

# **OIST Research Funding Program**

**(OIST: Okinawa Institute of Science and Technology)**

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## **Summary of Research**

Title of Project	A Computational Approach to Molecular Mechanisms of the Mind
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Abstract	<p>The goal of this research is to understand the neurobiological substrate of human mind by combining top-down computational modeling and bottom-up neurobiological experiments. Recent advances in molecular biology revealed specific genes and molecules responsible for affective and cognitive disorders, such as schizophrenia and depression. However, those disorders are the result of complex interactions between the environment and multiple genes and molecules, most notably the neuromodulatory systems such as dopamine and serotonin. Understand of such interactions requires computational models including environmental dynamics. For that purpose, we will work on three major subjects: 1) development of a novel computational framework for system identification of biological networks; 2) neurobiological experiments to study the dynamic functions of neuromodulators in regulating adaptive behaviors; 3) robotic experiments to explore adaptive mechanisms necessary for survival and reproduction in dynamic environments. By combining theoretical, biological, and engineering approaches, the research shall produce novel software tools for dynamic modeling, highly adaptive robots with emotion-like regulatory functions, and new approaches to therapy and prevention of psychiatric disorders.</p>

# Detailed Description of Research

## 1. Research plan

### A. Research concept

The goal of this research is to understand the neurobiological substrate of our mind based on both bottom-up, biological evidence and top-down, computational perspectives. While studies of neural mechanisms of sensory perception and motor control have seen a dramatic progress in the last decade, the neural mechanisms of emotion and cognition are still far from clear. Recent advances in molecular biology and genetics have identified genes and molecules that affect functioning of our mind. However, there usually is a huge gap between a change in a gene and changes in the behavior, since phenotypic manifestations are results of complex interactions of multiple genes, molecules and the environment. Understanding of such complex interactions clearly requires synthetic models, since each experiment can tap into just a small part of the dynamical system.

In order to better understand the mechanisms of emotion and cognition in normal and disordered cases, we will put together three strategies. First, we will develop a novel system identification framework for complex biological networks using recent development in machine learning technique. Second, we will perform rodent experiments on the roles genes and molecules, especially those related to neuromodulatory systems, in regulating adaptive behaviors of animals. Third, we will build a rodent-like robotic platform for exploring adaptive mechanisms necessary for survival and reproduction. By combining these three strategies, we aim to clarify the dynamic mechanisms of our emotional and cognitive systems, and to apply the knowledge to therapies and preventions of psychiatric disorders and innovative methods for education and learning.

### B. Research background

#### *1) System Identification of Biological Networks*

After completion of human genome sequencing, the focus of current research is on the dynamic interaction between genes, molecules, and extracellular environments. Advanced technologies like gene micro arrays and optical recording provide us with massive data of activation time courses of genes and molecules, interpretation of which requires sound mathematical frameworks. Although the networks of genes and molecules are highly complex, nonlinear dynamical systems, the modeling methods used so far are quite primitive. Molecular biologists often draw "box and arrow" models, which are helpful for logical inference or "thought experiment" for predicting the system behaviors in extreme cases, such as a total blockade of a particular gene or molecule. However, in complex networks, a change in one factor has multiple pathways of effects, often both positive and negative, and immediate and delayed. Inference by a "box and arrow" model is very much limited, or often misleading.

There have been several attempts at building quantitative models of intracellular dynamical

system (e.g., Bhalla 1999, Tomita 1999). A big issue there is estimation of appropriate model parameters. While many of the parameters, such as reaction and diffusion constants, are taken from experimental literature, they are often in conflict or unreliable, due to differences in measurement conditions. Many of the parameters are not available yet, or cannot be measured by today's technology. Thus researchers have to resort to hand-tuning of unknown parameters to replicate known behaviors of the system, which compromises the objectivity of the model.

