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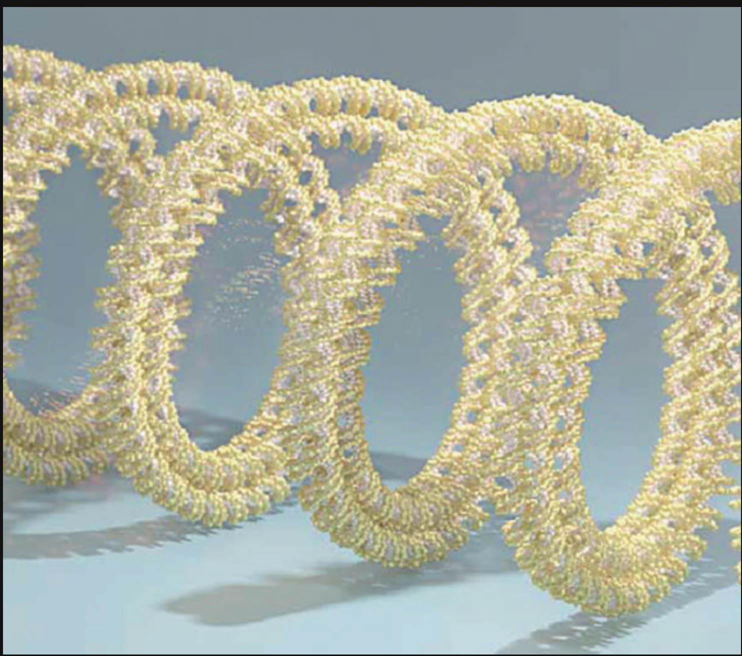
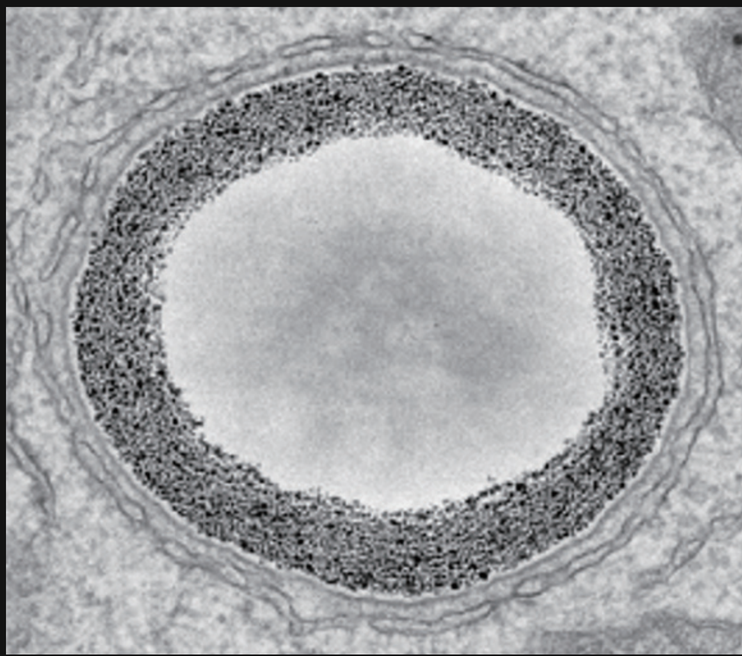
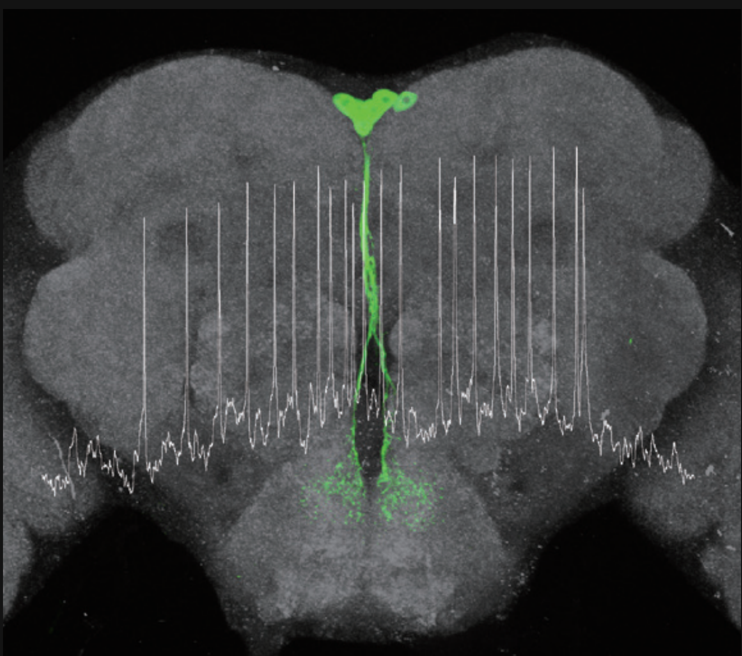
FEATURE Biology Inspired ICT: A Bridge to the Future

Round Table

Exploring the Frontiers of Information and Communications Technology using Biological Systems







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Round Table

Exploring the Frontiers of Information and Communications Technology using Biological Systems


TANAKA Shukichi
Leading the Kobe Frontier Research Center
Director General, Kobe Frontier Research Center, Advanced ICT Research Institute


KOBAYASHI Shouhei
Creating cellular information interface technology
Director of Bio-ICT Laboratory


FURUTA Ken'ya
Building and understanding biological systems
Research Manager, Bio-ICT Laboratory


MATSUDA Atsushi
Visualizing biological spaces at the nanometer level
Research Manager, Bio-ICT Laboratory


KOHATSU So
Exploring the mechanism of operation of the insect brain
Research Manager, Neuro-ICT Laboratory


SAKURAI Akira
Understanding the learning system of neurons
Senior Researcher, Neuro-ICT Laboratory

The origins of information and communication technology (ICT) go back to the start of wireless communication via electronic waves, which evolved to light-based digital communication, leading to the affluent information society of today where substantial information is exchanged via networks. However, a number of issues remain unresolved. For example, the amount of information processed will continue to increase, and the corresponding input of electricity and other sources of energy will become enormous. How should we manage and treat these difficult situations?

Possible solutions can be found in living organisms. Organisms survive in their environment by efficiently adapting themselves using small amounts of energy.

Learning from organisms—the ICT of the future. The present article features an interview with young researchers who are working at the Kobe Frontier Research Center in the Advanced ICT Research Institute to make the best use of biological mechanisms in the most advanced ICT.

First, I would like to talk with Director General Tanaka from the Kobe Frontier Research Center (Kobe FRC). You are conducting research into advanced fundamental technology that is expected to produce groundbreaking discoveries for the next generation. What is the position of the Kobe FRC in the Advanced ICT Research Institute?

TANAKA At our institute, we are conducting research to create innovative ICT technology. In particular, the Kobe FRC mainly undertakes basic research with the aim of creating a new paradigm for information and communication.

For example, given "Beyond 5G" that forms the current mainstream of research and development in ICT, our goal might be "Beyond 6G," or even further technical innovations.

Basic research usually takes a long time to produce the desired deliverables, and I believe important achievements and their social installations cannot be realized without working to "thicken the trunk of research based on the roots of science and harvest the fruit." We have recently been focusing on the creation of a new biotechnology-based paradigm for information and communication. Accordingly, today's interview features topics on this paradigm shift.

Round Table

Opening the Frontiers of Information and Communication Using Biological Systems

The most advanced basic research

What types of research are being conducted by the researchers working here?

