Quantitative Biology Center

Clarification of dynamic biological systems

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RIKEN Quantitative Biology Center

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Director’s Message

Advances in biological research have given us much deeper understanding of the underlying principles that create life. However, there are still a great number of problems to be solved, many of which require further integration of basic sciences like chemistry and physics into the biological sciences. Such integration is of particular importance when trying to examine the structure and function of intracellular elements at the nano-scale level, and then reconstructing how these elements assemble to form higher scale systems like cells and organisms.

This is the primary goal at QBiC. By developing and applying the latest in experimental techniques and technologies, we aim to reveal the mechanisms that allow basic elements to form complex and dynamical biological systems. In combination with new mathematical models, we expect to be able to predict and control the behavior of such systems with unprecedented ability.

Such a project will require bringing people of different fields together to one institute while at the same time developing and maintaining collaborations with laboratories from around the world. Furthermore, it means designing a training program that nurtures future scientists for such aims.

This is a truly ambitious effort. We hope you feel that its goals and structure are such that you too want to take part.

Along with being Director at QBiC, Toshio Yanagida is Vice-Director of the Osaka University Immunology Frontier Research Center (iFReC) and Director of the Center for Information and Neural Networks (CiNet). Formerly Dean of the Graduate School of Frontier Biosciences at Osaka University, he has won a number of national awards based on his work on the dynamics of biological motors.
The total number of Principal Investigators at QBiC now stands at 20, with labs based primarily in the Hanshin (Osaka-Kobe) area. (See below for specific locations). QBiC laboratories are organized into three main research cores: Cell Dynamics, Computational Biology, and Cell Design. There also exist externally funded projects that collaborate with the main research cores.

QBiC Organization as of May 1, 2012

**Cell Dynamics Research Core**
- Cell Dynamics Observation
- Single Cell Gene Dynamics
- Cell Signaling Dynamics
- Comprehensive Bioimaging
- Nano-Bio Probes
- Single Cell Mass Spectrometry
- Developmental Dynamics
- Cell Polarity Regulation

**Computational Biology Research Core**
- Computational Molecular Design
- Drug Discovery Molecular Simulation
- Biomolecular Function Simulation
- Biochemical Simulation
- MetaSystems Research
- Multiscale Biosystem Dynamics

**Cell Design Research Core**
- Synthetic Biology
- Cell-Free Protein Synthesis
- Integrated Biodevice
- Cardiovascular Molecular Dynamics
- Frey Initiative Research Unit

**Office for Multicellular Dynamics Research Collaboration**

**Office for Supramolecular System Dynamics Research Collaboration**

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**YOKOHAMA AREA**
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  Tsurumi-ku, Yokohama,
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**Advisory Council**
- Director of QBiC
- Office for Multicellular Dynamics Research Collaboration
- Office for Supramolecular System Dynamics Research Collaboration

**Research Collaboration**
- Office for Multicellular Dynamics Research Collaboration
- Office for Supramolecular System Dynamics Research Collaboration

**Frey Initiative Research Unit**
- OSAKA AREA
  Yoshihiro Shimizu
  Yo Tanaka

**KOBE AREA**
- Atsuo Kawahara
  Ura Frey

**YOKOHAMA AREA**
- Tsutomu Masaoka
- Shuzi Onani
- Yoshiki Sasai

**Integrated Biodevice**
- Todd Taylor

**International Medical Device Alliance (IMDA)**
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  Chuo-ku, Kobe 650-0047, Japan

**Frey Initiative Research Unit**
- Urs Frey

**Frey Initiative Research Unit**
- Todd Taylor

**Frey Initiative Research Unit**
- Yoshi Namba
Our Mission

A quantitative perspective of the life sciences

What is life? While we cannot yet say definitively, we do know life requires certain basic elements and that these elements build onto one another to form networks that are the foundation of complex living organisms. Understanding how these networks form is an essential part to answering this question.

The 20th century led to great advances in our understanding of life. Beginning with the discovery of the structure of DNA, genomic and proteomic studies have been invaluable to our understanding of how molecules function inside a cell. At the same time, population genetics and bioinformatics studies have provided a quantitative understanding of how genes regulate these molecules in order to execute the appropriate function at the appropriate time.

On the other hand, life depends on certain properties that remain a mystery. For example, cellular systems are able to function at energy levels that are far below the requirements of any equivalent artificial system. Properties like this make biological and artificial systems fundamentally different, and may therefore offer important clues for clarifying what is and what is not life.

QBiC aims to unveil the operating principles that regulate complicated biological systems by developing leading edge experimental and theoretical techniques, and then applying these principles to new technologies.

Combining advanced measuring equipment, modeling techniques, and design strategies

A primary focus at QBiC is the dynamics of biological phenomena that arise from basic elements like genes and their corresponding proteins, and then piecing together how these elements form networks that lead to higher-order systems. Realizing the principles that allow molecules and cells to integrate into tissues and organs is expected to be instrumental in our ability to control and design biological systems.

