RIKEN RESEARCH

SUMMER 2023

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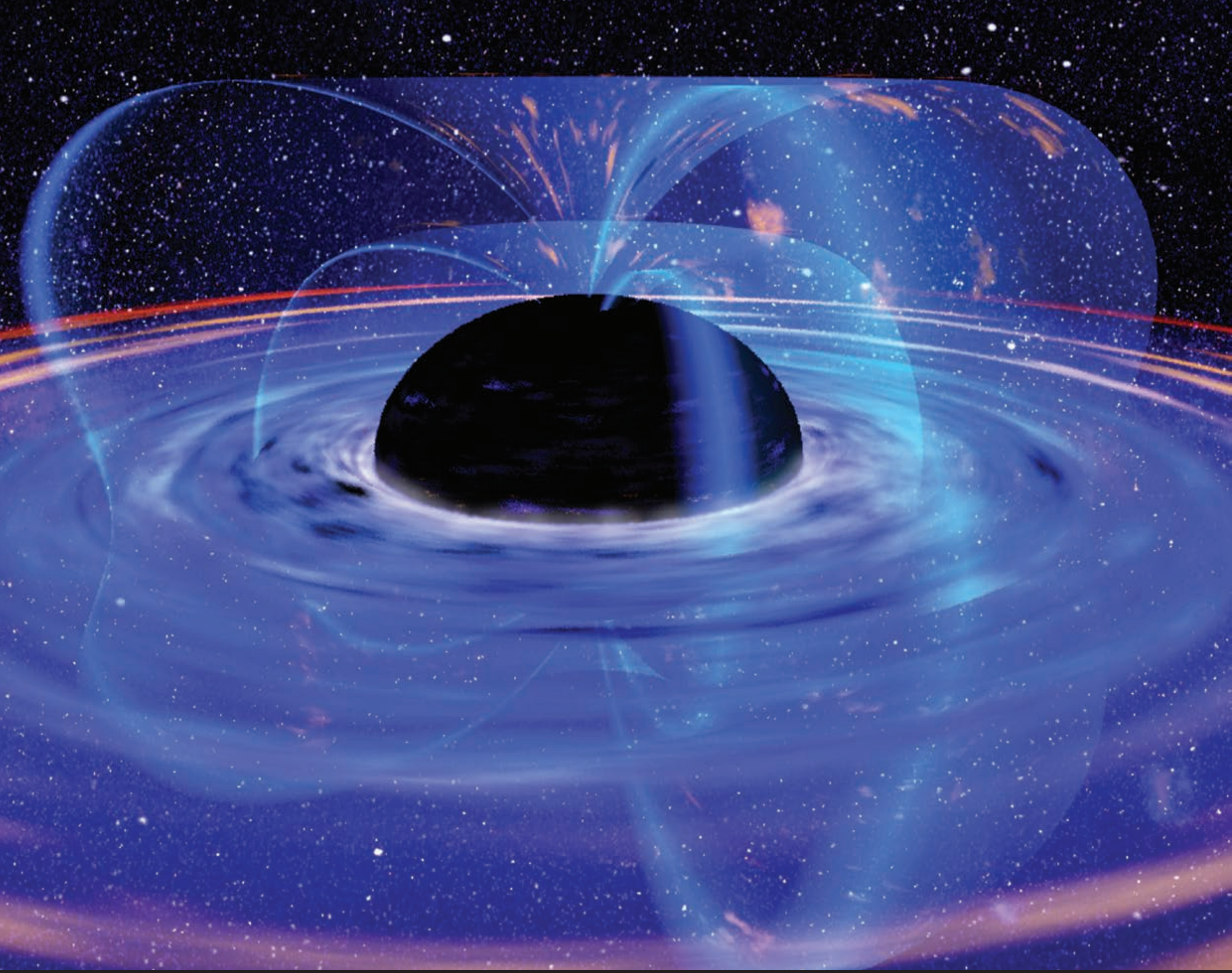
ONE DIRECTION

How embryos tell left from right

BENEATH THE SURFACE
Terahertz tech for non-destructive imaging

BIOLOGY IN A BOX
Making mini-organs in a lab

A KIND OF MAGIC
Quantum property key to black hole chaos



MAGICAL BLACK HOLE CHAOS
RIKEN researchers think that a quantum property dubbed 'magic' may explain black hole chaos. They have shown (page 13) that a chaotic system will almost always evolve into one that is ‘maximally magical’—a mathematical measure of how difficult a quantum state is to simulate.

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.

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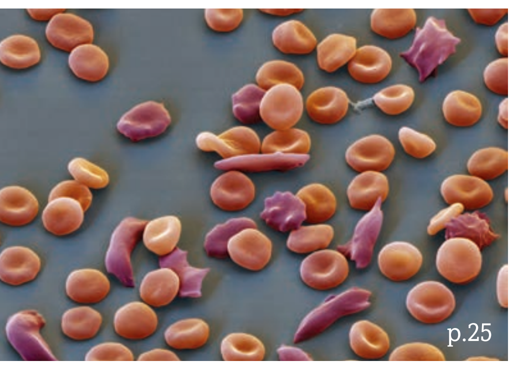
p.14

p.16

p.18



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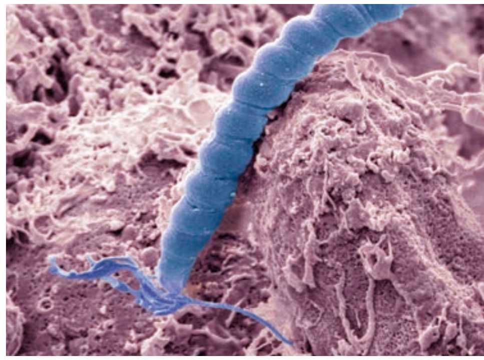

New early-career opportunities at RIKEN

Satoru Kagaya
Executive Director, RIKEN

I began my career at RIKEN four decades ago, and in April last year I was appointed to serve as an executive director in charge of administrative divisions, including human resources and general affairs, as well as facility and safety management. I am very pleased to be able to introduce a new program we have launched as part of our efforts to strengthen the nurturing of junior researchers.

As Japan's sole comprehensive research institute for the natural sciences, RIKEN is committed to promoting research and development as well as fostering junior researchers who will play a central role in global brain circulation.

This year, we decided to establish the RIKEN Early Career Leaders (ECL) Program to provide exceptionally talented junior researchers with the opportunity to carry out their research independently as laboratory leaders. It offers two fixed-term positions, team leader and unit leader, depending on the career stage and research plan of the researcher.

The first position, team leader, provides an opportunity for junior researchers who are ready to take on the challenge of ambitious research with high scientific and social impact to lead their own team as principal investigators. Its maximum term is seven years and its research budget provides up to 40 million yen per year.

The second position, unit leader, provides an opportunity for outstanding junior researchers who have recently earned their doctorate and are ready for the new challenge of leading a laboratory. Its maximum term is five years and its research budget provides up to 10 million yen per year.

In addition, as a means for providing extra incentives to outstanding female researchers, we have another program, the Sechi Kato Program—named after a prominent early female researcher at RIKEN—which provides both team leader and unit leader positions under the RIKEN ECL Program with an extra budget of 10 million yen per year.

We hope that you will take advantage of these programs to come to RIKEN yourself or encourage your own students or colleagues to apply.

加賀屋 悟

COVER STORY:
RIKEN biologists have discovered that tiny hairs that detect flowing fluid lead to the development of an embryo's distinct left and right sides. *Page 24*

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Watching spiraling disks in space

Mariko Kimura
Special Postdoctoral Researcher
Extreme Natural Phenomena RIKEN Hakubi Research Team,
Cluster for Pioneering Research

Please describe your role.
As materials around astronomical objects lose energy and angular momentum, and slowly spiral inward, they form accretion disks from accumulated gas, plasma, dust or particles. I am researching accretion disks that swirl around compact astronomical objects, such as black holes, white dwarfs and neutron stars. My targets are transient events related to these disks, such as a sudden brightening. If a transient event occurs, I observe the relevant star via x-ray and optical telescopes, and analyze the data to find out why. I also perform numerical simulations to try to explain the observed phenomenon.

Please describe your current research.
I study the physics related to the growth of binary stars composed of a compact object and a normal star. That binary system is the simplest astronomical system to feature accretion disks, so if we can understand them, we can try to understand more complex accretion systems. I do this by looking at them at x-ray, optical and radio wavelengths.

Some binary systems can also be the source of gravitational waves, so measurements of their binary parameters will help future gravitational-wave research. I also study gamma-ray bursts, which could reveal the mechanisms of black-hole formation and the origin of heavy elements in our Universe.

How did you become interested in your current field of research?
I liked physics in high school, then at university I attended my first seminar on astrophysics. It seemed to me like the professors really enjoyed their research, which was fascinating. Later, I did graduate research with one of those professors, who is a specialist in accretion physics.

What has been the most interesting recent discovery in your field?
The detection of electromagnetic counterparts to gravitational-wave sources, emanating from the merger of neutron stars, was big news, and meant research on compact objects flourished. While my interest is accretion physics, I am also trying to identify astronomical candidates for future gravitational wave observations.

> *“I am researching accretion disks that swirl around compact astronomical objects, such as black holes, white dwarfs and neutron stars.*

How has being at RIKEN helped your research?
I perform multi-wavelength observations. When I joined RIKEN as a special postdoctoral researcher in 2020, I finally had access to optical telescopes. However, I don’t have access to x-ray telescopes for multi-wavelength observations, so I also make observations and perform multi-wavelength analysis via data from my networks.

What excites you the most about your current research?
It is exciting when unexpected transient events occur and I find them in my data. I am then able to enjoy trying to understand the origin of these events via observations and simulations. ■

Magic moments with exotic nuclei

Pieter Doornenbal
Senior Research Scientist
Radioactive Isotope Physics Group,
RIKEN Nishina Center for Accelerator-Based Science

Please describe your research
I lead research at the RIKEN Nishina Center for Accelerator-Based Science revealing the structure of radioactive isotopes via in-beam gamma-ray spectroscopy. Radioactive isotopes, often called exotic nuclei, do not naturally occur on Earth. But their properties are fundamental to obtain a complete understanding of the forces that form atomic nuclei and hold them together. This is crucial to explaining the abundance of different elements in the Universe.

Describe an exciting, recent finding in your field
Complete filling of nucleus shells with protons and neutrons at nucleon numbers 2, 8, 20, 28, 50, 82 and 126 yields 'magic' numbers. Magic-number isotopes are spherical and very difficult to excite, among other things. Recent experimental results demonstrated that neutron numbers 32 and 34 are also magic in calcium isotopes. It is possible that 40 is a magic number, which is a research topic we're examining.

When did you join RIKEN?
After obtaining my PhD from the University of Cologne in 2007, I joined RIKEN as a Japan Society for the Promotion of Science fellow. I later became one of RIKEN's Foreign Postdoctoral Researchers, and was fortunate that a researcher position opened up in 2012.

How has being at RIKEN helped your research?
At the RIKEN Nishina Center for Accelerator-Based Science's Radioactive Isotope Beam Factory (RIBF), we have access to the most powerful machine of its kind. Equally important is that young researchers are encouraged to put forward scientific proposals and apply for machine time with their own ideas.

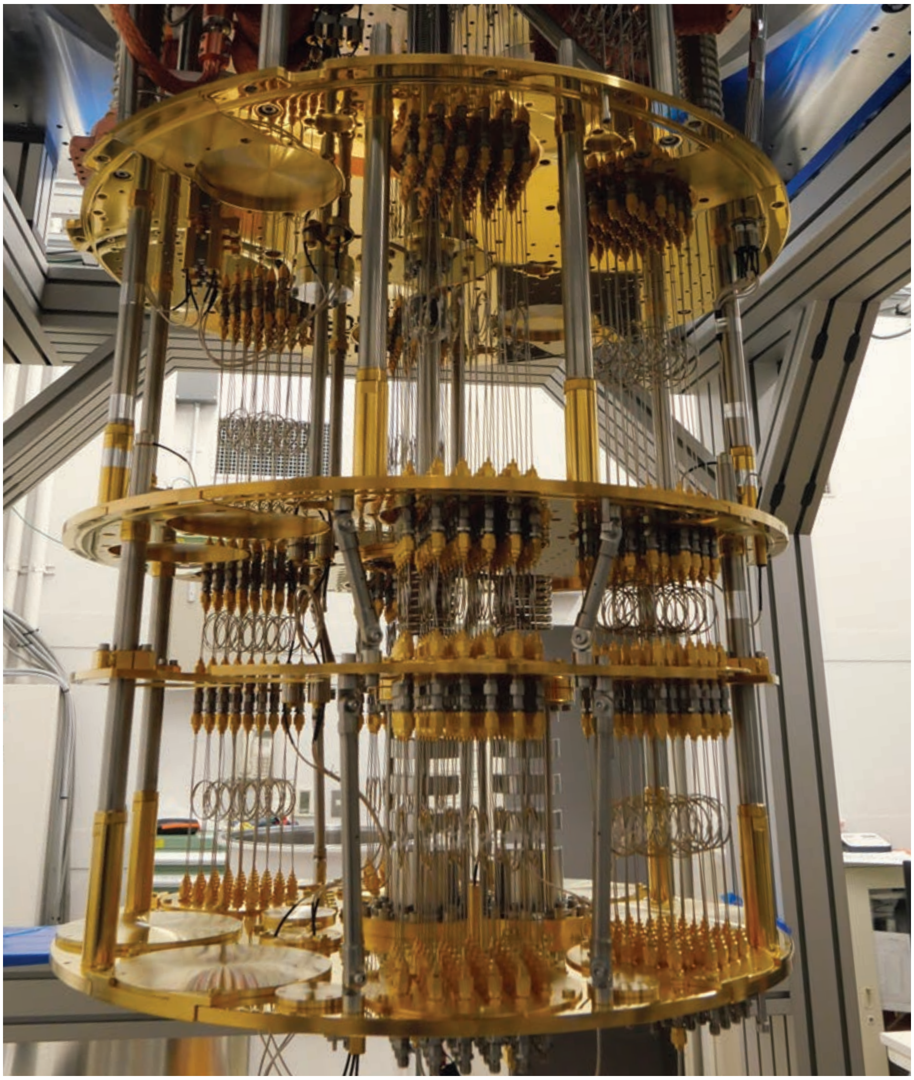
What technologies do you use?
The RIBF's Superconducting Ring Cyclotron accelerates stable isotopes to an energy of 345 MeV per nucleon. Accelerating the isotope ^{238}U corresponds to an energy for which the cyclotron in Wako was listed in GUINNESS WORLD RECORDS® on April 11, 2022, as 'Highest beam energy cyclotron'. Besides that, RIBF offers world-leading primary-beam intensities that help produce many exotic nuclei.

What has been your most memorable experience at RIKEN?
While it's not easy to pick a single event, I enjoy after-beam-time parties. Collaborators from all over the world come to the RIBF for beam time. This is typically very intense, as beam-time schedules are tight. Experiments are carried out night and day, and on weekends. Once the experiment is over, the stress levels drop, and one would typically gather in a local *izakaya*, sometimes with up to 40 people, to celebrate a successful experiment. Often this leads to new experimental ideas!