Construction of a dynamic model from observed time courses is a problem of system identification. While conventional system theory focused on identification and control of linear systems with Gaussian uncertainty, a new trend of research since 1980's, under the names like connectionism, graphical models, and statistical machine learning, extended their scope to nonlinear, non-Gaussian systems. In Bayesian estimation framework, both the goodness of fit to the data (likelihood) and the constraints and assumptions about the model (priors) are combined to give the posterior probability of the model in reference to the given data. In recent years, modern Bayesian estimation methods, such as Sequential Monte Carlo and Variational Bayes methods, have been successfully applied to variety of system identification and state estimation problems, such as computer vision and robot navigation.

Now the time is ripe to introduce those contemporary system identification methods in the field of systems biology. Instead of relying on heuristic hand-tuning, our knowledge and ignorance about the system should be represented in the words of probabilities, and the estimated models should be evaluated in the words of statistical reliability. This is essential process for making computational modeling from alchemy to science.

We have performed some leading studies on the application of contemporary Bayesian estimation techniques to neuroscience. For example, Sato et al. (2003), in my Computational Neurobiology Department at ATR, applied Variational Bayes estimation methods to signal source estimation of MEG signal. We also developed a Sequential Monte Carlo method for estimating internal variables of a learning agent from his behavioral data (Samejima et al. 2004). Ishii (2003), a member of my CREST research project, applied Variational Bayes method for constructing a dynamic model of gene activation from micro array data.

## *2) Dynamics of Neuromodulatory Systems*

Recent brain imaging techniques, most notably functional MRI, provided a flood of data about which parts of our brain are involved in what sort of cognitive and affective processing. However, those data do not tell us what kind of computation is performed in each brain area. Abundant data are available about localization of different neurotransmitters and their receptors in different brain areas, and their effects on the postsynaptic cells. Integration of such macroscopic and microscopic data clearly necessitates theoretical modeling. Convergence of the theory of reinforcement learning and the neurophysiological data from the basal ganglia and the dopaminergic systems (Schultz et al. 1997) has brought a major impact on our understanding of the

neural mechanisms of reward-based learning and decisions.

While the role of dopamine has been relatively well characterized, the roles of other neuromodulators, such as serotonin and noradrenaline, are less evident. Based on a wide review of literature and my own experience in reinforcement learning applications (Doya et al. 2001), I proposed a comprehensive theory on the roles of neuromodulators (Doya 2002). This theory posits that neuromodulators represent global variables and parameters for reward-based learning, namely,

- i) Dopamine signals reward prediction error.
- ii) Serotonin controls the time scale of prediction of future rewards.
- iii) Noradrenaline controls the width of exploration.
- iv) Acetylcholine controls the rate of memory updates.

In an inter-disciplinary research project supported by CREST, JST, we have performed both theoretical and experimental studies to test these hypotheses. For example, Ishii et al. (2002) and Schweighofer and Doya (2003) proposed biologically plausible models of regulation of these global parameters. In collaboration with Prof. Yamawaki at Psychiatry Department at Hiroshima University School of Medicine, we discovered parallel neural pathways involved in reward prediction at different time scales (Tanaka et al. 2004) and are now performing a new experiment to test how those pathways are modulated by the serotonergic system.

Understanding of the functions and interactions of neuromodulators is of immediate importance to psychiatric medicine, since most drugs used for therapies of psychiatric disorders, such as schizophrenia and depression, are either agonists, antagonists, or transport blockers of those neuromodulators.

### 3) *Robotic Approaches to Emotion and Cognition*

Psychiatric disorders can be regarded as runaway of adaptive systems that usually regulate diverse parts of our brain in the right domain of operation. What makes understanding of psychiatric disorders difficult is, first, our ignorance about the normal functioning of human cognitive systems, and second, the complex interaction between the brain and the physical and social environment.

Embodied robotics is emerging as a new methodology for understanding realistic interactions between the brain and the environment. As our capacity of thought experiments on complex dynamical systems is limited, experiments using real sensors and actuators in physical environment, or its realistic simulation, are necessary to understand what really are the problems for robustly adaptive behaviors, and to find what could be possible solutions.



Cyber Rodents and battery packs.

