TUT Research
e-Newsletter from Toyohashi University of Technology

No.17 May 2019

FEATURE STORY

Overcoming a major obstacle to the practical application of regenerative medicine: Paving the way for the mass production of iPS Cells

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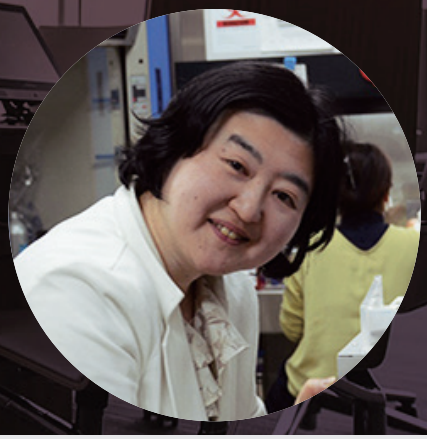


Research Highlights

Pick Up

Overcoming a major obstacle to the practical application of regenerative medicine: Paving the way for the mass production of iPS Cells

Rika Numano

There are high hopes that the innovative approach of using iPS cells for regenerative medicine will be capable of radically transforming the treatment of diseases. However, there are many barriers to its practical application. One of the major problems is that mass production of iPS cells with homogeneous properties cannot be efficiently achieved. Associate Professor Dr. Rika Numano has developed a water-in-oil droplet electroporation as a novel method of overcoming this obstacle, and is now working to achieve the mass production of iPS cells. When voltage is applied to an aqueous droplet containing cells and Yamanaka factors (reprogramming genes), tiny pores are formed on the surface of the cells. The genes can then be introduced into the cells through these transient pores in the cell membranes. This new technique has several advantages over conventional transfection techniques, in that it can be performed relatively easily using fewer cells, and in that it has a lower chance of inducing cancer. As a result there is growing interest in the potential of this method to realize the development of mass-produced implantable iPS cells in the future.

Interview and report by Madoka Tainaka

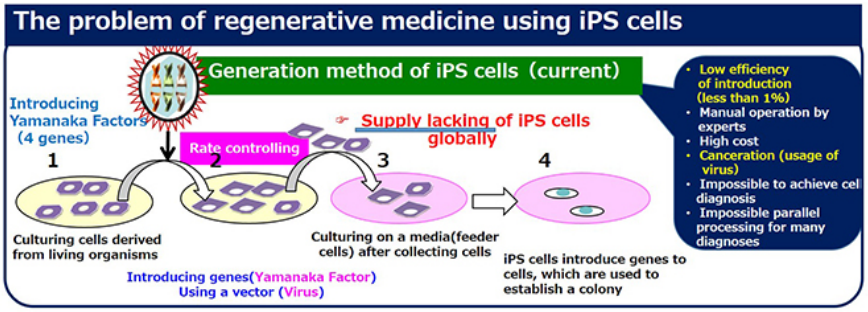
Creating iPS cells conveniently without using viruses

Professor Shinya Yamanaka of Kyoto University was awarded the 2012 Nobel Prize in Physiology or Medicine for his famous discovery that mature somatic cells such as skin or blood cells can be reprogrammed to become pluripotent iPS cells by introducing four transcriptional factors. Regenerative medicine is an innovative field of medicine which utilises iPS cells. It can potentially restore or replace damaged or lost physical functions as well as completely curing diseases or healing injuries.

A lot of clinical research has been conducted in the field of iPS cells, but there are some obstacles to its practical use, namely the difficulty in generating iPS cells that display consistent characteristics, and a very low production rate (about 1%).

Conventionally, the generation of iPS cells utilized viruses to introduce Yamanaka factors into cells, but these factors are also capable of inducing cancer in cells and creating tumors. Concerns have also been raised about the risk of parts of the viruses' gene sequence remaining in cells. Currently, there are various methods being developed for generating iPS cells without using viruses, but all of these methods have demonstrated even poorer rates of production efficiency. In addition, the generation and culturing of iPS cells can only be done by trained experts, and these activities require specialized conditions in facilities in order to prevent contamination.

Dr. Numano explains, "We have developed a novel method of generating iPS cells by using water-in-oil droplet electroporation. Cell membranes are made of layers of oils.



We have found that by momentarily applying several kilovolts to cells, with about the same voltage as static electricity, the cell membrane loosens and forms transient pores through which the Yamanaka factors can pass. This technique does not require the use of viruses.

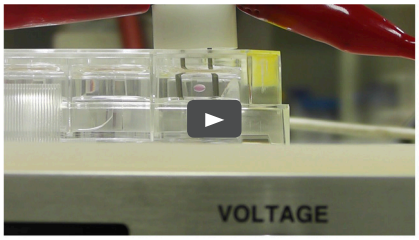
However, commercially available electroporation equipment requires a costly pulse generator and sends out high-voltage pulses that kill more than half of the cells. Therefore, rather than implement a method using commercial electroporation equipment, we decided to develop a machine that uses direct-current electric fields to generate iPS cells in a more cell-friendly, convenient and efficient way."

Aiming for chip-based mass production of iPS cells

The procedure for this novel technique is to take an aqueous droplet several microliters in volume containing cells and four Yamanaka factors, put this droplet inside insulating oil, and then apply a direct current from a metal electrode. When the aqueous droplet is exposed to an electric field between a pair of electrodes, the droplet moves back and forth in a rapid bouncing motion between the positive and negative electrodes several hundred

times in a minute.

"This technique uses the basic physical property that oil does not mix with water. When the electric field is first applied, the droplet might move to the negative electrode,



for example. However, the machine switches the polarity after the droplet contacts with this electrode, and so the droplet is repelled by the negative electrode and moves toward the positive electrode. This cycle is repeated many times, making the droplet move in a bouncing motion. This creates a minute electric current that loosens the cell membranes, allowing for the Yamanaka factors to be introduced into the cells.

Although this reactor is extremely small in size — a water droplet just a few microliters in volume — the droplet contains about ten thousand cells as well as the four types of genes known as Yamanaka factors. This arrangement allows for these genes to be efficiently introduced into the cells. The droplet is insulated by the oil surrounding it, and so there is no risk of contamination in the reactor," explains Dr. Numano.

One of the most striking points of this new method is that despite a high voltage being used to move the droplet, the electric current in the droplet is very small, and has little influence on the cells.

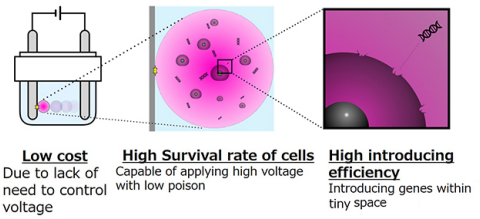
"We think that if we can conduct the same process in an even smaller reactor, such as picoliter-scale droplets in the micro-channels of a chip, we could further improve the diffusion efficiency of genes, allowing for better introduction of the genes into the cells.

