Chapter V
Synthetic Biology as a Proof of Systems Biology

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ABSTRACT

Biologists have used a reductionist approach to investigate the essence of life. In the last years, scientific disciplines have merged with the aim of studying life on a global scale in terms of molecules and their interactions. Based on high-throughput measurements, Systems Biology adopts mathematical modeling and computational simulation to reconstruct natural biological systems. Synthetic Biology seeks to engineer artificial biological systems starting from standard molecular compounds coding in DNA. Can Systems and Synthetic Biology be combined with the idea of creating a new science—'SYS Biology' that will not demarcate natural and artificial realities? What will this approach bring to medicine?

"We live in a society exquisitely dependent on science and technology,
in which hardly anyone knows anything about science and technology."
- Carl Sagan

INTRODUCTION

Sometimes, we are like the three blind Indian philosophers who tried to guess what kind of animal the elephant was by touching various parts of it. One blind man while touching the side of elephant announced the animal was like a wall. The second philosopher hugged its leg and declared that the animal was like a tree and the third blind man, while holding on to its tail said the animal was a snake. All three were correct, but all three had a distorted perspective of an elephant. This allegory captures a weakness of the analytical reductionist approach to biological science and illustrates a paradigm that the whole is greater than the sum of its parts. A system, holistic approach to Biology means the synthesis of knowledge from various sources and by different methods of data extraction. This approach starts with data collection and modeling to understand how components of the system interact, continues with experimentation and then returns to modeling to refine our understanding of interactions and to identify new questions to be addressed. This system of thinking emphasizes relationships rather than isolated entities.

The idea of a system-level understanding of Biology is not new. In 1943, Erwin Schrödinger published the book 'What is Life', a seminal work on scientific thought that examined the relationship between the laws of Physics and the mechanisms of life. In particular, it provoked the development of Molecular Biology and led to the research we know as *Systems Biology*. Norbert Wiener (1948) and Ludwig von Bertalanffy (1969) described a systems approach to living organisms i.e. the holistic view that 'mysterious' properties of life arise at the system level from dynamical interactions and diversity of system components. Breakthroughs in Molecular Biology during the last decades have enabled an analysis of dynamical interactions inside living cells and between them. Systems Biology appeared as a result of the Human Genome Project as well as from a growing understanding of how genes and their proteins give rise to biological forms and functions. Recent studies have involved high-throughput experiments in Genomics, Transcriptomics, Proteomics and Metabolomics. These '-omics' should be fused together to reach an understanding of Biology at a top system-level (Kitano, 2002a). The new field has attracted biologists, engineers, mathematicians, physicists and chemists who are tackling complex biological problems. The Internet allows researchers to distribute massive amounts of data. In particular, the theory of dynamical systems, agent-based approach and systems engineering methods provide the opportunity to study the collective behavior of biological entities. The challenge is to connect genetic circuits with physiological behavior.

Following Systems Biology, the goal of *Synthetic Biology* is both to improve our quantitative understanding of natural phenomenon and to establish an engineering discipline to design artificial biological systems. It will strongly depend on what possibilities there will be in the multi-scale modeling of whole organisms. Biological models often have numerous unknown parameters such as kinetic constants, decay rates and drift terms. A big problem for Systems/Synthetic Biology ('*SYS Biology*' for short) is that these parameters are often very difficult to measure. However, Systems Biology researchers believe that methods of dynamic analysis, modeling and simulation can provide a deeper understanding of life (Kitano, 2002b). Synthetic Biology, with the goal of synthesizing life from scratch, gives us other modern hype-and-hope, namely the 'understanding by building'. Regarding complex dynamical systems, Richard Feynman wrote: "What I cannot create I do not understand." By creating artificial life, we are beginning to answer Schrödinger's question: "What is Life?" This will give us new opportunities to distinguish the health and pathology for treating for example, schizophrenia, cancer and diabetes.

CONNECTION BETWEEN GENOTYPE AND PHENOTYPE

A current front of '-omics' research has moved from metabolic pathway analysis to the reconstruction of regulatory networks, identification of protein/DNA, protein/RNA and protein/protein interactions, simulations of signal transduction reactions, validation of experimental data available from high-throughput measurements and to studies on the correlation between gene expressions and phenotype. The relation between genotype and phenotype is a central question. Do selective forces which act on the phenotype affect individual genes? Or, is there an epigenetic influence arising from the complex interac-

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