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Stability of periodic solutions for a model of genetic repression with delays

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Abstract. A technique is discussed for locating the Hopf bifurcation of an n-dimensional system of delay differential equations which arises from a model for control of protein biosynthesis. Certain parameter values are shown to allow a Hopf bifurcation to periodic orbits. At the Hopf bifurcation the periodic orbits are shown to be stable either analytically or numerically depending on the parameter values.

Key words: Hopf bifurcation — Delay differential equations — Stability of orbits — Protein biosynthesis — Genetic repression

1. Introduction

There have been numerous studies of periodic enzyme syntheses for populations of prokaryotic and eukaryotic cells. A summary of some of the experimental studies can be found in Tyson [13, 14]. The oscillations are observed in both synchronous and asynchronous cell cultures which suggests that the autogenous oscillations in enzyme activity may be controlled by a negative feedback system for the synthesis of the enzyme. A variety of oscillatory phenomena in biology are thought to arise because of negative feedback, from high frequency neural activity to longer period circadian rhythms and endocrine oscillations [15]. There has been considerable interest as to whether or not the classical model of repression proposed by Jacob and Monod [6] could account for oscillations. In this paper we determine when oscillations can arise in a class of models for genetic repression with time delays and show that there is a stable periodic orbit. A stable periodic solution is one which could be observed experimentally.

Goodwin [4, 5] proposed a mathematical model for genetic repression which was developed from the theory of Jacob and Monod using biochemical kinetics. This model has been extended and studied extensively [see e.g., 2, 9, 10, 13, 15]. Previous work has been mainly concerned with the existence of periodic solutions to the systems of differential equations for this model. In this paper we are interested in studying the stability of small amplitude periodic solutions. Mahaffy [8] showed the existence of periodic solutions for an n-dimensional model of repression with delays and also demonstrated a technique for calculating when

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a small amplitude periodic solution from a Hopf bifurcation occurs. This technique for finding a Hopf bifurcation is combined with a technique developed by Stech [11, 12] for determining the stability of a Hopf bifurcation.

In Sect. 2 we present the model and find a region where periodic solutions may exist and then use a method for locating where a Hopf bifurcation occurs. A theorem is given that determines a region where a Hopf bifurcation can occur as the delay varies. For a collection of examples the critical delay is computed numerically. In Sect. 3 we present formulae which allow one to compute the stability of the Hopf bifurcation for the model. For a particular range of parameter values we show that the Hopf bifurcation is always stable. We also give numerical results which suggest that for the n-dimensional repression model the Hopf bifurcation always results in a stable periodic orbit.

2. The Hopf bifurcation in a genetic repression model

The mathematical model for genetic control by negative feedback or repression was first derived by Goodwin [5]. Using non-dimensional variables we present the n-dimensional model for repression with a discrete delay, r, representing transcription and translation. It is given by the following system of differential equations:

$$\begin{aligned} \dot{x}_1(t) &= \frac{1}{1+[x_n(t-r)+\bar{x}_n]^\rho} - b_1\bar{x}_1 - b_1x_1(t) \\ &\equiv f(x_n(t-r)) - b_1x_1(t), \\ \dot{x}_i(t) &= x_{i-1}(t) - b_ix_i(t), \qquad i=2,\dots,n, \end{aligned} \tag{2.1}$$

where b_i represent non-dimensional decay rates, ρ is the Hill coefficient for repression, and $\bar{x}_i$ are the constants used to translate the equilibrium of the model to the origin and can be found from the unique solution to the system of equations given by

$$f(0)=0 \quad \text{and} \quad \bar{x}_{i-1}=b_i\bar{x}_i, \qquad i=2,\dots,n.$$