Micro-channels are a completely closed system, with no danger of contamination. They also allow for Yamanaka factors to be introduced into the same cells, enabling a large number of iPS cells to be produced in a short period of time," she says.

This water-in-oil droplet electroporation was developed in a joint research project with Professor Takayuki Shibata and Assistant Professor Hirofumi Kurita from Toyohashi University of Technology. Professor Takayuki Shibata is a bio-MEMS (Micro Electro Mechanical System) researcher working on microneedle arrays for cells, and Assistant Professor Hirofumi Kurita is working on applications of electrostatic forces in life science. A patent has already been obtained for the device, and work is underway together with the electroporator manufacturer Nepa Gene Co., Ltd., in order to realize a practical implementation.

Dr. Numano adds, "Researchers at Juntendo University are conducting clinical research in regenerative medicine using iPS cells to treat Parkinson's Disease. We have requested Professor Wado Akamatsu, from the Center for Genomic and Regenerative Medicine in Juntendo University, to investigate the characteristics of functional differentiation in the iPS cells that we have generated.

Apart from Juntendo University, many clinical



studies are currently being conducted at Kyoto University, Osaka University, Keio University, and other institutions in order to seek treatments for neurodegenerative diseases that are considered difficult to cure. We also hope to accelerate our research on mass production methods for iPS cells in order to make the fruits of our research publicly available as soon as possible."

Utilizing this technology to treat diseases by manipulating many cells at once

Before she switched to working with iPS cells, the main focus of Dr. Numano's research was on circadian rhythms in mammals.

"All animals on the earth have a circadian rhythm, which is an internal clock that works in 24-hour cycles. The circadian rhythm is regulated by some 20 types of genes known as clock genes. These clock genes work together within the brains of mammals over 24-hour cycles. This is a very robust system, and is not easily disturbed by minor genetic mutations. If we want to control clock genes, we need to manipulate multiple genes at the same time," Dr. Numano says.

For example, when flying from Japan to the US, our eyes are stimulated by light from the outside, which influences the clock genes in our brain in order to make adjustments to follow local time. However, it is difficult to shift the entire human biological clock by many hours in an instant. As a result, we become jet-lagged because it takes longer for the tissues outside of the nervous system to adjust to the local time.

"I have been working on analyzing the mechanism of the circadian rhythm. I have thought a lot about finding ways to adjust the circadian rhythm instantly. This would allow us to control physiological processes, such as to cure jet lag instantly, or to discover treatments for diseases that are related to the circadian rhythm."

In her research, she came across the electroporation method, which can manipulate many genes at once. This method may allow genes to be introduced into CAR (Chimeric antigen receptor) T cells—a type of white blood cell that specifically attacks cancer cells—to improve their abilities, meaning that this method could also be employed for cancer treatment.

"In addition to iPS cells, this electroporation method can be applied to many other types of genetic manipulation. I would like to conduct further research to refine several aspects of the method, such as identifying how many more genes we can introduce in total, and the types of cells that can be regulated with the method," said Dr. Numano about the future prospects of her research.

[Reporter's Note]

Dr. Numano grew up in a family with many physicians: her father was a cardiologist and her mother was a pediatrician. She recalls her father's disappointment when he came home from his university hospital if one of his patients had died that day.

She says, "I thought of becoming a physician as well. However, through witnessing my parents' experiences, I decided to go into basic research where I could work on ways to fundamentally treat or prevent diseases."

The Human Genome Project commenced when she was a student, and many other research efforts made progress in treating disease preventatively or at early stages. She obtained her doctorate degree while working in the laboratory of our previous Dean Yoshiyuki Sakaki, a prominent Japanese researcher who took a leading role in the Human Genome Project. After graduating, she came to Toyohashi University of Technology, and she has worked over a decade in collaboration with many researchers and companies in order to achieve her dream. Her bright, graceful smile offers the reassurance of an expert physician. We look forward to witnessing further successes in her career.

再生医療普及のカギを握る「iPS細胞の量産化」への挑戦

iPS細胞を用いた再生医療は、病気を根本から治療する革新的な医療として大きな期待が寄せられている。しかし、その実用化には多くの壁が存在する。その一つが、均質な性質を持つ iPS細胞を大量に効率よく量産することができないことである。沼野利佳准教授は、その壁を破る革新的な技術として、液滴エレクトロポレーション法を開発し、新法によるiPS細胞の量産化を手がけている。これは、細胞と導入したい山中因子（細胞の初期化を促す遺伝子）を封入した液滴に、電圧を印加することで細胞表面に開いたわずかな孔から遺伝子が導入されるという革新的な手法だ。従来のウイルス感染法に比べて、iPS細胞ががん化しにくく、少ない細胞で簡便に作製できるという。将来、移植に適応可能なiPS細胞の量産化を実現する新手法として注目が集まる。

ウイルスに頼ることなく、簡便にiPS細胞を作製する

京都大学の山中伸弥教授が、皮膚や血液などの体細胞に4つの因子を導入することで、細胞が初期化し、分化多機能性を持つiPS細胞になることを示して、2012年にノーベル生理学・医学賞を受賞したことはよく知られている。このiPS細胞を用いた再生医療は、失われた身体の機能や欠損を取り戻し、病気や怪我の根治を実現する革新的な医療として、世界中から大きな期待が寄せられている。

現在、このiPS細胞を用いた臨床研究が進められているが、実用化の障壁となっているのが、均質な性質を持つiPS細胞の作製の難しさと、実際にiPS細胞になる細胞が1%程度という、作製効率の悪さだ。

従来、iPS細胞の作製には、山中因子を細胞に導入するためにウイルスが用いられてきたが、これが原因で細胞ががん化し、腫瘍ができることがあった。ウイルス由来配列の残存などの危険性も指摘されている。そこで現在、ウイルスを用いずにiPS細胞を作製する方法が検討されているが、そうするとさらに作製効率が落ちてしまう。また、iPS細胞の作製・培養には熟練した専門技術者が必要なうえ、コンタミネーション（汚染）を防ぐための特殊な施設管理体制も必要になる。

「そこで、私たちが開発したのが、液滴エレクトロポレーション（電気穿孔法）によるiPS細胞の作製です。細胞膜は油の層でできているのですが、瞬間的に静電気ほどの数kV級の電圧をかけてやると、細胞膜が緩んで、微細な孔ができ、そこから山中因子を取り込むことができると考えられるのです。つまり、ウイルスを用いる必要はありません。

