R&D Spirits

Understanding the Brain—Exploring the Mechanisms behind Neural Transmission

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The research of nano-bio science, a fusion of nanotechnology and bio-science, is beginning to attract attention in the world of information-communications. This field, which includes neural transmission mechanisms, is currently being researched by the Molecular and Bio-Science Research Group at NTT Basic Research Laboratories. To find out what possibilities this seemingly non-NTT-related field of research holds and how it may change the future of both NTT and society, we talked with Keiichi Torimitsu, the Group Leader of the Molecular and Bio-Science Research Group.

Searching for a biological-electronic interface for information-processing and health-care applications

—Dr. Torimitsu, could you tell us about the section that you belong to and the roles that you perform there?

Well, to begin with, research at NTT Basic Research Laboratories is centered on two main fields: quantum materials and nano-bio science [1]. The Materials Science Research Laboratory is concerned with the latter, and I am the executive manager of this laboratory. At first glance, it might appear that bio-science is not a field in line with the basic business of NTT. But the mission that we have established for ourselves is to create new materials and devices in combination with nanotechnology, which is a specialty of NTT, and to use these devices to promote technical innovation in the information-sharing society.

The Materials Science Research Laboratory is divided into three groups. These are the Thin-Film Materials Research Group, which targets materials such as gallium nitride, aluminum nitride, and diamond for high-output systems; the Low-Dimensional Nanomaterials Research Group, which researches carbon nanotubes and the formation of their circuits; and the Molecular and Bio-Science Research Group, which deals with nerve cells. These apparently disparate groups do have a common thread, and that's the research of functional materials. That is why I take a comprehensive view of their research results—I believe that these three groups, in combination, can come up with new and innovative devices and sensors. By the way, I also lead the Molecular and Bio-Science Research Group while managing these three groups in unison.

—What specific research is the Molecular and Bio-Science Research Group involved in?

We are involved with several projects in parallel. The first of these is the generation of artificial neural circuits. In this project, we experiment with the intentional growth of nerve tissue to examine the relationship between neural circuits and memory and learning functions. This research requires an understanding of neural-circuit functions, and for this reason, we are simultaneously developing tools for measuring those functions in an electrical and electrochemical manner. This is actually the work of our second project.

Next, in order to investigate the functions possessed by neural connections, or synapses, in nerve cells, we need to be able to visualize their behavior under various conditions, and we are developing an electrochemical measuring tool for this purpose. This is an 8×8 array of enzyme-treated electrodes on a substrate,

