Technische Universität München's Scientific Magazine
June 2014 | Edition 14

Faszination **Forschung**

Battery Research: A Look Inside the Black Box

Optoelectronics: Infrared Nanoscale Lasers
Biogenic Polymers: Guiding Algae to Do Delicate Construction Work
Medical Research: Heart Tissue from Stem Cells

ISSN 18653022
9 771865 302004
Nominal charge
9,- Euro

Dear reader, dear TUM friends and associates,

Scientific progress knows no boundaries – and it speaks English, even here in Germany and at our university. As English is the lingua franca of science, “Faszination Forschung” will be published only English from now on. We will not be translating the articles into German so we have even more space to bring you hot-off-the-press news from the world of research.

“Faszination Forschung” is read around the world, not least by our ever-swelling alumni ranks, many of whom return home after their stay at TUM to take up leading positions in their own countries. They are our most effective ambassadors because they live and share the standards of excellence they have learned at TUM. Similarly, “Faszination Forschung” sends a powerful signal about TUM, showcasing and communicating the most fascinating developments at our university.

In this issue we look at the work of Jonathan Finley of the Walter Schottky Institute. This physicist has succeeded in building the world’s first nanolasers capable of emitting light at wavelengths that could be useful across a variety of industrial and medical applications. Such nanophotonic technologies could be the key to optical information processing on silicon chips, thus paving the way for the optical computers of the future. Computer miniaturization is also driving a more networked world – referred to as the Internet of Things. This is also the subject of the German government’s Industry 4.0 project. Informatics expert Manfred Broy develops theories for the formal modeling of networked cyber-physical systems, which he uses to design these complex architectures.

Nanoscale structures are being created in the laboratory of TUM professor Cordt Zollfrank at the Straubing Competence Center for Renewable Resources. The TUM researcher received the Reinhart Koselleck prize from the German Research Foundation (DFG) for his ground-breaking project. It involves guiding algae with light so that they form delicate micro-structures which then act as templates for functional ceramics. Christian Große uses a variety of methods to find hidden defects in materials, components and structures. The non-destructive testing expert uses every tool in the physics toolbox to develop new measurement techniques for materials like the latest carbon fiber reinforced plastics. The aim of his research is to develop highly reproducible industrial quality control processes.

High-performance batteries will be a key building block in the renewable energy and electromobility landscape of the future. With the help of neutron beams at the Heinz Maier-Leibnitz neutron source research reactor (FRM II), Anatoliy Senyshyn studies the charge and discharge cycles in electrochemical electricity storage systems. He has discovered previously unknown mechanisms that open up new avenues for optimized battery concepts.

Karl-Ludwig Laugwitz and Alessandra Moretti are carrying out ground-breaking research on cardiac muscle cells using stem cells. Using a technique that won the 2012 Nobel Prize in Medicine, the TUM researchers grow cardiac muscle cells from the stem cells of patients with congenital heart conditions. By studying these cells, they have decoded the biomolecular mechanisms that cause these diseases. As a result of their work, new therapies are being developed and tested.

Yet again, “Faszination Forschung” is packed full of research excellence – giving you exciting new insights into life at TUM. Enjoy!

Wolfgang A. Herrmann

Prof. Wolfgang A. Herrmann

Foto / Picture credit: Eckert

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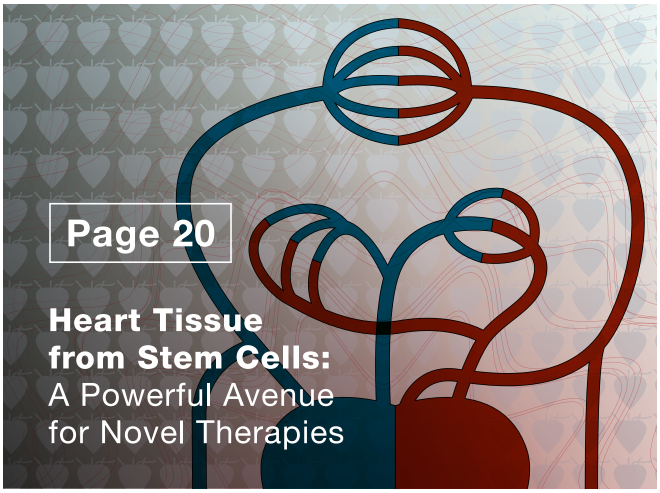
Cover Story:
A Look Inside the Black Box



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A Powerful Avenue for Novel Therapies

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The Wonders
of Nanowires on Silicon

Cover Story

> *"Despite the fact that there have been many advances in this technology, Li-ion cells still have some drawbacks which require careful and systematic research."*
>
> *Anatoliy Senyshyn*

Research and Technology

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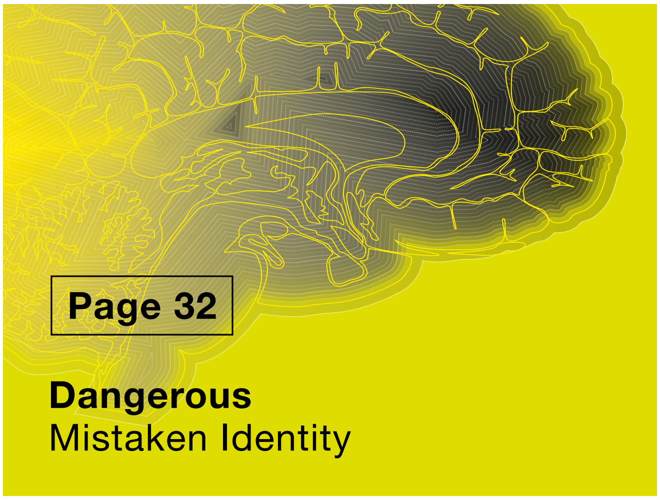
Light Touch:
Guiding Algae to Do Delicate Construction Work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Cordt Zollfrank uses light to guide the growth of algae. He wants to produce finest 3-D structures to be used as templates for functional ceramics

Headings

Airplanes contain up to **50%** fiber reinforced polymers (GFRP+CFRP)

Wind turbines are designed for a lifetime of only **20 years**

Concrete is the world's most widely used construction material, at more than **10 billion** tons per year

20% of all bridges in Germany are more than 50 years old

Electric cars are made of up to **50%** fiber reinforced polymers (CFRP)

Finding the reason for deteriorations inside museum pieces

Picture credit: ediundsepp

"Our job is to supply information **for a more sustainable future.**"

Christian Große develops new technologies for non-destructive testing, and employs a wide range of methods to discover hidden damage. The ultimate aim is to improve the quality and safety of structures, industrial production processes and many everyday objects, and to determine what causes deterioration

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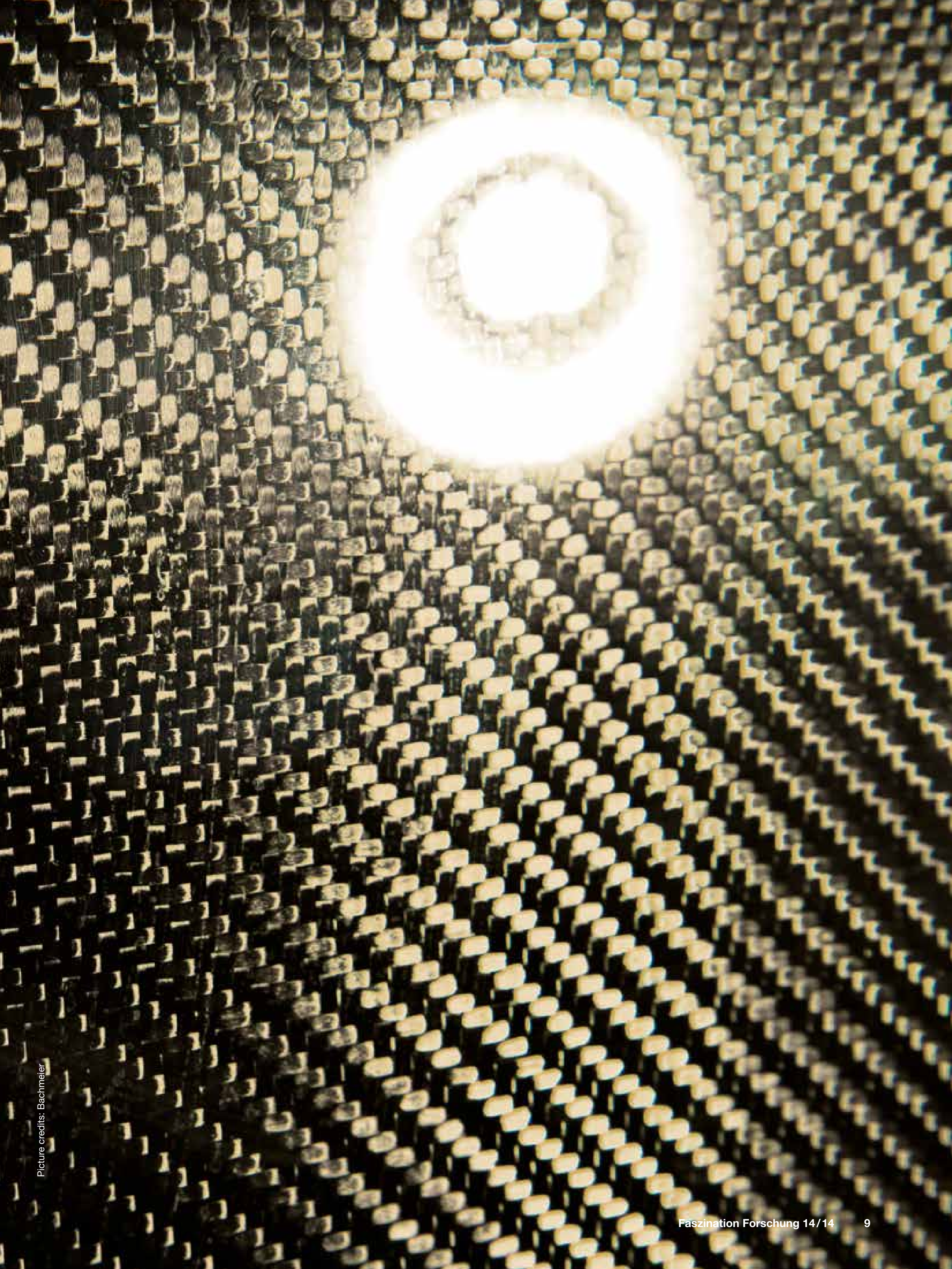
Carbon fiber reinforced polymers under scrutiny: Material defects show up under a light source using infrared thermography



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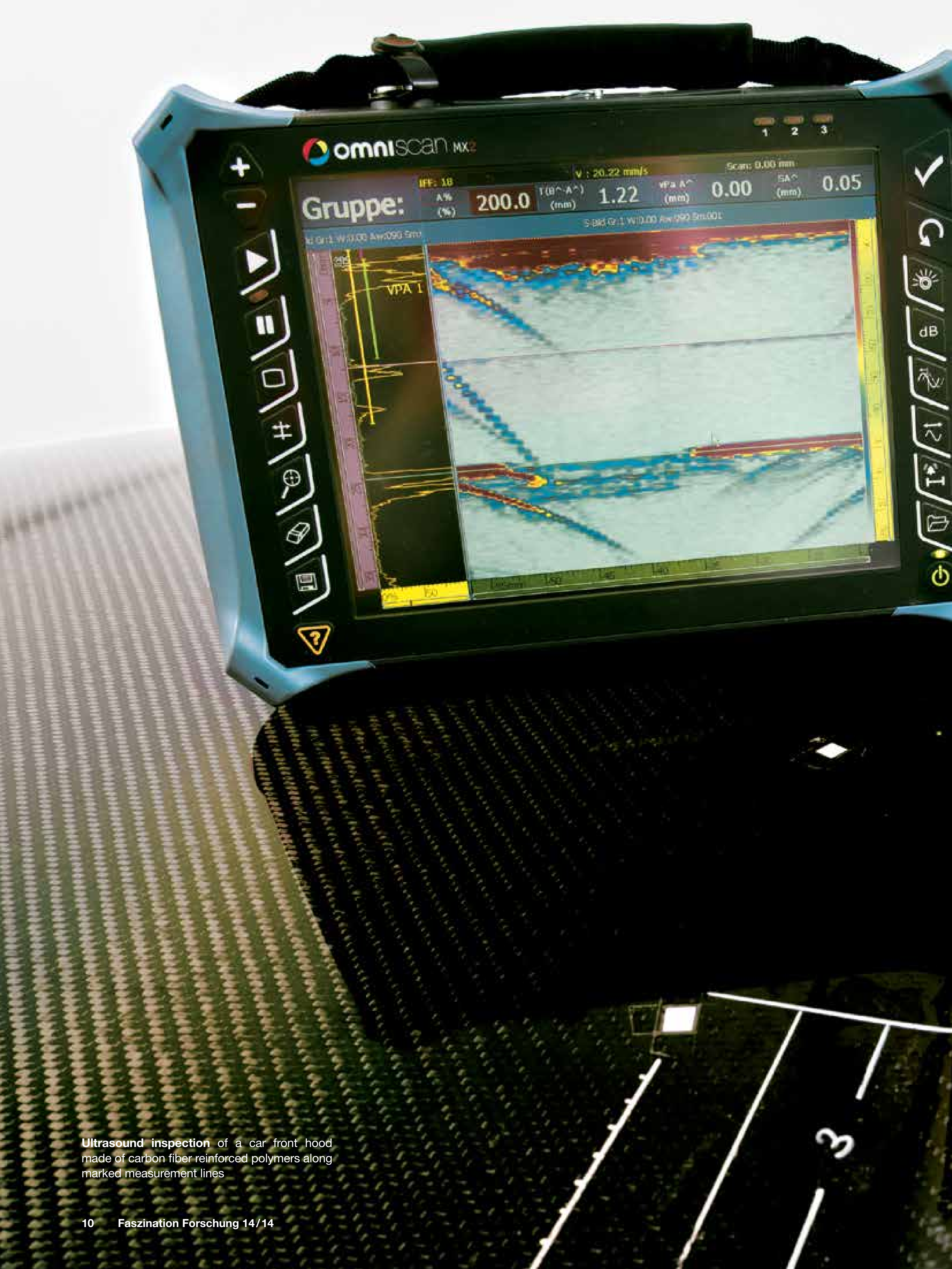
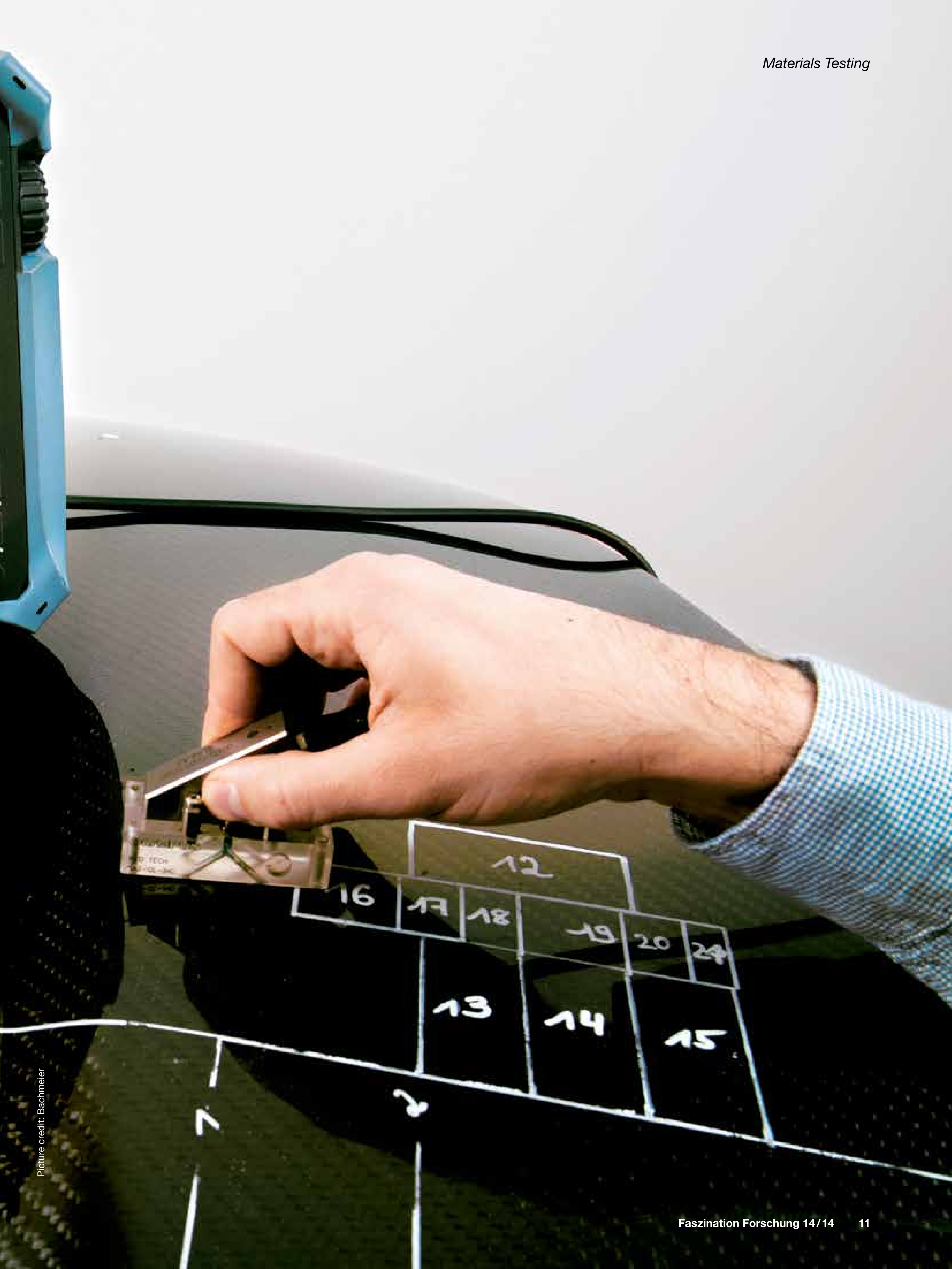


Ultrasound inspection of a car front hood made of carbon fiber reinforced polymers along marked measurement lines



Picture credit: Bachmeier

„Wir liefern die Information für Nachhaltigkeit“

Verborgene Schäden in Materialien, Bauteilen und Konstruktionen zu erkennen – das sind Ziele von Prof. Christian Große und seinem Team vom Lehrstuhl für Zerstörungsfreie Prüfung (ZfP). Mithilfe der verschiedensten Verfahren schauen die Wissenschaftler in Objekte hinein und ermitteln die physikalischen oder chemischen Eigenschaften. Heute ist ohne zerstörungsfreie Prüftechniken keine Gas- oder Ölversorgung, kein Start eines Flugzeugs, keine Herstellung eines Autos oder eines Zuges und kein Bau sicherheitsrelevanter Bauwerke wie Brücken, Tunnel, Hochhäuser und Fahrbahnen denkbar. „Als Informationslieferanten tragen wir dazu bei, Werkstoffe nachhaltig zu verwenden und damit die Umwelt, die wir Menschen gestalten, zu schützen“, bringt es Große auf den Punkt. Denn auf der Grundlage der Messungen lassen sich Qualität und Sicherheit von Bauteilen und Bauwerken erhöhen, aber auch die Kosten-, Zeit- und Energieeffizienz von Produktionsprozessen positiv beeinflussen. Ein Beispiel ist die Aushärtung der Harzmatrix bei Faser-Werkstoff-Verbundmaterialien: Lässt sich dank zerstörungsfreier Prüftechnik der richtige Aushärtezeitpunkt bestimmen, kann der nächste Gussprozess schneller eingeleitet werden.

Eine Querschnittswissenschaft, die nachhaltig wirkt

Von großer Bedeutung ist die Zerstörungsfreie Prüfung zudem bei Objekten unseres kulturellen Erbes, beispielsweise um Aufschluss über den Schädigungsgrad von Kunstgegenständen zu geben. Die Beispiele zeigen: Das Arbeitsgebiet der Zerstörungsfreien Prüfung erfordert Kompetenzen in vielen Schlüsseldisziplinen wie den Materialwissenschaften, der Messtechnik und der Datenverarbeitung – und es ist höchst abwechslungsreich. So kommt es vor, dass Große morgens im Museum arbeitet, mittags eine Brücke begutachtet und nachmittags bei einem Automobilunternehmen eine Arbeitssitzung hat. Die TUM hat dieser Vielfalt Rechnung getragen und den Lehrstuhl als Joint Appointment in den Fakultäten Bauwesen und Maschinenbau angelegt. *Gitta Rohling*

The world premiere of the BMW i3 was staged simultaneously in New York, London and Beijing. And it was more than its electric motor that created quite a stir. Equally impressive is the fact that the new vehicle is made of carbon fiber reinforced polymers (CFRP). Its launch therefore marks the start of a transition from metal to composite materials in the automobile industry. One of the advantages of CFRP is that, unlike metal panels, no cracks, bumps or dents show up on the surface. While this is undoubtedly a good thing in terms of esthetics, there is a downside: just because you can’t see the damage doesn’t mean it’s not there. Invisible flaws could even compromise the vehicle’s reliability.

This is where Professor Christian Große and his team from the Chair of Non-destructive Testing come in. They are able to identify and assess hidden defects in all kinds of materials, components and structures – including CFRP components.

The use of CFRP for the bodywork of series-produced vehicles may be new in the automotive industry, but the aircraft industry has been using CFRP for some time now. Not all CFRPs are the same, however, and testing methods cannot be simply transferred from one industry to another. That is why industry and research players teamed up for a three-year project dedicated to the development of methods for testing fiber composites for the automotive ▷

Did the front hood suffer from an incident? Non-destructive testing of the hood of a roadster would show material defects, since defects change the thermal flow in the material. This can be observed in the infrared spectrum

Using all sensors and senses to assess the innermost structure of an object without destroying it: Professor Christian Große develops testing technologies to investigate new materials such as fiber reinforced polymers for aircrafts. The scientist is equally fascinated by the capability of humans for non-destructive testing: "Visually examining an object, tapping on a piece of pottery or running a fingertip over a surface – these methods have been optimized by evolution and used throughout the ages"

Picture credits: Bachmeier

Inspecting the composite structure of an aircraft tail unit using infrared lock-in thermography and aeronautical industry. “Which was a challenge not to be underestimated,” stresses Große. There are in fact several hundred potential testing procedures. Many are derived from medical technology – such as microscopy, radiography and ultrasound – or from geophysics, which includes geoelectrics, magnetics and seismology. “For this project, we are using computer tomography (CT) reference measurements,” says Große. CFRP components that were, for instance, exposed to impacts are put into a computer tomograph. The computer then evaluates the X-ray images from the CT, exposing invisible damage. The project partners are now comparing the findings of the various different testing methods with the CT scans. “CT can tell us a lot, but it is not a universal solution. Besides, it is very expensive, so is not likely to become a standard testing procedure for high-volume production in the automotive industry,” adds Große. What the project partners are actually aiming for is the integration of cost-efficient non-destructive testing (NDT) into the manufacturing process. This includes automatic data-processing techniques or so-called big data solutions for a huge amount of NDT data.

From works of art to rotor blades to bridges – it can be measured

Developing suitable test methods for CFRP is just one of the areas that the Chair of Non-destructive Testing specializes in at TUM. “We cover a very broad range of activities,” declares Große. An important means of quality control and assurance, non-destructive testing is used for applications as diverse as assessing automobile components during manufacture, identifying damage in rotor blades for a wind farm, or predicting the lifespan of safety-critical structures like bridges, tunnels, high-rise buildings and rail tracks. NDT also plays an important role in preserving our cultural heritage, for instance by shedding light on the level of degradation suffered by works of art. Biomedical engineering is another area where NDT experts can make a useful contribution. Große and his team are cooperating with doctors from Klinikum rechts der Isar, TUM’s university hospital, to analyze how a human femur fractures. Their aim is to discover whether the fracture starts inside the bone and spreads outwards, or whether microfractures in the cortical bone are responsible for the break. If a conclusive answer is found, doctors will be able to develop improved prophylactic and treatment therapies for patients who suffer chronic pain, osteoarthritis and restricted movement following such a fracture.

An interdisciplinary field full of fascination and future potential

As the examples above show, non-destructive testing requires competence in multiple key disciplines, including materials science, measurement technology and data processing. It is also applied in incredibly diverse fields. A typical day for Große can involve working in the museum in the morning, examining a bridge at lunchtime and visiting a car manufacturer in the afternoon. To reflect this diversity, TUM has made the chair a joint appointment between the Department of Civil, Geo and Environmental Engineering and the Department of Mechanical Engineering. Große himself is a geophysicist by training who started out by studying the Earth – “in a non-destructive way, of course,” he smiles. After obtaining his doctorate and lecturer qualification, he conducted research into structural health monitoring at the prestigious University of California in Berkeley. He was appointed Associate Director and later Provisional Director of the Materials Testing Institute of the University of Stuttgart, and in 2010 he was appointed to the newly created Chair of Non-destructive Testing at TUM. “I was always interested in different fields of research,” he explains. That is why he takes his inspiration from his-

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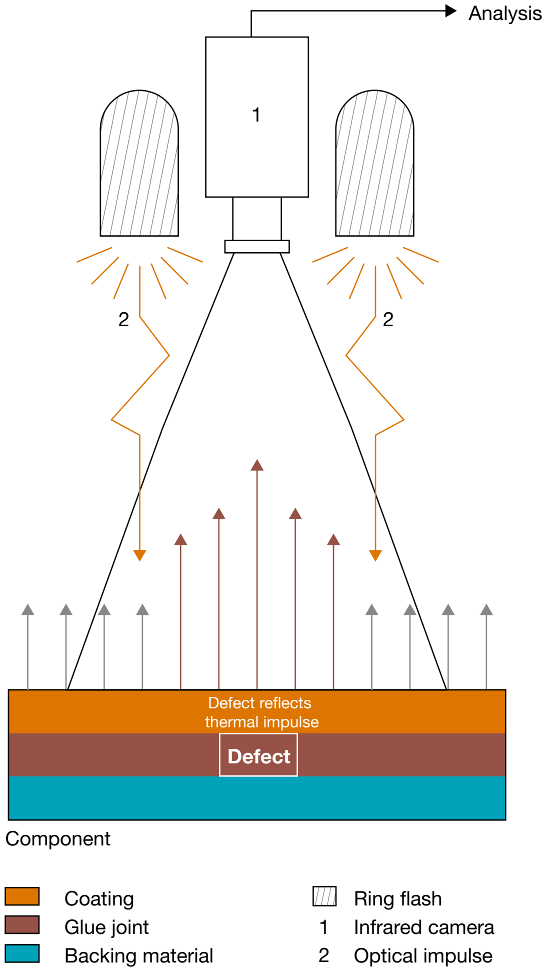


Defects inside carbon fiber reinforced polymers show up under a strong light source using infrared lock-in thermography. The light as an electromagnetic wave heats the material up and defects act as hot or cold spots, which alter the thermal flow in the material. Changes in this flow can easily be detected in the infrared spectrum using IR cameras

Picture credit: Bachmeier / Graphics: ediundsepp

torical figures like Galileo Galilei and Leonardo da Vinci. “Both men had access to limited information and hardly any opportunity to exchange ideas with other scientists. On top of that, they had to contend with religious and moral constraints. Yet despite all this, both men made some highly important discoveries,” continues Große.

