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]

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

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

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 $\mu_m = \mu_p = \mu$.

2. Stability of equilibrium

We begin by rescaling Eqs. (1) and (2). 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

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

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

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

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

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

Expanding for small values of η_d, Eq. (8) becomes

$$\dot{\xi} = -\mu\xi - K\eta_d + H_2\eta_d^2 + H_3\eta_d^3 + \cdots \tag{10}$$

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

$$K = \frac{n\beta}{p^*(1+\beta)^2}, \quad \text{where } \beta = \left(\frac{p^*}{p_0}\right)^n \tag{11}$$

$$H_2 = \frac{\beta n(\beta n - n + \beta + 1)}{2(\beta+1)^3 p^{*2}} \tag{12}$$

$$H_3 = -\frac{\beta n(\beta^2 n^2 - 4\beta n^2 + n^2 + 3\beta^2 n - 3n + 2\beta^2 + 4\beta + 2)}{6(\beta+1)^4 p^{*3}} \tag{13}$$

Next we analyze the linearized system coming from Eqs. (10) and (9)

$$\dot{\xi} = -\mu\xi - K\eta_d \tag{14}$$

$$\dot{\eta} = \xi - \mu\eta \tag{15}$$

Stability analysis of Eqs. (14) and (15) shows that for $T = 0$ (no delay), the equilibrium point (m^*, p^*) is a stable spiral. Increasing the delay, T, in the linear system (14) and (15), will yield a critical delay, T_{cr}, such that for $T > T_{cr}$, (m^*, p^*) will be unstable, giving rise to a Hopf bifurcation. For $T = T_{cr}$ the system (14) and (15) will exhibit a pair of pure imaginary eigenvalues $\pm\omega i$ corresponding to the solution

$$\xi(t) = B\cos(\omega t + \phi) \tag{16}$$

$$\eta(t) = A\cos\omega t \tag{17}$$

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. Then for values of delay T close to T_{cr},

$$T = T_{cr} + \Delta \tag{18}$$

the nonlinear system (3) and (4) is expected to exhibit a periodic solution (a limit cycle) which can be written in the approximate form of Eqs. (16) and (17). Substituting Eqs. (16) and (17) into Eqs. (14) and (15) and solving for ω and T_{cr} we obtain

$$\omega = \sqrt{K - \mu^2} \tag{19}$$

$$T_{cr} = \frac{\arctan\left(\frac{2\mu\sqrt{K-\mu^2}}{K-2\mu^2}\right)}{\sqrt{K-\mu^2}} \tag{20}$$

3. Lindstedt's method

We use Lindstedt's Method [5,6] on Eqs. (10) and (9). We begin by changing the first order system into a second order DDE. This results in the following form:

$$\ddot{\eta} + 2\mu\dot{\eta} + \mu^2\eta = -K\eta_d + H_2\eta_d^2 + H_3\eta_d^3 + \cdots \tag{21}$$

where K, H_2 and H_3 are defined by Eqs. (11)–(13). We introduce a small parameter ϵ via the scaling

$$\eta = \epsilon u \tag{22}$$

The detuning Δ of Eq. (18) is scaled like ϵ^2, $\Delta = \epsilon^2\delta$

$$T = T_{cr} + \Delta = T_{cr} + \epsilon^2\delta \tag{23}$$

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

$$\tau = \Omega t \tag{24}$$

This results in the following form of Eq. (21):

$$\Omega^2 \frac{d^2 u}{d\tau^2} + 2\mu\Omega \frac{du}{d\tau} + \mu^2 u = -Ku_d + \epsilon H_2 u_d^2 + \epsilon^2 H_3 u_d^3 \tag{25}$$