ところが、市販のエレクトロポレーション装置の場合、高い電圧の電気パルスを発生させるための高価なパルスジェネレーターが必要なうえ、これを用いると、半分以上の細胞が死滅してしまいます。そこで我々は、市販品と異なる直流電解を用いて、簡便に、高効率にiPS細胞をつくることができる、細胞にやさしい作製装置を開発しました」と、沼野准教授は説明する。

オンチップiPS細胞で量産化を狙う

そのしくみは、絶縁体である油相の中に、細胞と4つの山中因子を入れた数μlほどの液滴を垂らし、金属電極から直流電解をかけるというものだ。すると、球状の液滴が反応して、1分間に数百回ほど、プラス極とマイナス極の間を行ったり来たり、素早く往復運動を繰り返すようになる。

「水と油が混ざり合わない性質を利用しているわけですね。そして、最初の帯電で、液滴がたとえばマイナス極のほうに引き寄せられて接触すると、今度は極性がマイナスに反転して反発し、プラス極へ向かいます。これを何度も繰り返す中で、液滴が往復運動し、その間に微弱な電流が流れ、細胞膜が緩んで、山中因子が細胞の中に導入されるのです。しかも、反応場である液滴は数μl程度と小さいものの、この中に約1万個の細胞と山中因子である4種類の遺伝子が入っていて、効率よく遺伝子を細胞に導入することができます。液滴のまわりは油相で隔てられているため、反応場がコンタミネーションする心配もありません」（沼野准教授）

特筆すべきは、高い電圧をかけても液滴に流れる電流自体は非常に微弱で、細胞にはほとんど影響しないことにある。この液滴を採取して培養液に入れてiPS細胞を培養するまで、一連の工程には難しい作業は不要で、自動化もしやすいという特長がある。

「チップ状のマイクロ流路の中の数pl（ピコリットル）ほどの液滴でこの実験系を展開すると、さらに反応場が小さくなることで、遺伝子の拡散効率が高まり細胞により入りやすくなると考えられます。マイクロ流路は完全閉鎖系のためコンタミネーションの心配もありませんし、同時に山中因子を同じ細胞に導入することができ、短時間でiPS細胞を大量につくることができるようになるでしょう」

この液滴エレクトロポレーションの開発は、同大のバイオMEMS（Micro Electro Mechanical System）の研究者で、細胞穿刺用のマイクロニードルアレイの開発などを手がけてきた柴田隆行教授や、静電操作技術を生命科学へ応用されている栗田弘史助教らと共同で進めている。すでに特許を取得し、エレクトロポレーション装置を製造しているネッパジーン株式会社と共同で、社会実装に向けた検討も重ねている。

「現在、順天堂大学では、iPS細胞を使った再生医療としてパーキンソン病治療の臨床研究に取り組んでいますが、順天堂大学のゲノム・再生医療センター赤松和土先生に、私たちが作製したiPS細胞の機能分化の特性について調べていただいているところです。そのほか、京都大学、大阪大学、慶應義塾大学などでも、これまで治療が困難とされてきた神経の変性疾患に関する臨床研究が始まっています。こうした成果をできるだけ早く社会に還元できるよう、我々も量産化に向けた取り組みを加速させていきたいと思っています」

細胞をいっぺんに操作することで、病気の治療に役立てたい

ところで、沼野准教授自身がiPS細胞に関わるようになったのはここ数年のことだが、それまではおもに哺乳類の概日リズムを制御する研究を手がけてきた。

「地球上のすべての生物は24時間周期の概日リズムを刻んでいますが、これを支えているのが、20種類ほどある、時計遺伝子と呼ばれる遺伝子で、これらが脳の中で24時間周期で関連しながら機能しています。これは非常に強固なシステムで、数個の遺伝子変異が起こったくらいでは、簡単には壊れません。もし、時計遺伝子をコントロールしようとするなら、いっぺんにたくさんの遺伝子を操作する必要があるのです」と沼野教授は語る。

たとえば、日本から渡米した場合、目から入った光の刺激で、脳の時計遺伝子が影響を受けて、現地時間にリセットする調整を促す。しかし、体全体の時計を何時間も一気に動かすのは難しく、末梢組織の時計は脳の時計との同期に時間がかかるため、時差ボケに悩まされることになるのだという。

「そこで、遺伝子による概日リズム形成のメカニズムを解明し、それをいっぺんに調整することで、生理現象を変えられないか、たとえば時差ボケを一気に解消するとか、派生的に起こる病気の治療法に役立てられないかと考えてきました」

そうした中で出合ったのが、たくさんの遺伝子を一気に操る手段としてのエレクトロポレーションだった。また、この方法を活用すれば、がん細胞を特異的に攻撃するCAR（キメラ抗原受容体発現）-T細胞を改善するような遺伝子を入れて、がん治療に役立てることもできるかもしれない。

「この手法を発展させれば、iPS細胞だけでなく、さまざまな遺伝子操作にも活用できるでしょう。さらにどれくらいの遺伝子が入るのか、どういう種類の細胞なら機能調節ができるのかなど、研究を深めていきたいと考えています」と、沼野准教授は展望を語った。

（取材・文＝田井中麻都佳）

取材後記

お父様は循環器内科、お母様は小児科のお医者様で、親戚を含めて医者一家の中で育った沼野准教授。大学病院に勤めていたお父様が家に帰ってくるなり、「今日は患者さんが亡くなった」と肩を落とす姿を見ることもあったという。

「医者になろうかとも思いましたが、親の姿を見るにつけ、病気を根本から治したり、予防したりすることができればと考えるようになり、基礎研究の道に進むことにしました」と沼野准教授は語る。

折しも、学生時代にヒトゲノム計画が始まり、より上流で病気を食い止める研究が進展しつつあった。ヒトゲノム計画を牽引していた日本の代表研究者、榊佳之前学長の研究室で博士の学位を取得し、その後、豊橋技科大へ。以後、10年に渡り、多様な研究者や企業とのコラボレーションにより、夢を実現しつつある。その笑顔は、明るくたおやかで、ベテラン医師のような安心感がある。今後のさらなる活躍に期待しています。

Researcher Profile

Dr. Rika Numano

Dr. Rika Numano received her M.S. degree in engineering and PhD degree in doctor in 1997 and 2001 respectively from University of Tokyo, Japan. Since she started her career at Toyohashi University of Technology, had been involved in the chronobiology, molecular biology, and neuroscience. She is currently an associate professor at the Department of Applied Chemistry and Life Science, Toyohashi University of Technology.