What do you wish you had known before coming to Japan?
Prior to coming to Japan, I had two concerns: a rather strict working atmosphere, and hot and humid summers. For the former, I was quickly relieved that this wasn't the case at all, while for the latter, neck towels came in very handy. ■

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

Look to the clouds for quantum computing



The 64-qubit superconducting quantum computer, which RIKEN developed along with other partners, is now available for researchers throughout Japan via a cloud service.

Japan's first 64-qubit superconducting quantum computer will be made available for non-commercial use under a joint research agreement with RIKEN.

The consortium of joint research partners who developed the technology include RIKEN, the National Institute of Advanced Industrial Science and Technology (AIST), the National Institute of Information and Communications Technology (NICT), Osaka University, Fujitsu Limited (Fujitsu) and Nippon Telegraph and Telephone Corporation (NTT).

From March 27 this year, RIKEN has made the technology available as a quantum computing cloud service to researchers and engineers in Japan under joint research agreements. Users will be able to access the new superconducting quantum computer for tasks within the scope of the joint research agreement and can send data and receive results via the cloud.

The new technology represents a significant step toward the wider use of quantum computing in Japan.

SPECIAL FEATURES

The newly developed superconducting quantum computer uses integrated circuits with 64 qubits and two special features: two-dimensional integrated circuits and perpendicular wiring packages.

In the two-dimensional integrated circuits, four qubits are arrayed in a square, with each connected to its neighbors by inter-qubit connections. This basic four qubit unit can be arranged in two dimensions to form a qubit integrated circuit. The 64 qubit integrated circuit consists of 16 of these basic units formed on a two centimeter square silicon chip.

To sufficiently wire the qubits in the space available, the team adopted a design based on perpendicular wiring packages, in which the wiring to the chip for the qubits arrayed on a two-dimensional planar surface is connected perpendicularly. The research team is further developing a wiring package that enables wiring to the qubit integrated circuit chip.

Moving forward, the joint research group will enhance the new system to enable quantum computing operations with a higher number of qubits and increase the density of wiring inside the dilution refrigerator. The team will provide access to the superconducting quantum computer as a testbed for noisy intermediate-scale quantum computers.

FUTURE PLANS

Using the highly scalable integrated circuit as a core technology, the joint research team will continue to work toward the realization of quantum computers with 100 and 1,000 qubits. They will also promote further R&D toward the integration of 1 million qubits and the realization of fault-tolerant quantum computing for real-world applications.

By making this technology available as a cloud computing service, the research partners hope to further accelerate R&D in quantum computing through deeper collaboration with quantum software developers, quantum computing researchers and corporate developers.

rqc.riken.jp/en/

Reaching across the disciplinary divide

At an in-person event that exceeded pre-pandemic levels of attendance, 225 eager RIKEN personnel took the opportunity to share their work with colleagues from a range of disciplinary backgrounds.

The 26th Interdisciplinary Exchange Evening, was held at the Headquarters Building of Wako Campus on February 17 2023, with the aim of encouraging collaborative research projects and providing opportunities for all RIKEN staff to get to know each other.

In the first part of the event, three new principal investigators, Azusa Inoue, Tomotaka Kuwahara and Takuya Hashimoto, together with Cai Kunpeng, a research manager from Sysmex Corporation (Sysmex), shared their recent research activities and visions for the future.

In the second part of the evening, 90 presenters shared their research in a poster session. The top-five poster presenters were selected based on a vote by all attendees and awarded a certificate of merit and an Amazon gift card (10,000 JPY). The winners were Takuma Tagami from the Catalysis and Integrated Research Group, Jiawei Zhang from the Advanced Laser Processing Research Team, Alexandra Wolf from the Cognitive Behavioral Assistive Technology Team, and Sobi Asako and Ikko Takahashi, both from the Advanced Organic Synthesis Research Team.

Additionally, Sysmex generously founded the Sysmex Award to recognize the excellent research results of two poster presenters. The awardees, Akifumi Shiomi from the Microfluidics RIKEN Hakubi Research Team and Noriyuki Uchida from the Emergent Bioinspired Soft Matter Research Team, received certificates and invitations to give research seminars at Sysmex.

The event was organized by the RIKEN Scientists' Assembly Steering Committee together with Policy Planning Division Planning Section (RIKEN Science Council's Secretariat).

Financial support was provided by the RIKEN Mutual Benefit Society Wako, as well as RIKEN's president, executive directors and principal investigators.

Hiroyoshi Sakurai, director of the RIKEN Nishina Center for Accelerator-Based Science and Roger Eccleston, director of ISIS Neutron and Muon Source, signing a new research collaboration agreement.

30 years of RIKEN–RAL collaboration

On March 14 2023, a RIKEN–RAL commemoration ceremony was held at the Rutherford Appleton Laboratory (RAL) in the United Kingdom (UK) to honor more than 30 years of research collaboration.

RIKEN and RAL first signed an international research cooperation agreement on muon science in 1990. In the 30 years since, RIKEN has built and operated the RIKEN–RAL Muon Facility within the RAL Intense Pulsed Proton (ISIS) facility in the UK.

By the end of March 2023, the RIKEN–RAL Muon Facility will be upgraded and asset rights and operations control will be transferred to RAL, ending the current era of research collaboration.

In the past 30 years, the RIKEN–RAL collaboration has contributed to more than 500 papers, from basic research on condensed matter and chemical physics to applied research in areas such as battery materials. More than 90 Japanese institutions have participated in experiments and collaborations with 40 research institutes around the world. Their research has furthered the field of muon science, especially with Indonesia and other Southeast Asian countries.

"The partnership between RIKEN and RAL is one of the largest, longest-lasting and most successful examples of a scientific partnership between the UK and Japan," noted Philip King, director of the RIKEN–RAL Branch and associate director of ISIS.

A new research collaboration agreement has been signed between the RIKEN Nishina Center for Accelerator-Based Science and RAL ISIS.

www.isis.stfc.ac.uk/Pages/riken-timeline.pdf

Looking into marmoset minds

Marmosets grow and age more rapidly than other primates (including humans) making them useful for preclinical research in neuroscience.

Now, a group led by Junichi Hata and Hideyuki Okano of the RIKEN Center for Brain Science have published an open marmoset MRI database across a wide range of ages.

The Brain/MINDS Marmoset Brain MRI Dataset contains brain MRI information from 216 marmosets ranging in age from 1 to 10 years, as well as multi-contrast MRI images. At the time of publication, it is the largest publicly available dataset of its kind in the world.

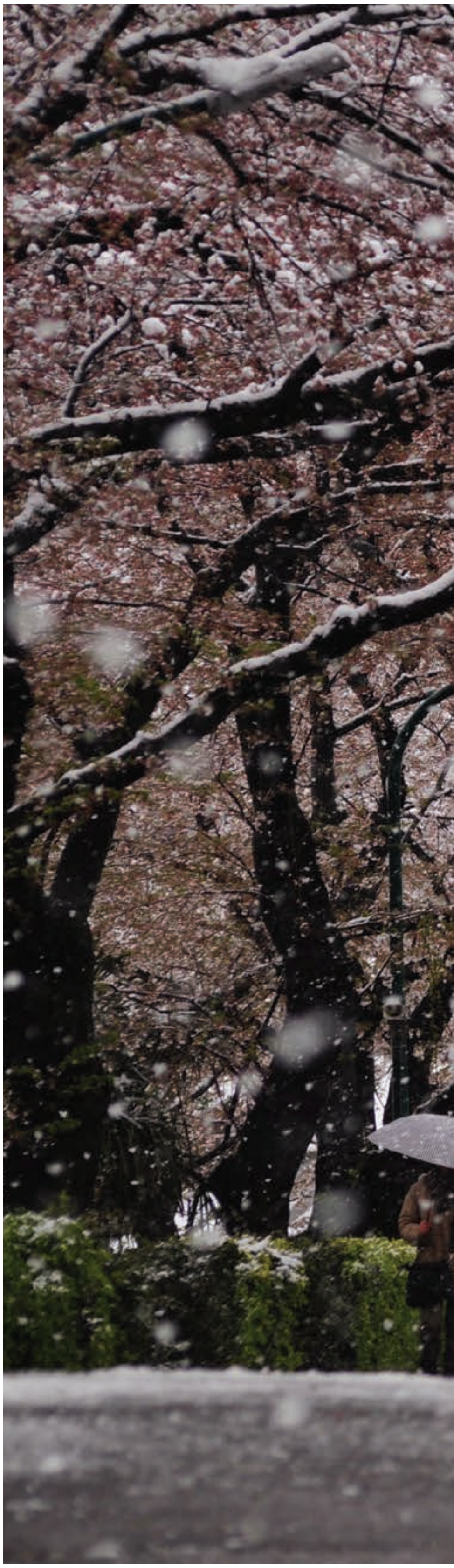
This database will help researchers understand how various factors such as age, sex, body size and fixation affect the brain, and will help accelerate brain science research around the world.

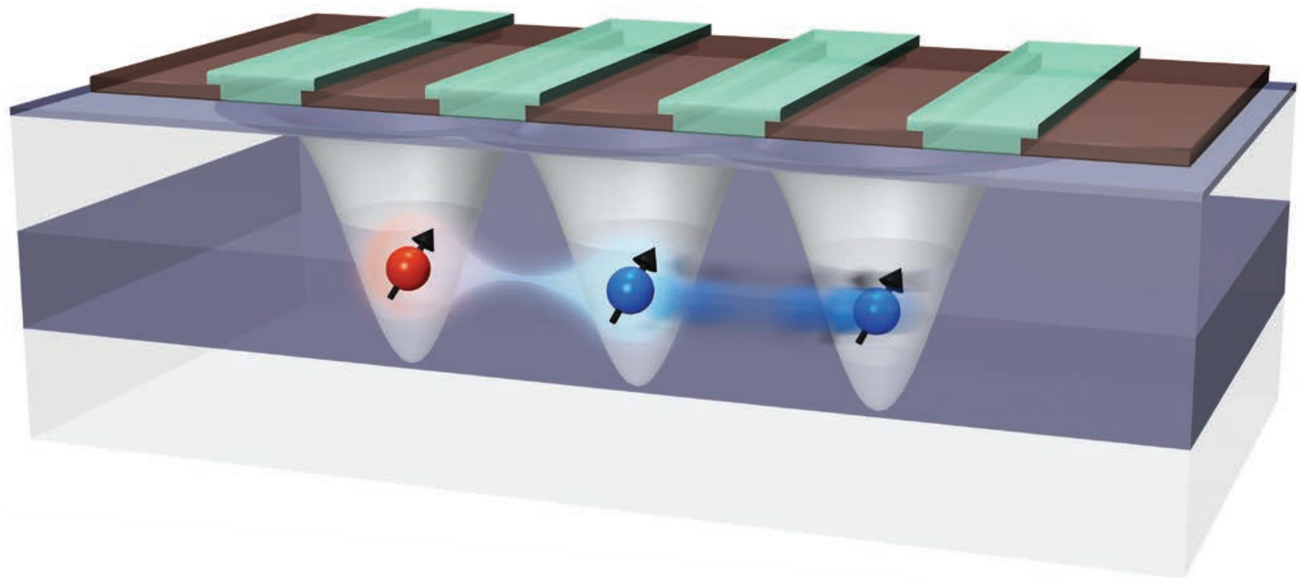
It can be freely accessed at: **dataportal.brainminds.jp/marmoset-mri-na216**

Snapshots of excellence

The winners of the second RIKEN image contest have been announced. Executive Director Makiko Naka presided over the awards ceremony at Wako on January 31 to celebrate the winners.

The winning images were chosen based on online voting that was open to all RIKEN personnel. First prize was awarded to Liang-Chun Wu of the RIKEN Cluster for Pioneering Research for his entry called 'White and Pink RIKEN' (right). Second place (below) went to Bolati Wulaer of the RIKEN Center for Brain Science, Thomas Chater of the RIKEN Center for Brain Science received third place and fourth place (bottom) went to Po-Yen Chen of the RIKEN Cluster for Pioneering Research.





RIKEN researchers have linked two distant qubits (red and blue spheres with black arrows in gray cones on the left and right) by coherent shuttling of one of the qubits (blue spheres).

QUANTUM COMPUTING

Connecting distant silicon qubits

The linking of two distant qubits will help to develop larger, more complex quantum computers based on silicon quantum dots

In a demonstration that promises to help scale up quantum computers based on tiny silicon dots, RIKEN physicists have connected two qubits—the basic unit for quantum information—that are physically distant from each other[1].

Many big IT players—including the likes of IBM, Google and Microsoft—are racing to develop quantum computers, some of which have already demonstrated the ability to greatly outperform conventional computers for certain types of calculations. But one of the greatest challenges to developing commercially viable quantum computers is the ability to scale them up from a hundred or so qubits to millions of qubits.

In terms of technologies, one of the front-runners to achieve large-scale quantum computing is silicon quantum dots that are a few tens of nanometers in diameter. A key advantage is that they can be fabricated using existing silicon fabrication technology. But one hurdle is that, while it is straightforward to connect two quantum dots that are next to each other, it has proved difficult to link quantum dots that are far from each other.

"To connect many qubits, we have to cram lots of them into a tiny area," says Akito Noiri of the RIKEN Center for Emergent Matter Science. "And it's very hard to use wires to connect such densely packed qubits."

Now, Noiri and co-workers have realized a two-qubit logic gate between physically distant silicon spin qubits (see image).

"While there has been a lot of work in this area using various approaches, this is the first time that anyone has succeeded in demonstrating a reliable logic gate formed by two distant qubits," says Noiri. "The demonstration opens up the possibility of scaling up quantum computing based on silicon quantum dots."

To connect the two qubits, the team used a method known as coherent spin shuttling, which allows single spin qubits to be moved across an array of quantum dots without degrading their phase coherence—an important property for quantum computers since it carries information. This method involves pushing electrons through an array of qubits by applying a voltage.

Although the physical separation between the two qubits was relatively short, Noiri is confident that it can be extended in future studies. "We want to increase the separation to about a micrometer or so," he says. "That will make the method more practical for future use." ●

Reference

1. Noiri, A., Takeda, K., Nakajima, T., Kobayashi, T., Sammak, A., Scappucci, G. & Tarucha, S. A shuttling-based two-qubit logic gate for linking distant silicon quantum processors. *Nature Communications* **13**, 5740 (2022).

CORRELATED ELECTRON SYSTEMS

Nickel crystal shows its stripes

A hidden pattern of electrons could provide clues to exotic quantum behavior

Hidden stripes in a crystal could help scientists understand the mysterious behavior of electrons in certain quantum systems, including high-temperature superconductors, an unexpected discovery by RIKEN physicists suggests[1].

