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NARA INSTITUTE of SCIENCE and TECHNOLOGY

RESEARCH HIGHLIGHTS 2023

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Outgrow your limits

SOCIAL BEHAVIOR

Computing COVID-19 vaccination attitudes p.8

MICROBIOLOGY

Tackling plastic pollution with PET-eating bacteria p.36

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Developing super-flexible semiconductors p.48

NAIST®

Outgrow your limits

The Nara Institute of Science and Technology (NAIST) was founded in 1991 as a Japanese national university with the aim of conducting advanced research and educating scientists and technologists to support the development of society. NAIST is comprised of the Graduate School of Science and Technology, which focuses on the areas of information, biological and materials sciences and the development of their interdisciplinary fields. At present, over 1,000 students—roughly 25% from overseas—are supervised by roughly 200 NAIST faculty.

With its cutting-edge facilities and a 5 to 1 student-to-faculty ratio, NAIST's world-leading research and education are a direct result of its rich, global environment and supportive infrastructure. The outstanding achievements of NAIST's faculty and students are shared worldwide through publications, patents, licenses and active exchange with overseas partners.

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NAIST Research Highlights

ISSN 2189-714X

For further information on the research published in *NAIST Research Highlights* or to arrange an interview with a faculty, please contact:

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Aims & Scope

NAIST Research Highlights showcases promising and important research achievements at NAIST and presents their current research and core technologies to the public. The publication distills highly technical research papers into short, easy-to-understand articles that appeal to a global audience of both specialists and non-specialists. *NAIST Research Highlights* aims to inform readers of the latest developments in NAIST's pioneering research and to stimulate new and existing international collaborations.

NAURA

NAURA (NAIST URA team) publishes *NAIST Research Highlights* under the auspices of the "Program for Promoting the Enhancement of Research Universities", which is funded by Japan's Ministry of Education, Culture, Sports, Science and Technology (MEXT). NAURA facilitates pioneering research developments, international research collaboration activities and interdisciplinary research projects to further strengthen NAIST's research capabilities.

NAIST Divisions and Laboratories

NAIST conducts advanced research in the core study areas of information, biological and materials sciences and engages in interdisciplinary studies to explore and seek solutions in the most challenging areas. NAIST actively addresses important social issues by generating international-level research products that will help to build a better society.

Division of Information Science

Computer Science

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- Cyber Resilience
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Division of Materials Science

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As of December 22, 2022

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Materials Science

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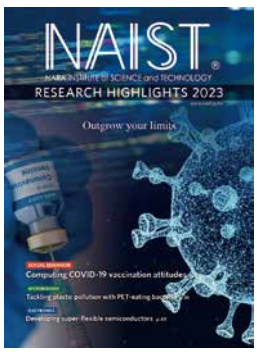
RESEARCH HIGHLIGHTS 2023

Nurturing discovery

Welcome to *NAIST Research Highlights 2023*. This publication provides an overview of recent research achievements of one of Japan's leading research bodies, the Nara Institute of Science and Technology. In these pages we present a view of recent extraordinary advances and breakthroughs, including 36 topics from the three divisions.

Of course, at the heart of such outcomes are our researchers. Each year NAIST attracts more leaders in scientific fields. We look forward to nurturing their important work and the careers of all our researchers in the atmosphere of cutting-edge discovery that will continue to be fostered at NAIST.



On the cover

By analyzing social concerns regarding COVID-19 vaccination based on search engine queries, NAIST researchers assist in improving online messaging about vaccination.

Page 8

INFORMATION SCIENCE

Dependable System

Prof. Michiko Inoue

Toward accurate modeling of power MOSFET electrical characteristics

Researchers at NAIST use automatic differentiation to dramatically speed up the calculation of model parameter extraction for metal oxide semiconductor field-effect transistor data, which may lead to more energy efficient power converters.

Scientists from NAIST have developed the mathematical method called automatic differentiation to find the optimal fit of experimental data up to four times faster. This research can be applied to multivariable models of electronic devices, which may allow them to be designed with increased performance while consuming less power.

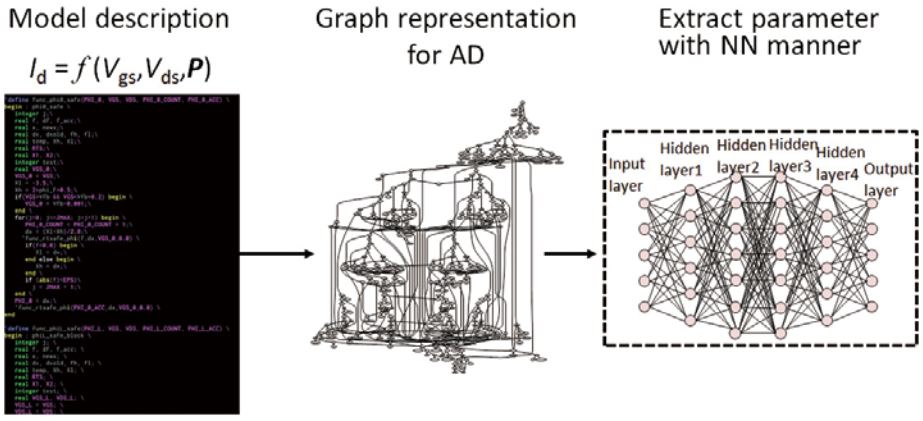
Wide bandgap devices, such as silicon carbide (SiC) metal-oxide semiconductor field-effect transistors (MOSFET), are a critical element for making converters faster and more sustainable. This is because of their larger switching frequencies with smaller energy losses under a wide range of temperatures when compared with conventional silicon-based devices. However, calculating the parameters that determine how the electrical current in a MOSFET responds as a function of the applied voltage remains difficult in a circuit simulation. A better approach for fitting experimental data to extract the important parameters would provide chip manufacturers the ability to design more efficient power converters.

Now, a team of researchers led by NAIST has successfully used the mathematical method called automatic differentiation (AD) to significantly accelerate these calculations. While AD has been used extensively when training artificial neural networks, the current project extends its application into the area of model parameter extraction. For problems involving many variables, the task of minimizing the error is often accomplished by a process of "gradient descent," in which an initial guess is repeatedly refined by making small adjustments in the direction that reduces the error the quickest. This is where AD can be much faster than previous alternatives, such as symbolic or numerical differentiation, at finding direction with the steepest "slope". AD breaks down the problem into combinations of basic arithmetic operations, each of which only needs to be done once. "With AD, the partial derivatives with respect to each of the input parameters are obtained simultaneously, so there is no need to repeat the model evaluation for each parameter," first author Michihiro Shintani says. By contrast, symbolic differentiation provides exact solutions, but uses a large amount of time and computational resources as the problem becomes more complex.

To show the effectiveness of this method, the team applied it to experimental data collected from a commercially available SiC MOSFET. "Our approach reduced the computation time by 3.5× in comparison to the conventional numerical-differentiation method, which is close to the maximum improvement theoretically possible," Shintani says. This method can be readily applied in many other areas of research involving multiple variables, since it preserves the physical meanings of the model parameters. The application of AD for the enhanced extraction of model parameters will support new advances in MOSFET development and improved manufacturing yields.

Reference

Michihiro Shintani, Aoi Ueda, Takashi Sato. 2022. Accelerating parameter extraction of power MOSFET models using automatic differentiation. *IEEE Transactions on Power Electronics*, 37, 2970-2982.



Overview of the mathematical method developed in this study.

Software Engineering

Prof. Kenichi Matsumoto

Software ecosystem: Everybody needs somebody

Researchers at NAIST employ network analysis methods from social science to study volunteer contributions to open-source software libraries, and find correlations between dependency networks and viability, which may identify libraries about to become dormant.

Using socio-technical techniques, researchers from NAIST have measured the congruence between the network of contributors to open-source programming libraries and the dependencies of that library within the ecosystem. This work suggests that the level of matching between the network of contributors and networks of dependencies could be used as an indicator of libraries at risk of becoming inactive.

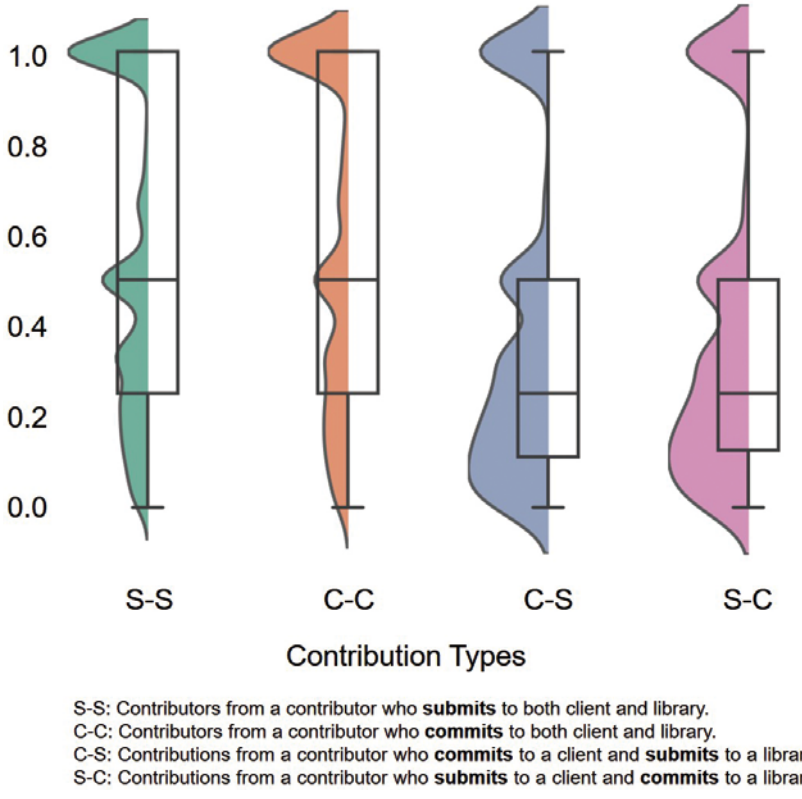
The modern computer programs that run your favorite apps or websites can be extremely large, often measured in millions of lines of code. This is obviously much more complex than can be handled by any one individual. Most programming languages therefore rely on specialized modules called third-party libraries to accomplish specific tasks. These libraries are often open-source and freely available to anyone who wants to download and use them. For example, programmers in JavaScript have access to over one million libraries, while there are more than 300,000 libraries for the Python community. The libraries themselves often rely on each other, with the typical library requiring the use of about five others. However, the ecosystem of interconnected libraries and their dependencies on each other is poorly understood, which is concerning since a failure in one could have cascading effects on the entire system. Sustained contributions are crucial, because the dependencies of any one library on others must be constantly updated in response to changes. However, maintainers of these libraries are often overworked and often contribute as unpaid volunteers.

Now, a team of researchers led by NAIST has studied these networks by defining a metric called "dependency-contribution congruence" (DC congruence), which measures how closely the network of library dependencies matches the network of contributor changes. The congruence metric is largest when the same contributor makes changes to both a library and its dependents. "We found that DC congruence shares an inverse relationship with the likelihood that a library becomes dormant. Specifically, a library is less likely to become dormant if the contributions are congruent with upgrading dependencies," says first author Supatsara Wattanakriengkrai. The team measured the DC congruence within the npm ecosystem of JavaScript libraries and analyzed over 5.3 million change commits across 107,242 different libraries. "Peaks in our generated metrics correlate with important ecosystem events," says senior author Kenichi Matsumoto.

This research may help keep software running and identify fragile points in the dependency network, and may ultimately encourage dependency contributions that support the maintenance of interdependent third-party libraries used in software development.

Reference

Supatsara Wattanakriengkrai, Dong Wang, Raula Gaikovina Kula, Christoph Treude, Patanamon Thongtanunam, Takashi Ishio, Kenichi Matsumoto. 2022. Giving back: Contributions congruent to library dependency changes in a software ecosystem. *IEEE Transactions on Software Engineering*, in press.



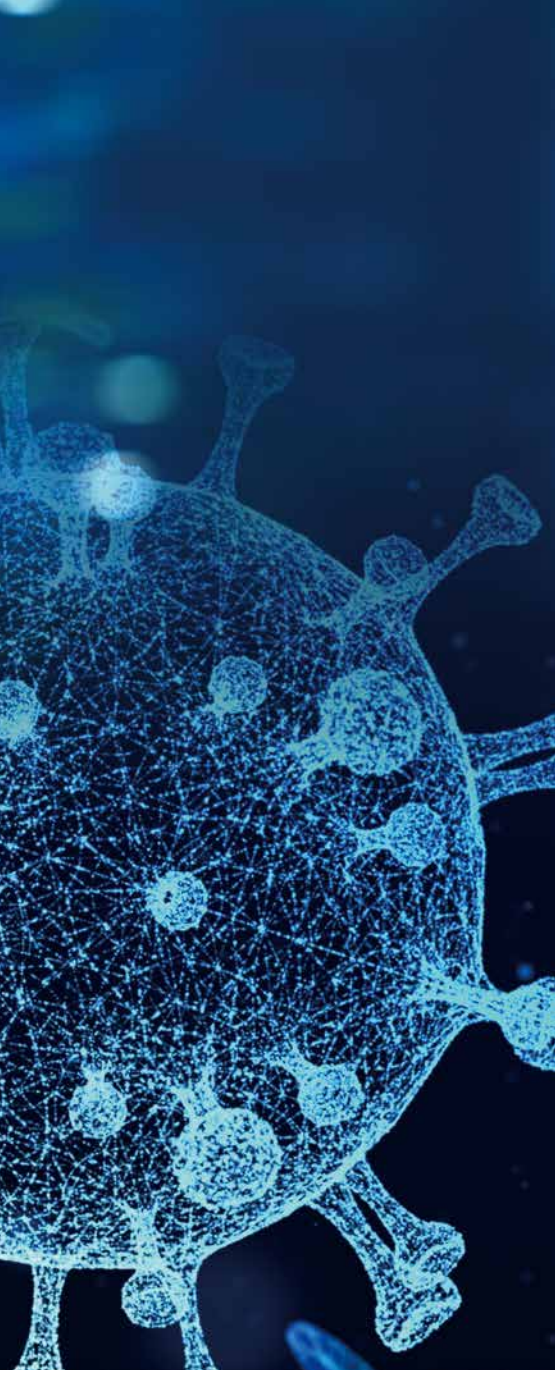
Library-level DC congruence in npm JavaScript Ecosystem.

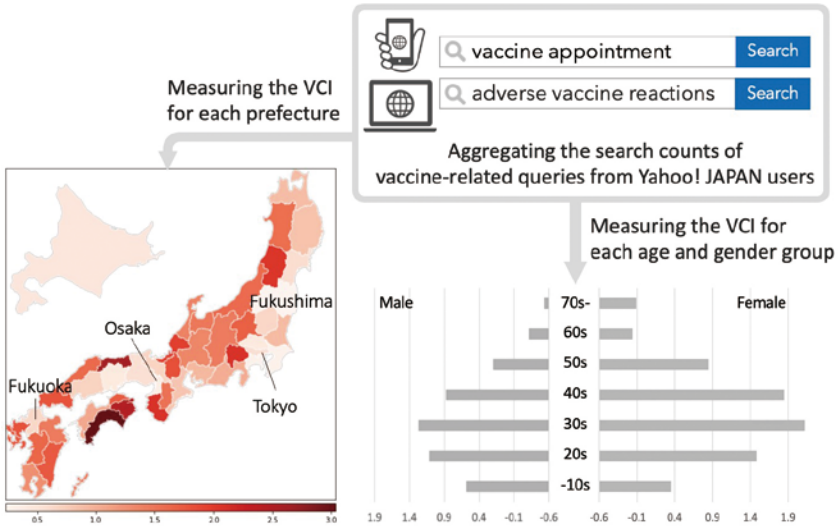
Social Computing

Prof. Eiji Aramaki

COVID vaccine: Who's searching for reassurance?

Using a vaccine concern index based on internet searches on the COVID-19 vaccine, researchers at NAIST find that "adverse reaction" searches positively correlate with adoption, which may help online resources encourage vaccination.





Societal concerns over COVID-19 vaccines as shown by the vaccine concern index that is calculated from vaccine-related queries searched on Yahoo! JAPAN.

Since becoming available, vaccines against COVID-19 have been vital in preventing deaths. However, vaccination rates in many developed countries are below expectations of public health officials, which is partly due to vaccine hesitancy. Scientists from Japan have found that searches related to vaccine side effects actually increased with adoption rates of vaccination. This work may help public health officials better understand vaccine hesitancy.

Vaccines against COVID-19 were remarkable in their rapid progress through development, manufacture, and introduction to the market. However, the rate of their uptake among health consumers did not match this speed. In Japan, a large survey found that many people expressed concerns about adverse reactions and vaccine effectiveness. Even before the pandemic, Japan had scored low on measures of trust in vaccines. Thus, being able to understand and measure people's concerns could help shape public relations outreach efforts with the goal of increasing vaccine adoption.

A team of researchers led by NAIST has examined online searches on Yahoo! JAPAN to quantify the degree of unease about getting the COVID-19 vaccine. They worked with Yahoo! JAPAN to develop a 'vaccine concern index' (VCI) based on the aggregated search counts of vaccine-related queries by prefecture for August and September 2021. The VCI captured searches of terms that may indicate vaccine hesitancy (such as adverse reactions and side effects) out of all vaccine-related searches (including searches for vaccination centers or appointments). The team found that the concern index tended to be lower in more populated areas, but higher in people in their 20s to 40s, especially female users. "This could be related to the online spread of misinformation that the vaccine causes infertility," says author Shoko Wakamiya, "and lower concerns among older people may be because they have limited familiarity with online searching."

The team found that the VCI was larger in prefectures with higher vaccination rates. This suggests that web searches for vaccine adverse reactions may be one step taken by health consumers before ultimately choosing to get vaccinated, which highlights the importance of providing complete and accurate information online. Conversely, individuals strongly hesitant towards vaccination may not be looking for online information, or are looking online less often. "As part of a collectivistic, Confucian culture, Japanese people often have an interdependent view of self," explains senior author Eiji Aramaki. "As a result, 'greater good' messaging and guidelines may be more effective in Japan." This work may pave the way for equally cost-effective examinations of societal attitudes towards COVID-19 vaccination in similar cultures, and ultimately improving online resources about these vaccines.

Reference

Makoto Uehara, Sumio Fujita, Nobuyuki Shimizu, Kongmeng Liew, Shoko Wakamiya, Eiji Aramaki. 2022. Measuring concerns about the COVID-19 vaccine among Japanese internet users through search queries. *Scientific Reports,* 12, 15037.

Optical Media Interface

Prof. Yasuhiro Mukaigawa

Turning the tables into touchscreens

Researchers at NAIST develop a projected touchscreen system that requires only one camera and one projector, allowing for the production of inexpensive large interactive displays and computer interfaces.

Scientists from NAIST have developed a touchscreen-like interface on a flat surface using a synchronized projector and camera. Because the camera only registered the user's fingers when actually in contact with the surface, the need for any additional cameras, depth sensors, or light sources was eliminated. This work may lead to portable projection systems that can be used to create large interactive displays nearly anywhere.

Everyday life is full of handheld devices that show videos and accept touch input. These include smartphones, tablets, or even the credit card reader at your local store. However, larger touchscreen interfaces remain expensive and slow to respond. Projection systems that are currently available need multiple detectors, because a single camera usually cannot distinguish depth. Now, a team of researchers led by NAIST has created a system that uses just one camera. "Typical cameras observe a three-dimensional situation as a two-dimensional plane. Thus, even if the position of a fingertip can be detected, it is difficult to know whether it is touching the surface or hovering above it," senior author Yasuhiro Mukaigawa says.

The researchers took advantage of "slope disparity gating," in which the projector scanning the table is synchronized with the camera, so that it captures only the region slightly above the surface. Using a dedicated image-processing algorithm, the touch of a finger could be localized with high efficiency. Because the same light source is used to produce the projected video as well as detect touch, the algorithm was not misled by the projected image.

"The method developed in the study can be used to produce a touch display on any flat surface. In the future, we will hope to expand to include touchless operations or even add gesture recognition," Mukaigawa says. Also, because the method captures only the region slightly above the surface, privacy concerns are reduced, as human faces and other identifying details are not recorded at all.

Reference

Mayuka Tsuji, Hiroyuki Kubo, Suren Jayasuriya, Takuya Funatomi, Yasuhiro Mukaigawa. 2021. Touch sensing for a projected screen using slope disparity gating. *IEEE Access*, 9, 106005–106013.

Optical Media Interface

Prof. Yasuhiro Mukaigawa

Keeping the light from fading

Researchers at NAIST develop a new mathematical method to calibrate scans of stained-glass windows to account for changes in natural light, which may help assist in the accurate preservation of famous artworks.

Scientists from NAIST have created a new approach to compensate for variations in illumination while scanning cathedral stained-glass windows. This work may be applied to other objects of cultural significance to help capture their colors in the most lifelike way.

It's hard to think of a more inspirational experience than watching the sun slowly set through historic stained-glass windows, such as those found in the cathedrals in Europe. While the changing light levels over time may be breathtaking, it also makes high-resolution scans of the windows more challenging. That is, if the scanning process requires minutes or even hours to complete, variations in the natural illumination can lead to inconsistent results.

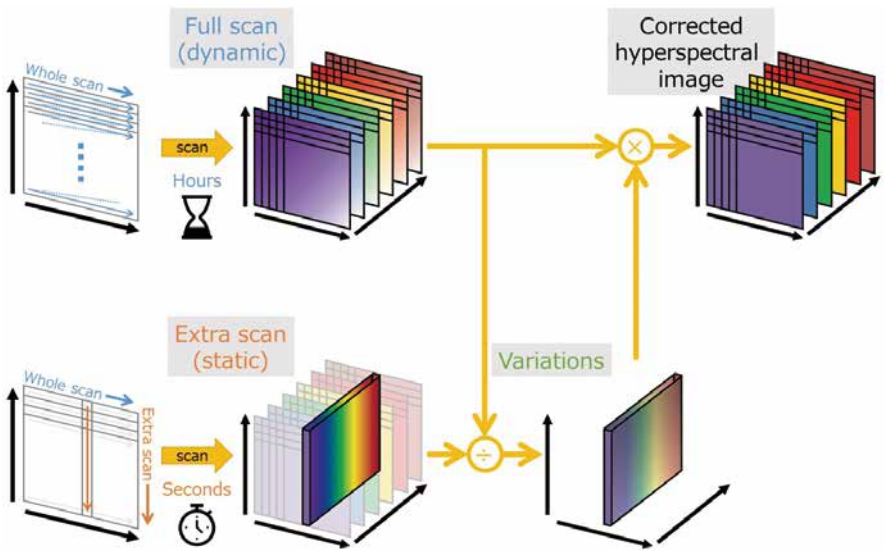
Now, a team of researchers led by NAIST has developed a new calibration method to help compensate for changes in the sun's illumination over the course of the scan. "It can take hours to capture thousands of spectral channels pixel by pixel. Thus, the measurement can be significantly affected by the perturbations in natural light," first author Takuya Funatomi says.

