University of Stuttgart
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HEALTH!

FORSCHUNG LEBEN

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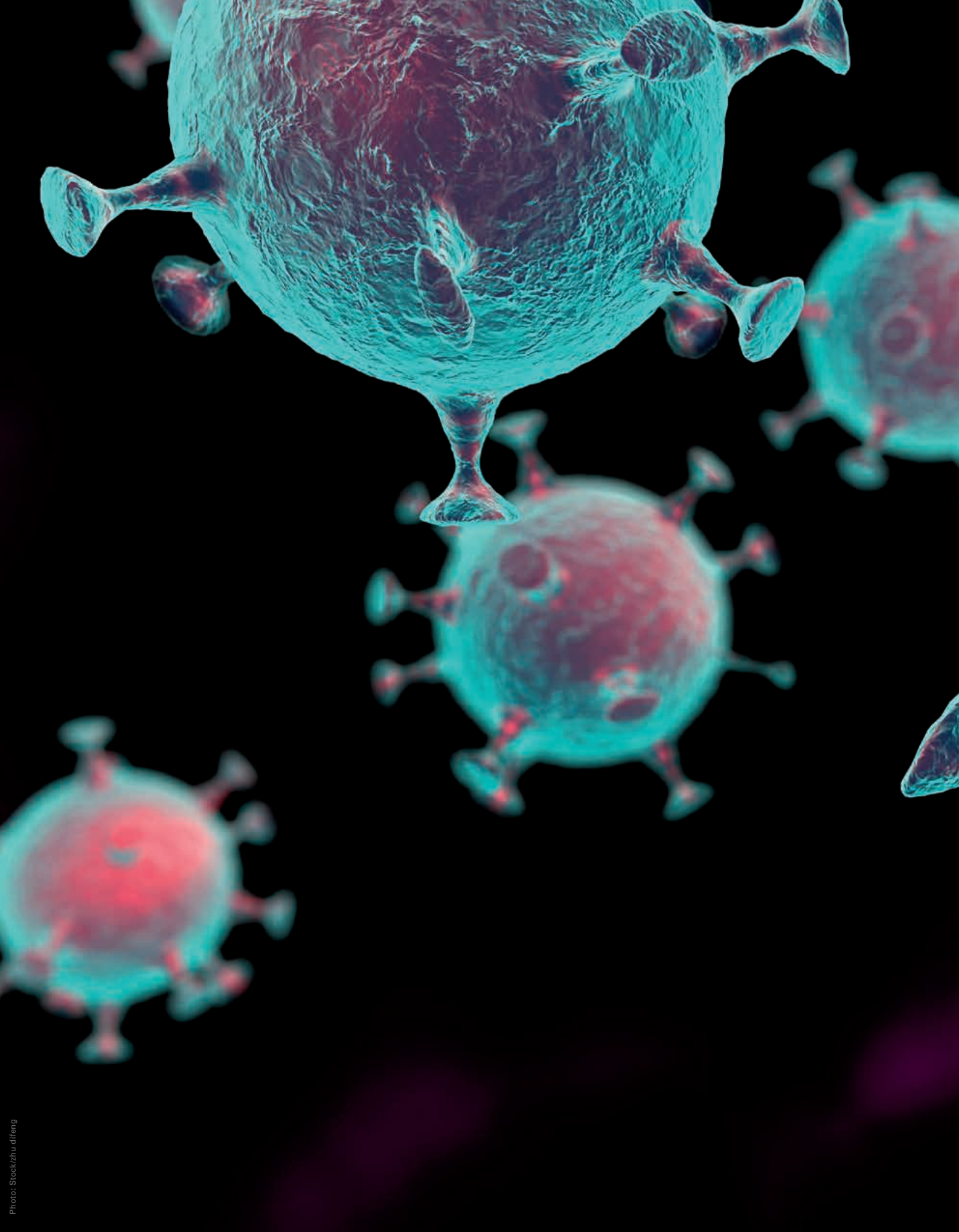

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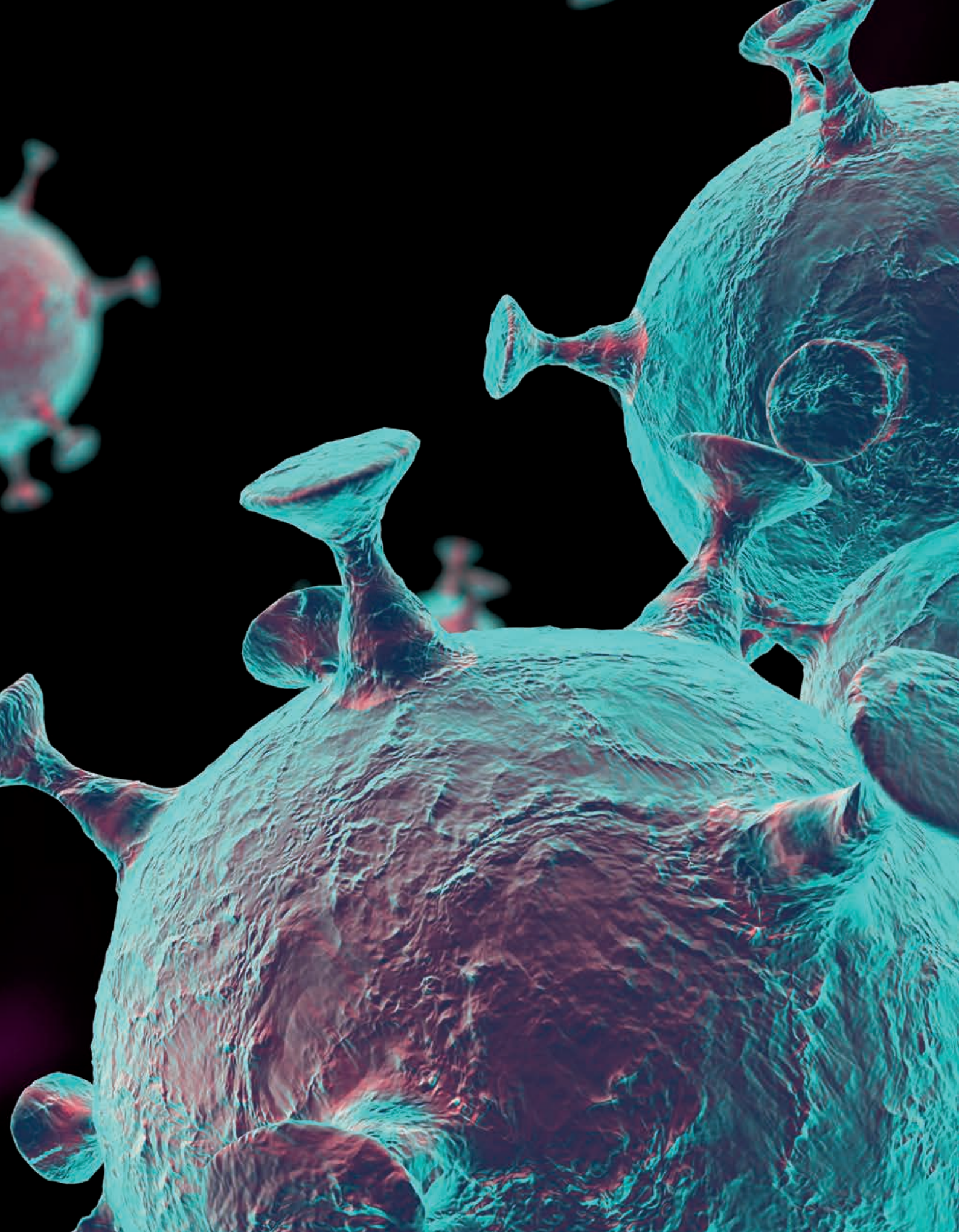

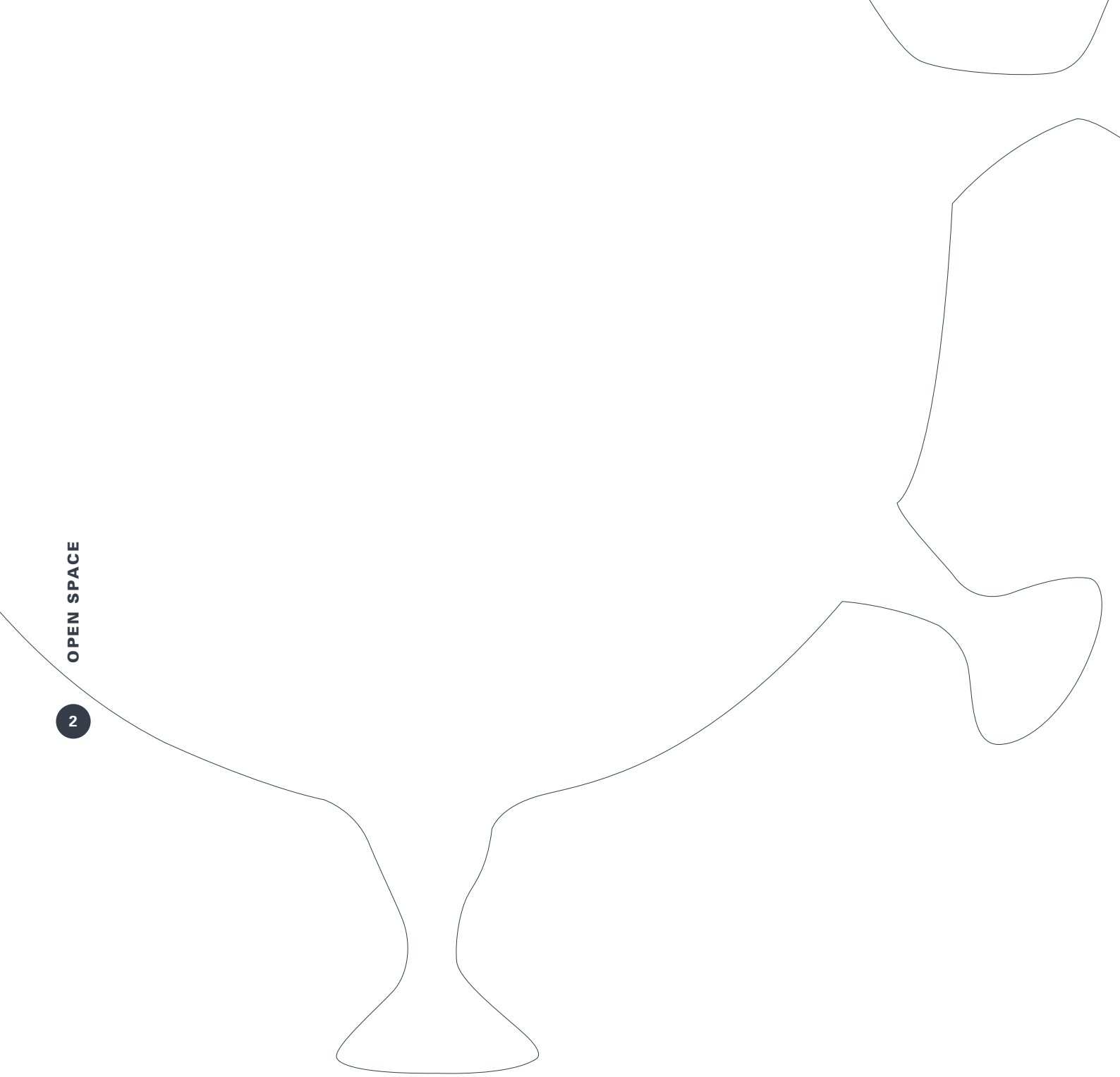

Dear Readers,

Photo: Uli Regenscheit

"the successful cutting edge research carried out at our university will continue to make valuable contributions to preserving or restoring human health in future".

Wolfram Ressel
Rector of the University of Stuttgart

Gesundheit! Health – is something we all wish to enjoy. Usually, this "greatest good" is ranked higher among the good wishes than categories such as happiness and success. Health-related research has a correspondingly high social value, whereby health research is often equated with medical science per se. However, being able to fully exploit this field of research for the benefit of mankind requires interdisciplinary collaboration between all specialist disciplines and faculties.

In accordance with our vision of "intelligent systems for a sustainable society", the University of Stuttgart will be focusing even more on the medically-oriented disciplines in the context of the engineering and natural sciences as well as the humanities. But, you can read about the latest findings and achievements in the field of health research that our university can already pass on to society at large in this edition of FORSCHUNG LEBEN. The various articles provide insights into interdisciplinary research projects in the fields of simulation technologies, quantum mechanics, the human as a system, medical engineering, personalized medicine, digitalization in medicine and nursing as well as sport and preventative medicine.

As the final preparations for this edition of FORSCHUNG LEBEN were being made, a decision was taken by the Excellence Commission to select two clusters with which the University of Stuttgart had applied for a grant in the context of the Excellence Initiative of the federal and state governments of Germany, which will now receive funding for seven years starting on the 1st of January 2019. The clusters in question are the "Data-Integrated Simulation Sciences Cluster of Excellence", whose objective is the development of a new class of modelling and computational methods to elevate the usability and precision of simulations, and consequently the reliability of decisions based on them, to a new level of quality, and the "Integrative Computer-Based Planning and Construction for Architecture Cluster of Excellence", which plans to exploit the full potential of digital technologies to reconceptualize planning and construction.

With these achievements, the University of Stuttgart will be putting everything into emphatically pursuing its objectives in the specified strategic fields over the next few years. Thus, the successful cutting edge research carried out at our university will continue to make valuable contributions to preserving or restoring human health in the future.

I would like to wish you an enjoyable read – hopefully in good health!

EXPERIENCE RESEARCH

Becoming a University of Excellence

The Data-Integrated Simulation Science Cluster of Excellence and the Integrative Computational Design and Construction for Architecture Cluster of Excellence Selected for Funding

There was great delight at the University of Stuttgart following the announcement of the winning projects for the new Strategy of Excellence on the 27th of September. Two of our clusters of excellence were selected for funding by experts from the German federal and state governments as well as the German Research Foundation and will be receiving funding worth millions of euros for the next seven years. Both the Data-Integrated Simulation Science Cluster of Excellence and the Integrative Computational Design and Construction for Architecture Cluster of Excellence were accepted.

"We're very, very happy", said Professor Wolfram Ressel, Rector at the University of Stuttgart. "The success of not one but two clusters, in the face of some extremely stiff competition, is testament to the successful development of collaborative research at the University of Stuttgart as well as the expertise established over the past few years in the fields of simulation technology as well as adaptive architecture. Spurred on by this success, and with the strategic focus of our research profile being on 'Intelligent systems for a sustainable society', we are now increasing our efforts in the competition for the title of 'University of Excellence'. I would like to thank everyone involved in the application process for their enormous commitment and passion; they all put their hearts and souls into it".

It is a shame, he continued, that the Commission chose not to select the other applications from the Understanding Understanding: Language and Text Cluster of Excellence and Quantum Sciences from the Basics to Application: Development of Quantum Instruments of the Future Cluster of Excellence. However, he pointed out, they have created important foundations, for example, for future collaborative research centers. "We will continue to pursue these important areas of research at our university and to advance them as far as we can". The application process for funding as a "University of Excellence" based on a vision of "intelligent systems for a sustainable society" is currently in full swing, with the final decision to be taken in the spring of 2019. "With the commitment of our staff and a small pinch of luck", said Ressel hopefully, "we'll all be working at a University of Excellence as of November 2019".

Simulation in the Era of Data Science

Given the enormous amount of data currently available from various sources, the Data-Integrated Simulation Science Cluster of Excellence is working on the development of a new class of modeling and computational methods, which will take the usability and precision of the simulations as well as the reliability of the decisions based on them to a whole new level.

Simulations have become an indispensable part of research and development in many different areas, and make a key contribution towards technological progress. In terms of models, methods and computing aspects from an engineering perspective, the "Simulation Technology (SimTech) Cluster of Excellence" at the University of Stuttgart has been advancing simulation technology in terms of scope and depth since 2007, and, with its interdisciplinary and methodical profile, has established it as an internationally visible research center. The University of Stuttgart can now develop its research findings and successes in a new direction.

"We are introducing a new paradigm into simulation sciences at the University of Stuttgart with data-integrated simulation", explains Prof. Thomas Ertl, spokesman for the Cluster of Excellence. "We are reaching our limits with the traditional approaches when it comes to simulating highly complex

Simulations have become an indispensable part of research and development in many different areas and make a crucial contribution towards technological progress.

Photo: University of Stuttgart / VISUS

phenomena, for example in environmental issues, in digital human models and in new materials, and we can only overcome this issue by integrating all the available data. We're convinced that the new methods emerging out of SimTech will fundamentally change research and development in many scientific disciplines."

Future-Oriented Research Questions

The focus of the Data-Integrated Simulation Sciences Cluster of Excellence reflects a variety of future-oriented research questions. The amount of data available today from sensor readings, data collections, experiments and simulations offers new and ever more significant opportunities to gain insights. Methods based purely on data analysis however are often difficult to understand, and previously could often not take physical conditions into consideration. An in-depth understanding of complex systems can only be gained based on scientific principles.

This is why the scientists want to systematically integrate the data they can extract from various sources into the modeling-simulation-analysis cycle. Their research objective is to develop a new class of both simulation and data-driven approaches, which will take the usability and precision of the simulations as well as the reliability of the decisions based on them to a whole new level. The research will be focused on simulating multiphase flows, porous materials, mechanical structures and biological systems, but also on overarching aspects of machine learning, the analysis of uncertainties and those arising from adaptive and ubiquitous IT infrastructures.

Reconceptualizing the Built Environment

The Integrative Computational Design and Construction for Architecture Cluster of Excellence is facing up to the challenge posed by the fact that, in the next 35 years, new urban accommodation will have to be created for some 2.6 billion people around the world. Yet the productivity of the building industry has been stagnating for decades, and even today construction accounts for more than 40 percent of the world's resources and energy consumption. New approaches for planning and building are urgently required. Digital technology promises one solution, though due to the fragmented nature of the building industry this has previously only led to improvements in isolated cases, and very slowly. The Cluster of Excellence has, therefore, decided to rethink the process of planning and building, whe-

The Architecture Cluster of Excellence will be rethinking the process of planning and building, whereby it will be concentrating on a holistic computer-based approach.

Photo: University of Stuttgart / ICD

reby it is concentrating on a holistic computer-based approach to enable pioneering innovations in construction.

"Architecture is very important to our society. However" as Cluster spokesman Prof. Achim Menges, Head of the Institute of Computational Design (ICD) at the University of Stuttgart, emphasizes: "the construction sector is facing enormous ecological, economic and social challenges. By taking an integrative and interdisciplinary research approach, we want to exploit the full potential of digital technologies to create the foundations for pioneering innovation and sustainable planning and building".

An Overarching Co-Design

A key objective is the development of an overarching "co-design" methodology of methods, processes and systems, based on interdisciplinary research between the fields of architecture, construction engineering, geodetic engineering, production and systems technology, informatics and robotics, as well as the social sciences and humanities. The research is not only focused on the question of how new digital technologies can be used to optimize existing processes and systems, but also how novel design, planning and manufacturing construction approaches can be developed.

The scientists are expecting to develop comprehensive approaches to solving the ecological, economic and social challenges, which cannot be mastered through an incremental (step-by-step) approach. They want to create the conditions for a high-quality, livable and sustainable built environment as well as for a digital building culture. Likewise, they want to increase Germany's competitiveness into the biggest industrial sector in the world. Here they can draw upon the many years of experience that the University of Stuttgart has as a pioneer in architecture and construction engineering, as well as its international profile. In particular, the results of the DFG's Collaborative Research Center SFB 1244 (Adaptive Shells and Structures for the Built Environment of Tomorrow, spokesman Prof. Werner Sobek), as well as the discontinued transregional Collaborative Research Center SRA-TR 141 (Designing and Construction Principles in Biology and Architecture, spokesman Prof. Jan Knippers), will be incorporated into future research.

red

... News flash!

Top spot for third-party funding

655,400 euro: According to figures recently released by the Federal Statistical Office of Germany (Destatis), that's how much third-party funding each professor at the University of Stuttgart was able to attract in 2016. This once again placed the University of Stuttgart in second place by national comparison. The professional group with the highest third-party funding revenues were the engineering sciences.
The national German average for third-party funding per professorship was just 258,000 euro. The University of Stuttgart achieved fourth place for third-party funding for the university as a whole ahead of far bigger institutes.

Rector Re-Elected, New Vice Rectors

The University Council and Senate were unanimous in their decision to reelect Professor Dr. Wolfram Ressel, who has already held the position of Rector for twelve years, for a further six years in the University of Stuttgart's top position. By contrast, changes were made among the Vice Rectors: Professor Dr. Hansgeorg Binz (Institute of Engineering Design and Industrial Design (IKTD)) is the new Vice President for Education and Qualifications, Professor Dr. Peter Middendorf (Institute of Aircraft Design (IFB)) is the new Vice Rector for Knowledge and Technology Transfer.

VR Expo in ARENA2036

A platform that connects industrial users, technology providers, content service providers and researchers from the fields of virtual reality (VR) and augmented reality (AR) – that's what the VR Expo, instated by LIGHTSHAPE and the Virtual Dimension Center (VDC) Fellbach, offers. This year, ARENA2036 and the University of Stuttgart participated as additional co-organizers so that the interactive exhibition could be held in the ARENA Research Factory for the first time. The VR and AR laboratories of the University of Stuttgart's High Performance Computer Center Stuttgart (HLRS) and Visualization Institute (VISUS) as well as the Fraunhofer Institute of Industrial Engineering (IAO) Center for Virtual Engineering (ZVE) also took part. The approximately 1500 visitors were able to try out a broad spectrum of innovations, from mobile smart glasses and head mounted displays to large format, high resolution power walls and CAVE systems from 47 exhibitors.

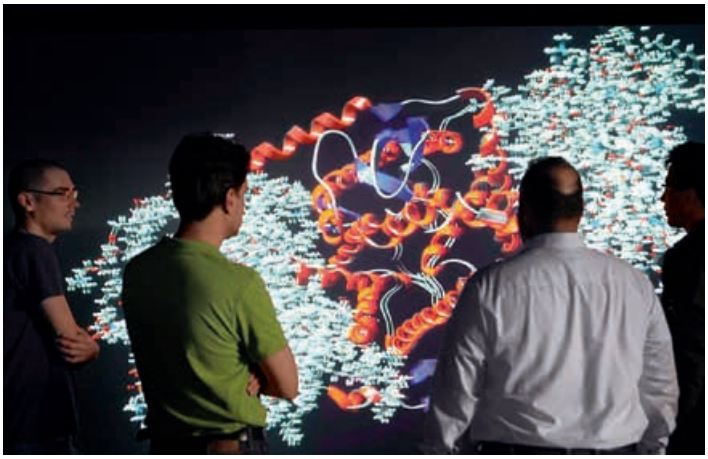

Photo: Universität Stuttgart / VISUS

Observant Computers

Shortly before moving to the University of Stuttgart, Andreas Bulling, the newly appointed Professor for Human-Computer Interaction and Cognitive Systems at the Visualization Center received an ERC Starting Grant from the European Research Council. In his project, which is known as "ANTICIPATE: Anticipatory Human-Computer Interaction", he is trying to find new user interfaces between humans and computers, which are modeled on interpersonal interactions. To this end, user attention and intentions are being analyzed to enable proactive adaptations to future user interactions.

Photo: Private

EXCELLENCE

Outstanding Quantum Chemists

The Society of German Chemists has awarded the Erich-Hückel Prize to Professor Hans-Joachim Werner, Head of the Institute of Theoretical Chemistry (ITheoC) at the University of Stuttgart. Werner has received the award, which includes a 7500 euro cash endowment, for his outstanding achievements in Theoretical Chemistry. He is considered one of the most internationally renowned researchers in the field of Quantum Chemistry and is known particularly for his numerous methodological contributions. The MOLPRO program package for wave-function-based electron structure calculations, for the development of which he was chiefly responsible, is used by over 500 groups around the world.

Photo: University of Stuttgart / Uli Regenscheit

Expertise in Timber Engineering

Dr. Simon Aicher, Leading Academic Director at the University of Stuttgart's Materials Testing Institute, and Head of the Timber Construction Department, was awarded the prestigious Carl-Olof Ternryd Prize. Aicher received the prize in recognition of his achievements in the field of Timber Engineering with particular relevance to the areas of glues, timber bonding, load-bearing timber constructions as well as, in particular, their non-destructive testing, standardization and quality assurance.

Photo: Universität Stuttgart / MPA

Exchange in South Korea

In mid-September, the Hanyang University in Seoul hosted visitors from the University of Stuttgart for an interdisciplinary alumni reunion and the inaugural Stuttgart-Hanyang Science Day, which focused on artificial intelligence and solid state quantum technology. The participants included former students, doctoral students and guest professors invited to an alumni reunion by the University of Stuttgart's Alumnus Office. The alumni reunion was incorporated into the university orchestra's Asia concert tour held to mark its 50th anniversary.

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Mobile Green Room

What will happen if it is not only hotter but also dryer in future? At which locations are green areas most effective as buffers against rising temperatures and how can the irrigation requirements of green areas be met during heat waves? The University of

Photo: Helix

Stuttgart is carrying out research into these highly topical questions in the new "Integrated Strategies for the Consolidation of Urban Blue-Green Infrastructures (INTERESS-I)" research project. The researchers want to identify alternative water resources, appraise their suitability for irrigation, test storage methods and develop new forms of climate-effective urban green spaces. A mobile green room was on display as a foretaste at Campus Stadtmitte in October.

Fewer Pharmaceutical Residues

The environment is being polluted by huge quantities of residual traces of Diclofenac, a widely used painkiller. A research team headed by Professor Bernhard Hauer of the University of Stuttgart's Institute of Biochemistry and Technical Biochemistry (IBTB) has been able to demonstrate for the first time how Diclofenac can be broken down in soils and what is preventing its decomposition.

Interactions between specific microorganisms are crucial to the success of this decomposition process. The decomposition of the compound is initiated by a so-called carboxylation, an unusual reaction in nature. Highly sensitive analyses were required to discover the metabolic product made by the microbes.

Outpatient Care Even in Stormy Weather

How can outpatient care for people in need of care and medical aid be assured when access routes are blocked, for example, by flood waters or lengthy winter storms, and when communication channels are restricted? In the KOPHIS research project, the Institute of Human Factors and Technology Management (IAT) at the University of Stuttgart is conducting research into how care services can be maintained by means of a structured collaboration between relevant stakeholder groups, such as the authorities and aid organizations including the fire brigade, the Federal Agency for Technical Relief (THW) as well as care services. The results of the study and concrete recommendations and training instructions are set out in the recently published guideline "Achieving a Successful Collaboration".

Asteroid Named After SOFIA

A great honor for the Stratospheric Observatory for Infrared Astronomy (SOFIA), for the scientific support of which the University of Stuttgart is responsible within Germany: the minor planet number 239672 has been named after the flying observatory. SOFIA (239672) inhabits the main asteroid belt of our solar system between Mars and Jupiter: one SOFIA year takes 4.81 Earth years.

