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THE EFFECTS OF DIMENSION AND SIZE FOR A COMPARTMENTAL MODEL OF REPRESSION*

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Abstract. The bifurcation of time periodic solutions in a compartmental reaction-diffusion model of a eukaryotic cell is studied as a function of various physical parameters including the size of the cell and the delays due to transcription and translation. The analytical results suggest a possible mechanism for the triggering of mitosis which is in qualitative agreement with observed behavior. These results are based on both detailed analyses of specific cases and on numerical solutions of the model equations.

Key words. compartmental reaction-diffusion system, delay partial differential equations, Hopf bifurcation, cell model, control by repression, cell clocking mechanism

AMS(MOS) subject classifications. 92A09, 34K99, 36K60

1. Introduction. We examine a compartmental model with diffusion and delays and propose a possible mechanism for triggering mitosis, the process by which a cell divides into two new cells. The model which we analyze is developed from the Jacob and Monod [12] theory for genetic control of biosynthetic pathways by negative feedback or repression. It is derived using basic biochemical kinetics and certain standard velocity approximations in a manner similar to that of Goodwin [7], [8] whose nonlinear mathematical models have been studied extensively (cf. [2], [7]-[9], [18], [19], [21], [23]-[25]). In his work Goodwin suggested that both delays from transcription and translation and the process of diffusion of the biochemical species could be significant in destablizing steady-state solutions of the mathematical models, while experimental evidence [1, Chap. 11], [6] supports the introduction of a compartmental model. The triggering mechanism for mitosis which we suggest involves the destabilization of the steady-state solution of the reaction-diffusion equations of our model. There are two possible ways in which this destabilization can occur. The first leads to a time periodic solution via a Hopf bifurcation and the second to a different steady state. The latter type of bifurcation is due to differences in the diffusion rates of the reacting species and was first proposed by Turing [22] as a possible cause for biological pattern formation. More recently, Hunding [10] and Hunding and Billing [11] have studied in detail a single compartment, two-species reaction-diffusion model where this second type of destabilization occurs and which they suggest as a possible cause of mitotic prepattern formation in the cell. In our model the steady-state solution is unique for a wide range of the pertinent parameters and this second type of destabilization does not occur. Hence, we study the first type of bifurcation which leads to a time periodic solution when the steady state loses its stability.

The model we treat includes the biochemical transcription and translation delays, the diffusion of the reactants and the compartmental nature of the cell. It is based on the generalization by Busenberg and Mahaffy [5] of an earlier model of Mahaffy and Pao [17]. The specific model diagrammed in Fig. 1.1 consists of two compartments enclosed within the cell wall and separated by a permeable membrane. The first compartment is labeled ω in Fig. 1.1 and is regarded as a well-mixed compartment

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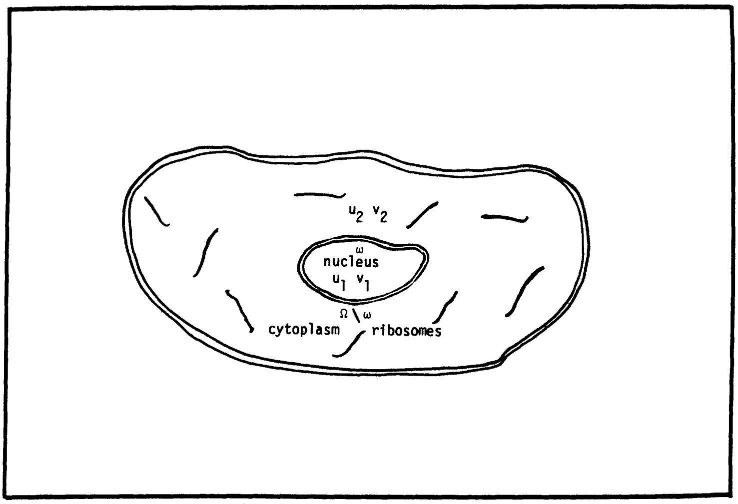

FIG. 1.1. *The two-compartment eukaryotic cell model.*

(the nucleus) where mRNA is produced. The second compartment denoted by $\Omega\backslash\omega$ consists of the cell interior Ω minus the nucleus ω and represents the cytoplasm in which the ribosomes are randomly dispersed. It is here that the process of translation and the consequent production of the repressor occurs. The communication between the nucleus and the ribosomes, where translation occurs, is by diffusion in the cytoplasm and transfer through the membrane bounding ω. Let u_i and v_i, $i=1,2$, denote the concentration of mRNA and repressor, respectively, in compartment ω for $i=1$, and $\Omega\backslash\omega$ for $i=2$, and assume ω is a well-mixed compartment. Then the repression model is given by the following system of equations:

$$\text{(1.1)}\quad \begin{aligned} \frac{du_1(t)}{dt} &= f(v_{1t}) - b_1u_1(t) + a_1\int_{\partial\omega}[u_2(x,t)-u_1(t)]\,dS_\omega, \\ \frac{dv_1(t)}{dt} &= -b_2v_1(t) + a_2\int_{\partial\omega}[v_2(x,t)-v_1(t)]\,dS_\omega, \\ \frac{\partial u_2(x,t)}{\partial t} &= \mu_1\Delta u_2(x,t) - b_1u_2(x,t), \\ \frac{\partial v_2(x,t)}{\partial t} &= \mu_2\Delta v_2(x,t) - b_2v_2(x,t) + g(u_{2t}(x)), \qquad x\in\Omega\backslash\omega \end{aligned}$$

with boundary conditions

$$\frac{\partial u_2(x,t)}{\partial n} = -\beta_1[u_2(x,t)-u_1(t)], \qquad x\in\partial\omega,$$

$$\frac{\partial v_2(x,t)}{\partial n} = -\beta_1^*[v_2(x,t)-v_1(t)], \qquad x\in\partial\omega,$$

$$\frac{\partial u_2(x,t)}{\partial n} = \frac{\partial v_2(x,t)}{\partial n} = 0, \qquad x\in\partial\Omega.$$

The subscript t is used to denote dependence on the past history of a variable. Thus $f(v_{1t}) = f[\int_{-\nu}^{0} v_1(t+s)\,d\eta(s))]$, and in particular, we can have discrete delays of the form $f[v_1(t), v_1(t-\nu_1), \cdots, v_1(t-\nu_n)]$, $0<\nu_i \leqq \nu$. The constants b_i are kinetic rates of decay through degradation and/or dilution from cell growth, while the a_i are the rates of transfer between compartments which we assume to be directly proportional to the concentration gradient. The μ_i are the diffusivity coefficients, and $g(u_{2t}(x))$ is the delayed production rate for the repressor. Following the model developed by Goodwin, we can take the simple form $g(u_{2t}(x)) = c_0 u_2(x, t-\nu_2)$, where ν_2 represents a delay for translation. The function f is a decreasing function in v_1 representing the production of mRNA and is often of the form $1/[1+k(v_{1t})^\rho]$, where v_{1t} represents the delayed concentration of v_1.

There have been several approaches to modeling the clocking mechanism for cell mitosis. We have already mentioned the destabilization of the unique steady-state solution of our model as a possible mechanism. Another theory postulates the existence of a trigger-protein which needs to accumulate to a threshold value before DNA replication can start [1, p. 617]. An alternative theory is provided by the "transition probability" model which postulates that the cell cycle time is regulated by a stochastic event [1, p. 618]. This model suffers from the lack of a physical or chemical basis of this stochastic trigger. This defect is partially removed by the "chaotic clock" model of Lasota and Mackey [13] where a chaotic biochemical stimulus is suggested as the basis for cell cycle time variability. This model has been further developed by Mackey [14] and its predictions have been fitted to experimental results by Mackey et al. [15]. The trigger protein model fits well with the variations in cell division times that have been observed; however, the trigger proteins have not been experimentally seen. In the next section we shall see that the trigger mechanism we are suggesting also explains the observed variations in cell division timing and has the advantage of being based on accepted cell biochemical processes; hence, it is a viable alternative theory for the trigger mechanism of cell mitosis.

We note that for prokaryotic cells (cells without a separate nucleus), Tyson [23] and Bliss et al. [4] present models which demonstrate that a biochemical repression process could lead to epigenetic oscillations of certain biochemicals with a cycle time which approximates that of cell division. Tyson's analysis demonstrates that dilution of certain species could be critical in this clocking mechanism.

In our model we shall demonstrate that, as the cell grows, the two-compartment equations (1.1) can undergo a change of stability. Through most of the cell cycle the biochemical concentrations u_i and v_i remain in a region of stability. However, as the cell's diameter increases, (1.1) exhibit a Hopf bifurcation, and hence the concentrations begin oscillating. These oscillating concentrations could trigger a gradient sensor in the cell and signal the beginning of DNA synthesis followed by mitosis. Alternatively, since the oscillations lead to peak concentrations which exceed the steady-state levels, triggering may occur when a critical component exceeds a threshold concentration level.

In order to better present the implications of these results on cell timing, we first give the main numerical results we have obtained in the special case where $f(v) = 1/(1+kv^4)$, $g(u)=c_0u$ and with spherical symmetry. Figure 1.2 shows bifurcation curves separating the region of stability of the steady state from the region where the oscillatory solution exists. The parameters that are varied are the radius R of the cell, the delay ν, and the ratio $\sigma = r_0/R$, where r_0 is the radius of the nucleus. Referring to Fig. 1.2, we can describe the details of the proposed triggering mechanism for the initiation of DNA synthesis preceding mitosis. As the cell grows from an initial size of radius R_0 to a final size of radius R_1, the steady state becomes unstable at radius $R_c(\sigma)$, triggering the gradient or threshold concentration sensing mechanism for the start of DNA synthesis. At size R_1, the cell divides into two daughter cells of radius

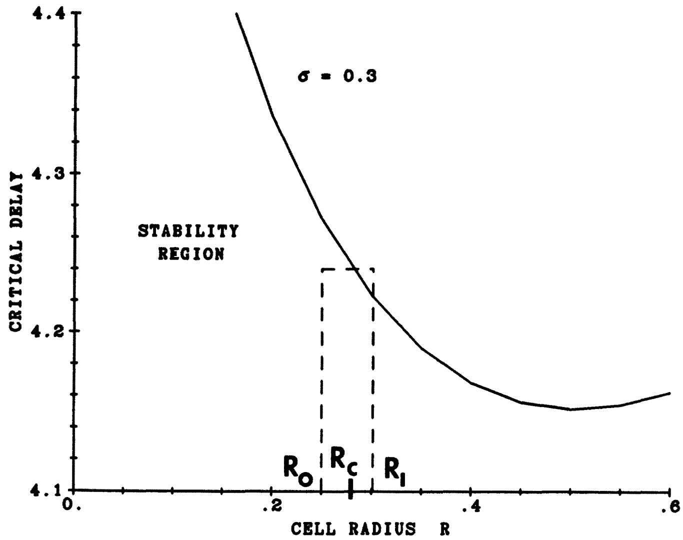

FIG. 1.2. *Dependence of the stability region on the cell radius and the delay.*

R_0 and the process starts again for each of these two cells. It is experimentally observed that the time from start of growth (R_0) to the initiation of DNA synthesis ($R > R_c$) can vary widely depending on the conditions under which the cell is growing. The time between the initiation of DNA synthesis and cell division (at R_1), on the other hand, is remarkably constant [1, Chap. 11]. Cells which are arrested in the pre-DNA synthesis threshold also stop growing even though their general biochemical reactions must continue to compensate for degradation of chemicals in this constant size state. This is consistent with the above triggering mechanism. Also, cells that are flattened and, hence, have a larger ratio σ of nuclear to cytoplasmic volume, have a faster division time. Even though our spherical model cannot simulate this flattening, the monotone decreasing nature of $R_c(\sigma)$, for fixed delay, under changes of σ (see Fig. 1.3)