In order to understand the adaptive mechanisms required under the basic constraints of

biological agents, we built a robotic experiment platform called "Cyber Rodent" (Doya 2003), with funding from CREST, JST. Cyber Rodents "survive" by foraging battery packs and "reproduce" in software by exchanging their programs through infrared (IR) communication ports. A Cyber Rodent has a wide-angle camera as its eyes, IR proximity sensors as its whiskers, two wheels for locomotion, and a three-color LED for emotional communication. It has a high-performance CPU (Hitachi SH-4) and a FPGA vision processor, and can "live" about one hour if fully recharged.

We have so far demonstrated the interactions between multiple regulatory systems, such as randomness and learning speed, depending on the environmental settings (Eriksson et al. 2003). However, more theoretical and experimental works are needed to elucidate biologically plausible regulation mechanisms of behavioral learning, and to test what kind of disorders can happen when the regulatory system goes out of balance.

### **C. Research contents**

In order to implement the three major strategies, we form three research groups in Okinawa:

- 1) *Dynamical Systems Group* for developing novel computational framework for modeling dynamic biological networks
- 2) *Systems Neurobiology Group* for elucidating functions and dynamics of neuromodulatory systems in rodent experiments
- 3) *Adaptive Systems Group* for exploring adaptive mechanisms and mal-adaptive phenomena using artificial rodents

These three groups work in synergy with the fourth group, Cognitive Systems Group, located in and supported by ATR Computational Neuroscience Laboratories, where the PI will retain his department head position as a part-time employee. This group will focus on psychophysics and brain imaging studies, for which ATR has excellent facilities, such as functional MRI and MEG, as well as leading researchers with good expertise.

Below is the plan for each research group. We divide the five-year project into roughly three phases: Phase 1 till March 2005; Phase 2 till March 2007; Phase 3 till December 2008.

#### *1) Dynamical Systems Group*

The goal of Dynamical Systems Group is to develop novel framework for modeling biological dynamical systems. Its major methodology is Bayesian estimation theory and computer simulations.

**Phase 1:** The main task in phase 1 is to develop original methods for applying Bayesian estimation techniques, such as Sequential Monte Carlo method and Variational Bayes method, for identification of biological dynamical systems, such as gene networks, intracellular signaling cascades, and neural networks for behavioral control and learning. The basic strategy is to represent such a network as a Bayesian network, and describe their dynamic interactions as conditional probability distributions of variables and parameters (Samejima and Doya 2004). Although standard algorithms for estimating unknown variables and parameters from available data and priors are

already established, we will make special efforts on incorporating particular types of uncertainties in experimental data as prior distributions, and deriving efficient algorithms that exploit the special structures of the network.

**Phase 2:** In the second phase, the main task will be coding the algorithms as software packages and to test them internally with benchmark tasks. The latter is best done in collaboration with local experimental group with which we can run experiments and modeling in an interactive manner.

**Phase 3:** In the final stage, we will make our modeling tool public for extensive tests and improvements. We will actively solicit collaborators internationally, to test and demonstrate the validity of our new methods.

## *2) Systems Neurobiology Group*

The major goal of Systems Neurobiology Group is to elucidate functions and dynamics of neuromodulatory systems. Its main methodology is rodent neurophysiology experiments, including multi-electrode recording, in vivo micro dialysis, and pharmacological manipulation.

**Phase 1:** In the preparatory phase, we will develop a novel behavioral paradigm with which we can maximally exploit the learning capabilities of a rodent. The reason for choosing a rodent for experiment is that there is a rich archive of experimental data on rodent neuromodulatory systems, and that we can utilize genetic manipulation. On the other hand, rodent cognitive capabilities are far primitive compared to primates and humans, which is why rodent models of psychiatric disorders so far has been incomplete. We will explore, by giving specially enriched developing environment, and even artificially enriched sensorimotor systems (e.g., Talwar et al. 2002), whether it is possible to let them make complex decisions or complex social interactions. We will also develop laboratory setups for multi-channel recording from behaving animals.