So what exactly does he find so fascinating about his current field of research? “The idea that human beings themselves are excellent non-destructive test systems.” Große smiles, then elaborates: “The human race developed a very good sensory system as we evolved – our sensory organs are wonderfully adept at carrying out NDT.” Visually examining an object, tapping on a piece of pottery or running a fingertip over a surface – these are non-destructive testing methods that have been used throughout the ages. For centuries, these simple tests were the only way to inspect components up to the point of failure or even destruction. However, when the Industrial Revolution took off around the middle of the 19th century, demand for raw materials increased sharply. So industry was suddenly faced with the need to conserve resources and at the same time guarantee workers’ safety. This prompted the intensive development of methods to test a material without destroying it.

Nowadays, non-destructive testing techniques are indispensable in many sectors of industry. Without them there would be no gas or oil pipeline systems, planes could not take off, cars and trains could not be manufactured and safety-critical structures like bridges, tunnels, high-rise buildings and train tracks could not be built. “Our job is to supply information for a more sustainable future – by helping to protect the environment that we are all shaping,” summarizes Große. The measurements he takes can help to improve the quality and safety of components and structures as well as the cost, time and energy efficiency of production processes. These are aspects of considerable importance to Germany as an industrial location in its bid to fend off competition from low-wage countries. One example of where NDT comes in useful is in curing the resin matrix for fiber reinforced composites: if the right curing time can be determined through non-destructive testing, the subsequent molding process can be started sooner.

What seems like science fiction is actually science fact

Große has an impressive example of the capabilities of NDT revolving around concrete – one of the most important materials of our time. Over 10 billion tons of concrete are produced annually across the world. This volume is enough to build 100,000 ten-story office buildings complete with underground car parks – assuming that each building would require 10,000 tons of concrete. “The quality assurance of concrete is still very much in its infancy, however,” maintains Große. He and his team are developing state-of-the-art ultrasound techniques to determine the properties of a concrete mix. “Our ultimate aim is to give every new building or structure a “birth certificate” documenting all of its properties. This should subsequently facilitate the job of maintenance,” he declares.

Cracks in a concrete structure could result in water or salt ingression. These can result in corrosion processes that attack the steel reinforcement and thus cause significant damage to the structure. Identifying the cause of deterioration requires experience – and intuition. Große reveals more by turning to another important project, focusing on concrete that is able to “heal” itself. He is investigating three self-healing mechanisms that were developed by colleagues from the Universities of Ghent and Delft. One of these involves bacteria that live within the concrete. These are dormant most of the time, but when they come in contact with water that has seeped into a crack, they “produce” calcium carbonate, which helps repair the cracks. Although this sounds like science fiction, it actually seems to work. The second approach uses hydrogels, which elsewhere are used in diapers to absorb moisture. The idea is that the hydrogel will swell on contact with water, thus filling the cracks. The third mechanism is based on tiny capsules filled with polymer-based resin which is released when cracks cause the encapsulation to break.

Self-healing concrete is of particular interest for structures that frequently come into contact with salt – such as highway bridges and buildings located by the sea. “Our job is to observe how cracks occur and how the healing

▷

Non-destructive Testing (NDT)

Non-destructive testing (NDT) uses measurement technologies and data analysis methods to investigate the physical or chemical properties of objects and inspect them for damage without needing to destroy them. The most commonly used techniques include ultrasound, radar, microwaves, infrared thermography, vibration and acoustic emission testing and radiography as well as visual techniques like microscopy. This type of testing is used to support quality assurance, inspections and continuous monitoring.

Quality assurance: Nowadays, non-destructive testing is included in most manufacturing processes to reduce the rate of defects and optimize process efficiency.

Inspection: NDT methods can be used to inspect objects for damage on a once-off or occasional basis.

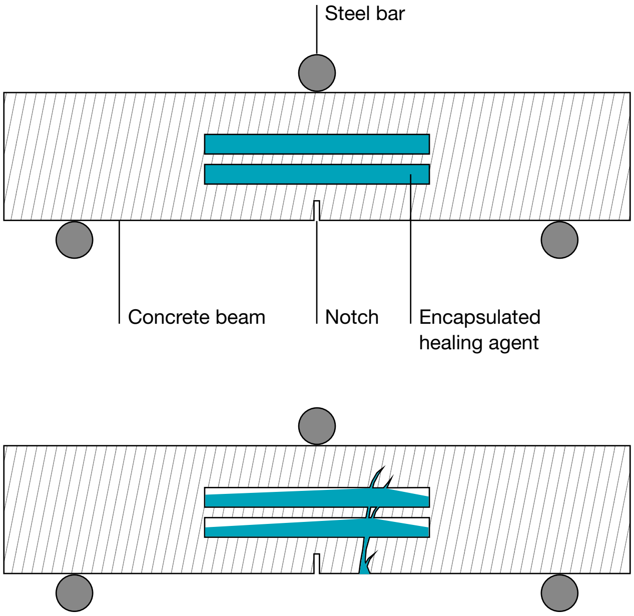
Continuous monitoring: Cracking processes that occur in microseconds can be monitored just as easily as damage to a bridge that happened over a period of years. The intervals between each measurement depend on the test object and range from seconds/minutes to hours/days.

NDT is an interdisciplinary field and – as a methodology – is not restricted to any particular material or application. It is a branch of materials testing and is mostly used for applications in civil or mechanical engineering.

Inspection of the wing of an aircraft made of a mix of glass and carbon fiber reinforced polymers. Measurements with ultrasound phased-array sensors help in determining material structure

Picture credit: Bachmeier

Left: Three-point bending test of concrete with self-healing capabilities. A technician prepares ultrasound sensors and sticks them onto a concrete beam containing capsules with a healing agent. The capsules break under pressure. Ultrasound and acoustic emission measurements show whether the agents are activated and all voids are properly sealed

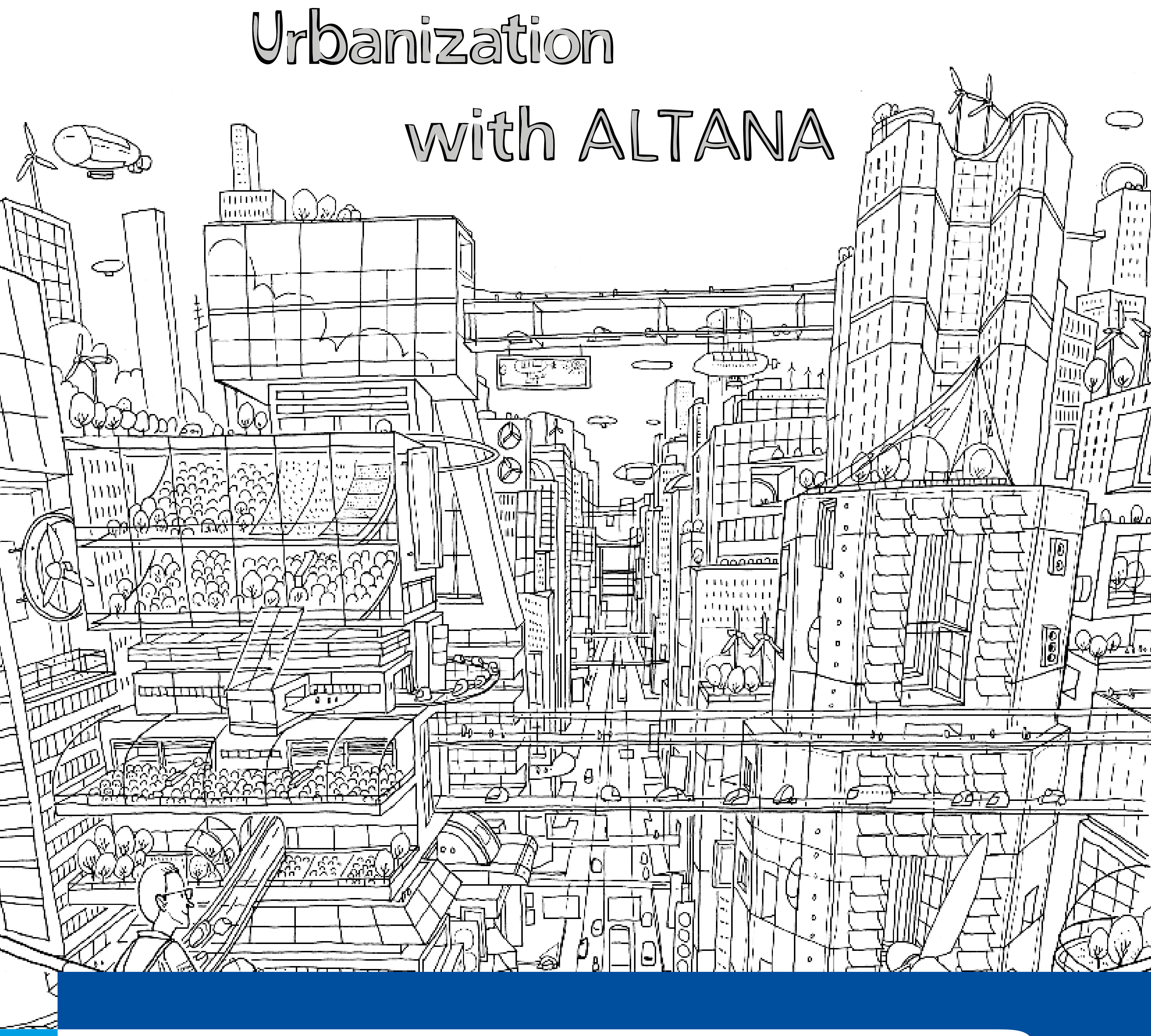


Self-healing concrete: Capsules containing a healing agent (blue) are incorporated inside a concrete beam. They break under pressure and the agents are activated releasing the resins into the cracks and seal them

agents are released. Then we assess how efficiently the healing agents did their job," says Große. He and his team have developed or refined many procedures with this in mind – from acoustic emission analysis for lab studies to wireless sensor nodes for non-stop monitoring. Initially, the mechanisms are tested on small objects before moving on to full-scale components. In the third phase, Große and his team perform their measurements on real structures. For this purpose the procedures have to be completely robust and practicable. Although self-healing concrete will be more costly, it has advantages that could compensate for this. For example, it can potentially increase the lifetime of a structure and reduce maintenance intervals. In addition, thanks to its special properties, it may save raw materials at the construction stage.

Whether it is concrete, CFRP or some other material, Große knows that he will be kept busy: "Safety and quality requirements are becoming stricter and stricter, and new testing methods need to be developed all the time. We have our work cut out for us." *Gitta Rohling*

Picture credits: Bachmeier/Graphics: ediundsepp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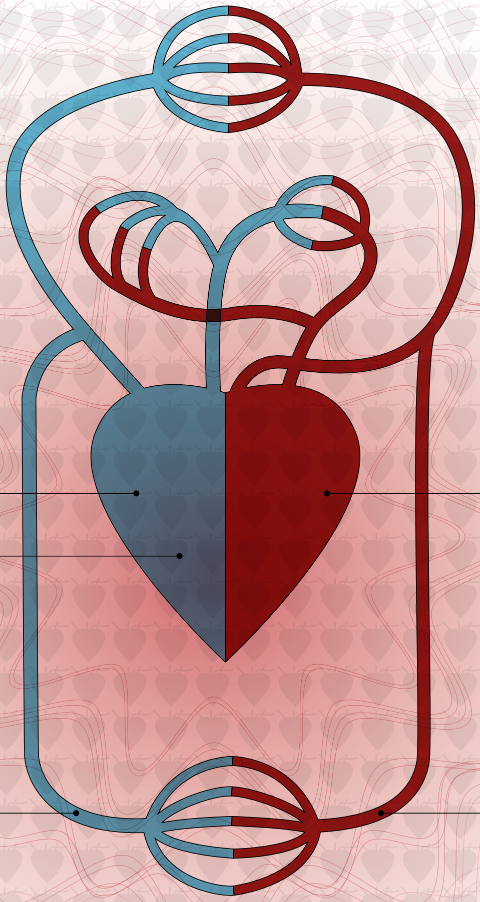


7000

liters of blood pump through
an average-sized human per day

60 to 90

heart beats per minute

2.5 to 3.8

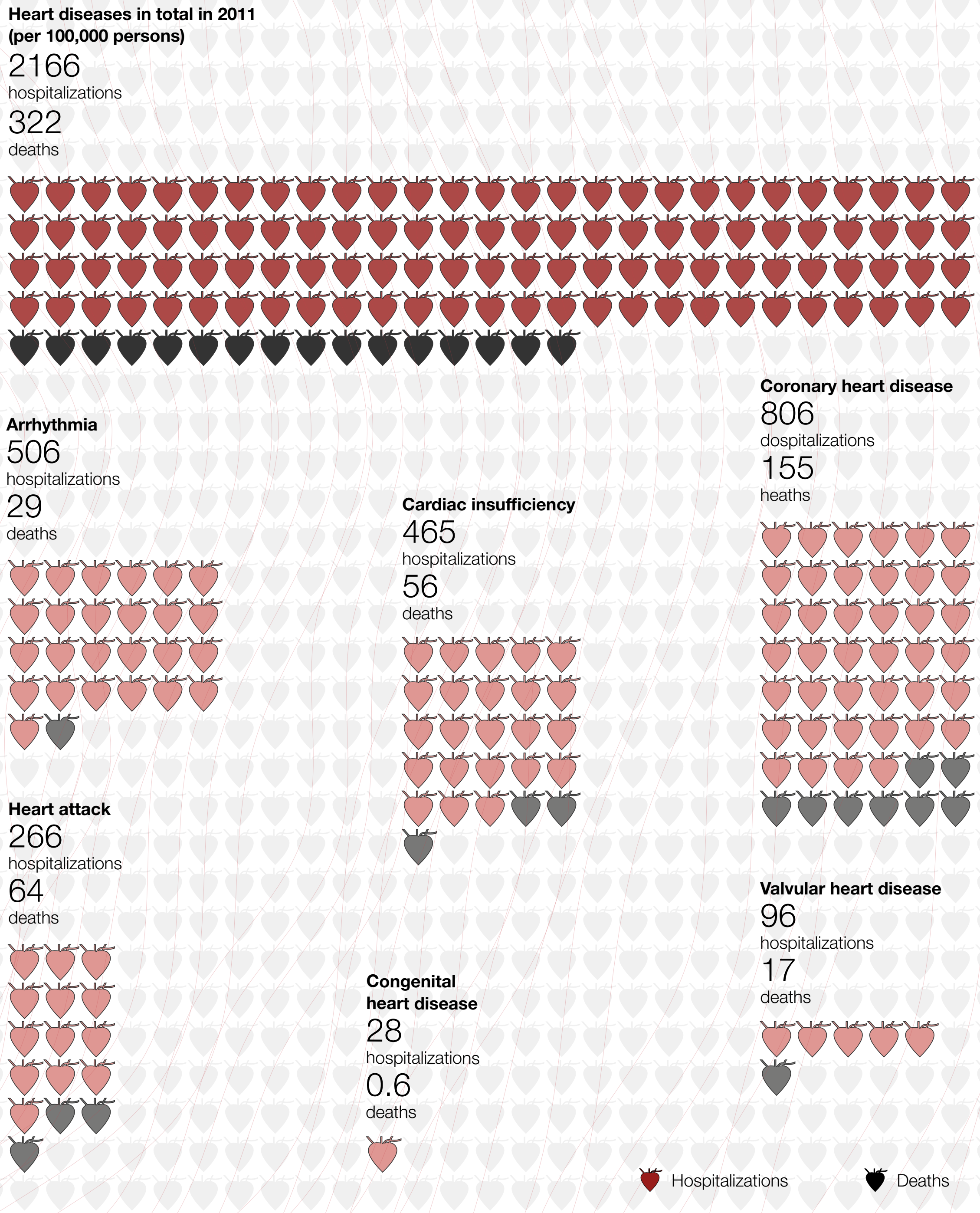
billion heart beats over a
lifetime of 80 years

2 blood circuits

The large, systemic circulation between the heart
and all other body tissue and the smaller, pulmonary
circulation between the heart and the lungs

Heart Tissue from Stem Cells: A Powerful Avenue for Novel Therapies

In an interview with Faszination Forschung, Alessandra Moretti and Karl-Ludwig Laugwitz explain how they develop models of human heart disease from patient-specific stem cells, why the cells serve as software and not hardware for therapeutic use, and how they pave the way for novel treatment options for patients



Illustrations: ediundsepp from data in: Neuer Deutscher Herzbericht 2014, DGK

Picture credit: Jooss

Dr. Alessandra Moretti & Prof. Karl Ludwig Laugwitz

Dr. Alessandra Moretti was born in Padua, Italy, in 1967 and completed a doctorate in pharmacology and toxicology at the university there in 1997. She worked at the University of California, San Diego from 2002 to 2005, followed by a year at Harvard. Since 2006, this stem cell specialist has been leading a working group for molecular and cellular cardiology at the First Department of Medicine, Klinikum rechts der Isar at the TUM.
Prof. Karl-Ludwig Laugwitz was born in 1968 in Berlin, Germany. He studied medicine at the FU Berlin and received his doctorate there in 1996. In 2000, Laugwitz moved as junior professor to TUM's First Medical Department, before starting as Heisenberg professor of the German Research Foundation at the University of California, San Diego in 2002. The cardiologist then returned to TUM's Klinikum rechts der Isar in 2006 and has been Director of its First Medical Department since 2012.
Moretti and Laugwitz have each received several awards for their research and they both have a long list of publications in high-impact journals. They have been married since 1996.

Picture credit: Jooss/Graphics ediundsepp (Source: TUM)

Doctor Moretti, Professor Laugwitz – you produce models of patients' hearts. What does that actually mean?

Moretti: "Heart" is slightly overstating it – but what we are actually able to obtain with iPS cells from every individual are cardiac muscle cells (myocytes) and heart tissue segments.

iPS cells?

Moretti: Induced pluripotent stem cells. Like embryonic stem cells, iPS cells can be grown into any cell type in the human body. And we are now able to generate iPS cells even from highly differentiated adult cells. Japanese researchers Shinya Yamanaka (ed. note: 2012 Nobel Prize winner along with John Gurdon) and Kazutoshi Takahashi pioneered this technology first in mice in 2006 and, one year later, in humans. So in 2007, when human iPS cells became possible, we quickly set up the technique in our laboratory. We saw the potential of a transformative novel tool for cardiac research.

How do you obtain iPS cells?

Moretti: First of all I would need a syringe of blood from you.

Oh dear!

Moretti (laughs): Well, ok, just a small syringe – eight milliliters is not a lot. We then isolate immunocompetent cells – T lymphocytes – from your blood and transfect them with the four proteins identified by Yamanaka as sufficient to reprogram differentiated cells into pluripotent stem cells. These "reprogramming factors" are OCT4, SOX2, KLF4 and c-MYC. They are transported into the cells by viruses, which we equip with the genes for the four factors beforehand.

What happens next?

Moretti: After about a month, iPS cells will be developing randomly in the culture dish. You can identify them by their appearance, to start with: very round, relatively small and usually clustered into tightly packed colonies. A colony looks a bit like a pizza through the microscope. For conclusive proof, we test for marker proteins of pluripotency and have to show that the cells are capable of differentiation into the body's various tissue types.

And that's where cardiac modeling comes in?

Moretti: Indeed. Around ten days after adding a specific differentiation cocktail, the iPS cells form an embryoid body.

An embryo?

Laugwitz: No. A type of tissue that generates various cell types but is not a functional embryo.

Moretti: After another few days, you can see cells here and there in the tissue that are beating regularly – just like cardiac muscle cells. Those are the ones we want, and we use them to culture myocardial tissue. In total it would take us five months to reach that stage with your blood sample. ▷

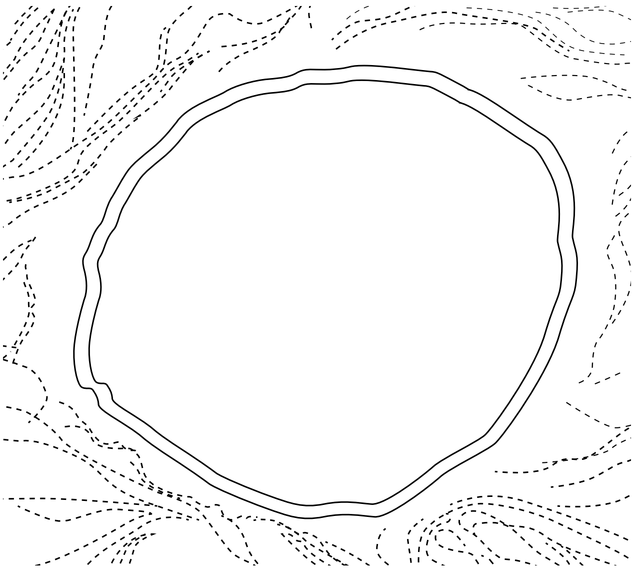
Ein neues Krankheitsmodell für die Herzforschung

Die Gruppe um Dr. Alessandra Moretti und Prof. Karl-Ludwig Laugwitz von der TUM arbeitet seit 2007 an der Nachzüchtung von patientenspezifischen Herzmuskelzellen. Möglich macht es ein Zweistufenprozess. In Schritt eins die Reprogrammierung differenzierter Immunzellen eines Patienten zu sogenannten iPS-Zellen. Aus diesen lassen sich – Schritt zwei – wieder differenzierte Körperzellen regenerieren – darunter Herzmuskelzellen, die sich bislang allerdings nur bis zu einem recht unreifen embryonalen Stadium entwickeln. Im Interview erklären die TUM Forscher, warum diese Zellen ihrer Ansicht nach derzeit keine therapeutische Option darstellen. Sehr wohl aber sehen sie in ihnen ein mächtiges Werkzeug für die Erforschung der genetischen Ursachen von Herzkrankheiten und für die initiale Erprobung von neuen Therapien.

Bahnbrechende Fortschritte

In einem international hochkompetitiven Umfeld schaffte die TUM Arbeitsgruppe dabei gleich mehrere Premieren:

- 2010 erbrachte sie den weltweit ersten Nachweis, dass sich mit diesen Zellen genetisch bedingte Krankheitsursachen tatsächlich neu aufklären lassen. Im konkreten Fall die einer bestimmten Form von Herzrhythmusstörungen, einer Variante des sogenannten Long-QT-Syndroms.
- 2013 konnte bei einer zweiten Form von Long-QT der zugrunde liegende genetische Defekt molekulargenetisch behoben werden – noch nur in der Zellkultur.
- 2014 gelingt durch sogenanntes Exon-Skipping die Korrektur eines genetischen Defekts bei einer Form von Herzmuskelschwäche, bei der das Strukturprotein Titin defekt ist. Solch ein Exon-Skipping lässt sich womöglich bald auch klinisch erproben. *Bernhard Epping*



iPS cells in a culture dish appear very round, relatively small and are clustered into tightly packed colonies

> *"Only now, with iPS cells, we can produce cardiac myocytes for every genetic heart condition and potentially from every individual. In fact, back in 2010, we were the first in the world to generate such cells from cardiac patients."*
>
> *Karl-Ludwig Laugwitz*

The cells have a pulse?
Laugwitz: Yes – some of them beat continually at the same rate as the human heart, so 60, 70 beats per minute. We can keep them in culture for up to a year.

Are you aiming to grow this kind of cardiac muscle tissue in the hope of surgically replacing damaged tissue in heart attack patients?
Laugwitz: No, we're a long way from that. There are various challenges to overcome, including the immaturity of these cardiac muscle cells.
Moretti: What we're currently obtaining are very young, immature myocytes – comparable with those of a newborn. But, for the first time, this system gives us access to human heart muscle cells for research.

Wasn't that possible before – in connection with organ transplants, for instance?
Laugwitz: Occasionally, yes. But adult cardiac myocytes survive just six hours in the lab. Only now, with iPS cells, we can produce cardiac myocytes for every genetic heart condition and potentially from every individual. In fact, back in 2010, we were the first in the world to generate such cells from cardiac patients.

What sort of patients were they?
Laugwitz: A father and son who both have long QT syndrom or LQTS.

Long … what?
Laugwitz: The name comes from the prolonged QT interval visible on electrocardiograms or ECGs for these patients. In healthy individuals, the frequency-adjusted QT interval lasts a maximum of 440 milliseconds but in people with this condition it is longer: up to 700 milliseconds. The T wave of the ECG represents the repolarization phase of the heartbeat, when the cardiac muscle relaxes following contraction. Since this takes longer in these patients, it can cause abnormal heart rhythms (arrhythmia).

What symptoms do these patients have?
Laugwitz: Often hardly any at first – the condition frequently goes undetected in the early stages. Warning signs can include fainting or an unexpectedly rapid heartbeat (tachycardia). Congenital heart arrhythmia is like a time bomb, increasing the risk of sudden cardiac death – particularly when under strain as a result of stress or sports, for instance.

Is there any treatment?
Laugwitz: There is no causal therapy. We usually prescribe beta-blockers. In severe cases, we recommend preventive placement of an implantable cardioverter-defibrillator (ICD). Fortunately, the condition is very rare, affecting maybe one in ten thousand people. And it was from two of those patients that we were able to generate iPS cells and, subsequently, cardiac muscle cells in the lab for the first time in 2010, giving us a better understanding of the mechanism of the disease.