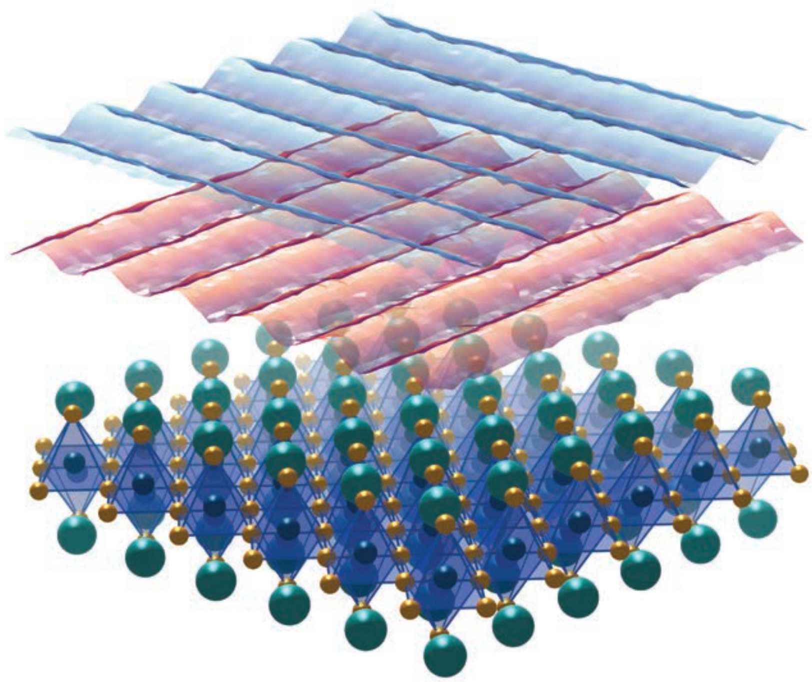
The electrons in most materials interact with each other very weakly. But physicists often observe interesting properties in materials in which electrons strongly interact with each other. In these materials, the electrons often collectively behave as particles, giving rise to 'quasiparticles'.

"A crystal can be thought of like an alternative universe with different laws of physics that allow different fundamental particles to live there," says Christopher Butler of the RIKEN Center for Emergent Matter Science.

Butler and colleagues examined a crystal in which a layer of nickel atoms was arranged in a square lattice, like a chessboard. Individual electrons have a small mass, but within this crystal, they appeared as massless quasiparticles.

The team set out to examine this odd effect using a scanning tunneling microscope, but this proved challenging. The walnut-sized microscope is housed inside a vacuum chamber, surrounded by a roomful of equipment that creates low temperatures and ultralow pressures comparable to that at the surface of the Moon.

"To examine the pristine surface of these crystals, we try to cleave off a small flake, much as geologists do," says Butler.



RIKEN physicists have observed that electrons (top two layers) formed striped arrangements above the square atomic lattice of a nickel crystal (bottom layer).

"But we have to do this inside the vacuum, and these crystals are so brittle they are prone to explode into dust."

After numerous attempts, they succeeded and used the microscope to scan the flake with a small needle—like a record player—with a voltage across it. Varying the voltage allowed them to probe different features.

The team confirmed the nickel atoms were arranged in a chessboard-like arrangement. But to their surprise, the electrons had broken this pattern and were instead aligned in stripes (see image). This is called nematicity—where interactions in the system make the electrons display less symmetry than the underlying material.

Butler likens the discovery to standing by a pond and throwing in a pebble. "You'd expect to see circular ripples, so if you saw ripples appearing in parallel lines, you would know something weird is going on," he says. "It demands an explanation."

Such experiments will help physicists test different proposed theories for the behavior of quantum systems with many particle interactions, such as high-temperature superconductors. These new results, for instance, fit with predictions made using a 'density-wave' framework proposed by the study's co-authors at Nagoya University in Japan.

"The behavior of many interacting electrons is hard to predict even with supercomputers," says Butler. "But at least we can observe what they are doing under a microscope."

Reference

1. Butler, C. J., Kohsaka, Y., Yamakawa, Y., Bahramy, M. S., Onari, S., Kontani, H., Hanaguri, T. & Shamoto, S. Correlation-driven electronic nematicity in the Dirac semimetal $BaNiS_2$. *Proceedings of the National Academy of Sciences* **119,** e2212730119 (2022).

COGNITIVE NEUROSCIENCE

Hidden links between vision and decision making

A behavioral task reveals interplay between the visual system and brain cells that guide decision making

An all-RIKEN team of neuroscientists has mapped out neurons in the mouse visual system that are selectively activated during decision-making, and may directly influence this process[1]. To achieve this, they combined a cleverly-crafted behavioral task with sophisticated imaging of neurons.

The choices we make involve diverse sectors of the brain, including those responsible for cognition, movement and other activities. This complexity has made it challenging for neuroscientists to tease out which neural circuits directly coordinate decision making.

Many important decisions start with responding to what we see in front of us. But the visual centers of the mammalian brain rely on much more information than is supplied by the eyes alone. “Most of the inputs come from within the brain,” says Andrea Benucci of the RIKEN Center for Brain Science. “And they carry a great diversity of non-visual signals.”

This led Benucci to hypothesize that these other sources of data may represent choice-guiding neuronal inputs. However, confirming this would require designing an experiment that minimized the confounding effects of other brain functions that intersect with the decision-making process.

To tackle this challenge, Benucci and his team used a behavioral task for mice that minimized the involvement of memory, body movements and responses to novel stimuli. This entailed training animals to earn a water reward by aligning the orientation of a projected image to match that of a target pattern. Once the animals had mastered this task, the researchers used a fluorescent ‘reporter’ protein to monitor the firing of neurons in different regions of the brain as animals pursued their reward.

By imaging neuronal activity in mice, researchers are learning how activity in specific parts of the visual system may produce a reciprocal interaction between vision and the decision-making process.

Their imaging data revealed subsets of neurons that appeared to be directly involved in choice. These were mostly located in regions of the brain within the ventral visual stream, a system of neurons primarily involved in identifying features in a visual scene. The strength of these signals depended both on the difficulty of the task and on the extent to which the animal’s attention was focused on the orientation task.

Benucci and colleagues validated the activity patterns they had observed with a neural-network-based computational model, which they trained using the actual data from animals.

“In this study, we not only uncovered signatures of choice, but we also found well-structured representational dynamics of choice signals that reflected the context-dependent nature of the decision-making process,” says Benucci. “The model confirmed that the recorded signals indeed reflect network computations associated with solving this specific task using choice strategies matching those of the mice.”

Intriguingly, the choice signals identified here were produced by a relatively small number of sparsely dispersed neurons within the ventral stream. Benucci’s team is now exploring the extent to which these ‘loners’ influence vision-based decision making. ●

Reference

1. Orlandi, J. G., Abdolrahmani, M., Aoki, R., Lyamzin, D. R. & Benucci, A. Distributed context-dependent choice information in mouse posterior cortex. *Nature Communications* **14,** 192 (2023).

A view of the M87 supermassive black hole.

QUANTUM INFORMATION

Quantum ‘magic’ could explain spacetime origins

Physicists relate the quantum property of ‘magic’ to the chaotic nature of black holes for the first time

A quantum property dubbed ‘magic’ could be the key to explaining how space and time emerged, a new mathematical analysis by three RIKEN physicists suggests[1].

It’s hard to conceive of anything more basic than the fabric of spacetime that underpins the Universe, but theoretical physicists have been questioning this assumption. “Physicists have long been fascinated about the possibility that space and time are not fundamental, but rather are derived from something deeper,” says Kanato Goto of the RIKEN Interdisciplinary Theoretical and Mathematical Sciences (iTHEMS).

This notion received a boost in the 1990s, when theoretical physicist Juan Maldacena related the gravitational theory that governs spacetime to a theory involving quantum particles. In particular, he imagined a hypothetical space—which can be pictured as being enclosed in something like an infinite soup can, or ‘bulk’—holding objects like black holes that are acted on by gravity. Maldacena also imagined particles moving on the surface of the can, controlled by quantum mechanics. He realized that mathematically a quantum theory used to describe the particles on the boundary is equivalent to a gravitational theory describing the black holes and spacetime inside the bulk.

“This relationship indicates that spacetime itself does not exist fundamentally, but emerges from some quantum nature,” says Goto. “Physicists are trying to understand the quantum property that is key.”

The original thought was that quantum entanglement—which links particles no matter how far they are separated—was the most important factor: the more entangled particles on the boundary are, the smoother the spacetime within the bulk.

“But just considering the degree of entanglement on the boundary cannot explain all the properties of black holes, for instance, how their interiors can grow,” says Goto.

So Goto and iTHEMS colleagues Tomoki Nosaka and Masahiro Nozaki searched for another quantum quantity that could apply to the boundary system and could also be mapped to the bulk to describe black holes more fully. In particular, they noted that black holes have a chaotic characteristic that needs to be described.

“When you throw something into a black hole, information about it gets scrambled and cannot be recovered,” says Goto. “This scrambling is a manifestation of chaos.”

The team came across ‘magic’, which is a mathematical measure of how difficult a quantum state is to simulate using an ordinary classical (non-quantum) computer. Their calculations showed that in a chaotic system almost any state will evolve into one that is ‘maximally magical’—the most difficult to simulate.

This provides the first direct link between the quantum property of magic and the chaotic nature of black holes. “This finding suggests that magic is strongly involved in the emergence of spacetime,” says Goto.

Reference

1. Goto, K., Nosaka, T. & Nozaki, M. Probing chaos by magic monotones. *Physical Review D* **106,** 126009 (2022).

NUCLEAR ASTROPHYSICS

A more accurate picture of how heavy elements form

Measurements on neutron-rich nuclei help to refine models of how heavy elements came into existence

Models for how heavy elements are produced within stars have become more accurate thanks to measurements by RIKEN nuclear physicists of the probabilities that 20 neutron-rich nuclei will shed neutrons[1].

Stars generate energy by fusing the nuclei of light elements—first hydrogen nuclei and then progressively heavier nuclei, as the hydrogen and other lighter elements are sequentially consumed. But this process can only produce the first 26 elements up to iron.

"So we're very close to having a good understanding of this part of the nuclei chart."

Another process, known as rapid neutron capture, is thought to produce nuclei that are heavier than iron. As its name suggests, this process involves nuclei becoming larger by rapidly snatching up stray neutrons. It requires extremely high densities of neutrons and is thus thought to occur mainly during events such as mergers of neutron stars and supernova explosions.

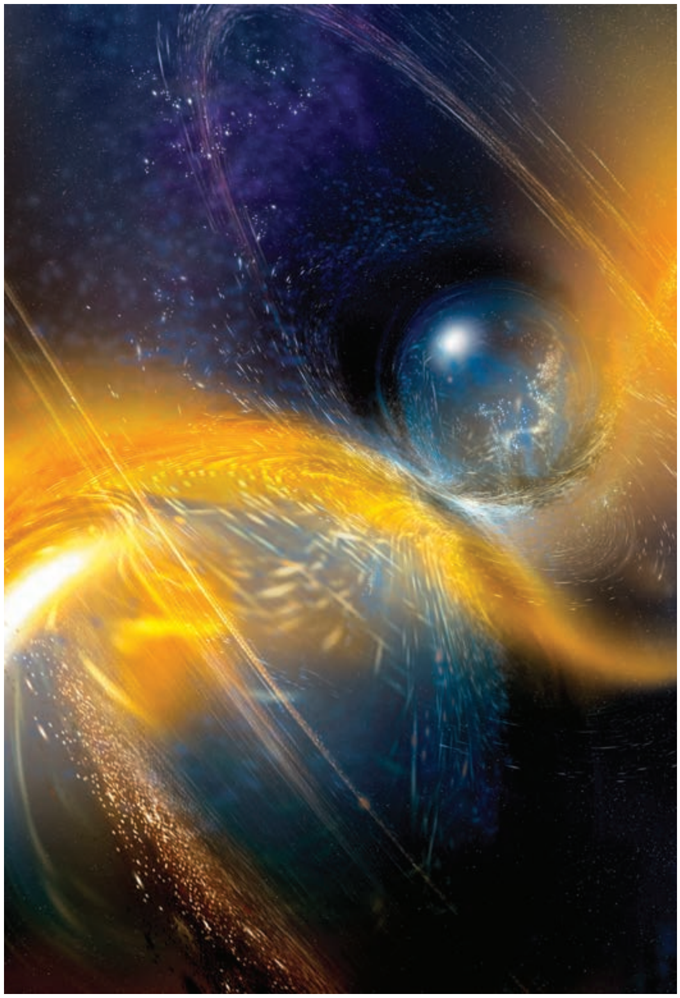
The neutron-rich elements produced by rapid neutron capture can lose neutrons through another process known as beta-delayed neutron emission.

Ultimately, astrophysicists dream of developing models that can accurately reproduce the natural abundances of the elements in the Universe. To achieve this goal, they need to combine astrophysical observations with measurements on nuclei in the lab.

Now, Shunji Nishimura of the RIKEN Nishina Center for Accelerator-Based Science and his co-workers have measured the possibilities that 20 neutron-rich nuclei will emit one or two neutrons.

Using the RIKEN Radioactive Isotope Beam Factory—one of only a handful of facilities in the world capable of performing such measurements—the team accelerated large uranium nuclei to about 70% of the speed of light and smashed them into beryllium, which produced unstable nuclei by a fission reaction. They then measured the probabilities of neutron emission when these unstable nuclei decayed.

When the results were put into models that predict the abundances of the elements, they improved their agreement with the abundances observed in the Solar System.



An illustration depicting two neutron stars merging. Such collisions are believed to be responsible for generating heavy elements by a process known as rapid neutron capture. Measurements by RIKEN researchers on neutron-rich nuclei have helped tighten models of element production by this process.

These measurements are important for tightening up theoretical models of element production, removing nearly 30% of their inherent uncertainty.

"While we still have a long way to go before we can determine the natural abundances of the elements, our measurements have helped close in on the fine structure in the region of elements near tin, which is determined by the so-called freeze-out time of rapid neutron capture," explains Nishimura. "So we're very close to having a good understanding of this part of the nuclei chart."

The team now intends to investigate the impact of about 200 delayed neutrons on the production of elements up to bismuth by rapid neutron capture. ●

Reference

1. Phong, V. H., Nishimura, S., Lorusso, G., Davinson, T., Estrade, A., Hall, O., Kawano, T., Liu, J., Montes, F., Nishimura, N., Grzywacz, R. *et al.* β-delayed one and two neutron emission probabilities southeast of ^{132}Sn and the odd-even systematics in *r*-process nuclide abundances. *Physical Review Letters* **129,** 172701 (2022).

