Strategic Programs for Innovative Research Field 1 Supercomputational Life Science

BioSupercomputing Newsletter

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SCLS

Theme 4 Large-scale analysis of life data

Large-scale analysis of life data toward and complexity of life programs

Aiming to analyze the biomolecular network by using the genome as the standard, promote development of a system for processing and analyzing a vast amount of DNA information, and contribute to medical application

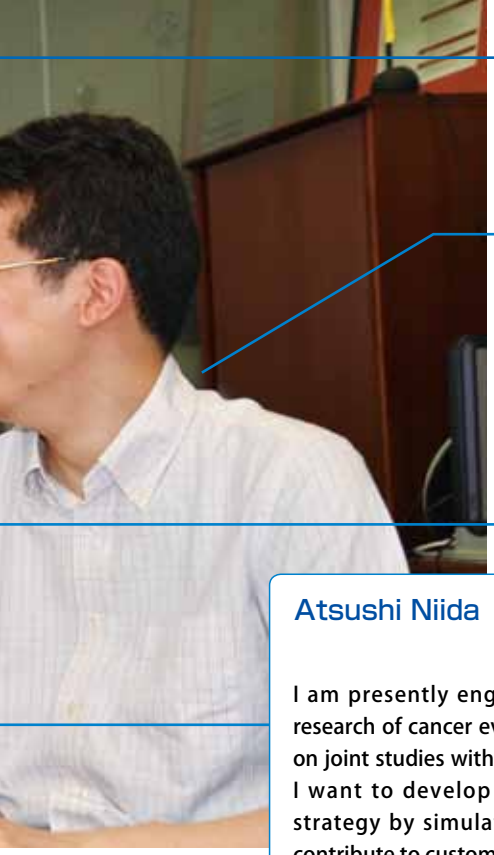
Various advanced measurement technologies such as cutting-edge sequencers are accelerating refinement and size increases of life system data. Theme 4 "Large-scale analysis of life data" (Leader: Prof. Satoru Miyano, The Institute of Medical Science, The University of Tokyo) aims to construct an infrastructure for cutting-edge, large-scale data analysis optimized for the K computer, understand the complexity, diversity and evolution of life programs, and promote analytical studies on biomolecular networks by using the genome as the standard. We interviewed three researchers who are struggling at the frontline of bioinformatics by utilizing state-of-the-art information processing technologies.

Encounter with bioinformatics

● How did you happen to get involved in bioinformatics studies?

Niida: In the undergraduate school, I worked on the molecular biology of cancer. Just when I finished my undergraduate course, the human genome project was completed. The encounter with genomic science aroused my interest in bioinformatics. I was not very good at computers, and so I studied it in my way. After I finished my graduate school, I came to the lab of Prof. Miyano and started to work on the methodology of bioinformatics. One day, Prof. Miyano invited me to the K computer project. I never imagined that I was going to use the fastest computer in Japan, but I'm continuing my studies with help from Dr. Ito and other members.

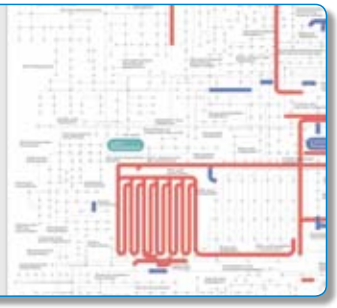
Ito: I graduated from the school of engineering and majored in computational fluid mechanics. My field is closely related to Field 4, "Industrial Innovation" of the Strategic Programs for Innovative Research. In the field of industrial innovation, computers have been used extensively (Computer Aided Design: CAD), and I was also performing simulation studies using supercomputers. However, technology development in the industrial field is so subdivided or narrow, and studies are conducted on almost every topic. Well, I felt that I wanted to study fundamental science. At that time, at Prof. Miyano' s invitation, I came to this laboratory in April last year. I still do not have a full understanding of biology, and am receiving guidance from Dr. Niida and other members. On the other hand, the members of the laboratory are not



Masanori Kakuta

Postdoctoral researcher, Akiyama Lab., Department of Computer Science, Graduate School of Information Science and Engineering, Tokyo Institute of Technology

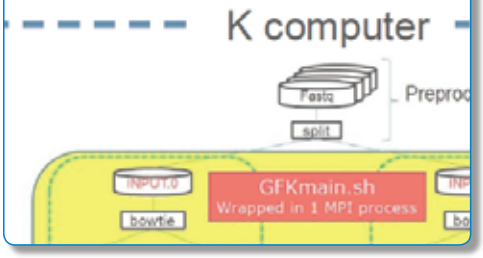
There is still room for improvement in large-scale data analysis using HPC. I want to develop information processing systems for actualizing faster and more efficient data analysis to make large-scale analysis possible.



Satoshi Ito

Project Researcher, Human Genome Center The Institute of Medical Science The University of Tokyo

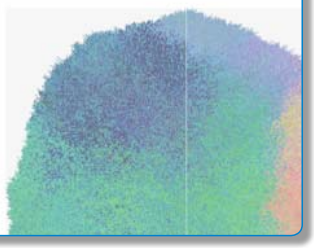
It is important to establish a collaboration between large-scale sequence data, bioinformatics for analyzing the data, and biologists and medical doctors. I want to develop software to help this collaboration.



Atsushi Niida

Project Assistant Professor, Laboratory of DNA Information Analysis, Human Genome Center Institute of Medical Science, The University of Tokyo

I am presently engaged in exploratory research of cancer evolution by simulation on joint studies with medical practitioners. I want to develop a cancer treatment strategy by simulation in the future to contribute to custom-made medicine.



disclosure of the diversity

yet accustomed to parallelization and optimization of the K computer, and I am supporting that part. We are thus cooperating together.

Kakuta: I was in the department of science during my undergraduate course. Then I went to a graduate school of agriculture to study applied engineering and started to use computer for the first time. In the graduate school, I studied interactions among proteins, and analyzed and estimated three-dimensional structures of proteins. I continued working at the lab for one year and a half after I finished my doctoral course. In the middle of 2011, I moved to the Akiyama Lab and started to participate in the Theme 4 project. I've been interested in HPC itself, but I also felt that working on large-scale computation would broaden my studies.

