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Waves that track time

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A penetrating view of viruses

The powerful x-rays from a RIKEN synchrotron can provide high-contrast images of biological specimens

X-ray diffraction is a widely used tool to probe the three-dimensional structures of crystals and large molecules. One of its first successes, in the 1950s, was to reveal the structure of the oxygen-binding proteins hemoglobin and myoglobin, and it has since found many other uses in biology.

More recently, researchers have used x-ray diffraction in a powerful new kind of microscope, which provides high-contrast images of biological cells, viruses or proteins. This so-called 'x-ray diffraction microscopy' requires extremely bright, coherent x-rays that are only available at large synchrotron facilities.

Now, Changyong Song at the RIKEN Advanced Science Institute and co-workers have used the synchrotron radiation source at the RIKEN SPring-8 Centre (Fig. 1) in Hyogo prefecture, Japan, to provide the first clear x-ray diffraction images of single, unstained viruses[1]. The viruses are the smallest objects ever resolved using this technique.

Figure 1: Aerial view of the powerful synchrotron radiation source (ring-shaped building) at RIKEN's SPring-8 Center, which can produce coherent x-rays for imaging viruses.

Crystal conundrum

It can be very difficult to crystallize biological samples into a state suitable for traditional x-ray diffraction studies. X-ray diffraction microscopy provides a solution to this problem. It works by measuring the diffraction patterns of non-crystalline samples and then 'oversampling' them with a computer algorithm to obtain a sample image at high resolution.

"I previously worked on resonant x-ray scattering, which can resolve complex ground states of many intriguing materials, but this was limited to high-quality crystallized samples," explains Song, who was previously based at the University of California in Los Angeles. "Later I heard about x-ray diffraction microscopy, which can unravel structures even from a non-crystalline specimen."

Unfortunately, non-crystalline samples do not amplify the x-ray signal in the same way that crystals do, so the scattered x-rays can be hard to detect. For this reason x-ray diffraction microscopy has so far been limited to imaging samples that are larger than a micrometer in size, or contain heavy elements.

The SPring-8 synchrotron changes all this. Its incredibly powerful x-rays provide very strong diffraction signals, allowing researchers to view much smaller objects.

Viral viewing

Song and co-workers positioned a pinhole aperture to filter x-rays from the synchrotron onto a mouse herpes virus (Fig. 2). The x-rays diffracted by the virus were captured on a CCD camera.

The researchers then recorded another image without the virus present, and calculated the difference between the two images. This important process removes unwanted scattering by the surrounding environment.

The resulting images resolved details as small as 22 nanometers. This was enough to clearly define both the outer virus envelope and the capsid—the protein shell at the centre of the virus which contains the DNA.

Comparing contrast

The researchers recorded images of similar stained viruses with a scanning electron microscope (SEM) and an atomic force microscope (AFM). These techniques revealed the same general virus structure.

X-ray diffraction microscopy currently has much lower resolution than electron microscopes. However it has two significant advantages—it does not require staining of the viruses, and it provides higher contrast because the background scattering is removed.

Most promisingly, the x-ray images taken by Song and co-workers revealed electron density variations inside the viral capsid, which might provide details on the packing of the genome. The capsid has only been visualized before by laboriously taking averages over thousands of images from an electron microscope held at cryogenic temperatures.

This proves that x-ray diffraction microscopy can reveal subtle variations in structure that cannot be picked out by other techniques. It has other advantages, as Song explains: "Both electron microscopy and x-ray diffraction microscopy are powerful probes in a different sense. However, x-rays can probe thick specimens in air, whilst electron microscopes need a high vacuum environment and thin specimens."

What's more, x-ray diffraction microscopy does not need an imaging lens, eliminating the possibility of distortion or focusing limits in the equipment.

Free-electron future?

In theory, x-ray diffraction microscopy is limited only by the coherence of the available x-ray flux. Unfortunately when the x-rays get too strong they can start to do irreversible damage to biological samples.

To avoid damage the samples can be cryogenically cooled, but with standard x-rays there is still a practical limit of around five nanometers resolution. Even so, Song is not perturbed.

"Diffraction microscopy, or lensless imaging, can be applied with any coherent source, from photons to electrons to neutrons," he says. "It can also be used with any wavelength."

The most promising candidates for diffraction microscopy are new 'fourth generation' synchrotron light sources called X-ray Free Electron Laser (XFEL). These devices use a relativistic beam of electrons to provide optical gain to a light signal.

Probing proteins

XFELs should produce coherent x-rays up to a billion times brighter than SPring-8's. This could mean diffraction resolution down to the size of single atoms—leading to the ultimate goal of imaging proteins such as those in cell membranes.

"Presently, lots of membrane proteins are extremely hard to make as a single crystal," explains Song. "This is a serious bottleneck given their importance in basic biological functions like single transduction. X-ray diffraction microscopy may find its most competitive application in resolving the structures of those proteins."

"RIKEN has the world's best facilities and well-established research infrastructures which can make this cutting-edge research happen. Japan's x-ray free-electron laser, one of the world's three XFELs, is currently under construction at the RIKEN SPring-8 Center, and we plan to generate the first x-ray laser beam by March 2011. I am eager to use this facility for 3D imaging of single molecules at near-atomic resolution." ■

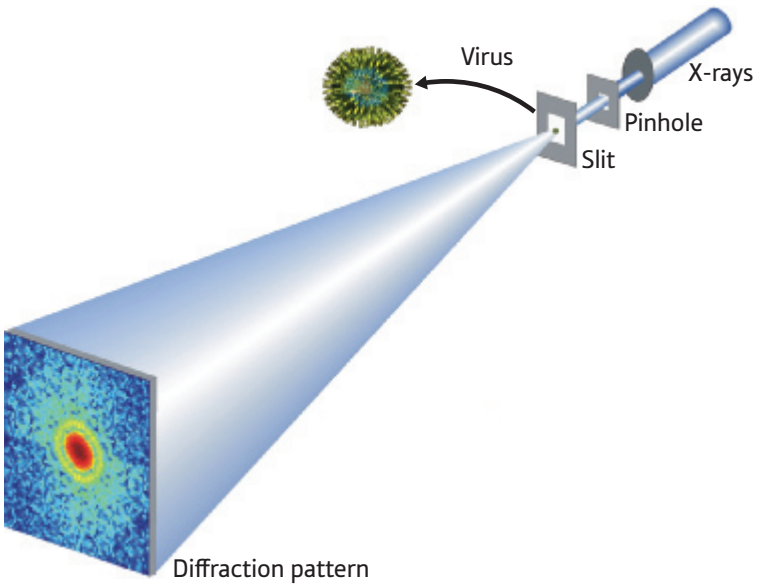


Figure 2: X-ray diffraction imaging of a virus, using the synchrotron radiation source at RIKEN's SPring-8 Center.

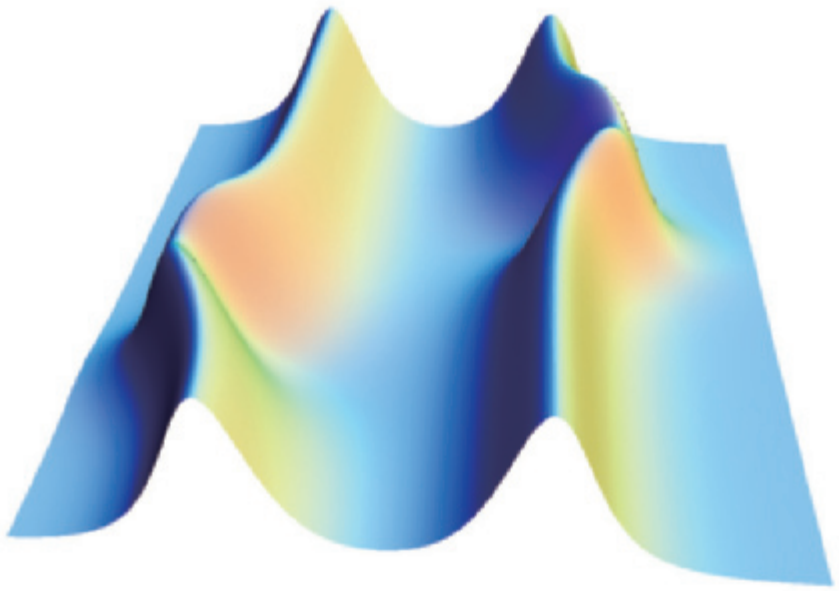
1. Song, C., Jiang, H., Mancuso, A., Amirbekian, B., Peng, L., Sun, R., Shah, S.S., Zhou, Z.H., Ishikawa, T. & Miao, J. Quantitative imaging of single, unstained viruses with coherent x-rays. *Physical Review Letters* **101,** 158101 (2008).

About the researcher

Changyong Song was born in Korea in 1972. After receiving a bachelor's degree from Physics Department of Jeonbuk National University in 1995, he went to the US in 1996 and obtained a Ph.D. in experimental condensed matter physics from Iowa State University (Ames, Iowa, USA) in 2001. On receiving the degree, he returned to Korea as a postdoctoral researcher, substituted service of his compulsory military duty and continued his research on resonant x-ray scattering at POSTECH until late 2004. Finishing the term in Korea, he moved back to the US as a postdoctoral researcher working on coherent x-ray diffractive imaging at UCLA. In March 2008, he joined RIKEN as an initiative research scientist at the Song Initiative Research Unit to develop an innovative x-ray microscope with the Japan X-ray Free Electron Laser (XFEL), one of the world's first three XFELs. Changyong Song aims to realizing near atomic resolution, single macromolecule 3D x-ray microscopy with XFELs.

