

RIKEN

SUMMER 2022

RESEARCH

SHOWCASING THE BEST OF JAPAN'S PREMIER RESEARCH ORGANIZATION • www.riken.jp/en/

MICROBE-MADE

The road to renewable rubber

LONELINESS HORMONE

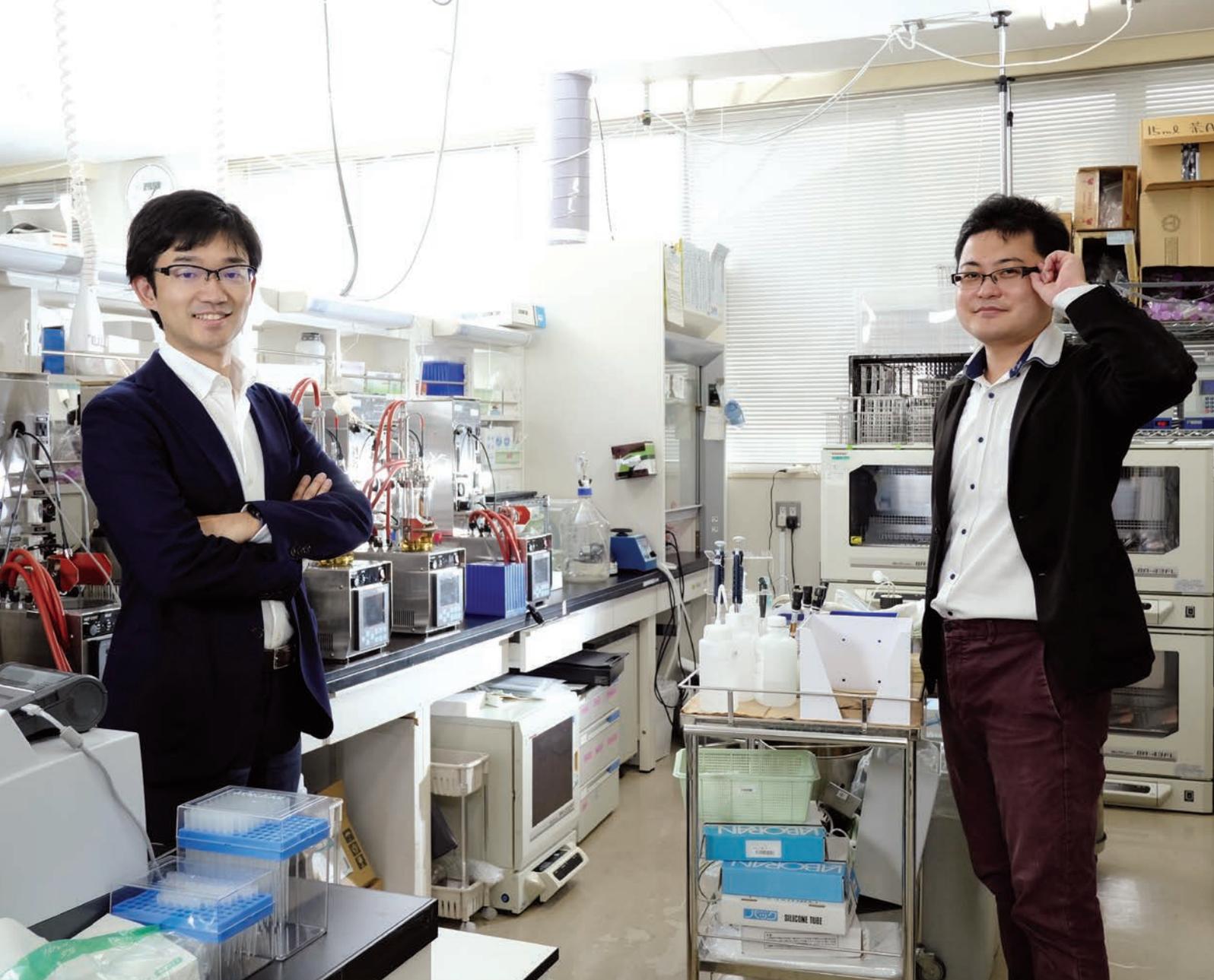
The brain chemistry born from social isolation

WEATHER WIZARDS

When mathematics and meteorology collide

DROID RAGE

Relatable robot conveys emotional range



▲ **Planting possibilities**

Tomokazu Shirai (left), a senior scientist within the Cell Factory Research Team, and Yutaro Mori, a member of Shirai's lab. Shirai's team has already created microbes that take glucose and convert it into maleic acid or 1,3-butadiene, which are chemicals used in polymers and rubbers (see page 26).

RIKEN RESEARCH

RIKEN, Japan's flagship research institute, conducts basic and applied research in a wide range of fields including physics, chemistry, medical science, biology and engineering.

Initially established as a private research foundation in Tokyo in 1917, RIKEN became a national research and development institute in 2015.

RIKEN Research is an online and print publication that highlights the best research published by RIKEN. This

publication is a selection of the articles published by RIKEN at: https://www.riken.jp/en/news_pubs/research_news/. Please visit the website for recent updates and related articles. Articles showcase RIKEN's groundbreaking results and are written for a non-specialist audience.

RIKEN Research is published by RIKEN in collaboration with Nature Research Custom Media, a part of Springer Nature.

For further information on the research in this publication or to arrange an interview with a researcher, please contact: RIKEN International Affairs Division
2-1, Hirosawa, Wako, Saitama, 351-0198, Japan
Tel: +81 50 3500 5438
rikenresearch@riken.jp

ISSN 1883-3519
www.riken.jp/en



ADVISORY BOARD

BIOLOGY

- Kuniya Abe (BRC)
- Makoto Hayashi (CSRS)
- Shigeo Hayashi (BDR)
- Joshua Johansen (CBS)
- Atsuo Ogura (BRC)
- Yasushi Okada (BDR)
- Hitoshi Okamoto (CBS)
- Kensaku Sakamoto (BDR)
- Kazuhiro Sakurada (R-IH)
- Harukazu Suzuki (IMS)
- Toshitada Takemori (IMS)
- Koji Yonekura (RSC)

COMPUTER / COMPUTATIONAL SCIENCE

- Toshiaki Iitaka (R-CCS)
- Takahito Nakajima (R-CCS)
- Hirofumi Tomita (R-CCS)

CHEMISTRY

- Hideki Abe (CSRS)
- Keisuke Tajima (CEMS)
- Katsunori Tanaka (CPR)

ARTIFICIAL INTELLIGENCE

- Hiroshi Nakagawa (AIP)
- Satoshi Sekine (AIP)

PHYSICS

- Akira Furusaki (CEMS)
- Erika Kawakami (RQC)
- Hiroaki Minamide (RAP)
- Yasuo Nabekawa (RAP)
- Shigehiro Nagataki (CPR)
- Atsushi Noguchi (RQC)
- Masaki Oura (RSC)
- Toru Tamagawa (RNC)
- Tomohiro Uesaka (RNC)
- Yasunori Yamazaki (CPR)

3 Editorial

Joining RIKEN's ranks

4 People

Astrocytes,
not just brain glue

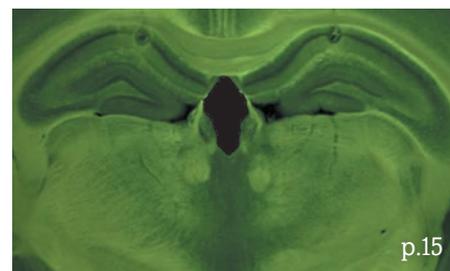
Jun Nagai
*Team Leader of Laboratory
for Glia-Neuron Circuit
Dynamics, RIKEN Center
for Brain Science*

Green hydrogen goals

Shuang Kong
*Postdoctoral Researcher,
Biofunctional Catalyst
Research Team, RIKEN
Center for Sustainable
Resource Science*

8 Research highlights

- 8 Quantum reboot gets a speed boost
- 9 Shrink-wrapped solar cells stick to anything
- 10 Astrocytes assist in making memories
- 11 Retinal transplant technique close to clinical trials
- 12 Better crops without genetic modification
- 13 Bringing fault-tolerant quantum computers closer
- 14 Novel tools for examining plant immunity
- 15 Cell circuit sparks synchronicity
- 16 Developing trust in AI diagnosis



6 Briefs

Makoto Gonokami takes office as
president of RIKEN

Japan Academy Prizes for chemistry and
brain-machine interfaces

Wako Open Campus

President of the Swiss Confederation visits
RIKEN–Max Planck Society symposium



17 Research highlights

- 17 Self-healing polymer bounces back
- 18 Worming out of the black-hole information paradox
- 19 The brain runs on free energy

COVER STORY

- 20 Is loneliness all in the head?

COVER STORY

- 21 Android head gets emotional
- 22 Plant mutations cause beneficial defects
- 23 Flitting between the wings of a butterfly
- 24 Dust grains gang up to seed new planets
- 25 Priming the pump



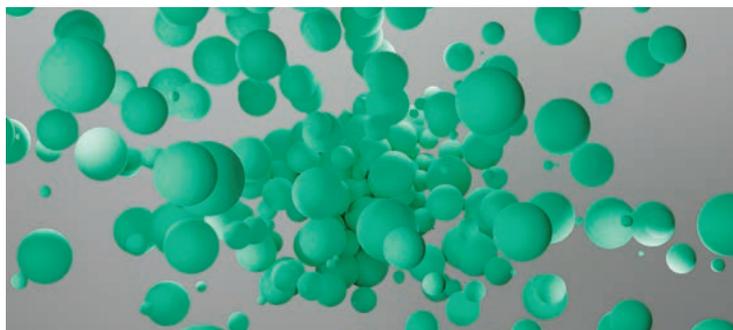
26 Perspectives COVER STORY

Nature's own assembly line: RIKEN-engineered microbes and plant lignin could soon help produce everything from car tires to engine components.



30 Feature COVER STORY

Cracking green hydrogen energy: An electrocatalyst that has a long shelf life is a major step towards realizing terawatts from green hydrogen.



32 Infographic

Japan's genes: RIKEN's BioBank Japan (BBJ) stores genetic data from 260,000 Japanese patients. This data is closing the gap between European and East Asian genetic risk score accuracy.



Joining RIKEN's ranks



Makoto Gonokami
President

As of April this year, I am honored to serve as RIKEN's president. I'm very proud to be able to join so many outstanding researchers working toward the creation of new knowledge, but I am also humbled by the heavy responsibility that comes with leading a research institute with such a long tradition.

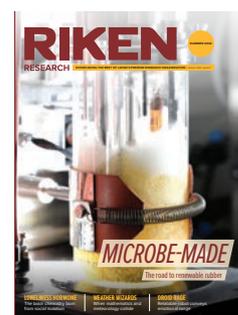
I feel that we are at a crucial point in the history of humanity. For the past 10,000 years or so, we have been blessed to live in exceptionally stable climactic conditions. With this stability as a foundation, civilization evolved from a hunter-gatherer society to an agricultural society, industrial society, and an information society.

However, we now face a major turning point as we confront global challenges that threaten our daily lives and future, including the COVID-19 pandemic, climate change caused by global warming, and tragic military invasions. What these challenges have in common is that they are fundamentally linked to a magnification of human activities by science and technology. Collaboration on a world scale, across borders, is essential if we are to resolve

them. However, the path to international cooperation is a steep and twisting one, and solving the challenges will not be easy.

Nevertheless, I believe in the power of science to continue the quest to find universal truths. I believe that the creation of new knowledge, driven by the joy of discovery, will allow us to overcome difficulties and provide sustenance that will lead the earth and humankind toward sustainable development. At RIKEN, I will dedicate myself to supporting this quest. Through RIKEN's activities, I hope to be able to convey to the world that building knowledge that results in the creation of something out of nothing is a light that will bring about future growth.

I hope that you will find the contents of this new issue exciting, and hope that the articles will perhaps help to stimulate new collaborations between RIKEN researchers and colleagues around the world.



COVER STORY:

RIKEN researchers have been working with tire manufacturers to engineer *E. coli* microbes to take glucose and convert it into 1,3-butadiene, a chemical used to make tires. *Page 26*

© 2022 RIKEN

Keep up to date



Online
www.riken.jp/en



Facebook
facebook.com/RIKENHQ



Twitter
twitter.com/RIKEN_en



LinkedIn
linkedin.com/company/riken

Astrocytes, not just brain glue

Jun Nagai

Team Leader of Laboratory for Glia-Neuron Circuit Dynamics
RIKEN Center for Brain Science



▣ **Please describe your role at RIKEN.**

I'm a team leader in the Laboratory for Glia-Neuron Circuit Dynamics at the Center for Brain Science, which was established 18 months ago. We are testing a hypothesis that neurons are not the only players in brain function: there are also key interactions between neurons and other brain cells. Glia are a type of brain cell that support neuronal insulation and communication, and nutrient and waste transport. While most people are familiar with neurons, glia occupy more than a half of our brain.

All brain disorders feature some alterations of glia, both in human patients and in the lab mice that we study. Despite their importance, glia are still a bit of a mystery, even to scientists.

▣ **What excites you about your current research?**

Small changes in the brain can have outsized effects on our behavior and health—so is there anything common across brain conditions? It's impossible to mention a brain disease that isn't related to glial cells. Glia is Greek for *glue* and for a long time scientists thought these cells just filled space in the brain, acting as a scaffolding structure for neurons. I focus on astrocytes, a type of star-shaped glial cell. Progress in the last decade has revealed that astrocytes are not

passive, but actively regulate neural circuits in healthy and diseased brains. We know this because scientists, including myself, have developed tools to monitor and manipulate glial cells. These include specialized multi-photon laser scanning microscopy and opto-/chemo-genetics, as well as *in silico* analysis pipelines.

▣ **Please describe your long-term research goals.**

Currently, there are no treatments or diagnoses for human neurological and neuropsychiatric disorders stemming from glial cells, so my hope is to provide a new perspective on brain function and dysfunction that will lead to new therapies or diagnoses.

“ *Mysterious glia occupy more than a half of our brain. All brain disorders feature some alterations of glia.* ”

▣ **How did you become interested in your current field of research?**

There aren't many jobs that let you be yourself, but as a scientist I can 100% be myself. This need stems from a keen sensitivity to individual differences that I developed early in life. I asked my parents why my siblings, who have developmental disabilities, are different: they said 'it's just the brain, everything else is the same'. To improve the recognition and acceptance of human differences, I realized that I have to study the brain.

▣ **What made you decide to become a scientist?**

I was tempted to become a medical doctor, but I realized my impact would possibly be more limited than I thought. You could treat patients every day, but you can't cure the incurable. Scientists have freedom to think out of the box to solve those problems, and though it could take tens of years, it could help millions of people. ■

Green hydrogen goals

Shuang Kong

Postdoctoral Researcher, Biofunctional Catalyst Research Team
RIKEN Center for Sustainable Resource Science

▣ Please describe your role at RIKEN.

I'm a postdoctoral researcher in the Biofunctional Catalyst Research Team at the RIKEN Center for Sustainable Resource Science. My research is linked to the center's Innovative Catalysts flagship project, and I'm focused on advanced catalyst development for efficient and sustained water electrolysis (the process by which water is split into oxygen and hydrogen by an electric current). If done with renewable energy, electrolysis can produce 'green hydrogen' for use as a cleaner fuel.

▣ Please describe your current research.

At the moment I'm seeking highly stable and active catalysts for polymer electrolyte membrane (PEM) electrolysis—where a cell transfers ions between the anode and cathode using a solid polymer electrolyte to create hydrogen from water. PEM electrolysis is a promising means of efficiently producing green hydrogen. Large-scale implementation is limited by the scarcity of the most efficient known oxygen evolution reaction catalyst, iridium. We want to find alternative catalytic materials in order to accelerate renewable energy transitions (see more about RIKEN's work in this area on page 30).

▣ "My research is important for sustainable development because..."