Reporter Profile

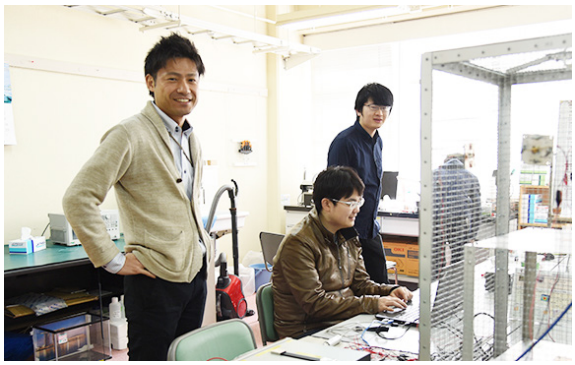
Madoka Tainaka is a freelance editor, writer and interpreter. She graduated in Law from Chuo University, Japan. She served as a chief editor of "Nature Interface" magazine, a committee for the promotion of Information and Science Technology at MEXT (Ministry of Education, Culture, Sports, Science and Technology).

Wireless power transfer in fresh water using capacitive coupling

Using underwater inspection robots to detect the early-stage deterioration of structures

By Masaya Tamura

A research team led by Associate Professor Masaya Tamura of the Department of Electrical and Electronic Information Engineering at Toyohashi University of Technology successfully achieved wireless power transfer in fresh water using capacitive coupling. In the field of wireless power transfer, it had been considered difficult to realize wireless power transfer in fresh water using capacitive coupling because fresh water behaves as a dielectric material with extremely high dielectric loss. In this research, the team elucidated the high-frequency properties of fresh water through experiments. The team also discovered the frequency band that enables power transfer with high efficiency using an electric field and an electrode structure that can realize this high efficiency.



Wireless power transfer has attracted attention within a wide range of fields, ranging from mobile terminals to automobiles. Previously, research was mainly done in dry-land environments, though expectations are high for studies in underwater environments as the next target of research. For example, with regard to structural health monitoring systems for pipes, cooling towers or dam walls, there is an urgent need to develop underwater inspection robots that can move freely and perform inspection, even in the event of a disaster. Because these robots are battery-powered, with conventional technology it is necessary to pull them out of the water, charge them, and have them dive back into the water repeatedly. The development of technology to transfer power and information wirelessly in water, therefore, (Figure1) will be key in improving the efficiency of this work.

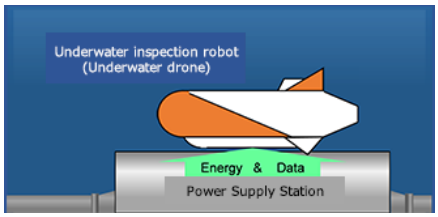


Fig.1 The underwater inspection robot parks on top of the power supply station, charges its battery and communicates information such as its collected data.

As a solution, the research team led by Associate Professor Masaya Tamura developed a capacitive coupler that can supply power wirelessly in fresh water with high efficiency.

The efficiency of wireless power transfer depends on the kQ product, which is the product of the coupling coefficient k of the coupler and the Q-factor of the coupler loss including the influence of the surrounding environment. The higher the kQ product, the better the transfer efficiency. Since the influence of water surrounding the coupler is dominant over the coupler itself in an underwater environment, the study focused on the high-frequency properties of fresh water. The team made its own cell for measurements and clarified the relationship between frequency and the Q-factor of fresh water.

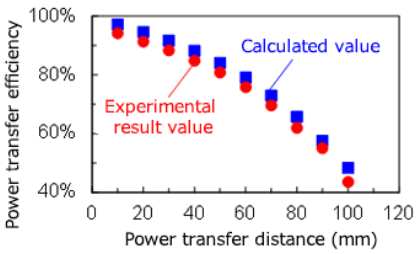


Fig.2 The calculated values and the experimental result values were in close agreement. The research team achieved a transfer efficiency of at least 90% at a distance of 2cm and at least 80% at 5cm.

Based on these results, the team used electromagnetic field analysis to find the frequency of power transfer and the structure of the coupler where the value of the kQ product in fresh water is at a maximum. The team achieved a power transfer efficiency of at least 90% at a transfer distance of 2cm and at least 80% at 5cm. The team also succeeded in activating a sensor module via wireless power transfer to conduct infrared data communication. Power transfer efficiency was maintained at 90% or higher over a distance of 2cm, even when transferring 400W of power. Considering that the robot will park on top of the power supply station, this technology is suitable for practical use.

The result of this study will allow for robots that inspect the pipes and cooling towers of power plants or dam walls to communicate information and charge their batteries within the areas of inspection. The research team believes the technology will contribute to drastic improvements in user safety as well as in the operational

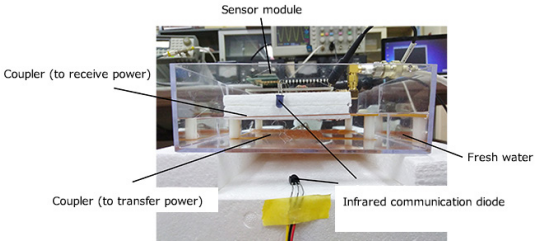


Fig.3 The sensor module was activated by wireless power transfer in fresh water to conduct infrared data communication in this experiment.

efficiency of the robots. The coupler newly developed by the team is simple and lightweight, and therefore the impact on the total weight of the underwater inspection robot is kept to a minimum. Use of this lightweight coupler can also eliminate the need for an extensive redesign of the buoyancy system. The team seek to soon achieve the communication of information with electric field coupling in fresh water, as well as highly efficient wireless power transfer in seawater. Their ultimate goal is to realize the wireless transfer of power and information transfer in both fresh water and sea water.

This research was supported by REFEC: Research Foundation for the Electrotechnology of Chubu and Japan Society for the Promotion of Science, Grant-in-Aid for Scientific Research (C)

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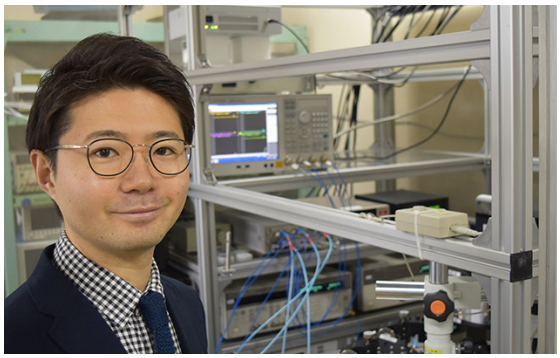
Expression of Stop Bands in Forward Volume Spin Waves

Contribution to the realization of super low-power spin wave integrated circuits

By Taichi Goto

A research group led by assistant Professor Taichi Goto at Toyohashi University of Technology have, for the first time in the world, demonstrated "stop bands" that prevent propagation of specific frequency components of "forward volume spin waves." Forward volume spin waves are transmitted through magnetic insulators without the flow of current, and are expected to be applied to the next generation of integrated circuits (ICs). Furthermore, among the spin waves that have been confirmed, forward volume spin waves are the most suitable for information transmission in IC chips, and there are high expectations for their application. However, until now, noise in forward volume spin waves was large, and the stop bands, which are one of the basic physical phenomena, could not be observed. In this demonstration, a magnetic insulator was combined with metal to suppress the noise in forward volume spin waves, and the expression of stop bands was confirmed experimentally.