Dilating time with superconductors

Solitary waves trapped in superconducting junctions could illustrate time dilation effects similar to those in special relativity



D.R. Gulevich

Figure 1: A two-dimensional magnetic field distribution of hill-shaped vortex lines in a superconducting Josephson junction, with smaller 'shape excitations' on top. These 'shape waves' can be considered as solitons propagating along other solitons. They can be used to measure a time dilation effect analogous to that in special relativity.

Solitary waves, known as solitons, can be striking. The first observation of a soliton was documented in 1834: a large moving heap of water formed by a boat on a canal in Scotland. Since then, solitons have been found in many areas of science including nonlinear optics, condensed matter physics, astrophysics (for example Jupiter's red spots), and biology (during energy transfer in DNA).

Solitons can also be found in a so-called Josephson junction, where a thin insulating layer is sandwiched between two superconductors. A team, including RIKEN scientists at the Advanced Science Institute in Wako, has discovered a new type of soliton excitation in a Josephson junction that could be used to measure time dilation effects similar to those in Einstein's special relativity[1].

In a Josephson junction, the role of a soliton is played by a 'Josephson vortex'—a lump of magnetic field that can be accelerated inside the material[2]. When a Josephson vortex approaches the speed of light for the material, it should start to experience relativistic effects. One of these effects, the Lorentz (length) contraction of solitons, has been observed in experiments. However the measurement of another relativistic effect, time dilation, has been a challenge.

"It has been difficult to observe time dilation for a moving Josephson vortex because we need something internal acting as a clock to measure time in its frame of reference," explains team member Franco Nori from RIKEN and the University of Michigan, USA. "We can't find such a clock in conventional Josephson junctions, but we found one that can exist in vortices in long, wide Josephson junctions."

The 'clock' discovered by Nori and co-workers is a nonlinear wave that propagates along Josephson vortices, and therefore belongs to the vortex frame of reference (Fig. 1). The excitations are associated with distortions in the Josephson vortices, and are similar to shear waves in solids. They can have almost any shape and retain it for a long time while the wave is propagating.

"The new excitation that we discovered can act as the 'minute hand' of a clock, keeping track of time in the frame of reference of a moving soliton," says team member Dmitry Gulevich from Loughborough University, UK, and RIKEN.

Feo Kusmartsev and Sergey Savel'ev, also from Loughborough University, add: "This effect could be used to transmit information, and as waveguides for Terahertz radiation." The research team plans to put the predicted effect into practice in the near future. ■

1. Gulevich, D.R., Kusmartsev, F.V., Savel′ ev, S., Yampol′ skii, V.A. & Nori, F. Shape waves in 2D Josephson junctions: Exact solutions and time dilation. *Physical Review Letters* **101,** 127002 (2008).
2. Gulevich, D.R., Savel′ ev, S., Yampol′ skii, V.A. Kusmartsev, F.V. and Nori, F. Josephson vortices as flexible waveguides for terahertz waves. *Journal of Applied Physics* **104,** 064507 (2008).

Spin currents heat up

Long-range spin currents induced by heat herald a new era for spintronic applications

Modern electronics is based on the transport of electrons, generated by a difference in electric voltage. In a bid for faster and smaller electronic devices, researchers have turned to the spin of electrons, or spintronics. However, sustaining spin currents has proven difficult. Now researchers from the RIKEN Advanced Science Institute in Wako with scientists from Keio University, Yokohoma, and Tohoku University, Sendai, have—for the first time—observed the so-called spin Seebeck effect, which is able to generate pure spin currents across macroscopic distances.

The classic Seebeck effect describes the generation of an electric voltage when the ends of a material are at different temperatures. As such, it is used in thermoelectric devices that convert heat into electricity.

In a similar fashion, as reported by the researchers in *Nature*[1], the spin Seebeck effect reported uses a temperature gradient in a magnetic material to create a flow of electron spins in the absence of any external voltage. As a result, spins of opposite polarization assemble at the two ends of the sample, creating a 'spin voltage' caused by the different spin polarizations at both ends. This use of thermal effects in spintronics is novel and unexpected. "The electron spin is usually controlled by magnetic fields, so nobody has thought about a thermoelectric response," says Wataru Koshibae from the research team.

The discovery of the spin Seebeck effect is enabled by the so-called spin Hall effect. Through interactions between the spin current and the atoms in a metal, electrons of different spin orientations get scattered to opposite ends of the metal, creating an electrical voltage. The spin voltage created by the spin Seebeck effect is then detected by thin platinum sheets placed at both ends of the sample (Fig. 1).

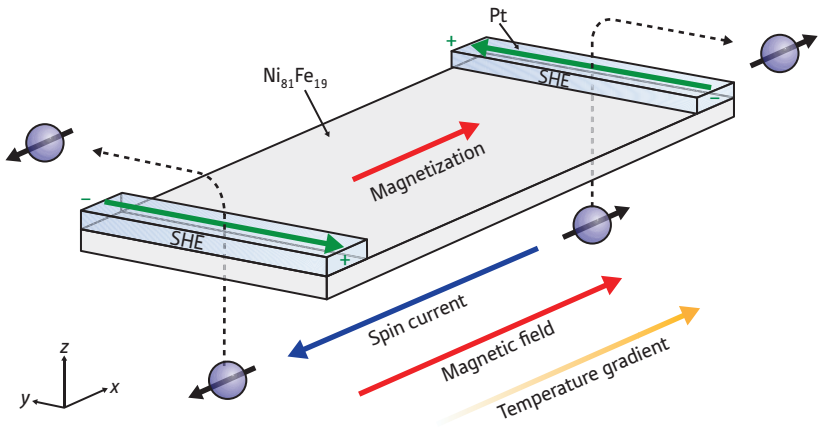


Figure 1: Schematic of the experimental setup for the spin Seebeck effect. A magnetic metal such as $Ni_{81}Fe_{19}$ is exposed to two different temperatures at its ends. With the magnetic magnetization (red arrow) in the plane of the device, a spin voltage results, so that spins of different orientation are at either ends of the sample. The spin voltage is measured through thin platinum (Pt) strips where the spin Hall effect (SHE) converts spin voltages into electric voltages.

Importantly, in this setup the electrons don't move at all, and only spins travel along the sample. This is markedly different to most other schemes where undesirable parallel electronic currents are unavoidable. In addition, there appears to be no limit to the distances along which spin currents can be sustained. "The spin Seebeck effect occurs in samples almost 1 cm long, much longer than the usual spin current decay lengths of 1 nm," comments Koshibae.

This first observation of the spin Seebeck effect therefore marks a new era in spintronics and opens the door to novel applications. Long-distance spin current are critical to the realization of spintronic devices, and these results offer the generation of spin currents simply through temperature effects. ■

1. Uchida, K., Takahashi, S., Harii, K., Ieda, J., Koshibae, W., Ando, K. Maekawa, S. & Saitoh, E. Observation of the spin Seebeck effect. *Nature* **455,** 778–781 (2008).

Spin currents: pure and clean

Switching the orientation of magnetization in a thin metallic film can be achieved using the diffusion of electron spins

A team of scientists in Japan has demonstrated the possibility of switching the magnetization of a thin magnetic film with a non-conventional and innovative method, achieving a considerable step forward in magnetic data storage and the field known as spintronics.

In magnetic memory devices, information is stored in magnetic elements and typically retrieved by applying a small, external magnetic field. More convenient, however, is the use of a spin-polarized current, in which moving electrons exert a torque on a magnetic element and can switch the direction of its magnetization.

Unfortunately, moving electrons can give rise to electrical noise, which reduces the efficiency of the magnetization control. Now, Yoshichika Otani from the RIKEN Advanced Science Institute in Wako and colleagues have overcome this problem by using a pure spin current[1], that is, a diffusion of electron spins without charge motion.

A spin current can be created by the process known as non-local injection: a current is injected into a junction between a metal and a magnetic layer (Fig. 1). When the magnetic element is magnetized, such as a metallic film, electron spins accumulate at the junction, and then diffuse away from the junction to re-equilibrate the spin population in the film. The trick is to then use this spin current to influence the magnetization of another magnetic element placed far from the accumulation point.

Previous attempts to create a pure spin current in this way have all met with limited success. Otani and co-workers therefore focused on optimizing the quality of the interface. In particular, they grew all the layers of their devices in sequence in a single high-vacuum chamber. This prevented possible contamination that could occur while moving a structure between growing chambers.

By examining the electronic transport properties of their device, the researchers were able to demonstrate that when the current injected into the first junction is high enough, it creates a spin current high enough to reverse the magnetization at the second junction. Most importantly, the magnetization can be reversed back by applying the same amount of current in the opposite direction.