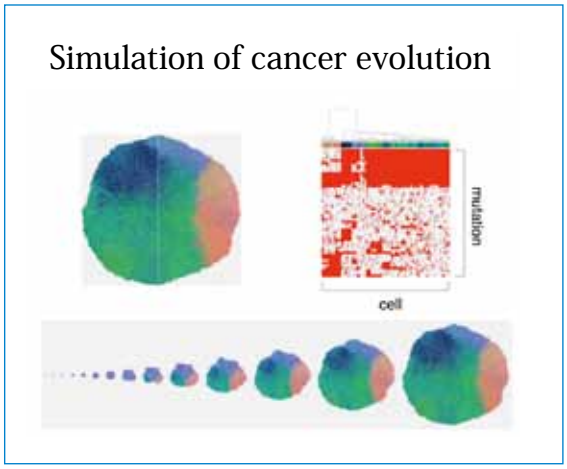


Fig. : Top left: Tumor obtained by simulation calculation
Top right: Profile of genomic mutations
Bottom: Visualized time-historical evolution of a tumor

Also working on simulation of cancer

● In Theme 4 project, what actual researches are you conducting?

Niida: The Miyano Lab is carrying out various joint studies with medical practitioners and experimental cancer labs. We receive a huge amount of data from them, which need to be analyzed quickly. One of our ongoing studies is to analyze the data from joint study laboratories by using a software called EEM (Extraction of Expression Module), which extracts expression modules, or genes that are co-expressed, from the mRNA expression data based on gene set information, and identify the transcription program of cancer by combining the analytical results with experimental data. Dr. Ito and other members are helping us to transfer EEM to the K computer. Another study is also simulation of cancer born out of joint studies. While it is well known that the

DNA of cancer differs among individuals, we found recently that the DNA is diverse even within a single patient, and differs depending even on the part within a single tumor. It has been found that, in cancer development, the first normal cell accumulates mutation and produces clones that have a mutation(s) different from the mother cell and each other. When we observe a formed tumor, there are many subclones that have mutations in completely different genes. Actually, when we conducted multi-sampling of a colorectal cancer or sampled DNAs from different parts of the tumor in a joint study, we obtained profiles of completely different genes. To answer why such a phenomenon occurs, we will investigate the mechanism of evolution by performing a simulation. Dr. Ito has converted our simulation model so that it runs on the K computer. We are running it while changing the parameters to search for key parameters involved in the development of non-uniformity in a tumor. We are planning to simulate the entire life of a cancer also to determine effective drugs, aiming to use the results in therapeutic strategy.

● Mr. Ito is also involved in the study, engaged in porting the software to the K computer.

Ito: Yes. Not only Dr. Niida, but also most members of the Miyano Lab are not familiar with MPI programs or massively parallel supercomputers such as the K computer. So my first task is to support running of existing software on the K computer. For example, let us assume that Dr. Niida wants to run a certain software on the K computer on a large scale. He tells me his intention, and I analyze the contents of the software, and judge whether the program can be ported to the K computer as it is or not. If it is not possible, I substitute another program for the software, or re-write the program directly to make it run on the K computer. It is also necessary to do parallelization, and I do the work so that Dr. Niida can use the software.

Niida: The K computer is a rather high hurdle for me in some respects. The K computer is designed for persons who have long used HPC, such as those engaged in astronomy and physics. I feel the K computer has parts that are difficult for biologists to use.

Ito: Yes. There are difficult parts. There are various bioinformatics software programs. Each of them is a combination of two or more programs and so, in many cases, they are written in two or more languages instead of one. For example, a pipeline software consists of C language mainly, R statistical language partially, and shell script for connecting C and R parts. Most software needs to resolve the flow before porting. Although there are people in bioinformatics who use supercomputers, there are few who have done parallelization. Therefore, there may be a great barrier to using the K computer without experience of using other HPCI supercomputers.

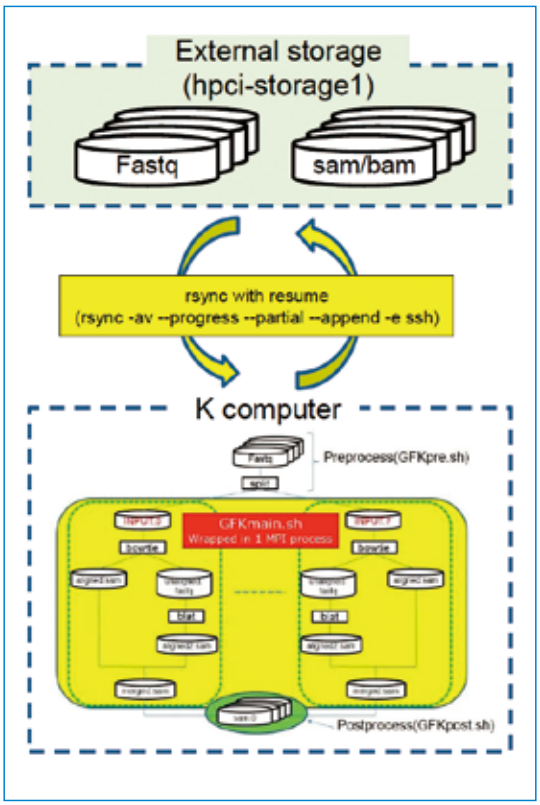


Fig. : **The concept of Genomon-Fusion for the K computer, a software for detecting cancer variants on a large-scale and comprehensively at the transcriptomic levels. Various improvements were made to port the program to the K computer such as integration of MPI processes, because multiple MPI processes would lose time due to the MPI barrier mechanism.**

Toward ultra-fast large scale analysis

Kakuta: I am mainly developing a metagenomic analysis pipeline using the K computer and also analyzing actual data using the pipeline. Metagenomic analysis is a method for analyzing the genome of the entire group of microorganims within a certain environment. There are various species of microorganisms within an environment, but it is possible to determine what species are present in which part of the environment and their amount by analyzing them as a mixture. It is also possible to investigate how microorganisms interact with the environment by measuring the percentages of the species. However, metagenomic analysis processes a

much larger amount of sequence data than genomic sequencing of one microorganism. The project in which I am involved aims to conduct large-scale computation by the K computer to analyze this enormous amount of data. The metagenomic analysis pipeline compares fractions of the genome, which is obtained via a next-generation sequencer, and sequences in the existing databases through a series of processes. The pipeline can identify genes contained in the sample data and analyze their relative abundance based on their functions. A parallelized homology search tool called GHOST-MP plays the central role in the analysis pipeline. Graduate students are writing programs to run on a processor, and I am converting them one by one into a parallelized program that runs on the K computer to enable large-scale analysis. We are aiming at highly precise analysis, but this requires a long computation time. To shorten the time, we are developing efficient and highly parallelized methods, and also increasing the speed of each subprogram. We are trying to develop an ultra-fast, large-scale analysis program by approaching it from both sides.

