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How do nerve cells communicate with each other? How does a complex organism evolve from a single fertilized egg cell? How is our “biological clock” controlled? Scientists at the Max Planck Institute for Biophysical Chemistry are on the trail towards unraveling the answers to these and other fundamental biological questions. However, observing the molecular mechanisms that control and regulate these vital cellular processes is not an easy feat. They occur deep within the nanocosmos of living cells and are therefore invisible to the naked eye. Conventional microscopes can detect bacteria or observe individual body cells. However, what occurs deep within the inner workings of a living cell remains an unsolved mystery.

One focus of the institute’s research is the development of special methods that provide a closer look into the world of molecules. The patch-clamp method allowing to measure ion currents at cell membranes (Nobel Prize for Physiology or Medicine 1991 to Erwin Neher and Bert Sakmann), ultra-high resolution fluorescence microscopy on the nanometer scale (Nobel Prize for Chemistry 2014 to Stefan W. Hell), nuclear magnetic resonance spectroscopy, cryo-electron microscopy, or computer simulations are just a few of the methods that are successfully used to investigate proteins.

Tricks of nature
The goal is to unravel the many tricks that proteins play to fulfill their diverse cellular functions as molecular motors, chemical plants, or photoelectric cells, for example.

The scientists are further investigating how a cell converts the basic blueprints of proteins into a readable format, and are revealing the roles that cellular nanomachines – DNA polymerases, spliceosomes, and ribosomes – play in these processes.

Nanomachines also function in cellular logistics. How specific proteins sort and transport different cargo between the various compartments of a cell is one of the topics explored in greater detail.

Moreover, researchers elucidate how protein aggregates damage living cells and which role these protein clumps play in neurodegenerative diseases. Scientists are further interested in how genetic defective regulation can lead to obesity and metabolic disorders and how – focusing on phenomena of inanimate nature – energy conversion processes at surfaces are controlled.

At the Max Planck Institute for Biophysical Chemistry, scientists from various disciplines and of different nationalities work together to shed light on such complex processes. The biologists, chemists, medical scientists, and physicists collaborate not only with their colleagues at the institute, but also with a large number of renowned experts from other institutions worldwide. Accordingly, as they exchange views on projects, ideas, and results, many different languages can be heard on the Max Planck Campus, which comprises the Max Planck Institute for Dynamics and Self-Organization and the Gesellschaft für wissenschaftliche Datenverarbeitung Göttingen (GWDG) as well.
Erwin Neher and Bert Sakmann were the recipients of the 1991 Nobel Prize for Physiology or Medicine. They explored the molecular structures that enable nerve cells to transmit electric signals. In 1976, the two Max Planck researchers developed a method for measuring the incredibly weak electric current that flows for extremely short periods of time when single ion channels open up—the so-called patch-clamp technique. Miniscule ion channels—pore-forming proteins—are embedded within the outer membrane of nearly all cell types. They not only transmit the electrical activity of nerve and muscle cells, but also translate physical and chemical sensory stimuli into neuronal signals. Blood cells, immune cells, and liver cells also use ion channels for communication. These nanomachines in the membrane are therefore not only involved in nerve cell signaling; they also play a crucial role in the messaging systems of organisms.

Stefan W. Hell was awarded the Nobel Prize for Chemistry in 2014 for his pioneering work in the field of ultra-high resolution fluorescence microscopy. With his invention of STED (stimulated emission depletion) microscopy and related processes, he revolutionized light microscopy. Conventional light microscopes already reach their resolution limit when two objects are closer than 200 nanometers (one nanometer is a millionth of a millimeter) from each other because the diffraction of light blurs them into a single image feature. This limit, discovered about 130 years ago by Ernst Abbe, had been considered an insurmountable hurdle. Stefan Hell was the first to radically overcome the resolution limit of light microscopes—which is no longer limited by diffraction. It allows an up to ten times better image resolution in living cells and makes structures visible that are much smaller than 200 nanometers. By applying this method, biologists and physicians can look deeper into the nanocosmos of living cells than ever before.

Like all other Max Planck institutes, the Max Planck Institute for Biophysical Chemistry primarily pursues basic research. Here, the researchers follow up on fundamental new ideas. This unrestrained research, excellent working conditions, and outstanding international reputation are the reasons why the institute has become a center of attraction for both students and renowned researchers from all over the world. The new findings gained from such scientific research have paved the way for many pioneering applications. For example, the chemical compound Miltefosine, which was synthesized here, turned out to be a cure for the tropical disease visceral leishmaniasis—also known as kala azar. If left untreated, this disease almost always leads to death within two years. The World Health Organization hopes to use this medicine to control leishmaniasis in the long-term and to finally defeat it.

Other researchers have provided groundbreaking ideas for revolutionizing magnetic resonance imaging and optical microscopy. Thanks to these new methods, processes in our body such as beating of the heart or blood flow can even be studied in real-time. Many of the scientists at the institute have received awards and prizes for their work, including the 13 recipients of the prestigious Leibniz Prize of the German Research Foundation. The highest scientific honor, the Nobel Prize, has been awarded three times for research carried out at the Max Planck Institute for Biophysical Chemistry—one in every generation of researchers.

Manfred Eigen was awarded the Nobel Prize for Chemistry in 1987. He succeeded in observing the course of very fast chemical reactions occurring in the range of nanoseconds. He thus broke down a fundamental barrier as, until then, these very fast reaction processes had been considered unmeasurable. His work is of fundamental importance far beyond the scope of chemistry.

Research without constraints
The Max Planck Institute for Biophysical Chemistry was founded at the Faßberg site on the outskirts of Göttingen on the initiative of Manfred Eigen. It was inaugurated in 1971, but its history can be traced back far beyond this date, extending back to the former Kaiser Wilhelm Institute for Physical Chemistry in Berlin. In 1949, after creation of the Max Planck Society, the physical chemist Karl Friedrich Bonhoeffer (photo) re-established the Berlin institute as the Max Planck Institute for Physical Chemistry in Göttingen. This institute and the Göttingen Max Planck Institute for Spectroscopy were then merged to form the Max Planck Institute for Biophysical Chemistry.

The focus of the newly founded institute on biological research also has its roots in the work and interests of Karl Friedrich Bonhoeffer. He pursued a strong interdisciplinary approach at a very early stage and applied physical-chemical methods to answer biological questions – a good reason to name the institute after him.

Manfred Eigen’s vision for the newly-established institute was to find answers to seemingly unsolvable scientific questions through inter- and multidisciplinary research and to apply the novel findings for the benefit of mankind: A vision which has played a decisive role in the institute’s success, and which still stands today in the departments and research groups.

At present, the Max Planck Institute for Biophysical Chemistry comprises 13 departments and 20 research groups, each with its own focus. With more than 800 staff members – including about 400 scientists – it is not only one of the largest institutes of the Max Planck Society, but is also unique in its inter- and multidisciplinarity covering a wide range of research areas.

The Directors of the individual departments are at the same time Scientific Members of the Max Planck Society and decide jointly on the course to be taken by the institute.

In order to ensure the maintenance of the institute’s high quality research, a Scientific Advisory Board of internationally renowned scientists regularly assesses the research performed here. A Board of Trustees, comprising not only scientists but also prominent representatives from business and politics, ensures good contact with the general public.
Science is based on more than just experience. The future of science depends on young scientists who drive the research forward. Hence, many researchers at the Max Planck Institute for Biophysical Chemistry are professors at the University of Göttingen as well as other universities. They are actively involved in collaborative research centers and graduate schools, and thereby keep close contact with students. Many students, on the other hand, come to the institute for their laboratory work during their bachelor and master courses or doctoral studies.

In the international competition for the best young minds, the Max Planck Society and various universities have established a special program of education and training for outstanding students: the International Max Planck Research Schools (IMPRS). The Max Planck Institutes for Biophysical Chemistry, for Dynamics and Self-Organization, and for Experimental Medicine have teamed up with the University of Göttingen to establish the International Max Planck Research Schools Molecular Biology, Neurosciences, and Physics of Complex and Biological Systems. A new program for Genome Science is in the developmental phase. The structured education and training, with excellent research and learning conditions, is tailored to prepare especially talented German and foreign students for their doctoral studies.

Additionally, the institute and the IMPRS are involved in the Göttingen Graduate School for Neurosciences, Biophysics, and Molecular Biosciences (GGNB), which contributed significantly to the success of the University of Göttingen in the national Excellence Initiative.

Structured doctoral studies

The award-winning GGNB offers intensive courses and tutoring and paved the way for structured doctoral studies in Germany. There are also programs for young scientists within the framework of further cooperation between the institute and the University, the Max Planck Institutes for Dynamics and Self-Organization and for Experimental Medicine as well as the German Primate Center. These include:

- the Bernstein Center for Computational Neuroscience (BCCN Göttingen), which investigates the neuronal basis of our brain activity with mathematical models,
- the European Neuroscience Institute (ENI), which concentrates on experimental research into functions and diseases of the nervous system,
- the Cluster of Excellence and DFG Research Center Nanoscale Microscopy and Molecular Physiology of the Brain (CNMPB), where researchers from various disciplines collaborate in the field of brain research in order to gain a better understanding of the molecular processes and interactions between nerve cells. Furthermore, the researchers aim at developing microscopy methods with resolution in the nanometer range and making them available on a practical level.
Whether in the field of nuclear magnetic resonance (NMR) tomography, laser technology, or microscopy – the findings of basic research solve many a practical problem that applied research was not able to overcome. Such findings are therefore also of economic importance.

Many scientists at the institute hold promising patents and founded companies in the area of medical diagnostics and therapy, metrology and environmental technology, or ultra-high resolution microscopy, for example.

Highly successful techniques

The newly developed FLASH (fast low-angle shot) method allows one to take NMR images 100 times faster. It has revolutionized NMR tomography and is now routinely used in hospitals worldwide with over 100 million examinations per year. The FLASH patent is the most successful patent of the Max Planck Society. A further acceleration of the NMR imaging now even makes it possible to generate movies from inside our body in real-time.

The RNA interference (RNAi) technique was successfully applied to mammalian cells for the first time at the institute. Using this method, individual genes can be switched to «mute», facilitating the investigation of their function. This technique might contribute to the treatment of certain hereditary diseases in the future.

DNA analysis from minimal traces of skin scales, root of a hair, blood, or saliva may be done with the help of the short tandem repeats (STR) technology, in whose development the scientists at the Max Planck Institute for Biophysical Chemistry had a substantial part. The method is applied for paternity tests. It is also used in criminological investigations to assign samples to specific individuals.

Scientists as company founders

The revenue from patents and licenses is invested into new projects at the Max Planck Institute for Biophysical Chemistry. The use of the patents creates new jobs for highly qualified staff members. In addition, there is a broad spectrum of further cooperative ventures with industrial companies, which include pharmaceutical companies and those that develop industrial measurement technology.

Moreover, former institute’s employees have been involved in the founding of more than a dozen companies. One of these spin-offs is OMHEV (now Bayer HealthCare AG), where an automated «evolution machine» is used to quickly find and optimize bio-pharmaceutical active substances.

Another example is Lambda-Physik (now Coherent), which specializes in developing ultraviolet lasers that operate with extremely short light pulses. The lasers are continuously undergoing further development and are nowadays also used in medicine and research, in addition to printing technology.

The biotechnology companies Evotec and DeveloGen (today also Evotec), are two more successful spin-offs of the institute. They connect research on genetic control processes in the development of different kinds of body tissues with the practical treatment of medical conditions such as obesity and diabetes.

The enterprise Abberior Instruments was also co-founded by employees of the institute. It specializes in ultra-high resolution microscopes and translates newest findings into innovative research equipment.
A t the Max Planck Institute for Biophysical Chemistry anyone interested will find that our doors are open. During guided tours through the institute or single labs, during presentations and discussions, everyone – be it a teacher, pupil, journalist, or interested person – can find out more about current research.

Teachers can also register with their school classes for visits to get to know our research during lectures and experimental demonstrations.

Moreover, every year in April, pupils are given the opportunity to become active themselves in our labs and workshops during the Zukunftstag für Jungen und Mädchen (Future Day for Boys and Girls) – up to 80 children visit the institute on that day. Teachers are also invited to deepen their knowledge on specific topics.

In cooperation with the XLAB – Göttinger Experimental-labor für Jüngste Wunder: ‘the institute offers training for teachers.

The Max Planck Institute for Biophysical Chemistry further takes part in the Nacht des Wissens (Science Night) where the scientific institutions at Göttingen Campus welcome the general public. Even more can be discovered at the Open Day – here, the entire institute presents itself to the general public with a wide spectrum of offers ranging from informative talks to fascinating experimental stations and a rally for children.

Together with four other Göttingen Max Planck Institutes, the Göttinger Literaturherbst GmbH, and the Göttingen State and University Library, the institute further participates in the Göttinger Literaturherbst – a literature festival – with a series of scientific lectures. Here, renowned researchers from all over the world present their latest results and discuss current topics with the audience.

Anyone interested can always stay up-to-date with the institute’s magazine MPIbpc News. It reports on research news, awards, events, and much more in ten issues per year. However, a larger audience can only be reached via the free media. We therefore not only publish press releases on current topics but also put journalists in touch with experts for enquiries and questions.

Last but not least, it should be noted that beside the science, there is also room for culture at the institute – such as the art exhibitions regularly hosted in the foyer.
How the unseen becomes measurable and visible

Without X-ray structural analysis, Francis Crick and James Watson would not have discovered that DNA, our prime genetic carrier, comes along as a double helix. And how would Robert Koch have detected the anthrax bacillus without a good microscope at his disposal? Top scientific achievements require high-end equipment. New spectroscopic and microscopic methods are needed, for example, to determine structural details at the single molecule level as well as to explore the dynamics of molecular or even atomic processes. Therefore, it is not surprising that many of the institute’s scientists work on methodological innovations, constantly pushing the boundaries of what is possible.
Stefan W. Hell received his PhD in physics at the University of Heidelberg in 1990 and worked from 1991 to 1993 at the European Molecular Biology Laboratory (EMBL) in Heidelberg. From 1993 to 1996, he carried out research at the Universities of Turku (Finland) and Oxford (Great Britain). Subsequently, he obtained his habilitation at the University of Heidelberg. In 1997, he went to the Max Planck Institute for Biochemistry as head of the High Resolution Optical Microscopy Research Group, where he has headed the Department of NanoBiophotonics since 2002. Stefan W. Hell has received many national and international awards for his research, among them the Kavli Prize in Nanoscience (2014) and the Nobel Prize in Chemistry (2014).

Making the smallest details visible using focused visible light – this is the objective of our ultra-high-resolution light microscopes, known in recent years as nanoscopes. Conventional microscopes reach their resolution limits when two similar objects are closer than 0.2 micrometers (1/5,000 of a millimeter) to each other, because the diffraction of light blurs them to a single image feature. Even the best microscope lenses cannot change this. Therefore, anyone who desires to image at nanometer or even molecular dimensions, starting from electron or scanning probe microscopy. However, the interior of living cells can only be observed with focused visible light. Fluorescence microscopy, where the molecules (proteins, lipids, nucleic acids) of interest are highlighted by tagging them with specific fluorescent molecules (fluorophores), is the most important light microscopy modality in the life sciences. But like any other light microscopy, standard fluorescence microscopy is also limited by diffraction.

Switching fluorescence off and on by light In order to outsmart the resolution-limiting role of diffraction, we first have to unravel the mechanisms underlying the resolution of adjacent molecules consecutively off and on makes them readily distinguishable. In this approach (called STORM, PALM, GSDIM), only one molecule in the detection area is switched on, but at an unknown, random position. The adjacent molecules indeed lie so close to each other, because the diffraction of light blurs them to a single image feature. Even the best microscope lenses cannot change this. Therefore, anyone who desires to image at nanometer or even molecular dimensions, starting from electron or scanning probe microscopy. However, the interior of living cells can only be observed with focused visible light. Fluorescence microscopy, where the molecules (proteins, lipids, nucleic acids) of interest are highlighted by tagging them with specific fluorescent molecules (fluorophores), is the most important light microscopy modality in the life sciences. Even if one molecule is excited at one point so that the wave fronts of the two lenses jointly focus on it, this procedure is impossible. The superposition of the two images results in a blurred image. Therefore, anyone who desires to image at nanometer or even molecular dimensions, starting from electron or scanning probe microscopy. However, the interior of living cells can only be observed with focused visible light. Fluorescence microscopy, where the molecules (proteins, lipids, nucleic acids) of interest are highlighted by tagging them with specific fluorescent molecules (fluorophores), is the most important light microscopy modality in the life sciences.