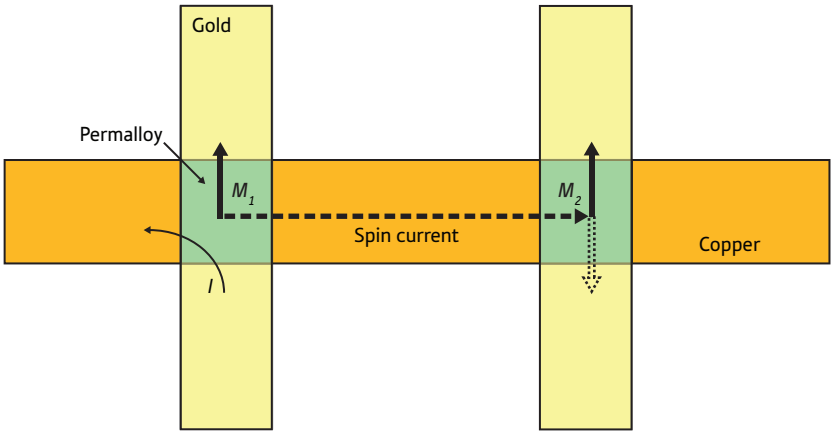


Figure 1: Top view of the device used to switch magnetization using a pure spin current. A current, I, is injected from the gold wire into the permalloy film with magnetization M_1. The copper wire creates a spin accumulation at the junction (green). The spin diffuses towards the second junction and can switch the magnetization M_2 of the second permalloy film.

Magnetization control using a pure spin current in this way in the high-quality devices fabricated by the team could lead to the realization of very advanced electronic devices. The team believes, for example, that it will be possible to achieve different types of transistors—which have no analogues in current electronics—based only on electron spin. ■

1. Yang, T., Kimura, T. & Otani, Y. Giant spin-accumulation signal and pure spin-current-induced reversible magnetization switching. *Nature Physics* **4**, 851–854 (2008).

Porous material sized up

A metal–organic framework that contains ordered channels of two different sizes can separate different gases

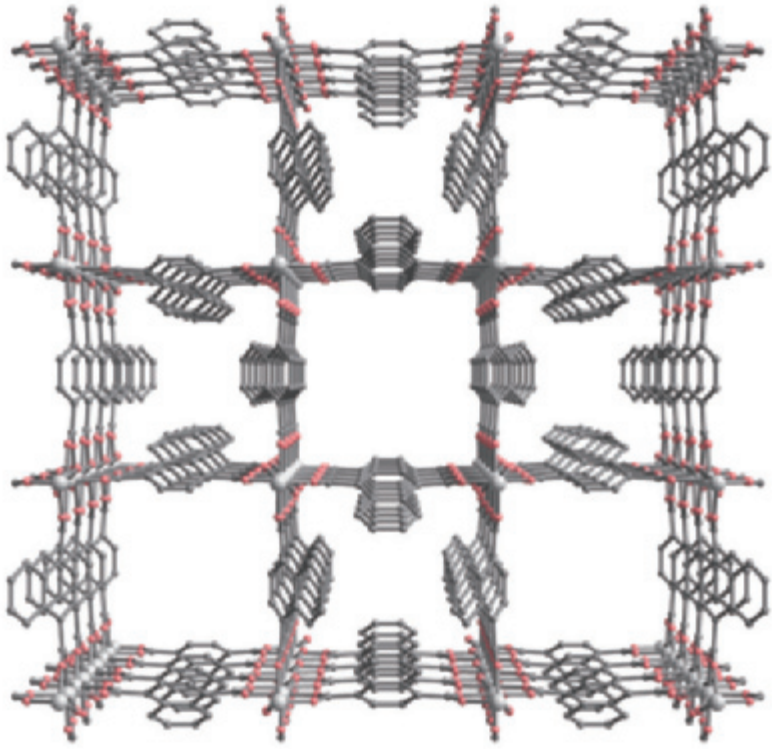


Figure 1: A schematic of the metal-organic framework, which contains a highly ordered network of small and large nanopores.

Scientists have developed a new type of porous material that could be used to separate mixtures of different gases.

The material's structure is based on a three-dimensional lattice of aluminum atoms, surrounded by oxygen atoms. These clusters are connected by a carbon-based molecule called 1, 4-naphthalene dicarboxylate (1, 4-NDC). Such metal–organic frameworks (MOFs) are finding uses in separating liquids or gases, acting as catalysts to speed up chemical reactions, or for safely storing large volumes of gas.

The international team of scientists that made the material, including Masaki Takata of RIKEN's Harima Institute, used x-rays to reveal that it contains ordered channels of two different sizes[1]. The smaller channels, crowded by napthalene units, are just 0.3 nanometers (billionths of a meter) across, while the larger channels are 0.77 nanometers across (Fig. 1).

"We expected the porous structure to some extent," says Satoshi Horike, now at the University of California, Berkeley, who was part of the team. "But the existence of two kinds of pores in our system is kind of surprising."

The team then used nuclear magnetic resonance (NMR), a technique which measures the magnetic behavior of atomic nuclei, to build up a more detailed three-dimensional picture of the MOF.

The scientists analyzed a sample of the inert gas xenon as it diffused through the MOF's pores. This experiment confirmed that the material has parallel, yet independent, pores. Xenon atoms have a diameter of about 0.44 nanometers, and did not fit down the smaller channels. However, it took mere milliseconds for the xenon to diffuse through the larger channels, which were not blocked by any other molecules, such as water.

Carbon dioxide could also seep through the material. The scientists calculate that each gram of the MOF can bind carbon dioxide to an internal surface area which is greater than 500 m^2, roughly the size of two tennis courts.

And while the small organic molecules methanol and acetone were easily absorbed, more pressure was required to squeeze water into the pores because of high hydrophobicity. This could make the material useful for separating water from alcohols, suggests Horike. "Gas separation between water and ethanol is important for obtaining liquid fuel from biomass sources," he says.

The smaller pores could also be useful for storing hydrogen gas, a potentially environmentally friendly fuel. "Hydrogen has a really small interaction with pore surfaces," explains Horike, "and the small pore would be able to bind hydrogen gas more tightly than the large one." ■

1. Comotti, A., Bracco, S., Sozzani, P., Horike, S., Matsuda, R., Chen, J., Takata, M., Kubota, Y. & Kitagawa, S. Nanochannels of two distinct cross-sections in a porous Al-based coordination polymer. *Journal of the American Chemical Society* **130,** 13664–13672 (2008).

Stay of execution

A new twist on an old technique helps researchers identify proteins with a regulatory 'death sentence'

The targeted destruction of specific proteins is an important means of regulation for many cellular pathways. This is typically managed through the process called ubiquitination, in which doomed proteins are chemically marked for entry into a degradation pathway by protein complexes known as ubiquitin ligases.

"Although the identification of substrates is essential for our understanding of cellular regulatory mechanisms involving ubiquitination, identifying them is quite difficult," explains Tsutomu Kishi of the Advanced Science Institute in Wako, whose work on ubiquitin ligase target recognition via subunits known as 'F-box proteins' has been impeded by the limitations of existing tools for protein–protein interaction analysis.

One popular method is the 'two-hybrid' system, which uses a gene-activating protein that has been split into two pieces: one capable of binding to a target DNA sequence, and one capable of inducing activation. The first piece is fused to a 'bait' protein, while the second piece is fused to various 'prey' proteins; both bait and prey are then introduced into yeast cells with an indicator gene containing an appropriate binding site for the bait. The indicator is only turned on if the DNA-binding domain and gene activation domain become linked via prey–bait interaction, making it easy to identify such associations.

When working with ubiquitination targets, however, prey fusions are in danger of being marked for rapid destruction by the host cell before interactions can be detected. Kishi and colleagues therefore modified the assay so that it could be performed under conditions in which the relevant degradation pathways are disabled, enabling straightforward two-hybrid analysis of substrates from these pathways[1].

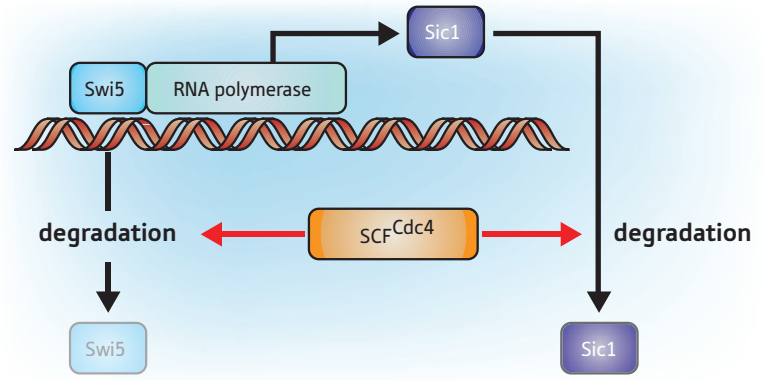


Figure 1: A schematic representation of the flow of SCF^{Cdc4} mediation.

Kishi's team applied their method to Cdc4, a component of the SCF^{Cdc4} ubiquitin ligase complex. They identified four interacting partners, but focused on Swi5, a protein that stimulates production of Sic1, a regulator that inhibits onset of S phase—and also a ubiquitination target. Subsequent experiments revealed that SCF^{Cdc4} mediates a two-pronged process of Sic1 downregulation by first reducing levels of the activator protein Swi5, and then by inducing direct degradation of Sic1 itself (Fig. 1).

These findings offer valuable insights into the regulation of the cell cycle and illustrate an important 'indirect' mechanism for ubiquitination-based regulation of protein levels via the targeting of relevant gene activators for destruction. They also demonstrate the effectiveness of a strategy that could be generalized for identifying other ubiquitination targets. "This methodology is widely applicable," says Kishi, "and in collaboration with other groups, we have succeeded in identifying targets of other F-box proteins." ■

1. Kishi, T., Ikeda, A., Koyama, N., Fukada, J. & Nagao, R. A refined two-hybrid system reveals that SCF^{Cdc4}-dependent degradation of Swi5 contributes to the regulatory mechanism of S-phase entry. *Proceedings of the National Academy of Sciences USA* **105,** 14497–14502 (2008).

