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Evolution comes to a head

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Coordinating connections between neurons

'Reverse signaling' orchestrates synaptic activity

The architecture of the brain is bewilderingly complex. Upwards of one hundred trillion connections between tens of billions of neurons—some individual neurons making thousands of connections to other neurons (Fig. 1)—collectively function to bring about thought, action, emotion, sight and memory. For any of these brain functions to occur, the myriad neuronal connections must be coordinated. Yet, the challenge of coordinating these many connections stems from the physical structure of the synapse.

Neuronal axons—the long 'arms' of neurons that carry signals to dendrites—end in terminals that function as exit points for chemical neurotransmitters that bind to receptor molecules expressed on the terminals of dendrites, called spines, which are variously sized and shaped projections from other neurons. Chemical-electrical signals that propagate along axons are 'delivered' across a cleft—or synapse—spanning 20–40 nanometers (Fig. 2), to neighboring dendrites that pass along the signals.

Because chemical and molecular activity at pre- and post-synaptic sites is required for successful propagation of signals across synapses, the two synaptic termini must be precisely coordinated. Although signs that regulation of pre-synaptic activity occurs from post-synaptic sites as been reported, the mechanics of such regulation are little understood.

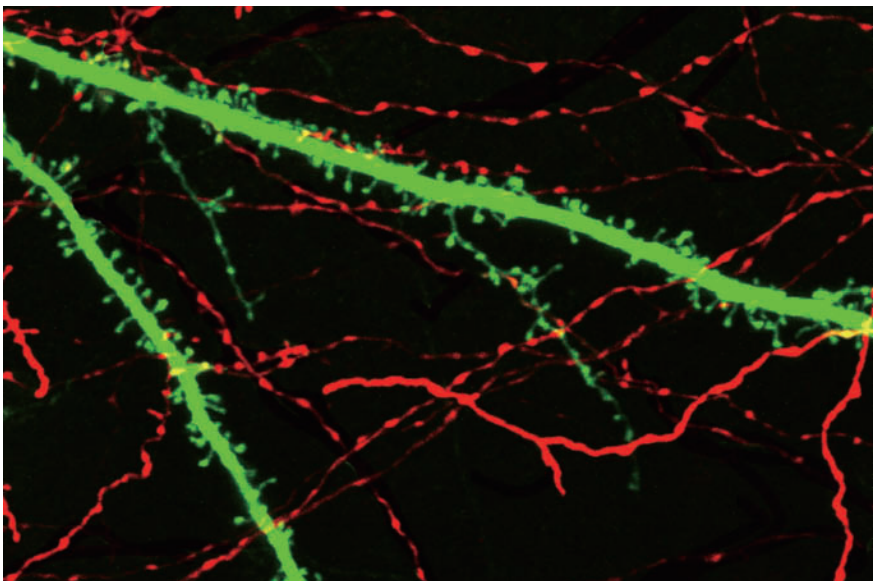


Figure 1: Neurons receive thousand of inputs (red) through post-synaptic sites (green) demonstrating the complex problem of coordination in the brain.

Pinning down the mechanism

Now, a collaboration of scientists led by Kensuke Futai, Tsutomu Hashikawa, Morgan Sheng and Yasunori Hayashi at the RIKEN-MIT Neuroscience Research Center, Cambridge, US, and the RIKEN Brain Science Institute, Wako, have determined the mechanism by which feedback regulation—or retrograde transmission—coordinates the activity of at least some synapses[1].

"Since Ramon Cajal established the synapse hypothesis in [the] 19th century, many people have believed that the major direction of synaptic transmission is the anterograde [or forward] transmission," remarks Futai on the rationale for the new work. Studies since Cajal's pioneering work by many scientists found that pre- and post-synaptic structures are tightly coordinated in both size and function, leading some scientists to speculate that feedback, or reverse signaling, by post-synaptic dendrites regulates pre-synpatic activity.

The RIKEN team's working assumption was that signals from the spines would physically travel 'in reverse' across synaptic clefts (Fig. 2) to influence the function and properties of pre-synaptic terminals. Initial experiments centered around three proteins known to connect post-synaptic and pre-synaptic activity: post-synaptic protein 95 (PSD-95), neuroligin and the pre-synaptic protein β-neurexin.

The team first explored the role of PSD-95 in coordinating synaptic activity. By altering the amount of PSD-95 in post-synaptic sites with state-of-the-art molecular biology techniques such as RNA interference and gene delivery with DNA-coated gold particles, and then measuring electrophysiological activity in the synapse, they found that post-synaptic PSD-95 regulates pre-synaptic activity.

They next turned their attention to neuroligin, which is also found in post-synaptic sites. But neuroligin also extends into synaptic clefts where it can interact with proteins on pre-synaptic neurons.

Speculating that neuroligin and β-neurexin—along with PSD-95—could function as a physical bridge linking post- and pre-synaptic neurons, the team measured the electrophysiological activity between neurons after altering the levels of either post-synaptic neuroligin or pre-synaptic β-neurexin. As with PSD-95, changing the amount of either protein altered activity of the synapse.

According to the model developed by Futai and colleagues, post-synaptic PSD-95 and neuroligin play a central role in directly regulating pre-synaptic

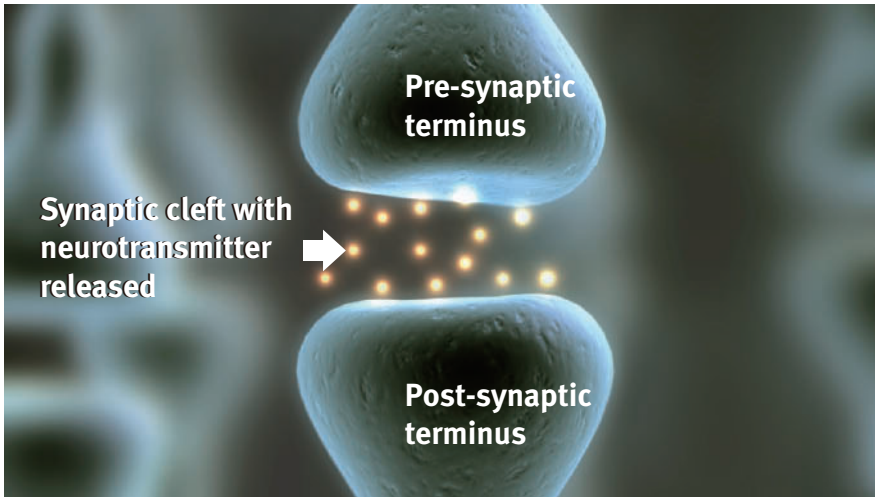


Figure 2: An artist impression of a synapse. Chemical neurotransmitter in the cleft passes from the pre-synaptic terminus to the post-synaptic terminus.

β-neurexin. But what is ultimately being regulated in the pre-synaptic terminals? The team focused on release of neurotransmitter into synaptic clefts, as β-neurexin had been linked to the molecular apparatus required for neurotransmitter release.

Indeed, by directly measuring the amount of neurotransmitter released from pre-synaptic terminals after altering PSD-95 and neuroligin levels in post-synaptic neurons, and inhibiting the β-neurexin function in pre-synaptic neurons, the team found that all of these manipulations affected neurotransmitter release. A relatively complete picture of the retrograde signaling mechanism was now evident: the PSD-95—neuroligin—β-neurexin complex physically spans synaptic clefts and regulates the release of neurotransmitter.

Importantly, the model posits that retrograde signaling depends on fluctuations in the amount of PSD-95 in post-synaptic terminals, which some studies have shown to be influenced by even simple tasks such as opening one's eyes. "We hypothesize that neuronal activity such as learning induces localization of PSD-95, and then PSD-95 strengthens the synaptic connection through the neuroligin—β-neurexin interaction," explains Futai.

Modulating synapses in diseased brain

The work by the RIKEN team may provide new avenues of research on several brain diseases. Retrograde communication may be critical for memory formation and in such diseases as Alzheimer's or in the development of autism. More generally, the work significantly adds to our understanding of how synapses in general are regulated.

"Beta-amyloid accumulation, which is a major symptom of Alzheimer's disease, causes the loss of PSD-95 from synapse," says Futai. "It's perhaps not unexpected that Alzheimer's patients have less PSD-95 since Alzheimer's patients cannot maintain memories, and because PSD-95 is important for synaptic function." Yet, increasing the amount of PSD-95 in Alzheimer-diseased neurons to treat memory problems is not very realistic at present, he adds.

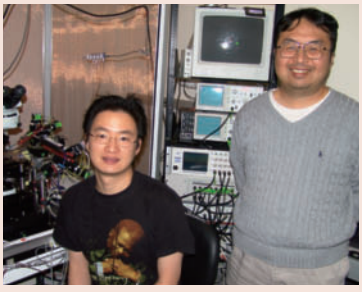
Other types of trans-synaptic molecules factors still await intensive study. "I would like to apply [the] same technology we used [in] the present study to other trans-synaptic and retrograde molecules. By doing further studies, I think we will understand better how synapses [memories] are maintained [stored] in the brain," says Futai. "Regarding further work on PSD-95–neuroligin–β-neurexin, I would also like to know if a relationship exists between these protein-protein interactions and the development of autism."

1. Futai, K., Kim, M.J., Hashikawa, T., Scheiffele, P., Sheng, M. & Hayashi, Y. Retrograde modulation of presynaptic release probability through signaling mediated by PSD-95–neuroligin. *Nature Neuroscience* **10**, 186–195 (2007).

About the researchers

Yasunori Hayashi (picture below, right) received his MD degree in 1990 and his PhD in Physiology in 1994, both from Kyoto University. He conducted postdoctoral work in AMPA receptor phosphorylation in Tomoyuki Takahashi's laboratory (the University of Tokyo). In 1996 he moved to Cold Spring Harbor Laboratory and conducted research in AMPA receptor trafficking with Roberto Malinow. He is currently a unit leader at the RIKEN Brain Science Institute, as well as an assistant professor at the Picower Institute for Learning and Memory at the Massachusetts Institute of Technology.

