RIKEN RESEARCH

SPRING 2021

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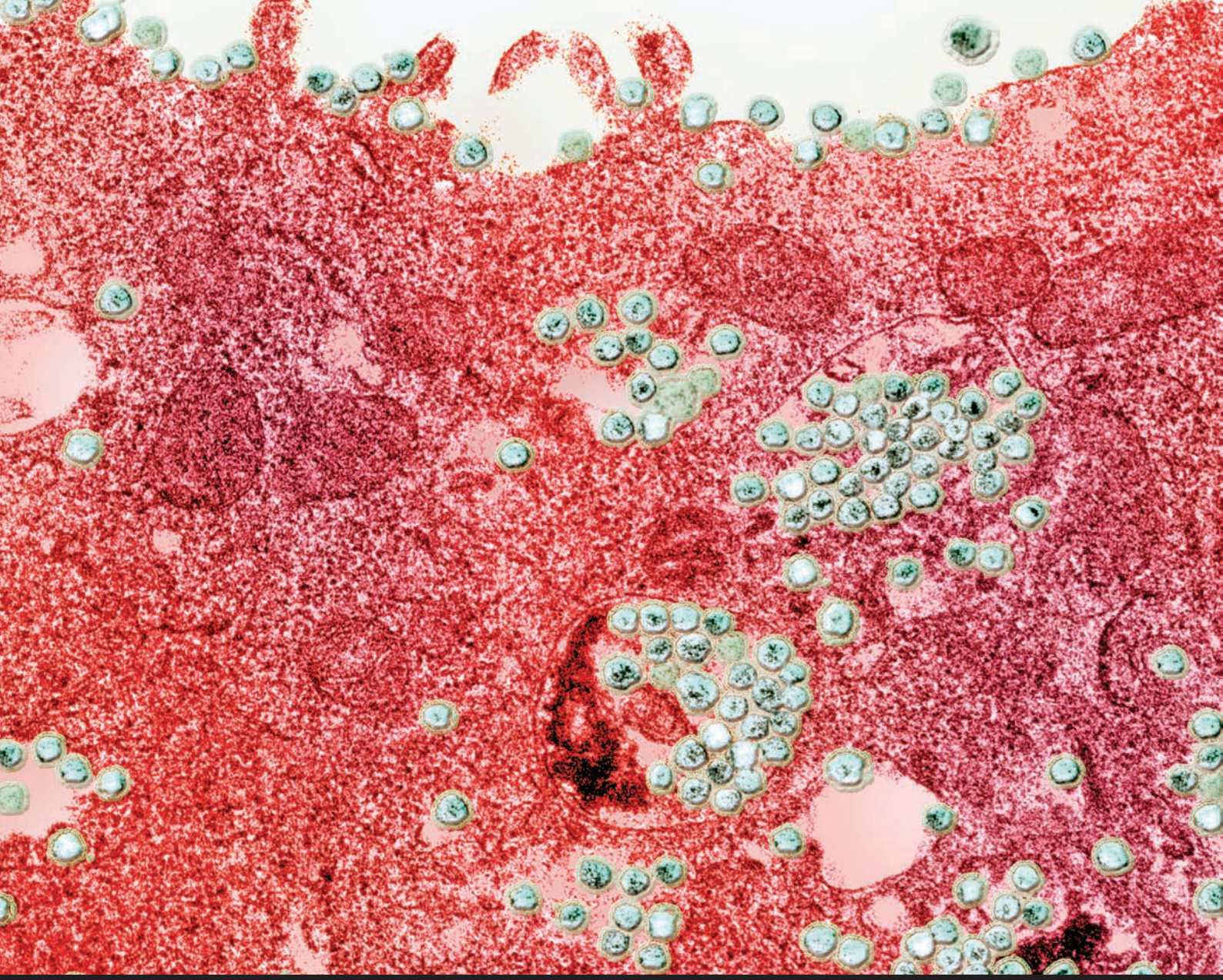
COVID-19
A dynamic response

HEAVY HITTERS
Streaks of light illuminate dark matter

BEEP FROM THE DEEP
Ultrasound-carrying rays map ocean floor

EVOLUTION STRIPPED BACK
E. coli mutation possibilities converge



▲ **Purpose in the pandemic**
Coronavirus particles (green) in a host cell. The virus is named for the corona (crown) of surface proteins (dark dots) used to penetrate cells. RIKEN is contributing to many aspects of coronavirus research (page 29) including modeling droplet spread with supercomputer Fugaku (page 32).

RIKEN RESEARCH

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

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

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

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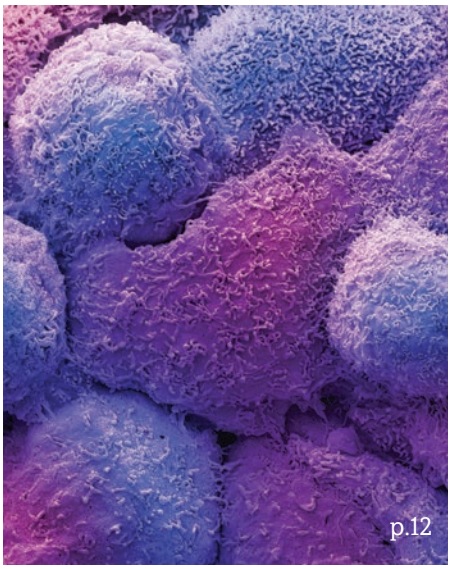
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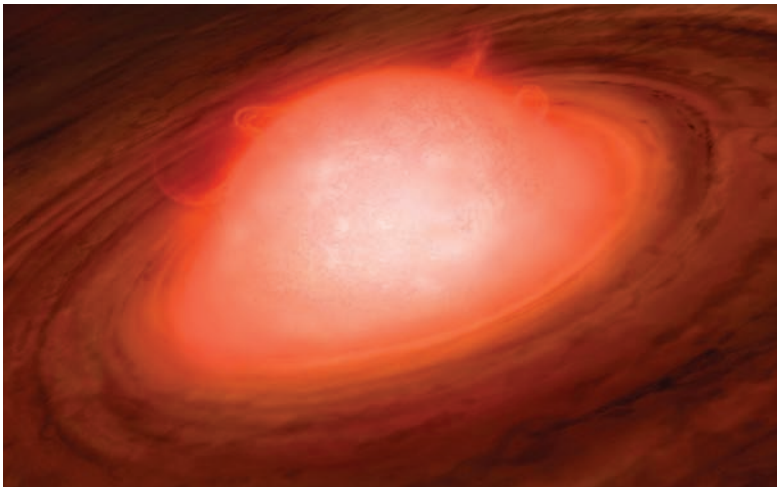

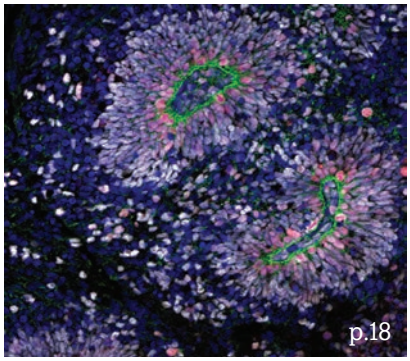
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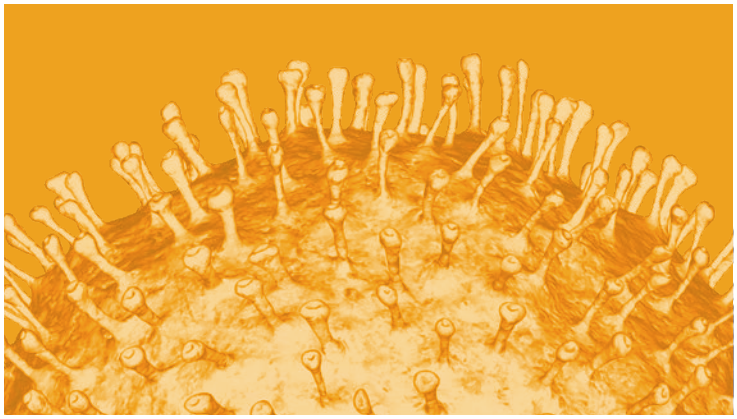

Creating our future ourselves

Shigeharu Kato
Executive Director, RIKEN

By the time this issue of *RIKEN Research* is published, vaccinations against COVID-19 will have begun in some countries. But that does not mean the struggle against COVID-19 is over. One thing is clear: we cannot return to the days before the pandemic. Rather, we must devise and adapt to a new way of life, including new ways of working, to give us more resilience toward future pandemics.

RIKEN has already taken steps in that direction. When the government declared a state of emergency in April last year, we quickly introduced teleworking (with the exception of essential personnel). We faced some hurdles: poor internet connections, hardware problems and a lack of face-to-face communication. However, teleworking brought benefits: more time to spend with our families, more flexible time management and relief from Japan's notorious commuter rush.

Based on my recommendations, our Board of Executive Directors decided in June to reform our administrative processes. The chief goal was to allow our administration to remain functional even under a state of emergency, but another goal was to enhance the quality of life of our administrative workforce by rationalizing work regulations and abolishing inefficiencies (including the need for stamps on documents) through the introduction of digital tools. Making administration more effective and efficient will also benefit our scientists, thus helping us to carry out our mission more effectively.

I brought young administrative staff into this project to encourage them to create their future themselves. We set up taskforces working on specific areas. They worked through the summer and autumn and came up with various proposals, and some of them have already been implemented.

The aim of this reform is not just the digitalization of documents, but rather the digital transformation of our administrative work. I am hopeful that this process, carried out by young staff, will help bring a new mindset to RIKEN administrators: "creating our future ourselves."

We are also looking forward to sharing experiences and ideas with our international partners, so please get in touch with us if you would like to work together on these changes.

COVER STORY:
The response of *Escherichia coli* bacteria to 95 different stresses reveals that the evolution of *E. coli* is less complex than previously thought, opening up new possibilities for countering antibacterial resistance. *Page 26*

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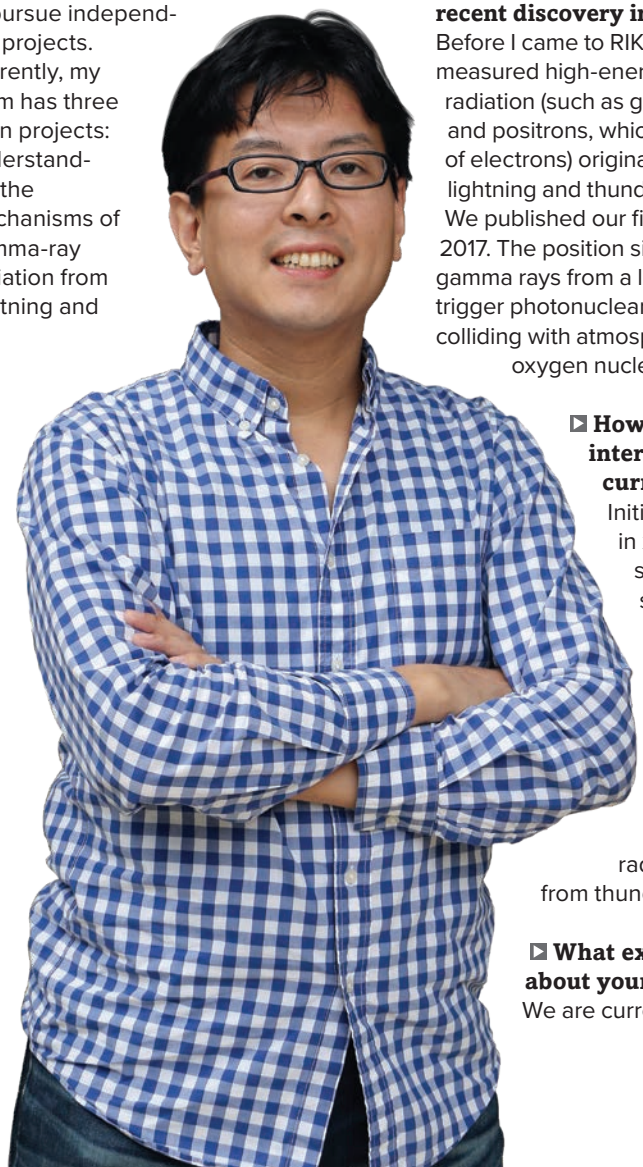
Repurposing storm and space tech

Teruaki Enoto

RIKEN Hakubi Team Leader, Extreme Natural Phenomena RIKEN Hakubi Research Team, RIKEN Cluster for Pioneering Research

Describe your role at RIKEN.
I lead the Extreme Natural Phenomena RIKEN Hakubi Research Team, a group that studies high-energy phenomena. In January 2020, my team became part of the second round of RIKEN Hakubi teams, a five-year program that allows young researchers to pursue independent projects. Currently, my team has three main projects: understanding the mechanisms of gamma-ray radiation from lightning and thunderclouds; exploring new astronomical techniques for observing black holes and neutron stars using CubeSats; and probing for hidden water on the Moon using neutron signals produced by cosmic rays.



What has been the most interesting recent discovery in your field?
Before I came to RIKEN, my group measured high-energy atmospheric radiation (such as gamma rays, neutrons, and positrons, which are antiparticles of electrons) originating from winter lightning and thunderstorms in Japan. We published our findings in *Nature* in 2017. The position signal indicated that gamma rays from a lightning discharge trigger photonuclear reactions when colliding with atmospheric nitrogen and oxygen nuclei.

How did you become interested in your current research?
Initially, I worked in x-ray astronomy, studying neutron stars and magnetars, which are compact objects formed after supernova explosions. Now, my team is using space-science technologies to explore the radiation emanating from thunderstorms on Earth.

What excites you the most about your current research?
We are currently making a new x-ray astronomical CubeSat (named NinjaSat) as part of collaborations with the RIKEN Tamagawa High Energy Astrophysics Laboratory and young researchers from a number of institutes. NinjaSat is a small 6U-sized spacecraft that will be used to observe bright x-ray sources in the sky. We can observe x-rays from accreting matter that falls into black holes or neutron stars. This small observatory will help gravitational-wave observatories to search for coherent gravitational waves from fast-rotating neutron stars.

My research is important to society because...
We are developing a new non-contact water sensor using our neutron-measurement technology. This device uses the fact that neutrons bounce off protons in water. The same techniques have been used to find corrosion in bridges and pipes, and to measure moisture in the soil. We're particularly interested in advancing space exploration by examining the possibility of hidden water on the lunar surface. We will work to develop new neutron detectors, which will be used for lunar rovers, and to look for the water signature in neutron signals, which are generated by cosmic rays striking the Moon's surface.

> *My team are using space science technologies to explore the radiation emanating from thunderstorms on Earth.*

How has being at RIKEN helped your research?
RIKEN's interdisciplinary environment has been very beneficial to my group, as its research targets cover physics, astronomy, geophysics and meteorology. Such a multidisciplinary approach is challenging to achieve at universities. RIKEN has shifted to an online research style due to COVID-19, which has allowed one of our members to work from home in Brazil. ■

Human-spun spider silk

Nur Alia Oktaviani
Special Postdoctoral Researcher, Biomacromolecules Research Team, RIKEN Center for Sustainable Resource Science

Describe your work at RIKEN.
I'm a special postdoctoral researcher in the Biomacromolecules Research team at the RIKEN Center for Sustainable Resource Science, where I study the self-assembly mechanisms of spider-silk proteins.

We are trying to create a spinning system that mimics the materials and conditions of the spider silk gland.

How did you become interested in your current field of research?
I've always been interested in investigating the molecular mechanisms underlying protein function. Spider silk is a protein-based material known for its extraordinary strength and elasticity, and it should have many industrial applications.

However, as spiders can't be farmed (due to their cannibalistic tendencies) researchers require artificial spider silk to be able to investigate its uses. To create this, we are trying to create a spinning system that mimics the materials and conditions of the spider silk gland. However, we don't fully understand the processes that transform the highly soluble silk proteins within the spider gland into an insoluble, strong and elastic biomaterial. So my research focuses on understanding the self-assembly mechanism of spider silk proteins.

What excites you the most about your current research?
I'm investigating spider silk self-assembly mechanisms at the molecular level. Alongside other biophysical techniques, I'm using the multidimensional nuclear magnetic resonance (NMR) spectroscopy facility at RIKEN's Yokohama campus. The most exciting part of my research is when I get good-intensity, high-resolution spectra data on spider-silk proteins. This allows me to do NMR chemical shift assignments, so I can analyze and interpret structural spider silk protein data at the molecular level.

