Perspectives on the Sixth International Conference on Systems Biology

Kwang-Hyun Cho, of the College of Medicine and Bio-MAX Institute at Seoul National University, Korea, is one of the two founding Editors-in-Chief of IEE Proceedings – Systems Biology. He laid the foundations for our journal during his sabbatical leave at UMIST in Manchester in 2002–3, together with Olaf Wolkenhauer (now at University of Rostock, Germany). He has been an active participant in the ICSB conference series since it started in 2000, and is on the programme committee for this year’s meeting, which, like the first, is to be held in Japan. He has followed the growth and maturing of the discipline of systems biology since the turn of the millennium. This growth, he believes, is reflected by the increasing popularity of the ICSB meeting, undoubtedly the largest international systems biology conference. “Many researchers, including some of my colleagues, were unable to attend ICSB in Boston, because registration closed early when it became fully booked”, he said. “I am confident that systems biology can now stand alone as a discipline in its own right, and not just as a way of doing interdisciplinary science.”

Cho also commended the number and popularity of the specialist workshops that were held immediately after the main meeting, in particular an oversubscribed session on the reverse engineering of gene regulatory networks.

Cho also believes that the scope and breadth of areas encompassed in “systems biology” is growing, and that this is reflected in the variety of topics covered in symposia at ICSB. He singled out synthetic biology for particular comment. This term refers to the “engineering” of systems with particular functions and properties from biological components. It interacts with systems biology and is now covered extensively in the systems biology literature, but he believes that it should be considered as a separate discipline. Other researchers commented on the fact that systems biology is now being applied to more practical biological problems, and is being integrated into disciplines such as microbiology and developmental biology. This is seen as a sign of the maturity of the field and the growing acceptance by experimental biologists of the insights being provided by systems biology.

To illustrate the variety of work presented at ICSB, I present profiles of Cho’s work and that of two ICSB speakers whose work he commended as being of particular interest: Hiroki Ueda from the Center for Developmental Biology, RIKEN, in Japan, and Jim Collins from Boston University, USA.

Jim Collins

Jim Collins is Professor of Biomedical Engineering at Boston University. His original training was in physics, and his first exposure to systems biology came during his PhD research at the University of Oxford, UK, in the late 1980s. There he met Denis Noble, whose pioneering models of cardiac systems exemplify the potential of systems biology in physiology, and even in clinical medicine.

Collins’ wide research interests at Boston combine several of the strands of systems biology highlighted in this report. His research group is involved in integrating systems biology with synthetic biology; in engineering synthetic gene networks out of well characterised biological components; and in reverse engineering models of gene networks in order, for example, to determine which pathways and gene products within those networks are the targets of potential drugs.

In the first section of his invited lecture at ICSB, Collins described a synthetic biology project to create a “toggle switch” out of two genes1. This work started in the late 1990s, when Timothy Gardner, now an Assistant Professor at Boston University, was a PhD student in the Collins lab. “The basic principle is the use of two genes that are co-responsive, so the protein product of each gene functions to shut off the other one”, says Collins.

Two technologies for the control of gene expression have been developed in recent years. These involve the use of repressor and activator proteins and, more recently, the use of RNA interference (RNAi) to decrease transcription. However, neither technique provides a precise and error-free method of switching genes on and off. Collins has developed synthetic techniques that provide more control, essentially by combining these approaches. In a recent paper in *Nature Biotechnology*2 the group describes a regulatory system in *E. coli* in which a sequence is inserted into the upstream region of a target gene that forms an RNA stem-loop when the gene is transcribed. This silences gene expression, but the gene is activated in turn when a small noncoding RNA interacts with the stem-loop to change its structure. A poster presented by current PhD student Tara Deans extends a similar principle to mammalian gene expression, coupling RNAi to the LacI repressor to effectively silence a gene. Transcription can be resumed by adding a substance that inhibits LacI binding. Most recently, Collins’ group has been developing methods of interfacing these “synthetic biological” switches with regulatory pathways in bacteria to create

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programmable cells that can act as biosensors. “One interesting example is the quorum sensing pathway, which bacteria use to sense how many others of the same type are in their vicinity”, says Collins. An engineered biosensor involving this pathway might have some very useful biotechnological applications.

The second part of Collins’ talk was concerned with one aspect of what might be termed “classical” systems biology: the reverse engineering of regulatory networks in E. coli from microarray data. Although this is one of the most closely studied bacteria, its known metabolic pathways still involve only about a quarter of its genes. Collins’ group collected expression data from E. coli under a wide variety of conditions and used a reverse engineering network algorithm to generate a comprehensive model of gene regulation for the organism. These models have been used to suggest previously unknown mechanisms for regulating processes such as DNA repair and iron transport, and to determine the protein targets of potential antimicrobial drugs. “We are now using this to investigate compounds that might induce the death pathway in bacteria, and that therefore might be useful to potentiate existing antibiotics”, says Collins. Collins has also extended this systems biology approach to eukaryotic systems, and shown that it can be used to identify the mode of action of antifungal compounds.

