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Minireview

The dynamic systems approach to control and regulation of intracellular networks

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Abstract Systems theory and cell biology have enjoyed a long relationship that has received renewed interest in recent years in the context of *systems biology*. The term 'systems' in systems biology comes from *systems theory* or *dynamic systems theory*: systems biology is defined through the application of systems- and signal-oriented approaches for an understanding of inter- and intra-cellular dynamic processes. The aim of the present text is to review the systems and control perspective of dynamic systems. The biologist's conceptual framework for representing the variables of a biochemical reaction network, and for describing their relationships, are pathway maps. A principal goal of systems biology is to turn these static maps into dynamic models, which can provide insight into the temporal evolution of biochemical reaction networks. Towards this end, we review the case for differential equation models as a 'natural' representation of causal entailment in pathways. Block-diagrams, commonly used in the engineering sciences, are introduced and compared to pathway maps. The stimulus–response representation of a molecular system is a necessary condition for an understanding of dynamic interactions among the components that make up a pathway. Using simple examples, we show how biochemical reactions are modelled in the dynamic systems framework and visualized using block-diagrams.

Keywords: Pathway; Biochemical reaction network; Dynamics; Feedback; Block-diagram

A cell is built up of molecules, as a house is with stones.
But a soup of molecules is no more a cell
Than a heap of stones is a house.

1. Pathways as dynamic systems

In an amusing article, Yuri Lazebnik [1] argues that with the ever increasing flood of information about the components that are involved in any of the cell functions, like apoptosis, we are failing to improve our understanding of cell functions. Put specifically, by simply collecting and cataloguing the components and their molecular properties, we lose sight of how the components interact functionally. By comparing an engineering approach to systems with that of biology, he argues that a more systematic and formal approach is necessary to move from molecular characterization towards an understanding of cell function through the interactions of the components involved. The functions of the cell do not reside in the molecules themselves but in their interactions, just as life is an emergent, rather than an inherent, property of matter. Although life, or the functions of the cell, arise from the material world, they cannot be reduced to a plain description of the component parts. A central dogma of systems biology is that it is the dynamic interactions of molecules and cells that give rise to biological function. The understanding of inter- and intracellular networks defines the agenda of the (re-)emerging area of systems biology. The principle aim is to understand intra- and inter-cellular processes [2]:

1. How do the components within a cell interact, so as to bring about its structure and function?
2. How do cells interact to develop higher levels of organization, including, cell clusters, tissue and organs?

To support an understanding of the functioning and function of cells, in our view systems biology ought to focus on mathematical modelling and simulation of the dynamics associated with biochemical reaction networks (pathways).

With the many reviews and special issues available on the subject, the present article instead focusses on the differential equation or dynamic systems approach that underlies the majority of noteworthy publications that may be attributed to this area. One notices a trend in the current literature that the term 'mathematical' is frequently avoided and replaced by 'computational' to make mathematical modelling and simulation more acceptable to experimentalists. Systems biology is trying to establish a close link between experimental data and mathematical models in molecular and cell biology. Central to any computational approach or simulation is a *model*, a mathematical model. Variables in a dynamic system change with

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Abbreviations: ODEs, ordinary differential equations; PDEs, partial differential equations

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time and for these changes to be ordered and meaningful they must be organized in a formal model. Control systems analysis provides a way of formalizing such organization by using structured mathematical descriptions of dynamical systems, and graphical representations of system component interactions. The purpose of this article is to provide a review of system- and signal-oriented methods for biologists. On the way, we learn about various ways to represent and visualize our understanding, including the biologist's pathway diagrams, the biochemists reaction equations, pathway maps, the mathematician's differential equation models, and the control engineer's block-diagrams. These tools serve as an interface between the practical experiment and a theoretical model of system dynamics.

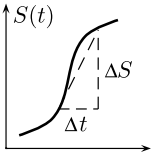
2. Differential equations as a language for observed changes

There are a range of formalisms available for modelling and/or simulation of biochemical networks, including formal languages, stochastic models and differential equations. The choice of a suitable framework is not only guided by which formalism would provide the most realistic representation. The large number of variables and nonlinear relationships force us to make assumptions. The experimental diffculties in quantifying intracellular concentrations renders most models in molecular and cell biology *phenomenological*. We are thus not in the business of building in silico replica models of actual physical interactions of molecules. Instead, we ought to choose a conceptual framework that is best suited to support the biologist's reasoning in making sense of observations.

