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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:

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

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

where $\zeta(t)$ 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 $-T \leq t \leq 0$. 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:

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

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

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

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

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

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

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

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).

Here T_{cr} represents the value of the delay T such that the characteristic equation of (1), (2) has a pair of pure imaginary roots, $\pm i\omega$, where from [12] we have

$$T_{\text{cr}} = \frac{\arctan\left(\frac{2\mu\sqrt{K-\mu^2}}{K-2\mu^2}\right)}{\sqrt{K-\mu^2}} \quad (11)$$

$$\omega = \sqrt{K-\mu^2} \quad (12)$$

$$\sin(\omega T_{\text{cr}}) = \frac{2\mu\sqrt{K-\mu^2}}{K} \quad (13)$$

$$\cos(\omega T_{\text{cr}}) = 1 - \frac{2\mu^2}{K} \quad (14)$$

The center manifold reduction is based on the idea of writing the solution x_t as the sum of vectors lying in the center subspace spanned by the eigenvectors s_1 and s_2 corresponding to the eigenvalues $\pm i\omega$, and the rest of the solution, w , which does not lie in the center subspace:

$$x_t = y_1 s_1 + y_2 s_2 + w \quad (15)$$

The eigenvectors s_1 and s_2 corresponding to the eigenvalues $\pm i\omega$ are calculated as the solution of the four-dimensional first order boundary value problem

$$\frac{d}{d\theta} s_1(\theta) = -\omega s_2(\theta) \quad (16)$$

$$\frac{d}{d\theta} s_2(\theta) = \omega s_1(\theta) \quad (17)$$

$$Ls_1(0) + Ms_1(-T_{\text{cr}}) = -\omega s_2(0) \quad (18)$$

$$Ls_2(0) + Ms_2(-T_{\text{cr}}) = \omega s_1(0) \quad (19)$$

Substituting Eqs. (8)–(10), (11)–(14) into (16)–(19) yields

$$s_1(\theta) = \begin{pmatrix} b\omega + a\mu \\ a \end{pmatrix} \cos(\omega\theta) + \begin{pmatrix} b\mu - a\omega \\ b \end{pmatrix} \sin(\omega\theta) \quad (20)$$

$$s_2(\theta) = -\begin{pmatrix} b\mu - a\omega \\ b \end{pmatrix} \cos(\omega\theta) + \begin{pmatrix} b\omega + a\mu \\ a \end{pmatrix} \sin(\omega\theta) \quad (21)$$

To simplify the equations, and without loss of generality, we take $a = 1$ and $b = 0$, whereupon Eqs. (20) and (21) become

$$s_1(\theta) = \begin{pmatrix} \mu \\ 1 \end{pmatrix} \cos(\omega\theta) - \begin{pmatrix} \omega \\ 0 \end{pmatrix} \sin(\omega\theta) \quad (22)$$

$$s_2(\theta) = \begin{pmatrix} \omega \\ 0 \end{pmatrix} \cos(\omega\theta) + \begin{pmatrix} \mu \\ 1 \end{pmatrix} \sin(\omega\theta) \quad (23)$$

In order to find the equations on $y_1(t)$ and $y_2(t)$, we need to project $x_t(\theta)$ onto the center subspace. In this system, projections are accomplished by means of a bilinear form [5]:

$$\langle v, u \rangle = v^*(0)u(0) + \int_{-T_{\text{cr}}}^0 v^*(\theta + T_{\text{cr}})Mu(\theta) d\theta \quad (24)$$

where $u(\theta)$ lies in the original function space, i.e. the space of continuously differentiable functions defined on $[-T_{\text{cr}}, 0]$, and where $v(\theta)$ lies in the adjoint function space of continuously differentiable functions defined on $[0, T_{\text{cr}}]$.