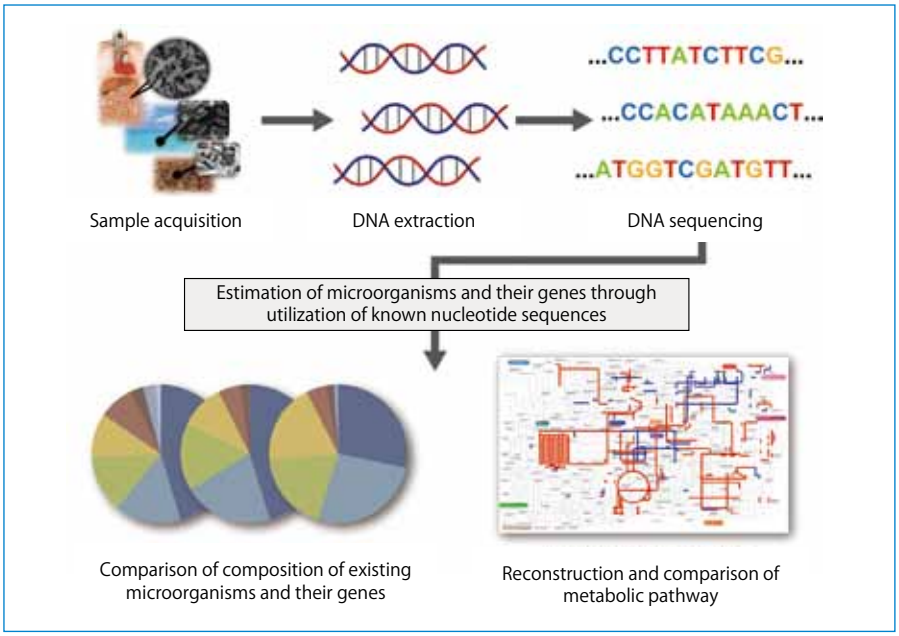
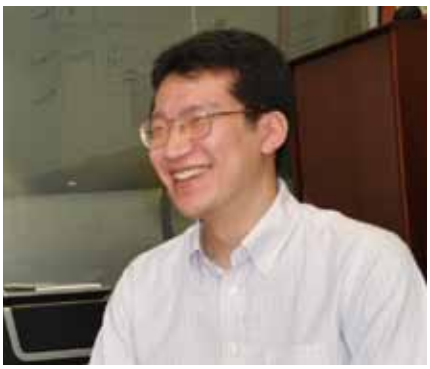


Fig. : Schematic illustration of metagenomic analysis using systematic and functional analyses



We want to utilize bioinformatics in medicine

● What do you want to accomplish through this and future studies?

Niida: In the ongoing simulation study, my goals are not only to identify parameters but also to find the principles of evolution and mechanisms that lead to diversity by comparing with experimental data, and to find a new concept of cancer research. To achieve the goals, it is important to improve simulation, but it is also crucial to communicate with in-service medical practitioners to acquire new knowledge, and to feed back experimental data to our own analysis. In the future, I want to make a discovery by using bioinformatics that is useful to medicine.

Ito: My first goals are to develop a pipeline for biologists to analyze a huge amount of data in public and restricted databases in order to acquire biological knowledge, and to carry out computation using the pipeline. Next-generation sequencing technologies are rapidly progressing, thus completely different approaches may be required in several years. To cope with such a situation, I want to develop software programs by merging the characteristics of supercomputers and the requirements of bioinformatics in a sophisticated way.

Kakuta: Not only in metagenomic analysis, but the amount of data is increasing in various kinds of experiments. Computers are already indispensable for analyzing experimental data, but I think that faster and larger-scale analysis by parallelization will be increasingly demanded in the future. I wish I could contribute as much as possible to meeting such a demand.

After SPECIAL TALK

After the interview, the interviewees answered questions from and talked freely with young researchers and students. Visit the URL below for more information.

● See the URL on the right for longer version of this discussion meeting. ***http://www.scls.riken.jp/eng/newsletter/vol.11/openup.html***

Designing and evaluating new medicines on a computer Aiming to construct the platform of IT-based drug discovery

Fujitsu working jointly with the University of Tokyo toward an innovative drug discovery process

Manager,Bio-IT R&D Office, Research & Development Division, Next-Generation Healthcare Innovation Center, Fujitsu Limited **Nozomu Kamiya** (left in the photo)

Bio-IT R&D Office, Research & Development Division, Next-Generation Healthcare Innovation Center, Fujitsu Limited **Takashi Mitsui** (right in the photo)

Theme 2 "Simulation Applicable to Drug Design" (representative: specially appointed professor Hideaki Fujitani, Research Center for Advanced Science and Technology, the University of Tokyo) aims to optimize MP-CAFEE, which is a method of calculating the binding free energy based on molecular dynamics, for the K computer, identify a low-molecular weight compound(s) that strongly interacts with a target protein that causes a disease, and develop and establish an efficient and quick technology for developing new drugs. Fujitsu started a joint study with the Research Center for Advanced Science and Technology, the University of Tokyo (hereinafter referred to as "RCAST") in 2011, and is tackling to conduct IT-based drug discovery. We interviewed the leading researchers in Fujitsu on the circumstances and objectives of the innovative drug discovery technology.

The IT-based drug discovery by Fujitsu

— Why is Fujitsu working on the R&D of IT-based drug discovery ?

Kamiya Fujitsu started to import and sell computational chemistry software and develop original software programs jointly with research institutes and companies in Japan in 1983, which is more than 30 years ago. At the time, Japan was behind the USA, etc., on software development. For example, let's say that a university bought a supercomputer, but they could not use it effectively. So we started in-house software development full-scale. In 2003, the sequencing of the human genome was completed, providing an impetus to the biotechnology industry. Fujitsu established the BioIT Business Development Unit (present Next-Generation Healthcare Innovation Center) in 2004 to accelerate the bio-related business, and has also concentrated its efforts on technologies called IT-based drug discovery, which use computational science, through its own research activities and collaboration with companies, universities and research institutes in Japan and overseas.

