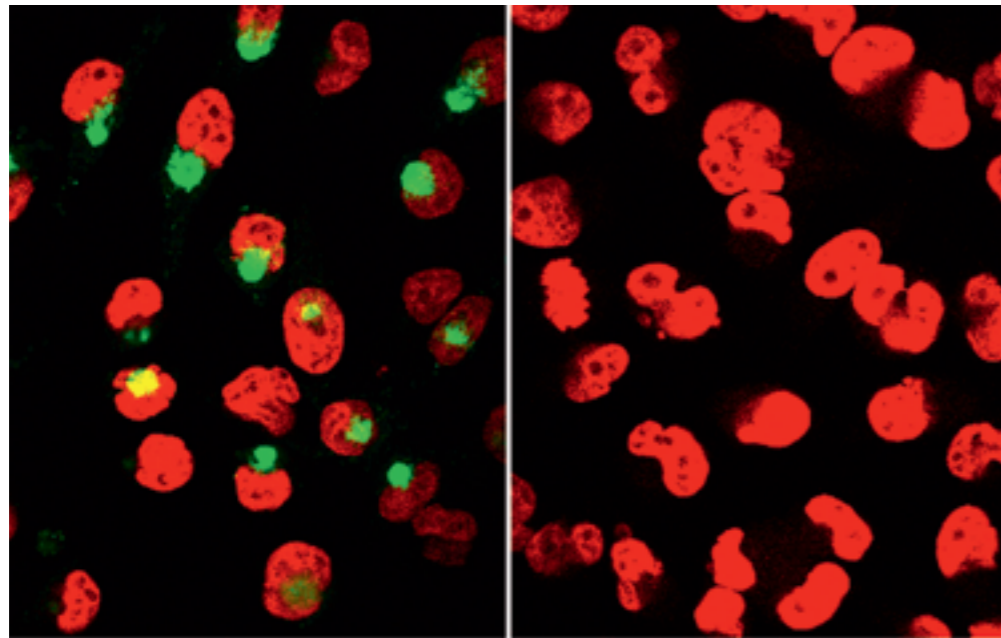




RESEARCH in Brief

Switching off the cause of Alzheimer's: Untreated cells show the activity of β -secretase, marked in fluorescent green (left), which leads to the production of β -amyloid. It is no longer present in cells in which the researchers in Dresden have inhibited β -secretase. This explains why only the cell nuclei that have been dyed red still show up in the image on the right.



CELL BIOLOGY

Rafting to Better Memory

Nerve cells disintegrate, and forgetfulness becomes the order of the day: Humans lose their ability to remember and their sense of time and place. Alzheimer's is an insidious disease of the brain. Researchers at the Max Planck Institute for Molecular Cell Biology and Genetics in Dresden have now inhibited the β -secretase enzyme, one of the most critical proteins in the onset of Alzheimer's disease. This enzyme is crucial in the formation of the peptide β -amyloid, the culprit in the development of the disease. Using a simple, yet very novel approach, the researchers in Dresden achieved effective inhibition of this enzyme, both in cultured cells and in animals. This novel strategy not only offers a promising therapeutic intervention for Alzheimer's, but also opens up new vistas in drug design and delivery.

Currently, there are around a million people in Germany alone who suffer from this progressive disease of the nervous system. As humans in industrialized countries are living longer, this number is likely to rise even further in the future. Alzheimer's disease is the most common age-related dementia. It results in the progressive decline in memory and cognition, and ultimately leads to death. Clumps of protein fragments or plaques, known as amyloid deposits, are considered the most visible change in the brains of Alzheimer's patients. According to the current school of thought, these accumulate over time and cause increasing damage to brain cells, until they eventually die. These deposits occur when the β -secretase enzyme splits the β -amyloid precursor protein (APP), which is a membrane protein. It is precisely this β -secretase that research-

In a daze: In the brain of an Alzheimer's patient (right), fewer areas shine bright yellow than in a healthy patient (left) – an indication of less activity.

