Title of Project : Software Foundations for Interoperability of Autonomic Distributed Data Based on Bidirectional Transformations

Zhanjiang Hu
(National Institute of Informatics, Information Systems Architecture Science Research Division, Professor)

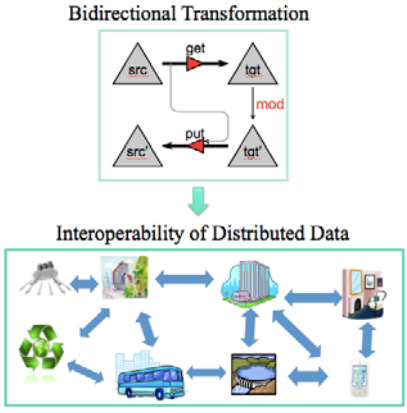
Research Project Number : 17H06099 Researcher Number : 50292769
Research Area : Software, Computing Infrastructure
Keyword : Programming Languages, Bidirectional Transformations, Data Interoperability

【Purpose and Background of the Research】

Big data processing is now widely employed in all aspects of our lives. Usually, parts or copies of a huge amount of data are stored in separate locations, and it is infeasible to collect all the parts and copies of the data and process them in a centralized manner, as it would be exceedingly inefficient to transfer them over the network. We therefore need new software foundations based on which big data can be efficiently analyzed and shared in a distributed way.

A highly relevant research area is bidirectional transformations, which provide a reliable mechanism for data synchronization. The study of bidirectional transformations originates from the long-standing problem of view updating in databases, and has led to a rich collection of bidirectional languages with new programming models tailored for data synchronization. Despite the potential in solving practical synchronization problems including data interoperability, bidirectional technologies are not widely employed yet, and most applications of bidirectional transformations remain only proof of concept.

In this research, we aim to further develop bidirectional technologies to make them more reliable, scalable, and efficient, so as to establish solid foundations for integration, sharing, and interoperability of autonomic distributed big data.



【Research Methods】

We will build on our previous research on bidirectional transformations to achieve the following three goals:

"Goal 1: To further develop bidirectional transformation technologies", to enable modular development, static analysis and automatic verification, strong debugging mechanism, and learning support for large-scale, reliable, and systematic construction of bidirectional applications.

"Goal 2: To build a new foundation with bidirectional transformations", which will feature a novel view-passing model that can achieve efficient asynchronous parallel data processing and facilitate interoperability of autonomic distributed data.

"Goal 3: To construct practical applications of bidirectional transformations", solving real-world problems using the view-passing model.

【Expected Research Achievements and Scientific Significance】

The unique contribution of this research is that we will push the scalability and reliability of bidirectional transformations to the limit, and be able to demonstrate its practical values using real-world applications about interoperability of autonomic distributed data.

This research continues our leading work on practical bidirectional transformations (e.g., bidirectional languages designed to offer full programmability), and is a groundbreaking step in solving important real-world problems using bidirectional transformations. By developing a system for autonomic distributed big data, we will eliminate the problem of centralized management in the current cloud-based computing environments, and provide a new methodology of distributed computing.

【Publications Relevant to the Project】

- H-S. Ko, T. Zan, Z. Hu, BiGUL: A Formally Verified Core Language for Putback-Based Bidirectional Programming, ACM PEPM 2016.
- S. Hidaka, Z. Hu, K. Inaba, H. Kato, K. Nakano, K. Matsuda, Bidirectionalizing Graph Transformations, ACM ICFP 2010.

【Term of Project】 FY2017-2021

【Budget Allocation】 133,500 Thousand Yen

【Homepage Address and Other Contact Information】

- http://research.nii.ac.jp/~hu/
- hu@nii.ac.jp

Title of Project : From Text Engineering to Text Science

Seiichi Uchida
(Kyushu University, Faculty of Information Science and Electrical Engineering, Professor)

Research Project Number : 17H06100　Researcher Number : 70315125
Research Area : Multimedia, database
Keyword : text science, text engineering, character recognition, machine learning, font design

【Purpose and Background of the Research】

Text and its component characters are one of the most important media for our intellectual activity and communication. In this project, we will establish new research field, called "text science". Its purpose is to fully understand multiple functions of text and characters, which are not analyzed in past researches. Specifically, we will analyze the following four functions objectively with a large amount of real data: disambiguation of scene context, ubiquitous message transmission, nonverbal impression expression by font design, and legibility against distortion.

【Research Methods】

(1) Disambiguation of scene context: We will analyze how textual information in scene helps to disambiguate its surroundings as a label. In other words, we will analyze the interaction between scene and textual information.
(2) Ubiquitous message transmission: We will analyze what kind of messages texts and characters send to us in daily life. In addition, we will compare information given as textual message with semantic information implicitly given from scene images.
(3) Nonverbal impression expression by font design: We will analyze the relationship between semantics and font design of words. Furthermore, we will try to realize an automatic font design method so that the font expresses specific impression.
(4) Legibility against distortion: We will investigate why characters can keep its legibility under various distortions and noise. In addition, we will generate a new alphabet (i.e., a set of character symbols) in an automatic way, where each symbol can be distinguished clearly from the others even under various distortions.

【Expected Research Achievements and Scientific Significance】

We expect to have multiple research achievements in both of fundamental and application.
(1) As fundamental achievements, we will establish a new scientific framework for communication utilizing multiple functions of text and characters. In addition, our research results of analyzing the simplest patterns, i.e., character symbols, will contribute to general pattern recognition and artificial intelligence research.
(2) In application fields, we contribute to environment, art and design, society and welfare, and humanity and life, because text and characters are related to all human activities. As application examples, we will realize a supporting system for scene understanding and a font design method so that the font expresses specific impression and keeps sufficient legibility under various distortions.

