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TUM

Faszination **Forschung**

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150 Years of TUM
Celebrating the Next Generation of Scientists

Remote Sensing: Watching Cities Grow
Immunology: How Plants Fight Back
Medical Imaging: Getting a Diagnosis from Pixels

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150 Jahre
culture of
excellence

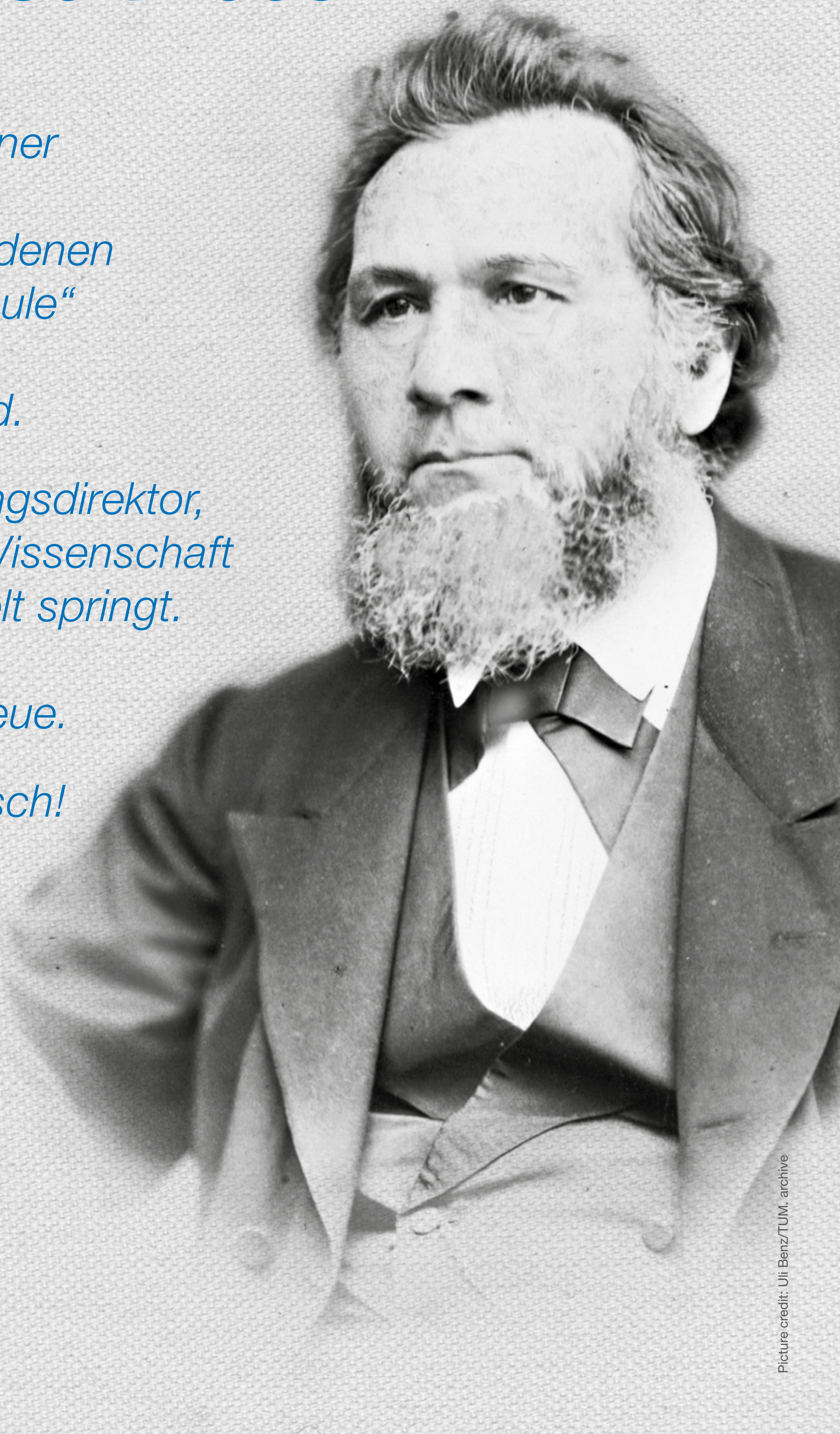
TUM

150 Jahre TUM.
Innovation seit 1868.

*Es war außerhalb meiner
Vorstellungskraft,
dass aus der bescheidenen
„Polytechnischen Schule“
eine internationale
Spitzenuniversität wird.*

*Ich wollte als Gründungsdirektor,
dass der Funke der Wissenschaft
auf die industrielle Welt springt.
Das gelingt der TUM
seither täglich aufs Neue.*

Herzlichen Glückwunsch!



*Karl Max von Bauernfeind
Gründungsdirektor 1868*

Picture credit: Uli Benz/TUM. archive

2018 marks a very special anniversary for us here at TUM. 150 years ago, Ludwig II, King of Bavaria, founded our university. With gratitude, we remember all those people who have shaped TUM and enriched our society with their curiosity and inventive spirit over the years since 1868. What started out as a polytechnic school has grown into one of the world's top-ranking universities.
This anniversary finds our university in good spirits, evidenced by the fact that we can look to the future with optimism and confidence. As a leading research university, we have a key role to play in the quest for solutions to the major challenges of our time: Health & Nutrition · Energy & Natural Resources · Environment & Climate · Information & Communications · Mobility & Infrastructure.

In recent years, we have attracted numerous young scientists from all over the world to tackle these topical issues. Building on their excellent qualifications, they are ideally equipped to think outside the box and look beyond their individual disciplines – which is precisely the approach we foster at TUM. Our Integrative Research Centers, such as the Munich School of Engineering, bring together specialists from a variety of disciplines. Similarly, our TUM Institute for Advanced Study gives leading lights in their field the freedom to try out new ideas, knowing that they could inspire a breakthrough, but also that their endeavors may not be successful. After all, if there is no risk, there is no reward. The TUM Faculty Tenure Track career model offers talented young researchers realistic prospects for advancement to a permanent professorship.

From junior research group leader to tenured professor, many young and excellent scientists are now teaching and researching at TUM. We are delighted to introduce ten of them to our readers in this issue of our magazine.

Bjoern Menze conducts his research at the interface between computing and medicine, "teaching" computers to detect and classify brain tumor indicators based on hundreds of X-ray images. Also seeking new approaches through large-scale data analytics are Stefanie and Kilian Eyerich, whose focus lies on personalized treatment of chronic skin conditions.

Meanwhile, Xiaoxiang Zhu is investigating the impact of urbanization. She uses machine learning algorithms to analyze data from earth observation satellites and social media networks, taking this as the basis for high-precision 4D models of the world's cities. Remaining in the urban environment, Jia Chen is using a new method to track the volume and spatial distribution of greenhouse gas emissions in our cities.

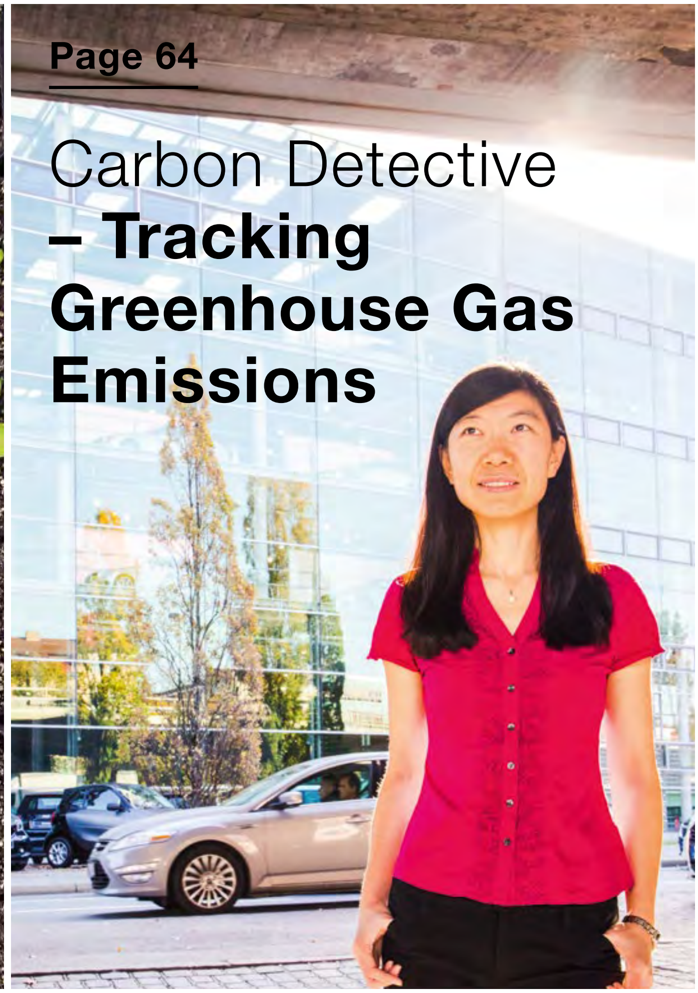
Picture credit: Astrid Eckert/TUM

Next, we step inside the laboratory of Stefanie Ranf, who discovered a receptor that is used by plants to sense pathogenic bacteria and combat these pathogens. We also watch Tim Czopka at work as he tracks the lifecycle of myelin-forming cells in the central nervous system in a bid to gain new insights into neuroplasticity.

In addition, this issue brings you new approaches to energy research: Christoph Hackl harnesses complex mathematics to develop new control technology for renewable energy systems. And Harald Oberhofer uses computer models able to analyze thousands of chemical compounds in a quest for organic semiconductors to enable the solar cells of the future.

Finally, Leibniz Prize winner Hendrik Dietz – a pioneer in the field of bionanotechnology – shares his thoughts on success factors for a career in research. In his view, productivity is key, as is a willingness to never stop learning. Indeed, his conviction that it's best to pick a topic that inspires you personally is a fitting summary of the interview as a whole – and something the young researchers featured in this issue have evidently all achieved. I trust you will agree that this makes for inspiring reading.

Prof. Wolfgang A. Herrmann



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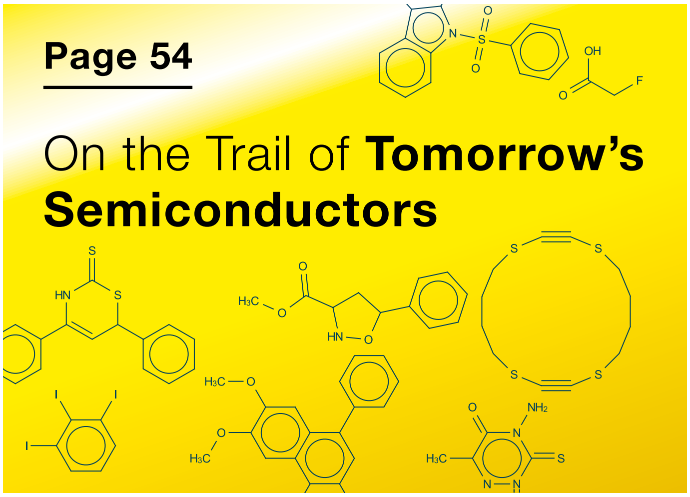
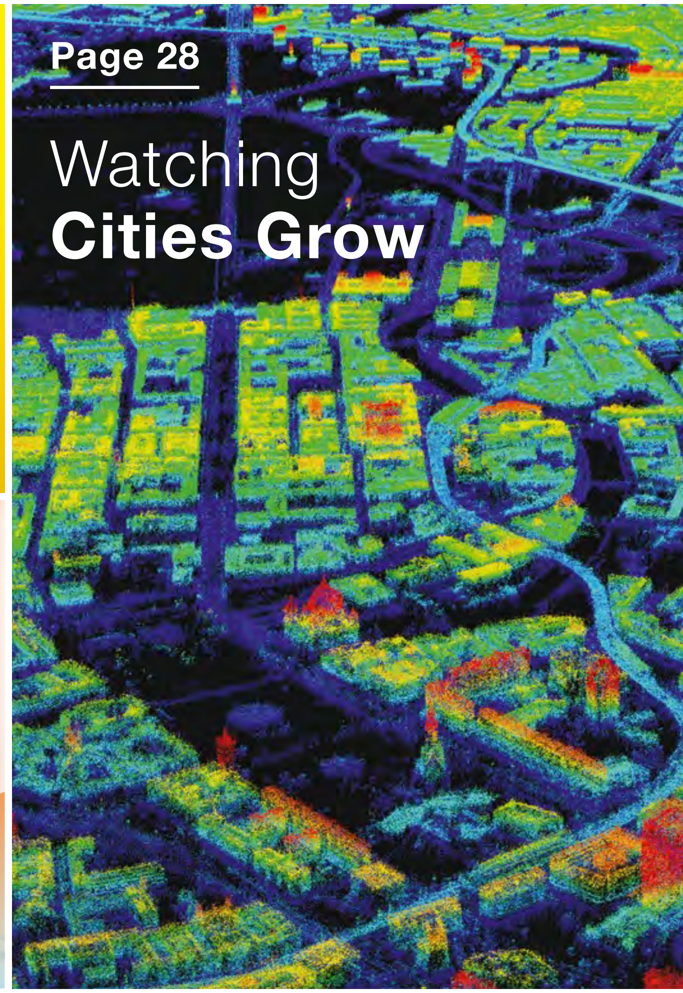




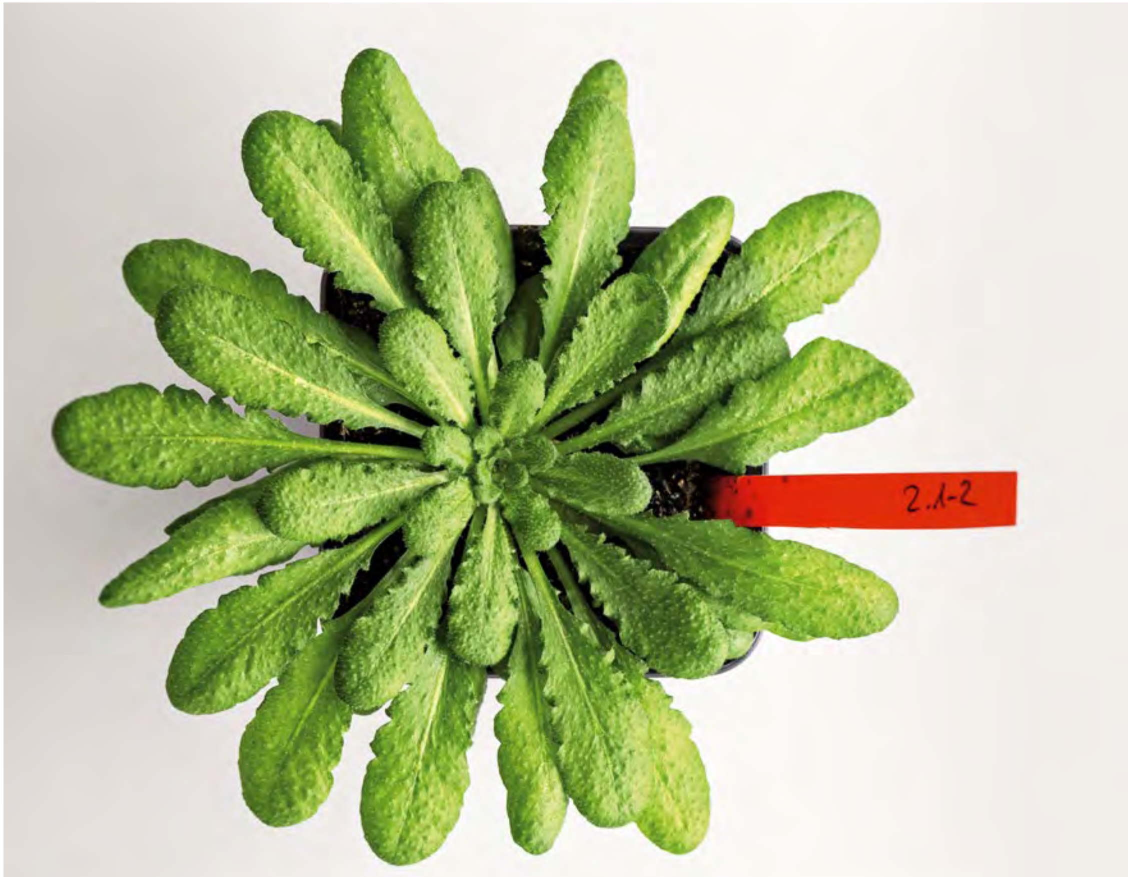
In every Issue

Research group: “The functions of lipopolysaccharide in plant-bacteria interactions”
www.ranf.wzw.tum.de

How Plants **Fight Back**

The immune system of plants is currently a hotbed of research. How do plants detect disease-causing agents such as bacteria and how do they combat these pathogens? Stefanie Ranf is interested in answers to these questions. She hopes that the findings from her research will help equip plants with natural protection against pathogens and secure our food supplies.

Picture credit: Astrid Eckert/TUM



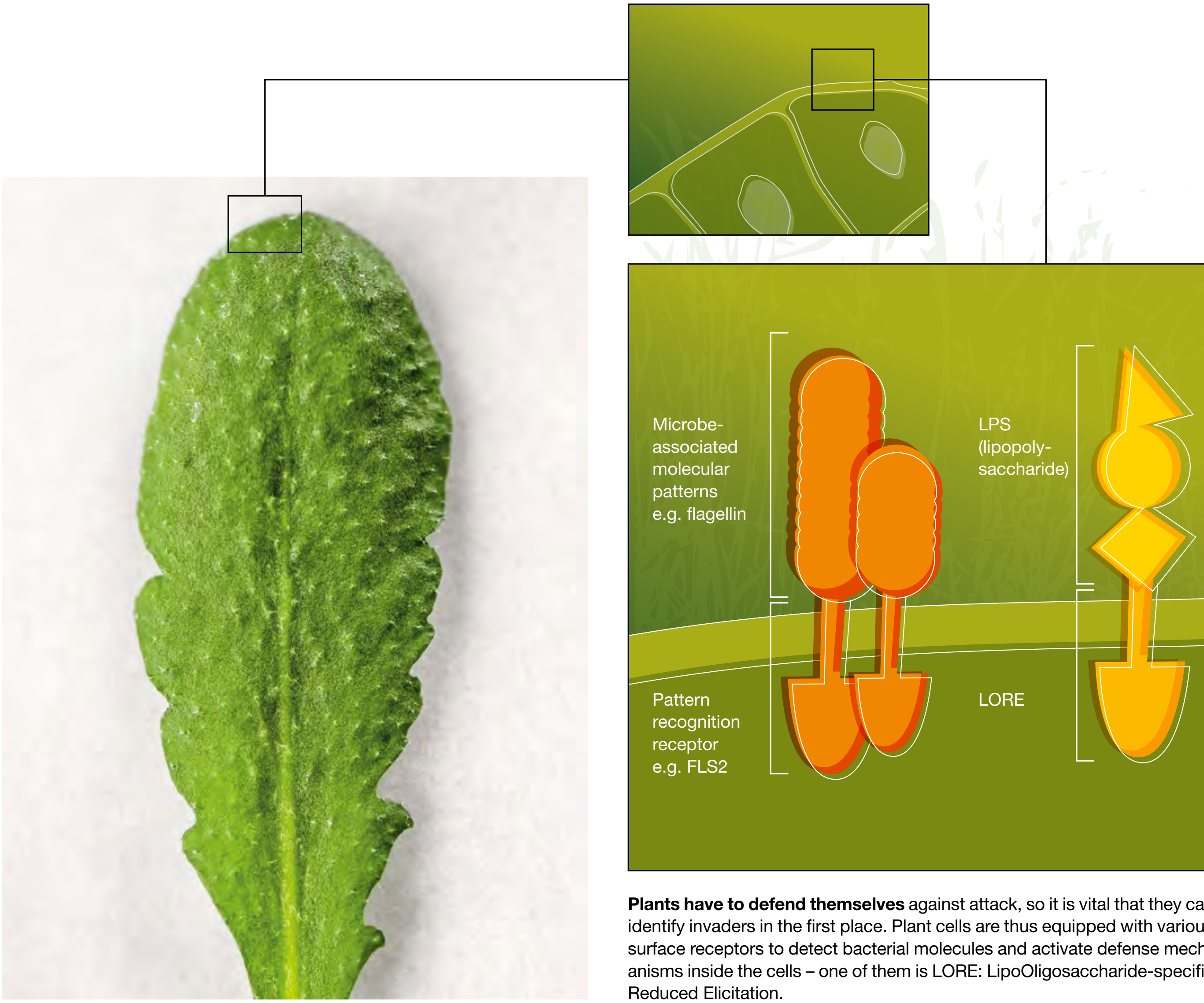
The model plant *Arabidopsis thaliana* (thale cress) is often used for laboratory testing. Its relatively small genome is fully sequenced and can easily be genetically manipulated for research purposes.

Claudia Doyle

Wie Pflanzen sich wehren

Pflanzen müssen sich genau wie Tiere gegen Krankheitserreger verteidigen. In einer Pflanze sind nahezu alle Zellen in der Lage, eine effiziente Abwehrreaktion gegen Krankheitserreger in Gang zu setzen.
Voraussetzung für eine Immunreaktion ist, dass der Angriff überhaupt bemerkt wird. Meist nutzen Pflanzen dazu Immunrezeptoren auf der Zelloberfläche. Sie funktionieren wie eine Antenne. Die Rezeptormoleküle durchspannen die äußere Zellmembran und schauen an beiden Seiten hinaus. Erkennen sie außerhalb der Zelle verräterische Bakterienmoleküle, so leiten sie die Information ins Zellinnere weiter.
Einen besonders wichtigen Rezeptor namens LORE hat Dr. Stefanie Ranf vor Kurzem entdeckt. LORE erkennt das bakterielle Molekül Lipopolysaccharid, kurz LPS genannt. Jedoch besitzen nur Kreuzblütler wie Kohl, Senf oder Raps den LORE-Rezeptor. Mithilfe von gentechnischen Verfahren ließe sich LORE von Kreuzblütlern auf wichtige Nahrungspflanzen übertragen. Dies hätte keine Auswirkungen auf Geschmack, Aussehen oder Ertrag der Pflanzen. Es würde sie lediglich resistenter machen.

Stefanie Ranf interessiert sich nicht nur dafür, wie Pflanzen ihre Feinde wahrnehmen. Die Biochemikerin will auch herausfinden, mit welchen Strategien die Bakterien sich tarnen und vor dem pflanzlichen Immunsystem verstecken. „Es ist ja nicht so, dass die Bakterien nur darauf warten, von der Pflanze entdeckt und umgebracht zu werden“, sagt die 39-Jährige, die am Wissenschaftszentrum Weihenstephan der TUM eine eigenständige Forschungsgruppe leitet.
Vermutlich verändern die Bakterien auch ihr LPS dermaßen, dass Pflanzen es nicht mehr erkennen können und sie gleichzeitig resistenter gegen die Abwehrreaktionen der Pflanzen sind. Von Bakterien, die Tiere infizieren, ist ein solches Verhalten bereits bekannt.
Ranfs Forschung ist nicht nur wichtig für die Züchtung krankheitsresistenter Kulturpflanzen. Auch die Sicherheit von Lebensmitteln soll davon profitieren. „Es wäre schön zu sehen, dass das, was wir machen, auch einen nachhaltigen Effekt hat. Das wäre die beste Belohnung für unsere Arbeit.“ □



Plants have to defend themselves against attack, so it is vital that they can identify invaders in the first place. Plant cells are thus equipped with various surface receptors to detect bacterial molecules and activate defense mechanisms inside the cells – one of them is LORE: LipoOligosaccharide-specific Reduced Elicitation.

Graphics: ediundsepp (source: TUM); Picture credits: Astrid Eckert/TUM

Around a year ago, Dr. Stefanie Ranf took the stage in an auditorium in the German city of Hamburg. She opened her laptop, picked up the microphone and began to talk about her research into plant immunity. Her audience consisted solely of fellow researchers – all of whom were investigating the immune systems of humans and animals, as well as bacteria and their toxins.

What Ranf had to say astonished her listeners. They began whispering and murmuring how fascinating it was to hear that even plants have an immune system. “I was really very surprised that there was so little awareness around our research up until that point,” recalls Ranf. A group leader at the TUM School of Life Sciences Weihenstephan, she specializes in plant-bacteria interactions.

Of course, just like animals, plants also have to defend themselves against pathogens. Both animals and plants thus possess a natural, innate immune system. Animal cells are additionally equipped with an adaptive immune system, which uses specialized immune cells and antibodies to ward off invaders. Plants, however, lack this type of system.

On the other hand, in plants, almost every cell is able to trigger an efficient immune response to pathogens. “The plant system isn’t weaker; it’s just different,” confirms Ranf. And exploration of plant immunity is now advancing by leaps and bounds.

The 39-year-old biochemist is interested in understanding how plants detect pathogens, how they defend themselves against them, and what processes take place inside the cells as this occurs. Plants with healthy defenses are essential to secure human food supplies. Our ability to harvest sufficient volumes of healthy foodstuffs in the future depends on crop resistance to disease. ▷

Dr. Stefanie Ranf

An inquisitive mind

Stefanie Ranf studied biochemistry at the University of Regensburg. With a degree under her belt, she decided to spend time abroad, joining the University of South Carolina in Columbia (USA) as a visiting researcher investigating MAP kinase signal transduction. “I learned to work independently over there,” recalls Ranf. “It would never have crossed my mind to ask my boss what I should do next.”

Her interest in plant research also stems from that period. On returning to Germany, she thus sought out a green topic for her doctoral thesis, which she completed at the Leibniz Institute of Plant Biochemistry in Halle/Saale (Germany).

In 2013, Ranf started leading her own research group at the Chair of Phytopathology (Prof. Ralph Hückelhoven) at the TUM School of Life Sciences Weihenstephan. The 39-year-old particularly appreciates the interdisciplinary collaboration between the various faculties at TUM. “Life is really easy here, because people are genuinely keen to achieve things together,” she affirms.

Ranf is now trying to foster the same autonomous work ethic in her students that she previously benefitted from herself. “If someone wants to produce lab equipment with a 3D printer or test a new approach to an experiment, I certainly won’t stand in their way.”

Since 2015, Stefanie Ranf has also been a member of the Collaborative Research Center 924 (SFB924), which investigates molecular mechanisms regulating yield and yield stability in plants. In 2016, she was awarded an Emmy Noether fellowship by the German Research Foundation (DFG). Since then, Ranf has been researching both the plant immune system and pathogenic bacteria with an independent research group.

"It would be great if we could make a lasting difference through our work."

Stefanie Ranf

Picture credits: Astrid Eckert/TUM

Every plant cell has a natural immunity mechanism

To trigger an immune response, a plant obviously has to first detect an attack. Plants usually use immune receptors for this purpose: molecules that traverse the external cell membrane and protrude from each side. These work like antennas. If they sense telltale bacterial molecules outside the cell, they transmit this information to its interior.

It has been clear since at least the 1970s that bacterial molecules trigger immune responses in plants. The molecules in question are often common to multiple different types of bacteria. A case in point here is flagellin, the protein forming the bacterial flagellum that enables microorganisms to move. Another is lipopolysaccharide, or LPS – the main component of the outer membrane of Gram-negative bacteria. These include the Salmonella and coliform bacteria dangerous to humans, for instance, as well as others pathogenic to plants.

However, the receptors plants use to recognize these molecules went undetected for a very long time. The initial breakthrough came when the flagellin receptor was identified seventeen years ago. But the LPS receptor was to evade discovery until relatively recently.

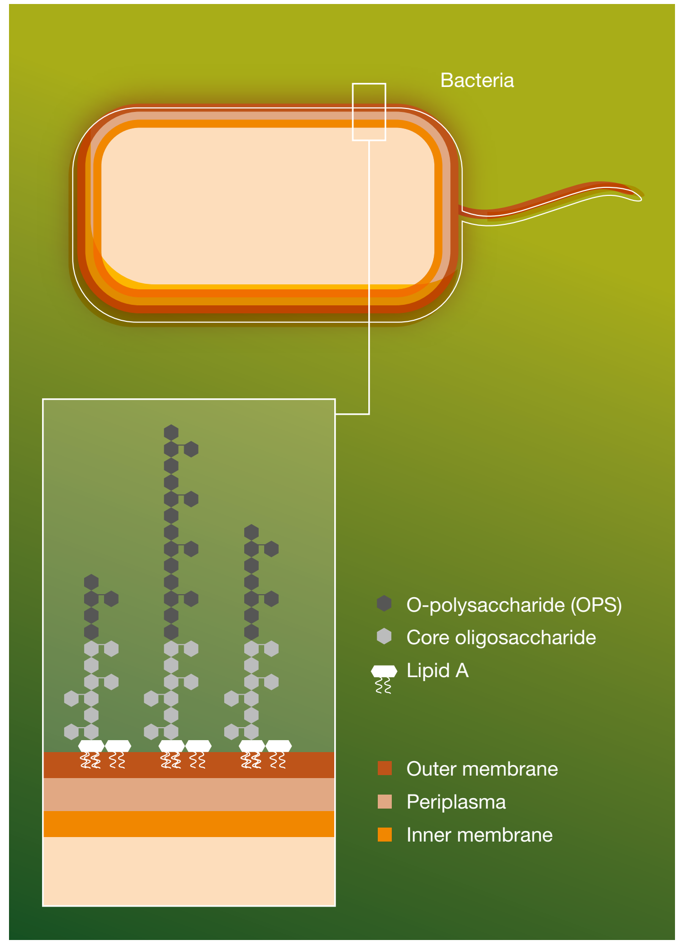
Initial contradictions

Since LPS occurs in so many types of bacteria, the LPS receptor is an important checkpoint in efforts to improve the plant immune system. Soon, plant researchers all over the world were carrying out tests to determine which plants were equipped with the right antennas to “pick up” LPS. Yet as the findings streamed out of the labs, contradictions emerged. Each working group was investigating different bacteria in different plants, leading to a jumble of individual studies and little meaningful progress.

In part, this was due to the elusive nature of LPS – an extremely complex and variable molecule with challenging chemical properties. Its size and structure vary from one bacterial species to another, and even bacteria of the same species form extremely different LPS variants. Only its basic composition always remains the same.

“Another problem was that no one knew how plants sense LPS,” Stefanie Ranf explains. The LPS receptor in animals had already been identified but it has little in common with the plant-specific equivalent. The two systems evolved independently of each other.