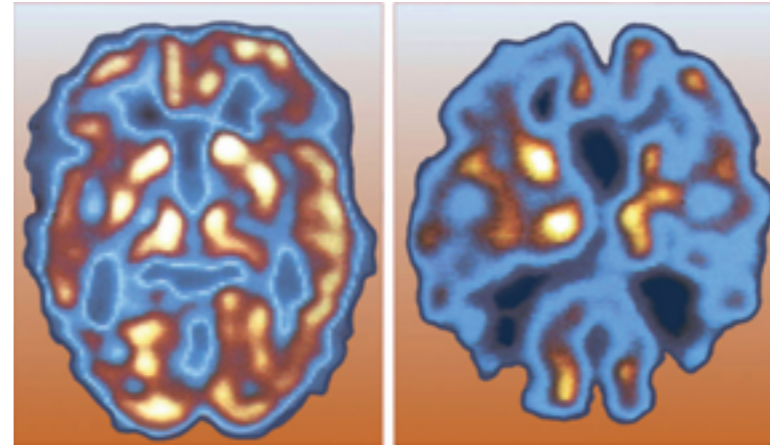


IMAGE: GRAFIK-ATELIER RIEDIGER

ing attention ever since. Now, using cholesterol as a lipid anchor, the scientists enriched the inhibitor not only in the endosomal membrane, but also in the vicinity of the enzyme. This strategy enormously increased the effective concentration of the inhibitor at the precise site of action. "The inhibitor travels into the

cell as a stowaway on the little raft, so to speak," says Lawrence Rajendran. "We thus use a cellular mechanism that transports the inhibitor into the endosomes, precisely where it is supposed to act." Initial experiments in both cell cultures and living organisms have shown that these endosome-specific inhibitors are many times more effective than the soluble preparations that have been available on the market to date. In an animal model in which Alzheimer's was simulated, the new inhibitor reduced the formation of β -amyloid by 50 percent in just four hours, whereas the previously available inhibitors showed no effect whatsoever.

"The new β -secretase inhibitors hold great potential for the development of new, effective medication to fight Alzheimer's," says Kai Simons. And he is already thinking ahead. "We believe that we will soon be able to apply this principle to other therapeutic inhibitors in other diseases." In virus-mediated diseases such as Ebola and HIV, the viruses use rafts to move from cell to cell. In the future, drugs just might be able to block these routes.

First, however, employees at JADO Technologies, of which Kai Simons is a co-founder, are trying to harness the stowaways on the membrane rafts as potential therapies for Alzheimer's disease. In order to do this, one of the things they need to work out is how to introduce the β -secretase inhibitor into the brain without directly injecting it. Before such effective inhibitors can become available as drugs, scientists must also find out more about the biological function of β -amyloid. They know that β -secretase helps wrap children's growing nerve cells in an insulating myelin sheath. Blocking this in Alzheimer's patients, who are predominantly older, is not expected to yield any undesirable side effects. However, neuroscientists at the Ludwig Maximilian University in Munich recently discovered that β -amyloid is not just a useless or even damaging waste product. It might be involved in the construction and function of synapses, the contact points between neurons, which means that it may also play a role in learning. However, even if a β -secretase inhibitor should make learning more difficult, it at least prevents "the great forgetting."

ers are attempting to block, with the aid of the right inhibitors. A group of scientists working with Kai Simons at the Max Planck Institute for Molecular Cell Biology and Genetics have now designed the inhibitor such that it blocks the enzyme directly in the cell where the target is located. Almost four years ago, Lawrence Rajendran, a post doc in Kai Simons lab, studied the cell biology of the processing of APP and found that β -secretase, though physically present on the cell surface, is not active until it gets internalized into intracellular compartments called endosomes. The enzyme and the amyloid precursor protein must therefore be transported into the cell, where the pH is so low that the enzyme can split the membrane protein.