The researchers set out to capture hyperspectral images of the famous stained-glass windows in the Amiens Cathedral in France. With some window panels dating back to the 13th century, this location which has been designated as a UNESCO World Heritage Site. A whisk-broom scanner was used to acquire hyperspectral images. This kind of sensor uses a movable mirror to slowly scan across an object. Each pixel is measured one at a time as its light is reflected onto the single detector with the sky in the background. However, when it is applied to outdoor cultural heritages, temporal illumination variations become an issue due to the lengthy measurement time. Hyperspectral scanning is not limited to the wavelengths of light that are visible to humans. For this research, the team used a spectrometer that recorded more than 2,000 channels over a spectrum ranging from about 200 nm to 1100 nm, which includes ultraviolet, visible and infrared colors.

An extra single column scan was added to help calibrate the images. Using matrix methods, variations in temporal illumination could be removed. This allowed for much more accurate results compared with simply normalizing the total brightness, because each color might be impacted differently by the changing light. "Our method provides a new modality for the digital preservation of large cultural assets," senior author Yasuhiro Mukaigawa says. This method can be easily adapted to other situations in which outdoor scanning has to occur over long time periods.

Reference

Takuya Funatomi, Takehiro Ogawa, Kenichiro Tanaka, Hiroyuki Kubo, Guillaume Caron, El Mustapha Mouaddib, Yasuyuki Matsushita, Yasuhiro Mukaigawa. 2022. Eliminating temporal illumination variations in whisk-broom hyperspectral imaging. *International Journal of Computer Vision*, 130, 1310–1324.



Color compensation procedure developed in this study.

Optical Media Interface

Prof. Yasuhiro Mukaigawa

A technology for embedding data in printed objects

Researchers at NAIST develop a new method to embed information in a 3D printed object without modifying the shape of the object and retrieve it using a single image of a commercially available document scanner.

Digital watermarking is a technology that embeds information inside digital contents such as image, audio, video, and 3D models. Some methods including barcode and QR code embed information in a visible way. Other methods embed it covertly, with additional hidden information that is not perceivable by the user. Since 2010, the 3D printing technology has increasingly gained popularity, leading to a growing interest in the watermarking technology for 3D printed objects.

In the study published in *IEEE Transactions on Multimedia,* researchers from NAIST have developed a new method to embed information in a 3D printed object and retrieve it using a consumer document scanner. Information such as a serial ID can be embedded without modifying the shape of the object, and simply extracted from a single image of a commercially available document scanner.

Several technologies have been developed for 3D printing, including the Fused Deposition Modeling (FDM) that is most commonly used. It consists of deposing layers of molten plastic on top of each other. The desired shape is obtained by precisely controlling the position and flow of a printing nozzle such that the deposed plastic layers have a controlled path and thickness. The plastic flow is generally controlled to produce a constant layer thickness.

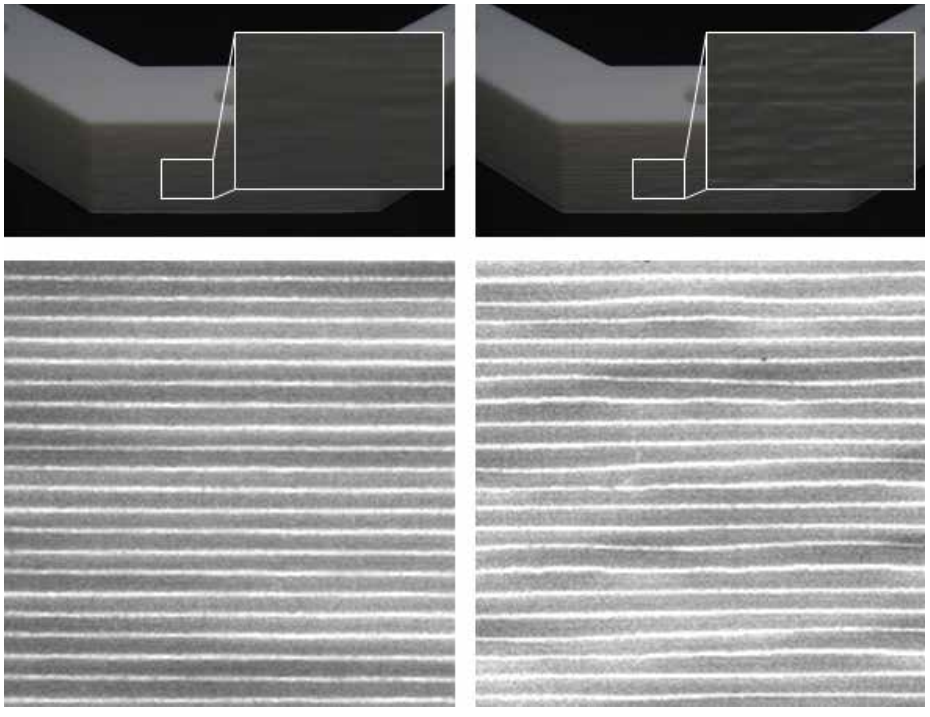
In the new method developed by the NAIST researchers, the plastic flow is modified during the print to locally change the layer thickness and embed some additional information. In order to prevent the degradation of the external surface of the object, pairs of vertically adjacent layers are selected and the ratio of their respective thicknesses is modified while keeping constant the sum of the two layer thicknesses. Since a standard layer thickness is about 0.2mm, information can be embedded in a relatively small area ranging from several millimeters to a few centimeters.

To retrieve the embedded information, it is necessary to measure the thickness of the layers. The new method conducts this procedure only with a common document scanner, and does not require any special equipment. The FDM printing process naturally produces some layering artifacts that are visible in images obtained by a document scanner. These artifacts enable to measure the thickness of the layers and extract the information.

The new approach makes it possible to embed various types of information such as an URL that can be linked to Web services, a unique ID that can be used for product tracing, and a printer ID and printing date for batch quality managements.

Reference

Arnaud Delmotte, Kenichiro Tanaka, Hiroyuki Kubo, Takuya Funatomi, Yasuhiro Mukaigawa. 2020. Blind watermarking for 3D printed objects by locally modifying layer thickness. *IEEE Transactions on Multimedia,* 22, 2780–2791.



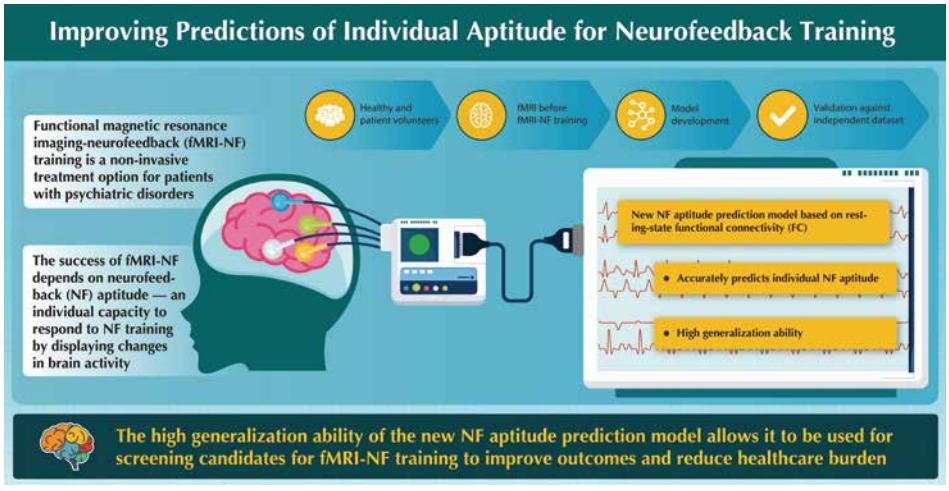
Scanned images of normal (left) and newly developed printing methods (right).

Prof. Kazushi Ikeda

New model can predict a patient's responsiveness to fMRI-based mental health treatment

Researchers at NAIST develop a new machine-learning based model that can forecast a person's aptitude for neurofeedback training treatments with a high generalization ability.

Advancements in medical science have allowed the treatment of psychiatric disorders like major depressive disorder (MDD) with functional magnetic resonance imaging neurofeedback (fMRI-NF) training. fMRI-NF training is a type of treatment that provides a non-invasive way to control and reinforce brain functions in patients with mental disorders through the use of real-time fMRI monitoring. However, the effectiveness of the treatment is not universal—it is influenced by a parameter called neurofeedback (NF) aptitude.



The high generalization ability of the new neurofeedback (NF) aptitude prediction model offers a quick, simple and non-invasive method to screen candidates in clinical settings for whom fMRI-NF training would be most beneficial.

NF aptitude refers to an individual's capacity to respond to NF training by displaying changes in brain activity. But NF aptitude varies from individual to individual. Thus, predicting a patient's NF aptitude becomes important not only for the success of fMRI-NF training, but also to reduce the physical and economic burden on the patient and healthcare system. Thus far, NF aptitude prediction models have focused on specific target regions in the brain, where the NF training was focused. Now, in a new study published in *NeuroImage*, a group of researchers, led by Junichiro Yoshimoto from NAIST, has successfully developed a mathematical model for the prediction of NF aptitude with a high generalization ability.

Speaking about their research, Yoshimoto says, "We applied machine learning, which is an offshoot of artificial intelligence (AI) technology, on data obtained from heathy individuals and patients with major depressive disorder to successfully develop a mathematical model that can predict individual fMRI-NF training aptitude, based on their pre-recorded brain activity at the resting state."

To arrive at the model, the scientists first studied fMRI images of healthy patients and patients with MDD before fMRI-NF training. They then used these images to calculate the resting state functional connectivity (FC), which describes the correlated or anti-correlated activities in different areas of the brain. They then applied a technique called 'partial least squares regression' (PLS) to transform the FC patterns into participants' NF aptitude. Furthermore, they determined which FCs were most effective for predicting NF aptitude.

They found that the PLS model could be generalized to the independent dataset from other institutes, i.e., it could successfully predict the NF aptitude of individuals based solely on resting-state fMRI scanning. They also found that a part of the brain called the posterior cingulate cortex was the functional hub among the brain regions, suggesting that it plays a major role in NF aptitude. "We believe that our research will help fMRI-NF training become more popular as a non-invasive treatment with minimal side effects for patients with mental health disorders," concludes Yoshimoto.

Even though the study focused on MDD, the generalizability of the model developed in this study ensures that it can be applied to different neuropsychological disorders, providing hope to patients suffering from mental illnesses and neurological disorders.

Reference

Takashi Nakano, Masahiro Takamura, Haruki Nishimura, Maro Machizawa, Naho Ichikawa, Atsuo Yoshino, Go Okada, Yasumasa Okamoto, Shigeto Yamawaki, Makiko Yamada, Tetsuya Suhara, Junichiro Yoshimoto. 2021. Resting-state brain activity can predict target-independent aptitude in fMRI-neurofeedback training. *NeuroImage,* 245, 118733.

Mathematical Informatics

Prof. Kazushi Ikeda

How is the brain programmed for computer programming?

Researchers at NAIST analyze the brain activities of computer programmers of different skill level using fMRI and find that several regions of expert programmers' brains are fine-tuned for programming, which may provide better methods and tools for everyone to learn programming.

Countries around the world are seeing a surge in the number of computer science students. Enrolment in related university programs in the U.S. and Canada tripled between 2006-2016 and Europe too has seen rising numbers. At the same time, the age to start coding is becoming younger and younger because governments in many different countries are pushing K-12 computer science education. Despite the increasing popularity of computer programming, little is known about how our brains adapt to this relatively new activity.

A team of researchers led by NAIST has examined the brain activity of thirty programmers of diverse levels of expertise, finding that seven regions of the frontal, parietal and temporal cortices in expert programmer's brain are fine-tuned for programming. The finding suggests that higher programming skills are built upon fine-tuned brain activities on a network of multiple distributed brain regions.

"Many studies have reported differences between expert and novice programmers in behavioural performance, knowledge structure and selective attention. What we don't know is where in the brain these differences emerge," says Takatomi Kubo, one of the lead authors of the study.

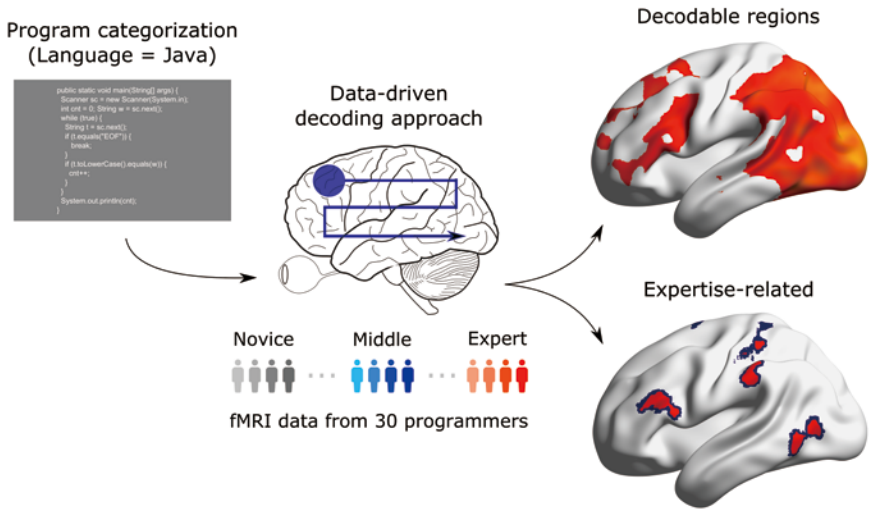
To answer this question, the researchers observed groups of novices, experienced, and expert programmers. The programmers were shown 72 different code snippets while under the observation of functional MRI (fMRI) and asked to place each snippet into one of four functional categories. As expected, programmers with higher skills were better at correctly categorizing the snippets. A subsequent searchlight analysis revealed that the amount of information in seven brain regions strengthened with the skill level of the programmer: the bilateral inferior frontal gyrus pars triangularis (IFG Tri), left inferior parietal lobule (IPL), left supramarginal gyrus (SMG), left middle and inferior temporal gyri (MTG/IT), and right middle frontal gyrus (MFG).

"Identifying these characteristics in expert programmers' brains offers a good starting point for understanding the cognitive mechanisms behind programming expertise. Our findings illuminate the potential set of cognitive functions constituting programming expertise," Kubo says.

More specifically, the left IFG Tri and MTG are known to be associated with natural language processing and, in particular, semantic knowledge retrieval in a goal-oriented way. The left IPL and SMG are

associated with episodic memory retrieval. The right MFG and IFG Tri are functionally related to stimulus-driven attention control.

"Programming is a relatively new activity in human history and the mechanism is largely unknown. Connecting the activity to other well-known human cognitive functions will improve our understanding of programming expertise. If we get more comprehensive theory about programming expertise, it will lead to better methods for learning and teaching computer programming," Kubo says.



Overview of the study. Multiple brain regions have fine-tuned representation of source code in proportion to the behavioral performance of program comprehension based on the fMRI data obtained from 30 subjects with different levels of programming expertise while performing the program categorization task.

Reference

Yoshiharu Ikutani, Takatomi Kubo, Satoshi Nishida, Hideaki Hata, Kenichi Matsumoto, Kazushi Ikeda, Shinji Nishimoto. 2021. Expert programmers have fine-tuned cortical representations of source code. *eNeuro,* 8, ENEURO.0405-20.2020.

Computational Behavioral Neuroscience

Associate Prof. Saori Tanaka

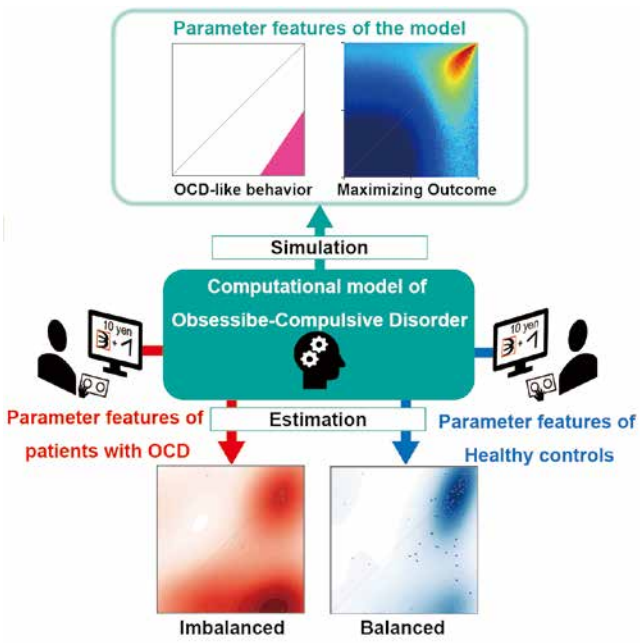
Studying the OCD cycle

Researchers at NAIST develop a new model of obsessive-compulsive disorder based on principles of reinforcement learning, which may lead to better treatment for obsessive-compulsive and related disorders.

A team of researchers led by NAIST has demonstrated that obsessive-compulsive disorder (OCD) can be understood as a result of imbalanced learning between reinforcement and punishment. On the basis of empirical tests of their theoretical model, they showed that asymmetries in brain calculations that link current results to past actions can lead to disordered behavior. Specifically, this can happen when the memory trace signal for past actions decays differently for good and bad outcomes. In this case, "good" means the result was better than expected, and "bad" means that it was worse than expected. This work helps to explain how OCD develops.

OCD is a mental illness involving anxiety, characterized by intrusive and repetitious thoughts, called obsessions, coupled with certain repeated actions, known as compulsions. Patients with OCD often feel unable to change behavior even when they know that the obsessions or compulsions are not reasonable. In severe cases, these may render the person incapable of leading a normal life. Compulsive behaviors, such as washing hands excessively or repeatedly checking whether doors are locked before leaving the house, are attempts to temporarily relieve anxiety caused by obsessions. However, hitherto, the means by which the cycle of obsessions and compulsions becomes strengthened was not well understood.

Now, the team has used reinforcement learning theory to model the disordered cycle associated with OCD. In this framework, an outcome that is better than predicted becomes more likely (positive prediction error), while a result that is worse than expected is suppressed (negative prediction error). In implementation of reinforcement learning, it is also important to consider delays, as well as positive/negative prediction errors. In general, the outcome of a certain choice is available after a certain delay. Therefore, reinforcement and punishment should be assigned to recent choices within a certain time frame. This is called credit assignment, which is implemented as a memory trace in reinforcement learning theory. Ideally, memory trace signals for past actions decay at equal speed for both positive and negative prediction errors. However, this cannot be completely realized in discrete neural systems. Using simulations, the researchers found that agents implicitly learn obsessive-compulsive behavior when the trace decay factor for memory traces of past actions related to negative prediction errors (v^-) is much smaller than that related to positive prediction errors (v^+). This means that, from the opposite perspective, the view of past actions is much narrower for negative prediction errors than for positive prediction errors. "Our model, with imbalanced trace decay factors ($v^+ > v^-$) successfully represents the vicious circle of obsession and compulsion characteristic of OCD", say co-first authors Yuki Sakai and Yutaka Sakai.



Memory trace imbalance in reinforcement and punishment systems can reinforce implicit choices leading to obsessive-compulsive behavior.

To test this prediction, the researchers had 45 patients with OCD and 168 healthy control subjects play a computer-based game with monetary rewards and penalties. Patients with OCD showed much smaller v^- compared with v^+, as predicted by computational characteristics of OCD. In addition, this imbalanced setting of trace decay factors ($v^+ > v^-$) was normalized by serotonin enhancers, which are first-line medications for treatment of OCD. "Although we think that we always make rational decisions, our computational model proves that we sometimes implicitly reinforce maladaptive behaviors," says corresponding author, Saori C. Tanaka.

Although it is currently difficult to identify treatment-resistant patients based upon their clinical symptoms, this computational model suggests that patients with highly imbalanced trace decay factors may not respond to behavioral therapy alone. These findings may one day be used to determine which patients are likely to be resistant to behavioral therapy before commencement of treatment.

Reference

Yuki Sakai, Yutaka Sakai, Yoshinari Abe, Jin Narumoto, Saori C. Tanaka. 2022. Memory trace imbalance in reinforcement and punishment systems can reinforce implicit choices leading to obsessive-compulsive behavior. *Cell Reports*, 40, 111275.

BIOLOGICAL SCIENCE

Plant Developmental Signaling

Prof. Keiji Nakajima

Switching roles: Key proteins evolved from activators to maintainers in plants

Researchers at NAIST find that the ancestral role of KNOX and BELL transcription factors in plants is zygote activation, later switching to meristem maintenance during plant evolution.

Sometimes in research, just as in other areas of life, answers to fundamental questions can be sitting in plain sight. Scientists have discovered a key piece of the puzzle of plant evolution previously overlooked by plant scientists.

In a study published in *eLife*, a team of researchers led by NAIST has revealed that an ancestral function of the plant KNOX/BELL proteins is activation of the zygote (the first diploid cell formed by the fusion of female and male gametes, also known as reproductive cells), and this role shifted toward the maintenance of organ development during the evolution of land plants.

One of the central questions of developmental biology is how parental genomes mix in a zygote and are activated to begin diploid development. Two proteins, KNOX and BELL, function as transcription factors—proteins that play an essential role in gene expression. KNOX and BELL activate diploid development in plants such as unicellular green alga, but in land plants such as angiosperms (flowering plants) they play a part in the maintenance of the shoot meristem—the tissue that generates the whole of the plant that grows above ground—and the process of organ formation in the later stages of diploid development.

