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Firefly mutation flashing before our eyes

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Transistor statistics add up

Better predictions of electron behavior could reduce the size of computer chips.

Tiny transistors that allow current to flow just one electron at a time could ultimately help to build even smaller computer chips. So an improved mathematical model of how the electrons move should excite scientists trying to accurately predict the behavior of these devices.

Transistors work like taps for electricity, where a voltage at one terminal controls the flow of current between two others. Conventional transistors used in circuit boards can either be 'on' or 'off', depending on whether current is flowing or not. These two states correspond to the 'ones' and 'zeros' that computers use to carry their binary information.

Single electron transistors (SETs) instead rely on just one electron dripping through the device to register a bit of information. Some SETs are made from individual molecules, and if they could be linked into a computing network it would significantly shrink the size of hardware inside electronic devices.

"I hope SETs have the potential to realise more powerful computers," says Yasuhiro Utsumi, a physicist at RIKEN's Discovery Research Institute in Wako, Japan. His new mathematical description of SETs, developed with Dmitri Golubev and Gerd Schön at the University of Karlsruhe, Germany, is a step in the right direction.

Tunnel to freedom

SETs were first built in the late 1980s and rely on an effect called quantum tunnelling. Inside the SET, electrons are confined to a particular spot of metal by an insulating gap just a few billionths of a metre wide, which acts like the high walls of a prison. The electron does not have enough energy to climb this

barrier, and yet because of the strange rules of the quantum world it still has a chance to reach the other side of the wall (Fig. 1).

This is because the probability of finding an electron in a particular place can be expressed as its quantum wavefunction, which does not abruptly fall off to zero when it hits the wall. Instead, it trails off smoothly to leave a small probability of finding the electron on the other side of the insulating gap. This means that any imprisoned electrons will slowly but surely tunnel through the wall and reach the other side.

Heavier particles find it exponentially more difficult to tunnel in this way, which is why solid objects rarely drop straight through tables. But electrons are particularly good at this sort of escapology, so reliable theoretical

models of their behavior, such as the Utsumi team's, are vital to predicting the behavior of devices relying on their individual properties.

Predicting the unpredictable

For electrons at the mercy of such quantum effects, fluctuations in their behavior can also decrease the predictability of a SET. Under certain conditions, electrons can pair up to escape from the transistor's core at the same time, and this 'co-tunnelling' can cause current leakage when the transistor is in its off state.

But the theoretical model of Utsumi's team can account for such quantum quirks, even when the device experiences the heavy traffic of electrons that is needed to maximise the working speed of the SET. Utsumi says he is particularly pleased that the model
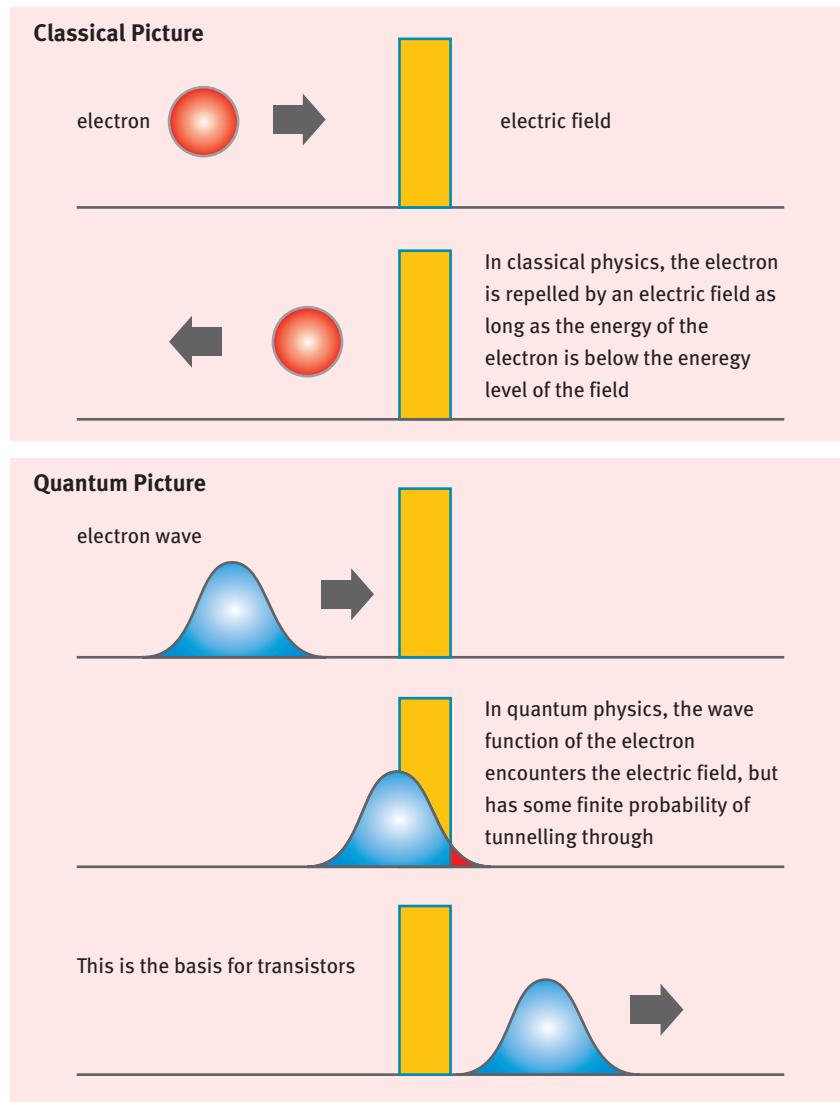
Classical Picture

electron

electric field

In classical physics, the electron is repelled by an electric field as long as the energy of the electron is below the eneregy level of the field

Quantum Picture

electron wave

In quantum physics, the wave function of the electron encounters the electric field, but has some finite probability of tunnelling through

This is the basis for transistors

Figure 1: Quantum tunnelling

seems to work under these conditions, where previous theories have been less successful. "In principle, we can find the optimum working conditions of a SET," he says.

The key to calculating the SET's current distribution is a mathematical method called full-counting statistics initiated by Levitov and Lesovik[1]. "It aims to count the electrons one by one to obtain the statistical distribution of the electron current, from which one can analyse their properties," explains Utsumi.

This means that changes in the current through the transistor can be predicted for different conditions, and Utsumi hopes that other research groups will soon be able to measure these current profiles in working devices. The team describe their method in the journal *Physical Review Letters*[2].

Super sensitivity

The mathematical method has also helped Utsumi to figure out how electrons move around in tiny fragments of material known as quantum dots, which can be made from less than a thousand atoms. In a paper posted to the arXiv preprint server[3], Utsumi shows that full-counting statistics can predict how electrical currents in the dot relate to the number of electrons there, and also how the electrons move in and out of the dot. With a better theoretical understanding of how quantum dots work, scientists can better explore how to link them together into networks that could form the basis of more powerful computers.

Utsumi adds that the model could soon benefit researchers who are already making the most of SETs. "In laboratories, SETs are actually used as ultra sensitive electrometers," he says. Electrometers can detect the movement of extremely small charges, "but the noise generated by the current flowing through the SET itself limits their performance," explains Utsumi. "So it is quite important to know the current distribution, from which one can get the noise properties." ■

1. Quantum Noise in Mesoscopic Physics, Vol. 97 of NATO Science Series II: Mathematics, Physics and Chemistry edited by Yu. V. Nazarov (Kluwer Academic Publishers, Dordrecht/Boston/London, 2003).

2. Utsumi, Y., Golubev, D. S. & Schön, G., Full counting statistics for a single-electron transistor: Nonequilibrium effects at Intermediate Conductance. *Phys. Rev. Lett.* **96,** 086803 (2006).

3. Utsumi, Y., Full counting statistics for number of electrons dwelling in a quantum dot. Preprint at <http://arxiv.org/PS_cache/cond-mat/pdf/0604/0604082.pdf> (2006).

About the Author

Yasuhiro Utsumi graduated from the Faculty of Engineering, Tohoku University in 1998, and earned his doctorate of information sciences at the same university in 2001. He served as a postdoc fellow at Max Planck Institute of Microstructure Physics in 2002-2004 and then at Institut für Theoretische Festkörperphysik, Universität Karlsruhe, both in Germany. In April 2005, Utsumi became a postdoc fellow at the Condensed Matter Theory Laboratory of RIKEN's Discovery Research Institute.
http://www.riken.jp/lab-www/cond-mat-theory/people-e.html

Upending a protocol to optimize gene analysis

Switching ends to analyse messenger RNA opens a door to reliable and unbiased global analysis of mammalian gene expression.

Genome scientists at RIKEN have improved and standardized a previously published protocol for rapidly cataloguing and quantifying all messenger RNAs present in a biological sample[1].

Messenger RNAs represent a critical link between the information encoded in individual genes on a genome and the protein makeup that determines an organism's fate. Analyzing the complexity of this information transfer process, called 'transcription', requires the development of sophisticated molecular tools that can capture both the qualitative and quantitative aspects of gene expression.

Yoshihide Hayashizaki from RIKEN's Genomic Sciences Center in Yokohama and colleagues from RIKEN in Wako and K.K. Dnaform in Tsukuba, Japan, have outlined a complete roadmap for obtaining high-quality measurements of mouse and human gene transcript levels. The researchers call their method 'cap analysis of gene expression (CAGE)' in reference to the 'cap' structures at the 5' end of messenger RNAs—the end of the molecule under analysis.