"Previous approaches to finding a therapy neglected the exact site of enzyme activity and acted only non-specifically – that is, scattered over a broad area," says Lawrence Rajendran, who played a crucial role in the present work. "This method allows us to increase the effectiveness of the β -secretase inhibitor enormously." This is a key to treating Alzheimer's disease effectively – or at least slowing the course of the illness.

How did they achieve this specificity in the inhibition? There are many β -secretase inhibitors in the cell, but most of them either do not enter the cell and, even if they do, the inhibitor is all over the cell interior. The Dresden-based scientists specifically targeted the inhibitor to the endosomes by linking the inhibitor to the lipid molecule called cholesterol. This makes the inhibitor readily attach to the membrane, and since part of the membranes continuously get internalized into the endosomes, this enabled the lipid-linked inhibitor to reach the endosomes. The authors cleverly chose cholesterol to be the lipid to anchor the inhibitor because they previously showed that the enzyme is enriched in the regions of the membrane that also contained cholesterol. These regions, called lipid rafts, play functionally relevant roles in both physiological and pathological processes. It is interesting to note that Kai Simons put forward the raft hypothesis more than a decade ago, and it has been gaining increas-

ing attention ever since. Now, using cholesterol as a lipid anchor, the scientists enriched the inhibitor not only in the endosomal membrane, but also in the vicinity of the enzyme. This strategy enormously increased the effective concentration of the inhibitor at the precise site of action. "The inhibitor travels into the cell as a stowaway on the little raft, so to speak," says Lawrence Rajendran. "We thus use a cellular mechanism that transports the inhibitor into the endosomes, precisely where it is supposed to act."

Initial experiments in both cell cultures and living organisms have shown that these endosome-specific inhibitors are many times more effective than the soluble preparations that have been available on the market to date. In an animal model in which Alzheimer's was simulated, the new inhibitor reduced the formation of β -amyloid by 50 percent in just four hours, whereas the previously available inhibitors showed no effect whatsoever.



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ASTROPHYSICS

A Jet-Propelled Black Hole



Shot from the core: For the first time, researchers have observed how a black hole is propelled from its parent galaxy by gravitational waves. This scenario is depicted in the illustration.

It sounds a little like science fiction: Two black holes at the heart of a galaxy merge and create gravitational waves that catapult the super-heavy black hole out of the galaxy. A few years ago, theoreticians created computer simulations of just such a spectacular scenario. Now a team working with Stefanie Komossa at the Max Planck Institute for Extraterrestrial Physics has indeed found a gravitational rocket like this one – with far-reaching consequences for our understanding of how galaxies were created and how they evolved in the early universe. (ASTROPHYSICAL JOURNAL LETTERS, May 10, 2008)

The discovery by the Max Planck scientists provides evidence of one of these extreme events for the first time; up to now, they have only been simulated. According to the theory, enormous gravitational waves emanate at the speed of light when two black holes coalesce. As the waves are emitted mainly in one direction, the black hole experiences a recoil, similar to when a gun is fired or a rocket is launched. The black hole is prevented from remaining at the core of the Milky Way system and it starts to move away, eventually leaving the parent galaxy.

The astrophysicists' attention was drawn to the black hole in the Sloan Sky Atlas by its very high speed: the gas around the black hole exhibited strong shifts in the spectral lines. This led the researchers to conclude that the cosmic heavy-weight – it is the equivalent of several hundred million solar masses – was moving at almost 3,000 kilometers per second. To put this into perspective: a person leaving Munich at this speed would

be in Africa in less than a second. The enormous force of this recoil catapulted the black hole out of its parent galaxy.

In addition to the spectral lines of the gas bound to the black hole, the physicists also noticed unusually narrow lines from the galaxy itself. This gas is not linked to the black hole, but is illuminated by its hot accretion disk.

