

STABILITY RESULTS FOR A MODEL OF REPRESSION WITH EXTERNAL CONTROL

By

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Abstract. A stability analysis is performed for a mathematical model with negative feedback, diffusion, and time delays. The model of a cell includes three biochemical species that interact to control the transport of an extracellular nutrient. This study examines the effects of diffusion, cell size, and extracellular nutrient concentration on the model. With certain assumptions the symmetry, a linearized version of the model is studied in detail. The characteristic equation is shown to have no solutions with positive real part when extracellular nutrient concentration or the diffusivities are sufficiently small or the radius of the cell is sufficiently large. These results are compared to an earlier study that showed that biochemical oscillations could occur for certain parameter values. A discussion is provided for how the bifurcations from regions of stability to regions of instability could affect the biological response of the cell.

1. Introduction. For survival a cell must extract essential nutrients from its external environment. The cell uses an active transport mechanism to raise its intracellular concentration of certain nutrients. The cell invests a great deal of energy to produce the enzymes required to transport important nutrients, so many of these transport systems are regulated by repressing the expression of the gene, a negative feedback system. An example of this type of regulatory system can be found in the uptake of iron (Fe^{+++}) by bacteria [5,10,11]. This work examines the stability of a mathematical model that includes repression as a control for a protein mediated transport across a cell membrane of some substance, possibly a critical nutrient for the cell. A two compartment model is formed for three interacting biochemical species. The mathematical model is composed of reaction diffusion equations and includes time

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delays for the processes of transcription and translation. The dynamics of the reacting biochemical species in the first compartment are governed by differential equations that have no spatial dependence. The second compartment represents the cytoplasm of the cell in which reactions and diffusion are considered. For a discussion of the biological details and development of the model see Mahaffy, Jorgensen, and Vanderheyden [8].

The three biochemical species examined are mRNA (u_i), permease (v_2), and the repressor nutrient (w_i). The subscripts, $i = 1, 2$, denote the two compartments in the mathematical model. The mRNA is formed in the first compartment and diffuses throughout the cytoplasm where it is translated to form the permease. The permease is restricted to the second compartment. The permease is necessary for transport of the nutrient across the cell wall. The nutrient comes from an external source, diffuses freely in the cell, and acts as a repressor or inactivates a gene activator for the production of its permease.

The development of the model is similar to a simpler repression model of Mahaffy and Pao [9]. The cell is assumed to be spherical with a radius, R , and with an inner radius, σR , for the first compartment. With this symmetry assumption, the model is given by the following system of equations:

$$\begin{aligned} \dot{u}_1(t) &= f(w_1(t-T)) - u_1(t) + \gamma_1[u_2(R\sigma, t) - u_1(t)], \\ \dot{w}_1(t) &= -\hat{b}_3 w_1(t) + \gamma_3[w_2(R\sigma, t) - w_1(t)], \\ \frac{\partial u_2}{\partial t} &= D_1 \nabla^2 u_2 - u_2, \\ \frac{\partial v_2}{\partial t} &= D_2 \nabla^2 v_2 - b_2 v_2 + c_0 u_2, \\ \frac{\partial w_2}{\partial t} &= D_3 \nabla^2 w_2 - b_3 w_2, \end{aligned} \tag{1.1}$$

for $t > 0$ and $R\sigma < r < R$ and with the boundary conditions:

$$\begin{aligned} \frac{\partial u_2(R\sigma, t)}{\partial r} &= \beta_1[u_2(R\sigma, t) - u_1(t)], & \frac{\partial u_2(R, t)}{\partial r} &= 0, \\ \frac{\partial v_2(R\sigma, t)}{\partial r} &= 0, & \frac{\partial v_2(R, t)}{\partial r} &= 0, \\ \frac{\partial w_2(R\sigma, t)}{\partial r} &= \beta_3[w_2(R\sigma, t) - w_1(t)], & \frac{\partial w_2(R, t)}{\partial r} &= k v_2(R, t), \end{aligned}$$

where $\nabla^2 = \frac{1}{r^2} \frac{\partial}{\partial r} \left(r^2 \frac{\partial}{\partial r} \right)$ and $f(w_1)$ is a positive decreasing function of w_1 reflecting the negative feedback of repression. The kinetic constants b_i are decay rates and γ_i are transfer rates. The D_i are coefficients of diffusivity and β_i related to the transfer across compartmental boundaries. The constant k is a parameter depending on the rate of transfer across the exterior membrane and the extracellular concentration of the nutrient. The delay, T , represents the time required for some biochemical

processes, such as transcription and translation. The constant c_0 represents the rate of translation of the mRNA to produce the permease.