In order to accomplish the projection onto the center subspace, we will need the adjoint eigenvectors. These are determined from a similar boundary value problem as above

$$-\frac{d}{d\theta}n_1(\theta) = \omega n_2(\theta) \tag{25}$$

$$-\frac{d}{d\theta}n_2(\theta) = -\omega n_1(\theta) \tag{26}$$

$$L^*n_1(0) + M^*n_1(T_{cr}) = \omega n_2(0) \tag{27}$$

$$L^*n_2(0) + M^*n_2(T_{cr}) = -\omega n_1(0) \tag{28}$$

where L^* and M^* are the transposed matrices. We proceed as above and obtain

$$n_1(\theta) = \begin{pmatrix} c \\ c\mu + d\omega \end{pmatrix} \cos(\omega\theta) - \begin{pmatrix} d \\ d\mu - c\omega \end{pmatrix} \sin(\omega\theta) \tag{29}$$

$$n_2(\theta) = \begin{pmatrix} d \\ d\mu - c\omega \end{pmatrix} \cos(\omega\theta) + \begin{pmatrix} c \\ c\mu + d\omega \end{pmatrix} \sin(\omega\theta) \tag{30}$$

Now we find the constants c and d by taking into account the conditions of orthonormality:

$$\langle n_i, s_j \rangle = \begin{cases} 0, & \text{if } i \neq j \\ 1, & \text{if } i = j \end{cases} \tag{31}$$

where, from Eq. (24),

$$\langle n_i, s_j \rangle = n_i^*(0)s_j(0) + \int_{-T_{cr}}^0 n_i^*(\theta + T_{cr})Ms_j(\theta) d\theta \tag{32}$$

The calculation yields

$$n_1(\theta) = v_1 \cos(\omega\theta) - v_2 \sin(\omega\theta) \tag{33}$$

$$n_2(\theta) = v_2 \cos(\omega\theta) + v_1 \sin(\omega\theta) \tag{34}$$

where

$$v_1 = \frac{2}{KC_0} \begin{pmatrix} 2\mu^2 T_{cr} - KT_{cr} + 2\mu \\ \mu KT_{cr} + 2K \end{pmatrix} \tag{35}$$

$$v_2 = \frac{2}{KC_0} \begin{pmatrix} 2(\mu T_{cr} + 1)\omega \\ KT_{cr}\omega \end{pmatrix} \tag{36}$$

$$C_0 = KT_{cr}^2 + 4\mu T_{cr} + 4 \tag{37}$$

Next we define the time dependent scalars

$$y_1(t) = \langle n_1, x_t \rangle \tag{38}$$

$$y_2(t) = \langle n_2, x_t \rangle \tag{39}$$

where y_1 and y_2 are the coordinates of x_t in the s_1 and s_2 directions, respectively. Differentiating Eqs. (38) and (39) we obtain (cf. [8])

$$\dot{y}_1 = \omega y_2 + h(y_1, y_2) \tag{40}$$

$$\dot{y}_2 = -\omega y_1 + g(y_1, y_2) \tag{41}$$

where we let

$$h(y_1, y_2) = n_1^*(0)f(x_t(0), x_t(-T_{cr})) \tag{42}$$

$$g(y_1, y_2) = n_2^*(0)f(x_t(0), x_t(-T_{cr})) \tag{43}$$

The next step is to look for an approximate expression for the center manifold, which is tangent to the y_1 - y_2 plane at the origin, and which may be written in the following truncated form by neglecting third and higher order terms (see Eq. (15)):

$$w(y_1, y_2)(\theta) = m_1(\theta)y_1^2 + m_2(\theta)y_1y_2 + m_3(\theta)y_2^2 \tag{44}$$

where the unknown vectors m_1 , m_2 , and m_3 will be calculated by equating the *time*-derivative of Eq. (44)

$$\dot{w} = -\omega m_2 y_1^2 + 2\omega(m_1 - m_3)y_1y_2 + \omega m_2 y_2^2 \tag{45}$$

and the *time*-derivative of Eq. (15)

$$\dot{w} = \dot{x}_t - \dot{y}_1 s_1 - \dot{y}_2 s_2 \tag{46}$$

$$= Ax_t + F(x_t) - \langle n_1, \dot{x}_t \rangle s_1 - \langle n_2, \dot{x}_t \rangle s_2 \tag{47}$$

$$= Aw + F(x_t) - \langle n_1, Fx_t \rangle s_1(\theta) - \langle n_2, Fx_t \rangle s_2(\theta) \tag{48}$$

