



RIKEN RESEARCH

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Rebuilding the brain

A method for deriving complex neuronal tissues from embryonic stem cells could yield major benefits for clinical research and the development of new therapeutics

The great hope for embryonic stem cell (ESC) research is that scientists will be able to develop effective strategies for coaxing these cells to develop into a wide variety of mature cell types and tissues, which could in turn be used for clinical studies or even outright transplantation into patients.

As one might expect, the brain poses a particular challenge, being composed of a diverse array of cell types arranged in highly complex and specialized structures. There have been some promising signs of early progress, however. For instance, Yoshiki Sasai's team at the RIKEN Center for Developmental Biology in Kobe recently described a technique for stem cell cultivation, SFEB, which enables the reliable derivation of a variety of cerebral precursor cell types from cultured ESCs¹.

At the same time, SFEB has shown only limited efficiency in obtaining some particular cell types, such as cerebral cortical neurons—the cells that mediate many of the mammalian brain's highest-order functions, including conscious thought and sensory processing.

To improve their method, Sasai and colleagues introduced a new twist—cultivating dissociated mouse ESCs under conditions that favor unrestricted aggregation in three dimensions, rather than in adherent cultures on a flat surface². The results of their 'quick aggregation' SFEB (SFEBq) method are striking—nearly 95% of the resulting neuronal progenitors differentiated into sheets of neuroepithelial cells, brain tissue precursors with a distinctive polarized structure, in which the 'upper' and 'lower' segments of the cells exhibit distinctive physical characteristics.

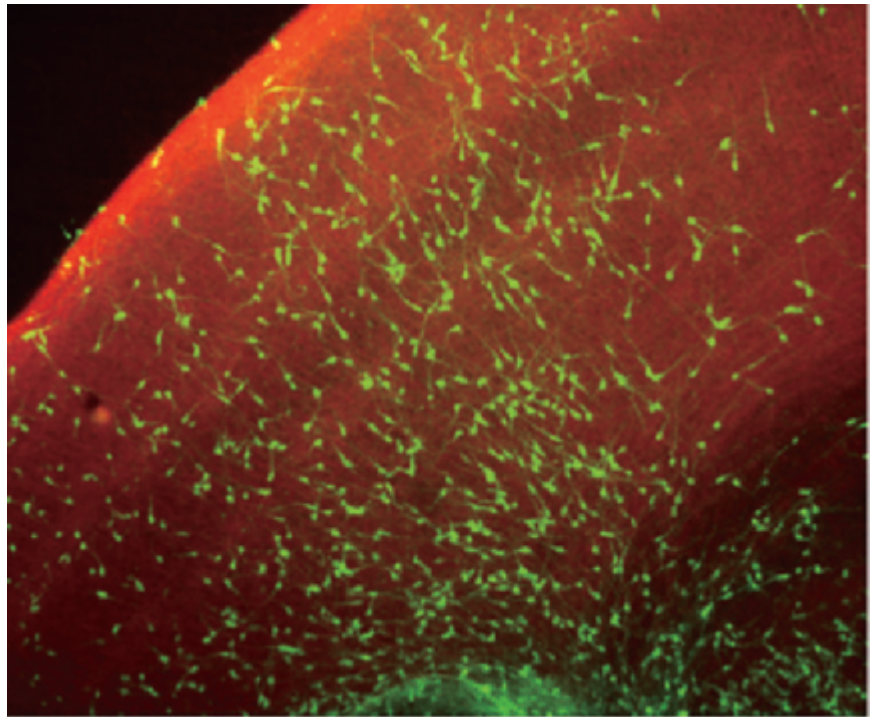


Figure 1: When cocultured with mouse brain slices, neuronal precursors derived from SFEBq cultures (green) develop into neurons that integrate with existing cerebral cortical structures.

Getting with the program

With further cultivation, these sheets reformed into spherical clusters that subsequently yielded functional cortical neurons, both in culture and after transplantation into mouse brains (Fig. 1). By further tweaking the culture conditions to include various cell signaling factors, Sasai's team was even able to derive neuronal subtypes from specific cortical structures, such as the olfactory bulb, as well as noncortical cells.

These cultures also behaved similar to embryonic cortical tissue, displaying spontaneous signaling activity and even network behavior. "The induced cortical tissues started to exhibit synchronized neural activity over a range of more

than one millimeter," he says, "which is characteristic of the neural activity seen in the neonatal cortex."

But there were other surprises as well. The cerebral cortex is composed of six parallel layers, each comprising a different cellular ecosystem of distinctive neuronal subtypes; these layers develop in a specific order, with outermost layer I appearing first, after which layers VI through II develop sequentially in an 'inside-out' manner. By examining changes over time in gene expression profiles in their SFEBq cultures, the researchers found that their ESC-derived cortical neuron progenitors were naturally entering into a stepwise developmental program of layer formation that closely mirrors normal

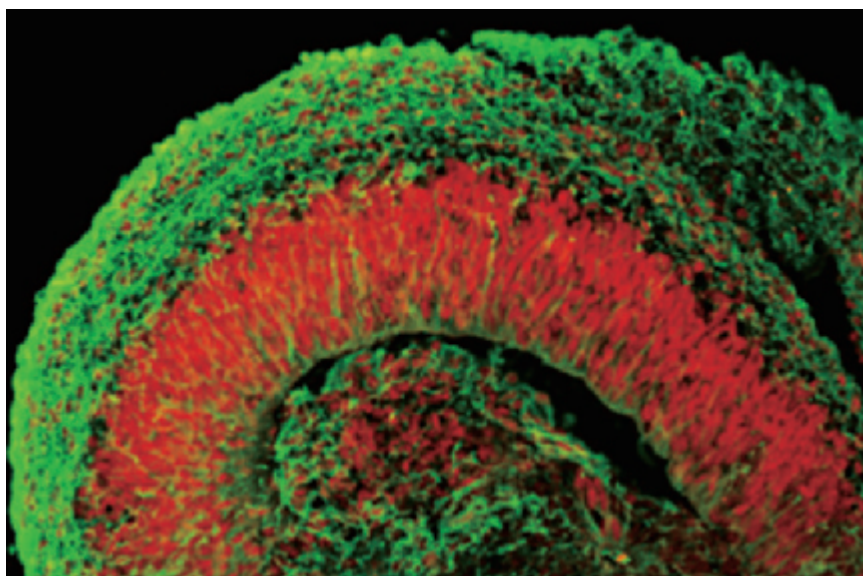


Figure 2: Human ESCs cultured via the SFEBq method develop into structures that resemble the early fetal cortex. Cells have been fluorescently stained for a cerebral marker (red) and to indicate cortical neurons (green).

embryonic cortical development (Fig. 2). “This is self-formation of a highly ordered pattern from patternless cells, which is quite impressive to me,” says Sasai. “In other words, it is the programmed nature of these cells to form such structures.”

The SFEBq cultures recapitulated the development of four of the six cortical layers in terms of timing, and the researchers were able to modify their culture protocol to isolate layer-specific neuron types. However, these layers did not exhibit appropriate physical arrangement, and two of the layers never developed at all, suggesting that considerably more remains to be understood about how this process is regulated. “It was really wonderful to see successful formation of the four-layered tissue,” says Sasai. “However, for basic scientists like me, it is even more exciting to understand why the next steps of corticogenesis fail to occur. What is missing? It may take a really long time to address this question.”

Sasai believes this work will provide a valuable starting point for exploring a number of mysteries about the early stages of cerebral development, and his team is actively working to develop new imaging tools that will allow them to monitor these SFEBq-derived cell clusters in real-time, and to attempt to better understand the processes involved in cortical differentiation.

A new approach to stem cell research

More generally, however, the ability to recapitulate and even control the complex developmental processes underlying tissue formation in culture is exciting from both a research and a medical perspective, and the successful extension of this and other techniques for neuronal cultivation and manipulation may ultimately be a game-changer for the field of neuroscience. “So far, stem cell projects have been aiming at the generation of useful cells,” says Sasai. “The present work demonstrates a new stage: the generation and use of functional tissues. This makes a large difference from working with ‘just cells’ in applications relating to drug discovery, toxicology, disease pathogenesis, and—in the long-term—tissue replacement, because such tissues mimic the *in vivo* situation much better than simple cell cultures.”

Of course, many of the more ambitious objectives relating to *in vitro* engineering of functional, transplantable nervous tissue currently remain solidly in the realm of science fiction. Nevertheless, Sasai perceives complicated ethical questions that may lie ahead as these technologies continue to advance, especially regarding how far scientists should be willing to pursue projects related to engineering of human brain tissue. “So far,” he says, “it is not difficult to answer, because the tissue we can produce right now is still very immature—far from our own cortical

tissues and their capacity for higher brain functions. However, in the long-term future, a day may come when we really need to consider the question more seriously.” ■

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2. Eiraku, M., Watanabe, K., Matsuo-Takasaki, M., Kawada, M., Yonemura, S., Matsumura, M., Wataya, T., Nishiyama, A., Muguruma, K. & Sasai, Y. Self-organized formation of polarized cortical tissues from ESCs and its active manipulation by extrinsic signals. *Cell Stem Cell* **3**, 519–532 (2008).