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

$$\Omega = \omega + \epsilon^2 k_2 + \cdots \tag{26}$$

Next we expand the delay term u_d

$$u_d = u(\tau - \Omega T) = u(\tau - (\omega + \epsilon^2 k_2 + \cdots)(T_{cr} + \epsilon^2 \delta)) \tag{27}$$

$$= u(\tau - \omega T_{cr} - \epsilon^2 (k_2 T_{cr} + \omega\delta) + \cdots) \tag{28}$$

$$= u(\tau - \omega T_{cr}) - \epsilon^2 (k_2 T_{cr} + \omega\delta) u'(\tau - \omega T_{cr}) + O(\epsilon^3) \tag{29}$$

Now we expand $u(\tau)$ in a power series in ϵ

$$u(\tau) = u_0(\tau) + \epsilon u_1(\tau) + \epsilon^2 u_2(\tau) + \cdots \tag{30}$$

Substituting and collecting terms, we find

$$\omega^2 \frac{d^2 u_0}{d\tau^2} + 2\mu\omega \frac{du_0}{d\tau} + Ku_0(\tau - \omega T_{cr}) + \mu^2 u_0 = 0 \tag{31}$$

$$\omega^2 \frac{d^2 u_1}{d\tau^2} + 2\mu\omega \frac{du_1}{d\tau} + Ku_1(\tau - \omega T_{cr}) + \mu^2 u_1 = H_2 u_0^2(\tau - \omega T_{cr}) \tag{32}$$

$$\omega^2 \frac{d^2 u_2}{d\tau^2} + 2\mu\omega \frac{du_2}{d\tau} + Ku_2(\tau - \omega T_{cr}) + \mu^2 u_2 = \ldots \tag{33}$$

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

$$u_0(\tau) = \hat{A} \cos \tau \tag{34}$$

where from Eqs. (17) and (22) we know $A = \hat{A}\epsilon$. Next we substitute (34) into (32) and obtain the following expression for u_1:

$$u_1(\tau) = m_1 \sin 2\tau + m_2 \cos 2\tau + m_3 \tag{35}$$

where m_1 is given by the equation

$$m_1 = -\frac{2\hat{A}^2 H_2 \mu \sqrt{K - \mu^2}(\mu^2 - K)(2\mu^2 - 3K)}{K(16\mu^6 - 39K\mu^4 + 18K^2\mu^2 + 9K^3)} \tag{36}$$

and where m_2 and m_3 are given by similar equations, omitted here for brevity. We substitute Eqs. (34) and (35) into (33), 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

$$A^2 = \frac{P}{Q} \Delta \tag{37}$$

where

$$P = -8K^2(\mu^2 - K)(\mu^2 + K)(16\mu^6 - 39K\mu^4 + 18K^2\mu^2 + 9K^3) \tag{38}$$

$$Q = Q_0 T_{cr} + Q_1 \tag{39}$$

and

$$Q_0 = 48H_3K^2\mu^8 + 16H_2^2K\mu^8 - 69H_3K^3\mu^6 + 32H_2^2K^2\mu^6 - 63H_3K^4\mu^4$$
$$- 162H_2^2K^3\mu^4 + 81H_3K^5\mu^2 + 108H_2^2K^4\mu^2 + 27H_3K^6 + 30H_2^2K^5 \qquad (40)$$

$$Q_1 = 96H_3K\mu^9 + 64H_2^2\mu^9 - 138H_3K^2\mu^7 - 16H_2^2K\mu^7 - 126H_3K^3\mu^5$$
$$- 308H_2^2K^2\mu^5 + 162H_3K^4\mu^3 + 296H_2^2K^3\mu^3 + 54H_3K^5\mu + 12H_2^2K^4\mu \qquad (41)$$

Eq. (39) depends on μ, K, H_2, H_3, and T_{cr}. By using Eq. (20) we may express Eq. (39) 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, where, from Eq. (26), we have $\Omega = \omega + \epsilon^2 k_2$

$$k_2 = -\frac{R}{Q}\delta \qquad (42)$$

where Q is given by (39) and

$$R = \sqrt{K - \mu^2} Q_0 \qquad (43)$$

An expression for the amplitude B of the periodic solution for $\xi(t)$ (see Eq. (16)) may be obtained directly from Eq. (9) by writing $\xi = \dot{\eta} + \mu\eta$, where $\eta \sim A\cos\omega t$. We find

$$B = \sqrt{K}A \qquad (44)$$

where K and A are given as in (11) and (37), respectively.

