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Next-Generation Integrated Simulation of Living Matter

ISLiM
Integrated Simulation of Living Matter

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In order to change from observation-type medical practice focusing on experience to prediction-type medical practice to construct the base of theoretical medicine

Professor, Department of Internal Medicine (Cardiovascular Medicine), Director of the Metabolic Disease Research Center, Bio-Research Medical Center, Tokai University Graduate School of Medicine, and Director, Department of Metabolic System Medicine, Tokai University General Medical Laboratory

Shinya Goto

For predictive, individual and "prospective" medical practice

You often say that the present medical practice is empirical, and lacks logic and predictability.

● Goto (dispensed with the Mr. and Mrs) If I, as a clinician engaged in the treatment of a large number of cardiovascular diseases, say this, patients may be shocked, but it is the present state of affairs that when doctors provide medical care, they do not fully appraise the system of the human body and disease scientifically, and do not provide medical care based on definite prediction like controlling an atomic power plant based on physical understanding, for example. Medical intervention based on an essential and sophisticated understanding of life phenomena is presently impossible. It is obvious considering the history of medical progress. Doctors know empirically what will happen if they do nothing for diseased people. By making a certain intervention considered to be effective without leaving patients as they are and observing whether the prognosis (catamnesis) is good or bad, we are repeatedly evaluating the propriety of intervention. Medical care has progressed by repeatedly comparing what result will be obtained if some other intervention is made. Evaluation of experience may be performed based on the doctor's own common sense, or based on a numerical database obtained by summarizing a large number of cases. The latter method for evaluation of a numerical database based on a certain standard is also called "Evidence-Based Medicine". However, even Evidence-Based Medicine which has incorporated scientific methodology is only a methodology in which cumulative past experience is quantified. Even if the experience is converted to a numerical database, there is no essential difference in that past medical practice still decides future directionality based on "retrospective" experience.

Comparing this to the history of the development of physics, it can be said that present medical science is still in the age of Galileo. By dropping a heavy ball and a light ball from a high place at the same time, Galileo revealed that the time taken for falling is not related to the weight of object. He revealed the basics of dynamics by an experiment, but he could not arrive at a future unified principle, that is, the gravity of the earth and the law of gravitation even control celestial motion. Before long, Newton extended the law of gravitation by mathematically discussing the motion of objects discovered by Galileo et al., and constructed the basis of modern physics. Current medical practice is conducted under circumstances where the universal life phenomena controlling the human body are not yet understood. Doctors only describe the patients' symptoms appearing as a change in life phenomena and their change according to the presence or absence of therapeutic intervention, and accumulate experience. Since we can understand only the "result with or without medical intervention," we only evaluate the patient population to determine the propriety of medical intervention. In order to introduce modern physics and science like chemistry into the world of medical care, it is necessary to understand the nature of life phenomena, to clarify the factors defining individual differences, and then to construct learning like architectural and prospective "theoretical medicine." Hence, it is necessary to resolve life phenomena into factors, and to understand them by fine mathematical expression of the causal relationship among factors. In the world of medical practice, a learning system is required which makes "theoretical prediction" and "individualization" possible. If we cannot have such a system, we will not be able to take even one step beyond the medical practice evaluated by accumulation of past experience.

Why can we give only empirical medical care?

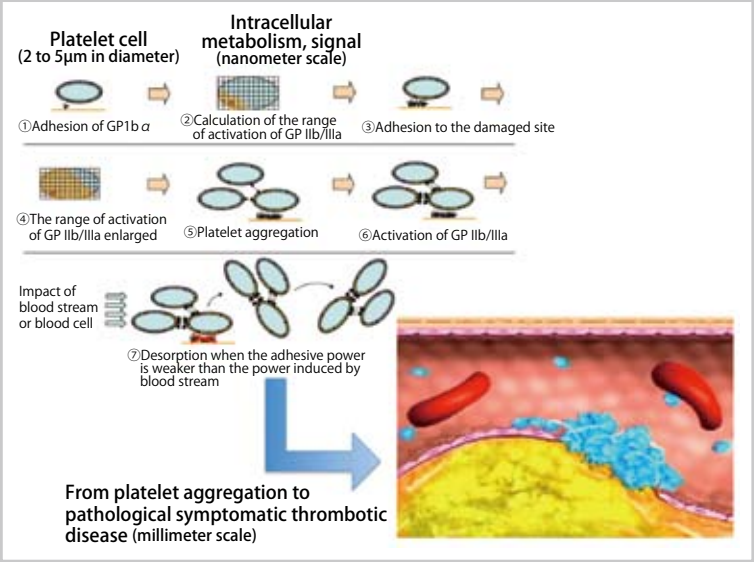
● Goto In a word, the nature of the problem is that, since the life phenomena constituting the human body are too complex and there are too many factors involved in the onset and progress of disease, we cannot precisely understand the causal relationship among these factors. In order to give the optimum treatment for individual patients, we have to understand the nature of life phenomena, the factors defining individual differences, and the sophisticated causal relationships among them. Genes, a design blueprint of an individual, are different individually, and exposure to environment and life style are different individually. Unless the system, from molecules through cells to the human body, that is, what disease is likely to occur in the human body when a person with a certain gene lives under a certain condition, can be understood architecturally, it is impossible to conduct medical practice and individual medical care with which the future can be predicted scientifically. In order to understand a system where the combination of slight positional differences in an enormous number of genes individually defines optimized therapeutic methods, moreover, it is necessary to handle an enormous amount of integrated time-dependent information such as information about genes, exposure to environment, life style and disease, at the same time. In order to reconstitute clinical medicine as information science, that is, the basis of a precise future-type medical practice in the 21st century, a high-speed supercomputer is absolutely required. We already know information about the design blueprint of the human body defining individual differences called the personal genome. We understand the system in which the design blueprint produces proteins. However, we have not understood the system in which those proteins constitute cells. It is the current state of affairs that although we can understand how the functions of biological molecules will change when a drug consisting of molecules is administered, we cannot understand how the change is constituted in cell response and biological response on the scale of the human body. If we understand the system in which cells and the human body are constituted by physical and chemical interactions of a huge number of molecules, we may be able to understand life phenomena exactly. By so doing, it may be possible to provide scientific treatment in the true sense for the first time.

What is the most promising point of the ten quadrillion speed computer "Kei"?

● Goto In order that we can understand life phenomena, I think that reproduction of life phenomena is important. If all the substances constituting one cell were arranged positioned spatially, it might be possible, in principle, to reconstitute the cell. At the present time, there are too many substances that make up cells, and we have no fundamental technique that can reconstitute the information. If we establish a technique to measure information about the arrangement of substances in cells precisely and enter the information virtually on a high-speed supercomputer, it should be possible to reproduce virtual cells. We can observe the aspect whereby cells gather together to constitute tissues and organs at the microscopic level. Such an approach is the basis of simulation biology, and the ten quadrillion speed computer is an important tool to realize it.