Making the switch for DNA

New switches could lead the way in controlling DNA duplex formation with potential nanotechnology applications

Two RIKEN researchers have developed a switch to control the formation and separation of DNA duplexes that may have implications in many biological processes, such as gene regulation.

Formation of complexes of our genetic building blocks, the nucleic acids, underlies many biological events. Hybridization of the nucleic acids, through interactions known as base pairing, forms the intricate complexes responsible for the formation of DNA duplexes. The ability to control hybridization, and consequently whether biological events take place, is a very important goal for scientists.

Now, Shinzi Ogasawara and Mizuo Maeda at the RIKEN Advanced Science Institute, Wako, have developed a light-controlled switch that directs the formation and destabilization of a series of DNA duplexes[1].

They designed the photoswitch, a photochromic nucleoside (PCN), with several fundamental properties and benefits. The switch can be easily incorporated into a DNA strand and its physical conformation can be altered reversibly when irradiated by an external light source. Change of the physical conformation, by isomerization, disrupts and destabilizes the hybridization of two DNA strands. Another benefit of the PCN switch is that installing it into DNA has little influence on the structure of the duplex when it forms. Further, the PCN can be used as molecular trace label because it is fluorescent. This PCN photoswitch is therefore easy to track in the body and could be used in living cells without disruption.

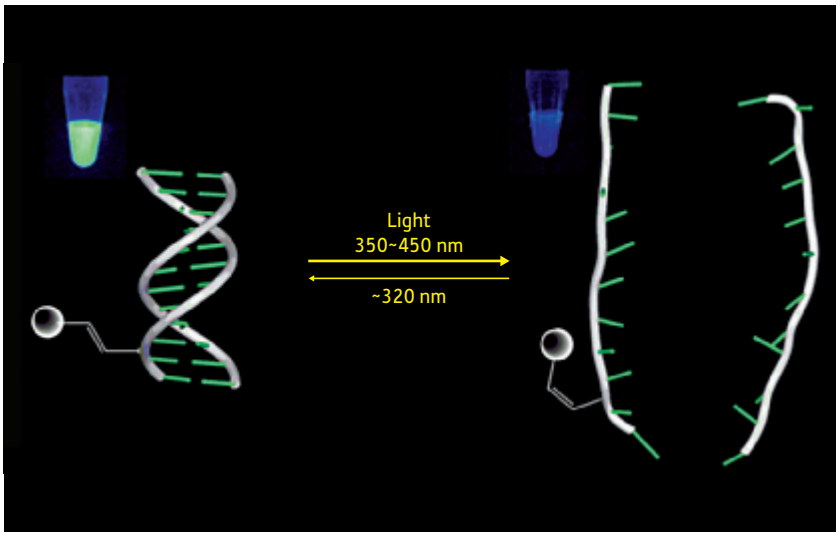


Figure 1: This figure shows the reversible formation and destabilization of a DNA complex by a photochromic nucleoside (PCN) that changes formation under differing light conditions. The changes are monitored by fluorescence.

The researchers irradiated a series of reaction mixtures containing PCN-modified DNA duplexes, which were fluorescent, with light at 370 nm for 5 minutes. After this time, only a slight fluorescence was seen. The PCN fragments had isomerized and the duplex broken. They then irradiated the mixtures at 254 nm for 2 minutes and the fluorescence returned, indicating a change back in conformation of the PCNs and importantly, hybridization to re-form the duplexes (Fig. 1). This switching showed good reversibility over two cycles.

Surprisingly, this easy switching system also works below room temperature. Ogasawara is naturally pleased with the current results. "There were no particular problems we had to overcome," he says. However, the synthesis of the PCNs was not as straightforward as they would have liked.

Ogasawara and Maeda now want to build on the results of this current study. "We plan to apply this technology to gene regulation such as antigene, antisense and siRNA," says Ogasawara. "We think that this light-switching technique can be applied to nanotechnology, for example [using] light [to] control DNA nanomachines and architectures." ■

1. Ogasawara, S. & Maeda, M. Straightforward and reversible photoregulation of hybridization by using a photochromic nucleoside. *Angewandte Chemie International Edition* **47,** 8839–8842 (2008).

Island hopping

Cells control interactions between two proteins with an important role in Alzheimer's disease by stranding them on discrete membrane 'islands'

The earliest known stage in the pathology of the neurodegenerative disorder Alzheimer's disease involves the accumulation of deposits of amyloid-β peptide (Aβ) in the brain. Aβ is a byproduct of cleavage of amyloid precursor protein (APP), a membrane protein that is particularly abundant at neuronal synapses.

Both APP and BACE1—the enzyme that cleaves it—are thought to associate with microdomains, patches containing specific lipid subtypes and membrane proteins that form discrete islands adrift in the plasma membrane. What remains unclear, however, is the role of these microdomains in the regulation of APP cleavage and Aβ production.

In order to better understand this process, Nobuyuki Nukina and his colleagues at the RIKEN Brain Science Institute in Wako set about isolating and characterizing microdomains containing APP[1]. They have found that APP normally forms part of a multi-protein complex that appears to stabilize its inclusion in certain types of microdomains, but BACE1 appears to be segregated to a completely distinct subset of microdomains, suggesting the need for an active process that reunites these two proteins in order to produce Aβ. "It is necessary for the substrate, APP, and enzyme, BACE1, to be in the same microdomain," explains Nukina.

Previous studies have indicated that increased neuronal activity is directly correlated with increased production of Aβ, and subsequent experiments by Nukina's group helped to reveal the chain of events underlying one mechanism by which this may occur. They found that prolonged synaptic activity stimulates a protein called cdk5, which introduces a chemical modification to the APP-containing protein complex; this modification leads to disruption of the multi-protein complex that helps anchor APP to its microdomain, releasing it and enabling it to associate instead with BACE1-containing microdomains—and thus undergo cleavage (Fig. 1).

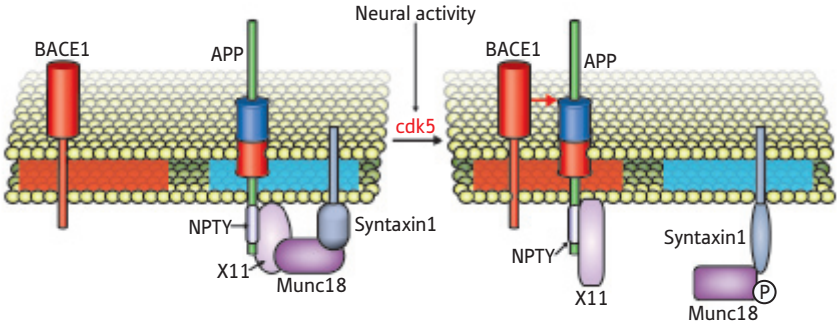


Figure 1: Cleavage dependent on neuronal activity. BACE1 and APP are normally sequestered in different types of microdomains (pink and blue boxes). This is mediated by a complex of proteins (syntaxin, munc18 and x11) that anchor APP. However, increased neuronal activity stimulates cdk5, which introduces modifications that disrupt this complex and allow APP to associate with BACE1-containing microdomains, resulting in elevated Aβ production.

In addition to providing new insights into the mechanisms involved in the initial stages of Alzheimer's pathology, these findings may further illuminate the functional importance of the various microdomain types. "It has been reported that different microdomains in the membrane contain particular protein complexes, but the significance of this has not been known," says Nukina. "Our report suggests that microdomain switching of APP to BACE1-containing microdomains regulates APP cleavage, [and] similar mechanisms may exist in the processing of other proteins." ■

1. Sakurai, T., Kaneko, K., Okuno, M., Wada, K., Kashiyama, T., Shimizu, H., Akagi, T., Hashikawa, T. & Nukina, N. Membrane microdomain switching: a regulatory mechanism of amyloid precursor protein processing. *The Journal of Cell Biology* **183**, 339–352 (2008).

A sweet success

Genomic analysis helps scientists to start determining how licorice plants produce a highly beneficial compound

Image courtesy of Kiminori Toyooka, RIKEN

Figure 1: Glycyrrhizin, a powerful sweetening agent which also possesses a wide range of pharmacological properties, is extracted from the root of licorice plants.

It turns out that licorice is good for treating more than just a sweet tooth—the licorice plant produces a chemical called glycyrrhizin that is not only a potent sweetener but also has wide-ranging pharmacological properties, including anti-inflammatory and antiviral activity (Fig. 1).

Although the value of glycyrrhizin has been understood for some time, it has proven difficult to unlock the multi-step process by which this molecule is produced from the precursor β-amyrin, a commonly found natural compound. Toshiya Muranaka of the RIKEN Plant Science Center in Yokohama has been studying plant metabolic processes for decades, and recalls considerable challenges in his early days of trying to uncover the mysteries of these pathways. "In those days, such biosynthetic pathways were hidden in a 'black box,'" he says. "Almost no information was available about genes involved in useful secondary metabolite production."

Fortunately, things have changed with the advent of the post-genomic era, and in a new article, Muranaka describes how he and a multidisciplinary team of colleagues from across Japan successfully identified an important component of the glycyrrhizin biosynthetic process through the careful analysis of a large library of licorice plant genes[1].

The newly identified gene, *CYP88D6,* is expressed specifically in underground portions of the plant, where glycyrrhizin is known to be produced and accumulate, and appears to catalyze the first step in the processing of β-amyrin.

