Unraveling what it means to be alive

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Dive into BDR's intriguing research

A new scheme for science

We are going to meet Dr. Kanda, who is operating "Maholo," a robot doing experiments. Although I have seen an online stream of Maholo in action, this is my first time seeing it in person.
I wonder what kind of themes we are going to talk about today. . .

Robot running experiments

I imagined that the moving robot would be making a lot of noise, but in fact, it moves relatively quietly.

That's because the robot is culturing cells, so it needs to move slowly. The noise from the fans is also quite loud. The robot can move a lot faster as well, and when it does, it makes more noise.

How do you send commands to Maholo?

Details of the movements are already programmed within each command, so we just enter instructions like, "transfer 100 μL of liquid A to tube 2."

Its movements are a bit creepy. . .

Maholo has seven joints in its arm, which makes its movements look a bit odd. But these joints also allow it to carry out a range of motions including raising both arms over its body to do experiments on a high shelf.

It's not easy to make robots conduct experiments

What part of the implementation process to robots is difficult?

Although there are slight lot-to-lot variations of plastic products like tubes and pipette tips, these small discrepancies can be overridden by making adjustments in movements, such as pressure or angle. In fact, these types of adjustments are know-how that we have been accumulating.

To be honest, it's hard to say that "everything can be done with robots." There are in fact many other factors that need to be adjusted besides the robots. Soft, flexible items, such as cords, hoses and paper, are also still difficult for robots to handle. There is a lot of human know-how that needs to be translated to robots when we consider biological experiments.

Since we need to consider what robots can do and their limitations, we cannot transfer the exact same process that humans undertake to robots. We need to prioritize every single step in the process. During the implementation process, we need to be aware of what robots can and cannot do, as well as what can and cannot be done with IT. We also need to understand biology, such as knowing that enzymes cannot be left out in the open for a long time. We need to understand all of these things, otherwise the transfer process cannot be implemented.

Genki N. Kanda

Research scientist in the Laboratory for Retinal Regeneration. He received his Ph.D. from Osaka University. He originally joined RIKEN as a biologist, but is now working to try and figure out how humans can work with robots.

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Hideki Yakushiji

Business developer based in Kobe. He has a broad background in areas such as analytical chemistry, optics, biotechnology and IT. He is involved in a wide range of activities to assist in commercializing technologies and ideas born from academia, including setting up opportunities for idea-sharing, finding investors, and strategic planning.

So, you mean that we need a person who serves as sort of a knowledge hub—someone who knows both sides?

There is probably no single person on this planet right now who is completely knowledgeable in both robotics and molecular biology. It's impossible to find someone like that right away, so the best we can do in the present situation is to ensure that we make a team in which the members are able to clearly communicate with each other.

This is a proof-of-concept experiment

It sounds like communication technology, rather than biology.

Basically, our research here aims to figure out the best way to set up a team for implementing experimental capabilities to a robot. In other words, we are not trying to make Maholo carry out specific tasks; rather, we are carrying out research to determine what steps should be taken and what kind of team is necessary when we want to use Maholo, AI or other robots to conduct experiments.

Even though Maholo is currently capable of doing many things, we still don't know what is the most suitable way to use it in a biological lab. Addressing this challenge requires an assembly of people with different expertise such as robotics, IT and biology. We need to figure out what kind of team is needed to resolve day-to-day problems that might crop up.

It's also important to consider how to communicate with one another, since these kind of teams involve a range of people with some working remotely. Even though nobody has determined the gold standard yet, we've been introducing tools and schemes that have worked in other fields, like IT.

So, what does science mean to human beings?

The images taken with a microscope can now be automatically uploaded to a network. We have almost implemented an automated system, in which AI can analyze those images and then plan the next experiment.

Does AI determine when to start as well?

That's right. Of course, humans need to make the first decision of when to initiate an experiment. But once initiated, we don't have to do anything. If we command the robot to "start the next experiment when cells are ready," only the AI system knows when it decides the cells are "ready" to start the next experiment.

It sounds like something from a sci-fi movie. . . It makes you wonder, if AI and robots also become capable of making hypotheses, will humans be needed at all to do experiments?

It's possible that humans may no longer be needed, if such a future comes to be. AlphaGo is a good example. Originally, AlphaGo was trained to become a strong Go player based on game records of a human player versus another human player, and in the second phase, it no longer learned from games played by humans. Instead, AlphaGo learned by playing games against itself, eventually becoming much, much stronger than even the world's high-ranked professional human players.