"It's unknown if the differing functions of KNOX and BELL were attained separately in land plants and algae," says senior author of the study, Keiji Nakajima. "Although mostly dismissed from the spotlight by plant biologists until now, the zygote-activating functions of algal KNOX/BELLs, and how they relate to those of land plants, were the focus of this study."

To investigate this, the research team looked at a basal land plant species, the liverwort *Marchantia polymorpha*, which has recently been recognized as a good model for studying the evolution of land plants, especially in sexual reproduction research. The team found that gamete-expressed *KNOX* and *BELL* genes are needed to begin zygote development by promoting nuclear fusion in the zygote in a way very similar to that previously found in the green alga *Chlamydomonas reinhardtii*.

"Our results suggest that the ancestral role of KNOX/BELL transcription factors is zygote activation," explains Nakajima. "As land plants evolved, this moved toward meristem maintenance."

The results of this study will be important to plant biologists working across a range of fields such as embryo and organ formation, sexual reproduction and evolution. These findings, in addition to the proposal of an equivalent scenario in groups such as fungi and animals, will also be relevant to researchers in the wider biological sciences.

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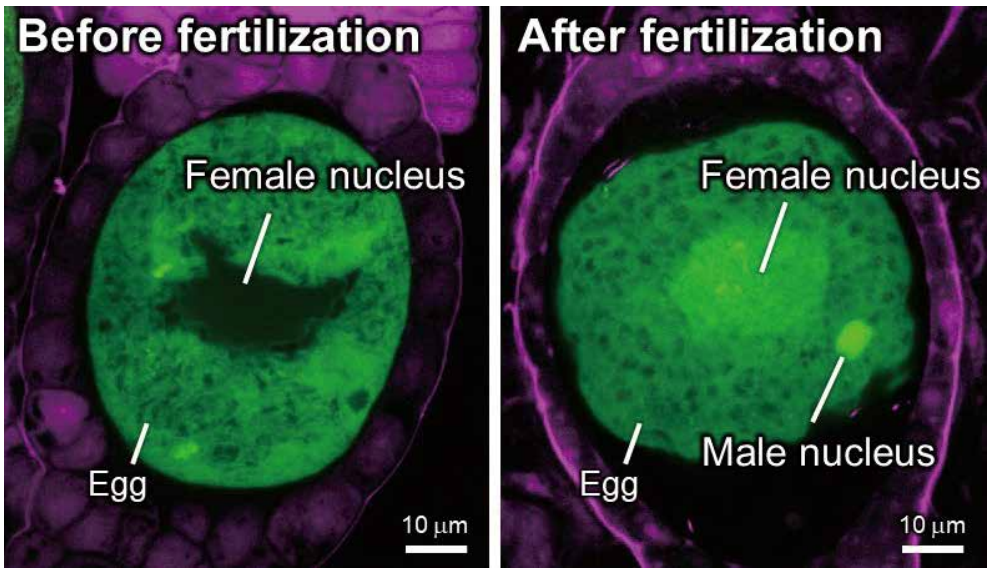
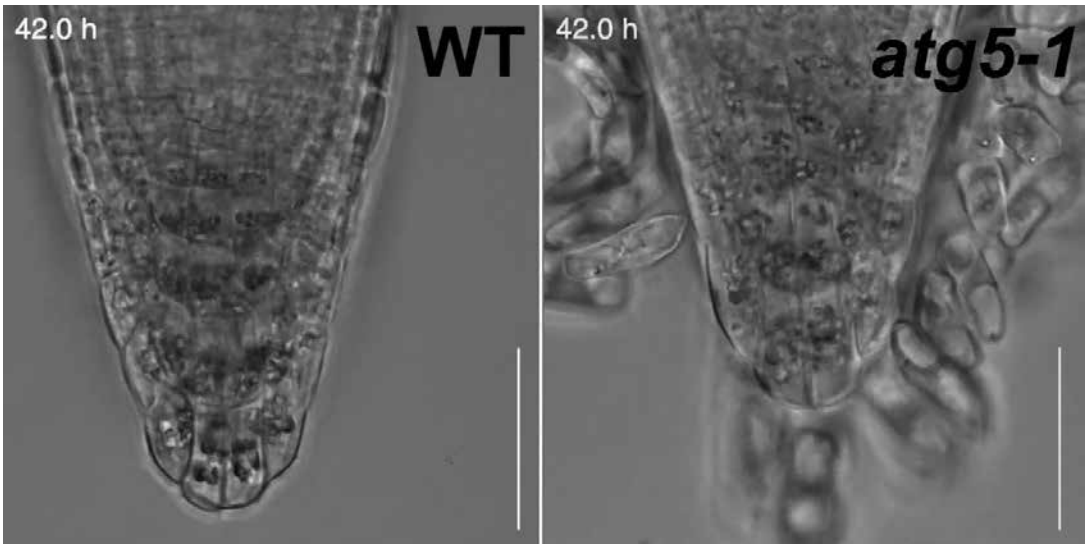
Tetsuya Hisanaga, Shota Fujimoto, Yihui Cui, Katsutoshi Sato, Ryosuke Sano, Shohei Yamaoka, Takayuki Kohchi, Frédéric Berger, Keiji Nakajima. 2021. Deep evolutionary origin of gamete-directed zygote activation by KNOX/BELL transcription factors in green plants. *eLife,* 10, e57090.



Egg cells of the liverwort *Marchantia polymorpha.*



Root cap cell detachment in wild type (left) and autophagy-deficient mutant *Arabidopsis thaliana* (right).

Prof. Keiji Nakajima

A new role of autophagy in plant cell differentiation revealed

Researchers at NAIST find that autophagy is required for root cap cell differentiation and separation in Arabidopsis.

A midlife career change is hard to pull off, because it can involve reinventing yourself and adopting a completely new professional role. Now, scientists show that some plant cells get a helping hand from autophagy when they switch primary functions partway through their lifespan.

In a study published in *Development*, a team of researchers led by NAIST has revealed that autophagy—self-digesting machinery that operates inside of eukaryotic cells—plays a crucial role in root growth. That is, autophagy supports root cap cells transition from the center of the cap, where they act as gravity sensors, to the outside of the cap, where they function as secretory cells and eventually slough off.

Root cap cells are unique among plant cells in that they are subject to constant turnover, while most of the other cells that make up the plant body are maintained throughout the plant's life. As the roots grow and lengthen, the outermost cells on the root cap slough off, and inner cells take their place, changing function as well as location.

"The concerted cell turnover and functional specialization of root cap cells require sophisticated subcellular reorganization," explains Tatsuaki Goh, lead author of the study. "However, the spatiotemporal dynamics of this reorganization and the molecular and genetic regulation of this process are not well characterized."

To investigate this process of subcellular reorganization, the researchers designed a microscopy technique that allowed them to watch *Arabidopsis* roots grow in real time while automatically tracking the tip of the extending root. "What we saw is that, right before the outermost layer of cells sloughed off of the root tip, there was a major shift in the location of organelles within the cells," says Keiji Nakajima, senior author of the study. "Importantly, the autophagy system needed to be intact for this shift to take place."

Having a functional autophagy system was also required for the cells to separate from the root caps in a highly ordered manner. "Our findings suggest that autophagy is an essential component of cell clearance and organelle rearrangement. These are both associated with the functional specialization of the outermost root cap cells as secretory cells, as well as with the cell separation process," says Goh.

Autophagy is an evolutionarily conserved process in eukaryotic cells, where it plays key roles in nutrient recycling and the stress response, although its role is less well understood in plants. Thus, the novel role for autophagy in plants revealed by this study has important implications for the conservation of core autophagy factors in plant genomes.

Reference

Tatsuaki Goh, Kaoru Sakamoto, Pengfei Wang, Saki Kozono, Koki Ueno, Shunsuke Miyashima, Koichi Toyokura, Hidehiro Fukaki, Byung-Ho Kang, Keiji Nakajima. 2022. Autophagy promotes organelle clearance and organized cell separation of living root cap cells in *Arabidopsis thaliana*. *Development,* 149, dev200593.

Plant Stem Cell Regulation and Floral Patterning

Prof. Toshiro Ito

How to beat the heat: Memory mechanism allows plants to adapt to heat stress

Researchers at NAIST find that plants adapt to heat stress via an epigenetic memory mechanism, where JUMONJI proteins control small heat shock genes.

"If you can't stand the heat, get out of the kitchen," as the old saying goes. But for organisms that can't leave the proverbial kitchen when things get too hot, there's another way: scientists have discovered that plants can gain heat tolerance to better adapt to future heat stress, thanks to a particular mechanism for heat stress 'memory'.

In a study published in *Nature Communications*, a team of researchers led by NAIST has revealed that a family of proteins that control small heat shock genes enables plants to 'remember' how to deal with heat stress.

Climate change, especially global warming, is a growing threat to agriculture worldwide. Because plants can't move to avoid adverse conditions, such as potentially lethal high temperatures, they need to be able to deal with factors such as heat stress effectively to survive. Therefore, improving the heat tolerance of crop plants is an important goal in agriculture.

"Heat stress is often repeating and changing," says lead author of the study Nobutoshi Yamaguchi. "Once plants have undergone mild heat stress, they become tolerant and can adapt to further heat stress. This is referred to as heat stress 'memory' and has been reported to be correlated to epigenetic modifications." Epigenetic modifications are inheritable changes in the way genes are expressed, and do not involve changes in the underlying DNA sequences.

"We wanted to discover how plants retain a memory of environmental changes," explains Toshiro Ito, senior author. "We examined the role of JUMONJI (JMJ) proteins in acquired temperature tolerance in response to recurring heat within a few days."

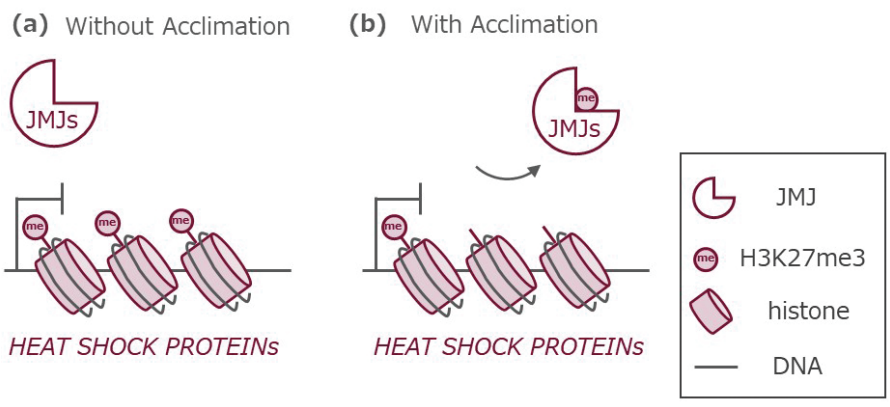
JUMONJI proteins are histone demethylases. Demethylases are enzymes that remove methyl groups from molecules such as proteins, particularly histones, which provide structural support to chromosomes. The team revealed that plants are able to maintain heat memory because of lowered H3K27me3 (histone H3 lysine 27 trimethylation) on small heat shock genes.

"We found that these proteins are necessary for heat acclimation in *Arabidopsis thaliana*. These results, along with future studies, will further clarify the mechanisms of plant memory and adaptation," says Yamaguchi.

This research will be relevant to genetic research in a number of fields, including biology, biochemistry, ecology, and environmental and agricultural sciences, and is applicable to the study of animals as well as plants. Understanding the epigenetic memory mechanism revealed in this study will help in working with heat tolerance to maintain the food supply in natural conditions.

Reference

Nobutoshi Yamaguchi, Satoshi Matsubara, Kaori Yoshimizu, Motohide Seki, Kouta Hamada, Mari Kamitani, Yuko Kurita, Yasuyuki Nomura, Kota Nagashima, Soichi Inagaki, Takamasa Suzuki, Eng-Seng Gan, Taiko To, Tetsuji Kakutani, Atsushi J. Nagano, Akiko Satake, Toshiro Ito. 2021. H3K27me3 demethylases alter *HSP22* and *HSP17.6C* expression in response to recurring heat in *Arabidopsis*. *Nature Communications*, 12, 3480.



Removal of H3K27me3 in response to heat.

Plant Stem Cell Regulation and Floral Patterning

Prof. Toshiro Ito

The flower clock: How a small protein helps flowers to develop right and on time

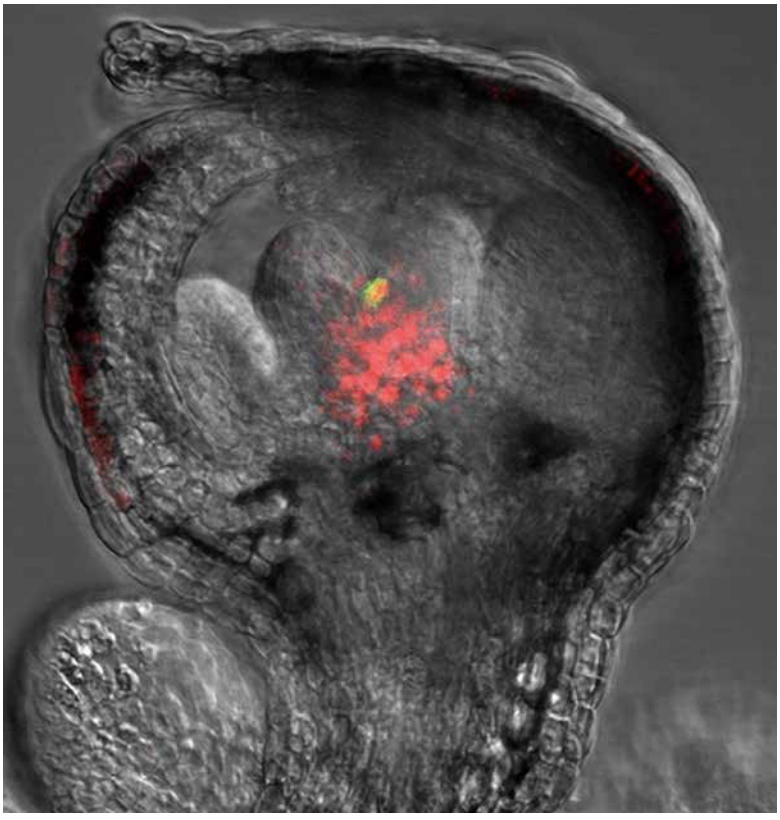
Researchers at NAIST find that KNUCKLES, a small multi-functional protein, supports the correct timing of floral development for the proper formation of flower reproductive organs.

How flowers form properly within a limited time frame has been a mystery, at least until now. scientists have discovered how a multi-tasking protein helps flowers to develop as expected.

In a study published in *Proceedings of the National Academy of Sciences U.S.A.*, researchers have revealed that a small protein plays multiple roles to ensure that floral reproductive organs are formed properly within a short space of time.

Flowers develop from floral meristems, which differentiate to produce the sepals, petals, stamens, and carpels. The proper development of these floral organs depends on meristem development being completed within a certain time period. In the early stages of flower development, stem cells provide the cell source for floral organ formation. In floral meristems, stem cell activities are maintained via a feedback loop between *WUSCHEL* (*WUS*), a gene that identifies floral stem cells, and *CLAVATA3* (*CLV3*), a stem cell marker gene that is activated and sustained by *WUS*.

"A small protein called KNUCKLES (KNU) represses *WUS* directly, which leads to the completion of floral stem cell activity at the right time," says lead author of the study Erlei Shang. "What isn't fully understood is how the robust floral stem cell activity finishes within a limited time period to ensure carpel development."



KNUCKLES expression in floral meristem of *Arabidopsis thaliana*.

"The team's research revealed that in *Arabidopsis thaliana*, KNU can completely deactivate the robust floral meristems at a particular floral stage, thanks to the multiple functions that KNU carries out via its position-specific roles," says senior author Toshiro Ito at NAIST.

KNU both represses and silences *WUS*, and directly represses *CLV3* and *CLV1* (a gene that encodes a receptor for the CLV3 peptide). Consequently, KNU eliminates the *CLV3-WUS* feedback loop via transcriptional and epigenetic mechanisms (i.e., those that do not involve changes in the underlying DNA sequences). Additionally, KNU interacts physically with the WUS protein, which inhibits *WUS* from sustaining *CLV3*, disrupting interactions that are required for the maintenance of floral meristems.

"Our results reveal a regulatory pathway where KNU plays a key role in supporting the completion of floral meristem development within a short time window, and ensures that flower reproductive organs are properly formed," says corresponding author Bo Sun.

The results of this research will be useful for genetic studies of food crop species such as rice, tomatoes, and maize. An understanding of the floral meristem termination mechanism discovered in this study will benefit crop yields for food production globally.

Reference

Erlei Shang, Xin Wang, Tinghan Li, Fengfei Guo, Toshiro Ito, Bo Sun. 2021. Robust control of floral meristem determinacy by position-specific multifunctions of KNUCKLES. *Proceedings of the National Academy of Sciences U.S.A.*, 118, e2102826118.

Plant Physiology

Prof. Motomu Endo

The circadian clock makes sure plant cells have the time of their lives

Researchers at NAIST find that the circadian clock regulates cell cycle progression and cell differentiation in Arabidopsis*, using a novel algorithm to reconstruct actual-time gene expression patterns from single-cell RNAseq datasets.*

They say timing is everything, and that couldn't be more true for cell cycle progression and differentiation. Now, a team of researchers led by NAIST has found that the circadian clock is crucial for proper plant development. In a study published in *Cell Reports*, they showed that the circadian clock plays a guiding role in plant cell differentiation.

The circadian clock is involved in both cell-cycle progression and cell fate transitions. The involvement of circadian clocks in the process of differentiation has been shown in many multicellular organisms; however, how plant circadian clocks regulate cell differentiation remains unclear.

"Elucidating how the circadian clock is involved in cell differentiation is important to understand the basis of cell fate determination," explains Motomu Endo, senior author of the study. "However, this has been difficult to investigate in plants because it is challenging to isolate single plants' cells, and existing analytical methods rely on "pseudo-time" analysis that does not accurately reflect normal circadian rhythms."

To address these challenges, the researchers used tiny glass tubes to isolate individual cells from developing plants and analyzed the expression of various genes related to circadian rhythms and cell differentiation in each cell. They then developed a new algorithm called PeakMatch to reconstruct actual-time gene expression patterns from the single-cell datasets.

"Using this powerful approach, we were able to show that the expression profile of clock genes is changed prior to cell differentiation," states Endo. "Specifically, in early differentiating cells, the induction of the clock gene LUX ARRYTHMO directly targets genes involved in cell-cycle progression to regulate cell differentiation."

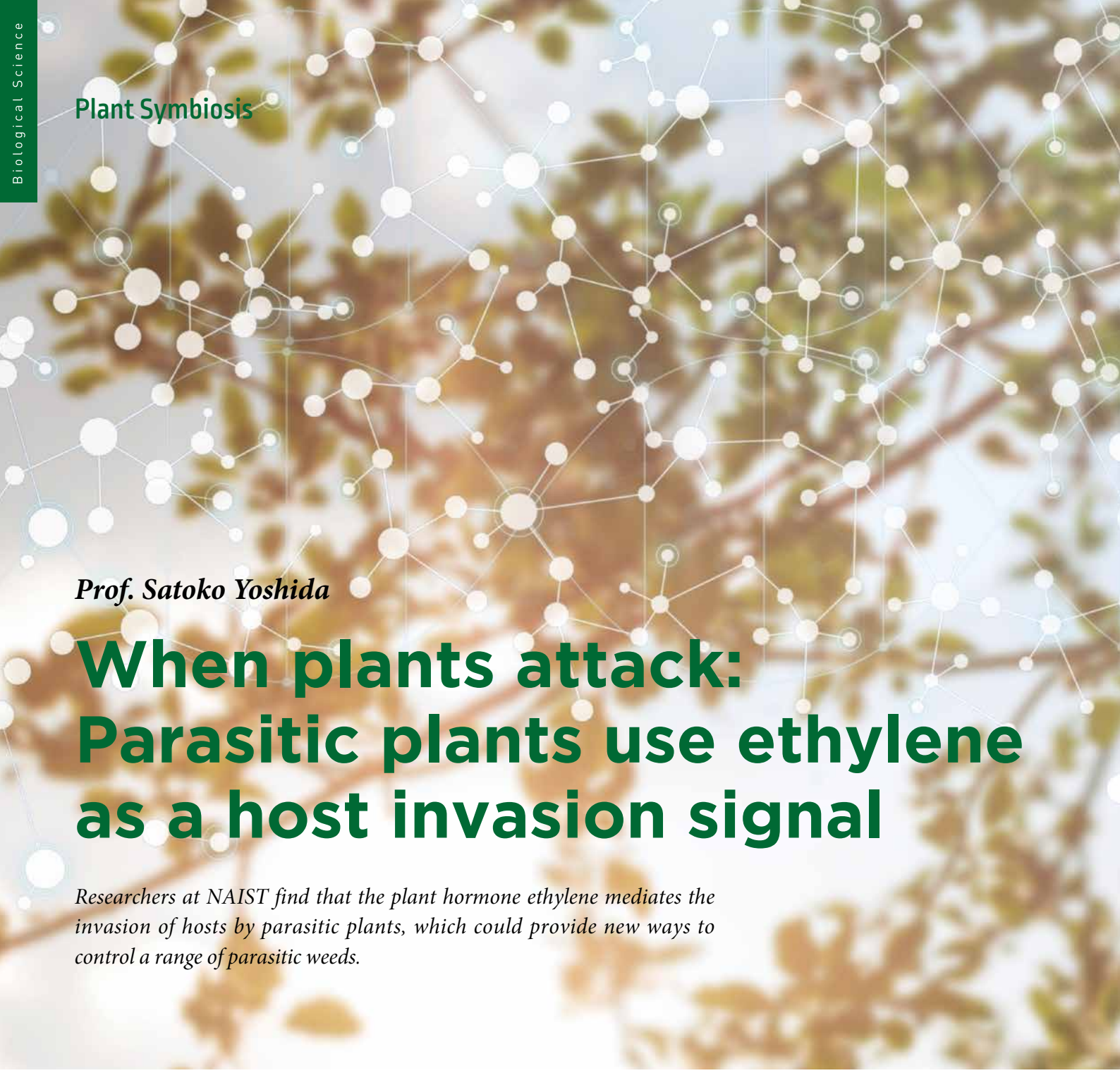
Further investigation showed that large-scale changes in the circadian clock profile in undifferentiated cells induce the expression of the clock gene LUX, which directly triggers cell differentiation. "Taken together, our results show that the plant circadian clock plays a guiding role in cell differentiation," says Endo. "Importantly, our study also provides an approach for time-series analysis at single-cell resolution."