【Publications Relevant to the Project】

Uchida S., Text Localization and Recognition in Images and Video, in Handbook of Document Image Processing and Recognition, Springer-Verlag, London, 2014.
Zhu A., Gao R., Uchida S., Could Scene Context be Beneficial for Scene Text Detection? Pattern Recognition, vol.58, pp.204–215, Oct. 2016

【Term of Project】 FY2017-2021

【Budget Allocation】 116,000 Thousand Yen

【Homepage Address and Other Contact Information】

http://human.ait.kyushu-u.ac.jp
uchida@ait.kyushu-u.ac.jp

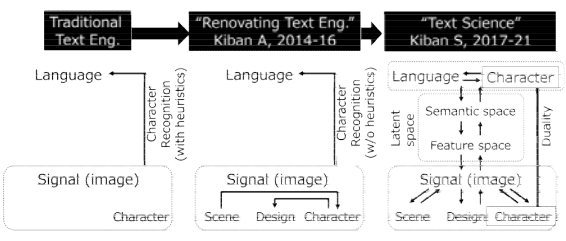


Figure 1　From text engineering to text science

Title of Project：Next Generation Speech Translation Research

Satoshi Nakamura
(Nara Institute of Science and Technology, Graduate School of Information Science, Professor)

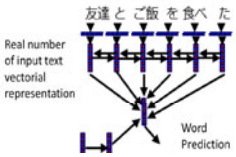
Research Project Number：17H06101　Researcher Number：30263429
Research Area：Informatics, Human Informatics, Perceptual Information Processing, Speech Processing
Keyword：Speech Translation

【Purpose and Background of the Research】

The conventional speech translation, which translates a sentence after each utterance in a simple domain such as travel conversation, is advancing for a practical use, but the simultaneous translation still faces difficulties for practical use. Especially for the translation between Japanese and English, as they have different sentence structures, the system cannot start translation until the verb or negation is recognized. The goal of this project is to develop a next generation speech translation system that is able to start translation instantly without waiting for a sentence end as human interpreters do. It conveys the message of speakers by avoiding a breakdown caused by the structure sentence difference.

【Research Methods】

①A) Noise reduction based on DNN by using the noise database, integration with independent low-rank matrix analysis, and development of target voice extraction and enhancement with multiple distributed microphone arrays, B) improvement of continuous speech recognition system for lectures based on the system for national congress, C) upgrading simultaneous translation by predicting a potential tree structure of the next utterance from the current parsing analysis result, and utilizing a tree-to-string model, D) trial to compress input/ output layers of attentional NMT based on LSTM, E) introduction of dialogue management technologies

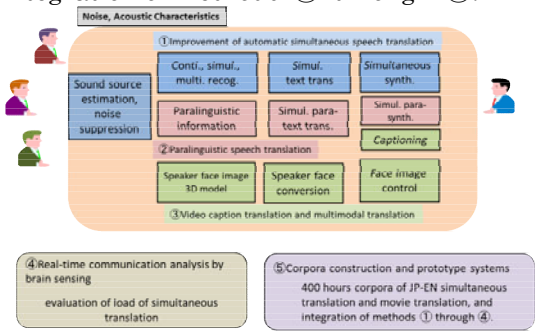


②A) Paralinguistic translation of speech emphases and emotional expressions, B) speech synthesis with paralinguistic information
③A) captioning of speech translation based on summarization technologies, B) multimodal translation by using lip sync for videos


Model Fitting


Mouth Model

④Real-time communication analysis by brain sensing for evaluation of load of translation
⑤A) Corpora construction, B) prototype systems by integration of methods ① through ④.



【Expected Research Achievements and Scientific Significance】

①Continuous noisy speech recognition of multiple speakers and automatic incremental speech translation with consideration of sentence structure difference between languages. ② Paralinguistic speech translation to extract, preserve and reproduce speaker's emotion, emphasis, and individuality. ③Video captioning and translation for lectures and movies. ④Data analysis of brain activity sensing during translation. ⑤ 400 hours corpora of JP-EN simultaneous translation and movie translation, prototype systems.

【Publications Relevant to the Project】

・Yusuke Oda, Satoshi Nakamura et al., "Syntax-based Simultaneous Translation through Prediction of Unseen Syntactic Constituents", ACL 2015, pp. 198-207. July 2015.
・Satoshi Nakamura, "Speech Translation Technologies, Past and Beyond," The Journal of the IEICE, vol.96, no.11, pp865-873, 2013.11

【Term of Project】 FY2017-2021

【Budget Allocation】 157,100 Thousand Yen

【Homepage Address and Other Contact Information】

Not yet available

Title of Project : Computational Optical Imaging for Endoscopic Surgery

Hajime Nagahara
(Osaka University, Institution for Datability Science, Professor)

Research Project Number : 17H06102 Researcher Number : 80362648
Research Area : Information Science
Keyword : Computational Photography, Optical Sensing, Medical Sensing

【Purpose and Background of the Research】

An endoscopic surgery is getting attention and the number of the patients has been increased in these days, since the patients have less load to have the surgery and early to recover. However, a surgeon must see only 2D displaying images with limited field of view and view points during the surgery. The endoscopic surgery requires a surgeon to have higher skills and experiences, since it is more difficult and less safe than regular surgeries. In this project, we will develop a new optical imaging technique for measuring 3D shape of organ tissues.

Existing 3D measurement methods using time of flight (TOF) modulate an intensity of projecting light as sinusoidal pattern and measures the reflective light from an object. It calculates an object depth from the delay of the light by phase difference between projecting light and received light. A regular TOF method assumes that there is only direct reflection, although, actual reflection contains scattering and multipath factors. So the existing TOF cannot apply to the organ tissues, since there are a scattering and multipath in this situation and they causes a large estimation error.

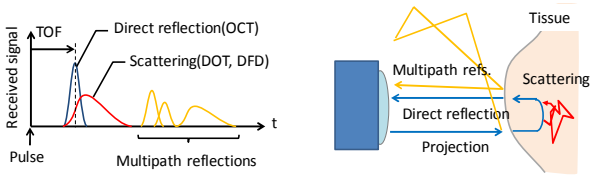


Figure 1 Responses of multiple reflections

【Research Methods】

We propose a sensing hardware and a method to obtain direct, scattering and multipath reflections from a single captured image. We develop an optical comb inference camera that consists of comb leaser and reference laser sources, inference optics, temporal modulation CMOS sensor. We propose a 3D reconstruction method from the captured inference image. The proposed method is combined with the different types of estimation methods; TOF, OCT, and DFD/ODT utilizing the different depth ques separating from the single captured image. We will fuse these results with the different range of the depth and resolutions to generate an single general 3D model. We will apply the proposed 3D measuring method to endoscope surgery supporting system to show a generated free view images. We will also evaluate the system by actual endoscopic surgery situation in experiments. Figure 2 shows the overview of our project and each essences of the project.

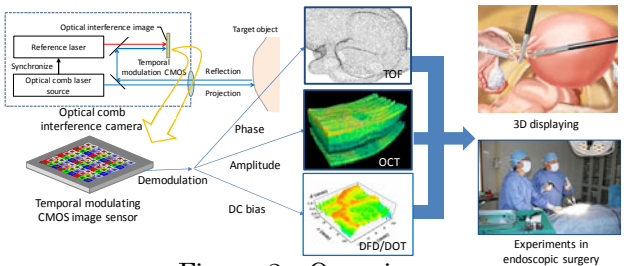


Figure 2 Overview

【Expected Research Achievements and Scientific Significance】

Our group consists of optics, sensor, and informatics expertise. we are only able to realize this new methodology of computation optical imaging corroborative with different areas.