**Phase 2:** While the rodent performs the above task, we will perform multi-electrode recording from neuromodulatory centers (e.g., substantia nigra, dorsal raphe, locus coeruleus, basal forebrain) as well as their major afferents and efferents (e.g., dorsal and ventral striatum, amygdala, hippocampus, and ventromedial prefrontal cortex). This requires most up-to-date electrode and data acquisition systems (e.g., Nicolelis and Ribeiro 2002), as well as spike sorting software, some of which would have to be developed in house.

A particular goal of the experiment is to measure the activities of different neuromodulatory centers at different events and contexts of the behavioral task, and how they change in the course of learning and with the change of environmental settings. We will also complement the results with micro dialysis measurement of modulator concentration and pharmacological blockade of particular receptors. In conjunction with the method given by Dynamical Systems Group and experiments by the Adaptive Systems Group, we will develop a dynamic model of interactions of the neuromodulatory systems, the environmental setting, and the animal's experience.

**Phase 3:** We will further test the model using genetically altered animals. Specifically which

knock-out or knock-in animals to use will depend on the results of the second phase.

### 3) *Adaptive Systems Group*

The aim of the Adaptive Systems Group is to explore adaptive mechanisms required for life-like agents and to test how such mechanisms can fail with defunct components, under extreme environments, or both. In order to take into account challenges in real physical and social environments, the group will use a colony of artificial rodents and its simulator software.

The specific issues to be tested are

- a) how design of reward function affects the learned behaviors of agents
- b) what regulation mechanisms are necessary for robust learning in changing environments
- c) what malfunctions can happen when the reward systems or the regulatory systems are

imperfectly set. While development is primarily top-down inference of computational necessities and efficacies, we will always try to make relevant connections with the real biological systems.

**Phase 1:** In the first phase, we will focus on developing meta-learning algorithms for tuning higher-level parameters, such as time scale of prediction and width in action exploration.

Experiments will be performed by using the Cyber Rodent platform and its simulator developed at ATR. We will also design a second-generation platform, which is more compact, economical, and can be distributed to other laboratories.

**Phase 2:** We will build the second generation of Cyber Rodents, preferably in collaboration with a company that has a good expertise in mechanical design and an interest in commercial distribution of the products. We will also revise our simulator to match the structure of the new Cyber Rodents. Using these hardware and software, we will perform experiments of collaborative behaviors, such as foraging, nest making, and defensive behaviors.

**Phase 3:** Based on the meta-learning and communication mechanisms developed in the second phase, we will develop "robotic" models of behavioral and cognitive disorders, such as schizophrenia, depression, and autism. The new Cyber Rodent hardware will be made available in collaboration with a company, and its simulator software will be publicly available.

### **D. Related research, originality and advantage**

#### 1) *Simulation of biological networks*

There have been several studies that reconstructed network dynamics of genes and intracellular molecules (e.g., Bhalla 1999). Projects of simulating an entire cell, e.g., E-cell Project, are under way (Tomita 1999). However, in these modeling projects, many of the parameters are hand-tuned by trial and error, which compromises the objectivity and reliability of the models.

Some attempts have been made at applying machine learning techniques for system identification of biological network. Most notably, Dr. Shin Ishii's group at NAIST have applied Variational Bayes method for building a linear state space model of gene activation using DNA chip activation data (Ishii 2003). We have been in collaboration with his group as a part of CREST project and will be recruiting their members into our new project in Okinawa. We have also applied

Variational Bayes method for estimation of brain activation from fMRI and MEG data (Sato et al. 2003) and Sequential Monte Carlo method for prediction of brain activities from observable variables (Samejima and Doya 2004).

These put us in a uniquely advantageous position to put together a team of people to develop a novel computational tool for system identification closely based on experimental data and domain knowledge.