What has been the most interesting discovery in your field in the last few years?
For many years, researchers used organic solvents to spin artificial spider-silk fibers. However, they were not as strong or tough as natural silk. A few years ago, researchers tried to mimic the environment in the spider gland and greatly improved the mechanical properties of artificial spider silk, even though it is still not quite as good as native spider silk. This discovery prompted me to look for better understandings of the mechanisms underlying natural spinning processes.

How and when did you join RIKEN?
I joined RIKEN in February 2015 as a postdoctoral researcher. My family and I moved to Japan because my husband had been given a position at RIKEN. Soon after I arrived, I found a vacant role as postdoctoral researcher in the Biomacromolecules Research Team and applied for the job.

How do you balance family life with your work at RIKEN?
My husband and I are both researchers at RIKEN and we have two children. Balancing family life sometimes isn't easy, but RIKEN is incredibly flexible and supportive of researchers with families, which helps a lot. ■

Careers at RIKEN

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

Akito Arima (far right), then president of RIKEN, greets an expert invited to discuss best practice managment of research at the 2nd RIKEN Advisory Council in 1995.

Remembering Akito Arima (1930–2020)

Akito Arima, who served as president of RIKEN from 1993 to 1998, passed away on December 6 at the age of 90.

Arima, a nuclear physicist who helped substantially simplify representations of the atomic nucleus, was focused on the international expansion of RIKEN during his tenure.

His achievements included the opening of RIKEN Facility Office at the Rutherford Appleton Laboratory (RAL) in the United Kingdom and the RIKEN BNL Research Center at Brookhaven National Laboratory (BNL) in the United States.

In addition, he devoted his efforts to the establishment of a number of strategic research centers such as the Brain Science Institute (BSI), now the Center for Brain Science (CBS) and the SPring-8 synchrotron facility in Harima. These centers are still at the core of RIKEN's research structure.

Arima also served as president of the University of Tokyo and president of the Japan Association of National Universities. In these and various other roles, he made great contributions to the development of science and technology as Japan prepared to enter the 21st century.

Akito Arima.

The journal *Nature* published an obituary on January 28, 2021, that detailed how Arima had helped promote centers of excellence in advanced research in Japan.

The article describes how, during his tenure at RIKEN, Arima lobbied for a law to inject more funding into Japanese science. Japan's Basic Law for Science and Technology came into force on November 15, 1995. It helped double the number of postdoctoral fellows in Japan by the end of the decade.

After RIKEN, Arima became minister for education and state minister of science and technology under Prime Minister Keizo Obuchi. In this time, he strengthened graduate programs and corporate sponsorship of research.

RIKEN President Hiroshi Matsumoto issued a statement regarding the passing, saying, "We would like to express our deepest condolences to the family of former president Arima. All of the RIKEN community will continue to work hard to further develop the foundation he laid during his tenure here and in various other roles."

More on the RIKEN news website:
https://www.riken.jp/en/news_pubs/news/2020/20201208_2/index.html

Read Akito Arima's obituary in *Nature*:
https://www.nature.com/articles/d41586-021-00189-7

First clinical trial of cancer immunotherapy using iPS-NKT cells

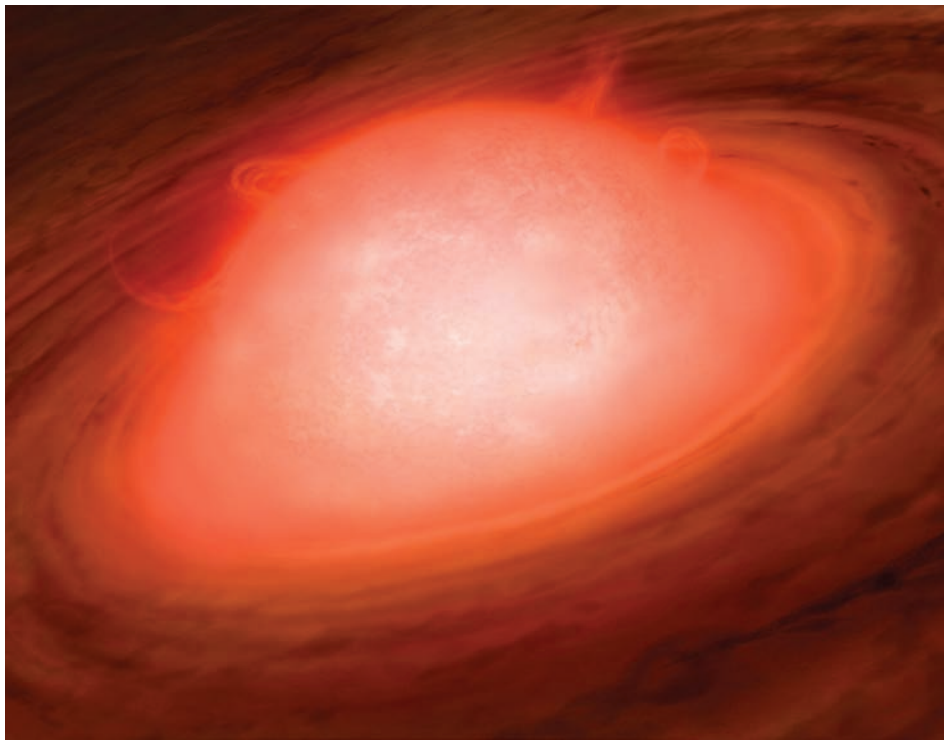
In October 2020, a research team from Chiba University Hospital and the RIKEN Center for Integrative Medical Sciences transplanted natural killer T (NKT) cells made from induced pluripotent stem (iPS) into neck-cancer patients in a clinical trial. It was the first case of the injection of NKT cells derived from iPS cells into humans in the world.

In this doctor-initiated clinical trial, iPS cells made from the blood of healthy individuals were made into NKT cells; some 50 million of these were injected into blood vessels connected to the cancer.

The injections occured every two weeks and three times in total, and the teams kept a careful eye on whether the cells triggered inflammation.

After noting no significant adverse reactions, the team plan to start the second clinical trial in 2021, with hopes for third and fourth trials in the near future.

Natural killer cells and T cells are the body's first line of defence against cancers.



Nami Sakai is a leading female researcher trying to understand the connections between physcial and chemical observations in space.

Star chemist awarded JST prize

Late last year, Nami Sakai, Chief Scientist at RIKEN's Star and Planet Formation Laboratory won the Brilliant Female Researcher Award (The Jun Ashida Award) from the Japan Science and Technology Agency. The award comes with prize of one million yen (about US$10,000).

Sakai's team is examining the differences in chemical composition at the formation sites of exoplanetary systems. She wants to know how planets similar to Earth might differ in atmosphere or minerals. Her work will help researchers understand how different forms of life might be created under different environmental conditions, if at all.

Sakai's work introduces chemical methods to traditional astronomy, such as capturing changes in molecular composition using spectroscopic observation to reveal the mechanisms involved in the formation of exoplanetary systems.

For example, in September 2020, Sakai was part of a group of astronomers working with the Atacama Millimeter/submillimeter Array (ALMA) who spotted a pair of massive baby stars shrouded by a gaseous disk of molecules that included sodium chloride (commonly known as table salt) and heated water vapor. By analyzing the radio emissions from the salt and water, the team found that the disks are counter rotating.

Nami Sakai.

These types of observations will go a long way to explaining more about the link between the physical and chemical in space, says Sakai.

By leading teams using state-of-the-art radio telescopes, including ALMA, located in the Chilean desert, Sakai is investigating the chemical and physical histories of exoplanetary systems around solar-type protostars. These, she says, can be revealed by observing the formation sites of protoplanetary disks.

By understanding these elements, Sakai says her team will help us understand how our Solar System is unique.

The supercomputer Fugaku is based at RIKEN's Kobe campus and currently leads all four major supercomputing rankings (see right).

The future is Fugaku

Simulations confirm benefit of masks

The supercomputer Fugaku was deployed ahead of schedule to combat the COVID-19 pandemic. One areas in which the new machine has made an impact is by simulating viral particle spread. For example, one simulation has shown that 20 minutes of maskless conversation is equivalent to a single cough.

Droplet and aerosol spread has been modeled in situations ranging from restaurants and classrooms to airplanes (see page 32). Without protective gear, such as masks and face shields, large amounts of virus-laden droplets and aerosols were shown to spread easily and quickly. Even with masks and face shields, viral aerosols were shown to escape through material or the gap between a mask/shield and the face, and these contaminate the air for a long time, particularly in highly air-conditioned settings, meaning modeling of ventilation was also vital.

https://www.r-ccs.riken.jp/en/fugaku/covid-19/msg-en.html

The coders behind the rankings

Fugaku is currently the fastest computer in the world (see right), but how this was proven is a story in itself.

The prep work for Masahiro Nakao of the Programming Environment Research Team at R-CCS, the man who ran the code on Fugaku for the Graph500 benchmark, started nearly a year in advance. In the summer of 2019, Nakao was first asked to lead the effort.

Fugaku's eventual specs had been defined, and its theoretical performance could be estimated. There was, however, no code to run on Fugaku for the Graph500 benchmark. Unlike other benchmarks, the Graph500 allows leeway in how to measure it. That means that getting to the top of the list requires a superior machine and custom-designed code that brings the best out of it. Determined to live up to the challenge, Nakao spent many hours learning the code used for the K computer and modifying it for Fugaku.

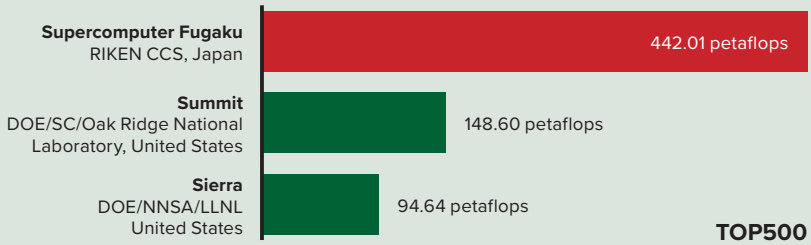
During a single-node evaluation that started in September 2019, as well as later multiple-node evaluations and large-scale trials, there were numerous challenges overcome only through hours of testing and re-testing. "It was very difficult to determine whether it was a hardware problem or a problem with the code," explains Nakao.

The code that worked beautifully for the K computer is not the best for Fugaku, he adds. By writing what is best suited for Fugaku, Nakao thinks there is still room for a significant improvement in the next round of benchmarking.

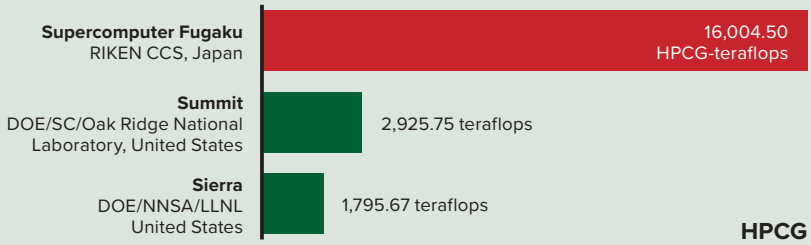
FUGAKU TOP SPOTS

(as of November 2020)

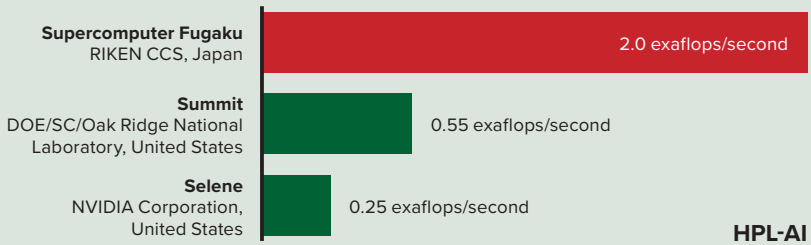
Following its impressive debut in June 2020, the supercomputer Fugaku again swept the top spot in four major rankings of world supercomputers—TOP500, HPCG, HPL-AI and Graph500. This time, all 158,976 of the system's nodes were used for the measurements, improving the scores in all four benchmarks and further widening its lead over the second-ranked machines. **Fugaku was made publicly available from 9 March 2021.**



TOP500



HPCG



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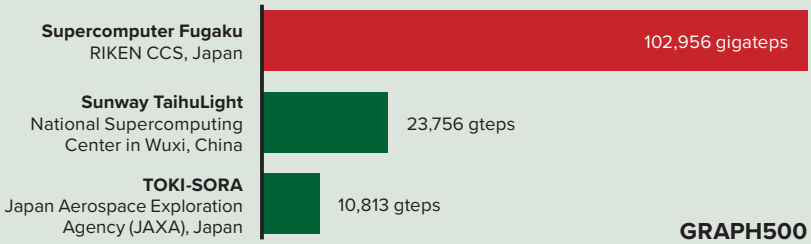
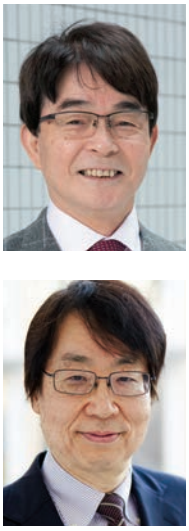


GRAPH500

Two join the Japan Academy



Toshio Yanagida (top) and Yasushi Miyashita (bottom).

Two RIKEN researchers, Toshio Yanagida and Yasushi Miyashita, have been elected as members of the prestigious Japan Academy. The Japan Academy, which was established in 1879 and is based on bodies such as the Royal Society in the United Kingdom, is an elite group with only 150 members in both the natural sciences and humanities. Yanagida, who previously served as director of the RIKEN Quantitative Biology Center (QBiC) and currently serves as an Honorary Scientist, was chosen by the academy in recognition of his contribution to the development of molecular imaging techniques and their application to biology and biophysics. Through his work he made it possible to study the movements of single molecules under the biologically important conditions of ambient temperature and liquid medium. Miyashita, who is head of the Laboratory for Cognition Circuit Dynamics at the RIKEN Center for Brain Science (CBS) and previously served as director of CBS, was chosen by the academy in recognition of his contribution to the development of biological methodologies for studying cognition in non-human primates, leading to the discovery of brain mechanisms of memory and metamemory, though which we can feel introspection toward our own memory states, creating a higher level of cognition toward our own cognition.

https://www.riken.jp/en/news_pubs/news/2020/20201222_1/index.html

AUTISM

Picking up on autism earlier in life

Measuring the levels of a protein could lead to autism spectrum disorder being detected sooner in preschool children

Children with autism spectrum disorder (ASD) may be diagnosed and treated earlier thanks to the discovery of a potential biomarker by RIKEN researchers[1]. This could help to better manage their long-term symptoms.

A developmental disorder that starts appearing in early childhood, ASD affects learning, communication and social behavior. The severity of its symptoms falls on a broad spectrum, which are believed to be related to genetic and environmental factors that interact during brain development.

Neurons in the mouse brains had similar shapes and structures as those in postmortem brains from people with ASD

Because young children with ASD are at particular risk of being overweight, a team led by Takeo Yoshikawa of the RIKEN Center for Brain Science (CBS) wondered whether ASD may be linked to the metabolism of fat cells.

