Plant Systems Biology
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Introduction to systems biology

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Abstract

The developments in the molecular biosciences have made possible a shift to combined molecular and system-level approaches to biological research under the name of *Systems Biology*. It integrates many types of molecular knowledge, which can best be achieved by the synergistic use of models and experimental data. Many different types of modeling approaches are useful depending on the amount and quality of the molecular data available and the purpose of the model. Analysis of such models and the structure of molecular networks have led to the discovery of principles of cell functioning overarching single species. Two main approaches of systems biology can be distinguished. *Top-down* systems biology is a method to characterize cells using system-wide data originating from the Omics in combination with modeling. Those models are often phenomenological but serve to discover new insights into the molecular network under study. *Bottom-up* systems biology does not start with data but with a detailed model of a molecular network on the basis of its molecular properties. In this approach, molecular networks can be quantitatively studied leading to predictive models that can be applied in drug design and optimization of product formation in bioengineering. In this chapter we introduce analysis of molecular network by use of models, the two approaches to systems biology, and we shall discuss a number of examples of recent successes in systems biology.

From a molecular to a systems perspective in biology

In the last century many of the molecular details of living organisms have been deciphered. The identification of molecular constituents was greatly speeded up by genome sequencing. Many of the processes occurring in cells have been characterized. For simple organisms, such as *Escherichia coli* or yeast, large parts of the metabolic network structure, the operon structure and their transcriptional regulators are now known [1–3].

This knowledge allows for combined molecular and system-level studies applying a synergistic approach involving modeling, theory, and experiment under the name of *Systems Biology*. Dynamics of entire cells cannot yet be modeled with detailed kinetic models but we anticipate that this may happen within a decade or two. Detailed stoichiometric models of entire organisms have already been studied [1, 4–6]. Those cannot deal with the dynamics of cells for they do not contain any kinetic data; they focus on distributions of steady-state flux or study network organization. However, the dynamics of a number of subsystems of cells have already been modeled in great detail (e.g., [7–12]). Such models describe the molecular mechanisms operative in cells. They contain all the molecular knowledge available of the systems under study; they are near replica of the real system. We term such models *silicon-cell models*. They allow for a 'completeness' test of our knowledge (e.g., [7, 9, 10]). This form of scientific rigidity is unprecedented in biology. In addition, those models allow for analysis of the system *in silico* in ways not (yet) achievable in the laboratory (e.g., [13, 14]). More importantly, they may allow for rational strategies of drug design in medicine and optimization of product formation in bioengineering (e.g., [11, 15, 16]). Also more qualitative models are of importance in systems biological approaches to illustrate principles (re-) occurring in molecular networks [17, 18]. Such models may be model reductions of complicated silicon-cell models to facilitate explanation of phenomena by focusing on the core mechanism responsible for some phenomenon of interest. In other cases, such models may be approximations of the real system to describe phenomena too complicated to grasp without usage of mathematical modeling [14, 18, 19].

Systems biology aims to provide a firm link between the molecular disciplines in biology, such as genetics, molecular biology, biochemistry, enzymology, and biophysics, and the disciplines within biology that study entire organisms, i.e., cell biology and physiology [20, 21]. It does so by quantitatively characterizing the molecular mechanisms in organisms on a molecular and system level. Such combined molecular and system-level studies are therefore a sort of unification; they 'unify' the molecular characterization of organisms with their physiological – behavioral or functional – characterization. That is, they indicate how the properties of organisms are brought about by the properties of their molecular constitution and organization and how the system can be altered molecularly to have it behave as desired.

Many associate this kind of strategy with reduction, i.e., that properties of organisms are reduced to properties of molecules; that properties of organisms are *just* properties of molecules. We disagree with such kinds of statements [22]. Rather, the type of reduction achieved here is that of mechanistic explanation [23, 24]. Properties of organisms that are unique to organisms – not found on the level of single molecules or simpler systems thereof – are explained in terms of the molecular mechanisms that manifest those properties. Accordingly, organisms display emergent behaviors not displayed by any of their molecules in isolation, such as adaptation, growth, robustness, and natural selection [22, 25]. Those emergent system properties do depend on the properties of the molecular constituents *but* even more