In recent years, electronic devices using semiconductor materials have had difficulty in responding to the demands of the rapidly growing information society. For example, due to increases in energy density due to increased integration, chip temperatures have become high, causing defects. Therefore, the development of spin wave IC chips which can process information not by moving electrons themselves but by transmitting spin only, greatly reducing the generation of heat, is attracting attention.

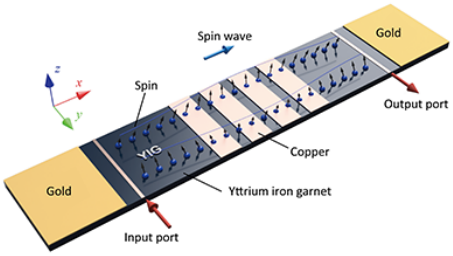


Fig.1 A model of a spin wave device realized by combining yttrium iron garnet, gold and copper.

Specifically, spin waves traveling through magnetic insulators have the advantage of low energy loss and long-distance transmission. Furthermore, among the spin waves whose existence has been confirmed, forward volume spin waves that transmit in all directions are said to be most suited for ICs because they can be wired diagonally or in curved shapes as well as linearly. On the other hand, these forward volume spin waves are noisy, and several fundamental spin wave phenomena have not yet been demonstrated. Demonstration of these fundamental principles is indispensable for the development of IC chips and has become an important issue.

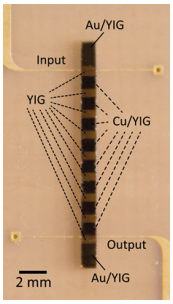


Fig.2 Photograph of the fabricated spin wave device.

Now a research group led by Taichi Goto, of Toyohashi University of Technology, has successfully combined an Yttrium iron garnet (YIG) – an oxide single crystal well known as a magnetic insulator – with two metals (gold and copper) to suppress noise. Through this approach the research team was able to confirm the expression of stop bands in forward volume spin waves experimentally for the first time in the world. In this research, firstly, a system that could simulate the propagation of spin waves was prepared using a three-dimensional model (Figure 1) with the same scale as real spin waves. Using this system, a sample structure was determined where noise was small and the "stop bands," which are one of the fundamental spin wave phenomena, was confirmed. A stop band is a phenomenon that does not allow spin wave components of a specific frequency to pass through, and stop bands are also expressed in other waves such as electromagnetic waves including light.

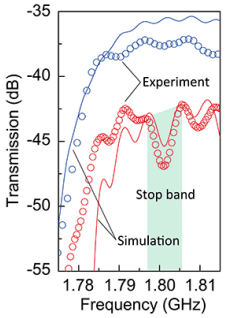


Fig.3 Transmission characteristics of the fabricated spin wave device.

Next, samples were made to be as close as possible to the simulation. Figure 2 shows a sample prepared using materials from Shin-Etsu Chemical Co., Ltd. Both ends of the yttrium-iron garnet (which was processed into a wire shape) were covered with gold film to suppress noise generation, and by arranging a copper film in stripes like a pedestrian crossing, the research team tried to hinder the propagation of specific frequencies. Spin waves of various frequencies were passed through this sample and the transmission characteristics were measured.

As a result, the "stop bands" were confirmed as shown in Figure 3. By comparing these with the characteristics of samples without stripe-arranged copper, it can be seen that the expression of stop bands is due to the stripe-arranged copper. Also, the experimental results and the calculation results are in good agreement. From this, the results can be predicted by simulation before experiment, leading to the potential for efficient spin wave IC development.

The promising results of this research can be used for applications such as spin wave filters in spin wave IC chips in the future. In addition, they can also be used to slow down the transmission speed of spin waves and to control the direction of travel, contributing to the development of smaller chips capable of more dense information processing.

This research was jointly conducted by Assistant Professor Taichi Goto, PhD student Kei Shimada, Associate Professor Yuichi Nakamura, Professor Hironaga Uchida, and Professor Mitsuteru Inoue of the Toyohashi University of Technology. Additionally, the samples used for the experiment were prepared under a joint research initiative with Shin-Etsu Chemical Co., Ltd.

This research was supported by JST PRESTO Number JP JPR 1524 and JSPS KAKENHI Nos. 17K19029, 16H04329, 26220902.

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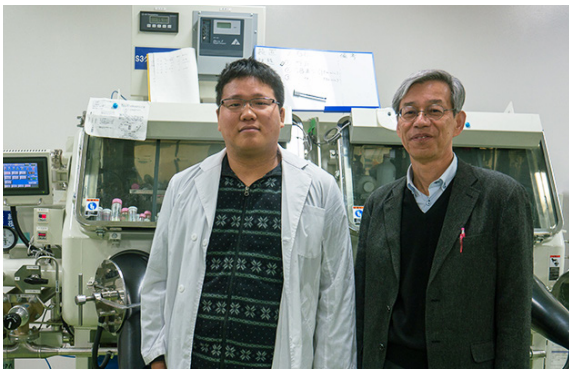
Structure of Electrolyte Controls Battery Performance

Toward implementation of calcium-ion batteries

By Yoshiaki Murata

A research team at the Department of Electrical and Electronic Information Engineering, Toyohashi University of Technology has revealed that adding water into electrolyte improves the function of vanadium oxide, which is one of positive electrode materials used in calcium-ion batteries. Although water in electrolytes is known to produce many negative effects, it has now been found to bring about a phenomenon that speeds up the conventionally slow reaction of calcium-ion batteries. The results of the present study indicate that this phenomenon is caused by changes in the electrolyte structure. It is believed that this discovery will greatly benefit the development of electrolytes for implementing calcium-ion batteries in the future.



Yoshiaki Murata (left) with his adviser, Prof. Yoji Sakurai.

Secondary batteries are valuable resources that support various industries. Nowadays, secondary batteries are required to be even more powerful to cope with increased use of reusable energy and electric vehicles. Lithium-ion secondary batteries are already widely used as powerful secondary batteries. However, in recent years, the safety of secondary batteries has been brought into question with countless reports citing combustion. Going forward, the need for batteries in our current society is expected to increase exponentially along with the rise in electric vehicles. This means a higher demand for lithium, which in turn is expected to cause problems such as higher prices and potential resource depletion.