Because the development of circadian rhythms during cell differentiation is observed in animals as well as in plants, the finding that clock genes directly regulate cell fate determination and cell division may help understand how cell differentiation is controlled in multicellular organisms. The newly developed PeakMatch algorithm can also be applied to all kinds of single-cell transcriptomes in other organisms.

Reference

Kotaro Torii, Keisuke Inoue, Keita Bekki, Kazuya Haraguchi, Minoru Kubo, Yuki Kondo, Takamasa Suzuki, Akane Kubota, Kyohei Uemoto, Hanako Shimizu, Masato Saito, Hiroo Fukuda, Takashi Araki, Motomu Endo. 2022. A guiding role of the *Arabidopsis* circadian clock in cell differentiation revealed by time-series single-cell RNA sequencing. *Cell Reports*, 40, 111059.

Plant Symbiosis



Prof. Satoko Yoshida

When plants attack: Parasitic plants use ethylene as a host invasion signal

Researchers at NAIST find that the plant hormone ethylene mediates the invasion of hosts by parasitic plants, which could provide new ways to control a range of parasitic weeds.

Mutants that reveal the secrets of how plants attack? No, it's not a scene from a science fiction movie, but you could be forgiven for thinking that. Instead, it's a scene from real life. A team of researchers led by NAIST has reported in a new study in *Science Advances* that parasitic plants use the plant hormone ethylene as a signal to invade the roots of host plants.

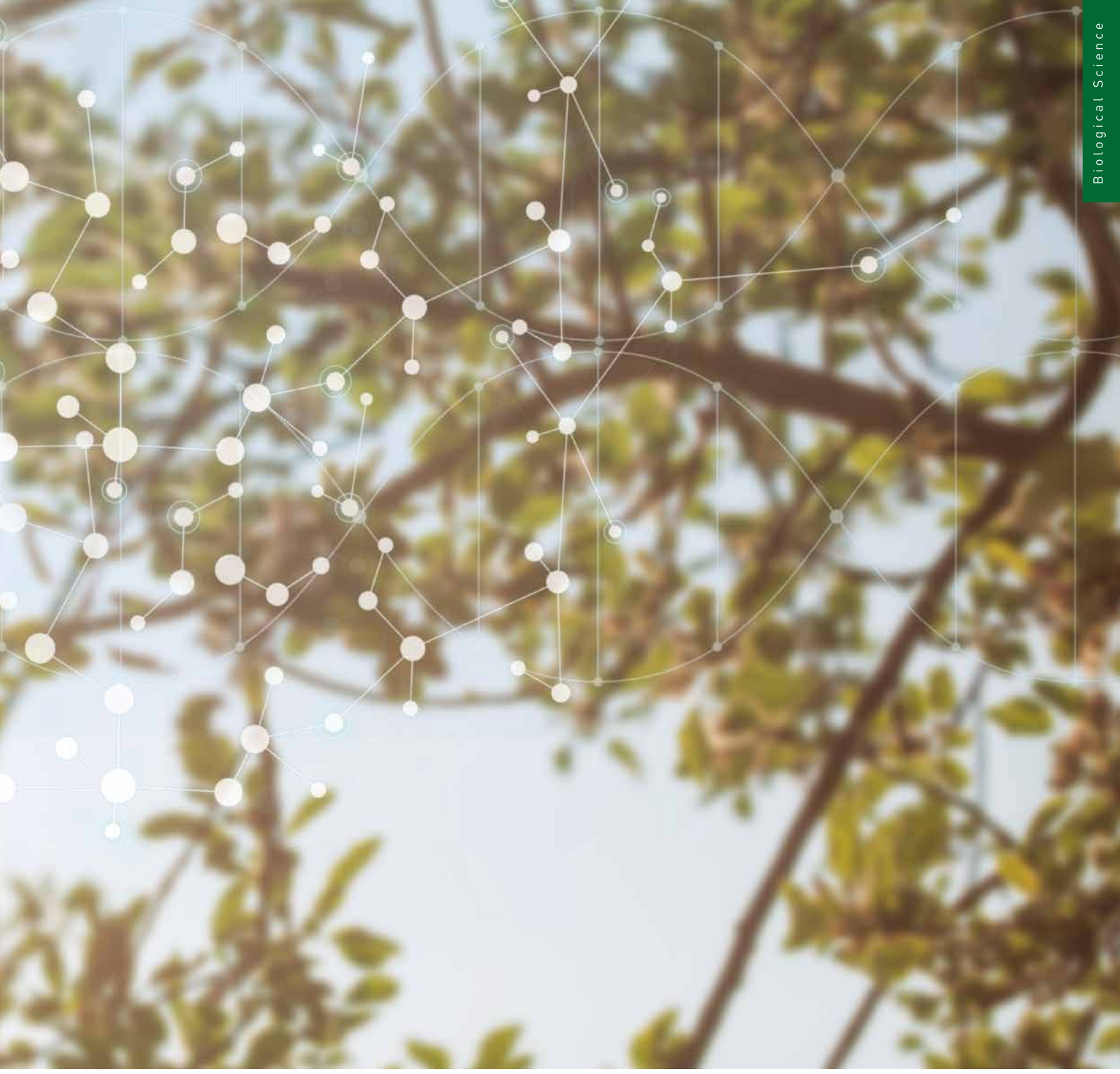
To develop a successful parasitic relationship, parasitic plants form a specialized structure, the haustorium which attaches to and invades the host plant. The formation of haustoria is regulated by signal molecules derived from the host plant and allows the parasitic plant to absorb water, nutrients, and small materials from the host plant.

"To understand the genetic programs for haustorium development, we identified mutants that displayed haustorial defects on host invasion," says lead author of the study Songkui Cui. "Genome sequencing showed that these mutants have defective ethylene signaling, and it turned out that ethylene signaling genes are crucial for the parasitic plant to infect its host plant."

Ethylene is a gaseous plant hormone that is involved in fruit ripening, aging of leaves, and the formation of root nodules. Ethylene is also widely involved in plant interactions with viruses and numerous organisms, such as insects and bacteria, lending either resistance or susceptibility to plants depending on the types of pathogens.

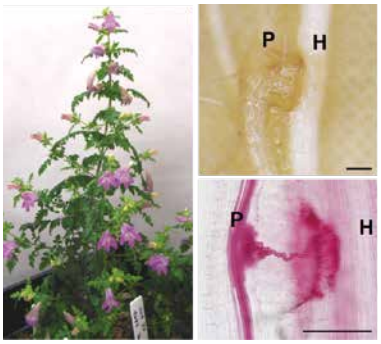
"Our results indicate that ethylene mediates host recognition in parasitic plants for host invasion," explains project leader Satoko Yoshida. "This is the first time that the mediation of host invasion by parasitic plant genes has been identified via forward genetics. Our findings offer a new understanding of how a parasitic plant uses the ethylene molecule to tweak haustorium development and host invasion."

Forward genetics is used to identify genes,



or sets of genes, that produce a particular characteristic in an organism. The model species used in this study is from a family of parasitic plants that includes destructive weeds. But the molecular basis for their parasitism has been largely unexplored until now.

"Our results suggest that parasitic plants have taken over ethylene signaling for parasitism at multiple stages of their life cycle, such as germination, haustorium growth termination, and host invasion. This knowledge could provide new ways to use ethylene and ethylene inhibitors to control a broader range of parasitic weeds, including those that don't rely entirely on hosts to complete their life cycle, by manipulating haustorial function," says Cui.



The model parasitic plant, *Phtheirospermum japonicum*, and its haustorium. The right lower photo shows xylem connection between the parasitic (P) and host plants (H).

Reference

Songkui Cui, Tomoya Kubota, Tomoaki Nishiyama, Juliane K. Ishida, Shuji Shigenobu, Tomoko F. Shibata, Atsushi Toyoda, Mitsuyasu Hasebe, Ken Shirasu, Satoko Yoshida. 2020. Ethylene signaling mediates host invasion by parasitic plants. *Science Advances*, 6, eabc2385.

Plant Growth Regulation

Prof. Masaaki Umeda

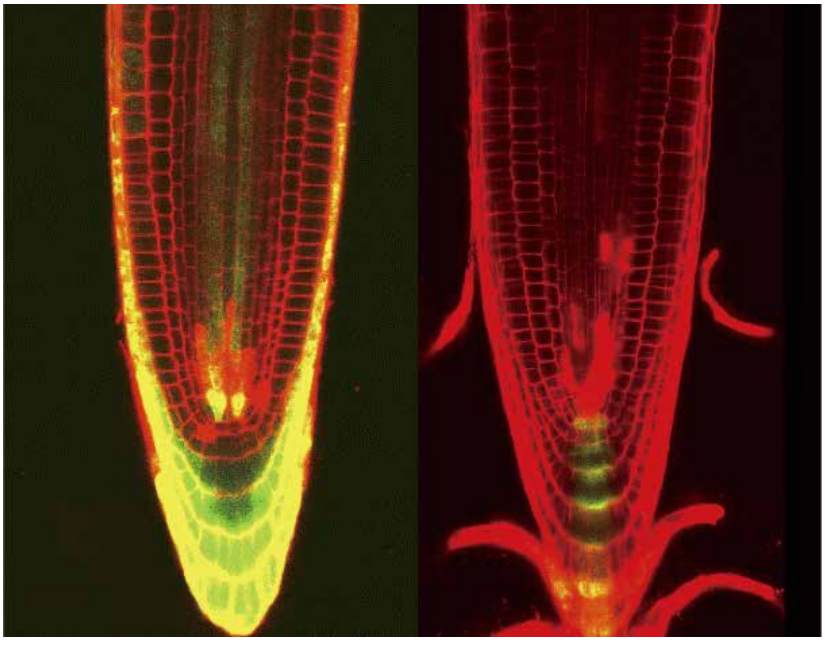
Damage control: Plants juggle genome maintenance and growth by being organized

Researchers at NAIST find that control of the plant hormones cytokinin and auxin help damaged plants to minimize cell death while maintaining their genomes and organ development.

Humans pride themselves on being able to multitask, especially under pressure. But it turns out that we aren't the only ones who are organized: scientists have discovered that plants balance genome maintenance with organ growth by organizing different responses to DNA damage.

In a study published in *Science Advances*, a team of researchers led by NAIST has revealed that plants use combined control of the plant hormones cytokinin and auxin to organize DNA damage responses while maintaining growth.

Plants are highly adaptable organisms that never stop growing, thanks largely to the functions carried out by their roots. Because of the essential role that roots play in plant growth, root development is highly responsive to fluctuating conditions underground, including environmental stresses. These stresses tend to limit root growth, and can damage DNA.



***Arabidopsis* root tips with increased cytokinin (left) and decreased auxin signals (right) in response to DNA damage.**

"Plants actively respond to DNA damage, and these responses are controlled by the cell cycle checkpoint mechanism," says project leader Masaaki Umeda. "The cell cycle is stopped at a certain stage so that DNA can be repaired, or in extreme cases, cell death initiated. What we wanted to know was how the DNA damage responses are organized to allow continuous root growth."

Unlike animal cells, plant cells aren't mobile, so plants can't replace dead cells with surrounding living cells. To simultaneously maintain their genomes and allow organ development, plants initiate different DNA damage responses that are dependent on the different types of cells in tissues.

"We found that the combined control of two plant hormones, cytokinin and auxin, organizes different DNA damage responses at the cost of minimized cell death," explains first author Naoki Takahashi. "This is a sophisticated way to retain stem cells while maintaining their genomes in damaged plants."

A decrease in auxin triggers stem cell death and stops the cell cycle at the G2 phase, while increased cytokinin signals support early endoreplication—a cell cycle variant where the genome is duplicated without cell division.

The study explains previously unidentified mechanisms of keeping genomes stable in a developmental setting, which allow continuous organ growth in fluctuating environments. The results of this study will have wide-ranging applications to research on agricultural technologies, particularly for plant growth and development in extreme environments. Future studies will illuminate how plants develop organs beyond the embryonic stage via the maintenance of genome stability in changing conditions.

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Naoki Takahashi, Soichi Inagaki, Kohei Nishimura, Hitoshi Sakakibara, Ioanna Antoniadi, Michal Karady, Karin Ljung, Masaaki Umeda. 2021. Alterations in hormonal signals spatially coordinate distinct responses to DNA double-strand breaks in *Arabidopsis* roots. *Science Advances*, 7, eabg0993.

Associate Prof. Yasumasa Ishida

A single allele deletion in gene encoding *Zbtb38* leads to early embryonic death

Researchers at NAIST find that heterozygous loss in gene encoding methyl-CpG binding protein Zbtb38 leads to early embryonic death via the suppression of transcription factors Nanog *and* Sox2.

DNA methylation is a major epigenetic modification that is crucial for mammalian development. For instance, DNA methylation is central to inexhaustible biological processes, such as gene regulation and cell fate decisions. In mammals, DNA methyltransferases are key for blastocysts to re-establish global DNA methylation patterns during implantation. This is critical for passing on epigenetic information to the next generation. On the other hand, the role of methyl-CpG binding proteins (MBPs) that bind methylated CpG as part of the DNA methylation processes is still unclear. However, a previous study conducted by researchers at NAIST clarified that; Zbtb38, also known as CIBZ, is a zinc finger type of MBP that is pivotal for the growth of mouse embryonic stem (ES) cells. They further demonstrated that Zbtb38 facilitates the expression of *Nanog*, which is fundamental for the growth of ES cells. However, what Zbtb38 does in real life, is still a mystery.

In a further quest to solve this mystery, the same scientists at NAIST, led by Eishou Matsuda, used Cre-loxP technology to make conditional *Zbtb38* knockout mice. Their ground-breaking research revealed that a single *Zbtb38* allele deletion in the germline led to a decrease in epiblast cell growth and an increase in apoptosis soon after implantation, which led to early embryonic death. *Nanog*, *Sox2* and genes that control epiblast growth and differentiation became dysfunctional when *Zbtb38* was lost in heterozygous embryos.

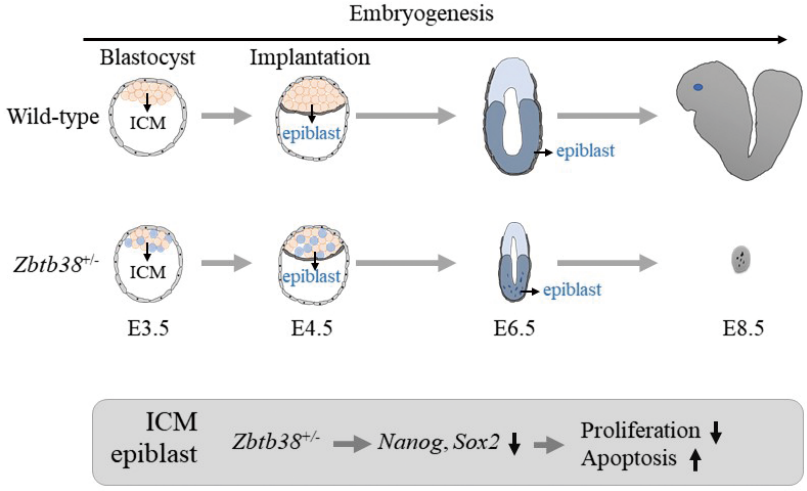
"Our findings indicate that germline loss of the *Zbtb38* single allele reduces epiblast cell proliferation and increases apoptosis shortly after implantation, resulting in early embryonic lethality. Heterozygous *Zbtb38* deficiency reduced the expression of *Nanog*, *Sox2* and genes involved in epiblast proliferation, differentiation and cell viability. This finding shows that a methyl-CpG binding protein has a role in controlling embryonic phenotype," explains Matsuda.

"For the first time we demonstrated a link to an embryonic function for a protein that has long been known to bind methyl-CpG," says co-author Yasumasa Ishida. "This presents a huge opportunity for further research to find out how Zbtb38 works during embryogenesis. More research needs to be done to elucidate the specific molecular mechanisms. Zbtb38 is found in all tissues, and it is linked to height, cancers, neurodegenerative diseases and rheumatoid arthritis, etc. Thus, the creation and analysis of tissue-specific Cre-mediated knockout mice will help us understand Zbtb38's physiological functions and Zbtb38-linked diseases," concludes Matsuda.

The findings of this work will interest developmental biologists as it emphasizes the epigenetic significance of DNA methylation during the early stages of pregnancy.

Reference

Miki Nishio, Takuya Matsuura, Shunya Hibi, Shiomi Ohta, Chio Oka, Noriaki Sasai, Yasumasa Ishida, Eishou Matsuda. 2022. Heterozygous loss of *Zbtb38* leads to early embryonic lethality via the suppression of *Nanog* and *Sox2* expression. *Cell Proliferation*, 55, e13215.



Heterozygous loss of *Zbtb38* causes decreased epiblast cell proliferation and increased apoptosis shortly after implantation, leading to early embryonic lethality.

Molecular Immunobiology

Prof. Taro Kawai

Tropical ginger treatment for blocking inflammation

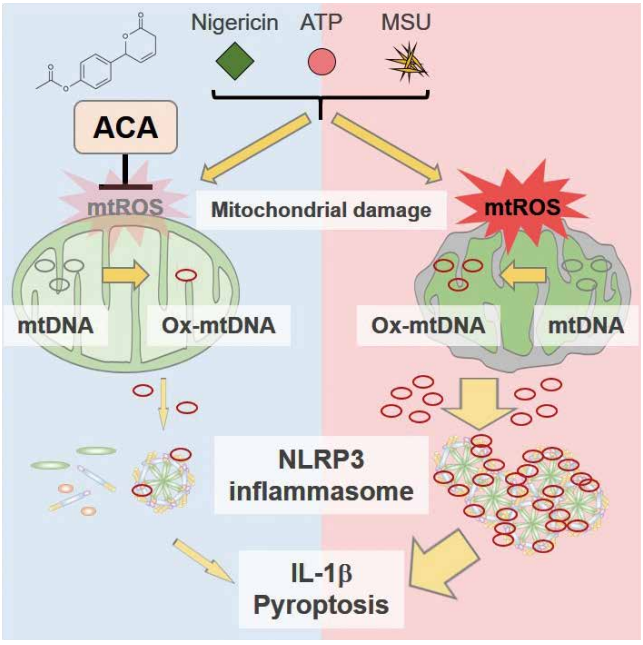
Researchers at NAIST identify antioxidant properties of a ginger-derived compound that may help fight inflammatory diseases.

Many natural compounds have various anti-inflammatory and other beneficial properties that humans have been utilizing for medicinal purposes for hundreds of years. However, the specific molecular mechanisms behind these health-promoting effects are not always clear. One such compound is 1'-acetoxychavicol acetate, or ACA, which comes from the tropical ginger *Alpinia* plant. Now, a team of researchers led by NAIST has identified how ACA can help in the treatment of inflammatory diseases.

In a report published in *International Immunology*, they found that ACA attenuates mitochondrial damage through decreasing mitochondrial reactive oxygen species (ROS), blocking activation of a crucial protein complex known as the nucleotide-binding oligomerization domain-like receptor family pyrin domain-containing protein 3 (NLRP3) inflammasome. Many inflammatory diseases, like inflammatory bowel disease, display improper and chronic activation of this complex.

Previous work has suggested that the NLRP3 inflammasome plays a significant role in promoting inflammation by secreting a molecule called IL-1β. This acts as a messenger that recruits various immune cells to the site of injury or infection. Additional studies described how production of ROS can help trigger activation of the NLRP3 inflammasome. Because other groups showed that ACA can reduce ROS production in certain immune cells, the researchers became curious how this compound would impact the NLRP3 inflammasome and its functions.

"Many disease pathogeneses involve dysregulation of the inflammasome," says Daisuke Ori, co-lead author of the study. "Blood cells from people suffering from rheumatoid arthritis or other autoimmune disorders frequently have increased levels of inflammasome-derived IL-1β. Therefore, targeting the NLRP3 inflammasome with a compound like ACA may be a promising therapeutic strategy."



ACA ameliorates mitochondrial damage, leading to the suppression of NLRP3-inflammasome activity and subsequent IL-1b release.

The researchers grew immune cells in culture that were obtained from mouse bone marrow, and also used a mouse model of colitis. ACA was added to the growing cells and the live mice were given the compound in their food. The researchers then examined the effects on ROS production, secretion of IL-1β, and other markers of inflammation.

"Cells treated with ACA had significantly reduced IL-1β production, as well as lower levels of ROS," explains Taro Kawai, senior author. "ACA could also inhibit NLRP3 inflammasome activation in the colitis mouse model." These *in vivo* results are promising, as they suggest ACA has the potential to treat or prevent the development of inflammatory diseases. "Interestingly, we did not observe high levels of immune cell death when using ACA, which means that it may be relatively safe," continues Ori.

This work provides novel evidence for a specific molecular mechanism governing the previously observed anti-inflammatory properties of ACA. Furthermore, it highlights the potential of ACA for therapeutic use in diseases mediated by IL-1β molecules, or associated with cytokine storm occurrence, as seen in patients suffering from severe COVID-19.

