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WINTER 2023

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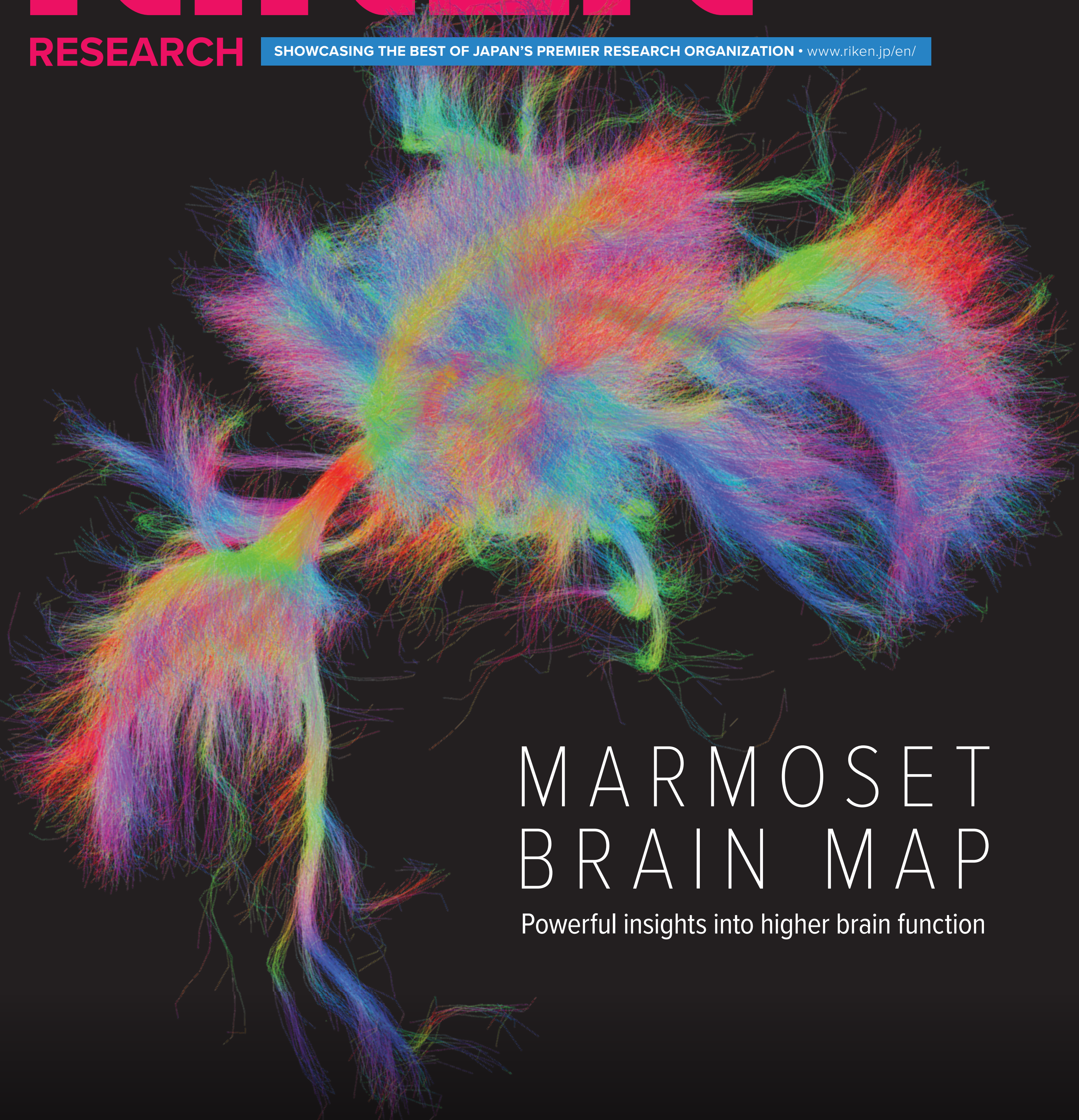

MARMOSET BRAIN MAP

Powerful insights into higher brain function

ICE LASERS
Shining a light on paleoclimates

WEIGHTY MATTER
New scale sheds light on Earth's core

PRECISE PREDICTIONS
Infrared satellites that could monitor flood risk

NEW LASER METHOD ALLOWS RESEARCHERS TO REVEAL CLIMATE CLUES FROZEN IN TIME
A laser sampler developed at RIKEN has high depth resolution, and also preserves oxygen and hydrogen isotope ratios in water, which will accelerate the detection of ancient temperatures from ice cores (see page 16).

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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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Please visit the website for recent updates and related articles. Articles showcase RIKEN's groundbreaking results and are written for a non-specialist audience.

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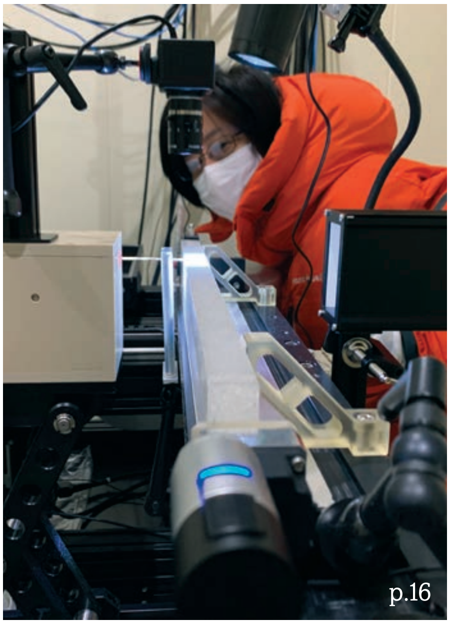

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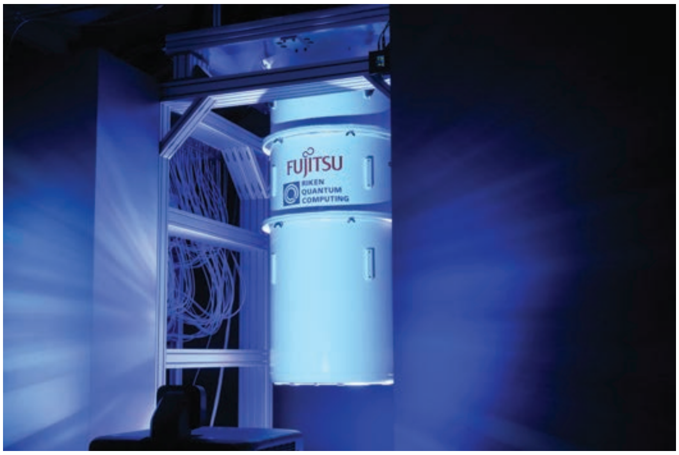

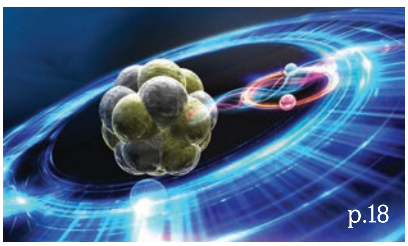
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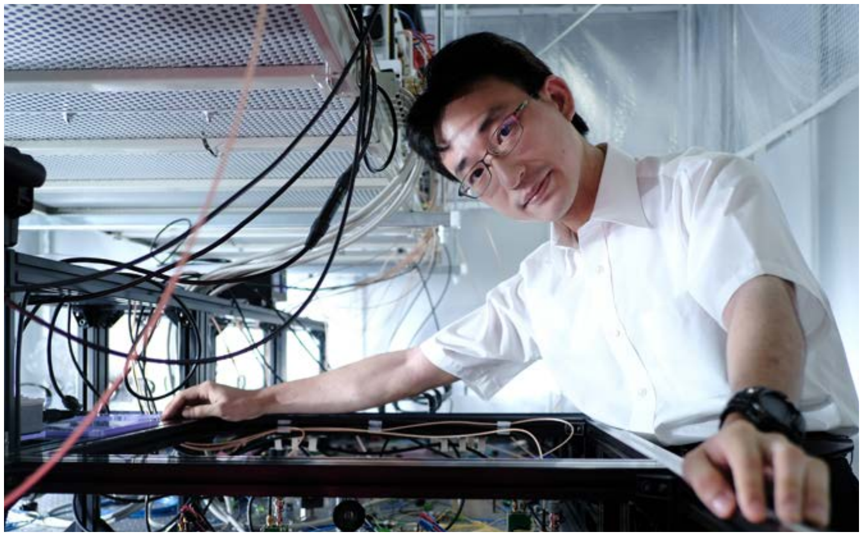


Scientists and global leaders gather in Kyoto in the autumn

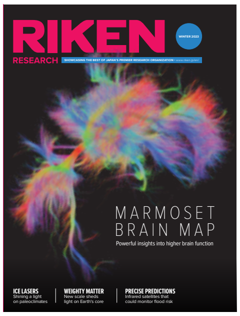
Makoto Gonokami
President, RIKEN

This autumn, I had the chance to visit beautiful Kyoto for the annual meeting of the STS forum and for the Global Summit of Research Leaders (RIL), a satellite event that we host together with the National Institute of Advanced Industrial Science and Technology (AIST). For us, the STS forum and RIL offer us a precious occasion each year to meet new and old friends from around the world.

This year, the STS forum brought together nearly 1,500 leaders from over 80 countries, regions, and international organizations to discuss the benefits of advances in science and technology, and also the issues they raise.

At the RIL this year, we took up a very timely issue, namely challenges facing research institutions from potentially disruptive technologies, in particular generative AI. We had a very constructive discussion on the benefits and risks of generative AI and how we as research institutes can make use of it, and also how we can support its benefits for society while mitigating the risks. The challenges and prospects related to developments in AI also featured prominently in the discussions at the STS forum itself. In this regard, I would like to mention RIKEN's activities for "AI for Science" to explore the use of generative AI, including the development of infrastructure and environment, in order to revolutionize the research process under the Transformative Research Innovation Platform of RIKEN platforms (TRIP) initiative. Through this we plan to further accelerate the research cycle and lead advanced science to have a social impact.

In addition to the Global Summit, we had the chance to meet with a number of organizations from around the world to discuss the possibility of collaborating in various fields on the important scientific topics of today. It seems that there is an increasing focus now on international collaboration on these globally important challenges, and we are happy to be able to play a part in that. I hope that the research highlights and other news we have included in this issue will give you hints on the research we are conducting and where we might be able to work together.



COVER STORY: Research on the marmoset brain map has revealed that the primate's prefrontal cortex—the region responsible for regulating thoughts, emotions and actions—has two types of connections to other cortical areas. This may have implications for better understanding the human brain. *Page 13*

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AI augmented scientific simulations

Mohamed Wahib

Team Leader, High Performance Artificial Intelligence Systems Research Team, RIKEN Center for Computational Science

Please tell us about yourself.
I was born in Egypt and spent most of my childhood there, except for a couple of years in an elementary school in the United States. After graduating from university, I traveled to several countries. I now head the High Performance Artificial Intelligence Systems Research Team in Kobe and Tokyo.

What excites you the most about your current research?
Currently, we are looking into how artificial intelligence can augment and compliment key numerical methods in scientific simulations. For instance, to model a mouse brain, we could use artificial intelligence technology to build a comprehensive map of neural connections in the brain.

What do you think has been the most interesting discovery in your field in the last few years?
The realization that we can use huge amounts of data and computing power to train neural networks to outperform humans in a wide range of tasks. Previously, it was thought that for computers to learn a task, such as playing chess, you needed to teach computers the first principles of the task in hand (chess rules and strategy, for example). Surprisingly however, simply providing data—such as records of chess games—to neural network models is enough to help computers to learn a task without additional human expertise or knowledge.

When and how did you come to Japan?
I first came to Japan in 2006. I always admired the country and I wanted to experience the challenge of living and studying in a new environment. I was so happy with my lab and university during my Master's degree, that I continued and did my PhD there. Fast forward, it's now 17 years since I arrived in Japan!

What are your workplace and colleagues like?
RIKEN is a national research center, but it feels very much like a university. While my center is in Kobe, I spend most of my time in the central Tokyo office because my team is located there. It's a very relaxed and nice environment and the people are flexible.

> *To model a mouse brain, we could use artificial intelligence to build a map of neural connections.*

Would you encourage foreign researchers to work at RIKEN?
Yes, definitely. RIKEN has a lot of resources and facilities. For instance, it has one of the world's most powerful supercomputers. And these facilities attract bright people from all areas of science, so career-wise, it's a smart move. Japan is a great country to live in and life in RIKEN is good because it's a very relaxed environment, and there are professional support personnel in the background looking after all the necessary administrative tasks. Doing a postdoc at RIKEN was the most productive phase of my life because I had minimal distractions and could focus on my work.

Do you enjoy life in Japan?
Yes, very much so. Outside of my research, I have a lot of hobbies. I like to exercise and like to do sports, so I try to make them a part of my daily life. For example, I cycle to the Tokyo office whenever I can. Also, Japan is really good for food and there is a wide selection of different cuisines. Japan is a great place to live and it offers a very vibrant environment.

Looking at abnormal synapse function

Akiko Hayashi-Takagi
Team Leader, Laboratory for Multi-scale Biological Psychiatry
RIKEN Center for Brain Science

Please describe your role at RIKEN.
I'm a former practicing psychiatrist, but now I use my knowledge to conduct basic research into understanding psychiatric disorders. While there are many excellent neuroscientists at RIKEN, few have clinical expertise and I want to act as a bridge to integrate basic psychiatry, clinical psychiatry and basic neuroscience.

Please briefly describe your current research. Why is it important?
Several lines of evidence, including human genetics, strongly suggest that abnormalities in the function of synapses are an underlying cause of psychiatric disorders. However, no-one knows which synaptic abnormalities alter the function of neurons and neural circuits and ultimately lead to behavioral changes. Our strategy has been to search for causal relationships between synapses, neurons, neural circuits and behavior in a multiscale manner.

> *The physiology of psychiatric disorders is so poorly understood, and it is shocking that there are so few curative treatments.* ”

How did you become interested in your current field of research?
When I was a psychiatrist, I was shocked by how unexplored the physiology of psychiatric disorders were, so I decided to move into basic science. The more research I did, the more I realized the importance of synapses.

What excites you the most about your current research?
It is most gratifying when, after conducting difficult experiments, we obtain reliable data and the results are published in a decent academic journal. I am particularly proud of a recent paper that indicated that abnormal synaptic strength is involved in the physiology of schizophrenia.[1]

What made you decide to become a scientist?
The physiology of psychiatric disorders is so poorly understood, and it is shocking that there are so few curative treatments. I wanted to contribute to the understanding of these disorders through basic research.

What do you think has been the most interesting discovery in your field in the last few years? How has it influenced your research?
Electrophysiological experiments with human neurons by a group led by Matthew Larkum at Humboldt University of Berlin have provided fascinating insights. They uncovered a unique human dendritic computational mechanism. This result was such an eye opener to me that I decided my lab would start studying primates, including humans, rather than mice. I believe it is one of the essential strategies for understanding psychiatric disorders in people.

"My research is important for sustainable development or society because...."
... the acquisition and maintenance of mental health is one of the most important things for human beings.

How has being at RIKEN helped your research?
The staff at RIKEN are the best of all the institutions I have belonged to. Not only are they extremely competent, but they are dedicated and supportive of my research. There is a strong sense of camaraderie, and a sense that we are working as a team. ■

Reference
1. Obi-Nagata, K. *et al. Sci. Adv.* **9**, eade5973 (2023)

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

Visitors talked to members of the Biofunctional Catalyst Research Team at the Wako Campus, ouside Tokyo.

RIKEN Wako Open Campus

On October 14, 2023, the RIKEN Wako Open Campus was held both on-site and online. Participants that attended on-site in Wako, Japan, were able to join lectures, booth tours, hands-on showcases, and lab tours.

During the lectures, Takaomi Saido of the RIKEN Center for Brain Science talked about the status and future prospects of Alzheimer's disease research. Okito Yamashita of the RIKEN Center for Advanced Intelligence Project (AIP) also introduced research on identifying mental disorders using brain science and machine learning.