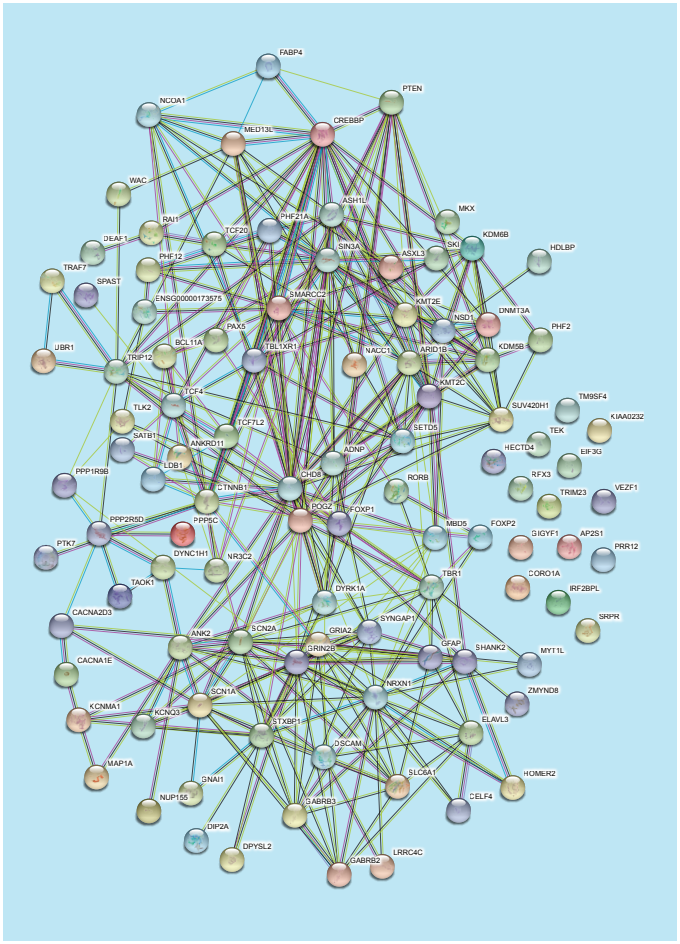
Fat cells make hundreds of important biomolecules called adipokines, some of which regulate brain activity. The researchers compared the adipokine levels of blood samples taken from preschool-aged children with and without ASD. Specifically, they examined adipokines associated with ASD as well as the protein FABP4.

"We had previously found lower levels of FABP4 in the hair follicles of patients with schizophrenia," explains Motoko Maekawa, also of CBS. "Although the disorders themselves are very different, we knew that FABP4 was an adipokine that can modulate brain function, especially during development."

The team found that preschool-aged children with ASD had much lower levels of FABP4 in their blood than other children, but that other adipokines did not differ between the two groups. A second test in two other groups of children confirmed these results. This makes FABP4 a potential early biomarker for ASD.

"The identification of FABP4 as a biomarker that can detect ASD in four-to-six-year-old children is good news," says Maekawa. "Especially because early diagnosis and intervention can lead to better long-term prognosis."

Further analysis showed that the story is a little more complex. Similar comparisons in older children and in postmortem brains showed equal levels of FABP4 between ASD and non-ASD groups. This means that FABP4 levels differ during a critical period of brain development, making it more than just a biomarker: its lack could be a factor that leads to the disease, rather than being just a byproduct.



A network showing how the protein FABP4 (top-most blue sphere) interacts with 102 candidate proteins that are associated with autism spectrum disorder (ASD). FABP4 could be used as a biomarker for ASD, RIKEN researchers have shown.

To confirm the importance of FABP4, the researchers created mice lacking the *FABP4* gene. These mice interacted less with unknown mice and had more difficulty with spatial learning and memory than normal mice, all reminiscent of difficulties shared by those with ASD. The team also found that neurons in the mouse brains had similar shapes and structures as those in postmortem brains from people with ASD.

The team intends to continue studying the FABP4 mouse model of ASD to determine exactly how the FABP4 protein affects the developing brain. ●

Reference

1. Maekawa, M., Ohnishi, T., Toyoshima, M., Shimamoto-Mitsuyama, C., Hamazaki, K., Balan, S., Wada, Y., Esaki, K., Takagai, S., Tsuchiya, K. J. *et al.* A potential role of fatty acid binding protein 4 in the pathophysiology of autism spectrum disorder. *Brain Communications* **2,** fcaa145 (2020).

SEABED MAPPING

Hitching a lift on rays to map the ocean floor

Harnessing rays that hug the ocean floor could provide a cheap way to map uncharted territory

Electric rays and stingrays equipped with pingers—devices that emit ultrasound—could provide a much cheaper way to map the seabed than conventional methods, a feasibility study by RIKEN researchers indicates[1].

The ocean has an abundance of natural resources, including fossil fuels, minerals and marine animals. However, many of them are on the ocean floor, which is largely unexplored territory.

Currently, automated vehicles, sonar and satellites are used to explore the ocean floor, but a team led by Yo Tanaka of the RIKEN Center for Biosystems Dynamics Research is developing a very different system for investigating the ocean floor—one that relies on the natural swimming behavior of electric rays and stingrays.

"Electric rays and stingrays spend most of their time swimming around on the ocean floor," explains Tanaka. "By combining simple pinger technology and digital cameras with this natural behavior, we think we can use rays to map the ocean floor, and at the same time collect meaningful data about ocean wildlife, biota and resources."

This method could be much more cost effective than conventional ones, and Tanaka's team has shown that small pingers can be powered by the electricity generated by electric rays.

When several receivers pick up the pinger's sound, its position can be calculated from the receivers' positions and the times when they detected the sound. By placing cameras on rays and linking the timing of the recorded video to the timings and locations determined by the pingers, the researchers believe they can accurately map the ocean floor.

Stingrays fitted with pingers and cameras could be used to map the ocean floor, a feasibility study by RIKEN researchers suggests.

The researchers initially tested the concept in a water tank. Cameras in three planes verified that both types of ray swam near the bottom of the tank. The ray's movements could be reconstructed in three dimensions from the camera images. The researchers also verified that cameras attached to the rays could be used to record videos of their exploration.

The team then tested their system off the coast of Okinawa, Japan. They attached pingers to stingrays and electric rays and lowered them into the ocean from a boat along with four ultrasound receivers. The researchers recorded the pinger-derived positions as the rays swam near the boat for about two hours. Afterward, they compared the data with an existing seabed map of the area and found that the rays' positions lay within about 10 centimeters of those in the map.

"In our ocean experiment, in addition to the pinger positioning, we were able to confirm that electric rays actually move around the seabed," says Tanaka. "In the near future, we will test the system for long-term monitoring." ●

Reference

1. Funano, S., Tanaka, N., Amaya, S., Hamano, A., Sasakura, T. & Tanaka, Y. Movement tracing and analysis of benthic sting ray (*Dasyatis akajei*) and electric ray (*Narke japonica*) toward seabed exploration. *SN Applied Sciences* **2,** 2142 (2020).

BIOORTHOGONAL CHEMISTRY

Pulling a golden trigger to kill cancer cells

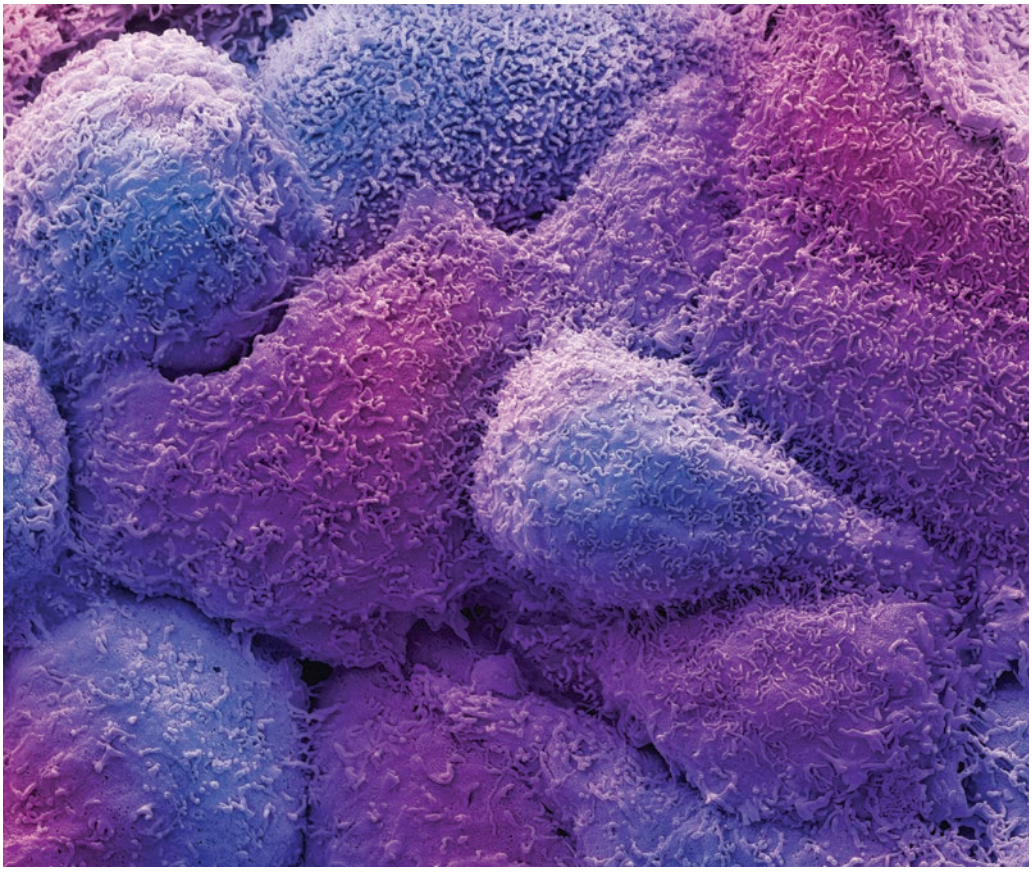
Masked drugs can be unleashed inside the body using gold to activate them

Drugs that are activated inside the body with catalytic quantities of gold could offer a new option for treating cancer and other diseases, four RIKEN researchers have shown[1].

Using metals to convert masked 'pro-drugs' into their active forms inside the body is an emerging area of biomedical research. These drug-release reactions are designed to be triggered by metals that are not naturally present in the body, providing a new way to trigger drug release that promises to increase the efficacy and reduce the side effects of a therapy.

"Research groups worldwide have done a lot of beautiful work showing that transition metals like ruthenium and palladium can be used in biological settings to catalyze the unmasking of drugs," says Katsunori Tanaka, who leads the RIKEN Biofunctional Synthetic Chemistry Laboratory. In many clinical scenarios, however, it may be useful to deploy several masked drugs in tandem, each triggered using a different metal. "We identified a lack of studies focusing on gold, and so we set out to tackle this unique challenge," Tanaka says.

Many active drugs contain nitrogen-based amine functional groups, so Tanaka, Kenward Vong and their colleagues developed 2-alkynylbenzamide (Ayba), an amine-masking group that would be clipped off in the presence of gold. Ayba features a triple-bonded carbon–carbon alkyne group that, when activated by gold, triggers a cyclization reaction that ultimately cleaves the bond between Ayba and the masked nitrogen atom, releasing the active drug.



Scanning microscopy micrograph of breast cancer cells. RIKEN chemists have used a gold catalyst to convert a pro-drug into a drug, and demonstrated this strategy against breast cancer cells.

In testing, the team used Ayba to create prodrugs of two amine-containing anticancer compounds. Adding gold to these prodrugs in cancer cells released the active drug to kill the cells, the team showed. Other metals did not trigger the unmasking reaction, and the Ayba-protected drugs could be used in tandem with prodrugs released by ruthenium and palladium. "We believe Ayba-based prodrugs performed with a lot of promise," Tanaka says.

Another advantage of the Ayba prodrug platform was that it could be easily modified. The researchers added various chemical side chains to the Ayba structure, enabling them to fine-tune the overall properties of the prodrug, such as its inability to cross cell membranes. "Having the ability to make derivatives makes the Ayba group much more functional than other approaches," Tanaka says.

"We hope this work gives us the chance to start collaborations and to look for specific systems where our chemistry can benefit the most," Tanaka adds. "Our end goal is to work towards developing novel therapeutic applications."

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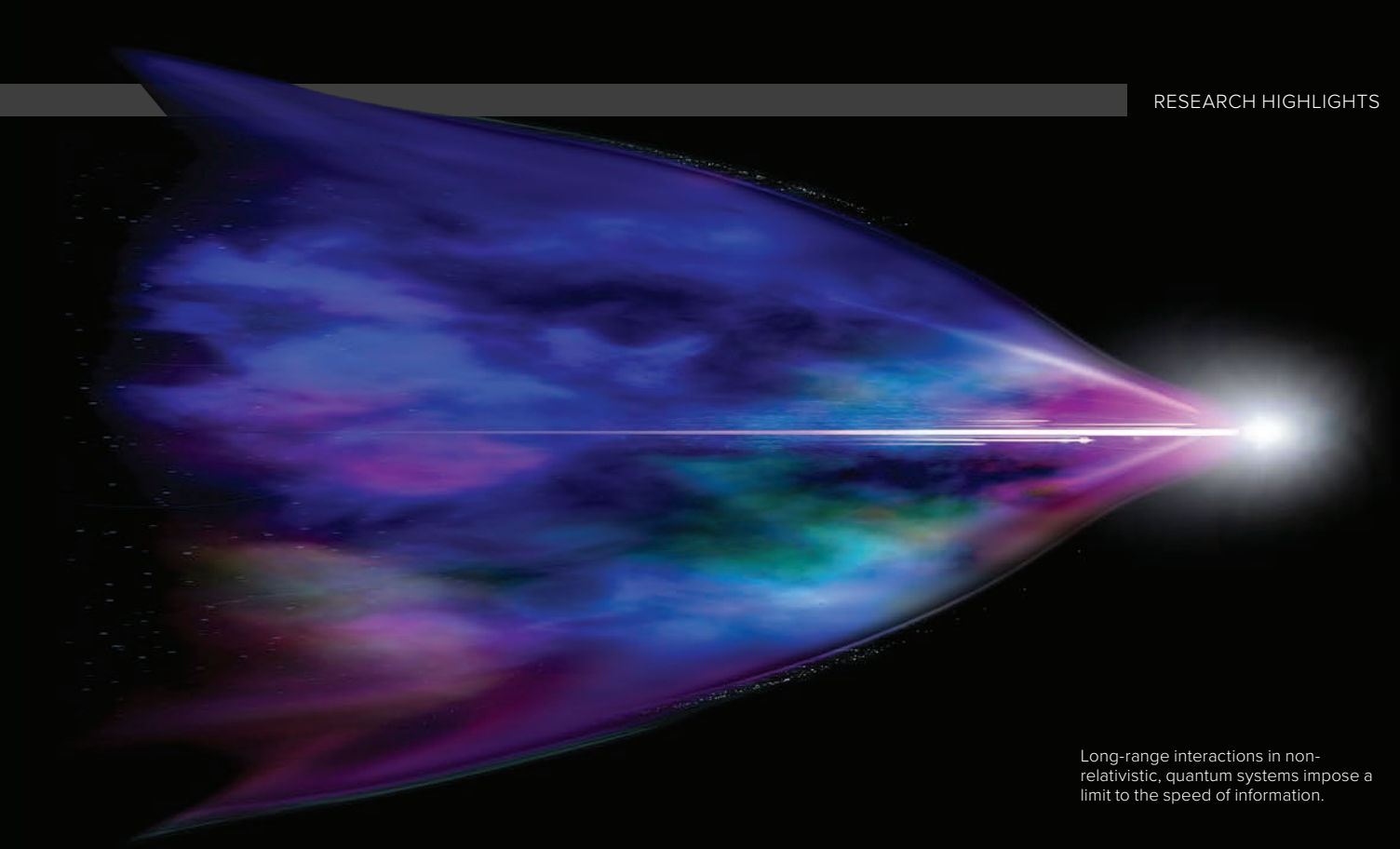

Long-range interactions in non-relativistic, quantum systems impose a limit to the speed of information.

QUANTUM OPTICS

Quantum mechanics sets speed limit

Long-range interactions between quantum particles can impose a limit on the speed at which information can travel

The speed of light is not the only fundamental limitation, at least not in quantum systems, a RIKEN physicist and his collaborator have shown[1]. The mathematical proof could have implications for the development of algorithms used in quantum computation and quantum machine learning.

Einstein's theory of special relativity imposes a speed limit on the Universe—information cannot travel faster than the speed of light. Relativistic systems—those with particles moving at velocities approaching this limit—exhibit a wide range of weird effects not seen in our everyday, non-relativistic experience. But do non-relativistic systems also have an information speed limit? Classical mechanics says no, but does quantum mechanics define one?

Two theoretical physicists, Elliott Lieb and Derek Robinson, investigated this question in the early 1970s. They considered a lattice of particles with a quantum property known as spin: each spin in the lattice interacts strongly with the next. By mathematically imposing a theoretical upper limit on the speed at which information can propagate in non-relativistic quantum systems, Lieb and Robinson showed that information cannot travel instantaneously, even in quantum theory.

But as is often the way in physics, an answer raised more questions: what happens if the quantum particles interact over longer distances and not just their nearest neighbors in the lattice?

Now, almost half a century after Lieb and Robinson's work, another pair of theoretical physicists—Tomotaka Kuwahara from the RIKEN Center for Advanced Intelligence Project and Keiji Saito from Keio University—has shown that there is indeed a limit even for quantum systems with such long-range interactions.