Reference

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Molecular Immunobiology

Prof. Taro Kawai

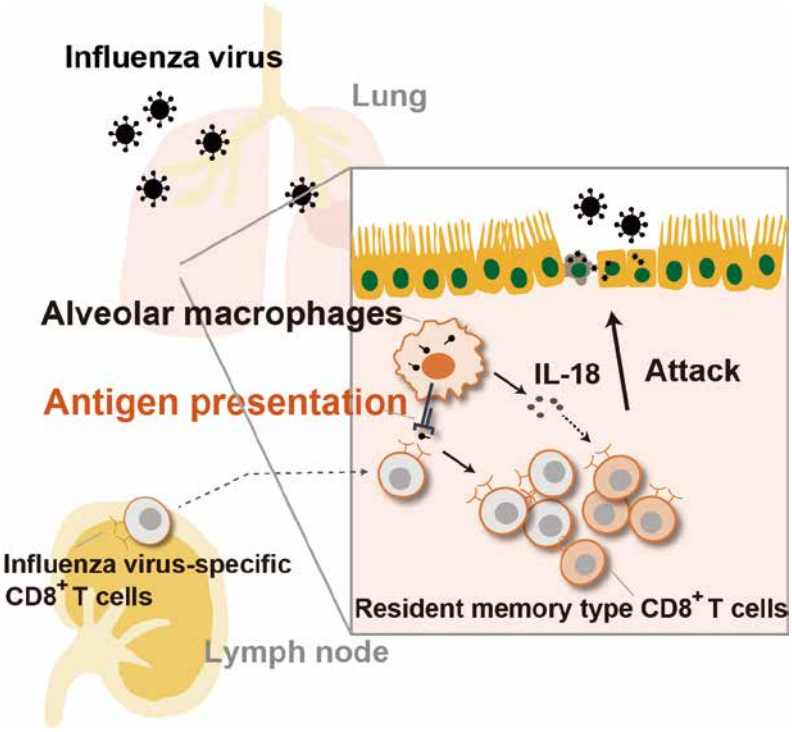
Alveolar macrophages help CD8$^+$ T cells go (anti-)viral

Researchers at NAIST find that lung-resident alveolar macrophages act as antigen-presenting cells to prime CD8$^+$ T cell expansion in the lungs in response to viral infection.

The human immune system is a highly complex network of cells, signals, and responses that is tightly regulated to ensure that the body can fight off infection without damaging its own tissues. Now, scientists report a new way in which the immune system protects lung tissue from viral infections.

In a study published in *Cell Reports*, a team of researchers led by NAIST has revealed that antigen-specific killer T cells (CD8$^+$ T cells) rapidly expand in the lungs when they encounter antigen-presenting alveolar macrophages (AMs) to protect against viral infection.

CD8$^+$ T cells confer protective immunity against infection with respiratory viruses, such as influenza A virus (IAV) and severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), by killing infected cells. In order to target the correct cells for killing, naive CD8$^+$ T cells must be primed by contact with antigen-presenting cells (APCs), which mediate the uptake of virus-infected cells and present their antigens, in a process known as cross-presentation. The primed CD8$^+$ T cells then clonally expand and differentiate into effector or long-lived antigen-specific memory T cells.



Influenza virus-specific CD8$^+$ T cells induced in lymph nodes as a result of influenza virus infection or vaccination circulate throughout the body.

"Multiple cell types can present antigen to CD8$^+$ T cells in the lungs, although the role of tissue-resident macrophages in this process is unclear," explains Takumi Kawasaki, lead author of the study. "AMs are the first cells in the lungs that encounter infectious materials, environmental particles, surfactants, and dying cells, and they are important for the host defense against bacterial and fungal infection, so we suspected that they were also important in protecting against respiratory virus infection."

To test this, the researchers explored the mechanisms by which APCs instruct antigen-specific CD8$^+$ T cells in the lungs. First, mice were primed by vaccination with a specific antigen or infection with IAV, and then they were subjected to secondary immunization or re-infection. "We determined that antigen-presenting AMs present inhaled antigen to memory CD8$^+$ T cells," says senior author of the study, Taro Kawai, "and that this resulted in a rapid expansion of antigen-specific CD8$^+$ T cells in the lungs."

Furthermore, the researchers found that AMs help to develop resident memory-type cell population by producing interleukin 18. Importantly, administration of antigen-loaded AMs to mice induced the proliferation of resident memory-type CD8$^+$ T cells. "This strategy may improve the efficacy of CD8$^+$ T cell-dependent cellular immunity," says Kawai.

Given that the lung is a major tissue for IAV and SARS-CoV-2 infection, the findings from this study regarding the mechanism of lung-resident memory CD8$^+$ cell expansion are expected to lead to the development of new vaccines that induce cellular immunity. Virus-specific antigen-presenting AMs could be delivered as a type of "cell transplant vaccine" in the future.

Reference

Takumi Kawasaki, Moe Ikegawa, Kosuke Yunoki, Hifumi Otani, Daisuke Ori, Ken J Ishii, Etsushi Kuroda, Shiki Takamura, Masahiro Kitabatake, Toshihiro Ito, Ayako Isotani, Taro Kawai. 2022. Alveolar macrophages instruct CD8$^+$ T cell expansion by antigen cross-presentation in lung. *Cell Reports*, 41, 111828.

Prof. Shiro Suetsugu

How cellular fingertips may help cells "speak" to each other

Researchers at NAIST broaden the known functions of an under-appreciated cell structure, with possible applications in wound closure and cancer therapy.

What if you found out that you could heal using only a finger? It sounds like science fiction, reminiscent of the 1982 movie E.T. Well, it turns out that your body's own cells can do something similarly unexpected. A team of researchers led by NAIST has reported in *Developmental Cell* a means by which cells may use "fingers" to communicate instructions for wound closure.

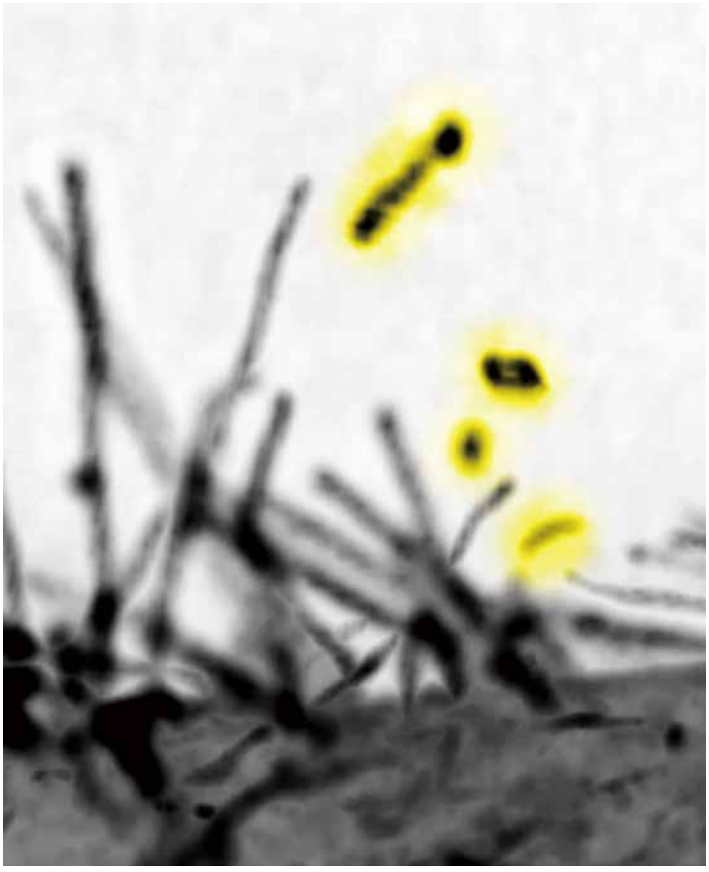
NAIST project leader Shiro Suetsugu has devoted his career to studying how cells shape themselves, initiate and accept communication among one other. An under-appreciated means of doing so is through filopodia, small finger-like cellular projections that are more commonly known to help certain cells crawl in the body. "Filopodia are well-recognized as cellular locomotion machinery. Less understood is how filopodia help cells communicate, and the molecular details of how this is done," says Suetsugu.

A focus of this line of research should be the proteins known by the acronym I-BAR. I-BAR proteins are well-known to help bend the plasma membrane, the "skin" of many cells, for filopodia formation and thus facilitate movement. "We identified an I-BAR protein that severs filopodia," says Suetsugu. An important element of this scission may be mechanical force, a stimulus that your body commonly applies to cells. "Laser experiments showed that the force required for scission is approximately 8–20 kilopascals. These forces are similar to the 4–13 kilopascals, experienced by cells in blood capillaries," Suetsugu says.

Severed filopodia go on to form structures called extracellular vesicles, a popular research topic in biology. Extracellular vesicles were used to basically be considered the trash bags of cells, used for disposing cellular waste. However, the vesicles are now considered to be communication packets rather than waste bags. "The pertinence of these vesicles to cancer metastasis has piqued researchers' and clinicians' interest," notes Suetsugu.

What does this have to do with cell-cell communication? A simulated cell-scale wound healed faster when it was treated with filopodia-derived extracellular vesicles than if untreated. In other words, an I-BAR protein first induced filopodia scission and vesicle production. These vesicles then sent cellular signals that promoted cell migration toward one another, in a way that may promote wound closure.

By understanding how cells fully use their molecular machinery to send instructions to other cells, Suetsugu is optimistic that medical practitioners will develop new means to safely treat cancer and other diseases. "Certain BAR proteins are pertinent to cancer cell biology. BAR proteins are also pertinent to cell locomotion. By learning more about how these proteins aid cell-cell communication, we may find better ways to stop cancer cells from spreading," he says.



The lattice light sheet microscopic images of the filopodia by expressing the I-BAR domain protein MIM.

Reference

Tamako Nishimura, Takuya Oyama, Hooi Ting Hu, Toshifumi Fujioka, Kyoko Hanawa-Suetsugu, Kazutaka Ikeda, Sohei Yamada, Hiroki Kawana, Daisuke Saigusa, Hiroki Ikeda, Rie Kurata, Kayoko Oono-Yakura, Manabu Kitamata, Kazuki Kida, Tomoya Hikita, Kiyohito Mizutani, Kazuma Yasuhara, Yuko Mimori-Kiyosue, Chitose Oneyama, Kazuki Kurimoto, Yoichiroh Hosokawa, Junken Aoki, Yoshimi Takai, Makoto Arita, Shiro Suetsugu. 2021. Filopodium-derived vesicles produced by MIM enhance the migration of recipient cells. *Developmental Cell*, 56, 842–859.

Prof. Shiro Suetsugu

AI knows where your proteins go

Researchers at NAIST find that machine learning can predict the subcellular locations of functionally related proteins.

Facial recognition software can be used to spot a face in a crowd; but what if it could also predict where someone else was in the same crowd? While this may sound like science fiction, scientists have now shown that artificial intelligence can accomplish something very similar on a cellular level.

In a study published in *Frontiers in Cell and Developmental Biology*, researchers from NAIST have revealed that a machine learning program can accurately predict the location of proteins related to actin, an important part of the cellular skeleton, based on the location of actin itself.

Actin plays a key role in providing shape and structure to cells, and during cell movement helps form lamellipodia, which are fan-shaped structures that cells use to "walk" forwards. Lamellipodia also contain a host of other proteins that bind to actin to help maintain the fan-like structure and keep the cells moving.

"While artificial intelligence has been used previously to predict the direction of cell migration based on a sequence of images, so far it has not been used to predict protein localization," says lead author of the study, Shiro Suetsugu. This idea came in during the discussion with Yoshinobu Sato at the Data Science Center in NAIST. "We therefore sought to design a machine learning algorithm that can determine where proteins will appear in the cell based on their relationship with other proteins."

To do this, the researchers trained an artificial intelligence system to predict where actin-associated proteins would be in the cell by showing it pictures of cells in which the proteins were labeled with fluorescent markers to show where they were located. Then, they gave the program pictures in which only actin was labeled and asked it to tell them where the associated proteins were.

"When we compared the predicted images to the actual images, there was a considerable degree of similarity," states Suetsugu. "Our program accurately predicted the localization of three actin-associated proteins within lamellipodia; and, in the case of one of these proteins, in other structures within the cell."

On the other hand, when the researchers asked the program to predict where tubulin, which is not directly related to actin, would be in the cell, the program did not perform nearly as well. "Our findings suggest that machine learning can be used to accurately predict the location of functionally related proteins and describe the physical relationships between them," says Suetsugu.

Given that lamellipodia are not always easy for non-experts to spot, the program developed in this study could be used to quickly and accurately identify these structures from cell images in the future. In addition, this approach could potentially be used as a sort of artificial cell staining method to avoid the limitations of current cell-staining methods.

Reference

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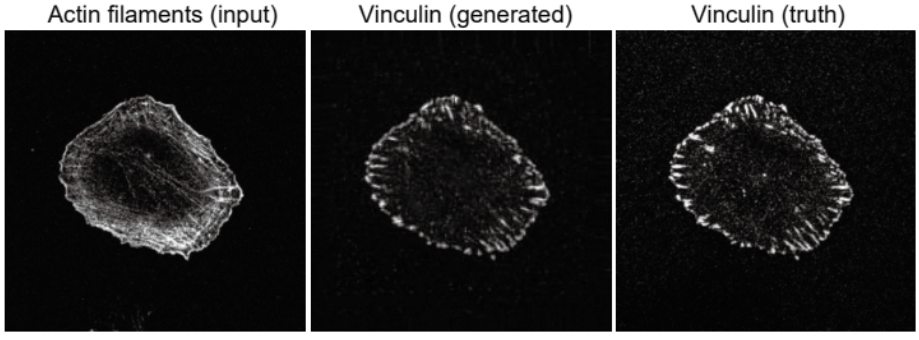
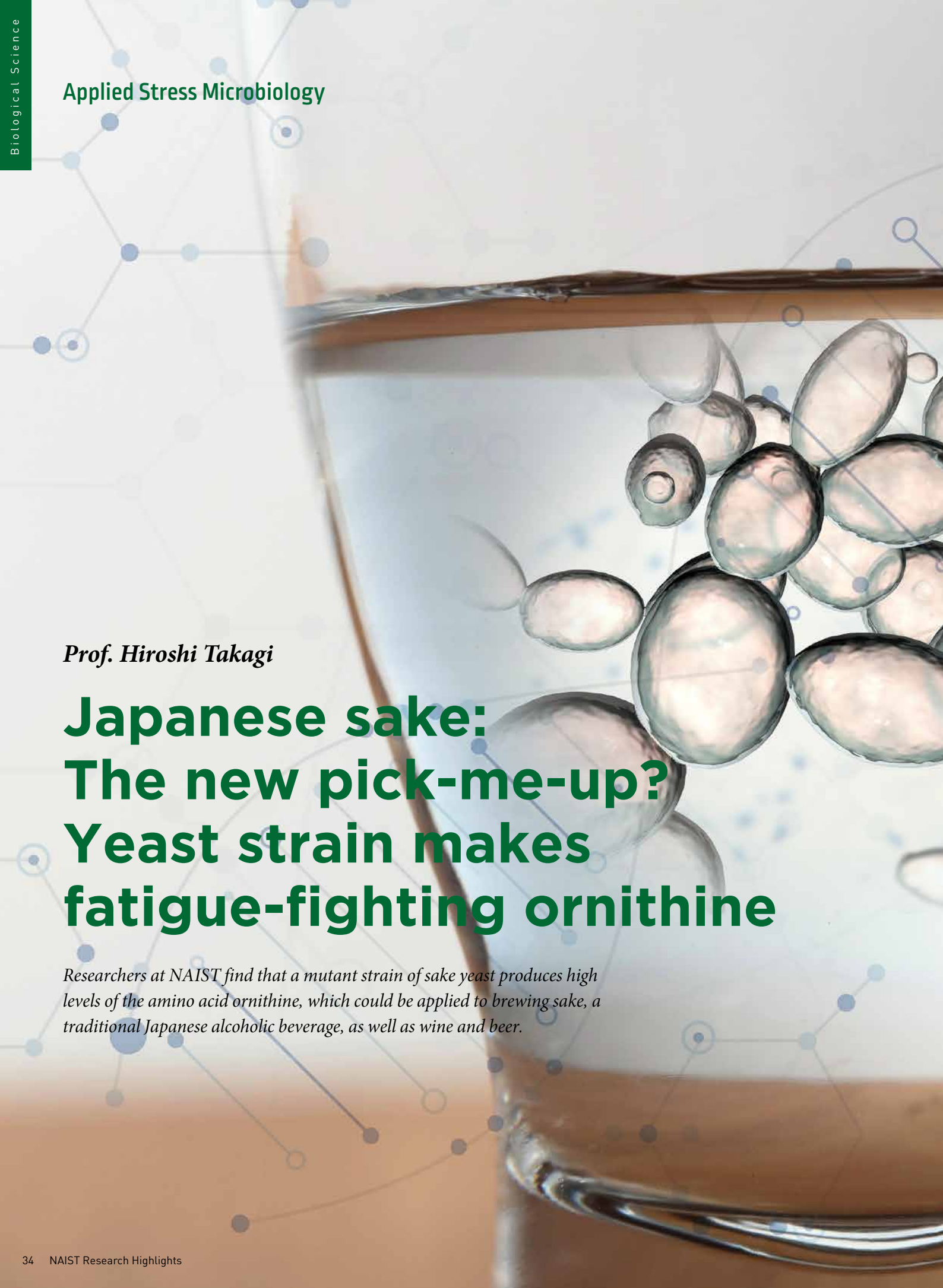


An example of a generated image of focal adhesion protein (center), which anchors actin filaments, from an image of actin filaments (left).

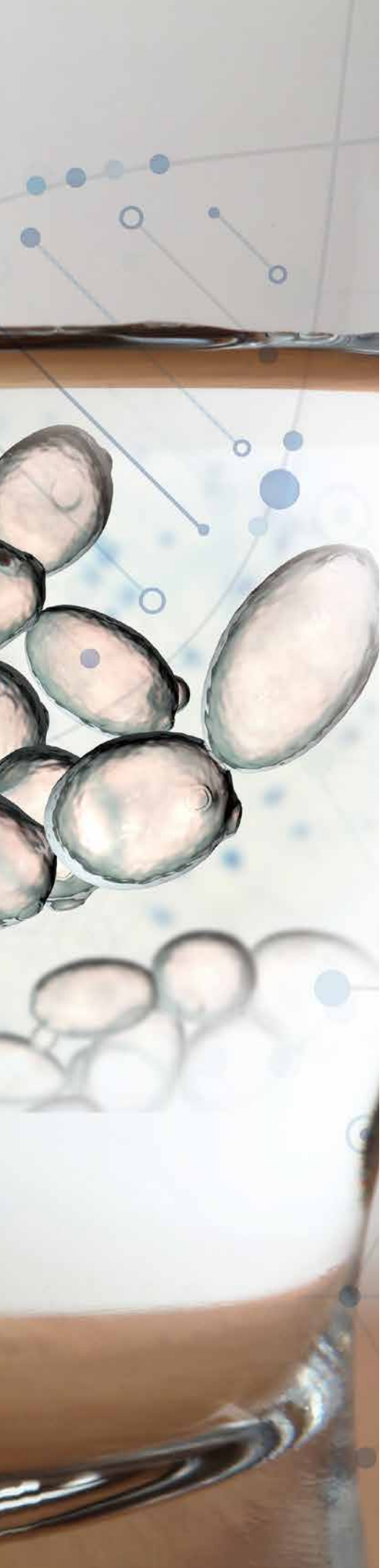
Applied Stress Microbiology



Prof. Hiroshi Takagi

Japanese sake: The new pick-me-up? Yeast strain makes fatigue-fighting ornithine

Researchers at NAIST find that a mutant strain of sake yeast produces high levels of the amino acid ornithine, which could be applied to brewing sake, a traditional Japanese alcoholic beverage, as well as wine and beer.



Fans of sake, the traditional Japanese alcoholic beverage, may have even more reason to enjoy it now: Japanese scientists have discovered that a mutant strain of sake yeast produces high levels of the amino acid ornithine.

In a study published this month in *Metabolic Engineering*, a team of researchers led by NAIST has revealed that a mutant strain of sake yeast produces 10 times the amount of the amino acid ornithine compared with the parent yeast strain.

Ornithine is a non-protein-making amino acid and a precursor to two amino acids—arginine and proline. It has been found to perform several physiological functions, such as reducing fatigue and improving sleep quality.

"We wanted to obtain sake yeast strains with improved ethanol tolerance," says first author of this study, Masataka Ohashi. "During sake fermentation, the yeast is exposed to high concentrations of ethanol, which impedes yeast cell growth, viability and fermentation. Increased ethanol tolerance in sake yeast strains could improve ethanol production and reduce fermentation time."

To find ethanol-tolerant yeast strains, the researchers isolated mutants that accumulated proline, which can alleviate ethanol toxicity, using a conventional mutagenesis (i.e., one that doesn't involve genetic modification). They also conducted whole genome sequencing analysis, and performed brewing tests with sake yeast strains. Then they identified and analyzed a new mutation in a gene that encodes a variant of *N*-acetyl glutamate kinase that increases intracellular ornithine level.

"We previously constructed self-cloning industrial yeast strains that accumulate proline to increase ethanol tolerance and productivity of yeast," explains Hiroshi Takagi, corresponding author. "But those yeasts have not been yet acceptable to consumers because they're considered to be genetically modified, even though a self-cloning yeast has no foreign genes or DNA sequences—they only have yeast DNA."

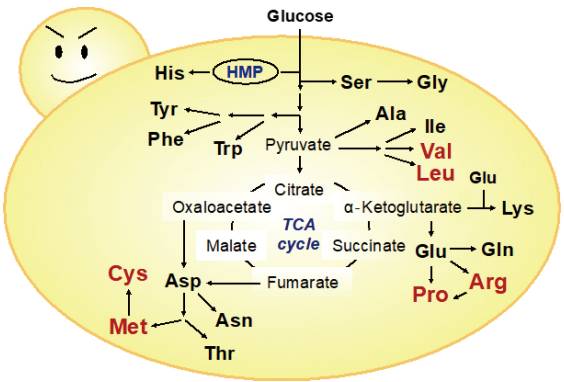
The researchers successfully isolated non-genetically modified yeasts that produced 10 times the amount of ornithine compared with the parent strain, which is widely used in Japanese sake breweries, and the sake brewed with them contained 4–5 times more ornithine.

Takagi notes "There are two major purposes for breeding of industrial yeast: improvement of fermentation ability with enhanced tolerance to environmental stresses during fermentation processes and diversity of product taste and flavor with modified metabolic pathways. In yeast, amino acid metabolisms vary under different growth environments and the metabolic styles form a complicated but robust network. The elucidation of metabolic regulatory mechanisms and physiological roles for amino acids is important fundamental research for understanding life phenomenon. The yeast is reliable and safe in food production, and thus the development of novel strains that overproduce 'functional amino acids' such as ornithine, proline and branched-amino acids, would greatly contribute to food-related industries."

The results of this study will contribute to the development of improved yeast strains for production of high levels of ornithine, and the strain obtained in this study could be readily applied to sake, wine, and beer brewing. Ornithine-accumulating yeast strains could also be used in the production of ornithine-rich dietary supplements made from these yeasts and their products.