KOBAYASHI Our Kobe FRC has two biotechnological laboratories. One is the Bio-ICT Laboratory, for which I am serving as the Director. The other is the Neuro-ICT Laboratory, to which Research Manager Kohatsu and Senior Researcher Sakurai belong. At the Bio-ICT Laboratory, I and my colleagues are working on ICT using biomolecules produced by organisms. Our research focuses on the manipulation of molecular communication for our use as ICT. Specifically, we aim to establish a technology to measure and sense molecular communication performed by organisms. Another aim is to artificially modify biological molecular communication to produce easily operable devices by means of the cellular capacity of information processing and communication.

What is molecular communication?

KOBAYASHI In our body, various forms of information are exchanged via molecules. Hormones secreted in the brain, for example, are transported to various organs to relay information. This exchange of information achieved by molecules is called molecular communication. Molecular information is exchanged in special environments such as our body. To allow its efficient use for ICT, it is important to elucidate the mechanism of this molecular communication and to develop technology to control it. Additionally, this mechanism enables organisms to achieve system control with extremely low levels of energy. Therefore, if we can feedback such knowledge to ICT, we can create an extremely efficient system.

TANAKA The concept of molecular communication for information exchange via molecules emerged around 2008, and research on this has been internationally active just over the past decade.

KOBAYASHI We are now working to develop a technology that controls cellular functions via artificial materials incorporated in the cell, which is the minimum functional unit of organisms, and a fundamental experimental system has just been formed. In talking about research prospects, I plan to realize something like a microrobot that works in ICT environments such as in the body, where molecular communication serves as the major means of information transmission.

FURUTA While Dr. Kobayashi conducts research at the cellular level, we start at the component level for our research. A component as mentioned herein refers to a molecular machine that constitutes cells. An example is a molecular motor. It may be described as an energy converter that converts chemical energy in the body into physical motion and force. It is characterized by extremely high energy efficiency. I want to understand this mechanism and link it to the development of efficient devices.

In this field, recently emerging generative artificial intelligence (generative AI) is accelerating research to allow us to predict protein structures. However, the mechanism behind the “motion” of proteins is not well understood, so I think a more extensive understanding of this aspect will show us how to design energy conversion functionality.

MATSUDA An enormous number of molecules are present in organisms, and their density is extremely high, and we are conducting research to view them functioning in real time. Such achievements are expected to resolve some of the long-standing mysteries in bio-ICT that have yet to be uncovered. When visualizing target biological molecules, we usually use a fluorescence microscope, but this does not allow us to watch living cells in high resolution in real time. We are working hard on this issue.

We are developing a new technology known as computational adaptive optics, which enables us to clearly observe cells in a cell population that normally do not come into focus, as they are located deep in the cell population. The molecular motor under development by Dr. Furuta measures less than 100 nanometers, and our goal for the time being is to achieve at least this level of visibility. I want to further increase resolution to enable us to observe the motion of the molecular motor in real time.

KOHATSU In our project, we are investigating the functions of the brain of the fruit fly *Drosophila* melanogaster. The field of biomimicry has long focused on the body structures of an organism and the physical properties of biomaterials, but our interest is in information processing in the insect brain. The insect brain is capable of generating a wide variety of behaviors relying on limited information that can be processed by its limited computational resources. For example, fruit flies use visual information captured by their compound eyes, which consist of only 1,600 optical units (“pixels”) in total, for motor control such as flight, walking and escaping from threats. We are trying to extract the information processing algorithm that underlies such vision-dependent behaviors in the small brain of an insect, and apply it to information processing in small devices such as Internet-of-Things sensors and microrobots.

SAKURAI My research interests include the mechanisms of learning and memory utilized by organisms. We have been exploring phenomena that occur at the molecular level in brain neurons during learning, using Drosophila as an experimental model. We have found that neurons with the role of governing a given behavior form new linkages with otherwise nonlinked neurons to form memory. Thus, for the first time, we have become able to analyze in real time the process of formation of new linkages between neurons as the entity behind learning and memory in the brain.

TANAKA Research on the insect brain represents one of our important themes. Until recently, what was happening at the synaptic and molecular level in the brain was unknown. However, recent advances in experimental technology have increasingly enabled us to topically observe phenomena that occur in the brain at the level of a single synapse in real time. Our research is positioned at the edge of such a breakthrough. Attempts have commenced to analyze and model brain functions by linking acquired information and fly dynamics to establish new principles of information processing.

Although there have been rapid advances in AI research and development, the present mainstream approach cannot avoid substantial resource consumption, and I think it will be difficult to create AI that functions in an equivalent manner to a biological brain without resolving this issue. What happens in the biological brain? To answer this question, it is necessary to thoroughly understand the fundamentals. We believe we can create a major paradigm shift by incorporating the biological mechanism of information understanding therein.

KOBE Frontier Research Center
The KOBE Frontier Research Center consists of five laboratories: the Superconductive ICT Device Laboratory, Nano-scale Functional Assembly ICT Laboratory, Bio-ICT Laboratory, Neuro-ICT Laboratory, and DUV ICT Device Laboratory.

Research goal

What is your future goal?

KOBAYASHI We aim to create a technology using single cells to manipulate other cells and control their population as a whole. If we can move cells as desired to arrange them in place, we will be able to apply them in specific ways in the molecular communication environment. To this end, in addition to using natural cells as they are, it is useful to manipulate living cells in combination with artificial materials.

FURUTA In talking about devices to aid weak vision, hearing, or other sensations, it matters how power sources are secured. A large and heavy battery cannot always be carried, and worrying about battery depletion causes a great deal of stress. Hence, we want to create devices that derive their electric power from inside the body, like those that operate as we eat meals, and those that operate even better if we eat delicious meals (laughter).

MATSUDA I want to develop a technology that produces stereoscopic images in high resolution, including depth, from a single photograph. At present, clear images in high resolution are acquired from a large amount of image data through complex processes, and I want to achieve it in a single step.

KOHATSU Insects use their tiny brains to recognize complex environments and perform adaptive behavior, but the mechanism involved is not fully understood. I hope that by applying the mechanism of information processing in the insect brain, we will be able to produce a highly efficient information processing system, such as an autonomous microrobot that operates on very limited power.

SAKURAI The mathematical model used in current AI (McCulloch-Pitts Model 1943) is based on the mechanisms of production and transmission of electrical signals in neurons. On the other hand, it is poorly understood as to what is happening in the neurons during learning. One of the keys to create new AI may reside in the answer to this question.

TANAKA All the young researchers here will carry forward the future of our institute.

They have their own ideas and technical expertise that are unique to them. I hope they will maximize such talent to conduct research and development that aims to realize a completely new paradigm of ICT using biological mechanisms as leverage.

Research and Development of Molecular Communication Control Technology using Biological-non-biological Hybrid Devices

KOBAYASHI Shouhei
Director of Bio-ICT Laboratory, Kobe Frontier Research Center, Advanced ICT Research Institute
After completing a doctoral course, Dr. KOBAYASHI joined NICT in 2005. He has been engaged in researches on understanding cellular responses against invading artificial materials.
Ph.D. (Engineering).

Our lifestyles have changed dramatically over the past few years. This is due to the proliferation of various electronic devices such as smartphones, the implementation of measures against COVID-19, and the promotion of work style reform. We now live in an era where an enormous amount of information is generated and used across all aspects of society. As existing information and communications technology (ICT) based on radio waves and light continues to evolve, we face increasingly serious challenges related to information explosion, energy shortages, and other issues. As a new approach to radically addressing these problems, research and development of ICT that takes advantage of the characteristic properties of living organisms and biomaterials has recently gained attention.

