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RESEARCH HIGHLIGHTS 2021

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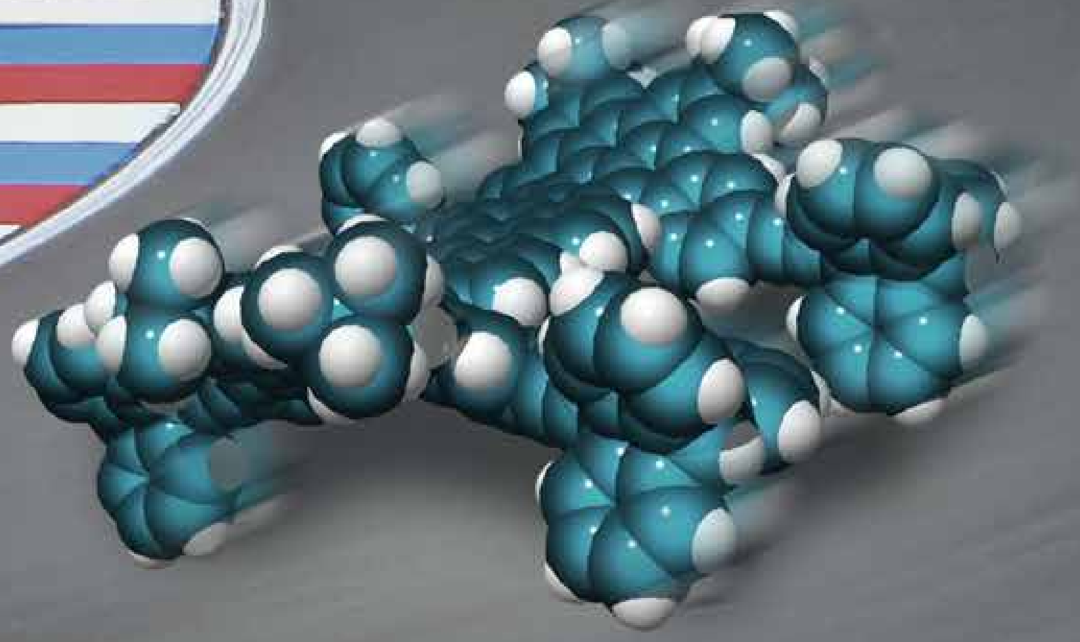
– Outgrow your limits –



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NAIST®

Outgrow your limits

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

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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). Through this program, NAIST further supports its cutting-edge research while expanding into new interdisciplinary fields in science and technology toward becoming a globally recognized education and research center.

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.

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As of February 1, 2021

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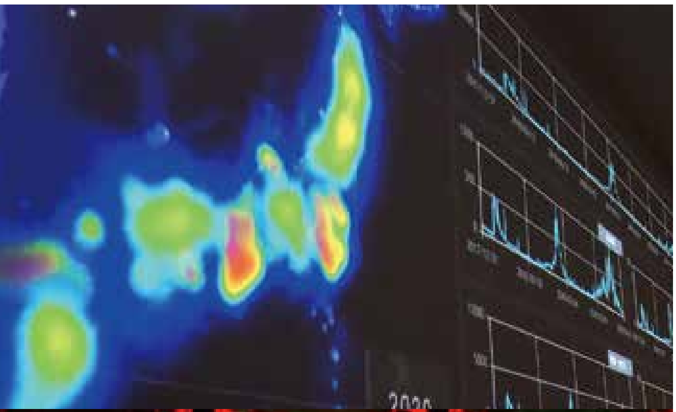

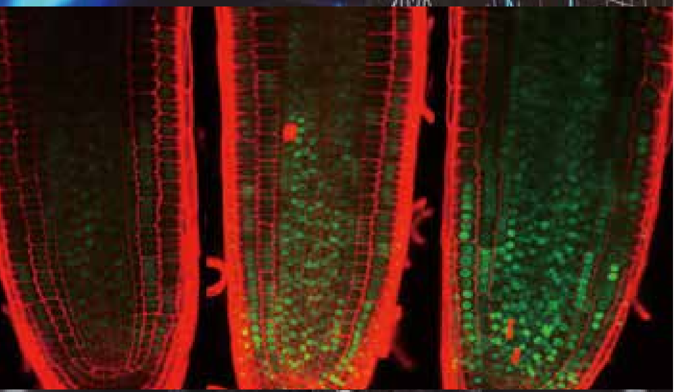

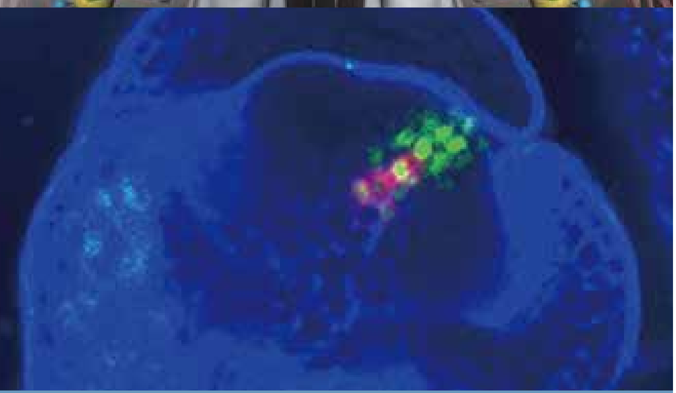

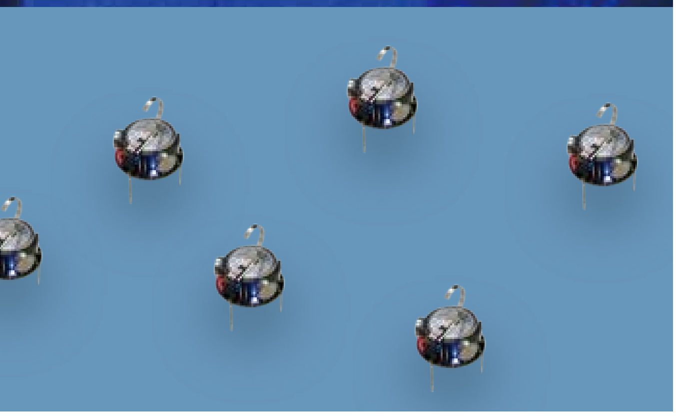

NAIST®
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RESEARCH HIGHLIGHTS 2021

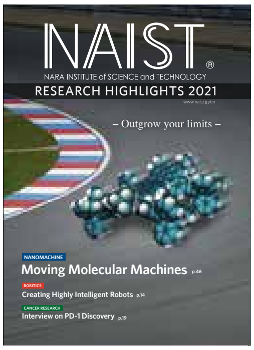
Nurturing discovery

Welcome to NAIST Research Highlights 2021. This publication provides an overview of the work and people of one of Japan's leading research bodies, the Nara Institute of Science and Technology. In these pages we present a view of the institute's achievements in two different formats.

Research Highlights are short features that cover recent extraordinary advances and breakthroughs, including 16 topics from 16 laboratories. Twelve longer **Impact** profiles explore some of our research achieving significant outcomes in 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 synthesizing moving molecular machines, NAIST researchers are one step closer to their goal of going beyond the boundaries of nanoworld.

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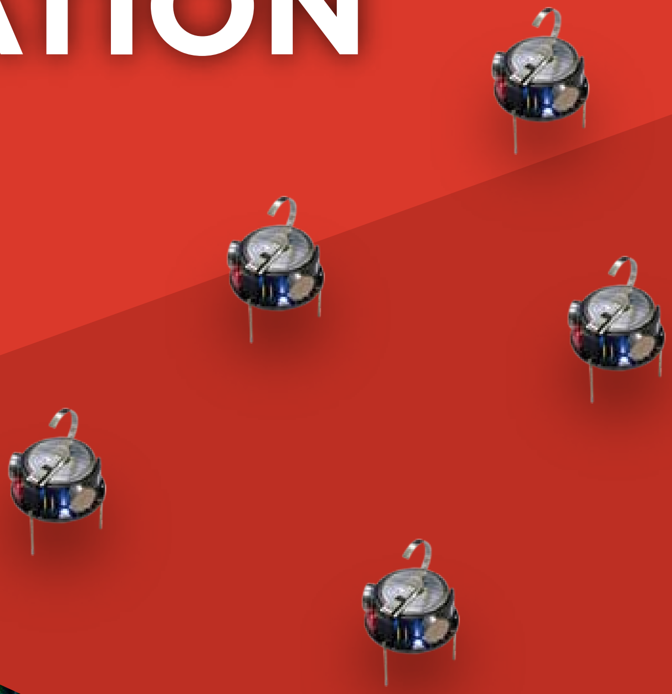
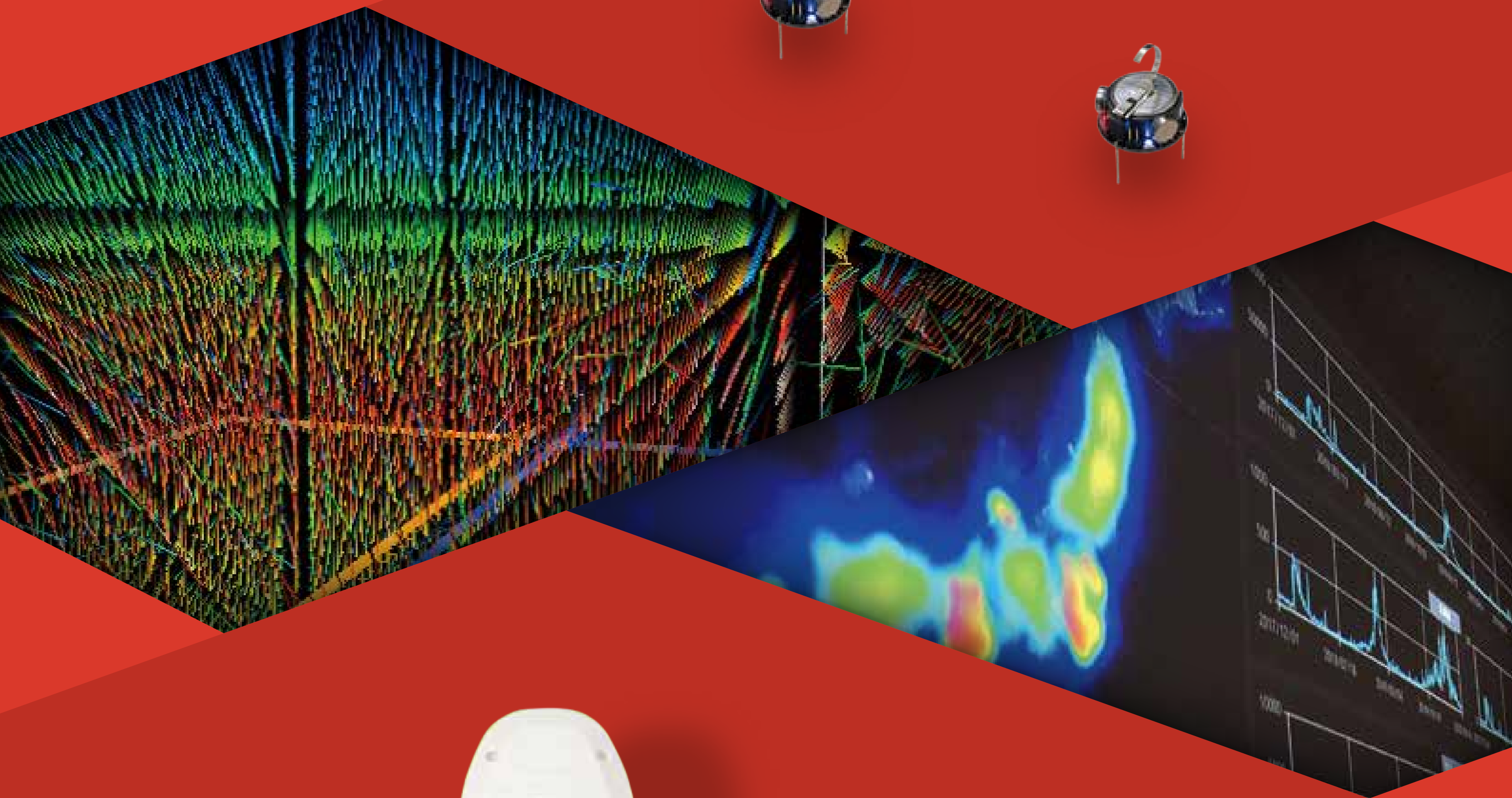
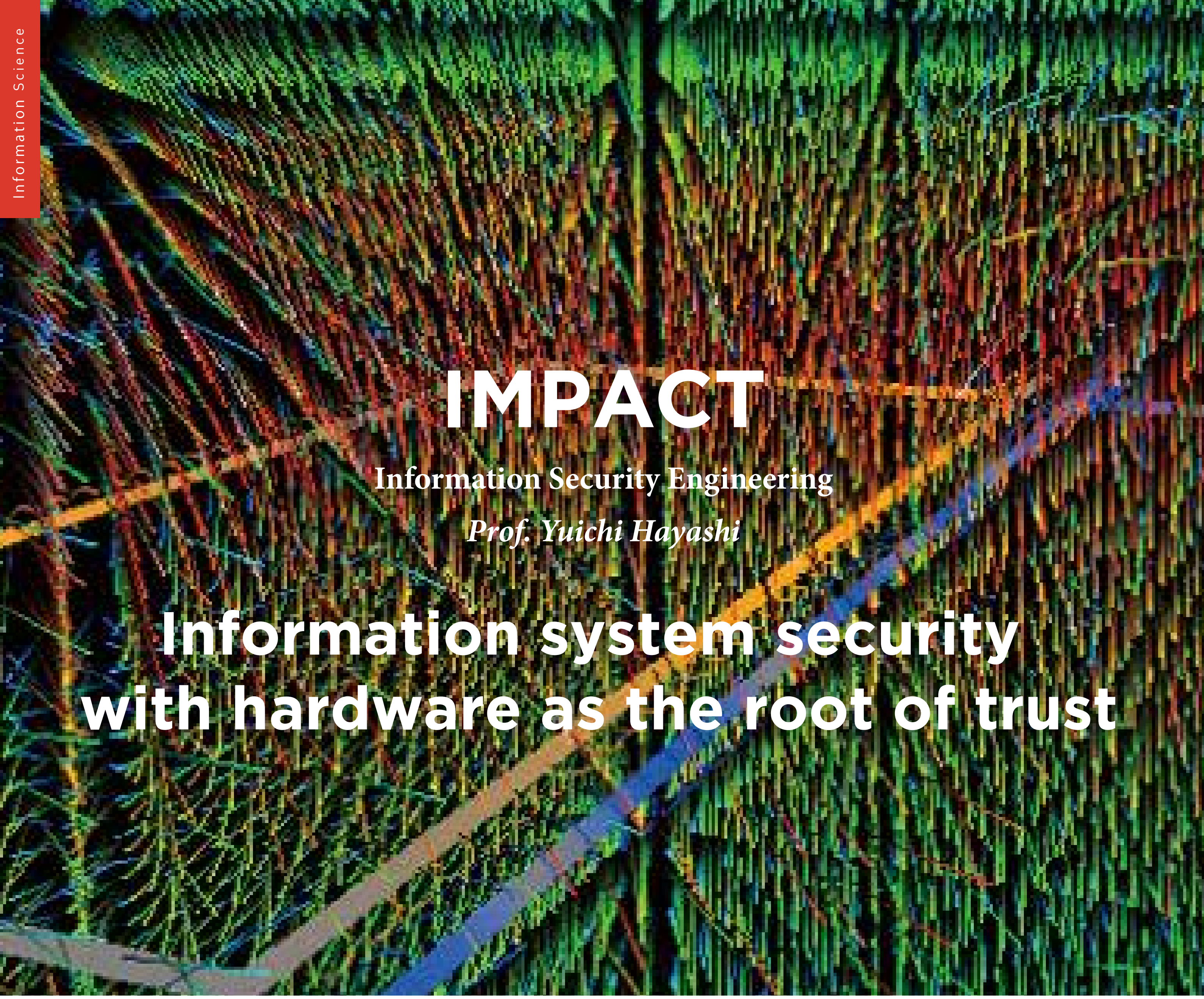
INFORMATION SCIENCE







IMPACT

Information Security Engineering

Prof. Yuichi Hayashi

Information system security with hardware as the root of trust

Rapidly increasing physical attacks on hardware

With computer information networks spreading to every corner of the Earth, and enormous amounts of information flow, building security to counter system interference and information leaks due to cyberattacks is now critical. While strong defenses have been developed against the intense threats faced by software, including networks and applications, countermeasures have also become essential to protect hardware such as PCs and mobile information devices that operate over the Internet as well as storage devices. For example, if a malicious integrated circuit (IC) chip is input into a system, the IC can cause serious damage that adversely affects the entire system; addressing such damage would be highly expensive. As the Internet of Things (IoT) spreads, various Internet-connected devices are under direct attack. Thus, hardware security has become crucial.

The Information Security Engineering Laboratory is studying the security of entire systems, focusing on the hardware. Professor Yuichi Hayashi says, "Hardware is essential for operating systems and applications to work. Therefore, if there is vulnerability in the hardware, the security of the entire system is compromised. Ensuring the security of the hardware, which is key to trust, becomes an important challenge that must be examined in the same way as that for applications and networks." The devices that attackers use are rapidly evolving, and their price is decreasing with improving performance. This is the backdrop to the increasing damage that cyberattacks are causing.

Developing sensors for detecting attacks

Hayashi's group has developed a sensor to detect information leaks occurring via electromagnetic waves from the hardware. In this case, the attacker does not target the regular input and output of information to attack the hardware. Rather, using a physical method such as an electromagnetic field probe, the attacker surveys the operations of the encryption device to acquire highly confidential information such as the privacy key. However, it is difficult to conduct this survey without disturbing the electromagnetic waves around the hardware according to the laws of physics; hence, a disturbance occurs in the electromagnetic field. The developed sensor can detect this disturbance with a high level of accuracy over a wide range, and detect probing by attackers. Thus, in this case,

group has shown that by installing a hardware-version computer virus, composed of cheap circuits costing a few dozen yen, on a device during a manufacturing process, it enables an attacker to access the device from areas that would have been difficult to operate without the virus. They are developing a sensor to detect the malicious circuits that attackers install on devices by visualizing such circuits using a principle similar to that of SONAR.

Hayashi has established a technical subcommittee to discuss the information security of electromagnetic waves on consumer devices at the Institute of Electrical and Electronics Engineers (IEEE), the world's largest technical professional organization for the advancement of technology. In the subcommittee, he exchanges opinions with foreign researchers.

Hayashi studied computer networks, information security, and electromagnetism in graduate school, leading him to the advanced subject of hardware security. "When I look at issues in a different field from the perspective of the field in which I am conducting research, I am able to find new solutions and open a new path of research," he says.

Circuit design with security

Assistant Professor Daisuke Fujimoto is conducting research on the design of semiconductor electronic circuits. When he was a student, he discovered that information leakage occurred not only through electromagnetic waves but also through the silicon substrates of IC chips. This inculcated in him an attitude of "getting at the root of the problem rather than covering it up" by designing safe circuits and installing encryption circuits for protection. The range of his research has broadened to include measuring information leakage from the attacker's perspective, the design of circuitry for a sensor that detects the installation of malicious IC, and a method to prevent the manipulation of analytics data of vehicle location information, which has become a problem in automated driving technology.

"We can have new realizations in scientific research, when we learn about both hardware and software, and see the whole picture," he says.

Interviewed by Yoshinori Sakaguchi

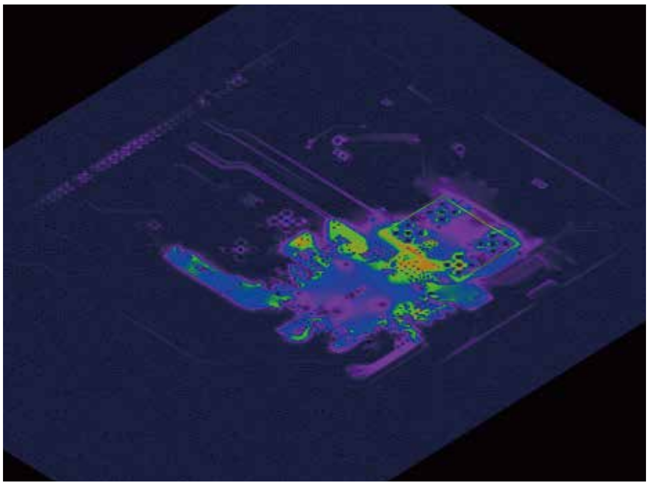
damage can be prevented by blocking the attack at the beginning.

Furthermore, when information is touch-input on the screen of a portable device such as a smartphone, the attacker can get the operation information from a distance using the leaking electromagnetic waves. To counteract this, they have developed technology that can prevent information leakage, both electromagnetically and optically, by combining a polarizing filter and transparent shield sheet with a metal mesh that blocks the electromagnetic waves. When attached to a smartphone's screen, this technology can limit the extent of electromagnetic information leakage to within a 50-cm range.

Changing perspective

In addition, attacks known as "fault injections" are being continually researched. This attack causes a temporary breakdown in some of the processes performed in the hardware. The resulting error output information is analyzed to acquire confidential information such as the privacy key used for encryption.

Moreover, from viewpoint of offensive security, Hayashi's



Visualization of information leakage paths based on large-scale EM field simulation techniques.

More information about the group's research can be found at https://isw3.naist.jp/Contents/Research/cs-09-en.html

IMPACT

Dependable System

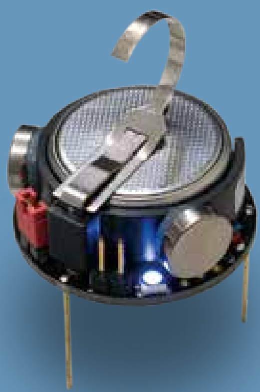
Prof. Michiko Inoue

Improving the reliability of a system through teamwork using devices connected to a network

Toward distributed processing from centralized management

With the widespread of Internet of Things (IoT) where information devices that perform various tasks connect to the Internet, and the development of complex and large-scale information networks, considerable attention has been directed toward distributed algorithms (algorithms for distributed systems) to realize dependable and efficient information systems. The concept of dependability encompasses several desired properties such as fault-tolerance, reliability, availability, safety, and security.

The Dependable System Laboratory is studying distributed algorithms based on mathematical theories of computation and also addressing the issue of quality for highly densified very large-scale integration (VLSI), considering "what is a dependable system for users?" Professor Michiko Inoue emphasizes, "For example, even though each device connected to the IoT detects an abnormality only in the range of its own view, problems such as system failures can be solved appropriately and quickly based on collective intelligence obtained through communication between the related devices. We aim to develop algorithms that are more suitable for distributed processing rather than centralized management."



