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Mathematical analysis of a biochemical oscillator with delay

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ABSTRACT

In this work we analyze a nonlinear delay differential equation (DDE) model with negative feedback and constant time delay. The model is constructed from a previously studied biochemical reaction network of gene transcription and protein synthesis. Linear analysis of the associated DDE model gives a critical time delay beyond which a periodic motion is born in a Hopf bifurcation. The method of multiple scales is then used to analyze the nonlinear system to obtain expressions for the amplitude and frequency of oscillation as a function of the system parameters. We use our closed form analytical expressions to study the importance of a well-balanced ratio between synthesis and degradation rates in the existence of periodic solutions. We show that our theoretical results are in agreement with numerical simulations and with experimental evidence found in the biological literature.

1. Introduction

It is well known that some physiological processes of living organisms are periodic [1]. Although the time period can be in the range of seconds, days, months, or even years, all of these processes have a profound importance in our lives, and they are among the main regulators of many of our biological functions such as body temperature, sleeping habits, heartbeat, breathing, and even hormonal concentration changes [2,3].

The periodicity of a physiological process is usually endogenously generated, that is, driven by the organism itself [4]. Recent experimental evidence suggests an intracellular negative feedback of gene expression [5] as one of the main responsible mechanism generating these periodic oscillations. Mathematical models of gene expression with oscillations driven by feedback inhibition loops were first studied by Goodwin [1], who showed that protein concentrations can vary rhythmically due to negative feedback. In more recent studies, Monk [5] and Scheper et al. [6] showed that the oscillations can be driven by a single constant delay associated to the total duration of the feedback loop. In [5] Monk shows that the regulatory pathways of the Hes1 gene has a delay associated mainly due to the transcription process. The main result of his work shows that the system exhibits oscillations for certain critical delay values. This was later confirmed rigorously by Verdugo and Rand [7]. In [6] Scheper studies a similar model and gives strong arguments that negative feedback, delay and nonlinearity are necessary conditions for oscillations.

In this paper we study a gene expression model similar to that in [5,6] with negative feedback, nonlinear synthesis of mRNA and protein, and a single constant time delay (see Fig. 1). We show that oscillations are always possible by using a perturbation method called the method of multiple scales for our mathematical analysis [8]. Although other perturbation methods have been used previously [7,9] for these gene expression models with delays, our analytical investigations of the model afford insight into the biological importance of protein synthesis and degradation on the amplitude and periodicity of the oscillations. By means of detuning the system parameters we are able to study and understand the importance

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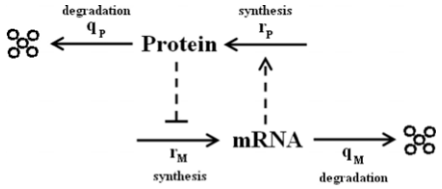

Fig. 1. Biochemical network diagram representing the synthesis and degradation of mRNA and protein. Solid and dashed lines represent chemical reactions and indirect regulatory signals, respectively. The three main properties in this biochemical network are (1) negative feedback, (2) nonlinear mRNA and protein synthesis, and (3) delay. The synthesis and degradation rates are given by r and q, respectively. Five small circles represent degradation products.

of a well-balanced ratio between synthesis and degradation rates in the existence of periodic solutions. The biological applications of our computational results should motivate biochemists to quantify these processes (delay, nonlinearity, synthesis, degradation) through appropriate experimental techniques. Since our results show the importance of negative feedback, sufficiently long time delay, a critical synthesis/degradation ratio, and enough nonlinearity in the reaction rate laws, then our findings should provide computational evidence on some of the important features necessary for oscillations in a two-component biochemical network. These numerical findings will hopefully prove to be useful to computational researchers in the field of biochemical rhythms.

The rest of the paper is organized as follows. In Section 2 we present the differential equation model and its linear stability analysis. The details of the method of multiple scales are given in Section 3 along with the slow flow equations. In Section 4 we validate our perturbation results by using MATLAB's DDE-BIFTOOL on the full nonlinear system to obtain numerical plots which confirm our theoretical results. Here we also extract information about the ratio between the system's degradation and synthesis parameters and the period of oscillation. Finally, in Sections 5 and 6 we compare our results with previous models and discuss our findings.

2. Linear stability analysis

The biochemical reactions in Fig. 1 can be translated into the following set of delay differential equations (DDEs) [5,6]

$$\dot{M} = r_M \frac{1}{1+P^n(t-T)} - q_M M(t), \tag{1}$$

$$\dot{P} = r_P\, M(t) - q_P P(t), \tag{2}$$

where M and P are the concentrations of messenger RNA and protein, respectively. The parameters r_P, r_M are production rate constants and q_P, q_M are degradation rate constants for protein and mRNA, respectively. The time delay T is due to gene transcription and n is the so-called Hill coefficient, which is a measure of the nonlinearity in the inhibition of mRNA production.

By taking the time derivative of Eq. (2) and substituting Eq. (1) we may transform the first order system (1)–(2) into the following second order DDE

$$\ddot{P} + (q_M + q_P)\,\dot{P} + q_M q_P\, P = \frac{r_M r_P}{1+P^n(t-T)}. \tag{3}$$

Assuming $q_M = q_P = q$ and introducing dimensionless time $\xi = qt$ we have

$$x'' + 2x' + x = \frac{\gamma}{1+x^n(\xi-\tau)} \tag{4}$$

where $' \equiv \frac{d}{d\xi}$ and

$$x(\xi) = P(\xi/q), \qquad \gamma = r_M r_P/q^2, \qquad \tau = qT. \tag{5}$$

To find the steady state solutions, x^*, of Eq. (4), we set $x'' = x' = 0$ and $x^* = x(\xi) = x(\xi-\tau)$ to obtain

$$(x^*)^{n+1} + x^* - \gamma = 0. \tag{6}$$

Since $x^* > 0$ (x^* is a concentration) then $y_1 = \gamma$ and $y_2 = (x^*)^{n+1} + x^*$ (which is a monotonic increasing function) intersect at least once for $\gamma > 0$. Thus there exists a real positive solution for $(x^*)^{n+1} + x^* - \gamma = 0$ for any $n \in \mathbb{R}$.

From Eq. (4) and letting y be a small deviation from equilibrium $y = x - x^*$, we obtain the following nonlinear system

$$y'' + 2y' + y = \frac{\gamma}{1+(y(\xi-\tau)+x^*)^n} - x^*. \tag{7}$$

To study the behavior of y close to the steady state solution, $y^* = 0$, we expand Eq. (7) about $y = 0$ and keep terms up to third order

$$y'' + 2y' + y = -\mu\, y_d + \mu_2\, y_d^2 + \mu_3\, y_d^3 + \cdots \tag{8}$$