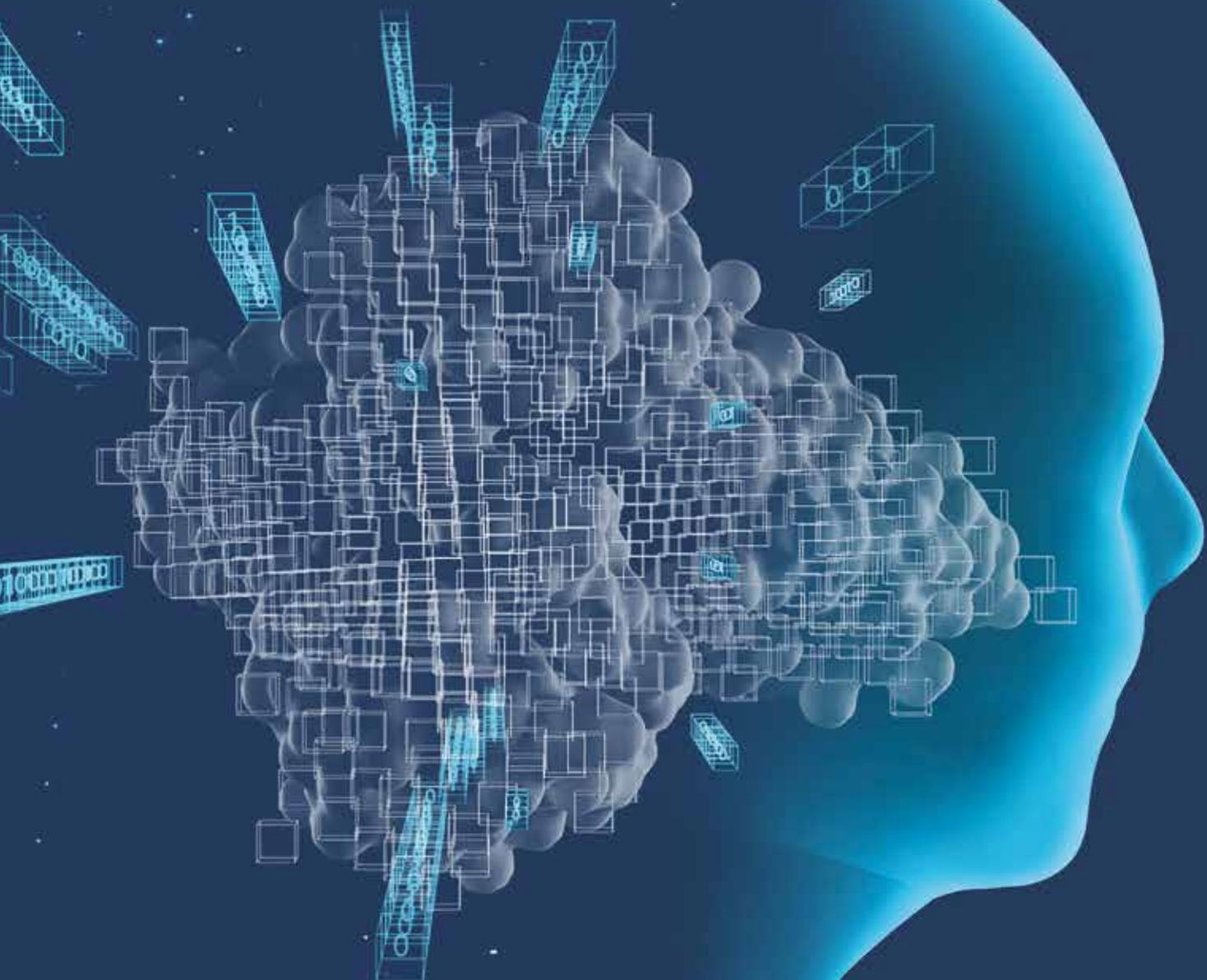


# femto

The DESY research magazine – Issue 01/24



## Life sciences

Human beings at the centre  
of intelligent research

Neutrinos from  
the Milky Way

AI in the accelerator  
control room

Cooking eggs  
for science



# Arsenic and top place

There are thousands of areas contaminated by arsenic around the world. The poison leaks into the environment through mining, for example, but certain microorganisms also release arsenic. There is a tropical fern, however, called *Pteris vittata*, which has the exceptional ability to naturally accumulate arsenic into its living tissues. The image of the fern (top right), taken at DESY's X-ray source PETRA III, won second place in the 2023 Helmholtz Imaging Award competition for the best scientific images.

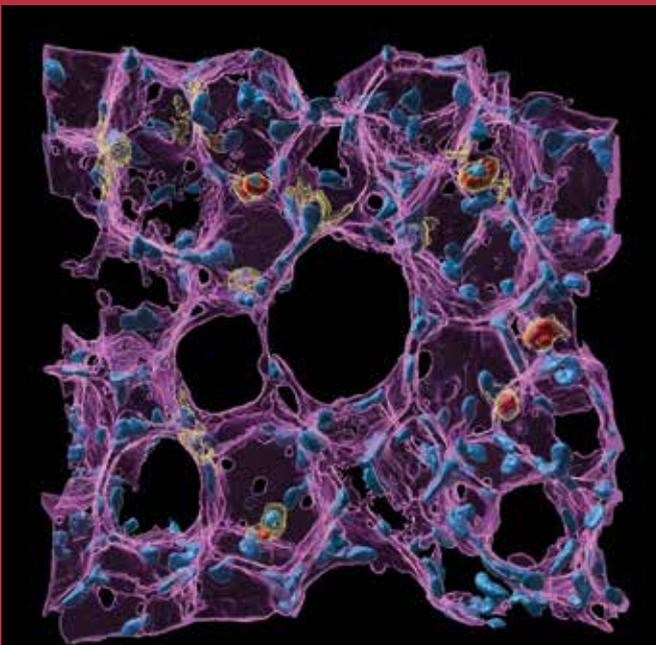
This cross section is a microfluorescence computed tomographic reconstruction (i.e. a micro X-ray image) of the fern stem. The arsenic is shown in green. DESY researchers Kathryn Spiers and Dennis Brückner, together with plant ecophysiologicalist Anthony van der Ent from Wageningen University in the Netherlands, have investigated exactly where the fern stores the metalloid. The image shows the arsenic in the fern's endodermis and pericycle – the inner and outer layers around the plant's water-conducting bundles. The arsenic map helps to better

understand the molecular and physiological mechanism of arsenic tolerance in the fern.

It was the third time that Helmholtz Imaging called for the best scientific images. First place in the jury's selection went to Lin Yang from Helmholtz Munich for an image of the delicate architecture of lung alveoli (bottom left). Third place went to Angelika Humbert from the Alfred Wegener Institute and Tilman Bucher from the German Aerospace Center for an aerial photograph of a drained glacial lake in Greenland (bottom right).



<https://helmholtz-imaging.de>



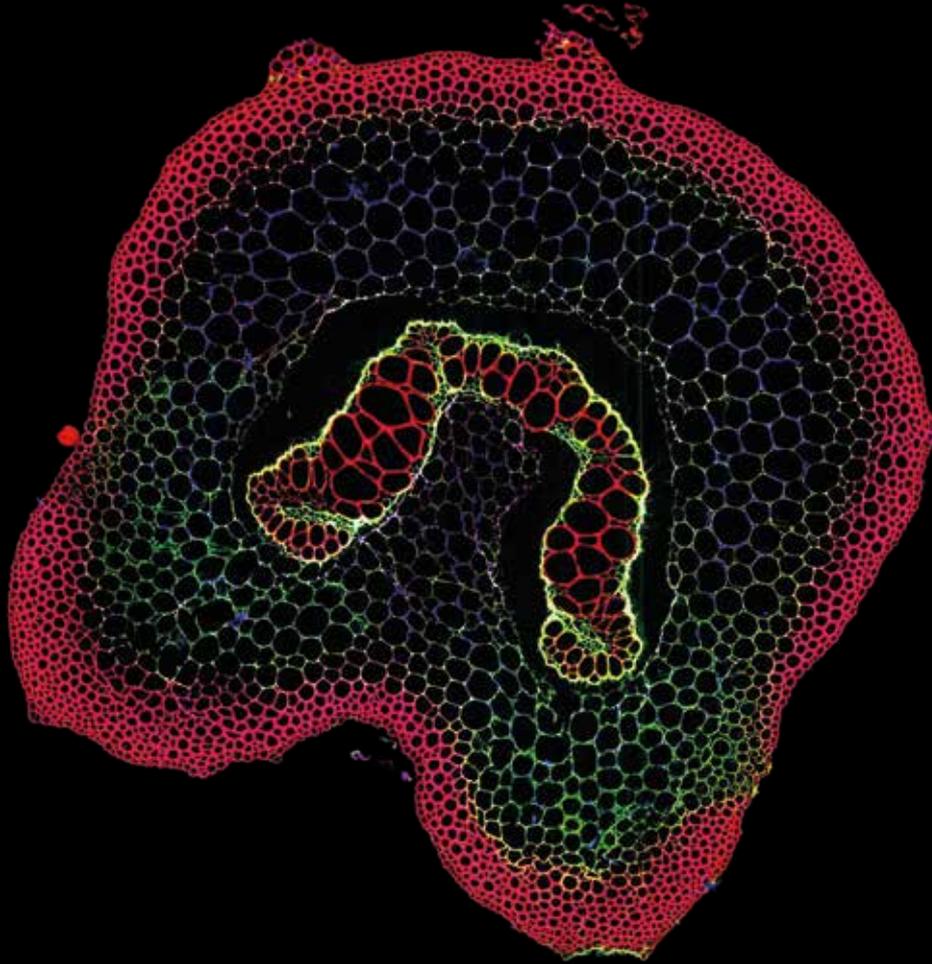
## First place

This image shows the spectacular and fascinating architecture of lung alveoli, consisting of interconnected alveoli, microvessels and capillaries (all in purple) as well as numerous locations of lung macrophages (yellow) engulfed with foreign pollutants (here fluorescent particles in red). The cell nuclei are coloured light blue.

### Second place

Cross section through the stem of the tropical fern *Pteris vittata* with arsenic glowing in bright green

femtoscope



### Third place

This image was created by means of aerial photographs that monitor ice dynamics in the Arctic. The fish-shaped supraglacial lake – i.e. a lake on the surface of the glacier – was located in north-east Greenland. It was drained by a crack in the ice, leaving dust and sediment on the former lake bed.



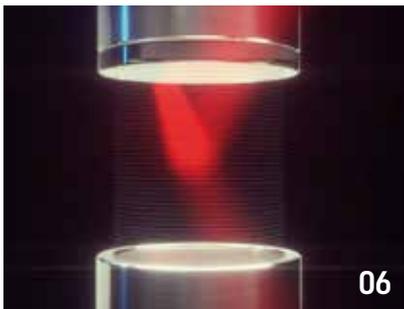
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A stellar moment

Dear readers,

Health research is undergoing rapid changes – in terms of the speed with which research into biological processes is progressing, the speed of medical research and the intelligent combination of high-precision data from high-tech systems with artificial intelligence. In other words, knowledge in the field of life sciences is advancing at a tremendous pace. This calls for a holistic approach, in which highly qualified scientists specialising in fundamental research work together in interdisciplinary partnerships. They need state-of-the-art methods of structural analysis, high-performance X-ray sources and an infrastructure that provides the best possible support for researchers, with everything close at hand and opportunities for networking. All of this inspires and unites the scientists on the DESY campus in the growing field of health research. They are working on the foundations for developing new drugs and vaccines, for example against Alzheimer's and Parkinson's disease, on new, gentle radiotherapy procedures for treating tumours and on innovative materials for implants that could prevent the need for further surgery.

In this issue, we are presenting the sophisticated and in some cases unique methods used for health research at DESY. The idea of taking a closer look at this topic was proposed by our late colleague Till Mundzeck. As one of the creators of femto, he was also the editor-in-chief of this issue. An outstanding science journalist and a highly esteemed colleague at DESY, we owe him a great debt of gratitude. This issue is dedicated to Till.

The femto team,

Diana von Ilseman, Frank Grotelüschen, Barbara Warmbein, Joseph Piergrossi, Ilka Flegel, Jutta Krüger, Cristina Lopez Gonzalez, Thomas Zoufal, Kerstin Straub

# Full blast for laser beams

Innovative concept deflects laser light through air

**T**he patent is already pending: Using a new process that includes the use of loudspeakers, laser beams can be deflected in the air without contact. The invention could have a major impact on research areas such as high-performance optics. The key to the new technology is an invisible optical grating made of air, which is not only immune to damage by the laser beam, but also ensures that the beam does not lose quality.

The grating is created by sound waves that modulate the air in the area crossed by the laser beam.

“We’ve generated an optical grating with the help of acoustic density waves,” explains DESY researcher Yannick Schrödel from the interdisciplinary development team, the main author of the article. Using powerful special loudspeakers, the researchers imprint a striped pattern of dense and less dense areas in the air. Just as layers of air of different

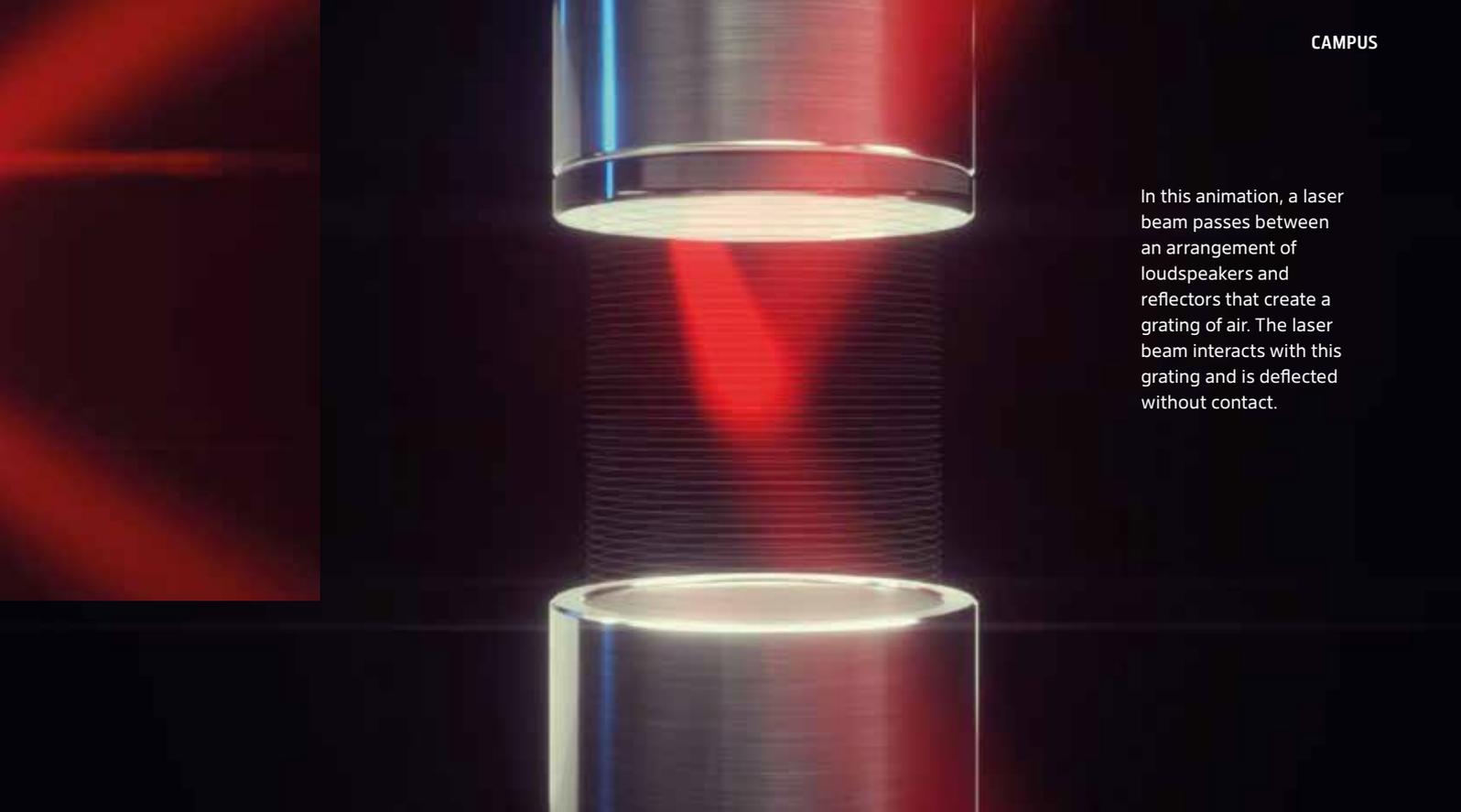
densities deflect light in the Earth’s atmosphere, the density pattern in the air acts as an optical grating that diffracts the laser beam. The deflection of the laser light can be controlled very precisely. “The properties of the optical grating are influenced by the volume of the sound waves,” explains Schrödel.

## Ultrasound instead of shiny mirrors

Initial laboratory tests have shown that a strong infrared laser pulse can be deflected with an efficiency of 50 percent. Based on their modelling, the researchers hope to achieve significantly higher efficiencies in the future. For the first test, the scientists had to crank up their special loudspeakers. “We are dealing with a sound level of around 140 decibels, the equivalent of a jet engine at a distance of just a few metres,” explains research leader Christoph Heyl from DESY and the Helmholtz Institute Jena. “Fortunately, the noise is in the ultrasound range, so the human ear cannot perceive it.”



The development team in the cleanroom working on the acoustic laser optics



In this animation, a laser beam passes between an arrangement of loudspeakers and reflectors that create a grating of air. The laser beam interacts with this grating and is deflected without contact.

The team sees great potential in the technology for high-performance optics. In their experiments, the experts used an infrared laser pulse with a peak power of 20 gigawatts – the equivalent of around six billion LED bulbs. Lasers of this and even higher power classes are used

**“The potential of contactless control of light can currently only be imagined”**

*Christoph Heyl, DESY and Helmholtz Institute Jena*

for material processing, in fusion research or for the latest particle accelerators, for example. “In this power range, the material properties significantly limit the use of mirrors, lenses and prisms, and such optical elements are easily damaged by strong laser beams in practice,” explains Heyl. “In addition, the

quality of the laser beam suffers. In contrast, we’ve managed to deflect laser beams in a quality-preserving way without contact.”

**From grating to lens**

The principle of acoustic control of laser light in gases is not limited to the generation of optical gratings, the scientists emphasise. It can probably also be transferred to other optical elements, such as lenses and waveguides. “We’ve been thinking about this method for a long time and quickly realised that extreme sound levels are necessary. At first, these seemed technically unfeasible,” explains Heyl. “However, we didn’t give up and finally found a solution with the support of the Technical University of Darmstadt and the company inoson. First, we tried out our technique with ordinary air. Next, for example, we will also use other gases in order to tap into other wavelengths and other optical properties and geometries.”

The already demonstrated direct light deflection in ambient

air opens up promising applications, especially as a fast switch for high-power lasers. “The potential of contactless control of light and its extension to other applications can currently only be imagined,” emphasises Heyl. “Modern optics is based almost exclusively on the interaction of light with solid matter. Our approach opens up a completely new direction.”

