In silico modeling of biochemical pathways

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Abstract

We present *in silico* modeling methods for the investigation of dynamical properties of *biochemical pathways*, that are chemical reaction networks underlying cell functioning. Since pathways are (complex) dynamical systems, in-silico models are often studied by applying numerical integration techniques for Ordinary Differential Equations (ODEs), or stochastic simulation algorithms. However, these techniques require a rather accurate knowledge of the kinetic parameters of the modeled chemical reactions. Moreover, in the case of very complex reaction networks, in-silico analysis can become unfeasible from the computational viewpoint. Consequently, in the last few years several approaches have been proposed that focus on estimating or predicting dynamical properties from the analysis of the *structure* of the biochemical pathway. This means that the analysis focuses more on the interaction patterns than on the kinetic parameters, and this usually makes it possible to deduce the role of each molecule and how each molecule qualitatively influences each other, by abstracting away from quantitative details about concentrations and reaction rates.

In silico approaches for the analysis of biochemical pathways allow reducing *in vitro* and *in vivo* experiments by performing preliminary computational investigations.

Biochemical pathways can be represented as *graphs* (also called *networks*) that are abstract mathematical structures consisting on *nodes* connected by *arcs*. In the graph representation of a pathway, typically nodes represent molecules and arcs represent interactions (*i.e.* chemical reactions) between the molecules they connect. Sometimes, in a more accurate representation, also chemical reactions are represented as nodes, and in this case an arc between a molecule node and a reaction node represents the fact that the molecule is a reactant, a product, or a modifier (promoter/inhibitor) of such a reaction.

Most of the approaches that have been proposed for the structural analysis of pathways perform explorations of the graph representation. For instance, if we are interested in finding molecules that can influence the dynamics of a specific target molecule (*e.g.* during drug design) we can apply an algorithm that computes the *paths* in the graph from candidate molecules to the target in order to identify the most promising ones. Other approaches apply standard graph-theoretic measurements (*e.g.* centrality) in order to identify the key molecules in the whole pathway.

Recently, we proposed different approaches that aim at predicting dynamical properties, such as robustness or monotonic response to perturbations, without the need of performing a huge number of numerical or stochastic simulations. On the one hand, we proposed approaches that allow such properties to be assessed by checking whether the graph representation of the pathway satisfies some structural conditions we identified.[1,2] On the other hand, we developed methods based on machine learning on graphs that can automatically infer a model of the relationship between pathway structure and dynamics in order to make predictions of dynamical properties directly from the graph representation of the pathway.[3,4]

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