Switching fluorescence off and on by light In order to outsmart the resolution-limiting role of diffraction, we first have to unravel the mechanisms underlyina the resolution of adjacent molecules consecutively off and on makes them readily distinguishable. In this approach (called STORM, PALM, GSDIM), only one molecule in the detection area is switched on, but at an unknown, random position. The adjacent molecules indeed lie so close to each other, because the diffraction of light blurs them to a single image feature. Even the best microscope lenses cannot change this. Therefore, anyone who desires to image at nanometer or even molecular dimensions, starting from electron or scanning probe microscopy. However, the interior of living cells can only be observed with focused visible light. Fluorescence microscopy, where the molecules (proteins, lipids, nucleic acids) of interest are highlighted by tagging them with specific fluorescent molecules (fluorophores), is the most important light microscopy modality in the life sciences. Even if one molecule is excited at one point so that the wave fronts of the two lenses jointly focus on it, this procedure is impossible. The superposition of the two images results in a blurred image. Therefore, anyone who desires to image at nanometer or even molecular dimensions, starting from electron or scanning probe microscopy. However, the interior of living cells can only be observed with focused visible light. Fluorescence microscopy, where the molecules (proteins, lipids, nucleic acids) of interest are highlighted by tagging them with specific fluorescent molecules (fluorophores), is the most important light microscopy modality in the life sciences.
Structural and Dynamic Analysis of Mitochondria

Mitochondria are the power plants of the cell. Through the process of cellular respiration, they provide the chemical energy required to keep cellular metabolism moving. When the mitochondria do not function properly, the consequences are correspondingly fatal. Defective mitochondria can lead to disorders such as cancer, Parkinson’s, or Alzheimer’s disease.

But how are mitochondria constructed in detail, and which molecular mechanisms are behind this architecture? Mitochondria are so nanoscopically small that their internal structure could previously only be examined with electron microscopes. However, for this cells must be chemically fixed and cut into ultra-thin slices, which are then examined individually. We therefore learned relatively little about what occurs in the mitochondria of living cells.

In contrast, fully intact cells can be examined by means of light microscopes. However, even with the best conventional microscopes, the spatial resolution is not nearly high enough to examine the interior of the cell’s power plants more closely. Therefore, we use new light-microscopic methods, such as stimulated emission depletion (STED), or reversible saturable optical linear fluorescence transitions (RESOLFT), nanoscopy, with which the optical resolution can be dramatically increased.

A glimpse into the interior of the cellular power plant. To this end, we label selected proteins in the cell with dyes or fluorescent proteins. This enables us to subsequently localize the proteins of interest in the mitochondria. In this manner, we have, for example, discovered that some protein complexes are concentrated in a specific part of the mitochondrial inner membrane where they influence membrane curvature. Other protein complexes form very large structures that ensure a regular architecture inside of mitochondria – an essential prerequisite for proper cellular growth. In addition to microscopic methods, we also use biochemistry and molecular biology methods to elucidate how such structures are organized and how they support the tiny power plants in their function. We are aiming to understand what consequences it has for the cell when the inner architecture of the mitochondria or the interaction between the different proteins is disturbed.

Novel proteins for nanoscopy

For super-resolution light microscopy, we always require novel fluorescent proteins. These provide completely new possibilities for exploring the inner workings of living mitochondria, cells, and even whole tissues.

Contact
sjakobs@mpibpc.mpg.de
www.mpibpc.mpg.de/jakobs
www.mitoweb.de


*) co-corresponding authors

References
increased life expectancy leads to a higher risk of developing diseases such as cancer, Alzheimer’s, and Parkinson’s. Therefore, new possibilities for treating such diseases becomes increasingly important. In our work, we seek a better understanding of how these diseases arise.

We concentrate our research activities in two major areas. The first has to do with the molecular mechanisms of signal transduction controlled by external growth factors in normal and tumor cells. The second focus is on the molecular mechanisms underlying the pathogenesis of Parkinson’s disease (PD). Characteristics of this and other related neurodegenerative disorders, for example Alzheimer’s disease (AD), is the appearance of protein aggregates – clumped proteins – in and around neurons of affected areas, primarily in the brain. In PD, the protein in question is alpha-synuclein.

Unfortunately, how the so-called amyloid aggregates are formed and how they and other different oligomeric species exert their toxic effects is largely unknown. Answers to these questions are required before one can rationally design drugs to inhibit or reverse the progress of PD and AD. We approach this challenge with molecular and cellular approaches and biological techniques that can be applied in vitro as well as in studies of cells and tissues. We employ established laboratory cell lines and isolated plasmacytoma stem cells derived from PD patients.

Tracking molecules in Living cells

For the cellular studies, we develop and utilize novel fluorescent probes based on nanoparticles, for example semiconductor nanocrystals Quantum Dots, and information-sensitive organic compounds. These sensors are introduced into biomolecules and cells by chemical, physical, and cell expression techniques.

In vitro studies help shed light on the mechanism of cell dysfunction in Parkinson’s disease. The picture compares induced stem cells from a healthy individual (left, control), from a Parkinson’s disease patient with a triplication in the alpha-synuclein gene SNCA (right), and from the same Parkinson’s disease patient after SNCA gene knockdown. Neurons were partially restored by the SNCA gene knockdown. The expression has been reduced by 2-fold (bottom). Cell lines with SNCA triplication impaired neuronal differentiation compared to lines from healthy individuals. The ability to differentiate into dopaminergic neurons was partially restored by the SNCA gene knockdown.

For the application of such probes, we initiated – already in 1997 – a long-term development of a programmable array microscope (PAM) for sensitive, optically-sectioned imaging of living cells with high spatial, temporal, and spectral resolution. The instrument is based on a micrometer array for exciting the fluorescent probes as well as detecting the fluorescent emission in two different channels corresponding to the in-focus and out-of-focus signals. In a parallel effort, a new fluorescence lifetime imaging microscopy (FLIM) method denoted eEFLIM has been devised using long rather than the conventional ultra-short light pulses. Donna Ardnt-Jovin is responsible for the cell biological research on signaling is being extended to use in the operating room, for example for detecting and identifying tumor cells in resected tissue as well as in the surgical margins remaining in patients.

Department of Director and chairman of the Society in 1969 and functioned as Scientific Member of the Max Planck (United States). He became a Hopkins Medical School in Baltimore was awarded his M.D. (Doctor of Medicine) in 1967. Thomas M. Jovin has received honorary degrees from the University of Limburg (Belgium) and the University Medical School of Debrecen (Hungary). He is an honorary professor of the University of Buenos Aires and a member of the European Molecular Biology Organization (EMBO).

Contact

Jovin, T. www.mpib-berlin.mpg.de

T.M. Jovin, E. A. Jares-Erijman:

Oliveira et al.: 2015)

B A C

Live multispectral optical sectioning with the fourth generation iPAM: Human epidermoid carcinoma cells expressing the protein EBD3 bound to mCitrine (yellow) and labeled with Quantum Dots-EGF (625 nanometers, red). The nucleus is stained blue. (A) Conjugate, in-focus image of the cells. (B) Non-conjugate, out-of-focus image of the cells. (C) The final image is produced by subtracting the non-conjugate from the conjugate image. (De Vries et al 2015)

A B C

Donna Ardnt-Jovin is responsible for the cell biological research focusing on growth factors and the effects of over-expressed or fetal maternal alpha-synuclein on primary neurons and on patient-derived induced pluripotent stem cells. The basic research on signalising is being extended to use in the operating room, for example for detecting and identifying tumor cells in resected tissue as well as in the surgical margins remaining in the organism.
Electron-Spin Resonance Spectroscopy

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gardless of whether one is considering simple water or complexed proteins, electrons usually occur pairwise in molecules. By means of their spin – a form of angular moment-

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Contact

marina.bennati@mpibpc.mpg.de

www.mpibpc.mpg.de/bennati

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Electron-Spin Resonance Spectroscopy

Regardless of whether one is considering simple water or complexed proteins, electrons usually occur pairwise in molecules. By means of their spin – a form of angular momentum – they generate a microscopic magnetic field. However, since the spins are oriented in opposite directions, their magnetic effects cancel each other. As a consequence, we are only interested in unpaired electrons, which are magnetically active and serve as highly sensitive probes in our experiments. These so-called paramagnetic centers can provide us with unique information on how complex biomolecules change their structures while they are fulfilling their specific function. With different methods of electron paramagnetic resonance (EPR) spectroscopy we can observe biomolecules under nearly natural conditions or learn about how they act in the living cell.

In our group, we develop EPR techniques to simultaneously excite several paramagnetic centers with microwaves or radio frequency in order to manipulate their magnetic interactions. In this manner, we cannot only measure distances between the paramagnetic centers of a protein down to the nanometer range, but also gain important information on their orientations in the biomolecule. Since EPR sensitivity and resolution substantially increase with the applied static magnetic field, we perform experiments at fields up to ten tesla and excitation wavelengths down to the sub-millimeter range, which is in the regime where sophisticated microwave technology and novel spectrometer designs are required. Therefore, in our group, biophysical investigations are conducted hand-in-hand with methodological and technical developments.

Observing the interior of proteins

Paramagnetic centers are involved in many fundamental biological processes. Representative examples are provided by photosynthesis or the respiratory chain, but also in the biosynthesis of our hereditary material, the DNA. There, enzymes called ribonucleotide reductases (RRs) play a pivotal role. From bacteria to humans, the RRs catalyze the last step in the formation of the individual building blocks, the DNA. In this process, paramagnetic states are generated as a result of the translocation of electrons and protons through and between proteins. With the aid of different EPR techniques, we have succeeded in elucidating several intermediate steps in the catalytic cycle. While paramagnetic centers occur naturally in proteins such as RNR, they have to be inserted artificially into other proteins. To achieve this, we introduce spin labels at selective positions of the proteins. Following this protocol, we investigate the structure of representative classes of biomolecules such as nucleic acids, aggregating proteins, and membrane proteins in collaboration with other research groups of the institute.

Polarization of nuclear spins

In our research we further use EPR in parallel with nuclear magnetic resonance, thereby combining the advantages of both techniques. The magnetic moment of an electron spin is subject to three orders of magnitude larger than that of protons. If those nuclear spins interact with electron spins, spectra of nuclei can be observed with much higher sensitivity – a feature that can considerably expand the application fields of magnetic resonance. These types of experiments are called electron-nuclear double resonance (ENDOR) if electron spins are detected, or dynamic nuclear polarization (DNP) if nuclear spins are detected. We have been investigating fundamental principles of polarization transfer between electron and nuclear spins and have recently introduced a new concept to allow fast and coherent electron-nuclear polarization transfer. We have been exploring these phenomena also in the liquid state, driven by relaxation mechanisms. We foresee exciting applications in a variety of research fields, ranging from biology to nuclear magnetic resonance imaging (MRI) and material sciences.

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M. Luchinat, M. Bennati: One thousand-fold enhancement of high field liquid nuclear magnetic resonance at room temperature. Nat. Chem. 2017, accepted manuscript.


The image shows an EPR experiment to observe the active site of an enzyme. Represented are: A) the structure of a protein radical; B) a radical with surrounding amino acids and C) a high-frequency (GHz) gigahertz electron-nuclear double resonance (EENDOR) spectrum of proteins that are in the vicinity of this radical. Background: View of the microwave bridge for EPR in quasi-optical regime.
Diamons are brilliant not only as gem stones. Also scien-
tists have become increasingly interested in these precious
carbon crystals. Although as a jewel the colors and flawless
variant sparkles brightly, in science the defective diamonds are
much more desirable. One such defect is due to impurities in the
diamond lattice, for example nitrogen. If a nitrogen atom occu-
pies a vacancy – an empty spot – in the carbon crystal lattice, the
diamond gets a characteristic pink color. This defective diamond
can be used as a very sensitive and precise quantum sensor. This
ability is based on a property of the nitrogen atom’s electrons –
their so-called spin, which magnetically interacts with nearby
atoms and molecules. We can use this one-atom sensor to
very precisely measure nanoscale magnetic fields, electric fields,
spins, charge, temperature, and pressure. The atomic size and
exponential sensitivity of the single nitrogen-vacancy (NV) sen-
or is a unique combination that outperforms most other sen-
sors and offers possibilities that are beyond the current state-of-
the-art technologies.

Our research group is developing new methods and technolo-
gies based on this diamond sensor for biophysical and bio-
medical applications which are beyond the current possibilities.
Structural biology has revolutionized life science, yet several
molecules of biomedical importance remain unexplored and still
pose a challenge to be investigated using current techniques.

The nuclear magnetic resonance (NMR) technique has been
used for many years to elucidate the structure of biological
molecules. However, until now, scientists could only measure
many molecules at the same time, making the result an aver-
age, and therefore, minute variations are overlooked. Our group
is developing nano-NMR technology that will allow us to create
precise three-dimensional images of single molecules and com-
plexes.

Furthermore, we have established interdisciplinary collabora-
tions with other groups to explore unique applications for the
NV sensor. Our efforts include developing quantum control strate-
gies for sensing applications as well as techniques for enhancing
magnetic resonance signals. Due to the very promising prospect
of using diamond sensors, our research aims to contribute new
tools and technologies towards the betterment of science and society.

Images from atomic spin
Atoms, which make up biomolecules, have a spin, which acts like
a tiny compass needle that aligns along magnetic field lines.
When a biological molecule – for example a protein – is placed
in a magnetic field, the spins of its hydrogen atoms orient in this
field. If we then subject the molecule to a short electromagnetic
pulse, the spins are deflected briefly. We can measure this deflec-
tion with the NV sensor. By changing the direction of the mag-
netic field that is used to align the spins, we record images from
different projections or perspectives. We analyze such images
using image reconstruction algorithms to obtain the three-
dimensional image of a single biomolecule.

The research is developing new imaging techniques that could overcome
limitations and complement the structural landscape in under-
standing the molecular mechanism or function of diseases and
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Biological Micro- and Nanotechnology

Thomas Burg studied physics at the Swiss Federal Institute of Technology (ETH) Zurich (Switzerland) and earned his doctorate in 2005 at the Massachusetts Institute of Technology (MIT) in Cambridge (United States). From 2005 to 2008, he conducted research as a research associate at the MIT Department of Biological Engineering. Since 2009, Thomas Burg has been head of the Max Planck Research Group Biological Engineering, which is developing new physical methods with which we can observe, measure, and manipulate the world on the micro- and nano-meter scale. Using biologically inspired artificial nanopores, for example, we are investigating new methods to separate subtly different molecules, and with the help of nanomechanical sensors, we are hoping to better understand why proteins sometimes clump together and give rise to disease. Furthermore, we are interested in new opportunities provided by microsystems technology in the field of microscopy.

Modern microscopes can render complex three-dimensional cellular structures visible with stunning clarity and detail. However, whenever any of these structures are changing or moving quickly, it often is impossible to follow the dynamics in real time. This is an especially challenging problem when different methods, such as light and electron microscopy, must be combined in order to understand complex processes. To solve this problem is simply to freeze the object. To avoid damaging delicate structures, however, the water inside cells must be kept from crystallizing. Today, all existing methods to accomplish this have significant shortcomings. Firstly, due to the need for complex sample preparation, researchers today have no way to freeze an object at an exact point in time. Secondly, there is no way to observe the object until just prior to solidification. Both would be important in order to understand which function is carried out by certain structures in the cell, or in what sequence and how quickly a specific process occurs.

At a fundamental level, this challenge is due to the fact that there is no way in nature to extract an arbitrary amount of heat from an object on command. The only way to initiate cooling is to bring the sample into contact with a cold environment, for example by dipping it in liquid nitrogen. To do this, the sample must be removed from the microscope, thus creating a gap of several seconds in the observation.