Another thing that we hope to do is to make a lot of doctors and health professionals understand that past medical practice and medical science are only an accumulation of experience, and do not offer any understanding

of nature at all. We can do this by showing examples of the possibility of predictable medical practice and individual medical care using a ten quadrillion speed computer. Moreover, they may be able to understand that "future life science, medical practice and medical science will proceed in such a direction." Even if I say that "the present time is at the stage of Galileo," the people in clinical practice cannot understand this. If we can show concrete examples, however, I believe that our message, "we have to change our thinking in the future", can be delivered.



Research and development of platelet cell simulator

What is the platelet cell simulator that you are addressing now?

● Goto Platelet cells are divided by voxels, and the properties of subcellular organelle and membrane protein are included in each voxel to reconstitute platelet cells. If the number of divisions is increased, it can be expected that it can be reduced to a single cell. As concerns the adhesive protein of a cell membrane, at the present time, we are aiming at coupling with information about adhesiveness obtained in a molecular scale structural analysis. Since treatment with antiplatelet drugs for prevention of recurrence of myocardial infarction that we provide as clinicians is intervention to molecules such as cyclo-oxygenase in platelets, platelet membrane protein and receptor protein, we are aiming at a simulation of how molecular scale intervention with a drug may change the behavior of platelet cells. Finally, I want to simulate whether or not organ-perfusing arteries which perfuse important organs such as the heart and brain may be thrombotically occluded by aggregation of a large number of platelet cells, and whether or not the occlusion can be inhibited by intervention with a drug of molecular scale.

As for the molecules constituting platelet cells, moreover, there are molecules with obvious biological characteristics such as adhesive proteins having special adhesion modes. I therefore think that the platelet cell simulator will be useful for combination of the molecular scale with the cell scale. Since it is known that aggregation of a large number of platelet cells may cause myocardial infarction, moreover, the simulator will promote a combination of the cell scale with the organ and body scale. Moreover, this is a system to prepare the basis of a 2-step coupling of the molecular scale with the cell scale, and the cell scale with the organ and body scale, mainly with platelet cells, by coupling the associations between molecules and platelet cells theoretically by simulation, and by quantitatively simulating the process in which platelet cells of micrometer scale lead to occlusion of blood vessels of millimeter scale, that is, the impact of cells on the organs and body.

A platelet cell has no nucleus and is not divided. Moreover, there is less production of new substances. Its function is specialized in hemostasis and thrombus formation. Since platelet cells have a simple structure and function, it is suitable for reproduction by simulation. I will show an actual example using platelet cells. Moreover, it is clear from clinical studies that platelet cells are importantly involved in the onset of myocardial infarction and cerebral infarction and that, if the function of platelet cells is reduced, the onset of myocardial infarction and cerebral infarction is inhibited. From the viewpoint of clinical medicine, the association of the intervention with a drug on the molecular scale and the outcome of the organ and body scale are obvious. Finally, whether or not a correct simulation can be performed from the viewpoint of physics and technology is important. However, biological cells are very complex, and it is very difficult to perform a precise simulation. Collection of actual information in the body and modeling it on a computer should progress like two wheels of a cart. It cannot be said that the information to be entered into the computer is sufficient, and its quantitative capability is also low. Platelet cells are relatively easily handled, but this is a very difficult challenge as a project.

What is the most difficult thing in developing a simulator?

● Goto I recognize that the biggest problem is that we have not understood the whole picture. Even if Kei becomes available, it is still impossible to reproduce the complex biological body. A certain simplification is essential. Simplification by us who have not understood the whole picture may be beyond the mark. Since calculation resources are limited, we are selecting the information to be omitted in our brain. You might think that the computer is fully automatic, but it is the human brain that enters important information to make a model. Our worst problem is that we do not know whether or not modeling can be done by selection of appropriate information. Comparing the secret of the human body pursued in medical science to the secret of the universe, I do not know whether, in the vast universe, our current anxiety is because we only know the circumference of the earth, we only know the solar system, we only know up to the galaxy, or we actually know a considerable amount. Even if we only knew up to the solar system, it might still be possible to clarify the basic principle controlling the universe. At the present time, we have to try to predict the phenomena of the human body and the outcome of disease using a principle which we definitely understand. By substantiating the validity of the predicted result, the validity of the prediction will be confirmed. In simulation science on a subject that has not revealed its true aspect, it is essential to repeat prediction and substantiation. It is a challenging academic field from the viewpoint that the validity of modeling is repeatedly being confirmed, while the truth has not yet been observed. I am a clinician and actually provide medical care. I actually feel that much of clinical practice depends on my experience and feeling. Although we cannot find a scientific rationale, moreover, we are practicing individualized medical care based on my experience and feeling. I am always puzzling over how to select the direction in which we should go for logical performance and digitization of individualized medical science, not based on science conducted empirically by a lot of doctors.

How about the reaction of medical practice to your approach?

● Goto I think that the meaning of what I want to show can be understood by everybody. Particularly, the leaders in academic societies say, "certainly, we have to go in such the direction." The leaders in global academic societies commonly recognize that the method called Evidence-Based Medicine, that is, a scientific approach to medical practice by building a numerical database by accumulating present experience, has got stuck.

Medical practice and medical education are suffering from a flood of information to the numerical database of experience. It is difficult to get healthcare professionals to change their mind and realize that predictive and individual medical care is required. In order that the validity of our approach is understood by healthcare professionals, moreover, it is important to show an actual example of antiplatelet treatment using a platelet cell simulator as an example. I want a lot of people to understand that even life phenomena are ultimately an accumulation of physical and chemical phenomena, and its descriptive term is mathematics. Moreover, I expect that young doctors, researchers and students will participate in the field of simulation medicine. I think that the quadrillion speed computer is the gateway to it.

It is expected that new possibilities in nutrition science and health control will be opened up by simulation science

EXECUTIVE PROFESSIONAL
Health infomatics DEPT., Ajinomoto Co., Inc.
Toshihiko Ando

A new viewpoint born from simulation

You have played a central role in the Life Sciences Application Subcommittee Meeting of the Industrial Committee for Supercomputing Promotion. Have you always been interested in simulation?

● Ando (dispensed with the Mr. and Mrs) Describing the present state of affairs, it can be said that there are very few cases using simulation in the food industry. For example, in heating frozen food, simulation has been performed to develop the form of tray with the best heat efficiency, and simulation has been used to design the manufacturing processes for foods. However, the Research and Development Division of this company is addressing research and development on an "Amino index" useful for health control by measuring the concentrations of amino acids in the blood. This aims at development of new products using amino acids and at new commercial prospects such as providing information useful for health checks and diagnosis of disease, and prediction of drug efficacy and adverse reactions, based on an idea that health conditions can be analyzed using the pattern in the concentration of amino acids, the center of the metabolite network (aminogram), as an index. I am also engaged in this research and development, in which I thought that I can make good use of simulation. For example, the pattern of amino acids in the body changes when we are getting sick. The reason for this change has not been clarified, but the amino acid balance changes because a certain amino acid increased or another amino acid decreases. It is very difficult to understand the change in balance and its mechanism, but it may go smoothly by using simulation. So, I am looking forward to doing research and development on a metabolism simulator at the cellular level, which has been progressing in the field of biosupercomputing.

It's certainly different from medical science, but it may be possible to utilize simulation for nutrition science and development of health foods.

