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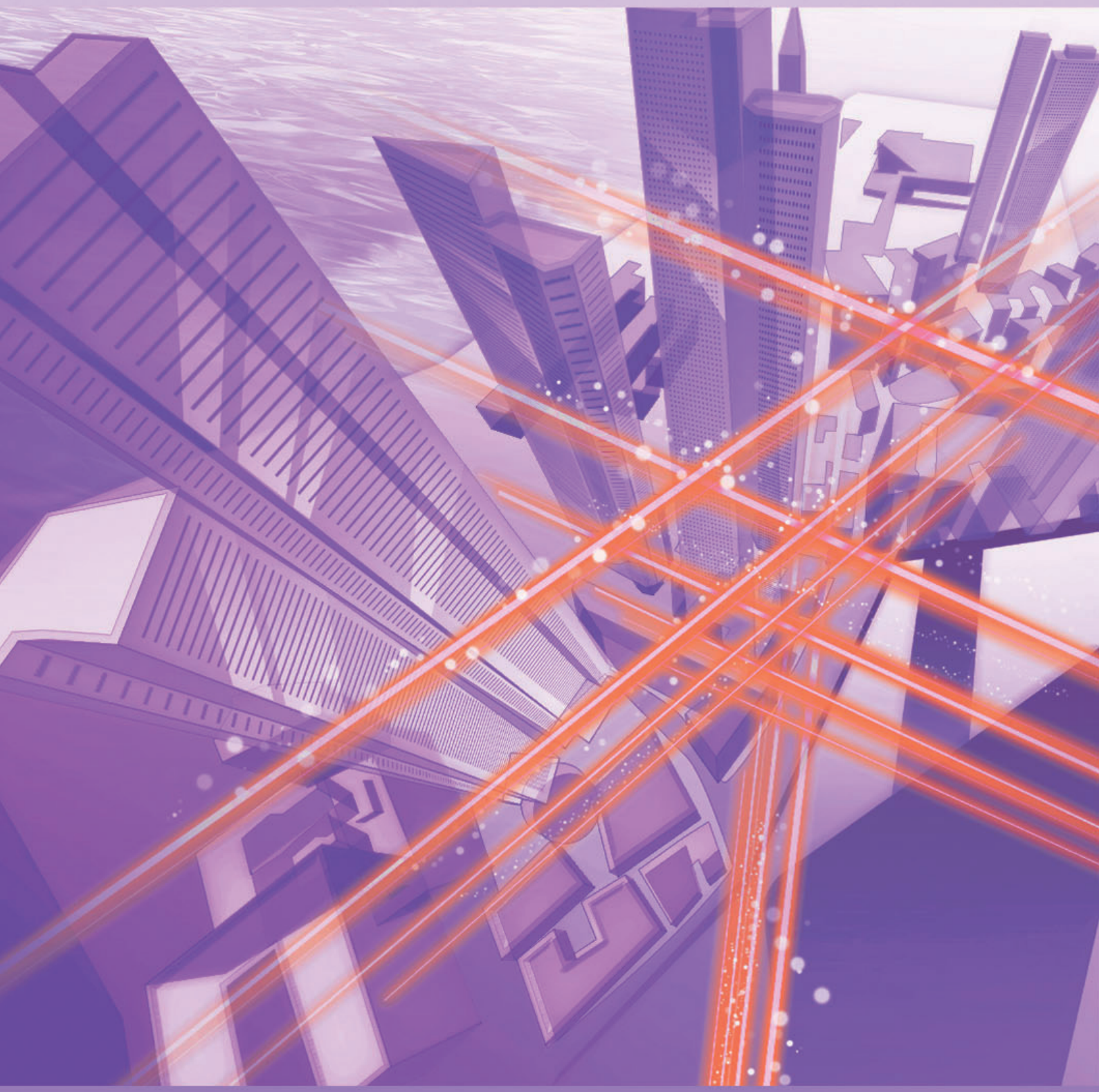

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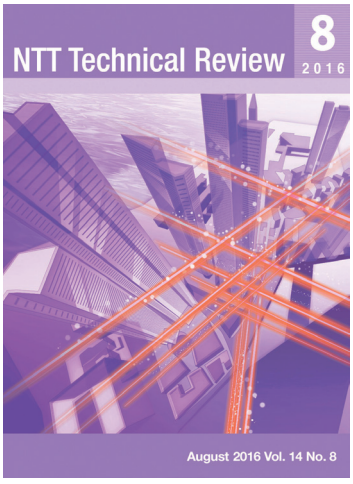
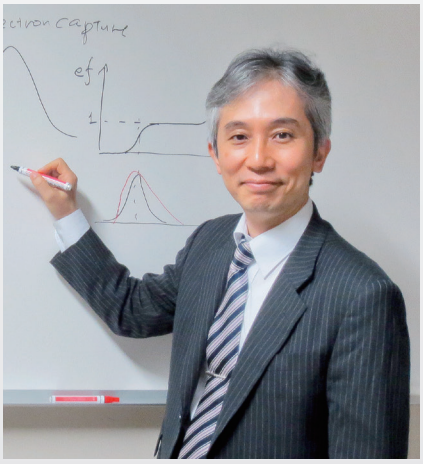


Research and Development that Will Be Valued 100 Years from Now—Making Dreams a Reality with Single-electron Devices Manipulating Individual Electrons



Akira Fujiwara
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Overview

Semiconductor technology—the backbone of information and communication technology—has made amazing progress over the years, and more recently, attention has come to focus on the ultimate-level control of single electrons and single atoms using nanofabrication and crystal-growth techniques. What kind of breakthroughs can we expect from NTT's research on ultimate electronics? We asked Dr. Akira Fujiwara, Senior Distinguished Researcher at NTT Basic Research Laboratories, to update us on recent research achievements and to tell us about his life as a researcher.

Keywords: semiconductor, single-electron device, current standard

"Ultimate electronics" based on new principles and concepts

—Dr. Fujiwara, please tell us about your current research activities.

The computers, smartphones, and other information terminals and devices that surround us today all embed a countless number of current switches to process large amounts of information at high speed. Semiconductor technology provides the backbone for this processing. "Semiconductor" is the name given to a material that exhibits properties halfway between a metal (good conductor) and an insulator. The transistors used in integrated circuits (ICs) consist of semiconductor material, and controlling the current flowing through the ICs enables various types of information processing to be done.

Up to now, the research in this area has focused on a means of downsizing IC chips and increasing the integration density as much as possible. It has so far become possible to integrate more than 100 million transistors interconnected by massive amounts of wiring on a 1-cm-square chip.

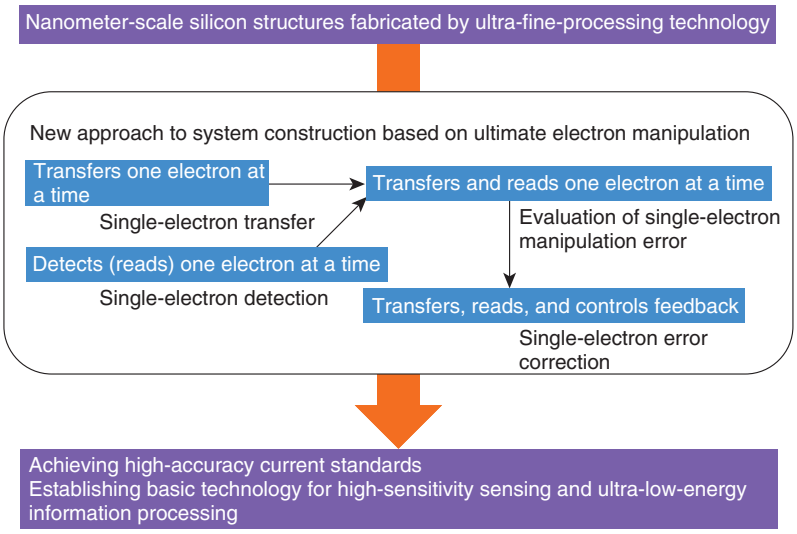

Fig. 1. Ultimate electronics.

However, the present mechanism for charging such wiring requires the flow of more than 10,000 electrons per one bit of information. At this rate, simply increasing the integration density will drastically increase power consumption. This is a serious issue in terms of the environment and energy-related costs. With this in mind, we are researching single-electron devices that can manipulate individual electrons with the aim of achieving devices and circuits that operate on new principles and concepts. If this can be achieved, we foresee the creation of a form of electronics having ultimate performance (in accuracy and sensitivity) and low-power characteristics that are different from the functions and performance of today's simple electron switches (**Fig. 1**).

—This is certainly the seed of new technology arising from unconventional ideas. In what kind of research and in what fields would this technology be useful?

The basic functions of transistors that make up an IC are often compared to the holding back and releasing of the flow of water. This analogy, however, only holds for bulk semiconductors of a sufficiently large size.

In contrast, the field of research that we are currently pursuing is low-dimensional semiconductors that trap electrons in a small space. This concerns technology that confines electrons in nanometer-scale spaces by forming a laminated structure of semiconductors and insulators and contracting its dimensions using ultra-fine-processing technology. In such low-dimensional semiconductors, quantum-mechanical wave properties intrinsic to electrons and repulsive forces between electrons are particularly prominent. Here, the structure that we are dealing with is called a quantum dot, which is considered to be zero-dimensional. Within this structure, we can confine an electron in a small space and use the repulsive forces that arise between electrons to individually control electrons one by one. Such an electron-confining space is often called a single-electron island (**Fig. 2**). Electrically controlling the movement of electrons into and out of this single-electron island enables high-speed and high-accuracy transfer of electrons. In addition, preparing a high-sensitivity charge detection device near the island enables the detection of transferred electrons one electron at a time.

A hot topic of late is a "current standard" for accurately measuring electrical current using silicon single-electron devices that can precisely manipulate individual electrons (**Fig. 3**). A resistance standard using semiconductor devices and a voltage standard using superconducting devices are already in practical use, but if a current standard using a single-electron device can be achieved, it should be possible to construct a more solid electrical standards and units system.

Research on low-dimensional semiconductors has been going on for some time, and various devices have been studied. This is because it's an attractive

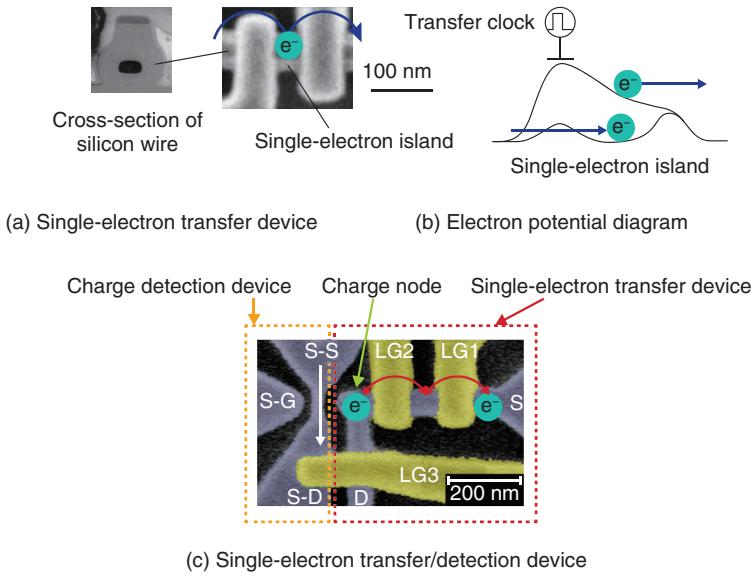

Fig. 2. Single-electron transfer and detection using silicon transistors.

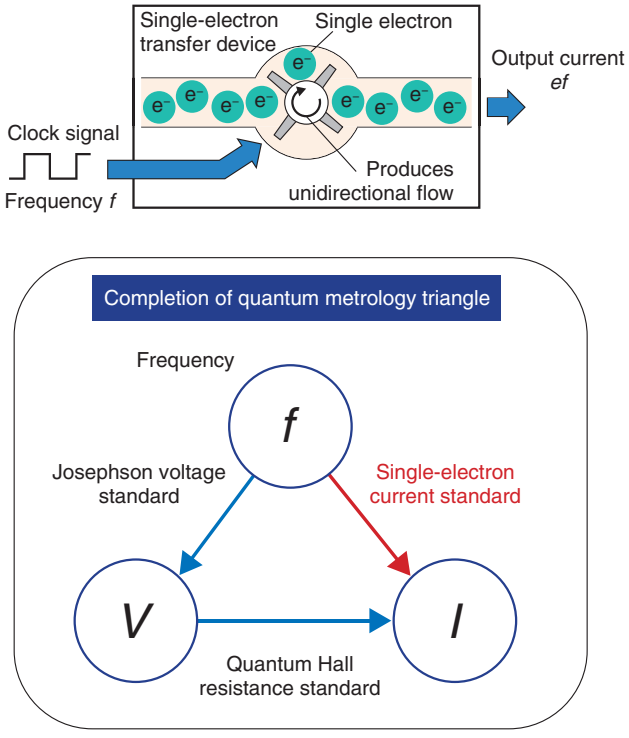

Fig. 3. Application of single-electron current standard.

research theme that has much potential not only in the realm of fundamental physics but also in the field of engineering applications.

We began our research on single-electron manipulation and transfer devices around the year 2000, and in March 2001, we published our research results on the

first silicon-based device for manipulating elementary charge in *Nature*, the distinguished British scientific journal [1]. Later, in research focusing on high-speed operation of this device, we succeeded in achieving single-electron transfer by a gigahertz clock in 2008 [2]. Next, through assistance received from the Funding Program for Next Generation World-Leading Researchers (NEXT Program) of the Cabinet Office of the Japanese government, we conducted research on silicon low-power nanodevices based on the control of single or a few electrons over a three-year period starting in 2011. In this research, we developed a different approach to using an artificially fabricated single-electron island. That is, we proposed and successfully demonstrated high-speed single-electron transfer using a localized state within a semiconductor crystal to trap an electron in an even smaller space. We published the results of this research in *Nature Communications* in 2014 [3]. In more recent research, we have been quantitatively evaluating the accuracy of single-electron transfers and making sound progress while setting new world records in this field [4, 5].

From a "Why not?" attitude at first, to a totally committed love of research

—Why did you choose physics as your research theme? Have you made steady progress as a researcher?

It all started during my studies in high school and college; physics struck me as something "very beautiful." But I also enjoyed studies related to nature and the environment, so there was a period in which I was in a quandary over which to choose as a major: physics or the environment. In the end, knowing that I was someone who liked to probe deeply into matters, physics seemed like a good fit, so that's what I chose. However, I can't say that this decision was a firm reflection of my career objectives. At the time, it was more like "Why not?"

I think that people who can say "This is my life's calling!" from the start are extremely rare. For this reason, I believe that it's best to first get involved in something that you are somewhat skilled in or that you feel is worthwhile or rewarding from a social perspective. Then, by moving forward even without a clear understanding of your objectives, your calling in life should one day come into view. Looking back to the time when I entered NTT, I remember how motivated I felt as a corporate researcher on a clear career path. Today, I still have fond memories of the emotion I felt in my second year at the company, when I worked on the fabrication of transistors and actually got them to work under the instruction of my superiors and senior colleagues. In Japanese, the Chinese characters for the word "device" include the character for "child," and the emotion that I felt on creating a device was much like the emotion one might feel on the birth of one's child. This feeling motivated me to advance to the next step in my research career.

Later on, I shifted to what is now my current line of research—the manipulation of single electrons. My research activities have not necessarily been smooth and steady, but one reason why I have been able to persevere in my research is that I have been blessed with great superiors and colleagues, and a great family too; there has always been someone to consult with whenever I hit an impasse in my work.

Starting in 2004, I also spent two years in charge of recruiting staff at NTT laboratories, and because I could not do any research during that time, I became quite frustrated. However, this period proved to be a great learning experience for me on what drives people and an organization. What may appear to be a negative environment at first glance can be turned into a positive environment with the right mindset.

—Where do good ideas come from in research?

If there is anything that I feel to be true in my research activities up to now is that discoveries lie in laboratory experiments. I really don't feel much insight from desktop thinking and contemplation. In the laboratory, however, I start by acquiring data, which may generate a response from me such as "Say, something is strange here!" Then, by probing deeper here and there, I can obtain many useful results. In fact, results that are different from those expected are food for an inquiring mind. This, in short, is my research style.

It's exactly at these key moments that I am particularly focused rather than in regular, everyday research. At such times, I find myself deep in thought even on the train or in the middle of a meal. When I was younger, staying up all night to work on a problem was a matter of course. I remember sleeping only six hours over a three-day period when writing my doctoral thesis.

In regards to the paper we published in *Nature* in 2001, what supported our achievement in manipulating single electrons was our detection method for

verifying whether an individual electron was actually being manipulated. This detection method was unprecedented and highly creative, and it enabled us to obtain and analyze experimental results that were not expected on the basis of previous experiments. It took about three or four years from the discovery of this detection method to the manipulation of single electrons, but I was totally absorbed in everyday experiments, and I enjoyed the entire process.

Digging deeply into the cause of observed phenomena leads to the discovery of new research themes. And the criterion for assessing such a discovery is insight based on hard physics, so logical thinking is very important here.

Brilliant researchers look for brilliant partners

—What is important for producing good results as an active researcher?

Starting in 2003, I spent a year as a researcher at the National Institute of Standards and Technology in the United States. At that time, I was already researching high-speed, high-accuracy single-electron transfer, and I thought that this institution would be a good place to move my research forward. I faced a variety of challenges there, such as assembling experimental equipment, devising measurement techniques, and coming up with good ideas. These challenges tested my competence as a researcher in an American style that evaluates not only one's position but one's actual abilities as well. It took several months for my abilities to be recognized, but once that happened, my research activities began to change in a big way. As my ideas came to be accepted, I began to win the confidence of those around me and to engage in lively discussions.

An internationally active researcher places great importance on whom to hold discussions with. In other words, such a researcher wants to be stimulated by a brilliant partner and is always on the lookout for such a person to team up with. A researcher will not grow by withdrawing into a shell. It is imperative to seek out situations enabling contact and stimulating discussions with excellent researchers. Researchers need to challenge themselves with an open frame of mind.

It is also important for a researcher to have a personality that is conducive to direct interaction in a face-to-face manner. At present, we are involved in a joint research project with the National Physical Laboratory of the United Kingdom, and I believe that making visits is one important way of earning the trust of other team members. This is my research style; when it comes to gaining the confidence of others, personality matters more than research results. Deciding whom I would like to establish a rapport with is very important. Of course, scientific credentials are necessary in a partner, but what counts in the end is whether I think that I would like to team up with that person over the long term.

Moreover, to achieve breakthroughs as a researcher, it is important to maintain an interest in other researchers and research studies and to keep the channels of communication open. It is also important to ask insightful questions at international conferences and other gatherings to keep others interested in you and your activities. Even if you are unable to ask questions at a presentation for whatever reason, you can always make your voice known later in one way or another. In addition, simply chatting about common interests or hobbies is a great way of promoting communication. Such an approach can open your heart to that country's culture and to human-interest conversations outside of research.

—Can you say a few words to our young researchers?

Please value intellectual curiosity and teamwork. Research results cannot be achieved by one person. In short, amassing wisdom and working hard together are essential components. You cannot achieve effective teamwork with a reserved attitude. It goes without saying that the technologies of *monozukuri* (manufacturing) are important, so I would like to see all of you make an active effort in accumulating and sharing know-how within your teams. There are three criteria for doing significant work in the world of basic research. The first is "Do work that can be recognized by the world." The second is "Do work that can be evaluated and cited by other researchers in the same field." And the third is "Do work that includes content that has the potential of being praised in the future even if it appears at first glance to be out-of-fashion research." In other words, are you doing work that includes useful data or information that later researchers will have the urge to reference?

To fulfill these criteria, keep asking yourself, "Am I falling victim to the Galapagos syndrome?" "Am I becoming a frog in the well?" Take a broad look at your research field and its history and do some objective self-analysis. Find out exactly where your research lies in the lineage or historical flow of that research. Contributing to the progress of science and

technology means leaving one's footprint on a long list of results achieved to date by other researchers. Pay homage to past research and continue to ask yourself "Am I really doing something meaningful?"

—Dr. Fujiwara, what challenges will you take up going forward?

We expect an electric current standard using single-electron transfer to be used as a means of directly establishing the ampere, the unit of current, which is scheduled to be redefined as part of a new International System of Units after 2018. The aim is to complete the quantum metrology triangle as a milestone toward achieving applications of this current standard. This is an experiment that aims to check the relationships among the electric current standard using single-electron transfer, the Josephson voltage standard, and the quantum Hall resistance standard. I mention here that discoverers of the Josephson effect and the quantum Hall effect each received a Nobel Prize in Physics. Our work, meanwhile, is an engineering challenge that seeks to determine the extent to which an electron can be accurately controlled. We are undertaking this work as an exit path for ultimate electronics. At present, our joint research with a team at the National Physical Laboratory of the United Kingdom is moving forward, and research projects centered particularly about Europe are progressing. Over the long term, I hope to connect this research with the further pursuit of ultimate electronics, the application of sensors, and the achievement of low-power information processing systems.

In addition, while pursuing my research goals, I would like to convey my thoughts and opinions to my younger colleagues. This is not to mean that I want to push my ideas on others. Rather, I would hope to stimulate their intellectual curiosity and assist them in any way that I can.

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■ **Interviewee profile**

Akira Fujiwara

Senior Distinguished Researcher, Senior Manager of Physical Science Laboratory and Group Leader of Nanodevices Research Group, NTT Basic Research Laboratories.

He received his B.S., M.S., and Ph.D. in applied physics from the University of Tokyo in 1989, 1991, and 1994. He joined NTT in 1994 and has been engaged in research on silicon nanostructures and their application to nanodevices and single-electron devices. He was a guest researcher at the National Institute of Standards and Technology, Gaithersburg, MD, USA, in 2003–2004. He was a director of the Japanese Society of Applied Physics (JSAP) in 2010–2011 and a visiting professor at Hokkaido University in 2013. He received the International Conference on Solid State Devices and Materials (SSDM) Young Researcher Award in 1998, the SSDM Paper Award in 1999, and JJAP (Japanese Journal of Applied Physics) Paper Awards in 2003, 2006, and 2013. He was awarded the Young Scientist Award from the Ministry of Education, Culture, Sports, Science and Technology in 2006. He was supported by the Funding Program for Next Generation World-Leading Researchers (NEXT Program), Japan Society for the Promotion of Science, during 2011–2014. He is a member of JSAP and a senior member of IEEE (Institute of Electrical and Electronics Engineers).

Overview of Bio-soft Material Research at NTT

Hiroshi Nakashima

Abstract

At NTT Basic Research Laboratories, we are aiming to create a novel nanobiointerface that allows direct access to the human body and brain by utilizing the functions and structures of biomolecules and soft materials. We are also attempting to understand the fundamental principles of bioinformation processing by managing the combination of nanotechnology and biotechnology. The Feature Articles in this issue introduce our bio-soft material research in relation to the fabrication of nanobiodevices, which constitute one of the components of a future artificial synapse. We also present a highly sensitive and long-term stable biosensing system.

Keywords: bio-soft material, nanobiointerface, bioelectrode

1. Introduction

Soft and flexible materials now play an important role in supporting modern society in the same way as hard materials such as metals, semiconductors, and ceramics. Soft materials include rubber, plastic, gel, colloid, and liquid crystal, and biological tissue also consists of large and complex soft materials. In the 20th century, hard materials played major roles in the evolution of various industries.

In the 21st century, the manufacture of soft materials including their biological applications has been greatly expanded. The size, shape, and function of soft materials are easily controllable over a wide range. These materials provide us with the potential to discover unknown physical and chemical properties through the synthesis of novel soft and flexible materials or by precisely controlling their composition and structure on a nanometer-scale. In addition, these materials are not simply an interesting target for basic research; in fact, a wide range of industrial applications have also been developed.

In the field of information technology and electronics, for example, plastic optical fiber and organic electro-luminescent (EL) material have been put to practical use. A tough and flexible polymer material is used as a surface coating material for mobile phones, and its surface is both highly waterproof and scratch-resistant.

In recent years, it has become increasingly important to ensure that the production, use, and recycling of materials have as little effect on the environment as possible. Therefore, organic and soft materials that are people- and environment-friendly have been widely used.

Another issue in the current aging society in terms of the development of medical implant materials and medical and healthcare devices is that it is important that we construct a biointerface that enables direct contact with biological systems. A sophisticated biointerface design is thus required that employs soft material with a high affinity to soft biological tissue, without causing it any damage.

2. Biointerface application

If we are to produce a functional biointerface that is compatible with biological systems, it is essential that we understand fundamental biostructures and design the biointerface by mimicking these biostructures. Proteins, nucleic acids, polysaccharides, and the lipid molecules of a cell membrane are often used to produce biointerfaces. These molecules have a specific feature, namely that the shape and characteristics

vary greatly depending on the external environment and external stimulus. Deoxyribonucleic acid (DNA) or protein chips, various biosensors, and a drug delivery system have been developed using these molecules.

In recent years, high-performance biointerfaces have been reported that can be applied to advanced medical treatments. For example, soft and highly biocompatible silicone enables us to produce an implant material that can be flexibly bent and that does not result in inflammation or rejection by the body. Damage to the spinal cord caused by an injury or an accident can result in paralysis, and to restore bodily functions, it is necessary to repair the damage site using artificial biomaterials. Thus far, it has been difficult to repair such damage. However, a research group has reported exciting results in which a paralyzed laboratory animal began to move after silicon material was embedded in the damaged part and electrical stimulation provided.

Another research group has reported a functional film material that can adhere to the surface of a beating heart for a long time without falling off and without the need for sutures or adhesive. A metal or semiconductor device is printed on the film, and it features various sensor functions for detecting distortion, pH, and temperature; it also includes an actuator function that can provide electricity, heat, and a light stimulus. There is the potential to add further utilities to the functional film, and thus, it is expected that we will be able to enhance clinical applications in relation to the study and medical treatment of heart disease.

Biointerface research has been conducted at NTT Basic Research Laboratories since the 1980s, and the research target is to understand neural information processing in the brain and realize a similar bioprocess using artificial devices. As an example, we have cultured a nerve cell in an artificial environment and have tried using various approaches to elucidate the nerve cell function and control neural growth. There is a synapse at the terminal of a nerve cell that transmits electrical signals to the corresponding neuron. It is well known that synapses control information processing in the brain with respect to memory and learning.

The fundamental mechanism of bioelectrical signal transmission via a synapse is as follows: 1) the nerve action potential is transmitted to the synapse of a neuron; 2) the electrical signal is converted into a chemical signal (neurotransmitter), and the neurotransmitter is then released from the synapse to the outside; 3) the neurotransmitter is received via a receptor protein of the recipient cell; and finally, 4) the chemical signal is converted back to an electrical signal in the synapse of the recipient cell, and the electrical signal is then propagated in the cell. Here, the synapse that releases the neurotransmitter is called a *pre-synapse*, and the other part that includes a receptor protein is called a *post-synapse*. Information is coded by changing either the release amount or the release frequency of the neurotransmitter and modified by changing the receptor sensitivity at the synapse.

Certain phenomena and functions regarding the exchange of information at the synapse are as yet unexplained. Therefore, one of our research targets involves using nanotechnology and biotechnology to artificially develop a post-synapse structure that works as an interface with a neural signal receiver. In the future, we will attempt to fabricate an *artificial synapse* with a simple and basic structure through the fusion of our post-synapse device and an actual nerve cell extracted from a biological pre-synapse (**Fig. 1**). Furthermore, we will explore the principles of bioinformation processing and clarify the information signaling mechanism in the brain. We also hope to fabricate a distinctive and valuable nanobiodevice that can work as a substitute for damaged neurotransmission elements.

3. Bio-soft material research at NTT

In our research group, we are attempting to access fundamental bioinformation processing by utilizing a nanobiointerface or nanobiodevices, which we have fabricated by combining nanotechnology and biotechnology. We are also undertaking the research and development of novel and highly sensitive biosensors and long-term biomonitoring systems (**Fig. 2**). Here, we outline the research topics of each group.

