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Short communication

Hopf bifurcation in a DDE model of gene expression

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Abstract

We analyze a model of gene transcription and protein synthesis which has been previously presented in the biological literature. The model takes the form of an ODE (ordinary differential equation) coupled to a DDE (delay differential equation), the state variables being concentrations of messenger RNA and protein. Linear analysis gives a critical time delay beyond which a periodic motion is born in a Hopf bifurcation. Lindstedt's method is applied to the nonlinear system, resulting in closed form approximate expressions for the amplitude and frequency of oscillation. A parameter study shows that the Hopf bifurcation may not occur if the rates of degradation are too large.

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1. Introduction

This work deals with a mathematical model of gene expression [4]. The biology of the problem may be described as follows: A gene, i.e., a section of the DNA molecule, is copied (*transcribed*) onto messenger RNA (mRNA), which diffuses out of the nucleus of the cell into the cytoplasm, where it enters a subcellular structure called a ribosome. In the ribosome the genetic code on the mRNA produces a protein (a process called *translation*). The protein then diffuses back into the nucleus where it represses the transcription of its own gene.

Dynamically speaking, this process may result in a steady state equilibrium, in which case the concentrations of mRNA and protein are constant, or it may result in an oscillation. In this paper we analyze a simple model previously proposed in the biological literature [4], and we show that the transition between equilibrium and oscillation is a Hopf bifurcation. The model takes the form of two equations, one an ordinary differential equation (ODE) and the other a delayed differential equation (DDE). The delay is due to an observed time lag in the transcription process.

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Oscillations in biological systems with delay have been dealt with previously in [1–3]. Mahaffy [1] studied a system in which concentrations of mRNA and cell repressor are analyzed by varying several parameters, such as diffusivity and cell radii. Delay is introduced into the system and the model is linearized to find stability changes and associated critical delays which give rise to Hopf bifurcations. In a later study, Mahaffy et al. [2] investigated a transport mechanism in cells to obtain nutrients. Their model examined how the change in diffusivities and cell radii caused biochemical oscillatory responses in the concentrations of the nutrients. Their model was reduced to a system of DDEs and stability analysis was used to show that the system can undergo Hopf bifurcations for certain parameter values. In a more recent study, Mocek et al. [3] studied biochemical systems with delay. They approximated the DDE system with an ODE system by means of characterizing critical delays. In all of these works, the presence of Hopf bifurcations was indicated by the existence of a periodic solution in the linearized equations. In the present work we go beyond the linearized equations, and by considering nonlinear effects we are able to predict the amplitude and frequency of the resulting limit cycle, and its stability.

The model equations investigated here involve the variables $M(t)$, the concentration of mRNA, and $P(t)$, the concentration of the associated protein [4]

$$\dot{M} = \alpha_{\mathrm{m}}\left(\frac{1}{1+\left(\frac{P_d}{P_0}\right)^n}\right) - \mu_{\mathrm{m}}M \tag{1}$$

$$\dot{P} = \alpha_{\mathrm{p}}M - \mu_{\mathrm{p}}P \tag{2}$$

where dots represent differentiation with respect to time t, and where we use the subscript d to denote a variable which is delayed by time T. Thus $P_d = P(t-T)$. The model constants are as given in [4]: α_{m} is the rate at which mRNA is transcribed in the absence of the associated protein, α_{p} is the rate at which the protein is produced from mRNA in the ribosome, μ_{m} and μ_{p} are the rates of degradation of mRNA and of protein, respectively, P_0 is a reference concentration of protein, and n is a parameter. We assume $\mu_{\mathrm{m}} = \mu_{\mathrm{p}} = \mu$.

2. Stability of equilibrium

We begin by rescaling Eqs. (1) and (2). We set $m = \frac{M}{\alpha_{\mathrm{m}}}$, $p = \frac{P}{\alpha_{\mathrm{m}}\alpha_{\mathrm{p}}}$, and $p_0 = \frac{P_0}{\alpha_{\mathrm{m}}\alpha_{\mathrm{p}}}$, giving

$$\dot{m} = \frac{1}{1+\left(\frac{p_d}{p_0}\right)^n} - \mu m \tag{3}$$

$$\dot{p} = m - \mu p \tag{4}$$

Equilibrium points, (m^*,p^*), for (3) and (4) are found by setting $\dot{m} = 0$ and $\dot{p} = 0$

$$\mu m^* = \frac{1}{1+\left(\frac{p^*}{p_0}\right)^n} \tag{5}$$

$$m^* = \mu p^* \tag{6}$$

Eliminating m^* from Eqs. (5) and (6), we obtain an equation on p^*

$$(p^*)^{n+1} + p_0^n p^* - \frac{p_0^n}{\mu^2} = 0 \tag{7}$$

Next we define ξ and η to be deviations from equilibrium: $\xi = \xi(t) = m(t) - m^*$, $\eta = \eta(t) = p(t) - p^*$, and $\eta_d = \eta(t-T)$. This results in the nonlinear system

$$\dot{\xi} = \frac{1}{1+\left(\frac{\eta_d + p^*}{p_0}\right)^n} - \mu(m^* + \xi) \tag{8}$$

$$\dot{\eta} = \xi - \mu\eta \tag{9}$$