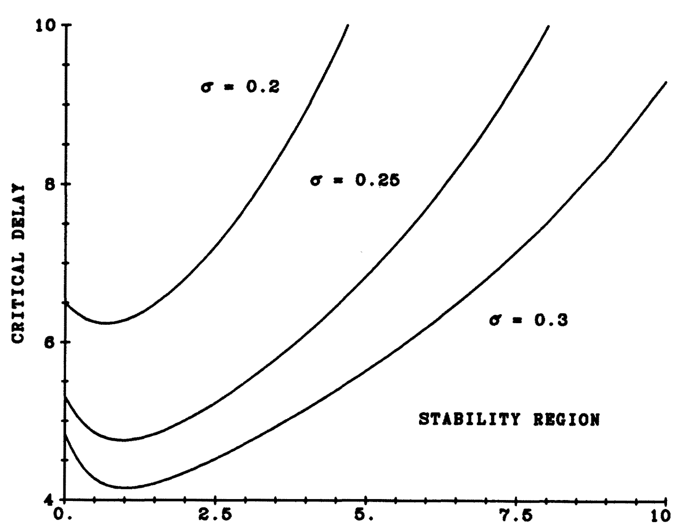

FIG. 1.3. *Variation of the stability region with the diameter ratio.*

is consistent with this observation when we recall that the time to go from $R_c(\sigma)$ to R_1 is fairly constant. Finally, the two daughter cells of a dividing cell are not exactly equal in volume but vary about a mean whose radius we denote by R_0. This distribution of initial sizes about R_0 leads to a distribution of time of growth from R_0 to R_c; hence, since the time between R_c and R_1 is constant, this implies a distribution of cell division cycle times about a mean corresponding to the size R_0. This is a possible mechanism, implied by our triggering hypothesis, for the variability of cell cycle times on which the transition probability models are based. The general results which we have presented in our theorems and illustrated with the above special numerical example show that this type of bifurcation behavior is a consequence of a reaction-diffusion process with biochemical control by repression in a compartmentalized cell. The triggering mechanism we presented does not require any contrived forces or effects. It is affected, however, by environmental or other factors that change the growth rate, the shape, and the reaction and diffusion constants in ways that are consistent with experimental observations.

Our mathematical and numerical results are summarized in the next section. Section 3 contains the proofs of our theorems. We conclude with a presentation of our numerical techniques and a discussion of these results. In this article we concentrate on the mathematical development of the model. In a subsequent article we shall discuss the details relating our results to known biological data.

2. Results. In this section we perform a detailed analysis of the two-dimensional and three-dimensional models of repression for symmetric geometries involving concentric cylinders and spheres, respectively. We consider the model (1.1) for a region as diagrammed in Fig. 2.1. If the cell radius is given by R and the inner radius is given by σR, then the following dimensionless parameters are introduced: $\tau = tb_1$, $a_i = a_i R^{k-1}/b_1$, $c_0 = c_0/b_1$, $\mu_i = \mu_i/b_1R^2$, $r = x/R$ and $\beta_1 = R\beta_1$, where $k = 2$ or 3 depending on the dimension of the system. We assume the linear form of $g(u_{2t}(x))$ given above and make a change of variables to shift the delay into the nonlinear function f only. We start with a preliminary reduction of the problem which is similar to the one we

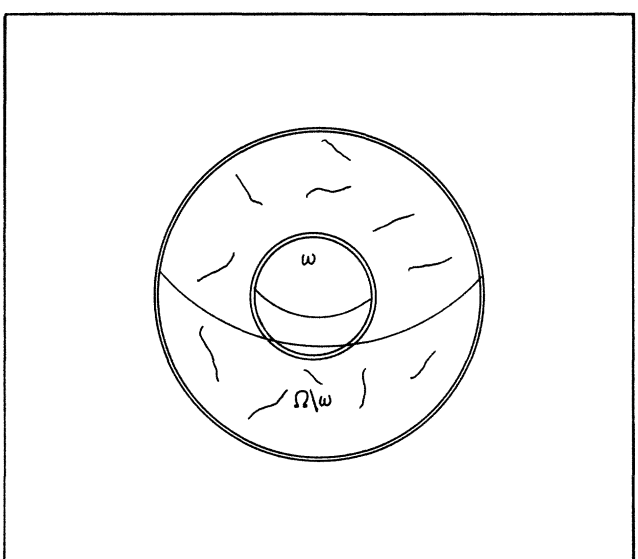

FIG. 2.1. *Concentric sphere model of the two-compartment cell.*

gave for the one-dimensional case [5] and which we only outline here. The unique, radially symmetric, steady-state solution, $(\bar{u}_1, \bar{v}_1, u_2^s, v_2^s)$, is computed for the model (1.1). After a change of variables to make the equations dimensionless and a translation of the steady-state solution to make the boundary conditions homogeneous, we have the following system of partial differential equations with delays:

$$
\begin{aligned}
u_1'(\tau) &= f(v_1(\tau-\nu)+\bar{v}_1) - u_1(\tau) + \gamma_1 u_2(\sigma,\tau) + \gamma_1 u_2^s(\sigma) - (1+\gamma_1)\bar{u}_1 \\
&\equiv F_1(u_1(\tau), v_{1\tau}, u_2(\sigma,\tau)), \\
v_1'(\tau) &= -b_2 v_1(\tau) + \gamma_2 v_2(\sigma,\tau) \equiv G_1(v_1(\tau), v_2(\sigma,\tau)), \\
\frac{\partial u_2(r,\tau)}{\partial \tau} &= \mu_1 \Delta u_2(r,\tau) - u_2(r,\tau) - u_1(\tau) - F_1(u_1(\tau), v_{1\tau}, u_2(\sigma,\tau)) \\
&\equiv \mu_1 \Delta u_2(r,\tau) - u_2(r,\tau) - F_2(v_{1\tau}, u_2(\sigma,\tau)), \\
\frac{\partial v_2(r,\tau)}{\partial \tau} &= \mu_2 \Delta v_2(r,\tau) - b_2[v_2(r,\tau)+v_1(\tau)] + c_0[u_2(r,\tau)+u_1(\tau)] \\
&\quad - G_1(v_1(\tau), v_2(\sigma,\tau)) \\
&\equiv \mu_2 \Delta v_2(r,\tau) - b_2 v_2(r,\tau) - G_2(u_1, u_2(r,\tau), v_2(\sigma,\tau)).
\end{aligned} \tag{2.1}
$$

The parameter ν is the dimensionless delay for the system. The parameters γ_i, $i=1,2$, are given by $\gamma_i = 2\pi\sigma a_i$ in two dimensions and $\gamma_i = 4\pi\sigma^2 a_i$ in three dimensions. The Laplacian Δu is

$$
(1/r)\frac{\partial}{\partial r}\left[r\frac{\partial u}{\partial r}\right] \quad \text{and} \quad (1/r^2)\frac{\partial}{\partial r}\left[r^2\frac{\partial u}{\partial r}\right]
$$

for two and three dimensions, respectively, when u is radially symmetric. The boundary conditions are given by

$$
\frac{\partial u_2(\sigma,\tau)}{\partial r} = \beta_1 u_2(\sigma,\tau), \qquad \frac{\partial v_2(\sigma,\tau)}{\partial r} = \beta_1^* v_2(\sigma,\tau),
$$

$$
\frac{\partial u_2(1,\tau)}{\partial r} = \frac{\partial v_2(1,\tau)}{\partial r} = 0,
$$

where β_1 and β_1^* are as before.

We proceed in these higher-dimensional cases as we did in the one-dimensional case [5] and obtain a characteristic equation whose roots determine the stability of the steady-state solution. This equation takes the form

$$
\begin{aligned}
&(\lambda+1)(\lambda+b_2)\left(1+\gamma_1\int_0^\infty K(s,\sigma)\,e^{-\lambda s}\,ds\right)\left(1+\gamma_2\int_0^\infty K^*(s,\sigma)\,e^{-\lambda s}\,ds\right) \\
&\quad - c_0\gamma_2 f'(\bar{v}_1)\,e^{-\lambda\nu}\left[\int_0^\infty K^*(s,\sigma)\,e^{-\lambda s}\,ds - (\lambda+1)\int_0^\infty \sum_{n=1}^\infty \mathcal{K}_n(s)\,e^{-\lambda s}\,ds\right] = 0
\end{aligned} \tag{2.2}
$$

where the kernels K, K^*, and $\mathcal{K}_n$ depend on the region and on the boundary conditions and will be given explicitly later.

For high diffusivity we compare system (2.1) to the related well-mixed two-compartment model which was analyzed in [17] and has the characteristic equation:

$$
(\lambda+1)(\lambda+b_2)(\lambda+1+a_1+a_3)(\lambda+b_2+a_2+a_4) - c_0 a_2 a_3 f'(\bar{v}_1)\,e^{-\lambda\nu} = 0, \tag{2.3}
$$

where the kinetic parameters are as given in [17]. For this well-mixed model, Mahaffy and Pao [17] give conditions when there exists a critical value of the delay $\nu = \nu_0$ which gives a Hopf bifurcation. The two-compartment diffusion model given by (2.1) would be expected to behave in a manner similar to a well-mixed two-compartment model if the diffusivities μ_i are sufficiently large relative to the other parameters. The next theorem compares the local behavior of the model (2.1) to the well-mixed model.

THEOREM 2.1. *Assume that the nondimensional diffusivities μ_i tend to infinity and $\beta_1\mu_1$ and $\beta_1^*\mu_2$ are finite. Consider λ such that* $\mathrm{Re}\,\lambda > \max\{-1, -b_2\}$. *Then, in the limit, the solutions λ which satisfy the characteristic equation* (2.2) *for the model* (2.1) *equal the solutions λ to the characteristic equation* (2.3) *for the well-mixed two-compartment model with $\gamma_1 = a_1$, $\gamma_2 = a_2$, $\beta_1\mu_1 = a_3$ and $\beta_1^*\mu_2 = a_4$.*

Let $\alpha = -c_0a_2a_3f'(\bar{v}_1)$, where $\bar{v}_1$ is the equilibrium solution for the well-mixed model analyzed in [17]. Theorem 5.1 in [17] shows that if $b_2(1+a_1+a_3)(b_2+a_2+a_4) < \alpha$, then there exists a critical delay ν_0 such that for all $\nu > \nu_0$, (2.3) has at least two roots with $\mathrm{Re}\,\lambda > 0$. If either $b_2(1+a_1+a_3)(b_2+a_2+a_4) > \alpha$ or $0 \leqq \nu < \nu_0$, then all solutions of (2.3) have $\mathrm{Re}\,\lambda < 0$. From this we see that a Hopf bifurcation occurs for (2.3) at $\nu = \nu_0$ with appropriate conditions on the other parameters. Combining this information with Theorem 2.1, we obtain the following theorem.

THEOREM 2.2. *Assume $b_2(1+a_1+a_3)(b_2+a_2+a_4) < \alpha$ and that ν_0 is the critical delay for a Hopf bifurcation of the well-mixed model. If μ_i are sufficiently large, $a_3 = \beta_1\mu_1$ and $a_4 = \beta_1^*\mu_2$, then the system* (2.1) *has a Hopf bifurcation for some delay $\hat{\nu}_0$ with $\hat{\nu}_0 \in [-\varepsilon + \nu_0, \nu_0 + \varepsilon]$, $\varepsilon > 0$ small.*

The proof of this theorem is immediate from work done on the well-mixed model, Theorem 2.1, and the continuous dependence of a Hopf bifurcation for functional differential equations.