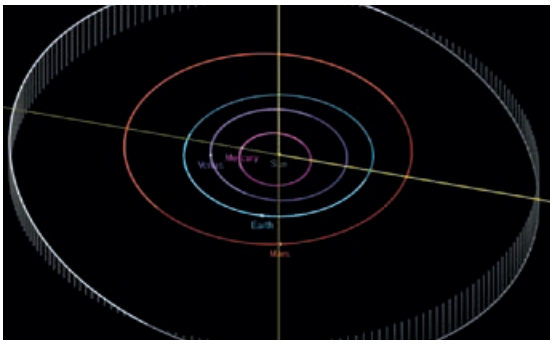


Photo: JPL Small Body Database Browser

Teacher Training Quality Campaign

The Federal Ministry of Education and Research (BMBF) will be supporting the Professional School of Education Stuttgart-Ludwigsburg (PSE) for a further five years with funding totaling around 5.3 million euro. The money will be used to fund joint activities aimed at the provision of top quality teacher training by the Universities of Stuttgart and Hohenheim, the Ludwigsburg University of Education, the State Academy of Fine Arts Stuttgart and the State University of Music and Performing Arts Stuttgart. The partner universities are pooling their strengths in the science disciplines, subject-related didactics, educational sciences and teaching practice under the auspices of the PSE. Specific topics include course offerings, evaluation and quality assurance, studies into teaching practice, scientific and technical studies (STEM), digitalization, inclusive education and heterogeneity as well as learning-teaching and student laboratories for teacher training.

Only those who help to shape the future will stay on top

The healthcare industry is facing a transformation, which will require a rethink in science and research.

Within Germany, Baden-Württemberg's healthcare industry is at the top of the league. Yet, changes, such as digitalization and new licensing regulations are presenting the front runners with certain challenges. In his guest article, the Managing Director of the state-affiliated BIOPRO organization, Professor Ralf Kindervater, sets outs four propositions to explain what health researchers should do to ensure that Baden-Württemberg stays ahead.

"Gesundheit!" That's something we hear more and more often these days: after all, the seasons in which people most often catch cold are upon us. Today, we're in the fortunate position to be able to do a great deal for our health and to treat illnesses. The part of the economic sector that deals with health issues is known as the health economy. The part of the health economy concerned with production is the healthcare industry, which encompasses the biotechnology, pharmaceutical and medical engineering sectors. There are over 1000 companies active in Baden-Württemberg's healthcare industry, which are involved in production, development and research. Speaking of research – research is the foundation for all progress, including within the healthcare industry. This is evident in new treatment methods, diagnostic processes and technical devices. Everything we know today about the functional connections within the body, disease patterns and their causes, medicines, germs, genes, treatments, diagnostic processes, environmental factors, such as stress and nutrition as well as the promotion of good health, is thanks to research. The spectrum of research disciplines relating health is broad: biology, biotechnology, pharmaceuticals, medical engineering, information technology, physics but also the sports and nutritional sciences to name just a few examples.

Yet, the fact that research is indispensable for health certainly doesn't mean that everything will stay the way it is. It's becoming apparent that various changes are approaching that will affect both academic and corporate research. I shall now provide an overview of these changes based on the following four propositions.

Proposition 1: Data is the new capital

This proposition is not new. Google, Facebook, Apple, Amazon, IBM are just a handful of examples for the economic importance of data. There are IT companies that use code, content and CPUS to analyze, processes and apply data. All sectors work with data in one way or another, and the healthcare industry is no exception to this. What is changing, however, is the importance of data in medical research. Until now, doctors have been able to treat illnesses using a plethora of diagnostic processes, medical devices and pharmaceutical agents or drugs, in other words, the three Ds. There is now a fourth D – data. This means a fundamental change for medical research. So far, researchers have been concentrating on processes, devices and drugs. There were few connections between these different areas, because doctors tended to apply the respective resources successively as part of a graduated process: First, a blood test (diagnostic device), then ultrasound (medical device) to complete the diagnosis after which some type of medication (drug) was used to treat the complaint. At an event hosted by BIOPRO Baden-Württemberg, Professor Jochen Maas from Sanofi, a pharmaceutical company, recently provided some examples of the links between diagnosis, devices and drugs. Insulin pumps, which automatically dispense the correct amount of insulin within the patient's body, are a case in point. The patient's blood sugar level is measured by a sensor within the body and the insulin pump is activated as required. Diagnostics,

Photo: BIOPRO Baden-Württemberg GmbH

a medical device and a drug all act in harmony. However, there are very few companies within the pharmaceutical sector that have mastered this triad. So, when the medical research sector is inundated by huge data volumes, it will not exactly be easier for established companies to expand their own portfolios. Data-savvy companies, such as Google and Apple are working on driverless cars, which can be seen as evidence for the fact that these companies have no reservations about working with other sectors. They work at a high level of abstraction, identifying data pools, thinking about how they could be exploited and then developing new applications. So the medical research sector needs to look beyond existing analytic and diagnostic parameters. IT-related topics, such as artificial intelligence, the Internet of Things, virtual and augmented reality must also be considered in relation to applications in the healthcare economy. And, additional data needs to be taken into account and processed for health profiles. Which data and precisely how it can be used and protected is a challenge for the research community.

The university-based research community will need to deploy campus resources in new ways. Until now, high-performance computers have primarily been used by the engineering sciences. However, the desire for computing performance is now increasing in the life and medical sciences, as the synthesis between the biosciences, computer sciences and mathematics is already in full swing under the heading "system biology", the objective of which is to map complex cellular processes with the aid of mathematical models and simulations. The data volumes generated during the simulation of metabolic cascades and intracellular signaling paths are enormous, but they deliver results that can be used in practice. Such data-based procedures are already established in the field of biotechnology. We should not fail to utilize these new methods in healthcare research.

"Professors ought to be keeping an eye out for start-up potential and be sensitizing and their students to chances and opportunities and motivating them".

Professor Ralf Kindervater, Managing Director of BIOPRO Baden-Württemberg GmbH

Proposition 2: Medical research must take account of research right from the start.

The regulatory standards applicable to the medical engineering and pharmaceutical industries are very demanding. Progress has even created situations in which both sectors, i.e., the pharmaceutical and medical engineering sectors mesh. In such cases, it needs to be decided whether a given products is more characteristic of a medicament or a medical engineering application. In addition, the authorization modalities pertaining to the production of medicines, in particular, are currently undergoing a radical upheaval.

So, it can happen that a given product suddenly lands in a high risk medical technology class, although this was not intended at the start of the development

process. It then needs to comply with much more stringent requirements, the costs increase and its profitability is called into question. Researchers need to be up-to-date on the subtle distinctions between the respective regulations as well as their ramifications. Contact centers should, therefore, be created where questions about licensing and approvals could be clarified in the early stages of research. For scientists active in medical research, the main question then changes from "can it be done?" to "how can we get this through the approvals process?" Ultimately then, it is the approval criteria that set the boundaries of feasibility, not technical sophistication. Greater support with regulatory issues right from the start would make research, particularly in the medical engineering field, more efficient and faster.

Proposition 3: The basics of starting a business should be taught as a standard part of the university curriculum

In every academic year, there an immense number of potential entrepreneurs, whose ideas and technologies could transform the relevant markets. Some of them will capitalize on their capacities, but most will abandon their ideas and seek careers outside of the business incubators and innovation highways. This is a significant loss both for the healthcare economy and patients, which could result in certain diagnostic processes or treatments only emerging at a later time or being developed elsewhere. 50 companies were launched in Baden-Württemberg's healthcare sector between January 2015 and June 2018, about half of which are biotechnology companies specializing in the development of novel therapeutic agents. That's extremely encouraging, both in terms of future therapeutic achievements and for the region. But, in my view, a few more would be very welcome.

We already have structures and programs in place to support new ventures. Nevertheless, in my opinion, the start-up culture still has too few supporters at the institutional level. We need to generate some enthusiasm for start-ups, precisely because the healthcare sector is so strictly regulated and can appear rather daunting to young entrepreneurs. Professors ought to be keeping an eye out for start-up potential and be sensitizing and their students to chances and opportunities and motivating them. It would be better still if the subject of entrepreneurship were a standard part of the academic curriculum. Then it would finally become what it should be – a strategic instrument for business development in Germany as a high-tech region, embedded within our universities.

Proposition 4: Reward collaboration and networks with an impact factor

If one considers the questions with which the healthcare industry is concerned, one has to conclude that the solutions can no longer be developed at the level of individual institutes or professorial chairs. For diseases such as cancer, we can hardly talk in terms of a clinical picture. The cellular and molecular-biological entanglements and the many consequences for the organism are more reminiscent of a collage made up of hundreds of images, so complex are the influencing factors involved. Thanks for technological developments and our high level of knowledge, we can now look at things from multiple perspectives. And yet, we still often get the impression that we can only recognize a small excerpt from the overall picture.

To be able to advance medical research going forward, we will be more reliant than ever on establishing, exploiting and continuously pushing long-term collaborative arrangements. We need many collaborators to enable us to take in all the various perspectives on a given disease incidence. We need more consortia and more collaboration beyond the consortia, because more specialist disciplines need to be involved.

In our capacity as an innovation agency, we at BIOPRO Baden-Württemberg repeatedly find that many stakeholders know nothing about each other, but would be a good fit in terms of content. In the health economy, that applies particularly to the connections between academia and the business sector. Clearly, the old adage of the need to network is still as applicable as ever, but what we often forget when it comes to networking is that rapid successes are rare. The commitment to a given network requires two things: a lot of reciprocal visits and a preparedness to get involved.

The science community likes to cite the journal impact factor, in other words, the relative ranking of the journal in which one publishes one's findings, as a mark of quality. Regardless of how one feels about this practice , the fact remains that, if healthcare research is to have an impact where it is urgently required, namely on people, then networking is more important than the prestige of any journal. We should first increase our network impact factor and only then worry about journal ranking lists.

The healthcare industry in Baden-Württemberg is at the top position within Germany in terms of employment, gross value added and export volume. In 2017 alone, some 88026 employees generated 16.5 billion euro gross value added. So, there's not much to complain about. But, enough of the self-congratulations! As everyone knows, it doesn't do to rest on one's laurels.

Professor Dr. Ralf Kindervater

As a Graduate Chemist specializing in biochemistry and biotechnology, Professor Dr. Ralf Kindervater earned his doctorate at the Technical University of Braunschweig for his work in enzyme technology with the Gesellschaft für Biotechnologische Forschung mbH (Research Center for Biotechnology) in Braunschweig.

Following stints at the Eberhard Karls University of Tübingen and the Fraunhofer Institute of Interfacial Engineering and Biotechnology IGB in Stuttgart, Kindervater held interim board memberships and managing directorships in several biotech companies.

He has been the Managing Director of BIOPRO Baden-Württemberg GmbH in Stuttgart since 2003 with responsibility for the healthcare industry and bio-economy. Dr. Kindervater has held an honorary professorship at the Karlsruhe Institute of Technology since 2014, where he is active in the Faculty of Chemical and Process Engineering.

Glass tumor
On the system biology of personalized cancer treatment

Today's new cancer drugs that are customized to patients and their specific tumors are enabling sufferers to survive much longer. However, many cancers are resistant even to targeted drugs. Researchers at the University of Stuttgart's Stuttgart Research Center Systems Biology (SRCSB) are currently analyzing tumor cells as a whole, in all their complexity, and using their findings to predict the efficacy of such drugs, both to develop new treatments and to be able to develop potential new drug candidates more rapidly.

It has long been known that tumors are as different as the people they affect. Even the cancer cells inside an individual person can differ, which is why chemotherapy, an undifferentiated chemical cosh aimed at all cancer cells, is increasingly being replaced by cancer drugs that target and attack individual changes within the cancer cells themselves, which promote the growth of tumors. Yet, even such personalized therapies often only show short-term results or none at all.

To ensure the success of a customized treatment, it is usually not enough to search for specific biomarkers in patients, such as gene mutations within their tumors or certain tumor-relevant proteins that may be being produced in greater or lesser quantities. The biology of tumors is far too complex for this. "That's like dismantling a radio and spreading the components across the table" as Morrison, Head of the Institute of Cell Biology and Immunology (IZI), explains: "the system will only function if I connect the heap of parts in a specific way". In future, it will be about not simply considering individual pieces of the puzzle, but rather trying to understand the tumor in its entirety, to develop drugs with more targeted effects. This discipline is known as system biology. Morrison's research group, which predominantly includes cell biologists and systems biologists, is currently looking into the complex intracellular signaling paths, which seal the cell's fate, i.e., they either tell it to divide and multiply or self-destruct. In cancer, these signaling paths are often impaired and the cells start to divide uncontrollably, whereby the tumor cells usually exhibit multiple mutations in different, but often interconnected, signaling paths. Therefore, simply treating a single signaling path with drugs is unlikely to halt the growth of the tumor.

Understanding the signal twitter in tumor cells

Usually, each cell continuously scans its environment via its receptors, and forwards information about external stimuli, such as growth stimuli or stress signals, via a series of messenger molecules within the cell. At the same time, the information flow branches out, is reinforced or incorporates data from other signaling paths. If the sum of all signals reach a certain threshold value, the information flows culminate in an order to the cell either to cease growing or to initiate the programed cell death process.

It is easy to lose track of things among all the signaling noise, which is why Morrison's group is feeding high-performance computers with enormous amounts of data. They are linking data relating to signal messenger substance volumes from their own experiments on individual cells and animals to information about how the various messenger substances are interconnected and adding clinical data from cancer patients and their tumor properties. From this they can produce circuit diagrams – like those produced for radios – for cancer cells and then run the signaling network and consequent changes on the computer.

"Based on the mathematical models, we then try to predict, whether certain cancer cell lineages or

New active agents can be developed more rapidly and cost-effectively using virtual signaling networks and computer simulations. If one wanted to analyze all possible modifications to drugs purely through empirical experimentation, it would take an inordinate amount of time and the task would be practically intractable.

Photo: University of Stuttgart / Max Kovalenko

tumors will be amenable to treatment with a given drug or what the best possible strategy is for making the tumor more sensitive again" says Morrison. The researchers' predictions about colorectal and skin cancer cells have an 80 to 85 per cent probability of being correct, which, says Morrison, is already pretty good. His team then carries out empirical testing on the simulation so that they are able to configure the models with increasing precision. In future, the predictions could help protect patients from undergoing ineffective treatments and suffering their side effects.

But, the virtual signaling network can also be used to develop novel drugs more cost-effectively and faster, as their effects on the signaling networks of tumor cells can be simulated on the computer. If one wanted to analyze all possible interventions in the network or modifications to drugs purely through empirical experimentation, it would take an inordinate amount of time and the task would be practically intractable.

The Angle of Death – redesigned

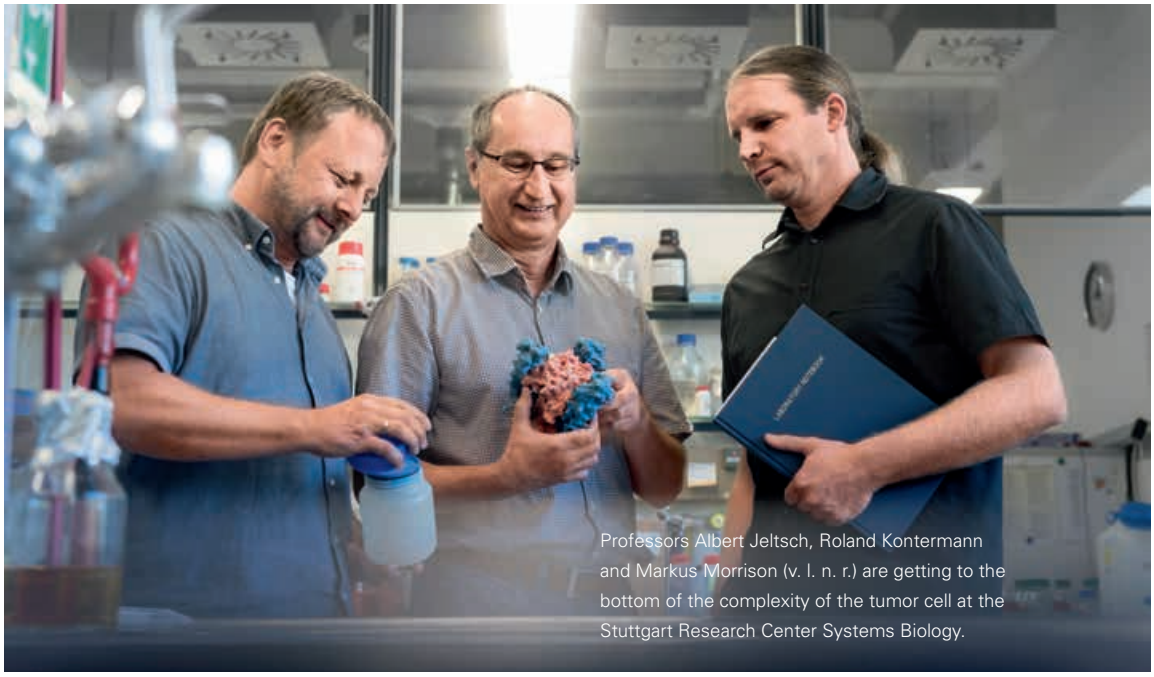
The "Biomedical Development" and "Cell Biology" groups headed up by Roland Kontermann and Morrison's predecessor at the institute Klaus Pfizenmaier respectively have already developed one very promising drug candidate together. It consists of a fusion protein, which drives cells to commit suicide, known as apoptosis, in targeted manner. The biologists modeled their creation on the TRAIL (TNF-related apoptosis inducing ligand) protein, which is produced by certain immune cells and triggers apoptosis in cancer cells, but has a negligible effect on normal healthy cells. "Tumor cells", as Kontermann explains, "are already teetering on the brink; they just need a little shove. You need to put a bit more effort in when it comes to healthy cells, as they can protect themselves much better".

However, clinical studies on the natural suicide messenger substances have so far delivered disappointing results. To trigger the cell death mechanisms in cancer cells more effectively, the protein engineers in Kontermann's team first used genetic engineering to link the three subcomponents of the TRAIL protein to form a single molecular chain. They then fused two such chains together, such that the designer protein they created can activate six death receptors on the cancer cells simultaneously. Finally, they appended another antibody fragment, which specifically binds to certain surface molecules on tumor cells thus guiding the active substance to its target with

a high degree of accuracy. “It looks very promising when used in colorectal and skin cancer cell cultures”, says Kontermann: “the TRAIL fusion protein also shows beneficial activity in mouse tumor models”. In the meantime, he goes on, three companies have indicated an interest in further developing the active substance in clinical studies. Meanwhile, the researchers working with Kontermann and Morrison are trying to completely destabilize tumor cells and give them the coup de grâce through a combination of the TRAIL fusion protein and chemo therapy drugs as well as newer substances. In the meantime, Morrison's team is augmenting its prediction model so that it can be applied to the combination therapy.

Misrouted gene switches as a cause of cancer

Albert Jeltsch, Head of the Biochemistry Section at the Institute of Biochemistry and Technical Biochemistry (IBTB) is taking a different approach towards personalized cancer treatment. The 52-year-old is researching reversible mechanisms, which regulate when which genes within the cell nucleus are switched on or off without altering the genetic information. It is thanks to this second level of DNA-mediated information that our bodies produce the various different cell types and cells are able to react in a flexible manner to environmental influences, such as hunger and trauma, whereby errors sometimes occur. Accidentally turning off genes that control cell growth and division, or switching on marginally active growth genes can fuel the formation of cancer. Whether genes are read and transcribed or not depends on small groups of chemicals on the DNA or DNA packaging proteins in the cell's nucleus, which are placed there or removed by enzymes. If enzymes attached methyl groups to the DNA base Cytosine at the starting area of a gene, they usually block



Professors Albert Jeltsch, Roland Kontermann and Markus Morrison (v. l. n. r.) are getting to the bottom of the complexity of the tumor cell at the Stuttgart Research Center Systems Biology.

Photo: University of Stuttgart / Max Kovalenko

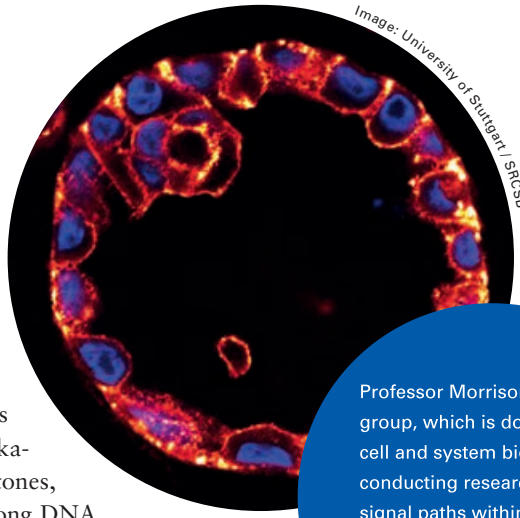


Image: University of Stuttgart / SRCSB

Professor Morrison's research group, which is dominated by cell and system biologists, is conducting research into those signal paths within the cell that seal its fate – i.e., decide whether it will divide or self-destruct.

the path of the gene transcription mechanisms. On the other hand, methyl, acetyl, phosphate or ubiquitin groups appended to the packaging proteins, the histones, cause the two-meter long DNA thread to wrap itself around a single histone complex, sometimes tighter, sometimes less tight, like a string of pearls. Genes in densely packed DNA areas are also not transcribed and are virtually switched to silent mode.

Researchers have discovered over 60 epigenetic markers thus far. In addition, there is also the fact that certain modifications usually interact in groups, which influence one another reciprocally. "We have 100 times more epigenetic than genetic information, because the human body comprises around 200 cell types, which carry different epigenetic markers" says Jeltsch. One of the objectives of a biochemist is to create a bit of order in this jungle of modifications and to understand which combinations of epigenetic markers work in which ways and may potentially trigger cancer.

Cataloging tool for modifications

Jeltsch's group has taken a first system-biological step in this direction by developing a new tool for detecting two adjacent epigenetic markers on histones at the same time, which they have since patented. The trick: Jeltsch's team fused two different epigenetic protein transcription domains, which specifically attach to histones if they are carrying certain markers. In theory, the researchers could combine any two different transcription domains, which would enable them to analyze every possible pair combination of histone modifications across the entire genome. To date, researchers have had to search for pairs of epigenetic markers in two sequential steps using specific antibodies. "We're faster with our one-step process and need less source material", Jeltsch says. Moreover, the properties of antibodies could vary from batch to batch, so that the experiments are not always repeatable.

Another of Jeltsch's research focuses are methyltransferases, attach methyl groups to DNA or histones. Mutations in these epigenetic enzymes have been discovered in some cancer patients. Jeltsch and his team are interested in how these mutations affect the function of methyltransferases. "Ideally, if we understand what is happening there", Jeltsch continues, "we could adjust the therapeutic treatment of patients, who have these mutations accordingly". Methyltransferase inhibitors could be useful against some mutations, for example. That would be personalized medicine in the true sense.

The researchers recently discovered, for instance, that the most common mutation in the DNA methyltransferase DNMT3A results in an altered DNA methylation pattern in a certain type of leukemia. Because methyltransferases unfold their effects across the entire genome, an altered DNA methylation pattern could affect many cancer-relevant genes. In the experiment, the researchers first analyzed just 56 different DNA locations. The goal now is to find out which methylation sites are marked incorrectly throughout the genome, and which genes are affected by this. "The individual pieces of experimental data then need to be recombined", Jeltsch explains: "to do this, we need the help of our colleagues in

the system sciences, who view the whole thing as a network to discover how all these modifications are interconnected and result in diseases such as cancer". Whoever has an insight into the tumor cell network and knows which adjusting screw they can twist, will also be better placed to discover the tumor's Achilles heel.

New insights by tearing down inter-disciplinary boundaries

To facilitate interdisciplinary exchanges between the bio-scientists, system scientists and engineers, Germany's first Center for System Biology was established as far back as 2005. The current successor organization, the SRCSB, has members from 19 institutes and eight faculties. Both Jeltsch and Morrison are members of the six-person management team. The Center not only focuses on novel active agents and cancer treatment methods but also on applications in industrial biotechnology. For example, other SRCSB have targeted the metabolism of microorganisms to get them to manufacture specific products.

The researchers are closing in on the tumor cells by microscope and image analysis to identify – to paraphrase Goethe – "what holds the world together at its core".

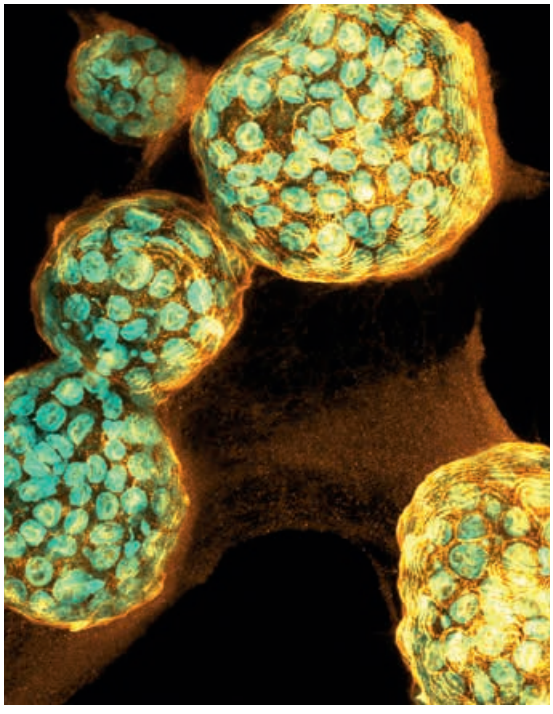


Image: University of Stuttgart / SRCSB

The regular meetings at the Center, such as the "System Biology" seminar series, conferences, but also internships and workshops on the topic for up-and-coming scientists are all conducive to the desired exchange. "One cannot help but become acquainted with the contents of other disciplines" Morrison finds, "which, of course, expands one's own horizons". Jeltsch and Morrison both agree that many interdisciplinary projects would never have come about without the SRCSB. On the one hand, the bio-scientists would never even have known what the system scientists, for example, were researching at the university at any given moment. On the other hand, it is an advantage when applying for third-party funding. "One would never expect to find expertise in mathematical models for predicting therapeutic outcomes at an institute of cellular biology," says Morrison: "however, the SRCSB can convince an expert evaluator that we do have the expertise in house". In the current five-year funding period, which finishes at the end of the year, the members were able to attract funding for 60 projects in the fields of system and synthetic biology.

Jeltsch and Morrison's research has also benefited from the collection of microscopes and large-scale image analysis equipment, which the institutes contribute and which are centrally managed and maintain by an SRCSB appointee, who also advises and supports the researchers with their measurements. "Normally, there is no one who exclusively deals with these things and trains people properly in their use", Morrison says. In the coming funding period,

the SRCSB intends to establish a similar technology platform to carry out system-biological research into proteins and metabolic byproducts.
In previous years, the biosciences at the University of Stuttgart have undergone an increasing change away from traditional subject areas toward system-oriented research approaches, which is evident just from the new professorships in such subjects as computational biology and system biology. Morrison is convinced: “if we want to focus on system biology and establish an international reputation in this field, then that is only possible in the context of a structure such as the SRCSB”. Cancer research could also benefit from this.

Helmine Braitmaier

Researching nutrition
Jens Brockmeyer sniffs out allergens and counterfeit food

People with food allergies usually have to completely avoid any contact with the food in question. Jens Brockmeyer would like to be able to identify the trigger allergens directly and to understand what makes a protein into an allergen. His primary "sniffer dog" in this undertaking is the mass spectrometer. The professor has headed up the recently created Food Chemistry Department at the University of Stuttgart's Institute of Biochemistry and Technical Biochemistry (IBTB) since 2016.

Jens Brockmeyer's main focus is on the protein pool in foods, the so-called proteomics. He sniffs out rogue substances among the food proteins that trigger an immunological reaction in food allergy sufferers. In Germany, almost one in twenty people have an allergy to at least one type of food. The most common trigger substances are milk, egg, soya, wheat, peanuts and tree nuts, fish and crustaceans. Even minute concentrations of allergens can trigger an allergic reaction in some suffers, sometimes culminating an anaphylactic shock. Others can consume a comparatively large amount until they notice the first signs of tingling or itching.

