BioSystems 129 (2015) 1–18

Contents lists available at ScienceDirect

BioSystems

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

Review Article

Methodologies for the modeling and simulation of biochemical networks, illustrated for signal transduction pathways: A primer

Nesma ElKalaawy*, Amr Wassal

Department of Computer Engineering, Faculty of Engineering, Cairo University, Giza 12613, Egypt

ARTICLE INFO

Article history:
Received 26 June 2014
Received in revised form 23 January 2015
Accepted 23 January 2015
Available online 28 January 2015

Keywords:
Biochemical networks
Signal transduction pathways
Modeling and simulation
Stochastic methods
Ordinary differential equations
Partial differential equations

ABSTRACT

Biochemical networks depict the chemical interactions that take place among elements of living cells. They aim to elucidate how cellular behavior and functional properties of the cell emerge from the relationships between its components, i.e. molecules. Biochemical networks are largely characterized by dynamic behavior, and exhibit high degrees of complexity. Hence, the interest in such networks is growing and they have been the target of several recent modeling efforts. Signal transduction pathways (STPs) constitute a class of biochemical networks that receive, process, and respond to stimuli from the environment, as well as stimuli that are internal to the organism. An STP consists of a chain of intracellular signaling processes that ultimately result in generating different cellular responses. This primer presents the methodologies used for the modeling and simulation of biochemical networks, illustrated for STPs. These methodologies range from qualitative to quantitative, and include structural as well as dynamic analysis techniques. We describe the different methodologies, outline their underlying assumptions, and provide an assessment of their advantages and disadvantages. Moreover, publicly and/or commercially available implementations of these methodologies are listed as appropriate. In particular, this primer aims to provide a clear introduction and comprehensive coverage of biochemical modeling and simulation methodologies for the non-expert, with specific focus on relevant literature of STPs.

Contents

1. Introduction

Studying the individual components of a biological system is an important initial step; however, this alone is not sufficient to arrive at a derivation of the system behavior. Many properties arise at the

* Corresponding author.
E-mail addresses: kalaawy@eng.cu.edu.eg (N. ElKalaawy), wassal@eng.cu.edu.eg (A. Wassal).

http://dx.doi.org/10.1016/j.biosystems.2015.01.008
0303-2647/

system level only. Therefore, biology has shifted from the molecular characterization of the biological system, towards the integration of its components, their behavior, and their relationships. The latter gave rise to the notion of systems biology. Systems biology attempts to determine a system-level understanding of biological systems through the examination of the structure and dynamics of cellular and organismal functions, rather than the characteristics of the isolated parts of a cell or an organism (Ideker et al., 2001; Kitano, 2002).

Static diagrams, which merely describe a system by a collection of components and their interconnections, are of little help when it comes to understanding how the different components interact to achieve a certain function (Kitano, 2002). The inherent complexity of biological systems and the accumulation of huge amounts of biological data mandate a systematic approach.

Using computational and mathematical models for biological processes allows discovering emergent properties, examining system behavior, and generating new hypotheses. Such models allow performing *in silico* experiments that would be very expensive or impossible to perform in the laboratory (Decraene and Hinze, 2010). In light of these benefits, new user-friendly modeling languages and tools that allow biologists to represent biological systems more intuitively are emerging. Moreover, formal approaches are being incorporated in biological research, standardized representations of biological data are being established, and biological systems modeling is gaining better ground (Fisher and Henzinger, 2007).

Biochemical networks constitute examples of biological systems that have been modeled extensively. Such networks are classified into three broad categories: metabolic networks, gene regulatory networks, and signaling networks. *Metabolic networks* comprise the set of reactions that occur in living organisms for the production and degradation of organic compounds needed for an organism's vital functions (Liiving et al., 2011).*Gene regulatory networks* are concerned with the control of transcription, i.e., how genes are up- and down-regulated in response to signals. *Signaling networks* describe how cells receive, process, and respond to stimuli from the environment, as well as stimuli that are internal to the organism. In this primer, we present an introduction to the modeling and simulation of biochemical networks, illustrated for the class of signaling networks.

