

Interaction of spatial diffusion and delays in models of genetic control by repression

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Abstract. A class of models based on the Jacob and Monod theory of genetic repression for control of biosynthetic pathways in cells is considered. Both spatial diffusion and time delays are taken into account. A method is developed for representing the effects of spatial diffusion as distributed delay terms. This method is applied to two specific models and the interaction between the diffusion and the delays is treated in detail. The destabilization of the steady-state and the bifurcation of oscillatory solutions are studied as functions of the diffusivities and the delays. The limits of very small and very large diffusivities are analyzed and comparisons with well-mixed compartment models are made.

Key words: Genetic control — Repression — Diffusion — Delays — Compartmental models — Bifurcation — Stability — Oscillations

1. Introduction

The Jacob and Monod [9] theory of genetic repression for control of biosynthetic pathways in cells has been the basis of several mathematical models. Goodwin [6, 7] derived a system of nonlinear ordinary differential equations in the formulation of such a model. He also suggested that time delays from the processes of transcription and translation as well as spatial diffusion of reactants could play a role in the behavior of this system. Since this early work, there have been extensive studies of such models which include either time delays [1, 2, 3, 4, 8, 12, 13, 20] or diffusion [10, 15, 17, 18, 19], but no studies that combine these and compare their relative effects.

We consider a class of models based on the theory of Jacob and Monod [9] which include both spatial diffusion and time delays. We analyze the dynamic stability of the model and study the relative effects of diffusion and delays. The basis of our method is a transformation that imbeds the spatial diffusion in specific functional delay terms, thus effectively reducing a problem including partial differential equations with delays to a problem containing only delay

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terms. Using this reduced system, we study the local stability and the bifurcation of time periodic solutions. We show that, in some cases when the diffusion becomes large, these models approach the corresponding models with well-mixed compartments. However, in other basic cases, the large diffusion limit does not lead to a standard well-mixed compartment model. Thus our conclusions partially support the heuristic arguments that time-delays can be used to model the effects of diffusion. However, they show that the types of delays that have been suggested to describe diffusion (see MacDonald [11], for example) are not adequate, and that rather subtle hereditary distributive delays are needed to perform this reduction. Also, we show that in certain basic situations, well-mixed compartment models cannot describe systems where reactants diffuse in space from one compartment to another, even in the large diffusion rate limit. Similar conclusions hold for certain population models and physiological models.

The model we consider regards the cell as consisting of two compartments enclosed within the cell wall and separated by a permeable membrane (see Fig. 1.1). The first compartment is labeled ω in the figure and is regarded as a well-mixed compartment (the nucleus) where mRNA is produced. The second compartment denoted by $\Omega \setminus \omega$ consists of the cell interior Ω minus the nucleus ω and represents the cytoplasm in which the ribosomes are randomly dispersed. Here occurs the process of translation and the consequent production of the repressor. The communication between the ribosome sites where translation occurs and the nucleus uses the processes of diffusion in the cytoplasm and transfer through the membrane bounding the nucleus.

The regions Ω and ω are three-dimensional in the actual situation, however, both a two-dimensional and a one-dimensional spatial domain can be considered as simplified versions of this model. The one-dimensional model was introduced by Mahaffy and Pao [14] where it is discussed together with a related three compartment model which we shall describe below. In a subsequent paper we will describe a more general situation which includes the above models and which can still be analyzed by using the techniques that we develop here. For now, we follow [14] in considering only a one-dimensional model with two biochemical species whose concentrations we denote by u_i and v_i , $i = 1, 2$, where $i = 1$ refers to the concentration in compartment ω , and $i = 2$ to that in $\Omega \setminus \omega$. These two species interact to control each other's production and have production sites which are spatially separated. We will compare the dynamic behavior of these species with the behavior of the concentrations in a model of genetic repression with two well-mixed compartments.

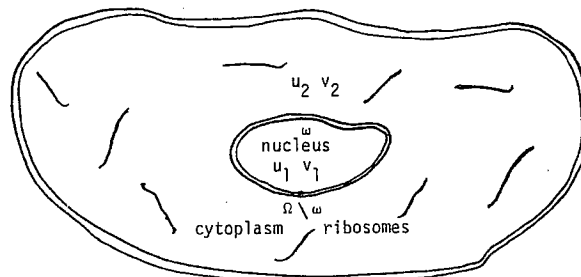


Fig. 1.1. Model of the cell as a two-compartment system

In our model the cell nucleus ω , is viewed as a well-mixed compartment where mRNA (whose concentration is denoted by u_1) is transcribed from the gene at a rate depending on the concentration of the repressor protein v_1 . The mRNA leaves ω and enters the cytoplasm, $\Omega \setminus \omega$ where it diffuses and reacts with the ribosomes. Through the delayed process of translation, a sequence of enzymes is produced which in turn produces a repressor v_2 (or possibly one of the enzymes itself is the repressor). This end-product repressor then diffuses back to ω where it inhibits the production of u_1 . The cell wall acts as a barrier through which neither biochemical substance can pass.

From these assumptions and from kinetic arguments similar to those of Goodwin, we can write the system of equations governing the kinetics of u_i and v_i inside Ω . These equations are as follows:

$$\begin{aligned} \frac{du_1(t)}{dt} &= f(v_{1t}) - b_1 u_1(t) + a_1 \int_{\partial\omega} [u_2(x, t) - u_1(t)] dS_\omega \\ \frac{dv_1(t)}{dt} &= -b_2 v_1(t) + a_2 \int_{\partial\omega} [v_2(x, t) - v_1(t)] dS_\omega \\ \frac{\partial u_2(x, t)}{\partial t} &= D_1 \Delta u_2(x, t) - b_1 u_2(x, t) \\ \frac{\partial v_2(x, t)}{\partial t} &= D_2 \Delta v_2(x, t) - b_2 v_2(x, t) + c_0 u_{2t}(x), \quad x \in \Omega \setminus \omega \end{aligned} \quad (1.1)$$

with boundary conditions

$$\begin{aligned} \left. \begin{aligned} \frac{\partial u_2(x, t)}{\partial n} &= -\beta_1 [u_2(x, t) - u_1(t)] \\ \frac{\partial v_2(x, t)}{\partial n} &= -\beta_1^* [v_2(x, t) - v_1(t)] \end{aligned} \right\}, \quad x \in \partial\omega, \\ \frac{\partial u_2(x, t)}{\partial n} &= \frac{\partial v_2(x, t)}{\partial n} = 0, \quad x \in \partial\Omega. \end{aligned}$$

The constants b_i are kinetic rates of decay, while a_i are the rates of transfer between compartments which we assume to be directly proportional to the concentration gradient. D_i are the diffusivity coefficients and c_0 is the production rate for the repressor. The function f is a decreasing function in v_1 representing the production of mRNA and is of the form $1/(1+(v_{1t})^\rho)$. The terms v_{1t} and $u_{2t}(x)$ are delayed concentrations which may have discrete delays, i.e. $v_{1t} = v_1(t-r_1)$ and $u_{2t}(x) = u_2(x, t-r_2)$, or more generally a distributed delay of the form

$$z_{it} = \int_{-r}^0 z_i(t+\theta) d\eta(\theta)$$

where the above integral is a Stieltjes type integral with $\int_{-r}^0 d\eta(\theta) = 1$. The β_1 and β_1^* are Fick's law constants for flux across the boundary of ω denoted by $\partial\omega$ and n is the normal component to the boundary. We assume the boundaries of ω and Ω are smooth.

By considering the second compartment to also be well-mixed, we obtain the following system of differential equations with only delays describing the corresponding well-mixed compartment system.

$$\begin{aligned}u_1'(t) &= f(v_1, t) - b_1 u_1(t) + a_1(u_2(t) - u_1(t)) \\v_1'(t) &= -b_2 v_1(t) + a_2(v_2(t) - v_1(t)) \\u_2'(t) &= -b_1 u_2(t) + a_3(u_1(t) - u_2(t)) \\v_2'(t) &= c_0 u_2(t) - b_2 v_2(t) + a_4(v_1(t) - v_2(t)).\end{aligned}\tag{1.2}$$

The constants a_1 , a_2 , b_1 , b_2 and c_0 in this system have the same interpretations as for the model with diffusion. The constants a_3 and a_4 are transfer rates between the two compartments and are equal to the net transfer rates across $\partial\omega$ in the diffusion model. Taking this boundary to have unit area, we then have $a_3 = \beta_1 D_1$ and $a_4 = \beta_1^* D_2$. This well-mixed model has been analyzed in Mahaffy and Pao [14] for a particular class of interaction terms with discrete delays. For certain parameter values, (1.2) was shown to have a unique globally attracting equilibrium, while for other parameter values one could show the existence of a Hopf bifurcation to a periodic solution. One of the aims of this paper is to extend these results for the well-mixed model (1.2) to the reaction diffusion model (1.1).