About the author

Yoshiki Sasai was born in Hyogo, Japan, in 1962 and received his MD from Kyoto University School of Medicine in 1986. From 1986 to 1988, he performed an internship in general and emergency medicine. In 1993, he earned a PhD from the same university for work on neural specific transcriptional regulators. From 1993 to 1996, he was a visiting research fellow at UCLA School of Medicine, California, and then appointed as an associated professor at Kyoto University School of Medicine. From 1998 to 2003, he served as a professor at the Institute for Frontier Medical Sciences, Kyoto University. From 1998 to 2003, Sasai served as a professor at the Institute for Frontier Medical Sciences at Kyoto University. During that time, in 2002, he also became a group director at the RIKEN Center for Developmental Biology. Since 2003, Sasai has been concurrently serving as an affiliated professor at Kyoto University Graduate School of Medicine. <http://www.cdb.riken.jp/sasai/index-e.html>



Quantum force on the edge

A standard measurement of resistance, the quantum Hall effect, changes dramatically at the edge of a sample

When a conductor carrying electrical current is placed in a magnetic field, the flowing electrons experience a force perpendicular to both the magnetic field and the current. The production of voltage, or potential difference, by this (Lorentz) force is known as the Hall effect (Fig. 1). It is exploited in several electronic devices such as flow sensors, joysticks, car ignitions and even spacecraft propulsion.

At very low temperatures, the classical Hall effect breaks up and displays some striking quantum characteristics. In fact, this so-called integer quantum Hall effect reveals quantizations that are so precise they have been used to accurately determine some important numbers in quantum mechanics, including the fine-structure constant that characterizes the strength of electromagnetic forces.

Now, Akira Furusaki at the RIKEN Advanced Science Institute in Wako and co-workers in Japan and the USA have shown that the quantum Hall effect is strongly affected by boundaries at the edge of a material¹. Their findings could alter the underlying quantum theories of condensed matter.

Quantum quirkiness in the Hall effect

During the classical Hall effect, the electrons moving under the influence of the Lorentz force experience resistance to their flow. This ‘Hall resistance’ increases linearly with the strength of the magnetic field (Fig. 2a).

The quantum version of the Hall effect was discovered in 1980 when researchers measured the properties of electrons confined to just two dimensions at very low temperatures near absolute zero. Here, the Hall resistance looks very different—it jumps up in quantized steps

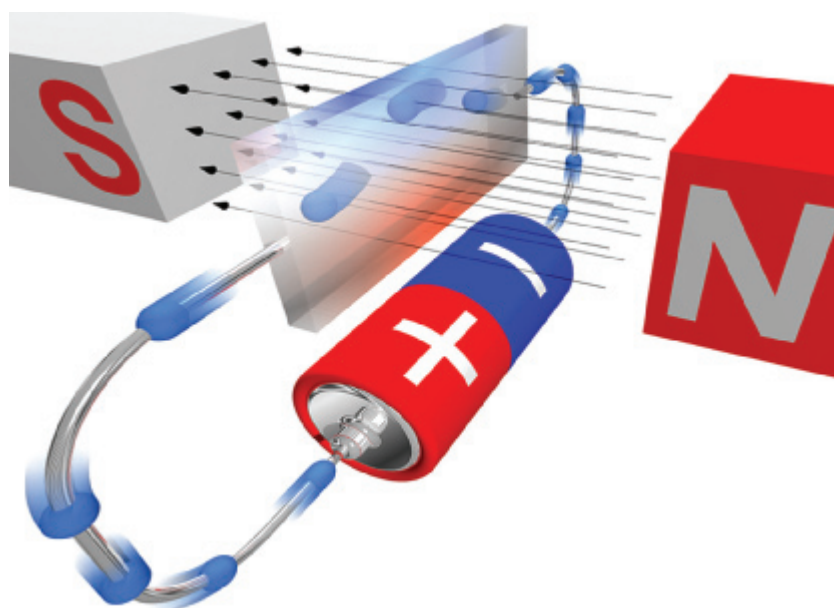


Figure 1: The classical Hall effect—electrons (moving blue spheres) flowing in an external magnetic field (between ‘S’ and ‘N’) experience a force at right angles to both the field and the current flow. At very low temperatures this transforms to the quantum Hall effect.

as the magnetic field strength increases, producing a series of plateaus (Fig. 2b).

The size of each step is determined by two fundamental constants, the electron charge e and Planck’s constant h , regardless of the material being studied. This quantum Hall effect is so precisely quantized that it is now used as a standard of resistance measurement.

Many theories have been proposed to explain exactly how electrons move between the resistance plateaus in the quantum Hall effect.

At such low temperatures the electrons experience a phenomenon called Anderson localization—they are scattered so much that they cannot propagate over any distance, and effectively stay in one place. This means that their wavefunctions

are very narrow, and the sample effectively acts as an insulator against the Hall effect.

The main theoretical challenge is to work out what happens to delocalize the wavefunctions, allowing the system to jump between adjacent plateaus.

Finding fractals

Previous research completed by Furusaki and co-workers has helped them to explain the Anderson localization. In one study², they examined the electron wavefunctions in materials that can undergo transitions from metallic (electrically conducting) to insulating behavior.

They found that the electron distribution obeys so-called multifractal statistics, meaning that they follow similar patterns on both small and large scales. However,

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the electrons at the sample's boundary edges showed quite different distributions from those in the bulk of the sample.

The researchers realized that the boundary differences will influence the quantum Hall effect. Previous calculations have missed this subtlety by using bulk physical quantities that are valid only in the center of a sample.

"We showed that boundary multifractal properties are different from bulk multifractal properties," explains Furusaki. "It was a very natural next step for us to study boundary multifractality in the integer quantum Hall effect."

Examining the edge

The quantum Hall effect depends on impurities or defects in the sample, which can be thought of as hills that the electrons must climb over or skirt around. At the sample edges, there are limits to the directions the electrons can travel to overcome these obstacles, so their dynamics are different. However, it turns out that these restrictions at the edges are crucial in producing the quantum Hall effect.

"In a sample showing the quantum Hall effect, electron wavefunctions in the bulk are all localized and cannot carry electric current. Instead, there are 'edge wavefunctions' extended along the edge of the sample which can carry current," explains Furusaki.

"When the electrons undergo a transition between two successive resistance plateaus, the number of edge

states changes by 1. At the transition point the wave functions, both at bulk and at boundary, are neither extended nor localized; they are called critical."

Furusaki and colleagues recalculated these critical wavefunctions for electrons undergoing a transition between plateaus near the edge of a sample. They found that the transitions do not follow the same multifractal statistics that have been assumed in previous studies.

Edging towards a new future

Any new theories for the quantum Hall effect will have to take these constraints into account. Furusaki looks forward to unraveling the final details of this remarkable example of quantum physics in action.

"Some recent experiments are using scanning tunneling microscopy to observe electrons in a quantum Hall sample, but they are still at a primitive stage and resolution is not high," he says. "I suspect that the edge states in the quantum Hall effect should indirectly affect the electron distribution at boundaries, but it will take more work to get a good understanding of it."

In the future, the quantum Hall effect could become important in the world of electronics. In a different study³, Furusaki and his collaborators have already explained an unusual quantum Hall effect caused by the relativistic nature of electrons in graphene, which could eventually replace silicon in integrated circuits. ■

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2. Obuse, H., Subramaniam, A. R., Furusaki, A., Gruzberg, I. A. & Ludwig, A. W. W. Multifractality and conformal invariance at 2D metal-insulator transition in the spin-orbit symmetry class. *Physical Review Letters* **98**, 156802 (2007).
3. Nomura, K., Ryu, S., Koshino, M., Mudry, C. & Furusaki, A. Quantum Hall effect of massless Dirac fermions in a vanishing magnetic field. *Physical Review Letters* **100**, 246806 (2008).

About the author

Akira Furusaki was born in Saitama, Japan, in 1966. He graduated from Faculty of Science, the University of Tokyo in 1988 and obtained his PhD in physics in 1993 from the same university. He became a research associate at Department of Applied Physics, the University of Tokyo in 1991, and worked as a postdoctoral associate for two years at Department of Physics, Massachusetts Institute of Technology in USA, before being appointed as an associate professor at Yukawa Institute for Theoretical Physics, Kyoto University in 1996. Since October 2002 he has been a chief scientist of Condensed Matter Theory Laboratory at RIKEN. His research focuses on developing theories of quantum electronic transport, superconductivity and magnetism in solids. He received Nishinomiya Yukawa Commemoration Prize in Theoretical Physics (2004).