The article “Fabrication of Nanobiodevices that Utilize the Function of Membrane Proteins” [1] explains our effort to focus on a cell membrane and a membrane protein as an interface for configuring nanobiodevices. The artificially created cell membranes (artificial lipid membranes) are deposited on a silicon substrate containing a nano- or microscale hole array, and the composed structure constitutes the basic and pseudo-skeletal structure of an artificial cell. In addition, the membrane proteins, which work as a biosignal receiver, are reconstituted in the artificial lipid membrane, and this provides a platform for measuring a single protein function. The platform structure works as a post-synapse in the designed

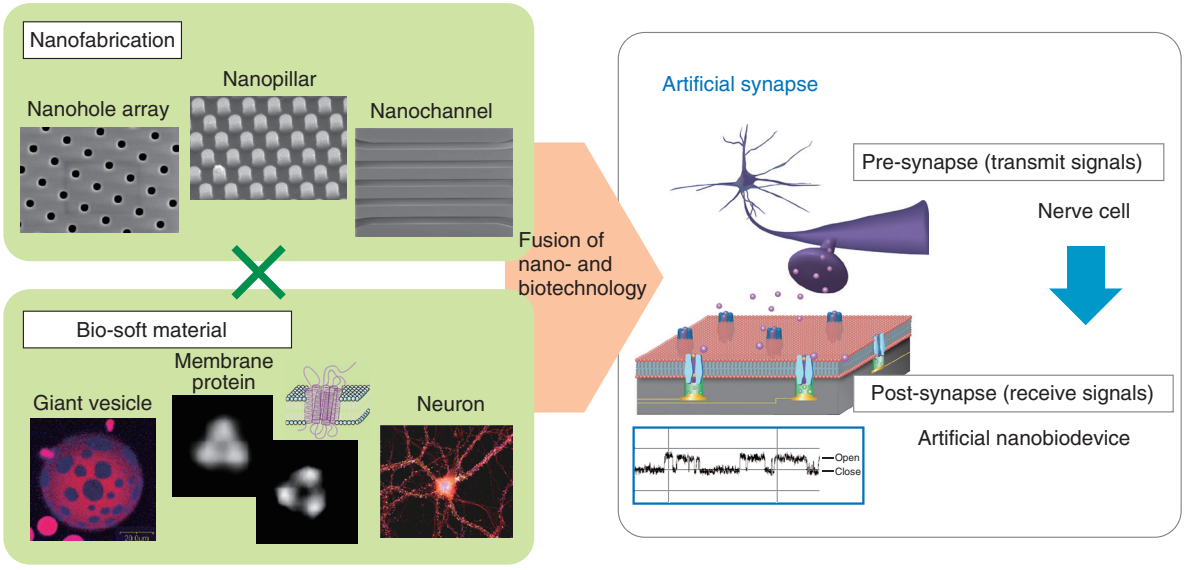

Fig. 1. Nano-bio fusion technology: artificial synapse.

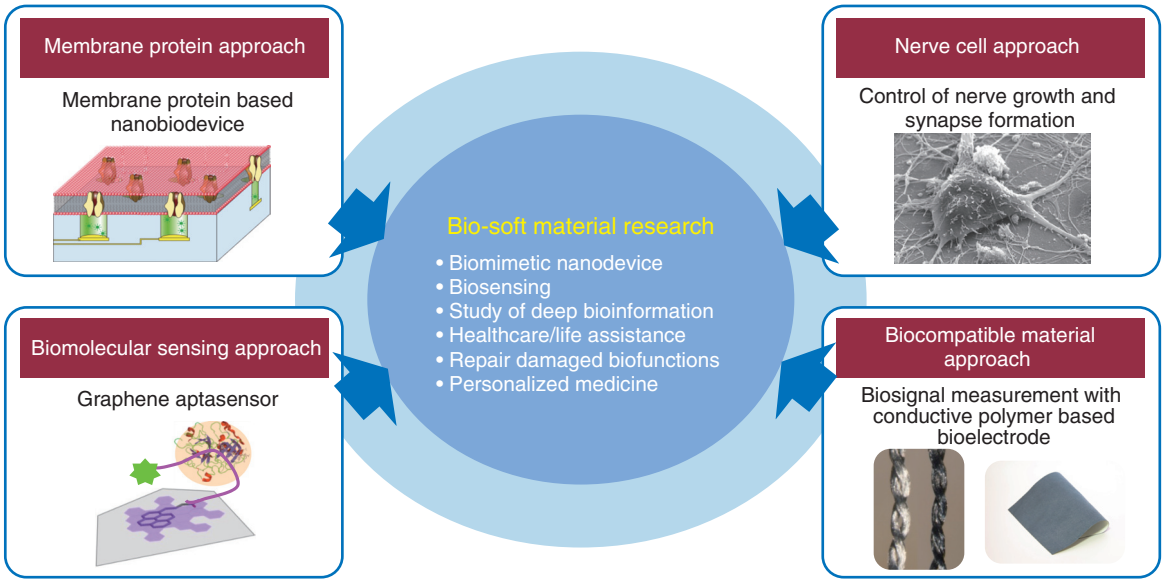

Fig. 2. Bio-soft material research at NTT.

artificial synapse.

The artificial lipid membrane is a soft molecular film with high fluidity, and its dynamic characteristics are an interesting research subject. In the article "Pattern Formation of Supported Lipid Bilayer for Molecular Manipulation" [2], we present an original technique for forming an artificial lipid membrane on a nanostructured surface in a precisely controlled manner. Furthermore, we describe how the lipid membrane is used as a dynamic molecule carrier.

We use nerve cells to investigate the structural control of a pre-synapse that is responsible for the signal transmission of the artificial synapse. The article entitled "Neuronal Growth on Artificial Structures with Different Materials" [3] describes our study of the interfacial structure of nerve cells cultured on

various substrates for which we use a technique that combines a focused ion beam with a scanning electron microscope. The topic also includes direction control in the process of nerve cell growth on a substrate with a nanopillar structure, which leads to the patterning of the nerve cell network. Moreover, in "Time-lapse Imaging of Neural Morphological Changes Relating to Cellular Functions" [4], we describe how we have used a scanning ion conductance microscope for the time-lapse imaging of the change in nerve cell structure in a physiological solution. Here, we have focused on an apoptotic process, which plays an important role in forming the most appropriate and effective neural network structure. We have clarified the correlation between morphological cell changes and the biological function by employing live imaging of the apoptotic process.

In "On-chip Graphene Biosensor" [5], we describe a novel biosensor based on a graphene platform where an aptamer molecule (single-stranded DNA), which binds with a specific protein, is bound to the graphene surface. We have succeeded in selectively detecting very small amounts (below 1 μL) of proteins such as cancer or blood coagulation markers by combining a microchannel device with this biosensor. We are currently undertaking proof-of-concept experiments on the sensor, but our aim is to fabricate an on-chip biosensor that can be universally used for the qualitative and quantitative analysis of very small amounts of biomolecules.

The article "Conductive Composite Material for Vital Data Measurement" [6] introduces the fabrication of a flexible and non-cytotoxic bioelectrode made of a composite consisting of silk protein and a biocompatible conductive polymer. We have used this bioelectrode to measure the electrical properties of single cells, and we have also demonstrated the long-term and stable detection of biosignals acquired from the surface of the body.

4. Evolution to wearable bioelectrode

The bioelectrode, which is composed of two soft materials, was originally produced as a soft and fibrous microelectrode for recording very weak signals emitted by neurons in the brain. When a conventional rigid metal electrode is used, necrosis of the cells around the electrode occurs immediately. However, this soft bioelectrode has the great advantage of being hydrophilic and biologically friendly. Therefore, we can measure the nerve action potential of an experimental animal with little cell damage.

By expanding this knowledge and collaborating with Toray Industries Inc., we developed a conductive fabric material called "hitoe" based on the coupling of an advanced fiber material nanofiber and a conductive polymer. "hitoe" has excellent flexibility, stretchability, breathability, and biocompatibility, and it can accurately detect biological signals such as heart rate, and provide electrocardiograms (ECG) and electromyograms (EMG) [7]. A single nanofiber is approximately 700 nm in diameter. Thanks to the fine fiber structure, adhesion with the skin is greatly improved. In addition, the high conductivity and durability of "hitoe" both help to achieve stable and long-term biological signal monitoring. Moreover, by combining "hitoe" with an undershirt, we have successfully developed a bioelectrode system that can measure the heart rate and ECG simply by having the subject wear the undershirt and by monitoring the results on a smartphone. Thanks to our collaborative work with GOLDWIN INC. and NTT DOCOMO, the undershirt has been marketed for sports applications (**Fig. 3**).

"hitoe" is expected to be used with a medical quality electrode for help in the early detection and treatment of heart disease. This is because "hitoe" can monitor biological information comfortably and conveniently during normal daily life without placing a burden on the wearer. Our goal is to couple "hitoe" with various wearable devices and information and communication technology, and we are therefore conducting research that will allow us to utilize bioelectrodes in a wide range of fields including medicine, healthcare, worker safety, sports, and entertainment.

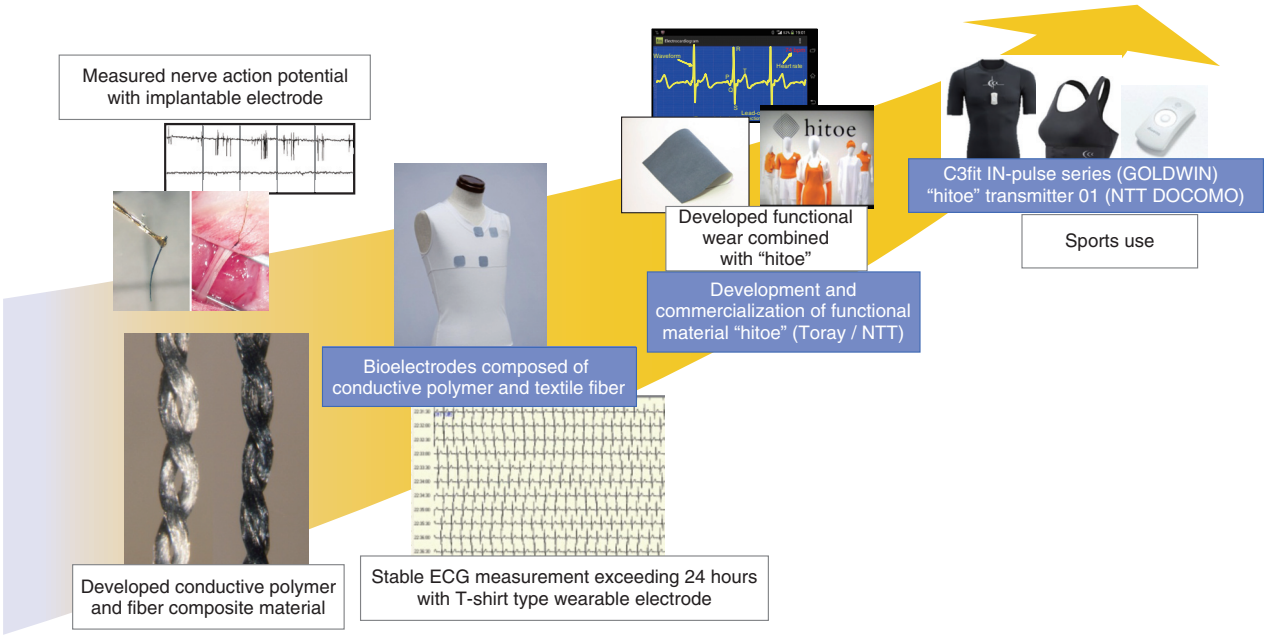

Fig. 3. Evolution of wearable-type bioelectrode.

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Fabrication of Nanobiodevices that Utilize the Function of Membrane Proteins

Yoshiaki Kashimura, Azusa Oshima, and Koji Sumitomo

Abstract

Membrane proteins play vital roles in a wide variety of functions in living organisms. The development of nanobiodevices that fuse semiconductor nanotechnology and membrane proteins makes it possible to understand various biological processes as well as engineering applications. In this article, we introduce the fabrication of nanobiodevices that are functionalized by membrane proteins and designed to mimic the synaptic signal transmission mechanism in the nervous system.

Keywords: lipid bilayer, membrane protein, nanobiodevice

1. Introduction

Membrane proteins have attracted interest as a post-genome target since the mapping of the human genome was completed in 2003. Membrane proteins that are located in cell membranes perform a variety of functions vital to the cell membrane. There are several types of membrane proteins. Most of them are transmembrane proteins that span the membrane and in most cases work as gateways that permit the transport of specific chemicals across the membrane. Transmembrane proteins can be classified into three types based on their transport mechanisms: channels that form transmembrane passive pores and transport molecules and ions; transporters that require conformational changes when transporting substances; and pumps that move ions against a concentration gradient by consuming energy sources such as ATP (adenosine triphosphate).

Among channel proteins, ion channels that allow ions to flow into cells play an important role in the signal transduction in living organisms. The nervous system responsible for informational signal transmission consists of a network of neurons. A synapse is a connection that is formed at a narrow gap between neurons. At this connection, an electrical signal is converted into a chemical signal such as the release of a chemical called a neurotransmitter. The neurotransmitter is released from a presynaptic neuron and binds to ion channels called receptors located in a postsynaptic neuron. This causes the ion channels to form passive pores leading to an influx of ions into the postsynaptic neuron, and consequently induces a synaptic potential that spans other neurons. Thus, ion channels play pivotal roles in the signal transduction in living organisms. Therefore, a loss or a gain of a channel function can cause brain diseases such as depression, addiction, dementia, and anxiety disorders.

As described above, membrane proteins including ion channels are biomolecules associated with many physiological and behavioral functions such as drug response, immune response, and the outbreak of a disease. Membrane protein research will become increasingly important since it is known that more than 60% of commercially available pharmaceuticals are targeted at membrane proteins. The transport rate through an ion channel is typically 10^6 ions per second or greater. This is interesting from the viewpoint of technological applications because the channel gating is controlled solely by the attachment of a molecule to a channel. The fusion of semiconductor nanotechnology and membrane proteins should lead to further progress on diagnostic tools, the medical

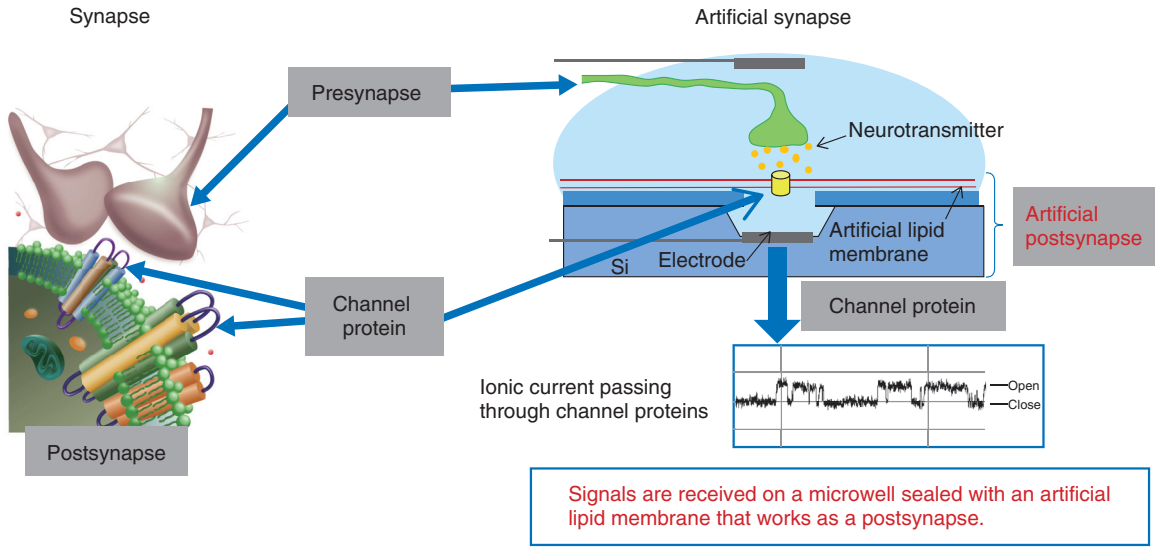


Fig. 1. Nanobiodevice that mimics the neuronal transmission mechanism.

treatment of diseases, and environmental applications in addition to basic research in nanobioscience.

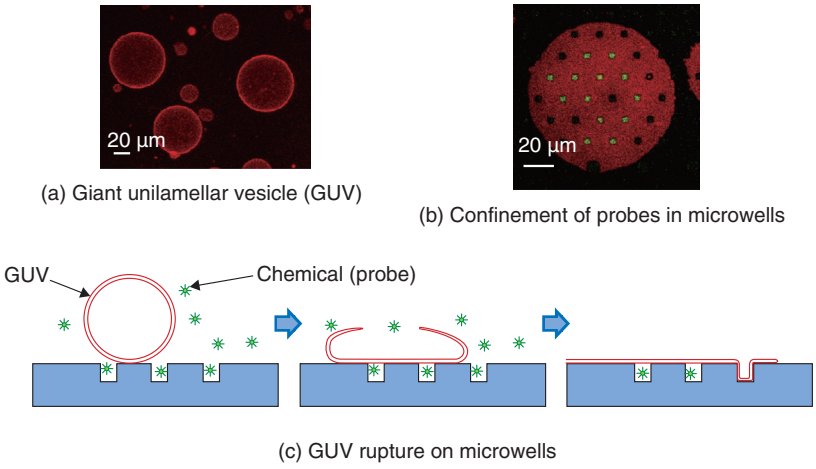
Despite its importance, research in this field remains a challenge. One reason is that membrane proteins are very difficult to handle compared with DNA (deoxyribonucleic acids), which has already been put to practical use. For example, membrane proteins denature on a semiconductor substrate or under atmospheric conditions. In this article, we introduce our efforts to overcome these hurdles and to create nanobiodevices that are functionalized by membrane proteins.

2. Construction of artificial cells

A schematic diagram of a nanobiodevice that utilizes membrane protein functions is shown in **Fig. 1**. We have designed a new type of nanobiodevice called an artificial synapse that mimics the structure of a postsynaptic neuron, which is the signal-receiving part of the synapse. One difficulty when using membrane proteins is that they can only function within lipid membranes. If the proteins are simply disposed on a substrate, they are deformed as a result of an unfavorable protein-substrate interaction, which leads to their denaturation. Membrane proteins account for half the weight of a cell membrane. The other main membrane component is a lipid molecule, which is an amphiphilic molecule containing both a hydrophilic head group and a hydrophobic tail group. In an aqueous solution, lipid molecules arrange themselves into topologically closed structures that protect the hydrophobic part from being exposed to the surrounding aqueous solution. This results in the formation of a lipid bilayer membrane, which is a fundamental component of a cell membrane.

Membrane proteins can diffuse laterally within a lipid membrane *in vivo*. Our first goal was to reproduce a biological cell-like environment on a semiconductor substrate. A promising way to achieve this is to use microwells on a Si (silicon) substrate sealed with a lipid membrane. A sealed microwell is comparable in size to a biological cell and has a suspended lipid membrane area that works as a cell-mimetic field on the substrate. When membrane proteins are reconstituted within a suspended lipid membrane, they can diffuse within the membrane and function in the same way as those *in vivo*. Thus, individual microwells can be considered the simplest model of a biological cell.

An example method to fabricate the above-mentioned artificial cell is illustrated in **Fig. 2**. First, lipid vesicles (or liposomes), which are one stable form of a lipid membrane, were prepared by electroformation [1]. We used giant unilamellar vesicles (GUVs) with diameters in the 10–100 μm range, which should be larger than those of the microwells. We used a lithographic technique to fabricate microwells (2–4 μm in diameter and 1 μm deep) on a silicon dioxide (SiO_2) substrate [2]. The microwells were sealed with lipid membranes by rupturing the GUVs in an electrolyte solution such as calcium chloride ($CaCl_2$). We



(a) Giant unilamellar vesicle (GUV)

(b) Confinement of probes in microwells

(c) GUV rupture on microwells

Fig. 2. Fabrication of microwells sealed with a lipid membrane.

confirmed that the microwells were sealed by confining fluorescent probes in them. A fluorescent image of a lipid membrane patch labeled with red fluorescent rhodamine B, where green fluorescent calcein was confined in the microwells, is shown in Fig. 2(b). The fluorescence was clearly observed from the calcein confined in the microwells. This result shows that the lipid membrane successfully seals the microwells. Depending on our target functions, other chemicals can be confined in the microwells using the same protocol instead of fluorescent probes.

3. Biodevice functionalized by membrane proteins

A functional analysis of ion channel activity requires first reconstituting the ion channels within a lipid membrane. To demonstrate this, we began by using α-hemolysin, which is widely studied and is known as a bacterial exotoxin with a membrane-damaging function [3]. We inserted α-hemolysin monomers into the lipid membrane and then oligomerized it to form a heptameric transmembrane pore through which ions or small molecules pass. The function of α-hemolysins is easily identified by their ability to pass ions through unregulated pores, thus providing a good prototype for confirming the operating principle of the device.

For this purpose, a calcium ion (Ca^{2+}) indicator (fluo-4) that emits green fluorescence in the presence of Ca^{2+} was confined in the microwells instead of calcein. Then, to analyze the Ca^{2+} transport through the ion channels, a Ca^{2+} concentration gradient between the outside and inside of the microwells was created by adding a $CaCl_2$ solution to the outer solution. When α-hemolysin was added to the outer solution, it diffused into the suspended lipid bilayer and formed ion channels. Time-lapse images of the fluorescent intensity of microwells containing fluo-4 after adding the $CaCl_2$ solution (t = 0) are shown in **Fig. 3**. The obtained images reveal that most of the microwells became bright after several minutes and their fluorescence intensity gradually increased. This result indicates that Ca^{2+} were transported from the outer solution to inside the microwells through the ion channels formed by α-hemolysin.

A fluorescence intensity analysis revealed that the detection limit for Ca^{2+} transport was estimated to be several tens of ions/s/µm^2, which is much smaller than the ion current in a standard electrophysiological measurement. This is because the small microwell volume, which is a minimum of several hundred attoliters, induces a large change in the ionic concentration even when the ion permeation is small. This demonstration enables us to mimic a local ion concentration change in the biological cells when we use more sophisticated membrane proteins.

4. Toward electrophysiological detection of ion channel activity on a device

The most widely used methods for studying ion channel functions are related to electrophysiological techniques that directly measure the ionic current through channel proteins. Among them, the patch clamp technique is the gold standard, and it can be

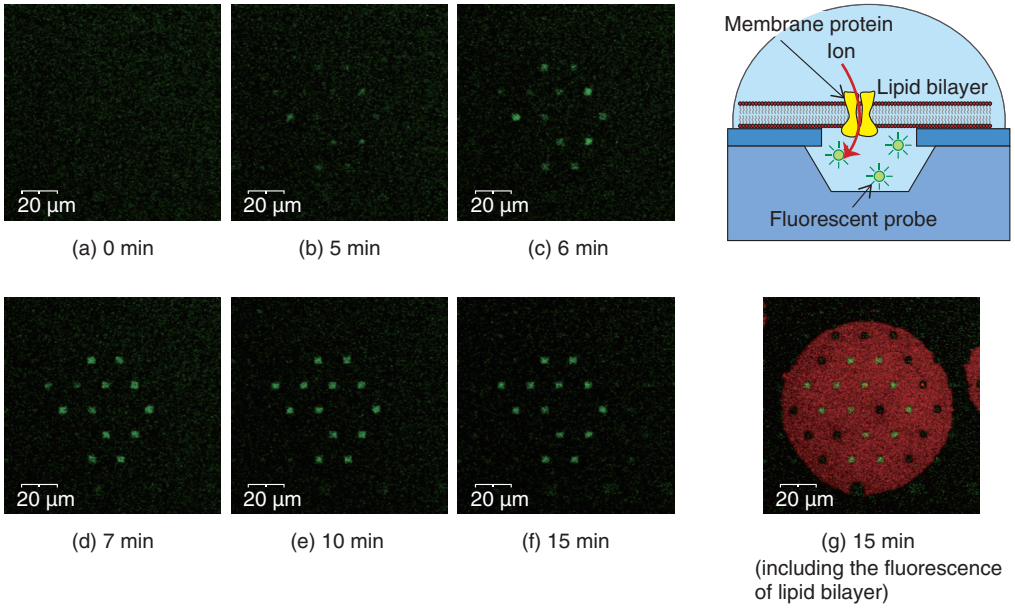


Fig. 3. Functional analysis of α-hemolysin with fluorescent microscopy.

applied to cells and tissues using a glass micropipette as a recording electrode. However, the use of an electrophysiological technique to detect an ion channel current on a semiconductor device still remains challenging. One difficulty is that the ion channel current is very low and comparable to the background noise (several pA). Although we succeeded in observing Ca^{2+} transport through ion channels with fluorescent microscopy using our proposed microwell device, when we try to achieve electrophysiological detection we are faced with the problem of ion leakage through the water layer between the lipid bilayer and the substrate, as shown in **Fig. 4** [4]. This phenomenon did not cause any serious changes in the optical measurements; however, it is not negligible in an electrophysiological measurement, which detects a very small signal.

To overcome this problem, we proposed a newly designed microwell structure that uses a self-assembled monolayer (SAM) on a gold (Au) surface to prevent ion leakage from/into the microwells, as shown in **Fig. 5** [5]. Microwells with a slightly offset Au ring were fabricated using a lithographic technique. A SAM of octadecanethiol, which has a similar structure to a lipid, was created on the Au surface. By rupturing GUVs on the structure, a lipid monolayer was formed with the hydrophobic tails of both molecules facing each other to minimize unfavorable interactions with the aqueous regions. A supported

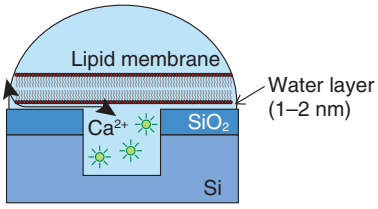


Fig. 4. Schematic illustration of microwell structure sealed by a lipid bilayer showing the passage of Ca^{2+} through the water layer.

lipid bilayer was formed in the SiO_2 regions of the surface, and a suspended lipid bilayer was formed at the microwell aperture.

The fluorescence from the rhodamine B-labeled patch of a lipid membrane suspended over the structure is shown in Fig. 5(c). The green fluorescence from the microwell indicates that fluorescent probes are successfully sealed with the lipid membrane. There is no fluorescence on the Au ring, probably owing to the energy transfer between dyes and gold. The fluorescence recovery after the photobleaching observation revealed that lateral fluidity is maintained across the Au ring. This result supports the structural geometry predicted in Fig. 5(a).

The time course of the fluorescence intensity of the Ca^{2+} indicators confined in the microwells when

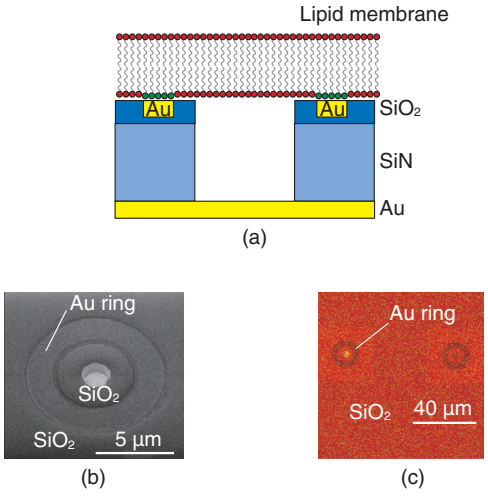


Fig. 5. (a) Schematic illustration of microwell structure. (b) SEM image of the Au ring substrate. (c) Fluorescence from the rhodamine-B labeled lipid membrane. The green fluorescent probe is confined in the microwell.

