【Grant-in-Aid for Scientific Research(S)】
Integrated Science and Innovative Science (Comprehensive fields)

Title of Project：Higher-Order Model Checking and its Applications

Naoki Kobayashi
（Tohoku University, Graduate School of Information Sciences, Professor）

Research Area：Computer Science
Keyword：Program verification, Model checking, Type theory

【Purpose and Background of the Research】

The reliability of computer software is critical, as infrastructure such as transportation and banking systems are nowadays controlled by computers. Model checking is a promising technique for formal verification of software, but traditional model checking has a limitation in the expressive power of the mathematical models, so that it is not suitable for verification of software written in high-level programming languages.

We have recently studied higher-order model checking, and shown that (i) many program verification problems reduce to higher-order model checking, and that (ii) despite its high worst-case complexity, higher-order model checking can often be solved efficiently. Based on those results, we have constructed the first higher-order model checker and implemented an automated program verification tool. The project aims to further advance this work on higher-order model checking and program verification, and also to find new applications of higher-order model checking such as data compression.

【Research Methods】

We set up the following three sub-topics, and study them in parallel.

(1) Theory and implementation techniques for higher-order model checking: We refine model checking algorithms and implementation techniques by advancing the underlying theories for higher-order model checking. We also study open problems about higher-order model checking.

(2) Software model checkers for full-scale programming languages: We extend the prototype program verification tool to obtain a more efficient verification tool that supports full-scale programming language features.

(3) New applications of higher-order model checking: We study other potential applications of higher-order model checking, such as data compression. For example, we can compress tree data as a program that generates it, and use higher-order model checking to apply pattern matching operations on data without decompression. Data compression may also lead to discovery of knowledge hidden in data.

【Expected Research Achievements and Scientific Significance】

This project will establish a new method for software verification based on higher-order model checking, and contribute to the reliability of computer software. From a scientific viewpoint, the project will contribute to a broad area of theoretical computer science, by combining and advancing results from many fields of theoretical computer science, including formal languages and automata, type theory, model checking, program transformation, etc. The project may also influence other disciplines through applications to data compression and knowledge discovery.

【Publications Relevant to the Project】

・Naoki Kobayashi, Types and Higher-Order Recursion Schemes for Verification of Higher-Order Programs, Proceedings of the 36th ACM SIGPLAN-SIGACT Symposium on Principles of Programming Languages (POPL 2009), pp.416－428, 2009.
・Naoki Kobayashi, Model-Checking Higher-Order Functions, Proceedings of the 11th International ACM SIGPLAN Conference on Principles and Practice of Declarative Programming (PPDP'09), pp. 25 – 36, 2009.

【Term of Project】 FY2011-2015
【Budget Allocation】 105,800 Thousand Yen

【Homepage Address and Other Contact Information】

http://www.kb.ecei.tohoku.ac.jp/

Title of Project : Development of the Innovative Specification Verification System based on Proof Scores

Kokichi FUTATSUGI
(JAIST, School of Information Science, Professor)

Research Area : Informatics-Software
Keywords : Specification Construction/Verification, Formal Methods, CafeOBJ, Proof Scores

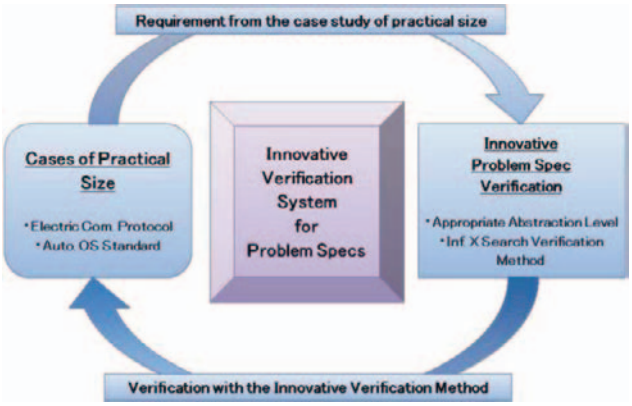
【Purpose and Background of the Research】

Construction of reliable and secure problem specifications (i.e. specifications or models of processes, activities, rules, and/or organizations in problem/application domains) is one of the most important issue in software technology of 21st century. For example, many company or government agencies are currently trying to provide new services on the Internet, and reliable and secure specifications of requirements in problem domains are vital important. In the automotive embedded software area where the shift to electric cars is apparent, it is an urgent issue to prepare fundamentals for the social system where many companies can collaborate flexibly in producing reliable and secure automotive software. Establishment of reliable and secure standards (i.e. problem specifications) for basic automotive software is an inevitable prerequisite for the end.

This research project is aiming at the development of the innovative verification system that can verify reliability and security of problem specifications of practical sizes. The verification system is going to be developed based on the CafeOBJ proof score methodology, which is an original research achievement of Prof. Futatsugi's research group. The developed verification system will be an important foundational contribution to the formal methods in software engineering.

【Research Methods】

To improve the current verification method for making it applicable to problem specifications of practical sizes, the following two are going to be achieved. (1) Construction of specifications in the appropriate abstraction levels. (2) Verification with the seamless combination of inferences and searches. The verification system is going to be developed in parallel with the case studies in the following two domains. (a) Electric commerce protocols. (b) Automotive software standards. With these approaches, the methods for constructions and verifications of problem specifications of practical sizes are going to be clarified. The obtained methods will be embodied into the revised CafeOBJ language system, which will be distributed worldwide through the Internet.



【Expected Research Achievements and Scientific Significance】

(1) The verification system (i.e. a revised CafeOBJ language system) for problem specifications that can be used to construct problem specifications in appropriate abstraction levels and to verify the specifications with the seamless combination of inferences and searches. The system can prove and/or disprove the problem specifications of practical sizes.
(2) The verified formal problem specifications of practical sizes in the domains of electric commerce protocols and of automotive software standards.
(3) The developed verification methods, verification system, and verified problem specifications will be the foundational contributions to the core part of software technology.

【Publications Relevant to the Project】

Kokichi Futatsugi: Fostering Proof Scores in CafeOBJ, Proc. of 12th International Conference on Formal Engineering Methods (ICFEM 2010), LNCS 6447, Springer, pp.1-20, 2010. (invited keynote paper)

【Term of Project】 FY 2011-2015

【Budget Allocation】 134,300 Thousand Yen

【Homepage Address and Other Contact Information】

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Title of Project : Fault Tolerant Infrastructure Toward Billion of Parallelization and Exa-scale Supercomputer

Satoshi Matsuoka
(Tokyo Institute of Technology, Global Scientific Information and Computing Center, Professor)

Research Area : Comprehensive fields – Computer science
Keyword : Exa-scale system, Fault tolerant

【Purpose and Background of the Research】

"Simulation" is becoming attractive tools as 3th methodology following after theoretical and experimental basis methodology. Thanks to Supercomputers, the large-scale simulations can be achieved. Recently, the performance of Supercomputers increases exponentially every year with increasing demands for computational power. In 2018, exa (10^{18}) flops supercomputers are expected to emerge.

However, the constant increasingly number of nodes and components will lead to a very high failure frequency for Exa-scale supercomputers. In an optimistic scenario, where the reliability of each component increases several times, the failure frequency will still be dozens of times higher, therefore, the mean time between failures will be no more than tens of minutes, which means computing node doesn't work in effect. A lot of fault-tolerance techniques are proposed, but current techniques can't accommodate Exa-scale systems.

We will seek a solution to the problem by using post-petascale TSUBAME3.0, which is successor to TSUBAME2.0 and expected to emerge in 2014.

【Research Methods】

We will focus on the following five techniques to establish fault-tolerant infrastructure for Exa-scale supercomputers. (1) Extension of our mathematical fault tolerant models for Exa-scale system: We extend our mathematical models for fault tolerant to accommodate billions of threads. We validate applicability of the fault tolerant model to Exa-scale system from historical records of fault of TSUBAME1, which is predecessor to TSUBAME2.0, in the past four and half years and validate (2) Development of new fault-tolerant method for large-scale and fine-grain heterogeneous supercomputer: We apply our extended fault tolerant model to hybrid supercomputer consisting many core processor (e.g. GPU) and multi core processor (e.g. CPU), which is most promising architecture for exa-scale systems. (3) Overhead minimization of the fault-tolerant system: We archive high dependable but high performance computation with minimization of the overhead in fault tolerant system by using next-generation non-volatile memory (e.g. SSD) distributed among nodes. (4) Development of fault recovery methods: We add autonomous fault detection, prediction and dynamic fault recovery selection mechanism to our fault tolerant model. (5) System integration and the performance evaluation: We integrate our fault tolerant systems and conduct performance evaluation toward TSUBAME3.0.

【Expected Research Achievements and Scientific Significance】

Our research achievements are expected to contribute to development of TSUBAME3.0 and Exa-scale supercomputer. Nowadays, supercomputers are used in a wide range of scientific fields, such as biology, geology and statistics and becoming an essential tool for simulations and data analysis. Exa-scale supercomputers enable high precision and high performance simulation and have a significant impact on science academic fields.

【Publications Relevant to the Project】

- Hideyuki Jitsumoto, Toshio Endo, Satoshi Matsuoka."Environmental-Aware Optimization of MPI Checkpointing Intervals", Proc. IEEE Int'l Conf. Cluster Computing (Cluster 2008)
- Leonardo Bautista Gomez, Naoya Maruyama, Franck Cappello, Satoshi Matsuoka. "Distributed Diskless Checkpoint for Large Scale Systems", Proc. 10th IEEE/ACM Cluster, Cloud and Grid Computing (CCGrid 2010)

【Term of Project】 FY2011-2015

【Budget Allocation】 164, 400 Thousand Yen

【Homepage Address and Other Contact Information】

http://matsu-www.is.titech.ac.jp/

Title of Project：Understanding Human's Adaptive Bipedal Walking by Using a Cadaver Feet/ Artificial Muscular-Skeleton Hybrid Robot

Koh Hosoda
（Osaka University, Graduate School of Information Science and Technology, Professor）

Research Area：Informatics, Intelligent Robotics
Keyword：Intelligent Robot

【Purpose and Background of the Research】

Habitual bipedal walking is one of most fundamental features of humans over other animals, and understanding its adaptability is very important for study on human intelligence. It is supposed that soft feet and complicated structure of foot bones largely contribute to the adaptability. However, it is very difficult to observe the dynamic behavior of the foot even though its anatomical structure is, to some extent, known. In this study,
(1) we construct a cadaver feet/ artificial muscular-skeleton hybrid robot, and observe its precise dynamic behavior by using X-ray, force sensors, pressure sensors, and high-speed cameras, (2) we build a precise dynamic simulator based on the anatomical data of the foot and validate it by comparing with the hybrid robot, (3) we realize an adaptive biped walking robot by understanding the mechanism.