And so Ranf took matters into her own hands, testing more than twenty thousand different seedlings of the model plant thale cress *(Arabidopsis thaliana)* to determine whether their immune system was activated by LPS. And since good LPS is hard to source, she asked her colleagues at Germany’s Research Center Borstel (Leibniz-Center for Medicine and Biosciences) to show her how to isolate it from bacteria so she could do it herself. ▷



Bacteria are surrounded by multiple membranes. The outer membrane includes LPS molecules (lipopolysaccharide). They don’t all look the same, differing significantly in size and structure. However, their basic composition always remains the same, with lipid A – a di-phosphorylated di-glucosamine carrying four to seven fatty acids – embedded in the outer cell membrane. Chains of sugar molecules – some lengthy and branching – protrude from the cell surface.

Graphics: ediundsepp (source: TUM); Picture credit: Astrid Eckert/TUM

Various mutations were created in the genome of these *A. thaliana* plants, occurring at random points. Possibly also in the gene encoding the immune receptor? Stefanie Ranf harvests the seeds from this first plant generation.

Ranf's first few weeks in the lab brought her no further. In the end, though, she was able to identify four plants that displayed no response to contact with LPS. Could it be that their LPS receptor was faulty? She tested this hypothesis by genetically mapping and sequencing the mutation, then comparing it with the reference genome for thale cress. Sure enough, she found that all these plants exhibited a mutation in a gene that coded a receptor whose function was previously unknown. She named this receptor LORE.

Only cruciferous plants recognize LPS

Other cruciferous plants such as cabbage, mustard and rapeseed are also equipped with the LORE receptor on the surface of their cells and are thus able to detect LPS. Or, to be more precise, not LPS in its entirety but the section at the end of the molecule known as lipid A – a sugar molecule with fatty acids of varying lengths.

Interestingly, LORE does not recognize LPS in coliform or Salmonella bacteria. However, it reacts very strongly to LPS in bacteria of the Pseudomonas and Xanthomonas genera. Depending on the species, pseudomonads affect olive trees, cucumbers and tomatoes, among others. Meanwhile, targets for Xanthomonas include citrus fruits, bananas and rice. All of these plants have one thing in common: they lack LORE – the antenna that would enable them to recognize LPS.

LORE could be transferred from cruciferous plants to other important food crops using genetic engineering. The benefits of this type of genetic crop protection are clear. To understand how it works, however, we need to look a little more closely at the plant immune system.

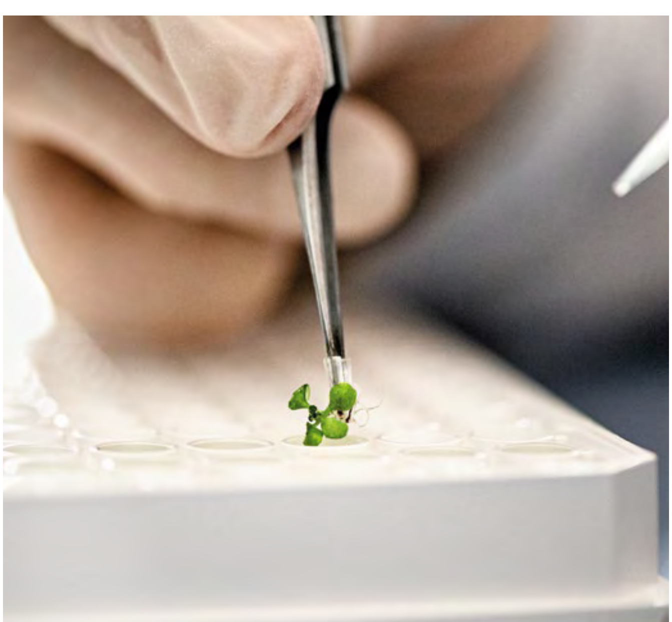
Receptors activate defenses

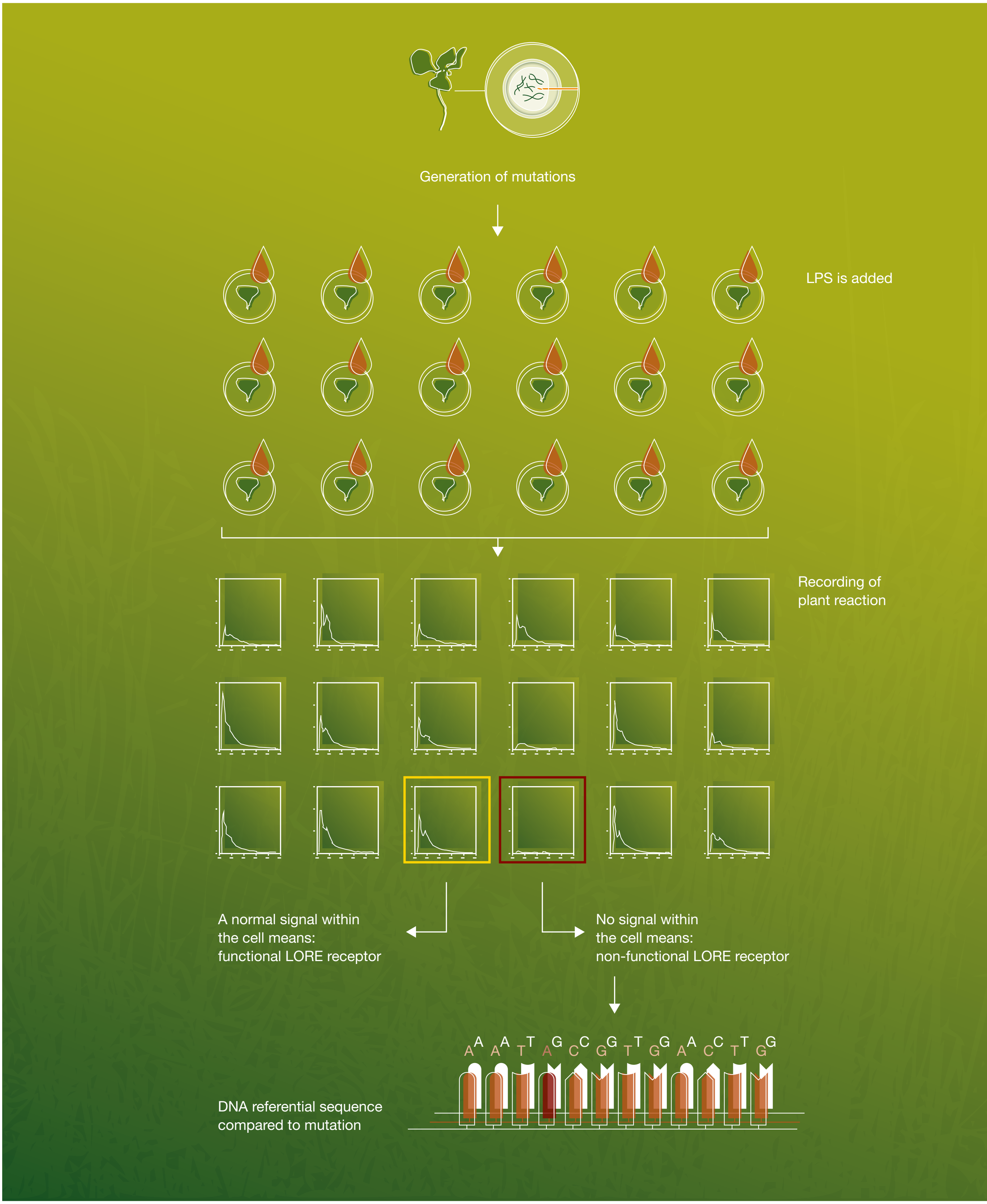
Plants have hundreds of different receptors on the surface of their cells, which they use to sense the surrounding environment. As soon as they detect a pathogen, their defense mechanism kicks in. They strengthen their cell walls to hold back intruders, switch their metabolism to defense mode and produce oxygen radicals and antimicrobial substances to kill off invaders.

"All plants are equipped with this system – the receptors just switch it on," describes Ranf. Transferring LORE from cruciferous crops to other plants would have no impact on their taste, appearance or yield, she explains. It would simply improve their resistance.

To date, though, the use of green genetic engineering has been viewed with suspicion in Germany. So Ranf is continuing her quest to identify LORE or other LPS receptors in other plants. With clever cross-breeding, these receptors could then be introduced to specific plants to create stronger lines. ▷

The seedlings grow in a sterile medium. When they reach a sufficient size, each seedling is placed in an individual compartment.





Graphics: ediundsepp (source: TUM); Picture credits: Astrid Eckert/TUM

The seedlings from the mutated plants are germinated in a sterile medium, then LPS is added. If the plants react to LPS, there is a spike in the graph. If this is missing, the plants are not reactive to LPS and are likely missing the relevant receptor to sense it. These LPS insensitive plants all exhibit a mutation in a gene that codes for the LORE receptor.

After 8 to 10 days, the LPS molecule from pseudomonad bacteria is added by doctoral candidate Milena Schäffer to the young plants. Will they identify it and react to it?

The monitor shows which plants are activated by LPS, with a significant upswing in their graphs. If this curve is missing, it means the plant does not react to LPS. There may be a mutation in its LPS receptor.

Stefanie Ranf tests if mature plants with a mutation in the LORE gene are more susceptible to infection with pathogenic bacteria. To this end, cultures of *Pseudomonas syringae* bacteria are grown under sterile conditions.

Picture credits: Astrid Eckert/TUM

In the next step, leaves are infected by simply pressure-infiltrating a solution containing the bacteria into the leaf interior using a needleless syringe.

However, for Stefanie Ranf, the scope extends beyond the way plants recognize their enemies. She is also keen to expose the strategies bacteria use to camouflage themselves and hide from the plant immune system. “It’s not as though bacteria just hang around waiting to be discovered and destroyed by the plant,” she points out.

Under cover

To remain undetected, some bacterial species simply shed their telltale flagella. Ranf suspects the bacteria also adapt their LPS in such a way that plants no longer recognize it. This change also improves their own resistance to the plant’s defense mechanisms. It seems probable that relatively small modifications are sufficient here. Discarding one or two fatty acids from lipid A renders bacteria virtually invisible to the plant’s immune system. That is the theory at least.

This type of behavior has already been observed in bacteria infecting humans and animals. The plague’s causative agent *Yersinia pestis*, which is transmitted by fleas, deduces from the temperature change that it has successfully made the leap from flea to human. Once there, it swiftly discards two fatty acids from lipid A and is thus hardly recognizable by the human immune system. Salmonella bacteria, which trigger severe diarrheal diseases, also go into stealth mode by slightly modifying their lipid A.

“It’s not as though bacteria just hang around waiting to be discovered and destroyed by the plant – they go under cover.”

Stefanie Ranf

***A. thaliana* plants harboring** a functional LORE receptor sense the bacterial LPS and initiate immune responses to halt pathogen spread. If the LORE receptor is not functional, bacteria proliferate and cause disease symptoms – yellow and wrinkled leaves (left).

Most likely, bacteria also make use of this type of mechanism when attacking plants. Furthermore, a single bacterial species never occurs alone in a plant, but shares its environment with numerous other microorganisms. “These are all interlinked,” explains Ranf, “and our aim is to determine how the communities interact.” Some of them are even good for the plant, promoting growth or helping to defend against pathogens. Ranf is aiming to establish a better understanding of this interplay between bacteria and their plant hosts, supported since 2016 by funding from the German Research Foundation (DFG) through the Emmy Noether Programme.

Plants as intermediate hosts

Not only does Ranf’s research have important ramifications for breeding disease-resistant crops; it also has the potential to enhance food safety. This is because some bacteria such as coliforms and Salmonella, which mainly target mammals including humans, use plants as intermediate hosts.

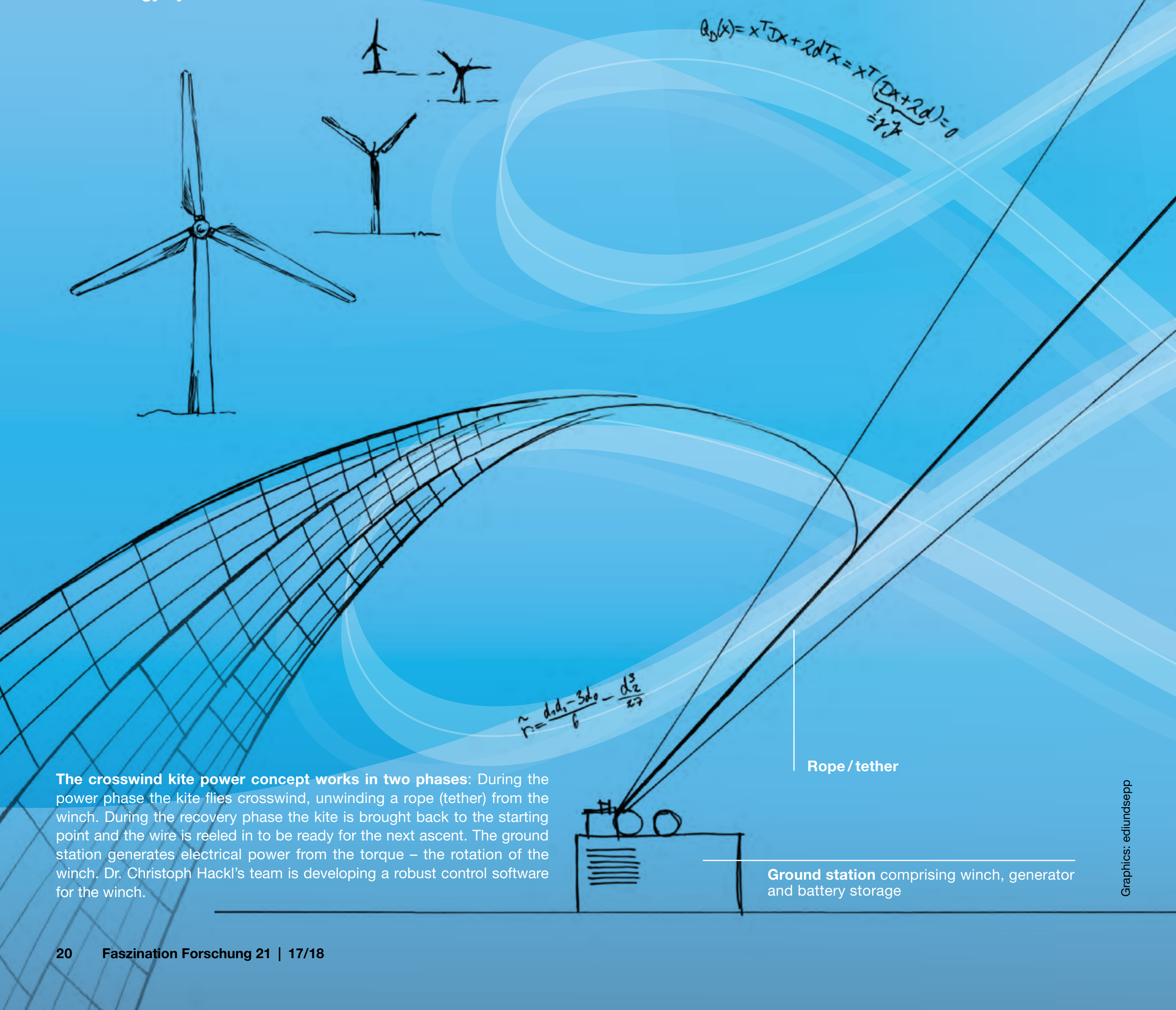
Coliform and Salmonella bacteria are known to survive in plants and can produce toxic substances there. It then makes no difference how thoroughly food is washed, as the bacteria and their toxins reside inside the plant tissue. So if plants improve their defenses, humans also stand to gain.

“It would be great if we could make a lasting difference through our work. That would be the best possible reward for our research,” concludes Ranf. *Claudia Doyle*

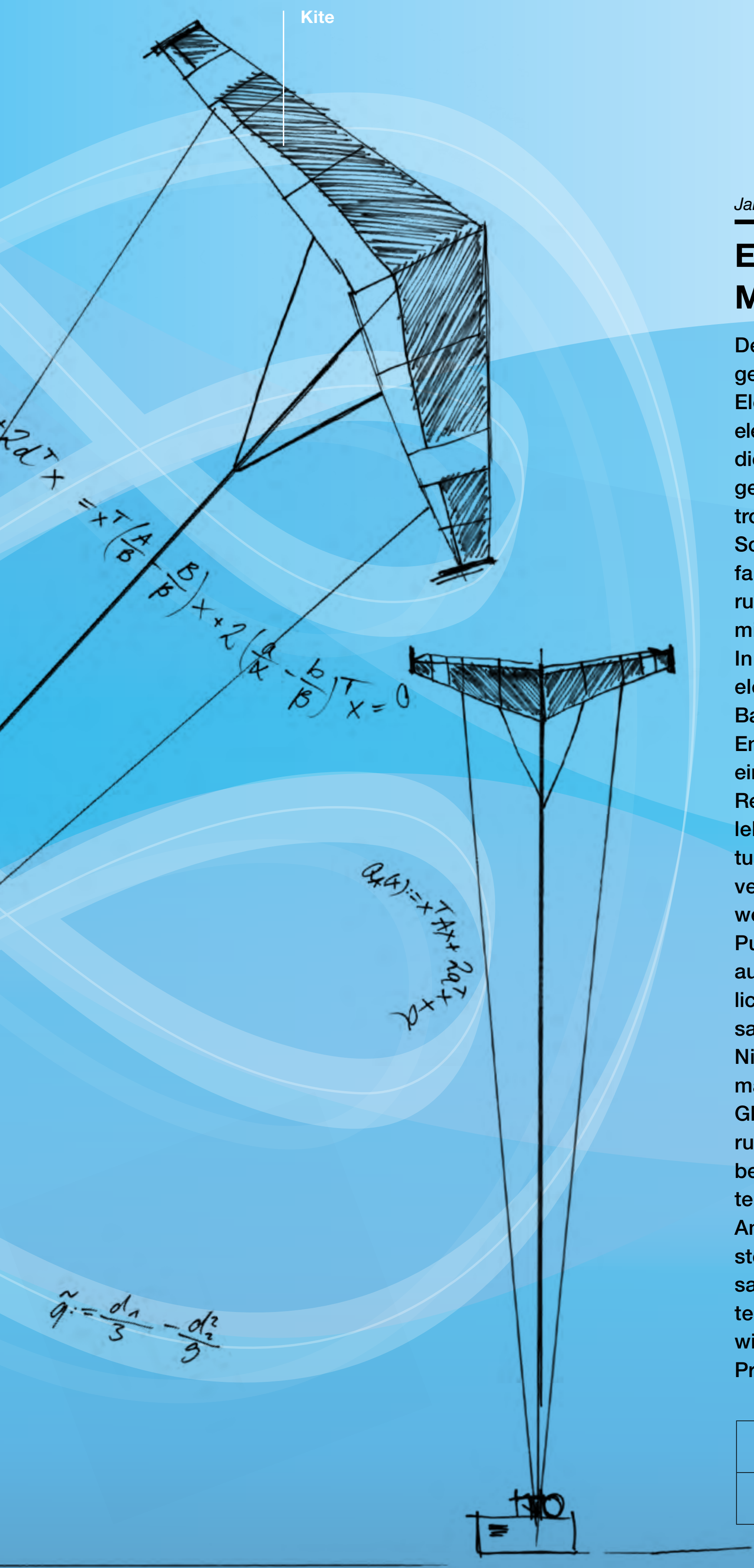
Picture credits: Astrid Eckert/TUM

Energy Transition – **Efficiency Gains through Mathematics**

With the help of advanced mathematical methods, Christoph Hackl develops control technology for energy systems. His aim is to enhance the efficiency and robustness of power electronics in electric vehicles and renewables, such as wind energy systems.



The crosswind kite power concept works in two phases: During the power phase the kite flies crosswind, unwinding a rope (tether) from the winch. During the recovery phase the kite is brought back to the starting point and the wire is reeled in to be ready for the next ascent. The ground station generates electrical power from the torque – the rotation of the winch. Dr. Christoph Hackl's team is developing a robust control software for the winch.



Jan Oliver Löfken

Energiewende – Effizienzschub durch Mathematik

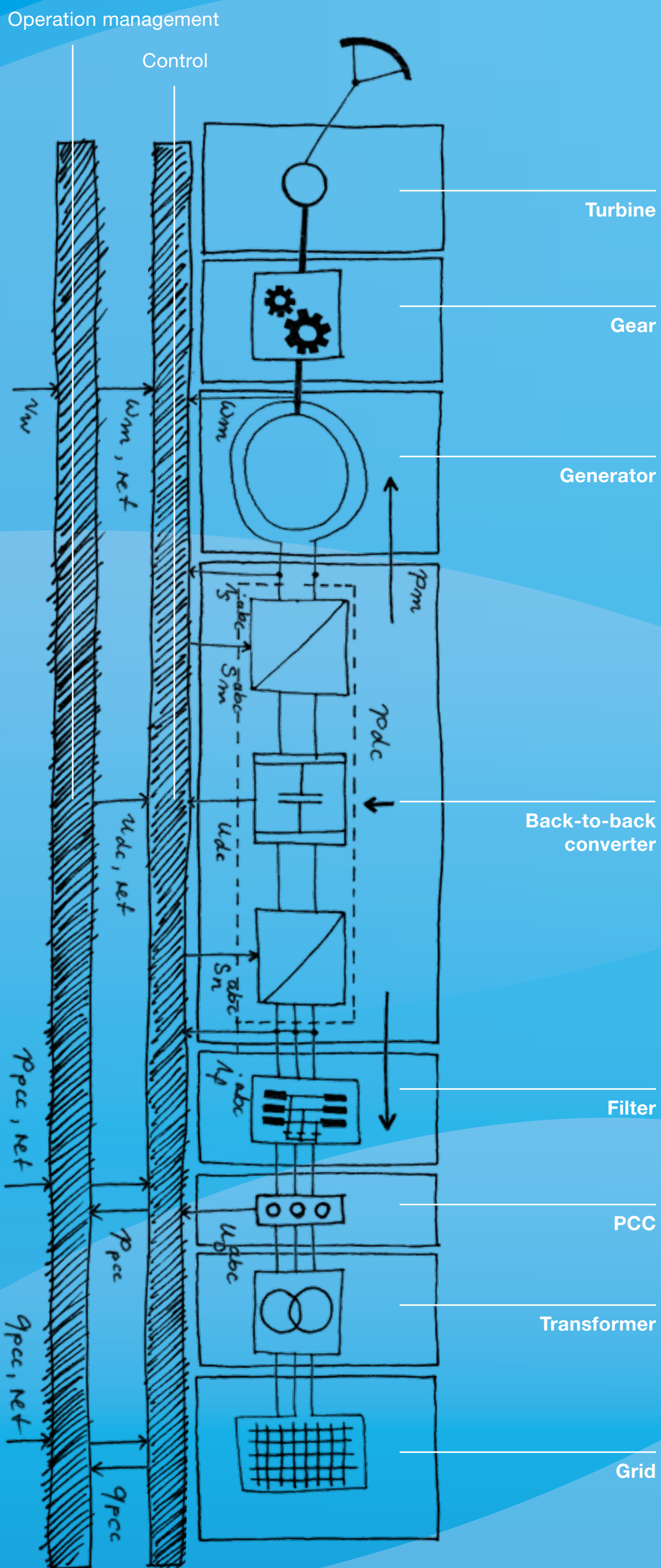
Der Systemtheoretiker Dr. Christoph Hackl reizt bisher ungenutztes Potenzial von erneuerbaren Energiesystemen und Elektroautos aus. Allein mit intelligent gesteuerter Leistungselektronik und komplexer Regelungstechnik will der 39-Jährige die Effizienz von Kraftwerken um mehrere Prozentpunkte steigern. Erste Resultate erzielte die Forschungsgruppe „Control of Renewable Energy Systems“, die Hackl an der Munich School of Engineering der TUM leitet, bereits bei einer Störfallregelung von Flugdrachenkraftwerken und bei der Steuerung klassischer Windkraftwerke, Elektroautos oder Geothermiekraftwerke.

In all diesen Anlagen stecken elektrische Maschinen und elektronische Module wie beispielsweise Umrichter. Diese Bauelemente der Leistungselektronik bereiten die elektrische Energie etwa für die Einspeisung in ein Stromnetz vor. Zum einen entwickelt Hackl dafür eine auch bei Störfällen robuste Regeltechnik. Zum anderen analysiert er das komplexe Eigenleben dieser Energiesysteme. Denn lange Kabel und leistungselektronische Bauteile führen zu Schalt- und Leitungsverlusten, metallische Bauteile in elektrischen Maschinen werden magnetisiert oder die Leistung von Generatoren und Pumpen schwankt. „Um das Potenzial eines Kraftwerks voll auszuschöpfen, müssen wir die Physik der Anlage mit möglichst all diesen nicht-linearen Effekten komplett verstehen“, sagt Hackl.

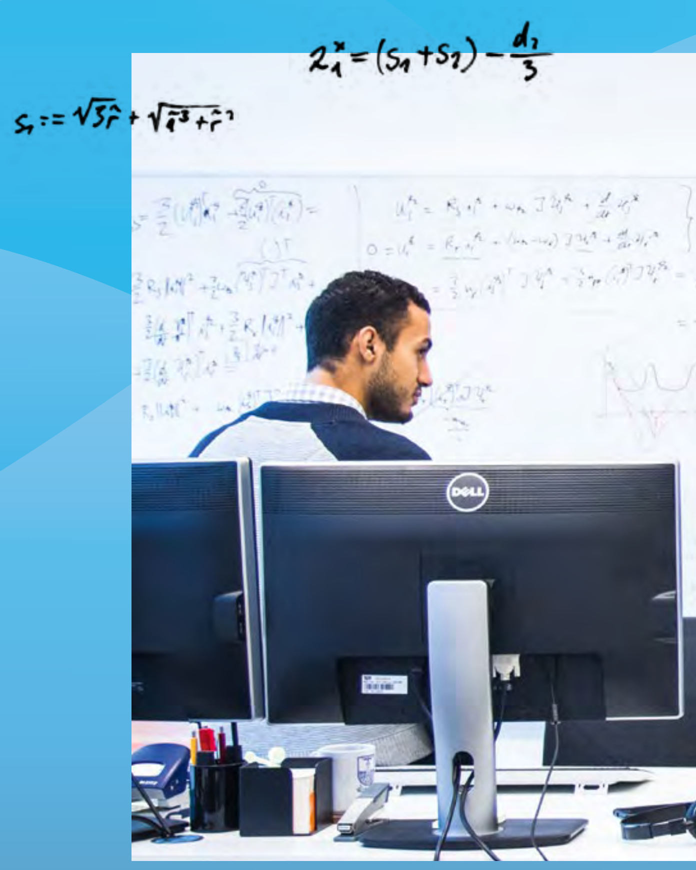
Nicht-lineare Effekte verlangen auch nach nicht-linearen mathematischen Verfahren. So lassen sich mit komplizierten Gleichungssystemen am Computer relevante Zustandsänderungen wie Temperatur, Leitfähigkeit oder Magnetisierung berechnen. Es folgt die Simulation einer Anlage am Computer, auf der dann eine Regelungssoftware aufbaut. „Je nach Anlage können wir die Effizienz um mehrere Prozentpunkte steigern und so die Gewinnmargen entsprechend erhöhen“, sagt Hackl. Seinen Ansatz – die Verknüpfung von Energietechnik mit Systemtheorie – bringt er mit Projektpartnern wie BMW, Volkswagen und den Stadtwerken München in die Praxis. □

Research group “Control of renewable energy systems”

www.cres.mse.tum.de



> *“We have to overcome our fear of complex mathematics.”*
>
> *Christoph Hackl*



The scheme shows the electronic components of airborne wind energy systems. By optimizing for instance the electric currents within the generator, Christoph Hackl is able to minimize power losses.

Within seconds the kite is spiralling in a tight figure-eight pattern up to 300 meters above a field near Pritzwalk in the German state of Brandenburg. As it soars, it unwinds a rope, a so-called tether, from a winch below. Linked to a generator and battery storage, the winch and kite form an unusual power plant: As the kite rises higher, the rotation of the winch is converted to electrical power. After a controlled descent, the kite loses altitude and the rope is reeled in to be ready for the next ascent. The prototype automatically repeats this maneuver at one-minute intervals. It utilizes the steady and strong winds at higher altitudes. With this concept for airborne wind energy systems – still in its infancy – the start-up company Enerkite plans to start supplying electric power to remote areas by 2019. That would eliminate the need for the diesel generators often used in such locations.

Dr. Christoph Hackl heads the "Control of Renewable Energy Systems" research group at TUM's Munich School of Engineering. A partner of Enerkite within a European research project, he fosters the development of airborne wind energy systems. His aim: to develop a robust and intelligent control concept for the winch system. The concept has to be flexible enough to reel in the tether and permit a safe and controlled landing of the kite even in case of malfunctions such as short circuits or a partial disruption of the electronics. His tools: a well-founded knowledge of power electronics and mechatronics combined with complex mathematics.

Smart control despite breakdowns

"When faults occur, conventional control systems can easily fail, resulting in a loss of control," he explains. Hackl, who earned his doctorate in system theory, wants to gain a detailed understanding of these faults, simulate them with computers and make them tangible with complex formulas. These will be used as the basis for control software developed by his team for the flexible and above all secure operation of power plants. "But the applications for this approach are certainly not limited to kite-based high-altitude wind power," says Hackl. The list of projects pursued by his research group includes conventional wind power, electric cars, geothermal power stations, solar energy and biogas systems. They all use power electronic modules such as rectifiers and converters. These power electronics components convert the electric energy before being fed into a power grid, for example. They can be actively controlled and optimized using Hackl's expertise. ▷

Christoph Hackl (second from the right) and his team work on a wide variety of energy systems, from geothermal power stations and wind power facilities to electric cars.

Graphics: ediundsepp; Picture credit: ediundsepp/TUM

But possible malfunctions are only one aspect. The energy systems under consideration lead complex and dynamic lives of their own: Long wires combined with power electronics components result in critical resonances as well as switching and conduction losses. Metal components in electric machines become magnetized to greater or lesser degrees, and the performance of generators or pumps can vary depending on their operating point or external influences. "Those are only a few examples of complex, non-linear behavior with a direct impact on the operation of a power station or an electric drive," says Hackl. Non-linear means that these effects are difficult to predict and cannot be calculated using simple mathematical formulas.