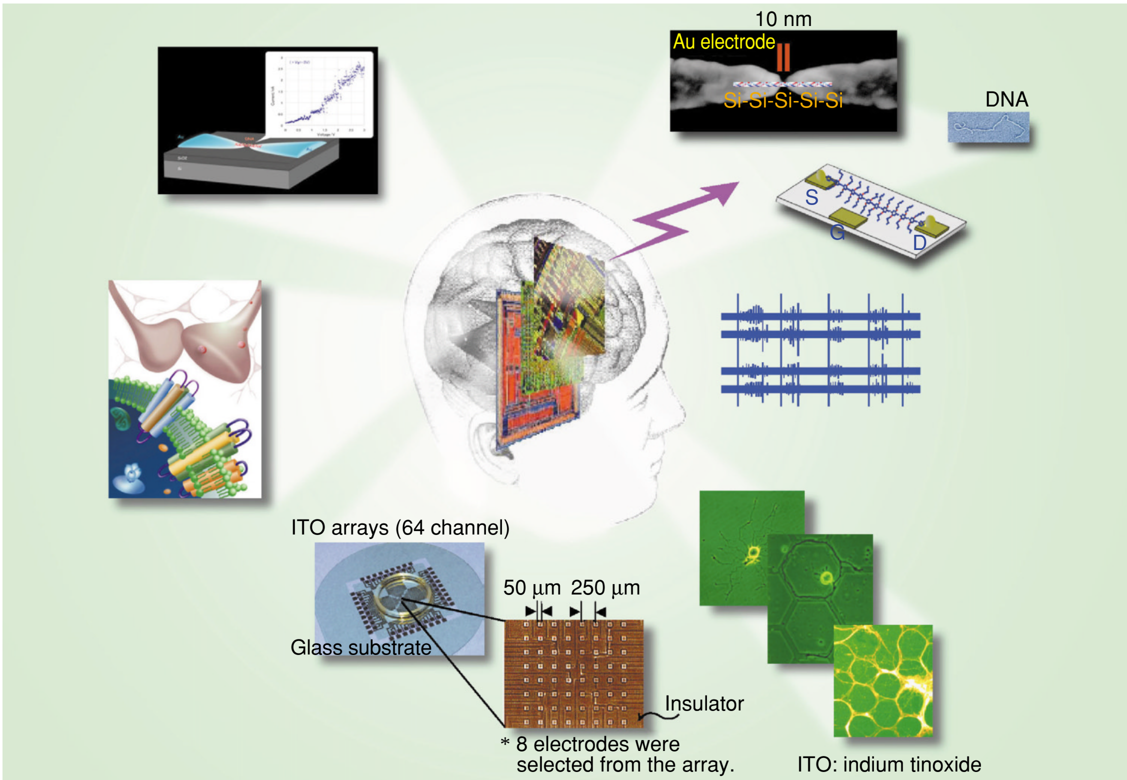

Fig. 1. Nano-bio science: towards a bio-information link through a biological-electronic interface

which we use to determine the spatial and temporal distribution of neurotransmitters released from the brain's hippocampus. With this information, we can investigate the functions and reactions of specific regions of the brain. This is the work of our third project.

Finally, our fourth project is the study of brain receptors. As you know, brain signals are transmitted through the process of converting electricity into chemical substances and back into electricity. The intermediary in this process is a receptor, but much of its function is still unexplained. In this project, we focus on the receptor protein and research its response to stimuli using an atomic force microscope.

These projects are all concerned with interaction between nerve tissue and substances. If we can explain this interaction, we may be able to explain the mechanism behind human information processing, which might then lead to a technological revolution in communications in the information-sharing society.

—In what ways might this research benefit society?

Well, if we can clarify the mechanisms underlying memory and learning in the brain, the application of that knowledge might give birth to new forms of information processing. It might even result at long last in biocomputers, which have long been the subject of much research. And it could even lead to more efficient grid computing. That being said, it is going to take some time to reach that point, at least 10 to 20 years.

But during that time, we will come to understand many things, and I think that from time to time we will be able to provide the world with various bioproducts that make use of that knowledge. The most likely target of such products is the health care field. Our research on nerve cells is actually research on biological-electronic interface technology. If we can make this technology practical, we can envision its use in health care, medical treatment, and sensing by providing a bio-information link between people and computers. We think bioproducts of this type might be attainable within ten years. Although NTT is not directly involved in the business of health care, it should be able to cultivate new business areas by developing new devices and providing health-related information-communication networks.

—What specific bioproducts are being considered?

For example, we can imagine the realtime monitoring of health-related information by attaching a very small device to the human body or embedding one in it. This could be part of a tailor-made health care system that sounds an alarm whenever an abnormal condition arises. And if this system can be further enhanced, it might prove useful in the treatment of