"Our current problem is that many foodstuffs are labeled with such statements as: 'may contain traces of ...'", says Brockmeyer angrily. Manufacturers apply this label to foods as a precautionary measure if there is any risk of accidental contamination with allergens during the manufacturing or filling processes. Whether and in what quantities the substance actually contains any allergens whatsoever remains unclear. If allergy suffers want to ensure that they avoid triggering a reaction, they have to avoid the suspect substance completely. "That places huge restrictions on their everyday lives", says Brockmeyer. It would be better, Brockmeyer continues, to specify the allergen concentration that is just sufficient to trigger an allergic reaction in a suffer as a threshold value for foodstuffs. The necessary clinical data has been gathered for many allergens over the past few years. Finding even minute traces of specific allergens in a given foodstuff requires highly sensitive detection methods. However, the two most common methods currently used in routine laboratories both have their weaknesses.

The immunological ELISA-tests involve fishing antibodies out of the food sample not only of the sought-after allergen but also structurally similar molecules. The second so-called Polymerase Chain Reaction (PCR) method requires food analysts not to verify the presence of the protein, which triggers the allergy, but a fragment of DNA typical of the allergenic foodstuff. However, because all of an organisms cells contain the identical DNA information, the analysts are not able to differentiate between a hens egg and a chicken. This also goes for milk and beef. "Nor would I be able to use PCR to determine whether a product contains albumen or not, because albumen contains practically no DNA", Brockmeyer explains, "but it is full of allergens".

Processed food cracked

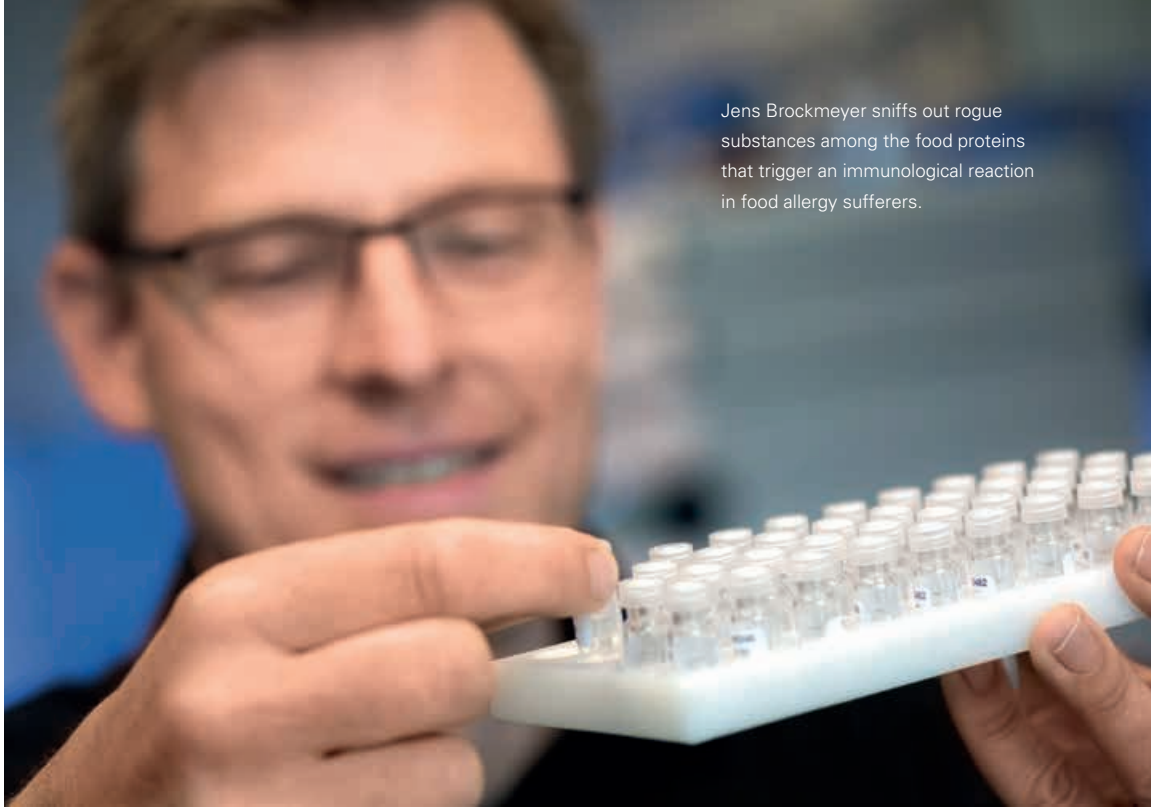
In particular, the current detection methods fail against processed foods, partially, it is thought, because proteins become denatured through heating and are no longer recognized by the antibodies, or because the DNA in acidic foodstuffs, for example, decomposes long before the allergens and, therefore, escapes detection.

Brockmeyer uses mass spectroscopy to detect the allergens. The devices in the adjacent laboratory are on every day around the clock. With this method, Brockmeyer's team can detect the most minute quantities of allergens, even in processed foods, for example traces of nuts in bread, chocolate and ice cream.

“The exciting thing about food chemistry is that it can be used to solve tangible issues. On the other hand, trying to understand the composition of food is fascinating”

Jens Brockmeyer

Photo: University of Stuttgart / Max Kovalenko



Jens Brockmeyer sniffs out rogue substances among the food proteins that trigger an immunological reaction in food allergy sufferers.

Photo: University of Stuttgart / Max Kovalenko

Mass spectroscopy involves crushing protein fragments from the food samples, which have been cut into little pieces by enzymes, so-called peptides, to charged fragments, which are then separated by charge. A peptide's mass spectrum is, as it were, its "finger print" from which its structure can be inferred. Brockmeyer and his colleagues can scan the food sample for the known peptide finger prints of various allergens simultaneously.

At first, it was particularly tricky to identify those marker peptides that are specific to a single allergen from among the millions of different protein fragments from the food sample. For example, one of Brockmeyer's colleagues had to wash every single hazelnut with various solutions, because nuts are nearly always contaminated with traces of other nuts. Only then would she scrape a piece from the surface to analyze all the proteins it contained in the mass spectrometer and to select those marker peptides that were easiest to detect. In the meantime, the group has successfully identified the marker peptides for the most common allergens responsible for over 90 per cent of all allergic reactions.

"We have to use every trick in the book to get to the sensitivity range we need with our high-resolution mass spectrometer" Brockmeyer admits. Routine laboratories, which already use less sensitive mass spectrometers to detect traces of residual pesticides and mycotoxins in food, cannot compete with this.

Bait molecules increase sensitivity

To make this method usable for normal mass spectrometers, the team is currently developing bait molecules from DNA and RNA aptamers, which fish out only the sought-after marker peptides from the millions of peptides, thus concentrating them for detection in the mass spectrometer. In addition, the group wants to automate the sample preparation process to enable the simultaneous rapid analysis of as many food samples as possible.

Brockmeyer also uses the mass spectrometer to track down counterfeit food – for the first time, without even having to know what he is searching for. Today, he would be in a position to rapidly uncover things such as the beef lasagna scandal in 2013, in which the beef was laced with cheaper horse meat, because the proportion of beef-specific peptides in the total quantity of mammalian marker peptides would be lower. If, as happened in the USA back in 2014-15, spices containing cumin have been, probably deliberately, contaminated with peanuts then the counterfeit food puts allergy sufferers in real danger.

What excites Brockmeyer about food chemistry is that it can be used to solve tangible issues. "You know why you're analyzing a given substance", he explains. On the other hand, he is fascinated by questions such as what food is composed of, and why certain food allergens trigger an immunological response in the small intestine, whereas structurally

similar molecules are able to pass without incident. His team is currently playing through the passage of food through the digestive tract in the model system and analyzing the structure of the allergen peptides that arrive in the small intestine. It may be possible at some point to use them for a specific immune therapy for the treatment of food allergies.

Were it not for his brother, who is 13 years older than him and works as a food chemist in toxin analysis, Brockmeyer may well have chosen a different career path. "We've already agreed that we'll do a few joint experiments using our machines here" says the younger brother happily. Right from the start, his career seemed like a vocation – even if the way there was not always straightforward. Even at school in Osnabrück, the now 43-year-old was enthusiastic about chemistry but also about physics. After completing a vocational training course as a laboratory chemist, the pendulum swung in the direction of chemistry. But he likes to get to the bottom of things and went back to school to pocket his university-entrance diploma so that he could study. Again, he vacillated, this time between biochemistry and food chemistry before finally deciding to follow in his brother's footsteps.

Detective in forensic medicine

As a freshly qualified food chemistry graduate from the University of Münster, Brockmeyer first took a detour via forensic medicine in Bonn. As he tells it, he wanted to do something relevant, not just "analyzing the number of raisins in Christmas cake". The analytical methods are the same, regardless of whether he is searching for residues in food or of drugs in blood or urine. Following a murder case involving a drug that paralyzes the muscles of respiration, he attempted to detect the substance using mass spectroscopy but came up against technical limits. His doctoral studies at the Münster University Hospital were supervised by the renowned microbiologist Helge Karch. Karch is credited with the discovery of a certain type of dangerous (EHEC) diarrhea pathogen, which had been responsible for all major outbreaks in Germany and primarily spreads via contaminated food. This time, Brockmeyer used biochemical and molecular biological tools to investigate the structure and function of an EHEC virulence factor – for which he received the German Microbiology Association Doctoral Prize.

Since then, he has always maintained contact with his "alma mater": time and again he attended seminars at the University of Münster's Institute of Food Chemistry, where he also carried out various analyses for his doctoral thesis. Finally, he was offered the opportunity to do a post-doctoral qualification at the institute. His research on EHEC continued augmented by his current fields of research, food allergens and the authenticity of food, which he brought with him to Stuttgart along with a number of colleagues.

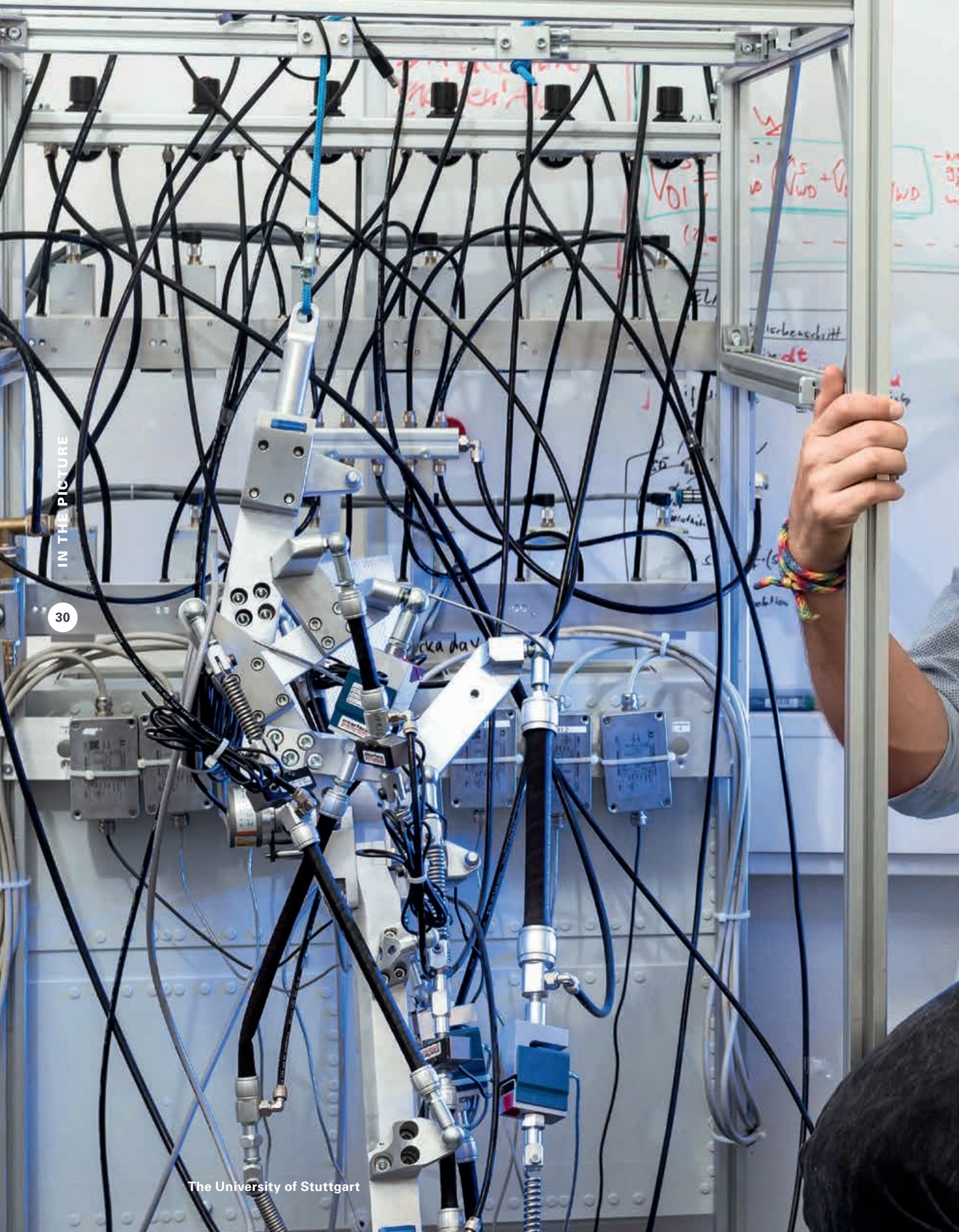
The fact that Brockmeyer has now settled in as the Head of Food Chemistry at the Institute of Biochemistry and Technical Biochemistry (IBTB) seems like a stroke of destiny. "The exciting thing about Stuttgart is that collaborative projects that I never would have dreamed of are a frequent occurrence here", Brockmeyer says. His department will shortly be conducting research into whether the nutritional value and protein composition of algae change under the zero gravity, high radiation conditions of space, or if they could be used as astronaut food or for generating oxygen in future without any issues. The Institute of Aeronautics and Astronautics has already provided an algae bioreactor, which will soon be sent to the International Space Station (ISS).

Helmine Braitmaier

The people modelers

For centuries, scientists have used models to describe complex phenomena.
Simulations enable us to understand important aspects of the systems described in this way, to predict their states and to decide how such systems could be controlled. In our contemporary society, simulations have become an indispensable part of research and development in many different areas and make a key contribution towards technological progress. In terms of models, methods and computing aspects from an engineering perspective, the "Simulation Technology (SimTech) Cluster of Excellence" at the University of Stuttgart has been advancing simulation technology in terms of scope and depth since 2007, and has established it as an internationally visible research center with its interdisciplinary and methodical profile.
Building on the scientific findings and insights from the SimTech Cluster of Excellence, the successful new "Data Integrated Simulation Science Cluster of Excellence" (SimTech), established as part of the strategy of excellence for the promotion of cutting edge research at universities is now tackling a plethora of new pioneering research questions and a new class of modeling and computational methods. Its main focus is, in particular, on the simulation of multiphase flows, porous materials, mechanical structures and biological systems as well as overarching aspects of machine learning, the analysis of uncertainties and adaptive, ubiquitous IT infrastructures. But above all, SimTech is also contributing toward medical progress in the field of digital models of human beings.

Photo: University of Stuttgart / SimTech / Storz Medienfabrik GmbH



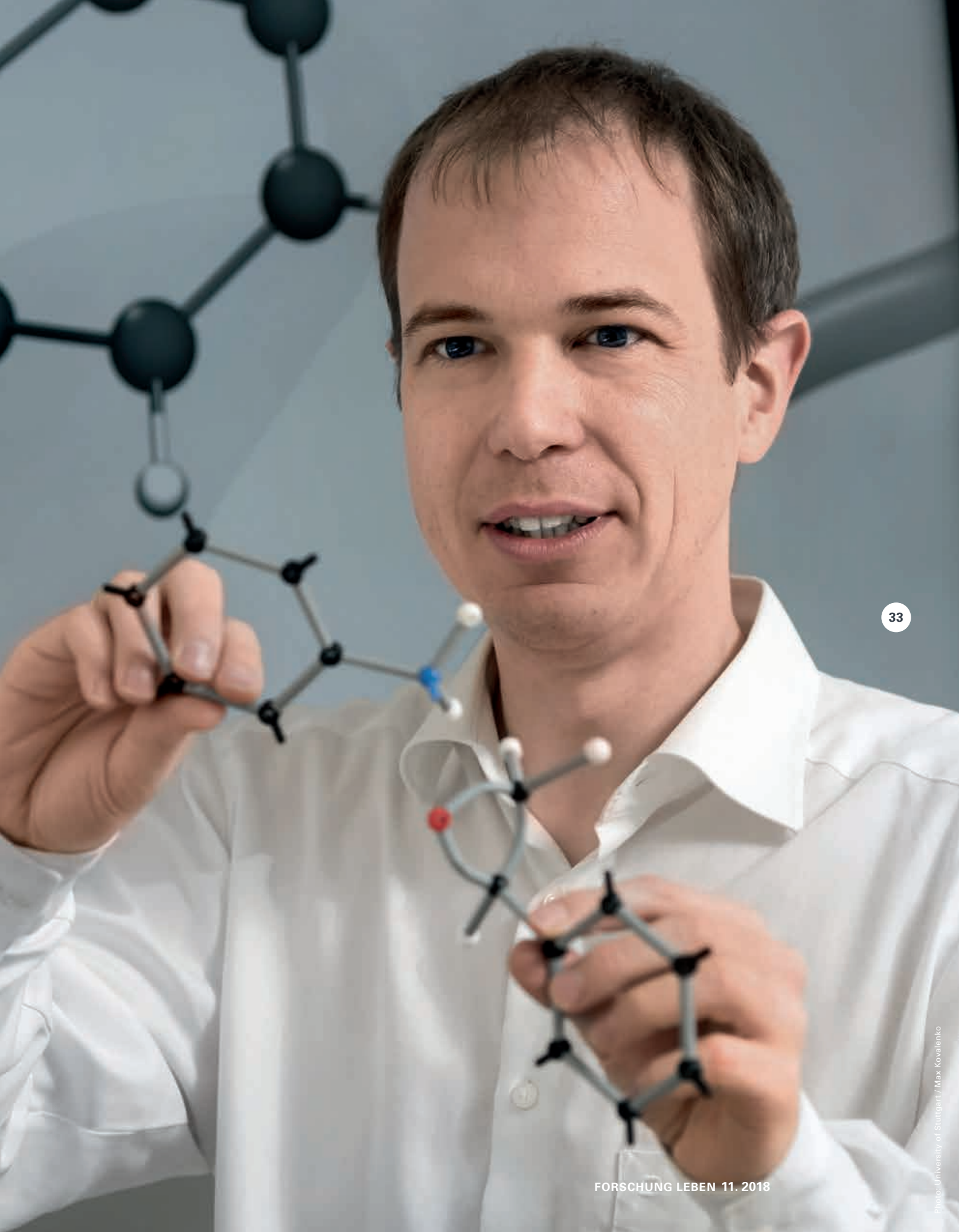
The University of Stuttgart

The human being is a highly complex biological system characterized by a finely tuned, intelligent interaction between individual subsystems. It is considered to be energy efficient, fault resilient and highly integrated. A new project involving neuromuscular motion control is analyzing the generation and control of active biological movements to provide the foundations for functional assistance systems in the field of rehabilitation robotics. The group headed up by Professor Syn Schmitt and the junior research group under Daniel Häufle of the University of Tübingen's Hertie Institute of Clinical Brain Research are collaborating in the development of simulation models and technical bio-robots. (Also see the article on p. 82)

Photo: University of Stuttgart / Max Kovalenko

Thanks to simulations, it is possible to analyze the smallest building blocks of life. Professor Johannes Kästner and his team are investigating how enzymes, such as salicylate-dioxygenase, are able to take up and use oxygen to break down poisons and digestive waste products within the body and to excrete them. Such biochemical processes at the smallest scale could explain the function of larger units within the organism, such as the organelles or cells. In the course of the study, experimental data from the field of system biology will be combined with quantum-mechanical simulations.

The University of Stuttgart



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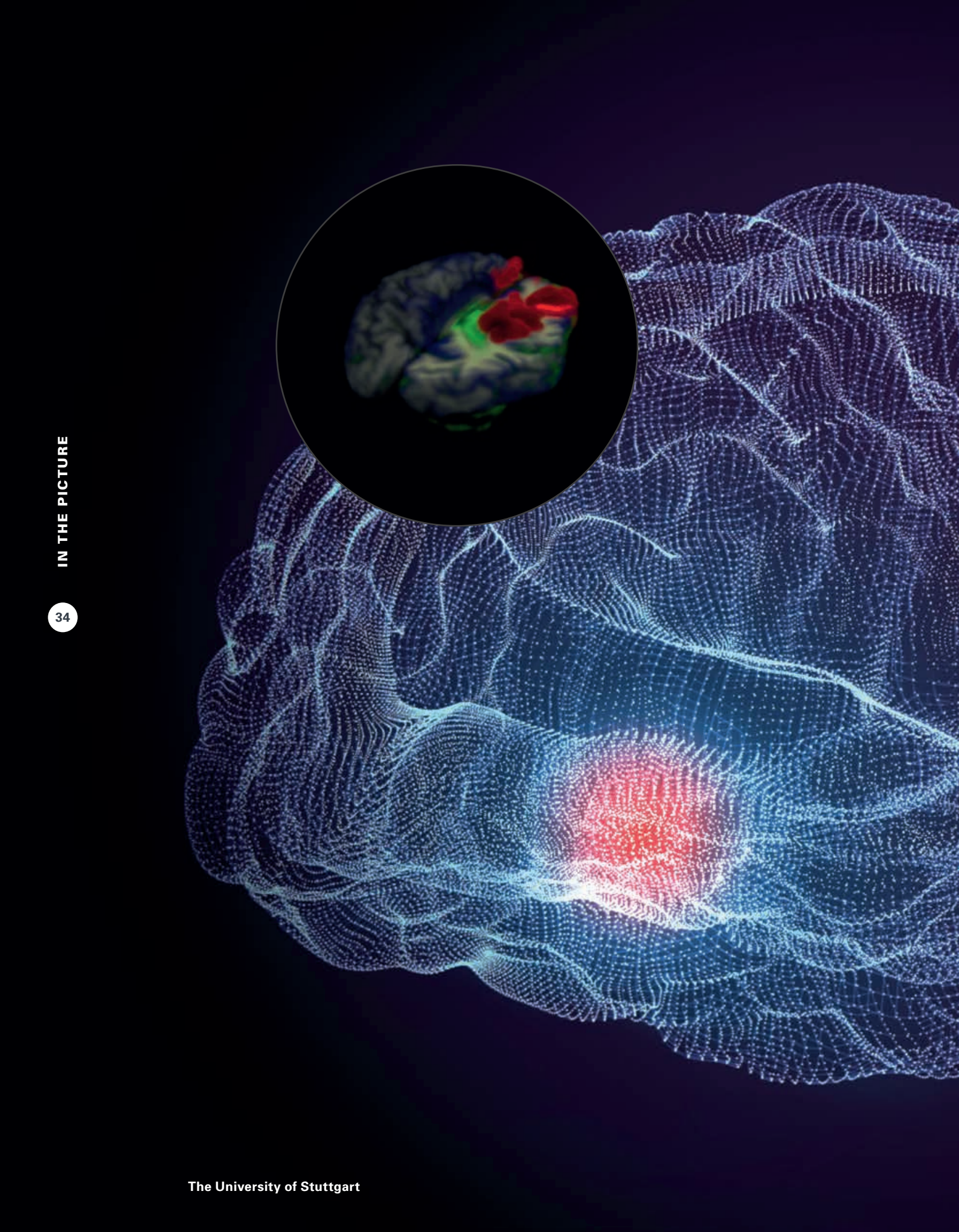


The University of Stuttgart

A glioblastoma is a currently incurable type of brain tumor. Research is being conducted at the "Simulation of Large Systems" Department run by Professor Miriam Mehl in collaboration with a group headed up by Professor George Biros (ICES, UT Austin) and the University of Pennsylvania on a software tool for the inverse simulation of the growth of the tumor.