The above theorems consider the stability for large diffusivities. Next a result is presented that shows 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, 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. As we shall see in the numerical studies reported in § 4, the dependence of the critical delay value at the 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 results for small diffusivity are summarized in the following theorem.

THEOREM 2.3. *Suppose that $\beta_1\mu_1 = a_3$, $\beta_1^*\mu_2 = a_4$, with a_3, a_4 fixed and suppose that μ_1, μ_2 tend to zero. Then there exists $d > 0$ such that if $0 < \mu_i < d$, all solutions λ, which satisfy the characteristic equation* (2.2), *have real parts less than zero.*

What happens when the cell grows is of particular interest in studying cellular dynamics. In this case the parameters such as the decay constants, membrane permeabilities, and diffusivities are kept fixed, while the cell radius is allowed to vary. For analysis of this system we must consider the system (2.1) in the dimensionalized form. The appendix provides some of the details about this conversion. For large cell radii, we have the following analogue of Theorem 2.3.

THEOREM 2.4. *Let $\tilde{a}_i$ denote the parameters of the well-mixed model, $\hat{\beta}_i$, $\hat{\mu}_i$ the dimensioned parameters of the diffusion model, and suppose that $\hat{\beta}_1\hat{\mu}_1 = \tilde{a}_3R$ and $\hat{\beta}_1^*\hat{\mu}_2 = \tilde{a}_4R$ with the constants $\hat{\beta}_1$, $\hat{\beta}_1^*$, and $\hat{\mu}_i$ fixed from the dimensionalized form of* (2.1). *When $R \to +\infty$, there exists a constant $M > 0$ such that if $R > M$, all solutions λ, which satisfy the characteristic equation of the dimensionalized system, have real parts less than zero.*

Heuristically, in Theorem 2.3 we are examining the case where low diffusivity does not allow sufficient diffusion of the chemical species into the cytoplasm before decay to low concentrations occurs. In Theorem 2.4 the flux rate per unit surface area is kept constant. Since the volume increases by a factor of R times the boundary area, the chemical species reacting in the cytoplasm are diluted as R increases to the point where, for sufficiently large R, the feedback induced oscillations cannot be maintained regardless of the value of the delay. Numerical results show a parameter region of increasing stability as $R \to 0$.

Another result that can be examined with our techniques is the case when σ, the ratio of the radius of the nucleus to that of the cell, tends to zero. For this case we may assume $R=1$. We assume the diffusivities μ_i and the transfer coefficients β_1 and β_1^* remain fixed. With these assumptions the decrease of σ will mean that the nucleus cannot transfer large quantities of mRNA to the cytoplasm which allows a dominance of the decay terms and stability of the system. This result is stated in the following theorem.

THEOREM 2.5. *Consider the radially symmetric system of equations given by* (2.1) *in three dimensions. Assume that the parameters b_2, μ_1, μ_2, c_0, β_1 and β_1^* are fixed. Let $\sigma = r_0/R$, then there exists a critical value σ_0 such that for $\sigma < \sigma_0$ the solution of the characteristic equation* (2.2) *have real parts less than zero and the steady state is stable.*

3. Proofs of the theorems. The proofs of our main results are based on some preliminary analysis of (2.1) which is similar to our treatment of the one-dimensional version of this problem [5]. Before starting this analysis we note that the existence and uniqueness of solutions to (1.1) follow either from the reasoning described in [5] or from the analysis of a similar problem treated by Pao [20] where the integral over the boundary $\partial\omega$ does not appear and the terms of (1.1) which involve this integral are replaced by $a_1[u_2(x,t)-u_1(t)]$ and $a_2[v_2(x,t)-v_1(t)]$. Since these proofs in the present case involve only straightforward technical changes of those of Pao [20], we will not present details here. The existence and uniqueness of a radially symmetric steady state involves a fairly direct analysis which we omit.

In (2.1) let $u_2(r,\tau)=R(r)T(\tau)$ and use the technique of separation of variables. For the two-dimensional model we obtain the eigenvalues λ_n to the Sturm–Liouville problem in $R(r)$ by satisfying the equation:

$$\lambda[J_1(\lambda\sigma)Y_1(\lambda)-J_1(\lambda)Y_1(\lambda\sigma)]-\beta_1[J_1(\lambda)Y_0(\lambda\sigma)-J_0(\lambda\sigma)Y_1(\lambda)]=0 \tag{3.1}$$

from which we obtain the normalized eigenfunctions:

$$\phi_n(r)=\frac{\pi\lambda_n\sqrt{2}[Y_1(\lambda_n)J_0(\lambda_n r)-J_1(\lambda_n)Y_0(\lambda_n r)]}{[4-\sigma^2\pi^2(\lambda_n^2+\beta_1^2)(J_0(\lambda_n\sigma)Y_1(\lambda_n)-J_1(\lambda_n)Y_0(\lambda_n\sigma))^2]^{1/2}}. \tag{3.2}$$

We also need the expression for $\delta_n \equiv \langle\phi_n, 1\rangle = \int_\sigma^1 \phi_n(r)r\,dr$ which is given by

$$\delta_n=\frac{\sigma\pi\sqrt{2}[J_1(\lambda_n)Y_1(\lambda_n\sigma)-Y_1(\lambda_n)J_1(\lambda_n\sigma)]}{[4-\sigma^2\pi^2(\lambda_n^2+\beta_1^2)(J_0(\lambda_n\sigma)Y_1(\lambda_n)-J_1(\lambda_n)Y_0(\lambda_n\sigma))^2]^{1/2}}. \tag{3.3}$$

In the three-dimensional model we obtain the eigenvalues λ_n to the Sturm–Liouville problem for $R(r)$ by satisfying the equation:

(3.4)

$$(\lambda^2\sigma+1)\sin\lambda(1-\sigma)-\lambda(1-\sigma)\cos\lambda(1-\sigma)-\beta_1\sigma(\lambda\cos\lambda(1-\sigma)-\sin\lambda(1-\sigma))=0$$

and the corresponding normalized eigenfunctions are

(3.5)

$$\phi_n(r)=\frac{2\sqrt{\lambda_n}(\lambda_n\cos\lambda_n(1-r)-\sin\lambda_n(1-r))}{r[(\lambda_n^2+1)(2\lambda_n(1-\sigma))-2\lambda_n+2\lambda_n\cos 2\lambda_n(1-\sigma)+(\lambda_n^2-1)\sin 2\lambda_n(1-\sigma)]^{1/2}}.$$

Similarly, we compute $\delta_n\equiv\langle\phi_n,1\rangle=\int_\sigma^1\phi_n(r)r^2\,dr$ which becomes

(3.6)

$$\delta_n=\frac{2[(1+\lambda_n^2\sigma)\sin\lambda_n(1-\sigma)-\lambda_n(1-\sigma)\cos\lambda_n(1-\sigma)]}{\lambda_n^{3/2}[(\lambda_n^2+1)(2\lambda_n(1-\sigma))-2\lambda_n+2\lambda_n\cos 2\lambda_n(1-\sigma)+(\lambda_n^2-1)\sin 2\lambda_n(1-\sigma)]^{1/2}}.$$

For both the two- and three-dimensional models we define $A_n=1+\lambda_n^2\mu_1$ and $\alpha_n=\langle u_{20},\phi_n\rangle$, where $u_{20}(r)$ is the initial concentration distribution of u_2. Then from the variation of constants formula we obtain:

$$(3.7)\qquad \begin{aligned} u_2(r,\tau)&=\sum_{n=1}^{\infty}\alpha_n e^{-A_n\tau}\phi_n(r)-\int_0^\tau\sum_{n=1}^{\infty}\delta_n\phi_n(r)e^{-A_n(\tau-s)}F_2(s)\,ds\\ &\equiv\sum_{n=1}^{\infty}\alpha_n e^{-A_n\tau}\phi_n(r)-\int_0^\tau K(\tau-s,r)[\tilde f(v_1(s-\nu))+\gamma_1u_2(\sigma,s)]\,ds,\end{aligned}$$

where $K(\tau,r)=\sum_{n=1}^\infty\delta_n\phi_n(r)e^{-A_n\tau}$ and $\tilde f(v_{1s})=f(v_1(s-\nu)+\bar v_1)+\gamma_1u_2^s(\sigma)-(1+\gamma_1)\bar u$.

We evaluate (3.7) at $r=\sigma$ to obtain the following linear Volterra equation in $u_2(\sigma,\tau)$:

$$u_2(\sigma,\tau)=\sum_{n=1}^{\infty}\alpha_n e^{-A_n\tau}\phi_n(\sigma)-\int_0^\tau K(\tau-s,\sigma)[\tilde f(v_{1s})+\gamma_1u_2(\sigma,s)]\,ds.$$

A similar procedure is applied to the v_2 equation. We obtain eigenvalues ζ_n from the equations:

$$(3.8)\qquad \zeta[J_1(\zeta\sigma)Y_1(\zeta)-J_1(\zeta)Y_1(\zeta\sigma)]-\beta_1^*[J_1(\zeta)Y_0(\zeta\sigma)-J_0(\zeta\sigma)Y_1(\zeta)]=0$$

and

(3.9)

$$(\zeta^2\sigma+1)\sin\zeta(1-\sigma)-\zeta(1-\sigma)\cos\zeta(1-\sigma)-\beta_1^*\sigma(\zeta\cos\zeta(1-\sigma)-\sin\zeta(1-\sigma))=0$$

for two and three dimensions, respectively. The corresponding normalized eigenfunctions are given by

$$\psi_n(r)=\frac{\pi\zeta_n\sqrt2[Y_1(\zeta_n)J_0(\zeta_nr)-J_1(\zeta_n)Y_0(\zeta_nr)]}{[4-\sigma^2\pi^2(\zeta_n^2+\beta_1^2)(J_0(\zeta_n\sigma)Y_1(\zeta_n)-J_1(\zeta_n)Y_0(\zeta_n\sigma))^2]^{1/2}}$$

and

$$\psi_n(r)=\frac{2\sqrt{\zeta_n}(\zeta_n\cos\zeta_n(1-r)-\sin\zeta_n(1-r))}{r[(\zeta_n^2+1)(2\zeta_n(1-\sigma))-2\zeta_n+2\zeta_n\cos 2\zeta_n(1-\sigma)+(\zeta_n^2-1)\sin 2\zeta_n(1-\sigma)]^{1/2}}.$$

We define $\delta_n^*=\langle\psi_n,1\rangle$ similarly to the manner in which δ_n was defined, and thus it is easy to obtain the values for δ_n^* by (3.3) and (3.6) with λ_n replaced by ζ_n. Also, we define $B_n=b_2+\zeta_n^2\mu_2$ and $\alpha_n^*=\langle v_{20},\psi_n\rangle$, where $v_{20}(r)$ is the initial concentration distribution of v_2. Then as before the variation of constants formula gives

$$\begin{aligned} v_2(r,\tau)=&\sum_{n=1}^{\infty}\alpha_n^* e^{-B_n\tau}\psi_n(r)+\int_0^\tau\sum_{n=1}^{\infty}\delta_n^* e^{-B_n(\tau-s)}\psi_n(r)[c_0u_1(s)-\gamma_2v_2(\sigma,s)]\,ds\\ &+c_0\int_0^\tau\sum_{n=1}^{\infty}\langle u_2(\cdot,s),\psi_n(\cdot)\rangle e^{-B_n(\tau-s)}\psi_n(r)\,ds.\end{aligned}$$

When $r=\sigma$, then

$$v_2(\sigma,\tau)=\sum_{n=1}^{\infty}\alpha_n^*\,e^{-B_n\tau}\psi_n(\sigma)+\int_0^{\tau}K^*(\tau-s,\sigma)[c_0u_1(s)-\gamma_2v_2(\sigma,s)]\,ds$$
$$+c_0\int_0^{\tau}\sum_{n=1}^{\infty}\langle u_2(\cdot,s),\psi_n(\cdot)\rangle\,e^{-B_n(\tau-s)}\psi_n(\sigma)\,ds.$$

where $K^*(\tau,r)\equiv\sum_{n=1}^{\infty}\delta_n^*\,e^{-B_n\tau}\psi_n(r)$, $\langle x,y\rangle=\int_\sigma^1 x(\xi)y(\xi)\xi^{n-1}\,d\xi$, and n equals the dimension of the problem. This is a linear Volterra equation in $v_2(\sigma,\tau)$.