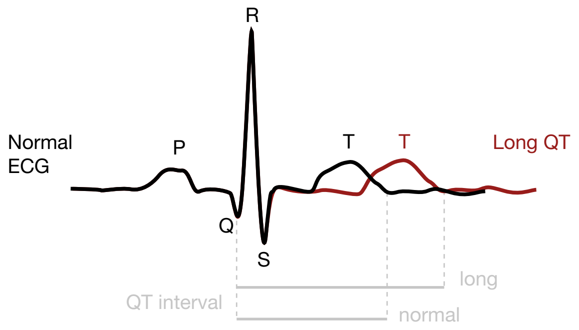
What did you find out?
Laugwitz: Well, we have known for a while that, in most long QT patients, certain ion channels in the heart cells no longer function properly. In the most common variant, LQT1 – also the type affecting these two patients – the functionality of specific channels for potassium ions is reduced. After the cell contracts, it is immediately flooded with positively charged ions. These KCNQ1 channels then open up to allow the positively charged potassium ions to flow back out of the cell, neutralizing the excess charge so the cell is ready for the next contraction.

Which, of course, takes longer if the channel doesn't work properly. So you already know all about the disease? Then why the heart models?
Moretti: No, that's not true – no one knew what was really going on with the diseased channels inside human heart muscle cells before.
Laugwitz: The great thing about iPS technology is that we can now for the first time examine in patient-specific cardiac muscle cells exactly where and how many of which channels are synthesized and how they behave. At the same time, we are able to measure electrical activity even at the level of a single channel. This puts us in the position to analyze the concrete implications of individual genetic defects on cardiac activity of the patient. In the end, we were able to identify a transport defect in both patients.

What sort of transport defect?
Moretti: The KCNQ1 channel is made up of four identical subunits within the cell, which then reaches the cell membrane. These patients have one normal and one mutated copy of the gene for the subunit and their cells combine ▷

Picture credits: Jooss

Picture credit: Jooss/Graphics: edlundsepp



Patients with long QT syndrome show a longer QT interval in their electrocardiograms

both forms during synthesis. What we have seen is that a channel with more than one defective subunit cannot reach the cell membrane. So the patients have less functioning channels in their membrane compared to a healthy person. In a nutshell, that also explains why the repolarization phase of the action potential in their cardiac muscle cells and thus the sum signal of all cells – the QT interval on the ECG – is prolonged. The potassium doesn't leave the cells quickly enough because the channels to enable it are missing.

So do your investigations benefit the patients?
Laugwitz: Not directly, at this stage, but we are definitely a step closer. With these two patients, we now know that drugs could help resolve the transport issue and ensure that more of the defective channels reach the membrane, where they would then function sufficiently. But such pharmacological agents don't exist yet – they still need to be developed by industry.

Couldn't you glean this information just as well from animal models?
Laugwitz: Not at all. The mouse, in particular, has very little relevance here, since its heart physiology is completely different from ours. Mice don't die from cardiac arrhythmia, even if they lack the ion channels that are essential for the human heart function. No – we are only able to explore the exact causes of these conditions in detail now that we have access to human heart cells. Long QT alone has 14 variants, with genetic defects in a wide variety of channels, so we have a lot more projects ahead of us.

And yet the value of these human heart models is controversially discussed even among experts. A dozen groups around the world are working, like you, with these iPS-derived models. Just last year, the Circulation Research journal published a heated exchange between you and a colleague, Björn C. Knollmann from Vanderbilt University in the US. According to Knollmann's calculations there, a single heart model generated in this way would cost over 15,000 US dollars …
Laugwitz: It is expensive, yes.

… and he argues that, while the models might be helpful in investigating genetically determined arrhythmia, these conditions are so rare that the industry would not invest in developing drugs for such a small market.
Laugwitz: We take a different view. The cost of these models will decrease – industry itself will make it possible.

Why is that?
Laugwitz: A test for QT-interval prolongation is now mandatory for every novel drug compound before reaching the ▷

> *"Before we could investigate the long QT syndrome using cardiac muscle cells produced from iPS cells, no one knew what was really going on with the diseased channels inside patients' hearts."*
> *Alessandra Moretti*

Induced pluripotent stem cells (iPS cells)

… were first created in the lab of the Japanese researchers Shinya Yamanaka and Kazutoshi Takahashi, who succeeded in using four specific proteins to generate pluripotent stem cells from mature, differentiated somatic cells in mice in 2006 and in humans in 2007. Pluripotency is the ability of a cell to form all of the roughly 220 differentiated cell types present in the organism.
A counterpart of iPS cells are embryonic stem cells (ES cells), which can also be obtained from humans through somatic-cell nuclear transfer (SCNT) since 2013. Here, the nucleus of a differentiated, somatic cell is injected into an egg whose genetic material was previously removed. Once ES cells are harvested from the early-stage embryo produced in the lab, the latter is destroyed. ES cells are regarded as easier to cultivate and propagate than iPS cells. However, iPS cells raise fewer ethical issues, since their generation bypasses the need for early-stage embryos.

market and being used in the clinic. Indeed, many pharmacologically active substances carry the risk of prolonging the QT interval and, depending on the circumstances, might then not be authorized for human use. Right now, animal models are used for these tests, but human cardiac cell culture systems offer so many advantages that the pharmaceutical industry is making intensive efforts to establish human iPS-based models for drug development. Which then could also reduce the costs sufficiently to enable the use of personalized models to test whether a long QT patient would tolerate a specific drug. Even many authorized drugs, such as antibiotics, can increase the risk of arrhythmia in these patients. If someone with this condition needs antibiotics, there are risks that we are not yet able to evaluate properly.

But as you've explained, it takes almost half a year to develop such a model. So there surely wouldn't be time to test the antibiotics in case of acute infection?
Moretti: We could generate for long QT patients prophylactic iPS-based heart models. But of course we also have a more ambitious aim – developing actual treatments. We are currently conducting a study showing the feasibility of this.

Can you tell us more?
Laugwitz: Well, more common than long QT are cardiac diseases known as dilated cardiomyopathies, in which the heart muscle is enlarged and weakened. In every second patient, mutations in the gene encoding the protein titin are responsible for this disease. Titin is a component of elastic structures – sarcomeres – in the cardiac muscle cells. If titin defects are present, these sarcomeres stretch out and the heart pumps with less force.

And how does your new treatment work?
Laugwitz: The gene for titin consists of numerous coding regions, called exons. In our patients, the genetic sequence is defective in just one exon. But as a result, protein synthesis in the cell is interrupted at this exon and no viable titin is produced. Through tests on iPS-generated heart models from these patients, we have now been able to show how we could prevent this synthesis stop on the part of the protein – by using exon skipping.

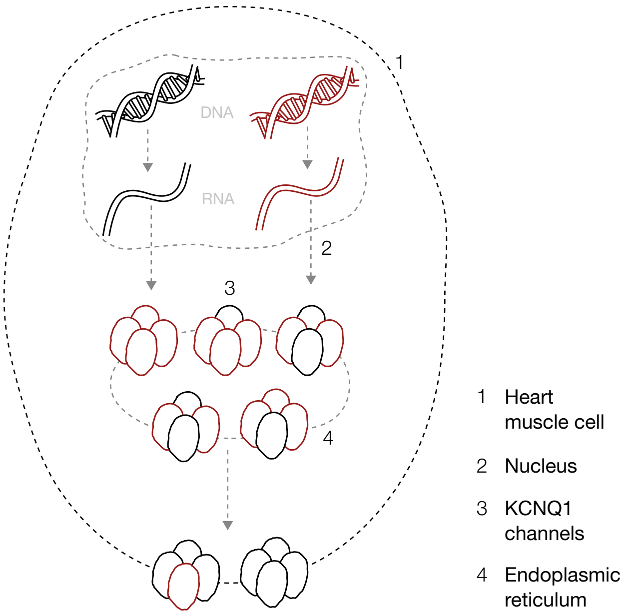
What is that?
Moretti: It's a method that involves the smuggling of nucleic acid particles, or oligomers, into cells so that the protein synthesis mechanism simply skips over the faulty exon of the gene and completes the rest of the protein. This results in generation of largely functional titin within the cells. And, most importantly, the sarcomeres gain stability and cell contractility increases. Clinical trials with exon skipping are already ongoing for other conditions, particularly muscular dystrophies, and we also see potential for its use in cardiology.

And now a practical question to finish off with: do you plan your experiments together or does each of you do your own thing?
Laugwitz: Oh, definitely together.

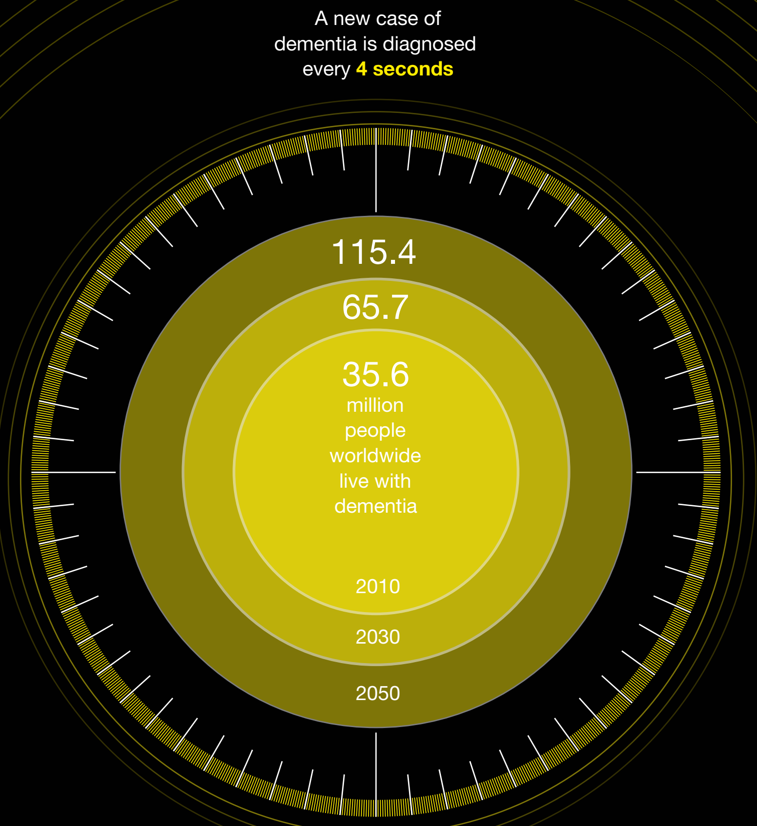
Even at home over the dinner table, I suppose?
Moretti (laughs): I wouldn't rule it out. But some of our best ideas come when we're visiting my family in Padua and relaxing in the vineyards.

Interview by Bernhard Epping

Long QT syndrome patients suffer from a genetic defect (red), which affects the subunit proteins that co-assemble into KCNQ1 channels. Only channels with zero or one mutated subunit reach the cell membrane. The others are retained in the endoplasmic reticulum



Picture credit: Jooss/Graphics: edlundsepp (Source: TUM)



Dangerous **Mistaken Identity**

Chaperone binds protein responsible for Alzheimer's disease – scientists unveil the molecular recognition mechanisms behind the process

Link

www.madllab.ch.tum.de/

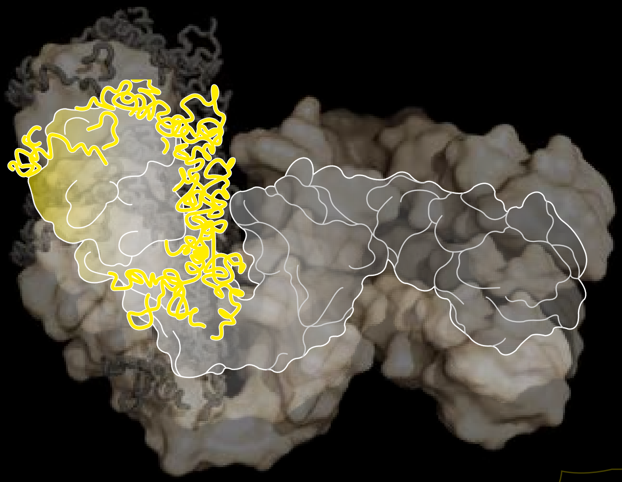
Tau proteins, which are responsible for Alzheimer's disease, bind to the folding protein Hsp90. The molecular recognition mechanisms that play a role here have been unveiled by an international team of scientists led by the Technische Universität München (TUM) and the Helmholtz Zentrum München (HMGU). This might open the door for new approaches for the treatment of Alzheimer's disease. Proteins like the so-called heat shock protein Hsp90 play an important role in almost all processes within human cells. They help other proteins fold into their three-dimensional structure or return damaged proteins back into their proper shape. Recently, there has been increasing evidence indicating that the heat shock protein Hsp90 may also be involved in the folding processes ▷

Graphics: ediundsepp (Source: WHO),
Picture credit: mammamaart (istockphoto.com)

USD 604 billion
was the estimated global societal cost
of dementia in 2010.
This corresponds to **1.0%** of the
worldwide gross domestic product

60 – 70%
of global dementia cases may be caused
by Alzheimer’s disease

2 – 8%
of all people aged **60** and over
suffer from dementia



Tau proteins, which are responsible for Alzheimer's disease, bind to the folding protein Hsp90. Scientists have now unveiled the structure and dynamics behind the interactions between the two biomolecules. The image shows a structural model of the Hsp90-tau protein complex aquired with magnetic resonance spectroscopy (NMR) and small-angle X-ray scattering (SAXS). (light grey: Hsp90; yellow: tau protein)

of the tau protein. Deposits of tau proteins in brain cells are typical for Alzheimer's disease and are held responsible for decaying nerve cells. However, while dissolved tau proteins look more like long, stretched chains, Hsp90 binds predominantly proteins that have already been prefolded. This contradiction has now been resolved by an international team headed by Dr. Tobias Madl, leader of the BioSysNet Working Group, TUM Junior Fellow and leader of the Emmy-Noether Group Structural Biology of Signal Transduction at the Institute of Structural Biology at the Helmholz Zentrum München, as well as Prof. Stefan Rüdiger from the Dutch University of Utrecht.

How the heat shock protein Hsp90 and the tau protein interact

Using a combination of very different techniques like magnetic resonance spectroscopy, small-angle X-ray scattering and computer modeling, they successfully determined structure and dynamics of the interactions between the two biomolecules: for Hsp90, the tau protein looks like a prefolded larger protein. Furthermore, they were able to deduce how Hsp90 influences the aggregation of tau proteins with one another.

"Deposits of tau proteins can cause Alzheimer's disease. We have discovered the protein regions in which the proteins interact. This is a novel and important starting point for influencing structural formation and for developing future therapies for Alzheimer's disease," says Madl. In addition to Alzheimer's disease, further neurodegenerative diseases are caused by protein aggregation. Chaperones also play a role in the development of cancer and cystic fibrosis. These scientific insights thus provide an important basis for better understanding the disease mechanisms. *Andreas Battenberg (TUM)*

Picture credit: Tobias Madl/TUM/HMGU


// PIONIERGEIST UND BODENHAFTUNG
MADE BY ZEISS

A Look Inside
the Black Box

What happens inside lithium-ion batteries when they are being charged and discharged? Anatoliy Senyshyn and his team are taking a close look – with the help of neutrons

Blick in die Blackbox

Neutronen sind ein geeignetes Werkzeug, um zu beobachten, was im Inneren von Lithium-Ionen-Batterien beim Laden und Entladen geschieht. Dies beweisen Arbeiten von Dr. Anatoliy Senyshyn und seinen Mitarbeitern an der Forschungs-Neutronenquelle Heinz Maier-Leibnitz (FRM II) der TU München. Die Wissenschaftler positionierten handelsübliche Li-Zellen der Bauart 18650 in einem Neutronenstrahl. Die ungeladenen Elementarteilchen werden am Elektrodenmaterial der Zellen abgelenkt. Die Winkel, unter denen dies geschieht, lassen Rückschlüsse auf den Aufbau und die Zusammensetzung der Batteriekomponenten zu. Mit anderen Methoden war es bisher nicht möglich, den Zustand während des Betriebs zu untersuchen. Denn öffnet man die Zelle, kann das Auswirkungen auf ihr elektrochemisches Gleichgewicht haben und die Ergebnisse verfälschen.

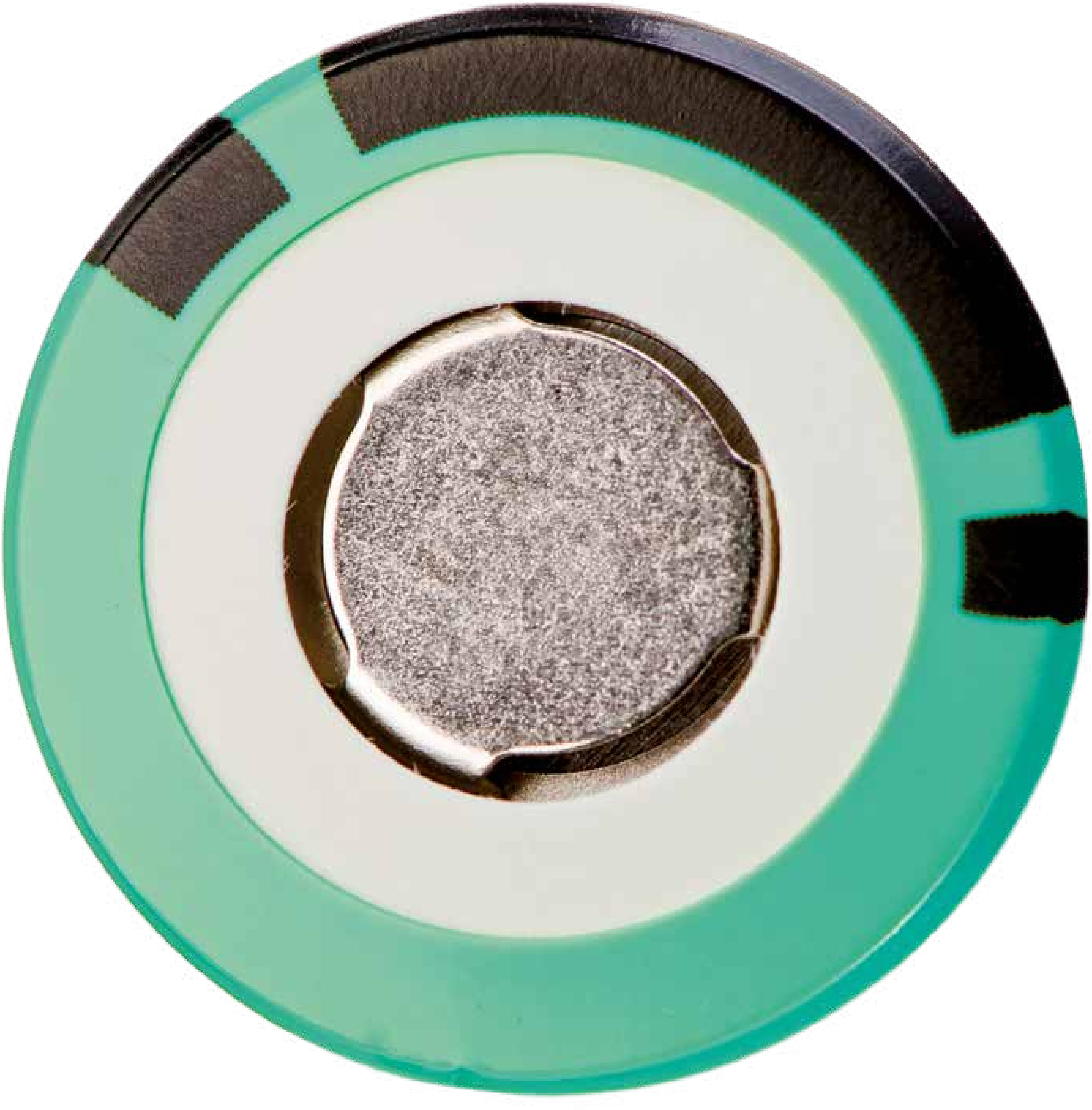
Neue Mechanismen bei der Einlagerung von Lithium-Ionen
Bei der Untersuchung des Ermüdungsverhaltens konnten die Forscher zeigen, dass sich bei fortschreitendem Betrieb der Zellen einige Lithium-Ionen irreversibel auf der Anode ablagern und dann nicht mehr zur Verfügung stehen, was die Kapazität der Batterie verringert. In weiteren Analysen beobachteten die Wissenschaftler Beugungsmuster, die auf einen bis dahin unbekannten Mechanismus bei der Einlagerung von Lithium-Ionen in die Grafitanode hindeuten. Bei ihren neuesten Messungen fanden sie heraus, dass sich die Menge des Elektrolyten in den Zellen nach vielen Ladungszyklen verringert, gleichzeitig mit der Menge der aktiven Lithium-Ionen. Künftige Analysen sollen die Ursache dafür finden. *Brigitte Röthlein*

Link

www.mlz-garching.de/spodi
www.mlz-garching.de/englisch/instruments/structure

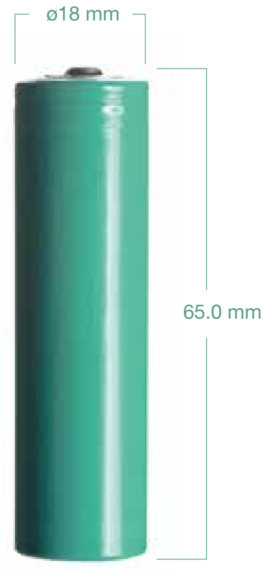
Technology has become pervasive in many facets of our modern lifestyle. But many of the gadgets we have come to rely on – laptops and smartphones included – would not be possible without lithium (Li)-ion batteries. These rechargeable batteries are designed to undergo thousands of charging and discharging cycles – which they do with no problem most of the time. Sometimes, though, we hear reports of the tiny power packs suddenly bursting into flames. Such incidents are very rare, however, considering that billions of batteries are in use worldwide. They usually occur as a result of cell damage or misuse followed by a thermal runaway. Which is why lithium-ion batteries are typically protected against short-circuits, overcharging and deep discharge.

High capacity – at a comparatively low price – makes Li-ion batteries the energy storage solution of choice for today's electric cars. They are even used in modern aircraft. ▷



Picture credit: Heddergott

Picture credit: ediundsepp (Source: TUM)



Left: Commercially available 18650 Li-ion cells are used in most laptop battery packs. Recently they have also been making their way into electric cars
Below: Martin Mühlbauer mounts a Li-ion cell on the sample table of the high-resolution powder diffractometer SPODI

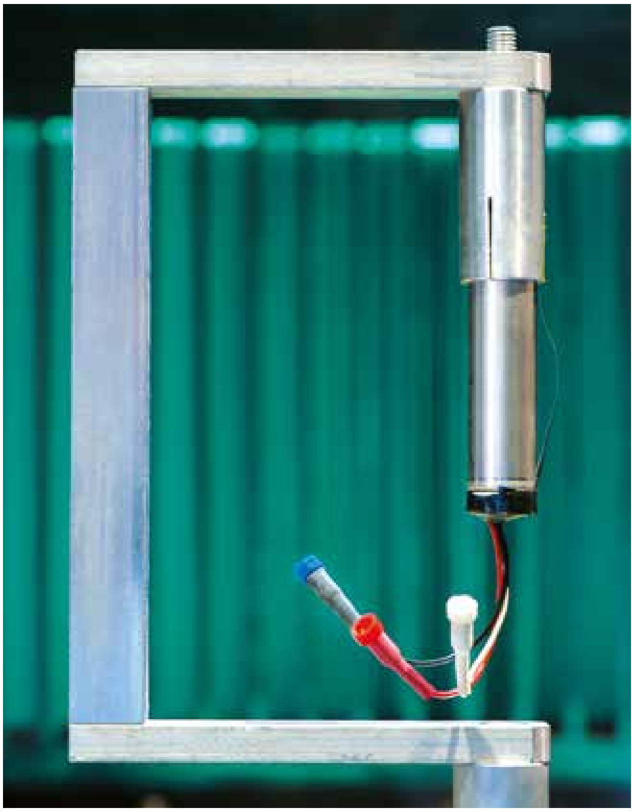
For these applications, however, the batteries are of course scaled up and the internal stress is much higher. Particularly when it comes to mobility, safety – besides weight and energy density – is one main concern. So understandably, the public was hugely disturbed when the battery of a Dreamliner passenger plane burned in early 2013, and when a Tesla electric car caught fire because of battery damage. “Despite the fact that there have been many advances in this technology, Li-ion cells still have some drawbacks, which require careful and systematic research,” admits Dr. Anatoliy Senyshyn. “That is why we decided to undertake a study on safety issues, the stability of the electrode material and ways to increase capacity.”

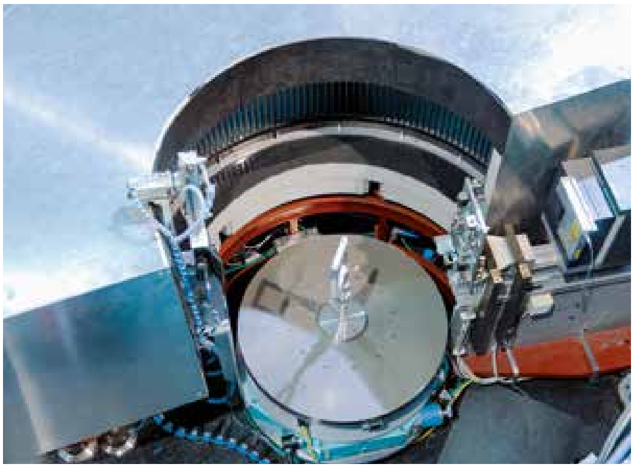
Using neutrons to look inside batteries

The physicist works at the Forschungs-Neutronenquelle Heinz Maier-Leibnitz (FRM II) of TU München (TUM). Along with colleagues from the Institute for Applied Materials – Energy Storage Systems (IAM-ESS) at Karlsruhe Institute of Technology (KIT) and the Materials Science Department at TU Darmstadt, he uses neutrons to look inside Li-ion batteries – more closely than it was ever possible before. “We have the great advantage of being able to see what is happening inside the battery while it is being charged and discharged,” he explains. “With other methods, it is usually only possible to examine the battery beforehand and afterwards. During the actual charging process, the cell is a black box. If it is opened for examination, this can disturb the equilibrium of its chemical components in some cases and thus impact the validity of the study findings.”

