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The circuit-breaking algorithm for monotone systems

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In earlier work, we have introduced the circuit-breaking algorithm (CBA) for the analysis of intracellular regulation networks. This algorithm uses the network topology to construct a one-dimensional circuit-characteristic whose zeros correspond to the fixed points of the system.

In this study, we apply the CBA to monotone systems whose flow preserves a partial order with respect to some orthant cone. We consider relations between stability of fixed points and the derivative of the corresponding zeros of the circuit-characteristic. In particular, we derive sufficient conditions for instability in case of global asymptotic stability of the open-loop system. Furthermore, we fully characterize stability of the fixed points if in addition the system is monotone. Combined with the theory of monotone systems, our results are used to characterize the long-term behavior of two models for different intracellular regulation processes.

1. Introduction

Modeling the dynamic behavior of biochemical regulation networks with ordinary differential equations has become a standard approach in systems biology. In the last decades many models for different signaling pathways or molecular regulation mechanisms have been built and made available in databases. Some of these have a highly complex interaction graph (I-graph) topology and can show a rich variety of behaviors. Feedback circuits are important network motifs that are crucial for the qualitative dynamic behavior of such networks. The role of single feedback circuits has intensively been investigated for general model classes. On the contrary, there are only few approaches going beyond numerical studies for the investigation of more complex networks. However, an increasing number of studies show the importance of the network topology for a robust and reliable functioning (see e.g. Wagner [22]). Therefore, methods that operate on the I-graph topology are highly desirable, and can facilitate a mechanistic understanding of these networks.

An example for such an approach is the circuit-breaking algorithm (CBA), which constructs a one-dimensional circuit-characteristic based on the I-graph topology [11]. This characteristic provides important information about the system. Its zeros correspond to the fixed points of the system. The CBA exploits the dependencies among the variables in a circuit, thereby reducing the dimension of the implicit equations that have to be solved. This can make the calculation of fixed points highly efficient, depending on the network topology. Moreover, the characteristic contains even more information about the role of the network topology for the long term behavior of the system. Once the characteristic has been calculated, our approach allows for example to visualize the influence of parameters on the set of fixed points. Furthermore, it allows to identify subnetworks that are responsible for a certain dynamic behavior, or that are necessary for the occurrence of phenomena such as fixed point bifurcations and multistability [14,15].

In order to characterize the long-term behavior of a system, knowledge about the stability of fixed points is important. Thus, in Radde [13] we started to investigate relations between the circuit-characteristic and the stability of fixed points and derived conditions for the case that there is a universal node that is part of all feedback circuits in the network.

Here we extend this work for general networks by investigating the role of the CBA for monotone systems whose flow $\Phi_t(x)$ preserves a partial ordering with respect to some orthant K of the coordinate system. Our main results are illustrated in Fig. 1. We determine sufficient conditions for stability or instability of a fixed point based on the slope of the circuit-characteristic. Furthermore, we fully characterize stability of the fixed point set and the long-term behavior of the system in case of monotone systems. We apply our approach to characterize the long-term behaviors of a

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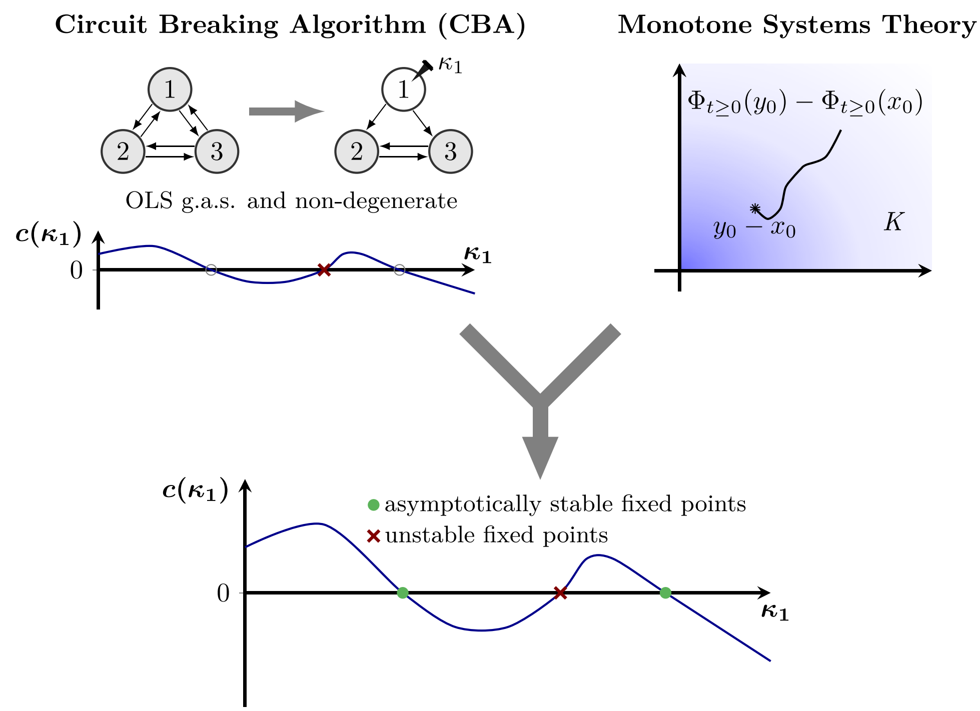