Using the full potential of power stations

"Equipment manufacturers and engineers are aware of these non-linear effects," says Christoph Hackl. "However, they are rarely exploited in detail." Instead it is standard practice to make more or less rough guesses of their possible impact. To avoid unpleasant surprises when operating electric equipment, the customary approach is to exceed the required performance parameters or to use additional cooling to prevent overheating. This safety buffer is where Hackl sees the potential for greater efficiency.

"To exploit this efficiency potential, we need to understand a system completely, including having the best possible understanding of all non-linear effects. And we have to overcome our fear of complex mathematics," says Hackl. Non-linear effects call for non-linear mathematical processes. In some cases this requires highly complicated systems of equations. However, these can be worked out using computers, taking into account all of the relevant changes in state such as temperature, conductivity and magnetization.

"With our intelligent control of the power electronics we can boost the efficiency of power production by several percentage points."

Christoph Hackl

Industry showing interest in complex mathematics

Once the physics is understood and systems of equations are formulated and solved, a power system can be simulated on a computer. This serves as the basis for the control software that Christoph Hackl and his team are testing in their own laboratory on small converters and electric machines. He never loses sight of practical applications. "With a supercomputer we can generally take into account any effect that might arise, for example in wind power generators, no matter how small," says Hackl. But that would simply be too costly. He therefore scales the control software back to cover only the most important effects. The computer power needed for the electronic control of a system – whether airborne wind energy, a solar park or a geothermal power station – should not greatly exceed that provided by a cheap industrial computer.

"With our intelligent control of the power electronics and the electric machines, we can boost the efficiency of power production by several percentage points, depending on the system, and thus greatly improve profit margins," says Hackl. And that is possible without making costly adjustments to the system itself. It's hardly surprising that his research approach is meeting with growing interest not only for new developments such as the wind kite, but also among established companies. Other project partners include BMW, Volkswagen and the municipal utilities provider Stadtwerke München. His methodology – combining energy technology with system theory – could thus become a competitive advantage. "At the international level, our work is rather unique," says Christoph Hackl, not without a hint of pride. *Jan Oliver Löfken*

Dr.-Ing. Christoph Hackl

Striking a balance between energy and mathematics

Christoph Hackl has taken an unusual route in pushing the development of power electronics with the help of complex mathematical models. The electrical engineer completed his doctorate at TUM in 2012. In his doctoral thesis on the control of mechatronic systems, mathematical methods of system theory played an essential role.

In 2014 Hackl established the research group “Control of Renewable Energy Systems”. The group works within the Munich School of Engineering – an Integrative Research Center at TUM that engages in interdisciplinary research and teaching.

His 10-member team works on a wide variety of energy systems, from geothermal power stations and wind power facilities to electric cars. Hackl is a senior member of the Institute of Electrical and Electronics Engineers (IEEE).

The 39-year-old sees himself as a scientist conducting fundamental research with clear links to real-world applications. When teaching up-and-coming engineers about the opportunities opened up when straddling those two worlds, his enthusiasm is very much in evidence. Christoph Hackl’s goal: For all of his students to acquire comprehensive interdisciplinary knowledge of drive technology, mechatronics and, of course, system theory.

Xiaoxiang Zhu

Watching **Cities Grow**

Highly precise computational models of the world's mega-cities could help to improve urban planning. Working towards this goal, Xiaoxiang Zhu is combining petabytes of earth observation satellite data and social media data for the first time.

Bjoern Menze

Getting a **Diagnosis from Pixels**

Bjoern Menze is training computer programs to "learn" how to detect brain tumors and propose individualized treatments.

Machine **Learning**

A lot of scientists are using machine learning methods in order to unveil information hidden in huge amounts of data. Remote sensing (p. 28) and medical image recognition (p. 38) are two examples highlighted in this issue. How does machine learning work and what impact does it have in research? We explore the key points.

What is machine learning?

Machine learning involves a computer autonomously developing knowledge from experience – similar to human learning – and independently coming up with solutions to new and previously unknown problems. To enable experience-based learning, a computer program analyzes examples and uses algorithms in an attempt to identify specific patterns and rules in the data. These are then applied to new cases.

How does it work?

Machine learning works along the same lines as human learning. Similar to the way a child learns to recognize certain objects in pictures, for instance, a computer can also "learn" to identify objects or distinguish between people. To enable this, a learning software program must first be populated with data and trained. Programmers will tell the system that a specific object is "a dog" and another "not a dog", for example. Next, the learning software receives continual feedback from the programmers, using the algorithm to adapt and optimize the model. Improving with each new data set, the model is ultimately able to make a clear distinction between dogs and non-dogs.

What is deep learning?

Deep learning is the most successful machine learning technique to date. Its methods are based on artificial neural networks. Following the example of the human brain, these simulate a network of connected neurons. Learning from experience is achieved by changing the strength of the connections between simulated neurons. In this way, machines can acquire abilities such as seeing, hearing, speaking, reading and writing. Deep learning eliminates many stages of conventional neural networks, since the computer covers all the intermediate steps.

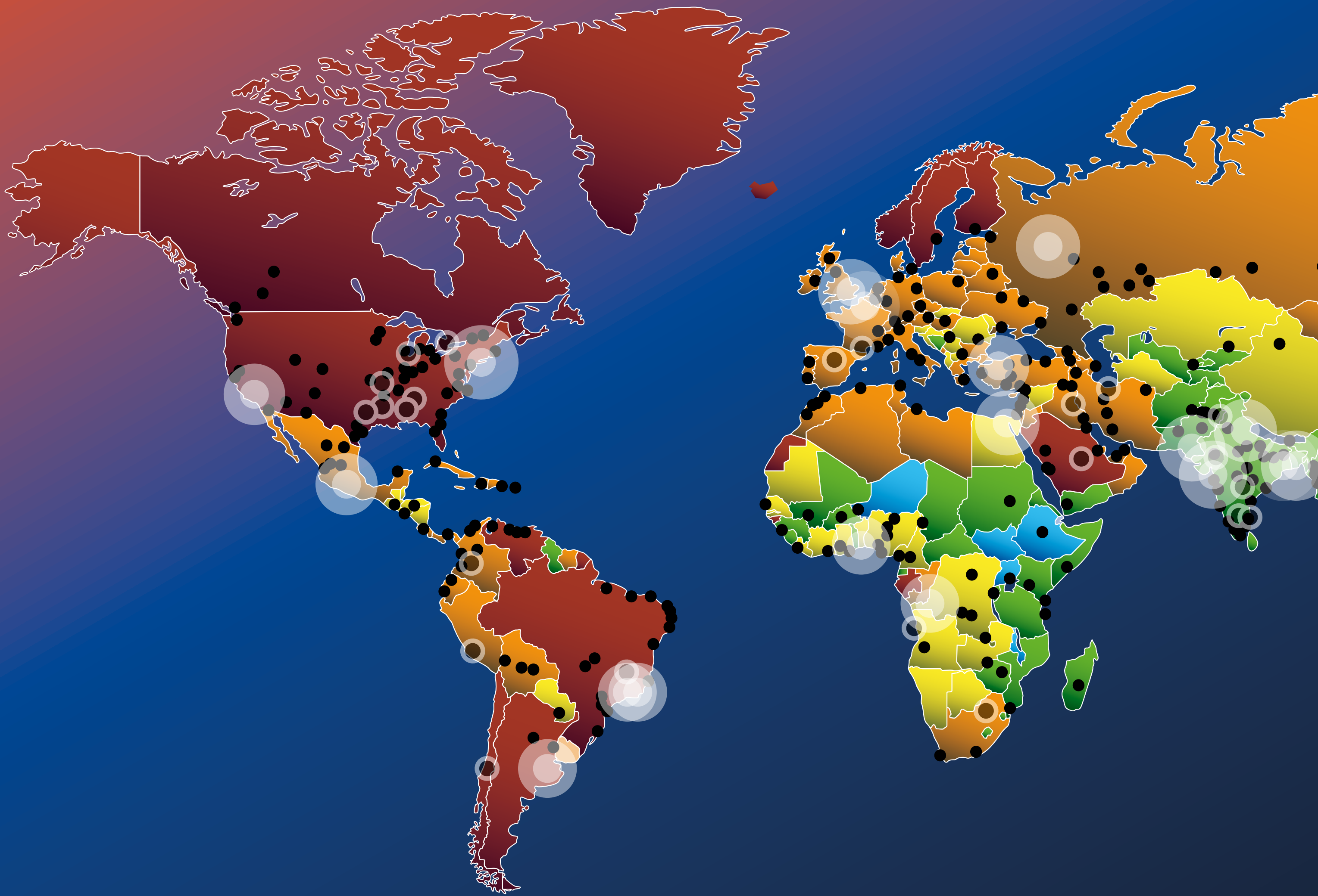
Why machine learning and why now?

Machine learning stands to benefit both science and business. In science, it can be used to identify patterns and derive rules from data, for instance. Fields such as text analysis, machine translation and speech and image recognition are beginning to undergo radical changes thanks to machine learning.

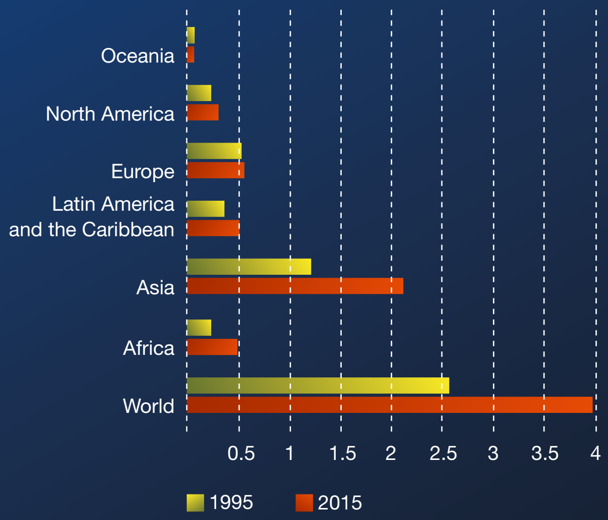
Machine learning was originally based on research in the field of pattern recognition, carried out as far back as the 1980s. Technical constraints meant the area then lay dormant for quite a long time. However, just a few years ago, machine learning experienced a breakthrough in the form of parallel data processing capabilities, enabled by graphics processing units (GPUs) originally developed for the video gaming industry. GPUs are equipped with thousands of processing cores, making them significantly faster than standard processors.

Further developments such as multi-core architectures, improved algorithms and ultrafast in-memory databases have also had a positive impact. Another substantial factor is the growing availability of large amounts of structured and unstructured data from a wide range of sources – from sensors to digitalized documents and images – which can be used to "train" learning algorithms.

Klaus Manhart



Urban population at mid-year
(1995–2015) in billions



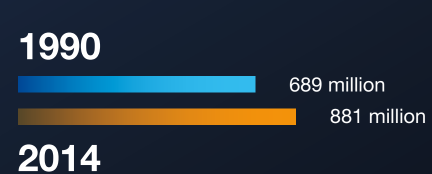
The urban population of the world has grown from 2.6 billion in 1995 to approx. 4 billion in 2015.

30%

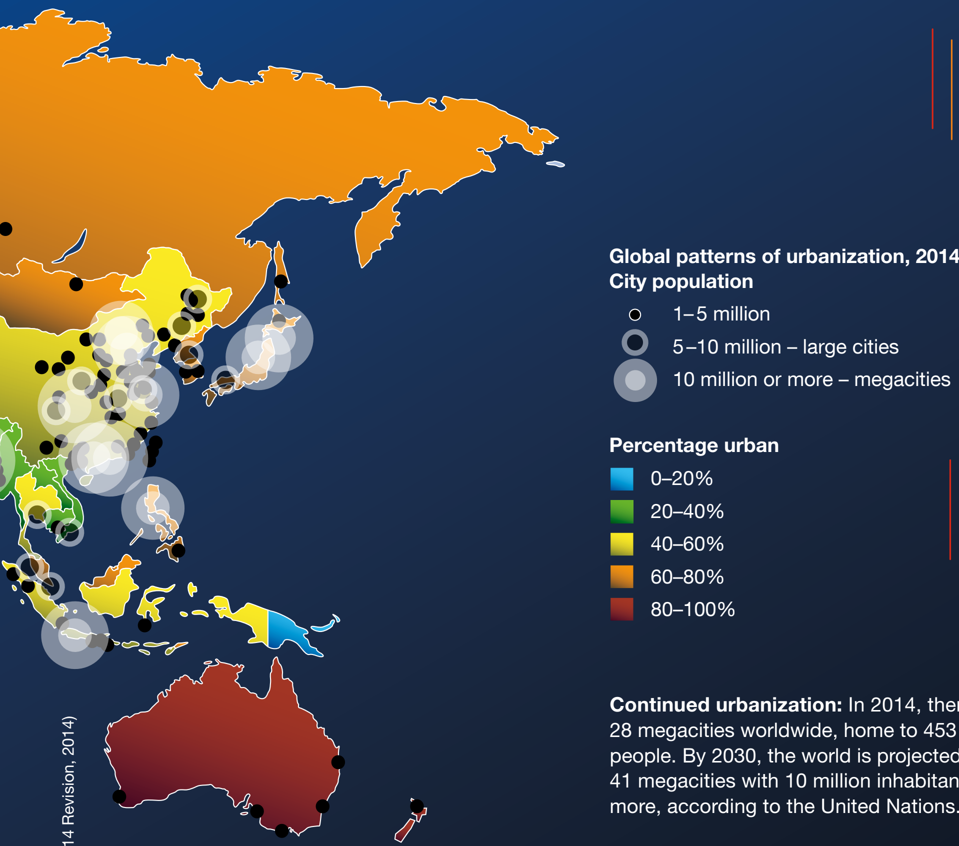
of the urban population

of developing countries reside in slums (2014).

Number of urban residents living in slums



UN-Habitat's estimates show that there were 881 million people living in slums in developing country cities in 2014 compared to 689 million in the year 1990.

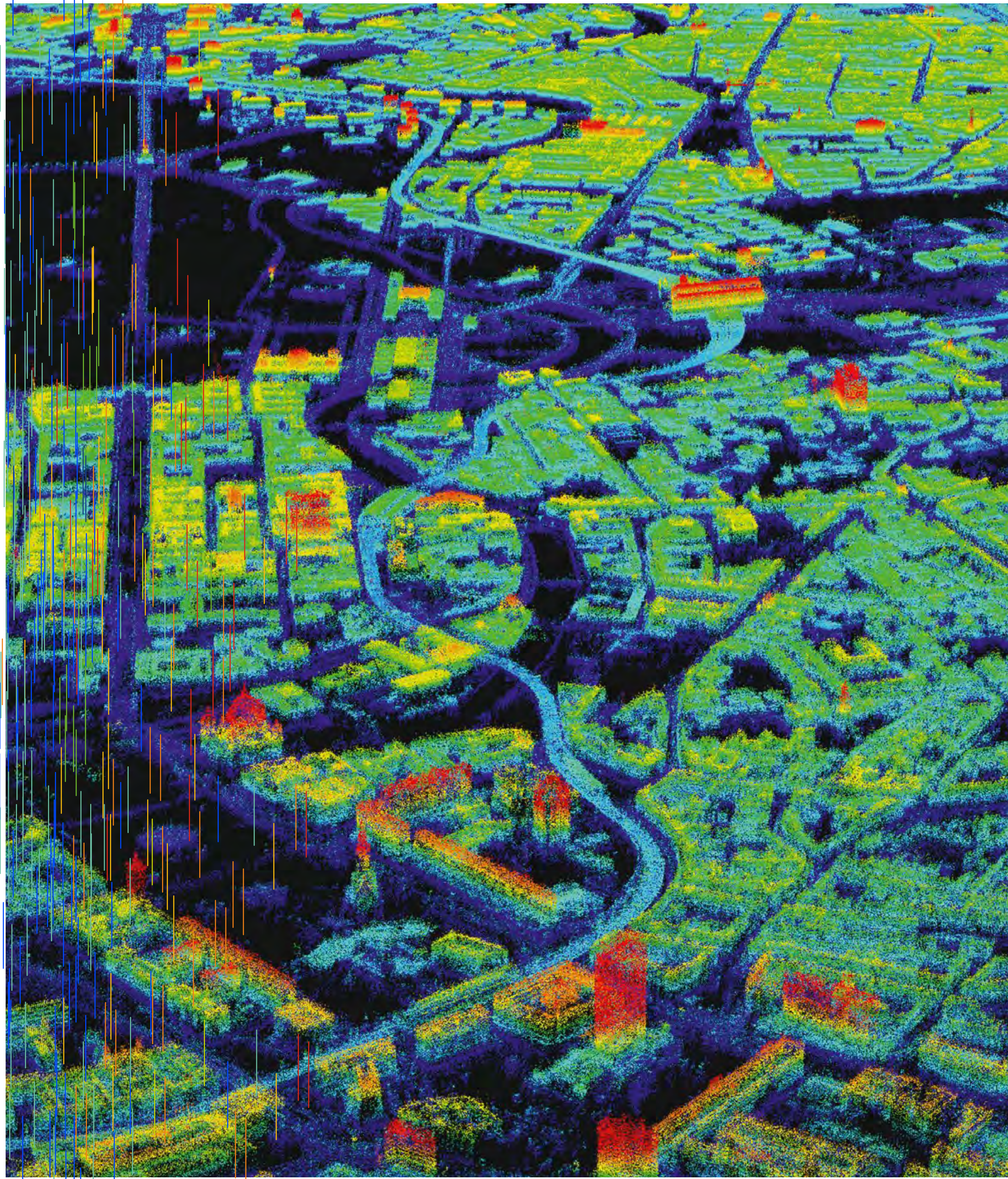


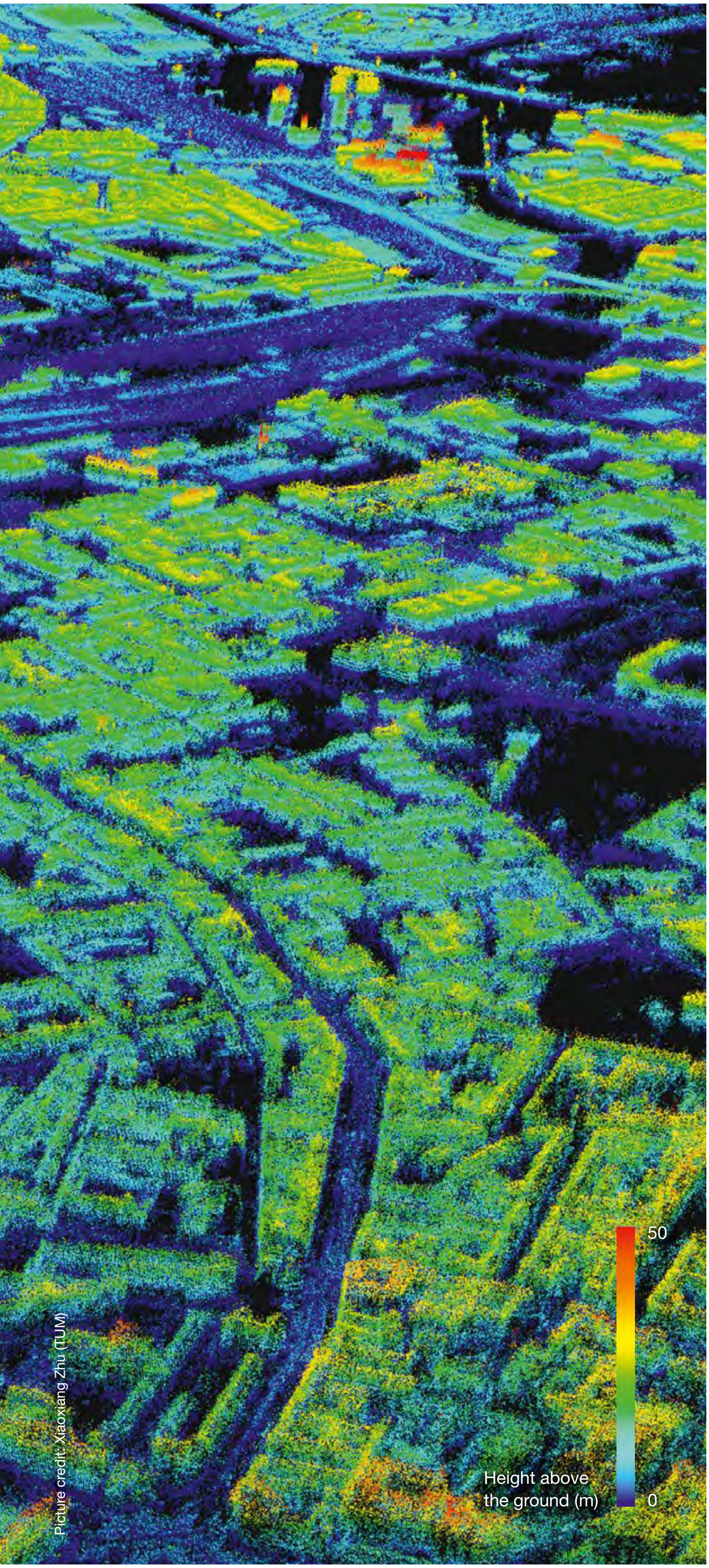
Continued urbanization: In 2014, there were 28 megacities worldwide, home to 453 million people. By 2030, the world is projected to have 41 megacities with 10 million inhabitants or more, according to the United Nations.

Graphics: ediundsepp (source: UN-Habitat: World Cities Report 2016, UN DESA: World Urbanization Prospects: The 2014 Revision, 2014)

Watching **Cities Grow**

Xiaoxiang Zhu has developed new algorithms for analyzing geographical data collected by satellites and is aiming at creating 4D models – including three spatial dimensions and time – of all cities in the world. With this goal in mind, she is combining petabytes of earth observation satellite data and social media data for the first time.





Signal Processing in Earth Observation
www.sipeo.bgu.tum.de

Monika Weiner

Städten beim Wachsen zusehen

Wie Magneten ziehen die Metropolen der Erde die Menschen an. Schon heute lebt nach Schätzungen der Vereinten Nationen mehr als die Hälfte der Weltbevölkerung in Städten. 2050 werden es zwei Drittel sein. Das Wachstum der urbanen Gebiete ist eine gewaltige Herausforderung für Planer, Verwaltungen und Einsatzkräfte. Vielerorts fehlen Informationen über das Wachstum von Stadtteilen und die notwendige Infrastruktur.

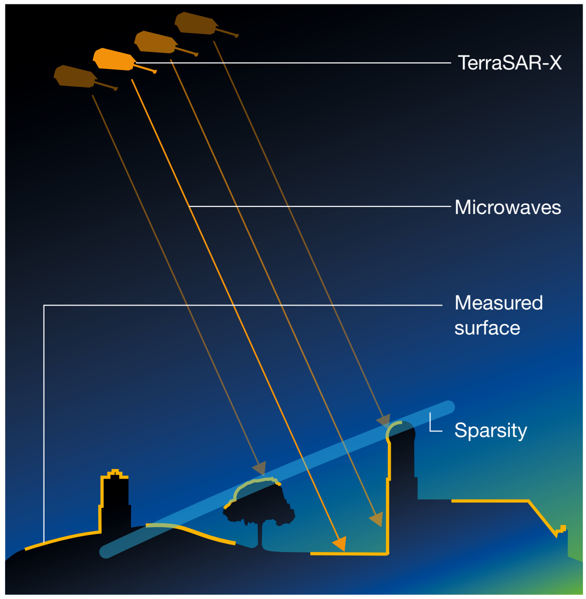
Mit neuen Datenanalyseverfahren will Prof. Xiaoxiang Zhu jetzt diese Wissenslücken schließen. Die 32-jährige Wissenschaftlerin forscht als Professorin für Signalverarbeitung in der Erdbeobachtung an der TUM und leitet eine Helmholtz-Nachwuchsforschungsgruppe am Deutschen Zentrum für Luft- und Raumfahrt (DLR).

Zusammen mit ihrem Team entwickelt Zhu neue Algorithmen für die Auswertung von Satellitendaten. Mit ihren Verfahren ist es ihr gelungen, hochpräzise 3D-Modelle verschiedener Metropolen zu erstellen, aber auch kleinste Veränderungen sichtbar zu machen – und damit eine vierte Dimension hinzuzufügen.

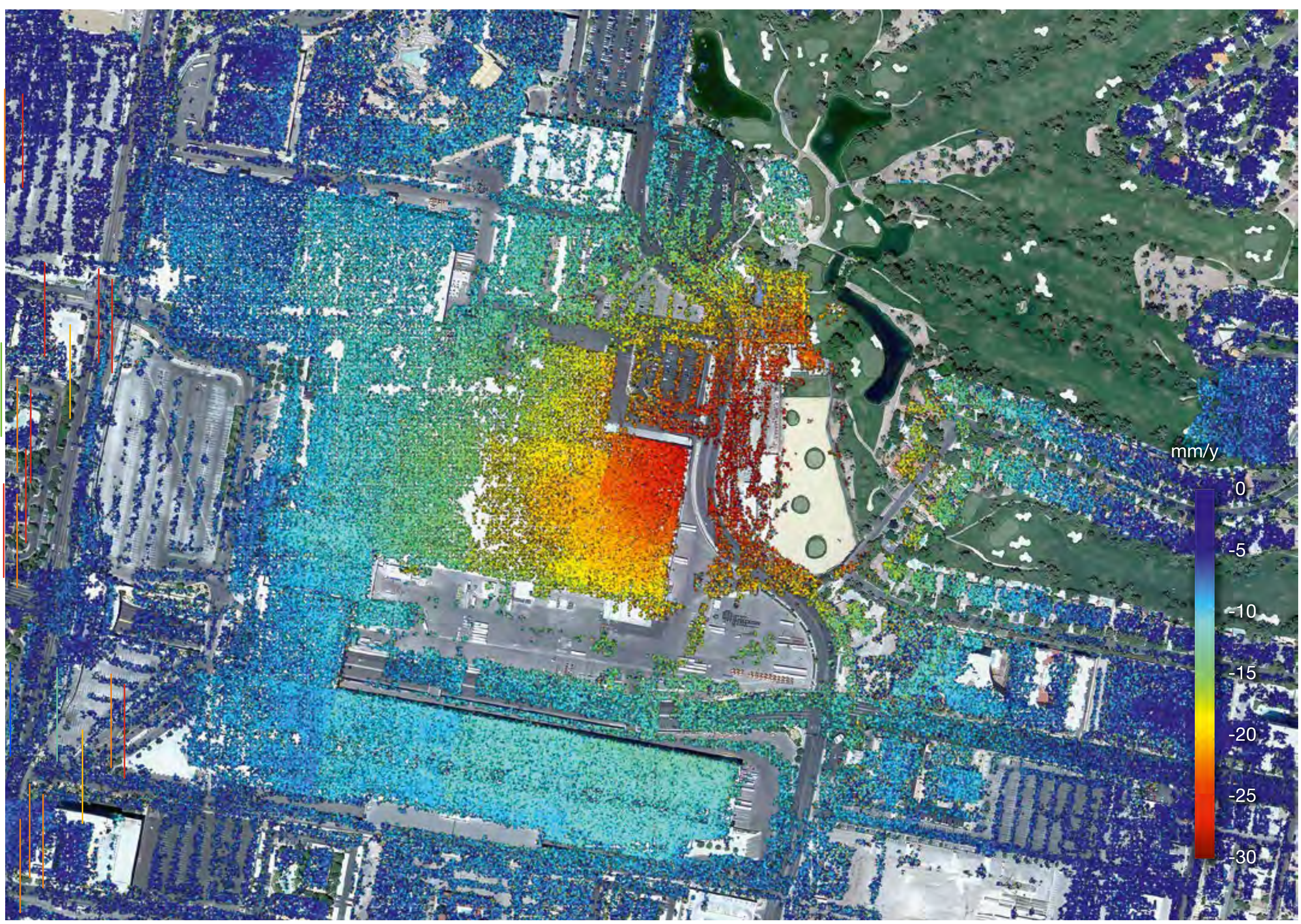
In ihrem aktuellen Forschungsprojekt So2Sat, für das Zhu einen Starting Grant des European Research Council (ERC) erhält, will sie jetzt auch Social-Media-Daten in ihre Auswertung einbinden: Durch Kombination ihrer Modelle mit Open-Source-Kartenmaterial aus dem Internet, aktuellen Fotografien, die Handynutzer ins Netz stellen, und den Tweets, die von einem Standpunkt aus gesendet werden, lassen sich Informationen über Ort und Funktion von Gebäuden sowie die Bevölkerungsdichte gewinnen und in die Modelle integrieren.

Der urbane Fußabdruck, der so entsteht, zeigt, wie sich Stadtgrenzen, Bevölkerungsdichte und Art der Bebauung verändern. Er soll künftig dabei helfen, eine nachhaltige Entwicklung der Städte zu planen und das Leben von Milliarden Stadtbewohnern einfacher und sicherer zu machen. □

A new way of global urban mapping: Using radar measurements from the TerraSAR-X satellite, Xiaoxiang Zhu and her team generate three-dimensional, high-resolution computational models of Berlin (left) and other major cities.



Radar tomography: Orbiting the earth at an altitude of approximately 500 kilometers, the TerraSAR-X radar satellite sends microwave pulses to the earth, in turn measuring the distance between the satellite and the buildings in the area in question. Initially, these measurements are received in a two-dimensional image.
In order to establish 3D or 4D city models, Xiaoxiang Zhu's team uses images taken from slightly different perspectives and at different times. The satellite flies over the same area every 11 days and each time takes an image from a slightly different orbit position. Comparable to a computed tomography of the earth, the method allows the localization of all reflecting points, which are sparse – a three-dimensional surface in the full three-dimensional space.



High resolution: Since the satellite images are taken at different times, the researchers are able to look for deformation patterns by noting even the tiniest changes (the 4th dimension) in a building's distance from the satellite. The 4D model shows a ground subsidence of up to three centimeters per year around the Las Vegas Convention Center, indicated by the red zone (center). This deformation is probably due to ground water being pumped up.