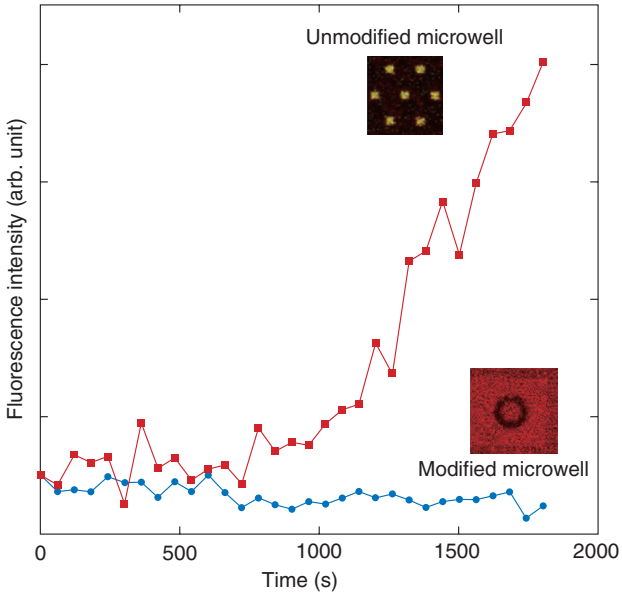


Fig. 6. Change in fluorescence intensity from fluo-4 confined microwells as a function of time.

$CaCl_2$ solution was added to the outer solution is shown in **Fig. 6**. Unmodified substrates (without a Au ring) caused a significant increase in the fluorescence intensity within 20 min. However, with a modified substrate (with a Au ring), there was no increase in fluorescence intensity during the observation time. Separating the microwells and the outer regions effectively reduced the ion diffusion through the water layer. Toward the aim of achieving the electrophysiological detection of ion channel activity, we estimated the membrane resistance by using a conventional patch-clamp amplifier. The membrane resistances for the modified microwells were one order higher than those of the unmodified microwells, leading to a reduction in background noise. The improved membrane resistance and background noise for the modified microwells resulted from the reduced ion leakage. The device structure used in this study therefore has the potential to be used as a platform for the very low signal-to-noise ratio measurement of ion channels.

In addition to the ion leakage problem, there are certain other hurdles to overcome such as the purification and alignment of membrane proteins. In our group, researchers from a variety of backgrounds including physics, chemistry, and medical engineering are working hard to overcome such hurdles in their efforts to achieve nanobiodevices.

5. Conclusion

Despite recent developments in biological information transmission, many important problems remain unsolved such as the synaptic plasticity associated with learning and the understanding of mechanisms at the neuronal circuit level. In addition, the mechanisms of neurological disorders such as Alzheimer's disease, which are caused by synapse abnormalities, have not yet been described in detail. One of our aims for our proposed nanobiodevice is to artificially replace synapses, which will allow us to access our information transmission system. By constructing a model synapse system in a controlled manner in an artificial environment, it will be possible to elucidate the mechanisms and functions in as simple a way as possible. The acquisition of information at a single protein level allows us to reveal the biological information transmission mechanism at the molecular level and, furthermore, to find ways of treating incurable diseases.

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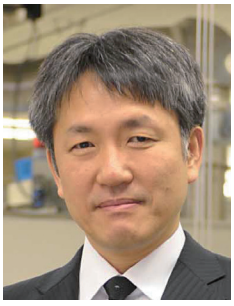

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Pattern Formation of Supported Lipid Bilayer for Molecular Manipulation

Kazuaki Furukawa

Abstract

A supported lipid bilayer (SLB) is an artificial membrane formed on a solid support. We have developed an original technique for controlling the position of an SLB using a pattern fabricated on a solid surface. In this article, I report on two new results obtained using our technique; one involves the use of an SLB microarray for protein detection and the other a molecular gate device that can control a few individual molecules within an SLB.

Keywords: lipid bilayer, self-spreading, molecule manipulation

1. Introduction

Ten years have passed since we published our first paper describing the positional control of a supported lipid bilayer (SLB) and its application to microfluidic devices [1]. Our achievements in the early stages were detailed in a previous review [2]. I will focus on new developments in this article, especially on research using an SLB for transporting and manipulating biological molecules.

Cell membranes are formed by various biological molecules. The main components of a membrane are lipids, which are molecules with both hydrophilic and hydrophobic parts. Therefore, a monolayer formed by lipid molecules has a hydrophilic surface and a hydrophobic surface. In aqueous conditions, the hydrophobic surfaces of two monolayers face each other to form a lipid bilayer, which is the basic structure of a cell membrane. Here, the lipid molecules can be obtained by extraction from natural products such as egg yolk and/or by chemical synthesis.

A schematic drawing of self-spreading is shown in **Fig. 1**. First, the lipid molecules are placed on a hydrophilic solid surface. The solid surface is immersed gently in a buffer solution such as physiological saline. The lipid molecules form an SLB at the boundary between the lipid source and the solid surface, and it spreads across the solid surface over time. This phenomenon is driven by the self-organization process exhibited by the lipid molecules. Self-spreading occurs selectively on hydrophilic surfaces. Thus, when a solid has a hydrophilic/hydrophobic pattern surface, we can grow an SLB only on the hydrophilic surface. This is a very important technique for NTT Basic Research Laboratories in terms of accelerating our research in this field [1, 3].

We observe SLBs using a fluorescence microscope. For the observations, we add a small quantity (~1%) of lipid molecules containing a fluorescent dye to the lipid source. Because the dye-conjugated lipid

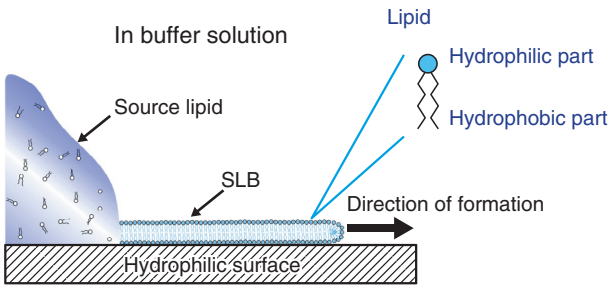
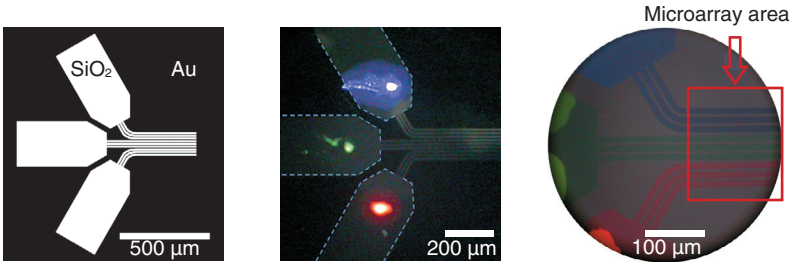


Fig. 1. Fabrication of SLB by self-spreading technique.



(a) Designed pattern (b) With lipid sources (c) After self-spreading

Fig. 2. Fabrication of dense SLB microarray.

distributes homogeneously in the SLB, fluorescence images correspond to the shape of the SLB.

2. Fabrication of SLB microarray

A microarray is a two-dimensional array of biological molecules on a solid surface, which is useful for high-throughput medical screening. The best-known microarray is a deoxyribonucleic acid (DNA) chip. It can detect complementary DNA molecules in a sample solution on the basis of the hybridization of DNA fixed on a solid surface. Recent research has started to extend the technique to protein targets. This means proteins instead of DNA must be fixed on a solid surface. DNA is a stable molecule, and it maintains its activity when fixed on a solid surface. However, proteins are usually delicate molecules, and they often lose their activity as the result of fixation. One way to overcome this problem is to use an SLB as a cushion for proteins. If we are to develop the protein microarray on the basis of this idea, we must fabricate an SLB microarray with a high integration density. Our technique is useful for this purpose [4].

Our original proposed technique for fabricating a dense SLB microarray is shown in **Fig. 2**. Our strategy is to use pattern-guided self-spreading for the integration. A gold (Au) pattern fabricated on silicon dioxide (SiO_2) is shown in Fig. 2(a). Different kinds of lipid sources, which show blue, green, and red fluorescence, are placed on the 500 × 250-µm areas (Fig. 2(b)) of the surface pattern on the solid. The sample is then immersed in buffer solution to initiate the self-spreading. As shown in Fig. 2(c), SLBs grow along the surface guide. At the end of the guide, we can obtain a linear pattern formed of 10-µm-wide SLBs with 5-µm intervals. The different colored dyes do not mix with each other because the lipid molecules are not soluble in aqueous media.

A technique for fabricating a dense SLB microarray was reported before our work. The technique is based on dropping vesicle solutions from different sources. One problem with the technique is that the droplets must not mix with each other during fabrication. Another problem is that of drying when the droplets are too small. The integration limit is thus determined by the droplet size. By contrast, SLBs are grown in a single buffer in our process. The integration limit is thus determined by the pattern size. This is the advantage of our technique, which yields an SLB microarray with a much higher integration density than the previous approach.

3. Protein detection by SLB microarray

We applied our microarray to protein detection using the specific binding of streptavidin and biotin [4]. The results are shown in **Fig. 3**. The microarray has three different sets of SLBs, each formed of three lines. The first set contains 1% of nitro-benzoxadiazole (NBD)-conjugated lipid, the second set contains 1% of biotin-conjugated lipid, and the third set contains them both.

A fluorescence image of the microarray is shown in Fig. 3(a). In the initial stage, only NBD has green fluorescence. Thus, in Fig. 3(a) we observe green fluorescence in the first and third sets. Here we add a streptavidin solution. The streptavidin we used was labeled with red fluorescent dye, and thus, the red fluorescence must be observed from an area where the streptavidin is present. The fluorescence image of the microarray after the reaction is shown in Fig. 3(b). It can be separated into the green and red fluorescence images shown in Fig. 3(c). The red fluorescence, which corresponds to the position of streptavidin, is observed only in the second and third sets of SLBs, which include biotin-conjugated lipid. This

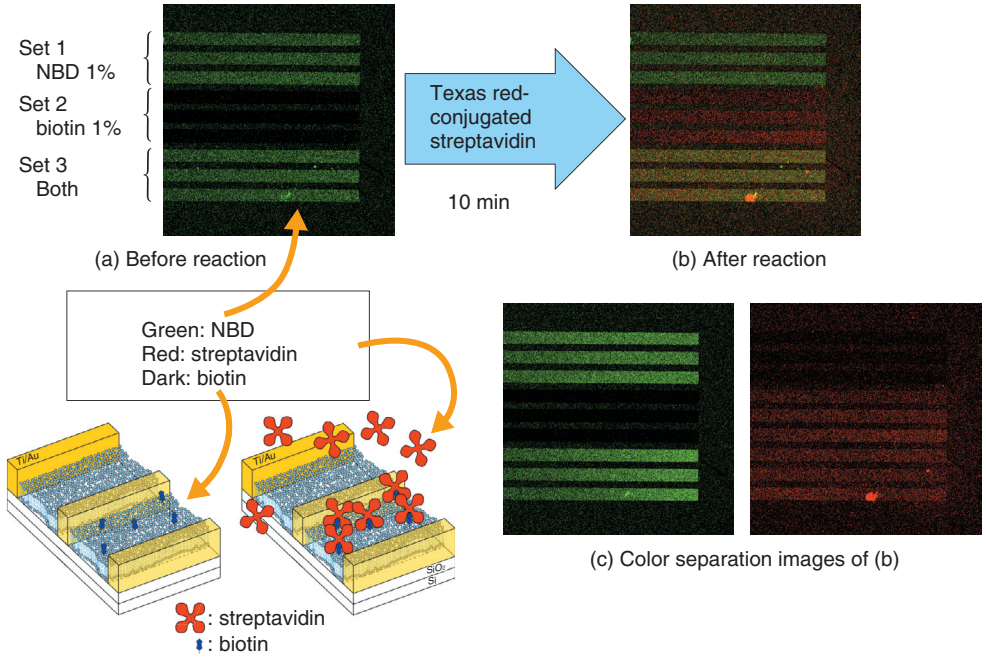


Fig. 3. Demonstration of protein detection with SLB microarray.

confirms that our microarray works for protein detection.

4. SLB in nanostructures

We can grow an SLB in the desired area by using a surface pattern as described above. Our next question concerns how narrow the area is in which an SLB can grow. To find the answer, we performed the following experiments [5, 6].

We designed the new structure shown in **Fig. 4**. It has a pair of gold electrodes with a 10–100 nm gap. The SLB is about 4 nm thick, and the gap is slightly larger than the thickness. The nanogap structure is much smaller than the resolution of an optical microscope. We therefore use a scanning electron microscope to observe the nanogap structure.

A self-spreading SLB passing through a nanogap is shown in **Fig. 5(a)**. The SLB grows inside a 10-μm-wide line (1) and reaches the nanogap position (2). It continues to grow through the nanogap, which is located in the center of the line (3). The SLB keeps growing and reaches the other side of the nanogap (4–6).

The most common way to fabricate SLBs is the vesicle fusion technique. However, it is difficult to determine if the SLB exists or not when we intend to

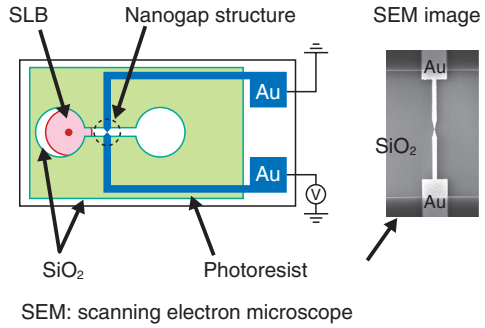


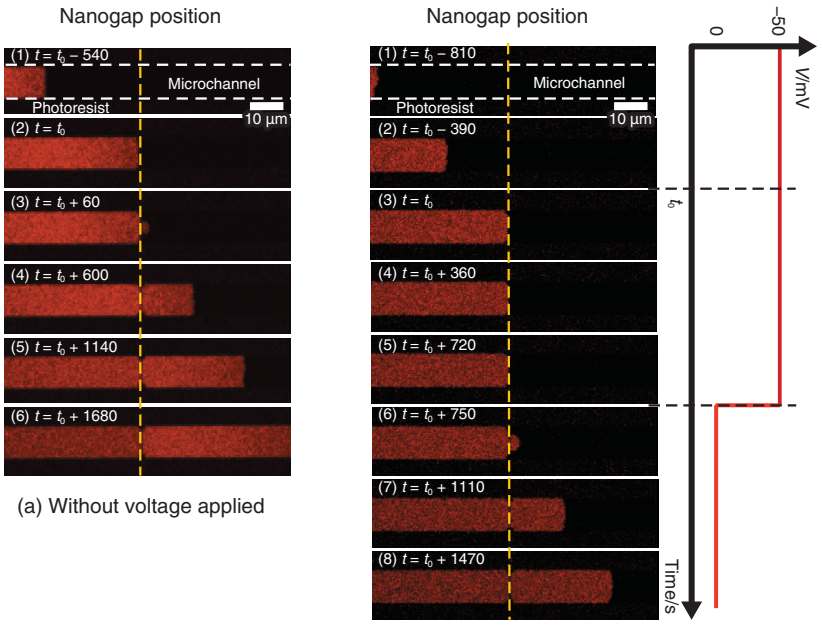
Fig. 4. Design of new pattern with nanogap structure.

fabricate the SLB in a nanostructure area such as the space in a nanogap structure. With our self-spreading method, it is clear that the SLB certainly grows on the nanogap area.

5. Manipulation of molecules inside SLB

We can use our nanogap structure as a pair of electrodes because they are made of Au metal. Next, we examined self-spreading when voltage was applied to the electrode.

The self-spreading when –50 mV was applied



Red fluorescence is SLB. White dotted holizontal line indicates 10-μm-wide line pattern, and yellow dotted vertical line indicates nanogap position. The time at which SLB reached the nanogap position is set as t_0.

Fig. 5. Self-spreading through nanogap structure.

between the electrodes is shown in **Fig. 5(b)** [5, 6]. The self-spreading behavior is no different from the example shown in Fig. 5(a) until the SLB reaches the nanogap (1–2). However, when the SLB reaches the nanogap (3), the SLB growth stops (4). After a certain period, the voltage is turned off (5), and the self-spreading restarts through the nanogap (6). The self-spreading after that is no different from that of the previous experiments shown in Fig. 5(a).

We explain the results with the following model. When an effective electric field is generated in the nanogap by the applied voltage, the field traps the molecule inside the SLB. This blocks the flow of the lipid molecules for SLB growth. In an electrolyte solution such as a physiological buffer, the electric field is only effective at nanometer-scale distances (called Debye length) from the electrode surface. In our experiments, we show that an effective electric field can be generated by using a nanometer-scale gap.

If we reapply the voltage in Fig. 5(b)(8), we can again stop the growth. It stops the supply of the lipid molecules required for the growth by trapping them in the nanogap. Because the nanogap is very narrow and the effective electric field is applied to a limited area, we think that few molecules are trapped. This means we can control a macroscopic event such as self-spreading simply with a small number of molecules, which is analogous to a gate in a field-effect transistor [5]. The conditions for trapping molecules are determined by the gap distance and the Debye length, which varies depending on the electrolyte concentration in the solution. We checked the effect of these parameters by performing thorough experiments and revealed the validity of our model.

6. Future perspectives

I have described some of our recent results—especially those related to biosensing applications—that we have obtained as a result of our basic research activities. One of the goals is to develop a protein chip using our SLB microarray.

A technique for manipulating molecules with nanogap electrodes can be further extended to single-molecule manipulation. It will constitute an original tool that will help NTT Basic Research Laboratories to undertake pioneering work in the new nano-bio

research field.

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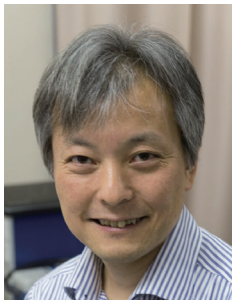

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Neuronal Growth on Artificial Structures with Different Materials

Nahoko Kasai and Toichiro Goto

Abstract

Neuronal guidance on a device is a key issue to achieve artificial synapses towards the goal of developing artificial post-synaptic structures. NTT Basic Research Laboratories has established a method for examining the *in vitro* affinity of neurons to a substrate by observing in detail the interface between a neuron and a substrate surface using a focused ion beam/scanning electron microscope at the single neuron level. With this knowledge in hand, we fabricated nanostructures using materials with a high affinity to neurons and examined the ability to control neuronal growth on the structure. We demonstrated the possibility of achieving neuronal guidance on a nanopillar substrate of amorphous silicon, which solves one of several difficulties related to the realization of artificial synapses.

Keywords: neuron, FIB/SEM, nanostructure

1. Introduction

Recent advances in nanotechnology and measurement technology have enabled us to obtain highly accurate biological information at high speed. Nanotechnology has been useful not only for diagnostics and treatments but also for developing nanobiodevices, which are nanometer-scale devices with biological functions. Nanobiodevices that utilize the superior functions of biological molecules such as high selectivity and high efficiency have limitless potential for medical care, innovative drug development, and science applications.

There are more than 100 billion neurons in a human brain, and they develop their function from a complicated network by delivering signals through synaptic connections. The goal of NTT Basic Research Laboratories is to realize an *artificial synapse* as a nanobiodevice by mimicking this synapse. A schematic illustration of our artificial synapse is shown in **Fig. 1**. The artificial synapse can be achieved with neurons forming a synaptic connection with an *artificial post-synapse*, which can be fabricated by combining nanotechnology and biomolecules. Thus, the mechanism of the brain can be investigated from the signal of each synapse at the molecule and synapse level. For example, we can identify the membrane proteins needed to induce a synaptic connection, and elucidate the mechanism of synapse signal transmission.

We require various elemental techniques if we are to achieve an artificial synapse. One such technique involves moving neurons towards the artificial post-synapse to achieve a synaptic connection. To do this, it is necessary to prepare an environment in which neurons can grow *in vitro* to adhere to the substrate, and to elongate the neurites properly. However, to provide an environment for a post-synapse membrane, proteins should be capable of being reconstituted into a lipid bilayer because they can function only when reconstituted into a lipid bilayer *in vivo*. This means that the device should be covered with a lipid bilayer as shown in Fig. 1(a). However, neurons cannot grow on or adhere to a substrate covered with a lipid bilayer. Therefore, at NTT Basic Research Laboratories, we have proposed nanopillars, which are nanostructures, as a scaffold on which the neurons can grow without adhering to the lipid bilayer (Fig. 1(b)). If neurons grow on nanopillars used as scaffolds, the nanopillars may control the neuronal growth direction, namely providing guidance.

We succeeded in evaluating the neuronal affinity with the substrate material at the single cell level by

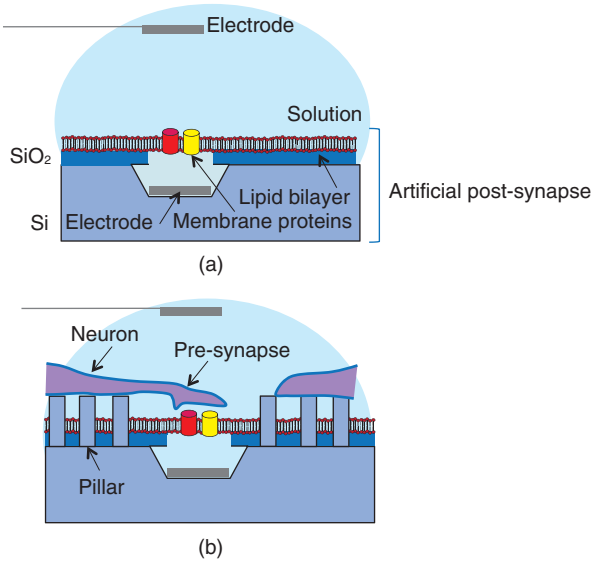


Fig. 1. Artificial synapse to communicate with neuron using artificial post-synapse via synaptic connection.

observing their interface by combining a scanning electron microscope (SEM) and a focused ion beam (FIB) to examine the substrate material for neuronal growth control so that the material could be utilized as a nanostructure for a scaffold.

Then, with the knowledge we obtained, we showed that neurons grew on the nanostructures by patterning them using the materials for which neurons show high affinity. In this article, we introduce our examination of the interface between neurons and a substrate, and neuronal growth control, namely guidance, using a nanostructure.

2. Evaluation of neuronal affinity and growth with different substrates

Neuronal *in vitro* cultivation has been widely used with the aim of elucidating neuronal signaling mechanisms and for applications in the neural engineering field. Our group has cultivated neurons on various substrates to create interfacial devices for neuronal guidance and thus realize artificial synapses.

The interfacial state between neurons and substrates is important information in regard to controlling neuronal growth when we fabricate neuron-integrated devices. Detailed information about the interface between single neurons and substrates, especially nanostructures, can be important in terms of controlling neuronal growth on nanostructured substrates.

Several techniques can be used to observe biological samples, ranging from the use of optical microscopes through scanning probe microscopes such as atomic force microscopes. These optical and scanning probe microscopes enable us to observe cell surfaces in detail. However, they cannot be used to directly observe the internal structure of the cells or the interface between the cells and the substrate.

NTT Basic Research Laboratories has succeeded in evaluating the interfaces between single neurons and substrates by using FIB milling and subsequent SEM. FIB can process samples by accelerating a gallium ion beam by high voltage [1]. This FIB with an SEM enables us to observe both the cross-sectional and three-dimensional structure of the neurons at a single cell level. In this study, a cell sample was sliced with an FIB/SEM dual system, and its cross-section was observed very precisely [2]. This article introduces the result of observing neurons cultivated on either a gold (Au) or titanium (Ti) substrate obtained with a fluorescent microscope or an FIB/SEM dual system.

Neurons were obtained from a rat cerebral cortex. Au has been widely used in the nanotechnology field because its surface chemical characteristics can be modified by functionalizing the surface through self-assembled monolayers of thiols. Ti has superior biocompatibility, and its oxide is used for medical applications such as implants. Thus, the evaluation of the neuronal affinity to different materials can lead to the optimization of neuronal growth scaffolds using nanostructures.

Fluorescent images of neurons cultivated on Au and Ti are respectively shown in **Figs. 2(a)** and **2(b)**. Green indicates neurons stained with fluorescent dye. A relatively large green grainy lump was observed on the Au, suggesting the aggregation of neurons. In contrast, the neurons on the Ti were observed to be elongated, which means they had dispersed without aggregating. This suggests Ti is more cytophilic than Au. To investigate the neuronal affinity expected from the fluorescent results in more detail, neurons cultivated on Au or Ti were examined using cross-sectional images of the interface between the neurons and the substrate obtained with an FIB/SEM dual system (**Figs. 2(c)** and **2(d)**). The neuron-Au interface exhibited partial adhesion. In contrast, almost all the neurons adhered to the Ti interface. These results are consistent with an assessment made using fluorescence microscopy, and the difference reflects the

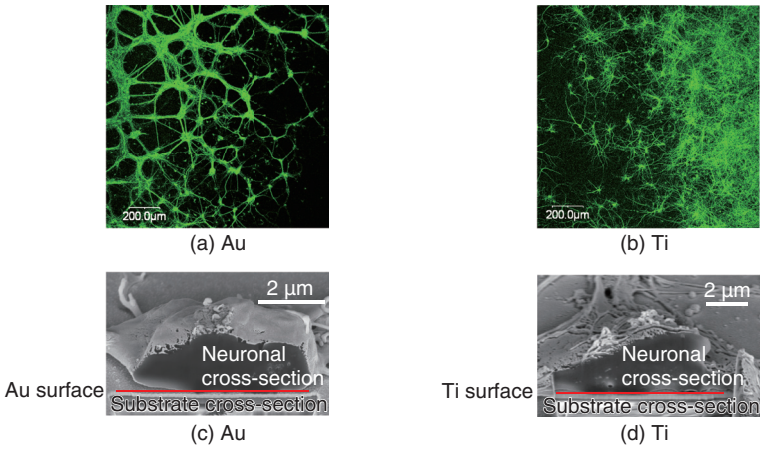


Fig. 2. Microscopic images of neurons cultivated on Au and Ti surfaces. Red lines show the substrate surface [2].

neuronal affinity of the materials.

A fluorescent microscope can be used to evaluate the affinity of the multiple cells, but a combination of FIB and SEM can examine the difference in the affinity of a single neuron, and a precise evaluation can be made of the substrate surface. An SEM can provide us with more detailed information because of its much higher spatial resolution, and a detailed interfacial examination will be possible even for nanostructures.

In the future, we will aim for an evaluation that includes two-dimensional interfacial mapping and that uses low temperature (cryo) FIB/SEM, which requires fewer samples in the preparation process of fixation and dehydration and thus avoids changing the cellular topologies.

3. Neuronal guidance using nanostructures

Neuronal guidance using nanometer-scale structures including grooves, fibers, and pillars has been attracting attention since the late 2000s, and the structural influences on neuronal adhesion and growth have been examined [3]. However, little attention has been paid to nanostructure materials.

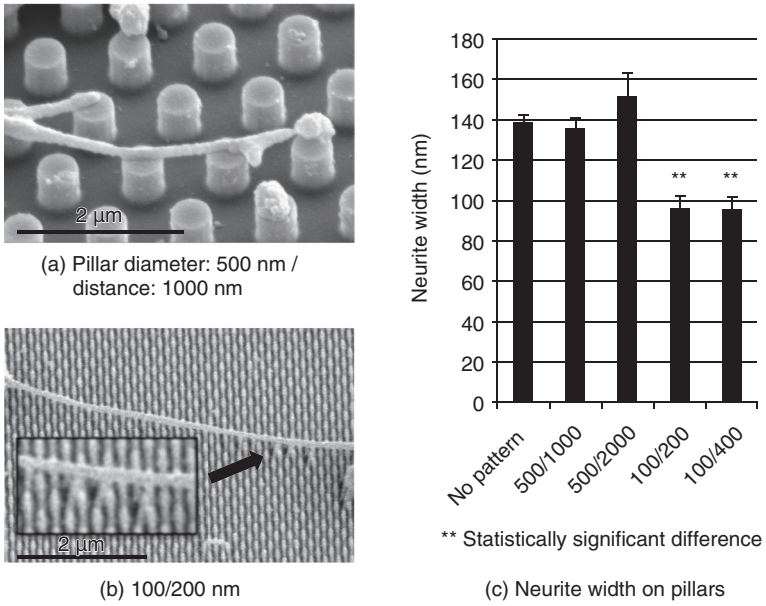
As stated above, we examined neuronal affinity with different substrates using the cross-sectional observation of a single neuron. In this section, we examine neuronal growth and guidance capability using nanopillar arrays made of amorphous silicon (a-Si) and Au fabricated as scaffolds for neuronal growth.

