Intervention in biological phenomena: Applying results to create and adapt a model, or identify systems

Interviewer: Takashi Mikuriya

——First, could you please talk about your lab's research in Systems Biology and Medicine?

Well, I was born in 1953, the year Watson and Crick published their famous paper on the double helix. When I was studying biology in high school, I became very interested in DNA. As a student in the school of medicine at university, I did research on the genetic causes of disease. After graduation I searched around for a research topic and got interested in atherosclerosis, so I began to research on cholesterol.

Researchers begin with a theory and then proceed from there with their research. But nobody knows better than a researcher how unreliable theories actually are. In 1990, when I was in the United States, I succeeded in cloning a gene that codes for storing cholesterol in fat tissue, and I published an article about it in the journal Nature. Some people misinterpreted my findings as a discovery of the gene that causes atherosclerosis. But based on my experiments, I knew that the identified gene was not the direct cause of atherosclerosis. I was surprised at how my research got oversimplified.

After returning to Japan, I did some more experiments using mice. Atherosclerosis generally doesn't occur in mice, so I crossed a mouse lacking the gene I discovered and two other types of mice with genetic irregularities that make them more susceptible to atherosclerosis. As a result, on one hand, the mice that were prone to atherosclerosis improved-again I published my findings in Nature. On the other hand, atherosclerosis worsened in the mice lacking the gene that codes for cholesterol storing. Generally this way of thinking does not work; what would happen if you take gene A, which makes atherosclerosis worse, and combine it with gene B, which makes atherosclerosis better? It's easier to publish an article in a world-renowned journal like Nature if your work is easy to understand and confirms preexisting theories. It's harder to publish complicated findings about a phenomenon that flies in the face of popular opinion. This sort of "reductionism" is especially prevalent in the scientific community in Europe and America, but it won't bring us even one step closer to finding the cause of atherosclerosis. So when I moved to RCAST, I stopped doing "reductionism"-type research and began taking a careful look at the relationships between elements. That's how I hit on the notion of "systems."

When I moved to RCAST, I stopped using mice on my research. In one sense, my experiments on altering mouse genes create black boxes. I wasn't satisfied with just focusing on one gene by itself-I really wanted to see all the genes together. As luck would have it, in 2000 the human genome was decoded and mapped, giving us a picture of all the genes in the human body. The total number is huge but at least it's finite, so we set about collecting exhaustive data that would hopefully enable us to identify systems.

Around the same time, Systems Biology was developed-mostly from research done in the US-which allows scientists to make biological predictions using computer models. Now, this is a kind of high-level reductionism, which basically says that everything can be solved in terms of differential equations. My own view is that it seems strange to talk about solving differential equations when you don't even know whether what you want to study can be expressed as differential equations. The popular view now on dealing with any complex system is to choose a model and then plug whatever phenomenon you're dealing with into it. Now, in

contrast to this, what we at RCAST call Systems Biology and Medicine is not simply about positing systems. The system as a whole may be too complex to fully understand, but by intervening in a biological process, we can see whether a given phenomenon occurs the way we predicted it would, or whether something different happens. If you're just going to look at phenomena and create models, you could come up with any number of different models. What we do instead is to intervene in an actual biological process and then alter and adapt our model based on the results, or identify a system-we take that as the most important first step.

——Predicting mechanisms one step beyond gene activation to create new medications with fewer side effects

How do you feel about your research now?

What I've become most acutely aware of is that the special characteristic of a system is that in it, biological phenomena are repeated over and over with incremental changes. When an activating stimulus is introduced, it triggers a signal that terminates it-what we call an autotermination signal. Usually activation will cease at that point, but if a continuous stimulus is introduced, it sets up a cycle; when the stimulus is repeated for a certain amount of time, the number of activated factors increases. This increases the number of inactivating factors, and activating effect is suppressed. But when activated factors become fewer, the number of inactivating factors also decreases. If the stimulus continues, then the number of activated factors increases again-this is what we call oscillation. Oscillation is a basic biological principle. For example, it determines the number of our vertebrae-if a certain protein activates and inactivates itself seven times-seven oscillations-then we get seven vertebrae. That is to say, the periodicity of oscillation functions like a clock.