Before finding the m_i 's we calculate the nonlinear term $\langle n_1, Fx_t \rangle$ as follows (see Eq. (24)):

$$\langle n_1, Fx_t \rangle = n_1^*(0)f(x_t(0), x_t(-T_{cr})) \tag{49}$$

$$= v_1^* \begin{pmatrix} H_2 \eta(-T_{cr})^2 + H_3 \eta(-T_{cr})^3 \\ 0 \end{pmatrix} \tag{50}$$

$$= \frac{2H_2}{KC_0} (2\mu^2 T_{cr} - KT_{cr} + 2\mu)(s_{12}(-T_{cr})y_1 + s_{22}(-T_{cr})y_2)^2 + \text{h.o.t.} \tag{51}$$

$$\approx C_1(2\mu^2 - K)y_1^2 + 4\mu\omega C_1(2\mu^2 - K)y_1y_2 - 4C_1\mu^2(\mu^2 - K)y_2^2 \tag{52}$$

where

$$\eta(-T_{cr}) = y_1 s_{12}(-T_{cr}) + y_2 s_{22}(-T_{cr}) + w_2(-T_{cr}) \tag{53}$$

and

$$C_1 = \frac{2H_2(2\mu^2 T_{cr} - KT_{cr} + 2\mu)}{K^3 C_0} \tag{54}$$

In Eq. (53), s_{12} represents the second entry of the vector s_1 , and w_2 represents the second entry of the vector w , and so on.

Similarly,

$$\langle n_2, Fx_t \rangle \approx C_2(2\mu^2 - K)y_1^2 + 4\mu\omega C_2(2\mu^2 - K)y_1y_2 - 4C_2\mu^2(\mu^2 - K)y_2^2 \tag{55}$$

where

$$C_2 = \frac{4\omega H_2(\mu T_{cr} + 1)}{K^3 C_0} \tag{56}$$

Now we equate Eqs. (45) and (48), substitute the expressions for A , F , s_1 , s_2 , n_1 , and n_2 , and set the coefficients of y_1^2 , y_1y_2 , and y_2^2 to zero to obtain the following six-dimensional first order boundary value problem

$$m'_1 - (\mu^2 - \omega^2)(C_1 s_1 + C_2 s_2) = -\omega m_2 \tag{57}$$

$$m'_2 - 4\mu\omega(\mu^2 - \omega^2)(C_1 s_1 + C_2 s_2) = 2\omega(m_1 - m_3) \tag{58}$$

$$m'_3 - 4\omega^2\mu^2(C_1 s_1 + C_2 s_2) = \omega m_2 \tag{59}$$

$$Lm_1(0) + Mm_1(-T_{cr}) - (\mu^2 - \omega^2)(C_1 s_1(0) + C_2 s_2(0) + C_3 \hat{e}) = -\omega m_2(0) \tag{60}$$

$$Lm_2(0) + Mm_2(-T_{cr}) - 4\mu\omega(\mu^2 - \omega^2)(C_1 s_1(0) + C_2 s_2(0) + C_3 \hat{e}) = 2\omega(m_1(0) - m_3(0)) \tag{61}$$

$$Lm_3(0) + Mm_3(-T_{cr}) - 4\omega^2\mu^2(C_1 s_1(0) + C_2 s_2(0) + C_3 \hat{e}) = \omega m_2(0) \tag{62}$$

where

$$C_3 = -\frac{H_2}{K^2} \tag{63}$$

$$\hat{e} = \begin{pmatrix} 1 \\ 0 \end{pmatrix} \tag{64}$$

The solution to this problem is:

$$m_1(\theta) = u_{11} \sin 2\omega\theta + u_{12} \cos 2\omega\theta + u_{13} \sin \omega\theta + u_{14} \cos \omega\theta + u_{15} \tag{65}$$

$$m_2(\theta) = u_{21} \sin 2\omega\theta + u_{22} \cos 2\omega\theta + u_{23} \sin \omega\theta + u_{24} \cos \omega\theta + u_{25} \tag{66}$$

$$m_3(\theta) = u_{31} \sin 2\omega\theta + u_{32} \cos 2\omega\theta + u_{33} \sin \omega\theta + u_{34} \cos \omega\theta + u_{35} \tag{67}$$

where

$$u_{11} = -\frac{1}{2}u_{22} = -u_{31} = C_4 \begin{pmatrix} -\omega(12\mu^6 - 34K\mu^4 + 27K^2\mu^2 - 3K^3) \\ 2\omega^3\mu(2\mu^2 - 3K) \end{pmatrix} \tag{68}$$

