Journal of Theoretical Biology 264 (2010) 334–346

Contents lists available at ScienceDirect

Journal of Theoretical Biology

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

Thresholds in transient dynamics of signal transduction pathways

Katja Rateitschak *, Olaf Wolkenhauer

Systems Biology and Bioinformatics Group, University of Rostock, 18051 Rostock, Germany

ARTICLE INFO

Article history:
Received 1 October 2009
Received in revised form
1 February 2010
Accepted 2 February 2010
Available online 6 February 2010

Keywords:
Signal transduction
Transient dynamics
Lyapunov exponents
Metabolic control coefficient
Hill equation
Relative instability exponent

ABSTRACT

Transient dynamics of signal transduction pathways play an important role in many biological processes, including cell differentiation, apoptosis, metabolism and DNA damage response. Recent examples of quantitative methods to characterize transient signals include transient metabolic control coefficients and finite time Lyapunov exponents. In our work we compare these quantitative methods to characterize transient phenomena and specifically discuss their predictive power for three examples. We focus on the identification of thresholds that separate different transient dynamic behaviors. Our investigation leads to the following results: The spectrum of the finite-time Lyapunov exponents unambiguously and reliably identifies putative thresholds in transient dynamics. Metabolic control coefficients do not reliably detect all thresholds and suffer from false positives.

1. Introduction

The behavior of cellular processes can be classified into steady state and transient dynamics, whereby we include biochemical oscillations with constant amplitude as examples of steady state processes. While steady state processes are most important in metabolic systems (Heinrich and Schuster, 1996), transient dynamics play an important role in cell communication (Aldridge et al., 2006; Bolouri and Davidson, 2003; Kao et al., 2001; Cheong et al., 2005; Hao et al., 2003; Sasagawa et al., 2005).

Transient dynamics describe the transition from some initial state of the system into a steady state. For an understanding of signaling pathways and their targets transient dynamics are often more important than steady state dynamics as demonstrated by the following examples: Aldridge et al. (2006) have established a mathematical model which describes the regulation of active caspase 3 dynamics in apoptosis. The temporal duration depends on the initial condition (concentration) of the protein xiap. Bolouri and Davidson (2003) have shown by mathematical modeling that genes are activated successively in a regulatory network cascade, long before steady states are attained. The EGFR stimulated MAPK cascade in the PC12 cell line shows a transient activation of ERK with a peak at 5 min and a return to its basal level after 30 min, which leads to cellular proliferation (Kao et al., 2001). Using mathematical modeling Cheong et al. (2005) have predicted that the dynamic profile of the IKK signal must transiently peak at all TNFα doses in order to generate the observed NFκB activity which they could experimentally validate.

Aldridge et al. have employed direct finite-time Lyapunov exponents to identify domains in the transient dynamics of high sensitivity to initial conditions (Aldridge et al., 2006). These separatrices delineate regions with different transient dynamics and can be considered as a threshold. Furthermore, for the activation of a signaling pathway often threshold concentrations of proteins are required to prevent the unintentional activation of signaling pathways through random fluctuations.

The relevance of thresholds in biology is demonstrated by a large number of publications about ultrasensitive responses ranging from Goldbeter and Koshland (1981) and Ferrell (1996) to the recent work of Buchler and Cross (2009). Ferrell has concluded, on the basis of experimental data, that the MAPK cascade is optimized to convert a graded input into a switch-like output (Ferrell, 1996). Ultrasensitive responses leading to sigmoidal stimulus-response curves have been related to activation thresholds of biochemical networks in the literature (Goldbeter and Koshland, 1981; Ferrell and Machleder, 1998; Nash et al., 2001; Bhalla et al., 2002; Huang and Ferrell, 1996; Bentele et al., 2004; Gunarwardena, 2005; Salazar and Höfer, 2007). Experimental measurements in networks with multiple phosphorylations have shown that the stimulus has to exceed a threshold concentration to activate downstream events (Buchler and Cross, 2009; Ferrell and Machleder, 1998; Nash et al., 2001; Bhalla et al., 2002). Mathematical models for the MAPK cascade with dual phosphorylation (Huang and Ferrell, 1996) and general models for multisite phosphorylations (Salazar and Höfer, 2007) have shown that multisite phosphorylation give rise to more threshold like responses than single site phosphorylation. So far,

* Corresponding author. Tel.: +49 381 498 7682; fax: +49 381 498 7572.
E-mail addresses: katja.rateitschak@uni-rostock.de (K. Rateitschak), olaf.wolkenhauer@uni-rostock.de (O. Wolkenhauer).
URL: http://www.sbi.uni-rostock.de.

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doi:10.1016/j.jtbi.2010.02.001

however, mathematical modeling has focused on network properties leading to sigmoidal stimulus-response curves in the steady state dynamics.

In small networks, stimulus-response curves of the transient and steady dynamics can be studied in detail, leading to the identification of putative thresholds. In larger biochemical networks the identification of putative thresholds would become very time consuming because the network components could show sigmoidal-stimulus response curves during different time intervals. Therefore quantitative measures to identify putative thresholds in transient dynamics are required. They should be designed such that an inspection of trajectories is not necessary, i.e. they should deliver initial conditions (concentrations) of proteins and respective time intervals where a response shows a threshold. Recent examples of quantitative methods to characterize transient signals include transient metabolic control coefficients (MCC) (Ingalls and Sauro, 2003; Hornberg et al., 2005) and finite time Lyapunov exponents (FTL) (Aldridge et al., 2006). We here focus on system structures that generate thresholds in transient dynamics and investigate quantitative measures to identify such thresholds.