When a black hole is ejected from the center of a galaxy, it takes most of the matter immediately surrounding it along with it, which provides it with fuel for many million more years. It continues to absorb gas from the disk, and this gas shines in X-ray light. The team headed by Stefanie Komossa also discovered the X-ray light around the black hole, which is ten billion light years away. By chance, this area of space was scanned by the ROSAT satellite; at the very edge of its field of view, there was a source of X-rays whose position corresponded to that of the distant galaxy.

Astrophysicists are strongly interested in gravitational waves, which were predicted by Albert Einstein. They bend space-time almost like a stone thrown into a lake ripples the surface of the water. In 2006, researchers first merged black holes in computer simulations and calculated the signal from the gravitational waves created in this way.

The latest discovery proves indirectly that black holes do indeed merge, for which there was previously no clear evidence. Another conclusion from the observation is that there must be galaxies that do not have a black hole at their core – and, conversely, that there are black holes that drift in intergalactic space for all eternity. ●

ILLUSTRATION: MPE/HST ARCHIVE



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DEVELOPMENTAL BIOLOGY

Accelerating Plant Breeding

Rice is the most important staple food for around half of the world's population, and its many different varieties are constantly being improved through breeding. Scientists at the Max Planck Institute for Developmental Biology in Tübingen, working with colleagues from the International Rice Research Institute in the Philippines, are now making use of small, artificially created RNA molecules to accelerate this breeding process significantly. (PLOS ONE, March 19, 2008)

Many varieties of rice are very well adapted to the region in which they grow. Transferring a single gene to these varieties without affecting the genes that ensure their adaptation to their location normally takes years of conventional breeding. Researchers at the Max Planck Institute for Developmental Biology in Tübingen, working with colleagues from the International Rice Research Institute in the Philippines, have now developed a tool that could enormously accelerate the development of rice varieties with specific characteristics. Norman Warthmann and his staff have switched off genes using artificial microRNAs.

A useful modification in a plant often requires the inactivation of a single gene. The loss of the gene that makes rice plants grow tall and thus topple over under the weight of many heavy grains of rice is an example of this. Rice breeders are therefore very interested in transferring inactivated genes.

This process has now been successful with microRNAs: RNA molecules consisting of 20 to 22 base pairs that assist in gene regulation. As the microRNAs bind to the complementary base sequence of messenger RNA – scientists refer to this

as RNA interference – they stop these base sequences from being translated into a protein. This silences the gene. "Using artificial microRNAs, we can quickly transfer reduced gene function to other varieties and even species," says Norman Warthmann.

The research group working with Detlef Weigel, Director at the Max Planck Institute for Developmental Biology, developed this technique using the model plant *Arabidopsis thaliana*. They have now tried out this method on rice plants, including the gene *Eui1*. When this gene is inactive, the uppermost part of the rice plant and parts of the flowers grow taller and the plants can more easily pollinate neighboring plants. Breeders use this genetic trick to produce hybrid seeds.

Originally discovered as a spontaneous mutation, *eui1* has been transferred to Indica varieties through years of breeding. With artificial microRNA targeting the messenger RNA of the *Eui1* gene, researchers at the International Rice Research Institute were able to create plants of two rice varieties with the desired characteristics within weeks. One of these was the Indica variety IR64, one of the most important varieties grown in southeast Asia. The stable integration of the gene that carries the information for the microRNA in the plants' genome allows it to be passed on to future generations.

"Artificial microRNAs will also accelerate the identification of important genes and the discovery of new gene functions," says Norman Warthmann. They could also improve immunity to pathogens and pests, by switching off pathogen-derived genes. "We have found microRNAs in all the plant varieties examined so far. It should therefore be possible to apply this technique to other crops as well," says Detlef Weigel. ●

A boost for rice cultivation: Small pieces of RNA accelerate the breeding of new varieties that exhibit new characteristics.



PHOTO: PIRELLO



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ATMOSPHERIC RESEARCH

Shedding Light on a Methane Source



A methane source in sunlight: Plants create the greenhouse gas under UV radiation, which is part of sunlight. A large percentage of the gas is released from pectin – a biopolymer from which the supporting structures of flowers and leaves are made.