In the next section we reduce model (1.1) to a system of delay differential equations. In Sect. 3 we consider in more detail a simplified version of this model where the spatial domain is assumed to be one-dimensional. We show that, as the diffusivities D_i become large while the products $\beta_1 D_1$ and $\beta_1^* D_2$ tend to a_3 and a_4 , the system (1.1) goes through a Hopf bifurcation creating an oscillatory solution which is analogous to the bifurcation that occurs for the system (1.2) which describes the well-mixed two-compartment model. In fact, the limiting characteristic equation for (1.1) is the same as that for (1.2). We note that the products $\beta_1 D_1$ and $\beta_1^* D_2$, which are flux gradients multiplied by diffusivities, represent the net flux per unit area across the boundary $\partial\omega$ of ω . So, the limiting form, as the D_i tend to infinity, of (1.1) is equivalent to (1.2) as far as this local bifurcation of periodic solutions is concerned. We also consider the case where the D_i become small with $\beta_1 D_1$ and $\beta_1^* D_2$ remaining constant, and show that there is a cut-off value of the diffusivities below which the steady state solution always remains stable regardless of the value of the delay. This analytical result has the intuitive explanation that the damping effect of the diffusion process when sufficiently pronounced neutralizes the destabilizing effect of the delayed negative feed-back control mechanism.

Between the two extremes of very small and very large diffusivities there is a range where the damping effect and the delaying effect of the diffusion mechanism are in balance. For this case we have only numerical results which we present in Sect. 5. We compute the parameter values where the Hopf bifurcation occurs for (1.1) from the limiting characteristic equation found in Sect. 3 and show that spatial diffusion has the net effect of an added delay in this case. We also study the period of the oscillatory solution as a function of the diffusivity when the delays due to transcription and translation are kept fixed.

In Sect. 4 we describe our results for a similar three compartment system discussed by Mahaffy and Pao [14]. Unlike the previously described two-compartment

ment system, the limiting form of this model as D_1 and D_2 tend to infinity, while $\beta_i D_i$ and $\beta_i^* D_i$ tend to constants, usually does not lead to a characteristic equation of a well-mixed three compartment system. In fact, rather special restrictions need to be imposed in order that the large diffusion limit correspond to a well-mixed three compartment model. This serves to show the limitations of traditional compartmental analysis in describing systems where reactants are transferred via a diffusion mechanism.

We conclude by noting that the distributive delay terms caused by the spatial diffusion in the reduced version of our models are strongly dependent on the spatial dimension and, in the case of two and three dimensional domains, also the shape of these domains. Consequently, the methods that we develop here can be used to study the changes in the dynamic behavior of these models as the dimension of the domain changes, and also as its shape changes. We do not address these questions here, but will treat them in a subsequent paper.

2. Reduction of the two compartment diffusion model to a system of delay differential equations

In this section we outline the first step of our analysis and show that the reaction diffusion problem (1.1) can be reduced to a problem involving only delay differential equations. In the case of a one-dimensional spatial domain, all of the steps we take here are explicitly computed in Sect. 3 and the reader who is mainly interested in that case may go directly to that section after reading up to Eq. (2.2) below.

We begin by making a change of variables that shifts the equilibrium solution of (1.1) to the origin and transforms the boundary conditions to homogeneous boundary conditions. Let $u_1^s, v_1^s, u_2^s(x), v_2^s(x)$ be the unique equilibrium solution of (1.1) whose existence is shown in [14], then making the substitutions $U_1(t) = u_1(t) - u_1^s, V_1(t) = v_1(t) - v_1^s, U_2(x, t) = u_2(x, t) - u_2^s(x) - U_1(t), V_2(x, t) = v_2(x, t) - v_2^s(x) - V_1(t)$, into Eqs. (1.1) we obtain the following system of equations:

$$\begin{aligned} \frac{dU_1(t)}{dt} &= f(V_{1t} + v_1^s) - b_1 U_1(t) + a_1 \int_{a\omega} U_2(x, t) dS_\omega - b_1 u_1^s \\ &\quad + a_1 \int_{a\omega} (u_2^s(x) - u_1^s) dS_\omega \equiv F_1(U_1(t), V_{1t}, U_2(t)) \\ \frac{dV_1(t)}{dt} &= -b_2 V_1(t) + a_2 \int_{a\omega} V_2(x, t) dS_\omega \equiv G_1(V_1(t), Y_2(t)) \\ \frac{\partial U_2(x, t)}{\partial t} &= D_1 \Delta U_2(x, t) - b_1 U_2(x, t) - b_1 U_1(t) - F_1(U_1(t), V_{1t}, U_2(t)) \\ &\equiv D_1 \Delta U_2(x, t) - b_1 U_2(x, t) - F_2(U_1(t), V_{1t}, U_2(t)) \\ \frac{\partial V_2(x, t)}{\partial t} &= D_2 \Delta V_2(x, t) - b_2 V_2(x, t) - b_2 V_1(t) + c_0 U_{2t}(x) + c_0 U_{1t} - G_1(V_1(t), Y_2(t)) \\ &\equiv D_2 \Delta V_2(x, t) - b_2 V_2(x, t) - G_2(U_{1t}, V_1(t), U_{2t}(t), Y_2(t)) \end{aligned} \quad (2.1)$$

with the homogeneous boundary conditions

$$\left. \begin{aligned} \frac{\partial U_2(x, t)}{\partial n} + \beta_1 U_2(x, t) &= 0 \\ \frac{\partial V_2(x, t)}{\partial n} + \beta_1^* V_2(x, t) &= 0 \end{aligned} \right\}, \quad x \in \partial\omega \quad (2.2)$$

$$\frac{\partial U_2(x, t)}{\partial n} = \frac{\partial V_2(x, t)}{\partial n} = 0, \quad x \in \partial\Omega$$

where $\underline{U}_2(t) \equiv \int_{\partial\omega} U_2(x, t) dS_\omega$ and similarly for $\underline{V}_2(t)$.

The next step in the reduction is to form the fundamental solution to the linear part of the partial differential equations in (2.1) such that a variation of constants formula can be used. Let $T_i(t)$ be the semigroup generated by $D_i\Delta - b_i$, $i = 1, 2$, with boundary conditions (2.2), on the space of continuous functions with uniform norm on $\bar{\Omega} \setminus \omega$. $T_i(t)$ is an analytic semigroup on this space [16]. The function $F_2(U_1(t), V_{1b}, \underline{U}_2(t))$ is continuously differentiable in t with range in the space of continuous functions on $\bar{\Omega} \setminus \omega$, thus $U_2(x, t)$ satisfies (2.1) with boundary conditions (2.2) if and only if it satisfies the mild version of this problem ([16] Corollaries 2.2 and 2.5) which is simply a variation of constants formula. If we let $U_{20}(x) = u_2(x, 0)$ denote the initial distribution of U_2 in $\bar{\Omega} \setminus \omega$, then

$$U_2(x, t) = T_1(t)U_{20}(x) - \int_0^t T_1(t-s)F_2(U_1(s), V_{1s}, \underline{U}_2(s)) ds. \quad (2.3)$$

When (2.3) is integrated over the boundary of ω , it becomes a Volterra integral equation for $\underline{U}_2(t)$ given by the following:

$$\underline{U}_2(t) = \int_{\partial\omega} \left[T_1(t)U_{20}(x) - \int_0^t T_1(t-s)F_2(U_1(s), V_{1s}, \underline{U}_2(s)) ds \right] dS_\omega. \quad (2.4)$$

From the form of F_2 , it is easily seen that this equation is linear in $\underline{U}_2(t)$. Thus, by the continuity of F_1 and exponential bounds on T for $t \geq 0$, (2.4) has a unique, continuous and exponentially bounded solution for all $t \geq 0$.

The final step in the reduction is to perform similar steps to the $V_2(x, t)$ equation from (2.1). First, we note that from (2.4) $\underline{U}_2(t)$ depends only on U_1 , V_{1b} , and the initial data, hence, from (2.3) $U_2(x, t)$ can be expressed as a function depending only upon U_1 , V_{1b} , and the initial data. This implies that G_2 may be written as a function which depends on U_{1b} , V_{1b} , $\underline{Y}_2(t)$ and initial data. Suppressing the initial data dependence, we write $\tilde{G}_2 = G_2(U_{1b}, V_{1b}, \underline{Y}_2(t))$. From the solution operator $T_2(t)$ and the variation of constants formula we follow a similar procedure as before and obtain

$$V_2(x, t) = T_2(t)V_{20}(x) - \int_0^t T_2(t-s)\tilde{G}_2(U_{1s}, V_{1s}, \underline{Y}_2(s)) ds. \quad (2.5)$$

And, as before, by integrating over $\partial\omega$, we obtain a linear Volterra integral equation for $\underline{Y}_2(t)$ given by:

$$\underline{Y}_2(t) = \int_{\partial\omega} \left[T_2(t)V_{20}(x) - \int_0^t T_2(t-s)\tilde{G}_2(U_{1s}, V_{1s}, \underline{Y}_2(s)) ds \right] dS_\omega. \quad (2.6)$$

By the continuity of \tilde{G}_2 and exponential bounds for $t \geq 0$, (2.6) has a unique, continuous and exponentially bounded solution for all $t \geq 0$.