We fabricated nanopillars 100 and 500 nm in diameter on quartz substrates using electron-beam lithography; then we cultivated rat cortical neurons on them. The samples were then fixed and observed by using either an SEM or confocal laser scanning microscope (CLSM) after the treatment. The first process in the treatment was fixation to stabilize the protein, which is the main structural molecule of the cell. Thus, the observed cell structures resembled their intact structures after fixation. The sample for SEM observation was further dehydrated and freeze-dried, and the sample for CLSM was also immunostained to identify the specific protein localization.

SEM images of neurites (axons or dendrites) elongated from neurons cultivated for 7 days on a-Si nanopillars are shown in **Fig. 3**. The neurites were observed to adhere to the nanopillars, and they grew on pillars with diameters of 500 and 100 nm. Some of the narrower pillars were bent by the neurite growth (magnified in the inset in Fig. 3(b)).

By comparing the widths of neurites cultivated on different nanopillar patterns, we found that the neurites were significantly wider on wider-diameter pillars (Fig. 3(c)). Neurites on the wider pillars were almost as wide as neurites on a plane substrate. This suggests that the size of the neuronal adhesion area affects neurite width. The neuronal width can be determined by the adhesion area; a neurite adhering to a substrate promotes the expression of cytoskeletal proteins. This result shows that 500-nm-diameter pillars allow neurites to grow in the same manner as on a plane substrate.

Then, we examined neurons on different pillar materials, as shown in **Fig. 4**. Neurons grew longer along with the patterns on a-Si pillars (Fig. 4(a), thick arrow) while they elongated randomly on both Au pillars and a quartz substrate (Fig. 4(b)). A quantitative

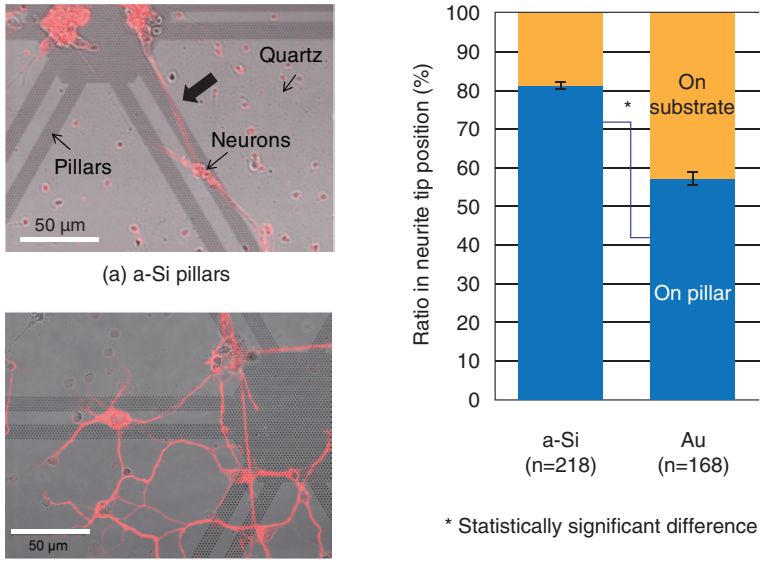


(a) Pillar diameter: 500 nm / distance: 1000 nm

(b) 100/200 nm

(c) Neurite width on pillars

Fig. 3. SEM images of neurites on pillars, and neurite width [4].



(a) a-Si pillars

(b) Au pillars

(c) Neurite tip positions

Fig. 4. (a)(b) Fluorescent images of neurons cultivated on pillars of different materials. (c) Neurite tip positions [4].

analysis revealed that there was a higher ratio of neurite tips on the a-Si pillars than on the Au pillars (Fig. 4(c)) [4]. This low affinity of neurons for Au corresponds to neuronal cross-section results obtained using FIB/SEM. These results demonstrate the possibility of achieving neuronal guidance using nano-pillars made of appropriate materials.

4. Realizing an artificial synapse

We established a method of evaluating the *in vitro* neuronal affinity to a substrate with different materials

using a single neuron by observing neuronal cross-sections. Furthermore, we demonstrated the possibility of controlling the neuronal growth using nanopillars made of high affinity materials. The neuronal growth direction can be controlled by controlling the nanopillar array. Then, neurons can be expected to grow towards the device, namely the artificial post-synapse, which would be fabricated in advance. Thus, in the future, we will investigate the mechanism of synaptogenesis by realizing an artificial synapse by the bottom-up examination of molecules; for example, the identification of proteins (synaptogenesis factors) for synapse formation.

Acknowledgments

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Time-lapse Imaging of Neural Morphological Changes Relating to Cellular Functions

Aya Tanaka

Abstract

The human body is composed of trillions of cells. The association between the cells with specialized functions is important in the formation of the skeleton and organs, whose integration is vital for human activity. The nervous system plays a central role in effectively integrating the functions of the skeleton and organs. Here, we introduce research aimed at understanding the relationship between neural function and morphology in the early stages of apoptosis, which plays an important role in the process of neural network formation.

Keywords: bioimaging, SICM, neuron

1. Introduction

The human body is composed of several trillion cells. The association between the cells with specific functions plays a vital role in the formation of the skeleton and organs, whose integration is crucial for human activity. The nervous system plays a central role in integrating their functions so that they operate effectively. The nervous system is classified into two parts: the central nervous system, which is composed of the brain and spinal cord, and the peripheral nervous system, which is composed of the nerves throughout the body. In the nervous system, external stimuli detected by the peripheral nervous system are transmitted to the central nervous system. The central nervous system processes the information and sends the responses to the peripheral nervous system. For the nervous system to operate efficiently, a neurotransmission pathway network must be formed between neurons or between neurons and other cells. Therefore, it is important to understand the processes that form a neural network.

There are two main processes involved in the formation of a neural network inside the brain. One is the neural maturation of individual neurons; this maturation provides functions for neurotransmission and the formation of a platform for neurotransmission, namely a synapse, between cells during neural network formation. The neural maturation processes can be classified into five stages based on established morphological criteria (**Fig. 1**). These consist of immature neurons lacking neurites (stage 1), neurons with multiple short neurites without established polarity (stage 2), and neurons that have achieved polarity and that possess neurites considerably longer than the rest, namely axons, which act as transmission paths (stage 3). The remaining neurites mature as dendrites with functions for receiving neural information from axons (stage 4). With further maturation, the axon and the dendrites elongate to form synapses among target cells (stage 5).

The other process is the formation of a neural network. One of the key biological events in this process is apoptosis. Apoptosis is defined as programmed cell death. In a developing nervous system, apoptosis occurs as a homeostatic mechanism to maintain cell populations in a neural network. It is a highly regulated and controlled process, and apoptotic cells are quickly eliminated without causing any damage to surrounding cells. In the neural network formation process, target cells secrete signals such as neural growth factors, which are essential for neural survival.

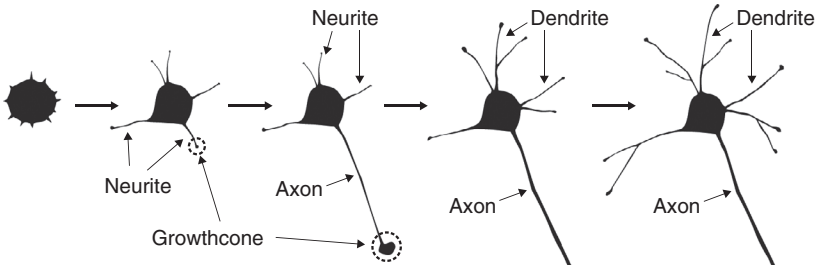


Fig. 1. Morphological changes in neural network formation process.

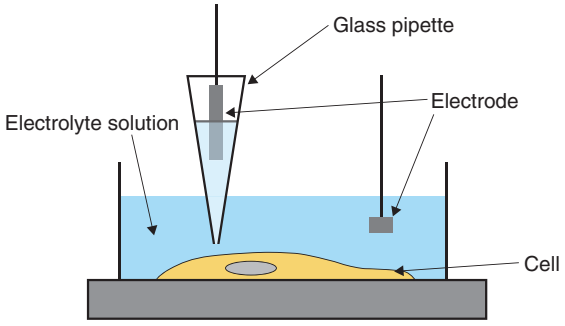


Fig. 2. Experimental system overview of SICM.

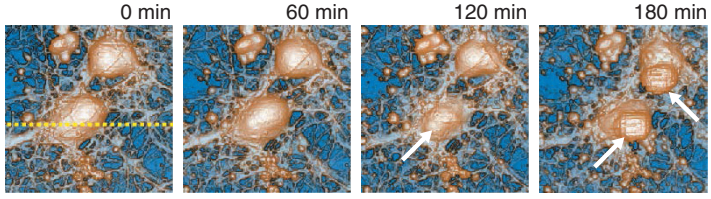
Neurons that successfully receive the signals continue growing in the direction of the target cells. In contrast, neurons that fail to receive the signals are eliminated from the network formation process via several biological processes. If we are to understand this apoptotic process, we must investigate cellular functions at molecular and morphological levels.

2. Observation of biological samples by microscopy

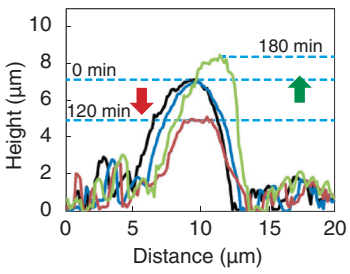
Cellular morphologies are observed using some form of microscopy. Fluorescence microscopy is used to visualize biological samples by attaching fluorescence probes to them. This technique helps us to visualize the interaction between biological samples during biological events, although it is limited in terms of imaging morphological detail. Electron microscopy has been the conventional method for obtaining structural information about cells with higher resolution than optical microscopy, but it requires a fixed sample [1]. Therefore, it is impossible to obtain dynamic morphological images of living cells. One effective dynamic imaging technique, scanning probe microscopy [2, 3], and specifically, scanning ion conductance microscopy (SICM) [4], is expected to be a powerful tool for obtaining images of living cells (**Fig. 2**). This technique uses a glass pipette filled with an electrolyte that senses an ion current and feeds back its position relative to samples completely immersed in a liquid buffer containing electrolytes. Since the tip-sample distance is maintained at the radius of the pipette during the scan by keeping the ionic current constant, SICM enables stable and non-contact imaging of soft and sticky biological samples at a resolution of better than 100 nm. Because the application of external stimuli to living cells may induce cell death, SICM will allow us to image the morphological dynamics of living cells.

3. Neurons during apoptosis

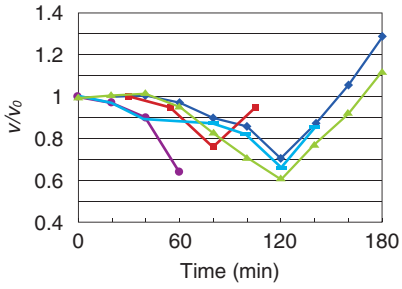
As described above, apoptosis plays an important role in the neural network formation process. It exhibits a distinct set of the biological changes including apoptotic volume decrease, the formation of cell buds or membrane blebs, and phosphatidylserine (PS) translocation. The cell membrane is



(a) Time-lapse images of neural morphological changes observed by SICM



(b) Cross-sectional graph of (a)



(c) Time-course volume change of single neurons

Fig. 3. Morphological changes in neurons in early stages of apoptosis.

composed of the inner and outer leaflets of a lipid membrane. PS normally resides in the inner leaflet of the cell membrane and is translocated from the inner to the outer leaflet in the early stages of apoptosis. This PS translocation is considered to be a key biological event in relation to phagocytosis. As regards morphological changes during the early stages of apoptosis, the cell volume decreases, and membrane blebs are subsequently formed on the surface of the cell membrane. Despite the importance of these apoptotic morphological changes, no one has yet revealed the morphological dynamics at a resolution of better than a micrometer, or revealed the relationship between biochemical changes such as PS translocation and the cellular morphology. SICM is a suitable technique for investigating a series of these changes because it allows us to observe the morphology of living cells without any mechanical interactions between the probe and the sample surface with a high resolution. In this article, we discuss the morphological changes that occur in neurons in the early stages of apoptosis including apoptotic volume decrease and membrane blebbing. In addition, we explain our investigation of the relationship between membrane blebbing and PS translocation. Additionally, we use the results of these experiments to discuss the order of morphological dynamics during apoptosis and the relationship between biochemical and morphological changes [5].

4. Bioimaging of neurons

We investigated the morphological changes in apoptotic neurons by exposing cultivated neurons to staurosporine (STS), which is an apoptosis inducer. The morphological changes in a single neuron are shown in **Fig. 3(a)**, and line scans for the SICM image indicated by the dashed line in Fig. 3(a) are shown in **Fig. 3(b)**. In the first 120 min after exposure to STS, bulge-like structures known as membrane blebs were observed at the neuron (Fig. 3(a), white arrows). The number and size of the blebs increased with time. A graph of the volume change over time as a ratio of volume to initial volume, v/v_0, shown in **Fig. 3(c)**, was obtained from five neurons, and individual time-course images were obtained in an independent experiment. The v/v_0 ranged from 0.6 to 0.8, meaning that the volume decreased from 20 to 40% in the first 120 min after exposure to STS. Once the volume reached its minimum value, it increased again, and membrane bleb formation was observed. The SICM results indicate that the time course of the morphological changes begins with an apoptotic volume decrease, followed by membrane blebbing.

We used fluorescence microscopy to investigate the relationship between membrane blebbing and PS translocation by detecting the PS translocation with Annexin V, which binds to the PS residing in the outer leaflet of the cell membrane in the presence of calcium

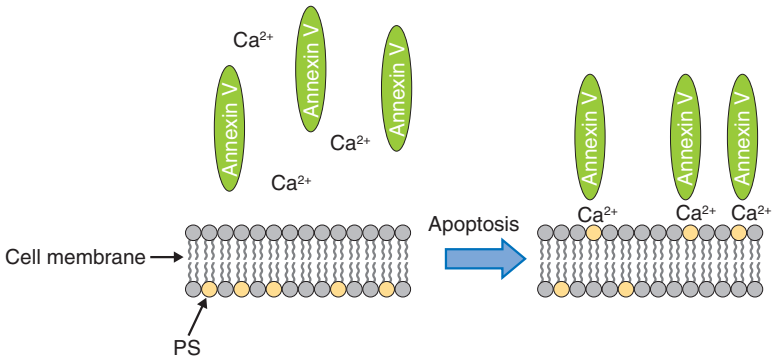


Fig. 4. Detection of PS translocation using Annexin V.

ions. Normally, PS exists in an inner leaflet of the cell membrane. Apoptosis induces the translocation of PS from the inner to the outer leaflet without changing the permeability of the cell membrane. This translocation can be detected via binding with fluorescently labeled Annexin V (**Fig. 4**). After the neurons were exposed to STS, we monitored the binding of the Annexin to the neurons (**Fig. 5**). The Annexin V-positive ratio without exposure to STS ranged from 0% to 10% during 180 min of observation, whereas the ratio with the exposure to STS increased more than 20%. This indicates that PS translocation induced by STS occurred around 120 min after exposure to STS.

These results obtained by SICM and fluorescence microscopy show that apoptosis induces a reduction in cellular volume and subsequent membrane blebbing. Moreover, the membrane blebbing had a similar onset time to the PS translocation. It has been difficult to observe the time series of morphological changes in living cells, especially that of soft and deformable structures. A non-contact imaging technique such as SICM provides us with the morphological details of neurons in the early stages of apoptosis.

5. Future perspectives

The Molecular and Bio Science Research Group at NTT Basic Research Laboratories is focusing on fabricating a nanobiodevice based on biological systems. To achieve this, it is essential to understand how many biological systems are orchestrated inside organisms as well as to investigate individual biological materials and cells. The combination of conventional and new imaging techniques such as fluorescence microscopy and SICM will provide new insight into the relationship between individual biological events and applications to information technologies and medical technologies.

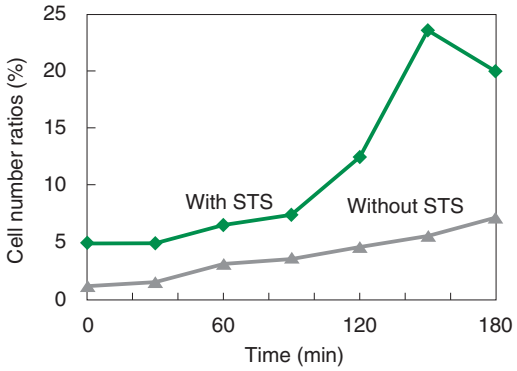


Fig. 5. Ratios of cells binding to Annexin V.

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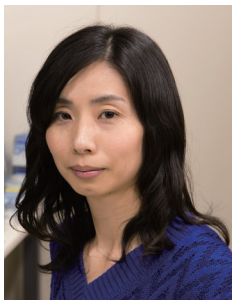

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On-chip Graphene Biosensor

Yuko Ueno

Abstract

This article describes our recent research on an on-chip biosensor that uses the surface of graphene, an atomically thin carbon sheet modified with specific DNA (deoxyribonucleic acid) molecules, which binds selectively to a target molecule. Biologically important proteins such as cancer markers can be detected simply by adding a sample solution smaller than 1 microliter to the sensor chip. Quantitative detection of multiple proteins on a single graphene biosensor chip is demonstrated by using a microchannel configuration. Our findings have the potential to lead to a simple assay technique for disease markers.

Keywords: graphene, biosensor, protein

1. Introduction

Graphene is an atomically thin two-dimensional sheet consisting of a hexagonal honeycomb lattice of carbon atoms. It has been attracting great attention owing to its unique properties, which include extremely high mechanical strength, thermal conductivity, electronic mobility, and thermal and chemical stability [1]. Graphene was isolated in 2004 by Profs. Geim and Novoselov of the University of Manchester, who won the 2010 Nobel Prize in Physics for their pioneering work. The mass production of graphene was difficult at that time but has progressed greatly. It is now possible to obtain a monolayer of graphene several tens of centimeters square by using synthetic techniques typified by the chemical vapor deposition process.

At the same time, graphene oxide (GO), the most widely known chemical derivative of graphene, is also attracting considerable interest. GO is an oxidized form of graphene, and it also has an atomically thin sheet-like structure, which contains nanometer-sized graphene-like domains. In GO, many of the bonds between the carbon atoms in graphene are broken and link with oxygen to form carbon-oxygen bonds. GO is prepared very differently from graphene and is rather easy to mass-produce. We can chemically synthesize GO by oxidizing graphite powder in strong acid. This yields a large quantity of GO in a glass container; however, it is difficult to obtain synthesized GO larger than a millimeter square. Therefore, GO is not suitable as a replacement for graphene in electronic materials that require high mobility, but is applicable to optical devices and sensing materials [2].

On the surface of graphene (or the graphene-like domains in GO), energy transfer occurs when molecules are located close to the surface. The energy transfer yield depends on the degree of molecular interaction between the adsorbed molecules and the graphene surface. For example, when a fluorescent molecule such as a dye is located very close to the graphene surface, the dye does not exhibit fluorescence. Here, graphene works as an excellent acceptor for fluorescence resonance energy transfer (FRET) over the entire visible wavelength region. By using the energy transfer reaction on a graphene surface, we can visualize biological/chemical reactions by converting those invisible molecular behaviors into the measurable physical quantities such as light and electricity. This makes graphene a promising material for a novel biosensor.

We have proposed and developed a unique type of biosensor, which works on a graphene surface, by modifying it with a specific deoxyribonucleic acid (DNA) called an aptamer for the detection of biologically important proteins such as cancer markers (aptasensor, aptamer-based biosensor). We call a solid surface functionalized by biological molecules a *biomolecular interface*. First, we achieved biomolecular interfaces using GO and confirmed their usefulness for protein detection. We also fabricated

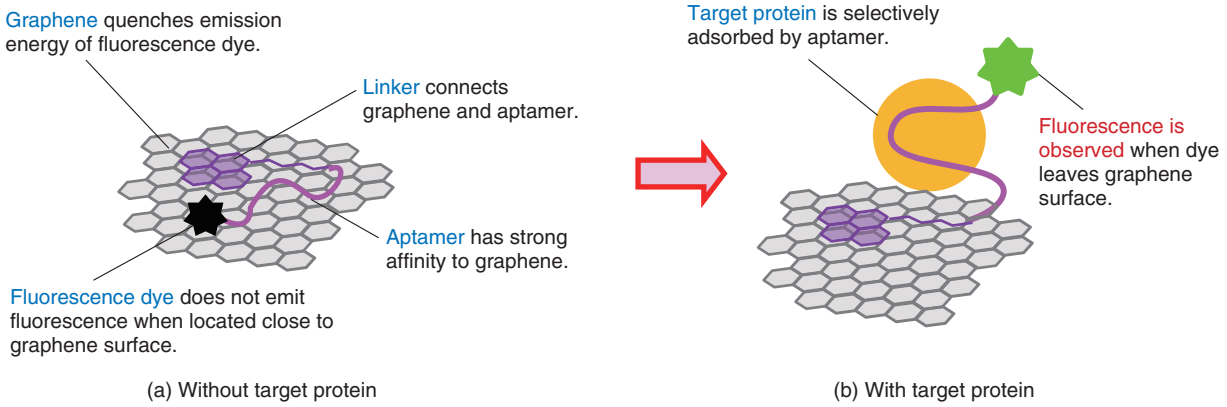


Fig. 1. Design of protein detection system with graphene aptasensor.

on-chip sensors by combining the system with microfluidic techniques. Then we demonstrated protein detection by replacing GO with graphene to achieve an aptasensor with better performance than one with GO.

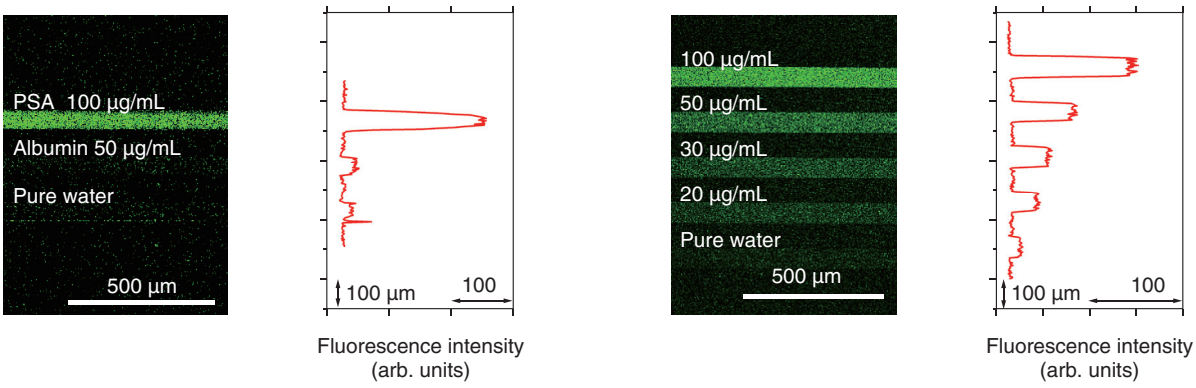
2. Mechanism of graphene aptasensor

Our graphene aptasensor uses a graphene surface modified with an aptamer, which is a selected single-strand (ss) oligonucleotide that binds to a specific target. One end of the aptamer is labeled with a fluorescent dye, and the other end is connected to a pyrene linker molecule, which shows a strong affinity to the graphene (graphene-like domains in the case of GO). Thus, the aptamer is firmly fixed to the graphene surface. The graphene aptasensor detection process is as follows. In the initial stage, the dye-conjugated aptamer is adsorbed on the graphene surface via physical adsorption (π-π interactions), and thus, the dye is located close to the graphene surface. Here, the fluorescence of the dye is well quenched by graphene via FRET and is barely observable (**Fig. 1(a)**). If the target of the aptamer is present in the system, the aptamer forms a complex with the target and leaves the graphene surface. At the same time, the dye molecule also leaves the graphene surface, and the dye recovers its fluorescence (**Fig. 1(b)**). We can detect the target molecule by using the fluorescence [3].

Aptamers have a wide variety of targets and offer many advantages as molecular recognition probes. Aptasensors are generally versatile because they can be extended to the detection of many different targets by replacing the aptamers. We confirmed the versatility of our on-chip graphene aptasensor by using it to detect three different proteins, namely, thrombin (a blood clotting marker), prostate specific antigen (PSA; a cancer marker), and hemagglutinin (an antigenic glycoprotein found on the surface of influenza viruses), simply by changing the aptamers but retaining the same sensor composition. Moreover, aptamers can be flexibly designed without loss of bioactivity. Thus, we can design and construct various kinds of biomolecular probes by conjugating additional functions with an aptamer. Lastly, aptamers are chemically stable. We confirmed that the aptasensors that had been stored at a normal temperature and pressure for more than a month operated normally as if they had just been made.

3. Multichannel configuration for quantitative detection and linear-array for multiple protein detection

We first studied the sensing performance of our aptasensor by using GO and confirmed their usefulness for protein detection. An advantage of using an on-chip sensor is that it enables us to realize a parallel analysis system such as a sensor array. A multichannel system allows us to make a precise quantitative sample-reference comparison. It also enables us to perform simultaneous observations of the sample and reference signals, which can be used to eliminate the effect of fluorescence degradation caused by laser exposure and other noises. This is an advantage of our on-chip graphene aptasensor. Moreover, the on-chip aptasensor requires no out-of-chip processes such as labeling or mixing the sample, and thus, the human errors that can occur during the sample preparation



(a) Selectivity (b) Concentration dependence

Fig. 2. Selectivity and concentration dependence of PSA detection.

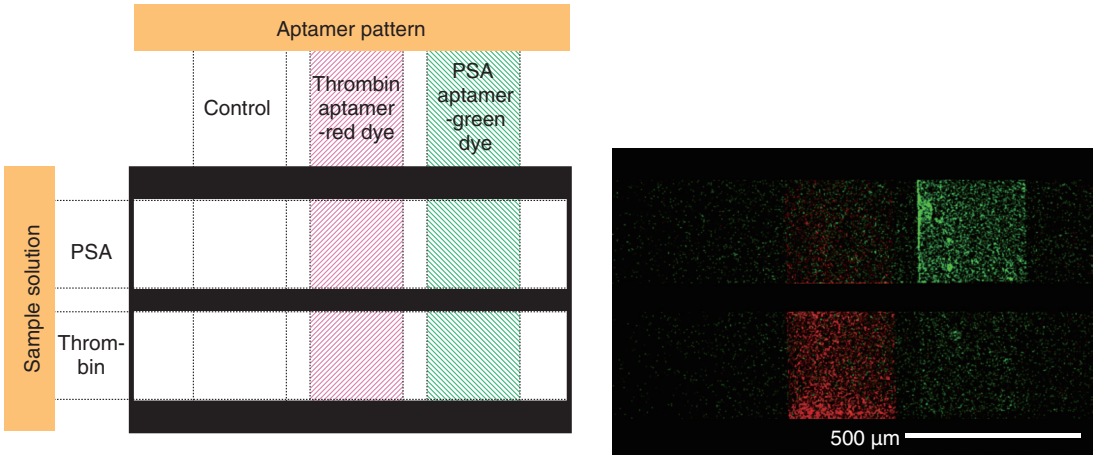
procedure can be minimized. We fabricated an on-chip multichannel aptasensor by placing a polydimethylsiloxane sheet with microchannels on a solid substrate, and we formed the graphene aptasensor on its surface. The target protein was detected in about a minute simply by adding a sample solution smaller than 1 microliter to the sensor chip. We measured the fluorescence emitted from the graphene surfaces located in each microchannel simultaneously and compared the intensities of the channels. For comparison, a commercially obtained ELISA (enzyme-linked immunosorbent assay) kit—one of the most common protein detection methods—requires a sample volume of at least 100 microliters and an assay time of three hours.