● Ando I may get scorched by the doctors of nutrition science, but I think that the teaching in nutritional science has not changed much from the past. I think that it is very important that a new viewpoint using simulation is created in the field of nutrition science.

As written in the book by Mr. Shinichi Fukuoka, "Dynamic Equilibrium," the human body is totally replaced in 3 or 4 months. As concerns amino acids, firstly, we take protein from foods in an amount of about 70 g per day. It is digested, decomposed and absorbed into the blood, and by this, about 180 g is synthesized into proteins such as for muscle tissue. On the other hand, about 180 g is decomposed to amino acids, and about 50 g is pooled as free amino acids in the body, 45 g of which exists in cells, about 5 g of which exists in the intercellular space and about 1 g of which exists in the blood. They are in this kind of balance. In this cycle, moreover, 70 g is discharged together with feces and urine through the blood (see Figure). Moreover, this cycle is totally renewed in 3 or 4 months. Amino acids which we ate are not used as amino acids as they are, but metabolized in various ways to become organic acids or amines and taken into the body. There is such a fast metabolic turnover, but the form of the human body does not change. The same form can be maintained, that is, equilibrium is maintained. It is a dynamic equilibrium. I myself think that amino acids are present at the center of this dynamic equilibrium, and in any case, the protein turnover is very important. It can be said that it supports the equilibrium of body. The turnover is very fast, but there is only 1 g of amino acids in the blood. A person weighing 50 kg has about 10 kg of muscles but has only 1 g in the blood. One part per 10 thousand. Even so, a constant level is maintained, and amino acids are maintained in equilibrium. It may be good if nutrition science were not limited to calories by a thorough understanding of something like this.

My other interest is chrononutrition. In a simple term, nutrients are different according to the time of intake, and the timing is important. For drugs, there are some doctors studying when a drug shows least adverse reactions and highest efficacy, before sleeping at night or at waking up in the morning, considering the pattern of drug metabolism. Similarly, there are some doctors of nutrition science studying when and how to take foods effectively to maintain health in balance. I feel that simulation may be useful in the field of new nutrition science to which the concept of time is added. If we can simulate the change in the metabolism of the human body with time when a perturbation like eating some food occurs, we may be able to provide information concerning the nutritional management suitable for a person, such as what nutrients are the most efficient and good for the body and when they should be taken. Moreover, nutrition and metabolism are very complex, and there are many molecules involved, so it is very difficult to control them. Their balance may be changed by something, but it is important to maintain it. If such a thing were clarified by simulation, I think that it would be very useful for many reasons.

Health simulator can also be realized

The use of simulation in nutritional management is also a new viewpoint.

● Ando Mainly in Europe, nutritional societies around the world are addressing a campaign called "Fight against all malnutrition". Malnutrition is considered to be a problem of developing countries. Apparently there are a many cases leading to malnutrition because of poverty and food shortage, but in countries like Japan, there may still be some malnutrition. There are a many elderly people with malnutrition. For example, there are many people who cannot eat because of decreased digestive function and loss of desire to eat. Moreover, there are some people who come to suffer malnutrition due to dietary limitation for lifestyle-related diseases. Simulation may be used for research concerning what parameters we should control to prevent malnutrition.

It is of course important to cure illness, but I think it is very important to maintain the body in health as long as possible. In this respect, I think that simulation can help. For example, health care to identify some parameter such as a health barometer and to provide a method to maintain individual health may be acceptable. It is like a dream, but I hope for a system in which, if my parameter data is determined every 3 months or 6 months and analyzed, various prescriptions to maintain my health would be identified.

If this were made visible, it might be more interesting. How about such a health simulator? If several tens of millions of people could register to collect

data, a health trend might emerge, and we might be able to issue a "health forecast" that it is necessary to prepare for some disease in the future. It may be interesting if the whole world of industry were to address such an attempt.

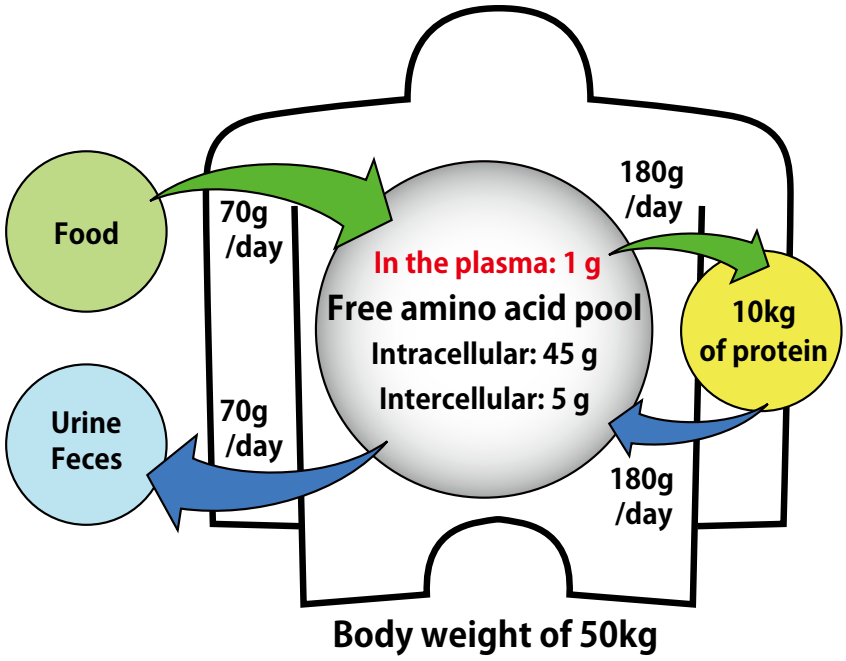
The world of industry may move if we can show evidence of success.

— Do you feel that the reaction of the world of industry to simulation is still weak?

● Ando I think so. I think it is different depending on the field. There are many companies working hard in the field of making things. Generally speaking, however, in order that simulation is utilized in the world of industry, I think it is very important to achieve not only academic results but also economic effects. Unless everybody understands that major successes will be obtained by using simulation, they may think that "it may be difficult to use it." I think it is necessary to show some example of a major economic success. Every category has a rule for success. Unless we can show a paradigm of success cases using supercomputers to become winners, I feel that the number of people who use supercomputers will not much increase. A lot of success cases are not required. However, it might be OK if there were only one case of major success. I hope that the present field of life sciences will reveal such a case. If we focus on possible cases for promotion instead of wide and shallow promotion and achieve results which might turn out to be a breakthrough, the awareness of the world of industry may change.

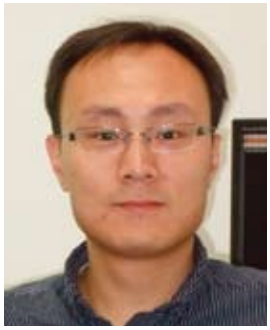
Moreover, it may be difficult to use supercomputers abruptly. I think that the hurdle is too high. We need a certain mechanism like a "trial system." In such a context, it is necessary to design a way of collaboration between industry and the academic world. It may be necessary to examine how each area of specialty is used amongst ourselves, such that simulation is entrusted to the academic world.

Dynamic equilibrium of amino acid metabolism: Proteins in the body are replaced with amino acids, etc. taken from foods in a few months.