The Volterra equations (2.4) and (2.6) give U_2 and V_2 as smooth functions of the initial data and of the variables U_{1t} and V_{1t} , so entering this information into (2.1) we obtain the following system of functional differential equations for the variables in the well-mixed compartment:

$$\begin{aligned} \frac{dU_1(t)}{dt} &= F_1(U_1(t), V_{1t}, U_2(U_{1t}, V_{1t})) \\ \frac{dV_1(t)}{dt} &= G_1(V_1(t), V_2(U_{1t}, V_{1t})). \end{aligned} \tag{2.7}$$

The above transformations show that the reaction diffusion problem (1.1) can be reduced to a system of retarded functional differential equations (2.7) which involve only U_1 , V_1 and the initial data. The components U_2 and V_2 in the diffusing compartment are given via explicit expressions (2.3) and (2.5) which can be written in terms of the components U_1 , V_1 and initial data after solving the linear Volterra equations (2.4) and (2.6). Details showing the equivalence of the problem (1.1) to the functional differential equation (2.7) with the effects of diffusion incorporated as explicit general delay terms in (2.7) will be presented for a general class of models that includes those we treat here in a subsequent paper.

3. The one-dimensional two-compartment model

In the special case when the region Ω is one-dimensional we can obtain significantly more information from the reduced system of functional differential equations and develop certain local stability results. We establish three main results in this section. The first result shows that the diffusion problem is equivalent to an explicit delay differential equation problem and exhibits the specific delay terms that are caused by the diffusion process. The second result shows that this model in many respects reduces to a well-mixed two-compartment model in the limit when the diffusivities tend to infinity. In particular, the value of the transcription-translation delay at which a periodic cycle bifurcates is the same in the infinite diffusion limit as in the well-mixed two-compartment model. The third main result addresses the opposite extreme of very small diffusivities, and shows that there is a positive cut-off value of the diffusivities below which the stationary steady state is stable regardless of the size of the transcription-translation delay. Hence, for small enough diffusivities no oscillatory solution bifurcates from the stationary steady state. These three results, when coupled with the numerical results that will be presented in Sect. 5, serve to delineate the dual effect of diffusion as both a delaying and a dissipative damping mechanism. In Sect. 4, we will demonstrate yet another basic aspect of diffusion in compartmental models which does not occur in the present setting.

Let us consider the case where $\bar{\Omega}$ is the interval $[0, 1]$, then (2.1) is given by

$$\begin{aligned}\frac{dU_1(t)}{dt} &= \tilde{f}(V_{1t}) - b_1 U_1(t) + a_1 U_2(0, t) \\ \frac{dV_1(t)}{dt} &= -b_2 V_1(t) + a_2 V_2(0, t) \\ \frac{\partial U_2(x, t)}{\partial t} &= D_1 \frac{\partial^2 U_2(x, t)}{\partial x^2} - b_1 U_2(x, t) - \tilde{f}(V_{1t}) - a_1 U_2(0, t) \\ \frac{\partial V_2(x, t)}{\partial t} &= D_2 \frac{\partial^2 V_2(x, t)}{\partial x^2} - b_2 V_2(x, t) + c_0 U_{2t}(x) + c_0 U_{1t} - a_2 V_2(0, t)\end{aligned}\quad (3.1)$$

with the boundary conditions

$$\begin{aligned}\frac{\partial U_2(0, t)}{\partial x} - \beta_1 U_2(0, t) &= 0 \\ \frac{\partial V_2(0, t)}{\partial x} - \beta_1^* V_2(0, t) &= 0 \\ \frac{\partial U_2(1, t)}{\partial x} = \frac{\partial V_2(1, t)}{\partial x} &= 0\end{aligned}\quad (3.2)$$

where $\tilde{f}(V_{1t}) = f(V_{1t} + v_1^*) - v_1 u_1^* + a_1 [u_2^*(0) - u_1^*]$.

We start by applying the separation of variables method on the linear homogeneous problem

$$\frac{\partial U_2}{\partial t} = D_1 \frac{\partial^2 U_2}{\partial x^2} - b_1 U_2 \quad (3.3)$$

satisfying the boundary conditions (3.2). By letting $U_2(x, t) = X(x)T(t)$ we solve the Sturm-Liouville problem for X to obtain the complete set of eigenvalues $\lambda_n = w_n^2 D_1$ where w_n satisfies

$$\cot w_n = w_n / \beta_1$$

and eigenfunctions (normalized so that $\langle \phi_i, \phi_j \rangle = \int_0^1 \phi_i(x) \phi_j(x) dx = \delta_{ij}$)

$$\phi_n(x) = \frac{2\sqrt{w_n} \cos w_n(x-1)}{\sqrt{2w_n + \sin 2w_n}}$$

Defining: $A_n = b_1 + w_n^2 D_1$, $\alpha_n = \int_0^1 U_{20}(x) \phi_n(x) dx$,

$$\delta_n = \int_0^1 \phi_n(x) dx = \frac{2 \sin w_n}{\sqrt{w_n} \sqrt{2w_n + \sin 2w_n}}, \quad K(t, x) \equiv \sum_{n=1}^{\infty} \delta_n \phi_n(x) e^{-A_n t}$$

and using the variation of constants formula, we obtain the following relation:

$$U_2(x, t) = \sum_{n=1}^{\infty} \alpha_n e^{-A_n t} \phi_n(x) - \int_0^t K(t-s, x) [\tilde{f}(V_{1s}) + a_1 U_2(0, s)] ds \quad (3.4)$$

Evaluating (3.4) at $x=0$, we obtain

$$U_2(0, t) = \sum_{n=1}^{\infty} \alpha_n e^{-A_n t} \phi_n(0) - \int_0^t K(t-s, 0) [\tilde{f}(V_{1s}) + a_1 U_2(0, s)] ds \quad (3.5)$$

The problem for V_2 is similar to the one for U_2 , but now the eigenvalues are $\lambda_n = z_n^2 D_2$ where z_n satisfies $\cot z_n = z_n / \beta_1^*$ and the normalized eigenfunctions are $\psi_n(x) = 2\sqrt{z_n} \cos z_n(x-1) / \sqrt{2z_n + \sin 2z_n}$. Defining

$$B_n = b_2 + z_n^2 D_2, \quad \alpha_n^* = \int_0^1 V_{20}(x) \psi_n(x) dx, \quad \delta_n^* = \int_0^1 \psi_n(x) dx, \quad (3.6)$$

$K^*(t, x) = \sum_{n=1}^{\infty} \delta_n^* e^{-B_n t} \psi_n(x)$ and $\langle z_1, z_2 \rangle = \int_0^1 z_1(x) z_2(x) dx$, and using the variation of constants formula, we obtain a linear Volterra equation for $V_2(0, t)$:

$$V_2(0, t) = \sum_{n=1}^{\infty} \alpha_n^* e^{-B_n t} \psi_n(0) + \int_0^t K^*(t-s, 0) [c_0 U_{1s} - a_2 V_2(0, s)] ds + c_0 \int_0^t \sum_{n=1}^{\infty} e^{-B_n(t-s)} \psi_n(0) \langle U_{2s}, \psi_n \rangle ds. \quad (3.7)$$

The first two equations of (3.1) together with the Volterra equations (3.5) and (3.7) for $U_2(0, t)$ and $V_2(0, t)$ are the reduced system of equations that incorporate the diffusion process in (3.1) as distributive delay terms.