Much like a fingerprint contains all the information needed to uniquely identify a person, a DNA copy of a short sequence from one end of the RNA strand, the so-called 5' end, provides a specific 5' end sequence marker (tag) for every messenger RNA.

Previously researchers have extensively analyzed the other end of the messenger RNA, the so-called 3' end. Profiling the 5' end of the molecule increases the resolution and reliability of gene expression analysis because it contains sequence information directly involved in orchestrating the transcription process.
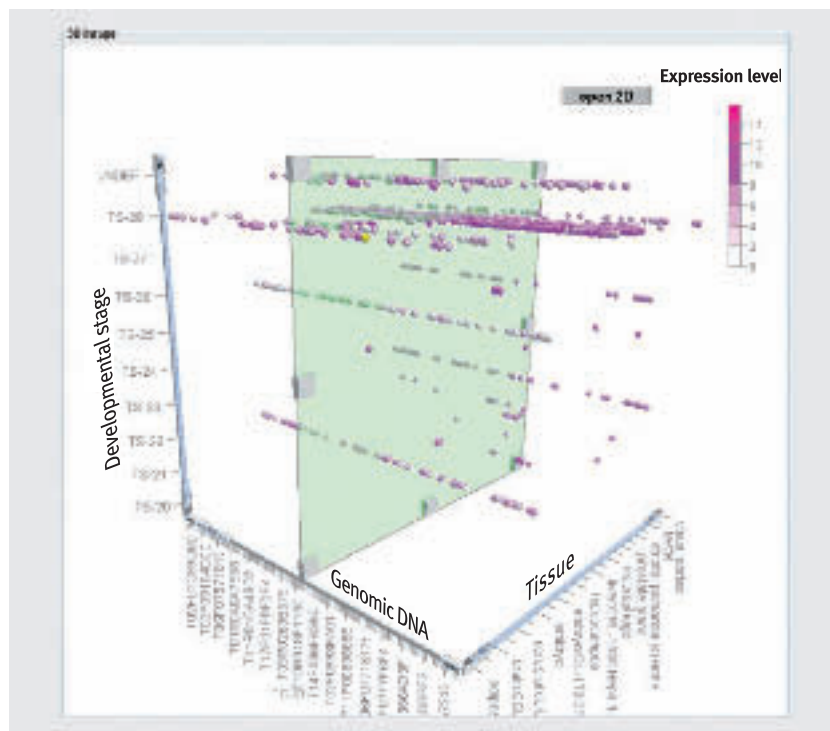

Figure 1: 3D visualistation of CAGE transcripts expression

The thousands of short tags generated from a 5' end sample are each 20 nucleotides long (a nucleotide is the basic building block of RNA and DNA strands), and can be best decoded by applying conventional DNA sequencing to chains of 10 to 20 tags at a time.

In order to allow for efficient tag generation and subsequent concatenation, the authors attached short recognition sequences to the 5' end of the full-length DNA copies of the messenger RNAs to serve as anchors for an enzyme that cuts the DNA strand at a distance of exactly 20 nucleotides and leaves 'sticky' ends on the newly formed tags to facilitate their attachment to other equally sticky tags.

The protocol published by Hayashizaki and colleagues provides an optimized approach to gene expression analysis that could be used by laboratories around the world to generate unified, comprehensive catalogues of expressed sequence tags from mouse, human and other organisms for medical or biotechnological purposes.

The work is reported in *Nature Methods*, March, 2006[2]. ◾

1. Shiraki, T. *et al.,* Cap analysis gene expression for high-throughput analysis of transcriptional starting point and identification of promoter usage. *Proc. Natl. Acad. Sci. USA* **100**(26): 15776–15781 (2000).

2. Kodzius, R. *et al.,* CAGE: cap analysis of gene expression. *Nat. Methods* **3**(3): 211–222 (2006).

An axis of embryonic development

Details revealed of a molecular mechanism that determines the position of cells in vertebrate embryos, and how they will develop.

Researchers at RIKEN have uncovered details of a molecular mechanism which marks out where cells are with respect to the ventral (front) and dorsal (back) sides of early embryos of vertebrate animals. At this stage, the position of a cell determines what it will eventually become, so the establishment of such a dorso-ventral axis is a significant step in development. The research team also identified a protein in zebrafish which controls setting up the axis.

Knowledge of such molecular mechanisms affecting early embryonic development could well find application in regenerative medicine.

Earlier work in amphibian and fish embryos by other researchers showed that the establishment of the dorso-ventral axis is a result of antagonistic interactions between bone morphogenetic proteins (Bmp) and a group of molecules, known collectively as the dorsal organizer molecules and derived from the most dorsal part of the embryo.

Sections of a key dorsal organizer molecule, Chordin, are cleaved off serially by enzymes the further it moves away from the dorsal side. As Chordin becomes progressively broken up in this way, its ability to counter the activity of Bmp weakens. So the Chordin-Bmp interaction marks out a gradient from the dorsal region, where Chordin is fully active and Bmp is repressed, to the ventral region where Bmp is fully active and Chordin is repressed. The details of the control of this process, however, were unknown.

While many mutants cause the overdevelopment of dorsal tissues in zebrafish, only two are known to lead to ventral overdevelopment. The research team from RIKEN's Center for Developmental Biology in Kobe, Japan,

Figure 1: A comparison of a normal (wild-type) embryo with mutant embryos lacking Chordin (chordino) and Sizzled (ogon).

worked primarily with one of these two. This mutant occurs in a gene which codes for a protein known as 'Secreted Frizzled' or 'Sizzled'.

The researchers found that the Sizzled protein exerts its impact only in association with Chordin. In fact, the Sizzled protein inhibits the enzymes which break down Chordin, and in this way controls the establishment of the Chordin-Bmp activity gradient along the dorso-ventral axis. This is the first time such an important role has been recognized for the Sizzled protein. These findings are published in *Nature Cell Biology*[1].

"The enzymes which cleave Chordin have been implicated in many pathological processes, such as inflammation and cancer," says the leader of the research team, Masahiko Hibi. "The Sizzled protein may find a role in treating these conditions," he says.

The research group is now searching for what triggers the determination of the dorsal region, a process which takes place just after fertilization. ■

1. Muraoka, O., Shimizu, T., Yabe, T., Nojima, H., Bae, Y-K., Hashimoto, H. & Hibi, M., Sizzled controls dorso-ventral polarity by repressing cleavage of the Chordin protein. *Nature Cell Biology* **8**, 329-340 (2006).

Firefly mutation flashing before our eyes

One amino acid substitution changes Japanese fireflies from yellow-green to red.

For centuries, on dark evenings in early summer, Japan's *Genji-botaru* firefly (*Luciola cruciata*) has delighted villagers with its luminous mating manoeuvres over local streams.

Like most of the world's 10,000-odd firefly species, *L. cruciata* glows yellow-green, but a few species display their ardour with an orange to red blush (Fig. 1).

In 1991, Japanese researchers[1] created three *L. cruciata* mutants that glow orange, or in hues of red. The mutations subtly alter the amino-acid sequence of an enzyme in the firefly, luciferase, which catalyses the reaction for luminescence.

RIKEN Harima Institute X-ray crystallographer Toru Nakatsu[2] and his colleagues have now shown that the mutations result in changes in flexibility of a side chain that loops out from the luciferase molecule to bind to another molecule luciferin that provides a substrate for the enzyme.

In the binding process, Luciferase accelerates the oxidation reaction of luciferin through specific intermediate, yielding a high energy state of oxyluciferin. When electrons in the oxyluciferin molecule move from a high energy 'excited' state to a lower energy 'ground' state, light is emitted and the color is dependent on the difference in energy between the two levels.

The RIKEN researchers looked for differences between the wild-type and red-emitting mutant enzymes, after determining their crystal structure.

Using a synthetic mimic of the specific intermediate of the reaction, they compared its interactions with wild-type and mutant luciferase during luminescence. They found that, as wild-type luciferase binds to luciferin, the side chain changes shape, but this does not occur in the red-emitting, mutant. As a result, the red-emitting mutant loses a portion of energy and the energy difference between exited and ground state electrons is different resulting in a different color of emission.

The RIKEN researchers generated two more novel, mutant luciferases, with medium- and small-volume side chains based on the above hypothesis. As they predicted, they produced orange and red luminescence further confirming their interpretation of the cause of color variation. ■

1. Kajiyama, N., Nakano, E., Isolation and characterization of mutants of firefly luciferase which produce different colors of light. *Protein Engineering* **4**(6), 691–693 (1991).
2. Nakatsu, T., Ichiyama, S., Hiratake, J., Saldanha, A., Kobashi, N., Sakata, K. & Kato, H., Structural basis for the spectral difference in luciferase bioluminescence. *Nature* **440,** 372–376 (2006).

KAZUO UNNO

Figure 1: One of the world's 10 000-odd species of firefly that glows yellow-green

Noisy whirlpools ousted to improve magnetic sensitivity

A technique that moves troublesome whirlpools of current in superconductors could help to boost the performance of these materials.