The functions of a multidrug discharging transporter were verified by coarse graining molecular simulation

Graduate School of Science, Kyoto University
(From the above) Shoji Takada, Xin-Qiu Yao, and Hiroo Kenzaki



Multidrug resistance where most drugs become ineffective leads to serious social problems in nosocomial infection and cancer chemotherapy, etc. This multidrug resistance arises due to different mechanisms. In the case of Pseudomonas aeruginosa which was a large problem in nosocomial infection, the main cause of multidrug resistance was that expression of a multidrug discharging transporter of RND type in Pseudomonas aeruginosa increases and discharges antibiotics from the bacteria. The multidrug discharging transporter of RND type is driven by transfer of H+ (proton) using the difference in acidity (pH) inside and outside cells, and discharges the drug by using this ability. The atomic structure of the Escherichia coli-derived RND type multidrug discharging transporter "AcrB" was elucidated by Mr. Satoshi Murakami (presently Professor of Tokyo Institute of Technology), et al. using X-ray crystal structural analysis in 2002 and 2006. In the structural analysis done in 2002, it was shown that AcrB is a trimer of 3 similar molecules, having three-fold symmetry, while in the structural analysis in 2006, it was found that each molecule has the function of a membrane proton transporter and drug discharger, and that the trimer of AcrB has an asymmetric structure. In the first molecule of this asymmetric AcrB trimer structure, a route considered as an entrance for the drug facing into the cell opens (incorporation type), in the second molecule, the drug binds to the center (binding type), and in the third molecule, a drug discharge port facing outward from the cell opens (discharging type). Murakami et al. considered that the 3 molecules of the AcrB trimer discharge drugs by mediating these 3 functional states in turn. Since it seems that the whole structure rotates 120 degrees by changing the respective states of the 3 molecules step by step, this mechanism of drug discharge was named a "functional rotation mechanism." However, since the verification experiment using this experimental system was difficult, it was impossible to verify this hypothesis.

We have independently developed a technique for coarse graining molecular simulation of biomolecules as part of the project "Research and Development of Next-Generation Living Matter Integrated Simulation Software" of the Ministry of Education, Culture, Sports, Science and Technology. In this research, we conducted a functional simulation attributable to fluctuation of the multidrug discharge transporter AcrB by applying this new technique.

(1) Functional rotation of AcrB trimer and drug discharge: In the asymmetric AcrB trimer structure, when a proton binds to the drug-bound AcrB molecule (blue on the left side of Figure 1) from the extracellular space, the drug is discharged outward (center of Figure 1), and subsequently, the other 2 AcrB molecules also changed their state, and a functional rotation occurred (right side of Figure 1). By this, it was shown that functional rotation occurred according to proton binding and that drug discharge could occur.

(2) Resting state of AcrB trimer: It was found that, if a drug is removed from the asymmetric AcrB trimer structure, the structure having three-fold symmetry becomes stable. This structure is near the structure elucidated in 2002. That is, the structure obtained in the structural analysis in 2006 is a snapshot of the way the AcrB trimer discharges the drug, and the structure in 2002 is considered to correspond to the resting state.

Reference
Xin-Qiu Yao, Hiroo Kenzaki, Satoshi Murakami & Shoji Takada, Drug export and allosteric coupling in a multidrug transporter revealed by molecular simulations *"Nature Communications.* 1, 117 (8 pages) (2010)

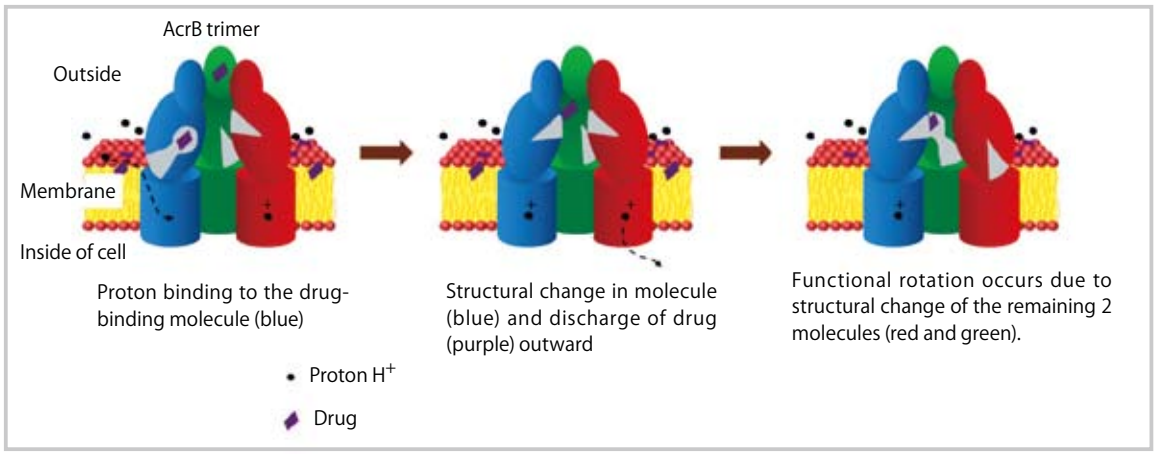


Figure 1 : Drug discharge and functional rotation of AcrB due to proton binding
The AcrB trimer is of asymmetric structure. In the first molecule, the route considered as an entrance for the drug, which faces into the cell, opens (green in the left figure: incorporation type), in the second molecule, the drug binds to the center (blue in the left figure: binding type), and in the third molecule, the drug discharge port facing outward opens (red in the left figure: discharging type). When a proton binds to the second drug-binding molecule from the outside of a cell (arrow of dotted line in the left figure), the drug of this molecule is discharged to the outside of the cell (figure at the center), and the other 2 molecules change their states (right figure).

Cell simulation considering time-space

Computational Science Research Program, RIKEN
Yasuhiro Sunaga

All living things consist of units called cells. More than 10 million kinds of living things including single-cell organisms such as Escherichia coli and multicellular organisms such as humans exist on the earth, and the functions and forms of cells are different so that they are optimum for their living things survival. However, it is known that living things basic living cell functions have many things in common.

A cell has a very complicated and compact structures, and in the cell, various biochemical reactions occurs actively for each compartment which is known as an organelle. Due to this, molecules and reactions are differentiated to implement various living functions efficiently.

So far, much cell simulation research ignoring cell structures has been done by grinding up organs, the aggregates of cells, to understand the biological systems of organisms and to explore methods of treating diseases. In the cells, life is maintained by complex phenomena such as biochemical reactions (metabolism) and signaling. To reproduce these biochemical reactions, many simulators were developed, and it became possible to replicate intracellular metabolism and signaling. However, these simulators calculate a nondimensionalized field and replicate a chemical reaction uniformly in the cell, a so-called 'closed bag'. In actual cells, biochemical reactions differ for each organelle, and uneven reactions go on in the cell depending on the intracellular transfer of substances, inside and outside the cell, and entry and exit of substance from and to the inside and outside of the cell. We, the Cell Scale Research and Development Team, have been looking at these things, and are now developing the RIKEN Integrated Cell Simulator (RICS) which aims to perfect an intracellular time-space simulation. With this system, we undertook a coupled analysis of intracellular biochemical reactions and substance diffusions with the equations of reaction diffusion. This system uses the voxel analysis framework developed by the VACD research program of RIKEN for spatial expression, which is a simulation system that can represent the special complex space structures of the cell.