NEUROMORPHIC COMPUTING

Brain-inspired system 'reads' handwriting

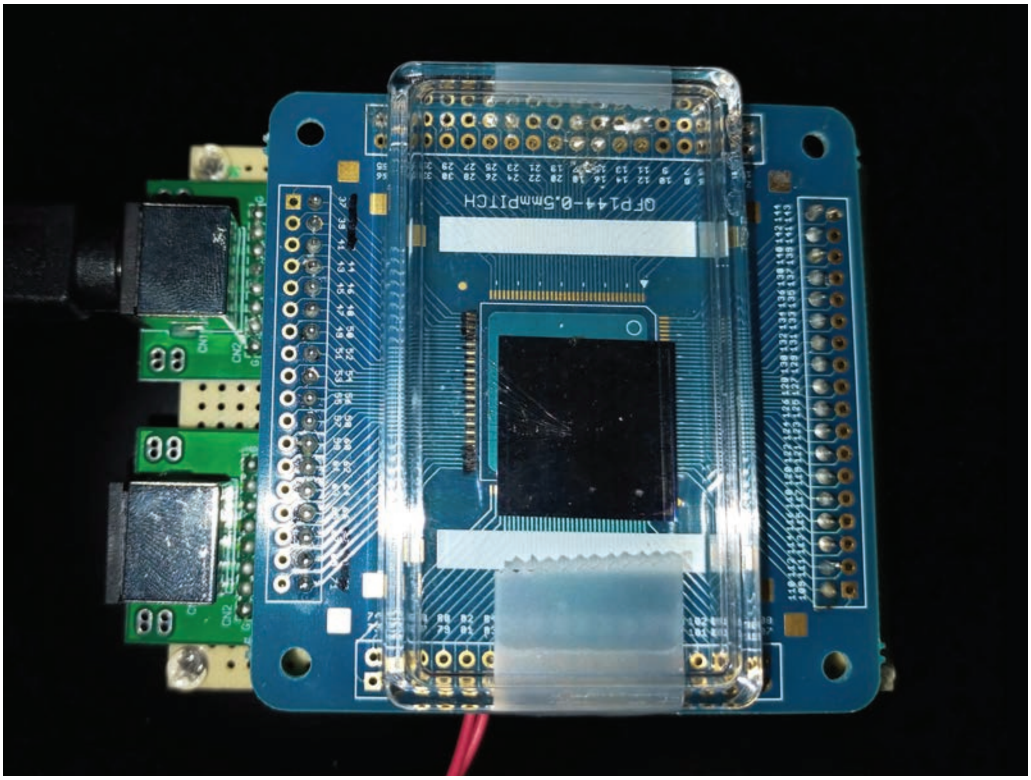
Tiny magnetic swirls help to process data in a pattern-recognition device that mimics brain networks

A computing device that uses swirling magnetic whirlpools to process data has been trained to recognize handwritten numbers[1]. Developed by RIKEN researchers, the device shows that miniature magnetic whirlpools could be useful for realizing low-energy computing systems inspired by the brain.

Our brains contain complex networks of neurons that transmit and process electrical signals. Artificial neural networks mimic this behavior, and are particularly adept at tasks such as pattern recognition.

But artificial neural networks consume a lot of power when run on conventional silicon chips. So researchers are developing alternative platforms that are specially designed for brain-inspired computing, an approach known as neuromorphic computing.

The new neuromorphic device (see image), created by researchers including Tomoyuki Yokouchi of the RIKEN Center for Emergent Matter Science, relies on a type of artificial neural network known as the reservoir computing model. One feature of this model is its short-term memory—its output depends on both past and present inputs to the system.



This neuromorphic computing device uses skyrmions to perform image-recognition tasks.

That's where tiny magnetic whirlpools known as skyrmions come in. These magnetic patterns have an in-built memory effect, because their structure and behavior reflect previous exposure to magnetic fields.

Skyrmions can also run on low energies. "Another advantage of using skyrmions is energy saving, because skyrmions can be controlled using very small current densities," says Yokouchi.

The team's device contains a series of bars covered in a platinum–cobalt–iridium film, which can host skyrmions a few micrometers wide.

To put data into the device, the researchers encoded information into a magnetic field that, when applied to the skyrmions, generates a voltage. This output voltage depends on the number and size of the skyrmions present.

The researchers trained the device using more than 13,000 images of handwritten digits from 0 to 9. They converted the images into magnetic input signals, and tuned the device so that the output voltage signals accurately represented the correct digit.

The team then tested the device using another 5,000 images, and found that it could recognize the numbers with about 95% accuracy—outperforming rival neuromorphic devices.

"Our work indicates that energy-saving neuromorphic computing can be realized using skyrmions," says Yokouchi.

The team hopes to develop a similar device that uses an electrical current for its input, rather than a magnetic field, which should improve its performance and further reduce its energy consumption. "If we succeed, we may be able to demonstrate more complex tasks such as speech recognition and motion tracking," Yokouchi says.

Reference

1. Yokouchi, T., Sugimoto, S., Rana, B., Seki, S., Ogawa, N., Shiomi, Y., Kasai, S. & Otani, Y. Pattern recognition with neuromorphic computing using magnetic field–induced dynamics of skyrmions. *Science Advances* **8**, eabq5652 (2022).

DEVELOPMENTAL BIOLOGY

How female embryos turn off an X chromosome

Two protein complexes play key but different roles in silencing one X chromosome in female mammals

RIKEN researchers have shed new light on the roles two protein complexes play in the enigmatic process of turning off one X chromosome in female mammals[1]. This finding could help researchers discover how certain cancers occur in women.

Males have one X chromosome and one Y chromosome, whereas females have a pair of X chromosomes. This redundancy of having two X chromosomes generally provides female mammals with extra robustness against genetic disorders and cancers compared with males.

During development, females employ a mechanism for turning off one of the X chromosomes, known as X-chromosome inactivation. When this process goes awry, women can develop major health problems such as breast cancer. A deeper understanding of proper X-chromosome inactivation could help to prevent or treat these types of tumor-fueling events in humans.

Now, by using mouse embryos, a team led by Haruhiko Koseki of the RIKEN Center for Integrative Medical Sciences (IMS) has shown how two protein clusters—known as polycomb repressive complex 1 (PRC1) and PRC2—serve independent and crucial roles in helping to keep one X chromosome in the developing embryo in a dormant state.

Notably, the researchers found that only embryonic-support tissues rely on PRC1 and PRC2 to maintain gene silencing on the inactive X chromosome. In contrast, embryonic tissues themselves can keep the same chromosome in an idle position without using these epigenetic regulators, and thus must rely on some other molecular machinery to get the same job done.

Illustration of two female X chromosomes. RIKEN researchers have discovered how two protein complexes turn off one X chromosome in female mammals.

“This finding could contribute to our understanding of how female-specific tumors form”

“This study points out differential features of two major tissue lineages in developing embryos,” says Osamu Masui, also of IMS.

The researchers pinpointed the functions of PRC1 and PRC2 by studying mice genetically engineered to lack one or the other protein complex. These experiments showed how each PRC changes the winding of DNA in different ways to each silence a unique set of genes on the inactive X chromosome.

Both complexes are needed for proper X-chromosome inactivation in extra-embryonic tissues that will form organs such as placenta. Yet both are also dispensable in the embryo tissue itself.

“This study clearly demonstrates that both PRC1 and PRC2 independently accumulate on the inactive X chromosome and differentially maintain X-linked gene silencing,” says Masui. “This finding could contribute to our understanding of how female-specific tumors form.”

The team is now trying to uncover the molecular mechanisms that allow embryonic tissues to tightly maintain X-chromosome inactivation. “These studies should help us further establish the fundamentals of gene regulation in the genome,” says Masui. ●

Reference

1. Masui, O., Corbel, C., Nagao, K., Endo, T. A., Kezuka, F., Diabangouaya, P., Nakayama, M., Kumon, M., Koseki, Y. Obuse, C. *et al.* Polycomb repressive complexes 1 and 2 are each essential for maintenance of X inactivation in extra-embryonic lineages. *Nature Cell Biology* **25,** 134–144 (2023).

In the absence of a chemical gradient, nematodes usually move in random directions. But when placed on a special hydrogel developed by RIKEN researchers, nematodes tended to move toward one side of the hydrogel.

METAMATERIALS

A one-way material for mechanical energy

A material that flexes in one direction, but not the other, has promise for harvesting waste energy

A material developed by RIKEN scientists can channel mechanical energy in one direction but not the other[1]. It could thus be used to harness waste energy in the form of random vibrations to move matter in a preferred direction.

Channeling energy in a preferred direction is an important property that makes life possible since many basic biological functions, such as photosynthesis and cellular respiration, occur by channeling random fluctuations in nature in one direction.

Devices that allow energy to move preferentially are used in many areas, including electronics, photonics, magnetism and sound. However, it has been more challenging to create devices that channel mechanical energy, which could have many potential uses.

Now, a team led by Yasuhiro Ishida of the RIKEN Center for Emergent Matter Science has developed a remarkable material that can perform this function and is relatively easy to produce.

"It was a remarkable and surprising result, seeing how mechanical energy could be channeled in one direction preferably, in such a clear way, and using a material that is rather easy to make and quite scalable," says Ishida.

The team made the material using a hydrogel—a soft material made mainly of water—that consisted of a polymer network with graphene oxide nanofillers embedded in it. The nanofillers were angled clockwise from top to bottom.

The team fixed the bottom of the hydrogel, whereas its top part could move in response to a shear force. When they applied a shear force to it in the direction that the nanofillers were tilted toward, they tended to buckle and lose their resistance. But when it was applied in the opposite direction, the nanofillers stretched and maintained their strength. As a result, the material was about 60 times more resistant to deformation in one direction than the other.

When a block of the material was placed on a vibrating stand, it could channel the vibrational energy to make droplets move to the right or left, depending on the tilt direction of the nanofillers. The vibrational motion could also drive a circular motion, either clockwise or anticlockwise.

In a further demonstration, the team placed nematodes on the material. Although nematodes normally move randomly, they all moved to one or the other side of the hydrogel, depending on the tilt direction of the embedded nanofillers.

The team is now exploring how this material could be used. "We plan to find applications for this material, with the hope that we can use it to make effective use of vibrational energy that, up until now, has been seen as waste," says Ishida.

Reference

1. Wang, X., Li, Z., Wang, S., Sano, K., Sun, Z., Shao, Z., Takeishi, A., Matsubara, S., Okumura, D., Sakai, N. *et al.* Mechanical nonreciprocity in a uniform composite material. *Science* **380,** 192–198 (2023).

Grasses such as barley employ a unique strategy to obtain iron from the soil. RIKEN researchers have now determined the molecular structure of a transporter protein that these plants use to import iron into their cells.

PLANT PHYSIOLOGY

A nifty trick to help plants thrive in iron-poor soils

Insights into molecular structure could improve fertilizers that help plants gather iron from alkaline soils

After almost a decade of effort, scientists at RIKEN have determined the structure of a key transporter protein that helps plants gather iron from soil[1]. This finding could guide the development of new high-potency fertilizers that will help plants extract iron from iron-deficient soils.

Roughly a third of all land globally is alkaline because its soil contains large quantities of the alkaline salt, calcium carbonate. Iron does not dissolve well in these alkaline soils, and the resulting iron deficiency can severely restrict plant growth.

"Iron uptake from the soil is not easy," says Atsushi Yamagata of the RIKEN Center for Biosystems Dynamics Research.

However, common grasses, including wheat and barley, have evolved a unique strategy to capture iron. They release compounds called phytosiderophores that are released into the soil, where they bind with iron and form a complex that the plants can absorb through their roots.

The phytosiderophores are compounds known as mugineic acids. While carrying their cargo of iron they are reabsorbed into plant cells by a transporter protein in cell membranes. But much is still unknown about the molecular mechanism of this process.

Now, Yamagata and his co-workers have determined the structure of the transporter protein for the first time.

"We have solved the structure of the transporter protein—both in the unbound state and when combined with an iron-carrying phytosiderophore," says Yamagata. This is critical because it helps the researchers understand the fine molecular details of how the iron-containing complex interacts with the transporter to be carried into cells.

The RIKEN team had been trying to determine the transporter protein's structure for nearly ten years. "We couldn't even obtain the crystals needed for analysis by x-ray crystallography," says Yamagata. The breakthrough came with recent advances in a technique called cryo-electron microscopy, which revealed the structures by firing electrons at frozen samples of the protein.

This research is now guiding work to develop derivatives of mugineic acids, which the team believe could become a new generation of highly effective fertilizers for alkaline soils.

"One synthetic derivative, developed by our collaborator Kosuke Namba of Tokushima University, can improve plant growth better than the natural compound at only around a thousandth of the cost," says Yamagata. Called proline-2′-deoxymugineic acid (PDMA), the derivative is stable for a month in soil, compared to only a day for the natural compound.

Namba is now working with a Japanese manufacturer to scale up production of PDMA for commercial use as an agricultural fertilizer.

Reference

1. Yamagata, A., Murata, Y., Namba, K., Terada, T., Fukai, S. & Shirouzu, M. Uptake mechanism of iron-phytosiderophore from the soil based on the structure of yellow stripe transporter. *Nature Communications* **13**, 7180 (2022).

SEISMIC MODELING

Neural networks may help predict earthquakes

Machine-learning method could offer a more reliable way to predict deformations in the Earth's crust

An artificial neural network has taken its first steps toward predicting the timing and size of future destructive earthquakes, according to RIKEN researchers[1].

Earthquakes typically occur when parts of the Earth's crust suddenly move around a fracture, or fault, in the rock. This releases a huge amount of strain energy that shakes the surrounding region, sometimes unleashing enormous destruction, such as in the case of the 2023 February earthquake in Turkey and Syria.

Predicting an earthquake before it hits could give people enough time to evacuate threatened areas, potentially saving many thousands of lives. But earthquake prediction is notoriously difficult.

To create mathematical models of earthquakes, researchers often draw an analogy to defects within the structures of crystals—cracks within crystals resemble faults in the Earth's crust. When applied to the motion of crustal faults, these 'dislocation models' describe the movement and deformation of the Earth's crust during earthquakes.

In contrast, a team led by Naonori Ueda of the RIKEN Center for Advanced Intelligence Project (AIP) considered applying a neural network that learns physical laws, called a physics-informed neural network (PINN). Conventional neural networks learn functional relationships between inputs and outputs, whereas PINNs differ in that they learn to satisfy a physical model described by partial differential equations.

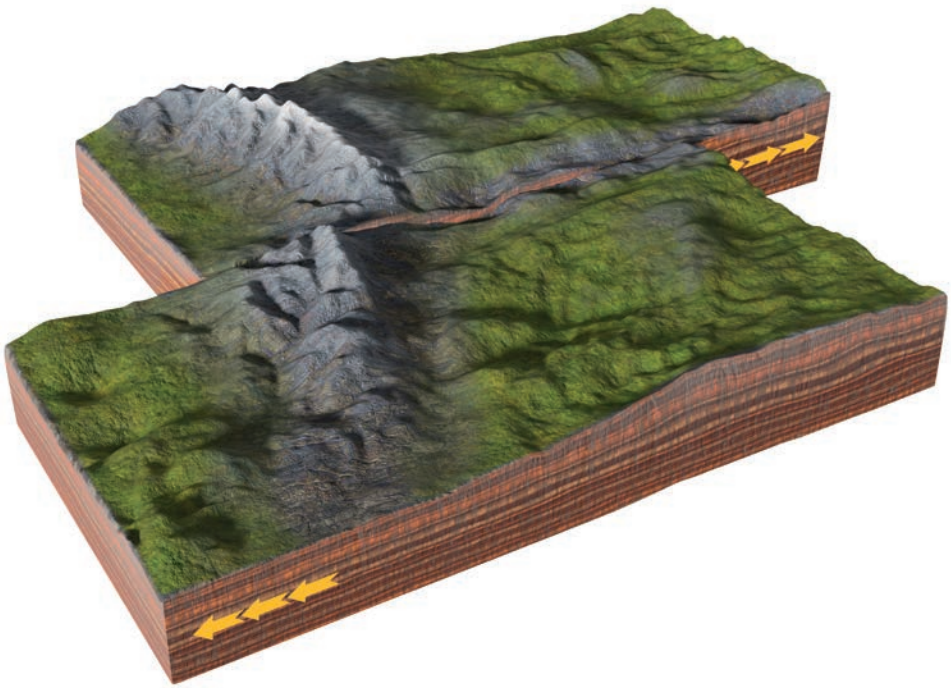


Illustration of a strike-slip fault at a tectonic plate boundary. The tectonic plates move parallel to each other, leading to so-called strike-slip earthquakes with relatively little deformation. RIKEN researchers have used artificial neural networks to accurately predict the behavior of the Earth's crust at a strike-slip fault.