The rest of this primer is organized as follows. Section 2 discusses signaling networks in detail. Section 3 presents the different methodologies used for modeling and simulation of biochemical networks, with specific reference to models of signaling networks. Relevant surveys describe similar methodologies (Andrews et al., 2009; Decraene and Hinze, 2010; Eungdamrong and Iyengar, 2004a; Eungdamrong and Iyengar, 2004b; Fisher and Henzinger, 2007; Gilbert et al., 2006; Hughey et al., 2010; Materi and Wishart, 2007; Meng et al., 2004; Pahle, 2009; Pinney et al., 2003; Sreenath et al., 2008; Turner et al., 2004). Some of these focus on only a subset of methodologies and/or overlook the fundamental differences between the methodologies. On the other hand, this primer covers a large number of methodologies and particularly aims to provide a clear introduction and comprehensive coverage of the methodologies for the non-expert. In particular, by using signaling networks as an example, we try to establish a clear understanding of the fundamentals of biochemical modeling and simulation. By discussing relevant signal transduction models from the literature, we aim to illustrate how the different formalisms capture different behaviors of biochemical systems, and how modelers are guided at their choice of method and at their modeling process. In Section 4, we discuss modeling and analysis tools that are widely used in the biochemical community. Finally, Section 5 provides a summary and comparison of the methodologies, and the conclusions are given in Section 6.

2. Signaling networks

In order for an organism to respond to internal and external stimuli, its cells have to communicate together. Cells communicate using *intercellular signaling*, i.e., either by sending out signaling molecules in the extracellular space, or by direct contact between neighboring cells (Krauss, 2004). When a signal arrives at a recipient cell, certain proteins, called *receptors*, are activated. Activated receptors pass on the signal to other proteins inside the cell and this initiates a chain of *intracellular signaling* processes. Such chains ultimately result in generating different cellular responses, such as proliferation, differentiation, or apoptosis.

The set of successive events that take place as part of an intracellular signaling chain are often termed a *signal transduction pathway*, (STP). Generally, a 'pathway' is an abstraction that biologists use to describe the core of a biochemical network, comprising a sequence of events (Gilbert et al., 2006). It is used in the context of signaling, metabolic, and gene regulatory networks. A common example of an STP is the mitogen activated protein kinase (MAPK) pathway. MAPKs are a family of protein kinases that mediate signals from cell-surface receptors to different cellular compartments and regulate various cellular activities. They are conserved in many organisms, and they play an important role in many pathological conditions, including cancer and other diseases (Zhang and Liu, 2002). Orton et al. (2005) compared three different models of the MAPK pathway and illustrated how the models focus on different parts of the same pathway. Different models include different subsets of molecules and reactions and stop at different points in the pathway, depending on the questions that they seek to answer.

STPs have been traditionally viewed as separate linear entities. However, this description can no longer account for the complex patterns observed in these pathways. STPs are very dense, and have a large number of molecular species that dynamically move between cellular organelles. These species do not only make linear connections with other upstream and downstream components, but they also exhibit a lot of branching, horizontal interconnections, and even feedback loops (Mellman and Misteli, 2003). Moreover, STPs are rarely isolated, i.e., there is usually crosstalk between the different pathways.

Like their biological counterparts, models of STPs display sophisticated structures. This is further complicated by the fact that information about a particular pathway comes from various databases and research work, possibly with different representations (Heiner et al., 2004). Several methods have been used to model STPs, of which the most common are ordinary differential equations (ODEs). However, new methods are being continuously proposed and investigated. In general, models of STPs are classified into two main categories: structural network models and dynamic analysis models. *Structural network models* are based solely on connectivity information. They can generate hypotheses regarding the structure of the global network, as well as the function of individual proteins. Such models reconstruct the topology of a signaling network. On the other hand, *dynamic analysis models* require, in addition to the network connectivity, numerical values of the kinetic rate constants and the initial concentrations of signaling proteins and complexes. These models measure the time-variant properties of a network. In other words, once the associated quantitative data are known, dynamic analysis of a reconstructed signaling network can be carried out (Papin et al., 2005). It is believed that signaling molecules interact dynamically and non-linearly to achieve specificity of responses, i.e., the ability to selectively activate a specific cellular response (Pawson, 2004). For this reason, dynamic modeling has been the conventional method for modeling STPs. However, since dynamic analysis models build upon structural network models, it is necessary to first verify the consistency and correctness of the latter (Heiner et al., 2004).