.....  
*Nature Photonics,*  
*DOI: 10.1038/s41566-023-01304-y*

Using the X-ray pulses from the European XFEL, researchers were able to trigger processes in the nucleus of scandium atoms that can generate a signal with an unprecedented precision of one second in 300 billion years.

# The nucleus sets the pace

## X-ray laser points the way to improved precision timekeeping with nuclear clocks

**C**urrently, no clock measures time as precisely as an atomic clock: Over a period of 300 million years, it is accurate to one second, which is very important for exact positioning in satellite navigation, for example. However, an international research team wants to make the next generation of clocks a thousand times more precise – achieving an accuracy of one second in 300 billion years. The team has now taken a decisive step at the European XFEL X-ray laser: By using the element scandium, the experts have created a much more precise pulse generator.

Atomic clocks make use of a property of electrons: These can be raised to a higher energy level with microwaves of a known frequency. In the process, they absorb the

microwave radiation. The electrons are located in the atomic shell of chemical elements, for example caesium. An atomic clock shines microwaves at caesium atoms and regulates the frequency of the radiation in such a way that the absorption of the microwaves is maximised; experts call this a resonance. The quartz oscillator that generates the microwaves can be kept extremely stable with the help of resonance.

Crucial to the accuracy of an atomic clock is the width of the resonance used – which, however, can practically no longer be improved by exciting electrons. Therefore, teams around the world have been working for several years on the concept of a nuclear clock, which uses transitions in the atomic nucleus rather than in the atomic

shell as the pulse generator. Nuclear resonances are much more acute than the resonances of electrons in the atomic shell, but also much harder to excite.

### Nuclear clocks open up completely new possibilities

At the European XFEL, the team has managed to do just that in the nucleus of the element scandium. In the groundbreaking experiment, the scientists irradiated a 0.025-millimetre-thin scandium foil with X-ray laser light. They were able to detect a characteristic afterglow emitted by the excited atomic nuclei, clearly demonstrating the extremely narrow resonance line of scandium. The new method promises an accuracy of 1:10 000 000 000 000 000 000. “This corresponds to one second in 300 billion years,” explains DESY researcher Ralf Röhlsberger.

The researchers also need to know the exact energy of the X-ray laser radiation at which the resonance occurs, which they were able to achieve through sophisticated, extreme noise suppression and high-resolution crystal optics. “The breakthrough in the resonant excitation of scandium and the precise measurement of its energy opens new avenues not

**“The accuracy corresponds to one second in 300 billion years”**

*Ralf Röhlsberger, DESY and Helmholtz Institute Jena*

only for nuclear clocks, but also for ultrahigh-precision spectroscopy and precision measurements of fundamental physical effects,” explains Yuri Shvyd’ko from Argonne National Laboratory in the USA, the project leader of the experiment. The team is now exploring further steps towards the realisation of such a nuclear clock.

*Nature, DOI: 10.1038/s41586-023-06491-w*

# Highest-energy cosmic gamma rays ever from a pulsar

H.E.S.S. observatory records 20-teraelectronvolt photons from the Vela pulsar

Using the H.E.S.S. observatory in Namibia, an international research team has detected the highest-energy gamma rays ever from a burnt-out, dead star called a pulsar. The detected radiation has around ten trillion times as much energy as visible light. The observation is difficult to reconcile with the current theory on the generation of such pulsed gamma rays.

Pulsars are the left-over corpses of stars that spectacularly exploded in a supernova. The explosion leaves behind a tiny, dead star with a diameter of just some 20 kilometres, rotating extremely fast and endowed with an enormous magnetic field. “These dead stars are almost entirely made up of neutrons and are incredibly dense: A teaspoon of their material has a mass of more

than five billion tonnes, or about 900 times the mass of the Great Pyramid of Giza,” explains H.E.S.S. scientist Emma de Oña Wilhelmi, a co-author of the publication working at DESY.

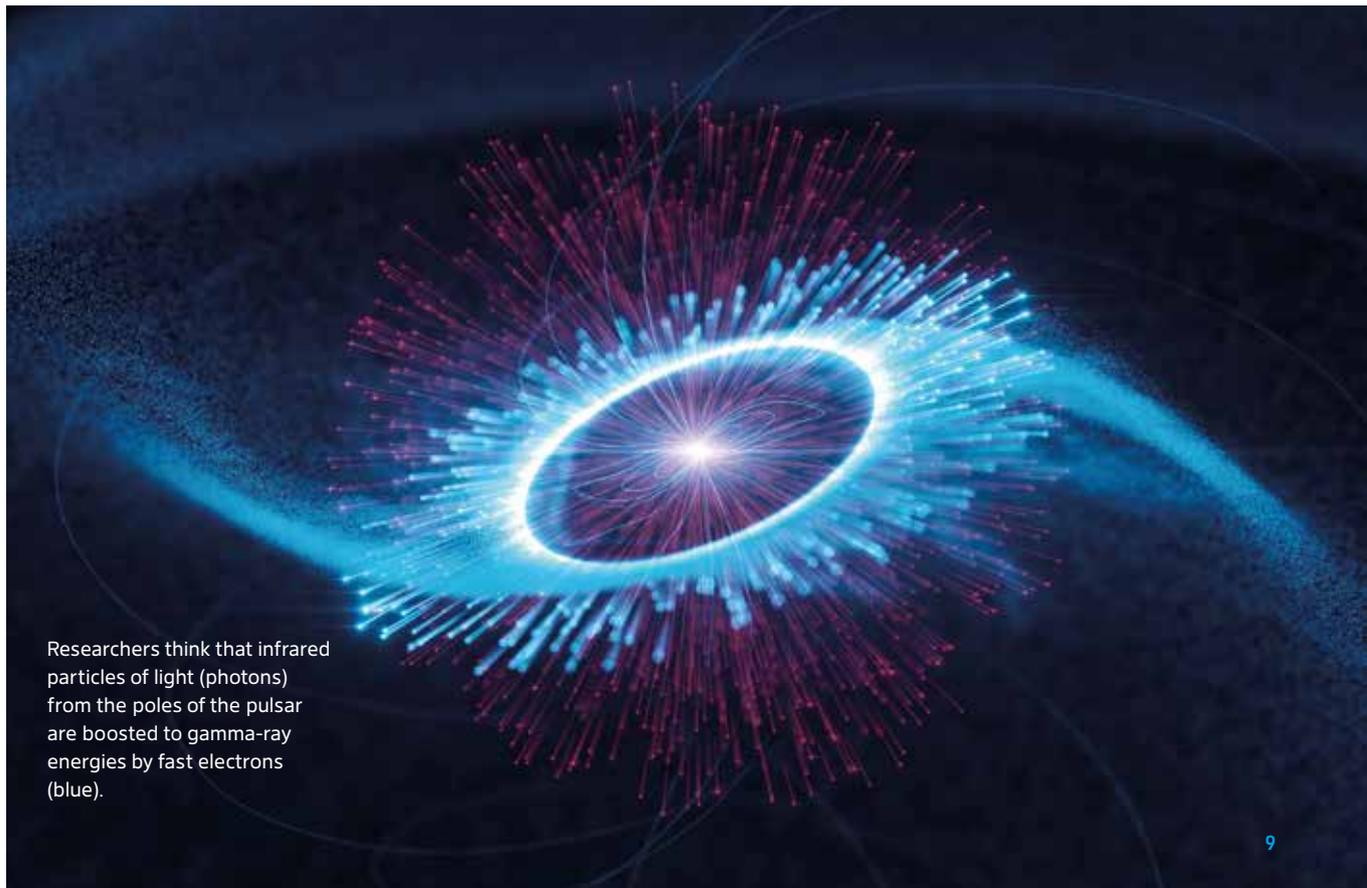
## The brightest pulsar lighthouse

Pulsars emit rotating beams of electromagnetic radiation, somewhat like cosmic lighthouses. If their beam sweeps across our solar system, we see flashes of radiation at regular time intervals. These flashes can be observed at various wavelengths of the electromagnetic spectrum, from radio waves to gamma rays. According to current theory, the radiation originates from fast electrons that are accelerated and deflected by the pulsar’s strong magnetic fields while they are

moving outwards from the surface of the pulsar to the edge of its magnetosphere. “On their outward journey, the electrons acquire energy and release it in the form of the observed radiation beams,” says Bronek Rudak from the Nicolaus Copernicus Astronomical Center (CAMK PAN) in Poland, also a co-author. The area in which this happens is called the light cylinder.

The Vela pulsar, located in the Southern sky in the constellation Vela (sail of the ship), is the brightest pulsar in the radio band of the electromagnetic spectrum and the brightest persistent source of cosmic gamma rays in the giga-electronvolt (GeV) range. It rotates about 11 times per second. However, above a few GeV, its radiation ends abruptly, presumably because the electrons reach the end of the

»



Researchers think that infrared particles of light (photons) from the poles of the pulsar are boosted to gamma-ray energies by fast electrons (blue).

pulsar's magnetosphere and escape from it.

### Impossible to explain with conventional models

But it turns out that this is not the end of the story: H.E.S.S. has recorded a new radiation component at even higher energies. These cosmic gamma rays have energies of up to 20 teraelectronvolts (TeV). "That is about 200 times more energetic than all radiation ever detected before from this object," says co-author Christo Venter from the North-West University in South Africa. This newly discovered component appears in synchronisation with the radiation observed in the GeV range. However, to attain these enormous energies, the electrons would have to be accelerated more strongly than is actually possible in the

magnetosphere. And the rotational emission pattern would need to remain intact.

"This result challenges our previous knowledge of pulsars and requires a rethinking of how

magnetosphere cannot sufficiently explain our observations. Perhaps we are witnessing the acceleration of particles through the so-called magnetic reconnection process beyond the light cylinder, which still

**"This result challenges our previous knowledge of pulsars and requires a rethinking of how these natural accelerators work"**

*Arache Djannati-Atai, Astroparticle and Cosmology laboratory (APC), France*

these natural accelerators work," says Arache Djannati-Atai from the Astroparticle and Cosmology laboratory (APC) in France, who led the research. "The traditional scheme according to which particles are accelerated along magnetic field lines within or slightly outside the

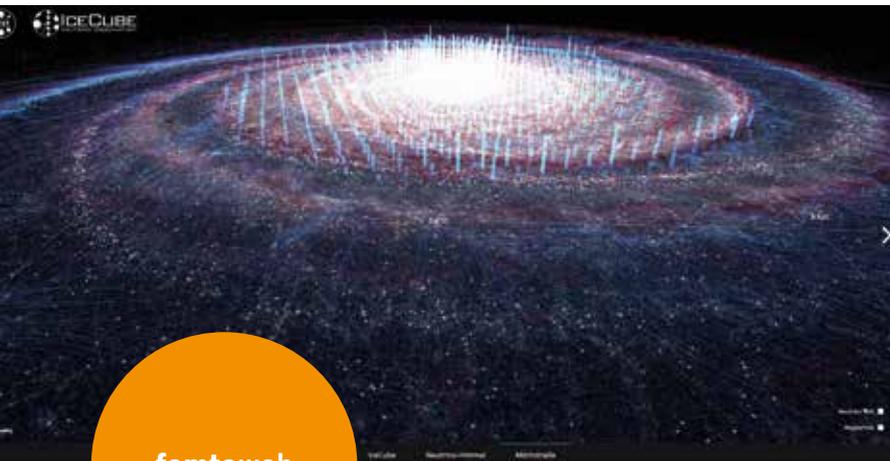
somehow preserves the rotational pattern? But even this scenario faces difficulties to explain how such extreme radiation is produced." Theorists therefore have to develop new models.

### Searching for other pulsars

Whatever the explanation for this mysterious radiation, the Vela pulsar – alongside its other superlatives – now officially holds the record as the pulsar with the highest-energy gamma rays discovered to date. "This discovery opens a new observation window for the detection of other pulsars in the tens of teraelectronvolt range with current and upcoming more sensitive gamma-ray telescopes, hence paving the way for a better understanding of the extreme acceleration processes in highly magnetised astrophysical objects," says Djannati-Atai.

*Nature Astronomy,*

*DOI: 10.1038/s41550-023-02052-3*



femtoweb

## Computer safari through the Milky Way

The award-winning Science Communication Lab in Kiel has created an interactive module for DESY to visualise the IceCube observations of galactic neutrinos (see "A new view of our cosmic home", right). Viewers can navigate through the neutrino data in the Milky Way and compare the neutrino distribution with electromagnetic radiation from our home galaxy at different wavelengths. The IceCube detector can be explored as well.



<https://neutrino-map.science>

**Neutrinos from the Milky Way:**

Bright areas symbolise measurements with high significance, dark areas those with low significance.

# A new view of our cosmic home

## The IceCube detector in the Antarctic captures neutrinos from the Milky Way

Using the IceCube observatory at the South Pole, researchers have for the first time detected neutrinos from our home galaxy, the Milky Way. Neutrinos are elementary particles that usually originate from high-energy processes in space and effortlessly penetrate all matter. With their help, we can learn more about the processes in which the neutrinos are generated.

Neutrinos are ubiquitous: From the nuclear fusion reactions in the sun alone, about 60 billion of these ghostly elementary particles pass through us unnoticed every second – per square centimetre, that’s about the area of a thumbnail. Neutrinos hardly ever interact with the matter they pass through.

To nonetheless be able to observe neutrinos from the cosmos, researchers have set up the world’s largest neutrino detector in the perpetual ice of Antarctica: IceCube lies below the surface and encompasses an entire cubic kilometre of ice, in which it scouts for the extremely rare neutrino reactions. From the light trail that a neutrino occasionally produces after interacting with the ice, its direction of origin and energy can be determined.

### Where are the Milky Way’s neutrino sources?

Nevertheless, the neutrino signal from our Milky Way is not easy to detect. “What’s intriguing is that – unlike the case for light of any wavelength in the electromagnetic spectrum – in the neutrino regime, the distant universe far outshines the nearby sources in our own galaxy,” says Francis Halzen, a professor at the University of Wisconsin–Madison in the USA and principal investigator of IceCube. It took a sophisticated analysis of some 60 000 neutrino events recorded over ten years, to which artificial intelligence methods made a crucial contribution, to isolate the neutrino panorama of our Milky Way.

The energy of the neutrinos now detected by IceCube is many millions of times greater than the energy of the steady neutrino stream from nuclear fusion reactions in the sun. Thus, they clearly do not originate from the stars of the Milky Way itself. “Now the next step is to directly identify specific neutrino sources within our galaxy,” says Ignacio Taboada, a professor at the Georgia Institute of Technology in the USA and IceCube spokesperson.

From the search for the neutrino sources, the researchers

also hope to learn something about the sources of so-called cosmic rays, a shower of electrically charged atomic nuclei that bombards the Earth uniformly from all directions. Sources of the energetic neutrinos may also be sources of cosmic rays, which still have not been satisfactorily elucidated more than 100 years after the phenomenon was discovered.

*“In the neutrino regime, the distant universe far outshines the nearby sources in our own galaxy”*

*Francis Halzen, University of Wisconsin–Madison, USA*

“The new IceCube observations open a new window on the Milky Way and give us confidence that we can use neutrinos to identify the sources of cosmic rays in our galaxy in the coming years,” underlines Marek Kowalski, leader of the IceCube group at DESY and a professor at Humboldt University Berlin.

Science, DOI: 10.1126/science.adc9818

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Deciphering the  
building blocks of life

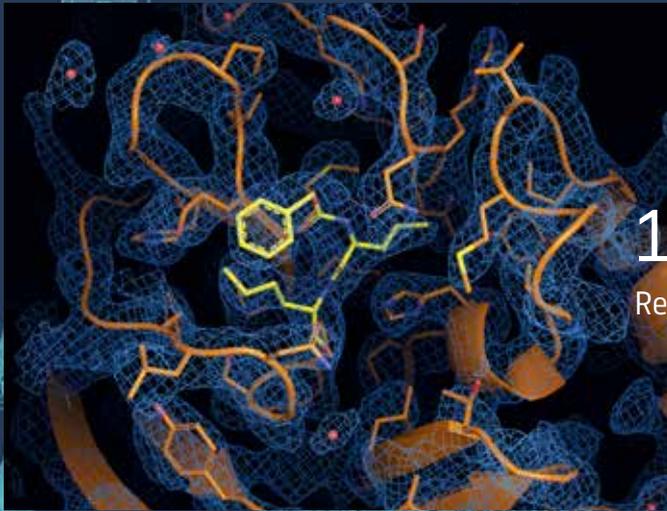
# Life sciences

## Human beings at the centre of intelligent research

Over the years, medicine has made enormous progress. And the developments go on. The aim is to devise drugs that are more effective and have fewer side effects, vaccines that offer perfect protection against infectious diseases and radiotherapy that targets tumours more precisely. DESY and its partners are laying the foundations for these developments – with a toolbox that offers a wide range of sophisticated and in some cases unique methods.

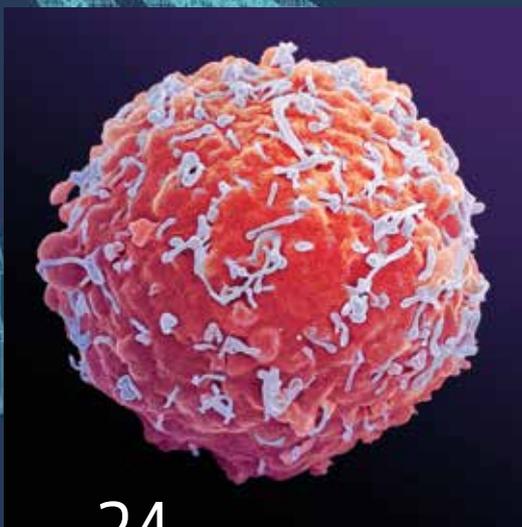
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reactions

# Proteins, vaccines and sticky biofilms

Various teams on the DESY campus are conducting health research

The atomic structure of proteins can be deduced from the diffraction pattern of X-rays scattered by the protein crystal. The regular pattern of the atoms forming the crystal lattice produces strong reflections in the diffraction pattern, represented here by coloured spheres.

**P**eering down the microscope, we see crystals with sharp corners and edges, somewhat like tiny gemstones. In reality, though, these are the objects of biomedical research. The microscope is located at the outstation of the European Molecular Biology Laboratory (EMBL) in Hamburg. It is part of a measuring station at one of the most powerful X-ray sources in Europe: the particle accelerator PETRA III on the DESY campus in Hamburg Bahrenfeld.