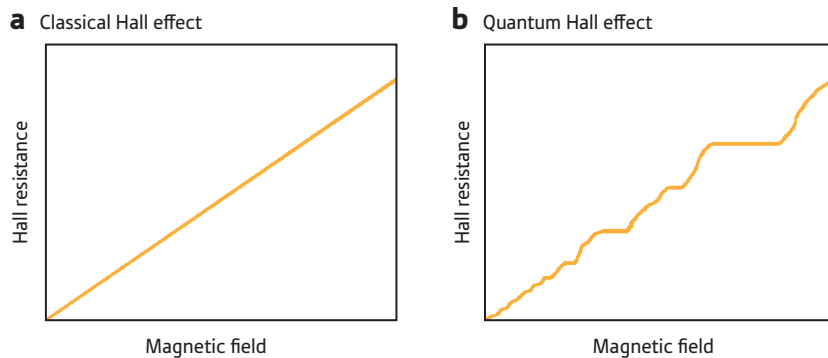


Figure 2: Changes in Hall resistance. (a) Electrons moving under the influence of the classical Hall effect experience resistance to their flow, which increases linearly with magnetic field strength. (b) At very low temperatures this transforms to the integer quantum Hall effect, where the resistance jumps up in steps.

The single photon switch

Little more than a system of two energy levels could be used to control a single particle of light

Modern electronics is built upon the control of electric charges through an electric field. Computing based on photons rather than electrons, on the other hand, promises significantly faster computation and information processing. An international team of researchers has now developed a theoretical system that would allow single photons to be controlled reliably. “The system we propose can be used as a quantum switch to control the transport of single photons,” says team member Franco Nori from the Advanced Science Institute, Wako, and the University of Michigan, USA.

In contrast to electrons, exercising control over photons is rather difficult to achieve, because light travels at high speeds and hardly interacts with matter. This has hampered the realization of schemes such as all-optical computing. The use of resonators, however, offers a solution to better control the way light propagates. Resonators are small cavities, bound by mirrors at both ends that

bounce light back and only occasionally let light out.

As reported in the journal *Physical Review Letters*¹, the researchers studied a chain of resonators coupled together so that photons propagate along this line. A system with two energy levels was placed in the center of this coupled-resonator waveguide (Fig. 1). To facilitate the interaction between light and the two-level system the separation of the two energy levels is close to the photon energy.

When there is a perfect match between the photon energy and the separation of energy levels, the two-level system interacts with the photon; physics then dictates that the photon will be reflected. However, when the energies of the photon and the two-level system do not match, the photon will be transmitted towards the other end of the waveguide.

“Such a two-level system with adjustable energy levels could be used as a switch that controls the propagation of a single photon in the same way a transistor

controls the transport of electrons,” says team member C. P. Sun from The Chinese Academy of Sciences, Beijing.

To realize this two-level system the researchers suggest using so-called superconducting qubits, used in connection with superconducting resonators, which have been demonstrated already, as the waveguides. The separation of the qubit energy levels can be easily controlled and could even be done with another single photon. The researchers have demonstrated theoretically that, with the right choice of system parameters, switching can be easily achieved. “We believe such a system is well within reach of current technology,” says RIKEN’s Lan Zhou. ■

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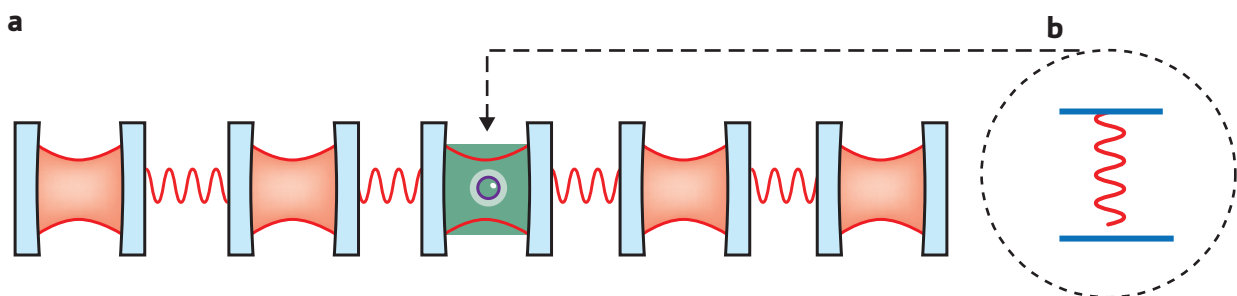


Figure 1: Schematic diagram of the single photon switch. (a) A photon (red) propagates along a line of coupled resonators (blue). (b) Depending on the match between the energy of the photon and the energy of a two-level system (located in one of the resonators, shown in green), the photon is either reflected back or allowed to propagate further.

Warming up to the Casimir force

The Casimir force between objects in a vacuum shows a complex dependence on temperature

When two uncharged objects are placed in a vacuum with no external fields, we wouldn't expect them to have any force between them other than gravity. Quantum electrodynamics says otherwise. It shows that tiny quantum oscillations in the vacuum will give rise to an attraction called the Casimir force (Fig. 1).

Scientists at the RIKEN Advanced Science Institute in Wako, and co-workers at the National Academy of Sciences of Ukraine (NASU), have shown for the first time that the Casimir force has a complex dependence on temperature¹. They propose a related experiment that could clarify the theory around this important interaction, which has widespread applications in physics and astronomy, and could eventually be exploited in nano-sized electrical and mechanical systems.

"The Casimir force is one of the most interesting macroscopic effects of vacuum oscillations in a quantum electromagnetic field," says Franco Nori from RIKEN and the University of Michigan in the USA. "It arises because the presence of objects, especially conducting metals, alters the quantum fluctuations in the vacuum."

The Casimir force was first predicted in 1948, but has only recently been measured in the laboratory because experiments are difficult—the force is negligible except when the distance between objects is very small. More experiments are needed to understand how the force depends on temperature, an important practical consideration.

"As the temperature increases, metal objects in a vacuum experience two competing effects," explains Sergey Savel'ev from RIKEN and Loughborough

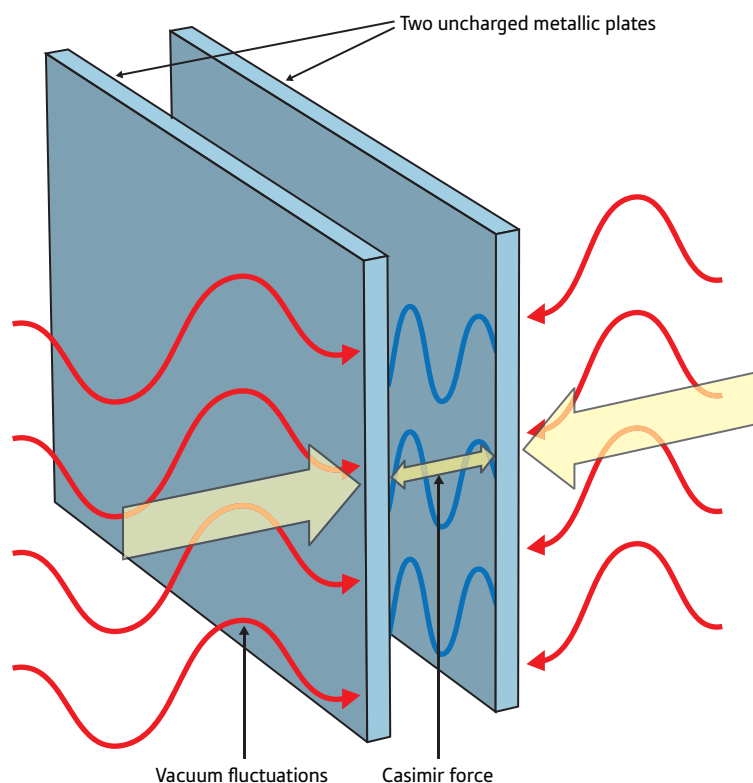


Figure 1: Quantum electrodynamics shows that two uncharged plates in a vacuum will experience an attractive force called the Casimir force, which arises because the plates alter the fluctuations in the vacuum.

University in the UK. "They lose some of their electrical conductivity, which tends to cause a decrease in the Casimir force. At the same time they are bombarded with more radiation pressure from the thermal heat waves, and this increases the Casimir force."

Nori and co-workers derived the temperature dependence for Casimir attractions between a thin film and a thick flat plate, and between a thin film and a large metal sphere. They found that the Casimir force will tend to decrease near room temperature, but can increase again at higher temperatures as the thermal radiation effects take over.

RIKEN's Valery Yampol'skii, who also works at NASU, says that "if these temperature effects were observed in an experiment, they would resolve some fundamental questions about electron relaxation in a vacuum". Such an experiment would be near-impossible with pieces of bulk metal, but could be done using extremely thin metal films. ■

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Free from approximations

A novel numerical technique permits researchers to study the interaction between elementary particles within a material without approximations

An international team of researchers has developed a numerical modeling technique to study specific types of particles called excitons, which consist of a positively and a negatively charged electron and hole, respectively. The technique includes the influence of a material's internal structure—the so-called host lattice—without the need to make approximations of any sort¹.