Combining the above information, we obtain the reduced system of equations which incorporates diffusion as a distributed delay and is given by

$$u_1'(\tau)=\tilde{f}(v_1(\tau-\nu))-u_1(\tau)+\gamma_1u_2(\sigma,\tau),$$
$$v_1'(\tau)=-b_2v_1(\tau)+\gamma_2v_2(\sigma,\tau),$$
$$u_2(\sigma,\tau)=\sum_{n=1}^{\infty}\alpha_n\,e^{-A_n\tau}\phi_n(\sigma)-\int_0^{\tau}K(\tau-s,\sigma)[\tilde{f}(v_1(s-\nu))+\gamma_1u_2(\sigma,s)]\,ds,$$
$$v_2(\sigma,\tau)=\sum_{n=1}^{\infty}\alpha_n^*\,e^{-B_n\tau}\psi_n(\sigma)+\int_0^{\tau}K^*(\tau-s,\sigma)[c_0u_1(s)-\gamma_2v_2(\sigma,s)]\,ds$$
$$+c_0\int_0^{\tau}\sum_{n=1}^{\infty}e^{-B_n(\tau-s)}\psi_n(\sigma)\langle u_2(\cdot,s),\psi_n(\cdot)\rangle\,ds.$$

To proceed with the local stability analysis, we linearize the above system, which becomes

$$u_1'(\tau)=f'(\bar{v}_1)v_1(\tau-\nu)-u_1(\tau)+\gamma_1u_2(\sigma,\tau),$$
$$v_1'(\tau)=-b_2v_1(\tau)+\gamma_2v_2(\sigma,\tau),$$
$$u_2(\sigma,\tau)=\sum_{n=1}^{\infty}\alpha_n\,e^{-A_n\tau}\phi_n(\sigma)-\int_0^{\tau}K(\tau-s,\sigma)[f'(\bar{v}_1)v_1(\tau-\nu)+\gamma_1u_2(\sigma,s)]\,ds,$$
$$v_2(\sigma,\tau)=\sum_{n=1}^{\infty}\alpha_n^*\,e^{-B_n\tau}\psi_n(\sigma)+\int_0^{\tau}K^*(\tau-s,\sigma)[c_0u_1(s)-\gamma_2v_2(\sigma,s)]\,ds$$
$$+c_0\int_0^{\tau}\sum_{n=1}^{\infty}e^{-B_n(\tau-s)}\psi_n(\sigma)\langle u_2(\cdot,s),\psi_n(\cdot)\rangle\,ds.$$

As in the one-dimensional case, we must find the limiting Volterra equations to study the local stability of the system. One can show that

$$\lim_{\tau\to\infty}\sum_{n=1}^{\infty}\alpha_n\,e^{-A_n\tau}\phi_n(\sigma)=\lim_{\tau\to\infty}\sum_{n=1}^{\infty}\alpha_n^*\,e^{-B_n\tau}\psi_n(\sigma)=0.$$

The analysis for the two- and three-dimensional cases is identical to that found in [5], from which the limiting linear system of delay differential equations and Volterra equations is written:

$$
\begin{aligned}
&u_1'(\tau)=f'(\bar{v}_1)v_1(\tau-\nu)-u_1(\tau)+\gamma_1 u_2(\sigma,\tau),\\
&v_1'(\tau)=-b_2 v_1(\tau)+\gamma_2 v_2(\sigma,\tau),\\
&u_2(\sigma,\tau)=-\int_0^\infty K(\tau-s,\sigma)[f'(\bar{v}_1)v_1(s-\nu)+\gamma_1 u_2(\sigma,s)]\,ds,\\
&v_2(\sigma,\tau)=\int_0^\infty\Bigg[K^*(\tau-s,\sigma)[c_0u_1(s)-\gamma_2 v_2(\sigma,s)]\\
&\qquad -c_0[f'(\bar{v}_1)v_1(s-\nu)+\gamma_1 u_2(\sigma,s)]\sum_{n=1}^\infty \mathcal{K}_n(\tau-s)\Bigg]\,ds,
\end{aligned}\tag{3.10}
$$

where $\mathcal{K}_n(s)=\psi_n(\sigma)\int_0^s e^{-B_n t}\langle K(s-t,\cdot),\psi_n(\cdot)\rangle\,dt$. From (3.10) we can write the characteristic matrix whose determinant can be expanded to give (2.2). This characteristic equation is similar to the one in [5], so again we may interchange the summation and integration to obtain

$$
\begin{aligned}
&\int_0^\infty K(s,\sigma)\,e^{-\lambda s}\,ds=\int_0^\infty\sum_{n=1}^\infty \delta_n\phi_n(\sigma)\,e^{-A_n s}\,e^{-\lambda s}\,ds=\sum_{n=1}^\infty\frac{\delta_n\phi_n(\sigma)}{\lambda+A_n},\\
&\int_0^\infty K^*(s,\sigma)\,e^{-\lambda s}\,ds=\sum_{n=1}^\infty\frac{\delta_n^*\psi_n(\sigma)}{\lambda+B_n},\\
&\int_0^\infty\sum_{n=1}^\infty \mathcal{K}_n(s)\,e^{-\lambda s}\,ds=\sum_{n=1}^\infty\sum_{m=1}^\infty\frac{\psi_n(\sigma)\delta_m\langle\phi_m,\psi_n\rangle}{(\lambda+A_m)(\lambda+B_n)}.
\end{aligned}
$$

We multiply the characteristic equation by $(\lambda+A_1)$ and $(\lambda+B_1)$, and obtain the following:

$$
\begin{aligned}
&(\lambda+1)\Bigg[\lambda+1+\lambda_1^2\mu_1+\gamma_1\delta_1\phi_1(\sigma)+\gamma_1\sum_{n=2}^\infty\frac{\delta_n\phi_n(\sigma)(\lambda+1+\lambda_1^2\mu_1)}{\lambda+1+\lambda_n^2\mu_1}\Bigg]\\
&\quad\cdot(\lambda+b_2)\Bigg[\lambda+b_2+\zeta_1^2\mu_2+\gamma_2\delta_1^*\psi_1(\sigma)+\gamma_2\sum_{n=2}^\infty\frac{\delta_n^*\psi_n(\sigma)(\lambda+b_2+\zeta_1^2\mu_2)}{\lambda+b_2+\zeta_n^2\mu_2}\Bigg]\\
&\quad-c_0\gamma_2 f'(\bar{v}_1)\,e^{-\lambda\nu}\Bigg[(\lambda+1+\lambda_1^2\mu_1)\Bigg[\delta_1^*\psi_1(\sigma)+\sum_{n=2}^\infty\frac{\delta_n^*\psi_n(\sigma)(\lambda+b_2+\zeta_1^2\mu_2)}{\lambda+b_2+\zeta_n^2\mu_2}\Bigg]\\
&\quad-(\lambda+1)(\lambda+1+\lambda_1^2\mu_1)(\lambda+b_2+\zeta_1^2\mu_2)\sum_{n=1}^\infty\sum_{m=1}^\infty\frac{\delta_m\psi_n(\sigma)\langle\phi_m,\psi_n\rangle}{(\lambda+1+\lambda_m^2\mu_1)(\lambda+b_2+\zeta_n^2\mu_2)}\Bigg]=0.
\end{aligned}
$$

When $\beta_1=\beta_1^*$, $\lambda_n=\zeta_n$, $\phi_n(\sigma)=\psi_n(\sigma)$, and $\langle\phi_m,\psi_n\rangle=\delta_{mn}$, the Kronecker delta, the characteristic equation can be written in the simpler form

$$
\begin{aligned}
&(\lambda+1)\Bigg[\lambda+1+\lambda_1^2\mu_1+\gamma_1\delta_1\phi_1(\sigma)+\gamma_1\sum_{n=2}^\infty\frac{\delta_n\phi_n(\sigma)(\lambda+1+\lambda_1^2\mu_1)}{\lambda+1+\lambda_n^2\mu_1}\Bigg]\\
&\quad\cdot(\lambda+b_2)\Bigg[\lambda+b_2+\lambda_1^2\mu_2+\gamma_2\delta_1\phi_1(\sigma)+\gamma_2\sum_{n=2}^\infty\frac{\delta_n\phi_n(\sigma)(\lambda+b_2+\lambda_1^2\mu_2)}{\lambda+b_2+\lambda_n^2\mu_2}\Bigg]\\
&\quad-c_0\gamma_2 f'(\bar{v}_1)\,e^{-\lambda\nu}\Bigg[\lambda_1^2\mu_1\delta_1\phi_1(\sigma)\\
&\qquad+\sum_{n=2}^\infty\frac{\delta_n\phi_n(\sigma)\lambda_n^2\mu_1(\lambda+1+\lambda_1^2\mu_1)(\lambda+b_2+\lambda_1^2\mu_2)}{(\lambda+1+\lambda_n^2\mu_1)(\lambda+b_2+\lambda_n^2\mu_2)}\Bigg]=0.
\end{aligned}\tag{3.11}
$$

In the proofs of both Theorems 2.1 and 2.3 a detailed examination of the quantity $\delta_n\phi_n(\sigma)$ for the two and three dimensions is needed. In the proofs of each of the theorems we write only the case when $\beta_1=\beta_1^*$ though the proof extends to the more general case. For the two-dimensional case with (3.2) and (3.3)

$$\delta_n\phi_n(\sigma)=\frac{2\pi^2\sigma\lambda_n[J_1(\lambda_n)Y_1(\lambda_n\sigma)-Y_1(\lambda_n)J_1(\lambda_n\sigma)][J_0(\lambda_n\sigma)Y_1(\lambda_n)-J_1(\lambda_n)Y_0(\lambda_n\sigma)]}{[4-\sigma^2\pi^2(\lambda_n^2+\beta_1^2)[J_0(\lambda_n\sigma)Y_1(\lambda_n)-J_1(\lambda_n)Y_0(\lambda_n\sigma)]^2]}.$$

With the eigenvalue equation (3.1) we can write

$$\delta_n\phi_n(\sigma)=\frac{2\pi^2\sigma\beta_1}{(4/[J_1(\lambda_n)Y_0(\lambda_n\sigma)-Y_1(\lambda_n)J_0(\lambda_n\sigma)]^2)-\sigma^2\pi^2(\lambda_n^2+\beta_1^2)}. \tag{3.12}$$

