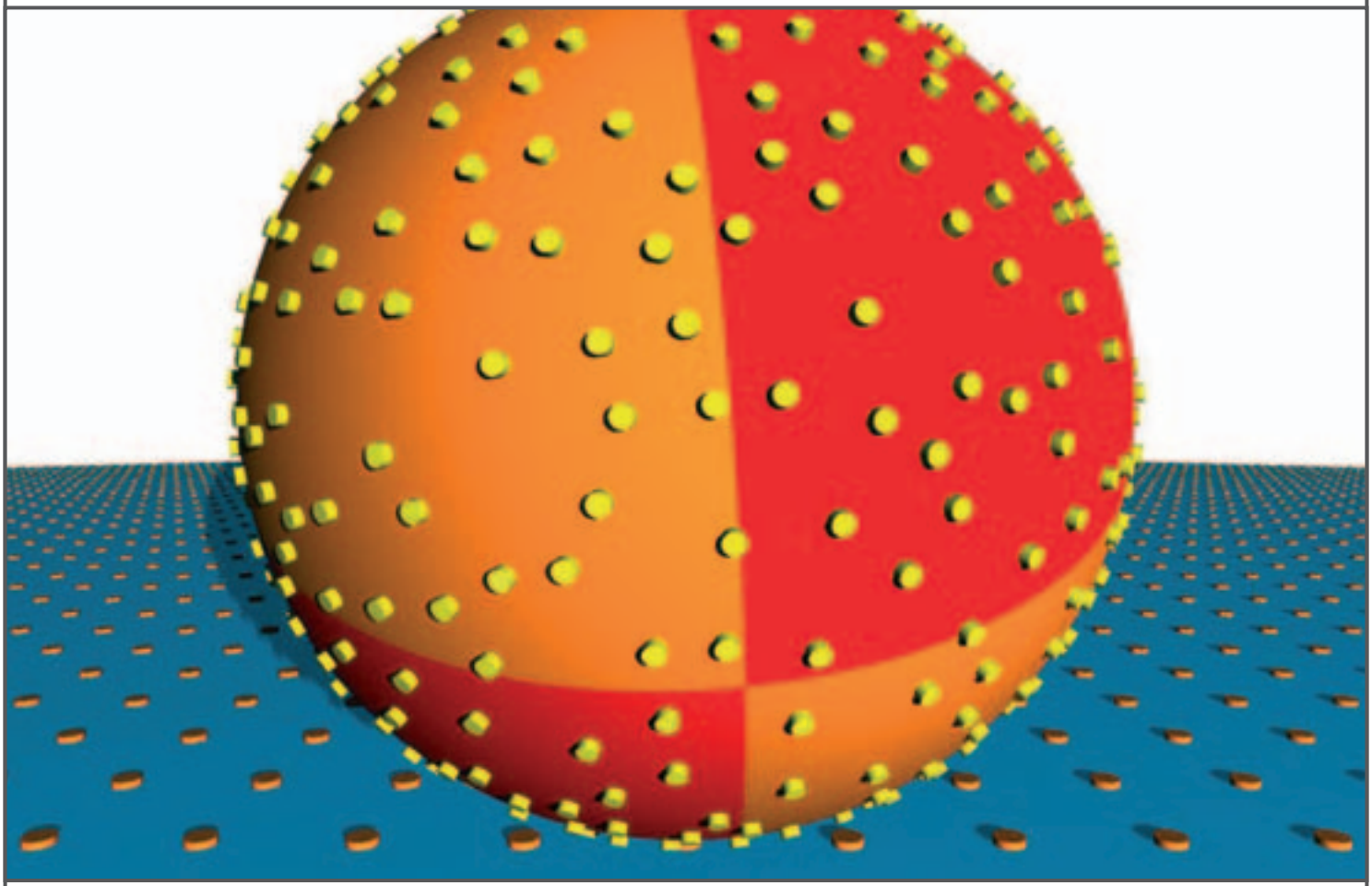
“Our findings open up new perspectives for regenerative medicine, e. g. the design of artificial tissue.”