In an exciton, the electron and the hole are bound together by an electric attraction—known as the Coulomb force (Fig. 1)—in a fashion very similar to that of an electron and a positron in a hydrogen atom. The presence of the host lattice and its thermal and magnetic excitations that consist of phonons and magnons, respectively—known collectively as the ‘bosonic’ field—can affect the excitons considerably.

The researchers, including Andrei Mishchenko from the RIKEN Advanced Science Institute in Wako, aimed to develop a technique to study the excitons' interaction with phonons in an exact way. In particular, they focused on taking into consideration the fact that phonons do not act instantaneously as occurs in the Coulomb attraction. “Previously, the only way to treat the exchange [between electrons and holes] by bosons was an instantaneous approximation, where the influence of particle–boson interaction was included into the model by renormalization of the instantaneous coupling,” explains Mishchenko.

Mishchenko and colleagues' technique is known as a Diagrammatic Monte Carlo Method and is based on the diagrams that the Nobel laureate Richard Feynman

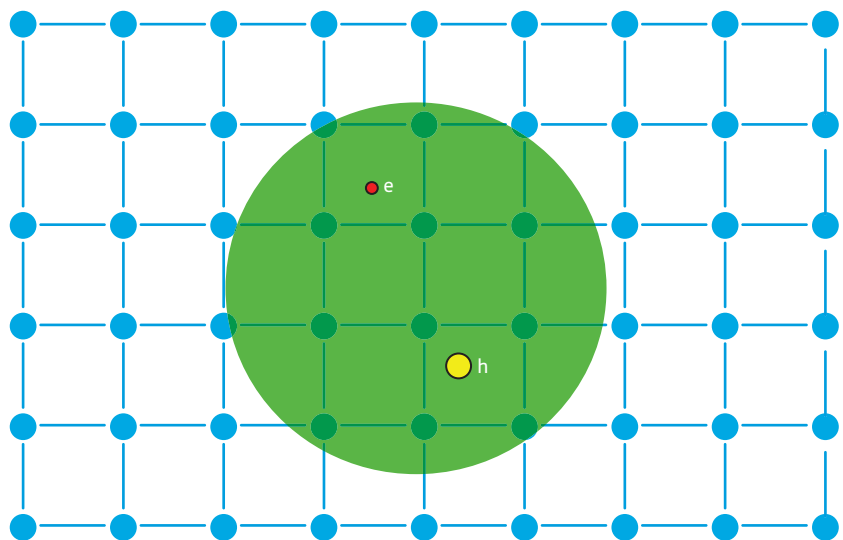


Figure 1: Schematic of an exciton in a host lattice. The electron (red) and the hole (yellow) that constitute the exciton are held together by the Coulomb attraction (represented by the green circle).

introduced to quantum field theory. The method per se existed already and was normally used with all variables expressed as a function of spatial coordinates. This, however, limits the size of the area that can be examined in a calculation. The team therefore formulated the algorithm for momentum space. This provides the “possibility to overcome the limitation of the direct space method [for] finite systems and handle the problem [in] a macroscopic system,” says Mishchenko.

Like any new theoretical method, the team's numerical technique must be compared with known scenarios to verify its validity, so Mishchenko and colleagues used it to study excitons with different

values for the electron and hole masses. They found very good agreement with previous theories within the limit in which it is reasonable to neglect any retardation effect. Importantly however, the results show that in standard conditions it is incorrect to neglect the retardation.

As Mishchenko explains: “Our ‘free-from-approximations’ results show that the domain of validity of the instantaneous approximation is very limited.” ■

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Escape from frustration

When the bonds between atoms suddenly alter in strength, structural changes in symmetry result

Everyone prefers to avoid the frustration of failing to achieve a desired outcome. Now it seems this even applies to materials and the arrangement of their atomic magnets, referred to as spins. Researchers from RIKEN's Nishina Center for Accelerator-Based Science in Wako, in collaboration with researchers from the University of Hyogo and Kyoto University, have uncovered an intriguing interplay between the arrangement of atomic spins and atomic interactions in the metallic compound Mo_3Sb_7 .

The molybdenum (Mo) atoms in Mo_3Sb_7 crystals are arranged in octahedra. Unusually, the atomic bonds between the Mo atoms at the tips of the octahedra are stronger than between the Mo atoms in the plane. This leads to the formation of 'dumbbells' of Mo pairs along the three main crystal directions (Fig. 1). "The unusual arrangement between the dumbbells and the other Mo atoms makes this material unique and interesting to study," comments Isao Watanabe from the research team.

Of particular interest is a sudden structural change that occurs at temperatures below 50 K (-223.15 °C). The origin of this phase transition has now been unveiled by a number of experiments that probe the magnetic and electric properties of the Mo atoms¹. These measurements present clear evidence that the phase transition is accompanied by symmetry changes in the crystal.

The symmetry changes are triggered by the spins associated with Mo atoms. The researchers found that an unusual competition in interaction between

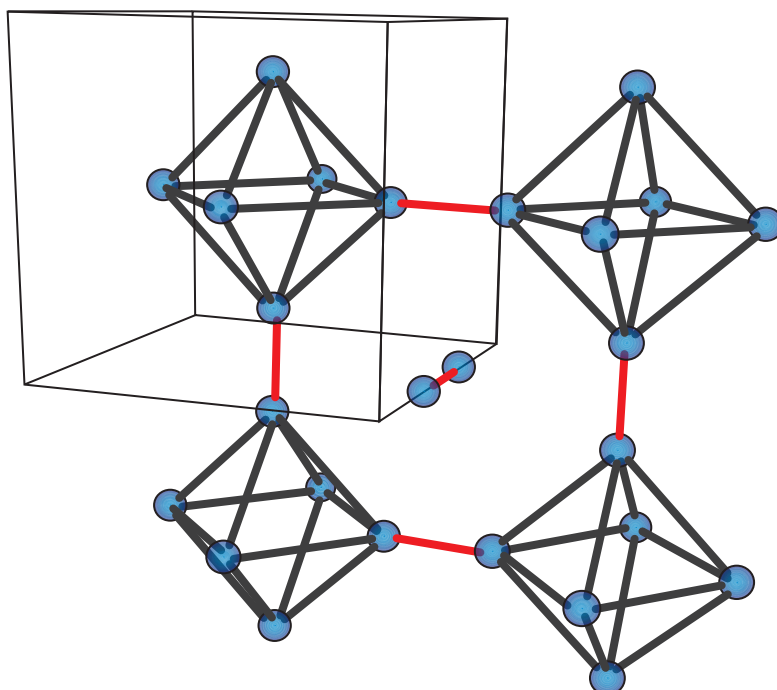


Figure 1: The octahedral arrangement of Mo atoms within the crystal structure of Mo_3Sb_7 . Strongly coupled Mo atoms at the tips of the octahedra form dumbbells (red lines) throughout the structure.

the Mo atoms takes place. At the phase transition, the strength of the interaction between the Mo atoms in the octahedra becomes comparable to the bond between the Mo atoms in the dumbbells. Consequently, the Mo atomic spins then begin to arrange in an up-and-down fashion along the entire crystal rather than within the dumbbells. However, owing to the particularities of the three-dimensional crystal structure, a periodic up-and-down arrangement, which is homogeneous across the entire crystal, is impossible. Frustration is the result.

To break this frustration the Mo octahedra elongate in one direction, breaking the crystal symmetry. This in turn finally allows the Mo dumbbells to

order themselves periodically throughout the crystal in an arrangement termed a 'valence bond crystal'.

The unusual competition of the atomic bonds between the Mo atoms in Mo_3Sb_7 has led to dramatic consequences involving crystallographic, electronic and magnetic properties. "This is the first example of its kind and we expect that this opens a new field to study similarly complex systems," say Watanabe and his colleagues. ■

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Electronic recoil

RIKEN researchers have revealed an unexpectedly large recoil of ‘free’ electrons emitted from a simple metal

Photoelectron spectroscopy is a powerful technique for studying the composition and physical properties of a material. Despite its maturity, Yasutaka Takata from the RIKEN SPring-8 Center, Harima, and colleagues have discovered that there are still new things to learn about the physical phenomena on which it is based. They have observed an unexpected shift in the energy of electrons emitted by hard x-rays from the valence band of aluminum¹—an effect that has implications for the interpretation of photoelectron data obtained at similar energies.

When a photon of light of sufficiently high energy is absorbed by a sample, it can cause the ejection of an electron. The kinetic energy the emitted electron depends on the energy of the light absorbed and the energy level the electron came from (Fig. 1). By using light with a well-defined energy and measuring the energies at which electrons emitted from a sample, it is possible to determine its chemical composition, how its atoms are bonded together, and its electronic structure, which determines its electronic, thermodynamic and optical properties.

When an electron is emitted from a sample, it transfers momentum to the sample, similar to the recoil that occurs when a bullet is fired from a gun. At the low energies at which photoelectron spectra are usually collected, the small mass of an electron relative to an atom makes this recoil negligible. But at higher energies, it becomes important.

