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Leroy Hood expounds the principles, practice and future of systems biology

Interview by Stephen L. Carney

Leroy Hood, President, Institute for Systems Biology

Leroy Hood is recognized as one of the world's leading scientists in molecular biotechnology and genomics. In 2000, Hood co-founded, and is currently President of, the Institute for Systems Biology in Seattle (http://www.systemsbiology.org), which pioneers systems approaches to biology and medicine. He earned an MD from Johns Hopkins University in 1964 and a PhD in Biochemistry from the California Institute of Technology in 1968. His professional career began at Caltech where he and his colleagues pioneered four instruments, sequencers and synthesizers for DNA and protein. Hood was also one of the first advocates of, and a key player in, the Human Genome Project. In 1992, he moved to the University of Washington to create the cross-disciplinary Department of Molecular Biotechnology as the William Gates III Professor of Biomedical Science. He has played a role in founding numerous biotechnology companies, including Amgen, Applied Biosystems, Systemix, Darwin, Rosetta and MacroGenics. In a distinguished career, Hood has been honoured many times, most notably receiving the 1987 Lasker Award for his studies on the mechanism of immune diversity and the 2002 Kyoto Prize in Advanced Technology. He has a life-long commitment to making science accessible and understandable to the general public, especially children. One of his foremost goals is bringing hands-on, inquiry-based science to K-12 classrooms.

For the benefit of our readers who might not be familiar with the idea, could you briefly define the concept of systems biology?

Systems biology is the ability to look at all of the elements in a biological system – by elements, I mean genes, messenger RNA, proteins, protein interactions and so forth – and to measure their relationships to one another as the system functions in response to biological or genetic perturbations. Then one can attempt to model the behaviour after integrating the different levels of information, either graphically or mathematically, so that, ultimately, you will be able to describe the behaviour of the system given any kind of perturbation. In the future, we will be able to redesign systems by modification or drugs to have completely new systems properties. What distinguishes systems biology from the more classical biology of the past 35 years or so, which looked at genes and proteins one at a time, is the attempt to look at all, or at least most, of the elements and their interrelationships.

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What, in your opinion, are the essential elements that underpin and drive the development of a systems biology department?

The key elements are: first, to create a cross-disciplinary faculty environment where one has physicists, computer scientists, engineers, chemists, biologists and mathematicians all working together. The challenge is to create a language that can be commonly shared to allow them to communicate with one another with the aim of creating a focus on particular systems problems. The second challenge would be to create an environment that has all of the high-throughput platforms that one needs for gathering biological information. In genomics, that would be large-scale DNA sequencing, DNA arrays and large-scale genotyping. In proteomics, that would be the ability to identify and quantify proteins, to look at their interactions and measure their compartmentalization and chemical modification, and so on. Metabolomics is the ability to look at the small molecules that operate in the context of systems. A third requirement would be the development of new global technologies and powerful new computational tools for gathering, classifying, analyzing, integrating and, ultimately, modeling biological information. That is one of the reasons you need a cross-disciplinary environment. In all cases, the systems biology itself should drive the nature and strategy of tool development, be it technical or be it computational.

Another element that is essential for doing good systems biology is being able to partner effectively with academia and, perhaps equally importantly, with industry. This is because one scientific entity is not going to be able to invent all the technologies or all the computational tools, nor will they have access to all the biology that one can explore. So you need partnerships to be able to facilitate the integration of technology, computation and biology. Another challenge is how you can then keep these new tools that have been developed and mature them into high-throughput platforms that can be used to inexpensively generate enormous amounts of data. Finally, there are issues of how you can integrate what I call systems biology, which is hypothesis-driven, iterative and integrative – a cyclical kind of process – with discovery science, which is identifying all the elements in a transcriptome or the proteome of a particular cell type. Discovery information is useful for disease stratification (classification) and provides the elements for beginning systems biology. I would draw a sharp distinction between performing array analyses and doing systems biology; systems biology has to be necessarily integrative of many different types of biological information. So, in the end, I think the challenge for systems biology is how the academic or industrial scientific entities can effectively integrate technology with computation, biology and, ultimately, medicine.