【Research Methods】

We will focus on the following three points:

(1) we construct a cadaver feet/ artificial muscular-skeleton hybrid robot, and observe its precise dynamic behavior by using X-ray, force sensors, pressure sensors, and high-speed cameras. During walking, some of the ligaments are pulled by artificial pneumatic muscles. We conduct lesion experiments by getting rid of ligaments, too.
(2) we build a precise dynamic simulator based on the anatomical data of the foot and validate it by comparing with the hybrid robot
(3) By understanding the underlying mechanism, we realize an adaptive biped robot whose adaptability is superior to the existing humanoid robots

【Expected Research Achievements and Scientific Significance】

Anatomical structure of a human foot is well investigated. There are many reports on the observable features from outside, e.g., contact situation of the sole during walking. Recently, to verify the dynamics of the foot, there are a few studies to push the cadaver foot against the floor, and observe the dynamic process. However, in these experiments, they observe behavior of an isolated foot pushed against the floor, which may be different from the one in the context of real walking. They try to reproduce the same loading condition, but is very difficult to be realized.
In this study, the cadaver foot is driven by anthropomorphic muscular-skeleton robot, and it is observed by X-ray, force sensors, pressure sensors, and high-speed cameras. We can expect to observe precise micro motion of the bones in the foot as well as macro information such as force, pressure, and gross motion of the foot. We expect that we can investigate fundamental mechanism of the foot-leg system. The knowledge obtained from this study will contribute to clarify the foundation of the mechanism of the foot for adaptive bipedal walking. It also contributes to the plastic surgery aiming at treatment of broken foot/ leg, and to the sports science to develop new shoes that can absorb impact against the floor.

【Publications Relevant to the Project】

Koh Hosoda, Takashi Takuma, Atsushi Nakamoto, and Shinji Hayashi, "Biped robot design powered by antagonistic pneumatic actuators for multi-modal locomotion", Robotics and Autonomous Systems, Vol.56, No.1, pp.46-53, January 2008.

【Term of Project】 FY2011-2015

【Budget Allocation】 166,100 Thousand Yen

【Homepage Address and Other Contact Information】

TBA. Currently, http://www-hi.ist.osaka-u.ac.jp

Title of Project: Development of an Environment to Share Legal Information of Countries of Chinese Ideograms in Plain Language

Yoshiharu Matsuura
(Nagoya University, Graduate School of Law, Professor)

Research Area : Comprehensive fields
Keyword : Legal Information; Comparative Law, Standard Translation Dictionary

【Purpose and Background of the Research】

There is a growing demand for sharing legal information of Japan, China, Korea and Taiwan (the countries of Chinese ideograms). This project will develop full-scale standard translation dictionaries (STD) of these four countries and link them for cross reference. The project will promote joint research on various topics and produce useful annotations about relevant statutes, cases and social information.

In order to achieve deeper understanding of legal information and to encourage more sophisticated study of comparative law, three conditions are essential: (1) development of STDs that will help consistent translation, (2) effective link of STDs and (3) inclusive information about legislation, cases, and contextual information about each state, society, history, culture and social reality.

The project has already developed a tool to display aligned legal text in two languages and a work flow to develop STD from the statutory texts. Legal text is widely perceived as "hard to read" or "abstruse." If we translate abstruse Japanese legal text into English, we will not be able to achieve global sharing of legal information in plain language. The European Union practices translation of its laws into all languages of member countries. Their manuals for plain legal drafting and sophisticated translation system are very inspiring. The project will attempt to develop an environment, learning from the experience of the EU.

【Research Methods】

The project will pursue its research under four headings.

(1) Development of STDs will be promoted based on MOU between the project and the Ministry of Government Legislation, Korea, and National Chung Cheng Univ. of Taiwan. Research team consists mainly of lawyers and information scientists.

(2) The project will digitize the English edition of the Japanese Gazette published postwar days. The project will also digitize translation of European laws during the late 19 century Japan and will use the processed results to trace how legal concepts in Chinese ideograms were coined, exported and imported in Asia.

(3) The project will develop standard formats to add annotations (English and other languages) to share the information in Asia. An environment to assist translation will be researched.

【Expected Research Achievements and Scientific Significance】

An extended comparison of STDs will clarify similarities and differences of basic legal concepts represented by Chinese ideograms. It will lead to more precise comparison of laws in Asian countries and will produce deeper understanding of Asian laws.

Proposed comparative study of law assisted by IT tools is a first attempt in Asia and will contribute to harmonization of legal concepts in Asia, particularly in countries of Chinese ideograms.

The project will add annotations to legal texts by international cooperation. The annotation offered in some languages will include the relevant information such as legislative history, cases, and social background of a new legislation. The result will be useful as a common basis of advanced comparative law.

STDs of Asia will be linked to the EU legal terminology in 23 languages and become an important source of information about legal concepts of the world.

【Publications Relevant to the Project】

Y. Matsuura, "Translation of Japanese Statutes and Cases and Its implications for Transparency of Japan" 1394 ***Juristo*** 24-28 (2010). (in Japanese)

Y. Matsuura, "A Perspective: Significance of the Project of Japanese Law Translation—Global Marketability of Japanese Law and Institutions" 1377 ***Juristo*** 2-7 (2009). (in Japanese)

【Term of Project】 FY2011-2015

【Budget Allocation】 162, 600 Thousand Yen

【Homepage Address and Other Contact Information】

http://jalii.law.nagoya-u.ac.jp/

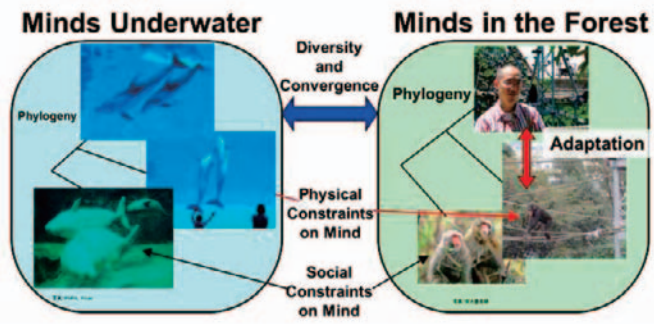
Title of Project：Minds Underwater, Minds in the Forest Comparative Cognitive Science of Primates and Cetaceans

Masaki Tomonaga
（Kyoto University, Primate Research Institute, Associate Professor）

Research Area：Comprehensive Fields
Keyword：Primates, Cetaceans, Evolution of Mind, Body, Comparative Cognitive Science

【Purpose and Background of the Research】

What is human unique in our mind? To answer this issue, we need to dissociate the properties shared with the other animals from our mind. We investigate the evolutionary factors emerging these two faces of mind, that is, uniqueness and commonality, from the perspective of comparative cognitive science. Nonhuman primates are frequently used for the study of comparative cognition. In addition to them, however, our project also focuses on the other group of mammals, Cetaceans, who adapted to the completely different environments from ours, the sea. Unique minds have evolved in each species under the constraints of phylogeny and adaptation. Our goal is to clarify the similarities and differences of these "Minds Underwater" and "Minds in the Forest". We also pay much attention to developmental perspective. Our project tries to understand "What is Human?" from the broader and hierarchical perspectives of comparative cognitive science.



【Research Methods】

We mainly study the two groups of animals. One is Primates, such as chimpanzees (including humans) and the other is Cetaceans, especially dolphins. Studying the effects of phylogenetic relations and adaptation on the cognitive abilities in these two groups concurrently enables us to promote the projects in the more dynamical manner. Experimental and observational studies with Primates are mainly conducted in the Primate Research Institute, Kyoto University, and the collaborating zoos. Studies with captive dolphins are mainly conducted in collaborative aquariums, such as Port of Nagoya Public Aquarium, and Kujukushima Aquarium. We also investigate the behavior and cognition of wild dolphins. Research Topics are as follows. 1) Behavioral synchronization and social cognition, 2) Imitative and observational learning, 3) individual recognition, 4) Understanding of the physical causality, 5) Physical constraints on object manipulation and tool use, 6) Social intelligence and its development, 7) Physical and social cognition in wild dolphins.

【Expected Research Achievements and Scientific Significance】

This is the first big project of cognitive studies of dolphins in Japan. Furthermore, it is quite unique that the principal investigators are the Primate researchers. We will provide new perspective to the cetacean studies and promote the breakthrough. At the same time, cetacean researchers in our team will also provide new perspectives to the primate studies. These bi-directional promotions will establish the long-lasting bases of comparative studies of dolphin cognition and behavior in Japan. Our results will further provide the good opportunities for the people to pay much more attention to the conservation of these two minds underwater and in the forest.

【Publications Relevant to the Project】

Kaneko T, Tomonaga, M (2011) The perception of self-agency in chimpanzees (*Pan troglodytes*). *Proc B Roy Soc* doi:10.1098/ rspb.2011.0611

Tomonaga et al. (2010). Bottlenose dolphins' (*Tursiops truncatus*) theory of mind as demonstrated by responses to their trainers' attentional states. *Int J Comp Psychol* 23: 386-400.

【Term of Project】 FY2011-2015

【Budget Allocation】 162,000 Thousand Yen

【Homepage Address and Other Contact Information】

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Title of Project：Exploring the genomic basis for the species difference in the neural circuitry for male courtship in *Drosophila*

Daisuke Yamamoto
(Tohoku University, Graduate school of Life Sciences, Professor)

Research Area： Neuroscience in general
Keyword： Molecular and cellular neuroscience

【Purpose and Background of the Research】

We cloned the gene *fruitless (fru)*, whose loss-of-function mutations enhance male-to-male courtship in *Drosophila* males. The Fru protein masculinizes the nervous system because the ectopic expression of Fru in females results in the generation of male-specific muscle of Lawrence (MOL) and male-typical courtship behavior in such females. Some of the *fru*-expressing neurons exhibit conspicuous sexual dimorphism, which is indeed *fru*-dependent. One of the *fru*-expressing interneuron clusters, P1, is male-specific. Ectopic formation of a P1 MARCM clone in the female brain allows her to display male-typical courtship, indicating that P1 plays a role in triggering male-typical courtship behavior. These observations led to the hypothesis that *fru* orchestrates the transcriptional network of genes that function to form the male courtship circuit, just as a master control gene, *eyeless*, does in eye development.

In the proposed project, we endeavor to disclose the mechanism whereby the *fru* genes of different *Drosophila* species organize the neural circuitry in species-specific ways, thus, enabling males to perform behaviors with conspecific patterns. This study is expected to open up an avenue for the study of molecular and cellular bases for the divergence in behavioral patterns, which is probably not just a result of, but also a cause of, speciation.

【Research Methods】

1. Clone the genomic sequence 5' to the most distal promoter of *fru* for up to 30 kb in both *subobscura* and *melanogaster*, 2. Construct a series of transgenes, *sub-fru5'-Gal4* and *mel-fru5'-Gal4*, each carrying a *fru5'* fragment of different length, 3. Generate transgenic lines harboring these transgenes in *melanogaster*, 4. Identify exhaustively the Gal4 expressing neurons in all transgenic flies generated as above by MARCM, 5. Express dTrpA1 in all neurons composing the *mel-fru5'* and *sub-fru5'* circuitries, activate them with temperature increases and see if this forcible activation of each circuitry induces courtship behavior characteristic of respective species, 6. Determine which neurons are crucial for the determination of species-types of courtship behavior by restricting the number of cells to be activated by MARCM, and 7. Establish causality among the species differences at three levels; the *fru cis*-element, identified neuronal connections and courtship behavioral patterns.