According to Muranaka, since the identification of this first enzyme, which is now known as β-amyrin 11-oxidase, his group has made considerable further progress in building a complete understanding of the four-stage glycyrrhizin biosynthetic pathway. "We have already cloned the second gene, and we have obtained a strong candidate for the last gene," he says, "which means that the only one gene—the third gene—remains."

Large-scale production of glycyrrhizin has proven a considerable challenge; currently, this compound is still extracted directly from harvested plants, a process with potentially severe long-term environmental consequences. As such, the ability to recapitulate this biosynthetic pathway in the laboratory could be a tremendous asset.

However, Muranaka is also excited about the opportunities to explore the properties of intermediates from glycyrrhizin synthesis. "By designing the metabolic pathway we can increase the amount of intermediates in engineered cells, which might be very useful bioactive compounds," he says. "We may even produce unnatural bioactive compounds through combinations of these genes." ■

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Staying true to the code

By turning enzymes into better editors, Japanese scientists achieve improved results in protein engineering

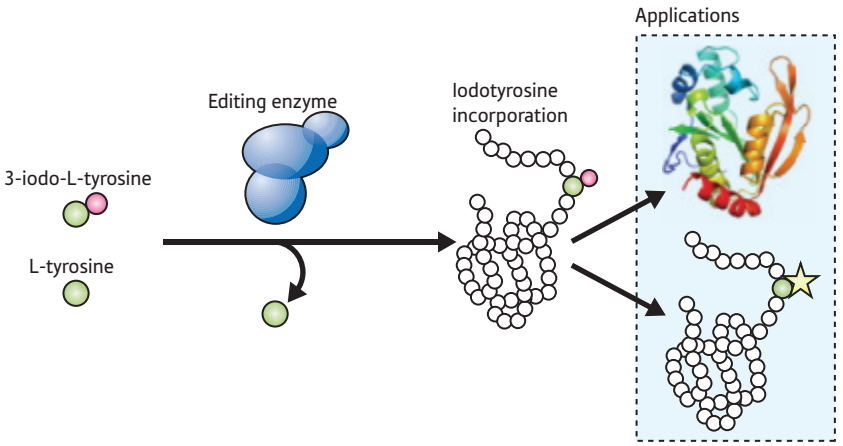

Figure 1: Schematic of the synthetase editing functionality. Synthetase enzymes with a clear preference for 3-iodo-L-tyrosine will occasionally introduce L-tyrosine by accident. The integration of an editing domain prevents this by cutting L-tyrosine molecules loose, so that proteins synthesized from RNAs containing the appropriate codon will consistently incorporate only the modified amino acid.

Cells achieve astonishing protein diversity with a fairly limited palette: just 20 naturally occurring amino acids. However, there is sufficient flexibility inherent in the protein-coding and -translation processes that has allowed enterprising scientists to develop clever means for introducing additional, unnatural amino acids into otherwise normal proteins.

As cellular translation machinery reads an RNA transcript, it identifies nucleotide triplets known as codons that indicate what amino acid is needed—these are then delivered through the assistance of a family of enzymes called aminoacyl-tRNA synthetases, which ensure proper placement of the proper molecule.

In previous work, Shigeyuki Yokoyama from the RIKEN Systems and Structural Biology Center in Yokohama and colleagues demonstrated that these enzymes can be engineered to introduce alternative amino acids into proteins[1]—in this case, substituting L-tyrosine with 3-iodo-L-tyrosine, a synthetic analog with uses in imaging and structural biology applications.

Unfortunately, this approach was not a total success, as the mutated synthetase enzyme (iodoTyrRS) still processes L-tyrosine at a reduced, but still significant, frequency. "Any further changes made in the amino-acid-binding pocket [of the enzyme] could not reduce the error rate," explains Kensaku Sakamoto, a member of Yokoyama's team. "We had to change the approach to achieve satisfactory selectivity."

The team's solution was to teach iodoTyrRS to be a better proof-reader. In new work, Yokoyama and colleagues have further engineered a version of the synthetase, one that incorporates a transplanted enzymatic domain that specifically recognizes and purges L-tyrosine[2].

They began by analyzing various synthetase enzymes that exhibit this editing functionality, in an effort to zoom in on the domains that confer this ability. Once these had been identified, they grafted these domains onto different sections of iodoTyrRS. One of the variants, iodoTyrRS-ed, showed strong specificity for 3-iodo-L-tyrosine alone (Fig. 1), while the original iodoTyrRS enzyme and other variants would regularly make use of L-tyrosine when the synthetic amino acid was no longer available. This specificity was greatly reduced when the editing domain was inactivated by mutation, indicating that this functionality is highly important for establishing strict amino acid preference.

The team is now looking to move their modified enzymes out of the test tube and into living cells, but they are generally quite pleased with this demonstration of grafting two sophisticated enzymatic activities together seamlessly. "Our approach may facilitate developing other enzymes required for incorporating non-natural amino acids into proteins site-specifically," says Sakamoto, "so that the list of available non-natural amino acids can thus be further extended." ■

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2. Oki, K., Sakamoto, K., Kobayashi, T., Sasaki, H. & Yokoyama, S. Transplantation of a tyrosine editing domain into a tyrosyl-tRNA synthetase variant enhances its specificity for a tyrosine analog. *Proceedings of the National Academy of Sciences USA* **105,** 13298–13303 (2008).

Immune cell activation under the microscope

The application of sophisticated imaging techniques illuminates spatio-temporal regulation critical for T cell activation

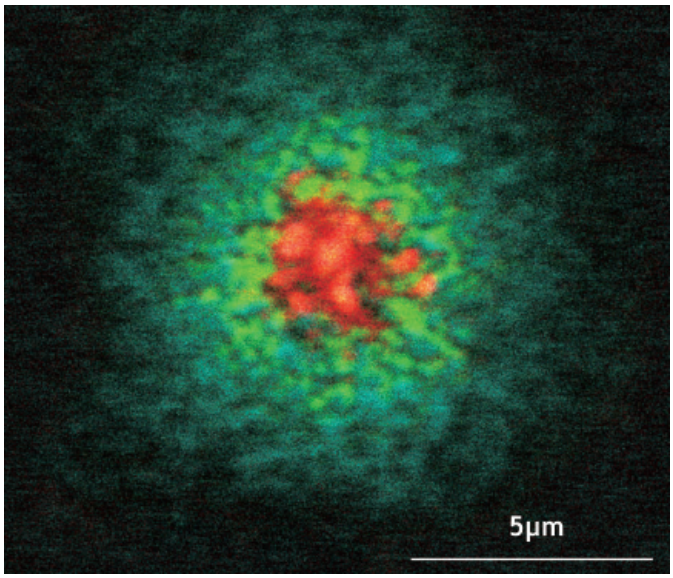

Figure 1: An immunological synapse showing the central supramolecular activation cluster containing both T cell receptors (red) and PKCθ (green).

T cells are central to an organism's defense against invading pathogens. But scientists have long puzzled over how they are activated and regulated after pathogen recognition. Now a team of researchers, led by Takashi Saito from the RIKEN Research Center for Allergy and Immunology in Yokohama, has succeeded in imaging molecular events that are crucial for these processes.

Full activation and differentiation of T cells requires a primary signal from T cell receptors (TCRs) upon interaction with an antigen-presenting cell (APC), and a second, distinct signal transmitted through 'costimulatory' receptors.

The receptor CD28 plays a predominant role in T cell costimulation. CD28-mediated signals augment many T cell functions, such as cytokine production and cell proliferation.

Modulation of these costimulatory signals has been applied in clinical trials by increasing tumor immunity and reducing autoimmune diseases. But the precise roles of molecules implicated in CD28-mediated costimulatory signals and their relationship with TCR signals require clarification.

Antigen-specific T cells 'communicate' with APCs through an 'immunological synapse', which forms at their interface and contains a central (c-) and a peripheral (p-) supramolecular activation cluster (SMAC).

At initial activation, TCRs form microclusters, which contain receptors, kinases, and adaptor proteins to induce activation signals at the interface between a T cell and an APC. These microclusters translocate to the center of the interface, resulting in c-SMAC formation.

The role of microcluster translocation in T cell signaling has been unclear, and the concept that they function as signaling centers for T cell activation has raised questions as to how CD28-mediated costimulation is regulated.

Using sophisticated fluorescence microscopy techniques to study CD28-mediated costimulation at the molecular level, Saito and colleagues have found that the accumulation of microclusters at c-SMAC is important for T cell costimulation[1]. CD28 is initially recruited together with TCRs to microclusters. PKCθ—a protein kinase acting downstream of CD28—is also recruited to microclusters by association with CD28 (Fig. 1), thereby resulting in the initial activation of T cells.

CD28 also plays a role in retaining PKCθ at a spatially unique subregion of c-SMAC, leading to sustained signals for T cell activation. "Thus, costimulation is mediated by the generation of a unique costimulatory compartment in the c-SMAC via the dynamic regulation of microcluster translocation," say the researchers.