The eigenvalues λ_n asymptotically approach $(n-1)\pi/(1-\sigma)$ [3, p. 303] with $\lambda_n>(n-1)\pi/(1-\sigma)$. For n sufficiently large, hence λ_n and $\lambda_n\sigma$ large, we use the asymptotic approximations of the Bessel functions given by

$$J_n(x)\simeq\sqrt{2/\pi x}\cos(x-\pi/4-n\pi/2),$$
$$Y_n(x)\simeq\sqrt{2/\pi x}\sin(x-\pi/4-n\pi/2).$$

It is important to note that these asymptotic approximations depend only on n and σ. From (3.1) with λ large and the above asymptotic approximations for the Bessel functions, we obtain

$$\begin{aligned}\lambda[(2/\pi\lambda\sqrt{\sigma})[\cos(\lambda\sigma-3\pi/4)\sin(\lambda-3\pi/4)-\cos(\lambda-3\pi/4)\sin(\lambda\sigma-3\pi/4)]]\\ \simeq\beta_1[(2/\pi\lambda\sqrt{\sigma})[\cos(\lambda-3\pi/4)\sin(\lambda\sigma-\pi/4)-\cos(\lambda\sigma-\pi/4)\sin(\lambda-3\pi/4)]],\end{aligned}$$

which is equivalent to

$$\lambda/\beta_1\simeq\cot[\lambda(1-\sigma)]. \tag{3.13}$$

Equation (3.13) is similar to the eigenvalue equation for the one-dimensional case (see [5]). With these approximations which are independent of β_1, we can show

$$[J_1(\lambda_n)Y_0(\lambda_n\sigma)-Y_1(\lambda_n)J_0(\lambda_n\sigma)]^2\simeq\frac{4}{\pi^2\lambda_n^2\sigma}\cos^2[\lambda_n(1-\sigma)].$$

Using (3.13) we find $\cos^2[\lambda_n(1-\sigma)]\simeq\lambda_n^2/(\lambda_n^2+\beta_1^2)$. Now substituting these approximations into the expression for $\delta_n\phi_n(\sigma)$, we obtain

$$\delta_n\phi_n(\sigma)\simeq\frac{2\beta_1}{(\lambda_n^2+\beta_1^2)(1-\sigma)}. \tag{3.14}$$

Similar computations are performed for the three-dimensional case. Using (3.5) and (3.6), we find that

$$\delta_n\phi_n(\sigma)=$$
$$\frac{4[(1+\lambda_n^2\sigma)\sin\lambda_n(1-\sigma)-\lambda_n(1-\sigma)\cos\lambda_n(1-\sigma)][\lambda_n\cos\lambda_n(1-\sigma)-\sin\lambda_n(1-\sigma)]}{\lambda_n\sigma[(\lambda_n^2+1)(2\lambda_n(1-\sigma))-2\lambda_n+2\lambda_n\cos2\lambda_n(1-\sigma)+(\lambda_n^2-1)\sin2\lambda_n(1-\sigma)]}.$$

We can use the eigenvalue equation (3.4) to eliminate the trigonometric functions from the expression for $\delta_n\phi_n(\sigma)$. After some algebraic manipulations one obtains

(3.15)

$$\delta_n\phi_n(\sigma)=\frac{2\beta_1\sigma^2(1+\lambda_n^2)}{\beta_1^2\sigma^2[\lambda_n^2(1-\sigma)-\sigma]+\beta_1\sigma[(2-\sigma)\lambda_n^2-\sigma]+(1-\sigma)\lambda_n^2(1+\sigma+\sigma^2+\lambda_n^2\sigma^2)}.$$

With these preliminary computations we are ready to proceed with the proofs of our theorems. We begin with the proof of Theorem 2.1. The assumption that $\beta_1\mu_1$ is finite with $\mu_1 \to \infty$ implies $\beta_1 \to 0$. With this in mind, we examine the eigenvalue equations (3.1) and (3.4). In (3.1) when series expansions are used for $J_0(z) = 1 + \mathcal{O}(z^2)$, $J_1(z) = (z/2) + \mathcal{O}(z^3)$, $Y_0(z) = (2/\pi)\ln(z/2) + \mathcal{O}(1)$, and $Y_1(z) = -(2/z\pi) + \mathcal{O}(z\ln(z))$ we see that for λ_1 near zero $\beta_1 = [(1-\sigma^2)\lambda_1^2/2\sigma] + \mathcal{O}(\lambda_1^3)$. In (3.4) when series expansions are used for sine and cosine near zero we obtain $\beta_1 = [(1-\sigma^3)\lambda_1^2/3\sigma^2] + \mathcal{O}(\lambda_1^4)$.

For two dimensions we can use the above order arguments in (3.12) to show that as $\mu_1 \to \infty$, $\beta_1 \to 0$, and $\lambda_1 \to 0$, then $\lim_{\lambda_1 \to 0} \delta_1\phi_1(\sigma) = 1$. In three dimensions we substitute the expansion of β_1 in powers of λ_n into (3.15) and again we find that $\lim_{\lambda_1 \to 0} \delta_1\phi_1(\sigma) = 1$ from the order arguments.

It remains to show that the infinite sums from $n = 2$ to $n = \infty$ all tend to zero as $\mu_i \to \infty$, $i = 1, 2$. For the two-dimensional case the approximation in (3.14) is only valid for $n \geqq N(\sigma)$ a fixed positive number. To handle the expression with the Bessel functions for $n \leqq N$, we need another result. As this result will be used in the subsequent theorems, a lemma is presented for the dimensionalized two-compartment model. For more information on the change of coordinates and the definitions of the dimensioned variables $\hat{\delta}_n$, $\hat{\beta}_1$ and $\hat{\phi}_n$ see the appendix.

LEMMA 3.1. *For the two-dimensional model in dimensionalized coordinates, given an N, there exists $M(N) > 0$, such that*

$$|\hat{\delta}_n\hat{\phi}_n(R\sigma)| \leqq \frac{M(N)R\sigma\hat{\beta}_1}{(1-\sigma^2)(1+R^2\sigma^2\hat{\beta}_1^2)}, \qquad n = 2, \cdots, N.$$

Proof. For notational convenience we shall drop the ^ in the proof of this lemma. We consider the Prüfer transformation [3, p. 228],

$$P(r) = (\phi_n^2 + r^2[\phi_n']^2)^{1/2} > 0, \qquad \theta(r) = \arctan(\phi_n/r\phi_n),$$

where the normalized $\phi_n(r)$ satisfy Bessel's equation, $d/dr[r\phi_n'(r)] + \lambda_n^2 r\phi_n(r) = 0$, with boundary conditions $\phi_n'(R\sigma) = \beta_1\phi_n(R\sigma)$ and $\phi_n'(R) = 0$ in our cellular model. It can be shown that

$$P' = -(\lambda_n^2 r - 1/r)P\sin\theta\cos\theta, \qquad R\sigma \leqq r \leqq R.$$

Clearly, $P' \geqq -\lambda_n^2 rP$ for this model which implies

$$P(r) \geqq P(R\sigma)\exp[-\lambda_n^2R^2/2].$$

From the definition of $P(R\sigma)$ we obtain

$$P(r) \geqq |\phi_n(R\sigma)|(1+R^2\sigma^2\beta_1^2)^{1/2}\exp[-\lambda_n^2R^2/2].$$

With $\langle\psi, \eta\rangle \equiv \int_{R\sigma}^R \psi(r)\eta(r)r\,dr$,

$$\langle P, P\rangle \geqq |\phi_n(R\sigma)|^2(1+R^2\sigma^2\beta_1^2)[R^2(1-\sigma^2)/2]\exp[-\lambda_n^2R^2].$$

However, $\langle P, P\rangle = \langle\phi_n, \phi_n\rangle + \langle r\phi_n', r\phi_n'\rangle \leqq 1 + R^2\langle\phi_n', \phi_n'\rangle$, as $R\sigma \leqq r \leqq R$. From the Sturm–Liouville problem,

$$\int_{R\sigma}^R \phi_n[(r\phi_n')' + \lambda_n^2 r\phi_n]\,dr = -R\sigma\,\phi_n(R\sigma)\phi_n'(R\sigma) - \langle\phi_n', \phi_n'\rangle + \lambda_n^2 = 0,$$

which implies

$$\langle\phi_n', \phi_n'\rangle = \lambda_n^2 - R\sigma\beta_1\phi_n^2(R\sigma) \leqq \lambda_n^2.$$

Combining these results we obtain

$$|\phi_n(R\sigma)|^2 \leqq \frac{(1+R^2\lambda_n^2)\exp[\lambda_n^2R^2]}{(1+R^2\sigma^2\beta_1^2)(R^2(1-\sigma^2)/2)},$$

which forms a bound on $|\phi_n(R\sigma)|$ depending on λ_n, β_1, R, and σ. Furthermore,

$$\int_{R\sigma}^{R} [(r\phi_n')' + \lambda_n^2 r\phi_n]\,dr = -R\sigma\phi_n'(R\sigma) + \lambda_n^2\delta_n = 0;$$

hence,

$$\delta_n\phi_n(R\sigma) = R\sigma\beta_1\phi_n^2(R\sigma)/\lambda_n^2 \leqq \frac{2R\sigma\beta_1(1+R^2\lambda_n^2)\exp[\lambda_n^2R^2]}{R^2\lambda_n^2(1-\sigma^2)(1+R^2\sigma^2\beta_1^2)}.$$

As $(n-1)\pi < R\lambda_n(1-\sigma) < n\pi$, for $n = 2, \cdots, N$, there exists a constant $M(N)$ such that

$$\delta_n\phi_n(R\sigma) \leqq \frac{M(N)R\sigma\beta_1}{(1-\sigma^2)(1+R^2\sigma^2\beta_1^2)},$$

which completes the proof of the lemma.

A comment is appropriate at this point. One can readily see that as $\beta_1 \to 0$, the Sturm–Liouville problem is approaching a Neumann problem and the first eigenvalue, $\lambda_1 \to 0$. On the other hand, as $\beta_1 \to \infty$, the Sturm–Liouville problem is approaching a Dirichlet problem and $R\lambda_1(1-\sigma) \to \pi/2$. In the proof of the lemma, the constant $M(N)$ used the idea that the eigenvalues λ_i for $i \geqq 2$ are bounded away from zero. It is clear that if $\beta_1 \geqq \varepsilon$, $R \geqq \varepsilon$, and σ fixed for some fixed $\varepsilon > 0$, then λ_1 is bounded away from zero and Lemma 3.1 holds for $n = 1$.