Reference

Masataka Ohashi, Ryo Nasuno, Shota Isogai, Hiroshi Takagi. 2020. High-level production of ornithine by expression of the feedback inhibition-insensitive *N*-acetyl glutamate kinase in the sake yeast *Saccharomyces cerevisiae*. *Metabolic Engineering*, 62, 1–9.



Overview of amino acid metabolism in yeast.

Environmental Microbiology

Prof. Shosuke Yoshida

How a bacterium may help solve the plastic pollution crisis

Researchers at NAIST find that the bacterium Ideonella sakaiensis *can not only degrade environmentally problematic petroleum-based plastics but can also sustainably produce biodegradable plastics, which has promising environmental implications.*

Plastic pollution is one of the most pressing environmental issues of our time. The accumulation of petroleum-based plastics is having devastating effects on our environment, wildlife, and human health. In a study published in *Scientific Reports*, a team of researchers led by NAIST has revealed a bacterium that is not only able to degrade difficult-to-recycle petroleum-based plastics but can also sustainably produce more environmentally friendly biodegradable plastics.

Petroleum-based plastics, including poly(ethylene terephthalate) (PET), are extensively used in everyday products, such as single-use plastic bottles, textiles, and food wrappers. While such products are disposed of rapidly after use, they persist in the environment for hundreds of years. The plastic pollution resulting from our throw-away culture has now exceeded manageable levels and is overwhelming the planet's ability to deal with it. The environmental impacts are becoming increasingly obvious, with wildlife and human health increasingly threatened.

Although reducing the manufacture of unnecessary single-use plastics and improving waste management systems will help ease the pollution crisis, our reliance on the convenience of plastic products is unlikely to be abated any time soon. Researchers are therefore looking at alternative approaches to "clean up" the more persistent plastics from our environment and it appears that microbes may offer some promising solutions.

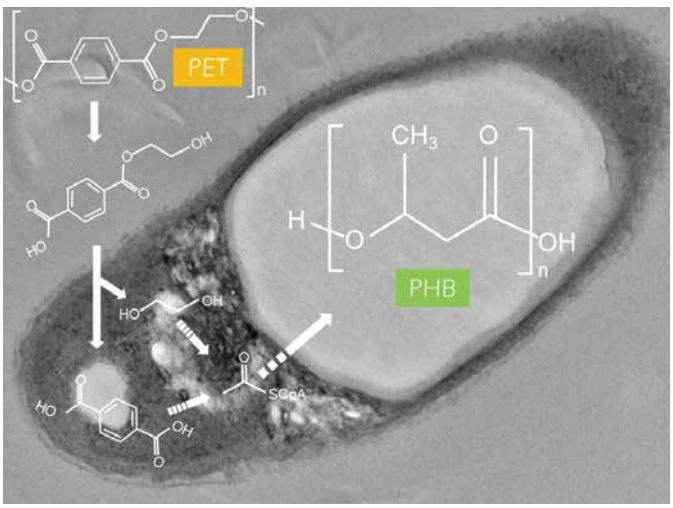
"Certain bacteria harbor the necessary enzymes to degrade PET, the most problematic plastic environmentally," explains senior author Shosuke Yoshida. "Our research has shown that the bacterium *Ideonella sakaiensis* converts PET into poly(3-hydroxybutyrate) (PHB), a type of poly(hydroxyalkanoate) (PHA) plastic that is biodegradable," he continues.

This finding is particularly promising because it addresses two current problems for the sustainability of plastics: degrading the most persistent form of petroleum-based plastic while sustainably producing biodegradable plastics.

"We believe that this discovery could be significant in tackling plastic pollution," Yoshida states, "as we show that the PET-degradation and PHB-synthesis pathways are

functionally linked in *I. sakaiensis*. This might provide a novel pathway where a single bacterial species breaks down difficult-to-recycle PET plastics and uses the products to make biodegradable PHA plastics."

Given the overwhelming challenge of dealing with worldwide plastic pollution, this novel bacterial approach may be a significant part of the solution.



***Ideonella sakaiensis* cultured on poly(ethylene terephthalate) (PET) accumulates poly(3-hydroxybutyrate) (PHB).**

Reference

Ryoga Fujiwara, Rikako Sanuki, Hiroharu Ajiro, Toshiaki Fukui, Shosuke Yoshida. 2021. Direct fermentative conversion of poly(ethylene terephthalate) into poly(hydroxyalkanoate) by *Ideonella sakaiensis*. *Scientific Reports*, 11, 19991.

Structural Life Science

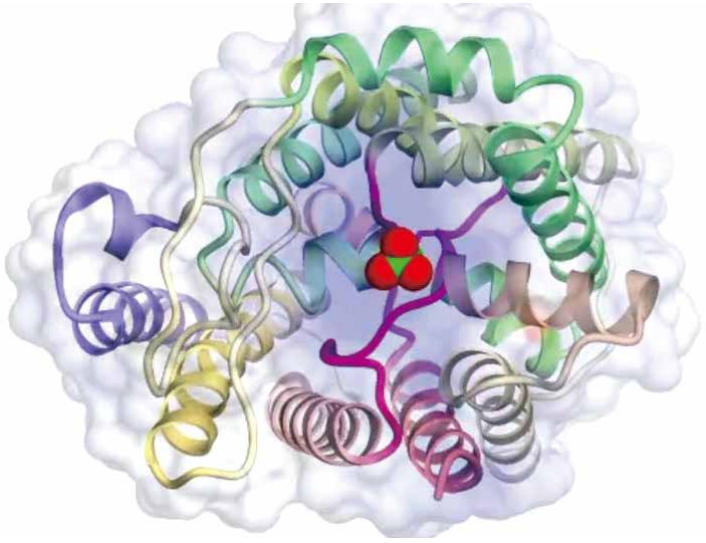
Prof. Tomoya Tsukazaki

A protein with an unprecedented fold helps bacteria uptake thiosulfate as a sulfur source

Researchers at NAIST discover that the YeeE protein allows bacteria to uptake thiosulfate from the environment for cysteine synthesis, showing a unique hourglass shape that allows YeeE to undergo minimal conformational changes for the uptake compared with other transporter proteins.

A new study led by researchers at NAIST, in *Science Advances* has reported the crystal structure of YeeE, a membrane protein that allows bacteria to uptake thiosulfate from the environment in order to synthesize L-cysteine. The structure reveals that YeeE has a characteristic hourglass shape that results in a sophisticated mechanism for the uptake, providing fundamental information that could greatly lower cysteine production costs in industry.

Most people know that water is made of hydrogen and oxygen atoms, and carbon compounds are found in all life on earth. However, other elements like sulfur are also indispensable for life, and sulfur-based molecules like L-cysteine are essential for many of our proteins. L-cysteine is also commercially important, as it is heavily used by the food, cosmetic and pharmaceutical industries.



YeeE structure.

"In nature, L-cysteine is produced by microorganisms that collect inorganic sulfur in the soil. If the secretion and production efficiency of L-cysteine by microorganisms can be dramatically improved, this procedure will be superior to existing methods, such as in the production of glutamic acid by *Corynebacterium glutamicum*," says Tomoya Tsukazaki, an expert in structural biology.

Bacteria can take up both sulfate and thiosulfate ions from the environment in order to synthesize L-cysteine. The efficiency of the synthesis from thiosulfate is higher because of fewer chemical reaction steps. To examine which proteins are crucial for thiosulfate uptake, the researchers conducted a series of genetic studies, finding YeeE.

To understand how YeeE physically conforms for the transport, the researchers uncovered crystal structures of YeeE that revealed an unprecedented fold forming an hourglass shape. "Both the inner and outer surfaces of YeeE are indented toward the center. We think this shape is crucial for initiating the uptake and conducts thiosulfate," explains Yoshiki Tanaka, the first author of the study.

Molecular dynamics simulations implied that the uptake occurs by passing the thiosulfate ion through three key sites in the YeeE structure. In the model, the first site attracts a thiosulfate ion to the positively charged surface. Then using S-H-S type hydrogen bonds, YeeE passes the ion to the other two sites and on to the cytoplasm without itself undergoing any major conformational changes.

This mechanism for uptake is quite unusual among membrane transporters according to Tanaka. "There is a lot less movement compared with transporters that have inward- and outward-facing structures or use rocking bundle motions. YeeE is not structurally designed to use these other mechanisms," he says.

Tsukazaki adds that the new mechanism expands our knowledge of nutrient transport into a cell, knowledge that can be exploited for industrial purposes. "Comparatively little is known about the YeeE family of transport proteins. Through more study of the structure for the uptake and genetic modifications, we might be able to artificially design 'super' YeeE that enhance L-cysteine productivity via high thiosulfate uptake" he says.

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Systems Neurobiology and Medicine

Prof. Naoyuki Inagaki

Shootin1a – The missing link underlying learning and memory

Researchers at NAIST find that the shootin1a protein is crucial for allowing dendritic spines to change in size, which is an important process underlying learning and memory.

In neurons, changes in the size of dendritic spines—small cellular protrusions involved in synaptic transmission—are thought to be a key mechanism underlying learning and memory. However, the specific way in which these structural changes occur remains unknown. In a study published in *Cell Reports*, a team of researchers led by NAIST has revealed that the binding of cell adhesion molecules with actin, via an important linker protein in the structural backbone of synapses, is vital for this process of structural plasticity.

Actin proteins make up an important part of a cell's structure, or cytoskeleton, and allow for dynamic changes in this structure by forming microfilaments when growth or movement is required. It was originally thought that the polymerization of actin was all that was needed for dendritic spines to change size in response to synaptic activation, but researchers at NAIST found that this process alone was not enough to cause structural plasticity, and decided to address this problem.

"Current models of structural plasticity in dendritic spines do not take mechanical force into account," says Naoyuki Inagaki, corresponding author. "We had already identified the role of shootin1a, a protein involved in neuronal development, in axon growth and so we wanted to investigate whether this protein might also have a role in the structural plasticity of dendritic spines."

To explore this question, the researchers used neurons of control and shootin1a knockout rodents to examine whether shootin1a was involved in the formation of dendritic spines. The researchers wanted to determine if mechanical force was generated in dendritic spines by the shootin1a-mediated coupling of actin and cell adhesion molecules—cell-surface proteins that bind cells together at synapses—similar to what they had observed in axons.

"The results were clear," explains Inagaki. "We found that shootin1a mechanically linked polymerizing actin with cell adhesion molecules in dendritic spines, and revealed that synaptic activity enhanced this coupling, thus allowing the actin filaments to push against the membranes and enlarge spines." The results of this study are the first to link mechanical force with synaptic activity-dependent dendritic spine plasticity and provide new insights into the mechanisms of structural plasticity in these spines.

Given that changes in activity-dependent dendritic spine plasticity have been implicated in multiple neuropsychiatric and neurodegenerative disorders, including autism spectrum disorder and Alzheimer's disease, these findings are important because they suggest that shootin1a disruption may lead to the development of neurological disorders. Future studies into this mechanism of structural plasticity in dendritic spines might provide new drug targets for these disorders.

Reference

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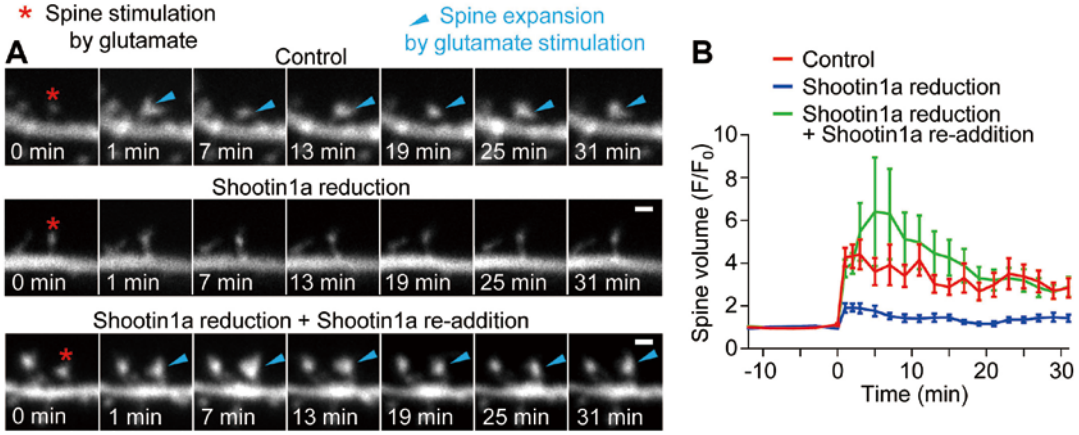

Fluorescence time-lapse images of dendritic spines (A) and time course of their volume changes (B) of hippocampal neurons in slice culture.

Plant Cell Function

Prof. Takashi Hashimoto

Hired blade: Anchoring complex in plant cells recruits its own katana sword

Researchers at NAIST find that an anchoring complex stabilizes microtubule creation sites within plant cells, then recruits katanin—named after the katana sword—to cut new microtubules.

The katana, a Japanese sword, may be thought of solely as a weapon used by the samurai. But scientists from Japan have discovered that not only do plants wield their own katanas within their cells, they recruit them to specific locations within those cells to do their work.

In a study published in *Nature Communications*, a team of researchers led by NAIST has revealed that the enzyme katanin, which is named after the katana, is used by an anchoring complex to cut microtubules at specific locations of the framework within individual plant cells.

Katanin severs microtubules in cells, which is an important step in cell division and central to the development of many organisms, including plants and animals. Microtubules form part of the cytoskeleton, a complex network of protein filaments found in all cells. The severing performed by katanin enables mobility, which is important during development, and treadmilling—a phenomenon where one end of a filament lengthens as the other shrinks, which results in a section of filament that seems to 'move' like a treadmill.

"Katanin severs microtubules at specific locations in plant and animal cells, and this leads to active reorganization of the microtubule cytoskeleton," says senior author of the study Takashi Hashimoto. "But the mechanisms for targeting this extraordinary enzyme at specific sites within the cell are not well understood—these are what we wanted to investigate."

The team's genetic and cell biology research results showed that the microtubule anchoring complex Msd1-Wdr8 is used to stabilize microtubule nucleation sites (where microtubules are formed) in plant cells to prevent early release of the new microtubules (called 'daughter microtubules'). But in a seemingly counterintuitive twist, Msd1-Wdr8 then turns around and recruits katanin to the same location to enable the efficient release of daughter microtubules.

"These 'glue-and-cut' functions performed by Msd1-Wdr8 and their effects on microtubule stability may seem confusing at first, but they probably enable strict control of microtubule release by the katanin activity," explains Hashimoto.

This study will inform future research on whether the Msd1-Wdr8 complex in animal cells also recruits katanin, and whether other sites use similar mechanisms for the stabilization and release of daughter microtubules. The results of this study will be of interest to cell biologists, especially those working on cytoskeletons, in plants and other organisms.

Reference

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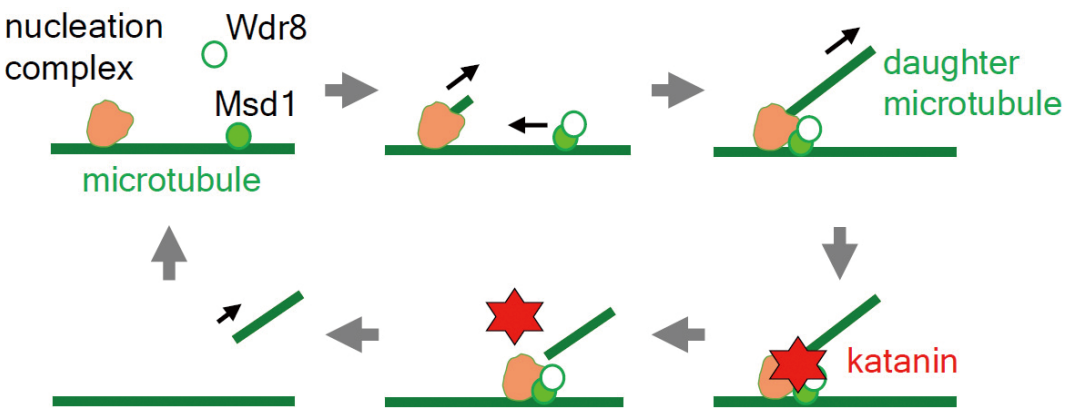


The anchoring complex Msd1-Wdr8 stabilizes the base of the Y-shaped nucleation structure and recruit katanin to sever the basal end of the daughter microtubule.

MATERIALS SCIENCE

Bio-Process Engineering

Prof. Yoichiroh Hosokawa

Antibiotic resistance testing no longer impeded by time

Researchers at NAIST develop a novel method for antibiotic resistance testing that might transform microbial screening in clinical and research labs.

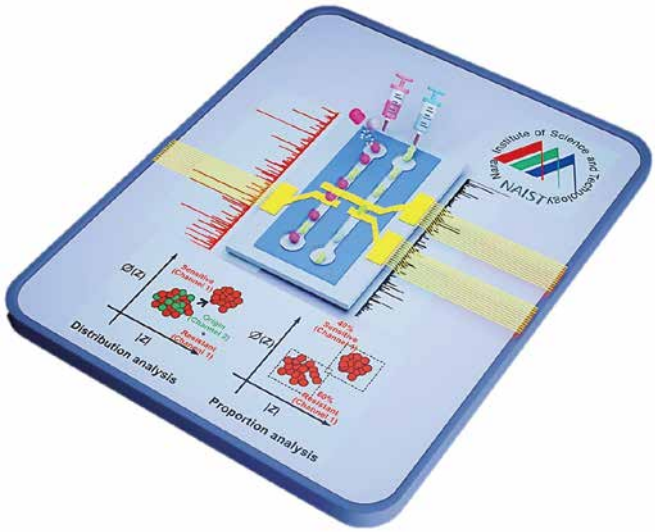
Significant time is needed to determine the drug susceptibility profile of a bacterial infection. Now, a team of researchers led by NAIST has published reports on a technology that will dramatically speed up this otherwise slow process and possibly help save lives.

The U.S. CDC states that antibiotic-resistant infections are responsible for killing over a million people worldwide every year. Central to managing resistant infections is quickly identifying an appropriate treatment to which the infective bacteria are susceptible. "Oftentimes susceptibility results are needed much faster than conventional tests can deliver them," says Yaxiaer Yalikun, senior author. "To address this, we developed a technology that can meet this need."

The group's work is based on impedance cytometry which measures the dielectric properties of individual cells with high throughput—over a thousand cells per minute. Because the electrical readout of a bacterium corresponds to its physical response to an antibiotic, one has a straightforward means of determining whether the antibiotic works against the bacteria. Conventional impedance cytometry involves analyzing the test (antibiotic treated) and reference (untreated) particles in one sample followed by calibrating the impedance of the two particles—both steps require technical specialists to carry out extensive post-processing, which was a major limitation the group was determined to overcome.

In a study published in *ACS Sensors*, the group develops a novel impedance cytometry method that simultaneously analyses the test and reference particles in separate channels, creating easily analyzable separate datasets. This cytometry had nanoscale sensitivity, allowing for detection of even minute physical changes in bacterial cells. In a concurrent study published in *Sensors and Actuators B*, the group designed a machine learning tool to analyze the impedance cytometry data. Because the new cytometry method splits the test and reference datasets, the machine learning tool could automatically label the reference dataset as the "learning" dataset and use it to learn the characteristics of an untreated bacterium. By real-time comparison with antibiotic-treated cells, the tool can identify whether the bacteria are susceptible to the drug and can even identify what proportion of bacterial cells are resistant in a mixed-resistance population. "Although there was a misidentification error of less than 10% in our work, there was a clear discrimination between susceptible and resistant cells within 2 hours of antibiotic treatment," explains Yoichiroh Hosokawa, another senior author in the group.

This work is not limited to rapid evaluations of infections in clinical settings. For example, drug discovery researchers could use it to conduct quick initial investigations of drug efficacy against any cell, as long as the cellular response results in a change in dielectric properties. Impedance cytometry might become a staple of clinical and research labs in the coming years.



Schematic of the intelligent impedance system, consisting of a parallel impedance cytometry and a machine learning-based detection system.

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Bio-Process Engineering

Prof. Yoichiroh Hosokawa

Feeling the pressure

Researchers at NAIST refine the equations for mechanical stiffness to apply to plant cell walls based on elastic shell theory and verified using finite element simulations, which may lead to a better understanding of how plants resist stress.

A team of researchers led by NAIST has shown how the stiffness of plant cell walls depends on their elasticity and internal turgor pressure using elastic shell theory. By utilizing atomic force microscopy (AFM) combined with finite element computer simulations, they were able to show that cell stiffness is very sensitive to internal turgor pressure.

Many people will have fond memories from their school days looking at onion peels under a microscope. While the individual cells might have seemed then like simple rectangles, the stability of plant cells reflects complex combinations of forces. In addition to the cell membrane which is similar in animals, plant cells also have a rigid cell wall that provides structural integrity. Turgor, meaning the normal rigidity of cells due to the pressure from its contents, is also a critical factor in maintaining balance with the environment. Too little pressure can cause the cell to shrink. Cells can regulate their turgor pressure osmotic flows that tend to balance the salt concentrations between the interior and the outside of the wall. However, the resulting mechanical properties of plant cells remain nebulous. For example, using AFM alone to determine the stiffness from cell wall deformation makes it difficult to separate the contributions from the tension of the cell wall, cell geometry and turgor pressure.

Now, the research team led by NAIST has used finite element method (FEM) simulations to verify a new formula based on elastic shell theory. This allowed them to interpret the apparent stiffness observed using AFM. The team studied onion epidermal cells, which are a model system for understanding the physical properties of plant cells. "Looking at the force versus indentation data suggested that the standard equations were not sufficient for interpreting the apparent stiffness of plant cells," senior author Yoichiroh Hosokawa says.

Based on the FEM simulations, the elastic shell theory equation was shown to be better at describing the AFM response of the onion cells, compared with the conventional model used for objects without internal turgor pressure. Moreover, their findings suggest that tension caused by turgor pressure regulates cell stiffness, which can be modified by slight changes, on the order of 0.1 megapascals. "Our theoretical analysis paves the way for a more complete understanding of the forces inherent in a plant cell," Hosokawa says.

The work helps generalize our understanding of stiffness for living systems. This knowledge can be applied to help ensure that plants maintain their structure even under stressful situations, such as during periods of water deprivation.