【Expected Research Achievements and Scientific Significance】

Our proposed project will attempt to reconstitute the *subobscura* neural circuitry for courtship in the *melanogaster* brain by "transplanting" the *cis* element of *subobscura fru* into the *melanogaster* genome in the form of the Gal4 fusion transgene. This will allow us to visualize and genetically manipulate the neurons in which the *cis* element of *subobscura fru* (*sub-fru5*) is active.

This study will elucidate the hitherto unknown mechanism whereby genomic changes and the selective forces upon them shape the brain circuitry and therefore drive the evolution of behavior. The principles thus unveiled would help us to understand how the diversification in behavior took place, and possibly even help us to learn know how we acquired the uniquely human brain.

【Publications Relevant to the Project】

Goto, J., Mikawa, Y., Koganezawa, M., Ito, H. and Yamamoto, D. (2011) Sexually dimorphic shaping of interneuron dendrites involves the Hunchback transcription factor. J. Neurosci. 31, 5454-5459.

Kohatsu, S., Koganezawa, M. and Yamamoto, D. (2011) Female contact activates male-specific interneurons that trigger stereotypic courtship behavior in *Drosophila*. Neuron 69, 498-508.

【Term of Project】 FY2011-2015
【Budget Allocation】 165,200 Thousand Yen

【Homepage Address and Other Contact Information】

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Title of Project : Molecular physiological study for the elucidation of mechanisms for modulation of neurotransmitter release

Toshiya Manabe
(The University of Tokyo, Institute of Medical Science, Professor)

Research Area : Neuroscience (general)
Keyword : Molecular and cellular neuroscience

【Purpose and Background of the Research】

The induction and expression mechanism for synaptic plasticity in postsynaptic cells has been examined extensively; however, the mechanism for presynaptic plasticity of neurotransmitter release, which is also critical for postsynaptic plasticity, is largely unclear. In this research plan, we will try to elucidate (1) the mechanism for modulation of neurotransmitter release by Ca^{2+} dynamics in presynaptic terminals and (2) the mechanism by which the content of neurotransmitters in one synaptic vesicle is determined. For these purposes, we will perform functional analyses using mutant mice in which only presynaptic functional molecules are modified. Specifically, we will analyze functional molecules and intracellular organelles related to the regulation of Ca^{2+} dynamics and presynaptic plasticity of neurotransmitter release. Furthermore, we will try to elucidate the molecular mechanism for the determination of quantal size in the presynaptic terminal.

【Research Methods】

We will study electrophysiologically the mechanism for modulation of neurotransmitter release using mouse hippocampal slice preparations. We will focus on the molecules that regulate intracellular Ca^{2+} dynamics as well as the molecules whose functions are modulated by Ca^{2+}. We will also deal with intracellular organelles related to these modulations. In addition, we will generate mutant mice in which only presynaptic functional molecules are modified and analyze synaptic transmission using these mice. Furthermore, by analyzing miniature excitatory postsynaptic currents, which are the smallest unit of synaptic transmission, and evaluating quantal size using a low-affinity antagonist of AMPA receptors that mediate excitatory synaptic transmission, we will try to identify functional molecules that determine quantal size and analyze the functions of these molecules. Following these analyses, we will also perform neural behavioral analyses using mutant mice in which the molecules that we analyze are genetically modified.

【Expected Research Achievements and Scientific Significance】

In previous studies, the mechanism of neurotransmitter release itself has been examined extensively. In this research plan, we will be able to elucidate the mechanism for plastic modulation of neurotransmitter release processes. It is also unique and original that we will be able to elucidate the regulation mechanism of neurotransmitter release, which is mediated by accumulation and release of Ca^{2+} via intracellular organelles. As for quantal size, it is well known that glutamate is filled into synaptic vesicles by glutamate transporters; however, it is largely unknown how the content of glutamate in each synaptic vesicle is determined. In this study, we will be able to understand the molecular and cellular mechanism for the determination of quantal size by presynaptic factors for the first time in the world. These expected research achievements would provide novel insights into presynaptic plasticity.

【Publications Relevant to the Project】

● Sakisaka, T., Yamamoto, Y., Mochida, S. et al. Dual inhibition of SNARE complex formation by tomosyn ensures controlled neurotransmitter release. ***J. Cell Biol.*** 183:323-337, 2008.
● Shimizu, H., Fukaya, M., Yamasaki, M., et al. Use-dependent amplification of presynaptic Ca^{2+} signaling by axonal ryanodine receptors at the hippocampal mossy fiber synapse. ***Proc. Natl. Acad. Sci. USA*** 105:11998-12003, 2008.

【Term of Project】 FY2011-2015

【Budget Allocation】 165,000 Thousand Yen

【Homepage Address and Other Contact Information】

http://www.ims.u-tokyo.ac.jp/NeuronalNetwork/Neuronal_Network/Index.html

Title of Project : Molecular and cellular mechanisms underlying memory update system

Kaoru Inokuchi
(University of Toyama, Graduate School of Medicine & Pharmaceutical Sciences (Faculty of Medicine), Professor)

Research Area : Neuroscience
Keyword : Memory, Update, Association, Reconsolidation, Hippocampus, Conditioning

【Purpose and Background of the Research】

Formation of knowledge is one of the bases of a human mental activity. Knowledge is not simply formed by the accurate storage of information as memory. New information is usually compared with previously stored old memories. Old memories are sometimes re-written if new information is related to the old ones (memory update). For instance, memories about an already-known person are usually modified by a new episode with that person. "Update mechanism" is necessary for the flexible adjustment to changes in environment, and becomes basic of the mental activity through the formation of knowledge.
In this study, using animal models we aim to clarify the memory update mechanisms. Memory update of three different time span will be considered:【1】association between two information that takes place in seconds ~ minutes ~ hours. 【2】 interaction between information that enters at intervals of days ~ month, and【3】rewriting by "change in the brain region where the memory is stored" that happens during week ~ month.

【Research Methods】

【1】Update by the association of memories: Identify the memory allocation and molecules that are required for memory association *per se*. Moreover, "behavioral tag" that is related to the memory association will be analyzed.
【2】 Update by memory reconsolidation: Analyze the molecular and cellular mechanism underlying memory reconsolidation by using a model system at the synapse level *in vivo* (hippocampal LTP) and a behavioral analysis system.
【3】 Memory allocation: The allocation of writing and storing in various learning paradigms will be analyzed.

【Expected Research Achievements and Scientific Significance】

The update mechanism of the memory is one of strategies that constructs advanced information by relating a lot of information, and an indispensable for survival of animals. In human beings, the memory update system is extremely important for the formation of knowledge. Understanding the whole image of memory update system leads not only to the understanding of the memory mechanisms but also to an approach to a philosophical proposition, for example the formation of one's character, from a natural science.

【Publications Relevant to the Project】

1. Kitamura, T., Saitoh, Y., Takashima, N., Murayama, A., Niibori, Y., Ageta, H., Sekiguchi, M., Sugiyama, H. & Inokuchi, K. Adult neurogenesis modulates the hippocampus-dependent period of associative fear memory. ***Cell*** 139, 814-827 (2009).

2. Okada, D., Ozawa, F. & Inokuchi, K. Input-specific spine entry of soma-derived Vesl-1S protein conforms to synaptic tagging. ***Science***, 324, 904-909 (2009).

3. Inokuchi K. Adult neurogenesis and modulation of neural circuit function. ***Curr Opin Neurobiol,*** 21, 360-364 (2011).

【Term of Project】 FY2011-2015

【Budget Allocation】 164,700 Thousand Yen

【Homepage Address and Other Contact Information】

http://www.med.u-toyama.ac.jp/bmb/index.html
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Title of Project：Functional analyses of axon guidance cue, draxin, and its signaling mechanism

Hideaki Tanaka
（Kumamoto University, Graduate School of Medical Sciences, Professor）

Research Area：Neuroscience, Neurochemistry
Keyword：molecular and cellular neurobiology, development and differentiation

【Purpose and Background of the Research】

Proper brain function depends on the precise establishment of intricate network of billions of neuronal connection. Developing axons from neurons have exquisite motile structures at its tip called, growth cones, which can detect and respond to a variety of attractive and repulsive guidance molecules in its surrounding environment and navigate to its targets in a highly stereotyped and directed manner. Through genetic, biochemical and molecular approaches four conserved families of axon guidance molecules have been identified: netrins, semaphorins, ephrins and slits. Although these molecules have prominent developing effects, considering the immense complexity of nervous system much more await identification. We have found a new axon guidance molecule, which we named draxin (dorsal repulsive axon guidance protein). Since *draxin* gene-deficient mice showed agenesis of all forebrain commissural fibers (corpus callosum, hippocampal commissure and anterior commissure), draxin is considered to be an important guidance cue for brain development. The present study has three major purposes: analyzing the draxin receptors and its signaling mechanism; clarifying draxin functions by using genetically modified mice; and elucidating the molecular basis of the maintenance of the brain.

【Research Methods】

To clarify the role of draxin in brain formation and maintenance mainly we plan to perform the following three research projects in parallel. (1) Elucidation of draxin receptors and signaling, (2) analysis of draxin functions by using transgenic and conditional knockout mice using a variety of Cre mice, (3) evaluation of draxin function after its re-expression in the dentate gyrus granule cell layer of adult transient ischemic brain .

【Expected Research Achievements and Scientific Significance】

In *draxin* knockout mice brain we have found that forebrain commissuers are not formed, indicating that draxin is an important cue for forebrain commissures formation. Despite the absence of sequence homology with other known axon guidance molecules, draxin binds specifically all netrin receptors: DCC, Neogenin, UNC5s, and DSCAM. Netrin is essentially attractive and draxin is repulsive. It would be an interesting and important breakthrough in the field of developmental neurobiology to clarify how the signals though guidance molecules are segregated by the identical set of receptors. Draxin is not only adding one more new guidance cue to the list of axon guidance molecules, but also its signal becomes a new breakthrough in understanding the regulatory mechanisms between axon guidance molecules, and thus elaborate further the basic principles of neural circuit formation.

【Publications Relevant to the Project】

・Ahmed G., Shinmyo Y., Ohta K., Islam S., et al. Draxin Inhibits Axonal Outgrowth through the Netrin Receptor DCC. **J. Neuroscience** (in press).

・Zhang, S., Su, Yuhong, Shinmyo, Y., Islam, S. M., Naser, I. B., Ahmed, G., Tamamaki, N., Tanaka, H. Draxin, a repulsive axon guidance protein, is involved in hippocampal development. **Neurosci. Res.** 66, 53-61 (2010).

・Islam S.M., Shinmyo, Y., Okafuji, T., Su, Y., et al. Draxin, a Repulsive Guidance Protein for Spinal Cord and Forebrain Commissures. **Science** 323, 388-393 (2009).

【Term of Project】 FY2011-2015
【Budget Allocation】 132,700 Thousand Yen

【Homepage Address and Other Contact Information】

http://www.medphas.kumamoto-u.ac.jp/research/bunya/41.html

Title of Project : Identification of factors endowing the genome with a high plasticity in the mouse and their applications to biomedical researches

Atsuo Ogura
(RIKEN, Bioresource Center, Division head)

Research Area : Comprehensive fields, Laboratory animal science
Keyword : Genomic reprogramming, mouse, genomic plasticity, nuclear transfer, ES cell

【Purpose and Background of the Research】

The fact that cloned animals are born following somatic cell cloning and pluripotent cells can be established by inducing reprogramming factors unequivocally indicates that the epigenetic changes imposed on the genome during differentiation are reversible and can be reprogrammed to the initial stages. However, these reverse epigenetic changes are too artificial and therefore prone to many kinds of epigenetic errors and incomplete reprogramming.