Kensuke Futai (picture below, left) was born in Madison, USA, in 1971. He studied at the Department of Biology in Kyusyu University for his undergraduate and Master's degrees from 1991 to 1997, before obtaining his PhD at the Department of Neurophysiology at the University of Tokyo in 2001. In the same year, he joined the RIKEN-MIT Neuroscience Research Center, the Picower Center for Learning and Memory (now the Picower Institute for Learning and Memory since 2002) and the Department of Brain and Cognitive Science at the Massachusetts Institute of Technology, as a postdoctoral fellow. Between 2002 and 2005, he held an appointment as a special postdoctoral researcher at the Laboratory for Neural Architecture, in the Advanced Technology Development Group of the RIKEN Brain Science Institute in Japan. His research interests include the investigation of the functional significance of trans-synaptic molecules.



A careful catalyst

A catalyst based on rare-earth metals has been developed that can make high-performance synthetic rubber in a highly selective reaction

Figure 1: The structure of a catalyst precursor based on the rare-earth element lutetium (purple). The nitrogen and phosphorus atoms of the PNP ligand are shown in blue and pink, respectively. An oxygen atom is shown in red, the silicon atoms in green, and the carbon atoms in gray.

Rubber is a naturally occurring elastic material that is used to make many different products, ranging from tires to surgical gloves. The main component of natural rubber is a polymer called polyisoprene, which is made from a large number of smaller identical building blocks (an organic molecule called isoprene) linked in a chain.

Because natural sources are limited, chemists have devised ways to make synthetic rubber in the laboratory by polymerizing isoprene with metal catalysts. This is not straightforward, however, because there are many different ways in which isoprene molecules can be joined together. In particular, it is desirable for them to be linked at each end (1,4 substitution) with the carbon-carbon double bonds all adopting the same arrangement, known as '*cis*'.

"Although a variety of catalyst systems have been reported for the polymerization of isoprene, none have been able to produce polymers with both a narrow distribution of chain lengths and a high (>99%) *cis*-1,4-content," says Zhaomin Hou from RIKEN's Discovery Research Institute in Wako.

Hou and co-workers have now developed[1] a catalyst system (Fig. 1) based on the rare-earth metals—a group of elements that comprises scandium, yttrium and the lanthanides—that can be used to make, in a highly selective fashion, *cis*-1,4-polyisoprene. The catalysts, which are positively charged, contain a central metal atom that is bonded to a carbon chain and an organic ligand containing one nitrogen and two phosphorus atoms—known as a bis(phosphinatophenyl)amido or PNP group.

The catalysts react with isoprene and related compounds to make polymers in which there is little variation in the length of the chains. Such polymerizations are referred to as 'living', because once a growing chain is formed, it remains active (alive) and does not terminate (die). Since all of the chains start growing at roughly the same time with the same rate—and do not die—they grow to roughly the same size.

In this way, Hou and co-workers were also able to make polymers containing two different segments. After the catalyst had polymerized butadiene to give polybutadiene, the active catalytic sites at the ends of the 'living' chains were used to grow polyisoprene blocks when isoprene was added to the reaction.

Although rare-earth-based polymerization catalysts are not yet as widely recognized as those of group 4 metals (such as titanium and zirconium), Hou comments that, "they do possess unprecedented potential, and a prosperous future in this area can be confidently anticipated". ■

1. Zhang, L., Suzuki, T., Luo, Y., Nishiura, M. & Hou, Z. Cationic alkyl rare-earth metal complexes bearing an ancillary bis(phosphinophenyl)amido ligand: A catalytic system for living *cis*-1,4-polymerization and copolymerization of isoprene and butadiene. *Angewandte Chemie International Edition* **46**, 1909–1913 (2007).

Superconductors' dripping faucet

New insights on how magnetic fields trickle through stacks of high-temperature superconductors

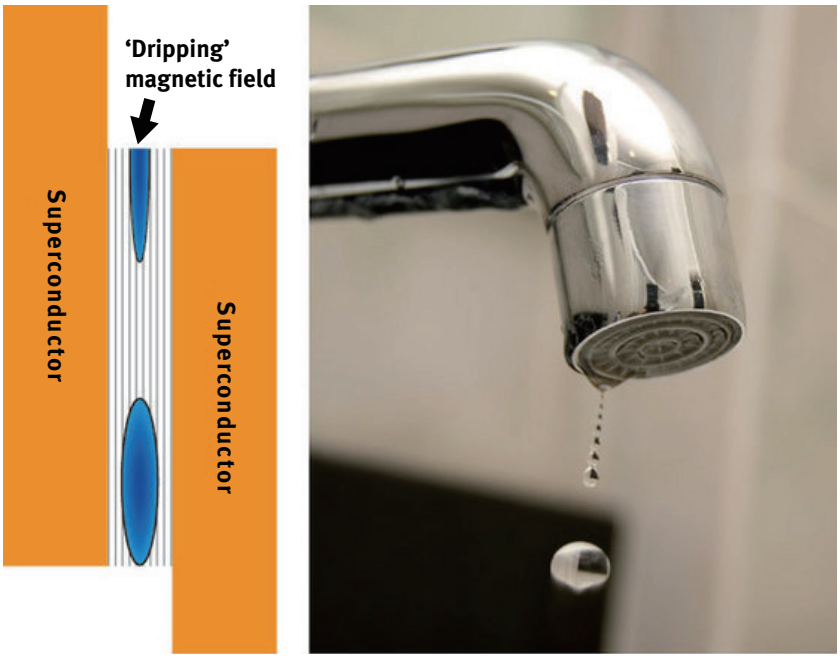


Figure 1: Dripping faucets. The schematic diagram (left) shows how quanta of magnetic flux (blue ellipses) first form and then successively slide down between stacks of Josephson junctions between by two high-temperature superconductors (orange). The process is similar to a dripping water faucet (right).

Superconductors show many intriguing magnetic phenomena including their well-known penchant for expelling magnetic fields. This effect is the origin of popular images where superconductors hover weightlessly above a magnet. However, sufficiently strong magnetic fields can enter certain superconductors in tiny units known as magnetic flux quanta. In particular, magnetic field infiltration of so-called Josephson junctions formed by the interface of two superconducting materials is complex, and how such flux quanta tunnel across these junctions is not clearly understood.

Now, a team of researchers from RIKEN's Frontier Research System in Wako and the University of Michigan has established a theory that describes tunneling across Josephson junctions of layered high-temperature superconductors[1]. Until its recent experimental demonstration, this process was considered to occur only in conventional superconductors and be suppressed in high-temperature ones, as the latter show fundamentally different properties.

A complex quantum theory developed by the researchers now explains these observations. "The tunneling of a magnetic flux quantum has a close analogy with water dripping from a tap," explains Franco Nori, who is part of the team. If a tap is not turned off tightly, water slowly leaks out and forms a droplet. As soon as a critical mass is reached, the droplet falls (Fig. 1).

A similar effect occurs in layered superconducting materials. When the externally applied electric current across the Josephson junction is far below the maximum superconducting current, the 'droplets' of magnetic flux quanta cannot pass through the junction: the tap is closed. However, sufficiently high external currents can result in the leakage of magnetic flux quanta, says Sergey Savel'ev from the RIKEN team. "As soon as a flux quantum is created, it passes through the junction, just like a falling drop of water."

According to Nori, the discovery of this novel behavior could have practical implications. "These results could open a new avenue of using such high-temperature layered superconductors for quantum electronics applications," he says. In particular, such structures could be used as sensitive read-out devices for superconducting quantum computers.

While such applications will not be realized in the near future, the theory proposed by the researchers offers a fundamentally new view into the subtle interactions between magnetic flux quanta and the superconducting state. ■

See also animations at:
http://dml.riken.jp/MQT/mgt.swf

1. Savel'ev, S., Rakhmanov, A. L. & Nori, F. Quantum terahertz electrodynamics and macroscopic quantum tunneling in layered superconductors. *Physical Review Letters* **98**, 077002 (2007).

How the brain gets its message across

Timing is essential when it comes to the distribution of information across the brain

Our brain handles huge amounts of information about everything we see, hear, taste, feel, think and do. All this information needs to be processed and transported across different sections of the brain. This is a huge task and the brain's solution is to process everything in parallel through a network of brain cells, the neurons.

Neurons are interconnected and, depending on the input they receive from other neurons, they 'fire' and send spikes of signals to other cells (Fig. 1). This is a very dynamic process and the feedback the neurons receive from each other is essential to it.

The challenge for scientists, however, is to understand how neurons are able to handle such vast quantities of information in order to realize parallel processing of information. Transmitting such a huge amount of information across the brain creates a significant logistics problem, and previous theoretical simulations have not achieved a sufficient amount of variety in neuronal spike patterns to explain the complexity in the brain's activity. Now, as reported in *Physical Review Letters*[1], Pulin Gong and Cees van Leeuwen from the RIKEN Brain Science Institute at Wako have discovered an answer to this problem.

The researchers have developed a theoretical model that is able to simulate a much larger transfer of information than previously thought possible. The model assumes long delays in the time it takes for feedback from other brain cells to reach a neuron—much longer than previously assumed. Once that period has passed, "the system gets a kick from the past" says van Leeuwen, which is important for the system to reach a meta-stable state of sufficient complexity. During the period between feedback loops, individual neurons send signals in a carefully orchestrated manner. Significantly, the time difference between those individual neuron spikes is not fixed between sequences and can vary strongly. Taking signalling times into account, Gong and van Leeuwen found that the number of possible combinations of firing sequences is very large.