For their investigations, the researchers focus on commercially available 18650 Li-ion cells with a diameter of 18 mm and a length of 65 mm. These cylindrical cells are found in the majority of laptop batteries, and recently they have also been making their way into flashlights and increasingly into electric cars. Their anode is made of carbon – graphite to be exact – and the cathode consists of a lithium metal oxide, often lithium cobalt dioxide. For each electrode, the powder based materials are mixed with a binder to form a solid paste. A film is inserted to separate the two layers. This separator electrically isolates the two electrodes. ▷

Picture credit: Heddergott





Looking inside batteries with the powder diffractometer SPODI (bottom): Mounted 18650 cell (top, with removed plastic cover) as seen by the neutron beam. Elastically scattered neutrons have to pass neutron collimators (green background) installed in front of the neutron multidetectors

It is permeable for the lithium ions, however, and these then create the current flow. During charging, they move inside the graphite, and to the metal oxide while discharging. On both sides they are intercalated into the respective crystal lattice. The electrode material is coated on electrically conductive foils made of aluminum or copper, which act as a supply line or contact to the outside. The stacked layers comprising electrodes and separator are rolled up and fitted inside the cylindrical housing. This is filled with a liquid electrolyte, which acts as a medium for lithium transport.

Thermal neutrons are a good way to gain insight into a rechargeable battery during operation as they have very little energy and therefore do not effect changes in the cell. The uncharged elementary particles move through many materials almost unhindered, but they are diffracted by ordered systems like the crystalline electrode material. The angles at which this happens allow conclusions to be drawn on the structure and the elemental composition of the battery components. The researchers made use of this effect and placed the cells in a thermal neutron beam. At the same time, detectors arranged in a semicircle around the sample recorded the distribution of the neutrons scattered at the corresponding angle. The resulting graphs show peaks of varying heights at various scattering angles depending on the charge status of the cells.

At the same time, the researchers generated radiographs using a procedure similar to medical X-ray tomograms. “We measured the intensity of the neutrons penetrating the sample at various angles and then generated tomograms of the interior of the cells,” explains KIT researcher Dr. Martin Mühlbauer. The images obtained can be compared with the X-ray tomograms of the batteries previously recorded at a nearby chair at TUM. “With X-rays, the spatial resolution is actually better than with neutrons,” points out Mühlbauer, “but only neutrons enable us to trace the distribution of the lithium ions.”

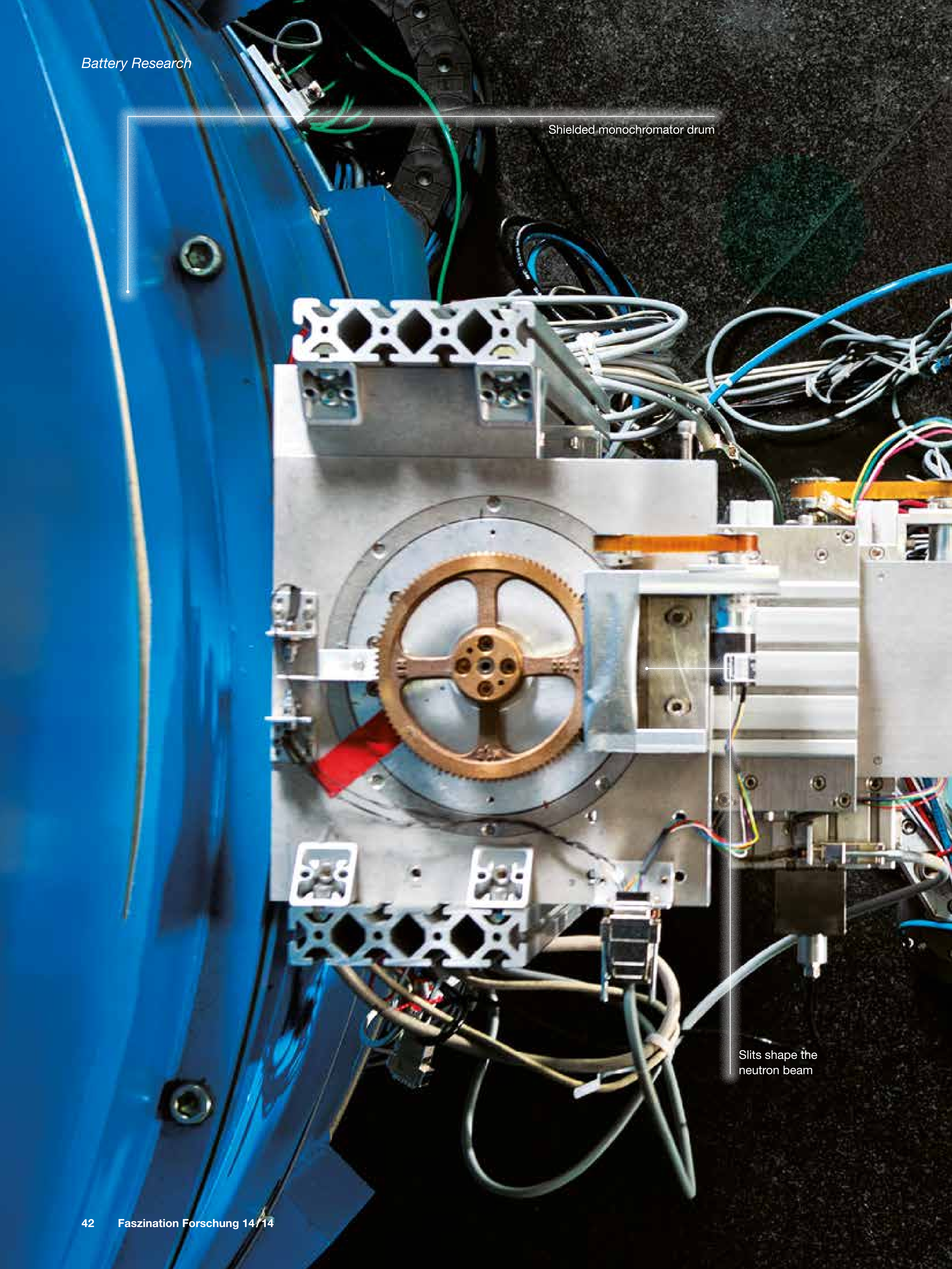
Lithium ions stick to the anode

During evaluation of the measurement graphs, numerous geometric, physical and metrological factors have to be taken into account. Based on a model representation of the material, individual parameters are adjusted by the computer until – in an ideal case – the measured values fully correspond with the calculated values. If this does not happen, the researchers modify the model until they achieve the best possible match.

Already two years ago the researchers made a discovery, showing that when the cells are used continuously, some of the lithium ions are irreversibly deposited at the anode and are therefore lost for subsequent cycles, which reduces the battery’s capacity. “This enabled us to prove that there are processes at the anode, which affect the performance of the storage system. These are not yet fully understood, however,” comments Senyshyn. One thing is clear at this stage: the process is temperature-dependent. Electrochemical analysis allowed for monitoring a decrease of the battery capacity down to only about 80 percent of the original capacity after 1000 cycles. Neutron measurements confirmed a corresponding decrease in the number of lithium ions exchanged between the two electrodes. At 25 degrees Celsius, the effect was much more pronounced ▷

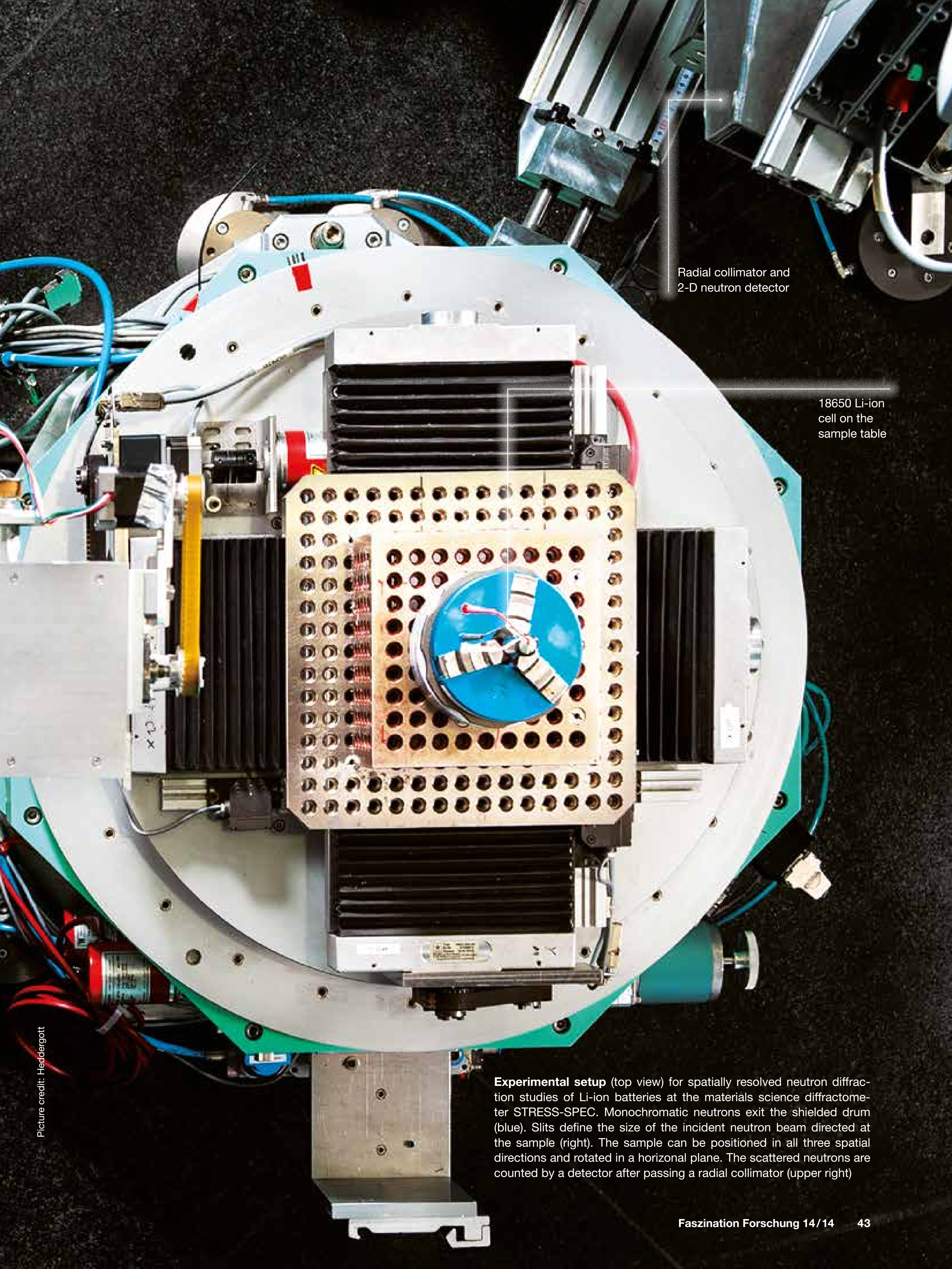
Picture credits: Heddergott

The materials science diffractometer STRESS-SPEC is one of the instruments used by Anatoliy Senyshyn (right) and Martin Mühlbauer to analyze the charge and discharge processes inside batteries



Shielded monochromator drum

Slits shape the neutron beam



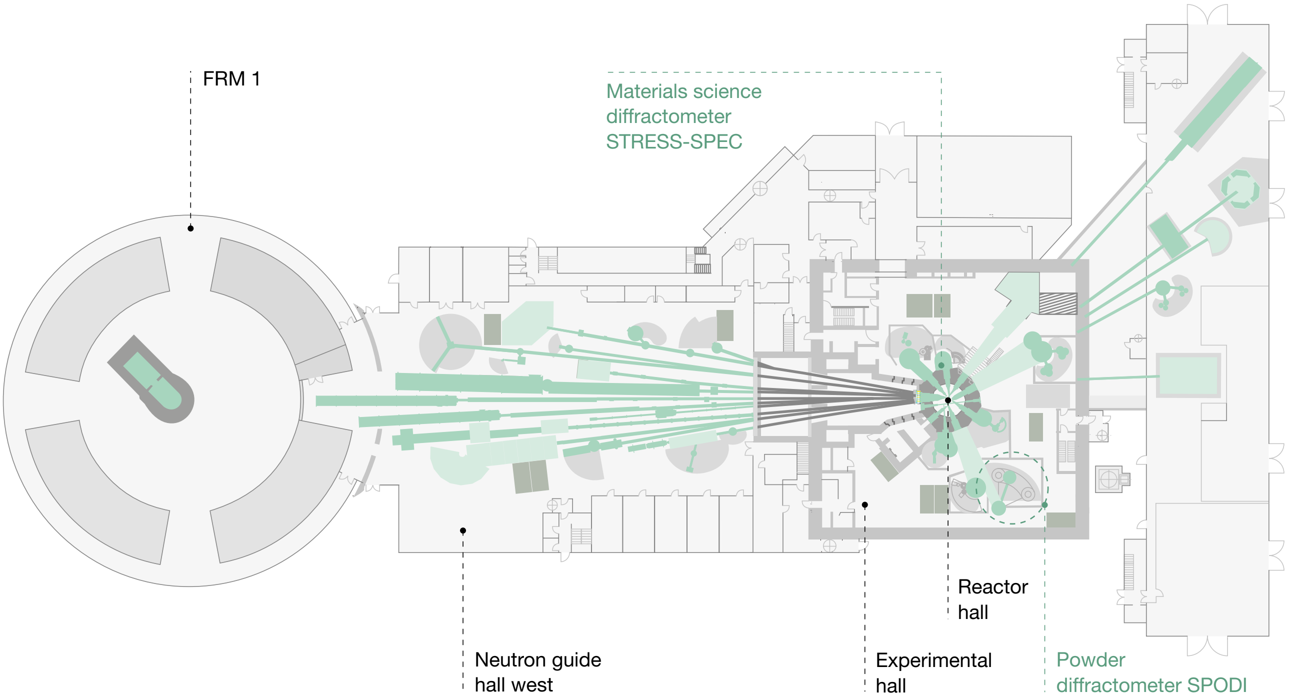
Radial collimator and
2-D neutron detector

18650 Li-ion
cell on the
sample table

Picture credit: Heddergott

Experimental setup (top view) for spatially resolved neutron diffraction studies of Li-ion batteries at the materials science diffractometer STRESS-SPEC. Monochromatic neutrons exit the shielded drum (blue). Slits define the size of the incident neutron beam directed at the sample (right). The sample can be positioned in all three spatial directions and rotated in a horizonal plane. The scattered neutrons are counted by a detector after passing a radial collimator (upper right)

Right: The FRM II reactor building. The neutron guide hall occupies the space between the new and the old reactor, the so-called Atomic Egg. Soon a new neutron guide hall east will start its operation. The high-resolution powder diffractometer SPODI and the materials science diffractometer STRESS-SPEC are located in the experimental hall
Bottom: Side view of the setup for spatially resolved powder diffraction studies of 18650 Li-ion batteries at the instrumtent STRESS-SPEC. The red laser beam marks the center of the neutron beam for sample alignment



than at 50 degrees Celsius. Batteries operated at the higher temperature only showed about two thirds of the capacity loss observed at room temperature after 1000 cycles. Apparently the Li-ions retain greater mobility at elevated temperatures and can overcome transport barriers built up due to fatigue more easily.

Neutron measurements indicate unknown mechanisms

Meanwhile, more detailed measurements revealed that the process of charging and discharging lithium-ion batteries is different to previous assumptions. The researchers observed an intensity distribution inside the diffraction pattern, indicating a previously unknown mechanism occurring during the intercalation of lithium ions into the graphite anode. Contrary to the accepted opinion that this intercalation only takes place in well-defined stages, they only found two of these states forming defined stages at high lithium concentrations, where each lithium ion is coordinated with either six or twelve carbon atoms. These stages are known as LiC_6 and LiC_{12}. At lower lithium concentrations, the transformation from graphite to LiC_{12} is a quasi-continuous process, whereby intercalated lithium forms "islands" in every second layer of graphite. These gradually grow as lithium concentrations rise until a stage corresponding to LiC_{12} is reached.

"These findings force us to reconsider the intercalation of the lithium ions into the anode's graphite layers close to the discharged state," says Senyshyn. "The deviations we have observed may have considerable influence on critical battery properties like quick-charge behavior, low-temperature performance or depth of discharge." All of this information could be extremely valuable to battery manufacturers and users – if it is incorporated into the design and testing of new products. "Beyond an academic environment, industry undoubtedly faces financial constraints in funding research projects such as these," reckons Mühlbauer, "or the persons in charge are simply unaware of these possibilities."

Money could be saved, however, by developing optimized battery concepts. The researchers in Garching have discovered in their latest measurements, for instance, that the amount of electrolyte in the cells decreases after numerous charging/discharging cycles, simultaneously with the number of active lithium ions. "Opinions are divided on what actually happens to the electrolyte," relates Senyshyn. "We cannot say with certainty, however, which theory is the valid one." The geometric structure of the cells is another area that could be optimized: "In some types of rechargeable batteries, we have found areas where a comparatively small amount of lithium is intercalated. That is a waste of material," states Mühlbauer. "One might be able to prevent this by improving the structure, at the same time increasing cell capacity without using additional material." So the researchers still have a lot of work to do. They are currently investigating different cell types and materials. "The electrolyte in particular is an extremely critical component," Senyshyn points out. "So analyzing its temperature behavior will be a top priority. Battery cells have many parameters allowing for changes. They look like simple structures, but are extremely complicated in terms of how they work. We assume there are many opportunities for optimization." *Brigitte Röthlein*

Picture credit: Heddergott, Graphics: ediundsepp (Source TUM)

Tracing Unique Cells **with Mathematics**

Stem cells can turn into heart cells, skin cells can mutate into cancer cells; even cells of the same tissue type exhibit small heterogeneities. Scientists use single-cell analysis to investigate these heterogeneities. But the method is still laborious, and considerable inaccuracies conceal smaller effects. Scientists at TU München (TUM), the Helmholtz Zentrum München and the University of Virginia (USA) have now found a way to simplify and improve the analysis by mathematical methods

Link

www-m12.ma.tum.de
www.helmholtz-muenchen.de/icb/index.html

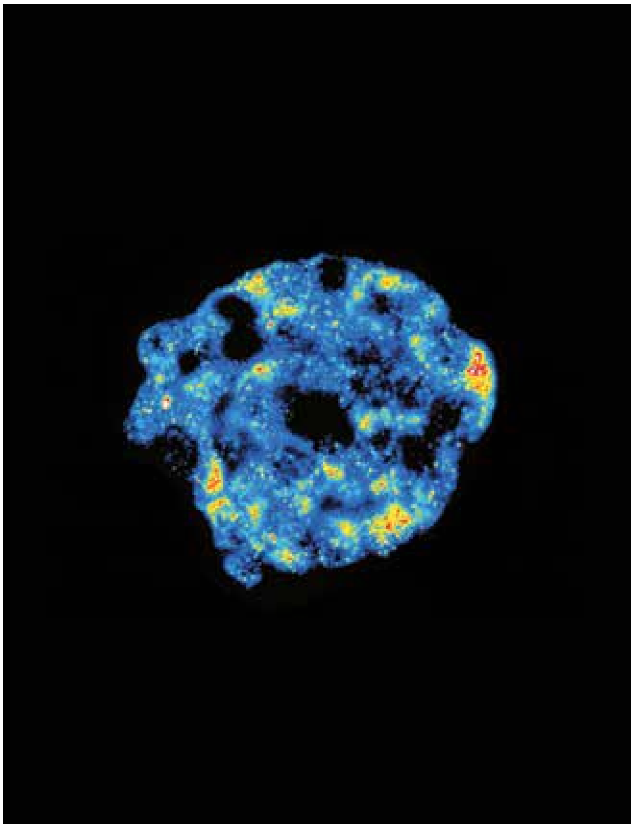
Each cell in our body is unique. Even cells of the same tissue type that look identical under the microscope differ slightly from each other. To understand how a heart cell can develop from a stem cell, why one beta-cell produces insulin and the other does not, or why a normal tissue cell suddenly mutates into a cancer cell, scientists have been targeting the activities of ribonucleic acid, RNA. Proteins are constantly being assembled and disassembled in the cell. RNA molecules read blueprints for proteins from the DNA and initiate their production. In the last few years, scientists around the world have developed sequencing methods that are capable of detecting all active RNA molecules within a single cell at a certain time. At the end of December 2013 the journal Nature Methods declared single-cell sequencing the “Method of the Year.” However, analysis of individual cells is extremely complex, and the handling of the cells generates errors and inaccuracies. Smaller differences in gene regulation can be overwhelmed by the statistical “noise.”

Easier and more accurate, thanks to statistics

Scientists led by Professor Fabian Theis, Chair of Mathematical Modeling of Biological Systems at TUM and Director of the Institute of Computational Biology at the Helmholtz Zentrum München, have now found a way to considerably improve single-cell analysis by applying methods of mathematical statistics. Instead of just one cell, they took 16 to 80 samples with ten cells each. “A sample of ten cells is much easier to handle,” says Professor Theis. “With ten times the amount of cell material, the influences of ambient conditions can be markedly suppressed.” However, cells with different properties are then distributed randomly on the samples. Therefore, Theis’s collaborator Christiane Fuchs developed statistical methods to still identify the single-cell properties in the mixture of signals.

Combining model and experiment

On the basis of known biological data, Theis and Fuchs modeled the distribution for the case of genes that exhibit two well-defined regulatory states. Together with biologists Kevin Janes and Sameer Bajikar at the University of Virginia in Charlottesville (USA), they were able to prove experimentally that, with the help of statistical methods, samples containing ten cells deliver results of higher accuracy than can be achieved through analysis of the same number of single-cell samples. In many cases, several gene actions are triggered by the same factor. Even in such cases, the statistical method can be applied successfully. Fluorescent markers indicate the gene activities. The result is a mosaic, which again can be checked to spot whether different cells respond differently to the factor. The method is so sensitive that it even shows one deviation in 40 otherwise identical cells. The fact that this difference actually is an effect and not a random outlier could be proven experimentally. *Andreas Battenberg (TUM)*



Fluorescence in-situ hybridization shows mRNA activity in a tissue sample. Blue indicates low activity, and red, high

Picture credit: S. S. Bajikar / University of Virginia, Charlottesville (USA)