From the eigenvalue equation (3.4) for the three-dimensional case, one can write the following expression:

$$\cot[\lambda_n(1-\sigma)] = \frac{\lambda_n^2\sigma + 1 + \beta_1\sigma}{\lambda_n(\beta_1\sigma + 1 - \sigma)}. \tag{3.16}$$

As in the two-dimensional case which has its eigenvalues approximated by (3.13), we find that the solutions λ_n to (3.16) are such that $\lambda_n \to (n-1)\pi/(1-\sigma)$ as $n \to \infty$ with $\lambda_n > (n-1)\pi/(1-\sigma)$ for all n. For the three-dimensional case we see from (3.15) that

$$|\delta_n\phi_n(\sigma)| < \frac{2\beta_1\sigma^2(1+\lambda_n^2)}{(1-\sigma)\lambda_n^2(1+\sigma+\sigma^2+\lambda_n^2\sigma^2)} < \frac{2\beta_1}{(1-\sigma)\lambda_n^2} < \frac{2\beta_1(1-\sigma)}{(n-1)^2\pi^2}. \tag{3.17}$$

Similarly, in two dimensions if $n \geqq N$ for some N independent of β_1, we can use (3.14) to show that

$$|\delta_n\phi_n(\sigma)| < \frac{2\beta_1}{(1-\sigma)\lambda_n^2} < \frac{2\beta_1(1-\sigma)}{(n-1)^2\pi^2}. \tag{3.18}$$

For $n = 2, \cdots, N$, we apply Lemma 3.1 with $R = 1$, σ fixed, and β_1 small to see that $|\delta_n\phi_n(\sigma)| < M_1\beta_1$ for some constant $M_1(N, \sigma)$. Now with inequalities (3.17) and (3.18), whenever $\operatorname{Re}\lambda > \max\{-1, -b_2\}$,

$$\begin{aligned}\left|\sum_{n=2}^{\infty} \frac{\delta_n\phi_n(\sigma)(\lambda+1+\lambda_1^2\mu_1)}{\lambda+1+\lambda_n^2\mu_1}\right| &< \sum_{n=2}^{\infty} |\delta_n\phi_n(\sigma)| \\ &= \sum_{n=2}^{N-1} |\delta_n\phi_n(\sigma)| + \sum_{n=N}^{\infty} |\delta_n\phi_n(\sigma)| \\ &\leqq (N-1)M_1\beta_1 + \sum_{n=N}^{\infty} \frac{2\beta_1(1-\sigma)}{(n-1)^2\pi^2} \\ &\leqq \hat{M}\beta_1\end{aligned}$$

for some constant $\hat{M}(N,\sigma)$. Note that $N=2$ for the three-dimensional case. The second infinite sum in (3.11) is handled identically. For the third infinite sum we see that

$$\left|\sum_{n=2}^{\infty}\frac{\delta_n\phi_n(\sigma)\lambda_n^2\mu_1(\lambda+1+\lambda_1^2\mu_1)(\lambda+b_2+\lambda_1^2\mu_2)}{(\lambda+1+\lambda_n^2\mu_1)(\lambda+b_2+\lambda_n^2\mu_2)}\right|<|\lambda+1+\lambda_1^2\mu_1|\sum_{n=2}^{\infty}|\delta_n\phi_n(\sigma)|$$
$$\leqq|\lambda+1+\lambda_1^2\mu_1|\hat{M}\beta_1.$$

In each of these cases the infinite sum is bounded by a constant multiplied by β_1; hence, as $\beta_1\to 0$, the infinite sum vanishes. As $\delta_1\phi_1(\sigma)\to 1$ for $\beta_1\to 0$, it is easily seen that in the limit (3.11) approaches (2.3) with $\gamma_i=a_i$, $i=1,2$, $\lambda_1^2\mu_1=a_3$ and $\lambda_1^2\mu_2=a_4$, which completes the proof of the theorem.

Proof of Theorem 2.3. As in Theorem 2.1, we consider only the case when $\beta_1=\beta_1^*$. The other case is analogous. When $\beta_1=\beta_1^*$ we can write (3.11) as follows:

$$(\lambda+1)(\lambda+b_2)(1+\gamma_1S_1)(1+\gamma_2S_2)=c_0\gamma_2f'(\bar{v}_1)\,e^{-\lambda\nu}[S_2-(\lambda+1)S_3], \tag{3.19}$$

where

$$S_1=\sum_{n=1}^{\infty}\frac{\delta_n\phi_n(\sigma)}{\lambda+1+\lambda_n^2\mu_1},\qquad S_2=\sum_{n=1}^{\infty}\frac{\delta_n\phi_n(\sigma)}{\lambda+b_2+\lambda_n^2\mu_2},$$
$$S_3=\sum_{n=1}^{\infty}\frac{\delta_n\phi_n(\sigma)}{(\lambda+1+\lambda_n^2\mu_1)(\lambda+b_2+\lambda_n^2\mu_2)}.$$

Since we are concerned with solutions λ of (3.19) with real parts greater than zero, again it suffices to consider only $\operatorname{Re}\lambda>\max\{-1,-b_2\}$.

We begin by estimating the sums S_i, $i=1,2,3$. Let $\lambda=\xi+i\eta$, with $\xi>\max\{-1,-b_2\}$, and use $\lambda_n\geqq(n-1)\pi/(1-\sigma)$ and $\mu_i=a_{i+2}/\beta_1=\sigma^k\gamma_i/\beta_1(1-\sigma^k)$, where $k=2$ or 3, depending on the dimension of the problem. The first sum is estimated as follows:

$$|S_1|\leqq\frac{1}{\xi+1}\sum_{n=1}^{\infty}\frac{|\delta_n\phi_n(\sigma)|}{[1+C^2(n-1)^2/\beta_1]}, \tag{3.20}$$

where $C^2=[\pi^2\sigma^k\gamma_1]/[(1-\sigma)^2(1-\sigma^k)(\xi+1)]$. In this proof, we must show that $|\delta_n\phi_n(\sigma)|$ is $\mathcal{O}(1/\beta_1)$ for all values of n.

In two dimensions the approximation in (3.14) holds for $n\geqq N$ for some N independent of β_1. Thus $|\delta_n\phi_n(\sigma)|<2/[\beta_1(1-\sigma)]$, for $n\geqq N$. In three dimensions with (3.15) we can easily show that for $n\geqq 2$, $|\delta_n\phi_n(\sigma)|<3/[\beta_1\sigma(1-\sigma)]$ with the fact that $\lambda_n(1-\sigma)>\pi$. Let $R=1$ and fix σ, then the result of Lemma 3.1 for β_1 large shows that $|\delta_n\phi_n(\sigma)|\leqq M_1/\beta_1$ for some $M_1(N,\sigma)$ and $2\leqq n\leqq N$. By the comment following Lemma 3.1, if $\beta_1\geqq 1$, then we have $|\delta_n\phi_n(\sigma)|\leqq M_1/\beta_1$ for some $M_1(N,\sigma)$ and $1\leqq n\leqq N$. Also, using that comment about λ_1 being bounded away from zero, we can use (3.15) to show that in three dimensions $|\delta_1\phi_1(\sigma)|\leqq M_2/\beta_1$ for some M_2. Let $M=\max\{M_1,M_2,3/\sigma(1-\sigma)\}$. It follows that (3.20) can be written

$$\begin{aligned}|S_1|&\leqq\frac{M}{\beta_1(\xi+1)}\left[\sum_{n=1}^{\infty}\frac{1}{[1+C^2(n-1)^2/\beta_1]}\right]\\&\leqq\pi M/[2C(\xi+1)\beta_1^{1/2}].\end{aligned} \tag{3.21}$$

From (3.21) we see that $|S_1|=\mathcal{O}(1/\beta_1^{1/2})$. Similar computations can be used on $|S_2|$ and $|S_3|$ to show that they are $\mathcal{O}(1/\beta_1^{1/2})$.

We next note that if $f'(\bar{v}_1)$ remains bounded as $\beta_1 \to \infty$ (or equivalently, $\mu_i \to 0$), then it is easily seen that the left-hand side of (3.19) remains bounded away from zero and the right-hand side of the equation tends to zero. Thus, no solutions λ exist with $\operatorname{Re} \lambda > \max\{-1, -b_2\}$ which satisfy (3.19). This excludes the possibility that the linearized system (3.10) is unstable. Since $f(v_1)$ is taken to be $1/[1+k(v_1)^\rho]$ in our model, $f'(\bar{v}_1)$ is clearly bounded independent of $\bar{v}_1 \geqq 0$. This completes the proof of the theorem.

Proof of Theorem 2.4. We examine only the case when $\hat{\beta}_1 = \hat{\beta}_1^*$. To show this result we need to repeat the process used to transform the dimensionless system (2.1) into the reduced system of delay differential equations and Volterra equations in (3.10) without the normalization of cell size, i.e., omit the change of variable $r = x/R$. In keeping with the notation used in the appendix we use $\hat{}$ over the dimensionalized parameters. (Note that without loss of generality we can leave the time change $\tau = \hat{b}_1 t$.) The principal change in (2.1) is to replace the boundary evaluations at σ by $R\sigma$ and at 1 by R.

The eigenvalue equations (3.1) and (3.4) are transformed by substituting $\hat{\beta}_1 R$ for β_1 and $\hat{\lambda}_n R$ for λ_n. Obviously, there are corresponding changes in (3.8) and (3.9). We find $\hat{\delta}_n$ and $\hat{\phi}_n(R\sigma)$, and replace δ_n and $\phi_n(\sigma)$ in (3.2), (3.3), (3.5), and (3.6) with similar substitutions. With these changes we can write (3.19) in the form:

$$(3.22)\qquad \begin{aligned}&(\lambda+1)(\lambda+\hat{b}_2)[1+(\hat{\gamma}_1 S_1/R^{k-1})][1+(\hat{\gamma}_2 S_2/R^{k-1})]\\ &\quad = \hat{c}_0(\hat{\gamma}_2/R^{k-1})\hat{f}'(\bar{v}_1)\, e^{-\lambda\nu}[S_2-(\lambda+1)S_3],\end{aligned}$$

where k is the dimension of the system,

$$S_1 = \sum_{n=1}^{\infty} \frac{\hat{\delta}_n \hat{\phi}_n(R\sigma)}{\lambda+1+\hat{\lambda}_n^2 \hat{\mu}_1}, \qquad S_2 = \sum_{n=1}^{\infty} \frac{\hat{\delta}_n \hat{\phi}_n(R\sigma)}{\lambda+\hat{b}_2+\hat{\lambda}_n^2 \hat{\mu}_2},$$

$$S_3 = \sum_{n=1}^{\infty} \frac{\hat{\delta}_n \hat{\phi}_n(R\sigma)}{(\lambda+1+\hat{\lambda}_n^2\hat{\mu}_1)(\lambda+\hat{b}_2+\hat{\lambda}_n^2\hat{\mu}_2)}.$$

As in the proof of Theorem 2.3, we must estimate the sums S_i, $i = 1, 2, 3$. To accomplish this we must evaluate $\hat{\delta}_n \hat{\phi}_n(R\sigma)$ for the two- and three-dimensional cases. From the results of the appendix we can write

$$(3.23)\qquad \hat{\delta}_n \hat{\phi}_n(R\sigma) = \frac{2\hat{\beta}_1 R\sigma\pi^2}{(4/[Y_1(\hat{\lambda}_n R)J_0(\hat{\lambda}_n R\sigma) - J_1(\hat{\lambda}_n R)Y_0(\hat{\lambda}_n R\sigma)]^2) - R^2\sigma^2\pi^2(\hat{\beta}_1+\hat{\lambda}_n^2)},$$

for the two-dimensional model in dimensioned variables and

(3.24)

$$\hat{\delta}_n \hat{\phi}_n(R\sigma) = \frac{2\hat{\beta}_1 R\sigma^2(1+\hat{\lambda}_n^2 R^2)}{\begin{aligned}&\hat{\beta}_1^2 R^2\sigma^2[\hat{\lambda}_n^2 R^2(1-\sigma)-\sigma] + \hat{\beta}_1 R\sigma[(2-\sigma)\hat{\lambda}_n^2 R^2 - \sigma]\\ &\qquad + (1-\sigma)\hat{\lambda}_n^2 R^2(1+\sigma+\sigma^2+\hat{\lambda}_n^2 R^2\sigma)\end{aligned}},$$

for the three-dimensional model in dimensioned variables. In a manner similar to our handling of the dimensionless system, we use the asymptotic approximations for the Bessel functions and find $\lambda/\beta_1 \simeq \cot[R\lambda(1-\sigma)]$ becomes the equivalent of (3.13) in the dimensioned form of the eigenvalue equation. From this we can show

$$[J_1(\hat{\lambda}_n R)Y_0(\hat{\lambda}_n R\sigma) - Y_1(\hat{\lambda}_n R)J_0(\hat{\lambda}_n R\sigma)]^2 \simeq \frac{4}{\pi^2\hat{\lambda}_n^2 R^2\sigma}\cos^2[\hat{\lambda}_n R(1-\sigma)].$$