Shohei Shimizu of the AIP talked about causal inference in statistics. Ichiro Takeuchi, who is also from the AIP, talked about AI and machine learning techniques for discovering and evaluating hypotheses in scientific research. There were roughly 3,500 visitors on-site and up to 1,300 online lecture views. Open days were also held at RIKEN campuses in Sendai, Harima, Yokohama, Tsukuba, and Kobe, Japan.

www.riken.jp/en/about/visiting/

RIKEN 2023 Summer School

The RIKEN Summer School gives students at RIKEN the opportunity to network with other researchers, across disciplines and centers.

At the summer school in September, 103 student researchers working at RIKEN each presented a poster of their research, and shared an introductory slide during icebreaker events.

RIKEN Executive Director Makiko Naka opened the day by encouraging the participants to actively get to know one another and build bridges between their respective fields. Ryusuke Hamazaki of the Nonequilibrium Quantum Statistical Mechanics RIKEN Hakubi Research Team also told the story of how he ended up leading a RIKEN Hakubi Team.

A number of young principal investigators also gave inspiring talks on their work, including Yasuhiro Ishida of the Emergent Bioinspired Soft Matter Research Team, Terufumi Fujiwara of the Adaptive Motor Control RIKEN Hakubi Research Team and Yuka Iwasaki of the Laboratory for Functional Non-coding Genomics.

Twelfth Global Summit of Research Institute Leaders

In September 2023, leaders from 25 public research institutes around the world attended the Twelfth Global Summit of Research Institute Leaders in Kyoto, Japan. They discussed the challenges facing research institutions from potentially disruptive technologies, in particular generative AI.

Elanor Huntington of the Commonwealth Scientific and Industrial Research Organisation in Australia and Takashi Usuda of the National Institute of Advanced Industrial Science and Technology (AIST) in Japan presented on potentially disruptive technologies. After this the participants at the summit discussed the effect that generative AI and other technologies are having on their institutions and societies and shared experiences of their own introductions to such technologies.

In a subsequent statement, the group recognized that AI will have an increasingly important role in research, and research activities and management, by providing new tools and technologies. The members also noted that generative AI also poses threats and that they "believe that we have a significant role to play in responding to such challenges". As a result, they stated that they "will continue to work together and share information as appropriate in order to take advantage of the opportunities brought by generative AI, while making every effort to make sure they are trustworthy, reliable, and equitable".

The Global Summit of Research Institute Leaders was co-hosted by RIKEN and AIST and co-chaired by RIKEN's President Makoto Gonokami and President Iain Stewart of the National Research Council Canada. It is an annual event held in Kyoto, Japan, in tandem with the Science and Technology in Society forum, an meeting designed to provide a framework for open discussions regarding the progress of science and technology for the benefit of humankind and the control of ethical, safety and environmental issues.

www.riken.jp/en/news_pubs/news/2023/20231108_1/

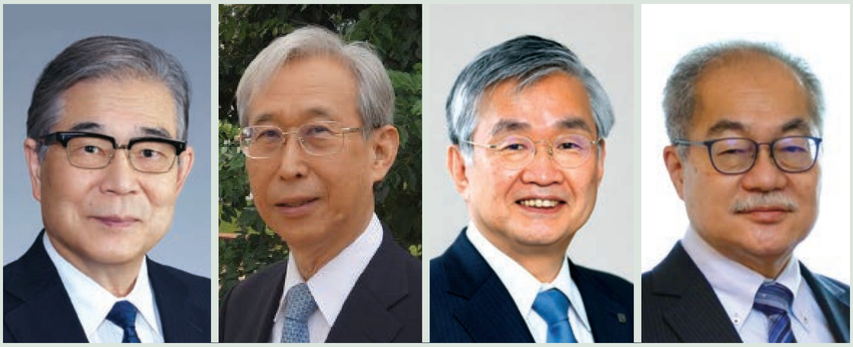
The new 64-qubit superconducting quantum computer (pictured) is open to companies and research institutions for joint research via a hybrid platform.

RIKEN and Fujitsu develop a 64-qubit quantum computer and accessible hybrid platform

RIKEN and Fujitsu have collaborated to develop a new 64-qubit superconducting quantum computer at the RIKEN Center for Quantum Computing-Fujitsu Collaboration Center in Saitama, Japan. The new quantum computer leverages technology previously developed by RIKEN and a number of research partners, including Fujitsu, for Japan's first superconducting quantum computer. A new hybrid platform will harness the newly developed quantum computer and a world-leading Fujitsu-developed 40-qubit quantum computer simulator. The hybrid platform enables an easy comparison of the calculation results of noisy intermediate-scale quantum computers against error-free results from quantum simulators. As a result the platform will be used to accelerate research on many topics, such as performance evaluations of quantum-application error mitigation algorithms. Fujitsu and RIKEN began providing their new platform to companies and research institutions with which they were conducting joint research in October 2023.

www.fujitsu.com/global/about/resources/news/press-releases/2023/1005-01.html

The Japanese government honors RIKEN leaders



(From left) Kohei Tamao, Kazuo Shinozaki, Kohei Miyazono and Hiroshi Ohno.

KOHEI TAMAO
Order of Culture
RIKEN Honorary Science Advisor Kohei Tamao, who is also director of the Toyota Physical and Chemical Research Institute and a professor emeritus of Kyoto University, has been selected to receive a 2023 Order of Culture. Between 2008 and 2013, Tamao served as director of the RIKEN Advanced Science Institute.

The Order of Culture is awarded by the Japanese government to individuals who have made particularly outstanding contributions to the development of science, technology, art, and other aspects of culture. His achievements include the creation of new materials, in particular using nickel-catalyzed cross-coupling based on a process known as Kumada-Tamao coupling, as well as Tamao oxidation, a process for synthesizing alcohols based on hydrogen peroxide oxidation of carbon-silicon bonds. He has also contributed to science outreach activities, by helping create a popular periodic table published by the Ministry of Education, Culture, Sports, Science and Technology.

"I am truly overwhelmed by this honor, and am honestly happy that our research utilizing silicon and nickel has been so highly evaluated, and I would like to share the honor with my colleagues," Tamao said upon receiving the award.

KAZUO SHINOZAKI
Order of the Sacred Treasure Gold and Silver Star
RIKEN Honorary Scientist and Honorary Scientific Advisor, Kazuo Shinozaki, has been selected to receive the 2023 Order of the Sacred Treasure, Gold and Silver Star. This Japanese government order is awarded to persons who have been engaged for many years in the public service, or in non-public services that are equivalent to public service.

Shinozaki has been a world leader in introducing molecular biological techniques to help explain the molecular mechanisms behind the acquisition of the environmental stress response and tolerance in plants. Shinozaki has served as director of the RIKEN Plant Science Center and the RIKEN Center for Sustainable Resource Science.

"I believe that [my] research results were made possible thanks to the many researchers I worked with, and those who supported the research. Science progresses based on the efforts of many of our predecessors. I would like to express my gratitude to my mentors, who have guided me on the path of science, and to my family, who have supported me," Shinozaki said upon receiving the award.

KOHEI MIYAZONO
Person of Cultural Merit
RIKEN Executive Director Kohei Miyazono has been selected as a 2023 Person of Cultural Merit. Miyazono is also team leader of the Laboratory for Cancer Invasion and Metastasis at the RIKEN Center for Integrative Medical Sciences.

The designation is a recognition by the Japanese government of those who have contributed to the advancement and development of Japanese culture in a variety of fields, including academia, arts, science and sports.

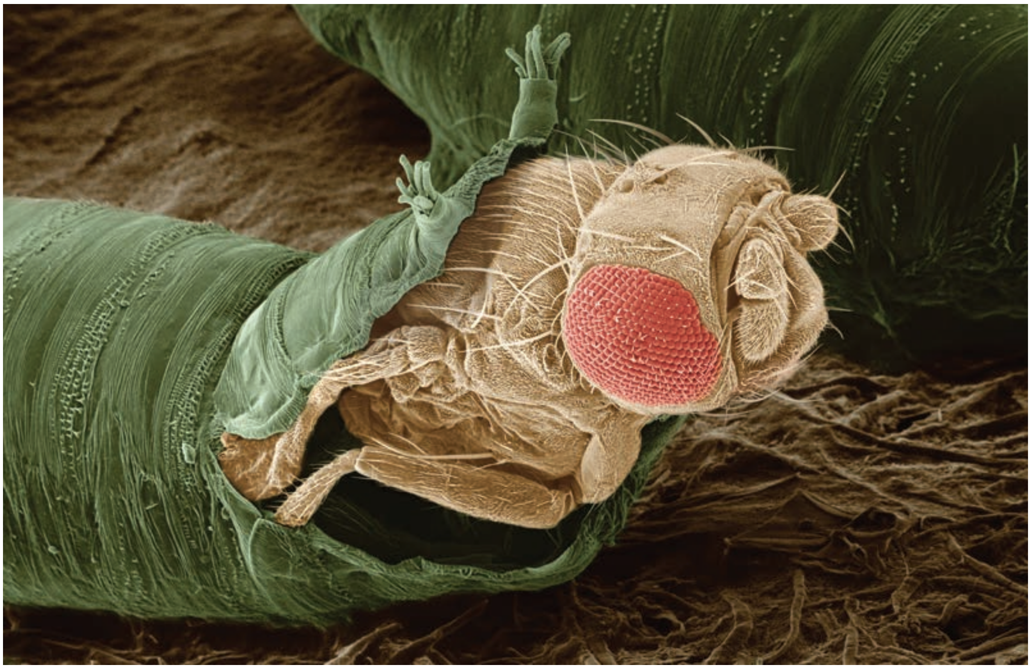
Miyazono received the distinction for his research on the relationship between transforming growth factor-β signaling and its relation to progression of cancer, and revealing the mechanisms behind cancer invasion and metastasis.

HIROSHI OHNO
Medal of Honor (purple ribbon)
Hiroshi Ohno, deputy director of the RIKEN Center for Integrative Medical Sciences received a 2023 Medal of Honor (purple ribbon), given out by the Japanese government to individuals who have contributed to academic and artistic developments, improvements and accomplishments, in recognition of his achievements in immunology and gut bacteria research.

CANCER CACHEXIA

How cancer can affect the whole body

The connection between local tumors and body-wide changes to metabolism has been revealed in fruit-fly larvae



Scanning electron micrograph of a fruit-fly emerging from a puparium. RIKEN researchers have discovered that, in larvae with cancer cells, the protein Netrin reprograms the metabolism of the organism.

Local, tumor-induced stress in fruit-fly larvae releases a signaling molecule that reprograms the metabolism of the animals, an all-RIKEN team has discovered[1]. If the same thing happens in humans, it could lead to new ways of treating cancer-induced complications, which are often fatal.

How cancer kills people is often mysterious. In some cases, it causes a vital organ to misfunction. But more frequently, cancer kills by causing changes that affect the body as a whole.

A case in point is cancer-induced cachexia, a wasting syndrome that causes muscle and fat loss. It contributes to the emaciated appearance of many cancer patients. Cachexia is estimated to occur in 80% of people with advanced cancer and to directly cause 30% of all cancer deaths.

But how cancer gives rise to these body-wide complications has been unclear. "There are still a lot of things that we don't understand about cancer cachexia," says Morihiro Okada of the RIKEN Center for Biosystems Dynamics Research. "And there are very limited options for treating it."

Now, Okada, Sa Kan Yoo and co-workers have discovered that cancer-induced stress in fruit-fly larvae produces a protein known as Netrin, which reprograms the metabolism of the larvae.

This is the first time that Netrin, which plays a role in guiding cell and nerve axon migration during development, has been implicated in spreading the effects of a local cancer to the metabolism of the organism.

The team engineered fruit flies with a mutant gene that causes tissue that normally develops into eyes in larvae to become tumors. Even though the cancer cells did not multiply excessively, about 80% of the larvae with the mutation died within days.

"Almost all the larvae survived after knocking down Netrin"

The researchers conjectured that factors secreted by the cancer cells were negatively impacting the entire body. They identified 20 factors, including Netrin, the expression of which was upregulated in cancer cells. Follow-up analysis revealed that inhibiting the expression of Netrin markedly increased the survival rate of larvae, even though it didn't affect the cancer cells. "Almost all the larvae survived after knocking down Netrin," says Okada.

Human cancer patients often have elevated levels of Netrin, suggesting that the same mechanism may occur in people. "Recently a lot of researchers have been focusing on Netrin in tumor cells because it's highly expressed in tumors, which leads to very high levels in the blood," says Okada. "But so far nobody knows what role Netrin plays in the blood."

The finding by Yoo's team suggests that it may be possible to improve patient survival by altering the metabolic state of tissues far from the cancer site.

The team now intends to extend their investigation to mice. ●

Reference

1. Okada, M., Takano, T., Ikegawa, Y., Ciesielski, H., Nishida, H. & Yoo, S. K. Oncogenic stress-induced Netrin is a humoral signaling molecule that reprograms systemic metabolism in *Drosophila*. *The EMBO Journal* e111383 (2023).

SCHIZOPHRENIA

Extra-large synapses could be a cause of schizophrenia

The discovery that some cases of schizophrenia may be due to an overabundance of extra-large synapses in the brain could lead to new treatment approaches

Schizophrenia may be associated with the excessive formation of oversized and hyperactive synaptic connections between nerves in the brain, a mouse model and a human post-mortem study by RIKEN researchers suggests[1]. This finding points to potential new modes of treatment for this challenging brain disorder.

"The dominant explanation for schizophrenia suggests it is due to changes in the density of synapses, but the strength of the synapses has been overlooked," says Akiko Hayashi-Takagi from the RIKEN Center for Brain Science. "We've now found evidence implicating the appearance of a small number of extra-strong synapses."

The research has potentially profound implications for treating schizophrenia

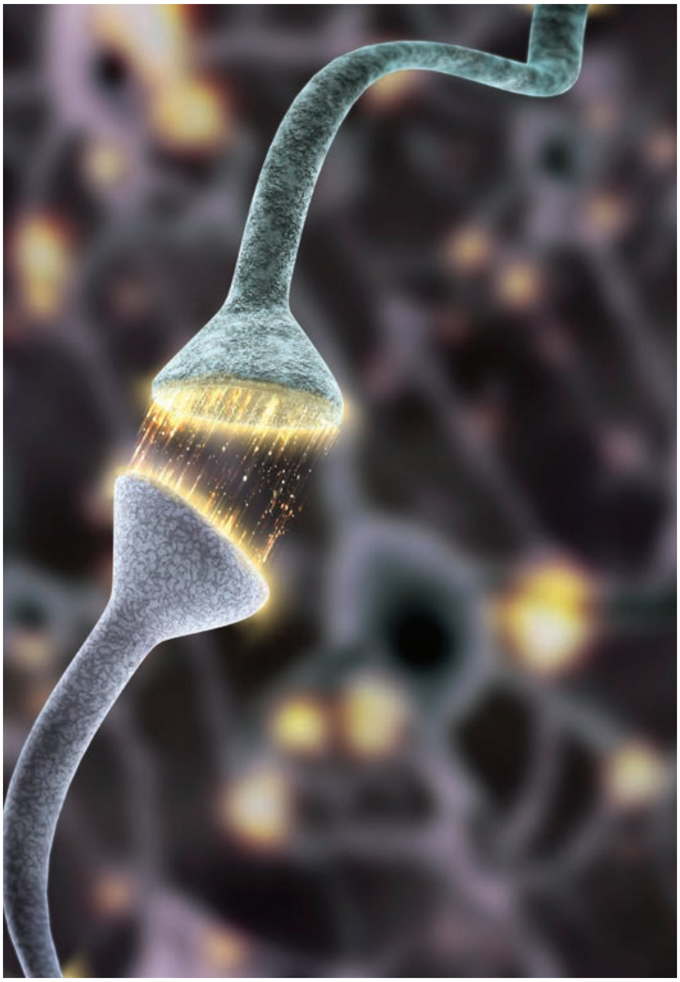
Synapses are locations in the brain where nerve cells connect and send messages to each other (see image). Hayashi-Takagi says these extra-large, extra-strong 'aristocratic' synapses can bypass the normal 'democratic' integration of input from all synapses, thereby taking control over the firing of neurons receiving input from the synapses. This is thought to affect the performance of the working memory—a key aspect of schizophrenia symptoms.

The extra-strong synapses were found in two forms of genetically modified mice that are generally accepted as being animal models of schizophrenia.