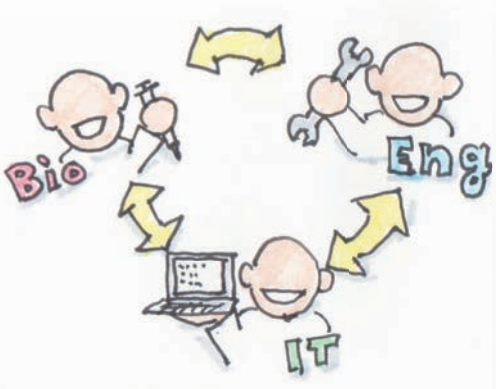
This suggests that the science being carried out by humans may actually be quite biased and we are seeing only a very narrow image of a bigger picture.

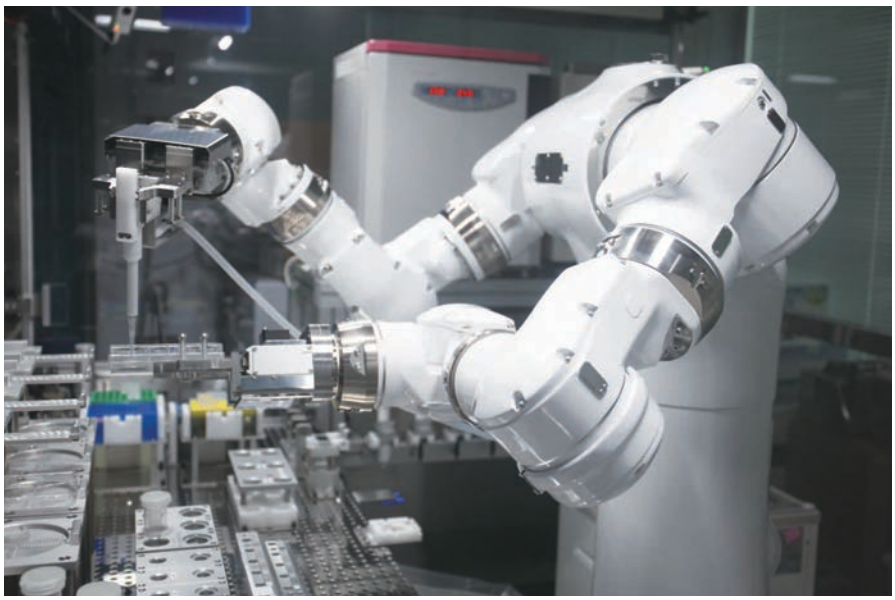
The world would be completely different then, if that becomes the case.

But, it wouldn't be limited just to research, you know.

Some might say that if there are no longer jobs in research, people can switch to listening or composing music or drawing pictures. But, it may not be as simple as that. In fact, AI systems capable of composing music and making drawings have been developed, and it's hard to recognize that the end product was created by AI.

We are now realizing that such a future is near since AI and robots have come out into the real world. We are entering a phase in which we may need to reflect on one of the most fundamental themes of being human—what it means to be human.





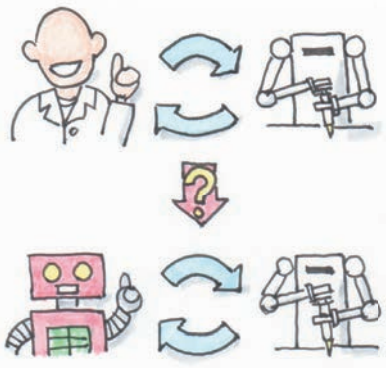
Changing the world

There has not been much sharing of information on fundamental aspects, such as what points to keep in mind when using machines to run experiments. Thus, many researchers within Japan and around the world working in automation are facing similar troubles and hurdles. There are also some robots built for a particular purpose and used by only one lab. It can be challenging working on your own. So, we have begun to organize monthly study meetings which are held alternatingly in Tokyo and Osaka as a place for people to share their own experiences and hurdles. These meetups appear to be well received as once the next meeting is announced, spaces fill up fairly quickly.

It's like a new research discipline, already. . .

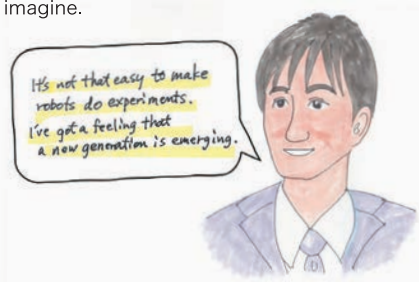
In the future, I think it would be great to have a textbook of sorts that contains the experiences of the pioneers of biological automation—what they did and how they were able to implemented it. Once there is a textbook, this will become the first source of information for beginners. At the moment, there is no textbook.

For me, working closely with people with different expertise, from biologists, hardware developers and software developers, but who all have the same goal is a lot of fun, to say the least.



It seems that a new generation with a completely different mindset will arise in the future.