The proposed optical imaging realizes to measure 3D shape organs and make the endoscopic surgery safer in actual application.

【Publications Relevant to the Project】

H. Nagahara, “Computational 3D imaging”, Display week, Aug. 2016 (Invited talk).

【Term of Project】 FY2017-2021

【Budget Allocation】 115,800 Thousand Yen

【Homepage Address and Other Contact Information】

http://www.ids.osaka-u.ac.jp/organization/
nagahara@ids.osaka-u.ac.jp

Title of Project : Advanced Reasoning Support for Judicial Judgment by Artificial Intelligence

Ken Satoh
(National Institute of Informatics, Principles of Informatics Research Division, Professor)

Research Project Number : 17H06103 Researcher Number : 00271635
Research Area : Logical Foundation of Artificial Intelligence, Juris-informatics
Keyword : Artificial Intelligence, Judicial Judgement, juris-informatics

【Purpose and Background of the Research】

In the trial process, the intellectual tasks that the judges are carrying out are roughly divided into the fact finding process, the subsumption process, and the judgement process. The fact finding process is a process of recognizing facts actually occurred in the case from evidence, the subsumption process is a process of making the facts correspond to legal concepts, and the judgement process is a process of making a judgement according to the legal concepts corresponding the facts based on legal rules. Furthermore, in court cases, there are conflicting structures of plaintiffs and defendants, and prosecutors and an accused. Therefore, in the trial process, various complicated high-order inferences are executed, and more accurate and prompt high order inference should be realized by support by artificial intelligence.

For this research, we aim to develop a system that supports advanced reasoning by using the following fundamental technologies and a system that analyzes argumentation in each process (Figure 1) .

1.Fact finding process support system using evidence reasoning based on Bayesian network
2.Subsumption process support system by acquiring subsumption rules based on natural language processing
3.Judgement process support system by extending the existing civil code reasoning system PROLEG to handle criminal cases and administrative cases
4.Argumentation analysis system based on argumentation theory

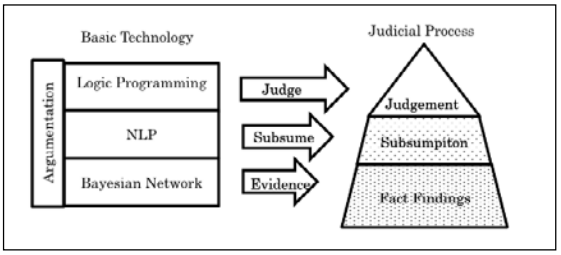


Figure 1 System Configuration

【Research Methods】

In FY2029, we investigate technologies of each trial process and argumentation analysis and the law scholar group considers the virtual judicial cases which can be used commonly in each process . In FY2030, we construct a prototype system and confirm each process execution using the above virtual judicial cases. In FY2031, we integrate each system and verify whether we can comprehensively solve the entire virtual judicial case, and the legal school group will evaluate the result. In FY2032, this system is applied to actual cases (including both civil and criminal). In FY2033, we ask the attorneys to use this system to verify applicability.

【Expected Research Achievements and Scientific Significance】

If this research is succesful, we can improve the accuracy and the efficiency of the judicial system using AI technology and increase the trust for the judicial system. This allows the public to access the judicial system easily, and it can be expected that a proper society (legalized society) will be created in which dispute resolution by law is properly considered.

【Publications Relevant to the Project】

Satoh, K., et al.,"PROLEG: An Implementation of the Presupposed Ultimate Fact Theory of Japanese Civil Code by PROLOG Technology", New Frontiers in Artificial Intelligence: JSAI-isAI 2010 Workshops, Revised Selected Papers, LNAI 6797, pp. 153-164 (2012).
Satoh, K., ``Logic Programming and Burden of Proof in Logic Programming", New Generation Computing, Vol. 30, No.4, pp.297-326 (2012).

【Term of Project】 FY2017-2021

【Budget Allocation】 113,600 Thousand Yen

【Homepage Address and Other Contact Information】

http://research.nii.ac.jp/~ksatoh/juris-informatics/

Title of Project : Understanding the interaction between ice sheets, ocean and atmosphere under large scale climate changes of the past

Ayako Abe-Ouchi
(The University of Tokyo, Atmosphere and Ocean Research Institute, Professor)

Research Project Number : 17H06104 Researcher Number : 30272537
Research Area : Environmental science, Environmental dynamic analysis
Keyword : environmental change, paleoclimate modeling

【Purpose and Background of the Research】

During the past 1 million years, there were glacial-interglacial climate cycles with periodicities of around 100,000 years. We have, for the first time, used a full scale numerical model to simulate the glacial cycles of the past 400,000 (Abe-Ouchi et al, 2013). We now extend our experiments to cover the past 1.5 million years to elucidate the processes leading to ice sheet collapse, the interaction with the global climate and the cause of the transition of the periodicity from 40,000 to 100,000-years. Using an atmosphere-ocean coupled climate model, we challenge to propose the mechanism of the millenial scale climate change, such as Dansgaard-Oschger oscillation, B/A and Younger Dryas events. Another important issue that needs to be addressed is whether abrupt climate changes are the cause or effect of deglaciation.

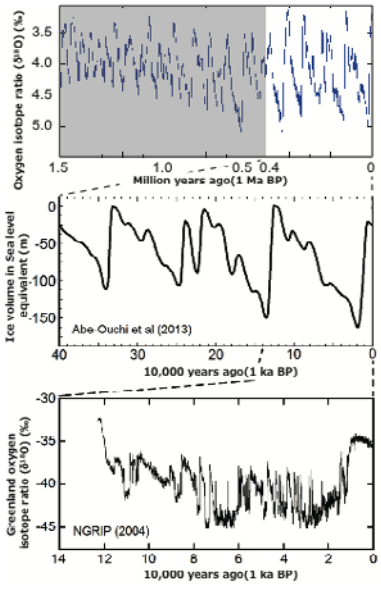


Figure 1 Glacial cycles of the past 1.5 Million years

【Research Methods】

We will carry out various numerical experiments to simulate the climate and ice sheets by using coupled atmosphere-ocean, ice sheet and vegetation models, with orbital parameters and greenhouse gas levels as model input. We will use ocean biogeochemical and isotope-incorporated models to compare with paleoclimate data and validate climate model results. Changes in the periodicity of the glacial cycle, changes in the climate, ice sheets and ocean during the Last Glacial Termination, reproduction of the millennial scale abrupt climate changes and prerequisites for these changes to occur will be investigated.