The nonlinear system (2.1) may be written

$$\dot{x}(t) = Ax(t) + Bx(t-r) + H(x(t-r)), \tag{2.2}$$

where $A=[a_{ij}]$ is an $n\times n$ matrix whose only non-zero elements are $a_{ii}=-b_i$ on the diagonal and 1's on the subdiagonal and B is an $n\times n$ matrix whose only non-zero element is $f'(0)$ in the $(1,n)$ position. $H(\psi)$ is a nonlinear n-vector function with an expansion of the form

$$H(\psi) = \sum_{j=2}^{3} H_j(\psi) + \mathcal{O}(\|\psi\|^4)$$

where $H_j(\psi)$ are the appropriate symmetric, bounded j-linear forms on the Banach space $C([-r,0];\mathbb{R}^n)$ with the usual sup norm. A more detailed description of $H_j(\psi)$ is presented in Sect. 3.

The characteristic equation for (2.1) is given by $\det[A+B\,e^{-\lambda r}-\lambda I]=0$, which upon expansion becomes

$$\prod_{i=1}^{n}(b_i+\lambda)-f'(0)\,e^{-\lambda r}=0 \tag{2.3}$$

where $f'(0)=-[\rho\bar{x}_n^{\rho-1}/(1+\bar{x}_n^{\rho})^2]$. If we assume that for $r=0$ (the ordinary differential equation case) all solutions λ of (2.3) have $\operatorname{Re}\lambda<0$, then it was shown in Mahaffy [7] that whenever

$$-f'(0)>\prod_{i=1}^{n} b_i\equiv\beta \tag{2.4}$$

then there exists an $r_0>0$ such that for $r=r_0$, (2.3) has two purely imaginary solutions $\pm\lambda_0=\pm i\nu_0$ and all other solutions λ have $\operatorname{Re}\lambda<0$. If we consider r as the bifurcation parameter then as r increases we have a transverse crossing of the imaginary axis by a pair of eigenvalues λ, thus a Hopf bifurcation occurs. If $f'(0)<\beta$, then all solutions λ of (2.3) have $\operatorname{Re}\lambda<0$, hence the system (2.1) is locally asymptotically stable. For the special case when $\rho=1$, it has been shown that (2.1) is globally asymptotically stable [1, 3].

When (2.4) is satisfied and (2.1) is locally stable for $r=0$, Mahaffy [7] gives a technique for computing the critical value r_0 at which the Hopf bifurcation occurs. If we define

$$P(i\nu)\equiv\prod_{j=1}^{n}(b_j+i\nu),$$

then compute ν_0 such that $|P(i\nu_0)|=|f'(0)|$ which has a unique solution as $|P(0)|<|f'(0)|$ and $|P(i\nu)|$ increases monotonically with ν. The critical value of the delay r_0 is found by the formula

$$r_0=\frac{\pi-\arg P(i\nu_0)}{\nu_0} \tag{2.5}$$

where

$$\arg P(i\nu_0)=\sum_{j=1}^{n}\arctan(\nu_0/b_j).$$

It is of particular interest to determine for a fixed ρ what values of b_i allow there to be an $r\geqslant 0$ such that the system (2.1) is locally unstable. We summarize our findings in the following theorem:

Theorem 2.1. *Let* $\beta_0=\rho^{-1}(\rho-1)^{(\rho+1)/\rho}$. *If* $0<\beta<\beta_0$, *then there exists an* $r_0\geqslant 0$ *such that* (2.1) *is locally unstable for all* $r>r_0$. *If* $\beta\geqslant\beta_0$, *then all solutions* λ *of* (2.3) *have* $\operatorname{Re}\lambda<0$ *for all* $r\geqslant 0$.