My research is important for sustainable development because efficient water electrolysis will further the widespread use of renewable, relatively clean hydrogen energy. Hydrogen is

light, easy to store and energy dense. It can be converted into chemicals, fertilizers and pharmaceuticals, as well as fuels. It could replace industrial processes that consume fossil fuels and produce huge emissions. For example, green hydrogen can be used for ammonia synthesis, which accounts for about 2% of the world's fossil fuel primary energy consumption.

▣ What excites you about your current research?

My work is able to extract hydrogen, a clean energy vector, from ordinary water. I feel very excited when I see a large amount of bubbles generated by a catalyst, not only because it indicates high-performing catalysis, but also because of its raw beauty.

▣ What has been your most memorable experience at RIKEN?

I will never forget RIKEN's 2019 open day. It was the first time I'd explained our group's research to the public in Japanese. I was grateful that even though I couldn't speak Japanese fluently, the audience listened patiently. I was especially impressed by the children in the group, and their curiosity and ability to unravel riddles.

▣ How has being at RIKEN helped your research?

RIKEN gives young people many opportunities to apply for funds and collaborations. I was honored to receive an Incentive Research Project Fund in 2021, which gave me more confidence to pursue my research goals.

In terms of technology, RIKEN has its own beamline at the SPring-8 synchrotron radiation facility. This means I can easily do advanced characteristic experiments on potential catalysts to further understand the properties of each material. To do this, I use advanced crystallography and spectroscopy techniques, such as X-ray absorption spectroscopy and pair diffraction. ■

Careers at RIKEN

For further information, visit our Careers page:
Website: www.riken.jp/en/careers
E-mail: pr@riken.jp



Makoto Gonokami takes office as president of RIKEN

On April 1, 2022, Makoto Gonokami, who previously served as president of the University of Tokyo, succeeded Hiroshi Matsumoto as president of RIKEN. In addition, there have been a number of changes to the Board of Executive Directors. The new appointments to the board are pictured below. www.riken.jp/en/news_pubs/news/2022/20220401_1

Makoto Gonokami, President of RIKEN

“Now at RIKEN, I will dedicate myself to supporting the earnest activities of researchers. I believe that collaboration across traditional academic disciplines is once again becoming critical. But collaboration should not be limited to the natural sciences and engineering. Rather, it should extend to fundamental questions for humanity, such as what a person is and what society is.”



President of the Swiss Confederation visits

On April 20, 2022, a delegation led by Ignazio Cassis, president of the Swiss Confederation, visited the RIKEN Center for Computational Science (R-CCS) in Kobe.

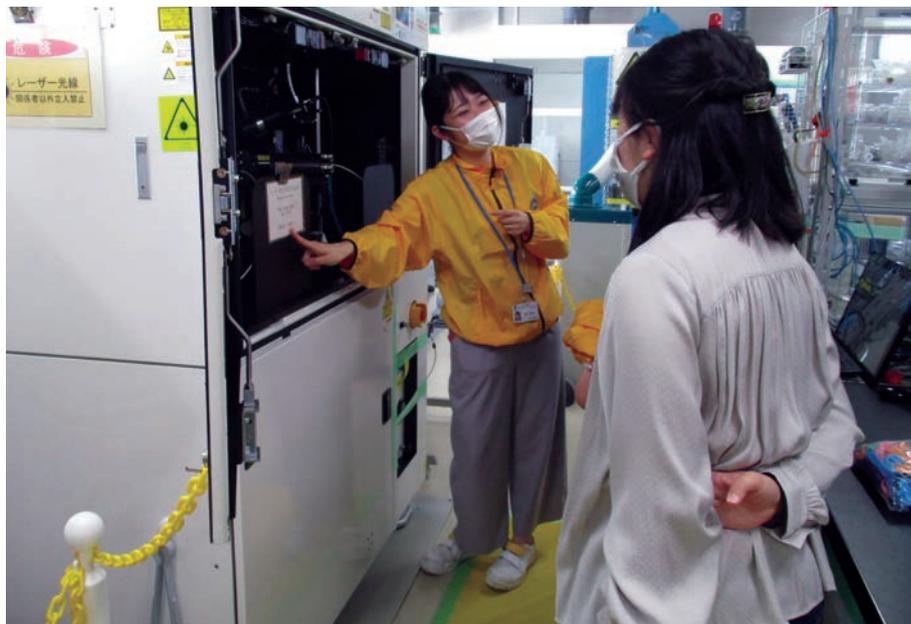
At the event R-CCS Director Satoshi Matsuoka gave an introduction to the supercomputer Fugaku, the center's flagship, which has won the world's top benchmarking awards for four consecutive terms, and discussed some research results including countermeasures against the COVID-19 pandemic. Then, with the aim to encourage the use of Fugaku to produce research results through partnerships with Switzerland, a ceremony was held to conclude a basic agreement for new collaboration in the field of supercomputing between the Swiss National Supercomputing Center and the R-CCS.

www.riken.jp/en/news_pubs/news/2022/20220425_2/

RIKEN–Max Planck Society symposium

On October 26, 2021, RIKEN and the Max Planck Society (MPS) held an online symposium on systems chemical biology. The symposium began with addresses from RIKEN Executive Director Yuko Harayama, MPS Vice President Klaus Blaum, and RIKEN Center for Sustainable Resource Science Director Kazuki Saito. Then, from the MPS, Herbert Waldmann spoke about small molecules for systems biology, and Peter Seeberger spoke on using synthetic tools to understand biological processes and create novel treatments. Following them, from RIKEN, Katsunori Tanaka talked about therapeutic *in vivo* synthetic chemistry using glycoconjugates, and Hiroyuki Osada spoke about chemical biology on small molecules that affect cellular events, growth, and death.

www.riken.jp/en/news_pubs/news/2022/20220325_2



Participants who were able to make it to RIKEN's Wako Open Campus in person were given a tour of the labs.

Wako Open Campus

On April 23, 2022, the RIKEN Wako Open Campus was held both on site and online. Participants on site were able to join special lectures, booth tours, hands-on showcases, and lab tours. At one lecture, Yoshihiro Iwasa of the RIKEN Center for Emergent Matter Science talked about making superconductors with nanotech devices, and Yasuo Tabei of the RIKEN Center for Advanced Intelligence Project lectured on

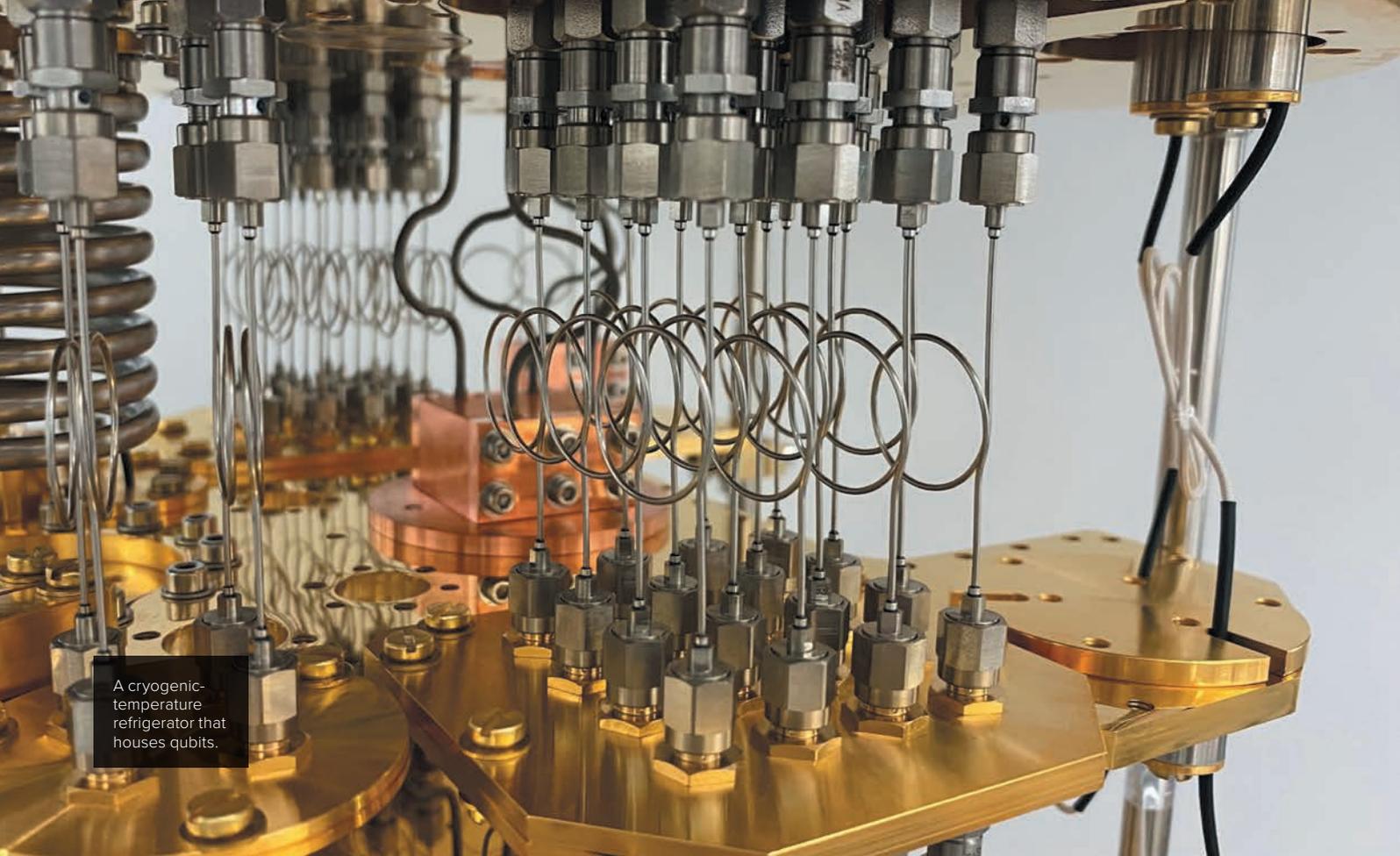
succinct data structure for large-scale data analysis. Teruaki Enoto of Extreme Natural Phenomena RIKEN Hakubi Research Team talked about the citizen scientists helping to track lightning and thunderstorms, and Shinichi Yorozu of the RIKEN Center for Quantum Computing talked about quantum computers. On the event's website, visitors enjoyed live streamed lectures, virtual open laboratories and lab tour videos.

Japan Academy Prizes for chemistry and brain–machine interfaces

On March 14, 2022, RIKEN's Zhaomin Hou was awarded the Japan Academy Prize for his work on the development of organo rare-earth chemistry and exploration of new synthetic methods. RIKEN advisor Mitsuo Kawato was awarded the same prize for his study of brain functions using computational neuroscience, and the development of brain–machine interfaces.

Upon hearing the news, Hou, chief scientist of the Organometallic Chemistry

Laboratory and deputy director of the RIKEN Center for Sustainable Resource Science, said: "I am deeply honored to receive this award for my research in organo rare earth chemistry, which I have continued for the past 30 years since joining RIKEN." Kawato, a senior advisor to the RIKEN Center for Advanced Intelligence Project, said: "The field for which I received the award is computational neuroscience, which is, so to speak, a boundary area between brain science and the field of artificial intelligence. I would like to express my gratitude for the support I have received over the years from the RIKEN Brain Science Institute, the Center for Integrated Research on Innovative Intelligence, and the Center for Brain Science."



A cryogenic-temperature refrigerator that houses qubits.

QUANTUM COMPUTING

Quantum reboot gets a speed boost

Simulations suggest a new technique for resetting ‘qubits’ in a quantum computer without harming them

Rebooting a quantum computer is a tricky process that can damage its parts, but now two RIKEN physicists have proposed a fast and controllable way to hit reset.

Conventional computers process information stored as bits that take a value of zero or one. The potential power of quantum computers lies in their ability to process ‘qubits’ that can take a value of zero or one—or be some fuzzy mix of both simultaneously.

“However, to reuse the same circuit for multiple operations, you have to force the qubits back to zero fast,” says Jaw Shen Tsai, a quantum physicist at the RIKEN Center for Quantum Computing. But that is easier said than done.

One of the best current ways to hit reset for qubits built from tiny superconductors is to link the qubit to a photon—a particle of light—in a tiny device called a resonator. The qubit transfers its energy to the resonator, after which the photon in the resonator decays, releasing its energy to the environment. This process causes the qubit state to drop back to the ground state (zero). The trouble with this method is that permanent entanglement to a decaying photon rapidly degrades the qubit’s quality, so that it rapidly ceases to be useful for future operations. “It’s bad for the qubit, whose lifetime becomes short,” says Tsai.

Now, Tsai and his RIKEN colleague Teruaki Yoshioka have

devised a simulation to help find a better way of resetting the qubit, without harming it.

Based on their calculations, the pair proposed building a resonator that can be controlled using an additional junction made by sandwiching a superconducting material with an insulator, a normal metal, another insulator and another superconductor. This layered junction is controlled by applying a voltage. While the qubit operation is being carried out, the set-up is tuned so that the photon cannot decay. Only when the operation has been completed do the physicists change the voltage, allowing the photon to release energy. “This adjustable resonator is the key to our proposal,” says Tsai.

The best current lab record for resetting a qubit is 280 nanoseconds, with 99.0% fidelity. “Our simulations suggest we could reset the qubit in 80 nanoseconds, with 99.0% fidelity,” says Yoshioka.

The team is testing this set-up, which is held at low temperatures using a cryogenic-temperature refrigerator. “This device should be very useful if we can implement it in a quantum circuit,” Tsai says. ●

REFERENCE

1. Yoshioka, T. & Tsai, J. S. Fast unconditional initialization for superconducting qubit and resonator using quantum-circuit refrigerator. *Applied Physics Letters* **119**, 124003 (2021).

ORGANIC ELECTRONICS

Shrink-wrapped solar cells stick to anything

Ultrathin electronics can now be laminated onto curved surfaces using heat-shrinkable polymers

Heat-shrinkable technology developed by an all-RIKEN team could allow solar cells and touch sensors to be attached to objects that have shapes that make them challenging to laminate¹.

Recent studies have indicated that curved solar-cell panels capture sunlight more efficiently than flat ones on cloudy days. One way to produce curved electronics is with rubber-like substrates, but solar cells on such substrates usually have relatively low performance. In contrast, solar cells fabricated on flexible sheets have high efficiency, but can be difficult to attach to curved surfaces—a fact that anyone who has tried to gift wrap a soccer ball can attest to.

Researchers led by Takao Someya of the RIKEN Center for Emergent Matter Science realized that this problem could be overcome using heat-shrinking films, which are commonly used to encapsulate products such as over-the-counter medications. While most electronics are too rigid or fragile to be attached to shrink film, the team specializes in producing ultrathin devices with unique properties.

“When a material becomes thinner, it becomes more flexible—that’s why we can crumple aluminum foil by hand, but can also use aluminum to make bicycles,” explains postdoctoral researcher Steven Rich. “Although we use rigid materials such as metals and plastics, they are three times thinner than a grocery bag and can bend very sharply without breaking.”

Rich and three RIKEN



RIKEN researchers have used their heat-shrinking technology to attach organic photovoltaic films to spheres of different sizes.

The team also used shrink wrapping to laminate the handle of a teacup with an electronic touch sensor

colleagues attached a non-stretchable but flexible polymer sheet to a shrink film. They then used microscopy to observe the layered structure during various exposures to heat. These tests revealed that, as the device’s area shrank by up to 70%, the ultrathin sheets relieved the strain of compression by forming tiny wrinkles and folds.

By controlling the size of these wrinkles and choosing materials capable of surviving both heat and severe wrinkling, the RIKEN team found they could shrink prefabricated organic photovoltaic modules onto round objects (see image) as well as ones with sharp angles and irregular curvatures, including plastic rocks and traditional Japanese *Daruma* dolls.

Although the researchers anticipated that shrinking might damage the photovoltaic components and reduce device performance, the opposite occurred. Experiments indicated that the photonic properties of the shrink-induced wrinkle structures improved light absorption, boosting power conversion efficiencies by up to

17% over planar devices.