Convincing evidence of the relevance of the mouse findings to humans came with the discovery that the extra-strong synapses were more abundant in post-mortem brain tissue samples from patients with schizophrenia than in those of matched controls.

One reason why synapse strength had been largely ignored previously is that synapses are very challenging to manipulate and study, Hayashi-Takagi thinks. "I've been working on this issue for seven years to get to this point," she says.

Hayashi-Takagi and her team now intend to look for evidence supporting their hypothesis in human tissue from living brains. While samples cannot ethically or safely be taken directly from a patient's brain, they can be extracted from surgically removed tissue surrounding glioma brain tumors.



Extra-strong synapses could play an important role in psychiatric disorders such as schizophrenia, a study by RIKEN researchers finds.

"Glioma is an invasive malignant cancer, so the surgeon must remove the tumor along with a margin that contains healthy neurons," Hayashi-Takagi explains. "We would like to quantify the human synapse parameters in these samples and integrate these human data into a computational model. As far as I know, no simulation has ever been implemented by using actual data from human synapses."

The research has potentially profound implications for treating schizophrenia. Since extra-strong synapses are very stable and difficult to disrupt, Hayashi-Takagi thinks drugs might not be the best solution. A better approach might be to explore techniques that affect the circuits in the brain using neurofeedback, electrical or magnetic stimulation, she suggests. ●

Reference

1. Obi-Nagata, K., Suzuki, N., Miyake, R., MacDonald, M. L., Fish, K. N., Ozawa, K., Nagahama, K., Okimura, T., Tanaka, S., Kano, M. *et al.* Distorted neurocomputation by a small number of extra-large spines in psychiatric disorders. *Science Advances* **9**, eade5973 (2023).

QUANTUM COMPUTING

Feedback system could fix quantum-computing errors

Quantum circuit can reset quantum bits carried by electron spins in silicon

A method to reset the data held in silicon-based, quantum-computing devices has been developed by RIKEN researchers[1]. This could help to enhance the reliability of quantum computers by forming a crucial part of an error-correction system.

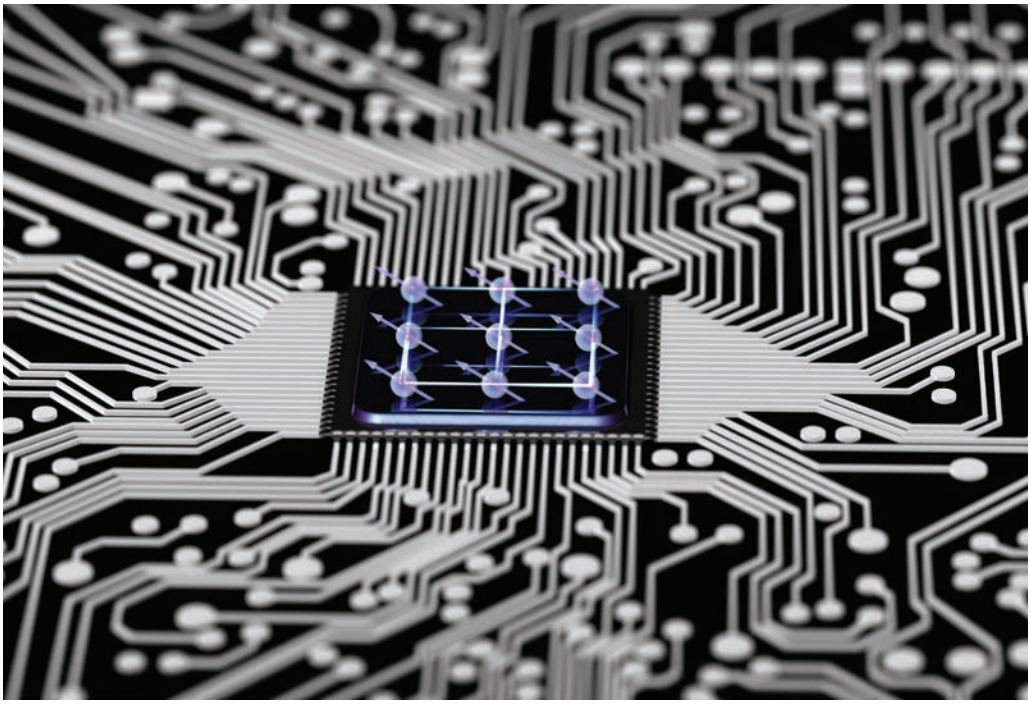
Quantum computers promise to dramatically increase our computing power, but these highly sensitive devices are prone to errors.

Data in quantum computers is encoded by the quantum states of particles, such as the spin of an electron. These quantum bits (qubits) can be linked together through a phenomenon called entanglement, and then process information through a combination, or superposition, of their quantum states. This enables quantum computers to perform certain complex calculations much more rapidly than conventional computers.

Electrical confinement in silicon formed by metallic electrodes, known as quantum dots, is a promising candidate to host an electron-spin qubit. But quantum states can be delicate, and the qubits often acquire errors that need to be corrected.

To help address this problem, RIKEN researchers have devised a way to rapidly and accurately read a spin qubit, and then reset it. This kind of control system will be essential to build fault-tolerant quantum computers based on silicon quantum dots.

One challenge the team faced is that a qubit loses correlation between the readout result and the qubit state after reading. To overcome this, the team



Conceptual illustration of a computer microchip with a grid of quantum spin states. RIKEN researchers have shown how a quantum circuit can reset quantum bits carried by electron spins in silicon.

used a pair of silicon quantum dots to accommodate two entangled qubits. While one qubit carried data, the other served as an auxiliary. By using a charge sensor to read the auxiliary qubit, the researchers could estimate the state of the data qubit without destroying its information—a method known as a quantum non-demolition (QND) measurement. Depending on the outcome of the measurement, the system could then deliver a microwave pulse that reset the data qubit.

"The time for the protocol might be reduced to a few microseconds"

The team constructed a quantum circuit to repeatedly perform the QND measurements, producing a single microwave pulse to reset the data qubit with cumulatively improved reliability. "Since the quantity measured by a quantum non-demolition measurement is not disturbed by the measurement, it can be measured again and again to estimate the data-qubit state more accurately," says Takashi Kobayashi of the RIKEN Center for Quantum Computing.

The whole reset process currently takes about 60 microseconds at least, which might be too slow for a practical quantum computer. To shorten this time, the researchers suggest adding a second auxiliary qubit, which would allow them to use a faster measurement method.

"The time for the protocol might be reduced to a few microseconds," says Kobayashi. "This would pave the way to feedback-based quantum error correction." ●

Reference

1. Kobayashi, T., Nakajima, T., Takeda, K., Noiri, A., Yoneda, J. & Tarucha, S. Feedback-based active reset of a spin qubit in silicon. *npj Quantum Information* **9,** 52 (2023).

SPINAL DISEASES

New genes implicated in an incurable spinal disease

An expanded genomic association study reveals previously unknown genetic links to a debilitating spinal disease

The discovery of eight new genes associated with a disease known as ossification of the 'posterior longitudinal ligament of the spine' (OPLL) is a key step toward the development of effective treatments for this currently incurable disease[1].

OPLL is a painful and debilitating condition in which a ligament that travels the length of the spinal cord turns to bone over time, severely restricting movement and causing motor and sensory issues, pain and numbness.

"OPLL is more common in East Asian populations than in Western populations, and is particularly prevalent in Japanese people," notes Shiro Ikegawa of the RIKEN Center for Integrative Medical Sciences. "This points to a genetic susceptibility to the condition, hence our investigations into the causal genes involved."

Previous research has suggested links between certain health traits, such as type 2 diabetes and a high body mass index (BMI), and the development of OPLL. However, OPLL is likely a 'polygenic' disease, meaning that complex genetic and environmental factors combine to drive its progression.

Ikegawa and his co-workers conducted an initial genome-wide association study (GWAS) of OPLL in Japanese patients in 2014, and identified six significant genetic loci linked to the disease. More recently, they discovered a susceptibility gene, CCDC91, in one of the loci.

Now, the team has expanded on this earlier study by conducting a meta-analysis of GWASs comprising data from 22,000 Japanese individuals. This revealed a further eight previously unreported genetic loci and specific candidate genes that warrant future study.

The team observed enrichment in genes related to connective tissue and bone cell groups, as well as blood and immune cell components. Analysis of 96 different traits showed that OPLL also has positive correlations with type 2 diabetes and increased BMI.

"We found a significant causal effect of increased BMI and high bone mineral density on OPLL," says Ikegawa. "These insights could point toward novel treatment targets."

"Crucially, although our data confirms a link, we didn't find causal effects of type 2 diabetes on OPLL development," adds Ikegawa's colleague Chikashi Terao.

The team also found genetic differences between cervical (neck) and thoracic (trunk) variants of OPLL, with a stronger influence of BMI fueling the latter. These differences between subtypes may inform the basis for precision medicine for OPLL—the two related conditions require different treatments and care, notes Ikegawa.

The researchers are planning to further examine the candidate genes they have uncovered, and will conduct additional GWASs using data from Korea, Taiwan and China to gain insights into OPLL in different ethnicities.

Genetic studies reveal new gene candidates that might be responsible for the debilitating and incurable disease known as ossification of the posterior longitudinal ligament of the spine (OPLL).

Reference

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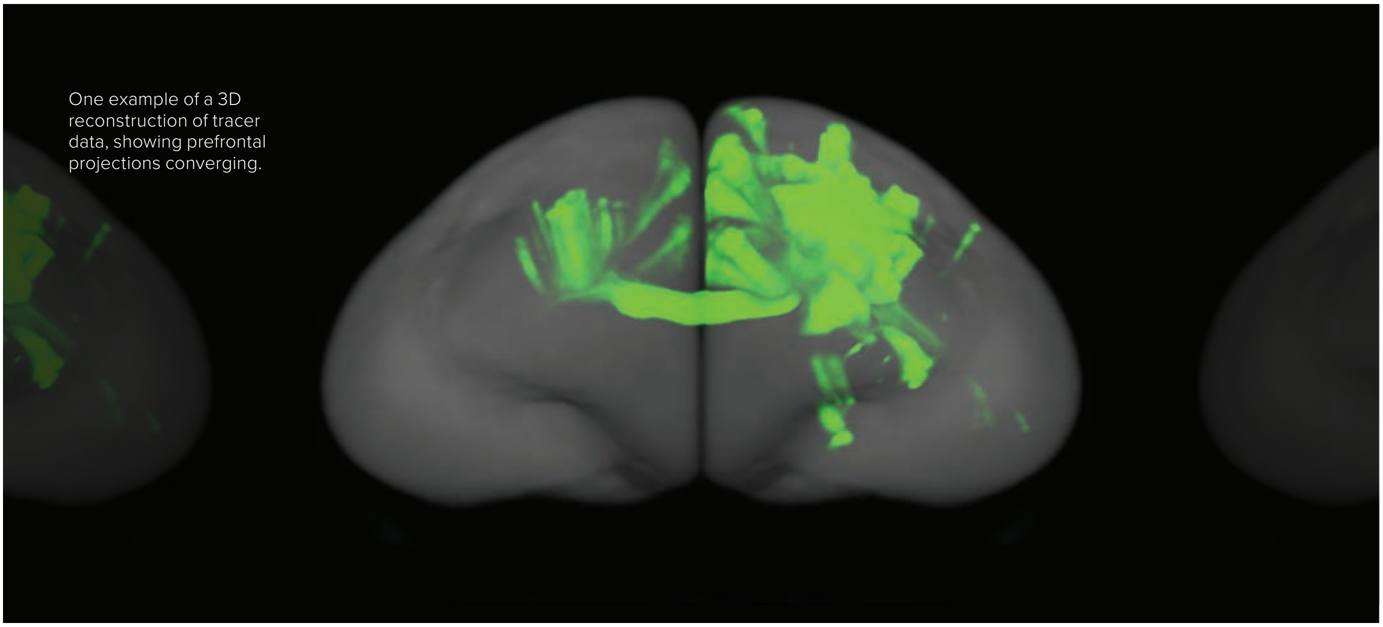

NEUROSCIENCE

Mapping connections of the marmoset prefrontal cortex

The prefrontal cortex in the marmoset has two distinct types of connections to other cortical areas

A comprehensive map of the marmoset brain by RIKEN neuroscientists has revealed that two types of connections link the prefrontal cortex to other cortical areas[1]. This finding could provide insight for addressing neurological disorders involving the prefrontal cortex.

A lot of what we know about the human brain comes from experiments on rats and mice. But unlike humans, rodents lack a well-developed prefrontal cortex—the brain region housed immediately behind the forehead that regulates our thoughts, emotions and actions. Knowledge of the prefrontal cortex gained from rodent studies may thus be providing only a partial picture of the human prefrontal cortex.

"One of the most remarkable features of the human brain is its large prefrontal cortex, which is much more evolved and highly specialized than the rodent counterpart," says Akiya Watakabe of the RIKEN Center for Brain Science (CBS). "It controls the emotions and thoughts, so in a sense it's a center of higher brain functions."

Primates such as marmosets provide a helpful stepping stone between rodents and us since their prefrontal cortex is much more developed than rodents'. One thing that was largely unknown is how the prefrontal cortex connects to and interacts with the other brain areas.

Now, Watakabe and Henrik Skibbe, also of the CBS, and co-workers have identified two types of projections—patchy and diffuse ones—that connect the prefrontal cortex to the cortex and striatum. The patchy connections had multiple column-like structures that were smaller than a millimeter in size. In contrast, the diffuse connections spread out widely across the cortex and striatum.

"We uncovered two kinds of connectivities: the patchy one connects two points very strongly with each other, whereas the diffuse one connects to very large regions, but only very loosely," explains Watakabe. "So we expect that the two connections have different functions."

The team uncovered this structure by injecting viral tracer into more than 40 locations and then observing the paths they took. It took about seven years to collect and analyze all the data.

This is the first time such a comprehensive and detailed projection map has been generated for primates. "Whole-brain analysis at this high resolution hasn't been done before for primates because it generates too much data," says Watakabe. Skibbe took the data generated from the different brains and mapped it onto a common brain template. He also used deep learning to accurately detect the tracer signal for quantitation. "When I saw his processed data, it was so beautiful to look at," recalls Watakabe.

The whole-brain map of the prefrontal cortex projections in the marmoset is freely available on the Brain/MINDS data portal [https://dataportal.brainminds.jp/]. ●

Reference

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Storm surges that are produced by typhoons can cause great devastation and loss of life in coastal areas.

STORM SURGE PREDICTION

Deep learning method saves time but keeps accuracy

Deep learning allows storm surges produced by typhoons to be quickly and accurately forecasted

A deep learning method developed by RIKEN researchers can accurately predict the destructive power of typhoon-induced storm surges on coastal regions in a fraction of the time of conventional models[1]. It promises to buy precious time for coastal residents without compromising accuracy.

The powerful winds and torrential rain generated by typhoons can wreak destruction and loss of life in inland regions. But coastal regions bear the full brunt of their destructive power through a phenomenon known as storm surges. The combination of strong winds and low pressure causes the sea level to rise well above its normal level, resulting in inundation of low-lying areas.

"When the bulge in the water surface reaches the coastline, it can cause flooding similar to that of tsunamis but spread out over two or three days," explains Iyan Mulia of the RIKEN Prediction Science Laboratory.

Currently, two kinds of computer models are used to forecast wind and pressure fields for simulating storm surges. Parametric models use statistical calculations determined from past observations. They are quick to perform but can be unreliable under certain conditions. In contrast, numerical weather prediction (NWP) models, which account for the physics involved, are more accurate but take much more time and computing power to perform.

"Parametric models are computationally more efficient but less accurate than NWP models," says Mulia. "Our goal is to develop a model that is as efficient as parametric models but as accurate as NWP models."

Now, Mulia and his co-workers have used deep learning to combine the advantages of both models. "Our deep learning model can produce comparable accuracy to NWP models with significantly less computational effort," says Mulia.

Their model uses deep learning to convert the results of a parametric model into realistic wind and pressure fields within a few seconds on a normal desktop computer. These are then used to calculate the effect on the sea. The team employed this approach because it is much more demanding to calculate atmospheric conditions than water ones.

