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DELAY DIFFERENTIAL EQUATIONS IN THE DYNAMICS OF GENE COPYING

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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. The delay is assumed to depend on the concentration of mRNA and is therefore state-dependent. 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.

INTRODUCTION

This work deals with a mathematical model of gene expression (Monk, 2003a),(Lewis, 2003). The biology of the problem may be described as follows: A gene, i.e. a section of a DNA molecule, is copied (*transcribed)* into messenger RNA (mRNA), which is transported out of the nucleus of the cell into the cytoplasm, where it enters a subcellular structure called a ribosome. In the ribosome the genetic information encoded in the mRNA produces a protein (a process called *translation).* The protein then enters the nucleus where it represses the transcription of its own gene.

This process has been modeled by two differential equations (Monk, 2003a):

$$\dot{M} = \alpha_m \left(\frac{1}{1 + \left(\frac{P}{P_0}\right)^n} \right) - \mu_m M \tag{1}$$

$$\dot{P} = \alpha_p M - \mu_p P \tag{2}$$

where $M(t)$ is the concentration of mRNA and $P(t)$ is the concentration of the associated protein, and where dots represent differentiation with respect to time t. The model constants are as given in (Monk, 2003a): 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 known as a Hill coefficient. After (Monk, 2003a), we assume μ_m=μ_p=μ.

In laboratory experiments, the dynamics of the process of gene copying has been observed to sometimes result in a steady state equilibrium, in which case the concentrations of mRNA and protein are constant, and to sometimes result in an oscillation in which these concentrations vary periodically in time. However, it is easy to see that the system (1),(2) cannot support oscillations, as follows: Differentiating (2) and substituting (1) into the result gives the second order equation:

$$\ddot{P} + (\mu_m + \mu_p)\dot{P} + F(P) = 0 \tag{3}$$

where

$$F = \mu_m \mu_p P - \frac{\alpha_m \alpha_p}{1 + \left(\frac{P}{P_0}\right)^n} \tag{4}$$

Eq.(3) is a linearly damped oscillator with nonlinear conservative restoring force F and as such cannot oscillate.

A natural question arises as to how the model (1),(2) can be changed to be more realistic so that it will oscillate.

One possibility involves coupling a series of such systems together. For example, (Elowitz and Leibler, 2000) have shown that three such systems (a "repressilator") can be coupled in such a way as to exhibit a periodic motion. Another approach involves introducing delay into the model.

Sources of the delay include the time required for transcription and translation to occur. (Monk, 2003a) states that transcription has an average delay time of about 10-20 min while translation delays are about 1-3 min. He posits the following delayed version of Eqs.(1),(2):

$$\dot{M} = \alpha_m \left(\frac{1}{1 + \left(\frac{P_d}{P_0} \right)^n} \right) - \mu_m M \tag{5}$$

$$\dot{P} = \alpha_p M - \mu_p P \tag{6}$$

where the subscript d denotes a variable which is delayed by time T, that is, $P_d = P(t-T)$. In (Monk, 2003b) it is shown that (5),(6) are equivalent to a system which contains both transcriptional and translational delays.

Oscillations in the system (5),(6) have been studied previously for constant delay in (Verdugo and Rand, 2007a) and (Verdugo and Rand, 2007b). **In the present work we extend previous results to include delays which are state-dependent, that is, where the delay T depends on M, the concentration of mRNA.** This effect is important in systems where the mechanisms which transport the mRNA from the nucleus to the cytoplasm (through the nuclear membrane) become saturated, in which case the delay will increase with the concentration of mRNA.