The three approaches to studying the dynamics of biological phenomena

Combining advanced measuring equipment, modeling techniques, and design strategies

Such an achievement will have a tremendous impact on an assortment of medically related fields including better patient treatment and drugs. Moreover, these studies are also expected to make an impact on nano-based and energy efficient technologies as molecules and cells can be thought of nano-machines. Thus, our studies will contribute to a diverse number of fields ranging from medicine to engineering.

Applications

Design new pharmaceuticals

Innovative diagnostic techniques

Nanotechnology and energy efficient technologies

New concepts

Predicting and detecting cellular dynamics

Manipulating cellular states

Understanding the principles that regulate complex biological phenomena

Measuring complex biological phenomena

Modeling complex behavior with new mathematical principles

Designing self-organizing systems

Cell

Tissue and Organs

Gene and Protein

Understanding the principles that regulate complex biological phenomena

Applications

Design new pharmaceuticals

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Cell

Tissue and Organs

Gene and Protein
Measuring cell dynamics

Japan is a world leader in high-resolution equipment for measuring real-time intracellular phenomena. These established techniques and Japan’s competitive advantage in the field are our foundation for building better spatial-temporal resolution imaging systems to observe the mechanical and electrical properties of various basic cellular components like mRNA, proteins and ions. Furthermore, these imaging technologies are currently being used to observe the dynamics of single molecules in a cell and of single cells within a tissue or organ. Complementing these experimental techniques with advanced modeling tools will allow us to study the dynamical behavior of these response networks in order to reveal the fundamental principles regulating them.

Intracellular imaging of single molecule dynamics

One example of Japan’s lead in the world of molecular and cellular imaging is the ability to observe the dynamic behavior of molecular motors or membrane receptors. With improving spatial-temporal resolutions and other developments, these imaging systems promise to offer great insight on the function and dynamics of various intracellular phenomena like signal transduction pathways. To accomplish this, however, the following are needed:

- nanometer size spatial and millisecond time resolutions
- 3D analysis of intracellular molecular movement
- simultaneous imaging of multiple molecules

Such improvements in imaging systems are expected to allow for a vast number of quantitative studies. These include changes over space and time in gene expression and receptor distribution in response to a stimulus. Understanding such reactions will give a quantitative framework on how changing specific cellular features can have much greater effects on more complex systems like immunity. To do such experiments, however, a concerted effort will be needed to build better lasers, microscopy systems, and chemical and optical probes.

Intracellular detection of single molecules

We intend to complement the ability to observe single molecules with techniques that allow for these molecules to be manipulated, aiming to observe how various intracellular molecules change in number, size, and dynamics and how such changes regulate cell function. Finally, such techniques will then be applied to the real-time observation of intracellular phenomena.

Analysis of single cells inside tissue and organs

Stem cell research has great promise in medical therapy. To harness this potential requires far deeper understanding of the mechanisms that determine a stem cell’s fate. Therefore, we aim to investigate how stem cells differentiate and how they interact with their surrounding cells by quantitatively observing cells and their intracellular components so that we can eventually control their function.

Principal Investigators in Cell Dynamics Research Core

Dr. Toshio Yanagida
Dr. Masahiro Ueda
Dr. Tomonobu Watanabe
Dr. Takashi Jin
Dr. Tsutomu Masujima
Dr. Shuichi Onami
Dr. Yasushi Okada
Dr. Yuichi Taniguchi

A key technological innovation will be the non-invasive imaging of tissues for the observation of gene expression, protein expression and single cells. From these studies will come an understanding of the operating principles that determine a cell’s behavior, which is a crucial step to determining a stem cell’s fate. Overall, this type of study is an excellent example of the diverse skills and techniques needed to make QBIC a leader in biological systems research.
Simulation and statistical analysis of biological phenomena

In general, biological systems are complex, non-linear systems. This makes their quantitative analysis very difficult. Furthermore, current modeling techniques are limited in what they can predict due to the lack of experimental data. That makes the development of the experimental technologies mentioned earlier all the more important. New techniques for faster processing and the development of better prediction models will therefore also be needed to analyze new data from the Measurement Group.

Different biological tiers like molecules and tissues operate on different time scales. For example, the molecular dynamics of a protein is on the time scale of femtoseconds. However, their effects on a cell measure out to milliseconds. Therefore, an extraordinary number of protein dynamics need to be considered when modeling the dynamics of a cell. A similar problem of scale arises spatially. Cells show an incredible sensitivity to even the slightest concentration gradients, meaning a difference of a small number of molecules at one end of a cell compared to the other can have profound effects on cell behavior. Accurate models must account for this fact. Therefore, a new generation of supercomputers and mathematical algorithms are needed.

Millisecond scale simulations of molecules

Currently, our understanding of protein dynamics mostly comes from crystallography studies, which really only offer a series of static images that are then reconstructed to describe the dynamics. Understanding structural and functional changes requires temporal information, particular at the millisecond scale. Future supercomputers and analysis techniques for multi-scale simulations are expected to capture the molecular dynamics driving these changes. The ability to predict these dynamics will give great insight on enzymatic reactions, which should improve drug design strategies.