With this system, using the cell morphology obtained from actual microscopic data, we simulated the transporters, reactions and diffusion of calcium ion (Ca^{2+}) in the cell. As concerns the cell morphology, we acquired the cell morphology and the form of the nucleus and mitochondria with a confocal laser microscope using a HepG2 cell, human liver-derived cells (Figure 1). The nucleus is the largest structure in the cell, and it packs DNA. Mitochondria have the function of producing energy for cellular activity, and are an important location for biochemical reactions such as metabolism. We prepared three-dimensional Volume data from microscopic images to use in the present calculation (Figure 2). We established 10 molecules involved in buffering reactions in the cell and 24 biochemical reactions. A channel passing Ca^{2+} only was localized in part of the cell membrane shown by an arrow in Figure 2, and simulated by influx of Ca^{2+}.

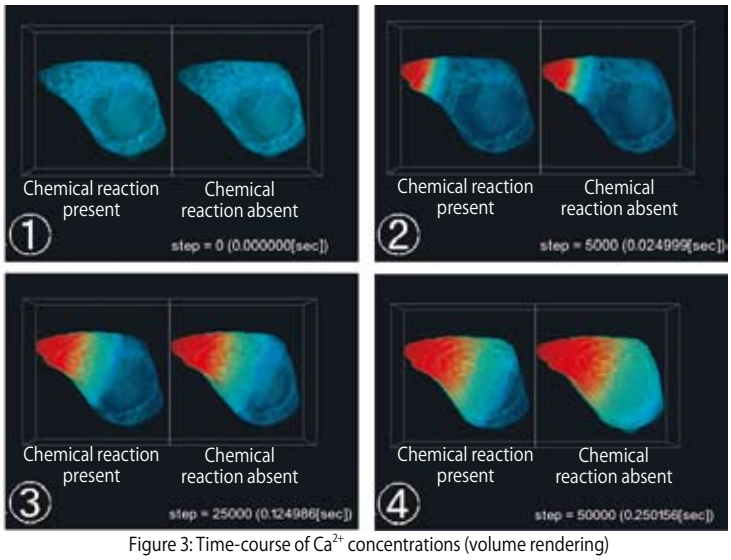


Figure 3: Time-course of Ca^{2+} concentrations (volume rendering)

The result of simulation is shown in Figure 3. When the buffering reaction of Ca^{2+} in the cell was set up (expressed as "reaction present"), the apparent diffusion speed of Ca^{2+} in the cell was decreased as compared with the case of no biochemical reaction (expressed as "reaction absent"). This suggested that kinetics of Ca^{2+} close to that in actual cells can be simulated.

This RICS makes it possible to calculate the phenomena occurring in cells such as biochemical reactions and diffusions, considering their location. In the future, we want to model various cell functions, and to show that the model can be utilized to elucidate the cause of drug reactions and disease. Moreover, we want to make this system a tool that can examine a mass of cells that functions as a tissue.

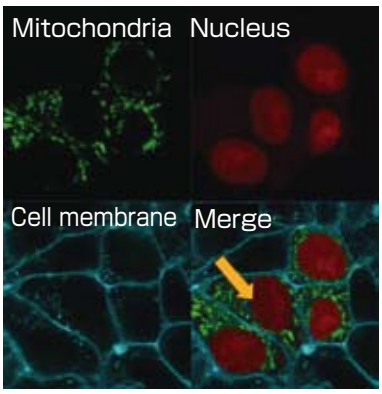


Figure 1 : Cross section image of a cell photographed using a confocal laser microscope

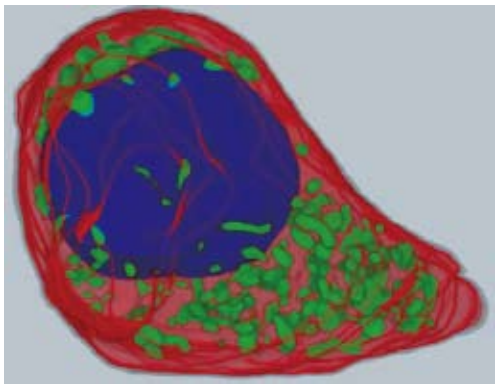


Figure 2 : Cell morphology reconstructed three-dimensionally from successive cross section images of cells

Development of HIFU simulator for non-invasive treatment with high-intensity focused ultrasound

VCAD System Research Program, RIKEN
Kohei Okita

An ultrasonic imaging diagnostic system with which the inside of the body can be investigated using inaudible ultrasound has been widely used in clinical practice. There is a therapeutic method by which ultrasound stronger than that used in this ultrasonic imaging diagnostic system is focused on a target such as a tumor to necrotize tissues by heating, which is referred to as HIFU (High Intensity Focused Ultrasound). The main characteristic of HIFU is that treatment can be performed without incision, and the low impact on the body is of great advantage. The treatment of uterine fibroids and prostatic hyperplasia with therapeutic equipment using this HIFU has already been approved in other countries, and clinical studies on the treatment of liver tumors, etc., are being conduced and awaiting application for approval, but some problems remain. In the treatment of a deep-seated liver tumor, for example, the ultrasound transmitted from the HIFU system runs from the skin through organs such as fat, muscles, bones and liver to a focal point (right side of Figure 1). At this time, the ultrasound may be absorbed so that it decays when it passes through various organs, the ultrasound may be refracted so that it bends, and part of the ultrasound may be reflected. Thus, in treating deep-seated tumors with HIFU, the energy required to heat the target may be insufficient due to decay of the ultrasound, the focal point may be blurred because of reflection or refraction of the ultrasound, and the position of the focal point may deviate from the target. In order to control the HIFU system so that the ultrasound focuses on the target, it is therefore necessary to know how the ultrasound passes through the body, and using the biological information obtained by CT or MRI, we are trying to reproduce the behavior of ultrasound transmission in a biological body by simulation.[1]

So far, the result of a simulation of HIFU treatment for a liver tumor has been obtained as shown in Figure 1.[2] It is seen that the ultrasound sent from the HIFU system is transmitted in a complex way as shown in Figure 2, and focuses short of the target. In such a case, the normal part is heated instead of the site of tumor to be treated. In order to focus the ultrasound onto the target by controlling the ultrasound delivered by the system, a method called the time-reversal method[3] is therefore used. The time-reversal method is to emit ultrasound from a sound source placed at the target point, to receive the ultrasound with the HIFU system, and to send the received signals by reversing the time. The result of simulation by controlling the HIFU system by this time-reversal method is shown in Figure 3, showing that the ultrasound focuses appropriately on the target. When ultrasound is transmitted in a complex way in the body as in this case, it is expected that it will be possible to treat a deep-seated tumor more precisely by controlling the HIFU system. Actually, since it is difficult to place a sound source at the target depth in the body, it is possible to perform highly precise HIFU treatment using the time-reversal method by determining the controlling parameter of the HIFU system by simulation in advance. Since a highly precise HIFU simulation is therefore required, we will increase the precision of a HIFU simulator by verifying the simulation result by comparison with experiment, and by introduction of a more advanced physical model. For realization of a highly precise and non-invasive HIFU treatment in the near future, we will contribute to the design and control of a HIFU system, and clinical studies for approval and examination of a preoperative treatment plan, etc., using the HIFU simulator.