Proof. From Mahaffy [8] we see that the critical value β_0 is when $\beta_0=|f'(0)|$. Solving for the equilibrium solution we find that $\beta\bar{x}_n=1/(1+\bar{x}_n^{\rho})$, so $f'(0)=-\rho\bar{x}_n^{\rho-1}/(1+\bar{x}_n^{\rho})^2=-\rho\beta^2\bar{x}_n^{\rho+1}$. Hence $1=\rho\beta_0\bar{x}_{0n}^{\rho+1}$ but $1=\beta_0\bar{x}_{0n}+\beta_0\bar{x}_{0n}^{\rho+1}$ from the equilibrium solution. Combining these we see that

$$\beta_0=\rho^{-1}(\rho-1)^{(\rho+1)/\rho}\quad\text{and}\quad\bar{x}_{0n}=(\rho-1).^{-1/\rho}$$

Now from above we see that

$$|f'(0)| = \rho\beta^2\bar{x}_n^{\rho+1} = \rho\beta^2\left[\frac{1}{\beta} - \bar{x}_n\right] = \beta + \beta[(\rho-1) - \rho/(1+\bar{x}_n^\rho)].$$

If $\beta < \beta_0$, then $\bar{x}_n > \bar{x}_{0n}$ which implies $\bar{x}_n^\rho > (\rho-1)^{-1}$. From this we see that

$$|f'(0)| = \beta + \beta[(\rho-1) - \rho/(1+\bar{x}_n^\rho)] > \beta + \beta[(\rho-1) - \rho/(1+(\rho-1)^{-1})] = \beta.$$

If $\beta > \beta_0$, then a similar argument gives $|f'(0)| < \beta$. By applying Theorem 1 of Mahaffy [7] which uses the argument principle and including any regions which are locally unstable in the ordinary differential equation case ($r = 0$), we establish our result.

Formula (2.5) gives a technique which computes numerically where a Hopf bifurcation occurs for the parameter r when parameters ρ, b_i and n are fixed. In Fig. 2.1 let $n = 4$ and $b_i = 1$, $i = 1, 2, 3$, then for different values of ρ and b_4 the critical value is r_0 where the Hopf bifurcation occurs. Note that $b_4 = \beta$ in this case. When $\rho = 8$ the region $0.3 < b_4 < 0.35$ is where (2.1) with $r = 0$ is locally unstable.

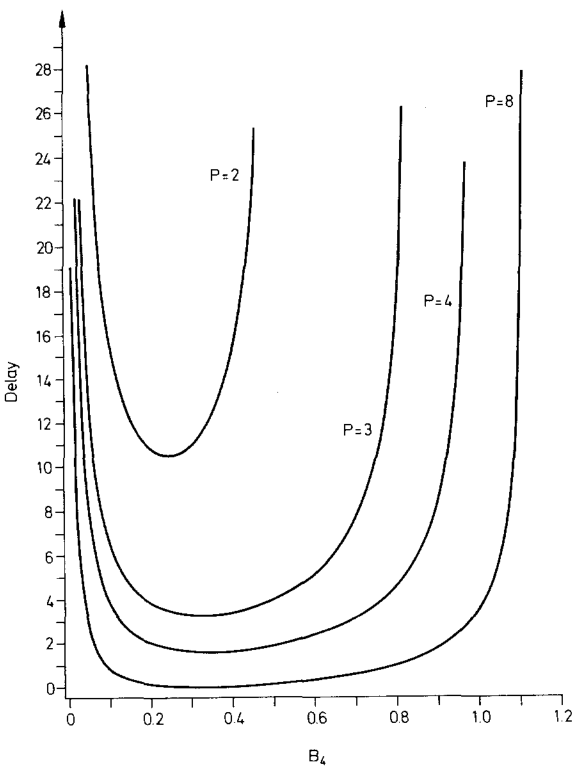

Fig. 2.1. A series of curves for different ρ values across which a Hopf bifurcation to a periodic solution occurs in the delay r and b_4 phase space. Here $b_1 = b_2 = b_3 = 1$ and $n = 4$

3. Computing the stability of the Hopf bifurcation

In the previous section a technique was presented to determine where a Hopf bifurcation occurs for (2.1). In this section we apply a method developed by Stech [11, 12] to determine the stability of the bifurcation. The notation used below parallels that of Stech [12] for a generic Hopf bifurcation.