Ulrich Schwarz



Mammalian tissue cells, here a fibroblast, exert forces (red arrows) through discrete sites of adhesion (white spots) to the extracellular matrix. Quantitative analysis with traction force microscopy shows that a linear relation exists between the size of the adhesions and the force transmitted through them.

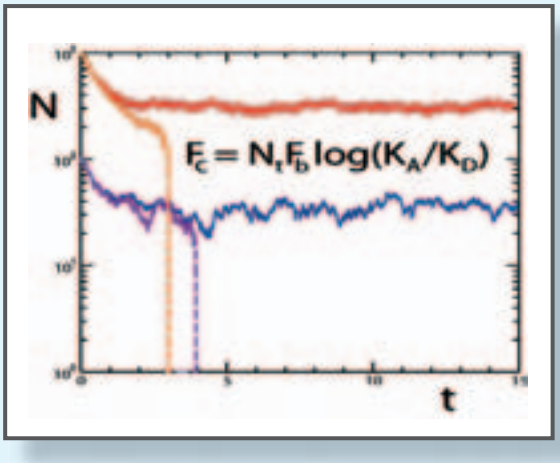
In addition, our cooperation with the experimental scientists in Israel has indicated that forces exerted from the outside cause contacts to grow. Physical force also plays an important part in a cell-biological phenomenon called “rolling adhesion”. This kind of cellular movement precedes the extravasation of white blood cells from the blood vessels into the surrounding tissue. The same phenomena are also observed for stem or cancer cells. In collaboration with a research group from the Weizmann Institute we have used high-resolution video microscopy to demonstrate that rolling adhesion based on very few adhesion bonds only occurs above a critical flow rate. This is probably designed to ensure that white blood cells do not extravasate at the wrong places.



Rolling adhesion of cells in the vasculature is mediated by specific binding between receptors on the cell and ligands on the substrate. In computer simulations one can investigate in a quantitative manner how the spatial positioning of receptors and ligands determine rolling adhesion.

One main focus of our research group is to develop theoretical models with which we can explain and predict the role of mechanical forces in cell adhesion. For example, we want to know how individual proteins and protein groups are coupled chemo-mechanically and how physical forces influence the transduction of signals into the interior of the cell. We are also working on the simulation of the rolling adhesion phenomenon. For example, one of our theoretical concepts enables us to predict the extent to which the average life-span of adhesion clusters depends on their size and mechanical load.

Stochastic dynamics of biomolecular bonds



The dynamics of biomolecular bonds depend on mechanical loading. Here the number of closed bonds (N) is simulated as a function of time (t). This shows that adhesion clusters (both for N_t = 100 and 1000 overall bonds) are stable for small force, but dissociate in an abrupt way at large force. The critical force (F_c) depends logarithmically on the ratio of association (K_A) to dissociation rate (K_D). Fb is the internal force scale of the bonds.

Self-organization of tissues and organs

Another focus of our work concerns the way in which mechanical properties of the cellular environment determine the decisions of individual cells or their self-organization to form tissues or organs. The most important concept involved in this context is continuum mechanics, notably linear elasticity theory. One important aspect of our work centers around the behaviour of cells in "soft matter", which includes biological materials. For multicellular systems in which individual cells interact with their elastic environment we have been able to predict an interesting feature of cell behaviour. Depending on the material properties of the environment and the density of cells, disordered arrays of cells suddenly change into ordered ones. This may be an explanation for the fact that wound healing sometimes involves large-scale, undesirable contraction of skin tissue. In the long term we plan to make our methods and insights available for the design of innovative cell environments, for example biomedical diagnosis chips or artificial tissue.

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The Container System of the Cell

The cell transports valuable cargo from one place to another in little containers called vesicles. These tiny membrane-coated bubbles also supply the material for the preservation and renovation of cellular membranes. As of yet, little is known about these cellular transportation routes their dynamics and regulation. Matthias Weiss, head of the BIOMS Cellular Biophysics research group elucidates the ingenious container system of the cell and the role of transport problems in diseases.