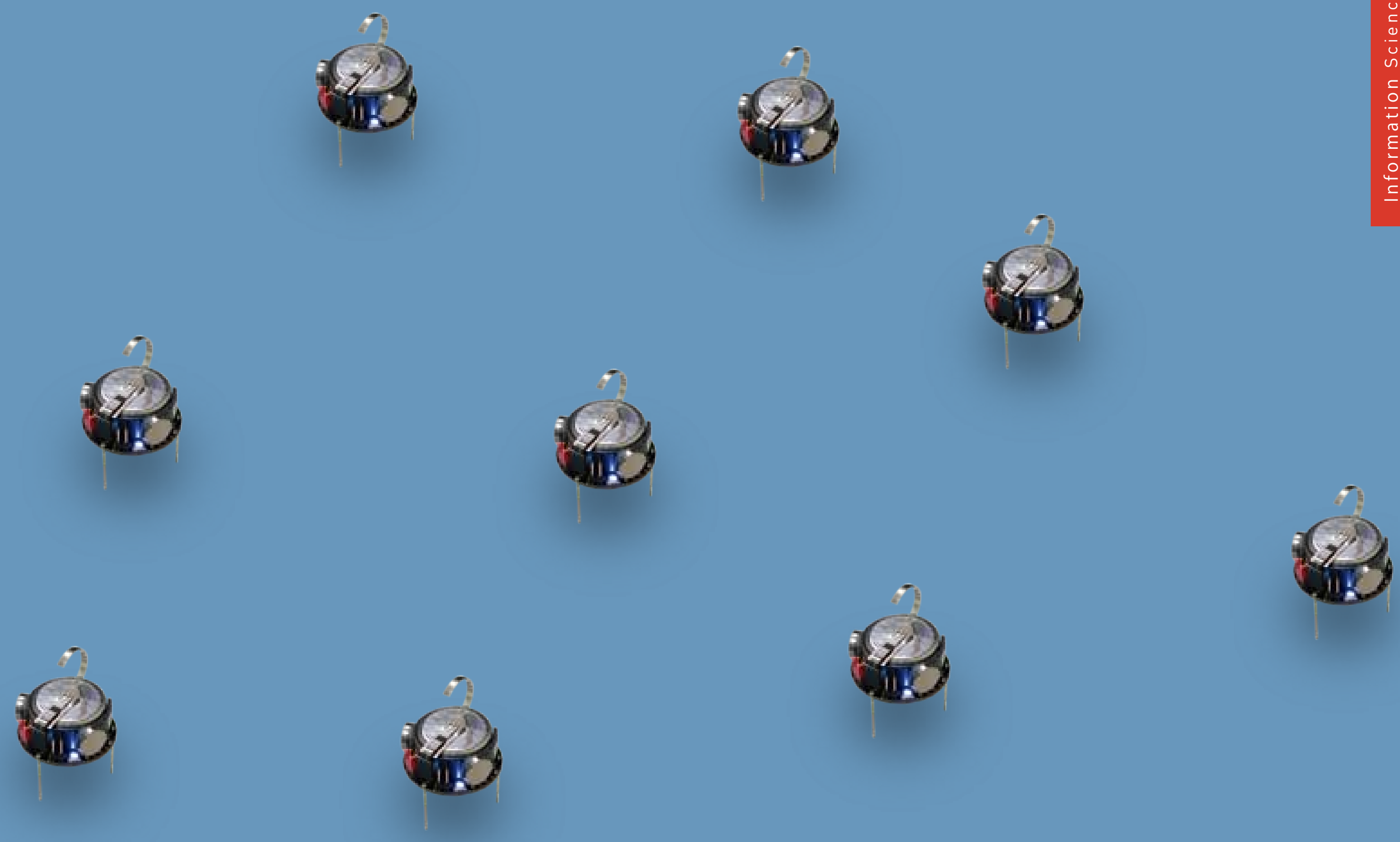
Mobile robot.

Her research topics also include a near-future system that comprises nanometer sized machines, i.e., nanomachines, despite being based on the current system. Concerning this topic, Inoue's group has proposed an algorithm that can effectively divide numerous low-performance individuals (molecular robots) into two groups with the same number of individuals exhibiting similar performances, and assign separate tasks to the groups. They developed this efficient algorithm minimizing the number of individual states used for the computation. When the algorithm is used, molecular robots rearrange groups so that they can work efficiently according to internal environmental changes, enabling the creation of a flexible and effective system.

Introducing deep learning

Inoue's group is also conducting research on quality control of VLSI devices, including topics such as circuit design to facilitate production test. Despite comprehensive test of circuits at the time of shipment, one test escape can occur within several tens of millions, which leads to problems under special conditions during operation. Thus, they developed a quality test that adopted the deep learning of AI, with satisfactory results. In this test, AI learns the pattern of a perfectly-made VLSI in advance and shows predicted values of defective devices that do not match the perfect pattern.

Inoue has excelled at mathematics and science since her time in primary and middle school. She is an advisor to the President for Gender Equality at NAIST. Five years ago, she started hosting an annual symposium for supporting female researchers. "I want to increase the opportunity for brilliant women to succeed in the scientific field, as the number of researchers is decreasing owing to the declining birthrate," Inoue says.



Clarifying essence of cooperative problems

Associate Professor Fukuhito Ooshita has continued studying the distributed algorithm to allow many computers to operate cooperatively. In addition to the molecular robots mentioned above, he has developed an algorithm for low-performance mobile robots that can move in spaces autonomously and can detect only nearby robots; this algorithm allows them to patrol environments cooperatively or gather together in one place for further cooperation.

"I am keen on elucidating essence of the cooperative problems for future practical use by clarifying minimum equipment of individual robots and simple algorithms to solve the problems with a theoretical model," Ooshita says.

Elucidating the deterioration mechanism

Assistant Professor Michihiro Shintani is conducting research on circuit designs that detect the degradation of VLSI systems overtime early on. After clarifying the mechanism of actual degradation, he postulated a theory based on the collected degradation data and developed a method to be reflected in the design. He found that the degradation of the threshold voltage occurred because defects are preexisting in the gate electrode, which was incorporated into a model. Consequently, he succeeded in mathematically formulating the degree of degradation predicted via temperature and an elapsed time at the time of operation.

In addition, Shintani has built a circuit simulation model for operating the power semiconductors used for power converter, which is receiving considerable attention from related companies. Recently, he has been also working on a highly reliable design of neuromorphic-type circuits that imitate the neural circuits of the human brain.

Evaluation circuit of semiconductor device reliability.

Shintani transitioned into academia after conducting research on the design of integrated circuits in a company for nine years. "While in a company, I sought short-term success; however, at a university, I can start with fundamental studies and look ten years into the future. I would like to conduct research from scratch while not buying into the common wisdom and take the technology in the direction of much improved performance," Shintani says.

Interviewed by Yoshinori Sakaguchi

More information about the group's research can be found at https://isw3.naist.jp/Contents/Research/cs-02-en.html

RESEARCH HIGHLIGHT

Augmented Human Communication

Prof. Satoshi Nakamura

One class in all languages

Advances in communication technology have had a major impact in all sorts of industries, but perhaps none bigger than in education. Now anyone from around the world can listen live to a Nobel Prize Laureate lecture or earn credits from the most reputable universities with nothing more than internet access. However, the possible information to be gained from watching and listening online is lost if the audience cannot understand the language of the lecturer. To solve this problem, scientists at NAIST, presented a solution with new machine learning at the 240th meeting of the Special Interest Group of Natural Language Processing, Information Processing Society of Japan (IPSJ SIG-NL).

Machine translation systems have made it remarkably simple for someone to ask for directions to their hotel in a language they have never heard or seen before. Sometimes the systems can make amusing and innocent errors, but overall achieve coherent communication, at least for short exchanges usually only a sentence or two long. In the case of a presentation that can extend past an hour, for example, an academic lecture, they are far less robust.

"NAIST has 20% foreign students and, while the number of English classes is expanding, the options these students have are limited by their Japanese ability," explains NAIST Professor Satoshi Nakamura, who led the study.

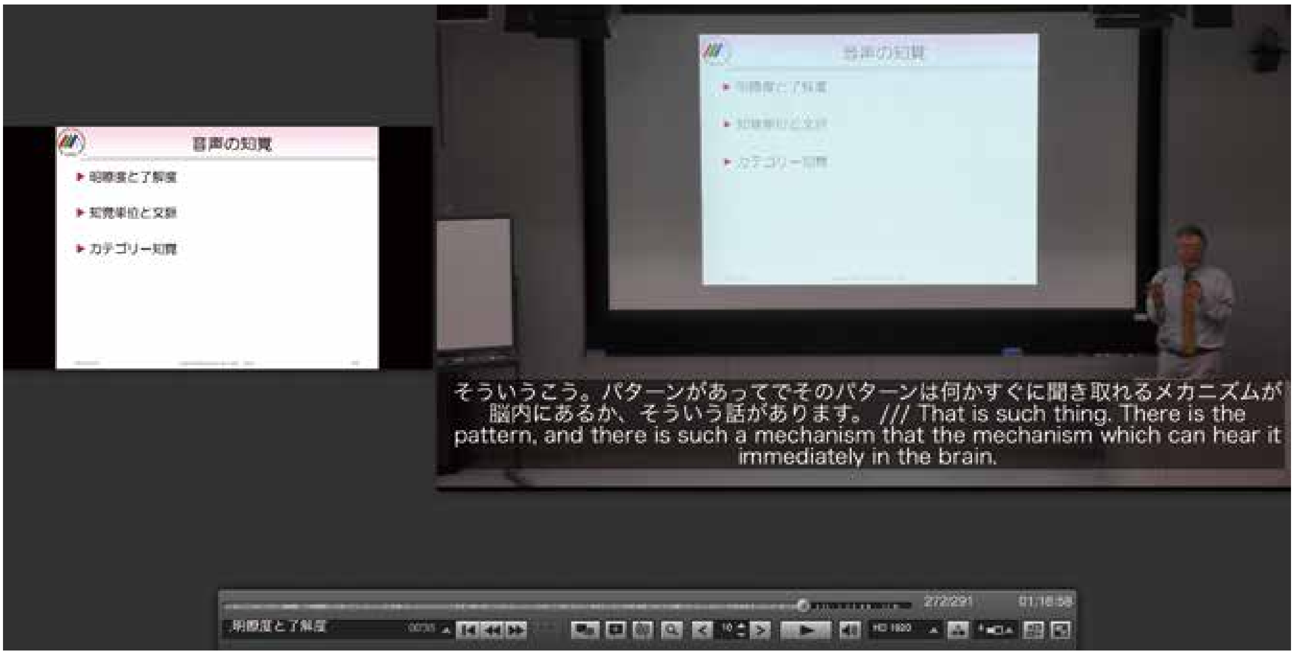
Nakamura's research group acquired 46.5 hours of archived lecture videos from NAIST with their transcriptions and English translations, and developed a deep learning-based system to transcribe Japanese lecture speech and to translate it into English. While watching the videos, users would see subtitles in Japanese and English that matched the lecturer's speaking.

One might expect the ideal output would be simultaneous translations that could be done with live presentations. However, live translations limit the processing time and thus the accuracy.

"Because we are putting videos with subtitles in the archives, we found better translations by creating subtitles with a longer processing time," he says.

The archived footage used for the evaluation consisted of lectures from robotics, speech processing and software engineering. Interestingly, the word error rate in speech recognition correlated to disfluency in the lecturers' speech. Another factor from the different error rates was the length of time speaking without pause. The corpus used for the training was still insufficient and should be developed more for further improvements.

"Japan wants to increase its international students and NAIST has a great opportunity to be a leader in this endeavor. Our project will not only improve machine translation, it will also bring bright minds to the country," he continues.



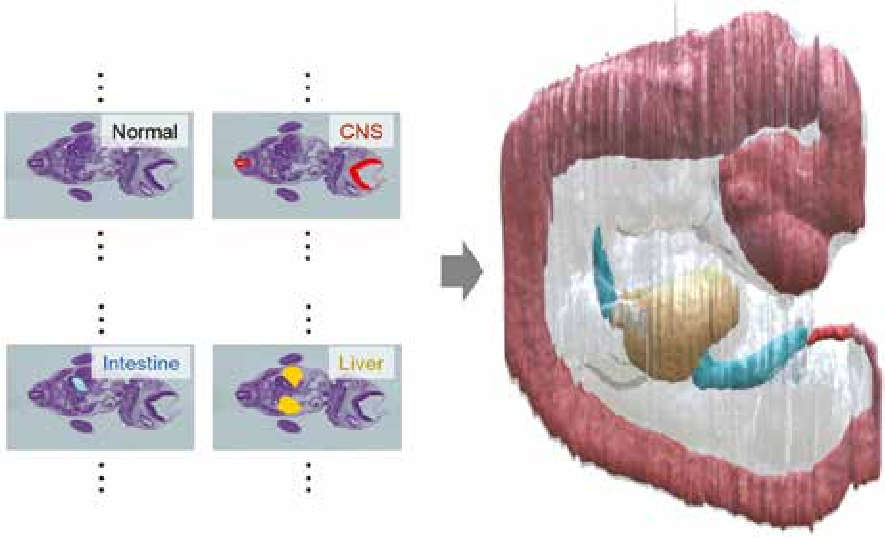
A deep learning-based system to transcribe Japanese lecture speech and to translate it into English.

More information about the group's research can be found at http://isw3.naist.jp/Contents/Research/mi-02-en.html

Optical Media Interface
Prof. Yasuhiro Mukaigawa

Reconstructing histological slices into 3D images

Japanese scientists report in *Pattern Recognition* a new method to construct 3D models from 2D images. The approach, which involves non-rigid registration with a blending of rigid transforms, overcomes several of the limitations in current methods. The researchers validate their method by applying it to the Kyoto Collection of Human Embryos and Fetuses, the largest collection of human embryos in the world, with over 45,000 specimens.



A set of histological serial sections of a human embryo with organ annotations (left) and 3D reconstruction (right).

MRI and CT scans are standard techniques for acquiring 3D images of the body. These modalities can trace with unprecedented precision the location of an injury or stroke. They can even reveal the microscopic protein deposits seen in brain pathologies like Alzheimer's disease. However, for the best resolution, scientists still depend on slices of the specimen, which is why cancer and other biopsies are taken. Once the information desired is acquired, scientists use algorithms that can put together the 2D slices to recreate a simulated 3D image. In this way, they can reconstruct an entire organ or even organism.

Stacking slices together to create a 3D image is akin to putting a cake together after it has been cut. Yes, the general shape is there, but the knife will cause certain slices to break so that the reconstructed cake never looks as beautiful as the original. While this might not upset the party of five-year olds who want to indulge, the party of surgeons looking for the precise location of a tumor are harder to appease.

In fact, the specimen can undergo a series of changes when prepared for sectioning.

"The sectioning process stretches, bends and tears the tissue. The staining process varies between samples. And the fixation process causes tissue destruction," explains NAIST Associate Professor Takuya Funatomi, who led the project.

Fundamentally, there are three challenges that emerge with the 3D reconstruction. First is non-rigid deformation, in which the position and orientation of various points in the original specimen have changed. Second is tissue discontinuity, where gaps may appear in the reconstruction if the registration fails. Finally, there is a scale change, where portions of the reconstruction are disproportional to their real size due to non-rigid registration.

For each of these problems, Funatomi and his research team proposed a solution that when combined resulted in a reconstruction that minimizes all three factors using less computational cost than standard methods.

"First, we represent non-rigid deformation using a small number of control points by blending rigid transforms," says Funatomi. The small number of control points can be estimated robustly against the staining variation.

"Then we select the target images according to the non-rigid registration results and apply scale adjustment," he continues.

The new method mainly focuses on a number of serial section images of human embryos from the Kyoto Collection of Human Embryos and Fetuses and could reconstruct 3D embryos with extraordinary success.

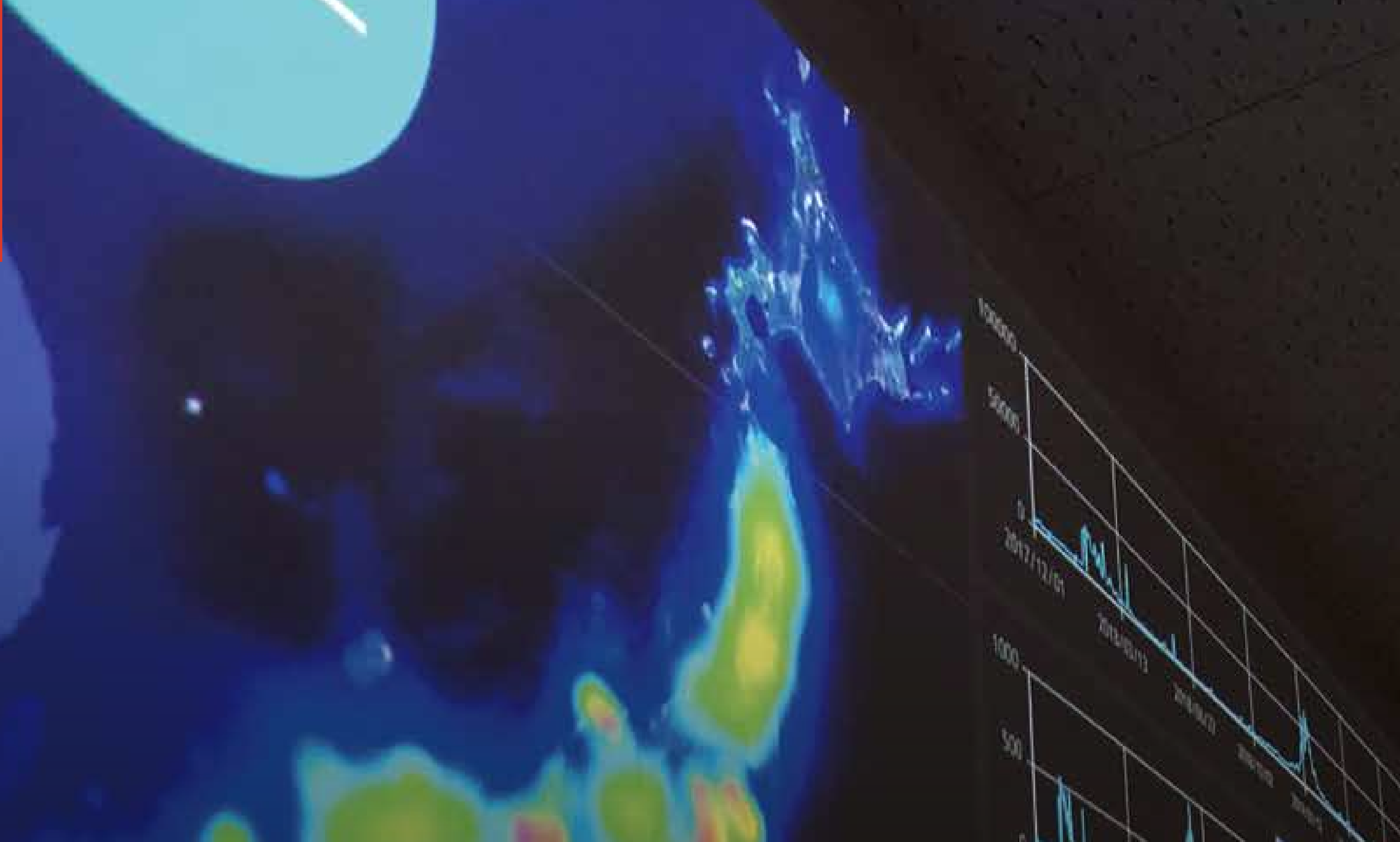
Notably, there are no MRI or CT scans of the samples, meaning no 3D models could be used as a reference for the 3D reconstruction. Further, wide variability in tissue damage and staining complicated the reconstruction.

"Our method could describe complex deformation with a smaller number of control points and was robust to a variation of staining," says Funatomi.

Reference

Kajihara, T., Funatomi, T., Makishima, H., Aoto, T., Kubo, H., Yamada, S. & Mukaigawa, Y. 2019. Non-rigid registration of serial section images by blending transforms for 3D reconstruction. *Pattern Recognition*, 96, 106956.

More information about the group's research can be found at http://isw3.naist.jp/Contents/Research/mi-06-en.html



IMPACT

Social Computing

Prof. Eiji Aramaki

Automatically reading internet information to track viral infection trends

Analyzing language data

Conversations on social media on the Web, such as Twitter, represent trends of phenomena influencing social life, e.g., influenza epidemics, at a certain point in time. The Social Computing Laboratory, led by Professor Eiji Aramaki, is conducting research to develop technologies for investigating various social phenomena based on language data that manifest according to communication patterns on social media. Aramaki's group is also conducting research that can be utilized in less-explored areas of information science, e.g., the applications of natural language processing in medical care.

Twitter is a powerful source of information

Aramaki is supporting efforts to understand the infection status of the novel coronavirus that has broken out worldwide. "Regarding the infection-related information posted on the internet through Twitter, we are investigating whether locally concentrated cases are clusters (small outbreaks) and analyzing information that could be viewed as wild rumors and fake news," Aramaki explains. Aramaki's group provides their research data to national research institutes for reference. The amount of retrieved information in English, Chinese, and Japanese, with the words "novel coronavirus" and related terms as a clue, reaches about 10,000 per day.

Aramaki has proven that social media can become an influential source of information for creating countermeasures for and preventing infectious diseases, including influenza. First, the proposed method automatically infers the meaning of a sentence using a natural language processing technique that converts vague expressions from everyday conversation into language that can be understood by computers. Then, keywords such as “influenza” and secondary terms such as “feverish” and “coughing” are searched, and extracted data are classified using artificial intelligence (AI). Based on location information obtained from Twitter, the areas showing more tweets are identified, enabling the prediction of increased infections. When the results based on the tweet data were compared with data on the numbers of patients released by the National Institute of Infectious Diseases, the correlation was so high as to almost match perfectly, thereby receiving global attention.

Improving accuracy by removing noise

Furthermore, Associate Professor Shoko Wakamiya has proposed a calculation model that considers the gap between the estimated number of patients with tweets and the real number of patients to improve the accuracy of the developed method. The research paper describing this model was awarded best paper by the International Medical Informatics Association (IMIA) in 2018. “When examining a particular area, the number of tweets decreases once the information is posted because the people’s interest fades, whereas a temporary surge of tweets is observed after a news report. Therefore, we compensated for them by additionally considering information about the infection posted from other areas and also considering components that become noise in the count,” Wakamiya explains. The subjects of the surveys conducted so far are wide-ranging, including infectious food poisoning due to norovirus and hay fever. Recently, studies are also conducted based on symptoms such as fever, chills, diarrhea, and runny nose, attempting to narrow down the characteristics of even unknown viruses based on symptoms and aiming to investigate the conditions of infection at an early stage.

“We are exploring the possibility of acquiring effective data by expanding our methods, such as selecting frequently searched words on internet search engines, detecting the location history of people who have installed specific applications on their smartphones and examining applications that allow the patient to report actively,” Aramaki says.

Determining decline in cognitive function

Using techniques of speech recognition and natural language processing, a study is currently underway on using medical care to predict the difficult-to-detect signs of dementia by analyzing speech characteristics when an individual speaks freely. Based on examination data collected at hospitals, certain speech characteristics signify dementia, such as “a reduced amount of vocabulary (the total number of words) and nouns” and “delayed utterance.” Based on these data, a dementia-screening system called KOTOBAKARI has been developed. The simplified version of this examination method automatically calculates the number of words in a response to a question; e.g., “Have you had any fun lately?” If the calculated value is significantly lower than the reference, it implies a decline in cognitive function.

“A decline in cognitive function is thought to be related not only to dementia but also to depression in elderly people and to the side effects of anticancer drug treatment. Thus, through the proposed system, we are additionally examining the relationship between diseases such as cancer and decline in cognitive function,” Aramaki explains.

Studying ethical issues

Research is also underway for cases requiring long-term treatment, such as breast cancer. A website called EPISODE BANK has been established, wherein patients are encouraged to post their experiences of fighting illnesses to share and ease their concerns. Furthermore, the nation’s first large-scale analysis technology is being developed that analyzes large quantities of clinical data, including specialized medical terms, through a natural language processing technique, extracts accurate information and turns them into text using AI.

As research on medical treatment such as the handling of medical examinations and clinical data is being undertaken with doctors as well as other medical personnel, it is expected that the field of information science will expand into the medical field in the future. Therefore, collaborative research is also being conducted with biotechnology research institutes regarding the ethical issues related to handling personal medical information.

“Going forward, ethical issues pertaining to handling a variety of information will become important. Furthermore, I want to continue to explore undeveloped fields, such as the connection between information technology and creative concepts like art, which AI cannot create,” Aramaki says.