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If you were to highlight only one success that has arisen from systems biology, what would it be and why?
Together with Eric Davidson at Caltech and Hamid Bolouri here at the Institute for Systems Biology, we have used systems approaches to define the gene regulatory network that controls the development of the endoderm of the sea urchin. This is a 55 gene network. We know the linkages and the interrelationships in some detail. From that network you can begin to make predictions about how you could change development if you made modifications to the network. To give you one example of engineering the system, Eric and his colleagues perturbed the network in a defined manner and quite predictably generated an organism with not one gut, but two. This is a graphical illustration of how, if you rationally understand the gene regulatory networks that control development, you can redesign those networks to get completely new systems properties. You can predict the behaviour of a network, given a particular perturbation in the system. This could never have been done in a million years with the classical, one-gene one-protein-at-a-time, approach to understanding gene regulatory networks.

What would you consider the role for systems biology within the pharmaceutical industry? How would you envisage this approach driving the discovery of new pharmaceutical agents?
Systems approaches to human systems (immune, cardiovascular, cancer, and so on) have the chance to enormously facilitate the process of target selection and the various aspects of pharmacogenomics; that is, the ability to identify adverse side effects or individuals that genetically do not react effectively to drugs. My feeling is that systems biology is going to usher in a new kind of medicine, which I call predictive, preventive and personalized medicine. The predictive will deal with, and be able to identify, hundreds if not thousands of variant genes that may predispose, in particular combinations, to various late-onset diseases (e.g. heart disease, cancer, autoimmune disease, and so on). It would therefore be possible to actually write out a probabilistic health history for the individual. Disease prevention will use systems biology to place defective genes in the context of the networks in which they operate. As I described with the sea urchin, it would then be possible to circumvent the genetic limitations with newly designed drugs, or modified proteins or genes, and thus be able to say 'a prediction for you is that you have a 70% chance of getting breast cancer when you are 60 years of age, but if at the age of 40, you start taking this drug, you need never get breast cancer, because we can circumvent whatever limitations the genes might create.'

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I'll say parenthetically that disease arises either as a consequence of gene defects or a combination of gene defects and/or pathologic, environmental cues, and we can learn to deal with the circumvention of pathologic, environmental cues in exactly the same way using systems biology. My feeling is that systems biology will be a central strategy for discovering, initially, therapeutic drugs and, eventually, preventive drugs.

In the future, the question is, how effective big pharma will be in utilizing systems biology? It requires a lot of integration that they are not very well set up to do. One possible alternative scenario is that a few successful systems biology companies could emerge and focus on the early stage processes of drug target discovery and drug identification, stratification of disease and pharmacogenetics.

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The outcome for drug discovery is that you will probably identify targets that are significantly more complex than have been the case in the past. How likely is it that medicinal chemistry will be able to deliver selective tools that can act upon multiple, possibly diverse, targets?
I do not think that the targets will be more complex, rather they will be more effectively chosen. I think what the pharmaceutical industry has objected to is the concept that any given disease, such as prostate cancer, is almost certainly stratified into a multiplicity of different diseases caused by differing combinations of genetic and environmental factors, even if their initial phenotypic outcome is similar. For example, prostate cancer may be considered as a disease that can be stratified on the basis of systems approaches into a number of disorders that we will treat in different ways. The tools of discovery and the tools of systems biology will be ideal for this process of stratification. By stratifying disease entities and putting them individually through clinical trials, you increase enormously the probability that the drugs undergoing trial are actually going to work on a significant fraction of patients. Consider a hypothetical disease in which there are 10 different genetic predispositions giving similar phenotypes. Each of these predispositions accounts for 10% of the total, and you have one drug that works perfectly in one of them. The resultant global efficacy of 10% would not appear to be a particularly effective clinical trial. With the systems approach, we can stratify disease and look at the individual types of disease in the context of which drugs work. Then we can conduct clinical trials on the patient population predicted to be responsive to the drug. In this case, the success rate will be 100%. I think we can enormously increase the efficiency of defining drugs that are going to be effective on a very high proportion of selective stratified populations. Now the argument that has to be made is that for each of these approaches, we're going to cut down the total cost of creating the drug because the markets will be smaller than for the current blockbuster drugs, and because the disease is going to be highly stratified and the market fragmented.