However, the team found that a PINN, which learns continuous functions, would be difficult to directly apply to cases such as crustal deformation models, where the displacement is discontinuous across a fault line.

Ueda and his co-workers have overcome this difficulty by using a specially designed coordinate system to deal with the discontinuity across faults. This allowed them to accurately model the deformation of the Earth's crust, even in regions close to faults.

"The proposed modeling has the potential to realize a high-precision prediction," says Ueda.

The researchers trained their neural networks using physical laws rather than data, which is ideal for applications where data acquisition can be difficult.

To demonstrate the effectiveness of the approach, the researchers applied their physics-informed neural networks to model strike-slip faults, in which two blocks of the Earth's crust move horizontally about a vertical fracture (see image). The network could turn information about a particular location inside the Earth into a prediction of the amount of crustal displacement at that point.

"This work demonstrated PINN's ability to accurately model crustal deformation on complex structures," says Tomohisa Okazaki, also of AIP.

PINNs represent a relatively new form of machine learning, and the researchers hope that their approach could be applied to many other problems involving crustal deformation.

Reference

1. Okazaki, T., Ito, T., Hirahara, K. & Ueda, N. Physics-informed deep learning approach for modeling crustal deformation. *Nature Communications* **13,** 7092 (2022).

SOLID-STATE QUBITS

Keeping quantum holes spinning

The development of quantum computers will benefit from a new model of spin in tiny silicon dots

A theoretical model developed by three RIKEN physicists for optimizing semiconductor nanodevices will be helpful for scaling up quantum hardware[1].

An electron trapped in a semiconductor device offers a promising building block for future quantum computers. Electrons have a property called spin, which, when measured, exists in one of two states—like the binary information, or bits, used in conventional computing. But due to its quantum nature, spin can exist in a superposition of the two states. These quantum bits, or qubits, lie at the heart of quantum information processing.

> **“We can find sweet spots at which the silicon hole-spin qubits are remarkably robust against electric noise”**

Electrons, or their positively charged counterparts known as holes, can be isolated in tiny semiconductor blobs called quantum dots.

But electron and hole spins only maintain their quantum state for a limited time. Disruption, or noise, from the spin's environment can alter the spin state. “Once a quantum state is assigned to a qubit, it immediately starts to fade away,” explains Peter Stano from the RIKEN Center for Emergent Matter Science (CEMS).

This inevitable decay, or dephasing, is a fundamental limit and a major difference to classical information, which can be made permanent. Understanding dephasing is vital for developing methods to mitigate it, and thus aiding the design of large-scale quantum computers.

Now, Stano, along with CEMS colleagues Ognjen Malkoc and Daniel Loss, has theoretically modeled a hole trapped in a silicon quantum dot. Using this model, they demonstrated that the length of time for which the hole spin maintains its quantum state depends on the quantum dot size and shape and the magnetic and electric fields applied to it.

The team identified robust configurations of quantum dots by going beyond the established theoretical model.

“Our results show that by carefully designing a quantum dot and by placing the electric and magnetic fields in certain ways we can find sweet spots at which the silicon hole-spin qubits are remarkably robust against electric noise,” says Stano.

This highlights one of the main advantages of spin qubits—they are largely immune to electric noise, which is the strongest type of noise present in every semiconductor device.

But dephasing is just one of the design considerations when optimizing quantum dots for quantum information processing. Speed and reliability of reading, writing and operating on the quantum information are also important.

“All these aspects will have similar sensitivity on the quantum dot design,” says Stano. “Our goal is to exploit the sensitivity also seen here and optimize the spin-qubit design.”

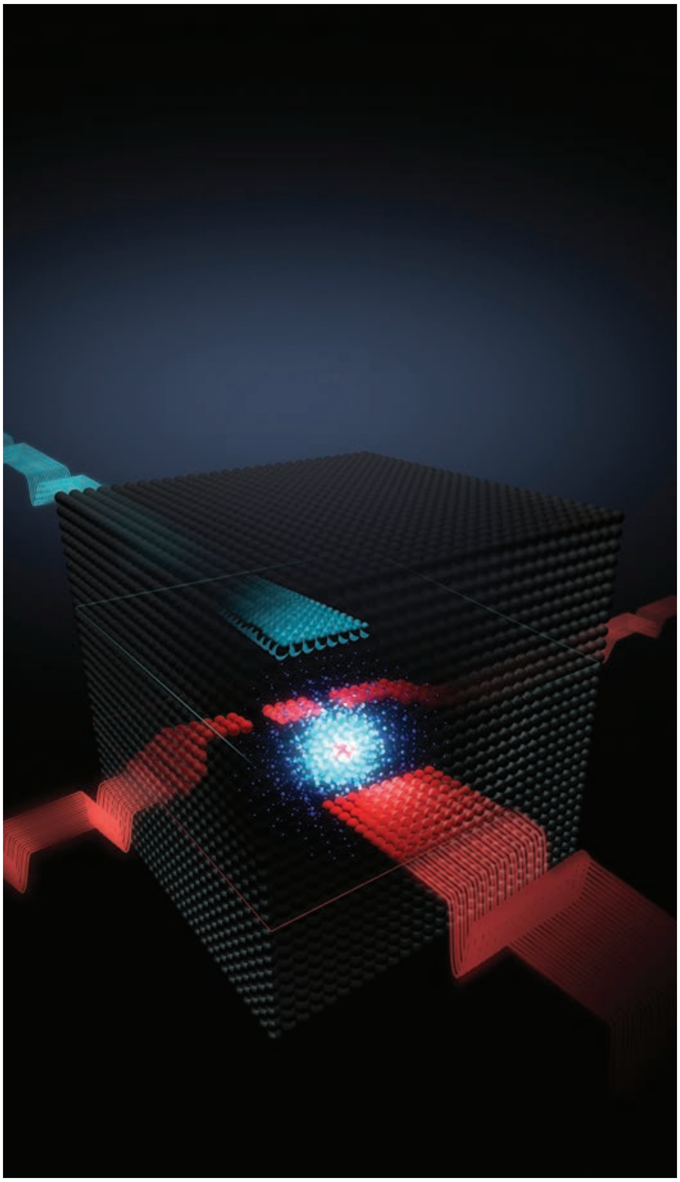


Illustration of a qubit in a silicon quantum dot. Optimizing the size, shape and geometry of a quantum dot leads to longer-lived hole spins.

Reference

1. Malkoc, O., Stano, P. & Loss, D. Charge-noise-induced dephasing in silicon hole-spin qubits. *Physical Review Letters* **129,** 247701 (2022).

QUANTUM COMPUTERS

Simplifying quantum computation

A novel protocol for quantum computers could reproduce the complex dynamics of quantum materials

A quantum-computational algorithm that could be used to efficiently and accurately calculate atomic-level interactions in complex materials has been developed by RIKEN researchers[1]. It has the potential to bring an unprecedented level of understanding to condensed-matter physics and quantum chemistry—an application of quantum computers first proposed by physicist Richard Feynman in 1981.

Quantum computers bring the promise of enhanced number-crunching power and the ability to crack problems that are out of the reach of conventional computers.

Qubits, the building blocks of quantum computers, are essentially tiny systems—nanocrystals or superconducting circuits, for example—governed by the laws of quantum physics. Unlike bits used in conventional computers, which can be either one or zero, qubits can have multiple values simultaneously. It is this property of qubits that gives quantum computers their advantage in terms of speed.

An unconventional way of computation also requires a new perspective on how to efficiently process data in order to tackle problems too difficult for conventional computers.

One notable example of this is the so-called time-evolution operator. "Time-evolution operators are huge grids of numbers that describe the complex behaviors of quantum materials," explains Kaoru Mizuta of the RIKEN Center for Quantum Computing. "They're of great importance because they give quantum computers a very practical application—better understanding quantum chemistry and the physics of solids."

The prototype quantum computers demonstrated to date have achieved time-evolution operators using a relatively simple technique called Trotterization. But Trotterization is thought to be unsuitable for the quantum computers of the future because it requires a huge number of quantum gates and thus a lot of computational time. Consequently, researchers have been striving to create quantum algorithms for accurate quantum simulations that use fewer quantum gates.

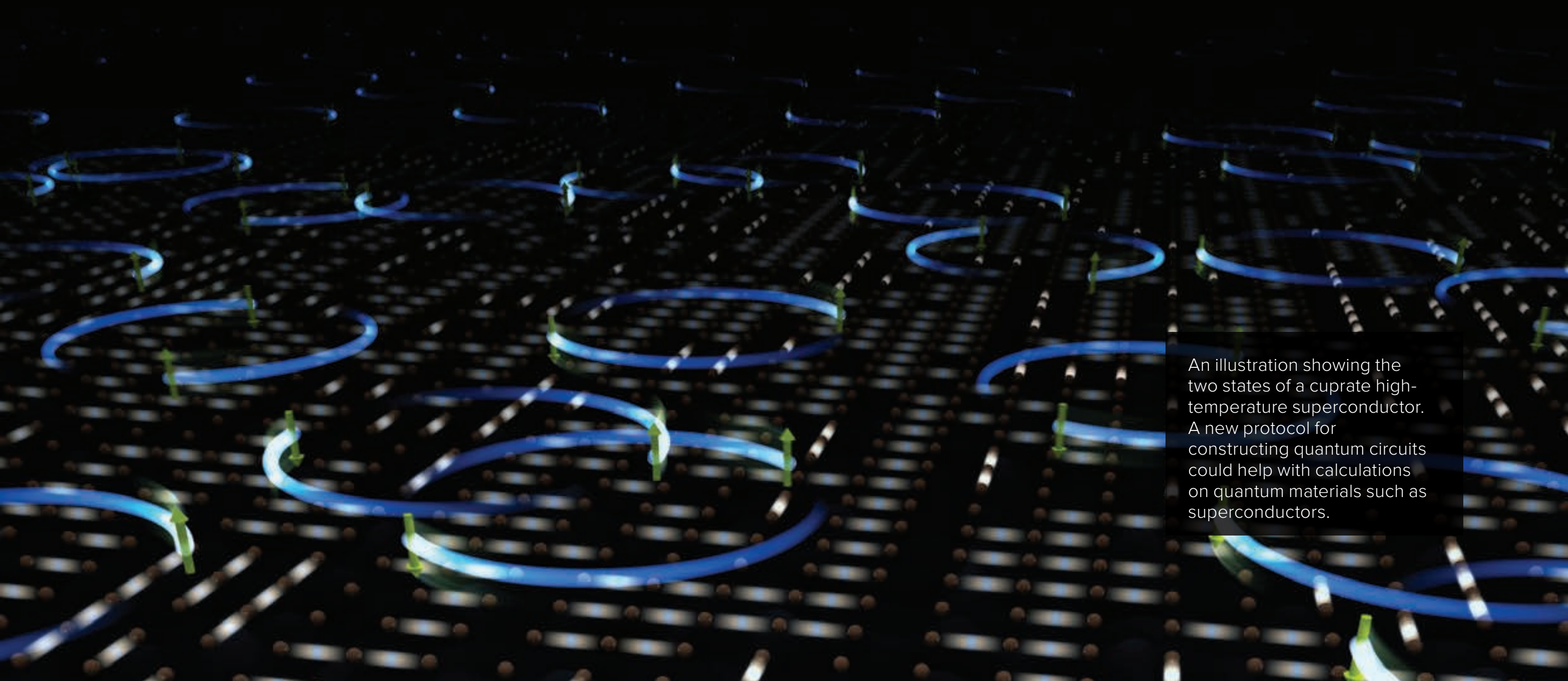
Now, Mizuta, working with colleagues from across Japan, has proposed a much more efficient and practical algorithm. A hybrid of quantum and classical methods, it can compile time-evolution operators at a lower computational cost, enabling it to be executed on small quantum computers, or even conventional ones.

"We have established a new protocol for constructing quantum circuits that efficiently and accurately reproduce time-evolution operators on quantum computers," explains Mizuta. "By combining small quantum algorithms with the fundamental laws of quantum dynamics, our protocol succeeds in designing quantum circuits for replicating large-scale quantum materials, but with simpler quantum computers."

Mizuta and his team next intend to clarify how the time-evolution operators optimized by their method can be applied to various quantum algorithms that can compute the properties of quantum materials. "We anticipate that this work will demonstrate the potential of using smaller quantum computers to study physics and chemistry."

Reference

1. Mizuta, K., Nakagawa, Y. O., Mitarai, K. & Fujii, K. Local variational quantum compilation of large-scale Hamiltonian dynamics. *PRX Quantum* **3,** 040302 (2022).



An illustration showing the two states of a cuprate high-temperature superconductor. A new protocol for constructing quantum circuits could help with calculations on quantum materials such as superconductors.

SLEEP

Protein tags govern sleep dynamics in mice

Adornments made to a critical sleep-promoting protein mediate the onset and duration of slumber in mice

The function of a key sleep-promoting protein in the mouse brain depends on how it is chemically tagged, RIKEN researchers have found[1]. This discovery could lead to new medications for inducing and maintaining sleep.

The sleep–wake cycle is a physiological function that determines the rhythms of when we fall asleep and wake up. While the cycle has been much studied, there is still a lot that we don't know about its molecular mechanisms.

Previously, Hiroki Ueda from the RIKEN Center for Biosystems Dynamics Research and his colleagues had identified sleep-promoting proteins whose activity could be modulated by phosphate tags. Based on this observation, they proposed that this tagging of phosphate groups—or phosphorylation—regulates the sleep–wake cycle.

> "Control of sleep and wakefulness can be carried by the state of a specific enzyme in the brain."