## *2) Rodent experiments*

Techniques of multiple electrode recording have seen a remarkable progress in these years. It is possible to record from hundreds of neurons simultaneously (Nicolelis and Ribeiro 2002). It is even feasible to connect the neural recoding output to robotic hardware and to guide the animal behavior by intracranial stimulation precisely timed with the animal behaviors (Talwar et al. 2002).

While many previous rodent experiments focused recordings from the neocortex and the hippocampus, the activities of more primitive parts of the brain, which may subserve more fundamental functions in life, have not been sufficiently explored yet. While it is technically feasible to simultaneously record from multiple neuromodulatory nuclei, without a clear theoretical principle, it is difficult to decide what behavioral paradigm to use and how to analyze resultant massive data. With our theoretical paradigm (Doya 2002), we can predict in what kind of situation a particular neuromodulatory system should be activated, and evaluate the resulting data in reference to our theoretical predictions.

## *3) Robotic experiments*

The Khepera robot (by EPFL and K-TEAM) has been popularly used in modeling studies, e.g., in exploring the interaction between learning and evolution (Nolfi and Floreano 2002). Developer's kit for AIBO robot was recently made public, which can also be used in various experiments. The use of Khepera robot is hampered by its humble sensory and computing capabilities. The complex body kinematics of AIBO robot requires extensive tuning of basic control routines before any learning experiments can be performed.

Self-recharging function has been implemented in recent AIBO robots. Embodied evolution by exchange of program parameters has been tested in a colony of mobile robots (Watson et al. 2002). However, our Cyber Rodent is the first robotic platform that enables both self-preservation and self-reproduction, by means of foraging battery packs and local communication through IR ports, respectively. It also has a real-time image processing FPGA module and a high-power CPU (Hitachi SH-4), which is comparable in its computing power as a Pentium chip a few years ago.

Through our experiments of learning and evolution with current Cyber Rodent robots and simulators, we are developing concrete ideas about how the platform could be improved by changes in its basic designs and incorporation of more recent technologies. For example, incorporation of artificial retinal chips, which are recently applied to mobile phone cameras, would drastically reduce the robot size and also make its visual system more biologically realistic.

## **E. Major challenges**

The first major issue is how to recruit talented and motivated researchers from around the world. While some of my colleagues and collaborators have already expressed their enthusiasm in joining this Okinawa research project, we definitely need more personnel, including experienced researchers, graduate students, and computer engineers to fully implement the plan. This requires active international recruitment and extensive promotion of our research project.

The second requirement is to establish strong partnership with other research institutes and industry. In extending our research results to understanding of human cognitive functions, collaboration with research groups at ATR Computational Neuroscience Laboratories will be essential. We will also actively seek partnership with companies in designing, manufacturing, and distribution of a new generation of Cyber Rodents.

## **2. Expected achievement**

### **A. Scientific achievement**

The primary achievement of the research will be a better understanding of neural substrates of affective and cognitive systems. If the research plan is fully executed, we will have much clearer ideas about the origins and functions of our affective system, and why damages in particular genes and molecules, or certain environmental factors lead to affective and cognitive disorders.

More specifically, we will produce a computational paradigm that can be practically used for building and analyzing dynamic models of biological networks, including gene networks, intracellular signaling cascades, and combined dynamics of neurons and environments.

On the basis of this methodology, we will construct and a computational model of interactions of the neuromodulatory system in regulating our behaviors, and justify the model through rodent experiments.

### **B. Social impact**

Our scientific achievement of understanding the neuromodulatory functions have direct implications on the therapy and prevention of psychiatric disorders, such as Schizophrenia, depression, and autism.

The new platform of Cyber Rodent, both in hardware and software, will not only become useful research tools in cognitive science and artificial intelligence, it would serve as a new generation of entertainment robots. Its advanced capability of learning and communication would require more devotion and deeper affection on the side of caretaker.

We will secure any new development in the therapeutical use of our research as our intellectual properties. Core technologies in the design of new Cyber Rodents may also be patented.

In the widest sense, our research, in conjunction with development in other laboratories, would change the way people consider our affective system; from the subject of philosophy and mystery to the subject of science and quantitative prediction.

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