One very promising treatment method for deep seated glioblastomas is the "convection method". Research is being carried out at the Institute of Applied Mechanics (Civil Engineering) (MIB) headed by Professor Wolfgang Ehlers into multiphase continuum mechanic models to provide the means to describe the dispersal of an injected drug in complex brain tissue and its effect on the tumor. In addition, data from tumor growth experiments will be included in the models in collaboration with the group run by Professor Markus Morrison of the Institute of Cell Biology and Immunology (IZI)

Perfusion MRI is a promising method for the supportive treatment of multiple sclerosis. However, the precise characterization of MS lesions remains difficult using contemporary approaches. Detailed, small-scale simulations of the MR contrast agent in the brain provide insights into the mechanisms that result in the characteristic MRI images of MS lesions and help to better interpret them. (Also see the article on p. 78)

The University of Stuttgart

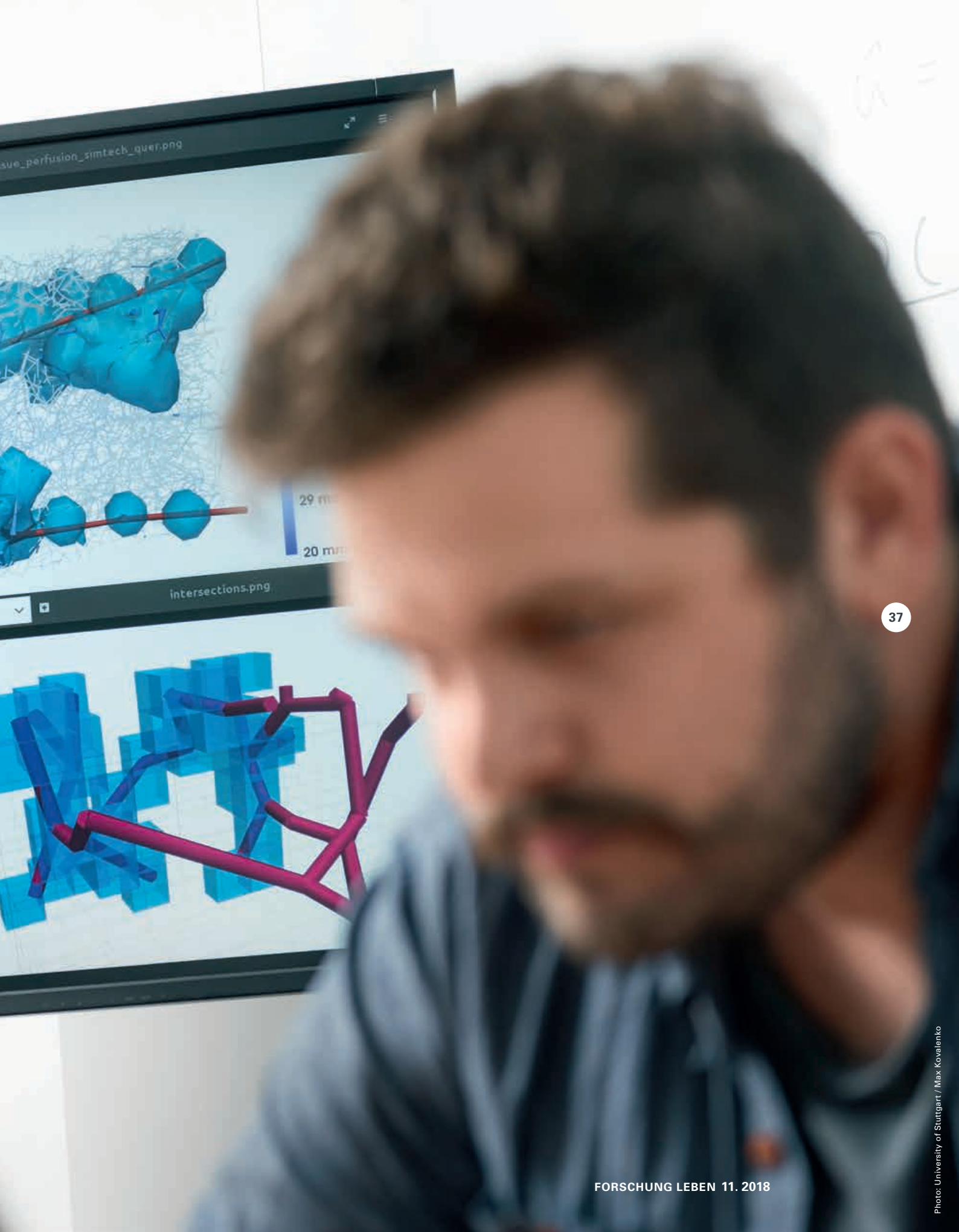


Photo: University of Stuttgart / Max Kovalenko

The objective of the interdisciplinary and simulation-oriented research approach is to gain a holistic, integrative understanding of the neuromuscular system, whereby the focus is on obtaining a better understanding of the three-dimensional structure and bio-physical structure and functionality of skeletal muscles. Professor Oliver Röhrle and his team are attempting to model the chemo-electro-mechanical properties and development of new homogenization methods for the patient-specific material modelling of skeletal muscles. In addition, the scientists are developing forward-looking dynamic musculoskeletal system models.
(Also see the article on p. 50)

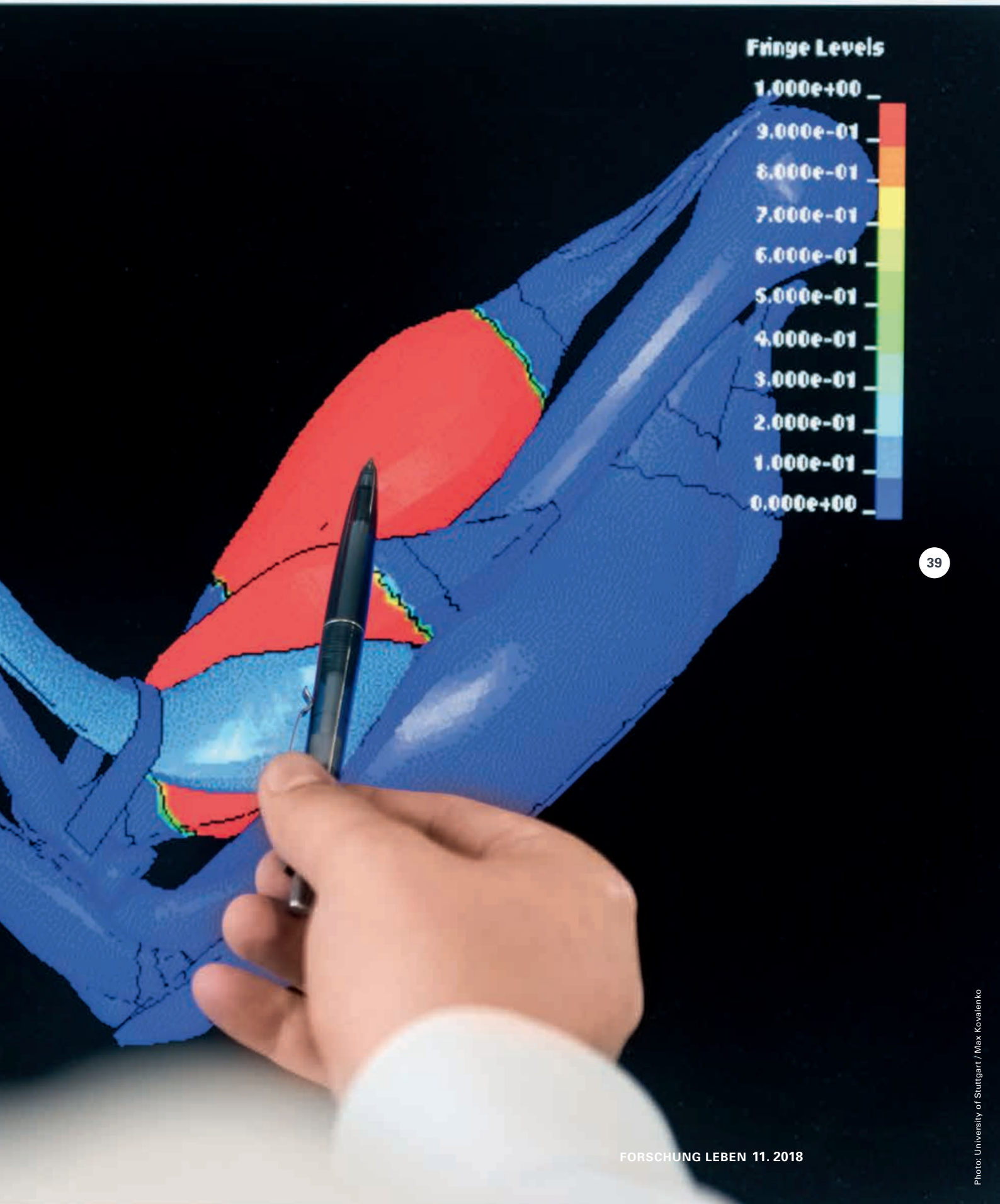
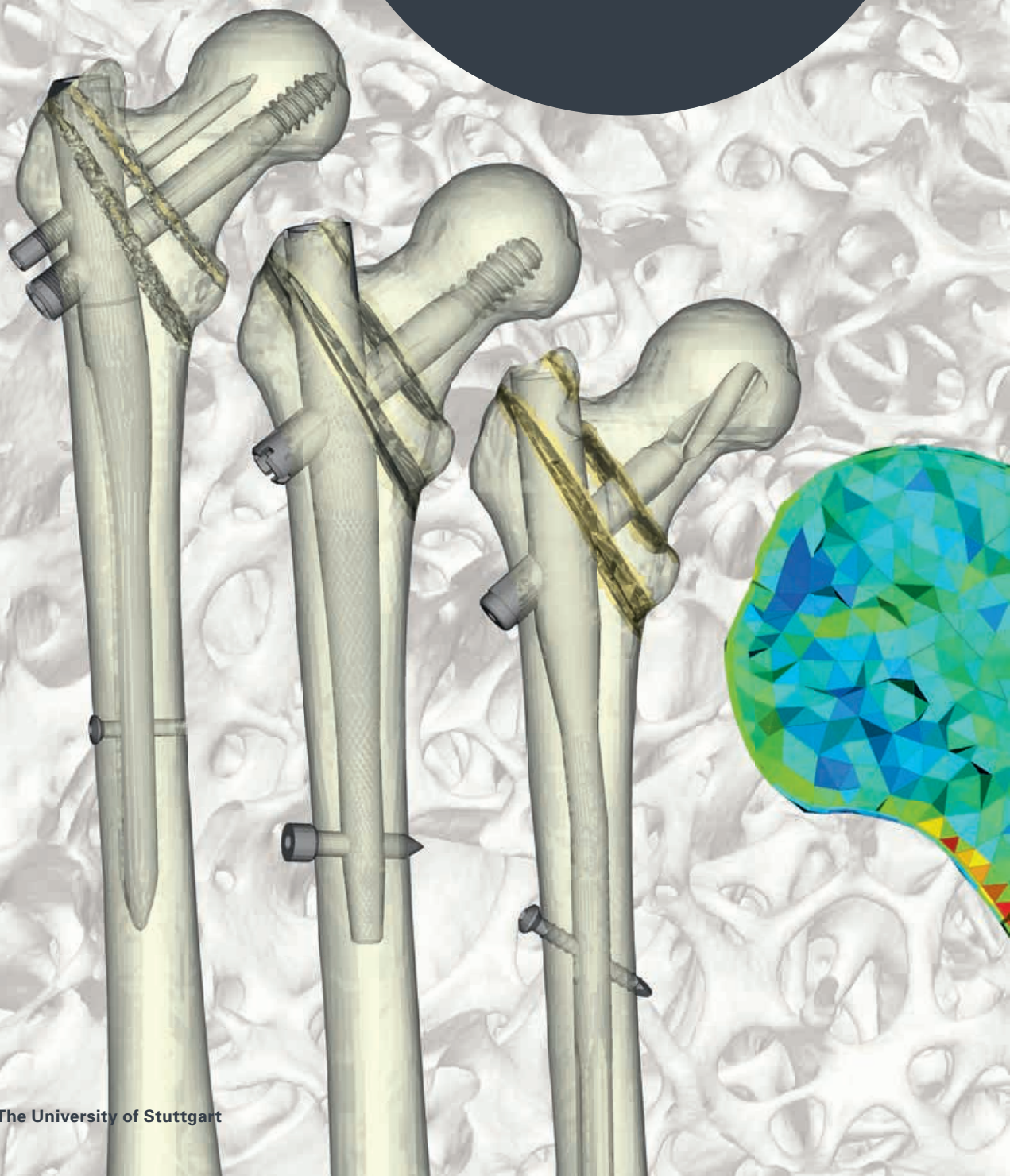


Photo: University of Stuttgart / Max Kovalenko

One medical application from the field of structural mechanics is the numerical simulation of bone implant systems, which includes artificial hip joints and implants for healing bone fractures. These simulations should make it possible to support the development of new implants and to configure their functionality and design in as physiological-ly-compatible a way as possible to ensure an optimum healing process, the objective being to use them in everyday clinical practice.
The micro-mechanical analysis of cancellous bone tissue, which is found in around the joints and is particularly affected by implants, also falls within the scope of structural mechanical simulation . It is hoped that a detailed mechanical analysis at the micro-structural level will pro-vide further insights into the internal processes of human bone growth.



The University of Stuttgart

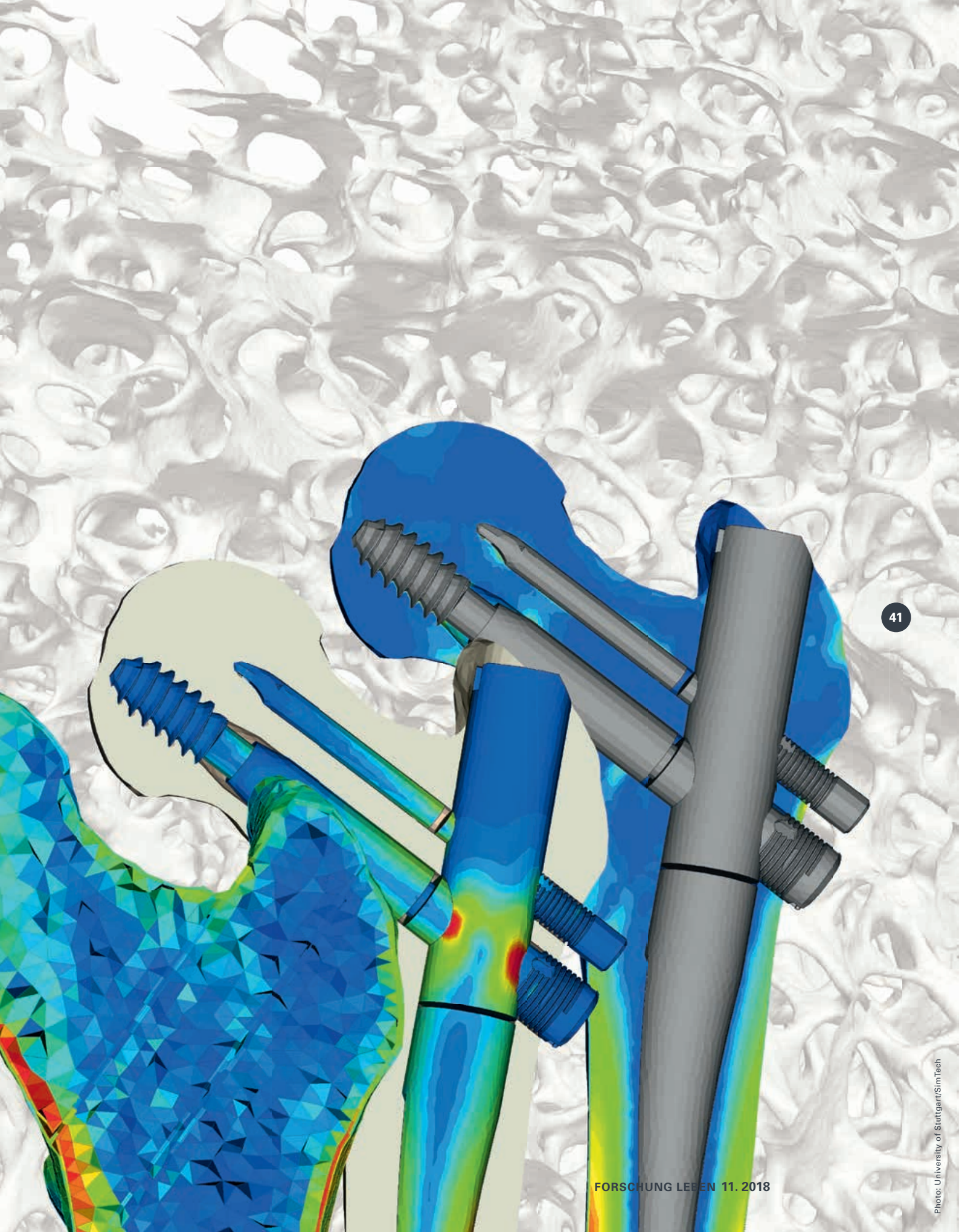


Photo: University of Stuttgart/SimTech

To be able to deploy complex biomechanical models in support of everyday clinical practice, projection-based model reduction methods are becoming increasingly important. Lengthy computational times and the cost of elaborate numerical simulations can be significantly reduced by using appropriate reduction methods, whereby the complex theoretical principles of the model formation are retained via previously generated simulations (offline calculations), enabling time-efficient numerical simulations (online calculations) with variable patient-specific parameters.

The University of Stuttgart

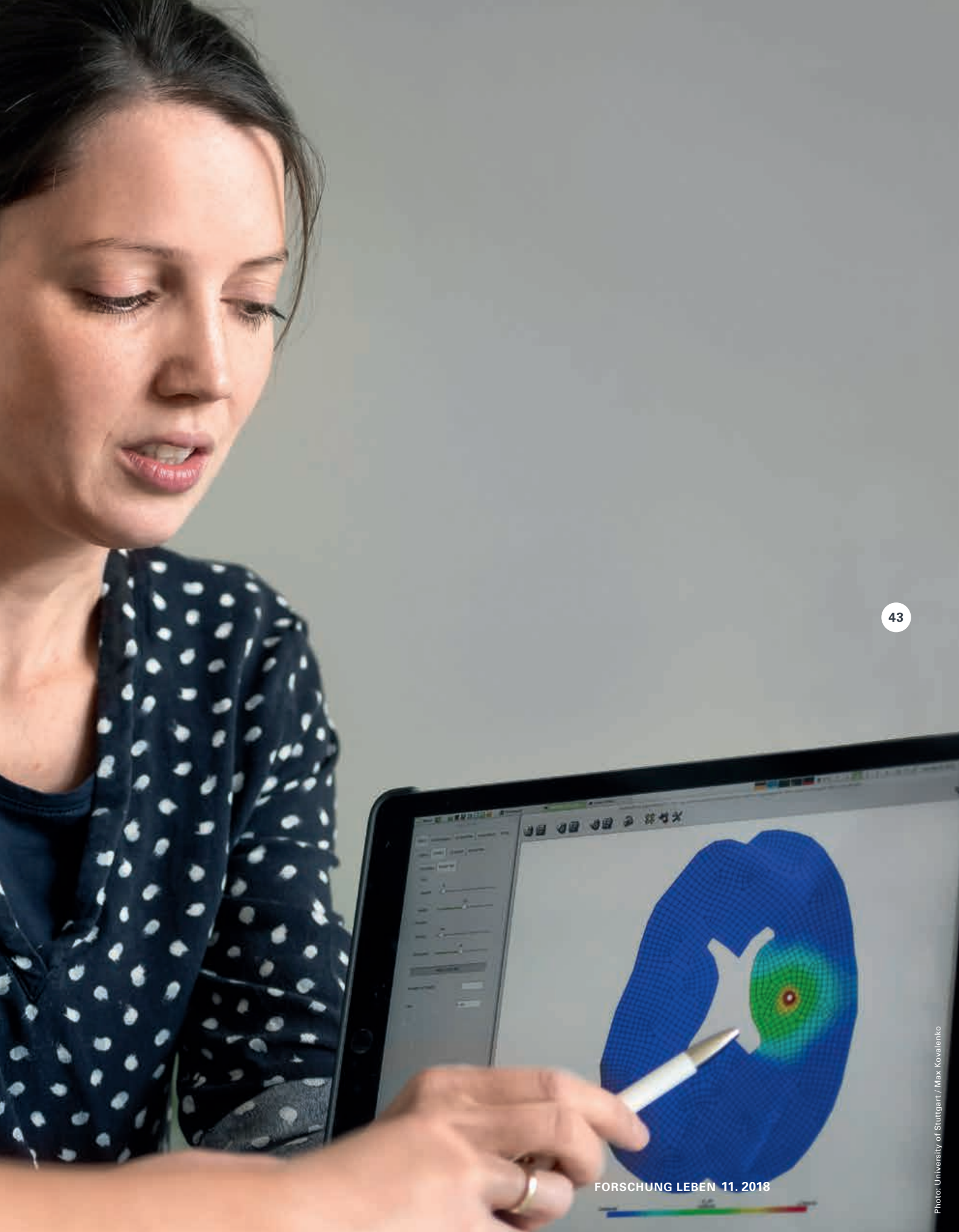
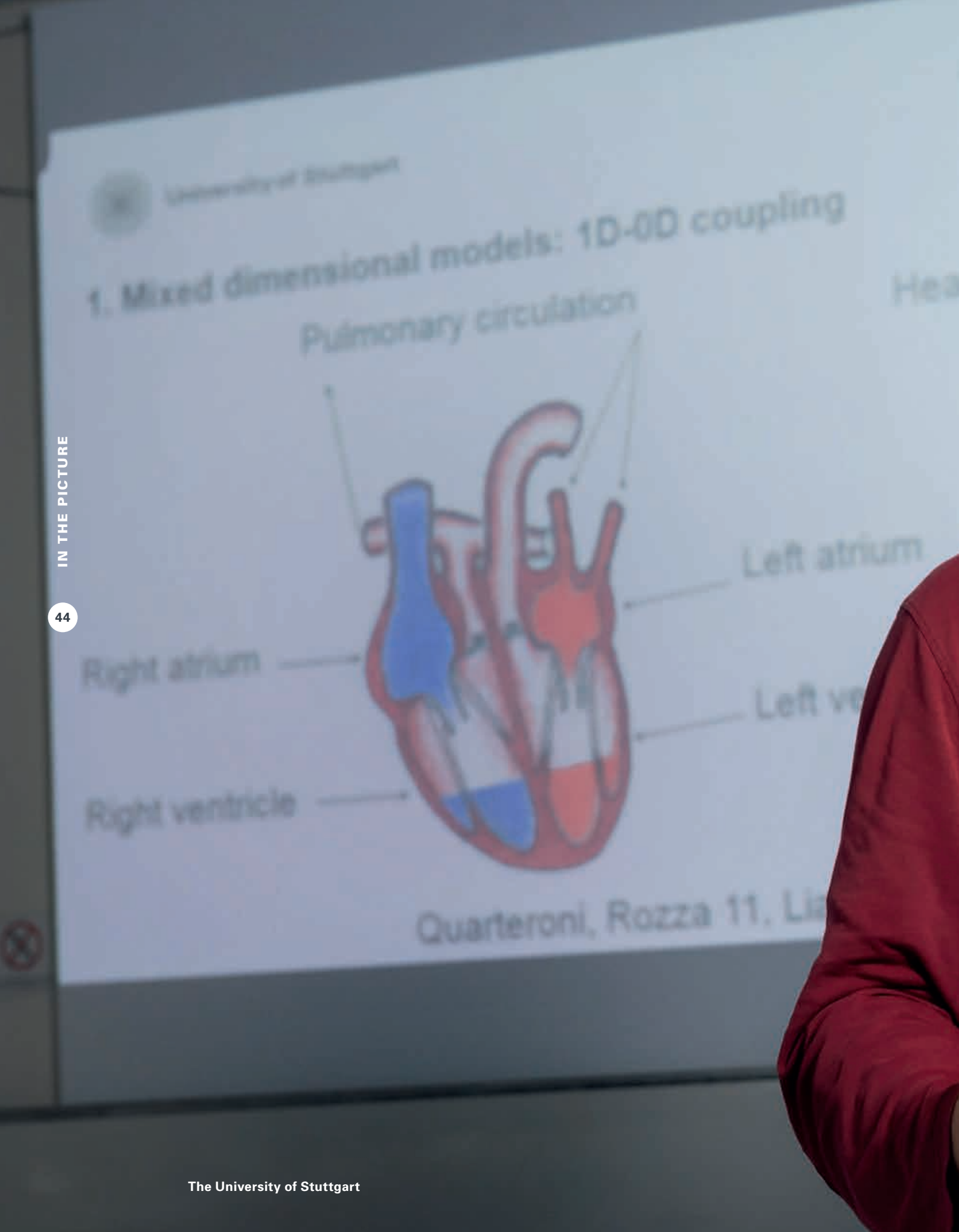
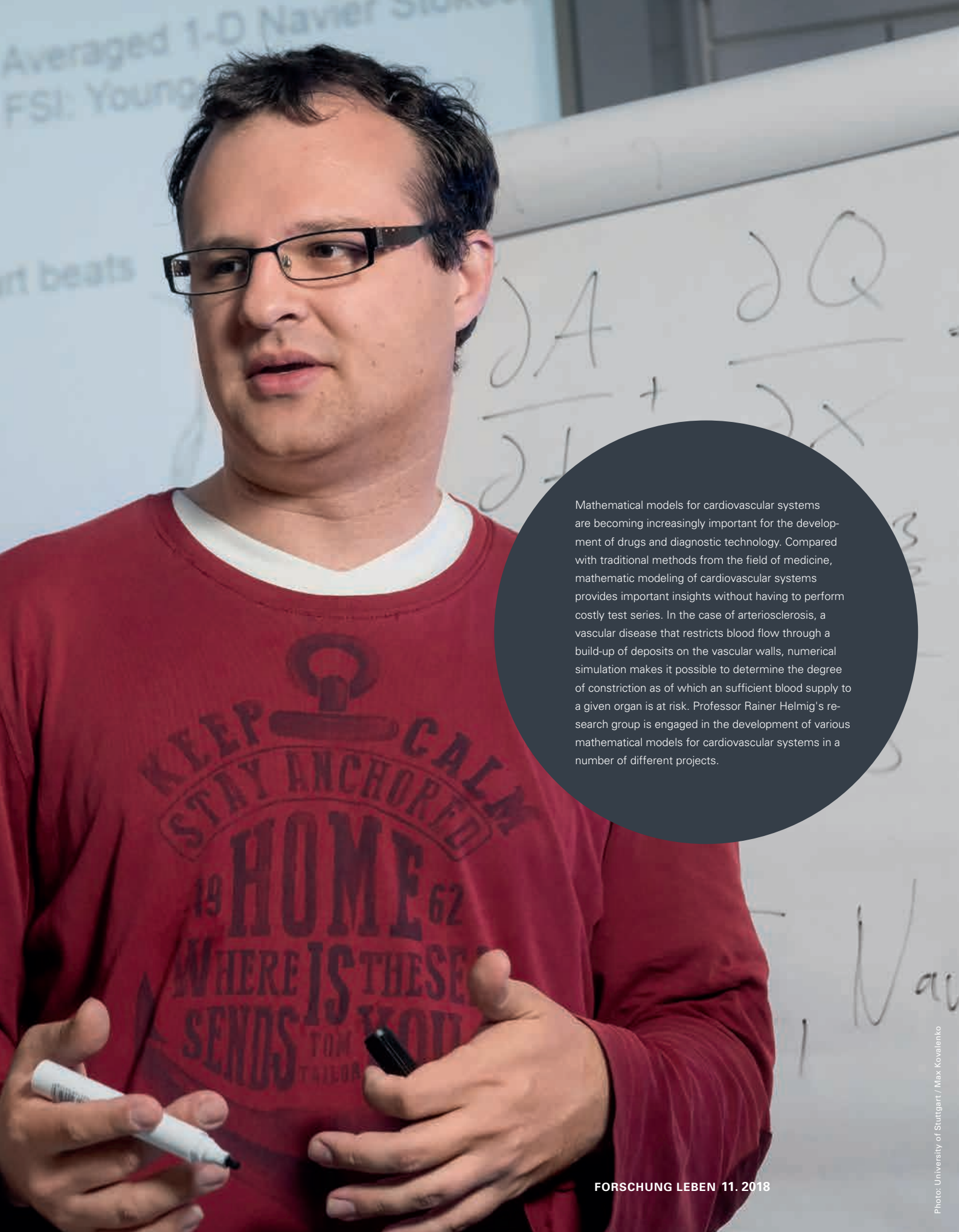


Photo: University of Stuttgart / Max Kovalenko


1. Mixed dimensional models: 1D-0D coupling
Pulmonary circulation
Left atrium
Right atrium
Right ventricle
Quarteroni, Rozza 11.



Mathematical models for cardiovascular systems are becoming increasingly important for the development of drugs and diagnostic technology. Compared with traditional methods from the field of medicine, mathematic modeling of cardiovascular systems provides important insights without having to perform costly test series. In the case of arteriosclerosis, a vascular disease that restricts blood flow through a build-up of deposits on the vascular walls, numerical simulation makes it possible to determine the degree of constriction as of which an sufficient blood supply to a given organ is at risk. Professor Rainer Helmig's research group is engaged in the development of various mathematical models for cardiovascular systems in a number of different projects.

Photo: University of Stuttgart / Max Kovalenko

Followers of a special kind

Computer linguists analyze what patients are reporting on the Internet

Patients talk about their illnesses, treatment and side effects in various online forums, blogs and social networks. However, until now, this broad wealth of experience has not been available to medical practitioners and pharmaceutical researchers. But at the same time, these communication flows have also served as fertile ground for misinformation. Computer linguists from the University of Stuttgart's Institute of Natural Language Processing (IMS) are working on ways to automatically search networks for content of this kind and to structure it.

"Watch out!", the Twitter user warns all those following her updates on her microblog network: "I might be grumbling about pain more often in the next few weeks". She goes on to say that she is switching from one painkiller to another. For Dr. Roman Klinger, Senior Lecturer at the IMS, tweets like this are extremely interesting: he is developing ways to automatically search information exchanged in social networks for biomedical knowledge and to link it to what is known from medical research, whereby he and his team have to deal with two completely different challenges.

A combination of expertise and emotion

First, there is medical expertise, which, says Klinger, is usually hidden away in the form of data that is not easy to access. Researchers, medical practitioners and laypeople nearly always have to plough through vast amounts of literature to collate all relevant information pertaining to a given illness. "If I, for example, want to know which proteins or genes are known to play a role in the emergence of some type of cancer, then there are databases for that", Klinger explains. "However, the most recent findings are only ever available in scientific publications". This is why one of his projects involves looking into how to automatically extract this information from such publications and enter them into the relevant databases, which can then be parsed by a search engine. "This way, I can simply search on the name of the disease and the search engine will find all documents in which it is mentioned and list all the proteins listed in these texts".