— What is the IT-based drug discovery targeted by Fujitsu?

Mitsui Conventional drug discovery involves the selection of possibly promising candidates for drugs among a vast number of low-molecular weight compounds by using the experience and knowledge of researchers, and repeating synthesis and experiments. According to one's estimate, out of a total number of candidate compounds, only one out of thirty thousand is finally approved as a new drug. The process requires a long time, may be a decade or longer, and costs several tens of billions of yen. Our drug development technology involves using computer simulation to design the structure of a compound, virtually on the computer, that has drug efficacy based on the structure of the target protein, and creating a new compound in a short period of time at a low cost. We also have developed technologies for predicting and evaluating the activities of drug candidates by molecular dynamics simulation that assumes a biological environment.

Kamiya The technology is characterized by the capability of designing diverse chemical structures, which may not be found in existing compounds, and narrowing them down to promising ones before synthesis and evaluation. For this purpose, Fujitsu developed original software for designing low-molecular weight compounds, which is called OPMF (Optimum Packing of Molecular Fragments). Based on the three-dimensional X-ray structural analysis of the (target) protein, a new compound that can bind to the active site is designed by connecting fragments. The efficacy of the chemical structure so obtained is then predicated by using MAPLE CAFEE for an environment that reproduces biological conditions, including the water molecules surrounding the protein.

— Is MAPLE CAFEE different from MP-CAFEE?

Kamiya When Prof. Fujitani was in Fujitsu Laboratories, he constructed a force field that uniformly processes biopolymers such as proteins and organic molecules, and developed a method for calculating the molecular dynamics from the state in which the protein and compound are separate until they are bound, and determining the binding free energy. This calculation method is called MP-CAFEE. MAPLE CAFEE is the name of the system constructed by Fujitsu by using this calculation method.

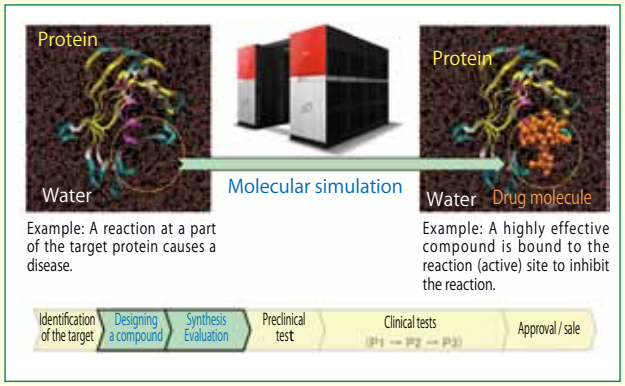


Fig. 1: **Fujitsu developed OPMF, a software for designing a low-molecular weight compound which strongly binds to and inactivates the target protein which causes a disease, enabling highly effective novel compounds to be created in a short period of time at low cost.**

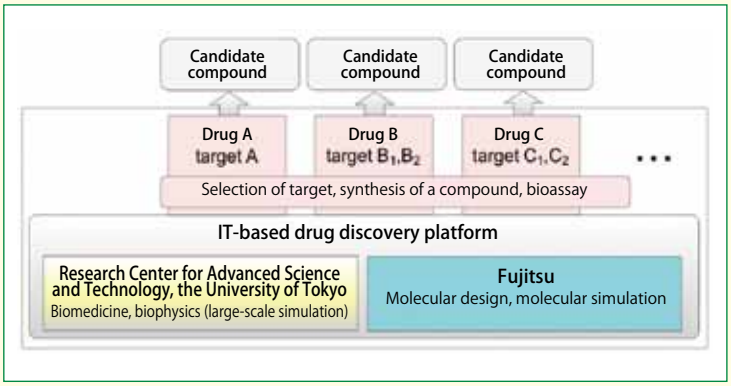


Fig. 2: **Schematic view of joint studies on IT-based drug discovery between Fujitsu and RCAST and pharmaceutical companies.**

Construction of IT-based drug discovery platform jointly with RCAST

—You started joint studies with RCAST in 2011.

Mitsui During the process of doing R&D toward the creation of low-molecular weight drugs by using computer simulation, RCAST appreciated the technologies of Fujitsu for designing and evaluating low-molecular weight drugs; and we started joint studies. In concrete terms, Fujitsu designs low-molecular weight drug candidates by using OPMF, narrows them down to likely promising ones, and provides the information to Fujitani Laboratory in RCAST. At the Fujitani Laboratory, they calculate the extent the compound acts on the protein via simulation. They notify the results of the analysis to Fujitsu, and Fujitsu feeds back the data into the design. Through this joint study, we are also using the computational power of the K computer, although indirectly.

Kamiya For the Theme 2 in FY 2012, Fujitsu designed about 300 compounds for a target protein in cancer therapy, and the binding free energy was calculated using the K computer. Last fiscal year, the results were used to improve studies and further elaborate the designs of the compounds. We chose 25 compounds from them, and calculated their binding free energy. Eight compounds were predicted to have strong binding free energy, and studies will start jointly with the experimental group toward development of drugs for a cancer remedy.

—What is the goal of Fujitsu in the joint study with RCAST?

Mitsui We aim to construct a platform for IT-based drug discovery, which innovates the development process, by using the excellent study knowhow and results of RCAST, the large-scale simulation technology performed by Prof. Fujitani et al., and the molecular design and simulation technologies of Fujitsu. We will also conduct joint studies with a pharmaceutical company to produce the fruits of new drugs by IT-based drug discovery.

—What are the current issues in R&D?

Mitsui The biggest problem is the computational power. We want to quickly check how the efficacy changes by a change in the design of a compound, and reflect the results for improving the compound. In other words, we want fast cycles. However, calculation of binding free energy requires a vast amount of computation, and thus we want to use as high a computational power as possible. It would be meaningless to use IT-based drug discovery if it is faster to actually synthesize the compound than calculating.

—What do you think about the future of IT-based drug discovery ?