4. Numerical example

Using the same parameter values as in [4]

$$\mu = 0.03/\text{min}, \quad p_0 = 100, \quad n = 5 \qquad (45)$$

we obtain

$$p^* = 145.9158, \quad m^* = 4.3774 \qquad (46)$$

$$K = 3.9089 \times 10^{-3}, \quad H_2 = 6.2778 \times 10^{-5}, \quad H_3 = -6.4101 \times 10^{-7} \qquad (47)$$

$$T_{cr} = 18.2470, \quad \omega = 5.4854 \times 10^{-2}, \quad \frac{2\pi}{\omega} = 114.5432 \qquad (48)$$
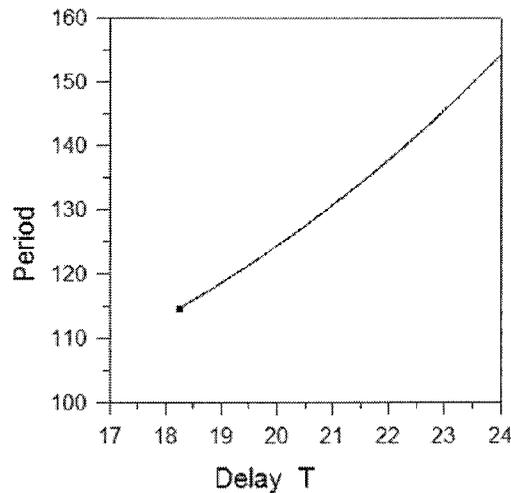
Fig. 1. Period of oscillation, $2\frac{\pi}{\Omega}$, plotted as a function of delay T, where Ω is given by Eq. (52). The initiation of oscillation at $T = T_{cr} = 18.2470$ is due to a supercritical Hopf bifurcation, and is marked in the figure with a dot.

Here the delay T_{cr} and the response period $2\pi/\omega$ are given in minutes. Substituting (46)–(48) into (37)–(44) yields the following equations:

$$A = 27.0215\sqrt{\Delta} \tag{49}$$

$$k_2 = -2.4512 \times 10^{-3}\delta \tag{50}$$

$$B = 1.6894\sqrt{\Delta} \tag{51}$$

Note that since Eq. (49) requires $\Delta > 0$ for the limit cycle to exist, and since we saw in Eqs. (14) and (15) 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.

Multiplying (50) by ϵ^2 and substituting into (26) we obtain

$$\Omega = 5.4854 \times 10^{-2} - 2.4512 \times 10^{-3}\Delta \tag{52}$$

where $\Delta = T - T_{cr} = T - 18.2470$. Plotting the period, $\frac{2\pi}{\Omega}$, against the delay, T, yields the graph shown in Fig. 1. These results are in agreement with those obtained by numerical integration of the original Eqs. (1) and (2) and with those presented in [4].

5. Effect of changing parameters

An advantage of the closed form approximate solution presented in this paper is that the effect of changes in parameters may be easily studied. In this section we present a few results obtained from our solution.

The equilibrium concentration p^* is determined by solving Eq. (7) for given values of μ, p_0, and n. Fig. 2 shows p^* displayed as a function of μ for $p_0 = 10, 50, 100,$ and 200. Here and in the following plots we follow [4] and take $n = 5$.

