Interdisciplinary Area

Title of Project : Non-equilibrium-state molecular movies and their applications

IWATA So
(Kyoto University, Graduate School of Medicine, Professor)

Research Project Number : 19H05776 Researcher Number : 60452330

【Purpose of the Research Project】

In order to understand the functions of biological macromolecules essential for life, it is most effective to capture their chemical reactions and structural changes in real time. X-ray free electron laser (XFEL) is a unique tool to observe these reactions and changes with outstanding time and spatial resolutions. Promote and develop this method as a versatile technology applicable to a wide range of biological macromolecules, we will integrate various methodologies including organic chemistry, computational science and biophysics to understand basic questions such as switching and signalling mechanisms of proteins and reaction mechanisms of enzymes. Based on these results, we will also develop controlling methods of biological macromolecules using light and other stimulations.

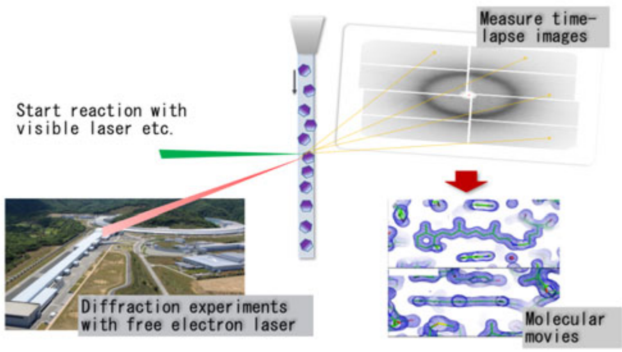

Figure 1. Making molecular movies

【Content of the Research Project】

We use XFEL's femtosecond pulses like strobes for making molecular movies to study macromolecular dynamics with a wide range of time resolution from femtoseconds to seconds. This research field is new and includes a wide range of disciplines such as physics, engineering, chemistry and biology. The group to study the chemical reactions and structural changes (A01, in the figure) in a wide variety of macromolecules, which forms the core part of this project, will closely collaborate with the group responsible for technical development of molecular movies (B01) and the group of computational science and physical chemistry (C01). In the group A01, we will study a variety of interesting biological and chemical systems to understand these molecular mechanisms. For this purpose, we will introduce and develop a wide range of new technologies. In addition, by using computational science, we aim to understand these systems theoretically and quantitatively to design proteins and compounds with new functions.

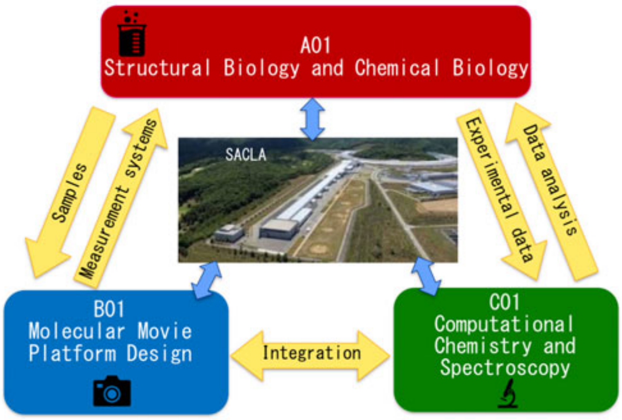

Figure 2. Project design

【Expected Research Achievements and Scientific Significance】

Outstanding time and spatial resolutions of the method will be used to study structural changes and chemical reactions in biological macromolecules to understand their functions at molecular level. Based on the results, rational molecular design will be carried out to produce proteins controlled by various stimulations and compounds switched *in vivo* controlling protein functions. Integrated research in a wide range of fields such as structural biology, protein engineering, chemical biology, and computational science is also expected to accelerate the further development of each field.

【Key Words】

X-ray free electron laser (XFEL): An X-ray laser characterized by ultrahigh brightness, ultrashort pulse duration and high spatial coherence. Using the source, one X-ray diffraction image can be collected within 10 femtosecond.

