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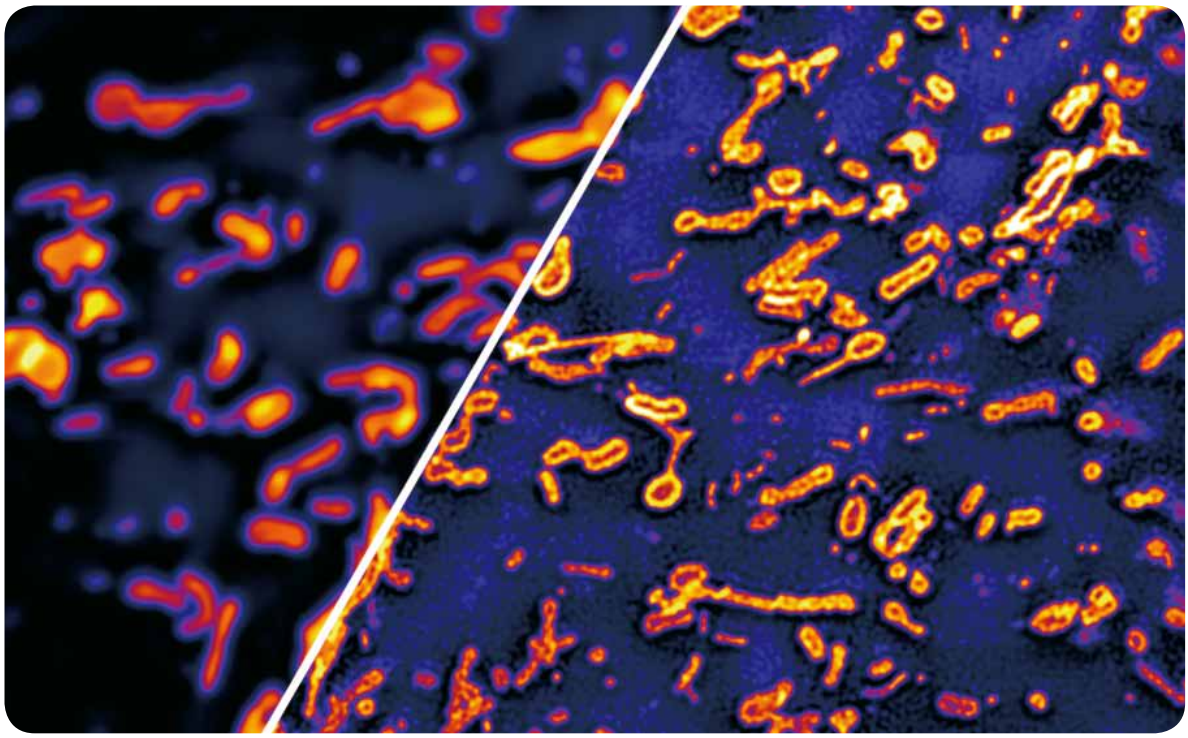
QBiC

NEWSLETTER OF RIKEN Quantitative Biology Center

QBiTs



Ultrafast Super-resolution mitochondria

Combining the powers of spinning disc confocal microscope optics and structured illumination microscopy, a new frontier of live imaging has opened at RIKEN QBiC. Organelles, such as the mitochondria above, can now be seen with unprecidented resolution in live cells. A conventional fluorescence microscope image (left) is compared to a Spinning Disc Super-Resolution Microscope (SDSRM) image. Team Leader Yasushi Okada received a MEXT award for creating this microscope, details on page 8.

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CATCHING UP WITH

Professor Shin-ichi Tate

Shin-ichi Tate, Director of the Research Center for the Mathematics on Chromatin Live Dynamics (RcMcD), a biodynamics research center in Hiroshima University sat down with QBiTs during a break at the 2017 Molecular Mechanisms and Mathematics of Life Dynamics Symposium at QBiC. He was joined by his colleague and QBiC visiting scientist Yuichi Togashi.

QBiTs: How did your research center come to be?

Shin-ichi Tate: The RcMcD developed out of the Department of Mathematical and Life Sciences at Hiroshima University. About ten years ago this department sought to train mathematicians and physicists to work on problems of biological interest. We had some excellent researchers in that program, including QBiC's Tatsuo Shibata, and because of the success of that program we were able to get funding and support to further develop into the RcMcD, biodynamics research center.