Even Mulia was surprised at how well the deep learning model performed. "We didn't expect that the deep learning model could achieve such high accuracy given how complex typhoon structures are," he says. "For instance, it clearly captures the topographic effect on the wind, which is difficult to achieve using standard parametric models. We're very happy with the result."

More testing using larger data sets is needed before the method can be deployed in operational forecasting systems, Mulia notes.

The team is now applying the same approach to other fields such as environmental science and engineering.

Reference

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HIBERNATION

Animal resistance to cold reflected in stem cells

The ability to use stem cells to explore cold resistance offers a convenient way to explore hibernation-like states in animals

A mouse's stem cells possess the same level of cold resistance as the animal itself, RIKEN researchers have shown[1]. This indicates that mouse stem cells could be used to investigate organ preservation and even human hibernation.

Organs can be irreparably damaged if they are stored at low temperatures for too long prior to transplantation. In contrast, hibernating animals can survive for months with a low body temperature.

Genshiro Sunagawa's team at the RIKEN Center for Biosystems Dynamics Research is investigating how they survive under such conditions. They are studying lab mice rather than wild hibernators because they offer greater control over genetic variables.

If mouse stem cells could be used to study organ preservation and hibernation, this would open up the field to experimental systems already developed for studying stem cells and reduce the need to use live animals in hibernation research.

Mice don't hibernate but can enter a hibernation-like state called torpor for about an hour. The researchers tested strains of inbred lab mice and found one strain with shallow torpor, one with deep torpor, and one in between.

After establishing embryonic stem cell lines from the mouse strains, the team examined cell metabolism near mouse body temperature and at a lower temperature.

Cells produce energy in two ways. Glycolysis involves breaking down sugar molecules and does not require oxygen, while oxidative phosphorylation occurs in mitochondria and needs oxygen.

The organs of hibernators such as this woodland jumping mouse can withstand low temperatures for months. RIKEN researchers have shown that stem cells from lab mice can be used to explore this phenomenon.

At the lower temperature, stem cells from the shallow- and medium-torpor mice switched to glycolysis, whereas those from the deep-torpor mice did not. Those stem cells consumed high levels of oxygen at all temperatures.

Further tests revealed that the deep-torpor stem cells generated energy using oxygen in the mitochondria differently from those of the other two strains, with the oxygen coming from an outside source.

The researchers investigated whether this finding applied to adult mice by examining liver tissue from the three mouse lines. As in the stem cells, the tissue from the deep-torpor mice did not rely on glycolysis in the cold but consumed a high amount of oxygen. So even when not in torpor, tissue from these mice was preserved better at lower temperatures.

"We've proven that the distinct responses to lower temperatures, unique to each strain, are preserved even at the cellular level," says Sunagawa. "This provides a huge opportunity to conduct *in vitro* studies of cold tolerance in tissues from torpor-capable animals."

The team eventually hopes to induce similar cold resistance in tissue from any animal. "In the long-term, insights from this system will help us develop ways to implement human hibernation or human organ cryopreservation," says Sunagawa. ●

Reference

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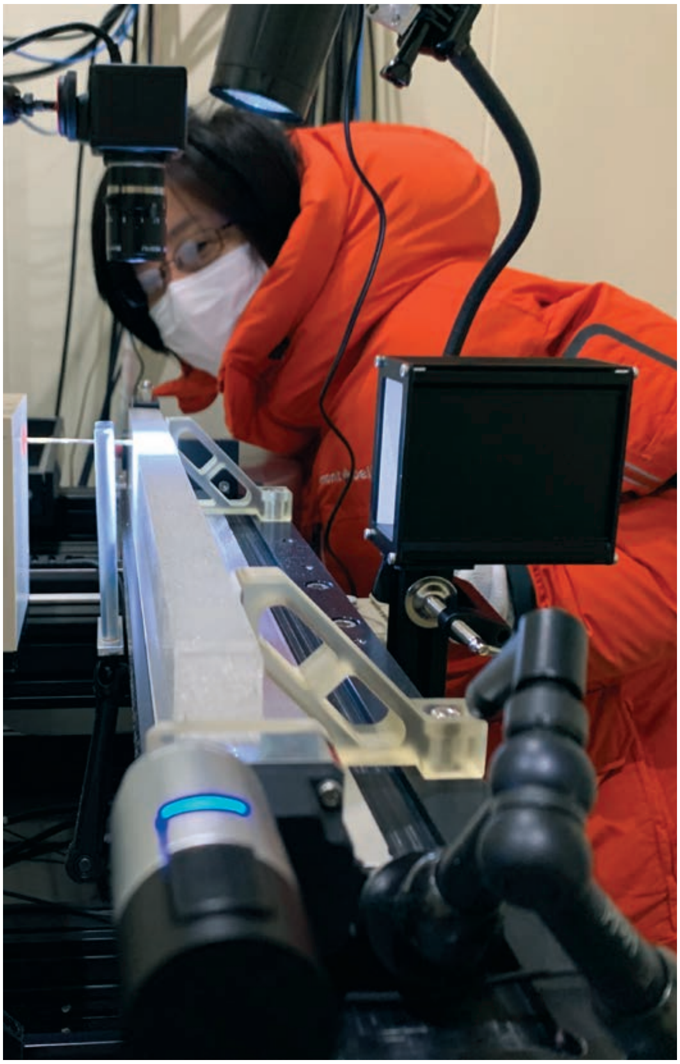
ICE-CORE SAMPLING

Shining a light on climate change over a million years

A sampling system that uses a laser to melt ice can accurately determine past temperatures even for highly compacted samples



An Antarctica Dome Fuji ice core being sampled by a laser-based system developed by RIKEN researchers.

A laser-based sampling system developed by RIKEN researchers for analyzing the composition of ice cores taken from glaciers will help scientists understand climate change in the past and present[1].

Tree rings can reveal information about the local climate during the tree's lifetime. The annual growth of glaciers can provide similar information, but over much longer periods—thousands of years to more than a million years. By sampling at regular intervals along cylindrical ice cores taken from glaciers, scientists can construct continuous temperature profiles, allowing them to investigate past changes in climate.

"It's now possible to analyze stable water isotopes at a few-millimeters depth resolution"

However, this isn't possible with samples from deep locations, where annual accumulation is often compressed into layers smaller than a centimeter.

Two main methods are used to sample ice cores. One has a depth precision of more than 1 centimeter. Since it cannot obtain data from those years with accumulation less than 1 centimeter, it could miss key, one-off climate events. The other method has good depth precision but cannot analyze the water content—the main way for determining past temperatures.

Now, a laser melting sampler developed by a team led by Yuko Motizuki of the RIKEN Nishina Center for Accelerator-Based Science overcomes both problems: it has a high depth resolution of about 3 millimeters, and it preserves the oxygen and hydrogen isotope ratios in water needed to infer past temperatures.

A laser beam delivered through an optical fiber in a special silver nozzle melts the ice, which is rapidly pumped out and collected in stainless-steel vials.

The researchers optimized three aspects: the laser power, the nozzle insertion speed, and the rate at which the liquid is sucked out. This optimization melted the ice as fast as possible, prevented the laser from overheating, and stopped the meltwater from becoming too hot, which would destabilize the critical isotopic ratios and prevent accurate temperature determinations.

To demonstrate the system, the team took 51 samples at 3-millimeter intervals along a 15-centimeter segment of an ice core from about 92 meters below the ice surface in East Antarctica. The stable oxygen and hydrogen isotopes in the meltwater from the samples matched well with those taken by hand segmentation, a process that is considered precise. This indicated that the inferred temperatures were accurate.

"With our laser melting method, it's now possible to analyze stable water isotopes at a few-millimeters depth resolution," says Motizuki. "This will allow researchers to obtain continuous, long-term, annually-resolved temperature profiles, even in deep ice cores collected at low accumulation sites in Antarctica."

The team plans to use their laser melting sampler to study climate change related to natural variations in solar activity. ●

Reference

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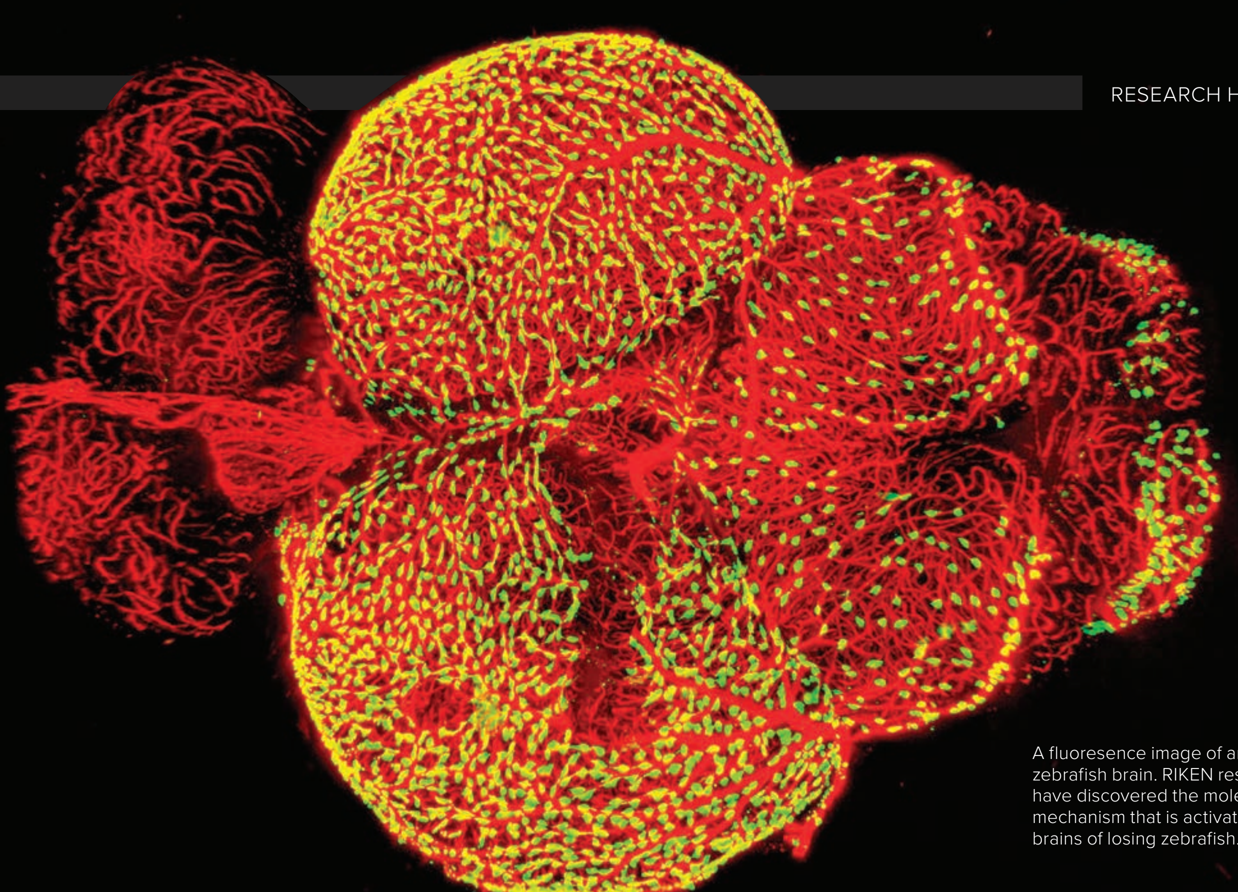

A fluoresence image of an adult zebrafish brain. RIKEN researchers have discovered the molecular mechanism that is activated in the brains of losing zebrafish.

EXPLORATORY LIFE SCIENCES

The neuroscience behind losing a fight

The molecular mechanism in the brains of zebrafish that causes a fish to quit a fight has been identified

Two RIKEN neuroscientists have uncovered a molecular switch in the zebrafish brain that causes a fish to stop fighting against another zebrafish[1]. This discovery could shed light on various mood disorders in people.

Like many animals, two male zebrafish placed close to each other will start fighting. They will circle and take lunging bites at each other until eventually one of them acquiesces and exhibits loser-like behavior such as fleeing.

Knowing when to bow out of a fight is critical since continuing beyond a certain point risks serious injury or even death. Researchers are interested in discovering what happens in the brains of losing fish to induce this behavior, both because many animals exhibit similar behavior and because it could help illuminate mood disorders in people such as social withdrawal and social anxiety.

Previously, a team led by Hitoshi Okamoto of the RIKEN Center for Brain Science (CBS) had found that a deep-brain structure known as the habenula contains two neural circuits that play a key role in determining whether a fight is won or lost. But the molecular activation of these circuits was not known.

Now, Okamoto and Masae Kinoshita, also at CBS, have found a molecular mechanism in the brains of losing zebrafish that is probably behind the switch in behavior.

Okamoto and Kinoshita placed two zebrafish in a tank and allowed them to fight. They then sliced the brains of both the winner and the loser, and examined them under a microscope. The researchers found that in losers, the neurotransmitter acetylcholine causes the receptor for glutamate—another neurotransmitter—to move from the inside to the surface of the postsynaptic membrane of the neurons in the interpeduncular nucleus, the target of the two neural circuits from the habenula. This transfer of the glutamate receptor did not occur in winners.

The implications of this finding extend far beyond fish. “This circuit from the habenula to the interpeduncular nucleus exists in all vertebrates,” says Okamoto. “So I’m quite confident that it plays a similar role in other animals.”

In particular, it may be relevant to mood disorders in people. “There’s lots of research implicating the habenula in severe depression, but the part of the habenula connected to the interpeduncular nucleus hasn’t been studied very much,” explains Okamoto. “I’m sure that this circuit is probably involved in conditions such as social withdrawal.”

The pair plans to continue exploring the roles of the winner and loser circuits. “Our ultimate goal is to identify the real roles of these two circuits,” says Okamoto. “Our current hypothesis is that the winner circuit makes fish focus on their internal state, whereas the loser circuit causes fish to look to the external world. We’re currently performing experiments to test this hypothesis.”

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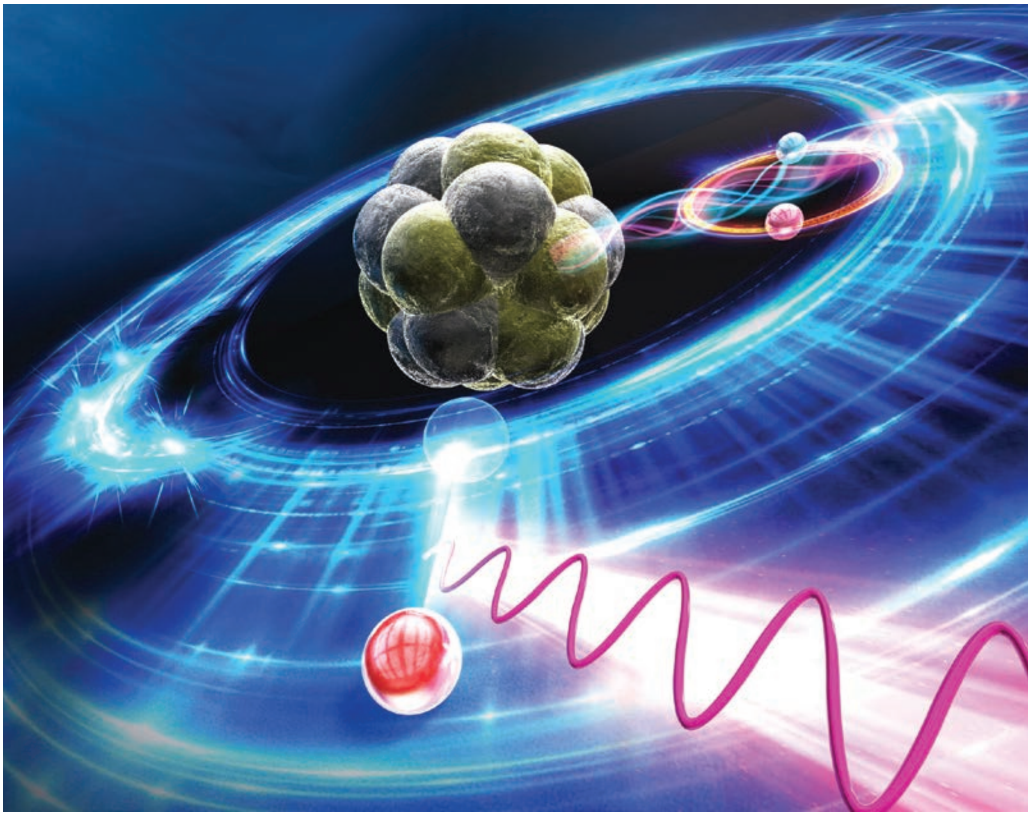
QUANTUM ELECTRODYNAMICS

Quantum electrodynamics passes high-field test

A quantum theory of electrodynamics is accurate even at the very high electric fields of exotic atoms



A conceptual image depicting a muonic neon atom and quantum electrodynamic (QED) effects.

