

## Chapter 6

# The Present and the Future Perspectives of Biological Network Inference

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### **ABSTRACT**

*Biological network inference is based on a series of studies and computational approaches to the deduction of the connectivity of chemical species, the reaction pathway, and the reaction kinetics of complex reaction systems from experimental measurements. Inference for network structure and reaction kinetics parameters governing the dynamics of a biological system is currently an active area of research. In the era of post-genomic biology, it is a common opinion among scientists that living systems (cells, tissues, organs and organisms) can be understood in terms of their network structure as well as in term of the evolution in time of this network structure. In this chapter, the authors make a survey of the recent methodologies proposed for the structure inference and for the parameter estimation of a system of interacting biological entities. Furthermore, they present the recent works of the authors about model identification and calibration.*

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## **1. NETWORK INFERENCE: GOALS AND METHODOLOGICAL APPROACHES**

To define the network structure of a biological system, network biology researchers use data generated by experimental methods, including high-throughput proteomic, genomic, and metabolomic data, as well as computational capabilities to identify and infer the topology and the causality of the interactions. It is beneficial to conceptualize a cell or higher units of biological organization as systems of interacting elements, i. e. as networks of influences, physical or statistical, between components. High-throughput experimental methods enable the measurement of expression levels for thousands of genes and the determination of thousands of protein–protein or protein–DNA interactions. It is increasingly recognized that theoretical and computational network inference methods are needed to make sense of this abundance of information. Viewing biological systems in terms of their underlying network structure is a powerful concept. All networks share common characteristics, and, consequently, common mathematical frameworks can be developed to understand their structure and how they can be regulated. For such conceptual framework, that is the basis for a systems-level description, one needs to know (i) the identity of the components that constitute the biological system; (ii) the dynamic behavior of the abundance or activity of these components; and (iii) the interactions among these components (Kitano, 2002). Ultimately, this information can be combined into a network that, if it is validated and revealed to be consistent with current knowledge, provides new insights and predictions, such as the behavior of the system in conditions that were previously unexplored.

Currently methodological approaches and algorithms have been proposed to determine reaction mechanisms from time series data which are collected for gene and protein interactions and for metabolic pathways and networks. The

aim of these techniques is to infer the system of biochemical reaction mechanisms from time series data on the concentration or abundance of different reacting components of a network, with little prior information about the pathways involved. The great majority of these methods belongs to the class of the mechanistic approaches to the network inference knowledge. Crampin et al. (Crampin, Schnell, & McSharry, 2004) provide a survey of mathematical and computational mechanistic techniques proposed to deduce complex biochemical reaction networks. The majority of the reviewed techniques require the generation and analysis of significant quantities of experimental data in terms of composition and concentration time series.

The mechanistic view of a system of biochemical reactions is widespread among the modelers. It is considered important for several reasons: (i) an improved understanding of the functional role of different molecules can be achieved only with the knowledge of the mechanism of specific reactions and the nature of key intermediates; (ii) the control (or regulation) of different biochemical pathways can best be understood if some hypothesis for the reaction mechanism is available; (iii) kinetic modelling, which forms the basis for understanding reaction dynamics, is based on comprehensive information about the reaction mechanism. Kinetic models allow simulation of complicated pathways, and even whole-cell dynamics, which is proving to be an increasingly important predictive tool (Noble, 2002; Crampin, Schnell, & McSharry, 2004).

The data required for kinetic modelling are typically time series data of the response of a biochemical system to different conditions and stimuli. The reason why these data are used is that time series data reveal transient behavior, away from chemical equilibrium, and contain information on the dynamic interactions among reacting components. From time resolved data of reagent concentration, the mechanistic inference methods deduce the nature of reagents and their interactions

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