Stability results are demonstrated for a cell with a large radius or one with very small diffusivities. Physically, one would expect that if the radius of the cell is too large, then the decay of the biochemical species would dominate the behavior of the system and lead to stability of the system. Similarly, if the diffusivity constants are too small, then the slow diffusion of the biochemical species would be equivalent to increased cell size, which again results in stability. The analysis of the mathematical model parallels the work on a related model by Busenberg and Mahaffy [1,2].

Of particular interest is a result that demonstrates that there is a region of stability for k sufficiently small. Since k depends on the external concentration of the nutrient and since it was shown that there are parameter values where (1.1) is locally unstable [8], it follows that for certain parameter values as the concentration of the external nutrient increases (k increases), (1.1) has a Hopf bifurcation from a region of stability for a low nutrient concentration to a region of instability. If the nutrient is a morphogen then this instability could represent a trigger for the cell to change its behavior, i.e., undergo morphogenesis.

The proofs of the theorems rely on a technique of reducing the system of partial differential equations with delays to an equivalent system of delay differential equations and Volterra equations that depend only on the state variables at the boundary. The method uses the variation of parameters formula with the semigroup operator coming from the linear part of the partial differential equations after the change of variables that makes the boundary conditions homogeneous. The resulting system has its spatial component occurring only in an exponentially damped term depending on the initial conditions. Next a related system is formed by linearizing the previous system and examining the limiting Volterra equations. The stability of this linear system is studied by analysis of its characteristic equation.

In the next section the main results are stated, and the background material is presented for stability analysis of the model. This includes some notation necessary for the understanding and development of the characteristic equation. Section 3 gives the details of the proofs of the theorems. The last section provides a discussion of the work performed on this model.

2. Main results and background information. The main results presented here demonstrate conditions on certain parameters in system (1.1) that result in asymptotic stability of the system. To show these results there are several conditions that are used in the proofs of the theorems. The nonlinear negative feedback function f can be shown via biochemical kinetics to satisfy the hypothesis below.

(H1) Hypothesis. Assume the function f representing the negative feedback of repression has the form $f(w) = 1/(1 + kw^\rho)$, where K is a kinetic constant and $\rho > 1$ is the Hill coefficient.

In fact, the proofs of the theorems only require that f is negative, decreasing, continuously differentiable with $f'(0) = 0$.

Another assumption in the mathematical model is that the rate of transfer across the boundary of the first compartment per unit area is a constant times the gradient

of the concentration of the biochemical species. Creating a model where the second compartment is also well mixed, we find that the active transfer of nutrient across the outer membrane per unit area is proportional to the concentration of the permease v_2 in the second compartment. Let κ be this constant of proportionality with κ depending on the external nutrient concentration, which is assumed to be constant. From the mass balance relations for the cell as detailed in [8], we find that

$$\gamma_1 = \frac{3D_1\beta_1}{R\sigma}, \quad \gamma_3 = \frac{3D_3\beta_3}{R\sigma}, \quad \text{and} \quad \kappa = \frac{3D_3k}{R(1-\sigma^3)}, \quad (2.1)$$

where γ_1 and γ_3 are fixed transfer rates across the boundary in the well-mixed first compartment. From the divergence theorem, we see that our assumption implies that $\beta_1 D_1$, $\beta_3 D_3$, and $k D_3$ are fixed constants.

The first theorem examines the case when the diffusivities, D_i , in the model become small. In order to compare this model to a corresponding well-mixed model, (2.1) show that the transfer rates β_1 , β_3 , and k must become proportionately larger as diffusivities decrease. With this information the following stability result supports the intuitive concept that the restricted motion of the biochemical species allow decay rates to dominate reaction rates.