Membranes form the outer envelope of every living cell. In higher organisms, the so-called eukaryotes, membranes also contribute to the formation of organelles in the interior of the cell by creating separate reaction spaces (so-called compartments) that perform different tasks: the cell nucleus membrane encloses the genetic code, the DNA, containing the information for the building of proteins; protein synthesis and quality control takes place on the membranes of the tubular endoplasmatic reticulum; modifications to the proteins are undertaken in the Golgi apparatus. One consequence of this division of labour is that proteins have to be transported back and forth between the organelles. This task is entrusted to special transport vesicles, tiny bubbles budding off from specific sites on organelles membranes. These "domains" are found on the membranes of almost all organelles. Without them, the living cell cannot organize itself and hence cannot survive.

How vesicles originate

On the membrane of the endoplasmatic reticulum the transport vesicles originate at small specialized domains. These so-called "exit sites" are highly dynamic structures. Before a cell divides, they disintegrate. When division is over, they materialize once more. When a new vesicle needs to be formed, special proteins accumulate at the exit sites. At the precise point where these proteins are located, the membrane bulges outwards and a bubble – the transport vesicle – buds. During this process, cargo proteins are sorted into the vesicle. Ultimately the vesicle detaches and transports its cargo towards the Golgi apparatus.

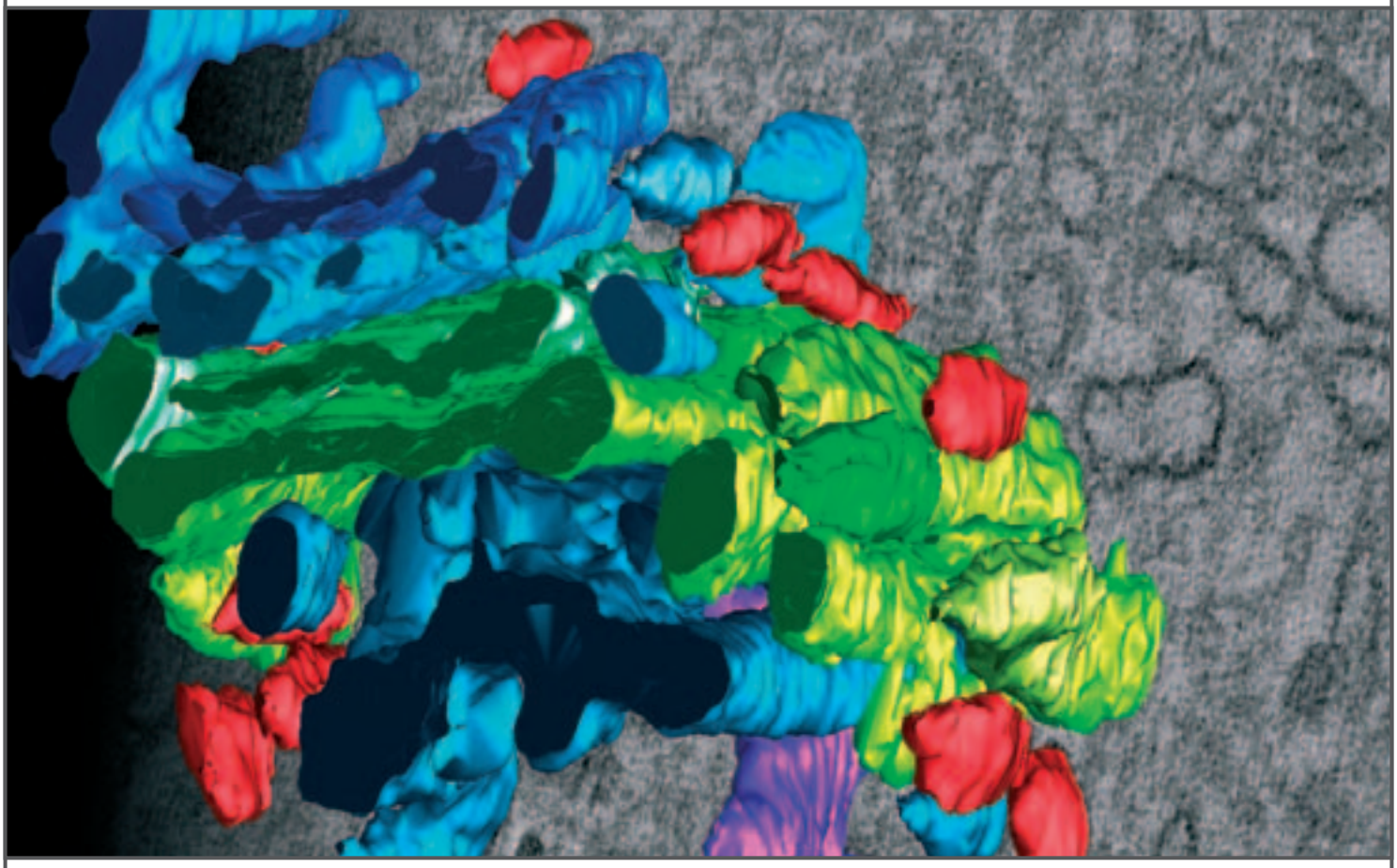
Thus the entire membrane system of the Golgi apparatus is derived from the exit sites of the endoplasmic reticulum. And it is preserved in the same way. If the export of proteins from the endoplasmatic reticulum is obstructed, the Golgi apparatus