Background

Towards the realization of Beyond 5G (6G), research and development of ICT using electromagnetic waves such as radio waves and light is progressing in various fields. However, our daily lives contain a vast amount of information that is challenging to handle directly with existing ICT, such as that associated with chemical substances. For example, quarantine dogs play an active role in airports. This is because it is difficult for existing ICT systems to quickly and sensitively detect and process information associated with chemical substances as the source of odors in real time. Another example is that it is extremely difficult to apply existing ICT to monitor intercellular exchanges of chemical substances in living organisms because electromagnetic waves are attenuated in aqueous environments. Thus, ICT based on information associated with chemical substances has not yet been fully established, although such information is very familiar and important.

In response to these circumstances, the Bio-ICT Laboratory is advancing research and development of ICT that learns from information and communication via molecules (molecular communication) in living organisms. Our efforts aim to enrich society by leveraging the information technology associated with chemical substances. Our research is proceeding based on two main approaches: The first is related to the development of measurement and evaluation technologies for information associated with biomolecules; and the second aims to create sensors, processors, and actuators that can operate in an environment where molecular communication takes place using molecules, cells, and other biomaterials. This article presents the results of "cellular ICT research" from our research group, which focuses on cells, the smallest functional unit of life, primarily using the latter approach.

Research on Cell-artificial Material Interfaces using Biological-non-biological Hybrid Devices

Cells survive by constantly exchanging information with the outside world. To understand the mechanisms of molecular communication by cells, or the "language" of cells, and to harness these mechanisms, it is essential for humans to not only investigate the cells themselves in detail but also to research from an engineering perspective in order to artificially manipulate cell functions. For that purpose, we initially fabricated biological-non-biological hybrid devices by combining various biomolecules and artificial materials. We introduced these devices into cultured living cells (HeLa cells) to analyze the outcome in detail (Figure 1). In other words, we explored how to design the interface between the cell and the artificial device in order to manipulate cell function using such devices. We mainly used polystyrene beads bound to biomolecules, such as DNA and proteins, as models of biological-non-biological hybrid devices. The key advantage of this experimental system is the use of non-degradable beads as observational markers, which allows for detailed observations specific to the cellular response to the biomolecules bound to the bead surface.

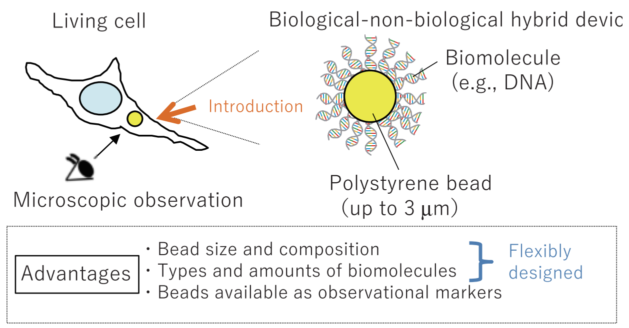


Figure 1 Overview of technology for measuring cellular responses using a biological-non-biological hybrid device

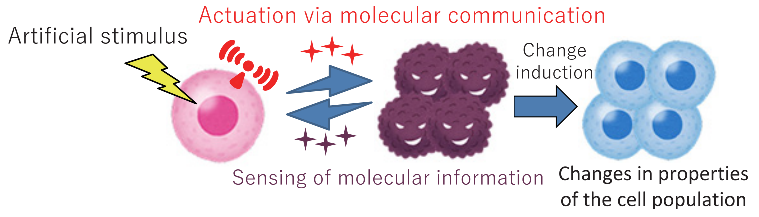


Figure 2 Schematic illustration of the regulation of cell population function through molecular communication control

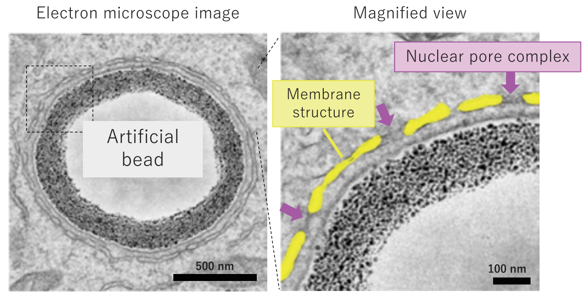


Figure 3 Nuclear membrane-like structure formed around a biological-non-biological hybrid device
Transmission electron microscope image of a nuclear membrane-like structure artificially formed within a cell using an artificial bead coated with nuclear membrane-pore components (left), and a magnified view of part of the structure (right)

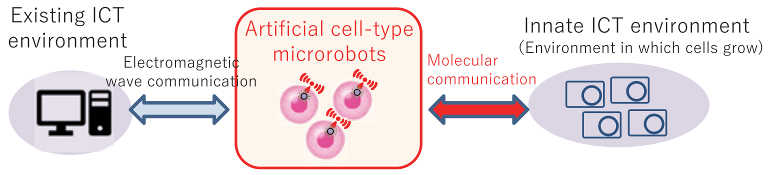


Figure 4 Artificial cell-type microrobots connecting existing ICT and innate ICT environmentsFigure 4 Artificial cell-type microrobots connecting existing ICT and innate ICT environments

Cellular Response to Biological-non-biological Hybrid Devices

Once biomolecule-bound beads are introduced into cells, various cellular responses can be observed depending on the type of biomolecule involved*. For example, when a polystyrene bead coated with a protein called avidin was introduced into a living cell, autophagy—the process in which a cell digests its own proteins—was induced around the bead. This means that the cell attempts to degrade the avidin-coated bead, believing it to be an invader. However, subsequent studies have indicated that this autophagic reaction does not target the invading bead itself, but the cell membrane that was ruptured when the bead entered. This is an excellent defense mechanism in that the cell can respond to various types of invaders.

Another example is a bead with DNA bound to its surface. When such a bead was introduced into the cell, DNA sensor molecules present within the cell immediately detected the bead and prevented it from being degraded by autophagy. This means that cells have a mechanism, apart from the autophagy defense mechanism, to retain invaders if they are recognized as DNA (or DNA-coated materials). We believe that if we can fully understand the mechanisms by which cells flexibly recognize and process foreign substances, and then create cells with elements that can freely control these functions, we can apply them to regulate the behavior of cell populations and other systems (Figure 2).

Constructing Artificial Structures within Cells

In general, cell functions are modified by altering the genome—rewriting life's blueprint—using genome editing technologies. However, these modifications are passed on to subsequent generations through cell division and proliferation. In contrast, our research focuses on creating artificial structures (or spaces) with specific functions that do not modify genomic information (i.e., outside the genome or around a bead) and utilizing the structures to manipulate cellular functions. When cells with such beads undergo division and proliferation, the beads do not increase in number. Therefore, the effect on subsequent generations of cells is minimized, and various controls, such as killing only bead-containing cells, are possible if needed. The nucleus is responsible for controlling the genetic ON/OFF state in the cell. We have already succeeded in artificially constructing nuclear membrane-like structures, corresponding to the "vessel" of the cell nucleus (Figure 3).

Future Prospects

By using biological-non-biological hybrid devices, we have successfully established a fundamental technology for artificially constructing targeted structures within living cells. We plan to develop technologies to control the timing of bead entry into cells and to induce gene expression around the beads. Molecular communication is expected to take place not only between cells but also between microrobots composed of biomaterials. In the future, we would like to take on the challenge of creating artificial cell-type microrobots with specialized functions that can connect the existing ICT environment and the innate ICT environment inherent to living organisms, including the molecular communication environment (Figure 4).

Reference

* Shouhei Kobayashi, "Understanding and Control of Cellular Functions Using a Biological-non-biological Hybrid Device," NICT Research Journal, vol.66, pp.31-35, 2020 (in Japanese).

