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Foundations of Systems Biology

THE BOOK

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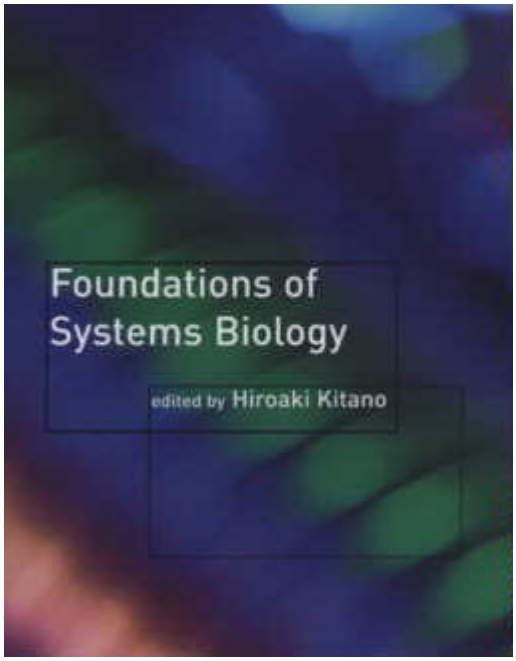
UNDERSTANDING BIOLOGICAL PROCESSES AS A WHOLE

Foundations of Systems Biology *edited by* Hiroaki Kitano, hard cover
The MIT Press, Massachusetts Institute of Technology, Cambridge, Massachusetts 02142: xvi + 297 Pages: Publication Date: 2001: ISBN 0-262-11266-3: Price $45.00



Although it may not be readily apparent, there is an eerie similarity between man and machines. Among other things, both work on a feedback mechanism. This similarity may be most apparent when we, say, compare the functioning of an air conditioner (a machine) with temperature regulation in man. An air conditioner will continue cooling till the temperature of the room drops down to a particular predefined point (we set it by turning the knob to "cool", "cooler" or "coolest"

etc). After that it will stop working, and shall begin working again only after some time when the temperature of the room has risen above our predefined point. Our bodies work in much the same way. There is a minor difference though. We can not willingly set a temperature here; it has already been set at 37 degrees Celsius by nature. If you run, the body temperature rises, and the cooling mechanisms start (sweating, increased respiration etc), and you will continue to sweat till the temperature of the body comes back to 37 degrees. After that - just as the air conditioner stops - the perspiration stops too.

Many might take it to be an interesting and trivial similarity, but it is not. Much can be learnt by comparing the two systems. In fact engineers are trying to make better machines by learning feedback mechanisms from living beings. Conversely biologists borrow freely from complex engineering equations to mathematically describe the workings of the human body. The first scientist who raised this comparison to the level of a new science was the American mathematician Norbert Wiener, who in 1948 coined the term cybernetics to describe and study this interesting comparison. The word comes from Greek *kubernetes*, meaning "steersman". This field now studies self-regulating systems, whether these are machines, living beings, or even groups of living beings such as organizations.

Hiroaki Kitano



Hiroaki Kitano is a Director at Sony Computer Science Laboratories, Inc. and a Project Director of Kitano Symbiotic Systems Project, Japan Science and Technology Corporation. He is also a President of The Systems Biology Institute. He received a B.A. in physics from the International Christian University, Tokyo, and a Ph.D. in computer science from Kyoto University. Since 1988, he has been a visiting researcher at the Center for Machine Translation at Carnegie Mellon University. Kitano received The Computers and Thought Award from the International Joint Conferences on Artificial Intelligence in 1993, Prix Ars Electronica 2000, Japan Design Culture Award 2001, and Good Design Award 2001. His research interests include AI, Robotics, and Systems Biology..

The book under review deals with a similar subject - systems biology. It is an attempt to understand biology at the system level. The editor Hiroaki Kitano says rightly in his preface that at the time of Norbert Wiener, molecular biology was in its infancy. So comparisons between man and machines were made at a physiological level (as we have done in the example above). Much water has flown down the Ganges during this time. Lot more is known about molecular biology now, and comparisons are now made at a molecular level.