With the approximation for the eigenvalue equation we see that for n sufficiently large, $\cos^2[\hat{\lambda}_n R(1-\sigma)] \simeq \hat{\lambda}_n^2/(\hat{\lambda}_n^2+\hat{\beta}_1^2)$. With this approximation we obtain the following approximate expression for (3.23):

$$(3.25) \qquad \tilde{\delta}_n \hat{\phi}_n(R\sigma) \simeq \frac{2R\hat{\beta}_1}{(\hat{\lambda}_n^2 R^2 + R^2\hat{\beta}_1^2)(1-\sigma)}.$$

Similar to our previous analysis we note that the quantity $R\hat{\lambda}_n(1-\sigma)$ asymptotically approaches $(n-1)\pi$ with $R\hat{\lambda}_n(1-\sigma) > (n-1)\pi$, hence our approximations above depend only on n and not R. With this information it is easy to see that for $n \geqq N$ for some N, (3.25) is an expression which is $\mathcal{O}(R)$ for small R and $\mathcal{O}(1/R)$ for large R. Equation (3.24) is clearly $\mathcal{O}(R)$ for small R and $\mathcal{O}(1/R)$ for large R for $n \geqq 2$. In the two-dimensional model for $2 \leqq n \leqq N$, Lemma 3.1 shows that $|\hat{\delta}_n\hat{\phi}_n(R\sigma)|$ is $\mathcal{O}(R)$ for small R and $\mathcal{O}(1/R)$ for large R.

For large R and $\hat{\beta}_1$ and σ fixed the comment after Lemma 3.1 applies. This implies that $|\hat{\delta}_1\hat{\phi}_1(R\sigma)|$ is $\mathcal{O}(1/R)$ in two dimensions. Similarly, $\hat{\lambda}_1 R$ is bounded away from zero in three dimensions, so (3.24) shows $|\hat{\delta}_1\hat{\phi}_1(R\sigma)|$ is $\mathcal{O}(1/R)$ in three dimensions. With this information we see that in either two or three dimensions $|\hat{\delta}_n\hat{\phi}_n(R\sigma)| \leqq M/R$ for some constant M, $n \geqq 1$.

We return to the estimates of the sums S_i in (3.22). Let $\lambda = \xi + i\eta$, with $\xi > \max\{-1, -\hat{b}_2\}$. For fixed $\hat{\mu}_i$ and with $R\hat{\lambda}_n \geqq (n-1)\pi/(1-\sigma)$, $\hat{\lambda}_n^2\hat{\mu}_i$ is $\mathcal{O}(1/R^2)$. With this information and the bound on $|\hat{\delta}_n\hat{\phi}_n(R\sigma)|$ from above, we can make the following estimate for large R:

$$|S_1| \leqq \sum_{n=1}^{\infty} \frac{M/R}{1+[K^2(n-1)^2/R^2]},$$

for some constants M and K. The integral test is applied to this infinite sum, and we obtain S_1 is $\mathcal{O}(1)$. From the appendix we see that $\hat{\gamma}_1 = \tilde{a}_1 R^{k-1}$ and by assumption $\tilde{a}_3 = \hat{\beta}_1\hat{\mu}_1/R$, which implies $\hat{\gamma}_1$ is $\mathcal{O}(R^{k-2})$. By making an order argument with the terms S_i and $\hat{\gamma}_i$ in (3.22), it is easily seen that as $R \to \infty$, the left-hand side of the equation is $\mathcal{O}(1)$ while the right-hand side of the equation is $\mathcal{O}(1/R)$. Hence, there are no solutions λ with $\text{Re}\,\lambda > \max\{-1, -\hat{b}_2\}$, i.e., the system is locally asymptotically stable. This completes the proof of Theorem 2.4

Proof of Theorem 2.5. We only prove this result for the three-dimensional case to avoid the details necessary to handle the Bessel functions for two dimensions. A comment following the proof provides a heuristic argument for why this result should work in two dimensions as well. As in our previous theorems we must examine $\delta_n\phi_n(\sigma)$. From (3.15) we can readily see that for $n \geq 2$:

$$|\delta_n\phi_n(\sigma)| \leqq \frac{2\beta_1}{(n-1)^2\pi^2}.$$

For $n=1$ we apply a Maclaurin series expansion to (3.4) to obtain

$$\lambda_1^2 = 3\beta_1\sigma^2 + \mathcal{O}(\sigma^3).$$

With this estimate in (3.15) we see that as $\sigma \to 0$, $\delta_1\phi_1(\sigma) \to 1$. These estimates can be used in the infinite sums in (3.11) in a manner similar to our proofs of the previous theorems.

From the appendix we find $\gamma_i = \mu_i\beta_1 k/\sigma$. From the above we have estimates on the infinite sums in (3.19), which is another expression for (3.11). If we divide both sides of (3.19) by $\gamma_1\gamma_2$, then we can easily see that for $\text{Re}(\lambda) > \max\{-1, -b_2\}$ the left-hand side of the resulting equation is $\mathcal{O}(1)$ while the right-hand side is $\mathcal{O}(\sigma)$. Thus, for small σ no solutions exist with $\text{Re}(\lambda) > \max\{-1, -b_2\}$ which satisfy (3.19), so the linearized system (3.10) is stable.

With the parameters μ_i, β_1, and β_1^* fixed in the system of equations, as $\sigma \to 0$, the problem is approaching the singular problem which behaves more like a Neumann problem. This implies that the system of equations is acting like there is one insulated compartment with decay which will be a stable situation. From this heuristic argument one would anticipate the two-dimensional model to behave similarly. The proof was not attempted for the two-dimensional case as the trigonometric approximations to the Bessel functions are not uniform in σ which prevents the use of the approximation (3.14) and Lemma 3.1 which we used in our other proofs.

4. Numerical computation of the bifurcation curves. The numerical computation of the bifurcation curves separating the region where the steady-state solution is stable from that where a periodic solution exists is based on calculating zeros of the characteristic polynomials (2.3) and (3.19). Since we are interested in the three-dimensional model with radial symmetry, the eigenvalues, λ_n, the eigenfunctions, ϕ_n, and the δ_n are given by (3.4), (3.5), and (3.6), respectively. Numerically, the λ_n are computed by using a bisection method to localize them, then a secant method is used to refine their values to the desired accuracy. Once this is done, the sums S_1, S_2, and S_3 in (3.19) can be computed. There remains to compute $f'(\bar{v}_1)$ to complete the calculations of the coefficients of (3.19), where $\bar{v}_1$ is the steady-state value of $\bar{v}_1$. This is done by using a Newton method on a nonlinear equation satisfied by $\bar{v}_1$. The equation satisfied by $\bar{v}_1$ is obtained by an elementary but tedious reduction of the system (1.1) with its time derivatives set equal to zero. Once all of these coefficients have been computed, the critical eigenvalues $\lambda = i\omega$, ω real, which define the bifurcation curve are computed. The method followed is described by Mahaffy [16] and uses a special form of the argument principle.

Numerical results illustrating Theorems 2.4 and 2.5 for large diffusivities (Theorem 2.1), as shown in Figs. 1.2 and 1.3, are discussed in the Introduction and are based on (2.3). In Fig. 4.1, we show the variation of the bifurcation curve with respect to the delay and the diffusion coefficient. It is clear that as the diffusion coefficient tends to infinity, the critical delay approaches the value of the critical delay of the well-mixed model, illustrating Theorem 2.2. Figure 4.1 does not illustrate the result of Theorem 2.3 as clearly, since the value of the diffusion coefficient below which stability occurs regardless of the delay is extremely small; however, the curve does demonstrate the increase in the critical delay as the diffusivity tends to zero.

Finally, in Fig. 4.2 we show the variation of the critical period at the Hopf bifurcation. This period is plotted against the cell diameter (also shown is the critical delay for comparison). Observe that the period varies markedly with the cell diameter. This allows for the possibility that the variation in frequency could play a role in the triggering mechanism.

Appendix. Comparing the parameters. In this section we compare the different parameters for the two-compartment model with diffusion in dimensional and dimensionless form and contrast the parameters in these models with the parameters in the well-mixed two-compartment model. The well-mixed model developed in Mahaffy and Pao [17] is given by the following system of equations:

$$
\begin{aligned}
u_1'(t) &= \tilde{f}(v_{1t}) - \tilde{b}_1 u_1(t) + \tilde{a}_1[u_2(t) - u_1(t)],\\
v_1'(t) &= -\tilde{b}_2 v_1(t) + \tilde{a}_2[v_2(t) - v_1(t)],\\
u_2'(t) &= -\tilde{b}_1 u_2(t) + \tilde{a}_3[u_1(t) - u_2(t)],\\
v_2'(t) &= \tilde{c}_0 u_{2t} - \tilde{b}_2 v_2(t) + \tilde{a}_4[v_1(t) - v_2(t)],
\end{aligned} \tag{A.1}
$$

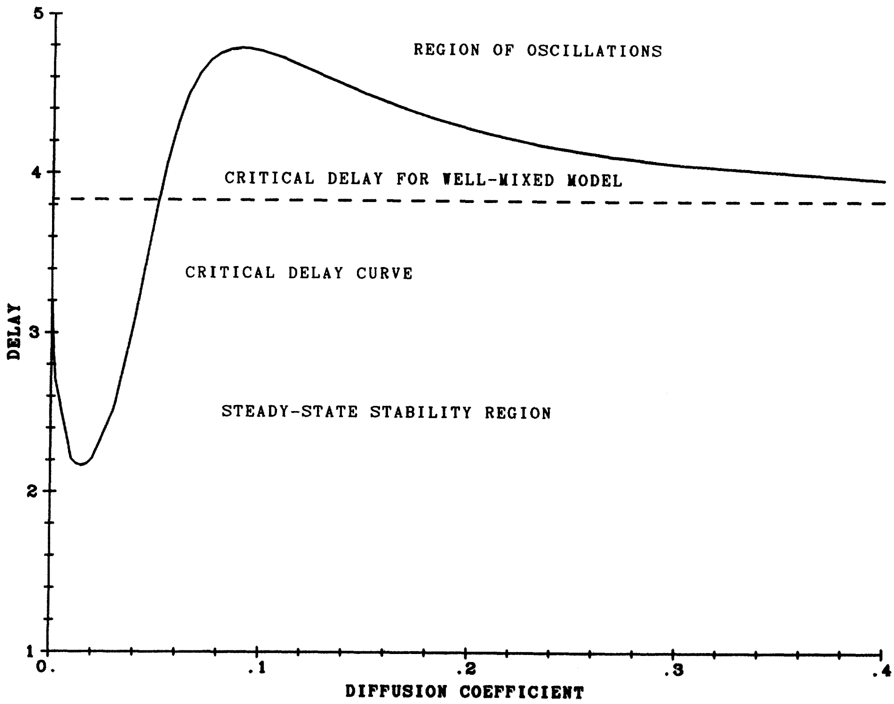

FIG. 4.1. *Dependence of the stability region on the diffusion rate and the delay.*