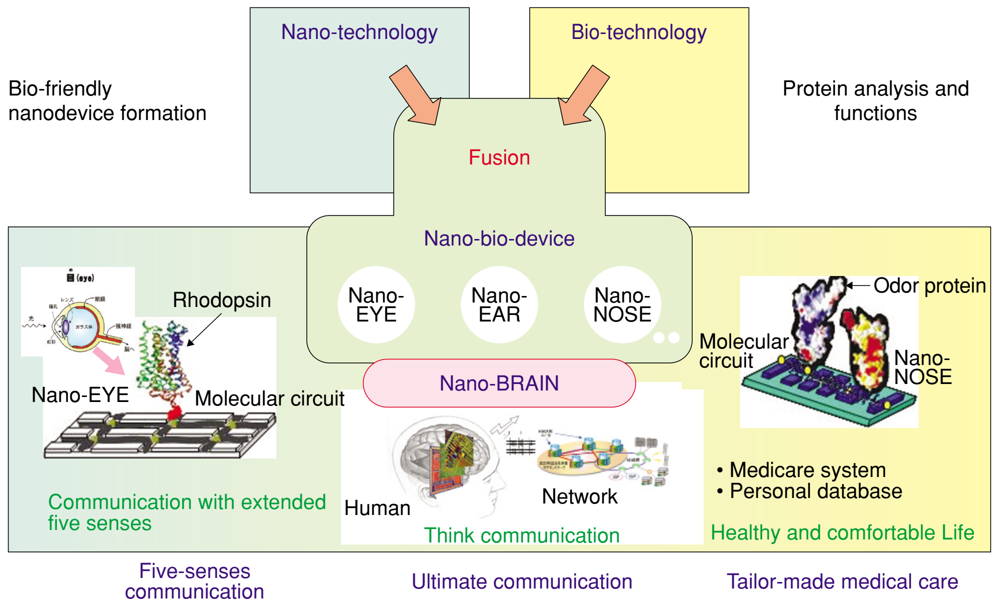

Fig. 2. Strategy of Nano-bio research.

diseases such as Parkinson's disease. A person with Parkinson's disease loses control of body movement as the secretion of a particular neurotransmitter becomes impaired. If a device were able to detect the lack of such neurotransmitter production, it could stimulate nerve cells in a specific region of the brain and promote the secretion of that chemical. This is quite possible, at least from a theoretical point of view.

Another application would be to transmit visual or aural signals directly to the brain to give visually or aurally impaired people an artificial sense of vision or hearing as a substitute or supplement. These nano devices, which we call "nano-eye" and "nano-ear," could lead to even more advanced products such as artificial communications based on the five senses and even "synchronous communications" whereby a certain image can act as a trigger for establishing a link with another party.

—What has been the most important technical accomplishment in this research?

That would be the 8 × 8 electrode substrate that I mentioned earlier. This is indeed a biological-electronic interface, but I must admit that it is not especially new. Similar tools are being developed and implemented in Germany and by other companies in Japan. But from a functional point of view, I think we are out ahead. At the experimental level, our device can record data continuously for a period of about 50 days, and in terms of simply exchanging information, it can be used for about six months. There are no other devices of this type that can be used for so long. If we can continue to decrease the size and raise the performance of this device, it should expand to various types of nano-devices in the future.

Attracting worldwide attention by superior fine-processing technology and an original approach

—Dr. Torimitsu, what are some recent trends in nano-bio science?

In research targeting nerve cells and receptors as we are doing, Oxford University in the U.K. is analyzing receptor functions at the molecular level, while the University of Basel in Switzerland is performing structural observations by atomic force microscopy and Newcastle University in the U.K. is concentrating on nerve cells from a health care perspective. There is also research in this area at universities and government-related institutions in Sweden, Canada, Australia, and other countries, but I would say that there is no organization covering as wide a research area as ours. And in the United States, the scale of research is large, but the approach taken there, if anything, is more oriented toward commercialization than fundamental research. The trend there is to create biodevices using existing technology.

—What is the position taken by NTT Laboratories in this regard?

A truly unique position. NTT, needless to say, excels in fine-processing technologies for the development of LSIs and other advanced devices. Bringing bio-science knowledge and techniques to this area as we are doing is an approach that cannot be found elsewhere. The general approach to research that includes different fields of study as in nano-bio science is to have that research performed jointly by specialized research institutions. In our case, in contrast, a single research group deals with both bio-science and nanotechnology. This is our most outstanding feature and strength.

—Are you nevertheless involved in any collaborative research with other institutions?

With the idea that two groups with complementary knowledge and strengths can go far, yes, we are involved in various joint-research projects. For example, a branch of the Institute of Medical Science of the University of Tokyo has been set up in the Materials Science Research Laboratory, and overseas, a branch of our research laboratory was set up last year at Oxford University where I have become a guest professor. We are also working with universities in Sweden. We are planning to collaborate with several other institutions in the near future.

—What has been the response so far, both from inside and outside Japan, to your research results?

We have received various acknowledgments of our work. The year before last, we received an award for a new method of measuring neural activity in relation to magnesium from the respected Gordon Research Conference in the United States. Participation in this conference is generally by invitation only, and it is considered to be a gateway to joining societies in this field. We were very glad to have been recognized in this way. We have also been interviewed by reporters from Newsweek, Time, and other magazines for special issues on nano-bio science, and researchers in the field of information processing, such as SIGGRAPH, have shown great interest in our results to date.