Molecular movies: Using XFEL, it is possible to capture extremely fast motions of molecules such as chemical reactions, at the time resolution of femtoseconds and spatial resolution of Angstroms and to visualize them as "molecular movies".

【Term of Project】 FY2019-2023

【Budget Allocation】 1,064,000 Thousand Yen

【Homepage Address and Other Contact Information】

http://www.molmovies.med.kyoto-u.ac.jp
s.iwata@mfour.med.kyoto-u.ac.jp

Interdisciplinary Area

Title of Project：Hyper-adaptability for overcoming body-brain dysfunction: Integrated empirical and system theoretical approaches

OTA Jun
(The University of Tokyo, School of Engineering, Research into Artifacts, Center for Engineering (RACE),Professor)

Research Project Number：19H05722　Researcher Number：50233127

【Purpose of the Research Project】

With coming of a super-aging society in Japan, we are facing the urgent problems of sensory-motor impairments, declining higher-order brain functions, cognitive impairment, loss of motivation, and mood disorders caused by aging, and in turn extreme decline of bodily and neurological functions. All of these problems have a common source: inability to adapt appropriately to a brain-body system changed with aging and impairments.

The human body has a high degree of redundancy. For example, “when a hand is paralyzed by a spinal cord injury, the ipsilateral motor cortex immediately joins its control by reactivating its pre-existing neural pathway, which is normally suppressed and preserved in the course of development” (Isa, 2019).

In light of such facts, we believe that clarifying the brain’s “hyper-adaptability” may resolve the abovementioned issues. The goal of our research project is to elucidate the neural and computational principles of hyper-adaptability in which the brain manages impairment of brain functions by linking neuroscience with systems engineering in order to comprehensively understand acute/chronic impairments and disorders, and the principle of frailty.

【Content of the Research Project】

When a person experiences acute/chronic impairment or disorder due to aging, the brain reorganizes neural networks by disinhibiting pre-existing neural network that is normally suppressed and searching for latent but available network that has long been unutilized through course of evolution and development. We call this process of functional compensation as “reconstruction of neural structure”, i.e. a neural entity that achieves hyper-adaptability. In order to implement practical functions to this reconstituted neural network, the network should acquire a new control policy of motor effectors based on precise recognition of the present states of the brain and the body. Here, the brain has to activate the new network by repeatedly performing neural computations and updates the network based on prediction error. We call this learning cycle in a new control space as “reconstitution of sensorimotor control rules”, i.e. neural computation principle that enables hyper-adaptability.

In order to verify the hypotheses described above, knowledge of neuroscience is essential. However, with only the “bottom-up” approach relying on experiments and analyses, it would be difficult to clarify hyper-adaptability that is manifested by systematic behavior of a neural network. Therefore, we apply an interdisciplinary approach that integrates the mathematical modeling technology of systems engineering with neuroscience (Fig. 1). We adopt two new analytical approaches: (a) Robotic-interventional neuroscience, i.e. combinatory use of well-controlled robotic technologies and biological approaches of viral vector, optogenetics, chemogenetics and brain stimulation. This allows verification of cause-effect relationship of neural activity and its generated functions and behaviors. (b) Function-oriented neural encoding, which constitutes a model that may incorporate any knowledge of brain functions into gray-box modeling or hypothesizes the structure of a model based on statistical methods.

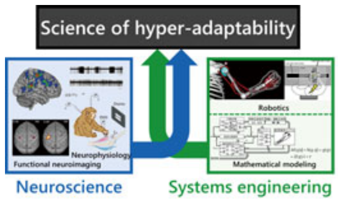

Fig. 1 Whole constitution of the project

【Expected Research Achievements and Scientific Significance】

1. Systematization of “science of hyper-adaptability” by elucidating its underlying neural mechanisms and through its computational modelings
2. Construction of mathematical modeling (gray-box model), which can describe brain functions by integrating multi-modal experimental data such as electrophysiology, brain imaging, and behavior.
3. Construction of a comprehensive theory that can explain adaptation principle from its neural entity to its neural computation principle.