The team also used shrink wrapping to laminate the handle of a teacup with an electronic touch sensor—a delicate feat that serves as an example of how this technology could be widely applied. “We could incorporate sensors along with displays, power-generation systems, and transistors to create interactive interfaces,” Rich says. ●

REFERENCE

1. Rich, S. I., Lee, S., Fukuda, K. & Someya, T. Developing the nondevelopable: Creating curved-surface electronics from nonstretchable devices. *Advanced Materials* 2106683 (2021).

NEUROSCIENCE

Astrocytes assist in making memories

Brain cells known as astrocytes play a prominent role in tuning changes in neuronal activity that enable memories to be stored

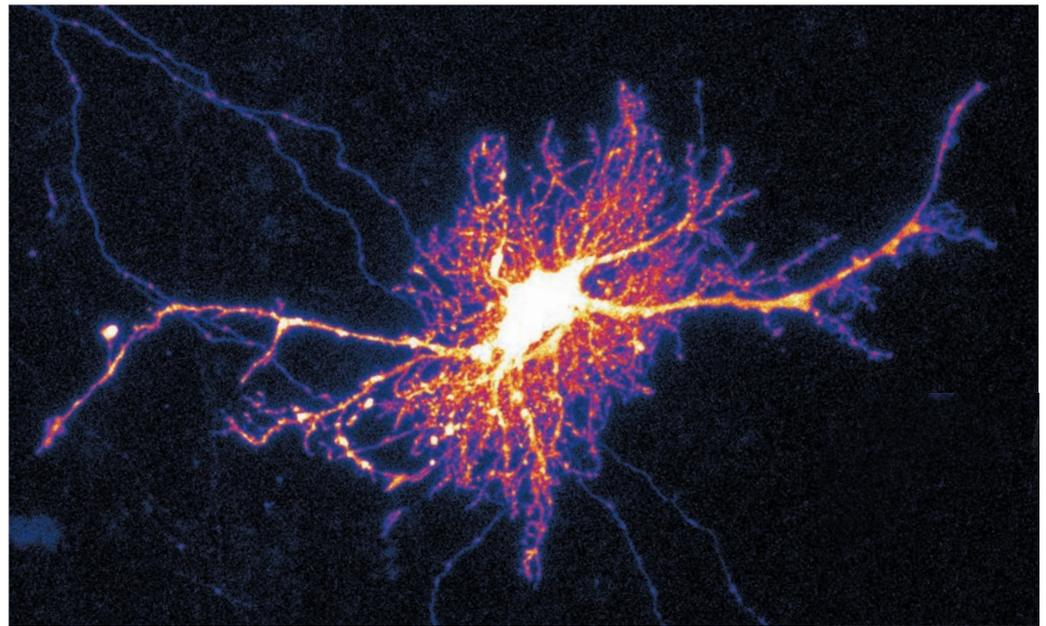
RIKEN neuroscientists have discovered a surprising mechanism for how neuronal activity in mice is dynamically tuned to promote the process of learning and memory formation¹. This finding provides new insights into the role brain cells called astrocytes play in memory creation.

A team led by Yukiko Goda of the RIKEN Center for Brain Science has been seeking to understand the neural processes underlying learning and memory formation. “One of our major goals is to understand how the strengths of individual synapses are set and dynamically modified,” says Goda.

In a 2016 study, Goda’s team used rat brain cell cultures to study the behavior of simple systems in which multiple input neurons formed synaptic connections with the dendrite of a single recipient neuron. They determined that astrocytes—a highly abundant population of cells that play various essential supporting functions in the brain—facilitated the strengthening of active synapses, while weakening less-active synaptic connections.

Now, the team has probed this regulatory mechanism more deeply. In particular, they focused on the role of receptors for the neurotransmitter N-methyl-D-aspartate (NMDA) in the mouse hippocampus, the brain region where memories are formed.

“NMDA is a well-established component of neuronal signaling in the hippocampus,” explains Goda. “But the idea of astrocyte



A micrograph showing a labeled astrocyte. Yukiko Goda and her team have demonstrated how astrocytes play a prominent part in tuning the changes in neuronal activity that enable memory formation.

NMDA receptors has met with some skepticism.” Nevertheless, her team’s prior work offered compelling evidence that such receptors are directly involved in tuning the connections between nearby neurons.

In the latest study, Goda and colleagues used various interventions to selectively interfere with NMDA receptor activity in mouse astrocytes. These treatments clearly affected activity on the presynaptic side of synapses, modulating the terminals of input neurons, rather than the dendrites of the neurons that received those signals. Consequently, synaptic activity between input and recipient neurons became more uniform overall, rather than shifting dynamically to

favor activity at some synapses relative to others.

Mathematical modeling, done in collaboration with a team led by Tomoki Fukai at the Okinawa Institute of Science and Technology Graduate University (OIST), revealed that these changes in synaptic function greatly reduced neural plasticity in the hippocampus, namely the selective reinforcement of memories through the strengthening and weakening of synapses between neurons.

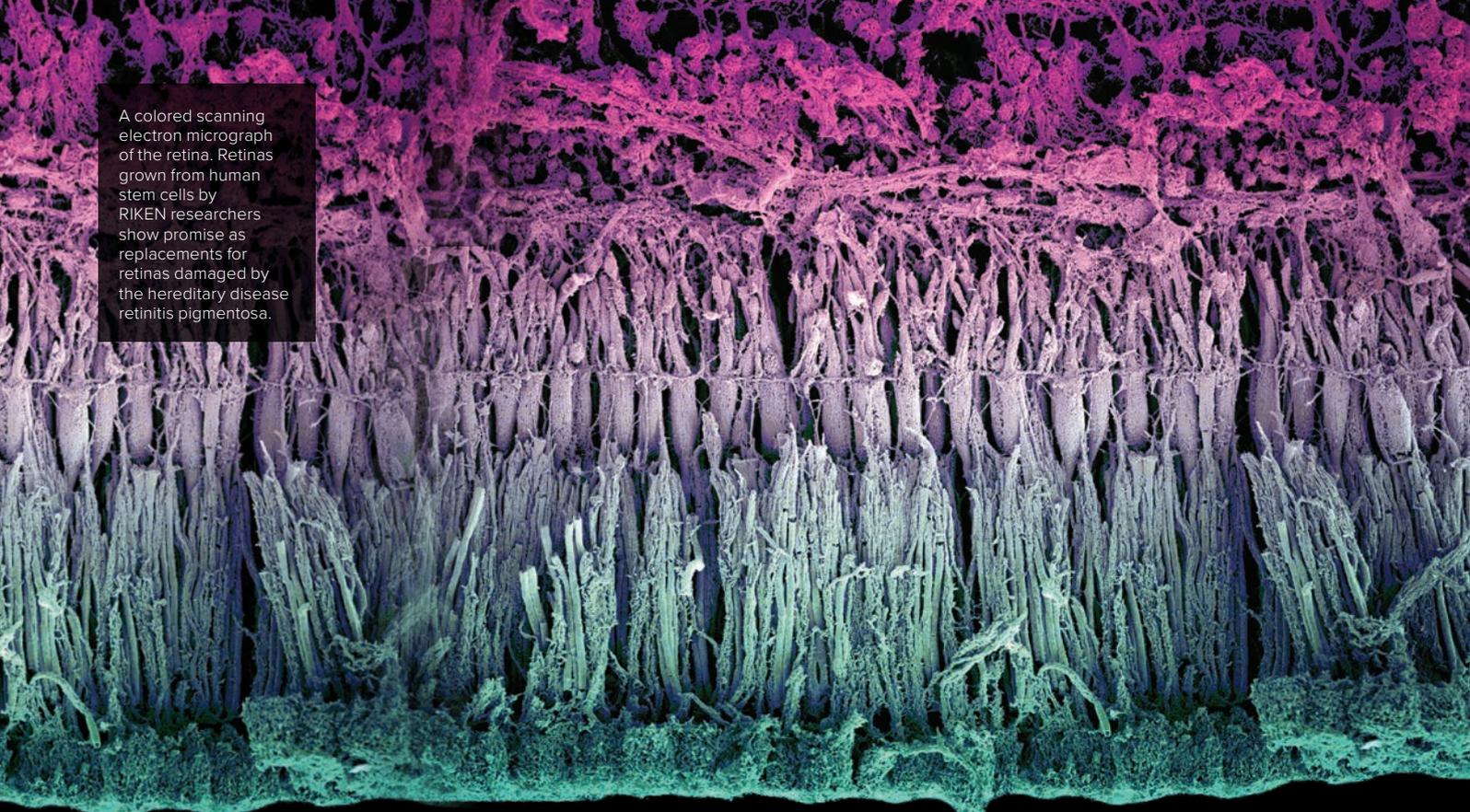
“Our work demonstrates that astrocyte signaling helps ensure the broad distribution of presynaptic strengths,” says Goda.

The team is now trying to better understand the organization, activity and distribution of NMDA receptors in

hippocampal astrocytes, and the broader influence of these non-neuronal receptors on animal behavior. “We want to discover whether mice with impaired astrocyte NMDA receptors show altered hippocampal network activity, and, if so, whether those changes relate to spatial and contextual learning,” says Goda. ●

REFERENCE

1. Chipman, P. H., Fung, C. C. A., Fernandez, A. P., Sawant, A., Tedoldi, A., Kawai, A., Gautam, S. G., Kurosawa, M., Abe, M., Sakimura, K. *et al.* Astrocyte GluN2C NMDA receptors control basal synaptic strengths of hippocampal CA1 pyramidal neurons in the *stratum radiatum*. *eLife* **10**, e70818 (2021).



A colored scanning electron micrograph of the retina. Retinas grown from human stem cells by RIKEN researchers show promise as replacements for retinas damaged by the hereditary disease retinitis pigmentosa.

REGENERATIVE CELL THERAPY

Retinal transplant technique close to clinical trials

Improved retinal sheets grown from human stem cells connect better with degenerated rat retinas

A new technique that seeks to treat a hereditary eye disease by transplanting retinas grown from human stem cells will soon be ready to test in human clinical trials thanks to a genetic modification by RIKEN researchers that improved retina transplants in rats¹.

Retinitis pigmentosa is a hereditary disease in which photoreceptors in the retina die, leaving people with complete loss of vision or progressive loss in certain spots. One promising therapy is to replace the part of the retina at the back of the eye with a retinal sheet grown from stem cells that includes photoreceptors.

For this regenerative therapy to work, the new light receptors in the graft must connect to neurons in the host retina, thereby allowing light from the outside world to be relayed to the

brain, which is how we see.

Connecting the grafted sheet to bipolar cells in the host retina is critical, but bipolar cells in the retinal sheet hinder this. “Bipolar cells are inevitably born when the retinal sheet develops properly and photoreceptors mature,” says Michiko Mandai of the RIKEN Center for Biosystems Dynamics Research. “But it’s their very connection to the bipolar cells in the retinal sheet that prevents the photoreceptors from connecting to the bipolar cells in the host.”

The solution was to engineer retinal sheets that would lose their bipolar cells during the final stages of photoreceptor maturation. The researchers targeted a gene necessary for maturation of bipolar cells that connect to photoreceptors. They began with a line of human stem cells and made clones lacking

the gene. The team then grew retinal organoid sheets from these clones. These retinal sheets initially developed the same way as those grown from normal stem cells, but later they lacked mature bipolar cells.

The researchers then transplanted these retinal sheets onto degenerated rat retinas lacking almost all photoreceptors. The photoreceptors in the retinal sheet matured properly after transplantation, and made better contact with the host eye than normal retinal sheets.

The team found that retinal ganglion cells, which form the optic nerve and relay visual information from bipolar cells to the brain, had better responses to light than those that received a normal retinal sheet transplant. “The genetic modification in human stem-cell derived retinas showed a substantial functional

improvement compared with the wild-type graft retinas,” says Mandai.

Applying this technique to human cells is a significant milestone, says Mandai. “We can now move forward to applying this strategy in clinical studies,” she says. “We expect it will improve clinical outcomes and be useful in general for stem-cell based therapies targeting retinal degeneration.” ●

REFERENCE

1. Yamasaki, S., Tu, H.-Y., Matsuyama, T., Horiuchi, M., Hashiguchi, T., Sho, J., Kuwahara, A., Kishino, A., Kimura, T., Takahashi, M. *et al.* A genetic modification that reduces ON-bipolar cells in hESC-derived retinas enhances functional integration after transplantation. *iScience* **25**, 103657 (2022).

Soybean is one crop that stands to benefit from a method that can make plants more drought or pest resistant by simply spraying them.



PLANT GENETICS

Better crops without genetic modification

An approach that improves crops by spraying them gives the benefits of genetic modification without the expense and public backlash

A method developed by RIKEN plant geneticists to spray crops with a bioactive compound that makes them more drought or pest resistant promises to be cheaper, faster and easier than genetic modification¹.

Technology allows us to genetically modify plants, but this takes time and money, and it has yet to gain widespread public support.

Now, a team led by Masaki Odahara of the RIKEN Center for Sustainable Resource Science has developed an alternative method that can overcome these problems.

Rather than altering a plant's genome so that it doesn't express a particular gene, their method

suppresses the gene by using a carrier that can penetrate plant cell walls to insert a specific bioactive compound into the plant's cells.

Implementing this simple concept proved challenging. "We had to consider a delivery method that would be practical for cultivated crops under real agricultural conditions," says Odahara. The team concluded that a spray deployable over large fields relatively easily would be best.

The team investigated cell-penetrating peptides (CPPs) because they can target specific structures inside plants cells, such as chloroplasts. To determine the best CPPs for a spray, the team tagged natural

and synthetic CPPs with fluorescent yellow, sprayed them on the leaves of thale cress and several types of soybeans and tomatoes, and measured the amount of fluorescence in the leaves at different times. This revealed several natural CPPs that could penetrate the outer layer of leaves, and in some cases even deeper.

This technique worked well when plasmid DNA was attached to the CPPs. After being carried into the cells via an aqueous spray, genes were expressed in the leaves of thale cress and soybeans.

Crop yield can improve by inserting or knocking out genes. After creating a transgenic plant that overexpresses yellow fluorescence in the leaves, the team attached RNA that interferes with fluorescent protein expression to a CPP. As hoped, spraying the leaves with this complex silenced yellow-fluorescence expression. "This result was critical because it is important that any alternative to genetic modification be able to achieve the same functional outcome," says Odahara.

The researchers were able to similarly silence genes specific to chloroplasts when they included a chloroplast-targeting peptide to a specific CPP–RNA complex. "Mitochondria and chloroplasts regulate much of a plant's metabolic activity," explains Odahara. "Targeting these structures with bioactive molecules delivered via spray could effectively improve economically desirable quality traits in crops."

The team next intends to improve the efficiency of the delivery system. "Ultimately, we hope this system can be used to safely protect crops from parasites or other harmful factors," says Odahara. ●

REFERENCE

1. Thagun, C., Horii, Y., Mori, M., Fujita, S., Ohtani, M., Tsuchiya, K., Kodama, Y., Odahara, M. & Numata, K. Non-transgenic gene modulation via spray delivery of nucleic acid/peptide complexes into plant nuclei and chloroplasts. *ACS Nano* **16**, 3506–3521 (2022).