Aiming to contribute to information-communications and health care: the two major industries of the 21st century

—Dr. Torimitsu, could you tell us something about your academic background?

My background is actually not in the biological sciences, but rather in engineering. My university major was instrumentation engineering, and in our research laboratory, one of our measurement targets was plant physiology. That was during a time when many people warned of an imminent food crisis, and it was thought that growing larger plants using engineering techniques was worth a try. Our research in this regard focused on the relationship between the electrical properties of mung bean root and its growth, and we found that growth could be significantly promoted by applying a certain voltage. This result came to be used by a certain company in actual agricultural production. As I was just a student at the time, that in itself—the achievement of actually useful results—was very satisfying, but looking back, it might not have been such a bad idea to apply for a patent. For my doctoral thesis, by the way, I measured the chemical shift of phosphoric acid in cell vacuoles and cytoplasm in order to estimate intracellular pH using nuclear magnetic resonance. My goal here was to analyze and explain the mechanism behind the way a cell keeps its environment fixed in the face of external stress.

—What research activities have you been involved with so far?

My first job at NTT was the preparation of soil as part of bio-research. I should mention here that 1986, the year that I entered NTT, was the same year that NTT Laboratories embarked on bio-research. There was consequently almost a complete lack of know-how and facilities to support this research, and I was first sent to the University of Tokyo for one year as a form of preparation. I received my instruction there from then Assistant Professor Jun Fukuda (now professor at National Defense Medical College) under the direction of Professor Masao Ito, a world authority in brain research and now a Group Director at the RIKEN Brain Science Institute. My research theme was to control the growth of nerve cells, which is usually a random process, using semiconductor fine-processing technology. After returning to NTT, I was given the chance to undertake actual research while setting up facilities for NTT Laboratories, but this time, I was sent to the U.S. National Institutes of Health for about a year and a half starting in 1990. My research there involved the measurement of a neurotransmitter called gamma aminobutyric acid (GABA). This research, which continues to this day, relates to the development of sensors based on electrode substrates, which I talked about earlier. I can therefore say that my research activities have always centered on one major theme, namely, the control of cell growth. One part of this research has been to examine the correlation between fine-processing technology and cell growth.

—What, in particular, have you been pursuing through your research?

I have been looking for the answer to the very simple question: "How does the brain remember?" Man has created an artificial brain called the computer, which, in one sense, far exceeds the ability of the human brain, but in another, falls far short. Consider the task of recognizing a particular person, which is a form of information processing. When you encounter someone who is included in your memory, you generally need only a few tens of milliseconds or at most a few seconds to be able to recognize that person. A computer, on the other hand, requires several minutes at best. What is the source of this difference? While it is known that the human brain is vastly different from a computer, I would still like to know what kind of information processing is actually performed by the brain. My research has centered, in particular, on my desire to explain those mysterious parts of the brain involved with memory and learning.

For that matter, there is also the question of "What does it mean to be alive?" This may sound a bit childish, but when you are involved with biology, fundamental questions like this one tend to bother you quite frequently. For example, it is possible with current technology to measure the behavior of even a single cell receptor. It is also possible now to artificially prepare deoxyribonucleic acid (DNA), the source of life. These, however, are not "living things," and you sometimes wonder what is the difference between them and actual living things. I find this question very interesting.

—How would you like to see this research develop over the years to come?

To begin with, I would like to see it become truly useful for the health care and medical treatment fields. It would also be nice if it could generate new business opportunities for NTT. In this way, our research should become part of information communications and health care, the two major industries of the 21st century. But as I mentioned earlier, it's going to take at least ten years for us to reach that point. Furthermore, there is the economics-related issue of how to achieve a good balance between corporate profit and public good in terms of research results. I cannot solve all of these problems on my own, but I hope to be part of their solution as my fellow researchers increase in number.

Having a strong will: an essential attribute of researchers

—Dr. Torimitsu, what are some current issues in your research work, and what are your aspirations for the future?