Define

$$\Delta(\alpha, \lambda) \equiv [I\lambda - A - B\,e^{-\lambda r}]$$

where A and B are defined in (2.2). Hence $\Delta'(\alpha) = \partial\Delta(\alpha, \lambda)/\partial\lambda$ is an $n \times n$ matrix with 1's on the diagonal and $rf'(0)\,e^{-\lambda r}$ in the $(1, n)$ position. From the sparsity of $\Delta(\alpha, \lambda)$, it is easy to find $\Delta^{-1}(\alpha, \lambda)$. In fact we shall later show that only the first column of Δ^{-1} is needed, so with this information we write

$$\Delta^{-1}(\alpha, \lambda) = \frac{1}{\det \Delta(\alpha, \lambda)} \begin{bmatrix} \prod_{i=2}^{n} (b_i + \lambda) & \cdots \\ \prod_{i=3}^{n} (b_i + \lambda) & \cdots \\ \vdots & \\ 1 & \cdots \end{bmatrix}$$

A left eigenvector for $\Delta(\alpha, \lambda)$ at $\lambda = \lambda_0 = i\nu_0$ is $\xi^* = (1, c_2, \ldots, c_n)$ where

$$c_k = \prod_{i=1}^{k-1} (b_i + \lambda_0), \qquad k = 2, \ldots, n.$$

A right eigenvector for $\Delta(\alpha, \lambda)$ at $\lambda = \lambda_0$ is $\xi = (d_1, d_2, \ldots, d_{n-1}, 1)^T$ where

$$d_{n-k} = \prod_{i=n-k+1}^{n} (b_i + \lambda_0), \qquad k = 1, \ldots, n-1.$$

When the linearization of (2.1) is considered, we obtain the fundamental solutions on the 2-dimensional center manifold $\phi(s) = \xi\,e^{\lambda_0 s}$ and $\bar{\phi}(s) = \bar{\xi}\,e^{-\lambda_0 s}$ where $\lambda_0 = i\nu_0$. For the generic Hopf bifurcation which appears to be the only case for the n-dimensional model of repression first compute the trilinear form $H_3(\phi^2, \bar{\phi})$ and the bilinear forms $H_2(\phi^2)$ and $H_2(\phi, \bar{\phi})$ where $H_j(\psi)$ are the jth Frechet derivatives of the nonlinear $H(\psi)$ in (2.2). To compute these multilinear forms first write an expansion for $f(\zeta)$ which is given by

$$f(\zeta) = f'(0)\zeta + \frac{f''(0)}{2!}\zeta^2 + \frac{f'''(0)}{3!}\zeta^3 + \mathcal{O}(\|\zeta\|^4)$$

where

$$f''(0)/2! = h_2(0) = \frac{-\rho(\rho-1)\bar{x}_n^{\rho-2} + \rho(\rho+1)\bar{x}_n^{2\rho-2}}{2[1+\bar{x}_n^{\rho}]^3} \tag{3.1}$$

and

$$f'''(0)/3! = h_3(0)$$
$$= \frac{-\rho[(\rho-1)(\rho-2)\bar{x}_n^{\rho-3} - 4(\rho+1)(\rho-1)\bar{x}_n^{2\rho-3} + (\rho+2)(\rho+1)\bar{x}_n^{3\rho-3}}{6[1+\bar{x}_n^{\rho}]^4} \tag{3.2}$$

As f is the only nonlinearity and it appears in the first component with a dependence upon the nth component in the system (2.1), it can be readily shown that

$$H_3(\phi^2, \bar{\phi}) = h_3(0)(e^{-i\nu_0 r}, 0, \ldots, 0)^T$$
$$H_2(\phi^2) = h_2(0)(e^{-2i\nu_0 r}, 0, \ldots, 0)^T$$
$$H_2(\phi, \bar{\phi}) = h_2(0)(1, 0, \ldots, 0)^T.$$