Electricity can flow through superconducting materials with no resistance, making them an extremely efficient way to carry electrical currents that can produce large magnetic fields, such as those required for medical imaging. They can also be used in instruments that measure very small magnetic fields, called Superconducting Quantum Interference Devices (SQUIDs).

But superconductors are so sensitive to magnetic fields that even the Earth's own magnetism can induce tiny whirlpools of current in the material. Each of these vortices produces a small magnetic field of their own, and their fluctuating motion introduces random 'noise' into a superconducting device, reducing its sensitivity. The vortices can be pushed around by electrical currents, or trapped by defects, like scratches, in the material.

"So we propose a way to remove these trapped magnetic flux lines that move around and produce noise in the measurements," says Franco Nori, a materials scientist at RIKEN's Frontier Research System at Wako, Saitama, Japan, and also at the University of Michigan in the USA.

Nori and his colleagues in Japan and the United Kingdom have coaxed the unwanted vortices into areas where they interfere less with the material's performance, by using an unusual alternating current that shifts quickly in one direction, and then slowly in the reverse direction. This 'sawtooth current' focuses them on the center (see Fig.1), or gently nudges the vortices towards the edges of the superconducting sample, where they pose fewer problems.

They tested the idea in a layered, crystalline material made from the

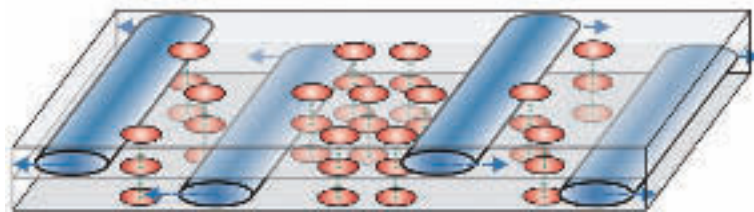**H^{AC} slowly increasing**
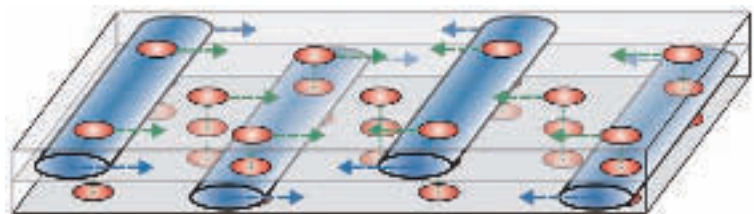
H^{AC} fast decrease

Figure 1: The 'sawtooth current' focuses the magnetic flux lines (i.e., vortices) on the center of the sample.

elements bismuth, strontium, calcium and copper, known as Bi2212, which becomes a superconductor when cooled to about -182°C. The team found that the vortices could be transported from the central part of the crystal to the edges in just a few minutes. They have published their results in *Nature Materials*[1].

Previously, researchers have tried to control these vortex currents by modifying the material itself, an extremely expensive and time-consuming procedure. The beauty of Nori's approach is that both magnetic field and electrical current can easily be tweaked so that the vortices are moved around with much greater control. The alternating current does not affect the overall operation of the device, Nori adds.

"These advantages, and its simplicity of implementation, should allow the approach to be transferred to different

systems," comments Akira Tonomura of the Hitachi Advanced Research Laboratory, Saitama, Japan and RIKEN FRS [2].

For example, the team hope that the same general technique could also be used to move 'cargo' around inside devices. This cargo could be in the form of individual units of electrical charge, or even microscopic charged particles. "This is a major thrust in our research program," says Nori. ■

1. Cole, D., Bending, S., Savel'ev, S., Grigorenko, A., Tamegai, T. and Nori, F., Ratchet without spatial asymmetry for controlling the motion of magnetic flux quanta using time-asymmetric drives. *Nature Materials*, **5**, 305–311 (2006).
2. Tonomura, A., Conveyor belts for magnetic flux quanta. *Nature Materials*, **5**, 257–258 (2006).

More to a blink than meets the eye

The molecular details of how mice learn are beginning to be revealed through eyeblink research.

Researchers from RIKEN and universities in the US and Japan have assembled evidence that, at a molecular level, training mice to blink in response to an environmental stimulus is a two-stage process which takes place in different parts of the brain's cerebellum (near the brain stem).

Such eyeblink conditioning could be a useful system with which to investigate the role of stress in brain function, the researchers say, and in particular whether stress tends to augment learning or not.

Although earlier work suggested that the cerebellum was where the memory traces of eyeblink conditioning were laid down, the molecular details of the process were not clear. So the research team, based at RIKEN's Brain Science Institute in Saitama, used a range of techniques to investigate the activity of the genes inside the nerve cells of
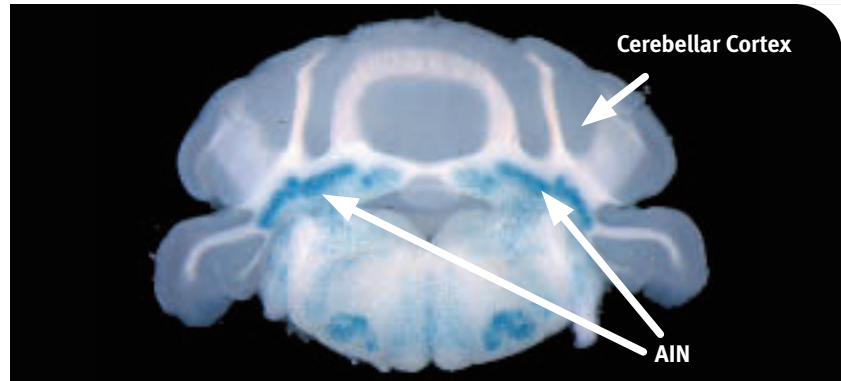
the cerebellum during the conditioning process.

Over the course of a week, the researchers trained mice to blink in response to a tone. The playing of the tone was followed by and associated with a small electric pulse to the muscles of eyelid. The researchers found that while many different genes were switched on and off during the week-long conditioning process, they fell into two distinct groups, with little overlap between the two.

One group of genes showed highest activity at the first day. The activity of the other group increased slowly over the week peaking on the seventh day (Fig. 1). The activity of the 'early' group was broadly distributed throughout the

cerebellum, whereas that of the 'late' group was localised in a deep cluster of cells, the anterior interpositus nucleus (AIN) (Fig. 2).

The data suggests that conditioning to an environmental cue initially involves laying down memory in the cortex of the cerebellum[1]. The 'emotional learning' phase primes the cerebellum tissue for a second, 'motor learning', phase of memory formation which controls the details of the blinking motion of the eyelids. The motor learning is restricted to the AIN.

While emotional learning is associated with the release of stress hormones and seems to involve the cortex on both left and right sides of the cerebellum, the motor learning for each eye tends to be dominated by memory formation in the AIN on its own side.

"In our future work, we will continue to identify the memory trace and to analyse the effects of stress on learning, particularly the differential effects in males and females," says research team member, Shigeyoshi Itohara of the RIKEN Brain Science Institute. ■
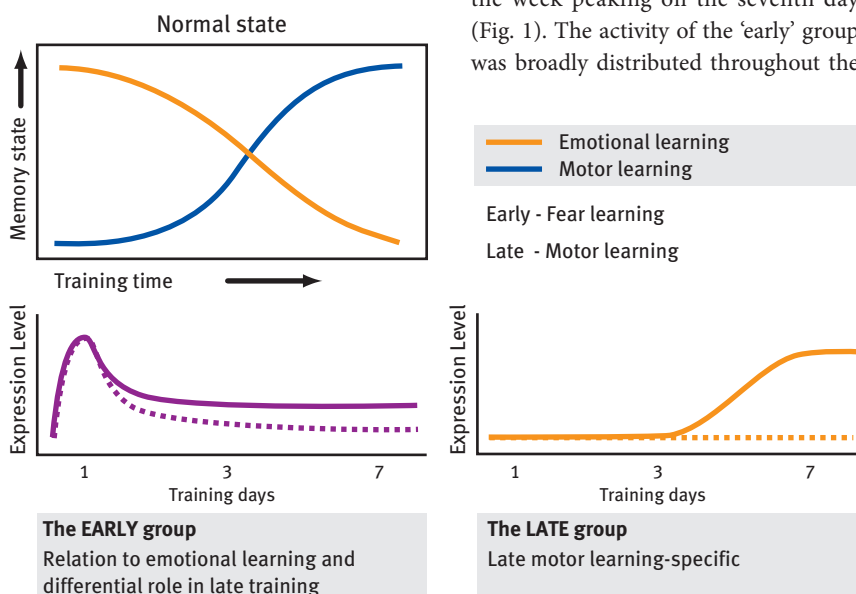

Figure 2: The anterior interpositus nucleus (AIN) of a mouse brain

1. Park, J-S., Onodera, T., Nishimura, S., Thompson, R.F. and Itohara, S., Molecular evidence for two-stage learning and partial laterality in eyeblink conditioning of mice. *Proc. Natl Acad. Sci. USA* **103**(14), 5549–5554 (2006).