Interviewed by Yoshinori Sakaguchi

More information about the group’s research can be found at https://isw3.naist.jp/Contents/Research/mi-08-en.html

IMPACT

Robot Learning

Associate Prof. Takamitsu Matsubara

Creating highly intelligent robots using skillful machine learning

Effective learning using small-scale data

For a robot to be integrated into and act as a capable companion in an environment where people work and live, the robot must have advanced perception and flexible judgment. The Robot Learning Laboratory is developing artificial intelligence (AI) using machine learning algorithms in which data from the neighboring environment and objects are automatically input and analyzed to infer rules regarding optimal action. Further, studies are being conducted to explore the future of robotics in fields where automation has been challenging; e.g., providing the robot operational skills to work with flexible and amorphous cloth and providing an automated driving functionality to small vessels that are susceptible to the effects of wind, waves, and tides.

This laboratory was established in January 2019 via a tenure-track system, with an outstanding young researcher as principal investigator. The leader, Associate Professor Takamitsu Matsubara says, “We are developing algorithms that can make stable calculations with the efficiency required for practical use from the autonomous collection of necessary data to machine learning and deep learning that infer optimal action rules based on the collected data, in accordance with the robot’s particular purpose.”

Within machine learning, significant advancements have been made in reinforcement learning, in which the robot selects the optimal action through repeated trial-and-error, and deep learning, in which the robot automatically extracts feature points based on a neural network, resembling nerve cells of a human brain. However, these types of learning require substantial data and are unsuitable for practical use when considering the effort and failures the robot encountered during data collection. Thus, a technology is being developed that can perform deep reinforcement learning with small-scale data within a range that robots can collect.

Learning complicated cloth-handling skills

Matsubara’s group has achieved a significant success using the above technology. They developed robots that can efficiently learn the task of flipping a handkerchief and folding children’s clothes. While such amorphous and flexible objects are a challenge for robots to handle, the learning process that took at least 10 h or more in the past was significantly shortened to 4 h.

“We accumulated experience data while viewing images of the robots picking up and dropping a cloth. Since the amount of data was limited, we designed the algorithms where they provided a stable answer that was roughly presumed to be the best,” explains Matsubara.

In this study, he employed the stochastic control theory to estimate errors in experimental data and compensate for them. The challenge concerning the insufficiency and unevenness of data was successfully addressed by applying this theory.

In 2013, Matsubara studied at Radboud University in the Netherlands for the Project for International Brain Circulation of NAIST for one year. He avoided studying modern robotics and focused on learning the underlying fundamental mathematical and physical theories instead. “There were theories I learned there that had been developed independently without being linked to AI, and then, I tied one of them to robot learning, paving a new path,” he emphasizes.

Automated driving of small vessels

Matsubara’s group is currently working on more than 10 project topics. A collaborative research with a maritime business company aims to provide an automated driving function for small-sized vessels, which are susceptible to the effects of weather and tides. After collecting data on weather and sea areas by randomly navigating for 1 h, the algorithm learns the data and infers the vessel’s movement to derive action rules to manage the given operations. If the vessel arrives at a specified destination on the sea for fishing, the algorithm operates the steering wheel to stop there.

“Similar to the study on the cloth-handling robots, this technology utilizes a small amount of data but uses another theory. As various fundamental theories are available, it is our policy to design AI algorithms that meet specific purposes,” says Matsubara.

In collaboration with a major restaurant chain, they are also developing a robot that can arrange Japanese food on platters. For Japanese food, the robot must show delicacy on par with a professional chef; e.g., the robot must be able to place the food properly, taking into account various requirements. Thus, they employed a pioneering AI technology called generative adversarial imitation learning, a type of deep learning. After converting chef’s demonstration into data, they are mixed with an enormous amount of practice data obtained from the robot, from which point it is determined whether the data sufficiently resemble the demonstration. Studies are being conducted to learn delicacy by repeating this process such that the robot outputs food arrangements closely resembling those prepared by a Japanese chef.

Furthermore, contributions are being made to the introduction of AI technology in several fields, such as automating fine adjustments in chemical plants with reinforcement learning to significantly shorten the time spent on such adjustments.

Aiming to increasingly automate the machinery around us

After entering the Graduate School of Information Science of NAIST in 2003, Matsubara interned at the Advanced Telecommunications Research Institute (ATR), in which one of NAIST’s collaborative laboratories is located. Here, Matsubara encountered the ongoing robot study and was instantly absorbed in it. “I worked on a study of biped locomotion with reinforcement learning, but there was no GPU or deep learning in those days. Compared with the current situation where there are many social demands, the atmosphere was such that I could conduct research calmly,” he says.

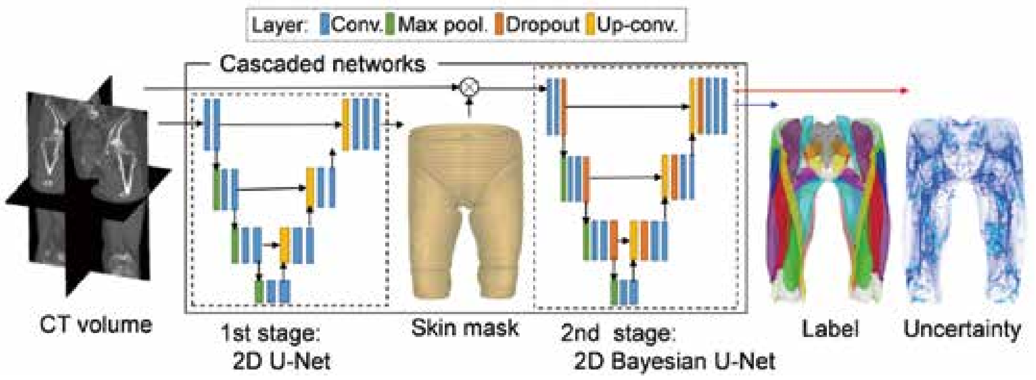
Concerning future studies, Matsubara says, “There still are more machines that can be automated with current technology. I want to continue to make breakthroughs in the research. I found that the issue of ensuring safety without making a dangerous mistake when AI performs trial-and-error and learning is also critical, and I am addressing the issue by going back to fundamental studies.”

Interviewed by Yoshinori Sakaguchi

More information about the group’s research can be found at https://isw3.naist.jp/Contents/Research/ai-08-en.html

RESEARCH HIGHLIGHT

Imaging-based Computational Biomedicine
Prof. Yoshinobu Sato



Muscle segmentation from CT volume using Bayesian U-net. Skin mask is obtained using conventional U-net during the first stage, and then Bayesian U-net is utilized to assign a muscle label as well as uncertainty to each pixel.

Artificial intelligence learns muscle anatomy in CT images

Personalized medicine has stirred the imagination of drugs and therapies that are individually tailored to patients. In the future, there will no longer be a need to worry about side effects, and patients will be screened to identify which treatment will be most effective for them, instead of for the average population. Deep learning is one tool that will be key to realizing personalized medicine. A new study by Japanese researchers describes a new deep learning tool that will advance personalized medicine for musculoskeletal diseases. The tool can segment individual muscles for a comprehensive model of the musculoskeletal system, which is expected to advance personalized biomechanics.

Accurate measurements of the musculoskeletal system can have a tremendous impact for the extremely ill, like those suffering from ALS or other severe forms of atrophy, to influence the design of rehabilitation devices, and for the extraordinarily gifted, like high-performance athletes who want to take their game to the next level. These measurements come from computed tomography or other imaging modality with which researchers build computer models to study the forces and stresses on muscles and bones.

"Once we have the CT images, we need to segment the individual muscles for building our model," explains Professor Yoshinobu Sato of NAIST, who led the study.

"However, this segmentation was time consuming and depended on expert-knowledge. The figure shows an overview of our system. We used deep learning to automate the segmentation of individual muscles to generate a musculoskeletal model that is personalized to the patient," he continues.

While it is normal to expect a physician to evaluate the images, this adds a level of subjectivity to the diagnosis. The system is especially beneficial for patients in remote areas with limited access to expert orthopedic surgeons, for decisions based on a more quantitative interpretation should improve outcomes.

The method depends on Bayesian U-net architecture.

"U-Net is a deep learning framework based on a fully convolutional neural network for the precise segmentation of images. Our colleague, Dr. Yuta Hiasa, extended U-net by combining Bayesian inference to formulate Bayesian U-net, in which uncertainty is associated with segmentation results," says Sato.

The challenge in segmenting individual muscles is the low contrast of the imaging at border regions of neighboring muscles. To test their system, the researchers examined 19 muscles in the thigh and hips. Bayesian U-Net had better segmentation accuracy than other methods including the hierarchical multi-atlas method, which is viewed as state-of-the-art, and did so while reducing the time to train and validate the system by a surgeon.

"Some pixels in the images had high uncertainty. It was these pixels that especially need confirmation by surgeons," notes Sato.

The researchers thus defined an uncertainty threshold to identify which pixels required human verification.

"Bayesian U-Net learned the musculoskeletal anatomy to create segmentations that would have been created by experts with high fidelity and our collaborator orthopedic surgeon, Prof. Nobuhiko Sugano of Osaka University Hospital, is quite satisfied with this achievement," says Sato.

Reference

Hiasa, Y., Otake, Y., Takao, M., Ogawa, T., Sugano, N. & Sato, Y. 2020. Automated muscle segmentation from clinical CT using Bayesian U-net for personalized musculoskeletal modeling. *IEEE Transactions on Medical Imaging*, 39, 1030-1040.

More information about the group's research can be found at http://isw3.naist.jp/Contents/Research/ai-05-en.html

Mobile Computing
Associate Prof. Naoki Shibata

All Bitcoin mining should be environmentally friendly

The rise in popularity of cryptocurrencies such as Bitcoin has the potential to change how we view money. At the same time, governments and societies are worried that the anonymity of these cashless transactions could allow criminal activities to flourish. Another less remarked issue is the energy demands needed to mint new coins for these cryptocurrencies. A new report by Associate Professor Naoki Shibata of NAIST presents a blockchain algorithm, which he calls "proof-of-search" (PoS), that retains the attractive features of most cryptocurrencies at a lower cost to the environment.

While the economics of cryptocurrencies gets most of the attention, it is becoming readily apparent that cryptocurrencies have a massive environmental cost. The energy used in the world to mine for Bitcoins alone equals almost that of the energy consumption of all of Ireland, while in Iceland, Bitcoin mining consumes more energy than households. In the end, it could be environmental implications, not economic ones, that halt the mainstream adoption of cryptocurrencies.

The basis of all major cryptocurrencies is the blockchain. Ironically, while the blockchain provides pure anonymity to the human user, it is remarkably transparent in all its transactions, meaning the digital owner of the digital coins is clear, even the actual person represented by the digital owner is not.

"Bitcoin uses a proof-of-work [PoW] system to decide the chronological order of transactions. PoW works anonymously because the order is identified by IP addresses," explains Shibata.

When a transaction in the Bitcoin blockchain is made, a user makes a request. PoW makes a series of calculations to confirm the validity of the transaction, calculations that consume energy. In PoS, users in the blockchain are invited to use this energy to request a job for finding a solution to an optimization problem.

"There are three kinds of users in the PoS blockchain. The first two are those who want to use the blockchain as a payment system or mine for e-coins, which is the same as PoW. The third group wants to use the PoS blockchain as grid computing infrastructure," says Shibata.

The energy lost in the PoW is redirected to finding an approximate solution to the submitted problem. Thus, energy can be devoted to adding new blocks to the blockchain or to another problem, namely, the optimization proposed by a user, so that the amount of energy used is not reduced, but neither is it wasted.

PoS is the newest of more than a dozen alternative algorithms to PoW that all aim to reduce energy cost. PoW has remained the standard algorithm through which cryptocurrencies operate, because it is extremely decentralized and democratic, which prevents any one user from having an outstanding influence on the currency value.

"The problem with the alternatives is that they lose their democracy or are more vulnerable to outside attacks," notes Shibata.

By adding the feature of an approximate solution, PoS also invites possible corruption to which PoW is immune. Therefore, as a deterrent, PoS demands that the user who submits the problem be the one who pays the user who proposes the solution. This prevents users from colluding together to submit problems for which they already know the solution.

Another appeal of PoW is its robustness. PoS preserves this robustness by introducing miniblocks each time an optimization problem is submitted.

Shibata envisions the optimization problems that can be solved by redirecting the wasted energy with PoS will include diverse problems from medicine to the beginnings of the universe.

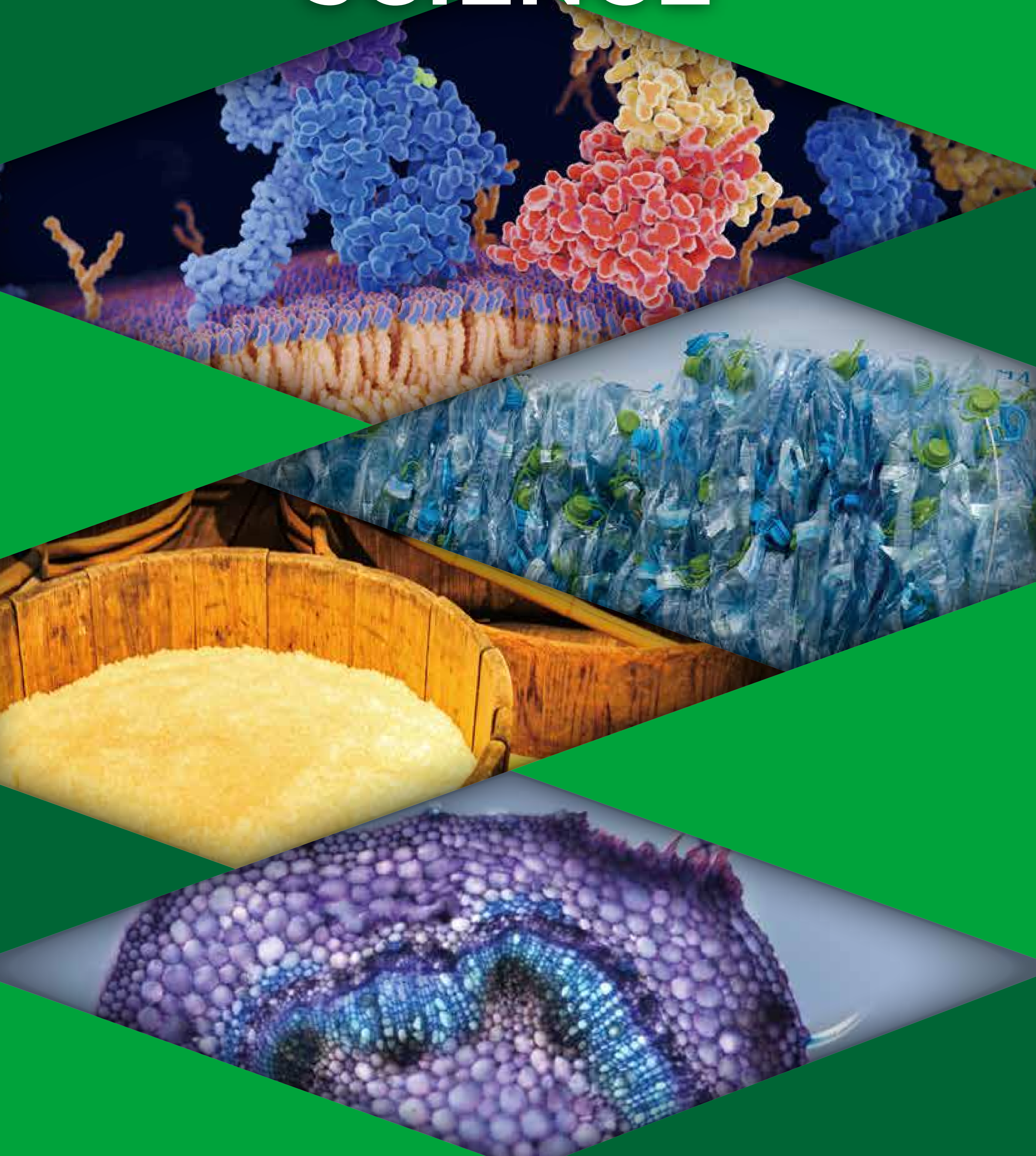
"PoS could help solve problems in protein folding, the dynamics of interstellar formations and finance," he says.

Reference

Shibata, N. 2019. Proof-of-Search: Combining blockchain consensus formation with solving optimization problems. *IEEE Access*, 7, 172994-173006.

More information about the group's research can be found at https://shibata.naist.jp/~n-sibata/

BIOLOGICAL SCIENCE



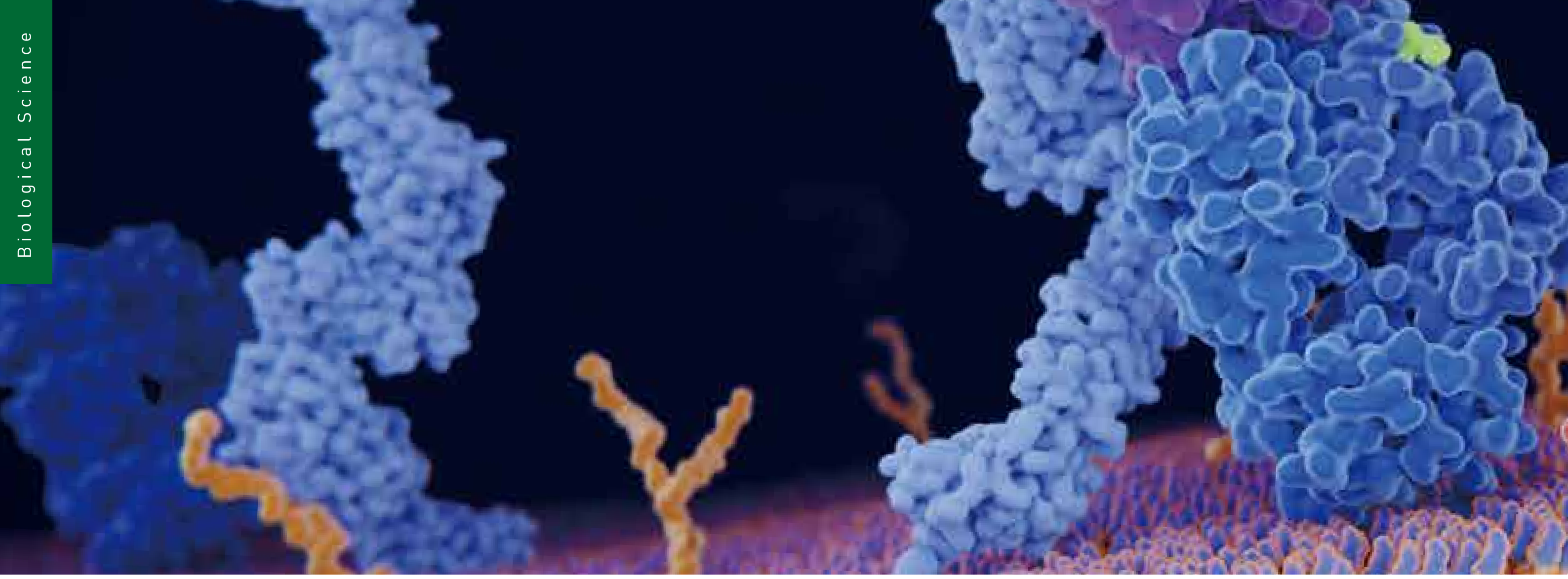
IMPACT

Functional Genomics and Medicine

Associate Prof. Yasumasa Ishida

Interview with Associate Professor Yasumasa Ishida, who discovered the protein PD-1, the basis for the research on drugs for cancer immunotherapy developed by Dr. Tasuku Honjo, a Nobel laureate in physiology or medicine

After the Nobel lecture of Dr. Honjo (right), the photo was taken during the reception at Karolinska Institutet in Stockholm.



Dr. Tasuku Honjo, a Distinguished Professor of Kyoto University, received the Nobel Prize in Medicine or Physiology in 2018 for his achievement in developing a breakthrough drug for cancer immunotherapy (therapeutic anti-PD-1 antibody) based on the receptor protein PD-1 that mediates immunosuppression. PD-1 was discovered and named by Dr. Yasumasa Ishida, an associate professor in the Division of Biological Science at NAIST, who is conducting basic medical studies, including research on the detailed mechanisms that enable specific targeting of cancer cells. Associate Professor Ishida shared with us about the relationship he has had with Dr. Honjo as his former mentor and the prospects for PD-1 research.

Tenacity of purpose was the key

—Professor Tasuku Honjo won a Nobel Prize. How do you feel about it now?

I simply feel so happy and am thrilled. Since the drug was first approved for the treatment of malignant melanoma, a type of skin cancer, in 2014, it has been used to treat several different types of carcinomas in over 60 countries; this is undoubtedly an award-winning achievement. The only question was when Dr. Honjo would win the award, and I was looking forward to hearing that he won. I was honored and grateful to attend the Nobel Prize awarding ceremony in Sweden with him.

—Did you have any contact with Dr. Honjo on the day the award was announced?

On the day the award was announced, Dr. Honjo was overwhelmed with press conferences and etcetera, so I did not call him. I simply sent a congratulatory e-mail to him. Surprisingly, that night, Dr. Honjo replied briefly from his smartphone that "It was your tenacity of purpose that made everything possible. Thank you!" When I read it, I felt rewarded for the numerous experiments I have diligently conducted. It still astounds me that he found my e-mail from a flood of e-mails.

Interested in self- versus non-self-discrimination

—When you discovered the gene for this protein in 1991, was the gene named programmed cell death-1 (PD-1) because you were searching a gene that is turned on when immune competent T cells (T lymphocytes) spontaneously die, that is, when they undergo apoptosis?

We named it PD-1 hoping that it would be a gene involved in self- versus non-self-discrimination at the initial stage of T cell death. A subsequent study by a graduate student who continued my research project indicated that the gene was not directly involved in T cell death. However, because the gene is deeply involved in self- versus non-self-discrimination, the immune system can detect and begin attacking cancer cells—which fluctuate between self- and non-self—when the PD-1 function is weakened via the use of OPDIVO or a similar antibody. Thus, the role of PD-1 was to delineate and determine between self and non-self.

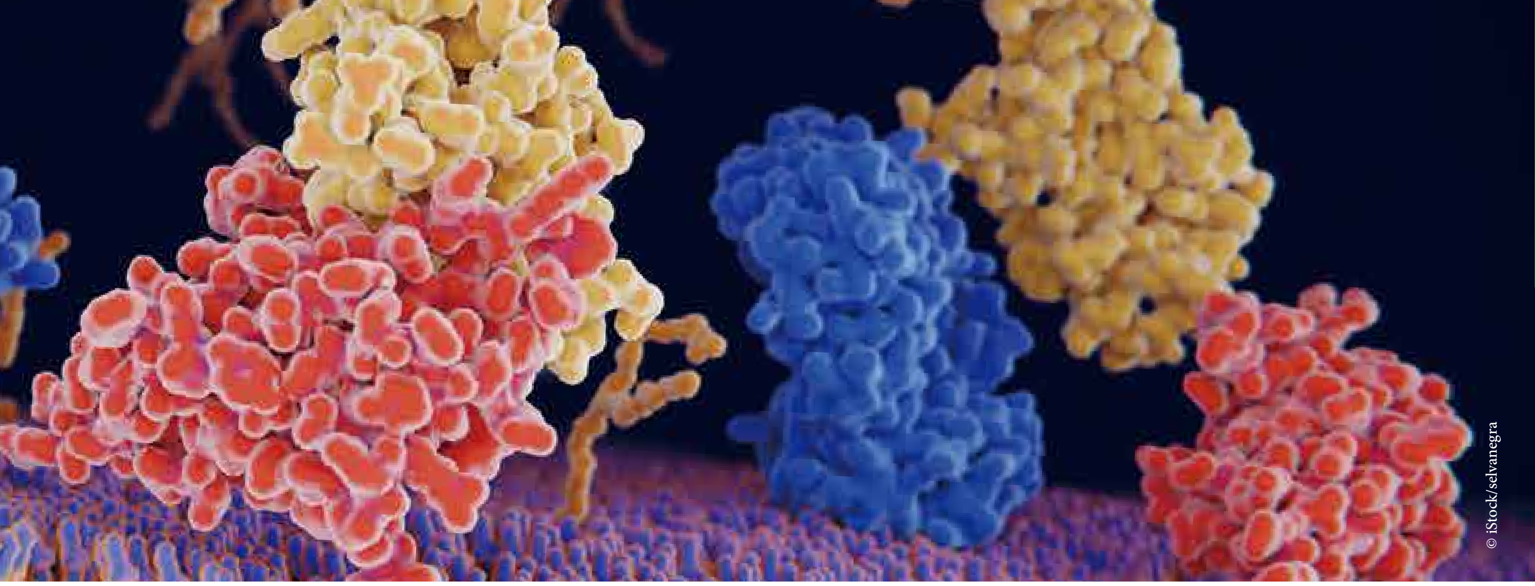
—Was tenacity of purpose also the key in the experimental method used to discover this gene?

