

SPECIAL FEATURE

The impact of systems biology on medicine

At the 7th International Bio Forum & Bio Expo Japan (Bio Expo), held in Tokyo in July 2008, Dr. Leroy (Lee) Hood¹, the president of the Institute for Systems Biology, Seattle, USA, shared his views with A-IMBN counselor Chris Y. H. Tan² on how systems biology is transforming our understanding of biology and disease, and how it will revolutionize our approach to medicine.

TAN: As the founder of the Institute for Systems Biology in Seattle, USA, how would you explain systems biology in an elevator speech?

HOOD: I would say that systems biology is very much like what an engineer would do in trying to figure out how radio waves work; how you convert radio waves into sound waves. The first thing you do is to take a radio apart, look at the individual components, and try and understand what each one does. And that is exactly what molecular and cell biologists have done for the last 40 years. What was transformational about the Human Genome Project, for example, is that it gave us — for the first time — the complete ‘parts list’ of all the genes. And, by inference, all the proteins that are essential in systems biology.

The second thing [a systems biologist does] is put those components together in a circuit to understand how they individually and collectively carry out this conversion process — again, as with converting radio waves to sound waves. Systems biology is all about understanding how living organisms handle information by virtue of biological circuits that operate in exactly the same kind of way. Organisms take in information, or acquire it from the genome, transmit it and modulate it, and then integrate it and put it out into little molecular machines that actually execute the function.

Systems biology essentially applies to human health — understanding how systems work, and how those systems are perturbed such that their altered activities lead to the disease process.

TAN: How do you overcome the resistance of star academics, who have been working on their favorite signaling pathways all their lives, to systems biology since this area needs good biologists?

HOOD: You get them to play by attracting them with success. I will give you an analogy. When we started talking about the Human Genome Project in 1985, I would guess that 90% of the biologists were totally resistant on doctrinaire grounds. The perception was that big science is bad, and you’re never ever going to find anything very interesting. Those people were very hard to convince until they looked at it carefully in detail. Actually, that was what the National Academy Committee in the US did in 1988, and they argued that the genome project should go ahead.

The biggest opponent to the genome project at that time was the US National Institute of Health (NIH). They were bitterly opposed to it. Eventually, they created a new institute, the NIH National Center for Human Genome Research (NCHGR) that later became the National Human Genome Research Institute (NHGRI), which was responsible for



the Human Genome Project.

I would say the same has been true for systems biology. When we first set up the Institute for Systems Biology in 2000, there was enormous skepticism. I remember going to see Bill Gates and telling him I was leaving the university. He tried to dissuade me from doing that, but I said I felt I had to. So he asked me: “How are you going to fund it?” I replied that that is part of the reason why I came was to see you. He just said: “I never fund anything that I don’t think is going to succeed.” So I spent the next four years making sure that it was going to succeed — which it did. We have a good relationship now and he is supporting the institute.

I think you persuade skeptics by proving it is going to work. Older people are harder to persuade than younger ones, because the younger scientists, I think, can see the future more fully in many cases.

TAN: What impact will systems biology have on medicine?

HOOD: First let me tell you what I think the systems biology approach to disease is going to do for us over the next 10 to 20 years. I think the combination of a systems approach to disease, plus new transformational technologies — next generation sequencing, protein measurements, imaging and so forth, plus new computational and mathematical tools to handle enormous amounts of data — are going to move us from our current reactive medicine to one that I call 4P medicine: predictive, personalized,

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preventive, and participatory. My feeling is that this conversion process will take somewhere between 10 to 20 years, and within the next 10 years we will have predictive and personalized medicine in full force.

Let me give you an idea of what I mean by that. I would say there are two major components to predictive medicine. One is from your genome sequence: in 10 years many of us will have our own individual genome sequenced if not rapidly and extensively, we will begin to make probabilistic statements about our future health history. Now they have to be constrained by environmental exposures but we will begin to do that very successfully too. So we can say to you: "You have an 80% chance of having prostate cancer by the time you are 50."

The second thing we will do is have a little hand-held device that will prick your finger, take a drop of your blood and measure two or three thousand proteins. Those proteins will be 'fingerprints' that reflect the activities of the major organ systems in an individual. The levels of activity, as determined by the protein concentrations, will affect the biological network activity in each of these organs.

If you have a normal liver, you will get a particular set of protein ratios. If you have liver cancer, your body will modify a few of those proteins and the ratios will be different. So this will allow us to distinguish health from disease. And, it will allow us to distinguish the transition to disease very early on, which should allow us to detect many cancers pre-clinically. Ordinarily, most cancers can likely be cured if they are detected pre-clinically.