We note from Eq. (20) that the quantity $K - 2\mu^2$ must be non-negative in order that $T_{cr} > 0$, that is in order that parameters corresponding to the Hopf bifurcation occur in a *delay* equation. (If $T_{cr} < 0$ then we would have a *future* equation, which is physically unreasonable.) Fig. 3 shows that this condition restricts the values of degradation rate μ for a given value of reference concentration p_0. For values of μ which are greater than this critical value $\mu_{critical}$, the system will not exhibit a Hopf bifurcation and no oscillation will result.

From Eq. (37) we see that the amplitude A of protein oscillation is the product of $\sqrt{\frac{P}{Q}}$ and $\sqrt{\Delta}$. Fig. 4 displays $\sqrt{\frac{P}{Q}}$ as a function of μ for $p_0 = 10, 50, 100,$ and 200 and for $n = 5$. Note that the maximum permissible value of μ depends on p_0 as shown in Fig. 3.

Eqs. (26), (42), (43), (19) and (23) give that $\Omega = \omega(1 - \frac{Q_0}{Q}\Delta)$, where Ω is the frequency of oscillation for delay $T = T_{cr} + \Delta$, and ω is the frequency of oscillation for delay $T = T_{cr}$. Fig. 5 displays $\frac{Q_0}{Q}$ as a function
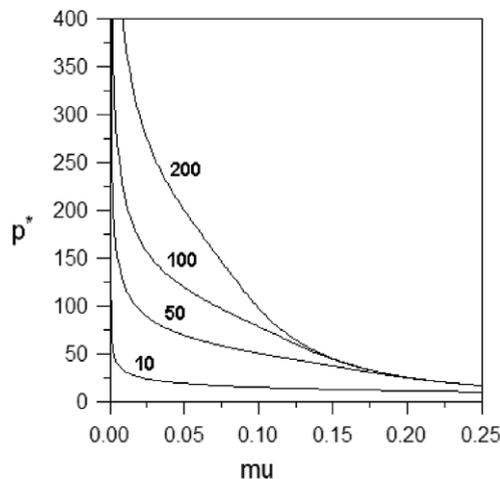
Fig. 2. The equilibrium concentration p^* displayed as a function of μ for $p_0 = 10, 50, 100$ and 200 and for $n = 5$.
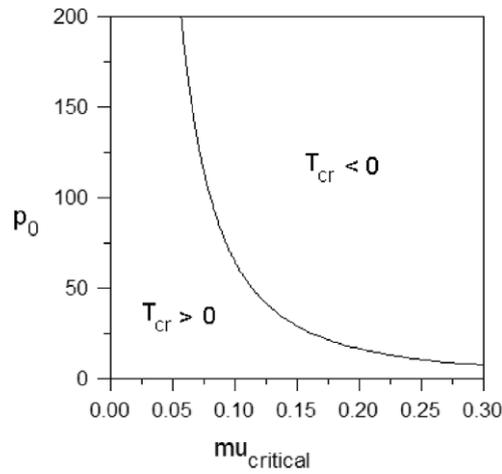
Fig. 3. Values of degradation rate μ which are greater than $\mu_{critical}$ correspond to negative values of T_{cr} and will prevent the system from oscillating. Here $\mu_{critical}$ is shown to depend on the reference concentration p_0.
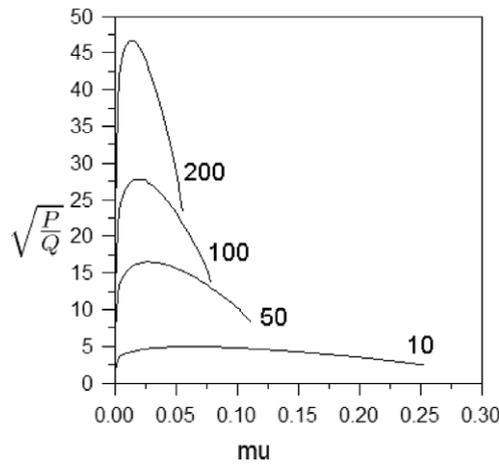
Fig. 4. Eq. (37) shows that the amplitude A of protein oscillation is the product of $\sqrt{\frac{P}{Q}}$ and $\sqrt{A}$. Here $\sqrt{\frac{P}{Q}}$ is displayed as a function of μ for $p_0 = 10$, 50, 100 and 200 and for $n = 5$.
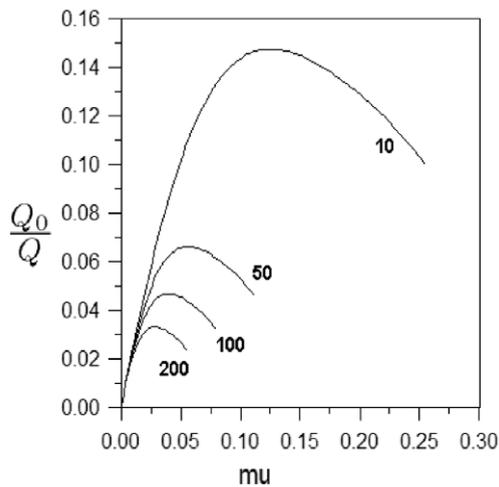
Fig. 5. Our solution gives that $\Omega = \omega(1 - \frac{Q_0}{Q}A)$ where Ω is the frequency of oscillation for delay $T = T_{cr} + A$ and ω is the frequency of oscillation for delay $T = T_{cr}$. Here $\frac{Q_0}{Q}$ is displayed as a function of μ for $p_0 = 10$, 50, 100 and 200 and for $n = 5$.

