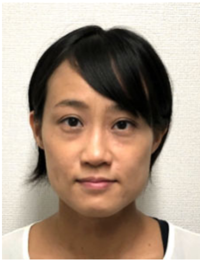


Title of Project： Innovative multiplex imaging with functional Raman probes

KAMIYA Mako
(The University of Tokyo, Graduate School of Medicine, Associate Professor)

Number of Research Area：20B201 Researcher Number：90596462

【Purpose of the Research Project】

Fluorescence imaging has been used as an indispensable life science research tool that allows observing dynamics and functions of various biomolecules in live cells and organisms. However, fluorescence imaging suffers from a ‘color barrier’ (i.e. the number of simultaneously resolvable targets is limited to 4-5) owing to the intrinsically broad fluorescence spectra of fluorescent molecules. On the other hand, in recent years, Raman imaging with specific Raman tags such as alkyne, nitrile, and polyyne have been attracting attention as a method for highly multiplexed detection, because the Raman spectral linewidth can be 50-200 times smaller than the fluorescence peak width and can be tunable by structural modification such as isotope editing. However, multiplex imaging with these reported Raman tags generally requires more than 10 minutes for acquiring one image, which makes it difficult to track the biological phenomena in real time. Further, most of the pre-existing Raman tags show constant Raman signal intensity (“always-on” Raman probes), and thus their application has been limited to the labeling of molecules of interest in cells. Although there are a few reports of Raman probes that show a shift in Raman frequency or show Raman signal activation by chemically producing alkynes by externally added reagents, it has generally been believed that the Raman signal cannot be switched on and off, since it arises from molecular vibration.

In this research project, we aim at establishing a first-in-class general design strategy of “activatable-type” Raman probes that can react with endogenous biological targets and show an increased Raman signal under physiological conditions. We will also optimize and sophisticate our stimulated Raman scattering (SRS) microscopy to achieve real-time observation of biological phenomena, then validate the utility of our method for simultaneous detection of plural biomolecules in live cells and tissues. For this purpose, three groups with different expertise are working closely together to develop new functional Raman imaging probes (Mako Kamiya Group: Chemical Biology), to optimize and upgrade the high-speed, multi-color Raman spectroscopic microscopy (Yasuyuki Ozeki Group: Optics), and to apply the developed technology to biological samples (Fumiaki Obata Group: Molecular Biology).

【Content of the Research Project】

In this research project, we aim to establish a molecular design strategy to precisely control Raman signal (to switch Raman signal on and off), and to establish a method for multiplexed detection of biomolecules in live cells and tissues with superior functionality compared to conventional methods. Specifically, we will focus the following three projects.

(Project 1) Multiplex imaging of enzyme activities

We will develop activatable Raman probes whose Raman signal can be activated upon reaction with target enzymes, and establish a method for multiplex detection of multiple enzyme activities in living cells and tissues.

(Project 2) Multiplex detection of target structures

We will develop Raman probes whose Raman signal can be activated upon labeling to target proteins and structures, and develop a method for multiplex detection of target structures in live cells and tissues without washing procedure.

(Project 3) Multiplexed super-resolution imaging

We will develop photoswitchable Raman probes and Raman microscopy that induces photoswitching of the developed Raman probes to confine Raman signals to a small area to establish multiplexed super-resolution Raman imaging method.

【Expected Research Achievements and Scientific Significance】

The multiplex imaging methods using functional Raman probes to be established in this research project will dramatically expand the applicability of Raman imaging as a bioanalysis tool. Therefore, we can expect that our research project will lead to the creation of new interdisciplinary research fields, and the technologies to be developed will affect a wide range of research fields.

【Key Words】

Raman tags/probes: A general term for molecules with unique molecular vibrations that can be detected by Raman scattering. Raman tags/probes with different molecular vibration frequencies allows us to perform multiplex detection of multiple molecules. Since the molecular vibration spectrum is narrower than the fluorescence spectrum, Raman probes are advantageous for multiplexed detection.