To determine the stability of a generic Hopf bifurcation Stech [12] showed that it suffices to determine the sign of κ where:

$$\kappa = \mathrm{Re}\left\{\binom{3}{2}\xi^* H_3(\phi^2, \phi)/\xi^*\Delta'\xi\right.$$
$$+2\binom{1}{1}\binom{2}{0}\xi^* H_2(\phi, \bar{e}^{2\lambda_0^{\cdot}}\Delta^{-1}(0, 2\lambda_0)H_2(\phi^2))/\xi^*\Delta'\xi$$
$$\left.+2\binom{1}{0}\binom{2}{1}\xi^* H_2(\phi, \Delta^{-1}(0,0)H_2(\phi, \bar{\phi}))/\xi^*\Delta'\xi\right\}.$$

From before we find that

$$\xi^*\Delta'(\alpha)\xi = \sum_{i=1}^{n}\prod_{j\neq i}^{n}(b_j+\lambda_0) + rf'(0)\,e^{-\lambda_0 r} \equiv \gamma, \tag{3.3}$$

$$H_2(\bar{\phi}, e^{-2\lambda_0 r}\Delta^{-1}(0, 2\lambda_0)H_2(\phi^2))$$
$$= H_2\left(\bar{\phi}, e^{-2\lambda_0 r}\frac{h_2(0)\,e^{-2\lambda_0 r}}{\prod_{i=1}^{n}(b_i+2\lambda_0) - f'(0)\,e^{-2\lambda_0 r}}\left(\prod_{i=2}^{n}(b_i+2\lambda_0), \ldots, 1\right)^{\mathrm{T}}\right)$$
$$= \frac{[h_2(0)^2]}{\prod_{i=1}^{n}(b_i+2\lambda_0) - f'(0)\,e^{-2\lambda_0 r}}(e^{-3i\nu_0 r}, 0, \ldots, 0)^T,$$
$$H_2(\phi, \Delta^{-1}(0,0)H_2(\phi, \bar{\phi})) = \frac{[h_2(0)]^2}{\prod_{i=1}^{n} b_i - f'(0)}(e^{-i\nu_0 r}, 0, \ldots, 0)^T.$$

Stech [12] showed that the Hopf bifurcation is stable when $\kappa < 0$, so for our model of genetic repression to have small stable periodic orbits it suffices to show that

$$\mathrm{Re}\left\{\frac{3h_3(0)}{\gamma}e^{-i\nu_0 r} + \frac{2}{\gamma}\frac{[h_2(0)]^2}{\prod_{i=1}^{n}(b_i+2i\nu_0) - f'(0)\,e^{-2i\nu_0 r}}e^{-3i\nu_0 r}\right.$$
$$\left.+\frac{4}{\gamma}\frac{[h_2(0)]^2}{\prod_{i=1}^{n} b_i - f'(0)}e^{-i\nu_0 r}\right\} < 0. \tag{3.4}$$

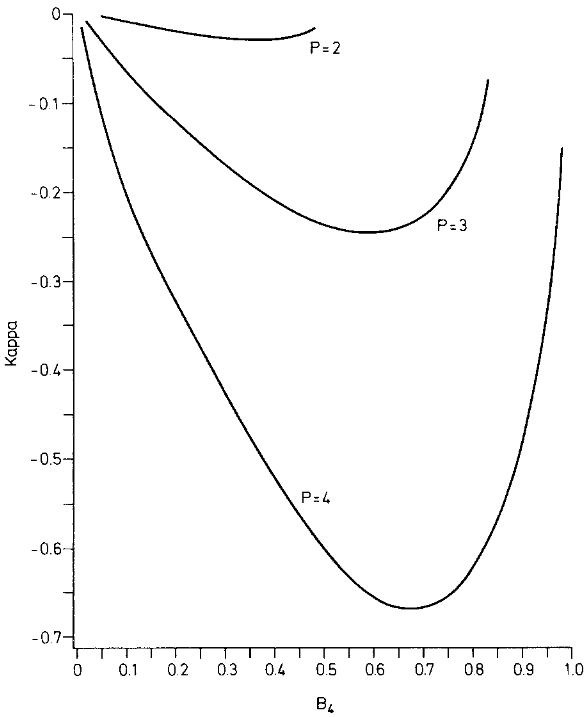

Fig. 3.1. A series of curves for different ρ values showing the value of κ at the Hopf bifurcation as b_4 varies. Note that κ is always negative implying a stable Hopf bifurcation.