To identify genes that are expressed only when T cells are dying, I initially created an experimental plan to subtract genes that are expressed when T cells are not dying. Dr. Honjo told me, "More than 100 candidate genes may be found with that method. That is not acceptable." Therefore, we used myeloid progenitor cells, which are different from T cells, to investigate genes expressed during cell death in the same manner and select genes common to both cells. We found only one gene—the PD-1 gene.

Why only cancer cells are targeted

—What is your research plan at NAIST?

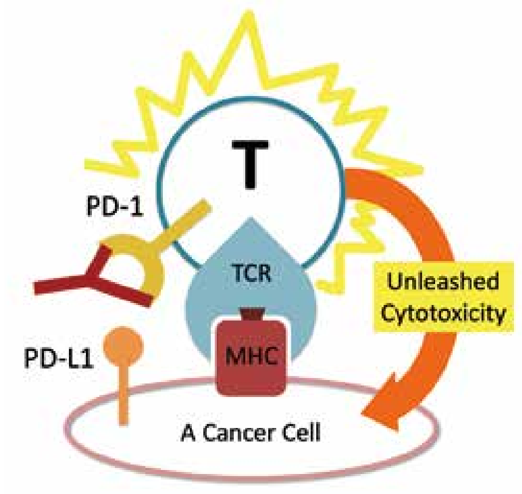
To date, our knowledge about PD-1 is that it plays the role of a brake, i.e., a negative regulator, in immune responses. Therefore, when an antibody binds to PD-1 and its function is weakened, the brake is released; the immune system can then attack cancer cells at its maximum capacity, and some patients can be cured of cancer. However, there remains an unsolved question: Why is the immune response to cancer cells selectively enhanced? If overall immune



responses are enhanced, it may lead to the development of autoimmune diseases; however, patients receiving the PD-1 antibody have only experienced minor adverse reactions. This is a research question whose solution requires a basic medicine approach. For example, knockout mice with no PD-1 gene remained healthy when they are young, but they required PD-1 to suppress autoimmune disease occurrence with increase in age. What are the mechanisms involved? I would like to investigate the mechanisms in relation to self- versus non-self-discrimination.

—What are being discovered?

We have proposed a hypothesis. Gene/DNA mutations gradually accumulate with age, even in normal somatic cells. Consequently, mutant proteins are produced in various places in the body. The immune system quickly detects and begins attacking by considering those as non-self, resulting in autoimmune diseases. We believe that the PD-1 gene was acquired in the process of evolution to prevent the occurrence of this phenomenon. There are tens of trillions of cells in the body; and it would be uncontrollable if each of them started producing a different set of mutant proteins. PD-1 might have widened the boundary between self and non-self to prevent immune responses to normal cells with slight mutations. Cancer cells, being slightly different from normal cells, are apparently trapped in the gap created by this widened boundary. When the PD-1 antibody is administered, cancer cells are eliminated as non-self because the antibody restores the boundary. At that time, some slightly mutated normal cells are also attacked. I believe that this is the mechanism underlying the occurrence of certain adverse reactions. Cancer cells appear to be selectively attacked simply because they have higher number of mutations and are thus more readily discriminated as non-self.



Antibody-mediated blockade of inhibitory signaling through PD-1.

Having a clear goal

—Based on your achievements in basic research on PD-1, what advice do you have for young researchers?

It is crucial to "clearly know what you want to know." These are the words of Dr. Honjo. It is not sufficient to attempt something owing to a vague thought that it seems interesting. If you have a clear goal of elucidating something, then you would be able to determine what is required to achieve it and develop an experimental plan. In my case, I was interested inself-/non-self-discrimination even before I joined Dr. Honjo's laboratory at Kyoto University as a graduate student, and I still am interested in that subject. I believe that such kind of tenacity is necessary.

Interviewed by Yoshinori Sakaguchi

Application characteristics of PD-1 to develop drugs for cancer immune therapy

PD-1 is a receptor expressed on the surface of immune-competent T cells on activation. When a particular substance (ligand) binds to this receptor, the immune function of T cells is weakened. Some cancer cells express a similar substance on the surface, which binds to PD-1 on T cells and facilitate cancer cells to escape the attack by T cells. Therefore, artificial antibodies are used to mask PD-1 to ensure that the ligand-like substance on cancer cells can no longer bind to PD-1, and the therapeutic efficacy is enhanced. Such antibodies have been used to treat numerous types of cancer, such as malignant melanoma, non-small cell lung cancer, renal cell cancer, Hodgkin's lymphoma, head and neck cancer, bladder cancer, and gastric cancer. However, the treatment is effective in only 20%–30% of patients with lung cancer and 30%–40% of those with malignant melanoma. Ishida and other researchers are conducting studies to improve these rates.

More information about the group's research can be found at https://bsw3.naist.jp/eng/courses/courses211.html

RESEARCH HIGHLIGHT

Tumor Cell Biology
Prof. Jun-ya Kato

Stressing cancer with spice

A new study by scientists in Japan and Indonesia reports how an experimental drug agent stops cancer cells from growing. A little over a decade ago, Indonesian scientists first reported pentagamavumon-1 (PGV-1), an analogue of a molecule found in turmeric and that has been since discovered to have anti-cancer effects. In the new study, tests on cancer cells and animals reveal that these anti-cancer effects come from PGV-1 inhibiting a series of enzymes responsible for the metabolism of reactive oxygen species. This finding is expected to clarify how modifications to PGV-1 will lead to its use for cancer treatment.

The popular spice turmeric has for centuries been used not just as a flavoring, but also as medicine, with history having shown it to have a number of anti-inflammatory and even anti-cancer benefits. These medicinal benefits come from the compound curcumin, which is commonly sold as an herbal supplement. Several studies have examined curcumin's anti-cancer properties, but the high doses required and poor understanding of the chemical process through which curcumin acts have limited these efforts.

The team of Professor Jun-ya Kato, at NAIST, had previously identified that curcumin acts on the same reactive oxygen species enzymes as its analogue, PGV-1. By suppressing the enzyme activity, reactive oxygen species are allowed to cause stress on cells, ultimately leading to cell death. Indeed, many anti-cancer drugs operate similarly, but sometimes with severe side-effects due to stress on healthy cells.

In the new study, Kato's team compared the effects of curcumin and PGV-1 on cancer, finding that they shared many of the same properties, but that PGV-1 did so at higher efficiency and lower dose.

"We found that PGV-1 arrests cells in the cell cycle at M phase" and that "it inhibits many ROS-metabolic enzymes," says Kato.

This arrest prevents the cancer cells from dividing, and the enzyme inhibition causes the cancer cells to die.

Intriguingly, PGV-1 was effective on numerous types of cancers. Moreover, when administered to mice injected with human cancer cells, the mice showed no evidence of the cancer and no side-effects. Furthermore, unlike some other anti-cancer drugs, the anti-cancer effects persisted even after the cessation of PGV-1 administration.

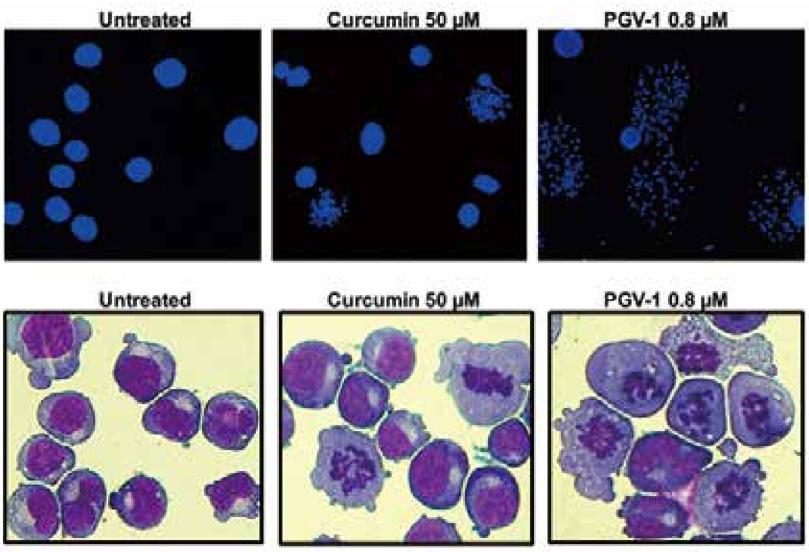
"Our results suggest that PGV-1 inhibits the enzyme activity more effectively in cancer cells than in normal cells. This may be the reason why PGV-1 selectively suppresses tumor cell proliferation with few effects on normal cells," notes Kato.

Scientists have long looked at the potential of curcumin to treat cancer. Kato believes PGV-1 could provide a breakthrough.

"Considering the high drug efficacy and low amount of side effects in animals, we propose that PGV-1 should be pharmaceutically developed as an orally administered drug for cancer," he says.

Reference

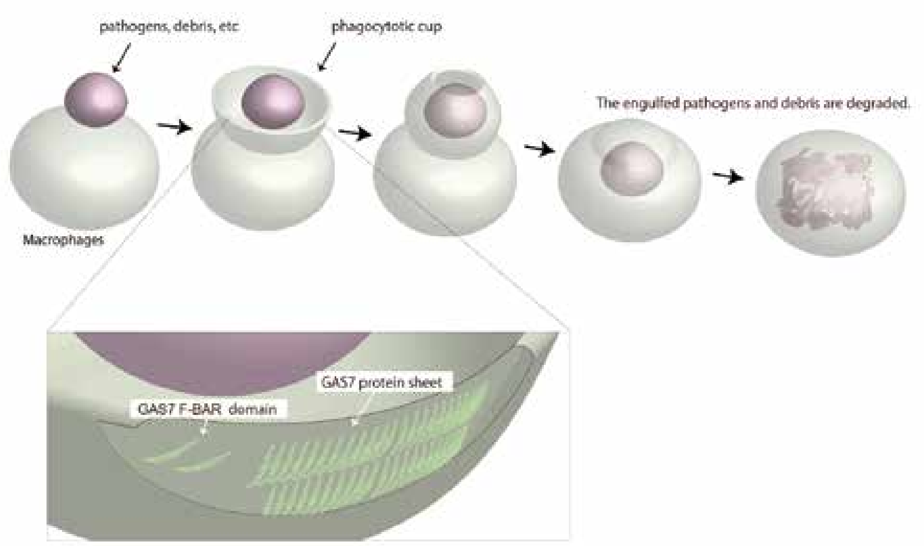
Lestari, B., Nakamae, I., Yoneda-Kato, N., Morimoto, T., Kanaya, S., Yokoyama, Y., Shionyu, M., Shirai, T., Meiyanto, E. & Kato, J. 2019. Pentagamavunon-1 (PGV-1) inhibits ROS metabolic enzymes and suppresses tumor cell growth by inducing M phase (prometaphase) arrest and cell senescence. *Scientific Reports*, 9, 14867.



Tumor cells were treated with curcumin (middle) and PGV-1 (right) and subjected to mitotic spread assay (upper) and Giemsa staining (lower). PGV-1 treatment markedly arrested tumor cells in the M phase of the cell cycle.

More information about the group's research can be found at https://bsw3.naist.jp/eng/courses/courses208.html

Molecular Medicine and Cell Biology
Prof. Shiro Suetsugu



Phagocytosis and the sheet model of GAS7 assembly in the phagocytotic cup.

GAS7 protein allows cells to eat

Without hands or feet, a single human cell has little to protect itself from surrounding threats like bacteria or viruses. In this way, the cell membrane has evolved to be much more than a wall that keeps cell content inside and everything else outside. By dynamically changing its shape, the membrane allows the cell to purge itself of waste and also attack nearby threats. Japanese scientists now report how the assembly of the protein Growth Arrest Specific 7 (GAS7) into two-dimensional sheets is crucial for this second process.

Phagocytosis describes a universal mechanism through which cells consume debris from the outside. The cell membrane will deform into a curvature known as phagocytic cup that rapidly wraps around nearby debris. Once fully engulfed, the debris will be passed into the specific organelles that will dispose of it. Immune cells such as macrophages use this process to consume and destroy infected or cancerous cells.

GAS7 is expressed in many cell types, but its function in membrane deformation is only partially understood.

"GAS7 is expressed in macrophages, and macrophages highly depend on phagocytosis, but we don't know the function of GAS7 in these cells," explains NAIST Professor Shiro Suetsugu, who led the study.

Even though macrophages are only 20 or so microns wide, the phagocytic cup themselves measure in microns. In other words, the membrane deformation required for phagocytosis makes the cell like a snake that dislodges its jaw to eat something as small as a mouse or as big as a cow.

The study shows that the presence of GAS7 could mark which sites on the macrophage membrane would deform into phagocytic cups. By exposing macrophages to zymosan, a type of glucan that scientists use to model microbes, the researchers found GAS7 along with an assortment of other molecules indicative of the beginnings of phagocytosis accumulated.

Of particular interest to Suetsugu was a specific region in GAS7, the Bin-Amphiphysin-Rvs167, or BAR, domain. BAR domains come in several types and are responsible for a protein's ability to bend the cell membrane. Crystal structures revealed a distinctive morphology of the GAS7 BAR domain to be the F-BAR domain with small protrusion on its surface.

"These domains formed filamentous oligomers with flat surfaces. The oligomers had an asymmetry due to two GAS7-specific loops so that one side is more positively charged than the other. The positively charged side, we supposed, could be the membrane-binding surface," says Suetsugu.

Mutants in these loops compromised the macrophage phagocytosis for zymosan.

"Our findings indicate that the oligomerization and membrane binding of GAS7 are essential for phagocytic cup formation," continues Suetsugu.

GAS7 is just one of many but essential proteins that have evolved to support phagocytosis. Elucidating the roles of the many proteins involved in this universal mechanism will explain not only the dynamics of the membrane, but also insights on how cells could thrive and thus grow into multicellular organisms.

"Further analyses will clarify how GAS7 oligomers cooperate with other proteins to regulate membrane deformation in phagocytosis," says Suetsugu.

Reference

Hanawa-Suetsugu, K., Itoh, Y., Ab Fatah, M., Nishimura, T., Takemura, K., Takeshita, K., Kubota, S., Miyazaki, N., Wan Mohamad Noor, WNI., Inaba, T., Nguyen, NTH., Hamada-Nakahara, S., Oono-Yakura, K., Tachikawa, M., Iwasaki, K., Kohda, D., Yamamoto, M., Kitao, A., Shimada, A. & Suetsugu, S. 2019. Phagocytosis is mediated by two-dimensional assemblies of the F-BAR protein GAS7. *Nature Communications*, 10, 4763.

More information about the group's research can be found at https://bsw3.naist.jp/eng/courses/courses210.html

IMPACT

Applied Stress Microbiology

Prof. Hiroshi Takagi

Revealing the mechanism of stress tolerance by cells to create stress-resistant yeast

Proline protects cells

Yeast, which is familiar to us as an essential microorganism for producing fermented foods, such as sake, miso, soy sauce, and bread, is used as a model microorganism to reveal fundamental mechanisms of life. Professor Hiroshi Takagi and colleagues have elucidated complicated but sophisticated intracellular mechanisms underlying adaptation by yeast to various environmental stresses, such as freezing, ethanol, temperature, osmotic pressure, reactive oxygen species (ROS) generation, and nutrient starvation. They applied the findings to construct stress-tolerant yeast strains that contribute to development of fermentation process and commercial production.

Takagi says, "After working for 13 years as a researcher in a food company (Ajinomoto), I decided to change my carrier to the academic position in Fukui Prefectural University, and moved to NAIST. Therefore, I have always been conscious of the balance between basic science and biotechnological application." He first encountered yeast at the company when working on the evaluation of frozen dough for bread making. It was the time he learned about the need for baker's yeast which is tolerant to freeze damage.

Numerous bacteria and plant cells protect themselves from osmotic and salt stresses by accumulating the amino acid proline; however, yeast cells normally do not induce proline synthesis upon exposure to stress. This fact captured his attention. He isolated yeast mutants capable of intracellular accumulation of proline and found that proline protected yeast cells from freezing and various other stresses, such as desiccation, oxidation, osmotic pressure, and ethanol. This achievement is expected to be applied to breeding industrial yeast strains (e.g., baker's yeast and sake yeast) with high fermentation ability.

Nitric oxide (NO) transmits information

During the proline research project, Takagi discovered a novel *N*-acetyltransferase named Mpr1 in yeast. This enzyme is considered to accelerate the synthesis of arginine related to proline metabolism. Furthermore, it was found that nitric oxide (NO) is produced by the diflavin reductase Tah18 via proline/arginine metabolism, and NO protects cells from high-temperature stress.

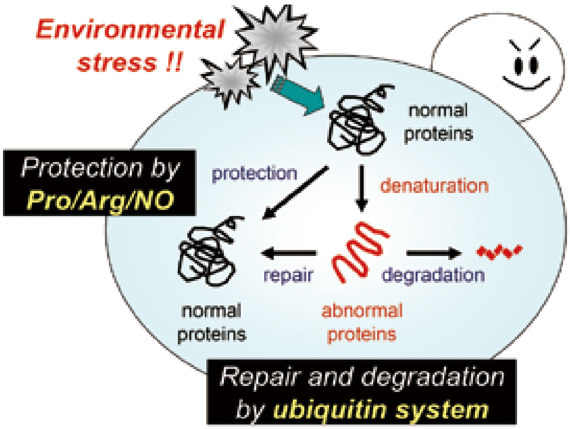
Regarding NO, scientists in the US found that NO is an essential signaling molecule in mammals and was awarded a Nobel Prize in Physiology or Medicine in 1998. However, NO synthase (NOS) in yeast has not been identified, and research conducted on this subject was limited.

"Because NO is highly reactive, it has two opposed functions—it is cytoprotective if it is produced in a small amount when needed but it can be cytotoxic if it is produced in higher quantities. I want to clarify the detailed mechanism in yeast and molds (filamentous fungi)," says Takagi.

Fruity awamori

Another major research theme for Takagi is "functional amino acid engineering"—to elucidate mechanisms of metabolic regulation and physiological functions of various amino acids produced in yeast cells. In terms of application, control of amino acid composition and content contributes to an improvement in productivity and add the value of alcoholic beverages. He has established an efficient method for isolation of yeast mutants capable of producing a specific amino acid in a large amount and has successfully developed highly functional brewery yeast strains. For example, he isolated some yeast mutants that accumulate leucine in the cell and overproduces "isoamyl acetate" known as the key flavor for sake and bread, which is produced from the leucine synthetic pathway. By brewing with his yeast, the Okinawa sprit "awamori" increased a unique fruity flavor and three different types of awamori have already been commercialized.

Currently, Takagi serves as the chair of the international academic society on yeast (International Commission on Yeasts); he is proud of introducing Japanese excellent yeast technology for fermentation and brewing in the world. Regarding NAIST, he says, "There are several researchers and students from various nations. Our laboratory also has many graduate students and accepts short-stay researchers from overseas, such as Southeast Asia, the US and European countries. I really enjoy to work under this diverse environment."



Novel stress-tolerance mechanisms in yeast.

Getting to the essence of life

Assistant Professor Ryo Nasuno is extensively investigating NO signaling in yeast. He is searching for enzymes and nitrogen sources directly involved in NO production, and also trying to identify enzymes involved in the attachment (modification)/detachment of NO to/from the relevant amino acid residues on protein when it serves as a signaling molecule. "I investigate easy-to-handle yeast to discover the mechanism common to all living organisms," he says.

Assistant Professor Akira Nishimura discovered NO production during experiments when he was a student at the Takagi Laboratory. He became an assistant professor at Tohoku University, School of Medicine after graduation and then returned to NAIST. During his research on sulfur (S) at Tohoku University, he discovered that the antioxidant effect of the amino acid cysteine was enormously enhanced when its SH group was replaced by the SSH group. In yeast experiments, he has demonstrated that this type of molecule is a possible cellular lifespan regulator. "This molecule appears to be involved in the energy metabolism of cells, and this study may lead to drug discovery," he says.

Unraveling the anomaly sensing system

Associate Professor Yukio Kimata is studying a system that responds to and processes stresses, such as the accumulation of proteins denatured into an abnormal shape in the endoplasmic reticulum, an intracellular organelle producing membrane proteins. In this system, when a sensory protein (Ire1) in the endoplasmic reticulum membrane detects stress, it is activated and transmits the information to the quality control protein, i.e., molecular chaperone. Thereafter, the increased chaperone levels result in processing of the abnormal molecules.

Kimata investigates the detailed mechanism underlying the phenomenon that Ire1 certainly detects abnormal proteins and activates itself to induce the remaining response using yeast. He presented the following mechanism for the first time: when abnormal molecules are accumulated, Ire1 releases the bound chaperone and then aggregates. Furthermore, abnormal molecules bind directly to the aggregated Ire1. Following two-step checking, Ire1 is activated and increases the amount of chaperone. Microscopic observation of the red fluorescent protein-labeled endoplasmic reticulum and green fluorescence-labeled Ire1 revealed that Ire1 aggregates as dots scattered across the endoplasmic reticulum in response to stress.

"Similar biological response mechanisms are found in animals. While yeast is occasionally used for manufacturing drugs, I intend to do research that is widely useful for human, such as functional enhancement by increasing the amount of chaperone in yeast," he says.

Interviewed by Yoshinori Sakaguchi

More information about the group's research can be found at https://bsw3.naist.jp/eng/courses/courses305.html

IMPACT

Environmental Microbiology

Associate Prof. Shosuke Yoshida

Discovering PET-eating bacteria and elucidating the underlying mechanism to employ them for environmental improvement

Disposal of waste plastics is a global issue

Reducing waste plastics, such as polyethylene terephthalate (PET) used for drinking water containers, is a major issue worldwide because they accumulate in and have adverse effects on the natural environment. Although PET produced through chemical synthesis is disposed via artificial processes, including recycling and incineration, capacity and cost limitations for collecting and disposing enormous quantities of waste plastics are present.

Therefore, finding and applying a natural system that microorganisms acquired to decompose artificial materials has begun attracting attention. Associate Professor Shosuke Yoshida and his colleagues were the first in the world to discover a bacterium (*Ideonella sakaiensis*) that possessed the ability to degrade PET. Furthermore, they demonstrated that this bacterium decomposes as well as consumes PET by metabolizing it. These research results, which have the potential of accomplishing dramatic environmental improvements, have been published in the journal *Science*.

“We were fortunate to find this bacterium in a PET recycling plant. This bacterium appears to have special enzymes that can utilize PET to produce the microbial body constituents and energy. No other bacteria like this one have been reported,” Yoshida emphasizes.

Two enzymes work together

This bacterium can grow using PET as a sole carbon source. In their experiment, approximately 250 environmental samples were cultured with a PET film. Various types of microorganisms were found to gather around the film. *Ideonella sakaiensis* was isolated from this population. When the film surface was observed under an electron microscope, countless dimples were formed, indicating that the bacterium was feeding on the PET film.