【Term of Project】 FY2020-2022

【Budget Allocation】 121,500 Thousand Yen

【Homepage Address and Other Contact Information】

https://sites.google.com/view/i-raman/

Title of Project： Challenge to the new generation cloud-resolving climate simulation

MIURA Hiroaki
(The University of Tokyo, Faculty of Science, Associate Professor)

Number of Research Area：20B202　Researcher Number：70415991

【Purpose of the Research Project】

In "Challenge to the new generation cloud-resolving climate simulation", we will strive to bring about revolutionary advances to the climate science by the realization of the 6th generation climate model simulation, in which atmospheric phenomena are reproduced through spontaneous organization of clouds. Inclusion of explicit cloud microphysics schemes in addition to equations for atmospheric flows and radiation will enable models to reproduce clouds as physical entities with dimensions and will include spontaneous generation and dissipation of clouds. As a result, behaviors of aggregated cloud systems such as tropical cyclones and rainbands will be more realistically represented in the models. Moreover, this approach will eliminate low-order approximations and enable comprehensive evaluation of the cloud-radiation interaction, which is one of the most difficult aspects of climate predictions.

One of the distinctive characteristics of the atmospheric phenomena is their hieratical structure much similar to what is observed in biology. In analogy with the biological systems in which DNAs provide the blueprints for cells and organs, we perceive the cloud microphysics as the microscopic blueprints for the hierarchy of cloud systems. Thus, we entitled the novel approach to climate science with the 6th generation climate model that simulates cloud systems from cloud microphysics as DNA climate science.

【Content of the Research Project】

Taking advantage of the Earth Simulator launched in 2002 and K-computer launched in 2011, Japanese climate modeling groups have contributed to the Intergovermental Panel on Climate Change (IPCC) with the climate model MIROC and have led the world in the field of global cloud resolving modeling with a prototype of the 6th generation climate model, NICAM, for almost 10 years.

In this project, the plan A for realizing the 6th generation climate model is to modify the global cloud-resolving model NICAM to enable climate simulations, and back up with a plan B, in which we aim to add cloud-resolving processes on to MIROC. We aim to enhance cooperation between the developers of NICAM and MIROC so that the two models can complement each other to connect the intraseasonal time scales of typhoons and MJO and the longer timescales of Asian monsoon and climate, which NICAM and MIROC respectively excel in. Furthermore, aiming at the 7th generation standard, young researchers will take the lead in research for advanced modeling, such as general-planet model that positions the Earth as one of the planets and calculates flow phenomena of gas, liquid, and solid phases of the planetary surface layer, and a multiple-hierarchical model that dramatically increases parallel computing efficiency by incorporating the intrinsic hierarchical nature of fluid phenomena.

【Expected Research Achievements and Scientific Significance】

With the rise of exascale computers in sight, the development of the 6th generation climate models is in full swing in Europe and the United States and is expected to become the norm of climate predictions within a decade. This will lead to a paradigm shift from estimating the effects of clouds on climate from hypothetical clouds to the direct analysis of realistically reproduced clouds. This will contribute to resolving the grand challenges set by the World Climate Research Program (WCRP).

Furthermore, by providing more reliable climate predictions, we will contribute to solving global-scale issues such as the SDGs (Sustainable Development Goals) set by the United Nations. The WCRP has identified Digital Earths (a digital twin of the Earth) as one of the Lighthouse Activities that identify the core issues for the next generation climate science. Our research project is also in line with this global trend toward the realization of the Digital Earths.

【Key Words】

Climate model: A program consisting of several hundred thousand lines that computes equations for fluid dynamics, thermodynamics, and optics that are associated with the energy and water budgets of the atmosphere, land, and the oceans.

The 6th generation climate model: An interpretation of the generations of the models as 1st generation (1970's) as 1D radiative-convective equilibrium model with static clouds, 2nd generation (1980's) as 3D atmosphere general circulation model, 3rd generation (1990's) as an atmospheric model coupled to a static ocean, 4th generation (2000's) as atmospheric model coupled to 3D ocean circulation model, and 5th generation (2010's) as the modern climate model that includes atmospheric chemistry and carbon cycle processes.