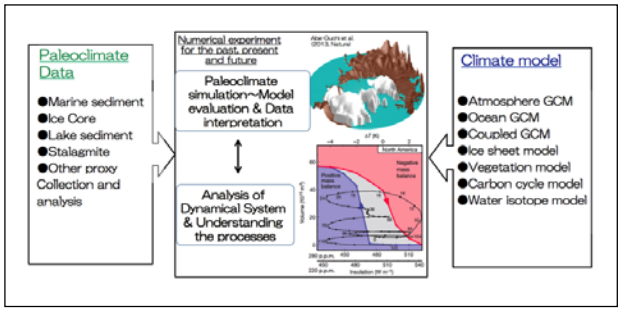


Figure 2 Outline of research

【Expected Research Achievements and Scientific Significance】

Various sensitivity experiments with climate models should yield temporal and spatial reconstructions of air temperature, precipitation, ocean circulation, ice sheet and vegetation distribution, ocean biogeochemical state, and a better understanding of the mechanisms involved. Clarifying the mechanisms behind glacial climate change by carrying out long-term simulation, while also establishing a research base to systematically tie model and data through international cooperation together presents an opportunity to contribute to the science of past-to-future climate.

【Publications Relevant to the Project】

・Abe-Ouchi, A. et al. (2013, *Nature*, 500, 190-193, doi:10.1038/nature12374.
・Kawamura et al (2017), *Science Advances*, 3, e1600446, doi:10.1126/sciadv.1600446.

【Term of Project】 FY2017-2021

【Budget Allocation】 157,600 Thousand Yen

【Homepage Address and Other Contact Information】

http://ccsr.aori.u-tokyo.ac.jp/~abeouchi/
abeouchi@aori.u-tokyo.ac.jp

Title of Project : Environmental diagnosis with isotopologue tracers

Naohiro Yoshida
(Tokyo Institute of Technology, School of Materials and Chemical Technology, Professor)

Research Project Number : 17H06105 Researcher Number : 60174942
Research Area : Environmental Cycle Analysis, Environmental Chemistry
Keyword : Material cycle, Biogeochemistry, Stable isotope, Isotopomer, Isotopologue

【Purpose and Background of the Research】

Since the 1950's, the stable isotope composition of natural samples has proved to be a unique tool for the study of geological and biological processes, their evolution and effect on Earth's surface environment. However, due to technical and conceptual limitations, the complete set of information potentially contained in the different modes of isotopic substitution remains largely unexplored. In this project, using new methodological developments that allow analysis of more isotopically substituted molecules, we will develop new tracers in 3 isotopologue modes (Fig.1), fully integrated in the study of geological, biological and anthropogenic processes which affect the evolution of the Earth's surface environment.

【Research Methods】

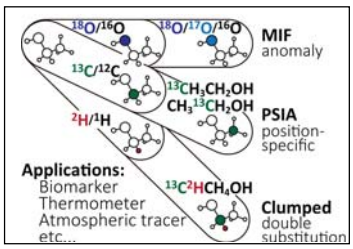


Fig.1. Et-OH isotopologues

1) Position specific isotope analysis (PSIA): Our group has pioneered PSIA of N_2O[1,2] and organic molecules using classic isotope mass spectrometry[3] and nuclear magnetic resonance[4,5]. We have shown that PSIA of hydrocarbons and organic acids allows to distinguish between biological and non-biological processes[4,6].

2) Mass-independent fractionation (MIF): The discovery of MIF of sulfur and oxygen in terrestrial samples has revolutionized environmental geochemistry and our understanding of the evolutionary history of the Earth's environment and life[7-9].

3) Clumped isotopes (i.e. isotopologues with 2 minor isotopes) provide unique information about the temperature history of molecules such as carbonates[10] or organic compounds[11-13].

We will develop new and improved tracers of environmental and biogeochemical processes and apply them to the environmental diagnosis (Fig. 2).

【Expected Research Achievements and Scientific Significance】

We will establish and standardize new methods for the analyses of every 3 complex modes of isotopic substitution, and unifying them to develop ultimate environmental diagnosis.

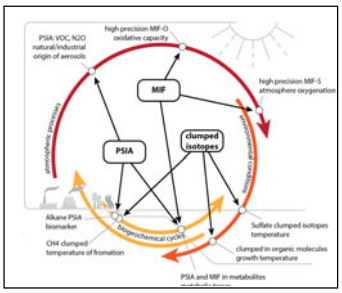


Fig. 2. Ultimate diagnosis

The development and application of these new isotopic tools to the environment evolution, in modern and more ancient eras, represents an important conceptual advance in Earth and life sciences. This will open new areas of research about, for example, the geological production of some atmospheric gases, metabolic processes and the biological fixation of atmospheric CO_2, the production and cycling of pollutant gas by industrial processes.

As a whole, these new tracers will be integrated together for diagnosis of the Earth's environment.

【Publications Relevant to the Project】

1)Yoshida & Toyoda, 2000 *Nature*; 2)Yamazaki, Toyoda, Yoshida, et al., 2014 *Biogeosciences*; 3)Yamada, Yoshida, et al., 2002 *RCM*; 4)Gilbert, Yamada, Yoshida, 2013 *Anal. Chem*., and 5) 2014 *Anal. Chim. Acta*; 6)Gilbert, Yamada, Ueno, Yoshida 2016 *Geochim. Cosmochim. Acta*; 7)Danielache, Ueno, Yoshida et al., 2008 *J. Geophys. Res.*; 8)Hattori, Danielache, Ueno, Yoshida et al., 2013 *PNAS*, 9)Ueno, 2015 *Science*; 10) Yoshida, Abe, Yamada et al., RCM, 2013; 11)Tsuji, Yamada, Yoshida et al., 2012 *Sensor*; 12)Ono et al., 2014 *Anal. Chem.*; 13)Stolper et al., 2014 *Science*.

【Term of Project】

FY2017-2021

【Budget Allocation】

162,400 Thousand Yen

【Homepage Address and Other Contact Information】

http:// nylab.chemenv.titech.ac.jp/
yoshida.n.aa@m.titech.ac.jp

Title of Project : Renovating Assessment for the Future: Design-Based Implementation Research for a Learning-in-Class Monitoring System Based on the Learning Sciences

Hajime Shirouzu
(The University of Tokyo, Center for Research and Development on Transition from Secondary to Higher Education, Professor)

Research Project Number : 17H06107 Researcher Number : 60333168
Research Area : Educational technology
Keyword : Learning assessment, Learning Sciences, Collaborative learning

【Purpose and Background of the Research】

Assessment reform requires a radical shift from a "summative assessment which ranks individuals" to a "formative assessment of the learning environment that helps all the students reach the next level of learning". Educational policy makers are also aiming for a similar shift in the revision of the Courses of Study and in high school/university articulation reform. The newly revised Courses of Study introduced "active learning", emphasizing its use of formative assessment. However, teachers lack appropriate tools to do this. Therefore, this study develops a "Learning-in-Class Monitoring System" and tests it in educational settings and assessment situations, in order to check whether it can serve as a foundation for assessment.