**Hiroki Ueda**

Hiroki Ueda, laboratory head of systems biology at the Center for Developmental Biology at RIKEN in Japan, is one of the very few research leaders in this discipline to have first trained as a medical doctor. His rise to prominence in systems biology in the past few years has been meteoric. After undergraduate studies under Hiroaki Kitano at Tokyo University, he attended the first ICSB in Tokyo as a first year graduate student, becoming a group leader at Yamanouchi Pharmaceuticals and then a laboratory head at RIKEN before completing his Ph.D. studies. His research applies systems and network biology to one of the most intricate and complex biological mechanisms: the circadian clock.

A wide range of physiological and metabolic processes in mammals and other organisms are controlled by cycles that have a period of approximately 24 hours and are known as circadian clocks. In humans, the disturbance or breakdown of these cycles is present in a number of more or less serious conditions, ranging from simple and rapidly reversible jet-lag through insomnia to depression and dementia. On a genetic level, these mechanisms are controlled by a network of transcription factors that regulate the expression patterns of other genes in a periodic manner. Analyses of gene expression patterns have revealed the intricate complexity of these networks, with some clock genes being regulated by others.

Ueda and his colleagues developed an assay that used luciferase to monitor transcription in clock-controlled processes in real time. Using this, they have identified the upstream regulatory sequences that control time-dependent gene expression in sixteen of these transcription factors, and classified them into three types known as “E/E’ boxes”, “D boxes” and “RevERB/ROR binding elements (or RREs)”. Each transcription factor can be categorised in two ways, by the element that it binds to as a regulator and by the element that other factors bind to regulate it. Despite this complexity, only two simple temporal regulation patterns were recorded. In E/E’ box and RRE regulation, expression of regulators always preceded that of activators, whilst in D-box regulation expression patterns of repressors were almost completely out of phase with those of activators. Ueda developed an *in silico* model of these patterns that replicated the observed finding that the first, “repressor precedes activator” model gives rise to delayed transcription and the second, antiphasic model gives rise to high amplitude transcription.

Furthermore, Ueda demonstrated the use of expression patterns in over 100 “time-indicating genes” in wild type and mutant mice to detect “internal body time” (which will affect, for example, drug metabolism) in individuals. This has implications for the diagnosis of rhythm disorders.

Ueda is delighted to have been given this opportunity to present his work at the largest ICSB meeting so far. “It is very exciting to see, and to contribute to, the growth of the systems biology community”, he said.

**Kwang-Hyun Cho**

Kwang-Hyun Cho, the director of the Systems Biology Laboratory at the Korea Bio-MAX Institute at Seoul National University, Korea, received his initial training in electrical engineering, although his current faculty position is at the College of Medicine there. The work of his group is applied explicitly to biology and medicine. The group is involved in collaborations with “wet lab” biologists, applying *in silico* techniques including signal transduction pathway analysis and the “reverse engineering” of regulatory networks to specific, practical biological problems. They participate in the Korean Systems Biology Initiative (KoSBI), which was set up in 2003 with a grant from the Korean Ministry of Science and Technology and now concentrates on the study of calcium signalling systems in the heart.

The essential role played by calcium ions in cell signalling is now extremely well known; changes in the concentration of these ions in cells are associated with a wide range of

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biochemical processes\textsuperscript{8}. Scientists working under the aegis of KoSBI, including Cho and his colleagues, have been examining calcium-signalling pathways in normal and diseased mouse hearts. The contribution of Cho’s group to this work was presented at ICSB as a poster with Do Han Kim, from Gwangju Institute of Science and Technology (GIST) in Korea, as first author. The group has identified a number of genes and proteins that are both involved in calcium signalling and highly expressed in mouse heart, and has been developing a hierarchical model of the mouse calcium signalling system. This model focuses particularly on one type of cardiac myocyte and a calcium-dependent protein kinase that plays an important role in this cell type. Cho and his colleagues are now examining the validity of this kinase as a drug target for some cardiovascular diseases.

For the 2006 conference, Cho and colleagues will be organising a session on “complex systems biology”; this will be the first time that a dedicated session is given over to this topic, which applies the insights learned in this half-century old discipline involving the study of systems with simple components but complex overall behaviour, in computing, maths and engineering, to biological problems. He hopes that Mihajlo Mesarovic, who first mentioned the term “systems biology” in a book published as long ago as 1968, will be able to speak there.

ICSB 2006 will take place in Yokohama, Japan from October 9–13 (http://www.icsb-2006.org/). And it appears that the centre of gravity of the systems biology world will be firmly fixed in the Far East this year. Another significant international conference, the International Conference on Computational Systems Biology, will be taking place in Shanghai, China from August 3–5, 2006. Readers in other continents, especially those without large travel budgets, may be particularly interested to know that both these conferences will be covered in full in this journal.