One great concern of mine is how to go about making our research more widely acknowledged both inside and outside the company. Nano-bio science is a minor field at NTT, and to gain a more solid foothold, we must endeavor from time to time to explain what it's all about and convey its value. At the same time, we must make our research attractive to outside organizations and establish its position clearly.

I mentioned earlier that I undertook the research of bio-science with a background in engineering. My research today still involves both these fields. I also have many opportunities to talk with experts in medicine and chemistry. These experiences have allowed me to see how different fields come to view the same thing in different ways. For example, when discussing the same substance, an engineer may view it in terms of its electrical properties, while a bio-scientist may consider only its functional aspects. A chemist, moreover, may see only its composition or reactive properties. In short, the language used to describe the same thing can differ from person to person even if that thing is sitting right in front of their eyes. Of course, this may only be a case of different means of expression, but it can nevertheless cause an unexpected bottleneck in actual joint research. I feel a need for more researchers who can talk in more than one "language" much as I have had to do. While it would be an exaggeration to say that I am a bridge between engineering and bio-science, I sometimes think that perhaps that should be my personal mission.

—What is your ultimate goal as a researcher?

I really haven't thought much about an ultimate goal, but in terms of a long-term outlook, I would like to uncover the mechanisms behind brain activities such as recognition, memory, and learning. Perhaps I am being too naïve, but I would like to understand the foundation of brain activities that have defied explanation. Of course, I would want to produce useful bioproducts along the way, and this long-term goal is not to say that I have no interest in the business aspects of our research. As a researcher, however, I must not forget the search for scientific truth, which should anyway turn into something useful for people in the form of health care or medical treatment.

—What is it like working at NTT Laboratories?

From the perspective of my research field, I find it unique that NTT places importance on the public good despite being a private company. I believe that research undertaken not only with an eye to the market but also out of concern for the needs of people can only happen in an organization like NTT. At the same time, when our research enters the implementation stage, the key technology will be fine processing, which is quite a different field from bio-science, but is NTT's specialty. We are also blessed at NTT with excellent facilities and research funding. All in all, from the viewpoint of our group, NTT Laboratories is the closest thing to an ideal research environment. To be able to pursue research that one likes in an environment such as this one is very gratifying.

—Could you leave us with a message for young researchers?

Yes, I would love to. My experiences have told me that if you have the determination to keep moving in the direction of something that you want, there's a good chance that you will eventually get it. Having a strong will and a deep desire for something gives you the power to bring the people around you to your side. It also has the power to reveal your latent abilities. The most important thing for you as a researcher to do is to let other people know what it is you want to pursue. If you do that well, then I think you cannot help but reach your desired goal eventually even if some mishaps occur along the way. That is the kind of researcher that I myself aspire to be.

Reference

[1] K. Torimitsu, "Nano-Bio Science," NTT Technical Review, Vol. 2, No. 2, pp. 12-20, 2004.

Interviewee profile

■ Career highlights

He received the B.E., M.E., and Ph.D. degrees in instrumentation engineering from Keio University, Yokohama in 1980, 1982, and 1986, respectively. In 1986, he joined NTT Basic Research Laboratories and worked in the bio-computer project. His research interests range from neuroscience including signal transduction, neuro-imaging, and neurochemistry to surface science and molecular science. He is currently focusing on nano-bio science and nano-bio device fabrication. He studied cell physiology and developed a novel measurement system using magnetic resonance spectroscopy from 1980–1986. From 1986 to 1987, he studied neurophysiology at the Laboratory of Physiology, Faculty of Medicine, the University of Tokyo as a guest researcher. For the year 1990–1991, he was a visiting researcher at the National Institute of Health and studied GABA physiology at the Laboratory of Neurophysiology, NINDS. From 1997–1998, he was a guest researcher at National Institute for Minamata Disease. He is now a Visiting Professor in Physics at Oxford University. He received Research Awards from NTT BRL in 1993, 1998, 2003 and the Distinguished Award in 1994. He received the Poster Award at the Electrophoresis'99 and the SLOWMAG Award at the Gordon Research Conferences in 2002. He is a member of the Society for Neuroscience, International Brain Research Organization, Japan Neuroscience Society, etc.