Lesson improvement requires a collaborative PDCA (plan-do-check-act) cycle of the teachers, but for most teachers, too much time and effort is required in completing this cycle. Thus, we put forward two ideas: first, a reciprocal collaboration between human beings and AI, and second, application of the teachers' usual efforts of assessment as a resource to advance the knowledge of both humans and AI.

【Research Methods】

Figure 1 represents an overview of the system, which depicts a teachers' PDCA cycle in its inner circle. The support systems shown in the outer circle help teachers turn the cycle in a timely manner. In addition, as teachers use these systems to plan, discuss, conduct, look back, and share the lessons iteratively, the entire system including the AI becomes smarter. For example, when a teacher creates a lesson plan, s/he predicts keywords that students will refer to in the lesson. Other teachers simulate this lesson plan from multiple perspectives, adding new keywords. If the teacher registers appropriate keywords in the transcription system beforehand, the speech recognition rate, which is the most difficult part of the dialogue analysis, becomes higher (shown in red letters in Figure 1).

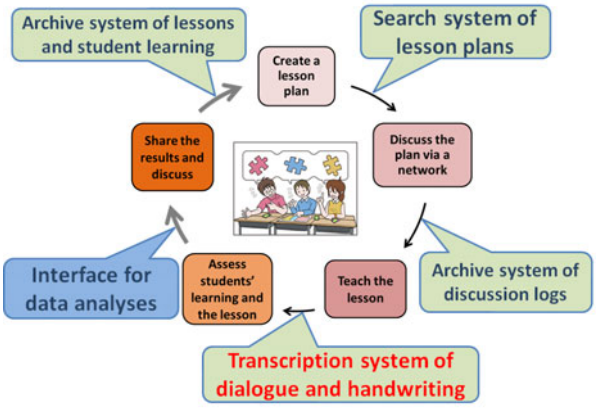


Figure 1 Learning-in-Class Monitoring System

【Expected Research Achievements and Scientific Significance】

As expected research achievements, we would like to examine if such kind of speech-to-text translation is capable of promoting in-depth analyses of collaborative learning by researchers, high-quality lesson improvements by teachers, and context-driven approaches to semantic analyses of learning by engineers. Scientific significance lies in bringing forth a perspective that sees an intertwined cycle of teaching and assessment as an arena of mutual growth for humans and AI.

【Publications Relevant to the Project】

Shirouzu, H., et al. "Building on cultural capacity for innovation through international collaboration: In memory of Naomi Miyake." Looi, C-K., et al. (Eds.) *ICLS 2016 Conference Proceedings*, Singapore. 2016, 1074-1081.

【Term of Project】 FY2017-2021

【Budget Allocation】 154,500 Thousand Yen

【Homepage Address and Other Contact Information】

http://coref.u-tokyo.ac.jp/legacy/en

【Grant-in-Aid for Scientific Research (S)】

Integrated Disciplines (Complex Systems)

Title of Project : Fusion of sensing and simulation of tsunami damage assessment towards innovation of disaster medical system

Shunichi Koshimura
(Tohoku University, International Research Institute of Disaster Science, Professor)

Research Project Number : 17H06108 Researcher Number : 50360847
Research Area : Natural Disaster
Keyword : Tsunami, Disaster Medicine, Simulation, Sensing

【Purpose and Background of the Research】

More than 150 of preventable disaster death at medical institutions were reported in the areas affected by the 2011 Great East Japan Earthquake and Tsunami. Devastating damage, lack of disaster information, insufficient resources in the hospitals, disrupted lifelines and transportations, and delayed medical intervention constituted the major contributing factors of preventable death. On the basis of the lessons from the 2011 event, there have been many new findings, insights, and progress on disaster observation/monitoring, simulation, modeling, and damage assessment methods. This project aims to utilize these advanced technologies towards enhancement of disaster medical system.

【Research Methods】

To achieve the goal of innovating disaster medical support system, five issues are adressed;

(1) Nation-wide real-time tsunami inundation and damage forecasting and advanced sensing for assessing tsunami impact with particular regard to the damage on medical facilities.
(2) Establishing a quasi-real-time estimation of the number of affected people in the affected areas and clarifying the relationship between the exposed population and medical demand.
(3) Clarifying relationship between the damage amount and medical demand from the medical records in the 2011 event, and developing a statistical model to estimate the medical demand using the damage data obtained immediately after the event occurs.
(4) Developing a multi-agent system with Markov Decision Process to simulate the medical activities in the affected areas with use of damage information, medical demands, and resources in the medical facilities to provide better guidance for decision making of medical response.
(5) Developing multi-agent-based medical support system by fusion of real-time tsunami inundation forecasting and simulation, and implementation as disaster medical support system.

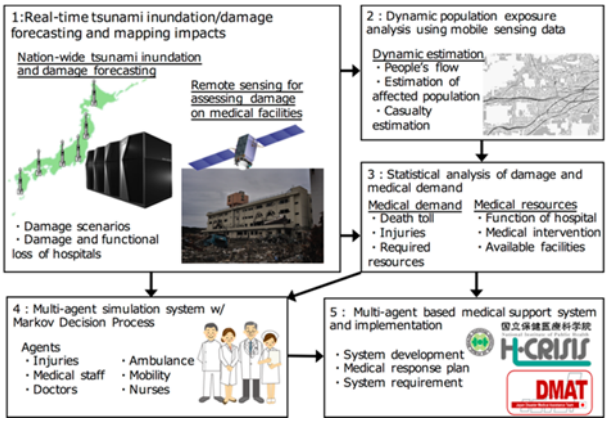


Fig.1 Structure of Research

【Expected Research Achievements and Scientific Significance】

The key outcome expected from this project is to create an innovative disaster medical support system to reduce preventable disaster death. To accomplish the goal, researchers in the fields of earth science, engineering, and medical science are working together to enhance the society's resilience against future catastrophic tsunami disaster.