While we undertook many series of nuclear transfer cloning experiments in mice, we found that the genome of a certain strain of mice (129 strain) can be precisely reprogrammed in terms of the quality of cloned embryos (e.g., their global gene expression patterns) and the birth rates of clones. The 129 is the strain by which the first embryonic stem cells were established about 30 years ago and have been implicated to have some genomic plasticity. As the recipient ooplasm are common in all nuclear transfer experiments, we thought that the secret of this high genomic plasticity should reside within its genome. In other word, some factor(s) inside the 129 genome endow itself a high plasticity.

The goal of the present project is to identify the genomic plasticity factors in the 129 genome by employing the so-called “forward genetics”. We define the candidate genomic regions, surmise the candidate genes from the list in the relevant regions, and estimate the factors from their known biological functions. Finally, we expect that we will be able to transfer the factor(s) to other mouse strains and other mammalian species to establish iPS cells having a high quality and to generate healthy cloned animals efficiently.

【Research Methods】

We employ the principle of forward genetics throughout the project. We analyze phenotypes and gene expression patterns in embryos or pups reconstructed from recombinant inbred strains or consomic strains between C57BL/6 and 129 strains. Then we can define one or a few genetic regions responsible for correct genomic reprogramming comparable to that in the 129 genome. By combining gene modification techniques in mice, we identify the responsible factor(s). If possible, they will be transplanted into other mammalian species, which then will provide high quality iPS cells and efficient nuclear transfer cloning technology.

【Expected Research Achievements and Scientific Significance】

Generation of safe iPS cell and healthy cloning animals has been a long-awaited technology not only in basic science but also for future industry and medical practice. The results and information obtained from this project will enable us to reprogram the genome from a broad range of organisms more safely and more efficiently. This will also facilitate development of new strategies for human regenerative medicine and pharmaceutical sciences.

【Publications Relevant to the Project】

Inoue K, Kohda T, Sugimoto M, Sado T, Ogonuki N, Matoba S, Shiura H, Ikeda R, Mochida K, Fujii T, Sawai K, Otte AP, Tian XC, Yang X, Ishino F, Abe K, Ogura A. Impeding Xist expression from the active X chromosome improves mouse somatic cell nuclear transfer. Science 330: 496-499, 2010.

Inoue K, Kohda T, Lee J, Ogonuki N, Mochida K, Noguchi Y, Tanemura K, Kaneko Ishino T, Ishino F, Ogura A. Faithful expression of imprinted genes in cloned mice. Science, 295: 297, 2002.

【Term of Project】 FY2011-2015

【Budget Allocation】 158,600 Thousand Yen

【Homepage Address and Other Contact Information】

http://www.riken.go.jp/r-world/research/lab/brc/engineering/index.html
http://www.brc.riken.go.jp/lab/kougaku/

Title of Project : Computational nano-biomechanics for diagnosis, treatment, and prediction of human diseases

Takami Yamaguchi
(Tohoku University, Graduate School of Biomedical Engineering, Professor)

Research Area : Biomedical engineering
Keyword : Biomechanics

【Purpose and Background of the Research】

We will establish computational nano-biomechanics by modeling multi-scale physical and biomedical phenomena, from the molecular level to the cellular, tissue, and organ levels, and finally to the whole-body level. We will study physiological and pathological conditions at the macro-, micro-, nano-scale in our body, and will develop a new medicine for diagnosis, treatment and prediction of the blood, cardiovascular, digestive, and respiratory diseases.

【Research Methods】

At the molecular level, we will model receptor-ligand interactions. This model will be integrated into cellular level modeling, to investigate thrombogenesis, adhesion of red blood cells infected by malaria, and that of cancer cells. The cellular model will be integrated into multicellular simulations at the tissue level to determine macroscopic properties. We will study flow, mass transport, and infection in small blood vessels. We will also apply our method to the metastasis of cancer cells and bacterial flora in the intestines. Finally, a new continuum model will be developed for simulating flows in large arteries, pulmonary airways and the gastrointestinal tract at the organ level.

【Expected Research Achievements and Scientific Significance】

By establishing computational nano-biomechanics, we will be able to reveal physiological and pathological conditions from mechanical point of view. This will provide a novel tool for clinical treatment, and the reliability of treatment should be improved considerably compared to existing empirics based treatments. Computational nano-biomechanics will also accelerate the development of new medicine, since one will be able to discuss the effects of medicine by computational simulations.

【Publications Relevant to the Project】

Shimogonya et al., J Biomech 42, 550 (2009).
Imai et al., J Biomech 43, 1386 (2010)

【Term of Project】 FY2011-2015

【Budget Allocation】 165, 800 Thousand Yen

【Homepage Address and Other Contact Information】

http://www.pfsl.mech.tohoku.ac.jp
takami@pfsl.mech.tohoku.ac.jp

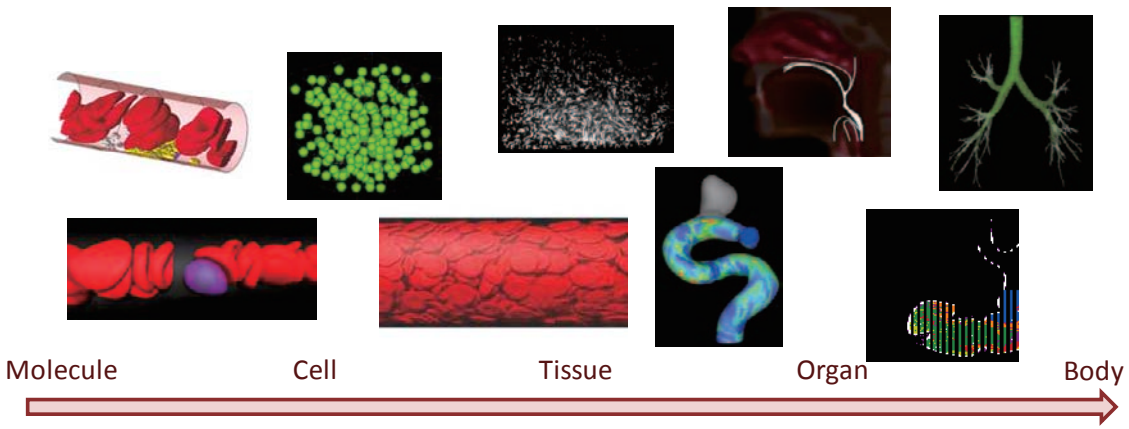


Fig. 1. Computational nano-biomechanics.

【Grant-in-Aid for Scientific Research(S)】
Integrated Science and Innovative Science (Comprehensive fields)

Title of Project : Explorations into development of autonomic neuromodulation system to treat refractory heart failure

Kenji Sunagawa
(Kyushu University, Graduate School of Medical Sciences, Distinguished Professor)

Research Area : Comprehensive Fields
Keyword : Neuromodulation, Treatment, Autonomic regulation, Cardiovascular regulation

【Purpose and Background of the Research】

Despite major progresses in latest medicine, cardiovascular diseases remain the number one killer of human. Among them, heart failure (HF), the common final stage of every cardiovascular disease, has unacceptably poor prognosis (5 year survival <50%). There is an urgent need to promote medical science to save those patients.

Thanks to extensive investigations on HF, it has been well established that cardiovascular dysregulation plays a central role in the pathogenesis of HF. HF induced metabolic as well as hemodynamic disturbances excessively activate the regulatory system and worsen HF. Since the most powerful regulatory mechanism is the autonomic nervous system (ANS) and conventional treatments cannot totally control ANS, we developed an intelligent mechanism that electrically controls ANS by feedback regulation of the afferent autonomic nerves. We called such artificial systems integrated with physiological systems as *bionic systems*. The purpose of this investigation is to develop bionic systems to treat refractory HF.

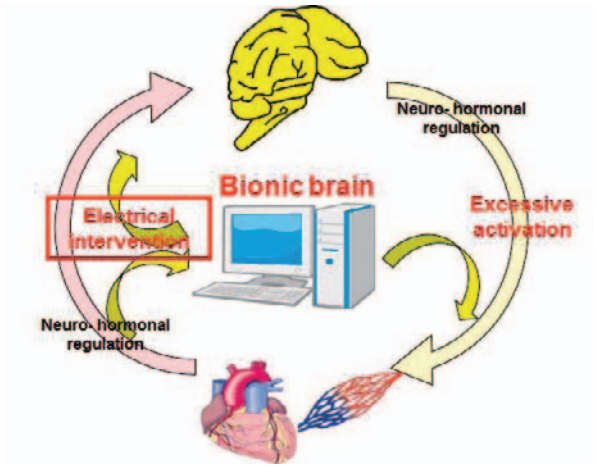


Fig.1 Schematic diagram of bionic system. See text for details.

【Research Methods】

Recent investigation indicated that systolic dysfunction accounts only for 50% of HF. The rest of patients have well preserved systolic function. We will develop bionic systems that are tailored for specific pathophysiology.

1. HF with impaired systolic function: In animal models, we will develop a bionic system that modulates the afferent baroreceptor nerve to deactivate sympathetic tone and activate vagal tone. We will evaluate its impact in terms of cardiac function and survival.
2. HF with preserved systolic function does not have effective treatments. Patients are known to be old, women and hypertensive and intolerant to volume overload. We hypothesized that atherosclerosis induced baroreflex failure plays a significant role in this pathophysiology. We will develop a bionic system to restore normal baroreflex function.

【Expected Research Achievements and Scientific Significance】

Most of the anti-HF agents work by intervening in the regulatory system. Their impact on survival, however, remains limited. In this investigation, we will electrically stimulate the afferent ANS to optimally regulate the systemic ANS. Electrical regulation of ANS could immediately adapt to incessantly changing physiological conditions. Therefore, it would have more powerful therapeutic impacts on HF than conventional treatments.

【Publications Relevant to the Project】

Sugimachi M, Sunagawa K. Bionic cardiology: exploration into a wealth of controllable body parts in the cardiovascular system. IEEE Rev Biomed Eng. 2: 172-186, 2009.

Li M, Zheng C, Sato T, Kawada T, Sugimachi M, Sunagawa K. Vagal nerve stimulation markedly improves long-term survival after chronic heart failure in rats. Circulation. 2004;109(1):120-4.