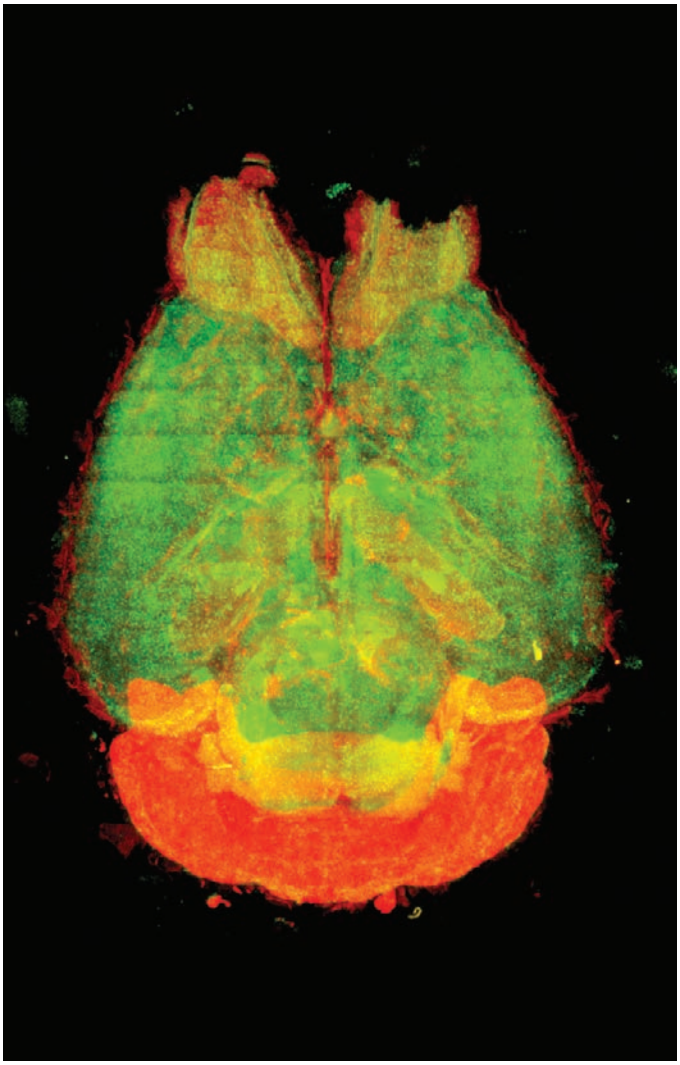
Now, by focusing on one sleep-promoting protein in particular—a neuronal enzyme called CaMKIIβ—Ueda and his team have shown how different phosphorylation patterns on this critical protein in mice can control different sleep induction and maintenance processes in their brains (see image).

For example, mice with a mutant form of CaMKIIβ that mimics an 'always on' phosphorylation state tended to transition more readily from wakefulness to slumber. In contrast, mice with mutations that resemble a different multisite phosphorylation pattern tended to stay asleep longer, and the transition to waking up was suppressed.

"These findings are consistent with our proposal that sleep-promoting enzymes such as CaMKIIβ can store information about wakefulness in the form of phosphorylation events," explains Ueda. "In turn, control of sleep and wakefulness can be carried by the state of a specific enzyme in the brain."

The results could potentially have practical applications, since they highlight new potential avenues for developing sleep-enhancing medications.

Ueda and his team showed that the inhibition of CaMKIIβ could dramatically reduce sleep duration in the mice to less than 10 hours, while the induction of CaMKIIβ could greatly extend sleep duration to more than 15 hours (mice tend to sleep a lot more than humans do).



To investigate the effect of CaMKIIβ on sleep, RIKEN researchers measured the expression of the neuronal enzyme in different regions throughout the mouse brain.

"Pharmacological agents that similarly augmented CaMKIIβ activity may have the same sleep-promoting effects," says Daisuke Tone, a member of Ueda's lab. "And by tweaking phosphorylation specifically, drug companies could develop different CaMKIIβ-targeted therapies that either put people to sleep or keep them asleep longer."

The latter approach has rarely been tried before. "But it may lead to the development of sleep-maintenance drugs, which could offer a new therapeutic strategy for sleep disorders," says Tone. ●

Reference

1. Tone, D., Ode, K. L., Zhang, Q., Fujishima, H., Yamada, R. G., Nagashima, Y., Matsumoto, K., Wen, Z., Yoshida, S. Y., Mitani, T. T. *et al.* Distinct phosphorylation states of mammalian CaMKIIβ control the induction and maintenance of sleep. *PLoS Biology* **20,** e3001813 (2022).

ORGANOIDS

Cubes create complex organoids

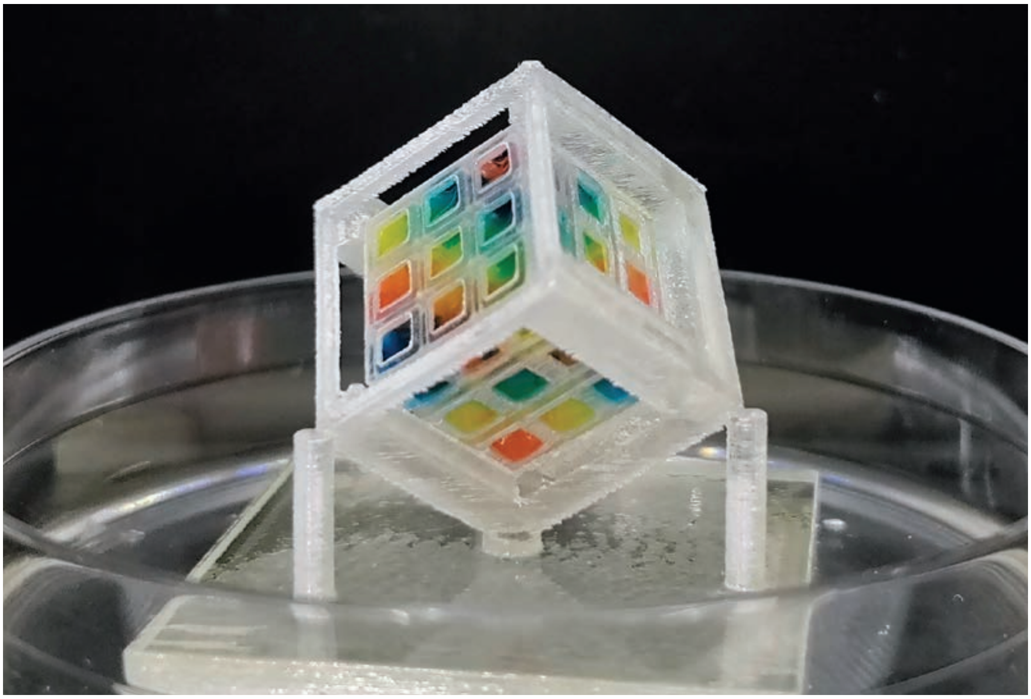
Complex organoids that mimic real organs can be easily made in the lab using a system based on cubes

Complex 3D organoids—organ-like tissues grown in the lab—that reproduce the genetic expression observed during the development of actual organisms can be readily constructed using a device developed by RIKEN researchers[1,2]. In addition to providing new insights into how tissues develop, the device could revolutionize drug testing.

Organoids hold promise for gleaning insights into the process of development. They are also important for developing new medicines, since they can reveal how drugs move through various tissues. And organoids are a stepping stone to growing whole organs for patients.

However, creating life-like organoids has proven difficult. In nature, tissues develop through an elaborate dance whereby chemical gradients and physical scaffolds guide cells to adopt specific 3D patterns. In contrast, lab-grown organoids typically develop either by allowing cells to grow in uniform conditions—creating simple balls of similar cells—or by using 3D printing or microfluidic devices, which require sophisticated equipment and technical skills.

Now, Masaya Hagiwara of the RIKEN Center for Biosystems Dynamics Research and co-workers have developed an innovative technique that allows them to spatially control the environment around groups of cells based on cubes, using nothing more elaborate than a pipette.



One configuration of a cube-based platform for creating complex organoids. Each cube making up the larger cube contains a different hydrogel.

See infographic on organoids on **page 32**.

"The new system will make it possible for researchers to quickly, and without difficult technical hurdles, recreate organoids that more closely resemble the way that organs develop in actual organisms," says Hagiwara.

The method involves confining layers of hydrogels—substances consisting mostly of water—with different physical and chemical properties inside a cube-shaped culture vessel. A pipette was used to insert different hydrogels into the scaffold. Cells were inserted into the cubes either within the hydrogels or as pellets that could move into the different layers, thus making it possible to create a range of tissue types.

The device could recreate the head/rear and back/stomach patterning of cell differentiation observed during the development of vertebrates. Though important for the creation of organoids that faithfully recreate what happens in actual organisms, this had been difficult to reproduce in the lab.

The team even recruited a junior high school student to perform the work, showing that seeding the cells does not require a high level of expertise.

"We hope that a range of researchers will use our method to create various new organoids and contribute to research on different organ systems," says Hagiwara. "Eventually, we hope that it will also contribute to understanding how we can build actual artificial organs that can help patients." ●

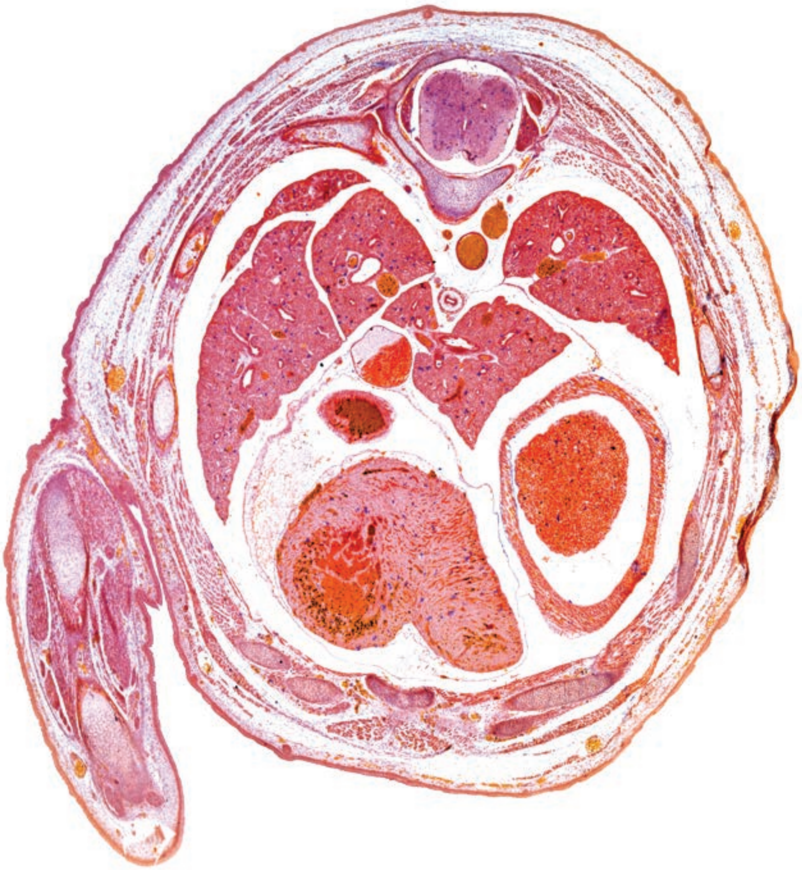
Reference

1. Suthiwanich, K. & Hagiwara, M. Localization of multiple hydrogels with MultiCUBE platform spatially guides 3D tissue morphogenesis in vitro. *Advanced Materials Technologies* **8,** 2201660 (2023).
2. Koh, I. & Hagiwara, M. Gradient to sectioning CUBE workflow for the generation and imaging of organoids with localized differentiation. *Communications Biology* **6,** 299 (2023).

DEVELOPMENT

How mouse embryos determine left from right

Resolution of a two-decade debate enhances our understanding of how embryos develop differences between their left and right sides



A light micrograph of a section through the thorax of a mouse embryo, which shows left–right asymmetry. RIKEN researchers have discovered how cilia detect fluid flow, which eventually leads to this asymmetry.

RIKEN biologists have discovered how tiny hairs in embryos detect flowing fluid, which ultimately leads to the left and right sides of the embryo developing differences[1]. As well as resolving a long-standing debate, this finding will inform research into disorders that arise when this process malfunctions.

Viewed from the outside, the left and right sides of vertebrate bodies usually appear indistinguishable. But the situation is very different on the inside, with many organs such as the heart, liver and spleen being positioned to either the left or right of the central left–right axis.

By contrast, embryos begin as symmetrical bundles of cells. Researchers have long been interested in how differences between the left and right sides develop in embryos.

Tiny hair-like structures, called cilia, in a mouse embryo gyrate clockwise, setting up a leftward flow in the surrounding fluid. This fluid flow is then picked up by static cilia, called immotile cilia, located to the left and right of the moving cilia. This detection of fluid movement causes the left and right sides of the embryo to develop differently.

However, debate surrounds how the immotile cilia sense the fluid flow. Two mechanisms have been proposed: one in which the movement is detected through chemicals in the flow and another in which it is detected via the mechanical force. But no-one had shown experimentally which one is correct until now.

Hiroshi Hamada and Takanobu Katoh of the RIKEN Center for Biosystems Dynamics Research and co-workers have put this debate to rest by showing that the cilia in mice embryos detect the movement mechanically.

Using microbeads trapped in a laser beam, the team manipulated a single cilium and observed a signal involving calcium ions. This showed that mechanical stimulus of just one cilium can determine left–right asymmetry in embryos.

Using advanced microscopy techniques, they also found that left and right cilia are bent in opposite directions. Furthermore, they discovered that the cilia sense the bending direction because channels within them are not symmetrically distributed. Consequently, calcium signals are only triggered when fluid strikes them in one direction, explaining why only cilia on the left side of an embryo are activated.

“Our research has finally answered one of the most important questions for left–right determination, namely why leftward nodal flow activates only the left side,” says Katoh. “This represents an important step towards understanding the mechanism of left–right determination.”

These findings could have practical applications. “Our results provide useful information for studies of how organs form,” says Katoh. “They might also be helpful for finding ways to treat cilia-related disorders.” ●

Reference

1. Katoh, T. A., Omori, T., Mizuno, K., Sai, X., Minegishi, K., Ikawa, Y., Nishimura, H., Itabashi, T., Kajikawa, E., Hiver, S. *et al.* Immotile cilia mechanically sense the direction of fluid flow for left–right determination. *Science* **379,** 66–71 (2023).

Colored scanning electron micrograph of red blood cells in sickle cell disease. Normal red blood cells (rounded) contrast with elongated sickle-shaped cells (darker). RIKEN researchers have identified a new target for sickle cell disease, which could result in safer, more effective treatments.

SICKLE CELL DISEASE

A safer way to treat sickle cell disease?

A new target could result in drugs that are safer and more effective at treating sickle cell disease

RIKEN researchers have identified a novel candidate for treating sickle cell disease (SCD), a heritable genetic disorder that affects millions of people worldwide[1].

Caused by mutations in the β-globin gene, SCD results in deformed, crescent-shaped red blood cells that can clog blood vessels and tend to have very truncated lifetimes. This can cause symptoms such as anemia, bouts of pain and stroke, symptoms that can be offset by inducing the production of fetal γ-globin. Some promising therapeutic agents for combating SCD are inhibitors of the protein methyltransferase G9a that are associated with silencing γ-globin and fetal hemoglobin production. However, just how they worked had been unclear.

Now, a team led by Minoru Yoshida at the RIKEN Center for Sustainable Resource Science has not only uncovered the mechanism of G9a inhibitor action but also discovered the therapeutic potential of a novel G9a inhibitor called RK-701.

"We succeeded in developing RK-701, a specific and low-toxic inhibitor of the histone methyltransferase G9a, with a novel chemical scaffold," says Akihiro Ito at the Tokyo University of Pharmacy and Life Sciences. "RK-701 induces fetal γ-globin expression in human erythroid cells as well as embryonic globin expression in mice and shows greater efficacy than hydroxyurea, an existing therapeutic agent that is used to treat SCD."

Although hydroxyurea has long been used to treat SCD, its toxicity is a serious concern. In contrast, RK-701 is highly selective since it does not bind non-specifically to off-target locations. Furthermore, it does not damage host DNA. RK-701 seems to be superior to hydroxyurea in terms of both efficacy and safety.