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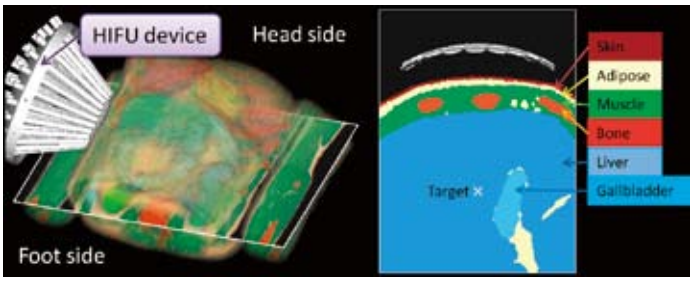


Figure 1 : HIFU simulation of liver tumor using a numerical human body model
The figure on the rights shows the distribution of tissues lying in the path of ultrasound transmission.

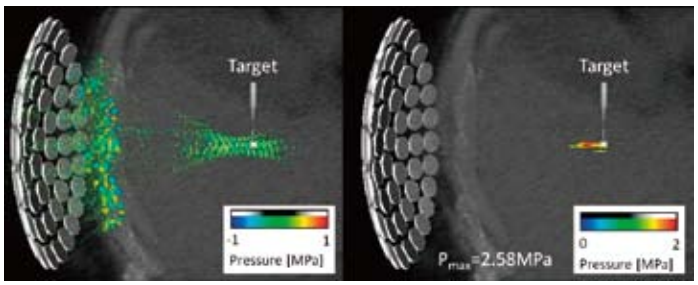


Figure 2 : Condition of ultrasound transmission (left) and the position of focal point (right) when the HIFU system is not controlled

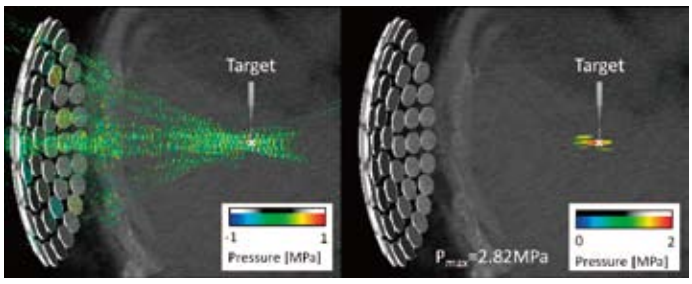
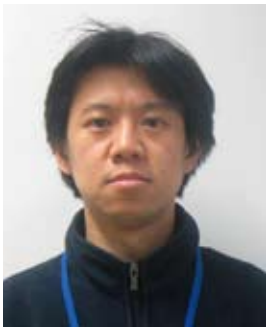


Figure 3 : Condition of ultrasound transmission (left) and the position of focal point (right) when the HIFU system is controlled by the time-reversal method

PLATO: Platform for a collaborative brain system modeling toward development of large scale mathematical model.

Keiichiro Inagaki ①
Takayuki Kannon ②
Nilton L. Kamiji ②
Koji Makimura ②
Shiro Usui ①②

① Computational Science Research Program, RIKEN
② Brain Science Institute, RIKEN



The elucidation of information processing fulfilled by the brain is regarded as the most difficult problem in natural science. In the brain, about 100 billion nerve cells form a network consisting of about 1 trillion contacts known as synapses. It is thought that various information obtained from the external world, such as vision and audition, is processed flexibly and appropriately by this network in the brain. The function of such complicated information processing in the brain is being revealed mainly by electrophysiological experiments. Together with the recent dramatic progress made in computational science, research to elucidate brain functions from the perspective of computational science has also been conducted by structuring part of the brain in detail as a mathematical model, and carrying out simulations. However, it is still difficult to describe the whole brain as a large-scale mathematical model for simulation.

Since a vast amount of knowledge and sophisticated techniques are required to construct a large-scale brain model, it is difficult for a researcher to achieve this by working alone. Therefore, it is considered rather important to collect and accumulate the knowledge obtained by the collaborative work of various researchers, and to integrate it as a large-scale model running on a computer. We are now designing a method to integrate the knowledge and mathematical models concerning various sites of the brain obtained from conventional physiological and computational research as a novel approach for constructing a large-scale brain model. In our approach, we are constructing an integrated development environment consisting of tools for collecting and managing the data required for development and simulation of models registered in the database server such as ModelDB at Yale University and various platforms of Neuroinformatics Japan-Node, simulators, simulation server, and a result visualization tool (Figure 1). In order to facilitate interconnection of multiple models, we are studying and developing a data format to standardize the input and output of the model for data exchange, and its supporting library. The common format, for example, would make it possible to connect mathematical models produced with different programming languages and/or simulators, such as C language and Python. Since the model input and output are standardized, we can modify and update a model into a large-scale model and install a new mathematical model in a plug-in manner. Interconnected models are simulated in parallel by a system called Agent. During the simulation, data communication between models is also adjusted automatically by accounting the progress of each model. By providing a unified library for such a common format and Agent, it is expected that the creator of the model can develop a mathematical model that can bind to other models without changing most of the program codes.

For describing the information processing underlying "vision", one of the brain functions, we are constructing a large-scale model of the whole visual system by the approach we have described. The human visual system consists of eyes, optic system, retina and cerebral cortex, where information from the external world are processed at these multihierarchicall sites to achieve functions such as recognition of objects and transition of visual lines. By constructing mathematical models for various sites in the brain, integrating them by the method we described and doing simulations, we hope to visualize the information processing that occurs when humans look at an object, for example visual illusion such as in Figure 2. In the future, by describing all the sites in the brain involved in “vision” in collaboration with various researchers involved in this field, integrating them by the approach that we proposed, and performing computer simulation as a large-scale model of "vision" using K computer, it will become possible to elucidate the visual information processing that occurs in the brain.

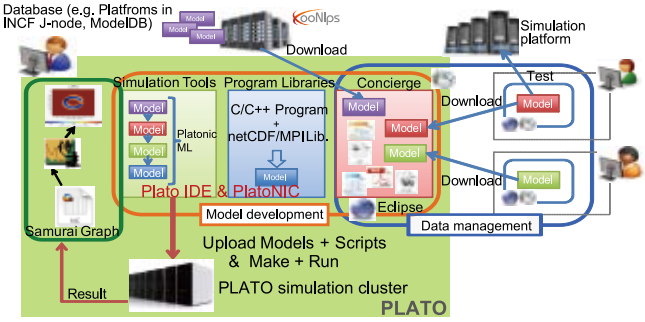


Figure 1 : PLATO system environment
PLATO consists of 4 environments including a data management tool (http://concierge.sourceforge.jp/), model development environment, simulation server and the result drawing tool.