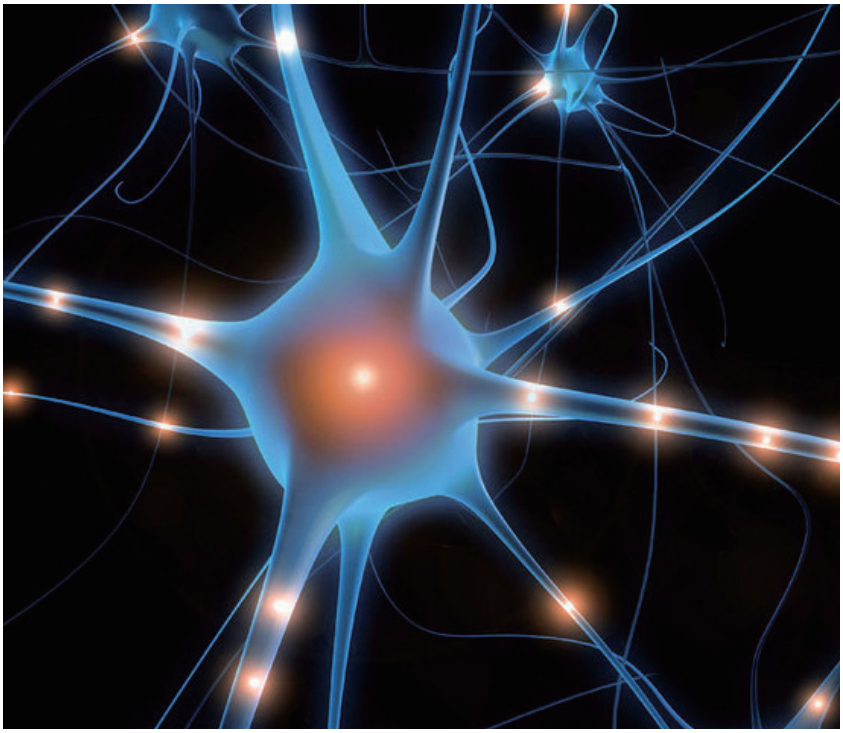


Figure 1: Depiction of a neuron in the process of firing and sending a number of signal spikes.

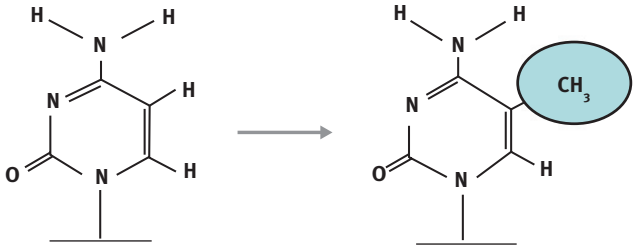
Experimental evidence appears to support this model, as generally the spiking times and patterns correspond to observations made in animal brains. However, "the role of the inhibitory neurons in generating these patterns is yet to be tested in experiments", explains van Leeuwen. While the details of the model therefore remain to be verified, their work represents a significant change in our understanding of how the brain processes large quantities of information. ■

1. Gong, P. & van Leeuwen, C. Dynamically maintained spike timing sequences in networks of pulse-coupled oscillators with delays. *Physical Review Letters* **98**, 048104 (2007).

Gene silencing at long range

Researchers demonstrate the role of methyl groups in regulating early mammalian development

Genes & Development



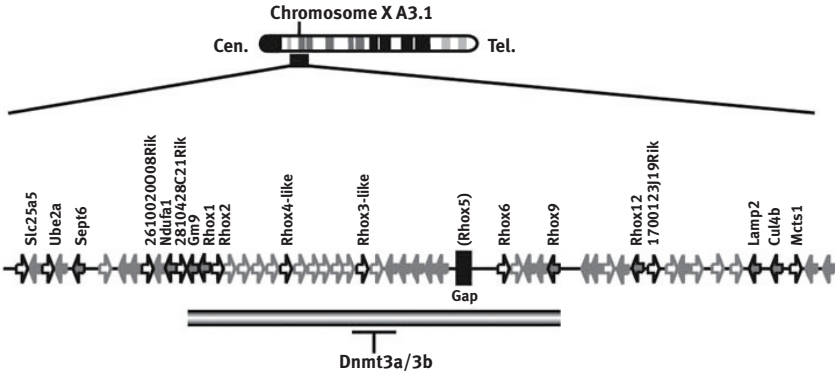


Figure 2: An example of methylation (top). The cluster of genes on the X-chromosome affected by Dnmt3a/3b (bottom).

Researchers at RIKEN and their US colleagues have provided solid evidence of the way in which early mammalian development is regulated. The team has demonstrated how enzymes keep selected genes inactive during periods of development by adding methyl (-CH_3) groups to them.

The work has specific relevance to the means by which stem cells are programmed and reprogrammed, and also to cloning procedures. Abnormal methylation may also explain the body's failure to suppress tumors in some cancer patients.

Development of multicellular organisms is achieved by switching genes on and off in a highly controlled manner over time and space. It has long been known that the addition of methyl groups to genes shuts them down. Enzymes known as DNA methyltransferases (Dnmts) are involved. Dnmt3a and Dnmt3b establish methylation, and Dmnt1 maintains it.

In a recent paper in *Genes and Development*[1] the research team based at the RIKEN Center for Developmental Biology in Kobe and at the Novartis Institute for Biomedical Research in Cambridge, US, reports on studies on the reproductive homeobox or *Rhox* family of genes at the blastocyst stage of embryonic development in the mouse. The blastocyst is a ball of about 100 cells which implants in the uterus. At implantation, the *Rhox* genes are switched off in those cells of the blastocyst which become part of the developing embryo (Fig. 1), but many of the *Rhox* genes remain active in cells which will eventually form the placenta.

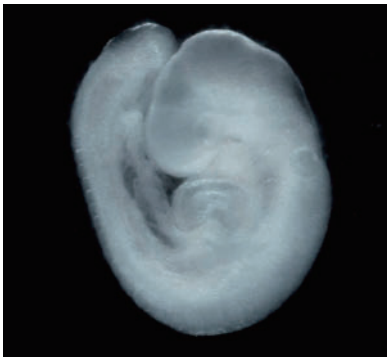


Figure 1: A developing mouse embryo.

The researchers focused on *Rhox6* and *Rhox9* in both embryonic and placenta tissue before and after implantation. They were able to show that these genes became highly methylated only at implantation and only in embryonic tissue. So the process was time and space dependent.

When the *Dnmt3a* and *Dnmt3b* genes are disabled individually the level of methylation of the *Rhox* genes in embryonic tissue is reduced. Knocking out both genes at once shuts down methylation completely. In fact, the impact of *Dnmt3a/3b* was found to extend over a substantial cluster of genes including the *Rhox* family and its neighbors (Fig. 2). Using stem cells as models in the laboratory, the research team showed that the methylation of many of these genes could be restored by adding active *Dnmt3a* genes.

"The study provides a solid demonstration of a specific regulatory role for DNA methylation in mammalian development," says team leader, Masaki Okano. The group now wants to elucidate details of the mechanism of the process and discover the key molecules that determine its specificity. ■

1. Oda, M., Yamagiwa, A., Yamamoto, S., Nakayama, T., Tsumura, A., Sasaki, H., Nakao, K., Li, E. & Okano, M. DNA methylation regulates long-range gene silencing of an X-linked homeobox gene cluster in a lineage-specific manner. *Genes & Development* **20**, 3382–3394 (2006).

Heading in the right direction

Fish and mice provide insight into the evolution of the head

RIKEN researchers and colleagues in the US have determined that, with the exception of the bony fishes, the molecular regulators of head development have been deeply conserved during the evolution of vertebrates, the animals with backbones.

On an evolutionary line from primitive skate species through to the mouse, the researchers found that the gene known as *Otx2*, which directs development of the head region and the brain, is activated at different times and places by at least two distinct enhancers. In the bony fishes or teleosts that branch off this line early on, however, only one of these enhancers is employed.

The head is the structure that has undergone the most change during vertebrate evolution, and its development helps set the body plan for all vertebrates. The work is important because it reinforces suggestions that significant evolution in vertebrates can result not only from changes in genes themselves, but also from subtle variation in the way those genes are regulated.

The regulator conserved in all vertebrates is known as the forebrain/midbrain (FM) enhancer, because it switches *Otx2* on at the time of development of that particular region of the head. But in all vertebrates, except for the bony fishes, there is a second regulator in addition to FM. The anterior neuroectoderm (AN) enhancer activates the *Otx2* gene at an earlier time than FM to initiate development of what becomes the bulk of the brain in mammals–the cerebellum and hypothalamus.

The researchers from RIKEN's Center for Developmental Biology in Kobe and the Benaroya Research Institute in Seattle, US, recently published details of the activity of the teleost FM enhancer in zebrafish[1]. They found that this enhancer also takes on the role of the AN enhancer. But the teleost FM enhancer does not use the same mechanism as that of AN in activating *Otx2* at the appropriate time. It binds with a different set of compounds to act upon the gene. These compounds are also present in mouse embryos (Fig. 1). And, using transgenic mice, the researchers found that the zebrafish FM enhancer was active in mice and, in the absence of AN, could switch on *Otx2*.

The researchers also analyzed *Otx2* DNA sequences in species of skate and coelacanth, considered to represent an earlier stage of evolution than either mice or zebrafish. These species both carried AN and FM enhancers closely related to those found in mice. So, the researchers infer that this was the ancestral condition. ■

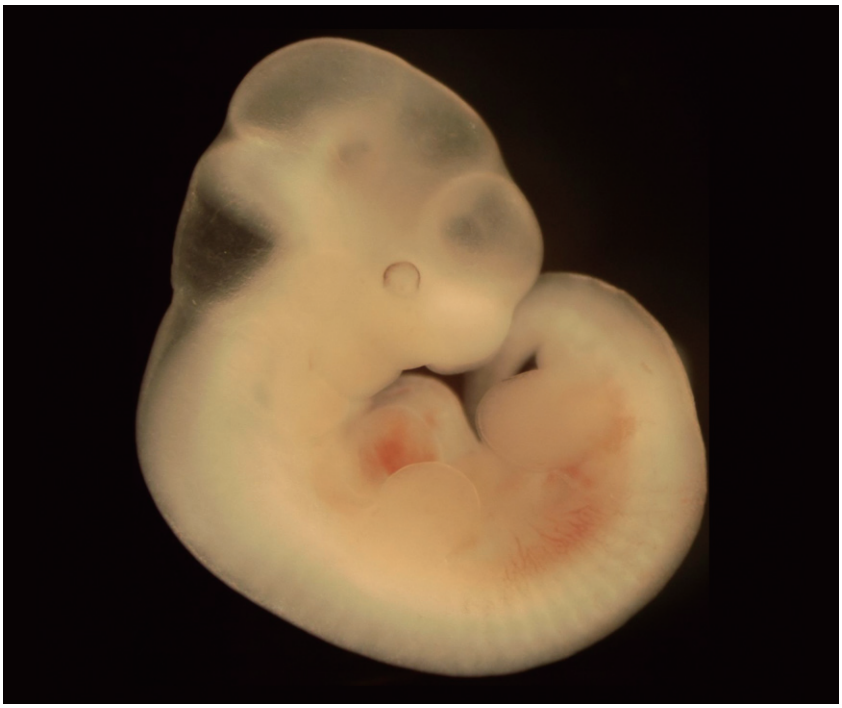


Figure 1: A mouse embryo. The gene that initiates development of the brain in the mouse can be activated by a zebrafish enhancer, even though the biochemical mechanism differs.