Plants store one greenhouse gas, but emit another: While they absorb carbon dioxide, they release methane – albeit in small quantities. Scientists from the Max Planck Institute for Chemistry, the University of Utrecht and the Agri-Food and Biosciences Institute in Belfast have now confirmed this. They have also discovered that some of the greenhouse gas comes from pectin, an important component with which plants build their supporting structure. (New Phytologist, May 9, 2008; Biogeosciences in press)

The announcement caused considerable controversy two years ago: Frank Keppler and his colleagues at the Max Planck Institute for Nuclear Physics in Heidelberg had observed for the first time that plants release methane under aerobic conditions – that is, in the presence of oxygen – and not the anaerobic conditions under which bacteria usually produce the methane that bubbles up out of bogs and marshes. This study further indicated that plants could contribute a substantial proportion of all the methane in the atmosphere.

The global significance of these methane emissions was not the only issue that subsequently gave rise to intense debate: doubt was even cast as to whether plants released methane – a greenhouse gas that is 25 times more damaging to the climate than carbon dioxide – at all. However, Frank Keppler, who is now conducting research at the Max Planck Institute for Chemistry, and his colleagues have produced more evidence from detailed experiments that unequivocally show that plants do indeed produce methane, and that in especially high quantities when they are irradiated with UV light.

Tom Dueck, a scientist at the University of Wageningen in the Netherlands, has now acknowledged the validity of Keppler's new findings. Keppler is particularly pleased with this, as Dueck had strongly contested his original results, not least

because he and his colleagues were unable to reproduce them. However, they had grown plants in greenhouses under artificial light that did not emit UV radiation.

Frank Keppler and his colleagues, some of whom are now working at the University of Utrecht, examined both dry and fresh material from more than 20 different plants. "This time, we deliberately used only parts of the plants, such as leaves, because it is possible that there are processes taking place in living plants that distort the result," explains Keppler. In one series of experiments, the researchers irradiated the specimens with different UV light energies; in another, simultaneously irradiated and heated the plants to 100°C; and in a third, without UV light, examined the plants at temperatures ranging from 20°C to 100°C.

In the process, they established that the more energetic the light shone on the specimens, the more methane the plants emitted. Production reached even higher rates when the temperature was simultaneously increased. Without UV radiation, the emission rate rose to levels comparable with those reached with UV radiation only when the temperature was around 80°C.

One plant component from which UV light forms the greenhouse gas is pectin, a plant structural material. Keppler and his colleagues have now proven the existence of this mechanism by replacing certain hydrogen atoms in pectin with deuterium – the heavier form of hydrogen. They subsequently found the deuterium in the methane again. This does not, however, explain the presence of all the methane, as some is also formed without deuterium. "We still have no idea what this alternative mechanism might be," says Frank Keppler. He adds that, "Since we currently understand only some of the processes that underlie methane emissions from plants, it is difficult to estimate their true extent on a global scale." ●