【Key Words】

Hyper-adaptability: Capability of central nervous system (brain and spinal cord) to manage impairment of sensory, motor and cognitive functions including ageing-related ones, by reactivating and recruiting pre-existing, latent but available network with being implemented by new computational principles and practical functions.

【Term of Project】 FY2019-2023

【Budget Allocation】 1,165,800 Thousand Yen

【Homepage Address and Other Contact Information】

http://www.hyper-adapt.org

Title of Project：Integrated Biometal Science: Research to Explore Dynamics of Metals in Cellular System

TSUMOTO Kouhei
(The University of Tokyo, School of Engineering, Professor)

Research Project Number：19H05760　Researcher Number：90271866

【Purpose of the Research Project】

Several trace metal elements including iron, zinc, and copper play important roles in physiological functions such as energy conversion, material conversion and signal transduction. We call such metal and metalloid elements required to sustain life of all living organisms as “Biometal”. Dynamics of Biometals *in vivo* such as their uptake, transport, sensing and utilization are strictly regulated, and its failure causes diseases. Some other metal elements are toxic, and their toxicity is emerged by perturbation of the dynamics of Biometal *in vivo*. In this project, our goal is to unravel the dynamics of Biometal *in vivo* comprehensively through all levels of biological organization and to establish a novel research field of “Integrated Biometal Science”, in which the present research fields related to Biometal could be integrated. We will elucidate the strategy of living organisms, which was acquired during their evolution, to utilize effectively metal and metalloid elements for life and growth. Thus, “Biological Metal Element Strategy” will be established in this project.

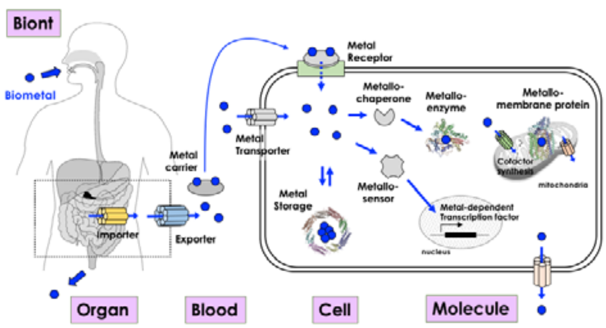

Fig 1 Dynamics of Biometal *in vivo* in physiologies

【Content of the Research Project】

In the research item A01, the functional roles of Biometal to maintain cellar homeostasis will be elucidated by studying the structure, interaction and function of proteins responsible for dynamics of Biometal *in vivo*. In the research item A02, the mechanisms of *in vivo* Biometal dynamics will be elucidated to develop its control method. In the research item A03, the mechanisms of development of toxicity of toxic metals will be elucidated in connection with *in vivo* Biometal dynamics. In the research item B01, measurement and analysis methods for Biometal research will be highly upgraded through collaboration with the project members in A01～A03.

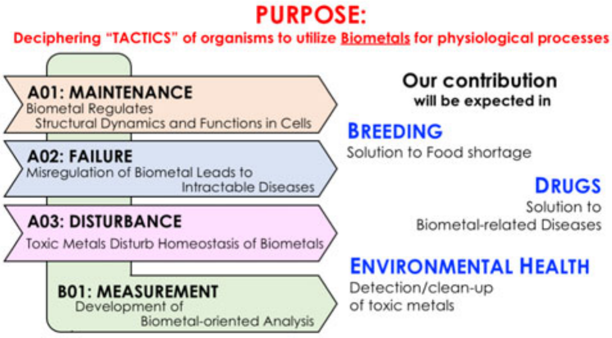

Fig 2 Integrated Biometal Science and its future

【Expected Research Achievements and Scientific Significance】

The scientific principle and interaction of researchers in the Biometal research will be established, which will contribute further development of the research field.