We can fabricate a microchannel with the desired design using photolithographic techniques. The number of channels is also variable. Here we prepared an on-chip aptasensor with a triple microchannel configuration. We measured the fluorescence images when PSA, human albumin solution, and water were injected into the top, middle, and bottom channels, respectively (**Fig. 2(a)**). Albumin, the most abundant protein in human blood plasma, caused no change in the fluorescence intensity, just as with water. This proved the selectivity of our aptasensor for PSA detection. We also examined the dependence of the fluorescence intensity on the PSA concentration (**Fig. 2(b)**). We used a quintuple microchannel configuration and injected PSA solution with four different concentrations and water as a reference into each microchannel. The results showed that the fluorescence intensity became weaker as the PSA concentration decreased.

We fabricated a 2×3 linear-array aptasensor by using two different aptamers for different targets, namely thrombin and PSA, which we labeled with red and green fluorescent dyes, respectively (**Fig. 3(a)**). Bright fluorescence was only observed in the areas where we assumed that the correct aptamer-target pair had been formed (**Fig. 3(b)**). The simultaneous detection of multiple target molecules on a single chip was successfully demonstrated [4].

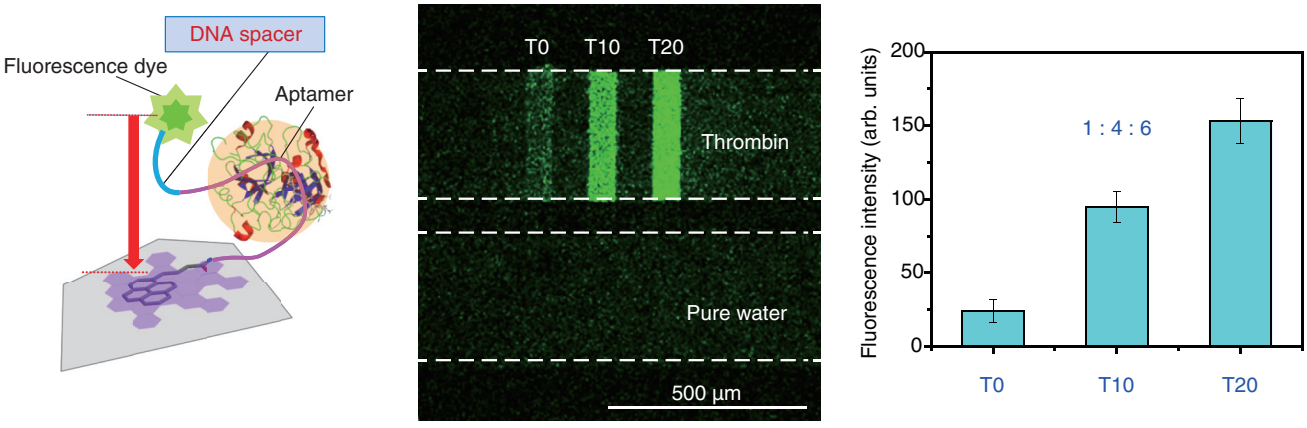
4. Molecular design for enhanced sensitivity

The most interesting feature of aptasensors is that we can design and construct various kinds of biomolecular probes by incorporating additional functions with an aptamer. We can improve the sensitivity of an on-chip GO aptasensor by modifying an aptamer with an ssDNA spacer (**Fig. 4(a)**). The strategy was to increase the distance between the fluorescence dye and the graphene surface, which is crucial for FRET-based sensors, when forming a complex with the target protein. We fabricated a 2×3 linear-array GO aptasensor by using three different probes and introducing ssDNA spacers with 0, 10, and 20 thymine segments between the aptamer and the dye. The fluorescence intensity increased significantly with increases in the spacer length (**Figs. 4(b)** and **4(c)**). The limit for thrombin detection was about 1 nM, which corresponds to the *in vivo* concentration range during blood clotting by using the probe with 20 thymine segments, the best design in our present study. The results showed that introducing an ssDNA spacer at the correct position is an effective way of enhancing sensor sensitivity [5, 6].



(a) Layout of 2×3 linear array sensor (b) Fluorescence image of protein detection

Fig. 3. Demonstration of simultaneous multiple protein detection.



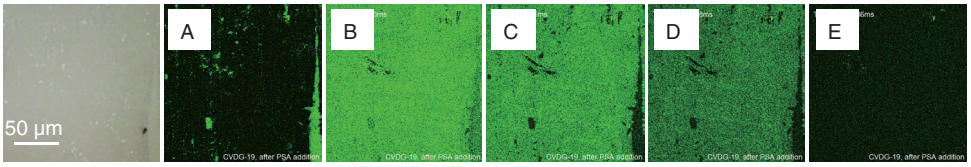
(a) Design of molecular probe (b) Dependence of spacer length (c) Comparison of fluorescence intensity

Fig. 4. Enhanced sensitivity by using molecular probe modified with DNA spacer.

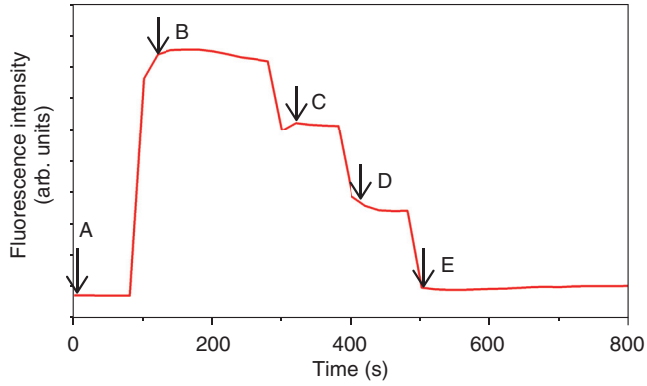
5. Aptasensor built on continuous single-layer graphene surface

In our GO aptasensor, we used a pyrene linker that showed a strong affinity with the graphene-like domain to immobilize the aptamer. However, the surface area of the graphene-like domain reached at most 50% that of a GO flake. By changing the platform from GO to graphene, we were able to achieve a solid surface with a 100% graphene structure.

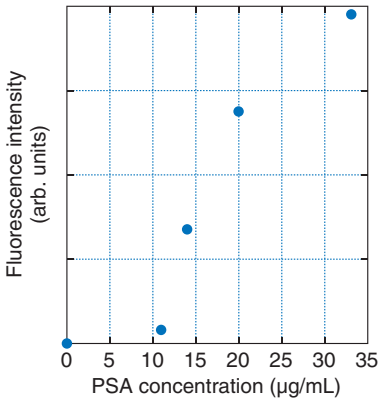
We prepared a PSA aptasensor on a commercially available single-layer graphene surface fixed on a solid substrate. We confirmed that the substrate was almost fully covered with a single layer of graphene by observing optical and Raman images before measuring the sensing performance. The fluorescence intensity was initially small (**Figs. 5(a)** and **5(b)**, A), increased steeply after PSA was added (B), and then decreased rapidly as water was added to dilute the sample solution (C - E). It is noteworthy that the fluorescence intensity was almost homogeneous in the observed area of more than 100 µm × 100 µm. The maximum fluorescence intensity was larger than that of a GO aptasensor prepared in the same manner; namely, the ratio reaches 3.3. Thus, we can improve the sensitivity by changing the sensing platform from



(a) Microscope image and fluorescence images for PSA detection



(b) Change in fluorescence intensity of graphene aptasensor with PSA concentration



(c) Plot of average fluorescence intensity against PSA concentration

Fig. 5. PSA detection using graphene aptasensor.

GO to graphene. An investigation of the mechanism behind the improvement in sensitivity is ongoing [7].

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Conductive Composite Material for Vital Data Measurement

Tetsuhiko Teshima, Shingo Tsukada, and Hiroshi Nakashima

Abstract

As the interest in healthcare has grown in recent years, the technologies needed to monitor vital data have been attracting a lot of attention with a view to disease diagnosis and prevention as well as lifestyle improvement. At NTT Basic Research Laboratories, we are working on the research and development of conductive composite materials by coating or mixing conductive polymer with biocompatible substrates. We utilize these materials as electrodes for measuring biological signals from, for example, the skin or the heart, with high biocompatibility and sensitivity. We report here on composite electrodes made of conductive polymer (PEDOT:PSS) and silk substrates that are used when measuring biomedical signals via human tissue.

Keywords: biocompatible material, conductive polymer, vital data

1. Introduction

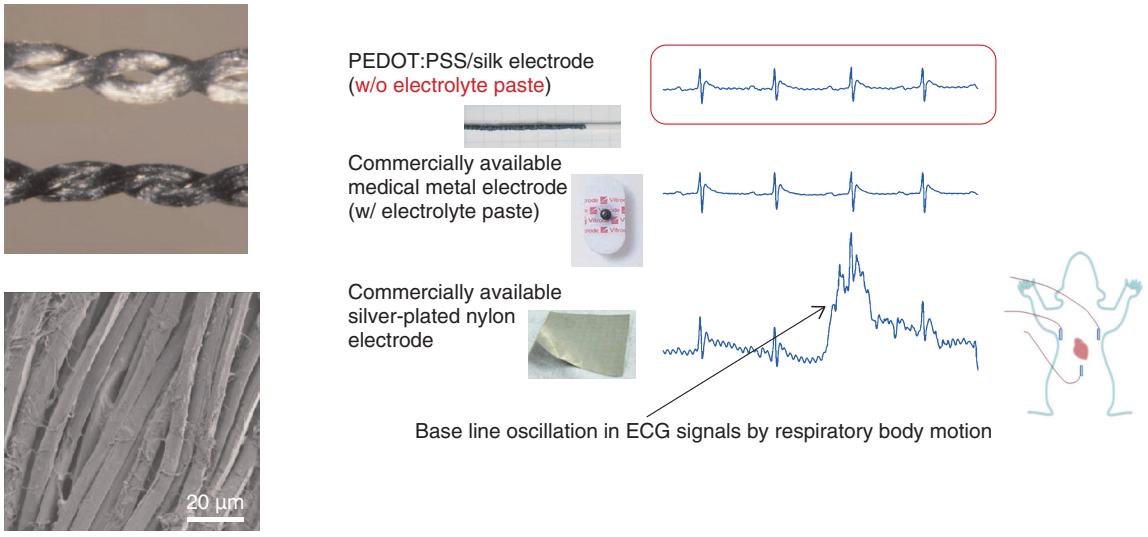
In recent years, rapid diagnosis and early-stage treatment of disease have become important with the aim of reducing the risk of contracting serious diseases. In particular, there is a strong need to develop methods for continuously monitoring heart rate and for measuring electrocardiographic (ECG) waveforms in order to prevent heart diseases such as heart attack and arrhythmia. Conventionally, metal electrodes and metal-plated fibers have been widely used to measure heart rate and ECG waveforms. However, metal-based electrodes lack flexibility and biocompatibility. As a result, the obtained signals are often affected by high noise, and the patient's skin may be allergic or sensitive to metal. Furthermore, electrolyte paste is needed to attach medical electrodes to the skin surface, and this may induce a rash and/or itching during long-term use.

Our group has focused on the use of PEDOT:PSS (poly(3,4-ethylenedioxythiophene) poly(styrenesulfonate)) as an electrode material that is non-toxic and stable in wet conditions. This molecule, which consists of a π electron-conjugated compound (PEDOT) and a polyelectrolyte (PSS), is widely used as a transparent electrode for touchscreens and displays, and is a replacement for rare metals such as indium tin oxide (ITO). We have been taking advantage of the high hydrophilicity and biocompatibility of PEDOT:PSS to carry out research and development of electrodes designed to measure the action potential of nerve cells [1]. In this article, we introduce biocompatible electrodes that we achieved by integrating PEDOT:PSS with a base substrate such as fibers, without using a metal-based electrode and electrolyte paste.

2. Conductive silk fiber

The high hydrophilic property of PEDOT:PSS molecules means that they swell into a gel in humid environments. Therefore, these molecules exhibit reduced mechanical stiffness, water resistance, and processability, leading to limitations in their use. We avoided these limiting factors by immobilizing PEDOT:PSS on the surface of silk fibers in an electrochemical manner [2].

Images of silk bundles coated with PEDOT:PSS are shown in **Fig. 1(a)**. We can clearly observe the micrometer-scale fine structure of silk fibers that



(a) Optical microscope (above) and SEM (below) images of silk fiber bundle coated with PEDOT:PSS

SEM: scanning electron microscope

(b) ECG measurement of rats using PEDOT:PSS/silk electrodes, conventional metal-based medical electrodes, and silver-plated nylon electrodes

Fig. 1. PEDOT:PSS/silk composite electrode.

were thinly and uniformly coated with PEDOT:PSS. When we employed PEDOT:PSS/silk electrodes for ECG measurements with experimental animals, electrodes located on the surface of the skin provided us with ECG data that were comparable to data obtained with conventional metal-based electrodes (**Fig. 1(b)**).

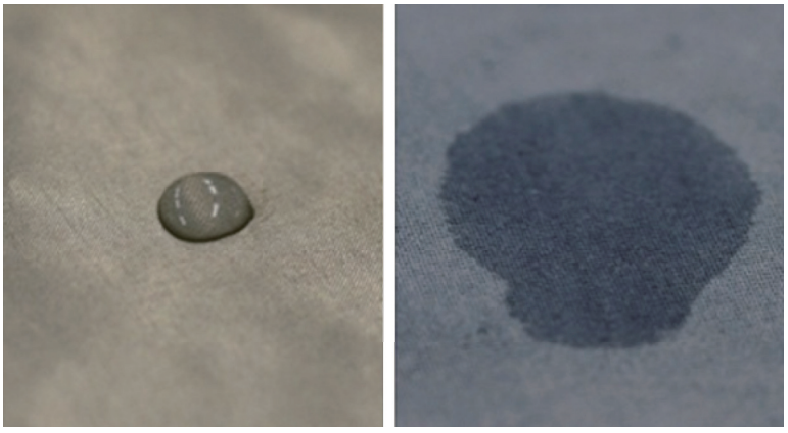
In contrast, it is difficult for the silver-plated nylon electrodes to make good contact with the skin surface. There was also a baseline oscillation in the ECG signals caused by respiratory body motion, which made it difficult to obtain a stable measurement of the ECG waveform. The water-repellent surface of conventional metal-based electrodes caused this difficulty, whereas the PEDOT:PSS/silk composite electrodes with high hydrophilicity meant that the moisture was rapidly absorbed by the fiber, as shown in **Fig. 2**.

The hydrophilic electrodes tended to absorb sweat and water vapor from the skin, which increased their flexibility and adhesion, making it possible to perform stable measurements. The PEDOT:PSS coating technology is not only applicable to silk fibers but also to a wide range of fibrous materials including polyester and nylon.

3. Conductive silk hydrogel electrode

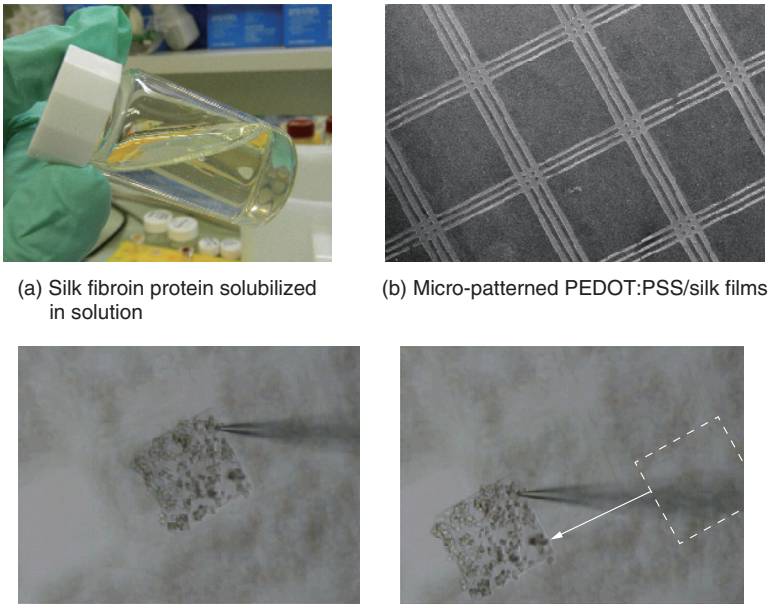
To broaden the application range of the PEDOT:PSS/silk composite, we are developing silk substrates with various shapes by solubilizing and molding silk fibers. When this technique was applied to a solution of silk fibroin obtained by chemically treating silk fibers, the solution retained its biocompatibility, hydrophilicity, and processability (**Fig. 3(a)**). The water solubility of both silk fibroin and PEDOT:PSS enabled them to mix and disperse well, yielding composites with high hydrophilicity.

The fibroin protein gelation process with alcohol produced conductive silk-hydrogel electrodes with arbitrary shapes. We employed this process to fabricate a cell-electrode interface for electrical measurements and for the activation of an adherent cell through a photolithographic technique, as shown in **Fig. 3(b)**. A thin-film electrode was formed into the desired shape applicable for cell morphology and function, and it possessed sufficient stiffness to withstand the cell traction force (**Fig. 3(c)**). By culturing the cells on the surface of films, we were able to collect the cell-laden films and manipulate them into the desired position. When the electrodes were inserted inside the silk hydrogel electrodes, voltage was



(a) Silver-plated nylon electrode (b) PEDOT:PSS/silk composite electrode

Fig. 2. Hydrophobic silver-plated nylon electrode (a) and hydrophilic PEDOT:PSS/silk composite electrode (b).



(a) Silk fibroin protein solubilized in solution

(b) Micro-patterned PEDOT:PSS/silk films

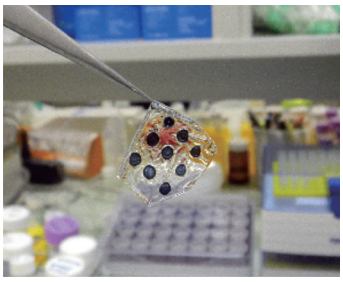
(c) Manipulation of cell-laden film

Fig. 3. Micrometer-sized PEDOT:PSS/silk fibroin electrodes.

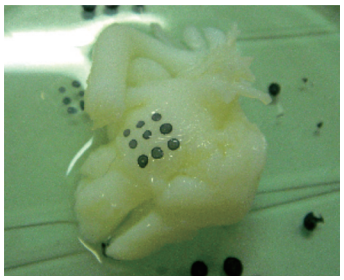
applied to the entire targeted film. By using this method, we electrically activated the cells to specifically stimulate the voltage-dependent channels expressed on the cells. In the future, we will employ this method to measure the cell action potential of various cells and tissues.

The addition of a photocurable hydrogel to the base material enabled us to produce a large-scale silk-hydrogel based electrode by light irradiation. An image of PEDOT:PSS/silk hydrogel arrays that were patterned on extremely flexible silk hydrogel thin film with high hydrophilicity and biocompatibility is shown in **Fig. 4(a)**.

Changing the shape of the mold to fill the precursor during light irradiation made it possible to build an *in vivo* implantation hydrogel electrode with the desired three-dimensional shape such as a fiber or a suction cup. The fabricated hydrogel electrodes exhibited



(a) Thin silk hydrogel electrode with embedded PEDOT:PSS/silk hydrogel arrays



(b) Attachment of silk hydrogel electrodes on three-dimensional heart tissue-like structures

Fig. 4. Large-scale PEDOT:PSS/silk composite electrodes.

high breaking strength, flexibility, and stretchability both in air and water in the tensile test because of their high viscoelastic properties. When these electrodes were introduced into the brain tissue of experimental animals, their structure was retained inside the tissue over a long period of time without damaging it. This facilitated the stable recording of brain electrical signals over a period of more than one month.

The PEDOT:PSS/silk hydrogel electrodes proposed in this study exhibited little cell toxicity, shape stability, and little change of conductivity even in the body. Thus, we are now working on optimizing the structure of these biocompatible electrodes so that they adhere stably to the surface of pulsating tissue such as the heart (**Fig. 4(b)**).

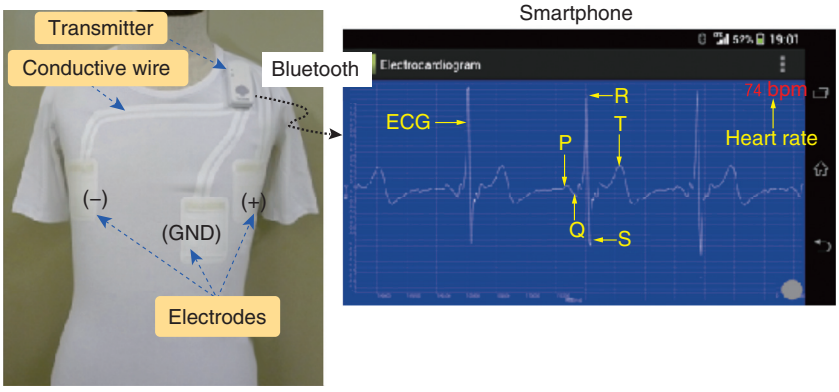
4. Development and practical application of "hitoe"

By taking advantage of the fibrous form of conductive silk fibers, we developed electrode-integrated innerwear that can record the heart rate and ECG waveforms when the subject wears it. The composite electrodes embedded inside the innerwear are located so that they measure the potential difference between two points on the body surface, thus obtaining biological signals with a high signal-to-noise ratio, as shown in **Fig. 5(a)**. The obtained data were sent via Bluetooth* from a transmitter to a smartphone. The ECG waveform shown in Fig. 5(a) indicates not only a sharp QRS waveform, but also a clearly identified P/T waveform and the heart rate estimated from the number of R wave peaks. The electrodes in the innerwear were attached to the body without the need for electrolyte paste, thus enabling long-term, almost noiseless, and stable measurement of ECG waveforms.

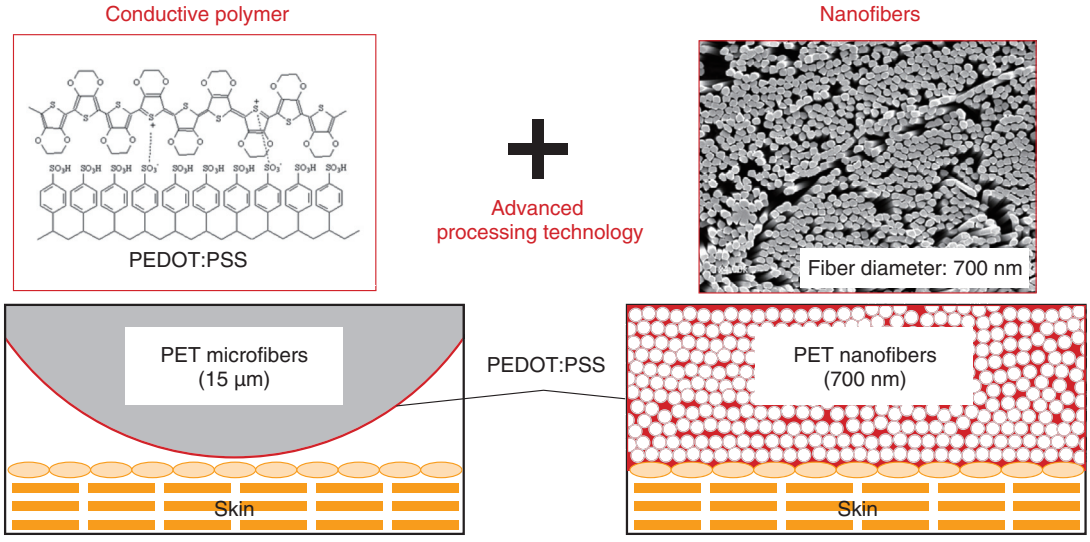
To further improve the adhesion to the skin and the moisture-retaining ability of the electrodes, we jointly developed with Toray Industries, Inc. the functional material "hitoe" by employing nanometer-scale fibers. The diameter of a single nanofiber is about 700 nm, and the continuous layers of PEDOT:PSS are highly impregnated within the gaps between nanofibers **(Fig. 5(b))**. Since the ultra-thin nanofibers increased the contact area and moisturizing effect on the skin, the sensitivity with which bioelectrical signals were detected was greatly improved. In addition, we achieved high functionality by integrating required components. This allowed us to rearrange electrodes, control the wearing pressure, employ electrical wiring suitable for use in clothing, and include a structure to prevent short circuits caused by perspiration and rain.

As hardware for measuring heart rate, biomedical signal measuring innerwear incorporating "hitoe" is being marketed—in collaboration with GOLDWIN INC. and NTT DOCOMO—as a way to monitor the load imposed on the body during exercise. We can expect the combination of heart rate data obtained during exercise with traveling distance and calorie consumption measurements to improve sports performance and to enhance training management efficiency. Moreover, the monitoring of a wearer's physical condition using "hitoe" will be demonstrated for use as a labor management tool for professionals engaged in dangerous work, long-distance bus/truck drivers, and night workers, or as safety management

* The Bluetooth word mark and logos are registered trademarks owned by Bluetooth SIG, Inc.



(a) Electrode-integrated innerwear with loaded Bluetooth transmitter



(b) Functional wearable electrode "hitoe"

GND: ground
PET: polyethylene terephthalate

Fig. 5. Development and practical application of "hitoe".

hardware for the prevention of work-related accidents such as heat stroke and heart attack.

5. Summary

If we are to measure vital data accurately, the electrode components should be in close contact with the target tissue at all times. The PEDOT:PSS/silk composite electrodes that our group has been working on offer high electrical conductivity, biocompatibility, and flexibility. Therefore, the electrodes are capable of measuring biological signals with long-term stability even when attached to the skin and *in vivo* tissue. By integrating them with innerwear, we have developed wearable bioelectrodes for measuring heart rate and ECG waveforms with high precision without burdening the wearer. Simply by wearing these bioelectrodes, we can easily undertake our own health management for longer periods regardless of whether we are engaged in normal activity or are exercising or sleeping.

Furthermore, by solubilizing silk fibers, we produced PEDOT:PSS/silk composite electrodes with the desired shapes. For example, we fabricated micrometer-sized thin electrode films in order to apply voltage to cells, and millimeter-sized implantable

electrodes to record electrical signals from tissue. Since these electrodes are derived from aqueous silk fibroin solution, they can be blended with any types of additives such as ethylene glycol to increase the conductivity or cell differentiation/growth factors corresponding to the types of cells and tissues. Currently, we are further developing these technologies to realize a complex and three-dimensional multi-electrode array. We expect them to be applicable as *in vivo* implantation electrodes that are attached to the surface of tissues and that measure signals from multiple points within them, in order to obtain basic knowledge of the profound information contained inside the human body.

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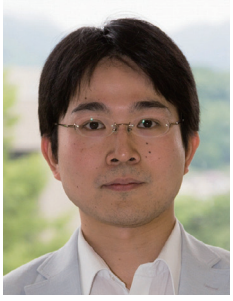

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Substrate-transfer Technique Using h-BN for GaN-based High-power Transistors

Masanobu Hiroki, Kazuhide Kumakura, and Hideki Yamamoto

Abstract

We transferred AlGaN/GaN (aluminum gallium nitride/gallium nitride) high electron mobility transistors from a sapphire substrate to a material with high thermal conductivity using a substrate-transfer technique that involves the use of an h-BN (hexagonal boron nitride) release layer. We succeeded in suppressing the self-heating effect and obtained good power performance in direct current characteristics. The transfer technique can overcome thermal problems in power transistors.