The United Nations estimate that city dwellers already account for half the global population. By 2050 that proportion may increase to two thirds. In particular, around a billion people live in slum conditions, their absolute number continuing to grow. Global urbanization, especially the uncontrolled kind, places enormous challenges in the path of urban planners, local administrators, utilities and emergency services. Basic data is often lacking: How many inhabitants live in a square kilometer? How quickly are urban areas growing? Where are people at risk in case of floods, earthquakes or tornadoes? Are there enough roads for an emergency evacuation? Where are hospitals located? How about schools? “All of this information is essential if we want to improve the planning of urban growth, develop security concepts and provide adequate infrastructure,” explains Xiaoxiang Zhu. The 32-year-old scientist is a professor of Signal Processing in Earth Observation at TUM and the German Aerospace Center (DLR).

Virtual city tour

With the methods she has developed for analyzing earth observation data, Zhu can watch cities grow without leaving her office. With one mouse click, a 3D image of Berlin is displayed on one of the two monitors mounted on her desk. Another click and Paris appears, followed by Las Vegas. “There we can see, using data from the radar satellite TerraSAR-X, that the golf course has sunk by three centimeters within a year – probably because ground water is being pumped up to water it,” reports the researcher. The next stop on the virtual city tour: Mumbai. An animation shows the steady spread of slums within just a few years, with the accompanying rise in population density indicated by a dark red shading of the areas.

So far this extremely detailed view of urban areas throws a spotlight on just a few of the world’s cities. To date Zhu has examined around a dozen metropolises. “The examples show that the use of large quantities of earth observation data can reveal changes triggered by urbanization – both in 3D and over time. In other words, in the fourth dimension.”

Pioneering work in data mining

The actual challenge is in the sheer quantity of data to be processed. It’s “Big Data” in every sense of the word. The German earth observation satellites TerraSAR-X and TanDEM-X and the Sentinel-1 and Sentinel-2 satellites of the EU Copernicus program alone transmitted to date already 10 petabytes of data to the ground stations. In the DLR Earth Observation Center, a room as big as a gymnasium, barely 200 meters from Zhu’s office in Oberpfaffenhofen, the information is catalogued and stored on magnetic tapes and discs. Scientists studying changes in urban areas can access this resource with a mouse click whenever they need it.

How can the information relevant to the global development of cities be filtered out of this enormous mountain of data? “It’s true that nobody would live long enough to complete this task by hand. Not even the 20 million core hours of computing time that the Leibniz Supercomputing Center allocated to me as a TUM professor would be long enough,” acknowledges Zhu. “Analysis can succeed only with special machine learning and artificial intelligence algorithms.” Developing these mathematical rules that enable computers to solve complex problems one step at a time is Zhu’s field of specialization.

From the second to the fourth dimension

Xiaoxiang Zhu was already writing algorithms that used images from the then newly launched TerraSAR-X for urban mapping purposes in her doctoral thesis. The radar satellite bounces microwave signals off the earth and receives the echo. These images are of limited information value, however, the reflections of different objects equally distant from the satellite overlap in the final image. This effect reduces the three-dimensional world to two dimensions.

But the images can be expanded into three or even four dimensions if tens of satellite measurements taken at slightly different positions and different times are included in the calculations: If the satellite flies over every region of the earth at 11-day intervals, its position is not always exactly the same. These orbital variations can be utilized to calculate the spatial locations of objects such as buildings from varying angles – similar to computed tomography, where multiple measurements are used to create an image of the human body. In addition to this third dimension, Zhu was able to derive a fourth dimension from the satellite data – showing the development of cities over time. ▷

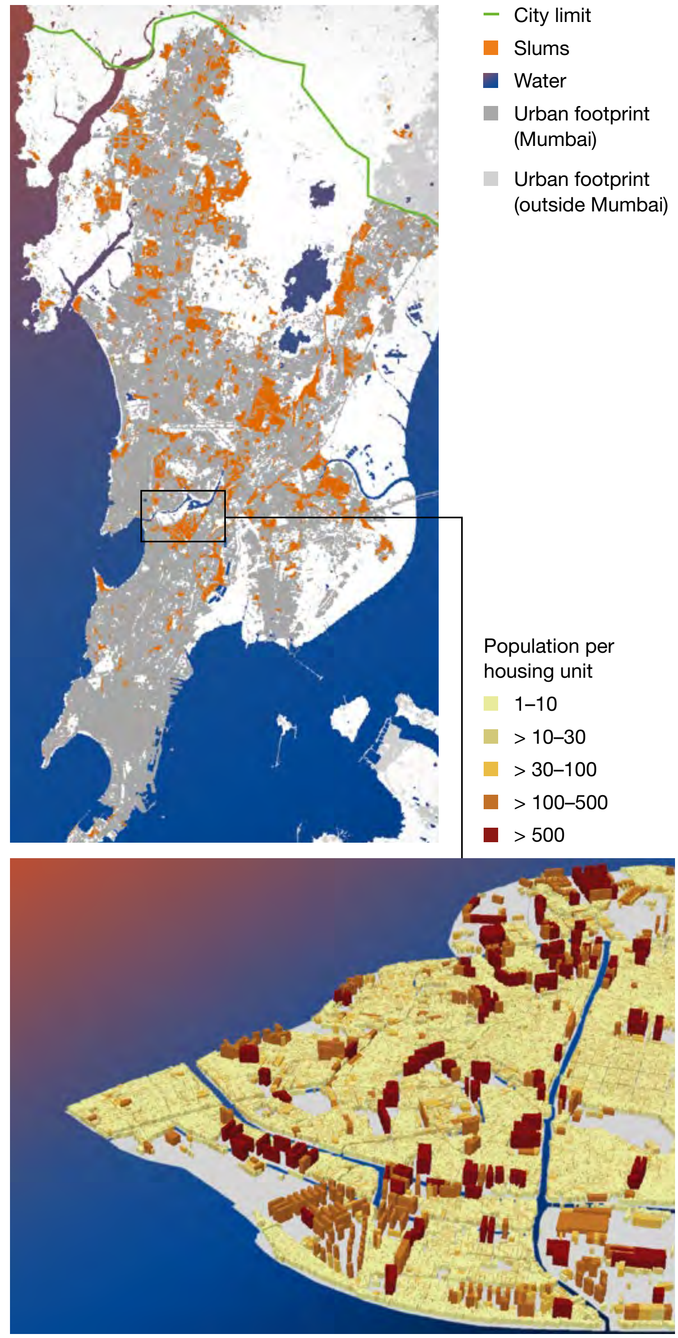
Paris on the one hand – Mumbai on the other: Xiaoxiang Zhu’s methods are suitable for all types of cities and settlements. Her aim is to create thematic footprints of all cities in the world.

Graphics: ediundsepp (source: TUM); Picture credits: Xiaoxiang Zhu, ediundsepp

In the recently completed 4D-City project, she worked with her team to generate high-resolution models of Las Vegas, Paris and Berlin, setting a new world record in this technology: The system reconstructed three million measurement points per square kilometer.
More importantly, the analysis recognizes deformations of buildings or soil subsidence of just one millimeter. “We demonstrated that this technology is suitable for detecting danger points, for example impending damage to bridges, dams or tracks,” reports the scientist.

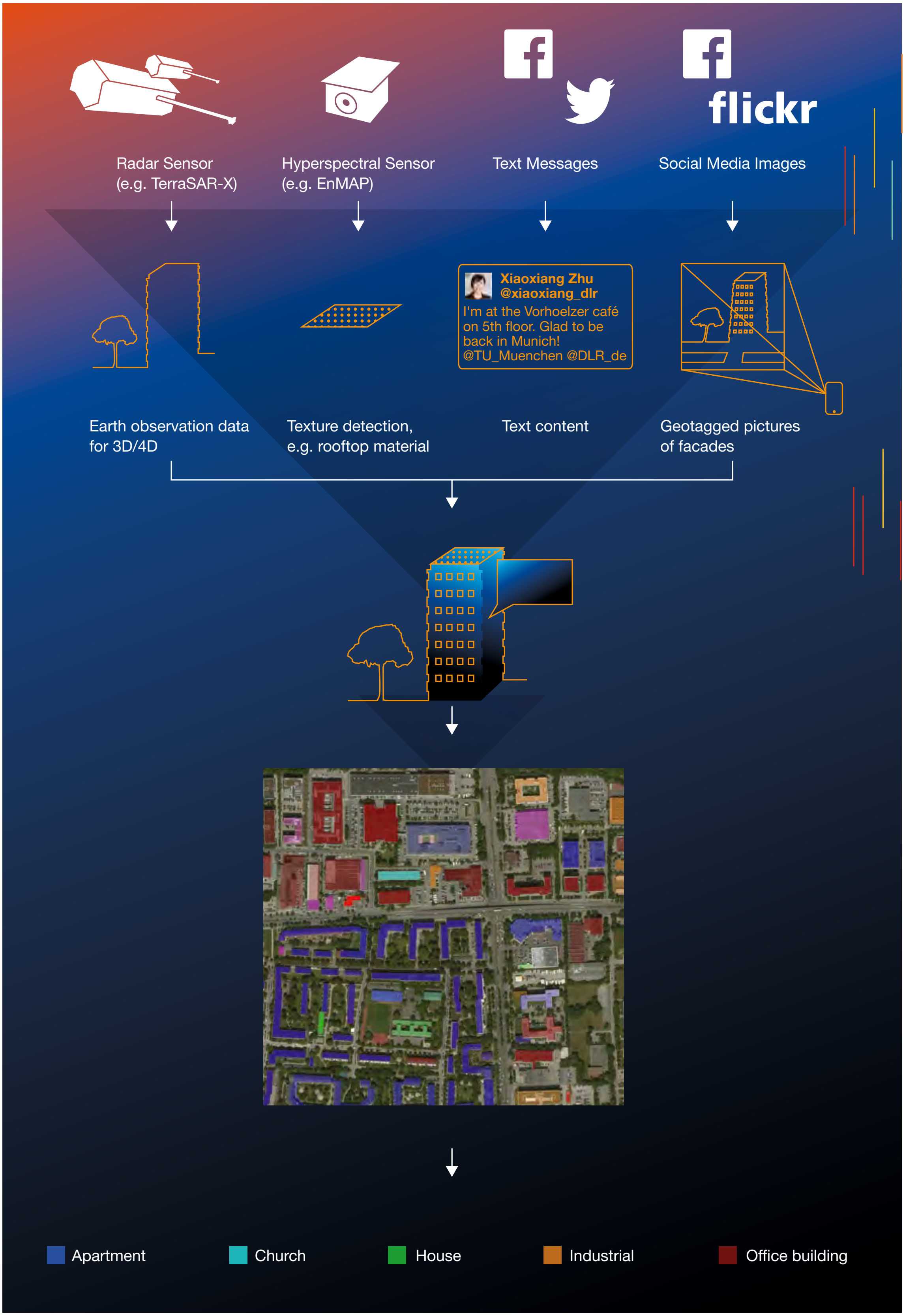
Deep learning for earth observation

Her experience in dealing with mountains of data now pays off when faced with even more massive quantities of information: The satellite fleet of the European Copernicus program has been in orbit for a few years. These Sentinel satellites, as they are called, are the world’s first large source of free and open earth observation data. In addition, the German EnMAP satellite, scheduled for launch in 2020, will transmit information to earth around the clock in an entirely new form: The sensors will detect 242 wavelengths for every pixel in various ranges of the spectrum, from short wave infrared to blue. This high spectral resolution allows the material to be identified and thus conclusions to be drawn on the properties of the mapped objects – differentiating for example tiled roofs typical of residential buildings from metal roofs typical of industrial zones. “This will give us an innovative and powerful earth observation technology that we want to be ready for,” says Zhu. With her colleagues she is now developing algorithms to enhance the resolution of the images and filter out signal noise. “At the same time, we have to explore new paths to convert the wealth of measurements into usable information quickly.” That will not be possible with traditional computational methods.
In her research project “Big Data for 4D Global Urban Mapping – 10^{16} Bytes from Social Media to EO Satellites” – “So2Sat” for short – the scientist is therefore exploiting the ability of computers to learn: Instead of analyzing every image pixel by pixel, the information will be compared against known patterns. This process will utilize deep learning, a technology based on artificial neural networks.
Deep learning is characterized by neural networks involving many layers, for this reason, they are called deep. As their shallow counterpart, deep neural networks exploit feature representations learned exclusively from data, instead of hand-crafting features that are mostly designed based on domain-specific knowledge. From massive labeled data they learn to recognize structures such as houses, churches or trees. Based on these structures, building settlement types are classified, displayed and verified by the researchers. In particular, with transfer learning techniques — one possible way to handle the challenge of limited annotated data — deep learning helps the analysis of images from all cities across the globe, with labeled data from only tens of cities. “This technology ▷



The 3D model of the Dharavi district in Mumbai showing changes in population density, is an exception. For the vast majority of slums, information on location, extent and morphology is lacking. Xiaoxiang Zhu and her colleague Dr. Hannes Taubenböck at DLR want to change that.

Picture credits: Taubenböck H, Wurm M, Esch T & Dech S (Hrsg.) (2015): Globale Urbanisierung – Perspektive aus dem All. Berlin Heidelberg, SpringerSpektrum. p. 297.



Data fusion: With the help of deep learning techniques, Xiaoxiang Zhu can "teach" algorithms to automatically classify houses, churches or industrial buildings, as shown here for a mixed urban area of Munich: Building instance footprints based on GIS maps are merged with geotagged street view images of facades as well as with text messages referring to the function of the building.

Graphics: ediundsepp (source: TUM); Picture credits: Xiaoxiang Zhu allows us to significantly reduce the manpower required for preparing labeling data of a large number of cities. We teach the machine to label data, in a sense," says Zhu.

New data source: social media

For Prof. Zhu, however, the final objective goes beyond that. "For comprehensive mapping and analysis of the urban footprint, we need more than just 4D models. We also want to know what the buildings look like, how they are used and how many people live in them. And the best way of collecting this information is through social media: from images uploaded to Instagram and Facebook, the number of text messages and tweets sent from a location at certain times of day or night, and open-source map materials such as Open Street Map," Zhu explains. In 2017 she was awarded a 1.5 million euro Starting Grant by the European Research Council (ERC) for her project.

Pictures, tweets and text messages – the fact that social media usage has generated billions of new data records to be analyzed leaves Zhu unfazed. On the contrary: "The ability of algorithms to learn improves with the quantity of data. The only problem is that the complexity of that learning also increases. We are therefore developing new algorithms that permit compressed assessment and analysis," she says.

Pilot applications have shown that the team is on the right track: They succeeded in combining the 3D model of Munich, generated using satellite data, with photos uploaded by smartphone users. The researchers also digitally combined the city map of Mumbai with data from messages and tweets to visualize the population density in the slums.

Xiaoxiang Zhu's hope is that, "Merging earth observation data with social media will make entirely new applications possible in the future. In case of a disaster such as a flood, city models can be updated using smartphone images and tweets for an immediate damage assessment without having to wait for a satellite to pass overhead."

A goldmine for science

As the next step, Zhu and her colleagues want to optimize the new processes to the point where a thematic urban footprint can be created for every major city in the world: This will include information on the expansion of urban boundaries, the population density in various areas and the type and function of buildings – with everything in 3D and precise to the meter.

"The possibility of comprehensive mapping will help planners and architects as well as security experts to take steps towards sustainable development", Zhu concludes. "This will help to make the lives of billions of urban residents easier and safer." *Monika Weiner*

Prof. Xiaoxiang Zhu

Aiming high

Looking at the sky has fascinated Xiaoxiang Zhu since the age of five, when she happened to see a book with pictures of space. After completing High School in Changsha, China, she studied aeronautics at the university there.

At TUM, the young researcher then specialized in the analysis of earth observation data. She completed her doctorate and established a Helmholtz junior research group at the German Aerospace Center (DLR) and TUM. This was followed by numerous stints as a visiting researcher in China, Japan, Italy and the USA. At the age of 30, in 2015, she was appointed as a professor of Signal Processing in Earth Observation at TUM as a joint appointment together with DLR.

Zhu has not regretted leaving aeronautical engineering behind to enter the field of earth observation for even a minute. "It was not so much an interruption as a development," the researcher says. "In our team we have specialists from engineering sciences, physics, mathematics and computer science. Without that interdisciplinary dimension, we could never tackle projects like the global mapping of urban development."

Xiaoxiang Zhu has already received many grants and awards, including an ERC Starting Grant (2016), a renowned Helmholtz Excellent W3 Professorship (2017), and the Heinz Maier-Leibnitz Prize of the German Research Foundation (DFG), the highest honor granted to young scientists in Germany.

“Only with the help of specialists from different disciplines can we tackle the global mapping of urban development.”

Xiaoxiang Zhu

Picture credits: ediundsepp

At her office at the German Aerospace Center (DLR) in Oberpfaffenhofen, Xiaoxiang Zhu has access to several petabytes of earth observation data. With a double appointment, she works as a professor at TUM and as a group leader at DLR.

Getting a Diagnosis from Pixels

Computer scientist Bjoern Menze is training computer programs to “learn” how to detect brain tumors and propose individualized treatments. His work shows how medical image analysis is opening up completely new perspectives.

Klaus Manhart

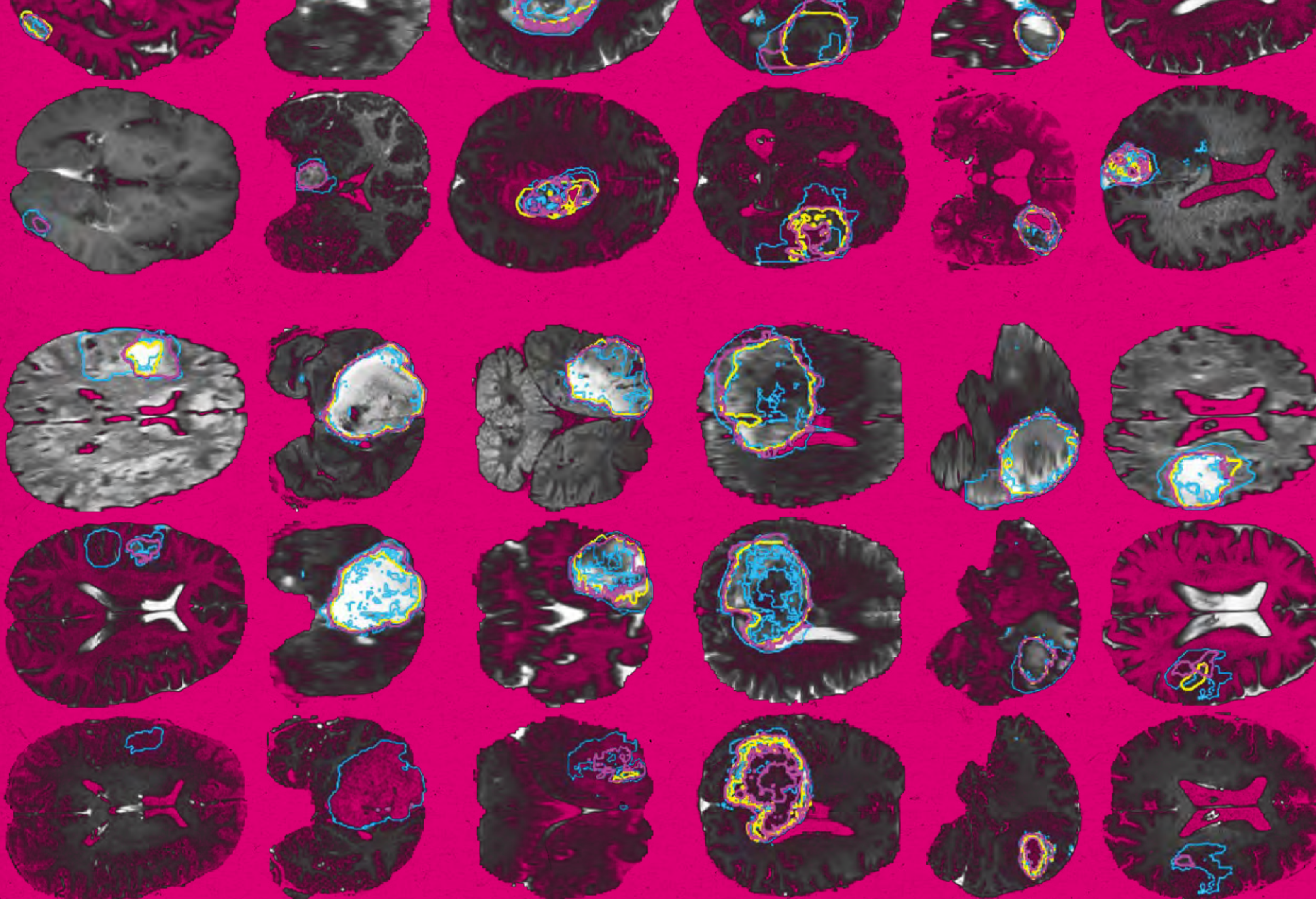
Wenn aus Pixeln Diagnosen werden

Medizinische Bilder von Krebstumoren liefern Ärztinnen und Ärzten wichtige Informationen. Allerdings liegen auf den Bildern die Tumormerkmale nur als unstrukturierte Pixelansammlungen vor. Die qualitativen Eigenschaften von Tumoren – ihre Größe, Lage, Form, Oberflächenbeschaffenheit und Substrukturen – sind schwer in objektive und quantifizierbare Daten zu überführen. Bjoern Menze, Professor für Bild-basierte biomedizinische Modellierung an der TUM, versucht diese Lücke zu schließen.

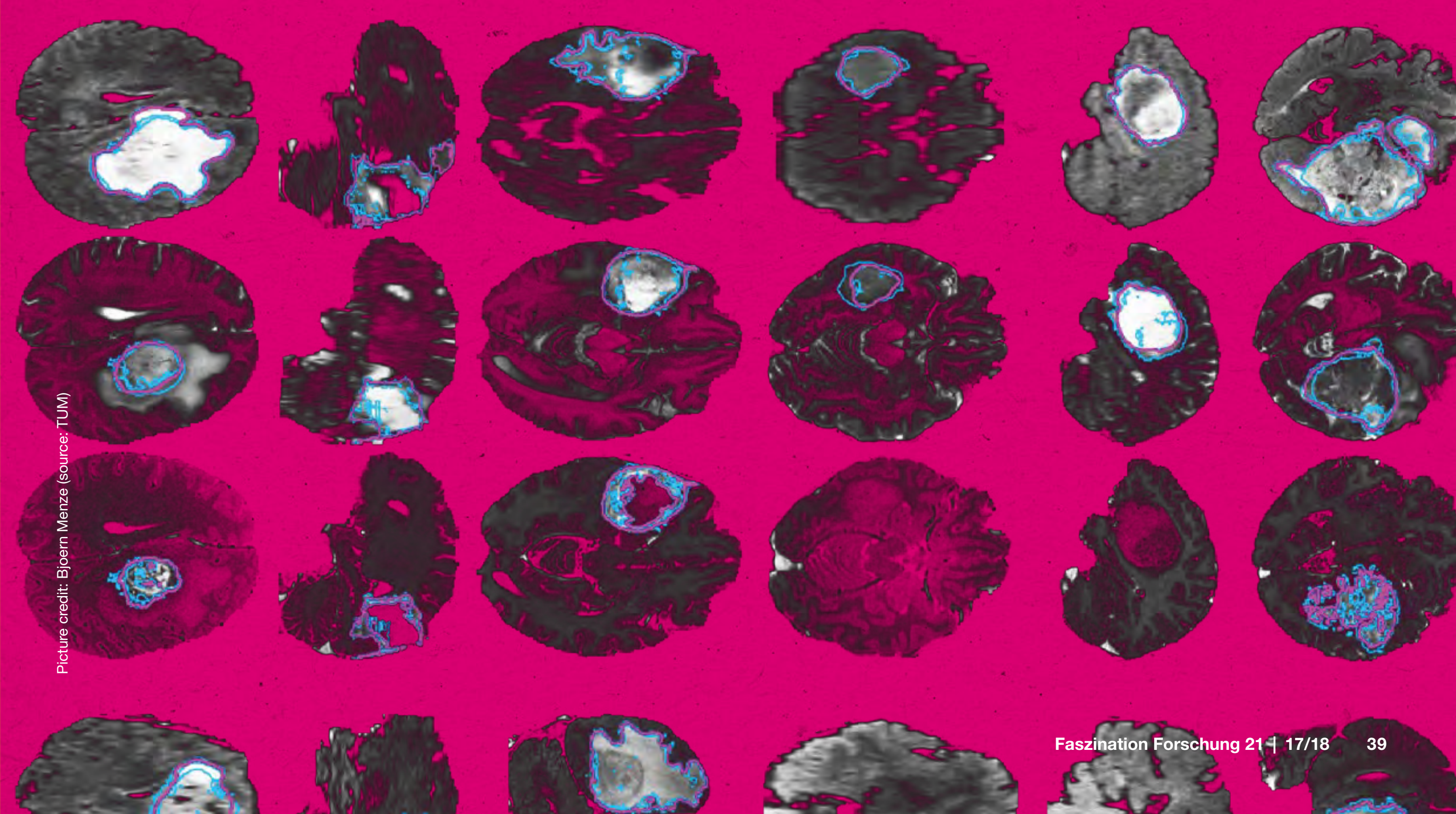
Der Informatiker entwickelt Verfahren des maschinellen Lernens, mit deren Hilfe in den biomedizinischen Bildern automatisch anatomische Strukturen, Organe und Tumoren erkannt werden. Diese werden dabei nicht nur identifiziert, sondern auch so bewertet und analysiert, dass die extrahierten Tumormerkmale die Diagnostik und Therapieentscheidungen verbessern können. Aktuell konzentriert sich die Forschung des 40-jährigen Wissenschaftlers auf die Erkennung und Analyse von Gehirntumoren.

Mit seiner Forschungsgruppe konnte er zeigen, dass maschinelles Lernen viel mehr Informationen zu Tage fördert, als das medizinisch geschulte Auge erfassen kann. Der Computer wertet Bilder dreidimensional aus. Auf diese Weise werden auch komplexe 3D-Strukturen und Texturen erfasst, die für den Arzt nicht unmittelbar einsehbar sind. Gleichzeitig verbessert die Computeranalyse die Qualität der Information: Die Algorithmen können subtile Unterschiede, wie verschiedene Grauwerte, berücksichtigen und sehr genau bestimmte Muster erkennen, die Menschen entgehen.

Damit verbessern die Lernalgorithmen mit der quantifizierten Auswertung der Bilder die ärztliche Diagnose. Sie geben Medizinern objektive und fundierte Informationen an die Hand und sorgen für eine Qualitätssicherung. Letztendlich wird damit auch die personalisierte Medizin gestärkt und es werden Therapieempfehlungen und automatisierte Entscheidungen möglich. Die letzte Entscheidung wird jedoch immer beim Arzt oder der Ärztin bleiben. □



Tumor areas in magnetic resonance images of the brain are automatically measured using machine learning techniques. The picture shows two different types of tumor segmentations. Top images: Individual algorithms (blue) are consolidated to produce an optimized algorithm (magenta), which matches or exceeds the measuring accuracy of an individual medical expert (yellow). Bottom images show findings established by individual medical professionals (blue) and findings through group consensus (magenta). Computer algorithms are trained to reproduce the experts' consensus segmentations, which are taken as a benchmark.



Picture credit: Bjoern Menze (source: TUM)

“The algorithm can detect specific patterns with extremely high precision – more accurately than this would be possible for a human.”

Bjoern Menze

Picture credit: Kurt Bauer/TUM

Medical images are a mine of information. Radiologists and medical specialists scrutinize computer tomography and magnetic resonance images, looking for anomalies and signs of disease. However, hidden in this vast sea of pixels is another layer of information that is not visible to the naked eye. And transforming this unstructured image information into objective, quantifiable data is no easy task.

Bjoern Menze, Professor of Image-Based Biomedical Modeling at TUM, wants to turn the information hidden in medical images into useful insights by converting the pixels into meaningful metrics. His aim is to support and validate today's qualitative, visual diagnostics with quantifiable values extracted from the imaging data.

This entails using computer algorithms from the fields of machine learning and computer vision to detect, analyze and evaluate anatomical structures in images from radiology, neuroradiology and nuclear medicine. And Prof. Menze's research efforts are already beginning to pay off, yielding better markers for tumor assessment and improvements to radiotherapy for brain tumor patients.

Computer-based tumor analysis

Menze's research team started out by programming a computer to recognize specific organs of the body. Here, the computer examines the pixels in medical images and classifies particular pixel structures as heart, liver or kidney. To train the computer, researchers first show it relevant images with the anatomical structures identified by an expert. Using artificial neural networks, the algorithm then learns how to categorize these organs and is ultimately able to interpret new images by itself (see FAQ on Machine Learning p. 27).

The team then took these algorithms developed to recognize organs and applied them to cancerous tumors in the human brain, so-called gliomas. "In terms of methodology, the task of locating an organ is very similar to that of identifying a tumor or tumor substructure," explains the 40-year-old researcher. "Rather than taking an array of pixels and asking whether they represent the left kidney or the liver, we now ask: Is this a tumor? And perhaps a particular tumor substructure?" ▷

Prof. Bjoern Menze

Medical computer scientist with an interest in archeology

Bjoern Menze is Professor of Computer Science and heads the Image-Based Biomedical Modeling at the Munich School of BioEngineering. The 40-year-old computer scientist is a fellow of the TUM Institute for Advanced Study (TUM-IAS) and conducts his research at the Center for Translational Cancer Research (TranslaTUM).

He develops algorithms that analyze biomedical images using models from computational physiology and biophysics. The emphasis of this work is on applications in clinical neuroimaging and the personalized modeling of tumor growth.

Bjoern Menze originally studied physics in Uppsala (Sweden) and Heidelberg (Germany), going on to complete his doctorate in computer science. Following postdoc periods at Harvard University in Cambridge and Harvard Medical School in Boston (USA), he continued his research as a member of the CSAIL Medical Computer Vision group at the Massachusetts Institute of Technology in Cambridge (USA), the Asclepios team at the Inria research center in Sophia-Antipolis (France), and the Computer Vision Lab at ETH Zurich (Switzerland). His work to transfer medical image analytics to Near Eastern archeology applications has been featured in Nature, Geo Magazin and Spiegel.