Establishing the underlying mechanisms should lead to new treatments for autoimmune diseases, such as rheumatoid arthritis and psoriasis, as well as the prevention of graft versus host disease in transplantation, more effective vaccinations, and augmented anti-tumor immunity. ■

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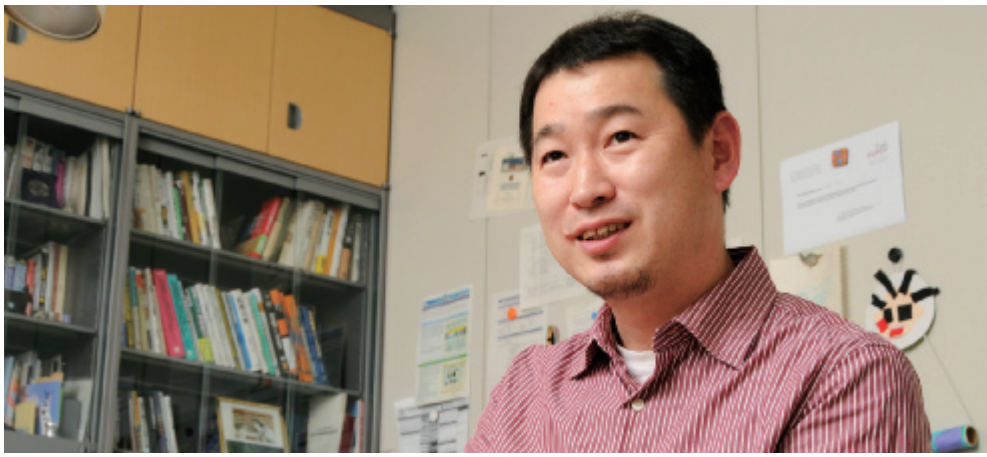
From skilled manufacturing to medical services—practical use of the VCAD system

Kenji Ono

Laboratory Head, Functionality Simulation and Information Team
VCAD System Research Program
Center for Intellectual Property Strategies



"The aim of the Functionality Simulation and Information Team is to develop tools that support skilled manufacturing and to make them practical tools in companies," says Kenji Ono, Team Leader, who worked at the Nissan Research Center for 11 years. He joined RIKEN in 2004 after having worked as Associate Professor at the University of Tokyo. Ono has enhanced research and development with an intense and consistent concern for making a "contribution to society" since he first started working in the field of skilled manufacturing. "I have experienced difficulties faced on site while working in the company and come across a large variety of technical 'seeds' in the university. I want to take advantage of my experience to develop new technology for solving problems encountered in skilled manufacturing, and return the technology to society." This article reports the leading technology of a VCAD-system-based simulation that has the potential to be used in the field of skilled manufacturing in Japan.

Using the VCAD system for rapid modeling

To highlight issues that are faced on site in skilled manufacturing, Ono refers to automobile development in this way: "Today, automobiles cannot be designed without using computers. For example, CAD (computer-aided design) systems are used to draft engineering drawings. A digital geometric object is created from engineering drawings. The object is a reproduced model of an automobile; it has a complicated shape and is used as the basic model while computer simulations are repeated. Simulated results are managed by a computer database program and fed back to the engineering drawings and the model. Today, a new car can be developed in a minimum time of only ten months. In comparison with the past, when prototyping and experiments were carried out repeatedly, the time and cost required for product development have been reduced significantly. Nevertheless, a further reduction in development period is much needed if we are to address market trends more quickly, improve product quality, increase the attraction factor of products, and enhance competitiveness. It is therefore very important to improve simulation accuracy and reduce the time and cost required for simulation."

It is said that the construction of simulation models can significantly influence the improvement in the simulation accuracy and reduction in simulation time. For example, about one to two weeks are required for constructing the simulation model of an automobile engine with a very complicated shape from CAD data. Most current CAD data are obtained from 'solid models' that can represent three-dimensional shapes; however, the data are limited to information about the outer surfaces of solid models. Data in their original format cannot be used for computer simulation, so they are converted into a suitable format. The simulation model is then divided into small elements called meshes. The model also requires information on boundary conditions and physical properties. This is a very time-consuming process. Errors may accumulate during conversion processes, causing a reduction in simulation accuracy.

"The proposed VCAD system is completely different in concept from conventional CAD systems. The letter

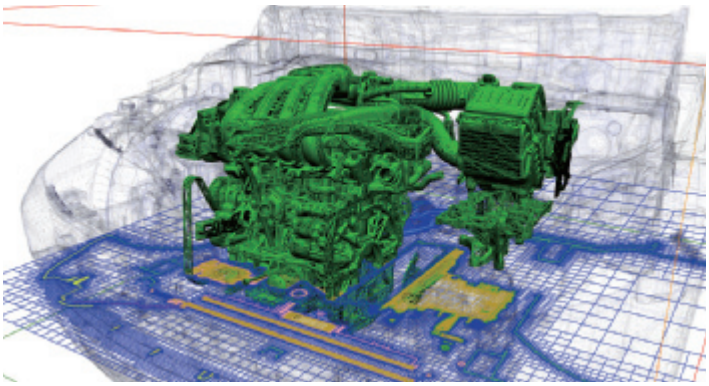


Figure 1 : VCAD model in the engine bay of a passenger car.
The VCAD system permits users to construct a simulation model or an 'electronic blueprint' from original CAD data in only about 3 min, whereas conventional systems require one to two weeks for the same purpose. The VCAD system uses a combination of 'voxels' to construct a three-dimensional shape. As mentioned in the text, a voxel is a cubic element that includes information on materials and positions.

'V' in 'VCAD' stands for 'volume.' In the VCAD system, a three-dimensional simulation model is a combination of cubic elements termed 'voxels,' in which all information such as that on materials and positions is stored. In addition, the voxels can be partly expressed by polyhedral approximation, thereby yielding a highly detailed design of shapes." The VCAD system is based on the concept that all manufacturing processes from design to manufacture should be performed consistently with a central focus on volume data. The VCAD system can significantly reduce simulation time, minimize errors, and improve simulation accuracy. Ono considers that no other research activities undertaken worldwide are based on such a concept. The VCAD system enables a user to construct an automobile engine model comprising eight billion cells in just three minutes (Fig. 1). This is one of the most advanced levels of technology in the world.

In the VCAD system, the quantity of data is reduced by using large cubic elements for simple or functionally insignificant portions and small cubic elements for complicated and significant portions. This is one of the advantages of the VCAD system; as a result, computers of only moderate speed can be used for simulation. Furthermore, the VCAD system can deal not only with artifacts but also with natural objects such as the human body. No engineering drawings are available for natural objects; however, data on natural objects can be obtained by computed tomography (CT) or magnetic resonance imaging (MRI) scanning.

Supporting skilled manufacturing

The Functionality Simulation and Information Team has been working a wide variety of fields. First, the team has been developing a system that allows users to construct a model from CAD data. This system aims at minimizing the time required for modeling by introducing automated processes wherever possible. Second, the team intends to use this model to develop an application program for various simulations such as thermal and fluid phenomena. Third, the team is planning to develop a system for analyzing simulation results. Simulation results will be compared with experimental results, and errors will be fed back to simulation models and application programs for improving the accuracy of simulation.

"The development process of a product is generally divided into several stages such as model construction, development of a simulation program, analysis of the simulation result, and experimentation. Each of these stages includes specialist researchers or system engineers. However, we undertake developmental activities in all these stages."

The major reason for this is that the voxel-based approach is unique: RIKEN is the only research institute promoting the development of this kind of system, into which peripheral technology is integrated. Ono considers it very important to support current skilled manufacturing by designing a voxel-based system that can function effectively as a whole, taking a broad perspective that includes processes from the start of product manufacture to its completion.

Ono pays special attention to a user interface when he develops application programs and systems: "A user interface relates to the operability or user-friendliness of application programs or systems. A poor design of user interface will result in a large simulation turnaround time because the time required for each operation will add up to a significant total even if each operation requires a very short time. The user interfaces of commercial application programs and systems are designed very carefully. In contrast, hardly any researchers pay much attention to the design of efficient user interfaces because they do not show an interest in user interface designs. However, researchers should do this because our programs should be sufficiently competitive with commercial products for them to be used by many companies."

Ono developed the concept during 11 years of working in product development at the automotive company. "I obtain the greatest pleasure when the application programs or systems developed by our team are used in companies, aiding in the manufacture of high-quality products."

What Ono is most concerned about at present is the development of a data analysis system. "The computation scale is increasing rapidly, and the volume of output data is also increasing in proportion to the computation scale. How can we obtain and analyze the required information from this vast quantity of data? Visualization and analytic systems are becoming increasingly important."

The term visualization may bring to mind image display. Image display, however, is not always limited to precise and detailed display. An image such

as a drawing, for example, can help a viewer to comprehend the entire image. Furthermore, a partly enhanced image helps the viewer to obtain necessary information (Fig. 2).

It should be noted that the term visualization is frequently used to imply, in a large sense, the analysis not only of images but also of any kind of data and the retrieval of necessary information from the data. The important challenge in visualization is therefore to depict the results retrieved from a vast amount of data accurately, quickly, and in an easily understood manner. The success or failure of visualization is directly linked to cost reduction and the acceleration of the entire product development process.

Supporting treatment for stones and tumors

The Functionality Simulation and Information Team is developing a simulation system targeted at the human body. "The system aims at supporting the treatment of kidney stones, gallstones, and tumors," says Ono. This research is being conducted in collaboration with Yoichiro Matsumoto, of the University of Tokyo, and Shu Takagi, Team Leader of the Organ/Whole Body-scale Research and Development Team, Research Program for Computational Science in RIKEN.