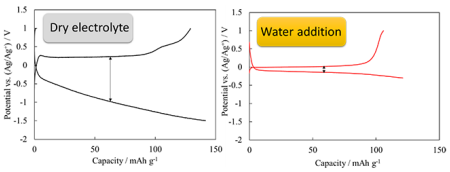


Fig.1 Changes in charge/discharge characteristics due to water addition.

Calcium-ion batteries are a type of next-generation secondary battery that do not use lithium and can achieve a battery voltage that rivals that of lithium-ion batteries. Compared to lithium-ion batteries, calcium-ion batteries are safer, cheaper to produce and their resources are much more plentiful. While calcium-ion batteries are currently attracting attention for these reasons, they are still subject to a number of issues. One such issue is that they operate at a speed much lower than that of lithium-ion batteries. In this study, Toyohashi University reported that the slow operating speed of calcium-ion batteries could be improved by adding water into the electrolyte. The graphs of the test results show that overvoltage that occurs during charge/discharge greatly decreases as the amount of added water increases and that reaction proceeds without any problems. As a result of various tests, it was proved that this phenomenon is caused by the fact that the structure of the electrolyte is greatly changed by the addition of water.

Yoshiaki Murata, PhD student and first author of the study explains that, “The electrolyte is made up of positive ions (calcium ions), negative ions and solvent molecules, and the state around the calcium ion greatly changes when water is added. What that means is that, in order to improve the performance of a calcium-ion battery, preferably no negative ion is attached to the calcium ion in the electrolyte and a solvent molecule that easily separates is attached to the calcium ion. While we still need to discover an electrolyte with these characteristics that does not include water in order to achieve calcium-ion batteries, the discovery of this phenomenon will surely help with future electrolyte development.

The result of the present study was actually a secondary result obtained while studying new electrolytes. Electrolytes need to be sufficiently dehydrated when they are developed, but this dehydration process is difficult. The present study arose when it was noticed that the characteristics of a battery which had an insufficiently-dehydrated electrolyte actually improved during tests. Although there have been reports of a phenomenon in which the performance of magnesium-ion batteries for example had improved after the addition of water, the

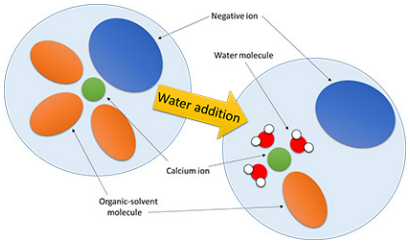


Fig.2 Adding water causes the organic solvent around the calcium ion to decrease and water to increase. Water also causes an important structural change in that the negative ion separates from the calcium ion.

mechanism behind this was not clearly understood. It was surprising that the same phenomenon could be seen in calcium-ion batteries, and we believe that elucidating the mechanism behind this behavior will prove useful for the future development of electrolytes.

Our research team is looking to develop and assess new electrolytes based on this newly discovered electrolyte structure that improves the performance of calcium-ion batteries. Further, we have not been the only ones to study this; there has been rapid increase in the number of studies of calcium-ion batteries in recent years. Ultimately, we would like to develop a calcium-ion battery that has the capability to rival or overtake lithium-ion batteries.

This work was partly supported by JSPS KAKENHI Grant Numbers JP24360109, JP18H01427 from the Japan Society for the Promotion of Science (JSPS).

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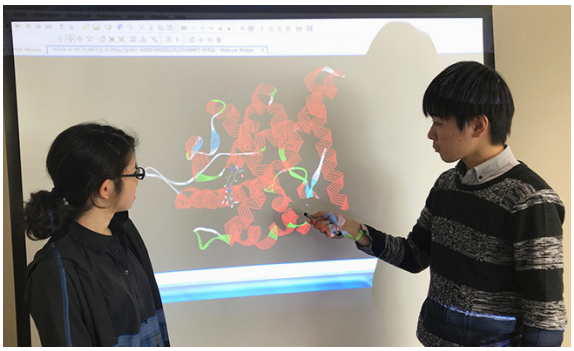
Chirality of vitamin-D derivative affects the protonation states of its receptor protein

Ab initio molecular orbital calculations with K Computer for development of novel and potent drugs.

By Noriyuki Kurita

A team of researchers lead by Noriyuki Kurita at Toyohashi University of Technology, in cooperation with researchers at Teijin Pharma Ltd. and Teikyo University, have highlighted the possibility that chirality of vitamin-D derivatives can affect the protonation states of histidine residues in the vitamin-D receptor protein via ab initio molecular simulations and biomedical analyses. This finding emphasizes that protonation states should be considered more precisely in molecular simulations, when investigating specific interactions between candidate drugs and target proteins related to disease pathogenesis.



Associate Prof. Kurita's student, Rie Suzuki and Sousuke Suzuki (from left)

Vitamin-D is understood to play many important roles in the onset of immunological diseases, as well as the regulation of calcium level in the blood. These physiological actions caused by active vitamin-D are triggered by the specific interaction of active vitamin-D with the vitamin-D receptor (VDR); many types of vitamin-D derivatives have been developed as potent ligands against VDR. The binding affinity between human VDR and vitamin-D derivatives has been reported to depend significantly on the chirality of the derivative.

However, the reason for the dependence has not been clarified, which makes it a bottleneck in the development of novel and potent drugs against immunological diseases, whose onset is related to the activation of VDR.

Now, researchers at the Department of Computer Science and Engineering at Toyohashi University of Technology and at Teijin Pharma Ltd. and Teikyo University have demonstrated the potential of the chirality of vitamin-D derivative to affect the protonation states of histidine residues in the VDR protein based on the results evaluated by state-of-the art molecular simulations and the K computer of RIKEN.

Researchers have observed the specific interactions between VDR and some vitamin-D derivatives with different chiralities using ab initio fragment molecular orbital (FMO) calculations. The FMO results reveal that two histidine residues in the VDR contribute significantly to the binding of the VDR with the derivatives and that the protonation states of these residues can affect the specific interactions.

Therefore, the researchers considered the other possible protonation states of these histidine residues and determined the most stable states using the ab initio FMO calculations. The results illustrated, for the first time, the possibility that the difference in the chiralities of vitamin-D derivatives can induce changes in protonation states of the histidine residues in the VDR that exists near the derivative. Due to this change in the protonation state, the derivatives can bind more strongly to the VDR and can thus produce more stable complexes with it.

This finding provides an important and essential warning for the molecular simulations to consider protonation states of histidine residues in proteins more precisely while investigating the specific interactions between proteins and ligands.