【Term of Project】 FY2011-2015

【Budget Allocation】 165,200 Thousand Yen

【Homepage Address and Other Contact Information】

http://www.med.kyushu-u.ac.jp/cardiol/research_units/baio/index.html

Title of Project : Regulation of functions and differentiation of ES/iPS cells by designing cell-recognizable chimera matrices

Toshihiro Akaike
(Tokyo Institute of Technology, Frontier Research Center, Professor)

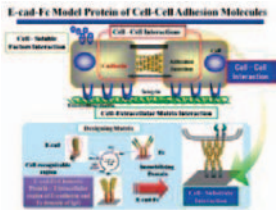
Research Area : Biomedical engineering/ Biological material science
Keyword : Materials for regenerative medicine and engineering, Cell-cooking plate, E-cadherin-Fc, ES/iPS cells, Matrix engineering

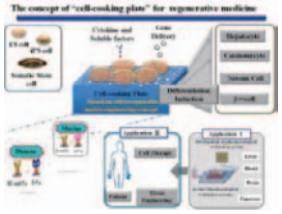
【Purpose and Background of the Research】

Pluripotent stem cells (ES/iPS cells) are considered to hold great promise in regenerative medicine. However, most of the studies reported that proliferation of undifferentiated state and induced differentiation of somatic cells from ES and iPS cells have been based on cell-cell aggregated colony culture system. In which, stimulating factors fail to interact with all cells homogeneously and directly in the same time, leading to generate heterogeneous cell population system.

To overcome these problems, we purposed in this project to establish a novel uniform single cell level culture system for controlling ES/iPS cells functions and differentiation process based on E-cad-Fc chimeric protein which was developed as a new type of extracellular matrix for modeling cell-cell adhesion molecules of E-cadherin in our labratory. Previously, we reported the possibility of highly efficient and homogenous differentiation induction of hepatocytes and cardiomyocytes from ES cells at single cell level, less stress and *Xeno*-free conditions. Recently, based on 30 years experience of designing cell recognizable matrix for tissue engineering and artificial organs, we proposed a new concept which was named “cell-cooking plate” and expected to be widely applicable in the fields of regenerative medicine and bio-artificial organs. Utilizing the concept of “cell-cooking palate”, we aimed to develop novel cell culturing system for regulating pluripotent ES/iPS cells functions and the differentiation process to somatic cells.

【Research Methods】





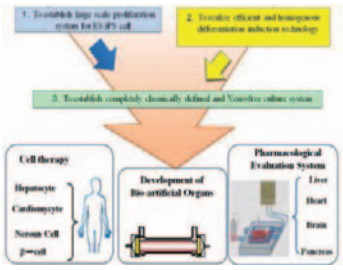
First of all, we will establish large scale culture system for undifferentiated ES/iPS cells based on E-cad-Fc protein. Subsequently, we will complete chemically defined culture system for human ES/iPS cells in the first year. In the second year, we will realize high efficient homogeneous differentiation induction system to hepatocytes and cardiomyocytes from human ES/iPS cells through delivering specific gene and co-immobilizing certain bioactive stimulating factor with E-cad-Fc matrix. Moreover, we will establish purification system of objected somatic cells through combining E-cad-Fc and other cell recognizable matrix to provide clinically applicable culture system and objected cells.

【Expected Research Achievements and Scientific Significance】

The following research achievements are expected in this project.

To generalize single cell level culture system of ES/iPS cells based on E-cad-Fc protein

To establish large scale proliferation culture system for undifferentiated ES/iPS cells.



To realize efficient homogenous induction system at single cell level for ES/iPS cells.

To complete chemically-defined and *Xeno*-free culture system.

【Publications Relevant to the Project】.

- Nagaoka M, Koshimizu U, Akaike T et al: E-Cadherin-Coated Plates Maintain Pluripotent ES Cells without Colony Formation. PLoS ONE., **1**: e15, 2006.
- Haque, A. Hexig, B. Akaike, T. et al: The effect of recombinant E-cadherin substratum on the differentiation of endoderm-derived hepatocyte-like cells from embryonic stem cells. Biomaterials., 32 2032-2042, 2011.

【Term of Project】 FY2011-2014

【Budget Allocation】 157,300 Thousand Yen

【Homepage Address and Other Contact Information】

http://www.akaike-lab.bio.titech.ac.jp/akaike/english/index.html

Title of Project : Integrated studies of aerosol-cloud-precipitation system in Asia based on measurements and model calculations

Yutaka Kondo
(The University of Tokyo, Graduate School of Science, Professor)

Research Area : Environmental science, Environmental dynamic analysis
Keyword : Environmental change

【Purpose and Background of the Research】

The effects of aerosols on clouds and precipitation (aerosol indirect effect) are one of the most uncertain factors in predicting the future global climate change. The key parameters required for understanding the role of aerosols in cloud and precipitation processes are the number concentrations and their size distributions of aerosols. Conventional mass-based studies do not take into account them properly.

To reduce the uncertainty in aerosol indirect effect, we make studies to greatly improve our understanding of the aerosol and cloud interaction by the greatly updated measurements and modeling of key parameters and processes of aerosols and clouds. We also evaluate the heating effects of aerosols (aerosol semi-direct effect) accurately by the combination of measurements and model calculations.

【Research Methods】

Measurements: We develop advanced measurement techniques and deploy them for field measurements. Surface (3 sites) and aircraft measurements (2 seasons) will be conducted in East Asia to study the impacts of aerosol emitted from anthropogenic activities. We will measure the size distribution, chemical composition, and mixing states of aerosols, size distribution and liquid water content of cloud and rain droplets, and meteorological components, including radiative parameters.

Numerical models: We plan to develop a new radiative transfer model to efficiently calculate aerosol radiative effects with improved accuracy. The calculations are validated by comparison with the measurements of radiation at surface. The validated radiative transfer model is integrated into regional scale 3-D models to calculate aerosol impacts on regional scale circulation. We also develop a new generation regional three-dimensional model, which considers aerosol-cloud interactions explicitly based on particle number concentrations and their size distributions. We will validate this model by comparison with the observations for each step of aerosol-cloud process. Using the validated models, we will evaluate aerosol indirect effects and their uncertainties in Asia.

【Expected Research Achievements and Scientific Significance】

There are strong needs to improve the accuracy of the predictions of climate change by greatly reducing the uncertainties of the effects of aerosols. Conventionally, global models have been used to assess the indirect and semi-direct effects of aerosols. However, the detailed processes of aerosol generation, transformation, and its uptake by clouds are not fully expressed by these models because they are mass-based models. In order to overcome these difficulties essentially, we make a completely new scheme to express number concentrations and their size distributions of particles. This scheme will greatly improve the calculation of aerosol and cloud processes in a self-consistent way. This study will greatly contribute to the improvement of climate predictions.

【Publications Relevant to the Project】

- Y. Kondo, H. Matsui, N. Moteki, L. Sahu, N. Takegawa et al., Emissions of black carbon, organic, and inorganic aerosols from biomass burning in North America and Asia in 2008, J. Geophys. Res., 116, D08204, doi:10.1029/2010JD015152, 2011.
- Kondo, Y., N. Takegawa, H. Matsui, T. Miyakawa, M. Koike et al, Formation and transport of aerosols in Tokyo in relation to their physical and chemical properties -A review-, J. Metorol. Soc. Japan, 88, 597-624, 2010.

【Term of Project】 FY2011-2014

【Budget Allocation】 165,500 Thousand Yen

【Homepage Address and Other Contact Information】

http://www-sys.eps.s.u-tokyo.ac.jp/~kondo/

Title of Project : Changes in hydrological cycle in East Asia during the Holocene and their implication for Global Monsoon

Ryuji Tada
(The University of Tokyo, Graduate School of Science, Professor)

Research Area : Earth System Dynamics, Environmental Change Analysis
Keyword : East Asia, hydrological cycle, monsoon, Holocene, Yangtze River, Lake Suigetsu, East China Sea, flood, ESR

【Purpose and Background of the Research】

This project aims to reconstruct temporal changes in intensity and spatial pattern of East Asian Summer Monsoon [EASM] since the middle Holocene (last 5,000 years) and clarify the ultimate driving forces of such changes. It will also explore the temporal and spatial relationships between flood events associated with tropical cyclones and EASM precipitation. The project is composed of three sub-projects, i) reconstruction of spatio-temporal variations of EASM precipitation and flood events in the Yangtze River drainage, ii) investigation of the linkage between EASM precipitation and the Kuroshio intensity, and iii) reconstruction of spatio-temporal variations of the position of the westerly jet axis over East Asia and EASM precipitation over the Japan Sea side of Honshu. Based on the synthesis of these results and exploration of the relationships with behaviors of other monsoon systems on different continents, we hope to understand the dynamics of the global monsoon system and properly evaluate changes in EASM precipitation pattern with in the global monsoon context.

【Research Methods】

1) We plan to collect sediments, suspended particles, and water samples from major tributaries of the Yangtze River to characterize the provenance and understand water and sediment budgets in the modern Yangtze River.
2) We also plan to drill Yangtze delta and Dongting Lake to recover the continuous Holocene record of sediment discharge from the Yangtze River. We will reconstruct provenance changes in response to changes in area of heavy EASM precipitation using ESR signal intensity of detrital quartz based on the result of 1).
3) We reconstruct changes in the Yangtze River discharge during the summer based on SST and SSS estimations in the northern East China Sea [ECS] using Mg/Ca ratio and $\delta^{18}O$ of planktonic foraminifera from cores.
4) We also plan to take cores from E-W transect in the central Okinawa Trough to reconstruct changes in Kuroshio intensity based on changes in the thermocline gradient along the transect using two planktonic foraminifera species with different depth habitat.
5) We plan to drill Lake Suigetsu to reconstruct changes in the westerly jet axis position using ESR signal intensity of eolian quartz within the sediments.

【Expected Research Achievements and Scientific Significance】

From this project, we hope to reconstruct spatio-temporal changes in patterns, speeds, and magnitudes of EASM precipitation during the middle to late Holocene in millennial to decadal time-scales. We also hope to clarify their relationships with tropical storm tracks and frequency, westerly jet axis position, and Kuroshio strength. Ultimately, we hope to understand the relationship between EASM and global climate with special emphasis on the global monsoon.

【Publications Relevant to the Project】

1) Tada, R., Onset and evolution of millennial-scale variability in Asian monsoon and its impact on paleoceanography of the Japan Sea, in Clift, P. et al. (eds.) Continent-ocean interactions within east Asian marginal seas, AGU Monograph Series 149, 283-298, 2004.
2) Kubota, Y., Kimoto, K., Tada, R., Oda, H., Yokoyama, Y., Matsuzaki, H., Variations of East Asian summer monsoon since the last deglaciation based on Mg/Ca and oxygen isotope of planktic foraminifera in the northern East China Sea, Paleoceanography, 25, PA4205, doi:10.1029/2009PA001891, 2010.
3) Nagashima K., Tada R., Tani A., Sun Y., Isozaki, Y., Toyoda, S., Hasegawa, H. Millennial-scale oscillations of the westerly jet path during the last glacial period, *Journal of Asian Earth Sciences*, 40, 1214-1220, 2011.

【Term of Project】

FY2011-2015

【Budget Allocation】

166,300 Thousand Yen

【Homepage Address and Other Contact Information】

http://www-sys.eps.s.u-tokyo.ac.jp/~tada/
ryuji@eps.s.u-tokyo.ac.jp

Title of Project : A study on inventory and distribution of nutrient in seawater together with higher comparability

Michio AOYAMA
(Meteorological Research Institute, Geochemical Research Department, Senior Scientist)

Research Area : environmental science, geochemistry
Keyword : marine chemistry, measurements, global warming

【Purpose and Background of the Research】

The comparability and traceability of nutrient data in the world's oceans are fundamental issues in marine science, and particularly for studies of global change. The oceanography community has been continuing to improve comparability of nutrient data from the world's oceans in many ways, including international inter-laboratory comparison exercises and also development of nutrient reference materials. However, as the Climate Change 2007 – The Physical Science Basis (IPCC2007) report stated, adequate comparability and traceability have not yet been achieved. Recent comparison study at the 120 crossings of WOCE and CLIVAR cruises revealed that nutrients concentrations show larger differences up to 10 %. Therefore, previously stated distribution and inventory of nutrient should have lager uncertainty. This means that present nutrients dataset used in biogeochemical models for global warming should also have lager uncertainty, too.