Designing, Understanding, and Controlling the Mechanical Information Processing Systems in Living Organisms

Aiming to develop ultra-energy-efficient computers and intra-body ICT for hearing · touch sensation

IWAKI Mitsuhiro

Senior Researcher
Bio-ICT Laboratory,
Kobe Frontier Research Center,
Advanced ICT Research Institute

After completing graduate school, Dr. IWAKI worked as an assistant professor, a specially appointed associate professor at Osaka University, and deputy team leader at RIKEN before joining NICT in 2022. Engaged in research and applications of mechanical information processing in biology. Also appointed as an associate professor at Osaka University. He holds a Ph.D. in Science.

Biological studies to date have uncovered that in the course of evolution, brain neural networks and similar systems utilize electrical, molecular, and mechanical information communication to handle complex information processing in an energy-efficient manner. Understanding and applying these natural information processing systems could revolutionize society. To this end, we are aiming to develop ultra-energy-efficient systems and intra-body ICT for hearing and touch sensations by designing and analyzing information processing systems based on mechanical communication just as takes place in muscles, as well as molecular-level elastic components (nanosprings).

Background

The electrical information communication technology that emerged in the 18th century and the optical communication technology of the present day have become indispensable in today's society through telephones, television, computers, and the Internet. On the other hand, when it comes to living organisms, electrical information communication utilized by brain neural networks, molecular interactions (molecular communication), and communication methods using mechanical forces (mechanical communication) have evolved over billions of years to achieve complex information processing with minimal energy consumption. For example, the human brain is considered to maintain its system while consuming only about 20 W of energy for complex information processing. Technologies for understanding these natural ICT systems to devise a new information processing concept and to design and control their interior workings are unexplored fields that have significant potential to evolve society. One of the characteristics of natural ICT is that due to the minimal energy available to living organisms, it is difficult to suppress thermal fluctuations in a system, causing information processing to become a complex and probabilistic process. Despite ongoing studies on probabilistic information processing by the brain, an overview has yet to be clarified due to its ultra-complex system comprising a large number of nerve cells in a network. Our research is therefore focused on biomolecular systems, which are of a relatively small scale in the layers of life, and whose design has recently become possible.

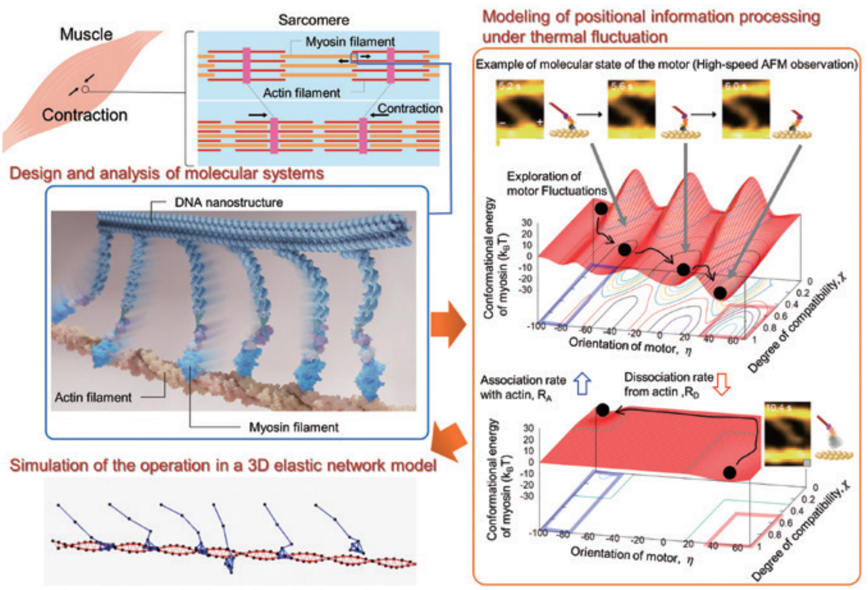


Figure 1 Design of a Biomolecular System and Operation Simulation

Designing Biomolecular Systems and Analyzing the Internal Operation Thereof

Inside living organisms, various biomolecules self-assemble to comprise a system and internally exchange information in a mechanical manner. For example, all animals have muscles, in which a molecular system referred to as "sarcomere" is present as the smallest unit structure. In a sarcomere, biological molecular motors ("myosins") cooperatively function through mechanical communication with one another. Individual myosin molecules thermally fluctuate and flexibly process their respective positional information through mechanical communication inside and outside the system.

Therefore, a sarcomere can be referred to as an intelligent microbot that handles information processing using mechanical communication. Because it moves utilizing thermal fluctuation, high energy-efficiency can be achieved at a level unparalleled to an artificial actuator. To understand and apply this mechanism, we have artificially designed a molecular system akin to a sarcomere (Figure 1) by utilizing DNA nanotechnology and developed a technology to accurately observe the internal operation of the designed system.[1] At the same time, we have also established a simulation model that quantitatively reproduces the internal operation for analysis from the viewpoints of operation forecasting and information physics, thereby striving to achieve comprehensive control and understanding of ultra-energy-efficient information processing.

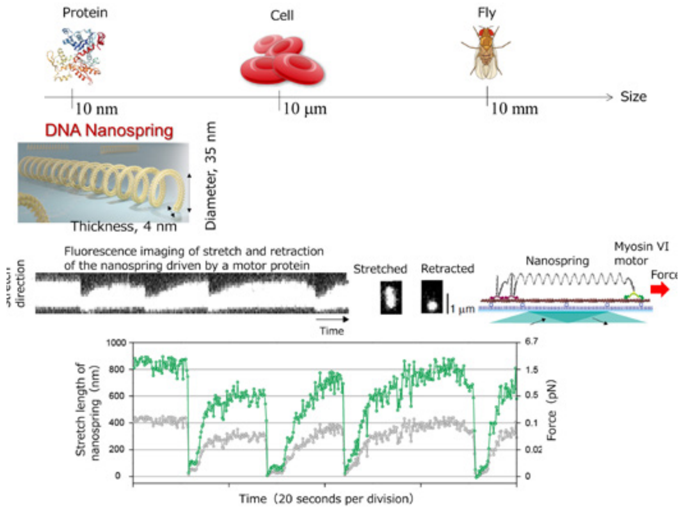


Figure 2 Size Comparison of a Nanospring with the Layers of Life (Top), and Fluorescent Observation and Force Detection of Nanospring Stretch and Retraction via One Motor Molecule (Myosin VI) Functioning in Hearing Sensation (Bottom)

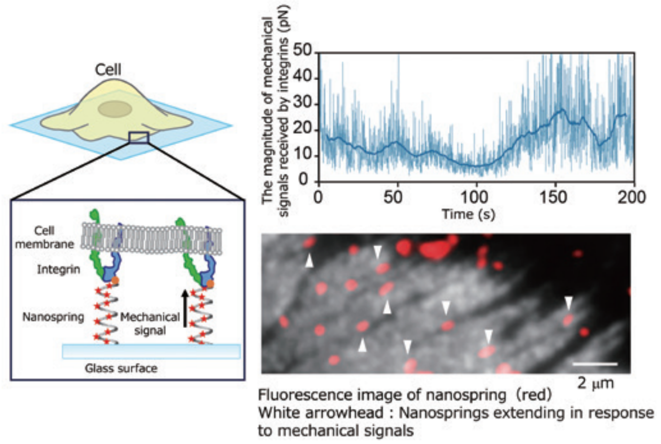


Figure 3 Ultra-high-sensitivity Detection of Mechanical Signals Received by Integrin Molecules on the Cell Membrane