In the case of atherosclerosis, the problem is that white blood cells adhere to the arterial wall and pass into it. Superficially, the way they adhere appears the same, but we've discovered that the phenomena occurring during the first oscillation and second oscillation are in fact different. We believe that when genes are activated during the first oscillation, what's more important than the fact that the oscillation occurs, is that a system of oscillation with incremental change is established. Cholesterol lowering medications are designed on the presumption that when a gene oscillates, you can introduce a certain stimulus and such-and-such will occur. But what we're doing is taking it one step further. In other words, we're trying to predict what phenomena will occur after the gene is activated, and design a medication accordingly. This could reduce side effects. We believe such drugs would have a high social value, so we're trying to use this process to predict mechanisms one step beyond gene activation to create new medications.

——So it's rather like letting the first wave go past and then making your decision based on what the next wave looks like?

Simplifying one's predictions is fine, but in fact medications work by activating genes, so if its effect is prolonged, genes will continue to oscillate and trigger various phenomena. In such a case, the first wave might well occur just as predicted, but the second wave will occur differently. You end up considering such things when you try to understand the relationships between elements. The problem is, with the third wave and beyond, so many elements come into play that it's impossible to calculate or predict-right now two waves are the limit, I think.

——Last year you and Professor Masaru Kaneko of Keio University published Reverse Systematology (I wanami Shoten). Could you tell us about that?

The impetus behind the book was what you might call "pop evolutionary biology"-for example, when people talk about things like the "love gene" or the "criminal gene." The public tends to think genes are responsible for everything. But as one should realize from the fact that we talk about "gene activation," genes are in fact passive, not active, and are only one part of a system that is subject to control. There may be such a thing as an "intelligent system," but there's no such thing as an "intelligent gene"-that's what we believe. But in society at large it's exactly the opposite; genes are the active agent and people are just vehicles. I've even heard people theorizing about "selfish genes" and that sort of thing. Anyway, a while back I was talking to my old friend Kaneko (Professors Kodama and Kaneko attended junior high and high school together). He was saying that even in economics people hold some very simplistic views, such as the performance principle. He argued that once you boil down a complex process to one mechanism or element, you threaten the integrity and sustainability of the entire organization.

——What sort of responses have you had to Reverse Systematology?

Well, because I quoted some people in the book by name, I thought I'd get a lot of angry responses from people who practice elemental reductionism, but in fact I haven't received a single serious objection. Of course, I've heard a lot of, "What you say is fine in theory, but it doesn't have any practical validity." My response to that is not simply to assert that elemental reductionism is wrong-the main issue now is what individual results can we produce, what medications can we create, what prescriptions can we give to patients, using the methodology that emerges from this new system we've identified called "Reverse Systematology."

I think the decisive factor in making this a field of study with practical validity will be the question of temporal dynamism. You see this not only in biological cycles, but take Chinese history, for example, with the rise and fall of dynasties, or economics, with cycles of boom and bust. When you look at these, they're not simply about repetition, but repetition with incremental change-that's what's critical. I suspect that a variety of control mechanisms underlie these cycles, and the interaction between them is also strong. When an economic bubble bursts, the ripples created by these various mechanisms produce an interference phenomenon, which

can result in a massive wave-then you get a meltdown of the entire control system. If not-if the ripples simply dissipate-you can get long-term economic stagnation that just simmers without setting up a cycle.

Because cells and biological organisms age and die, it's impossible to control an entire system, so we end up with small cycles, like those we experience in our daily lives, and larger historical cycles-it's those larger cycles that I believe impact the rise or fall of an entire nation or civilization. What we need to do is understand the relationship between small cycles and large cycles.

——So you're saying that these large waves represent cultural shifts, and at each historical turning point there are always lots of small disturbances. That probably explains what's happening now at the beginning of the 21st century with all the upheaval in the world. What's fascinating about the book is how it interweaves history and biology to make its points.

