

Inverse Eigenvalue Problems for Exploring the Dynamics of Systems Biology Models

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Abstract. This paper describes inverse eigenvalue problems that arise in studying qualitative dynamics in systems biology models. An algorithm based on lift-and-project iterations is proposed, where the lifting step entails solving a constrained matrix inverse eigenvalue problem. In particular, prior to carrying out the iterative steps, *a-priori* bounds on the entries of the Jacobian matrix are computed by relying on the reaction network structure as well as the form of the rate law expressions for the model under consideration. Numerical results on a number of models show that the proposed algorithm can be used to computationally explore the possible dynamical scenarios while identifying the important mechanisms via the use of sparsity-promoting regularization.

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1 Introduction

Over the past decade, there has been much focus on the field of *systems biology*, with the fundamental goal being to understand how genes act together to bring about the wide-ranging regulatory functions within cells [1]. Various processes are controlled by networks of genes, including the cell division cycle and the circadian rhythm clock [12]; moreover, gene regulatory networks possess robust dynamical properties such that they are able to withstand fluctuating environmental conditions and the imprecision of the underlying biochemical components [2]. To shed light on the many questions that arise, various modeling paradigms have been developed, ranging from boolean models, ODE, PDE, delay-differential equations to stochastic models [12].

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In this paper, we focus exclusively on ODE models of the form,

$$\dot{x}(t) = f(x(t), q), \quad (1.1)$$

where $x(t)$ denotes the n -dimensional state vector and q the m -dimensional parameter vector. In systems biology modeling, one rarely has a detailed knowledge of the parameter values and sometimes even the knowledge of the network topology is incomplete. However, there often exist a direct relation between the qualitative dynamics of system (1.1) as captured in the bifurcation diagram with the cell physiology [33]. In this paper, we examine an inverse problem associated with the qualitative dynamics of (1.1) which commonly arise at the initial stages of modeling gene regulatory networks, namely: given a set of genes as well as their known and hypothetical interactions, can the network be bistable or oscillatory for some choice of parameter values? If so, what are the minimal sets of parameters that one could vary in order to obtain these dynamical phenotypes? Such questions are of practical relevance to the modelers, who may wish to explore or eliminate different hypothetical reaction network topologies and mechanisms. It needs to be emphasized that the dependence of qualitative dynamics on the choice of parameters cannot be neglected: it has been shown that even with a fixed reaction network topology and biochemical mechanism, different choices of parameters can result in oscillators of various qualitative types [7]. At the initial modeling stage, there is no prior knowledge on the influence of its parameters and inverse eigenvalue analysis could be a useful first step by bringing the system to a relevant parameter regime where a more complete picture of its dynamical characteristics would be obtained by carrying out a (forward) bifurcation analysis [19] followed by possible inverse bifurcation analysis [22, 23].

This paper is organized as follows: In Section 2, we describe the underlying methodology and the proposed lift-and-project algorithm. In particular, we discuss in detail the matrix inverse eigenvalue problem that arises and give an illustrative example using a MAP kinase model. In Section 3, we demonstrate the proposed algorithm by applying to a number of systems biology models. The ODE systems for the numerical examples are given in the Appendix.

2 Methodology and algorithms

Let (df/dx) be the Jacobian matrix of the ODE system (1.1). Motivated by such a need to explore qualitative dynamics of gene networks, a computational method has been developed in the systems biology context [5] to find parameters that give rise to limit-point (LP) and Hopf (H) bifurcations [19], which satisfy the spectral conditions $0 \in \sigma(df/dx)$ and $\sigma(df/dx) \supset \{\pm i\omega\}$ respectively.

A minimization problem is formulated, with the objective being functions of eigenvalues of (df/dx) whose minimum are attained by limit-point and Hopf bifurcations [5]. To locate parameters that could bring about the corresponding bifurcations, genetic algorithms are applied. The proposed method has been applied to a number