In a previous study, Takata and colleagues observed a shift in the energy of electrons emitted from the inner shells of carbon atoms by high-energy, hard

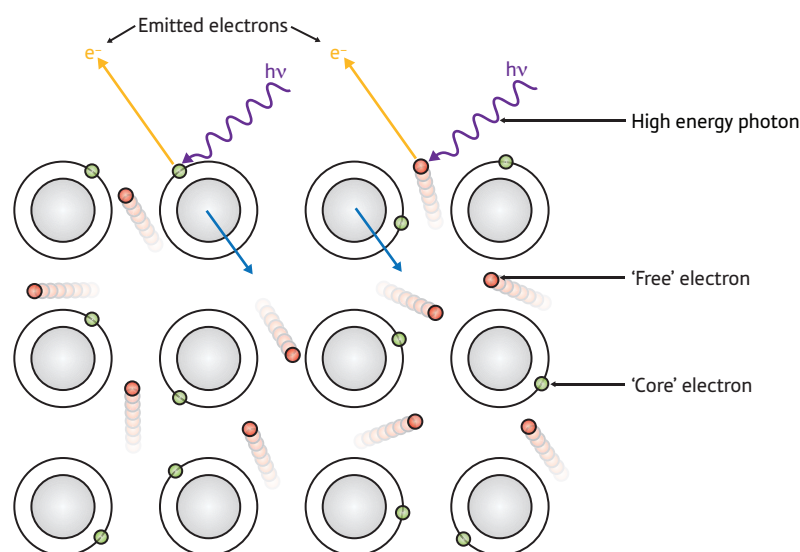


Figure 1: When a photon ($h\nu$) of sufficient energy hits a sample, it can excite the emission of electrons. For a metal, these electrons can come either from specific atoms (green circles) or from the sea of ‘free’ valence electrons (red) that extends over the whole sample.

x-rays². Their calculations showed that this shift could be explained, as expected, in terms of the loss of energy caused by the recoil of a high energy electron being ejected from a carbon atom.

What they found in their latest study, however, they did not expect. Analysis of high resolution hard-x-ray photoelectron spectra obtained aluminum revealed a shift in the energy of so-called ‘free’ electrons coming from its valence band (Fig. 1). This is surprising because unlike core electrons, which are associated with individual atoms, valence band electrons belong to the sample as a whole. The recoil effect of these electrons should therefore be very small.

Such effects will need to be taken into account when interpreting hard x-ray

photoelectron spectra. Takata suggests it might also provide a new tool for probing composite materials. ■

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Missing piece gets a work over

New pathways for the biological activity of two little-understood enzymes emerge from a theoretical investigation

Researchers working in Japan have developed a new theory that may explain the activity of two unusual, but vitally important, enzymes that were discovered over 40 years ago.

The enzymes, indoleamine 2,3-dioxygenase (IDO) and tryptophan 2,3-dioxygenase (TDO), known as dioxygenases, are responsible for the cleavage of the essential amino acid, L-tryptophan. Both enzymes contain heme—a metal-containing organic ring structure—to which molecular oxygen is bound before being transferred to L-tryptophan. This important oxidation reaction releases energy into the body in all cells in mammals, but its mechanism is little understood.

Now, Hiroshi Sugimoto and colleagues at the RIKEN SPring-8 Center, Harima, in collaboration with Keiji Morokuma, Lung Wa Chung and colleagues at Kyoto University, have studied the structures of these enzymes and modeled some potential reaction pathways to better understand how they work¹.

Recently, crystal structures of IDO (Fig. 1)² and TDO with tryptophan or similar compounds were obtained. Surprisingly, these structures showed different active sites for these enzymes compared to other heme systems. Consequently, the researchers concluded that different mechanistic pathways must also be operating for the dioxygenase reaction.

The researchers used a detailed modeling method, called Density Functional Theory, to calculate and evaluate the energy of the starting compounds, products, possible reaction intermediates and transition states. They then used comparisons to provide insight

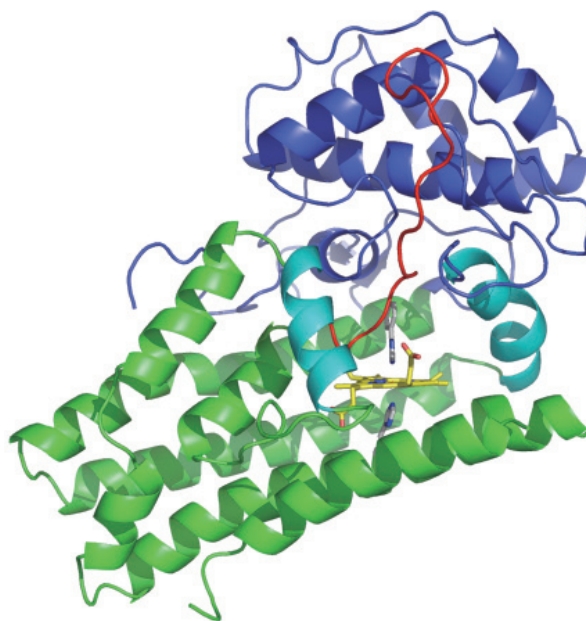


Figure 1: An illustration of the crystal structure for Indoleamine 2,3-dioxygenase (IDO) bound to an inhibitor molecule.

into which reaction pathways are the most energetically favorable and, therefore, which mechanism is most likely to take place in the body.

They found that one proposed mechanism involved a highly distorted transition state, which would lead to a very high energy barrier, making this route doubtful. Instead, they suggest that a new and energetically favorable mechanistic pathway explains the unusual dioxygen activation and oxidation reactions for the enzymes. This proposed mechanism is sharply distinct from other mechanisms for heme-containing oxygenases.

The enzyme-bound oxygen was found to react directly with the electron-rich indole carbon on the tryptophan via either a 2-electron (electrophilic) or 1-electron (radical) transfer pathway. Either of these reactions would lead to the formation of a low-energy intermediate making it a much more realistic possibility. Sugimoto and colleagues are now investigating exactly how oxygen binds to the heme

and evaluating the contribution of the enzyme to the mechanism.

“[The research] might also be informative for rational drug design because IDO is emerging as an important new therapeutic target for the treatment of cancer, chronic viral infections, and other diseases characterized by pathological immune suppression,” says Sugimoto. ■

1. Chung, L.W., Li, X., Sugimoto, H., Shiro, Y. & Morokuma, K. Density Functional Theory study on a missing piece in understanding of heme chemistry: the reaction mechanism for Indoleamine 2,3-dioxygenase and tryptophan. *Journal of the American Chemical Society* **130**, 12299–12309 (2008).
2. Sugimoto, H., Oda, S., Otsuki, T., Hino, T., Yoshida, T. & Shiro, Y. Crystal structure of human indoleamine 2,3-dioxygenase: catalytic mechanism of O₂ incorporation by a heme-containing dioxygenase. *Proceedings of the National Academy of Sciences USA* **103**, 2611–2616 (2006).

An 'opening' role

Non-coding RNAs play a role in regulating the expression of genes in yeast

Much debate has surrounded the mostly unknown function of non-coding RNAs, which have recently been shown to constitute a surprisingly large proportion of gene transcripts, rather than encoding proteins. Now, as reported in *Nature*¹, a research team led by Kunihiro Ohta of the RIKEN Advanced Science Institute, Wako, has discovered a new role for such non-coding RNAs in gene expression in the fission yeast, *Schizosaccharomyces pombe*.

Most DNA is wrapped up in chromatin of the cell's nucleus, which in turn is packaged in chromosomes. Chromatin can be in either a 'closed' or an 'open' configuration, affecting the accessibility of the DNA to proteins called transcription factors that regulate gene expression.

Ohta and colleagues showed that non-coding RNAs are involved in the step-wise conversion of chromatin from the closed to the open configuration during the induction of one particular gene in fission yeast. This supports some previous suggestions that non-coding RNAs could play an important role in regulating gene expression.

The gene studied by Ohta and colleagues is induced when yeast cells are starved of glucose. The most common transcript encodes the protein product of the gene. However, they also showed that three rarer, longer RNA transcripts are also produced, and that their expression is initiated far upstream of the main coding sequence of the gene.

