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Qualitative simulation of the nonlinear dynamics of gene regulatory networks

We consider a specific class of ODEs well-accepted in the literature as adequate to model the essential features of the complex dynamics of Gene Regulatory Networks (GRN). In these models, the actions of transcriptional factors on genes depend on their concentration values, and can be modeled by either binary on-off or continuous steep sigmoidal functions around certain threshold concentrations. The network dynamics is modeled by either Boolean or piecewise linear equations in the former case, and by highly nonlinear equations in the latter one.

In a continuos framework, the mathematical problem related to such networks deals with the analysis of the behavior in narrow domains, called *switching domains*, where at least one variable is close to one of its thresholds. The current lack of precise and quantitative information on the biochemical reaction mechanisms underlying regulatory interactions, on kinetic parameters and threshold concentrations along with the size and interaction complexity of the GRNs makes, on the one hand, the solution of this problem particularly challenging, and, on the other hand, the design and implementation of an automated symbolic tool necessary. For piecewise linear models, with Heaviside dose-response functions, a computational analyzer, called GNA, of the qualitative dynamics of GRNs has been proposed (de Jong et al., 2004). The assumption GNA is based on considerably simplifies the analysis but it raises the problem to find a proper continuous solution across threshold hyperplanes. To this end, it adopts the Filippov approach that is not flawless when applied to approximate the limit solutions of a continuous model (Bacciotti, 2003).

In this talk, we consider models with sigmoidal response functions that vary continuously from zero to one with a steep rise around certain threshold concentrations. The ensuing dynamics is both linear and nonlinear with different time scales, and is analyzed with the singular perturbation method adapted to the considered class of models (Plahte and Kjøglum, 2005). The equations of motion for switching domains may raise several mathematical difficulties that lead to an heavy, or even intractable, computational problem. But, the biologically reasonable assumption that each transcriptional factor only regulates one gene at each of its threshold simplifies the problem and allows us to establish sound rules, computationally tractable, that determine the calculation of trajectories as the sequence of phase space domains through which the system passes. When suitable conditions are fulfilled (Ironi et al.,2011), the simulation outcomes do capture the network dynamical properties dependent on the model structure and invariant for ranges of model parameter values. The proposed algorithm has been designed for GRNs but is applicable to study the multi-scale dynamics of threshold-dependent regulatory systems from other application contexts that may be reasonably modeled by the class of ODE models and assumptions we consider.

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