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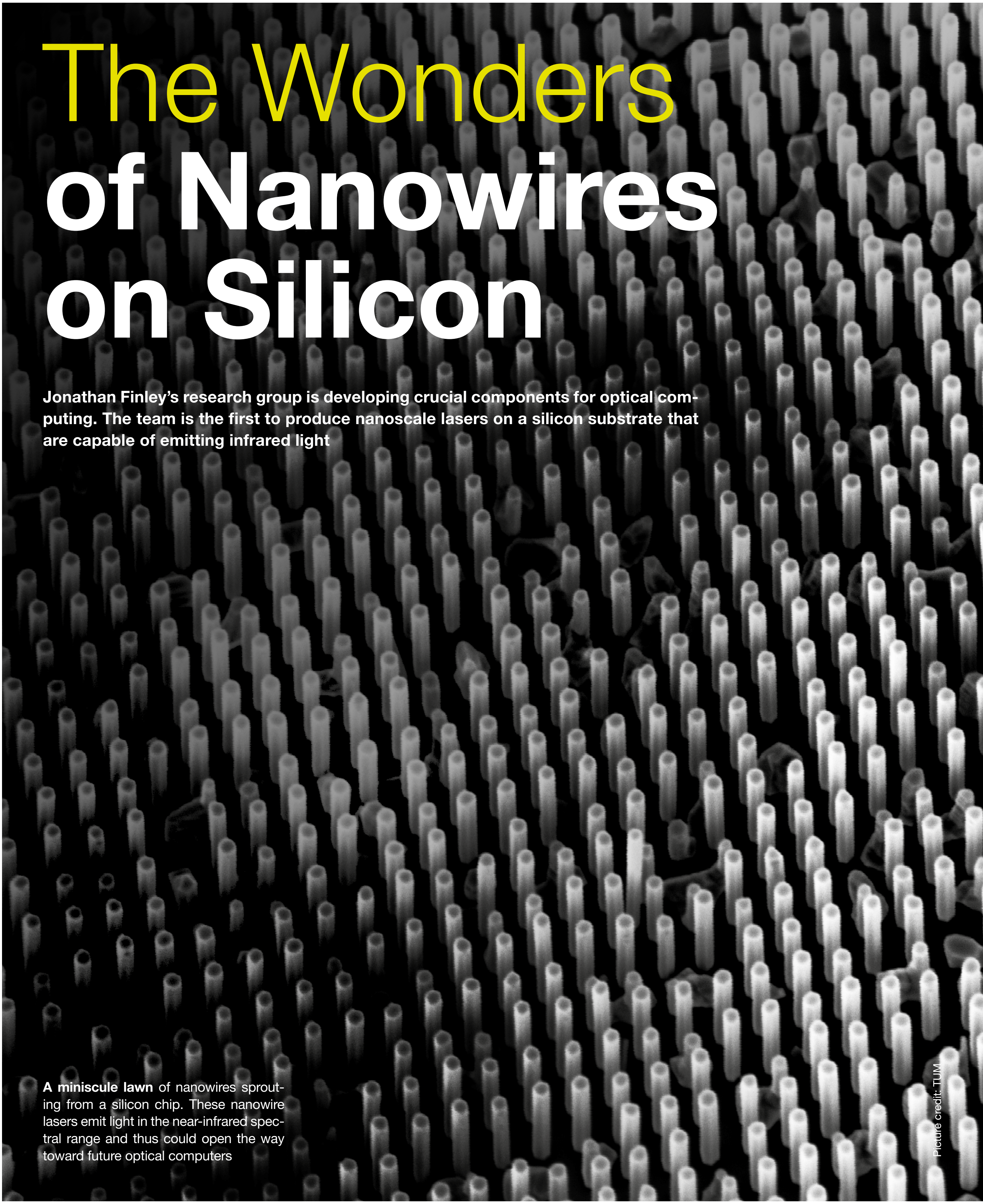
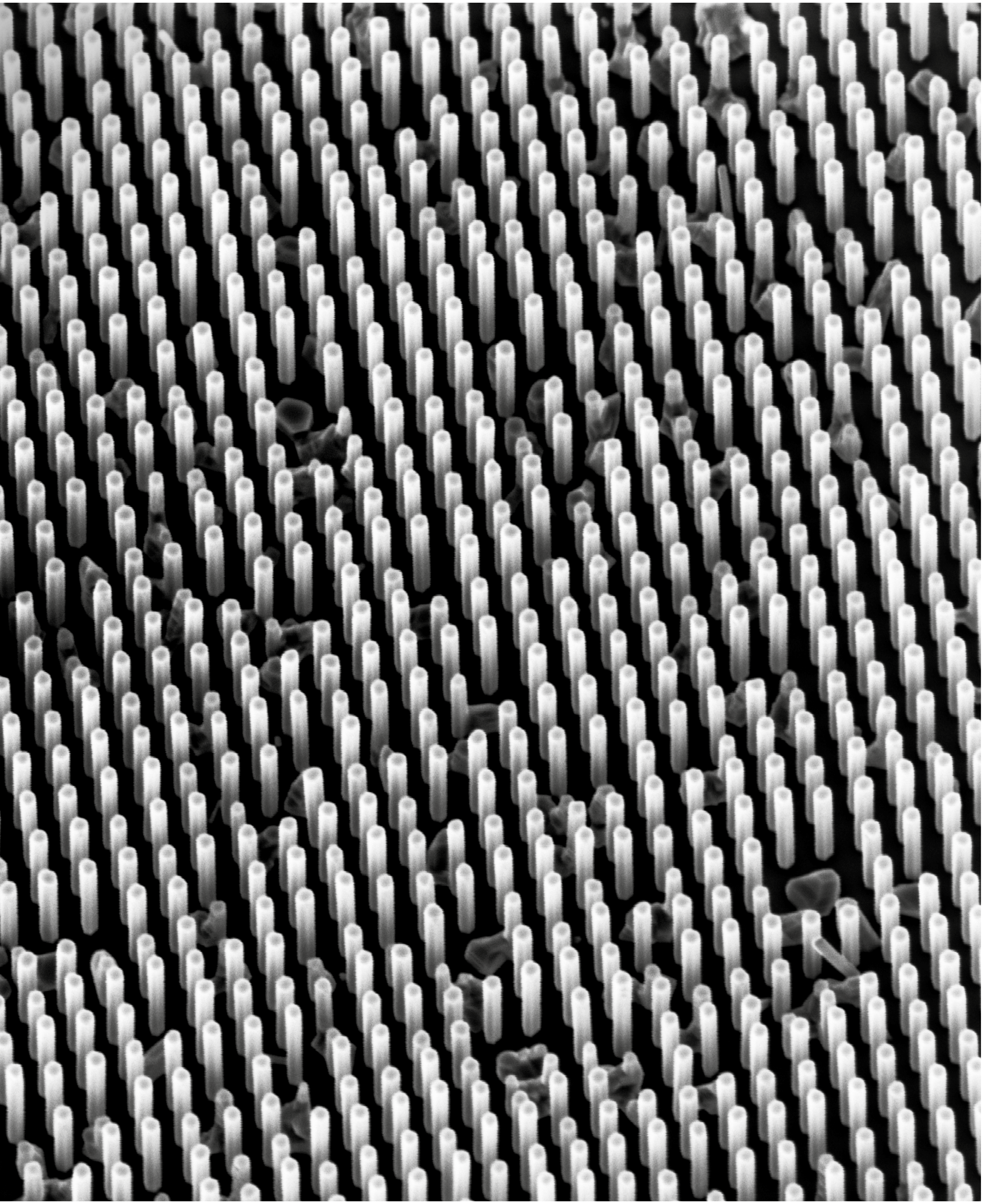
The Wonders **of Nanowires on Silicon**

Jonathan Finley's research group is developing crucial components for optical computing. The team is the first to produce nanoscale lasers on a silicon substrate that are capable of emitting infrared light



A miniscule lawn of nanowires sprouting from a silicon chip. These nanowire lasers emit light in the near-infrared spectral range and thus could open the way toward future optical computers

Picture credit: TUM



Zauberhafte Nanodrähte auf Silizium

Prof. Jonathan Finley, Direktor des Walter Schottky Instituts (WSI) der TU München, und seinem Team ist es gelungen, eine wichtige, bisher noch fehlende Komponente für optische Computer zu entwickeln: Sie züchteten erstmals auf einer Silizium-Oberfläche Laser im Nanobereich, die Licht im Infraroten erzeugen. Es handelt sich um Nanodrähte aus Galliumarsenid, nur ca. 300 Nanometer dick und etwa zehn Mikrometer lang, die direkt auf der Silizium-Oberfläche hochwachsen und dann zum optischen Pumpen mit Licht bestrahlt werden. Durch die Ummantelung mit einer fünf Nanometer dicken Schicht aus einer Aluminium-Galliumarsenid-Legierung konnten sie zum Lasern gebracht werden. Die Messungen der Garchinger Forscher zeigten, dass diese Core-Shell-Struktur die optische Effizienz um den Faktor 1000 erhöht, verglichen mit einem reinen Galliumarsenid-Draht.

Nanolaser als optisches Schaltelement

Hergestellt werden die Nanodrähte mithilfe von Molekularstrahlepitaxie. Damit lassen sich die Strukturen durch Selbstorganisation Atom für Atom aufbauen, indem man in einem Hochvakuum entsprechende Materialien verdampft und sich auf einer geeigneten Oberfläche absetzen lässt. Da es möglich ist, die Nanolaser exakt auf einem Silizium-Substrat zu positionieren, eignen sie sich zur Integration auf mikroelektronischen Chips, wo sie als optisches Schaltelement dienen können. Im nächsten Schritt entwickelten die Wissenschaftler ein Verfahren, die Nanolaser elektrisch zu pumpen, was für einen Computer vorteilhafter ist als das optische Pumpen.

Brigitte Röthlein

Link

http://www.wsi.tum.de

For the first time in my scientific career, I was actually too pessimistic," concedes a smiling Professor Jonathan Finley, Director of TUM's Walter Schottky Institut (WSI). "But Benedikt Mayer, my Ph.D. student, was confident of success – and he was quite right. Perhaps I'm getting old!" The 41-year-old head of the Chair for Semiconductor Nanostructures and Quantum Systems is referring to research into nanowires made of gallium arsenide, only around 300 nanometers thick and about ten micrometers long. The plan was to turn this into a tiny infrared laser – something many research groups around the world had already attempted without success. Various researchers managed to fabricate the necessary nanostructures and pump them with energy, but dissipation to the nanowire surface was so fast such that lasing action could not be achieved – or at least never at the desired wavelength.

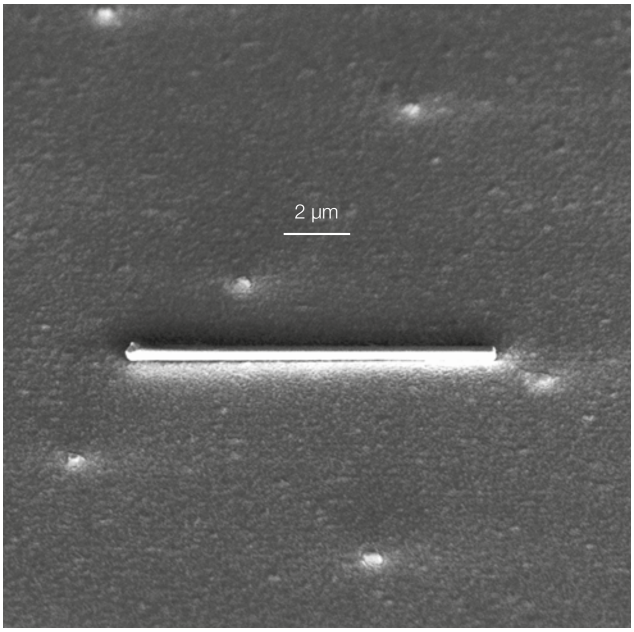
In November 2013, the Garching-based WSI researchers coated their nanowires with a passivation layer just five nanometers thick and set about putting it to the test. And, as it turned out: "We grew the sample on a Monday, and by Thursday of the same week, we were already able to show that it was lasing," recounts Finley. "I thought we would probably need to try out several variants, but then we tested the first sample and it worked straight away. It was one of those champagne moments. In fact, we really did open a bottle and toast our success."

Optical computing, here we come

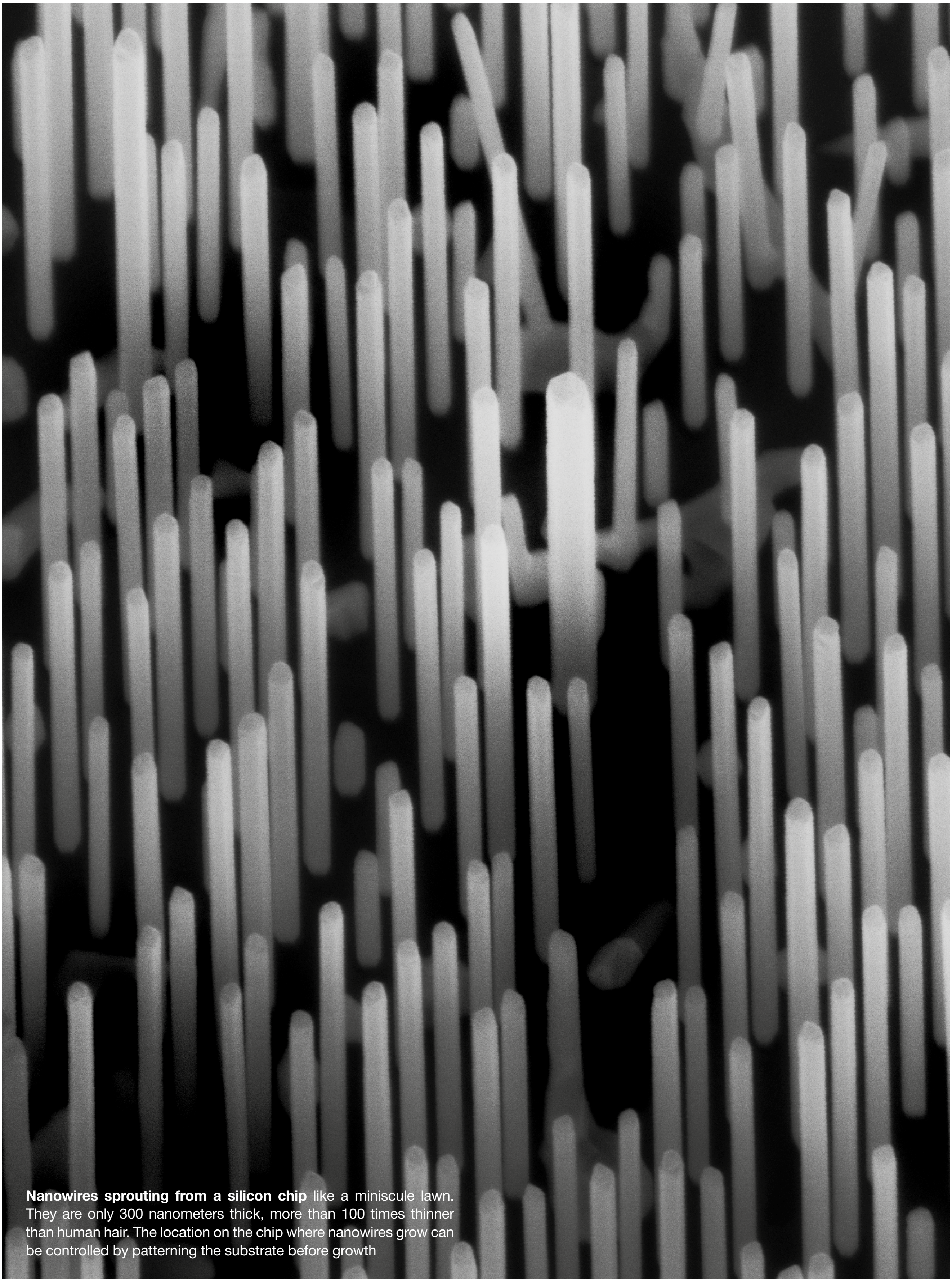
This type of tiny laser is no gimmick, but a long-awaited breakthrough in the world of optical information technologies. Moore's law predicts that the number of transistors that can be incorporated in a computer chip will double every 18 months or so due to their steadily shrinking size. "However, we are gradually reaching the limit," declares Finley. "The Haswell processors on today's Intel chips use transistors measuring just 20 to 30 nanometers in size, which means just a few hundred atoms between the contacts. If it carries on like that, we'll soon be down to a few tens of atoms per transistor." Beyond that stage, making computers faster and, above all, more energy-efficient calls for entirely new approaches. One of the main ones is to transmit information between components optically rather than electrically. Electrons move along wires and tend to heat them up in the process. By contrast, a light beam offers a multitude of benefits, including high capacity to transport information and the ability to cross other light beams without disturbance – not so easy with electrical interconnects. Most of all, information technologies based on light bring speed – nothing in the world is faster than light.

Using light for information transmission requires optical components – meaning light sources, waveguides and photodetectors on the chip. The latter two components ▷

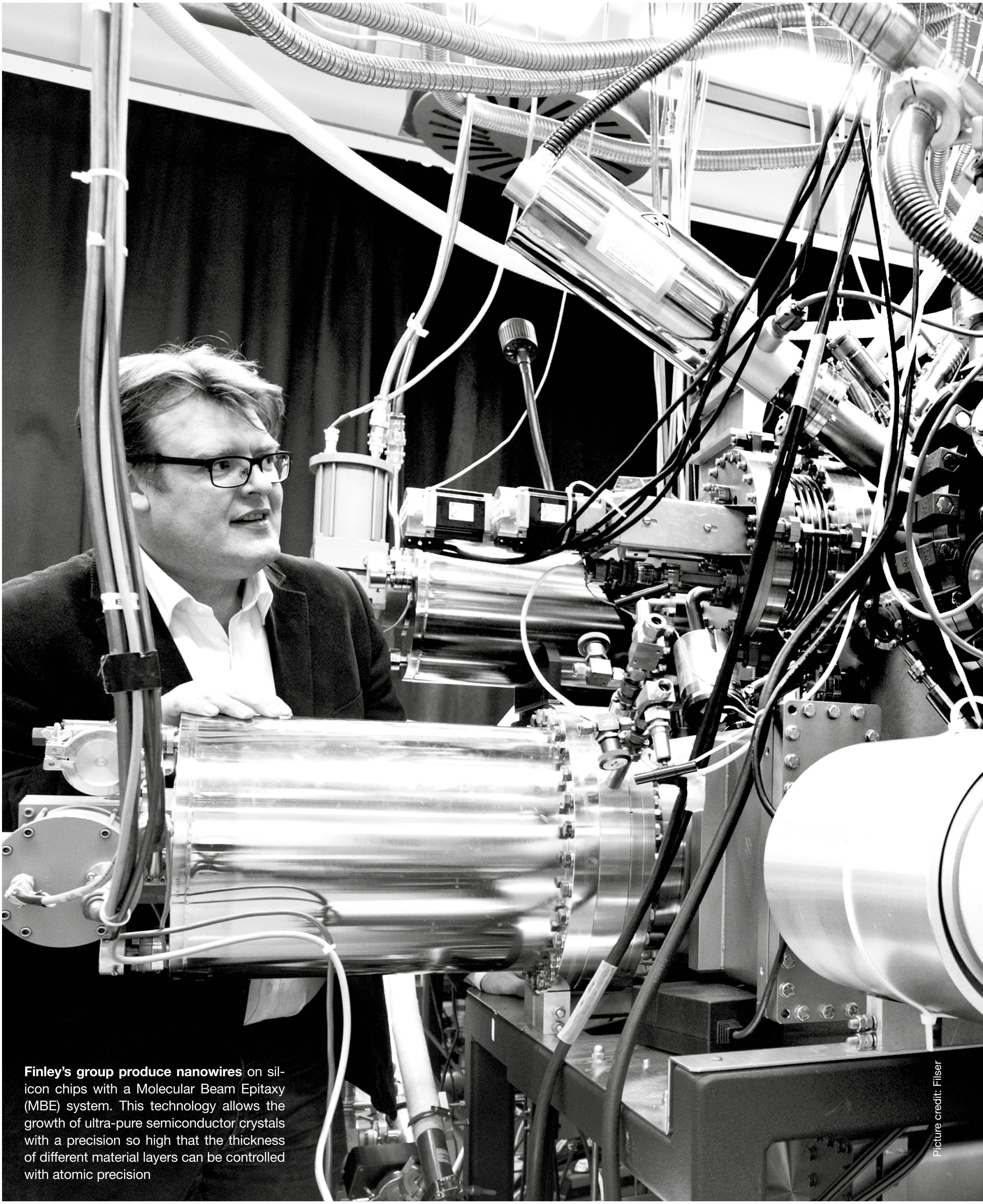
Scanning electron microscope image of a single GaAs-AlGaAs nanowire that has been removed from the silicon substrate and placed onto glass for study



Picture credits: TUM

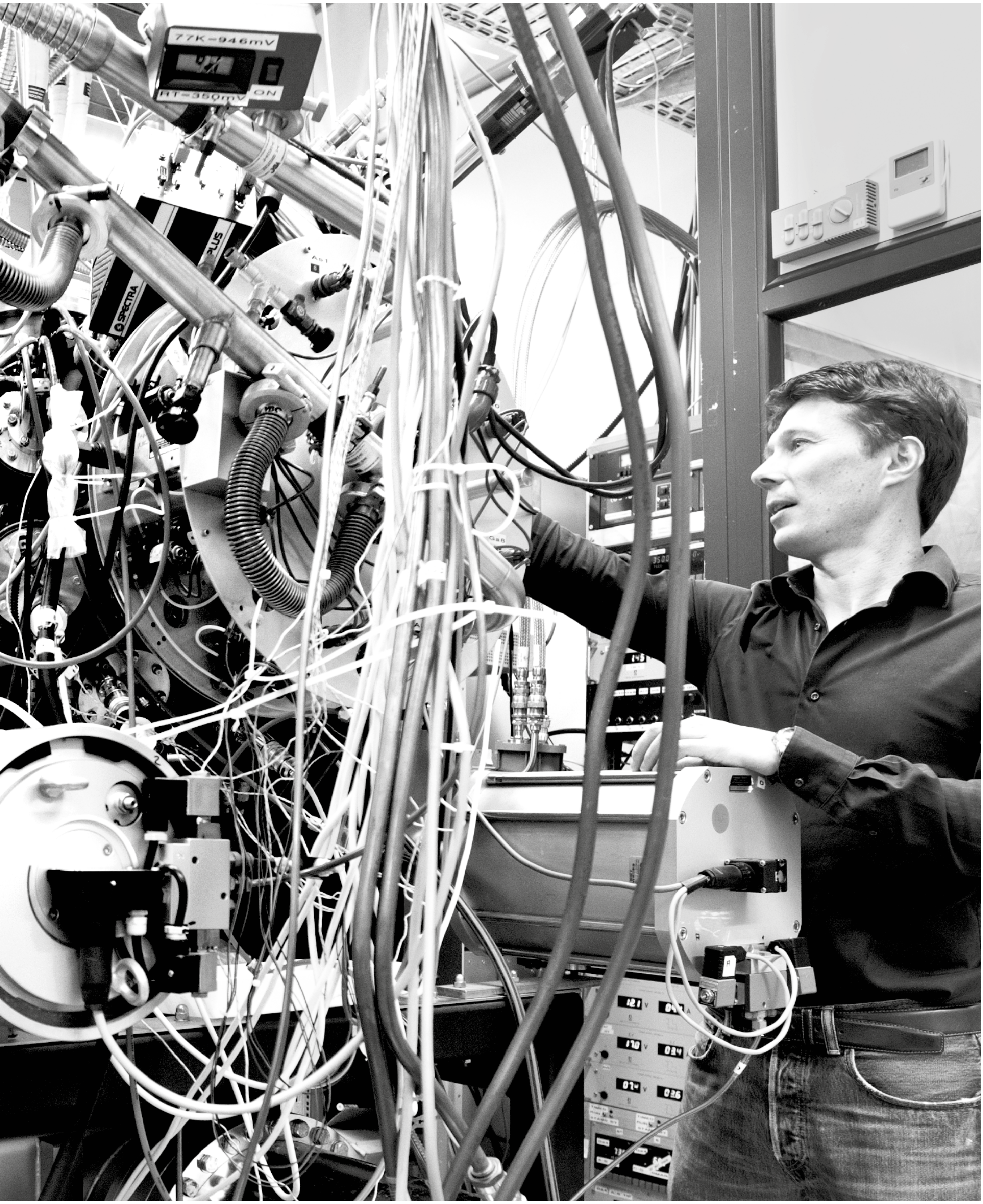


Nanowires sprouting from a silicon chip like a miniscule lawn. They are only 300 nanometers thick, more than 100 times thinner than human hair. The location on the chip where nanowires grow can be controlled by patterning the substrate before growth



Finley's group produce nanowires on silicon chips with a Molecular Beam Epitaxy (MBE) system. This technology allows the growth of ultra-pure semiconductor crystals with a precision so high that the thickness of different material layers can be controlled with atomic precision

Picture credit: Filser



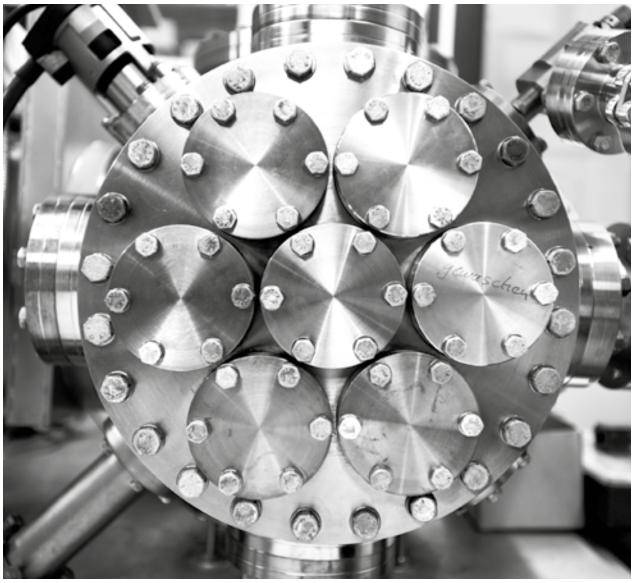
are already available, but growing the required high-performance light sources directly on silicon (Si) chip substrates previously posed a stumbling block for researchers. These sources must emit light at the correct wavelength – that is, in the infrared spectral region – since silicon structures are non-transparent for visible light. An infrared laser that can be directly integrated on a chip is thus precisely the missing link that computer manufacturers are looking for.

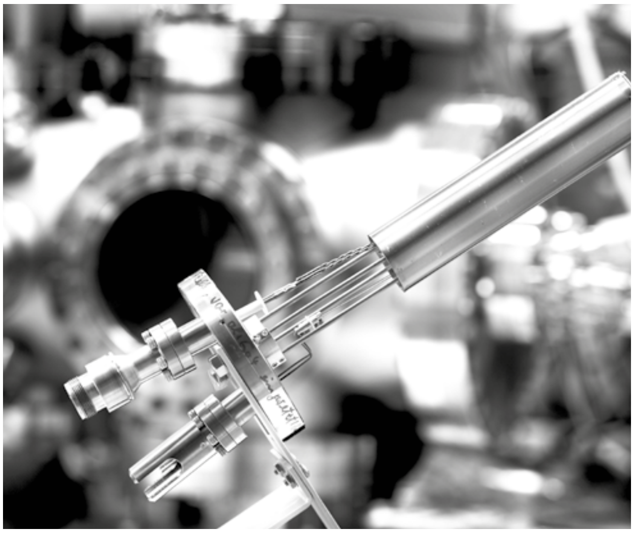
Building wires atom by atom

A freestanding nanowire that sticks out of a silicon chip like a tiny bristle and emits laser beams would be an ideal solution. So WSI research groups led by Finley and Professor Gerhard Abstreiter spent years exploring how to build nanowires – which can, in fact, be used for other purposes, too. By now, the researchers have pretty much perfected their method. Dr. Gregor Koblmüller and his students operate the molecular beam epitaxy (MBE) system, which allows the formation of these nanowires, with artistic finesse. They know how they can build up nanowires atom by atom by vaporizing the relevant materials and depositing them onto a substrate in high vacuum.

Ordinarily though, the vapor would condense over the entire surface of the chip, but this is clearly no way to produce nanowires. Essentially, nanowires are simply tiny monocrystals of semiconductor material, such as gallium arsenide (GaAs). If you supply both gallium and arsenic vapor and deposit these onto a silicon substrate, the natural tendency is to coat the whole surface and thus grow into a flat (planar) layer. “That wouldn’t be bad in itself, but it causes huge tensions at the interface with the substrate, which can only be relieved through the formation of a high number of crystal lattice defects,” explains Koblmüller. “These defects eat up a lot of energy, so we can’t build efficient lasers that way.”