【Publications Relevant to the Project】

Koshimura, S., Establishing the Advanced Disaster Reduction Management System by Fusion of Real-Time Disaster Simulation and Big Data Assimilation, Journal of Disaster Research, Vol.11 No.2, pp.164-174, 2016. doi: 10.20965/jdr.2016.p0164

【Term of Project】 FY2017-2021

【Budget Allocation】 156,900 Thousand Yen

【Homepage Address and Other Contact Information】

http://www.regid.irides.tohoku.ac.jp

Title of Project : Development of heteroduplex oligonucleotide crossing the blood-brain barrier

Takanori Yokota
(Tokyo Medical and Dental University, Graduate school of Medical and Dental Sciences, Professor)

Research Project Number : 17H06109 Researcher Number : 90231688
Research Area : Complex Systems
Keyword : Oligonucleotide, Biotechnology, Glucose transporter, Recycling

【Purpose and Background of the Research】

We developed heteroduplex oligonucleotide having a new molecular structure and mechanism of action, which is a breakthrough platform technology from Japan showing 10 to 1000 times the effectiveness of existing oligonucleotides (Nat Commun 2015). Moreover, we also developed a delivery system for polymeric drugs efficiently crossing the blood brain barrier (BBB) to reach the central nervous system by manipulating the blood glucose level of animals (Nat Commun [in revision]).

In this study, we aim to develop an innovative heteroduplex oligonucleotide that conjugates to the glucose transporter (Glut), crosses the BBB, and enables the regulation of arbitrary genes in the central nervous system.

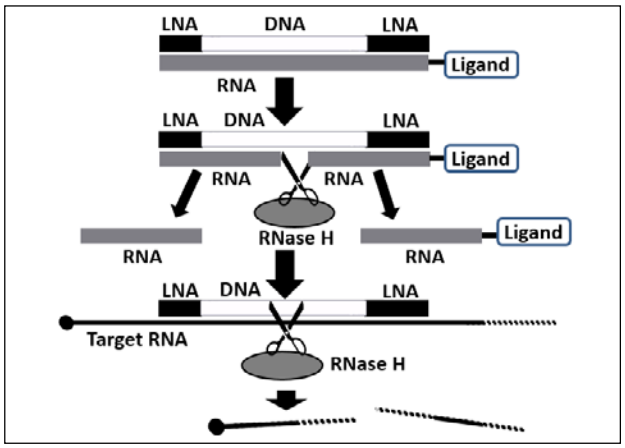


Figure 1 Gene silencing mechanism of heteroduplex oligonucleotide

【Research Methods】

We perform the screening of antibody clones that bind to Glut and create a linker that increases cell transduction efficiency and blood retention. We also elucidate the biological mechanism of and optimize the efficiency of BBB-crossing. In addition, we control the blood kinetics of heteroduplex oligonucleotide and to create technologies that increase RNase resistance. Furthermore, we optimize the oligonucleotide sequence and structure for the treatment of neurodegenerative diseases, and examine the therapeutic effect and safety in model mouse.

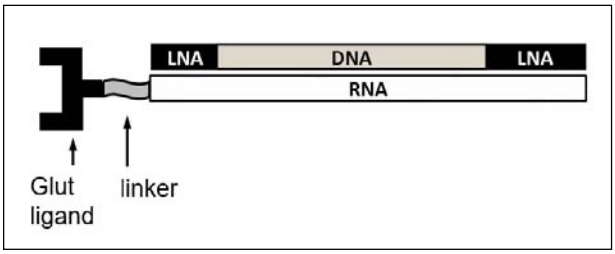


Figure 2 Structure of heteroduplex oligonucleotide crossing the blood-brain barrier

【Expected Research Achievements and Scientific Significance】

Our heteroduplex oligonucleotide is expected to become useful to achieve gene regulation in the central nervous system by systemic administration. We expect that this innovative platform technology opens a new field of drug development to treat many intractable neurological and psychiatric disorders, such as Alzheimer's disease, in the future super aging society.

【Publications Relevant to the Project】

Nishina K, Piao W, Yoshida-Tanaka K, Sujino Y, Nishina T, *et al.* DNA/RNA heteroduplex oligonucleotide for highly efficient gene silencing. Nat Commun 6: 7969, 2015.

Anraku Y, Kuwahara H, Fukusato Y, Mizoguchi A, Ishii T, *et al.* Crossing the BBB: Glycaemic control boosts glucosylated nanocarrier transport into the brain. Nat Commun (in revision).

【Term of Project】 FY2017-2021

【Budget Allocation】 133,100 Thousand Yen

【Homepage Address and Other Contact Information】

http://www.tmd.ac.jp/med/nuro/
tak-yokota.nuro@tmd.ac.jp

Title of Project : Expanding the medicinally relevant chemical space with architecturally complex natural products and their synthetic analogues

Masayuki Inoue
(The University of Tokyo, Graduate School of Pharmaceutical Sciences, Professor)

Research Project Number : 17H06110 Researcher Number : 70322998
Research Area : Natural Product Synthesis, Bioorganic Chemistry
Keyword : Synthetic Chemistry, Total Synthesis, Natural Products, Drug Design, Biological Activity

【Purpose and Background of the Research】

Natural products provide a crucial foundation for novel drug discovery. Architecturally complex natural products with multiple functional groups and molecular weight over 500 often exhibit potent bioactivities, and represent privileged structures for the development of pharmaceuticals (Fig. 1). The biological profiles of most of these natural products are not well understood, because both practical isolation and synthetic preparation have been highly challenging. In this research, we will develop new synthetic routes to the complex natural products and their analogues, and expand the medicinally relevant chemical space.

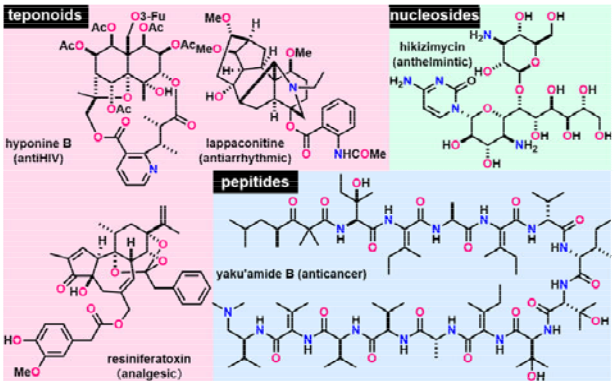


Figure 1 Architecturally complex natural products

【Research Methods】

First, the architecturally complex terpenes and nucleosides will be chemically constructed based on the radical-based convergent strategies (Fig. 2), and the peptides will be synthesized via a full solid-phase strategy. By employing the developed synthetic routes, a medicinally relevant chemical space will be expanded by preparation of 10 to 10,000 analogues of these natural products. Structure-activity relationship studies of these natural and artificial analogues will enable us to determine biologically significant structural features within their structures, and to elucidate their mode of actions. Thus obtained information will provide a chemical basis for the design of novel molecules with more potent and selective biological activities.