1. Kurokawa, D., Sakurai, Y., Inoue, A., Nakayama, R., Takasaki, N., Suda, Y., Miyake, T., Amemiya, C. & Aizawa, S. Evolutionary constraint on *Otx2* neuroectoderm enhancers – deep conservation from skate to mouse and unique divergence in teleost. *Proceedings of the National Academy of Sciences US* **103**, 19350–19355 (2006).

Picking up the scent of olfactory neuron differentiation

New findings may explain how the body generates a diverse population of neurons capable of detecting an array of distinct odors

A recent study identifies a signal that ensures that the fruit fly brain can sense a variety of smells. The olfactory sensory system of flies, which closely resembles those of vertebrates, contains many olfactory receptor neurons (ORNs), each of which expresses one of 60 odor receptors. Upon detection of its specific odor, each olfactory receptor fires a signal into the neuron. Each neuron routes this signal through an appendage called the axon, towards a structure called the glomerulus. Each glomerulus gathers and processes signals from neurons expressing a given odorant receptor.

Keita Endo and colleagues in the laboratory led by Chihiro Hama, a scientist at RIKEN's Center for Developmental Biology in Kobe, set out to determine how precursor cells can give rise to the diverse assortment of ORNs found in the antennae, an external organ of the fly head. Their work is published in *Nature Neuroscience*[1].

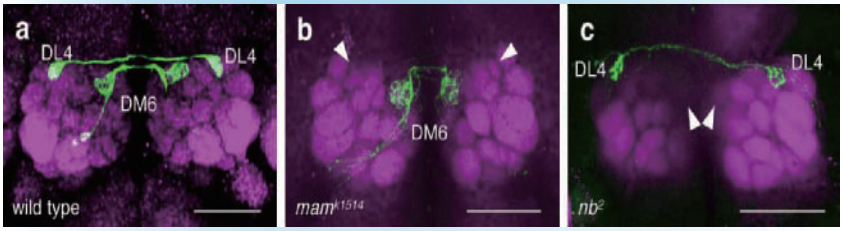
The researchers hypothesized that flies having a flaw in a signaling pathway required for ORN diversification might exhibit altered odorant receptor expression and targeting of ORN axons. They used chemical mutagenesis to create a collection of flies containing genetic defects, and examined ORN axon–glomeruli connections and odorant receptor expression patterns in each mutant fly.

In unmanipulated flies, each ORN within a pair of ORNs projected an axon toward a distinct glomerulus. However, in one mutant fly, both ORNs in a pair sent axons toward a single glomerulus (Fig. 1).

Extensive genome mapping tracked the chemically induced alteration to a gene called *mastermind* (*mam*). This gene is required for transmission of signals emanating from the cell surface receptor Notch, a protein previously implicated in the generation of asymmetry among 'sibling' precursor cells. ORN–glomeruli connections were altered in a reciprocal fashion in flies expressing a defective version of the *numb* gene, which encodes a protein needed to shut down Notch signals.

These data indicate that some ORN–glomeruli connections are forged only in the presence of Notch signaling whereas others are made only in the absence of Notch signaling. Similar observations were made with regard to odorant receptor expression patterns.

Thus, variations in Notch signaling bestow upon ORNs distinct axon targeting cues and odorant receptor profiles. However, "Notch signaling is only one of the mechanisms regulating neuronal diversity," cautions Hama. "More extensive studies are necessary to uncover the whole story. We suspect that Notch-mediated diversification may contribute to the framework of the olfactory circuitry by controlling connectivity between ORNs and second-order neurons." ■



Nature Neuroscience

Figure 1: Two classes of ORNs derived from the same precursor cells normally project to two distinct glomeruli (DM6 and DL4) (a). Mutations in the *mam* (b) and *numb* (c) genes cause reciprocal phenotypes.

1. Endo, K., Aoki, T., Yoda, Y., Kimura, K. & Hama, C. Notch signal organizes the *Drosophila* olfactory circuitry by diversifying the sensory neuronal lineages. *Nature Neuroscience* **10**, 153–160 (2007).

Protecting pigs with modified maize

The introduction of a foreign gene into maize plants may help reduce the damage done by fungal infections

Maize is one of the world's primary agricultural crops, although the majority is used to feed livestock rather than humans. It is also vulnerable to infection by a variety of fungal pathogens, many of which produce compounds that are toxic both for infected plants and the animals that ultimately consume them.

Genetically-modified (GM) crops have been viewed as a promising solution for thwarting fungal infections, although progress to date has been limited. "The difficulty in developing disease-resistant GM crops is the lack of appropriate transgenes that efficiently control disease, [and] kill invading microbial pathogens either directly or through the activation of plant defense mechanisms," explains Makoto Kimura of the RIKEN Discovery Research Institute in Wako.

In collaboration with Isamu Yamaguchi, former Group Director of the RIKEN Plant Science Center in Yokohama, Kimura and his colleagues have been pursuing strategies for protecting maize against the ear rot fungus *Fusarium graminearum*. Among other toxins, *Fusarium* produces the estrogen-like compound zearalenone (ZEN), which can cause a variety of breeding problems in swine that consume infected maize. Maize has no natural means for eliminating ZEN; however, recent work by Kimura and colleagues has identified *zhd101*, a fungal gene encoding an enzyme with efficient ZEN-degrading activity, which the group subsequently cloned[1].

Having established *zhd101*'s potential as a detoxifying transgene, Kimura's group has now generated transgenic maize crops that express this enzyme[2]. Initial *in vitro* experiments demonstrated that seed extracts from the transgenic seeds were capable of rapidly degrading ZEN in solution. In subsequent *in vivo* experiments, entire seeds were soaked in a high-concentration ZEN solution; at the end of the experiment, the wild-type seeds contained more than 15 times as much ZEN as the transgenic seeds.

Transgenic seeds proved equally capable of eliminating the ZEN mycotoxin following actual infection with *Fusarium*—a promising indicator of this transgene's potential for crop protection. However, Kimura cautions that this fungus also produces other, unrelated mycotoxins like deoxynivalenol (DON), which is not affected by *zhd101* expression. "Removing only ZEN is not sufficient for consumption as animal feed—it is also necessary to develop a strategy to decontaminate DON," he says.

Rather than targeting individual compounds, however, Kimura's top priority now is to better understand general mechanisms for maize disease resistance. "The isolation of fungal molecules essential for pathogenesis—and affected target proteins from host plants—will be indispensable," he says. "With such knowledge…GM crops may offer a possible solution for the problems caused by phytopathogenic fungus in the future." ■

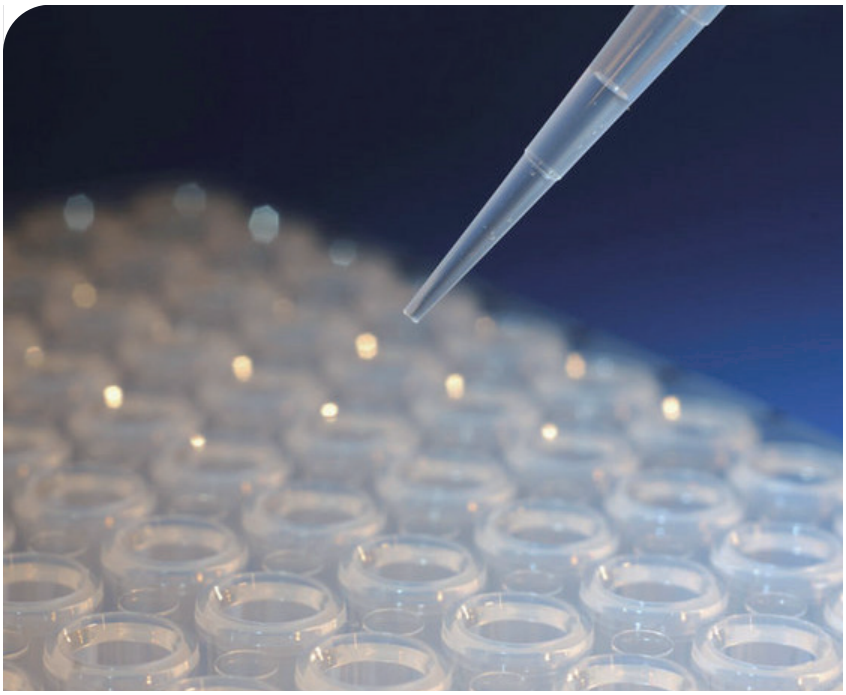
1. Takahashi-Ando, N., Kimura, M., Kakeya, H., Osada, H. & Yamaguchi, I. A novel lactonohydrolase responsible for the detoxification of zearalenone: enzyme purification and gene cloning. *Biochemical Journal* **365**, 1–6 (2002)
2. Igawa, T., Takahashi-Ando, N., Ochiai, N., Ohsato, S., Shimizu, T., Kudo, T., Yamaguchi, I. & Kimura, M. Reduced contamination by the *Fusarium* mycotoxin zearalenone in maize kernels through genetic modification with a detoxification gene. *Applied and Environmental Microbiology* **73**, 1622–1629 (2007).

Better folds and yields with zinc

Laboratory-based production of zinc-binding proteins optimized

Researchers from several Japanese research institutes have determined the best conditions to synthesize zinc-binding proteins in a test tube. Zinc ions are a critical co-factor needed by many proteins for their proper folding and function. Indeed, it has been estimated that 3% of the human genome encodes zinc-binding proteins, including those that are involved in gene transcription, DNA replication, metabolism and cell signaling.