THEOREM 2.1. Assume (H1), suppose that $\beta_1 D_1$, $\beta_3 D_3$, and $k D_3$ have fixed finite values, and suppose that the diffusivities D_i , $i = 1, 2, 3$, tend to zero. Then there exists a $d > 0$ such that if $0 < D_i < d$, all solutions λ that satisfy the characteristic equation of the model (1.1) satisfy $\text{Re}(\lambda) < -\varepsilon < 0$.

The second stability result examines (1.1) for an increasing radius, R . The increased distance for diffusion of biochemical species does not allow oscillatory behavior as in the previous theorem.

THEOREM 2.2. Assume (H1), suppose that the transfer rates between compartments remain fixed, and suppose that the radius of the cell, R , increases. Then there exists a constant $M > 0$ such that if $R > M$, all solutions λ that satisfy the characteristic equation of the model (1.1) satisfy $\text{Re}(\lambda) < -\varepsilon < 0$.

The last result for (1.1) shows that as k decreases with all other parameter values fixed there is a region of local stability. This result demonstrates that if the nutrient concentration is sufficiently small, then (1.1) does not have oscillatory solutions.

THEOREM 2.3. Assume (H1) and suppose that the parameter k , which reflects the rate of transfer across the exterior membrane and the extracellular concentration of the nutrient, decreases while all other parameters in (1.1) are fixed. Then there exists a constant $k_0 > 0$ such that if $0 < k < k_0$, all solutions λ that satisfy the characteristic equation of the model (1.1) satisfy $\text{Re}(\lambda) < -\varepsilon < 0$.

The first step in proving these theorems is to make a change of variables that transforms (1.1) to an equivalent system of equations with the equilibrium solution translated to the origin and homogeneous boundary conditions. If we let variables with an s superscript represent the unique steady state solution of (1.1), then the

following change of variables is used:

$$\begin{aligned}
 U_1(t) &= u_1(t) - u_1^s, \\
 W_1(t) &= w_1(t) - w_1^s, \\
 U_2(r, t) &= u_2(r, t) - u_2^s(r) - U_1(t), \\
 V_2(r, t) &= v_2(r, t) - v_2^s(r), \\
 W_2(r, t) &= w_2(r, t) - w_2^s(r) - W_1(t) - kh(r)V_2(R, t),
 \end{aligned}$$

where h must satisfy $h'(R\sigma) = \beta_3 h(R\sigma)$ and $h'(R) = 1$ to make the last two boundary conditions homogeneous. The resulting mathematical model can be written as follows:

$$\begin{aligned}
 \dot{U}_1(t) &= \tilde{f}(W_1(t - T)) - U_1(t) + \gamma_1 U_2(R\sigma, t), \\
 \dot{W}_1(t) &= -\hat{b}_3 W_1(t) + \gamma_3 W_2(R\sigma, t), \\
 \frac{\partial U_2}{\partial t} &= D_1 \nabla^2 U_2 - U_2 - \tilde{f}(W_1(t - T)) - \gamma_1 U_2(R\sigma, t), \\
 \frac{\partial V_2}{\partial t} &= D_2 \nabla^2 V_2 - b_2 V_2 + c_0(U_2 + U_1(t)), \\
 \frac{\partial W_2}{\partial t} &= D_3 \nabla^2 W_2 - b_3 W_2 + (\hat{b}_3 - b_3)W_1 - \gamma_3 W_2(R\sigma, t) \\
 &\quad + k \left[\left[\left(\frac{D_3}{r^2} \right) \frac{d}{dr} \left(r^2 \frac{dh}{dr} \right) - b_3 h \right] V_2(R, t) - h \dot{V}_2(r, t) \right],
 \end{aligned} \tag{2.2}$$

for $t > 0$ and $R\sigma < r < R$ and with the boundary conditions:

$$\begin{aligned}
 \frac{\partial U_2(R\sigma, t)}{\partial r} &= \beta_1 U_2(R\sigma, t), & \frac{\partial U_2(R, t)}{\partial r} &= 0, \\
 \frac{\partial V_2(R\sigma, t)}{\partial r} &= 0, & \frac{\partial V_2(R, t)}{\partial r} &= 0, \\
 \frac{\partial W_2(R\sigma, t)}{\partial r} &= \beta_3 W_2(R\sigma, t), & \frac{\partial W_2(R, t)}{\partial r} &= 0,
 \end{aligned}$$

where $\tilde{f}(W_1) = f(W_1 + w_1^s) + \gamma_1 u_2^s(R\sigma) - (\gamma_1 + 1)u_1^s$ and $h(r) = (r - R\sigma)^2 / (2R(1 - \sigma))$.