PHOTO: FRANK KEPPLER – MPI FOR CHEMISTRY

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BIOPHYSICS

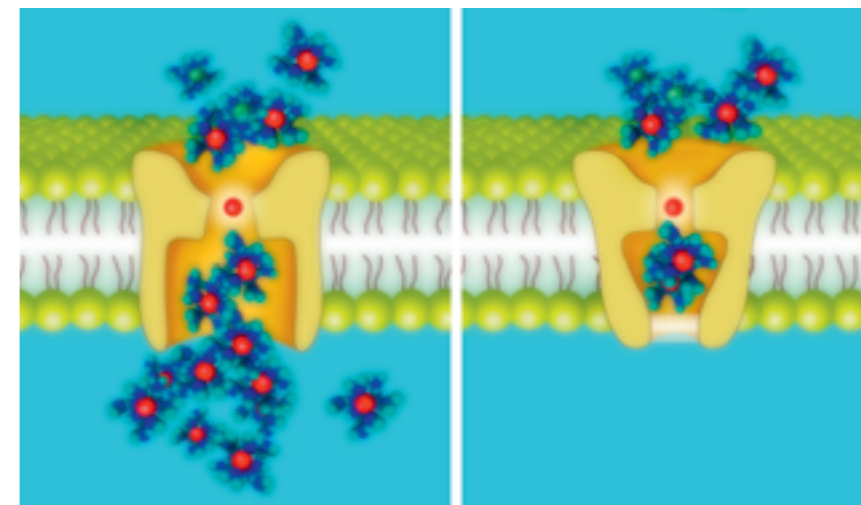
Barriers of Emptiness

Ion channels play an important role in organisms' communication systems: These proteins form tiny pores in the cell membrane through which charged particles, such as potassium and sodium ions, move, thus facilitating, for example, the electrical activity of nerve cells. Scientists at the Max Planck Institute of Metals Research in Stuttgart and their colleagues from Rush Medical School in Chicago and the Miller School of Medicine at the University of Miami have now identified, for the first time, a physical mechanism that might be responsible for opening and closing these ion channels. (BIOPHYSICAL JOURNAL 94, June, 2008)

When we have a cup of coffee for breakfast, and lift the cup to our mouth, our brain processes information about the weight of the cup and the position of our hand. It issues commands to the arm muscles to coordinate the cup-to-mouth movement. This dialog is conducted via nerve fi-

At 1.2 nanometers, the diameter of the part of the pore that is adjacent to this selectivity filter, which scientists call the gate, is much larger. In response to a change in the membrane potential, ion channels increase or decrease the diameter of the gate. However, this conformational change is not necessarily sufficient to halt the flow of ions. An important detail here is that, in most cases, the gate is slightly water-repellent. When the gate is wide enough, the mutual repulsion of water and protein is barely significant, as each water molecule is surrounded, on average, by several other water molecules.

However, if the gate becomes narrower and its diameter is reduced to less than a certain value, then it is very unlikely that there will still be water in the gate. The repellent effect between the water molecules and protein stops this from happening and the space remains empty. This emptiness has a function: ions that prefer to be in water encounter a barrier. The



An invisible barrier: Ions surrounded by water flow through the open gate (left). When the gate closes (right), the channel wall repels the water molecules, creating a barrier.

bers in the form of an action potential. The action potential constitutes a change in the electrical potential across the cell membrane, which results from sodium ions flowing into the cell and the subsequent outflow of potassium ions from the cell.

In itself, a cell membrane is impermeable to ions. In order for sodium and potassium ions to be able to slip through the cell membrane, there are special proteins called ion channels, which are proteins in the membrane that have microscopically small pores. Depending on their structure, they are open only to certain ions; they can distinguish, for example, between sodium and potassium ions. Their narrowest point functions as a filter: in the ion channel investigated here, this point has an approximate diameter of just 0.3 nanometers.

vacuum thus interrupts the flow of ions and closes the gate. "This bubble gating model helps us understand many of the observations that have been made in experiments with opening and closing ion channels," says Roland Roth, who has made a major contribution to the development of the model at the Max Planck Institute of Metals Research.

The bubble gating model could also explain the anesthetizing effect of inert gases, such as xenon. Breathing air with the right concentration of xenon is an almost perfect anesthetic. "Calculations using the bubble gating model have shown that even low concentrations of xenon increase the probability of bubbles forming, even if the gate is still relatively wide open," says Roland Roth. ●