Shigeyuki Yokoyama from the RIKEN Genomic Center in Yokohama and the University of Tokyo, and his colleagues from RIKEN and other Japanese research institutes report that adding zinc during the synthesis of zinc-binding proteins in a cell-free system optimizes their production. Their findings are published in the *Journal of Structural and Functional Genomics*[1].

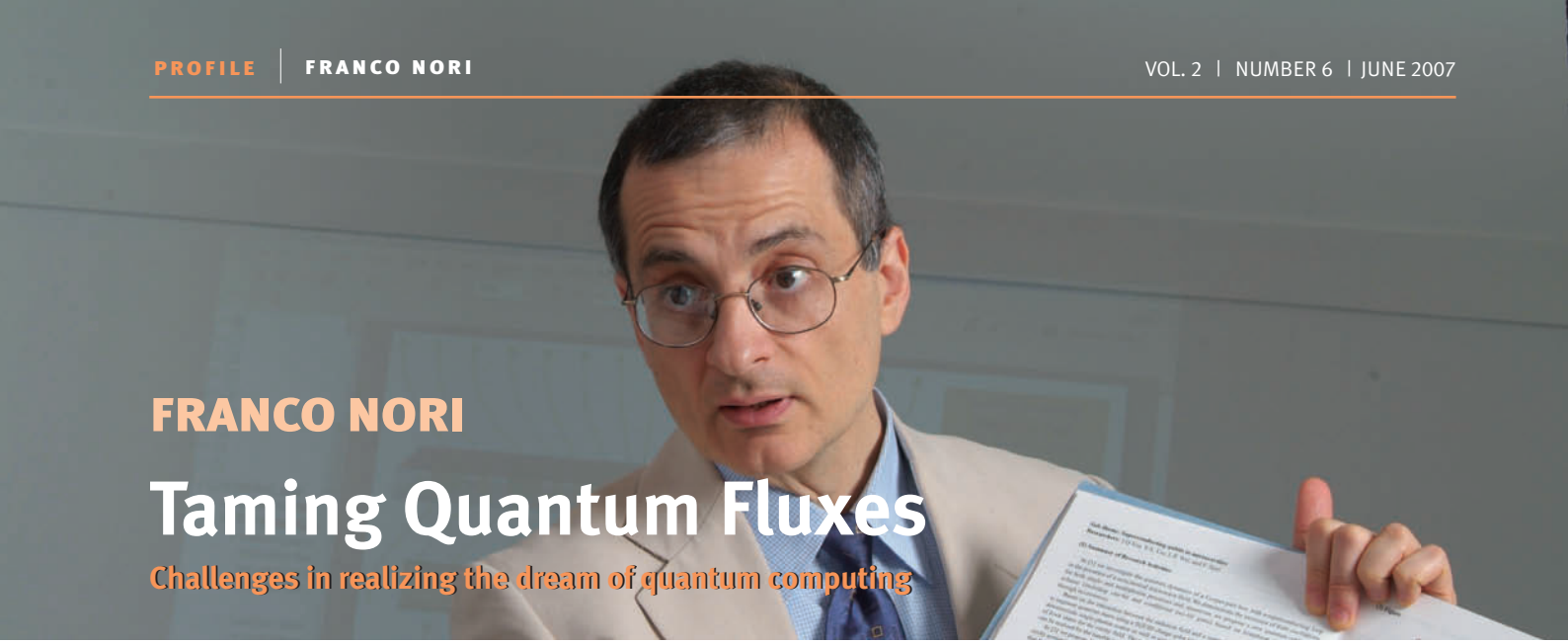


Cell-free systems are composed of extracts from cells that consist of all the cellular components needed to transcribe and translate a given gene. All that is needed to activate the system is the DNA encoding the gene of interest. Given that only this DNA will be present, all the energy of the system is then devoted to the synthesis of just a single protein. Thus, once the DNA is added, in a few hours large quantities of the protein encoded by the gene are soon available for purification by standard methods. The purified protein can then be used for further studies, such as structural and/or functional analysis.

Yokoyama and his team found that for zinc-binding proteins, the addition of zinc during the protein translation process increases both the yield and the stability of the protein due to more proper folding during its synthesis. They confirmed these results by measuring the folding of the purified protein using the technique known as nuclear magnetic resonance (NMR) spectroscopy. The team also demonstrated that the isolated protein had normal function, as shown by specific DNA binding.

According to Yokoyama, the advantage of the cell-free system over cell-based protein synthesis systems is that ligands or co-factors that are necessary for the proper folding and activity of a given protein can be added during its synthesis, even those that are usually unable to cross the cell membrane. These studies could be extended to proteins requiring other small molecule cofactors, such as copper or small metabolites, he notes. ■

1. Matsuda, T., Kigawa, T., Koshiba, S., Inoue, M., Aoki, M., Yamasaki, K., Seki, M., Shinozaki, K. & Yokoyama, S. Cell-free synthesis of zinc-binding proteins. *Journal of Structural and Functional Genomics* **7**, 93–100 (2006).



FRANCO NORI

Taming Quantum Fluxes

Challenges in realizing the dream of quantum computing

Future quantum computers are expected to solve problems within seconds that existing supercomputers couldn't solve in years. The Single Quantum Dynamics Research Group at RIKEN leads the world in developing this dream computer. The group studies quantum phenomena occurring in the microscopic world and aims to apply it to develop epoch-making devices and materials as well as information technology. Developing a quantum computer is one of the groups' ultimate objectives. This research is part of the activities of the Digital Materials Laboratory that oversees theoretical studies central to the genesis of new ideas to manipulate and utilize novel quantum phenomena.

Taming Flux Quanta

Superconductors exhibiting zero electrical resistance below a certain critical temperature are used to fabricate powerful magnets, or highly sensitive magnetic sensors in equipment such as magnetic resonance imaging systems (MRI) used in medical applications. Superconductors are also slated for use in power transmission lines and power storage equipment.

However, superconductors are sensitive to magnetic fields. When superconductors are exposed to an intense magnetic field, magnetic field lines penetrate the superconductor in the form of millions of ultra-fine threads, each one of these carrying a 'flux quantum' (Fig. 1). This quantum of flux is the minimum possible unit of magnetic flux, and is the magnetic analog of the electron charge, which is the quantum of electricity.

When applying a large current to a superconductor or when improving the accuracy of highly sensitive magnetic sensors based on superconducting devices, it is necessary to stop the motion of these flux quanta, since their motion dissipates energy. Flux quanta can be temporarily stopped, trapped, or 'pinned', by deliberately putting impurities in a pure crystal to form defects. However, for decades, precisely controlling the motion of flux quanta was difficult since their movement could not be observed.

Then, in the 1990s, a group at Hitachi, led by Akira Tonomura, developed the 'holography electron microscope' and directly visualized the movement of flux quanta. Tonomura went on to establish the Single Quantum Dynamics Research Group at RIKEN and was inaugurated as the group's director in October, 2001. He then visited the US and recruited Franco Nori as the Laboratory Head.

"Dr Tonomura told me to act as the 'glue' bonding several laboratories," laughs the Venezuelan-born Nori, since his name literally means 'glue' in Japanese. After graduating from the University of Illinois with a Masters and a PhD, Nori completed postdoctoral work at the University of California. He then became a professor at the University of Michigan before accepting the joint RIKEN position. Nori's lifelong curiosity and penchant for building and tinkering with machines, devices, and computers stood him in good stead for a scientific career that has produced achievements well-received by the international scientific community.

Nori pioneered the research area of controlling the motion of tiny particles and flux quanta. One method for manipulating these is to form regular microscopic structures in superconductors. For example, triangular magnetic structures can trap flux lines moving inside a nearby superconducting layer (Fig. 2). For certain values of the externally applied magnetic field, three flux quanta (red) will be caught in one of the triangular structures. The flux quanta (blue) outside of the triangular structures can move freely. If an AC current is applied, the flux quanta can move freely within a confined area as the direction of the current changes. In contrast, the flux quanta caught in the triangular structures jump in the same direction of the next triangular element. Therefore, with microscopic structures embedded in materials, the direction in which flux quanta move can be controlled. A mechanism allowing movement only in a certain direction like this acts as a 'quantum diode' and is called a 'ratchet structure' (Fig. 3).

In 2005, Tonomura and colleagues succeeded in using the holography electron microscope to observe in detail unidirectional movement of flux quanta in a ratchet structure. According to Nori, the ratchet structure may be applicable to control other types of particles, in addition to flux quanta, and may see the development of a minute motor exploiting the energy of Brownian movement, where particles move randomly in all directions.

Manipulating flux quanta with applied currents

Nori's group also proposed the novel idea of manipulating flux quanta by controlling an applied AC current—an idea that was recently verified by experiments. "Imagine plates on a tablecloth," says Nori. "If the tablecloth is pulled slowly, the plates will move with it. And, if the tablecloth is successively pulled slowly-and-quickly, the plates can move in one direction only: the direction of slow pull. Similarly, billions of flux quanta can be manipulated at will by properly controlling the applied AC current," he explains.

Since building a special microscopic structure in a superconductor is unnecessary using this approach, this method may be advantageous for practical applications. Controlling at will the motion of flux quanta can enhance the performance of superconducting devices.

Quantum computers for super fast calculations

An ultimate goal of Nori's group is to develop circuit designs that could be useful in next-generation quantum information processors. Still in its very early stages, some of these early prototypes now use flux quanta to complete simple operations.

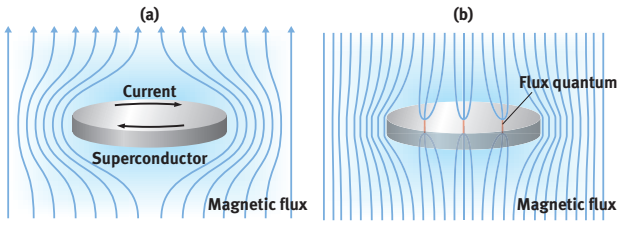


Figure 1: A flux quantum.
(a) A superconductor tends to repel magnetic fields. (b) However, when a superconductor is exposed to an intense magnetic field, this breaks up into billions of tiny magnetic filaments, each carrying a "flux quantum", the minimum possible amount of magnetic flux inside a superconductor.