Development of Nanosprings to Visualize Mechanical Communication

The Nobel Prize in Physiology or Medicine 2021 was awarded for the discovery of a mechanosensor molecule ("Piezo"), a receiving and responding element for mechanical information in living organisms. Myosins and other biological molecular motors are also mechanosensor molecules. It has recently been uncovered that a wide variety of molecules function as mechanosensors. However, it is difficult to visualize what types of mechanical information are exchanged by these molecules, causing delays in the understanding of information processing based on mechanical communication. We have therefore designed the world's smallest coil-shaped spring (nanospring), close to the size of a biomolecule (about 10 nm), and developed a technology to use this spring to connect between molecules and between cells and the extracellular environment and to sense changes in structure (stretching and retraction) and direction with high sensitivity (Figure 2). By assembling DNA molecules in a bottom-up manner, we have succeeded in exceeding miniaturization by several dozen times compared to springs produced by photolithography and other existing technologies. Because our spring uses biological materials, it has high biocompatibility, and it is expected to be incorporated into biomolecular systems or inside living organisms with no toxicity. As a demonstration experiment, we connected our nanospring to an integrin molecule, which senses the hardness of the scaffold to which a cell adheres. Through observational analysis, for the first time in the world, we succeeded identifying temporal changes on the order of seconds in the size and direction of miniature forces received by the cell via a single molecule of integrin (Figure 3).[2] Mechanical signals, which are not significantly different from thermal fluctuations that become noises, are able to be received and processed. By combining this with analyses of molecular systems and intracellular operations, we expect to gain a more advanced understanding of ultra-energy-efficient information processing based on probabilistic operation.

Future Prospects

Among other natural ICT systems, our research is focused on information processing based on mechanical communication, which is easier for evaluating energy consumption and efficiency.

By understanding the operating principle of ultra-energy-efficient information processing through the design and analysis of systems like muscles and by pursuing full control thereof, we are exploring new possibilities for its societal implementation. For example, we are seeking to obtain clues to help design ultra-low-power computers through an understanding of their operating principle. Among the five senses of living organisms, hearing and touch sensations detect and process mechanical signals external to the organism and communicate them to the brain. By incorporating sarcomere-like microbots that can be freely controlled into hearing and touch systems, it may become possible to increase sensitivity by multiplying specific signals or to supplement sensory functions that have been compromised by disease or aging. Furthermore, because a nanospring functions as a force sensor that converts mechanical signals into fluorescent signals, it may become possible to monitor the hardness of skin tissues, blood vessels, cancer tissues, etc., which is highly correlated with aging and malignancy, inside living organisms by incorporating nanosprings into a living body to detect fluorescent signals. This technology therefore has the potential of becoming a new intra-body ICT to diagnose the condition inside the body.

Reference

[1] FUJITA, K., OHMACHI, M., IKEZAKI, K.,YANAGIDA, T., IWAKI, M., "Direct visualization of human myosin II force generation using DNA origami-based thick filaments," Commun.Bio. l, 2, 437, 2019.

[2] MATSUBARA, H., FUKUNAGA, H., SAITO, T.,IKEZAKI, K., IWAKI, M., "A programmable DNA origami nanospring that reports dynamics of single integrin motion, force magnitude and force orientation in living cells," ACS Nano, 17, 13185–13194, 2023.

Witnessing the Creation of Memory in Real Time

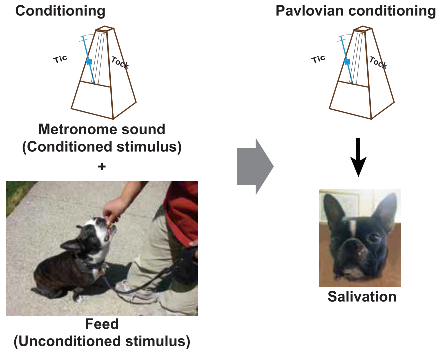


Figure 1 Pavlovian Conditioning Experiment

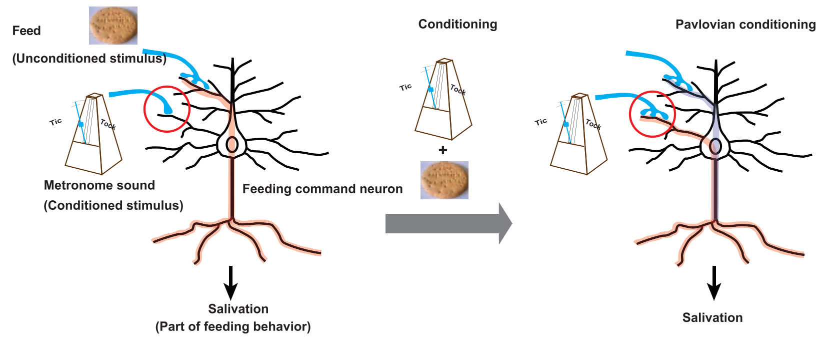


Figure 2 Change in the Neural Circuit in the Brain of Pavlov's Dog Presumed by Hebb

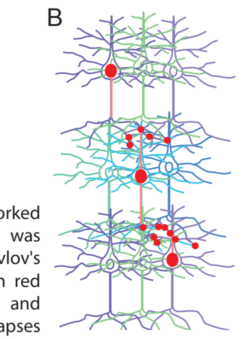


Figure 3
A The memory rule, worked out by Hebb, who was inspired by Pavlov's experiment. Parts in red indicate firing cells and the reinforced synapses connecting them.
B A series of cells linked via reinforced synapses, maintaining memory

YOSHIHARA Motojiro
Executive Researcher,
Kobe Frontier Research Center,
Advanced ICT Research Institute
Dr.YOSHIHARA received a Human Frontiers Science Program fellowship to do postdoctoral work at the City of Hope, California. After working as a visiting scientist at MIT, he joined the Department of Neurobiology at the University of Massachusetts Medical School as a faculty member in 2006. In 2013, he left University of Massachusetts Medical School to work as a visiting professor at MIT. In 2014, he moved back to Japan, and joined NICT as an Executive Researcher (PI). Ph.D.(Science)

We performed real time tracking of memory as newly formed synapses, or "acquired synapses," created on Drosophila feeding command neurons with conditioning, which we published in Nature in 2013. The first-ever direct observation of memory allowed identification of the site where two pieces of information link to form memories. In addition, as a growing body of evidence has recently supported the "local feedback hypothesis," a general hypothesis for memory I proposed in an article in Science in 2005, the probability has been growing that this hypothesis could be established as the basic principle of memory. To take it one step further, we are currently attempting to verify this hypothesis at the site where acquired synapses are formed and obtain definitive evidence.

Background

"Seeing is believing." As pursuing the phenomenon of memory, which has never before been visualized, would appear to be a wild-goose chase and an absurd endeavor, unrealistic discussions and incorrect research methods run rampant. Since the device that stores information as an array of 0s and 1s and is freely read out and copied on a computer was termed "memory," a word originally referring to brain memory, the brain memory system has tended to be misunderstood as working in the same way as computer memory. I was stunned to hear even some neuroscientists seriously say that "brain memories move from the hippocampus to the frontal lobe," which is impossible from a cell biology perspective. Furthermore, since I had given a warning, which was published in an editorial in Nature due to its svverious implications[1][2], meaningless biological papers based on experiments performed using a framework of faulty logic frequently appeared even in leading journals. This tendency is the most marked in current research being conducted on memory, for which methodology has not been well established, and pseudoscience on a massive scale is being passed on[3]. The focus of our memory neurobiology project is on understanding the entity of memory and establishing "memory neurobiology" that can be analyzed by reliable methods. We aimed to learn the basic principle of memory by a novel and certain methodology and utilize it to newly design information and communication devices.