QUANTUM COMPUTING

Bringing fault-tolerant quantum computers closer

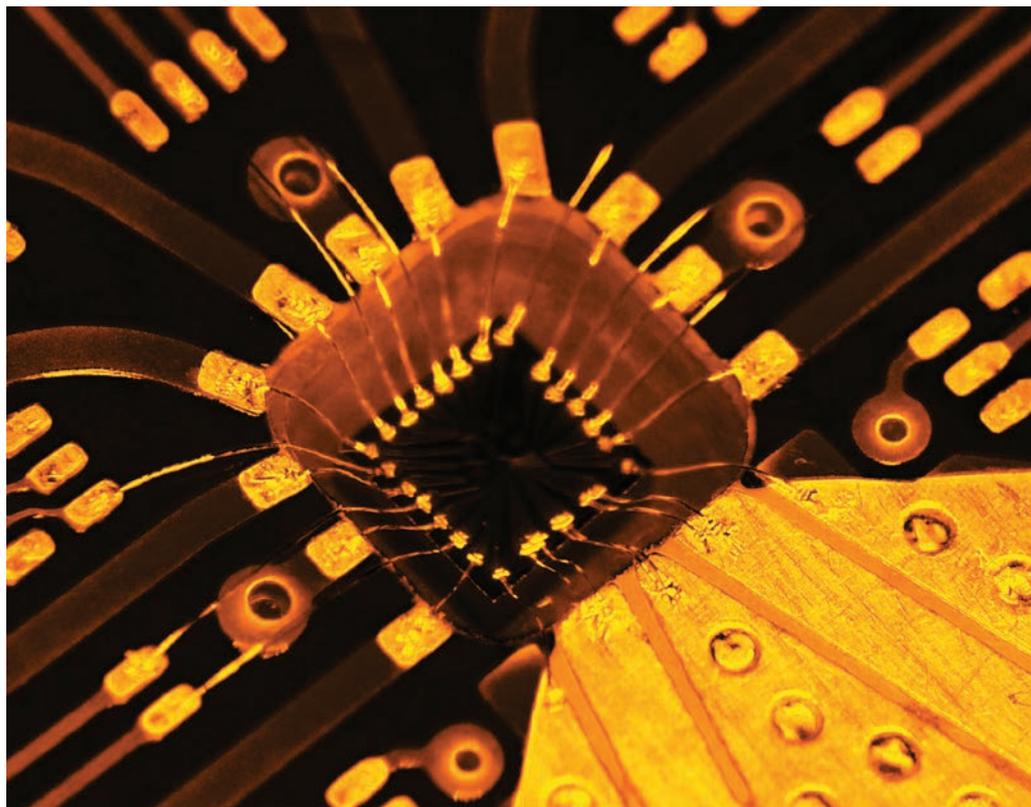
Realizing large-scale quantum computers based on silicon is closer to becoming a reality with the demonstration of high gate fidelities

A key milestone toward developing fault-tolerant quantum computers based on electron-spin qubits in silicon has been realized by RIKEN physicists, with the demonstration of a high two-qubit gate fidelity that exceeds the threshold needed for error correction¹.

Physicists around the world are racing to develop large-scale quantum computers that could vastly outperform classical computers in certain areas. However, the problem of noise generated in the qubits—the quantum equivalent of bits—has been hampering the scaling up of quantum-computing technologies, because it becomes more problematic with increasing numbers of qubits.

To achieve a large-scale quantum computer useful for real applications, a two-qubit gate fidelity of at least 99% is thought to be needed to correct errors. While this has been achieved in certain types of quantum computers, they are hard to scale up to the millions of qubits required to implement practical quantum computation with error correction. On the other hand, quantum computers based on electron-spin qubits in silicon are promising for large-scale quantum computers since the nanofabrication technology for building them already exists, but until now they have had two-qubit gate fidelities of lower than 99%.

Now, a team led by Seigo Tarucha of the RIKEN Center for Emergent Matter Science (CEMS) has exceeded this



The silicon-based quantum computer chip that has a two-qubit gate fidelity high enough to realize error correction.

threshold in a quantum-dot structure (see image) by realizing a two-qubit gate fidelity of 99.5%.

“We’re very happy to have achieved a high-fidelity universal quantum gate set, one of the key challenges for silicon quantum computers,” says Akito Noiri, also of CEMS.

In previous experiments, the gate fidelity was limited by a slow gate speed. To increase the gate speed, the team carefully designed the device and tuned its operation by applying voltages to the gate electrodes. This approach, which combined a fast single-spin rotation technique

using micromagnets and a large two-qubit coupling, enhanced the gate speed by a factor of ten compared to previous studies.

The team demonstrated that they could perform all the basic quantum operations with gate fidelities above the error-correction threshold. They tested the capabilities of their system by implementing two algorithms. It achieved correct results with high fidelities of 96–97%, showing that silicon quantum computers can perform quantum calculations with a high accuracy.

The team is excited about the implications of their results.

“This study demonstrates that silicon quantum computers are promising candidates, along with superconducting circuits and ion traps, for research and development toward the realization of large-scale quantum computers,” says Tarucha. ●

REFERENCE

1. Noiri, A., Takeda, K., Nakajima, T., Kobayashi, T., Sammak, A., Scappucci, G. & Tarucha, S. Fast universal quantum gate above the fault-tolerance threshold in silicon. *Nature* **601**, 338–342 (2022).

PLANT IMMUNITY

Novel tools for examining plant immunity

Drugs that inhibit plant immune responses by blocking key signaling pathways could enable novel approaches to genome editing

A group of non-steroidal anti-inflammatory drugs (NSAIDs) may prove valuable for investigating the molecular mechanisms inherent in plant immunity, according to plant scientists at RIKEN¹. Their results may also help improve genome-editing techniques for crops.

Many NSAIDs, including aspirin, are derived from a plant defense signaling hormone called salicylic acid. In plants, salicylic-acid levels increase in response to pathogenic attacks from viruses, fungi

The cell-culture system allowed them to rapidly screen thousands of chemicals

and bacteria. External treatment with salicylic acid can also boost the immune responses of plants. However, the precise mechanisms underlying salicylic-acid signaling pathways are unclear, partly because the compound plays multiple roles and acts differently in different species of plants.

Ken Shirasu at the RIKEN Center for Sustainable Resource Science has spent many years

studying plant immunity. Back in 1997, he demonstrated that salicylic acid induces immune signaling. When they encounter a pathogen, plants trigger salicylic-acid activity to induce local cell death as a key immunity response.

“Chemical genetics has come a long way since then, and so I decided to return to my initial experiment with my team here at RIKEN,” says Shirasu. “We re-established the assay using a cell-culture system of the model plant *Arabidopsis*.”

Since Shirasu’s team knew that salicylic acid interacts with a protein called NPR1, a critical regulator of immunity-related genes, they used the gene that encodes NPR1 as a marker of salicylic-acid activation in their model. The researchers explored whether other NSAIDs could boost plant immunity when challenged with the bacterium that causes bacterial speck disease. The cell-culture system allowed them to rapidly screen thousands of chemicals to find salicylic-acid functional mimics that caused immune-mediated cell death.

“Most of the chemicals we tested initiated immune responses similar to those of salicylic acid, but we found three ‘oxicam-type’ NSAIDs that instead suppressed immunity signaling,” says Shirasu. “This was



An *Arabidopsis* plant model enabled RIKEN researchers to test hundreds of chemicals to find out how they interacted with plant immune responses.

very curious.”

When the team examined the activity of the most potent of the three, tenoxicam, they found that tenoxicam prevents the NPR1 protein from accumulating in cell nuclei.

“We believe tenoxicam upregulates oxidative stress-related genes, inducing oxidation and altering cellular redox status,” says Shirasu. “NPR1 is regulated by redox status, so this disruption inhibits the plant’s salicylic-acid pathway.”

“These NSAIDs provide a unique tool to dissect the salicylic-acid signaling pathway and improve our understanding of plant immunity,” Shirasu adds.

A potential application of this finding could be in genome editing. *Agrobacterium* is often used to genetically transform plants, but some crops are resistant to infection. Oxicam-type NSAIDs may provide a way of switching off immunity so that transformation can work. ●

REFERENCE

- Ishihama, N., Choi, S.-W., Noutoshi, Y., Saska, I., Asai, S., Takizawa, K., He, S. Y., Osada, H. & Shirasu, K. Oxicam-type non-steroidal anti-inflammatory drugs inhibit NPR1-mediated salicylic acid pathway. *Nature Communications* **12**, 7303 (2021).

NEUROSCIENCE

Cell circuit sparks synchronicity

Neurons in the left and right hippocampal CA1 area coordinate their activity thanks to input from CA3 cells

RIKEN neuroscientists have uncovered the neural circuitry that permits a subregion in the hippocampus to communicate with its counterpart in the opposite hemisphere despite there being no direct connection between them¹. While not directly applicable to people, this finding is important for informing future studies of the mouse brain.

The hippocampus is well known for its role in learning and memory. Vertebrates have two hippocampi: one on the left side of the brain and the other on the right. Each hippocampus has various subregions, including the CA1 and CA3 areas.

In mice, cells in the left and right CA1 can communicate with each other and synchronize their

activity. But how this happens was unclear, because there are no direct connections between the left and right CA1.

Neurons in the CA3 subregion extend projections bilaterally into the CA1 area. Cells in the left CA3, for example, relay information to neurons in the left and right CA1, and cells in the right CA3 do the same thing. These projections may help cells in the left and right CA1 areas to coordinate their activity, but this had never been directly tested.

To find out, Thomas McHugh from the RIKEN Center for Brain Science and colleagues used a specially created transgenic mouse that enabled them to silence the activity of CA3 neurons, so that these cells could no longer communicate with CA1

neurons. Electrodes installed in the CA1 subregion of the mice (see image) allowed them to monitor the activity of place cells—special neurons in the CA1 that fire when the mouse is at a particular location—as the mice ran back and forth on a track.

“The nice thing is, if you record from enough of these cells, you see these repeatable sequences,” says McHugh. “As a mouse runs from left to right, cell 1 fires, then cell 2, then cell 3 and so on, and every time it runs down the track, you see the same pattern of sequences.”

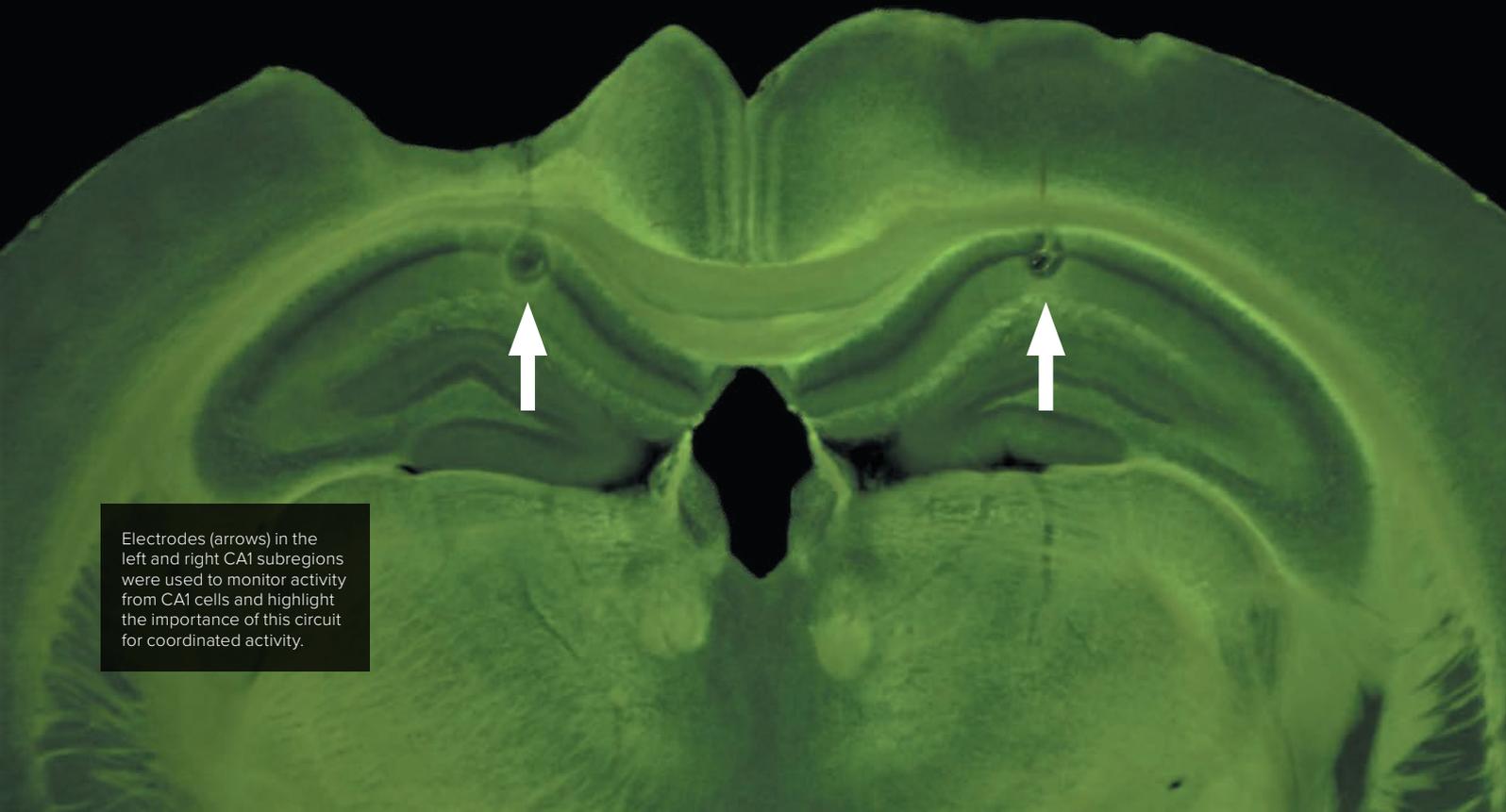
In normal mice, the patterns in the left and right CA1 regions were synchronized, whereas they were mismatched in the transgenic mice. This suggests that input from the CA3 region

really does underpin the coordinated activity of CA1 cells.

The story may be different in human brains, however, where imaging studies have shown that our hippocampi act in a more lateralized way—cells in the left CA1 often work independently of their counterparts in the right CA1. The mouse is a widely used laboratory model, so it’s important to highlight these differences. ●

REFERENCE

1. Guan, H., Middleton, S. J., Inoue, T & McHugh, T. J. Lateralization of CA1 assemblies in the absence of CA3 input. *Nature Communications* **12**, 6114 (2021).



Electrodes (arrows) in the left and right CA1 subregions were used to monitor activity from CA1 cells and highlight the importance of this circuit for coordinated activity.

DEEP-LEARNING DIAGNOSIS

Developing trust in AI diagnosis

An artificial-intelligence system that provides charts explaining diagnoses could help improve the diagnosis of congenital heart problems in fetuses

An explanatory artificial-intelligence (AI) system has enabled hospital residents and fellows to diagnose congenital heart disease in fetuses more accurately¹. It could assist with diagnosis when specialists are unavailable and also help train doctors.

Congenital heart problems account for almost one in five newborn deaths. Early diagnosis before birth improves the chances of survival but is extremely challenging because diagnosis is based on ultrasound videos, where fetus and probe movement can obscure subtle abnormalities. While experts can screen ultrasound images accurately, attending residents or fellows screen the vast majority of regular ultrasounds.

To address this problem, researchers led by Masaaki Komatsu at the RIKEN Center for Advanced Intelligence Project have been developing an AI system that can learn what a normal fetal heart looks like after being shown thousands of ultrasound images. It can then make diagnoses by classifying ultrasound videos as normal or abnormal.

Ensuring that the AI system works in a real-world setting requires gaining the trust of those who use it. “It’s difficult to build trust with medical professionals when the decisions made by AI take place in a ‘black box’ and cannot be understood,” says Komatsu.

Now, the researchers have tested an improved explanatory AI system that generates a chart representing its decisions. The



An artificial-intelligence system developed by RIKEN researchers can help doctors diagnose congenital heart disease in fetuses more accurately from ultrasound images.

charts were produced through another round of deep learning, which improved AI performance and allowed doctors to see whether abnormalities are related to the heart, blood vessels or other features.

Experts, fellows and residents were given the same sets of ultrasound videos and asked to provide two diagnoses: one without and one with the graphical representation of the AI’s decision (they were not given the actual AI decision). All three groups of doctors made more correct diagnoses when using the AI-based decision charts.

“This is the first demonstration in which examiners at all levels of experience were able to

improve their ability to screen ultrasound videos for fetal cardiac abnormalities using explainable AI,” says Komatsu.