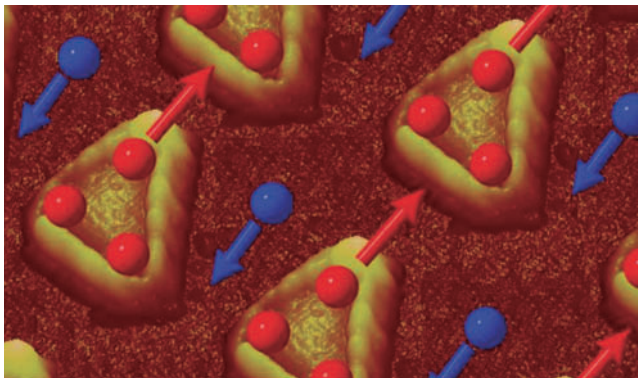


Figure 2: Triangular magnetic structures that can trap flux quanta.

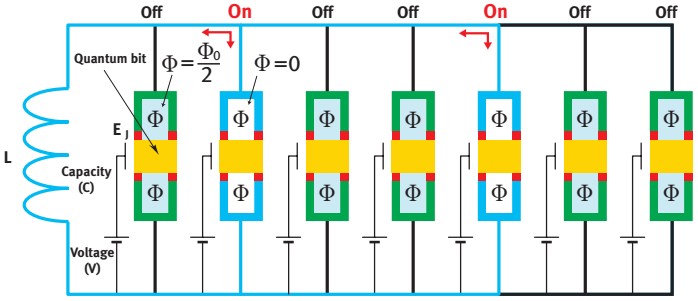


Figure 4: Circuit design for integrating quantum bits.
Quantum entanglement can be generated by coupling selected quantum bits, which are not necessarily adjacent to each other. This can be done by connecting several quantum bits with a common coil structure (inductance: L).

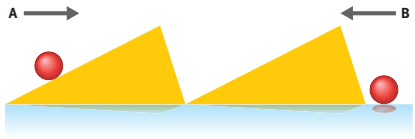


Figure 3: Schematic diagram of a simple ratchet structure. It is easy to move a ball in the direction of A, but hard in the direction of B due to the steep uphill slope.

Existing computers and quantum computers calculate by modifying the two bit states '0' and '1' in a logic gate, but a quantum bit can represent the states of '0' and '1' simultaneously, thus allowing parallel processing of vast amounts of data.

In the past few years, several groups have begun experiments testing possible circuit designs that might be useful for these future computing devices. However, to solve a practical numerical calculation with a quantum computer, it is necessary to integrate hundreds of quantum bits in complex circuits, and achieve 'quantum entanglement', or strong interaction of specific bits.

Building a quantum computer with a superconductor

In 1999, a group at NEC led by Jaw-Shen Tsai succeeded in creating a quantum bit using a superconducting (Josephson-type) solid-state device. Solid-state devices have the potential to facilitate the integration of quantum bits to design circuits. Tsai was inaugurated as the Laboratory Head of the Quantum Coherence Laboratory, Single Quantum Dynamics Research Group at RIKEN. His group succeeded in 2002 in producing a logic gate generating quantum entanglement of two quantum bits.

The logic gate created by Tsai and colleagues couples two quantum bits directly and generates quantum entanglement. However, at this stage, only adjacent quantum bits generate quantum entanglement. Nori's group has proposed a circuit design that selectively induces interactions between specific quantum bits by coupling several quantum bits with a common coil structure (inductance) (Fig. 4).

With this design, it is theoretically possible to generate quantum entanglement of specific bits by integrating hundreds of quantum bits necessary for realizing a quantum computer. Although quantum computing devices are now being studied at different laboratories worldwide using various methods, currently, the realization of quantum entanglement is difficult and ideas for entanglement-generating circuits are limited. The Digital Materials Laboratory has been proposing circuit designs to overcome the many obstacles present in building these complex devices.

"It is necessary to quickly generate quantum entanglement of specific quantum bits such that they do not influence other quantum bits," says Nori, outlining future challenges to be overcome. "It is also a challenge to confirm that quantum entanglement has actually occurred, or to do many operations, or to perform quick read-outs of the outputs. Although some manufacturing errors are inevitable in any solid-state device, it is necessary to develop circuits and computational procedures (algorithms) which are robust against component variations."

Nori's group has published a series of new ideas for overcoming these very difficult problems. Explaining how novel ideas are produced, Nori says: "We often actively discuss with experimental teams. We always have visitors from all over the world. An intense and dynamic exchange of ideas is a strong point of our laboratory."

On realizing the dream of developing future quantum information technologies, Nori believes that: "Since the study of quantum information processing has just started, it is too early to forecast the concrete time of utilization. It is not known now which device or system (e.g., ion traps, atoms, photons, spins) will be more fruitful in the long run for this task. The possibility is still open to all. Therefore, at this point this is a very exciting area of research, full of open problems and challenging questions."

Nori is grateful to the outstanding leadership of Tonomura, and of Kohei Tamao and Ryoji Noyori, also from RIKEN. "Scientific leaders of such high caliber motivate others to also do top-quality science of high international visibility."

About the researcher

Professor Franco Nori was elected Fellow of the American Physical Society in 2002 "for innovative theoretical contributions to the study of vortex dynamics in superconductors, dynamical instabilities, Josephson junction arrays, and quantum interference." In 2003, he was elected Fellow of the Institute of Physics in the United Kingdom. He has received an "Excellence in Research Award" and an "Excellence in Education Award" from the University of Michigan, USA. He has given more than 200 presentations worldwide, and published more than 200 papers on his research, including numerous publications in the highest impact journals (Science, Nature, Nature Materials, Nature Physics, as well as over 45 publications in Physical Review Letters, which is widely considered to be the top journal in physics). He obtained a Masters and a PhD in Physics from the University of Illinois and completed postdoctoral work at the University of California. He then became a Professor at the University of Michigan and afterwards Laboratory Head at RIKEN.

Using ultra-thin membranes to solve environmental problems across the world

Toyoki Kunitake

Laboratory Head, Topochemical Design Laboratory
Group Director, Spatio-Temporal Function Materials Research Group
Frontier Research System
RIKEN Wako Institute

It is said that in the 21st century we will face a shortage of water resources, which will be more serious than the problems with oil shortages. The Topochemical Design Laboratory successfully created a new material with the potential to contribute in a major way to solving such resource and environmental problems. The material is only 20 nm thick (two millionths of a centimeter), in the form of a huge nanomembrane, with an area of several square centimeters. It is expected that we will be able to produce inexpensive fresh water by using the huge nanomembrane as a reverse osmosis membrane in seawater desalination plants, and also improve power generation efficiency by using the film as an electrolyte membrane, which is the heart of the fuel cell.

The Essential function of huge nanomembrane is the 'separation'

The huge nanomembrane created by Toyoki Kunitake, who is Head of the Laboratory, is about 20 nm thick. Ten thousand films of this membrane laid on top of each other reach only the thickness of a postcard (about 0.2 mm). In fact, the human body has the same kind of ultrathin membrane with exquisite capabilities, namely the cell membrane. This is 5-10 nm thick, surrounds the cell, and is equivalent in thickness to two lipid molecules (Fig. 1).

Kunitake says, "The cell membrane plays the role of separator between the internal and external regions, taking in substances and information necessary for the cell, and discharging unnecessary substances. In other words, the cell membrane separates necessary compounds from unnecessary compounds. Both in living things and as an artificial material, 'separation' is the essential function of a membrane."

Kunitake successfully created this, the world's first artificial membrane, at Kyushu University, with a structure and thickness similar to those of the cell membrane. When molecules such as soap are dissolved in water, they naturally aggregate together and create a membrane structure. The phenomenon in which molecules naturally gather together and create a structure like this is called 'self-organization'. This phenomenon is actively applied in nanotechnology to manipulate molecules and atoms to produce new materials and devices with unconventional functions. Kunitake has used this self-organizational approach to create thin films with various kinds of properties. In 1999, he started the Topochemical Design Laboratory at RIKEN to work on the challenge of creating nano-structures, which were considered impossible to achieve in those days.

Creating a huge nanomembrane!

"All the other researchers knew that a huge nano-precision nanomembrane, with a large area, could drastically contribute to an expanding range of applications. Researchers had been able to create huge nanomembranes, but they

were easily torn. A good example is a huge soap bubble. However, a practical membrane material to be used for separating substances should be strong and free from pores. The vast majority of scientists thought that it would be a major challenge to create a huge membrane that could be used practically in industry."

Then, how did Kunitake succeed in creating these huge nanomembranes?

"We started to investigate how to create thin ceramic films at RIKEN. They are created on a substrate such as glass. It is comparatively easy to create even a nano-precision membrane with a huge area on a substrate. However, the membrane usually tears when it is peeled off the substrate. We therefore tried inserting a layer between the ceramic film and the substrate so that the ceramic film could be easily peeled off. This technique allowed us to create a strong membrane that was just barely suitable as a material, and we thought that we would be able to create a stronger, huge nanomembrane successfully if we could add a little more flexibility to the membrane. We then tried to incorporate flexible organic molecules into a strong ceramic film to create a hybrid membrane."

Many researchers have conducted research into creating inorganic-organic hybrid membranes, but they came up against a wall. To create a strong membrane, we need to entwine inorganic molecules with organic molecules. However, it was very difficult to entwine them in a thin film because inorganic and organic molecules have different properties. We made repeated attempts to choose good combinations of inorganic and organic molecules and were eventually successful in creating a huge nanomembrane."

In this huge nanomembrane, an inorganic material called zirconia, a kind of ceramic, and an organic material called acrylic polymer, are used to create individual web structures. These two structures, in turn, create a combined web structure (Fig. 2). It is this combined web structure that contributes to strength and flexibility (Fig. 3). The first huge nanomembrane was 35 nm thick, but we have successfully reduced the thickness of the nanomembrane down to about 20 nm.