Yes, I too am expecting the emergence of a new generation with a different mindset from our generation, and in fact, I feel that they are already in the process of emerging. We are in the transition phase, which is like a sort of social experiment. So, our team is trying out as many things as we can imagine.



Postscript

It was an intense discussion. Actually, all of the interviews I've done for this series have been equally intense. I went into the interview thinking that we would just be touching on robots and AI, and didn't expect to have discussions related to project management or the future. But, as these new things become reality, and not just a conception, we are forced to think about them regardless of whether we want to or not. Cars, electricity, telephones, the Internet, mobile phones, and smartphones. Coming up are AI and robots. I wonder what will be the things that only humans can do. . .

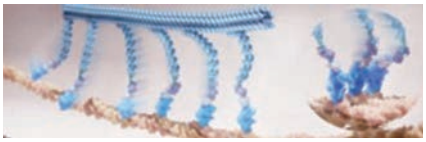
Read other interviews

01

Single motor proteins visualized in action for the first time

Muscles contract by sliding between two types of filaments—thick filaments of myosin and thin filaments of actin. But there has been a long-standing controversy about the dynamics of this molecular machine. A team led by Mitsuhiro Iwaki of the Laboratory for Cell Dynamics Research have now directly visualized the individual myosin molecules in action. Using DNA origami technology, they first created rod structures resembling thick filaments of muscle tissue to which they attached myosin proteins along this rod in precise positions. Then, using advanced single-molecule imaging, they snapped atomic-scale pictures of myosin interacting with actin under biologically realistic geometric conditions. Their achievement could aid in the hunt for new ways to treat diseases associated with myosin malfunction.

Fujita K, Ohmachi M, Ikezaki K, Yanagida T and Iwaki M. *Commun Biol* 2. 437 (2019)

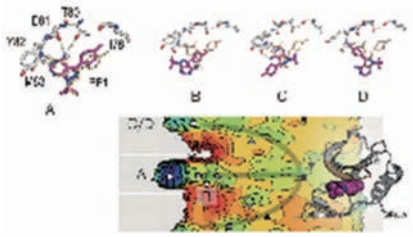


02

Faster modeling of interactions between ligands and proteins

Many drugs work by mimicking the natural interactions of small molecules known as ligands and large proteins involved in biological processes, thus, it is vital to accurately simulate such interactions when designing new drugs. Now, Yuji Sugita and Suyong Re in the Laboratory for Biomolecular Function Simulation and others have extended an existing molecular dynamics simulation method, allowing them to compute hundreds of binding and unbinding events between a protein and a ligand in about a month using the K computer, whereas conventional methods would take at least ten times longer. Their improved method promises to boost the speed and accuracy of designing new drugs.

Re S, Oshima H, Kasahara K, et al. *Proc Natl Acad Sci USA* 116. 18404-18409 (2019)

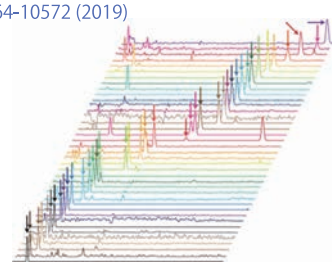


03

Detecting the metabolites of a single cell

There was no reliable technique for profiling the small molecules, or metabolites, produced by a single cell. Such a technique would provide valuable information for cancer biology, as cancer cells acquire different strategies for survival, thus, showing a different metabolite profile. A team led by Takayuki Kawai (Laboratory for Single Cell Mass Spectrometry) has now boosted the sensitivity of a conventional metabolomics analytical technique called capillary electrophoresis-mass spectrometry by up to 800 times, allowing them identify 40 metabolites from a single human cervical cancer cell. The team is now searching for good target molecules for clinical applications, such as drug discovery and diagnosis.

Kawai T, Ota N, Okada K, et al. *Anal Chem* 91. 10564-10572 (2019)



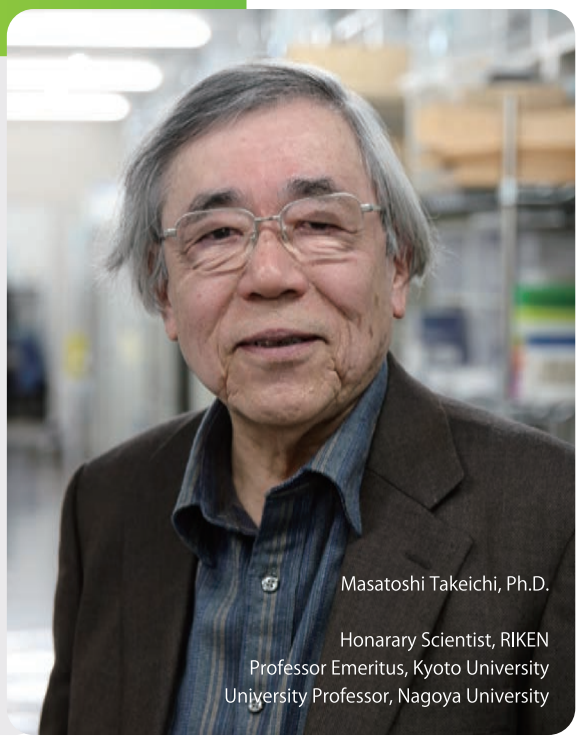
Masatoshi Takeichi to receive Canada Gairdner International Award