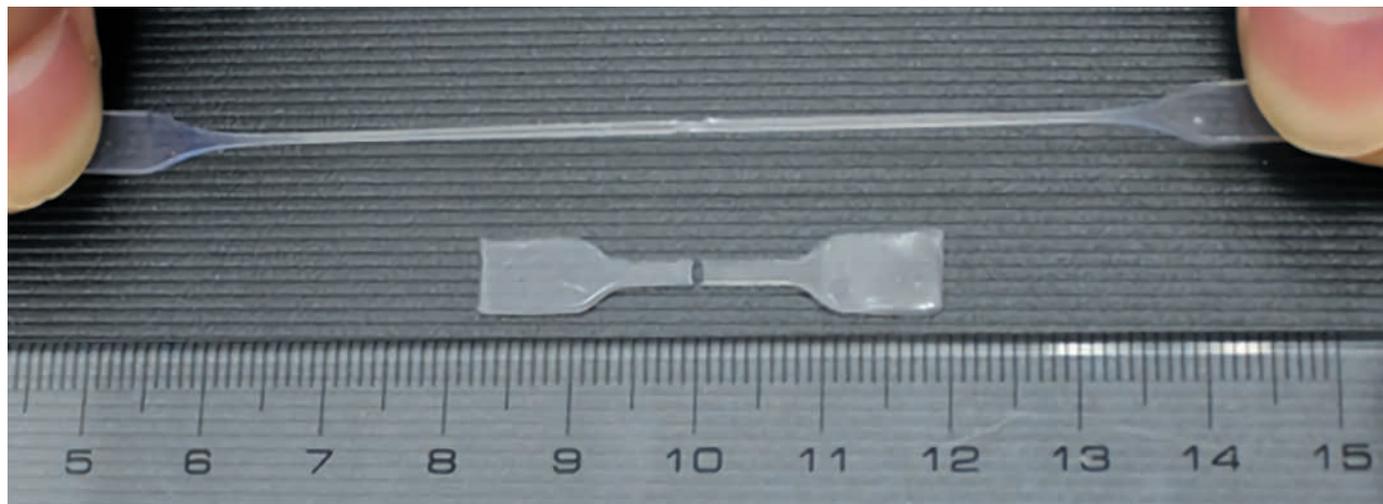
The least-skilled examiners—fellows and residents—became respectively 7% and 13% more accurate with AI’s help. While experts and fellows were able to improve on the AI-only diagnosis, residents were about 12% less accurate than the AI alone. Thus, in terms of clinical application, the AI is most useful for fellows, who usually perform fetal cardiac ultrasound screening in hospitals.

“Our study suggests that even with widespread use of AI assistance, an examiner’s expertise will still be a key factor

in future medical examinations,” says Komatsu. “In addition to future clinical applications, our findings show maximum benefit from this technology could be achieved by also using it as part of resident training and education.” ●

REFERENCE

1. Sakai, A., Komatsu, M., Komatsu, R., Matsuoka, R., Yasutomi, S., Dozen, A., Shozu, K., Arakaki, T., Machino, H., Asada, K. *et al.* Medical professional enhancement using explainable artificial intelligence in fetal cardiac ultrasound screening. *Biomedicine* **10**, 551 (2022).



After cutting the polymer (middle of image) with a razor blade, it largely self-healed (top of image) within a minute of the pieces being gently put together. After 5 minutes, it recovered 99% of its toughness and 97% of its tensile strength.

POLYMERIC MATERIALS

Self-healing polymer bounces back

A catalytic combination of multiple monomers generates a polymer that has an exceptional ability to self-heal

A polymer that heals itself with unprecedented speed and efficacy when cut—almost completely recovering its original strength within minutes—has been developed by RIKEN researchers¹. It was produced using an advanced catalytic method for combining multiple precursors into a single polymer in a controlled fashion.

Increasing the structural complexity of polymers offers great promise for developing new materials with novel or improved properties. The controlled synthesis of complex polymers remains challenging, however.

Zhaomin Hou of the RIKEN Center for Sustainable Resource Science and his colleagues recently developed a controlled catalytic method for combining non-polar and polar olefin monomers into a single polymer. “We previously discovered that we could synthesize multiblock

copolymers that exhibited excellent elasticity and self-healing by using the two-component copolymerization of non-polar ethylene and polar methoxyaryl-substituted propylenes by a half-sandwich scandium catalyst,” says Hou.

The two-component polymers’ properties depended strongly on the methoxyarylpropylene used. “This raised the intriguing question of whether a three-component ‘terpolymer’ of ethylene and two different methoxyaryl-functionalized propylenes would show unique synergistic effects on the mechanical and self-healing properties,” adds Hou.

Now, Hou and his co-workers have confirmed that terpolymers can show unprecedented mechanical and self-healing performance. Their elastomeric polymer could be stretched to almost 14 times its original length before breaking. And

when cut in two, the polymer healed itself within 5 minutes (see image) to recover 99% of its toughness and 97% of its tensile strength.

The material’s exceptional performance can be explained by its unique molecular structure, Hou notes. The polymer consisted of three nanoscale component subsections, or ‘blocks’, with quite different physical properties, the team showed. Each methoxyarylpropylene formed relatively long alternating ethylene–methoxyarylpropylene sequences. One methoxyarylpropylene formed sequences that were soft and flexible, whereas the other gave sequences that were hard. A third sequence type, consisting of relatively short ethylene–ethylene blocks, was crystalline in nature.

“The polymer’s excellent elastomeric and self-healing properties are due to the formation of

this nanoscale three-dimensional network,” says Hou. The long, soft sections form a highly flexible matrix, within which are hard and crystalline sections that rapidly re-aggregate after the material is cut, thereby self-healing any damage.

This polymerization method using a scandium catalyst offers many avenues for further polymer development. “We anticipate our approach will enable additional functions to be easily incorporated into this novel class of self-healing polymer,” says Hou. “And we expect our self-healing mechanism will guide the design and creation of various new self-healing polymers through microstructural control.” ●

REFERENCE

1. Yang, Y., Wang, H., Huang, L., Nishiura, M., Higaki, Y. & Hou, Z. Terpolymerization of ethylene and two different methoxyaryl-substituted propylenes by scandium catalyst makes tough and fast self-healing elastomers. *Angewandte Chemie International Edition* **60**, 26192–26198 (2021).

QUANTUM GRAVITY

Worming out of the black-hole information paradox

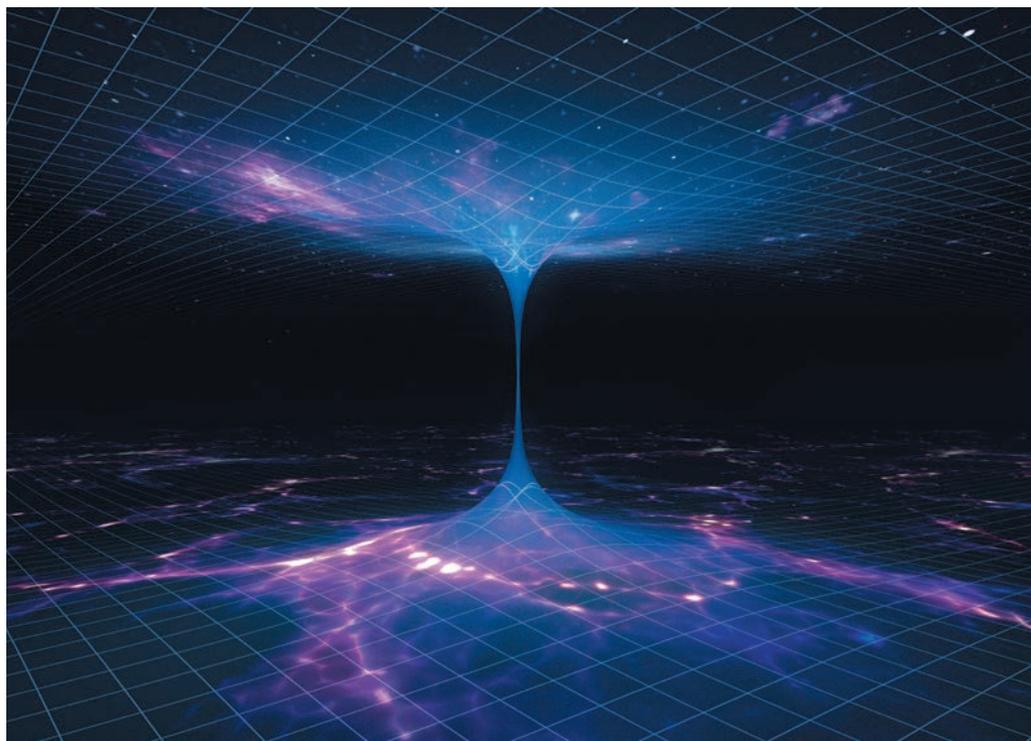
A mathematical analysis helps illuminate the puzzle over how information escapes from black holes

ARIKEN physicist and two colleagues have found that a wormhole—a theoretical bridge connecting distant regions of the Universe—may help to shed light on the mystery of what happens to information about matter consumed by black holes¹.

Einstein's theory of general relativity predicts that nothing that falls into a black hole can escape its clutches. But in the 1970s, Stephen Hawking calculated that black holes should emit radiation when quantum mechanics, the theory governing the microscopic realm, is considered. "This is called black hole evaporation because the black hole shrinks, just like an evaporating water droplet," explains Kanato Goto of the RIKEN Interdisciplinary Theoretical and Mathematical Sciences.

This, however, led to a paradox. Eventually, the black hole will evaporate entirely—and so too will any information about its swallowed contents. But this contradicts a fundamental dictum of quantum physics: that information cannot vanish from the Universe. "This suggests that general relativity and quantum mechanics as they currently stand are inconsistent with each other," says Goto. "We have to find a unified framework for quantum gravity."

Many physicists suspect that the information escapes, encoded somehow in the radiation. To investigate, they compute the entropy of the radiation, which measures how much information is lost from the perspective of someone outside the black hole. In 1993, physicist Don Page



As depicted in science fiction, a wormhole is a shortcut connecting two points in spacetime. A RIKEN physicist and two collaborators have used a new spacetime geometry with a wormhole-like structure to show that information is not necessarily irretrievably lost from black holes as they evaporate.

calculated that if no information is lost, the entropy will initially grow, but will drop to zero as the black hole disappears.

When physicists simply combine quantum mechanics with the standard description of a black hole in general relativity, Page appears to be wrong—the entropy continually grows as the black hole shrinks, indicating information is lost.

But recently, physicists have explored how black holes mimic wormholes—providing an escape route for information. This is not a wormhole in the real world, but a way of mathematically computing the

entropy of the radiation, notes Goto. "A wormhole connects the interior of the black hole and the radiation outside, like a bridge."

When Goto and his two colleagues performed a detailed analysis combining both the standard description of a black hole and one based on a wormhole, their result matched Page's prediction, suggesting that physicists are right to suspect that information is preserved even after the black hole's demise.

"We discovered a new spacetime geometry with a wormhole-like structure that had been overlooked in conventional

computations," says Goto. "Entropy computed using this new geometry gives a completely different result."

But this raises new questions. "We still don't know the basic mechanism of how information is carried away by the radiation," Goto says. "We need a theory of quantum gravity." ●

REFERENCE

1. Goto, K., Hartman, T. & Tajdini, A. Replica wormholes for an evaporating 2D black hole. *Journal of High Energy Physics* **2021**, 289 (2021).



Brain networks minimize the energy they expend through the free-energy principle.

NEURAL NETWORKS

The brain runs on free energy

Brain networks minimize the energy they expend via a principle that underpins many processes in nature

In a finding that promises to be useful for analyzing impaired brain function in thought disorders and for optimizing neural networks for artificial intelligence, RIKEN neuroscientists have shown that the efficiency of neural networks is optimized through the free-energy principle¹.

Biological optimization is a natural process that makes our bodies and behavior as efficient as possible. For example, cats switch from running to galloping at the exact speed when the energy expended by galloping drops below that needed to run. In the brain, neural networks are optimized to allow efficient control of behavior and transmission of information, while still maintaining the ability to adapt to changing environments.

A team led by Takuya Isomura of the RIKEN Center for Brain Science is seeking to discover the basic mathematical principles that underlie how neural networks self-optimize. The free-energy principle follows a concept called Bayesian inference. In this method, an agent is continually updated by incoming sensory data, as well as its own past outputs, or decisions.

The researchers compared the free-energy principle with well-established rules that control how the strengths of neural connections within a network are altered by changes in sensory input.

“We were able to demonstrate that standard neural networks, which feature delayed modulation of Hebbian plasticity, perform planning and adaptive behavioral control by taking their previous

‘decisions’ into account,” explains Isomura. “Importantly, they do so the same way that they would when following the free-energy principle.”

The team then tested this theory using simulations. Neural networks self-organized by changing the strength of their neural connections and associating past decisions with future outcomes. In this case, the neural networks can be viewed as being governed by the free-energy principle, which allowed it to learn the correct route through a maze by trial and error in a statistically optimal manner.

These findings point to a set of universal mathematical rules that describe how neural networks self-optimize. “Our findings guarantee that an arbitrary neural network can be

cast as an agent that obeys the free-energy principle, providing a universal characterization for the brain,” says Isomura.

These rules, along with the team’s reverse-engineering technique, could be used to study neural networks for decision making in people with thought disorders such as schizophrenia and predict the aspects of their neural networks that have been altered.

Another practical application is artificial intelligence. “Our theory can dramatically reduce the complexity of designing self-learning neuromorphic hardware to perform various types of tasks, which will be important for next-generation artificial intelligence,” says Isomura. ●

REFERENCE

1. Isomura, T., Shimazaki, H. & Friston, K. J. Canonical neural networks perform active inference. *Communications Biology* **5**, 55 (2022).



A mouse study has shown that the hormone amylin may be behind loneliness and the craving for social interaction.

MOLECULAR NEUROSCIENCE

Is loneliness all in the head?

A hormone expressed in a certain brain region may be behind loneliness and the craving for social interaction

In efforts to understand the neural basis for loneliness, RIKEN neuroscientists have found a hormone that both senses social isolation and drives social contact-seeking behavior in female mice¹. This finding could help to improve the prevention and treatment of mental health issues caused by loneliness.

As the social isolation imposed by the COVID-19 pandemic has highlighted, loneliness is a major stressor for social animals. It increases the risk of various mental and physical health issues including depression, substance abuse, obesity and premature death.

Previously, a team led by Kumi Kuroda of the RIKEN Center for Brain Science had shown that the drive for maternal care in mammals comes from neurons that respond to the hormone

amylin in the central medial preoptic area (cMPOA) of the brain. This discovery was serendipitous. “While studying amylin signaling in maternal care, we noticed that the amount of amylin in the cMPOA depended on the housing conditions of the mice,” recalls Kuroda.

Now, Kuroda’s team has examined the neural and behavioral responses to social isolation and reunion in female mice. They discovered that isolating mice for six days caused amylin to almost completely disappear, but that amylin returned to normal levels two weeks after reuniting mice with their cage-mates.

This was true even when a divider with windows was used to separate mice from their cage-mates, indicating that female mice needed physical contact with other mice to maintain amylin expression in the cMPOA.

The researchers also found that amylin-expressing neurons in the cMPOA are deactivated on isolation and activated on reunion.

When separated from their cage-mates by the windowed divider, female mice first vigorously bit the divider’s bars. Since this biting behavior was observed only when other mice were across the divider, the mice appear to be trying to break the window to reunite with their cage-mates.

This contact-seeking behavior was increased by activating amylin-expressing neurons using a chemical technique to artificially control neuronal activity. In contrast, contact-seeking behavior decreased after knocking down amylin in the cMPOA.

“Among other reported molecules, amylin is the one that

responds the most to isolation and reunion, and itself facilitates contact-seeking behaviors,” notes Kuroda. “With all these results, we became confident that amylin is the major player in the brain that is needed for sensing and seeking social contacts.”