Figure 3.1 shows κ for different values of ρ and b_4 at the Hopf bifucation r_0 computed in Fig. 2.1 where again $n=4$ and $b_i=1$, $i=1,2,3$. Numerically the value of κ is always negative indicating a stable periodic orbit near the Hopf bifurcation. Numerical integration of (2.1) does show the periodic orbits to be attracting or stable.

Because of the complexity of (3.4) we can not prove in general that κ is always negative; however, in a region near $\beta=\beta_0$ the following theorem holds:

Theorem 3.1. *There exists an* $\varepsilon>0$ *such that if* $\beta\varepsilon(\beta_0-\varepsilon, \beta_0)$, *then* (2.1) *has a small amplitude stable periodic solution.*

Proof. Theorem 2.1 shows that for $\beta\varepsilon(\beta_0-\varepsilon_1, \beta_0)$ for some $\varepsilon_1>0$ there exists a critical $r_0>0$ such that a Hopf bifurcation occurs. By the definition of ν_0 and (2.5) one can show that as $\beta\to\beta_0$, $r_0\to\infty$. As $|f'(0)|=\beta_0$ at β_0, then with the equilibrium solution one can show that $\bar{x}_{0n}^{\rho+1}=1/\rho\beta_0$ and $\bar{x}_{0n}=(\rho-1)/\rho\beta_0$. Substituting these into (3.1) and (3.2) we can show that

$$h_2(0)=-\frac{\beta_0^2\rho(\rho-3)}{2(\rho-1)}$$

$$h_3(0)=-\frac{\beta_0^3\rho^2(\rho-2)(\rho-7)}{6(\rho-1)^2} \tag{3.5}$$

at $\beta=\beta_0$.

At $\beta=\beta_0$ there is no Hopf bifurcation with respect to the parameter r; however, it is easily seen that the coefficients $h_2(0)$ and $h_3(0)$ vary continuously with respect to the parameter β. For β near β_0 the argument principle used in the proof of Theorem 2.1 gives ν_0 to be very small as $\beta\to\beta_0$; however, $\nu_0 r_0\to\pi$ as $\beta\to\beta_0$ from the argument principle and our definitions of ν_0 and r_0.

From the above information we examine $\gamma\kappa$ at $\beta=\beta_0$. At $\beta=\beta_0$, $\nu_0 r_0=\pi$, $\nu_0=0$, and $f'(0)=-\beta_0$, so we may substitute these values with (3.5) into (3.4) and obtain

$$\gamma\kappa=\frac{\beta_0^3\rho^2(\rho-2)(\rho-7)}{6(\rho-1)^2}-\frac{2}{2\beta_0}\frac{\beta_0^4\rho^2(\rho-3)^2}{4(\rho-1)^2}-\frac{4}{2\beta_0}\frac{\beta_0^4\rho^2(\rho-3)^2}{4(\rho-1)^2}$$
$$=-\frac{\beta_0^3\rho^2(\rho+1)}{4(\rho-1)},$$

which is strictly negative.

For $\beta<\beta_0$ but near β_0 we see from (3.3) that γ has a large positive real component with only a small imaginary component. Thus to complete our proof we use the continuous dependence of κ on the parameters to show that there exists an $\varepsilon<0$ such that for $\beta\varepsilon(\beta_0-\varepsilon,\beta_0)$, $\kappa<0$. Hence the result of Stech [11] gives the existence of a small amplitude stable periodic solution near the Hopf bifurcation.

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