The scientists in Finley’s team have solved this problem by growing the GaAs on a very small footprint instead of spreading it over a wider surface. “This means the material can grow upward in tiny columns,” reveals the British researcher. “The sharp rise in the surface-to-volume ratio of these nanocolumns means tensions that have built up can easily dissipate across the surface. Which allows us to grow the GaAs crystals on the silicon chip with almost zero defects.” To start with, the researchers exploited small ▷

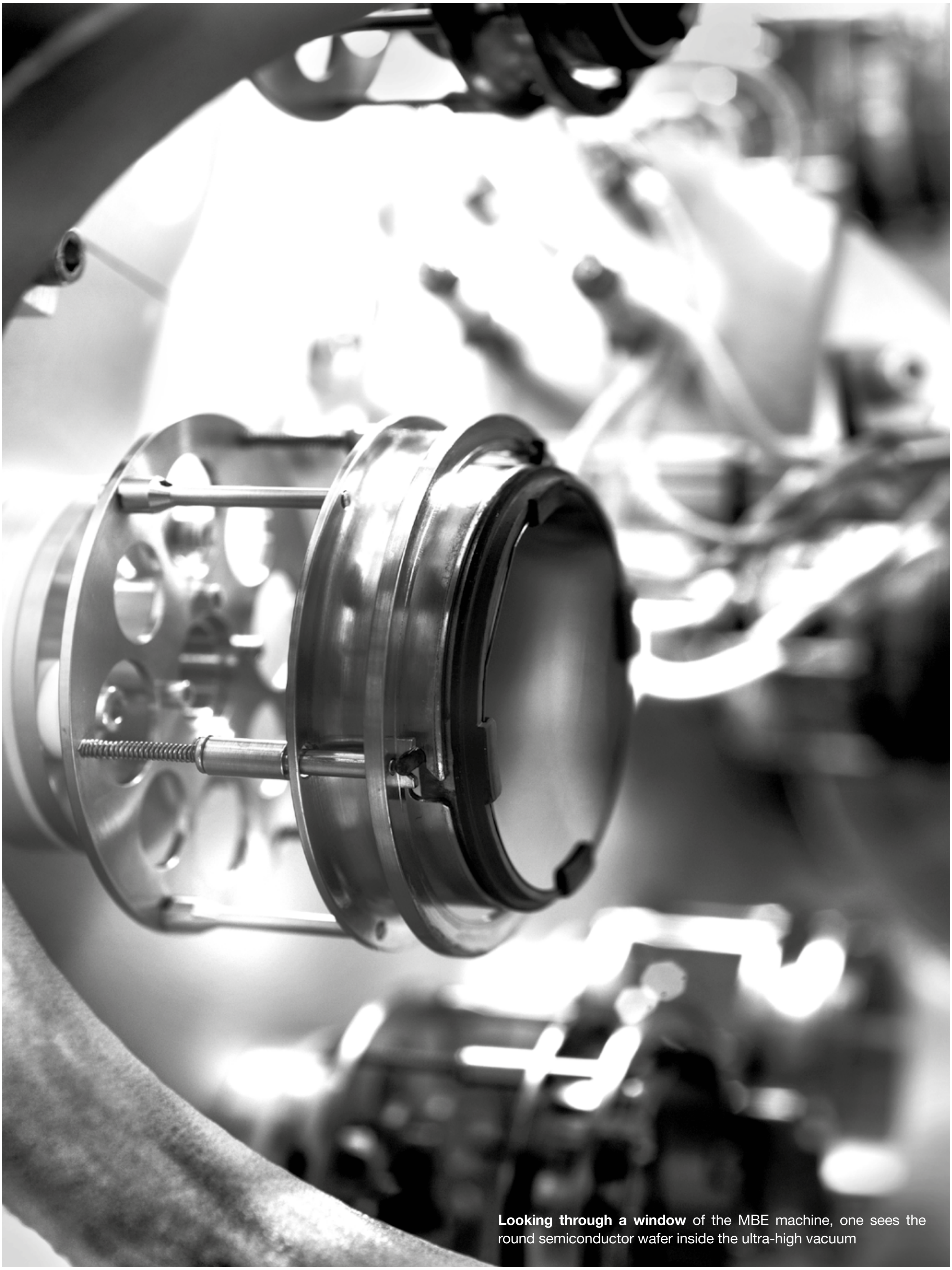




Inside the MBE system’s (top) ultra-high-vacuum chamber a Knudsen cell (middle) supplies ultra-pure beams of atoms to be deposited onto the chips. Max Bichler (bottom) examines a piece of wafer. One can see the area which contains nanowires with the naked eye

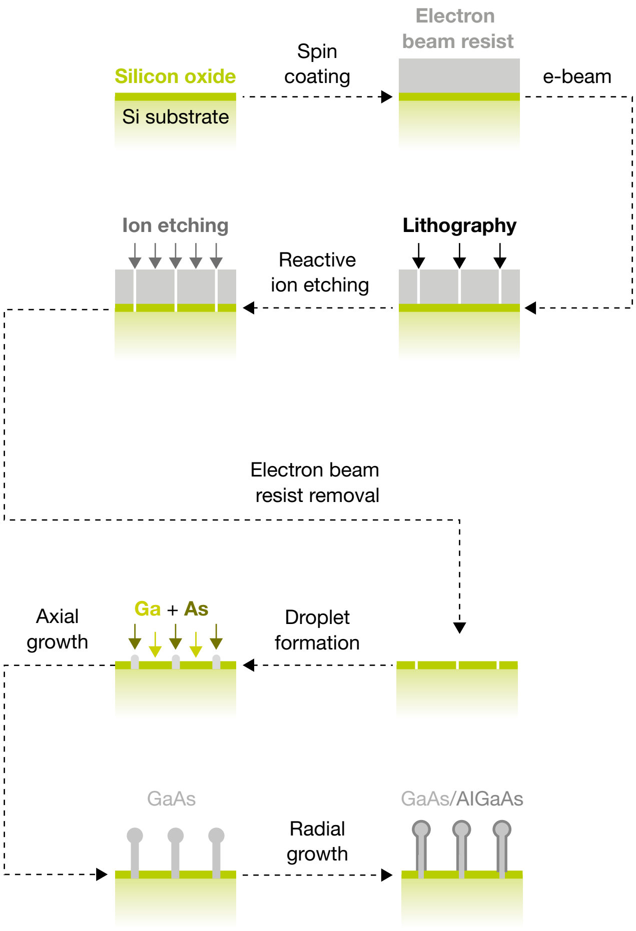
Right: In the laser laboratory, optical spectroscopy is used to analyze the properties of the semiconductor nanostructures. The measurements also allow scientists to test and optimize the performance of the nanowire lasers as external parameters such as temperature, etc. are varied

Picture credits: Filser



Looking through a window of the MBE machine, one sees the round semiconductor wafer inside the ultra-high vacuum

Picture credit: Filser/Graphics: ediundsepp



Nanowire production: Tiny holes are lithographically etched into a silicon oxide layer. Gallium and arsenide atoms deposited onto the chip can only grow upward from these holes. To reach the required optical efficiency to create laser beams, the nanowires are encapsulated with aluminum gallium arsenide

irregularities on the surface to seed the growth of these crystals. However, this was too random for them. So they began to use lithographic methods to etch tiny holes in the silicon oxide layer, which was specifically grown on the surface of the Si substrate. When gallium and arsenic atoms are deposited onto the chip under these conditions, the crystals can only grow upwards from these holes. “It works like a charm,” describes Finley. “The nanowires sprout from the chip like grass growing on a miniscule lawn. They are extremely pure and we can see through the electron microscope that they really are formed with great precision, layer by layer.” Koblmüller adds: “We are combining top-down and bottom-up procedures here. First we etch the holes – intervening from outside – and then we allow the monocrystals to grow, which is entirely a self-organizing process.” By now, the researchers know their way around the tiny wires – they can “mow” them with a piece of paper and then separate them; they can manipulate them with optical tweezers or use a polymer web to pull them out of the substrate (“just like waxing”) and move them from one site to another. And they can smooth off the end facets of the wire to produce a high-reflectivity mirror. Normally, every wire has a tiny drop of metal at its tip, which serves as the catalyst for its formation. To remove this, the team fills up the entire structure with a polymer, and can then etch away the tips with precision. The result is a smooth mirror, which is a key requirement for a good laser.

Wire with laser action

As exciting as the initial successes were, it was also clear that the nanowires alone would not suffice. Other research groups had already shown that energy pumped into these wires in the form of light was not amplified internally and then emitted again as a laser beam. Rather, it was found that the charge carriers released in the material discharged their energy again at the surface of the wires during recombination processes, without emitting light. So the WSI researchers began to consider ways of to prevent this effect. They decided to try applying a barrier to the surface of the nanowires to impede the charge carriers. Once again, Koblmüller’s expertise was called for. Together with Ph.D. student Daniel Rudolph, he devised a method of adapting the epitaxy process to permit radial growth. This way, the wires grew thicker rather than taller. The researchers then encapsulated them with an alloy layer of aluminum and gallium arsenide, forming a shell around the wire core. “This is only five nanometers thick, so equivalent to just 20 layers of atoms,” specifies Finley. “But our measurements showed that this was enough to increase the optical efficiency by a factor of a 1000.” And so the nanowire laser was born. GaAs is the optical medium inside it, while the outer layer serves purely as a barrier that prevents the charge carriers from reaching the surface and losing energy without emitting light. While laser activity was only detected at low temperatures to start with, it has now been shown that the nanowires emit infrared light even at room temperature.

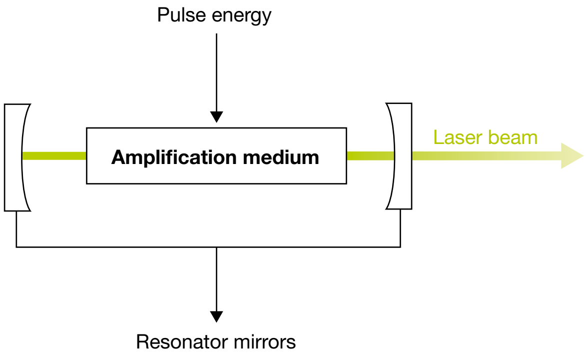
A bright future

There is still one downside to the tiny lasers: they require optical pumping. This means that, for the wires to emit infrared laser light, they first have to be irradiated with visible light. This would not be ideal for future use in computers, where electric pumping would be preferable – so this is the next challenge facing the Garching-based researchers. They have already devised processes to make the nanowires electrically conductive by doping (i.e. adding impurities). If they form a contact with the surface, they can apply voltage and electrically excite the wires. In general, too, the scientists are aiming to optimize the lasers further by varying the outer layer and the layer separating the wire and substrate. Clearing all the hurdles in terms of technology and phys-

▷

The principle of the laser

In a laser medium, most of the atoms and molecules are in a largely de-energized state. If energy is pulsed into the medium, in the form of a light source or an electrical discharge for example, the atoms become energized, transforming to an excited state. This energy can be released by exciting them with suitable photons. The parallel mirrors at each end reflect the light back and forth. The photons then encounter other excited atoms and molecules and cause them to release their energy. More and more photons are cumulatively released in this way. The laser beam composed of parallel light waves is then emitted through one of the end mirrors, which is semi-transparent.



ics takes years of detailed work and a great deal of practical experience in this area. So it is particularly important to Finley that all the key equipment for producing and testing the nanostructures is available at the institute. “That is a major advantage. We’ve been able to grow, process, structure and measure the wires right here on site. No need to wait until a collaboration partner can deliver samples – we are in the advantageous position that we can do it all ourselves. That means we can be innovative and react as quickly as possible to new requirements. If something doesn’t work, we can tailor the properties of the nanowire and try again.” The WSI researchers also work closely alongside the Nanosystems Initiative Munich (NIM) excellence cluster: “Nanoscience is exceptionally well established here in Munich, and one simply cannot overestimate the advantages of this strong base of expertise and capabilities,” emphasizes Finley.
Beyond computing, the nanowire lasers also have the potential to advance other fields, for instance providing a compact light source for biophysics or in environmental and biosensor applications. And the team has already received initial inquiries about using them as a tool in microsurgery or dentistry. However, Jonathan Finley is proceeding with caution: “I told them we’re not at a point where we could sell anything yet – that might still take another couple of years.”

Brigitte Röthlein

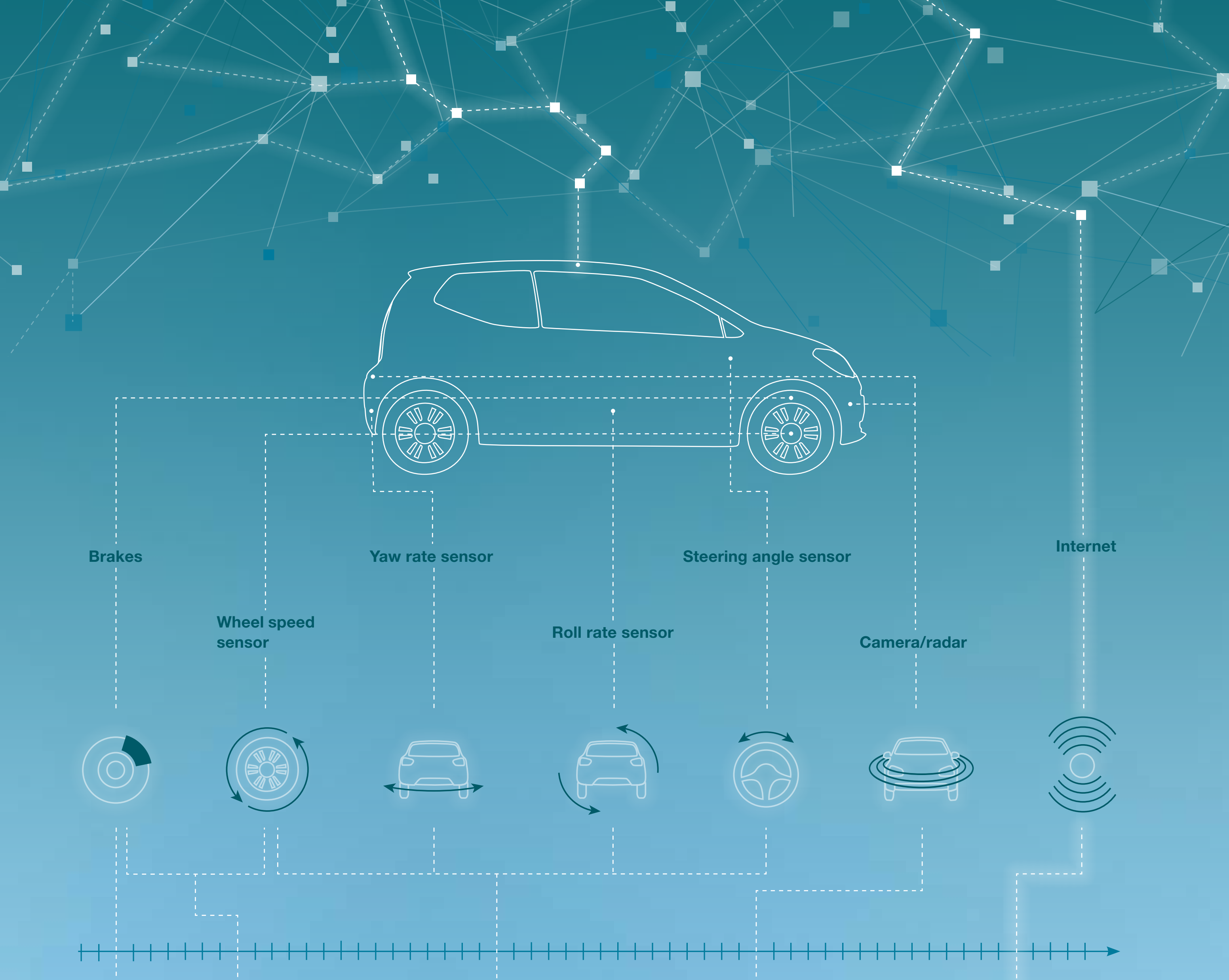
Professor Jonathan Finley and his team were among the first scientists to produce semiconductor nanowire lasers in the near infrared spectral range. Such nano-photonic technologies could pave the way toward chip-level optical information processing devices for future optical computers. Moreover, they also provide potential for use as a nanoscale light source that could be used in other fields, such as biophysics and nanoscale photonic sensing

Picture credit: Filser

Connecting **the World**

In future, everyday objects will be linked via the Internet, enabling them to interact autonomously. To realize this vision, computer scientists are developing virtual models they can use to test practical implementation and monitor the security, safety and reliability of connected systems

Graphics: ediundsepp / picture credits: fotolia.com – anbp, ehrenberg-bilder, imagedb.com, tournee, Denys Prykhodov, Luana R., fotohansel / photocase.de – Mr. Nico



Past
Mechanical
brake

1978
Reactive
brake
control

1995
Active
brake
control

2003
Autonomous
brake action
possible

Future
Brakes act
autonomously
and are
remote-controlled

Anti-lock Braking System (ABS)

One embedded system controls the brakes to prevent the wheels from locking up

Electronic Stability Program (ESP)

Several embedded systems monitor the driving behavior. They control the motor and the brakes at every wheel independently in order to keep the car stable

Active Brake Assist (ABA)

Several embedded systems monitor the driving behavior and the car's surroundings. They detect dangerous situations, warn the driver and automatically activate emergency brakes

Cyber Physical System (CPS)

The car is online and can autonomously react to incoming information about the road conditions or the traffic situation and thus avoid dangerous situations

Graphics: ediundsepp (Source: acatech, own research)

Die Verknüpfung der Welt

Internet der Dinge – so nannten Experten ihre Vision, Gegenstände übers Internet miteinander zu vernetzen und im Hintergrund agieren zu lassen. Heute sind die Voraussetzungen hierfür weitgehend erfüllt. In modernen technischen Geräten und Maschinen stecken unzählige eingebettete Systeme: winzige Rechner, die mittels Software Daten und Signale verarbeiten oder auf Basis von Sensordaten Zustände überwachen und Prozesse regeln. Forscher möchten diese um Aktoren erweitern und durch Informationstechnik miteinander verbinden: zu sogenannten cyber-physischen Systemen (CPS). Damit entsteht eine neue virtuelle Ebene, die ortsunabhängig intelligente Anwendungen und wissensbasierte Dienstleistungen ermöglicht.

Die Herausforderung für die Informatiker liegt darin, dass verschiedene Lebens- und Arbeitsbereiche miteinander verschmelzen und beim Entwurf von CPS die Komplexität steigt. Deshalb greifen sie auf virtuelle Modelle zurück, die einen Ausschnitt oder eine Situation aus der Realität in abstrahierter Form nachbilden. Der TUM Lehrstuhl für Software & Systems Engineering versucht, die Entwurfsarbeit mit Theorien zur formalen Modellierung von Systemen zu unterstützen, und erprobt darüber hinaus, in welchem Umfang diese dann praktisch eingesetzt werden können.

Zertifizierte Werkzeuge für die Software-Entwicklung

Ziel ist ein Baukasten, der auf einem geprüften mathematischen Regelwerk beruht, aus dem die Software-Entwickler standardisierte Werkzeuge kreieren können. Eines der Werkzeuge, die aus den Arbeiten des TUM-Lehrstuhls hervorgegangen sind, ist Autofocus. Das ist ein Programm, welches die gesamte Entwicklung eines Systems abdeckt und die rechnergestützte Software-Entwicklung unterstützt. Es reicht von der Beschreibung und Analyse der Anforderungen über das Design des jeweiligen Systems, die Software-Validierung und -Verifikation bis zur Codegenerierung.

Pilotprojekt erfolgreich

In einem Projekt mit einem Industriepartner haben die TUM Forscher mithilfe von Autofocus die elektronische Türsteuerung eines führerlosen Zugsystems an Zug– und Bahnsteigzugängen nachmodelliert. Inzwischen hat Autofocus den Praxistest bestanden: Das Programm hat Fehler in der Spezifikation der Türsteuerung nachgewiesen und Schwachstellen aufgedeckt. Als Nächstes soll Autofocus nicht nur Testfälle für die Türsteuerung in bestimmten Situationen erzeugen. Die Forscher werden sich auch ein Software-Programm automatisch generieren lassen, mit dem sie anschließend das echte System testen können. *Evdoxía Tsakiridou*

Link

http://livinglab.fortiss.org
www4.in.tum.de

Connected to the Internet, tomorrow's automobiles will become cyber-physical systems. Take the example of the braking system. Back in the 1970s, the mechanical brake was assisted by a single embedded system (ABS). In the next stage of brake evolution (ESP), several embedded systems worked together to keep the vehicle stable. Since the start of the millennium, automobiles have been able to react autonomously in the event of an emergency, thanks to the active brake assist (ABA) feature. This system uses cameras or a radar to monitor the immediate surroundings and apply the brakes if the vehicle is too close to another object. In the future, automobiles will be able to exchange information with other vehicles via the Internet. This will enable them to pre-empt situations or events that they have not yet detected – such as a slippery road surface 100 meters ahead

The conveyor belt stops in front of a filling machine. A hose descends and the plastic container below it promptly fills up with pink liquid. It then moves on to the next station, where the bottle is fitted with a pump dispenser and sealed. Meanwhile, a yellow liquid is now flowing into the next container at the filling line.

In this liquid filling plant, production is effectively driven by the product. Every product package is equipped with an RFID chip that acts as an electronic label, communicating with machines and the control center. It is able to "tell" them what each bottle should contain (pink handwash or yellow dish detergent), which packaging is required, which container the product should go in and when the product must reach the wholesaler at the latest.

Future factories are part of a large network

In the factory of the future, products are active information vehicles and equipment is networked. People and machines work together. Assistance systems display steps on a monitor for staff to follow. Components communicate with ▷

Theoretical groundwork for the development of complex software systems is the subject of Professor Manfred Broy's research. Manfred Broy heads the Chair for Software & Systems Engineering at TUM's Informatics Department. He is engaged in several initiatives for the advancement of technologies based on cyber-physical systems: As a member of the scientific advisory board of Plattform Industrie 4.0, a German initiative for the advancement of Industry 4.0 technologies, and as a member of the information and communication technologies network of acatech, the German national academy of science and engineering

machines and transmit data on their current status. Usage and sensor data is analyzed in real time, allowing faults or wear and tear to be predicted and prevented. All this, in turn, optimizes the production process, increases capacity utilization and improves product quality. In the future, plants will only produce what has actually been ordered. And customers will receive tailored goods, such as T-shirts or sports shoes, at mass-production prices.

The evolution from embedded to cyber-physical systems

At present, this scenario is still a vision, named Industry 4.0 in Germany's "High-Tech Strategy," referring to the fourth industrial revolution. At the same time, it describes part of the cyber-physical world, in which researchers anticipate that physical objects will be connected via the Internet and able to interact autonomously in the background. Technical devices and machines already feature embedded systems today – tiny computers that use powerful software to process information and signals or harness sensor data for status monitoring and process control. Expanding these systems to include actuators and connecting them up creates a new, virtual environment, enabling smart applications and knowledge-based services independent of location.

Professor Manfred Broy from TUM's Informatics Department gives a good example: "A car is currently a closed physical system, complete with electronic controls and embedded software. If, however, it communicates over a network to warn drivers behind about an accident or a patch of ice, it becomes a cyber-physical system."

Experts predict that, in the future, information and communication technologies will link up isolated physical systems in our everyday and working lives. Outlining the evolution from embedded to cyber-physical systems (CPS), the head of the Software & Systems Engineering Chair explains: "Cyber-physical systems are set to gain more and more ground in all areas of life – from intelligent power supply through smart logistics and transportation systems to

▷

Picture credit: Eckert

smart digital homes. And, one day, it will reach the point where systems can control and optimize themselves."

Mastering the complexity of cyber-physical systems

The design of closed physical systems remains relatively straightforward because it focuses on a specific scope. Like building a house, an underlying architecture describes the structures of the overall system – its components (hardware, mechanics, software) and their configuration and interaction, as well as the properties of software elements and the functions to be executed. In a factory, for instance, these structures would include equipment and systems, control and data communication software, transport and storage facilities, and the setup and interplay between these various building blocks during production. The factory turns into a CPS with the additional integration of IT systems connected to the outside world via communication networks. This enables it to interact or join forces with other facilities. If a company receives a major order that requires increased capacity, for instance, it could delegate part of the production work to a subsidiary. It is therefore particularly important that key information – such as instructions for retrofitting equipment, details of the production process, new measured values and set points, etc. – can be exchanged reliably and in real time between facilities, even if the network is overloaded.

From a technical perspective, CPS merges the previously discrete disciplines of machine building, electrical engineering and information technology into an overarching system of systems, forming ecosystems. The result is a dramatic increase in complexity, as the various domains intertwine. When buying a T-shirt via the Internet, for instance, this would apply to plant and production planning, the communication network and energy supply, the online shop, production status, and shipment tracking for the customer. Researchers are thus grappling with a raft of issues: What might CPS architectures look like? How should the human-machine interface be designed? And, last but not least, development and technical implementation pose plenty of challenges on the engineering side.

Smart grid architecture

Researchers at fortiss, a Munich-based institute affiliated with TUM, are investigating a possible cyber-physical architecture concept for an intelligent power network. In the Smart Energy Living Lab project, whose other participants include municipal utilities company Stadtwerke München, the fortiss office building functions as part of a decentralized network with a photovoltaic system on the roof. Staff members can use an app to call up data on power generation and consumption, while also receiving notifications about open windows or doors and energy-saving tips.

"We are in the process of developing a software architecture for a virtual power plant, joining up small local producers to form a large collective utility," reports project leader Dr. Markus Duchon. However, connecting producers and consumers and bundling several smaller storage batteries into a virtual interim storage solution for surplus green electricity is only part of the story. The IT specialists are also looking for mechanisms that will stabilize the network if a system is down or consumption suddenly increases. "The solution lies in pooling the various power sources into self-organizing groups," describes Duchon. An optimization program calculates the set values for each individual system based on a target for the overall cluster. The control center no longer needs to intervene as management of the individual systems has been dropped down. This hierarchical structure reduces the data traffic as well as control and optimization effort. At the same time, the flexibility and scalability of the network increases.

Standardized tools

To date, the disciplines mentioned have relied on their own (virtual) models when planning their specific systems. These models provide an abstract simulation of a real-world moment or situation, describe the properties of the required system and create a design blueprint. However, harmonized interplay between mechanical and electronic systems and software can only be checked once the final product is available. If it transpires that this interplay is not working as planned, subsequent reintegration can be extremely complex.

> *"Cyber-physical systems are set to gain more and more ground in all areas of life – from intelligent power supply and smart logistics and transportation systems to smart digital homes. And, one day, it will reach the point where systems can control and optimize themselves."* *Manfred Broy*

Researchers believe the solution lies in developing a comprehensive system model to support these three disciplines. This integrated approach brings two worlds together, merging abstract IT models for information processing with physical models focused on space and time. The challenge lies in modeling applications that fulfill precise, real-time requirements (such as in a chemical plant, in which all parameters and processes must be observed exactly) and run via dynamic communication networks whose behavior is modeled based on probabilities.

"Essentially, we develop theories into formal system models and examine to what extent their practical implementation is feasible," explains Broy, outlining his research focus. Developing new, computer-based design methods for networked technical systems is another priority – on one hand to reduce complexity, and on the other to devise and test new functions.