$$u_{12} = \frac{1}{2}u_{21} = -u_{32} = \frac{C_4}{2} \begin{pmatrix} \mu(24\mu^6 - 80K\mu^4 + 85K^2\mu^2 - 27K^3) \\ 8\mu^6 - 24K\mu^4 + 21K^2\mu^2 - 3K^3 \end{pmatrix} \tag{69}$$

$$u_{13} = \frac{C_5}{K\omega} \begin{pmatrix} K(4\mu^5T_{cr} - 8K\mu^3T_{cr} + 5K^2\mu T_{cr} - 8\mu^4 + 8K\mu^2 + 2K^2) \\ 8\mu^6T_{cr} - 12K\mu^4T_{cr} + 6K^2\mu^2T_{cr} - K^3T_{cr} + 8\mu^5 - 16K\mu^3 + 10K^2\mu \end{pmatrix} \tag{70}$$

$$u_{14} = -\frac{C_5}{K} \begin{pmatrix} K(4\mu^4T_{cr} + K^2T_{cr} + 16\mu^3 - 8K\mu) \\ 2(4\mu^5T_{cr} - 4K\mu^3T_{cr} + 3K^2\mu T_{cr} + 4\mu^4 + K^2) \end{pmatrix} \tag{71}$$

$$u_{15} = u_{35} = C_6 \begin{pmatrix} \mu \\ 1 \end{pmatrix} \tag{72}$$

$$u_{23} = \frac{2C_5}{K} \begin{pmatrix} K(4\mu^4T_{cr} - 6K\mu^2T_{cr} + K^2T_{cr} - 8\mu^3 + 4K\mu) \\ 2(4\mu^5T_{cr} - 4K\mu^3T_{cr} + 4\mu^4 - 6K\mu^2 + K^2) \end{pmatrix} \tag{73}$$

$$u_{24} = \frac{2C_5}{K\omega} \begin{pmatrix} K(4\mu^5T_{cr} - 2K\mu^3T_{cr} - K^2\mu T_{cr} + 16\mu^4 - 16K\mu^2 + 2K^2) \\ 8\mu^6T_{cr} - 12K\mu^4T_{cr} + 6K^2\mu^2T_{cr} - K^3T_{cr} + 8\mu^5 - 4K\mu^3 - 2K^2\mu \end{pmatrix} \tag{74}$$

$$u_{25} = \begin{pmatrix} 0 \\ 0 \end{pmatrix} \tag{75}$$

$$u_{33} = -\frac{2C_5}{K\omega} \begin{pmatrix} K(2\mu^5T_{cr} - 4K\mu^3T_{cr} + K^2\mu T_{cr} - 4\mu^4 + 4K\mu^2 - 2K^2) \\ 4\mu^6T_{cr} - 6K\mu^4T_{cr} + K^3T_{cr} + 4\mu^5 - 8K\mu^3 + 2K^2\mu \end{pmatrix} \tag{76}$$

$$u_{34} = \frac{2C_5}{K} \begin{pmatrix} K(2\mu^4T_{cr} - K^2T_{cr} + 8\mu^3 - 4K\mu) \\ 2(2\mu^5T_{cr} - 2K\mu^3T_{cr} + 2\mu^4 - K^2) \end{pmatrix} \tag{77}$$

and

$$C_4 = \frac{H_2}{K(16\mu^6 - 39K\mu^4 + 18K^2\mu^2 + 9K^3)} \tag{78}$$

$$C_5 = \frac{2H_2}{3C_0K^2} \tag{79}$$

$$C_6 = \frac{H_2}{2(\mu^2 + K)} \tag{80}$$

The flow on the center manifold is given by Eqs. (40) and (41), where we can now evaluate the expressions for $h(y_1, y_2)$ and $g(y_1, y_2)$ given in Eqs. (42) and (43) as follows:

$$h(y_1, y_2) = \frac{C_1 K^2}{H_2} \left(H_2 \eta(-T_{cr})^2 + H_3 \eta(-T_{cr})^3 \right) \tag{81}$$

$$g(y_1, y_2) = \frac{C_2 K^2}{H_2} \left(H_2 \eta(-T_{cr})^2 + H_3 \eta(-T_{cr})^3 \right) \tag{82}$$

where $\eta(-T_{cr})$ is given by Eq. (53). Note that $\eta(-T_{cr})$ involves our expression for the center manifold, Eq. (44), which in turn uses the expressions (65)–(80).