The colourful crystals consist of proteins – essential building blocks of life. In a moment, they will be carefully positioned on a high-precision rotating table, before PETRA III's narrowly focused X-ray beam is aimed at one

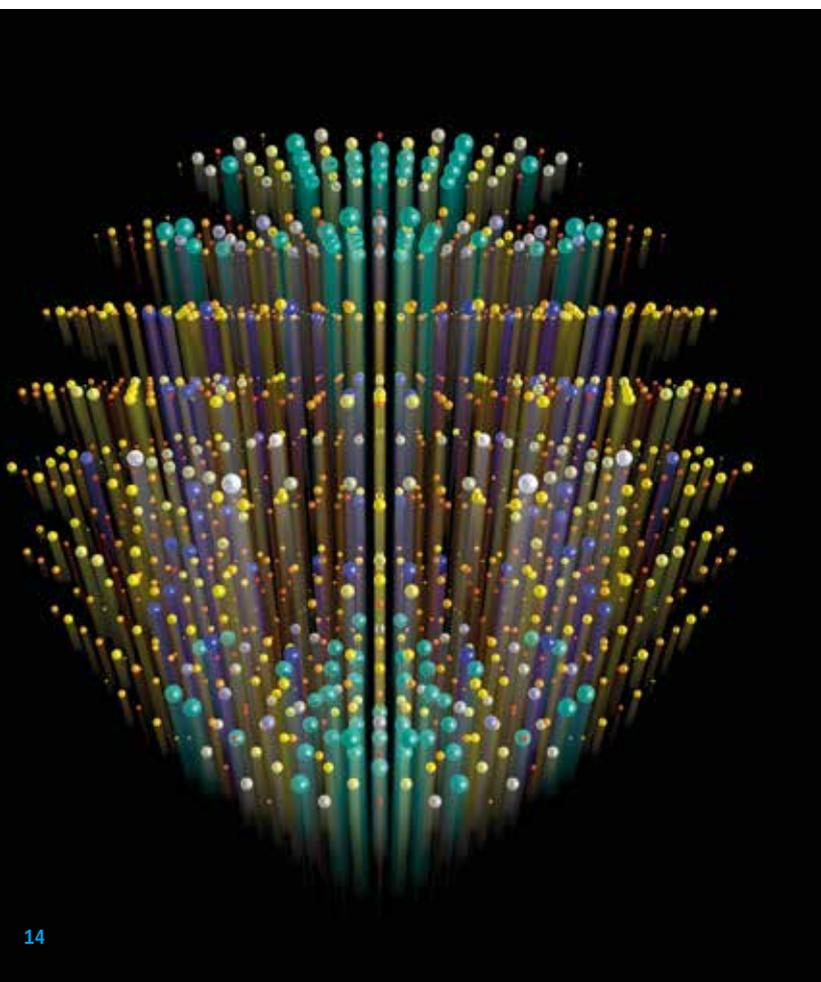
of the tiny objects. The miniature crystal deflects the beam slightly, creating a jumbled pattern of dots that is picked up by an X-ray detector. This is then analysed by a computer: Sophisticated algorithms convert the pattern of dots into a detailed image of the protein under investigation – a complex architecture of different groups of atoms linked by chemical bonds.

This method, known as protein crystallography, provides invaluable services to biomedicine. It can resolve the three-dimensional structure of an enzyme in great detail, sometimes down to the atomic level. Information like this is vital to the life sciences: Only by knowing the exact structure of a protein is it possible to determine the details of how it functions. Experts can use this information to identify targets for better drugs – such as binding sites that a new drug might block, thereby disabling a harmful viral protein.

## Detailed view of tuberculosis protein

In 2009, three scientists were awarded the Nobel Prize in Chemistry for a breakthrough they achieved using this method. The three, among them the Israeli biochemist Ada Yonath, had worked out the structure of the ribosome – a protein complex that serves as the body's protein factory. Yonath had done significant preliminary investigations at DESY, among other places. "I admire Ada Yonath for her patience," says EMBL researcher Matthias Wilmanns. "Analysing the ribosome was extremely difficult and time-consuming." Nowadays, though, other, more modern methods would be used.

Matthias Wilmanns's group too has managed to determine the structures of numerous proteins over the decades, in particular from the genome of the bacterium that causes tuberculosis. For some time now, the toolbox available to experts has been growing; entirely new methods have been added to it. "In recent years, we have seen a real revolution in structural



biology,” says Wilmanns enthusiastically. “On the one hand, there are AI algorithms that can calculate the shape of proteins with astonishing accuracy. On the other hand, a new technology can now also provide detailed images of proteins: the cryo-electron microscope.”

Wilmanns’s team achieved something remarkable with it: They determined the structure of a protein complex used by the bacterium *Mycobacterium tuberculosis* to introduce key substances for infecting the human body.

“With the help of cryo-electron microscopy, we were able to image this protein complex in such a way that every single atom could be discerned,” explains Wilmanns. “That was incredible; ten years ago, I would have said that’s impossible.”

In the meantime, the data have been published. They could give the developers of



“In recent years, we have seen a real revolution in structural biology”

Matthias Wilmanns, EMBL

tuberculosis drugs important clues as to which sites in the protein complex a new antibiotic might target to stop the infection process. In principle, Wilmanns emphasises, the two methods complement each other: The cryo-electron microscope is suitable for analysing relatively large protein complexes, but also viruses and even cells. Crystallography at the accelerator can be used to visualise smaller biomolecules in particular with high precision and to see how they interact with other substances, such as potential drugs.

EMBL in Hamburg also resorts to another method – small-angle X-ray scattering. This allows biomolecules to be analysed in solution, which more closely resembles their natural

>>

## ULTRACOLD, RAZOR-SHARP IMAGES

### How cryo-electron microscopes capture proteins and viruses

In the basement of the Centre for Structural Systems Biology (CSSB), Carolin Seuring points to a slit in the floor: “That’s where the special, vibration-damped foundations begin,” explains the biochemist. “They shield our microscopes from vibrations so that they can capture high-resolution images.” The microscopes that Seuring is in charge of are room-sized high-tech behemoths, each costing several million euros. Instead of light, they use electron beams. Because the temperature inside them reaches minus 150 degrees Celsius, experts refer to them as cryo-electron microscopes.

The technological breakthrough took place some ten years ago, when cameras were invented that could detect electrons directly and with great precision. Image resolutions increased tenfold as a result, making it possible to distinguish individual atoms. In 2017, the Nobel Prize in Chemistry was awarded for this advance, which is now being used by research teams around the world.

#### Shock-frozen proteins

The principle is as follows. An electron beam strikes a sample containing a protein, for example. To prevent the protein from being destroyed, it must first be shock-frozen. At the preparation benches, the researchers use special tweezers and liquid nitrogen to freeze their samples without allowing any ice crystals to form – because these could destroy the delicate structures. “The humidity in our laboratory is only 20 percent,” explains Seuring. “This helps us to freeze our millimetre-sized samples uniformly without significant contamination.”

The samples are then placed in a holder, 12 in each cassette. To prevent them from melting, the cassette is stored in a kind of thermos flask filled with liquid nitrogen. Seuring grabs the container, which is about the size of a coffee mug, and carries it over to the next room. She opens the casing of the microscope, revealing the inner workings: a vertical, evacuated tube for the electron beam, fitted with valves and surrounded by cables.

The scientist slots the deep-freeze container into a recess. A mechanism pulls the cassette upwards, ready to record the image. Electrons pass through the sample and are deflected by it. A detector records the deflection pattern and stores the data in the computer. “Thousands of images can be recorded every day,” says Seuring. “That’s two to three terabytes per data set, which are analysed with the help of our computing cluster.” The result is extremely detailed images of enzymes and protein complexes, of viruses and cells – the whole gamut of biological objects involved in an infection, the main topic of interest at CSSB.



Ruler over the ultracold microscopes: Carolin Seuring is the head of the cryo-electron microscope facility at CSSB.

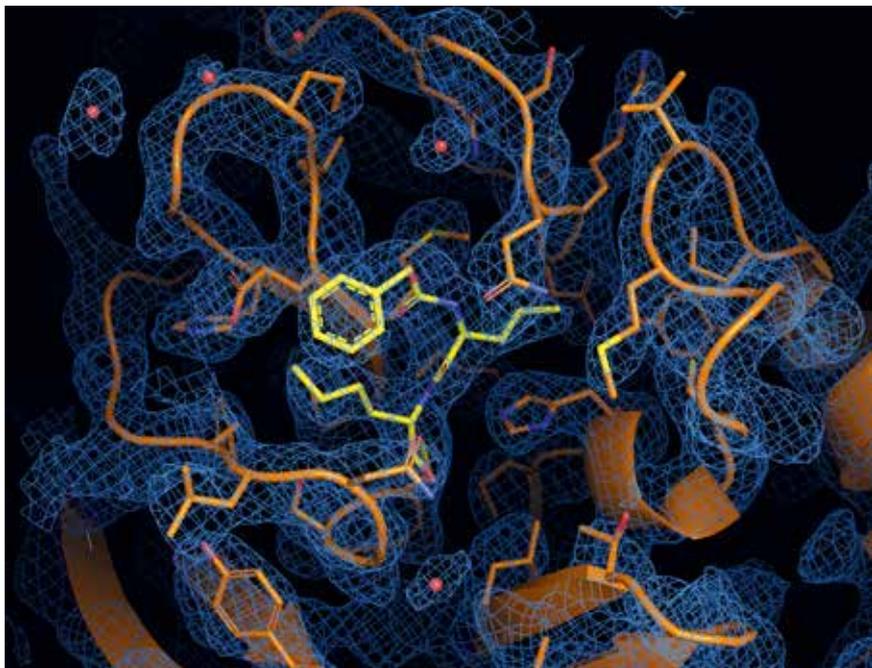
state. The method is a very useful supplement to crystallography and cryo-electron microscopy and can also provide insights into the structures of unfolded regions. Using this technique, EMBL and the Mainz-based company BioNTech were able to analyse the shape of so-called nanolipids. These serve as carriers for mRNA vaccines – and were a vital prerequisite for BioNTech’s COVID-19 vaccine.

“Our work helped to improve the biophysical properties of these particles,” explains Wilmanns. “This will have helped BioNTech to bring the vaccine to market as quickly as they did.” And the collaboration continues. In their latest joint project, the partners used small-angle scattering to determine the amount of mRNA contained in the nanolipid cages – potentially useful information for the company to improve its vaccines.

### Wide-ranging research setting

In recent years, the life sciences have become increasingly important at DESY. The Centre for Structural Systems Biology (CSSB), an interdisciplinary centre focusing on the biology of infections and involving various universities and research institutions, has been established on the campus in Hamburg Bahrenfeld. Universität Hamburg has put up a laboratory building, HARBOR, where the behaviour of molecular biological systems over time is studied. And the extremely powerful X-ray laser pulses from the European XFEL, in which DESY is a major stakeholder, are also used to analyse biological samples.

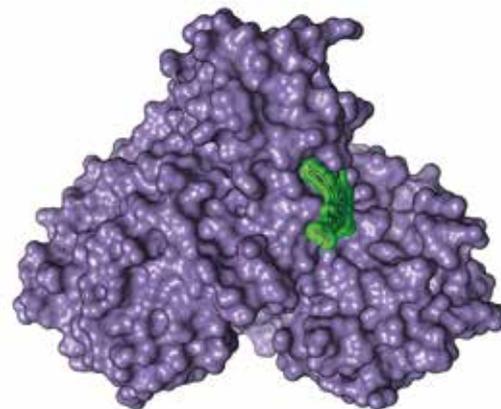
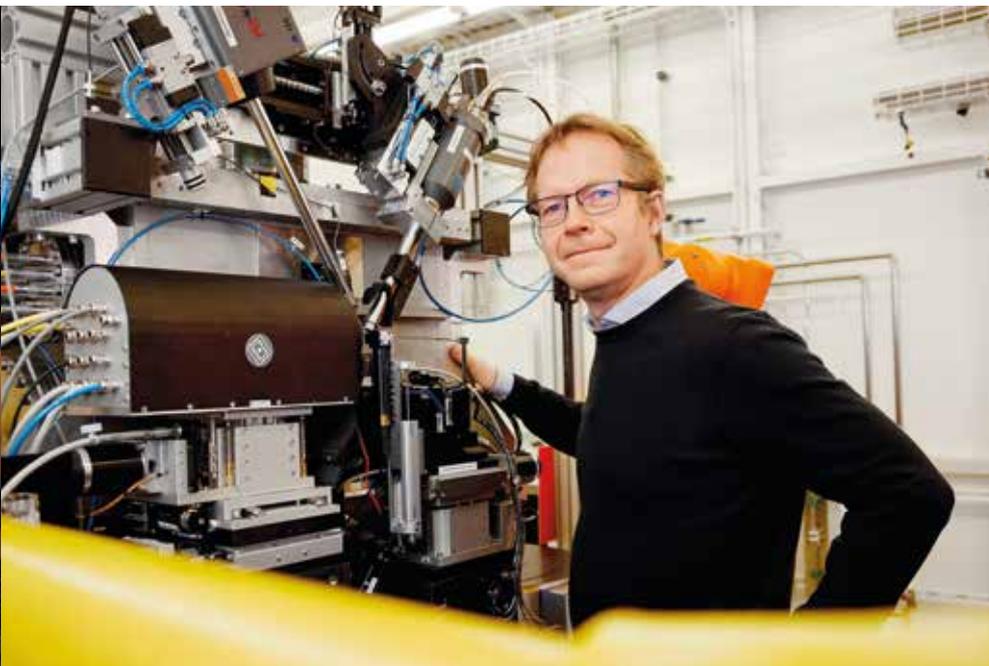
In addition, DESY is currently stepping up its cooperation with biomedical research institutions, such as the University Medical Centre Hamburg-Eppendorf, the Leibniz Institute of Virology and the Bernhard Nocht Institute for Tropical Medicine. Two start-ups are now also offering their services: BIOSAXS uses small-angle scattering to analyse medically relevant macromolecules for companies. And CrystalsFirst supports drug research by performing a targeted, AI-supported search for new active pharmaceutical ingredients.



## Searching for the superdrug

For some time now, experts have been using protein crystallography to systematically search for new drugs, for example against infectious diseases. The principle is straightforward. Thousands of drug candidates are combined with the protein they are meant to target and allowed to crystallise. The crystals are then irradiated with intense X-rays from DESY’s X-ray source PETRA III. The resulting data can be used to determine whether and how many of the drug candidates have bound to the protein.

This method was used at the beginning of the COVID-19 pandemic. A team led by DESY researcher Alke Meents managed to analyse almost 8000 crystals within a short time, each involving a different, already known drug candidate. And indeed, as Meents explains, “we found substances that bind to a specific protein in the virus, the main protease. If a drug could block this, it would disable the virus.” Closer examination of one promising drug candidate, calpeptin, revealed that it not only binds to the main protease of the virus, but also to the human protein cathepsin L, which the virus uses to enter human cells. As it turned out, calpeptin



The antiviral drug calpeptin (yellow) has attached itself to the main protease of the coronavirus (left). DESY researcher Alke Meents in front of his experimental apparatus at the X-ray source PETRA III (centre). The drug pelitinib (green) also binds to the main protease of the coronavirus (right).

blocks both the function of the main protease and that of cathepsin L, thus further inhibiting viral replication.

However, calpeptin appears to be unsuitable for routine COVID-19 treatment because of its expected side effects. Nevertheless, it could be used to treat other, much more serious viral diseases having a similar mechanism of infection: Ebola, for example, where side effects are less of a concern. “We are working with a research team in South Africa to see whether calpeptin can prevent the Ebola virus from entering cells,” explains Meents. Ideally, this could alleviate the threat of this often fatal disease. The experts also want to work with the Bernhard Nocht Institute for Tropical Medicine to see whether they can identify drug candidates against hantaviruses and Lassa viruses – pathogens that can cause epidemics or even pandemics.

### Screening within minutes

A new screening method currently being developed by the DESY team should be helpful in such investigations. Until now, each crystal has had to be individually positioned by a robotic arm so that the focused X-ray beam strikes it in just the right way. The protein crystal has to be cooled to extremely low temperatures to prevent it from being damaged by the intense X-rays. “Our new method allows us to grow hundreds of thousands of crystals simultaneously on a chip,” explains Meents’s colleague Sebastian Günther. “This chip can then be X-rayed in a single operation without

having to cool it, that is, at room temperature.” In a recent pilot experiment, the group demonstrated that the method works and that it achieves the same resolution as the conventional method – a breakthrough.

“The new method can largely be automated and will significantly speed up the screening process,” Günther points out. “We can test many

*“The new method means we can test many more drug candidates than before in the same amount of time”*

**Sebastian Günther, DESY**

more drug candidates than before in the same amount of time.” DESY’s planned X-ray source PETRA IV should even allow a protein crystal chip to be tested in a matter of minutes – an extremely interesting prospect not just for fundamental research but also for pharmaceutical companies looking for new, more effective drugs.



# Watching **proteins** at work

**W**hat is the sequence of events during a biochemical reaction? How does a crucial enzyme do its job? Radiation from X-ray sources like PETRA III can help answer these questions. By taking repeated measurements over time, it is possible to observe proteins reacting with other substances almost like watching a film. Such experiments require sophisticated, yet user-friendly methods. Developing such procedures is one of the tasks of HARBOR, the Hamburg Advanced Research Centre for Bioorganic Chemistry, which opened on the Hamburg Bahrenfeld campus in 2020. HARBOR is home to Universität Hamburg's Cluster of Excellence "CUI: Advanced Imaging of Matter" and works closely with local research institutions.

*"The corrected data were used by drug researchers"*

*Arwen Pearson, Universität Hamburg and CFEL*

One of the challenges is to trigger a biochemical reaction at just the right moment so that it can be observed. The HARBOR groups led by Pedram Mehrabi and Eike Schulz are developing several methods in collaboration with EMBL and the Max Planck Institute for the Structure and Dynamics of Matter. One of these is a sophisticated mixing technique: Tiny droplets are sprayed onto the previously crystallised protein through a fine nozzle. The droplets contain a ligand that reacts with the protein. Because the crystals are only 10 to 20 micrometres across, the droplets can rapidly penetrate them. The biochemical reaction begins – starting the stopwatch for the X-ray image at PETRA III's T-REXX measuring station.

## Swift nozzle

"This method can be used to track reactions that take place within milliseconds," explains biophysicist Arwen Pearson as she starts a video demonstrating the process. A magnified image of a silicon chip appears, with a chequered surface. Each square contains a microscopic protein crystal. "That shadow is a small piezoelectric nozzle," says Pearson. "The nozzle scans across the squares, spraying a droplet of the ligand onto the crystal in each square – those are the dark patches." The ingenious spitting mechanism is aptly named: LAMA.

Andrea Thorn's HARBOR team took on another important task, right in the middle of the COVID-19 pandemic. In order to fight the pandemic effectively, numerous research teams around the world were measuring the structure of the virus proteins and immediately publishing their findings. Some mistakes and inaccuracies crept in because of the time pressure. To deal with these, Thorn launched the Coronavirus Structural Task Force, a team of predominantly young researchers from around the world. It systematically reviewed all the newly published structures, identified shortcomings and made sure the data were supplemented and corrected. "The corrected data were then used by drug researchers," says Pearson. "So the work of the task force probably had a positive impact on overcoming the coronavirus crisis."