Separating noise from signals: What signals can tell us about how micro phenomena turn into macro phenomena

Earlier I said it's impossible to calculate the third oscillation and beyond, but for biological organisms we can try to orchestrate the overall system. For example, as long as blood pressure, blood sugar, and cholesterol are each kept with a certain range, there are mechanisms we can use to control the system even as oscillation occurs, thereby maintaining homeostasis. To do this, I think there are two main biological issues we need to address.

The first is the question of noise versus signals. In terms of how we can separate out signals from background noise, we now know that signals are interpreted in a time sequence. It's easier to understand if you think about music-if you hear a bit of the middle of a song you might not recognize it, but if you hear it sung form the beginning you will. In the same way, we know that biological signals are sequenced chronologically. So if something happens within a temporal framework, we can interpret that as a signal. That's the dynamism of signals.

The other is the question of how micro phenomena become macro phenomena. Various phenomena are occurring all the time on a micro level, just as there are always lots of important social phenomena around us, but what gets everyone's attention is when they emerge on a macro level, like the bursting of Japan's bubble economy or the long-term recession. I'm interested in the mechanisms at work behind the transformation of micro problems into macro ones. Methodologically speaking, on a micro scale we need to separate out signals from noise, and then figure out what these perceived signals can tell us about how micro phenomena will become macro phenomena-these are two areas of research I plan to pursue.

Repetition with incremental change: Its historical implications, and how to predict the next big wave

——Professor Kodama, you started the Future Drug Discovery we're looking for, in other words, is a "development of genome based antibody therapeutics" that works as both a diagnostic drug and a therapeutic drug-one that can create the antibodies that detect the extra protein created by gene oscillation, and then use the same antibodies to help fight cancer as well. In other words, the Future Drug Discovery Project is not part of our systems research per se-we plan to use the large amount of data we've collected to narrow in on a target and then, in the next stage, move to development of a drug that combines diagnosis and treatment.
Separate from that, the funds we've received from the Kowa Endowment will immediately enable us to build up our system base with new drugs. The Future Drug Discovery Project is a response to the scientific tidal wave unleashed by the decoding of the human genome, and we think of it more as a commercial enterprise. The Kowa Endowment, on the other hand, will give us the freedom to undertake a long and sustained examination of the principles of systems research, and look for new drugs to treat diseases.

——The Systems Biology and Medicine Laboratory that you direct, Professor Kodama, now employs some 100 researchers. Where do you think you'll go from here?

I think my future lies outside the university in the private sector. Take the drug Pitavastatin, which I helped Kowa Pharmaceuticals develop, for example-it now has sales of about 20 billion yen per year, and its main competitor Lipitol has annual sales of about 1.2 trillion yen. Taking that into consideration, I think I will probably end up branching out from RCAST and going commercial. If the Future Drug Discovery Project proves to be a success, I'd most likely turn it into a research center independent of the university. To me, that seems to be the direction I'm headed in.

In that respect there's one thing I find very difficult. Speaking as a member of a research project team, a private-sector lab has more advantages than a university lab because its part of a much bigger research effort. On the other hand, while a university lab has fewer advantages, the relative freedom it provides often yields very interesting material. The problem is that if you don't attain a critical mass then the research you produce ends up being worthless. The problem is how to motivate researchers and maintain a high level of motivation. Motivation research in science hasn't been talked about much in Japan. The challenge is how to develop a research style that combines science's intellectual component-data-oriented, labor-intensive intellectual skills-with its creative component-one that utilizes the individuality and imagination of your researchers.

——Listening to you, it strikes me it's the human, creative component of research which is exciting for you, isn't it?

What interests me most is the historical element of repetition and change, and trying to figure out when incremental changes will build into a great big wave. One of the keys to doing that is creating a dynamic synergy among researchers in the laboratory.

Today's discussion has been very illuminating. Even for someone like me who's basically a social scientist, this has

confirmed my sense that the context of your work in the natural sciences is essentially the same as ours in the social sciences. The idea of transformation through incremental change, and second and third oscillations, is very sociological. Thank you very much.

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Links

RCAST
http://www.rcast.u-tokyo.ac.jp

Laboratory for Systems Biology and Medicine
http://www.lsbm.org/site_e/index.html

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