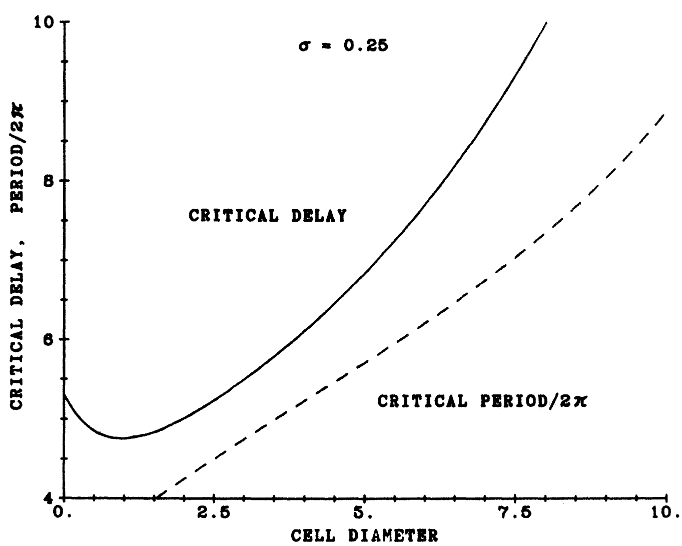

FIG. 4.2. *Variation of the period with the cell diameter at the bifurcation boundary.*

and is shown to have the following characteristic equation:

$$(\lambda+1)(\lambda+\tilde{b}_2)(\lambda+1+\tilde{a}_1+\tilde{a}_3)(\lambda+\tilde{b}_2+\tilde{a}_2+\tilde{a}_4)-\tilde{c}_0\tilde{a}_2\tilde{a}_3\tilde{f}'(\bar{v}_1)\,e^{-\lambda\nu}=0,$$

where we scale so that $\tilde{b}_1=1$ and assume a discrete delay ν as before. For clarity of argument, the parameters for the well-mixed model will all have $\tilde{}$ over them. The dimensional two-compartment model with diffusion will have $\hat{}$ over its parameters, and the dimensionless two-compartment model's parameters will have no special markings. To transform system (1.1) into the dimensionless form (2.1), the dimensionless variables $\tau = t\hat{b}_1$, $a_i = \hat{a}_i R^{k-1}/\hat{b}_1$, $c_0 = \hat{c}_0/\hat{b}_1$, $\mu_i = \hat{\mu}_i/\hat{b}_1 R^2$, $r = x/R$, $\beta_1 = R\hat{\beta}_1$, and $\beta_1^* = R\hat{\beta}_1^*$ are introduced, where $k = 2$ or 3 is the dimension of the system. By integrating around $\partial\omega$ in the symmetric two- and three-dimensional cases, where the inner radius is σR in the dimensioned form of the model, we obtain $\hat{\gamma}_i \equiv 2\pi\sigma R\hat{a}_i$ in two dimensions and $\hat{\gamma}_i \equiv 4\pi\sigma^2 R^2 \hat{a}_i$ in three dimensions. For the dimensionless form of the equation, we obtain $\gamma_i \equiv 2\pi\sigma a_i$ and $\gamma_i \equiv 4\pi\sigma^2 a_i$ in two and three dimensions, respectively. Thus, $\gamma_i = \hat{\gamma}_i/\hat{b}_1$.

Next we must relate the parameters of the well-mixed model to the parameters in the dimensionless two-compartment model. We begin by using a mass balance relationship to relate $\tilde{a}_1$ to $\tilde{a}_3$. A similar argument will relate $\tilde{a}_2$ to $\tilde{a}_4$. Let V_i be the volume of the ith compartment and suppose that $V_1 = \kappa V_2$. We use the system of (A.1) with no reactions and a conversion from concentration to mass to obtain $\kappa\tilde{a}_1 = \tilde{a}_3$. From the volume ratios in two and three dimensions with the inner radius, σR, and the outer radius, R, we obtain $\tilde{a}_3 = \sigma^2\tilde{a}_1/(1-\sigma^2)$ and $\tilde{a}_3 = \sigma^3\tilde{a}_1/(1-\sigma^3)$, respectively. Since the first equation in (A.1) is related to the first equation in (2.1), we have $\tilde{a}_i = \gamma_i = \hat{\gamma}_i/\hat{b}_1$.

Finally, we perform a mass balance across $\partial\omega$ for the dimensioned system (1.1). This implies that the net flux into ω must equal the term $\hat{\gamma}_1[u_2(\sigma, t) - u_1(t)]$. However, the total flux across $\partial\omega$ given by

$$\text{(A.2)}\qquad \begin{aligned}\int_{\partial\omega} \hat{\mu}_1 \frac{\partial u_2}{\partial r}\, dS &= \hat{\mu}_1\hat{\beta}_1 \int_{\partial\omega} [u_2 - u_1]\, dS \\ &= 2(k-1)\pi(\sigma R)^{k-1}\hat{\mu}_1\hat{\beta}_1[u_2(\sigma, t) - u_1(t)],\end{aligned}$$

where $k = 2$ or 3 depending on the dimension. To make (A.2) into a change in concentration we must divide by the volume of ω, which is $2(k-1)\pi(\sigma R)^k/k$. It is easily seen that $\hat{\gamma}_1 = \hat{\mu}_1\hat{\beta}_1 k/\sigma R$.

Analysis for small R and σ. In § 3 we needed to show that for small R and σ, $\hat{\delta}_n\hat{\phi}_n(R\sigma)$ tended to one for $n = 1$ and was $\mathcal{O}(R\sigma)$ for $n > 1$. Here, $\hat{\delta}_n = \int_{\sigma R}^{R} \hat{\phi}_n(r) q(r)\, dr$ with $q(r) = r^{k-1}$ where $k = 2$ or 3 depending on the dimension. To show this result we must use the formulae for $\hat{\delta}_n\hat{\phi}_n(R\sigma)$ and the equations for finding the eigenvalues. For convenience we drop the $\hat{}$ notation and use λ for λ_n. With these conventions we have the eigenvalue equation in three dimensions given by

$$\cot \lambda R(1-\sigma) = \frac{\lambda^2 R^2 \sigma + 1 + \beta_1 R\sigma}{\lambda R[(1-\sigma) + \beta_1 R\sigma]},$$

and

$$\delta_n\phi_n(R\sigma) = \frac{2\beta_1[\lambda R \cos \lambda R(1-\sigma) - \sin \lambda R(1-\sigma)]^2}{\lambda[(\lambda^2 R^2 + 1)\lambda R(1-\sigma) - 2\lambda R \sin^2 \lambda R(1-\sigma) + (\lambda^2 R^2 - 1) \sin \lambda R(1-\sigma) \cos \lambda R(1-\sigma)]}.$$

The eigenvalue equation allows us to express $\delta_n\phi_n(R\sigma)$ without any trigonometric functions. After some algebraic manipulations we can obtain the following expression for $\delta_n\phi_n(R\sigma)$:

$$\delta_n\phi_n(R\sigma) = \frac{2\beta_1 R\sigma^2(1+\lambda^2 R^2)}{(1-\sigma)\lambda^2 R^2(1+\sigma+\sigma^2+\lambda^2 R^2\sigma^2) + \beta_1 R\sigma[\lambda^2 R^2(2-\sigma) - \sigma] + \beta_1^2 R^2\sigma^2[\lambda^2 R^2(1-\sigma) - \sigma]}.$$

For $n > 1$, $\lambda_n R(1-\sigma) > (n-1)\pi$, so the above expression is easily seen to be $\mathcal{O}(R)$ for σ fixed and $R \to 0$ and is $\mathcal{O}(\sigma^2)$ for R fixed and $\sigma \to 0$. For $n = 1$, $\lambda_1 R(1-\sigma)$ is small for both R and σ small. We use the Maclaurin series expansions for sine and cosine in the eigenvalue equation and obtain

$$(\lambda^2 R^2 + 1)\left[\lambda R(1-\sigma) - \frac{\lambda^3 R^3 (1-\sigma)^3}{6} + \mathcal{O}(z^5)\right] - \lambda R(1-\sigma)\left[1 - \frac{\lambda^2 R^2 (1-\sigma)^2}{2} + \mathcal{O}(z^4)\right]$$
$$= \beta_1 R\sigma\{\lambda R[1 - \mathcal{O}(z^2)] - [\lambda R(1-\sigma) - \mathcal{O}(z^3)]\}.$$

where $z = \lambda R$. This expression can be reduced to the expression

$$\lambda^2 R^2 (1-\sigma^3) = 3\beta_1 R\sigma^2[1 - \mathcal{O}(z^2)]. \tag{A.3}$$

In the denominator of the expression for $\delta_1\phi_1(R\sigma)$, we observe that $\lambda^2 R^2(1-\sigma^3) - \beta_1 R\sigma^2$ is the dominant term for small R and σ. With (A.3) this expression can be written as $2\beta_1 R\sigma^2[1-\mathcal{O}(z^2)]$. In the limit as $R \to 0$, $\lambda_1 R \to 0$ and it is easily observed from the above information that $\delta_1\phi_1(R\sigma) \to 1$. Also, as $\sigma \to 0$, again $\lambda_1 R \to 0$ and it follows that $\delta_1\phi_1(R\sigma) \to 1$.

The arguments are similar for two dimensions. The eigenvalue equation in this case is given by

$$\lambda[J_1(\lambda R) Y_1(\lambda R\sigma) - J_1(\lambda R\sigma) Y_1(\lambda R)] = \beta_1[J_0(\lambda R\sigma) Y_1(\lambda R) - J_1(\lambda R) Y_0(\lambda R\sigma)].$$

It can be shown that

$$\delta_n\phi_n(R\sigma) = \frac{2\pi^2 R\beta_1\sigma[Y_1(\lambda R)J_0(\lambda R\sigma) - J_1(\lambda R)Y_0(\lambda R\sigma)]^2}{4 - R^2\sigma^2\pi^2(\beta_1^2 + \lambda^2)[Y_1(\lambda R)J_0(\lambda R\sigma) - J_1(\lambda R)Y_0(\lambda R\sigma)]^2}.$$

We examine the case when $n = 1$, so $\lambda_1 R$ is small and we can apply the asymptotic limits $J_0(z) = 1 + \mathcal{O}(z^2)$, $J_1(z) = z/2 + \mathcal{O}(z^3)$, $Y_0(z) = (2/\pi)\ln(z/2) + \mathcal{O}(z^2 \ln(z))$, and $Y_1 = -2/\pi z + \mathcal{O}(z)$. Using this information in the eigenvalue equation, we find that

$$\lambda_1^2 R^2(1-\sigma^2) + \mathcal{O}(z^3) = 2\beta_1\sigma[1 + \mathcal{O}(z^2 \ln z)],$$

where $z = \lambda_1 R$. Using these same asymptotic limits, we find that

$$\delta_1\phi_1(R\sigma) = \frac{2\pi^2 R\beta_1\sigma[(2/\pi\lambda R) + \mathcal{O}(z)]^2}{4 - R^2\sigma^2\pi^2(\beta_1^2 + \lambda^2)[(2/\pi\lambda R) + \mathcal{O}(z)]^2}$$
$$= \frac{2R\beta_1\sigma[1 + \mathcal{O}(z^2)]}{\lambda^2 R^2(1-\sigma^2) - R^2\sigma^2\beta_1^2}.$$

It is clear from the information on the eigenvalue equation that in the limit for either small R or σ, $\delta_1\phi_1(R\sigma) \to 1$.

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