"We have used sophisticated molecular simulations and the K computer to find that the protonation states of the histidine residues in the VDR change significantly with alterations in the chirality of ligand", explains Associate Professor Noriyuki Kurita, "Since histidine residues exist in many proteins involved in the pathogenesis of diseases, we should consider their protonation states more precisely via in silico drug design based on molecular simulations."

The first author, graduate student Yuta Terauchi, said, "Our final goal is to develop novel and potent drugs capable of activating VDR based on our ab initio molecular simulations, as well as on the basis of biomedical studies performed by our collaborators."

The authors are participating in an in silico drug design consortium – the fragment molecular orbital drug design (FMODD) consortium – in which various researchers from universities, drug companies, and national institutes are investigating the specific interactions between disease-related proteins and many types of candidate drugs using ab initio molecular simulations based on the FMO method and the K computer. Similar molecular simulations are underway now for a huge number of vitamin-D derivatives in order to propose novel ligands for VDR, which can act as candidates for potent new drugs against immunological diseases, such as cancer.

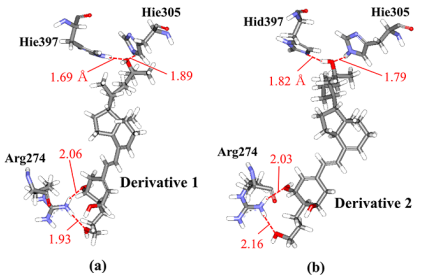


Fig.1. Hydrogen bonding interactions between vitamin-D derivatives and amino acid residues in VDR.

A part of this research was undertaken during activities of the FMODD consortium. A part of the results was obtained using the K computer (project ID: hp170183 and hp180147).

Reference

Yuta Terauchi, Rie Suzuki, Ryosuke Takeda, Ittetsu Kobayashi, Atsushi Kittaka, Midori Takimoto-Kamimura and Noriyuki Kurita (2018). Ligand chirality can affect histidine protonation of vitamin-D receptor: ab initio molecular orbital calculations in water. Journal of Steroid Biochemistry and Molecular Biology, in press. https://doi.org/10.1016/j.jsbmb.2018.09.020

電界結合で水中無線電力伝送を実現

水中点検ロボットで構造物の劣化をいち早くキャッチ

田村　昌也

豊橋技術科学大学 電気・電子情報工学系 田村昌也准教授らの研究チームが、電界結合を用いて淡水中での無線電力伝送に成功しました。無線電力伝送の世界では、淡水は非常に損失の大きな誘電体としてふるまうため、電界結合による水中での無線電力伝送は困難だとされてきました。今回、淡水の高周波特性を実験により明らかにし、電界でも高効率に伝送可能な周波数帯と高効率化を実現する電極構造を発見しました。

無線電力伝送はモバイル端末から自動車まで幅広い分野で注目を浴びています。これまでは陸上環境での研究が主でしたが、次のターゲットとして水中環境が期待されています。例えば、配管や冷却塔、ダムの堤体壁面など構造ヘルスモニタリングシステムにおいては、自由に移動でき、災害時でも調査が可能な水中点検ロボットの開発が急務となっています。このロボットはバッテリ駆動のため、充電のために何度も引き上げ、再び潜航させるという作業を繰り返す必要があります。このような作業による運用効率の低下を改善するには、給電ステーションを介した水中での無線電力情報伝送（図1）の技術開発がキーとなります。

そこで、田村昌也准教授らの研究チームは淡水中でも高効率に無線で給電できる電界結合器を開発しました。無線電力伝送における電力伝送効率は伝送用結合器のもつ結合係数kと周辺環境の影響も含めた結合器の損失を表すQ値の積であるkQ積に依存します。kQ積が高いほど伝送効率も向上します。水中では結合器よりも結合器を取り巻く水の影響が支配的であることから本研究では淡水の高周波特性に注目し、自作の測定セルを用いて測定を行い、周波数と淡水のQ値の関係を明らかにしました。

その結果を用いて電磁界解析から淡水中でkQ積が最大値を示す電力伝送周波数と結合器構造を明らかにしました。これにより送電距離2cmで90%以上、5cmで80%以上の電力伝送効率を実現しました。実際に淡水を介した無線電力伝送でセンサモジュールを駆動し、赤外線によるデータ通信にも成功しました。また、400Wの電力を送電距離2cmで送電しても電力伝送効率90%以上を維持できています。給電ステーションに着底することを考えると、実用に耐えうる効率と考えられます。

研究チームは、本研究成果により発電所の配管や冷却塔、ダムの堤体壁などの水中点検ロボットに対し、点検区域内での通信・充電が可能となり、使用者の安全性やロボットの運用効率の飛躍的向上に貢献できると考えています。開発した結合器は非常にシンプルかつ、軽量であるため、水中点検ロボットの総重量に与える影響を最小限に抑え、浮力システムの大掛かりな再設計も不要になることが期待されます。また、電界結合による淡水中での情報通信や海水中での無線電力伝送効率も高効率化が見えてきており、最終的には、淡水・海水のどちらでも無線電力情報伝送を実現したいと考えています。

前進体積スピン波のストップバンドの発現を実証

超低消費電力なスピン波集積回路実現に貢献

後藤　太一

豊橋技術科学大学の後藤太一 助教らは、「前進体積スピン波」の特定の周波数成分の伝搬を妨げる「ストップバンド」を実証しました。前進体積スピン波は、電流を流さずに磁性絶縁体中を伝わることから、次世代の集積回路への応用が期待されています。また、確認されているスピン波の中で集積回路チップ内の情報伝達に最も適しており、応用が強く期待されているものです。しかし、これまで、前進体積スピン波のノイズは大きく、基本的な物理現象の1つであるストップバンドが観測できていませんでした。今回の実証では、磁性絶縁体と金属を組み合わせ、前進体積スピン波のノイズを抑制し、ストップバンドの発現を実験で確認しました。

近年の半導体材料を利用した電子デバイスは、高集積化によるエネルギー密度の増加に伴い、チップの温度が高くなり、不具合を生じるなどして、急成長する情報化社会からの要求に答えることが難しくなってきています。そこで、電子自体は移動せずスピンだけを伝えることで情報処理を行い、熱の発生が大幅に低減可能なスピン波集積回路チップの開発が注目を集めています。

この中でも、磁性絶縁体中を伝わるスピン波は、エネルギーの損失が小さく、長距離伝送が可能という利点を持っています。さらに、存在が確認されているスピン波の中でも、あらゆる方向に伝わる前進体積スピン波は、直線状の配線だけでなく、斜めや曲線の配線が可能なため、最も集積回路に適すると言われています。その一方で、この前進体積スピン波はノイズが大きく、いくつもの基本的なスピン波の現象が実証されていませんでした。このような基本原理の実証は、集積回路チップの開発には必要不可欠であり、重要課題となっていました。