3. Averaging

The foregoing computation has permitted us to replace the infinite dimensional DDE problem (1), (2) by the two dimensional flow (40) and (41), where $h(y_1, y_2)$ and $g(y_1, y_2)$ are known and involve quadratic and cubic terms in y_1 and y_2 (to the order of truncation to which we have been working). This two dimensional system can be treated by traditional methods such as averaging, two variable expansion or normal forms [3,8,9]. The results can be most conveniently stated in terms of polar coordinates:

$$y_1 = r \cos \theta \tag{83}$$

$$y_2 = r \sin \theta \tag{84}$$

By means of a near-identity transformation, the flow (40) and (41) on the center manifold may be shown to give the following approximate equations on r and θ :

$$\frac{dr}{dt} = Qr^3 + O(r^5), \quad \frac{d\theta}{dt} = \omega + O(r^2) \tag{85}$$

We refer the reader to pp. 154–156 in [3] where it is shown that Q is given by the following expression:

$$16Q = h_{111} + h_{122} + g_{112} + g_{222} - \frac{1}{\omega} (h_{12}(h_{11} + h_{22}) - g_{12}(g_{11} + g_{22}) - h_{11}g_{11} + h_{22}g_{22}) \tag{86}$$

where the subscript i represents a partial derivative with respect to y_i , and where all terms are to be evaluated at $y_1 = y_2 = 0$. For the functions h and g in Eqs. (81) and (82), we obtain

$$Q = -\frac{2\omega^2}{C_0 P} (Q_0 T_{cr} + Q_1) \tag{87}$$

where P , Q_0 , and Q_1 are defined as follows:

$$P = -8K^2(\mu^2 - K)(\mu^2 + K)(16\mu^6 - 39K\mu^4 + 18K^2\mu^2 + 9K^3) \tag{88}$$

$$Q_0 = 48H_3K^2\mu^8 + 16H_2^2K\mu^8 - 69H_3K^3\mu^6 + 32H_2^2K^2\mu^6 - 63H_3K^4\mu^4 - 162H_2^2K^3\mu^4 + 81H_3K^5\mu^2 + 108H_2^2K^4\mu^2 + 27H_3K^6 + 30H_2^2K^5 \tag{89}$$

$$Q_1 = 96H_3K\mu^9 + 64H_2^2\mu^9 - 138H_3K^2\mu^7 - 16H_2^2K\mu^7 - 126H_3K^3\mu^5 - 308H_2^2K^2\mu^5 + 162H_3K^4\mu^3 + 296H_2^2K^3\mu^3 + 54H_3K^5\mu + 12H_2^2K^4\mu \tag{90}$$

The importance of the result (87) is that, from (85), the sign of Q determines the stability of the origin.

4. Unfolding the center

In this section we use the center manifold computation to approximate the amplitude of a periodic motion (a limit cycle) which is born as parameters change in the neighborhood of a center (i.e. in a Hopf bifurcation). The idea is to compute the real part of the eigenvalues of the linear system due to a small change in delay off of the critical delay T_{cr} . Let

$$T = T_{cr} + \Delta, \quad |\Delta| \ll T_{cr} \tag{91}$$

and suppose the resulting eigenvalues are $\lambda = R \pm i\Omega$, where R and Ω have the approximate expressions $R = R_1\Delta$ and $\Omega = \omega + \omega_1\Delta$. Then Eqs. (40) and (41) will take the approximate form

$$\dot{y}_1 = Ry_1 + \Omega y_2 + h(y_1, y_2) \tag{92}$$

$$\dot{y}_2 = Ry_2 - \Omega y_1 + g(y_1, y_2) \tag{93}$$

and Eq. (85) will be replaced by the approximation

$$\frac{dr}{dt} = Rr + Qr^3 + O(r^5), \quad \frac{d\theta}{dt} = \Omega + O(r^2) \tag{94}$$