HOPF BIFURCATION WITH STATE-DEPENDENT DELAY

In this section we use Lindstedt's perturbation method to investigate periodic solutions to the system (5),(6) in the case that the delay depends on the state of the system. Hopf bifurcations in state-independent delay equations have been treated previously by (Hassard et al., 1981) and (Kalmar-Nagy et al., 2001). State-dependent delay equations have recently been investigated by (Insperger et al., 2005) and (Insperger et al., 2007), who have provided linearized constant delay DDE's which govern the stability of an equilibrium solution. Periodic solutions of Eqs.(5),(6) in the case that the delay is constant have been investigated earlier by (Verdugo and Rand, 2007a) and (Verdugo and Rand, 2007b). We will follow (Verdugo and Rand, 2007a) in our treatment of the state-dependent delay problem.

As stated in the Introduction, the delay associated with the transport of mRNA from the DNA copying site to the ribosome, will increase with the concentration of mRNA in systems where passage through the nuclear membrane is saturated. This leads us to propose the following form for the state-dependent delay T:

$$T = T_0 + \bar{c} M \tag{7}$$

where T_0 and $\bar{c}$ are parameters, and where $M(t)$ is the concentration of mRNA.

Stability of Equilibrium

We begin by rescaling Eqs.(5) and (6). We set $m = \frac{M}{\alpha_m}$, $p = \frac{P}{\alpha_m \alpha_p}$, and $p_0 = \frac{P_0}{\alpha_m \alpha_p}$, giving:

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

$$\dot{p} = m - \mu p \tag{9}$$

In Eq.(8), $p_d = p(t-T) = p(t - T_0 - \bar{c}M) = p(t - T_0 - cm)$, where $c = \bar{c}\alpha_m$.

Equilibrium points, (m^*, p^*), for (8) and (9) are found by setting $\dot{m} = 0$ and $\dot{p} = 0$

$$\mu m^* = \frac{1}{1 + \left(\frac{p^*}{p_0} \right)^n} \tag{10}$$

$$m^* = \mu p^* \tag{11}$$

Solving Eqs.(10) and (11) for p^* we get

$$(p^*)^{n+1} + p_0^n \, p^* - \frac{p_0^n}{\mu^2} = 0. \tag{12}$$

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

$$\dot{\xi} = \frac{1}{1 + \left(\frac{\eta_d + p^*}{p_0} \right)^n} - \mu(m^* + \xi) \tag{13}$$

$$\dot{\eta} = \xi - \mu \eta \tag{14}$$

Expanding for small values of η_d, Eq.(13) becomes:

$$\dot{\xi} = -\mu\xi - K \, \eta_d + H_2 \, \eta_d^2 + H_3 \, \eta_d^3 + \cdots \tag{15}$$

where K, H_2 and H_3 depend on p^*, p_0, and n as follows:

$$K = \frac{n\beta}{p^*(1+\beta)^2}, \qquad \text{where} \quad \beta = \left(\frac{p^*}{p_0}\right)^n \tag{16}$$

$$H_2 = \frac{\beta\, n\, (\beta\, n - n + \beta + 1)}{2\, (\beta+1)^3\, p^{*\,2}} \tag{17}$$

$$H_3 = -\frac{\beta\, n\, \left(\beta^2\, n^2 - 4\,\beta\, n^2 + n^2 + 3\,\beta^2\, n - 3\, n + 2\,\beta^2 + 4\,\beta + 2\right)}{6\, (\beta+1)^4\, p^{*\,3}} \tag{18}$$

Next we analyze the system coming from Eqs.(15) and (14):

$$\dot{\xi} = -\mu\,\xi - K\,\eta_d \tag{19}$$

$$\dot{\eta} = \xi - \mu\,\eta \tag{20}$$

Although this equation would be linear for a constant delay, it is nonlinear for a state-dependent delay due to the term η_d:

$$\eta_d = \eta(t - T_0 - cm) = \eta(t - T_0 - cm^* - c\,\xi) \tag{21}$$

where m^* is the equilibrium value of m, related to the protein equilibrium p^* by Eq.(11). In order to linearize eq.(19), we must develop η_d in Eq.(21) in a Taylor series for small values of ξ and η. We obtain