"Membrane traffic is crucial for the viability and health of cells. By revealing the basic mechanisms and regulation of membrane protein transport, we wish to support the development of novel therapies for severe diseases."

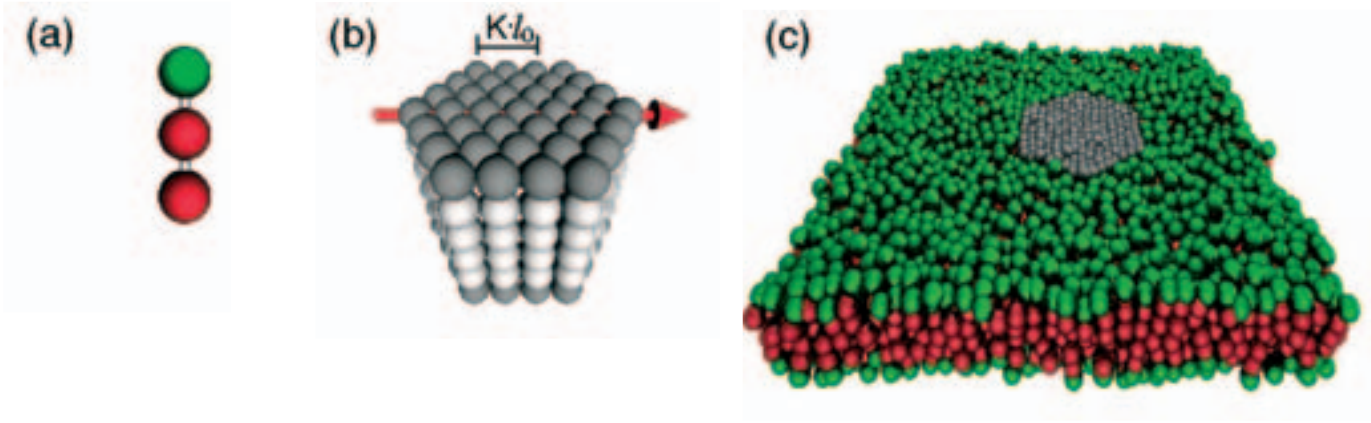
Matthias Weiss

may disintegrate within minutes and it is only restored when the block is removed. Accordingly, exit sites of the endoplasmic reticulum can be regarded as precursors of the Golgi apparatus.