Kamiya IT-based drug discovery is a highly promising new-generation process for developing innovative and highly effective compounds in a short period of time at low cost. We believe that establishment and application of this innovative technology will help to create new therapeutic drugs for various diseases. It would be wonderful if computational science can contribute to improving medicine, such as making it possible to cure diseases that are difficult today. We mentioned that the success rate of a new drug is one out of 30 thousand. This means that we need to synthesize thirty thousand compounds to develop one drug. If such experiments can be replaced by computation, it would sharply reduce the labor and difficulties for developing a drug. Also to achieve this goal, we want to produce results as early as possible.

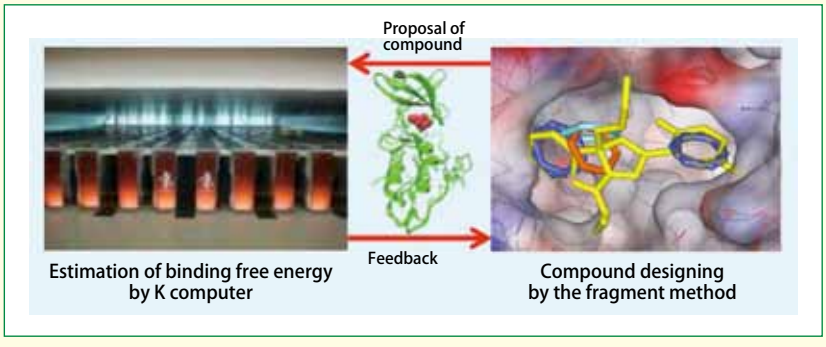
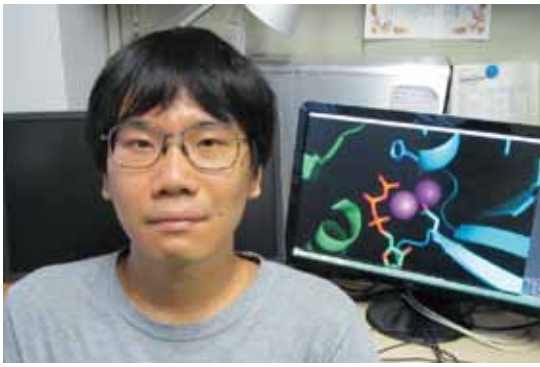


Fig. 3: **Schematic view of the joint study between Fujitsu and RCAST on Theme 2. Fujitsu designs candidate compounds, and the results of binding free energy calculation are fed back and used to elaborate the design.**

See the URL on the right for detailed information on this report http://www.scls.riken.jp/eng/newsletter/vol.11/sclseyes.html

Structural analysis of protein in solution by molecular dynamics simulation and small angle X-ray scattering

Computational Life Science Laboratory, Graduate School of Medical Life Science, Yokohama City University
Yuichi Kokabu



Biopolymers such as proteins exist in solution. A protein in solution does not have a single determined structure, but undergoes structural fluctuations by thermal fluctuation. Therefore, determining the structure of a protein in solution including its structural fluctuations is a key for understanding the *in vivo* functions of the protein. In this article, two methods for determining (or estimating) the protein structures in solution, namely molecular dynamics (MD) simulation and small angle X-ray scattering (SAXS), are explained by taking our recent study results for example.

MD simulation reproduces behaviors of a protein in solution by solving the equations of motion. With this method, the atomic-level behaviors of a protein can be estimated. We estimated the structure of Rad51 protein filaments in solution, which catalyzes strand exchange in homologous recombination, by performing MD simulation of a dimer as a minimal unit of the filament (Fig. 1).

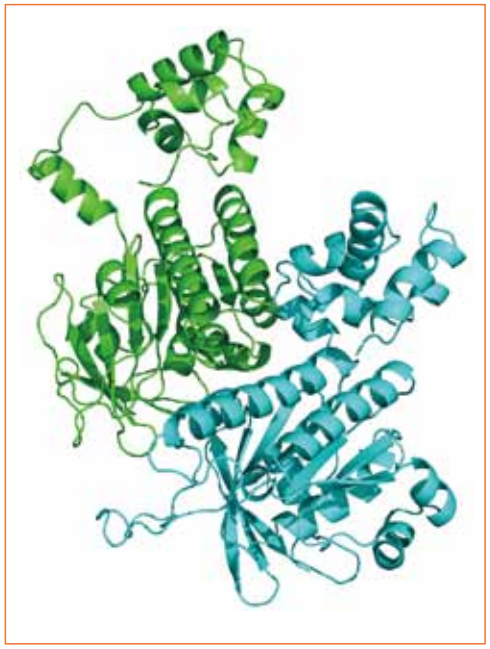


Fig. 1 : Structure of a dimer of Rad51 estimated by MD simulation

On the other hand, SAXS irradiates X-rays directly to the protein in solution and determines the general form of the molecule from the scattering pattern. Although the resolution is low, SAXS can measure the protein structure in solution including its structural fluctuations by thermal fluctuation. This time, we analyzed the structure of a protein called Swi5-Sfr1 complex (S/S) in solution, which is an activator of Rad51, by using SAXS, and found that the protein takes an extremely elongated form in solution.

This elongated structure fits well to the groove of the estimated Rad51 filament model (Fig. 2). Therefore, we hypothesized that Rad51 filament is activated by binding of S/S to the groove, and are verifying it.

MD simulation can estimate a structure including fluctuations at an atomic-level resolution, and its confidence factor can be increased by experimental verification. Aiming to verify the results of MD simulation by comparing with the experimental data of SAXS, we developed a theoretical method for calculating the SAXS scattering pattern from the results of MD simulation. We can judge that a result of MD simulation is valid if the SAXS pattern calculated from the MD simulation agrees with the experimental SAXS pattern. This method was applied to a mutant protein Swi5-Sfr1dN177, in which the 177 residues from the N terminus of Sfr1 are lost, to analyze the protein structure in solution including fluctuations at an atomic level.

Today, we are using the method for a DNA-binding protein called a nucleosome. A nucleosome is a huge molecule, and it would require enormous computation, i.e., too much time, to estimate its structure by all-atom MD simulation. Therefore, we are using coarse-grained MD simulation, which calculates the structure by substituting a particle for an amino acid, to analyze the fluctuations in the DNA terminus of the nucleosome and its SAXS scattering pattern.

