General model of a cascade of reactions with time delays: Global stability analysis

Marek Bodnar

Institute of Applied Mathematics and Mechanics, University of Warsaw, Banacha 2, 02-097 Warsaw, Poland

Abstract

The problem considered in this paper consists of a cascade of reactions with discrete as well as distributed delays, which arose in the context of Hes1 gene expression. For the abstract general model sufficient conditions for global stability are presented. Then the abstract result is applied to the Hes1 model.
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1. Introduction

The paper is motivated by the problem of global stability of a positive steady state in the system of delay differential equations that describes gene expression of Hes1 protein. A scheme of biochemical reactions connected with this process is shown in the left-hand side panel of Fig. 1. The mathematical model proposed by Monk [21] consists of two ordinary differential equations with time delays that reflect protein production time and mRNA transcription. Local stability of the positive steady state of the model was extensively studied in literature (e.g. [2,3,9,23] and the references therein). It is known, that if degradation rates of Hes1 protein and its mRNA are sufficiently large, the positive steady state is locally asymptotically stable and stability does not depend on time delay (see [2,3]). On the other hand, for other values of degradation rates of Hes1 protein and its mRNA, the stability depends on the sum of delays in transcription of
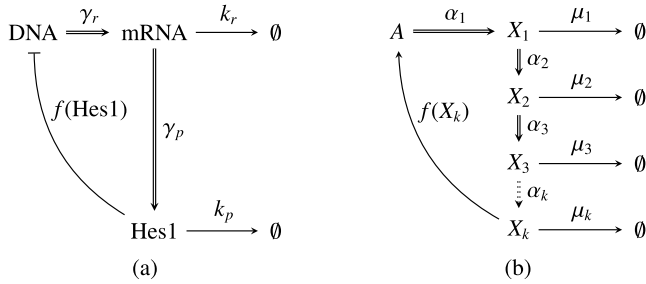
Fig. 1. (a) Sketch of negative feedback loop for the Hes1 system. (b) Sketch of simple signalling pathway with feedback.

mRNA and protein's production and if the delay exceeds some critical value, Hopf bifurcation occurs (see [2,3]). In [3] a direction of the bifurcation was studied, and conditions guaranteeing existence of the supercritical bifurcation was found. However, we are not aware of any results that address the question of global stability of the steady state of this system. In this paper we study global stability of the positive steady state in the Hes1 gene expression model and we generalise the result for similar systems as those shown on the right-hand side of Fig. 1. This kind of systems can be also considered as a simple signalling pathway. Gene expression models as well as signalling pathways are involved in many more complicated biological phenomena, including carcinogenesis (see e.g. [4,5,12,14,19] and the references therein). We hope the results as well as the methods presented in the paper could be used to various, even more complicated models, and also to tumour growth models.

Standard tool used in proving global stability is the method of Liapunov functionals. However, although the method is well known, the construction of suitable functional is usually a "bottle neck". Recently, Liz and Ruiz-Herrera [16] proposed the method for proving global stability of the steady state of delay differential equations by investigating the asymptotic behaviour of some corresponding discrete dynamical system. The method was developed for Hopfield's model of neural networks. Here, we adapt this method to other type of delay differential equations that arises from the model of Hes1 gene expression. The main idea of the Liz–Ruiz-Herrera method is to determine global stability of the trivial steady state of the equation

$$\dot{x}_j(t) = -x_j(t) + F_j\big(x_1(t - \tau_{j1}), x_2(t - \tau_{2j}), \ldots, x_k(t - \tau_{jk})\big), \quad j = 1, 2, \ldots, k, \quad (1.1)$$

where $F: \mathbb{R}^k \to \mathbb{R}^k$, $\tau_{j\ell} \geq 0$, by assuming suitable asymptotic properties for the discrete system

$$y_j(n + 1) = F_j(y(n)), \quad y = (y_1, \ldots, y_k), \quad j = 1, 2, \ldots, k, \quad n = 1, 2, 3, \ldots. \quad (1.2)$$

In fact, if we rewrite Eq. (1.1) as

$$\varepsilon \dot{x}_j(t) = -x_j(t) + F_j\big(x_1(t - \tau_{j1}), x_2(t - \tau_{2j}), \ldots, x_k(t - \tau_{jk})\big), \quad j = 1, 2, \ldots, k,$$

and let $\varepsilon \to 0$ we arrive at (1.2). Clearly, after time rescaling, which is equivalent to set new delays $\tilde{\tau}_{j\ell} = \tau_{j\ell}/\varepsilon \to +\infty$ (see [18] for extensive study of one singularly perturbed differential equation), we may say the Liz–Ruiz-Herrera method investigates the behaviour of (1.1) for very large delays. The main weak point of the method is a strong assumption made on the discrete system, which requires the steady state to be a strong attractor. We precise this notion in the