Further, to determine the mechanism of PET decomposition, they investigated enzymes possessed by the bacterium. PET is a polymer (multimer) in which ethylene glycol and terephthalic acid (TPA) are connected alternately together as a chain. Ethylene glycol is an alcoholic compound, and TPA is an acidic compound with aromatic ring (benzene ring) composed of carbon atoms connected in a hexagonal shape. The bonds connecting these units are ester bonds. Typically, ester bonds are readily cleaved by enzymes in an organism. However, PET is resistant to enzymatic degradation because the aromatic ring of TPA affects the structure of the entire PET molecule and renders it difficult to break its ester bonds. Therefore, they anticipated that enzymes with an unknown function are present in the PET-eating bacterium.

Yoshida analyzed the entire genome of this bacterium. Using enzymes that were previously reported to be capable of slight degradation of PET as a suggestion, they explored the bacterial genome

sequence and found PETase, a PET-specific hydrolase. This enzyme is powerful and can create cavities in a PET film overnight when the film is covered with this enzyme; however, PET decomposition by this enzyme occurs only until the production of MHET—a compound in which a single molecule ethylene glycol and TPA are connected. Accordingly, they predicted the existence of another enzyme capable of cleaving the bond of MHET into two molecules to facilitate metabolization and found MHETase. These two enzymes appear to work together.

Ideonella sakaiensis **on PET film (Yoshida** ***et al.***, ***Science***, **2016).**

For production of useful substances

The overall picture of the PET-eating mechanism is being elucidated. “There must be other factors that assist in the efficient functioning of this mechanism. We will identify those factors and engineer this bacterium to produce an industrially useful strain capable of more rapid conversion of PET into useful substances under mild conditions,” Yoshida says. “This mechanism is also interesting from the viewpoint of evolution of microorganisms. If the mutation of simply one of the amino acids that constitute an enzyme can impart a new function to a microorganism, an environment where PET is the sole available carbon nutritional source can serve as selection pressure to make the PET-eating bacterium the champion, thereby leading to the selective survival of mutant microorganisms,” he continues.

Yoshida enrolled in university to study environmental issues and encountered research exploring PET-degrading bacteria. “I have been aiming at research that will produce results that people find interesting. I want to work on carefully selected and interesting research subjects with students,” he says. Regarding NAIST, he says, “NAIST is actively accepting both domestic and international students, similar to colleges in Europe and the United States. The university’s educational support system for teaching individual students is outstandingly helpful.”

Research into evolution of PET-eating bacteria

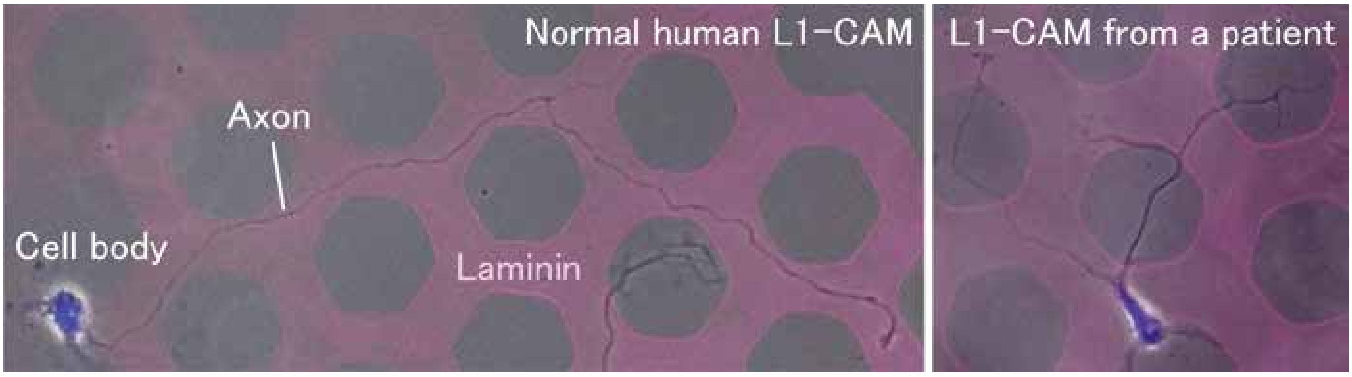
Members of his laboratory are working on the major research subject of functional characterization and the application of PET-degrading microorganisms from various perspectives. They have established a method to knockout specific genes in *I. sakaiensis*. They have successfully disrupted the PETase gene, rendering it possible to identify the systems that are working and determine the role of this enzyme. Moreover, they are interested in the evolution of new bacteria that have acquired the PET-degrading capacity.

Interviewed by Yoshinori Sakaguchi

More information about the group’s research can be found at https://bsw3.naist.jp/eng/courses/courses312.html

RESEARCH HIGHLIGHT

Systems Neurobiology and Medicine
Prof. Naoyuki Inagaki



Mutation in CRASH syndrome leads to dysfunction of the grip & slip mechanism and disrupts laminin-induced axonal haptotaxis.

Axons grip and slip their way around the brain

In a new study, NAIST scientists, in collaboration with researchers at the Osaka National Hospital and University of Tokyo, report that the L1 Cell Adhesion Molecule (L1-CAM) is crucial for directed axon migration. The study shows that L1-CAM grips and slips on laminin to steer axons to their final destination. It further explains how disruption of this L1-CAM system leads to CRASH syndrome, which describes an assortment of neural disabilities that are all attributed to an underdeveloped brain. The study can be read (open access) in the *Proceedings of the Natural Academy of Sciences of the United States of America* (*PNAS*).

Axons sprout from neurons and then migrate to specific parts of the developing brain where they interact with other neurons to form neural networks. The axons move in response to gradients of attractants with extraordinary sensitivity; the sudden stops and sharp turns they make during their migration resemble cars stopping and turning at an intersection.

"Laminins function as attractive chemical cues for haptotaxis of axonal growth cones," explains NAIST Professor Naoyuki Inagaki, whose lab studies how forces are generated in the cellular microenvironment to create directed axonal migration.

Axons migrate in response to laminin on the microenvironment. The new study by the Inagaki lab showed that neurons will produce four times more traction force when placed on adhesive substrates coated with laminin than those without laminin, assuring the axons reach their final destination.

"The force reduced the F-actin retrograde flow," says Kouki Abe, a doctoral student in the lab who conducted the experiments. "We looked at the movement of L1-CAM because it is linked to F1-actin flow."

Actin is a crucial molecule for cell motility throughout the body. However, in axons, it does not directly interact with laminin. Rather, L1-CAM acts as the intermediary. As expected, additional experiments by Abe showed that the F1-actin flow was dependent on L1-CAM interactions with laminin.

"We found L1-CAM switches between an immobilized state, or what we call 'grip' state, and a 'slip' state. The ratio of grip state increased with laminin," says Inagaki. This increased grip state strengthens the traction force produced by the axon onto the adhesive substrate, allowing the axon to turn and change its direction on cue. The scientists further found that disrupting the increased grip ratio compromised the directional migration, a discovery that could explain the pathogenesis of several diseases.

"We examined L1-CAM from a patient with CRASH syndrome in which L1-CAM was mutated. The different grip ratio seen between laminin and polylysine was lost, and the directional axon migration was disturbed," explains Inagaki.

"L1-CAM controls migration not only in the brain, but also in cancer. Grip-and-slip is a new mechanism that could explain other diseases," he says.

Reference

Abe, K., Katsuno, H., Toriyama, M., Baba, K., Mori, T., Hakoshima, T., Kanemura, Y., Watanabe, R. & Inagaki, N. 2018. Grip and slip of L1-CAM on adhesive substrates direct growth cone haptotaxis. *Proceedings of the National Academy of Sciences of the United States of America*, 115, 2764-2769.

More information about the group's research can be found at https://bsw3.naist.jp/eng/courses/courses204.html

Plant Metabolic Regulation
Prof. Taku Demura

Plant polymers do not always act together to make beautiful shapes

Animals and plants are distinguished by many features, one of which is the cell wall. In plants, this structure acts like a skeleton, providing support and stability, and also like muscle, passing water from the ground all the way to the highest leaves and branches. The structure responsible for water transport is the secondary cell wall, which NAIST Professor Taku Demura has been studying because it is constituted of xylem.

"Xylem is an important resource for land plant biomass. Modifications of xylem cell differentiation are important for strategies to improve plant biomass resources," believes Demura.

The secondary cell wall is composed of three types of polymers, cellulose, hemicellulose, and lignin. In a new study that can be read in *Plant Cell*, Demura's laboratory found that these three polymers in xylem cell mutants contribute to secondary cell wall formation independently of each other, challenging the contemporary model of plant growth.

Interaction between cellulose and hemicellulose is critical for giving cell walls their strength and elasticity to push water upward. Interaction with lignin adds the hydrophobicity that gives an electrical charge to the push. Studies in the early 1980s had convinced scientists that the formation of the secondary cell wall occurs in consecutive events, beginning with the synthesis of cellulose at the cell surface, followed by the deposition of hemicellulose that bonds to the cellulose, and finally the migration and polymerization of lignin.

These interactions result in the three polymers taking an obvious spatial pattern in xylem cells. However, xylem cells in a mutation of *Arabidopsis thaliana*, a small plant commonly used by scientists to study plant growth, made by the Demura lab, showed disrupted cellulose synthesis without disruption of the spatial patterning of hemicellulose or lignin.

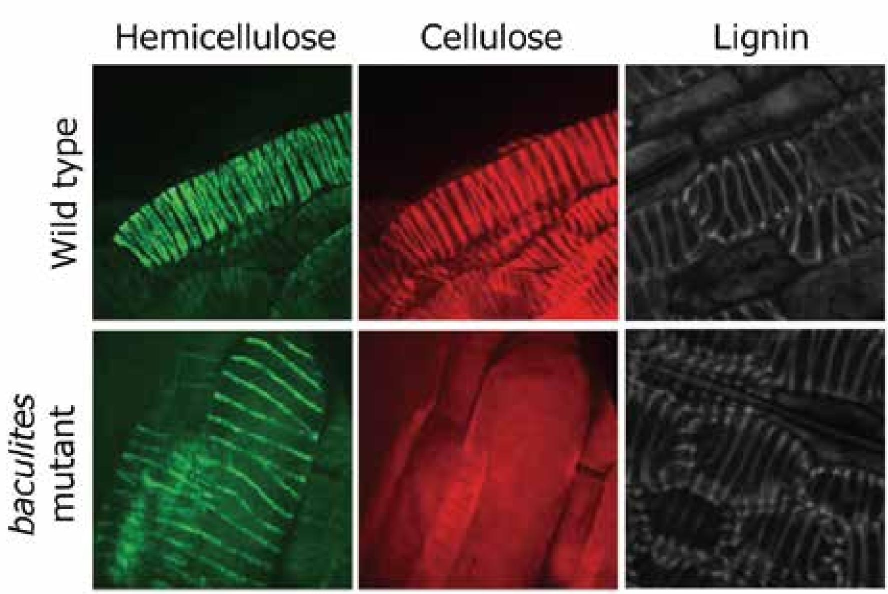
"We made a mutation in the cellulose synthase gene CESA7. This mutation prevented the formation of cellulose. Despite the lack of patterned cellulose deposition, we saw patterned deposition of hemicellulose and lignin," explains Dr. Misato Ohtani, who contributed to the project.

Additional study revealed that the sustained patterning could be attributed to microtubules, molecules seen in just about all life, including humans, and is responsible for transporting materials within cells.

"We were able to disrupt the hemicellulose and lignin patterning when we disrupted the microtubules with a drug. This suggests that during secondary cell wall formation, the hemicellulose and lignin are regulated by microtubules and not cellulose," continues Ohtani.

Considering the increasing efforts to bioengineer plants that can produce resources at higher efficiencies or withstand extreme changes in climate, Demura notes that elucidating the mechanisms of how fundamental plant structures like the secondary cell wall develop will help scientists achieve these goals.

"Identifying the independence of cellulose, hemicellulose and xylan suggests we can modify one without modifying the other in plants," he says.



Patterns of different polymers in xylem cells.

Reference

Takenaka, Y., Watanabe, Y., Schuetz, M., Unda, F., Hill, JL. Jr., Phookaew, P., Yoneda, A., Mansfield, SD., Samuels, L., Ohtani, M. & Demura, T. 2018. Patterned deposition of xylan and lignin is independent from the secondary wall cellulose of Arabidopsis xylem vessels. *Plant Cell*, 30, 2663-2676.

More information about the group's research can be found at https://bsw3.naist.jp/eng/courses/courses104.html

IMPACT

Plant Growth Regulation

Prof. Masaaki Umeda

Revealing astute strategies employed by stress-tolerant, long-lived plants

Stem cells underlying vitality

In evolution, plants have developed astute strategies to adapt themselves to various environmental stresses, such as ultraviolet rays and high temperatures, for the survival of individuals and prosperity of species. The Plant Growth Regulation Laboratory has revealed detailed mechanisms underlying ingenious functions of individual plant cells at the DNA level and employed this knowledge into applications, such as increased food and biomass production.

Professor Masaaki Umeda says, “Our research subjects include an extension of plant lifespans and enlargement of plant sizes. Regarding lifespan, we are attempting to elucidate the mechanisms underlying the maintenance of pluripotent stem cells, which undergo differentiation to various organs and support the foundation of vitality, as well as the mechanisms underlying high-stress tolerance. Regarding enlargement, we are studying ‘DNA polyploidization,’ which results in volume increases of individual cells.”

Information exchange between cells

Trees continue to grow throughout their lives, and some become massive trees after more than a thousand years. “Permanently repeated proliferation and regeneration of stem cells represent the unlimited source of power,” Umeda believes. “Principles of pluripotent stem cells underlying plant vitality," led by Umeda, was launched as Scientific Research on Innovation Areas, a MEXT Grant-in-Aid Project; it comprises multidirectional collaborative studies with universities and research institutions across Japan.

At the root tip of *Arabidopsis thaliana*, stem cells surround cells called the quiescent center. "The division cycle of stem cells is controlled by an enzyme called CDK, and the stem cells undergo differentiation when a CDK-inhibiting factor acts on this enzyme," Umeda explains. Investigations in columella stem cells, which undergo only a single cell division, have shown that a factor called WOX5 migrated from the quiescent center only to the adjacent stem cells, where it stops the CDK inhibitory action and maintains the stem cell function.

"WOX5 determines whether stem cells continue to remain as stem cells. A plant cell is encapsulated in a hard cell wall and is unable to move within tissues. Therefore, stem cells are likely to be kept maintained at a proper place via cell–cell information exchange," Umeda says.

Super stress-tolerant plants

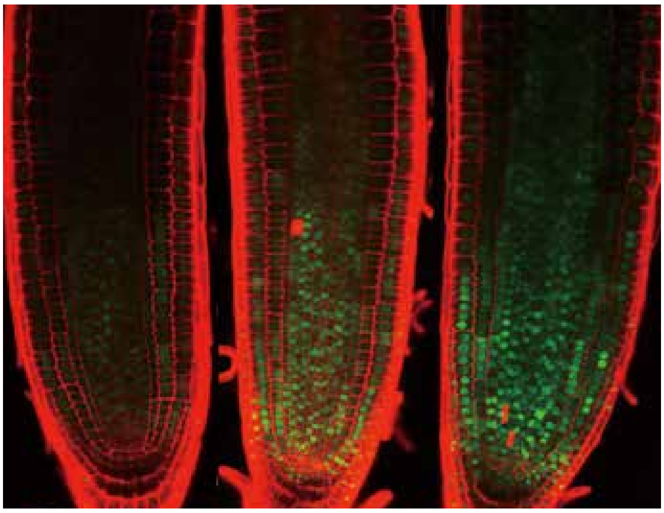
Plants actively arrest cell division, thereby suppressing growth and saving energy consumption to concentrate on stresses, such as DNA damage. Umeda has elucidated the signal transduction pathway between stress detection and cell division arrest. Specifically, two transcription factors (such as ANAC044) controlling gene expression are induced and stabilize different transcription factors (such as MYB3R3), thereby suppressing genes involved in the progression of cell division.

Because these factors are induced in response to various environmental stresses, Umeda predicts that, conversely, if the genes can be suppressed to prevent these factors from being produced, one can create super stress-tolerant plants that continue to grow regardless of environmental stresses that the plants are exposed to. Indeed, some rice varieties that are highly tolerant to stresses in the soil reportedly have lost the genes of these factors during selective breeding.

Chromatin loosens

A discovery was made in the research on plant body enlargement. During the cell cycle, DNA in a cell is replicated and doubled in amount, following which the cell is divided into two with the original amount of DNA. Therefore, duplication of DNA in cells, called polyploidization, can be induced by blocking and skipping the division step. Large crops can be produced by applying this method to increase the amount of DNA per cell. However, some trees, such as poplars, do not undergo DNA polyploidization. Umeda discovered that DNA polyploidization is likely to occur when chromatin is loosened. Chromatin is a string-like complex, which comprises DNA wrapping around a protein called histone. He is also investigating compounds that promote DNA polyploidization.

"The foundation of this research was the cell cycle of plants. This research subject attracts more attention and more researchers, although it used to be mundane and unpopular. Rather than going after popular research subjects, I choose ones that excite and inspire me. Discoveries and breakthroughs happen from such research," he emphasizes.


Arabidopsis **root tip treated with DNA-damaging agents.**

Life and death occur side-by-side

Assistant Professor Naoki Takahashi investigates the mechanism via which root meristems are maintained to allow for the continuous growth of plants in a stressful environment. In plants, cell death as a means to eliminate abnormal cells due to DNA damage is a phenomenon observed only in stem cells, and the phytohormone auxin inhibits the induction of cell death. Furthermore, when stem cells die, stress-resistant cells in the quiescent center initiate cell division to regenerate stem cells. Takahashi found that another phytohormone—brassinosteroid—is involved in the process. These findings indicate that the life and death of stem cells occur in cells adjacent to each other.

"For a long time, I have been engaged in this field of research, such as intracellular monitoring mechanisms, to determine if cell cycle steps are normal (e.g., cell division and DNA polyploidization). In the future, I intend to extend my research to more application-oriented subjects, such as stress tolerance," he says.

New functions of phytohormones

Assistant Professor Shiori Aki has discovered that *Marchantia polymorpha*, a liverwort that is the ancestor of land plants, has a signal transduction pathway responding to the phytohormone cytokinin, which promotes cell division. The pathway controls differentiation into various organs, including the gemma cup required for asexual reproduction.

"I wanted to become a plant researcher because I grew up in a rural area, noticing how various plants change their appearance. I am interested in basic research, and I intend to make discoveries that are going to be described in textbooks," she says.

Interviewed by Yoshinori Sakaguchi

More information about the group's research can be found at https://bsw3.naist.jp/eng/courses/courses105.html

RESEARCH HIGHLIGHT

Plant Growth Regulation

Prof. Masaaki Umeda

Plants grow less in hotter temperatures

Plants have developed a robust system that stops their cell cycle in hostile environments such as abnormally hot temperatures. In response, they direct their energy to survival rather than growth. A new study led by scientists at NAIST reports in *eLife* that two transcription factors, ANAC044 and ANAC085, are critical for this response in the flowering plant *Arabidopsis*. The findings give clues on ways to modulate the growth of crops and other agriculture products.

Upon DNA damage, plants and animals halt cell division and execute DNA repair. This response prevents the damaged cells from proliferating. NAIST Professor Masaaki Umeda has made a career studying the molecular biology behind this protective measure.

"We reported that SOG1 is activated by DNA damage and regulates almost all genes induced by the damage," he says. Another study from the lab showed "Rep-MYBs are stabilized in DNA damage conditions to suppress cell division," he adds.

In the laboratory's newest study, Umeda's research team shows that ANAC044 and ANAC085 act as a bridge between SOG1 and Rep-MYB.

The scientists disrupted DNA in *Arabidopsis* cells by treating the cells with bleomycin, a compound commonly used to halt the growth of human cancer cells. The *Arabidopsis* cells failed to proliferate as expected unless they possessed a mutation in ANAC044 or ANAC085. In the mutant cases, the cells proliferated as though they were never exposed to bleomycin.

"We found that ANAC044 and ANAC085 are essential for root growth retardation and stem cell death, but not for DNA repair," says Umeda.

Specifically, ANAC044 and ANAC085 were responsible for preventing the cell cycle from proceeding from G2 phase to mitosis in response to the DNA damage.

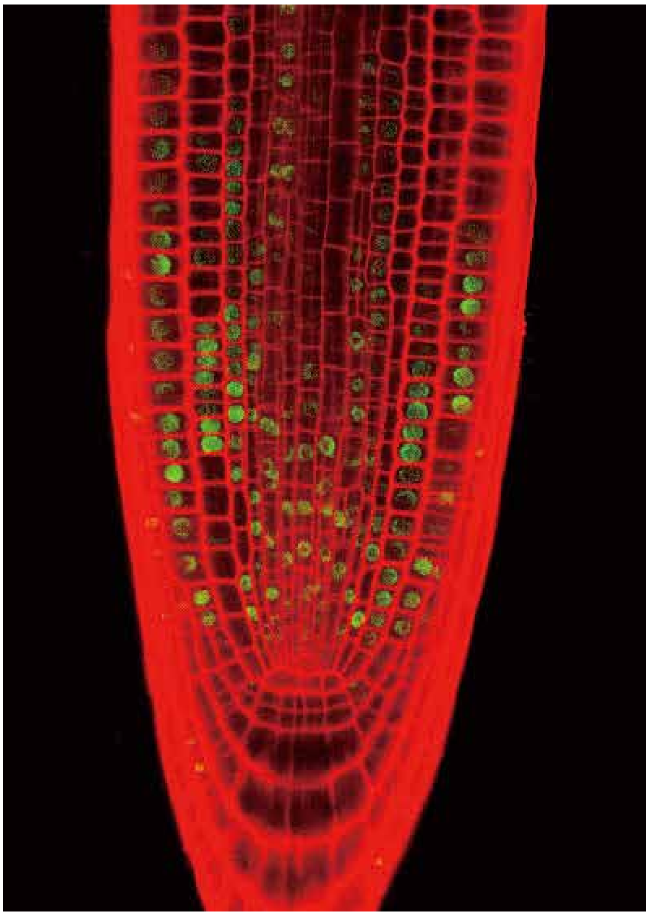
Rep-MYBs cause the same arrest in the cell cycle. Consistently, in normal cells, bleomycin caused a rise in the accumulation of Rep-MYBs, but not in cells with ANAC044 and ANAC085 mutations. These findings suggest ANAC044 and ANAC085 act as a bridge between SOG1 and Rep-MYBs in the halting of the cell cycle upon DNA damage.

DNA damage is just one form of stress that can cause the cell cycle to pause. To investigate whether ANAC044 and ANAC085 act in response to other forms of external stress, the researchers exposed the cells to different temperatures and osmotic pressure which cause the retardation in G2 and G1 progression, respectively.

Growth arrest was observed in both mutant and normal cells at a high osmotic pressure, but higher temperatures only caused pauses in the cell cycle in normal cells, indicating that ANAC044 and ANAC085 act as gatekeepers in the progression from the G2 phase in the cell cycle under abiotic stress conditions.

The fact that ANAC044 and ANAC085 operate in response to different types of abiotic stress suggests to Umeda that they may be at the core of new technologies designed to modulate plant growth.

"The research illuminates a new mechanism that optimizes organ growth under stressful conditions. When trying to increase plant productivity, scientists should consider ANAC044 and ANAC085," he says.



***Arabidopsis* root tip treated with DNA-damaging agents. Cells (red units) with green color, which indicates Rep-MYB stabilized by ANAC044/085, are stopping cell division.**

Reference

Takahashi, N., Ogita, N., Takahashi, T., Taniguchi, S., Tanaka, M., Seki, M. & Umeda, M. 2019. A regulatory module controlling stress-induced cell cycle arrest in *Arabidopsis*. *eLife*, 8, e43944.