This study can solve the problem above. This study will conduct global observation of nutrient using Reference Material of Nutrients in Seawater, RMNS, and create new global nutrient dataset to reveal more accurate distribution and inventory of nutrient.

【Research Methods】

To ensure comparability of nutrient dataset which will be obtained in this study, we use nutrient data from more than 30 cruises without RMNS these are corrected by the factors estimated at each crossing between previous cruise and latest cruise with RMNS. We already have 10 cruises data with RMNS and will also conduct more than 6 cruises during this study period. Therefore we can cover the world's oceans by nutrient data which have higher comparability. A dataset (0.5 deg. X 0.5 deg in horizontal grid and vertically 136 layers) with 3% uncertainty will be created. We also create the sigma coordinate dataset together with the depth coordinate. Estimations of inventory and distribution of nutrient will be done based on the new dataset.

【Expected Research Achievements and Scientific Significance】

This study is based on new RMNS developed by our group and new nutrients manual (Hydes et al., 2010) both can ensure comparability of nutrient data. We also work to establish International Nutrients Scale System.

Obtained dataset of nutrient with considerably high comparability can provide 1) accurate inventory of nutrient and distribution of nutrient. This could not be achieved until today, 2) The dataset would also enable to estimate accurate increase of anthoropogenic carbon in the ocean, 3) re-evaluation of global ocean circulation based on revised nutrient distribution.

This means that our study can contribute progress of geochemistry of nutrient, provide more accurate initial condition of global biogeochemical models.

【Publications Relevant to the Project】

Aoyama, M., D. J. Hydes, How Do We Improve the Comparability of Nutrient Measurements?. In: Aoyama, M., A. G. Dickson, D. J. Hydes, A. Murata, J. R. Oh, P. Roose, E. M. S. Woodward, (Eds.), Comparability of nutrients in the world's ocean INSS international workshop 10-12 Feb. 2009, Paris. Mother Tank, Tsukuba, pp. 1-10. (2010)

Aoyama, M., D. Hydes, A. Daniel, K. Bakker, A. Murata, T. Tanhua, E. M. S. Woodward, Joint IOC-ICES study group on Nutrient standards (SGONES) First Meeting UNESCO Headquarters, Paris, France 23-24 March 2010. IOC Reports of Meetings of Experts and Equivalent Bodies, 223. UNESCO 2010.(English) ,223, (2010)

【Term of Project】 FY2011-2013

【Budget Allocation】 59,600 Thousand Yen

【Homepage Address and Other Contact Information】

http://www.mri-jma.go.jp/Dep/ge/INSS.html

Title of Project : Effects of snow impurities and glacial microbes on abrupt warming in the Arctic

Teruo Aoki
(Meteorological Research Institute, Physical Meteorology Research Department, Head of laboratory)

Research Area : New multidisciplinary fields
Keyword : Polar environmental monitoring, Cryospheric change, Global warming

【Purpose and Background of the Research】

Many climate models cannot simulate recent abrupt snow/ice melting in the Arctic. One of the possible causes is albedo reduction due to light absorbing snow impurities such as black carbon (BC) and glacial microbes. To clarify that, we will conduct field campaigns in Greenland, where the abrupt melting is occurring, and continuous meteorological and snow observations in Japan. Based on those data, snow metamorphism and albedo process (SMAP) model and glacial microbe model (GMM) will be developed and incorporated into earth system model (ESM). We will simulate the recent and future climates, by which the quantitative contributions of BC and glacial microbes on the recent abrupt melting in the Arctic will be clarified. We will also reproduce the atmospheric aerosols and snow impurities after the Industrial Revolution from Greenland ice core. Furthermore, we will retrieve the temporal-spatial variations of snow physical parameters with satellite remote sensing.

【Research Methods】

(1) Field campaigns for meteorological and radiation observations, snow pit work, and glacial microbial survey will be conducted from 2011 to 2013 in Greenland.
(2) Continuous meteorological and snow observations will be performed at three sites in Japan from 2011 to 2015. Using those data including (1), SMAP model and GMM will be developed and validated.
(3) Climate simulation and numerical sensitivity experiment with ESM, in which SMAP model and GMM are incorporated, will be made for the present and future Arctic.
(4) Shallow ice core drilling will be conducted in Greenland to obtain the record of atmospheric aerosols, snow impurities, and glacial microbes after the Industrial Revolution.
(5) Long term and spatial variations of snow physical parameters and albedo in the Arctic will be retrieved with satellite remote sensing.

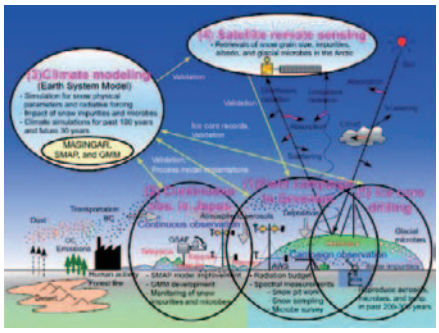


Fig. 1 Five research subjects in this study.

【Expected Research Achievements and Scientific Significance】

Snow pollution by BC in the Arctic is elucidated from in-situ and satellite measurements. Radiative forcing due to light absorbing snow impurities such as BC and glacial microbes are estimated with ESM, by which quantitative contributions of BC and glacial microbes on the recent abrupt snow/ice melting in the Arctic can be clarified. If the BC contribution to snow/ice melting cannot be ignored, these estimates could be scientific basis for the emission restriction.

【Publications Relevant to the Project】

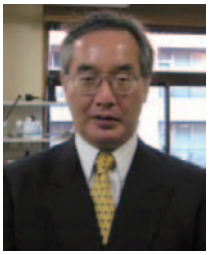
Aoki, T., K. Kuchiki, M. Niwano, Y. Kodama, M. Hosaka, and T. Tanaka: Physically based snow albedo model for calculating broadband albedos and the solar heating profile in snowpack for general circulation models, *J. Geophys. Res.*, **116**, D11114, doi:10.1029/2010JD015507, (2011).
Takeuchi, N., and Li, Z.: Characteristics of surface dust on Ürümqi Glacier No. 1 in the Tien Shan Mountains, China. *Arctic, Antarctic, and Alpine Research*, **40**(4), 744-750, (2008).

【Term of Project】 FY2011-2015

【Budget Allocation】 165,400 Thousand Yen

【Homepage Address and Other Contact Information】

http://www.mri-jma.go.jp/Dep/ph/ph3/ph3-e.html



Title of Project : Mutants deficient in DNA repair pathways provide high throughput assays for genotoxicity of chemicals and contribute to development of *in silico* methods for predicting genotoxicity of chemicals from their structure

Shunichi Takeda
(Kyoto University, Graduate School of Medicine, Professor)

Research Area : Radiation Biology, Toxicology, Molecular Biology
Keyword : Mutagen, toxic chemical compounds, ionizing radiation, Tox21 program

【Background of the Research】

Chemicals used industrially and commercially are required by law to be assessed for their genotoxic potential. However, all currently used bioassays, including the Ames test and the *in vitro* micronucleus assay, yield unacceptably large proportions of false-positive results. This limitation causes another problem. The ultimate goal of detecting toxicity associated with test chemical compounds is to develop a method for *in silico* prediction of toxicity from their chemical structures. Since this *in silico* prediction depends on the quality of the database, numerous false-positive results from currently used bioassays make development of reliable *in silico* prediction impossible.

To solve this problem, we have proposed new bioassays, where we evaluate genotoxicity using a Toxico-Genetic approach (Ref. 1). Previous bioassays employ only *wild-type* DNA-repair-proficient cells, while our new approach analyzes cellular responses to test chemicals by comparing between *wild-type* cells and isogenic DNA-repair-deficient mutant clones. If one of the mutants shows higher sensitivity to test chemicals than *wild-type* cells, it is concluded that their toxicity is certainly related with a relevant disabled DNA-repair enzyme, and is most likely to be attributable to DNA damage and resulting mutagenesis caused by these chemicals. It should be noted that in this Toxico-Genetic approach *wild-type* cells are served as a negative control to monitor false-positive results. Resulting high quality of data would be useful for establishing tools for the *in silico* prediction.

We have created more than 100 chicken DT40 clones deficient in individual DNA repair genes. We then proposed our bioassay of identifying mutagenic chemical compounds to scientists of National Toxicology Program (NTP) in USA. They agreed to let us join the Tox21 program, and we did the following preliminary experiment in National Institute of Health Chemical Genomics Center (NCGC) in 2008. We exposed five isogenic DT40 mutants and a *wild-type* control to 1405 chemical compounds, biological effects of which are well characterized by NTP.

【Purpose and Research Methods】

The purpose of our study is as follows:

(1) We optimize and validate the method noted above for the high throughput screening of mutagenic chemical compounds in NCGC. All data obtained in NCGC, including our data, must be deposited and open to public in the PubChem site.
(2) We develop a reliable *in silico* prediction tool by mining data deposited in the PubChem site.
(3) We create new bioassays to identify chemical compounds that damage mitochondria and endoplasmic reticulum (ER), and cause oxidative stress. To this end, we will generate DT40 mutants each deficient in the mitochondria quality control, ER stress response, or cellular response to oxidative stress.
(4) We analyze molecular mechanisms underlying the induction of mutations by ionizing radiation and various chemical compounds. To this end, we will disrupt genes involved in DNA repair and develop new phenotypic assays.

【Expected Research Achievements and Scientific Significance】

The Japanese Government will be able to improve methods to prevent the pollution of the environment by toxic chemical compounds.

【Publications Relevant to the Project】

(1) DNA Repair (Amst). 9: 1292-8, 2010

【Term of Project】 FY2011-2015

【Budget Allocation】 165,300 Thousand Yen

【Homepage Address and Other Contact Information】

http://rg4.rg.med.kyoto-u.ac.jp/
stakeda@rg.med.kyoto-u.ac.jp

Title of Project : Innovation of genotoxicity tests —DNA damage, Mutation, Chromosome—

Tomonari Matsuda
(Kyoto University, Graduate School of Engineering,
Associate Professor)

Research Area : New multidisciplinary fields
Keyword : Genotoxicity tests, DNA adductome, Mutation assay, Protein-complex analysis

【Purpose and Background of the Research】

Genotoxicity tests are essential for pre-marketing hazard assessment of newly-developed chemicals. However, the major genotoxicity tests have been developed several decades ago and are poor in prediction of carcinogenicity. Recent development of analytical equipments and cell biology allow us to make innovation in this area. In this study, we tried to develop innovative genotoxicity tests which focused on DNA damage, mutation and mechanism of chromosomal aberration.

【Research Methods】

We are going to develop three kinds of genotoxicity tests as described following.