Kunitake and members of the Laboratory have clarified that huge nanomembranes exclusively composed of organic molecules can be created by using a much finer web structure. In practice they have succeeded in creating a huge nanomembrane composed of two kinds of organic molecules: epoxy oligomer and polyamine.

Producing inexpensive fresh water from seawater

What specific applications can we expect from huge nanomembranes? "A study in applications has not been conducted yet, but I think that huge nanomembranes can contribute in a major way, especially in environmental fields related to resources and energy, because technology that can separate necessary chemicals from unnecessary chemicals is important in these fields. For example, we may be able to produce inexpensive fresh water from seawater."

There is a fear that we will face more serious shortages in water resources because of rapid population growth, economic progress, changing climate due to global warming, and especially desertification. The worldwide water shortage is also a matter of life and death for Japan, which imports food produced overseas using water resources in large quantities; water resource shortages are directly linked to food production, which requires large volumes of water.

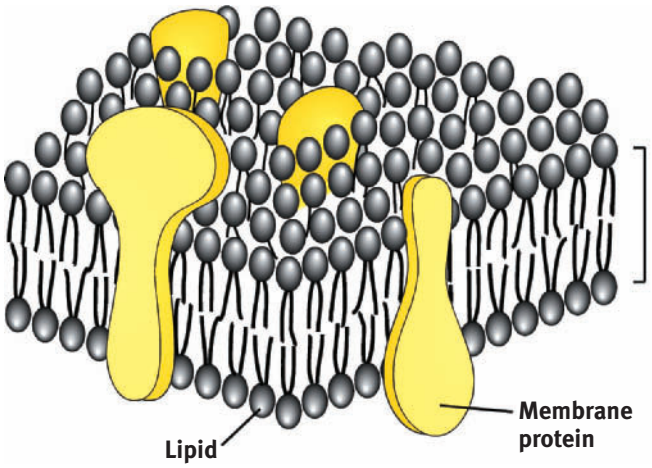


Figure 1 : The Structure of a cell membrane.

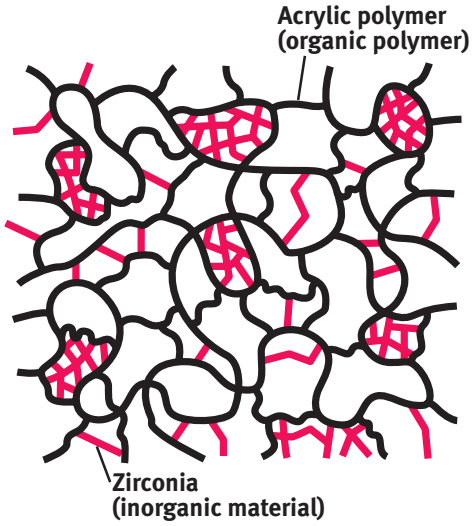


Figure 2 : The Structure of a huge nanomembrane.

It is hoped that technology to produce fresh water from seawater can solve water resource shortages. Oil-producing countries in the Middle East have tried various approaches, in which large amounts of energy were consumed to produce fresh water from seawater.

However, many countries are beginning to adopt an alternative approach based on a less energy-consuming reverse osmosis membrane technique, in which seawater under pressure is used to drive fresh water through a reverse osmosis membrane. This approach not only greatly helps to sanitize environments because of its applicability to purifying polluted water, but is also used in wastewater reclamation and producing the high-purity water necessary for semiconductor manufacturing.

"The world needs technology that can produce fresh water or clean water from seawater or polluted water with the least amount of energy, and at the lowest cost. The approach based on the reverse osmosis membrane technique also uses a certain amount of energy to pressurize the seawater or polluted water, but the thinner the reverse osmosis membrane, the less pressure needed, exerted by the seawater or polluted water."

The lowest thickness of reverse osmosis membrane currently used is several hundred nanometers. Thus, if we can use a huge nanomembrane that is one-tenth of that thickness as the reverse osmosis membrane, we will be able to greatly reduce energy consumption, and produce fresh water or clean water at low cost.

"The use of huge nanomembranes may lead to efficient recovery of scarce resources, such as uranium or gold dissolved in seawater in minute amounts," says Kunitake, expanding his dream.

The use of huge nanomembranes will make it possible to improve the power generation efficiency of fuel cells, which have been under development for clean power generation systems. Several types of fuel cells are available, but the fuel cell based on electrolyte membranes has been attracting attention as one type suitable for automobiles and household use.

"The electrolyte membrane is a membrane that allows only hydrogen ions to pass through it. The thinner this electrolyte membrane, the higher the power generation efficiency of the fuel cell."

Electrolyte membranes currently used are about 10 to 100 μm thick. Application of large-area nanomembranes as electrolyte membranes can reduce this thickness by three to four orders of magnitude or more, and significantly improve the power generation efficiency.

Using the advanced capabilities of the cell membrane

The cell membrane functions in an advanced way because membrane proteins called 'ion channels' or 'receptors' penetrate through the membrane (Fig. 1). The membrane protein acts as a sensor that accepts information from outside, or a pathway that allows specific substances to move in and out of the membrane.

"A single membrane protein several nanometers in size has this kind of advanced capability. If we can embed many membrane proteins in a huge nanomembrane, we will be able to use these advanced capabilities of the membrane protein on a large scale."

It has been very hard to extract pure membrane proteins from the body and to use their capabilities because we could not produce a membrane with an area large enough, which is thin enough for a membrane protein to penetrate.

What applications can we expect from huge nanomembranes that replicate the capabilities of the cell membrane?

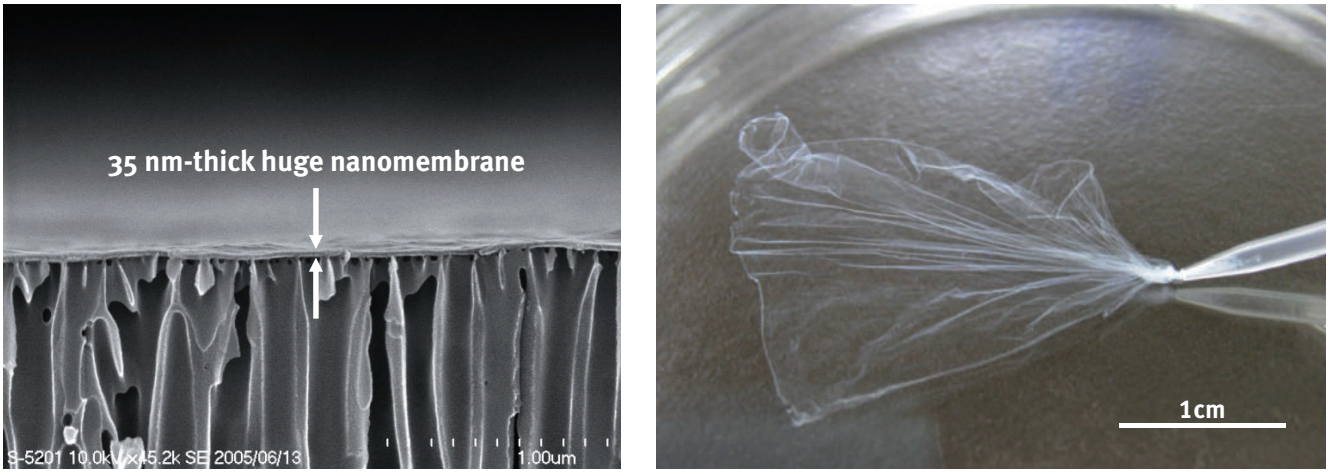


Figure 3 : A huge nanomembrane.
Left, a huge nanomembrane only 35 nm thick. This huge nanomembrane is so strong and flexible that it does not tear off, even if it is sucked into a pipette and discharged again (shown on the right).

"For example, a huge nanomembrane could be used as a high-sensitivity sensor to detect signs of disease," says Kunitake. When a person gets sick, certain molecules of the person's blood may increase. Thus, the development of a highly sensitive sensor capable of detecting extremely small quantities of molecules would greatly contribute to early disease detection.

The great potential of huge nanomembranes

A lipid molecule that constitutes a cell membrane has hydrophilic and hydrophobic repgions. In water, lipid molecules create a membrane structure on the basis of the self-organization principle, keeping each of their hydrophobic regions enclosed (Fig. 1).

"When we create an artificial membrane based on self-organization, the governing chemical principle itself is very simple. However, creating structures envisioned on the basis of such a simple principle requires sophisticated condition settings for molecular design and synthesis. To begin with, we make a hypothesis, and carry out experiments under various conditions. Of course, we will face repeated failure at first, but in the face of these experimental difficulties, the moment will come when we realize, "This is what I am looking for." That is the moment when the sophisticated conditions come into harmony with a simple principle and a new material is created, and also the most interesting moment in the research process. Once the material is created, we will soon find that what we did is only a simple thing. However, it is this simple thing that we cannot easily anticipate."

Finally, Kunitake talked about the significance of these findings as follows: "The significance lies in the fact that once we can create huge nanomembranes, many other researchers will start creating similar nanomembranes using different materials. The current Spatio-Temporal Function Materials Research Project is to end in the fall of 2006, but we want to put this potentially promising material to practical use in some way."

A new material is created when a simple principle is combined into harmony with sophisticated experimental conditions for molecular design and synthesis. ■

1. Thin membranes tough it out. *Riken Research* 1, 8 (August 2006).

About the researcher

Toyoki Kunitake was born in Fukuoka, Japan, in 1936. He received his BEng and MEng in applied chemistry from the Faculty of Engineering, Kyushu University, in 1958, and subsequently earned his PhD from the University of Pennsylvania in 1962. He then pursued the study of chymotrypsin catalysis kinetics at the California Institute of Technology. On returning to his alma mater as associate professor, he started research on polymerization processes and polymeric enzyme models. He then obtained his full professorship in the same department and began directing his research group in an extensive study on synthetic bilayer membranes. On the administration side, Kunitake served as Dean of Engineering at Kyushu University and has acted as principal investigator for various large national projects. Since his retirement from Kyushu in 1999, he has been head of the Spatio-Temporal Function Materials group at the Frontier Research System of RIKEN, as well as serving as Vice President of the University of Kitakyushu.