Information speed limits are visualized by so-called light cones: a map of the spatial limit across which the information can spread over time. A linear light cone indicates a fundamental speed limit. "Previous studies had obtained light cones that were only nearly linear," explains Kuwahara. "Strictly linear light cones couldn't generally be obtained in long-range interacting systems."

Kuwahara and Saito have now shown mathematically that for a D-dimensional system of particles whose interaction strength decreases over distance to the power of $-\alpha$, a linear light cone exists so long as α is greater than $2D + 1$.

The pair's theoretical finding could have practical implications. "This regime includes various practically important long-range interacting systems that can be created using trapped ions, Rydberg atoms or ultracold atoms and molecules," says Kuwahara. "The concept of the light cone is also deeply related to the implementation of faster quantum algorithms by quantum computers."

Reference

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FLOWERING

Cassava flowering cues

Cassava plants flower in the dry season in mountainous areas

New knowledge about the flowering mechanism of a popular cassava cultivar, gleaned by a RIKEN-led study, could help efforts to produce improved breeds of the crop[1].

Cassava is a major tropical crop that provides sustenance to people throughout Latin America, Africa and South Asia. The crop is produced through vegetative propagation and does not normally flower in agricultural fields. The difficulty in inducing cassava to flower and produce seeds slows down traditional breeding, and also poses a challenge to molecular breeding efforts. "Without flowering and producing seeds, an introduced gene might be lost if it is chimera," explains Motoaki Seki of the RIKEN Center for Sustainable Resource Science.

"Our findings suggest low temperature or drought conditions might induce flowering"

An international collaboration, led by Seki, investigated the environmental factors that control cassava flowering. Hiroki Tokunaga, the lead author of the study, explains the conundrum: "Plants generally control flowering timing by recognizing changes in temperature and day length, but in tropical areas the day length and temperature do not change much during the year."

Cassava generally produces flowers in the dry season in mountainous areas.

The team monitored the growth and flowering of cassava at five sites in Vietnam and Cambodia. Plants in Bac Kan and Lam Dong produced flowers, while those grown in Hanoi, Dong Nai and Battambang did not. Since the sites at Bac Kan and Lam Dong were higher than those in the other locations, this suggests that flowering is accelerated in high or mountainous regions.

To see if plants were flowering in response to a specific cue or after a certain amount of time had passed, the researchers varied the planting data at the Bac Kan site. The plants consistently flowered in August and September, showing that flowering occurs in response to an environmental cue. "Our findings suggest low temperature or drought conditions might induce flowering, but we don't have direct evidence for that," says Tokunaga.

The team also monitored changes in the expression of genes related to flowering in the plants. They found that expression of the *MeFT1* gene increased during the transition to flowering. They also identified 14 other flowering-related genes that had expression correlated with *MeFT1*, as well as a collection of environmental response genes that are coexpressed.

"In general, flowering is not directly related to stress-response genes, but our findings suggest an interaction between flowering and abiotic stress," says Seki. "That was a very big surprise for me."

The team now plans to investigate the interaction between stress response and flowering, with the aim of assembling a full picture of the environmental, molecular and genetic underpinnings of flowering in cassava. ●

Reference

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ACCELERATOR PHYSICS

A harmonic marriage between light and mechanics

A common type of oscillating motion surprisingly mimics the wave behavior of light

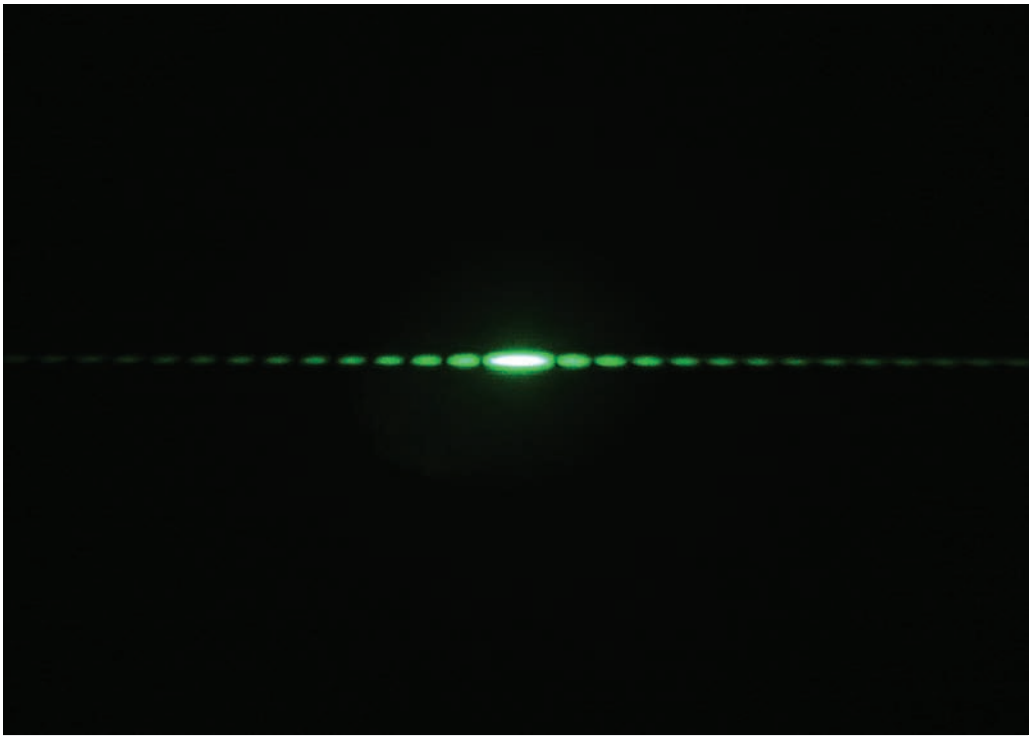
An unexpected mathematical connection between a special kind of mechanical motion and the behavior of light has been uncovered by three RIKEN physicists[1]. This strange link could help physicists to design future particle accelerators as well as investigate hot ionized gases known as plasmas.

Hitoshi Tanaka and his colleagues from the RIKEN SPring-8 Center made the discovery by accident. They were designing a next-generation synchrotron radiation source in which beams of electrons travel around a large circular track, emitting x-rays as they travel. Accelerating cavities periodically accelerate the beams to keep them at a constant energy.

The team wanted to find a way to safely and efficiently absorb the beam's energy by spatially expanding beams. "We have a sharp, high-intensity beam that can melt a steel vacuum chamber," Tanaka says.

The team mathematically modeled the electrons circulating in the synchrotron radiation source. A core part of the built model is equivalent to a forced harmonic oscillator, with a natural frequency of oscillation that varies slowly. A simple example of a forced harmonic oscillator is a child on a swing, being pushed by a parent at just the right moment to increase the swing's amplitude. In Tanaka's case, the electrode provides this driving force, causing the electrons to vibrate slightly while traveling around.

The team solved the equation to find the optimal frequency needed to increase the electrons' oscillation amplitude for spreading electron beams. Surprisingly, the solution looked similar to one describing a totally different system—the way light waves interfere when a beam of light passes through a narrow slit. When a screen is placed far from the slit, a pattern of bright and dark stripes appears on the screen (see image). The bright parts correspond to regions where the peaks of the light waves combine constructively, while the dark stripes are areas where the peaks of some waves combine with the troughs of others, cancelling each other out.



The mechanical motion of a forced harmonic oscillator shows a strange similarity to the interference pattern (shown here) created when light passes through a narrow slit.

Surprisingly, the solution looked similar to one describing a totally different system

"At first we didn't understand why we were seeing this, because our system is mechanical, not optical," Tanaka says.

The team then calculated that any simple forced harmonic oscillator with a slowly varying frequency will also behave analogously to light. When the driving force is applied with the right frequency, the system resonates and the amplitude of oscillation increases—just like when two light waves constructively interfere.

"Harmonic oscillators are important in many types of physics, such as plasma physics and accelerator physics," says Tanaka, who hopes that the results will be useful in these fields and others. ●

Reference

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ARTIFICIAL SKIN

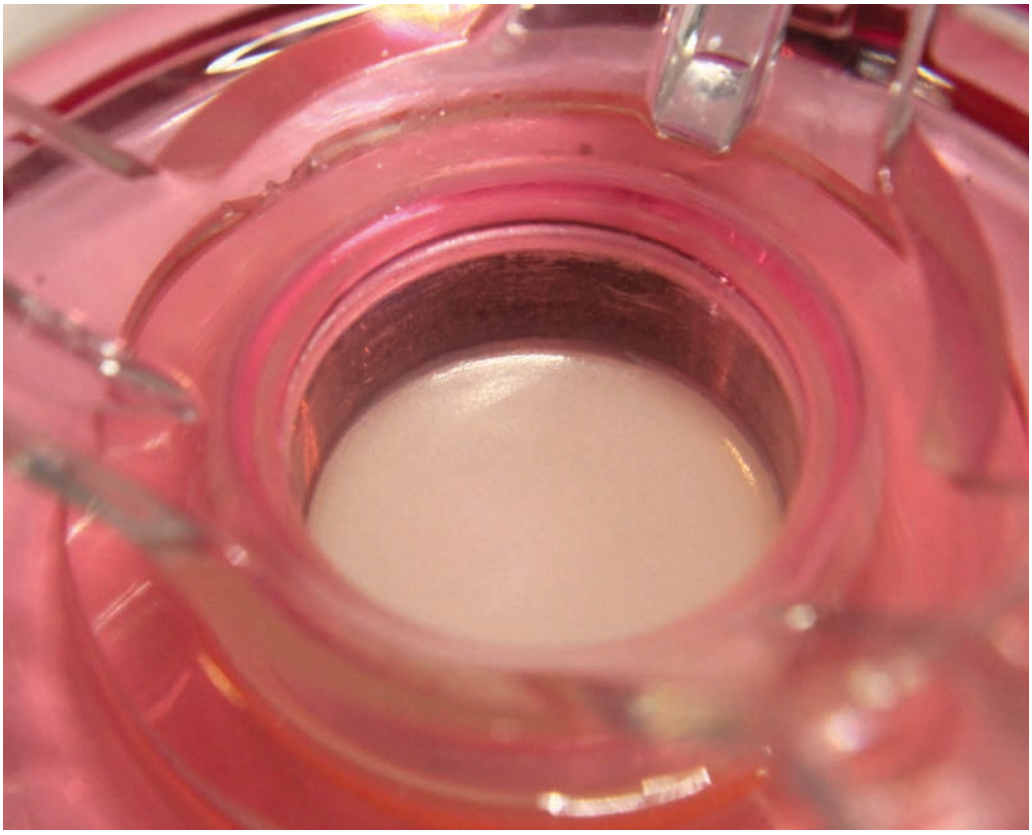
Artificial skin could save animals' skins

A new artificial skin that is tauter than conventional ones better reproduces natural skin

There could be less need to test skincare products on animals thanks to an artificial skin developed by RIKEN researchers that better mimics the tension of real skin[1].

The skin protects the body from the external environment. It is constantly in a state known as tensional homeostasis in which the cells near the outer layer of skin maintain a stable and steady tension through collagen fibers. This tension helps keep internal structures strong, yet flexible.

While synthetic skin models have been developed as alternatives to animal testing when developing safe and functional skincare products, it is difficult to study the tension distribution in the body because of its complexity. Furthermore, conventional skin models shrink during formation, eliminating the tension. Consequently, collagen and cells in the dermis—the second outermost layer of skin—are not properly oriented.



A photograph of an artificial skin developed by RIKEN researchers that reproduces the tension balance of natural skin.

Now, a team led by Takashi Tsuji of the RIKEN Center for Biosystems Dynamics Research, in collaboration with a Japanese pharmaceutical company, has developed a human-skin equivalent that reproduces the tension balance of natural skin.

The team developed a new model by sandwiching the artificial skin in a culture vessel and fixing the degree of contraction. This reproduced a natural tensional homeostasis so that the model did not shrink during culture. It had a similar tissue structure as natural skin, with collagen fibers and cells aligned in the same lateral direction as the tension. In addition, dermal fibroblast cells in this model stretched uniformly in the lateral direction, indicating that reproduction of the tension equilibrium is important for maintaining the orientation of skin tissue.

The researchers then explored the role of tensional homeostasis in controlling skin structure and function. They found that their synthetic skin with tension equilibrium had more collagen fibers in the dermis, produced more primary skin cells, and had greater expression of certain genes than artificial skin without tension. This means that tensional homeostasis facilitates healing and regeneration of the human-skin equivalent and makes it more responsive to some drugs. The researchers suggest that skin-tension balance regulates skin functionality via mechanical stress signals.

There are increasing social demands to reduce the use of animals in research, especially for skincare products. "Human-skin equivalents have crucial roles for scientific evidence-based skin health care and disease research that can help us reduce research in animals," Tsuji says. "We believe that our human-skin equivalent model will greatly contribute to the technological developments of next-generation skincare and improve quality of life."

Reference

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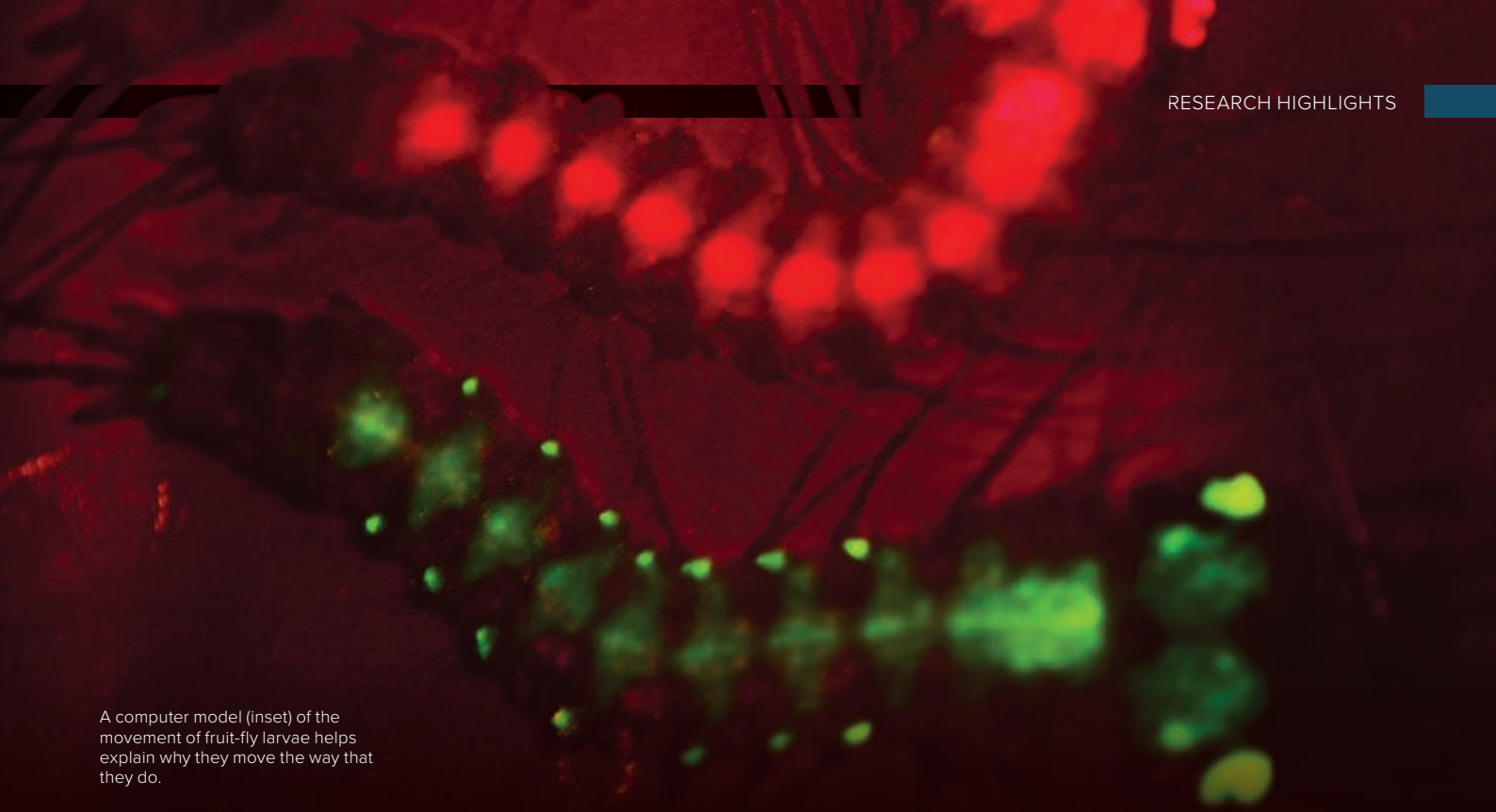


A computer model (inset) of the movement of fruit-fly larvae helps explain why they move the way that they do.