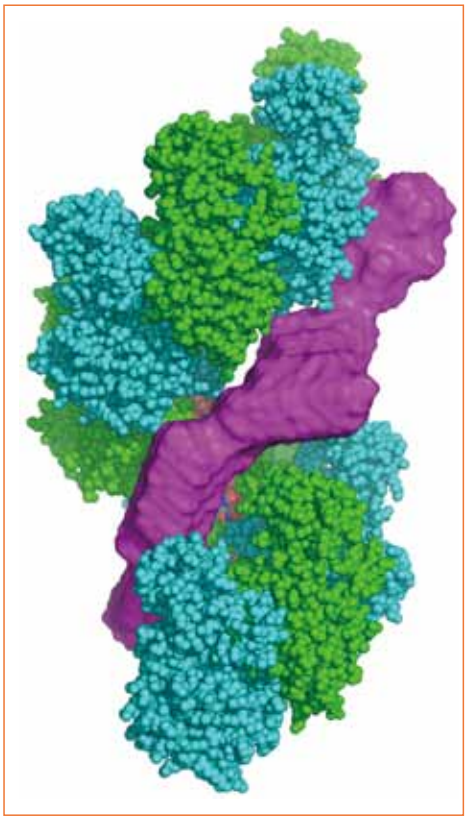


Fig. 2 : Model of Swi5-Sfr1 (magenta) binding to the groove of Rad51 filament in solution

● See the URL on the right for detailed information on this report and profile of the author.
http://www.scls.riken.jp/eng/newsletter/vol.11/zoomin01.html

Coarse-grained simulation : Investigation of the molecular mechanism of signaling pathway using CafeMol

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Division of Biological Sciences, Graduate School of Science, Kyoto University
Ryo Kanada

For cells to adapt to the environment, mechanisms are required for transmitting signals from outside of the cell to the nucleus, amplifying the signals, and expressing a gene and/or changing the activity of a protein. These mechanisms are called a signaling pathway. In our project, we are focusing on mitogen-activated protein kinase (MAPK) cascades, which are a typical signaling pathway model.

For example, in a mammalian MAPK cascade (one of pathways) shown in Fig. 1, a stimulus from outside activates upstream Ras and Raf (MAPKKK), which phosphorylates and activates another protein MEK1 (MAPKK) downstream, and then ERK2 (MAPK). Proteins are thus successively activated (Ras→ Raf (MAPKKK)→ MEK1 (MAPKK)→ ERK2 (MAPK)) until the signal reaches the nucleus. The cascade not only determines the fate of the cell (whether to undergo proliferation, differentiation, or apoptosis, etc.), but is also known to be closely related to canceration (cancer development). Therefore, elucidation of the activation mechanism in signaling pathways is strongly demanded also from a medical point of view. However, the precise molecular mechanism still remains unclear

One of the reasons for the difficulty of understanding the mechanism is that it is challenging to experimentally determine how the upstream protein (for example, MEK1) approaches the downstream protein (for example, ERK2), and forms a complex in terms of atomic-level structure. In our study, we aim to estimate the structure of the MEK1-ERK2 complex and its formation dynamics by using a theoretical approach, and the structures of MEK1 and EKR2 which are already known.

For this purpose we are using CafeMol*, which is a coarse-grained molecular dynamics simulation program developed by our research team. CafeMol assumes each amino acid that constitutes a protein as a bead, and calculates the dynamics. Therefore, the computation cost is significantly reduced compared to all-atom molecular dynamics methods (even a physical event of a millisecond order in a huge system such as a chromatin fiber can be reproduced by making full-scale use of the K computer, a supercomputer). By using our original atomic interaction based coarse grained (AICG) model to represent the interactions (force field) among beads, we can perform more practical calculations than conventional coarse-grained simulation, as our method considers the dependency on the amino sequence and the secondary structures of the proteins.

A complex structure estimated from the coarse-grained simulation using CafeMol is shown in Fig. 2. This structure was compared with the structure estimated from existing docking servers (ClusPro, etc.), and they were found to agree well with each other. CafeMol can also reproduce the time-dependent progress of protein binding, which cannot be performed with a docking server. We are planning to use this advantage to investigate the effects of the presence of a scaffold protein(s) (KSR) and crowded environments within the cell on the dynamics of complex formation, and reveal the molecular mechanism of signal transmission.

Note :
* H. Kenzaki et al., *J. Chem. Theory Comput.*, **7**, pp 1979-1989 (2011) [http://www.cafemol.org/]