Normal state

Emotional learning
Motor learning

Early - Fear learning
Late - Motor learning

The EARLY group
Relation to emotional learning and differential role in late training

The LATE group
Late motor learning-specific

Figure 1: Molecular evidence for two-stage learning in mice

Missing link in antiviral immune response revealed

Deciphering of a key step in a biochemical pathway is a mighty leap forward in understanding how mammalian immune systems work.
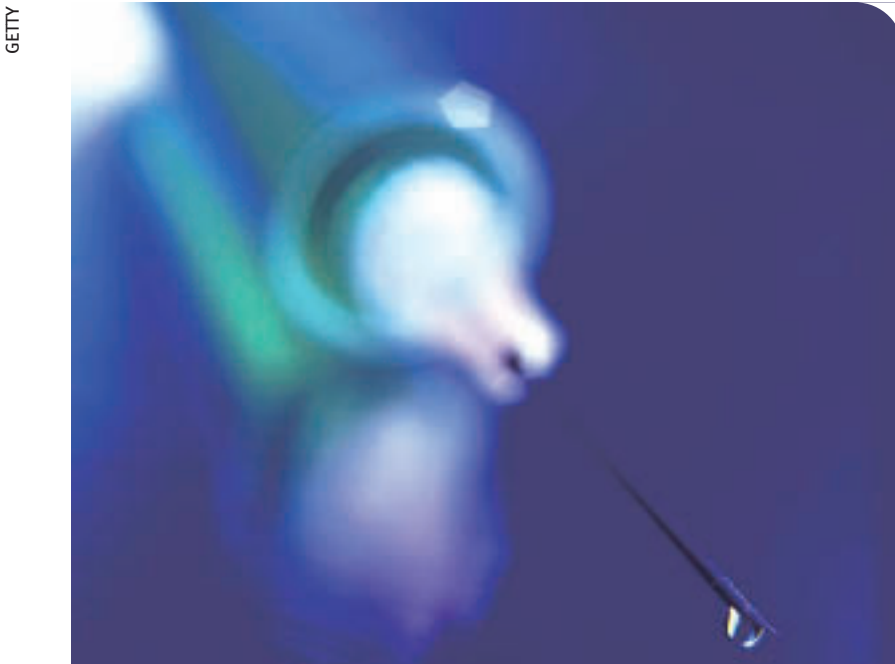
Immunologists at RIKEN have characterized a key component of the biochemical chain of events that leads to the release of interferon-α, an antiviral factor, following detection of viruses by specialized sensors expressed on the surface of dendritic cells, a kind of immune cell.

Humans and other animals are born with a sophisticated defence mechanism against viral and other microbial invasions. This so called 'innate immune response' consists of first detecting an invading particle via specific, pre-programmed sensors, also called 'receptors', followed by transmission of the signal through a unique intracellular signalling pathway, a 'signalling cascade', which leads to a 'first line of defence' immune response such as the release of interferon-α.

Tsuneyasu Kaisho from RIKEN's Research Center for Allergy and Immunology in Yokohama and colleagues from the University of Tokushima, the Research Institute for Microbial Diseases and ERATO in Osaka and Kazusa DNA Research Institute in Kisarazu, Japan, have worked out the key molecular step that mediates interferon induction by two members of the Toll-like receptor (TLR) family, TLR7 and TLR9. These receptors specialize on detecting single-stranded RNA and DNA viruses such as the influenza virus and herpes virus, respectively.

Previously, researchers had described the different components of the signalling cascade triggered by TLR7 and TLR9. It consists of an 'adaptor', MyD88, which transmits the signal detected by the receptors to an interferon 'regulatory factor', IRF7, which in turn is responsible for activating the interferon response[1,2]. How exactly the signal is transmitted from MyD88 to IRF7 remained a mystery, however.

As reported recently in *Nature*[3], Kaisho and colleagues have now determined that a kinase, IκB kinase-α, an enzyme that could potentially activate IRF7 by chemically attaching a phosphate group to it, is the key player in this step. In a series of experiments with human kidney cells, the RIKEN authors first show that IRF7 is indeed modified by IκB kinase-α. They then proceed to demonstrate that an inactivated version of the kinase inhibits MyD88-induced interferon-α production. Finally, they prove that in mice lacking IκB kinase-α, interferon-α production is greatly reduced.

The mechanistic insights gained by Kaisho and colleagues could aid the design of drugs that activate or block the TLR7- and TLR9-induced interferon-α pathway. This would be useful in the treatment of viral infections where interferon-α serves as an antidote. In addition, the treatment of autoimmune diseases such as lupus, in which the interferon response is constantly activated, could benefit from drugs that reduce IκB kinase-α activity. ■

1. Kawai, T. *et al.,* Interferon-α induction through Toll-like receptors involves a direct interaction of IRF-7 with MyD88 and TRAF6. *Nat. Immunol.* **5(10)**: 1061–1068 (2004).

2. Honda, K. *et al.,* IRF-7 is the master regulator of type-I interferon-dependent immune responses. *Nature* **434**: 772–777 (2005).

3. Hoshino, K. *et al.* IκB kinase-α is critical for interferon-α production induced by Toll-like receptors 7 and 9. *Nature* **440**: 949–953 (2006).

A common key regulator for both of two immunities

IRAK-4, an important immune defence protein, signals for both innate and adaptive immune responses.

The immune system is classified as either 'innate' or 'adaptive'. Innate immune responses rapidly detect and defend against invading pathogens. Adaptive immune responses act later, and ensure that the immune system 'remembers' invading pathogens, so that the body is equipped to respond more rapidly should the same pathogen be encountered again. Cells participating in both innate and adaptive immune responses express an array of receptors on their surface, which are able to 'sense' components of dangerous pathogens. Once triggered, each receptor activates a cascade of intracellular molecules that transmit stimulatory signals deep into the cell interior, which ultimately results in expression of defence genes.

At the RIKEN Research Center for Allergy and Immunology in Yokohama, Japan, Takashi Saito and colleagues demonstrated that IRAK-4, an intracellular molecule well-established as essential for transmission of signals in innate responses, also plays a crucial role in transmitting signals of T cells, that are in charge of adaptive immune responses (Fig. 1).

To gauge the role of IRAK-4 in T cell signalling, Saito and colleagues subjected IRAK-4-deficient T cells to a battery of immune function tests. In response to viral infection, normal T cells either mature into 'killer' cells capable of eliminating infected cells, or secrete defensive molecules called cytokines. IRAK-4-deficient T cells exhibited defective killing activity and cytokine production. Because T cells in transplant recipients perceive donor tissue as 'foreign', graft rejection occurs. Compared to normal recipients, IRAK-4-deficient recipients showed delayed rejection of foreign skin grafts. By
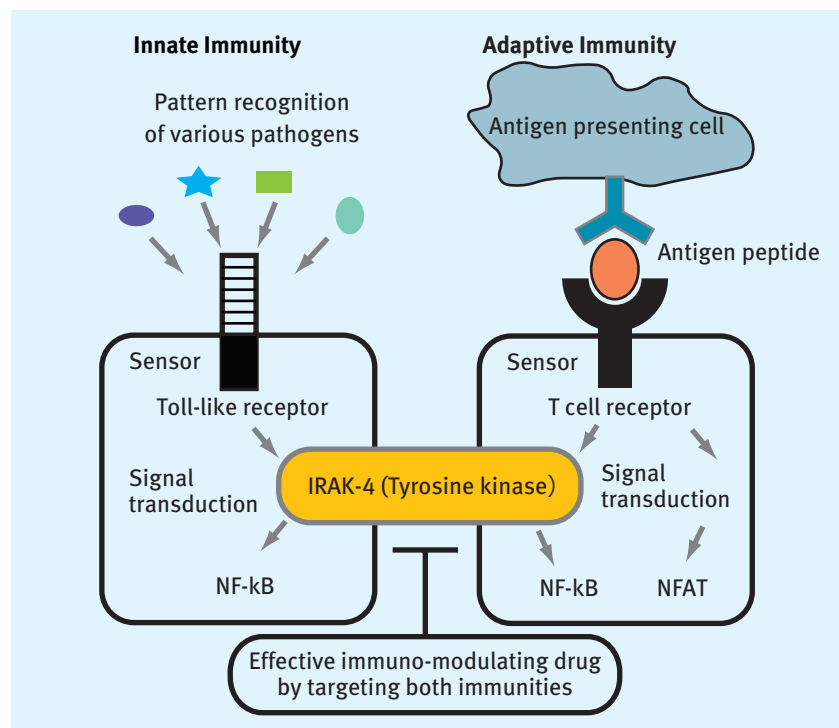

Figure 1: The role of IRAK-4 in innate and adaptive immunity

monitoring the activation status of T cell signalling molecules, the researchers traced these abnormalities to defective activation of NF-κB, a factor required for expression of defence genes. Importantly, these defects occurred even when IRAK-4-deficient T cells were placed in an otherwise normal immune system.

Previous studies identified 'adaptive' immune roles for two proteins, RIP2 and TRAF6, which were established participants in 'innate' signalling cascades. These studies, together with the study of Saito and colleagues, illustrate that the distinction between molecules contributing to innate and adaptive immune responses may not be

as sharp as previously thought. Innate and adaptive immune responses work in concert towards the common goal of defending the body against immune insults. Exactly how both arms of the immune system came to exploit the multi-functional IRAK-4 protein remains to be determined.

This work is reported in *Science*, 31 March, 2006[1]. ∎

1. Suzuki, N. *et al.,* A critical role for the innate immune signaling molecule IRAK-4 in T cell activation. *Science* **311:** 1927–1932 (2006).