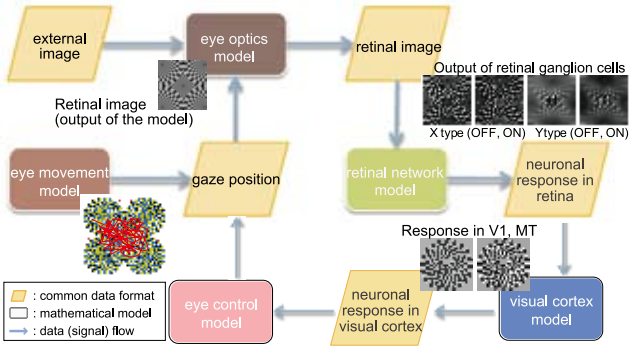


Figure 2. Configuration diagram of a large-scale visual system model
Schematic diagram of an integrated mathematical model of the visual system comprising of the eye movement, the optic system, the retina and the cortex, and sample image of each model output at simulation. The mathematical model at each site is described as an individual model, and each model is connected by the common format (Common data format).

Report

Report on the workshop in BMB2010 (Joint Meeting of the 33rd Congress of the Molecular Biology Society of Japan and the 83th Congress of the Japanese Biochemical Society)

The Molecular Biology Society of Japan and the Japanese Biochemical Society are both large academic societies representing biology study in Japan which have more than 10,000 members. In 2010, particularly, the annual congress of both societies was held as a joint meeting under the name BMB2010. We, the "Integrated Simulation of Living Matter" project, held a workshop at this congress to appeal for research in the biological field.

This project is a challenge for various problems in life science from the viewpoint of computational science, while on the other hand, expectations for computational science have also been increasing tremendously in the field of biology in recent years. This workshop was a timely project from these two aspects.

In this program, the major point of the project and outline of the whole project were explained, and then multi-scale research for life phenomena from the micro-scale to the macro-scale was introduced.

On the day of the workshop, the conference room with a capacity of more than 100 was so crowded that some people had to stand, which suggested the level of interest in this project in the biology field. A question-and-answer session was also held interactively, and the project members obtained meaningful opinions from biologists.

It is considered that the computational scientific method in life science will become increasingly important in the future. In the future, life science, and communication between the experimental method and the computational scientific method will become essential. It can be said that this workshop played a part in the creation of such bidirectional communication.

Report

Winter School 2011 for the Integrated Simulation of Living Matter

Computational Science Research Program, RIKEN
Yasuhiro Ishimine (Organ and Body Scale WG)
The Institute of Medical Science, The University of Tokyo
Hidetoshi Urakubo (Brain and Neural WG)
Computational Science Research Program, RIKEN
Yasuhiro Sunaga (Cell Scale WG)
Computational Science Research Program, RIKEN
Gen Masumoto (High-Performance Computing Team)
Computational Science Research Program, RIKEN
Keiji Misawa (Data Analysis Fusion WG)
Computational Science Research Program, RIKEN
Hisayuki Miyashita (Molecular Scale WG)

On January 6 and 7, 2011, the Winter School 2011 for the Integrated Simulation of Living Matter in the "Research and Development of the Next-Generation Integrated Simulation of Living Matter (ISLiM)" was held. ISLiM usually consists of a Molecular Scale Team, Cell Scale Team, Organ and Body Scale Team, Data Analysis Fusion Team, Brain and Neural Team, and High-Performance Computing Team. ISLiM is developing a software to perform a numerical simulation related to life science in various spatiotemporal scales of organisms and a large scale data analysis by harnessing the full range performance of the ten quadrillion speed computer "Kei", aimed at research leading to drug discovery and development of therapeutic methods.

This winter school was planned and managed mainly by young researchers participating in ISLiM projects, and there were 48 participants. In opening the school, Koji Kaya, a program director, made an opening speech. Next, Ryutaro Himeno, a vice program director, delivered a lecture about how to manage the future ISLiM.

In the next session, the High-Performance Computing Team consisting of experts in high-speed computation made a speech. Mr. Keigo Nitori related the episode when he received the Gordon Bell Award in the price/performance section of SC in 2009 with a computer consisting of a GPU together with Mr. Hamada, Nagasaki University. Mr. Yosuke Ohno explained the review process of the Gordon Bell Award from the experience when he became a finalist for the Gordon Bell Award. Also, Mr. Hiroshi Koyama in the High-Performance Computing Team spoke harshly about the implementation of high-performance computing with "Kei."

The next section was held by dividing participants into 4 subcommittees. In each subcommittee, recent research articles were selected from the 4 fields of molecular dynamics, blood flow, brain and genome, and brainstorming was done based on the articles. In order to climb over a fence among teams that usually cannot meet together, members were allocated to each subcommittee so as to crossover from their usual teams. An active discussion was held from the viewpoint of high-performance computing.

Thereafter, a convivial party was held, a poster presentation was made, and we had the opportunity to hear a presentation of the research carried out by all members. The discussion continued hotly until the time for the room expired at midnight.

First thing in the morning on the next day, the discussions of the subcommittees were summarized and presented in about 15 minutes. In the subcommittee on molecular dynamics, advances in protein research considering the cellular environment were discussed by taking virus capsid protein as an example. In the subcommittee on blood flow, thrombus formation was considered as a main theme of simulation by including platelets in simulation, aiming at infarction utilizing thrombus formation. In the subcommittee on the brain, the real-time behavior of animals in the cat family, for example the lion, was considered, and real-time processing of multi-channel data about brain activity, and construction and its real-time processing in an internal model including a neural network, were discussed. Moreover, there was a joke that they should search for a place to keep lions on the site of "Kei." In the subcommittee on the genome, an algorithm to search for a place where only incorrect consistency among genome sequences can be obtained due to mutation was discussed. All the subcommittees aimed at close collaboration with the High-Performance Computing Team as to the method of computation.

In the last section, Mr. Hiroo Kenzaki, Kyoto University, talked about the "coarse-grained biomolecular modeling and simulation program CafeMol" disclosed as one of the first runner softwares of ISLiM at the end of last year (http://www.cafemol.org/). Moreover, Mr. Akihiro Fujimoto, Center for Genomic Medicine, delivered a lecture with the title "Determination and comprehensive analysis of genome sequences in Japanese subjects using a super parallel sequencer" published in the journal, NatureGenetics. This

BMB2010 Workshop "Integrated Simulation of Living Matter of the Next-Generation"

14 : 30 -16 : 30, December 9 (Thursday)
at 2B Conference room of Kobe International Exhibition Hall

Organizer: Atsushi Mochizuki (Advanced Science Institute, RIKEN)
Hideo Yokota (Computational Science Research Program, RIKEN)

Ryutaro Himeno (Computational Science Research Program, RIKEN)	Grand challenge in next-generation supercomputers and life science
Yuji Sugita (Advanced Science Institute, RIKEN)	Analysis of structural change in a membrane transport system Sec Translocon by dynamic calculation of all atoms and molecules
Shoji Takada (Kyoto University School of Science)	Research on the operative mechanism of a multidrug resistance transporter by molecular simulation
Makoto Suematsu (Keio University School of Medicine)	Development and application of a hepatocellular metabolic simulation considering intracellular compartments enhanced by mass spectrometric techniques
Koichi Takahashi (Advanced Science Institute, RIKEN)	Advanced cell simulation – Where can we go with Kei?
Shu Takagi (Computational Science Research Program; The University of Tokyo, Faculty of Engineering)	For construction of a circulatory multi-scale simulator

research was taken up in several newspapers.