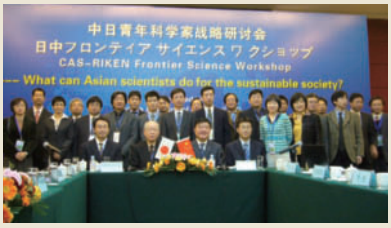
CAS-RIKEN Frontier Science Workshop at Beijing

From February 23 to 25, young researchers from China and Japan gathered in Beijing to discuss the theme 'What can Asian scientists do for the sustainable society?'

This workshop developed as the result of a meeting held in May 2006 between Zhu Chen, vice president of the Chinese Academy of Sciences (CAS), and Ryoji Noyori, president of RIKEN. The participants included 25 Chinese and Japanese researchers in their 30s and 40s who are organizing their own research groups and are expected to lead the future scientific community in each field. From RIKEN, the moderator, Hiroyoshi Sakurai from the Nishina Center for Accelerator-Based Science, and nine other researchers attended.

In the keynote speech, President Noyori exemplified some RIKEN research that could contribute to the sustainable society as: the salt-resistant rice crop generated by heavy-ion irradiation, recyclable organic conductors and a huge membrane of nanometer-order thickness that could aid the development of filtration and fuel cells. He also mentioned Bhutan, a country that has introduced gross national happiness (GNH) as a figure of merit instead of gross national product (GNP) and has continued to develop in its own way. He explained that in the 21st century, we should develop civilization based on each culture.

At the workshop, the participants discussed whether it was possible to understand nature



or life phenomena as a whole rather than by the reductionism and piecemeal analysis characteristic to modern science, and whether the science originating from native Asian culture could be developed.

Next year's workshop will be held in Japan and further discussion is expected to unfold.

Symposium on Reviving Measurement and Observation Technique in Japan

On May 10, a symposium entitled 'The Foundation of a Science and Technology Nation—Reviving Measurement and Observation Technique in Japan' was held, sponsored by the Science Council of Japan, the Ministry of Education, Culture, Sports, Science and Technology and RIKEN. There were many discussions among a full house of 250 attendees.

At the symposium, various Japanese measurement and observation techniques were presented, such as the photomutiplier that contributed to the detection of the neutrino by Masatoshi Koshiba, a Nobel Prize winner in Physics, and the electron microscope that enabled the structural analysis of water channels and the intraflagellar transport motor in cells. However, according to Akira Tonomura of the RIKEN Frontier Research System, recently, the government has been formulating a science and technology policy that tends to give higher priority to intensive short-term project research. Consequently the amount of long-term research to develop novel measurement and observation techniques is decreasing. Regarding this problem, some of the participants argued that building a common recognition of the concept of 'instrumentation' is necessary in Japan.

Koichi Tanaka from Shimadzu Corp. explained one reason for his success in the development of soft desorption ionization methods for proteins, which won a Nobel Prize in Chemistry, and attracted considerable attention. He said that it was 'team work', that is, the attitude of also taking an interest in other people's work and sometimes trying to help them if necessary. This attitude has been regarded as a problem for Japanese researchers as it can prevent people from inventing original ideas of their own. However, Tanaka said that to know other ways of conducting research and practicing science inspires further original research.

11th East Asian Workshop on Chemical Dynamics

Chemical dynamics, a science that elucidates the mechanism of chemical reactions at the level of quantum-mechanical motions of electrons and nuclei, now extends into a much broader range of research fields from gas-phase reactions to surface or biomolecular chemistry. With the aim of making a network among young Japanese, Taiwanese, and Korean scientists who have the potential to become world-class scientists, and of building a research community in Asia, the East Asian Workshop on Chemical Dynamics was first organized by Toshinori Suzuki of the RIKEN Discovery Research Institute (DRI) 10 years ago. It has now been held annually ever since.

The 11th Workshop was held in Tokyo for three days from May 8. Research results were presented in the fields of reactive scattering and cluster, interface, surface, protein, and nanostructures. Three DRI researchers talked about their research: Yousoo Kim explained the manipulation of a single molecule on a metal surface with a low-temperature scanning tunneling microscope, Syoichi Yamaguchi proposed a novel method for interface-selective nonlinear spectroscopy and Hiroshi Kohguchi described his crossed molecular-beam imaging study of chemical reactions. The workshop was full of lively discussions among the participants, who all contributed freely to the debate as if members of the same research group. It seems the research community in Eastern Asia has been building step by step, and RIKEN, at the core of this community, is certainly playing a leading role.

The 12th workshop will be held next year in Seoul, Korea.

World Brain Awareness Week held

The annual World Brain Awareness Week campaign was held from March 12 to 18 for the purpose of promoting a general understanding of the meaning of brain science and its social importance, and 15 regions in Japan took part. On March 17, the RIKEN Brain Science Institute (BSI) held a science day under the theme 'Approaching the Wonder of the Brain' and more than 100 senior high-school students and members of the public participated. Manabu Tanifuji and Tadaharu Tsumoto gave lectures during the program, which began with a greeting by the special advisor for RIKEN BSI, Masao Ito. Following them, participants were divided into smaller groups to observe experiments using functional magnetic resonance imaging and electroencephalography, and to visit the various laboratories. Lively question-and-answer sessions occurred throughout the day, proving that the science course was an unqualified success.

Frontier spirit is proven

RIKEN introduced a new center with a flexible approach to reach the forefront of many research fields

The year 1985 marked a significant step for Japan's science and technology research. Two government advisory councils issued separate reports stressing the importance of ceasing to follow the US and Europe and starting to tackle on its own new research fields that could lead the world.

At that time, more than 20 years had passed since RIKEN became a public corporation. It was actively adding new research groups in fields ranging from life science and lasers to solar power. But senior management felt RIKEN needed innovative measures to promote further progress.

RIKEN established the 'Frontier Research Program' (FRP) in 1986. This new center aimed at achieving basic research breakthroughs, rather than commercial applications. Top-level scientists were recruited worldwide and put on contract—a rare system of employment in Japan at that time. Each program was allocated a maximum 15 years comprised of two phases. Chief researchers were given authority and responsibility for personnel and budgets.

RIKEN invited Ryogo Kubo to head up the FRP. Kubo was one of the world's leading authorities on theoretical physics and a professor emeritus at the University of Tokyo. The FRP started with two programs: one designed to study bio-homeostasis, the system that controls the physiological equilibrium of plants and animals, and the other aimed at developing new functional materials by studying the mechanisms of ultra-small metals and molecules.

RIKEN added a third program in 1988—research into the thinking function of the brain—and appointed neuroscientist Masao Ito as the group director. In 1991, Ito became the second director of the FRP. RIKEN's neuroscience research has since expanded and resulted in the establishment of the Brain Science Institute in 1997.

Also in 1991, the two initial programs completed their first phase and were reorganized. The bio-homeostasis program became more focused on studying the hormone functions of plants and their capability to receive and transmit environmental stimuli, and a new project on glycochains was added. The materials program shifted its focus to nanoscopic materials.

In the early 1990s, the FRP made aggressive improvements on several fronts including infrastructure and project diversity. For example, it launched a new scheme to support research in collaboration with companies; a step beyond the original concept of adhering to basic research. Between 1991 and 2004, there were five projects created under the scheme, including research into the quantum limit and into drug development by analyzing the behavioral mechanisms of insects.

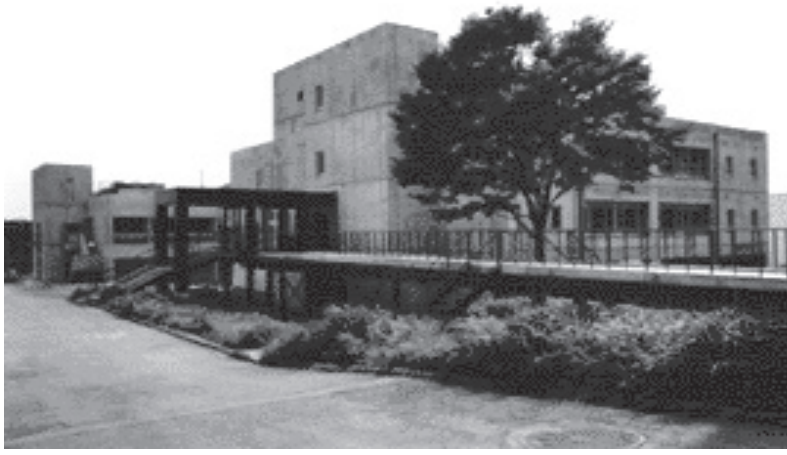


Figure 1: From small beginnings, the Frontier Research System is now one of the core research centers of RIKEN.

Senior management decided to open remote research centers where many key scientists are based in order to raise research efficiency. The first such center, the Photodynamics Research Center, was created in Sendai in 1990 to comprehensively investigate interactions between light and materials or organisms. Three years later, the Bio-Mimetics Control Research Center opened in Nagoya to investigate the highly sophisticated control functions of living systems.

After the great earthquake in the Kobe area in 1995, the government asked RIKEN to commence seismic research. The FRP started a project on earthquake prediction in 1996 that finished in 2002. In 1998, the Earthquake Disaster Mitigation Research Center was temporarily transferred to the FRP and then moved to an outside institute in 2001.

The FRP was renamed the 'Frontier Research System' (FRS) in 1999 (Fig.1) (http://www.riken.jp/lab/frs/frontier/indexE.html). In the same year, the bio-homeostasis program made a fresh start as the Supra-Biomolecular System Research Group and the materials program became the Spatio-Temporal Function Materials Research Group. In 2001, the Single Quantum Dynamics Research Group started to recruit top-class researchers from industry to further promote collaboration with industry.

Now with 32 laboratories and some 310 researchers, advancing to greater achievements, FRS is a core research center of RIKEN with strong representation in its overall management. ■

www.rikenresearch.riken.jp

RIKEN, Japan's flagship research institute, conducts basic and applied experimental research in a wide range of science and technology fields including physics, chemistry, medical science, biology and engineering. Initially established as a private research foundation in Tokyo in 1917, RIKEN became an independent administrative institution in 2003.

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