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I think that is consistent with what we can expect from systems biology. Microfluidics and nanotechnology are going to enormously decrease the cost of doing the global and integrative studies that underlie both systems biology and the multiparameter analyses of predictive medicine. For example, in the future we will sequence an individual genome for under US$1000, compared with today's cost of maybe US$50 million or more. This

will give you an idea of the scaling factors that we can think about as we move these new technologies first towards the discovery and then towards targeted ways for designing drugs and ways to circumvent gene defects and environmental cues.

With the exception of Eli Lilly's US$140m investment in a Centre for Systems Biology in Singapore, there seems little big pharma involvement at present – do you think they are waiting for the results of the Lilly foray or do you think the drug discovery industry is not receptive to the concept of systems biology at the moment?

I think big pharma in general has a wait and see attitude about new approaches, as they should. The pharma business is not to invent new approaches, but rather to apply successful approaches. The key issue for them is to determine when a new approach should be applied. Systems biology is a nascent discipline and the most interesting systems in which we have demonstrated its power are in microbes, yeast and sea urchins, and not humans, to date. There is scepticism about systems biology, possibly not whether it's going to be fruitful but how long it will take to get to a point where it will be useful to a drug company. But having said that, many of the executives in the drug industry don't understand systems biology. They have no idea about its potential but you've got to persuade the executives that it deserves the investment. I am on Lilly's Advisory Board and their Centre for Systems Biology is a marvellously interesting experiment.
I think the challenge for the pharmaceutical industry is going to be the challenge of the integrations necessary for systems biology; that is, the integration of new technologies with new computational tools with hypothesis-driven systems biology all focused on medicine.

In the end, the important word in systems biology is biology. The biology has to drive the development of the computational tools. It also has to drive the development of the new technologies. It should also be noted that many academics are sceptical of systems biology. Some sceptics feel systems biology really isn't anything new beyond the integrative physiology that has been practiced for years. This was exactly the same argument we heard in 1985 and 1986 from the National Institutes of Health when they said they didn't need a Human Genome Project; they were already spending US$300,000,000 a year on genetics and that was the same as the Human Genome Project. At the time, they didn't understand how profoundly different those things really were.

In retrospect we can see that the arguments of doing things the same old way have always been a barrier to advancing new opportunities. The pharmaceutical industry widely believes that genomics really hasn't advanced their cause very much. The reason for that is totally understandable. Genomics alone is a single dimension of information. Systems biology looks at many dimensions of biological information. Genomics alone is good for classification; it isn't necessarily good for understanding biology and ultimately providing powerful approaches to drug discovery. I think many in pharma and academia do not understand the difference between a one-dimensional view of information that you see with DNA arrays and the global, integrative, iterative and hypothesis-driven approach of systems biology.

Freeman Dyson said that if you really want to transform the field of science, invent a new technology. You clearly have a history in this with DNA and protein sequencers and synthesizers – what would you see as being a key enabling technology in the next 10 years?

I think without a doubt it's the synthesis of microfluidics, microelectronics and nanotechnology for integrating, automating and creating high-throughput production of tools for data production and analysis. It is nanotech we will use to sequence individual DNA molecules; it is nanotech we will use to measure RNAs and protein concentrations and protein interactions. Microfluidics is the way nanotechnology communicates with the outside world and, in the future, the two will be beautifully integrated together.
My very strong feeling, is that every analytic technique in biology and medicine will be transformed by microfluidics and nanotechnology.

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What would you see as being the next milestone achievement that might be delivered by a systems biology approach?

I think it's going to be a series of incremental steps, rather than one big achievement. It will require the development of novel technologies, powerful new computational tools, as well as their integrated application to the problems of biology and medicine. One of the biggest challenges in systems biology is how to develop computational tools for integrating the many different types of biological information, DNA, RNA, protein, protein interactions and the phenotypes, that are required by systems biology approaches. The ultimate aim will be to develop graphically integrated models that can be converted into mathematical descriptions of systems.
I think that these computational challenges are some of the biggest we face at the Institute for Systems Biology. We are incrementally moving towards success, but it isn't going to be one big development like the DNA sequencer; it's going to be an incremental series of integrative plug-in algorithms to digital and network platforms. I think developing the computational tools to handle, analyze integrate and model information is, however, one of the very biggest challenges of the day.

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