Image-Based Biomedical Modeling Group

www.translatum.tum.de/research-groups/image-computing/

Imaging techniques such as magnetic resonance imaging are used to generate numerous images of a brain tumor before treatment decisions are made. Bjoern Menze (left) and his colleague Dr. Jan Kirschke, senior physician at the Department of Diagnostic and Interventional Neuroradiology at TUM's university hospital Klinikum rechts der Isar, discuss the assessment of magnetic resonance images of a glioma patient.

The really crucial step, however, involves measuring the tumor once it has been identified. Here, the algorithm records its size, shape and relative location in the brain. Key analytical indicators include the image intensity and surface properties of the tumor in question – that is to say, its texture. The computer can differentiate between light and dark areas, detect whether the tumor is homogeneous or inhomogeneous and identify subareas worthy of attention. Training examples are initially used to teach the computer these core indicators, which it is then able to apply to new data sets.

Improving diagnostic accuracy

This type of automation benefits medicine in a number of ways. Machine analysis brings significantly more information to light than doctors are able to extract by themselves. While medical professionals generally focus on particular image sections and surface characteristics, the computer conducts a three-dimensional image analysis. This also identifies complex 3D structures and textures not immediately visible to the physician. At the same time, computer analysis improves the quality of the information: "The algorithm can factor in subtle variations, such as different gray tones, and detect specific patterns with extremely high precision – more accurately than would be possible for a human," underscores Menze.

By delivering detailed and quantified image analysis, the learning algorithms can enhance medical diagnostics. They provide doctors with additional information and provide a quality assurance net. They also facilitate well-founded treatment recommendations and can automate decision-making. Based on the pooled analyses, for instance, the computer can calculate the probability that a tumor belongs to a particular subgroup – perhaps determining that subgroup 6 is more likely than subgroup 4. The learning algorithm can also integrate additional information, such as genetic or histological data. Ultimately, however, the doctor will continue to reach a diagnosis and make clinical decisions. "We are supporting professionals in their assessment, not replacing them," emphasizes Menze. ▷

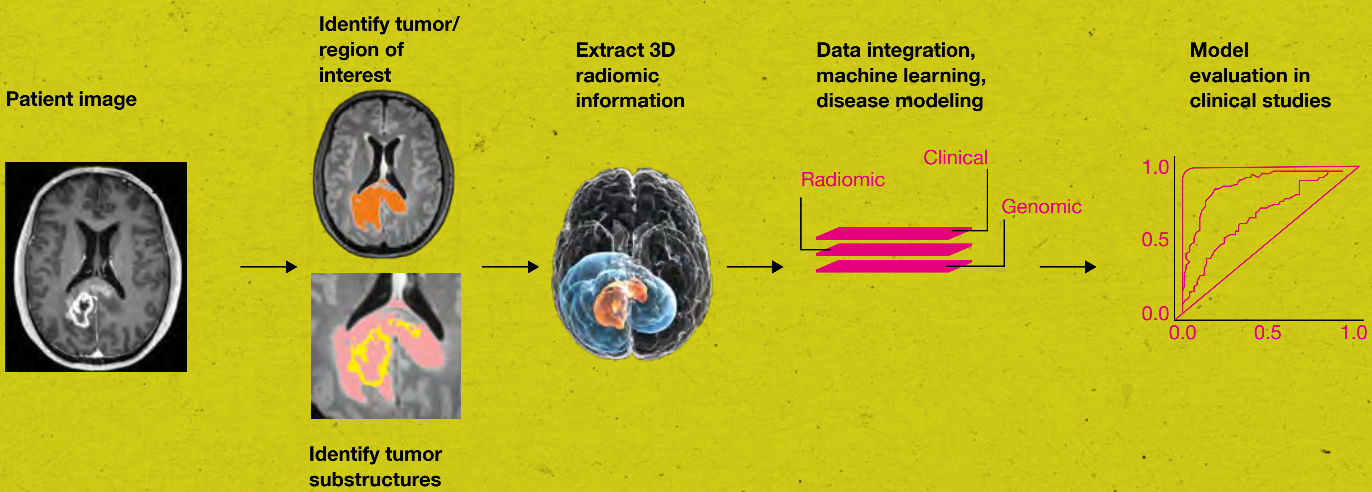
Computer vision and machine learning methods enable automated recognition and measurement of anatomical structures in computer tomography images. Data such as lung size, shape and texture are converted into a series of measurements, known as vector, that can subsequently be analyzed with statistical methods.

Picture credit: Kurt Bauer/TUM; Marie Bieth/TUM

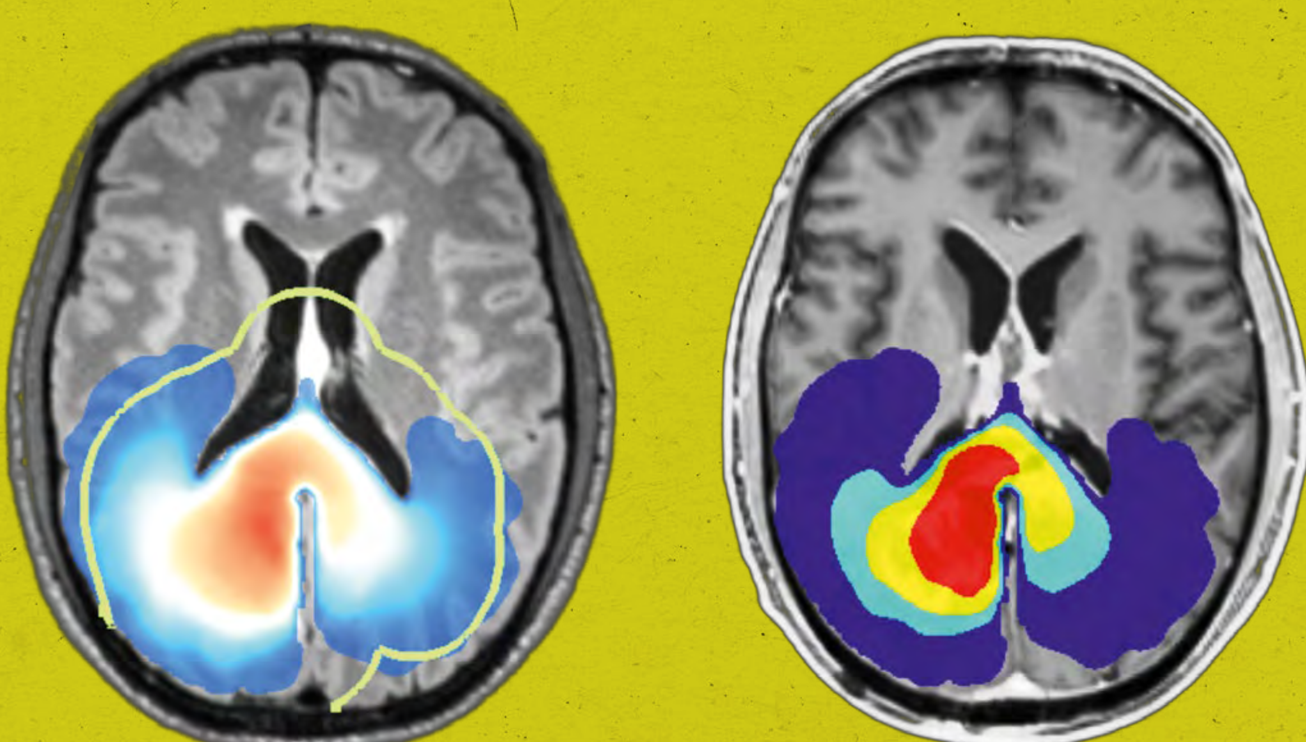
Computer Vision

Computer vision is a discipline that focuses on teaching computers specific capabilities that approximate the human visual system. At present, the primary focus of this field is the ability to identify specific objects within images, describe them, measure their properties and classify them. The outcomes can then serve as a basis for decision-making or determining subsequent processes. Many of the methods used by Bjoern Menze for medical image recognition and analysis stem from this area. Computer vision now also plays an important role in the development of self-driving cars. Here, the computer not only needs to "see" the street and everything happening on it, but must also be able to draw conclusions and learn from what it sees.

Extracting diagnostic image information and predicting disease progression



The flowchart shows the different steps in the process of image-based biomedical modeling that lead to the automated analysis of medical images. The information this yields could improve radiotherapy plans and reduce the side effects of radiation (lower image).



Improving radiotherapy plans for glioma patients – the target area and local radiation dose is adjusted to the tumor site and individual anatomy. In standard cases, the tumor is uniformly irradiated with a surrounding safety margin that is the same for all patients. Left: Conventional radiation chart. Right: Refined radiation chart derived from patient-specific tumor growth model.

Graphics: ediundsepp; Picture credit: Bjoern Menze/TUM

Following through on major advances in terms of technology and methods, Menze's next big challenge lies in clinical applications. The computer scientist also views his work as contributing to progress in personalized medicine. Here, patient populations are divided into small subgroups to optimize treatment delivery. With the availability of imaging data, patients can be assigned with greater precision to subgroups that respond well to a specific type of treatment.

Adapting learning algorithms

Menze's research group often adopts mature algorithms – including a deep learning algorithm from Google – as well as ones devised by other researchers, such as that developed by computer vision expert Prof. Daniel Cremers, also based at TUM. "The fact that big data and techniques like deep learning are also hot topics in business right now is certainly to our advantage," says Menze.

These algorithms cannot simply be adopted as is, however. They have to be adapted and further developed for biomedical applications. Menze and his team thus work in close collaboration with neuroradiologists, radiation therapists, neuropathologists and neurosurgeons to incorporate clinically relevant factors such as findings from tissue analysis or genetic markers into the learning algorithms. As well as healthcare professionals, the research team also liaises with physicists, biologists and mathematicians – who are working on tumor growth models, for instance.

Menze sets great store by this strong culture of interdisciplinary collaboration: "It's tremendously exciting to interact with so many different experts," he says. "All of these stakeholders are working with these images because they hold the information they need. But we are the ones capable of extracting quantitative data from them."

Even seemingly unrelated disciplines are benefiting from Menze's research efforts. As a PhD student at an archeology lecture in Boston (USA), Menze realized that the methods he was devising for medicine could also be applied to archeology. Together with archeologists from Harvard University, he used satellite images and his image recognition algorithms to locate ancient settlements – just like tumors in the human body. The computer scientist continues to pursue this "hobby" from his student days – whenever he can find the time.

Klaus Manhart

"The fact that big data and techniques like deep learning are also hot topics in business right now is certainly to our advantage."

Bjoern Menze

Brain tumors

Brain tumors occur relatively rarely compared to other types of cancer such as lung, breast and colorectal cancer. Worldwide, more than 256,000 brain and other Central Nervous System tumors were estimated to have been diagnosed in 2012, with incidence rates varying across the world (Cancer Research UK).

The groups most frequently affected are people between the ages of fifty and seventy and children (to a lesser extent). Benign gliomas and malignant medulloblastomas are the most prevalent forms in children. Conversely, malignant gliomas and benign meningiomas predominate in older people.

The outcome of a brain tumor cannot generally be predicted. Some forms of tumor have favorable treatment prospects, whereas others do not. The chances of successful treatment depend on the location of the tumor, the type of tumor cells, and sensitivity to radiation and chemotherapy.

Stefanie and Kilian Eyerich record several hundred attributes for each patient – an extract of the database is listed above. By analyzing this data, the researchers hope to improve the diagnosis and treatment of individual skin complaints.

Graphics: ediundsepp (source Eyerich); Picture credit: ediundsepp/TUM

The Right Treatment **for Every Skin Type**

Two scientists with one objective: Stefanie and Kilian Eyerich want to understand how inflammatory skin diseases occur and why they become chronic for some people. They are using the most advanced methods available and one of the world's most comprehensive dermatology databases.

Claudia Doyle

Für jede Haut das Richtige

Chronisch-entzündliche Hautkrankheiten wie zum Beispiel Neurodermitis (atopisches Ekzem) oder Schuppenflechte (Psoriasis) plagen immer mehr Menschen. Die Haut rötet und schuppt sich, oft kommt noch unerträglicher Juckreiz dazu. Neurodermitis tritt meist schon bei Kleinkindern auf, oft ohne erkennbaren Grund. Zwischen 15 und 20 Prozent aller Kinder leiden daran, Tendenz steigend. Schuppenflechte manifestiert sich meist erst später im Leben. Auch bei dieser Krankheit ist die genaue Ursache unklar.

Der Mediziner Kilian Eyerich ist Professor für Experimentelle Dermato-Immunologie an der Technischen Universität München (TUM). Stefanie Eyerich ist Biologin und leitet eine Forschungsgruppe am Zentrum Allergie und Umwelt der TUM und des Helmholtz Zentrums München. Gemeinsam haben sie sich das Ziel gesetzt, die Diagnose von Hautkrankheiten mithilfe von molekularen Markern zu verbessern und dem Patienten eine Prognose über den Verlauf seiner Erkrankung zu geben. In ihrem neuen Projekt erheben sie umfassende Daten von 400 Patienten, die entweder Schuppenflechte oder Neurodermitis haben. Von den Betroffenen entnehmen sie je eine gesunde und eine geschädigte Hautprobe. Zudem erfassen sie Werte wie Alter, familiäre Vorbelastung und Zeitpunkt des Krankheitsausbruchs. Sie analysieren die Blutwerte, die Bakterienpopulationen der Haut und die RNA-Sequenzdaten aus den Hautbiopsien. Dann suchen sie nach Gemeinsamkeiten zwischen den Fällen. Bioinformatiker helfen dabei, die Datenmengen in beherrschbare Häppchen zu zerlegen.

Sobald ein Gen identifiziert ist, das bei vielen Patienten einen Einfluss auf die Hautgesundheit zu haben scheint, geht es zurück ins Labor. Dort testen die Biologin und der Mediziner, was passiert, wenn Hautzellen zu viel oder zu wenig von diesem Gen exprimieren. Sie nutzen für ihre Experimente dreidimensionale Zellkulturmodelle, also Hautzellen, die in Petrischalen speziell für diese Versuche gezüchtet werden. Diese reagieren relativ ähnlich wie echte Haut, die Ergebnisse lassen sich also gut aus dem Labor in die Klinik übertragen. Bisher verlassen sich Dermatologen bei der Diagnose von Hautkrankheiten vor allem auf ihre Augen. Bald sollen sie zuverlässigere Methoden zur Hand haben. □

Kilian Eyerich's group "Experimental Dermato-Immunology"
www.derma-allergie.med.tum.de/forschung/experimentelle-dermato-immunologie.html

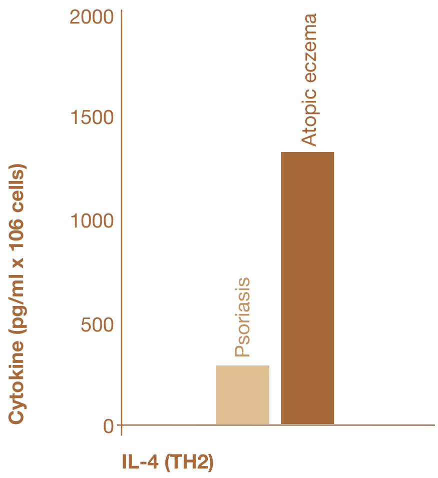
Stefanie Eyerich's group "Skin Immunology and Allergy"
www.zaum-online.de/research/lab-eyerich

One day a young patient came to the clinic to see Prof. Kilian Eyerich. Since earliest childhood, the teenager had suffered from atopic eczema, also known as neurodermatitis. This skin condition often makes its first appearance when the patient is still a child. For reasons that are not understood, the number of cases is steadily increasing. Today about 15 to 20 percent of all children suffer from the condition, which is accompanied by a red rash and sometimes itchy or oozing sores. The eczema generally comes and goes for no apparent reason. That was also true for this patient.
In puberty the atopic eczema suddenly vanished, but now he was plagued by scaly patches of skin: a condition known as psoriasis. This skin condition, which is to some extent hereditary, affects at least 100 million individuals worldwide.
Psoriasis and atopic eczema: two illnesses characterized by red, scaly and itchy skin. However, it is practically unknown for one patient to have both. For Stefanie and Kilian Eyerich, this patient was the starting point for a major insight into the contribution of different T helper cells to disease pathology.

Faszination Forschung: Professor Eyerich, Dr. Eyerich, how were you able to help this patient?
Kilian Eyerich: We treated his psoriasis and the therapy proved very effective.
Stefanie Eyerich: But the more the psoriasis improved, the faster the atopic eczema returned.
So as soon as you fought against one illness, the other flared up again?
K.E.: That's what happened, and we had never seen that before. We do have a few patients who suffer from atopic eczema as children and later develop psoriasis. In those cases, however, the atopic eczema disappears entirely. This interaction is very rare. We found only a few such patients in all of Europe.
Did that arouse your curiosity as a researcher?
S.E.: Yes, because we couldn't explain it. So we started looking at which kind of immune cells play a dominant role in the two skin conditions.
K.E.: And it is indeed two different types of T helper cells, present at the same time, that can trigger an entirely different skin reaction.

T helper cells (Th) are a group of white blood cells that form part of the adaptive immune system. They recognize hostile intruders such as viruses and bacteria on the basis of certain protein structures on their surfaces and then trigger an immune response. For a long time, only two types of T helper cells were known: Th1 and Th2. It was only 10 years ago when a third type was discovered: Th17.
The role of Th17 lymphocytes is to maintain homeostasis in tissues, for example when wounds are healing: In case of skin wounds, the body has two tasks. First, it has to close the

With large numbers of the population suffering from chronic inflammatory skin diseases, Stefanie and Kilian Eyerich want to gain a better understanding of these conditions through personalized medicine.



In atopic eczema, the Th2 lymphocytes are dominant. These damage the skin barrier and prevent wounds from healing. The skin becomes dry and prone to weeping at the same time.

Atopic eczema

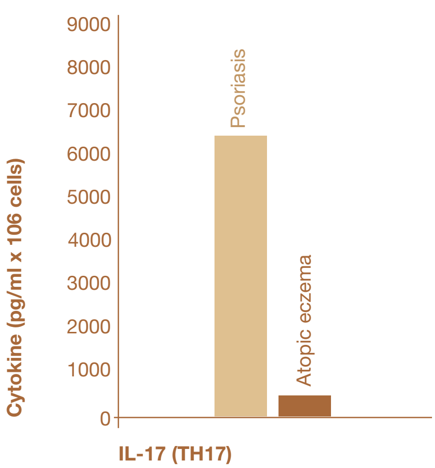
// Affected areas not clearly defined
// Over 20 million adult sufferers in Europe
// Red, scaly, itchy skin
// Skin is both dry and prone to weeping; formation of blisters
// Occurrence: Crook of the arm, back of the knee, face

Graphics: ediundsepp (source Eyerich); Picture credit: Magdalena Jooss/TUM

wound. It does this by instructing the skin cells to divide and to migrate. Second, it has to prevent pathogens from invading the tissue. It is exactly these two tasks that the Th17 lymphocytes perform. They not only trigger growth in the skin cells, but also the production of antimicrobial substances.
In a patient with psoriasis, this program takes place although there is no wound. The cells multiply wildly at breakneck speed, resulting in flaking of the skin.

How can this insight be used in treatment?
K.E.: The most effective therapy for psoriasis today is to block interleukin 17, the messenger substance sent out by the Th17 cells. That is now the gold standard.
But the Th17 lymphocytes do not play any role in atopic eczema?
K.E.: In atopic eczema, it is the Th2 lymphocytes that are the dominant factor.
S.E.: Th2 lymphocytes are known as a driving force behind allergies. In the skin they can also become part of a misguided immune response: They damage the skin barrier and thus interfere with the healing of wounds by preventing strong connections from forming between the new skin cells. This allows moisture to escape, resulting in extremely dry skin. At the same time, micro-organisms such as bacteria or fungi can colonize the area, sometimes even penetrating down to the deeper skin layers.
K.E.: Th2 lymphocytes have the exact opposite effect of Th17 lymphocytes. And it was ultimately this patient who showed us this. He had either atopic eczema or psoriasis lesions, but never both at once.

In 2015 Kilian Eyerich was awarded a Starting Grant by the European Research Council (ERC). The goal of the project is to improve diagnostics for skin diseases. Today dermatologists rely above all on their eyes when diagnosing illnesses. A look at the patient followed by a look at the skin cells under the microscope: in most cases, this makes it possible for clinicians to make a reliable distinction between atopic eczema and psoriasis. In most cases.
There are patients where it is not clear which of the two conditions is present. Especially when the changes in the skin occur in the hands, it can be quite difficult to tell the difference between atopic eczema and psoriasis.
It has also proved impossible until now to make accurate prognoses on the future course of these conditions. There is still no way of predicting whether a patient will develop asthma from their atopic eczema or arthritis from psoriasis. Stefanie and Kilian Eyerich have therefore made it their goal to improve the diagnosis of skin diseases with the help of molecular markers and provide patients with a prognosis on how their condition will develop over time. ▷



In psoriasis, Th17 lymphocytes dominate. They instruct the skin cells to divide, but if this happens at an accelerated rate, the characteristic scales will form.

Psoriasis

- // Affected areas clearly defined
- // 20 million sufferers in Europe
- // Red, scaly, itchy skin
- // Skin forms silvery-white scales which fall off easily
- // Occurrence: Elbow, knee, scalp

Picture credit: Magdalena Jooss/TUM

“Our goal is personalized medicine for chronic inflammatory skin diseases.” *Kilian Eyerich*

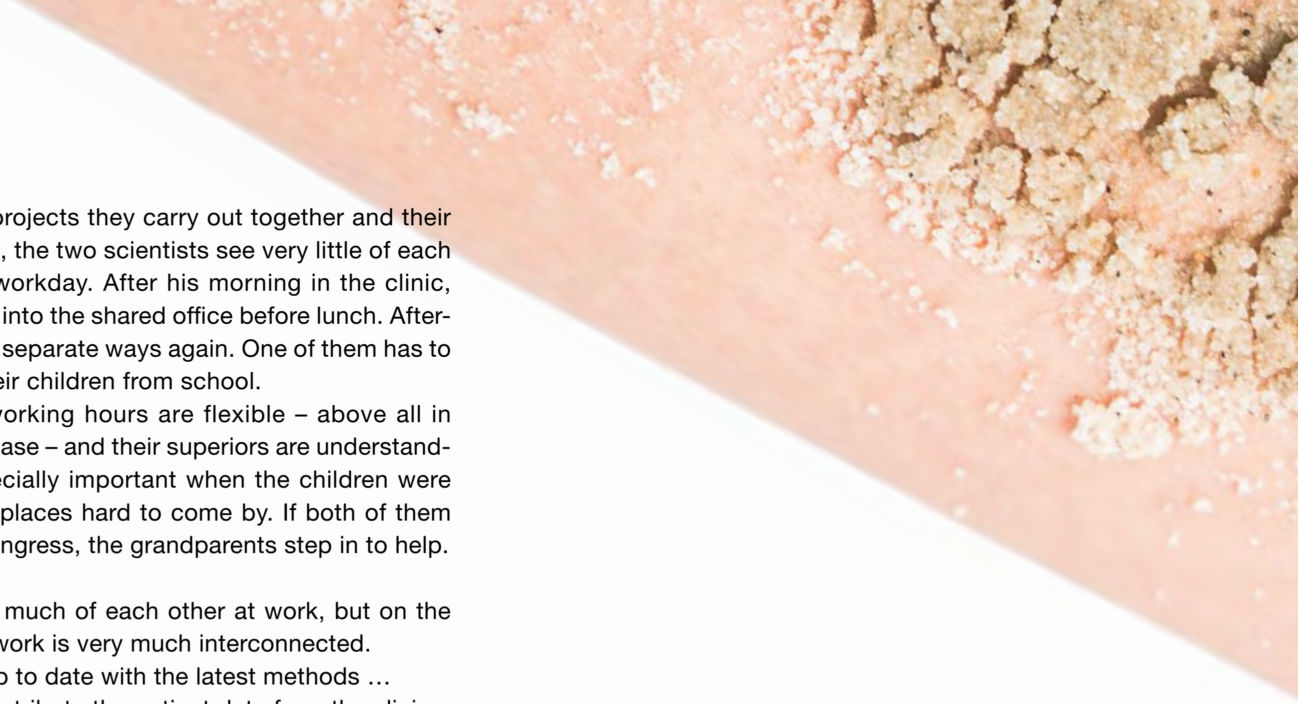
Dr. Stefanie Eyerich and Prof. Kilian Eyerich

Better Together

In search of an area for her doctoral research at TUM, biologist Stefanie Eyerich (39) knew she wanted a subject in the field of medicine. She found dermatology – and her husband. She took on a topic that the medical student Kilian Eyerich (38) had examined in his own doctoral research.
After completing her thesis, Stefanie Eyerich went to pursue her studies in London. And Kilian Eyerich went to Rome where he worked as a postdoctoral researcher.
They both returned to Munich in 2009. She went to the Center of Allergy and Environment (ZAUM), a joint research institution of TUM and Helmholtz Zentrum München (HMGU). He began his residency as a dermatologist. During that time, Kilian Eyerich also intensified his research activities and completed his Ph.D. That meant days in the clinic and evenings in the laboratory. At that time, financial support – or role models – for this career path were virtually non-existent. Although the structures have improved since then, many young doctors are still hesitant to take on that kind of double workload.
In 2012 Kilian Eyerich became a senior physician at the Department of Dermatology and Allergy of TUM’s university hospital. In 2014 he was appointed to a Heisenberg Professorship at TUM, funded by the German Research Foundation (DFG).
Stefanie Eyerich was appointed head of a joint junior research group at ZAUM and HMGU in 2013.

Today dermatologists have to rely on their eyes alone to arrive at a diagnosis. What are the advantages of molecular markers such as genes or proteins?
K.E.: A molecular diagnosis is more specific, which means that treatments can be targeted more precisely. When a drug costs 25,000 euros per year, it should go to a patient who will presumably benefit from it. There is enormous variation in eczema conditions, and we still know very little about them. Our goal is personalized medicine for chronic inflammatory skin diseases.
How do you aim to achieve that?
S.E.: By collecting highly detailed patient data and comparing it with the RNA sequencing data from the skin biopsies.
K.E.: In our database there are around 400 patients who either have psoriasis or atopic eczema. And we have characterized every one of them on the basis of hundreds of attributes.
Which ones?
K.E.: For example, which area of the skin is affected? Is there any family history? Are there other accompanying conditions? When did the condition occur for the first time? You can’t seriously compare a six-month-old infant with an 80-year-old adult. But that is still happening today.
And you also include biological parameters?
K.E.: Of course. We look at the immune cells, blood vessels, endothelial cells, blood results, the bacterial populations on the skin. And then we look for common factors linking the patients.
S.E.: For that we need bioinformatics experts who break down the data into smaller packages.
K.E.: It takes an interdisciplinary approach.

The scientists have been working on the project since July 2016. From each patient they took samples of both healthy and damaged skin and sequenced the RNA. Whereas the DNA in all cells is identical, the RNA profile reveals which genes are expressed in the individual cells. An RNA analysis therefore provides information on what is currently happening in the cell. Now the analysis is being carried out.
When a gene is identified that may have an effect on the skin health of many patients, the laboratory work begins again. Stefanie Eyerich tests what happens when skin cells express too much or too little of the gene in question. For her experiments she uses three-dimensional cell culture models, specially grown in Petri dishes for this purpose. Their responses are quite similar to those of real skin, so that it is relatively easy to transfer the results from the laboratory to a clinical setting. ▷



Despite the many projects they carry out together and their shared laboratories, the two scientists see very little of each other in a normal workday. After his morning in the clinic, Kilian Eyerich pops into the shared office before lunch. Afterwards they go their separate ways again. One of them has to leave to pick up their children from school.
Fortunately their working hours are flexible – above all in Stefanie Eyerich's case – and their superiors are understanding. That was especially important when the children were small and daycare places hard to come by. If both of them want to attend a congress, the grandparents step in to help.

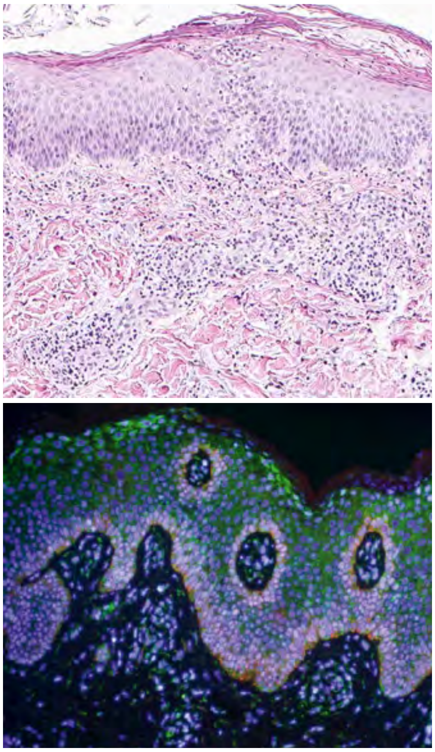
S.E.: We don't see much of each other at work, but on the scientific level our work is very much interconnected.
K.E.: You're right up to date with the latest methods …
S.E.: … and you contribute the patient data from the clinic.
K.E.: Each half perfectly complements the other.

Claudia Doyle

"We need bioinformatics experts who break down the data into smaller packages." *Stefanie Eyerich*

Atopic eczema

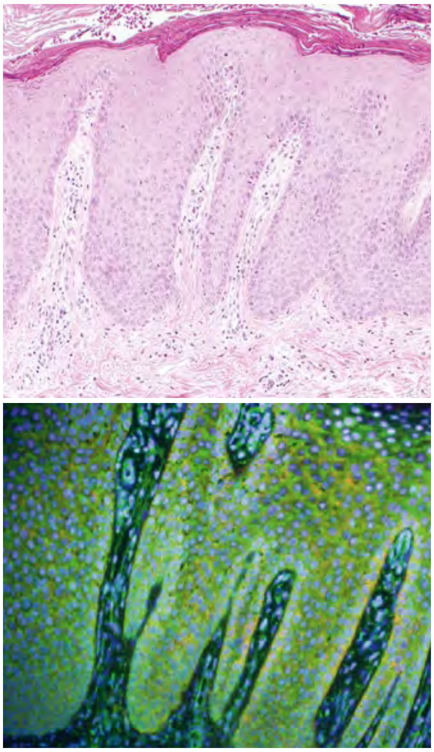
// Top: Light microscopy
// Bottom: Fluorescence microscopy



In atopic eczema, the connections between the epidermis and skin cells (keratinocytes) are damaged. The skin cells create more of a semiochemical called CCL27 (red staining in lower picture).