Dynamic processes in real time under the microscope, Microtechnology allows us to bypass this problem with a trick, so that continuous live cell microscopy and cryo-microscopy can be combined seamlessly. For this purpose, we slowly cool the whole environment of the sample with liquid nitrogen, while at the same time the sample is heated electrically. While the heater is active, a steep temperature gradient between the sample and the cold stage is maintained. The object thus always remains at room temperature, unaware of its chilly environment. At the same time, the sample is heated electrically. While the heater is turned off, the fragile temperature gradient collapses rapidly, much like the filament in a light bulb cools rapidly when the current is switched off. Numerous interesting questions can already be investigated with the above technology. For example, the possibility to heat and cool at controlled rates of more than 100,000 degree Celsius per second is of interest for studying mechanisms that may be relevant for the long-term cold storage of oocytes or sperm. To achieve these rates, the object must be thinner than approximately one hundredth of a millimeter, and the walls that surround it must be made from materials that can withstand the rapid temperature change. For this purpose, we are developing microfluidic cryo-fixation for correlative microscopy.

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Microsystems are used by our laboratory to enable ultra-rapid freezing of biological samples in the light microscope for high-resolution studies at cryogenic temperature. The microscopic cells that make up all living organisms are amazingly complex. Tiny molecular machines are constantly on the move to create, shape, or recycle intricate structures only nanometers – or millions of a millimeter – in size. To improve our ability to study these processes experimentally, our group is developing new physical methods with which we can observe, measure, and manipulate the world on the micro- and nano-meter scale. Using biologically inspired artificial nanopores, for example, we are investigating new methods to separate subtly different molecules, and with the help of nanomechanical sensors, we are hoping to better understand why proteins sometimes clump together and give rise to disease. Furthermore, we are interested in new opportunities provided by microsystems technology in the field of microscopy.

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Contact
lib@mpibpc.mpg.de
www.mpibpc.mpg.de/burg

Ultra-precise nanofabricated filter membranes are used for experimental studies of complex molecular transport mechanisms in artificial nanopores.


Microfluidic systems for rapid freezing of the nematode Caenorhabditis elegans.

Microsystems are used by our laboratory to enable ultra-rapid freezing of biological samples in the light microscope for high-resolution studies at cryogenic temperature.
Spectroscopy and Photochemical Kinetics

Many phenomena in nature can be traced back to molecular processes. Thus, many molecules, radicals, and atoms react with one another in the atmosphere after they have been produced and excited by solar radiation. Amazingly, these processes are very similar to those which occur in fire and in internal combustion engines. Such processes even play an important role when new stars form in interstellar molecular clouds. What is more, elementary photochemical processes, such as photochemistry, follow similar basic principles in their intra- and inter-molecular dynamics.

In order to investigate such molecular processes, the reactants can be generated by means of photochemical activation or by collisions in hot gases. Molecules absorb light and reach highly active states as a result of the added energy, or active particles are formed which start a series of reactions. We investigate the temporal course of these reactions and the subsequent, frequently rapid processes by analyzing the very specific absorption of light by the molecules with spectroscopic methods. On the basis of their respective spectra, we are even able to distinguish molecules which differ in nothing but their energy state. As a central part of our work we theoretically model intra- and intermolecular processes by means of classical and quantum-mechanical dynamics. One starts with the calculation of interaction forces and follows the reaction dynamics governed by them.

Reactions of atoms, radicals, electrons, and ions At present, we are increasingly focusing on reactions of molecular ions in so-called plasmas, that is in the gaseous state of matter in which electrically neutral and charged particles exist in parallel. This state is present on earth in the ionosphere or in electrical discharges such as lightning. In outer space the majority of matter exists in this state.

In addition we are interested in reactions of atoms and radicals generated by sun light and determining the structure of the earth’s atmosphere. Such studies help to understand the consequences of air pollution caused by man. The same processes as in the atmosphere – although at much higher temperatures – also play a central role in combustion. Thus, our studies can help to minimize the use of energy and to minimize pollutant emissions in technical applications.

The theoretical models following from our research are useful in many areas: from astrochemistry and atmospheric chemistry to plasma- and photochemistry to combustion chemistry. Even large-scale industrial processes can be described with them.
Simone Techert received her PhD in 1997 from the University of Göttingen. After her postdoctoral period at the European Synchrotron Radiation Facility in Grenoble (France), she returned to the Max Planck Institute for Biophysical Chemistry in 2000 with an Emmy Noether junior research group. After her habilitation in physical chemistry in 2005, she directed a Minerva working group until 2011. Since 2012, Simone Techert has been head of the Research Group Structural Dynamics of (Bio)Chemical Processes at the Max Planck Institute for Biophysical Chemistry, and she is professor at the University of Göttingen as well as senior scientist at the German Electron Synchrotron in Hamburg.

H ow quick and how agile is a molecule? How do individual atoms move when one molecule interacts with another in a chemical reaction? What are the elementary time scales? These are the questions we are investigating in our research group. As the smallest units in a molecule, atoms can move within one hundred trillionths of a second. This is also the time period in which the fastest processes occur in a chemical reaction. On the other hand, however, processes in complex systems such as living cells can extend to minutes or hours. We investigate the extent to which these different time scales depend on each other, and which structural patterns have to be present (or not present) in order to influence these different time scales.

Choreography of molecules

For this purpose, we are developing measuring instruments and methods using optical lasers, high-brilliance synchrotron X-ray sources, and X-ray lasers, that span the different chemical reaction time scales and allow us to determine in real-time exactly where an atom is at a certain point in time. For example, we use ultra-fast X-ray spectroscopy and ultra-rapid X-ray diffraction to observe what remains of an X-ray flash after a part of the light quanta was collected by the molecules «standing in the way». Thus, we can identify the motions with which single atoms of the molecules under investigation are involved in the choreography of a chemical or biochemical reaction.

Based on the very accurate understanding of chemical and biochemical processes gained from this operation, we are developing new materials that convert electrical energy more efficiently into light energy. Such light-active materials are, among other things, used in new types of photovoltaic systems or as biosensors.

In more complex systems, such as living cells, we determine so-called «transient structures», that is, structures that exist only for a very short time. For example, we transfer nucleotides, peptides, or proteins into very short-lived non-equilibrium states by means of external stimuli such as photons, and we demonstrate the rapid change in their structure by combining time-resolved, chemical-analytical measurement techniques with time-resolved X-ray imaging methods.

Ultra-fast X-ray spectroscopy and X-ray diffraction are complementary methods. Combining these, it is possible to monitor ultra-fast bonding changes in chemical reactions very closely. In this way, changes in poorly-structured biosystems can be recorded in real-time with atomic resolution.


Dynamics at Surfaces

When hearing the term «crash tests», most people will have the same picture in mind: A vehicle collides with another vehicle or an obstacle with full force. Such crash tests are used to investigate how a vehicle behaves in a collision and which forces are at work. One can thus identify weak points and potential for improvement.

Crash testing atoms and molecules

But crash tests are not only performed on huge objects like cars. Scientists can make atoms and molecules collide in the laboratory. With such mini-crash tests, it is possible to investigate the physical laws of chemical reactions. Researchers can thus learn more about how energy is stored and converted on an atomic level or how chemical catalysts can be improved. The corresponding field of research is termed chemical dynamics.

In this field, chemical reactions are categorized depending on the relative state of the precursor molecules, which are called reactants. These reactants can exist in the gaseous, liquid, or solid phase. If reactants are in different phases and, moreover, not «thoroughly» mixed, they encounter each other at their interface. This special case is dealt with in so-called surface chemistry. Our group is particularly interested in what exactly happens when atoms and molecules from the gas phase impinge upon solid surfaces. If you think of these collisions as a crash test, our mission is to report on damage control. To do this, we work according to the guiding principle «follow the energy of the products». When atoms or molecules collide with solid surfaces, other atoms and molecules form as products, which exhibit a different energy than the initial reactants. By monitoring with quantum specificity how the total energy of the reactants is conserved and distributed amongst the interfacial reaction products, we are able to gather valuable information about the crash scene – meaning that we can receive the circumstances of the collision and answer questions such as: What caused these results? What are the forces at work between the interacting particles? Can we optimize the reaction for a certain purpose? And what are the rate-determining steps?

Collisions in ultra-high vacuums

In order to measure as precisely as possible, we need a very complex experimental set-up. It is essential that we control the molecular encounter completely, and this means completely isolating our reactants from other particles and environmental influences. Therefore, we perform our experiments in ultra-high vacuums with about one trillion times less than atmospheric pressure, where no unmeasured molecules skitter about, which might interfere with the experiment. Also, we need to carefully clean the surface from atomic-dust. The temperature and morphology of the surface is also carefully probed and controlled.

When everything is set up and ready, the crash test follows. We spray our gas phase molecules into the vacuum using a high-tech version of a common atom and molecule beam jet. By controlling the temperature of the jet, we control the speed of the molecular beam. With lasers, we precisely tune the vibration and rotation of the molecules before they strike the surface. Following the collision, we measure the product molecule’s energy. We have recently pioneered a new tool for this: We take a picture of the molecular debris as it flies to the detector where their time of arrival is recorded. From the image data, we can calculate, for instance, the rate constant of the chemical reaction or how the energy was redistributed during the encounter. Therefore, we perform our experiments in ultra-high vacuum to ensure, where no unwanted molecules skitter about, which might interfere with the experiment. Also, we need to carefully clean the surface from atomic-dust. The temperature and morphology of the surface is also carefully probed and controlled.

Contact

A.M. Wodtke
alec.wodtke@mpib-berlin.mpg.de

A.M. Wodtke received his bachelor’s degree in chemistry from the University of Utah (United States) in 1981 and his PhD degree in physical chemistry from the University of California in 1986. After a two-year postdoctoral research appointment in Göttingen, he served on the faculty of the Department of Chemistry and Biochemistry at the University of California, Santa Barbara (United States) from 1986 until 2010. Following a joint proposal of the University of Göttingen and the Max Planck Institute for Biophysical Chemistry, he was awarded the prestigious Alexander von Humboldt Professorship in 2010. Since then, he has been a Professor at the University of Göttingen and Director at the Max Planck Institute for Biophysical Chemistry, where he heads the Dynamics at Surfaces team. His research interests are in the field of chemical dynamics, in particular the study of how chemical reactions occur on solid surfaces. He is a member of the German National Academy of Sciences Leopoldina and The Royal Society of Chemistry. He is also the author of two scientific textbooks and over 200 research papers.
C areful measurements have shown that the proton, the particle at the center of every hydrogen atom, is about 1836.15267389 times heavier than the electron orbiting it. This value seems quite arbitrary, and so far, no theory has been developed that can predict this number. This has led some scientists to speculate that, over time, one of these particles might actually be getting slightly heavier relative to the other. If the ratio were changing, the change must be very slow: Previous measurements have ruled out any change larger than 0.1 parts per trillion per year.

Vibrating molecules

Vibrational oscillations of molecules can provide a sensitive way to detect any changes of the electron-proton mass ratio. Our group is focused on developing and optimizing laser systems which can measure molecules with extreme precision and possibly detect changes that previous experiments missed.

In our experiments, we primarily investigate vibrations of the hydrogen (OH) molecule, consisting of one oxygen and one hydrogen atom. Hydroxyl molecules react quickly with other molecules in the environment, so in order to better study them, we create them in a vacuum chamber, where they can fly freely and undisturbed by other molecules.

The OH molecules in our vacuum chamber will not normally vibrate on their own. In order to cause them to start vibrating, we need to excite them with invisible infrared light from a laser. Laser light has a single, well-defined frequency, and the molecules will only start to vibrate if this frequency exactly matches the frequency of the vibrational oscillation. If the frequency is even just a bit off, the molecules will not be affected by the laser at all. By measuring the exact laser frequency that excites the molecules, we can effectively determine the oscillation frequency of the molecules.

Once excited, the molecules will continue vibrating for many milliseconds, retaining the energy they received from the laser. This can make it difficult to tell whether they have been excited at all. To determine how many molecules have been excited, we introduce a second laser, emitting UV light. The light from this laser causes the molecules to glow, but only if they are vibrationally excited. We can then measure this glow with a sensitive light detector.

A need for extreme precision

How precisely can we determine the vibrational frequency of the molecules is limited by how long we can measure them. Normally, the molecules fly through the vacuum chamber with a velocity of hundreds of meters per second, passing through the laser beam in only a fraction of a millisecond. In order to be able to observe them longer, we make use of a decelerator that slows the molecules using electric fields. Such a device can slow OH molecules to a small fraction of their original velocity, greatly increasing the observation time.

Measuring the energy levels of atoms and molecules more precisely has often helped advance our knowledge of fundamental physics. Nearly 70 years ago, the measurement of the Lamb shift in atomic hydrogen opened up the field of quantum electromodynamics, and in recent years, precise measurements of electronic transitions in hydrogen have indicated that the proton might be smaller than previously thought. Similar measurements on molecules can be used to look for other effects, such as whether fundamental physical constants vary over time, or how the weak nuclear force affects the motions of electrons in a molecule. To see these effects, it will be necessary to construct even more precise lasers and frequency standards.

Sophisticated molecules

How structure is related to function

For every purpose the right protein – the human body has hundreds of thousands available. Just take for example our immune system with its vast selection of antibodies, which protect us from pathogens. However, for many proteins the biological task remains elusive. Even less is known about specific functional details: Which forces are at work within and between the proteins? How do the proteins move and change their shape while fulfilling their tasks? Which proteins are present at which point in what amount, and how do they cooperate? To answer these questions, the scientists at the institute apply a wide range of methods, such as nuclear magnetic resonance spectroscopy, mass spectrometry, ultra-high resolution microscopy, or computer simulations.
Practically all processes in the human body are performed and controlled by highly specialized proteins. They transport cellular cargo, receive and transmit signals, convert energy, facilitate chemical reactions, or ensure growth and movement. These molecules can undoubtedly be characterized as the biochemical nanomachines of the cell; they developed in the course of a thousand million years of evolution. As is also the case with man-made machines, it is often the motions of individual parts of a protein which implement its function. Accordingly, the internal protein dynamics is extremely well-orchestrated. In many cases the movement of individual atoms is decisive.

No wonder that minute construction errors can have fatal consequences. Some hereditary diseases, for example sickle cell anemia, are attributable to the fact that a specific protein differs from the normal version by only a few atoms—and that although proteins frequently are composed of many ten thousands of atoms. Even though the exact structure of proteins can be measured with atomic resolution in many cases, the movements of proteins at an atomic level are very rapid and, therefore, are extremely difficult to access by experiment. In order to find out how these nanotechnological marvels function, we use computer simulations. State-of-the-art, high-performance parallel computers and increasingly more sophisticated algorithms allow us to calculate the movement of each individual atom in a protein complex with sufficient precision. To understand complex processes of life on the basis of the known physical laws in detail, we cooperate closely with experimental research groups.

Proteins at work – the smallest motor in the world
A particularly impressive example of a protein at work is the molecular motor ATP synthase. This protein complex of only 20 nanometers (millionth of a millimeter) in size works in the power plants of the cells and supplies the required energy for most processes in the body. With the aid of this protein machine, the human body transforms approximately 75 kilograms of the energy storage molecule ATP daily, in peak physical activities even much more. In fact, the similarity between ATP synthase and an Otto engine is astonishing: In both cases there are force strokes, a turning «crankshaft» and moving «cylinders». The decisive difference is the efficiency: Whereas the Otto engine achieves only a fraction of the thermodynamical efficiency limit, ATP synthase reaches nearly 100 percent. We were able to resolve how this efficient mechanism works in detail by means of computer simulations. The simulations revealed true «nano-mechanics». The rotational movement of the shaft is translated into an atomically coordinated movement at the synthesis site such that the ATP molecule is synthesized through elaborate assembly.
The function of a machine can be much more easily understood if we can observe it in action. The same is true for the tiny machines in our cells – the proteins. Billions of these nanomachines enable, control, or support nearly all the processes occurring in our bodies. Accordingly, the consequences are frequently severe when proteins do not function properly. Many diseases are caused by such dysfunctions.

Which interactions give rise to aggregation of proteins and thus cause disorders such as Alzheimer’s or Parkinson’s disease? How do cells regulate the influx and efflux of molecules such as water, ions, and nutrients? How does molecular recognition function? These are some of the questions we investigate in the Research Group Computational Biomolecular Dynamics.

To understand the function and dysfunction of proteins, it is usually insufficient to know their three-dimensional structure. Many proteins fulfill their respective task only by means of well-orchestrated movements. Our objective is to understand protein dynamics at the molecular level and to unravel the mechanisms underlying such dynamics.