Next, Klinger wants to link this data to subjective information relating to people's personal experiences. In the past few years, researchers have been trying to figure out how to determine the type, cause and objective of emotions in texts. So Klinger started to ask himself: "What information pertaining to biomedical knowledge is there on social media"? Sufferers generally talk about their illness and medication in emotional terms. "Emotions can be implicitly formulated in a number of very different ways", Klinger explains, citing the aforementioned Twitter user, who suffers from neuralgia, as an example. Just four days after her first tweet, she wrote: "The pain is much better. But the insomnia is getting worse every night". Even this short period is interesting for Klinger from an analytical perspective: "It demonstrates that she's expecting rapid results". The fact that the drug did work quickly, he goes on, in turn enables an analysis of the emotions involved. "On the face of it, her statement is an endorsement of the new medication as well as a deprecation of the old one. But then she talks about a side effect – insomnia. That casts doubt on the new drug".

What was previously hidden is now in plain sight

However, before all this it was important to clarify who sends out tweets or posts blogs about diseases. One of Klinger's master students looked into this. "We developed a process with which we can

A different approach to bird-song research. Roman Klinger is developing ways to automatically search social networks for bio-medical knowledge.

Photo: University of Stuttgart / Max Kovalenko

automatically identify the category to which a given author belongs. Is it a doctor, a patient, a relative or perhaps and industry expert"? Building on this, Klinger now wants to come up with a set of rules for analyzing the actual contents. Of interest in this context are the disease profile and resulting medical circumstances, the drug taken and any side effects that may have been experienced as well as the patient's feelings about them. "We want to be able to recognize all these things in social media and, in about two years' time, to be able to link the statements to scientific texts", Klinger states. "Then, not only could you find the scientific findings relating to a given illness in the databases, but also information provided by those affected". The twitter feeds from the above-mentioned neuralgia suffers demonstrate why that would be useful: she was advised to take yet another drug to counteract the insomnia. "When you analyze conversations like this on a large scale", Klinger says, "you discover which drugs are being combined and why". To date, he continues, practically no research has been carried out in this area, and certainly not involving texts written in German. The relevance is obvious In this way, side effects could be identified about which doctors and pharmaceutics had known nothing before.

In more drastic cases, the research being done at the IMS could even save lives, as Klinger demonstrates with another example. In 2014, the current President of the USA, Donald Trump sent out a tweet about a healthy child that allegedly became autistic after being inoculated and that he knew of many such cases. "Statements like this are very common. We can make it our task to ensure that, whenever anyone tweets anything like this, we can supply the facts". For, it has been scientifically proven that there can be no link between inoculations and autism. "Fact checking has been around for a while – but not for pharmaceutical drugs and illnesses. And, there is no program available that automatically collates false information of this kind with what has been published in the scientific literature". Not yet.

Daniel Völpel

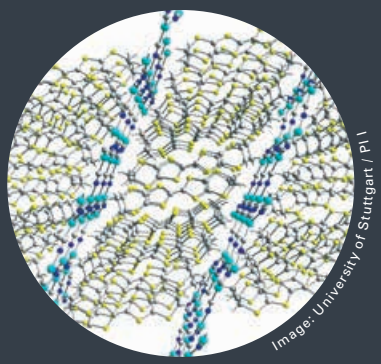


Image: University of Stuttgart / PI I

Make conductors from insulators

Physicists differentiate between metals, which conduct electricity very well and insulators, which do not conduct electricity. The latter are known as Mott insulators. Whilst they contain sufficient electrons to conduct electricity well, these impede each other so much that they can barely move. So, at low temperatures, the electrons are as trapped as the ice floes on a river.

Researchers working under Professor Martin Dressel of the Institute of Theoretical Physics I at the University of Stuttgart have, together with colleagues from the USA, Russia and Japan, succeeded in exploring the so-called Mott transition, i.e., the point at which non-conducting metals become conducting metals. This could be a starting approach for the construction of electronic components with entirely novel properties, perhaps even the crucial piece needed to solve the mystery of high-temperature superconductivity.

DNA duplicated without the use of enzymes

The ability to transfer genetic information to subsequent generations is a basic requirement for life. To ensure that every daughter cell receives the necessary genetic information following a cell division, the cell's DNA first has to be duplicated. In nature, these replication processes are catalyzed by enzymes. Now, for the first time, the research group headed by Professor Clemens Richert at the University of Stuttgart's Institute of Organic Chemistry (IOC) has succeeded in reproducing the DNA replication processes without the use of enzymes. In addition, the team acquired insights into how the transfer of genetic information might have functioned in lifeforms at an earlier evolutionary stage, knowledge, which is of particular relevance to research into the origins of life.

Altitude test facility XXL

The University of Stuttgart's altitude testing facility is unique in Germany. Tests can be carried out there to see how aircraft engines or their modules behave at high cruising altitudes under various air-pressure, temperature and humidity conditions perform, without having to actually fly them. The operating area of the altitude test facility is currently being upgraded at a cost of 4.5 million euro to facilitate testing of the next but one generation of aircraft engines as part of a joint research project involving the University of Stuttgart's Institute of Aircraft Propulsion Systems, MTU Aero Engines and Rolls-Royce Germany. These should consume less fuel and emit less CO2.

At the heart of the new facility is a heat exchanger the size of a large detached house. The entire roof of the main hangar area had to be removed specially to accommodate the delivery of the 19-tonne boiler and the 22-meter high smokestack. A 300-tonne crane then hoisted the components into the air.


Photo: Uli Regenscheit

Photo: Saskia Suetterlin / KSat e.V.

Pumps for outer space

For three days, the Falcon 9 rocket was travelling through space before docking with the International Space Station ISS. On board was the PAPELL Experiment, built by some 30 students at the University of Stuttgart's Small Satellites Group (KSat) and which will be supervised by astronaut Alexander Gerst on board the ISS.

The experiment involves a prototype pump with no mechanically moveable parts. It is designed to demonstrate that the maintenance-free pump can be used in space for transporting gas (air), liquid (ferrofluid) and solids (spheres). There are various potential applications for a pump of this kind, from fuel transportation to thermal regulation by cooling hot structures to a low-noise ventilation system for manned spacecraft.

The students were able to observe a relatively rare rocket plume as the rocket was launched (image), a phenomenon whereby the rocket exhaust gasses reflect the sunrays.

The right dose at the right time

The majority of over-60s take two to three pharmaceutical drugs every day – tendency rising. Dosage errors are a daily occurrence with considerable consequences for both patients and the health system. The University of Stuttgart's Institutes of "Industrial Automation and Software Engineering" and "Engineering Design and Industrial Design" as well as the medical engineering company "CompWare Medical" are collaborating on research into a novel, computer-supported tablet dispensing system designed to increase safety. The system, known as "Tantum", comprises a tablet dispenser, a safety and communication center, an app and a pharmacy loading system. The essentially novel aspect of "Tantum" is the overall concept. The device dispenses the drugs at the specified time and in precise dosage, reminds the patient to take them and, optionally, can inform the caregiver if the tablets have not been taken.

Photo: Adobe Stock / nik.bernadsky

Up close and personal with the Muscle
Simulations of the complex processes that take place within the human musculoskeletal system

It is not yet fully understood in detail how the nervous system, muscle cells and entire muscle groups interact in motion sequences. Three-dimensional simulations of the skeletal muscles of the type being researched by biomechanics at the University of Stuttgart, are set to change that and help with the development of control systems for exoskeletal neuro-prosthetics.

Reaching for a cup of coffee in the morning looks so easy; most people even manage to do it whilst still half-asleep. Yet, what has to happen in the human body just for this movement alone is by no means trivial. For the hand to reach for the cup, the brain has to initiate the sequence in the spinal nerve cells. The electrical signals then reach the so-called neuromuscular junctions via the nerve fibers, which transfer the signal to the muscle fibers within the skeletal muscles, which are responsible for voluntary movements. To this end, the electrical signal is transformed into a mechanical force. Calcium ions serve as a messenger substance, which causes certain cells to contract. The mechanical force generated at the cellular level is transferred via the muscles to the tendons resulting in the arm moving towards the cup. Then the hand has to close around it with a carefully controlled pressure before the cup is moved towards the mouth. Many muscle groups are involved in this simple sequence, controlled by countless nerve cells. Just how complex this pattern of movements actually is always becomes especially clear when it is impaired as the result of an illness or accident or when engineers attempt to train a robot to perform human-like movements.

Neuromuscular question mark

Every movement originates in physical and biochemical processes within the cells, which have not yet been entirely researched in terms of their rela-

The total electrical potentials of movements can be measured using electromyography, a type of ECG.

Photo: University of Stuttgart / Max Kovalenko

How is movement generated: The interdisciplinary team headed up by Professor Oliver Röhrle is working on obtaining a holistic understanding of the neuromuscular system.

Photo: University of Stuttgart / Max Kovalenko

tionship to entire musculoskeletal groups and their interactions with the central nervous system. Oliver Röhrle, Professor of Continuum Biomechanics and Mechanical Biology at the University of Stuttgart, wants to change that with and a team of experts from various disciplines. “Our interdisciplinary approach”, says Röhrle, “is based on a holistic understanding of the neuromuscular system”. Simulations are their chosen tool for this, which is why computer scientists, mathematicians and visualization specialist are on board. Sports scientists, electrical engineers, biologists and physiologists provide the bridge to application-based issues. Ultimately, Röhrle explains, their work addresses the question: “how is movement generated?”.

“The total electrical potentials of such movements can be measured using electromyography, a type of ECG, for the muscle, for example on the surface of the arm or leg”, the mathematician explains. “But this only provides us with extremely noisy signals and it is difficult for us to draw conclusions about the individual muscular processes from them”. It is precisely on the upper thigh that electromyography reaches its technical limits because it can only measure down to depths of one to two centimeters – but the musculature only starts to become really interesting below that level. “We want to use realistic simulations to get a much deeper understanding of the movements and electrical potentials to deliver results that our colleagues can then validate”, says Röhrle.

Neuronal control in the model

His research group uses three-dimensional skeletal muscle models for their calculations and bases their simulations on the principle of: “activation in, movement out”. These models are extremely detailed, thus they take account of a large number of muscle fibers and their neuronal control systems. “Among the probably 20 research groups around the world who model skeletal muscles in three dimensions, we're the only ones who approach it in this way”, the scientist explains. It is still fundamental research at this stage, but simulations used in various areas, such as the sports sciences, will benefit from it in future. But the results could also be useful for achieving as natural a connection for protheses as possible or for crash tests. One example of a research project that is already much closer to application maturity is known as KONSENS NHE, which, in addition to Röhrle's team, involves the university hospital and the University of Tübingen as well as

In the KONSENS NHE research project, Leonardo Gizzi and his team are developing an exoskeleton for the hand that will be controlled via the nervous system, not the least reason for which is to make life easier for stroke victims.

Photo: University Hospital Tübingen / Nicola Vitiello

Reutlingen University. The objective of the project, which began in 2017 and is scheduled to go on for three years, is to produce an exoskeleton for the hand controlled via the nervous system, which is suitable for everyday use. “In terms of the development of this orthosis, we're thinking of stroke victims, who often suffer from limited limb mobility, either long-term or short-term”, Dr. Leonardo Gizzi, who is responsible for the project within Röhrle’s team. The orthosis will ensure that stroke victim are able to grip things firmly enough and move their hand without restrictions. A prototype model of a brain controlled exoskeleton for a hand developed by an international team under the auspices of the University of Tübingen served as the starting point, which successfully restored the function of the hand in paraplegics almost completely. However, this exoskeleton was not portable and it could only be used with the aid of trained personnel. That's why the objective of the current project is to produce an exoskeleton that is fit for everyday use. If a stroke patient is suffering from a unilateral paralysis, for example, he or she should still be able to put it on themselves.

Communications between the patient and the orthosis

To be able to reach for something accurately, the exoskeleton should ideally be controlled by measured brain waves combined with eye-movements and a three-dimensional object recognition ability. “We use electromyographic electrodes for patients whose hand muscles are still active, but cannot exert enough force to be able to grip things securely”, Gizzi explains. The voltage that occurs naturally within the muscle can be measured using this type of electrode. These signals are also, as it were, the direct connection to the research work being carried out in Röhrle’s team on the simulations of skeletal muscle movements. “However, the orthosis doesn't only receive control signals from the patient but also provides him or her with haptic feedback via vibra-

tion motors", Gizzi continues. This is intended to enable as natural an interaction with the exoskeleton as possible.

Hardware and the electronic control system are currently being created by the project team: Gizzi is responsible for the layout of the electromyographic electrodes on the forearm. "We're trying to find the optimum layout with as few sensors as possible", says the scientist. This will be followed be comprehensive functional testing, initially with healthy test subjects. The real work will begin as soon as the project participants reach the stage where they can attach the orthosis to a patient for trials: "That will be a crucial phase, because, ultimately, only those affected can tell us how using the orthosis feels to them", Gizzi explains. "How it looks, the weight, operating it – all of that will play into it and may well differ from our expectations". After that it will no longer be about technology and functionality, as Gizzi explains citing prosthetics as an example. "Experience there has shown that, whilst older people want an artificial replacement limb that looks as natural as possible, a prosthesis can't look robot-like and technical enough for children".

Michael Vogel

Combined Sharpness
Better images of the body's interior through artificial intelligence

Imaging processes play a significant role in nuclear medicine both for diagnostic purposes and treatment. However, every examination method has its weaknesses, some of which can only be compensated for by combining two procedures. Scientists at the Universities of Stuttgart and Tübingen want to eradicate this problem with new machine learning methods. The initial results are encouraging.

It is often not good news if a patient needs to be examined using a positron-emission tomography (PET) scan. According to the German Society for Nuclear Medicine (DGN), a tumor, suspected dementia and epilepsy are typical indications for which this expensive examination method is considered appropriate. For the layperson, this device does not seem much different from the more familiar computed tomography (CT) or magnetic resonance imaging (MRI). The results of a PET scan also seem the same: two-dimensional sectional images of a particular region of the body. But experts, such as radiographers, are well aware of the differences between these procedures. CT and MRI produce images in which anatomic structures, such as bones, tissues and organs, can be identified. A PET scan, on the other hand, show metabolic processes, i.e., flows, at the molecular level. With specific reference to a tumor, one could say that CT and MRI images show where and how big the tumor is. The PET images, on the other hand, primarily provide insights into its activity, so that one can see how aggressive it is.
“However, it isn't the case that PET images contain no information at all about the anatomic structure”, says Karim Armanious, a doctoral student at the University of Stuttgart's Institute of Signal Processing and System Theory (ISS), which is headed up by Professor Bin Yang. “But this data is so insufficient that a PET scanner often has to be operated in combination with a CT or MRI scanner” – so that each of the imaging processes can contribute its respective strengths. Currently, this is everyday medical practice,
and means that the examination of a patient in such a tandem device takes a very long time, because the radiologist has to take double the amount of pictures. The consequences are additional stress for the patient but also fewer examinations per day for the operator and therefore a reduction in the device's economic efficiency. Moreover, the patient is exposed to an additional radiation load through the CT scans. “That’s why radiologist want PET images that don’t require any additional images and still provide sufficient anatomical information”, Armanious explains. He and his ISS colleagues are working towards this goal in collaboration with radiologists from the University Hospital of Tübingen (UKT).

New stars of the machine learning process

To achieve this, they are using machine learning processes, the so-called Generative Adversarial Networks (GANs). “This is a new process, first introduced just four years ago, which is currently really popular among researchers”, says Armanious, who earned his master's degree in Information Technology with a special focus on Communication Engineering and Media Technology. The GANs principle can be explained by way of an analogy: an art forger wants to paint the Mona Lisa so well that it is not possible to tell the difference between his painting and the original. An art expert compares the forged picture with the original, not knowing which is which. The forger will be told whether or not the expert has been able to identify the original, but not how he was able to spot the fake. So, with each new attempt, he changes the style, colors, perspective and appearance of the sitter and again

PET images, that suffice without the need for time-consuming, costly additional images and still contain a lot of anatomical information – that's what researchers from the Universities of Stuttgart and Tübingen are working on with the aid of so-called Generative Adversarial Networks, or GANs for short.

Photo: University of Stuttgart / Max Kovalenko

presents the results to the expert, who gives every picture the thumbs down as long as he can tell it apart from the original.

A human art forger would probably lose heart at some point and try to come up with some other scam. However, in Armanious' experiments, forger and expert are both GANs, algorithms running on a computer; they have no concept of disappointment and never get tired. Nor is it about the Mona Lisa, but about CT images. "After 36 hours of computer time on a high-end graphics card, the training of our two GANs had advanced to the point that the synthetic CT images were barely discernible from the real ones", he says. "Our quantitative tests on the computer then produced a concordance score of over 90 per cent". But that's not all: Armanious and his team showed the synthetic and real CT images to six doctors, who have to assess CT data routinely as part of their daily practice. They were asked to rate the quality of the images on a scale of one (low quality) to four (high quality), without knowing which of the images were based on real data and which had been general synthetically. "The doctors gave the real images an average score of 3.3 and the synthetic ones a 3.0)", says the scientist: a pretty convincing result!

Artificial intelligence is on the increase

"Until now", Armanious adds, "the research community has only used GANs that were originally designed for other applications to tackle medical issues. We're the first to have developed a GAN right from scratch specifically for medical purposes". One of the results is significantly shorter processing times. Creating synthetic CT images is just the first step for the researchers. Now, work is starting on the data to correct PET images such as to render CT images in tandem devices superfluous. "To do this", Armanious continues, "we compare the traditional imaging method with the new approach using PET imaging data from Tübingen". This involves one GAN attempting to reconstruct anatomical information from the pure PET data to render the CT data superfluous, whilst the other GAN compares the images generated in this way with those images based – as they have been to date – on combined PET and CT data. Then the competition between the original and the "forgery" enters the next round.

Michael Vogel

On the Trail of Superman
Novel views under the skin

At first, it all sounds a bit unreal: Scientists are attempting to peer inside the body through the intact skin – without the aid of x-rays or magnetic fields. The process is called imaging with new scattering media, and medicine would be the primary beneficiary. The fact that the research community has been gripped by a downright spirit of pioneering optimism is also evident in a research project at the University of Stuttgart's Institute of Applied Optics (ITO).

You would have to be Superman, who, as is well known, could look through any material except lead. Compared with this, the desiderata of medical practitioners seem rather modest: they would be satisfied with the ability to see through tissues, such as skin, which would enable them to identify changes to organs, cells or blood vessels without the need for surgical procedures. But we do already have a few of Superman's powers at our disposal: There are x-rays, computed tomography and magnetic resonance imaging (MRI) with which, for example, bones or organs can be examined. However, the resolution of these methods is rather poor and requires exposure to radiation or strong magnetic fields.

If, on the other hand, doctors could work with visible light, the results would be far more useful, because it significantly increases the achievable resolution, and because light interacts with many molecules within the body, which would provide additional information. To some extent, this is already possible today. For example, optical coherence tomography (OCT) makes it possible to look a few millimeters deep under the surface of the retina, which facilitates the early recognition of certain eye diseases. However, the light only has to penetrate the transparent eyeball to do this: Skin represents a more formidable barrier, being between one and a half and three millimeters thick and apparently impenetrable by visible light.

However, that is, in fact, not true as physicist Stephan Ludwig knows. Ludwig, a research assistant at the ITO, explains why the skin appears to be opaque in the following manner: "Rather than being absorbed by the skin", he says, "the majority of ambient light that falls on it is scattered, in other words, reflected back in multiple directions". For his doctoral studies, Ludwig is looking into the potential ramifications of this fact for new microscopes, still to be developed, which would enable doctors to see through skin.

Optical component with skin properties

Until now, Ludwig has been undertaking fundamental research in the context of a project funded by the German Research Foundation, so there is currently no complete device standing in his laboratory. Instead, one finds all the technology that will be important for a so-called diffusion disc microscope in future. A simple test structure with lines placed at varying distances apart serves as the object to be examined. "But we've also already imaged onion cells, wood and plankton", the physicist adds.

An optical microscope consists of a lens, a short distance in front of which the object to be examined is placed, and another lens with which the magnified image of the object can be viewed, or a camera, which can photograph the magnified image. The ITO researchers have exchanged the lens with a comparatively cheap diffusion disc – a glass disc roughened on one side – which can be bought for just 20 euro. This represents human skin, whose optical properties are similar to those of the human skin. From a physical perspective, this diffusion disc works as a lens, because it too produces an optical image. But, whilst a lens produces a sharp image of the object to be examined, the diffusion disc produces a pretty poor, out-of-focus image, just as skin

Photo: University of Stuttgart / Max Kovalenko

With his diffusion disc microscope, physicist Stephan Ludwig is able to achieve a 40 x magnification and, therefore, can resolve structures down to the millimeter range.

Photo: University of Stuttgart / Max Kovalenko

A major advantage of the diffusion disc microscope compared with its conventional counterpart is that the desired magnification level can be changed simply by varying the distances between the camera, diffusion disc and lens.

would do. “But”, Ludwig interjects immediately, “in principle, this image still contains all the information about the object to be examined”. And this information can be distilled out with some computational effort.

Thus, taking a picture of something, such as a piece of wood, with the diffusion disc microscope involves two steps. First, a point light source serves as the object, whose characteristic light pattern created by diffusion disc is captured by the camera. “That gives us an image of the simplest object there is – a single point of light”, Ludwig explains. In the second step, the piece of wood is photographed through the diffusion disc, which is illuminated for this with light of the same color as the point light source. At first glance, this image also looks pretty chaotic. “But, because we know from the image of the point of light how the diffusion disc alters the image, we can also reconstruct the image of the piece of wood using mathematics.

Resolution in the millimeter range

It is true that the camera has not captured all of the scattered light, so that some information is, in fact, lost. Nevertheless, the quality of the image reconstructed in this way is astonishing. With his diffusion disc microscope, Ludwig is able to achieve a 40 x magnification and, therefore, can resolve structures down to the millimeter range. In addition, the diffusion disc microscope has other advantages over its conventional counterpart apart from a cheap lens. For example, the scientists can change the desired magnification level simply by varying the distances between the camera, diffusion disc and lens; in traditional microscopes the lens has to be changed for this. Another benefit is that the principle of the process can be transferred to other wavelength ranges from infrared to x-ray.

Yet, there are some downsides: in principle, the smaller the magnification level and the smaller the captured image, the better the image quality. Till now the ITO researchers have limited themselves to monochrome photographs. “But color images are our goal”, says Ludwig. Moreover, for an application that would actually go beneath the skin, for example, there is still no specific concept for how the object to be examined could be illuminated. “We might be successful with fluorescent nano particles injected into the body”, says the physicist, explaining one possible approach. “Ultimately”, and Ludwig makes no bones about this, “researchers still don't know the limits of this method”. However, imaging by means of scattering media has only really taken off experimentally in the last decade. “But, there has been incredible progress”, Ludwig finds. And even if peering through the skin turns out to be much too costly and complex for too small an added information yield, the relevant research could result in so many findings that it inspires applications outside of the medical field, such as for driverless navigation in foggy conditions, security checks or identifying paint delamination in works of art. Superman sends his regards.

Michael Vogel

The right nose for precise diagnostics
Precision spectroscopy uses Rydberg excitation to measure minute traces of nitrogen oxide

Dogs' noses are a hundred times more sensitive than our own. With the appropriate training, "man's best friend" can even detect certain human diseases by smell alone. Physicists at the University of Stuttgart have thrown down the gauntlet to our four-legged friends and are constructing an artificial nose that is even more sensitive that its natural prototype.

By contrast with a dog's nose, the new measuring process will not only detect specific substances, but also their precise concentrations over time. The process that Professor Tilman Pfau and his team from the University of Stuttgart's Institute of Theoretical Physics V will be using, in collaboration with the Interdisciplinary Center for Integrated Quantum Science and Technology (IQST), for their analyses is known as optogalvanic Rydberg spectroscopy. The physicists are initially concentrating on measuring nitrogen monoxide (NO). "We use our lasers to put certain molecules – nitrogen monoxide molecules in this project – in a highly excited state", Harald Kübler, one of the project staff, explains. "In this so-called Rydberg state, electrons are only loosely attached to the atomic nucleus. As soon as the molecules within the gas cloud collide with one another they become ionized". The resulting electrical charges are counted allowing inferences to be drawn about the number of nitrogen monoxide molecules in the sample. "Our gas sensor is able to detect NO concentrations of less than 10 ppm, i.e., ten molecules in every one million molecules. It works at normal atmospheric pressure and is currently only limited in terms of precision by the method we use to rarefy the gas", Pfau says, summarizing the current research status. Another benefit, apart from the precision of the measurements, is that the gas flow can be analyzed relatively quickly, which makes it possible to measure more rapid changes in the NO concentrations.

Collaboration with the University of Ulm

For some time now, the importance of Rydberg atoms, named after the Swede Johannes Rydberg, for quantum technology has been increasing. Possible longer-term industrial uses of Rydberg states based on novel processes are being investigated at the IQST. The IQST's current project is about ascertaining the extent to which optogalvanic gas sensors based on Rydberg gases could be useful in the field of precise medical diagnostics and may produce new medical findings. To this end, the process is being theoretically assessed and further optimized at Pfau's institute and, in collaboration with the University of Ulm's Institute of Analytical and Bioanalytical Chemistry, headed up by Professor Boris Mizaikoff, compared with existing measuring processes.

"Initially, we were motivated by something else entirely", experimental physicist Pfau explains: "We wanted to improve our spectroscopic technology and install electronic components into a gas cell of this type. In the course of this, we realized that a novel sensor principle would be possible using this combination of highly miniaturized electronics and Rydberg atoms with which it would be possible to detect minute quantities of certain atomic or molecular gases". In a subsequent step, the scientists want to use and test this sensor

Photo: Stock/synto

Professor Tilman Pfau and his team from the University of Stuttgart's Institute of Theoretical Physics V have developed the so-called optogalvanic Rydberg spectroscopy process in collaboration with IQST Ulm. The process components still cover an area about the size of an outsized ping-pong table. As soon as it starts delivering flawless results, the plan is to shrink the cumbersome spectroscopic laboratory onto a chip the size of a fingernail and to fit it into a gas cell.

principle for analyzing relevant molecules, such as the aforementioned nitrogen oxide, a biomarker for inflammation and other nitrogen oxides (NOx) in exhaled respiratory gas. This is where the expertise of biochemist Boris Mizaikoff becomes relevant. In addition to increased precision, it will then mainly be all about parameters such as increasing ease of use, and lowering costs both in the manufacturing process and in everyday practice.

Relevance for environmental analysis

The gas sensor technology is not only suitable for the analysis of respiratory gasses but also for measuring nitrogen oxide concentrations in the environment. To put it in only slightly exaggerated terms, if this process had already been marketable and rolled out across the board, the Diesel scandal may never have happened. A small metering device of this level of precision and size could easily have been installed in vehicles and would have immediately indicated the discrepancy between the target and actual concentrations of nitrogen oxide emissions. Of course the requirements for car exhaust sensors are highly demanding, particularly due to the high operating temperatures of around 1000 degree Celsius. Nevertheless, even if there are still a few technical hurdles to overcome before Rydberg gas sensor technology can be deployed in cars, the benefits outweigh the drawbacks by far: it can be used selectively for any specific molecule and can determine its concentration in a gas mix with an extremely high degree of precision. In the case of car exhausts, for example, hundreds of different molecules are emitted. Despite this complex mix, it is possible to excite specific molecules – just like the nitrogen monoxide in the respiratory gas mix – and to precisely measure their concentration.