Analysis of human chromosome 11 complete

Researchers poised to mine a rich resource of novel genes on chromosome 11.

The most complete analysis of one of the most gene-rich chromosomes reveals a raft of novel genes and a rich resource for researchers studying the genetic basis of disease.

Chromosome 11 is of great interest to scientists because it has a very high density of genes. It also has an intriguing history, housing the first gene identified for a human genetic disease — the haemoglobin beta gene, which is mutated in sickle cell anaemia.

A team led by researchers at the RIKEN Genomic Sciences Center developed a new gene prediction program, called DIGIT, to analyze the complete sequence. According to Todd Taylor, a member of the team led by Yoshiyuki Sakaki, DIGIT combines the gene predicting power of several different programs. "It takes the best of the programs and reduces the number of false positives," says Taylor.

"Because chromosome 11 is so gene dense, it was a time consuming process to identify all the genes," says Taylor, "We also found many overlapping genes that complicated the analysis". The authors identified 2,347 genes, of which 230 were previously unknown and 765 are likely non-functional.

Because of its high-gene density, not surprisingly many diseases have been linked to chromosome 11, including various cancers and psychiatric conditions. However, the precise identity of the genes involved remains a mystery and, with the fully characterized sequence to hand, researchers are optimistic it will accelerate disease gene discovery.

Nearly half of the olfactory receptor genes are nestled on chromosome 11 and the authors thoroughly characterized their clustered arrangement. According to Taylor, some scientists have postulated that olfactory genes originated on chromosome 11 and then duplicated within the chromosome, before duplicating further and spreading elsewhere in the genome.

During the study, the authors made an unexpected discovery: they found several cases of two adjacent genes producing a third transcript — in addition to their own transcripts — that is a hybrid of the two genes. In some cases, these transcripts make proteins, revealing a new potential group of proteins "and another layer of complexity to the genome," says Taylor.

The draft genome sequence was published in 2001 and the finished genome sequence in 2004. This study is the latest in a series of publications in *Nature*, which provide the most comprehensive analysis of each chromosome[1]. ■

1. Taylor T.D., *et al.*, Human chromosome 11 DNA sequence and analysis including novel gene identification. *Nature* **440**, 497–500 (2006).
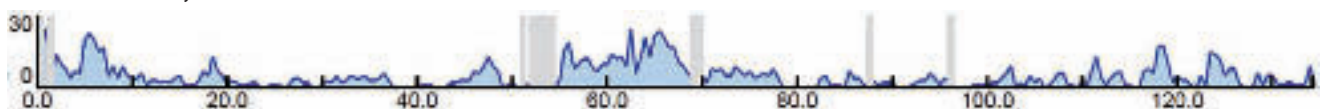
Human Chromosome 11

Figure 1: Chromosome 11. Shown in the figure from bottom to top are (1) the chromosome cytogenetic banding pattern, (2) the protein-coding gene distribution along the chromosome (# genes per 500 kilobases), (3) the olfactory receptor gene distribution, and (4) a few examples of disorders (diabetes: IDDM2 & IDDM4; leukaemia-related: BCL1) which are mapped to the chromosome but for which the causative gene has not yet been identified.

Zhaomin Hou

Tapping the potential of fragile metals

A bold insight has led a Chinese researcher to invent novel catalysts from rare earth metals.

Chemists around the world have been competing with each other to develop novel metal catalysts. But few are as daring as Zhaomin Hou at RIKEN, who enjoys tackling the extremely difficult elements called rare earth metals.

Working with those metals, Hou has been developing a number of unusual catalysts that could lead to new materials – from films to synthetic rubbers – with much better qualities than existing products.

Rare earth metals form a group of 17 chemical elements in the periodic table, including scandium, yttrium and the lanthanides (see Table). They acquired their name because they were considered scarce when they were first discovered in the late 18th century. Later it was found that rare earth metals exist in abundance, but they are highly brittle, and difficult to mine and extract from other metals. So many chemists have shied away from handling them.

Hou, however, bet on the potential of rare earths as early as the mid-1980s, when he was a graduate student at Kyushu University on the southern Japanese island of Kyushu. It was a time when, in the search for better catalysts than common metals, some chemists were just beginning to learn about rare earths. The research population is still small.

"The study of rare earth metals lags far behind other metals. I found it interesting because few people are researching them, and so many things have yet to be uncovered," says Hou, 44, now Chief Scientist at RIKEN's Discovery Research Institute in Saitama, near Tokyo.

Unexpected move to Japan

Hou's interest in rare earth metals was triggered by his supervisor at Kyushu University, who had just started researching them when Hou arrived from China at his laboratory in 1983. When Hou graduated from the University of Petroleum in eastern China in 1982, he passed a competitive examination to study abroad. At that time, Chinese students lacked the freedom to choose where to study in a foreign country, and the Chinese government decided to send him to Kyushu University, which was famous for applied chemistry.

The hardest part of starting his new life was learning Japanese, recalls Hou, who now speaks the language fluently. In 1989, after Hou earned his PhD, his supervisor introduced him to RIKEN, then the only research institute in Japan to accept postdocs. There were times when Hou thought about returning home, but given the political disorder at that time in China he decided to continue working abroad.

Table: Rare earth metals (highlighted in yellow) are highly fragile and difficult to handle, but they have great potential as novel catalysts.

Hou found that RIKEN, with its fine research environment and friendly culture, was where he could maximize his potential. He returned there in 1993 after a two-year fellowship at the University of Windsor in Ontario, Canada, and in 2002 was appointed Chief Scientist at the Organometallic Chemistry Laboratory, which has a longstanding history as one of the most prominent laboratories at RIKEN.

Flash of insight

Over the past few years, Hou's achievements have been impressive. He focuses on catalysts that can promote copolymerization, in which two or more monomers are reacted to become a copolymer that often has better properties than each of original monomers. The major breakthrough came in 2004, when his team developed a catalyst based on scandium[1] (see Fig. 1).
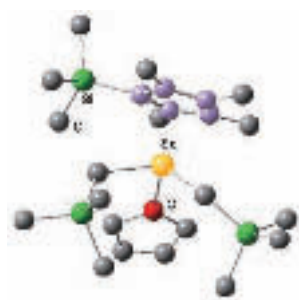

Figure 1: the scandium-based catalyst bearing a special organic support (the purple-coloured, five-membered ring compound above Sc) can realise unique olefin polymerization.

Sc = scandium
C = carbon
O = oxygen
Si = silcon

In the past, researchers have paid little attention to scandium as a polymerization catalyst because of its difficult characteristics. But based on his experience, Hou thought scandium might have similar or even better properties to titanium, which is widely used as a catalyst for some kinds of polystyrene, a common source of sheet plastic. But titanium makes polystyrene brittle, and therefore difficult to process and this limits its applications. "Polystyrene has good properties, but it's a shame that we couldn't fully enjoy their benefit," Hou says.

Researchers worldwide had been trying in vain to introduce ethylene into stereo-regular polystyrene to make it more durable and elastic. Hou thought a scandium-based catalyst could manage to copolymerize styrene and ethylene in a stereospecific fashion.

"The study of rare earth metals lags far behind other metals. I found it interesting because few people are researching them, and so many things have yet to be uncovered."

By experimenting with different organic compounds, Hou was able to create a special organic support (ancillary ligand) for the scandium, that provided an excellent catalytic system for the preparation of styrene-ethylene copolymers having the desired structures and properties. Hou says the scandium catalyst is quite unique and versatile. It can, for example, co-polymerize cyclic organic compounds (olefins) with ethylene in specific ways to make new polymer materials that can be used for optical lenses, CD discs and films.

By changing the ancillary ligand, Hou has also succeeded in developing new rare earth metal catalysts which can help synthesize polyisoprene, a man-made form of rubber, with well-controlled structures and properties superior to those of natural rubber. Although rare earth metals are rather expensive, they have shown very good cost performance because of their high

activity and the high value of the resultant products. A joint development with a Japanese chemical company is underway.

The challenge ahead

Hou's challenge has moved to far more complicated catalysts. He has been working hard to develop a new type of catalyst: multinuclear complexes containing both rare earth elements and non-rare-earth elements, based on rare-earth-metal hydride clusters developed recently by his group[2]. "We are aiming at developing a novel type of catalyst, in which the metal centers with different properties can act cooperatively on reactant molecules", Hou says (see Fig. 2).
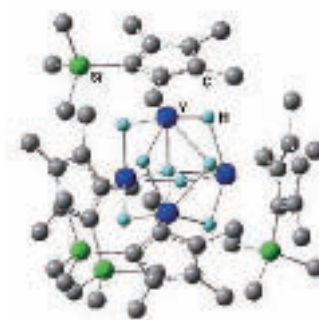

Figure 2: A multinuclear complex that has four "yttrium" rare-earth metals connected with eight hydrides.

Y = yttrium
H = hydride ion
C = carbon
Si = silicon

The search for better catalysts is always tough – but Hou never backs off. When he hits a wall, he tries to refresh his mind by sipping a favourite alcoholic beverage and chatting with his fellow researchers. When experiments fail, he discusses the problem thoroughly with colleagues and nails down the issues. Then those efforts come to fruition.