Potassium channels – highly selective ion filters

One class of proteins investigated in the group are ion channels. They form pores in the cell membrane, which function as perfect, highly selective ion filters and allow only specific ions to pass through. This is, for example, the basis of signal transduction in nerve cells. What is the physical basis of such a remarkable selectivity, which simultaneously enables a high efficiency close to the diffusion limit? Molecular dynamics simulations facilitate resolving these questions at the atomic level.

In addition, we are investigating a truly multi-talented protein: ubiquitin. It is part of a sophisticated recycling system in the cell, which marks certain proteins as cellular «trash». But how does ubiquitin manage to recognize and bind to a multitude of different partner molecules? With the aid of molecular dynamics calculations and experiments in cooperation with the Department of NMR-based Structural Biology, we were able to demonstrate that ubiquitin is surprisingly mobile. Like a Swiss army knife it continuously changes its shape extremely rapidly – within a millisecond of a second – until it incidentally fits its partner.

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Christian Griesinger studied chemistry and physics at the University of Frankfurt and received his doctorate in 1986. From 1986 to 1989, he worked as a postdoctoral fellow at the Swiss Federal Institute of Technology (ETH) Zurich (Switzerland). He became professor at the Institute of Organic Chemistry at the University of Frankfurt in 1990. In 1999, the Max Planck Institute for Biophysical Chemistry appointed him as Director, where he has been heading the Department of NMR-based Structural Biology ever since. Christian Griesinger has received numerous awards, including the Sommerfeld Prize, the Leibniz Prize, the Bayer Prize, the Ampere Prize, and the Prize of the Korean Magnetic Resonance Society. He is a member of the European Molecular Biology Organization (EMBO) and of several scientific academies. His work on protein dynamics was supported by an ERC Advanced Grant.

Contact
cigr@nmr.mpibpc.mpg.de
www.mpibpc.mpg.de/griesinger

NMR-based Structural Biology

In the case of molecular «inventories» of the cell, whether proteins or nucleic acids, spatial structure and dynamics are just as important as chemical composition. The functional consequences of a defect in the shape can be caused in the cell by various diseases such as Alzheimer’s, Parkinson’s and Creutzfeldt–Jakob disease. In all three cases, deformed protein molecules accumulate in brain cells and destroy them. However, only if proteins and nucleic acids retain their shape can they fulfill their biological function. We are interested in questions where structural details are important for this and at which time scales the different three-dimensional structures interconvert.

The heart of the matter

Our method of choice is nuclear magnetic resonance (NMR) spectroscopy. NMR makes use of the fact that most atomic nuclei have a magnetic moment. They can be regarded as electrically charged gyroscopes, which try to align themselves with an external magnetic field. Because of this property, the atomic nuclei can absorb electromagnetic radiation of specific energy. The frequency that is absorbed depends on the chemical environment. In a molecule with many atomic nuclei in different positions, a correspondingly large number of different energy portions is required.

This results in an NMR spectrum which contains detailed information about the arrangement of the individual atomic nuclei and thus about the atomic location in three-dimensional space. However, deciphering this information in an art in itself. And the larger the molecule under investigation, the more difficult this task becomes. To accomplish this, we use so-called triple-resonance experiments, which yield three-dimensional or even higher-dimensional spectra. In the case of protein molecules

![Spatial structure of the open form of the molecular channel VDAC](Image)

...of more than 200 amino acids – the building blocks of all proteins – even this form of NMR spectroscopy reaches its limits. But we are attempting to push these limits even further.

Going beyond the limits

Among other things, we work with magnetically active isotopes of carbon. From 1986 to 2000, we used so-called triple-quantum experiments for a selected set of proteins. In the NMR spectrum we can then make either one or the other isotope visible. This way, proteins which are normally too large to be used as radiation detectors, can be used as NMR radiation detectors. This can also be analyzed.

In order to be able to use such labeling strategies, which make the spectra simpler and thus interpretable, we must first produce the protein. To accomplish this task, we use genetically modified bacteria that produce the protein in large amounts. Further, electrons, which have a much greater magnetic moment, can be used in NMR experiments. This is the case of the so-called electron nuclear double resonance (ENDOR) technique, which helped to elucidate, for example, the spatial structure and functioning of one of the most common human membrane proteins, the VDAC channel, the cell’s fuel pipeline. These channels in the outer membrane of mitochondria provide the cell with chemical energy in the form of adenosine triphosphate (ATP). We apply this approach also to other vital membrane proteins. Furthermore, we use electrons for signal amplification.

Focus on drugs

We can already investigate very easily how small molecules interact with large proteins with the so-called PHIPMA method. With this technique, medically relevant compounds can be optimized and tested in an early phase. In another project, we work with Armin Giese at the Ludwig Maximilian University (Munich) on a small molecule from our own production, named anle138b, which prevents the above-mentioned misfolding of proteins such as alpha-synuclein (Parkinson’s disease), Aβ and Tau (Alzheimer’s disease), the prion protein (Creutzfeldt–Jakob disease), and the skel amyloid protein (diabetes).

The compound delays diseases such as Alzheimer’s, Parkinson’s, and Creutzfeldt–Jakob as well as diabetes – at least in the animal model. Using anle138b, the lifetime of a mouse is extended by an average of 200 days when treated with the compound. We are currently studying the spatial structure of anle138b, which promises a molecule in a complex with its target molecule and are preparing the substance for clinical trials at the company MOUAG.

4. Mice can be used as a model for Creutzfeldt–Jakob disease. If these mice are treated with a compound named anle138b directly after the onset of the disease (Aβ), their survival time from day 120 (d120) onwards, their survival time on average increases by 200, 70, or 50 days, respectively. We also observe positive effects in Parkinson, Alzheimer, and Diabetes II mouse models.

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Structure Determination of Proteins Using NMR

More and more people, particularly the elderly, suffer from neurodegenerative diseases such as Alzheimer’s or Parkinson’s. In Germany alone, there are 300,000 new cases every year. These diseases often develop because certain proteins do not function properly anymore. This may have various reasons: Often, the shape of these proteins – their three-dimensional structure – is altered. This can have far-reaching consequences: It is the protein’s structure that determines whether the protein can bind to other proteins, whether it can be usable as a tool, how well it is soluble, and much more. All these things influence how and to what extent a protein can execute its function in the cell. Therefore, it is important to find out how the three-dimensional structure of a protein is altered in certain neurodegenerative diseases to find new therapeutic approaches.

In order to uncover the structural transformation of proteins, there are few methods more suitable than nuclear magnetic resonance (NMR) spectroscopy. Using NMR spectroscopy, it is possible to determine the structure of even exceptionally stubborn proteins. These include proteins embedded in membranes as well as very flexible and dynamic proteins, which, similar to photography with moving motifs, appear blurred when viewed under the microscope. Furthermore, with NMR spectroscopy, one can even analyze so-called intrinsically unfolded proteins in atomic detail. These special proteins do not follow the general rule that proteins find their spatial structure by folding in a determined pattern. Instead, in the cell, these proteins switch back and forth between different conformations. The importance of knowing a protein’s structure in detail is well illustrated through Tau. It has been known for a long time that the Tau protein plays a crucial role in a number of neurodegenerative diseases such as Alzheimer’s. How precisely Tau contributes to neuronal malfunction, however, has remained elusive. In recent years, using NMR spectroscopy, we discovered how the diverse structures Tau may take, and how it can be chemically modified and thus regulated by the addition of a phosphate group by the cell, and how it interacts with microtubules – the cell’s transport rails.

Membrane proteins in 3D

Another research area of our group is targeting the structure of mitochondrial membrane proteins. Mitochondria serve as the cell’s power plants, supplying it with energy. They differ from other parts of the cell in their unique structure and functional characteristics. Moreover, there is increasing evidence that mitochondria play a central role in age-related neurodegenerative diseases. This makes mitochondria a possible target for drugs to improve the treatment of these diseases. Here, research is focused on mitochondrial membrane proteins, many of which are important for the transport of metabolites and proteins over the mitochondrial membrane.

In recent years, our laboratory determined the three-dimensional structure of two important mitochondrial membrane proteins. One of them, called VDAC, acts as a «gatekeeper» and controls which metabolites may enter and exit the mitochondrion. The TSPO structure also shows a small molecule bound to the protein, which serves as a diagnostic marker. This detail is important as TSPO is targeted by pharmaceutical agents in diagnostics and therapy.

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Bioanalytical Mass Spectrometry

Henneking Urlaub

study of protein complexes and cellular compartments, and it is also reflected by their protein patterns. We determine and compare protein patterns of protein complexes and cellular compartments, but also entire cells and tissues. This type of research is generally known as “proteomics.” The differences that we observe in this context not only help us understand cellular processes – they also allow conclusions about what occurs inside (how it develops from a progenitor cell (for example in the bone marrow)) to a highly specialized cell such as an immune cell. Moreover, we can investigate how cellular processes change in certain diseases. Besides these “classical” proteomics approaches, we are also interested in how proteins directly interact in the cell with other proteins, with RNA, or with DNA. To address these questions, we apply various cross-linking techniques. These involve using cross-linking reagents or UV light, both of which permanently connect individual binding partners, thus allowing us to identify them as an entity in the mass spectrometer.

Manageable protein fragments

To achieve the various types of protein identification, we do not usually analyze intact proteins in the mass spectrometer. On the contrary, we initially cleave proteins that have been isolated from cells into smaller, more manageable protein fragments termed peptides. Subsequently, we determine with high precision not only the masses of the peptides, but also the sequence of their individual building blocks – the amino acids. As soon as we know the mass and amino acid sequence of one or more of these peptides, we can reliably identify the corresponding intact protein in databases and determine its quantity.

The properties of proteins depend on both the sequence and the degree of modification of their amino acids. This must be taken into consideration during analysis. These proteins that are components of cell membranes and carry, for example, bound sugar molecules will require a different procedure for sample preparation and analysis than those that bear phosphate residues (which can switch some genes “on” and “off”). Experiments that determine the modifications of proteins in a quantitative manner are extremely important when we compare normal and altered cells, like for example cancer cells. Differences in protein modification shed light on which biochemical pathways are followed in the respective cell types and which key molecules are involved in altered cells.

Cellular proteins are not only frequently modified; they are also hardly ever isolated in the cell because they form complexes with other proteins and with biomolecules such as DNA, RNA, or lipids. It is of general interest to acquire knowledge of which proteins interact with which other molecules. We achieve this, as described above for protein modifications, by cleavage of cross-linked proteins and protein complexes, followed by determining the sequences of the still cross-linked peptides in the mass spectrometer. Such studies can be performed on isolated complexes, but also – more challengingly – on cross-linked cellular organelles. Such studies can be performed on isolated complexes, but also – more challengingly – on cross-linked cellular organelles.
In complex multicellular organisms like the human being, cells share the work: Nerve, immune, or skin cells are specialists in their respective fields. However, also within every individual cell, the division of labor is crucial so that it can reliably fulfill its various functions. For this, a multitude of different molecules must smoothly work together as nanomachines, for example to translate the genetic information into proteins. Which molecular machines are at work here? How do they function in detail? And how is their interaction organized? Such questions are addressed by several departments and research groups by applying biochemical, molecular genetic, microscopic, fluorescence spectroscopic, and computational methods.
Molecular Biology

Our body is comprised of billions of cells. But regardless of whether muscle, skin, love, or nerve cell – they all contain the same genome. It consists of DNA and stores all the information required for the development and maintenance of life. To ensure that each of our cells carries out its dedicated functions, only the required genes are switched on and activated.

Genes are activated in a process called gene expression. Our laboratory investigates the first step in this event – the transcription process. During gene transcription, DNA is copied into RNA, which then serves as a blueprint for protein production. The resulting proteins are the «workhorses» of living cells and fulfill numerous functions, such as the transport of cargos, energy conversion, signal transduction, or catalysis of enzymatic reactions. The regulation of gene transcription forms the basis of cell growth, differentiation, and organism development. Accordingly, it is not surprising that its deregulation causes severe diseases, including cancer.

Our goal is to understand the molecular mechanisms of gene transcription and the principles of transcriptional regulation in living cells. In one approach, we combine different methods to determine the three-dimensional structures of large protein complexes involved in transcription, since shape determines function. This work resulted in a movie depicting many aspects of the transcription process in atomic detail. The main actor in this movie is a molecular nanomachine called RNA polymerase II (Pol II), which transcribes DNA into RNA. The nanomachine, made of twelve protein subunits, cooperates with dozens of accessory proteins to initiate transcription at the beginning of a gene, to elongate the RNA chain as it passes through gene bodies, and to terminate transcription at the end of the gene.

Unravel how genes are switched on

As one example, we recently developed a method called transient transcriptome sequencing, which uses metabolic RNA labeling to map the entire range of RNA species in cells, including very short-lived RNAs. In the future, we will study the transient transcriptome.

To study how transcription in cells is regulated on a genome-wide level, we also developed and applied techniques based on DNA sequencing and computational approaches. Recent work has enabled us to monitor gene activity in cells and to relate it to the underlying DNA sequence features and the distribution of regulatory protein factors over the genome. A picture emerges from this work about how DNA, RNA, and proteins form functional dynamic networks that regulate cellular life.

As a recent highlight from our research, we succeeded in determining the structure of the transcription machinery during the initiation phase, when transcription begins. We assembled a complex of 35 proteins with DNA and resolved its architecture by combining cryo-electron microscopy and X-ray crystallography. In the future, we will extend this work to even larger complexes of the transcription machinery during the elongation phase, when transcription is activated.

The three-dimensional structure of the transcription initiation complex derived from a combination of cryo-electron microscopy and X-ray crystallography.
It is one of the great enigmas of life how a single fertilized cell can develop into a complex, multicellular organism composed of hundreds of different types of cells. The organism's genome dictates the cells to follow individual molecular programs in which the expression of proteins is switched on and off, depending on the exact time and cell type.

Changing research with high-throughput sequencing

Experiments based on determining the sequences of DNA or RNA can now probe with unprecedented breadth and depth these mechanisms by which cells regulate the expression of genes into proteins. The rapid improvement of high-throughput sequencing technology in the last decade is thus boosting the pace of progress in biological research.

Sequencing technologies are also gaining increasing importance in medical research. In systems medicine, researchers aim to understand the origins of most common diseases by investigating what changes in the genomes of patients predispose to these diseases and what the mechanisms are by which these changes influence disease risk. These insights will help us to develop better drugs to prevent and treat common diseases.

A great advantage of the novel high-throughput, data-driven approach to biological research is that it is unbiased and can lead to unexpected discoveries, as it allows us to ask many questions to the data in little time without the need to formulate concrete hypotheses before the experiment is done.

But the data are often noisier than measurements from conventional, low-throughput methods. Our group develops statistical and computational methods to make better use of the information hidden in these data. In this way we aim to facilitate data-driven approaches to cell and developmental biology, genetics, microbiology, and systems medicine.

Software tools for biological research

First, our group develops computational methods for predicting the structure, function, and evolution of proteins, the most important building blocks of cells. We develop statistical methods that enable us to make use of the vast amount of sequence information that is becoming available at an ever-increasing pace. The goal is to provide life scientists with more and more powerful tools in order to guide their experimental work. Our software for the detection of remote common ancestry between proteins (MMseqs, MMseqs2) is widely used to predict the function and structure of proteins. Our software PHMMPs combines high sensitivity to detect related proteins with an extremely high search speed, which is required to analyze the huge datasets of DNA and RNA sequences from environmental probes in the burgeoning field of metagenomics.

Understanding the genome’s ‘regulatory code’

Second, we want to help in understanding how the most important level of the regulation of gene expression, namely transcriptional regulation, is encoded in each gene's regulatory regions. We develop computational methods to make better use of the information hidden in these data. In this way we aim to facilitate data-driven approaches to cell and developmental biology, genetics, microbiology, and systems medicine.

The group develops statistical and computational methods to analyze these regions of the genome’s regulatory code, which we believe play a key role in determining the expression of genes into proteins.

The binding site motif models that our motif discovery method PROFVEGF learns from regulatory sequences can predict binding strengths of transcription factors (here CTCF) more accurately than the commonly used models (left). The plot on the right shows the information added by learning dependencies between neighboring positions in the binding site sequences.

Cellular Biochemistry

Regardless of whether muscle, skin, or liver – in every tissue there is an abundance of diverse proteins. The blueprints for all of these protein molecules are present in encoded form in the genes found in the cell nucleus. In order to be able to produce proteins according to these blueprints, a gene is initially transcribed into a precursor messenger RNA (pre-mRNA). However, pre-mRNAs (draft versions) cannot be immediately utilized for protein production, because the blueprints for a protein is not normally present in one piece, but rather in several segments – the exons. Between these exons there are regions that have to be excised from the precursor version – the introns. Only after this operational step (termed splicing) has occurred of the (pre-)requisite exons are constitutionally connected in a ready-to-use messenger RNA.