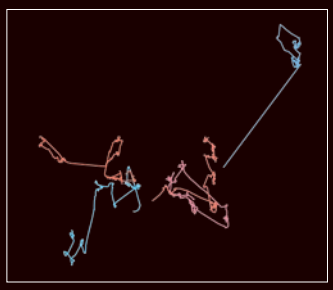
ANIMAL BEHAVIOR

Taking a walk on the random side

A computer model of fruit-fly larvae reveals the benefits of a ubiquitous form of random movement

A common form of random motion benefits animals by enabling them to flexibly switch between grazing and exploring, a computer model of fruit-fly larvae developed by a RIKEN scientist has revealed[1]. In addition to shedding light on the origins of this type of motion, the research could help engineers to develop artificial-intelligence systems that mimic natural ones more closely.

Named after the French mathematician Paul Lévy (1886–1971), a Lévy walk is a type of random movement in which an organism takes many small steps interspersed by the occasional longer one. It crops up everywhere in nature, from people wandering around at Disney World to immune cells in the brain. However, it is not clear how this movement arises, nor what advantages it offers over other movement strategies.



To explore the origins and advantages of Lévy walks, Masato Abe of the RIKEN Center for Advanced Intelligence Project created a mathematical model that imitates the motion of the larva of a fruit fly—a commonly used model organism.

The model was based on two elements that oscillate like a pendulum and a link connecting them. The larvae exhibited three different behaviors depending on the strength of the link. When the link was weak, the larvae basically followed a different kind of random motion, one resembling that of microscopic particles buffeted by molecules in a liquid or gas. And when the oscillators were tightly linked together, the larvae just walked in straight lines. However, when the link was intermediate, the larvae exhibited Lévy walks.

Interestingly, Lévy walks emerged suddenly near critical points—places where an animal's behavior changes flexibly. Abe wondered if this might benefit animals in some way. He found that in these areas, animals were able to respond strongly to even mild environmental stimuli. Thus, the motion could help animals make finely tuned decisions about whether to exploit the food in one area or to go searching in other areas. Observations of the actual movements of fruit fly larvae showed that they did indeed act in a manner consistent with the model.

"Thanks to this model, we can now explain why Lévy walks, emerging near critical points in a system, make sense for organisms performing tasks such as foraging for food, as well as searching for words in their memory," says Abe. "This work will help us in the field of artificial intelligence to create autonomous agents that can behave more closely like living organisms."

Reference

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PSYCHOSIS

The origins of psychosis

Tissue culture models of the fetal brain reveal psychosis-associated changes in the cell behavior of the early brain

The brain changes that occur at the onset of psychiatric conditions such as schizophrenia and bipolar disorder could originate from a disturbance in neuronal signaling pathways during brain development, RIKEN neuroscientists have found[1]. This knowledge could provide researchers with new strategies for treating these conditions.

Schizophrenia and bipolar disorder are some of the hardest mental health disorders to manage, in large part due to their complexity. In particular, the cellular mechanisms that underpin these conditions remain poorly understood. Diverse genetic and environmental factors give rise to psychosis, and it can be difficult to disentangle their various contributions.

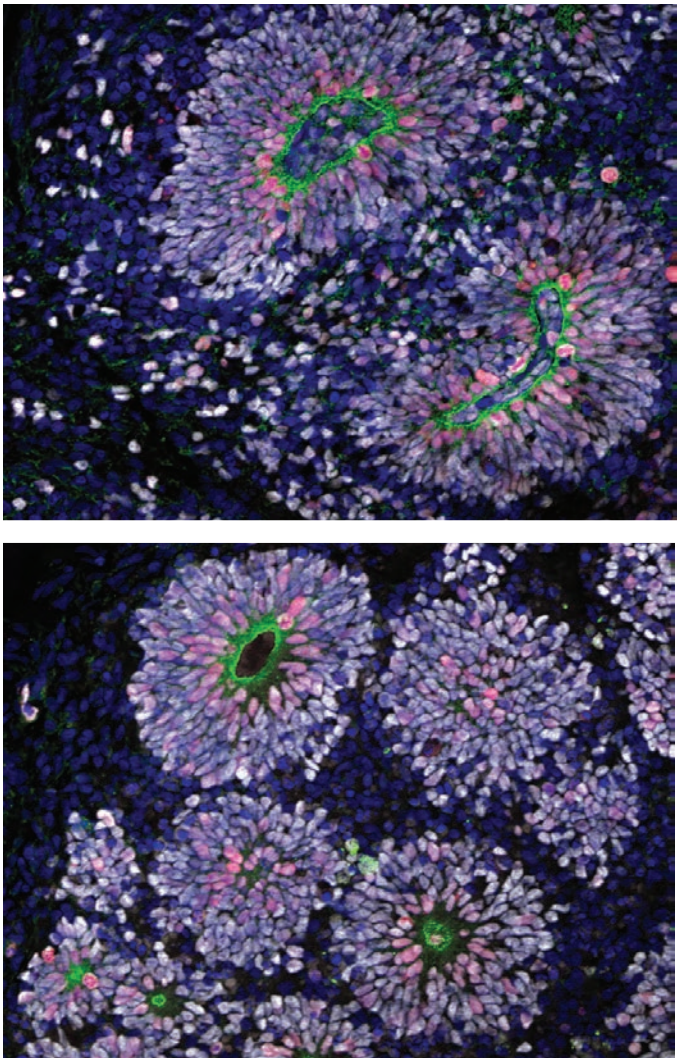
To overcome this problem, Tomoyo Sawada of the RIKEN Center for Brain Science (CBS) and her co-workers recruited a pair of identical twins where only one twin suffered from schizoaffective disorder, bipolar type—a condition characterized by both schizophrenic and bipolar disorder symptoms. Since identical twins are genetically identical, this provided a controlled genetic background for the study. The researchers validated their findings through further investigations involving two more pairs of identical twins where one twin had schizophrenia.

To model the early stages of brain development, the researchers took cells from participants' blood and reprogrammed them into stem cells (induced pluripotent stem cells, or iPSCs). These iPSCs were differentiated into neurons, which formed three-dimensional tissue cultures known as organoids.

The team used single-cell RNA sequencing to profile neuron activity in the organoids. They found that cell-to-cell signaling pathways between organoids derived from each twin differed significantly. In the psychosis-affected twin, 'Wnt signaling'—a critical mediator of cellular processes and embryonic development—was reduced. This subsequently reduced excitatory signaling of glutamate and dopamine, and, conversely, increased inhibitory gamma-aminobutyric acid (GABA) signaling compared to the healthy twin.

Postmortem analyses of patients with schizophrenia and bipolar disorder had previously shown reduced expression of inhibitory neurons. "Such a paradoxical phenomenon has also been reported in autism," explains Tadafumi Kato, also at the CBS. "The brain volume is larger than controls during the developmental stage, but it is smaller in the adult stage." This suggests that the lower numbers of inhibitory neurons found in adults with psychosis may be due to their enhanced production during early brain development.

The study was a first of its kind. "This is the first detailed analysis of cerebral organoids for studying psychiatric disorders," says Sawada. "It also represents the first use of single-cell RNA sequencing to compare brain organoid data for psychiatric disease markers." Sawada's team now intends to determine the link between enhanced early GABA signaling and psychosis development by adapting brain organoids derived from iPSCs to model the adult brain. ●



Cerebral organoids derived from a psychosis-affected twin (bottom image) exhibited significantly smaller ventricular zone-like structures than that derived from the healthy twin (top image). (White: neural progenitor marker; red: proliferative marker; green: apical surface marker).

Reference

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PARTICLE ASTROPHYSICS

Exotic space matter remains elusive

A search for visible traces of 'heavy compact objects' hitting the Earth's atmosphere could help to refine theories about dark matter

In the search for the source of the mysterious dark matter that is predicted to make up 85% of the Universe's mass, astrophysists at RIKEN have limited the likelihood that dark matter is made up of 'heavy compact objects'—a special form of matter that is simultaneously very dense and small[1].

Dark matter can be inferred from the movement of galaxies and other phenomena, but it has never been directly detected. Heavy compact objects have been proposed as one candidate for dark matter. One type of these objects—nuclearites, which were hypothesized in 1984—would contain extremely dense forms of exotic material, so-called strange quark matter, made up of nearly equal numbers of three types of quarks.

When space rocks strike the Earth's atmosphere, they become meteors that heat up and generate rather short, variable streaks of light in the upper atmosphere, until they cool down or disintegrate. In contrast, heavy compact objects such as 'nuclearites' are predicted to travel at hundreds of kilometers per second—several times faster than meteors—and would produce long tracks of almost constant brightness in the lower atmosphere.

Lech Piotrowski at the RIKEN Computational Astrophysics Laboratory and colleagues have now trawled through telescope images in search of these nuclearite traces. The data came from the Pi of the Sky project, a system of robotic telescopes in Spain and Chile. The very wide angle of view and large amount of data collected over several years of this project made it suitable for searching for bright, rare phenomena such as trails left by heavy compact objects.

Shooting stars, such as in this shower seen in China, are caused by small particles burning up in the upper atmosphere. Heavy compact objects, including nuclearites, which are candidates for dark matter, would travel faster than meteors and produce long tracks of almost constant brightness in the lower atmosphere.

The researchers developed a computer algorithm to look for nuclearite traces in hundreds of thousands of images from these telescopes. After the algorithm had removed events caused by cosmic rays, meteors and satellites, the astronomers narrowed down the pool of images to just 20 that did not have an obvious explanation. However, none of these were a good match for the traces expected from nuclearites. This implies that nuclearites, if they exist, are very rare. If nuclearites reached Earth at an equal rate from all directions, the absence of traces suggests that no more than two nuclearites with masses of 100 grams will hit a square kilometer of the Earth's atmosphere every decade. Heavier nuclearites are even scarcer—a 100-kilogram nuclearite would pass through a square-kilometer area less often than once per century.

"Our limits can be used to put constraints on specific types of heavy compact objects, not necessarily nuclearites, and their distribution in the Universe," says Piotrowski. "But it is important to improve on the limits." He hopes that future experiments using ground-based and orbiting telescopes will conduct an even more sensitive search for nuclearites. ●

Reference

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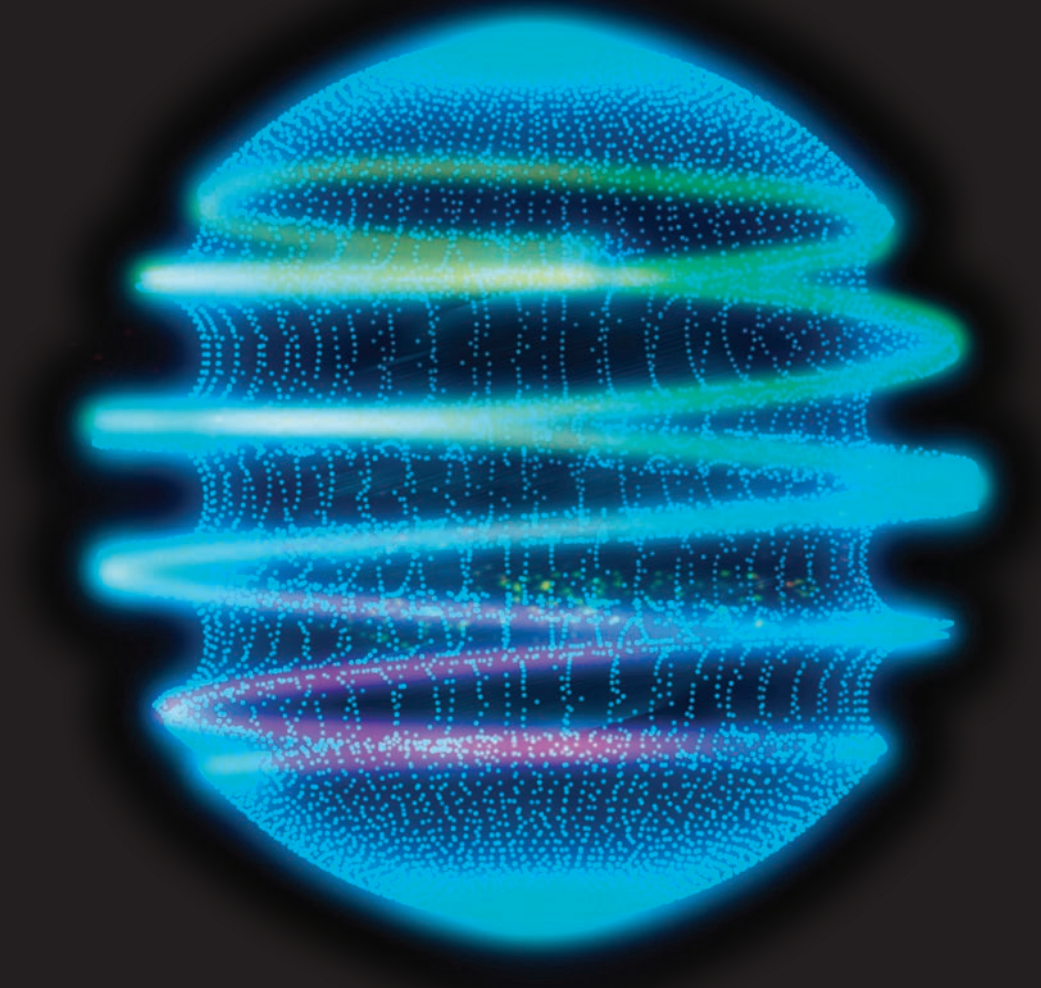
AXION PHYSICS

Stringing together dark matter

Calculations show how theoretical 'axionic strings' could create odd behavior if produced in exotic materials in the lab



An artist's impression of an axion, a hypothetical elementary particle, which has been invoked to explain why charge–parity symmetry is preserved in quantum chromodynamics. They have since been proposed as a leading candidate for dark matter.

A hypothetical particle that could solve one of the biggest puzzles in cosmology just got a little less mysterious. A RIKEN physicist and two colleagues have revealed the mathematical underpinnings that could explain how so-called axions might generate string-like entities that create a strange voltage in lab materials[1].

Axions were first proposed in the 1970s by physicists studying the theory of quantum chromodynamics, which describes how some elementary particles are held together within the atomic nucleus. The trouble was that this theory predicted some bizarre properties for known particles that are not observed. To fix this, physicists posited a new particle—later dubbed the axion, after a brand of laundry detergent, because it helped clean up a mess in the theory.

Physicists soon realized axions could clear up a cosmic conundrum too. More than 80% of the matter in the Universe is thought to be made up of a mysterious invisible substance, dubbed dark matter. "Axions are a candidate for dark matter, but we have not found them yet," says Yoshimasa Hidaka, of the RIKEN Interdisciplinary Theoretical and Mathematical Sciences Program. Axions might have the right properties, so physicists have been searching for signs they exist in numerous experiments. In June 2020, the XENON1T experiment at the Gran Sasso Laboratory in Italy reported hints they may have detected the axion—but that result has yet to be confirmed.

But there is another arena where axion properties can be studied. In the lab, physicists can prepare exotic materials, called topological insulators, which display strange properties, such as conducting electricity on their surfaces while remaining electrical insulators within. Such materials display other weird behavior. Sometimes, their electrons group together and move in such a way that the material appears to be made from 'quasiparticles' with unusual properties. This can create an unexpected voltage across the material, called the anomalous Hall effect.

The axion is also predicted to arise in this way, in topological insulators, where it should interact with particles of light, or photons, in a different way to regular particles.

Hidaka and his two colleagues have now examined the theory governing the interaction between axions and photons. Even though axions are point-like particles, the team calculated that within materials, light might actually interact with extended thread-like configurations made of axions, called axionic strings. That would lead to the anomalous Hall effect, which is observed in experiments.