More information about the group's research can be found at https://bsw3.naist.jp/eng/courses/courses105.html

Plant Stem Cell Regulation and Floral Patterning

Prof. Toshiro Ito

Proper flower growth depends on the activation and suppression of floral stem cells (left). KNUCKLES and WUSCHEL expression are seen to colocalize in the nucleus to suppress floral stem cell activation (right).

Turning off growth to make flowers grow

The beautiful colors and smells of flowers serve a much greater purpose than just decorating one's home. Flowers are where the plant's reproductive organs are found, and those same colors and smells that make a room beautiful also attract bees and other animals for pollination. Floral stem cells are crucial for the growth of the flower and its organs. That growth must eventually terminate for the flower to fully develop and set seeds. A new study led by scientists at NAIST and seen in *The Plant Cell shows* that the transcription factor KNUCKLES is a key regulator of this stem cell arrest by initiating a serious of epigenetic events to repress the stem cell determinant WUSCHEL.

"Floral stem cell activity vanishes when WUSHCEL is suppressed and silenced through changes in its chromatin state. What we did not know was how this change begins and how it is sustained," explains NAIST Professor Toshiro Ito, who led the study.

Ito's team looked at the activation and suppression of floral stem cells from Arabidopsis. Stem cell activation was marked by a clear expression of WUSCHEL, but that changed when the cells also began to express KNUCKLES, which bound to the *WUSCHEL* locus and led to *WUSCHEL*'s expression almost halving four hours later.

Then at 8-12 hours after the *KNUCKLES* expression, the group found that the *WUSCHEL* locus showed signs of H3K27me3 histone methylation, a marker of sustained gene suppression.

The question Ito wanted to answer was what were the events that took place from the KNUCKLES binding to the *WUSCHEL* locus to the H3K27me3 histone methylation that could terminate the stem cell activation.

"H3K27me3 is catalyzed by Polycomb Group complexes, but nothing is known about how the complexes are recruited to the *WUSCHEL* locus," says Ito.

The researchers discovered that KNUCKLES binding to *WUSCHEL* jettisoned SPLAYED, a chromatin remodeling protein that activates *WUSCHEL*. This effect leads to rapid transcriptional repression of *WUSCHEL*, followed by the recruitment of Polycomb Group complex to *WUSCHEL*, where it formed H3K27me3 marks on the chromatin to suppress gene expression.

"KNUCKLES binding was essential for the rapid removal of active H3K4me3 marks and the following deposition of repressive H3K27me3 marks," explains Ito.

The recruitment was done by KNUCKLES interacting with a specific component of the Polycomb Group complex known as FERTILIZATION-INDEPENDENT ENDOSPERM.

"Our study reveals the temporal steps from KNUCKLES binding to H3K27me marks that silence the *WUSCHEL* chromatin. Understanding how stem cell activation is terminated will assist in new food technologies," says Ito.

Reference

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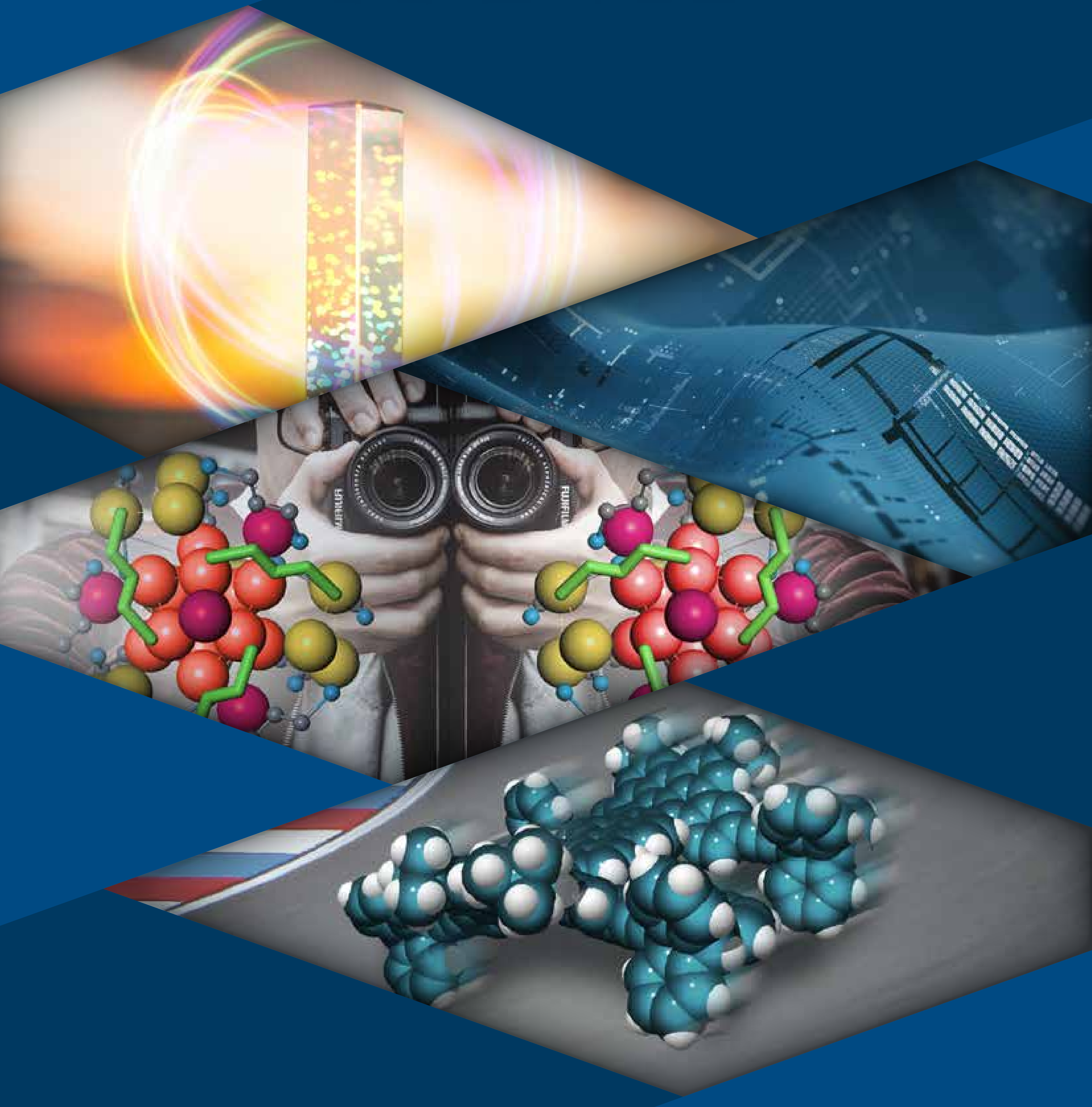
More information about the group's research can be found at https://bsw3.naist.jp/eng/courses/courses112.html

MATERIALS SCIENCE



RESEARCH HIGHLIGHT

Bio-Process Engineering
Prof. Yoichiroh Hosokawa

Measuring metabolites in algae one cell at a time

In the search for new sources of consumables, scientists have come to realize that life itself could be the solution. Metabolic engineers have altered the metabolism of living organisms to make new drugs, biodegradables and biofuels. One of the best examples in modern times is penicillin. Metabolic engineering bacteria has improved the production rate of this drug more than 100 times.

A major challenge in this field is identifying which cells are the most productive. It is relatively easy to study bulk populations, which results in information about the metabolism of the overall cell population. However, it remains extremely difficult to identify which cells in the bulk population stand above the rest in terms of metabolite production and are therefore the best to copy and imitate. This identification requires observing inside individual cells in real time while the metabolite is made. Scientists at NAIST report a new system that achieves this goal in microalgae cells. The system, which can be read about in *Scientific Reports*, combines fluorogenic aptamers with femtosecond laser photoporation.

"Algae have a number of attractive qualities for metabolic engineering. First, they are extremely adaptive, as they have the ability to live in a broad range of environments, from the equator to the poles and even in heavily saline or polluted waters," says Professor Yoichiroh Hosokawa, who led the study.

Normally, scientists use fluorescence microscopy to look inside a cell. This strategy involves attaching a molecule that fluoresces to the metabolite of interest. However, because of cell wall protection, it has been difficult to introduce fluorescent molecules that detect specific metabolites in microalgae cells from outside.

Hosokawa's team has therefore been developing fluorescent aptamers that emit fluorescence upon binding to the metabolite paramylon and manufacturing methods that can introduce them into the cell by laser pulses.

"We synthesized a peptide aptamer binding to paramylon, and introduced it into *Euglena gracilis* cells by single cell laser processing," says Dr. Takanori Maeno, who first-authored the study. "Paramylon is produced only by *Euglena* and functions like fiber. It can be refined into biofuels," he adds.

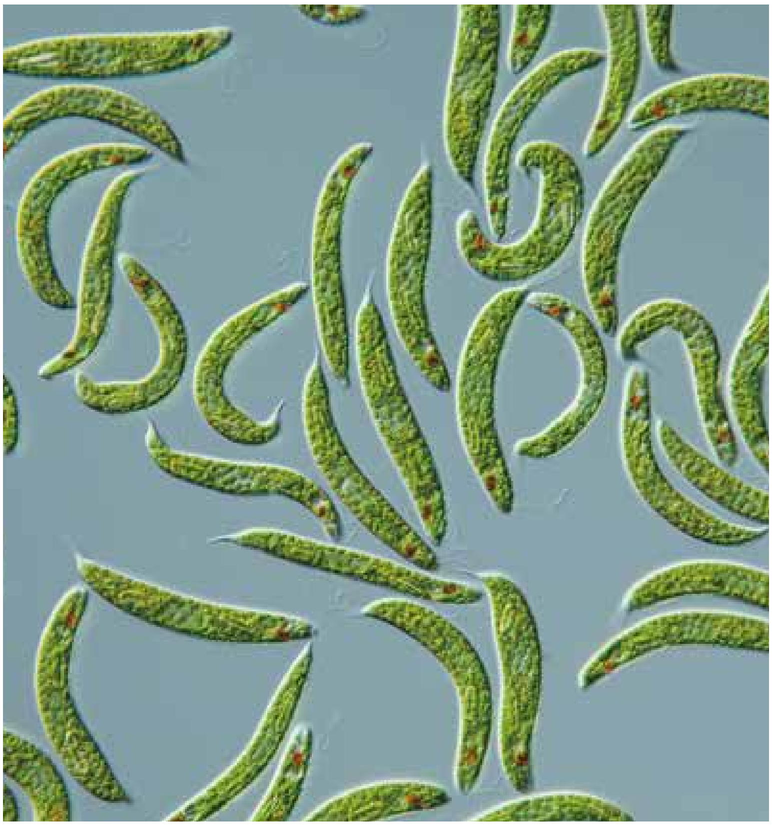
To get the aptamer inside the cell, the scientists shot the cells with laser pulses only femtoseconds long. These pulses created temporary pores big enough for the aptamers to enter. Once inside, the cells turned green only in places where the aptamers bound to paramylon. Using this technique, Hosokawa's group could measure the accumulation of paramylon with time, thus discriminating efficient cells from their unproductive neighbors.

While the system was only tested on paramylon, Hosokawa states that other metabolites will be detectable with appropriate aptamers.

"Our method gives spatial and temporal information about target intracellular paramylon, but should work for any kinds of metabolites in future. It will be useful for selecting high-performance cells," he says.

Reference

Maeno, T., Uzawa, T., Kono, I., Okano, K., Iino, T., Fukita, K., Oshikawa, Y., Ogawa, T., Iwata, O., Ito, T., Suzuki, K., Goda, K. & Hosokawa, Y. 2018. Targeted delivery of fluorogenic peptide aptamers into live microalgae by femtosecond laser photoporation at single-cell resolution. *Scientific Reports*, 8, 8271.



Euglena

More information about the group's research can be found at https://mswebs.naist.jp/english/courses/list/labo_11.html

IMPACT

Quantum Materials Science

Prof. Hisao Yanagi

Light is created with quanta; quanta are manipulated by light

Lasers realized using organic materials

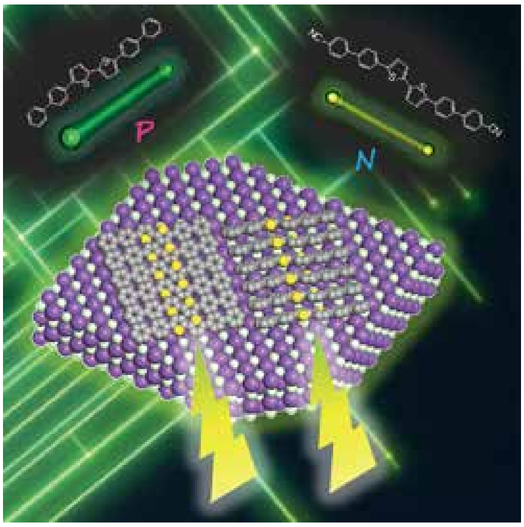
A number of photonic network projects are underway to accelerate information processing and communications by exclusively using light, with the aim of curbing the rapidly increasing energy consumption. A significant challenge is to replace the current situation in normal households, wherein light signals from the outside are converted into electric ones, to a situation wherein the light signals are directly utilized by circuits and devices to improve the energy-saving effect.

Professor Hisao Yanagi says, “We are developing an organic laser for light emission, including the light source of optical communication, sufficiently utilizing the characteristic of organic materials whose molecular design is easy.” He emphasizes, “We have also been studying the technology that will become the basis for realizing the super-high-speed quantum computer, which is the pivot of next-generation information processing and communication.”

His group’s study is based on quantum mechanics, a physics that elucidates phenomena occurring at the atomic or molecular level. Light and electrons in a substance are quanta that exhibit particle properties as well as wave properties. If the position of the peaks and valleys in multiple waves is aligned, they strengthen each other; otherwise, they cancel each other out. This characteristic phenomenon is called "interference." The electrons in a substance are enclosed in a molecular box (quantum box), and they behave as a wave on an orbital according to each energy level. The light emission mechanism is that when an electron is excited to a higher orbital, subsequently returning to a lower orbital, it releases energy, which becomes light.

There was a delayed response

The material studied by Yanagi's group is an organic compound called thiophene phenylene co-oligomer (TPCO) with characteristics of an organic semiconductor. Various optical functions from only the organic material have been elucidated. "When the number or order of ring structures contained in this molecule is changed, various wavelengths of visible light, from blue to red, can be emitted. We have also been able to confirm the effect of confining light in a crystal, which is a type of resonator that amplifies the light," Yanagi explains.



A molecular crystal-based organic laser.

Using this compound, they succeeded in optically pumped organic laser. After deviating electrons to a higher energy orbital (a state called population inversion), photons were generated in a chain reaction through a phenomenon called "stimulated emission." A strong laser beam with wavelengths of various colors in the visible light region were generated by amplifying photons through phase-matched waves.

In a series of such achievements, Yanagi's group made a significant discovery concerning organic material. When they excited an organic material via laser irradiation for a short period of time (1/10,000,000,000,000 of a second), they observed "delayed luminescence" in which light emission was delayed by ~3/10,000,000,000 of a second at a certain range of excitation energy. "The electron waves in the material interfered with each other, matched the phase of the waves, and behaved as one luminous body. This delay constituted the time taken for synchronism," Yanagi explains. This phenomenon is called "quantum coherence" and could be related to superfluorescence and used for the basic technology in quantum computers. "In addition to the organic laser of the optically pumped type, going forward, we will advance our studies to that of the electrically pumped type," Yanagi says.

Basic technology for quantum computer

Associate Professor Hiroyuki Katsuki has undertaken research on "quantum coherence control" to operate the quantum wave inside a crystal with ultrashort light irradiation, and has succeeded in controlling and reading the quantum state with a time accuracy of 1/1,000,000,000,000,000 of a second or less. If this technique is used for quantum computers, substantial information could be simultaneously processed in parallel using the superposition of waves. Furthermore, if a special state called "polariton", where the light and molecules in the excited state are mixed at room temperature using an organic material, is available, it could enable the application of the quantum coherence control technique under convenient conditions such as on a laboratory table at room temperature.

Furthermore, Katsuki is studying the state known as "vibrational polariton," wherein molecular vibrational motion and light are mixed. Using this state, the reaction path that could not be realized through conventional chemical reactions can be controlled and products can be selectively controlled.

Organic crystals for new developments

"When the brain is stimulated, nerve cells quickly and simultaneously process information in parallel through quantum interference. In plants, photosynthesis utilizes 100% of the available sunlight by absorbing the energy in an aggregate of chlorophyl molecules and transmitting it through quantum waves. Organic compounds that can utilize quanta at room temperature will provide new developments in the field," Yanagi expects.

Assistant Professor Hitoshi Mizuno says, "As laser oscillation from TPCO crystal shows a specific phenomenon like delayed emission at low excitation energy, further applications such as devices that temporarily record optical information can be expected."

Interviewed by Yoshinori Sakaguchi


Luminescence from impuritydoped semiconductor nanoparticles.

More information about the group's research can be found at https://mswebs.naist.jp/english/courses/list/labo_01.html

IMPACT

Organic Electronics

Prof. Masakazu Nakamura

Developing a new field of electronics with flexible organic semiconductors

Electronics for any surface

Research and development using soft organic compounds as materials for next-generation electronics has entered the practical stage. Bendable high-definition organic electroluminescence displays have been commercially manufactured, and the practical use of organic thin-film solar cells and organic transistors is also underway. Organic materials exhibit unique characteristics against their counterparts, such as silicon, including being lightweight, flexible, and enabling the manufacturing of large-area devices using low-cost printing techniques. The performance of organic devices has been markedly improved by the scientists' efforts to utilize the characteristics of organic molecules.

The Organic Electronics Laboratory is researching a range of themes, predominantly on organic devices that generate electrical power from the surrounding environment. Studies are being conducted from multiple perspectives, such as condensed matter physics, electronic engineering, surface science, and materials chemistry. The Laboratory is tackling various themes from the basics to applications while focusing on the fundamental understanding of the inside of phenomena. Their initiatives include the development of the world's only one instrument that can analyze the nanoscale distribution of electric potential in a material in which electric current flows and also the use of theoretical calculations for analyzing unmeasurable parameters of the materials.

Professor Masakazu Nakamura says, "I have continually conducted studies to elucidate various interactions in organic materials and their applications, keeping in mind that we can enrich our lives by adding the functions of electronics to the surface of various objects (any surface), such as electronic devices that can be folded like paper and power-generating clothes." The current application research is directed to organic thermoelectric materials, next-generation plastic solar cells, and super-flexible organic logic circuits.

Converting exhaust heat into electric energy

The aim of studying organic thermoelectric materials is to collect exhaust heat from the living environment and the human body and convert it into electric energy, using a phenomenon called the Seebeck effect, in which a temperature difference in the materials generates an electromotive force and thus a current in a circuit. Typically, when the Seebeck coefficient and electrical conductivity are higher and the thermal conductivity is lower, the efficiency becomes higher.

Regarding this effect, Nakamura's group encountered a significant discovery. A fullerene film with sufficiently increased purity exhibited a giant Seebeck effect, generating a high voltage that is approximately 100-fold the conventional theoretical value. Later, a similar phenomenon was found with many other organic small-molecule semiconductors; however, this is not explainable by the conventional theory of inorganic materials. When it is practically implemented, a thermoelectric converter with an extremely simple structure, reminiscent of that of a dry cell, can be realized, in which the flexible organic thermoelectric material is sandwiched by two electrodes. "A unique nature of organic solid such that the molecules are condensed by a weaker interaction than inorganic materials might be related to the novel phenomenon," Nakamura explains.

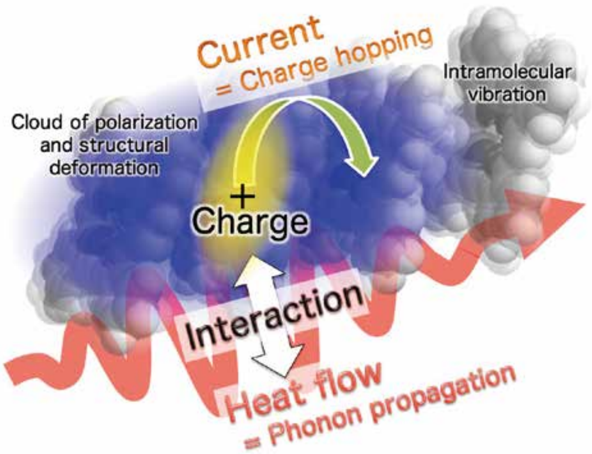
One of the nanocarbon materials called carbon nanotubes (CNTs) has the issue of extremely high thermal conductivity; however, Nakamura's group has also succeeded in developing a nanocomposite material that inhibits the thermal conductivity to as low as 1/1,000 by adding a special protein in between CNTs. Furthermore, a study on "power-generating clothes" is underway, in which threads are fabricated with CNTs and sewn into the fabric to make clothes that generate electricity using body heat. "The organic thermoelectric materials can exert their strength by developing them such as not to aim at the champion data on conversion efficiency but rather to prioritize their usability," Nakamura says.

Solar cells made of "plastic"

Plastic solar cells are fabricated by mixing two types of organic semiconductor materials called conjugated polymers that carry either a positive or a negative charge and dropping their solution onto a transparent electrode to form a thin film. By putting another electrode on the other side, they absorb light and generate electricity. Plastic solar cells can be fabricated with a low-cost process and are usable even when attached to a curved wall surface. Furthermore, they can absorb light of different wavelengths depending on the types of conjugated polymers used. Although their practical use has been promoted due to their superior characteristics, the quantitative understanding of the photocarrier generation/recombination/transport mechanisms required for further technological advancement has not yet been achieved.

Associate Professor Hiroaki Benten says, "The conjugated polymer layer is thin (100 nm), and the internal structure that determines the power-generation performance is even smaller. Therefore, we are using original approaches, such as visualizing various local functions using the cantilever tip of a scanning probe microscope (SPM) as a nanoelectrode to examine the factors that determine the performance. The photoelectric conversion is deeply related to how the polymers are mixed, and we aim to clarify the concealed nanostructures and mechanisms."

Transistors are essential for almost all kind of electronic circuits and this simple device has been blended in our lifestyle in an indistinguishable manner. We use conjugated polymers as a next-generation semiconductor for transistors because of their unprecedented flexibility and relatively high carrier mobility along orientation direction of the polymer backbone when it is aligned. "We are developing such fabrication methods that can be print large-area thin films of oriented conjugated polymers to produce high-performance super-flexible electronic circuits," Nakamura says.



Schematic illustration explaining the mechanism of the Giant Seebeck effect in organic semiconductors which is discovered in the NAIST Organic Electronics Laboratory.

"My research started in the field of inorganic semiconductors based on applied physics. Unlike such inorganic materials, however, organic semiconductors show a semiconducting property even in one molecular unit. Desired functions can be freely tailored by combining molecules as building blocks to form various structures, piling up heterologous molecules, or allowing them to be self-organized. I was attracted to these functions," Nakamura says. His motto is, "research begins from analyzing and measuring materials to understand their properties," and he has developed many unique instruments for characterizations. "Many staff members from different fields work together at my laboratory and proceed with multidisciplinary integrated studies, and this is an advantage of NAIST, which is a research-oriented graduate university that enables such a fusion," he explains.

Interviewed by Yoshinori Sakaguchi

More information about the group's research can be found at https://mswebs.naist.jp/english/courses/list/labo_10.html

Photonic Device Science
Prof. Jun Ohta

Miniaturized infrared cameras take colored photos of the eye

Look into one's eye and you might be able to see their soul. Or at least you can see signs of a stroke or diabetes. By looking at the blood vessels in the eyes, doctors can tell a lot about a person's health. This can be done using fundus photography, which has been around for almost two centuries and is the standard imaging tool used by ophthalmologists. However, for many, especially the poor, traveling to a clinic is not practical. Researchers at NAIST, in partnership with scientists at the University of Tokyo, have devised a new fundus camera small enough to fit on a smartphone that could get around this problem. The study was described at the 2018 IEEE Symposium on VLSI Technology this month.