In their efforts to implement cyber-physical systems, the TUM researchers are able to draw on groundwork for model-based development of embedded systems. Backed by Germany's Federal Ministry of Education and Research (BMBF), a joint project with partners in science and industry aims to develop a software platform for embedded systems (SPES) by 2020.

Theories for formal system models

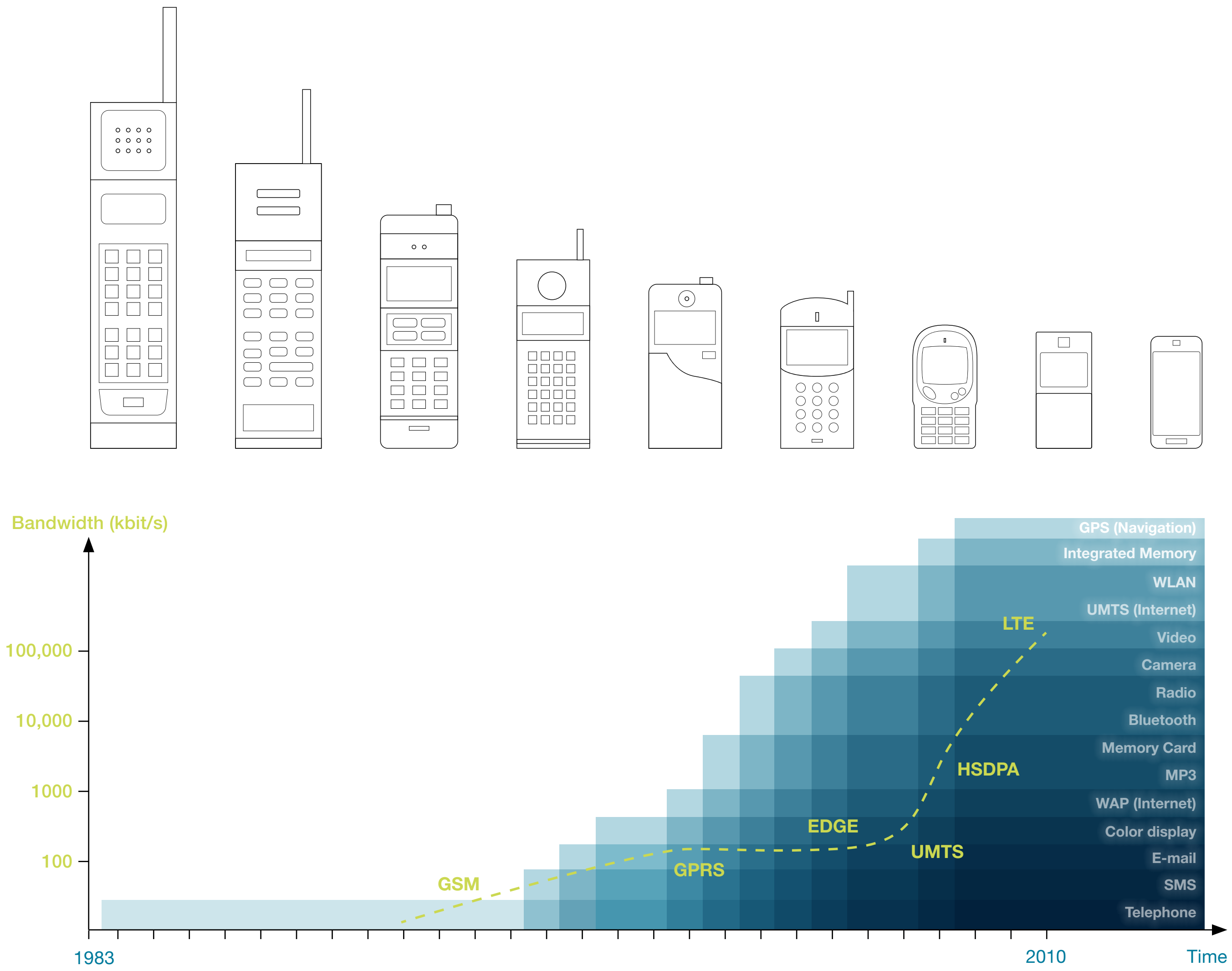
In the same way that bricklayers, plumbers and electricians all refer to the same plans when constructing a new building, the aim is to incorporate information from the three disciplines here into a shared underlying model. Ideally, the result will be a design kit based on a verified mathematical – and thus reliable – set of rules. Developers can then use this to create standardized tools, for instance to generate program codes for individual systems or analysis and inspection methods, or for upstream testing of software and components.

One of the tools to emerge from this Chair's efforts is a program called Autofocus, which extends along the entire ▷

Picture credit: Eckert

Human interaction with cyber-physical systems: In the future, networked software services will shape just about all aspects of our lives. We will use Web-based services to do everything from arranging to go for a drink with friends through working out how best to get there to checking that everything is OK back at home. These services will have access to our data, working out the shortest route for hay fever sufferers, automatically activating our home automation systems, or transmitting blood work details to our doctor to support long-term therapies

Graphics: ediundsepp



Highly capable mobile devices are one of the prerequisites for the future trend toward cyber-physical systems. Within 30 years, mobile phones developed from devices that were 30 cm long and offered 30 minutes of talking time to smartphones that feature many standard computer functions

development cycle of a system and supports computer-aided software development. It covers everything from describing and analyzing requirements and designing the actual system to software verification and validation, code generation included.

In a project with an industry partner, TUM researchers used Autofocus to replicate the electronic door control functionality of a driverless train on arrival and departure. In other words, it looked at train and platform access. “We wanted to find out whether the formal model behind Autofocus would work, so we put the tool and our methods to the test with a concrete application,” reports project leader Dr. Wolfgang Böhm. As a first step, the participants used Autofocus to convert the technical description or specification of the door control system – for instance, exactly when and how long the doors should open – into a formal language. The next, computer-assisted stage involved modeling the functional architecture to describe system behavior and operation in relation to the environment, but disregarding internal design.

Autofocus – a successful pilot project

“The tool helps reduce complexity and makes it quicker for users to identify errors. That means we are contributing to a product’s quality right from the beginning of development,” emphasizes Böhm. Autofocus passed its field test with flying colors, detecting errors in the automatic door control specification and discovering and exposing vulnerabilities. The industry partner was able to review their system architecture as a result. In the research project now under way, the project partners will derive test cases for the door control system in specific situations and use Autofocus to automatically generate a suitable software program, which they can then use to test the real system.

Evdoxía Tsakiridou

Graphics: ediundsepp

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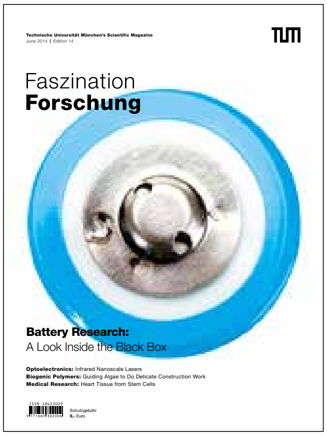

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Imprint

Faszination Forschung
Technische Universität München’s Scientific Magazine
Sponsored by the Excellence Initiative of the German federal and state governments

Publisher
Prof. Dr. Dr. h.c. mult. Wolfgang A. Herrmann, President
of Technische Universität München
Editorial Office
Tina Heun-Rattei (Editor-in-chief),
Dr. Christine Rüth (Managing Editor)
Translations
Capella & McGrath GmbH, München
Copy-editing
Angela Obermaier / Baker & Harrison
Design
ediundsepp Gestaltungsgesellschaft, München
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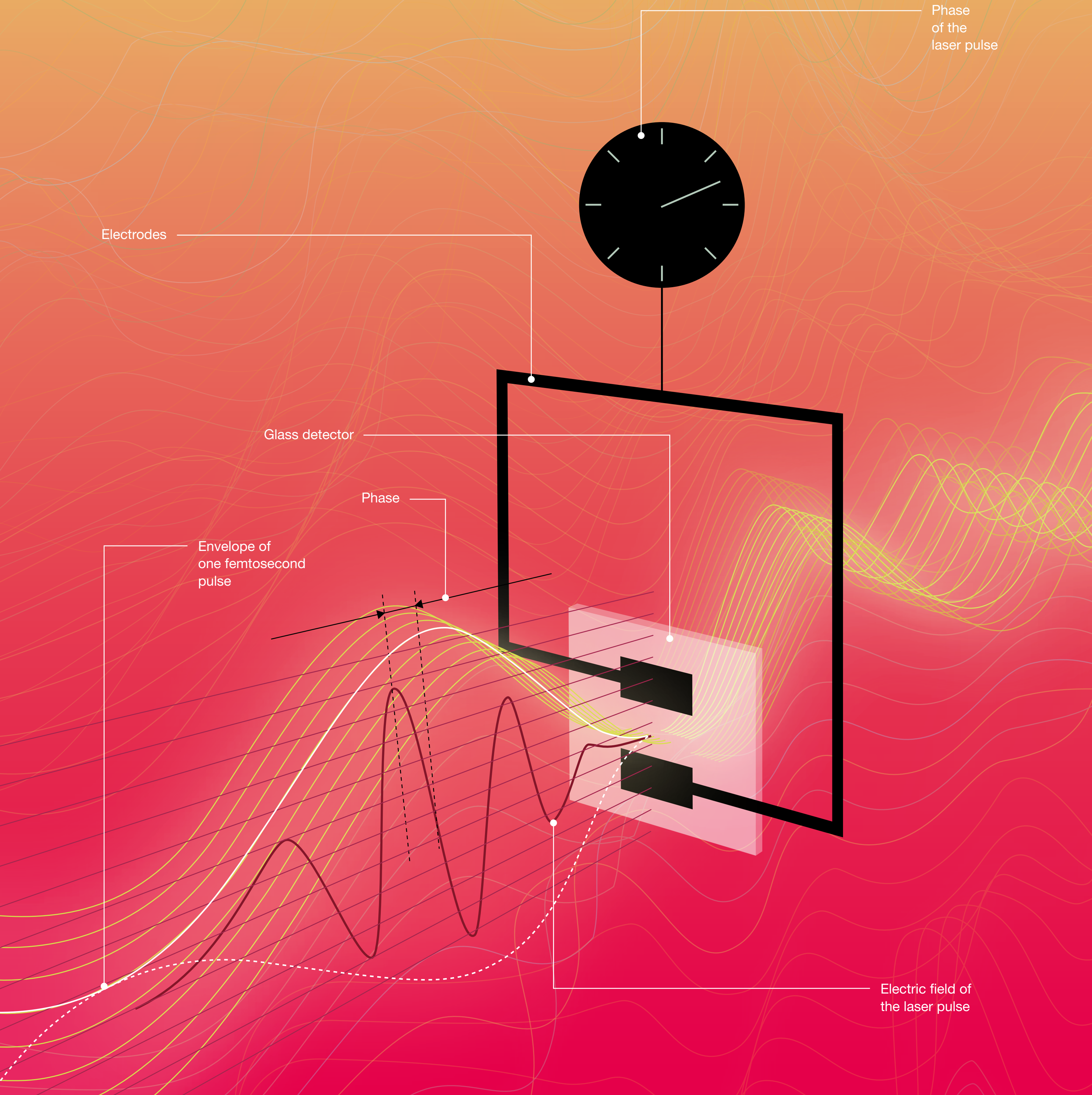
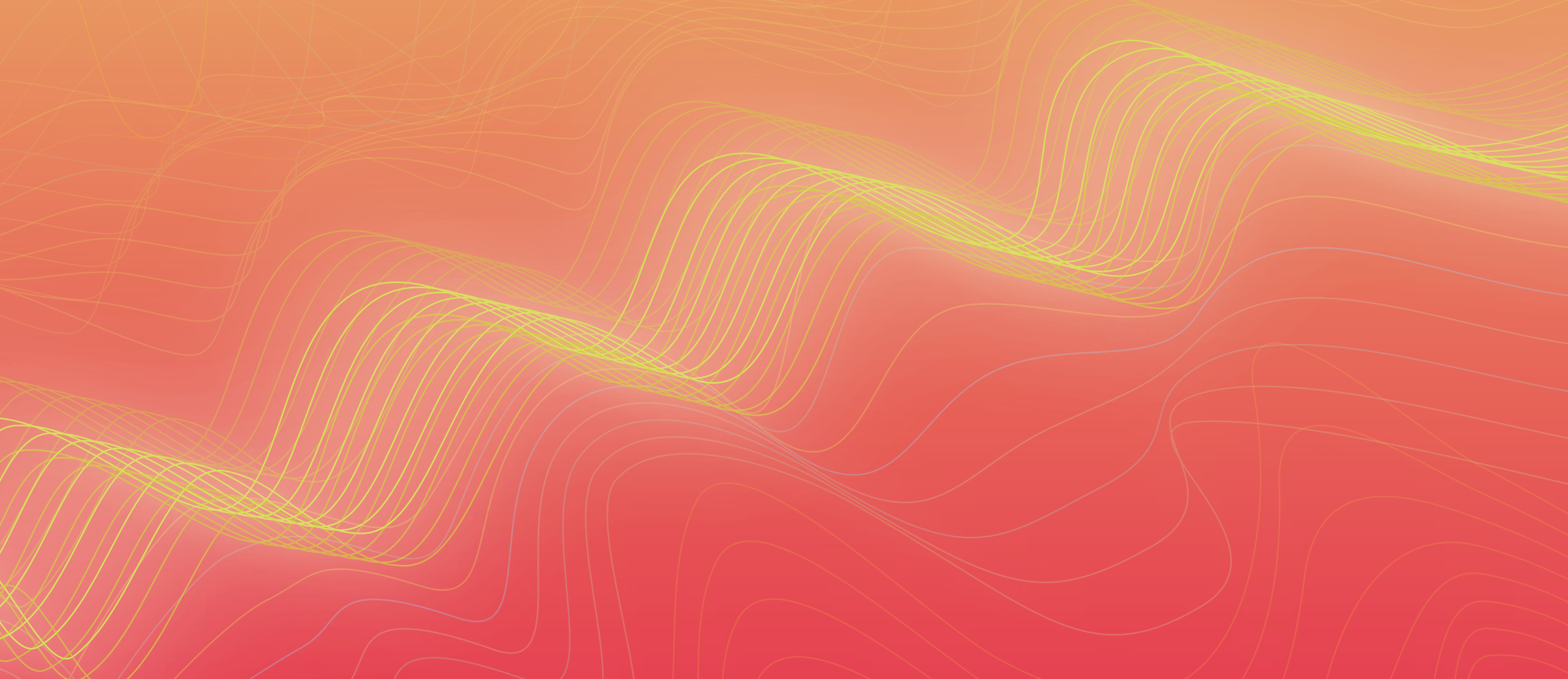
Address of the Editorial Office
Technische Universität München, Corporate
Communications Center, 80290 München
E-Mail
faszination-forschung@zv.tum.de
Printing
Druckerei Joh. Walch GmbH & Co. KG, Augsburg
Circulation
45,000
ISSN: 1865-3022
Frequency
Twice a year
Responsible for the editorial content and advertisements
Tina Heun-Rattei
Photographers
Astrid Eckert, Andreas Heddergott, Kurt Bauer, Werner Bachmeier
Wolfgang Filser
Cover picture
ediundsepp

Link
http://www.attoworld.de/ http://www.e11.ph.tum.de



Toward Perfect Control of Light Waves

Scientists developed a glass detector, which helps them determine the waveforms in a femtosecond laser pulse. These insights are the key to generating even shorter attosecond light pulses, which are used to study extremely fast processes taking place at atomic levels



Graphics: ediundsepp (Source: Hackenberger/LMU)

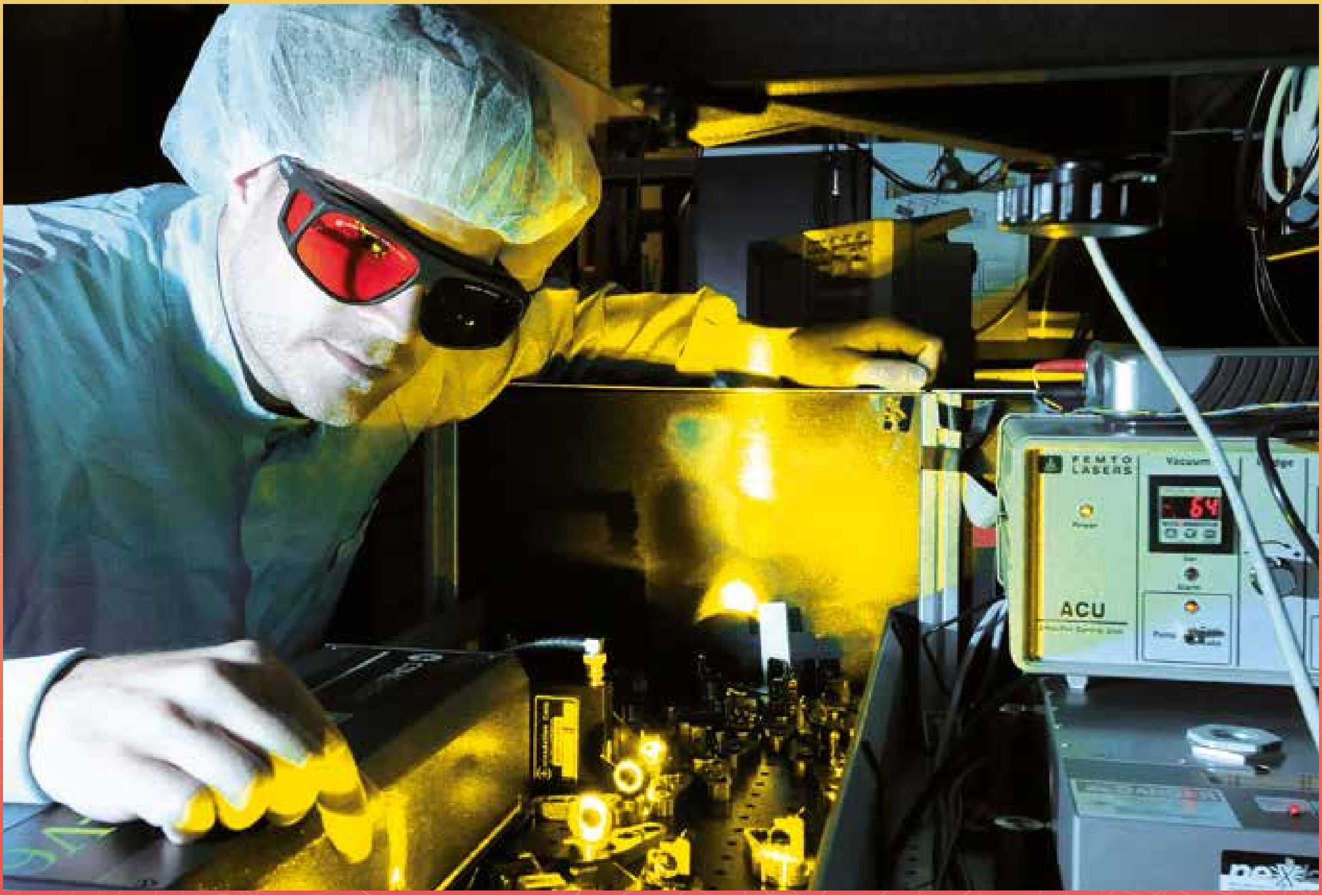
A team at the Laboratory for Attosecond Physics (LAP) has constructed a detector, which provides a detailed picture of the waveforms of femtosecond laser pulses (1 fs = 10^{-15} seconds or one millionth of a billionth of a second). Knowledge of the exact waveform of these pulses enables scientists to reproducibly generate light flashes that are a thousand times shorter – lasting only for attoseconds – and can be used to study ultrafast processes at the molecular and atomic levels. The team included scientists from Technische Universität München (TUM), Ludwig-Maximilians-Universität (LMU), the Max Planck Institute for Quantum Optics and further cooperation partners.

High-intensity laser pulses induce electric current

Modern mode-locked lasers are capable of producing extremely short light flashes that last for only a few femtoseconds. In one femtosecond light, which rushes from the Earth to the Moon in just one second, advances only three ten-thousandths of a millimeter. Such short pulses consist of only one or two oscillations of the electromagnetic field, which are preceded and followed by waves of lower amplitude that are rapidly attenuated. For them to be utilized in an optimal manner to probe ultrashort processes that occur at the level of molecules and atoms, it is important to know the precise form of the high-amplitude oscillations.

The team of scientists at the Laboratory for Attosecond Physics at the Max Planck Institute for Quantum Optics (MPQ) has now developed a glass-based detector that allows accurate determination of the form of the light waves that make up an individual femtosecond pulse.

In the course of experiments performed over the past several years, physicists in the group led by Professor Ferenc Krausz (MPQ/LMU) and Professor Reinhard Kienberger (TUM) have learned that, when pulsed high-intensity laser light impinges on glass, it induces measurable amounts of electric current in the material. Krausz and his colleagues have now found that the direction of flow of the current generated by an incident femtosecond pulse is sensitively dependent on the exact form of its wave packet. In order to calibrate the new glass detector, the researchers coupled their system with a conventional instrument used ▷



A mode-locked laser at the Max Planck Institute of Quantum Optics emits flashes of light that last for a few femtoseconds. A new glass-based phase detector now enables simpler and more precise control of their waveforms

to measure waveforms of light. Since the energy associated with the laser pulse is sufficient to liberate bound electrons from atoms of a noble gas such as xenon, the "classical" detector measures the currents caused by the motions of these free electrons. But there is a catch – the measurements must be done in a high vacuum.

Enormously reduced measurement efforts

By comparing the currents induced in the new solid-state detector with the data obtained using the conventional apparatus, the team was able to characterize the performance of their new glass-based setup, so that it can now be used as a reliable phase detector for few-cycle femtosecond laser pulses. The new instrument enormously simplifies measurements in the domain of ultrafast physical processes, because one can dispense with the use of cumbersome vacuum chambers. Moreover, in its practical application, the technique is much more straightforward than the methods previously available for the mapping of waveforms.

Reproducible generation of attosecond light flashes

If the precise waveform of the femtosecond laser pulse is known, it becomes possible to reproducibly generate stable trains of ultrashort attosecond light flashes, each one a thousand times shorter than the pulse used to induce them. The composition of the attosecond flashes is in turn highly dependent on the exact shape of the femtosecond pulses. Attosecond flashes can be used to "photograph" the motions of electrons in atoms or molecules. In order to obtain high-resolution images, the length of the flashes must be tuned to take account of the material one wants to investigate.

Highly sensitive and reliable measurements of physical processes at the level of the microcosmos with the aid of single attosecond light flashes of known shape should become easier to perform because, thanks to the new glass-based phase detector, the source of the energy to drive them – the waveform of the laser pulses – can now be controlled much more easily than before.