今回、豊橋技術科学大学の後藤太一らは、酸化物で磁性絶縁体として有名な単結晶のイットリウム鉄ガーネット（Yttrium iron garnet、YIG）と2つの金属（金と銅）を組み合わせ、ノイズを抑制し、前進体積スピン波のストップバンドの発現を実験で確認しました。本研究では、最初に、現実と同じスケールの三次元モデル（図1）を用いて、スピン波の伝搬がシミュレーションできるシステムを整えました。これを用いて、ノイズが小さく、基本的なスピン波の現象の一つである「ストップバンド」が発現する試料構造を決定しました。ストップバンドとは特定の周波数のスピン波成分を通さない現象であり、光を含む電磁波など他の波についても表れるものです。

次に、このシミュレーションと、できる限り同じ試料を作製しました。図2が信越化学工業株式会社から材料提供を受け作製した試料であり、線状に加工したイットリウム鉄ガーネットの両端を金膜で覆うことでノイズ発生を抑え、銅の膜を横断歩道のように周期配列することで特定の周波数の伝搬を妨げるようにしました。

この試料に、さまざまな周波数のスピン波を流し、透過特性を測定したところ、図3のように、ストップバンドが発現しました。周期配列した銅がない試料の特性と比べると、ストップバンドの発現が周期配列した銅による影響であることが分かります。また、実験結果と計算結果がよく一致しました。このことから、実験をする前にシミュレーションで結果が予測でき、効率的なスピン波集積回路開発に繋がると期待できます。

今回得られた成果は、将来のスピン波集積回路チップの中では、スピン波のフィルター等として使うことができます。他にも、スピン波の伝わる速度を遅くしたり、進む方向をコントロールしたりすることにも使うことができ、より小型で、高密度で情報処理を行うチップの開発に寄与します。

本研究は、豊橋技術科学大学の後藤太一 助教、島田馨 博士前期課程生、中村雄一 准教授、内田裕久 教授、井上光輝 教授らが共同で行ったものです。また、実験に用いた試料は、信越化学工業株式会社との共同研究のもと作製されました。

電解液の構造が電池の性能を支配する

カルシウムイオン電池の実現に向けて

村田　芳明

豊橋技術科学大学電気・電子情報工学系の研究チームは、カルシウムイオン電池の正極材料の一つである酸化バナジウムの性能が、電解液に水を添加することで向上することを明らかにしました。電解液に含まれる水は、様々な悪影響を及ぼすことが知られていますが、従来非常に低速だったカルシウムイオン電池の反応が高速化される現象が見出されました。今回の研究結果から、この現象は、電解液の構造の変化によって引き起こされていることが明らかとなりました。今後、カルシウムイオン電池実現のための電解液開発に向けて、重要な指標を与えると考えられます。

二次電池は、再生可能エネルギーの利用普及や、電気自動車の普及を支える重要な技術として、更なる性能の向上が必要です。性能の良い二次電池として、リチウムイオン電池が既に広く普及しています。その一方で、近年発火事故の報告は絶えず、二次電池の安全性は社会問題化しています。また、これからの社会では電池の需要は電気自動車の普及と共に爆発的に増加すると予想され、これによって生じるリチウムの需要増加は、資源枯渇リスクや価格高騰の観点で考慮すべき問題です。

カルシウムイオン電池は、リチウムを用いない次世代二次電池の一つです。カルシウムは次世代二次電池の中でも特に、リチウムイオン電池に匹敵する電池電圧を実現可能であり、リチウムイオン電池と比較して安全性が高く、資源量も豊富で、低コストであることから注目を集めています。しかしながら、カルシウムイオン電池は未だ多くの問題を抱えています。その一つが、リチウムイオンと比較してカルシウムイオンの動きが非常に低速なことです。

研究では、電解液に水を添加することで、この遅い動きを改善することを報告しました。実験結果の図から、放電・充電時に発生する過電圧が、水添加によって大きく減少し、反応がスムーズに進行していることが分かります。様々な検討の結果、この現象が電解液の構造が、水の添加によって大きく変化していることが原因となって引き起こされていることが明らかとなりました。

「電解液は、プラスイオン（カルシウムイオン）、マイナスイオン、溶媒分子で構成されており、水を添加した際には、カルシウムイオンの周りの状態が大きく変化します。具体的には、カルシウムイオン電池の性能を向上させるには、電解液の中でカルシウムイオンにマイナスイオンが付いておらず、さらには剥がれやすい溶媒分子が付いていることが好ましいです。カルシウムイオン電池を実現するためには、水を含まずにこれらの特徴を有する電解液を発見することが必要ですが、これらの現象を発見できたことはこれからの電解液開発にも必ず役立つはずです。」と筆頭著者である博士後期課程の村田芳明は説明します。

今回の成果は、新しい電解液の検討中に副次的に得られた成果です。電解液の開発の際には、電解液を十分に脱水する必要があります。脱水方法が難しく、脱水が不十分な状態の電解液を試験した際に、電池の特性が向上したのがこの研究の始まりです。水を添加した際に電池の性能が向上するという現象は、マグネシウムイオン電池などでは報告されていましたが、未だその機構が正確には解明されていません。カルシウムイオン電池でも同様の現象が起こった、という驚きと共に、この現象が発生する機構を解明すれば、これからの電解液開発に役立つと考えました。

研究チームは、今回発見できたカルシウムイオン電池の性能を向上させる電解液構造をもとに新たな電解液を開発・評価したいと考えています。また、我々の研究だけではなく、ここ数年でカルシウムイオン電池の研究例は急速に増加しつつあります。最終的には、リチウムイオン電池に匹敵、あるいはリチウムイオン電池を上回る性能を持ったカルシウムイオン電池の開発を行っていきたいと考えています。

Pick Up

TEDxToyohashiUT - The first TEDx event held in Toyohashi University of Technology

TEDx is a program of local, self-organized events that bring people together in the spirit of hearing ideas worth spreading, in other words to share a TED-like experience.

TEDx ToyohashiUT (Toyohashi University of Technology) executive committee was voluntarily established in early 2018 by an enthusiastic group of TUT students who had been impressed by TED Talks.

The goal of hosting TEDx ToyohashiUT is to stimulate fresh thinking at TUT which, allied with our technological knowhow will help us to develop novel and unique ideas. We will share these ideas with the world, while always retaining our curiosity to learn more.

“SURF THE FUTURE” - Ride the wave of the times, and spread your ideas as wide as the ocean

Under this theme, the first TEDxToyohashiUT was held on March 17th 2019, and several guest speakers were invited to talk. 120 audience participated (includes partners, staff and other speakers)

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Toyohashi University of Technology

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