The following concrete results will be obtained by this project.

i　New antimicrobial drugs will be developed.
ii. Therapeutic and diagnostic drugs that are able to regulate metal excess/deficiency in molecular level will be developed.
iii. New methodology to reduce metal toxicity will be developed.
iv. Novel metalloproteins will be discovered. New chemical model mimicking *in vivo* Biometal dynamics will be developed.

【Key Words】

Biometal: Metal and metalloid elements required to sustain life of all living organisms

In vivo Biometal dynamics: uptake, transport, sensing, storage, and utilization of metal ions or metal complexes in living organisms, which are involved in the various phenomena of life with many proteins and enzymes.

【Term of Project】 FY2019-2023

【Budget Allocation】 1,166,600 Thousand Yen

【Homepage Address and Other Contact Information】

https://bio-metal.org
k-tsumoto@protein.t.u-tokyo.ac.jp

Interdisciplinary Area

Title of Project：Information physics of living matters

OKADA Yasushi
(The University of Tokyo, Graduate School of Science, Professor)

Research Project Number：19H05794 Researcher Number：50272430

【Purpose of the Research Project】

Information or signaling has been one of the core concepts to understand the biological systems. Recent progress in technologies has enabled quantitative measurements of biological phenomena even at a single molecule level. However, theoretical framework(s) are still missing that can handle information in biological systems in a quantitative and unified manner.

Meanwhile, in physics, a new theory is emerging at the interface of the thermodynamics and the information theory. Now, information can be treated as a physical quantity just like heat or mechanical works.

In this project, we aim at establishing a new interdisciplinary research field by applying this new information physics to biological systems. The theoretical frameworks of information physics will deepen our understanding of the biological systems. For example, we will be able to discuss the design principles of the existing biological systems through the quantitative analyses of their efficiencies, which will be enabled by the theoretical tradeoff relations among various (thermo) physical quantities and information. At the same time, many good model systems or interesting questions will be found in the real biological systems, which will stimulate the further development of the theory of information physics. We would build a research group to explore this new research field through active feedbacks between biologists and physicists.

【Content of the Research Project】

The goal of this project is to establish a new physics theory that unites information with other physical quantities based on the real biological problems. To explore such interdisciplinary area, it would be essential to establish real collaborations between biologists and physicists. Therefore, each of the three groups in this project has both physical theorists and biological experimentalists, so that they can collaborate to tackle the problems.

The main target of the group A is to dissect the biological molecular machineries, such as molecular motors. The behavior of a single protein will be measured and analyzed in the non-equilibrium environment of the cytoplasm. Moreover, the interactions between the biomolecules in the cytoplasm will also be discussed, which would help us to understand the basic physical principles of liquid-liquid phase separations in the cytoplasm.

Group B will work on the cellular level, such as the chemical reaction networks of the signal transduction or chemotaxis. The information thermodynamics theory will be extended by the application of the information geometry or other mathematical concepts to handle those problems. Quantitative measurements and perturbation experiments would enable us to examine the theory, and would guide the further development of the theory.

Group C will work on the emergence of the functions in the multi-cellular systems, such as the collective cell movement or the developmental processes of multi-cellular organisms. The theory would further cover the adaptation or evolution. These processes include the noisy feedbacks between individual cells and a whole population via a macroscopic field. Information physics will be expanded to discuss such processes.

【Expected Research Achievements and Scientific Significance】

The current abstract theory of information thermodynamics will be materialized by solving the real biological problems. For example, the discussion of the theoretical limits of the efficiency of the cell signaling pathways would not only deepen our understanding how good the existing biological systems is, but also enable us to establish a general theory of the efficiency of information-heat engines.

At the same time, such approach would also enable us to discuss the (design) principles of the biological systems rather than making up a list of the molecules involved in some specific functions.