In a recently used method for treating kidney stones, an intense shock wave is applied to a bedridden patient from the backside to crush kidney stones in the bladder. The crushed pieces pass naturally through the ureter. The burden imposed on patients' bodies by this method of kidney stone removal is less than that caused by an operation for the same purpose; however, intense shock waves affect the entire bladder, causing it to bleed significantly. Furthermore, some crushed pieces may have sharp edges or be relatively large, causing severe pain to the patient.

To avoid these problems, Ono and his joint researchers are planning a method that uses ultrasonic waves. "Because ultrasonic waves have a shorter wavelength, this method is able to crush kidney stones into smaller pieces, just like pulverizing small rocks with a sharp needle. Smaller pieces of crushed kidney stones cause less pain to the patient as well."

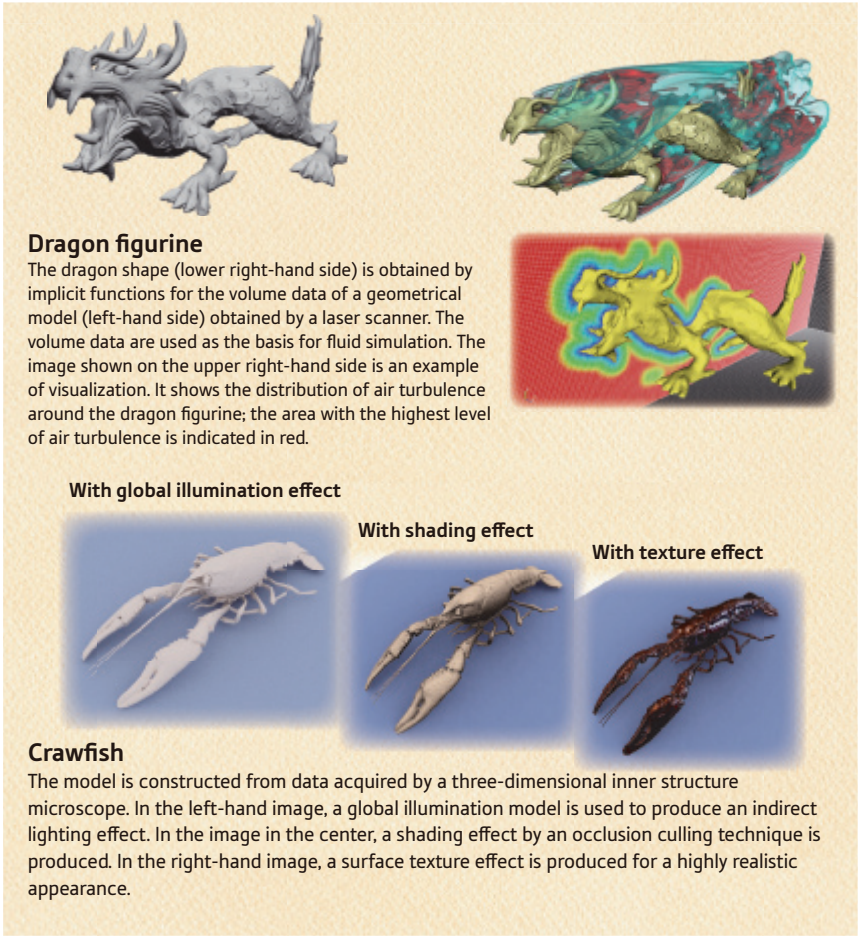


Figure 2: Examples of simulation and visualization based on VCAD system.

When ultrasonic waves are emitted from a parabolic transmitter, they converge on a single point. The sound pressure and the temperature become very high at this focal point, which enables the destruction of kidney stones and the burning of tumors (Fig. 3). Ultrasonic waves have been used in an ultrasonic pulse–echo technique. They are known to have little adverse effect on the body. However, not every problem has been solved by their use. "It is difficult to adjust the position of the focal point to precisely the point at which kidney stones or tumors are located. Internal organs usually move when a patient breathes. In such a case, further dynamic control is required," says Ono.

The body is composed of various tissues, including skin, fat, muscle, and bone. It is difficult to adjust the focal point to the target position because ultrasonic waves reflect or refract differently when they pass from one medium to another. In these circumstances, simulation based on the VCAD system comes into its own. Ono says, "Initially, CT or MRI techniques are used to obtain information on the body of a patient. Next, the VCAD system is introduced to construct the simulation model for the patient. Then, simulation is performed using the model to analyze how ultrasonic waves reflect and refract. On the basis of simulation results, doctors can determine techniques for controlling ultrasonic waves beforehand. We are planning to examine the entire process in real time."

The technology is expected to be practical for use within five to six years. "Biomedical simulation is so complicated that present computers cannot handle it. We intend to perform the simulation

with a next-generation supercomputer, which is under development at RIKEN; it is planned that this supercomputer will start in service in 2012. We intend to make the simulation fit for practical use by obtaining accurate results."

Ono is part of the team for the Research Program for Computational Science and has been working toward developing software programs for the next-generation supercomputer. "I have something you might be interested in," says Ono. "The next-generation supercomputer is aiming at a computational speed of 10 petaflops (10 peta (10^{16}) floating point operations per second, or 10 quadrillion operations per second), which is expected be one of the fastest in the world at the date of completion. The performance of computer simulations is not always determined by the hardware-based computational speed because performance is significantly affected by the software programs used. People tend to be fascinated by the term 'the fastest computer in the world'; however, the development of software is as important as that of the computer hardware itself."

Promoting the appeal of computational science

Ono considers that there is a shortage of qualified personnel, and that there have recently been fewer researchers wanting to study computational science. "This is a big problem. Information science was very popular when we were at college, whereas life sciences seem to be more popular now. However, life sciences always involve simulation, so I would like to promote the appeal of computational science so that young researchers become interested in it and work together with us."

What does Ono believe to be the appeal of computational science? "When observing a natural phenomenon, people may want to know how it occurs. Simulation can provide them with the answer. On the basis of observations of and insight into physical phenomena, we attempt to formulate rules that explain the phenomena mathematically (modeling) and develop programs based on the modeling to determine whether or not it provides a good explanation for the physical phenomena. This process is really interesting."

What Ono wants to do in the future is 'brain simulation': many papers have been written on the simulation of signal transmission in nerve cells. In nerve cells themselves, an action potential is transmitted. In addition, materials such as neurotransmitters are transported in the same manner as ordinary cells. An integrated simulation of the transport phenomenon and signal transmission in nerve cells is therefore an interesting topic. 'Live cell modeling,' which refers to the modeling of an entire living cell, is one of the research areas of the VCAD System Research Program. At present, metabolism simulation is being performed as an example of live cell modeling. Advancements in modeling technology in the near future may enable the simulation of signal transmission in nerve cells. "At RIKEN, we have researchers in the field of brain science who are working at the same site as us. I would like to take advantage of the favorable environment at RIKEN."

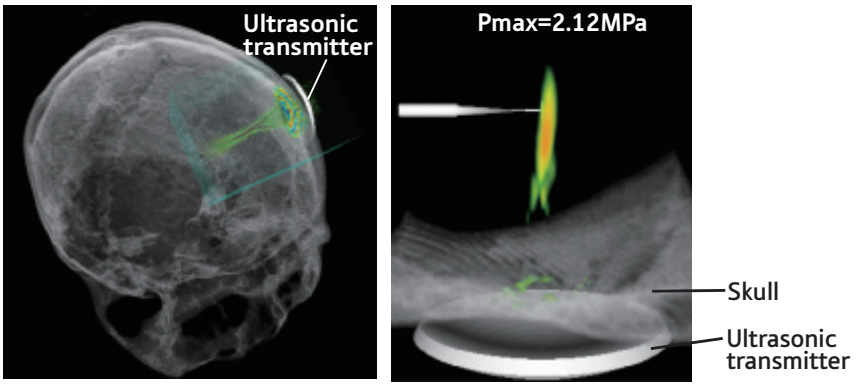


Figure 3: Examples of simulations illustrating ultrasonic treatment for stones and tumors.
The picture on the left shows an instantaneous sound field (sound pressure distribution) produced by an incident ultrasonic wave applied to the temporal region of a patient's head. The picture is an example of visualization, which shows how the ultrasonic wave is transmitted within the human body. It shows that most of the incident wave is reflected from the skull and only a small part is transmitted through the brain. The picture on the right shows the maximum sound pressure of the incident ultrasonic wave applied to the temporal region of the head. If a wave emitted from an ultrasonic transmitter travels uniformly in a homogeneous medium, the maximum sound pressure is observed at a geometric focal point (the end of the white bar). In this picture, however, the maximum sound pressure is observed in front of the focal point. This is because skin, fat, muscle, and bone have different physical properties, causing the ultrasonic wave to be absorbed or refracted differently in each case. Therefore, to focus ultrasonic waves on a target position, it is necessary to construct a model beforehand based on image data obtained by ultrasonic echo, CT, or MRI techniques and to control the model by computer simulation.

About the researcher

Kenji Ono was born in Oita Prefecture in 1966. He graduated from the master's course at the Graduate School of Engineering, Kumamoto University, and started work at the Nissan Research Center in 1990. He was admitted to the doctoral program at the Graduate School of Science and Technology at the same university in 1999, and received Doctorate of Engineering in 2000. He went on to become Associate Professor at the Department of Mechanical Engineering, Faculty of Engineering, the University of Tokyo in 2001. After three years he was appointed as Laboratory Head of the Product Performance Simulation Team, Integrated VCAD System Research Program, RIKEN. He has also held the additional post of a visiting associate professor at Hokkaido University since 2005, and a visiting professor at Iwate Prefectural University since 2008. He has been in his current position since 2007, also as a member of the High-Performance Computing Team, Integrated Simulation of Living Matter Group, Computational Science Research Program. His area of expertise is voxel-based fluid simulation and information visualization, which are useful for product design.