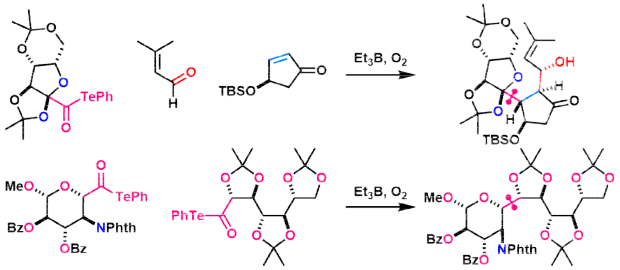


Figure 2 New radical-based convergent strategies

【Expected Research Achievements and Scientific Significance】

At the core of this research program is the development of new ideal strategies for assembling architecturally complex natural products. Efficient syntheses of these natural products will enable divergent syntheses of new analogues. These studies will expand a biologically relevant chemical space, and lead to the discovery of novel therapeutic agents based on the natural product templates. In this regard, this research will lead to a myriad of applications in future pharmaceutical and biological sciences.

【Publications Relevant to the Project】

· M. Koshimizu, M. Nagatomo, M. Inoue, "Unified Total Synthesis of 3-*epi*-Ryanodol, Cinnzeylanol, Cinncassiols A and B, and Structural Revision of Natural Ryanodol and Cinnacasol,"
Angew. Chem., Int. Ed. **2016**, *55*, 2493-2497.
· K. Masuda, M. Nagatomo, M. Inoue, "Direct Assembly of Multiply Oxygenated Carbon Chains by Decarbonylative Radical–Radical Coupling Reactions,"
Nature Chem. **2017**, *9*, 207-212.

【Term of Project】 FY2017-2021

【Budget Allocation】 157,800 Thousand Yen

【Homepage Address and Other Contact Information】

http://www.f.u-tokyo.ac.jp/~inoue/
inoue@mol.f.u-tokyo.ac.jp

Title of Project : Comprehensive understanding of molecular mechanism underlying the piRNA pathway

Mikiko C. Siomi
(The University of Tokyo, Graduate School of Science, Professor)

Research Project Number : 17H06111 Researcher Number : 20322745
Research Area : Complex Systems
Keyword : PIWI, piRNA, transposon, RNA silencing, Drosophila

【Purpose and Background of the Research】

The germ cells have specific chromatin organization that enables them to express germline-specific genes. However, this permits the amplification and insertion of transposable elements, including transposons, into other sites in the genome, leading to injury in the genome, defects in gametogenesis and finally infertility. To avoid this, piRNA-mediated RNA silencing represses transposons. piRNAs are mainly derived from piRNA clusters and loaded onto PIWI proteins. Both piRNAs and PIWI proteins are necessary for repressing transposons in the germline. However, the underlying molecular mechanism remains elusive. In this study, we will dissect the molecular mechanism by mainly focusing on piRNA biogenesis and piRNA-driven transcriptional silencing of transposons.

【Research Methods】

We will use biochemical approaches to understand the mechanism underlying the piRNA pathways. We will also use techniques such as genome wide-sequencing, bioinformatics and immuno-EM. Our first goal is to understand the

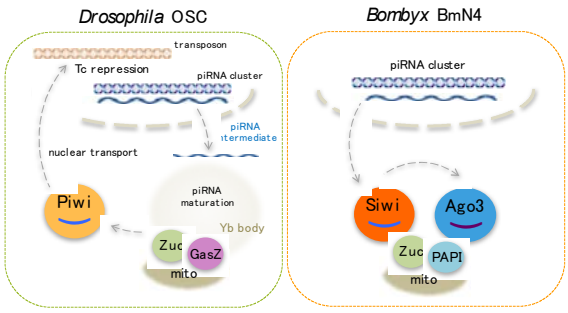


Figure 1. Model of the piRNA pathway in OSC and BmN4

molecular mechanism of piRNA biogenesis. We will focus on the primary piRNA processing pathway and the amplification loop. Our second goal is to identify the molecular functions of piRNA factors. The targeted goal of this proposal is to use biochemical-based techniques to understand the mechanisms controlling germline cell synthesis and function with a view to biotechnological and therapeutic applications.

【Expected Research Achievements and Scientific Significance】

We aim to use a unique biochemical-based aspect to understand the role of RNA silencing in germ cell fate determination, maintenance, and differentiation. Our group has established cultured OSCs, an ideal tool to perform biochemical analyses. We also have the ability to carry out RNAi-based gene screening in the OSC line, monoclonal antibody production, immunoprecipitation, and small RNA library construction. Our expertise allowed us to biochemically analyze the functions of piRNA factors in the piRNA pathways, and gain new insights into the molecular function of Piwi.

【Publications Relevant to the Project】

Matsumoto N, Nishimasu H, Sakakibara K, Nishida KM, Hirano T, Ishitani R, Siomi H, *Siomi MC, and *Nureki O. Crystal structure of silkworm PIWI-clade Argonaute Siwi bound to piRNA. ***Cell*** 167: 484-497. 2016 (*double corresponding authors)
Sumiyoshi T, Sato K, Yamamoto H, Iwasaki YW, Siomi H, and Siomi MC. Loss of l(3)mbt leads to acquisition of the ping-pong cycle in *Drosophila* ovarian somatic cells. ***Genes & Development*** 30: 1617-1622. 2016

【Term of Project】 FY2017-2021

【Budget Allocation】 155,800 Thousand Yen

【Homepage Address and Other Contact Information】

http://www-siomilab.biochem.s.u-tokyo.ac.jp/index.html

Title of Project : Search for novel modulators of cereblon, the target of thalidomide that regulates neural stem cell proliferation and differentiation

Hiroshi Handa
(Tokyo Medical University, Department of Nanoparticle Translational Research, Professor)

Research Project Number : 17H06112 Researcher Number : 80107432
Research Area : Integrated Disciplines(Complex Systems)
Keyword : Brain･Neuron, Development, Regenerative medicine, Biomolecules, Pharmacy

【Purpose and Background of the Research】

Using our original affinity nanobead technology, we identified cereblon (CRBN) as a target of thalidomide teratogenicity, and demonstrated that CRBN is a substrate receptor of E3 ubiquitin ligases (Science, 2010). Furthermore, through collaborative research with Celgene Corp. in the US, we clarified the involvement of CRBN in the anti-cancer effects and immunomodulatory effects of immunomodulatory drugs (IMiDs), including thalidomide. In addition, we identified the novel thalidomide derivative CC-885, which exerts therapeutic effects without immunomodulatory effects against acute myelocytic leukemia, and clarified its mechanisms of action (Nature, 2016). We therefore named thalidomide and its derivatives that exert therapeutic effects via CRBN as “CRBN modulators”, and we showed that each modulator recruits, ubiquitinates and degrades specific ates (Nature, 2015).

