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Self-organization in biology

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"*Synergy means the behavior of whole systems unpredicted by their parts taken separately*"
Buckminster Fuller
Synergetics: Explorations in the Geometry of Thinking (1975)

At a glance

One of the great challenges in biology is "putting it all together." There is a large and rapidly growing body of information about the building blocks of cells—proteins, RNA, DNA, lipids—but how these molecules form organelles, and how cells form tissues and organisms, is still a mystery. The principles of self-organization, borrowed from physics and engineering, in which mathematical modeling is used to predict the behavior of networks of interacting components, is beginning to provide insight into biological systems.

Definition of self-organization

Self-organization is a process by which a system—several components together with interaction rules—becomes ordered in space and/or time. Often, self-organization leads to emergent properties, meaning that the whole system has characteristics that differ qualitatively from those of the component parts without the interactions. Self-organization is usually distinguished from self-assembly because self-organized structures rely on a continuous input of energy to be maintained.

Background

Much of the success of the sciences has relied on a reductionist approach in which complex systems are systematically taken apart to examine the individual components and how they interact together. Historical examples are the isolation and characterization of the elements of the periodic table and the discoveries of the particles that make up atoms. In the biological sciences, reductionism has also been very successful: examples range from the purification of proteins, DNA and RNA and the study of their structures and activities, to the sequencing and analysis of whole genomes.

While the reductionist approach will continue in biology, there is increasing interest in understanding the properties of the systems that arise out of the interactions of biomolecules. There are many open questions. In systems biology, how do networks of proteins and genes integrate and respond to signals impinging on cells? In cell biology, how do dynamic structures such as the organelles and the mitotic spindle form, and what controls growth and division? And in developmental biology, how does the genome create

an organism? Self-organization plays a central role in all these processes (Karsenti, 2008; Rafelski and Marshall, 2008).

Biological systems challenge us because they consume energy, and are therefore far from thermal equilibrium. Thus classical thermodynamics, which has been so successful in developing an atomic understanding of physical and chemical properties such as temperature and pressure, does not apply to these systems. Instead of self-assembling into a lowest energy state, such as a crystal, these energy-dissipating components self-organize into highly dynamic structures, through which there us a constant flux of energy and material.

Understanding the principles underlying self-organization in biology will require, and inspire, new theoretical approaches. However, the theory does not need to be developed de novo. Biology can borrow from physics and engineering where systems theory is already well developed. For example, control theory arose from the practical need to regulate the speed and stability of engines (Maxwell, 1867). And the theory of dynamical systems (e.g. Andronov et al., 1987), which led to the discovery of chaos, grew out of simple questions about the orbits of three or more bodies. While established theory is expected to provide a foundation for understanding self-organization in biology, the unique properties of biological systems—the huge number of components, the multiplicity of energy dissipation mechanisms and the wide range of time and distance scales—pose great intellectual challenges.

Status of the art, and beyond

Systems and quantitative biology

Systems biology is currently seen as a highly productive approach to solving complex biological problems. While it means different things to different people, most agree that systems biology is the application of mathematical and theoretical approaches to understand how the interaction of metabolites, proteins, RNA, genes and cells can lead to systems-level behaviors that are often unintuitive and unexpected.

There are several examples where a systems approach has led to profound insight into a biological process. Early examples include the reaction-diffusion theory of morphogenesis by Turing in which spatial patterns emerge from simple molecular rules (Turing, 1990), and the action potential of nerve cells in which the voltage-dependent opening of ion channels leads to an all-or-nothing change electrical response (Hodgkin, 1964). A central concept in systems theory is that positive feedback, mediated by chemical, electrical or mechanical signals, can lead to instabilities and switching, which in turn can lead to spatial and/or temporal patterns or oscillations. More recently, successful models have been developed for the cell cycle (Tyson et al., 2003), bacterial chemotaxis (Bray, 2009), cell differentiation in response to growth factors (Santos et al., 2007), the heart beat (Noble, 2002) and the flagellar beat (Howard, 2009).

Omics

The above examples deal with small systems of interacting components. Systems biology has also come to mean modeling of systems at the level of the whole organism. Such an ambitious agenda has been motivated by the development of “omics” techniques, starting with the genome sequencing projects. It is now possible to measure the levels of all the proteins in a comparatively small number of cells using mass spectrometry (Cox and Mann, 2007), to quantify gene expression using microarrays and next-generation sequencing, and to use genome-wide RNAi screens to accelerate the discovery of new genes involved in cell biological processes such as membrane trafficking and motility (Sonnichsen et al., 2005; Pelkmans et al., 2005). The data being generated are vast, and the analysis is a long way behind. However, important discoveries have been made that give hope that general principles will be uncovered. For example, within networks of transcription factors that control gene expression there are motifs that occur far more often than random, indicating an underlying structure (Alon, 2007).

Synthetic cell biology

The rapid increase in the number of solved protein structures, together with improvements in sample preparation for electron cryomicroscopy, has led to the ability to fit the protein structures into the electron densities (Leis et al., 2009). Already there are atomic models of the leading edge of crawling cell, the axoneme, and filamentous structures in bacteria. These developments are fueling a dream that a full atomic model of a cell can be realized. This is a staggering feat to contemplate—even a bacterium contains some 10^{12} atoms, excluding water.