① DNA adductome

This technology, we have described previously, enables us to detect known- or unknown-DNA damages directly by using LC/MS/MS. In this study, we tried to apply this method as an genotoxicity test. We will expose various chemicals to cultured cells, extract DNA, analyze their DNA damage by the DNA adductome method.

② Direct sequence of gene mutations

To evaluate the cancer risk of chemicals, many mutation assays have been developed, most using sophisticated genetic technologies. However, recent advance in DNA sequencing technology, at least in principal, enables us to detect chemically induced small frequency of gene mutations by direct DNA sequencing. For example, a leading-edge next generation DNA sequencers can analyze more than 100 Giga bases per analysis. Assume that a chemical induce one mutation per 1 Mega bases, 100,000 mutations are expected to be detected. In this way, applying a DNA sequencer to a mutation assay is very promising. We will develop a method for DNA-template preparation and data-treatment for this new mutation assay.

③ Evaluation of DNA damage-independent clastogenic mechanisms

Chromosomal aberration test is one of the important genotoxicity tests. However, the weak point of this test is having much false-positive results in terms of carcinogenicity. For example, caffeine and curcmin have a clastogenic potential at higher doses, but have no carcinogenicity. Chromosome is composed of DNA and various protein-complexes. Such protein-complexes are important for maintaining function and structure of chromosome. So that, the molecular targets of clastogen should be not only DNA but also these protein-complexes. In this study, we will carry out proteome analysis of important protein-complexes, and develop evaluation methods for stability of the protein-complexes against clastogens.

【Expected Research Achievements and Scientific Significance】

Proper strategy for genotoxicity-evaluation is becoming world-wide concern. These innovative genotoxicity tests will be useful tools for hazard assessment of chemicals and contribute to public health and environmental protection.

【Publications Relevant to the Project】

Matsuda, T. (2010) Anticipated Mutation Assay Using Single-molecule Real-time (SMRTTM) Sequencing Technology. Genes and Environment, 32, 21-24.

Chou, P. H. and Matsuda, T. et. al. (2010) Detection of lipid peroxidation-induced DNA adducts caused by 4-oxo-2(E)-nonenal and 4-oxo-2(E)-hexenal in human autopsy tissues. Chem Res Toxicol, 23, 1442-1448.

【Term of Project】 FY2011-2015

【Budget Allocation】 146, 400 Thousand Yen

【Homepage Address and Other Contact Information】

http://www.eqc.kyoto-u.ac.jp/local/
matsuda@z05.mbox.media.kyoto-u.ac.jp

Title of Project : Compound Semiconductor Nanowires and Their Optical Device Application

Takashi Fukui
(Hokkaido University, Graduate School of Information Science and Technology, Professor)

Research Area : New multidisciplinary fields
Keyword : Compound Semiconductor, Nanowire, Optical Device, Solar cell

【Purpose and Background of the Research】

Semiconductor nanowires (NWs) have attracted much attention for use in future nanometer-scale electronic and optical device, because NWs have a small diameter and large surface area that enables high density integration of active devices on various platforms and fabrication of various kinds of functional devices by using hetero-structures. The surface area for the growth of the radial hetero-structures enables the formation of core-shell (CS) NWs. Moreover, a top surface with a small diameter achieves a formation of axial heterostructures regardless of lattice mismatches. The use of core-shell or axial NWs gives some functionality to NW-based applications.

The purpose of this study is to develop low a cost and low power consumption CSNW light emitting diode (LED), which is very promising for the next generation of LED. For solar cell development, we fabricate a tandem nanowire solar cell with three (or four) different bandgap and lattice constant semiconductors in a stacked structure with high energy conversion efficiency.

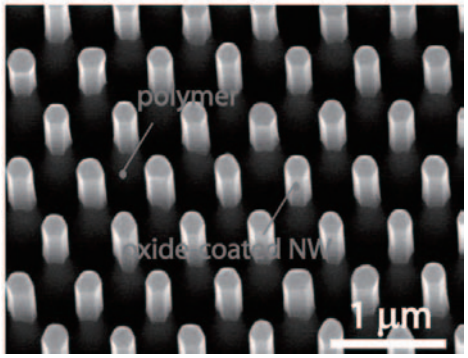


Fig.1 Scanning electron microscope image of semiconductor nanowires

【Research Methods】

We used selective-area metal-organic vapor phase epitaxy (SA-MOVPE) for III-V nanowire growth and hetero-epitaxial technique of forming NWs on a Si substrate for optical applications. The crystal growth of SA-MOVPE is based on faceting growth without catalyst. This growth technique enabled the position-controlled growth of vertically-aligned III-V NWs on lithography patterned substrates. Also, the growth temperature altered the axial NW growth direction and radial growth directions, resulting in formation of CSNWs. For light emitting diode (LED) applications, we fabricated AlGaAs/GaAs CSNW (infrared emission), and InGaP CSNW (visible light) on silicon substrates. For solar cell applications, we used InP lateral pn junction CSNWs. We also fabricate an InGaP/GaAs/InGaAs tandem solar cell with high energy conversion efficiency.

【Expected Research Achievements and Scientific Significance】

It is very important to develop low cost and low power consumption LEDs. The CSNW LED is very promising for the next generation of LEDs. For solar cell development, we fabricate tandem nanowire solar cell with three (or four) different bandgap and lattice constant semiconductors in a stacked structure, achieving energy conversion efficiency more than 50%. That means the NW solar cell has great potential for high efficiency solar cells.

【Publications Relevant to the Project】

1. K. Tomioka, J. Motohisa, S. Hara, K. Hiruma and T. Fukui, “GaAs/AlGaAs core multishell nanowire-based light-emitting diodes on Si”, NANO LETTERS, vol. **10**, pp.1639-1644,(2010)
2. H. Goto, K. Nosaki, K. Tomioka, S. Hara, K. Hiruma, J. Motohisa and T. Fukui, “Growth of Core-Shell InP Nanowires for Photovoltaic Application by Selective-Area Metal-Organic Vapor-Phase Epitaxy”, APPLIED PHYSICS EXPRESS, vol. **2**, pp.035004, 1-3 (2009)

【Term of Project】 FY2011-2015

【Budget Allocation】 163, 200 Thousand Yen

【Homepage Address and Other Contact Information】

http://www.rciqe.hokudai.ac.jp/

Title of Project : Development of Novel Spin Dynamics Devices

Teruo ONO
(Kyoto University, Institute for Chemical Research, Professor)

Research Area : New multidisciplinary fields
Keyword : Spin devices

【Purpose and Background of the Research】

The purpose of this project is to develop novel spin devices that utilize the current-induced spin dynamics in non-uniform spin structure, such as a magnetic domain wall and a magnetic vortex. Specifically, we aim to confirm the basic operations of three types of spin dynamics devices: vortex core memory, race-track memory, and domain wall oscillator. The vortex core memory is a non-volatile memory in which bit data is stored as the direction of the vortex core magnetization. In this memory, the direction of the core magnetization is controlled by the current-induced core switching phenomena which was found by our group, and the direction of the core magnetization is read out by using the tunnel magnetoresistance effect. The race-track memory is a non-volatile multi-bits memory which was proposed by IBM. In this multi-bits memory, domain walls are used to store bit data, and the current-induced domain wall motion is used for data shifting. The race-track memory is expected to overwhelm the Hard Disk Drive and Flash memory by its low power consumption and low bit cost. The domain wall oscillator is a device that converts the current-induced domain wall rotation into microwave, and the microwave frequency can be tuned by the current flowing through a domain wall.

【Research Methods】

To develop novel spin dynamics devices described above (vortex core memory, race-track memory, and domain wall oscillator), we plan to perform the following items.

(1) Elucidation of physics of the current-induced spin dynamics

(2) Confirmation of the basic operations of three types of spin dynamics devices: vortex core memory, race-track memory, and domain wall oscillator.

【Expected Research Achievements and Scientific Significance】

In general, the magnetic devices like Hard Disk Drive have high energy saving performance due to its non-volatility, i.e., data can be retained even if the electrical power is turned off. In this project, the vortex core memory and the race-track memory are developed as new novel non-volatile memories. The vortex core memory is expected as a fast non-volatile memory and it could be used in non-volatile logic devices in the future. The race-track memory is a novel device that satisfies high recording density, low bit cost, and reliability. The domain wall oscillator is a microwave generator based on the completely different operating principle from the conventional ones. These new spin dynamics devices proposed in this project can be integrated into the conventional silicon technology, leading to the seamless development of present electronics.

【Publications Relevant to the Project】

T. Koyama, D. Chiba, K. Ueda, K. Kondou, H. Tanigawa, S. Fukami, T. Suzuki, N. Ohshima, N. Ishiwata, Y. Nakatani, K. Kobayashi and T. Ono, “Observation of the intrinsic pinning of a magnetic domain wall in a ferromagnetic nanowire”, Nature Materials 10 (2011) 194.

K. Yamada, S. Kasai, Y. Nakatani, K. Kobayashi, H. Kohno, A. Thiaville, T. Ono, “Electrical switching of the vortex core in a magnetic disk”, Nature Materials, 6 (2007) 269.

【Term of Project】 FY2011-2015

【Budget Allocation】 165, 700 Thousand Yen

【Homepage Address and Other Contact Information】

http://www.scl.kyoto-u.ac.jp/~ono/onolab/public_html/indexj.html

【Grant-in-Aid for Scientific Research(S)】
Integrated Science and Innovative Science (New multidisciplinary fields)

Title of Project : Prediction of catchment runoff changes based on elucidating a nested structure consisting of the developments of topography, soil and vegetation

Makoto Tani
(Kyoto University, Graduate School of Agriculture, Professor)

Research Area : Natural hazards, Hydrology
Keyword : Forest influences, Hillslope hydrology, Land slide, Prediction in ungauged basins

【Purpose and Background of the Research】

A difficulty of predicting runoff characteristics from catchment properties such as geology. topography, soil and vegetation is caused by their heterogeneous spatial distributions. The regularities are derived from a nested structure of developments with different time scales: topography is evolved due to orogenic movement and erosion, soil development is repeated through landslide occurrences, and plants have a life cycle. Revealing the nested structure must be a key for evaluating an effect of catchment properties on the runoff prediction.

This study challenges a unique simulation for a recurrence process consisting of landslide and soil development supported by roots. We aim at an assessment of runoff buffering potential of forest through a new parameterization of catchment properties into runoff models.

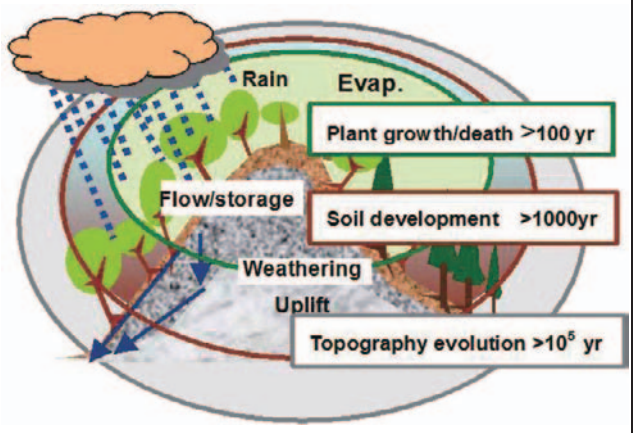


Fig. 1. Nested structure with various time

【Research Methods】

Effects of geology, weathering and land uplift velocity on catchment topography are first assessed by a simulation of topography evolution. Dependencies of runoff characteristics on the complicated underground structure are investigated through hydrometric observations and tracing tests using water quality and stable isotope. Root slope reinforcement effects are evaluated by field experiments. Field investigations are also conducted to know the history of landslide occurrences and the estimation of soil age.