Pavlov's Dog and Hebb's Rule

The first experiment on memory as a definitive subject of experimental biology is the well-known Pavlov's dog experiment (Figure 1), in which dogs that had been fed after the sound of a metronome led to salivate upon hearing the metronome sound alone. Inspired by this experiment, Donald Hebb[4], a Canadian psychologist, assumed that reinforcement of the synapses to feeding command neurons underlies Pavlov's dog experiments, as illustrated in Figure 2, and proposed that when two neurons sequentially fire, the synapses connecting those neurons are specifically reinforced, with other synapses remaining unreinforced—known as "Hebbian synapses" (Figure 3A). He believed that many connections are successively formed in this way to create the neural circuit carrying memory (Figure 3B). Many people believed this to be the case. However, the process had never actually been observed, and our first target was to actually visualize this process for the first time.

Basic Principle of Memory—Local Feedback Hypothesis

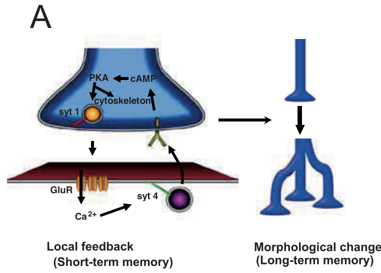
I thought out the local feedback hypothesis to explain Hebb's rule, and published it in Science[9] (Figure 4A). Under this hypothesis, I assumed that two active cells release substances to each other locally at the synapses bridging them, thereby strengthening the synapses immediately, as a short-term plasticity. However, this hypothesis, although well-consistent with previous findings, has no way to be tested. We have to observe synaptic changes at the micro level with being linked to memory formation as behavior at the macro level, and it is command neurons that serve as the link between the micro-level and macro-level.

Command Neurons and Pavlov's Fly

The behavior screening conducted through the all-out efforts of the whole Yoshihara lab at the University of Massachusetts Medical School led to the discovery of the "feeding neuron," a feeding command neuron, as depicted in Figure 2 (2013, Nature)[6]. Based on this discovery, Dr. Akira Sakurai, who worked at the laboratory as a post-doctoral fellow researcher (currently a senior researcher of the memory project at NICT)[7], conducted Pavlovian conditioning experiments with Drosophila brain using "rod removal" instead of the metronome sound for dogs as the conditioned stimulus and found that the responsiveness of feeding neurons in the Drosophila brain changed, causing Drosophila to act in response to the conditioned stimulus of "rod removal" (Figure 4B). Thus, it was demonstrated through the use of a relatively simple fly experimental system that the change in the neural circuit as proposed by Hebb, which was difficult to investigate in the complicated dog brain, had actually taken place.

On-site Observation of Memories ("Acquired Synapse") and Hypothesis Verification

We discovered by carefully examining the dendrites of feeding neurons upon conditioning that new synapses are formed at the same time as memory formation, and we named those synapses "acquired synapses" according to the term used by Hebb. Furthermore, we succeeded in witnessing the actual moment when acquired synapses form in real time, and thus achieved the target of "witnessing the site of memory creation" (Yoshihara, Sakurai, Yoshihara; in preparation). Moreover, in search of the fundamental principle of memory, we are attempting to verify the "local feedback hypothesis" at the site of formation of acquired synapses.



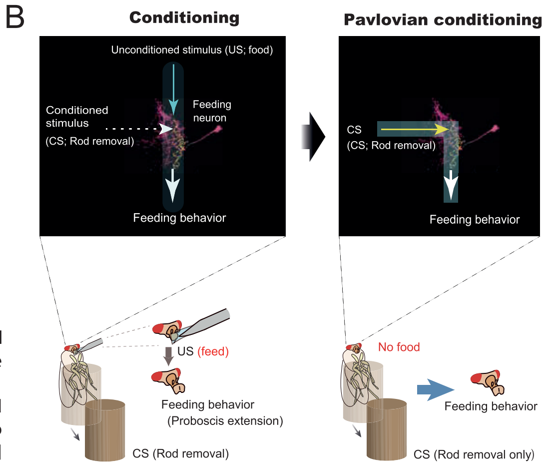


Figure 4
A "Local feedback hypothesis"[5] as a cell mechanism that follows Hebb's rule (reprinted with permission from Science)
B "Feeding neuron," a feeding command neuron, connects the micro and macro aspects of Pavlovian conditioning[7] (reprinted with permission from Current Biology).

Conclusion

The 50th anniversary of the Apollo 11 moon landing vividly brought that day back to me when I was strongly moved by the news as a kid. At the same time, I realized that I had never experienced such a strong impact in my scientific career, and I felt that in order to feel so strongly moved, I would have no choice but to succeed in witnessing the "creation of memories." Now that we have finally made it here, a subsequent discovery that would make a great impact akin to the moon landing, not only on me but everyone, would be defining the basic principle of memory. I started my own lab in the U.S. to verify the "local feedback hypothesis" I conceived of 20 years ago and proposed in the Science paper as a candidate for memory principle, and every piece of recently accumulated circumstantial evidence suggests that my hypothesis represents the fundamental principle of memory. Even more decisive hypothesis verification is possible through observation of miniature synaptic currents, which are currently undetectable in the brain, at the time of memory formation, and a new approach for this is gradually taking shape. Now, elated that the "moon's surface" is approaching, I relish the achievements of our longstanding challenge.

References

[1] Yoshihara and Yoshihara (2018) Journal of Neurogenetics 32, pp.53–64.
[2] Nature Editorial (2018) 558, p162
[3] Motojiro YOSHIHARA, "The Era of Pseudoscience," NICT NEWS 2018 No.5, pp11.
[4] Hebb D.O., The organization of behavior; a neuropsychological theory, New York: Wiley, 1949.
[5] Yoshihara, M., Adolfsen, B., Galle, K.T., and Littleton, J.T., "Retrograde signaling by Syt 4 induces presynaptic release and synapse-specific growth," Science 310, pp.858–863, 2005.
[6] Flood, T.F., Iguchi, S., Gorczyca, M., White, B., Ito, K., and Yoshihara, M., "A single pair of interneurons commands the Drosophila feeding motor program," Nature 499, pp.83–87, 2013.
[7] Sakurai, A., Littleton, J. T. Hiroaki Kojima, H. and Yoshihara, M., "Alteration in information flow through a pair of feeding command neurons underlies a form of Pavlovian conditioning in the Drosophila brain," Curr. Biol. 31, pp.4163–4171, 2021.

Learning to Small Brains

Towards the development of efficient ICT inspired by insect brain

KOHATSU Soh
Research Manager
Neuro-ICT Laboratory,
Kobe Frontier Research Center,
Advanced ICT Research Institute

After completing graduate school, Dr. Kohatsu did his postdoctoral work at Tohoku University and then joined NICT in 2018. His primary research interest is in neural circuit mechanisms of behavior in organisms with simple nervous systems. Ph.D. (Information Sciences).

The diversification of information and communication technology (ICT) applications in recent years has created an urgent need to improve the functionality of compact information devices such as drones and IoT devices. These devices pose severe constraints on computational resources and motive power, which in turn require technologies that can efficiently perform a minimum number of tasks with the least amount of computational overhead. To tackle these challenges, we are taking a unique approach to research and development by looking into information processing in the small brains of insects.