【Term of Project】 FY2020-2022

【Budget Allocation】 122,000 Thousand Yen

【Homepage Address and Other Contact Information】

https://dna-climate.org/
h_miura@eps.s.u-tokyo.ac.jp

Title of Project： Precision Degradation of Polymer and Polymeric Material

NUMATA Keiji
(Kyoto University, Graduate School of Engineering, Professor)

Number of Research Area：20B203 Researcher Number：40584529

【Purpose of the Research Project】

Polymer materials such as plastics are used in a wide range of material fields due to their excellent physical properties and processability. The decomposition of polymeric materials during or after use causes serious problems in various usage environments. Generally, it is still difficult to predict the polymer decomposition precisely, partly due to the lack/delay of systematic research on the decomposition of polymers. Simultaneously, it is not easy to suppress deterioration and decomposition and improve the stability of polymeric materials. These problems are because the decomposition of macromolecules has not been understood in multiple layers from the macro-level to the molecular level via the mesoscale. Despite the demand for polymer design based on theoretical prediction of stability and degradability of polymeric materials in various fields, it has not been realized due to the lack of systematic research on polymer decomposition and degradation.

This research project aims to clarify the degradation mechanism of polymers and polymeric materials with considering the hierarchical structure in terms of physical deterioration, chemical decomposition, and biological degradation and metabolism. Furthermore, the long-term goal is to provide new polymer design guidelines that consider degradability and environmental impacts. For the molecular theory that experiments cannot approach, the level of coarse-graining is judged based on the information obtained from the experiments, and computational science is introduced to clarify it.

【Content of the Research Project】

This research project promotes four planned research topics and two fusion research subjects to construct a theory and guideline that enable the precise decomposition of macromolecules and macromolecular materials. The planned research includes “A01 Elementary process of physical deterioration using uniform polymer network (physical deterioration)”, “A02 Precise design and time-course analysis of polymer chain cleavage under usage environment (chemical decomposition)”, “A03 Precise characterizations of degradation products and evaluation of their impact on the biological environment (biological metabolism)”, and “A04 Polymer decomposition simulation by effective coarse graining (decomposition prediction)”. Through these planned studies, we will consistently study physical destruction processes such as deterioration and wear of polymer materials, chemical polymer chain breaks, and decomposition products and their effects on living organisms in nature. Computational science will promote the phenomena that are difficult for the experimental evaluations. At the same time, by linking the four research topics, this research project sets two fusion research subjects, namely, “P1: the theory of spatiotemporal effects” and “P2: the theory of homogeneity and heterogeneity”. P1 promotes research on polymer decomposition effects, focusing on its time scale and spatial scale, that is, the degradation rate and degradation product concentrations. In P2, we approach the precise decomposition of polymers based on the presence or absence of a hierarchical structure of macromolecules, that is, the homogeneity and heterogeneity in the structure.

As pointed out in the reviewers’ comments on our project application, there is a risk of dissipating research results due to the wide scope of this project. Thus, we decided to focus on rubber polymers that are feared to impact the natural environment as well as biodegradable thermoplastic (polyesters) as the main target polymers in this research project according to discussions in the kick-off symposium.

【Expected Research Achievements and Scientific Significance】

When this project is achieved successfully, we will be able to design and synthesize the polymers with precisely designed and controlled degradability, such as polymers that are safe to leak into the natural environment, biomaterials that can be safely used *in vivo* for a long time, and closed-loop recyclable polymer materials.

【Key Words】

・ Polymer materials: Human life is made up of many polymer materials including rubber, plastics, synthetic fibers.

・ Precision decomposition: Although research on the precision synthesis of macromolecules has been carried out for many years, the precision decomposition theory that systematically controls the decomposition process is insufficient so far.