Diagnostic terra incognita

Another unique selling proposition of the new process is its ability to monitor NO concentrations along a timeline, i.e., the concentrations present in the first and then subsequent milliliters of exhaled respiratory gas. Of course, it has long been known that is possible to excite specific molecules extremely selectively via Rydberg states, but, in terms of its practical application, this form of gas analysis is still in its infancy. “In the next few years”, says Pfau, “we will need to get more clarity on exactly what new information we can obtain with this sensor as well as its significance”. For example, it is not yet known what new medical evidence could be revealed

Photo: University of Stuttgart / Max Kovalenko

by continuous real-time measurements, for instance if it were found that the exhaled gas contained a lot of NO at the start of the exhalation and less towards the end; this is another research question that Pfau and Mizaikoff are working together to clarify. “If this measuring principle turns out to be as sensitive as we expect it to be, there will certainly be other potential applications”, say the scientists, feeding the desire for new diagnostic processes.

From industrial laboratory to chip size

The “artificial nose” is currently still about the size of an outsized ping-pong table. It is covered with a labyrinth of optical components, that focus the laser beam to enable precise measurements. This makes it easy to monitor the applied processes and adjust them as required. As soon as it starts delivering flawless results, the plan is to shrink the cumbersome spectroscopic laboratory with all its functions onto a chip the size of a fingernail and to fit it into a gas cell similar to a pipette. The actual sensor head can become extremely small, but lasers we use as a light source of the measuring process are still relatively big and it probably won’t be possible in the next few years to shrink them dramatically”, says Pfau. To facilitate progress on the miniaturization of this cell, the physicists have been working closely with electronics engineers under the auspices of Professors Norbert Frühauf and Jens Anders in Stuttgart. Early on, Frühauf, Head of the Institute of Large Area Microelectronics (IGM) and experts in high-resolution screen technology came up with the idea of integrating the electronics needed to process the gas stream directly into the Rydberg gas cell to produce a compact sensor. Anders, who heads up the Institute of Smart Sensors (IIS), has been working on the design of highly sensitive and, above all, rapid gas stream processing circuits for a long time. Anders and his team use so-called CMOS semiconductor technologies for their electronic designs, i.e., the same technologies used in computer CPUs. This means that the electronic components only need a tiny fraction of the area currently used by the cumbersome electronics at the Institute of Theoretical Physics V, and are, therefore, extremely suitable for the desired miniaturization of the cells.

The engineers are currently working on reducing the noise level of the electronic components. This could result in sensitivity levels in the parts per billion range, the relevant range for precise respiratory gas measurements. At that point, the electronic system could hold its own against, or even outdo the dog's nose. Because the microchips can be produced extremely cost effectively – especially in large batches – the approach adopted by Pfau, Frühauf and Anders is very promising in terms of long-term commercialization. As it stands, the three scientists have succeeded in producing the first prototype of an already significantly smaller Rydberg gas cell.

Susanne Roeder

Contructed wellbeing

Building physicists are carrying out research into office spaces capable of enhancing health and performance

One staff member wants to make a telephone call, two others are chatting and the fourth needs to concentrate on solving a task – a daily challenge in thousands of offices. But how, in addition to noise levels, spatial factors such as temperature and light can be regulated such that employees feel well and healthy and are able to perform well? Researchers at the University of Stuttgart's Institute of Acoustics and Building Physics (IABP) are currently looking into this question, with the intention of coming up with a set of recommendations for how the office of tomorrow might look.

When humans first began to build shelters for themselves, they wanted to protect themselves from the elements, and, of course, to make life more comfortable for and increase the wellbeing of themselves and their families. "Starting about 100 years ago, building regulations have come to be dominated by the idea that a building ought to offer more than just protection from the elements", as Professor Philip Leistner explains. He heads up both the IABP and the associated Fraunhofer Institute for Building Physics (IBP). The first building regulations published in the mid-20th century called for a minimum level of protection. However, the insight that the conditions in spaces in which people spend time is of central importance in terms of their health, wellbeing and ability to perform was only recognized to a limited degree, whereby the ability to perform should not be understood in the sense that "for example, the objective is to squeeze

One man's joy is another man's sorrow: "Conviviality" in open-plan offices makes some people more creative but makes it hard for others to concentrate.

Photo: Stock / mooshny

Which factors crucially affect our ability to perform? To find out, building physicists are asking users of the spaces in question whilst simultaneously measuring the physical parameters of the structures.

Photo: Fraunhofer IBP

every last drop of work out office workers", the scientist emphasizes. Instead, they should find themselves in conditions in which they can perform their allotted tasks in a motivated, concentrated and efficient manner, so that they can enjoy their leisure time after an eight-hour working day "and", according to Leistner, "eventually retire from working life in as healthy a condition as possible".

Not just a matter of opinion

Up to now, buildings have been regarded as static or stationary, despite the fact that external and internal conditions are continuously changing. That is why the building physicists are working on one future-oriented topic in collaboration with numerous other institutes from the University of Stuttgart's Collaborative Research Center 1244, "Adaptive Shells and Structures for the Built Environment of the Future". "We're looking into the question of how a building façade would have to react to changing temperature, wind and noise conditions to ensure that the climate inside the building always remains comfortable", says Leistner. The German Research Foundation is providing CRC 1244 with initial funding till 2021 worth ten million euro. Yet the pivotal starting point for the IABP team involves a "communication task" as Leistner calls it: "If we want to design a space, we can't ask people, 'how many degrees Celsius do you prefer?' or: 'What Decibel level or what amount of CO2 would you like in the air?'", he explains. "Yet, these are precisely the values that engineers have to plan for and configure". That is why the building physicists are consulting with the users of the spaces whilst simultaneously measuring the physical parameters of the structures, both in laboratory experiments and directly in their working environment. A laboratory test might, for example, involve asking the test subjects to complete certain tasks whilst the room temperature is adjusted bit-by-bit. This enables the building physicists to determine the conditions under which the test subjects can best complete the tasks in question and feel most comfortable. This provides the planners with the precise values that they need. "Interestingly", says the head of the institute, "the individual room parameters correlate to one another". The test subjects experience a given constant noise differently under different temperature conditions.

The ideal office depends on the work carried out there

Whether or not and the extent to which an office is comfortable and conducive to good health depends

on what goes on there. “The first thing we always ask is about the activity profile and work organization. We then correlate this information with the physical structural requirements and develop the workspace conditions that we need to aim for”, Leistner explains.

Not luxury – just good economic sense

The building physicists usually encounter one of two different attitudes towards their results and recommendations. On the one hand, there is the works council whose primary concern is how a building's physical shortcomings impact the somatic and psychological wellbeing of the occupants. On the other side of the fence are the directors, who want the building physicists to explain how productivity or even turnover could be increased by investing in such things as air conditioning, acoustics or adjustable lighting. Leistner explains the potential benefits as follows: if we assume 60,000 euro per annum in personnel costs per staff member, then a performance dip of two per cent that could be prevented by modifying a building's physical properties, costs the company 1200 euro per capita per annum! “Although spending on building physics is a good investment, it often falls foul of budgetary rigor”, Leistner complains, citing the summer of 2018 as an example, which, he points out, demonstrated that heat-related performance dips and workplace absences cost significantly more than an air-conditioning system. “Many people are still having to deal with building environments that compromise rather than promote health, comfort and efficiency”, says Leistner: “Our research findings may well often seem like recommendations for luxury accommodation, but, actually, they are geared towards the mundane 90 per cent of our lives that we spend indoors”.

Daniel Völpel

Energy efficiency plus comfort factor

Creating a comfortable indoor climate as energy-efficiently as possible – that is also a central concern of the University of Stuttgart’s Institute of Building Energetics, Thermotechnology and Energy Storage (IGTE), which was formed on the 1st of July following the merger of the Institute of Building Energetics (IGE), the Institute of Thermodynamics and Thermal Engineering (ITW) with its Research and Testing Centre for Thermal Solar Systems (TZS) and the Institute of Energy Storage (IES). Its research objectives include, among others, improving the energetic standards of buildings and plant engineering as a contribution towards lowering energy consumption and emissions, and to increase energy efficiency. The approximately 60 scientists also want to optimize the energetic function and indoor air quality of entire systems such as buildings and districts and contribute towards progress in the integration of renewable energies, especially solar thermal power, in heating, ventilation and air conditioning systems. *red*

Power steering for the knee

Auxiliary systems are being developed at the Institute of Medical Device Technology based on the KISS principle

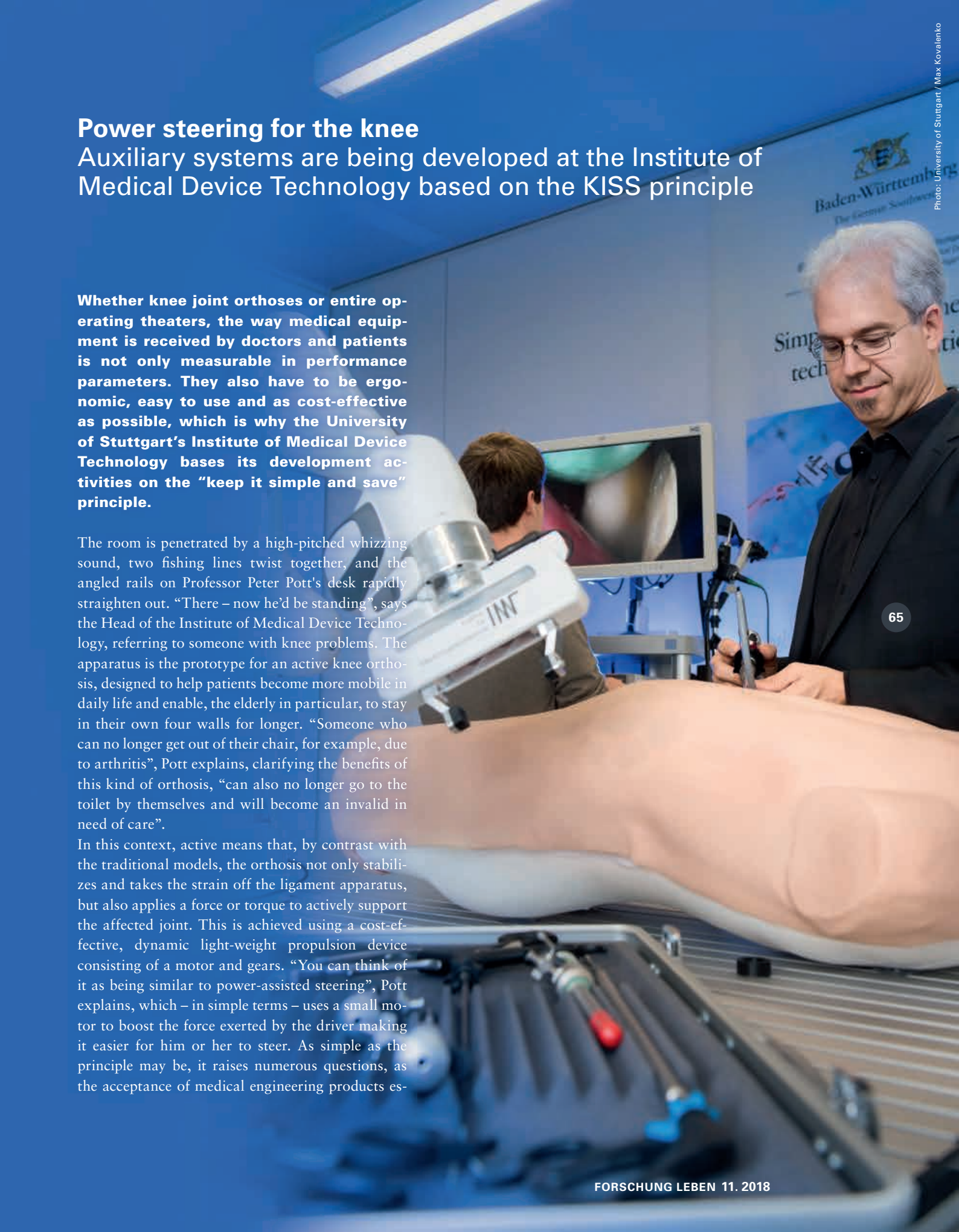


Photo: University of Stuttgart / Max Kovalenko

Whether knee joint orthoses or entire operating theaters, the way medical equipment is received by doctors and patients is not only measurable in performance parameters. They also have to be ergonomic, easy to use and as cost-effective as possible, which is why the University of Stuttgart's Institute of Medical Device Technology bases its development activities on the "keep it simple and save" principle.

The room is penetrated by a high-pitched whizzing sound, two fishing lines twist together, and the angled rails on Professor Peter Pott's desk rapidly straighten out. "There – now he'd be standing", says the Head of the Institute of Medical Device Technology, referring to someone with knee problems. The apparatus is the prototype for an active knee orthosis, designed to help patients become more mobile in daily life and enable, the elderly in particular, to stay in their own four walls for longer. "Someone who can no longer get out of their chair, for example, due to arthritis", Pott explains, clarifying the benefits of this kind of orthosis, "can also no longer go to the toilet by themselves and will become an invalid in need of care".

In this context, active means that, by contrast with the traditional models, the orthosis not only stabilizes and takes the strain off the ligament apparatus, but also applies a force or torque to actively support the affected joint. This is achieved using a cost-effective, dynamic light-weight propulsion device consisting of a motor and gears. "You can think of it as being similar to power-assisted steering", Pott explains, which – in simple terms – uses a small motor to boost the force exerted by the driver making it easier for him or her to steer. As simple as the principle may be, it raises numerous questions, as the acceptance of medical engineering products es-

sentially depends on their usability under everyday conditions, and this can often involve rather mundane requirements, including such things as whether or not the orthosis fits under long trousers, whether it is quiet and lightweight and works in an energy-efficient manner. So, “keep it simple and save” is Pott’s central idea, which is based on the frequently quoted KISS principle, a paradigm for the reduction of complexity. “For us”, Pott explains, “that means coming up with simple systems, and not just in the sense of basic and cheap, but rather so technically sophisticated that they are no longer laborious”. At times, this kind of thinking can be at odds with industry in which the Mannheim native worked for a year. “We're not interested in the ‘gold standard’, in ever increasing performance parameters, but rather in systems that help people”, including in countries that don’t invest so much money in the health system as they do in Germany.

Standard robots rather than special solutions

This way of thinking applies not only to the prototype orthosis, but also to the entire infrastructure currently being built by the institute, which was founded just one year ago. In the adjacent laboratory, for instance, stands a small commercially available industrial robot. Pott and his team want to find out if it would be possible to further develop the high-precision device to the point that it would be suitable for use in the specific conditions of robot-assisted surgery. This question encompasses the issues of sterilization, surgical instrument interfaces and the control system, whereby the latter is subject to extremely high stan-

“Keep it simple and save”: the active knee orthosis being developed at the Institute of Medical Device Technology helps patients to be more mobile in daily life.

Photo: University of Stuttgart / Max Kovalenko

dards in medical robots in the interests of preventing injury. The attempt to construct medical engineering systems using standard devices rather than special solutions could pay off. “The cost of surgical robots such as the DaVinci system, which is currently so popular, can soon spiral up to 1.5 million”, says Pott. “Prices for industrial robots such as this one, on the other hand, start at around 10,000 euro”. So the research could result in significantly cheaper and, therefore, more plentiful surgical robots.

Clean air in the operating theater

An experimental operating theater is currently being constructed in another laboratory, in which researchers and students can gain first-hand experience of what takes place in an operating theater from a technical perspective. Usability testing is also carried out there. At its heart is the interface between man and machine: how should instruments be arranged around a patient; where are the access points; where do the doctors stand? Following its metamorphosis to a medical device, the industrial robot next door might also be tested here to see how it interacts with the other operating theater element. Pott refers to this kind of investment in infrastructure as seed projects, facilities with which one can try things out and that are designed to become the nucleus for further projects.

A student is currently analyzing the airflows in the operating theater as part of her course work for her BSc in Medical Engineering. More specifically, this involves the so-called laminar airflow system, which ensures that the air in the operating theater is clean. In this system, turbulence-free air is directed from above and around the patient to that no germs are deflected downwards and eventually sucked up. The problem with this is that anesthetic signal lights, surgical devices and lamps disturb the airflow, because they present barriers and, in some cases, radiate heat, which causes turbulence. The infrastructure in the experimental operating theater also gives researchers and students the opportunity to analyze the influence of system components or peripherals on the airflow, in addition to hygiene-related factors and energy consumption.

Andrea Mayer-Grenu

Wireless energy for the strong hearts
Inductive energy transmission designed to improve cardiac support systems

When the heart weakens and medication no longer helps, many patients require a donor heart. To reduce lengthy waiting times, artificial heart pumps are used, which are powered via an external cable – which is a gateway for infection. Researchers at the University of Stuttgart's Institute of Electrical Energy Conversion (IEW) want to use inductive energy transmission to improve patient safety and quality of life.

When Professor Nejila Parspour earned her doctorate at the Technical University of Berlin over 20 years ago, artificial heart pumps were usually non-implantable machines that did not leave the patients much freedom of movement. Back then, in collaboration with the German Heart Center, the expert for energy conversion developed a drive system for a highly efficient implantable cardiac support system about the size of a fist, which was used successfully. Such systems are significantly smaller, more efficient and easier to use today. However, the problem of the cable, which connects the implanted pump with the external control system and batteries via an artificial exit point in the abdominal wall, continued to play on Parspours' mind. "This exit point is a gateway for life-threatening infections and limits the mobility of the sufferers", explains the current Head of the IEW at the University of Stuttgart. According to figures published by the German Society for Thoracic and Cardiovascular Surgery (DGTHG), some 1000 cardiac support systems were implanted in Germany in 2016 – almost three times as many as in 2005. In most cases, these were left ventricular support systems, i.e., pumps connected to the left ventricle and the aorta and pump blood around the body with a continuous flow and ensure that it gets sufficient oxygen.

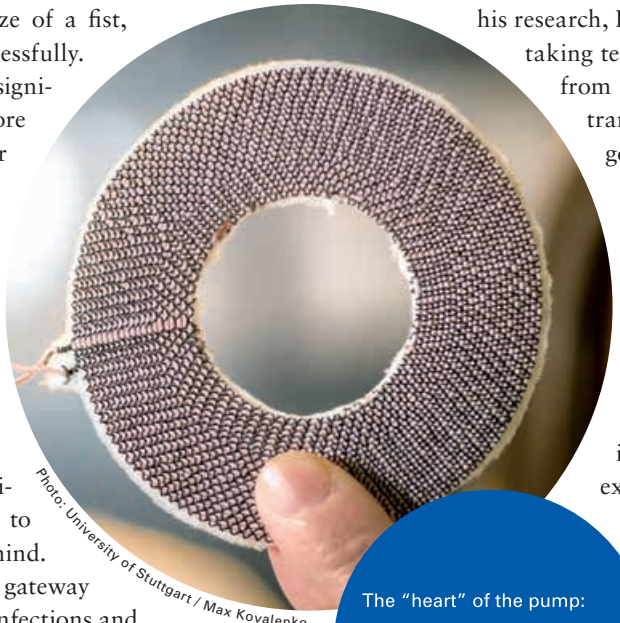
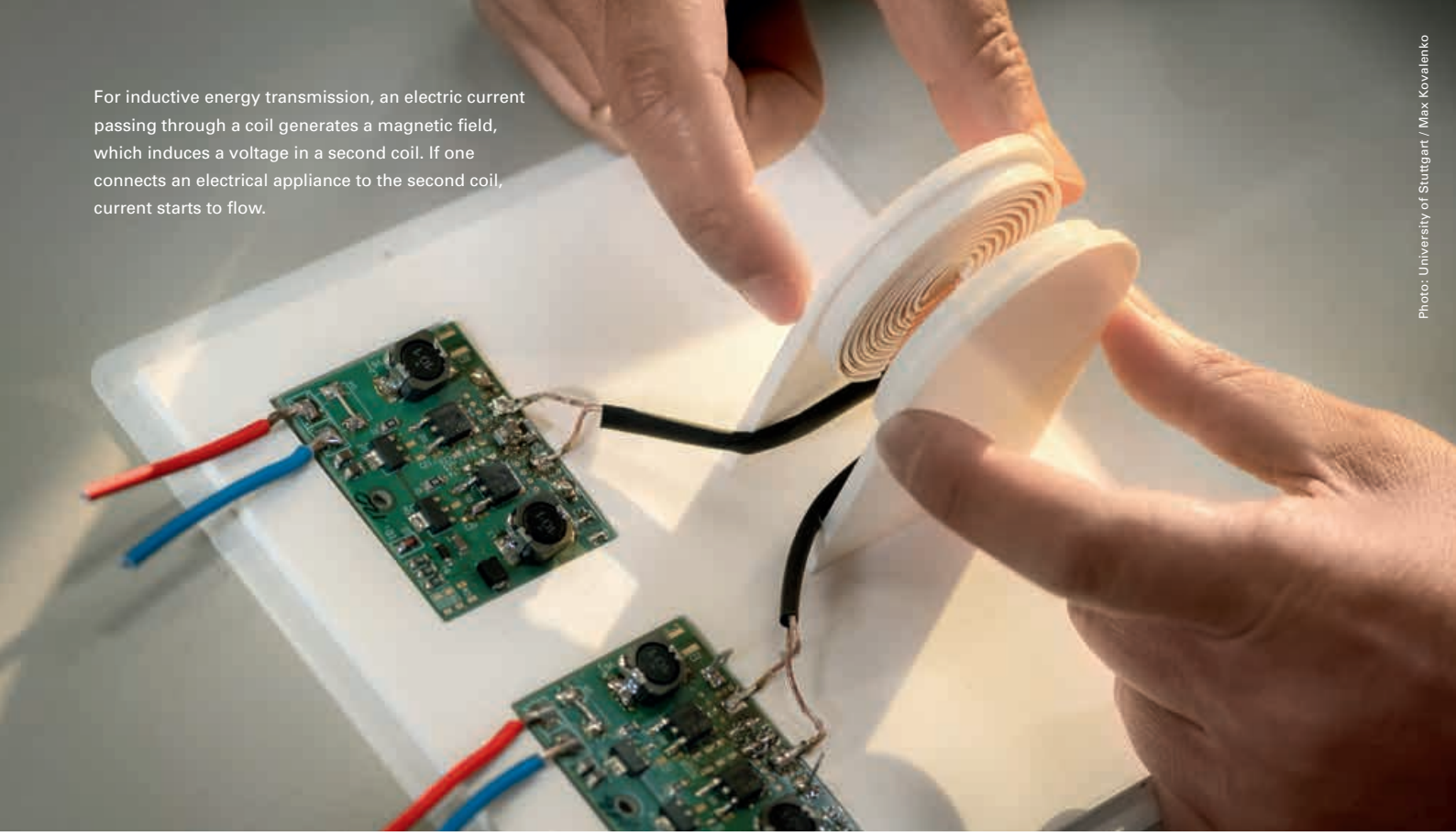


Photo: University of Stuttgart / Max Kovalenko

The "heart" of the pump: the prototype is based on two flat coils with a diameter of about eight centimeters.

Safety and quality of life

Patients always carry the external electronics around with them. Following their release from hospital, they have to keep the exit point scrupulously clean to prevent germs reaching the heart, which makes routine daily tasks, such as showering, problematic. "If we manage to transmit the energy wirelessly", IEW scientist Alexander Enssle explains, "we'll increase patient safety and make their lives easier". With his research, Parspour's doctoral student is taking technologies and developments from the field of inductive energy transmission that have so far gone into wireless charging systems for electric vehicles among other things, and transferring them to the life sciences. Cell phones, laptops, cars and now hearts too: "we're conducting fundamental research for applications that will enable improved mobility", Parspour explains. The physical phenomenon behind has been known for a long time. An electric current passing through a coil generates a magnetic field, which



For inductive energy transmission, an electric current passing through a coil generates a magnetic field, which induces a voltage in a second coil. If one connects an electrical appliance to the second coil, current starts to flow.

Photo: University of Stuttgart / Max Kovalenko

induces a voltage in a second coil. If one connects an electrical appliance to the second coil, current starts to flow. “Transferring this to a medical device inside the human body will take several years of research effort”, Enssle emphasizes.

A complex contact free system

The prototype, which the scientist developed in collaboration with cardiac surgery experts from the Hannover Medical School, is based on flat coils with a diameter of about eight centimeters. The first is outside the patient's body, and can be sewn into an item of clothing – for example in the chest region – and is connected to the external electronics. The second coil is implanted under the skin either in the stomach or chest region along with the control electronics, batteries and connection to the mechanical pump. The magnetic field generated by Coil 1 outside the body can transmit energy to Coil 2 without breaking the skin. However, what appears to be simple at first sight still requires some complex fine tuning,
to which end Enssle matches all implanted electronic elements to ensure that they function in miniaturized form, safely and as efficiently as possible. To achieve this, he uses magnet field calculations to design both coils such that he can optimize the magnetic coupling between the two but still leave a certain tolerance with respect to their positioning inside and outside of the body. Because heat is given off wherever energy is converted, the transmission system is also designed in a way that ensures that the thermal losses primarily take place outside of the body.
The patients can remove the external energy supply thus regaining their freedom of movement – currently for a maximum of one hour – and a bit more independence. In about three years the system, which has already undergone successful laboratory testing, and which should be useable with every type of cardiac support system, should enter the preclinical trial phase.

Jutta Witte

A life sentence for harmful substances
It is not short-term peak loads that cause long-term health impairments

Both the municipal authorities and politicians are concerned with the particulate and nitrogen dioxide contamination at the Neckartor in Stuttgart. The measured values are so high that they could be harmful to health. But, who actually spends all their time out there in the outdoors? In the context of an EU research project, Professor Rainer Friedrich and his team from the University of Stuttgart's Institute of Energy Economics and the Rational Use of Energy (IER) are looking into which contaminants people are exposed to in places where they spend the majority of their lives. Their findings show that action is not only required with respect to road traffic.

As Rainer Friedrich explains, a person's health is primarily influenced by two factors: the genome, i.e., hereditary factors, and the exposome which encompasses the totality of human environmental exposures. “Our assumption”, he says, “is that long-term exposures throughout one's entire life, and not short-term peak exposures, are responsible for chronic illnesses and a shortened life expectancy”. This is the starting point for the EU’s HEALS (Health and Environment-wide Associations based on Large population Surveys) project. The objective is to uncover potential links between environmental factors and ill health. Friedrich and two colleagues are contributing to the research project which involves participation from 30 partner organizations, by providing the calculation base for the exposome. “We're responsible for analyzing data and developing models with which health impairments due to noxious substances can be calculated for demographic groups with specific characteristics”, Friedrich explains, “for example gender, age, profession or place of residence. That's something completely new!” All previous studies have taken a single year of pollution into account at the most and have restricted themselves to concentrations in the outside air.

To arrive at their findings, the team uses basic data from databases that provide information on which demographic groups spend how much time at work, at home and in the car, and what they do there. The team has produced a time-activity matrix for Europe from this data. “We want to estimate the exposure of everyone characterized by each respective profile for their elapsed lifetimes and also prepare scenarios for the future”, says Friedrich. To achieve this, the IER team correlates the time-activity matrix with the noxious substance concentrations for the various locations, and not just for particulate matter and

A person's health is shaped by his or her genes and the environmental influences, both in the positive and the negative sense.

Photos, from left to right: Stock / markus_atelier, Stock / Claudia Otte, Stock / Ingo Bartussek, Stock / Grzegorz Polak, Stock / animaflora, Stock / Leo, Stock / mitifoto, Stock / rotschwarzdesign, Stock / Christian Hein Photo

nitrogen dioxide, but also for ozone, heavy metals and electromagnetic radiation. It was found that some 60 per cent of the most toxic of these noxious substances – particulate matter (PM) – with a diameter of 2.5 µm otherwise known as PM2.5, comes from outdoor air sources, primarily from road traffic but also the fumes from wood firing. In addition, manure and fertilizers used in agriculture produce ammonia emissions and, thus, secondary particulate matter. The most significant indoor sources, on the other hand, are passive smoking followed by frying food as well as operating wood burning stoves and burning candles and incense sticks. Using the methodology described, the researchers were able to calculate lifetime exposures to PM2.5.