Keywords: GaN, high-power transistors, epitaxial lift-off

1. Introduction

Gallium nitride (GaN) and its alloys are attractive materials for short-wavelength light-emitting devices and for high-power electronic devices due to their wide energy gap. Blue light-emitting diodes, blue-violet laser diodes, and high electron mobility transistors (HEMTs) have been widely used for room illumination, Blu-ray Disc* players, radio frequency amplifiers in Long Term Evolution mobile base stations, and in other applications. Other III-nitride semiconductor materials such as indium nitride (InN), aluminum nitride (AlN), boron nitride (BN), and their alloys are also attractive for new applications of III-nitride semiconductors. Indium nitride has a narrow bandgap (0.7 eV) and has been reported to have an electron mobility as high as 4400 cm^2/Vs [1]. Thus, InN and its alloys are attractive for infrared light-emitting devices and high-speed electronic devices. Aluminum nitride and BN have an extremely wide bandgap of around 6 eV, which enables the fabrication of ultraviolet-light-emitting devices and high-power transistors. We recently succeeded in growing high-quality single-crystal hexagonal boron nitride (h-BN) and found that it can be used as a release layer for nitride semiconductors [2, 3].

Epitaxial lift-off (ELO) and substrate-transfer techniques enable new ways to use semiconductor devices. These techniques have been used to fabricate a flexible GaAs (gallium arsenide)-based solar cell [4]. In addition, they help to reduce fabrication costs because we can reuse substrates. With III-nitride semiconductors, however, ELO from substrates is difficult because of their strong atomic bonding with the substrate as well as the lack of a suitable etchant for selective etching. We recently proposed using an h-BN release layer for ELO of III-nitride layers [3]. One of the benefits of the ELO and substrate-transfer techniques is the enhanced heat dissipation in GaN-based electrical devices. For HEMT on sapphire, the temperature rises significantly in operation with high current levels since a sapphire substrate widely used for the growth of GaN has low thermal conductivity (κ) of 40 W/m K. This self-heating degrades device performance and reliability. By transferring the devices to a material with high thermal conductivity, we can suppress the temperature rise in the active region of devices. This article describes the enhancement of

* Blu-ray Disc is a trademark of the Blu-ray Disc Association.

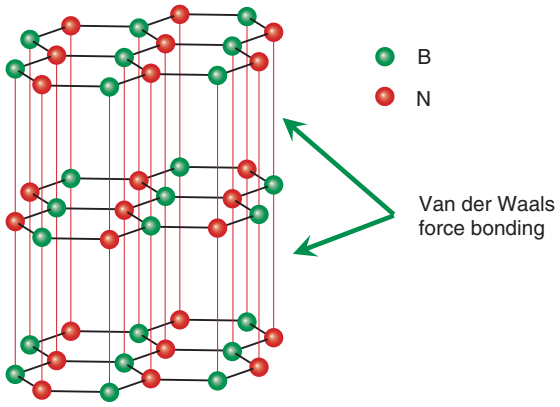


Fig. 1. Crystal structure of h-BN.

heat dissipation for aluminum gallium nitride/gallium nitride (AlGaN/GaN) HEMTs transferred to a copper plate with a thermal conductivity of 390 W/m K [5, 6].

2. Transfer technique for AlGaN/GaN HEMTs using h-BN ELO

First, we present our ELO technique based on the h-BN release layer. The crystal structure of h-BN is shown in **Fig. 1**. The h-BN crystal has a layered structure like graphite, and each layer is weakly bonded by van der Waals forces. Thus, the layers can be easily exfoliated. Moreover, single-crystal GaN layers can be grown on an AlN or AlGaN nucleation layer (NL) deposited on h-BN. Thus, the GaN layers can be released from sapphire substrates by mechanical forces.

The transfer process for AlGaN/GaN HEMT is illustrated in **Fig. 2**. First, the h-BN layer is grown on a C-plane sapphire substrate by metal organic vapor phase epitaxy (MOVPE). Next, a 100-nm-thick AlN NL is grown on the h-BN layer. Subsequently, an AlGaN/GaN heterostructure is grown by MOVPE at a temperature of 1000°C at a pressure of 300 Torr. These are the same as the conventional conditions for the direct growth on sapphire substrate. The heterostructure consists of a 3-μm-thick GaN buffer layer and 27-nm-thick AlGaN barrier layer. Two-dimensional electron gas (2DEG) with a 1×10^{13} cm^{-2} density is induced by a polarization charge at the AlGaN/GaN heterointerfaces, which forms a conductive path from the source to the drain.

AlGaN/GaN HEMTs were fabricated using conventional photolithography and lift-off techniques. The AlGaN barrier outside the active region was etched away by inductively coupled plasma etching to remove the 2DEG conductive channel for electrical isolation between devices (mesa isolation). We used electron-beam evaporation for metal deposition and rapid thermal annealing to form the ohmic contacts. The source/drain ohmic electrodes consisted of titanium (Ti; 15 nm)/ aluminum (Al; 80 nm)/ nickel (Ni; 30 nm)/gold (Au; 50 nm) annealed at 850°C for 30 s. The Schottky gate electrode was Ni (50 nm)/Au (100 nm). The gate length, source-drain spacing, and gate width were 1.5, 6, and 100 μm, respectively.

The next step in the process is to release AlGaN/GaN HEMTs from the sapphire substrate and transfer them to a copper plate. For that purpose, we first coated the sample surface with PMMA (polymethyl methacrylate) and adhered the sample to a glass plate. Then we mechanically released it from the sapphire substrate. For transfer to a copper plate, we used Au-Au thermocompression bonding [7]. We deposited Ti/Au on the back side surface of the HEMT, and we deposited Au on the copper plate. The two Au surfaces were brought into contact with each other, and then a pressure of approximately 20 MPa was applied at about 200°C. The cross-sectional transmission electron microscopy (TEM) image of the transferred HEMT is shown in **Fig. 3**. The TEM image reveals that the GaN layer strongly adhered to the copper layer at the Au-Au thermocompression interface.

3. Enhancement of heat dissipation of AlGaN/GaN HEMTs using substrate-transfer technique

Typical drain current (I_d)–drain bias (V_{ds})

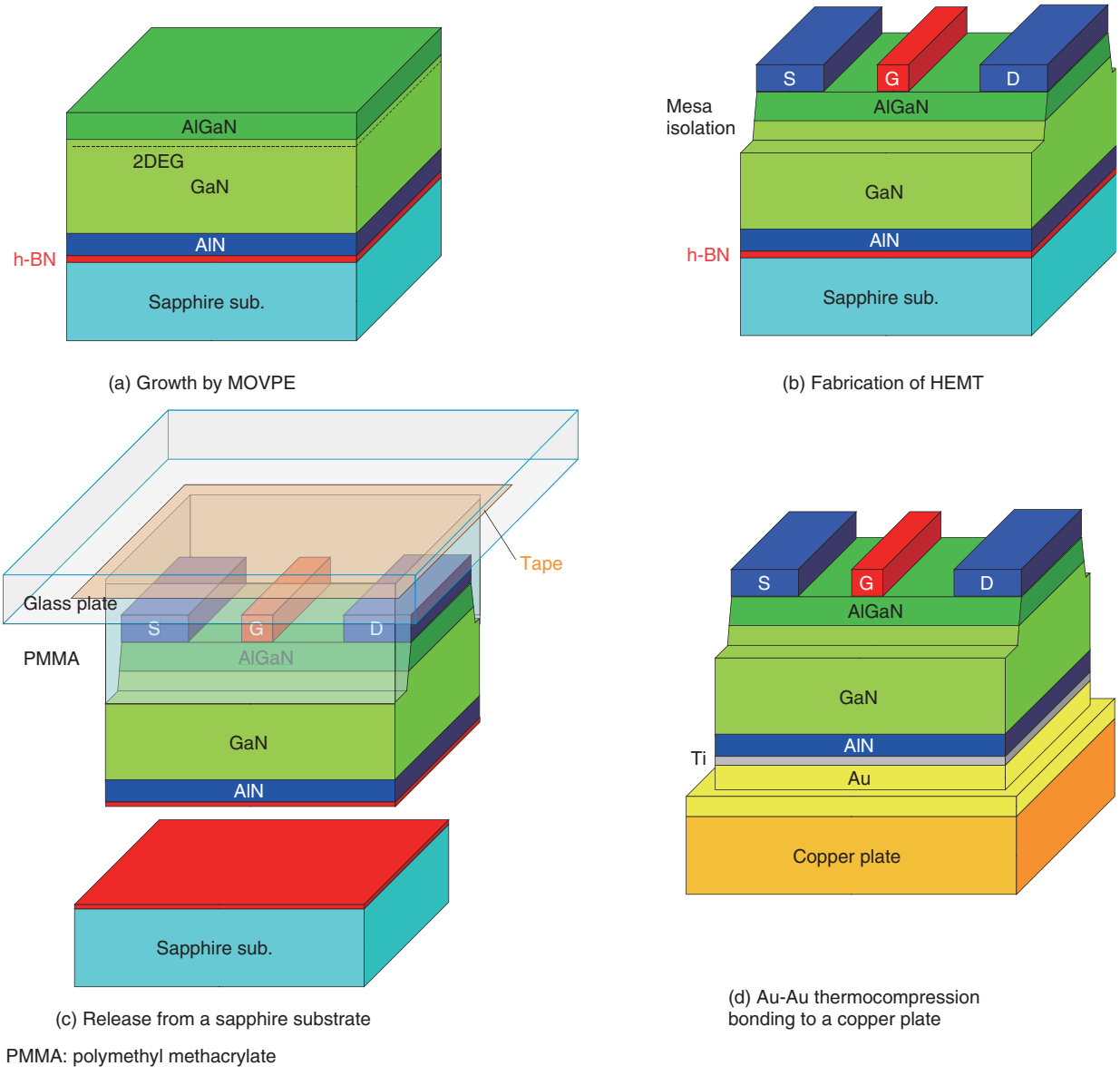
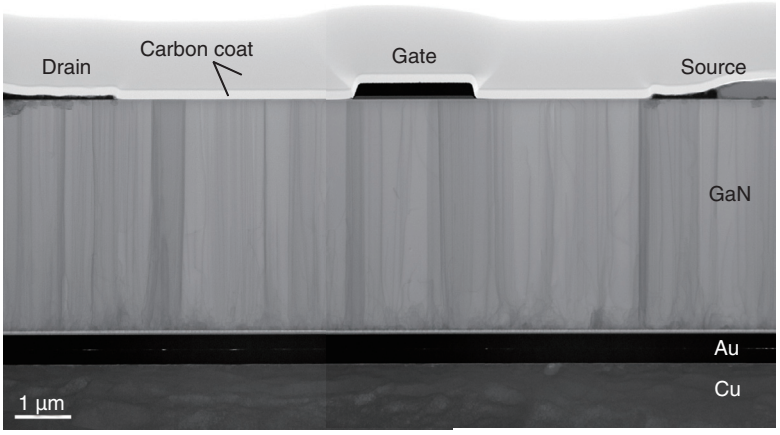


Fig. 2. Schematic views of h-BN ELO and transfer processes of AlGaN/GaN HEMT. (a) Growth of AlGaN/GaN heterostructures on AlN NL deposited on h-N/sapphire. (b) Fabrication of AlGaN/GaN HEMTs by conventional photolithography and lift-off technique. The labels S, G, and D indicate source, gate, and drain electrodes, respectively. (c) Mechanical ELO of the HEMTs from sapphire substrate. (d) Transfer of the HEMTs to a copper plate by Au-Au thermocompression bonding.

characteristics of the AlGaN/GaN HEMT before release from the substrate and after transfer to the copper plate are shown in **Fig. 4**. Good pinch-off and saturation characteristics were obtained even after the transfer, indicating that no degradation took place in the transfer process. The device performance significantly improved after transfer. The maximum I_d at a gate bias (V_{gs}) of 1 V significantly increased from 0.55 A/mm to 0.68 A/mm. Before release, a large reduction in I_d vs V_{ds} was observed in the saturation region at a large positive gate bias (V_{gs}). At V_{gs} = 1 V, the I_d decreased by 25% as the V_{ds} increased from 5 V to 20 V. In contrast, the decrement in I_d vs V_{ds} was as small as 3% for the transferred HEMT. The negative slope is commonly attributed to self-heating in the device operation [8]. The transfer from the sapphire to the copper plate improves the heat dissipation efficiency and thereby suppresses the decrease in



Cu: copper

Fig. 3. Cross-sectional TEM image of an AlGaN/GaN HEMT transferred to a copper plate by Au-Au thermocompression bonding. White and grey layers on the sample surface consist of carbon, which was coated for surface protection in TEM measurements. The difference in the colors is caused by the purity of carbon.

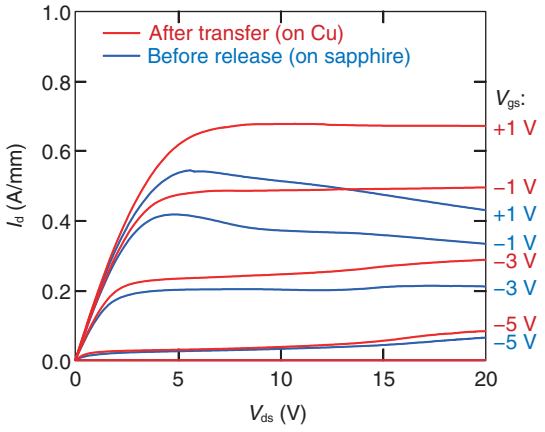


Fig. 4. I_d–V_{ds} characteristics of AlGaN/GaN HEMT before release and after transfer.

drain current under high-bias operation.

We also estimated the temperatures in the active region of HEMTs using micro-Raman spectroscopy. The temperatures of the devices can be estimated from the peak shift in the A_1 phonon mode [9, 10]. The temperature maps of an HEMT on a sapphire substrate and another HEMT transferred to copper are shown in **Fig. 5**. The highest temperature was observed at the center of the channel at the gate edge on the drain side. For the HEMT on sapphire (before its release), the temperature exceeded 200°C at a power dissipation (P) level of 0.68 W. In contrast, for the transferred HEMT, the temperature was only 110°C at P = 1.54 W. The channel temperature as a function of P in the HEMTs is plotted in **Fig. 6** before their release and after their transfer. The channel temperature is the average one in the center region of the channel at the gate edge on the drain side where the highest temperature was observed. A linear approximation revealed that the thermal resistances of the HEMTs before their release and after their transfer were 28 and 6.5°C mm/W, respectively, indicating a one-fourth reduction. The transfer to copper significantly improved the heat dissipation in the HEMTs.

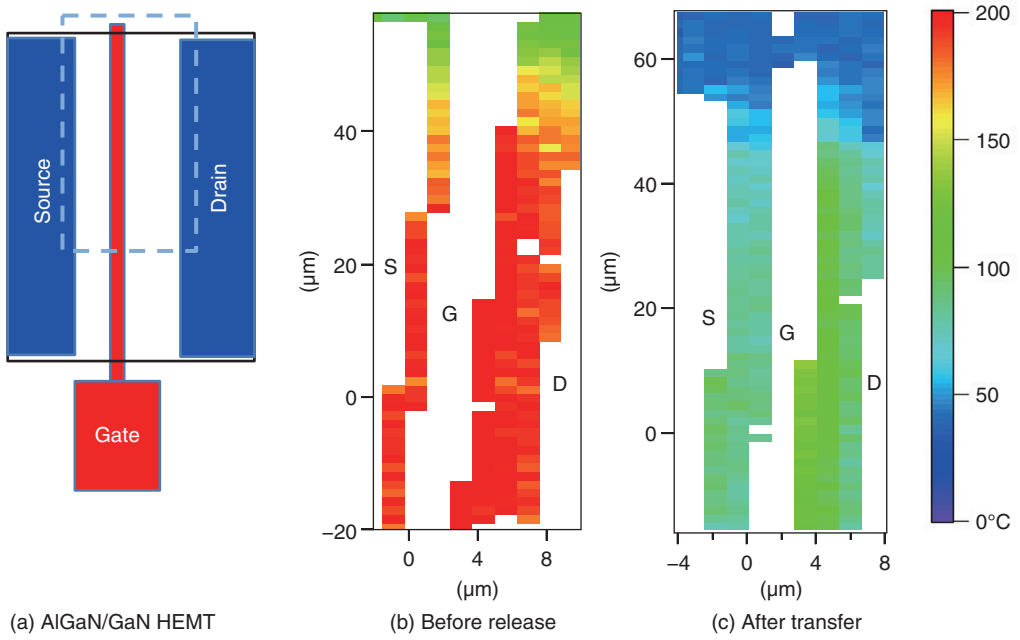


Fig. 5. (a) Schematic view of AlGaN/GaN HEMT. The dotted rectangle corresponds to the measurement area by micro-Raman spectroscopy. Temperature maps of (b) an HEMT on sapphire (before release) at a power dissipation of 0.68 W and (c) another HEMT transferred to a Cu plate at a power dissipation of 1.54 W. The white regions in each map represent the source, gate, and drain electrodes from left to right.

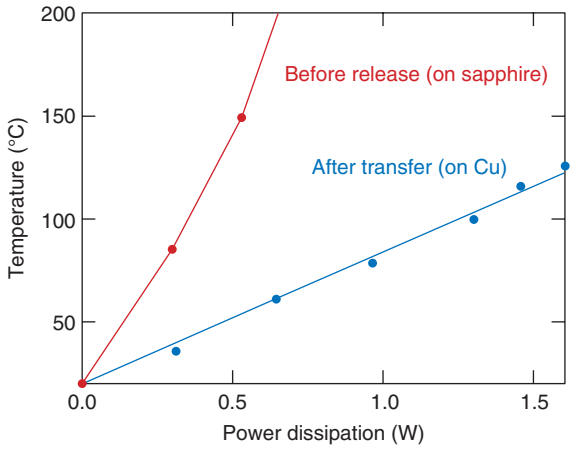


Fig. 6. Temperature at the gate edge on drain side as a function of power dissipation in HEMTs before release and after transfer.

4. Conclusion

We transferred AlGaN/GaN HEMTs from a sapphire substrate to a copper plate using the ELO technique with an h-BN release layer. The negative slope of I_d caused by the self-heating effect was reduced after the transfer. We also observed the temperatures in the active HEMTs using micro-Raman spectroscopy and found that the temperature rise was suppressed after the transfer to the copper plate. The temperature at P = 1.54 W was 110°C for the HEMT after transfer, whereas it exceeded 200°C at P = 0.68

W before the release. These results indicate that the transfer technique is effective for enhancing the heat dissipation in GaN-based devices.

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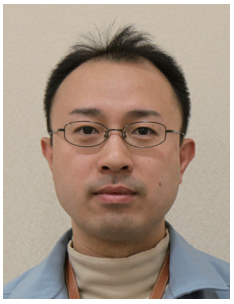

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Path Accommodation Design Engine for Simply and Reliably Designing Multi-layer Transport Networks

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Abstract

Core and metro transport networks continue to be simplified with the adoption of 100-Gbit/s packet transport systems. In line with this, the engineering work involved in path accommodation design and management is being carried out as a smooth flow, which is referred to as creating a flow-through operation. This article describes a multi-layer transport path accommodation design engine that takes into account the reliability demanded by each service in order to accommodate optical and multi-granular electrical paths from a few megabits per second to 100 Gbit/s.

Keywords: PTS, optical path, multi-layer, accommodation design

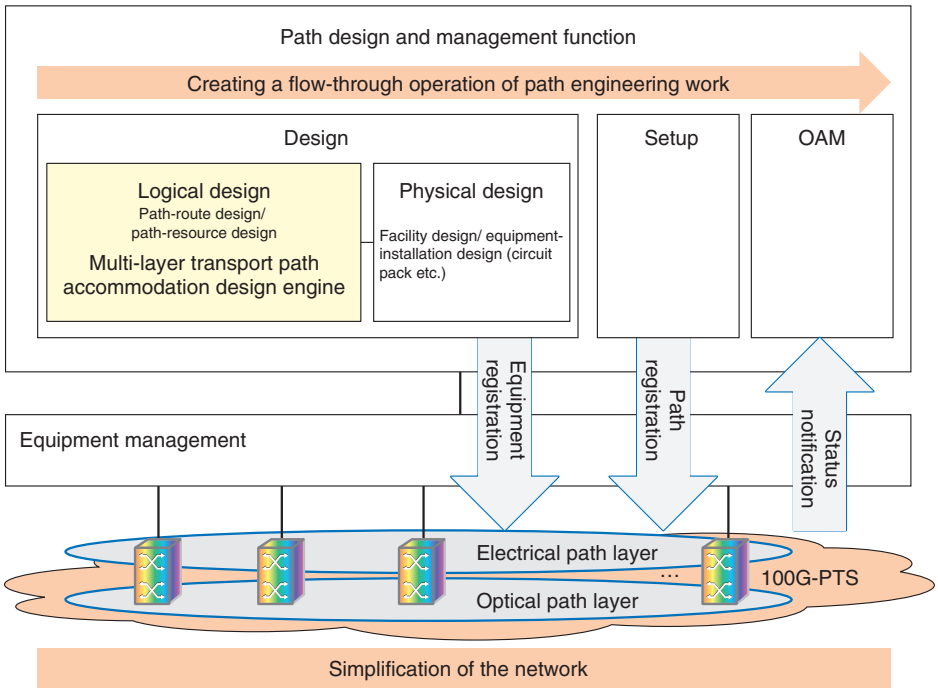
1. Introduction

To flexibly keep up with future increases in communication traffic, core and metro networks are evolving into multi-layers integrating optical and electrical paths on the 100-Gbit/s packet transport system (100G-PTS) [1]. Furthermore, to simplify networks while improving their quality, reliability, and interoperability, it is necessary not only to design networks in such a way that the closed paths in each layer of the optical-path or electrical-path layers are accommodated—which we refer to as *accommodation design*—but also to achieve a way to select routes that takes into consideration both path layers, the assignment of resources (i.e., wavelength and bandwidth used for paths), and the accommodation design of the optimal paths for each service on the basis of various conditions such as redundancy and reliability of routes.

2. Multi-layer transport path accommodation design engine

The multi-layer transport path accommodation design engine (hereinafter, *design engine*) was developed by NTT Network Innovation Laboratories and is positioned as part of a logical design function block, as shown in **Fig. 1**. An overview of the design engine is shown in **Fig. 2**. The assignment of wavelength or bandwidth and the route of optical or electrical paths are automatically designed in consideration of source and destination nodes as well as various design conditions, and the results are returned to the operator.

In developing the design engine, we assumed a usage scenario in which an operator handles the accommodation design of paths. The following suppositions were made regarding application scenarios involving automatic design: (i) routes and resources should be designed as a whole; (ii) routes should be designed by operators themselves, but resources should be designed automatically; (iii) routes and



OAM: operations, administration and management

Fig. 1. Image of application of the multi-layer transport path accommodation design engine.

resources should be designed by operators themselves, but delay times and other elements should be calculated; and (iv) not only optimal design results (best matched to the design conditions) but also quasi-optimal design results (approximately matched to the design conditions) should be looked at and judged in an integrated manner. Moreover, we considered requirements such as providing designs applicable to specific design policies for each service, future expandability such as the addition of equipment and equipment vendors, and easy of embedding in network operation systems.

The design engine has the following features: (1) functional partitioning based on the usage scenario; (2) multiple candidate routes in accordance with the design policy; (3) flexibility and expandability thanks to a configuration file that sets various design conditions and software startup parameters when adding other network elements and network equipment vendors; and (4) easy implementation of embedded equipment in network operation systems. These four features are first described here in terms of the entire design engine, and the primary functions and key features of the design engine are then explained.

2.1 Functional partitioning based on usage scenario

The design engine is composed of three function blocks configured in accordance with the above-described design scenarios concerning the operator as shown in Fig. 2: a route-design function block (for calculating candidate routes from a source node to a destination node); a resource-design function block (for assigning wavelengths to optical paths and assigning bandwidth to electrical paths); and an optimal route-selection function block (for selecting routes and ranking them according to evaluation priorities).

2.2 Multiple candidate routes in accordance with design policy

When a source node and a destination node are input, the design engine calculates optimal candidate routes and multiple quasi-optimal candidates. The multiple candidate routes are prioritized in accordance with a priority order set by means of the configuration file, ordered as optimal candidate routes and quasi-optimal candidate routes, and output as response results. This ordering of multiple candidates can be imagined as displaying multiple candidates

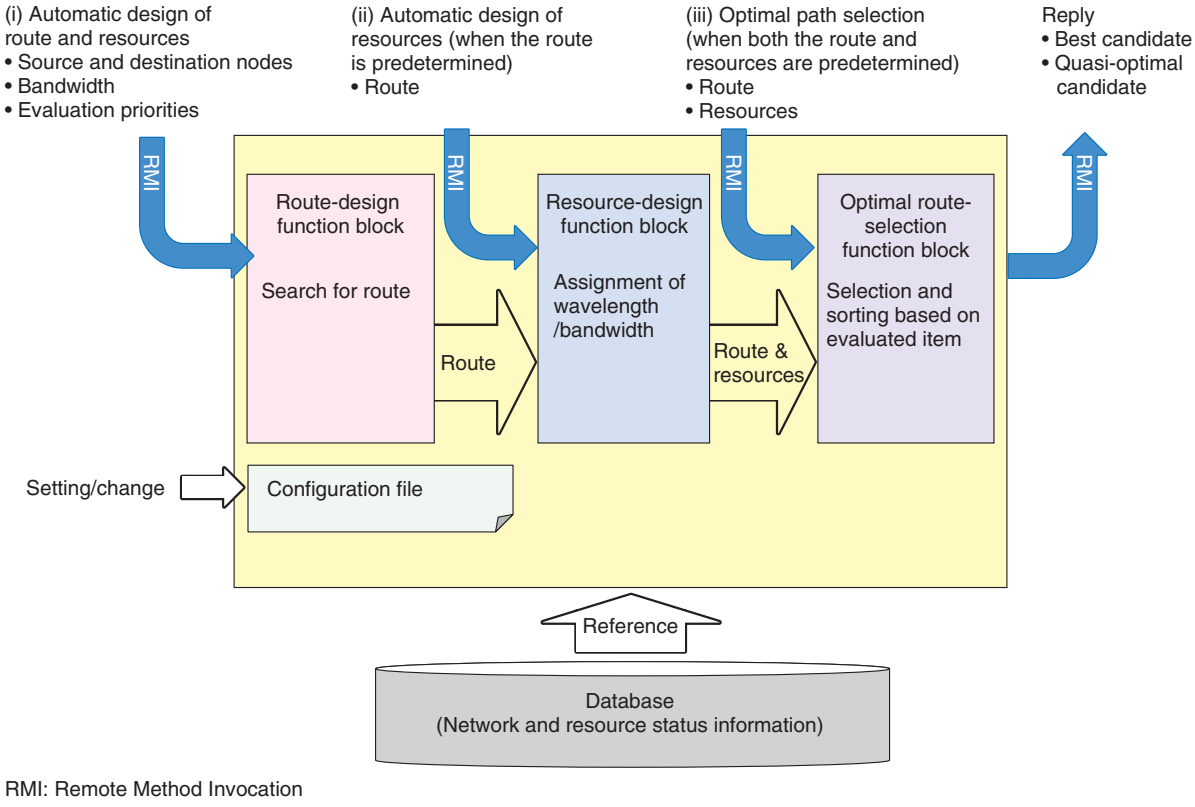


Fig. 2. Overview of multi-layer transport path accommodation design engine.

(e.g., trains) via a transfer-information app on smartphones in accordance with a display priority set by the user in terms of elapsed time, transport charge, and number of transfers. One usage scenario is that the operator can not only select optimal candidates; the operator has the freedom to select from multiple candidates including quasi-optimal ones whenever they please.