【Term of Project】 FY2020-2022

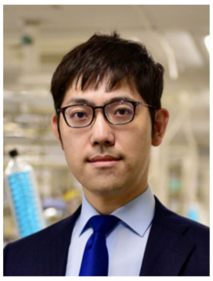
【Budget Allocation】 122,100 Thousand Yen

【Homepage Address and Other Contact Information】

http://pixy.polym.kyoto-u.ac.jp/pd/pd_index.html
numata.keiji.3n@kyoto-u.ac.jp

【Grant-in-Aid for Transformative Research Areas（B)】

Section II



Title of Project： Deuterium Science

NAKA Hiroshi
(Kyoto University, Graduate School of Pharmaceutical Sciences, Associate Professor)

Number of Research Area：20B204 Researcher Number：70431517

【Purpose of the Research Project】

Deuterium (^{2}H, D) is a non-radioactive, stable isotope of hydrogen (protium, ^{1}H) (Figure 1, left). Most properties of protium and deuterium are similar; however, there are major physical differences between the two isotopes which make their substitution with one another an interesting research field and they are: (1) D is twice as heavy as ^{1}H and (2) C−D bonds are stronger than C−^{1}H bonds. As a result, deuterated materials occasionally show quite different properties in comparison with their non-deuterated analogs. For example, the metabolic rate of C−D bond cleavage is slower by ten times or more as compared with that of C−^{1}H bond. This difference has led to the development of a heavy drug (deuterium-labeled medicines, namely, deutetrabenazine) approved by FDA (USA) as a new pharmaceutical in 2017 (Figure 1, right). Deuterium-control (isotope-control) on the material properties is an emerging yet immature concept in material design worldwide. The effect of deuterium substitution in materials can have positive or negative effect on the material properties depending on the position of the deuterium atoms and the metabolic pathways of the drug or the reaction mechanisms involved.

The purpose of this research project is to cultivate a deep understanding of the properties of deuterated materials and to explore the research field "deuterium science". Through this research activity, we wish to propose a new material design concept "Deut-Switch", which aims to maximize the material functions by precise and logical deuteration of materials and accurate prediction of the isotopic effect.

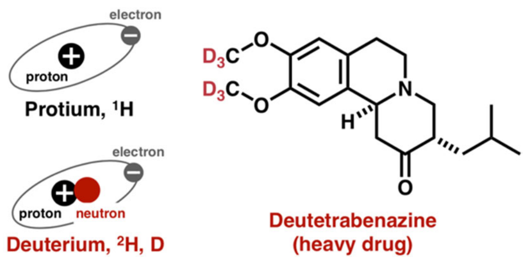


Figure 1. Isotopes of hydrogen (left) and heavy drug (right).

【Content of the Research Project】

To achieve our objectives, we promote the following four research items and collaborate closely with each other (Figure 2).

(1) **A01 Synthesis.** Development of synthetic methodology of deuterated materials;

(2) **A02 Calculations.** Understanding of the properties of deuterated materials by computational methods;

(3) **A03 Measurements.** Exploration of the reactivity of deuterated materials using spectroscopic measurements;

(4) **A04 Applications.** Application of deuterated drugs for metabolic research.

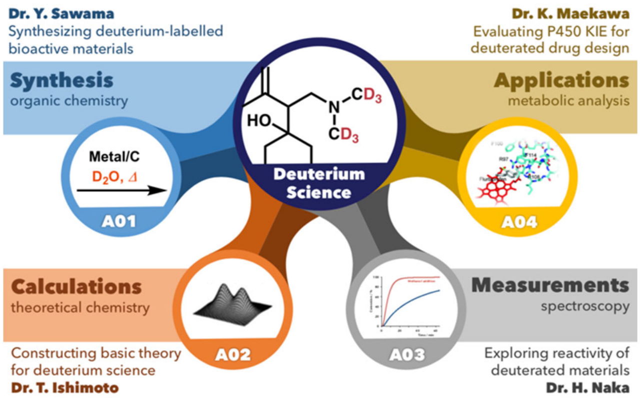


Figure 2. Framework of the project “deuterium science”.

【Expected Research Achievements and Scientific Significance】

This project will establish efficient methods for the synthesis and measurement of deuterated materials. New guides for the rational design of deuterated pharmaceuticals and agrochemicals will be provided.

