Progress in Biophysics and Molecular Biology 113 (2013) 358–368

Contents lists available at ScienceDirect

Progress in Biophysics and Molecular Biology

journal homepage: www.elsevier.com/locate/pbiomolbio

Original research

Systems biology: A biologist's viewpoint

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ARTICLE INFO

Article history:
Available online 16 July 2013

Keywords:
Systems biology
Complexity
Self-organization
Emergence
Reductionism

ABSTRACT

The debate over reductionism and antireductionism in biology is very old. Even the systems approach in biology is more than five decades old. However, mainstream biology, particularly experimental biology, has broadly sidestepped those debates and ideas. Post-genome data explosion and development of high-throughput techniques led to resurfacing of those ideas and debates as a new incarnation called Systems Biology. Though experimental biologists have co-opted systems biology and hailed it as a paradigm shift, it is practiced in different shades and understood with divergent meanings. Biology has certain questions linked with organization of multiple components and processes. Often such questions involve multilevel systems. Here in this essay we argue that systems theory provides required framework and abstractions to explore those questions. We argue that systems biology should follow the logical and mathematical approach of systems theory and transmogrification of systems biology to mere collection of higher dimensional data must be avoided. Therefore, the questions that we ask and the priority of those questions should also change. Systems biology should focus on system-level properties and investigate complexity without shying away from it.

1. Introduction

Are you a reductionist? This question may generate a puzzled expression from most experimental biologists. As experimental biologists, most of us peel out layers of causal relations between molecules and biological phenomena. How does it matter whether you call us reductionist or tag our activities as reductionism? Irrespective of such questions, most of us are indeed trained in reducing a given problem to a simple and linear molecule-to-phenomenon relation (see Box 1). In essence, we use reductionist approach. The basic premises of reductionism are to simplify a problem by dividing a complicated system into parts and studying the parts to understand the system. In this approach, one identifies the building blocks of a system, like cells of an organism, and studies the properties of those building blocks to explain a system-level phenomenon. This extends to the idea that all things in nature are made of a restricted set of indivisible elements and properties of these elements can explain the behavior of a complex system (see Box 2).

However, different shades of reductionism have been preached and practiced in science (Gatherer, 2010). Reductionism, as preached by Ernest Nagel, considers that all higher-level theories can be reduced to some basal-level theories (Ney, 2008). This is inter-theoretic reduction, an attempt to unify science through some fundamental theories explaining everything in nature. This discourse has its own share of debates (Gatherer, 2010). In this article, by 'reductionism' we do not mean inter-theoretic reductionism. The reductionism practiced in experimental biology can be considered as "Methodological Reductionism" (Brigandt and Love, 2012). This reductionism rests on the belief that we should decompose a system in its parts and then study the properties of those parts to understand the whole system. For most biologists this is merely a strategy to simplify a problem and get the answer. Through out this article, we have focused only on this form of reductionism.

Biology graduated from natural history by holding the hand of reductionism. Discovery of cells (Hooke, 1665) and development of "Cell Theory" (Schwann, 1847) gave the primary impetus to this. Subsequent development of biochemistry reinforced it. Following the principles of reductionism, biochemistry focuses on biochemical reactions, their mechanisms, and the structure–function relationship of biomolecules. As every organism is made up of molecules, a biochemist studies those molecules to understand phenomena at organism level (see Box 3). One essential requirement of reductionism in practice is to investigate the elementary objects or processes outside the original environment and in strictly controlled laboratory conditions. By this, we restrain unwarranted environmental factors to decipher the properties at their

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http://dx.doi.org/10.1016/j.pbiomolbio.2013.07.001

Box 1

Linear and non-linear

The words, ‘linear’ and ‘non-linear’ have different meanings when used in different contexts. The word ‘linear’ is often used to represent serial connections between objects. For example, metabolic pathways often have sequential connections without any branching, feed-forward or feedback paths. Such a pathway is called a linear pathway. On the other hand, a pathway with branching or feedback will be called non-linear. While discussing system behavior, linearity is used in a stricter mathematical sense. The change in output of a linear system is proportional to the change input to the system. A linear system satisfies the following mathematical properties:

If $f(x)$ is the output for an input x, then

$$f(x+y) = f(x)+f(y)$$
$$f(cx) = cf(x), \text{ where } c \text{ is constant}$$

A non-linear system does not satisfy these two properties. Linearity and non-linearity in casualty are often used in the same sense. In case of a non-linear casualty, change in the causal event will not lead to proportional change in the effect; rather in some cases, such change can cause very different effect. In a linear causal system, multiple independent events may add up to give rise to the effect. However, such additivity will not hold when the casualty is non-linear.

purest form. That is why a biologist would purify a biomolecule from a cell and then investigate its functions in a controlled condition in a test tube.