Quantum electrodynamics (QED) is a quantum theory describing the interaction of charged particles with electromagnetic fields. By creating special atoms, RIKEN physicists have tested what happens to—when the electric field is ramped up[1]. The demonstration opens the possibility of using the exotic atoms to perform further experiments at high fields.

QED is a highly successful theory that combines two pillars of modern physics—special relativity and quantum physics. The quantum equivalent of classical electromagnetics formulated by James Maxwell, QED was developed by some of the greatest minds of 20th century physics, including Richard Feynman, Julian Swinger and Shinichiro Tominaga.

So far it has passed every test thrown at it over the last 70 years with flying colors. But most experiments have been performed at low electric fields. Physicists are keen to discover if QED's untarnished record extends into high fields, especially since theoretical calculations become much harder to perform in this region.

"QED has not been well verified at all in the high-field regime of x-rays," notes Toshiyuki Azuma of the RIKEN Atomic, Molecular and Optical Physics Laboratory.

But since these high fields go beyond those that exist in normal atoms, such measurements have been challenging to perform.

Now, to test QED in the high-field regime, Azuma and his co-workers have performed high-precision measurements on special neon atoms, which they made using the facilities at the Japan Proton Accelerator Research Complex (J-PARC).

To create the atoms, the team stripped off all their electrons by adding a muon—a subatomic particle that has the same negative charge as an electron, but is about 207 times heavier. This larger mass means that the muon resides much closer to the atom's nucleus and thus experiences a much greater electric field from the protons in the nucleus.

Measurements of x-rays emitted by these atoms agreed well with values predicted by QED. While QED lives to see another test, the real value of the experiments was their demonstration of the usefulness of muonic atoms for probing high-field QED.

Both the measurements and the subsequent analysis were demanding. "Two things enabled us to succeed in performing this measurement," Azuma says. "One is we had highly sensitive detectors and the other is we had access to intense, low-energy muon beams that are only available in Japan right now." He notes that the detectors were originally developed for an x-ray satellite for astronomical observations. "It was also quite tough to analyze the results," Azuma adds. "We needed more than two years." ●

Reference

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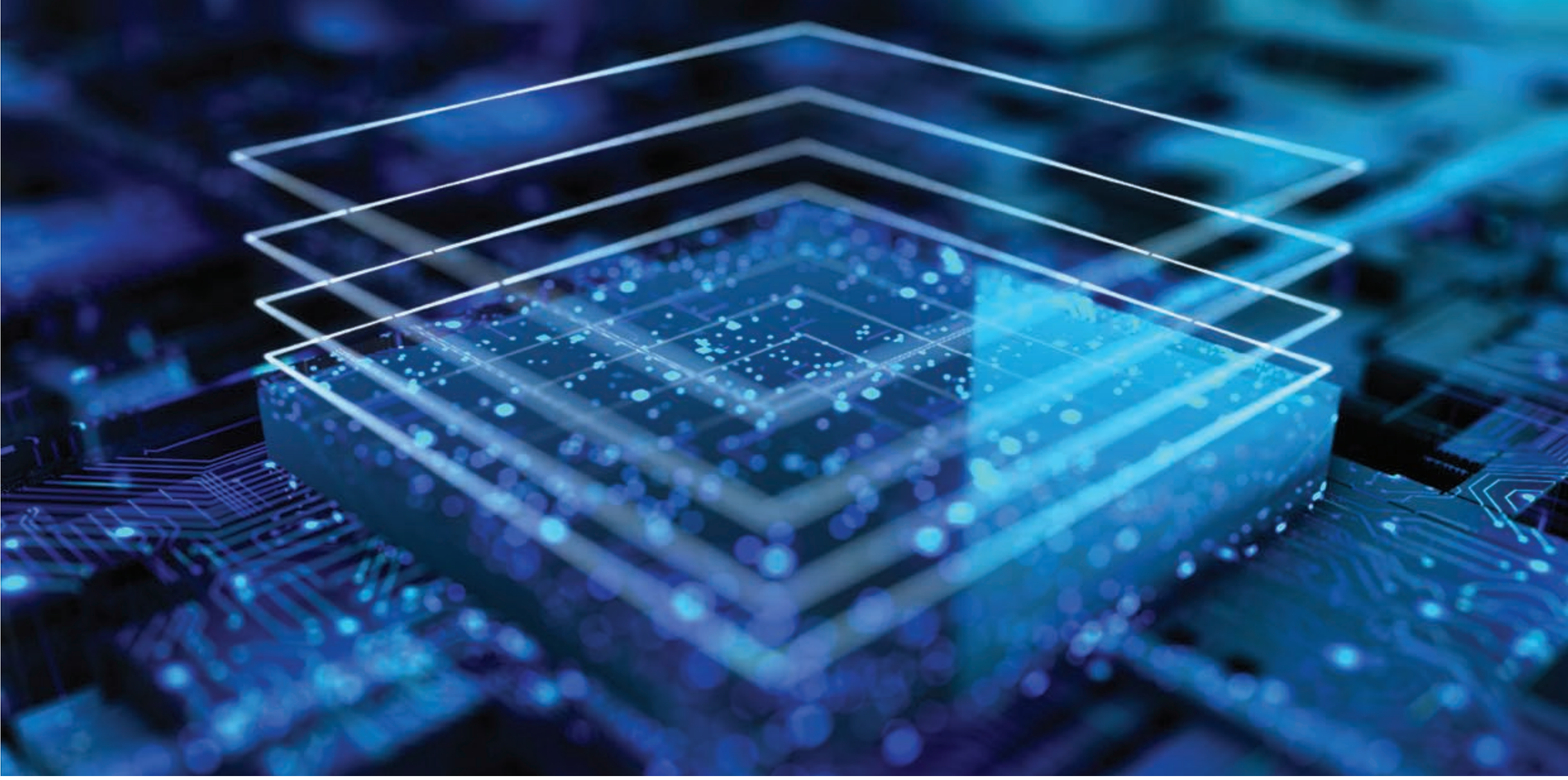

RIKEN researchers have used machine learning to help correct errors in quantum computers.

QUANTUM COMPUTING

Machine learning realizes better quantum error correction

Harnessing machine learning helps to correct errors that develop in quantum computers

In a step toward realizing practical quantum computers, RIKEN researchers have demonstrated that machine learning can be used to perform error correction for quantum computers[1].

Classical computers perform operations using bits, which can take the values 0 and 1. In contrast, quantum computers use qubits, which can assume any superposition of these two states. When combined with quantum entanglement—a quantum way of linking distant objects—qubits enable quantum computers to perform entirely new operations. This gives them a potential advantage over conventional computers for some tasks, such as large-scale searches, optimization and cryptography.

The main hurdle to realizing quantum computers for practical applications is the extremely fragile nature of quantum superpositions. Tiny perturbations from the environment can generate errors that rapidly destroy quantum superpositions.

To tackle this problem, sophisticated methods for quantum error correction have been developed. While they can, in theory, neutralize the effect of errors, they often greatly increase device complexity, which itself is error prone and thus potentially even increases exposure to errors. Consequently, full-fledged error correction has remained elusive.

Now, a team led by Franco Nori of the RIKEN Center for Quantum Computing (RQC) has leveraged machine learning in a search for error-correction schemes that minimize the device overhead while maintaining good error-correction performance.

The team adopted an autonomous approach to quantum error correction, where a cleverly designed, artificial environment replaces the need to perform frequent measurements to detect errors.

They also looked at 'bosonic qubit encodings', which are, for instance, available and utilized in some of the currently most promising and widespread quantum-computing machines based on superconducting circuits.

Finding high-performing candidates in the vast search space of bosonic qubit encodings was a complex optimization task. The team addressed this problem by using reinforcement learning, an advanced machine learning method in which an agent explores a possibly abstract environment to learn and optimize its action policy.

Using this approach, the team found a surprisingly simple, approximate qubit encoding that could not only greatly reduce the device complexity compared to other proposed encodings, but that also outperformed its competitors in terms of its ability to correct errors.

"Our work not only demonstrates the potential for deploying machine learning towards quantum error correction, but it may also bring us a step closer to the successful implementation of quantum error correction in experiments," says Yexiong Zeng, also of the RQC.

"Machine learning can play a pivotal role in addressing large-scale quantum computation and optimization challenges," says Nori. "Currently, we are actively involved in a number of projects that integrate machine learning, artificial neural networks, quantum error correction, and quantum fault tolerance."

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DIABETES

Bacteria treatment reduces insulin resistance in mice

A species of gut bacteria can reduce insulin resistance in mice, making it promising for protecting against type 2 diabetes

A type of gut bacteria that helps reduce insulin resistance in obese mice has been identified by RIKEN researchers[1]. It might protect people against the development of obesity and type 2 diabetes.

Insulin is a hormone released by the pancreas in response to blood sugar. Normally, it helps transfer the sugar into the muscles and liver so that they can use the energy.

But insulin becomes less effective in people who develop insulin resistance. Insulin resistance can lead to obesity, pre-diabetes and type 2 diabetes.

"The presence of gut Lachnospiraceae bacteria could be a good biomarker for pre-diabetes"

Our guts contain trillions of bacteria, many of which break down carbohydrates we eat. This phenomenon is likely to be related to obesity and pre-diabetes, but it has been difficult to verify because of the sheer variety of bacteria and a lack of metabolic data.

Now, a team led by Hiroshi Ohno at the RIKEN Center for Integrative Medical Sciences has discovered a type of bacteria that might help reduce insulin resistance.

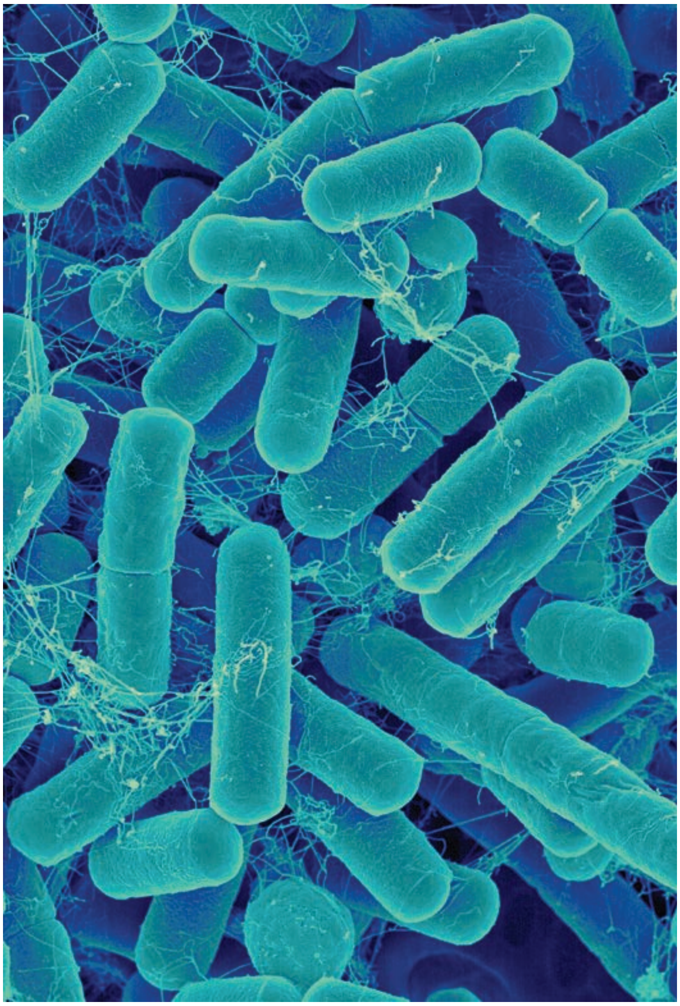
The team examined all the metabolites they could detect in the feces from over 300 adults, and they compared this metabolome with the insulin-resistance levels of the same people.

"We found that higher insulin resistance was associated with excessive carbohydrates in the fecal matter, especially monosaccharides," says Ohno.

The team characterized the gut microbiota of the participants and their relationship with insulin resistance and fecal carbohydrates. People with higher insulin resistance had more bacteria from one taxonomic order than from others in their guts. Additionally, gut microbiomes dominated by Lachnospiraceae were related to both insulin resistance and feces with excessive monosaccharides.

In contrast, insulin resistance and monosaccharide levels were lower in the guts of people that contained more Bacteroidales-type bacteria than other types.

The team then investigated the direct effect of bacteria on metabolism in culture and mice. In culture, Bacteroidales bacteria consumed the same kinds of monosaccharides as those found in the feces of people with high insulin resistance. The species



Bacteroidales bacteria consume the same types of monosaccharides as those found in the feces of people with high insulin resistance, a RIKEN team has found.

Alistipes indistinctus consumed the greatest variety.

Administering obese mice with *A. indistinctus* lowered their blood sugar levels, reduced insulin resistance and decreased the amount of fecal monosaccharides available.

These results have implications for the diagnosis and treatment of diabetes. "Because of its association with insulin resistance, the presence of gut Lachnospiraceae bacteria could be a good biomarker for pre-diabetes," says Ohno. "Likewise, treatment with probiotics containing *A. indistinctus* might reduce glucose intolerance in those with pre-diabetes."

But Ohno urges caution in the case that such probiotics become available over the counter. "These findings need to be verified in human clinical trials before we can recommend any probiotic as treatment for insulin resistance." ●

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ANOMALOUS HALL EFFECT

Anomalous Hall effect explained mathematically

A unifying description for the curving path of electrons in some magnetic materials has been derived

A mysterious magnetic effect that causes the path that electrons take through a material to bend—called the anomalous Hall effect—has been elucidated in a new mathematical analysis by two RIKEN physicists[1].

First discovered nearly a century and a half ago by American physicist Edwin Hall, the conventional Hall effect is a well-understood electrical and magnetic phenomenon. When an electric field alone is applied to a conducting material, the electrons will move in a straight line that is parallel to that field. But when a magnetic field is added too, it causes the electrons' path to curve.

The anomalous Hall effect is a related phenomenon that happens in some magnetic materials. In this case, no external magnetic field needs to be applied since the material supplies the magnetic field.

But the cause of the anomalous Hall effect seems to vary between materials. "The difficulty is that there are many possible mechanisms but no unifying explanation," says Hiroki Isobe of the RIKEN Center for Emergent Matter Science, who co-authored the analysis with RIKEN colleague Naoto Nagaosa. "This makes it very complicated, even for specialists."

The physicists' goal was to simplify this by finding an underlying explanation for all materials that display the anomalous Hall effect.

Following a mathematical analysis of the description of the energy of systems in which the effect occurs, the pair found a commonality based on two quantum features.

The first important quantum idea is that electrons can behave like both particles and waves. However, the wave-like nature of electrons can easily be disturbed as they move through the material, especially when they hit impurities and scatter in a different direction. The time it takes before this disruption happens is called the electron's lifetime.

The second relevant quantum feature is an internal magnetic property of electrons, called spin, which can point in one of two directions, up or down. Isobe and Nagaosa noted that in materials that display the anomalous Hall effect, electrons with a spin pointing up have a different lifetime to those with a spin pointing down. In particular, the pair has now demonstrated how this difference is captured mathematically in the energy description of such systems. "This provides a renewed perspective on the problem," says Isobe.

Isobe's goal for the future is to apply this mathematical description to real-world experiments. "Is this renewed perspective really useful for explaining real materials?" Isobe asks. "That's the next question to address."