Knowledge established in this project will be of high value in various academic and industrial fields. Examples include neutron scattering analysis of macromolecule structures, NanoSIMS isotopic imaging, organic electroluminescent display, solar battery, petroleum identification agent, nuclear-fusion power generation, and optical fiber.

【Key Words】

Heavy drug: medicine labeled with deuterium at specific molecular sites. The replacement of specific C−^{1}H bonds of medicine with the more stable C−D bonds results in better metabolic stability (isotopic effect). This effect contributes to reducing the frequency of taking medications and the occurrence of side effects as a result of unfavorable metabolic degradation pathways

【Term of Project】 FY2020-2022

【Budget Allocation】 121,800 Thousand Yen

【Homepage Address and Other Contact Information】

http://www.pharm.kyoto-u.ac.jp/deut_switch/
deuteriumscience@pharm.kyoto-u.ac.jp

【Grant-in-Aid for Transformative Research Areas（B）】

Section II

Title of Project：Science for virtual human development: Organ(s)-on-a-chips reveal systemic metabolic networks

SUGIMOTO Masahiro
(Tokyo Medical University, School of Medicine, Professor)

Number of Research Area：20B205　Researcher Number：30458963

【Purpose of the Research Project】

As an approach to understanding the human body through science and engineering, we aim to construct a virtual human that mathematically describes various responding reactions. The non-linear and dynamic response of the living body is reproduced to understand the rationality acquired by the living body.

Once mathematical models are sufficiently validated and the behavior of molecular networks is virtually reproduced, the data-driven science is realized. We will develop mathematical models, highly-sensitive omics-based measurement, and various types of organs-on-a-chip.

Such approaches potentially become a novel academic discipline that includes medicine, informatics, analytical science, and pharmacy, while being based on science and engineering, and finally, we will establish the “science of virtual humans”.

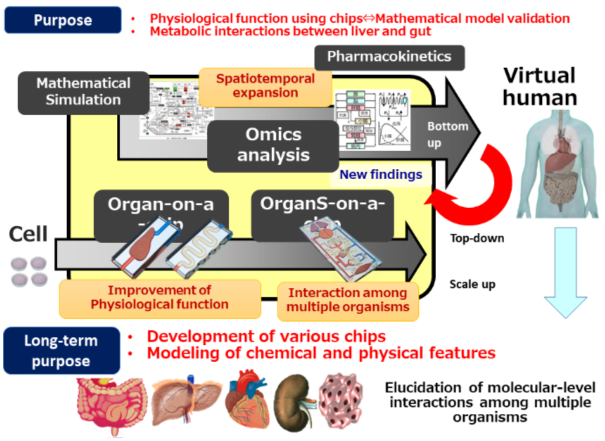


Figure 1. Overview

【Content of the Research Project】

Metabolic pathways were virtually reproduced using mathematical models and chip technologies. The physiological function of each chip will be improved, and subsequently, the multiple chips will be linked. Highly sensitive omics technology will analyze the molecules which induce the interactive reactions among organisms. Mathematical simulation models are also validated and will be used to analyze the robustness and fragility of biological systems. The interactive development and validations will accurately reproduce the dynamic responses of the systems.

【Expected Research Achievements and Scientific Significance】

The development and validation of mathematical simulation, highly sensitive omics, and organs-on-a-chip will yield the following.

First, the result of the new methodology for understanding the human body. These results will contribute to the sciences in physiology, medicine, and pharmacy, etc. The discrepancy between the current *in vitro* experimental system and the actual human body will be decreased. The methods to be developed will be used in pharmaceuticals, foods, chemical substances, and use as individual disease models.

Second, the mathematical model, measurement methods, and experimental systems will be used in the various fields. The integration of these research results will realize data-driven biosciences.