## "WE ARE SEEING A **RAPID TRANSFORMATION**"

**The life sciences are currently undergoing a significant transformation. Our understanding of how biological processes unfold at the level of individual molecules is rapidly growing. Experimental research and artificial intelligence are working hand in hand, explains Helmut Dosch, Chairman of DESY's Board of Directors.**

**femto:** Mr Dosch, what will health research look like in the future?

**Helmut Dosch:** We are currently seeing a rapid transformation in the life sciences. AI methods make it possible to carry out investigations at the molecular level that were previously unthinkable. Today, programs like AlphaFold can predict the spatial structure of proteins and thereby contribute enormously to our understanding of the machinery of life. This means that drug molecules can be pre-designed and pre-tested on a computer, which speeds up the development of new drugs enormously.

**femto:** Until now, the spatial structure of biomolecules has been determined using X-rays or electron microscopes. Will AI make this kind of equipment obsolete?

**Helmut Dosch:** On the contrary! AI depends on this type of experimental data. AlphaFold needs the data from high-resolution structural analyses in order to learn. This data should, of course, be of very high quality. That's why we are building a database of high-resolution analyses and feeding them to the AI; that then creates a kind of digital twin of the molecule to be used as input for further investigations. In the end, we have to optimise the structures at a molecular level. To do this, we need high-brilliance X-ray sources and specialised cryo-electron microscopes.

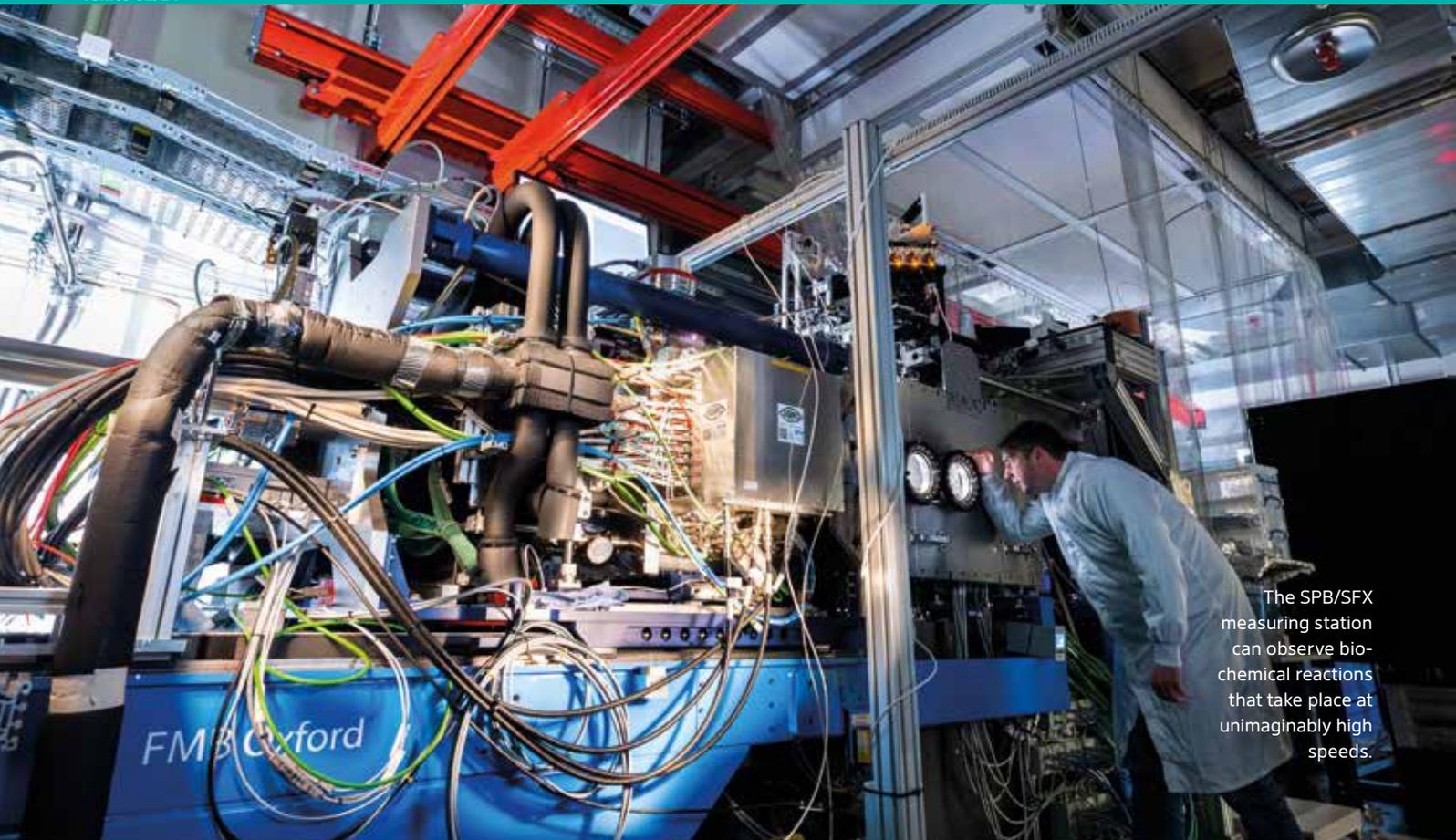
**femto:** In other words, measurement and simulation go hand in hand?

**Helmut Dosch:** Yes, and that's what makes our location in the Science City Hamburg Bahrenfeld so unique. We have all the tools for carrying out structural analyses – not just of proteins – and the AI expertise here on campus, both in house and through our partners. In other words, there are a number of X-ray sources, such as PETRA III and, in future, PETRA IV, the X-ray lasers FLASH and European XFEL, as well as cryo-electron microscopes. There are also partners such as EMBL, which co-developed

AlphaFold, and institutes such as CSSB, which brings together nine partners in the field of life sciences, as well as specialised laboratories for protein processing. You won't easily find such opportunities and concentrated expertise anywhere else in the world.

**femto:** Are they primarily used for fundamental research, or do medical applications also benefit, for example?

**Helmut Dosch:** Those two aspects cannot be separated. Firstly, we and our partners are doing fundamental research here, of course. I also see our analytical capabilities as a precautionary measure, to prevent further pandemics, for example. X-ray structural analysis allowed the central proteins of the coronavirus to be decoded extremely quickly. We then screened thousands of existing drugs in a fast-track procedure to see whether they could help fight the coronavirus – no other method could have done this so quickly. The mRNA vaccine against the virus consists of small snippets of genetic material that are delivered to our body's cells in tiny envelopes made of lipid molecules. How can this envelope be designed such that it can pass through the body intact, enter the cell and reliably release its payload once it gets there? That's no trivial task. Vaccine manufacturers used DESY's X-ray sources to study how these lipid beads, which ferry the mRNA snippets, could be optimised. In future, this could also be used for a vaccine against cancer, which would introduce cancer drugs into tumour cells by the same route. We have proposed to set up a comprehensive analytical centre at DESY. That would not only support health care, but would also make an important contribution towards developing new materials, which are analysed and designed at the molecular level just as drugs and proteins are today.



The SPB/SFX measuring station can observe biochemical reactions that take place at unimaginably high speeds.

## Short pulses for **high-speed imaging**

**A**nother facility in which DESY plays a key role also specialises in the analysis of fast bioreactions. Since 2017, the European XFEL X-ray free-electron laser has been producing what are currently the most powerful X-ray pulses in the world. It is based on a kilometre-long, superconducting linear accelerator, which accelerates electron bunches to almost the speed of light before sending them down long magnetic structures. The magnetic fields force the electrons to follow a precise undulating trajectory, which causes them to emit extremely powerful X-ray pulses. “The pulses are exceedingly short, 10 000 times shorter than those produced by a synchrotron like PETRA III,” explains Sakura Pascarelli, Scientific Director at European XFEL. “This allows us to track extremely rapid biological processes.”

### Rapid photosynthesis

Many things in nature happen very rapidly – for example when light is involved. When a ray of sunlight hits a plant, it can produce an electric charge in a receptor molecule within just a few femtoseconds (quadrillionths of a second). “This

charge then moves to a different region of the protein,” says Pascarelli. “Here, the plant is able to split water, and photosynthesis can take place.” A detailed understanding of these processes would make it possible to develop new types of biocatalysts in the future, for example in medicine or food technology.

Another advantage of the extremely powerful X-ray pulses is that only comparatively small protein crystals are needed to determine the exact shape of the biomolecules. This is a big advantage especially when studying protein molecules, which are reluctant to form crystals – such as medically relevant membrane proteins that transport vital substances into and out of a cell. Some bacteria even produce tiny nanocrystals naturally. These are used as insecticides in agriculture and can also be studied in detail at the European XFEL. In addition, the experts are working on how to analyse individual proteins using X-ray pulses. If their efforts are successful, proteins would no longer need to be grown into crystals – an invaluable advantage. However, the radiation produced at the European XFEL is so intense that a single pulse is enough



“The exceedingly short X-ray pulses allow us to track extremely rapid biological processes”

Sakura Pascarelli, European XFEL

to completely destroy a biosample. “Fortunately, by the time this happens, the X-rays have already passed through the sample, so the shot is in the can,” explains Pascarelli.

### Protein beams as fine as a hair

In an underground experimental hall the size of a football pitch in Schenefeld, Schleswig-Holstein, Pascarelli’s colleague Richard Bean shows us what the experiments look like. One of the massive containers houses the SPB/SFX measuring station, where most of the biomedical experiments at the European XFEL are performed. “It looks pretty complicated,” admits Bean. “A long apparatus made up of lots of metal boxes, connected by countless cables and wires.” But the principle is quite simple: The X-ray pulses are fired into the apparatus through a vacuum tube in the front wall and strike the sample in the centre, usually a tiny crystal of proteins. The pulses are deflected by the molecules and recorded by a detector, a shiny silver monster that can take up to 3500 pictures per second. Computer algorithms then process the recorded diffraction patterns to produce images in which, ideally, every single atom of the protein can be distinguished.

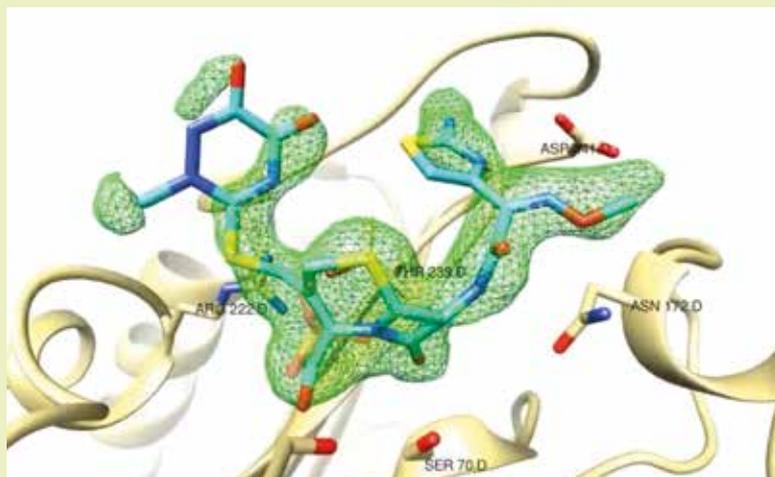
The biggest challenge when doing the experiments is this: “Because the crystals only survive a single shot, we constantly have to add new crystals,” explains Bean. “We do this by firing a fine jet of liquid from above, which contains the protein crystals.” The X-ray pulses intersect this stream of liquid in the centre of the chamber, typically every 900 nanoseconds (billionths of

a second). But the micrometre-fine jet of liquid is tricky to manipulate: Sometimes the protein crystals clump together, clogging the tiny, 3D-printed precision nozzles. The protein supply is interrupted and the crew has to intervene.

### Resistant to antibiotics

One research team at the European XFEL was able to perform a remarkable experiment. The team, which included members from DESY and the US universities of Cornell, Wisconsin-Milwaukee and Arizona, was able to monitor how the bacterium that causes tuberculosis disables an antibiotic. Experts have known for some time that the microbe uses a specific enzyme to do this: beta-lactamase. However, the team was able to watch the extremely rapid reaction between the enzyme and the antibiotic in slow motion. “This was only possible at the European XFEL because the facility can be used to analyse very small protein crystals,” explains DESY researcher Henry Chapman. “And we needed small crystals in order to capture the reaction between the antibiotic and the enzyme.”

Combined with other studies, the experts now have a detailed picture of how beta-lactamase deactivates the drug. “This gives us clues as to how the antibiotic might be modified to prevent the enzyme from cracking it,” explains Chapman’s colleague Dominik Oberthür. “We could also develop molecules that inhibit the enzyme effectively.” This could restore the efficacy of conventional antibiotics; ideally, the enzyme that blocks them would be rendered harmless. >>



**The enzyme beta-lactamase in the bacteria that cause tuberculosis** reacts with the antibiotic ceftriaxone. The reaction is extremely rapid. The high repetition rate of the pulses produced by the European XFEL, combined with a special injection technique, makes it possible to track the initial stages of the binding process in real time.

Working with researchers from Universität Hamburg and the University Medical Centre Hamburg-Eppendorf, Oberthür is developing methods of searching for such inhibitors using time-resolved techniques also at a synchrotron such as PETRA III – in this case, the scientists are interested in a different enzyme, also a lactamase. “We have found that compounds produced by boronic acid and its chemical relatives are very interesting,” says Oberthür. The team is now planning to do further experiments to test the suitability of these compounds in more detail.

However, “one of the current limits for drug screening at PETRA III is the throughput; the best measuring stations can record 800 data sets per day,” says Oberthür. “But we have designed a conveyor belt system that should allow us to collect 10 000 data sets per day in the future – this could make the method increasingly interesting for pharmaceutical companies as well.” And the people behind AI algorithms such as AlphaFold are also likely to benefit from the new conveyor belt technology. After all, they need as many high-quality and objective data sets as possible in order to refine their algorithms.



*“This was only possible at the European XFEL because the facility can be used to analyse very small protein crystals”*

Henry Chapman, DESY



## PARTICLE BEAMS AGAINST CANCER

Two facilities are exploring the potential for using high-energy electrons to treat tumours

**F**lorian Burkart passes through a safety door and enters a tunnel with metre-thick walls made of concrete. He stops in front of an extremely complex, 45-metre-long piece of research equipment: a thin, stainless steel tube, surrounded by special magnets, diagnostic sensors and devices that use radio waves to accelerate tiny electron bunches to almost the speed of light. The high-tech facility is also emitting an annoying high-pitched whistle – a side effect of its precision water cooling. “This keeps the accelerating structures at a constant temperature, to within a few hundredths of a degree,” explains the physicist.

The facility, known as ARES, is one of the smallest particle accelerators on DESY’s Hamburg campus. But it has a special feature: “It can produce extremely short electron bunches,” explains ARES coordinator Burkart. “These are just a few femto-seconds long, corresponding to a few nanometres.” This feature means that, in addition to other applications, ARES is suitable for medical research – just like another DESY facility, the PITZ photoinjector test facility at DESY’s Zeuthen site. Both are used to study



new, more effective methods of tumour radiotherapy.

### Flash effect

At PITZ, the focus lies on a recently discovered and promising phenomenon, known among specialists as the flash effect. "This means that a brief, very intense burst of radiation can damage the tumour tissue at least as much as conventional radiation treatment," explains PITZ group leader Frank Stephan. "But what makes it so remarkable is that the healthy tissue surrounding the tumour is spared." This would be an enormous advantage in practical applications. Until now, cancer patients

different intensities and lengths," explains Stephan. "This allows us to scan a wide range of parameters and determine where the flash effect is particularly effective." The first promising experiments took place at the end of 2022. Stephan's team is now expanding the test facility to optimise it for the required measurements. For example, the experts are planning to introduce a kind of scanner that will guide the electron beam, line by line, across the object under investigation – such as a culture of tumour cells. "Many medical research groups have already expressed their intention to study the flash effect here," Stephan points out. "They include the pioneering team from Lausanne as well as the German Cancer Research Centre."

### Diagnosis and therapy

ARES in Hamburg can supplement this work: On the one hand, its particle bunches are less intense than those of PITZ, simply because they contain fewer electrons. On the other hand, the accelerator gives them significantly higher energies. "That would allow the electrons to penetrate deeper into the tissue," explains Florian Burkart, "making it possible to treat not only tumours near the surface, but also those that are deeper inside the body." ARES has already presented the first results of this "Very High Energy Electron" method. The team is working with the University Medical Centre Hamburg-Eppendorf (UKE), among others – also to gain a better

Research teams from DESY and UKE are testing a new type of radiotherapy at the electron accelerator ARES. The high-energy electrons can easily penetrate centimetre-sized objects, such as so-called phantoms made of plastic.

## "The healthy tissue surrounding the tumour is spared"

Frank Stephan, DESY

have to undergo multiple radiotherapy sessions, sometimes dozens, over a period of several weeks. In future, a single session might be enough – with the same impact on the tumour, but significantly fewer side effects for the surrounding healthy tissue.

Some research teams have already demonstrated that the flash effect works in principle. But it is not yet clear which radiation doses and treatment times are most effective. This is where PITZ comes in. "The facility is very flexible and can produce electron pulses of very

understanding of the flash effect. In the long term, the UKE experts hope to use the new method to treat a rare type of brain tumour in children.

More far-reaching plans are already being pursued both at PITZ and at ARES. In principle, it should also be possible to use the electron accelerators for diagnostic purposes. The idea is to first fire weak electron pulses at the tumour, making it visible and allowing its precise location to be determined. Shortly afterwards, a far stronger electron pulse is released, targeting and destroying the tumour – if everything goes according to plan. At DESY, preparations are already underway for an accelerator that can be deployed in clinical settings. The centre is developing systems that use intense laser pulses to accelerate the electrons. Facilities like these could be much more compact than 45-metre-long ARES – and could thus easily fit into a hospital basement.

# The journey of immune cells

**A** team led by physicist Florian Grüner from Universität Hamburg is developing an innovative X-ray technique: X-ray fluorescence imaging (XFI) allows the movement of cells or drugs through an organism to be tracked. This promises to provide new insights in medicine. Certain diseases could be studied by observing how immune cells make their way to the site of the inflammation. And in the search for cancer drugs, one could see whether or not a particular drug is able to enter the tumour as intended.

The principle is to first label the structures you want to track in the body using a marker. “In the case of an active ingredient, such as an enzyme, you could label individual atoms, such as iodine,” explains Grüner. “To label larger structures, such as immune cells, we use nanoparticles or molecular contrast agents.” The labelled cells or active ingredients are injected into the organism, after which X-ray imaging takes place. When a focused X-ray beam strikes the marker, it responds with a characteristic “X-ray echo”. A detector records these fluorescence signals. The resulting images show how the markers – and hence the cells or active ingredients to which the markers are attached – disperse around the body after being injected.



*“At DESY, we were able to capture the image of immune cells as they spread throughout the body”*

*Florian Grüner, Universität Hamburg*

Lymphocytes are a type of white blood cell. They play a central role in the immune response by specifically recognising and destroying pathogens.

Grüner’s group is developing the markers in collaboration with the Fraunhofer Center for Applied Nanotechnology (CAN) and the Center for Hybrid Nanostructures (CHyN) on the Hamburg Bahrenfeld campus. They recently carried out a spectacular pilot study in association with the University Medical Centre Hamburg-Eppendorf (UKE). “At DESY’s X-ray source PETRA III, we were able to capture the image of immune cells that had been injected into live mice at UKE and to observe how they spread throughout the body,” reports Grüner. “No one had achieved this before with XFI.”