News Flash

Masatoshi Takeichi, former team leader of BDR's Laboratory for Cell Adhesion and Tissue Patterning, has been named a recipient of the prestigious 2020 Canada Gairdner International Award for "discovery, characterization and biology of cadherins and associated proteins in animal cell adhesion and signaling."

The animal body is made up of numerous cells. During the 1960s, Takeichi began investigating how animal cells stick together to form tissues and organs, and identified a key protein which he named 'cadherin.' He found that there are multiple kinds of cadherin within the body, each of which are made by different cell types. Cells with the same cadherins tend to cluster together, providing an explanation as to how different cells are sorted out and organized to form functional organs. Further studies led by Takeichi showed that cadherin function is supported by a number of cytoplasmic proteins, including catenins, and that their cooperation is essential for shaping of tissues.

The discovery of cadherins, which are found in all multicellular animal species, has allowed us to interpret how multicellular systems are generated and regulated. The knowledge of cadherin functions is expected to contribute to the development of effective treatments against diseases involving abnormal cell behavior like cancer.



Masatoshi Takeichi, Ph.D.

Honarary Scientist, RIKEN
Professor Emeritus, Kyoto University
University Professor, Nagoya University

Researcher Spotlight

BDR Team Leader
Wataru Kimura
Laboratory for Heart Regeneration
Interviewed by Emily Bian
(University of Wisconsin-Madison Intern)

Turning points and balance in a scientific career

You can read more about his research at the BDR website:

https://www.bdr.riken.jp/en/research/labs/kimura-w/index.html

Q▸So let me start by asking you about where and what you studied, and why you decided to become a researcher?

A▸I don't know when I decided to be a scientist. When I was a really young, I loved insects, bugs and dinosaurs. My father also worked for a pharmaceutical company, and I sometimes used to visit his institute—this may have triggered my interest. But I loved science, so I majored in science. I wanted to study molecular biology, so I went to Nagoya University. At the time, it was one of the few (Japanese) universities that had a department for molecular biology. My parents lived in Tokyo, so attending Nagoya University meant living away from home. But for graduate school, I had to pay for my own tuition which can be tough so I returned to Tokyo to go to a university there. As an undergrad and also a graduate student, I studied developmental biology. I really loved how embryos change in shape. So my first training was as a developmental biologist.

Q▸How did you get so good at English?

A▸I had many good opportunities to talk to students from abroad when I was a graduate student and postdoc. But the reason I got used to speaking and having conversations in English is because of where I went to in the U.S. to do my second postdoc—Dallas, Texas. I lived in Dallas for five years. There were not many Japanese people there, and I had to survive. There used to be many Japanese people living there maybe 10 or 20 years ago, but now there are not so many.

It was also in Dallas where I had the chance to change fields a little bit, and started to work on regenerative medicine, specifically, cardiac regeneration.

Q▸What kind of points do you focus on when you are going through your everyday lab routine?

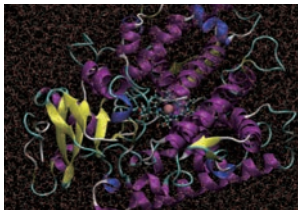
A▸I am sort of struggling with finding enough time for science and experiments. I always want to do experiments, but there is always a lot of paperwork, emailing and other stuff that also need to be done. RIKEN has been really helpful, and there is clearly less paperwork here than compared with universities and other places, but I am still struggling sometimes to find even a minute in a day or over a few days for my experiments—that is really tough.

Q▸Do you have any hobbies outside of research?

A▸Actually, I moved to Kobe about two years ago, and this is my first time living close to a lot of mountains, so I have recently started climbing these mountains. It's not that hard and it's really fun. The mountains don't take that long to climb, just two or three hours, and they are within walking distance from my apartment.

I usually climb on my own. But, people I meet on the mountains are very kind and feel very close for some reason. They greet each other in passing, which is something less likely to occur in Japan compared to the U.S. So, it reminds me of my days in the U.S.

On the cover!



Cytochrome protein containing heme (ribbon diagram) moving in water (tiny v-shaped lines). Snapshot from a simulation calculated by supercomputer MDGRAPE-4A. Image: Lab for Computational Molecular Design

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