Q: What do you think of QBiC?

ST: QBiC seems to be a quite an outstanding institute. Quantitative Biology is an interdisciplinary field and QBiC has excellent researchers and results. I think it is essential for RIKEN to support such interdisciplinary research centers because universities cannot maintain so many researchers in this field. We have less than ten people working in this particular field at Hiroshima University. We cannot get fruitful interdisciplinary collaboration without a critical mass of chemists, mathematicians, biologists, physicists, engineers and so on. QBiC's advantage is numerous representatives from each field coming together for collaboration.

Q: Isn't there a big difference in the perspectives of biologists and physicists?

ST: Yes! Well I am a chemist so I think I can see the perspectives of both the physicists and biologists. But sometimes mathematicians and physicist make very simplified or abstracted models of biological phenomenon. But they are looking for the most important, fundamental issue behind the phenomenon without preconceived notions.

In my research, I work on NMR structure of proteins, when working with biologist the question is always about the functional biochemistry of the protein but in working with mathematicians I've benefited from their insight into the fundamental mathematical principles of overall phenomena. And the protein biochemistry is only one element of that bigger picture. We get deeper insight into the phenomena.

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Recent Science Events

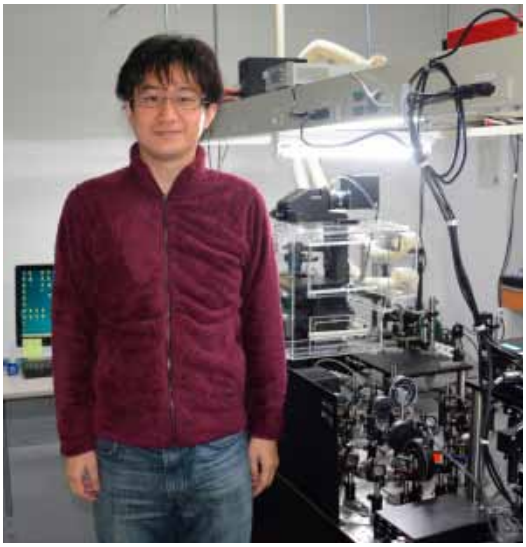
• Apr 11, 2017
QBiC-CDB Joint Seminar
Go Shioi
Genetic Engineering Team
RIKEN Center for Life Science Technologies

• Apr 3, 2017
QBiC-CDB Joint Seminar
Takeshi Sugawara
Center for the Mathematics on Chromatin Live Dynamics
Hiroshima University

MEET THE LAB

Observing single molecules in individual cells

Yuichi Taniguchi's Laboratory for Single Cell Gene Dynamics



We are pursuing systems-level biology of single cells by developing innovative technologies that quantify individual cell behaviors by their gene expression dynamics. Such single cell analyses are essential for understanding the causality of biological processes such as cell differentiation and disease occurrence. We aim to characterize single cells by precisely measuring molecular numbers and their spatiotemporal localizations with a broad scope across the epi-genome, genome, transcriptome and proteome. Ultimately, we aim to provide the key principles for the understanding and controlling of complex cellular systems.

The genome is the molecular basis of emerging cellular activities, however the causal relationships between its three-dimensional structure and its complex gene expressions remain unclear. To approach this issue, we developed a technique that characterizes 3D chromosome structure at high resolution. We achieved the highest resolution in the world for 3D chromosome conformation capture, able to capture both nucleosome contacts and orientations in chromosomes genome-wide for the first time. These results provide a general account for in vivo chromosome structure as an irregular, but ordered fiber and will help elucidate the interplay between nucleosome compaction, gene regulation and physiological outcomes.

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HOT OFF THE PRESS

Recent publications from QBiC researchers

◆Urs Frey and his team have moved on to Europe, with Urs leading MaxWell Biosystems, an ETH-Zurich associated start-up based on technology developed during his time at QBiC. Read the technical aspects in "Dielectrophoresis-Assisted Integration of 1024 Carbon Nanotube Sensors into a CMOS Microsystem" in *Advanced Materials*.

◆Yoshihiro Shimizu offers his cell-free protein synthesis expertise in *PNAS*, "Reaction dynamics analysis of a reconstituted *Escherichia coli* protein translation system by computational modeling."