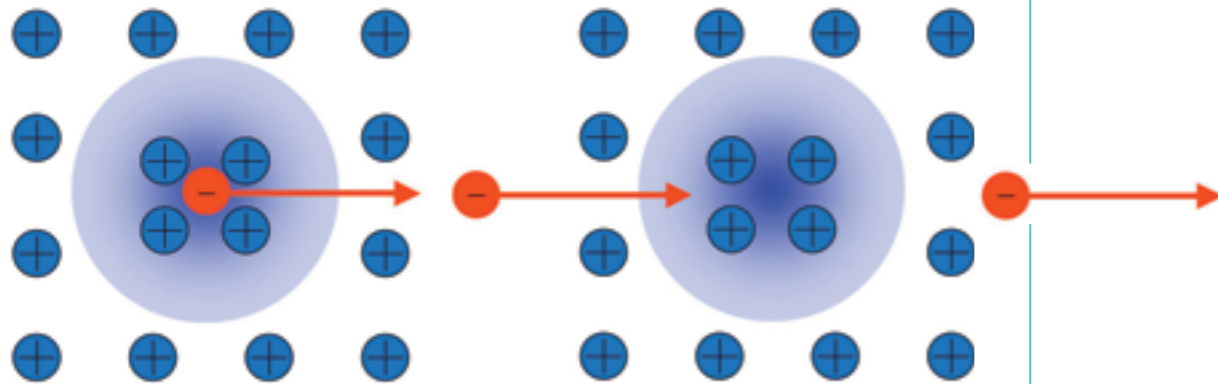
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SOLID-STATE PHYSICS

A Gap in the Superconductor

For more than 50 years, the problem had been considered solved – but apparently only because it had not been fully recognized: as early as 1957, John Bardeen, Leon N. Cooper and John R. Schrieffer explained why metals below certain temperatures conduct electricity without any losses. However, physicists at the Max Planck Institute for Solid State Research have now examined electrons in this superconductive state more closely and discovered a previously hidden detail in their energy distribution that cannot be explained with the theory as it currently stands. (SCIENCE, March 14, 2008)

At the same time, physicists observed a phenomenon in the two metals that, until then, had been considered completely separate from superconductivity. Using readings from spin-echo neutron scattering, a particularly sensitive method, they were able to draw conclusions from the details of the metal's Fermi surface. The scientists drew a relief map in which electrons with a certain momentum or a certain speed are assigned an energy level – mountains represent many electrons, valleys just a few. Previously unknown hills now appeared on this map where no one had expected any to be.



A question of the right attraction: Electrons in normal metals encounter resistance from the positive ions (left).

Some doctors claim that there are no healthy people – only those that have been poorly examined. There may well also be physics theories that are ailing unnoticed as long as they cannot be examined closely enough.

This is clearly the case with the BCS theory. This theory received its name from the initials of the three physicists Bardeen, Cooper and Schrieffer, and describes conventional superconductivity in metals. It states that, below a specific, very low temperature, their free conductive electrons save energy when they come together to form Cooper pairs. These are driven together by the resonance of the crystal lattice. As pairs, they can move through the metal lattice without colliding with its atoms.

A certain energy is required to break the bond in a Cooper pair. Physicists speak of electrons having to jump over an energy gap – a gap that opens only at the critical temperature at which a metal loses its resistance. "Lead and niobium provided a very good illustration of how the energy gaps open," says Bernhard Keimer, Director at the Max Planck Institute for Solid State Research, who also headed the study.

Physicists call these hills Kohn anomalies. At these points, it is particularly easy to nudge electrons away from vibrating atoms, as they carry a matching momentum – similar to the way a child on a swing needs to move its legs in the same rhythm in order to begin moving.

According to the physicists' measurements, the energy gap in the superconducting state grows only to a degree at which electrons with exactly these momentum or energy levels are incapable of forming Cooper pairs. "It can't be by chance that the Kohn anomalies coincide with the energy gaps, because they occur in both lead and niobium," explains Bernhard Keimer. "Without the Kohn anomaly, the metals would perhaps become superconductive at higher temperatures."