【Key Words】

Information thermodynamics = A theory to integrate the information theory into the framework of thermodynamics.

【Term of Project】 FY2019-2023

【Budget Allocation】 1,150,100 Thousand Yen

【Homepage Address and Other Contact Information】

http://infophys-bio.jp/

Interdisciplinary Area

Title of Project : Studies on intelligent systems for dialogue toward the human-machine symbiotic society

ISHIGURO Hiroshi
(Osaka University, Department of Systems Innovation, Professor)

Research Project Number : 19H05690 Researcher Number : 10232282

【Purpose of the Research Project】

In the near future, various home appliances and robots will act autonomously and will have intentions and desires. As they have intentions and desires, they will be able to establish relationships with humans in which they understand each other's intentions and desires by using natural language to interact with each other (see the figure below). This kind of world is a society in which humans and intelligent robots and information media coexist in the next stage of the information society.

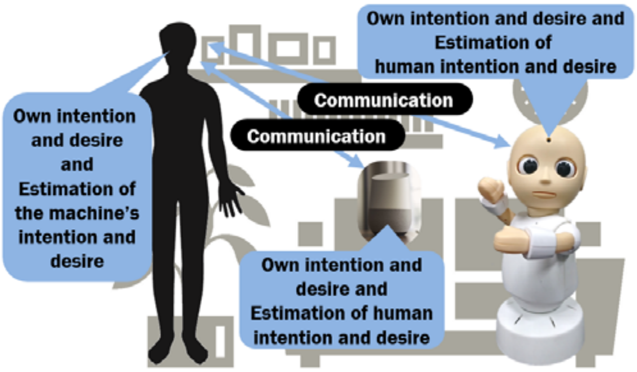

Figure1. Conversation with systems that have intentions and desires

In order to create an academic field that realizes this new symbiotic society, we will engage in research and development with four research groups: dialogue engagement and rapport research, communication understanding and generation research, behavioral decision model estimation research, and human-machine social norms research.

In addition, we will plan and manage field experiments and work on collaboration between the four research groups, as well as discovering and solving new research issues and fostering young researchers. We will study the influence of robots with intentions and desires on society, and propose social norms for a robot-symbiotic society.

【Content of the Research Project】

In order to achieve the above objectives, we will work on the following research while combining research in various fields.

Dialogue engagement and rapport research: we will realize the communication ability to maintain engagement and rapport even if the content of the communication is not completely understood.

Communication understanding and generation research: we will realize the communication ability to combine communication understanding and dialogue generation for a specific objective in a specific situation.

Behavioral decision model estimation research: we will realize the functions of robots that build behavioral decision models and that estimate the behavioral decision models of the other party.

Human-machine social norms research: Through public meetings held together with demonstrations of experiments, we will not only study the effects of robots with intentions and desires on people, but also propose social norms for a robot-symbiotic society.

Then, in this new academic field, under the leadership of the general manager group, we will work on field experiments using the developed information media and communication robots in the real world, and discover new problems to be solved through these field experiments. We will then prototype entirely new communication robots and information media with intentions and desires that can coexist with humans, and explore the possibilities of the intelligent robot/information media symbiotic society that will come after the information media society.

【Expected Research Achievements and Scientific Significance】

The research in this field departs from the unilateral tool-like relationship between humans and machines, where humans send instruction to machines, to establish a relationship between humans and machines where they mutually adapt to each other. Specifically, the autonomy of machines and information media will progress. In doing so, humans and machines and information media will create new relationships in which they interact with each other while deducing each other's intentions and desires through the use of natural language dialogue.

【Key Words】

Autonomous conversational robot: A robot that interacts autonomously based on its own intentions and desires.
Human-machine social norm: A social norm for building desirable relationships between humans and machines.