The next step is the reduction of the system of equations (2.2) by the method of variation of parameters to a system of delay differential equations with linear Volterra equations that depend only on the state variables at the boundary. The spatial component occurs only in an exponentially damped term depending on the initial conditions. Subsequently, this system is linearized about the zero solution, and the limiting linear Volterra equations are formed. Standard techniques are applied to this system to find the characteristic equation. The characteristic equation is analyzed to determine local stability properties of the mathematical model. This technique is developed in [1,2] and used on this particular model in [8].

Before the system of delay differential equations and limiting Volterra equations is presented with its characteristic equation as formulated in [8], several quantities must be defined that are used in the proofs of the theorems. From the homogeneous parts of the partial differential equations for U_2 , V_2 , and W_2 in (2.2) along with their boundary conditions, separation of variables is used to find the eigenvalue and eigenfunction equations. This leads to the eigenvalue equations:

$$\cot[\mu(1 - \sigma)] = \frac{\mu^2 \sigma + 1 + \beta_1 R \sigma}{\mu[(1 - \sigma) + \beta_1 R \sigma]}, \tag{2.3}$$

$$\cot[\nu(1 - \sigma)] = \frac{\nu^2 \sigma + 1}{\nu(1 - \sigma)}, \tag{2.4}$$

$$\cot[\omega(1 - \sigma)] = \frac{\omega^2 \sigma + 1 + \beta_3 R \sigma}{\omega[(1 - \sigma) + \beta_3 R \sigma]}, \tag{2.5}$$

for U_2 , V_2 , and W_2 , respectively, and their corresponding normalized eigenfunctions $\phi_n(r)$, $\psi_n(r)$, and $\xi_n(R)$.

For notational convenience the following quantities are defined:

$$\delta_n^u = \langle 1, \phi_n \rangle = \int_{R\sigma}^R 1 \cdot \phi_n(r) r^2 dr, \quad \delta_n^w = \langle 1, \xi_n \rangle,$$

$$A_n \equiv 1 + \frac{\mu_n^2 D_1}{R^2}, \quad B_n \equiv b_2 + \frac{\nu_n^2 D_2}{R^2}, \quad \text{and} \quad C_n \equiv b_3 + \frac{\omega_n^2 D_3}{R^2}.$$

Direct calculations show that

$$\delta_n^u \phi_n(R\sigma) = \frac{2\beta_1 R \sigma^2 (1 + \mu_n^2)}{G_{\text{nor}}(\mu_n, \beta_1)}, \tag{2.6}$$

and

$$\delta_n^w \xi_n(R\sigma) = \frac{2\beta_3 R \sigma^2 (1 + \omega_n^2)}{G_{\text{nor}}(\omega_n, \beta_3)}, \tag{2.7}$$

where the factor in the denominator that results from normalization of the eigenfunction is given by

$$G_{\text{nor}}(\chi, \beta) = (1 - \sigma)\chi^2(1 + \sigma + \sigma^2 + \chi^2\sigma^2) + \beta R \sigma(\chi^2(2 - \sigma) - \sigma) + \beta^2 R^2 \sigma^2(\chi^2(1 - \sigma) - \sigma).$$

The system of linearized delay differential equations and limiting Volterra equations is found from the system of differential equations (2.2) in accordance with the

procedure shown in [8] and is given by the following:

$$\begin{aligned} \dot{U}_1(t) &= f'(w_1^s)W_1(t - T) - U_1(t) + \gamma_1 U_2(R\sigma, t), \\ \dot{W}_1(t) &= -\hat{b}_3 W_1(t) + \gamma_3 W_2(R\sigma, t), \\ U_2(R\sigma, t) &= - \int_0^\infty K^u(t - s, R\sigma)[f'(w_1^s)W_1(s - T) + \gamma_1 U_2(R\sigma, s)] ds, \\ V_2(R, t) &= c_0 \int_0^\infty e^{-b_2(t-s)} U_1(s) ds + c_0 \int_0^\infty \sum_{n=0}^\infty e^{-B_n(t-s)} \psi_n(R) \\ &\quad \times \left[\int_0^s \sum_{m=1}^\infty \delta_m^u e^{-A_m(s-\tau)} \left[f'(w_1^s)W_1(\tau - T) + \gamma_1 U_2(R\sigma, \tau) \right] \right. \\ &\quad \left. \times \langle \phi_m, \psi_n \rangle d\tau \right] ds, \end{aligned} \tag{2.8}$$