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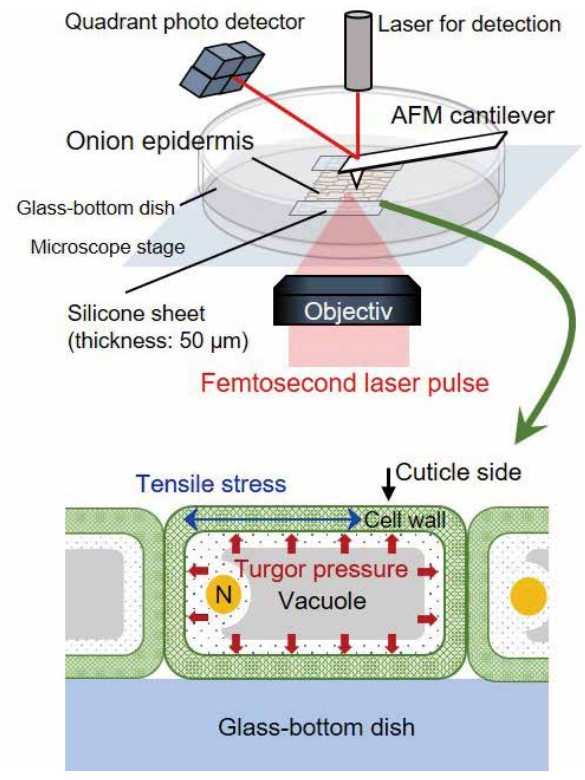


Overview of the study system that utilizes an atomic force microscopy (AFM) combined with finite element computer simulations.

Bio-Process Engineering

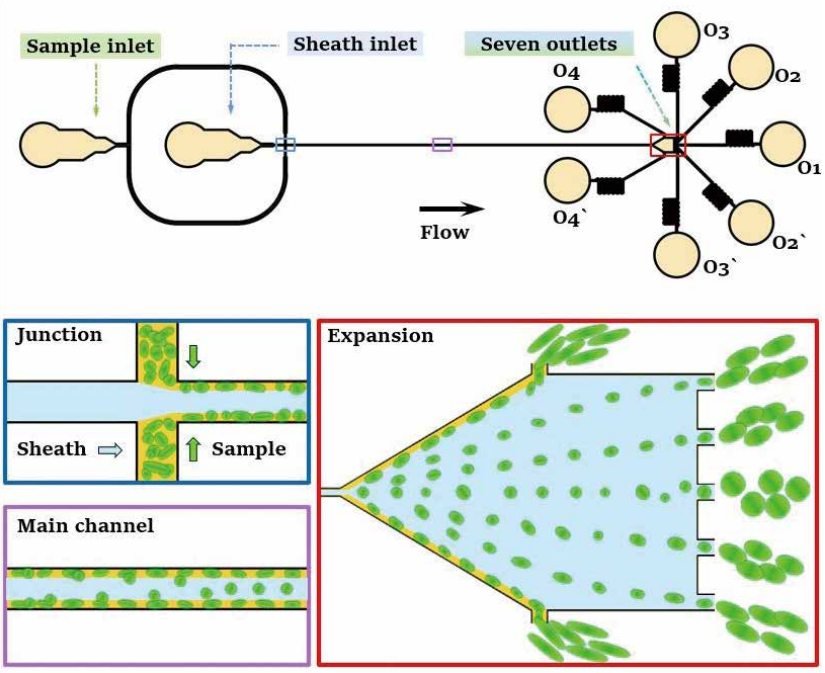
Prof. Yoichiroh Hosokawa

Separating tiny bacteria by shape: Simple techs for *E. coli* sorting

Researchers at NAIST create a lab-on-a-chip with a viscoelastic fluid that can separate spherical from elongated bacteria, which can help standardize biological research and improve medical testing.

A team of researchers led by NAIST has achieved shape-based separation of *Escherichia coli* (*E. coli*) bacteria using a viscoelastic fluid inside microfluidic channels. This "lab-on-a-chip" system has the capability to assist in making scientific experiments more reproducible, as well as provide more accurate assessments of the severity of bacterial infections based on patient samples.

The task of separating tiny bacteria based on their shape is a vital step in scientific and clinical applications, but also a difficult one. Whether an *E. Coli* bacterium is in a round or elongated configuration can indicate its state of biological function, and the ability to prepare homogeneous populations with uniform shapes may help improve experimental reproducibility. Moreover, being able to sort samples into sub-populations based on their shape may help diagnose patient health or assess environmental contamination. However, this ability has been difficult to achieve, especially at the scales needed to be practical.



The design of the viscoelastic microfluidic device for shape-based separation of drug-treated *E. coli*.

Now, the research team led by NAIST has been able to separate drug-treated *E. coli* bacteria using microfluidic channel containing poly-ethylene-oxide (PEO), a viscoelastic fluid. The elongation of the bacteria, as measured by the aspect ratio, ranged from 1.0 (spherical) to 5.5 (rod-shaped). Microchannels made of poly(dimethylsiloxane) were created with photolithography. PEO, which has both high viscosity and elasticity, was made to flow along the edges of an expanding V-shaped chamber. The elongated bacterium followed this flow to be collected at the edges of the device.

"The shape of a *E. coli* bacterium changes based on its attachment, motility, dispersal, predation and differentiation behaviors," author Yalikun Yaxiaer explains. A rod-like configuration is more efficient for swimming, while a spherical shape may help it form communities. These changes are important milestones for the progression of disease, and whether the bacteria are swimming free or forming communities. "This technology will allow downstream genomics experiments on the separated *E. coli* populations to determine linkage between cell shape, antibiotic susceptibility and gene function," author Yoichiroh Hosokawa says.

The team hopes the microfluidic platform they developed will be adopted by the broader scientific community for different applications in the fields of microbiology, molecular biology and biomedicine.

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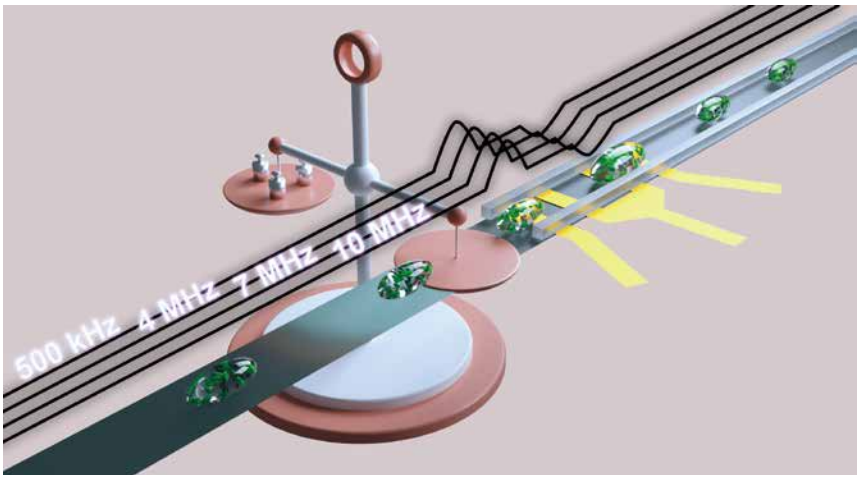

Precise total assessment of the cells with impedance signals.

Prof. Yoichiroh Hosokawa

From outside to inside: A rapid and precise total assessment method for cells

Researchers at NAIST show that using four frequencies of applied voltage can improve the measurement of cell size and shape during impedance cytometry, enabling to enhance the speed and accuracy of biological experiments.

Having a good eye for detail is an essential skill for many professions. In particular, biologists use special techniques and advanced technology to analyze individual cells with unprecedented precision. Impedance cytometry is one experimental method that can reveal specific characteristics of living single cells. This technique requires electrical penetration, in which high-frequency current can freely pass through the cell membrane, without damaging the cell. Now, a team of researchers led by NAIST has determined optimal conditions to perform impedance cytometry. Their work may lead to rapid assessment of cells during culture in biological experiments.

An improved method for measuring the morphology and biomass of single cells using impedance cytometry has been introduced in a recently published study in *Microsystems & Nanoengineering*. Impedance cytometry involves applying high-frequency voltages to electrodes to measure complex impedance, which can provide information about the shape and effective volume of the cell. In the study, the researchers used different phases of voltage signals at four frequencies. They showed that applied voltages with frequencies of around 7 MHz are able to pass through the membrane of *Euglena gracilis* cells. Higher frequencies can monitor changes in biomass, while lower frequencies can track volume changes.

When a high-frequency electrical field penetrates the cell membrane, the uneven intracellular distribution tilts the impedance pulses to the left or right, which has been verified in simulation and experiments. "Ultimately, our method for determining the conductivity of the cell membrane relies on the degree of tilt caused by the electrical pulses," says author Yoichiroh Hosokawa. The team also performed calibration studies using beads to better understand the underlying physical mechanisms of this effect.

"This research enables the easy determination of the electrical penetration of a cell membrane, and the proposed platform is applicable to multiparameter assessment of the organism's state during cultivation," says senior author Yaxiaer Yalikun. This platform may be easily integrated into microfluidic systems for the scalable monitoring of biological experiments.

The need for efficient and highly accurate analysis of living single cells may be met by this new impedance cytometry method developed by the research team. Future applications could be extended to cells in mammals to monitor specific membrane changes in fields such as oncogenesis and cell aging.

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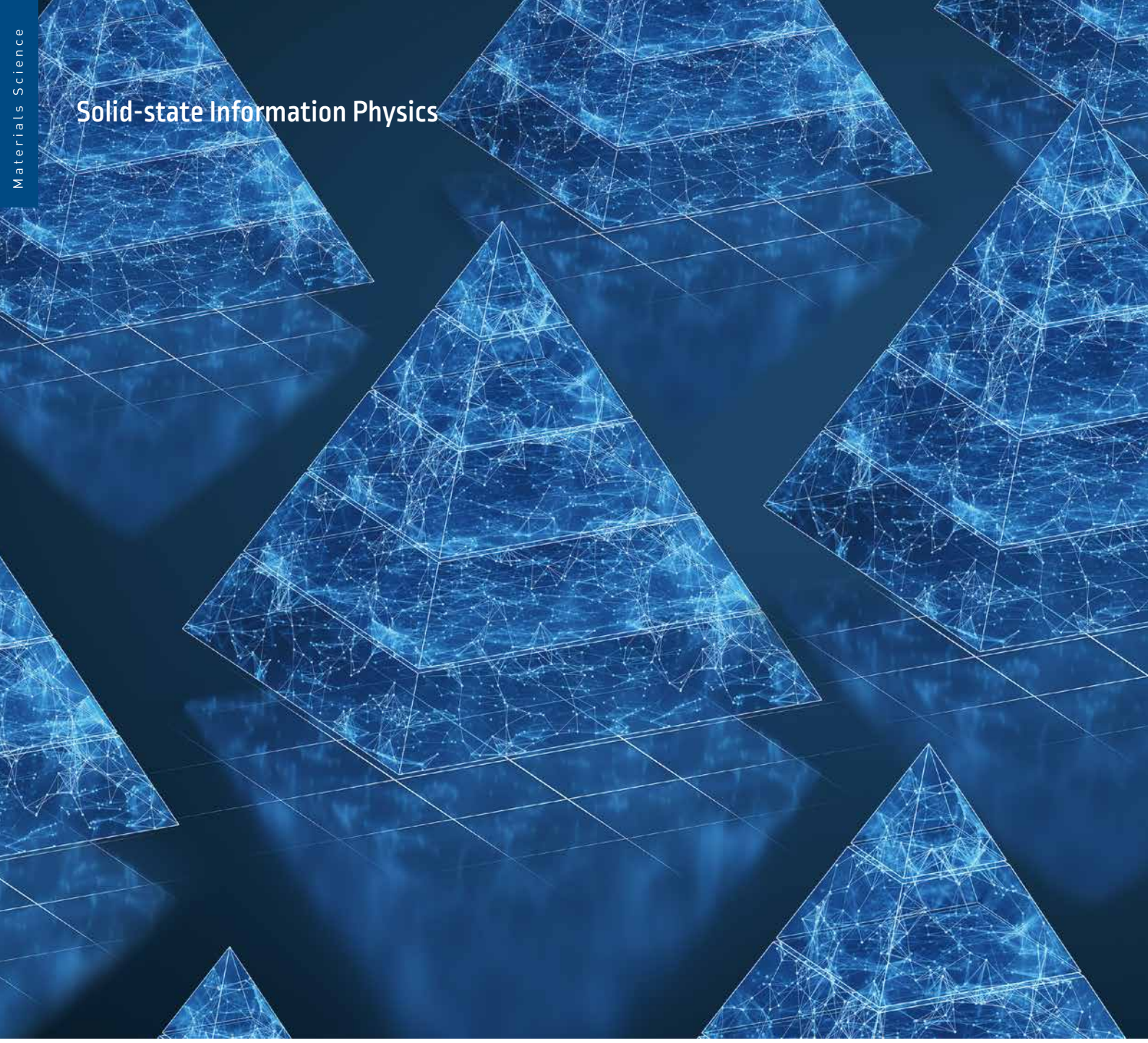
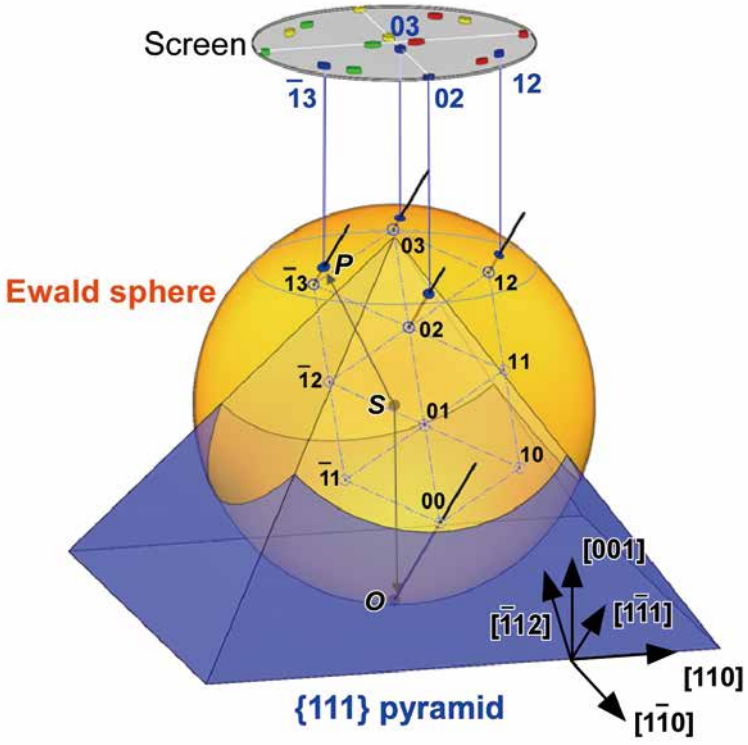
Solid-state Information Physics



Prof. Tomohiro Matsushita

Old silicon learns new tricks

Researchers at NAIST fabricate arrays of atomically smooth iron-coated silicon crystals pyramids with unusual magnetic properties, which could enhance the functionality of 3D spintronics and other technologies.



Schematics representing Ewald sphere and reciprocal lattice rods from a pyramid surface, reflecting diffraction patterns.

Ultra-small integrated circuits have revolutionized mobile phones, home appliances, cars, and other everyday technologies. To further miniaturize electronics and enable advanced functions, circuits must be reliably fabricated in three dimensions. Achieving ultrafine 3D shape control by etching into silicon is difficult because even atomic-scale damage reduces device performance.

A team of researchers led by NAIST has reported, in a new study seen in *Crystal Growth and Design*, silicon etched to adopt the shape of atomically smooth pyramids. Coating these silicon pyramids with a thin layer of iron imparts magnetic properties that until now were only theoretical. Ken Hattori at NAIST is widely published in the field of atomically controlled nanotechnology. One focus of Hattori's research is in improving the functionality of silicon-based technology.

"Silicon is the workhorse of modern electronics because it can act as a semiconductor or an insulator, and it's an abundant element. However, future technological advances require atomically smooth device fabrication in three dimensions," says Hattori.

A combination of standard dry etching and chemical etching is necessary to fabricate arrays of pyramid-shaped silicon nanostructures. Until now, atomically smooth surfaces have been extremely challenging to prepare. "Our ordered array of isosceles silicon pyramids were all the same size and had flat facet planes. We confirmed these findings by low-energy electron diffraction patterns and electron microscopy," explains lead author of the study Aydar Irmikimov.

An ultrathin—30 nanometer—layer of iron was deposited onto the silicon to impart unusual magnetic properties. The pyramids' atomic-level orientation defined the orientation—and thus the properties—of the overlaying iron. "Epitaxial growth of iron enabled shape anisotropy of the nanofilm. The curve for the magnetization as a function of the magnetic field was rectangular-like shaped but with breaking points which were caused by asymmetric motion of magnetic vortex bound in pyramid apex," explains Hattori.

The researchers found that the curve had no breaking points in analogous experiments performed on planar iron-coated silicon. Other researchers have theoretically predicted the anomalous curve for pyramid shapes, but the NAIST researchers are the first to have shown it in a real nanostructure.

"Our technology will enable fabrication of a circular magnetic array simply by tuning the shape of the substrate," says Irmikimov. Integration into advanced technologies such as spintronics—which encode information by the spin, rather than electrical charge, of an electron—will considerably accelerate the functionality of 3D electronics.

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Organic Electronics

Prof. Masakazu Nakamura

Easy fabrication of next-generation, super-flexible electronic circuits

Researchers at NAIST fabricate one-dimensional soft n-type semiconductors by a method that simplifies layer-by-layer assembly, which could be foundational to developing wearable electronics technologies with CMOS circuits.

Flexible semiconductors are essential for future wearable electronics technologies, but have been difficult to integrate into complex architectures. Now, in a study published in *Advanced Electronic Materials*, researchers from NAIST have developed a straightforward means of fabricating high-quality soft semiconductors for advanced electrical circuits.

Modern integrated circuit technology depends on basic elements known as complementary metal oxide semiconductor (CMOS) circuits. Silicon is the semiconductor component of most modern CMOS technology. However, because future CMOS circuits must (for example) mold to the shape of a body or integrate into clothing, much work has focused on developing soft, flexible, polymer-based semiconductors.

Several technical challenges must be overcome to integrate such semiconductors, especially n-type ones which flows electrons, into CMOS circuits. For example, preparing high-quality, layer-by-layer structures—important for CMOS device functionality—tends to be rather slow and challenging. Solving these challenges is the problem that the researchers at NAIST sought to address.

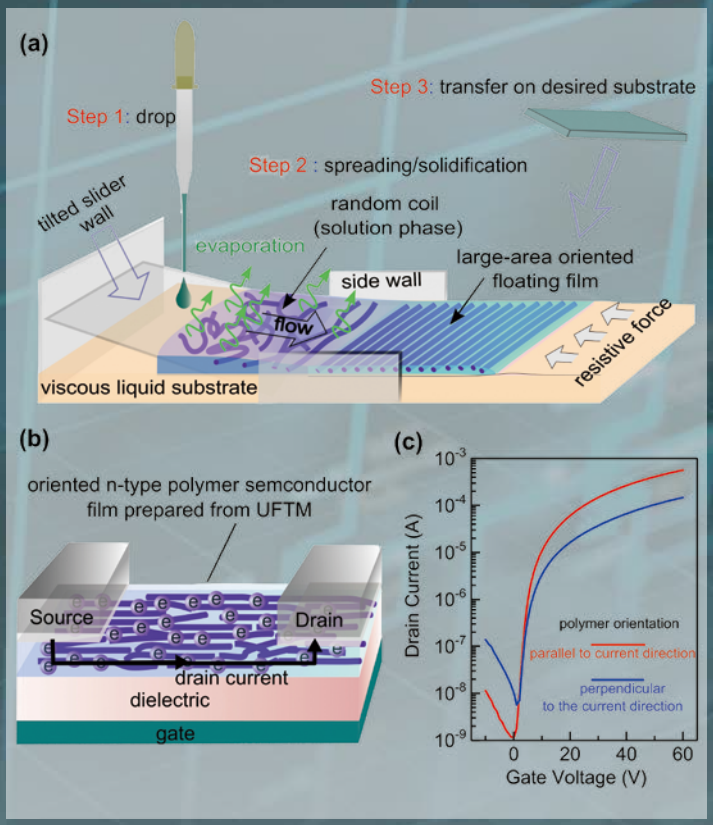
"Ideally, one would be able to deposit polymer films onto liquid substrates for ease of transfer to any other substrate," explains Manish Pandey, lead author. "Our strategy offers superior control over the resulting semiconductor film morphology, which is critical to the electrical properties, compared with conventional solution processing."

This work is based on unidirectional floating film transfer. By using a liquid substrate that does not dissolve the polymer, a solvent-dissolved polymer can be added dropwise onto the substrate, in a manner that forms a one-dimensional floating polymer film. Upon evaporation of the solvent, the polymer molecules orient perpendicular to the length direction of the film. This molecular morphology optimizes the electrical properties of the polymer film. Once the film solidifies, one can easily transfer it onto another substrate—e.g., for layer-by-layer deposition.

"We prepared an *n*-channel transistor that exhibited nearly no threshold voltage, which is important for maintaining power efficiency," says Masakazu Nakamura, senior author. "By using our approach, preparing and integrating *n*-channel as well as *p*-channel transistors into one device—based on flexible

semiconductors—should be straightforward."

This work succeeded in preparing one-dimensional, polymer-based semiconductor films in an inexpensive manner that is straightforward to replicate. The NAIST researchers' polymer film assembly methodology will be useful for advancing the prospects of flexible electronics, and helping to find replacements for silicon in upcoming wearable CMOS technology.



Overview and characteristics of the unidirectional floating film transfer method developed in this study.

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Organic Electronics

Prof. Masakazu Nakamura

Shedding light on polymer solar cells: Illuminating how solvent additives improve efficiency

Researchers at NAIST use photoconductive atomic force microscopy to investigate the role of solvent additives in the performance of all-polymer blend solar cells.

All-polymer blend solar cells are expected to play an important role in the transition to clean energy technologies because they can be easily produced in large-scale flexible sheets. However, their performance has lagged behind that of more traditional silicon alternatives, as well as other organic solar cells.