As these longer RNA transcripts do not appear to have any special protein coding function, and the researchers set out to explore whether they have important functions during expression of the gene. They showed that the chromatin at the

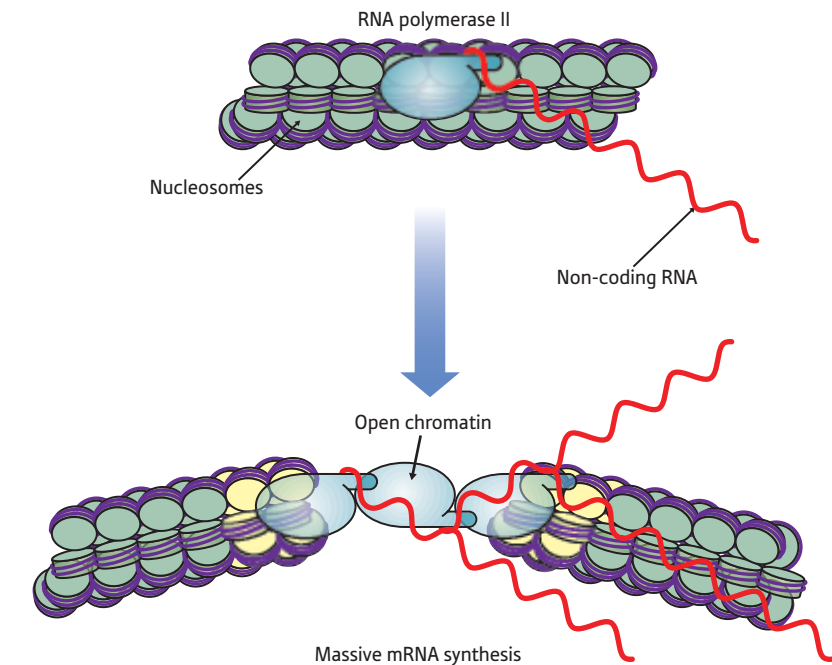


Figure 1: Conversion of chromatin from a closed to an open configuration.

gene is progressively converted to an open configuration, as the non-coding RNAs are transcribed by RNA polymerase II (Fig. 1).

Using various mutant yeast strains, the researchers then showed that transcription factors known either to induce or repress expression of the gene also regulate chromatin configuration in collaboration with the RNA polymerase.

Based on their findings, Ohta and colleagues propose a model for the regulation of the chromatin structure at the yeast gene.

"Transcription-mediated regulation of gene expression could also exist in

humans," say the researchers. Whether or not this turns out to be the case, the present study "demonstrates a new mechanistic role for non-coding RNAs in gene activation."

The hunt is now on to discover the exact mechanism by which the non-coding RNAs affect the configuration of chromatin. ■

1. Hirota, K., Miyoshi, T., Kugou, K., Hoffman, C. S., Shibata, T. & Ohta, K. Stepwise chromatin remodelling by a cascade of transcription initiation on non-coding RNAs. *Nature* **456**, 130–134 (2008).

Double trouble

Variations in a single gene simultaneously increase the risk of two autoimmune conditions

Japanese researchers have identified two single nucleotide polymorphisms (SNPs), each of which significantly increases susceptibility to the autoimmune diseases rheumatoid arthritis (RA) and systemic lupus erythmatosus (SLE). They occur in a gene for a protein that regulates immune system cells. While the SNPs have so far only been detected in East Asians, understanding their role in promoting the onset of both autoimmune diseases could lead to better treatments for all, the researchers say.

RA is a painful condition where the body's immune system attacks and degrades joints (Fig. 1). The disease affects up to one person in a hundred, and both genetic and environmental factors can increase susceptibility to it. Other researchers have uncovered several genes with variants that increase the risk of RA. Some, presumably for compounds involved in the autoimmune process at a generic level, simultaneously increase the risk of other autoimmune conditions, such as SLE.

The current study, recently published in *Nature Genetics*¹, was led by researchers from RIKEN's Center for Genomic Medicine in Yokohama. It focuses on a region of the long arm of human chromosome 1 which contains genes of the signaling lymphocyte activation molecule (SLAM) family. Proteins of the SLAM family are involved in regulating cells of the immune system, so there is a potential link with autoimmune conditions. The chromosome region had already been linked with increased risk of RA and SLE in previous studies.



Figure 1: Swollen joints affected by rheumatoid arthritis can make everyday tasks painful.

In two independent Japanese populations—one of 830 arthritis sufferers and 658 controls, the other of 1,112 arthritis sufferers and 940 controls—the researchers identified five SNPs closely associated with RA in the SLAM family gene, *CD244*. The researchers showed that these SNPs also increase susceptibility to SLE.

All the SNPs occurred in the gene's introns—segments of the DNA sequence that are chopped out before the final protein is synthesized. It has recently been suggested that introns may well play a role in regulating gene activity. So the researchers assayed the SNPs for their impact on the rate of transcription of *CD244*, and determined that two of five led to significant increases in gene activity.

As *CD244* is known to encode a protein which activates or inhibits the natural killer cells of the immune system, the researchers say they are not surprised that its SNPs are associated with susceptibility to autoimmune diseases. “But we don't yet know the precise molecular mechanisms involved,” says project leader, Kazuhiko Yamamoto. ■

1. Suzuki, A., Yamada, R., Kochi, Y., Sawada, T., Okada, Y., Matsuda, K., Kamatani, Y., Mori, M., Shimane, K., Hirabayashi, Y., *et al.* Functional SNPs in *CD244* increase the risk of rheumatoid arthritis in a Japanese population. *Nature Genetics* **40**, 1224–1229 (2008).

Setting the cellular clock

Synthetic genetic circuits enable researchers to uncover the mechanisms by which cells set their internal clocks

Many organisms live out their lives on schedules established by internal clock mechanisms, generated by the combined action of multiple regulatory networks that interlock like gears in a watch. The resulting circadian rhythms establish one's internal perception of day and night, as well as numerous time-points in between.

In 2005, a team led by Hiroki Ueda of the RIKEN Center for Developmental Biology in Kobe made significant progress in identifying the core components of the complex circadian circuitry¹. They found several regulatory elements that specifically mark genes for activation or inhibition in the morning, daytime or night, as well as numerous genes that mediate regulation via these elements.

"Our team identified a natural transcriptional circuit for mammalian circadian clocks," explain Maki Ukai-Tadenuma and Takeya Kasukawa, members of Ueda's team. "However, no one has yet confirmed the mechanism that generates practically continuous phases from these three, discrete basic phases."

However, the investigators had ideas about how such patterns might emerge, and were able to sketch a rough map of how the various time-specific regulatory loops may interact *in vivo* to produce a stable day-night cycle. To test their hypotheses, they constructed a series of synthetic circadian circuits within live cells based on their models, and examined the extent to which their activity replicated natural biological cycles².

In fact, these experimental scenarios provided strong support for their regulatory models. One of the synthetic circuits consisted of a bioluminescent



indicator gene under the regulation of a morning-specific activator and a nighttime-specific repressor, and the resulting pattern of indicator activity was a cyclic oscillation that very closely matches the natural expression pattern of daytime-specific genes.

They were similarly able to replicate night-cycle activity with a daytime-specific activator and morning-specific repressor, and were even able to generate novel 'late night' or 'dusk' output peaks by further tinkering with the timing of activation and repression. Most importantly, their experimental findings were all consistent with the predictions of their previously developed theoretical models. "Both our simulation model and the derived design principles successfully recapitulated the natural transcriptional circuit in the circadian clocks," say the researchers.

Although their modeling system has proven effective, the researchers have yet to fully reconstruct all the phases of the mammalian circadian cycle. "In our study, morning transcriptional regulation is still a 'missing link,'" they point out. The team's focus now is on successfully identifying the regulatory processes required to restore these final time-points to their reconstructed cellular clock. ■

1. Ueda, H.R., Hayashi, S., Chen, W., Sano, M., Machida, M., Shigeyoshi, Y., Iino, M. & Hashimoto, S. System-level identification of transcriptional circuits underlying mammalian circadian clocks. *Nature Genetics* **37**, 187–192 (2005).
2. Ukai-Tadenuma, M., Kasukawa, T. & Ueda, H.R. Proof-by-synthesis of the transcriptional logic of mammalian circadian clocks. *Nature Cell Biology* **10**, 1154–1163 (2008).

Balancing act

A recently discovered protein works behind the scenes to confer much-needed stabilization to an essential developmental pathway

Early in development, embryos transition from being simple spheres of cells into more structured forms in which the foundations of body patterning—such as distinct dorsal (back) and ventral (front) sides—have been established.

Dorsal–ventral patterning is primarily established by BMP signaling factors, which exhibit a gradient of activity along the length of the embryo: elevated BMP activity induces ventral development, while reduced BMP signaling induces dorsality. Reduction in BMP activity is mediated by a structure known as the Spemann organizer, which secretes factors like Chordin, which inactivates BMP and drives dorsalization.

However, BMP also represses Chordin expression, creating a seemingly fragile regulatory situation in which transient upregulation of Chordin could trigger a chain reaction of uncontrolled Chordin upregulation, with catastrophic results for body patterning.

This isn't the case; in fact, this process is surprisingly robust. Yoshiaki Sasai of the RIKEN Center for Developmental Biology in Kobe, suspected that additional failsafe mechanisms must exist to stabilize Chordin–BMP regulation, and decided to investigate the involvement of a protein recently discovered by his team, ONT1, which they thought might play a role in body patterning¹.