Our research group combines theoretical and experimental approaches to find out more about the domains of active biomembranes. The exit sites of the endoplasmatic reticulum and the subsequent structuring and preservation of the Golgi apparatus serve us as a model system. To understand these complex processes we use simulation methods enabling us to observe groups of atoms that have assembled to form functional units. This procedure allows us to determine the properties of molecular systems with an accuracy on the nanometer scale. For example, we can observe how lipids that have been immersed in water organize themselves into a lipid bilayer that is typical of cell membranes. We can also follow the complex interaction between molecules during vesicle budding. Other techniques enable us to investigate how vesicles are loaded with cargo, how exit sites



The Golgi apparatus is a complex membrane system in the cell's interior. Being responsible for the proper modification of secretory proteins, its main structure consists of a stack of 4-8 flattened membrane cisternae. While some cells make use of individual, dispersed Golgi stacks, the typical case rather is a centrally localized Golgi ribbon that consists of about 100 individual stacks.



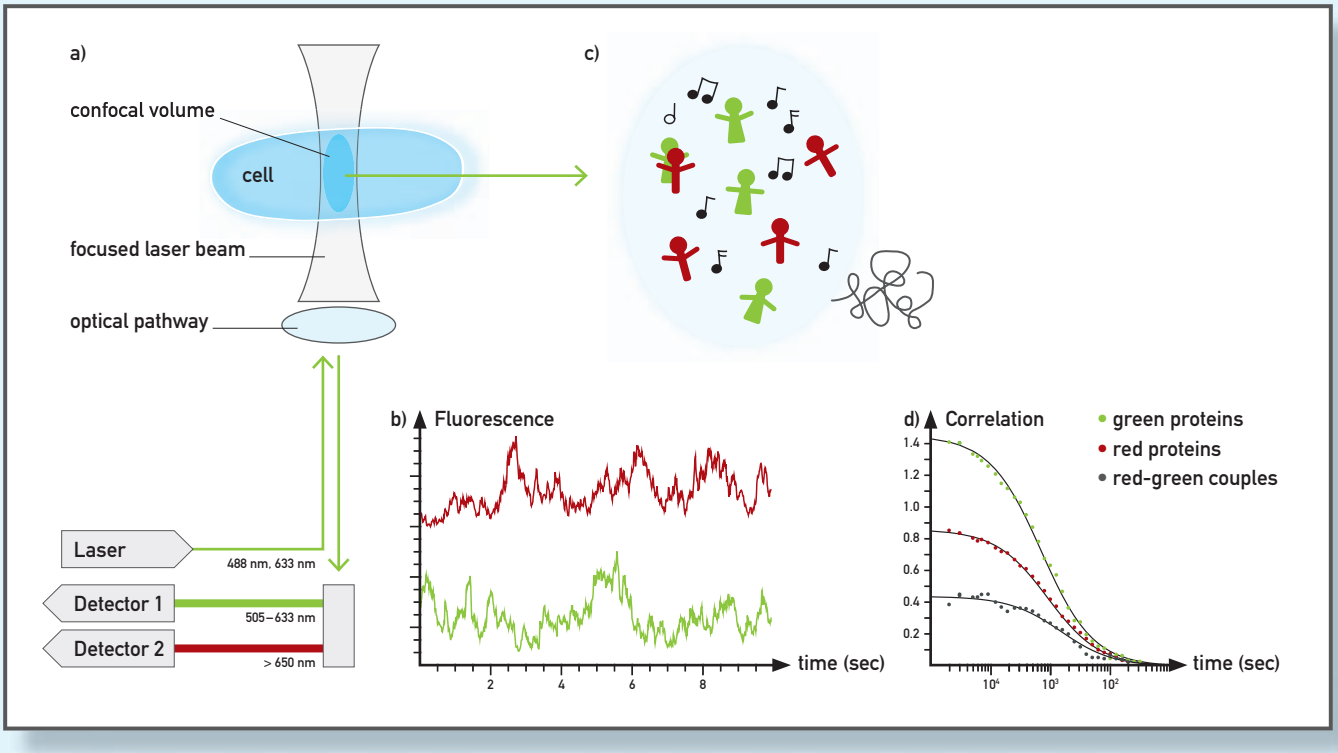
Simulations allow one to study the behavior of membranes and proteins down to the nanometer level.

originate and arrange themselves in the endoplasmic reticulum, and how the transport flux to the Golgi apparatus is maintained.