All-polymer blend solar cells are formed by combining two polymer solutions that solidify into a film on an electrode with in the form of interpenetrating networks, a kind of "phase-separation". The introduction of solvent additives to the polymer solution has been shown to increase the efficiency of all-polymer blend solar cells. However, the exact process underlying this improvement has not been fully understood. Now, in a study recently published in *ACS Applied Polymer Materials*, researchers from NAIST have investigated the performance enhancement mechanism using photoconductive atomic force microscopy (PC-AFM). Their findings are expected to help accelerate the widespread application of polymer-based solar cells.

"The empirical nature of solvent additive-mediated efficiency enhancement has hindered the optimization of all-polymer blend solar cell performance, so there has been an urgent need for a greater understanding of the process," explains senior author Hiroaki Benten. "To that end, we used PC-AFM to interrogate the nanoarchitecture that underpins the performance enhancement."

PC-AFM is an advanced microscopy technique that allows photocurrents to be visualized with nanometer-scale resolution. The researchers found that trace solvent additives improved the power conversion and photocurrent density of an all-polymer blend solar cell by a factor of up to ~3 by enhancing the ordering and crystallization of the polymer microstructure in the solar cell without damaging the phase-separated structure.

Absorption spectroscopy measurements further confirmed that the trace additives improved the ordering in the polymer microstructures. By forming a network that efficiently transports the photogenerated charges to the external electrode, the flow of photocurrent is increased.

"We found that local photocurrents were enhanced, somewhat like forming a new charge current highway, while the scale of phase separation that is critical to device functionality was retained," says coauthor Masakazu Nakamura. "We believe that this insight will be broadly applicable to all-polymer blend solar cells, not just those based on our choice of polymers."

The results of the study are expected to be important for optimizing the performance of all-polymer blend solar cells. By using the findings to minimize laboratory trial-and-error, it is hoped that researchers can speed up ongoing bench-to-market efforts, taking us a step closer to high-performance solar cells that are environmentally sustainable and easy to produce on a large scale.

Reference

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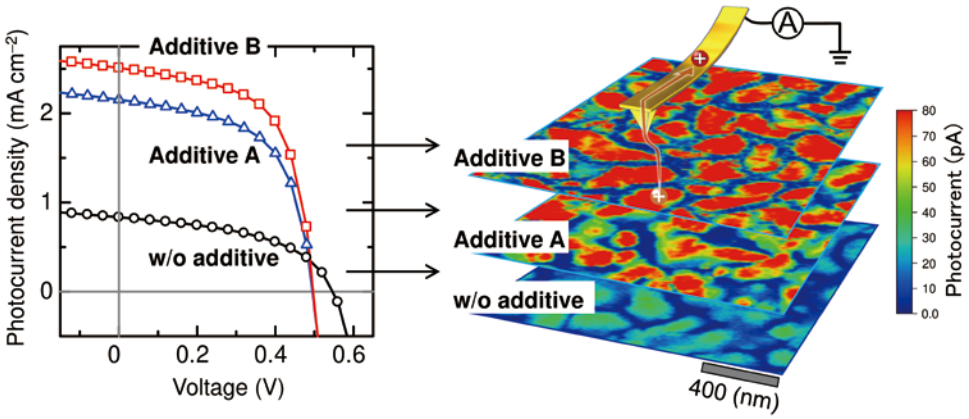

Improvements of the device performance by the introduction of solvent additives to the polymer solution.

Organic Electronics

Prof. Masakazu Nakamura

Fill me up: Improved efficiency of all-polymer solar cells

Researchers at NAIST reveal the science that underpins the efficiency of a versatile class of solar cells, which might help solve the environmental problems caused by relying solely on silicon-based solar cells.

Solar cells are an important contributor to a renewable energy supply, but solar panel waste will quickly become an enormous problem. Now, in a study recently published in *Journal of Materials Chemistry A*, researchers from NAIST have investigated the science that might help improve the utility of easily mass-producible, all-polymer-based solar cells.

Globally, approximately one-third of electricity currently comes from renewable sources. Silicon-based solar cells are the major contributor, but there's an increasing problem: what to do with the panels after their 30-year lifetime. A May 2022 article in *Chemical & Engineering News* lays out the problem: even when facilities recycle the frames and covers of the panels, the most valuable or even toxic elements are simply disposed. With a forecasted 80 million metric tons of solar panel waste to have been produced by 2050, this is a massive waste problem.

Polymer-based solar cells are a possible, less-wasteful solution. Such panels are thin and flexible, and thus are in principle quite versatile. Nevertheless, they have certain problems; e.g., a lower power conversion efficiency than silicon. "This efficiency is substantially limited by the fill factors: commonly less than 60%, even in advanced devices," says corresponding author Hiroaki Benten. "The science that underpins the limited efficiency of all-polymer blend solar cells remains insufficiently unexplored."

A ground-breaking result of this research is the high fill factor: ca. 70%, which remained ca. 60% even for polymer films several hundred nanometers thick. Competing polymer technology exhibits a ca. 40% fill factor at this thickness. This is because bimolecular recombination of free electrons with free holes substantially inhibited the fill factor prior work, but was suppressed in the current study.

What suppressed bimolecular recombination within the polymer blends? "There was substantial charge delocalization in the donor and acceptor domains," explains Masakazu Nakamura, senior author. "Appropriate aggregation of the polymer donors and acceptors led to a substantially ordered local structure of the polymer, which helped keep the separation of the electrons from the holes."

Even if researchers completely solve the efficiency problem of all-polymer solar cells, they'll still need to improve on the 10-year service life of the most advanced research prototypes. Additional research efforts include optimizing the film morphology, and even developing hybrid polymer/silicon solar cells, to optimize energy collection and efficiency. In the coming years, solar cells might look and function completely different from—and better than—modern technology.

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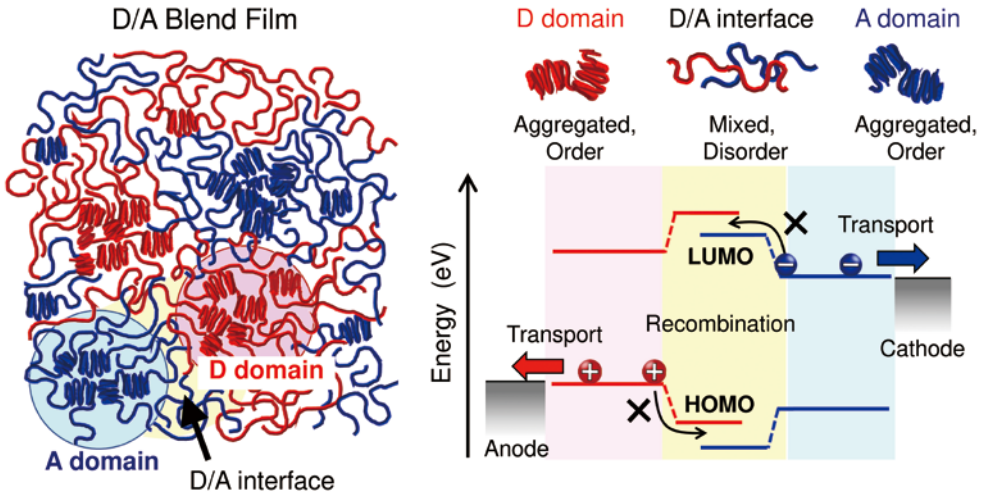


High fill factors of the all-polymer blend solar cells are achieved by long charge-carrier lifetimes owing to low bimolecular charge recombination coefficients.

Biomimetic and Technomimetic Molecular Science

Prof. Gwénaël Rapenne

Gearing up nanoscale machines

Researchers at NAIST in partnership with University of Paul Sabatier advance the science of molecular-scale gear trains for transmitting rotational force with the visualization of rotational snapshots by scanning tunneling microscopy.

Gear trains have been used for centuries to translate changes in gear rotational speed into changes in rotational force. Cars, drills, and basically anything that has spinning parts use them. Molecular-scale gears are a much more recent invention that could use light or a chemical stimulus to initiate gear rotation. Researchers at NAIST in partnership with University of Paul Sabatier, France, have reported in a new study published in *Chemical Science* a means to visualize snapshots of an ultrasmall gear train—an interconnected chain of gears—at work.

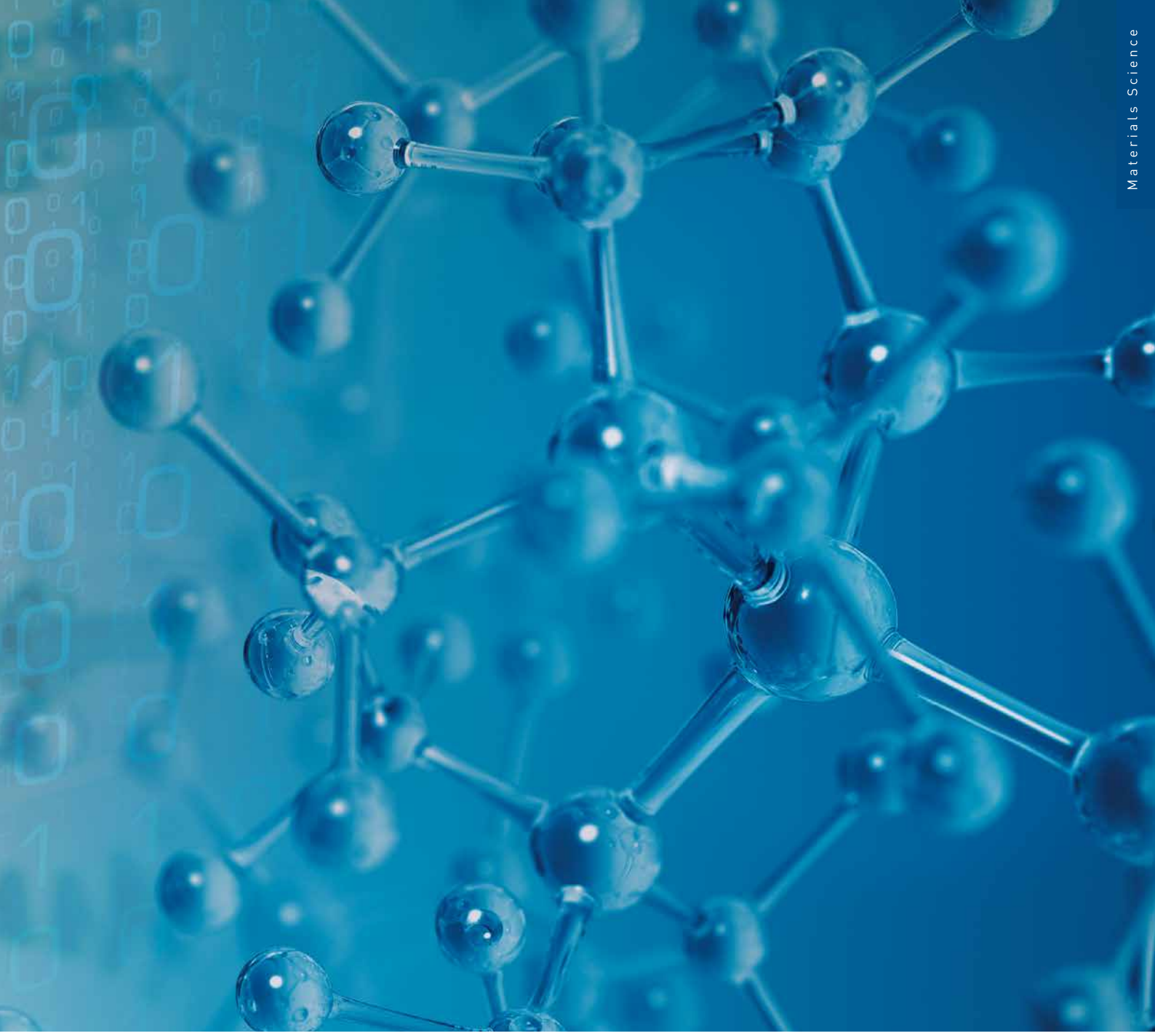
NAIST project leader Gwénaël Rapenne has devoted his career to fabricating molecular-scale mechanical devices, such as wheels and motors. Researchers recently designed a cogwheel for a molecular gear train but currently have no means to visualize the gears in action. "The most straightforward way to monitor the motion of molecular gears is through static scanning tunneling microscopy images. For these purposes, one of the teeth of the cogwheels must be either sterically or electrochemically distinct from the other teeth," explains Rapenne.

The researchers first created a molecular cogwheel comprising five paddles, where one paddle is a few carbon atoms longer than the other four paddles. However, as they showed last year, differences in paddle length disrupt the coordinated motion along the gear train. Thus, differences in paddle electrochemistry are a more promising design approach but synthetically more challenging.

"We used computational studies to predict whether electron-withdrawing units or metal chemistry could tailor the electronic properties of a paddle, without changing paddle size," says Rapenne. Such tailored properties are important because one can observe them as differences in contrast by using scanning tunneling microscopy, and thereby facilitate static imaging.

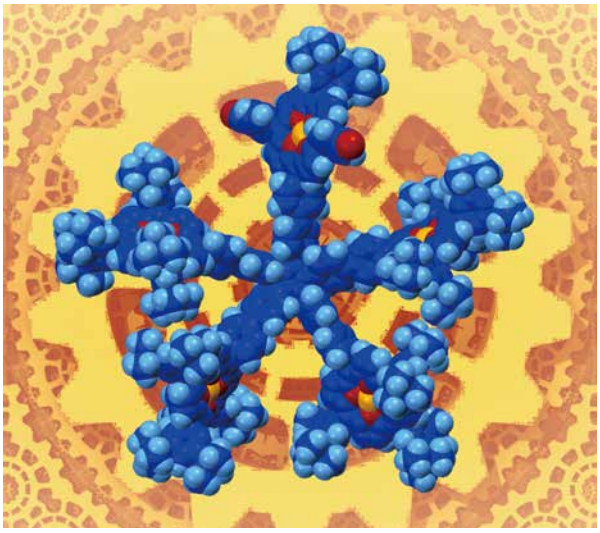
"Our pentaporphyrinic cogwheel prototypes contained one paddle with either a cyanophenyl substituent or a zinc—rather than nickel—metal center," explains Rapenne. "Various spectroscopy techniques confirmed the architectures of our syntheses."

How can researchers use these cogwheels? Imagine shining a highly focused beam of light, or applying a chemical stimulus, to one



of the gears to initiate a rotation. By so doing, one could rotate a series of cogwheels in a coordinated manner as in a conventional gear train, but on a molecular scale which consists in the ultimate miniaturizatio of devices. "We now have the means to visualize such rotations," notes Rapenne.

By using this development to carry out single-molecule mechanics studies, Rapenne is optimistic that the broad research community will have a powerful new design for integrated nanoscale machines. "We're not there yet, but are working collaboratively to make it happen as soon as possible," he says.



A train of molecular gears composed of star-shape molecules.

Reference

Seifallah Abid, Yohan Gisbert, Mitsuru Kojima, Nathalie Saffon-Merceron, Jérôme Cuny, Claire Kammerer, Gwénaël Rapenne. 2021. Desymmetrised pentaporphyrinic gears mounted on metallo-organic anchors. *Chemical Science*, 12, 4709–4721.

Photonic and Reactive Molecular Science

Prof. Tsuyoshi Kawai

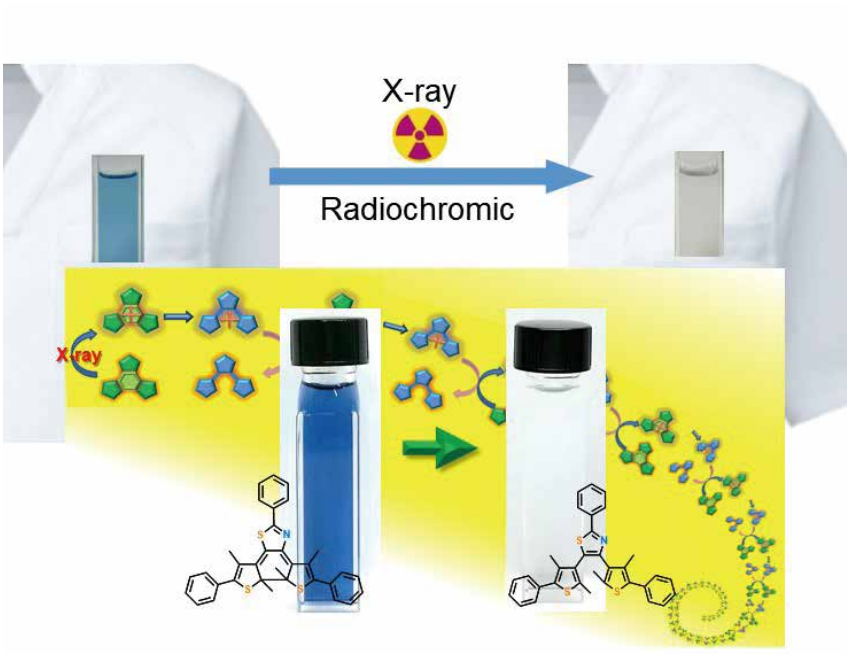
Invisible X-rays turn blue

Researchers at NAIST develop a new reaction system that can detect X-rays at the highest sensitivity ever recorded by using organic molecules.

A new reaction system can detect X-rays at the highest sensitivity ever recorded by using organic molecules. The system, developed by researchers at NAIST, involves the cycloreversion of terarylene, causing the molecule to switch reversibly between colorless and blue isoforms in the presence or absence of X-rays. With detection at safe doses, this reaction system is expected to detect even the faintest X-rays levels considered dangerous.

Photoreactive materials convert light input into chemical output and are standard in semiconductor and 3D printing technologies. Some of these materials are also used in eye-protection, such as how sunglasses can reduce UV exposure by changing the lens color. Similarly, workers at risk to X-ray radiation are required to wear monitoring badges that indicate dangerous levels through changes in photoreactive materials.

However, Tsuyoshi Kawai, project leader, stresses that these badges do not completely eliminate the risk. "Current materials for wearable detectors are sensitive to about 1 Gy. Ideally, safety management systems want about one hundred times more sensitivity," he says. Kawai is an expert at increasing the photoconversion efficiency of photoreactive molecules, having focused his attention primarily on terarylenes, organic molecules with which his research team has consistently achieved exceptionally high reaction efficiencies. "We have steadily improved the number of molecules that can undergo photoconversion in response to one photon. It was one to one in 2011 and today it becomes 33 molecules per one photon," he says.



The hazardous radiations such as Ultra-Violet and X-ray oxidative triggers the color-changing cascade of new dyes for 1000 times.

To increase the quantum yield of terarylenes, is to maximize the number of changes that can be induced by a single photon. They have selected terarylenes because of their reversibility, meaning that the molecule can be converted back to the starting blue isoform upon exposure to ultraviolet light allowing for the system to be reset for repeated use. Indeed, the color change is one of several reasons he believes organic molecules are preferable when considering X-ray detectors.

"Photochromic organic detectors can report X-rays through easily observed color changes and are recyclable and easy to process," Kawai says. The key modification to the terarylene molecules was the addition of a phenyl group to only one of the molecules two phenylthiophene groups, which allowed for reversible photoconversion between two isoforms. The result was a sensitivity of up to 0.3 Gy, making it more than 1000 times more sensitive than current commercial systems. Notably, 0.3 Gy is considered a safe exposure level, suggesting that no dangerous level will go undetected.

Photoconversion reactions like photosynthesis or neural stimulation in response to light in our eyes occurs at less than 100% efficiency (less than one molecule reacts to one photon). The system designed by the researchers, however, could achieve 3300% (33 molecules per photon), showing the potential of organic molecules in artificial systems. "I think this is the highest efficiency ever reported for photoconversion with an organic molecule," notes Kawai.

Reference

Ryosuke Asato, Colin J. Martin, Jan Patrick Calupitan, Ryo Mizutsu, Takuya Nakashima, Go Okada, Noriaki Kawaguchi, Takayuki Yanagida, Tsuyoshi Kawai. 2020. Photosynergetic amplification of radiation input: from efficient UV induced cycloreversion to sensitive X-ray detection. *Chemical Science*, 11, 2504–2510.

Innovative Research and Education Programs

NAIST constantly strives to renew its research and education programs toward producing science and technology researchers prepared to meet the demands facing tomorrow's global scientific community. These programs are regularly awarded external funding for their wide-ranging benefits.

Program for Promoting the Enhancement of Research Universities (2013-2023)

Japanese Ministry of Education, Culture, Sports, Science and Technology (MEXT) launched the Program for Promoting the Enhancement of Research Universities in October 2013, which is a new type of research funding in Japan that aims to enhance research capabilities by utilizing University Research Administrators (URA) who implement intensive reforms to strengthen the research environment at their respective universities. NAIST is one of 22 universities and research institutions selected to receive support through this program.

NAIST continues to conduct frontier-opening research while expanding into new interdisciplinary fields in science and technology. With the establishment of a university-wide strategic research infrastructure, NAIST endeavors to leverage its abundant resources to attain the new research materials and facilities necessary for next-generation research, to disseminate its achievements and human resources around the globe, and to further expand its global research and education network in order to contribute to the overall advancement of science and technology.

Projects being supported through this program include (1) the Creating New Research Streams Program which creates new research domains promising a high global profile, (2) the Sustainable Development of Research Capabilities Program which enhances NAIST's world-class research capabilities, and (3) the Joint International Research Program which raises the global visibility and standing of NAIST's research capabilities.

Formulating strategies and plans based on objective analysis data

Supporting the strategic acquisition of external competitive research funds

Enhancing the international collaborative research network

Reforming the research system to enhance NAIST's research capabilities

Top Global University Project (2014-2024)

In October 2014, NAIST was one of 37 universities selected to another prestigious MEXT initiative, the Top Global University Project. For a period of ten years, MEXT will support outstanding universities in their efforts to reform institutional governance and collaborate with top universities worldwide in order to strengthen international competitiveness.

Through the Top Global University Project, NAIST has committed to enhancing its international graduate courses by (1) including a joint degree scheme, (2) developing a new model for graduate education based on top-notch research, (3) reforming institutional governance and strategic agility, (4) creating a campus environment that supports trans-disciplinary education and cultural diversity, and (5) reorganizing its three graduate schools into a single entity toward establishing new, flexible research groups.





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