The above approaches rely on modeling to make the connection between components and systems. An alternative approach to understand how molecules lead to self-organization behavior is through reconstitution. In this approach, termed synthetic biology, increasingly complex cellular processes are reconstructed from purified components. Examples include motor and transport systems (Diez et al., 2004), membrane fusion (Ohya et al., 2009), the protein translation machinery, DNA and RNA synthesis (Liu and Fletcher, 2009). Recent breakthroughs in reconstituting the cell division machinery in bacteria—MinD/E (Loose et al., 2008), ftsZ (Osawa et al., 2008), ParM/R (Garner et al., 2007)—suggest it might be possible to produce a self-replicating protocell. This would then open the possibility of using selection strategies to rapidly evolve higher order capabilities.

Developmental biology

At the organ and organismal level, there have been impressive experimental successes. In a landmark paper, Sulston and Horvitz painstakingly reconstructed the entire cellular development of a nematode worm (Sulston and Horvitz, 1977). What took a decade, can now be visualized in real time and applied to other species, thanks to the development of new microscope techniques (Keller et al., 2008) and new image processing algorithms (Long et al., 2009).

The tremendous advances in genetic and imaging techniques gives hope that some of the long-standing and fundamental questions in cell and developmental biology can be answered. For example, Waddington proposed that the differentiation of cells during development takes place in an “epigenetic landscape” in which irreversibility is envisaged as corresponding to the ridges between valleys in which increasingly specialized cells are constrained (Waddington, 1956). Kauffman postulated that different cell types are distinguished by having different sets of activities in their genetic networks (Kauffman, 1969). These ideas have recently been reconsidered in the context of a modern molecular interpretation (Bar-Yam et al., 2009; Macarthur et al., 2009), opening a new way to understand the differentiation and reprogramming of cells using a systems theoretic approach.

International activities

Systems and Quantitative Biology
Institute of Systems Biology (Seattle), Department of Systems Biology (Harvard), California Institute for Quantitative Life Science, Integrative Cancer Biology Program (NIH)(US), Systems X (Switzerland), Life Sciences Interphase Programme (EPSRC, UK), Discipline Hopping (MRC, UK), HepatoSys (BMBF, Germany), Genome Network Project (Japan)

Synthetic Biology:
Synthetic Biology and Engineering REsearch Center (NSF)

Research opportunities and needs

In biology it is expected that a huge amount of data will be generated over the next several years. It will come from sequencing, proteomics and other omics such lipidomics and metabolomics. Cells will be visualized with unprecedented resolution by electron cryomicroscopy, and the total developmental program of organisms will be followed by light microscopy. It will be a computational challenge to put all this information into a form that can be easily comprehended and manipulated. Data must be integrated from different sources: gene expression profiles, proteomic maps, images.And it will be an intellectual challenge to understand the principles of self-organization that tell us how these parts (together with the interactions) make the whole.

Theory will play an increasingly important role. First, just handling and interpreting data will require major advances in bioinformatics and bioi**m**formatics (image processing). The demands on computer power will grow exponentially. And second, theory will be needed to make sense of it all. Biological processes are usually analyzed by a kind of reverse engineering approach: the individual components are measured, and the high-level organizational rules are deduced. However, there is paucity of systematic approaches to infer systems rules. The problem can be compared with the attempt to reconstruct the logic of a computer program by measuring the electric signals of individual transistors and logical elements. A huge logical gap remains between behavior of individual transistors and the systems behavior of the computer running that program.

We expect that new theoretical tools will need to be developed. The theory will have to bridge multiple scales: from single molecules, to complexes, to organelles, cells, tissues and organisms. The concepts of modularity and hierarchy will therefore be essential. The theory will have to take into account the complex connectivities in biological systems. And the theory will have to include often-significant delays associated with the interactions between the components, making the dynamics of biological systems depend on the history of the preceding activity. We anticipate that theory will become a driving force for biological discovery as it is in the physical sciences.

Expected outcome and benefit

In the next 10 years we will be able to “zoom” into all parts of the cell, as we go from the micron scale of light microscopy of organelles to the subnanometer scale of the individual atoms within the proteins, RNA and DNA. Likewise we will be able to zoom out from the cell to the tissue, organ and whole organism and see not just the arrangement of all the cells, but also how they got there during development.

Understanding the principles by which molecular interactions lead to self organization will be important in it own right. But it is also likely to change the way we think of cell differentiation and disease. The programming of pluripotent stem cells and the reprogramming of cancer stem cells might be best achieved using a systems approach. For example, it may be possible to selectively perturb and destabilize cancer regulatory networks by transient pharmacological intervention to ultimately cause cancer cell death while allowing normal cells to recover due to the natural robustness of their regulatory networks. Other complex chronic diseases such as metabolic disorders and diabetes may benefit from a more nuanced systems-level approach in which a magic bullet is replaced be a gradual guidance of metabolic networks back into the healthy regime.

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