Thorsten Naeser (MPQ) and Andreas Battenberg (TUM)

Picture credit: Naeser/MPQ/Graphics: ediundsepp

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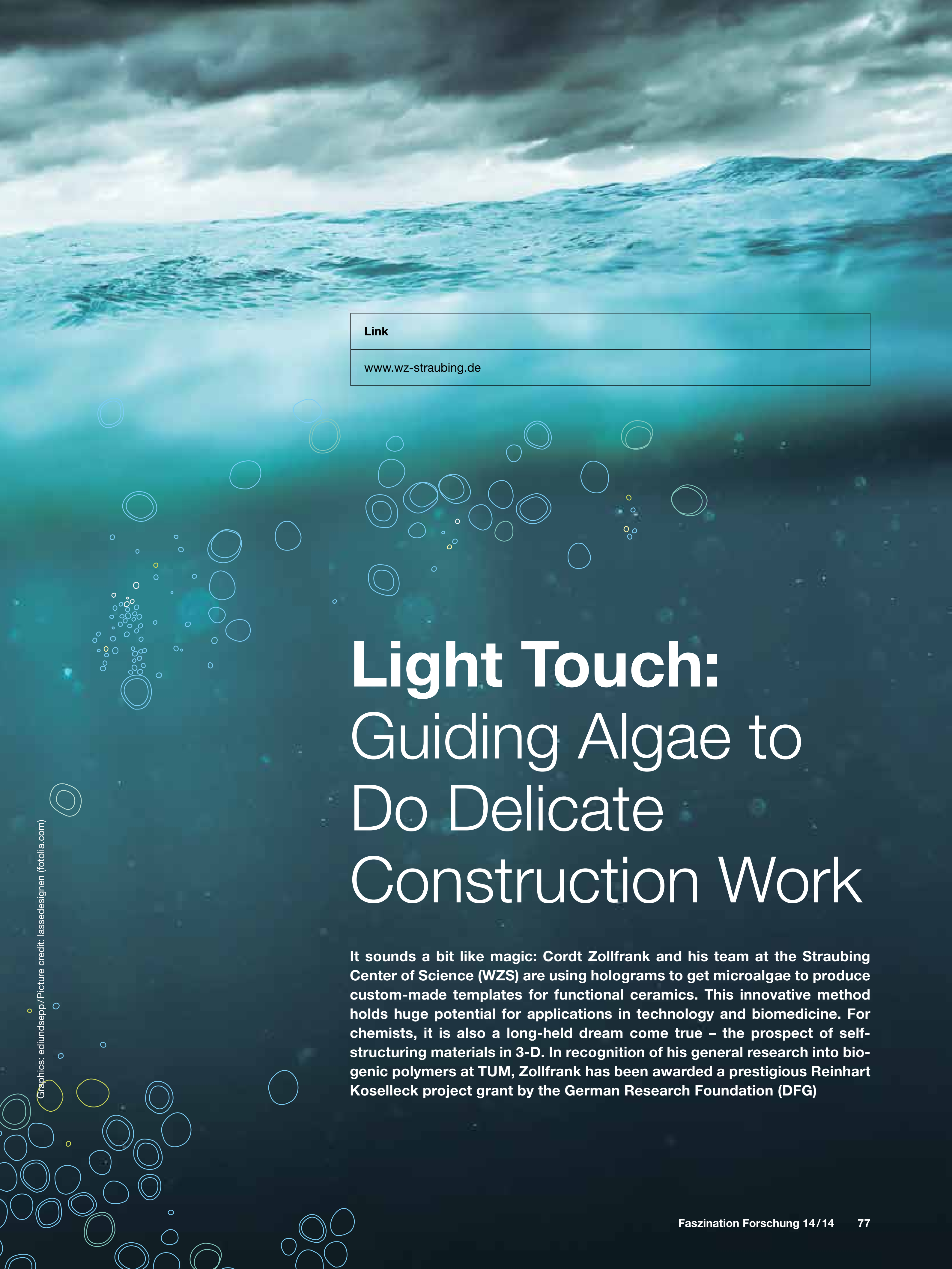

Light Touch: Guiding Algae to Do Delicate Construction Work

It sounds a bit like magic: Cordt Zollfrank and his team at the Straubing Center of Science (WZS) are using holograms to get microalgae to produce custom-made templates for functional ceramics. This innovative method holds huge potential for applications in technology and biomedicine. For chemists, it is also a long-held dream come true – the prospect of self-structuring materials in 3-D. In recognition of his general research into biogenic polymers at TUM, Zollfrank has been awarded a prestigious Reinhart Koselleck project grant by the German Research Foundation (DFG)

Link
www.wz-straubing.de

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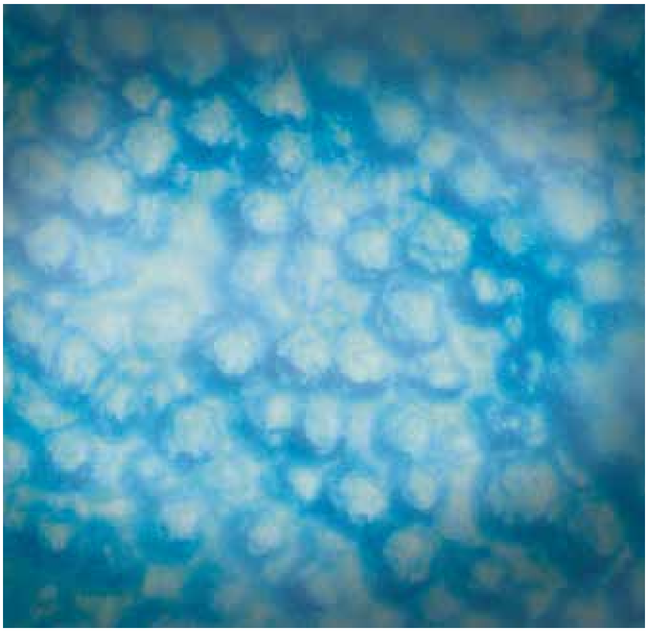
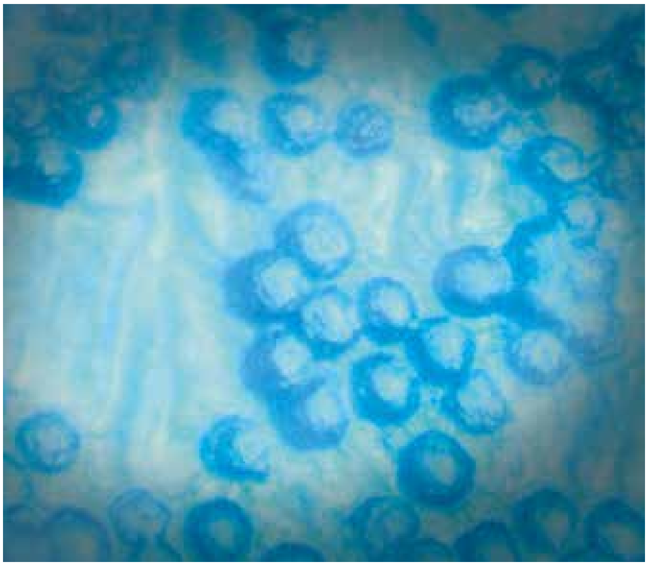
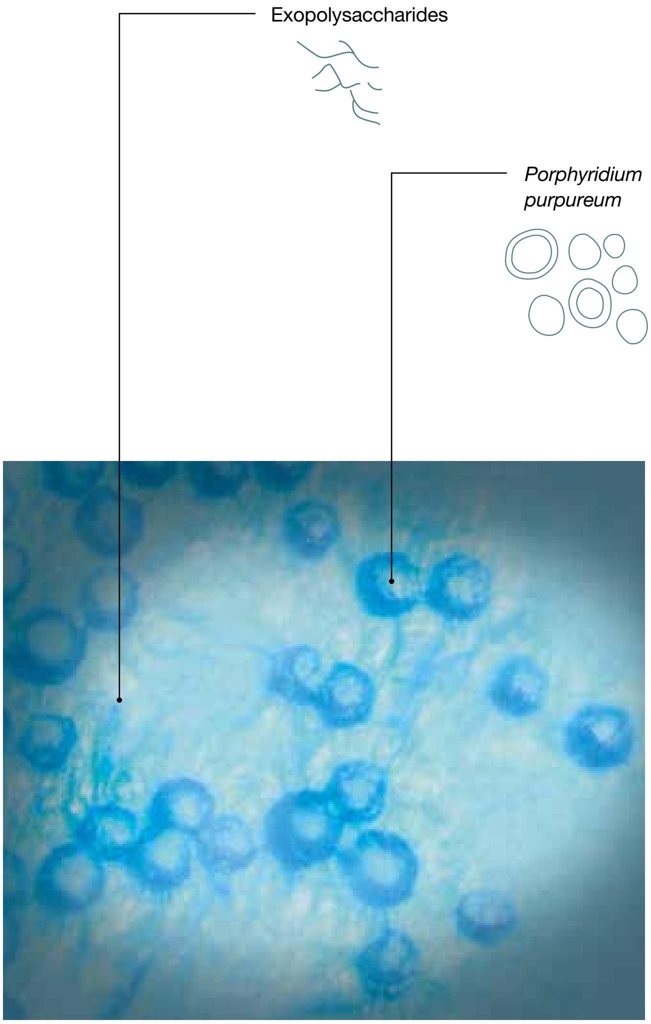
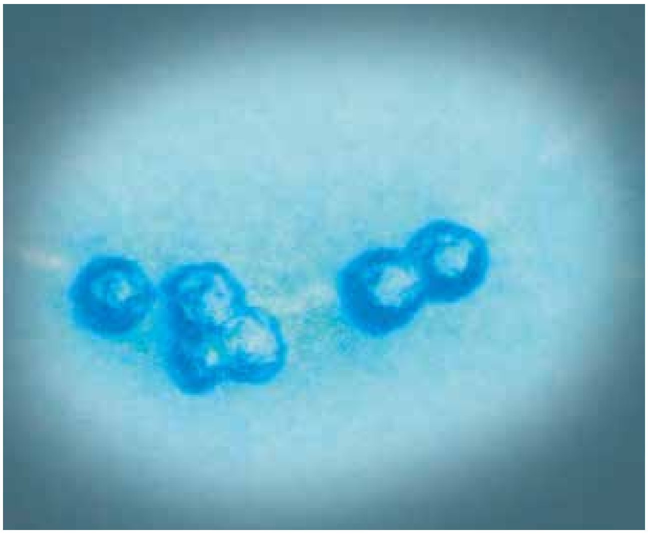
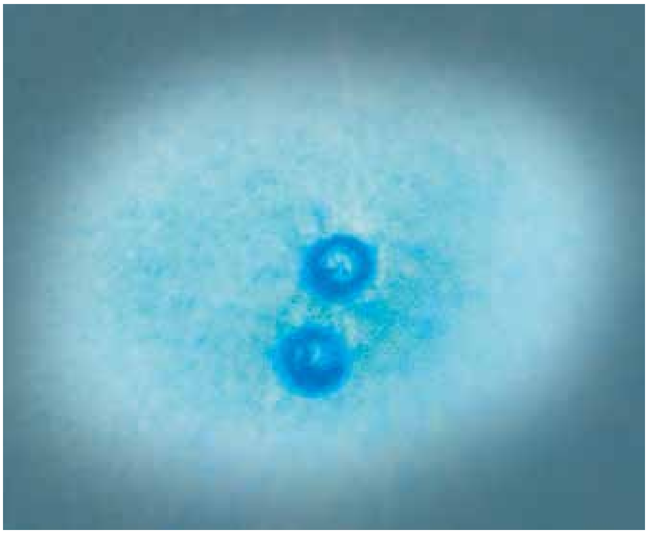


Tiny colonies of the red microalga *Porphyridium purpureum* surrounded by exopolysaccharides (EPS). These are excreted by the red algae during phototaxis, i.e. when they are moving towards the light. The resulting 3-D EPS structures serve as a template for the subsequent conversion into inorganic materials









Picture credits: TUM

Baumeister Licht: filigrane Algenkonstruktionen

Prof. Cordt Zollfrank und sein Team entwickeln am Wissenschaftszentrum Straubing (WZS) ein Verfahren, in dem die Forscher mit Hologrammen Mikroalgen dazu bringen, maßgeschneiderte Schablonen für Funktionskeramiken zu produzieren. Der innovative Ansatz verspricht großes Potenzial für Anwendungen in Technik und Biomedizin. Nebenbei erfüllt sich ein alter Chemikertraum: Material berührungsfrei in drei Dimensionen zu strukturieren. Für seine Grundlagenforschung erhielt Zollfrank mit seinem Fachgebiet Biogene Polymere der Technischen Universität München (TUM) von der Deutschen Forschungsgemeinschaft (DFG) eines der renommierten Reinhart Koselleck-Projekte.

Bioinspirierte holografische Materialsynthese

Die Forscher machen sich zwei Eigenschaften der Purpuralge zunutze: Der Photosynthese betreibende Mikroorganismus bewegt sich stets in Richtung des Lichts und sondert dabei Vielfachzuckerstrukturen ab. Die von der Alge hinterlassene dünne Makromolekülstruktur dient als Matrix, die über chemische Prozesse in Keramik umgewandelt werden kann. Die Vision des Projekts: Setzt man entsprechende Lichtreize, können mithilfe der Algen Werkstoffe in beliebig vielen Formen maßgeschneidert werden. Das Potenzial zur Erzeugung komplex strukturierter Materialien für bestimmte Einsatzgebiete ist enorm: von Elektroden für Batterien über Bestandteile von Spezialfiltern in der Wasserreinhaltung und neue Bildschirm- und Displaytechnologien bis hin zu Knochen- und Gewebeersatz. Wegen ihrer Formenvielfalt und ihrer Fähigkeit zum Selbstaufbau bezeichnet Zollfrank Polysaccharide als den idealen nachwachsenden Rohstoff für keramisches Funktionsmaterial. *Karsten Werth*

Bioinspired material synthesis using holograms – how would you even come up with the idea? “Our research area is biopolymers – or, to be more precise, the production, processing and properties of bioplastics,” explains Professor Cordt Zollfrank. “We develop ceramic materials with new structures and functions. Conventional production methods limit the assembly options for ceramics, so generating finer structures calls for an innovative, bioinspired approach.”

As a chemist and a forestry and materials scientist, Zollfrank has been working with biological materials for quite some time. After taking up his professorship at TUM in October 2011, he continued developing his concept of synthesizing materials using holograms and was able to convince the DFG to fund this new approach as part of its Reinhart Koselleck project program. Zollfrank is keen to emphasize that, alongside the innovative concept and his own track record, the excellent research infrastructure at the Straubing Center of Science was a key success factor in securing the funding. Here, six Bavarian universities cooperate within a TUM-led center of excellence for renewable resources, benefiting from excellent links with business and politics. The various labs work closely together and actively foster interdisciplinary exchange.

Over the next five years, 1.25 million euros will be available to fund a research group working on this visionary project. “This level of backing for higher-risk endeavors is very rare in the German research landscape,” underscores the 45-year-old researcher. “We are enjoying a high level of freedom here.” Alongside Zollfrank, “we” so far refers particularly to Daniel Van Opdenbosch, who recently completed his doctorate with distinction under Zollfrank’s supervision and is now setting up the new research group.

Inspired by nature

The field of biogenic polymers is – literally – all about natural science. Researchers work with any natural substance composed of biological macromolecules (biopolymers) – cellulose, polysaccharides, and collagen – and use them to develop bioplastics. In some cases, these have already been commercially adopted, one example being the wood-plastic composites now widespread in the construction sector as a replacement for tropical timber in outdoor decking. Biodegradable compounds are also available on the market, used for instance in plant pots made of elephant grass (miscanthus), which break down in the ground after the plants take root. But the TUM researchers are taking all this a giant step further. One of their focus areas is biotemplating – the transfer of biological structures to inorganic materials. By way of illustration, Zollfrank places a piece of rattan on his office table. The cross-section of this palm cane, extremely popular with furniture makers, reveals its porous structure – which offers astonishing possibilities. To start with, the rattan is heated in an inert atmosphere and converted into wood charcoal. A ceramic material is generated from this by infiltrating the carbon bodies with silicon heated to over 1400 degrees Celsius. This triggers the formation of silicon carbide, a heat-resistant substance that has also featured in the black protective tiles on space shuttles. In terms of the substance itself, this laboratory-generated ceramic is now far removed from rattan. But the new material completely mimics the rattan’s structure, albeit in slightly contracted form. The reward for all this effort lies in the detail, as Zollfrank reveals: “This method enables us to produce ceramics from naturally occurring, micron-sized structures. Silicon carbide is the second-hardest material in existence after diamond. You can’t even drill holes in that, no matter how small.”

Ceramic pine cones

The researchers are investigating both the structure and functionality of biogenic materials. Pine cones are one of the objects of interest here, and specifically the way they open and close in response to the surrounding air humidity. The interesting objective is that this motion is not due to cell metabolism but solely to material properties. The researchers are keen to gain an understanding of this type of process, allowing them to generate synthetic materials with similar functionality. One such example might be blinds on office windows that open and close themselves depending on the sun’s rays, without the need

▷

Picture credit: Bauer

Researchers from the field of biogenic polymers examine the quality of miscanthus (elephant grass). Besides its interest to applied archaeologists, miscanthus is also a valuable source of biomass. Working closely with local farmers (Martin Soetz, Pfatter) who grow this grass, researchers are busy exploring its full application potential

Taking advantage of highly efficient, natural microstructures: One focus area of Zollfrank's group is biotemplating, a method for the transfer of biological structures into inorganic materials. Here, researchers are inspecting wood samples for biotemplating. The process yields a ceramic with hierarchical, nanometer-precision replication of the wood's structure

Picture credit: Bauer

for electric operation. However, Zollfrank is careful not to raise undue expectations: “We still have a long way to go until we’ll really be able to build inorganic actuators.” Still, the foundations have already been laid: it transpires that, when the pine cone is converted into ceramic, not only the macrostructures in the wood, but even the nanoscale structures related to the microfibrils in the cell walls can be retained in the inorganic material. Summing up the main thrust of his research, Zollfrank declares: “We are looking to learn from nature as we work out what functional and design principles would be most useful for new materials. It is fascinating to take biological properties such as adaptation, self-organization, self-healing and energy autonomy and transfer them to ceramics.”

Harnessing phototaxis

The red microalga *Porphyridium purpureum* plays a key role in this new Reinhart-Koselleck project, granted funding in November 2013. The WZS researchers are exploiting two properties of these algae. Being photosynthetic microorganisms, they always move toward the light (phototaxis), and they secrete exopolysaccharides in the process. The fine macromolecular structures left behind during algal phototaxis serve as a matrix that could be transformed into ceramic, for instance. The vision shared by Zollfrank and Van Opdenbosch is that, if they can manage to manipulate the microalgae to produce one single template, they can probably adjust them to create any number of customized forms by applying the appropriate light stimuli. The researchers had already taken an important step prior to the DFG’s backing by using chemical processes to coat the microalgae with lead zirconium titanate (PZT), a piezoelectric ceramic. If these formations are heated to temperatures of 500 to 600 degrees Celsius, all organic matter is eliminated and what remains are hollow ceramic

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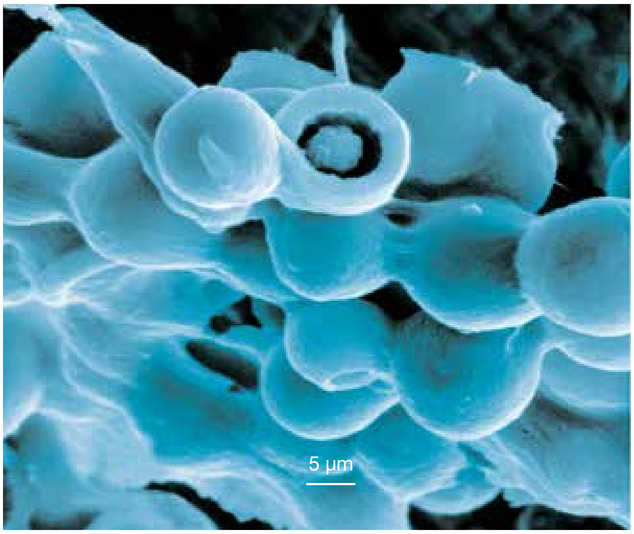

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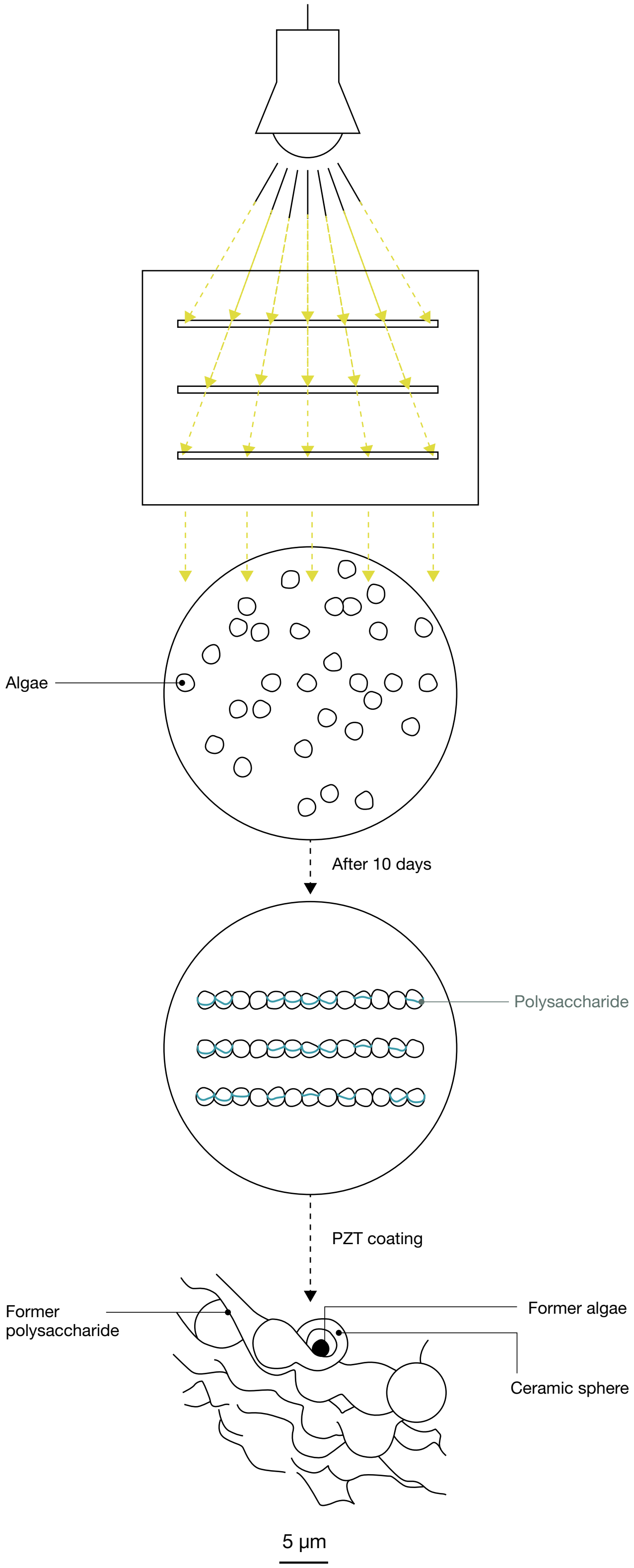

Finest structures created by algae: Light guides the growth of red microalgae, which secrete polysaccharides during the process. The researchers have managed to coat these structures with lead zirconium titanate (PZT), a piezoelectric ceramic. The formations are then heated to 500-600°C to eliminate all organic matter. The result is a structure made of hollow ceramic spheres

spheres. The next step was to solve the challenge of how to construct two-dimensional models from polymers. They accomplished this via an experiment that involves shining light through a mask into a Petri dish inoculated with the microalgae. After a certain amount of time, the microalgae align themselves with the pattern of the penetrating light.

Looking ahead, Van Opdenbosch explains: “The last, critical question is whether we will manage to construct a three-dimensional framework from polysaccharides – will phototactic structuring with microalgae succeed?” The plan devised by the researchers for bioinspired holographic synthesis is intended to work like this: A laser beam is directed at an object through a mask. This object reflects the light, and the superimposed object beam and reference beam form a hologram. A substrate with a microalgae suspension is placed in the immediate proximity of this three-dimensional light structure. The microalgae should then align themselves with the edges of the hologram and grow along them. After a few days, the culture medium is removed, and what remains should be the polymer structure secreted by the microalgae as they move – a ready-made template for conversion into inorganic material. Adding suitable reactants such as silicic acid or calcium compounds then produces a new substance. “Both the structure of the hologram and the choice of reacting agents for chemical conversion can be varied, so we hope to gain ceramic materials with a wide range of forms and functions,” says Van Opdenbosch. The potential for generating materials with complex structures for specific applications is huge: from electrodes for batteries and components for special water purification filters to new screen and display technologies, and bone and tissue replacements. Their variety of forms and ability to self-assemble leads Zollfrank to describe polysaccharides as the ideal renewable feedstock for functional ceramic materials. As the most common naturally occurring biopolymer, the cellulose they consist of is readily available, and large-scale industrial capacity to process cellulose products is already a given. That, then, is the vision. There are certainly still several issues to resolve – for instance, how the polysaccharide structure produced by the microalgae is to remain stable. The field of biogenic polymers is entering new territory in materials synthesis by generating three-dimensional structures directly from microorganisms. “We are harnessing a real biological principle to synthesize new materials – and there are very few examples of that in research to date,” confirms Zollfrank.

Baking without a mold

A major advantage of biotemplating over other methods of producing materials – such as 3-D printing – is that it enables synthesis of extremely fine structures. The process based on microalgae takes this to an unbeatable new level. Single algal cells are approximately five micrometers in size. The polysaccharide strands they secrete are significantly smaller still, at around a hundred nanometers across, so that we need an electron microscope to see them. This is the scale at which the scientists are building 3-D structures – and solely by means of specific light patterns. A dream come true for chemists, who have long sought ways to produce self-structuring 3-D materials without contact. “It’s like baking without a mold,” concludes Zollfrank. The current project is still in the early stages: equipping the lab, determining the number of participating colleagues and developing an interdisciplinary network for collaboration between biologists, chemists, materials scientists and physicists. Whether the vision will ultimately become reality is not yet clear. “But one thing is certain,” emphasizes Zollfrank: “We’ll learn a great deal along the way. Not just about material synthesis itself, but also about the mechanisms of phototaxis and the use of optical devices.”

Karsten Werth

As a chemist and a forestry and materials scientist, Professor Cordt Zollfrank appreciates the excellent research infrastructure at the Straubing Center of Science, where six Bavarian universities cooperate in the field of renewable resources research

Picture credit: Bauer


Hydraulik
Automation
Werkstofftechnik
440 Entwickler

Picture credit: Evonik Industries AG

Dr. Klaus Engel

Klaus Engel was appointed Chairman of the Executive Board of Evonik Industries AG, Essen, Germany in 2009 and he has been Member of the Executive Board since 2007. Klaus Engel studied chemistry at the Ruhr University in Bochum and received a doctorate there in 1984. He then worked for Chemische Werke Hülsl AG in Marl and Veba AG, Düsseldorf. In 1998 Engel became Managing Director of Creanova Spezialchemie GmbH, Marl and thereafter joined Stinnes AG in Mühlheim an der Ruhr. Since 1999 he has been Member of various Executive Boards: Degussa AG, RAG Aktiengesellschaft and Brenntag AG.

United in Diversity

Defining Integration for the 21st Century

Globalization has broken down barriers and enabled greater personal mobility. Germany must learn to embrace the growing riches of cultural diversity and harness it to drive innovation

Three Latin words appear on the seal of the United States of America. The same words are emblazoned on the crest of Benfica soccer club: “E pluribus unum”, or “one out of many”. The official motto of the European Union has the same idea translated into 24 different languages – the English version being “united in diversity”. There is another term that expresses this idea in a more abstract fashion: integration. How we define this word is crucially important – not just for a soccer team or for Europe, but for the entire globalized world.

New information technologies and the ever-expanding trade in goods and services between continents have transformed our world. Relaxed border controls make it easier to import different products, but also new ideas and lifestyles. This is a good thing, because we will need all kinds of innovations and fresh ideas if we are to solve the challenges of the future: How are we going to feed the planet’s growing population? How are we going to ensure adequate healthcare for all? And how can we conserve our limited resources?

The search for workable answers to these questions is fueling global demand for much-sought-after German products, allowing us to achieve sustainable growth and secure jobs. The rich diversity of cultures, mindsets and ideas that have come to Germany through immigration give us an advantage here. We need our immigrant population all the more in light of a recent study by the Bertelsmann Foundation, which estimated that, without this group, our population would shrink by 20 million by the year 2050, with the number in gainful employment falling by as much as 40 percent.

According to a recent opinion poll by broadcaster ARD, 68 percent of Germans believe that the domestic economy needs to import skilled workers. And 46 percent think that immigration provides more positives than negatives for the country as a whole. Most knowledgeable public commentators agree with these views: the jobs market, and above all the social security system, benefit considerably from the influx of new citizens.

In reality, most German companies have been “united in diversity” for some time now. For Evonik too, it is no longer a question of assimilating “foreign” employees into the workings of a German company. It is more about building understanding and grasping the opportunities presented by diversity. A strong mutual understanding leads to better cooperation, more creative teams and more innovative products. That, to me, is the current meaning of integration.

This perception of integration is also shared by leading universities and academic institutions. Back in 2007, TUM signed the German “Diversity Charter,” documenting its commitment to equal appreciation and acknowledgement of the world’s many individual talents. We also see diversity as a key driver of growth and prosperity. Reaching across cultural and geographic borders, it truly has the “power to create” a forward-looking, open-minded future for all of us. □


IN PQ 549