Moreover, RK-701 upregulates the long non-coding RNA of BGLT3. Long non-coding RNAs are not translated into proteins, but they have been increasingly found to be involved in regulating gene expression. RK-701 upregulates the BGLT3 gene, ensuring the expression of its long non-coding RNA, thus triggering the production of SCD-combating γ-globin and fetal hemoglobin.

"We noticed that the long non-coding RNA of BGLT3 upregulated by RK-701 has a universal role in inducing fetal hemoglobin expression, which underscores its efficacy as a therapeutic target for SCD," says Yoshida.

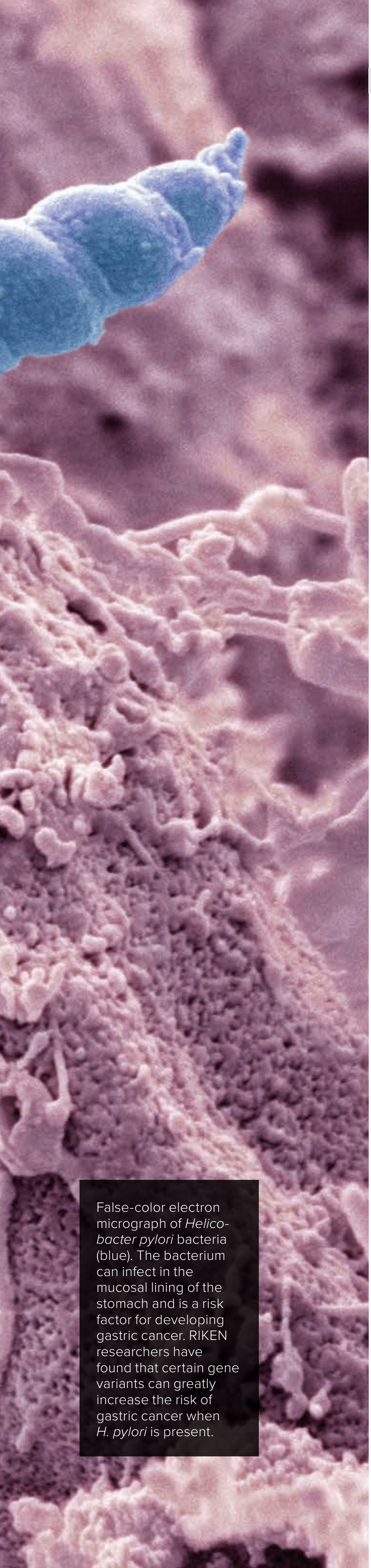
Experiments with adequate controls revealed the molecular mechanism of G9a-mediated γ-globin gene expression in human erythroid cells. "Remarkably, BGLT3 is indispensable for γ-globin induction by not only RK-701 but also hydroxyurea and other inducers," says Shohei Takase of the Tokyo University of Pharmacy and Life Sciences. "The universal role of BGLT3 in γ-globin induction suggests its importance in SCD treatment."

"Our study clearly demonstrates that BGLT3 is the universal activator for fetal globin gene expression," says Ito. "The essential role of BGLT3 lncRNA in the induction of fetal hemoglobin expression highlights its role as an extremely attractive therapeutic target for SCD."

Reference

1. Takase, S., Hiroyama, T., Shirai, F., Maemoto, Y., Nakata, A., Arata, M., Matsuoka, S., Sonoda, T., Niwa, H. *et al.* A specific G9a inhibitor unveils BGLT3 lncRNA as a universal mediator of chemically induced fetal globin gene expression. *Nature Communications* **14,** 23 (2023).

DOUBLE WHAMMY INFLATES RISK OF GASTRIC CANCER BY 45%



False-color electron micrograph of *Helicobacter pylori* bacteria (blue). The bacterium can infect in the mucosal lining of the stomach and is a risk factor for developing gastric cancer. RIKEN researchers have found that certain gene variants can greatly increase the risk of gastric cancer when *H. pylori* is present.

Working in tandem, a stomach microbe and rare variants found in nine genes greatly increase the risk of gastric cancer over a lifetime

Genetics has a greater influence in the development of gastric cancer—the fourth-most common cause of cancer death globally—than previously thought, RIKEN researchers have found[1].

In 2013, actress Angelina Jolie caused a stir when she announced that she had a double mastectomy as a preventative measure against breast and ovarian cancer, which had led to the death of her mother, grandmother and aunt.

She based the decision on the discovery that she carried a rare variant of the *BRCA1* gene that greatly increased her risk of developing breast cancer. The announcement generated much debate about the role that genetics plays in cancer, whether people should be screened, and what action they should take in light of their genome.

This debate was not thought to be directly relevant to gastric cancer, since genetics was not known to play big role in its development. Rather, its main cause was known to be a bacterium called *Helicobacter pylori*.

A CANCER-CAUSING INFECTION

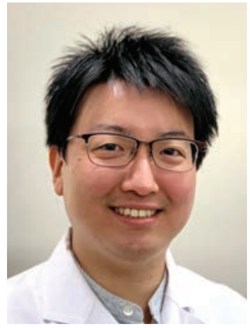
About half the people in the world have *H. pylori* in their stomachs, having most often acquired the bacterium via contact with another person's saliva, tooth plaque, vomit or stool, but also sometimes through contaminated food or water.

Most people are unaware they have the bacteria in their stomachs because it usually doesn't cause any symptoms. However, in the 1980s, two Australians, Barry Marshall and Robin Warren, discovered that the bacterium was behind the vast majority of stomach ulcers. Many scientists were initially dismissive of this claim since it flew in the face of the received wisdom that ulcers were primarily caused by stress and other lifestyle factors. However, further work vindicated Marshall and Warren, and they shared a Nobel Prize for the discovery in 2005.

Subsequently, *H. pylori* was linked with gastric cancer, earning it a classification in the highest class carcinogens, which include smoking, alcohol and excessive exposure to sunlight. The role of genetics was considered to be minimal, accounting for a mere 1% to 3% of cases.

A MORE NUANCED PERSPECTIVE

Now, Yoshiaki Usui and Yukihide Momozawa of the RIKEN Center for Integrative Medical Science



This feature looks
at the work of
YOSHIAKI USUI

Yoshiaki Usui is a Special Postdoctoral Researcher for the Laboratory for Genotyping Development at the RIKEN Center for Integrative Medical Sciences. He graduated from Okayama University in 2013. After working as a hematologist-oncologist, he started cancer epidemiology research at the Aichi Cancer Center in 2018. In 2020, he joined his current laboratory to conduct large-scale genetic analyses. He obtained his PhD from Okayama University in 2021. He is currently engaged in cancer research that combines epidemiological perspectives with large-scale genetic analyses.

and their co-workers have shown that the reality of the situation is more nuanced. They have discovered that having two risk factors—*H. pylori* infection plus carrying certain gene variants—causes the lifetime probability of getting gastric cancer to greatly increase.

Specifically, they found that the probability of someone getting gastric cancer over their lifetime was less than 5% regardless of their genetics if they were free of *H. pylori*. This risk increased to 14% for people infected with *H. pylori,* but who didn't carry one of the rare, high-risk gene variants. But the real surprise was that for people who had both *H. pylori* and one of the variants found in four genes (which includes the varient that Angelina Jolie has), the risk jumped to more than 45%. These results were published in *The New England Journal of Medicine* in March 2023.

"I suspected there might be an interaction between the gene variants and *H. pylori* on gastric cancer risk," says Usui. "But the actual impact was much larger than I had imagined."

EMPOWERING CARRIERS OF VARIANTS

Importantly, this finding offers hope for those carrying one of these gene variants—they can be tested for *H. pylori* and, if they are infected, they can take antibiotics to eliminate the bacterium, thereby dramatically reducing their risk of contracting gastric cancer. This aspect really appeals to Momozawa. "As a geneticist, a lot of my work involves identifying genetic risk, and sometimes we can provide only an assessment of risk to carriers, which isn't very satisfying," he says. "But this time we can provide genetic risk and an effective treatment. That's a key point of this study."

The finding also provides important insights into how gastric cancer develops. *H. pylori* is known to damage DNA by snapping its double strand in places. At the same time, four of the nine identified genes are involved in a process for fixing damaged DNA. If one of the high-risk variants of these four genes is present, the DNA-repair mechanism doesn't work and cells revert to another process for repairing DNA that is much more prone to introducing errors.

Thus, *H. pylori* damages DNA and the gene variants result in errors being introduced when this damage is repaired. This accounts for the high risk of getting gastric cancer when both factors are present.

This finding will also inform research on other cancers. Of the nine high risk gastric cancer genes (*APC*, *ATM*, *BRCA1*, *BRCA2*, *CDH1*, *MLH1*, *MSH2*, *MSH6* and *PALB2*) some, such as *BRCA1* and *BRCA2*, have been linked to breast, ovarian, prostate and pancreatic cancer, while *MLH1*, *MSH2* and *MSH6* increase the risk of colorectal cancer.

Gastric cancer was thought to be caused mainly by the bacterium *H. pylori*, but RIKEN researchers have found that *H. pylori* in combination with several gene variants greatly increases the probability of contracting gastric cancer over a lifetime.

REGIONAL DIFFERENCES

To conduct the study, the team analyzed DNA samples from nearly 12,000 patients with gastric cancer and more than 44,000 people without cancer by drawing on two Japanese cohorts. But since *H. pylori* is more prevalent in East Asia and the strain in the region is particularly virulent, the results may be far less dramatic in other regions. Usui speculates that had the same study been conducted in USA or Europe, the differences in the gastric cancer risks might have been too small to pick up. This highlights the importance of doing genetic studies in different regions.

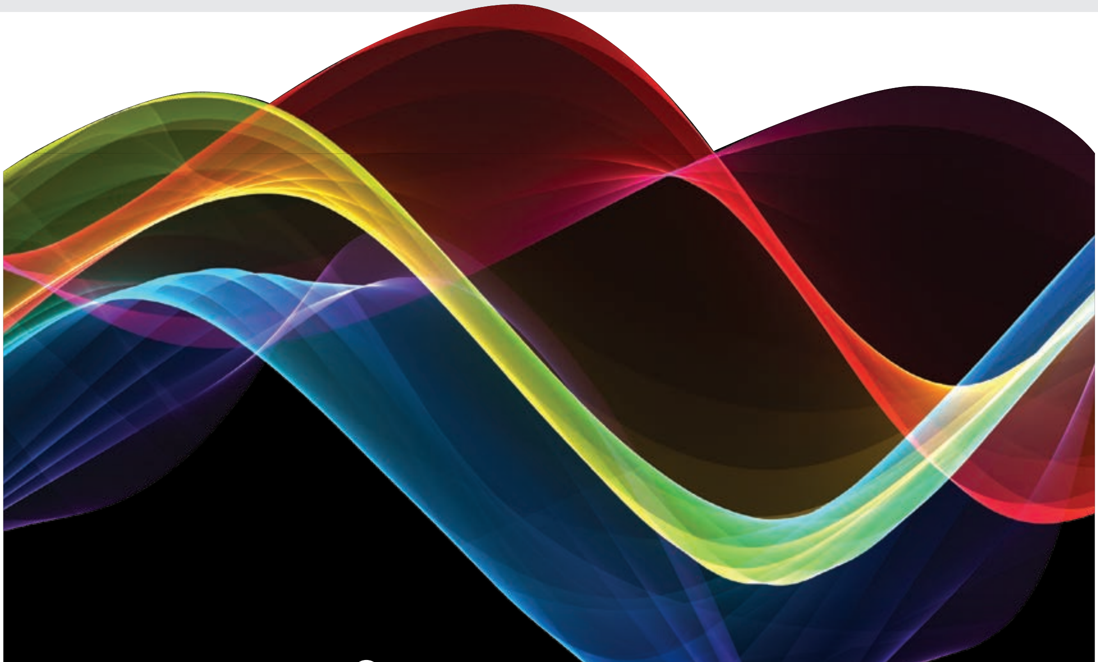
Commenting on the study, Nobel laureate Barry Marshall of the University of Western Australia says: "This landmark study by Momozawa *et al.* has convinced me that *H. pylori* is the detonator for all kinds of carcinogenic agents, either environmental or genomic. In brief, *H. pylori* makes everything worse. Much worse." ●

REFERENCE

1. Usui, Y., Taniyama, Y., Endo, M., Koyanagi, Y. N., Kasugai, Y., Oze, I., Ito, H., Imoto, I., Tanaka, T., Tajika, M. *et al. Helicobacter pylori*, homologous-recombination genes, and gastric cancer. *The New England Journal of Medicine* **388,** 1181–1190 (2023).

This feature looks
at the work of
YUKIHIDE MOMOZAWA

Yukihide Momozawa is the team leader of the Laboratory for Genotyping Development at the RIKEN Center for Integrative Medical Sciences. He graduated from the Department of Veterinary Medical Science at the University of Tokyo. He spent five years as a postdoc in the Unit of Animal Genomics at the University of Liège, Belgium, with Professor Michel Georges. He joined his current laboratory as a researcher in 2012 and became a team leader in 2015. He is interested in using genetic information to improve human and animal health, which can be revealed by large-scale genetic analyses with colleagues at RIKEN and other diverse collaborators.



Making waves with terahertz technologies

Using new palm-sized devices, RIKEN researchers may have finally harnessed the terahertz band of the electromagnetic spectrum to effectively 'x-ray' things without using harmful ionizing radiation.

HIROAKI MINAMIDE
Team leader, Tera-Photonics Research Team

Hiroaki Minamide is team leader of the Tera-Photonics Research Team and group leader of the Terahertz Research Group of RIKEN. He is also a visiting professor at Chiba University. He joined RIKEN in 1999 and, after working as a researcher and deputy team leader, has been working as a team leader since 2010 and as a group director since 2020. He received his undergraduate degree in communications engineering and his Masters and PhD in electrical engineering from Tohoku University, Japan, in 1993, 1996 and 1999, respectively. His research interests include high-power terahertz wave generation and ultrasensitive terahertz wave detection using nonlinear optics and their unique terahertz applications.

Countless technologies—from smartphones and TVs to infrared instruments on the James Webb Space Telescope and high-speed wireless telecommunication devices using microwaves—exploit sections of the electromagnetic spectrum.

But somewhere between commonly used microwaves and infrared light, lies a neglected region called the terahertz band. Terahertz waves have numerous exciting potential uses, not least because they can be used to see through or inside materials in a similar way to x-rays. Unlike x-rays, however, terahertz waves don't deliver damaging ionizing radiation.

But terahertz technologies have so far languished because it has been difficult to adapt microwave- or visible-light technologies to the terahertz range at useful sizes and power outputs.

For example, one approach to generate terahertz waves has been to develop electrical devices that produce higher frequency, ultra-short-wavelength microwaves. But this has been difficult in part because these devices need highly optimized parameters to produce greater electrical performance, which has proved challenging.

An alternative strategy is to produce terahertz waves by converting shorter, higher-frequency waves of infrared light, using materials known as nonlinear crystals.

At the RIKEN Center for Advanced Photonics, we are exploring this second strategy—producing terahertz waves by converting the output from an infrared laser.

This method has traditionally required enormous lasers to generate terahertz waves powerful enough for most practical applications. But this has limited the take-up of terahertz technology for real-world applications—where portable devices for in situ analysis would be far more valuable.