To proceed with the local stability analysis we shall consider the specific case of (3.1) with discrete delays. A simple change of variables can reduce the system to having a single discrete delay, r , in the nonlinear function f . We examine the system of functional differential equations (2.7) with the Volterra integral equations (3.5) and (3.7). These equations can be linearized to form the following system of linear equations:

$$\begin{aligned} u_1'(t) &= f'(v_1^s) v_1(t-r) - b_1 u_1(t) + a_1 u_2(0, t) \\ v_1'(t) &= -b_2 v_1(t) + a_2 v_2(0, t) \\ u_2(0, t) &= \sum_{n=1}^{\infty} \alpha_n e^{-A_n t} \phi_n(0) - \int_0^t K(t-s, 0) [f'(v_1^s) v_1(s-r) + a_1 u_2(0, s)] ds \\ v_2(0, t) &= \sum_{n=1}^{\infty} \alpha_n^* e^{-B_n t} \psi_n(0) + \int_0^t K^*(t-s, 0) [c_0 u_1(s) - a_2 v_2(0, s)] ds \\ &\quad + c_0 \int_0^t \sum_{n=1}^{\infty} \psi_n(0) e^{-B_n(t-s)} \langle u_2(\cdot, s), \psi_n \rangle ds. \end{aligned} \quad (3.8)$$

In (3.8) we find the limiting Volterra equations in order to study the local stability of the system. From standard arguments the limiting linear system of delay differential equations and Volterra equations is seen to be

$$\begin{aligned} u_1'(t) &= f'(v_1^s) v_1(t-r) - b_1 u_1(t) + a_1 u_2(0, t) \\ v_1'(t) &= -b_2 v_1(t) + a_2 v_2(0, t) \\ u_2(0, t) &= - \int_0^{\infty} K(t-s, 0) [f'(v_1^s) v_1(s-r) + a_1 u_2(0, s)] ds \\ v_2(0, t) &= \int_0^{\infty} (K^*(t-s, 0) [c_0 u_1(s) - a_2 v_2(0, s)] \\ &\quad - c_0 [f'(v_1^s) v_1(s-r) + a_1 u_2(0, s)]) \sum_{n=1}^{\infty} \mathcal{K}_n(t-s) ds. \end{aligned} \quad (3.9)$$

The characteristic equation for (3.9) is given by:

$$\begin{aligned}
 &(\lambda + b_1)(\lambda + b_2) \left(1 + a_1 \int_0^\infty K(s, 0) e^{-\lambda s} ds \right) \left(1 + a_2 \int_0^\infty K^*(s, 0) e^{-\lambda s} ds \right) \\
 &- c_0 a_2 f'(v_1^*) e^{-\lambda r} \left[\int_0^\infty K^*(s, 0) e^{-\lambda s} ds - (\lambda + b_1) \int_0^\infty \sum_{n=1}^\infty \mathcal{H}_n(s) e^{-\lambda s} ds \right] = 0.
 \end{aligned}
 \tag{3.10}$$

We shall investigate conditions on the parameters in (1.1) with discrete delays in the translation and transcription $f(v_{1t})$ and $c_0 u_{2t}$, that ensure asymptotic stability or demonstrate the existence of a Hopf bifurcation and thus small amplitude periodic solutions. The well-mixed model (2.1) is analyzed in [15] and its characteristic equation is given by

$$(\lambda + b_1)(\lambda + b_2)(\lambda + b_1 + a_1 + a_3)(\lambda + b_2 + a_2 + a_4) - c_0 a_2 a_3 f'(v_1^*) e^{-\lambda r} = 0, \tag{3.11}$$

where the kinetic parameters are as before. Mahaffy and Pao [15] give conditions when a critical value of the delay $r = r_0$ gives a Hopf bifurcation and a condition relating the other parameters when local asymptotic stability occurs for (2.1).

When $\text{Re } \lambda > \max\{-b_1, -b_2\}$ we can apply the Lebesgue dominated convergence theorem to the improper integrals in the characteristic equation (3.10) to interchange integration and summation. The integration of the functions $K(s, 0)$, $K^*(s, 0)$ and $\mathcal{H}_n(s, 0)$ transform (3.10) into the following:

$$\begin{aligned}
 &(b_1 + \lambda)(b_2 + \lambda) \left(1 + a_1 \sum_{n=1}^\infty \frac{\delta_n \phi_n(0)}{A_n + \lambda} \right) \left(1 + a_2 \sum_{n=1}^\infty \frac{\gamma_n \psi_n(0)}{B_n + \lambda} \right) \\
 &- c_0 a_2 f'(v_1^*) e^{-\lambda r} \left[\sum_{n=1}^\infty \frac{\gamma_n \psi_n(0)}{B_n + \lambda} - (b_1 + \lambda) \sum_{n=1}^\infty \sum_{k=1}^\infty \frac{\delta_k \psi_n(0) \langle \phi_k, \psi_n \rangle}{(A_k + \lambda)(B_n + \lambda)} \right] = 0.
 \end{aligned}
 \tag{3.12}$$

The two-compartment model given by (3.1) would be expected to behave in a manner similar to a well-mixed two-compartment model if the diffusivities D_1 and D_2 are sufficiently large relative to the other parameters in the system. For comparison of the local behavior of the model given by (3.1) to its well-mixed counterpart we have the following theorem:

Theorem 3.1. *Assume that the diffusivities D_i tend to infinity and $\beta_1 D_1$ and $\beta_1^* D_2$ are finite. Consider λ such that $\text{Re } \lambda > \max\{-b_1, -b_2\}$, then in the limit the solutions λ which satisfy the characteristic equation (3.12) for the two-compartment model equal the solutions λ to the characteristic equation (3.11) for the well-mixed two compartment model with $a_3 = \beta_1 D_1$ and $a_4 = \beta_1^* D_2$.*

Proof: To simplify the notation in the following presentation we consider the special case when the membrane permeabilities β_1 and β_1^* are equal. The arguments are similar for the case $\beta_1 \neq \beta_1^*$. If we multiply (3.12) by $(\lambda + b_1 + w_1^2 D_1)(\lambda + b_2 + w_1^2 D_2)$, and use the definition of $\delta_n, \gamma_n, \phi_n, \psi_n, A_n$ and

B_n , we obtain:

$$\begin{aligned}
 & (\lambda + b_1)(\lambda + b_2) \left[\lambda + b_1 + w_1^2 D_1 + a_1 \left(\frac{2\beta_1}{w_1^2 + \beta_1^2 + \beta_1} \right) \right. \\
 & \quad \left. + a_1 \sum_{n=2}^{\infty} \frac{(\lambda + b_1 + w_n^2 D_1) 2\beta_1}{(\lambda + b_1 + w_n^2 D_1)(w_n^2 + \beta_1^2 + \beta_1)} \right] \\
 & \cdot \left[\lambda + b_2 + w_1^2 D_2 + a_2 \left(\frac{2\beta_1}{w_1^2 + \beta_1^2 + \beta_1} \right) + a_2 \sum_{n=2}^{\infty} \frac{(\lambda + b_2 + w_n^2 D_2) 2\beta_1}{(\lambda + b_2 + w_n^2 D_2)(w_n^2 + \beta_1^2 + \beta_1)} \right] \\
 & - c_0 a_2 f'(v_1^*) e^{-\lambda r} \left[w_1^2 D_1 \left(\frac{2\beta_1}{w_1^2 + \beta_1^2 + \beta_1} \right) \right. \\
 & \quad \left. + \sum_{n=2}^{\infty} \frac{w_n^2 D_1 (\lambda + b_1 + w_n^2 D_1) (\lambda + b_2 + w_n^2 D_2) 2\beta_1}{(\lambda + b_1 + w_n^2 D_1) (\lambda + b_2 + w_n^2 D_2) (w_n^2 + \beta_1^2 + \beta_1)} \right] = 0. \tag{3.13}
 \end{aligned}$$

We have seen that w_n solves $\cot w_n = (w_n/\beta_1)$. First we note that $w_n > (n-1)\pi$, $n = 1, 2, \dots$, and that w_n asymptotically approaches $(n-1)\pi$ as n gets large. Secondly, from the Maclaurin series expansion for $\cot w_1$, we see that $\beta_1 = w_1^2 + w_1^4/3 + \dots$. As we are assuming that $\beta_1 D_i$ is finite and D_i is large, then it follows that β_1 approaches zero as $D_i \rightarrow \infty$ and $\beta_1 \approx w_1^2$. From this we obtain

$$\lim_{D_i \rightarrow \infty} \frac{2\beta_1}{w_1^2 + \beta_1^2 + \beta_1} = 1. \tag{3.14}$$

Now, we must show that the infinite sums in (3.13) can be made arbitrarily small. As we are assuming that $\text{Re } \lambda > \max\{-b_1, -b_2\}$, then $|(\lambda + b_1 + w_n^2 D_1)/(\lambda + b_1 + w_n^2 D_1)| < 1$, thus

$$\begin{aligned}
 \sum_{n=2}^{\infty} \left| \frac{(\lambda + b_1 + w_n^2 D_1) 2\beta_1}{(\lambda + b_1 + w_n^2 D_1)(w_n^2 + \beta_1^2 + \beta_1)} \right| &< 2\beta_1 \sum_{n=2}^{\infty} \frac{1}{w_n^2} \\
 &< \frac{2\beta_1}{\pi^2} \sum_{n=1}^{\infty} \frac{1}{n^2} = \frac{\beta_1}{3}.
 \end{aligned}$$

But as $D_i \rightarrow \infty$, $\beta_1 \rightarrow 0$ which shows the first two infinite sums tend to zero for the above limit. The third sum is seen to satisfy

$$\sum_{n=2}^{\infty} \left| \frac{w_n^2 D_1 (\lambda + b_1 + w_n^2 D_1) (\lambda + b_2 + w_n^2 D_2) 2\beta_1}{(\lambda + b_1 + w_n^2 D_1) (\lambda + b_2 + w_n^2 D_2) (w_n^2 + \beta_1^2 + \beta_1)} \right| < |\lambda + b_1 + w_1^2 D_1| \frac{\beta_1}{3},$$

so, from the remark below, this infinite sum can be made arbitrarily small.