These results provide molecular evidence for the notion that social affiliation among adults evolved from parental care. “Both parental care and female–female social contact depend on amylin and augment its expression,” says Kuroda. “This synergy might facilitate cooperative parenting, in which multiple females care for young together, as is observed in mice and humans.” ●

REFERENCE

1. Fukumitsu, K., Kaneko, M., Maruyama, T., Yoshihara, C., Huang, A. J., McHugh, T. J., Itoharu, S., Tanaka, M. & Kuroda, K. O. Amylin–Calcitonin receptor signaling in the medial preoptic area mediates affiliative social behaviors in female mice. *Nature Communications* **13**, 709 (2022).

ROBOTICS

Android head gets emotional

An android can express six emotions by adopting different facial expressions

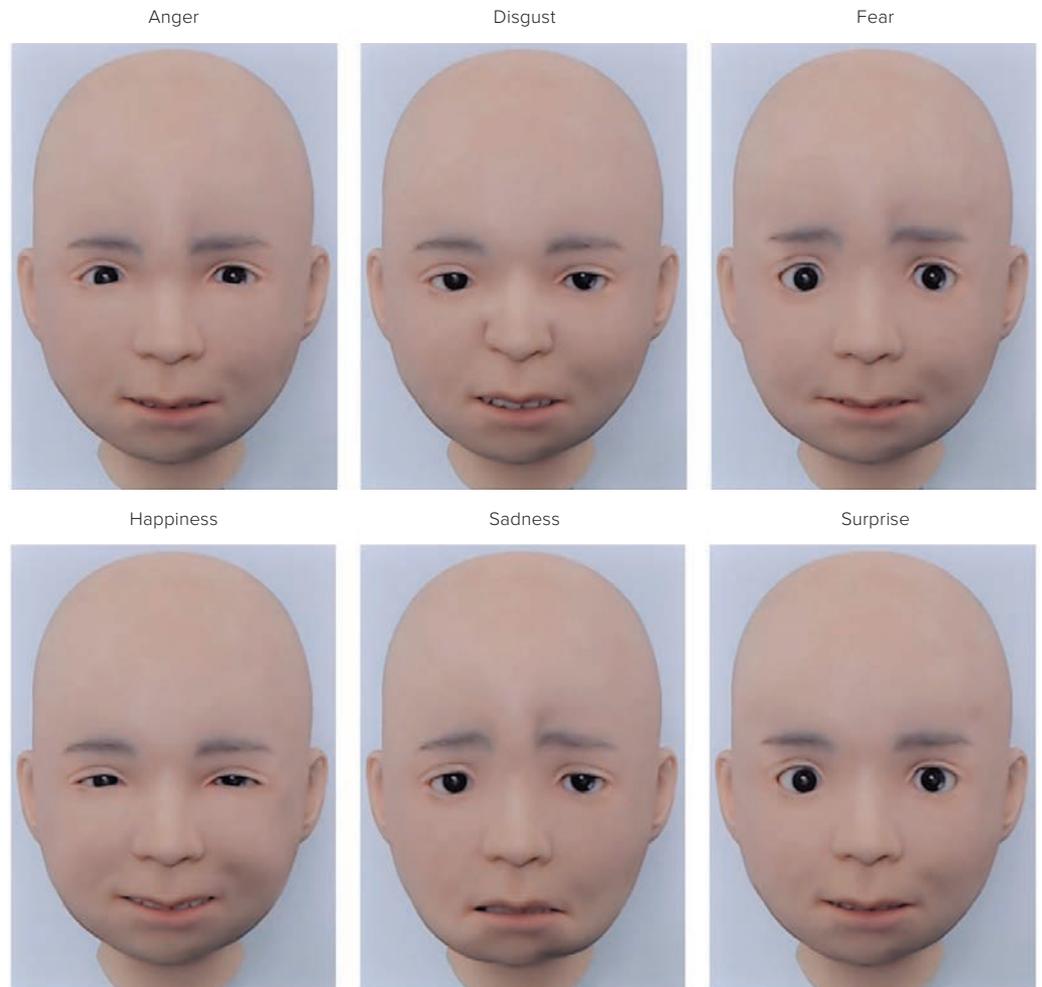
Through its facial expressions, an android head developed by RIKEN researchers can convey six emotions—happiness, sadness, fear, anger, surprise and disgust—that are recognizable to people¹. In the short term, the android promises to be useful for studies exploring human emotions, but it could eventually be used to help housebound people.

Rosie the robot maid was considered science fiction when she debuted on the Jetson's cartoon about 60 years ago. Although helpful robots are now closer to reality than fiction, they still need further development in several areas, including enabling robots to detect and express emotions.

Wataru Sato of the RIKEN Guardian Robot Project and his team have been developing Nikola, an android head that looks like a hairless boy. Now, they have enabled it to express six emotions through its facial expressions.

Nikola's face has 29 pneumatic actuators that control the movements of artificial muscles, while another six actuators control head and eyeball movements. Since pneumatic actuators are controlled by air pressure, the movements are silent and smooth.

The team arranged the actuators by referring to the



Nikola, an android head developed by RIKEN researchers, can convey six emotions that people can recognize.

Facial Action Coding System, which has been extensively used to study facial expressions. Past research has identified numerous facial action units—such as ‘cheek raiser’ and ‘lip pucker’—that convey emotions such as happiness or disgust, and these were incorporated in Nikola’s design.

In studies of emotions, it is difficult to conduct controlled experiments with live people interacting. The alternative approach of viewing photos or videos of people is less natural, and reactions aren’t the same. “The hope is that with androids like Nikola, we can have our cake and eat it,” says Sato. “We can control every aspect of Nikola’s

behavior, and at the same time study live interactions.” Sato believes that, in the near future, androids like Nikola could become important research tools in social psychology and social neuroscience.

In a test to see whether Nikola’s facial expressions were understandable, a person certified in FACS scoring was able to identify each facial action unit, indicating that Nikola’s facial movements accurately resembled those of a human. Another test showed that untrained people could recognize the six emotions in Nikola’s face, albeit with varying accuracies.

While Nikola still lacks a

body, the ultimate goal is to build an android that can assist people, particularly those with physical needs who live alone. “Androids that can emotionally communicate with us will be useful in a wide range of real-life situations, such as caring for older people, and can promote human wellbeing,” says Sato. ●

REFERENCE

1. Sato, W., Namba, S., Yang, D., Nishida, S., Ishi, C. & Minato, T. An android for emotional interaction: spatiotemporal validation of its facial expressions. *Frontiers in Psychology* **12**, 800657 (2022).

PLANT SALINITY TOLERANCE

Plant mutations cause beneficial defects

Defective molecular signaling in plants helps them survive in a salty medium

Genetic mutations that almost completely disrupt a natural molecular signaling system in plants can confer the surprising benefit of making them more tolerant to high salt levels, a RIKEN-led team has found¹. This discovery could help to develop new strategies for enabling crop plants to thrive in conditions of high salinity, which is a growing problem in many regions of the world.

“Salinity is a major threat to modern agriculture,” says Mostafa Abdelrahman of the RIKEN Center for Sustainable Resource Science (CSRS). “It is now estimated to affect somewhere between 20–50% of irrigated agricultural land worldwide as a result of irrigation with brackish water, inefficient drainage systems and global climate changes.”

To cope with high salinity, plants reprogram metabolic pathways in various subcellular compartments. However, how plants regulate these cellular processes has not been well understood until now.

Abdelrahman and his co-workers have now found that cellular signaling molecules known as cytokinins play a key role in regulating the metabolic pathways that control the levels of some metabolites that impart tolerance to salinity.

The researchers focused on mutations in two sets of genes coding for proteins that are involved in cytokinin signaling. They used two powerful systemic analysis techniques—transcriptomics and metabolomics—to tease out the connection between mutations and cytokinin activity.



Rice fields abandoned due to salinization in Thailand. Rising salinity levels due to climate change are a growing problem around the world. New insights into the role of cytokinin signaling in making plants more tolerant to a salty medium could lead to new strategies for producing crops that are more salt-resilient.

Transcriptomics involves analyzing entire transcripts produced by the genome in order to identify gene-expression profiles under specific circumstances. On the other hand, metabolomics involves analyzing the levels of a wide range of metabolites present in a cell.

Through this two-pronged analysis, the researchers found that mutations that almost completely disrupt the normal molecular signaling processes performed by cytokinins alter the levels of some lipid- and flavonoid-related metabolites, making *Arabidopsis* plants significantly more tolerant to a salty medium.

While *Arabidopsis* is not a crop

plant, these insights into the role of cytokinins in regulating its responses to environmental stresses may lead to new approaches for combating the problem of increasing salinity in soils worldwide.

“Genetic manipulation of cytokinin signaling might provide a promising avenue for developing salt-tolerant crops to help ensure global food security in this era of climate crisis,” notes Lam-Son Phan Tran, who led the team and is also at CSRS.

The team now intends to investigate the genetic manipulation of cytokinin signaling in major cereal crops using genome editing, as a promising strategy

for developing salt-tolerant cereal crops while maintaining superior productivity. ●

REFERENCE

1. Abdelrahman, M., Nishiyama, R., Tran, C. D., Kusano, M., Nakabayashi, R., Okazaki, Y., Matsuda, F., Chavez Montes, R. A., Mostafa, M. G., Li, W. *et al.* Defective cytokinin signaling reprograms lipid and flavonoid gene-to-metabolite networks to mitigate high salinity in *Arabidopsis*. *Proceedings of the National Academy of Sciences of the USA* **30**, e2105021118 (2021).

Two RIKEN researchers have explored the possibility of manipulating the weather by using a much simpler system known as the butterfly attractor, a chaotic system, with two tracks, or orbits, resembling butterfly wings.

DYNAMICAL SYSTEMS

Flitting between the wings of a butterfly

It may be possible to influence the weather by making only tiny changes

Just making small tweaks to certain variables could potentially modify extreme weather events such as sudden downpours, computer simulations by two RIKEN researchers have shown¹.

Scientists have long desired to develop ways to control the weather. Research in this area has intensified due to climate change, which is giving rise to more extreme weather events.

Present methods for modifying the weather have limited success. Seeding the atmosphere can induce rain, but only when the atmosphere is already in a state where it might rain. Geoen-gineering projects have been envisioned, but they have yet to be conducted due to concerns about unpredicted long-term effects.

As a promising approach,

Takemasa Miyoshi and Qiwen Sun, both of the RIKEN Center for Computational Science, have looked to chaos theory to assess the possibility of mitigating weather events such as torrential rain by making small changes. Instead of considering the weather system in all its complexity, they focused on a far simpler system—the butterfly attractor (see image). The butterfly attractor describes a chaotic system that has just three variables. When these variables are plotted, they follow one of two tracks, or orbits, which resemble butterfly wings. Small fluctuations in the system can cause it to switch between the two orbits.

The pair ran one weather simulation to serve as the control of nature itself. They then ran other simulations that had small

variations in several variables that described how heat moved through the system by convection. This revealed that small changes in several of the variables could cause the system to adopt a certain state after a certain amount of time.

“This opens the path to research into the controllability of weather and could lead to weather-control technology,” says Miyoshi. “If realized, this research could help us prevent and mitigate extreme storms, such as torrential rains and typhoons, whose risks are increasing with climate change.”

This is a completely new approach to controlling weather, Miyoshi stresses. “We have built a new theory and methodology for studying the controllability of weather,” he says. “Based on the observing-system simulation experiments used in previous predictability studies, we were able to design an experiment to investigate predictability based on the assumption that the true values

(nature) cannot be changed, but rather that we can change the idea of what can be changed (the object to be controlled).”

The pair intends to explore the use of more-complex models for weather. “In this study, we used an ideal, low-dimensional model to develop a new theory,” says Miyoshi. “In the future, we plan to use actual weather models to study the possible controllability of weather.” ●

REFERENCE

1. Miyoshi, T. & Sun, Q. Control simulation experiment with Lorenz's butterfly attractor. *Nonlinear Processes in Geophysics* **29**, 133–139 (2022).



Artist's impression depicting two protoplanetary disks. These disks of gas and dust host planetesimals, the seeds of new planets. RIKEN astrophysicists have developed a model that explains how dust avoids falling toward the star long enough to coalesce into kilometer-sized planetesimals.

PLANETARY FORMATION

Dust grains gang up to seed new planets

By amassing in high-density regions, dust grains avoid drifting toward the star they are orbiting

A key step in the formation of new planets may have been uncovered by a RIKEN astrophysicist and two collaborators¹. They have developed a new theoretical model of a protoplanetary disk that explains how dust in the disk overcomes a tendency to drift toward the star.

Planets are birthed from a swirling disk of dust and gas that surrounds a young star, but it is unclear how dust grains can grow into larger objects before they spiral inward toward the star.

In the classical theory of planet formation, minuscule dust particles collide and stick together to form centimeter-sized grains. These grains gradually build up to form kilometer-sized planetesimals, the first major step in producing a new planet.

But the dust grains feel a drag from the gas in the

protoplanetary disk. This slows the dust grains down, so that they fall toward the star. The speed at which they fall increases as the dust grains grow larger.

Previous studies have suggested that this effect should prevent the grains from forming objects larger than about a meter, which poses a major conundrum for astronomers. “Various mechanisms have been proposed to explain the formation of planetesimals, but they are still under debate,” notes Ryosuke Tominaga of the RIKEN Star and Planet Formation Laboratory.

Tominaga and two colleagues have now proposed a model that suggests a possible solution to this problem—small variations in the distribution of dust in the protoplanetary disk are quickly

amplified into regions of high and low dust density.

In areas having slightly higher densities, dust coagulates more efficiently, and it forms larger clumps that drift toward the star more quickly. When these clumps meet smaller dust particles, they form regions of even higher dust density, accelerating grain growth. Meanwhile, the regions vacated by the large clumps end up with relatively low densities.

The team found that this positive feedback creates multiple bands of high and low dust density in the protoplanetary disk. These bands can arise in a matter of 10,000 years or so, a remarkably short time for such astronomical processes. These high-density areas are ideal sites for further aggregation, allowing planetesimals to form

before the dust grains are pulled into the star.

“Unlike previous theories, this coagulation mechanism works even when there is far more gas than dust in the protoplanetary disk,” says Tominaga.

The team is now working on more-detailed models that include the formation and evolution of the disk itself, along with the eventual formation of planetesimals. ●

REFERENCE

1. Tominaga, R. T., Inutsuka, S. & Kobayashi, H. Coagulation instability in protoplanetary disks: A novel mechanism connecting collisional growth and hydrodynamical clumping of dust particles. *The Astrophysical Journal* **923**, 34 (2021).

MOLECULAR DYNAMICS

Priming the pump

Molecular dynamic simulations show how a protein pump transports calcium to help control muscle contractions

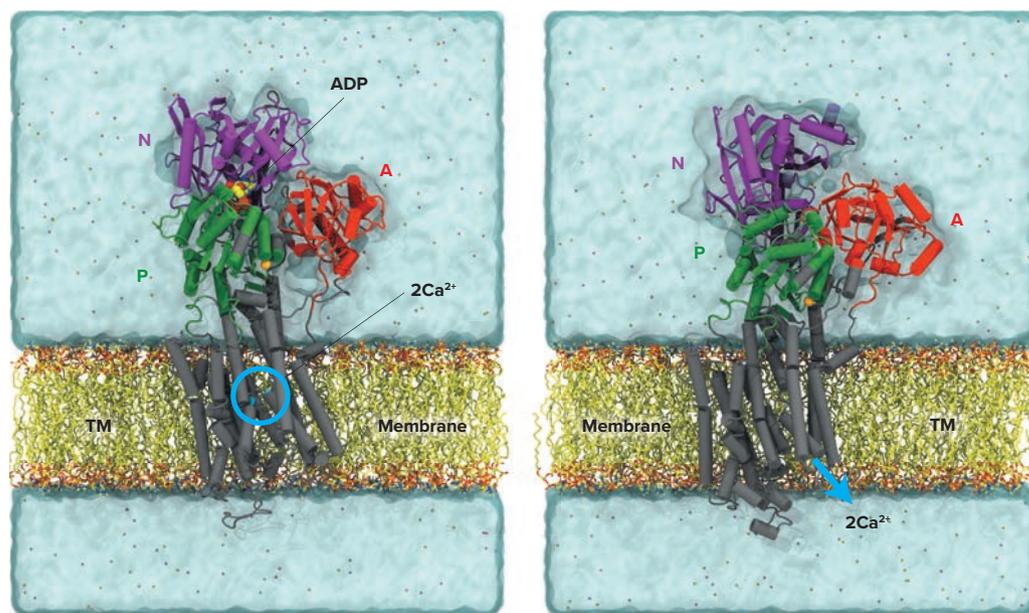
The pumping action of the calcium pump protein—an intricate molecular machine with several moving parts that helps control muscle contraction—has been detailed with exquisite precision by RIKEN biophysicists¹. By providing a blueprint of structural changes that occur during operation of the protein, the findings could aid the development of new treatments for skeletal myopathies and heart disease.