A simulation model for a long-term cycle including many landslides and soil development processes is established based on the findings above, and simulation results and runoff characteristics produced from this catchment are examined against the field investigations to parameterize catchment properties in a runoff model.

Runoff characteristics in various small catchments in Japan and Asia are characterized and findings derived deductively from the above simulations are validated through them.

【Expected Research Achievements and Scientific Significance】

This study contributes to applications of process understandings obtained from hillslope hydrology to runoff-prediction implementations and to an IHAS activity for prediction in ungauged basins (PUB). A new paradigm in hydrology may be created by innovating a concept of nested structure to runoff studies.

【Publications Relevant to the Project】

Tani M.: Analysis of runoff–storage relationships to evaluate the runoff-buffering potential of a sloping permeable domain. Journal of Hydrology 360: 132-146, 2008.

Tani M., Fujimoto M., Katsuyama M. et al. : Predicting the dependencies of rainfall-runoff responses on human forest disturbances with soil loss based on the runoff mechanisms in granitic and sedimentary-rock mountains. Hydrological Processes, 2011 (in press).

【Term of Project】 FY2011-2015

【Budget Allocation】 122,900 Thousand Yen

【Homepage Address and Other Contact Information】

http://www.bluemoon.kais.kyoto-u.ac.jp/start-jp.html

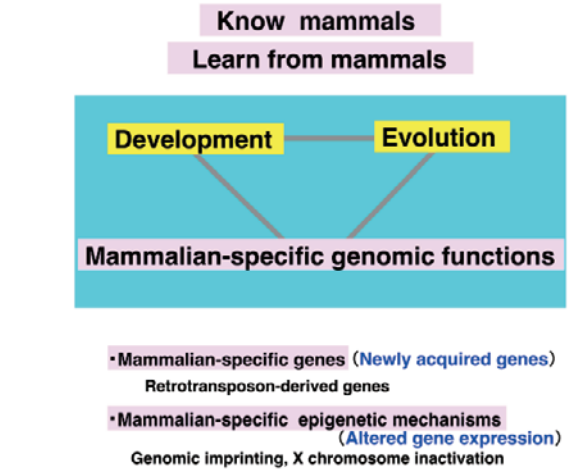
Title of Project : Mammalian-specific genomic functions

Fumitoshi Ishino
(Tokyo Medical and Dental University, Medical Research Institute, Professor)

Research Area : New multidisciplinary
Keyword : Genomic function, Genome evolution

【Purpose and Background of the Research】

Viviparity and placentation are representative characters in mammalian reproduction system. We have recently demonstrated that two retrotransposon-derived genes specific to mammals, *Peg10* and *Peg11/Rtl1,* play essential roles in placenta formation and functions. These are paternally expressed imprinted genes relating early embryonic lethality and late fetal/neonatal lethality, respectively. Genomic imprinting is one of mammalian-specific epigenetic mechanisms and known to be essential for mammalian development. How this mechanism emerged and how these mammalian-specific genes are acquired from retrotransposons? These questions are related to the origin or evolution of the mammals. The aim of this project is to dissolve these questions.



【Research Methods】

Our project comprises four subjects as below:

1. Biological function of *Peg10*: identification of functional domain of Peg10 protein and production of parthenogenons in mice.
2. Role of *antiPeg11/Rtl1*: biological functions of essential miRNAs in *antiPeg11/Rtl1.* Its roles in human pUPD14 and development of new miRNA therapy.
3. Biological function of *Sirh* genes: Analyses on *Sirh3*, *4-6*, *7* and *9* knockout mice.
4. Reprogramming of genomic imprinting memories in germ cells: molecular mechanism of DNA demethylation in PGCs.

【Expected Research Achievements and Scientific Significance】

Elucidation of evolution of mammals, a part of our history as human beings. Elucidation of the meechanism of epigenetic reprogramming for promoting regenerative medicine.

【Publications Relevant to the Project】

1. Kaneko-Ishino T and Ishino F. Retrotransposon silencing by DNA methylation contributed to the evolution of placentation and genomic imprinting in mammals. Develop Growth Differ **52**(6), 533-543 (2010).
2. Sekita Y, Wagatsuma H, Nakamura K, Ono R, Kagami M, Wakisaka-Saito N, Hino T, Suzuki-Migishima R, Kohda T, Ogura A, Ogata T, Yokoyama M, Kaneko-Ishino T and Ishino F. Role of retrotransposon-derived imprinted gene, *Rtl1,* in the feto-maternal interface of mouse placenta. Nat Genet **40**(2), 243-248 (2008).
3. Ono R, Nakamura K, Inoue K, Naruse M, Usami T, Wakisaka-Saito N, Hino T, Suzuki-Migishima R, Ogonuki N, Miki H, Kohda T, Ogura A, Yokoyama M, Kaneko-Ishino T and Ishino F. Deletion of *Peg10,* an imprinted gene acquired from a retrotransposon, causes early embryonic lethality. Nat Genet **38**(1), 101-106 (2006).

【Term of Project】 FY2011-2015

【Budget Allocation】 165, 200 Thousand Yen

【Homepage Address and Other Contact Information】

http:// www.tmd.ac.jp/mri/epgn/index.html
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Title of Project：Design and construction of new systems for regulating human cell fate

Tan Inoue
（Kyoto University, Graduate School of Biostudies, Professor）

Research Area：Chemical Biology
Keyword：RNA, protein, synthetic biology

【Purpose and Background of the Research】

Numerous numbers of DNA, RNA and protein molecules have been investigated at molecular level, starting from late 20th century till now. Moreover, the relationships between their intermolecular interactions and the functions have been revealed at atomic level on the basis of their 3D structures.

The accumulation of the data can be utilized as new tools for solving medical, food and energy problems in future. Along this line of thoughts, we would like to develop a new field in synthetic biology to contribute to medical engineering and other relevant fields by employing newly designed RNP (RNA-protein complex) containing naturally occurring tertiary interactions.

【Research Methods】

Two projects will be performed during the term of period.

Theme 1): Development of new RNP switches, which can be turned-on or –off in the presence of a marker protein expressed in cancer cells, for regulating human cell fate.

Theme 2): Multifunctional RNP will be constructed for detecting human cancer cells specifically and sensitively. After the establishment of the system, it will be employed to regulate signal transduction cascades connected to the cell surface receptors.

【Expected Research Achievements and Scientific Significance】

Establishmen of new methods for detecting and determining human cell fate will be expected.

The methods developed in the projects will be applicable not only for human cell but also for any other living organisms, because the materials used in the system are RNA and protein that are produced in any cell.

In addition, the RNP engineering employed in the projects can be applicable in a broad range of biological, medical and nanobiological studies.

【Publications Relevant to the Project】

・ Ohno H, Kobayashi T, Kabata R, Endo K, Iwasa T, Yoshimura SH, Takeyasu K, Inoue T, Saito H. Synthetic RNA-protein complex shaped like an equilateral triangle.
Nature Nanotechnology, 6, 116-20. (2011)
・ Saito H, Fujita Y, Kashida S, Hayashi K, Inoue T. Synthetic human cell fate regulation by protein-driven RNA switches.
Nature Communications, 2,160- (2011)
・ Hirohide Saito, Yoshihiko Fujita, Karin Hayashi, Rie Furushima, and Tan Inoue Synthetic Translational Regulation by an L7Ae-Kink-turn RNP Switch.
Nature Chemical Biology,6,71–78 (2010)

【Term of Project】 FY2011-2014

【Budget Allocation】 85,300 Thousand Yen

【Homepage Address and Other Contact Information】

http://kuchem.kyoto-u.ac.jp/seika/index.html

Title of Project: Conflict Resolution and Coexistence through Reassessment and Utilization of "African Potentials"

Itaru Ohta
(Kyoto University, Center for African Area Studies, Professor)

Research Area: Area Studies
Keyword: Africa, Reconciliation, Social Healing, Indigenous Knowledge and Institutions

【Purpose and Background of the Research】

One of the most serious problems in Africa is the disruption of the social order due to civil wars and regional conflicts. Conflicts in the 1990s and beyond are especially notable in their production of enormous numbers of refugees and IDPs. It is essential to the stability and growth of African societies to find effective means to ameliorate the varied problems these conflicts cause.

Both governmental and non-governmental international bodies have intervened in these conflicts in various ways, such as, peace keeping missions, supporting the establishment of post-war political institutions, and prosecuting violations of human rights and war crimes. These interventions have, however, achieved limited success, because they are based on ideologies, values and processes that are fundamentally Western in origin. This research project, in contrast, emphasizes the knowledge and institutions that African societies have themselves developed and utilized in resolving conflicts and maintaining co-existence. We thus aim to understand how this existing body of indigenous knowledge and institutions—which we term "African Potentials"—might most effectively be employed in settling conflicts, bringing about reconciliation, and healing post-conflict societies in Africa today.

These African Potentials have long been generated through encounters and clashes with European and Arabic Islamic societies and continue to undergo constant transformation, an ability we term "Interface Functions." As we identify and evaluate African Potentials, we also will explore how they are articulated with the external factors through the work of Interface Functions.

【Research Methods】

Drawing on a range of specific examples of conflicts, we will investigate three main areas based on intensive fieldwork, (1) how conflicts occur, continue, and were resolved, (2) What kind of African Potentials were effectively utilized in conflict resolution, and (3) The role of Interface Functions in these processes.

The project members are sub-divided into four "Research Units," focusing on specific topics (e.g. politics, culture), and four "Research Clusters," focusing on geographical areas (e.g. East Africa). Each member participates in at least one Unit and one Cluster. Plenary meetings will be held every two months in order to systematically unite Units and Clusters. An international forum, including African scholars and practitioners, will be held annually in various African countries. A "Data Archive on African Potentials" will be created to consolidate data on conflict resolutions in Africa.

【Expected Research Achievements and Scientific Significance】

This project is significant because of its focus on that which has previously been underplayed in previous studies of conflict resolution and peace-building: Namely, African Potentials and Interface Functions, and the ways to most effectively utilize such institutions. To further facilitate this goal, and disseminate findings, African scholars and practitioners will also participate in this project. We also believe that it is our duty to tackle the difficult problems of conflict resolution and coexistence in order to respond to the social needs of contemporary African societies.

【Publications Relevant to the Project】

Ohta, I., 2009. "Pastoralists are proficient in cultivating positive social relationships: Case of the Turkana in northwestern Kenya." *Mila (NS)*, 10: 24-38.

Ohta, I. and Y. D. Gebre, (eds.) 2005. *Displacement Risks in Africa*. Kyoto: Kyoto University Press.

【Term of Project】 FY2011-2015

【Budget Allocation】 157,600 Thousand Yen

【Homepage Address and Other Contact Information】

Our website is under construction. For the outline of the project, see the following URL:
http://jambo.africa.kyoto-u.ac.jp/kibans/index.html