## Surprisingly fast

This pilot experiment has already yielded some astonishing findings. Within six hours of being injected, the immune cells had spread to two thirds of the animal’s body – a surprisingly large proportion in an unexpectedly short space of time. The experts now hope to use this method to develop a better understanding of what causes Crohn’s disease, an immune-related disease of the bowels.

Another application is the search for better cancer drugs. Not all chemotherapy is as effective as hoped, because the chemicals administered do not penetrate far enough into the tumour. “A kind of internal pressure in the tumour prevents even the tiniest drug molecules from getting in,” explains Grüner. “We want to use our imaging technique to study this in detail and find out how to overcome this barrier.” Plans for the appropriate proof-of-concept studies have already been drawn up. Together with its partners, Grüner’s team intends to mark three separate chemicals and track their pathway to the tumour with high precision using the XFI method.



# Extremely sharp X-ray images

**H**ow can high-contrast X-ray images be taken of human tissue, such as the lungs, heart or brain? Experts led by the Göttingen physicist Tim Salditt have adapted a special imaging technique, known as phase contrast tomography, so that unstained tissue can be viewed in three dimensions and with high resolution. This requires intense X-rays like those produced by PETRA III. The principle is as follows: The beam passes through a sample, such as a slice of lung tissue. As it does so, the phase of the X-rays is shifted, creating tiny differences in the propagation time.

“It’s a bit like placing a couple of stones in the smooth current of a stream: The stones disrupt the flow and create small eddies,” explains Salditt. “In the tissue sample, it’s the atoms in the sample that disrupt the smooth flow of the X-rays.” The sample is then rotated in the X-ray beam so that images can be taken from different directions. In the end, a sophisticated algorithm calculates high-resolution 3D images from the small phase perturbations in the measurement data.

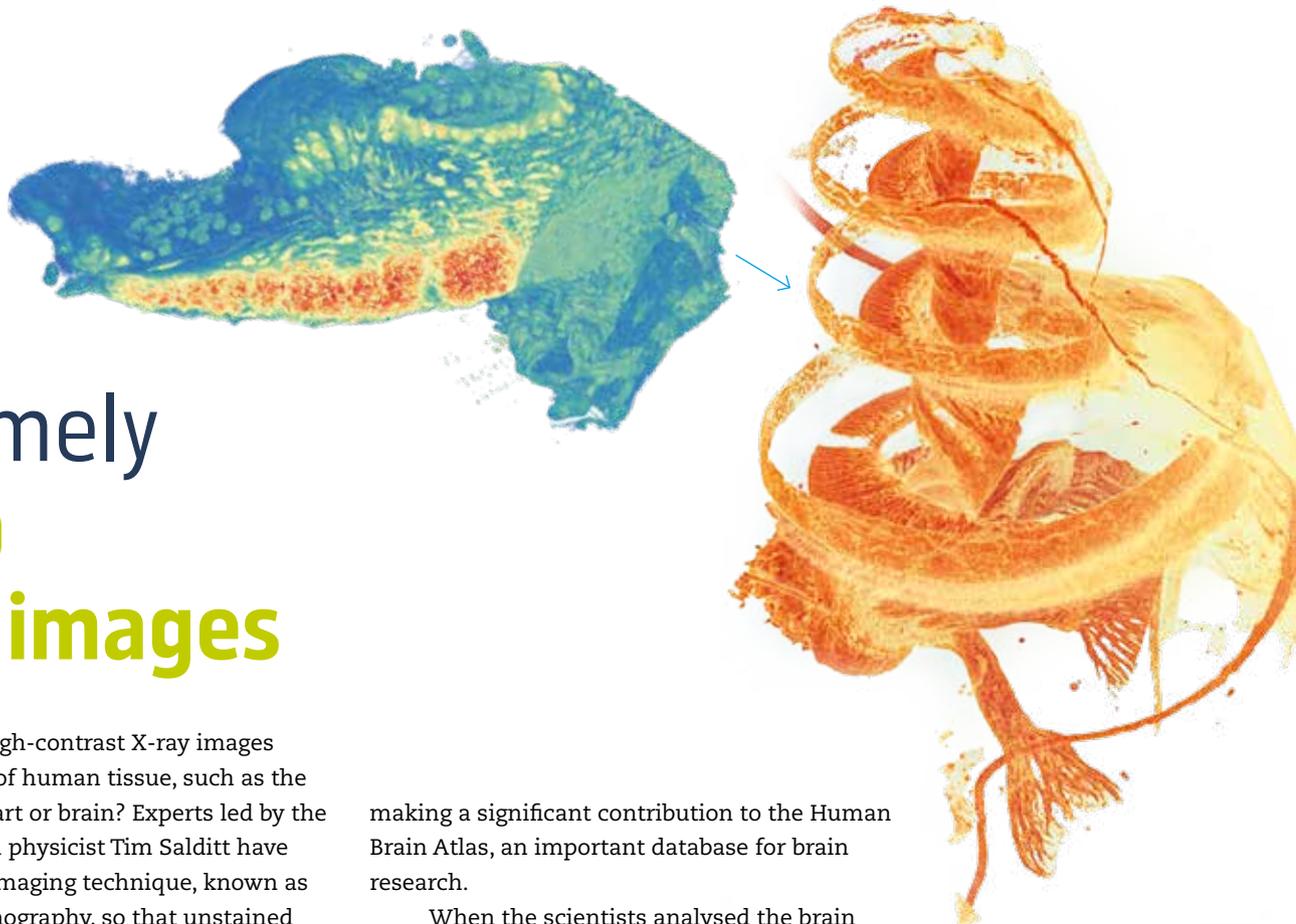
## Retired nerve cells

Several conditions have to be met for this process to work. “We need an X-ray beam that is as parallel as possible, like the one at PETRA III, and we had to design our own X-ray optical systems,” explains Salditt. In addition, highly sophisticated algorithms and enormous computing power are required to calculate meaningful images from the small phase differences in the measurement data. This allowed the team to obtain high-resolution images of the cerebellum and cerebral cortex –

making a significant contribution to the Human Brain Atlas, an important database for brain research.

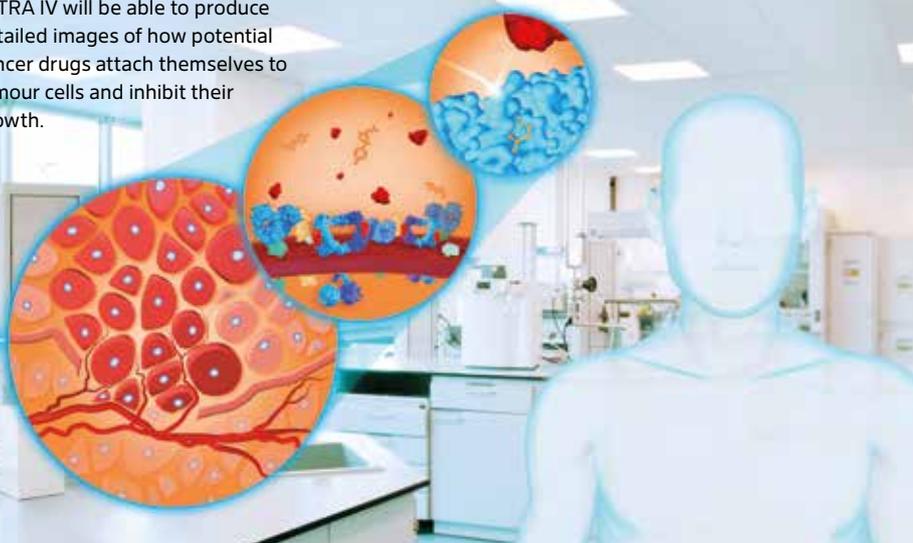
When the scientists analysed the brain tissue of Alzheimer’s patients, they came across an unexpected anomaly. “In one region of the hippocampus, where a sort of memory management takes place, we found evidence that many nerve cells were going into a kind of early retirement,” reports Salditt. Results like these can improve our understanding of the disease and lead to future therapeutic approaches. The method also provided important impetus for research into COVID-19: The experts were able to confirm that, under certain conditions, the virus leads to the formation of new blood vessels in the lungs, which can exacerbate the course of the infection. “This was important for the treatment of patients and contributed to our seeing fewer deaths towards the end of the pandemic than we had at the beginning,” says Salditt.

However, the potential of phase contrast tomography has not yet been exhausted. PETRA IV, the planned successor to the current X-ray source, could offer fresh perspectives. Its extremely fine X-ray beam would allow many more samples to be analysed in the same amount of time. “We could also increase the image resolution tenfold, down to ten nanometres,” notes Salditt enthusiastically. “This would make it possible to see how nerve cells are connected to each other, for example” – which would help the search for new drugs, for example against Alzheimer’s or Parkinson’s disease.



Phase contrast image of nerve tissue from the inner ear. Zooming in on the cochlea (orange) reveals tiny hair cells. These convert sound into electrical impulses, which are ultimately transmitted to the brain. That is where auditory perception actually takes place.

PETRA IV will be able to produce detailed images of how potential cancer drugs attach themselves to tumour cells and inhibit their growth.



## "THE WORLD'S MOST POWERFUL X-RAY SOURCE OF ITS KIND"

PETRA IV will open up entirely new possibilities for biomedical research

**H**amburg is home to some of the world's best X-ray sources. The high-intensity radiation from DESY's storage ring PETRA III can be used to analyse a wide variety of materials and view proteins down to the level of individual atoms. DESY also plays a significant role in the X-ray laser European XFEL. But technologies are constantly advancing, also in the field of high-power X-ray sources. In order to continue to offer research teams worldwide the best possible conditions, PETRA III is to be fundamentally upgraded, to produce an X-ray beam unlike any before. It will be much more powerful and more narrowly focused. As a result, PETRA IV will also give new impetus to biomedical research – for example in the search for new drugs or in the high-resolution imaging of organ tissue.

"PETRA IV will be up to a thousand times more powerful than the current machine. It will be the most powerful X-ray source of its kind in the world," Harald Reichert, overall project manager



**"PETRA IV will be up to a thousand times more powerful than the current machine"**

*Harald Reichert, DESY*

for PETRA IV, emphasises. "The X-rays produced by this facility will be much narrower and more focused – making them much more like a laser beam." This has several advantages for biomedical studies: On the one hand, the structure of proteins can be determined much more quickly using crystallographic

methods. And, as Reichert explains: "Whereas in today's experiments you essentially see the static image of a protein, PETRA IV will increasingly allow time-resolved measurements to be performed. You will literally be able to watch a protein molecule as it goes about its business on a timescale of microseconds."

### Unrivalled image resolution

Another important plus point is that PETRA IV will produce far better X-ray images of tissue samples – thanks to an unrivalled image resolution that can even distinguish between different types of cells. This should make it possible to identify the most subtle changes due to neurodegenerative diseases such as Parkinson's. And Reichert adds: "We will be able to observe with greater precision than before in which areas of an organ a drug is accumulating. Does it actually travel to its destination, or does it end up somewhere else?"

The upgrade to PETRA IV will also see the introduction of a new operating concept. "In future, we will offer a better service to biomedical research teams," announces Reichert. "That will make us far more accessible to this field of research." The idea is for DESY to handle much of the complex processing of the raw data generated by the X-ray experiments. New software tools will then make it possible to process this data largely automatically.

In future then, the specialists will be able to concentrate on their core competencies: the biomedical interpretation of the experimental data. "This should lower the entry threshold, not only for academic teams," Harald Reichert believes. "DESY will also become much more attractive for companies in the healthcare sector."

# Disappearing bone screws

**W**hen a bone is broken, it sometimes has to be reinforced using metal implants. After the fracture has healed, follow-up surgery is often necessary in order to remove the implant again. The Helmholtz Centre Hereon is working on an innovative method for avoiding such troublesome procedures in future. It is developing implants made of magnesium alloys that dissolve inside the body over time. Stents – mesh-like supports for obstructed or constricted cardiac vessels – could also be based on magnesium in the future, allowing them to dissolve inside the body once the tissue has stabilised.

## Top alloy wanted

One of the challenges the scientists face is finding suitable magnesium alloys. If the material dissolves too quickly, it will be unable to support the bone for long enough. If it dissolves too slowly, surgery may become necessary after all. The experts are therefore testing the suitability of a range of alloys in a series of long-term tests. An



*“That makes it possible to see more precisely how the surrounding tissue reacts to an implant”*

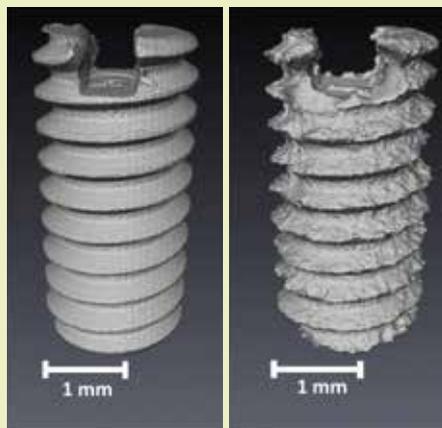
*Felix Beckmann, Helmholtz Centre Hereon*

For some time now, the researchers have also been using the so-called phase contrast method. “With this method, soft tissue, which is fairly indistinct in conventional images, can be visualised in much greater detail,” explains Felix Beckmann, a scientist at the Helmholtz Centre Hereon, which has an outpost at DESY. “That makes it possible to see more precisely how the surrounding tissue reacts to an implant, for example in terms of forming cartilage.”

## X-rays reveal bone structure

PETRA IV, the planned successor to the current X-ray source PETRA III, could lead to significant progress in this area. “Thanks to its narrowly focused X-ray beam, it could be used, for example, to analyse cartilage formation in much more detail than before,” says Beckmann’s colleague Berit Zeller-Plumhoff. “This precedes the formation of bone and marks an important stage in the healing process.” Research into dissolving stents would also benefit. At the moment, the blood vessels into which a stent is inserted are relatively difficult to see in X-ray images. The intense radiation from PETRA IV, on the other hand, would produce a detailed image of the shape of the vessel – which would allow researchers to see how the vessel reacts to the implant.

The examination at DESY’s X-ray source PETRA III showed that, after 56 days (right), the crests of the thread were the first to dissolve, gradually becoming rounded. In contrast, corrosion progresses more slowly at the root of the threads.



important method for monitoring the dissolution process is microtomography. It works like a CT scanner in a hospital, which produces 3D X-ray images of what is happening inside the body. Unlike in a CT scan, though, the samples are illuminated by the high-intensity X-ray beam of PETRA III. In combination with other X-ray methods, this allows a detailed analysis of how the implants gradually decompose and how the bone responds to this – for example, whether the implant stimulates bone growth.

# Slimy bacterial films



Biofilm colonies of the bacterium *Pseudomonas aeruginosa* formed under different conditions

Compared with higher life forms, bacteria are simple-minded organisms that just swim around aimlessly. That was the conventional wisdom when Holger Sondermann studied biology in the 1990s. Since then, the experts have come a long way. “We now know that bacteria are much more complex and that they establish communities. They join together to form biofilms,” says the scientist, who heads DESY’s Structural Microbiology team at CSSB. Microbes are often far better off in a community than on their own. This allows them to withstand harsh environmental conditions and defend themselves more effectively against antibiotics.

Biofilms are found in many places in nature, for example as a protective coating on plant roots. But they can also cause illness: “A large number of chronic infectious diseases can be traced back to them,” explains Sondermann. “In a biofilm, the bacteria are better protected from our immune system and from antibiotics. Living in a biofilm also facilitates the exchange of genes between microbes, which can lead to antibiotic resistance.”

With this in mind, Sondermann’s team is seeking to answer some fundamental questions: How do bacteria actually assemble to form a biofilm? How do the microorganisms communicate with each other, and could biofilm formation be prevented?

## Sticky proteins

One thing is clear: The chain of events is complex. “Microorganisms such as the pathogen that causes cholera have dozens of proteins for processes by which the bacteria recognise their environment and react to it,” explains Sondermann. Film formation can be triggered by nutrient molecules, but also by light. Receptors on the surface of the unicellular organisms pick up these stimuli and transmit them into the cell by means of membrane proteins, triggering a complex cascade of reactions. As a result, adhesive proteins are generated and a matrix is secreted through which bacteria can form communities and colonise surfaces, forming a biofilm. Sondermann’s team

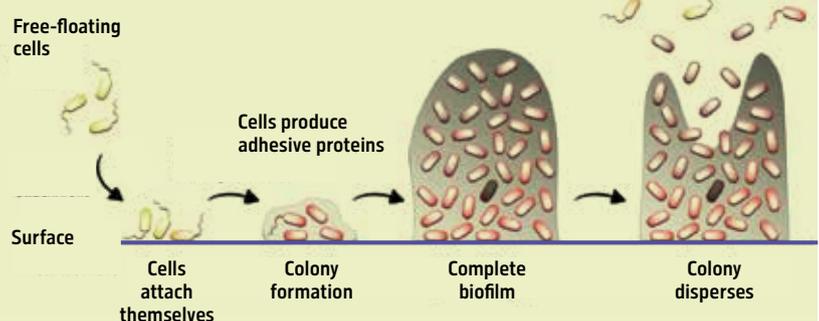
uses a wide variety of methods to analyse these processes. Using DESY’s X-ray source PETRA III and the cryo-electron microscopes at CSSB, the experts are elucidating the shapes of the enzymes involved, from which they can draw conclusions about how they function. In addition, AI algorithms such as AlphaFold can calculate the shape of a protein from its sequence with astonishing accuracy – a valuable extension to the experiments.

“A large number of chronic infectious diseases can be traced back to biofilms”

Holger Sondermann, DESY and Kiel University

Using this technique, the team managed to work out the role of certain receptor molecules in the chain of signals that tell the microbes to form a biofilm. “If we could intervene selectively, for example by administering suitable drugs, we might be able to prevent the formation of a biofilm,” says Sondermann. “That could weaken the stability of biofilms or discourage the microorganisms from creating a biofilm in the first place.” If such a deceptive strategy could prevent biofilm formation, traditional antibiotics would become more effective against microbes – a promising strategy against antibiotic resistance.

**How a biofilm forms:** Certain factors, such as light stimuli, can cause free-floating bacteria to attach themselves to a surface and establish a colony. When the environmental conditions change, the colony disperses again.



# THE PROTEIN FIBRE DETECTIVE

## Meytal Landau unlocks the secret of amyloids – using a variety of methods

She has not yet finished setting up her office, removal boxes still line the walls. Meytal Landau only recently moved into her new premises at CSSB, the Centre for Structural Systems Biology on the DESY campus in Hamburg. Before coming here, the biochemist worked at the Technion, the Israel Institute of Technology in Haifa. But even though she has not yet unpacked all her furniture, she has already settled in and feels at home. “I see many opportunities for scientific and personal growth here in Hamburg, for me and for my children,” explains Landau. In 2020, at the height of the COVID-19 pandemic, she came to Hamburg for a year as a guest researcher – and fell in love with the city. When a permanent position became available as a leading scientist at DESY, along with a professorship at the University Medical Centre Hamburg-Eppendorf, Landau didn’t think twice.