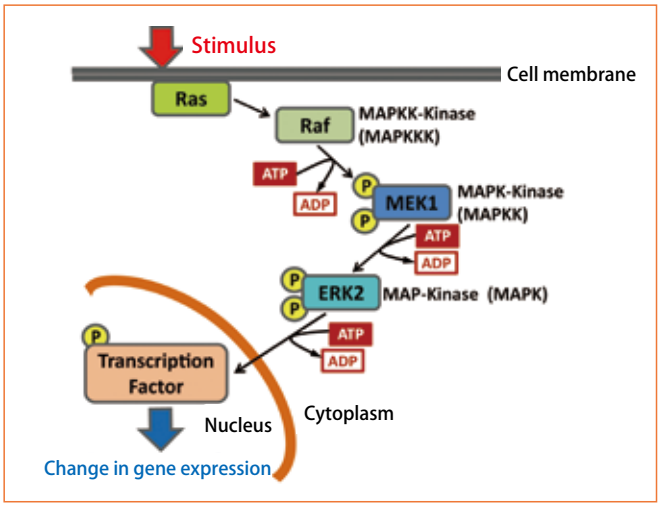

Fig. 1 : MAPK cascade signaling pathway

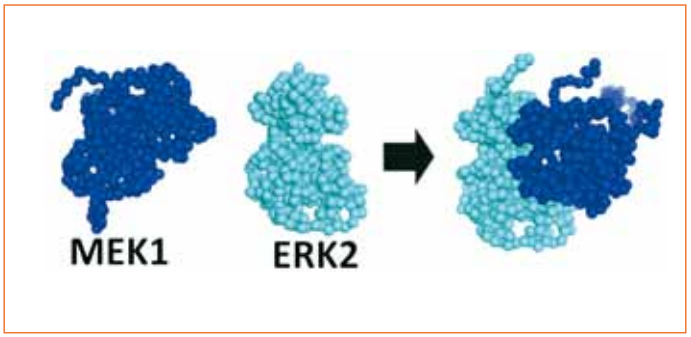

Fig. 2 : Coarse-grained simulation of MEK1 and ERK2 by CafeMol

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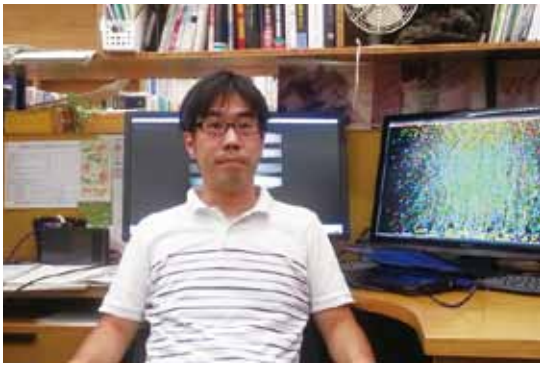
http://www.scls.riken.jp/eng/newsletter/vol.11/zoomin02.html

Development of a central nervous system model for elucidating the onset mechanism of Parkinson's disease

Neural Computation Unit, Okinawa Institute of Science and Technology Graduate University
Jun Igarashi



We are conducting simulation studies of the brain by using the K computer to elucidate the mechanisms whereby Parkinsonian symptoms develop, and investigate an effective remedy. Parkinson's disease is a disorder of the central nervous system and causes various symptoms mainly related to movement, such as slowness of movement, shaking of the body, muscle rigidity, and difficulty in maintaining posture. Parkinson's disease is the second most common neurodegenerative disease after Alzheimer's disease, and affects several million people in the world.

The cause of Parkinson's disease is loss of dopamine-generating cells in the substantia nigra compacta, the causes of which have been suggested to be mitochondria abnormality, and the effects of reactive oxygen. The resultant dopamine depletion triggers an abnormal and strong synchronous nervous activity of about 8-14Hz in the basal ganglia. The basal ganglia is interconnected with the thalamus and cerebral cortex forming a loop (basal ganglia→thalamus→cerebral cortex→basal ganglia); and the entire circuit is in charge of processing information that controls voluntary movement, etc. The abnormal synchronous nervous activity in the basal ganglia in Parkinson's disease is believed to affect the entire loop, inhibiting normal information processing and causing various symptoms. However, it is still poorly understood how the basal ganglia, thalamus and cerebral cortex affect each other and cause the various symptoms of Parkinson's disease. Factors obstructing elucidation of the mechanism include the limited number of nerve cells and the limited range of the brain that can be actually monitored, and the difficulty of measuring the interactions among nerve cells, which are connected in a complex way.

In brain simulation, the activities of all nerve cells and interactions are recorded, and the nerve activities can be investigated repeatedly for various conditions. We aim to simulate the entire nerve circuit of the basal ganglia, thalamus and cerebral cortex, and investigate their mutual interactions by using the enormous arithmetic capacity of the K computer, and investigate and improve deep brain stimulation and other remedies. At present, we are developing models of the basal ganglia, thalamus and cerebral cortex, separately. The basal ganglia is being modeled so as to reproduce the abnormal synchronous nervous activity. The pathological neural oscillation in Parkinsonian disease has been successfully reproduced by imitating the characteristics of nerve cells and synapses in the subthalamic nucleus and globus pallidus lateral segment under dopamine depletion. The thalamus and cerebral cortex are being modeled, focusing on elucidating the mechanism of Parkinsonian tremor. The tremor is known to synchronize with the neural oscillation (about 10Hz) at the thalamus and cerebral cortex, but at a half of the cycle. We are developing a neural circuit model of the thalamus that can reproduce the oscillation, and a model of the cerebral cortex that expresses the body movements involved in tremor. We are also testing the entire model that connects the models of the basal ganglia, thalamus and cerebral cortex. At the final stage, we are planning to evaluate the development mechanism of Parkinsonian symptoms by using a model of the whole body, which includes the spinal cord and musculoskeletal models that feed back sensory signals to the brain.

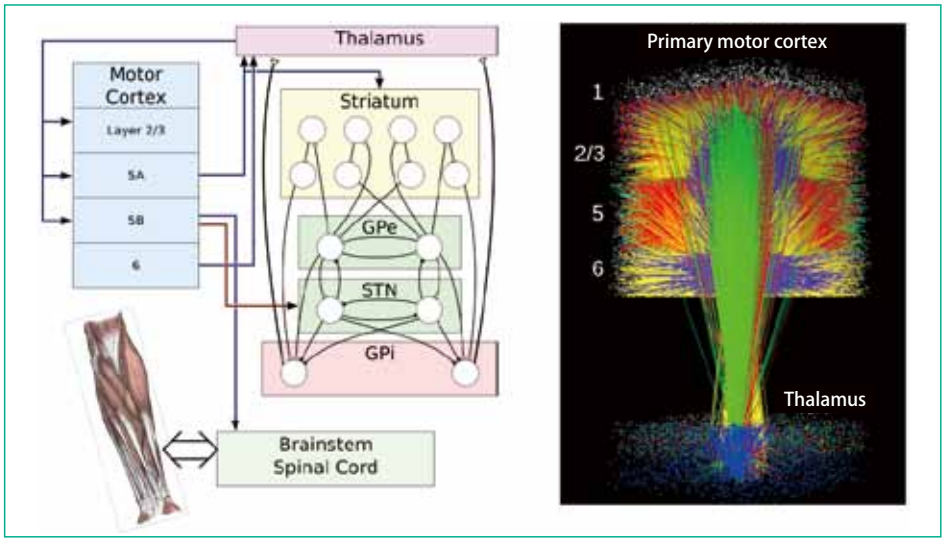


Fig. : Left: Schematic illustration of the connections between the basal ganglia, thalamus and cerebral cortex
Right: Three-dimensional illustration of the planned neural circuit model between the cerebral cortex and the thalamus

See the URL on the right for detailed information on this report and profile of the author.
http://www.scls.riken.jp/eng/newsletter/vol.11/zoomin03.html

SCLS Gotcha!