$$\begin{aligned} W_2(R\sigma, t) &= \int_0^\infty K^w(t - s, R\sigma)[(\hat{b}_3 - b_3)W_1(s) - \gamma_3 W_2(R\sigma, s)] ds \\ &\quad + k \int_0^\infty \sum_{n=1}^\infty \langle [D_3 \nabla^2 h - b_3 h], \xi_n \rangle \xi_n(R\sigma) e^{-C_n(t-s)} V_2(R, s) ds \\ &\quad - k \int_0^\infty \sum_{n=1}^\infty \langle h, \xi_n \rangle \xi_n(R\sigma) e^{-C_n(t-s)} \dot{V}_2(R, s) ds, \end{aligned}$$

where $K^u(s, r) = \sum_{n=1}^\infty \delta_n^u(r) e^{-A_n(s)}$ and $K^w(s, r) = \sum_{n=1}^\infty \delta_n^w \xi_n(r) e^{-C_n s}$.

Using standard techniques, Mahaffy, Jorgensen, and Vanderheyden [8] show that the characteristic equation for (2.8) is given by

$$P(\lambda) - Q(\lambda)e^{-\lambda T} = 0, \tag{2.9}$$

with

$$P(\lambda) = (\lambda + 1)(\lambda + b_2)(1 + \gamma_1 I_1)(\lambda + \hat{b}_3 + (\lambda + \hat{b}_3)\gamma_3 I_3) \tag{2.10}$$

and

$$Q(\lambda) = k\gamma_3 c_0 f'(w_1^s) I_4 [1 - (\lambda + 1)(\lambda + b_2) I_2], \tag{2.11}$$

where the integrals $I_j, j = 1, \dots, 4$ are appropriately defined below. To determine the stability of the system it suffices to consider the eigenvalues λ with $\text{Re}(\lambda) > \max\{-1, -b_2, -b_3\}$. With this restriction, the Lebesgue dominated convergence theorem can be applied to the integrals below and the order of integration and

summation can be interchanged to yield the following:

$$\begin{aligned}
 I_1 &= \int_0^\infty \sum_{n=1}^\infty \delta_n^u \phi(R\sigma) e^{-(\lambda+A_n)s} ds = \sum_{n=1}^\infty \frac{\delta_n^u \phi_n(R\sigma)}{\lambda + A_n} \\
 I_2 &= \int_0^\infty \sum_{n=0}^\infty e^{-(\lambda+B_n)s} \psi_n(R) \left[\int_0^s \sum_{m=1}^\infty \delta_m^u m e^{-(\lambda+A_m)\tau} \langle \phi_m, \psi_n \rangle d\tau \right] ds \\
 &= \sum_{n=0}^\infty \sum_{m=1}^\infty \frac{\delta_m^u \psi_n(R) \langle \phi_m, \psi_n \rangle}{(\lambda + A_m)(\lambda + B_n)}, \\
 I_3 &= \int_0^\infty \sum_{n=1}^\infty \delta_n^w \xi_n(R\sigma) e^{-(\lambda+C_n)s} ds = \sum_{n=1}^\infty \frac{\delta_n^w \xi_n(R\sigma)}{\lambda + C_n}, \\
 I_4 &= \int_0^\infty \sum_{n=1}^\infty [D_3 \nabla^2 h - b_3 h], \xi_n \xi_n(R\sigma) e^{-(\lambda+C_n)s} ds \\
 &\quad - \int_0^\infty \sum_{n=1}^\infty \langle h, \xi_n \rangle \xi_n(R\sigma) \lambda e^{-(\lambda+C_n)s} ds \\
 &= \sum_{n=1}^\infty \frac{\xi_n(R\sigma)}{\lambda + C_n} \left[\langle D_3 \nabla^2 h, \xi_n \rangle - (\lambda + b_3) \langle h, \xi_n(r) \rangle \right].
 \end{aligned}$$

It is the careful analysis of (2.9) that demonstrates the conclusions of the theorems.