ONT1 is produced and secreted by cells in the dorsal region of the embryo, where it appears to directly regulate Chordin function, and Sasai's team found that frog embryos with reduced ONT1 activity are far more vulnerable to excessive dorsalization in the presence of abnormally

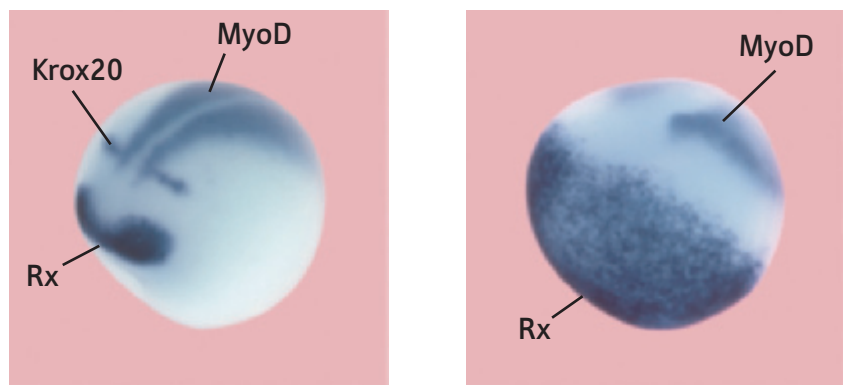


Figure 1: Frog embryos stained to reveal alterations in gene expression patterns in a normally patterned embryo (left) and in an embryo subjected to elevated Chordin levels under conditions of artificially reduced ONT1 activity (right). The latter embryo exhibits signs of profound dorsalization, as evidenced by expansion of the zone of expression for dorsal marker Rx, and reduction or loss of expression of ventral markers MyoD and Krox20.

elevated Chordin levels (Fig. 1). “We were really surprised to see how drastically the stability collapsed after knocking down ONT1 function,” he says.

They determined that ONT1 not only interacts directly with Chordin, but also binds to an enzyme known to degrade Chordin, and came to the surprising conclusion that ONT1 acts as a bridge that links the two proteins and thereby expedites destruction of the dorsalization signal. “There are a number of examples of intracellular scaffolds,” says Sasai, “but ONT1 is a rare example of a secreted scaffold for enzymes.”

There is another recently identified pathway for the regulation of dorsal–ventral patterning, mediated by ADMP, a protein that reduces Chordin levels by

activating BMP receptors, and ONT1 and ADMP appear to regulate parallel but independent pathways for ensuring robust control of dorsalization in the embryo.

The researchers now hope to delve deeper into this more complex model of organizer regulation. “One important approach will be to establish a mathematical model for this integrated view of organizer function,” says Sasai, “particularly to explain these phenomena in a spatial and real-time fashion.” ■

1. Inomata, H., Haraguchi, T. & Sasai, Y. Robust stability of the embryonic axial pattern requires a secreted scaffold for Chordin degradation. *Cell* **134**, 854–865 (2008).

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Exploring nuclear fusion and getting inside materials

The RIKEN-RAL Muon Facility, UK

Muons are obscure particles that only appear naturally on Earth when high-energy cosmic rays collide with the upper atmosphere. So why do RIKEN scientists travel all the way from Japan to study muons on a remote hill in England?

Since 1990, scientists from the RIKEN Nishina Center for Accelerator-Based Science in Wako have paid regular visits to the Rutherford Appleton Laboratory (RAL) in Oxfordshire, UK. The researchers have adapted part of the unique synchrotron facilities at RAL to create the world's strongest source of muons: The RIKEN-RAL Muon Facility. The muons, which are classified in the same group as electrons but have 207 times more mass, are used to examine the structure of materials and to explore fusion energy.

The Nishina Center has a distinguished history regarding muons—it is named after Yoshio Nishina, who discovered muons in cosmic rays. Scientists from the Nishina Center quickly spotted a unique opportunity when RAL built a new proton synchrotron, called ISIS, in 1985.

According to RIKEN researcher Katsuhiko Ishida, "ISIS was chosen because it is the only place in the world suitable for producing a pulsed muon beam." His colleague Isao Watanabe adds: "We began building in 1990 and observed our first muon beam in 1994. Today there are four permanent RIKEN researchers and some postdocs based at RAL, who are joined several times a year by visiting scientists from Japan, like myself."

Several steps lead to the production of muons for the RIKEN-RAL facility. Firstly, a beam of protons is accelerated to high energies in the circular ISIS synchrotron. The proton beam then passes into the experimental hall, where most of it generates neutrons for other experiments, but about 4% is used to make muons. A graphite target is inserted into the proton beam, producing lots of particles called pions that quickly decay into muons.

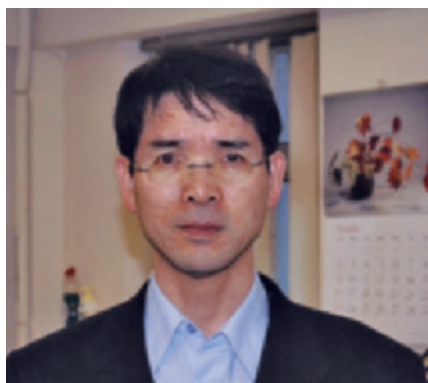
The experimental hall at ISIS is an impressive building the size of an aircraft hangar, with the huge proton beamline passing through the center. The RIKEN-RAL Muon Facility consists of four experimental ports encased in concrete and foam on one side of the beamline. On the other side is a UK group also studying muons—an arrangement which, according to Watanabe, fosters some healthy competition. However, the RIKEN team has the advantage of being able to generate both types of muons, positive and negative.

Ishida's research group uses the negative muons to investigate nuclear fusion, the 'Promised Land' for clean energy generation. The biggest advantage of this 'muon-catalyzed fusion' is that it could supply fusion energy without the need for extreme conditions such as high temperature and pressure.

How can muons make this happen? The central concept is that each negative muon has exactly the same charge as an electron, so it can knock an electron out of an atom and take its place in orbit



Isao Watanabe



Katsuhiko Ishida



Pavel Bakule

around the nucleus. These new ‘muonic’ atoms are much smaller in diameter than normal atoms.

“Muons can catalyze the fusion of two heavy versions of the hydrogen atom, deuterium and tritium, because the heavier muons orbit much closer to the nuclei than electrons,” explains Ishida. “This means the nuclei can move closer together in order to fuse. Thereafter, the muon can move on to catalyze more fusion.”

In theory, this chain reaction could go on thousands of times. However, in practice each muon only generates around 120 fused pairs of deuterium and tritium nuclei before they are lost by sticking to alpha particles. One of the RIKEN team’s biggest achievements was to precisely measure this so-called alpha-sticking effect.

The researchers hope to improve their experimental conditions so that fewer muons are lost by alpha-sticking. An even bigger challenge is to find a more energy-efficient way of producing muons in the first place.

Meanwhile, Watanabe and co-workers use positive muons to investigate the electromagnetic properties of substances. This is possible because positive muons have an intrinsic property called spin, which responds to nearby magnetic fields. When the positive muon decays it emits a positron which contains information on the magnetic field in the sample, and can be easily detected.

This technique, called Muon Spin Rotation, Relaxation and Resonance, or μ SR, can measure magnetic field fluctuations on a temporal scale in between those detected by neutron scattering and nuclear magnetic resonance (NMR). This means it can probe systems that have never been studied before.

“I collaborate with more than 50 groups in Japan and five or six in other countries, including semiconductor physicists, chemists studying metal complexes and biologists studying the electronic structure of proteins,” says Watanabe. “We have definitely proven the versatility of μ SR for exploring materials.”



Facility for preparing tritium and deuterium samples for muon-catalyzed nuclear fusion in the RIKEN-RAL Muon Facility

Watanabe has been particularly successful in using μ SR to explain the mechanisms in so called high- T_c oxides, which enter a superconducting state at relatively high temperatures.

“Metal superconductors, such as those used in levitating trains, need to be cooled with liquid helium, which costs about 2,000 yen per liter!” says Watanabe. “But high- T_c oxides could be put into a superconducting state using only liquid nitrogen, which is much cheaper.”

The RIKEN scientists obviously enjoy coming to RAL, and they hope that their collaboration will continue long into the future.

“Here at Rutherford, the working environment is excellent. The only problem is jet lag,” says Watanabe. “I’d like to develop a computerized system that could be remotely controlled from Japan. This could benefit other Asian scientists that would like to use the facility but cannot afford to travel to Europe. That is my dream.” ■

Pavel Bakule

Muons are unstable particles with an average lifetime of 2.2 microseconds—a long time in the world of particle decay. This means that when muons are used to probe materials, they penetrate deep into the sample before decaying to provide information on their surroundings.

But how can scientists investigate the surface layer of a sample, or study very thin films? Pavel Bakule, born in Prague, Czech Republic, is a postdoctoral researcher trying to solve this problem by producing very slow muon beams that decay just a few nanometers inside a sample.

Bakule trained as a laser physicist, and during his Doctor of Philosophy at Oxford University he worked on precision spectroscopy of muonium—an atom composed of an electron orbiting a positive muon. His experience with muonium is crucial to slowing muons down.

The basic idea is quite simple—the problems are more technical,” says Bakule. “We have a heated tungsten foil in which we physically stop the muons. The muons bind to electrons in the tungsten, and slow muonium atoms are emitted from the other side of the film.”