"Rare earth elements have a unique and fantastic potential in many aspects," Hou says. "However, if you handle a rare earth metal in the same way as other metals, you will fail in most cases. But if you treat it meticulously and persistently, you will eventually get some know-how, and it will not be at all a difficult metal. I hope more researchers will join in this wonderful world."

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About the researcher:

Hou graduated from China's University of Petroleum in 1982, majoring in applied chemistry, and earned his doctorate at Kyushu University in 1989. He became a postdoctoral fellow at RIKEN in 1990. After a two-year fellowship at the University of Windsor in Ontario, Canada, he became a research scientist at RIKEN in 1993, becoming Chief Scientist and Director of the Organometallic Chemistry Laboratory in 2002. Currently, Hou also teaches at Rikkyo University and Saitama University in Japan and Peking University in Beijing.

http://www.riken.jp/lab-www/organometallic/engl/index_e.html

Developing sensors that give intelligence to robots

Toshiharu Mukai

**Head of Biologically Integrative
Sensors Laboratory
Bio-mimetic Control Research Center
RIKEN Frontier Research System**

"I really hope to develop a robot that is immediately on hand, when necessary, to help us lift heavy weights but stays out of the way. We will feel comfortable with the robot at home, and the robot should also be useful for household chores, nursing care, and crime-prevention," says Toshiharu Mukai, Head of the Biologically Integrative Sensors Laboratory, relating his dream. He and his team members aim to develop a robot that has the ability to do whatever is necessary in our changing daily environment such as in the home, creating an intelligent robot that can live side-by-side with humans. Mukai points out, "Computers, which act as the brain of the robot, have advanced considerably in recent years. What is most required now in creating the intelligent robot, is to develop sensors that can respond flexibly to changes in the environment." In the laboratory, researchers are trying to develop sensors that can respond to environmental changes in the same way as humans, thus giving intelligence to robots.

From Left, Hiromichi Nakashima, Yo Kato and Toshiharu Mukai

Which have the better auditory perception, humans or robots?

On September 23, 2005, when the Bio-Mimetic Control Research Center (BMC) of RIKEN was opened to the public, noise was reproduced randomly from any one of six loudspeakers vertically arranged in two rows of three loudspeakers. Visitors to BMC were asked to compete with the robot that Hiromichi Nakashima and his colleagues have developed to see which was more effective in identifying which loudspeaker was on. How did the competition end up?

"You may turn round to look when someone calls to you. This is unconscious human behavior, but it is more difficult for current robots to perform than complicated mathematical calculations," says Mukai. The phrase "sound source localization" means locating the position of a sound source. The current mainstream approach in giving robots the ability of sound source localization is the "microphone array" technique with multi-microphones, which uses the differences in the sound signals picked up by multi-microphones to identify the direction of the sound.

However, what Nakashima is trying to develop is a sound source localization

robot with only two microphones. The robot tries to aim its camera at the estimated direction of sound, and repeatedly learns the most effective way to estimate the direction by confirming the difference between the real and the estimated directions. "Use of a larger number of microphones is, of course, advantageous to sound source localization. Strange to say, however, many animals have only two ears. There must be some benefits, such as easier data processing or learning, in the fact that they have only two ears. We want to know what the benefits are," says Nakashima.

However, how can we identify the direction of sound with only two microphones? A sound source is localized in the lateral direction on the basis of the difference of the loudness (sound pressure) and the arriving time between the sound arriving at the left and right microphones. For example, when a sound comes from the left side, the sound arrives at the left microphone earlier than the right microphone. Furthermore, the sound pressure at the left microphone is larger than that at the right microphone. What is more difficult is how to locate the vertical direction of a sound source. For performance improvement, Nakashima
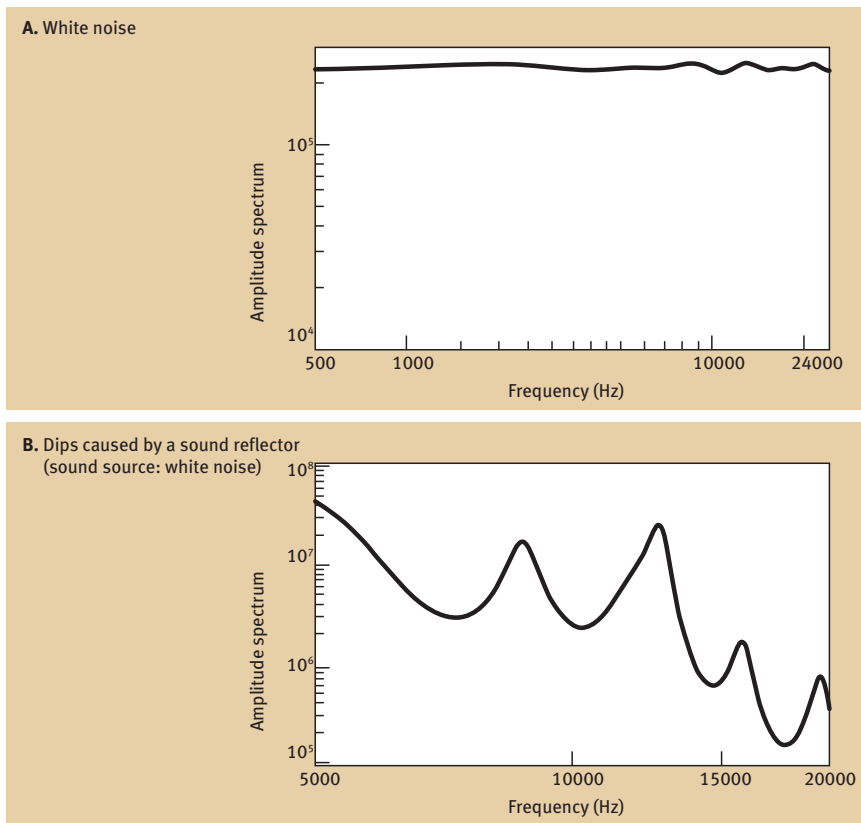
Figure 1: **Interference of sound by a sound reflector**
It is considered that both human beings and animals use the dip to obtain information for sound source location.

and his colleagues tried to install "outer ears" (sound reflectors) around the microphones. With the introduction of the outer ears, direct sounds from the sound source to the microphones interfere with the sounds reflected by the outer ears, thus causing sound wave cancellation between the direct and reflected sounds. The resulting sound, picked up by the microphones, exhibits some amplitude dips in the frequency spectrum because of the sound wave-cancellation (Fig. 1 B). The dip pattern varies with changes in the location of the vertical sound source, and is used to estimate the vertical direction of the sound source.

Now coming back to the result of the competition at the open house, it was not the visitors but the robot that won the game. However, the sound source that was used in the experiment was what we call "white noise," which contains an equal intensity of all wavelengths, and exhibits no dips in the frequency spectrum (Fig.1 A). When the white noise is used as a sound source, the robot can easily detect the dips caused by the interference of sound. Thus the robot won the game in its strongest field. However, a sound source generally exhibits some dips in

its frequency spectrum. "Since our robot is capable of analyzing a combination of four or five dips, it can distinguish the dips that are attributed to the sound source itself from those caused by the interference of sound," says Nakashima, referring to the features of the system.

However at the open house, there was a case when the robot could not locate the sound source with accuracy. It was the moment when a lot of noise was generated as the event captured a larger and larger audience. Humans have the ability to identify a talker's voice in a noisy environment such as at a cocktail party. Thus one of the future challenges for the robot is to develop a technique that gives the robot the ability to sort out only necessary sounds from amongst other noise.

Nakashima and his colleagues are planning to conduct original experiments where auditory information and visual information captured on camera are integrated for judgment processing. When we hear a sound, and when the situation of what we see in the direction of the sound is almost in agreement, we tend to think that the sound is generated at the position of what we see. This is how ventriloquism provides the illusion

of a doll speaking. However, when the ventriloquist is separated from the doll, we can easily tell that it is the ventriloquist who is actually speaking. Humans learn to tell the reasonable and appropriate distance that is necessary for matching the auditory and visual information. Nakashima says, "We will try to make the robot learn the appropriate distance." Maybe the day will come when a robot can enjoy ventriloquism.

Creating a smell identification robot

Mukai points out, "From among the five senses, the one in which robots are the most inferior to animals and humans is olfactory perception. The concentration of a known gas could be derived. However, if the kind of gas is unknown, the robot can neither tell the kind nor the concentration of the gas. The only thing the robot can detect is the existence of the gas. This is typified by the fact that some gas-leak detectors in kitchens are responsive to hot sake." "We are conducting research on how to identify the kinds and concentration of gases by using semiconductor gas sensors, which are considered to be the most durable, and used for gas-
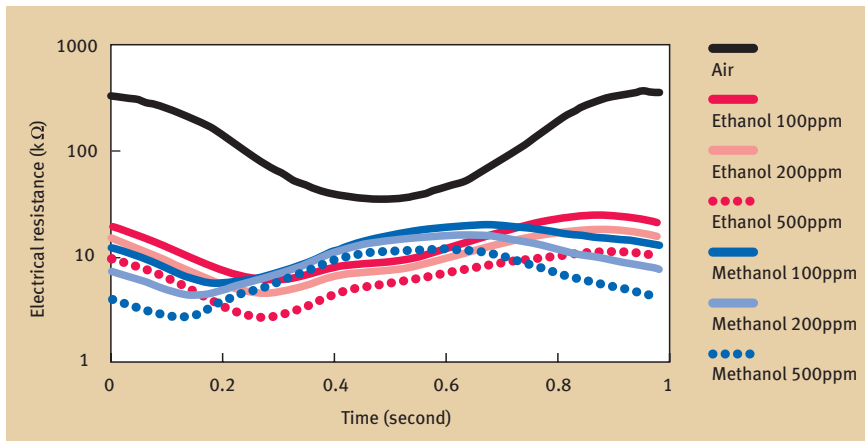
Figure 2: Identification of kinds and density of gasses by an active gas sensor

leak sensors," says Yo Kato, Research Scientist. When the semiconductor in a semiconductor gas sensor is heated to a high temperature, gases are absorbed or combusted (oxidative reaction) on the heated surface, and the semiconductor gas sensor uses the changes in electrical resistance to detect the concentration of gases. However, conventional gas sensors have been unsuccessful in identifying kinds of gases.

