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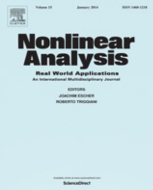

A proof of bistability for the dual futile cycle

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ABSTRACT

The multiple futile cycle is an important building block in networks of chemical reactions arising in molecular biology. A typical process which it describes is the addition of n phosphate groups to a protein. It can be modelled by a system of ordinary differential equations depending on parameters. The special case $n = 2$ is called the dual futile cycle. The main result of this paper is a proof that there are parameter values for which the system of ODE describing the dual futile cycle has two distinct stable stationary solutions. The proof is based on bifurcation theory and geometric singular perturbation theory. An important entity built of three coupled multiple futile cycles is the MAPK cascade. It is explained how the ideas used to prove bistability for the dual futile cycle might help to prove the existence of periodic solutions for the MAPK cascade.

1. Introduction

A pattern of chemical reactions frequently encountered in cell biology is one where n phosphate groups are attached to a protein by reactions catalyzed by one enzyme E (a kinase) and removed again by reactions catalyzed by another enzyme F (a phosphatase). This is sometimes called a multiple futile cycle. An introduction to this type of biological system and how it can be modelled mathematically using ordinary differential equations (ODE) depending on parameters can be found in [1]. It is proved in [1] that for an n-fold futile cycle, $n \geq 2$, this system of ODE exhibits multistationarity for certain values of the parameters, i.e. that there exist several different stationary solutions. Upper and lower bounds for the number of stationary solutions as a function of n were also proved in [1]. For $n = 1$ there is a unique stationary solution and it is globally asymptotically stable [2]. The results which follow concern the case $n = 2$ of this system, the dual futile cycle. In that case the maximal number of stationary solutions for any values of the parameters is three. Note for comparison that in the case $n = 3$ while the results of [1] only guarantee that the maximal number of stationary solutions is between three and five it was recently shown in [3] that the upper bound is sharp. In other words, for $n = 3$ there are parameter values for which there exist five stationary solutions.

Beyond the question of the number of stationary solutions it is of great interest to obtain information about their stability. This allows conclusions about the significance of the stationary solutions for the dynamics of more general solutions of the system. It is of particular interest to know whether there exist more than one stable stationary solution for fixed values of the parameters. This phenomenon is called bistability. (In ODE describing chemical systems there are often preferred invariant affine subspaces, the stoichiometric compatibility classes. When talking about fixed parameters it is understood that the stoichiometric compatibility class has been fixed.) In [4] it was concluded using numerical and heuristic approaches that

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there is bistability in the dual futile cycle. To the authors' knowledge there is no rigorous and purely analytical proof of this statement in the literature. The main result of the present paper is a proof of this type.

In [1,4] the reactions are modelled using a standard Michaelis–Menten scheme for the catalysis of each reaction and mass action kinetics for the elementary reactions involved. The resulting system will be called the MM–MA system (Michaelis–Menten via mass action) in what follows and it is the system of principal interest here. It is possible, via a quasistationarity assumption of Michaelis–Menten type, to pass formally to a smaller system, called the MM system (Michaelis–Menten) in what follows. The question of bistability in the latter system has been studied by methods which are partly numerical and heuristic in [5].

The strategy used in what follows is to first give a rigorous analytical proof of bistability in the MM system using bifurcation theory. It is shown that there is a generic cusp bifurcation and this implies bistability by well-known results [6]. Then bistability is concluded for the MM–MA system with the help of geometric singular perturbation theory [7] which gives control over the limiting process from the MM–MA system to the MM system and can be thought of as a far-reaching generalization of earlier work of Tikhonov (see [8, Section 39]) and Hoppensteadt [9]. The relevance of this type of result to the quasistationary approximation was pointed out in [10]. A similar strategy has been used in [11] to prove that there is a open subset of parameter space for which generic solutions of the system describing the dual futile cycle converge to stationary solutions.

The paper is organized as follows. In the next section the basic equations of the model studied in the paper are explained. Section 3 is a concise introduction to some of the main mathematical tools used. In Section 4 bistability is proved for the Michaelis–Menten system and in Section 5 this is used to obtain a corresponding result for the full system. In Section 6 some directions in which this research could be extended are indicated. These concern the MAPK cascade. In particular it is discussed how Michaelis–Menten reduction can be applied in that case and an explicit reduced system is presented.

2. The basic equations

Consider a chemical system consisting of a protein Y and the substances YP and YPP obtained by attaching one or two phosphate groups to Y. The reactions which attach phosphate groups are catalyzed by an enzyme E and those which remove phosphate groups by an enzyme F. It is assumed that the enzyme E can only add one phosphate group before releasing the substrate. This is what is called distributive phosphorylation in contrast to processive phosphorylation where more than one phosphate is added during one encounter between the enzyme and its substrate. It is also assumed that the phosphate groups are added at binding sites in a certain order. This is called sequential phosphorylation. It is assumed that dephosphorylation by F has corresponding properties and that phosphate groups are removed in the reverse order to that in which they are added. These assumptions about the nature of the phosphorylation and dephosphorylation processes are common in modelling approaches in the literature. Adopting them, the chemical reactions we are modelling can be written in the following form where the label k_i denotes the reaction constant of reaction i.

$$\begin{tikzcd} Y + E \arrow[r, bend left, "k_1"] & YE \arrow[l, bend left, "k_2"] \arrow[r, "k_3"] & YP + E \end{tikzcd}$$

$$\begin{tikzcd} YP + E \arrow[r, bend left, "k_4"] & YPE \arrow[l, bend left, "k_5"] \arrow[r, "k_6"] & YPP + E \end{tikzcd}$$

$$\begin{tikzcd} YPP + F \arrow[r, bend left, "k_7"] & YPPF \arrow[l, bend left, "k_8"] \arrow[r, "k_9"] & YP + F \end{tikzcd}$$

$$\begin{tikzcd} YP + F \arrow[r, bend left, "k_{10}"] & YPF \arrow[l, bend left, "k_{11}"] \arrow[r, "k_{12}"] & Y + F. \end{tikzcd}$$

An important biological example is the case where Y is the extracellular signal-regulated kinase (ERK), E is the MAPK/ERK kinase (MEK) and F is MAPK phosphatase 3 (MKP3). This is part of a mitogen activated protein kinase (MAPK) cascade,