This appears to be unnecessarily complicated, but it has a decisive advantage: Different exons can be selected and assembled to form different messenger RNAs as required. As a consequence, a single gene can provide the blueprints for many different proteins. This process, which is termed ‘alternative splicing’, explains how human beings can produce more than 100,000 different proteins from a rather modest complement of genes found in the cell nucleus.

In order to transform the precursor version of a messenger RNA into a functional end product, splicing must occur very precisely. Cutting to measure

In order to transform the precursor version of a messenger RNA into a functional end product, splicing must occur very precisely. Thus, it is no wonder that this process is performed by a very complicated molecular machine, the spliceosome. This machine is composed of more than 150 proteins and five small RNA molecules (the snRNAs U1, U2, U4, U5, and U6). Many of these spliceosomes are not scattered around the cell nucleus in an unordered manner, but form precisely organized complexes. Thus, for example, approximately 50 of these proteins associate with the snRNAs to form RNA-protein particles. These so-called snRNPs (pronounced ‘snurps’) bind to the pre-mRNA as prefabricated complexes and are the main building blocks of the spliceosome.

A molecular editing table

The spliceosome is assembled on site for each splicing event. To achieve this, snRNPs and other helper proteins are successively assembled on each pre-mRNA intron. Each of these five RNA-protein particles performs specific tasks. Thus, for example, the beginning and end of an intron must be recognized and brought closer to each other in order to immediately splice out the intron and couple the two exons originally separated by the intron.

The molecular scissors, which excise the intron, are successively activated during this process. In the course of splicing, a nick con- ing and going of snRNAs and proteins occurs; the timing of these molecular exchanges is exactly controlled. Presumably, this complex procedure ensures the exact excision of an intron and hence error-free assembly instructions for each protein.

Our objective is to record the dramatic structural dynamics of the spliceosome during splicing. For this purpose, we have stopped the spliceosome at different operational steps, isolated it in these states, and analyzed its components. In addition, we are able to measurably biological activity of spliceosomes from isolated components. By selectively removing or modifying individual components, we can observe how these manipulations affect the spliceosome.

In order to understand this fascinating molecular machine’s mode of operation in detail, we use an interdisciplinary approach. In addition to biochemical and biophysical methods, we primarily use high-resolution electron microscopy and X-ray crystal structure analysis. They provide us with three-dimensional models of individual snRNPs and entire spliceosomes, as well as details of the participating macromolecules.

Errors with grave consequences

The molecular analysis of the spliceosome, which is the focus of our interdisciplinary approach, will not only provide insights into the cause of molecular disorders that result from errors in the splicing of messenger RNA, but will also allow new therapeutic approaches for the treatment of such diseases. Recent estimates suggest that more than 20 percent of human genetic diseases are the result of mutations that impair the function of spliceosomes.
Vladimir Pena was trained in biochemistry at the University of Bucharest (Romania) from 1995 to 2000. He then went on to work as a research assistant. Subsequently, he joined the European Molecular Biology Laboratory (EMBL) in Heidelberg, where he received his PhD in 2005. He became a postdoctoral fellow at the Max Planck Institute for Biophysical Chemistry in Göttingen. He is now the group leader of the Crystallography Research Group at the Max Planck Institute for Biophysical Chemistry in Göttingen. Vladimir Pena has been heading his institute in 2009. Since 2014, Vladimir Pena has been heading his Research Group Macromolecular Crystallography as an independent group leader.

**DNA Enzymes**

DNA is known mainly for its capacity to encode information in the form of genes. However, twenty years ago, scientists identified DNA molecules that catalyze various chemical reactions. To date, not much is known about how such DNA enzymes function. We have now determined the first crystal structure of a DNA enzyme (Figure 2), in collaboration with the lab of Claudia Höbartner at the University of Göttingen. We plan to determine the structures of further DNA enzymes and to elucidate how they can catalyze reactions. We would like to use this knowledge to synthesize DNA enzymes for scientific applications – they could possibly be of medical importance in the future.

**Figure 1:** Crystal structure of the RNA helicase Aquarius. **Figure 2:** Crystal structure of a DNA enzyme (9DB1) catalyzing DNA splicing.

Claudia Höbartner at the University of Göttingen. We plan to place particular emphasis on the spliceosome’s regulation.

Helicases: the main driving forces of the splicing cycle

In a cyclic pathway, the spliceosome undergoes numerous stages, during which it varies in structure and composition as well as in its internal RNA-RNA and RNA-protein contacts. The driving forces and control mechanisms of these remodeling processes are provided by so-called RNA-helicases.

We recently determined the structure of an RNA helicase called Aquarius (Figure 1) and showed that it mediates important interactions within the spliceosome and helps to properly remove the introns and correctly join the exons. Aquarius also maintains the structural integrity of the intron-binding complex and helps to correctly position the exon junction complex. In the future, we would like to elucidate the molecular details of how Aquarius fulfills these tasks.

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Heli...
Marina V. Rodnina studied biology in Kiev (Ukraine) and received her PhD there in 1989. Subsequently, she went to the University of Witten/Herdecke on a research fellowship from the Alexander von Humboldt Foundation. She worked at this university as a research assistant from 1992 to 1998. After her habilitation in 1998, she was appointed university professor there; and from 2000 to 2009, she held the chair of physical biochemistry. She has headed the Department of Physical Biochemistry at the Max Planck Institute for Biophysical Chemistry as a Director since 2008. She has been a member of the European Molecular Biology Organization (EMBO) since 2004 and of the Leopoldina – National Academy of Sciences since 2008.

Contact rodnina@mpibpc.mpg.de

www.mpibpc.mpg.de/rodnina

in the cell, nothing happens without proteins. They maintain the cell’s shape, drive biochemical reactions, and provide for transport and communication. In all cells, proteins are produced by molecular machines called ribosomes. The ribosomes interpret the information encoded in the genes in order to produce functional proteins out of their building blocks, the amino acids. This process, termed translation, makes heavy use of the resources of the cell and consumes a large amount of energy. The well-being of cells depends on how many ribosomes they have and how well they work. On one hand, defective translation can result in a variety of diseases, including cancer as well as neurological, immunological, infectious, metabolic, and mitochondrial diseases. On the other hand, drugs that target ribosomes can be used to kill pathogens such as bacteria or fungi.

Our lab is interested in understanding how ribosomes work and how translation is regulated in health and disease. We use a wide range of experimental approaches including biophysical methods such as fluorescence spectroscopy, rapid kinetics, and single-molecule techniques, as well as biochemistry and genetics to study the mechanisms of action of this ancient macromolecular machine.

Precision work

Even when hundreds of amino acids are linked to each other to form a protein, each one of them can be important, as a single error or malfunction in the molecular machine can lead to severe damage. It is therefore essential that the cell have ways to control and clean-up procedures in the cell. We want to estimate how often the ribosomes make mistakes, how they manage to keep the error frequency manageable, and how they cooperate with other machineries in the cell to get rid of erroneously made products.

Programmed «errors»

Sometimes, the ribosomes make errors on purpose. These programmed errors can enrich cellular diversity by producing two different proteins from one coding sequence. Moreover, the ribosomes can sometimes re-code the message and incorporate special amino acids such as selenocysteine, which do not belong to the repertoire of the 20 standard amino acids. But which mechanisms allow such exceptions to the rule? Once we understand that, we also hope to be able to better understand how errors are normally avoided. Someday, such knowledge could also be used in medicine and biotechnology to synthesize «designer proteins».

Programmed -1 frameshifting by kinetic partitioning during impeded translocation

While the ribosome is progressively assembling a protein, it moves along its track, the messenger RNA (mRNA). We want to understand how the ribosome converts thermal and chemical energy into directed movement. What is the molecular choreography of the movement? Each time the ribosome steps along the mRNA, it moves by precisely one codon - the unit on the mRNA that tells the ribosome which amino acid it should add to the protein it is presently producing. How does the ribosome maintain this precise step? Answering these questions will give us a deeper understanding of how molecular motors work and how living cells utilize energy.

Defining the final shape of proteins

While proteins are essentially a chain of amino acids, they are not linear in their final form. To fully use their functions in the cell, proteins have to fold into complex, precisely defined three-dimensional structures. Folding starts while the proteins are still being produced on the ribosome. It will help prevent these diseases.

Marina Rodnina, Cristina Maracci, and Wolf Holtkamp (from left).
**Ribosome Dynamics**

Wolfgang Wintermeyer received his PhD in chemistry at the Ludwig Maximilian University in Munich. Subsequent to his habilitation in 1976, he did research in Munich supported by a Heisenberg fellowship from the German Research Foundation, at the Karolinska Institute in Stockholm (Sweden), and at the Massachusetts Institute of Technology (MIT) in Cambridge (United States). From 1987 until 2009, he held the chair for molecular biology at the Private University of Witten/Herdecke and thereafter became an emeritus professor. From 1991 until 2007, he was also Dean of the Faculty of Life Sciences there. Since 2009, he has been a Max Planck Fellow and head of the Research Group Ribosome Dynamics in the Department of Physical Biochemistry at the Max Planck Institute for Biophysical Chemistry.

A living cell is surrounded by a membrane, which separates the cell’s interior from its external environment. The membrane comprises a double layer of lipids (fat-like molecules), in which many proteins are embedded. The latter fulfill very specific functions. Some of them function as receptors for the reception of signals from the cell’s environment. Others serve as channels through which only certain substances to pass. Overall, about one third of all proteins of the cell are membrane proteins. But how are such proteins inserted into the cell membrane? For the most part their incorporation into the cell membrane occurs while the protein is being assembled from amino acids on the ribosome. Ribosomes which are assembling membrane proteins must therefore be directed to the cell membrane. How is a membrane protein recognized and how are the ribosomes that are assembling membrane proteins must therefore be directed to the cell membrane? We are studying how this complex process is executed and regulated in bacterial cells.

When a membrane protein is assembled on ribosomes, a specific label, the signal sequence, is incorporated, mostly in the early part of the protein. This signal is recognized by a ribonucleic acid-protein complex, the signal recognition particle (SRP). It directs the ribosome, assembling the membrane protein to the cell membrane (Figure 1). Interactions of the ribosome with SRP and helper proteins – among them the SRP receptor (SR) – ultimately result in the nascent protein being integrated in the membrane during the further course of synthesis. Membrane integration takes place in a protein complex localized in the membrane, the translocon. The translocon forms a pore through which the newly synthesized membrane protein can enter the membrane. The molecular events occurring in this process form one focus of our research.

Using a special fluorescence technique (photo-induced electron transfer, PET) we could show that the translocon opens laterally in the membrane protein has docked (Figure 2). We are studying how successful structural elements of the membrane protein are integrated into the membrane and the accompanying topological changes by single-molecule fluorescence analysis.

**Figure 1:** Interaction of protein biogenesis factors with the nascent peptide chain on the ribosome. The signal sequence, which is recognized by SRP, is highlighted in red.

**Figure 2:** Translocon opening involving ribosomes and signal peptide.

**Contact**

wolfgang.wintermeyer@mpibpc.mpg.de

www.mpibpcb.mpg.de/wintermeyer
Contact
holger.stark@mpibpc.mpg.de
www.mpibpc.mpg.de/stark

Holger Stark
studied biochemistry at the Free University of Berlin and completed his PhD at the Fritz Haber Institute in Berlin in 1997. Subsequently, he performed research at the Imperial College London (Great Britain), and from 1998 to 1999, he was a group leader at the University of Marburg. In 2000, he joined the Max Planck Institute for Biophysical Chemistry as research group leader. He was appointed Director and head of the Department of Structural Dynamics at the institute in 2015. He has also been a professor for molecular electron cryo-microscopy at the University of Göttingen since 2007.

Structural Dynamics

Cells keep their metabolism running with the help of molecular machines. Frequently, these are very complex structures, so-called macromolecules, comprising a large number of different components. However, in order to observe these machines directly in action in the «nanocosmos» of the cell, scientists must expend a great deal of effort.

Snapshots in a state of shock

In our group, we investigate dynamic macromolecules in a shock-frozen state with the aid of cryo-electron microscopy. This might sound paradoxical, but by means of flash freezing, the molecular machinery can be stopped in very different operational steps. With these samples, the electron microscope provides us with a complete series of images of a single macromolecule from different spatial perspectives and at different points in time. From these individual images, we ultimately assemble the three-dimensional structure using special computer programs. The structure shows us what the molecular machine looks like and how it changes during its functional cycle – and everything in 3D.

We apply this technique to a large number of different molecular machines, which are located at important switching points of cellular information processing. These machines frequently comprise not only proteins, but rather are complex associations of proteins and nucleic acids.

For example, we investigate how the cell’s protein factory, the ribosome, produces proteins by reading the genetic information. At present, we are also working with spliceosomes. They are triggered into action after the genetic blueprints for proteins have been copied into the draft version of a messenger RNA. Spliceosomes cut the unnecessary parts out of the messenger RNA and thus convert the blueprints into a legible form. In addition, we are studying a vital protein complex which plays an important role during cell division: the so-called anaphase promoting complex.

With cryo-electron microscopy, we cannot only determine the spatial structure at very high resolution. We can also observe the movements of such different molecular machines directly at work – and thus learn to understand their function in detail.

The ribosome schematically as a nanomachine «at work».

BioFuture Prize (2005), and the Ernst Ruska Prize (2013).

References
Communication and logistics

How cells transmit signals and distribute cargo

Catch a ball, recognize danger in time, remember something, or solve a mathematics problem – all seemingly effortless, our nervous system stores experiences from earliest childhood, controls complex movements, and creates our consciousness. The human nervous system comprises approximately 100 billion nerve cells. And each individual cell can make contact with thousands of neighbors. Tiny membrane vesicles release special messenger substances that affect the behavior of adjacent cells. How precisely this works on the molecular level is investigated by a number of labs at the institute. The researchers aim to shed light on the molecular processes which enable nerve cells to collect and process information – including complex brain functions such as learning and memory.

Also within every single cell the communication has to function flawlessly. Moreover, cellular logistics need to be well-organized. Scientists at the institute investigate how cells structure their interior, how molecules get into and out of the nucleus, and how cells transport proteins over membranes.
Neurobiology

Reinhard Jahn

Neurons are communication specialists. They receive and process signals and transmit them to recipient cells such as muscle cells or other neurons. Transmission is mediated by signaling molecules, called neurotransmitters. Within nerve endings, neurotransmitters are stored in small membrane-enclosed containers, termed synaptic vesicles. If electrical signals indicate that a message is to be sent, some of the synaptic vesicles fuse with the cell membrane and release their content, which, in turn, is recognized by the receiving cell.

Synaptic vesicles contain a fascinating array of proteins, which execute the main jobs the vesicles must perform. Some of them work as transporters and pump neurotransmitters into the vesicle. These transporters are driven by an ion gradient, or to be more precise, a proton gradient, and we want to understand how they are activated by signaling. Indeed, we already have a good idea of how they achieve this goal: If SNAREs that are attached to the vesicle and the plasma membrane meet, they become entangled and change their conformation. As a result, they exert a pulling force that pushes the membranes against each other until they fuse. This process, which is controlled by many additional proteins, can be reconstructed in the test tube. In our research, we want to find out how these proteins work together to achieve the precision and speed of synaptic vesicle fusion.

But SNAREs are not only needed for neurotransmitter release. They are also involved in the countless membrane fusion reactions that occur in every cell of our body. Biological membranes turn over continuously. They thereby generate small vesicles that are then transported to other membranes, where they fuse. We want to understand how these fusion reactions are controlled. After all, vesicles only fuse with their specific target membrane, and only if they are told to do so. Synaptic vesicles, for instance, only fuse if they need to transmit a signal. Intriguingly, some SNAREs are hijacked by pathogenic bacteria such as those responsible for Legionnaires’ disease. These bacteria create special vesicles in which they multiply, requiring fusion with intracellular vesicles.

One of our objectives is to find out what all these membrane fusions have in common and how they differ from each other.