3. Proofs of the theorems. In this section the details are given for analysis of the characteristic equation for (2.8). The technique follows similar stability results given by Busenberg and Mahaffy [2]. The stability results are established by showing that if $\text{Re}(\lambda) > -\varepsilon$, where $\varepsilon = \frac{1}{2} \min\{1, b_2, b_3\}$, then (2.9) has no solutions. This is accomplished by showing that under the hypotheses of the theorems, $|P(\lambda)|$ is bounded away from zero, while $|Q(\lambda)| \rightarrow 0$.

LEMMA 3.1. Suppose that $\beta_1 D_1$ and $\beta_3 D_3$ have fixed finite values. If the diffusivities $D_i \rightarrow 0$, $i = 1, 3$, and $\text{Re}(\lambda) > -\varepsilon$, then $|P(\lambda)|$ is bounded away from zero. Similarly, if the radius $R \rightarrow \infty$, while the transfer rates between compartments remain fixed, and if $\text{Re}(\lambda) > -\varepsilon$, then $|P(\lambda)|$ is bounded away from zero.

Proof. To demonstrate this result we examine (2.10) more closely. For $\text{Re}(\lambda) > -\varepsilon$, the formulae for I_1 and I_3 following (2.9) can be applied to give

$$\begin{aligned}
 P(\lambda) &= (\lambda + 1)(\lambda + b_2) \left(1 + \gamma_1 \sum_{n=1}^\infty \frac{\delta_n^u \phi_n(R\sigma)}{\lambda + A_n} \right) \\
 &\quad \times \left(\lambda + \hat{b}_3 + (\lambda + b_3) \gamma_3 \sum_{n=1}^\infty \frac{\delta_n^w \xi_n(R\sigma)}{\lambda + C_n} \right) \\
 &= (\lambda + 1)(\lambda + b_2)(1 + \gamma_1 S_1)(\lambda + \hat{b}_3 + (\lambda + b_3) \gamma_3 S_2).
 \end{aligned} \tag{3.1}$$

Since S_1 is analogous to S_2 , it suffices to show that $S_1 \rightarrow 0$ as $D_1 \rightarrow 0$ or $R \rightarrow \infty$. Note that the relations in (2.1) show that as $D_1, D_3 \rightarrow 0$, the parameters $\beta_1, \beta_3 \rightarrow \infty$. The proof closely parallels the work of Busenberg and Mahaffy [2].

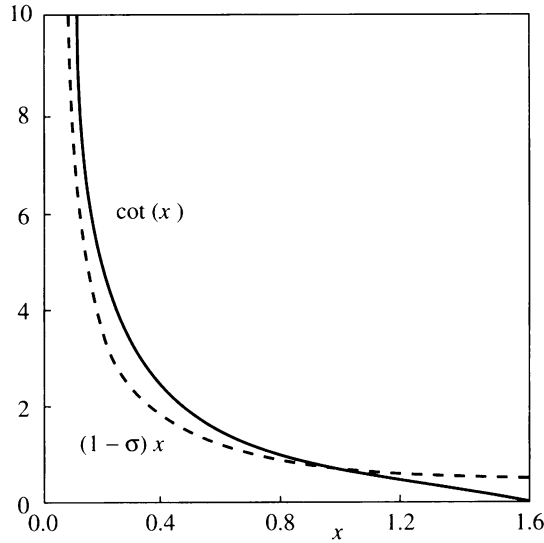


FIG. 3.1. Graphs of $\cot x$ and $(1 - \sigma)/x$ show how the curves intersect for the first eigenvalue $\mu_1 = x/(1 - \sigma)$. In this figure, $\sigma = 0.3$.

