Original articles

Nonlinear and temporal multiscale dynamics of gene regulatory networks: A qualitative simulator

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Highlights

- Simulation tool of the nonlinear dynamics of gene network models.
- Generation of *all* the possible trajectories in a *single* run.
- Characterization of the qualitative properties of predicted trajectories.
- Calculation of the probability of occurrence of each simulated trajectory.

Abstract

Advanced experimental technologies have made the disclosure of networks of intricate regulatory interactions between genes and gene products feasible and revealed their extreme complexity. Thus, understanding which particular dynamical behaviors derive from specific gene regulatory structures poses a challenging question, at both scientific and application level, that necessarily requires computational tools to be answered. Herein, we discuss the algorithmic aspects and the implementation of a mathematical method, grounded on singular perturbation analysis, for the study of the dynamics of regulated gene networks. This results in a gene regulatory network simulator of the full range of possible dynamics of a specific class of ordinary differential equations adequate to model gene regulatory networks. The considered class of equations represent phenomenological models of the long interaction chains in a network: genes are the main players and the interactions between them are modeled by steep threshold-dependent response functions. The simulator we propose operates in the presence of incomplete knowledge of parameter values. It assumes that threshold-dependent regulation is modeled by continuous steep sigmoid functions, and each transcription factor only regulates one gene at each of its thresholds. Under these assumptions, the simulator derives sound predictions of the nonlinear and temporal multiscale dynamics of a gene regulatory network from an initial state and parameter space, symbolically described by inequalities between parameters. Beside its predictive soundness, it outperforms other qualitative simulators as for characterization of trajectories and possible calculation of the probability of occurrence of each behavior when parameters are assigned stochastic values.

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Keywords: Gene regulatory networks; Nonlinear ODE models; Sigmoidal response; Qualitative simulation; Stochastic parameters

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1. Introduction

Networks of mutual interactions between molecular species (e.g., genes, RNAs, proteins, etc.) that regulate the concentration levels and temporal patterns of gene products, the so-called Gene Regulatory Networks (GRN), can be inferred by gene expression profiles as interaction graphs [16,5,1]. Also, interaction graphs represent the blueprint for synthetic GRNs that are engineered to have a certain function [40]. The analysis of these interaction graphs, based on graph theory, is suitable to gain new biological insights on the network structures underlying specific systems through the identification of important network properties such as interlocking positive and/or negative feedback loops, autoregulation, global interdependency, or signaling paths. But, the comprehension and prediction of the combined effects of these phenomena, and then of the overall dynamics of GRNs, are very rarely within the capacity of intuition and interaction graph analysis. Mathematical modeling and simulation frameworks are a must [2] to (1) capture the complexity of the mostly nonlinear network dynamics, (2) predict, in both normal and mutant organisms, the behavioral changes due to endogenous or exogenous perturbations or (3) test the coherence and completeness of regulation network structures hypothesized to underlie specific systems.

Several frameworks for modeling and simulating GRNs, in both deterministic and stochastic contexts, have been proposed [10,27,30,41]. They differ one from each other in goals, strengths and weaknesses, resolutions, discrete or continuous, at which they capture network dynamics as well as in the way they model the response functions. The suitability of either one or the other approach to study a specific network depends on modeling tasks, applicability and generalization.

Among the proposed approaches for modeling GRNs, a great attention has been paid to Ordinary Differential Equation (ODE) models that provide a continuous and accurate representation of the dynamics of the concentrations of gene products. Several computational frameworks for the thorough study of biochemical reaction networks are currently available, e.g. COPASI [22] and DBSolve [17], but their use is limited to quantitative ODE models where the equations describe the intracellular dynamic processes and values of kinetic parameters and molecular concentrations are given specific values. With exception of well-studied small GRNs, precise and quantitative information on the biochemical reaction mechanisms underlying regulatory interactions, and on values of kinetic parameters and molecular concentrations are frequently unknown and hard to estimate from noisy high-throughput data. Thus, the formulation of models that can be analyzed and simulated with the above-mentioned tools is typically hampered for a great number of cases. However, at the current state of knowledge, the key issue is to understand how specific activity patterns derive from given network structures and what different types of dynamical behaviors are possible. Thus, qualitative analysis and simulation of GRN dynamics is a rather appropriate solution.

Phenomenological ODE models, that are the continuous analogues of Boolean networks [44,42,45], can be derived from the interaction graphs of GRNs by using concepts and ideas from mathematical logic combined with earlier ideas on allostery and cooperativity [36], that lead to a sigmoidal rate dependence of key metabolites. Since their first introduction, these models have gained an increasing experimental support [23] that makes them reasonably acceptable and adequate to model gene regulation mechanisms. Following the pioneering efforts in this direction started in the early 1970s [19], several frameworks for modeling the dynamics of GRNs with interaction terms described by steep sigmoids around certain thresholds or approximated by binary on–off functions have been developed. In the former case, the effect of a transcription factor on the transcription rate of a gene, the *response function*, is described phenomenologically by a sigmoidal function of its concentration with a pronounced threshold behavior (e.g. Hill function), and the network dynamics is modeled by nonlinear ODEs [34]. In the latter one, a Heaviside step function approximates the response function and Piecewise Linear (PL) ODEs [18,13] model the network dynamics. The problem of analyzing the behavior of both classes of models has been tackled under a variety of assumptions and with the support of the available body of theory and methods for the analysis of dynamical systems.

The major problem with PL-ODEs is that they are not defined in the threshold hyperplanes where response functions discontinuously switch. Earlier investigations considered PL models under the further simplifying assumptions of single threshold per gene, uniform decay rates and no effective autoregulation, and developed mathematical methods for the calculation of continuous trajectories, also across the threshold hyperplanes, from given initial conditions [18,35,13]. Extensions of the proposed methods to models with multiple thresholds and non-uniform decay rates do not present particular difficulties as far as the calculation of trajectories but raise non-trivial problems when effective autoregulation is introduced. The problem of defining a continuous solution across threshold hyperplanes when PL models include autoregulation, ubiquitous in cellular systems, has been tackled by considering