Why do they fail to identify the kind of gas? Because the change in electrical resistance caused by a single type-A gas molecule absorbed at the surface can be the same as that caused by two type-B molecules absorbed at the surface. This leads to an inability to separate A from B. At present, the mainstream approach for gas identification is to prepare and arrange many kinds of sensors that have different relationships between the kind of gas and the resulting change in electrical resistance. However, only about 10 kinds of sensors are available now because manufacturing itself is limited.

On the other hand, Kato, Research Scientist, and his colleagues are trying to identify the kinds and concentration of gases by applying the concept of "active sensing," which actively changes the state of a sensor, thus periodically changing the surface temperature of the semiconductor. The electrical resistance shows different time characteristics with different kinds and concentrations of gases, which enables gases to be identified (Fig. 2). According to Kato, "When A burns at 80 ºC and B burns at 100 ºC, the difference in temperature can be used for identification. Our principle is based on this concept. So far, we have confirmed by experiment that just a single sensor

is capable of identifying eight kinds of gases. We think it possible to identify further kinds of gases by changing the period of the temperature variation on the surface of the semiconductor sensor, or by changing the upper and lower limits of the variation."

He and his colleagues are advancing a study on how to mount this gas sensor on disaster-relief robots. For example, these robots are expected to detect gas-leaks at disaster sites. However, they need to detect gases in real time in an ever-changing environment because they are expected to move about, sometimes under a strong wind at a disaster site. Kato and his colleagues have built a gas detecting system that is capable of

detecting gases in real time by providing a semiconductor surface area of 1 mm^2 with a heater that can change the temperature of the semiconductor from 80 to 320 per second. In the photo on the cover page, Kato (middle) is holding a robot that is equipped with this sensor. The robot has three sensors at each of the apexes of a triangle, and the robot finds its way to the region where a greater condensation of gas is detected.

Towards the birth of "RI-MAN" in 2006

At BMC, researchers are working on research into "bio-mimetic" control, which is a technology that mimics the highly-sophisticated control functions of living systems. Zhi-Wei LUO, Laboratory Head of the Environment Adaptive Robotic Systems Laboratory, has played the leading role to integrate main achievements of the center to develop their robot, which was unveiled in March. The robot is called "RI-MAN." "We aim to develop a robot that can directly contact humans, for example, a robot that is
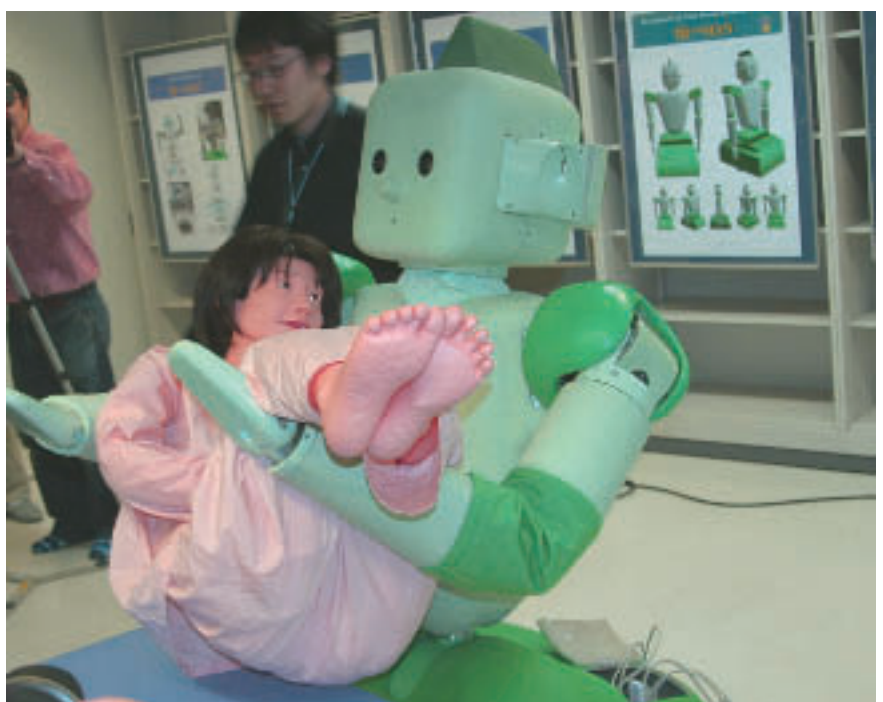

Figure 3: RI-MAN, the recently developed intelligent robot, holds a 12-kg doll.

Figure 4: Structure of the curved tacticle sensor
The array of 8 x 8 semiconductor pressure sensors, each 5.8 mm in diameter, and 18 mm apart is arranged on a single sheet. The distance between semiconductors can be shortened to about 8mm for higher accuracy. However, the minimum distance that human arms can identify is about 4 cm. thus the spatial resolution of the current array of semiconductors is enough for the robot to fold a person in its arms.

helpful for nursing care," says Mukai. So far, RI-MAN can hold a doll of about 12kg in its arms (Fig. 3), and Mukai's team aims to have the robot hold a real human in five years. "This will be a world-first challenge," says Mukai.

The robot cannot hold an infant in its arms without tactile sensors. When we hold an infant, we will try to feel the position where the pressure is located and control our arms accordingly. In the same manner, when the robot tries to hold an infant, it should control its arms by feeding back the information obtained from the tactile sensors.

Without tactile sensors, the robot may hold a person in its arms so strongly that it may cause harm to the person. However, existing tactile sensors for robots can detect only simple tactile senses such as "struck" or "touched," and the accuracy of signals from the sensors are insufficient to use for feedback signals. Why has the development of tactile sensors for robots been left on the back burner? "Basically because tactile sensors have not been required for conventional robots, which have been used in stable environments in factories, and only required to accurately perform routine operations. There has been no idea of covering a robot with tactile sensors that produce information signals on which the robot does its mechanical work," says Mukai.

He made up his mind to study the structure of the human skin so that he can develop curved-surface tactile sensors that can cover the entire body and accurately detect contact points and contact strength. The human skin includes a slightly hard layer of outer skin and a soft layer of inner skin. The complicated structure of the skin allows the contact pressure to be focused on the receptor organs of tactile sensation for accurate signal detection. Mukai and his team members have completed a structure where the contact pressure is focused on
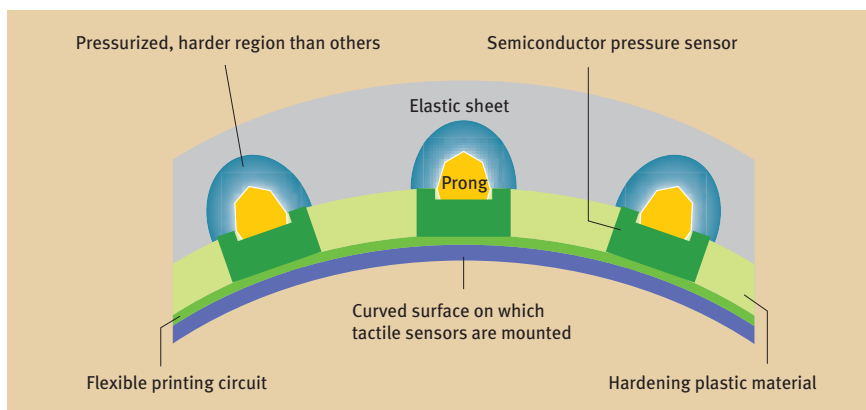
"It is the very moment when a system has just been completed, and when I make sure whether the system works well or not that I feel most excited."

high-precision semiconductor sensors by combining elastic bodies of different hardness and hard prongs (Fig. 4).

However, RI-MAN would be covered all over by cables if cables were used to directly connect the signals from the numerous semiconductor sensors mounted around RI-MAN to the central computer, which plays the role as the brain of the robot. To cope with this problem, they installed a small computer at the proximity of a sheet of semiconductor sensors (8 x 8 sensors), thus building up a system that can sort out and compress the information from the sensors and send the processed information to the central computer. For example, when one of the arms or legs of the robot bumps into something, one of the computers responsible for that portion issues a directive to withdraw it. This is analogous to the reflex action in human beings, because when a person touches something very hot, they instantaneously draw back their hand. In this reflex motion, a directive is issued from the spinal cord, not from the brain.