Reference

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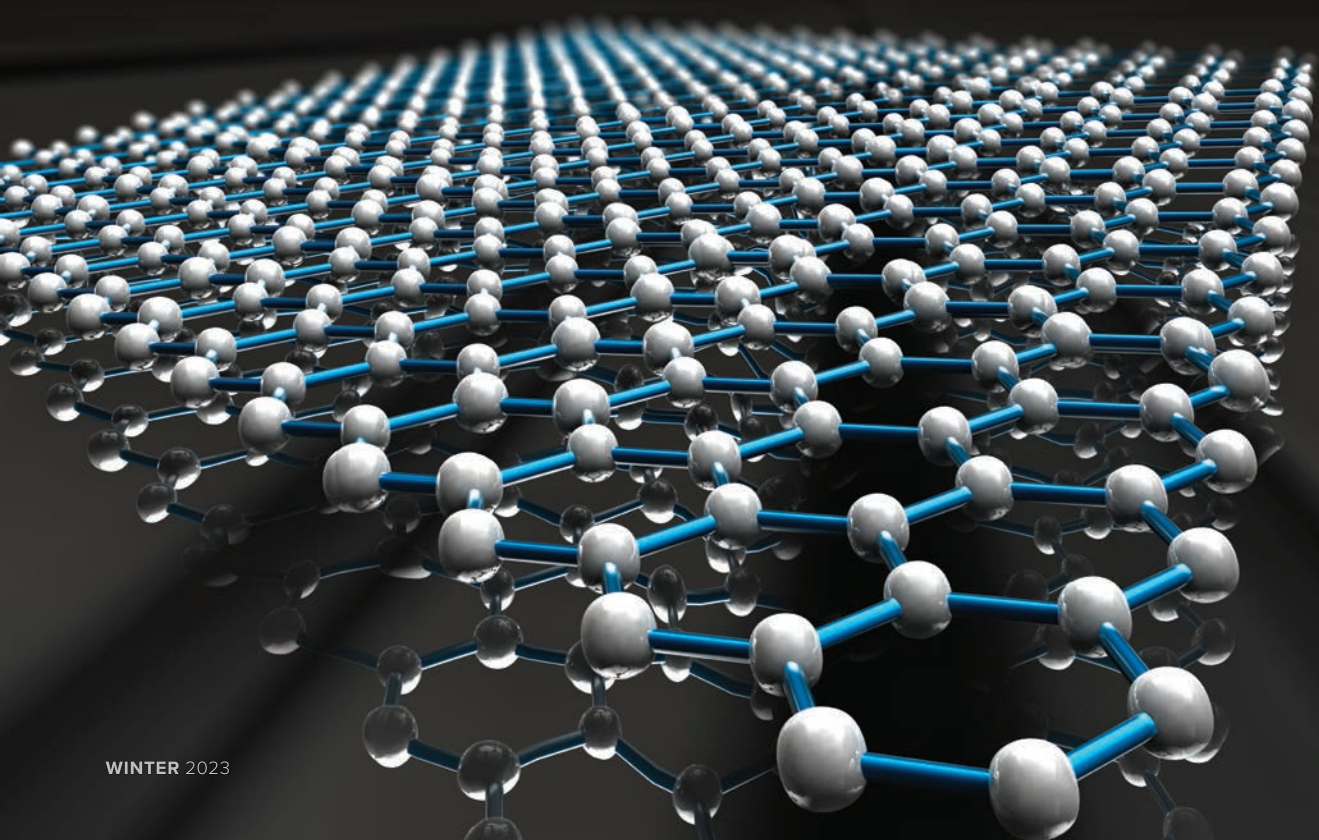
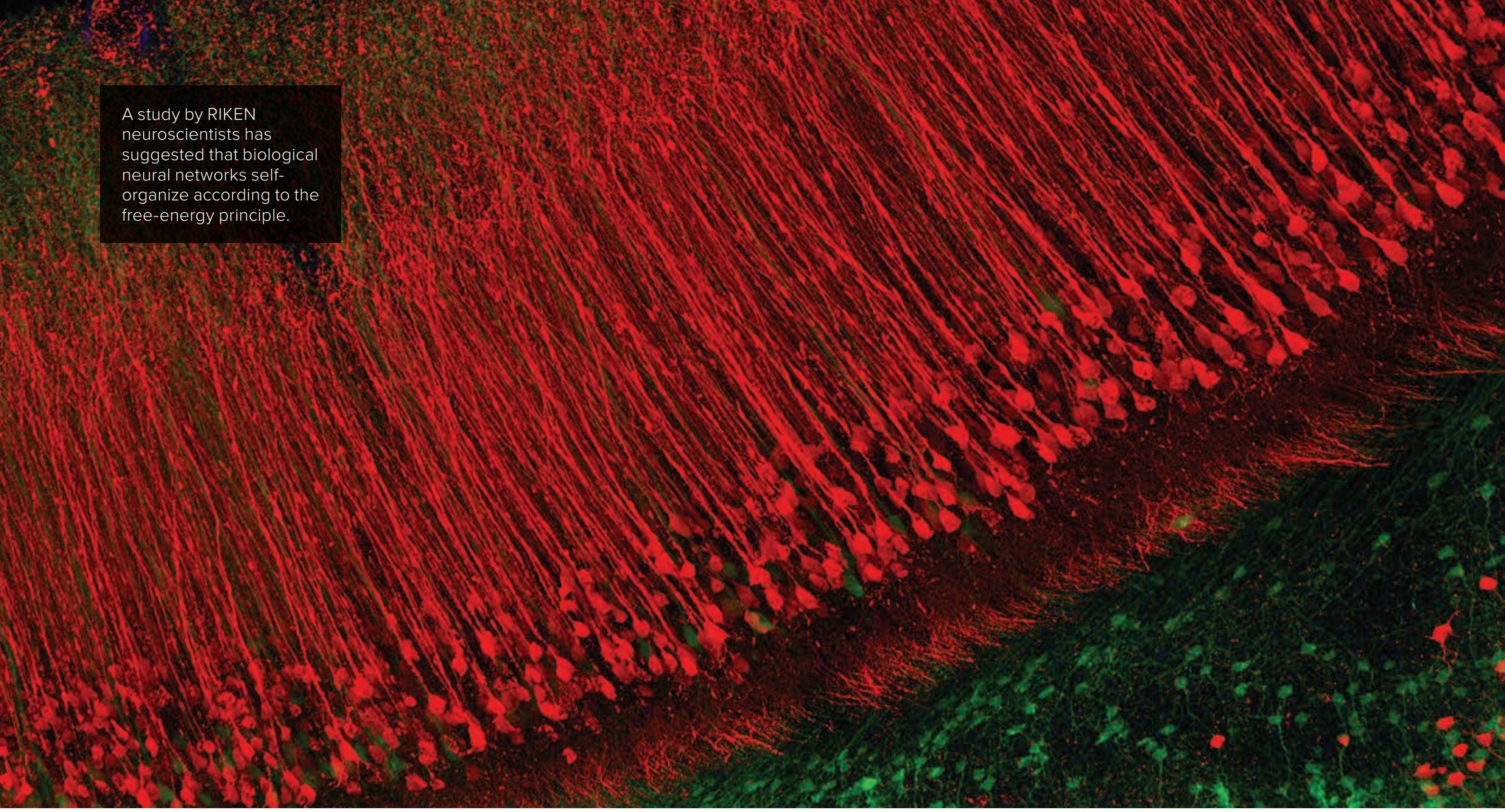


The anomalous Hall effect has been demonstrated in materials such as graphene (pictured).



A study by RIKEN neuroscientists has suggested that biological neural networks self-organize according to the free-energy principle.

COMPUTATIONAL NEUROSCIENCE

How neurons in the brain minimize their free energy

Self-organization of neurons, which underpins learning, is found to minimize the free energy of the system

RIKEN researchers have demonstrated that the self-organization of neurons as they learn follows a mathematical theory called the free-energy principle[1]. This finding has implications for developing animal-like artificial intelligences and for understanding cases of impaired learning.

When we learn to tell the difference between voices, faces or smells, networks of neurons in our brains automatically organize themselves. This process involves changing the strength of connections between neurons, and is the basis of all learning in the brain.

Recently, Takuya Isomura of the RIKEN Center for Brain Science and his colleagues predicted that this type of network self-organization follows the free-energy principle, which states that this self-organization will always minimize the system's free energy.

Now, Isomura's team has tested this hypothesis in neurons taken from the brains of rat embryos and grown in a culture dish on top of a grid of tiny electrodes.

Once you can distinguish two sensations, like voices, some of your neurons will respond to one of the voices, while others will respond to the other voice. This is the result of neural network reorganization, which underpins learning.

In their culture experiment, the researchers mimicked this process by using the grid of electrodes beneath the neural network to stimulate the neurons in a specific pattern that mixed two hidden sources. After 100 training sessions, the neurons automatically became selective—some responding very strongly to source 1 and very weakly to source 2, and others responding in the reverse.

Adding drugs prior to the experiment that raise or lower neuron excitability disrupted the learning process, indicating that the cultured neurons do just what neurons are thought to do in the working brain.

To determine whether this principle is the guiding force behind neural network learning, the team used the real neural data to reverse engineer a predictive model based on it. They then fed the data from the first 10 electrode training sessions into the model and used it to make predictions about the next 90 sessions.

At each step, the model accurately predicted the responses of neurons and the connectivity strength between neurons. Thus, simply knowing the initial state of the neurons is enough to determine how the network will change over time as learning occurs.

"Our results suggest that the free-energy principle is the self-organizing principle of biological neural networks," says Isomura.

"Ultimately, our technique will allow modeling the circuit mechanisms of psychiatric disorders and the effects of drugs such as anxiolytics and psychedelics," says Isomura. "Generic mechanisms for acquiring the predictive models can also be used to create next-generation artificial intelligences that learn as real neural networks do."

Reference

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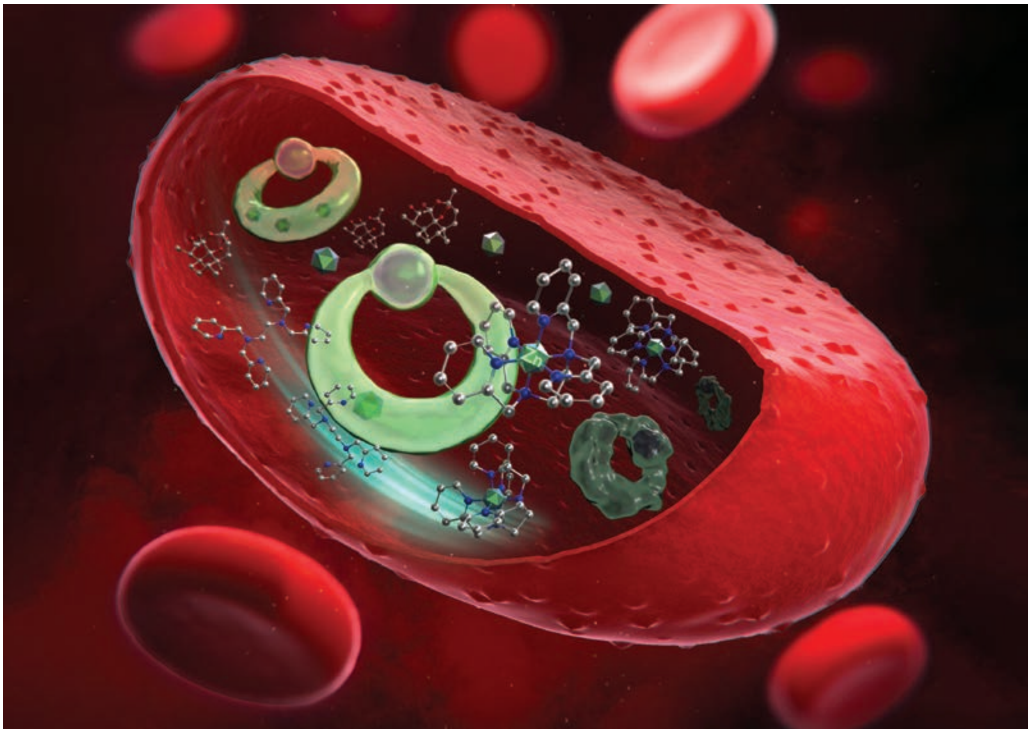
ANTIMALARIALS

Unraveling the action of an antimalarial drug

The discovery of how an antimalarial affects zinc levels in parasites could help combat drug resistance



A conceptual image showing *Plasmodium falciparum* (light green rings), the deadliest parasite that causes malaria in people, inside a red blood cell. RIKEN researchers have discovered how an antimalaria drug affects zinc levels in the parasite.

The crucial role of zinc depletion in the action of a key antimalarial drug against the deadliest malaria parasite has been uncovered by a team led by RIKEN researchers[1]. This finding provides valuable insights for developing new drugs against the disease.

Malaria poses a significant threat to nearly half of the world's population, with about 247 million people contracting the disease and nearly 620,000 lives lost in 2021 alone. While worldwide efforts against the disease had been made over the last two decades, malaria is on the rebound, with a sharp uptick in the past few years.

The antimalarial artemisinin and its derivatives (ARTs) are commonly used for a first-line treatment, usually in combination with other drugs, against infections of *Plasmodium falciparum*—the deadliest parasite that causes malaria in people. However, the recent emergence of artemisinin-resistant strains in South East Asia and southern Africa has raised serious concerns.

"In this context, there's an urgent need to develop new antimalarial drugs with mechanisms of action that are different from those of existing drugs, and to advance artemisinin-based combination therapy," says Akira Wada of the RIKEN Center for Biosystems Dynamics Research.

However, the underlying mechanism for how ARTs inhibit the growth of the malaria parasite had been unclear.

Now, Wada and his co-workers have discovered that the artemisinin derivative dihydroartemisinin (DHA) induces pyknosis, a state of developmental arrest, in *P. falciparum* in red blood cells. This effect was accompanied by decreased concentration of glutathione—a key component in the parasite's ability to tolerate oxidative stress.

"To gain a deeper understanding of the mechanism of action of DHA, we aimed to identify additional molecular factors that induce growth inhibition of *P. falciparum* through pyknosis," says Wada.

By analyzing the gene expression of *P. falciparum* treated with antimalarials, the team discovered a reduction of zinc-associated proteins following exposure to DHA. Measuring zinc levels in DHA-treated parasites revealed zinc depletion.

Disrupting zinc homeostasis enhanced the antimalarial action of DHA following pyknosis. Furthermore, the disrupted zinc and glutathione homeostasis synergistically resulted in parasite growth inhibition.

The findings provide valuable insights into the molecular processes that underpin the effectiveness of ART-based therapies. "They shed light on the antimalarial action of DHA, providing important clues for completely elucidating the underlying mechanisms of action of ARTs," says Wada.

This knowledge holds promise for developing novel strategies to combat drug-resistant malaria. "The development of specific compounds controlling zinc levels in *P. falciparum* can be expected to produce new companion drugs for enhancing the antimalarial activity of ARTs," notes Wada.

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EPIGENETICS

DNA's backup plan for genomic stability

Complementary epigenetic pathways safeguard against DNA failures that could lead to problems in gene regulation and stability

Complementary epigenetic pathways preserve the integrity of chromosomes by maintaining the form of heterochromatin.

The proper functioning of an important architectural component of our DNA, known as heterochromatin, is maintained by at least two pathways that can substitute for one another when either is lost, RIKEN researchers have found[1]. This finding provides a remarkable insight into how these complex biological systems include redundancy to keep our cells healthy.

Mammalian genomes are complex systems that require a wide variety of chemical tags known as epigenetic modifications to function properly. Heterochromatin—a tightly packed form of primarily genetically inactive DNA that is associated with gene repression and chromosome integrity—exists in large, condensed compartments, wrapped around histone proteins that are studded with such epigenetic modifications.

Kei Fukuda from the RIKEN Cellular Memory Laboratory and his colleagues have been studying this histone modification, known as the histone H3 lysine 9 trimethylation (H3K9me3) pathway, for some time.

Suspecting that this pathway is essential for the proper spatial organization and compaction of heterochromatin, the team decided to see what would happen when it was lost. They engineered mouse cells that lacked the five methyltransferase proteins responsible for the methylation pathway.

"Surprisingly, chromatin compaction and nucleus spatial organization remained largely unchanged in these cells," says Fukuda.

They saw that another kind of epigenetic modification, H3K27me3, which is usually seen on different parts of the chromosome, was redistributed to places where H3K9me3 is usually observed (mostly the centromeres and telomeres). This maintained the proper organization of the heterochromatin.