Muscle movement is fundamentally a calcium-driven process. When a muscle cell receives the signal to contract from its associated nerves, it releases a flood of calcium ions from a special intracellular container known as the sarcoplasmic reticulum. Those ions then set the muscle's molecular motors into action, spurring contractions until the calcium is removed.

“Our computational studies have filled in such missing information”

That's where the calcium pump comes in. After a frenzied wave of calcium-induced activity, the pump uses energy in the form of adenosine triphosphate (ATP) to return calcium ions to their intracellular storehouse.

Previously, scientists had relied on structural and biochemical techniques to infer how the calcium pump achieves



Structures of calcium pump before (left) and after (right) it has transported ions into the sarcoplasmic reticulum (A, N, P: three cytoplasmic domains; TM: transmembrane).

this molecular maneuver. However, structural techniques provide only snapshots of the protein at work while biochemical experiments indicate molecular states that are pertinent for the protein's function. These techniques give a good sense of what the pump looks like before and after completing its job of calcium transport.

The steps in between, however, were something of a mystery—that is, until Yuji Sugita at the RIKEN Center for Computational Science and his co-workers determined the pump's intermediate forms using molecular dynamic simulations. “Our computational studies have filled in such missing information and could give new insights into the molecular mechanisms

of ion pumping,” says Sugita (see image).

Using sophisticated computer models that account for structural changes and energetic profiles, the researchers identified a handful of transition states. They also demonstrated how the rapid exchange of calcium ions for protons at the pump's inner face is critical for releasing calcium into the sarcoplasmic reticulum.

Sugita first started interrogating the calcium pump's movements in the early 2000s, but his methods were fairly rudimentary by today's standards and he could only get a crude picture of the protein's dynamic nature. His success now, Sugita says, owes a lot to improvements in modeling techniques and software tools, along with

access to RIKEN's super-computer resources.

With continued innovations, Sugita hopes to unlock even more of the pump's structural secrets. A commentary on the study by Sugita's team says their work “provides opportunities for experimentalists, theoreticians, and simulators; their detailed picture advances our current understanding and points toward the next level.” ●

REFERENCE

1. Kobayashi, C., Matsunaga, Y., Jung, J. & Sugita, Y. Structural and energetic analysis of metastable intermediate states in the E1P–E2P transition of Ca^{2+} -ATPase. *Proceedings of the National Academy of Sciences USA* **118**, e2105507118 (2021).

NATURE'S OWN ASSEMBLY LINE

RIKEN-engineered microbes and plant lignin could soon help produce everything from car tires to engine components.

By Kazuki Saito, Director, RIKEN Center for Sustainable Resource Science and Tomokazu Shirai, Senior Scientist, Cell Factory Research Team, RIKEN Center for Sustainable Resource Science

Today the raw ingredients for virtually all industrial products, ranging from medicines to car tires, come from non-renewable chemical feedstocks. They are produced in fossil fuel refineries that emit greenhouse gases, such as carbon dioxide. However, future chemical factories might invert this dynamic, manufacturing some compounds using plants that naturally construct complex chemicals by drawing carbon dioxide molecules from the air.

Tomokazu Shirai taps into biology's native chemical capabilities, redirecting them so that plants and microbes cleanly produce the kinds of industrial chemicals currently derived from cracking crude oil. The synthetic biologist is senior scientist at the Cell Factory Research Team and joined the RIKEN Center for Sustainable Resource Science (CSRS, formerly, the RIKEN Biomass Engineering Program) in 2012. His team has already created the world's first microbes that take glucose and convert it into maleic acid or 1,3-butadiene. These valuable industrial chemicals are used in myriad products, including polymers and rubbers^{1,2}.

But this is just the first step for CSRS synthetic biologists. These engineered microbes need to be fed sugars to produce the target chemicals, but if plants are used as the host organism, their

ability to assimilate carbon dioxide directly from the atmosphere will result in the carbon-negative production of many valuable chemicals.

COMPUTER-AIDED DESIGN

Synthetic biology is an emerging area of research that combines chemistry, biology and engineering to rework the molecule-producing metabolic pathways of target organisms so that they produce valuable chemicals. CSRS scientists have expertise in catalytic chemistry and in chemical biology, but also many that specialize in large-scale data science, calculation and simulation, and AI.

The use of AI represents a departure from the traditional ways of doing synthetic biology. But this computational approach has been key to a collaboration with tire manufacturer, Yokohama Rubber, and Zeon Corporation. The joint venture has designed and created *E. coli* microbes that take glucose and convert it into 1,3-butadiene, a key synthetic chemical used to manufacture tires.

The first step in any synthetic biology project is to analyse the potential host's metabolic pathways to identify points that could be diverted to produce the desired chemical. Any modifications must not kill or significantly impair the growth of the host.

Since 2012, Shirai has been developing and refining the simulation tool BioProV to navigate this complex biochemical space. BioProV is an AI trained in metabolic pathway classification and enzyme reaction patterns that analyses the natural metabolic pathways of an organism. It proposes pathway modifications to produce a target chemical without affecting the host's overall metabolism. This *in silico* tool enables the design of artificial metabolic pathways and evaluation of their feasibility.

His team identified that *E. coli* naturally produces a molecule called muconic acid, which could be turned into 1,3-butadiene in two enzymatic reactions.

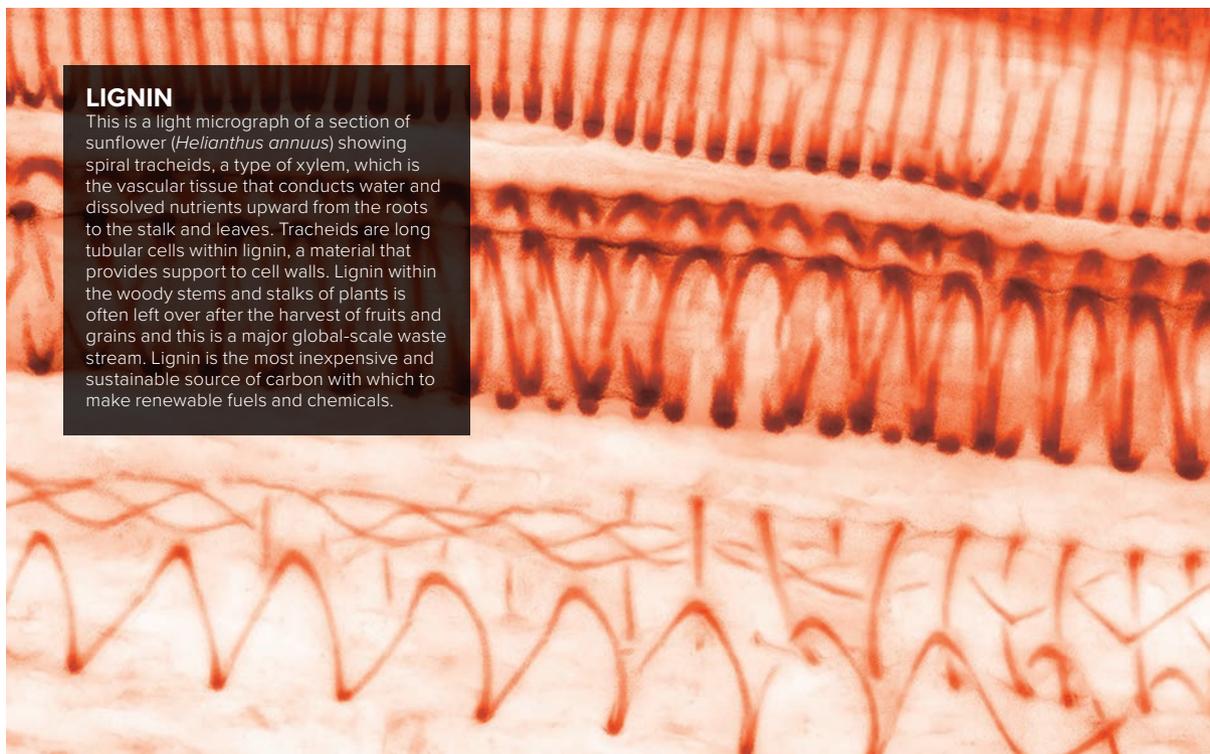
E. coli microbes have engineered to take glucose and convert it into 1,3-butadiene, a chemical used to manufacture tires.





KAZUKI SAITO
Director, RIKEN
Center for Sustainable
Resource Science

Kazuki Saito obtained his PhD in bio-organic chemistry and biochemistry from the University of Tokyo in 1982. In 1995, he became a professor at Chiba University, where he stayed until retirement in March 2020. He is currently a Professor Emeritus at Chiba University. Since 2005, he has also served as a Group Director at the RIKEN Center for Sustainable Resource Science (CSRS) (formerly, RIKEN Plant Science Center), where he directs metabolomics research. In April 2020, he became the Center Director. He has been a Highly Cited Researcher in the field of Plant & Animal Science since 2014.



LIGNIN

This is a light micrograph of a section of sunflower (*Helianthus annuus*) showing spiral tracheids, a type of xylem, which is the vascular tissue that conducts water and dissolved nutrients upward from the roots to the stalk and leaves. Tracheids are long tubular cells within lignin, a material that provides support to cell walls. Lignin within the woody stems and stalks of plants is often left over after the harvest of fruits and grains and this is a major global-scale waste stream. Lignin is the most inexpensive and sustainable source of carbon with which to make renewable fuels and chemicals.

To give the microbe the capacity to carry out the two missing steps, Shirai and his colleagues engineered enzymes for the necessary chemical conversion in 2021.

To do this, they identified known enzymes that could catalyze related reactions, and then modified them for the new reactions. Computational simulation was necessary to redesign and remodel the candidate enzymes' active sites to accept the new substrate. The team rationally designed enzymes that achieved a 1,000-fold increase in activity compared to the original wild-type enzyme.

The DNA codes for these improved enzymes were inserted into the *E. coli* genome and now the 1,3-butadiene produced by these engineered microbes is readily piped from their bioreactor. The project's commercial partners are currently scaling up the process to produce the kilogram quantities of 1,3-butadiene needed to manufacture and evaluate tires made using the bio-derived chemical.

Chemical companies employ many chemists, but few biological researchers, so to connect and collaborate with these companies to translate synthetic biology into the real world is a huge step.

WOODWORK

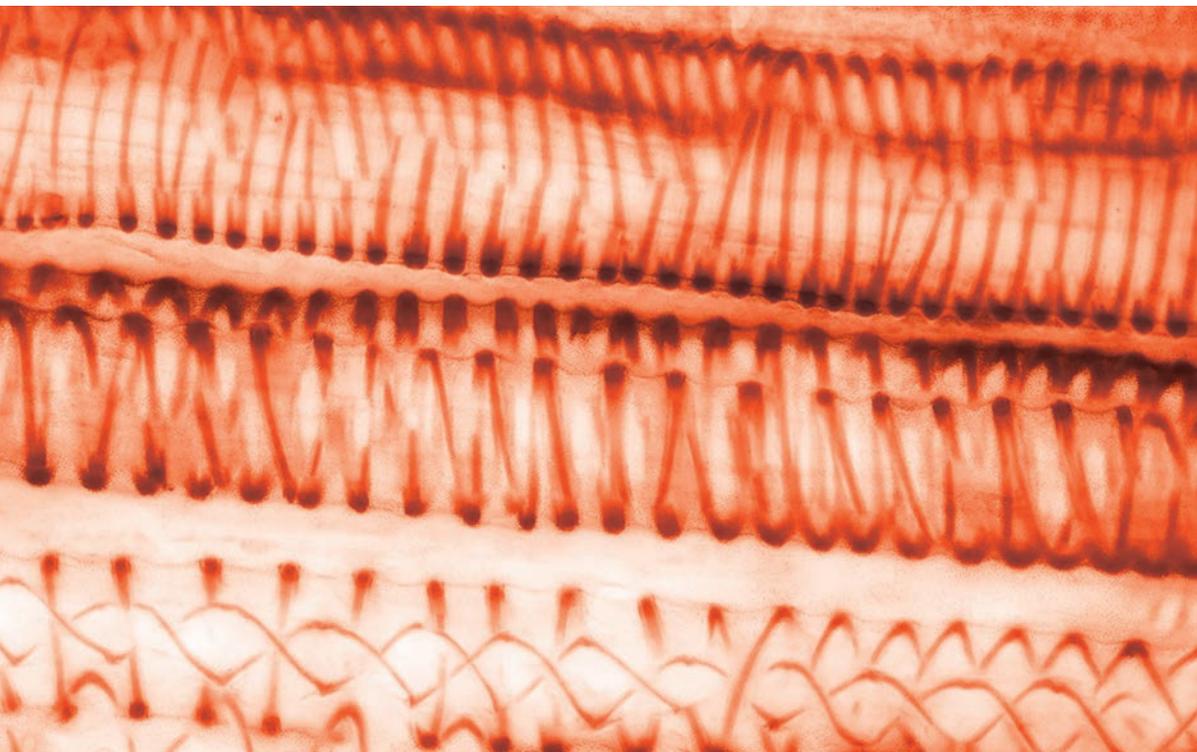
A sustainable alternative to traditional fossil fuel-derived chemical production is to take materials currently considered as waste, and chemically or

“ Lignin-derived acrylic resins showed **high strength**, and resistance to heat and chemical degradation, suggesting an array of uses, including for car body and engine components.

biologically convert them into valuable products.

The woody stems and stalks of plants left over after the harvest of fruits and grains is one global-scale waste stream. The main component of these inedible plant parts is lignin, a tough biopolymer. Lignin is the most abundant compound from plants and one of the most abundant compounds on Earth. It can be sourced from agricultural waste and is the most inexpensive and sustainable source of carbon with which to make renewable fuels and chemicals. To use it as a feedstock for high-value chemicals could be highly beneficial to society.

Lignin's complex chemical structure makes it difficult to break down and reassemble into new compounds. For example, a heat treatment known as fast pyrolysis can break lignin down into subunits called cinnamic monomers. These molecules feature a double bond that could potentially be used to recombine the monomers into advanced functional



polymers. However, side chains located around the double bond impedes chemical reactivity, hindering efforts to make polymers from this biowaste.

CSRS scientist Hideki Abe recently developed a method to overcome this limitation³. Rather than synthetic biology, Abe used organocatalysis to clip cinnamic monomers together. Organocatalysis is a sustainable chemistry technique, recognized by the 2021 Nobel Prize for Chemistry, which uses small organic molecules as catalysts in place of traditional catalysts based on rare or toxic metals.

The resulting acrylic resins showed high strength, and resistance to heat and chemical degradation, suggesting a wide array of potential uses, including for car body and engine components.

SEEDING FUTURE GROWTH

Another waste product in abundant supply is atmospheric carbon dioxide.

For the Cell Factory Research Team, the next major challenge is using synthetic biology to develop plants that could absorb that carbon dioxide from the atmosphere and turn it into industrially important chemicals.