From the above limits we see that the coefficients in (3.13) are arbitrarily close to the coefficients in (3.11) for D_i sufficiently large provided $a_3 = \beta_1 D_1$ and $a_4 = \beta_1^* D_2$. The continuous dependence of solutions to the characteristic equations completes the theorem.

Remark: From the highest power of λ it is easily seen that $\text{Im } \lambda$ remains bounded for λ in the above region. Also, as (3.12) is the characteristic equation for a delay equation the eigenvalues have their real part bounded above, thus there are at most finitely many eigenvalues λ with $\text{Re } \lambda > \max\{-b_1, -b_2\}$. However, this region

does include the eigenvalues which affect a change in stability or a Hopf bifurcation.

Let $\alpha = -c_0 a_2 a_3 f'(v_1^s)$, where v_1^s is the equilibrium solution for the well-mixed model analyzed in [14]. Theorem 5.1 in [14] shows that if $b_1 b_2 (b_1 + a_1 + a_3) (b_2 + a_2 + a_4) < \alpha$, then there exists delay r_0 such that for all $r > r_0$, (3.11) has at least two roots with $\text{Re } \lambda > 0$. If either $b_1 b_2 (b_1 + a_1 + a_3) (b_2 + a_2 + a_4) > \alpha$ or $0 \leq r < r_0$, then all solutions of (3.11) have $\text{Re } \lambda < 0$. From this we see that a Hopf bifurcation occurs for (3.11) at $r = r_0$ with appropriate conditions on the other parameters. Combining this information with Theorem 3.1, we obtain:

Theorem 3.2. *Assume $b_1 b_2 (b_1 + a_1 + a_3) (b_2 + a_2 + a_4) < \alpha$ and that r_0 is the critical delay for a Hopf bifurcation of the well-mixed model. If D_i are sufficiently large, $a_3 = \beta_1 D_1$, and $a_4 = \beta_1^* D_2$, then the system (3.1) has a Hopf bifurcation for some delay \hat{r}_0 with $\hat{r}_0 \in [-\varepsilon + r_0, r_0 + \varepsilon]$, $\varepsilon > 0$ small.*

The proof of this theorem is immediate from work done on the well-mixed model, Theorem 3.1 and the continuous dependence of a Hopf bifurcation for functional differential equations.

In the process of proving the result for a Hopf bifurcation for the well-mixed model, we utilized an argument principle analysis which can be extended by perturbation arguments to apply to (3.12). From this we were able to numerically compute the delay \hat{r}_0 for various values of D_i . These results are presented and discussed in Sect. 5.

We now turn to the analysis of the stability of the stationary solution when the diffusivity tends to zero. Heuristically, one can argue that, in the limit of very small diffusivity, the chemical species cannot move far into the second compartment before decaying to low concentration. Consequently, the delay needed to destabilize the stationary solution should increase as the diffusivity becomes very small. We will show that, in fact, as the diffusivity goes to zero there exists a positive cut-off value of the diffusivity below which the system is locally stable regardless of the size of the translation-transcription delay. So, the dissipative nature of the diffusion mechanism dominates for very small diffusivities, and as we shall see in the numerical studies reported in Sect. 5, the dependence of the critical delay value at bifurcation is a relatively complicated function of the diffusivity. Consequently, it is only in limited circumstances that an added discrete delay can be used to model the effects of diffusion in compartmental models of this type. The result for small diffusivity is summarized in the following theorem:

Theorem 3.3. *Suppose that $\beta_1 D_1 = a_3$, $\beta_1^* D_2 = a_4$, with a_3, a_4 fixed and that D_1, D_2 tend to zero. Then there exists $d > 0$ such that if $0 < D_i < d$, all solutions λ which satisfy the characteristic equation (3.13) have real parts less than zero.*

Proof: In order to simplify the proof we present the case $a_1 = a_3, a_2 = a_4, \beta_1 = \beta_1^*$, the general case being entirely analogous. When $\beta_1 = \beta_1^*$, Eq. (3.13) can be written as follows

$$(b_1 + \lambda)(b_2 + \lambda)(1 + a_1 S_1)(1 + a_2 S_2) = c_0 a_2 f'(v_1^s) e^{-\lambda r} [S_2 - (b_1 + \lambda) S_3] \quad (3.15)$$

where (recalling that $\beta_1 = \beta_1^*$ implies $z_n = w_n$)

$$S_i = 2\beta_1 \sum_{n=1}^{\infty} \frac{1}{(\lambda + b_i + w_n^2 D_i)(w_n^2 + \beta_1^2 + \beta_1)}, \quad i = 1, 2$$

$$S_3 = 2\beta_1 \sum_{n=1}^{\infty} \frac{1}{(\lambda + b_1 + w_n^2 D_1)(\lambda + b_2 + w_n^2 D_2)(w_n^2 + \beta_1^2 + \beta_1)}.$$
(3.16)

Since we are concerned with solutions λ of (3.15) with real parts greater than zero, we may take $\text{Re}(\lambda) > \max(-b_1, -b_2)$ without loss of generality.

We start by estimating the sums S_i , $i = 1, 2, 3$. The first two of these can be estimated as follows. Setting $\lambda = \mu + i\nu$ with $\mu > \max(-b_1, -b_2)$ and using the relations

$$(n-1)\pi \leq w_n \leq \frac{(2n-1)\pi}{2}, \quad D_i = \beta_1/a_i$$
(3.17)

we have

$$|S_i| \leq \frac{2}{\beta_1} \sum_{n=1}^{\infty} \left[\left(b_i + \mu + \frac{(n-1)^2 \pi^2 a_i}{\beta_1} \right) \left(\frac{(n-1)^2 \pi^2}{\beta_1^2} + \frac{1}{\beta_1} + 1 \right) \right]^{-1}$$

$$\leq \frac{2}{\beta_1(b_i + \mu)} \sum_{n=1}^{\infty} \left(1 + \frac{(n-1)^2 \pi^2 a_i}{\beta_1(b_i + \mu)} \right)^{-1}.$$
(3.18)

So,

$$|S_i| \leq \frac{2}{\beta_1(b_i + \mu)} \int_0^{\infty} \left(1 + \frac{x^2 a_i \pi^2}{\beta_1(b_i + \mu)} \right)^{-1} dx \leq 1/\sqrt{a_i \beta_1(b_i + \mu)}, \quad i = 1, 2.$$
(3.19)

From this we see that $|S_i| \rightarrow 0$ like $1/\sqrt{\beta_1}$ when $\beta_1 \rightarrow \infty$. Since $\beta_1 = a_i/D_i$, $a_i =$ constant and $D_i \rightarrow 0$, we do have $\beta_1 \rightarrow \infty$.

The estimate for S_3 is obtained in a similar manner. We again place the restriction $\lambda = \mu + i\nu$ with $\mu > \max(-b_1, -b_2)$ and obtain

$$|S_3| \leq \frac{2}{|b_1 + \lambda| \beta_1} \sum_{n=1}^{\infty} \left[\left(b_2 + \mu + \frac{(n-1)^2 \pi^2 a_2}{\beta_1} \right) \left(\frac{(n-1)^2 \pi^2}{\beta_1^2} + \frac{1}{\beta_1} + 1 \right) \right]^{-1}$$

$$\leq \frac{1}{|b_1 + \lambda| \sqrt{a_2(b_2 + \mu)} \beta_1}.$$
(3.20)

From (3.19) and (3.20) we now conclude that the norm of the right-hand side of (3.15) is less than or equal to $2c_0 \sqrt{a_2} |f'(v_1^s)| e^{-r\mu} / \sqrt{(b_2 + \mu) \beta_1}$, while the norm of the left-hand side of (3.15) is greater than or equal to $|b_1 + \mu| |b_2 + \mu| (1 - [\sqrt{a_1} / \sqrt{(b_1 + \mu) \beta_1}]) (1 - [\sqrt{a_2} / \sqrt{(b_2 + \mu) \beta_1}])$, whenever

$$\beta_1 > \max\left(\frac{a_1}{b_1 + \mu}, \frac{a_2}{b_2 + \mu}\right).$$

Hence, Eq. (3.12) has no solutions $\lambda = \mu + i\nu$ with $\mu \geq 0$ whenever

$$b_1 b_2 \left(1 - \sqrt{\frac{a_2}{b_1 \beta_1}} \right) \left(1 - \sqrt{\frac{a_2}{b_2 \beta_1}} \right) > 2c_0 |f'(v_1^s)| \sqrt{\frac{a_2}{b_2 \beta_1}},$$
(3.21)

or in terms of the diffusivities, (3.12) has no solutions $\lambda = \mu + i\nu$ with $\mu \geq 0$,

whenever

$$b_1 b_2 \left(1 - \sqrt{\frac{D_1}{b_1}}\right) \left(\sqrt{\frac{b_2}{D_2}} - 1\right) > 2c_0 |f'(v_1^s)|. \quad (3.22)$$

Since D_1, D_2 tend to zero, it is clear that (3.22) will hold for all D_1, D_2 sufficiently small. In fact, a simple estimate shows that if

$$0 < D_i < \min \left\{ \frac{b_1}{4}, \frac{b_1^2 b_2^3}{[b_1 b_2 + 4c_0 |f'(v_1^s)|]^2} \right\} = d \quad (3.23)$$

then inequality (3.22) holds, and the theorem is proved.