To begin with, what do we mean by the word "system", and what is "systems biology"? The book defines this concept at several places. Some of the best expositions of this word are given at pages 3, 23 and 24. System is basically an assembly of components in a particular formation. A component is an elementary unit of the system. In electronic machines the components are things like transistors, resistors and capacitors. In biological systems, the equivalents of components are genes

and proteins. And the system may be either a cell or even a whole organism, depending on your viewpoint.

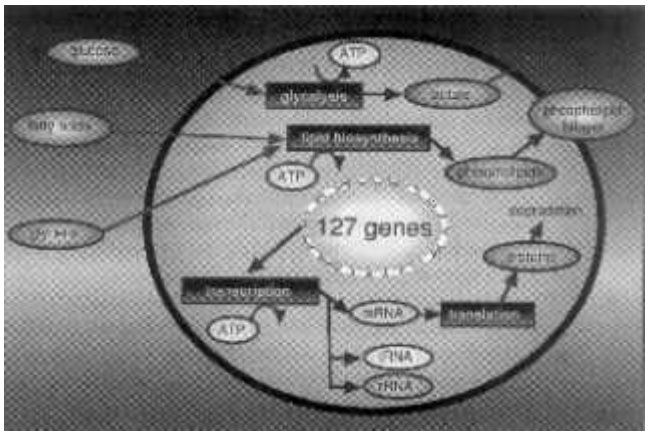
At a very basic level, systems biology may be construed as a combination of molecular biology and computing science. One of the purposes of this exciting new branch is to reverse engineer gene networks.

Systems Biology is now such an established branch of learning that three International conferences have been held on this subject. The First International Conference on Systems Biology (ICSB 2000) was held in Tokyo from November 14-16, 2000. It was supported by the Japan Science and Technology Corporation, an agency belonging to the Science and Technology Agency of the Japanese Government. The second conference was held at the California Institute of Technology from 4 November 2001 till 7 November 2001 (ICSB 2001, http://www.icsb2001.org/), and the third at Karolinska Institute, Stockholm, Sweden from 13 December 2002 till 15 December 2002 (ICSB 2002, http://www.ki.se/icsb2002/). The book under review is a loose collection of papers which were presented at the ICSB 2000. Hiroaki Kitano, the editor of this book and the Director of The Systems Biology Institute (http://www.systems-biology.org/) has compiled and arranged in a very logical fashion, beginning from the most basic and going on to the most advanced.

What's the purpose of this book? To my mind, the book serves two purposes. For one thing it puts in one place the current status of research on Systems Biology. Secondly and far more important, it sets forth the future challenges, the goals that must be achieved in this nascent science.

The main aims of systems biology - as we are told in chapter 1, written by Kitano himself -are four fold. These comprise of system structure identification, system behavior analysis, system control and system design. System design seems to be the ultimate goal, where biologists would attempt to design biological systems advantageous to us. For instance, how could one design a biological system which could enable us to harvest a genetically homologous organ from patients' own tissues. Such organ cloning techniques could quite obviously be enormously beneficial to us.

The book is well illustrated with diagrams such as this. This diagram appearing on page 244, shows an overview of the cell model, where the authors simulated the cell behavior using a program called E-CELL system

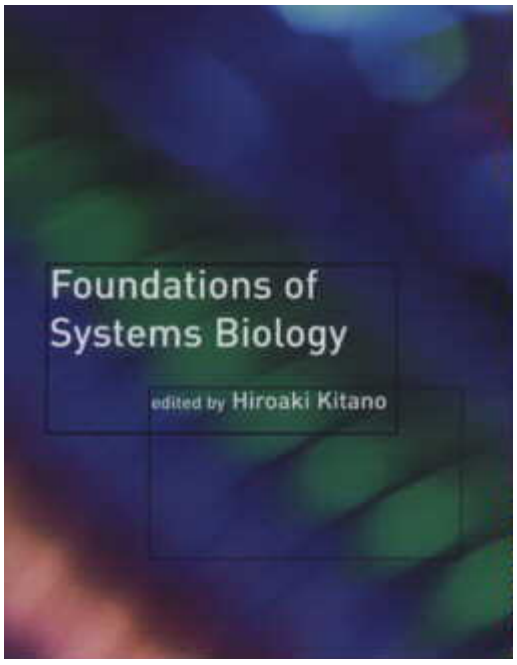


We talked about analogies between biological and engineering systems at the beginning. On page 16, the author gives us more analogies. Consider an airplane for example. If the atmosphere air flow were stable and the airplane did not need to change course, and if it didn't need to take off or land, it could be built with a very few components. Wright Brothers made their preliminary airplane with just about 100 or so components. But the modern Boeing 747 needs millions of