2.3 Flexibility and expandability by a configuration file

If the types of equipment and the equipment vendors are different, the values of parameters used for bandwidth calculations and design conditions may differ. Moreover, the design conditions may change when the equipment is modified. As for the design engine, flexibility and expandability are achieved by responding to changes in the design conditions and parameters by using the configuration file. Utilizing the path-route-design function block makes it possible to flexibly change design conditions such as the upper limit of delay times of end-to-end services and the upper limit of the number of nodes passed through. Moreover, it is possible to parameterize the evaluation priority used for ordering optimal candidates by the optimal route-selection function block using configuration files. For example, it is possible to set the order of priority such as delay times of end-to-end services and the number of nodes passed through as an evaluation priority. Setting the weighting of evaluation priority in this manner makes it possible to output optimal candidate paths in response to services and usage purpose.

2.4 Built-in easy implementation in network operation system

The design engine is implemented on the basis of a network model, path model, and object model specified in international standard TMF513 [2]. Furthermore, it adopts RMI (Remote Method Invocation)—an API (application programming interface) generally used with Java—as an interface, and it can be easily implemented by embedding it in the network operation system.

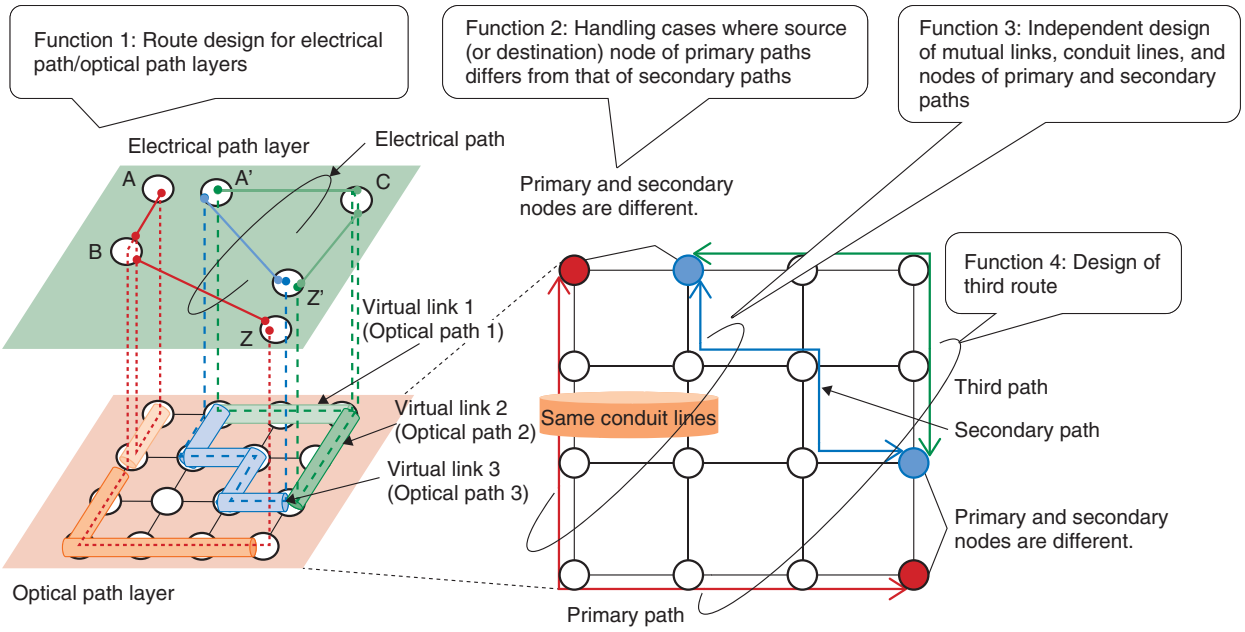


Fig. 3. Path-route-design function.

3. Path-route-design function block

The path-route-design function block provides integrated path designs in accordance with a variety of path-route-design conditions and the state of physical, optical, and electrical layers. To put that concretely, it makes it possible to select routes on the basis of design conditions such as the building that the system will be accommodated in, the number of nodes, links, and conduit lines for the physical layer, the delay time of paths in path layers, and the delay-time difference between paths of the currently used system and the backup system. The path-route-design function block has four primary functions, which are described below and shown in **Fig. 3**.

3.1 Batch design for multi-layer paths

With multi-layers (which mediate both optical paths and electrical paths) as targets, paths are designed in batches. For this batch design, first, optical paths that can accommodate electrical paths are searched for. An optical path is deemed to be a virtual link in the electrical-path layer; a virtual link that can accommodate the bandwidth number of the electrical path is searched for, and candidate routes are selected in order of the fewest number of virtual links passed through. As for the path accommodation design for nodes A' to Z' in Fig. 3, candidate routes are selected in order of paths via virtual link 3 and paths via virtual links 1 and 2. In contrast to the previously described example, in cases where there are no optical paths that can accommodate electrical paths, it is possible to design multi-layers as a whole by designing an optical path afresh and designing an electrical path on the virtual links. In addition, the assignment of a wavelength for the optical path at that time is executed by calling the resource-design function block (described below). This function makes it possible to independently design routes in the respective layers for optical and electrical paths.

3.2 Design when source (destination) nodes of primary and secondary paths differ

Path routes can be designed even if the paths do not have the same source or destination node for a redundancy path, which consists of primary and backup paths. In this way, the case in which the currently used system and backup system of the client equipment are installed at physically separate locations (or when equipment at the same location is installed separately) can also be handled as a redundant configuration.

3.3 Independent designs for nodes, links, and conduit lines of primary and secondary paths

It is possible to design routes that avoid duplication

of transit nodes and transit links of the primary path and the secondary path. It is also possible to design routes that avoid duplication of conduit lines that contain the respective transit links of the primary path and the secondary path.

3.4 Design of third path for primary and secondary paths

Reliable design that can handle changes in network configuration due to factors such as major disasters and fluctuations in the set number of nodes is possible. For example, when the existing primary or secondary path is disrupted, route design involving a third path [1] to rebuild a redundant configuration is implemented in order to avoid the disrupted points.

4. Resource-design function block

The resource-design function block provides wavelength and bandwidth for the routes calculated by the path-route-design function block or the routes set by the operator in advance. In the design of resources for assigning wavelengths to optical paths, a wavelength-continuity constraint is imposed on the links routed; that is, the same wavelength must be used between source and destination nodes. The concept of optical paths was advocated by NTT research & development laboratories in 1992; therefore, an algorithm for carrying out path accommodation design to allocate optical-path routes and wavelengths was proposed [3].

An algorithm called least fragmentation (LF) [4], which was devised by NTT Network Innovation Laboratories, is implemented in the resource-design function block. When multiple candidate wavelengths can be assigned to candidate routes, the LF algorithm selects a single wave number that minimizes fragmentation (i.e., a state in which wavelengths utilized for certain routes are fragmented) while considering the wavelength-utilization status of adjacent links on the candidate path routes. To put that more concretely, the wavelength-utilization status of links is expressed as two values: “0” (false) for unused and “1” (true) for used. The value of an exclusive OR (XOR) between adjacent links is taken as a linear measure, and the wave number that minimizes that XOR value is selected as the wavelength to be assigned. In this manner, the wavelength allocated to candidate routes is calculated in a short time—even in the case of a large-scale network—by a simple logic operation including the candidate path route and the wavelength-utilization status of adjacent links on that path.

As a conventional wavelength-assignment algorithm, the first fit (FF) algorithm (**Fig. 4**) for assigning wavelength in ascending order of wave number does not account for the wavelength-utilization status of adjacent links on the candidate route. Accordingly, to accommodate a new path request in the network (i.e., source node PTS-A and destination node PTS-C in Fig. 4), it is necessary to add links between nodes, for example, between nodes PTS-A and PTS-B in Fig. 4. In contrast, with the LF algorithm, the wavelength is selected so that the same wavelength can be assigned to maintain continuity for as many links as possible; consequently, new requests for paths can be accommodated in the network without having to add links in response to those requests, as shown in the example in Fig. 4.

In addition to the LF and FF algorithms, a random algorithm (which randomly selects allocable wavelengths) can be used. The results of a comparative evaluation of the three algorithms—on the basis of the number of paths that can be accommodated in relation to network configuration (i.e., scale)—are shown in **Fig. 5**. Over the entire network scale range, the number of paths that can be accommodated is largest when the LF algorithm is used. It can thus be concluded that the LF algorithm can effectively utilize network resources to the maximize extent possible.

5. Conclusion

We developed a multi-layer transport path accommodation design engine that achieves optimal path design and satisfies the required conditions for various services. From here on, we will continue to research and develop technologies for optical-path accommodation design while aiming to create core and metro networks for economically providing a multitude of broadband services.

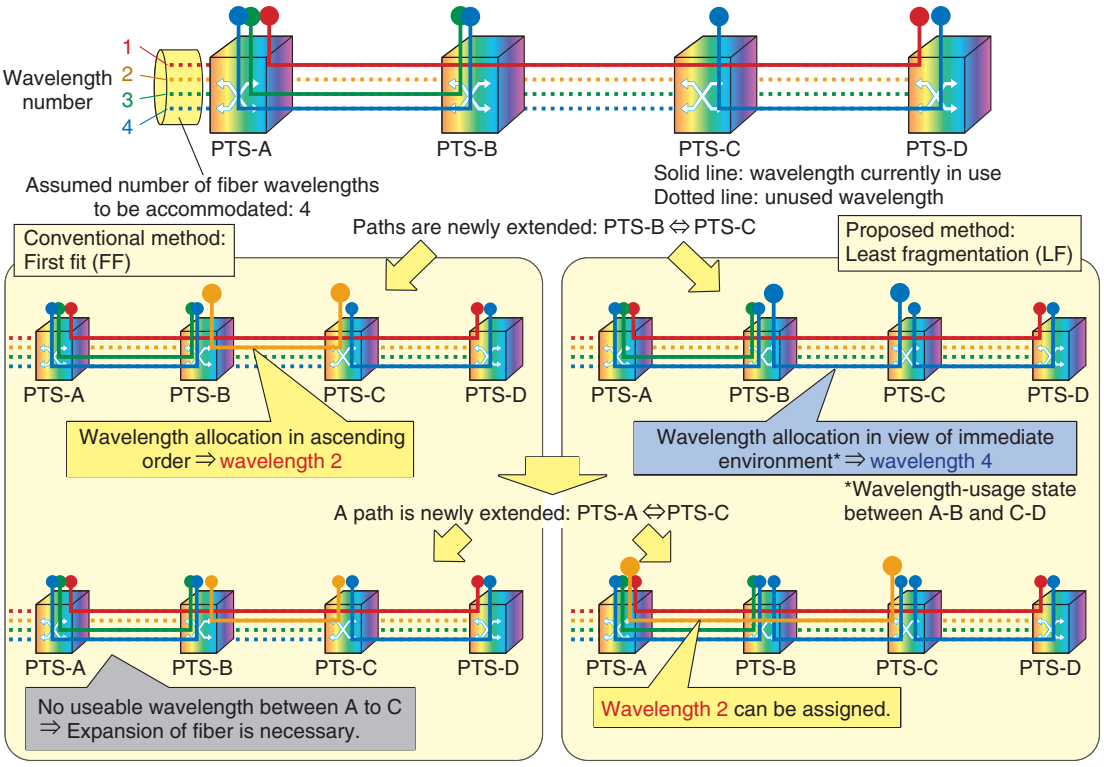
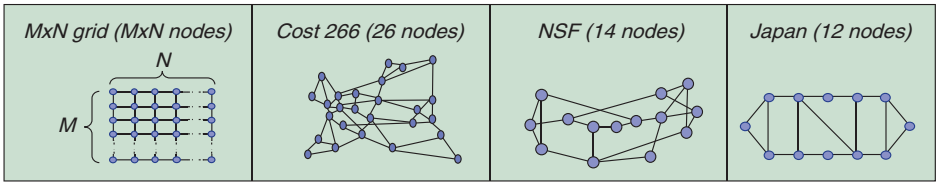
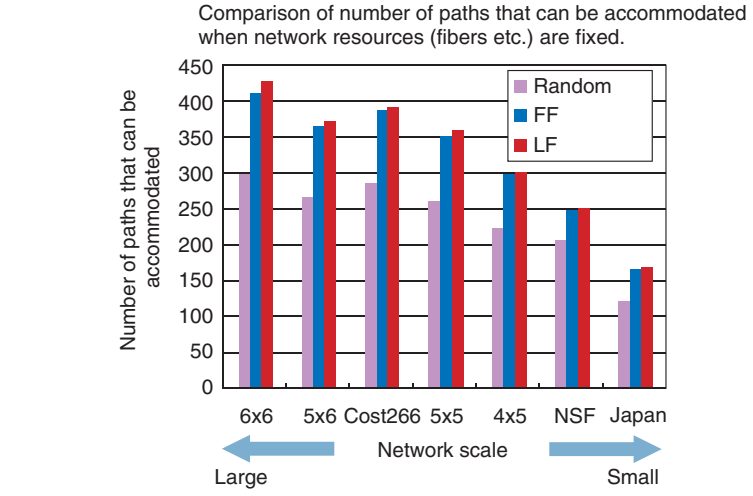


Fig. 4. Improved accommodation efficiency by LF algorithm.





NSF: National Science Foundation

Fig. 5. Quantitative evaluation of LF algorithm.

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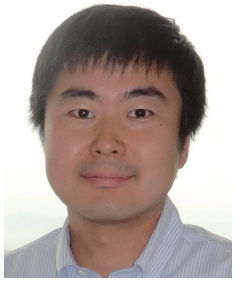

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Trajectory of ITU-T Standardization and Key Issues at the ITU-T CJK CTO Meeting

Masakatsu Fujiwara

Abstract

The ITU-T (International Telecommunication Union - Telecommunication Standardization Sector) CTO (chief technology officer) meeting for the CJK (China, Japan, and Korea) region was held in Seoul, Korea, on March 21, 2016. This article presents the main subjects of discussion at the meeting, namely, 5G (fifth-generation mobile communications system), IoT (Internet of Things), video, and other areas.

Keywords: ITU-T, IoT, 5G

1. Introduction

The International Telecommunication Union (ITU) Telecommunication Standardization Bureau (TSB) Director CJK (China, Japan, and Korea) CTO (chief technology officer) Consultation Meeting (hereinafter, "CJK CTO Meeting") serves as a consultative forum to the ITU's TSB Director. The participants of the meeting are tasked with applying feedback from the telecommunications industry to the ITU Telecommunication Standardization Sector (ITU-T)'s standardization activities. The meeting hosts CTOs and other representatives of major private sector firms from China, Japan, and Korea and fosters debate and discussion on relevant topics.

Discussions were held on expectations for future initiatives by ITU-T, predominantly centering on the fifth-generation mobile communications system (5G) and the Internet of Things (IoT), the key technological sectors the ITU-T intends to focus on, and the means of implementing such initiatives. A communiqué was prepared as a collection of proposals made to ITU-T. The following sections summarize the future standardization issues, which are all areas of great interest to the industry participants of the CJK CTO Meeting.

The CTO Meeting was established in 2008 by Resolution 68 of the World Telecommunication Standardization Assembly (WTSA), with the TSB Director assigned hosting and operations tasks. The meeting has been held annually since 2008. The CJK CTO Meeting, limited to the three CJK countries, was first launched by the current TSB Director Chae-sub Lee in April 2015. On the basis of the number of ITU-T personnel and articles contributed, the CJK region currently represents the majority at ITU-T.

The March 2016 CJK CTO Meeting was the second session of the event, following the first session in April of last year. The meeting is intended to increase cooperation around standardization among the three countries. At the meeting, CJK representatives exchanged opinions on future issues concerning standardization. These opportunities for collegial interaction are also beneficial from the standpoint of crafting better standardization strategies. For this meeting, the roster was largely made up of representatives of the private sector firms listed in **Table 1**, Director Chae-sub Lee of the TSB, and other members (**Photo 1**).

2. Thrust of meeting

This meeting explored four core subjects: networks in support of 5G, IoT and its applications, the future of video, and WTSA-16.

Table 1. Participating organizations at CJK CTO Meeting.

China	Alibaba Group
	FiberHome Technologies Group
	Huawei Technologies Co., Ltd.
	ZTE Corporation
Japan	Fujitsu Limited
	KDDI Corporation
	NEC Corporation
	National Institute of Information and Communications Technology
	NTT
	NTT DOCOMO
Korea	Electronics and Telecommunications Research Institute
	KT Corporation
	LG Uplus Corporation
	Samsung Electronics Co., Ltd.
	SK Telecom Co., Ltd.

Photo 1. Meeting participants.

2.1 Networks in support of 5G

The participants expressed their gratitude for the efforts of FG IMT-2020, a Focus Group (FG) established in May 2015 to discuss the issues of the IMT (International Mobile Telecommunications)-2020 system (5G). CJK members confirmed their intention to actively contribute to the activities of this group. The participants agreed that future key technical issues for networks supporting 5G include: 1) end-to-end network management, 2) network architecture and fixed-mobile convergence, 3) network softwarization and network slicing, including for fronthaul and backhaul, and 4) information-centric networking. In terms of the next steps for 5G standardization, the meeting called for collaboration with other standards-developing organizations (SDOs)

such as 3GPP (3rd Generation Partnership Project) so as to avoid duplication of efforts, and emphasized the importance of partnering with open-source organizations.

2.2 IoT and its applications

In addition to praising the 2015 establishment of the new Study Group (SG), SG20, the participants were in agreement about SG20's responsibility—pursuant to its enactment of international standards on IoT—to promote the growth of related technologies, including machine-to-machine (M2M) telecommunications and ubiquitous sensor networks, and to foster a climate in which stakeholders can collaborate to develop new technologies. The meeting also underscored the importance of improving collaboration and harmonization between SGs and other SDOs in order to prevent overlaps in issues such as oneM2M and other standards being explored by other groups.

2.3 The future of video

Given the rapid increase in the proportion of video data in network traffic and the forecast that this traffic will continue to increase markedly, the participants agreed that achieving image quality, stability, and availability is crucial to future networks. In addition, the participants agreed that with the presumed appearance of new video formats, among them real-time and immersive super realistic video, there is a growing need for networks to properly scale and handle these types of content, and a new host of key issues surrounding these technologies, such as the optimization of bandwidth consumption.

2.4 WTSA-16

It was announced that the WTSA-16 assembly will take place in Yasmine Hammamet, Tunisia, from October 25 to November 3, 2016. It was also announced that prior to the assembly, the CxO meeting would be held on October 23, and CTO participants were asked to attend. Because WTSA-16 will involve a rethinking of the structure of SGs and the selection of chairs and vice-chairs, as well as debate around methodologies used at ITU-T, the CJK CTO Meeting called for a contribution of articles regarding the proposals made by CTO members.

3. Future outlook

The first session of the CJK CTO Meeting in 2015 reported in its communiqué a plan to take greater steps towards involvement with the advance of IoT; evidence of this fact was seen in the formation immediately thereafter of SG20, a new Study Group focusing on the standardization of IoT protocols. This suggests that the TSB intends to emphasize the outcome of the meeting, and the communiqué would further indicate that this is an area of active interest for ITU-T. Details have been published on ITU-T's website and can be read by interested parties [1].

Reference

[1] TSB Director CJK CTO Consultation Meeting Communiqué, Mar. 2016.
http://www.itu.int/en/ITU-T/tsbdir/cto/Documents/160321/Final_communique.pdf

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Recent Case Study of Fault in IP Phone User System

Abstract

This article describes a problem a customer was having with disconnects in inter-office calling using IP-VPN (Internet protocol virtual private network) services and how we rectified it. This is the thirty-sixth article in a series on telecommunication technologies. This month's contribution is from the Network Interface Engineering Group, Technical Assistance and Support Center, Maintenance and Service Operations Department, Network Business Headquarters, NTT EAST.

Keywords: IP phone, IP-VPN, VoIP-GW

1. Introduction

With the spread of FLET'S HIKARI NEXT and other Internet protocol (IP) access services, individual customers of voice calling services have been increasingly shifting to IP phone services from conventional calling services such as *subscriber telephone* (analog line) and *INS-Net 64* (ISDN: integrated services digital network) services. Corporate customers have also been shifting to user systems that perform outside calling using IP phone services and inter-office extension calling using IP-VPN (virtual private network) services with the aim of reducing communication costs.

In this article, we introduce a case study involving occasional disconnects in inter-office calling using IP-VPN services; extension calling using the IP network.

2. Background of problem

The customer who experienced the problem has been using an IP-VPN service to make voice calls between the head office and branch offices by private branch exchange (PBX)-based IP extension calling. When both the voice-over-IP gateway (VoIP-GW) and PBX installed in the head office and branch offices were upgraded, a problem would occasionally occur in which an IP extension incoming call would disconnect on being answered, thereby terminating the call (**Fig. 1**). This event was not restricted to specific offices—it would occur at any office that used IP extension calling. Replacing the entire VoIP-GW or PBX package substrates did not solve the problem, so the Technical Assistance and Support Center was consulted to troubleshoot the problem.

3. On-site troubleshooting

Packet capture equipment was installed in the IP interval on the head-office side that had been experiencing a high frequency of disconnections in order to examine the conditions under which the event occurred. This equipment was used to collect and analyze IP packet traffic and PBX logs at the time of the event occurrence (**Fig. 2**).

The following results were obtained from this analysis. (1) Packet capture data revealed that the head-office VoIP-GW on the call-terminating side transmitted a BYE disconnect signal to the call-originating side (**Fig. 3**). (2) A *putt-putt* sound was output from the head-office VoIP-GW at the time of the disconnect, coinciding with the regeneration of voice data as indicated in packet capture data. (3) A survey of PBX logs over a period of about one month revealed that a disconnection (incomplete call) occurring within two seconds of answering an incoming call occurred 65 times on multiple phone sets. It was therefore concluded that the event was not caused by a defect in a phone set or by the intentional termination

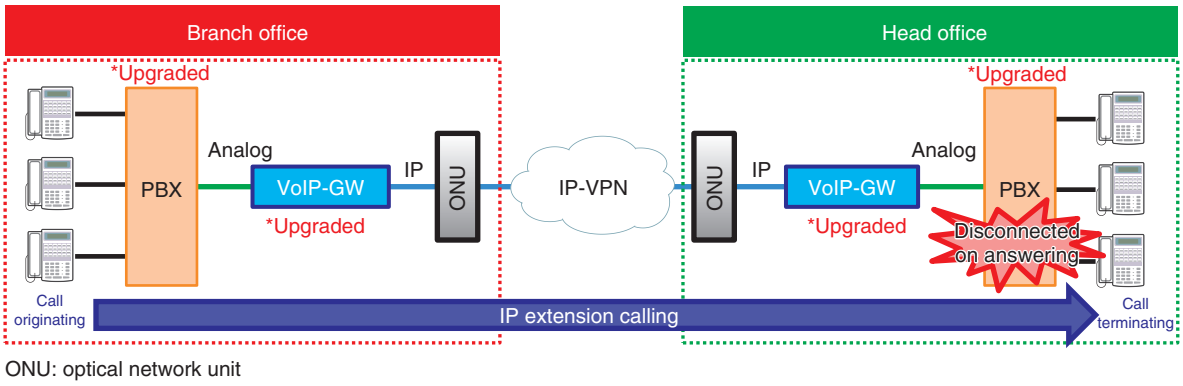

Fig. 1. Example of event occurrence.

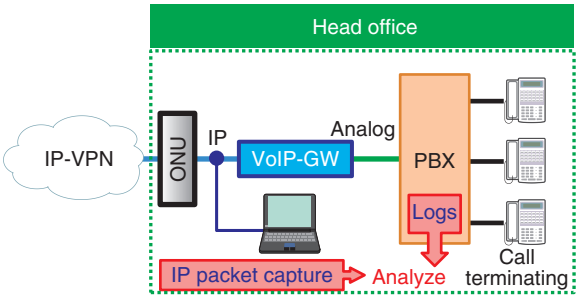

Fig. 2. On-site troubleshooting layout.

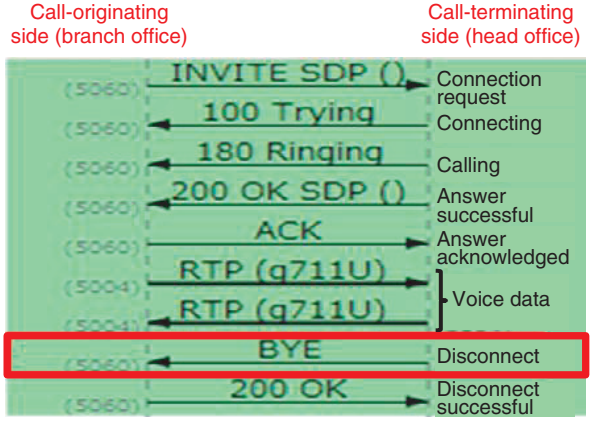

Fig. 3. Call control sequence at time of event.

of calls.

The above results suggested that the cause of this problem lie in either the VoIP-GW or PBX in the head office where the IP extension call terminated. With this in mind, the Technical Assistance and Support Center constructed a pseudo-environment of customer facilities to carry out more detailed testing.

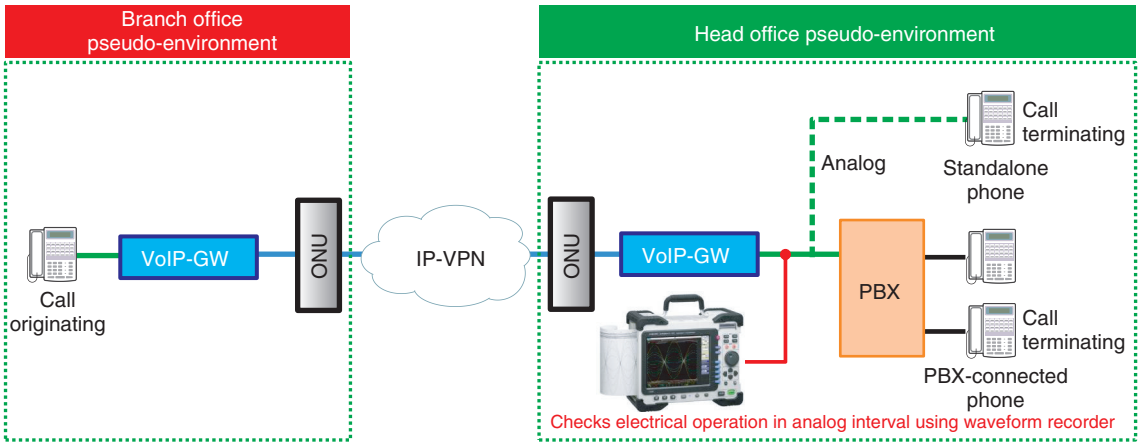

Fig. 4. Schematic of reproducibility test.

4. Reproducibility testing

To find the cause of this event, the Technical Assistance and Support Center conducted a reproducibility test by preparing VoIP-GW and PBX equipment and IP-VPN services as used by the customer and constructing an environment that emulated the system environment in which the event was occurring. Furthermore, to troubleshoot both the VoIP-GW and PBX at the event occurrence, a standalone phone set was prepared to check whether there were any differences between the call-terminating operation when connecting the standalone phone to the VoIP-GW and the call-terminating operation when connecting the PBX to the VoIP-GW. It was also decided to check for any changes in electrical operation in the analog interval below the VoIP-GW using a waveform recorder and to check the electrical operation between the VoIP-GW and terminals connected below the VoIP-GW when terminating a call (**Fig. 4**).

5. Results of reproducibility testing

(1) A reproducibility test was conducted several times when directly connecting a standalone phone set to the VoIP-GW and terminating a call, and not a single disconnection event occurred.

(2) A reproducibility test was also done several times when directly connecting the PBX to the VoIP-GW and terminating a call, and in this case, a call-disconnection event occurred on multiple occasions immediately after answering the incoming call.

Consequently, in reproducibility testing using the PBX, the technicians examined the voltage waveform between the layer 1 and 2 (L1–L2) lines during normal answering of an incoming call and the voltage waveform between the L1–L2 lines when a call was disconnected immediately after answering. First, for a normal connection, the VoIP-GW transmits a calling signal to the PBX on terminating the incoming call, and the PBX-connected phone goes off-hook. At this time, the polarity between L1–L2 is depolarized, and the call progresses (**Fig. 5**).

