BioSystems 149 (2016) 3–14

Contents lists available at ScienceDirect

BioSystems

journal homepage: www.elsevier.com/locate/biosystems

Geometric analysis of pathways dynamics: Application to versatility of TGF-β receptors

Satya Swarup Samal[a], Aurélien Naldi[f], Dima Grigoriev[b], Andreas Weber[c], Nathalie Théret[d,e], Ovidiu Radulescu[f,*]

[a] Algorithmic Bioinformatics, Bonn-Aachen International Center for IT, Dahlmannstraße 2, D-53113 Bonn, Germany
[b] CNRS, Mathématiques, Université de Lille, Villeneuve d'Ascq 59655, France
[c] Institut für Informatik II, University of Bonn, Friedrich-Ebert-Allee 144, 53113 Bonn, Germany
[d] Inserm UMR1085 IRSET, Université de Rennes 1, Rennes, France
[e] CNRS-Université de Rennes1-INRIA, UMR6074 IRISA, Rennes, France
[f] DIMNP UMR CNRS 5235, University of Montpellier, Montpellier, France

ARTICLE INFO

Article history:
Received 3 December 2015
Received in revised form 6 June 2016
Accepted 11 July 2016
Available online 21 July 2016

Keywords:
Tropical geometry
Cancer systems biology
Finite state automaton
Metastability

ABSTRACT

We propose a new geometric approach to describe the qualitative dynamics of chemical reactions networks. By this method we identify metastable regimes, defined as low dimensional regions of the phase space close to which the dynamics is much slower compared to the rest of the phase space. These metastable regimes depend on the network topology and on the orders of magnitude of the kinetic parameters. Benchmarking of the method on a computational biology model repository suggests that the number of metastable regimes is sub-exponential in the number of variables and equations. The dynamics of the network can be described as a sequence of jumps from one metastable regime to another. We show that a geometrically computed connectivity graph restricts the set of possible jumps. We also provide finite state machine (Markov chain) models for such dynamic changes. Applied to signal transduction models, our approach unravels dynamical and functional capacities of signalling pathways, as well as parameters responsible for specificity of the pathway response. In particular, for a model of TGFβ signalling, we find that the ratio of TGFBR2 to TGFBR1 receptors concentrations can be used to discriminate between metastable regimes. Using expression data from the NCI60 panel of human tumor cell lines, we show that aggressive and non-aggressive tumour cell lines function in different metastable regimes and can be distinguished by measuring the relative concentrations of receptors of the two types.

1. Introduction

Networks of biochemical reactions are used in computational biology as models of signalling, metabolism, and gene regulation. For various applications it is important to understand how the dynamics of these models depend on internal parameters, initial data and environment variables. Traditionally, the dynamics of biochemical networks is studied in the framework of chemical kinetics that can be either deterministic (ordinary differential equations) or stochastic (continuous time Markov processes). In order to cope with qualitative data, Boolean (Kauffman, 1969; Thomas, 1973) or multi-valued networks (Thomas, 1991; Naldi et al., 2007) are used instead of continuous models. For this reason, many efforts were focused on coarse graining dynamical networks described by ordinary differential equations (ODE) to Boolean networks (Davidich and Bornholdt, 2008). However, in spite of their advantages, dynamical properties of large Boolean or multi-valued networks are still difficult to study. The difficulty originates from the number of possible states, which for multi-valued networks with m levels (Boolean networks correspond to $m = 2$) and n nodes is m^n. Although there are efficient methods for computing attractors of Boolean networks (algorithms based on binary decision diagrams or on satisfiability solvers can handle synchronous networks with hundreds of variables, Dubrova and Teslenko, 2011), more intricate dynamical properties like the metastable regimes discussed in this

* Corresponding author.
E-mail addresses: samal@cs.uni-bonn.de (S.S. Samal), aurelien.naldi@gmail.com (A. Naldi), dmitry.grigoryev@math.univ-lille1.fr (D. Grigoriev), weber@cs.uni-bonn.de (A. Weber), nathalie.theret@univ-rennes1.fr (N. Théret), ovidiu.radulescu@univ-montp2.fr (O. Radulescu).

http://dx.doi.org/10.1016/j.biosystems.2016.07.004
0303-2647/

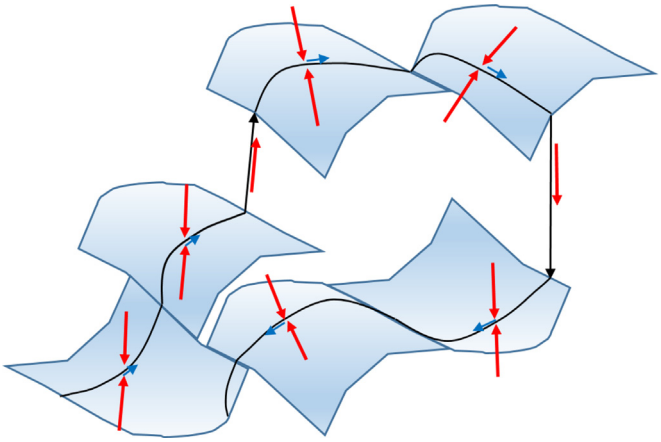

Fig. 1. Abstract representation of metastability as itinerant trajectory in a patchy phase space landscape. Dominant vector fields (red arrows) confine the trajectory to low dimensional patches on which act weak uncompensated vector fields (blue arrows). A typical trajectory contains slow segments within patches where dominant vector fields cancel, and transitions between patches in the fast direction of uncancelled dominant vector fields. Continuous (but non smooth) connections are also possible, corresponding to role reversal between dominant and dominated vector fields. The term *crazy-quilt* was coined to describe such a patchy landscape (Gorban and Radulescu, 2008). (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

paper, ask for comprehensive analysis of the state transition graph which is hard to perform and moreover for analysis of the hierarchy of time scales which is even harder for Boolean and multi-valued networks. The coarse graining method proposed in this paper leads to a drastic reduction of the number of states. This offers unprecedented possibilities for qualitative analysis of the dynamics.