◆The integrated biodevice super-team of Tanaka and Tanaka created a "Simple agarose micro-confinement array and machine-learning-based classification for analyzing the patterned differentiation of mesenchymal stem cells", published in *PLoS One.*

Recent Science Events

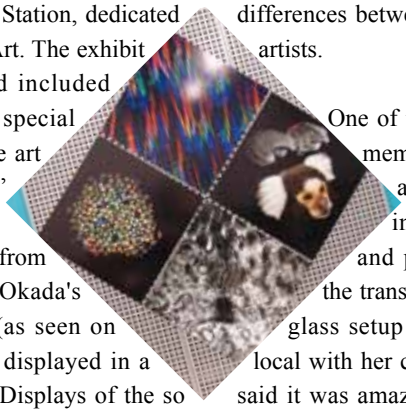
• Mar 8, 2017
QBiC-CDB Joint Seminar
Yuji Yamazaki
Lewis-Sigler Institute for Integrative Genomics
Princeton University

• Mar 17-18, 2017
QBiC Joint Symposium
With University of Tokyo, Hiroshima University,
Kyoto University, CREST and PRESTO

REACHING OUT

Science × Art at the Shizuoka Science Museum

The work of many RIKEN scientists was displayed at a special exhibit at the playfully named Ru Ku Ru, Shizuoka Science Museum. The museum which is conveniently located near Shizuoka Station, dedicated sections of two floors to Science × Art. The exhibit ran from March 18 to May 7 and included interactive installations and some special event days, such as the performance art piece "The world as seen by a robot."



Some aesthetically pleasing images from QBiC research including Yasushi Okada's mitochondria at super-resolution (as seen on the front cover of this issue) were displayed in a section dedicated to RIKEN work. Displays of the so called "UT Heart" and Hiroki Ueda's transparentized mouse were juxtaposed with similar work created by professional artists, including Iori Tomita. The thought provoking displays asked patrons to consider the differences between the works created by scientists and artists.

One of the professional artists, Akiko Sato is a member of Shoji Takeuchi's research group at the University of Tokyo. She created images with tiny bits of plant material and paintings of organs as machines. But the transparent mouse with a simple magnifying glass setup for better viewing was the big hit. A local with her children who were observing the mouse said it was amazing to be able to see such fine details of the bones and that "it really is art." The kids giggled, "Wow! It's small." ■

NEWCOMERS at QBiC

Mamiko Asano

Team Jin

Sports: Hiking

Hobbies: Listening to music (Jazz, blues, etc)

Food: Karaage-kun

Yuki Mori

Team Jin

Sports: American football and Ice Hockey

Hobbies: Playing the ukelele and sanshin (the Okinawan traditional instrument)

Food: Tacos

QBiC outreach activities

◆Feb 8, Mitsuhiro Iwaki, from Director Yanagida's lab, gave a RIKEN evening seminar for industry partners at RIKEN's new offices near Tokyo station.

◆Feb 15-16, Medical Japan, a huge industry exposition and conference in Osaka hosted talks by QBiC PIs Tanaka and Shimizu. Additionally, a group came to QBiC for a tour including Takashi Jin's lab and the MDGRAEPE-4 Supercomputer.

Spring course participants flanked by QBiC researchers Takas

In silico drug design in a gravity pipe

Makoto Taiji and team, who are developing the next generation of Molecular Dynamics GRAvity PipE (MDGRAPE) supercomputers, are hosting a forum series with the Japan Pharmaceutical Manufacturers Association (JPMA).

Dr. Kawakami, head of the research and development committee of JPMA, leads the forum but there is an alphabet soup of participants from computer venders, software houses, and semiconductor design companies. Representatives from Fujitsu, NEC, Hitachi, Alchip, Tokyo Electron Device, D-Clue, X-ability, Schroedinger Japan and others have joined the forum.

The purpose is to get input from these stakeholders on the design specifications of the MDGRAPE-4A, a rebuild of the current MDGRAPE computer at QBiC. This special purpose supercomputer is intended to do MD simulations which take several weeks run even on the most advanced supercomputers.