In the Tera-Photonics Research Team, which I lead, we hope to develop palm-sized, powerful terahertz wave sources for applications in industry and fundamental research. We have recently taken huge strides toward this goal and have multiple industrial collaborations underway.

PALM-SIZED DEVICES

We have focused on using lithium niobate, a nonlinear crystal that produces a beam of terahertz waves when irradiated with near-infrared laser light. When I assumed leadership of the team in 2010, it was impossible to produce sufficiently powerful terahertz waves using this method, despite many years of work.

In 2011, we had to stop lab research for several months after a major earthquake struck Sendai, Japan, where our campus is. During that period, I remembered the result of a previous experiment that had caught my attention, and, I found an exciting hint of a possible path forward.

At that time, we used a near-infrared laser with pulse durations in the nanoseconds. The results indicated that when shorter, sub-nanosecond laser pulses were used, terahertz-wave generation as a function of the input laser pulse was altered. I wondered why this was.

I then uncovered a 1993 paper[1] that reported the effects of laser pulse duration in nonlinear crystals. The study—analyzing visible light—implied that using shorter pulses reduced a light-scattering effect called Brillouin scattering. I wondered whether, by reducing our laser pulse duration, we could minimize Brillouin scattering from our lithium niobate crystals. This might allow us to convert more of the laser light into terahertz waves and increase the power output.

Once we returned to the lab and tested this theory, we were amazed by the result. Using sub-nanosecond laser pulses, we could escape Brillouin scattering to improve our terahertz wave power output by six orders of magnitude—from 200 milliwatts to 100 kilowatts[2]. We finally had powerful emission from a device only one meter square, much smaller than previous terahertz apparatuses, which filled entire rooms. But when we showed this device to industry, they told us that it was still too big for real-world applications.

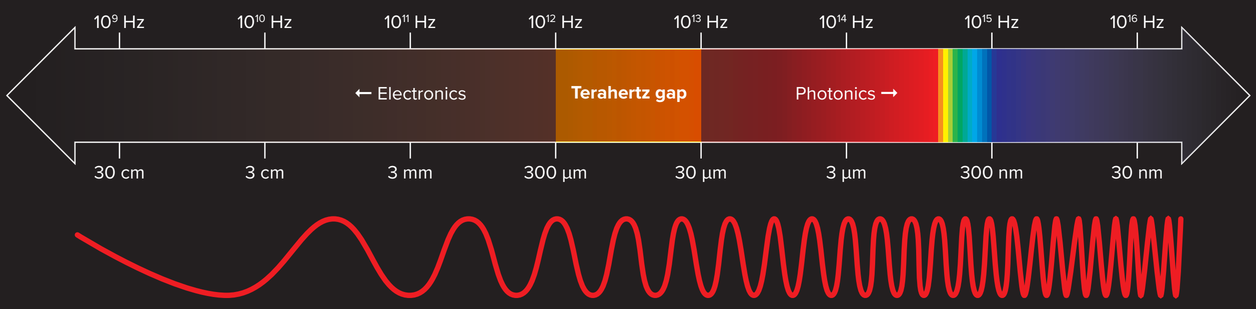
To further miniaturize our terahertz-wave source, we replaced the bulk lithium niobate crystal ingot we had previously used with a thin lithium niobate crystal with an artificial polarization-modulated microstructure, which is called a periodically poled lithium niobate (PPLN) crystal. Commonly employed in the visible-light region, the PPLN crystal enabled us to develop a handheld device due to its higher light conversion efficiency.

At the beginning of our PPLN research, there was no known way to efficiently generate terahertz waves using PPLN crystals. As we proceeded with our own experiments, we were initially very puzzled by the behavior of PPLN crystals. We saw no terahertz waves, just an unexpected light beam, produced from the crystal.

After carefully analyzing the properties of this light, we eventually realized that terahertz waves were being produced, but in an unexpected direction. The interaction between the light and the PPLN's

MIND THE GAP

Sandwiched between microwaves and infrared radiation on the electromagnetic spectrum, the terahertz gap has been underutilized in technologies until now. Like x-rays, terahertz waves have the ability to see through materials. But because terahertz waves have much lower frequencies (and hence energies) than x-rays, they do not pose the same risk to health that ionizing radiation does.



polarization-modulated structure caused terahertz waves to be generated at the rear of the crystal. When we moved our detector behind it, we found the terahertz wave[3]. We could finally make a palm-sized prototype with a high conversion efficiency and sufficient power.

Remarkably, we also discovered that simply by rotating the crystal, we could tune the frequency of the terahertz waves produced[4]. Our devices can completely cover the critical sub-terahertz region of the spectrum, which is especially important for non-destructive imaging applications.

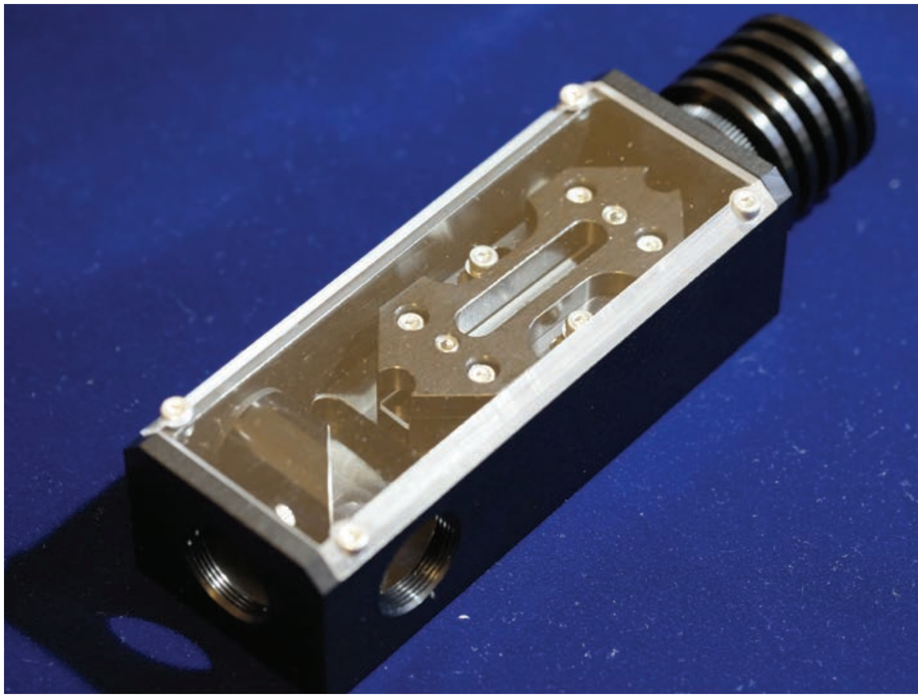
QUANTUM LEAP

Our research is based on photon conversion between light waves and terahertz waves by nonlinear optical effects based on mature photonic and laser technologies. We've achieved cascade oscillation in backward terahertz-wave parametric oscillation by using optical injection to lower the threshold and stabilize the output power—achieving a peak terahertz output power of 200 watts at a frequency of 0.3 terahertz; converted terahertz waves to light waves in a backward optical quantum conversion process; and succeeded in detecting ultraweak terahertz waves of approximately 50 attojoules, which is 1,000 times more sensitive than a 4 kelvin bolometer. These results provide new quantum research based on terahertz-to-light quantum photon conversion. Our most recent results are based on incorporating quantum theory into our work. And our future work will explore quantum entanglement—where one quantum particle mysteriously mirrors another far away—to improve the sensitivity of terahertz detectors.

Furthermore, our highly miniaturized, high-power terahertz waves systems are complemented by recent developments in compact, powerful photonic lasers. Our devices use a new microchip laser that produces far-infrared laser pulses at sub-nanosecond speeds and high powers.

We're now at the point where industrial collaborations form a key part of our work. The strong sub-terahertz emissions that our devices can generate are highly suited to imaging and analytical work. We're conducting joint research with Japanese companies specializing in electronics, optical and photonics—such as Ricoh, Topcon, Mitsubishi Electric and Hamamatsu Photonics—to develop non-destructive testing applications and terahertz-wave spectroscopy equipment.

To demonstrate the potential of our technology for security purposes, we have assembled a prototype terahertz imaging device. With it we showed that a plastic gun, which can fire plastic bullets, could be clearly detected when concealed behind bumpy glass that scatters light a lot. We could also clearly image a pair of scissors hidden in a thick leather bag.



A device created by Hiroaki Minamide and his team, which efficiently converts infrared radiation into terahertz waves. It can generate terahertz radiation over the entire range of the terahertz band.

Terahertz waves can also reveal the chemical composition of substances, due to characteristic 'fingerprint' absorption patterns. Different colorless liquids—such as kerosene and acetone—that look identical to the naked eye can be readily identified by this method, for example. Thus, applications under consideration for terahertz waves range from airport security scanners to the analysis of historic artworks.

Industrial paint and outer coatings can also be analyzed, from things as varied as new cars and pharmaceutical tablets—and non-destructively, unlike current methods. In the future, we could mount our devices onto robots to crawl along industrial pipework to inspect for corrosion or on drones to inspect paint on power transmission towers.

These and other uses could give us a better understanding of how materials interact and degrade in situ. If we can better understand these issues using non-destructive technologies, we can more easily tweak production processes in real time to improve efficiencies and make patches to extend the life span of structures, for example. The economic and environmental benefits should be exponential.

REFERENCE

1. Faris, G. W., Jusinski, L. E. & Hickman, A. P. *J. Opt. Soc. Am.* **8,** 87–99 (1993).
2. Minamide, H. *et al. J. Infrared, Millimeter, and Terahertz Waves* **35,** 25 (2014).
3. Nawata, K. *et al. Sci Rep-UK* **9,** 726 (2019).
4. Minamide, H. *et al.* in *2021 Conference on Lasers and Electro-Optics (CLEO)* (IEEE, 2021).

SCAFFOLDING FOR MINI-ORGANS

Researchers working on 'mini-organs'—or organoids—culture cells into forms that mimic organs and tissues for personalized drug testing and perhaps even transplants. Now, led by Masaya Hagiwara, the researchers from the Human Biomimetic System RIKEN Hakubi Research Team have developed a modular cube that makes it easier to culture different cells and tissues, as well as a technique to help mini-organs develop distinct sides and orientations.

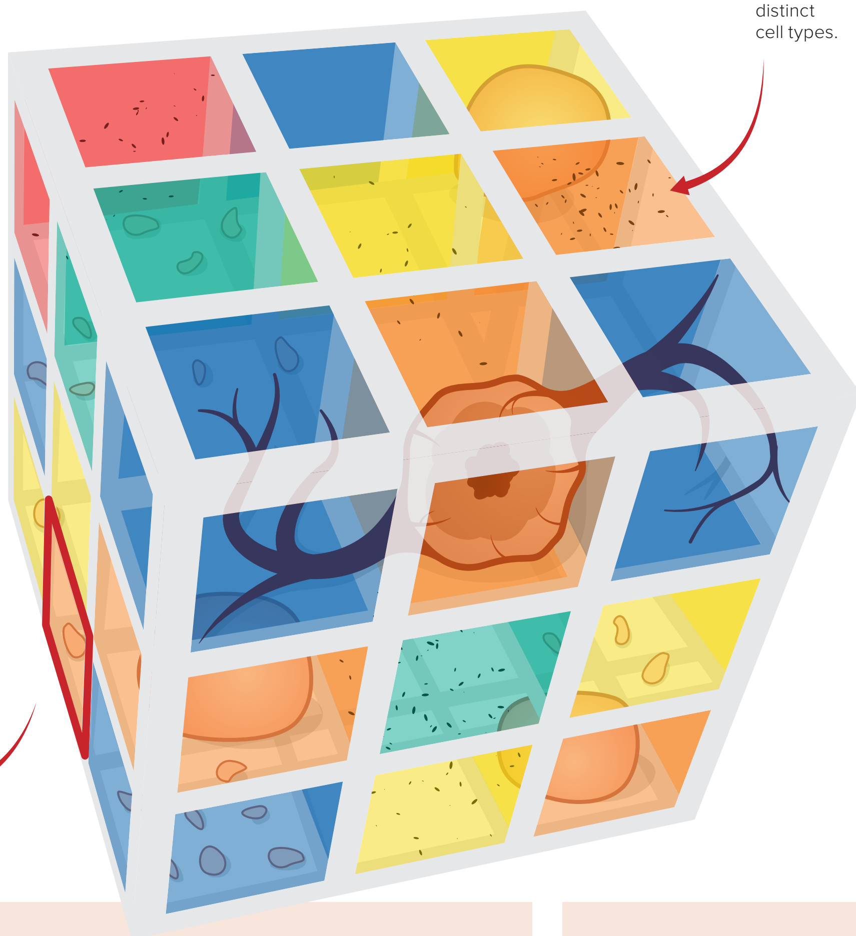
EASY AND ORIENTED

Culturing mini-organs is often done on well plates or dishes in a lab, which don't allow for great complexity. While sophisticated mini-organs can be made using 3D-bioprinting or microfluidic chips, a RIKEN team has now created a cube that can be populated via manual pipetting much more simply. In addition, the homogeneous environment found on well plates or dishes doesn't supply the spatial information that helps organs form distinct shapes. While microfluidic chips can be used to control fluids in ways that give cells signals about where they sit in space, fragile tissues tend not to fare well in these environments. A new gradient-in-a-CUBE system has been developed to address this.

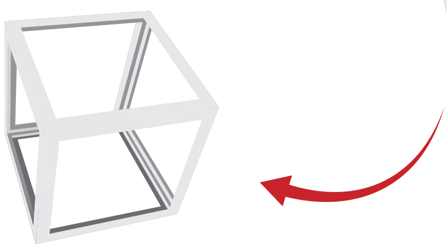
1 MULTI-CUBE

The RIKEN team made a device in which cells are separated into distinct hydrogel environments to help control their development into different types of cells and tissues[1].

Different environments to develop distinct cell types.

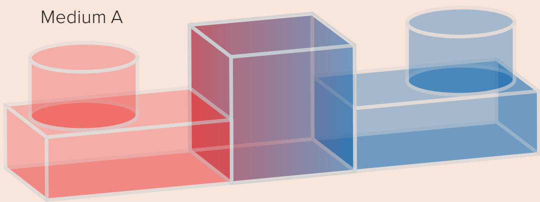


The dimensions of this 'L-shaped frame' and its surface wettabilities—intermolecular interactions that bring a solid surface and liquid together—enables several cubic millimeters of hydrogen to be simply pipetted in and trapped.



2 GRADIENT-IN-CUBE

The gradient-in-CUBE technology provides a gel gradient that helps cells to sense positional information and allows organs to form into appropriate shapes. The gel controls the amount of morphogen signalling proteins to reach different parts of tissue—these help to inform cell cultures about the shapes they should form[2].



Watch a live demonstration of MultiCUBE technology:

Watch a live demonstration of gradient-in-CUBE technology:

1. Suthiwanich, K. & Hagiwara, M. Localization of multiple hydrogels with MultiCUBE platform spatially guides 3D tissue morphogenesis In vitro *Adv. Mat. Tech.* **24,** 2201660 (2023).
2. Koh, I. & Hagiwara, M. Gradient to sectioning CUBE workflow for the generation and imaging of organoids with localized differentiation. *Commun. Biol.* **6,** 299 (2023).

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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.

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