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Global dynamics for steep nonlinearities in two dimensions

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ABSTRACT

This paper discusses a novel approach to obtaining mathematically rigorous results on the global dynamics of ordinary differential equations. We study switching models of regulatory networks. To each switching network we associate a Morse graph, a computable object that describes a Morse decomposition of the dynamics. In this paper we show that all smooth perturbations of the switching system share the same Morse graph and we compute explicit bounds on the size of the allowable perturbation. This shows that computationally tractable switching systems can be used to characterize dynamics of smooth systems with steep nonlinearities.

1. Introduction

This paper discusses a novel approach to obtaining mathematically rigorous results on the global dynamics of ordinary differential equations. The motivation is twofold. The first arises from applications, in particular the study of regulatory networks. Because of their centrality in the study of systems biology anything beyond the most cursory comments are beyond the scope of this introduction. Instead we refer the interested reader to [1]. The second arises from ongoing work of the authors to develop a mathematical framework, which we call a Database for Dynamics, that provides a computationally efficient and mathematically rigorous analysis of global dynamics of multiparameter nonlinear systems. Reasonable success has been obtained in the context of nonlinear systems generated by maps [2–5]. However, extending these methods to ordinary differential equations is proving to be technically challenging since the rigorous evaluation of a map needs to be replaced by the rigorous evaluation of solutions to a differential equation [6,7]. We return to this topic in the conclusion.

A regulatory network can be represented as an annotated directed graph. The vertices represent a regulatory object, e.g. a protein, and an edge from node m to node n indicates that m directly regulates n. The annotation on this edge indicates whether m activates (up regulates) or represses (down regulates) n. It is natural to think of modeling the dynamics of this system via an ordinary differential equation. In the context of gene regulatory networks, the associated proteins have a natural decay rate, and thus given a network with N genes one is led to a system ordinary differential equation of the form

$$\dot{x}_n = -\gamma_n x_n + f_n(x), \quad n = 1, \dots, N \tag{1}$$

where $\gamma_n > 0$ and f_n is independent of x_m if there is no edge from node m to node n. In the context of applications at this level of generality there is little that one can hope to say. However, it is typically assumed that the interactions have switch like behavior and thus the nonlinearities used to model interactions between individual nodes are often assumed to have a sigmoidal shape. A common construction is based on Hill functions

$$\frac{x^k}{\theta^k + x^k} \quad \text{or} \quad \frac{\theta^k}{\theta^k + x^k} \tag{2}$$

where the former and latter expressions are used to model activation and repression, respectively. However, it is important to keep in mind that there are other models that are probably more representative of the underlying biochemistry [8,9]. Even for N of moderate size the analysis of (1) with arbitrary Hill functions is intractable. A standard simplification is to let $k \to \infty$ in which

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case one obtains nonlinearities that take the form of piecewise constant functions. We refer to this as a *switching system* (for a precise definition see Section 3) and denote it by

$$\dot{x} = -\Gamma x + \Lambda(x), \quad x \in \mathbb{R}^N. \tag{3}$$

We view (3) as a computational model, the purpose of which is to give us insight into the behavior of the biologically motivated model (1) in which the nonlinearities f_n are Lipschitz continuous though a particular analytic form is not known. In particular, we are not concerned with identifying solutions to (3).

We recall [1] that there is a long tradition of associating *state transition diagrams*, which take the form of directed graphs, to regulatory networks. The paths through the state transition diagram are then used to represent the dynamics of the network. As is described in Section 6 we use (3) to define a particular choice of state transition diagram. Because our focus is on dynamics we find it convenient to represent this state transition diagram as a combinatorial multivalued map $\mathcal{F} : \mathcal{V} \rightrightarrows \mathcal{V}$. In this notation, $\mathcal{V}$ denotes the set of vertices in the state transition diagram and there exists a directed edge $u \to v$ in the state transition diagram if and only if $v \in \mathcal{F}(u)$.

The number of elements in $\mathcal{V}$ can grow rapidly as a function of the size of the regulatory network. In particular, in the approach we take here, if $O(n)$ denotes the number of out edges at node n, then the size of $\mathcal{V}$ is of order

$$\prod_{n=1}^{N}(O(n)+1).$$

Cataloguing all the paths in a graph of this size is not practical. However, there are efficient (both in time and memory) graph algorithms that allow one to identify essential dynamical structures: the *recurrent dynamics*, i.e. the nontrivial strongly connected components of $\mathcal{F}$; and the *gradient-like dynamics*, i.e. the reachability, defined by paths in $\mathcal{F}$, between the recurrent components (see [2,3] and references therein and [10] for an application of these techniques in the context of state transition diagrams). We encode this information in the form of a *Morse graph*, $\mathsf{MG}(\mathcal{F})$. This is the minimal directed acyclic graph such that each nontrivial strongly connected component is represented by a distinct node and the edges indicate the reachability information inherited from $\mathcal{F}$ between the nodes.