NAIST Professor Jun Ohta is researching the interface of photonic materials and biomedical treatments for the eye.

"We study photonic devices for biomedical uses. One of our goals is retinal prosthesis to restore vision. We work on highly sensitive imaging sensors for diagnostics of the eye," he says.

When taking a photo of the fundus, the camera must align itself with the path of light that travels through the retina to the back of the eye. The eye, however, makes regular and rapid movements, constantly changing this path. To resolve this problem, the new camera described at the symposium achieves 1000 images/s.

Another challenge when imaging the fundus is the wavelengths of light detected by the camera. To take a clear fundus image, a strong flush light must be introduced inside an eye through a pupil because it is completely dark inside the eye.

For this second problem, the researchers modified CMOS cameras. The cameras use microelectronics technology to acquire color images by using three kinds of invisible light or near infrared light. The new module was developed on a miniaturized sensor and incorporates three near infrared filters. These filters acquire three signals that can be given a red, green and blue value to generate a color photograph of the eye while using near infrared light that is not sensed.

Importantly, at 2.3 mm^2 in size, the module is small enough to be mounted on a smartphone without compromising the power necessary for capturing highly detailed images with which a user can take a fundus image by him/herself. Ohta imagines a future where patients can be diagnosed with nothing more than the phone in their pocket.

"People may be able to take a picture of their eye by themselves and know the status of their health from the fundus image. This could open the door for a personal healthcare system using fundus images. In addition, they could send it to a doctor over the internet. For people in countries like Japan perhaps, visiting an ophthalmologist is not difficult. However, in many countries, it is a real privilege. I want to see our technology improve people's health globally," he says.

Fundus image taken by portable near-infrared fundus camera.

Reference

Sumi, H., Takehara, H., Miyazaki, S., Shirahige, D., Sasagawa, K., Tokuda, T., Watanabe, Y., Kishi, N., Ohta, J. & Ishikawa, M. 2018. Next-generation fundus camera with full color image acquisition in 0-lx visible light by 1.12-micron square pixel, 4K, 30-fps BSI CMOS image sensor with advanced NIR multi-spectral imaging system. *2018 IEEE Symposium on VLSI Technology*.

More information about the group's research can be found at https://mswebs.naist.jp/english/courses/list/labo_03.html

Photofunctional Organic Chemistry
Prof. Hiroko Yamada

World's widest graphene nanoribbon promises the next generation of miniaturized electronics

With literally the thickness of one carbon atom and electrical properties that can surpass those of standard semiconductor technologies, graphene nanoribbons promise a new generation of miniaturized electronic devices. The theory, however, remains far ahead of reality, with current graphene nanoribbons falling short of their potential. A new collaborative study seen in *Communications Materials* by a project of CREST, JST Japan including NAIST, Fujitsu Laboratories Ltd. and Fujitsu Ltd., and the University of Tokyo reports the first ever 17-carbon wide graphene nanoribbon and confirms it has the smallest bandgap seen to date among known graphene nanoribbons prepared by a bottom-up manner.

Large-scale integrated circuits (LSIs) that use silicon semiconductors are used in a wide range of electronic devices, anywhere from computers to smartphones. They are actually supporting our lives and almost everything else these days. However, although LSIs have improved device performance by reducing the size of the devices, LSI miniaturization is approaching its limit. At the same time, commercial demand continues to put pressure on companies to make higher performing smartphones at smaller sizes, while industry pressure is demanding large-scale manufacturing with smaller equipment.

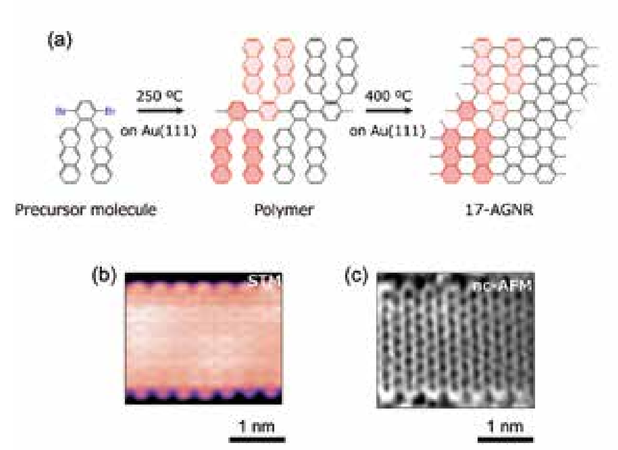
"Other methods and/or materials are definitely needed to solve these problems," says the group leader Dr. Shintaro Sato, Fujitsu Ltd.

"Silicon semiconductors are giving us better performance at smaller sizes. However, we are reaching the limit in how small we can make devices. Thus, we have high expectations for the performance of graphene nanoribbons, which have semi-conducting properties that are only one atom thick – a 2D material," he notes.

Graphene nanoribbons are honeycomb-like structures and, compared to graphene and carbon nanotubes, are the lesser known carbon-based semiconductor family member. Graphene nanoribbons exhibit unique electronic and magnetic properties that do not appear in two-dimensional graphene.

"Interestingly, the electronic and magnetic properties of graphene nanoribbons are widely tuned as a function of the width and edge structure." says Professor Hiroko Yamada at NAIST.

Armchair-type graphene nanoribbons, which are promising type of nanoribbon for device application, display width-dependent band gap. They can be classified into three subfamilies (3p, 3p + 1, 3p + 2), their band gaps being inversely proportional to the width of those families. Basically, wider armchair-edge graphene nanoribbons belonging to the 3p + 2 subfamily have the smallest bandgaps among different graphene nanoribbons, having considerable potential to be exploited in GNR-based devices. So far, 13-armchair graphene nanoribbons belonging to the 3p + 1 subfamily with a band gap of more than 1 eV have been reported, but Sato, Yamada and colleagues show the synthesis of a 17-graphene nanoribbon belonging to the 3p + 2 subfamily, which have even smaller bandgaps.



(a) Bottom-up synthesis scheme of 17-AGNR on Au(111), (b) high-resolution STM image, and (c) nc-AFM image of 17-AGNR.

The graphene nanoribbon synthesis was based on the bottom-up approach, called "on-surface synthesis," and a dibromobenzene-based molecule was used as a precursor for on-surface graphene nanoribbon synthesis.

"There are many methods to synthesize graphene nanoribbons, but to produce atomically precise graphene nanoribbons, we decided to use the bottom-up approach. The important point is that the structure of the precursor can define the ultimate structure of graphene nanoribbons if we use the bottom-up approach," explains NAIST's Dr. Hironobu Hayashi, who also contributed to the study.

Scanning tunnel microscopy and spectroscopy by Dr. Junichi Yamaguchi at Fujitsu. Ltd. and non-contact atomic force microscopy by Dr. Akitoshi Shiotari and Professor Yoshiaki Sugimoto at the University of Tokyo confirmed the atomic and electronic structure of the acquired 17-armchair graphene nanoribbons. Additionally, the experimentally obtained bandgap of 17-armchair graphene nanoribbons was found to be 0.6 eV, and this is the first demonstration of the synthesis of graphene nanoribbons having a band gap smaller than 1 eV in a controlled manner.

"We expect these 17-carbon wide graphene nanoribbons to pave the way for new GNR-based electronic devices," says Sato.

Reference

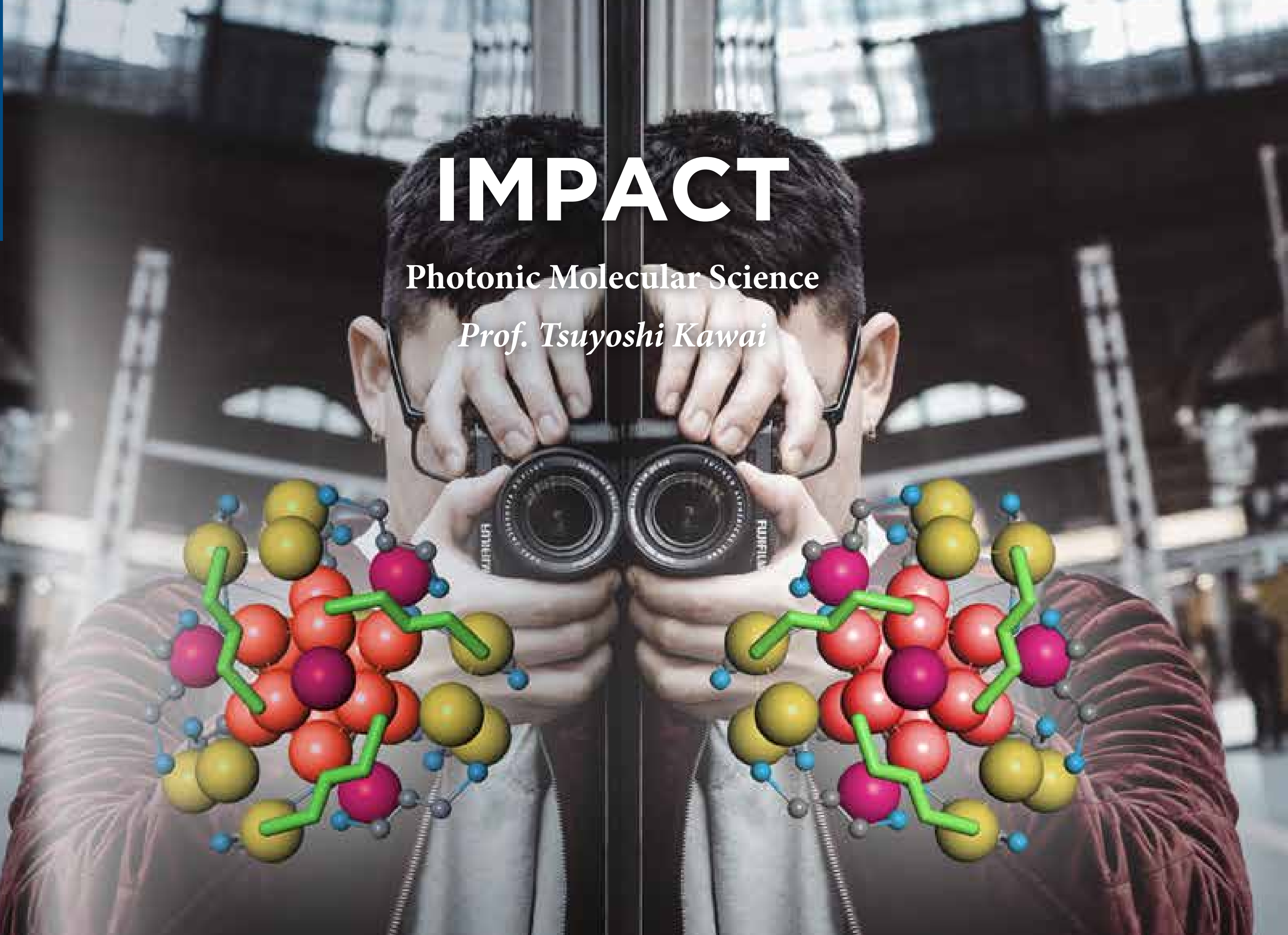
Yamaguchi, J., Hayashi, H., Jippo, H., Shiotari, A., Ohtomo, M., Sakakura, M., Hieda, N., Aratani, N., Ohfuchi, M., Sugimoto, Y., Yamada, H. & Sato, S. 2020. Small bandgap features achieved in atomically precise 17-atom-wide armchair-edged graphene nanoribbons. *Communications Materials*, 1, 36.

More information about the group's research can be found https://mswebs.naist.jp/english/courses/list/labo_08.html

IMPACT

Photonic Molecular Science

Prof. Tsuyoshi Kawai



Skillfully utilizing the power of light and heat to actualize next-generation high-performance molecules

More sensitive than the human eye

With the advancement in sophisticated information systems, energy-saving, and the use of renewable energy, expectations for developing new high-performance materials are increasing. The Photonic Molecular Science Laboratory is staying ahead of the curve and expanding its research themes, such as photochromic molecules whose molecular structure changes reversibly with light irradiation and materials that convert exhaust heat into electricity.

Professor Tsuyoshi Kawai talks about photochromic molecules, which are the basis of his research, saying, "The retina of the human eye has optical sensor molecules called the retinal, and its efficiency in reacting to photons (quantum yield) is as high as 65%. This is about twice higher than reptiles and has been essential for our ancestors to survive at the age of dinosaur. We aim to synthesize organic molecules with better efficiency."

Based on the molecular structure and other properties of the retinal, Kawai's group found that fluctuations in the diverse structures (referred to as "conformation") of artificial photochromic molecules result in the low efficiency, and achieved a high efficiency of 100% by fixing them to the planar structure through the method of molecular engineering. They claim first "photon-quantitative reaction". By expanding this molecular concept for practical functionality, they developed a highly sensitive photoacid generator. For example, semiconductor processing requires a reaction between a photosensitive material (resist) and an acid to transcript a circuit pattern. Such an acid could be yielded with light with an efficiency of approximately 70%, which is twice as efficient as the conventional materials. "Beyond the classic photoacid generators, our latest photoacid generator release no conventional acids but non-protic Lewis acids. We developed 'Photo-Lewis Acid Generator, PLAG' as the state-of-art photoactive material," Kawai says.

Endless domino reaction

Furthermore, Kawai's group made a discovery that significantly advanced the above study. When addressing the issue that the efficiency to erase color with light conversely decreased to approximately 0.5% as the performance of the coloration improved, they changed their approach to the idea that "when an electric current is applied, and a reaction that extracts an electron from a molecule occurs, the molecular structure changes, and the color disappears." They successfully developed an electrochromic molecule that erases the color with electricity with an efficiency ten times or higher than the ideal current efficiency (100%). When examining the reaction in detail, they discovered that a domino reaction occurred, wherein when one electron was removed, molecules reacted in succession, passing the electron to another. Furthermore, it is believed that this reaction endlessly continues as long as activated molecules are available.

"Approximately 1,000 molecules react with one-electron transfer now. In other words, the number of transferred electrons amplifies a reaction by 1,000 times or more, and the color visibly changes and becomes identifiable. For example, the color fading is triggered by week sky-light and even X-ray radiation of small dosage such as those at aircraft," Kawai explains. "Although studies on molecular materials reacting by light are progressing, they still only used 1% of the molecules' potential. I want to take on even more challenges for future manufacturing, sensing and energy applications," Kawai says.

The hazardous radiations such as Ultra-Violet and X-ray oxidative triggers the color-changing cascade of new dyes for 1,000 times.

Selectively manufacturing nanoparticles

Associate Professor Takuya Nakashima's theme concerns the field wherein metals and semiconductors exhibit superior characteristics by fabricating nanometer-sized crystals (nanoparticles). In the natural world, some minerals form two types of optical isomers, in which atoms are arranged in a clockwise or counterclockwise manner similar to a mirror image. Nakashima discovered a mechanism to selectively synthesize a crystal in either direction for the first time. In a study on the mineral mercury sulfide (HgS, cinnabar), he used an amino acid cysteine derivative (N-methyl-L-cysteine), an optically pure isomer, interacting with HgS. HgS selected the lattice structure with a counterclockwise arrangement. He was also able to prepare a crystal with a clockwise arrangement by changing the preparation condition. "Those asymmetric nanoparticles can be used as an asymmetric catalyst stimulating the reaction with a stereoselectivity," Nakashima explains. Such a mineral nanoparticle can also serve as material for new electronics and could be the key to addressing why more naturally occurring amino acids are left-handed.

"I am interested in chirality and will continue to conduct studies in this direction. I want to find basic characteristics that can be applied widely. My principle is to work through a mystery until it is understood," he says.

Light and durable thermoelectric conversion sheet

Assistant Professor Yoshiyuki Nonoguchi studies thermoelectric power generation to convert the temperature difference resulting from heat energy, such as exhaust heat, into electric energy. As the material used for this device requires high durability, he spread a carbon material called carbon nanotube (CNT), which is light and durable, to prepare a sheet of the material. Furthermore, when a substance containing positive sodium ions (Na^+), such as salt (NaCl), was added to a clathrate, negatively-charged electrons were effectively injected into the CNT. Consequently, the output property was improved approximately three-fold compared with the conventional method, and this performance was maintained at a relatively high temperature of 150 °C for over a month.

"The developed thermoelectric sheet has advanced to the demonstration experiment level. I want to make a breakthrough in IoT related devices, such as a power supply for sensors that automatically measure temperatures and humidity and transmits data, and in the health care and environmental power generation fields," Nonoguchi says.

Manipulating emission lifetime

Carbon materials with a ball-like or bowl-like curved skeleton, such as fullerenes, have a π-conjugated bond where the alternating double and single C–C bond share electrons, and their π-conjugation is distorted. Therefore, they exhibit characteristics properties such as strong emission and electrical conductivity, gaining research attention as a next-generation nanomaterial.

Assistant Professor Mihoko Yamada has researched on a compound called a metal complex by coupling metals to such curved organic molecules, and have been investigating their light-emitting property that is different from that of planar molecules. "A molecule with a curved surface has front and back sides owing to dents. The emission lifetime changes, depending on the side on which the organic substituent group is bonded," Yamada explains. Currently, she is investigating complexes with rare metals, including iridium, whose luminosity is large. "If we can control the fluorescence lifetime, the complex can be used as a catalyst that promotes a reaction by light. I intend to pursue this research with full commitment," she says.

Interviewed by Yoshinori Sakaguchi

More information about the group's research can be found at https://mswebs.naist.jp/english/courses/list/labo_07.html

Photonic Molecular Science
Prof. Tsuyoshi Kawai

Light burns with new acids

Researchers at NAIST report a photo-acid generator (PAG) that generates Lewis acids with a quantum yield that is vastly superior to PAGs that generate Brønsted acids. The new PAG is based on photo-chemical 6π-percyclization and is demonstrated to initiate the polymerization of epoxy monomers and catalyze Mukaiyama-aldol reactions.

PAGs are chemical species that release strong acids, either in solution or solid state, upon exposure to light. These acids can then be used to activate various biological and photo-polymer systems.

Most PAGs form Brønsted acids and do so with great efficiency. However, Brønsted acids limit options in terms of substrates and reaction mechanisms, particularly for organic synthesis when compared to Lewis acids. Some of chemical substances are easily decomposed with Brønsted acids but not with Lewis acids.

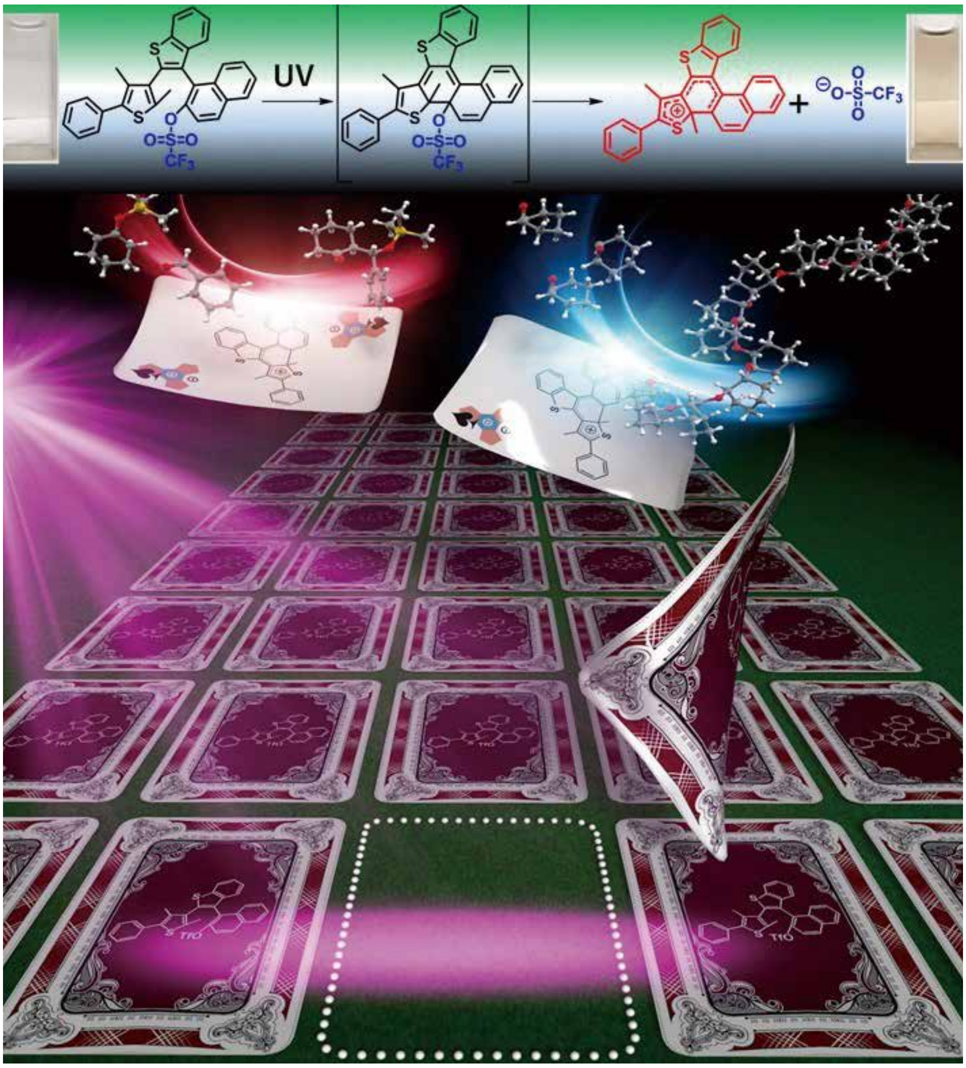
"Lewis acid catalysts are much useful but often unstable and require careful introduction to reaction systems. Preferably, we would induce Lewis acid catalysts remotely, like optical exposure," explains NAIST Associate Professor Takuya Nakashima, one of the lead researchers in the project.

The new PAG depends on the addition of a triflate group to terarylene. The triflate group showed a high propensity to release from the terarylene upon exposure to UV light.

"We have focused on terarylene because its very high light-sensitivity, compatibility into polymer films and no oxygen/moisture inhibition. We have also found non-linear responses that can be used to greatly enhance the light-sensitivity," says NAIST Professor Tsuyoshi Kawai, another lead researcher. Indeed, the photo-chemical quantum yield was 0.5, which is much higher than standard PAGs.

The resulting Lewis acid was generated without any radical intermediate and sustained for more than 100 days. It was then used to initiate the polymerization of epoxy monomers, SU-8, and Mukaiyama-aldol reactions for benzaldehyde and silyl enolates to produce silyl aldols of different stereoisomers, that were not possible with Brønsted acids formed with PAGs.

"This system opens new opportunities for Lewis-acid reactions. It is the first to generate photo-activated Mukaiyama-aldol reactions," says Kawai.