$$\eta_d = \eta(t - T_0 - cm^*) + \text{ nonlinear terms} \tag{22}$$

Thus the stability of the equilibrium point (m^*, p^*) will be determined by the linearized system:

$$\dot{\xi} = -\mu\,\xi - K\,\eta(t - T_0 - cm^*) \tag{23}$$

$$\dot{\eta} = \xi - \mu\,\eta \tag{24}$$

Stability analysis of Eqs.(23) and (24) shows that for $T{=}T_0{+}cm^*{=}0$ (no delay), the equilibrium point (m^*, p^*) is a stable spiral. Increasing the delay, T, in the linear system (23)-(24) will yield a critical delay, T_{cr}, such that for $T{>}T_{cr}$, (m^*, p^*) will be unstable, suggesting a Hopf bifurcation. For $T{=}T_0 + cm^*{=}T_{cr}$ the system (23)-(24) will exhibit a pair of pure imaginary eigenvalues $\pm\omega i$ corresponding to the solution

$$\xi(t) = B\cos(\omega t + \phi) \tag{25}$$

$$\eta(t) = A\cos\omega t \tag{26}$$

where A and B are the amplitudes of the $\eta(t)$ and $\xi(t)$ oscillations, and where ϕ is a phase angle. Note that we have chosen the phase of $\eta(t)$ to be zero without loss of generality. For values of delay T close to T_{cr}, we may introduce a detuning parameter Δ:

$$T = T_{cr} + \Delta + c\,\xi \tag{27}$$

Using (27), the nonlinear system (8)-(9) is expected to exhibit a periodic solution (a limit cycle) which can be written in the approximate form of Eqs.(25), (26). Substituting Eqs.(25) and (26) into Eqs.(23) and (24) and solving for ω and T_{cr} we obtain

$$\omega = \sqrt{K - \mu^2} \tag{28}$$

$$T_{cr} = \frac{\arctan\left(\frac{2\mu\sqrt{K-\mu^2}}{K-2\mu^2}\right)}{\sqrt{K-\mu^2}} \tag{29}$$

Lindstedt's Method

We use Lindstedt's Method (Rand, 2005),(Rand and Verdugo, 2007) on Eqs.(15) and (14). We begin by changing the first order system into a second order DDE. This results in the following form

$$\ddot{\eta} + 2\,\mu\,\dot{\eta} + \mu^2\,\eta = -K\,\eta_d + H_2\,\eta_d^2 + H_3\,\eta_d^3 + \cdots \tag{30}$$

where K, H_2 and H_3 are defined by Eqs.(16)-(18) and where η_d is given by Eq.(21). We eliminate the appearance of ξ in the expression for the delay in Eq.(21) by using Eq.(20):

$$\xi = \dot{\eta} + \mu\,\eta \tag{31}$$

We introduce a small parameter ϵ via the scaling

$$\eta = \epsilon u \tag{32}$$

The detuning Δ of Eq.(27) is scaled like ϵ^2:

$$T = T_{cr}{+}\Delta{+}c\,\xi = T_{cr}{+}\Delta{+}c(\dot{\eta}{+}\mu\,\eta) = T_{cr}{+}\epsilon^2\delta{+}c\epsilon(\dot{u}{+}\mu\,u) \tag{33}$$

Next we stretch time by replacing the independent variable t by τ, where

$$\tau = \Omega\, t \tag{34}$$

This results in the following form of Eq.(30):

$$\Omega^2 \frac{d^2u}{d\tau^2} + 2\,\mu\,\Omega \frac{du}{d\tau} + \mu^2\, u = -K\, u_d + \epsilon\, H_2\, u_d^2 + \epsilon^2\, H_3\, u_d^3 \tag{35}$$

where $u_d = u(\tau - \Omega\, T)$. We expand Ω in a power series in ϵ, omitting the $O(\epsilon)$ term for convenience, since it turns out to be zero:

