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Center manifold analysis of a DDE model of gene expression

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Abstract

We use center manifold theory to analyze a model of gene transcription and protein synthesis which consists of an ordinary differential equation (ODE) coupled to a delay differential equation (DDE). The analysis involves reformulating the problem as an operator differential equation which acts on function space, with the result that an infinite dimensional system is reduced to one of two dimensions. This work extends a previous CNSNS paper in which this problem was treated by Lindstedt's method. The present work is shown to provide approximations of general motions, including the *approach* to a periodic motion, in contrast to Lindstedt's method, which approximates only the periodic motion itself. In particular we show that the origin is asymptotically stable for the critical (bifurcation) value of the delay parameter.

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1. Introduction

This paper involves a mathematical model of gene expression [6]. As explained in [12], 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.

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. As shown in [12], the governing equations may be written in the following nondimensional form:

$$\dot{\xi} = -\mu\xi - K\eta_d + H_2\eta_d^2 + H_3\eta_d^3 \tag{1}$$

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$$\dot{\eta} = \xi - \mu\eta \tag{2}$$

where $\xi(t)$ and $\eta(t)$ are respectively the nondimensional deviations from equilibrium concentrations of mRNA and protein, where $\eta_d = \eta(t - T)$ represents the delay, and where μ, K, H_2 and H_3 are given constants.

In a previous paper, we used an approximate method called Lindstedt's method to investigate the foregoing problem [12]. Lindstedt's method provides a closed form asymptotic expansion for the periodic motion of a dynamical system [10]. The present paper complements the previous work by providing a center manifold analysis of the same problem. The advantage of the center manifold approach is two-fold. Firstly it can be used, together with an asymptotic method such as averaging, to provide approximations of general motions, including the *approach* to a periodic motion, in contrast to Lindstedt's method, which approximates only the periodic motion itself. Secondly, center manifold analysis is based on theorems [2] which place the results on a valid mathematical basis, in contrast to the strictly formal asymptotic analysis of Lindstedt's method.

2. Center manifold analysis

The idea of center manifold analysis is to reduce the DDE system, which is infinite dimensional, to a two dimensional system by projecting the original dynamics onto the eigenvectors corresponding to purely imaginary eigenvalues. The center manifold is a two dimensional surface which is tangent to those two eigenvectors. In order to accomplish this, the DDE is reformulated as an evolution equation on a function space. The idea here is that the initial condition for the DDE consists of a function defined on $-T \leqslant t \leqslant 0$. As t increases from zero we may consider the piece of the solution lying in the time interval $[-T + t, t]$ as having evolved from the initial condition function. In order to avoid confusion, the variable θ is used to identify a point in the interval $[-T, 0]$, whereupon $x(t + \theta)$ will represent the piece of the solution which has evolved from the initial condition function at time t. From the point of view of the function space, t is a parameter, and it is θ which is the independent variable. To emphasize this, we write:

$$x_t(\theta) = x(t + \theta) \tag{3}$$

We begin the center manifold analysis by transforming the DDE system (1) and (2) into the following operator differential equation, which acts on a function space consisting of continuously differentiable functions on $[-T, 0]$ (cf. [4,11,1,5,7,8]):

$$\dot{x}_t = Ax_t + F(x_t) \tag{4}$$

where the column vector x_t, the linear operator A, and the nonlinear operator F are defined as follows:

$$x_t(\theta) = \begin{pmatrix} \xi_t \\ \eta_t \end{pmatrix}(\theta) \tag{5}$$

$$Ax_t(\theta) = \begin{cases} \frac{\mathrm{d}}{\mathrm{d}\theta} x_t(\theta), & \theta \in [-T_{\mathrm{cr}}, 0) \\ Lx_t(0) + Mx_t(-T_{\mathrm{cr}}), & \theta = 0 \end{cases} \tag{6}$$

$$F(x_t)(\theta) = \begin{cases} 0, & \theta \in [-T_{\mathrm{cr}}, 0) \\ f(x_t(0), x_t(-T_{\mathrm{cr}})), & \theta = 0 \end{cases} \tag{7}$$

The matrix L in Eq. (6) is associated with the linear nondelayed terms of (1), (2). Similarly M is associated with the linear delayed terms. In (7) f is associated with the nonlinear terms of (1), (2). Thus for this system L, M, and f become

$$L = \begin{pmatrix} -\mu & 0 \\ 1 & -\mu \end{pmatrix}. \tag{8}$$

$$M = \begin{pmatrix} 0 & -K \\ 0 & 0 \end{pmatrix}. \tag{9}$$

$$f(x_t(0), x_t(-T_{\mathrm{cr}})) = \begin{pmatrix} H_2\eta_t(-T_{\mathrm{cr}})^2 + H_3\eta_t(-T_{\mathrm{cr}})^3 \\ 0 \end{pmatrix} \tag{10}$$

Note that the original DDE system (1) and (2) appears as a boundary condition at $\theta = 0$. The flow on the rest of the interval is based on the identity $\frac{\partial x_t(\theta)}{\partial t} = \frac{\partial x_t(\theta)}{\partial \theta}$, which follows from Eq. (3).