We use modern optical microscopy methods to test the predictions we can make on the basis of these simulations and the parameters involved in the simulations. With modern molecular biology methods we can induce cells to produce virtually any protein with a fluorescent dye. With techniques like confocal microscopy or fluorescence correlation spectroscopy we can measure the diffusion coefficients and the binding kinetics of single molecules in the living cell, for example the attachment and detachment of proteins involved in vesicle formation.

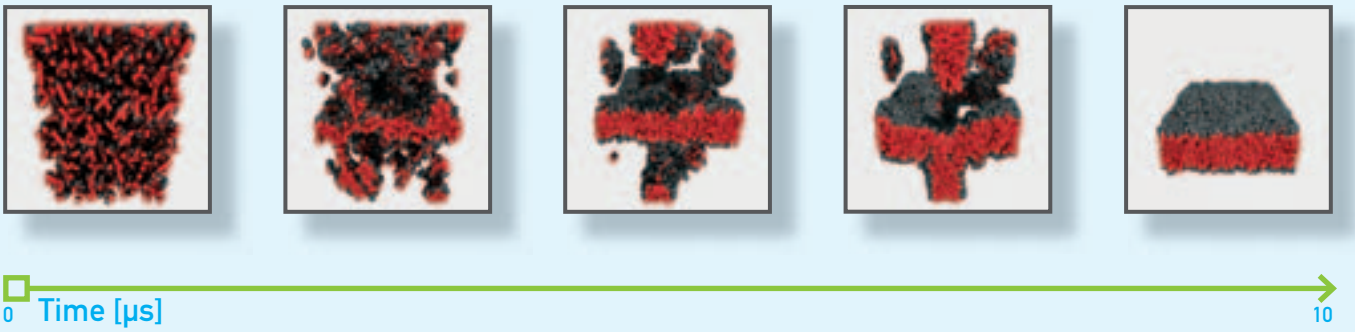
Correlation spectroscopy can even help us determine whether molecules display unusual behaviour, e.g. whether they are impeded on their way through the cell by other molecules or by

Fluorescence Correlation Spectroscopy



Fluorescence correlation spectroscopy (FCS) allows one to determine the mobility of proteins in the living cell on the level of single molecules. Focussing a laser beam into the cell (A), fluorescently tagged proteins move (e.g. via Brownian motion) through the detection volume of about 1 femtoliter (C). This gives rise to a fluctuating fluorescence in the detector (B). Analyzing these fluctuations yields a half-time (D) from which one can determine the mobility of the tracked particles. The amount of pairs of differently labeled, interacting proteins (‚dancing couples', C) can also be determined by this method.

Self-assembly of a membrane



The membrane, the envelope of the cell, is a lipid bilayer into which proteins are embedded. The picture shows the time course of the self-assembly of a membrane after lipids have been immersed in water.

components of the cytoskeleton. This combination of theoretical and experimental approaches is the ideal tool for casting light on the complex dynamic processes taking place in living matter.

In addition, we intend to investigate how special enzymes called lipases influence the properties of cellular membranes and the formation of vesicles. Other issues we address are the effects of obstructed diffusion on the activity of proteins and reaction networks, and the conditions favouring or restricting the passage of molecules through membranes.

Learning more about transport processes in the interior of the cell is of crucial importance. Membrane transport disorders are symptoms or causes of severe illnesses like cystic fibrosis, diabetes and cancer. By revealing the basic mechanisms that govern the secret life of living cells, our research aims at supporting the development of new therapies for these illnesses.

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Back: The embryo of the Nematostella polyp is covered by a "cilliar fur" (green) which propels the young animal through its aqueous environment. Single cells throughout the animal (red) connect to form a simple nervous and sensory system. The group of cnidarians are the first animals in evolution with a nervous system.

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