Remark. In the interest of simplicity, while proving Theorem 3.3 we have used rather strong estimates on the sums S_i defined in (3.16). These estimates can be easily refined to lead to a sharper bound on the cut-off value of the diffusivities (given in (3.23)) below which the stationary solution (u_i^s, v_i^s) is stable regardless of the values of the delay r . Such refinements may become of interest when reliable experimental values of the various parameters entering into the model become available.

4. The three compartment model

In this section we present our results on the three-compartment model studied by Mahaffy and Pao [14]. The analysis here is more involved than that of the two-compartment model and leads to some conclusions that differ significantly from those of the two-compartment model. In particular, in the limit as the diffusivities tend to infinity, this model does not approach what might at first appear to be the comparable well-mixed three-compartment model.

In this model the spatial region $(0, 1)$ corresponds to the cytoplasm and is a non-reacting compartment through which the components u and v diffuse. The nucleus is viewed as a well-mixed compartment located at 0, while the outer cell wall is another compartment located at position 1. The repressor is produced at the cell wall and diffuses through the cytoplasm region $(0, 1)$ to arrive at the nucleus where the mRNA is produced. The basis of this model is discussed in [14] where the following equations are derived:

$$\begin{aligned} \frac{du_1(t)}{dt} &= f(v_1(t)) - b_1 u_1(t) + a_1 [u_2(0, t) - u_1(t)] \\ \frac{dv_1(t)}{dt} &= -b_2 v_1(t) + a_2 [v_2(0, t) - v_1(t)] \\ \frac{\partial u_2(x, t)}{\partial t} &= D_1 \frac{\partial^2 u_2}{\partial x^2}(x, t) - b_1 u_2(x, t) \\ \frac{\partial v_2(x, t)}{\partial t} &= D_2 \frac{\partial^2 v_2}{\partial x^2}(x, t) - b_2 v_2(x, t) \\ \frac{du_3(t)}{dt} &= -b_1 u_3(t) + a_3 [u_2(1, t) - u_3(t)] \\ \frac{dv_3(t)}{dt} &= c_0 u_3(t) - b_2 v_3(t) + a_4 [v_2(1, t) - v_3(t)] \end{aligned} \quad (4.1)$$

with boundary conditions

$$\begin{aligned} \frac{\partial u_2(0, t)}{\partial x} &= \beta_1[u_2(0, t) - u_1(t)], \\ \frac{\partial v_2(0, t)}{\partial x} &= \beta_1^*[v_2(0, t) - v_1(t)], \\ \frac{\partial u_2(1, t)}{\partial x} &= -\beta_2[u_2(1, t) - u_3(t)], \\ \frac{\partial v_2(1, t)}{\partial x} &= -\beta_2^*[v_2(1, t) - v_3(t)]. \end{aligned} \tag{4.2}$$

We follow the same steps as in the analysis of the two compartment model and obtain a system of delay differential equations which is equivalent to (4.1). The details of the analysis can be found in [5].

In studying the stability of the steady state of (4.1), we restrict ourselves to the case where the delays due to transcription and translation are discrete, that is, we set $v_{1t} = v_1(t - r_1)$, $u_{3t} = u_3(t - r_2)$ in (4.1), and linearize about the steady state. There is a fundamental question that we wish to answer concerning this linear system: It is whether or not the limiting form of this system, when the diffusivities $D_i \rightarrow \infty$ (with $\beta_j D_i$ and $\beta_j^* D_i$ tending to constants), has the same characteristic equation as does a well-mixed three compartment system such as the one depicted in Fig. 4.1 below.

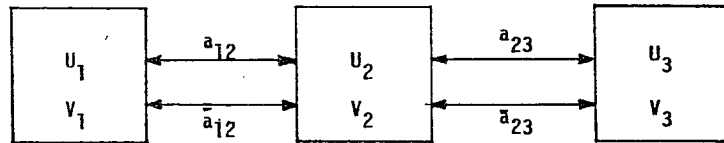


Fig. 4.1

The diffusion compartment in the model leading to Eq. (4.1) is now replaced by a well-mixed compartment communicating with compartments one and three. An alternate possible limit is a well-mixed three compartment system which has the following schematic form:

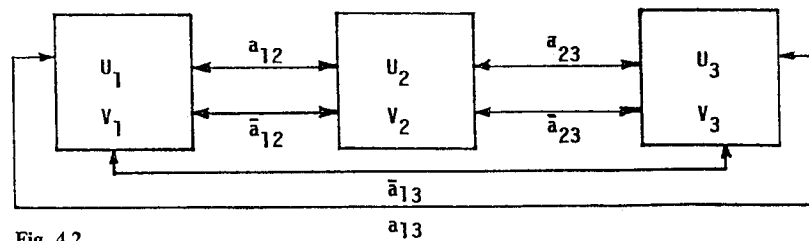


Fig. 4.2

Here there is direct communication between the first and third compartments, which can be thought as due to the effect of Fickian diffusion which allows for infinite velocity of propagation of disturbances, and which acts symmetrically in space (but not in time). Again we show that the diffusing three compartment model need not approach this well-mixed system as $D_i \rightarrow \infty$.

In choosing candidate well-mixed three-compartment systems we have placed the restriction that the transfer rates of a component (say u) from compartment i to j and from j to i are proportional to the gradient $u_i - u_j$ across the boundary separating these compartments. This leads to the conclusion that the net transfer rate a_{ij} from compartment i to compartment j equals a_{ji} the net transfer rate from compartment j to compartment i . This hypothesis is placed because in our diffusion models the membranes separating the different compartments do not store any of the chemical constituents and do have transfer rates that are proportional to the gradients across them. We assume the same decay and production rates for these well-mixed systems as for the limiting form when $D_i \rightarrow \infty$ of (4.1) and place the restriction

$$\beta_1 D_1 = a_1, \quad \beta_2 D_1 = a_3, \quad \beta_1^* D_2 = a_2, \quad \beta_2^* D_2 = a_4 \quad (4.3)$$

which correspond to the requirement that the transfer rates through the membranes separating contiguous compartments are constant. With these conditions we can write the characteristic equation of the linearization of the delay differential equation system which is equivalent to (4.1).

Theorem 4.1. *The characteristic equation of the linearization of the delay differential equation system which is equivalent to (4.1) with restrictions (4.3) does not approach the characteristic equations of either one of the two well-mixed compartment systems depicted in Figs. 4.1 and 4.2 when D_1 and D_2 tend to infinity, unless special restrictions are placed on the transfer rates a_1 , a_2 , a_3 and a_4 in the reaction-diffusion model.*

The second result is of a positive nature.

Theorem 4.2. *Let $a_1 = a_3$, $a_2 = a_4$ and let (4.3) hold. Set $a_{12} = a_{23} = a_1$, $\bar{a}_{12} = \bar{a}_{23} = a_2$ in the well-mixed three compartment system depicted by Fig. 4.1. Then the characteristic equation of this well-mixed system is identical to the characteristic equation of the linearization of the delay differential equation which is equivalent to (4.1) when $D_1, D_2 \rightarrow \infty$.*

Details on how these results are established can be found in [5].

We note that, in the case described by Theorem 4.2, the stability of the reaction-diffusion model, in the limiting case where $D_1, D_2 \rightarrow \infty$, is the same as that of the well-mixed three-compartment model depicted in Fig. 4.1. However, in general, even in this limiting case, the reaction diffusion model has a more complex structure than either of the two well-mixed three-compartment models depicted in Figs. 4.1 and 4.2.