The second thing then is 'personalized medicine'. We all differ from each other by 6 million nucleotides, so we are susceptible to different combinations of diseases. We have to be treated as individuals and, in fact, that is the premise of the first two predictive techniques that we just talked about. The really important point is that in 10 years we will probably have billions of data points for each individual. We are going to have to develop information technology for health care that can reduce such enormous data complexity to simple hypotheses for health and disease.

TAN: You are saying that management of the enormous amount of data collected from the general population in health and disease is the future. How is this going to lead to affordable and good medicine for the population?

HOOD: What will really make it affordable in the future are systems biology approaches, which will lead to preventive medicine that focuses on wellness rather than on disease. The basic idea is that if we can delineate disease-perturbed networks, we can rationally identify therapeutic targets — drugs would be made to behave in a more normal fashion with less aggregate deleterious effects. That will be even more important if we get to the point of saying: "You have an 80% chance of getting prostate cancer by the time you are 50." I will guarantee that we will be able to make drugs that can prevent the network from becoming perturbed, so we could then say: "Start taking this drug when you are 35 and by the time you are 50 you will reduce the probability from 80% to 2%." That is what we mean by a preventive drug.

TAN: How do you address ruling politicians who hold the view that the more money you pour into research the more expensive medicine becomes? Will systems biology reduce or increase healthcare costs?

HOOD: I think P4 medicine is going to push us rapidly to what I call the 'digitalization of medicine': the ability to extract information that is disease-relevant from a molecule, from a cell or from an individual. I would argue that the digitization of medicine would have exactly the same implication as the digitalization of communication and information technology.

Who would have ever have suspected 20 years ago that a woman in a small village in India could be using a cell phone to set up a business to support her family? That is what the digitalization of communication has done. In fact, the politicians 20 years ago would have said this is a pipedream that will never happen in a million years. I would say that

the digitalization of medicine will be easier to understand. There will be transformations in how we do diagnostics that will allow stratification of management of patients, and there will be transformations in how we create therapeutics and so forth. There will be transformations in moving towards wellness and eliminating disease.

If we just look at the social cost of disease, you can argue that this is going to be enormously effective in a 'dollar and wise' sense. The final point about this revolutionary technology is that with the new protein measurement technology we are working on now, using microfluidics and nanotechnology, rather than costing \$400 to measure a protein in a certain way, we can probably do it in the future for pennies. And, we will do thousands of them for pennies.

If you put all of those things together, I would argue that at some time in the future you will turn around sharply an escalating healthcare cost, and it will decrease to a point where we will be able to export P4 medicine to the developing world. In fact, it will be the foundation of global medicine. I have talked to a lot of people about this and, I am not saying that I can persuade them all, but I have not met anybody who could argue me down. Part of being able to accept this kind of idea is being able to see the future and not being confined to thinking in the short term.

TAN: Having seen your discoveries over the years and knowing that you are now the pioneer of systems biology, something compelling comes to mind: what makes you tick?

HOOD: I think what really excites me is I always have a good capacity to predict the future, whether it is technology or the application of technology. When I went to Caltech in the 1970s to do technology development most of the senior faculties were really against it. It was inappropriate to have engineering in biology. When I started to push for the Human Genome Project in 1984/85, almost all the world in biology was against it. I tried to persuade Caltech in the late 1980s to set up a different department — cross-disciplinary biology — but the biologists vetoed it. That is why Gates funded a department that I set up at the University of Washington and finally I set up the Institute for Systems Biology.

You know that I resigned from academia after 30 years of comfortable residence; I resigned because I realized it was too different in philosophies to ever fit into academic bureaucracy, which really is mostly run by the best. So we set this institute up and are successful beyond our wildest dreams. Of course, my future vision now is P4 medicine, so we are working on the science and the partnership to make that really happen.

TAN: Thank you very much Lee, I wish you every success in establishing the foundations of global medicine by combining the features of predictive, personalized, preventive and participatory medicine through systems biology.

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1. Lee Hood, who developed the first gene-sequencing machine, is the founder and director of the Institute for Systems Biology, Seattle, Washington, USA. He has been and continues to be one of the leading thinkers in the genetic engineering and biotechnology revolution.
 2. Chris Y.H. Tan is the founding and former director of the Institute of Molecular and Cell Biology, Singapore. He was amongst the first to bring high-impact science to Asia, which stimulated the creation of numerous centers of excellence in China, Hong Kong, Korea, Taiwan, Singapore and Okinawa in the last 15 years. He continues to link America and Asia through science and A-IMBN.