The switching system (3) has an N dimensional phase space, but an $N + 3E$ dimensional parameter space (E denotes the number of edges). In [11] we describe a set of algorithms that allows us to decompose parameter space into semi-algebraic sets, such that on each set the state transition diagram $\mathcal{F}$ is constant and hence the global dynamics as described by the Morse graph $\mathsf{MG}(\mathcal{F})$ is valid for each parameter value in the set. The algorithms have been implemented [12] and thus for moderate sized N we have the capability of describing via the Morse graphs the global dynamics associated with the state transition diagrams for *all* parameter values.

As is emphasized above we believe that from the biological perspective (1) provides a more realistic model than (3). Therefore, to justify the biological relevance of the combinatorial computations described above that are based on (3), it is important to be able to demonstrate that $\mathsf{MG}(\mathcal{F})$ provides correct and meaningful information about the dynamics of (1). Since a Morse graph is a directed acyclic graph it generates a poset. Our goal is to translate the poset structure associated with $\mathsf{MG}(\mathcal{F})$ into information about the structure of invariant sets for a flow generated by a smooth differential equation. For this we make use of Morse decompositions as defined by Conley [13]. Recall that given a continuous flow $\varphi : \mathbb{R} \times X \to X$ defined on a compact metric space X a *Morse decomposition* of X consists of a finite collection of mutually disjoint compact invariant sets called *Morse sets* indexed by a partially ordered set $(\mathsf{P}, \leq)$ with the property that if

$$x \in X \setminus \bigcup_{p\in\mathsf{P}} M(p),$$

where $M(p)$ denotes the Morse set indexed by p, then

$$\alpha(x,\varphi) \subset M(p) \quad \text{and} \quad \omega(x,\varphi) \subset M(q)$$

where $q \leq p$.

The primary goal of this paper is Theorem 8.4, which roughly states that given a regulatory network we can use (3) to construct a state transition diagram for which we can efficiently compute a Morse graph $\mathsf{MG}(\mathcal{F})$ from which we can determine lower bounds for a Morse decomposition for the dynamics defined by a smooth system of the form (1). The following outline indicates the tools and constructions that are used to obtain a proof of Theorem 8.4.

We begin in Section 2 with a brief description of Conley theory. Section 2.1 contains elementary ideas from lattice and poset theory and a statement of Birkhoff's theorem that relates finite distributive lattices and finite posets. Sections 2.2 and 2.3 presents the necessary definitions of Conley theory in the settings of combinatorial and continuous dynamics, respectively. Section 2.4 contains Theorem 2.17, which provides the theoretical framework by which we translate the information from the combinatorial dynamics to the continuous dynamics.

As indicated above Section 3 presents the definition of a switching system (3) and associated notation and definitions. The material in this section is restricted to two-dimensional systems, but can straightforwardly be extended to systems of arbitrary finite dimension. In Section 4 δ-constrained continuous switching systems

$$\dot{x} = -\Gamma x + f^{(\delta)}(x) \tag{4}$$

are defined. The definition begins with a given switching system, which determines Γ and a positive number δ, which indicates the width of a collar around the lines of discontinuity of Λ. The function $f^{(\delta)}$ is obtained by replacing Λ by a continuous function on this collar. Again, this construction is done in the setting of $\mathbb{R}^2$, but can be extended to $\mathbb{R}^n$.

The careful reader will note that we impose extremely weak constraints on the function $f^{(\delta)}$, thus on the level of individual invariant sets the dynamics can vary tremendously. However, what we prove is that the poset structure, which provides a rough description of the nonrecurrent dynamics, obtained from our combinatorial computations guided by Λ remains the same for the continuous dynamics generated by any $f^{(\delta)}$.

Theorem 8.4 states that the $\mathsf{MG}(\mathcal{F})$ derived from the switching system (3) determines a Morse decomposition for any associated δ-constrained continuous switching system (4) for any $0 < \delta < \delta^*$, where δ^* is explicitly determined by Γ and Λ (33). The strategy of the proof is as follows. We use the results of Section 2 and in particular Birkhoff's theorem to pass from the poset structure induced by $\mathsf{MG}(\mathcal{F})$ to a lattice of attractors for the state transition graph $\mathcal{F}$. We use Theorem 2.17 to guide the construction of a lattice of forward invariant sets for the δ-constrained continuous switching system. Birkhoff's theorem is then once more employed to identify the poset structure of the Morse decomposition for the δ-constrained continuous switching system.

The state transition graph $\mathcal{F}$ associated with a switching system (3) is defined in Section 6. This construction is presented in the setting of $\mathbb{R}^2$, but has been extended to $\mathbb{R}^n$ [11].

The major technical work of this paper is to construct a lattice of trapping regions for the δ-constrained continuous switching system (4) that is isomorphic an extension of the lattice of attractors for $\mathcal{F}$. This is done in two steps, both of which are restricted to $\mathbb{R}^2$.

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