"We have found the underlying mathematical structure for the phenomenon," says Hidaka.

Reference

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PULSARS

Pulsar distinctions are not so cut and dried

A recently discovered neutron star appears to bridge the gap between two different types of x-ray-emitting neutron stars

The study of a special type of neutron star with extremely high magnetic fields has received a boost thanks to x-ray observations by RIKEN researchers of a newly discovered x-ray-emitting neutron star[1].

Neutron stars are formed when massive stars run out of fuel and collapse under their own mass. They are small—just 20–30 kilometers in diameter—but incredibly dense, being composed mostly of neutrons.

Some neutron stars called pulsars emit intense beams of electromagnetic radiation that sweep through space like the beam of a lighthouse. The power source of these beams depends on the type of pulsar. The beams of conventional radio pulsars are powered by the rapid rotation of the star, whereas extremely strong magnetic fields are believed to power the x-ray beams for special pulsars known as magnetars. However, these phenomena are not well understood.

Recently, several magnetars have been found to emit radio waves—something previously thought to be limited to rotation-powered pulsars. These observations thus blur the boundaries between the two kinds of pulsars.

Now, observations by Chin-Ping Hu of the Extreme Natural Phenomena RIKEN Hakubi Research Team and colleagues have uncovered another connection between the two pulsar types.

On 12 March 2020, a new gamma-ray burst was detected by the Burst Alert Telescope aboard a space-based gamma-ray observatory.

Artwork illustrating a magnetar, a type of neutron star that has an exceedingly powerful magnetic field, trillions of times stronger than Earth's own field and even more powerful than regular neutron stars. Measurements on a new magnetar show that this new x-ray object has properties of both magnetars and rotation-powered pulsars.

Just four hours after the alert, the RIKEN team began making x-ray observations using the Neutron star Interior Composition Explorer (NICER), an x-ray instrument aboard the International Space Station. "The discovery of a new magnetar is exactly what our magnetar and magnetosphere science team of NICER was waiting for," says Teruaki Enoto, team leader of the Extreme Natural Phenomena RIKEN Hakubi Research Team.

The magnetar emitted a pulse every 1.36 seconds, the shortest pulsation period for a magnetar observed to date. The team investigated the basic x-ray behavior of this new magnetar.

Measurements of its surface magnetic field indicated that it was a young magnetar, formed only about 420 years earlier. The magnetar's youthfulness was confirmed by fluctuations in its rotational motion. However, its x-ray emission was lower than that of other magnetars, indicating that the star has the attributes of both magnetars and rotation-powered pulsars.

"The bridge between the two types of pulsars that we discovered has contributed to our understanding of these mysterious objects," notes Enoto.

"Our study has given us new understanding of the neutron stars with high magnetic fields," adds Hu. "Recent radio observations suggest that magnetars may be a cause of mysterious phenomena called fast radio bursts, so we look forward to investigating further." ●

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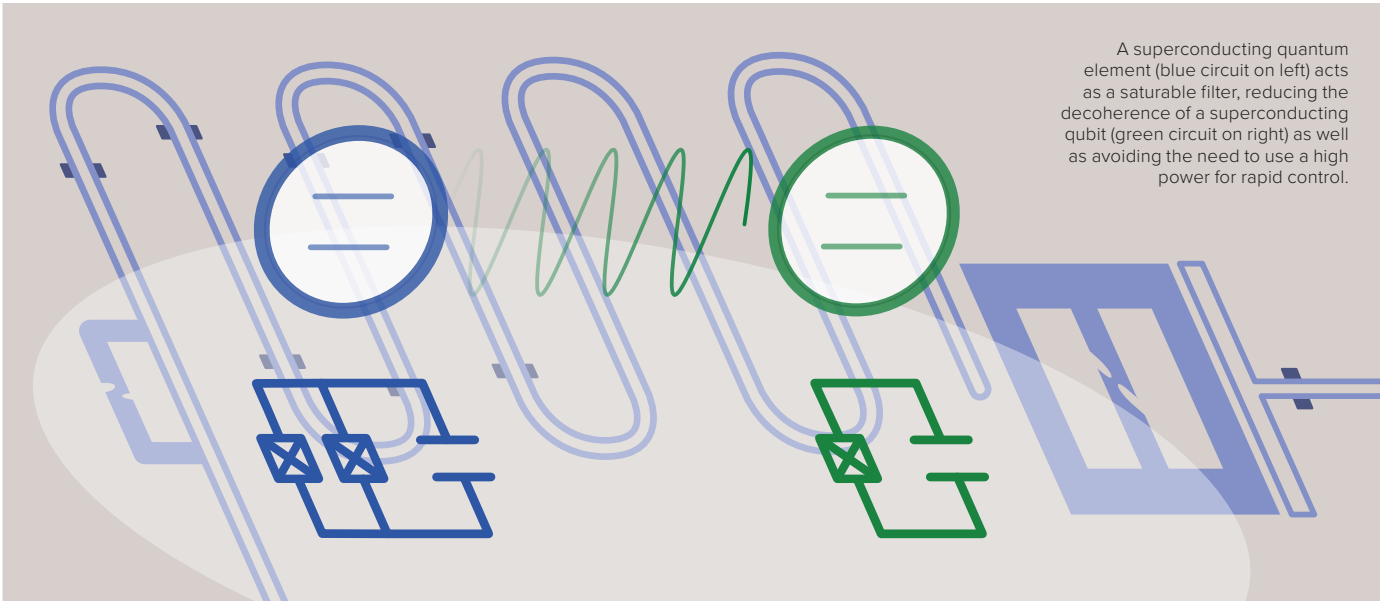

A superconducting quantum element (blue circuit on left) acts as a saturable filter, reducing the decoherence of a superconducting qubit (green circuit on right) as well as avoiding the need to use a high power for rapid control.

QUANTUM INFORMATION

Quantum filter allows qubits to have their cake and eat it

Rapid control of long-lived superconducting qubits is made possible by using a quantum filter

Superconducting qubits have become even more attractive for realizing quantum computers due to the demonstration by a RIKEN-led team of a quantum filter element that allows rapid control of superconducting qubits without sacrificing their long lifetimes[1].

In principle, any physical system with two energy levels can operate as a qubit—the memory element of a quantum computer. To work as a qubit, however, the system must be able to maintain its quantum properties for considerably longer than the time it takes for each operation to be performed. This duration is known as the coherence time of a qubit.

Superconducting qubits are one of the most promising qubit systems, in part because they are highly stable with respect to the environment. But to read and write information, a qubit has to be coupled with a control line, which introduces a source of decoherence. This decoherence involves the emission of a microwave photon.

The probability of photon emission can be minimized by turning down the coupling strength to the control line, but this requires using a high-power control signal to realize rapid control, which can affect other qubits in the circuit and generate undesirable noise. There thus exists a trade-off between a long qubit lifetime and the rapid control of superconducting qubits, and this trade-off will become more problematic as the number of qubits is increased.

"A linear filter connected to a qubit allows fast qubit readout and a long qubit lifetime, but it doesn't permit fast qubit control," explains Yasunobu Nakamura of the RIKEN Center for Emergent Matter Science. "We wanted to realize fast qubit control without reducing the qubit lifetime, leading us to the idea of using a saturable filter."

Now, Nakamura and colleagues have overcome this trade-off by demonstrating that a superconducting quantum element placed close to a qubit can effectively decouple the qubit from the control line by reflecting emitted photons.

The quantum filter consists of a superconducting qubit as well. It can absorb only one photon at a time. So when the qubit emits a photon, the filter can absorb the photon and then reflect it back, effectively suppressing the decay of the qubit. On the other hand, when a control signal with thousands of photons is sent to the qubit, the filter will absorb one photon but becomes transparent to the other photons, which can thus reach the qubit.

Using this quantum filter, the team were able to obtain a huge increase in qubit decoherence time. As a result, the filter reduces the power needed to control a qubit by several orders of magnitude.

The team is now designing a circuit made up of many qubits.

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HYDROGELS

Mimicking sea cucumbers using titanium

An inorganic material can flip between hard and soft states with changing temperature

Inspired by the flexibility of sea cucumbers, material scientists at RIKEN have created an inorganic material that switches between a hard and soft gel on raising or lowering its temperature[1]. This opens up the possibility of producing adaptive materials that have superior mechanical properties.

Adaptive materials that respond to stimuli such as temperature changes are almost always based on organic materials. However, using inorganic materials such as metals could be advantageous since they may have better mechanical properties. Thus, the RIKEN-led team wanted to recreate the behavior of organic hydrogels using inorganic materials.

The team was inspired by sea cucumbers, which are marine animals related to starfish. They can morph their skin from a hard layer to a jelly-like substance, allowing them to flee predators by jettisoning some internal organs (which eventually regrow). This change occurs when chemicals released by their nervous system trigger a rearrangement of a protein scaffold.

The researchers experimented with arranging nanosheets of titanium oxide in water. "The key to whether a material is a soft hydrogel or a harder gel is based on the balance between attractive and repulsive forces among the nanosheets," explains Koki Sano of the RIKEN Center for Emergent Matter Science (CEMS). "If the repulsive forces dominate, it is softer, but if the attractive ones are strong, the sheets become locked into a three-dimensional network, and it can rearrange into a harder gel."

A sea cucumber spawning. RIKEN scientists have created an inorganic hydrogel that mimics the skin of sea cucumbers in that it switches between a hard and soft gel on changing its temperature.

The researchers finely tuned the electrostatic repulsion to make a gel whose properties changed with temperature. At a temperature of about 55 degrees Celsius, their material changed from a softer, repulsion-dominated state to a harder, attraction-dominated state. Even after going through this transition many times, the material showed no significant deterioration.

"What was fascinating is that this transition process is completed within just two seconds even though it requires a large structural rearrangement," says Sano. "This transition is accompanied by a 23-fold change in the mechanical elasticity of the gel, reminiscent of sea cucumbers."

To increase the material's usefulness, the researchers added gold nanoparticles to it that could convert light into heat. This allowed them to heat the material and change its structure by shining laser light on it.

"This is really exciting work as it greatly opens the scope of substance that can be used in next-generation adaptive materials," says Yasuhiro Ishida, also of CEMS. "And it may even allow us to create a form of inorganic life." ●

Reference

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NEUROSCIENCE

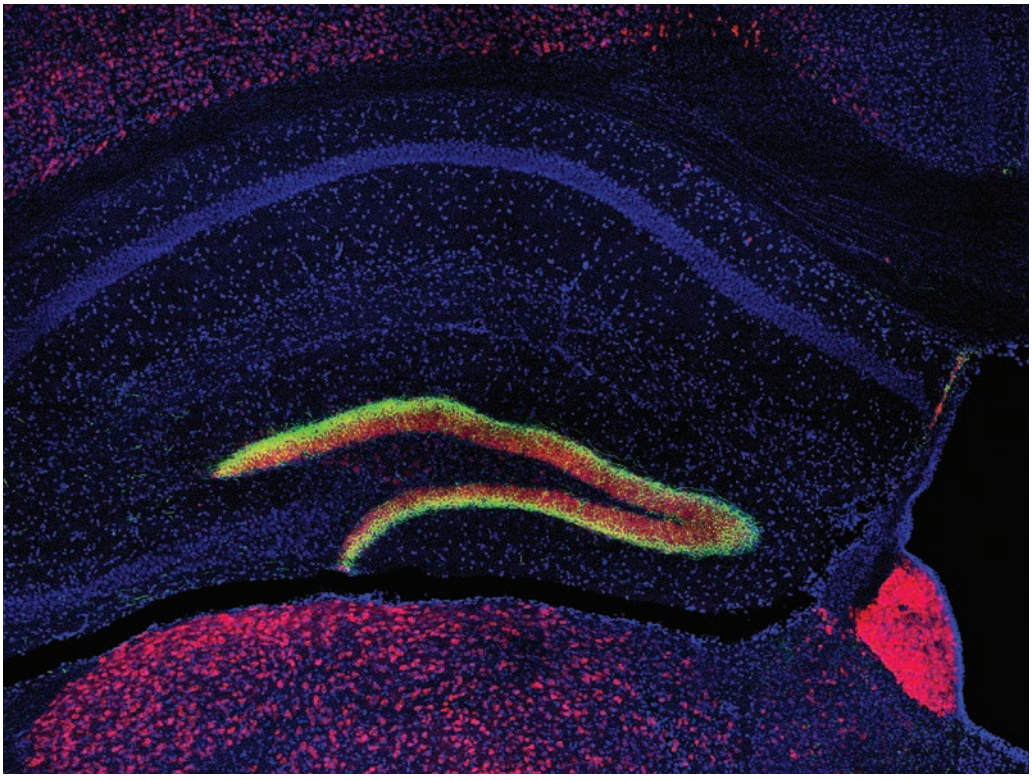
Brain region processes novel encounters

The neural pathways in mice responsible for processing new experiences have been found

A part of the mouse brain called the supramammillary nucleus (SuM) is specialized for detecting new experiences, RIKEN neuroscientists have discovered[1]. This discovery can illuminate both normal memory and conditions in which the recognition of and reaction to new information are impaired.

Meeting a new person or entering an unfamiliar house are very different experiences from meeting an acquaintance or walking into your own home. The ability to distinguish between the familiar and the unknown is essential for engaging in normal social interactions, performing daily functions and even surviving.

Since most animals seem to be born with this ability and other innate behaviors are connected with the hypothalamus region of the brain, a team led by Thomas McHugh of the RIKEN Center for Brain Science suspected that this ability might also involve the hypothalamus.



A fluorescence micrograph of a section of the hippocampus of a mouse. The green regions are axonal terminals of supramammillary nucleus (SuM) neurons, while the red areas are hippocampal neurons.

To test this, the team exposed mice to two types of novelty: an unfamiliar place (contextual novelty) and unknown individuals (social novelty). These novel situations caused much higher activity in the SuM, located in the hypothalamus, than when the mice were placed in familiar cages or near familiar mice.

"The hypothalamus is a very highly conserved region of the brain across evolution, mostly thought to be involved in innate behaviors like feeding, mating, parenting and fighting," says McHugh. "Our data suggest that it could also serve as a link between these survival-type behaviors and higher cognitive function."

Surprisingly, most neurons in the SuM responded to only one or the other type of novelty. This is the first time that a social and contextual split has been found in a novelty circuit in the brain.

Experiments on genetically altered mice revealed that neurons in the SuM connect with two hippocampus regions. Neurons selective for contextual novelty connected to the dentate gyrus (DG) region, while those that signaled social novelty connected to the CA2 region.

Stimulating specific neurons using laser light revealed that output from the SuM directly affected social and contextual memory. For example, exciting the SuM-to-CA2 connection caused mice to behave as if they had a selective deficit in social memory—they frequently approached familiar mice as if they had never seen them before—but they did not explore familiar rooms more than control mice. The reverse behavioral pattern was seen when the SuM-to-DG connection was excited.