However, at the time of the event occurrence, the L1–L2 loop state cannot be maintained after depolarization of L1–L2 polarity when the PBX-connected phone goes off-hook, and as a result, the circuit is released (disconnected), and the call is terminated (**Fig. 6**).

Additionally, on examining these waveforms in detail, it was apparent that the time from off-hook to depolarization was 50–575 ms when connecting normally, but 606–640 ms whenever the event occurred.

The above reproducibility test therefore showed that this event in which an incoming call failed to connect would occur whenever the time from off-hook to depolarization was 606–640 ms. In view of this fact, the settings related to the analog connection between the VoIP-GW and PBX were examined. It was found that the period for detecting the closing of the VoIP-GW TEL port (analog telephone port) circuit due to a terminal off-hook operation was set to 640 ms as a default value in the VoIP-GW. Meanwhile, on the PBX side, the guard time setting turned out to be 600 ms as a default value. This setting serves to prevent an unstable waveform generated at

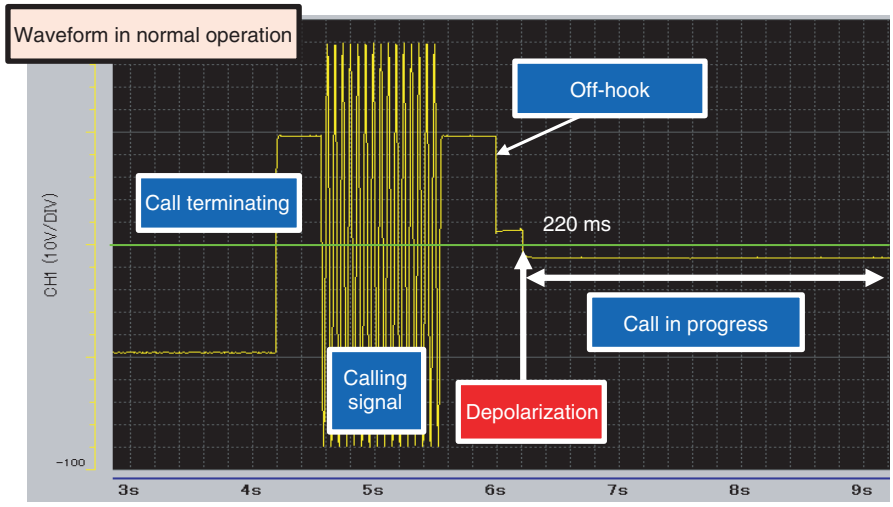

Fig. 5. Voltage between L1–L2 lines in normal connection.

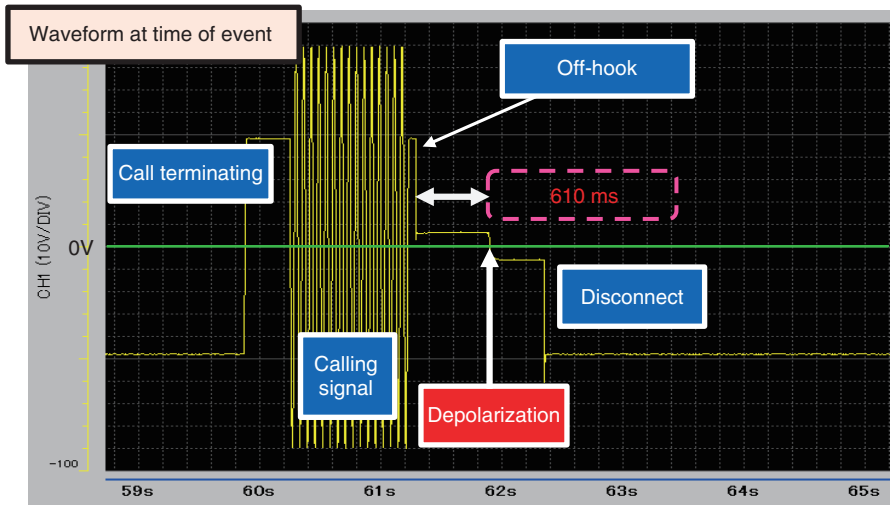

Fig. 6. Voltage between L1–L2 lines at time of event.

depolarization after the off-hook operation from being falsely recognized as an on-hook operation.

From these results, it was confirmed that changing any of the following settings in the VoIP-GW or PBX could avoid the problem of an incoming call being disconnected.

(1) In the VoIP-GW, change the default value of the period for detecting closing of the TEL port circuit from 640 ms to 560 ms.

(2) In the PBX, change the default value of the guard timer for preventing an unstable waveform from being falsely recognized as on-hook from 600 ms to 650 ms.

(3) Change the PBX on-hook signal detection method from its default value of *polarity detection or BT detection* to *BT detection* so that depolarization after the call is off-hook is not treated as if it were on-hook.

6. Countermeasure

On the basis of the results of this reproducibility test examining disconnections of incoming calls, the Technical Assistance and Support Center consulted

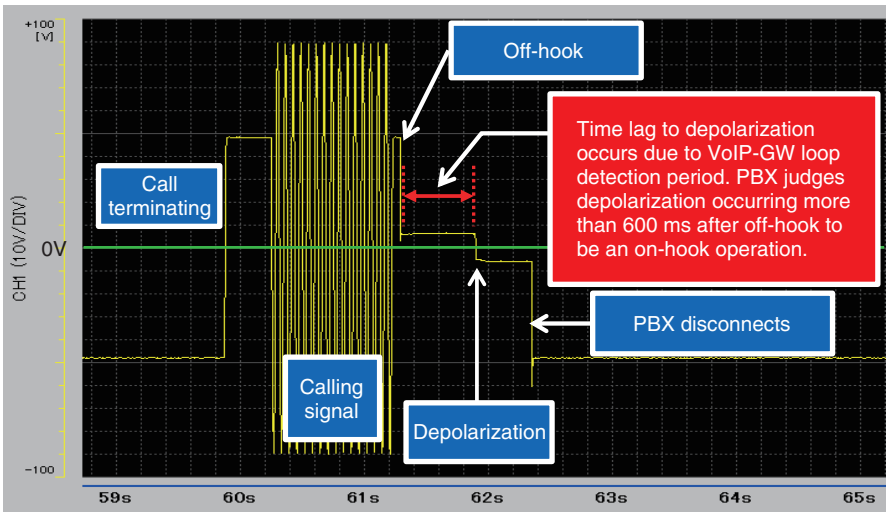

Fig. 7. Operation in customer's equipment at time of event.

with the customer and recommended that the setting for the PBX on-hook signal detection method be changed (item (3) above). This effectively eliminated the event in which an incoming IP extension call was disconnected upon answering.

7. Conclusion

The VoIP-GW used by the customer in this case study had a period of 640 ms for detecting the closing of the TEL port circuit due to a terminal off-hook operation. Thus, depending on the timing of this off-hook operation, a maximum time lag of 640 ms from VoIP-GW detection of the off-hook state to L1–L2 depolarization might occur. In the PBX, meanwhile, a time of 600–640 ms from off-hook to L1–L2 depolarization would exceed the guard timer (600 ms), which is used to prevent an unstable waveform at the time of depolarization from being falsely recognized as an on-hook operation. In such a case, it appears that the PBX would erroneously judge that an on-hook operation had occurred and would disconnect the circuit as a result (**Fig. 7**).

In this case study, the combination of specific VoIP-GW and PBX models resulted in the disconnection of incoming calls immediately after answering.

When equipment is selected for constructing a new user system or upgrading an existing one, it is important that system operation be checked beforehand as much as possible based on the customer's usage format. However, if a problem occurs that cannot be rectified by a straightforward measure such as replacing equipment, a technique that measures waveforms and signals to isolate the source of the problem can provide a shortcut to a solution.

External Awards

The 63rd JSAP Spring Meeting 2016, Poster Award
Winner: Masaaki Ono, Hideaki Taniyama, Masato Tsunekawa, Eiichi Kuramochi, Kengo Nozaki, and Masaya Notomi, NTT Basic Research Laboratories
Date: April 1, 2016
Organization: The Japan Society of Applied Physics (JSAP)

For "Demonstration of Efficient Mode Conversion to Slot Waveguides with λ^2/2000 Cross-sectional Area."
Published as: M. Ono, H. Taniyama, M. Tsunekawa, E. Kuramochi, K. Nozaki, and M. Notomi, " Demonstration of Efficient Mode Conversion to Slot Waveguides with λ^2/2000 Cross-sectional Area," The 63rd JSAP Spring Meeting, 20p-P4-8, Tokyo, Japan, Mar. 2016.

ISSJ 10th Anniversary Best Paper Award
Winner: Takeshi Morita and Yunki Hong, Keio University; Shinobu Saito, NTT Software Innovation Center; Tadashi Iijima and Takahira Yamaguchi, Keio University
Date: May 14, 2016
Organization: Information Systems Society of Japan (ISSJ)

For "A Support Tool for Production Management Process Modeling Based on SCOR Ontology."
Published as: T. Morita, Y. Hong, S. Saito, T. Iijima, and T. Yamaguchi, "A Support Tool for Production Management Process Modeling Based on SCOR Ontology," JISSJ, Vol. 11, No. 1, pp.13–47, Dec. 2015.

ITU-AJ Award, Encouragement Award: ICT Field
Winner: Kenjiro Arai, NTT Network Service Systems Laboratories
Date: May 17, 2016
Organization: The ITU Association of Japan

For his contribution to standardization in 3GPP (3rd Generation Partnership Project)/TTC (Telecommunication Technology Committee) call control signaling in IMS (Internet-protocol Multimedia Subsystem).

Best Paper Award
Winner: Doohwan Lee, Hirofumi Sasaki, Hiroyuki Fukumoto, and Tadao Nakagawa, NTT Network Innovation Laboratories
Date: May 17, 2016
Organization: 2016 International Workshop on Smart Wireless Communications (SmartCom2016) organizing committee

For "Toward Realization of a New Wireless Transmission Technology: Orbital Angular Momentum (OAM) Multiplexing."
Published as: D. Lee, H. Sasaki, H. Fukumoto, and T. Nakagawa, "Toward Realization of a New Wireless Transmission Technology: Orbital Angular Momentum (OAM) Multiplexing," IEICE Tech. Rep., Vol. 116, No. 29, SR2016-16, pp. 57–58, May 2016.

Best Paper Award
Winner: Thuan Ngo, Hiroki Nishiyama, and Nei Kato, Tohoku University; Satoshi Kotabe and Hiroshi Tohjo, NTT Network Innovation Laboratories
Date: May 18, 2016
Organization: 2016 IEEE (Institute of Electrical and Electronics Engineers) 83rd Vehicular Technology Conference (VTC2016-Spring) committee

For "A Novel Graph-based Topology Control Cooperative Algorithm for Maximizing Throughput of Disaster Recovery Networks."
Published as: T. Ngo, H. Nishiyama, N. Kato, S. Kotabe, and H. Tohjo, "A Novel Graph-based Topology Control Cooperative Algorithm for Maximizing Throughput of Disaster Recovery Networks," Proc. of IEEE VTC2016-Spring, Nanjing, China, May 2016.

Best Paper Award
Winner: Hideki Kuribayashi, Tohoku University; Katsuya Suto, University of Waterloo; Hiroki Nishiyama and Nei Kato, Tohoku University; Kimihiro Mizutani, Takeru Inoue, and Osamu Akashi, NTT Network Innovation Laboratories
Date: May 25, 2016
Organization: IEEE International Conference on Communications (ICC) Best Paper Award Selection Committee

For "A Mobility-based Mode Selection Technique for Fair Spatial Dissemination of Data in Multi-channel Device-to-device Communication."
Published as: H. Kuribayashi, K. Suto, H. Nishiyama, N. Kato, K. Mizutani, T. Inoue, and O. Akashi, "A Mobility-based Mode Selection Technique for Fair Spatial Dissemination of Data in Multi-channel Device-to-device Communication," Proc. of IEEE ICC 2016, Kuala Lumpur, Malaysia, May 2016.

Best Paper Award
Winner: Thuan Ngo, Hiroki Nishiyama, and Nei Kato, Tohoku University; Satoshi Kotabe and Hiroshi Tohjo, NTT Network Innovation Laboratories
Date: May 25, 2016
Organization: IEEE International Conference on Communications (ICC) Best Paper Award Selection Committee

For "GHAR: Graph-based Hybrid Adaptive Routing for Cognitive Radio Based Disaster Response Networks."
Published as: T. Ngo, H. Nishiyama, N. Kato, S. Kotabe, and H. Tohjo, "GHAR: Graph-based Hybrid Adaptive Routing for Cognitive Radio Based Disaster Response Networks," Proc. of IEEE ICC 2016, Kuala Lumpur, Malaysia, May 2016.

Best Industry Paper Award
Winner: Ho-Jin Song, Toshihiko Kosugi, Hiroshi Hamada, Takuro Tajima, Amin El Moutaouakil, Hideaki Matsuzaki, and Makoto Yaita, NTT Device Technology Laboratories; Yoichi Kawano, Tsuyoshi Takahashi, Yasuhiro Nakasha, and Naoki Hara, Fujitsu Limited; Katsumi Fujii, Issei Watanabe, and Akifumi Kasamatsu, National Institute of Information and Communications Technology
Date: May 27, 2016
Organization: IEEE International Microwave Symposium (IMS) 2016 committee

For "Demonstration of 20-Gbps Wireless Data Transmission at 300 GHz for KIOSK Instant Data Downloading Applications with InP MMICs."
Published as: H.-J. Song, T. Kosugi, H. Hamada, T. Tajima, A. E. Moutaouakil, H. Matsuzaki, M. Yaita, Y. Kawano, T. Takahashi, Y. Nakasha, N. Hara, K. Fujii, I. Watanabe, and A. Kasamatsu, "Demonstration of 20-Gbps Wireless Data Transmission at 300 GHz for KIOSK Instant Data Downloading Applications with InP MMICs," Proc. of IMS2016, San Francisco, CA , USA, May 2016.

Best Paper Award 2015

Winner: Yasuhiro Fujiwara, NTT Software Innovation Center; Makoto Nakatsuji, NTT Service Evolution Laboratories; Hiroaki Shiokawa and Takeshi Mishima, NTT Software Innovation Center; Makoto Onizuka, Osaka University
Date: June 2, 2016
Organization: The Institute of Electronics, Information and Communication Engineers (IEICE)

For "Fast Ad-hoc Search Algorithm for Personalized PageRank."
Published as: Y. Fujiwara, M. Nakatsuji, H. Shiokawa, T. Mishima, and M. Onizuka, "Fast Ad-hoc Search Algorithm for Personalized PageRank," IEICE Trans. Inf. & Syst. (Japanese Edition), Vol. J98-D, No. 5, pp. 774–787, May 2015.

Best Paper Award 2015

Winner: Hideya So and Atsuya Ando, NTT Network Innovation Laboratories; Tomohiro Seki, Nihon University; Munenari Kawashima, NTT Intellectual Property Center; Takatoshi Sugiyama, Kogakuin University
Date: June 2, 2016
Organization: IEICE

For "Multiband Sector Antenna with the Same Beamwidth Employing Multiple Woodpile Metamaterial Reflectors."
Published as: H. So, A. Ando, T. Seki, M. Kawashima, and T. Sugiyama, "Multiband Sector Antenna with the Same Beamwidth Employing Multiple Woodpile Metamaterial Reflectors," IEICE Trans. Electron., Vol. E97-C, No. 10, pp. 976–985, Oct. 2014.

IPSJ Fellow

Winner: Katsumi Takahashi, NTT Secure Platform Laboratories
Date: June 3, 2016
Organization: Information Processing Society of Japan (IPSJ)

For his contribution to the development and diffusion of privacy protection technology for the use of personal data.

Outstanding Paper Award

Winner: Ryohei Banno, Susumu Takeuchi, Michiharu Takemoto, and Tetsuo Kawano, NTT Network Innovation Laboratories; Takashi Kambayashi, NTT-AT IPS Corporation; Masato Matsuo, Japan Patent Office
Date: June 3, 2016
Organization: IPSJ

For "Designing Overlay Networks for Handling Exhaust Data in a Distributed Topic-based Pub/Sub Architecture."
Published as: R. Banno, S. Takeuchi, M. Takemoto, T. Kawano, T. Kambayashi, and M. Matsuo, "Designing Overlay Networks for Handling Exhaust Data in a Distributed Topic-based Pub/Sub Architecture," Journal of Information Processing, Vol. 23, No. 2, pp. 105–116, Mar. 2015.

IPSJ Nagao Special Researcher Award

Winner: Yasuhiro Fujiwara, NTT Software Innovation Center
Date: June 3, 2016
Organization: IPSJ

For his pioneering research on efficient mining techniques for big data.

Best Paper Award

Winner: Akihiro Shimoda, Keisuke Ishibashi, and Shigeaki Harada, NTT Network Technology Laboratories; Kazumichi Sato, NTT Communications; Masayuki Tsujino, NTT Network Technology Laboratories; Takeru Inoue, NTT Network Innovation Laboratories; Masaki Shimura, Takanori Takebe, Kazuki Takahashi, Tatsuya Mori, and Shigeki Goto, Waseda University
Date: June 6, 2016
Organization: Technical Committee on Internet Architecture, IEICE Communications Society

For "Inferring the Number of Accesses to Internet Services Using DNS Traffic."
Published as: A. Shimoda, K. Ishibashi, S. Harada, K. Sato, M. Tsujino, T. Inoue, M. Shimura, T. Takebe, K. Takahashi, T. Mori, and S. Goto, "Inferring the Number of Accesses to Internet Services Using DNS Traffic," IEICE Tech. Rep., Vol. 115, No. 307, IA2015-63, pp. 129–134, Nov. 2015.

Best Paper Runner-Up Award

Winner: Richard Chen, Takeru Inoue, Toru Mano, Kimihiro Mizutani, Hisashi Nagata, and Osamu Akashi, NTT Network Innovation Laboratories
Date: June 6, 2016
Organization: Technical Committee on Internet Architecture, IEICE Communications Society

For "Efficient Network Policy Checking with Multi-dimensional Graph Traversal Algorithm."
Published as: R. Chen, T. Inoue, T. Mano, K. Mizutani, H. Nagata, and O. Akashi, "Efficient Network Policy Checking with Multi-dimensional Graph Traversal Algorithm," IEICE Tech. Rep., Vol. 115, No. 256, IA2015-34, pp. 25–30, Oct. 2015.

Distinguished Service Award

Winner: Toshio Norimatsu, NTT Network Service Systems Laboratories
Date: June 21, 2016
Organization: The Telecommunication Technology Committee

For his contribution to the formulation of the standardized specifications for ENUM (E.164 number mapping)/DNS (domain name system) interfaces that enable number portability.

Distinguished Service Award

Winner: Takashi Kotanigawa, NTT Network Service Systems Laboratories
Date: June 21, 2016
Organization: The Telecommunication Technology Committee

For his contribution to the standardization concerning logical interfaces between networks of carriers such as MPSL-TP (multiprotocol label switching - transport profile) and Ethernet.

Papers Published in Technical Journals and Conference Proceedings

Multi-Service Fabric – An Any-vendor SDN Architecture for Service Provider Network

T. Iwai

SDN & OpenFlow World Congress, Düsseldorf, Germany, October 2015.

Many service providers are now investigating the employment of NFV (network functions virtualization). For SDN (software-defined network), however, the scope is usually limited to applications inside their datacenter networks. NTT, who announced the "NetroSphere" concept in which we aim to make maximum use of general-purpose servers and switches for carrier networks, is now challenging to replace the high-end core and edge routers to switch clusters controlled as SDN. We named this architecture as Multi-Service Fabric (MSF) architecture and have been developing the network systems based on the architecture. This architecture targets enabling "any-vendors" to join carrier networks. The presentation covers the architecture, technologies, challenges and the use-cases of MSF.

TMS over V5/hMT+ Disrupts Tactile Direction Discrimination

T. Amemiya, B. Beck, H. Gomi, and P. Haggard

Neuroscience 2015, 156.17, Chicago, IL, USA, October 2015.

Several human imaging studies have found that visual motion area V5/human medial temporal complex (hMT+) responds to tactile motion. A multivariate pattern analysis found specific patterns of activity in V5/hMT+ corresponding to leftward and rightward tactile directions. Some studies have also reported activations in the primary somatosensory cortex (SI) and posterior parietal cortex (PPC) during tactile motion, but they have not established a causal involvement of these areas in tactile direction processing. Here, we created an ecological tactile motion stimulus by varying the direction of a single object moving across the fingertip. We disrupted activity in SI, PPC (Brodmann's areas 7/40) and V5/hMT+ using online double-pulse transcranial magnetic stimulation (TMS) while participants judged tactile motion direction. TMS over both SI and V5/hMT+, but not over PPC, reduced tactile direction discrimination. Our results demonstrate, for the first time, that V5/hMT+ plays a causal role in tactile direction processing, extending previous studies that found directionally sensitive patterns of activity in V5/hMT+. Further, our findings are consistent with a serial model of cortical tactile processing, in which processing by higher-order perceptual areas depends upon the quality of input received from the SI. By contrast, our results do not provide clear evidence that the PPC is causally involved in discriminating tactile direction. This suggests that the pathway for tactile motion processing is not routed through inferior regions of the PPC.

Optical Linear Blending of Viewing Zones Using Convolution of Iris for Smooth Motion Parallax Autostereoscopic 3D Display

T. Kawakami, M. Date, M. Sasai, and H. Takada

Journal of Display Technology, Vol. 12, No. 2, pp. 143–151, February 2016.

A new autostereoscopic three-dimensional (3D) display is proposed. The use of only a small number of projectors and optical linear blending by optical convolution of the iris produces smooth motion parallax and the same depth regardless of viewing positions and interpupillary distance by applying the visual effects of dual edge perception in a depth-fused 3D (DFD) display. This is a breakthrough in overcoming the trade-off between 3D image reality and the number of video sources.

Techniques to Reduce Driving Energy of 1-pixel Displays

H. Manabe, M. Date, H. Takada, and H. Inamura

IEEE Transactions on Industry Applications, Vol. 52, No. 3, pp. 2638–2647, May 2016.

We propose a pair of techniques to lower the energy consumed by driving 1-pixel liquid-crystal displays (LCDs). The first one employs multiple capacitors while the other divides the LCD into two to lower the drive voltage. Simulations show that large capacitance values and many capacitors reduce the energy consumed, and stacking two thin low voltage LCDs maximizes the effect by decreasing the overhead consumed by the microcontroller. Actual polymer-dispersed LCDs (PDLCDs) were tested to confirm that the techniques worked as effectively as the simulations implied. The results show that the overall energy consumption of large PDLCDs is reduced more than 70% using multiple capacitors, and the combination of the two techniques successfully reduces the driving energy even for small LCDs. While the polarity reversal of the proposed technique does incur some delay, it was confirmed by a flicker test that the technique does not degrade image quality.

Optical Diversity Transmission Using WDM Signal and Phase-conjugate Lights through Multi-core Fiber

M. Koga, M. Moroi, and H. Takara

Optics Express, Vol. 24, No. 9, pp. 9340–9352, May 2016.

This paper proposes a maximum-ratio combining (MRC) scheme for a wavelength division multiplexing (WDM) signal and phase-conjugate pair (PCP) diversity transmission to cancel nonlinear phase-shift. A transfer function approximation for nonlinear phase-shift cancellation was formulated. It shows, with the help of numerical calculation, that span-by-span chromatic dispersion compensation is more effective than the lumped equivalent at the receiver. This is confirmed in a 2-core diversity 5-channel WDM transmission experiment over 3 spans of 60-km MCF (multi-core fiber) with 25 Gbit/s-QPSK (quadrature phase-shift keying) PCP. The peak Q-value was enhanced by 3.6 dB through MRC, resulting in a superior bitrate-distance product and optical power density limit compared to twice the single-core transmission.

Progress in LPC-based Frequency-domain Audio Coder

T. Moriya, R. Sugiura, Y. Kamamoto, H. Kameoka, and N. Harada

APSIPA Transactions on Signal and Information Processing, Vol. 5, e11, May 2016.

This paper describes the progress in frequency-domain linear prediction coding (LPC)-based audio coding schemes. Although LPC was originally used only for time-domain speech coders, it has been

applied to frequency-domain coders since the late 1980s. With the progress in associated technologies, the frequency-domain LPC-based audio coding scheme has become more promising, and it has been used in speech/audio coding standards such as MPEG-D unified speech and audio coding and 3GPP (3rd Generation Partnership Project) enhanced voice services since 2010. Three of the latest investigations on the representations of LPC envelopes in frequency-domain coders are shown. These are the harmonic model, frequency-resolution warping, and the Powered All-Pole Spectral Envelope, all of which are aimed at further enhancement of the coding efficiency.

Screen Free Floating 3D Image in a Crystal Ball Using Spatially Imaged Iris and Multiview DFD (Depth Fused 3D) Technologies

M. Date, T. Kawakami, M. Sasai, and H. Takada

Proc. of SID Display Week 2016 Digest, pp. 146–149, San Francisco, CA, USA, May 2016.

A method for displaying clear floating images in a crystal ball is proposed. Its symmetric optics can provide clear and natural 360-degree images with smooth motion parallax in horizontal and vertical directions using the directional selectivity of a spatially imaged iris method and natural 3D (three-dimensional) images of a multiview DFD display.

Flexible SDN Architecture for Carrier Networks

T. Iwai

Proc. of the 4th Annual Network Virtualization & SDN Europe, Madrid, Spain, May 2016.

Beyond NFV/SDN, NetroSphere concept & technologies, flexible SDN network architecture, Multi-Service Fabric (MSF), and the technologies and use cases of MSF are proposed.

Thickness Modulation and Strain Relaxation in Strain-compensated InGaP/InGaP Multiple-quantum-well Structure Grown by Metalorganic Molecular Beam Epitaxy on GaAs (100) Substrate

M. Mitsuhara, N. Watanabe, H. Yokoyama, R. Iga, and N. Shigekawa

Journal of Crystal Growth, Vol. 449, pp. 86–91, June 2016.

We have investigated the structural features of a strain-compensated InGaP/InGaP multiple-quantum-well (MQW) structure on GaAs (100) substrate with a band-gap energy of around 1.7 eV for solar cell applications. In transmission electron microscopy images, noticeable thickness modulation was observed in the barrier layers for a sample grown at the substrate temperature of 530 °C. Meanwhile, the X-ray diffraction patterns indicated that strain relaxation predominantly occurred in the well layers. Decreasing the substrate temperature from 530 to 510 °C was effective in suppressing both the thickness modulation and strain relaxation. Additionally, increasing the growth rate of the well layer further suppressed the thickness modulation. In room-temperature photoluminescence (PL) emission spectra, the sample grown at 510 °C showed approximately 50 times higher PL peak intensity than the one grown at 530 °C.

Single-source AlGaAs Frequency Comb Transmitter for 661 Tbit/s Data Transmission in a 30-core Fiber

H. Hu, F. Da Ros, F. Ye, M. Pu, K. Ingerslev, E. P. Da Silva, Md. Nooruzzaman, Y. Amma, Y. Sasaki, T. Mizuno, Y. Miyamoto, L. Ottaviano, E. Semenova, P. Guan, D. Zibar, M. Galili, K. Yvind, L. K. Oxenløwe, and T. Morioka

Proc. of Conference on Lasers and Electro-Optics, JTh4C.1, San Jose, CA, USA, June 2016.

We demonstrate an AlGaAs-on-insulator nano-waveguide-based frequency comb with high OSNR (optical signal-to-noise ratio) enabling a single source to fully load a 9.6-km heterogeneous 30-core fiber with 661-Tbit/s data achieved by 30xcores, 80xWDM (wavelength division multiplexing), 40 Gbaud, and PDM-16QAM (polarization-division multiplexed 16-level quadrature amplitude modulation).