The scientist explains further: "Our particularly accurate method of taking measurements has delivered new findings about materials that we thought we knew through and through. We can only speculate as to why Kohn anomalies and energy gaps coincide so unexpectedly." In the final analysis, physicists will probably have to broaden the BCS theory to explain this connection.

In the superconductive state, their charge attracts a second electron and they form Cooper pairs, which move freely through the lattice (right).

ILLUSTRATION: BERNHARD KEIMER – MPI FOR SOLID STATE RESEARCH

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Panorama

A RING AROUND RHEA, Saturn's second-largest moon, has been detected by instruments on board the *Cassini* space probe – making it the first ring system ever to be found around a moon. An electron detector from the Max Planck Institute for Solar System Research in Katlenburg-Lindau and a dust detector from the Max Planck Institute for Nuclear Physics in Heidelberg supplied important information about this ring. Both of these instruments have been orbiting Saturn with *Cassini* since 2004. They have also set their sights on Saturn's moons, including Rhea, which has a diameter of 1,528 kilometers and orbits its parent planet at an average distance of 526,000 kilometers every four and half days. Numerical simulations show that it is indeed possible for dust particles to circle around Rhea in a stable disc. However, there has, as yet, been no visual evidence of this dust ring, as the *Cassini* probe must first reach a position from which its cameras can point directly at the ring's edge.

BATS HEAR PLANTS and can, on the basis of their ultrasound echo, distinguish between deciduous and coniferous trees, as well as identify certain flowers as sources of nectar. Scientists at the Max

Planck Institute for Biological Cybernetics in Tübingen and at the University of Tübingen have been investigating these amazing feats. Using sonar, they imitated key elements of the bats' ultrasonic soundings. They also used machine-learning technology to analyze the vegetation echo they received. It was discovered

that, irrespective of their complexity, these echoes can be precisely matched to individual plants using surprisingly simple time and frequency identifiers. According to the researchers, the combinations of identifiers would also probably be easy for the bats' auditory system to analyze. They therefore supply a "biologically plausible" explanation for this previously elusive feat.

A SHORT CIRCUIT IN THE SIGNAL PATH between scent receptors and ion channels allows fruit flies to respond immediately to environmental scent stimuli. Researchers at the Max Planck Institute for Chemical Ecology and the Friedrich Schiller University, both in Jena, have found that the scent receptor in fruit flies is

closely bound to a second, structurally similar protein. This protein functions as an ion channel and, as such, controls the insect's behavioral response to olfactory signals – signals that indicate either food or a sexual partner. Depending on the concentration of the captured scent molecules, the signals are conducted via two different paths from the receptors to the associated ion channels. With low concentrations, namely, where high levels of sensitivity are important, the stimulus is conducted biochemically via special proteins that activate a messenger substance that eventually reaches the ion channels. Conversely, where the concentration of scent molecules is high, there is a short circuit between the receptor and the ion channel – and the scent stimulus acts directly on the ion channel without the biochemical diversion, thus triggering an immediate behavioral response.

PRIMITIVE ROCKS FROM THE OCEAN FLOOR have been brought to light from the Gakkel Ridge – an extension of the mid-oceanic ridge in the Arctic Ocean – during an expedition on the German research vessel *FS Polarstern*. The samples are of peridotite and originate in the upper sec-



Looking for sources of nectar: Bats identify plants using their ultrasound echo.

tion of the Earth's mantle. Researchers at the Max Planck Institute for Chemistry in Mainz have used isotope analysis to establish that these rocks formed from a melt two billion years ago and have remained unchanged ever since. This has led the scientists to conclude that this "fossilized" peridotite from the Earth's mantle lost its meltable components two billion years ago, which is why it has remained unaltered. Unlike other parts of the ocean floor, it was unable to remelt and become one of the common, younger basalts. These are often found in layers of several kilometers' thickness, forming the oceanic crust over the mantle. The primeval peridotite on the floor of the Arctic Ocean has provided the geosciences with a new look at the history of the Earth's mantle.

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 Further information is available at www.maxplanck.de