Project Group of Hans Dieter Schmitt

Hans Dieter Schmitt and colleagues also work on SNAREs. As a model organism, they use yeast because it is easy to genetically modify. Their main interest is focused on intracellular transport vesicles. These vesicles have to be covered by a protein coat in order to form and detach from the precursor membrane. The group found that the cost of this process is paid when vesicles com ing from the Golgi apparatus arrive at their target membrane, the endoplasmic reticulum (ER). In a large SNARE-associated tethering complex performs the first contact between the vesicle and the ER.


Mannfred Lindau studied physics at the Technical University of Berlin and the University of Hamburg, and received his doctoral degree in physical chemistry from the Technical University of Berlin in 1983. This was followed by post-doctoral training at the Max Planck Institute for Biophysical Chemistry and at the Free University of Berlin, where he has led his own research group since 1988 and habi-
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Contact
manfred.lindau@mpipb.mpg.de
www.mpipb.mpg.de/lindau

Nanoscale Cell Biology

C
tein the vesicle membrane interact with SNAP proteins on the cell membrane, pulling the two so close that they eventually fuse, opening a gate between them. To determine how exactly SNAP complexes accomplish their task, we combine two strategies: We perform experiments in which we characterize the opening of these gates using specially developed versions of the SNAP complex, and we utilize computer simulations that visualize the molecular mechanics.

SNARE complexes are of high medical interest: Tetanus toxin found in soil bacteria destroys essential components of this machine and can lead to death if untreated. Furthermore, the widely known Botulism treatment modifies the SNAP complex and thereby reduces transmitter release, which locally paralyses muscles. The precise understanding of the molecular mechanisms of SNARE-induced vesicle fusion may lead to new treatment strategies. It will also advance our understanding of the mechanisms by which viruses enter cells, since they use closely related mecha-

A transient change in SNAP complex structure opens the fusion pore. In mammalian neurons and neuroendocrine cells, the SNAP complex is composed of the proteins Synaptobrevin-2, Syntaxin-1, and SNAP-25. The discovery of the key components of vesicle fusion and their regulation was honored with the Nobel Prize for Physiology or Medicine in 2013. However, although the components are known, the question remains: How exactly do the nanomechanics of fusion pore opening work? When the SNAP complexes of two opposing membranes pull these membranes together, the proteins in the SNAP complex undergo so-called conformational changes—they slightly change their shape. We want to find out how such conformational chang- 

Figure 1: A) A SNAP-25 construct incorporating cyan and yellow fluorescent protein 
tests conformational changes. B-D) At the time of membrane fusion, yellow fluorescence increases and cyan fluorescence decreases, producing a transient change in the fluorescence ratio that indicates a temporary conformational change.

Figure 2: A) Computer simulation of a possible train (between two opposing membranes) SNARE complex conformation. Four SNAP-25 bridges a small portion of a membrane, a so-called nanoscopic (top) and a larger, planar membrane (bottom). Synaptobrevin-2 (blue), Syntaxin-1 (red), and SNAP-25 (green) are shown, as well as water surfaces in cyan. B) Movement of the transmembrane domains of Synaptobrevin-2 after 0.3 microsecond of simulating the MD. C) Fusion pore structure at 1.7 microseconds simulation time. The proteins of the SNAP complexes have opened up and water from both sides of the membranes are now connected.

This is especially useful in a microscopy technique called fluorescence resonance energy transfer (FRET). The FRET tech-

Neural plasticity refers to the brain’s ability to change and adapt in response to experience, with changes in synaptic strength playing an essential role in learning and memory. These changes can be both short-term and long-term, with short-term plasticity occurring within milliseconds to seconds, and long-term plasticity spanning hours to days.

**Short-term plasticity** is characterized by changes in synaptic strength that are temporary and do not alter the underlying synapse. This type of plasticity is often associated with changes in neurotransmitter release and can be induced by brief periods of high-frequency stimulation. Short-term potentiation (STP) and short-term depression (STD) are two examples of short-term plasticity, each characterized by different patterns of response to stimulation.

**Long-term plasticity**, on the other hand, involves more enduring changes in synaptic strength that can last for days to weeks or even longer. This type of plasticity is thought to underlie many forms of learning and memory, including both declarative (e.g., facts and information) and procedural (e.g., skills and habits) memories.

**Synapses** are the contact sites where neurons communicate with each other, and they can change in strength through a process called **synaptic plasticity**. The precise mechanisms by which synapses can change in strength are not fully understood, but involve changes in the number of neurotransmitter receptors on the postsynaptic cell, changes in the number of synaptic vesicles, and changes in the efficiency of neurotransmitter release.

**Neurotransmitter release** is a critical process in synaptic plasticity, and it involves the movement of vesicles containing neurotransmitters to the active zone of the synapse and the fusion of these vesicles with the plasma membrane to release neurotransmitters into the synaptic cleft. This process is controlled by several factors, including the number and type of neurotransmitter receptors, the availability of neurotransmitter molecules, and the electrical and chemical properties of the synaptic environment.

**Calcium ions** are key players in neurotransmitter release, as they act as second messengers that regulate the activity of vesicle-fusing proteins. The release of calcium ions into the synaptic cleft is triggered by the activation of voltage-gated calcium channels in the presynaptic membrane, and these channels are sensitive to the local electrical activity of the neuron.

**Voltage-gated calcium channels** are integral membrane proteins that are activated by changes in the membrane potential of the neuron. The opening of these channels leads to a rapid influx of calcium ions into the presynaptic terminal, which in turn triggers the fusion of vesicles containing neurotransmitters with the presynaptic membrane to release neurotransmitters into the synaptic cleft.

**Superprimed vesicles** are a specialized class of synaptic vesicles that are preloaded with a high number of neurotransmitter molecules and are released at times of high-frequency stimulation. These vesicles are thought to play a critical role in the regulation of synaptic strength, as they can release neurotransmitters in a rapid and efficient manner, even in the absence of additional vesicle replenishment.

**NMDA receptors** are ionotropic glutamate receptors that are activated by the binding of glutamate and are sensitive to the concentration of calcium ions in the synaptic cleft. The activation of NMDA receptors is thought to be a key mechanism by which changes in synaptic strength are mediated, as it can lead to the enhancement or inhibition of neurotransmitter release, depending on the specific characteristics of the synaptic connection.

**Early and late plasticity** are two different forms of short-term plasticity that occur in different time frames. Early plasticity occurs within a few minutes of stimulation and is mediated by changes in the number of neurotransmitter receptors. Late plasticity occurs over a longer time frame (hours to days) and is mediated by changes in the number and efficiency of neurotransmitter release.

**Long-term depression** (LTD) and long-term potentiation (LTP) are two well-studied forms of long-term plasticity that have been extensively studied in the visual system. LTD is associated with decreases in synaptic strength, whereas LTP is associated with increases in synaptic strength. These two forms of plasticity are thought to underlie the learning and memory processes that are essential for adaptation and survival.
Cellular Logistics

Dirk Görlich

studied biochemistry in Halle (Saale) and received his PhD at the Humboldt University of Berlin in 1993. After a two-year research period at the Wellcome/CRC Institute in Cambridge (Great Britain), he was first appointed head of a research group in 1996 and then, in 2001, professor for molecular biology at the ZMBH of the University of Heidelberg. Since 2007, he has been heading the Department of Cellular Logistics at the Max Planck Institute for Biophysical Chemistry. Dirk Görlich has received numerous scientific awards, among them the Leopoldina – National Academy of Sciences.

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goorlich@mpibpc.mpg.de

www.mpibpc.mpg.de/goerlich

How does the sorting unit of nuclear pores work?

Nuclear pores are extremely effective sorting machines and each of them can transport up to 1,000 cargo complexes per second. Nuclear pores have an extremely complex structure, and each pore comprises about 700 protein molecules or approximately 20 million individual atoms. In order to comprehend the functional principle of such a complex system, it has to be reduced to essentials. As a decisive step in this direction, we were recently able to reconstitute the nuclear pore's permeability barrier in a test tube. It consists of so-called FG repeats and forms an integral membrane protein complex of 40 subunits. It suppresses the passage of 'non-molecules' but accelerates the transport of proteins and nucleic acids. By using a combination of cryo-electron microscopy and high-speed imaging, we recently succeeded in separating the permeability barrier from the rest of the nuclear pore machinery and investigating it in isolation.

The permeability barrier of the nuclear pore is a hydrogel, that is, an elastic solid which consists primarily of water, similar to gum bases or the vitreous body of the eye. The transient red pattern of lines on the backgrounds provides an impression of the transparency of the object. Since the hydrogel comprises FG repeats, it is termed FG hydrogel. The permeability barrier of the nuclear pore is a hydrogel, that is, an elastic solid which consists primarily of water, similar to gum bases or the vitreous body of the eye. The transient red pattern of lines on the backgrounds provides an impression of the transparency of the object. Since the hydrogel comprises FG repeats, it is termed FG hydrogel. In the context of providing additional evidence for the selection function of the nuclear pore, we have recently shown that nuclear uptake of cargo molecules is highly selective and that the uptake rate is increased by the presence of pre-existing, pre-assembled cargo complexes at the nuclear pore. Nuclear transport is an energy-consuming process that is powered by ATP hydrolysis. Compartmentalization of energy-producing and energy-consuming processes is essential for the efficiency of macromolecular transport across the nuclear pore. Recent studies have revealed that the nuclear pore complex is a highly selective sorting machine and that the transport of cargo molecules across the nuclear pore is mediated by so-called importins and exportins. The mechanisms of recognition processes are the focus of our research.

Eukaryotic life forms, such as plants or animals, are characterized by a division of labor in their cells. The cell nucleus focuses on the administration of the genome, mitochondria on supplying energy to the cell, whereas the so-called cytosol has specialized in protein synthesis. The advantages of this organization can be impressively summarized by the fact that only eukaryotes have evolved to complex, multicellular organisms. But this also has its price and must be maintained by a sophisticated logistic system. Cell nuclei lack protein synthesis and therefore must import all required enzymes and structural proteins from the cytosol. In turn, nuclear import and export require components of the cytosol such as ribosomes to the cytosol and thus enable the whole cell's protein synthesis.

Gates and transporters

The cell nucleus is enclosed in two membranes that are impermeable for proteins and other macromolecules. An exchange of material can therefore not occur directly through these membranes. Instead, so-called nuclear pore complexes are embedded in the nuclear envelope. One can imagine them as highly selective gates, which make up the stationary part of an entire transport machinery system. The mobile part of this transport machinery is comprised of nuclear import receptors (importins) and exportins. Although the nuclear pores appear tightly closed to the majority of macromolecules above a certain size limit, importins and exportins have the privilege of being able to pass nearly unimpeded through the permeability barrier of nuclear pores. In this context, the decisive point is that they can also carry cargo or passengers on their way through the nuclear pore. Not every passenger is allowed on-board; instead, importins and exportins recognize with molecular precision which molecule is to be imported into the nucleus and which is to be exported. The mechanisms of these recognition processes are the focus of our research.
Membrane Protein Biochemistry

Not only cities rely on a properly functioning waste disposal system. Even living cells must eliminate “waste”. In particular, they tightly regulate the degradation of proteins. Proteins that are located in the cytoplasm are degraded by the so-called ubiquitin-proteasome system (UPS) in all highly developed cells. To accomplish this, enzymes called ubiquitin ligases first tag the proteins as waste by attaching chains of a small protein called ubiquitin to the proteins. These ubiquitin chains are recognized by a large cytoplasmic garbage collector, the proteasome, which breaks down the proteins into smaller blocks.

Degradation of non-cytosolic proteins

It has been known for some time that the UPS is also involved in the degradation of non-cytosolic proteins. After their production in the cytoplasm, these proteins are either incorporated into the membrane of a particular organelle, the endoplasmic reticulum (ER), or transported through the ER membrane. The degradation of non-cytosolic proteins by the UPS is called ER-associated protein degradation (ERAD).

A protein can be degraded by ERAD for several reasons: Some proteins cannot fold stably and are therefore discarded. This prevents misfolded proteins from clumping together and causing disease on the cell. Other proteins are degraded when they are simply no longer required.

ERAD differs from the conventional UPS in that the protein is recognized in a different compartment of the cell than where it is degraded. Since the two participating compartments – ER and cytosol – are separated by a membrane, the protein must first be transported through the ER membrane before it can be degraded. While scientists have been able to identify many proteins involved in ERAD, it remains largely unanswered how a protein that needs to be degraded is detected and then transported through the ER membrane.

Our work focuses on ubiquitin ligases in the ER membrane. We suspect that they not only attach ubiquitin to proteins which are intended to be degraded, but also form channels, through which ERAD substrates pass through the ER membrane. On the one hand, we investigate ERAD in living cells and try to find out which functions individual proteins have by specifically interfering with the process. For this, we use baker’s yeast as a model organism because we can easily manipulate it genetically. Furthermore, it allows conclusions about how this process, which is conserved in all higher developed creatures, generally works. On the other hand, we try to gain a better understanding of the ERAD mechanism by replicating the process in the test tube from purified components.

Transport of proteins into the apicoplast

In a second project, we examine how the ERAD process has been transformed in a completely different context. Some parasites, such as the pathogens of malaria or toxoplasmosis have a plastid-like organelle surrounded by four membranes. Since this so-called apicoplast hardly has any genetic information of its own and thus lacks instructions for building proteins, it has to import a large part of its proteins over the surrounding membranes. Evidently an ERAD-like apparatus is involved. We want to find out which proteins are part of this apparatus and transport other proteins into the apicoplast and define these proteins in molecular terms. By comparison with the ERAD process, we hope to understand how ERAD has been transformed into a pure protein import machine in these organisms in the course of evolution.
Heart and brain, liver and lung – all parts of our body originate from a single fertilized egg cell. But how is this egg cell formed? And how does it develop into a complex organism? How do the cells in the embryo form complex organs that interact reliably? Researchers at the institute unravel these fundamental processes on the molecular level using such different organisms as fly and mouse. Even though these animals do not appear to have much in common at first glance, their embryonic development as well as that of human beings follows similar genetic programs. Among other things, scientists use these organisms to investigate in how far diabetes and obesity are influenced by genes. This knowledge helps us to better understand and treat such diseases.

Furthermore, researchers at the institute are interested in the fascinating phenomenon of sleep: A large portion of our life is spent asleep – but why is this so? How is our «biological clock» controlled so that it stays in step? And how does sleep work in principle?

Last but not least, the scientists improve imaging methods like magnetic resonance tomography to obtain «live» images from inside our body and to visualize vital processes such as breathing or the beating heart in real-time.
Meiosis

Melina Schuh studied biochemistry at the University of Bayreuth. For her PhD, she worked at the European Molecular Biology Laboratory (EMBL) and received her degree from the University of Hidelberg in 2008. She then moved to Cambridge (Great Britain), where she was a group leader at the MRC Laboratory of Molecular Biology (MLBM) since the end of 2015. Since 2016, she is a group leader at the Max Planck Institute for Biophysical Chemistry and head of the Department of Molecular Biology of the Department of Meiosis. She received several awards for her work including the John Kendrew Young Scientist Award, the Biochemical Society Early Career Award, the Lister Research Prize, an EMBO Young Investigator Award, and the BINDER Innovation Prize.

H
uman life starts with the fertilization of an egg cell by sperm. During fertilization, the genetic material of the mother and the father – which is stored in the form of chromosomes – is united. Egg and sperm differ from all other cells in our body in one central aspect: They contain only half the number of chromosomes. Normally, each chromosome is present in two copies. In contrast, the egg has only one of the two copies of each of the mother’s chromosomes, and the sperm contains only one of the two copies of each of the father’s chromosomes.

An egg develops out of a progenitor cell, the oocyte, which still possesses two copies of each chromosome. To become a fertilizable egg, the oocyte has to eliminate one of the two copies. This happens once every menstrual cycle through a specialized cell division called meiosis. During meiosis, one of the two copies of each chromosome is eliminated from the oocyte and discarded in a small cell called polar body. Often, this does not work reliably, resulting in an egg with the wrong number of chromosomes. If such an egg is fertilized, the embryo will also have the wrong number of chromosomes. In most cases, an embryo with the wrong number of chromosomes will die. In other cases, the embryo may be viable, but it will suffer from congenital disorders such as Down syndrome, which is caused by an extra copy of chromosome 21.