The DESY campus offers the 47-year-old ideal conditions for her work: research into amyloids. These structures are formed when proteins stick together to produce extremely stable fibres, some of which are as strong as spider silk. Among other things, amyloid fibres stabilise bacterial cultures that have formed biofilms. They are also important in diseases such as Alzheimer’s and Parkinson’s. In these cases, amyloids form plaques, which are found in the brain cells of people with the disease. “Experts believe that these proteins are involved in the development of the disease,” explains Landau. “But we don’t know exactly how this happens; there doesn’t seem to be any link between the amount of these protein deposits and the symptoms that someone displays.”

### High-performance microscopes against amyloids

In the future, the scientist hopes to be able to identify such links at DESY.

“The conditions here on campus are unique in Germany,” she notes. “Well-equipped laboratories, several high-performance microscopes and PETRA III, an X-ray source that can be used to determine the shape of the amyloids with great precision.” Landau is fascinated by the protein fibres formed by bacteria. Although these are based on completely different genetic sequences to those in humans, the resulting structures are strikingly similar, as the researcher discovered in previous experiments. This remarkable result can be taken as a sign that amyloids played an important role in evolution. Some scientists even speculate that they were involved in the creation of life billions of years ago, together with RNA fragments and lipids, which include fat molecules.

## “Amyloids make bacteria more aggressive”

**Meytal Landau, DESY**

“Amyloids make bacteria more aggressive,” explains Meytal Landau. “If you are infected by a microbe that produces amyloids, the course of the infection may be much more severe.” This is because the bacteria release protein fibres that attack white blood cells, weakening the immune system. If a substance could be developed that prevents amyloid formation, the microbe would be deprived of one of its weapons – the body would be better able to fight off the infection. Landau and her team are working on the basic principles that could one day



make such drugs possible. Bacteria should be unable to develop a resistance to such drugs – giving these an advantage over conventional antibiotics.

### Millions in research funding

Since microbial amyloids are similar in structure to Alzheimer’s plaques, drugs developed in the course of Alzheimer’s research might also be effective against amyloid-forming bacteria. As it turns out, Landau has already identified two such drugs that make it more difficult for salmonella to form a biofilm out of amyloids. “In the future, we want to test other drugs,” says Landau. “However, studies like these require considerable resources.” So a multi-million-euro research grant from the European Research Council (ERC), which the scientist recently managed to secure, is very welcome.

It will allow her to study further questions in the future. For example, it has been speculated that amyloids actually have an important function: They can help humans and animals fight microbes. In the past, Landau’s team has managed to isolate dozens of amyloid-forming molecules that have an antimicrobial effect, for example in frogs and fish. “We are still at the very beginning here,” >>

the researcher emphasises. "We now want to determine the detailed structure of these molecules so as to learn more about how they work."

One day, it may be possible to translate such findings into practical applications, such as antimicrobial coatings on medical devices or hip implants. The wide range of research tools available in Hamburg should make it possible to significantly expand our basic understanding of amyloids.

### From Haifa to Hamburg

"I have the feeling that moving from Haifa to Hamburg was the right step," says Meytal Landau – even if it was not an easy one for her, as an Israeli whose grandfather lost his wife and two children in Auschwitz. "The first time I travelled to Germany, I bumped into some people in a bar, who were drunk and had shaved heads," she recalls. "That didn't feel very good." And on the Hamburg S-Bahn, she and her daughter endured the antisemitic outbursts of a drunk – and no one on the train intervened.

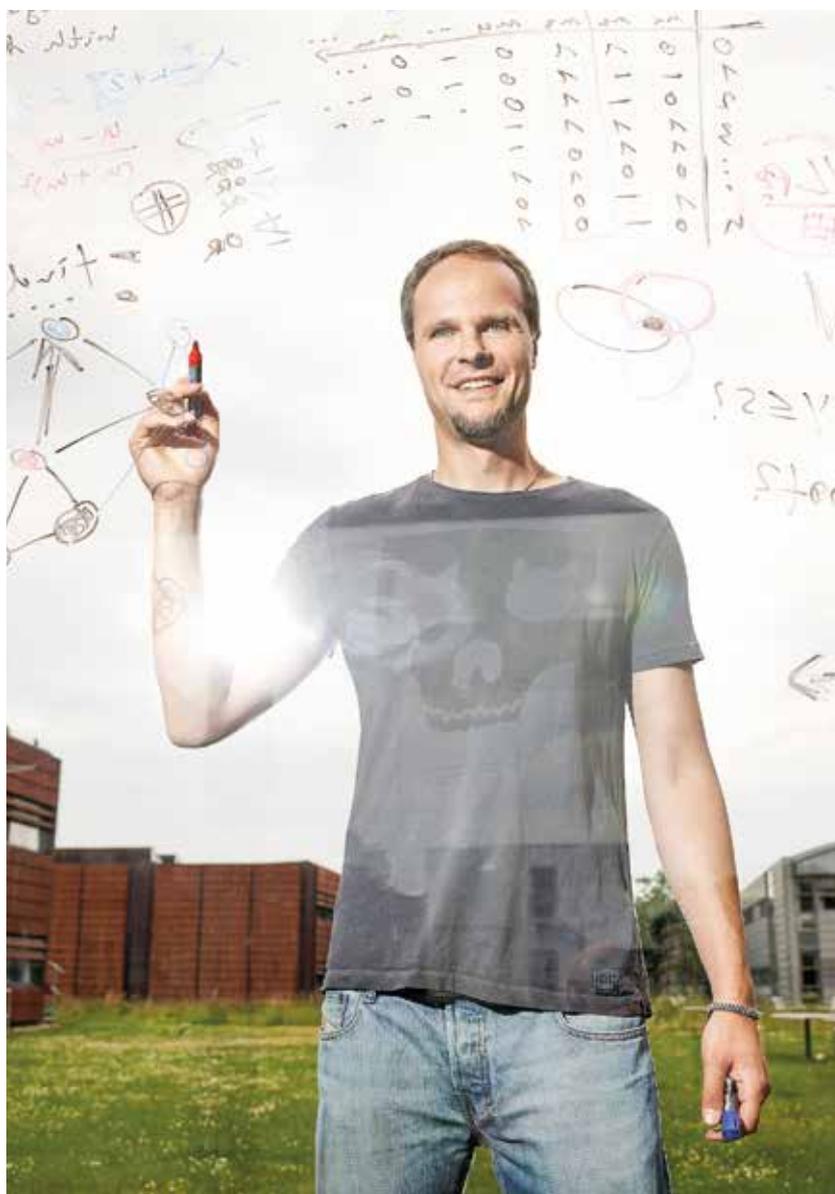
"But there have been other experiences too," says Landau. For example, when a 90-year-old neighbour, after some hesitation, told her son about her time in the Hitler Youth. Or when a woman at a New Year's party heard that Landau was from Israel and burst into tears – some time earlier she had learned that her grandfather had been a staunch Nazi. "She didn't want to be the granddaughter of a Nazi," says Meytal Landau. "It made me realise that some Germans also have their traumas – that changed my perspective."

# AI goes bio

## Why adaptive algorithms are becoming increasingly important in medical research

Computer science is playing an increasingly significant role in biomedical research. AI algorithms such as AlphaFold can calculate the spatial shape of numerous proteins with astonishing accuracy – providing the basis for determining the function of a protein. The calculations begin with the genetic sequence of a protein. The algorithms are trained on experimental data, for example from protein crystallography at DESY's X-ray source PETRA III.

In addition, machine learning can provide valuable services for other questions. Some of the findings are already being used in practical applications, for example in the treatment of breast cancer. "The question here is whether the cancer will return after an intervention," explains Jan Baumbach, a specialist in bioinformatics at Universität Hamburg. "Because this is difficult to predict, patients often receive relatively aggressive chemotherapy." AI algorithms can now identify specific patterns in the genetic



Picture: Ricky John Molloy

make-up of tumour tissue that contain information about the subtype of breast cancer – meaning that, in certain cases, chemotherapy may not even be necessary.

### Known drugs – used in new ways

Baumbach and his team are researching new IT procedures, for example in the search for drugs. It is quite possible that a well-known active ingredient could also be effective against a disease for which it was not originally developed. Such “off-label use” could provide a relatively quickly available weapon against pathogens, especially in the case of newly emerging infectious diseases – after all, the drugs in question have already been approved. The catch is that the number of proteins that might be targeted is vast. “To fish potential candidates out of this mass of data, we use programs inspired by nature, so-called ant colony optimisation algorithms,” explains Baumbach. “They simulate ants that solve the problem using collective intelligence.”

Baumbach’s team is also pursuing another strategy against infections – in collaboration with other institutions on the DESY campus, such as EMBL and CSSB. “This involves trying to produce so-called defective viruses,” explains the bioinformatics expert. “Although these are viable, they do not reproduce as effectively, and this makes them less dangerous.” The idea is to inject such defective viruses into the human body, where they would compete with the real viruses and ideally prevent them from reproducing – in the case of influenza, for example. The scientists are using AI software to work out what the genome of a likely defective virus should ideally look like – research that is still in its infancy.

One problem is that, to function properly, AI algorithms need to be trained with as much



DESY Zeuthen has access to IBM’s quantum computers – and can thus develop and test future algorithms.

data as possible, often genetic data. However, such data is usually personal, meaning that the individuals in question could be identified using their genetic fingerprint. Strict data protection rules must therefore be observed throughout AI training. Baumbach’s team is developing programs that comply with the data protection regulations. Instead of collecting the sensitive genetic data in a central cloud, the software travels from one hospital to the next – becoming smarter with each “visit”. The data itself never leaves the hospital, thereby ensuring data privacy.

### Quantum algorithms for medical research

One thing is clear: AI has revolutionised the field of biomedicine and is likely to continue to do so. Baumbach is focusing on a new type of computer here, the quantum computer. Instead of bits, it performs calculations using so-called qubits. These can carry out countless calculations simultaneously, making the machine far faster than today’s supercomputers. The technology is not yet ready to be applied to big real-world problems – current prototypes are only just beginning to outperform conventional computers. “However, I believe that, in a few years’ time, quantum computers will be able to execute various

AI applications more quickly,” says Baumbach. “That’s why we are already designing today’s algorithms so that they will be able to run on quantum computers in the future.”

DESY’s Zeuthen site is also working on quantum algorithms. Here, the Centre for Quantum Technology and Applications (CQTA) has cloud access to IBM’s quantum computers. “We are part of a group set up by IBM to carry out medical research,” says CQTA leader Karl Jansen. “For example, we are developing quantum algorithms that can calculate what cells will do from the way they aggregate.” This is based on sophisticated methods of pattern recognition, like those used in particle physics.

**“The algorithms simulate ants that solve the problem using collective intelligence”**

*Jan Baumbach, Universität Hamburg*

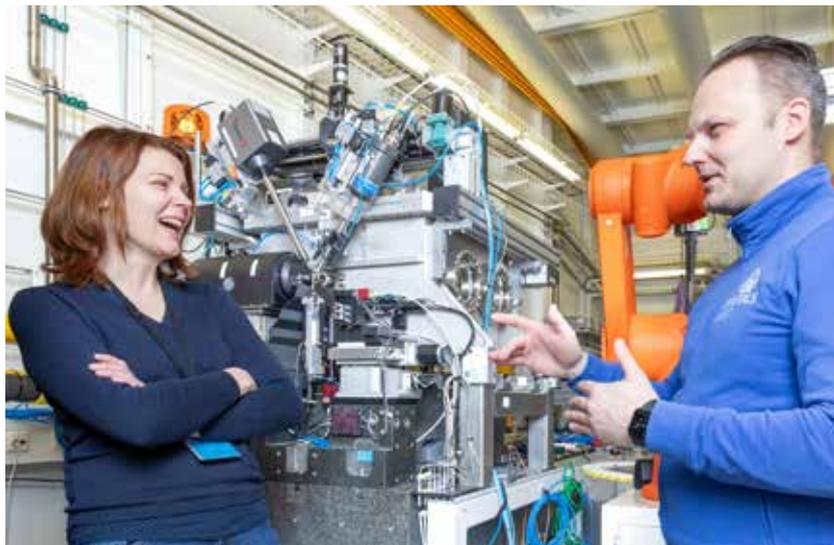
One of the CQTA projects is focusing on the early detection of cancer. The principle is to use algorithms to classify those regions on a gene that are actually active, for example those that cause a certain enzyme to be produced. If such regions – called exons – can be reliably classified, their distribution can be compared with that of a healthy gene. Any deviation would indicate an increased risk of cancer. “Conventional programs currently have a hit rate of around 80 percent,” says Jansen. “Self-learning quantum algorithms should be able to significantly improve this in the future – at least that’s the hope.” He estimates that quantum computers capable of running such programs productively could be on the market by 2030.

# Successful collaboration in biology

DESY is working with industry partners and taking part in networks. Why? Physical methods and novel accelerator technologies can facilitate faster drug development, more effective vaccines and the use of accelerators in diagnostics or treatment. Here are three examples:

## Developing drugs more quickly

Together with the start-up CrystalsFirst, DESY has launched the LigandML project, which aims to speed up the development of new drugs and make the process more cost-effective. The technique is based on protein crystallography: Protein crystals are combined with a huge number of ligands, i.e. drug candidates. PETRA III is then used to determine which drug has attached itself to the protein. CrystalsFirst has developed a method of stabilising the crystals



*“Our common goal is for LigandML to enable a more efficient, data-driven approach to developing new therapeutic drugs”*

*Johanna Hakanpää, DESY  
Serghei Glinca, CEO of CrystalsFirst*

effectively. In addition, an AI is able to analyse the X-ray data more quickly than before and learn which details are necessary for binding to occur. This can reduce the time it takes to identify a suitable drug from months to weeks or even days. The partners in the LigandML project are adapting the process for routine use to speed up the experiments at PETRA III.

## Optimising mRNA-based drugs

DESY is working with the Mainz-based biotechnology company BioNTech and Universität Hamburg. At PETRA III, the partners are investigating the imaging of lipid-based nanoparticles. These ultrasmall particles made from fats, known as “drug delivery” or “formulation” technologies, help to ensure that mRNA-based drugs are transported to their intended destination inside the body. More specifically, PETRA III is to make a technique known as X-ray fluorescence available for widespread use. For example, this method can provide information about the biological distribution of pharmaceutical nanoparticles. Such findings provide valuable information for the further development and optimisation of mRNA-based vaccines and medicines.



*“The approach is an innovative technique for evaluating the biological distribution of mRNA more efficiently. No comparable method currently exists for obtaining this information in a single measurement and with a resolution in the sub-micrometre range. The findings from these experiments can help us to further optimise formulation technologies for mRNA-based drugs and potentially develop new technologies”*

*Dr Jens Schumacher, Senior Director of Analytical Development at BioNTech SE*

### Accelerators for better radiotherapy

DESY is working on a promising new technology: plasma acceleration, which uses powerful laser pulses to accelerate electrons to considerable energies over very short distances. This makes compact X-ray sources conceivable, for example for use in hospitals. They could potentially improve the diagnosis and treatment of tumours – resulting in more successful treatments with fewer side effects. The Hi-Acts innovation platform coordinated by DESY aims to make the technology available for practical applications as quickly as possible. Industrial companies are cooperating with research institutes from the earliest stages of development.



*“Through the Hi-Acts innovation platform, we are strengthening the synergies between science and industry. Hi-Acts brings Helmholtz Centres together with companies and promotes new developments”*

**Wim Leemans, Director of the Accelerator Division at DESY**

## A GOOD REASON FOR STAYING IN GERMANY

**Dr Mathias Kraas is Director of Research and Development at Olympus Surgical Technologies Europe. He is also a member of DESY's Foundation Council and its Innovation Advisory Committee.**



**femto:** Olympus manufactures highly specialised devices for minimally invasive diagnosis and therapy. How much fundamental research goes into this kind of product?

**Mathias Kraas:** Laser research and materials science provide a crucial impetus. For some products, for example, we need ceramics that must function under very specific conditions. We can't search for such materials ourselves because we don't have that capacity. That's why the results from materials research are very important to us.

**femto:** DESY is in the process of further professionalising the transfer of research findings to industry. Where do you see the prospects for successful collaboration with the medical technology and pharmaceutical industries?

**Mathias Kraas:** There are many approaches, for example in information technology. DESY is proficient in structuring and analysing huge amounts of data, also with the help of AI. These tools can be very useful for our industry, for example when analysing medical imaging data. The pharmaceutical industry could also use DESY's

X-ray sources to find new tumour markers for cancer screening. And the compact accelerators that DESY is working on could open up new possibilities for hospitals in the diagnosis and treatment of tumours.

**femto:** What would you say are the best ways of improving cooperation between science and industry?

**Mathias Kraas:** It's important that research centres support start-ups and allow them to develop products in highly specialised laboratories. It's also important to deliberately open up the research centres to large companies. However, many companies are still unaware of the potential offered by facilities like DESY. This needs to be publicised even more. We should also raise awareness among policy-makers of the importance of fundamental research to Germany as a business location. More and more companies are thinking about moving abroad – there are not many reasons left for staying here. But centres like DESY are a good reason for a large company to continue operating in Germany.

# SPECTRUM

News from research

Thanks to machine learning, the properties of the electron bunches in the LUX plasma accelerator, such as charge and energy distribution (shown from top to bottom), can be controlled with high precision.

## Computer controls plasma accelerator

**A** team of researchers led by DESY scientist Sören Jalas has used machine learning to teach a compact particle accelerator to produce customised beams for a number of different applications. The technique expands the conceivable range of applications for innovative compact next-generation accelerators called laser plasma accelerators. Plasma accelerators can be around a thousand times smaller than conventional facilities. What promises to offer great advantages in terms of building, operating and using them in practical applications is, however, a challenge when it comes to controlling the beam parameters.

Basically, accelerator physicists must carefully adjust all of the control

settings at once to balance the different properties of the electron bunch. However, it is very difficult for human beings to find the right compromise between the many parameters involved – there were six of them in the present case.

“Computers are much more adept at finding their way around such high-dimensional parameter spaces,” says Jalas, the lead author of the study. “For our accelerator, we used a method called Bayesian optimisation. The computer effectively takes control of the accelerator. It tries out a number of configurations and measures the parameters of the electron bunches produced by the accelerator. From these measurements, the computer gradually builds up a kind of map and

hence finds tuning curves that show us the optimal way of adjusting the parameters to get the properties of the electron bunch that we need in a given situation.”

In their experimental plasma accelerator LUX, the researchers initially used the technique to adjust the energy and electric charge of the particle bunches. “But it could conceivably be extended to other beam properties, such as emittance,” says Jalas. The method is also to be used in the large plasma accelerator KALDERA, which is currently being built at DESY.