Irregularly scheduled meetings and teleconferences have been continuing throughout the year in various locations including a workshop in QBiC B-Building coinciding with cherry blossom season. ■

QBiC B-Building in spring
Suita, Osaka

shi Jin on the right and Shuichi Onami on the televsion screen

◆Mar 6-9, QBiC hosted university students from throughout Japan at the annual spring course. More than three dozen students enthusiastically participated in the three-day event including lectures, hands on experience in QBiC laboratories and student presentations.

◆Mar 13, A group of junior high school students came all the way from Niigata for a tour of QBiC and an overview of RIKEN. The students enjoyed the opportunity to see science in action in the Watanabe and M. Ueda labs and they also experienced the wind and noise of the MDGRAPE-4 Supercomputer.

Hiking in Osaka: Mount Kongo

Text and photos by Chew Wei Xiang, International Program Associate

Mountains and forest cover about seventy percent of Japan's land area, so it should come as no surprise that many cities including Osaka are situated close to the mountains. The mountains of Japan support a variety of ecological landscapes, from the subtropical natural forests of Yakushima to the evergreen forests of the Japanese Alps and from the mystic and mossy cloud forest to rocky and arid volcanic mountains. Despite the fact that the cities of Japan have undergone rapid industrialization and urbanization, I'm quite often surprised by the presence of wildlife during my hikes. Deer, wild boar, fox, wild rabbit, salamander, vipers, moles and macaques are some of the many animals that I've encountered. Thankfully I've not yet crossed paths with a bear.

Mountain trekking or hiking is a popular activity among the locals. I've met enthusiastic hikers of all ages motivated by various reasons. Some hike for the scenic view, some for health, some hike for the little adventure with friends and family, while some seek for solitary self-reflective times while immersing oneself in the mother nature. Most of the highest mountains in Japan are in Chubu and Kanto regions, while the mountains in Osaka's Kansai area are relatively lower and less exposed to the elements. One of my favorite mountains in the Kansai region is Mount Kongo, standing 1125 meters tall in between Osaka and Wakayama prefectures.

Viewed from afar, Mount Kongo might seem distant and dull, but that's deceiving as the mountain is very much alive throughout the seasons. Just after the spring rain, the new leaves and blossoming flower fields lift one's spirits for the new year ahead. In the hot summer months, dark forest shade and the murmuring streams together with the all-day, non-stop symphony of cicadas and bird songs offers a perfect escape from the concrete jungle. Autumn is the best time to witness a dramatic and vivid color display of the whole forest. While in winter, Mount Kongo is one of the few places in Osaka that transforms into a little winter wonderland decorated with frozen trees.

There are several trails that lead to the high plateau summit of Mount Kongo. The most popular and shortest is the Chihaya-hondo path which takes about 1 hour 40 min at a regular pace. The trail consists of a broad and gradual staircase that continues up to the peak. The trail is suitable for beginners and children. If you are a more adventurous type and like to go off the beaten track, there are few other options: the Katoratani trail with its secret flower garden blossoming during certain seasons and the Marutakidani trail where you hike through the valley and scale a few waterfalls. Once you reach the peak plateau, you can enjoy the beautiful view of the Osaka area and Mount Rokko range. If you are hungry, there is a tea house that serve hot coffee and delicious udon noodles. For the descent, you can either take the original route back or pay 750 yen to use the ropeway.

A few tips for preparation before the hike: wear quick-dry clothing during the spring and summer, add a breathable shell windbreaker as an outer layer for autumn and winter hikes to block out the freezing wind and maintain a comfortable temperature. A sturdy shoe or boot with good traction is enough for most of the local

mountains. Light-weight trail-running shoes are good for short distances and mid-cut hiking boot are excellent in supporting the ankles for a long-distance hike. A trekking pole is not a must but it helps in minimizing impact on the knees, especially during descent. Hydration is important, one litter is minimal for a two to three hour hike. On Mount Kongo there is a vending machine available at the peak. Although the hiking trails are well-marked with signboards at important junctions, having a map or a smartphone equipped with GPS would be useful. Last but not least, don't forget to check the weather forecast before you go. ■

Transport: One-way transport from Yamada Station near QBiC ¥1,460. From Yamada Station take a Tengachaya bound Hankyu train to the terminal. Change to Nankai-Koya line to Kawachi-Nagano station and change to a Nankai bus bound for Kongosan-ropeway-mae but stop at Kongozan-tozan-guchi bus stop. The trail head of Chihaya-hondo course is just around the corner.

