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Response to temporal parameter fluctuations in biochemical networks

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Abstract

Metabolic response coefficients describe how variables in metabolic systems, like steady state concentrations, respond to small changes of kinetic parameters. To extend this concept to temporal parameter fluctuations, we define spectral response coefficients that relate Fourier components of concentrations and fluxes to Fourier components of the underlying parameters. It is also straightforward to generalize other concepts from metabolic control theory, such as control coefficients with their summation and connectivity theorems. The first-order response coefficients describe forced oscillations caused by small harmonic oscillations of single parameters: they depend on the driving frequency and comprise the phases and amplitudes of the concentrations and fluxes. Close to a Hopf bifurcation, resonance can occur: as an example, we study the spectral densities of concentration fluctuations arising from the stochastic nature of chemical reactions. Second-order response coefficients describe how perturbations of different frequencies interact by mode coupling, yielding higher harmonics in the metabolic response. The temporal response to small parameter fluctuations can be computed by Fourier synthesis. For a model of glycolysis, this approximation remains fairly accurate even for large relative fluctuations of the parameters.

Keywords: Response coefficient; Fourier analysis; Metabolic control analysis; Correlated fluctuations; Resonance; Mode coupling

1. Introduction

Biochemical reaction networks, which implement both metabolism and signalling in cells, are subject to permanent perturbations. The velocities of single chemical reactions depend on kinetic parameters like rate constants or enzyme activities. These parameters may fluctuate due to external changes like temperature shifts, but also due to internal processes, for instance, changes of cell size and energy demand that go along with the cell cycle. Moreover, reaction rates show stochastic fluctuations (Gillespie, 1977, 2000) which play a role if only few molecules are present (McAdams and Arkin, 1997; Thattai and van Oudenaarden, 2001) as in cell signalling or in the control of gene expression. How will the dynamics of the entire biochemical network respond to such permanent, fluctuating perturbations of the individual reaction velocities?

It is well known that shifts of the kinetic parameters can have dramatic effects on the behaviour of metabolic systems: at bifurcation points, the system may undergo qualitative changes, for instance switch between stationarity, oscillations, and chaos. Usually, however, a small change of the parameters will only shift a steady state or deform a limit cycle (Demin et al., 1999; Reijenga et al., 2002). Metabolic control analysis (MCA) (Fell, 1992; Heinrich and Schuster, 1996; Hofmeyer, 2001) describes how a static parameter change will alter the system's metabolic variables, such as stationary metabolic concentrations or fluxes, or the system trajectories (Ingalls and Sauro, 2003). If the parameters are changed by a small amount, the resulting shift of the metabolic variables is approximately

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proportional to the parameter shift, and the linear coefficients are called the metabolic response coefficients (Heinrich and Schuster, 1996). For larger perturbations, a quadratic approximation involving second-order response coefficients has been proposed (Höfer and Heinrich, 1993).

How can we describe the effects of parameter fluctuations in time? Demin et al. (1999) assumed that each reaction velocity is the product of a static enzyme concentration and an oscillatory turnover rate: the Fourier components of the system's oscillations were then expanded with respect to static enzyme concentrations, for fixed oscillations of the external parameters. Along a slightly different line, Ingalls (2004) and Liebermeister (2004) analysed how a stable system responds to small harmonic oscillations of single parameters. A harmonic perturbation will lead to forced harmonic oscillations of all metabolic variables, each with a certain amplitude and phase shift. The oscillations of parameters and system variables are related to each other by frequency-dependent, complex functions termed the spectral response coefficients (Liebermeister, 2004). It turns out that this generalization of MCA to oscillatory perturbations requires only a slight modification of the existing formulae. A thorough treatment for linearized systems has been given in Ingalls (2004).

We extend this idea to general nonlinear systems and define spectral response coefficients by differentiating Fourier components of metabolic variables with respect to the Fourier components of the parameters: the first and second derivatives are then termed the spectral response coefficients of first and second order. For small parameter perturbations, the spectral response coefficients can be used to approximate the frequency spectrum of the metabolic variables. The respective time courses can then be obtained by Fourier synthesis. In this article, we first review responses to static parameter changes and linear systems with temporal parameter perturbations. Then, the spectral response are defined in Section 4. Section 5 is devoted to spectral control coefficients. In the remainder, we discuss how perturbations of certain frequencies can be amplified by resonance. Resonance can also occur with stochastic parameter fluctuations, giving rise to a peak in the spectral density of concentration fluctuations. We conclude the article with two illustrating examples: the propagation of perturbations along a linear reaction chain and a model of glycolysis with oscillating energy storage.