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*Physical Review Accelerators and Beams*, DOI: 10.1103/PhysRevAccelBeams.26.071302

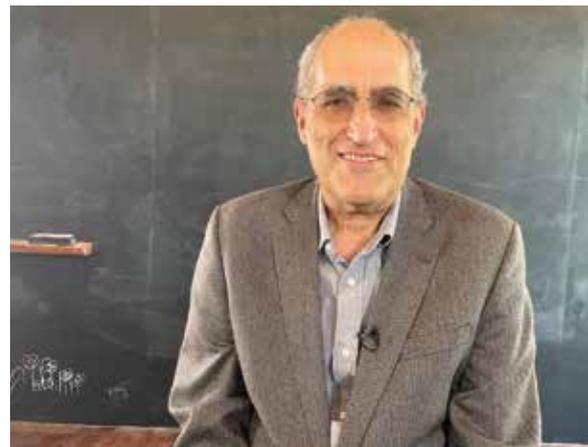
# String theorist Edward Witten receives Hamburg Prize for Theoretical Physics

The physicist Edward Witten was awarded the Hamburg Prize for Theoretical Physics 2023. The professor emeritus at the Institute for Advanced Study in Princeton, USA, was recognised for his groundbreaking contributions to a unified mathematical description of the fundamental forces of nature. His outstanding research on string and quantum theory has had a profound impact on our understanding of space, time, matter and the structure of the cosmos.

Witten ranks among the most renowned theoretical physicists of our time. For decades, he has been providing important impetus for the development of a grand unified theory of physics that describes all the forces and building blocks of the universe. String theory has been seen as a promising candidate for this unification since the 1970s because it builds a bridge between two established cornerstones of physics:

quantum theory, which governs the interaction of subatomic particles, and Albert Einstein's general theory of relativity, which describes gravity as a consequence of the curvature of space and predicts the evolution of stars, galaxies and black holes.

String theory suggests that quantum and gravitational theory can be unified under the umbrella of a new mathematical formalism. This involves looking at elementary particles as tiny line-shaped objects, the strings. All known elementary particles are consequently nothing other than different oscillation patterns of the same fundamental particle. In the 1980s, it became clear, with the significant participation of Edward Witten, that this paradigm shift would allow all four fundamental forces of nature – gravitation, electromagnetism, weak nuclear force and strong nuclear force – to be described by a unified quantum mechanical field theory.

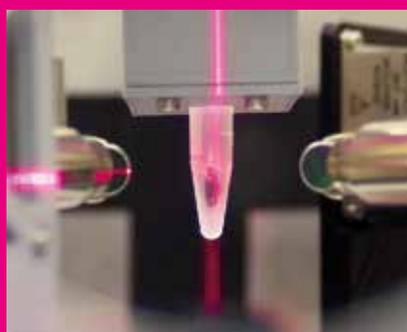


Witten has received many awards. In 1990, he was the first physicist to ever receive the Fields Medal, regarded as the highest award in mathematics.

The Hamburg Prize for Theoretical Physics is one of the most highly endowed science prizes for physics in Germany. The prize money amounts to 137 036 euros, a nod to Sommerfeld's fine-structure constant, which plays an important role in theoretical physics. It is awarded by the Joachim Herz Foundation together with DESY, the Wolfgang Pauli Centre of DESY and Universität Hamburg and the Clusters of Excellence "CUI: Advanced Imaging of Matter" and "Quantum Universe" at Universität Hamburg.

Picture: OFCLLC

## Innovation award for X-ray fluorescence technique



Experimental setup for X-ray fluorescence measurements

Florian Grüner, professor at Universität Hamburg and at the Center for Free-Electron Laser Science (CFEL), received the Innovation Award on Synchrotron Radiation of the "Friends of Helmholtz-Zentrum Berlin e.V.". He was recognised for his research on the tracking of molecules in biomaterials and living organisms using X-ray fluorescence imaging. His pioneering work paves the way for the precise tracking of immune cells, biomolecules, such as antibodies, and drug carriers in order to measure their distribution in living organisms in real time. The method can provide invaluable insights for medical research.

The key breakthrough achieved by Grüner and his team lies in the development of a method based on synchrotron radiation that allows scientists to precisely detect the smallest tumors or to track drugs or cells in living organisms. The cutting-edge approach holds significant potential for pharmaceutical research, drug development and even the study of the biological effects of pollution caused by micro- and nanoplastics. As it is a non-invasive method that can be used to measure an organism over many points in time, the method also promises to significantly reduce the number of animals required in preclinical trials.

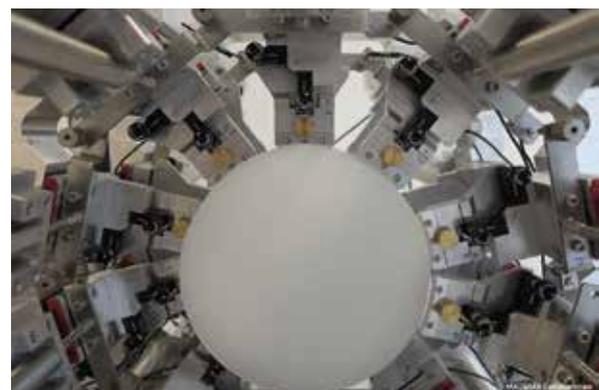
Picture: Universität Hamburg, Florian Grüner

# New German–French laboratory for researching dark matter

**T**he French research organisation CNRS and three research centres of the Helmholtz Association – DESY, GSI in Darmstadt and KIT in Karlsruhe – have joined forces to form the Dark Matter Lab (DMLab), an international research laboratory dedicated to the study of the mysterious dark matter. Dark matter is one of the greatest scientific puzzles of the universe: We know from astronomical observations that it accounts for about 26 percent of the total energy content of the universe, making it about five times more abundant than the normal matter we are familiar with.

The aim of the DMLab is to strengthen collaboration between the two countries and foster the potential for discovery. It is coordinated on the German side by DESY and has initially been established for five years.

The DMLab's scientific topics include direct searches for dark-matter particles, the development of innovative detector and accelerator technologies as well as the theoretical study of dark matter. In addition, activities of the lab encompass astroparticle physics with its multi-messenger approach, including gravitational waves, and scientific

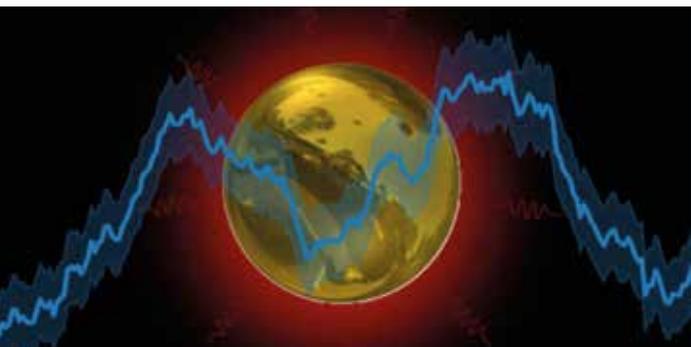


The axion experiment MADMAX is one of the experiments in which the DMLab will get involved.

computing with topics such as artificial intelligence and data management.

One joint project in which the DMLab will be involved is the MADMAX experiment. The international MADMAX collaboration was initiated by the Max Planck Society and formed at DESY in 2017. It aims to search for axions, hypothetical ultralight particles that could be building blocks of dark matter.

Picture: MADMAX Collaboration



## Displaced electrons cause gold nanoparticles to vibrate

**S**olar cells, sensors, photocatalysts: Nanoparticles that are sensitive to light hold the promise of a variety of applications – if the processes that determine their behaviour can be controlled. One of these processes is a kind of collective electron movement in the nanoparticle, called “plasmon”, which leads to an energy exchange that can be favourable or disruptive. The details of this collective movement were previously unclear. Using DESY's free-electron laser FLASH, a team has made observations in gold nanoparticles that cannot be explained by established models and proposed a new theoretical approach that describes the observed dynamics.

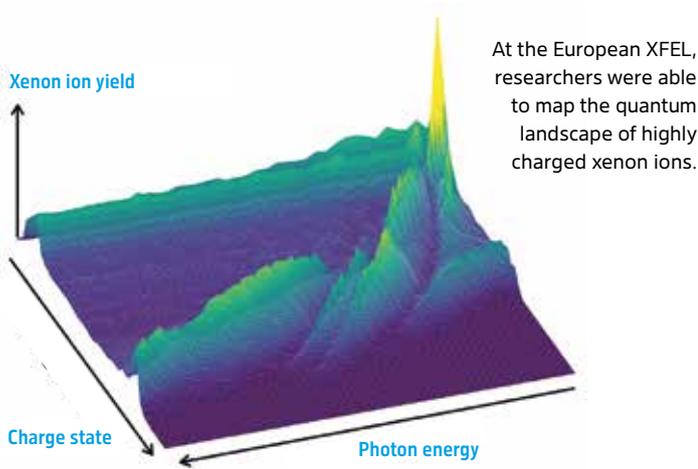
The established theory suggests that plasmons generate very energetic “hot” electrons, which then lose their energy by scattering off other electrons within the plasmon field, forming what is called a “warm” electron gas. This gas then heats up the nanoparticle, which eventually releases the excess energy into the environment. In the heating process, the entire nanoparticle

starts to oscillate collectively, almost as if it were a “breathing” sphere. The efficiency of the energy transfer between the hot and warm electrons and the nanoparticle is important for applications making use of these processes, such as in solar cells and sensors.

At FLASH and Universität Hamburg, the team used a laser to excite nanoparticles and study them. The particles expanded much faster than previously assumed – and well before the warm electron gas could form. The team used this insight to develop a new model of plasmon behaviour. To explain the “particle breathing”, it comprises a new effect in addition to the “classical” thermal expansion – a redistribution of the electrons triggered by the laser light, which directly induces the particle to oscillate. This new excitation contribution shows that so-called plasma dynamic processes are a lot more intertwined than assumed and that existing models of warm and hot electrons need to be questioned.

*Nano Letters*, DOI: 10.1021/acs.nanolett.3c00920

# Charting the quantum landscape of hollow atoms



**R**esearchers have identified exotic quantum states of heavy atoms missing up to six electrons in their core electron shells. The breakthrough was made possible by the unique capability offered by the European XFEL X-ray laser of scanning the X-ray energy over a wide range and by the application of a powerful computer program for predicting X-ray-driven quantum behaviour.

When an atom is hit by a photon – a particle of light – of sufficient energy, it can be ionised, i.e. an electron is knocked out of the atom, leaving behind a positively charged ion with a hole in its electron shell. The X-ray pulses generated by the European XFEL are so intense and have such short durations that the atoms they hit can absorb more than one photon at the same time. In this way, it should even be possible to create atoms with multiple holes in their core electron shells. In these innermost layers of the electron shell, the electrons are very tightly bound to the atomic nucleus and, unlike the valence electrons further out, they don't participate in chemical bonding.

In a joint theoretical and experimental study on xenon atoms, the team investigated the dependence of this “multiphoton” light-matter interaction on the X-ray energy for the first time. The measured spectra contained a multitude of quantum structures in the “landscape” formed by the photon energy and the charge state. These structures could be assigned to electronic transitions in corresponding ionic states with the help of state-of-the-art theoretical calculations. At specific photon energies and charge states, the spectra were found to be determined by massively “hollow” atoms featuring as many as six simultaneous holes in their core electron shells. The unusual atomic species discovered in the study could also be formed through collisions in outer space, making them potential candidates to explain unidentified X-ray emission lines in astrophysics.

*Nature Communications*, DOI: 10.1038/s41467-023-41505-1

Picture: DESY, Sang-Kil Son

femtomenal

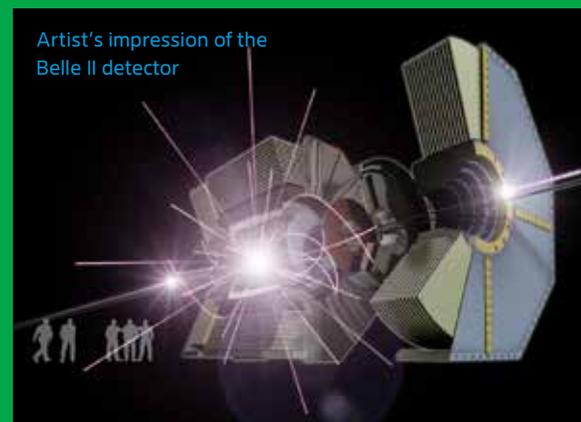
## 1777.09 ± 0.14 MeV: This figure is a record

**D**on't worry, you don't have to memorise this figure: 1777.09 ± 0.14 MeV. It's the most precise measurement to date of the mass of the tau lepton, a heavier cousin of the electron. But in the long term, it will tell us more about the rules of our universe. A research team led by DESY has determined it by analysing around 175 million decays of tau particles using the Belle II detector at the Japanese research centre KEK. Although the tau has similar properties to the electron, it is much more difficult to analyse because it only exists for an extremely short time.

While the current measurement agrees with earlier, less precise measurements, the tau is considered a good candidate for detecting processes beyond what we know today. In fact, there is a small difference between the theoretical prediction and the measured values. If this discrepancy increases with more precise measurements, this could be an indication of “new physics” beyond the Standard Model of particle physics.

So if the conversation at your next dinner party turns to the mass of the tau lepton, you now know where to look:

<https://arxiv.org/abs/2305.19116>



Picture: Rey Hori, KEK

The artist's impression shows how a series of pulsars is affected by gravitational waves coming from a pair of supermassive black holes in a distant galaxy.

# Who is making the **gravitational wave** here?

Data collected over 15 years provide evidence of a low-frequency background noise from gravitational waves in the universe – perhaps directly from the Big Bang

**T**hese waves are really long: Astrophysicists have found the first compelling evidence for the existence of gravitational waves that oscillate with periods ranging from years to decades. For their studies, the researchers evaluated data collected by the North American Nanohertz Observatory for Gravitational Waves, or NANOGrav, over 15 years. One of their hypotheses is that NANOGrav sees gravitational waves generated in the Big Bang.

## Pulsars help in the search

“After years of work, NANOGrav opens an entirely new window on the gravitational-wave universe and provides key evidence for gravitational waves at very low frequencies,” says Stephen Taylor from Vanderbilt University in the USA, who co-led the search

and is the current chair of the collaboration.

The NANOGrav collaboration, which brings together more than 190 researchers, including from the University of Münster, DESY, the Max Planck Institute for Gravitational Physics in Hannover and the University of Mainz, observes pulsars in our galaxy with large radio telescopes, searching for gravitational waves in the process. A pulsar is the ultradense remnant of the core of a massive star following its demise in a supernova explosion. Pulsars spin rapidly, sweeping beams of radio waves through space so that they appear to “pulse” when seen from Earth. “When the pulsar is correctly oriented, this highly regular signal can be measured from Earth. The effect can be compared with the light cone from a lighthouse that

flashes at certain intervals – except that pulsars blink much faster; and in the case of the pulsars observed by NANOGrav, they actually blink in intervals of milliseconds,” explains Kai Schmitz, associate professor at the Institute of Theoretical Physics at the University of Münster.

## Periods over decades

Albert Einstein’s general theory of relativity predicts precisely how gravitational waves should affect pulsar signals. By stretching and squeezing the fabric of space, gravitational waves affect the arrival time of each pulse in a small but predictable way, delaying some while causing others to reach the Earth earlier. Deviations following a certain pattern, which can be traced back to slowly undulating (low-frequency) gravitational waves, are now emerging in the data



The radio telescopes of the Very Large Array in San Agustin, New Mexico (USA), belong to the telescopes of the NANOGrav collaboration.

window on the gravitational-wave universe, providing insight into gigantic black holes merging in the hearts of distant galaxies, among other exotic sources.

The NANOGrav results thus open up a new frequency band in the gravitational-wave spectrum. This is because instruments on Earth, such as LIGO, the Laser Interferometer Gravitational-wave Observatory, can only see high-frequency gravitational waves – low-frequency gravitational waves can only be observed with the help of pulsars. In 2015, LIGO made the first direct measurements of high-frequency gravitational waves.

#### Wave maker black holes or Big Bang?

However, the signal measured by NANOGrav could also involve a cosmological contribution in the form of gravitational waves from the early universe. “In our work, we take a close look at the possibility that NANOGrav is seeing gravitational waves generated fractions of a second after the Big Bang – instead of a signal of astrophysical origin emitted by titanic black holes orbiting each other at the centres of galaxies”, explains DESY postdoc Andrea Mitridate.

“Many theories relating to new physics beyond the Standard Model of particle physics predict the generation of gravitational

waves in the Big Bang – including phenomena such as cosmic inflation, cosmological phase transitions or so-called cosmic strings,” says Schmitz. Mitridate adds: “In this sense, the NANOGrav data enable us to examine models of new physics at energies that are unachievable in laboratory experiments on Earth.” Further studies will be needed, however, to determine

**“We take a close look at the possibility that NANOGrav is seeing gravitational waves generated fractions of a second after the Big Bang”**

**Andrea Mitridate, DESY**

which argument will ultimately win through: the astrophysical interpretation in the form of binary systems of supermassive black holes, or the cosmological interpretation in the form of gravitational waves from the Big Bang.

*The Astrophysical Journal Letters,*  
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from 68 pulsars observed by the collaboration in 15 years of research work. Earlier results from NANOGrav had actually already uncovered an enigmatic timing signal that was common to all observed pulsars. However, it was too weak for any conclusions to be drawn regarding its origin.

NANOGrav’s most recent data set shows growing evidence for gravitational waves with periods of years to decades. These waves could arise from orbiting pairs of the most massive black holes in the entire universe: billions of times more massive than the sun, with sizes larger than the distance between the Earth and the sun. The superposition of the signals from many individual such pairs gives rise to a diffuse background noise of gravitational waves. Future studies of this signal will open a new

# Boson trio: ATLAS sees extremely rare process

DESY-driven analysis reveals three different bosons at once

**N**obody has ever seen this before: DESY scientists working with data from the Large Hadron Collider (LHC) at CERN in Geneva have uncovered a rare process in which three important force particles are produced at once. Using a data set collected by the ATLAS detector in the last few years, the team has seen evidence of a process that further details the relationship between two of the four fundamental

forces of the universe: the weak force and electromagnetism. The process involves the simultaneous production of the two particles that carry the weak force, the W and Z bosons, alongside the photon, the carrier particle of the electromagnetic force.