At this stage, the researchers use a laser to knock the electron off the muonium atoms, leaving a slow-moving beam of muons. This can be difficult, as Bakule explains.



“We can only generate a handful of muonium atoms, say about 200 in a space the size of an orange. Trying to hit them with a laser is very difficult, so we need a high intensity pulsed laser.”

The slow muons can provide information on useful materials for nanotechnology, or the emerging field of spintronics. Bakule hopes that the RIKEN team can soon investigate substances under various conditions.

“In future we could synchronize the implantation of muons with other excitations of the sample, for example irradiation with a laser or radiofrequency pulse.” ■

RIKEN-Nishina Memorial Symposium

On December 15, 2008, 150 people gathered at RIKEN's Wako campus for the RIKEN-Nishina Memorial Symposium on 'Charging Molecules: Fundamental Chemical Physics and Analytical Applications.'

The symposium was organized by RIKEN and the Japan Academy of Sciences, and cosponsored by the Nishina Memorial Foundation. Nobel prize winners Yuan T. Lee and Koichi Tanaka were invited as plenary lecturers.

Lee, who specializes in chemical reactions in crossed molecular beams, spoke about MALDI (matrix-assisted laser desorption/ionization), the basic process that was developed by Koichi Tanaka of Shimadzu Corp. Tanaka was a winner of the 2002 Nobel Prize in Chemistry, and also gave a talk at the symposium.

Several eminent researchers were also invited to present their research. Haruo Shiromaru

from Tokyo Metropolitan University described experiments in which he irradiated molecular ions in an electrostatic ion storage ring with a laser, and then examined the resulting configurations and reactions. RIKEN's Maki Kawai spoke about inducing molecular vibrations through the formation of a temporal negative ion state using a scanning tunneling microscope. They made the molecule react by injecting an electron from the point of the Scanning Tunneling Microscopy into a molecule that is adsorbed onto a solid surface.

Hisanori Shinohara of Nagoya University discussed nanofabrication of quantum metallic nanowires in carbon nanotubes. He also introduced research into a new material called peapod, in which metallic ions are wrapped in fullerene that is embedded in nanotubes. RIKEN's Toshinori Suzuki spoke about experiments on time-resolved photoelectron spectroscopy, in

which he discharged electrons from molecules with ultrashort laser pulses, making visible a state change in intramolecular electrons.

In his plenary address, Tanaka noted that breakthroughs in science require both creativity and teamwork. This research is expected to yield new discoveries in physics and chemistry, as well as a variety of applications. ■



RIKEN and Fujitsu host symposium on 'shogi intuition' research

RIKEN, Fujitsu Ltd. and Fujitsu Laboratories Ltd., in cooperation with the Japan Shogi Federation, held a symposium November 23 to discuss the results of their ongoing joint research into brain activity of *shogi* (Japanese chess) players, a project they have been pursuing since April 2007. The symposium, titled 'Results of research into activity of the brain while playing *shogi*,' was held at the Museum of Emerging Science and Technology in Odaiba, Tokyo.

Participants in the symposium included Tsuneo Kawatsuma of Fujitsu Ltd.; Kunio Yonenaga, the president of the Japan Shogi Association; Keiichi Sanada, a highly ranked professional *shogi* player; Yoko Yamaguchi a team leader at RIKEN's Brain Science Institute (BSI); three other researchers from BSI; Masao Ito a special advisor to BSI; Keiji Tanaka, the acting director of BSI, and Ryoji Noyori, the president of RIKEN.

The project aims to clarify the mechanism of information processing in *shogi* players' intuitive thinking, and thereby shed light on rapid perception and decision-making in the human brain. The researchers use functional magnetic-resonance imaging (fMRI) and brain-wave imaging to analyze both professional and amateur players and compare their brain activity. They have found that the professionals have unique brain activity that the amateurs lack, which accounts for their special intuitive way of playing.

Among other findings, the researchers have clarified for the first time that the renowned powers of intuition of professional *shogi* players' are due to the development of 'intuition circuits' in their brains, a result of many years of playing the game.

In one experiment, the players were shown both standard and random arrangements of *shogi* pieces. The professional players demonstrated rapid brain wave responses, indicating that they noticed the difference between the standard and random arrangements, much faster than the amateurs.

There were other reports related to intuition and the players' ability to react immediately through instinct. The researchers theorized that the cerebellum, known to be involved in motor control, should be also involved in instinctive thinking to operate unconscious model-based thought processes. An fMRI experiment based on this hypothesis is under exploration.

These results are still preliminary, since the project is ongoing, but they give an indication of some of the advancements waiting to be made in the field of human expertise. By elucidating the mechanisms of intuitive thought in *shogi* players, researchers are furthering our understanding of the human brain. ■

Molecular Imaging 2008

RIKEN and the National Institute of Radiological Sciences (NIRS) hosted an international conference, 'Molecular Imaging 2008 – Breaking New Ground in Drug Discovery and PET Diagnosis' in Kobe on Dec 14 and 15.

The audience of over 400 participants at the Kobe International Conference Center heard presentations on research into labeling chemistry and molecular probes; the recent revolution in drug discovery and PET diagnosis processes; and neuroscience and imaging methodology.

The session on 'Toward Clinical Applications' drew special attention. In June 2008, Japan's Ministry of Health, Labor and Welfare issued guidelines for microdose clinical trials that allow researchers to administer into human subjects very small amounts of new medicines and candidate materials, tagged with biomarkers, and then noninvasively examine them using various technologies, including PET, MRI and ultrasound. The guidelines have important implications for work on drug discovery, and the discussions at the conference focused on ways to improve research standards and overcome various barriers, such as regulatory and ethical issues, that exist in research.

The field of molecular imaging unites molecular biology and in vivo imaging into a multidisciplinary field that includes chemistry, life sciences, physics, engineering, computer science, medicine and pharmaceutical sciences. It plays an important role as a bridge between molecular, integrated systems, and basic and clinical research. The recent paradigm shift in drug discovery means molecular imaging is sure to become a core research area in evidence-based medicine. ■



Dr. Masahiko Iwasaki
 Chief Scientist
 Advanced Meson Science Laboratory
 RIKEN Nishina Center for Accelerator-Based Science
 Wako-shi, Saitama, Japan

Dear Dr. Iwasaki,

Almost five years have passed since I left RIKEN to join the Muon Science Laboratory at KEK (High Energy Accelerator Research Organization) in Tsukuba. Since then, I have been actively working on the design and construction of the new Muon Science Facility (named MUSE) at J-PARC in Tokai. At the beginning, it was quite hard to attend all the meetings related to the construction only in Japanese. When I was at RIKEN, I never needed to use Japanese so often. Now, I am doing much better, and I am enjoying my new position and working environment.

After a lot of effort by all our small muon group, the installation of the muon target and the primary proton beamline to the neutron target were completed successfully in 2007, and last year the first secondary muon channel was installed in the Materials and Life Science Facility (MLF) building. On the 26th of September, we proudly celebrated day one with our first muon beam at the J-PARC MUSE facility. Here, everybody was very excited about it. We will soon have the world's most intense pulsed muon source, but we still have a lot of work ahead to reach the level achieved by the RIKEN-RAL Muon Facility over all these years in terms of user-friendly support and very high scientific output. It will take us some time, but we are working hard at it.

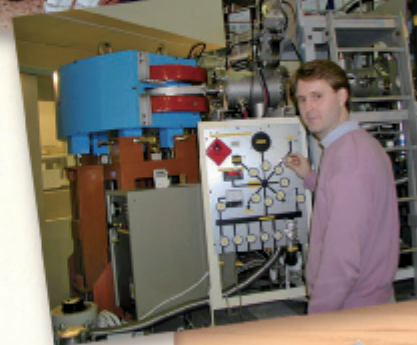
I have very good memories of my stay at RIKEN, especially of the last two years when you became the new chief scientist of the laboratory. Your fresh support and encouragement meant a lot to me, and gave me strong motivation for my research project at RIKEN-RAL on muon spectroscopy with implanted ions in solid hydrogen films. I am also grateful for the opportunity you gave me to collaborate briefly with your experiment E471 at KEK-PS for the search of deeply bound kaonic nuclear states, and the DEAR experiment at DAΦNE (Laboratori Nazionali di Frascati, Italy), which was measuring the shifts and widths of the K-series x-rays in kaonic hydrogen and deuterium. I learned to collaborate with a large group of people from many different countries. Until then, I used to work only with very few people on smaller experiments. This experience helped considerably in my new work at J-PARC.

Occasionally, I still have the opportunity to go to RIKEN-RAL to continue my experiment. Recently, with Akihiro Taniguchi, my new collaborator from Kyoto University, we succeeded in doing muon transfer experiments with trace alkaline-earth and rare-earth elements using a new surface ionization type ion source that we constructed. In the near future, we hope to realize the first muon spectroscopy experiment with long-lived unstable nuclei.

I hope that day one at the J-PARC Hadron will come soon as well.

Best regards,

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