The first of (94) gives the limit cycle amplitude r as

$$r^2 = -\frac{R}{Q} \tag{95}$$

In the case of the linearization of the system (1), (2), we have

$$\dot{\xi} = -\mu\xi - K\eta_d \tag{96}$$

$$\dot{\eta} = \xi - \mu\eta \tag{97}$$

which has solutions of the form

$$\xi = Be^{\lambda t} \tag{98}$$

$$\eta = Ae^{\lambda t} \tag{99}$$

Setting $\lambda = R \pm i\Omega$, we find

$$(R + \mu)^2 - \Omega^2 = -Ke^{-RT} \cos(\Omega T) \tag{100}$$

$$2\Omega(R + \mu) = Ke^{-RT} \sin(\Omega T) \tag{101}$$

Substituting Eq. (91) into (100), (101) and linearizing for small Δ , we obtain

$$R = \frac{2\omega^2}{KT_{cr}^2 + 4\mu T_{cr} + 4} \Delta \tag{102}$$

$$\Omega = \omega - \frac{\omega(2\mu + KT_{cr})}{KT_{cr}^2 + 4\mu T_{cr} + 4} \Delta \tag{103}$$

Substituting (102) and (87) into (95), we obtain the following approximation for the limit cycle amplitude r :

$$r^2 = \frac{P}{Q_0 T_{cr} + Q_1} \Delta \tag{104}$$

which agrees with the comparable result obtained by Lindstedt’s method in [12].

5. Conclusion

The idea of a center manifold reduction of a DDE is to replace an infinite dimensional system by a two dimensional system. In order to accomplish this, the delay T is chosen such that the linearized system possesses a pair of pure imaginary eigenvalues as well as an infinite number of eigenvalues with negative real parts. The center manifold theorem then guarantees that there exists a curved two dimensional subspace (the center manifold) which is tangent to the (flat) subspace spanned by the eigenvectors corresponding to those eigenvalues with zero real part, and which is invariant under the flow generated by the nonlinear equations. All solutions starting sufficiently close to the equilibrium point will tend asymptotically towards the center manifold. The stability of the equilibrium point in the full nonlinear equations will be the same as its stability in the flow on the center manifold. Any bifurcations which occur in the neighborhood of the equilibrium point on the center manifold are guaranteed to also occur in the full nonlinear system. In particular if a limit cycle is born in a Hopf bifurcation in the center manifold, then it will also be born in the full infinite dimensional system.

In the case of the DDE model of gene expression (1) and (2), we first solved for the eigenvectors s_1 and s_2 , Eqs. (22) and (23). These span a linear center subspace with coordinates y_1 and y_2 . Then we looked for the curved center manifold, $w(y_1, y_2)$, which is tangent to the y_1 - y_2 plane at the origin, in the form of a truncated

power series, Eq. (44). The coefficients m_1 , m_2 and m_3 of this series are 2-vectors which satisfy the ODE's (57)–(59) with the boundary conditions (60)–(62). The resulting expressions for the m_i , Eqs. (65)–(67), were then used to allow the original nonlinear system to be projected onto the center manifold, giving a two dimensional flow on the y_1 – y_2 phase plane, Eqs. (40), (41).

The familiar form of Eqs. (40) and (41) allowed averaging to be used to obtain the normal form (85), from which the stability of the origin could be determined from the sign of Q . Moreover, by detuning the delay T from the Hopf bifurcation value T_{cr} , we were able to generalize the normal form (94), yielding the amplitude of the resulting limit cycle (104).

The computations involved in this work were accomplished using the computer algebra package *macsyma*. As a check on the work, the final expression for the limit cycle amplitude (104) was shown to agree with the value obtained in [12] using Lindstedt's method. Although Lindstedt's method arrived at this result with less work than the present center manifold reduction, it gave only the periodic motion and not the associated slow flow (94). In particular, the work in [12] based on Lindstedt's method was unable to determine the stability of the origin at the bifurcation value $T = T_{cr}$. Using the same parameter values as in [6], we find that [12]

$$\mu = 0.03, \quad K = 3.9089 \times 10^{-3}, \quad H_2 = 6.2778 \times 10^{-5}, \quad H_3 = -6.4101 \times 10^{-7} \quad (105)$$

using which we compute from Eq. (87) that $Q = -1.100 \times 10^{-6}$, which implies that the zero solution is asymptotically stable for $T = T_{cr}$.

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