Mathematical notation: (1) Vectors and matrices are denoted by bold face letters. (2) If a subscript or superscript appears twice in a formula, as in $A_{ik}B_{kl}$, it is summed over by convention. (3) Functionals are written with square and round brackets: if a functional h maps the functions $f_1(\cdot),\ldots,f_n(\cdot)$ to a function $g: x \to g(x)$, then $h[f_1(\cdot),\ldots,f_n(\cdot)](x)$ denotes $g(x)$. (4) $\mathbf{I} = (\delta_{ik})$ denotes the identity matrix, while $\delta_\alpha(\omega) := \delta(\omega - \alpha)$ is Dirac's delta distribution. (5) Oscillations are described by circular frequencies (Greek letters), e.g. $\omega = 2\pi/T$, where T is the period. (6) If $x(t)$ is a time course, then $\hat{x}_\omega := \hat{x}(\omega)$ denotes its Fourier transform at frequency ω, $x(\cdot)$ denotes the entire function, and $\hat{x}(\cdot)$ denotes the Fourier transform as a function.

2. Static response coefficients

A thorough treatment of the metabolic response coefficients can be found in Fell (1992), Heinrich and Schuster (1996) and Hofmeyer (2001). As a reminder, let us briefly recall some basic definitions: the metabolite concentrations $x_l(t)$ in a biochemical reaction network follow the differential equations

$$\frac{\mathrm{d}}{\mathrm{d}t}\mathbf{x}(t) = \mathbf{N}\mathbf{v}(\mathbf{x}(t), \mathbf{p}), \tag{1}$$

given here in vectorial form. The velocities of the chemical reactions are given by the kinetics functions $v_k(\mathbf{x}, \mathbf{p})$ where the kinetic parameters are denoted by p_m. Each column of the stoichiometric matrix $\mathbf{N}$ contains the stoichiometric coefficients of a chemical reaction, describing the amounts of metabolites that are consumed and produced in this reaction. If the metabolite concentrations are constrained by conservation relations, then $\mathbf{N}$ does not have full row rank. In this case, we follow (Reder, 1988) and represent the system by a set of independent metabolites: first, we reorder $\mathbf{N}$ such that its top part $\mathbf{N}_R$ consists of a maximal set of linearly independent rows. Then $\mathbf{N}$ is split into the product $\mathbf{N} = \mathbf{L}\mathbf{N}_R$ where $\mathbf{N}_R$ is called the reduced stoichiometric matrix and $\mathbf{L}$ is called the link matrix.

The derivatives of the reaction kinetics v_k with respect to metabolite concentrations and kinetic parameters are called the unscaled reaction elasticities

$$\varepsilon^S_{kl} := \frac{\partial v_k}{\partial x_l}, \quad \varepsilon^P_{km} := \frac{\partial v_k}{\partial p_m},$$

$$\varepsilon^{SS}_{klj} := \frac{\partial^2 v_k}{\partial x_l \partial x_j}, \quad \varepsilon^{SP}_{klm} := \frac{\partial^2 v_k}{\partial x_l \partial p_m}, \quad \varepsilon^{PP}_{kmn} := \frac{\partial^2 v_k}{\partial p_m \partial p_n}. \tag{2}$$

The Jacobian matrix for the independent metabolites reads $\mathbf{M}^0 = \mathbf{N}_R\varepsilon^S\mathbf{L}$. We assume that with a parameter vector $\mathbf{p}^0$, the system exhibits a stable steady state $\mathbf{s}(\mathbf{p}^0)$ fulfilling

$$0 = \mathbf{N}\mathbf{v}(\mathbf{s}(\mathbf{p}^0), \mathbf{p}^0). \tag{3}$$

In the following, we shall assume that the steady state remains stable in a neighbourhood Ω_p around the unperturbed parameters.[1] The steady state concentrations and metabolic fluxes at parameters $\mathbf{p} \in \Omega_p$ are

[1]This is the case if the kinetics functions can be continuously differentiated twice with respect to both concentrations and parameters.