The outline of this paper is as follows. Following an introduction to MCCs and FTLs, we define thresholds in cellular signaling, discuss their properties and argue for the need of quantitative measures to identify them in transient dynamics. We then study two model structures that can generate thresholds in their transient response and we compare quantitative measures to identify thresholds in the transient dynamics. We first extend the analysis of thresholds by FTLs in an apoptosis decision network (Aldridge et al., 2006) by calculating the three largest FTLs and the MCCs. Next, we study a gene transcription network as an alternative model structure to generate thresholds in transient dynamics. Our analysis of the gene transcription network has motivated us to analytically quantify the threshold of a Hill equation and to discuss an alternative measure which combines properties of the FTLs and the MCCs.

Finally the results of our comparative study will lead us to an evaluation of the investigated quantitative measures regarding their ability to identify thresholds in transient signaling.

2. Quantitative measures to characterize transient dynamics

Metabolic control coefficients (MCC) measure the relative response of a state variable x_i, with respect to the relative perturbation by state variable x_j. They are a standard quantitative measure in sensitivity analysis (Heinrich and Schuster, 1996). MCCs can also be calculated for finite times as described in Ingalls and Sauro (2003) and Hornberg et al. (2005). They are defined by

$$C(x_i(t), x_j(0)) = \frac{\partial \log x_i(t)}{\partial \log x_j(0)}. \quad (1)$$

Comparing the influence of a perturbation at $t=0$ on different state variables at $t>0$ it is useful to consider relative changes of state variables because the values of different state variables can have different orders of magnitude. Thus control coefficients for different pairs (i,j) can be compared. In general one uses the same percentaged perturbation for all $x_j(0)$ resulting in the same denominator for all $C(x_i(t),x_j(0))$. To perturb simultaneously initial conditions of several state variables, global approaches have to be applied (Zhang and Rundell, 2006), which is not the focus of this work.

The MCC in Eq. (1) is also called "concentration control coefficient". Replacing in the denominator the initial condition $x_j(0)$ by a parameter, for example a reaction constant, leads to another type of concentration control coefficient. The concentration control coefficients can be calculated for the transient dynamics as well as in the steady state. In addition, flux control coefficients have been introduced to quantify the control of the flux of a metabolic system in the steady state (Heinrich and Schuster, 1996).

Lyapunov exponents measure the exponential divergence between a reference trajectory and d orthogonal perturbations to the trajectory, where d is the dimension of the related mathematical model which is equal to the number of state variables (Eckmann and Ruelle, 1985). Finite time Lyapunov exponents (FTL) have been introduced to quantify dynamical instabilities over a finite interval of time (Grassberger et al., 1988; Ott, 1994; Abarbanel, 1996; Haller, 2001). They depend on time and on the initial conditions of the dynamical system. The FTLs $\lambda_i(t,x(0))$, $i=1,\ldots,d$ can be calculated from the numerical solution of the ordinary differential equations (ODE) for a finite time t and initial state $x(0)$ at $t=0$:

$$\dot{x} = f(x) \quad \dot{u} = \frac{df}{dx}u,$$

$$\lambda_i(t,x(0)) = \frac{1}{2t}\log\left(\Lambda_i\left(u^T \cdot u\right)\right), \quad (2)$$

where $\dot{x}$ denotes a system of ODEs, and $\dot{u}$ a matrix differential equation for d initially orthonormal perturbation vectors which are the columns of the matrix u, and u^T being the transpose of u and $\Lambda_i(u^T \cdot u)$ denoting the eigenvalues of $u^T \cdot u$. Alternatively, λ_i can be calculated directly from differences between trajectories and initially perturbed trajectories (Aldridge et al., 2006).

The number of Lyapunov exponents is equal to d and the whole set of them is also called the Lyapunov spectrum. The largest Lyapunov exponent quantifies the exponential divergence of the most unstable direction and the lower Lyapunov exponents quantify the exponential divergence in the $d-1$ orthogonal directions.

Comparing the definitions of MCC and FTL the differences can be summarized as follows: The FTLs identify the most unstable direction of the state space and the stability in all orthogonal directions on the basis of absolute distances between the trajectory and perturbed trajectories. The MCCs measure the response-perturbation ratio on the basis of relative changes of state variables.

Recent experimental results show that biological responses can be absolute or relative: In EGF stimulated H1299 cells the absolute change of ERK2 response varies in different cells but the relative response is the same in different cells (Cohen-Saidon et al., 2009). An absolute response mechanism seems to occur in some bacterial systems (Shinar et al., 2007).

In our study we have numerically calculated the MCC according to Eq. (1) and the FTL according to Eq. (2). We have coded the calculations in Matlab (The MathWorks Inc, 2007). For the eigenvalues in Eq. (2) we have also coded an RQ decomposition but our results do not depend on it. The Matlab code can be obtained from the authors upon request.

3. Thresholds in transient dynamics

Cells respond to changes in protein concentrations, which suggests that concentration changes should be the basis for a definition of thresholds in cellular signaling. As it has been discussed in the introduction sigmoidal stimulus-response curves have been related to activation thresholds of biochemical networks (Goldbeter and Koshland, 1981; Ferrell and Machleder, 1998; Nash et al., 2001; Bhalla et al., 2002; Huang and Ferrell, 1996; Bentele et al., 2004; Gunarwardena, 2005; Salazar and Höfer, 2007). So far, experimental and modeling efforts have focused on sigmoidal stimulus-response curves in the steady state.

We suggest that a threshold value of a sigmoidal stimulus response curve can be defined by the stimulus that corresponds to the inflection point of the response curve. An alternative definition could be based on the highest curvature of the stimulus-response