$$\Omega = \omega + \epsilon^2 k_2 + \ldots \tag{36}$$

Next we expand the delay term u_d:

$$\begin{aligned} u_d &= u(\tau - \Omega T) && (37)\\ &= u(\tau - \Omega(T_{cr} + \epsilon^2\delta + c\,\epsilon(\Omega\, u'(\tau) + \mu u(\tau)))) && (38)\\ &= u(\tau - \omega T_{cr}) + \\ &\quad \epsilon[-c\,\omega(\omega u'(\tau) + \mu u(\tau))\, u'(\tau - \omega T_{cr})] + \\ &\quad \epsilon^2[\frac{1}{2} c^2\omega^2(\omega u'(\tau) + \mu u(\tau))^2\, u''(\tau - \omega T_{cr}) \\ &\quad -(\delta\omega + k_2 T_{cr}) u'(\tau - \omega T_{cr})] \; + O(\epsilon^3) && (39) \end{aligned}$$

where primes represent differentiation with respect to τ. Now we expand $u(\tau)$ in a power series in ϵ:

$$u(\tau) = u_0(\tau) + \epsilon u_1(\tau) + \epsilon^2 u_2(\tau) + \ldots \tag{40}$$

Substituting and collecting terms, we obtain equations on u_0, u_1 and u_2. Each of these involves the same linear differential-delay operator L:

$$L\, f \equiv \omega^2 \frac{d^2 f}{d\tau^2} + 2\mu\omega \frac{df}{d\tau} + K f(\tau - \omega T_{cr}) + \mu^2 f \tag{41}$$

$$\begin{aligned} L\, u_0 &= 0 && (42)\\ L\, u_1 &= H_2\, u_0^2(\tau - \omega T_{cr}) + \\ &\qquad cK\omega(\omega u_0'(\tau) + \mu u_0(\tau))\, u_0'(\tau - \omega T_{cr}) && (43)\\ L\, u_2 &= \ldots && (44) \end{aligned}$$

where $\ldots$ stands for terms in u_0 and u_1, omitted here for brevity. We take the solution of the u_0 equation as:

$$u_0(\tau) = \hat{A} \cos\tau \tag{45}$$

where from Eqs.(26) and (32) we know $A = \hat{A}\epsilon$. Next we substitute (45) into (43) and obtain the following expression for u_1:

$$u_1(\tau) = m_1 \sin 2\tau + m_2 \cos 2\tau + m_3 \tag{46}$$

where m_1 is given by the equation:

$$m_1 = \frac{\hat{A}^2\, \mu\, \sqrt{K - \mu^2}\, \Phi}{2\, K\, (16\,\mu^6 - 39\, K\,\mu^4 + 18\, K^2\,\mu^2 + 9\, K^3)} \tag{47}$$

where

$$\begin{aligned} \Phi &= 4\, c\, K^2\, \mu^4 - 8\, \mathrm{H}_2\, \mu^4 - 11\, c\, K^3\, \mu^2 + && (48)\\ &\quad 20\, \mathrm{H}_2\, K\, \mu^2 + 9\, c\, K^4 - 12\, \mathrm{H}_2\, K^2 && (49) \end{aligned}$$

and where m_2 and m_3 are given by similar equations, omitted here for brevity. We substitute Eqs.(45) and (46) into (44), and, after trigonometric simplifications have been performed, we equate to zero the coefficients of the resonant terms $\sin\tau$ and $\cos\tau$. This yields the amplitude, A, of the limit cycle that was born in the Hopf bifurcation:

$$A^2 = \frac{P}{Q}\,\Delta \tag{50}$$

where

$$\begin{aligned} P &= 16K^2\left(\mu^4 - K^2\right) \times \\ &\qquad \left(16\mu^6 - 39K\mu^4 + 18K^2\mu^2 + 9K^3\right) && (51)\\ Q &= Q_0\, T_{cr} \; + \; Q_1 && (52) \end{aligned}$$