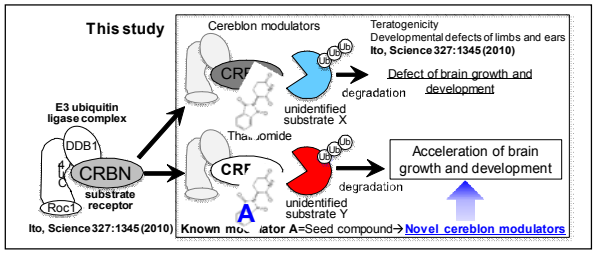


Fig. Conversion of substrate specificity by CRBN modulators

To understand the role of CRBN in brain growth and development, we demonstrated that treating zebrafish embryos with thalidomide inhibits brain development, and results in brain atrophy and a decrease in neural stem cell number via CRBN. Inhibition of CRBN expression also resulted in brain atrophy similarly to thalidomide, and CRBN overexpression resulted in brain enlargement and an increase in neural stem cell number. The aim of our research is to understand the role of CRBN in brain growth and development, to search for and identify novel CRBN modulators and substrate proteins, and to understand the mechanisms of action of CRBN modulators.

【Research Methods】

①We will identify downstream factors of CRBN and thalidomide using transcriptome and proteome analyses. ②We will establish zebrafish expressing human CRBN, and we will ③identify novel CRBN modulators that activate neural stem cell growth via chemical library screening. ④ Using our affinity nanobead technology, we will isolate and identify specific substrates of the novel CRBN modulators. ⑤We will characterize the substrates and their associated proteins, and ⑥ using cultured human neural stem cells and higher-order experimental animals, we will analyze the function of the identified substrates. ⑦We will clarify the mechanisms of action of novel CRBN modulators in neural stem cells during early development and in the mature brain, and ⑧using patient-derived cultured neural stem cells, we will explore the application of these modulators in the treatment of human brain disorders and regenerative medicine.

【Expected Research Achievements and Scientific Significance】

An epoch-making technology that enables brain regenerative medicine using endogenous neural stem cells has not been established to date. If novel CRBN modulators that can specifically control brain stem cells are established through our research, their application in the treatment of brain disorders, such as autism, depression, and dementia, as well as regenerative medicine are anticipated. Furthermore, our research is also expected to significantly contribute to basic neuroscience research, via clarification of the control network centered around CRBN, and the development of various CRBN modulators are also anticipated.

【Publications Relevant to the Project】

･Ito, T., Ando, H., Yamaguchi, Y., Handa, H., et al., Identification of a primary target of thalidomide teratogenicity. Science, 357, 1345-1350, 2010.
･Ito, T and Handa, H. Another action of a thalidomide derivative. Nature, 523, 167-168, 2015.

【Term of Project】 FY2017-2019

【Budget Allocation】 139,300 thousand yen

【Homepage Address and Other Contact Information】

http://www.tokyo-med.ac.jp/nanoparticle/
hhanda@tokyo-med.ac.jp

Title of Project : Dissection of molecules and neural circuits underlying a behavioral switch

Yuichi Iino
(The University of Tokyo, Graduate School of Science, Professor)

Research Project Number : 17H06113 Researcher Number : 40192471
Research Area : Brain Sciences
Keyword : The nematode *C. elegans*, Learning and memory, Synaptic transmission, Neural circuit

【Purpose and Background of the Research】

The nervous system is the most sophisticated information processing system that evolution of life has ever created. Unfortunately, much still remains unknown about its functions, due to the general difficultly of obtaining precise knowledge of the structure of neural circuits. However, in the small model organism *C. elegans*, all 302 neurons have been named and the structure of the entire neural circuit is known. In this study, by using *C. elegans* and extending the results of our previous study, we will elucidate how sensory inputs are processed to generate behavior and how molecular interplay reshapes the neural circuits to cause learning.

【Research Methods】

1) *C. elegans* are attracted to salt concentrations they have experienced in the presence of food, while they learn to avoid salt concentrations experienced while being starved. Our studies so far have revealed that a specific isoform of insulin receptor acts for the behavioral switch. We have also identified several other signaling molecules on which we will perform functional analyses, and we will clarify the relationship between the molecules, neurons and behavior.
2) We found that the sign of synaptic transmission between a specific pair of neurons changes via learning. We will clarify the mechanism by identifying the neurotransmitter, the receptor, the cells in which they act, and their change through learning.
3) We have developed a 4D imaging system in which all neurons in the head are observed at the same time. By using this method, we will identify the motor circuits and quantify the circuit dynamics and the change of these dynamics through mathematical modeling.
4) We will also generate a 4D optical system equipped with a tracking system that can observe the whole brain's activity in freely moving animals.

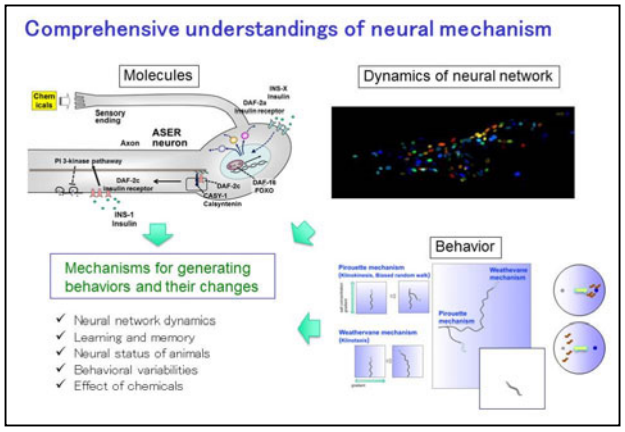


Figure 1 Outline of the study

【Expected Research Achievements and Scientific Significance】

Our analyses will cover the molecular, synaptic and neural circuit levels, and look at the whole brain's activity as well as behavioral patterns. Through these analyses, operational mechanisms of the neural circuit that have been previously unknown will be revealed.

【Publications Relevant to the Project】

Kunitomo, H. et al. "Concentration memory-dependent synaptic plasticity of a taste circuit regulates salt concentration chemotaxis in *Caenorhabditis elegans*." Nat. Commun. 4, 2210 (2013).
Ohno, H. et al. "Role of synaptic phosphatidylinositol 3-kinase in a behavioral learning response in *C. elegans*." Science 345, 313-317 (2014).

【Term of Project】 FY2017-2021

【Budget Allocation】 156,800 Thousand Yen

【Homepage Address and Other Contact Information】

http://molecular-ethology.bs.s.u-tokyo.ac.jp/
iino@bs.s.u-tokyo.ac.jp