Only when the researchers also blocked the H3K27me3 methyltransferases did the heterochromatin lose its spatial organization, leading to chromosome instabilities and abnormal gene expression. Even then, some regions of the genome were able to maintain their heterochromatin, suggesting there is at least one more epigenetic pathway that plays a role in heterochromatin maintenance.

"We thought H3K9 methylation was the main factor for maintaining heterochromatin organization," says Fukuda. "But we found that it wasn't essential—other chromatin modifications function in a redundant way to maintain heterochromatin."

Heterochromatin anomalies are seen in many diseases, including cancer and brain diseases, as well as during aging. In fact, decreased H3K9me3 and the redistribution of H3K27me3 have been seen before in aging cells, says Fukuda, although how the two are related is largely unknown.

This work could help to advance our knowledge in that area, Fukuda says. "Using our cells can help to address those questions about chromatin redistributions and redundant mechanisms of heterochromatin organization in aging or other diseases," he says. ●

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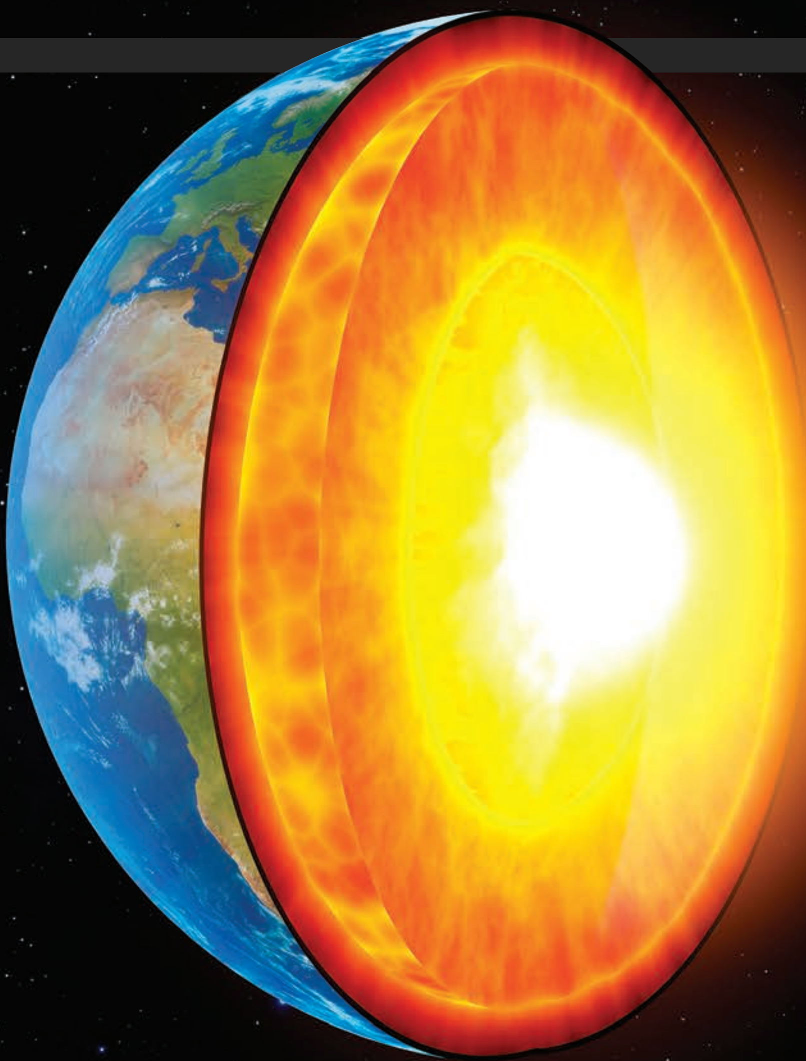

RIKEN researchers have found that the Earth's core may contain twice as much light material than previously thought.

GEOPHYSICS

Earth has more light material in its core

The Earth's core may contain twice as much light material than previously thought, according to a new pressure scale

RIKEN researchers have determined a new pressure scale, which has major implications for our understanding of the Earth's composition[1]. They discovered that the previous scale overestimated lab pressures by about 20% at pressures found in the Earth's core.

The composition of the Earth's core, which is important for understanding both our planet at present and the past evolution of the Solar System, is hotly debated. While it is generally accepted that the core is mostly iron, evidence from measurements of seismic waves generated by earthquakes suggests the core also contains lighter elements.

A key parameter in determining the composition of the Earth's core is the pressure, but it is difficult to accurately measure the pressure in laboratory experiments.

Now, by using inelastic x-ray scattering to measure the velocity of sound in a sample of the element rhenium under pressure, a collaboration initiated 15 years ago by Alfred Baron of the RIKEN SPring-8 Center has established an accurate way to measure pressures in the lab.

A tiny rhenium sample was subjected to extreme pressure by crushing it between two diamond crystals in a diamond anvil cell. The cell was placed in the inelastic x-ray scattering spectrometer at the RIKEN Quantum NanoDynamics beamline (BL43LXU) of SPring-8 and small shifts in the energy of x-rays scattered from the rhenium sample were measured, allowing the researchers to ascertain how fast sound traveled in it. From that measurement, and knowledge of the density, the researchers calculated the pressure the rhenium sample was subjected to.

The new pressure scale provided some surprises. When it was used to interpret the behavior of metallic iron under pressure and the results compared with the seismic model of the Earth, they found that the light material hidden in the inner core is probably about double what was previously expected.

This has implications for the interiors of other planets. Similar changes, perhaps even larger in magnitude, may be expected in considering the structure of other planets.

Other scientists stand to benefit from this establishment of a direct relationship between rhenium density and pressure since it allows them to determine the pressure from the density, which is much easier to measure. "The density of rhenium at high pressure is straightforward and fast to measure, and many facilities worldwide can make such measurements," explains Baron. "However, measuring the sound velocity is much more difficult, and, at these pressures, is probably only feasible using RIKEN's spectrometer at SPring-8's BL43LXU."

Reference

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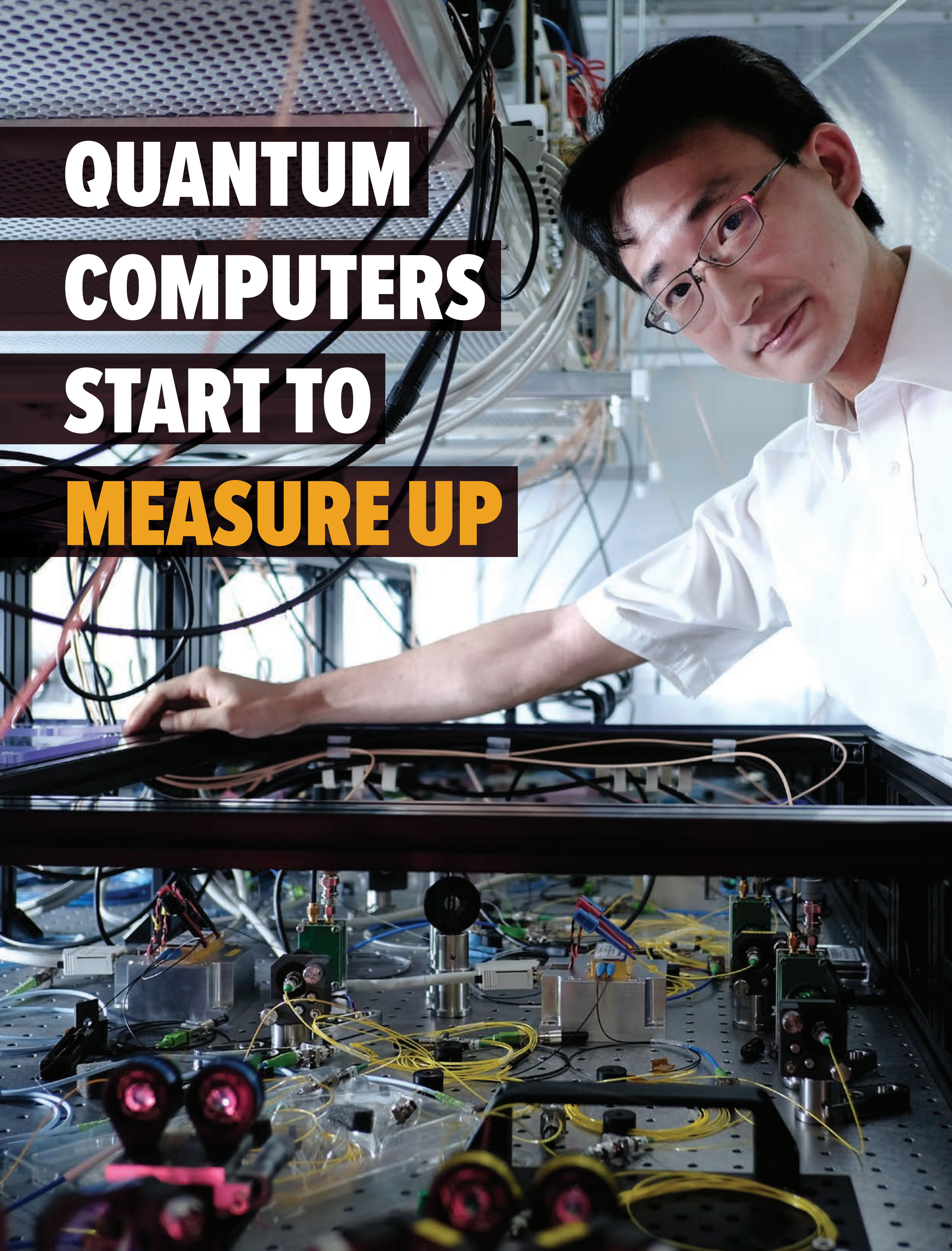
QUANTUM COMPUTERS START TO MEASURE UP



Atsushi Sakaguchi and his team are exploring the possibility of using light to produce quantum computers that are measurement based rather than gate based.

An alternative approach to quantum computers that stores and processes information as light could enable reprogrammable systems.

This feature looks **at the work of** **ATSUSHI SAKAGUCHI**

Atsushi Sakaguchi completed his PhD under the supervision of Akira Furusawa at the University of Tokyo in 2021. He then joined his current team, the Optical Quantum Computing Research Team at the RIKEN Center for Quantum Computing. Here he works on experimental quantum optics and quantum information research. He is currently collaborating on research into classical operations for quantum computing.

The race to develop quantum computers has really heated up over the past few years. State-of-the-art systems can now run simple algorithms using dozens of qubits—or quantum bits—which are the building blocks of quantum computers.

Much of this success has been achieved in so-called gate-based quantum computers. These computers use physical components, most notably superconducting circuits, to host and control the qubits. This approach is quite similar to conventional, device-based classical computers. The two computing architectures are thus relatively compatible and could be used together. Furthermore, future quantum computers could be fabricated by harnessing the technologies used to fabricate conventional computers.

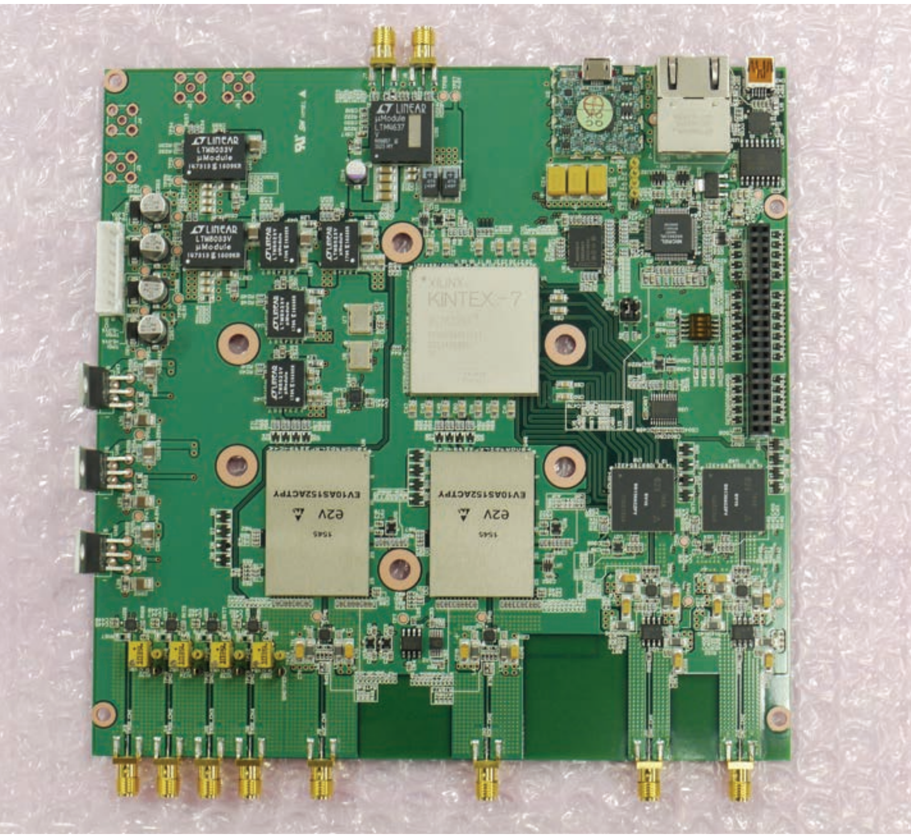
But the Optical Quantum Computing Research Team at the RIKEN Center for Quantum Computing has been taking a very different approach. Instead of optimizing gate-based quantum computers, Atsushi Sakaguchi, Jun-ichi Yoshikawa and Team Leader Akira Furusawa have been developing measurement-based quantum computing.

MEASUREMENT-BASED COMPUTING

Measurement-based quantum computers process information in a complex quantum state known as a cluster state, which consists of three (or more) qubits linked together by a non-classical phenomenon called entanglement. Entanglement is when the properties of two or more quantum particles remain linked, even when separated by vast distances.

Measurement-based quantum computers work by making a measurement on the first qubit in the cluster state. The outcome of this measurement determines what measurement to perform on the second entangled qubit, a process called feedforward. This then determines how to measure the third. In this way, any quantum gate or circuit can be implemented through the appropriate choice of the series of measurements.

Measurement-based schemes are very efficient when used on optical quantum computers, since it's easy to entangle a large number of quantum states in an optical system. This makes a measurement-based quantum computer potentially more scalable than a gate-based quantum computer. For the latter, qubits need to be precisely fabricated and tuned for



Gate-based quantum computers are becoming more common. But the Optical Quantum Computing Research Team at the RIKEN Center for Quantum Computing has been developing measurement-based quantum computing, with digital circuitry for electrical-optical control (pictured). Measurement-based systems are potentially more scaleable than gate-based quantum computing.

uniformity and physically connected to each other. These issues are automatically solved by using a measurement-based optical quantum computer.

Importantly, measurement-based quantum computation offers programmability in optical systems. “We can change the operation by just changing the measurement,” says Sakaguchi. “This is much easier than changing the hardware, as gated-based systems require in optical systems.”

But feedforward is essential. “Feedforward is a control methodology in which we feed the measurement results to a different part of the system as a form of control,” explains Sakaguchi. “In measurement-based quantum computation, feedforward is used to compensate for the inherent randomness in quantum measurements. Without feedforward operations, measurement-based quantum computation becomes probabilistic, while practical quantum computing will need to be deterministic.”

The Optical Quantum Computing Research Team and their co-workers—from the The University of Tokyo, Palacký University in the Czech Republic, the Australian National University and the University of New South Wales, Australia—have now demonstrated a more advanced form of feedforward: nonlinear feedforward.[1] Nonlinear feedforward is required to implement the full range of potential gates in optics-based quantum computers.

“We’ve now experimentally demonstrated nonlinear quadrature measurement using a new nonlinear feedforward technology,” explains Sakaguchi. “This type of measurement had previously been a barrier to realizing universal quantum operations in optical measurement-based quantum computation.”

OPTICAL COMPUTERS

Optical quantum computers use qubits made of wave packets of light. At another institutions, some of the current RIKEN team had previously constructed the large optical cluster states needed for measurement-based quantum computation.[2] Linear feedforward has also been achieved to construct simple gate operations, but more advanced gates need nonlinear feedforward.