of μ for $p_0 = 10, 50, 100$, and 200 and for $n = 5$. Note again that the maximum permissible value of μ depends on p_0 as shown in Fig. 3.

6. Conclusions

The biological literature [4] shows that long time behavior of gene expression dynamics can consist of both stable equilibrium as well as periodic behavior. By analyzing a DDE model originally proposed in [4], we have shown that the transition between these states is due to a Hopf bifurcation. Our nonlinear analysis provides approximate expressions for the amplitude and frequency of the resulting limit cycle as a function of the model parameters. Fig. 3 shows that the Hopf bifurcation may not occur if the rates of degradation μ are too large. Inspection of Fig. 4 shows that for a given detuning Δ off of the Hopf bifurcation, the amplitude of the oscillation depends on both p_0 and μ. We see that increasing p_0 for a fixed value of μ causes an increase in amplitude. However, for a fixed value of p_0, the limit cycle amplitude is largest for a certain optimal value of μ. Fig. 5 shows a similar behavior regarding the period of the limit cycle oscillation. Here again, for a fixed value of p_0 we see that the quantity $\frac{\Omega_0}{\Omega}$ achieves a maximum for a certain optimal value of μ. In this case the peak values of $\frac{\Omega_0}{\Omega}$ correspond to minimal values of frequency Ω of the limit cycle, and thus to maximal values for the period of the limit cycle.

References

[1] Mahaffy JM. Genetic control models with diffusion and delays. Math Biosci 1988;90:519–33.
[2] Mahaffy JM, Jorgensen DA, Vanderheyden RL. Oscillations in a model of repression with external control. J Math Biol 1992;30:669–91.
[3] Mocek WT, Rudbicki R, Voit EO. Approximation of delays in biochemical systems. Math Biosci 2005;198:190–216.
[4] Monk NAM. Oscillatory expression of Hes1, p53, and NF-κB driven by transcriptional time delays. Curr Biol 2003;13:1409–13.
[5] Rand RH. Lecture notes on nonlinear vibrations (version 52). Available from: http://www.tam.cornell.edu/randdocs/nlvibe52.pdf (2005).
[6] Rand R, Verdugo A. Hopf bifurcation formula for first order differential-delay equations. Commun Nonlinear Sci Numer Simul, in press, doi:10.1016/j.cnsns.2005.08.005.