Cell functions, including cell growth, cell differentiation, proliferation, stress response, etc. are dynamic processes. We observe through temporal changes in concentrations, counts or copy numbers. A natural approach to describe dynamic processes in terms of rates of change are differential equations. Differential equations come in two flavors: *ordinary* differential equations (ODEs), describing changes over time and *partial* differential equations (PDEs), describing changes in space and time. While the latter seem intuitively more appropriate for modelling intra- and inter-cellular processes, they require mathematical tools and experimental data that in most practical cases are not available. We hereafter focus, therefore, on ODEs as the most commonly adopted, although not only approach for modelling intra-cellular dynamic processes. To motivate differential equation modelling we use a very simple model of proteolysis. Let us consider a protease E, which cleaves a specific peptide bond in a substrate protein S, and thereby activating it to yield the modified cleaved form P. In the first step, we would assume or hypothesize the principle:

"The rate of proteolysis is inversely proportional to the amount of substrate."

Assuming the rate of cleavage (proteolysis) is inversely proportional to the amount of inactive substrate S, we can translate this into a mathematical model by first considering a notation for the rate of change of substrate S: $\mathrm{d}S/\mathrm{d}t$. The change over time is related to the slope of the concentration profile:



$$\frac{d}{dt}S = \lim_{\Delta t \to 0} \frac{\Delta S}{\Delta t}$$

The mathematical model for changes in the substrate concentration is subsequently obtained as

$$\frac{d}{dt}S = -k_p S(t)$$

k_p: variable (changes); $-$: parameter (fixed)

The parameter k_p defines the rate coefficient and includes assumptions about (constant) temperatures and volume. The concentration profile of the cleaved form, $P(t)$ is readily obtained from $P(t) = S_0 - S(t)$, where S_0 denotes the initial substrate concentration. The state of the system is, therefore, completely determined by $S(t)$. For simple differential equation models, we find an analytical or formal *solution*. This is another equation which describes the curve $S(t) = S_0 \cdot \mathrm{e}^{-k_\mathrm{p} t}$. For more complex systems, we will often not be able to find such solutions in analytical form but instead obtain solutions through numerical integration of the differential equations.

With the chosen framework of ODEs we now look at more complex networks. Pathways are the concept by which knowledge of interactions of proteins in cell functions is organized. A *pathway map* exhibits the names of the molecular components, whose interactions govern the basic cell functions. This leads us to a definition of pathways as biochemical *networks*. A large number of pathway maps are collected in biological databases (e.g., http://www.kegg.org). Whether we are aiming for stochastic models or a differential equation model, one possible approach to bring these static diagrams to life through modelling and simulation, is to decompose large reaction networks into a set of unidirectional *reaction channels* R_μ

$$\mathrm{R}_\mu : l_{\mu 1}\mathrm{X}_j + l_{\mu 2}\mathrm{X}_2 + \cdots + l_{\mu n}\mathrm{X}_n \xrightarrow{k_\mu} \ldots$$

where X denotes a chemical species participating in a reaction, the '+' signs represent a combination, the arrow represents a transformation proceeding with rate k_μ and $l_{\mu j} \geqslant 0$ defines the number of molecules of X_j involved in the reaction [3]. For instance, consider the following example

$$\mathrm{X}_1 + \alpha\mathrm{X}_2 \xrightarrow{k_1} \beta\mathrm{X}_3 \xrightarrow{k_2} \alpha\mathrm{X}_2 + \gamma\mathrm{X}_4 s$$

which can be split into two reaction channels

$$\mathrm{R}_1 : \mathrm{X}_1 + \alpha\mathrm{X}_2 \xrightarrow{k_1} \beta\mathrm{X}_3 \quad \mathrm{R}_2 : \beta\mathrm{X}_3 \xrightarrow{k_2} \alpha\mathrm{X}_2 + \gamma\mathrm{X}_4$$

When a reaction occurs, the changes to molecule populations can be summarized in form of vectors

$$v_1 = (-1, -\alpha, \beta, 0), \quad v_2 = (0, \alpha, -\beta, \gamma).$$

That is, if the first reaction channel is active, the population of X_1 molecules decreases by one, the population of X_2 by α molecules and so forth. Applying the *law of mass action*, a differential equation model is easily derived. Denoting with $x_1,\ldots,x_4$ the dynamic variables corresponding to chemical species $\mathrm{X}_1,\ldots,\mathrm{X}_4$, we have