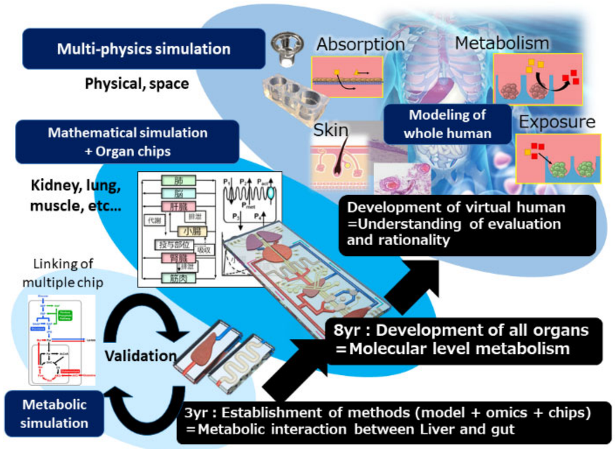


Figure 2. Expected achievements

【Key Words】

Mathematical model, Systems biology, Organ-on-a-Chip, OrganS-on-a-Chip, metabolome

【Term of Project】 FY2020-2022

【Budget Allocation】 121,900 Thousand Yen

【Homepage Address and Other Contact Information】

https://www.kasojintai.com/

Title of Project： Agile and Frequent Solar System Exploration with Innovative Microsatellite

FUNASE Ryu
(Japan Aerospace Exploration Agency (JAXA), Institute of Space and Astronautical Science (ISAS), Professor)

Number of Research Area：20B206　Researcher Number：70509819

【Purpose of the Research Project】

In space development activities conducted in the vicinity of the Earth, CubeSat, the world's first successful nano-satellite in 2003, was ridiculed as a "toy" due to its insignificant functions and performance at the time. However, such small satellites have developed explosively by extending their features of low-cost and short-term development. As a result, not only space agencies but also universities and venture companies are now using small satellites for space development, resulting in a situation where thousands of small satellites are orbiting the earth.

The purpose of this research project is to extend this active world to the deep space region outside the Earth's gravitational field by developing the small satellite technology cultivated in the near Earth region for deep space exploration, and to make the deep space region more easily accessible.

【Content of the Research Project】

Currently, there are three barriers to the realization of frequent and flexible deep-space exploration by small satellites: (1) limited opportunities for deep-space launches, (2) issues with the small satellite system itself, such as the reliability of the spacecraft for long-term missions, and (3) limited number of ground stations for spacecraft control.

In order to overcome these barriers, this research project aims to enable small spacecraft that can escape from Earth orbit on their own by kick motors and have the capability to carry out long-term deep space missions to perform orbit determination and control operations quasi-autonomously. This research area will be promoted by the following three research projects.

Project I: Research on kick motors to improve the accessibility to deep space
Project II: Research on small spacecraft systems that can carry out long-term deep space missions
Project III: Research on quasi-autonomous orbit determination and planning to reduce dependence on ground stations

【Expected Research Achievements and Scientific Significance】

The goal of this research project is to break through the limitations that prevent frequent deep space exploration, thereby paving the way for the realization of the ultimate goal of this area, namely, frequent and flexible exploration of the solar system. The results of this research will make it possible to increase the number of exploration missions currently carried out by space agencies to at least several dozen and is expected to bring new horizons to the world of solar system exploration.

If this research project is further promoted, it will lead to the integration of many fields other than aerospace engineering, including process engineering for designing and manufacturing a large number of spacecraft at low cost and in a short period of time, artificial intelligence technology for the spacecraft to act autonomously, and technology for semi-automatic trajectory design for deep space exploration without the need for a limited number of experts in orbital mechanics. The ultimate goal, a world in which an overwhelming number of ultra-small spacecraft can freely explore the solar system, is expected to be realized.

【Key Words】

Nano/Micro-satellite: Satellites that generally weigh from about 1 kg to less than 100 kg. Conventional satellites can weigh more than several tons, but small, lightweight, and low-cost nano/micro-satellites that incorporate the latest commercial technologies have been developed since the 2000s.

Kick motor: A propulsion device (engine) that accelerates a satellite launched into space by a rocket into a farther orbit. There are no examples of kick motors mounted on nano/micro-satellites yet.