Osaka University education program on high performance computing

Osaka University
Graduate School of Engineering Science

Osaka University Graduate School of Engineering Science has been conducting an "Education Program for Predictive Medicine and Drug Discovery on a High Performance Computing Infrastructure (HPCI)" jointly with the Graduate School of Information Science and Technology since 2011, as part of the "Supercomputational Life Science(SCLS)" . The core of this education program is the pair of classes "Biosimulation" and "Bioinformatics" provided for graduate students who will be main player in super-computational science/engineering. These subjects are also provided as part of the "Osaka University Graduate Program for Advanced Interdisciplinary Studies" through the Center for Advanced Medical Engineering and Informatics (MEI Center) educational program, and will accept students from all graduate schools by arranging the classes on Saturdays.

5th workshop on HPCI with the K computer as primary resource for drug discovery and medicine

These classes are, at the same time, open to engineers/researchers of industries and graduate students of other universities as part of the MEI Center Skill Course, an Osaka University Extension. In this framework, the auditors will be given certificates issued by the President of Osaka University.

As an outreach activity, a series of workshops on HPCI with the K computer as a primary resource for drug discovery and medicine has been held annually in Osaka and Tokyo. This provides a forum to translate the outputs of frontier research towards *in-silico* drug design, *in-silico* medicine and predictive medicine at academic and research institutions into advanced industrial technologies by inviting lecturers from cutting-edge research groups. Plenary/keynote lectures as well as sessions are organized at conferences hosted by academic societies/institutes in order to promote high performance computing in bioengineering, bioinformatics and life sciences, among others.

This year, an introductory class entitled "Introduction to Biosimulation" is being launched for university freshmen regardless of their academic study area to provide an opportunity to open their eyes to supercomputing science/engineering. These activities are aimed at encouraging the young generation, especially current students, to engage in computational pharmaceutics, medicine and bioengineering. For details, please visit the website at http://hpci.me.es.osaka-u.ac.jp/

SCLS Gotcha!

Past and future of acceptance of applications from the public to use the SCLS supercomputer system

RIKEN HPCI Program
for Computational Life Sciences

The objectives of SCLS are to drive breakthrough accomplishments by taking advantage of HPCI (High Performance Computing Infrastructure) with the K computer at the core, as well as to form a wider community for computational life science users by supporting research and developing human resources. To achieve these objectives, we have provided a SCLS supercomputer system highly compatible with the K computer and publicly invited research agendas that utilize this SCLS supercomputer system, as part of our support for the active and broad use of HPCI by life science researchers and engineers.

Next call **The FY2015 first round call planned to start invitations from February 2015**

Any researchers and engineers who are involved in life science can apply for the use of the SCLS supercomputer system, and actually we have had a number of applicants from research and educational institutions to private companies. An applicant who has a research agenda can use the SCLS supercomputer system free of charge, and also extend the use period by submitting a continuation request.

Acceptance of applications from the public to use the SCLS supercomputer system (the first call was in FY2012) has been made four times up to the FY2014 first round call. A total of 34 research agendas were adopted, and 144 persons have been involved in those agendas. As of the end of the FY2014 first round call (the system was available for use from April 2014; five agendas were adopted), 23 agendas including new ones had been going on, and 117 persons had been involved in those agendas.

Next, we plan the FY2015 first round call which starts looking for applicants from around February 2015. As we are approaching the end of the Strategic Programs for Innovative Research, the FY2015 first round call for the SCLS supercomputer system will be the last one that SCLS carries out. Although we do not have much time left for using the system, we look forward to your application.

Comments from users

We very much appreciate that you applied a patch to the software that could not run on the SCLS supercomputer system. The software became available in the system, and we were able to complete our research agenda as planned.

News & Events

"Rental Exhibition Panels" are now available to introduce research on computational life science and SCLS

To disseminate the research results and enhance understanding of computational life science, Supercomputational Life Science (SCLS) provides rental panels that can be used to introduce research to anyone, who are not researchers, at any time in a simple way. These panels can be exhibited at an event held in a school or an educational facility or an event for promoting awareness of science and technology, as well as used in class. We will notify the details on the website of SCLS as soon as they are fixed.

SCLS website redesigned

The redesigned website for SCLS has been launched!
We provide a variety of information that allows many people to enjoy SCLS activities. http://www.scls.riken.jp/

For researchers and engineers
S-cruise software, a portal that discloses the results from the software developed using the K computer, e-SCLS that provides training sessions for enhanced sampling, gene network analysis, etc., and public invitations relating to a SCLS supercomputer system compatible with the K computer

For students and working people
e-SCLS that offers academic seminars on our website where people can learn the basics of computational life science

For educators
SCLS on-site class in which people can enjoy SCLS courses, and SCLS rental exhibition that provides information on rental panels that introduce research on SCLS

People who are new to Computational Life Science and SCLS
Beginners which explains SCLS in an easy-to-understand way using Q&A and animations, and Biosupercomputing Newsletter that provides more information than publications

The SCLS website filled with information that makes people familiar with the world of computational life science. Search with the keyword "Field 1".

Information

October 2 (Thu) to 4 (Sat)

2014 Annual Convention, JSBi 2014 - the 3rd Joint Conference on Informatics in Biology, Medicine and Pharmacology

●Location : Sendai International Center (Sendai-shi, Miyagi)
October 4 (Sat): Sponsored sessions and training sessions are held together with the HPCI human resource development programs of AIST

Ocober 7 (Tue) 2014 to February 3 (Tue) 2015 ●Every Tuesday, 5:00 p.m. - 6:30 p.m.

Remote lecture with Kobe University Education Center on Computational Science and Technology

"Basics of Computational Life Science - from the intersection of Life science and Science and engineering to application to society" (total of 15 sessions)

●Location : Kobe University, Faculty of Engineering building, 1F
We will notify the details on the website of SCLS as soon as they are fixed.

Strategic Programs for Innovative Research Field 1

Supercomputational Life Science

SPIRE (Strategic Programs for Innovative Research) is a MEXT program aiming to produce ground-breaking results in computer science technology by maximizing the benefits of the HPCI (High Performance Computing Infrastructure) centered on the supercomputer K computer, and encouraging developments in five research fields that need to be strategically addressed.
"Supercomputational Life Science" has conducted research with the mission of understanding and predicting life phenomena based on large-scale simulation and advanced data analysis, and to apply these results to design and implement medicine and medical care with its research.

BioSupercomputing Newsletter Vol.11 2014.9 www.scls.riken.jp/en/

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