A theory for practical implementation of nonlinear quadrature measurement was proposed in 2016.[3] But this approach presented two major practical difficulties: generating a special ancillary state (which the team achieved in 2021[4]) and performing a nonlinear feedforward operation.

The team overcame the latter challenge with complex optics, special electro-optic materials and ultrafast electronics. To do this they exploited digital memories, in which the desired nonlinear functions were precomputed and recorded in the memory. “After the measurement, we transformed the optical signal into an electrical one,” explains Sakaguchi. “In linear feedforward, we just amplify or attenuate that signal, but we needed to do much more complex processing for nonlinear feedforward.”

The key advantages of this nonlinear feedforward technique are its speed and flexibility. The process needs to be fast enough that the output can be synchronized with the optical quantum state.

“Now that we have shown that we can perform nonlinear feedforward, we want to apply it to actual measurement-based quantum computation and quantum error correction using our previously developed system,” says Sakaguchi. “And we hope to be able to increase the higher speed of our nonlinear feedforward for high-speed optical quantum computation.”

“But the key message is that, although superconducting circuit-based approaches may be more popular, optical systems are a promising candidate for quantum-computer hardware,” he adds.

REFERENCES

For a full list of references, check the online version of this article: www.riken.jp/en/news_pubs/research_news/

TURNING THE TABLES ON WEATHER FORECASTING

With unprecedented supercomputing power, new data and AI, we are on the threshold of highly accurate weather prediction —and maybe even control, explains Takemasa Miyoshi. ➜

RIKEN researchers have been using infrared images from Japan's Himawari-8/9 geostationary satellites (pictured) to develop a system to provide flood and river discharge warnings. By assimilating the satellite images every 10 minutes, the team have shown they can monitor rapidly changing severe weather.

The basic equations used in meteorology have remained fundamentally unchanged since they were developed by Norwegian physicist Vilhelm Bjerknes in the early 1900s, based on calculations of atmospheric dynamics. Progress in weather prediction since then has principally been in the enormous expansion of weather monitoring resources around the world and in the supercomputers we use to solve the equations that use this influx of data.

We also now have the ability to combine newer observation technologies, including ground-based radar, satellite imagery and meteorological readings, to give an incredibly accurate snapshot of current conditions across most parts of the world. So the true challenge of weather prediction today is assimilating all of that data and running sufficient numbers of simulations quickly enough to enable timely prediction updates.

At the RIKEN Center for Computational Science, we are fortunate to have access to the Fugaku supercomputer, one of the most powerful computing facilities in the world. Using even a small fraction of Fugaku's power has allowed us to demonstrate what is possible at the cutting edge of weather prediction science.

AN OLYMPIC DEMONSTRATION

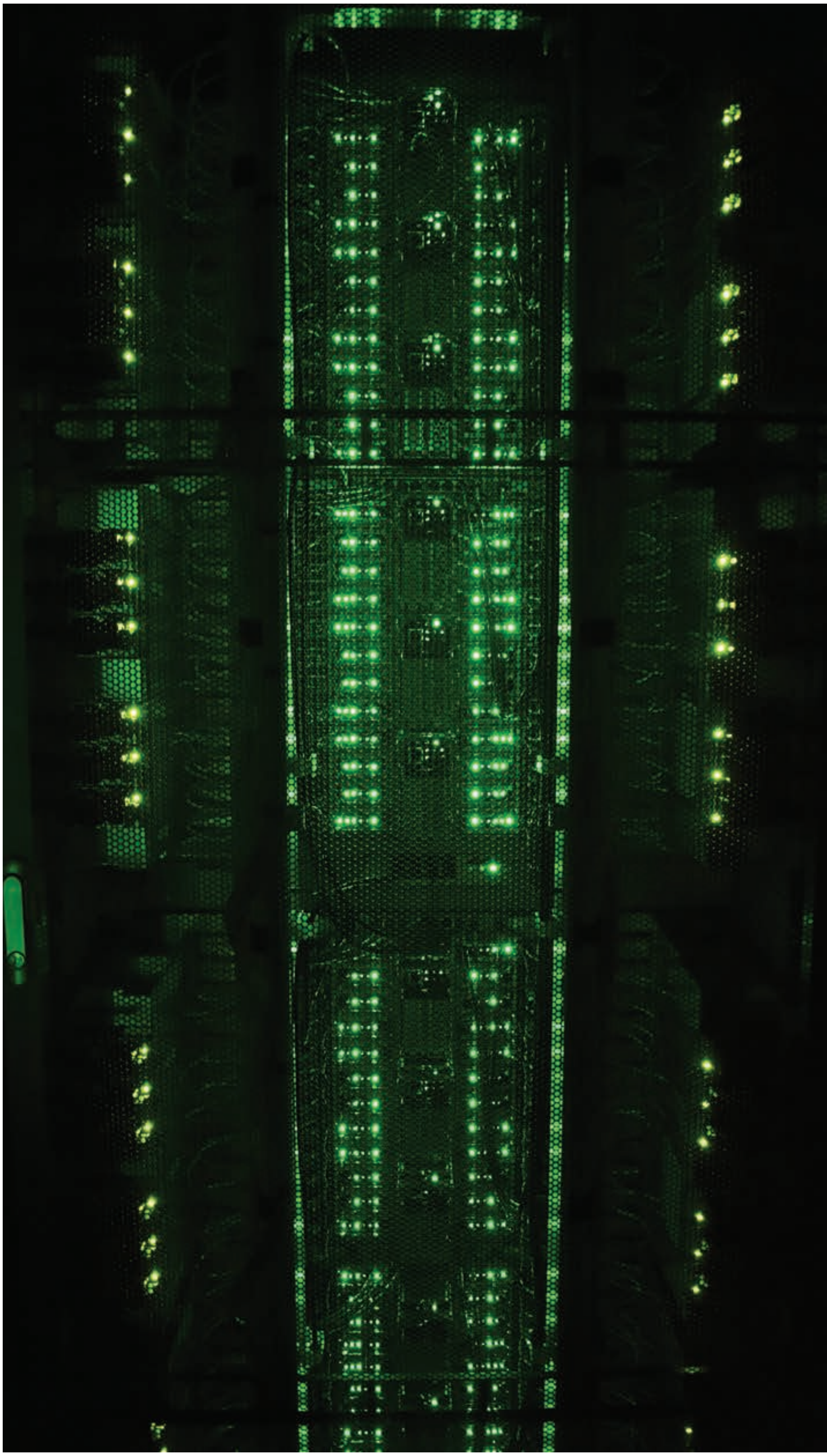
For the 2020 summer olympics, and paralympics, held in Tokyo in 2021 due to the COVID-19 pandemic, our group collaborated with researchers from other Tokyo institutions to develop a software system to move data from an advanced radar system direct to Fugaku, in order to deliver high-resolution coverage of the region within three seconds.

Working with computer scientists, we developed software that exploited Fugaku's full power by tailoring the data interconnections among its processing nodes to optimize computational speed.

Using just 7% of the available processing nodes, we were able to assimilate data from the radar and complete 1,000 parallel 'ensemble' simulations in just 15 seconds, allowing for a weather prediction update every 30 seconds.

The ensemble simulation approach is how we account for uncertainty in our predictions. We take the current set of observations and run multiple simulations with slight variations to the initial conditions and model a number of assumptions to generate multiple scenarios. The challenge for this olympic project was creating a computational environment that allowed us to complete the 1,000 simulations in the ensemble in an extremely short time period.

What was really groundbreaking about this prediction system was modeling the development of small individual 'convective clouds' for the first time. These are billowing, tall, rain-bearing clouds that form



In 2021, the Fugaku supercomputer (pictured) was used to complete 1,000 parallel high-resolution weather simulations in 15 seconds, allowing a Tokyo weather update every 30 seconds.

quickly when warm humid air rises through cooler surrounding air, typically in humid conditions.

Usually, the resolution of weather models is in the order of kilometers. But the resolution needed to model convective clouds is smaller than this. Weather models are also often only updated hourly, while these clouds can form, dissipate and evolve significantly in just minutes.

Our system, which ran for the duration of the olympics and paralympics, generated a 3D model of convective clouds every 30 seconds, and predicted the evolution and rain for the following half an hour. The model was accessible on a smartphone app developed with a partner for this purpose.

This demonstration showed the power of what is now possible using the latest technology, and it has been recognized by our nomination as a finalist for the 2023 Gordon Bell Prize for Climate Modelling. This prize is awarded annually by the world's largest computing association, the Association for Computing Machinery, to recognize outstanding achievement in high-performance computing.[1]

We have also been working on early warning of flood risk, flood development and river discharge with the integration of data from Japan's Himawari-8/9 geostationary satellites. These satellites capture regular infrared images covering the entirety of Japan. By assimilating this data every 10 minutes, we have shown that it is possible to monitor the flood risk associated with rapidly changing severe weather.[2]

Not only can this data provide warning of floods, it can improve the analysis of moisture transport and modeling of strong precipitation bands in the models we use for prediction.

AI EFFICIENCY

One of the problems with our current ensemble simulation approach for weather prediction is that it is computationally intensive and requires nationally-supported infrastructure to be available to the public. This type of investment is not possible in many countries.

Even in Japan, the current operational weather prediction run by the Japan Meteorological Agency is updated once every hour at a two-kilometer resolution and uses a relatively limited dataset. Upgrading this operational system to something like our olympic demonstration would require further investment in infrastructure and a permanent tenancy on Fugaku.

We are beginning to turn our attention to AI as a potentially more efficient and accessible platform for weather prediction. Could an AI model running on a single desktop graphics processing unit (GPU) predict the weather with comparable accuracy to what we currently achieve using supercomputers?

This is a very important question that is being explored. But we still need data—AI is only as good as the data it is trained on—but assuming we can train an AI model on a sufficiently large and complete dataset, we believe this revolution could be possible and would put sophisticated prediction in the hands of the people.

HARNESSING UNCERTAINTY FOR CONTROL

The key to prediction is uncertainty: those of us pushing the limits of weather prediction are consumed by it. In our ensemble simulations, each simulation is equally probable, so the more of these simulations we run for each point in time, the better out modeling is at representing uncertainty.

However, regardless of the number of ensemble simulations, all predictions become increasingly uncertain as they move further into the future, through an accumulation of more possible consequences.

What this ensemble approach also shows us is that the tiniest fluctuation in any of the starting conditions or model assumptions can result in very different weather evolutions over time, also known as the 'butterfly effect'.

This is a bane for forecasting, but it also raises an intriguing and potentially profound question: If the tiniest change can affect weather development so significantly in a simulation, could we not make that small modification in the real world to change the evolution of weather itself?

With our new ability to run thousands of ensemble simulations using high-resolution data, it is now feasible to accurately model the likely consequences of such a deliberate change to the weather.

My team has shown that it is technically feasible to run very large ensembles quickly to 'experiment' with the weather virtually, such as the consequences of small wind changes on the severity of typhoons or heavy rains. We think these experiments could one day lead to targeted weather modifications that could, for example, prevent the development of a predicted extreme event.[3] AI could help pinpoint the most efficient modifications.

This of course is not something that could, or should, be undertaken lightly. Great care needs to be taken that our control efforts don't have unintended consequences. But perhaps this is a way to turn the tables, to mitigate some of the weather impacts that we have caused as a result of climate change.

Our simulation sandbox is a great place to perform such experiments safely.

REFERENCES

For a full list of references, check the online version of this article: www.riken.jp/en/news_pubs/research_news/

TAKEMASA MIYOSHI,
Team leader,
Data Assimilation Research Team,
RIKEN Center for Computational Science

Takemasa Miyoshi started his professional career as a civil servant at the Japan Meteorological Agency (JMA) in 2000. In 2005, he gained his PhD at the University of Maryland (UMD) in the United States. He then became a tenure-track assistant professor at UMD in 2011. Since 2012, Miyoshi has led the Data Assimilation Research Team at the RIKEN Center for Computational Science (R-CCS). There he is working towards advancing science on data assimilation. Miyoshi has been recognized by several prestigious awards. These include the Meteorological Society of Japan Award (2016), the Yomiuri Gold Medal Prize (2018), a commendation by the Prime Minister for disaster prevention (2020), and an award for science and technology by the Minister of Education, Culture, Sports, Science and Technology (2022).

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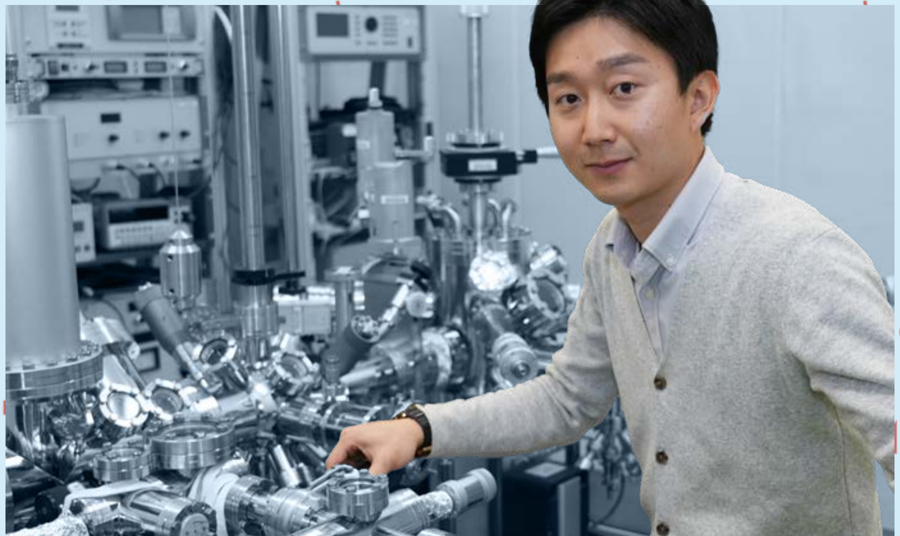
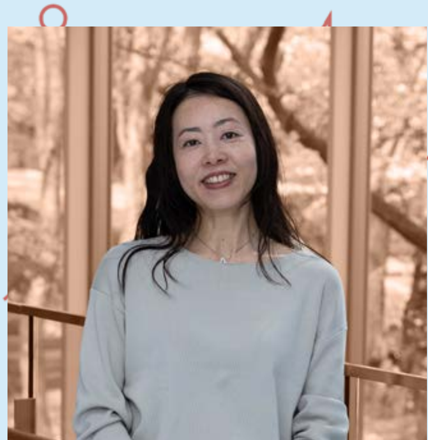


PROGRAMS FOR YOUNG RESEARCHERS



RIKEN HAKUBI TEAM LEADER

The RIKEN Hakubi Fellows Program provides junior principal investigator positions to exceptionally talented individuals, allowing them independent research at their own laboratories for up to seven years. Since 2018, 13 early career researchers have been hired as principal investigators under the RIKEN Hakubi Fellows Program.

RIKEN EARLY CAREER LEADERS

The RIKEN Early Career Leaders (ECL) Program is based on the RIKEN Hakubi Fellows Program, and provides further support to junior researchers who want to launch their own laboratory and project. The RIKEN ECL Program offers two types of positions: team leader and unit leader. The researchers are provided an appropriate research environment corresponding to their research plan and career stage. The program focuses on natural and mathematical sciences and research areas bordering the humanities and social sciences.

SPECIAL POSTDOCTORAL RESEARCHER

The Special Postdoctoral Researcher (SPDR) Program provides creative young scientists the opportunity to conduct autonomous and independent research that aligns with RIKEN objectives and research fields, for up to three years. Applicants must have a PhD awarded within five years of application or expect to be awarded a PhD by the date of hire.

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The Junior Research Associates (JRA) Program provides part-time research positions for young researchers, giving them the opportunity to carry out research alongside RIKEN researchers for up to three years (four years in special cases). By the time they are hired, candidates must be enrolled in a PhD program in a Japanese university that has a collaborative agreement with RIKEN, or are involved in joint research with RIKEN scientists.

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The International Program Associate (IPA) Program provides non-Japanese doctoral students the opportunity to carry out research for up to three years at RIKEN. This is undertaken through a joint supervision scheme run by RIKEN scientists and researchers from both local and overseas partner graduate schools or research institutions. Candidates must be enrolled in PhD program at a university that has (or is expected to have) a Joint Graduate Program agreement with RIKEN by their arrival date.

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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, 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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