Background

Insects are the most thriving group of organisms on Earth today, numbering over 1 million species. This is mainly thanks to their superb sensory and motor abilities, which are supported by the functionality of their nervous system. The brain of the fruit fly *Drosophila melanogaster* is less than 1 mm^3 in volume and contains only about 200,000 neurons, which is 100,000 times less than the approximately 100 billion neurons in the human brain. However, the extremely small brains of insects are capable of a whole series of information processing operations, which includes feature extraction from sensory input, information integration for decision making and motion control (Figure 1). Insects are capable of a wide range of behaviors such as exploration of the environment, escaping from predators, mating, and social interaction, to name but a few. Therefore, despite their compact size, insect brains can be likened to highly efficient information devices capable of interacting with the environment autonomously and in real time. We believe that their operating principles hold many clues that can be exploited for future ICT applications.

Our current research focuses on the visual system of *Drosophila*. The main visual organs of the fly, consisting of two compound eyes, have only about 1,600 ommatidia in total. If we can elucidate the mechanism by which the insect brain extracts information, such as temporal and spatial patterns, from these 1,600 "pixels" of visual input for behavioural control, it would be possible to apply the findings to the development of technologies that use visual information to control micro-robots and drones, which have severely limited computational resources and motive power. With this in mind, we are modeling the control mechanism of tracking behavior in fly, for example, a fly chasing another organism based on visual information.

Behavioral Analysis using a Locomotion Simulator

The tracking behavior that we study in our research is performed by males to court females. When a male fly detects a female, he quickly regulates the speed and direction of his movement, mainly based on visual information, in order to track the female as she moves. To establish a quantitative relationship between visual input and motor output during tracking, we use an experimental system called a locomotion simulator, in which a subject male fly "walks" while confined to the apparatus (Figure 2). This system presents the fly in the apparatus with artificial visual stimuli controlled with a degree of precision that exceeds the temporal and spatial resolution of the fly's visual organs, while recording the speed of the fly as it walks forward and backward, left and right. In principle, this system should enable us to analyze the behavioral responses of the male fly to various visual stimuli one by one. However, visual stimuli alone will not cause the male fly in the locomotion simulator to perform tracking, as male flies are programmed to engage in active tracking only when they detect females. Therefore, in order to analyze tracking, test male flies must first be artificially induced into ‘mating mode’, mainly by female pheromone stimulation.

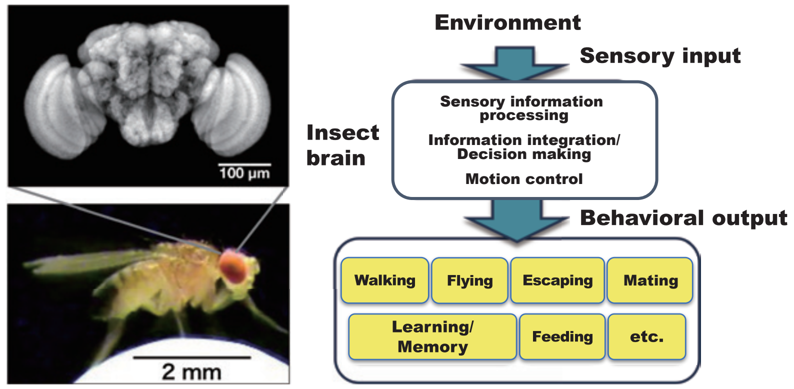


Figure 1　Information processing in the insect brain

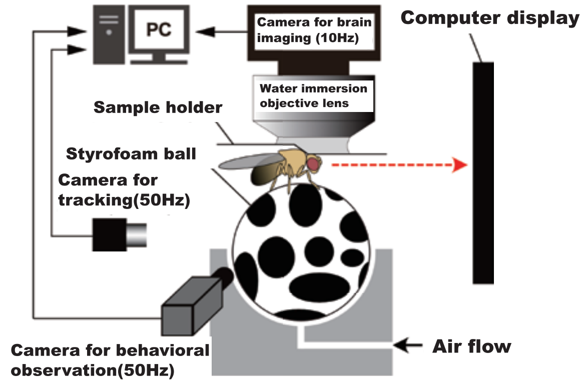


Figure 2　Locomotion simulator

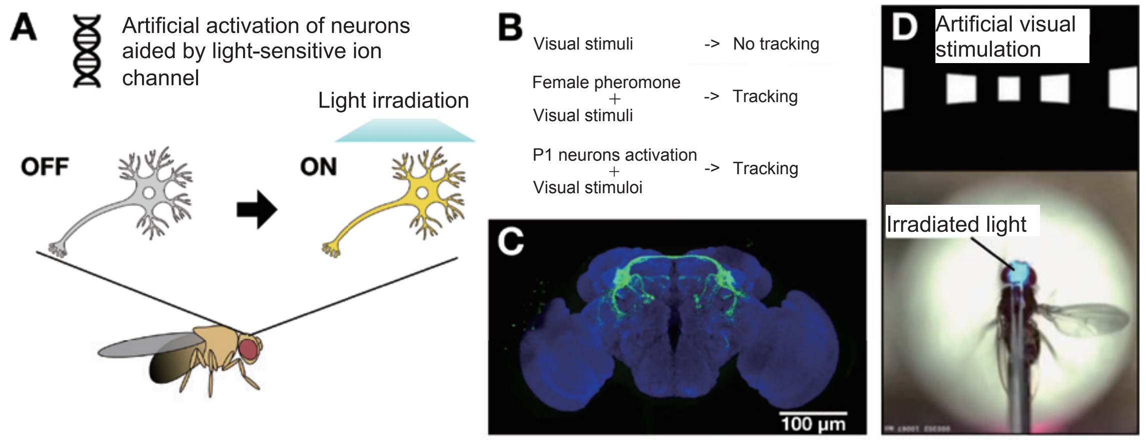


Figure 3　Tracking behavior triggered by artificial stimulation
(A) Neural activity manipulation by optogenetics　(B) Regulation mechanism of tracking behavior
(C) P1 neurons (green); counterstained brain (blue)　(D) A male fly on the locomotion simulator following artificial visual stimuli

Manipulation of Fly Behavior with Artificial Stimuli

Female pheromones are chemical substances and therefore pose experimental problems when used as stimuli, as they are difficult to control in terms of intensity and duration. Therefore, we have adopted the method of artificially stimulating the neurons in the brain that are activated when a male is exposed to female pheromones, rather than simply applying female pheromone stimulation to the subject (Figure 3). To do this, we use a technology called optogenetics, which involves introducing light-sensitive functional molecules into the neurons of the male fly so that the activity of the neurons of interest can be remotely controlled using light. With this approach, we successfully activated P1 neurons, a neuron group that triggers mating behavior in response to female pheromone information, for a male walking on a locomotion simulator. Thus, the two operations of light irradiation on the male fly’s head and presenting artificial visual stimuli enable us to efficiently reproduce for analysis the tracking behavior displayed by males only in mating mode. Based on behavioral analysis using this unique method, we are currently in the process of elucidating in detail the effects of the spatial distribution and moving patterns of visual stimuli on tracking behavior.

Exploring the Neural Circuit Mechanism Behind Tracking Behavior

We are also analyzing the structure and the function of the neural circuit that underlie vision-dependent tracking behavior. Behavioral screening using optogenetics has enabled us to identify the multiple candidate groups of neurons involved in both visual information integration and locomotion control. Moreover, by using an original system that combines the locomotion simulator and functional imaging technology, we are able to measure the neural activity that occurs during tracking in real time. We are nearing the stage where we can confirm that responses reflecting the position and speed of the tracking target occur in the higher visual areas of the fly brain. In the future, we expect to clarify the circuit mechanism that translates visual information into walking by analyzing the relationship between visual input, motor output, and neutral activity in greater detail.