Chromosome segregation is error-prone. To find out how often eggs frequently have the wrong number of chromosomes, we need to investigate how eggs develop. Our aim is to understand how the chromosomes become prepared for elimination into the polar body, and how the machinery distributing the chromosomes between polar body and egg works. This machinery is called the microtubule spindle and consists of protein fibers, which separate the chromosomes. If the spindle is abnormal, chromosomes cannot be separated accurately. Indeed, our work has revealed that chromosomes are frequently abnormally attached to the spindle in human oocytes, which may contribute to the high error rates in meiosis.

We are also investigating the causes of declining female fertility as women get older. We have found that chromosomes in human oocytes are disintegrating as women age. This leads to more and more errors during the segregation of chromosomes as women get older. This decline in oocyte quality may be due to the fact that eggs are as old as the woman. A 40-year-old woman has 40-year-old eggs.

New tools to study meiosis

To have a solid foundation for future research, we are developing new tools to study meiosis in mammalian oocytes. For instance, we have been able to carry out the first so-called high content screening directly in live human oocytes. This opened an exciting new area of research in our lab that we plan to expand significantly in the future.

Nuclear膜 breakdown
Chromosome segregation
Chromatid cohesion
Centrosome duplication
Prometaphase
Metaphase
Anaphase
Telophase
Recessive
Dominant
Meiosis
Meiotic纺锤体
Meiotic spindle
Stages of meiosis observed in live human oocytes.


Chromosome segregation in a human oocyte.
Molecular Developmental Biology

Herbert Jäckle

2014.

China. He served as Vice President of the Leibniz Prize, the Otto Bayer Award, and was subsequently appointed a professor for genetics at the Ludwig Institute of Molecular Developmental Biology in Tübingen. In 1987, he became the molecular control mechanisms that regulate developmental processes from egg to fly and to the control of the body's energy requirement, so that flies become neither obese nor underweight. The astonishing outcome of our analyses is that control factors which we found in the fly are present in similar form in the human genome. They are not some special achievement of flies, but rather a common genetic legacy of all animals. Drosophilin's genetic inventory, therefore, is also informative in medical questions: When developmental or metabolic processes occur in humans, in many instances the genes and entire control systems of the body design are identified, we aim at understanding their molecular interplay and the molecular mechanisms to solve the big puzzle that illustrates the path of a single cell, the fertilized egg, to a complex three-dimensional organism that interacts with its environment.

Setting up the body structure

The body structure of the fly has already been determined before the egg cell is fertilized. Female flies not only supply their eggs with nutrients, they also provide components which intervene as key factors in development. They are asymmetrically distributed in the egg and subsequently activate a gene cascade which determines the developmental fate of a cell at the proper position in the body via the interaction of signal substances with corresponding receptor molecules. While the molecular key players of the body design are identified, we aim at understanding their metabolic interaction and the molecular mechanisms to solve the big puzzle that illustrates the path of a single cell, the fertilized egg, to a complex three-dimensional organism that interacts with the environment.

Maintenance of body functions

All aspects of body function require energy, such as movements or metabolic actions of the organism as a whole, individual cells, or the internal cellular processes. Thus, we ask the question of how the body controls its energy budget since in nature, like all other animals, it is exposed to periods of sufficient food supply as well as famines. The big question is how an organism knows how much energy it must store or deliver to keep the genetically controlled body weight. Fat deposits are the main form of energy storage in the body. They cover the organism's energy requirements in times of famine. We address the question of how organismal energy homeostasis is maintained by showing how the metabolism adapts in response to food deprivation and resumption of food-intake.

Further, we analyze the genetic adaptations that allow flies to survive in environments with varying periods of starvation. These projects are also designed to help us better understand human obesity. Due to our life style, obesity – with its consequences such as cardiovascular diseases, diabetes, and certain types of cancer – is spreading pandemically around the globe. In our biomedical studies we use the fly as a model to contribute to improvement of diagnostic methods and development of new drugs that cure obesity in flies and later, hopefully, in humans.

The fruit fly Drosophila is a very popular scientific research object for good reasons. Undemanding and immensely prolific, this fly develops from a single, small egg cell. But how does a complex body with extremely diverse cell types and organs develop from this single cell? And, once the body is established, how does the animal regulate its energy requirement to maintain its organ functions?

To answer these great biological riddles, we delve deeply into the molecular control mechanisms that regulate developmental processes from egg to fly and to the control of the body's energy requirement, so that flies become neither obese nor underweight. The astonishing outcome of our analyses is that control factors which we found in the fly are present in similar form in the human genome. They are not some special achievement of flies, but rather a common genetic legacy of all animals. Drosophilin's genetic inventory, therefore, is also informative in medical questions: When developmental or metabolic processes occur in humans, in many instances the genes and entire control systems of the body design are identified, we aim at understanding their molecular interplay and the molecular mechanisms to solve the big puzzle that illustrates the path of a single cell, the fertilized egg, to a complex three-dimensional organism that interacts with the environment.

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The fruit fly embryo shortly after fertilization (top). The embryo is subdivided into increasingly smaller segments. As the anterior-posterior axis (red is anterior). About 90 minutes later (bottom), these factors have initiated the control of a hierarchy of about 20 interacting segmentation gene activities (three patterns are shown); red, green, blue, yellow are overlapping regions, which blueprint the not yet morphologically visible segmented body pattern (head region is to the left).
Gene Expression and Signaling

B
tiological processes in all organisms, including humans, are controlled by genes. But what controls genes in turn? A num-
ber of mechanisms that regulate gene activity have been discov-
ered. Among these regulators are tiny RNAs, called microRNAs (miRNAs), which are capable of silencing genes.

miRNAs can coordinate target one gene. This illustrates how complex mRNA-mediated gene regulation can be. Even
though we still do not know the complete repertoire of genes each miRNA regulates or how exactly miRNAs work, miRNAs have
already been developed as new therapeutic targets for many
diseases. To better understand the biological roles of miRNAs, we combine experimental and computational approaches and use
the fruit fly Drosophila melanogaster as a model organism.

Not just X and Y

Each cell has a sexual identity, meaning that male and female cells differ in sets of expressed proteins. Unexpectedly, we discovered that cellular sexual identity, which is established during embry-
genesis, does not only depend on X and Y chromosomes – it has to be actively maintained during its entire lifetime. This is con-
trolled by a sexually biased steroid hormone and its dependent
miRNA. We identified sets of miRNAs that are differentially ex-
pressed in male and female tissues across various stages of
development. We also found that miRNAs regulate other very important pro-
cesses. With the help of miRNAs, cells adjust their metabolism to fluctuations in nutrient composition and availability. Furthermore, miRNAs guide how cells develop from stem cells into specialized cells, a process called differentiation, and more importantly, how stem cells per se are maintained. As these two processes are affect-
ed in aging and cancer in humans, miRNAs have emerged as po-
tential therapeutics in regenerative medicine and cancer therapy.

Muscular dystrophy in the fruit fly

Furthmore, we study the role of miRNAs under stress conditions and
in disease. In particular, we focus on muscular dystrophies.

In Western Europe, more than 70,000 people suffer from forms of muscular dystrophy. Unfortunately, no cure exists for these dead-
ly neuromuscular disorders. The patients face neurological defects as well as progressive muscle weakness and loss. Drosophila’s easy-to-manipulate genetic system, relatively short life cycle, low
cost, and biological complexity make the fruit fly a perfect sys-
tem to investigate these hereditary muscle diseases. Previously, we developed a Drosophila model for studying different types of muscular dystrophy. We have shown that the phenotypes caused
dysfunction of Dystrophin-Dystroglycan complex interacts with miRNAs. This will help us understand the mechanisms contributing to
diabetic and dystrophic muscle degeneration and facilitate
the development of miRNA-based therapeutics.

Halyna R. Shcherbata
studied biology and chemistry at the Ivan Franko National University of
Lviv (Ukraine), where she also received her PhD and worked as an
assistant professor at the Department of Genetics and Biotechnology.
Until 2010, she became a postdoctoral fellow and later research professor at the Department of Biochemistry, University of Washington in Seattle (United States). Since 2010, Halyna R. Shcherbata has been head of the
Max Planck Research Group Gene Expression and Signaling at the Max
Planck Institute for Biophysical Chemistry. In 2012, she habilitated at the University of Göttingen.

Contact
halyna.shcherbata@mpipbg.mpg.de
www.mpipbg.mpg.de/shcherbata

mutations are remark-
dable similar to phenotypes observed in human muscular dystro-
phy patients. Mutant flies exhibit a shortened lifespan, decreased
mobility, age-dependent muscle degeneration, and brain defects.
Importantly, we have shown that several miRNAs regulate
Dystro-
phian expression. In the future, we plan to analyze in depth how
Dystrophin-Dystroglycan complex interacts with miRNAs. This will help us understand the mechanisms contributing to
brain defects and dystrophic muscle degeneration and facilitate
the development of miRNA-based therapeutics.

Deregulation of Dystroglycan expres-
sion in the brain causes the cobble-
stone brain or lissencephaly type II.

miR-9a targets the ECM receptor Dystro-
glycan to canalize myotendinous junction

M.M. Kucherenko, J. Barth, A. Fiala,
A.S. Yatsenko, A.K. Marrone, H.R. Shcherbata: miRNA-induced buffering of
the cobblestone-lissencephaly-associated extracellular matrix receptor dystroglycan via its alternative 3'-UTR. Nat. Commun. 6, 6995 (2015).


H.R. Shcherbata: Steroid-induced microRNA mir-4906 in Drosophila is a sterol sensor that acts as a spatio-temporal switch for neuronal cell fate in the developing Drosophila brain. JNEURO 31, 4511-4523 (2012).

Drosophila Dystroglycan
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Molecular Organogenesis

We breathe in and out approximately 20,000 times a day without thinking about it. Each time, the respiratory air flows through the delicate tube system of our lungs, which contain five to six liters of air and exchange approximately half a liter of air with every breath. Like the crown of a tree, the system transitions into increasingly finer branches down to the alveoli where oxygen migrates into the circulatory system.

Our research group wants to understand how these highly branched pathways for the respiratory air develop. However, examining the underlying molecular mechanisms is very difficult and time-consuming in mammals. As a consequence, we investigate complex questions on one of biology’s most popular model organisms: the fruit fly Drosophila melanogaster.

Drying out the respiratory system

The fly and the human being are more similar in many aspects than one might think. From a total of 13,600 Drosophila genes approximately 7,000 genes are also present in similar form in the human genome. The fruit fly indeed has no lungs, but instead a system of arboreally branched tubular pathways for the respiratory air, the trachea. In the meantime, we know that the development of this system of tubes is organized very similarly to the development of the lungs. A number of closely related steps during embryonic development ensure that the tubes branch at the proper locations and that they do not end up too narrow or too wide.

Common to both organisms is also that, during the developmental phase, the respiratory tubes are initially filled with liquid. The fly and the human being are more similar in many aspects than one might think. From a total of 13,600 Drosophila genes approximately 7,000 genes are also present in similar form in the human genome. The fruit fly indeed has no lungs, but instead a system of arboreally branched tubular pathways for the respiratory air, the trachea. In the meantime, we know that the development of this system of tubes is organized very similarly to the development of the lungs. A number of closely related steps during embryonic development ensure that the tubes branch at the proper locations and that they do not end up too narrow or too wide.

Common to both organisms is also that, during the developmental phase, the respiratory tubes are initially filled with liquid.

Among the 7,000 genes that are similar in humans and flies, we have discovered 20 genes which ensure that the tubes develop properly and are dried out at the right time. Now, we want to determine the molecular mechanisms in which these genes are embedded and whether they have kept their functions across species boundaries.

Therefore, before birth or hatching of the larva, they must be dried out at the proper time, otherwise severe respiratory problems will arise. Babies born prematurely, for example, are in danger of developing respiratory distress syndrome (RDS). Even in adult humans liquid in the lungs can result in life-threatening edemas.

High resolution electron microscopy of the tracheal cuticle. Transeptal folds (TF) are cuticle ridges that compose a helical structure running perpendicular to the tube length along the lumen.
Molecular Cell Differentiation

Wether it be heart or kidney, pancreas or brain, the organs in our bodies are equivalent to small factories, in which specialized «units» perform specific tasks. In the pancreas there are primarily two cell types which share the work. While the majority of them produce digestive juices, the smaller cell group produces hormones such as insulin, which regulates the blood sugar level. The mid-brain also comprises highly specialized cells such as nerve cells, for example, which produce the messenger molecule dopamine.

But as different as the specialized cells are, they all arise during the development of an organ from nearly identical progenitor cells. In our group, we are studying the underlying mechanisms behind this process. We already know that certain genes control the maturation of an organ and thus determine the subsequent fate of the cells. These control genes provide the blueprint for specific proteins, so-called transcription factors. These factors selectively switch on genetic programs or suppress them and thus transform progenitor cells into cells with specific characteristics. This has been shown by tests in which the control genes were inactivated. For example, without the control gene Pax4, no insulin-producing cells develop in the pancreas. Other factors cause cells to produce glucagon, insulin’s antagonist. Similar control mechanisms are at work in the mid-brain. There, for example, the factor Lmx1a activates a genetic program in a specific group of nerve cells, which enables them to produce dopamine. In order for cells with different tasks to be formed in the correct ratio in an organ, the respective transcription factors interact with each other and thus create the required balance.

Mouse research for human beings

We investigate the maturation of an organ in mice, because we can very easily modify this rodent genetically and can thus selectively examine the role of the participating factors. The information obtained in our research is also of fundamental importance for human medicine. For example, it can be used to find new strategies for the selective treatment of certain diseases. Such a therapy could be the conversion of glucagon-producing cells into insulin-producing ones to treat patients suffering from type I diabetes.

| Two islets of Langerhans in the pancreas, with insulin- (red) and glucagon-producing cells (green). The two hormones regulate blood sugar. |

Ahmed Mansouri

received his PhD in chemistry from the Technical University of Braunschweig in 1978. Subsequently, he performed research as a postdoctoral fellow at the Institute for Human Genetics at the University of Göttingen, in the Friedrich Miescher Laboratory of the Max Planck Institute for Immunobiology in Freiburg. In 1989, he became a scientist at the Institute for Molecular Cell Biology at the Max Planck Institute for Immunobiology in Göttingen. In 1999, he habilitated at the Medical Faculty of the University of Göttingen. Since 2002, he has been head of the Research Group Molecular Cell Differentiation at the Max Planck Institute for Biophysical Chemistry. Ahmed Mansouri has held the professorship of the Dr. Helmut Storz Foundation at the University Medical Center Göttingen since 2005.

Contact

amansouri@mpibpc.mpg.de

www.mpibpc.mpg.de/amansouri
time moves in one direction, and this sequence of events is irreversible. But this does not apply to biological systems! Many life processes show characteristic recurring patterns. A striking example is the strong influence of 24-hour rhythms on the physiology and behavior of living things. These internal clocks, also called circadian clocks, are the research topic of our department, where we examine this phenomenon using genetically modified mice. Much like in humans, a circadian clock is present in all cells of the mouse. One of the questions that interests us is how these clockworks are coordinated: Is there an overriding control center that regulates all the clocks of every cell and aligns them with each other, or are the individual clockworks controlled jointly?

We know that circadian clocks are controlled by positive and negative feedback (Figure 1). At the beginning of the day, activator proteins stimulate the production of inhibitor proteins, which then later in the evening block the activators. We are mainly focused on the nature of these circuits: Which proteins are responsible for the activation? As is already known, certain proteins (so-called transcription factors) play an important role here. But there are only vague ideas about what ultimately turns on the clock genes in the morning and how the inhibitors accomplish their negative feedback later in the day. By means of a gene-based screen, we discovered that a protein called TIP60 acetyltransferase is involved in the turning on of the clock genes, but is also a target of the negative feedback.

Molecular conveyor belts in the brain

We extend these molecular genetic studies to tissues. For example, we investigate the mode of action of circadian clocks in epithelial tissues lining the brain ventricles. Inside the brain of vertebrates, there are four interconnected ventricles which are filled with cerebrospinal fluid. Tiny cilia that extend into the ventricles are important for the transport of cerebrospinal fluid which is rich in signaling molecules. Through their synchronized beating pattern, the cilia create a complex network of dynamic flows that act like conveyor belts and transport molecular cargos. We were able to observe complex motion profiles in these flows. There are dividing lines and zones that change with the daily rhythm. The whirl in Figure 2, for example, can only be seen at the end of the night. Furthermore, vertical or horizontal barriers form depending on the time of day. For neurophysiologists the cilia-based flows indicate complex logistics through which the signaling molecules seem to be transported accurately, quickly, and under expenditure of energy inside the brain to where they are needed. We are investigating whether a circadian clock controls these rhythms and how this clock could influence such complex processes as the orientation of cilia. To get answers to our questions, we are combining mouse genetics with cellular and structural biology.