Psoriasis

// Top: Light microscopy
// Bottom: Fluorescence microscopy



In psoriasis, the epidermis becomes thicker. The skin cells form more of the enzyme iNOS (green staining in lower picture), which plays an important role in the immune system.

Picture credit: Stefanie and Kilian Eyerich/TUM; ediundsepp/TUM

On the Trail of **Tomorrow's Semiconductors**

In the quest for new semiconductors, researchers are no longer relying on experiments alone. In an approach that could be a game changer for photovoltaics and computing applications, physicist Harald Oberhofer and his team are developing computer models capable of analyzing just about every conceivable material.

Graphics: ediundsepp (source: TUM)

Harald Oberhofer's group at the Chair of Theoretical Chemistry

www.th4.ch.tum.de/oberhofer/

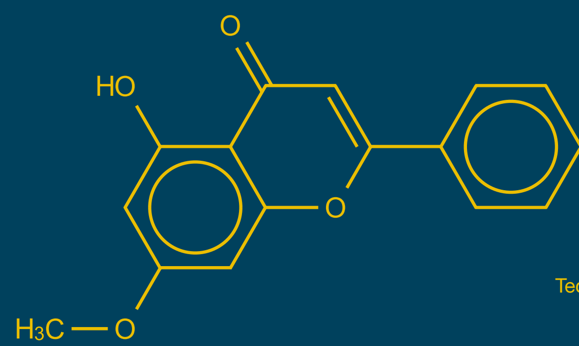
Reinhard Kleindl

Wo steckt der Halbleiter von morgen?

Mehr als 10.000 Materialien aus unterschiedlichen Einsatzbereichen wie etwa der Pharmakologie haben Wissenschaftler um Dr. Harald Oberhofer auf ihre Halbleiter-Eigenschaften hin untersucht. In Laborversuchen wäre das nicht durchführbar. Möglich wird es mithilfe ausgefeilter Computermodelle und riesiger Datenbanken, in denen die Eigenschaften hunderttausender Materialien gesammelt sind. Oberhofer ist Leiter einer Forschungsgruppe am Lehrstuhl für Theoretische Chemie der TUM – und das, obwohl er eigentlich Physiker ist. Das ist kein Zufall, auch die Chemie basiert auf physikalischen Vorgängen. Der 37-Jährige sucht mit seinen Computermodellen nach neuen Halbleitern, die nicht auf Silizium basieren, sondern auf Materialien der organischen Chemie, also Kohlenstoffverbindungen.

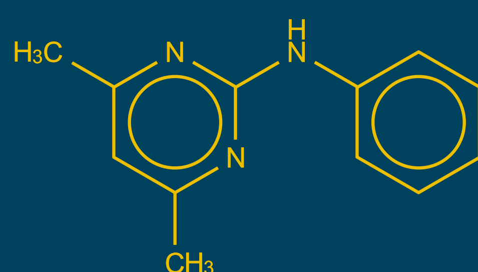
Einige dieser organischen Halbleiter haben längst ihren fixen Platz in der Technik, etwa organische Leuchtdioden, bekannt als OLED. Organische Solarzellen hingegen, die eine besonders kostengünstige Stromversorgung versprechen, kranken nach wie vor an der schlechten Haltbarkeit im Sonnenlicht. Dass es geeignetere Materialien gibt, ist nicht auszuschließen, die meisten organischen Halbleiter sind nach wie vor unerforscht.

Die Menge der theoretisch möglichen organischen Verbindungen ist zudem gigantisch. Oberhofer konnte unter den 10.000 untersuchten Materialien eine Handvoll organischer Stoffe identifizieren, die über eine ausreichende Leitfähigkeit verfügen, um als Halbleiter geeignet zu sein. Diese können nun einer genaueren Analyse unterzogen werden. Dann wird sich zeigen, ob sich darunter Materialien für beständigere Solarzellen finden. □



Techtochrysin

Perinone



Pyrimethanil

Using theoretical screening methods, Harald Oberhofer's team has identified several molecules with good semiconductor properties. These include:
// Techtochrysin, a flavonoid present in sour cherry
// Perinone, a red pigment that is already used as a semiconductor
// Pyrimethanil, a fungicide used in herbicides

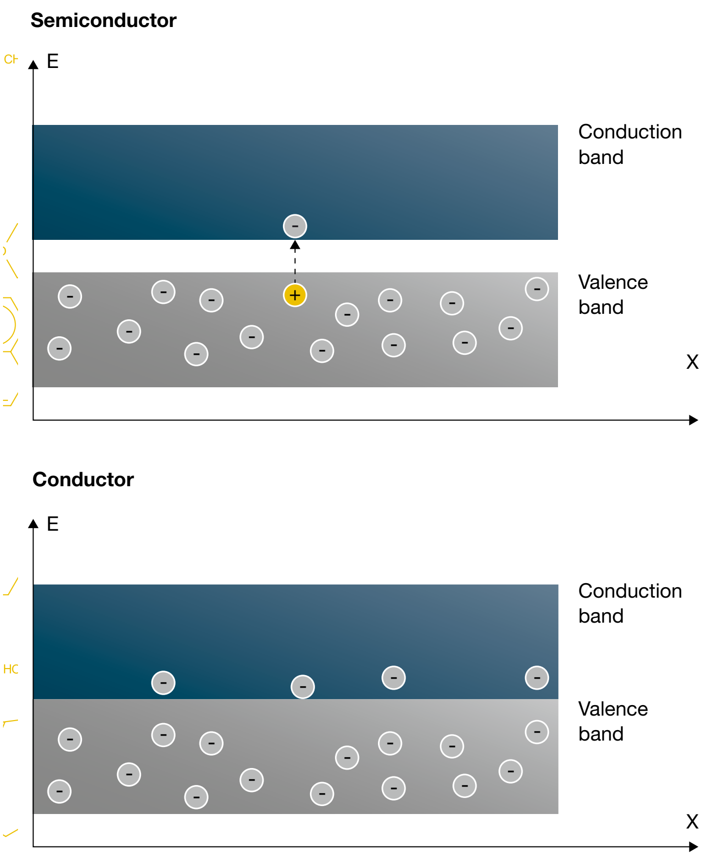
"With the help of computer simulations we can obtain very detailed insights – into the structure of 10,000 different molecules."

Harald Oberhofer

Breakthroughs in the history of technology have often been sparked by the discovery of new materials and exploration of their properties. New knowledge about semiconductors paved the way for the Information Age, just as the ability to produce bronze by smelting copper and other alloys marked an end to the Stone Age. In many cases, the discovery of new materials and their specific properties was simply a matter of luck.
Nowadays, the understanding of matter at a chemical level is so extensive that certain research groups are no longer willing to rely on chance. They have started to theoretically determine the properties of thousands of materials in the search for highly specific capabilities that would be promising for various technical applications. This process is known as "theoretical screening". One researcher involved in this field is physicist Dr. Harald Oberhofer from TUM. His mission is to find the semiconductors of the future and open up new opportunities in photovoltaics or the manufacture of energy-efficient electronics.

Virtual microscope

"This is the best microscope in the world," says Harald Oberhofer with a knowing smile. He works as a research group leader at TUM's Chair of Theoretical Chemistry on the Garching Campus. Sitting in his office, he looks at a screen as he writes lines of code in the Python and Fortran programming languages. The programs he is creating along with his research group will soon be running on one of Europe's fastest supercomputers. The SuperMUC is only a few buildings away at the Leibniz Supercomputing Center. Acting like a virtual microscope, it will provide in-depth insights into the electrical behavior of an extremely large number of chemical compounds. ▷

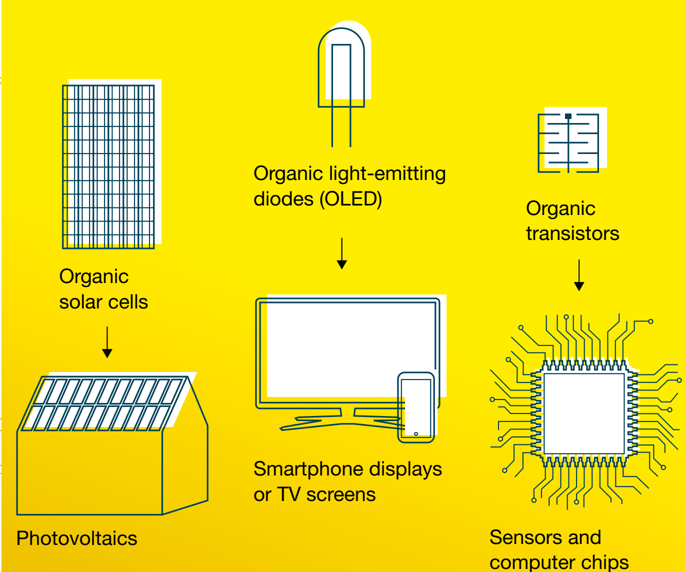


The difference between conductors and semiconductors lies in the way the electrons behave. Whereas conductor electrons (bottom) are highly mobile and begin to flow with the slightest external charge, electrons in semiconductors (top) need to reach a certain threshold energy before they can flow freely – illustrated by the gap in the middle of the image; also known as the "band gap". Absorbed light can energize the electrons to the required level, an effect that is used in photovoltaics.

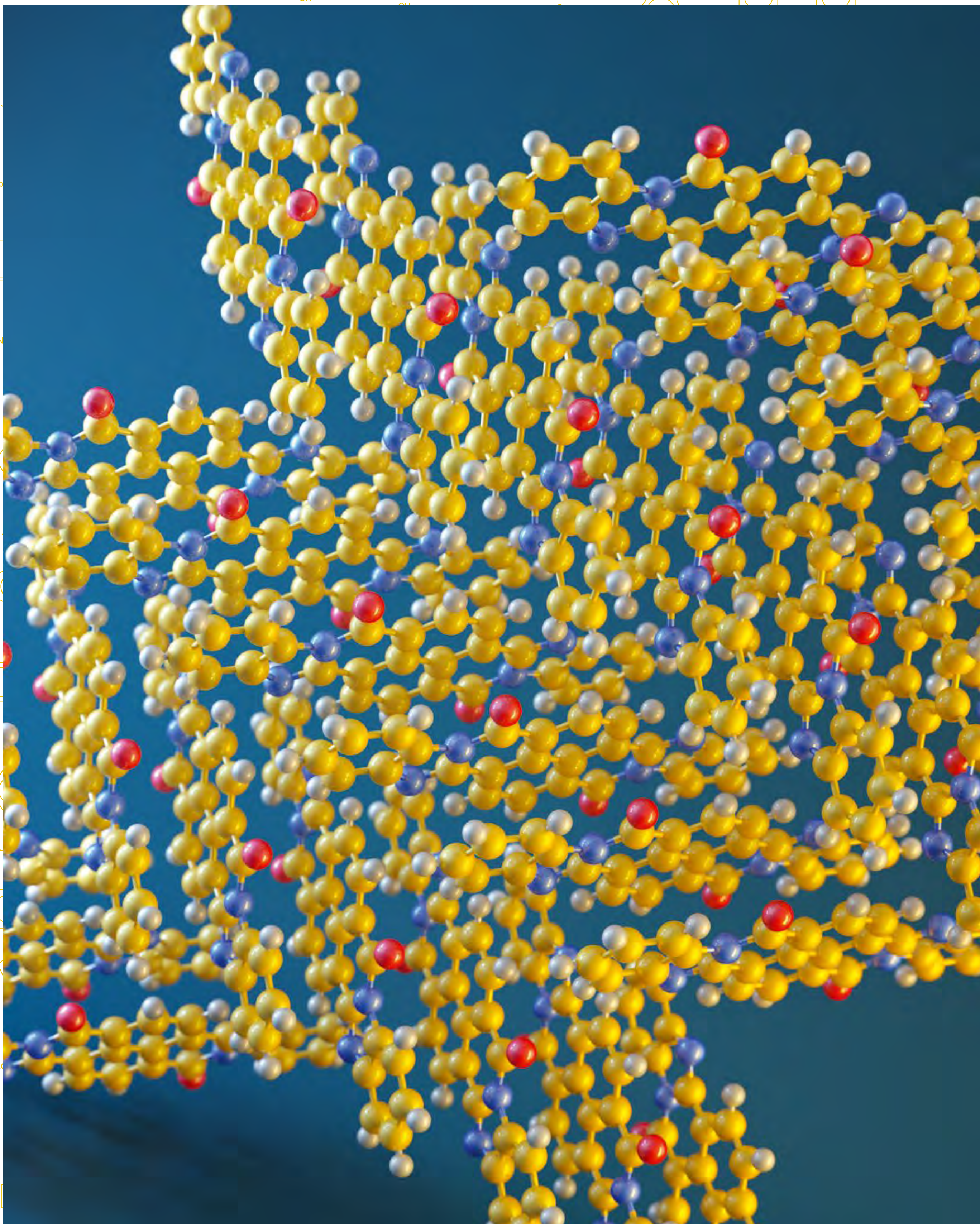
Semiconductors

Semiconductors are materials that conduct electricity under certain circumstances. The best-known example is the element silicon. Somewhere between insulators, which hardly conduct any electricity at all, and conductors, which have excellent conductive properties, semiconductors offer differing degrees of efficiency depending on various factors. One of these is temperature. At low temperatures, semiconductors do not conduct electricity whereas they do when the temperature rises to a certain point. The opposite is the case with conductors such as metals, for instance, where conductivity generally drops as the temperature rises. It is possible to selectively modify the electronic properties of a semiconductor material by doping it (i.e. by introducing foreign atoms). Semiconductors can be used to fabricate diodes, transistors and even computer chips – hence the reference to the "semiconductor industry".

Usage of organic semiconductors



Graphics: edundsepp (source: TUM)



In solid form, organic molecules can be organized into a structure known as a crystal. The scheme shows a crystal of perinone, a red pigment with semiconductor properties. The molecule is composed of oxygen (red), nitrogen (blue), carbon (yellow) and hydrogen (white).

Oberhofer is especially interested in organic materials, and wants to find out if they have potential as semiconductors. Here the word “organic” refers to the field of organic chemistry that deals with carbon compounds, including plastic in all its forms.
Organic semiconductors are already widely used by some manufacturers – smartphone screens being one good example. They work with what are known as OLEDs – organic light-emitting diodes.

Short-lived solar cells

The weakness of organic semiconductors lies mainly in their limited lifespan, in particular in the case of solar cells. The fact that they are continuously exposed to UV light means that they are subject to degradation to a certain extent. “Organic solar cells do have a lifespan problem,” admits Oberhofer. Which is why the researchers are keen to find materials that selectively convert the absorbed UV light without resulting in degradation. There is a good chance of success given that up to now, only a fraction of potential organic semiconductor materials have been investigated. This is what Oberhofer wants to change with his research. With the help of computer models, he calculates charge transfer in solids made of organic molecules. ▷

Theoretical screening

All modern natural science disciplines rely on theoretical research. Experiments are supplemented and supported by this type of research and, increasingly, computer simulations. Theoretical chemistry has two threads. On the one hand, research groups try to gain a detailed understanding of what happens within experiments and develop recommendations for improvements or new tests. On the other hand, independently of the experiment, they are on the quest for something completely new, such as identifying promising materials that were previously used in a completely different context. This process is known as “theoretical screening”. The line between theory and experiments is becoming somewhat blurred now that experimenting researchers are increasingly likely to carry out their own computer simulations.

Harald Oberhofer at the Leibniz Supercomputing Centre: His complex calculations run on the SuperMUC, one of Europe’s fastest supercomputers.

Graphics: ediundsepp (source: TUM); Picture credit: Kurt Bauer/TUM

"The big advantage of computer simulations is that we can obtain very detailed insights into the structure of molecules," describes Oberhofer. "We see where the electrons are located – something that is very hard to do in an experiment. We begin by looking at large international materials databases." These list all materials produced and characterized by various research groups over the decades, including everything from drugs to components of crude oil. "We use our computational models to screen for promising organic semiconductor candidates," says the 37-year-old physicist.

Sea of molecules

Oberhofer calls up a screen showing arrangements of colorful spheres representing molecules. "One of the things that determines whether a material has semiconductor potential is the ease with which individual electrons jump from one molecule to another," he explains. The greater the overlap between the electron orbitals, i.e. the higher the electron density, the more likely this is. Another criterion is the amount of energy an electron requires to make the switch from one molecule to another. When both effects are considered together, useful information can be gleaned about the material's conductivity.

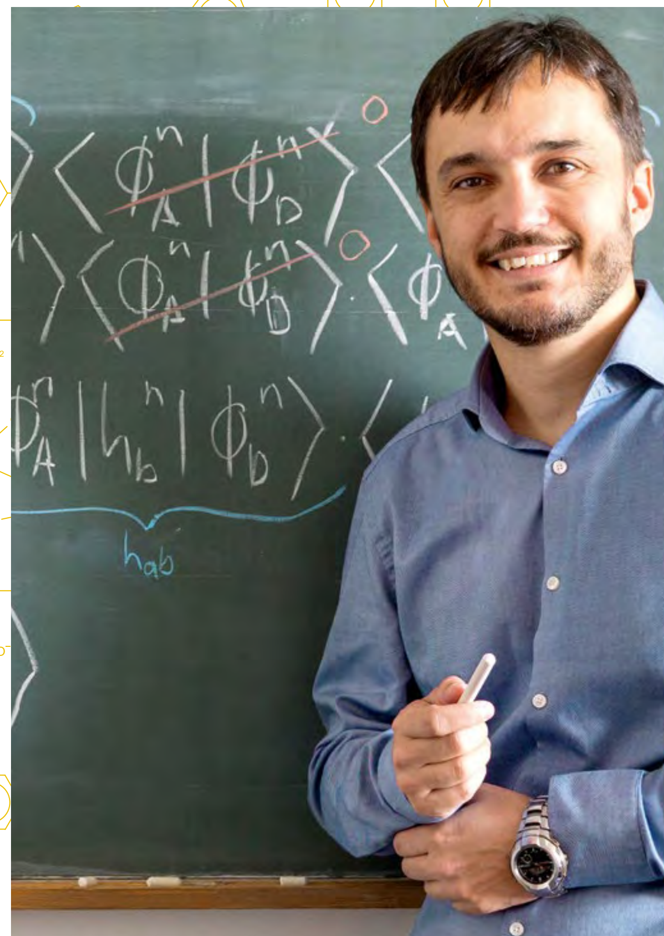
Oberhofer's analysis is based on what is known as the "density functional theory". This is a method from quantum physics which can be used to calculate the distribution of electrons in molecules.

According to Oberhofer, the only way to perform such analyses is by using theoretical methods: "The substances we are investigating can be costly and difficult to get a hold of. Some of them we even have to synthesize before we can obtain crystals and then run extensive tests," Oberhofer explains. "You can do that up to a certain point, but not for the 10,000 systems that we screened using our method. We only select the most promising candidates for more detailed investigation," says Oberhofer. Through this work, he produces valuable pointers for his colleagues' experiments. "The huge number of possible molecules gives us massive scope for semiconductor candidates," adds Oberhofer.

Interesting material discoveries

"We have managed to identify a few materials from completely different application scenarios that have good semiconductor properties. They include a pigment and a fungicide," says Oberhofer, who is now planning to investigate the most promising candidates using more precise theoretical methods. One of them could prove to be the ideal semiconductor for the solar cells of tomorrow.

Reinhard Kleindl



Dr. Harald Oberhofer

A theoretician at heart

Harald Oberhofer is head of a research group at TUM's Chair of Theoretical Chemistry (Prof. Karsten Reuter) even though he actually qualified as a physicist. That is not so unusual, however, since chemistry is also based on physical processes. "For me, the development of methodologies has always been my main interest. I really enjoy working away at intricate 'puzzles' like these," admits the 37-year-old scientist.

Originally from Vienna (Austria), he obtained his doctorate from the University of Vienna with a thesis on statistical mechanics. During three years of research at the University of Cambridge (UK), he developed an interest in the simulation of charge transfer. His current research is focused on the search for new organic semiconductors, photocatalysts and metal-organic frameworks.

Graphics: ediundsepp (source: TUM); Picture credit: Kurt Bauer/TUM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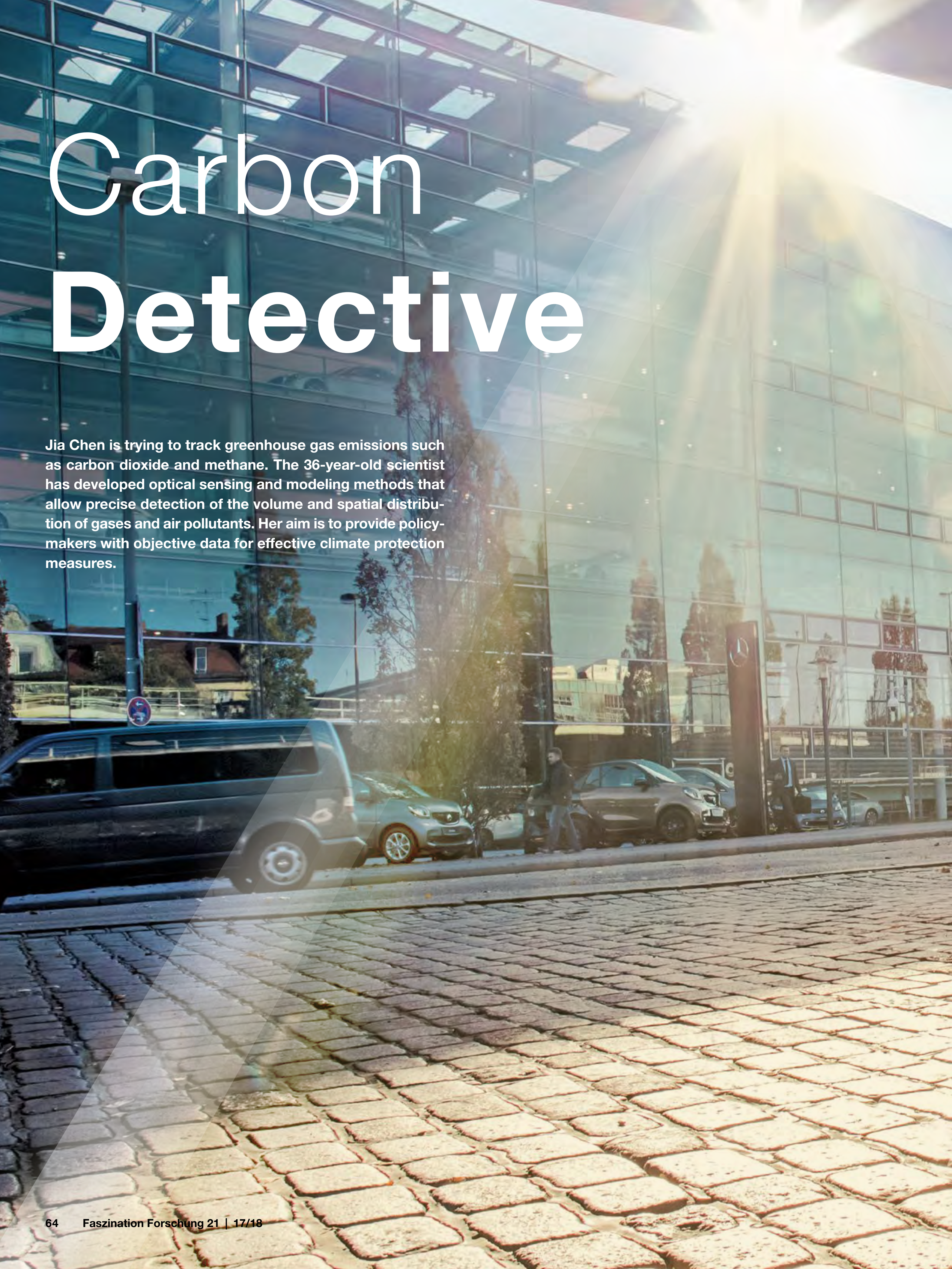


Carbon **Detective**

Jia Chen is trying to track greenhouse gas emissions such as carbon dioxide and methane. The 36-year-old scientist has developed optical sensing and modeling methods that allow precise detection of the volume and spatial distribution of gases and air pollutants. Her aim is to provide policymakers with objective data for effective climate protection measures.

Environmental Sensing and Modeling

www.esm.ei.tum.de

Picture credit: ediundsepp/TUM

Karsten Werth

Treibhausgasen auf der Spur

Der Klimaschutz ist eine der großen Herausforderungen für die Menschheit im 21. Jahrhundert. Prof. Jia Chen hat eine Messmethode entwickelt, um mit wenigen kompakten Sensoren die Treibhausgasemissionen einer Stadt zu erfassen. Ihr Ziel ist es, die Menge und Verteilung von klimaschädlichen Gasen wie Kohlendioxid, Methan und Kohlenmonoxid in der Luft exakt zu messen. „Um die Wirksamkeit von Klimaschutzmaßnahmen einzuschätzen, sind objektive Messungen notwendig. Berechnungen und Schätzungen mit vielen Unbekannten reichen nicht aus", sagt die Professorin für Umweltsensorik und Modellierung an der TUM.

Chen's Messmethode basiert auf Infrarotspektrometern, die sich nach der Sonne ausrichten. Weil jedes Gasmolekül einen ganz bestimmten Teil des Lichtspektrums absorbiert, lässt es sich anhand seines „spektralen Fingerabdrucks" eindeutig identifizieren. Da die Sonne als Lichtquelle genutzt wird, kann eine ganze Luftsäule erfasst werden. Vermessen werden solche atmosphärischen Säulen außerhalb und – in Windrichtung – innerhalb einer Stadt. Die Unterschiede zwischen den Messungen zeigen dann, wie viele Emissionen in der Stadt generiert werden. In Verbindung mit Winddaten lässt sich mit dieser sogenannten Differenzialsäulenmessung genau berechnen, wie sich die Treibhausgase räumlich verteilen. Im nächsten Schritt will die 36-jährige Ingenieurin auch die Erfassung von Stickoxiden in das Messkonzept integrieren.

Ein Netzwerk von automatisierten, kompakten Sensorsystemen soll als Pilotprojekt in München aufzeigen, wo Emissionen entstehen, wohin sie sich bewegen und welche Auswirkung ihre Verteilung auf die Luftqualität hat. „Die Stadt München könnte eine Vorreiterrolle einnehmen, wenn es darum geht, die Wirksamkeit von Klimaschutzmaßnahmen objektiv zu überprüfen", sagt Chen. □

When she steps out onto the roof terrace, Jia Chen is greeted by an impressive panoramic view of downtown Munich. Up here, however, the Professor of Environmental Sensing and Modeling is concerned less with the sightseeing highlights of the Bavarian capital and more with the equally prominent chimneys that tower over the city's heat and power plants. They may be among the cleanest of their kind, but – besides traffic – the municipal power and heating facilities are some of the city's biggest carbon dioxide emitters. The measurement instruments set up on the roof of TUM's Department of Electrical and Computer Engineering are intended to provide an accurate picture of urban air pollutants and their origins.

Conventional measurements fall short

"If you just take measurements at a single point, for instance on a power plant chimney, the results are not particularly meaningful because the pollutants spread out from there in a gas cloud," describes Chen, indicating plumes of exhaust gas in the sky. "You don't know in what direction the gases are moving and what effect their distribution will have on air quality." And horizontal dispersion of pollutants by the wind is not the only factor, she emphasizes. Measurements should also include vertical dynamics in the atmosphere: Depending on ground temperature, gases dissipate upwards at different speeds, mixing with the air. However, surface and point sensors are not able to measure this.

Bigger picture with new method

Chen specializes in optical gas sensors and their application in environmental monitoring. Together with Professor Steven C. Wofsy from Harvard University in Cambridge (USA), Jia Chen has developed a new method of quantifying the pollution emitted within a city using a few compact sensor systems. These are based on infrared spectrometers which track the sun. Since each gas molecule absorbs the light spectrum at a specific wavelength, it can be uniquely identified using its "spectral fingerprint". Carbon dioxide (CO_2), for instance, absorbs sunlight at wavelengths between 1565 and 1620 nanometers (nm) – methane, by contrast, at wavelengths between 1627 and 1696 nm. Since the sun is used as the light source, an entire column of air can be recorded in this way. These atmospheric columns are measured both outside (upwind) and inside (downwind) the city. The differences between the measurements reveal the level of emissions generated within the city. In conjunction with wind data, these differential column measurements enable precise calculation of greenhouse gas emissions. Thanks to their high sensitivity, the sensors work even on days with partial cloud cover. However, they are not suitable for use at night or in rainy weather. ▷

Graphics: ediundsepp, Source: Jia Chen

Tracking greenhouse gas emissions: An optical sensor measures the number of different gas molecules in the column of air downwind of an emissions source, in other words after the air column traveling through the emissions source or the city. A second sensor measures the gas in the air upwind. Based on the difference between the two air columns, Jia Chen then calculates how much carbon dioxide and methane was emitted and where, using atmospheric transport models. In the next step, this method will be applied to other air pollutants like nitrogen oxides. The method has been validated in measurement campaigns (Chen et al., 2016).

On the roof of TUM's Department of Electrical and Computer Engineering, Jia Chen and her team operate the only sensor system permanently installed in Munich that measures greenhouse gases such as carbon dioxide and methane. The sensor system is equipped with a FTIR spectrometer and a patent-pending automated weather-resistant housing (Heinle and Chen, 2017). Its cover follows the movement of the sun and automatically closes if it rains, in order to protect the optical and electronic components. The gas fired district heating plant Theresienstrasse operated by Munich City Utilities (SWM) is visible in the background (right).

"Objective measurements are the only way to answer questions about the effectiveness of climate protection activities"

Jia Chen

Helping to inform political decision-making

The advances in environmental sensing could help to reduce greenhouse gas emissions and thus slow global warming. Efficient, long-term monitoring of urban air quality also makes it easier to determine the success of climate and environmental protection measures. Chen and her team have been gathering data since 2015 using her sensor system. She clarifies: "It is important to review objectives and action plans on a regular basis and adjust them as necessary – which is where we can support policymakers."

Another of Chen's research interests lies in investigating technologies considered to be eco-friendly, such as the passive house concept, geothermal energy and e-mobility. Do all of these really lead to reduced emissions? "Answering this question calls for objective measurements. Calculations or estimates with unknown variables are not good enough," declares Chen.