Fig. 1. Characterization of stability of fixed points via the CBA. The CBA works on the network topology and calculates a one-dimensional circuit-characteristic $c(\kappa_1)$ whose zeros correspond to the fixed points of the system. A positive slope of this characteristic implies instability of the respective fixed point in case of global asymptotic stability (g.a.s.) of the open-loop system (OLS) and a negative slope implies asymptotic stability if the system is in addition monotone. A pair of ordered initial conditions is denoted by x_0 and y_0 here.

transcription factor network model for cellular differentiation of hematopoietic stem cells and of a model for the MAPK signaling pathway.

2. Materials and methods

In the following, the mathematical framework for our theory is introduced and the properties of monotone systems that are relevant for this study are summarized. Moreover, we shortly describe the general scheme of the CBA. More details can be found in Radde [11,13].

We consider regulatory network models of n interacting molecules. The dynamics of their concentrations or activity states are described by ordinary differential equations (ODE),

$$\dot{x}_i = f_i(x) \quad i = 1,\dots,n, \quad x \in U \subseteq \mathbb{R}^n, \tag{1}$$

defined on an open, convex and positively invariant subset U of $\mathbb{R}^n$. Lipschitz continuity of the vector field $f(x)$ guarantees the existence of a unique and smooth solution $\Phi_t(x_0)$ for an initial value problem with initial condition $x(t_0) = x_0$, in an interval $t \in I_{x_0}$ that contains t_0. All trajectories shall be bounded. Furthermore, we assume that the system has a state-independent underlying I-graph $G(V, E)$, whose vertices $v_1,\dots,v_n$ represent the molecular species. Edges $e_{j\to i}$ indicate regulatory influences, i.e.

$$e_{j\to i} \in E \;\Leftrightarrow\; \exists x \text{ such that } \frac{\partial f_i(x)}{\partial x_j} \neq 0 \text{ for } i \neq j \tag{2}$$

$$e_{i\to i} \in E \;\Leftrightarrow\; \exists x \text{ such that } \frac{\partial f_i(x)}{\partial x_i} > 0. \tag{3}$$

Note that negative self-regulations are omitted in this definition of the I-graph. We also remark that this definition is more general than others, which assume the partial derivatives to have constant signs, independent from the state of the system (see e.g. pioneering work of Thomas and D'Ari on gene regulatory networks [19,20], and subsequent work on positive and negative circuits and their relations to monotone systems and multistationarity [8,18]). However, in case of constant signs, edges might be labeled by the respective sign. In this framework it is intuitive to define the sign of a (directed or undirected) path in a graph in the usual way as the sign of the product of signs of all edges in this path. The same applies to directed and undirected circuits. Thus a circuit with an even (odd) number of negatively labeled edges is a positive (negative) circuit.

2.1. Monotone systems

The theory about monotone systems or systems with order preserving flow dates back to Hirsch and Smith [9,16] and was exploited for input/output control systems by Sontag, Angeli and coworkers [1–4].

We consider systems that have a flow which preserves a partial ordering with respect to some orthant K of the Cartesian coordinate system. Such a K can be described by

$$K = \{x \in \mathbb{R}^n : (-1)^{m_i} x_i \geq 0, i = 1,\dots,n\};\; m_i \in \{0, 1\}. \tag{4}$$

K is in particular a (convex and pointed) cone and generates a partial ordering $\preceq_K$ in the usual way:

$$x \preceq_K y \Leftrightarrow y - x \in K. \tag{5}$$

A flow of a differential equation system preserves a partial ordering with respect to K if forward trajectories of two ordered initial conditions preserve this ordering, i.e.

$$(x_0, y_0 \in U) \wedge (x_0 \preceq_K y_0) \;\Rightarrow\; \Phi_t(x_0) \preceq_K \Phi_t(y_0) \tag{6}$$

for all $t \geq 0$ for which both solutions are defined. Systems with order preserving flows are very well investigated (see e.g. Hirsch [9],

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