and

$$\begin{aligned} Q_0 &= 32\, c^2\, K^3\, \mu^{12} - 62\, c^2\, K^4\, \mu^{10} \\ &+ \left(7\, c^2\, K^5 + 140\, c\, \mathrm{H}_2\, K^3 - 96\, \mathrm{H}_3\, K^2 - 32\, {\mathrm{H}_2}^2\, K\right)\, \mu^8 \\ &+ \left(20\, c^2\, K^6 - 428\, c\, \mathrm{H}_2\, K^4 + 138\, \mathrm{H}_3\, K^3 - 64\, {\mathrm{H}_2}^2\, K^2\right)\, \mu^6 \\ &+ \left(-6\, c^2\, K^7 + 396\, c\, \mathrm{H}_2\, K^5 + 126\, \mathrm{H}_3\, K^4 + 324\, {\mathrm{H}_2}^2\, K^3\right)\, \mu^4 \\ &+ \left(42\, c^2\, K^8 - 84\, c\, \mathrm{H}_2\, K^6 - 162\, \mathrm{H}_3\, K^5 - 216\, {\mathrm{H}_2}^2\, K^4\right)\, \mu^2 \\ &- 33\, c^2\, K^9 - 24\, c\, \mathrm{H}_2\, K^7 - 54\, \mathrm{H}_3\, K^6 - 60\, {\mathrm{H}_2}^2\, K^5 \end{aligned} \tag{53}$$

$$
\begin{aligned}
Q_1 &= 96\,c^2\,K^3\,\mu^{11} \\
&+ \left(-354\,c^2\,K^4 + 48\,c\,\mathrm{H}_2\,K^2 - 192\,\mathrm{H}_3\,K - 128\,{\mathrm{H}_2}^2\right)\,\mu^9 \\
&+ \left(560\,c^2\,K^5 - 172\,c\,\mathrm{H}_2\,K^3 + 276\,\mathrm{H}_3\,K^2 + 32\,{\mathrm{H}_2}^2\,K\right)\,\mu^7 \\
&+ \left(-556\,c^2\,K^6 + 308\,c\,\mathrm{H}_2\,K^4 + 252\,\mathrm{H}_3\,K^3 + 616\,{\mathrm{H}_2}^2\,K^2\right)\,\mu^5 \\
&+ \left(368\,c^2\,K^7 - 340\,c\,\mathrm{H}_2\,K^5 - 324\,\mathrm{H}_3\,K^4 - 592\,{\mathrm{H}_2}^2\,K^3\right)\,\mu^3 \\
&+ \left(-114\,c^2\,K^8 + 156\,c\,\mathrm{H}_2\,K^6 - 108\,\mathrm{H}_3\,K^5 - 24\,{\mathrm{H}_2}^2\,K^4\right)\,\mu
\end{aligned}
\tag{54}
$$

Eq.(52) depends on μ, K, H_2, H_3, and T_{cr}. By using Eq.(29) we may express Eq.(52) as a function of μ, K, H_2, and H_3 only. Removal of secular terms also yields a value for the frequency shift k_2 (cf. Eq.(36) above):

$$k_2 = -\frac{R}{Q}\,\delta \tag{55}$$

where Q is given by (52) and

$$R = \sqrt{K - \mu^2}\;Q_0 \tag{56}$$

An expression for the amplitude B of the periodic solution for $\xi(t)$ (see Eq.(25)) may be obtained directly from Eq.(14) by writing $\xi = \dot{\eta} + \mu\eta$, where $\eta \sim A\cos\omega t$. We find:

$$B = \sqrt{K}A \tag{57}$$

where K and A are given as in (16) and (50) respectively.