Circadian rhythms in ecosystems

Unlike the recently discovered cilia-based complex flows in the brain, the daily recurring vertical migration of an entire ecosystem consisting of plankton has been known for a long time. Both in inland freshwaters and in the ocean this migration is controlled by a circadian clock, and very likely the planktonic components have such a clock. But there is still no clear answer to the question whether merely the change of light and dark or also additional factors, such as nutrients or the avoidance of planktonic sea creatures, play a critical role in migration. It is also unknown to what extent the circadian clocks in this ecosystem differ at the molecular level. Since the plankton population is complex, an individual spatio-temporal analysis of vertical movement is not feasible with classical approaches. Therefore, we use so-called metagenomic methods to capture the totality of the genome of an ecosystem in order to explore the diversity of the circadian clock and the rhythm coordination of these clockworks between organisms in the plankton ecosystem.
Cardiovascular applications are attractive for several reasons. First of all, real-time MRI — without the need for synchronization to the electrocardiogram and during free breathing — for the first time enables reliable studies of patients with cardiac arrhythmias. Moreover, a comprehensive real-time MRI protocol, combining access to cardiac function, blood flow, and myocardial tissue characterization, will lead to much shorter and more tolerable examinations. Finally, the possibility to monitor immediate physiologic responses of the cardiovascular system to stress or exercise offers new diagnostic opportunities, for example during early phases of heart insufficiency.

Future developments
Real-time MRI studies of body motions deal with movements of the wrist, knee, foot, or temporomandibular joint. We further expanded real-time MRI to completely new applications, for example in the oropharyngeal area, ranging from swallowing dynamics including reflux diagnostics. One specific real-time MRI result of utmost scientific and clinical interest is our discovery that inspiration rather than cardiac pulsation is the major regulator of human cerebrospinal fluid flow. For example in the oropharyngeal area, ranging from swallowing dynamics including reflux diagnostics. One specific real-time MRI result of utmost scientific and clinical interest is our discovery that inspiration rather than cardiac pulsation is the major regulator of human cerebrospinal fluid flow. This also applies to magnetic resonance imaging (MRI), which offers noninvasive, detailed, and quantitative insights into the brain, heart, and other organs.

Applications range from the visualization of structures and functions by imaging plays an important role in biomedical research and clinical practice. For example, MRI is used for the diagnosis of various diseases, ranging from cancer to heart disease. MRI is also used to monitor the progress of treatment and to assess the effectiveness of therapeutic interventions.

In summary, real-time MRI has the potential to revolutionize medical imaging by offering high temporal resolution and real-time monitoring of physiological processes. This technology is expected to lead to significant advancements in the diagnosis, treatment, and management of various diseases.
Sleep and Waking

Sleep and waking are part of life for every animal and every human. It appears obvious why we are awake. But why do we sleep? One moves less and is barely aware while asleep. Anyone who sleeps is more vulnerable. So why do animals enter such a hazardous state? Without sleep, we humans feel tired and are inefficient, and experiments show that animals can die from sleep deprivation. Today, researchers believe that sleep is not only important for energy conservation but also for learning and memory, fundamental cell biological processes as well as for nervous system regeneration.

In our research group, we are studying the regulation and functions of sleep. We want to find out how a nervous system falls asleep and wakes up, how it knows when it is tired and how to stop them. We also hope to understand how sleep carries out essential functions, thereby making it indispensable for animals and humans.

The sleeping worm

In C. elegans, sleep induction requires a network of so-called transcription factors that lead to the synthesis and release of a neuropeptide called FLP-11. Interestingly, these factors are also linked to human sleep disorders. This highly simplified, yet evolutionarily conserved system should make it possible to solve the molecular mechanisms of sleep in a controlled manner, allowing us to study the consequences of sleep loss on development, regeneration, aging, and general well-being.

Sleep-active neurons

Scientists already know that sleep is controlled by sleep-active, sleep-promoting neurons that specifically activate at the onset of sleep and release inhibitory signaling molecules (so-called neurotransmitters) such as GABA and neuropeptides. Such neurons are apparently quite different from each other, sleep in C. elegans appears to be highly similar to that of humans: Worms move less, exhibit reduced responsiveness, yet can be woken up, and sleep deprivation increases sleep pressure and thus a return to sleep. As sleep is an evolutionary ancient process, it is expected that many aspects of worm and human sleep are regulated by similar molecular mechanisms.

Another advantage of our model organism is its simple nervous system. It consists of 32 neurons only, and the connectivity between these neurons is known. Because the animals are transparent, we can observe and manipulate the nervous system in intact animals both during sleep and waking.

Our main objective is to find out how sleep is regulated on the molecular level. This then enables us to elucidate sleep as a controlled manner, allowing us to study the consequences of sleep loss on development, regeneration, aging, and general well-being.

Contact
henrik.bringmann@mpib-berlin.mpg.de
www.mpib-berlin.mpg.de/bringmann

A molecular machinery drives sleep in the roundworm. Sleep is induced by a single neuron called RIS. At the onset of sleep, the neuron degrades and releases inhibitory neurotransmitters, including GABA and FLP-11 neuropeptides to induce sleep. A) Wake: The transcription factor LIM-6 and AP-2 induce sleep-promoting RIS function by causing FLP-11 expression. B) Sleep: Calcium (Ca²⁺) transients trigger FLP-11 release at sleep onset.

Henrik Bringmann studied biology in Göttingen and Freiberg and completed his PhD at the Max Planck Institute for Cell Biology and Genetics in Dresden in 2007. Subsequently, he worked as a postdoctoral fellow at the MRC Laboratory of Molecular Biology in Cambridge (UK) until 2009. Since 2009, he has been heading the Max Planck Research Group Sleep and Waking at the Max Planck Institute for Biophysical Chemistry. Henrik Bringmann was awarded the Otto Hahn Medal of the Max Planck Society in 2008 and an ERC Grant in 2015.
Excellent service for cutting-edge research

What to do when an important element is missing, be it in a complicated experimental set-up or in one’s stock of knowledge? Outstanding research at the institute would not be possible without the corresponding service infrastructure. This is provided by top-trained colleagues in the central scientific facilities, workshops, administration, and additional service groups.
Service for scientists

- Advanced Light Microscopy
- Animal Facility
- Bioreactor
- Career Service for Junior Researchers
- Crystallization
- EU Liaison Office
- Proteomics
- Research Support
- Synthetic Chemistry
- Transgenic Cell Culture
- Scanning Electron Microscopy
- Transmission Electron Microscopy
Employees from 51 countries at the institute

<table>
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<th>Category</th>
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<tr>
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<td>Germans</td>
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How can one measure the success of basic research?

The most common criterion are scientific publications. How many articles are published in scientific journals, and how many of these have appeared in the renowned journals such as Nature, Science, and Cell?

However, outstanding research is never only an end in itself. Again and again, it promotes great discoveries and inventions. At the Max Planck Institute for Biophysical Chemistry this is not only documented by three Nobel Prizes – groundbreaking research findings from the institute are also of economical relevance: The list of successful patents granted to scientists at the institute is long. Furthermore, researchers transferred their insights from the lab to practical applications by founding numerous spin-offs, thus creating more than 1,000 jobs.

* Average number of publications per year from 2011 to 2016. Comprises scientific articles, reviews, books, and book chapters.
The Max Planck Society

The Max Planck Institute for Biophysical Chemistry is one of presently 83 institutes of the Max Planck Society for the Advancement of Science. As an independent, non-profit research organization, the Max Planck Society carries out basic research as service to the general public in the sections Biology & Medicine, Chemistry, Physics & Technology, and Humanities & Social Sciences.

The Max Planck Society is mainly financed by public funds of the Federation and the States. It recruits scientists who are leaders in their field worldwide as Directors, and allows them all freedom for their research. New and innovative ideas are especially promoted.

With this strategy, today, the Max Planck Society is one of the leading research institutions in the world. Since its foundation in 1948, many of its scientists have received renowned awards. 18 times the Nobel Prize has been awarded to Max Planck researchers.
Emeritus Directors of the institute

On Manfred Eigen’s initiative the Max Planck Institute for Biophysical Chemistry was founded in 1971. It was his vision to investigate complex processes of life with biological, chemical, and physical methods at this new institute. After his pioneering studies on ultra-fast reactions, for which he was honored with the Nobel Prize in Chemistry in 1967, he turned to biochemistry and worked on questions concerning evolution. His theories on self-organization of complex molecules and his development of revolution machines, with which he translated his theories into practice, established a new branch of the German biotechnology industry – the evolutionary biotechnology.

Manfred Eigen

Hans Kuhn †

Hans Kuhn worked on the chemistry of interfaces. He furthermore investigated the self-organization of molecular systems. In this context, he designed supra-molecular machines and analyzed the physicochemical conditions for the origin of life. His research contributed to the understanding of the mechanisms of photosynthesis, of proton pumps, and of ATP synthases. One of his associate researchers was the later Nobel laureate Erwin Neher.

Hans Strehlow †
Electrochemistry and Reaction Kinetics (1971-1984)

Hans Strehlow became Director at the Max Planck Institute of Physical Chemistry in 1965 and joined the Max Planck Institute for Biophysical Chemistry after its foundation in 1971. After having dealt with aspects of electrochemistry early in his career, Hans Strehlow was later interested in questions concerning reaction kinetics of elemental processes in solution. Important insights into the kinetics of ion reactions in liquid solution and detergent mixtures were born of his research. One of his doctoral students was Jens Frahm, head of the Biomedical NMR.

Albert Weller †
Spectroscopy (1971-1990)

Before the foundation of the Max Planck Institute for Biophysical Chemistry, Albert Weller was Director at the Max Planck Institute for Spectroscopy. His research dealt with the physicochemical basis of photochemistry. He worked on the molecular absorption and emission spectroscopy of crystals, solutions, and fumes as well as on electron-spin resonance spectroscopy. He additionally performed pioneering kinetic, thermodynamic, and spectroscopic experiments with electronically stimulated molecules.

Otto D. Creutzfeldt †
Neurobiology (1971-1992)

Otto D. Creutzfeldt made fundamental contributions to the understanding of epilepsy and the role of the cerebral cortex in seeing and speaking. Moreover, using intracellular derivation of cortical neurons he provided substantial insights into the neurophysiological basis of EEGs and the functioning of the visual system. He trained a number of important neurobiologists, among them Nobel laureates Bert Sakmann and Max Planck Directors Wolf Singer and Heinz Wässle.

Fritz Peter Schäfer †

Fritz Peter Schäfer applied spectroscopic techniques in order to investigate stimulated emission and quantum processes of chemical compounds. He furthermore worked with lasers and thus developed the dye laser (at the same time as Peter Sorokin) which was applicable on a broad spectral band. Later, he was also interested in X-ray lasers. He founded the Laser-Laboratorium Göttingen e.V. together with Jürgen Troe and Dirk Basting.

Manfred Eigen

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Hans Strehlow †
Electrochemistry and Reaction Kinetics (1971-1984)

Albert Weller †
Spectroscopy (1971-1990)

Otto D. Creutzfeldt †
Neurobiology (1971-1992)

Fritz Peter Schäfer †
Manfred Kahlweit †
Manfred Kahlweit’s research on crystal growth, phase diagrams of complex systems, and micro-emulsions provided important insights for the application of physicochemical methods and contributed to the elucidation of fundamental mechanisms of biological processes. As a member of the University of Bremen’s founding senate and as temporary head during the foundation of the Max Planck Institute of Colloids and Interfaces in Potsdam, he made important contributions to the development of the scientific landscape in Germany.

Thomas M. Jovin
Molecular Biology (1971-2007)
Two research areas are at the focus of interest of Thomas M. Jovin’s emeritus group: the activation of normal or cancerous cells with growth factors or other external factors as well as the molecular mechanisms of Parkinson’s disease. Thomas M. Jovin’s Emeritus Group Laboratory of Cellular Dynamics applies a number of methods in bio-physics, molecular, and cell biology to find the cause and possible preventive measures of the toxicity of so-called amyloid aggregates in the brain’s nerve cells.

Victor P. Whittaker †
Neurochemistry (1973-1987)
Victor P. Whittaker profoundly contributed to the understanding of neuronal synapses. He was the first to isolate so-called synaptosomes that made it possible to investigate synaptic signal transduction. He also succeeded in proving that synaptic vesicles contain neurotransmitters. Victor P. Whittaker trained a number of successful neurobiologists, among them later Nobel laureate Thomas C. Südhof, who performed his PhD research at the institute.

Klaus Weber †
Klaus Weber played an important role in the change in the scientific direction at the institute so that today it includes also key areas in molecular, cell, and developmental biology. His research focused on the cytoskeleton and biochemical anatomy of actin-containing structures such as stress fibers and microvilli, on microtubules, and intermediate filaments. He pioneered the use of immunofluorescence microscopy to visualize the arrangements of these and other structures in cells and tissues. Using protein chemistry, six different actins as well as five different intermediate filament types were defined. The development of monoclonal antibodies specific for each intermediate filament type provided reagents to classify human tumors.

Erwin Neher
Membrane Biophysics (1983-2011)
Together with Bert Sakmann, Erwin Neher received the Nobel Prize in Medicine or Physiology in 1991 for his ground-breaking discoveries concerning the function of single ion channels in the cell membrane. With his Emeritus Group Membrane Biophysics, Erwin Neher investigates the mechanisms of neurotransmitter release and synaptic short-term plasticity. Furthermore, the role of calcium ions in signal transduction is a focus of his interest.

Bert Sakmann
Cell Physiology (1985-1988)
Six years after his appointment as Director at the institute, Bert Sakmann received the Nobel Prize in Physiology or Medicine together with Erwin Neher for his ground-breaking discoveries concerning the function of single ion channels in the cell membrane. In 1988, he moved to the Max Planck Institute for Medical Research in Heidelberg. With his emeritus group at the Max Planck Institute of Neurobiology he studies the functional anatomy of circuits in the cerebral cortex and works on the in vitro reconstruction of a cortical column.

Emeritus Directors of the institute

Leo C.M. De Maeyer †
Experimental Methods (1971-1995)
Initially, as associate researcher with Manfred Eigen, Leo C.M. De Maeyer substantially contributed to further development of the so-called relaxation techniques. Besides these, he later investigated, among others, the kinetics of chemical processes and worked on electronic data processing and process control as Director at the Max Planck Institute for Biophysical Chemistry. His experimental methods have found broad application in many areas of biology, chemistry, and physics. He was deeply involved in the consolidation of the Max Planck Institute for Spectroscopy and the foundation of the Max Planck Institute for Biophysical Chemistry.

Manfred Kahlweit †

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Emeritus Directors of the institute

Dieter Gallwitz
Molecular Genetics
(1986-2004)

Peter Gruss
Molecular Cell Physiology
(1986-2014)

Jürgen Troe
Spectroscopy and Photochemical Kinetics
(1990-2008)
Page 32/33: Structure of a ribosome (Marina Rodnina, Department of Physical Biochemistry)

Page 68: Expression of the transcription factor Unccx4.1 (green) and the tyrosin hydroxylase (orange) in dopamin producing nerve cells, which play a role in Parkinson's disease (Tamara Rabe, Ahmed Mansouri; Research Group Molecular Cell Differentiation)

Page 79 (background): Structure of ubiquitin (Rogenbuck, Wikimedia Commons)

Page 80: Fruit flies (Drosophila melanogaster) in which to a mutation cannot produce the microtubule proteins (outer image), which develop structures such as follicles have epithelial defects and deposit fat. Cell membranes are colored in red, fat in green, cell nuclei in blue (Halyna R. Shcherbata, Ömer Çiçek; Max Planck Research Group Gene Expression and Signaling)

Page 100/101: Scanning electron microscopy of nuclear pores (Volker Cordes, Facility for Scanning Electron Microscopy), transgenic cell cultures (Ahmed Mansouri, Facility for Transgenic Cell Cultures), Career Service for Junior Researchers (Peter Heller)

Page 102: fotolia, macrovector

Page 107: Map of Germany (Max Planck Society)

Page 114: Imprint