5. Numerical results

In this section we present some numerical results for the two compartment model which consist of a numerical determination of the parameter values at which the bifurcation of the periodic solutions described in Sect. 3 occur, and of plots of the solutions for various parameter ranges. All these numerical solutions are for the case where $f(v_{1t}) = 1/(1 + v_{1t}^4(t - r))$.

The most significant numerical result that we present is in Fig. 5.1 which shows, in a diffusivity vs. delay plot, the curve along which the periodic solution

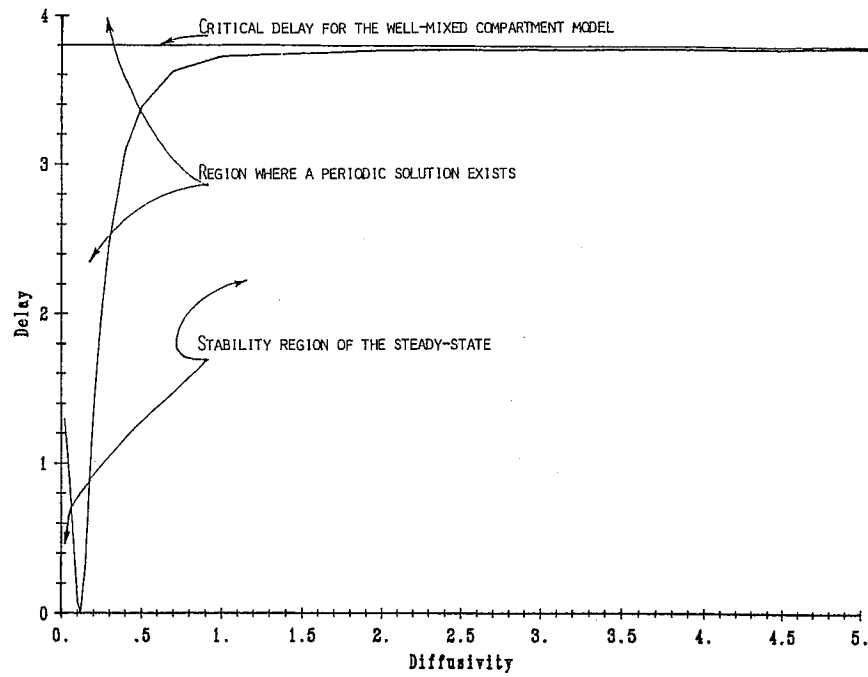


Fig. 5.1. The curve across which a Hopf bifurcation to a periodic solution occurs for the two-compartment model. Here $a_1 = a_2 = 2$, $b_1 = b_2 = 0.2$, $c_0 = 1$

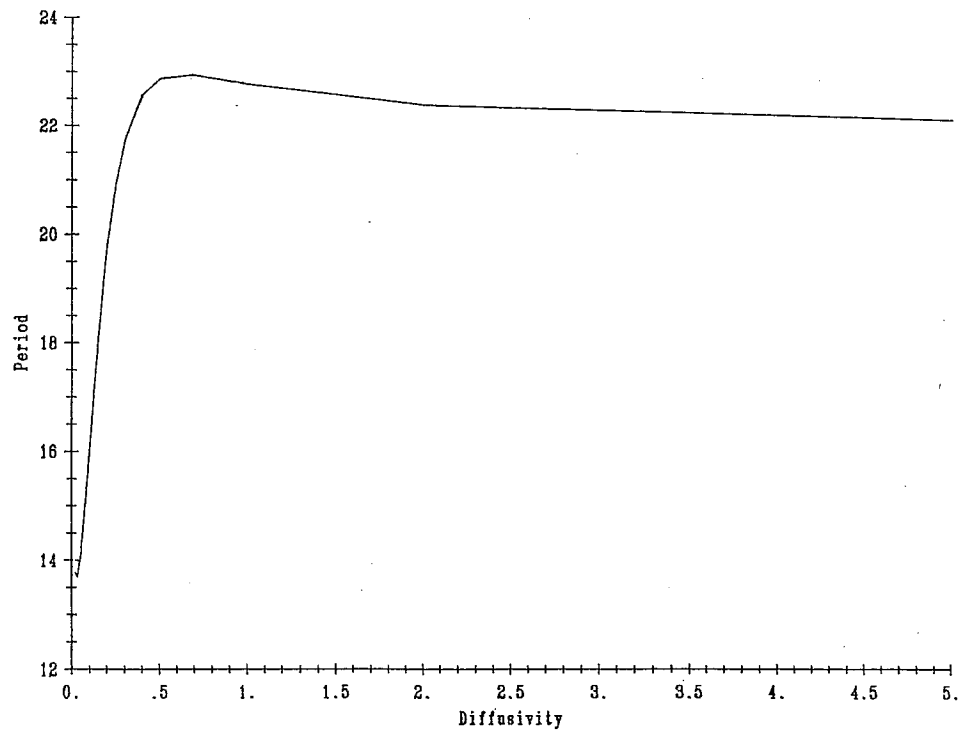


Fig. 5.2. The variation of the period with diffusivity for the two-compartment model. Here $a_1 = a_2 = 2$, $b_1 = b_2 = 0.2$, $c_0 = 1$

bifurcates and the steady-state becomes unstable for the parameter values $a_1 = a_2 = 2$, $b_1 = b_2 = 0.2$, $c_0 = 1$, and $D_1 = D_2$. As was proved in Theorem 3.1, when the diffusivity becomes large, this curve approaches the value $r_0 = 3.8$ where the well-mixed two-compartment undergoes a Hopf bifurcation. We know from Theorem 3.2 that, when the diffusivity approaches zero, the steady-state is stable for all values of the delay r . This is not seen clearly in Fig. 5.1 because the scheme we used for determining the bifurcation curve (this scheme is an adaptation of the one described in [14]) becomes very inefficient at low values of the diffusivity due to the large number of terms that have to be evaluated in order to accurately approximate the distributed delay terms that are due to the diffusion mechanism. The range between $D_i = 0.02$ and $D_i = 0.4$ on the graph shows the interesting behavior of having the delay required for destabilization first decrease then increase. Figure 5.2 shows the variation of the period of the periodic oscillation at the bifurcation point for the same parameter values as in Fig. 5.1 as the diffusivity varies. The period is seen to increase rapidly to a maximum value attained when the diffusivity is about 0.5 and then slowly decrease to the value for the well-mixed two compartment model. When $D = 0.2$, for example, the bifurcation occurs for r approximately equal to 1.3 time units and the period of

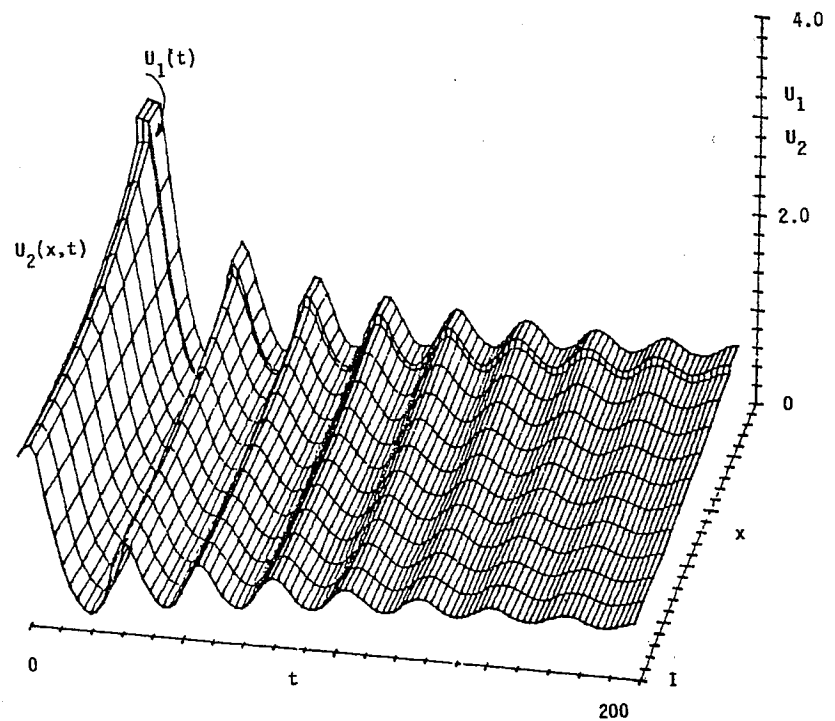


Fig. 5.3. Variation of U_1 and U_2 in space and time for the two-compartment model. Here $a_1 = a_2 = 2$, $b_1 = b_2 = 0.2$, $c_0 = 1$, $D_1 = D_2 = 0.2$, and $r = 3.0$