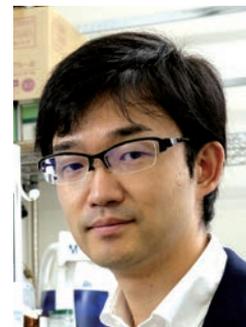
Compared to single-celled microbes, multicellular higher organisms such as plants are far more complex in their genome and metabolic pathways. This makes them significantly more challenging for synthetic biologists work with. Successfully re-engineering

the metabolic pathways of microbes has provided excellent training toward the ultimate goal of using plants as hosts. By collaborating with CSRS researchers specializing in plant science, the Cell Factory Research Team is translating its pioneering work in microbes into insights that can accelerate plant cell synthetic biology, particularly for the production of the terpenoids used in medicines and aromatics.

With the Japanese government recently announcing its aim to be carbon neutral by 2050, higher plants that can fix carbon dioxide using the energy from sunlight is the absolute ideal for future chemical production. ●

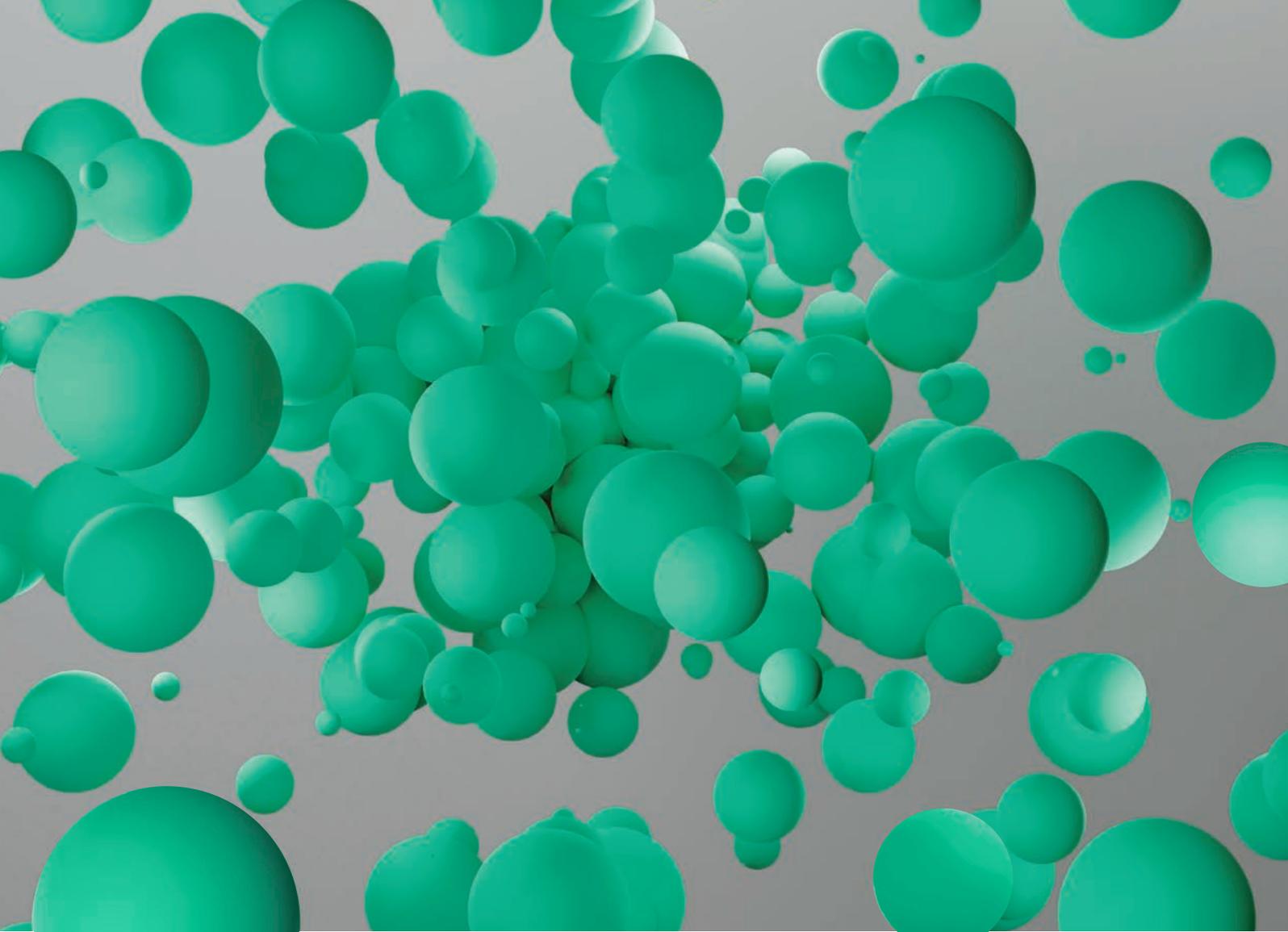
REFERENCE

1. Noda, S., Shirai, T., Mori, Y., Oyama, S. & Kondo, A. Engineering a synthetic pathway for maleate in *Escherichia coli*. *Nature Communications* **8**, 1153 (2017).
2. Mori, Y., Noda, S., Shirai, T. & Kondo, A. Direct 1,3-butadiene biosynthesis in *Escherichia coli* via a tailored ferulic acid decarboxylase mutant. *Nature Communications* **12**, 2195 (2021).
3. Imada, M., Takenaka, Y., Hatanaka, H., Tsuge, T., Abe, H. Unique acrylic resins with aromatic side chains by homopolymerization of cinnamic monomers. *Communications Chemistry* **2**, 109 (2019).



TOMOKAZU SHIRAI
Senior Scientist, RIKEN
Center for Sustainable
Resource Science

Tomokazu Shirai obtained a PhD in applied biotechnology from Osaka University in 2007. In 2008, he started working at Mitsui Chemicals, Inc., where he was involved in the development of isopropyl alcohol producing *E. coli* bacteria. In 2012, he joined Cell Factory Research Team, which was part of the RIKEN Biomass Engineering Program and later moved to the RIKEN Center for Sustainable Resource Science (CSRS). Since 2020, he has also been the Deputy Team Leader of the Biomonomer Production Research Team, a project jointly run by RIKEN, the ZEON Corporation and Yokohama Rubber Co. in the RIKEN Baton Zone Program.



CRACKING GREEN HYDROGEN ENERGY

An electrocatalyst that has a long shelf life is a major step towards realizing terawatts from green hydrogen.

A team of chemists at RIKEN has created a manganese and cobalt oxide electrocatalyst that represents an important step forward in the affordable production of cleaner hydrogen fuels.

Hydrogen can be made using electricity that induces a chemical reaction to split water into its

constituent elements: oxygen and hydrogen. “One of the biggest hurdles in generating industrial-scale hydrogen has been finding a suitable catalyst for the oxygen evolution reaction at one of the electrodes of this production system,” explains Ailong Li, who co-led the study at the RIKEN Center for Sustainable Resource Science.

The difficulty, he explains, has been finding an electrocatalyst that has high activity, but can also withstand the acidic conditions under which the reaction occurs. This newest catalyst is made from affordable materials, and is stable in acid for months while remaining highly active¹, says Li.

‘Green hydrogen’ is made using renewable sunlight or wind energy to generate the electricity

that splits water. It could hugely reduce global carbon dioxide emissions if it replaced fossil fuels at industrial scales, says Shuang Kong, who co-led the study. And when hydrogen is then combusted to produce energy, it reverts to water again, making it a truly pollution-free fuel.

The International Renewable Energy Agency, an intergovernmental organization supporting countries in their transition to a sustainable energy, predicts that generating green hydrogen on a large scale could become a cost-competitive option within the next decade. They've called it "a game-changer on the path to carbon neutrality".

“Both manganese and cobalt are vastly more abundant than iridium: the global annual production of manganese is more than 60,000 times greater than that of iridium.”

AFFORDABLY ACTIVE

While some electrocatalysts already exist that meet both conditions of stability and activity, they all suffer from one drawback—they contain one of the scarcest elements on Earth: iridium.

Since the global production of iridium is a mere seven tons per year (to put that into perspective, 170 tons of platinum, which is considered a rare metal, were mined in 2020), generating the terawatt levels of green hydrogen needed for industrial use would require four decades' worth of the world's iridium.

Then in a 2019 study, Li and his co-workers discovered that manganese oxide showed excellent stability in acid for catalyzing the oxygen evolution reaction². Now, they have shown that, by incorporating manganese into cobalt oxide—another electrocatalyst—to produce a mixed oxide, it is possible to increase the lifespan of the electrocatalyst in strong acid by a factor of about 100 without sacrificing activity. This takes the lifetimes of iridium-free electrocatalysts from just days or weeks to longer than two months.

Li was thrilled when he first saw the electrocatalyst in action. "Our electrocatalyst was very active," says Li. "Even before we made the measurements, it was a beautiful sight to see it generate a cascade of bubbles."

The manganese imparts stability to the electrocatalyst, while the cobalt gives the oxide its high activity. Kong describes manganese as "nature's catalyst for water oxidation." The team found that

the optimal mixture was two atoms of cobalt to every one of manganese.

Importantly, both manganese and cobalt are vastly more abundant than iridium: the global annual production of manganese is more than 60,000 times greater than that of iridium and it is the fifth most common metal in the Earth's crust.

CLEAN, GREEN INDUSTRIAL DREAM

There is still room for improvement in the catalyst's lifespan. While the activation barrier of the mixed oxide rivals that of iridium oxides, iridium catalysts can last for decades before needing to be replaced. But Li is encouraged by the advance. "In the long run, we believe that this is a huge step toward creating a sustainable hydrogen economy," he says.

Hydrogen, he adds, is also an important industrial chemical that is used to produce ammonia, a key component of fertilizers. The current industrial process for manufacturing ammonia is highly energy intensive and uses fossil fuels: it accounts for nearly 2% of the global emissions of carbon dioxide. Green ammonia produced from green hydrogen could help to slash these emissions.

An early inspiration, says Kong, was a 2004 speech by Nobel laureate Richard Smalley, in which Smalley describes a future in which trillions of watts (terawatts) of renewable energy is generated to drive industry instead of burning fossil fuels.

Looking forward, Li sees lots of ways to enhance their electrocatalyst and produce green hydrogen more efficiently. "There are so many avenues we can pursue to advance this technique," he says. "In addition to improving the electrocatalyst, we can also enhance the water-splitting membrane that is sometimes used."

Li points out that when you're dealing that terawatt-scale hydrogen production, even a small rise in efficiency can yield great gains. "Just a 1% increase in efficiency across today's large scale-industry could save 88 billion kilowatt hours per year and reduce carbon dioxide emissions by 34 million tons." ●

REFERENCE

1. Li, A., Kong, S., Guo, C., Ooka, H., Adachi, K., Hashizume, D., Jiang, Q., Han, H., Xiao, J. & Nakamura, R. Enhancing the stability of cobalt spinel oxide towards sustainable oxygen evolution in acid. *Nature Catalysis* **5**, 109–118 (2022).
2. Li, A., Ooka, H., Bonnet, N., Hayashi, T., Sun, Y., *et al.* Stable potential windows for long-term electrocatalysis by manganese oxides under acidic conditions. *Angewandte Chemie* **58**, 5054–5058 (2019).



This feature looks at the work of **AILONG LI** and **SHUANG KONG**

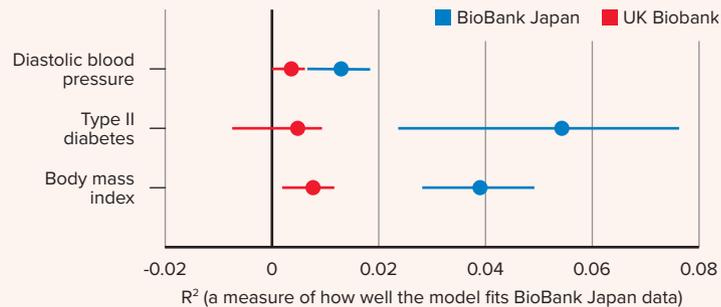
Ailong Li and Shuang Kong are postdoctoral researchers in the Biofunctional Catalyst Research Team at the RIKEN Center for Sustainable Resource Science (CSRS). They both moved to Japan in 2017. Li first worked as an International Program Assistant (IPA) between 2017 and 2019, while Shuang Kong worked on RIKEN's technical staff between 2018 and 2019. They are now working on finding alternative catalysts for iridium used in polymer electrolyte membrane (PEM) water electrolysis, funded by the New Energy and Industrial Technology Development Organization (NEDO).

JAPAN'S GENES

RIKEN's BioBank Japan (BBJ) stores genetic data from 260,000 Japanese patients. This data is closing the gap between European and East Asian genetic risk score accuracy.

GENETIC RISK SCORE GAP

Roughly 80% of all genome wide association study participants are of European descent. And genetic prediction accuracy is on average two-fold lower for East Asians than Europeans, using international models. This difference is even more pronounced in type II diabetes mellitus and coronary artery disease. To the right we see how using Japanese models is a better fit for Japanese subjects than UK models for phenotypes linked to these diseases.



NEW VARIANTS FOUND USING JAPANESE DATA

In a 2020 study published in *Nature Genetics*, researchers at the RIKEN Center for Integrative Medical Sciences used Japanese genome wide association study data from BBJ to link a number of variants to diseases for the first time.

VARIANT rs7721099

It is found on the gene **MEF2C** on chromosome 5. **MEF2C** had been shown to coactivate with another gene to increase levels of glucose transporter proteins. An inherited difference had previously been shown to weaken the binding of the two genes, increasing the risk of type II diabetes mellitus in a Chinese Han population.

New variants were found on the genes below. Some links to disease phenotypes are discussed at the left.

- Coronary artery disease
- Type II diabetes mellitus

VARIANT rs200525873

It is found on **CEP120** on chromosome 5. A 2022 study linked another variant on this gene with type II diabetes mellitus in South Asians. Variants near this gene have also been associated with increased waist circumference and BMI in East Asians.

- **Chromosome 5**
- **MEF2C**
- **TMEM16B**
- **CEP120**
- **PRDM6**

VARIANT rs39218

It is found on **STEAP1** on chromosome 7. A 2022 study published in *Nature* linked subcutaneous adipose tissue signals for type II diabetes to a different variant on the gene **STEAP1**.

- **Chromosome 7**
- **STEAP1**
- **ZNF804B**
- **Chromosome 11**
- **ATG16L2**

VARIANT rs11235604

It is found on **ATG16L2** on chromosome 11. **ATG16L2** has been linked to the degradation and removal of unnecessary or dysfunctional cell parts, particularly in immune cells. Previous studies have reported a link between variant rs11235604 on the **ATG16L2** gene and immune-related traits. This new link to coronary artery disease suggests that dysregulated degradation and removal of immune cells might play a role in disease development.

- **Chromosome 12**
- **PRIM1**
- **Chromosome 14**
- **IRF2BPL**
- **LRRC74A**

VARIANT rs17105012

It is found on **IRF2BPL** on chromosome 14. Different variants on the **IRF2BPL** gene have recently been linked to hip-to-waist ratios in Hispanic/Latino populations.

- **Chromosome 18**
- **SETBP1**
- **Chromosome 22**
- **ZNRF3**



RIKEN'S CENTERS AND FACILITIES

across Japan and around the world



Since relocating its original campus from central Tokyo to Wako on the city's outskirts in 1967, RIKEN has rapidly expanded its domestic and international network. RIKEN now supports five main research campuses in Japan and has set up a number of research facilities overseas. In addition to its facilities in the United States and the United Kingdom, RIKEN has joint research centers or laboratories in Germany, China, South Korea, India, Malaysia, Singapore

and other countries. To expand our network, RIKEN works closely with researchers who have returned to their home countries or moved to another institute, with help from RIKEN's liaison offices in Singapore, Beijing and Brussels.

For more information, please visit:
www.riken.jp/en/research/labs/
www.riken.jp/en/collab/research/



RIKEN RESEARCH

www.riken.jp/en



Science Blog

itaintmagic.riken.jp



Find us on
Facebook

www.facebook.com/RIKENHQ



www.riken.jp/en

 @riken_en

www.twitter.com/riken_en

 LinkedIn

www.linkedin.com/company/riken