The rapid economic growth in the post-war era went hand-in-hand with a significant increase in particulate matter emissions and precursor gasses, which form particulates in the atmosphere, a trend, which was only reversed in the 1980s. After 1990, exposure to particulate matter declined significantly due to the reunification of Germany in conjunction with the collapse of certain sections of the heavy industry sector as well as more stringent limit values for air pollutant emissions, but also no smoking rules in internal spaces and voluntary non-smoking at home. Since its zenith in the 1980s, exposure to PM2.5 has almost halved.

Life expectancy shortened by seven months

The results form the basis for the actuarial calculation. For instance, the life expectancy for a man who is currently 70 years old and whose exposome includes PM2.5 is shortened by an average of seven years plus-minus three months, if one accepts the concentration–response relationship for adults published by the WHO. Moreover, there is a direct proportional relationship between the lost life expectancy and the life-long exposure to particulate matter. “Those who die before their time”, says Friedrich, “lose an average of ten years of life”. He goes on to explain that, because the air is less polluted now than it was between the 1960s and ‘80s, things are looking better for anyone born after 1970. Their life expectancy is shortened by less than half of today’s 70-year-olds.

From the researcher’s point of view, therefore, it makes more sense to reduced long-term average values than to avoid short-term, peak loads. Reduction strategies should also take account of indoor sources: smoking in the house should be avoided, for example and the extractor hood should be switched on during frying.

Daniel Völpel

Minor muscle, major effect

Scientists are working on 3D models of the bladder to get a better understanding of its function and the diseases that can affect it.

A team at the University of Stuttgart is conducting research into the muscular physiology of the bladder and stomach both of which are still relatively unknown. The objective is to develop 3D models for a better understanding of how these organs work and become diseased.

To claim that the bladder holds a similar position in medical research as such things as the heart or brain would be a bare-faced lie, yet the widespread disregard for this small, hollow organ is entirely unjustified, because the bladder is vital to the life of man and all other vertebrates. If its function is compromised, the consequences can be grave.
The fact that the outer muscular sheath of the bladder is still largely not understood in terms of its functionality, makes it a very worthwhile object of research to Professor Tobias Siebert, Dr. André Tomalka and Mischa Borsdorf of the University of Stuttgart's Institute of Sports Science (InSpo). Since 2014, they have been working on gaining a better understanding of the bladder and the various illnesses associated with it.

Fascinating research object

When it is empty, the bladder of an adult human being is not much bigger than a child's fist, although it is capable of expanding its volume by several hundred per cent and of containing up to one liter of urine, at which point it is no longer spherical but more pear shaped.
"The great thing about the bladder is that it can always generate pressure across the entire volume spectrum", Siebert explains. That alone makes it interesting to the Stuttgart-based muscle physiologist. However, the focus of this research project, which is funded by the German Research Foundation (DFG) and carried out in collaboration with Professor Markus Böl of the Technical University of Braunschweig is on what happens when the bladder becomes diseased or scarred as the result of an illness or operation.

Digital model of the bladder and stomach

The objective of this research is to produce a three-dimensional electro-chemical and mechanical digital model of the bladder. En route to this end goal, research is being conducted into how precisely the contractions of the hollow organ, which is made of smooth muscle, work and how, for example, scar tissue affects the muscle. In parallel, the researchers in Stuttgart are working on a comparable model of the stomach, whose exterior muscle casing is, like the bladder, under researched. However, compared with the bladder, the structure of the stomach is significantly more complex, because the different regions of the organ each fulfill different tasks, which means that the muscular layers of the stomach also have to work differently to one another.

Data sets for models

"There are currently no models available, which realistically illustrate either the stomach or the bladder as entire organs" Siebert explains. The objective of the collaboration between Professors Siebert and Böl will be to generate such models on the computer. First, however, the necessary data must first be compiled – and that will require some real fundamental research.
"For a complete model", Siebert goes on, "we also need the complete data set, which cannot simply be adopted from previous studies into rodent bladders.
We're attempting to determine the muscle properties in different regions of the bladder and stomach. That is why, in this study, the researchers are working with strips from the muscle tissue of pig bladders, which they obtain from slaughterhouse waste. They use electrical impulses to stimulate the tissue, which is structurally and functionally very similar to the human bladder, whilst measuring their propagation and the distortions this causes in the muscle. From

The tissue from pig bladders bears a great structural and functional similarity to the human bladder. The researchers stimulate the tissue with electrical impulses then measure their propagation and the distortion of the muscle.

Photo: University of Stuttgart / Max Kovalenko

such experiments, the Stuttgart-based researchers are gradually piecing together the data set for the entire organ.

Terra incognita for researchers

At the same time, the team is entering a terra incognita, as they want to show for the first time how a muscle impulse spreads through the tissue. By contrast with skeletal muscles in which muscle fibers are activated in a targeted manner via nerves, the impulse conduction in smooth muscle spreads from cell to cell in an almost wavelike manner. “All that calls for some elaborate and costly experimentation”, the researchers emphasize, especially because the sample tissue used in the experiments can only be kept alive for about twelve hours.

Understanding highly efficient muscular activity

If the bladder and stomach models work, and the researchers are firmly convinced that they will, they could contribute to a reduction in or even replace animal testing. Ultimately, the models should work in such a precise and detailed manner, that diseases can be studied, operations and their outcomes planned or new treatment methods developed on the computer.

One of the diseases in question is the as yet still incurable interstitial cystitis (IC), a specific type of

Experimentally extremely laborious: Professor Tobias Siebert (right) and his team want to show how an impulse propagates through smooth muscle tissue.

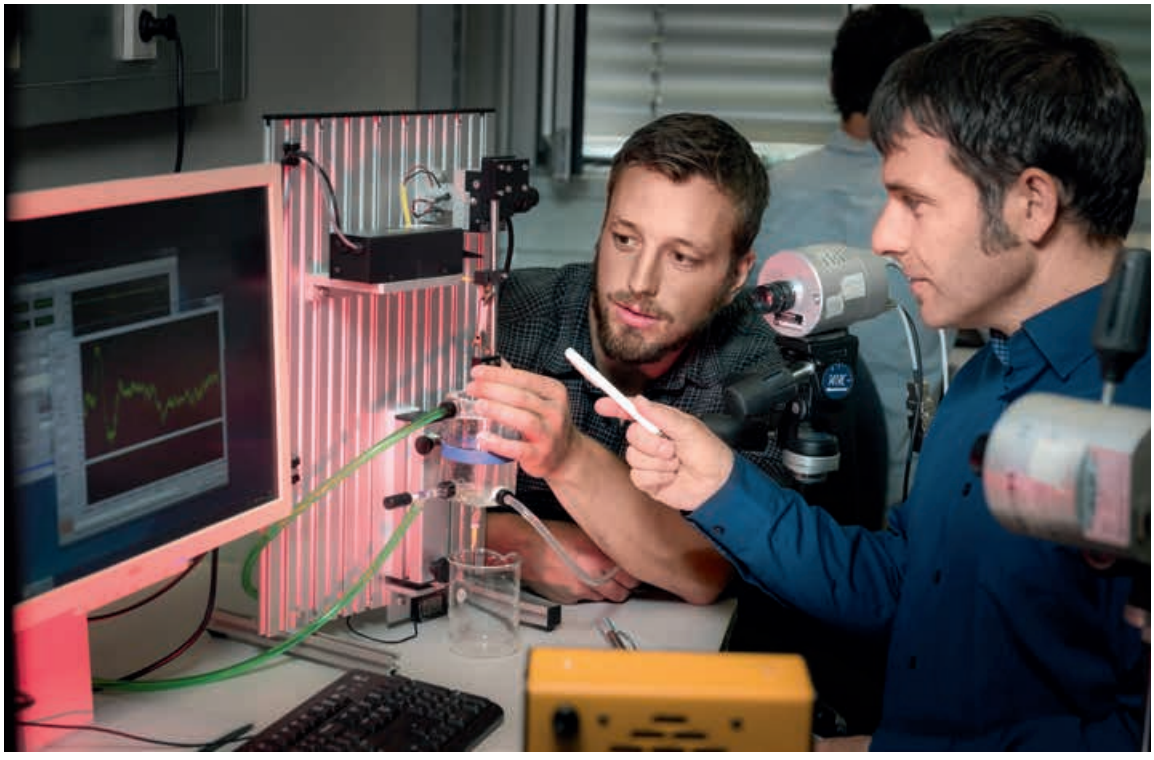


Photo: University of Stuttgart / Max Kovalenko

bladder inflammation that primarily affects middle aged women severely impairing their quality of life. IC results in scarring of the bladder as a consequence of inflammation, which has a serious affect on its mechanical properties.

In addition, the researchers are looking into the general principles of muscle physiology. According to Siebert, whilst the basic principle of musculature has existed for more than 500 million years and is found in all muscles, it is still unclear precisely how the muscle eccentric functions, whereby the eccentric motion by which, for example, skeletal muscles are "charged" for their contractions, is an important building block in the highly-efficient muscle work in vertebrates. "We are now attempting to gain a rudimentary understanding of this functionality", says Siebert. A total of five DFG projects involving muscle physiology and muscle modeling are currently being run within Professor Siebert's team. In addition, the researchers also want to look into the so-called layer dependency of muscle power. This phenomenon, known technically as "force enhancement", describes a muscle's force potentiation during eccentric movements. It is not yet clear whether this phenomenon is also at work in the bladder and stomach.

Jens Eber

When a human is unable to grasp it

Researchers are working on ways to improve the career profile in the intra-logistics sector

Existing logistics systems have primarily been planned on the basis of technical considerations and cater less to the needs of human beings. Researchers at the University of Stuttgart's Institute of Human Factors and Technology Management (IAT) and the Fraunhofer Institute for Industrial Engineering (IAO) want to improve interactions between people, technology and organization.

Bending, walking, stretching, lifting heavy loads, packing them and then on to the next rack: pickers have to walk up to 15 kilometers per day whilst working in the warehouse. Breaks are far and few between. “Logistics personnel come up against their limits – both physically and in terms of concentration”, says Dr. Dirk Marrenbach, who together with Dr. Martin Braun, is responsible for the Preventative Principles and Methods for Age-Appropriate and Market Conform Work System Organization in Intra Logistics (PREVILOG) project.

Intra logics encompasses the transportation, storage, picking and packing of goods within a company. The relevant jobs are generally considered to be unattractive and the pay is very poor. A high sick rate and permanent personnel shortages are widespread within the industry, which is where the PREVILOG project, which is funded by the German Federal Ministry of Education and Research comes in. Together, the IAT and IAO are attempting to structure job design measures in the intra-logistics sector such as to achieve a better balance between ergonomics, organization and behavioral prevention. “The objective is to make these jobs more attractive”, says Marrenbach.

Photo: Fraunhofer IAO / Martin Braun

Systems are being developed in Project PREVILOG that will literally make routine tasks in the intralogistics sector easier to handle.

Robots are no solution (yet)

Replacing intra-logistics with robots will not be feasible in the foreseeable future. “Because of their flexibility, human beings remain indispensable in this sector; they understand the bigger picture and can react quickly to instructions”.

In an initial step, Sven Schuler and his colleagues from the IAT have been analyzing existing work systems. They have developed an analytical tool with which they can determine the stress levels and demands of work systems in the intra-logistics sector. Based on the findings of the analyses, the IAO implements the subsequently derived measures within the companies.

“We’re still in the pilot phase”, says Marrenbach. One partner, for example, may need new work places but doesn't have enough space. “There we would organize a new room layout”, whereby we address concrete questions such as where the racks need to be placed to prevent people walking into them.

The project is also aimed at retaining experienced staff and their knowledge within the respective company. “Older workers, for instance, may start to suffer from impaired vision. So we install better lighting at work stations and also provide magnifying glasses”, Braun explains. How successful such measures are will be shown when the evaluation results are returned at the end of the project in July 2019.

Bettina Künzler

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The sponge as a role model
Using flow processes to understand how to improve therapies

Asphalt, soil, the brain and bones all have one thing in common: they are all considered to be so-called porous media. Researchers at the University of Stuttgart are using the similarities between their physical behaviors to support medical research through simulations, for example by making progress in the understanding of multiple sclerosis and in the treatment of osteoporosis.

The brains of infants are often compared with a sponge, because the soak up information at this age. However, beyond this linguistic image, there is a much stronger physical similarity between the brain and a sponge – both are porous media. This term refers to structures that contain hollow spaces through which liquids can flow. Bones are also included among the porous media as are asphalt and garden soil. This explains why engineer Timo Koch is looking into medical questions, and also why he is completing his doctoral studies at the University of Stuttgart's Institute of Modelling Hydraulic and Environmental Systems (IWS), where, actually, research is conducted into flows and transport processes in the subsurface terrestrial zone. Whilst entirely different parameters, chronological and dimensional scales are of relevance to the medical issues that Koch is working on in collaboration with Professor Bernd Flemisch under the professorial auspices of Professor Rainer Helmig, ultimately these also involve fluid mechanics, i.e., providing a physical description of the propagation of a fluid throughout the porous structures of a given medium. In the case of the brain, the "porous medium" that Koch is studying, the cells and blood vessels form the structure in which the pores – the so-called intercellular spaces – are found.

Immune defense off the beaten track

Koch's scientific research is based on multiple sclerosis (MS) an autoimmune disorder in which the nerves become damaged. According to the German Multiple Sclerosis Society, it affects some 2.5 million people around the world, more than 200,000 in Germany alone. Most cases are diagnosed between the ages of 20 and 40. The initial symptoms are usually unspecific and include, numb patches on the skin, a tickly or numb feeling in the legs and blurred vision, and usually fade within a few days. The adverse effects often manifest themselves in surges, which can be alleviated for many sufferers through pharmaceutical drugs, which can also extend the period between subsequent surges. However, the victims suffer motor impairments, which, in the worst case scenario, can result in their being confined to a wheelchair. They also suffer from attendant symptoms such as rapid exhaustion. The disease is incurable.

Parts of the immune system fail to work correctly in MS patients and attack their own healthy bodies, resulting in damage to nerve cells and fibers. To diagnose and track the progress of the disease, medical practitioners use computed tomography, among other things, to scan the brain" Timo Koch explains. "The resulting images reveal areas where the blood-brain barrier has been compromised. The capillaries in these so-called lesions are far more porous than those in healthy brain tissue. Magnetic resonance imaging (MRI) can also be used for regular checks to see if new lesions have been formed and others have healed over, so that the doctors can adjust the treatment regime accordingly.

In addition, a variant of this imaging process, the so-called perfusion MRI is also used in multiple sclerosis research, whereby the patient is injected with a contrast media, whose progress through the brain can be followed over time. "The type and changes to the MRI signal enables us to determine where the contrast media is seeping out of the capillaries into the intercellular space", Koch explains, and goes on to say that the immune system cells take the same

University of Stuttgart / Max Kovalenko

At the "boundary surface-driven multi-field processes in porous media" collaborative research center, efforts are being undertaken to gain an understanding of how boundary surfaces influence flows, transport and deformation in porous media. Picture (from left to right): Professor Bernd Flemisch, doctoral student Timo Koch, CRC Spokesman Professor Rainer Helmig.

path via these leaky areas to cause the unwelcome damage to the nerve cells and fiber. Koch's collaboration partners at the University of Bern's ARTORG Center for Biomedical Engineering and the Neuroradiology Department at the University Hospital of Bern have discovered that the precise course of the MRI signal reveals whether a given lesion is still in the acute phase, or has started to heal or has completely healed over. Because of the low resolution of the MRI images, the Swiss research team is unable to determine from the data how much of the contrast agent has leaked out at a specific point.

This is where Koch comes in, who simulates the propagation of the contrast medium on the computer. At first glance, the model that he uses for this looks nothing like a real brain. The researcher represents the capillaries as a row of tiny cylinders, which can cross over at various points. In the model, these capillaries cut through tiny, densely-packed cubes, which represent the intercellular space. Yet, the crucial factor is not what it looks like but rather how the characteristic physical equations – for such things as mass, pressure, velocity and concentration – change when the contrast medium seeps out through a leaky area in the capillary wall. "First", Koch explains, "I have separate model equations for the capillary system and intercellular space respectively, which relate to the two different grids, i.e., to the different reference systems for the cubes and cylinders. I only amalgamate the two grids in the calculation itself". One can envisage this so-called coupling as a process in which the two reference systems are reconciled or approximated to one another at the interfaces between the miniature cylinders and cubes.

Understanding flow processes within the brain

The result is a set of equations with around a million unknown variables, which Koch regards as "not that many" in terms of fluid mechanics per se. A single simulation for the propagation of the contrast medium takes about one to two minutes. "It takes several thousand iterations to be able to draw any reasonable conclusions – per pixel!", he says and goes on to say that processes do exist that could be used to expedite the simulations. "But, that's not necessary, as, for the time being it's about fundamental questions of identifying the appropriate model parameters and calibration", says the engineer.

The many iterations serve to estimate the parameters, i.e., the input variables, "whereby the results of the simulation are continually compared with

Photo: Stock / crevis

MRI images of the patient's brain, to determine the best fit and, at the same time, most physically useful, meaningful parameters", Koch explains. This process is done automatically, whereby the most relevant parameters are those that describe the physical properties of the materials. For instance, diffusion coefficients for the capillary walls can be found in the scientific literature or from the geometry of the capillaries. "A total of about ten parameters used in our model have an influence on the calculations", says Koch. "The concentration profile with which the contrast medium moves through the capillaries is ultimately unknown, which means that you have to play through a reasonable range of values". Finally, the researcher has to merge the flow model with the MRI images. Only then can useful conclusions be drawn about the development of the lesions. To this end, Koch also models the MRI imaging in a subordinated simulation. In this way, the researchers hope to gain a better understanding of the flow processes of an MS sufferer's brain than can be achieved with existing models.

Special research for porous media

The technical know-how about porous media available in Stuttgart is not just a reflection of Koch's research. In autumn 2017, the University received approval for a German Research Foundation (DFG) collaborative research center (CRC) focused on "boundary surface-driven multi-field processes in porous media". Over 20 scientists from several of the University's institutes participate in CRC 1313 as Principal Investigators: Professor Rainer Helmig is the current Spokesman. Together, they want to gain a full and fundamental understanding of how boundary surfaces influence flows, transport and deformation in porous media.

The boundary surfaces can be between two fluids or between one fluid and a solid body, whereby the CRC participants quantify which influencing factors, such as the geometry of the pores, the heterogeneity or cracks in the porous medium influence the dynamics of the flow processes. Important in this context is the development of mathematical and numeric models with which the effects of processes that play out on a much smaller scale can be integrated into flow simulations.

Therapy for osteoporosis

Although Timo Koch's research does not fall under the auspices of the CRC, it is closely related to the research questions being investigated there in terms of content. The recently initiated research into simulation of percutaneous vertebroplasty, a therapeutic treatment for osteoporosis (bone loss), on the other hand, is a CRC project, and falls under the directorship of Oliver Röhrle, Professor of Continuum Biomechanics and Mechanical Biology at the University of Stuttgart's Institute of Applied Mechanics (Civil Engineering) (MIB). "Using our models and simulations", the biomechanical specialist says, outlining the project objectives, "we want to help medical practitioners to better understand the processes involved in this method of treatment".

Avoiding complications during treatment

Percutaneous vertebroplasty involves injecting a so-called bone cement into the vertebrae of patients suffering from osteoporosis. The treatment is minimally invasive: the surgeon gradually injects a few milliliters of the bone cement whilst continuously

checking the results with x-ray images. “It's a standard treatment”, says Röhrle, “but, unfortunately, complications, such as bone cement leaking out of the vertebra, do occur from time-to-time. Moreover, the surgeon never knows how the bone cement will alter the mechanical behavior of the human musculoskeletal system”. Ultimately, the patient's vertebrae, ligaments, tendons and muscles will have adapted to the altered structure of the backbone. “Then there's the fact that, in the final analysis, the injected bone cement spreads differently in every patient”.

Photo: Stock / Prill Mediendesign

Sponges, brains and bones all have one thing in common – they are all porous media. Researchers are exploiting their similar physical properties to support medical research with the aid of simulations.

From a fluid mechanics perspective, percutaneous vertebroplasty is a typical example for the processes in porous media. The injected bone cement sets within the vertebra, so that when it first enters the bone it causes a volume change and then, after setting results in a phase change from fluid to solid. “We’re trying to use simulations to describe these processes”, says Röhrle. And, at the same time, to take account of the properties of at least three materials – bone, bone marrow and bone cement. To validate the Stuttgart model, the scientists will be collaborating with the AO Research Institute Davos. “They have experimental laboratory set-ups there as well as the clinical problems that we require for our model development”, Röhrle explains. Only once the results of this first phase are available will the project participants be able to approach the question in which they are really interested: what exactly happens when a vertebra breaks or cracks?

Michael Vogel

Coordination disorder at the push of a button
Using humanoid robots to get to the roots of neural disorders

The human system is highly complex To gain a better understanding of biological movement, researchers working under the auspices of the Regional Research Alliance "Human System", a collaboration between the Universities of Stuttgart and Tübingen have built a bio-robot.

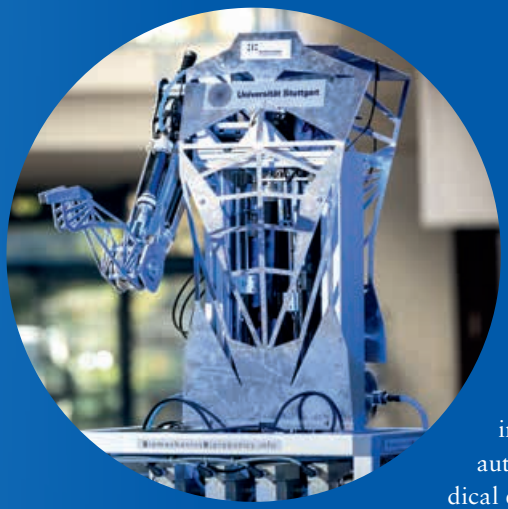
"Picture the human being as an orchestra: You can hear the overall result, but the contribution of the individual components is not immediately evident. That's what biological dynamics are like", says Professor Syn Schmitt of the University of Stuttgart's Simulation Technology (SimTech) Cluster of Excellence. To analyze and understand these individual, highly-complex movements in the human biological system, he and his colleague Dr. Daniel Häufle and their two junior research groups have built the bio-robot "ATARO" at the University Hospital of Tübingen (UKT).

ATARO moves its arm like a real human. It can mimic the movement exactly, as it moves its arm using muscles. in other words, the energy for the muscle movement is the result of the linear motion of a muscle contraction. "ATARO is already at the stage where it can throw a ball rapidly towards the ceiling and trace a circle with its hand", says Schmitt.

Among other things, their knowledge of the generation and control of these movements enables Schmitt and his team to carry out research into disorders that affect the central nervous system. They specialize in the study of cerebral ataxia, a movement coordination disorder triggered by circulatory disorders in the cerebellum. Those affected by the disorder can no longer accurately reach for a glass and end up knocking it over. "We want to produce a mathematical, theoretical model of the human system, which is capable of explaining ataxia". With ATARO, the team has already succeeded in being able to switch ataxia on or off at will. Instead of pointing at specific markings, the robot's finger moves in an uncoordinated manner and misses the target. "Studying this particular disorder has important ramifications for our overall understanding of the neurosciences". The knowledge gained through this project could be used in rehabilitation robotics or robotic care systems in future, which involve the robotic support or control of muscle movements.

Part of the Regional Research Alliance "Human System"

The ATARO project for neuromuscular movement control is part of the regional research alliance between the Universities of Stuttgart and Tübingen in Baden-Württemberg, the objective being to develop models of the highly-complex, biological human system. The models are designed to enable successful interactions between humans and machines, as well as to bring about a fundamental improvement in diagnosing and treating disease-based disorders.



The research alliance is part of the "Cyber Valley" initiative and exploits regionally available expertise in the fields of mechanical engineering, automotive engineering, robotics and medical engineering. Also involved are the Max Planck Institutes for Biological Cybernetics and Intelligent Systems and the Fraunhofer Institute for Manufacturing Engineering and Automation.

Bettina Künzler

ATARO moves its arm like a real human. Knowing how the movements are generated and controlled facilitates research into diseases of the central nervous system among other things.

Photos: University of Stuttgart / Max Kovalenko (circle); Stock / Pixelspieler (glass)

Wanted: the right knack
Medical technicians are developing age-appropriate control systems for everyday use

As an inter-university course between the Universities of Stuttgart and Tübingen, the Medical Engineering degree trains experts with a broad knowledge base, who can even find room for improvement in such commonplace components as the rotary knob.

We turn knobs when we switch on the oven or select the desired washing machine program. In many cars too, the Satnav, radio and other functions are operated by rotary controls, whereby we are not usually conscious of how these rotary controls provide us with information. But, what if we start to lose our tactile sensitivity, i.e., sense of touch, in old age? Are there rotary controls available whose function can be modified in an age-appropriate manner?Peter Schmid of the Technical Design Research and Teaching Department at the University of Stuttgart's Institute of Engineering Design and Industrial Design (IKTD) is conducting research into these questions. For his doctoral studies, the young researcher is looking into so-called haptic man-machine interfaces in a study funded by the German Research Foundation (DFG). What sounds quite complicated are actually simple, manually operated elements such as rotary knobs, slide controls and switches, which the industrial sector could design more precisely and better cater to the needs of older users in future.

Designed for senior citizens

"We're interested in age-appropriate product development", says Peter Schmid. The research is focused on the question of how a rotary knob would have to be changed to ensure that it also provides older people with the desired information, where-

Equipping rotary knobs with information, so that drivers can, for example, feel a menu change rather than taking their eyes off the road – that's what Peter Schmidt of the University of Stuttgart is working on.