A hiking map can be downloaded from the Nankai railway website while a digital trail map is available on Yamareco.com, a community-based hiking information sharing website.

Taniguchi continued from page 3

Biological noise, can be the basis for helping cells cope and survive with ever-changing environments. We have approached this mechanism by performing system-wide analyses of biological noise with single molecule sensitivity in the model organism *Escherichia coli*. Our next objective is to understand how such biological noise is derived from the transcription or translation process in eukaryotic cells. To directly examine this question, we achieved simultaneous counting of mRNA and protein expression in single living *Saccharomyces cerevisiae* cells with single molecule sensitivity. Our data will uncover linkages of stochastic dynamics between mRNA and protein expression in *S. cerevisiae* and typical differences in behaviors between prokaryotes and eukaryotes.

The causal relationship between the nucleosome-level chromosome structuring and gene regulation will be examined by measurements of *S. cerevisiae* in multiple growth conditions that give rise to alternate gene expression programs. In addition, applying our technique to other organisms will generalize our findings across eukaryotes to identify fundamental concepts of genome structure-function. Various kinds of bioinformatic and machine learning analyses can be applied to understand the complex nature of our genomic structural data. The obtained comprehensive datasets on high-resolution epi-genome, single cell transcriptome and proteome dynamics will provide fundamental data resources for whole cell modeling and the DECODE project. ■

AWARDS

Yasushi Okada, Team Leader of the Laboratory for Cell Polarity Regulation, received Commendation for Science and Technology from the Minister of Education, Culture, Sports, Science and Technology, in the Prizes for Science and Technology-Development Category, for his Spinning Disc Super-Resolution (SDSR) microscope.

Also receiving Commendation for Science and Technology, Unit Leader, Yo Tanaka received the Young Scientists' Prize as did visiting researcher Etsuo Susaki.

Yoshihiro Shimizu and his Laboratory of Cell-free Protein Synthesis won a research grant for international collaboration from the Human Frontier Science Program for "A PURE-ly synthetic ribosome biogenesis in DNA compartments on a chip," with Roy Bar-Ziv of the Weizmann Institute of Science in Israel.

QBiC was there

…in the Sankei Newspaper. QBiC researchers have published series of general audience science stories with fun, fascinating and controversial topics such as "Does Godzilla's transformation represent evolution or development?" written by Minako Izutsu, visiting researcher in the Furusawa lab. Minako explains a population geneticist's perspective on evolution in response to a line from the movie, "It's like evolution!"

Former particle physicist, Masaki Watabe, who is a postdoc in the Takahashi lab and Occam's razor personified, discussed the difference in culture between physics and biology research, and tackling the tough issues, Kazuho Ikeda, research scientist in the Okada lab discussed the ethics and science of genome editing in human embryos.

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ST: I was really impressed by the talks at this symposium. A typical example was the young speaker who developed mathematical models to investigate the archaic biological recapitulation theory, which says basically that evolutionary history can be witnessed in the development of an embryo. The speaker's point was that slow changing genes must be essential for this apparent relationship and he developed the conclusions strictly from a mathematical perspective. This may seem weird to biologists but it can provide a more fundamental understanding of the whole picture without being weighed down by investigating each individual part.

Q: Do you have any advice for other young researchers?

ST: Mathematicians and physicists frequently want to solve huge problems, like gravitational waves or particle physics. But biology is ripe with many small problems that can be solved with their skills. So, my advice to people in these fields is to find out what questions remain in biology and to work on that. They will find there are many questions and that they are relatively simple to solve and it is very interesting. For example, Dr. Togashi has worked on small number interaction systems, which reflect the sometimes very small numbers of certain molecules in a cell.

Yuichi Togashi: QBiC's Dr. Taniguchi made a very important finding, by counting the copy number of proteins in individual cells. It seems that some chemical reactions are mediated by proteins which only had one or two copies in each cell. This is very different from a chemical reaction in a test tube which might contain billions of molecules to achieve an equivalent concentration. Cells make a very unusual and very interesting system for mathematical investigation. ■

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