RIKEN scientists present research at AAAS 2009 annual meeting

A group of scientists from RIKEN presented their research at the 2009 Annual Meeting of the American Association for the Advancement of Science (AAAS) that was held in Chicago from February 12 to16.

In keeping with the theme of the meeting this year, 'Our Planet and Its Life: Origins and Futures', the RIKEN group that made presentations on their work included researchers doing cutting-edge work on environmental and life science-related topics.

Misao Itouga of RIKEN's Plant Science Center in Yokohama presented his team's findings on using moss to remove heavy metal contaminants from water.

Tetsushi Hoshida of RIKEN's Brain Science Institute and the Japan Science and Technology Agency Miyawaki Life Function Dynamics Project (part of the Exploratory Research for Advanced Technology (ERATO) program), discussed live imaging technologies with novel fluorescent proteins.

Kyoko Masuda of the RIKEN Center for Allergy and Immunology's Immune iPS Project, part of JST's CREST (Core Research for Evolutional Science and Technology) program, gave a talk on her research into the therapeutic potential of induced pluripotent stem (iPS) cells derived from mature lymphocytes.

Che-Hsiu Shih of the RIKEN SPring-8 Center in Harima talked about his work using X-ray charge density to directly observe chemical interactions at the molecular level, which can be applied to biomolecules such as proteins. A Taiwanese doctoral candidate who is conducting research as a RIKEN International Program Associate, he also talked about his life at RIKEN to university undergrads and post-doc students who are interested in working in Japan.

RIKEN shared a booth, which had a meeting area for presentations, at the conference with JST. The booth featured a presentation on the Omics Science Center, one of the primary life science centers at RIKEN's Yokohama Institute. The OSC presented an example of its stereoscopic high-vision movies illustrating the process of transcription and translation in a living cell with unique mechanical motifs. The booth also included a presentation on the X-ray Free Electron Laser (XFEL) currently being built at SPring-8.

The exhibition floor was filled with booths from almost 100 research institutes and universities. More than 300 people, including young researchers, high school students and teachers, business persons and journalists, visited the RIKEN/JST booth and enjoyed communicating with RIKEN's researchers.

Symposium provides update on XFEL construction

The hotly anticipated X-ray Free Electron Laser (XFEL) is nearing completion at the SPring-8 syncrotron facility in Hyogo Prefecture, and work is progressing toward startup in 2011. The 4th XFEL symposium was held on December 12, 2008, at the Tokyo International Exchange Center Heisei Plaza.

Speakers at the symposium gave detailed reports on the project's progress in the past year. The SPring-8 Compact SASE Source (SCSS) accelerator, a smaller-scale prototype XFEL, has begun operation ahead of the startup of the full-size XFEL. The SCSS succeeded in seeding the laser and achieved acceleration inclination and a high repetition rate.

Close observation of spider silk was done by users of the SCSS accelerator, and two-photon ionization was achieved using the light from SCSS. Because the distance needed for the laser to reach saturation has been greatly shortened, the quality of light may rise further, and even more compact XFELs may be possible in the future.

The speakers also reported on the progress of the XFEL construction. The XFEL building is almost complete, they noted, and mass production of C band tubes and klystrons began last year, as did construction of the electron beam transport tunnel from which the electron beam will be injected into the SPring-8 accelerator. Design work on the experiment hall and beamlines also began last year.

Participants were especially interested in practical uses of the XFEL, particularly in research laboratories and industrial applications.

The XFEL has been a high-priority national technology project since it began in 2006. When complete, the device will generate light a billion times brighter than existing X-ray sources, with pulses 1,000 times shorter. The laser's extremely fast femtosecond pulses will permit direct examination of the movements of objects at atomic-level resolution, and will help scientists break new ground in a variety of scientific fields, such as nanotechnology, materials science and life sciences. The facility should be available for experiments from April 2011.

Joint conference with MPG in Munich

The 'MPG RIKEN Bilateral Conference on Interdisciplinary Cooperation' was held at the Max-Planck-Gesellschaft (MPG) headquarters in Munich from January 21 to 23.

Science sessions in three areas - life science, materials science and physics - were held, with the subjects varying from the extremely small, such as manipulation of single molecules, to the entire universe. Lots of lively discussions ensued among the 28 participants from RIKEN and 28 researchers from eight Max Planck Institutes.

Kai Simons of the Max Planck Institute (MPI) of Molecular Cell Biology and Genetics gave a talk on cell membranes and phase separation, and Stefan W. Hell of the MPI for Biophysical Chemistry reported on a novel technology on fluorescence in nanoscopy and its application to lipid dynamics in plasma membranes.

Tetsuya Ishikawa of the RIKEN SPring-8 Center introduced the compact X-ray Free Electron Laser (XFEL) project. Masahiro Teshima of the MPI for Physics and Toshikazu Ebisuzaki of the RIKEN Advanced Science Institute (ASI) described their research in high-energy astrophysics by multi-wavelength carriers.

MPG-RIKEN joint meetings were held on the 23rd with RIKEN Executive Director Yoshiharu Doi, RIKEN ASI Director Kohei Tamao, its Deputy Director Yoshihito Osada, where they discussed the details of their further cooperation. They agreed to set up one or more associated research laboratories in certain areas and promote exchanges of researchers, especially young ones.

At a courtesy visit with MPG Secretary General Barbara Bludau to commemorate the 25th anniversary of the cooperation agreement, both institutions confirmed that they would enhance their collaboration in future.

Dr. Koji Ishibashi
Chief Scientist
Advanced Device Laboratory
Advanced Science Institute
Wako, Saitama, Japan

Dear Ishibashi-san,

As we draw ever closer to the twentieth anniversary (hard to believe!) of working on collaborative research together, this postcard gives me a good opportunity to reflect on the many great memories and experiences that this time has brought. It also allows me to express my profound appreciation for the many benefits that I have derived from the time that I spent working at RIKEN. As you will no doubt remember, we first met in 1991 when I was fresh out of my PhD study and you were a researcher in the newly initiated Frontier Research Program. There really was not much in Wako at that time; I remember quite clearly exiting the station and thinking that I must have mistakenly ridden the train too far into the countryside, as there was quite literally an open field in front of the station! Hard to believe now whenever one walks into the bustling community that Wako has become.

As I think back now to the five years that I spent at RIKEN, it was a time of great development; for me personally and for my scientific career, for RIKEN and the Frontier Program, and for Wako in general. I still remember the construction of the store Itō Yōkadō, and the excitement it caused in the community the day that it opened. My apartment was right next door, which was a great convenience once the store was built but not during construction!

More seriously, however, I can say without any doubt that my time at RIKEN was critical in projecting me along my career path, which has now led me to my current position in Buffalo. During my time in the Frontier Program, I was given enormous freedom to choose my research directions and was provided with a world-class facility to pursue them. Perhaps even more impressive was the fact that, in spite of being just a relatively inexperienced researcher, I was constantly given the opportunity to highlight my research to the many eminent scientists who would visit RIKEN, including Nobel laureates. For someone just embarking upon their scientific career, I cannot imagine a better experience.

It brings me a great sense of pride to recall that the joint work that we have undertaken in nanoelectronics, including the past eleven years since I left Japan, has achieved a significant impact. More important for me, however, are the many happy memories I have of the staff members at RIKEN, who helped me as I struggled to adapt to life in Japan and who have remained good friends until this day.

Thanks to all of you, I have some great memories of Japan, just some highlights of which include playing rugby for a local team of salarymen, overcoming my fear of karaoke, and—how could I forget—meeting my wife! Every time I am at RIKEN I learn something new and I look forward to many more happy joint memories in years to come.

With best wishes,

Jonathan Bird
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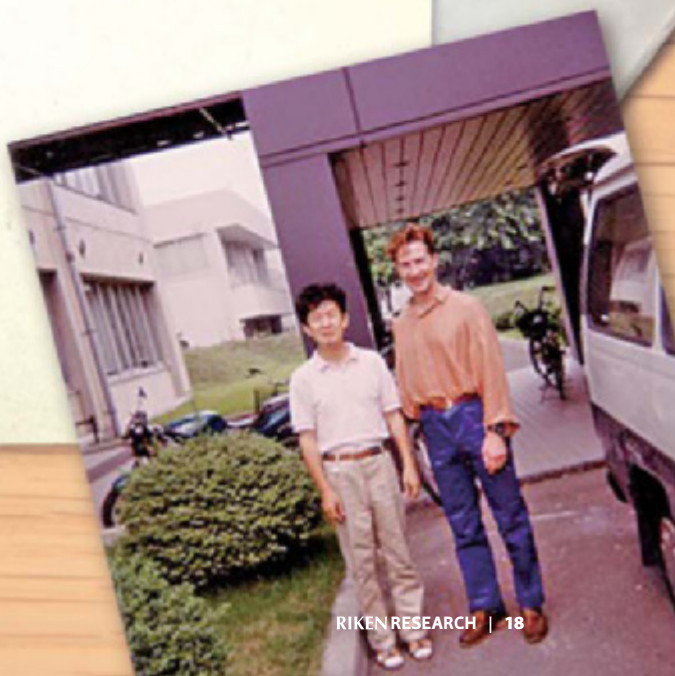

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