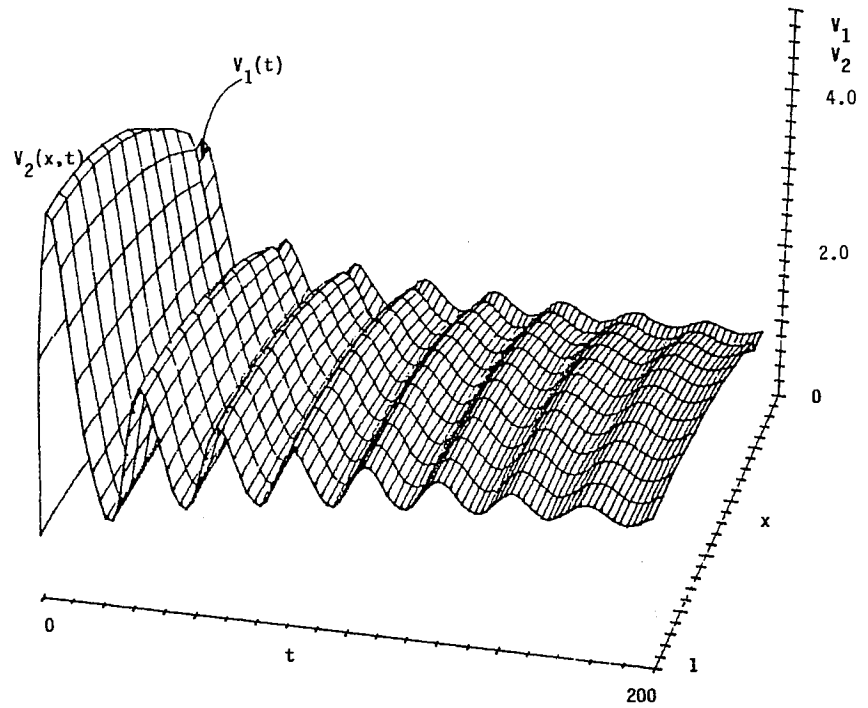


Fig. 5.4. Variation of V_1 and V_2 in space and time for the two-compartment model. Here $a_1 = a_2 = 2$, $b_1 = b_2 = 0.2$, $c_0 = 1$, $D_1 = D_2 = 0.2$, and $r = 3.0$

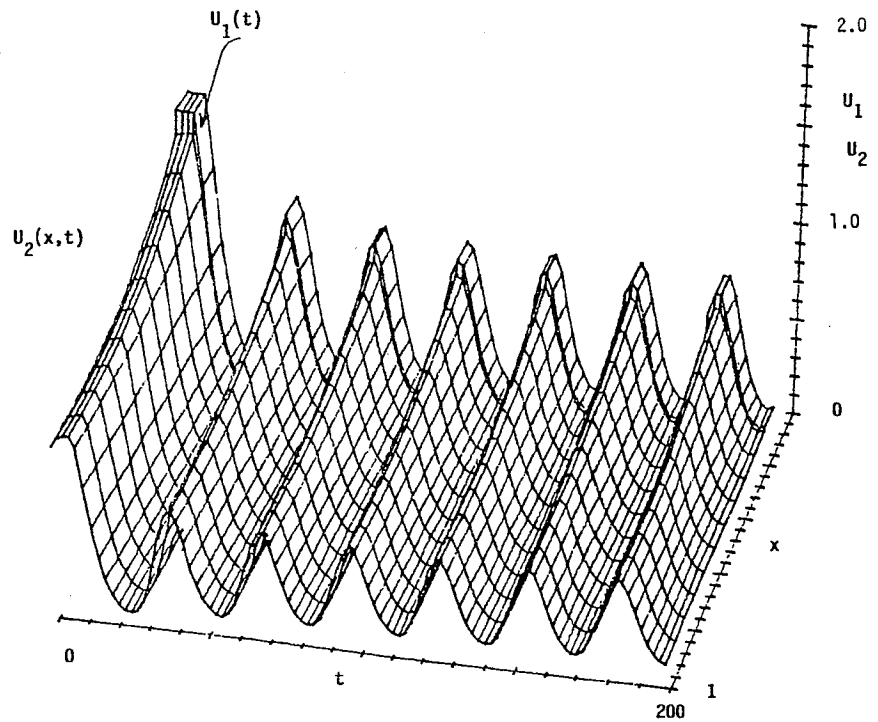


Fig. 5.5. Variation of U_1 and U_2 in space and time for the two-compartment model. Here $a_1 = a_2 = 2$, $b_1 = b_2 = 0.2$, $c_0 = 1$, $D_1 = D_2 = 0.2$, and $r = 5.0$

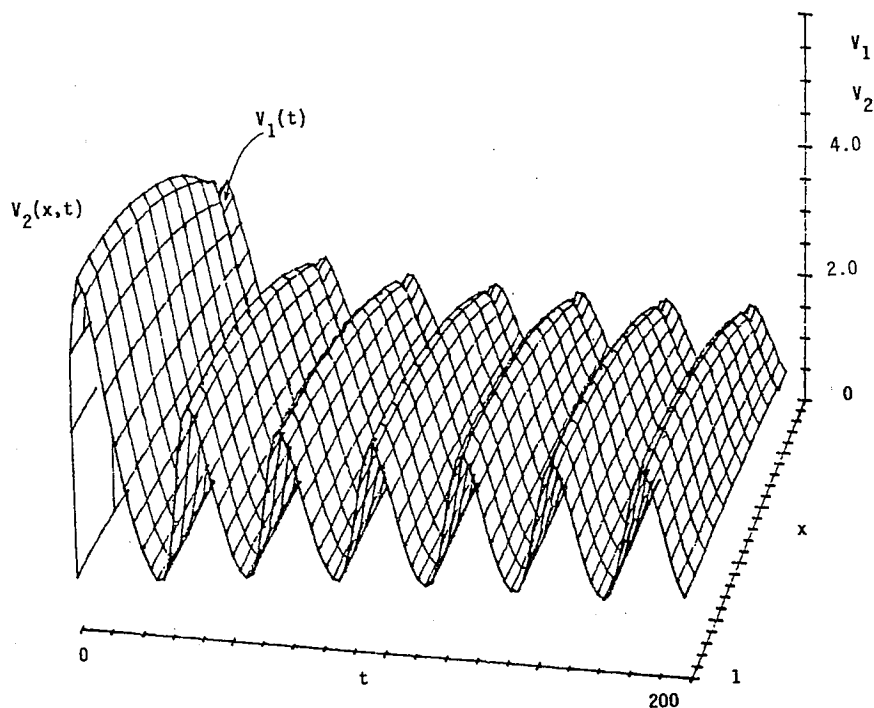


Fig. 5.6. Variation of V_1 and V_2 in space and time for the two-compartment model. Here $a_1 = a_2 = 2$, $b_1 = b_2 = 0.2$, $c_0 = 1$, $D_1 = D_2 = 0.2$, and $r = 5.0$

the oscillation is 22 time units. As the delay is increased from 0.2 to 7, keeping the diffusivity fixed, the period increases to 32 time units. So, in this region of diffusivity values, the diffusion mechanism acts as a means for increasing the period at a given value of the delay.

The remainder of the numerical results show the dependence of the solutions on time and spatial position. These plots were obtained by integrating the delay-differential equations for u_1 and v_1 using a one-step fourth order scheme that is similar to the Runge-Kutta scheme for ordinary differential equations and an implicit central difference scheme for the partial differential equations. The resulting plots for the two-compartment model with $a_1 = 2$, $a_2 = 2$, $b_1 = 0.2$, $b_2 = 0.2$, $c_0 = 1$, $D_1 = D_2 = 0.2$ and $r = 3.0$ (solutions approaching a small amplitude oscillation), and $r = 5.0$ (solutions approaching a large amplitude oscillation) are shown in Figs. 5.3-5.6. Numerical integrations of the three-compartment model show that it also can have time periodic solutions.

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Erratum

Interaction of spatial diffusion and delays in models of genetic control by repression
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An error was made in the proof of Theorem 3.3. Inequality (3.19) of the proof is incorrect as it stands but can be corrected by the addition of the term $2/\beta_i(b_i + \mu)$ to the right-hand side. The proof then goes through exactly as in the paper but with corresponding corrections to the steps that follow Eq. (3.19). Also a simpler estimate that can be used to replace (3.19) is: $|S_i| \leq (6 + \pi^2)/3\beta_i(b_i + \mu)$, $i = 1, 2, \dots$, for $\beta_i > \max(a_i\pi^2/(b_i + \mu))$. This implies that $|S_i| \rightarrow 0$ like $1/\beta_i$ as $\beta_i \rightarrow \infty$. Once this is done, the remainder of the proof parallels the one that is given. In the end one obtains the following revised estimate

$$0 < D_i < \min \left\{ \frac{3b_1}{2(6 + \pi^2)}, \frac{3b_1b_2^2}{(6 + \pi^2)(b_1b_2 + 4c_0|f'(v_i^*)|)} \right\} = d. \quad (3.23)$$

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