How much methane is escaping?

Even today, not much is known about actual levels of greenhouse gas pollution in city air, for instance. Chen explains that natural gas escapes from weak points in pipelines and storage facilities. In Boston (USA), her colleagues took measurements that show that leaky gas pipes are allowing around three per-

Side-by-side measurements: Jia Chen and her colleagues calibrate their sensors before a six-week series of carbon dioxide, methane, carbon monoxide and nitrogen oxide measurements in Munich in autumn 2017. The results will contribute to a larger international study. Left to right: Ralph Kleinschek (German Aerospace Center – DLR), Florian Dietrich, Jia Chen, Michael Wedrat (TUM).

cent of methane – the primary component of natural gas – to escape. “Natural gas is considered a greener fuel than coal because it generates less carbon dioxide when combusted. But what about the methane that seeps into the atmosphere before combustion? Methane has a much stronger greenhouse effect than CO_2. So we need to keep an eye on that,” points out Chen.

Munich as proof of concept

The measurement station developed and operated by Chen’s team is the only one permanently installed in Munich that measures greenhouse gases such as CO_2 and methane. The city’s CO_2 emissions are calculated according to a “bottom-up” approach – that is, upscaling individual emitters such as factories, power plants and vehicles with economic data or spatial proxies. However, this approach includes considerable uncertainties because many parameters are unknown. For example, combustion efficiencies cannot be clearly established. In addition, emitters that are unaccounted for, such as pipeline leaks, will not be included.

Chen’s goal is to determine the emissions by combining the concentration measurements taken by six automated stations with atmospheric transport modeling. To achieve this, she is liaising with city authorities and the municipal utilities provider Stadtwerke München. The planned monitoring network would reveal how much greenhouse gas and air pollutants are being emitted – and exactly where. As a next step, she is looking to integrate nitrogen oxide detection into the measuring system. “Objective measurements are the only way to answer questions about the effectiveness of climate protection activities,” asserts Chen. “So the city of Munich could play a pioneering role in the objective review of measures designed to protect the climate.”

Chen’s team uses sensors to help identify emissions sources and sinks. “If we know how many molecules of a particular gas are present in the atmosphere and how they are transported, we can work backwards to see where they come from – for instance a landfill site, natural gas storage unit or agricultural holding. We can also see how effectively forests and parks are absorbing carbon,” says Chen.

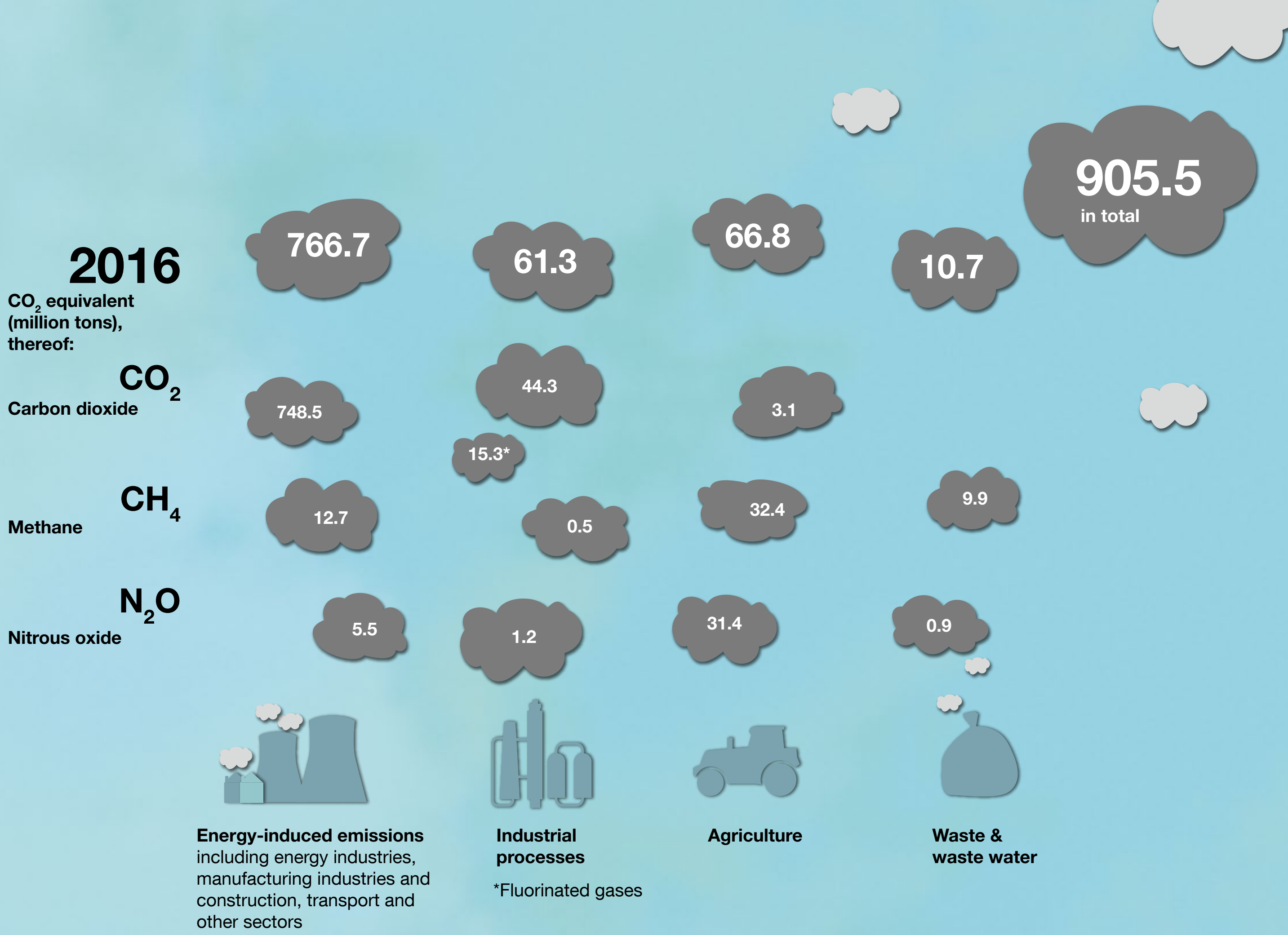
Getting started

A six-week series of measurements in autumn 2017 allowed Chen and her team to demonstrate what this type of urban sensor network can accomplish. Together with colleagues from Harvard University (USA) and Germany’s Ludwig-Maximilian University of Munich (LMU), the German Aerospace Center (DLR) and the Karlsruhe Institute of Technology (KIT), ▷

Picture credit: Andreas Heddergott/TUM

“What drives me in my work is the potential to improve the quality of air – and thus of people’s lives”

Jia Chen



Greenhouse gas emissions in Germany (2016 estimates by the German Environment Agency, UBA)
Close to 906 million tons of greenhouse gases were emitted in Germany in 2016. The energy sector, including heat and power plants, as well as road traffic were the main sources. Emissions from industrial processes also contributed to the total amount of greenhouse gas emissions, as well as agriculture with mainly methane (CH_4) and nitrous oxide emissions. Germany's goal is to reduce emissions by 40 percent through 2020, compared to 1990 levels. The current level of reduction achieved is only 27.6 percent.

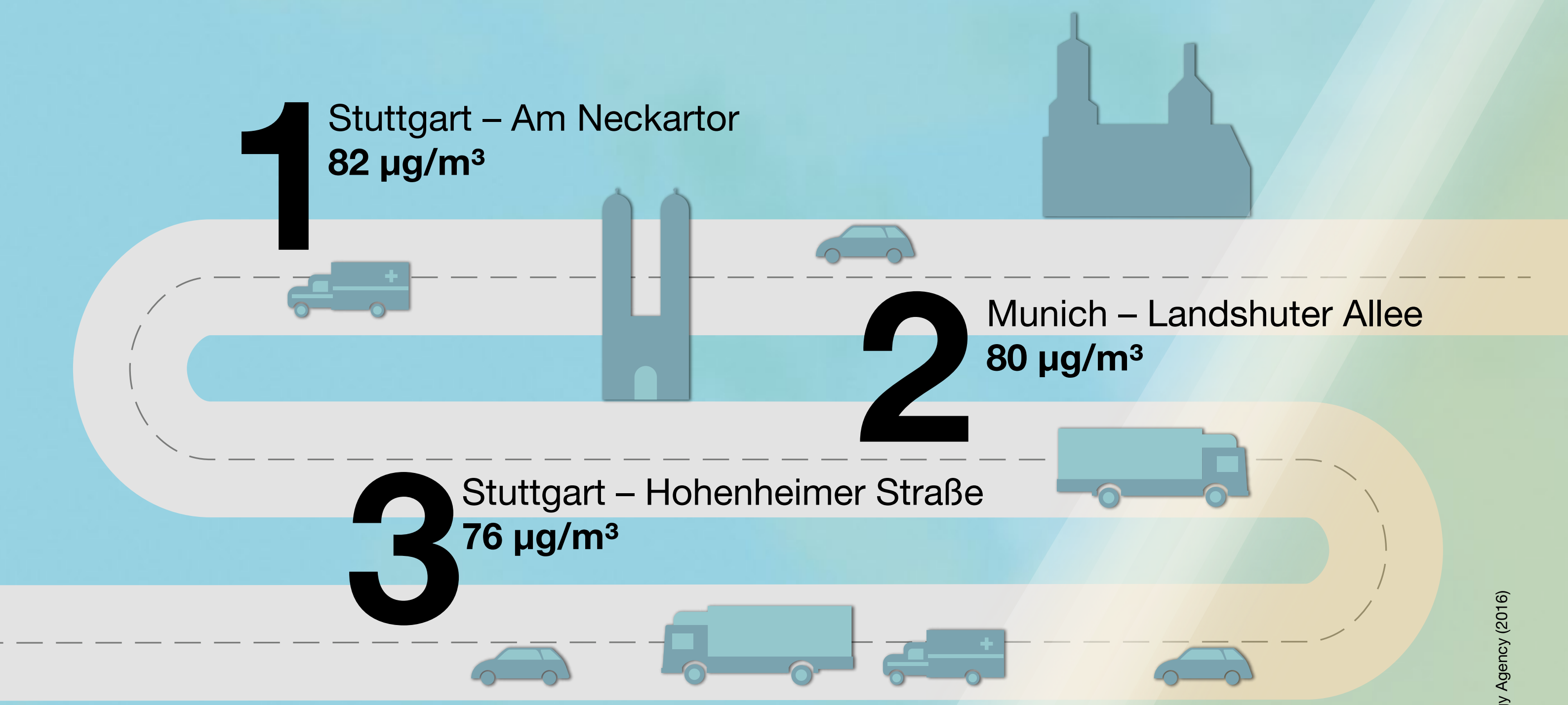
Picture credit: ediundsepp/TUM; Graphics: ediundsepp, Source: Federal Environmental Agency (UBA); Emissions data (March 2017)

Prof. Jia Chen

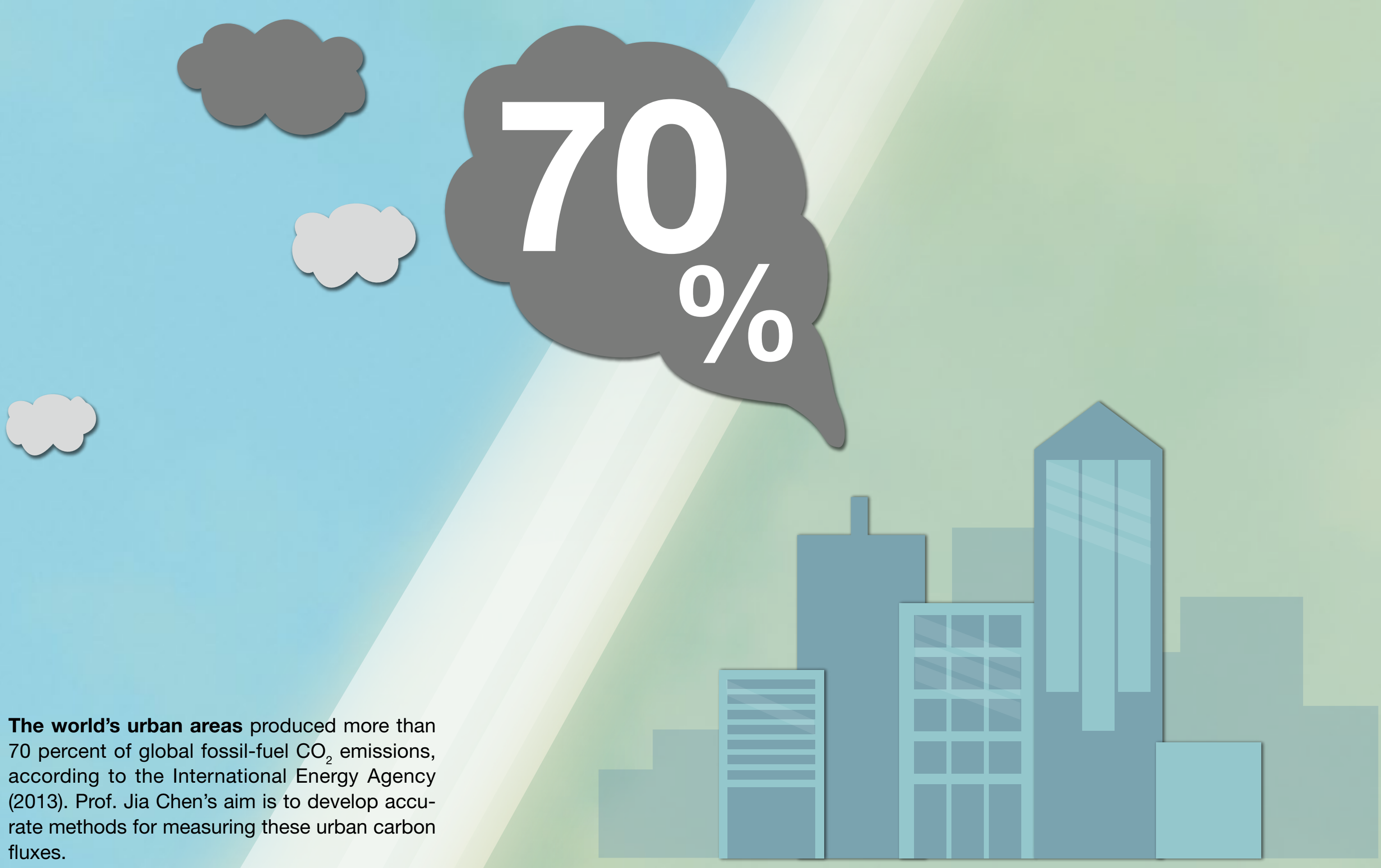
Always on the move

At the beginning of her presentations, Jia Chen likes to display a slide mapping her own mobility story. Her journey, stretching from China to the US, covers 180 degrees longitude: Jia Chen was born in Tianjin, "a small Chinese city with just twelve million inhabitants," she states with a smile. She started her studies in electrical engineering and information technology in Beijing and then transferred to Germany to continue studying at the Karlsruhe Institute of Technology (KIT), where she received her engineering degree in 2006. She completed her doctorate at TUM on the development of laser-based gas sensors.
In 2011, she moved on to Cambridge (USA), to pursue environmental research at Harvard University. Since 2015, Chen has been Professor of Environmental Sensing and Modeling at TUM. She is also a fellow of the TUM Institute for Advanced Study within the Rudolf Moessbauer Tenure Track program, and an associate at Harvard University.
"I started out by going west," acknowledges the 36-year-old. "But now I'm back in Munich, and this is a kind of geographical and research midpoint in my life. Munich's air quality index was 42 when I last checked – which is good, and as readers of Douglas Adams are well aware, also the answer to everything," shares the researcher with a wink.

Chen installed six measurement stations in and around Munich. The aim was to measure air pollution across time and space. The test included nitrogen oxide – a particularly hot topic in Germany following the diesel emissions scandal. When the analysis is completed, the results will be incorporated into an international measurement series comparing greenhouse gas emissions in major cities – research projects funded by the US Environmental Defense Fund (EDF) and the United Nations (UN).
Few people in Munich know as much about the city's greenhouse gas concentrations as Jia Chen. And although Munich may not top the list of cities with the cleanest air in the world, the researcher enjoys her time outdoors. "I spend an hour cycling from home to my downtown office and back every day," she confirms. "What drives me in my work is the potential to improve the quality of air – and thus of people's lives – around the globe." *Karsten Werth*

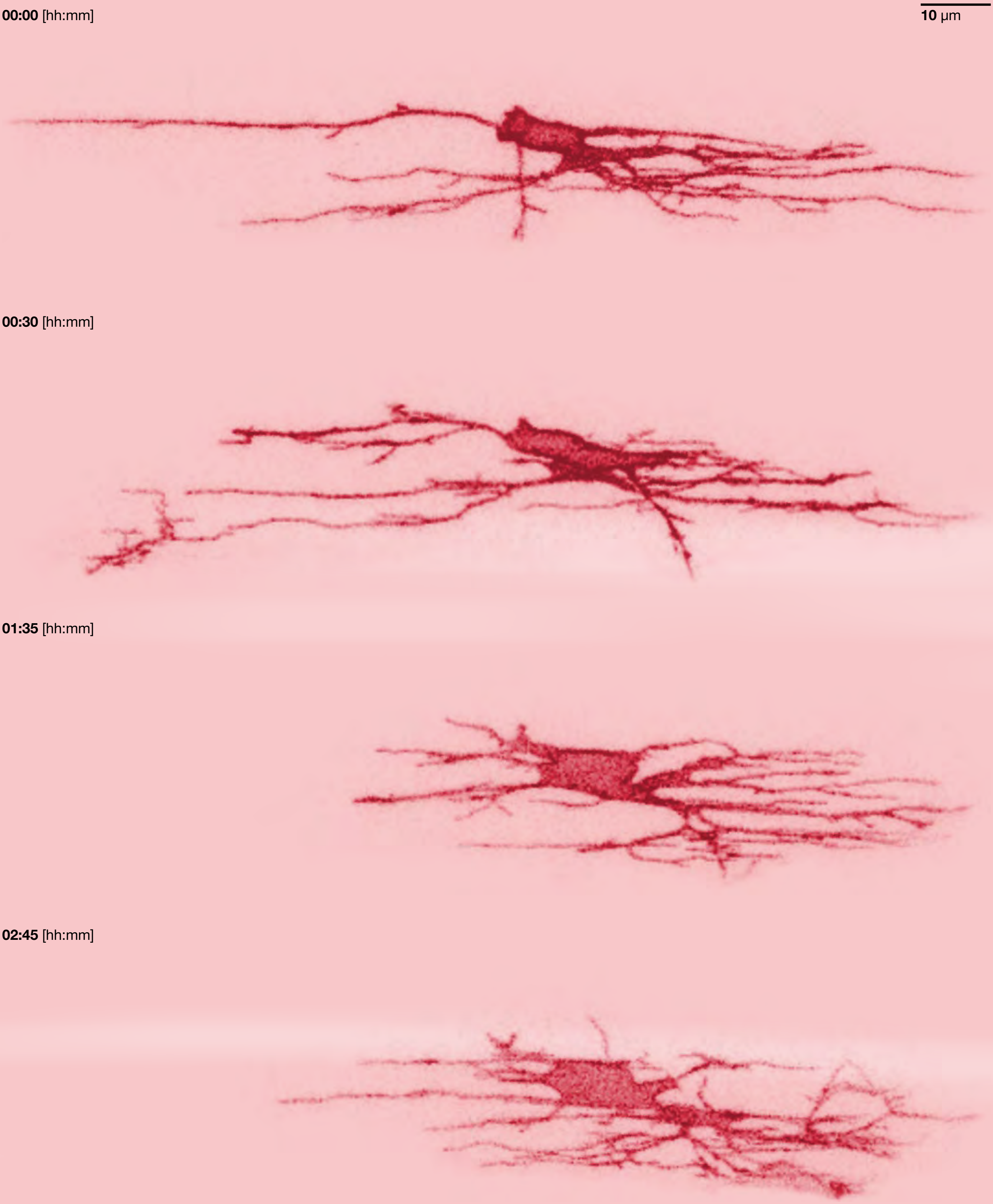


Nitrogen dioxide (NO_2) in 2016 (yearly average values in µg/m³)
This pollutant is a serious problem in German cities. The threshold value of 40 micrograms per cubic meter (µg/m³) on a yearly average was exceeded at about 57 percent of all the measuring stations located near major thoroughfares in 2016. The traffic intersections with the highest NO_2 concentrations were located in Stuttgart and Munich.



The world's urban areas produced more than 70 percent of global fossil-fuel CO_2 emissions, according to the International Energy Agency (2013). Prof. Jia Chen's aim is to develop accurate methods for measuring these urban carbon fluxes.

Graphics: ediundsepp, Source: Measurement data from the German federal states and the Federal Environmental Agency (UBA) (2016), International Energy Agency (2016)



Oligodendrocytes ensheath the axons of nerve cells by iteratively 'wrapping' them with their cell membranes. The images show an oligodentrocyte precursor cell observed with a confocal laser scanning microscope in a living zebrafish. At the beginning of the myelination process, the precursor cell makes its way along the nerve fibers (not pictured above), modifying its extensions in minute intervals.

Neuroplasticity – **a Matter of White Matter**

When adults learn a new skill – whether it be juggling or piano playing – this process modifies not only their gray matter, that is their neurons and synapses. It also changes what is known as white matter, areas of the brain where the nerve fibers are wrapped in a protective membrane called myelin. Tim Czopka is looking to better understand how this happens by investigating the cells that produce the myelin.

Karoline Stürmer

Neuroplastizität – neuer Blick auf die weiße Substanz

Jonglieren oder Klavierspielen – wenn Erwachsene neue Fähigkeiten erlernen, passen sich nicht nur die „grauen Zellen“ an, also die Nervenzellen und Synapsen. Auch die weiße Substanz unseres Gehirns verändert sich. So werden die mit einer weißen Myelinschicht umhüllten Nervenfasern bezeichnet, die Reize zwischen den Nervenzellen weiterleiten. Zuständig für die Bildung der schützenden Myelinschicht sind Oligodendrozyten, die zu den Helferzellen im Gehirn gehören. Dr. Tim Czopka untersucht, wie sich diese Zellen entwickeln, um die weiße Substanz zu bilden, diese plastisch zu verändern und sie nach einer Schädigung zu regenerieren. Der 37-jährige Biologe leitet eine Forschungsgruppe am Institut für Zellbiologie des Nervensystems der TUM.

Bisher konnte er zeigen, dass jeder einzelne Oligodendrozyt nur ein Zeitfenster von wenigen Stunden hat, um festzulegen, wie viele Myelinsegmente er an einer oder mehreren Nervenfasern ausbildet. Danach verliert er diese Fähigkeit und verändert sich kaum noch. Daraus folgert Czopka: Defektes Myelin kann nur durch neue Oligodendrozyten ersetzt werden, die sich aus sogenannten Vorläuferzellen entwickeln. Das sind Abkömmlinge von Stammzellen, die schon auf einen künftigen Funktionsbereich festgelegt sind. Czopkas Ziel ist es, die Vorläuferzellen der Oligodendrozyten über ihren gesamten Lebenszyklus zu verfolgen. Er untersucht, wie die Zellumgebung und die Gene darüber entscheiden, ob sich eine Vorläuferzelle weiter teilt oder stattdessen zu einem Oligodendrozyten entwickelt, und wie diese dann die Struktur und Funktion von Nervenzellen verändern.

Czopka arbeitet mit gentechnisch veränderten Zebrafischen als Tiermodell und mit hochauflösenden Mikroskopieverfahren. Weil die Larven der Fische durchscheinend sind, kann der Biologe in das Nervensystem der lebenden Tiere – also in vivo – blicken und Veränderungen einzelner Zellen im selben Tier verfolgen.

„Letztlich wollen wir die Stellschrauben der Myelinregulation identifizieren“, sagt Czopka. □

Tim Czopka’s research group at TUM’s Institute of Neuronal Cell Biology
www.neuroscience.med.tum.de www.czopka-lab.de

Picture credits: Tim Czopka/TUM

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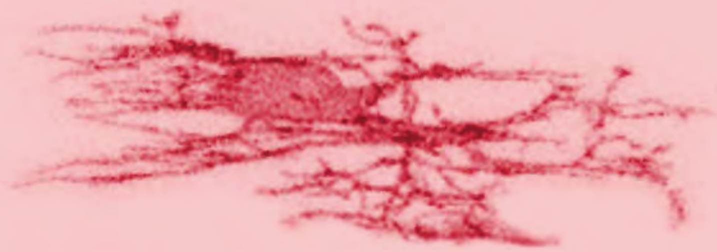

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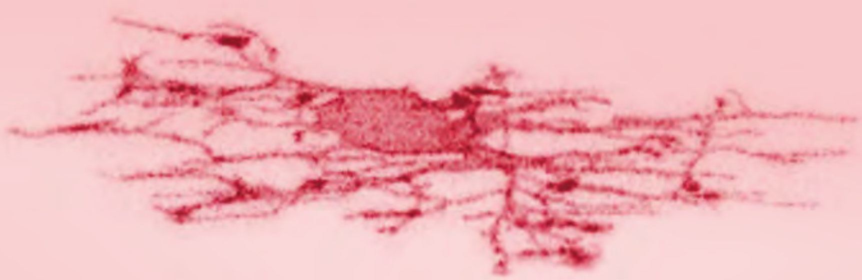

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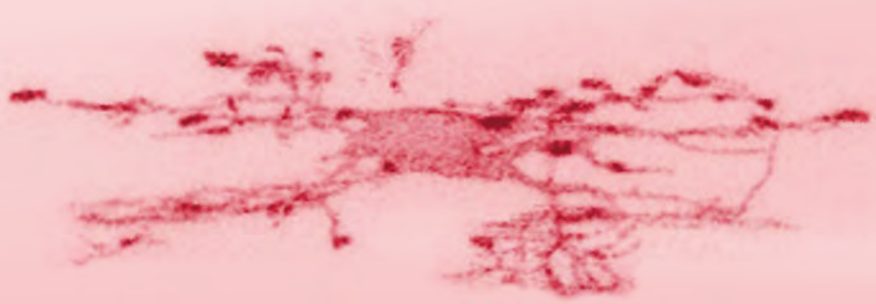


At a certain point in time, the cell starts forming myelin segments, also called internodes, recognizable as small horizontal tubes. Surplus extensions are also drawn back to the cell and eliminated at this time. As myelination progresses, the oligodendrocyte becomes less dynamic and loses the ability to form new myelin segments.

A cell slowly moves its fine extensions, which gradually grow in size and length. As soon as it comes into contact with a fiber of a neuron, called an axon, the cell begins to wrap itself around the axon.

Observed by Dr. Tim Czopka through his microscope, this process is known as myelination – the formation of a myelin layer around the connecting processes between neurons to protect and insulate them. The myelin layer surrounding the axons in the neural pathways is referred to as the white matter of the central nervous system. The cells responsible for myelination are called oligodendrocytes – a type of glial cell, which are helper cells in the brain. Czopka is investigating how these cells develop and what role they play in the formation, the remodeling and the regeneration of myelin. The 37-year-old biologist is a Junior Fellow at TUM's Institute of Neuronal Cell Biology, where he leads a junior research group funded by the German Research Foundation (DFG).

Myelination contributes to neuroplasticity

It is well established that neurons and synapses dynamically adapt to new challenges. New studies show that the role of myelination in this process was previously underestimated. Myelin is a biomembrane that provides electrical insulation, allowing signals between nerve cells to be transmitted quickly and efficiently. This is crucial when it comes to the timing of information processing within neural networks that is needed in the process of learning.

We now know that myelination can adaptively change in response to new experiences. For example, white matter changes occur when test subjects learn new motor skills such as juggling and piano playing. Another recent study showed that genetically modified mice incapable of forming new myelin were not able to perform complex learning tasks.

On the other hand, myelin is selectively attacked and degraded in autoimmune diseases such as multiple sclerosis, which leads to malfunction of the nervous system and varying rates of neurodegeneration.