The linear bottom–up (so called Cartesian) approach of reductionism was followed in genetics and in molecular biology. Discovery of gene as the basic unit of heredity, led to the idea that traits of an organism can be explained in terms of genes. Molecular biology followed the same string of thought. It swung the focus from mechanism of action of molecules to flow of information from gene to protein to trait. Though reductionist, tools of molecular biology gave us enormous power to manipulate biological systems at every level. From being passive observers, now we can manipulate a molecule and investigate it, in a test tube, in a cell and even in an organism. This lead to an explosion in cataloging functions of biomolecules. However, this catalog is mostly qualitative in nature. Biochemistry has focus on mechanisms of action, kinetic properties, and quantitative measurements. However, molecular biology focuses on the presence, absence, or modification of a molecule. We measure relative change in expression of a protein to explain a phenomenon. But we rarely investigate the dynamics of the processes involving this protein. For most cases, biology is now a simplified all-or-none system.

From biochemistry to molecular biology, we have followed the reductionism that reduces a complex biological process to a handful of molecules and explains the process in the linear scheme of molecule-to-phenomenon (Mazzocchi, 2011). This approach has paid rich dividends. We have used it to explain how our muscles work, to develop newer drugs, to develop diagnostic tools, to create transgenic crops, to create recombinant proteins for therapeutic and industrial uses and to understand hereditary diseases like haemophilia. This list goes on. But, there is another long list of questions that our current approach in biology fails to answer.

Box 2

Complex System

‘Complex System’ and ‘Complexity’ are two often-used terms in Biology. However, there exists no consensus definition and measure of ‘complexity’. Though inappropriate, ‘complex system’ and ‘complicated system’ are often used interchangeably. For our discussion, we will use simplified working definitions for these two terms. For this, we will use a system of gas as a metaphor. Consider a box filled with a gas. As per the kinetic theory of gas, we will consider this as a system of identical particles (i.e. gas molecules). These particles are in motion inside the box and except elastic collisions, there are no other interactions (or forces) between these particles. We will consider this as a ‘simple system’. In this system, the gas particles will follow the classical mechanics and we can calculate their trajectories. Now consider a system where we have more than one type of gas in the box and they still follow the assumption that there are no interactions among the particles except elastic collision. As we have more than one type of gas particles, with different sizes and masses, our calculations will be a bit difficult. Even then, as there are no interactions among the particles, we will be able to follow the trajectories. We will call this a ‘complicated system’. Now imagine a box filled with large number of different gasses where each gas particle has some additional interactions (like attraction/repulsion) with any other particle in the box. Here, dynamics of each particle will not only depend upon its own momentum, but also upon other interacting particles present around it at that moment. As those interacting particles also have similar dynamics, the trajectories of gas particles will be very different from what is observed in a simple or complicated system. In this system, several new and non-linear behaviors would emerge, depending upon the rules of interactions, which are not observed in a complicated system. We call this a ‘complex system’. A complicated system is made up of large number of different component. However, a complex system has large number of components with interactions between the components. Therefore, a complex system is an evolving time-variant system.

2. Problems in reduction

2.1. Searching for the master control

Metabolic pathways are visualized as cascades of enzymatic reactions. The rate-limiting step of a pathway is the step with slowest rate of reaction. The enzyme involved in that step is called the rate-limiting enzyme. The concept that one particular enzyme can control the overall rate of a pathway involving so many other molecules, in itself is a reductionist idea. Following this approach, one would assume that increase in the expression of this enzyme would increase the yield of metabolic products. However, such attempts failed to yield expected results (Moreno-Sanchez et al., 2008). Eventually, we realized that metabolic pathways are not linear and not controlled by one single master regulator. Rather, the control is distributed at various steps and local control is constrained by system-level properties like metabolic flux through the pathway (Fell, 1992; Thomas and Fell, 1998) (see Box 4). Developments in Metabolic Control Analysis (Wildermuth, 2000) and Biological Systems Theory (Voit, 2013) moved the focus from one molecule in a metabolic pathway to the system as a whole.