【Term of Project】 FY2020-2022

【Budget Allocation】 102,400 Thousand Yen

【Homepage Address and Other Contact Information】
https://www.isas.jaxa.jp/home/smallsat/tra-b/

Title of Project : Micro-meteorology control: Integrated technology of harmonic prediction and active monitoring of micro-meteorology for future autonomous society

ONISHI Ryo
(Tokyo Institute of Technology, Global Scientific Information and Computing Center, Associate Professor)

Number of Research Area : 20B207 Researcher Number : 30414361

【Purpose of the Research Project】

In future smart cities, various autonomous systems work collaboratively for maintaining sustainable, safe and comfortable society harmonized with nature (Fig.1).

Micrometeorology, which is directly linked to human life, is extremely important in order to realize such a future society. However, despite being related to various social issues, micrometeorology has been largely untouched academically. This project aims to bring new changes in the natural sciences and society by realizing the real-time micrometeorology prediction for the first time in the world and to show the feasibility of new social services based on the prediction information. Mere understanding and prediction of phenomena cannot ultimately create new social value. What is important here is the integration of observation and prediction that can hold the "spatio-temporal scale and accuracy" required for each issue. We will first focus on the integration of observation and prediction to initiate the new academic creation. Rather than simply linking cutting-edge observations and predictions, we will realize a right integration that creates value while sharing the appropriate "spatio-temporal scale and accuracy" according to the ultimate purpose.

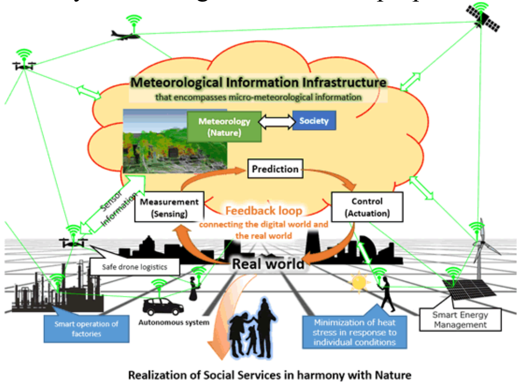


Fig.1: Autonomous society harmonized with nature

【Content of the Research Project】

The bottleneck of micro-meteorology prediction will be solved by fusing AI technology with the cutting-edge ultra-high-resolution micro-meteorology simulation that can consider the effects of artificial structures and human activities (Fig.2). The bottleneck of observation will be solved by active measurement that combines the mobility of a large number of autonomous drones and the adaptability to the unsteady environment.

Simply understanding and predicting phenomena is not enough to ultimately create new value to society. It is necessary to integrate observation and prediction in the right sense through the cooperation technology of observation, prediction, and control that correctly captures the "spatio-temporal scale and accuracy" necessary for solving social issues. In this project, we will build a micro-meteorology prediction system that combines harmonic prediction that has real-time performance and adaptability with active observation that has mobility and adaptability, and a social service infrastructure.

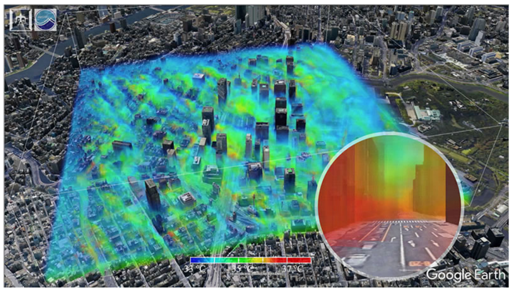


Fig.2: Snapshot of three-dimensional temperature distribution near Tokyo station obtained by our building-resolving urban micro-meteorology simulation.

【Expected Research Achievements and Scientific Significance】

Meteorological information infrastructure that includes micro-meteorology prediction information will be directly linked to the decision-making and control of things and human activities, and thus can provide a foundation for creating new social services. Furthermore, by treating weather and social networks at the same time, we can realize a safe and secure society with "zero victims of weather-related disasters" preventing unexpected disasters or accidents, and a sustainable society harmonized with nature.

【Key Words】

Micro-meteorology: near-surface atmospheric conditions, up to approximately 100 m in height, strongly affected by buildings and human activities.

【Term of Project】 FY2020-2022

【Budget Allocation】 119,900 Thousand Yen

【Homepage Address and Other Contact Information】

https://www.turb.gsic.titech.ac.jp/mmc/