EDITORIAL

Molecular Systems Biology: a new journal for a new biology?

Molecular Systems Biology 29 March 2005; doi:10.1038/msb4100009

While *Molecular Systems Biology* may be a new journal, there has been considerable debate as to whether systems biology itself represents a new approach to biology or whether it is really just a new and catchy name for what some biologists have been doing all along. The answer to this question of course depends on how one defines systems biology.

Terms that have already been used to describe systems biology include comprehensive biology, postgenomic biology, quantitative biology, mathematical modeling of biological processes, multidisciplinary biology, molecular physiology, the convergence of biology and computer science, and more. These terms do not actually describe systems biology as anything new. However, those who, like the author of this feature, believe that systems biology in fact does represent a new approach to the life sciences have therefore been challenged to produce a definition that reflects this view. Perhaps surprisingly, a concise definition of systems biology that most of us can agree upon has yet to emerge.

In order to come up with such a concise definition, we should first consider what systems biology aims to achieve, that is, the understanding of biological information, specifically the information encoded in the linear nucleotide sequence of a genome. Like written language texts, genome sequences can be represented as letters (nucleotides) and words (genes). However, understanding the lingual information of such texts requires knowledge not only of the letters and words, but also of the syntax, that is, the ordering of and relationship between the words in phrases and sentences. Likewise, understanding the biological information of genomes requires an understanding of not only the nucleotides and their arrangement into genes, but also of the syntax of biological information. A key part of such biological syntax is the organization of the elements encoded by the genome, particularly the proteins, into functional units such as complexes and organelles and the dynamic interactions between these units to control and carry out their various and complex biological functions. Thus, I would propose that systems biology can most simply be defined as *the search for the syntax of biological information*, that is, the study of the dynamic networks of interacting biological elements.

Explicitly or implicitly, much of the research in (molecular) biology over the last few decades has been based on the theory of deterministic genetics, which assumes a direct path from gene to protein to function and the presence of preset responses of a system to external perturbations. While this type of research has led to the accumulation of large amounts of detailed knowledge, its limitations have also become apparent: little is known how cells integrate signals generated

by different receptors into a physiological response, very few biological system have produced a density of data that has allowed the generation of mathematical models that simulate the dynamic behavior of the system, and the challenge of the pharmaceutical industry to identify new targets and molecular entities that interfere with them has dramatically increased. The root of these problems is the focus on letters and words rather than the syntax of biological information. Systems biology on the other hand, with its focus on the dynamic networks that represent this syntax, offers the potential to break through some or many of the limitations inherent in common current approaches to biological research.

Other areas of research are also now providing new and exciting perspectives for systems biology. For example, recent studies have indicated that the dynamic biological networks within living cells, while differing in size and composition, have structural properties in common with networks outside the biological world. The emergent theory that describes how such nonbiological networks constitute themselves, how they react dynamically to perturbations and how their behavior translates into predictable and measurable properties of the system, including adaptability and robustness, should provide a general theoretical framework for systems biology. Further development of such theory and its integration into biological research thus represents an exciting branch of systems biology.

Clearly, the models generated by the application of network theory, or any other theory for that matter, will only be as good as the data available to develop and test them. Thus the collection of quantitative, high-quality and validated data sets that reflect the syntax of biological information is critical for the success of systems biology. The techniques that have been successful for deterministic genetic approaches, including genomic sequencing, gene expression analysis, the identification of sequence polymorphisms, etc., are thus necessary but not sufficient for systems biology. It will therefore be incumbent upon system biologists to develop new quantitative technologies that are capable of systematically measuring the dynamics and ordering of, as well as the relationships and interactions between the molecules that constitute biological systems.

In the mid-1950s, Anfinsen began to concentrate on the problem of the relationship between structure and function in enzymes. Based on studies of ribonuclease, he proposed that the information determining the tertiary structure of a protein resides in the chemistry of its amino-acid sequence (the letters and words of the information), which was already known at that time. To this date however, even after decades of intense

research, the syntax of the information determining protein tertiary structure continues to evolve and produce new and surprising insights. Similarly today, the letters and words of systems biology are also largely known. Thus, it can be similarly anticipated that research into the syntax of the biological information of genomes will likewise continue to

produce important and unexpected insights into biology for decades to come. It is hoped that many of these insights will be described in *Molecular Systems Biology*.

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