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Review

Robustness analysis, prediction, and estimation for uncertain biochemical networks: An overview☆

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ABSTRACT

Mathematical models of biochemical reaction networks are important tools in systems biology and systems medicine, e.g., to analyze disease causes or to make predictions for the development of effective treatments. Models are also used in synthetic biology for the design of circuits that perform specialized tasks. Prediction, analysis and design require plausible and reliable models, that is, models must reflect the properties of interest of the considered biochemical networks. One remarkable property of biochemical networks is *robust functioning* over a wide range of perturbations and environmental conditions. The intrinsic robustness of a network should be reflected into its associated mathematical model. The description and analysis of robustness in biochemical reaction networks are challenging, however, because accounting explicitly for the various types of structural, parametric and data uncertainty in the description of the models is not straightforward. Furthermore, system properties are typically inherently uncertain and often only given by qualitative or verbal descriptions that impede a straightforward and comprehensive mathematical analysis. In the first part of this overview article, network functions and behaviors of interest are formally defined, and different classes of uncertainties and perturbations are consistently described. The second part reviews frequently used mathematical formulations and presents the authors' recent developments for robustness analysis, estimation, and model-based prediction. One biochemical network model is used to illustrate the capabilities of various methods to deal with the different types of uncertainties and robustness requirements.

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1. Introduction

Biochemical reaction networks form the structural basis of most cellular processes such as metabolism, signal transduction, and gene expression. In these networks, many species dynamically interact and are transformed by biochemical reactions to perform and maintain biological functions. Intertwined and possibly redundant feedback and feedforward mechanisms give rise to complex dynamical behaviors while their lack or improper functioning can result in dysfunctions or diseases. To minimize such risks, biological networks must perform their tasks reliably under various changes of the cellular environment and conditions [19,58,74,80]. This property is generally called *robustness* and refers to the *persistence of a behavior* or the *insensitivity of function characteristics* in the presence of (external or internal) perturbations [130]. Typical examples of *biological behaviors* that are robust to environmental changes are oscillations or multistability in the cell cycle, in apoptosis, or in adaptation [121,2]. The readers are referred to [1] for other examples and mechanisms of cellular regulation.

Robust functioning is of particular interest in synthetic biology or metabolic engineering. One core task in synthetic biology is the design of motifs or building blocks that perform a function robustly when connected into larger networks and under various perturbations of the cellular environment [99]. Function characteristics of interest include certain types of dynamic behavior such as the time derivation of inputs as required for adaptation to constant stimuli, logical combinations of different inputs, oscillatory behavior or multistability [113]. Note that these behaviors are described in a verbal and qualitative manner.

Besides the *robustness of qualitative behaviors* or function characteristics, *quantitative predictions* of system responses have become increasingly important, especially in therapy design and synthetic biology [145]. Often mathematical models are developed and employed to analyze and quantitatively predict, estimate, and control the response of the considered systems with respect to applied

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