"Understanding how we recognize and react to novel information is fundamental to understanding memory," says McHugh. "Not only does novelty strengthen memory, both in mice and humans, impairment in recognizing and reacting to new information often accompanies psychiatric conditions. This research can thus provide a biological target to examine in such cases." ●

Reference

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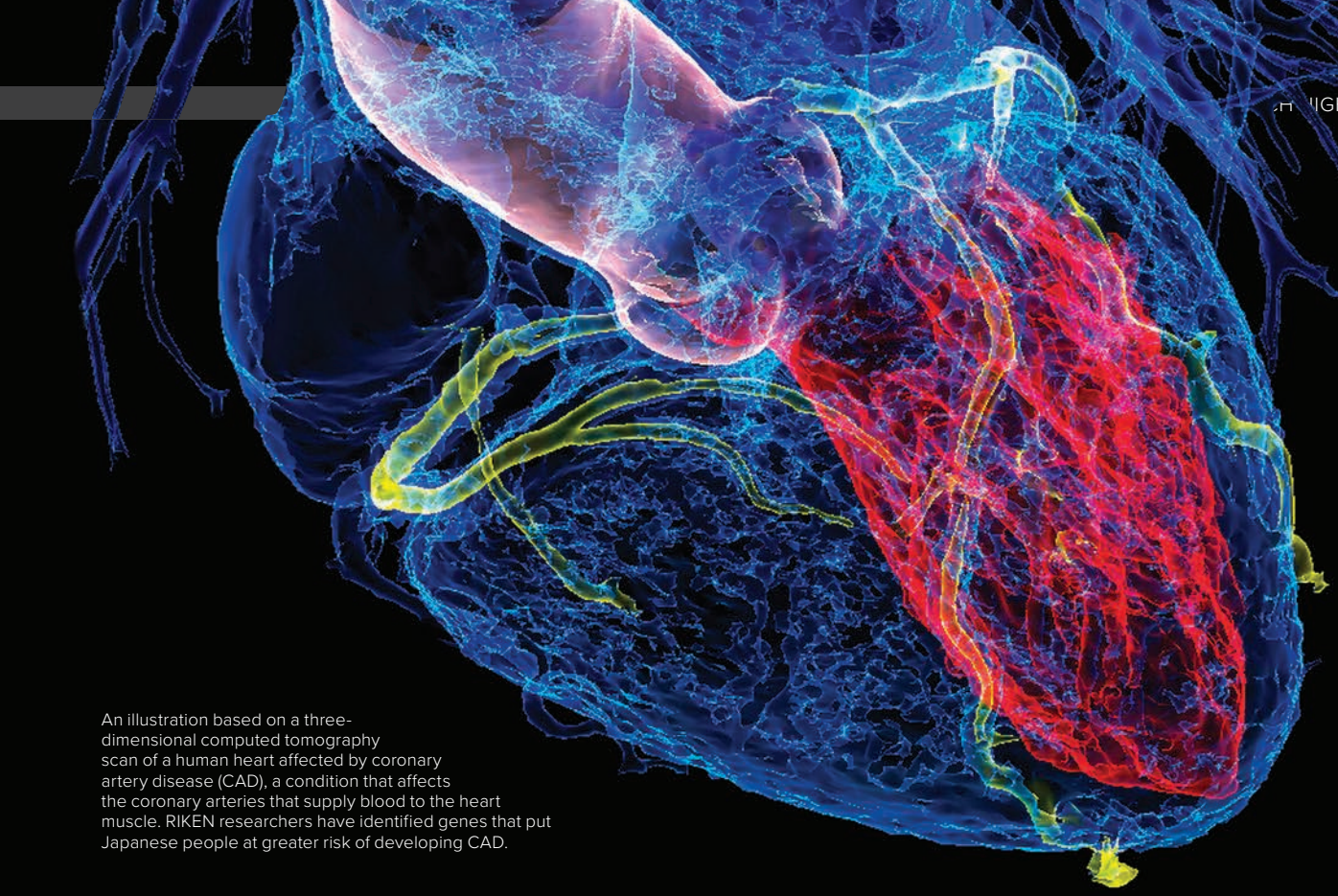

An illustration based on a three-dimensional computed tomography scan of a human heart affected by coronary artery disease (CAD), a condition that affects the coronary arteries that supply blood to the heart muscle. RIKEN researchers have identified genes that put Japanese people at greater risk of developing CAD.

CORONARY ARTERY DISEASE

The genetics of the Japanese heart

The possibility of developing coronary artery disease can be predicted with more accuracy thanks to a massive genetic study

By combining genetic data from Japanese and European populations, a RIKEN-led team has devised a more accurate predictor of coronary artery disease based on genetic factors[1]. In addition to identifying people with a high risk of developing the condition, the findings could help develop new treatments.

Coronary artery disease is the most common form of heart disease and the world's leading cause of death. It is highly heritable and genetic risk scores based on genetic information can accurately predict the onset of disease in individuals. But since studies have mainly focused on European populations, it is unclear how applicable these scores are for other populations of other ancestries.

To address this imbalance, the RIKEN-led team examined the genetics of the disease in a Japanese population by comparing the genome sequences of nearly 26,000 coronary artery disease patients and more than 142,000 controls. This made the study the largest genome-wide association analysis (GWAS) on coronary artery disease in a non-European population.

The team identified 43 genetic loci associated with a susceptibility to coronary artery disease, eight of which were previously unknown. In particular, they found one genetic variant in the *RNF213* gene, which is known to be associated with a cerebrovascular disease and which had never been identified in GWAS studies with European cohorts.

These results enabled the researchers to build a reference panel for the Japanese population, which can be used to gauge the risk of even variants found in a tiny proportion of the population. "We found one variant in the *LDLR* gene, which is not very common, but it has an important effect on cholesterol metabolism," says Kaoru Ito of the RIKEN Center for Integrative Medical Sciences. "Japanese people with this rare mutation have a five-fold higher likelihood of developing coronary artery disease."

By combining the results of nearly 170,000 Japanese subjects with two datasets from European populations—creating one of the world's largest trans-ethnic GWAS in coronary artery disease—the team identified 35 new loci associated with disease, one of which is the target of statin drugs.

The group used the combined GWAS to create a genetic risk score that outperformed the results of scores crafted from either. "This is exciting, as it means that, even when there are different frequencies of variants in different populations, we can combine GWAS studies from different ancestries and use this to create a risk score that is more accurate than any of the individual ones," says Ito. "This means that integrating existing data is a good way to develop genetic risk scores in non-European populations." ●

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MICROBES ARE PERHAPS MORE MANAGEABLE THAN WE THOUGHT

Escherichia coli (*E. coli*) has a genome with roughly 4,500 genes. The number of mutations possible defies most researchers' analysis resources, unless, as Chikara Furusawa and his team have done, fewer likely evolutionary directions can be identified.

The likely adaptive trajectories for viruses and bacteria might be fewer than previously thought, and there may be implications for the superbugs crisis.

Scientists at RIKEN have shown that correlated dynamics mean that the evolutionary pathways taken by microbes are fewer than previously thought—a finding that could significantly improve the predictions of how infectious bacteria will develop antibiotic resistance, and perhaps even help science to steer the course of microbial evolution.

Chikara Furusawa and his team at the RIKEN Center for Biosystems Dynamics Research have a long-standing interest in uncovering the dynamics that drive the evolution of bacteria. It isn't a research project for the faint hearted. Take the humble gut bacterium *Escherichia coli* (*E. coli*) for example. Its genome only contains around 4,500 genes—much fewer than the approximately 30,000 protein-encoding genes of a mouse. But that still creates an astronomical number of possible mutant bacteria, far exceeding present analysis capabilities.

"Biological systems are highly complex, consisting of a huge number of components," says Furusawa. "If we assume that the state of an *E. coli* cell can be described by the expression levels of its genes, the state of one cell can be represented by a point in a graph that has 4,500 axes—a very high dimensional state."

PHYSICS AIDS GENETICS

The ability of microbes to rapidly mutate and change has been making headlines with the emergence of a new highly virulent strain of the virus that causes COVID-19. The rise of strains of bacteria that are resistant to multiple antibiotics, which make readily treatable infections potentially life endangering, is also an acute concern globally. Both examples are reminders that microbes are constantly evolving under our noses (or in them!).

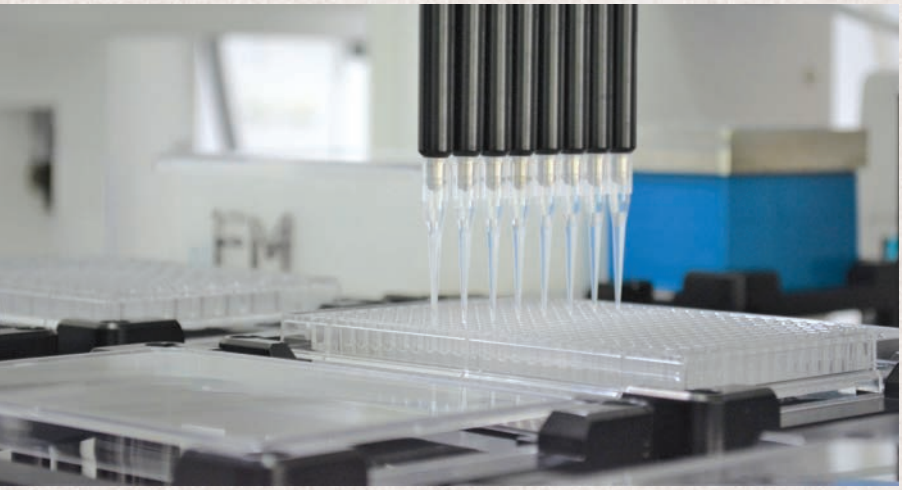
Furusawa brings a unique perspective. He's not a microbiologist or evolutionary biologist by training. Rather, he's a physicist who has studied the physics of complex interacting systems. The genius of physics is that it simplifies highly complex systems, stripping them down to their essential components. That is what Furusawa and his team are striving to do for the evolutionary dynamics of microbes.

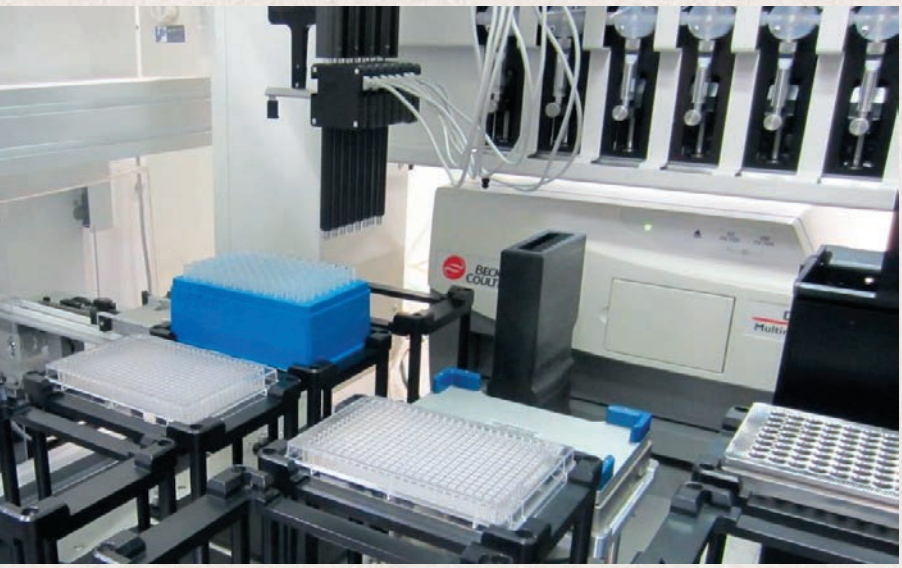
"My question is whether such a high-dimensional state is really necessary to describe the phenotypes of evolutionary dynamics," says Furusawa. "The expression levels of many genes may change in a very coordinated manner. Such correlated dynamics could greatly cut the number of variables needed to describe an *E. coli* cell."

Put simply, the expression levels of two genes may not be independent of each other: if the expression level of one gene changes, then that of the other gene may also change. Thus, the seemingly infinite number of possible paths that evolution offers may all converge into a few broad tracks. This concept has the potential to greatly simplify the problem of characterizing the evolutionary dynamics of microbes.

This feature looks **at the work of**
CHIKARA FURUSAWA

Chikara Furusawa received his Ph.D. from the University of Tokyo in 2000. His thesis focused on computational modeling of multicellular development. He launched his own lab at the RIKEN in 2011. The Laboratory for Multiscale Biosystem Dynamics at the RIKEN Center for Biosystems Dynamics Research now focuses on revealing evolutionary dynamics by integrating high-throughput experiments, data science and theoretical analysis. In 2011, he received the Nishinomiya-Yukawa Memorial Prize and The Young Scientists' Prize from Japan's MEXT.





Ninety-five bacteria stressors were used to induce mutations in *E. coli*. Each was replicated six times, including a control. Ultimately there were 576 culture series that went through 27 daily passages corresponding to ~250–280 generations. This was made possible using a robotic culture system at RIKEN (above).

95 WAYS TO STRESS BACTERIA

To test this, Furusawa's team effectively fast-tracked evolution in their laboratory. They exposed samples of a strain of *E. coli* to one of 95 antibiotics or other stressors. In the first round, the researchers divided each of the initial 95 samples into several vials, and exposed those vials to varying concentrations of the antibiotic, from low to high. The vial containing the highest antibiotic concentration whose *E. coli* survived was used in the next round of tests. Using this procedure, the team raised roughly 250 generations of each sample. For each of the evolved strains, they analyzed its genetic makeup, its gene expression and its resistance to other antibiotics.

Furusawa and his team found that 89 of the 95 samples of *E. coli* had developed resistance to the drug it had been exposed to. But more importantly, they discovered that the 95 strains could be clumped together into 11 broad groups. This provided strong evidence that their hypothesis was correct—that evolutionary pathways initiated by different stressors tend to converge to a few broad clumps. This finding implies that evolutionary trajectories are much less complex than they first appear.

The result didn't come as a surprise to Furusawa, as his team had previously run theoretical simulations that predicted that they would converge. "This is what we'd expected since computer simulations suggested that the number of possible phenotypic changes will be constrained to a low number," he says.

This demonstration has important implications for combating drug resistance in pathogens as it will allow researchers to predict in advance how drug resistance will develop, which could be vital in developing countermeasures. But beyond that, it may also allow scientists to steer the course of evolution. "We are now actually trying to control the evolutionary dynamics by dynamically changing the selection pressure," says Furusawa. This ability to funnel evolution pathways in certain directions could find application in the bioengineering industry, which uses microbes to produce a wide range of useful products.

LAB ROBOTS SPEED-UP EVOLUTION

What set the team's experiment apart was its sheer scope and scale. "Many studies on experimental evolution have been done using only a few antibiotics, but we have greatly expanded the number of stressors," says Furusawa. "We tried to comprehensively understand the evolutionary dynamics of the *E. coli* response to stress."

This was only possible due to a fully automated experimental system that uses robotics to handle the samples. It permits laboratory evolution to be simultaneously conducted on up to 700 strains. The system took Furusawa's team about a decade to develop and they had many initial teething problems. But this study has demonstrated its power to stimulate evolution in the lab on a scale never achieved before. "As far as we know, it has the highest throughput of any lab evolution system in the world," Furusawa says. The team is now planning to explore systems made up of multiple species of bacteria, which seeks to mirror what happens in our guts and other sites of bacterial interaction.

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RESPONDING TO THE CHALLENGE OF COVID-19

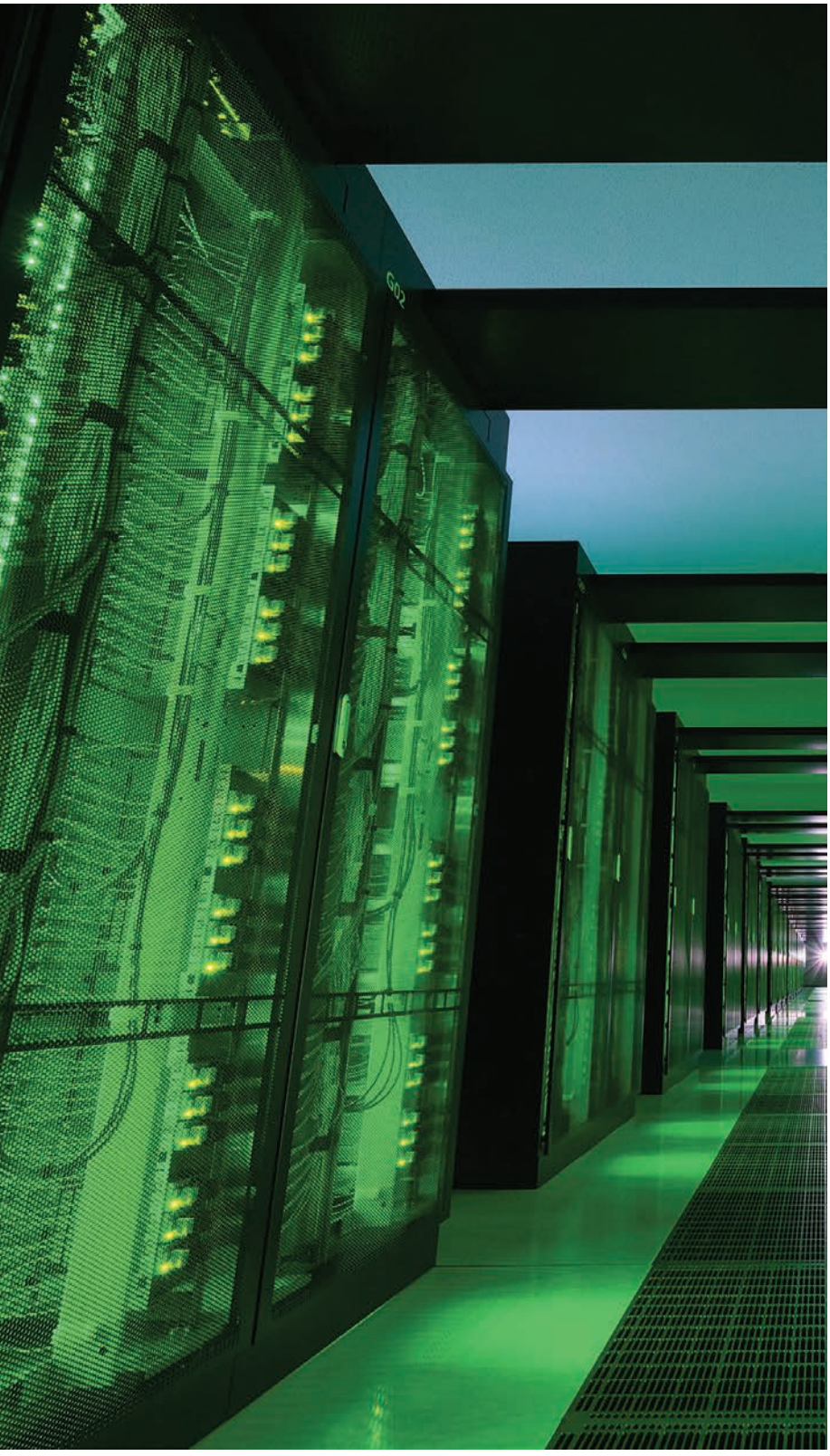
The arrival of COVID-19 in Japan in early 2020 prompted a concerted research effort at RIKEN. A strong research capacity in immunology, molecular biology and computational sciences, coupled with a culture of interdisciplinary collaboration and access to sophisticated infrastructure, gave RIKEN room to work on goals as diverse as diagnostics, therapeutics, vaccines and understanding social behavior.