Mukai and his team members, using an experimental robot arm wrapped with these tactile sensors, are advancing collaborative research with the Environment Adaptive Robotic Systems Laboratory on how to hold a person properly in the arms of a robot (top of the cover page, the two black sheets are tactile sensors). RI-MAN has speech recognition capabilities and is equipped with a sound source localization system and gas sensors

developed by the Biologically Integrative Sensors Laboratory. When a person gives RI-MAN an order by voice to hold the child in its arms, RI-MAN turns around and looks at the person. Then RI-MAN moves toward the child and uses its tactile sensors to hold the child in its arms. In the future, RI-MAN will be able to use a gas sensor to detect when the baby has wet its diaper. The development of RI-MAN must be a step toward practical application of an intelligent robot that can live side-by-side with humans.

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2. "Mobile Robot Control Using an Active Type Semiconductor Gas Sensor,"The 5th SICE System Integration Division Annual Conference (SI2004) (in Japanese).

3. "Development of Soft Areal Tactile Sensors for Robots with Skin," "The Frontiers of the Development of the Super-Five-Sense Sensors," NTS (2005) (in Japanese).

4. Japanese Patent Application No. 2005-189093: Soft Tactile Sensor and Its Fabrication Method (in Japanese).

About the researcher
Mukai earned his doctorate in matematical engineering and information physics at the University of Tokyo in 1995, and became a research scientist at the Bio-Mimetic Control (BMC) Research Center of RIKEN's Frontier Research System. In 2000 - 2001, he worked at Laboratoire de Neurobiologie in Marseille, France, as a post-doc fellow, and became the head of BMC's Biologically Integrative Sensors Laboratory in 2001.
http://www.bmc.riken.jp/~sensor/

The new Nishina Center for Accelerator Based Science, and the world's most powerful cyclotron

Next year will be the seventieth anniversary of the start of operation of the first Japanese cyclotron, built by Yoshio Nishina. On this occasion RIKEN is planning to start the full operation of the RIBF (Radioisotope Beam Factory), whose main accelerator is another cyclotron. The RIBF's final-stage superconducting ring cyclotron is especially remarkable, and will be the most powerful in the world. When used together with the new superconducting radioisotope beam separator, it will open the door to a realm of research on unstable nuclei that was previously thought unattainable.

This year, RIKEN, by collaborating with research institutes in other countries has gathered together all the labs related to the RIBF to form the new Nishina Center for Accelerator Based Science, named in honor of the man who created Japanese accelerator

science here at RIKEN.

The new center will be run as an international facility for joint use, and we expect it to make great contributions to nuclear physics and hadron research. Carrying

on Nishina's intention, it will also be used for medicine, agricultural science, and other fields. RIKEN has very high hopes for its future as a multidisciplinary research institute.

The Frontier Research System celebrates its twentieth birthday

In October 2006, it will be twenty years since the foundation of RIKEN's Frontier Research System (FRS), and on May 12 a symposium was held at the Wako Campus to mark this important milestone.

FRS plays a vital role in germinating new research fields in line with RIKEN's plans for the future. It occupies an intermediate position between the Discovery Research Institute, which engages in a wide range of curiosity-based basic research, and RIKEN's other centers and institutes, which conduct project-oriented research. Kohei Tamao, Director of FRS, states that, "It is no understatement to say that the future vitality of RIKEN as a whole comes from FRS."

The main purpose of the symposium was to allow younger researchers to demonstrate their work, to encourage lateral communication, and to promote the careers of the researchers themselves, as part of an all-FRS activity. Presentations on recent achievements were given by FRS researchers from nine groups, programs, and centers, including Molecular Imaging, Terahertz-Wave, Functional RNA, and the Initiative Research Units.

The symposium also included a ceremony for the presentation of the FRS Award for fiscal year 2005. The FRS Award was first started two years ago, and is designed for younger researchers and technical staff who have made especially impressive progress

in their work. This year the top prize was won by Tsuyoshi Yamamoto, for his work on "Quantum gate operation in Josephson charge qubits." Yamamoto and the other two winners each gave a short lecture. President Ryoji Noyori gave his congratulations, and said, "I hope that as researchers you will contribute to the further success of RIKEN in the future." He added, "I hope that you will enjoy rich personal lives as well."

FRS is planning further events to commemorate its twentieth anniversary, including a symposium for the national Japan Consortium for Glycobiology and Glycotechnology project.

Meeting of the Federation of International Mouse Resources

The fourth meeting of the Federation of International Mouse Resources (FIMRe) was held at the RIKEN BioResource Center (BRC) on May 22 and 23, attended by people from twenty-four major mouse resource centers from thirteen countries around the world. The FIMRe is a collaborative group of Mouse Repository and Resource Centers worldwide, whose goal is to archive and provide strains of mice as cryopreserved embryos and gametes, ES cell lines and live breeding stock to the research community. The FIMRe was formed in 2004. Dr. Barbara Knowles of the Jackson Laboratory serves as the chairperson, and Dr. Yuichi Obata of the

RIKEN BRC is one of four vice chairpersons.

As the whole human genome sequence has been determined, an obvious next step is to elucidate the function of all human genes. There are estimated to be approximately 30,000. A powerful method for analyzing gene functions is to delete them by homologous recombination. However, it is not feasible to conduct such experiments on humans. Projects to knock out of all genes in the mouse have started in Europe, the United States and Canada. In the coming years, a deluge of mutant mouse strains is anticipated. To make those mouse strains accessible, the FIMRe was formed. As a part of its activity, the worldwide "one-stop shop" for mouse strain database, International Mouse Strain Resources, has already been successfully launched.

At the meeting, the charter of FIMRe was agreed and finalized, and the formal agreement for mouse transfer between centers, and standard operating procedures, were almost completed. The RIKEN BRC invited seven centers in China, Korea, Singapore and Taiwan as observers and organized a special session for Asian centers, in which they presented their activities. Hopefully, these centers will be able to join the FIMRe in the near future.

By facilitating genetically manipulated mouse strains, the FIMRe hopes to contribute to understanding of human health and biology.

The metamorphosis of RIKEN

Japan's premiere research institute, RIKEN, has undergone a dramatic transition from its early beginnings as a private research foundation

Over the past 89 years, RIKEN has evolved into Japan's flagship research institute, through changes in style, active exploitation of business opportunities and expansion of research fields – which now range from physics to genomics. RIKEN's growing pains required endurance but its ambitious research spirit never flagged.

In 1917, RIKEN was established as a private research foundation in Tokyo. This was just four years after, Jokichi Takamine, a pharmacologist recently returned from the U.S., proposed that Japan create a national institute to conduct basic research into chemistry. Takamine believed this area would be the key for Japan to flourish, since it is a country scarce in natural resources. Japanese scientists, academics, government and business leaders all supported the idea, so joined forces to establish RIKEN.

RIKEN's first president died shortly after his appointment, and the second resigned quickly due to poor health. But the third president, Masatoshi Okochi, built RIKEN's first golden era during his 25-year tenure from 1919.

The significance of Okochi's presidency lies in two major reforms. First, he overhauled RIKEN's rigid research structure by reducing the power of division heads and allowing chief researchers to decide budget and personnel at their own discretion. Okochi also commercialized research results—laying the foundation for RIKEN's current venture system. In the early 1920s, RIKEN started to create actively venture companies based upon researchers' inventions, which included the copier-maker Ricoh—still found in offices around the world today—as well as a synthesized-alcohol brewer, a vitamin-A maker and an absorbent-material maker. By 1940, despite being a research institute, RIKEN owned 63 companies and 121 factories and was known as 'RIKEN *konzern*'—or the 'RIKEN conglomerate' in English.

But, following the outbreak of World War II in 1941, the shine of the golden era began to fade. By 1945, most of RIKEN's buildings and equipment had been destroyed. The General Headquarters of Allied Forces, which governed postwar Japan, even dumped RIKEN's two cutting-edge cyclotrons into the murky depths of Tokyo Bay.

RIKEN was on the verge of liquidation, but Yoshio Nishina, the cyclotron's developer and the fourth president, fought hard to avert the crisis. Still, the group of RIKEN venture companies was dissolved in 1947, and RIKEN entered a sluggish period that lasted 10 years. Although there was a bright spot: in 1948 RIKEN became Japan's first academic research institute to be incorporated and new projects were added including the development of medical products. But due to funding difficulties as hard times continued, RIKEN dropped its commercial section again in 1952 to concentrate on research.

RIKEN started as a private research foundation in this building in 1917 in Tokyo's Komagome area. It has now five research institutes and hundreds of laboratories nationwide, including three labs abroad.

In 1958, the government, aiming to promote Japan's science and technology, made RIKEN a semi-public organization. Then in 2003, RIKEN became an independent administrative institution, which its officials believe is the most ideal structure for the institute to date. RIKEN staff have more flexibility in using funds, but are required to be more competitive and more efficient at producing visible results.

During the last 48 years, RIKEN has also moved headquarters to Wako city in Saitama prefecture, and established a variety of research centers under its five parent research institutes. Many researchers have become leaders in advanced research areas ranging from heavy-ion accelerators and nanotechnology to brain and post-genome research. And they have generated a plethora of outstanding research results.

On his inauguration day, Ryoji Noyori, the current president of RIKEN, announced the five-point "Noyori Initiative" plan, which includes a pledge that "RIKEN should keep shining throughout the history of science and technology."

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