【Term of Project】 FY2019-2023

【Budget Allocation】 1,088,500 Thousand Yen

【Homepage Address and Other Contact Information】

http://www.commu-ai.org

Interdisciplinary Area

Title of Project : Post-Koch Ecology: The next-era microbial ecology that elucidates the super-terrestrial organism system

TAKAYA Naoki
(University of Tsukuba, Faculty of Life and Environmental Sciences, Professor)

Research Project Number : 19H05679　Researcher Number : 50282322

【Purpose of the Research Project】

The Earth is home to a system of super-terrestrial organisms, where the terrestrial environment and diverse living organisms interact. Microorganisms account for half of all living organisms in the biosphere. The number of microorganism species ranges in the millions, much greater than the numbers of animal, plant, and insect species. Therefore, understanding microbial ecology is essential for understanding the overall ecology of super-terrestrial living organisms.

Many microorganism species have been isolated from the environment; however, those that have been isolated still only constitute less than 1% of all microbial species on Earth. Establishing a novel microorganism isolation technique will be the key to understanding the entire picture of super-terrestrial living organisms.

We will create a novel post-Koch microorganism isolation technique that integrates science, engineering, and microbiology to find microorganisms that have yet to be isolated. Furthermore, we will use functional informatics to take full advantage of ecological and information science to establish a novel ecological system model that is centered on microorganism species as well as their functions and growing environment. This post-Koch functional ecology model will be the basis for elucidation of principles of the super-terrestrial organism system.

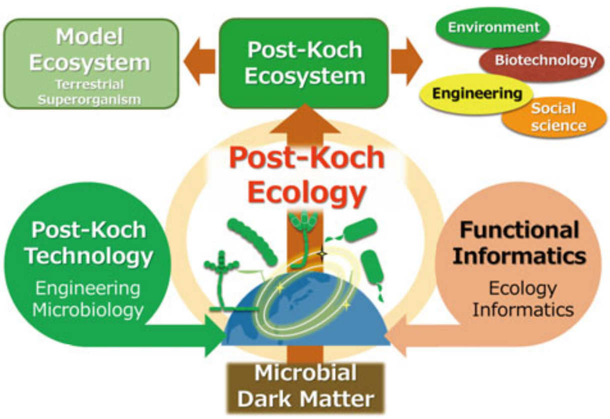

Figure 1 Research strategy and expected achievements

【Content of the Research Project】

Ten groups will advance research under two research tasks. Task A01 will be to develop an innovative post-Koch technique to isolate unknown microorganisms. Specifically, we aim to develop an innovative technique for the isolation, culturing, and analysis of microorganisms, utilizing diverse technologies such as micro-electronic mechanical systems, spectroscopy, and microscopic imaging. Discovery of new microbial species will elucidate their functions, and enhance the diversity of microorganisms. Task A02 will be to create a post-Koch ecology model by developing new bioinformatics technologies to integrate and perform network analysis on information about species, genes, functions, and the environment of microorganisms. The integrated analysis of environmental data and microorganism data will be addressed along with research on the functions of a complex organism system in the environment and technologies that transform enormous amounts of microorganisms into bioresources. Under these two research tasks, we aim to activate the whole research area through collaboration utilizing the shared experimental farm and data obtained therefrom.

【Expected Research Achievements and Scientific Significance】

A post-Koch functional ecology model that has one of the largest collections of information about species, genes, functions, and the environment of microorganisms will be established, allowing for ecology to be understood on the basis of the physiological functions of microorganisms in the environment. The outcomes from this research will contribute to agriculture, life science, engineering, biotechnology, and social sciences. Microorganisms are associated with many fields of study under the Sustainable Development Goals (SDGs). Therefore, this research area will evolve into a core academic area that supports SDGs beyond existing academic areas.

【Key Words】

Microorganism: A living organism that is too small to be seen with the naked eye. Microorganisms have the highest biodiversity on Earth and include bacteria, archaea, and fungi.

【Term of Project】 FY2019-2023

【Budget Allocation】 1,154,300 Thousand Yen

【Homepage Address and Other Contact Information】

http://postkoch.jp/