The first confirmed case of COVID-19 in Japan was reported in mid-January 2020. In early April, as case numbers increased, the Japanese government declared a state of emergency. RIKEN responded by diverting research resources and drawing on the expertise, not only of life scientists, but also mathematicians, physicists and engineers, including those not usually involved in virology or epidemiology.

Research priorities identified by the RIKEN President's Fund—an internal funding mechanism that was put to work for COVID-19—were:

- the publication of data and research using cutting-edge, large-scale, joint-use facilities;
- the development of diagnostic methods;
- the development of therapies;
- research to help people and communities overcome the crisis, and;
- basic research, including the development of technology to visualize the life cycle of the virus, genome analysis, epigenetic analysis and the study of host-gut microbiome interactions.

Basic research is currently being supported by the development of an artificial intelligence (AI) system that automatically analyzes biomedical big data from published papers. Early access to Japan's flagship supercomputer Fugaku (see pages 8 and 32, installation of which had begun in December 2019 under a RIKEN-led project) was central to many of the research goals. Projects given priority access to Fugaku included research on the characteristics of the new coronavirus, identification of compounds that could be used as therapeutic agents, improvement of diagnosis and treatment, understanding the socio-economic impacts of the pandemic and simulating the potential spread of infection through airborne droplets.



Among the projects given early access to the Fugaku supercomputer is one that is working to identify compounds that could be used as therapeutic agents.

DRUG DISCOVERY

One major aspect of RIKEN's response is the search for therapies for COVID-19. Some of the projects used Fugaku's massive computing power, for instance to search for drugs that target viral proteins and reduce the propagation of the virus in the early stages of disease. A project was also initiated by the RIKEN Program for Drug Discovery and Medical Technology Platforms (DMP), in collaboration with other RIKEN life-science centers and external research institutions, to help find effective drugs by investigating, for example, how well existing drugs bind to SARS-CoV-2 proteins.

These projects are now bearing fruit. One group of scientists used a protein-ligand docking method using large-scale molecular dynamics simulation (called ColDock) to calculate the binding affinities between virus proteins and more than 2,000 candidate drug compounds. Of these, 30 existing medications were earmarked as possibly effective COVID-19 treatments. These included drugs already in clinical studies such as remdesivir. The supercomputer Fugaku took 10 days to run the calculations, a feat that would have taken its predecessor, the K computer, at least a year.

Another group published molecular interaction data of 378 viral protein structures calculated by a quantum-mechanical method (called the fragment molecular orbital (FMO) method, developed by RIKEN researcher Kazuo Kitaura) on RIKEN's FMO database, the world's first database of quantum-mechanical data for proteins. The open database allows users to look at the mechanism by which a therapeutic drug candidate compound binds to a target protein, and the effect of stronger binding to the target.

An obvious viral protein target studied by RIKEN researchers was the structural spike protein (the protein involved in attachment to, and infection of, host cells). Others included non-structural proteins involved in the replication of the virus's genome and the synthesis of its proteins, such as the RNA-dependent RNA polymerase, the main protease (Mpro) and the papain-like protease (PLpro). The researchers also investigated a host cell surface protein, transmembrane serine protease 2 (TMPRSS2), which is involved in virus entry. These investigations are continuing, with the results freely available online for other researchers, as are the RIKEN-produced molecular simulation data on the structural dynamics of SARS-CoV-2 proteins.

Access to the SPring-8 (synchrotron) and SACLA (x-ray free-electron laser) facilities has also provided opportunities for structural analysis and for exploration of materials (such as those used in protective gear) that reduce the attachment of the virus.

Further therapeutic goals include the development of a COVID-19 antibody drug.

DETECTING VIRUS RNA MOLECULES

A major focus at RIKEN has been diagnostics.

Currently, the most widely used method for detection of SARS-CoV-2 is the polymerase chain reaction, which amplifies viral RNA to an easily detectable level. RIKEN went a different direction and developed a proprietary nucleic acid technology that does not require the amplification and can detect single molecules of viral RNA.

As one of five projects made possible by the RIKEN President's Fund, Rikiya Watanabe's team at the RIKEN Molecular Physiology Laboratory is developing a new detection method that uses this technology, alongside CRISPR–Cas13, a gene-editing technology, and a guide RNA specific to a sequence of the SARS-CoV-2 genome distinct from other coronaviruses.

The original nucleic acid technology investigation was used to study proteins, particularly membrane proteins such as ion pumps. The advantage of this method is that it can detect and identify single molecules and examine their behavior. In contrast, measurements on a collection of molecules only reflect average behavior. The method has now been applied to detect a wide variety of molecules, including RNA.

The method also uses a digital detection approach whereby the test sample is diluted into hundreds of compartments containing the guide RNA. Each compartment registers as either positive or negative according to whether a fluorescent tag is detected or not. Statistical analysis reveals the concentration in the original sample.

If quantification is not important, a result for something like SARS-CoV-2 can be obtained in 10 minutes. Although this new method detects the viral RNA at the sensitivity close to PCR, the method would need further development to be suitable for high-throughput mass screening. Future research will include analysis of clinical samples.

Other diagnostic approaches being examined by RIKEN researchers include methods of detecting antibodies to coronavirus proteins and development of an antibody-based rapid diagnosis kit.

NEW VACCINE APPROACH

A great deal of hope has been placed in vaccines, but there are potential difficulties facing current candidates. Firstly, coronaviruses mutate, changing their surface proteins. In addition, infection or vaccination can occasionally lead to antibody-dependent enhancement (ADE) which, through a variety of mechanisms (such as enabling viral entry into cells) can increase the severity of disease. RIKEN has developed a new vaccine technology 'mMAP' (mutation compatible multiple antigen peptides) to help to address these problems.

Database searches revealed regions of the spike protein conserved between SARS-CoV-2, the Middle East respiratory syndrome coronavirus (MERS-CoV) and severe acute respiratory syndrome coronavirus (SARS-CoV or SARS-CoV-1), the first identified strain of the SARS coronavirus species. These conserved regions are unlikely to mutate.

Using this information, another project was funded by the RIKEN President's Fund to construct a synthetic polypeptide containing multiple antigenic sites from the spike protein. The vaccine developed by Ken-ichi Masuda's team at the RIKEN Vaccine Innovation Laboratory has succeeded in producing antibodies against several different coronaviruses. Such a vaccine has the potential to be applicable to a wide range of coronaviruses, including those that are endemic in animals as well as mutant strains of SARS-CoV-2. The goal is to prevent spread from animals to humans.

A major advantage of the mMAP approach is that the vaccine elicits immunoglobulin M (IgM) antibodies and avoids the possible problem of ADE, which is mediated by immunoglobulin G (IgG) antibodies.

This may prevent problems seen in diseases such as Ebola, yellow fever, dengue and coronavirus infections, where the presence of antibodies, either from a primary infection or as a result of vaccination, can actually worsen disease.

FOCUSING ON THE FUTURE

RIKEN scientists are looking at other issues related to COVID-19. A major future focus will be understanding the variability in responses to infection and why certain people develop very severe symptoms. With Tomohiro Morio of Tokyo Medical and Dental University, RIKEN researchers are contributing to the COVID Human Genetics Effort. Working with samples collected from various hospitals and international consortia, scientists are carrying out genome analysis to identify genome sequences associated with individual differences in susceptibility to COVID-19 infection and predicting symptoms in those infected. Host microbiomes might also prove to be important in susceptibility.

Fecal samples from recovered patients are also being investigated for bacterial strains that could enhance antibody responses. This work around host-gut microbiota interactions will also help researchers develop therapeutic and preventive strategies, as any information gathered about individual susceptibility and immune responses will be crucial in preparing for future pandemics and identifying those at a higher risk.

It is also vital to understand individual responses to vaccination and whether vaccine effectiveness is influenced by genetic differences, the host microbiome or other environmental factors.

Though this article has focused on the life-science work, RIKEN scientists are also using machine learning and other AI methods in their research. These studies, which aim to help people overcome the crisis, will continue to examine the social impacts of COVID-19, such as the effects of teleworking, analysis of hate speech and misinformation and the social and legal measures needed to prevent the spread of infection. We will provide more detail on that work in a future article.

SHIGEO KOYASU
Executive Director, RIKEN

Shigeo Koyasu studied as an undergraduate and graduate at the University of Tokyo. He moved overseas to work at Harvard University between 1988 and 1995. He became the Chairman of Microbiology and Immunology at Keio University School of Medicine upon his return to Japan. Later he served as director of the RIKEN Center for Integrative Medical Sciences and is currently an executive director at RIKEN. Koyasu has served in board or council positions for the Japanese Society for Immunology (JSI), Molecular Biology Society of Japan, the International Union of Immunological Societies and the Federation of Immunological Societies of Asia and Oceania. He is currently president of JSI. His research team discovered group 2 innate lymphoid cells (ILC2), an innate lymphocyte population critical to allergic inflammation and immunity against helminth infection.

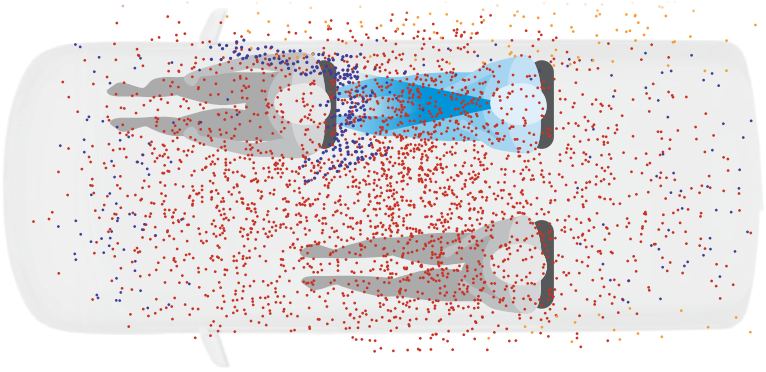
HOW DOES COVID-19 TRAVEL?

As the world settles into daily life in the presence of COVID-19, the RIKEN Center for Computational Science and its collaborators have been using RIKEN's supercomputer Fugaku to simulate droplet and aerosol spread dynamics in common travel settings. These accessible findings have now been widely distributed by the global media. The hope is that they help manage fears and better inform the public and administrators of the risks.

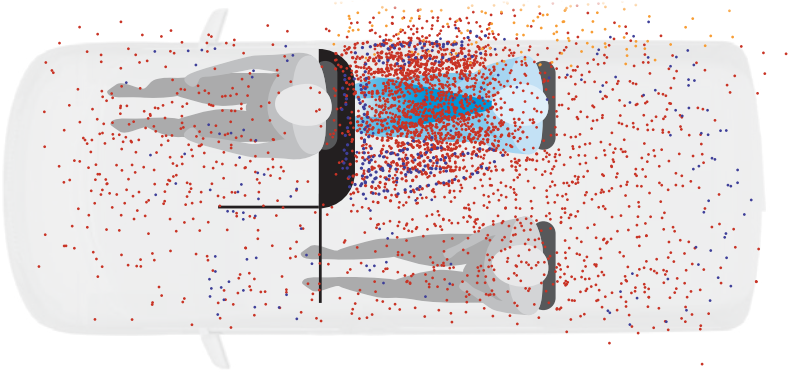
TURN UP THE A/C IN TAXIS

A car's air is typically replaced every two minutes. Masks reduce droplets by 70%. With no masks, emitted droplets and aerosols fill a car within 10 seconds. At a typical city driving speed (40 km/h) with the A/C 'fresh air mode' set to normal, opening a window improves ventilation by up to 25%. With no windows open, turning the A/C from normal to maximum increases ventilation efficiency by 90%.

- Particles floating in vehicle
- Particles near walls
- Particles floating outside vehicle
- Infected passenger
- Non-infected passenger
- Cough direction



Infected passenger sitting on the right, without barrier



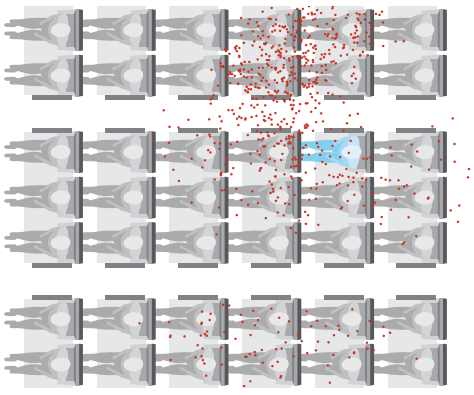
Infected passenger sitting on the right, with barrier

SIT IN THE REAR TWO-THIRDS OF A TRAIN CAR, WINDOWS OPEN

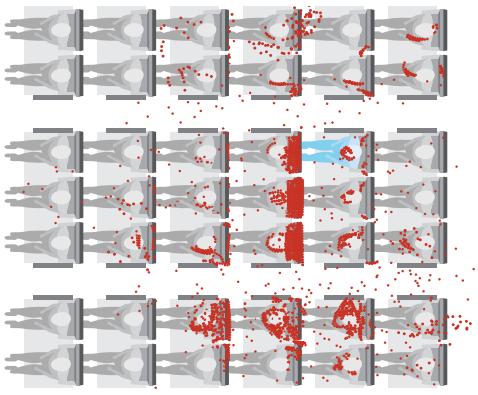
In Japan, masks are required on trains. However, aerosols and droplets can escape and ventilation is important. In rush-hour conditions, when a train is moving at 80 km/h with 228 passengers in a car, full air replacement occurs every six minutes or so. Air replacement proceeds from the upper middle towards the back of a car, while the air in the front remains relatively stale. Ventilation is better when the train stops frequently and the doors open (although the train is stationary). Ventilation also improves the wider the windows are open.

DON'T RECLINE ON PLANES

When seat backs are reclined, a large amount of emitted droplets will stick to the passengers in front. In the upright position, the back of the seat in front serves as a shield. Without a mask, small droplets are rapidly dehydrated and aerosolized due to the low humidity and high A/C airflow in the cabin. These can reach two rows front and back, and four seats either side. After a cough the air is cleared within three minutes or so.



Coughing while seats are upright, mask off



Coughing while reclining, mask off

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- ● Interdisciplinary Theoretical and Mathematical Sciences Program (iTHEMS)
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Since relocating its original campus from central Tokyo to Wako on the city's outskirts in 1967, RIKEN has rapidly expanded its domestic and international network. RIKEN now supports five main research campuses in Japan and has set up a number of research facilities overseas. In addition to its facilities in the United States and the United Kingdom, RIKEN has joint research centers or laboratories in Germany, Russia, 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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