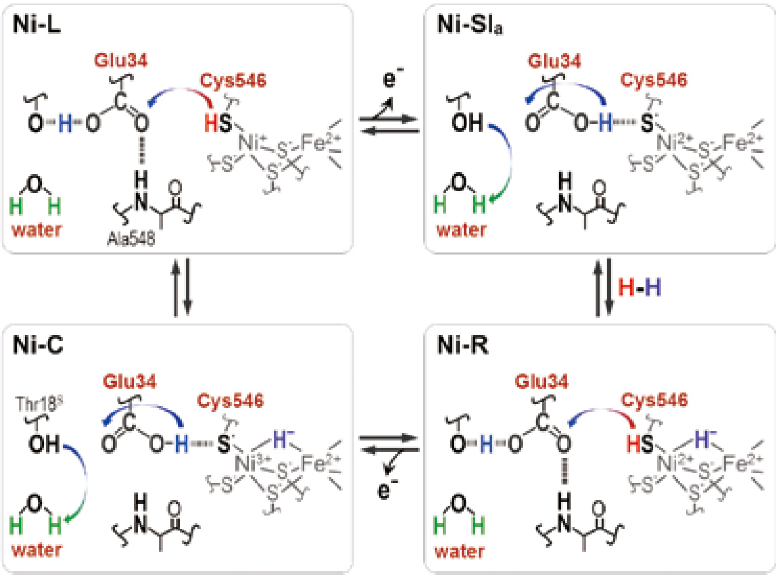
**Light irradiation onto the ambient inert new PLAG generates Lewis Acid as a versatile catalyst.
As the image depicts this process is like flipping a deck of cards and always coming up with the all-mighty card.**

Reference

Mizutsu, R., Asato, R., Martin, CJ., Yamada, M., Nishikawa, Y., Katao, S., Yamada, M., Nakashima, T. & Kawai, T. 2019. Photo-Lewis acid generator based on radical-free 6π photo-cyclization reaction. *Journal of the American Chemical Society*, 141, 20043–20047.

More information about the group's research can be found at https://mswebs.naist.jp/english/courses/list/labo_07.html

Supramolecular Science
Prof. Shun Hirota



Protons are transferred between the NiFe active site and protein surrounding through the Cyt546 and Glu34 residues during the catalytic reaction of [NiFe] hydrogenase.

Microorganisms build the best fuel efficient hydrogen cells

For all the advances technology has made throughout our lives, in many cases it stands behind what nature can do. Ants can carry 5000 times their weight, and spider webs are five times stronger than steel. Fuel efficiency is no different. In a new study seen in *Angewandte Chemie International Edition*, researchers from NAIST report new details on the proton transfer pathway of nickel-iron [NiFe]-hydrogenase using Fourier transfer infrared spectroscopy (FT-IR). This transfer is crucial for the hydrogen metabolism of micro-organisms, and the study gives scientists a better understanding of how to mimic nature in the construction of new biofuel cells.

Hydrogen metabolism is one of the oldest forms of energy production for life and one of the most intensely studied because of its significance in evolution. It has also attracted attention as it is a clean energy source. Among the enzymes responsible for hydrogen metabolism, [NiFe]-hydrogenase is the most abundant and ancient.

Much is known about the enzyme. It reversibly oxidases hydrogen atoms through its Ni-Fe active site, which is surrounded by specific amino acids. However, notes NAIST Professor Shun Hirota, who managed the study, certain fundamentals in the chemical reactions need to be understood before using this nanomachine to design biofuel technologies.

"Hydride and proton coordinate with the Ni-Fe site in the protonation-deprotonation cycle, resulting in four hydrogenase states. But the proton transfer pathway remains unknown," he says.

One reason for the lack of clarity has been an inability to resolve stretching frequencies of different hydrogen bonds. In the new work, Hirota's team, in collaboration with other researchers in Japan and China, solved this problem by observing photoconversions of three hydrogenase states with FT-IR spectra.

Distinct absorbance frequencies revealed that one of the four cysteines, cysteine 546, along with another amino acid, glutamic acid 34, and an ordered water molecule are crucial for the transfer. The scientists used the new information to deduce how the sulfur molecule of cysteine 546 and the acid group in glutamic acid 34 form hydrogen bonds to regulate the hydrogen transport.

"Our results show that cysteine 546 is a proton donor and acceptor in the [Ni-Fe] hydrogenase cycle. They also demonstrate how a low-barrier hydrogen bond for glutamic acid 34 is formed and cleaved during the catalytic cycle," notes Hirota.

Microorganisms have adapted to a wider range of environmental conditions than humans. They can be found in the comfortable climate of our bedrooms to the most hostile environments on earth. Thus, seeing how the [Ni-Fe] site of [Ni-Fe] hydrogenase transfers protons optimally provides a paradigm for researchers seeking to manufacture high efficiency energy catalysts under a host of conditions.

"Life has spent billions of years adapting to energy. We believe it gives us the best model for energy efficiency in the future," says Hirota.

Reference

Tai, H., Nishikawa, K., Higuchi, Y., Mao, Z-w. & Hirota, S. 2019. Cysteine SH and glutamate COOH contributions to [NiFe] hydrogenase proton transfer revealed by highly sensitive FT-IR spectroscopy. *Angewandte Chemie International Edition*, 58, 13285-13290.

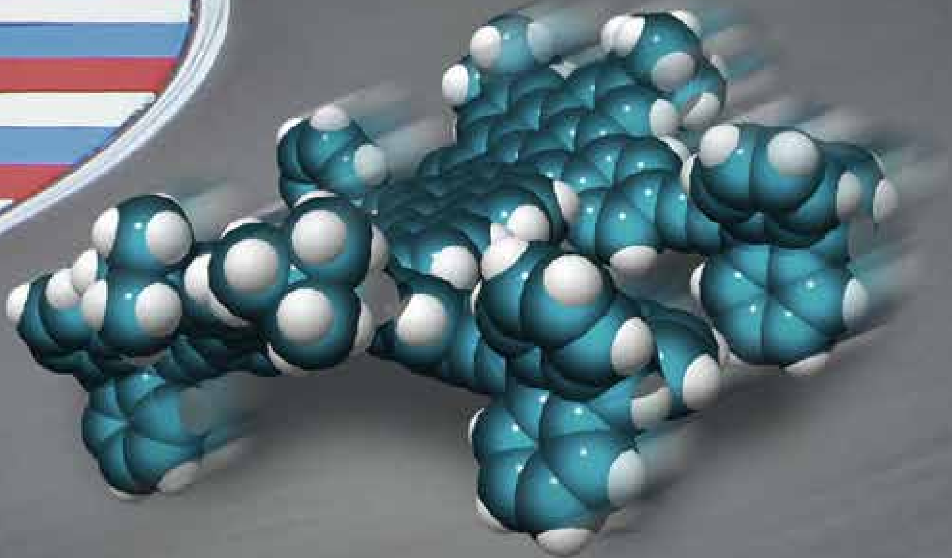
More information about the group's research can be found at https://mswebs.naist.jp/english/courses/list/labo_06.html

IMPACT

Biomimetic and Technomimetic Molecular Science

Prof. Gwénaël Rapenne

Synthesizing moving molecular machines and going beyond the boundaries of nanoworld



Inspired from living organisms and machines

Molecular machine (nanomachine) research to create molecular-level devices that work in the extremely small nanometer (one billionth of a meter) domain is a highly active research area. If one can develop molecules that respond to external stimuli, such as light and electricity, and act like robots, nanotechnological advances beyond the current technological boundaries can be achieved in medicine and industry.

The enzyme ATP synthase is a typical example of a biomolecule serving as a model of a molecular machine. ATP stores and releases energy for vital activities. The lower half of this enzyme is buried and fixed in the biological membrane. Owing to the potential difference inside the membrane, the molecule spins at high speed, similar to a motor, to incessantly produce ATPs.

Professor Gwénaël Rapenne, focusing on the mechanisms underlying such moving molecules,[1] has the ultimate goal of constructing devices using molecular machines. "We choose two approaches to achieve the goal: learning molecular structures from excellent functions of biological molecules and being inspired from machines, such as motors and gears," he explains.

Molecular gears were meshed

Rapenne has been studying the manipulation of molecular machines at the single-molecule level using a scanning tunneling electron microscope. In 2013, he published a molecular motor wherein the direction of rotation was switchable at will[2] depending which part of the molecule receive electrons.

Thereafter, in 2019, he succeeded for the first time in meshing gears of two adjacent propeller-shaped molecules and conveying a rotary movement from one to another.[3] This achievement has opened up the possibility of custom-made molecular-scale factories comprising multiple different molecular machines working together. This was followed by a new train of gears with rotative motions transferred up to three molecules.[4]

Synergy of chemistry and physics

Rapenne studied at Strasbourg University in France and received his Ph.D. in 1998 under Professor Jean-Pierre Sauvage, a Nobel laureate in chemistry for basic research on molecular machines. In 1999, he was appointed by Paul Sabatier University, where he began molecular machine research, specially focusing on single molecular level experiments and attained professorship in 2011. He holds the professorship at NAIST since 2018.

"In France, synergy was achieved via close collaboration in which chemists synthesized the molecules and physicists investigated the principles of molecular movement. At NAIST, I intend to conduct multidirectional studies via collaboration with experts of biomimetics," he says.

In addition, in the International Collaborative Laboratory of NAIST (Toulouse, France), research on the use of photochromic molecules, which change their structure in response to light, as switches for molecular motors is being conducted in collaboration with members of the Tsuyoshi Kawai laboratory. "I have continued molecular machine research for 20 years, and studies have produced results in directions that were unanticipated in the beginning. This may be the best part of the research," says Rapenne.

New functional molecules inspired by living organisms

Associate Professor Kazuma Yasuhara focuses on the role of biological membranes encapsulating cells and maintaining the intracellular environment. He developed an antimicrobial agent that interacts bacteria in the body and destroys their cell membranes to kill them without inducing drug resistance. Based on the molecular structure of a natural antimicrobial peptide that binds and penetrates into bacterial membranes, he designed a simple molecule by employing synthetic molecular frameworks with enhanced antimicrobial activity.[5]

In living membranes, some proteins work together with lipid bilayers to exert various functions and have attracted attention as an important class of drug discovery targets. Previously, isolation of membrane proteins without causing structural changes has been challenging. Yasuhara has developed a functional polymer that organizes membrane fragments in several tens of nanometers containing membrane proteins into disk-shaped stable molecular aggregates called "nanodisc."[6] Nanodisc is currently commercially available from Avanti Polar Lipids, a world-wide reagent supplier in the USA.

"Synthetic polymers can partially replicate the superior function of a protein with ingenuity. Molecules are designed and synthesized as well as thoroughly examined including their function. With the motto 'simply pursue what seems interesting,' we have a broad range of chemistry, physics, and biology interests. We pursue interdisciplinary research with our students," says Yasuhara.

Molecular memory

Assistant Professor Toshio Nishino is interested in the construction of molecular machines and their application for molecular memories. His research aims to realize ultra-high density, high-speed molecular memories by integrating molecular machines, each of which can move and express the digital signals 0 and 1.

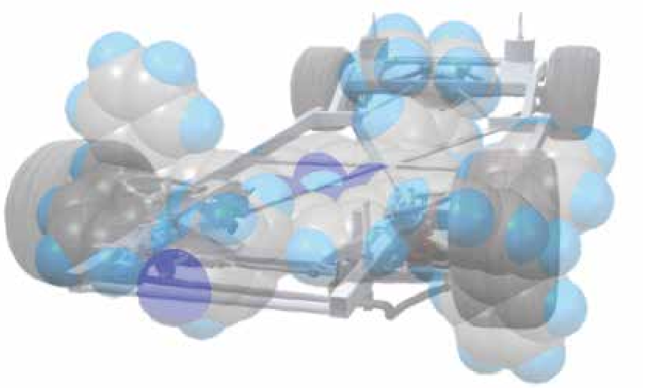
As components, he focuses on double-decker complexes, which have a sandwich-like structure composed of a rare earth metal ion and two macrocyclic ligands, such as porphyrins and phthalocyanines. "Ideally, I intend to create a molecular memory that works above the temperature of liquid nitrogen (approximately -196°C below freezing)," says Nishino.

Biological membrane-like porous materials

Assistant Professor Kenichiro Omoto is developing an entirely new porous material composed of lipid bilayers forming biological membranes. Although conventional solid-state porous materials, such as activated carbon- and zeolite-based materials, are composed of rigid backbone, his target material is characterized by the use of soft lipid bilayers as the wall which can bind biopolymers with complex structures, such as membrane proteins, without losing their activity. "I intend to develop porous materials that allow proteins to work in pores. Such porous materials are expected to work as catalysts and ion conductors utilizing functions of biomolecules," says Omoto.

Aiming at winning nanocar race

Rapenne is one of the founder of the "Nanocar Race," in which single-molecule cars compete to promote and disseminate molecular machine research. He participated in the first race in 2017 as a team member of the Center for Materials Elaboration and Structural Studies (CEMES), a French national research institute. He will participate in the second race to be held in the spring of 2022 as the leader of the NAIST-CEMES joint team. After joining the NAIST, they designed and synthesized a new nanocar[7] called "Blue Buggy". "We are fully prepared for this race, and I believe this time we can win," he says. The design of the molecules has been long thought. "To hope to win the race, you have to be fast but you need also to keep the control. The design is then a compromise between opposite requirements," he continues. The nanocar consists of a planar chassis made from porphyrin long of 2 nm and surrounded by four wheels to minimize contact with the ground and two legs which are able to donate or accept electron making the nanocar dipolar.



The Blue Buggy.

Interviewed by Yoshinori Sakaguchi

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More information about the group's research can be found at https://mswebs.naist.jp/english/courses/list/labo_13.html

Biomimetic and Technomimetic Molecular Science
Prof. Gwénaël Rapenne

A 2 nm sized nanomachine able to spin and transfer its rotational energy

With the celebration of the 50th anniversary of the moon landing this year, it could be argued that the greatest science of the 20th Century was about big machines that could travel the universe. The rise of nanotechnology is suggesting that the 21th Century will be dedicated to much smaller machines that can travel inside the smallest spaces including human cells. Researchers at NAIST in partnership with research teams in the University Paul Sabatier (France) and Professor Saw-Wai Hla in Ohio University (USA), report in *Nature Communications* the latest nanomachine, a propeller that can rotate at will in both clockwise and counterclockwise directions and transfer this motion to another molecule like gears.

Nature has proven exceptional at designing similar machines by using molecules that can convert optical, chemical or electrical energy into interactions with the surface to generate motion. “For many nanomachines, we look at nature as our model. There are many examples of propellers with which organisms move in dynamic environments. Surprisingly, these natural nanomachines take the shape of large-scale propellers,” says NAIST Professor Gwénaël Rapenne, who contributed to the new study.

Consistently, the propeller Rapenne and his colleagues designed consists of three components: three blades each composed of an indazole, a stator consisting of five phenyl groups, and a ruthenium atom that binds to the two and allow the rotation like a ball bearing.

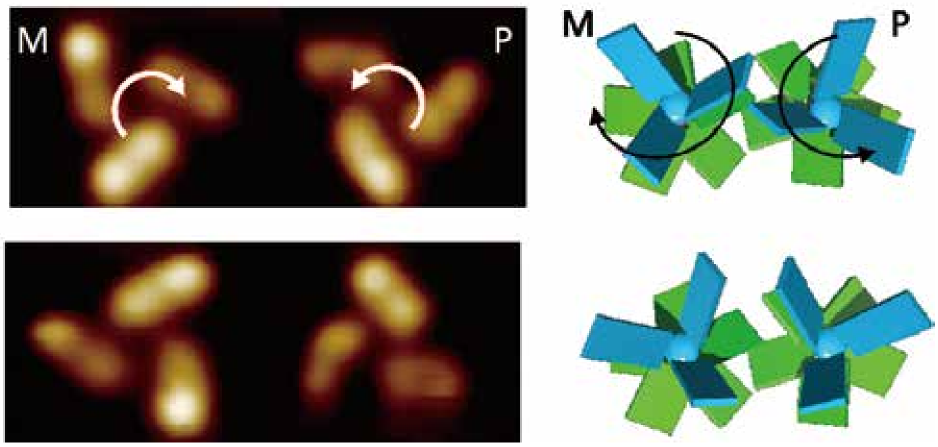
One of the major differences is the conditions in which artificial nanopropellers work. Where natural nanomachines tend to work in environments comfortable for life, artificial nanomachines can work in much harsher conditions. Rapenne demonstrates this point by attaching his machine to a gold surface and observing that some begin swirling at extremely cold temperatures (near -200 ºC). At the same time no propellers move at -275 ºC, verifying their ability to convert thermal energy into movement.

The propellers also showed the capacity to rotate in different directions in a controlled manner, but never to switch directions. This was the result of how the propeller was attached to the gold surface, which caused a slight tilt in the stator. The direction of the tilt determined the direction of the spin. This feature is reminiscent to macroscopic propellers we see in the real world.

“The stator acts as a ratchet-shaped gear that imposes a unidirectional rotation,” notes Rapenne.

This is not the first time Rapenne has used gold to prove the capabilities of his nanomachines. Two years ago, he and colleagues organized the world’s first nanocar competition using gold tracks. While he does not expect to follow that effort with the first nano single propeller competition, he does believe the new machines will serve an important purpose in the nanoworld.

“Our propellers can displace nearby molecules, showing that they can be used to move molecular loads for faster transfer of energy or information,” he says.



Two molecular gears in action: Rotation of the first one is transferred to the next one.

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More information about the group’s research can be found at https://mswebs.naist.jp/english/courses/list/labo_13.html

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)

The 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 for 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 transdisciplinary education and cultural diversity, and (5) reorganizing its three graduate schools into a single entity with a view to establishing new, flexible research groups.

The Graduate School of Science and Technology

NAIST's Guiding Concept: Education through Research

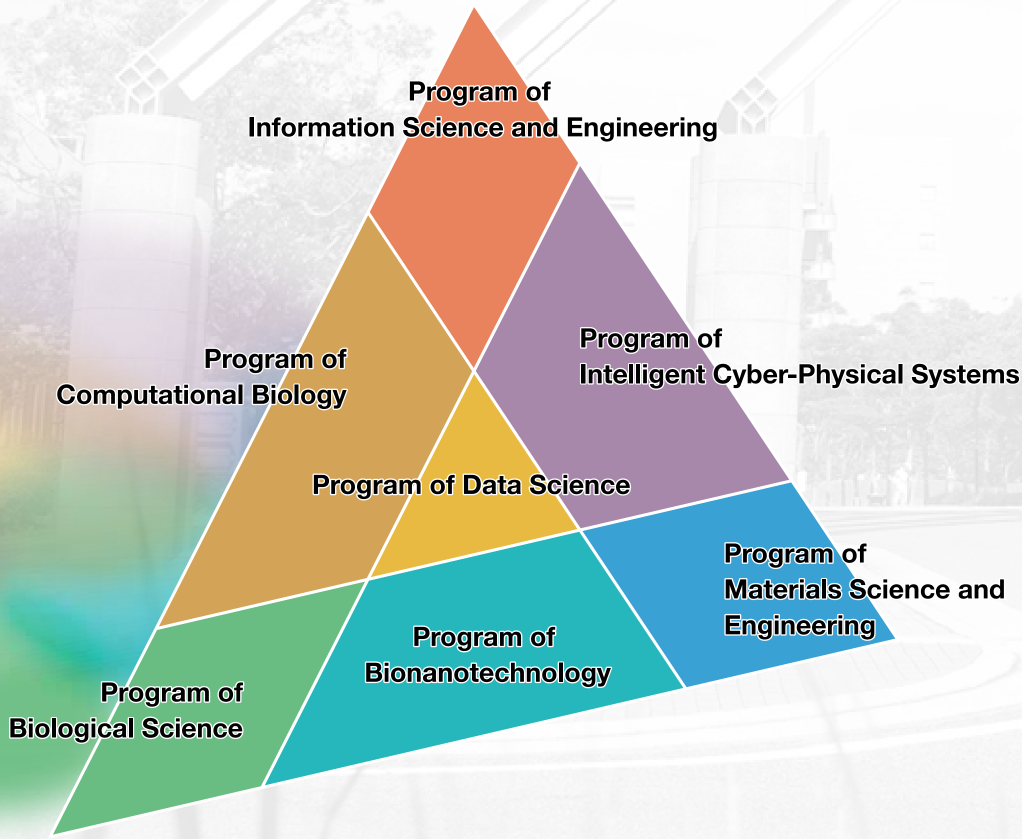
NAIST pursues research and education in an environment of interdisciplinary and international cooperation. Students and researchers have access to world-class facilities in an exciting atmosphere promoting individual achievements, collaboration across traditional research fields, and flexible course curricula.

Research-Focused Environment:
NAIST was established without undergraduate programs to allow the faculty to commit themselves towards achieving superior research results to lead their respective fields.

Research-Based Education:
Through the research of our accomplished faculty and collaboration with industry and academic partner institutions, NAIST's students learn both in traditional settings and through hands-on experience at the forefronts of science and technology.

Multidisciplinary-focused Educational Programs

The seven Education Programs of the Graduate School of Science and Technology span the three original fields of research at NAIST (information, biological and materials sciences) and include the developing interdisciplinary fields that emerge independent of traditional academic divisions to pursue current trends in science and technology. All laboratories belong to one or more Education Program and students choose the type of degree the will pursue depending on their studies and the focus of their research.



Program of Information Science and Engineering

A focused information science program which fosters students able to support today's dynamic advanced information society, implementing further achievements in information science in diverse fields and their wide-spread application. This program enriches students' broad interdisciplinary vision and cultivates cutting-edge specialized knowledge and skills covering computer hardware, software and information network technology; computer/human interaction and media technology; and various systems to fully utilize robotics and computer technology.

Program of Computational Biology

An interdisciplinary information science and bioscience program which fosters students who are able to collect and analyze the huge amounts of data related to the phenomena of life, such as medical imaging data and the enormous amounts of bio-information concerning genes, proteins, and metabolism, while fostering persons who will undertake the development of these technologies.

Program of Biological Science

A focused biological science program which fosters students able to facilitate societal development and environmental protection through activities concerning areas such as the environment, energy, food supply, resources, life quality and health maintenance, within industry and public institutions foreign/domestic. This program enhances students' knowledge and cultivate expertise in areas from the basic principles of the phenomena of life to the biodiversity found at the molecular, cellular and individual level of plants, animals and microorganisms.

Program of Bionanotechnology

An interdisciplinary bioscience and materials science program which fosters students who pursue new trends in bioscience based on materials science understanding, and cultivates abilities necessary for the creation of novel functional materials to contribute to the future of society, including development of pharmaceuticals and medical engineering materials, development of new polymers which imitate biological functions, development of novel compounds to increase farming productivity, and exploration of new cellular engineering to support regenerative medicine through an understanding of the molecular foundation of biogenic activity.

Program of Materials Science and Engineering

A focused materials science program which fosters students with the foundational knowledge of materials science and advanced knowledge to fully utilize their expertise through a program spanning solid state physics, device engineering, molecular chemistry, polymeric materials and bionano-engineering, and undertake next generation science and technology to maintain affluent living and support societal development.

Program of Intelligent Cyber-Physical Systems

An interdisciplinary materials and information science program which fosters students able to holistically grasp areas including functional material design, devices with new functions and real-world sensing, analytical device design, system structuring to fully utilize analyzation results, and machine and robot control systems, who have specific, specialized knowledge and experience to support the social systems of this IoT era.

Program of Data Science

An interdisciplinary information, biological and materials science program which fosters human resources with a wide range of expertise in data-driven and AI-driven sciences related to information, biological, and materials science who will find hidden 'value' and 'truth' through data processing, visualization, and analysis of huge amounts of collected data to contribute to next generation of science and technology, and societal development.

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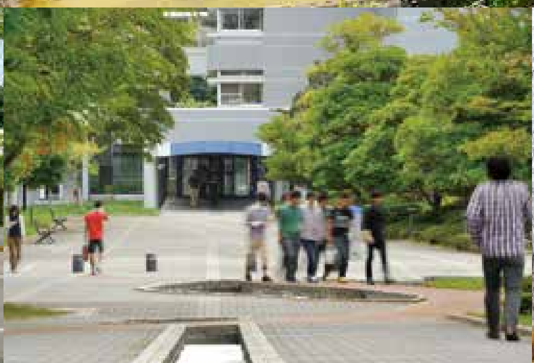




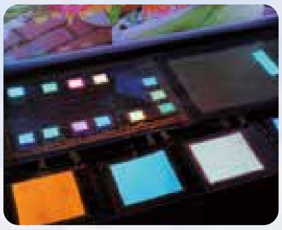



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