Variability of precursor cells

The principles underlying the formation and repair of myelin are precisely what Tim Czopka is investigating. To date, he has been able to show that each individual oligodendrocyte has a time span of just a few hours to determine how many myelin segments it will form on one or several nerve fibers. It then loses this ability to form new myelin segments and barely changes any further. From this finding, Czopka concludes that defective myelin, as well as new myelin generated during adaptive processes, can only be produced by newly formed oligodendrocytes from their precursor cells. ▷

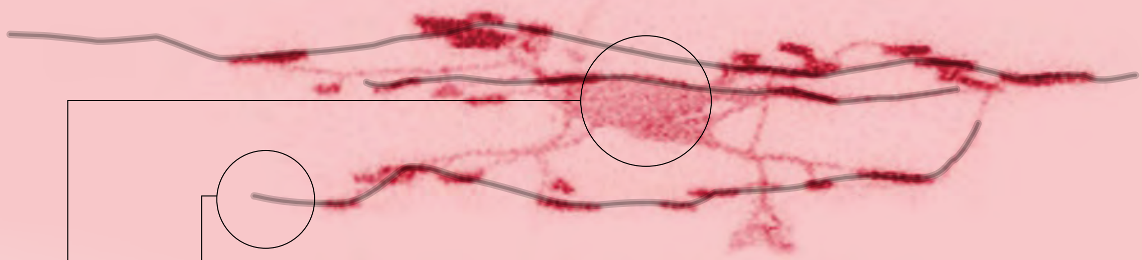
Dr. Tim Czopka

Combining molecular biology and neuroscience

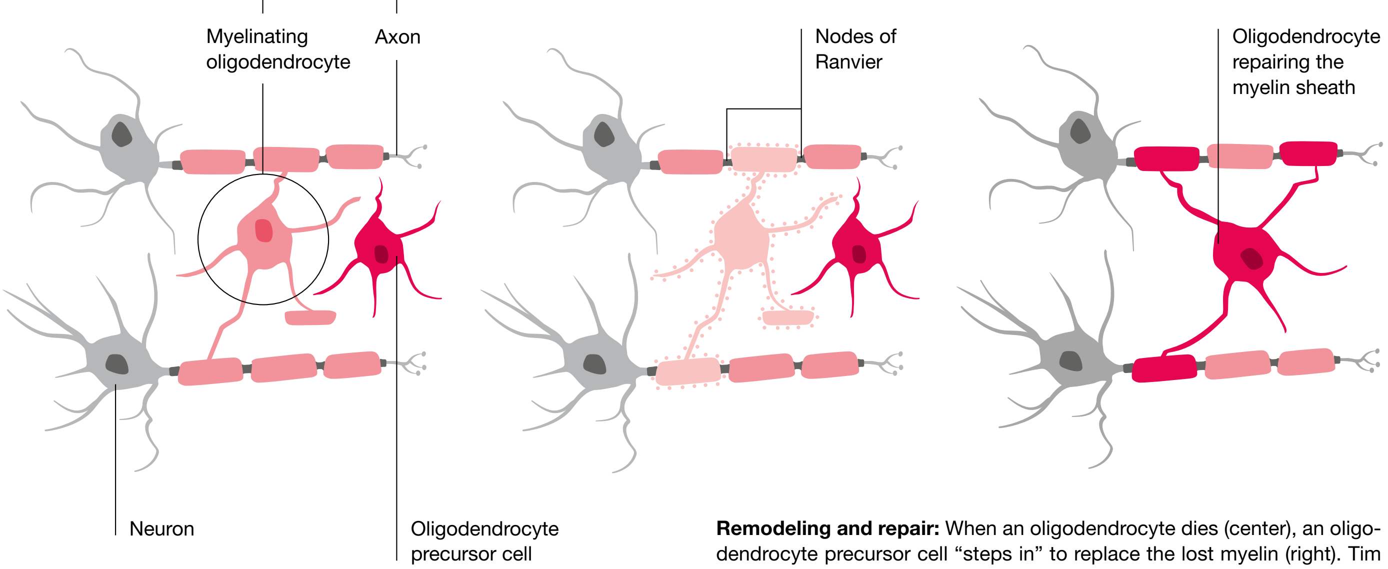
Tim Czopka studied biology at Germany's Ruhr-Universität Bochum, graduating in 2005 and completing his PhD in neuroscience in 2009. He then went on to the University of Edinburgh (UK) for postdoctoral training until 2014. The 37-year-old has been an Emmy Noether group leader at the TUM Institute of Neuronal Cell Biology since 2015. He was one of fourteen early-career scientists in the German state of Bavaria to receive a prestigious Starting Grant from the European Research Council in 2016. He is an associate of the Munich Cluster for Systems Neurology (SyNergy) and the Collaborative Research Center (Sonderforschungsbereich) 870 on the assembly and function of neuronal circuits.

Czopka investigates myelination mechanisms in the central nervous system, using young tropical zebrafish as a model organism. These are particularly well suited to genetic manipulation and in vivo live imaging using high-resolution microscopy.

Picture credits: Tim Czopka/TUM; Magdalena Jooss/TUM



Axons, or nerve fibers, transmit impulses to other nerve cells and to muscle cells. Each axon (visualized as grey lines above) is covered by consecutive myelin segments – also referred to as internodes – arranged one after the other like beads on a string. Some internodes originate from the same oligodendrocyte and some from different ones. The gaps between the internodes, known as the nodes of Ranvier, are unmyelinated.



Remodeling and repair: When an oligodendrocyte dies (center), an oligodendrocyte precursor cell "steps in" to replace the lost myelin (right). Tim Czopka wants to understand why the repair process is often less efficient than the original formation of myelin.

Oligodendrocyte precursor cells are found in the bodies of humans and other vertebrates in all stages of life. They are descendants of stem cells committed to form myelin. They divide swiftly and migrate through the tissue. Once they turn into oligodendrocytes, they lose this ability and begin forming dense layers of cell membrane around various neurons – the myelin. Because biomembranes have a high fat content, their tight stacking in heavily myelinated areas of the nervous system is even visible to the naked eye as white matter, standing out from the gray matter that contains less myelin. "The coating of neurons with myelin is an evolutionary adaptation in the brain of vertebrates," explains Czopka. "It is probably this that enabled the development of larger and increasingly complex nervous systems in the first place."

A glimpse of the living brain

In order to gain insights into mechanisms of myelin regulation, Czopka observes oligodendrocytes as they develop and interact with neurons – using zebrafish as the animal model and high-resolution imaging procedures. Zebrafish make ideal

Confocal laser scanning microscope: Tim Czopka and his team investigate interactions between neurons and glia using a combination of high resolution microscopy methods, genetics and modern data analysis.

"Our aim is to identify key success factors in the myelination process." Tim Czopka

model organisms for neurobiology. Many basic principles that apply to them can be directly transferred to humans. "The problem is, we can't see directly into the human brain," Czopka remarks. But he can see into the brain of a living zebrafish: In genetically modified zebrafish, cells can bear fluorescent tags such as green fluorescent protein (GFP). Since the fish larvae are transparent, researchers can look inside their nervous system – live and in vivo – and track changes to individual cells in the same fish with the aid of high-resolution imaging procedures.

Accompanying the "life cycle" of cells

In 2016 Tim Czopka was awarded a Starting Grant from the European Research Council (ERC) that will help him to pursue this goal: He intends to use this grant to accompany oligodendrocytes and their precursor cells in the nervous system throughout the entire development of an individual organism for the first time. To begin with, he is currently investigating what happens when he destroys individual myelin producing oligodendrocytes. "We see that the immune system clears away the cell debris, and other oligodendrocytes attempt to compensate for the loss," says Czopka. What is not yet clear is why the repair process is often substantially inferior to the original myelination. A general lack of oligodendrocyte precursor cells is not the issue, since they are present in large quantities in the nervous system of vertebrates.

Czopka suspects that various oligodendrocyte populations exist, not all of which are suitable for myelin repair. He is keen to understand what factors determine whether a precursor cell continues to divide or instead develops into an oligodendrocyte. To achieve this, his next step will be to explore the variables that may have an influence in the cellular environment, as well as various oligodendrocyte genes. "Our ultimate aim here is to identify key success factors in the myelination process," Czopka confirms. If he manages to do this, it would open up new insights into neuroplasticity as well as new strategies for treatment of myelin damage, which occurs in diseases like multiple sclerosis. *Karoline Stürmer*

Graphics: ediundsepp (source: TUM), Picture credits: Tim Czopka/TUM; Magdalena Jooss/TUM

Jumping from Postdoc **to Professor**

When Hendrik Dietz returned to Munich in 2009 after his postdoc period at Harvard University (USA), he became one of the youngest professors at TUM. Since then, he has built up the Chair of Experimental Biophysics there. For his work in bionanotechnology, he has received numerous grants as well as Germany's most prestigious research award.

Chair for Experimental Biophysics
www.dietzlab.org/

Picture credit: Astrid Eckert/TUM

Brigitte Röthlein

Der Sprung vom Postdoc zum Professor

Prof. Hendrik Dietz hält seit einigen Jahren die Fachwelt in Atem mit seinen Ideen und Arbeiten zum DNA-Origami. Er konzentriert sich darauf, aus DNA, Desoxyribonukleinsäure, dem Material, aus dem unsere Gene bestehen, „Dinge zu bauen, die noch nie jemand gebaut hat". Die DNA-Moleküle eignen sich gut dafür, denn sie sind kettenförmig, regelmäßig, stabil und in ihren physikalischen Eigenschaften gut verstanden.

Im Jahr 2009 entschloss sich Dietz, aus den USA zurück nach Deutschland zu gehen. An der Physik-Fakultät der TUM erhielt der junge Wissenschaftler eine Professur. „Es war eine harte Zeit", sagt der Professor für Experimentelle Biophysik in der Rückschau. „Ich musste nicht nur schnell Doktoranden finden, Forschungsgelder einwerben und eine Infrastruktur aufbauen, sondern gleichzeitig auch noch Vorlesungen halten."

Beim Aufbau seines Teams half es ihm, dass er im Rahmen zweier Exzellenzcluster Mittel und zudem im Jahr 2010 einen „Starting Grant", eine Förderung des European Research Council, erhielt. Für seine Arbeiten wurde er mehrfach mit Preisen und Stipendien ausgezeichnet, unter anderem 2015 mit dem Gottfried Wilhelm Leibniz-Preis der Deutschen Forschungsgemeinschaft (DFG), dotiert mit 2,5 Mio. Euro.

Heute verbringt der 39-Jährige seine Zeit mehr im Büro als im Labor. Er muss sie jetzt aufteilen zwischen Lehre, Management, Gutachtertätigkeit und der Betreuung seines Teams. „Wir diskutieren dann, wie man Probleme lösen und neue Ideen umsetzen könnte", sagt Dietz. In den letzten Jahren haben er und seine Forschungsgruppe ihr Verfahren weiter optimiert. Gleichzeitig fanden die Wissenschaftler wertvolle grundlegende Einsichten in Eigenschaften von Biomolekülen, etwa in die elementaren Kräfte, die zwischen ihnen wirken.

Neben Anwendungen seiner Nano-Objekte für die Mikroskopie oder die Grundlagenforschung verfolgt Dietz das Ziel, Werkzeuge zum Beispiel für die Medizin zu bauen. Sie sollen bestimmte Aufgaben in Zellen erledigen – etwa pharmazeutische Stoffe zielgerichtet im Organismus verteilen. Kürzlich ist Dietz gemeinsam mit Bioverfahrenstechnikern der TUM die Massenproduktion von DNA-Abschnitten in einem Bioreaktor mithilfe von Kolibakterien gelungen. Damit wird der Weg für breitere medizinische Anwendungen geebnet. □

DNA origami and molecular machines

In 2009, Hendrik Dietz and his colleagues published a paper outlining the method for producing all kinds of nanostructures – including tiny bricks, balls, and straight and twisted ribbons – from DNA, or deoxyribonucleic acid, from which our genes are also made. This became known as 3D DNA origami. DNA chains consist of the four bases adenine (A), cytosine (C), guanine (G) and thymine (T). These can attach to each other, but only in the pairs A-T and G-C. This is the property that Dietz and his team were able to turn to their advantage.

Their technique involves "stapling" single-strand DNA extracted from viruses, referred to as the "scaffold", together with tiny, synthetically produced DNA segments – known as staple molecules – according to a pre-programmed design. Like a puzzle putting itself together, the nanostructures emerge through self-organization – several million at a time. An electron microscope can be used to identify the shape and check all has gone to plan.

With time, the researchers gained more experience manipulating their new building blocks and were able to formulate systematic DNA assembly specifications and store them as a computer program. "We now have a set of rules that can be used to program the tiniest DNA building blocks. You can put them together however you want – almost like Lego," describes Dietz.

This might initially have looked like a game, but was in fact instrumental in advancing the method. Now that this has been established, it serves as a powerful tool to enable the assembly of nanoscale structures. These can then be used as the basis for medical delivery systems or molecular machines. Recently, Hendrik Dietz and Prof. Dirk Weuster-Botz of TUM's Chair of Biochemical Engineering devised a new method to produce large quantities of the necessary DNA segments from *E. coli* bacteria, paving the way for the use of DNA origami on an industrial scale.

Faszination Forschung: When you were appointed to TUM eight years ago, you had just turned 31. What has changed for you since then?

Hendrik Dietz: It's actually hard to believe that eight years have already passed. From a personal perspective, it seems as if not that much has changed, but actually there were many developments. At the outset, I was flying solo in my own small lab with very little in the way of research funding, whereas now I am part of a well-staffed, well-equipped research lab. A lot of ideas and concepts that only existed on paper eight years ago have since become reality. Staff have come and gone – the lab already has alumni – lab traditions have evolved, and we have developed our own lab culture.

▷

Intuitive design: A computer program with a graphical user interface enables rapid and simple development of three-dimensional nanostructures. These shapes are then converted into strands of DNA base pairs.

Picture credit: Astrid Eckert/TUM

> *"In the past, I saw research as more of a lone wolf activity, but now we work in teams to tackle more complex challenges."*
>
> *Hendrik Dietz*

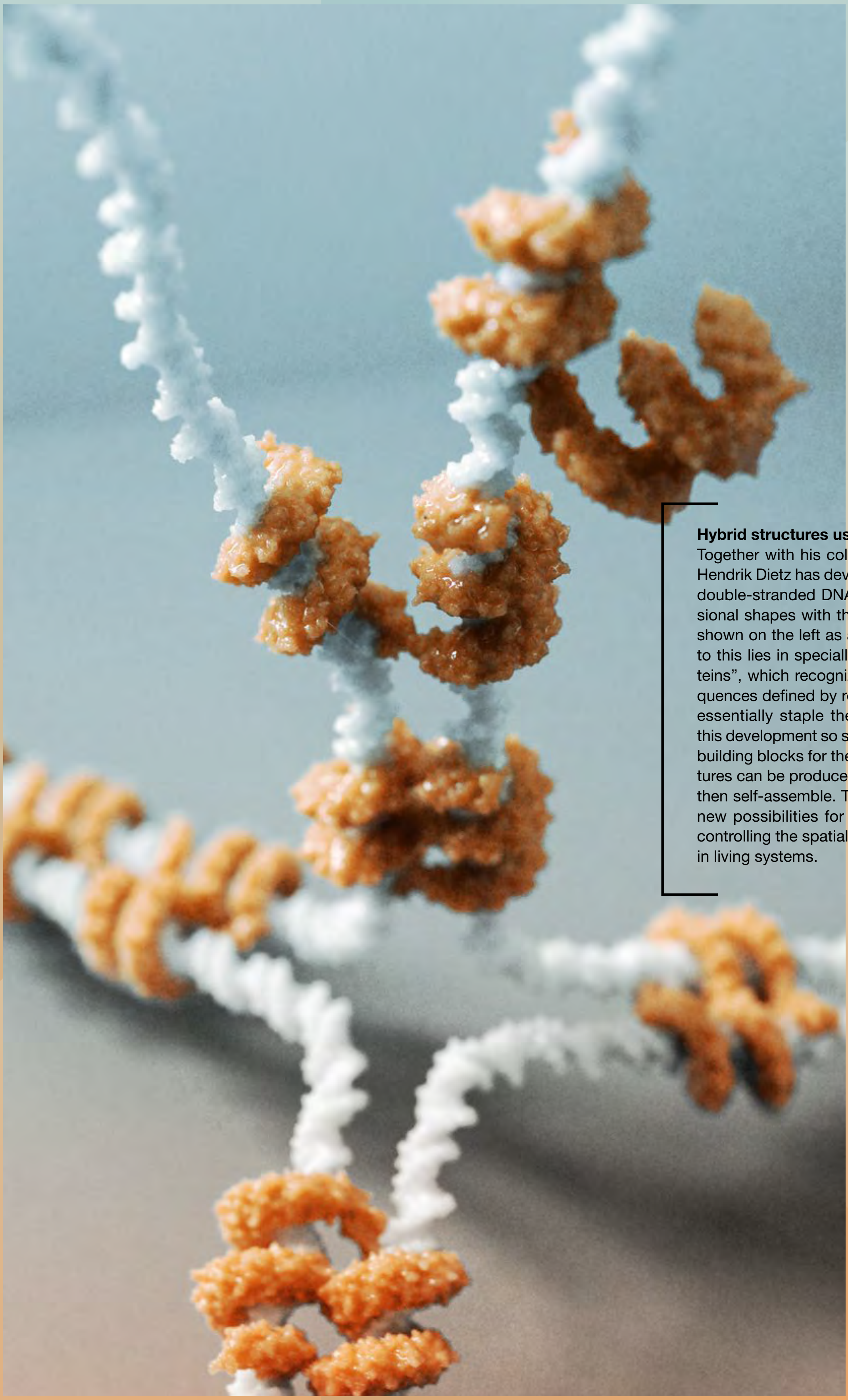
How many staff members do you have now?
We now have 25 full-time employees, as well as several young students who join us from their fourth semester onwards. This gives them very early insights into the true realities of research work. You see, it's not about reading a book and having the odd moment of illumination. You don't realize as a student that what you see on the pages of a textbook is often the product of decades of trial and error, and the huge effort that went into moving beyond those initial misconceptions or mistakes.

How has your way of working changed over the years?
My current role consists of analyzing data, discussing projects, making decisions about the direction we want to take, writing proposals and convincing funding bodies to invest in us. I was also in the lab myself for the first year or two but that quickly changed. Longer experiments requiring several consecutive days of lab work soon became impossible due to my schedule. I constantly have meetings (which is good) and need to look after my people. In the past, I saw research as more of a lone wolf activity, but now we work in teams to tackle more complex challenges.

Where do new ideas for your research come from?
The fundamental aims we are trying to achieve remain unchanged: building molecular machines with specific capabilities, such as transporting substances or producing chemical compounds. We've certainly learned a lot along the way, but haven't been able to turn these devices into reality as yet. So the vision is still there, along with plenty of ideas about how to take our research to the next level each time. The more difficult task is to filter out those ideas that have the best prospects of success and apply them in a practical context. And then it's not uncommon for everything to go wrong in the early stages. So that's when you need good and persistent people who believe in what they're doing and can cope with disappointments along the way. I'm very grateful to be working in that kind of environment.

In 2015, you were awarded the prestigious Gottfried Wilhelm Leibniz Prize, worth 2.5 million euros. What difference has that made?
Together with a series of publications in respected journals, that prize has boosted our credibility. In the early days, it was difficult when we promised to build something or other but didn't yet have anything to show for it. Now, though, I can point out that we're already halfway there. Mind you, we still regularly encounter skepticism – but there is less of it now.

You are known in scientific circles for your work on DNA origami – a method you have largely perfected at this point. What is your current research focus?
Well, to give an example: We have now used our method to build synthetic objects on the scale of viruses and cellular organelles. One of our goals is to use these DNA structures for medical treatments. We could envisage constructing ▹



Picture credits: Hendrik Dietz

Hybrid structures using DNA and proteins
Together with his colleague, Florian Praetorius, Hendrik Dietz has developed a method of folding double-stranded DNA (white) into three-dimensional shapes with the aid of proteins (orange), shown on the left as a 3D visualization. The key to this lies in specially constructed "staple proteins", which recognize two separate target sequences defined by researchers in the DNA and essentially staple them together. What makes this development so special is the fact that all the building blocks for the DNA protein hybrid structures can be produced by the cell itself and they then self-assemble. This method thus opens up new possibilities for better understanding and controlling the spatial arrangement of molecules in living systems.

("Science", 2017)

Synthetic lipid membrane channels based on DNA origami

In 2012, Hendrik Dietz and Prof. Friedrich Simmel, Chair of Physics of Synthetic Biological Systems at TUM, built synthetic membrane channels out of DNA, shown as a model above. These consist of a needle-like stem (red), which is 42 nanometers long and has an internal diameter of just two nanometers. The stem is partly sheathed by a barrel-shaped cap (white). A ring of cholesterol units (white and orange spirals) around the edge of the cap helps the device dock onto a lipid membrane, while the stem sticks through it, forming a nano-pore that appears to function just like the real thing. These synthetic membrane channels could be used as nano-needles to inject material or agents into cells.

("Science", 2012)

Reality check for DNA nanotechnology

In the same year, Hendrik Dietz and scientists from the MRC Laboratory of Molecular Biology in Cambridge (UK) were able to show that DNA objects can be assembled precisely as designed: They produced a relatively large, three-dimensional DNA-based structure, visualized on the left. This comprises more than 460,000 atoms. The researchers were able to map the object with subnanometer resolution, thus providing a crucial reality check for DNA nanotechnology.

("Proceedings of the National Academy of Sciences of the USA", 2012) a type of intelligent container, for instance, to transport active substances. Here, we would attach proteins or other molecule groups to the external coating. These would identify specific cell types, docking onto them and emptying the agent into the cells. The individual components for this type of container have all already been constructed – so the potential is definitely there. They have not yet been integrated into an overall system or tested in organisms, however.

Could you describe your most recent successes?

We now have a solution to a problem that has not been given much attention. In the past, it was much too expensive to produce DNA structures in large quantities. Using conventional origami methods, it would currently cost around 100,000 euros and take far too long to assemble a gram of DNA origami. To bring new medical applications to market, we first need to conduct experiments in animal models to observe how they respond to these types of structure – and this step alone requires quite a bit of material. That would be way too costly with the current process technologies. So to bring these costs down, we have developed new processes enabling us to produce our DNA structures in larger quantities.

Using our new method, individual strands of DNA can be produced with almost any length or sequence in cell cultures – as is already the case today for many protein-based substances, such as insulin. To this end, we harness *E. coli* bacteria, embedding our blueprints into their genetic code. When the bacteria multiply, they simultaneously multiply our DNA sequences too, which we can extract by purification at the end of the process. The difficulty here is that the DNA in cells is generally double-stranded, whereas we need single strands of DNA. Together with Prof. Dirk Weuster-Botz and his colleagues at TUM's Chair of Biochemical Engineering, we have now cleared this hurdle and produced our first actual macroscopic tablet from DNA origami powder. This symbolic gesture demonstrates that we have now reached the point of technical feasibility, while cutting costs for one gram of DNA origami from 100,000 euros down to only 100 euros. This paves the way for the development of medical applications based on this technology.

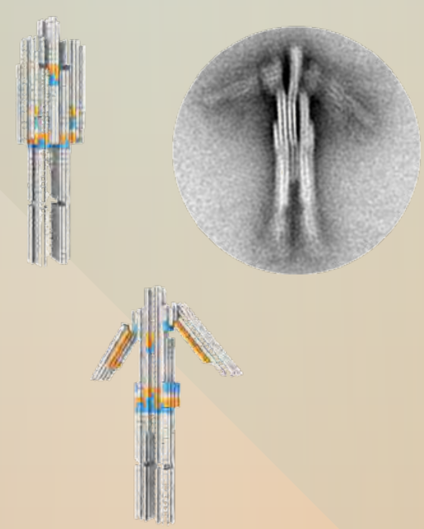
So what can we expect going forward?

Our next focus will be on medical applications. With the mass production challenge already resolved, now we need to investigate what actually happens to these structures within an organism. We have begun toxicity studies in collaboration with a partner to assess this. We also want to find out how long the biological half-life is – that is, how long such structures can survive inside the organism. Can we influence this with specific shapes or patterns? Or do we need to add on some kind of stabilizing structures? ▷

Moving nanomachines

If you change the ion concentration in the solution surrounding the "arms" of the nanorobot (below), they move up and down. To enable these synthetic DNA structures to move, Hendrik Dietz and his team turned a natural property to their advantage: nucleic acid molecules are capable of forming weak, easily reversible bonds with one another. The waving nanorobot (shown on the left and bottom as a model; on the right through the electron microscope) is based on a shape-complementary folding technique. Instead of zipping together strands of DNA base pairs, three-dimensional DNA building blocks are snapped together like pieces of a jigsaw.

("Science", 2015)



Picture credits: Hendrik Dietz

“Our next focus will be on medical applications.”

Hendrik Dietz

Prof. Hendrik Dietz

A pioneer in the field of DNA origami

Following his doctorate at TUM, physicist Hendrik Dietz moved to Harvard Medical School in Boston (USA) in 2007. There, he joined a research group led by William M. Shih, which set out to create three-dimensional objects from DNA. Together with computer scientist Shawn M. Douglas and other colleagues, Dietz then made the breakthrough that would establish his reputation as a pioneer of DNA origami.

At the outset, this entailed developing and testing the method that ultimately enabled production of all kinds of nanostructures from DNA: tiny balls, cogs and various other shapes – some of them highly intricate. Known as DNA origami, this method provides a powerful tool for assembling nanoscale structures, which can be used for example for medical applications. In 2009, Dietz took up an appointment at TUM as Professor of Experimental Biophysics. He is a Carl von Linde Senior Fellow of the TUM Institute for Advanced Study.

The 39-year-old scientist holds a Principal Investigator role in two clusters of excellence: Nanosystems Initiative Munich and the Center for Integrated Protein Science Munich (CIPSM). He received a Starting Grant from the European Research Council (ERC) in 2010, and a Consolidator Grant in 2016. In 2015, the German Research Foundation (DFG) awarded him the Gottfried Wilhelm Leibniz Prize, worth 2.5 million euros. In support of its decision, the DFG states: “Hendrik Dietz is among the world’s leading researchers in DNA nanotechnology – currently one of the most dynamic fields in basic biomolecular research.”

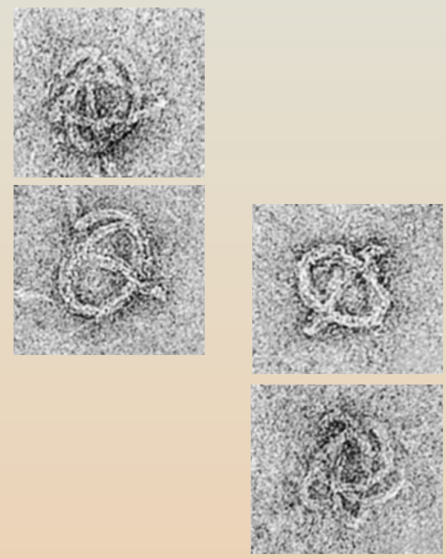
And where do you see yourself in five years' time?
I hope we'll have a string of new breakthroughs to show by then, since we still have many challenges to overcome. It would be great if our work continued as positively and productively as it has so far. Obviously, though, we are also looking to translate our research findings into practical applications. To facilitate this, we founded the company tilibit nanosystems in 2012 – where "tilibit" stands for "tiny little bit". The company distributes DNA components and shares our specialist know-how and I am delighted that we are seeing demand from all over the world. Tilibit gives us a good platform and an opportunity to gain practical experience in the business world.

What advice would you give to young people aiming for a career in research today?
In my view, a good doctoral thesis is certainly a solid and important starting point for a successful academic career. And after that, it is often worth making a break and working in another area of research as a postdoc. In this phase, too, productivity is key. It's probably better to pick a topic that inspires you personally rather than chasing trends – and ideally a topic still in its infancy, giving you room to make a significant scientific contribution. You need a certain instinct for that, and also some good luck. However, if it becomes clear that either of these two phases is proving too arduous, it might be better to pursue a different professional path. The academic world only becomes more competitive after that, while the number of positions shrinks. Of course you can also conduct research in an industrial setting. Each individual has to decide for themselves on the environment that offers them the best conditions to be happy and to develop their personal skills.

You are now a father of three – at four years old, does your oldest already understand what you do for a living?
I doubt it. I've tried to explain it to him but I think it's just too early. He's quite the little discoverer himself, though – he can spend hours watching a fly, for instance, or a spider roving about. So maybe science will appeal to him later on, too.

Brigitte Röthlein

DNA beach ball
Gears, coils and a beach ball made of DNA – in 2009, Hendrik Dietz published a method of producing curved and twisted DNA shapes. This is based on the fact that, in a DNA double helix, every seven base pairs rotate by 240 degrees. If base pairs are inserted or deleted between these segments, the structure is forced to over- or under-wind, thus bending itself. The bottom image shows a computer model of the DNA beach ball, while the top images are examples of actual objects under an electron microscope.
("Science"/"Nature", 2009)



Picture credits: Astrid Eckert/TUM; Hendrik Dietz

Prof. Alice Gast

Professor Alice P. Gast became President of Imperial College London in September 2014. Prior to her appointment at Imperial, Alice Gast was the 13th President of Lehigh University, Pennsylvania, USA. She also served as the Vice-President for Research and Associate Provost and Robert T. Haslam Chair in Chemical Engineering at MIT from 2001–2006.

Alice Gast's academic interest is in surface and interfacial phenomena, in particular the behavior of complex fluids. She has co-authored numerous scientific publications and a classic textbook on colloid and surface phenomena. She was a faculty member and professor at Stanford University, where she was also affiliated with the Stanford Synchrotron Radiation Laboratory. Alice Gast is a member of a number of UK and international advisory committees and boards.

An award from the Alexander von Humboldt Foundation brought her to Germany in 1999, and to TUM, where she worked in the research group of experimental physicist Erich Sackmann. 2015 saw her awarded the honorary title "TUM Ambassador" by TUM President, Prof. Wolfgang A. Herrmann.

International Cooperation – Building a New Foundation for the Future

Imperial College London is a global top ten university with a world-class reputation in science, engineering, business and medicine.

Globalization, advances in technology and changing political environments are dominant, interrelated forces in today's world. They are bringing about changes that have profound effects on individuals, institutions and governments. We know that with change come new and exciting opportunities. We also know that with changes like Brexit the future becomes more uncertain and setting strategy and planning become more difficult.

How then do we best approach these times of both opportunity and uncertainty? How do we continue to move forward? How do we deal with the present and approach the future with optimism and resolve?

I think the answer lies in staying true to the core values of excellence and international collaboration. Adhering to these core values fosters innovative solutions to complex problems that will benefit society in Europe and in the rest of the world.

For decades, institutions and individuals across Europe have established professional relationships that have created progress and prosperity. We see this in the beneficial discoveries arising from European funding of talented people working together. We need to continue to work together on areas of common interest and importance. International cooperation is essential. We must not let political change affect our commitment to thinking about the common goals we share.

We also see the value of collaboration in its lasting effect upon individuals and institutions. The exposure to different ideas and perspectives is intellectually enriching and advances excellence.

These values of excellence and international collaboration are evident in Imperial's relationship with Germany and with TUM. Germany is second only to the United States for research collaborations with Imperial. Our researchers have collaborated on more than 5,000 publications with their peers in Germany within the last five years. During the same period, Imperial and TUM have published almost 400 joint research papers.

One recent example of the Imperial-TUM relationship is our joint work on the important issue of urbanization. Over half the world's population now live in cities, and this will to grow to 66% by 2050. This creates many new challenges, including resource allocation, the integration of migrants, healthcare and strained transport systems. Our universities bring together talented doctoral students to explore solutions to this increasingly ubiquitous global issue. The participants in the Imperial-TUM Global Fellows are applying their knowledge and talents to these issues with the goal of improving the quality of life for current and future urban populations.

These are exciting, challenging and uncertain times. The impacts of the changes brought about by globalization, advances in technology and political uncertainty are felt throughout Europe. We need to make the most of the opportunities that await. That requires a renewed commitment to the core values of excellence, internationalism and collaboration. By continuing to work together, we will build a new foundation for the future in this changing world. □

Picture credit: Astrid Eckert/TUM

„Stiften stiftet Zukunft an.“

Prof. Wolfgang A. Herrmann,
Alumnus und Präsident der TUM

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