Photo: University of Stuttgart / IKTD

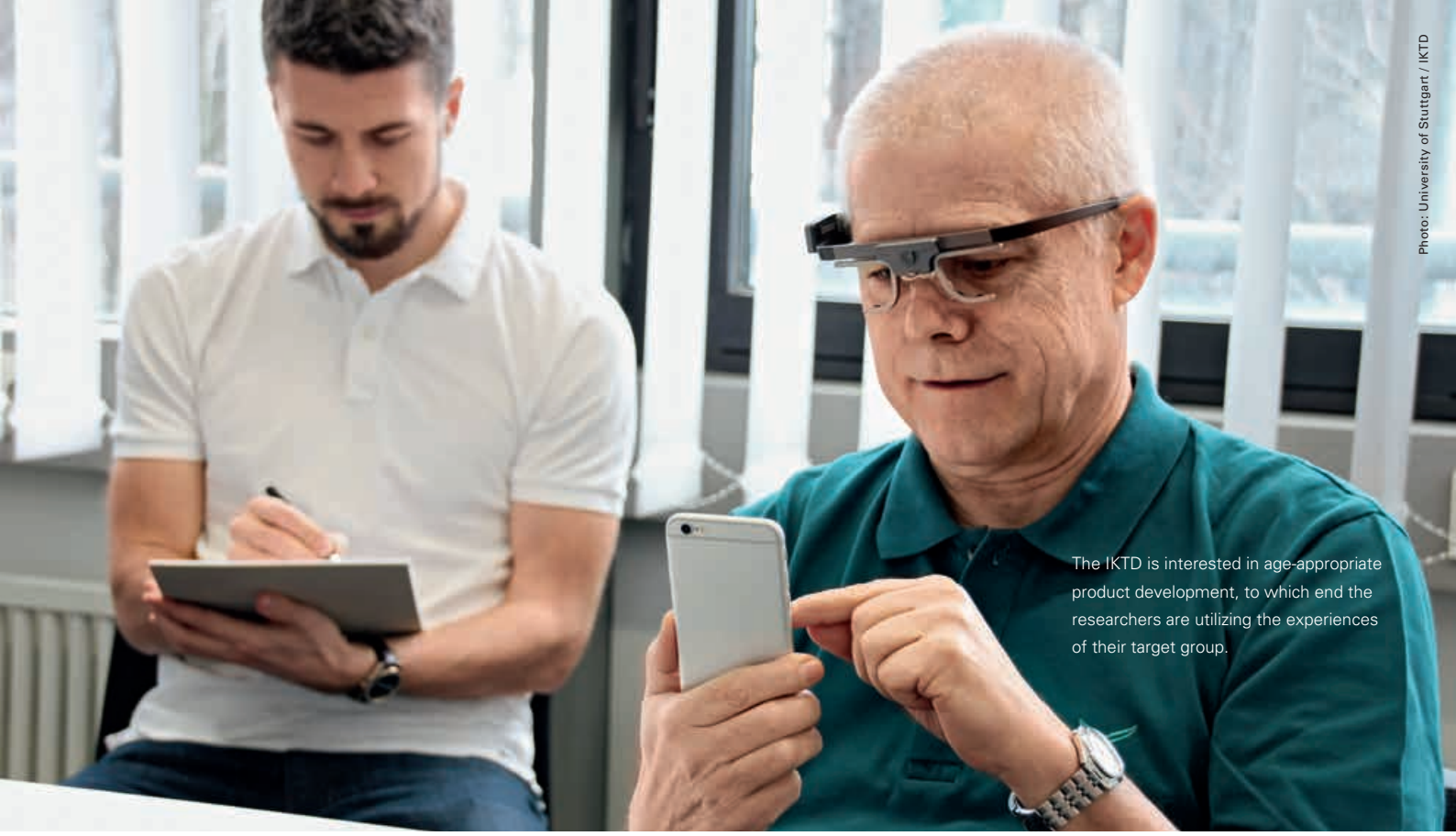


Photo: University of Stuttgart / IKTD

The IKTD is interested in age-appropriate product development, to which end the researchers are utilizing the experiences of their target group.

by there are more design options for such knobs as first meets the eye. On the one hand, developers could change the angle of rotation, i.e., the path of travel between one resting point and the next. On the other hand, the force required to overcome the resting point can also be adapted. These parameters are perceived solely through the sense of touch.

To refine the information transmitted passively via the knob even further, various angles of rotation and torque values can be combined. "We want to equip the rotary knob with information, so that people can, for example, feel a menu change in the car" Schmid explains.

And, it is not just about convenience: people who become distracted by an unclearly coded knob when driving could put themselves and others at risk. Clearly coded knobs in the home could, for example, help visually impaired users to operate their appliances correctly. For this reason, Schmid has used test subjects aged between 21 and 82 for his test series. Having first tested the fine motor skills of his test subjects, he then asked them to select pre-specified values on a rotary knob on the central console of a driving simulator. Among other things, Schmid measured the extent to which these tasks distracted the test subjects from their primary task of driving.

"We found significant discrepancies between younger and older test subjects in terms of the time taken to select the right setting and to complete the task, the ability to stay in lane and our accuracy assessment", the researcher explains. From this data, we were able to design a rotary knob configuration, which functions best across all generations. The knob turns through 30 degrees between the individual points of rest, whereby it takes 0.09 Nm of force to move it on from any given rest point.

Fingers more reliable than the eyes

"This is not just about research; we also have a specific application in mind", Professor Thomas Maier, Head of the Technical Design Research and Teaching Department at the KTD, emphasizes. The objective of the project, which ended in September 2018, was to produce a set of design guidelines for age-appropriate man-machine interfaces to enable companies to cater better to the needs of older users during product development. "In our opinion", says Maier, "touch screens are not always the optimum solution in every situation. The degree of distraction during driving is significant because users first have to look to see where to place their fingers on the control panel". Schmidt agrees: "Older people are glad

that rotary knobs still exist and that their sense of touch becomes an additional support for them when their sense of sight starts to deteriorate". Nevertheless – or precisely because of this – the researchers at the IKTD are hoping to get approval for a follow-up project in the course of which they want to explore design concepts for a tactile touch screen. This, according to Maier, could transmit minute impulses to the finger thereby practically producing a tangible scale.

It may be surprising that this research, which is aimed at such a wide range of practical applications, has its origins in the Medical Engineering degree. But, as Professor Maier points out: "It does involve medical engineering simply by dint of the fact that we are taking sensory and motoric impairments in consideration". Whist one usually associates medical engineering with developments for the treatment of medical disorders or for rehabilitation purposes, he continues, the rotary knob development "intervenes even before severe handicaps arise". Not only identifying these wide ranging approaches and potentials for medical engineering, but also to realize them in practically-oriented research is, in Maier's view, one of the major strengths of the still new Medical Engineering degree program.

Technical and medical skills

The Bachelor in Medical Engineering course was first offered in 2010. "It was created based on the idea of setting up an inter-university degree course in collaboration with the University of Tübingen", says Thomas Maier, one of the course founders. The ultimate idea was to combine the University of Tübingen's medical know-how with the University of Stuttgart's technical expertise. Right from the start, the project was met with a lot of enthusiasm: "In 2010, we had 100 places available, but received 456 applications", says Maier. There are up to 700 applications per year.

"Medical engineering degree programs are not a rarity in Germany", Maier admits, but points out that: "The fact that two such prestigious universities are collaborating so closely, remains unique to this day". The students are matriculated at both universities and commute between the lecture venues. The Masters in Medical Engineering degree program

Rotary knob versus touch screen: older people whose visual acuity is declining are glad of the extra support they get through their sense of touch in everyday life.

Photo: Stock / Tobias Langner

was launched with 36 students in 2013. Over 50 per cent of today's 300 students are women. Two professorships for optical design and medical device construction have also been established since then. And, not to be forgotten: the demand for course graduates has been considerable right from the start. "Most of them go into industry, where there is a huge demand for our graduates", says Professor Maier. In the past, he continues, medical engineering companies were often forced out of necessity to employ mechanical engineers, and to provide them with further medical training, or else trained medical professionals who were retrained as design engineers. The Medical Engineering degree program, he goes on to say, produces experts with a broad set of skills and know-how. Peter Schmid was among the first intake into the Medical Engineering degree. "I was motivated by the desire to help people and, at the same time, I'm a bit of a technology geek", the doctoral student explains, and goes on to say that this field offers many challenges even beyond traditional medical devices for hospitals and clinics.

Jens Eber

How can senior citizens stay mobile even when faced with health challenges and still reliably call for help in an emergency? These are the questions that interest the recently founded company AGE-Ing (ageing), which was established by engineers Benedikt Janny and Matti Schwalk both former academic staff at the Technical Design Research and Teaching Department at the IKTD. They have developed a so-called wearable device, a high-tech' product in the form of a chain or bracelet, which is easy to operate and ensures personal safety using a mix of mobile communications and GPS technology.

By contrast with many smart and emergency call watches, AGE-ing's emergency call system depends on functionality that is as reduced and clear as possible without putting the wearer at risk of stigmatization due to its design. The interesting thing about it is that potential users were integrated into the development process right from the start. "We concentrated on user-centric technology design and organized a test subject pool during our doctoral studies", Benedikt Janny explains. Some 65 senior citizens are involved in the design process, trying out prototypes and providing valuable feedback. Additional test subjects are always welcome, says Schwalk. The start-up is also working on other projects in collaboration with this pool of test subjects, such as the optimization of technology to meet the needs of older users, for example the electrification of walker frames.

AGE-Ing is the first spin-off from the IKTD. The company was launched in early 2018 with start-up capital from a research scholarship. Professors Thomas Maier and Hansgeorg Binz of the University of Stuttgart serve as mentors.

The two entrepreneurs see the interdisciplinary Medical Engineering degree program as a major advantage. According to Janny, the former course manager: "The connection between man and technology as well as biological, medical and technical principles is a great field to work in, and students graduate with a broad basis of expertise in preparation for it". In addition, say Schwalk and Janny, given the breadth of the subject, it takes personal commitment on the part of the students to acquire more detailed expertise. *je*

The spaghetti effect
Biophysicists track proteins as they pass through the cell membrane

Does spaghetti have anything to do with biophysics? Not at first glance. But, when Professor Stephan Nußberger of the University of Stuttgart explains his highly-complex research, pasta becomes a highly illuminating didactic tool. A look at the mysterious world of organelles and proteins.

Professor Stephan Nußberger, Head of the University of Stuttgart's Institute of Biomaterials and Biomolecular Systems (BIO), is one of those passionate scientists, and conducts research into natural processes in what initially appears to the initiated as an inaccessible dimension. But because Nußberger talks about and explains it in such captivating terms, one leaves his office after a few hours with the feeling of having peered into a fascinating universe. It's all about translocases, i.e., certain proteins that permit molecular chains to pass through cell walls. And this is crucial to human life for one of the fundamental requirements for the functioning organism is that proteins, for example, arrive within the mitochondria, i.e., the "the power stations" found in every cell of our bodies, in the correct numbers and at the right time. Over 1400 different protein polymers need to be threaded through these pores into the human mitochondria. Any disruption to this never ending transfer results in serious illnesses. Of course, this knowledge is based on thoroughgoing fundamental research: the American biochemist, Günter Blobel, won the 1999 Nobel Prize for Medicine for his discovery of the fact that every one of a cell's organelles requires pores as well as specific receptors to be able to thread proteins through. It is also clear that proteins succeed in getting through the cell membrane countless times in every moment of our lives. But – how?

The science magazine Nature once described the process as "the art of sucking spaghetti", says Nußberger, dishing up an extremely pithy image. The idea of slurping up long, sauce-covered noodles with gusto immediately conjures up a mental picture, at least among pasta-fans. Yet, who or, rather what is pulling the protein chains in? "How nature manages this is still not understood", says the biophysicist and adds: "but that's why I'm here! As a physicist, it's all about the scientific challenge of finding that out!".

Diving down to unimaginable dimensions

To give an idea of why it is so difficult to observe molecules or polymers as they transgress the cell membrane, Nußberger uses another analogy. The sun, he says, is about 150 million kilometers away from earth. One needs to imagine a similarly immense distance between us and the scale of a few atoms, because this is the dimension at which the activities of the translocases play out. Even with the hugely powerful microscopes available to the biophysicists in Nußberger's department, it is still extremely difficult to observe proteins in motion the way one might, for example, observe a worm burrowing into the soil. However, the Stuttgart-based researchers have managed to do something else,

The scientists are conducting their research into translocases in dimensions that are unimaginable to the layman.

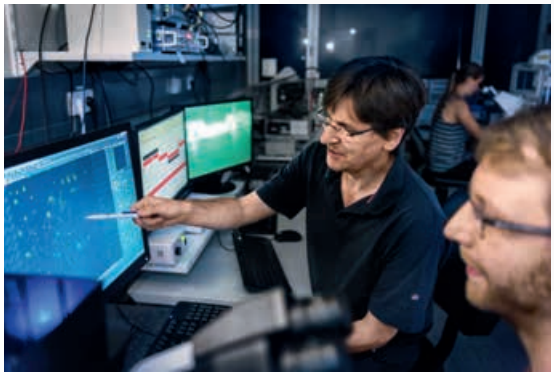


Photo: University of Stuttgart / Max Kovalenko

Photo: Stock / Melica

which Professor Nußberger described in a noteworthy article, co-authored with Professor Werner Kühlbrandt of the Max-Planck Institute of Biophysics in Frankfurt am Main, which was published in the respected journal Cell.

In the summer of 2017, the two biophysicists in Stuttgart and Frankfurt succeed in creating a translocase with a resolution of 6.8 ångströms, whereby one ångström equates to about the size of an atom. In the image that Nußberger presents, one can see the structure of the translocase as well as its two openings, each with a diameter of elven ångströms, which bears a slight resemblance to a Viennese mask. As the professor says, he had already discovered ten years ago that mitochondrial translocases of this type – a TOM-translocase or "translocase of the outer mitochondrial membrane" to use the correct technical jargon – have two pores. However, the fact that this finding is now available as a three-dimensional image with a resolution of almost atomic dimensions is, as Nußberger puts it with charming understatement "an elegant scientific result".

Stubbornness and routine laboratory work

This result was achieved via routine, tangible work in the laboratory, where the scientists cultivated bread mold in 100-liter tanks, from which highly purified mitochondria as well as, ultimately TOM was isolated in a multi-stage process, which was then observed using Cryo-Electron Microscopy (Cryo-EM) technology, which won the 2017 Nobel Prize for chemistry. "What's fascinating about our work is that we are penetrating down to dimensions that no one has ever seen before us", says Nußberger, explaining that his team is searching for structures whose appearance they don't even know. "But I'm also glad that it is possible to pursue this stubborn desire to understand fundamental biological questions in our academic landscape", the scientist adds. The open questions include such things as the actual mechanics of the "slip through", i.e., whether the protein-spaghetti is pushed through or pulled in. At the same time, the biophysicist's work absolutely provides the basis for practice-oriented applications. For example, initial efforts are already underway to use this type of nano pore for DNA sequencing. The findings from Nußberger's department are also useful to cell biologists studying mitochondrial disorders.

Jens Eber

“We’re nowhere near the end of the flagpole”
Artificial intelligence in medical science

Digitalization is set to open up entirely novel avenues in medical engineering. That’s the view of Alexander Kunz, a graduate of the University of Stuttgart, who now works as a product manager for Fresenius Medical Care, a medical engineering and healthcare company. His interests include such things as how dialysis machines can be upgraded for the future Industry 4.0.

Medical dressing, injections and implants: the range of medical materials encompasses everything from simple everyday products to highly-complex technical devices. The history of medical engineering – or, more correctly “medical products” – goes back a long way and is intimately entwined with the developmental history of mankind. Much has changed since the first primitive forms of treatment, which involved treating wounds with tree bark or the leaves of medicinal plants, and not only with respect to dressing materials.

Chronically ill patients in particular are able to enjoy significantly longer lives and an existence more worth living thanks to sophisticated technology such as dialysis machines when the kidneys no longer properly function or fail completely. Based in Bad Homburg, Fresenius Medical Care is one of the companies that have made a substantial contribution to the development of dialysis products. Over the past few decades, the company, which specializes in products and services for chronic kidney failure, has advanced the relevant medical and technical progress through intensive research. Yet, as Alexander Kunze knows: “we’re nowhere near the end of the flagpole”. Because the digital transformation is paving the way to a plethora of promising new possibilities in the medical products sector. Kunze is certain that: “artificial intelligence and big data will play a major role in medical engineering going forward”.

Smart machine maintenance

In his role as product manager within the company, he represents the interface between the Development Department and the customers, and is, therefore, involved in the entire product lifecycle from the initial planning phase to active product support following the market launch. His earliest experiences in product development were acquired during his studies at the Furtwangen University of Applied Science and in his role as research associate at the Fraunhofer Institute for Manufacturing Engineering and Automation (IPA). The Master’s in Medical Engineering that he gained at the University of Stuttgart provided him with the necessary tools for his areas of interest, orthopedic technology and cardiology. “On the one hand”, he says, “we did of course have close connections to the research community here, whilst on the other there were close links to practical applications. That opened many doors to the industrial sector to me during my studies”. Today, almost three years after completing his studies, he and three of his colleagues form the “Smart Dialysis Clinic” within the company. Among other things, this still very new business unit focuses on the development of new and existing systems and devices in the wake of digitalization. The 30-year-old has sole responsibility for artificial intelligence. “This involves such things as the development and application of algorithms that analyze data for prognoses”, he says: Primarily, this plays a significant role in the maintenance of the devices”. What increases productivity in other sectors of industry, i.e., the ability to predict and, therefore, avoid machine outages in good time, could be life-saving in this context.

New requirements and business models

However, the primary focus of the “Smart Dialysis Clinic” is the development and implementation of new business models, which is why Kunze keeps a watchful eye on the market to ensure that he recog-

Gazing into the future of medical engineering: product manager and maverick, Alexander Kunze, is pushing the development of artificial intelligence for dialysis machines at Fresenius Medical Care.

Photo: University of Stuttgart / Uwe Nölke

nizes customer demand and requirements in a timely manner, whereby it appears that the hardware itself no longer plays such an essential role. “By now, we've already achieved an extremely high quality in this area”, Kunze explains: “if anything, the most important thing now is our promise to guarantee it”. For Fresenius Medical Care as a technology provider, that means a comprehensive restructuring of their portfolio; a transition from a device developer to a service provider. “Doctors should be able to depend 100 per cent on the technology so that they can concentrate fully on treating patients. what we’ll be selling in future will no longer be our own product but the results, just as if the customer were no longer to purchase a drill but rather the finished hole”.

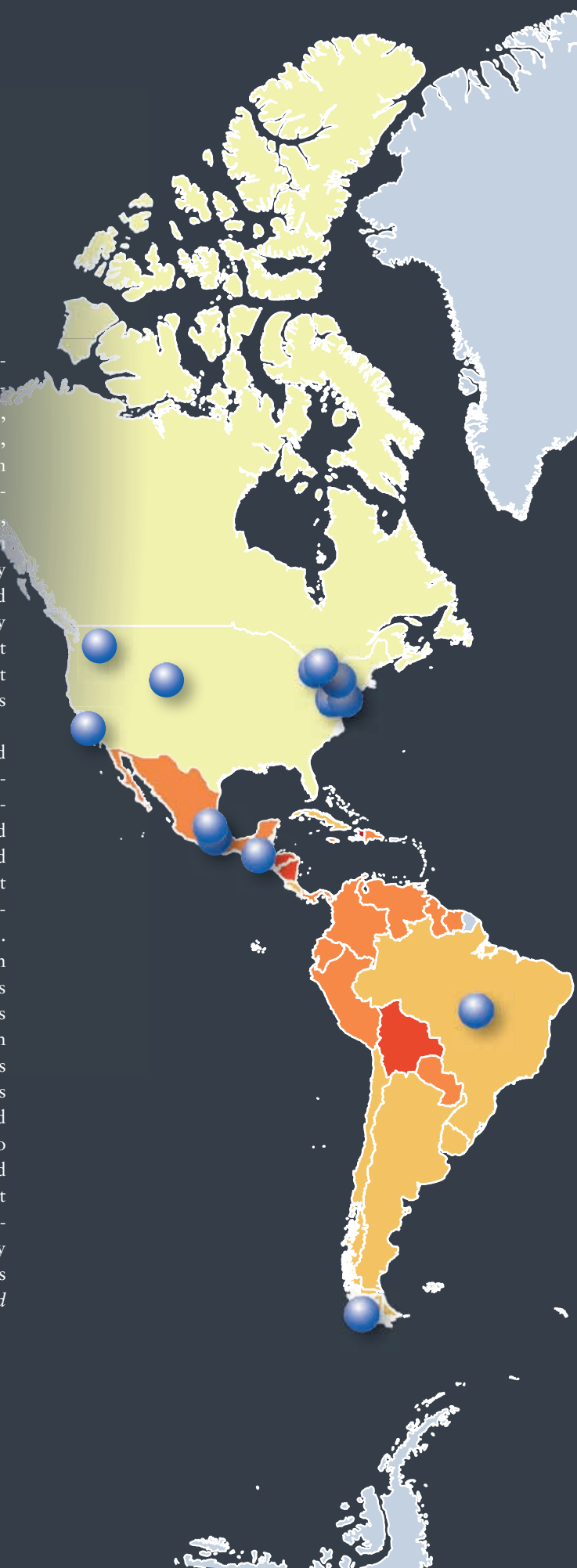
As if that were not enough, the ambitious 30-year-old is also busy launching his own start-up on the side, which, totally in line with the spirit of the age and his own expertise, is also concerned with digitalization in the healthcare system. “Our business idea is based on an Internet platform for brokering and coordinating patient transport services”. Although the project is still in its infancy, he and his business partners have set themselves no less an objective than “revolutionizing the organization of patient transport”. Indeed, the product manager has a heart-felt desire and drive to ensure the wellbeing of patients: “since my paramedic’s training at the latest, I have been passionate about doing my very best to help patients. We're well provided for in this country, but there is still room for improvement”.

Constanze Trojan

Vulnerability – Measuring the Unmeasurable

Risks and damages due to extreme events and climate change not only depend on the force and frequency of natural events, such as floods and storms, but also on the vulnerability of infrastructures, towns and cities and, therefore, ultimately of human beings. The question of how to measure vulnerability represents one of the central challenges of science, as evidenced by the heatwave that gripped Europe in 2003, during which many people died, particularly the elderly. Yet, in their responses to a household survey currently being conducted by the University of Stuttgart's Institute of Regional Development Planning (IREUS) in Ludwigsburg, a major district center, older people, in particular, deem themselves to be not especially vulnerable to heat.

Measuring vulnerability to extreme events and climate change at the global level is of central importance to the relevant risk analyses and adaptative measures. According to calculations performed at the IREUS, countries in Sub-Saharan Africa and the Pacific island states have a high and persistent vulnerability rating. Vulnerability, resilience and adaptation are the topics of current global discussions. As a result of the internationally recognized research into vulnerability being carried out at IREUS, its head, Professor Jörn Birkmann, has been selected as the coordinating lead author for the IPCC's Sixth Assessment Report. In collaboration with experts from 90 countries, he will be analyzing the effects of climate as well as questions of vulnerability and adaptation during the next four years. The first two conferences will be held in 2019 in South Africa and Nepal respectively and the publication of the report is planned for 2021. The Summary for Policy Makers will be read word-for-word and discussed by over 180 governments – hardly any scientific reports garner such widespread attention. *red*



Ludwigsburg
ZURES

Universität Stuttgart

Thailand
RiskNAP

93

Vulnerability Level

- very low (25 – 35)
- low (35 – 43)
- middle (43 – 49)
- high (49 – 63)
- very high (63 – 75)
- no data

Research Projects Being Conducted under the Auspices of the University of Stuttgart

Coordinating lead authors of the

Dr. Do and the detectives
… and the Internet-wide search for code errors

Since 2017, Dr. Quoc Huy Do has been working on making life difficult for hackers at the University of Stuttgart's Institute of Information Security (SEC). Together with his colleagues at the SEC the Vietnamese native has been searching for security loopholes in basic Internet standards and protocols.

By comparison with the corridors throughout the SEC, with their many seating areas and mirrored kitchenettes, Dr. Quoc Huy Do's office appears almost Spartan. There are no papers on his desk, just a laptop, flat screen and a cup of tea. A photo of his family is his only concession to his private life. It appears as if the 36-year-old wants to protect his work from all distractions so that he does not make the same mistakes that many programmers fall victim to: they program security loopholes into Internet code, and nothing motivates a hacker more than a security loophole. “We work very hard here”, is Do's smiling summary of the office environment.
In terms of the data-hunter and collector powerplay, Dr. Do is one of the good guys. With his research group colleagues at the SEC the Vietnamese native has been searching for security loopholes in basic Internet standards and protocols. Asked if he is a kind of detective searching for clues to possible points of attack with persistence and intelligence, Do nods and agrees one could say that.

Not a traditional crime scene

Of course – and this is where the complexity of the subject already starts – the Internet is not like a crime scene that detectives search thoroughly for fingerprints, murder weapons and traces of DNA. Whilst the Internet appears to be something physical when presented on screens of every kind, it is, in reality, intangible; nor is it invulnerable. On the contrary, the Internet is a kind of developing organism, continuously expanding in every dimension. The fact that loopholes, points of attack for hackers, arise in the course of this is the result of natural human fallibility. “Nothing in the world is perfect, and no code either”, says Dr. Do. That’s why the institute team, which works under the directorship of institute leader, Professor Ralf Küsters, has set its sights on the development of a tool designed to reveal vulnerabilities in code to web developers before they put it online, a kind of non-bribable auditor that identifies code errors on a logical-mathematical basis.
The outlines of the tool have already been sketched out on paper – and this was a highly-complex project. By the end of the year, Do hopes, a structural framework of the auditing tool should also have been programmed.

Rooted in computer science

Computer science has been a constant aspect of Quoc Huy Do’s career right from the start of his university studies. And, with each subsequent step, the Vietnamese national probed deeper into the material, till now when he has practically reached the foundations of the Internet here in Stuttgart.
Born in Hanoi, the capital of Vietnam, Do attended the People's Security Academy, where he first studied the basics before going on to conduct his initial research into program verification at the National University in Hanoi – “the best university in Vietnam”. Of course, there was no hint at that time of the route that would finally lead him to Stuttgart.
For his doctorate, Do conducted research at the TU Darmstadt in a research group headed up by Professor Reiner Hähnle. “There, I work on dataflow security”, Do explains. Whilst that sounds similar to non-experts, the researcher assures us that it was “something entirely different: we programmed a tool for Java developers, which checks whether a piece of software contains hidden dataflows”.

However, Quoc Huy Do had already become obsessed with the topic of security whilst there: “After getting my doctorate, I wanted to carry on working in this direction”. And, an opportunity to do just that seemed to open up at the University of Stuttgart: Professor Küsters had been working on a comprehensive security analysis of the OAuth-2.0 protocol in Trier and had just transferred to the University of Stuttgart at that time.

Do was fascinated by the research being carried out in a newly inaugurated research group and applied for a post there, and, although he also received other offers at the same time, opted for Stuttgart. “The atmosphere and close collaboration are great and Stuttgart is also a beautiful city”, says the research fellow, who took up his post at the SEC in September 2017.

Do first lived with his family in the University guest house, but the City of Stuttgart's Welcome Center soon introduced him to potential landlords, assisted him with various official questions (“a nightmare”) and even organized a Christmas party for the new arrivals. “My kids thought it was great” he says. In the meantime, not only has the family found accommodation, it has also grown: “My son was born in Stuttgart”, Do says, adding that his two daughters are attending primary school here.

Photo: University of Stuttgart / Max Kovalenko

Fan of research freedom

“I hadn’t originally planned to become a researcher”, says the security expert. Today, the 36-year-old feels very comfortable in the world of academic research. “I like to learn and to tackle new challenges. Research is a great opportunity to do precisely that”. Even though he has never worked for a company, he says, he places great store in research freedom. “We focus on specific topics, whereas, in industry, you always have to keep the final product in mind”.

OAuth 2.0 (Open Authorization), a popular Internet authorization and authentication protocol, is at the center of the project that Quoc Huy Do and his colleagues are working on. It is designed to ensure the secure authorization of web-services and applications without giving third-party providers access to confidential data. In practice, one uses one's private data to dial-in to a specific service provider after which one can also use the services of third-party providers without having to log in again every time. There have already been several hacker attacks on OAuth 2.0 in the past, which have usually been responded to by rapid program code fixes. The tool on which the SEC is working is intended to help identify potential gateways for criminals at an early stage by using the pattern of known points of weakness in OAuth.

Do's contract of employment at the Institute ends in September 2019. He is not yet sure whether or not he will continue to work in Stuttgart after that. He is, on the other hand, certain that he will continue to work in the field of cyber security.

Jens Eber

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Address: University of Stuttgart, Keplerstraße 7, 70174 Stuttgart
Telephone 0711 685-82211, Fax 0711 685-82291
hkom@uni-stuttgart.de, www.uni-stuttgart.de

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Tobias Blocher,
Projektingenieur

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