Cell analysis at the single molecule level

Using the above techniques to understand how individual molecules coordinate inside a cell to determine the cell’s behavior offers a new horizon for biological research. It is especially important to connect how a vast number of molecules integrate to make reliable, functioning cells despite individually behaving in what appears to be a random, erratic manner. This should lead to the ability to predict, manipulate and design similar biological systems.

Tissue analysis at the single cell level

Along with being able to quantify cellular properties at the single molecule level, we aim to examine the development and function of tissues and organs for understanding pathologies at the cellular example. One example is clarifying how cellular changes can lead to cancer.

Principal Investigators in Computational Biology Research Core

Dr. Makoto Taiji
Dr. Yuji Sugita
Dr. Koichi Takahashi
Dr. Todd Taylor
Dr. Chikara Furusawa
Designing cells based on biological principles

Biological systems are inherently complex, non-linear systems. As a result, subtle changes in individual elements can cause large changes in a system. This makes it difficult to predict the impact an elementary change has on an entire network when looking only at individual or a small cluster of elements inside a network. Therefore, to reveal the principles behind the complexity and non-linearity, more holistic studies are needed. At the same time, however, it is easy to neglect the contribution individual elements make to complex biological networks. To balance these two problems, we aim to reconstruct and manipulate artificial systems that mimic their biological counterparts.

Challenges in designing biological systems

A variety of problems must be overcome when designing the above systems. First is to bring together individual elements to form a functional complex network. Another issue is controlling the behavior of the individual elements. One approach is the design of simulation methods that can predict the effects of certain mutations on a molecule and on the subsequent network. In conjunction with this is the need for new experimental methods that can confirm these predictions, especially in real-time.

New biological fields emerging from such biological designs

The work described above is expected to open the door to new branches in the biological sciences. Below are five examples of the type of fields that will arise or rapidly progress due to these efforts.

1. Protein synthesis

There already has been great progress in protein synthesis. Nevertheless, more efficient systems are needed to pursue grander and more challenging projects. The aforementioned design efforts will push forward such technologies.

2. Membrane division

Cell division is a distinguishing characteristic of life, and is considered to be a vital step in evolution. A basis for cell division is membrane division, which will be a starting point for designing our artificial biological systems.

3. Spatial control

The realization of therapeutic fields like regenerative medicine is very dependent on our understanding of the mechanisms that drive cell proliferation. In particular are the mechanisms that determine how elements distribute within a biological system like molecules in a cell to regulate function. One example is to examine how spontaneous intracellular changes, like changes in a cell’s polarity, affect the spatial distribution of the cell.

4. Temporal control

Parallel to the spatial distribution of a cell is its temporal distribution. The dynamics of many molecular systems are like clockwork, and regulate processes like hormone secretion, metabolic rates, and changes with age or the environment.

5. Logic Systems

The properties and functions of a cell are determined by gene networks, which make the cell a self-functioning machine. Cells possess a number of intangible skills like logic, memory, and learning that arise from their networks. We aim to reconfigure the logic of these gene networks in order to control a cell’s output.
**Next Program**

This program is funded by Japan Society for the Promotion of Science (JSPS) and will provide opportunities for young researchers to make use of the most advanced technologies developed by the core programs to promote their research projects. One beneficiary is Dr. Atsuo Kawahara, who runs Laboratory for Cardiovascular Molecular Dynamics. His group is performing functional analysis on zebrafish mutants defective in the cardiovascular system using fluorescent proteins to visualize the cardiovascular formation.

**The Initiative Research Unit Leader Program**

This program affords opportunities to outstanding non-Japanese young scientists to pursue independent research at RIKEN and to promote international collaborations. One beneficiary of this program is Dr. Urs Frey, who runs his Initiative Research Unit. The lab focuses on bioelectronics and biosensors, a multidisciplinary research field at the interface of engineering, biology and nanotechnology.

**Dynamic Biological Systems Collaborations Program**

This program will provide a platform for researchers outside of QBiC to conduct feasibility studies with Core Program researchers. The Office for Multicellular Dynamics Research Collaboration (Dr. Yoshiki Sasai) focuses on area of Quantitative Developmental Biology. It hosts workshops to support developmental biologists to learn quantitative analysis theories and apply them to experimental biology. The Office for Supramolecular System Dynamics Research Collaboration (Dr. Keiichi Namba) promotes the research collaborations with the leading-edge research infrastructure in the RIKEN and Osaka University.

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**Outreach**

**Annual Symposium**

Every year, QBiC hosts an international symposium, inviting world leading scientists in quantitative biology and related area.

**QBIC training course**

This two - day course is designed for graduate students to learn various aspects of quantitative biology including imaging, computing, and designing.

**QBIC Seminar**

Every month or so, QBIC PIs host this open-to-public seminar series.

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**Quick Statistics 2011 - 2012**

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<th>Budget (FY2011)</th>
<th>Competitive funds from government (123)</th>
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<td>Others</td>
<td>RIKEN operating grant (2,086)</td>
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<td></td>
<td>JSPS Strategic fund for strengthening leading-edge research and development (387)</td>
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**Total funding (2,520)**

<table>
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<td>Visiting Scientists</td>
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