In this paper we propose a new method for model analysis that uses coarse grained descriptions of continuous dynamics as discrete automata defined on finite states. These states will not be obtained by discretization of network variables, but by identification of a finite number of collective modes describing possible coordinated activity of several variables.

For large networks with ordinary differential equations dynamics and multiple timescales it is reasonable to consider the following property: a typical trajectory consists in a succession of qualitatively different slow segments separated by faster transitions. The slow segments, generally called metastable states or regimes, can be of several types such as attractive invariant manifolds (Gorban and Karlin, 2005), Milnor attractors (Rabinovich et al., 2006) or saddle connections (Rabinovich et al., 2012). The notion of metastability generalizes the notion of attractor. Like in the case of attractors, distant parts of the system can have coordinated activity for metastability. The dynamical states of large networks can be represented as points in a high dimensional space, called phase space. In this representation each coordinate represents the concentration of a molecular species. Coordinated activity means that many of the species concentrations are correlated, which can be geometrically represented by the proximity to a lower dimension hypersurface in the phase space. A system remains in the proximity of an attractor after entering its basin of attraction, but can leave a metastable regime after a relatively long time (much longer than the time needed for transitions between two different regimes). Fig. 1 summarizes this geometrical picture. The term *crazy-quilt* was coined to describe such a patchy landscape of multiscale networks dynamics (Gorban and Radulescu, 2008).

This phenomenon, called itinerancy, received particular attention in neuroscience (Tsuda, 1991). Itinerant behaviour is shown by mathematical models with stable heteroclinic sequences (defined as open chains of saddle fixed points connected by one-dimensional separatrices) and was also observed in transient activity of antennal lobe neurons involved in insect olfaction or in the activity of high vocal centers controlling songbird patterns (Rabinovich et al., 2006). We believe that similar phenomena occur in molecular biology for chemical reaction networks. A well studied example sustaining this picture is the biochemical and gene expression dynamics guiding the orderly progression of the cell cycle. The main feature of this dynamics is the sequential activation of cyclin dependent kinase/cyclin complexes. More than 30 years since cyclins were discovered the main cell cycle control events are now well understood and it is agreed that each of them involve the collective action of several regulator molecules. In addition, studies of periodic gene expression in synchronized cell division of yeast show the existence of waves of coordinate expression corresponding to different cell cycle phases or transitions (Rustici et al., 2004). Furthermore, mathematical models of the cell cycle machinery (currently more than 150 published models, Weis et al., 2014) illustrate the stage dependent coordination of biochemical variables. As an example, the structure of steady state branches of the Wee1-Cdc25 module in yeast lead Tyson et al. (2002) to consider that the exit from mitosis is a collective phenomenon that can be described as a saddle-node bifurcation. Our analysis of such models also showed that branches and bifurcations of states occur naturally in the context of cell cycle modelling (Noel et al., 2012). In a more general context, geometric analysis of single-cell expression data from human and mouse tissues showed that gene expression is structured in clusters but also in continua of states within polyhedra whose vertices can be understood as specialized key tasks (Korem et al., 2015). These findings were interpreted in terms of multi-objective optimization solutions (Korem et al., 2015), but could also suggest transient behaviour between specialized states. The idea of associating cell lineage commitment to collective behaviour of gene networks variables was used in many other contexts including cancer genomics where it was proposed that cancer cells are trapped in some abnormal attractors (Huang et al., 2009).

In this paper we propose a method to compute metastable dynamical regimes and the transitions between such regimes for chemical reaction networks. This will provide a precise meaning to the “crazy-quilt” metaphor illustrated in Fig. 1. To this aim we will use tropical geometry methods. Tropical methods (Litvinov, 2007; Maclagan and Sturmfels, 2015), also known as idempotent or max-plus algebras owe their name to the fact that one of the pioneer of the field, Imre Simon, was Brazilian. These methods found numerous applications to computer science (Simon, 1988), physics (Litvinov, 2007), railway traffic (Chang, 1998), and statistics (Pachter and Sturmfels, 2004). Recently we have applied these methods to model order reduction (Noel et al., 2012, 2014; Radulescu et al., 2015b; Samal et al., 2015b). In these works we have used tropical methods to rank monomial terms into rate vectors according to their orders of magnitude and to identify lowest order, dominant terms. When there is only one dominant term or when the dominant terms have all the same sign, the dynamics is fast and the system tends rapidly towards a region in phase space where at least two dominant terms of opposite signs are equilibrated. We have called the latter situation tropical equilibration (Noel et al., 2014; Radulescu et al., 2015b; Samal et al., 2015b). In this paper, we use tropical equilibrations to identify metastable dynamic regimes of chemical reaction networks. We show that tropical equilibrations can be grouped into branches and describe the qualitative network dynamics as a sequence of transitions from one branch to another. The complexity of the qualitative dynamics depends on the number of branches. Therefore, we would like to know how this number depends on the number