We ardently hope that the communication in this winter school will bring out the performance of "Kei", and lead to drug discovery and development of therapeutic methods. At the end of the winter school, we visited the facility of the ten quadrillion speed computer "Kei." There may be no space for keeping lions. (Author: Misawa)

Program of Winter School 2011 for the Integrated Simulation of Living Matter

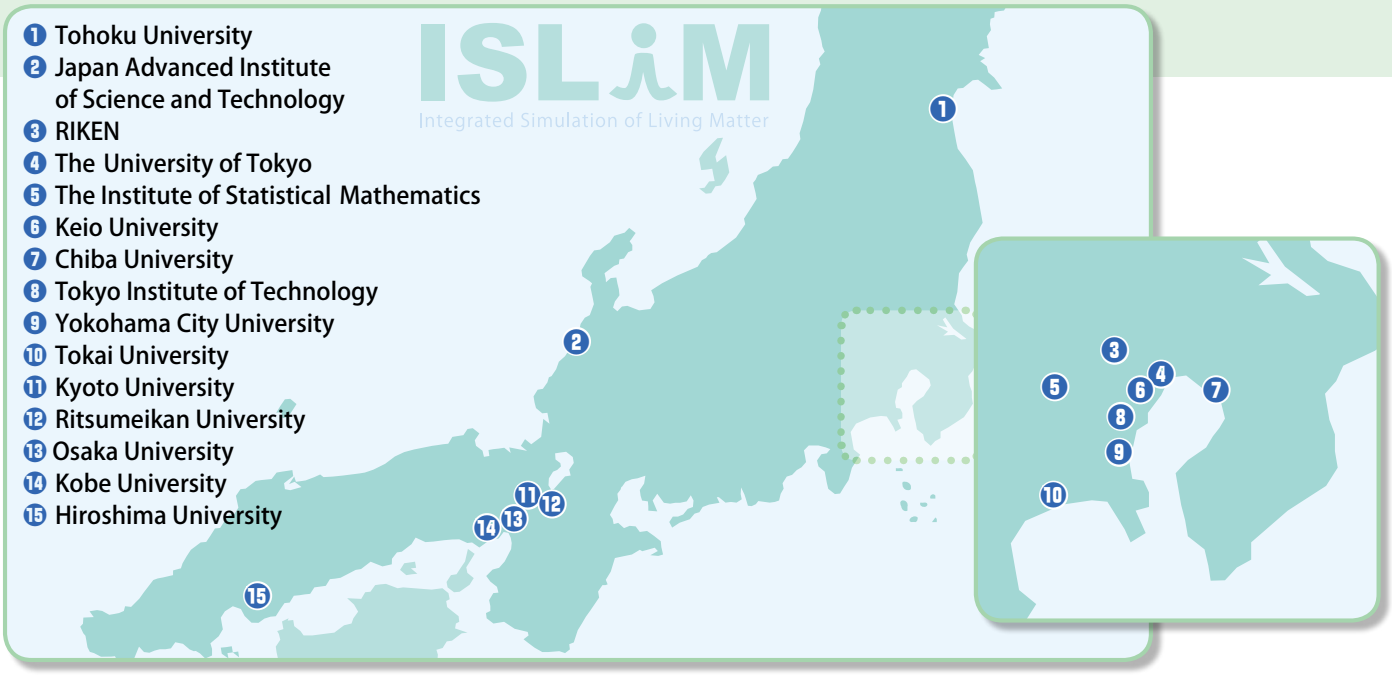
[Day 1] January 6 (Thursday)

13:15 - 13:45	Opening greeting **Koji Kaya** (Program Director)
13:45 - 15:15	Future ISLiM **Ryutaro Himeno** (Vice Program Director)
15:15 - 16:15	Break and check-in
16:15 - 17:15	About the Gordon Bell Award **Yosuke Ohno** (High-Performance Computing Team) **Hiroshi Koyama** (High-Performance Computing Team) **Keigo Nitori** (High-Performance Computing Team)
17:15 - 19:15	Study meeting on computational science for biology Molecular dynamics – Chairperson : **Miyashita** (Molecular Scale Team) Brain – Chairperson : **Urakubo** (The University of Tokyo) Blood flow – Chairperson : **Nanasawa** (Tokai University) : **Ishimine** (Organ and Body Scale Team) Genome – Chairperson : **Misawa** (Data Analysis Fusion Team)
19:15 - 19:30	Break
19:30 - 24:00	Convivial party and night session Poster presentation Poster tour

[Day 2] January 7 (Friday)

8:00 - 9:00	Breakfast
9:00 - 10:15	Presentation of the study meeting on computational science for biology By the groups of molecular dynamics, brain, blood flow and genome
10:15 - 10:30	Break
10:30 - 11:00	Coarse-grained biomolecular modeling and simulation program CafeMol **Hiroo Kenzaki** (Kyoto University School of Science)
11:00 - 11:30	Determination and comprehensive analysis of genome sequences in Japanese subjects using super parallel sequencer **kihiro Fujimoto** (Center for Genomic Medicine, RIKEN)
11:30 - 12:00	General discussion Closing greeting
12:30 - 13:30	Lunch
13:30 - 14:30	Visiting Advanced Institute for Computational Science, RIKEN

ISLiM Participating Institutions



Event information

■ Seminar held by Institute for Protein Research, Osaka University/ (co-hosted by) BioSupercomputing Research Community

- Date : March 4 (Friday): New Era of Biosimulations with Super Computers
  March 5 (Saturday): Training session: Practice of molecular simulation and intracellular network analysis
- Location : Seminar Room, 1st floor, main building of Institute for Protein Research, Osaka University (Suita Campus)
  3-2, Yamadagaoka, Suita, Osaka, Japan 565-0871
- Contact person: Haruki Nakamura (harukin@protein.osaka-u.ac.jp)

Event report

■ Next-Generation Supercomputing Symposium 2010 and 1st Joint Workshop for 5 Strategic Programs

On January 17, 2011, the "Next-Generation Supercomputing Symposium 2010 and 1st Joint Workshop for 5 Strategic Programs" was held on the Port Island, Kobe. The RIKEN Advanced Institute for Computational Science, which operates the 10 quadrillion speed "K computer", and interested persons from 5 research fields doing research using the K computer, gathered together for the first time. The symposium was highly successful, and there were about 300 participants. From the active discussion, there was a feeling that this project is making a contribution to life and society due to collaboration between the field of computational science and that of computer science to achieve new breakthroughs.

BioSupercomputing Newsletter Vol.4 2011.2

The "Next-Generation Integrated Simulation of Living Matter" is a project sponsored by the Ministry of Education, Culture, Sports, Science and Technology, in which research and development of simulation software to understand various phenomena occurring in the biological systems, including molecules and the human body, have been undertaken to realize a petascale simulation by making full use of the performance of a ten quadrillion speed computer known as "Kei."

Issued : February 2011

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