The electromagnetic and weak forces have a close relationship. Since the first description of general relativity, theorists have been working backwards to figure out

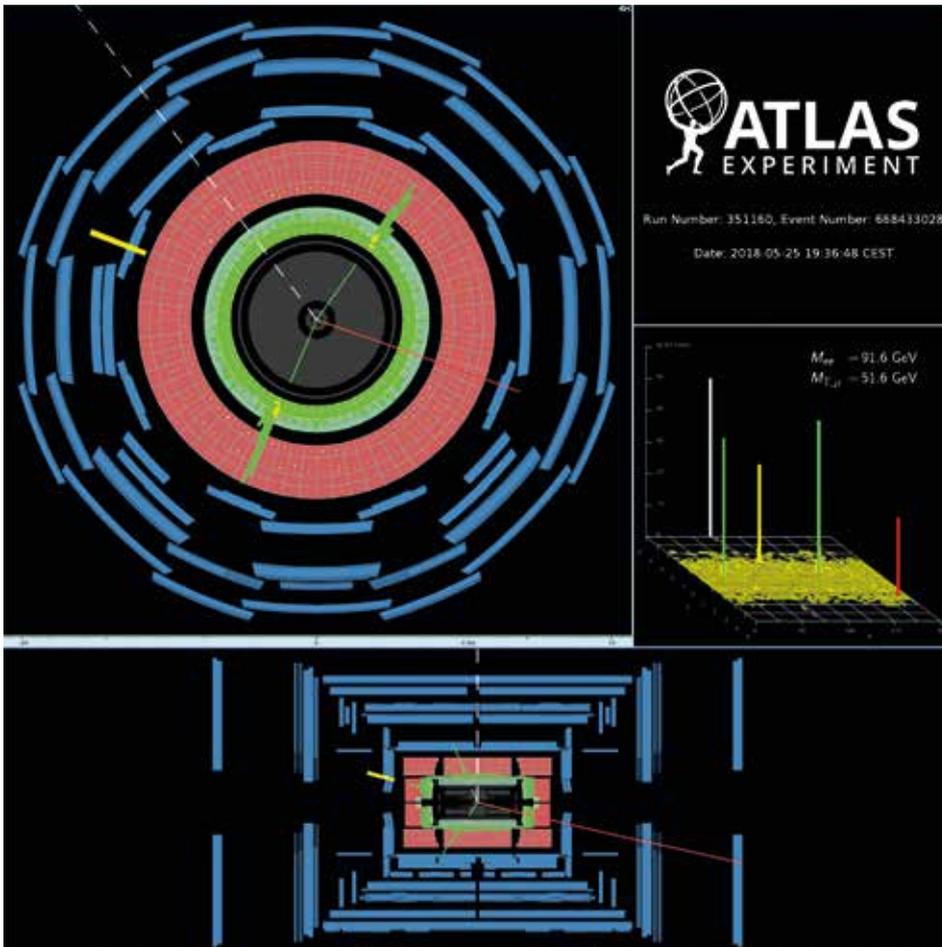
how the four fundamental forces – electromagnetism, the weak force, the strong force and gravity – were once a single force that emerged from the Big Bang. Based on these calculations, the electromagnetic and weak forces must have been united for the longest time. Many experimental results edify these calculations. The two carrier particles of the weak force, the electrically charged W boson and the electrically neutral Z boson, have already been observed individually with the photon. Now, for the first time, all three have been spotted emerging together from a single collision.

## Idea for the analysis comes from DESY

The proposal to use the huge amount of data from the last LHC run to find evidence for the simultaneous production of all three bosons comes from DESY Particle Physics Director Beate Heinemann. “By using the full data set, you can find such rare processes,” says Ludovica Aperio Bella, a DESY ATLAS scientist who led the analysis.

“I am excited that we have observed for the first time the simultaneous production of all three electroweak gauge bosons,” says Heinemann. “This is a very rare process, so we have only been able to see it now, almost 15 years after the start of the LHC, and on the basis of a huge amount of data. Understanding how these bosons interact is at the heart of understanding our early universe.”

Part of the challenge in the analysis was to locate the grouped signatures of the W and Z bosons and the photon – a signal that is



Better analysis methods, more precise values of the collision rate at the LHC and a brilliant idea make images like this possible. It shows a rare collision in the ATLAS detector featuring three bosons – one W boson, one Z boson and one photon.

unfortunately not exceptionally distinct from many other traces of particles careening out of the collision site. The researchers therefore had to find ways to identify the signal they were looking for more easily, developing new statistical methods to do so. “Only with these techniques, which are more complex than any we’ve had before, can we see three-boson production,” says Bella.

### Statistically and physically significant

Just as critical to the team’s success was a new value of the LHC’s luminosity, updated with intensive involvement of DESY. The luminosity is a figure describing the average number of proton collisions, which, when revised more accurately, increases the precision of all measurements. The results were calculated at a significance of 6.3 sigma, meaning that the three-

“Understanding how these bosons interact is at the heart of understanding our early universe”

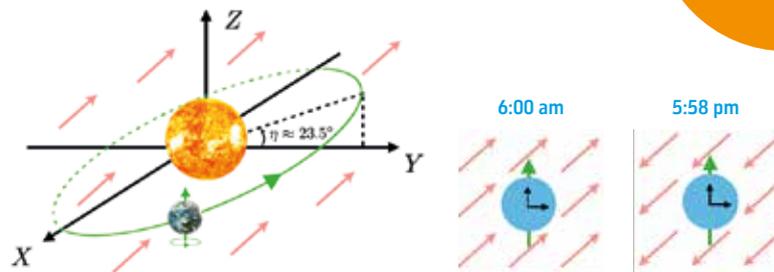
Beate Heinemann, DESY

boson observation can be stated to be 99.99966 percent certain – the probability that the phenomenon was observed in error is about three in a million.

“This result is important to finding physics beyond the Standard Model, because whenever we observe a rare process like this, we force our theory colleagues to put it into context. That context helps to make future results much more precise, so that we know what to look for,” says Bella.

## DO QUARKS INTERACT WITH THE COSMOS?

femtopolis



Quarks preserve rotation and Lorentz invariance, a study based on data from the ZEUS experiment shows.

Any experiment taking place on Earth has, at any given time, a well-defined orientation and velocity with respect to the centre of the solar system, the centre of our galaxy and the rest frame of the universe. Rotation and Lorentz invariance state that these two symmetries should not have any effect on the particles in the experiment. While this can be verified with many particles in the Standard Model of particle physics, with quarks it is slightly trickier. Whether they also preserve these basic symmetries of nature was unclear for a long time.

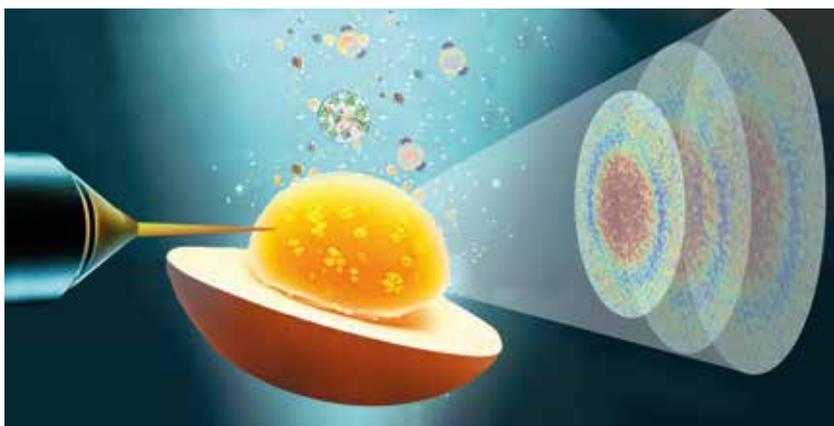
Quarks make up hadrons – for example the proton and the neutron – and so belong to the fundamental building blocks of the atomic nucleus. As building blocks go, they are difficult to examine: They cannot exist in isolation, meaning that they always bind with other quarks.

This is where HERA comes in, DESY’s a one-of-a-kind collider for probing hadrons, which was decommissioned in 2007. Thanks to HERA, we know essential details about the behaviour of quarks and the structure of the proton – knowledge that is crucial to experiments at current colliders, such as the Large Hadron Collider (LHC) at CERN.

Almost two decades on from HERA’s shutdown, new details are still emerging. Recently, two theoretical physicists from Indiana University in the USA and Sussex University in the UK joined the ZEUS team at DESY to study rotation and Lorentz invariance and the behaviour of quarks.

Using the data taken by the ZEUS detector at HERA between 2003 and 2007, they re-analysed collisions, looking for anomalies among the quarks. Such anomalies could have been an indication that the experiment – and thus the space around the Earth – was passing through a yet unknown field that could not otherwise be seen. However, the results show that rotation and Lorentz invariance hold for quarks – meaning that either such fields do not exist, or, if they do, quarks do not significantly interact with them.

“We have thus established some of the world’s best limits on the violation of these invariances and contributed important details for finding physics beyond the Standard Model,” says DESY scientist Achim Geyser, who was part of the analysis team.



# Cooking **eggs** for science

X-ray source PETRA III reveals phenomena in gelling egg yolk

**S**ome like their eggs hard-boiled, some soft-boiled, some like them sunny side up. A group of researchers has used DESY's X-ray source PETRA III to analyse the structural changes that take place in egg yolk during cooking. The study shows how different constituents in the yolk of a chicken egg contribute to the development of the typical soft-grained microstructure when heated. The results could be of interest to the food industry and serve as a model for the physics behind biological processes associated with a number of serious diseases.

## Determining factors: temperature and speed

Heated egg yolk is widely used in our kitchens, in the food industry and in biotechnology. However, only little is known about the processes that occur in the egg yolk during cooking. Using coherent synchrotron radiation at PETRA III, the researchers investigated the contribution of proteins, fat molecules – so-called LDLs, or low-density lipoproteins – and yolk granules to the development of the grainy gel microstructure and

the microscopic dynamics during cooking.

For the experiments, the scientists used the yolk of conventional chicken eggs. During the heating process, they observed the samples at temperatures from 63 to 100 degrees Celsius over time intervals of up to two hours at a time resolution of down to 10 milliseconds. "We observe that the mechanism that leads to the formation of the grainy gel microstructure is identical irrespective of the cooking temperature, but the speed of these processes depends on the temperature," says Nimmi Das Anthuparambil, lead author of the study from the University of Siegen.

Apart from its food, biological and therapeutic value, the diversity of proteins and high concentration of LDLs make egg yolk also an ideal candidate for studying the physics behind biologically relevant non-equilibrium processes. Denaturation and aggregation of proteins and LDLs are generally undesirable and harmful in biological systems; they are associated with diseases such as Alzheimer's, Parkinson's and atherosclerosis. Protein-based

At PETRA III, researchers discovered how the components of egg yolk contribute to the development of its soft-grained microstructure when heated.

drugs are susceptible to changes in their environment, for example temperature, pH value or ionic strength, which represents one of the greatest challenges for the pharmaceutical industry. A good understanding of nanoscopic non-equilibrium processes is therefore extremely valuable.

## Even better results with PETRA IV

"These experiments make ideal use of the coherent fraction of the X-ray radiation produced at PETRA III," explains DESY scientist Fabian Westermeier, a co-author of the study. "This fraction is limited, however." According to Westermeier, DESY's future project PETRA IV would be even better suited for investigating these processes. "The coherent part of the beam at PETRA IV will be a 100 times larger, enabling up to 10 000 times better time resolution for measuring and understanding these processes."

**"PETRA IV will enable up to 10 000 times better time resolution for measuring these processes"**

*Fabian Westermeier, DESY*

"We expect our results to be relevant beyond egg yolk," says Christian Gutt from the University of Siegen. Future research will explore the aggregation of egg yolk proteins caused by deviations from optimal conditions of salt and pH. This could provide insights on suitable conditions for stabilising the proteins, which has implications for storage conditions of future protein-based drugs.

*Nature Communications,*  
DOI: 10.1038/s41467-023-41202-z

# High-pressure view of Earth's interior

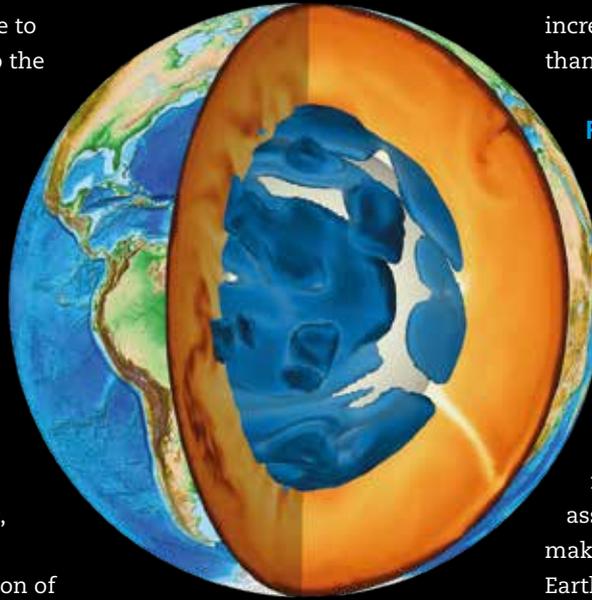
High-pressure experiment shows that hot iron oxide slows down seismic waves

**W**e may not be able to look directly into the Earth's interior, but we can use sophisticated experiments in the lab to at least partially simulate some of the conditions inside the Earth. A research team has done so using a high-pressure experiment at DESY's X-ray source PETRA III, providing new insights into the Earth's lower mantle and the second most abundant mineral there, ferropericlase. The results are important for the interpretation of seismic waves, for example.

## Material softens under pressure

Ferropericlase is a magnesium-iron oxide. At high pressures, an unusual phenomenon occurs: Ferropericlase temporarily becomes softer. This has a direct effect on seismic-wave velocities, which are slowed down by the softening of the mineral. This behaviour of ferropericlase can be explained at the atomic level. The electrons of the iron reorganise themselves to form pairs of electrons with opposite spin – that is, they “rotate” in opposite directions. This redistribution of electrons, known as spin crossover, reduces the diameter of the iron atoms.

The team measured how spin crossover affects the compressibility of ferropericlase and hence the velocity of seismic waves for the first time at high temperatures approaching those occurring in the Earth's mantle. To do this, the scientists used a heatable high-pressure cell in which they heated ferropericlase to almost



Model of the Earth with temperature variations: Cold, sinking material is depicted in dark colours, light colours stand for hot, rising material. The blue surface shows where half of the iron in the ferropericlase has undergone spin crossover – illustrating the strong temperature dependence of the phenomenon.

1200 degrees Celsius. At one of PETRA III's measuring stations for extreme states, they X-rayed the sample and were thus able to measure how compressible it is.

“The spin crossover is highly dependent on temperature,” says lead author Viktoria Trautner from the University of Oxford in the UK. “At room temperature, the spin crossover begins at around 400 000 times atmospheric pressure,” adds Hauke Marquardt, also from the University of Oxford, who led the study. “At 1000 degrees, on the other hand, it doesn't start until around 500 000 times atmospheric pressure.” Using a new theoretical model, the team was able to extrapolate the results of their measurements to the temperatures found in the Earth's mantle, which

increase with depth and reach more than 3000 degrees Celsius.

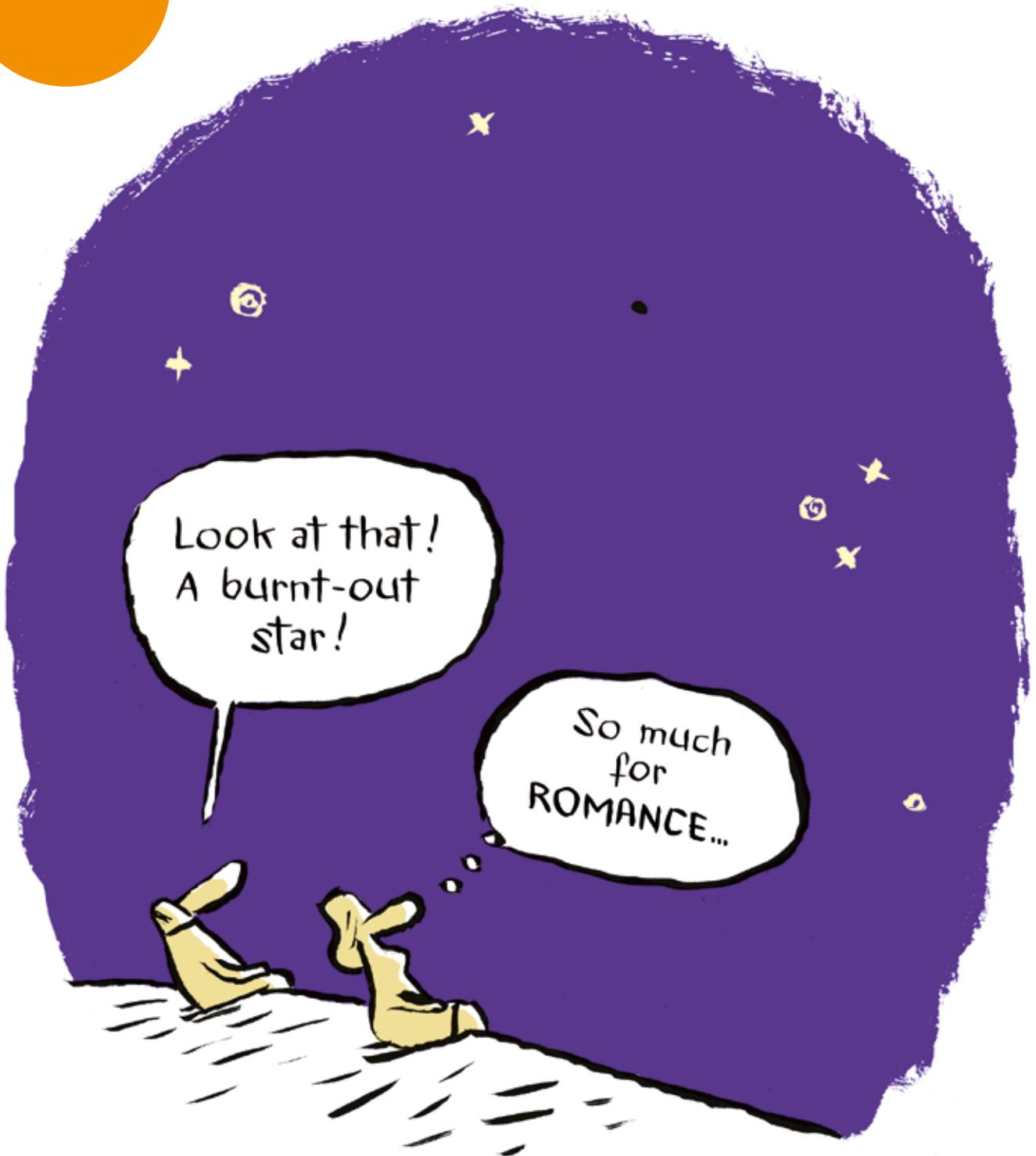
## Ferropericlase in the high-pressure cell

The scientists then used 3D modelling of the Earth's interior to simulate the effect of spin crossover on the behaviour of seismic waves and compared this with actual seismic measurements. Their initial analyses support the assumption that ferropericlase makes up about 20 percent of the Earth's lower mantle, which extends from a depth of 660 kilometres to about 2900 kilometres. “There is no way of exploring the Earth's lower mantle directly. Experiments like ours are the only way to learn about mantle mineral properties,” says co-author Hanns-Peter Liermann, who is in charge of the beamline at PETRA III where the experiment was carried out.

The behaviour of seismic waves can be used to study the structure and composition of the Earth's mantle, which strongly affect the physical properties and dynamics of the Earth's interior. A more accurate modelling of the Earth's lower mantle will in turn aid the interpretation of seismic waves. The researchers hope that, in future, they will even be able to measure the temperature at certain depths using the behaviour of seismic waves under the influence of spin crossover, but they will need more detailed seismic measurements and models than are currently available.

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