Numerical Example

Using the same parameter values as in (Monk, 2003a)

$$\mu = 0.03/\mathrm{min}\,,\ p_0 = 100\,,\ n = 5 \tag{58}$$

we obtain

$$p^* = 145.9158\,,\ m^* = 4.3774 \tag{59}$$

$$K = 3.9089{\times}10^{-3}\,,\ H_2 = 6.2778{\times}10^{-5}\,,\ H_3 = -6.4101{\times}10^{-7} \tag{60}$$

$$T_{cr} = 18.2470\,,\ \omega = 5.4854\times10^{-2}\,,\ \frac{2\pi}{\omega} = 114.5432 \tag{61}$$

Here the delay T_{cr} and the response period $2\pi/\omega$ are given in minutes. Substituting (58)-(61) into (50)-(57) yields the following equations:

$$A = \frac{27.0203}{\sqrt{0.0544\,c^2 - 0.05656\,c + 1.0}}\,\sqrt{\Delta} \tag{62}$$

$$k_2 = \frac{-8.39065\cdot10^{-5}\,c^2 - 4.00072\cdot10^{-4}\,c - 0.00245}{0.0544\,c^2 - 0.05656\,c + 1.0}\,\delta \tag{63}$$

Note that since Eq.(62) requires $\Delta > 0$ for the limit cycle to exist, and since we saw in Eqs. (23) and (24) that the origin is unstable for $T > T_{cr}$, i.e. for $\Delta > 0$, we may conclude that the Hopf bifurcation is supercritical, i.e., the limit cycle is stable. This conclusion is based on the assumption of the existence of a two dimensional center manifold. This has been proven in the case in which the delay is state-independent in (Verdugo and Rand, 2007b), but has not been proven for the case of state-dependent delay. Nevertheless numerical simulation has shown that the limit cycle is stable in the latter case.

Figure 1 shows a plot of p versus t for $c = 1$ and $\Delta = 0.16$ in which the results of the perturbation theory (solid line) are compared to those of numerical simulation (broken line) in Matlab using the function ddesd.

CONCLUSIONS

In this paper we investigated the effect of state-dependency on delay by using a perturbation method valid in the neighborhood of a Hopf bifurcation. We showed how Lindstedt's method can be used to deal with state-dependent delays. Figure 1 shows that the resulting approximate expressions for amplitude and frequency of the steady state oscillation are in good agreement with those obtained by numerical integration. On the other hand, Eqs.(62) and (63) show that the effect of c on amplitude and frequency is small for O(1) values of c.

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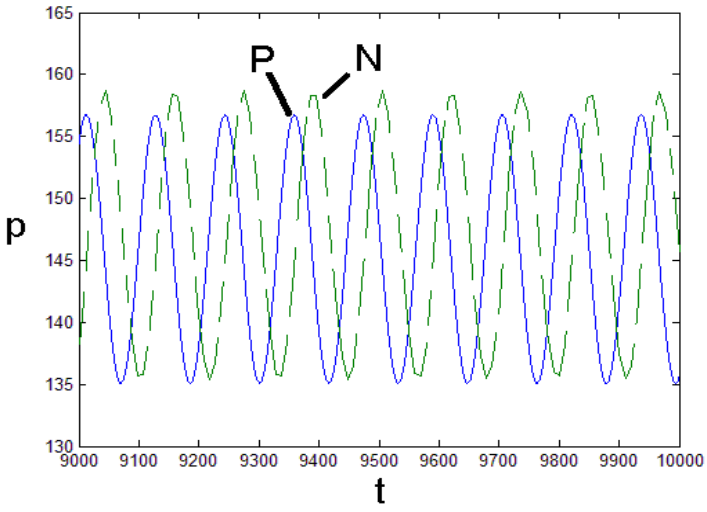

Figure 1. Comparison of perturbation results (P) with those of numerical integration (N) for $c = 1$ and $\Delta = 0.16$. The perturbation solution is $p(t) = 145.91 + 10.82\ \cos(0.05438\ t)$. Since the system is autonomous, the phase of the steady state solution is arbitrary, which accounts for the difference in phase between the displayed solutions.