Future Prospects

Using the behavioral and neural activity data that we have obtained through our original approach, we are currently modeling a tracking control mechanism in collaboration with a research group specialized in mathematical modeling. In recent years, interest has been growing in ICT research focusing on information processing that occurs in the small nervous systems of living organisms, with a number of private businesses entering this research domain. However, technology development inspired by the functionality of living organisms, or biomimicry, has so far mainly focused on physical properties and structures of biomaterials, and not much has been done in the field of information processing. We hope that our research activity will contribute to the expansion of this under-explored research area.

Towards the Development of Ultra-Efficient Energy Conversion Devices Inspired by Biological Systems

FURUTA Akane

Researcher
Bio-ICT Laboratory,
Kobe Frontier Research Center
Advanced ICT Research Institute
Ph.D (Science)

Biography

2001 Graduated from the Division of Natural Sciences, College of Liberal Arts, International Christian University
2009 Completed a doctoral course at the University of Tokyo
2011 Joined NICT
2018 to 2021 RPD Research Fellowship for Young Scientists at the Japan Society for the Promotion of Science

Q&As

Q What is the biggest failure in your life so far?

A In my student days, I found myself in a poster presentation hall, completely unaware that I was explaining the intricacies of molecular motor cytoplasmic dynein to its discoverer.

Q What are you interested in other than research?

A I enjoy cooking using recipes shared with my foodie friends. Since I live near the Akashi coast, I would like to try to catch fish and cook them using good recipes.

Q What advice would you like to pass on to people aspiring to be a researcher?

A Immerse yourself in what interests you. Even if it's an incredibly niche topic, having knowledge (or expertise) that surpasses anyone else will undoubtedly be a strong foundation for your career as a researcher.

As humans, we can walk around for about two hours with the energy from just a single slice of bread. If you try to make a battery-powered robot equipped with electric motors walk around for about two hours, the robot, being quite heavy including control mechanisms and other equipment, would stop in a few minutes using the same amount of energy generated from that slice of bread. But, if we were able to harness a system that could perform this much work using only one slice of bread, it might hold the potential to address the energy consumption challenge in modern info-communication, which has resulted from an explosive increase in the energy consumption of AI systems and, for example, people who send videos to each other. The driving force behind the movement of living organisms lies in molecular machines known as molecular motors, which are about one thousandth the diameter of a human hair. They perform a myriad of tasks related to motion, including muscle contractions, cell division, and material transport.

A molecular motor is very small. In muscle, they are arranged at an incredible density of 2 trillion units per centimeter. They can directly convert chemical energy, called ATP, into mechanical work without heat generation to successfully minimize energy loss and obtain a large amount of energy. Moreover, while robots are provided with an energy source in the form of electrical energy, living things are provided with energy in the form of substances like bread. They chew it to break it into smaller pieces, and then digest it with enzymes to break it down to a molecular level and extract energy from it. To understand the design principle of molecular machines, we have established an experimental approach of assembling and reconstructing these molecular machines from the component level, like playing with toy blocks. To date, we have succeeded in creating molecular motors with new functions that do not exist in nature. And through the approach of "create to understand", we are beginning to understand the design principle of molecular motors. Moving forward, we aspire to leverage the secrets of molecular machinery to develop novel, ultra-efficient information and communication systems that harness the remarkable features found in living organisms.

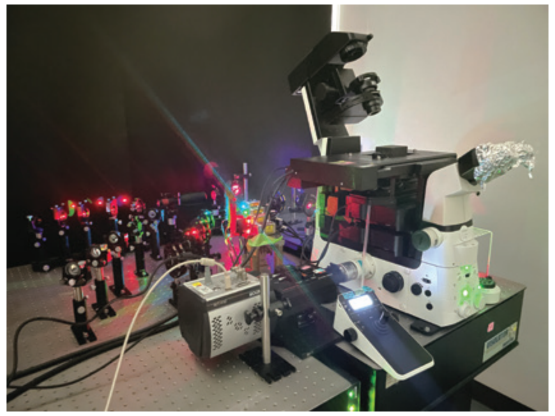


Figure Simultaneous four-color fluorescence microscope system under construction

Holding of "NICT Diversity Day 2024," the First Event of the Diversity Promotion Office

Diversity Promotion Office

The Diversity Promotion Office, newly established in FY2023, held its first event, "NICT Diversity Day 2024," on March 8, International Women's Day, at the NICT Innovation Center (Tokyo Nihonbashi Tower). About 200 NICT executives and personnel participated in the event both at the venue and online.

At the opening of the event, Dr. TOKUDA Hideyuki, President, expressed his aim of not only acquiring excellent human resources and international competitiveness by promoting diversity, but also of strengthening NICT's creativity and innovative ability as a whole to enable NICT to become a more flexible organization. The president also expressed his expectations for the activities of the Diversity Promotion Office, saying that although the proportion of female personnel in the ICT field is not particularly high or low at present, he hopes to achieve a level of 30% or more in the future.

The next speaker, MORIAI Shiho, Senior Executive Director and Director of the Diversity Promotion Office, reported on the results of a NICT internal survey conducted by the Diversity Promotion Office in conformity with the "Survey on Unconscious Assumptions Based on Gender (Unconscious Gender Bias)" by the Gender Equality Bureau of the Cabinet Office.

The average percentage of answers to the question on awareness of unconscious gender bias for NICT was 10%, which is significantly lower than the average (20.7%) in the Cabinet Office survey, indicating that gender role awareness within NICT is much lower than the general figures for Japan. While this is evaluated as one of NICT's strengths, there was a large gender gap with regard to the experience of being assigned gender-based roles by others or feeling that such an atmosphere existed (49.1% for females and 24.2% for males). Furthermore, Senior Executive Director MORIAI pointed out that one difference among positions was also observed in the lower scores for managerial positions compared to career-track and general positions, indicating that gender role awareness within NICT is low compared to the general public, but nonetheless remains.

In addition to gender-related bias, as many asked for initiatives based on diversity perspectives such as age, nationality, LGBTQ, and disability status, Senior Executive Director MORIAI expressed her vision of strengthening communication to gain the empathy of personnel with diverse values.

The second half of the event featured a trialogue among President TOKUDA, Senior Executive Director MORIAI, and Specially Appointed Professor SASAKI Narie of the Institute for Gendered Innovations, Ochanomizu University.

Gendered innovation is the concept that discoveries and innovations can be made in the field of science and technology by incorporating analyses of sex/gender differences into research and technological development. Professor Sasaki introduced issues using examples of familiar technologies such as seat belts and medical care, where sex and gender analysis has not been incorporated to date. The panelists exchanged opinions on four themes, including gender bias latency in AI technology, such as bias reproduction due to biased AI training data, and new innovations beyond measures to improve the proportion of minorities in organizations. A lively Q&A session was held with participants at the venue and online.

Dr. DOI Miwako, Auditor, took the podium for the closing remarks, concluding that she had wondered how scientists could contribute to the Equity part of DE&I, but became convinced of the possibility when she learned about the concept of Gendered Innovation, and would like to share this knowledge with others.

Details of this event will be posted on the official NICT Diversity website at a later date.

Specially Appointed Professor SASAKI Narie giving a lecture

A snapshot of the Trialogue

Surrounding Specially Appointed Professor Dr. SASAKI Narie, from the left are Auditor Dr. DOI, Professor SASAKI, President Dr. TOKUDA, Senior Executive Director Dr. MORIAI

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4-2-1 Nukui-Kitamachi, Koganei, Tokyo
184-8795, Japan
TEL: +81-42-327-5392 FAX: +81-42-327-7587

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