components, simply because it is so complex, can be maneuvered in so many different ways, and has so many built-in safety mechanisms. The same is true of organisms. A simple microorganisms, with hardly any complexity - such as Mycoplasma - needs only about 400 genes (equivalent to components of an airplane). But since it has so few components, it can only live under specific conditions. It is very vulnerable to environmental fluctuations. To make a more robust organism, nature would need more components (genes). *E.coli*, a slightly more complex organism has over 4000 genes and can live under varying environments. Humans - perhaps the most complex organism nature has ever made - have almost 100,000 components or genes.

There are further analogies. In engineering systems, robustness is ensured by four features (i) System control (ii) Redundancy (iii) Modular design and (iv) Structural stability. Each of this is well-explained in the book, but I will take just one here - redundancy. It is the name given to a method or mechanism, whereby there are more than one way to achieve a goal. If, say, four different roads lead to my college (from my home), I can still steer my car through to the college, if one were damaged due to some reason. This is an example of redundancy. A modern airplane has a high level of redundancy; a Boeing 747 has four independent hydraulic control systems. The same is true of robust biological systems. There are often multiple metabolic pathways to burn up the same chemical. Then there are duplicated genes and genes with similar functions. This is also an example of redundancy.

Almost all chapters in this book impressed me, but I might as well mention those, which appealed to me the most. Chapter six (by Michael Hucka, Andrew Finney, Herbert Sauro, Hamid Bolouri, John Doyle and Hiroaki Kitano) appeared quite interesting, in which we are told of a new computer language - the Systems Biology Markup Language - or SBML. It is a language which enables one to exchange models between simulation/analysis tools. We are told that the complete specification of SBML Level 1 is available at http://www.cds.caltech.edu/erato/. Readers might want to visit this site. On page 138-9, an example of a model encoded in XML using SBML is shown. It starts with the tag (like the usual) and ends in .



" .. I would recommend this book very highly to all biologists, computer engineers, mathematicians, computer programmers - and above all system biologists. It has

something to offer to each one of them. I am only a forensic pathologist, and yet I enjoyed this book thoroughly - perhaps because I love both biology and programming so much. ... "

Another chapter that impressed me very much was chapter 10 by Thomas Simon Shimizu and Dennis Bray in which we are told of a stochastic approach in computational cell biology. The conventional approach of representing biochemical reactions is by continuous, deterministic rate equations. We are told that if the molecules taking part in a reaction are very few, probabilistic (or stochastic, as the authors put it) factors begin to weigh heavily. On page 215, we are given an actual example of such a situation. We are told that only about 200 K^+ and Na^+ channels responsive to changes in intracellular Ca^{2+} are responsible for a key step in many neutrophil signaling pathways. At such small numbers, deterministic rate equations frequently break down, and what takes over is the stochasticity. To take care of such cases, the authors have devised a program called STOCHSIM. The authors describe its working in great detail, which is extremely fascinating - to say the least. The program is compared with another similar program, the Gillespie algorithm. On page 218, we are told that the latest version of STOCHSIM can be obtained via FTP from ftp://ftp.cds.caltech.edu/pub/dbray/.

I am tempted to write about rest of the chapters, but if I did that, I would end up summarizing the whole book. Suffice it to say, that the book is extremely interesting. I would recommend it very highly to all biologists, computer engineers, mathematicians, computer programmers - and above all system biologists. It has something to offer to each one of them. I am only a forensic pathologist, and yet I enjoyed this book thoroughly - perhaps because I love both biology and programming so much.

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-Editor-in-Chief

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