The next step in the proof of the lemma is the analysis of $\delta_1^u \phi_1(R\sigma)$ using (2.3) and (2.6). For either $\beta_1 \rightarrow \infty$ or $R \rightarrow \infty$, we find $\cot[\mu_1(1 - \sigma)] \simeq 1/\mu_1$. Let $x = \mu_1(1 - \sigma)$ and consider $\cot x = (1 - \sigma)/x$. For $\sigma \geq 1 - \frac{\pi}{4}$, it is clear that the graphs $\cot x$ and $(1 - \sigma)/x$ intersect with $\frac{\pi}{4} \leq x < \frac{\pi}{2}$. (See Fig. 3.1.) Thus,

$$\mu_1^2(1 - \sigma) - \sigma \geq \frac{\pi^2 - 16\sigma(1 - \sigma)}{16(1 - \sigma)} > \frac{\pi^2 - 4}{16(1 - \sigma)} > 0,$$

which is a bounded, positive value for fixed $1 - \frac{\pi}{4} \leq \sigma < 1$. This argument can be extended to smaller values of σ with some work.

To show a similar result for σ small, $\sigma > 0$, we examine the Laurent series for $\cot x$:

$$\cot x = \frac{1}{x} - \frac{x}{3} - \frac{x^3}{45} - \dots, \quad 0 < |x| < \pi.$$

Thus, $\cot x \simeq (3 - x^2)/(3x)$ for small x . This implies that

$$\cot x \simeq \frac{3 - x^2}{3x} \simeq \frac{1 - \sigma}{x}$$

or $\mu_1(1 - \sigma) = x \simeq \sqrt{3\sigma}$, which is readily borne out by numerical calculations. Thus,

$$\mu_1^2(1 - \sigma) - \sigma \simeq \frac{3\sigma}{1 - \sigma} - \sigma > 0$$

is again a bounded positive number for fixed σ .

To obtain a bound on $\delta_1^u \phi_1(R\sigma)$, we omit the terms in the denominator ($G_{\text{nor}}(\mu_1, \beta_1)$) that have powers of β_1 or R less than two. Combining this information with the previous results, we see that for $0 < \sigma < 1$ fixed there exists a

constant $M(1) > 0$, such that for β_1 or R sufficiently large

$$\delta_1^u \phi_1(R\sigma) < \frac{2\beta_1 R \sigma^2 (1 + \mu_1^2)}{\beta_1^2 R^2 \sigma^2 [\mu_1^2 (1 - \sigma) - \sigma]} \leq \frac{M(1)}{\beta_1 R}.$$

For $n \geq 2$, $\delta_n^u \phi_n(R\sigma)$ can be bounded using (2.6) with the fact that $(n - 1)\pi < \mu_n(1 - \sigma) < n\pi$. From (2.6),

$$\delta_n^u \phi_n(R\sigma) < \frac{2(1 + \mu_n^2)}{\beta_1 R [\mu_n^2 (1 - \sigma) - \sigma]} < \frac{2(1 + n^2 \pi^2 / (1 - \sigma)^2)(1 - \sigma)}{\beta_1 R [(n - 1)^2 \pi^2 - \sigma(1 - \sigma)]} \equiv \frac{M(n)}{\beta_1 R}.$$

An easy calculation shows that $M'(n) < 0$ for $n \geq 2$, which implies that

$$\delta_n^u \phi_n(R\sigma) < \frac{M(2)}{\beta_1 R},$$

with

$$M(2) = \frac{2[(1 - \sigma)^2 + 4\pi^2]}{\beta_1 R (1 - \sigma) [\pi^2 - \sigma(1 - \sigma)]}.$$

Next we consider the denominator of the term in the infinite sum.

$$|\lambda + A_n| = \left| \lambda + 1 + \frac{\mu_n^2 D_1}{R^2} \right| \geq \left| \operatorname{Re}(\lambda) + 1 + \frac{(n - 1)^2 \pi^2 \gamma_1 R \sigma}{3\beta_1 R^2 (1 - \sigma)^2} \right|,$$

as $\mu_n(1 - \sigma) \geq (n - 1)\pi$ and $D_1 = \gamma R \sigma / (3\beta_1)$. If we let

$$C^2 = \frac{\gamma_1 \pi^2 \sigma}{(\operatorname{Re}(\lambda) + 1) 3(1 - \sigma)^2}$$

and $M = \max\{M(1), M(2)\}$, then from (3.1) we have

$$|S_1| \leq \left| \frac{M}{(\operatorname{Re}(\lambda) + 1)\beta_1 R} \sum_{n=1}^{\infty} \frac{1}{1 + C^2(n - 1)^2 / (\beta_1 R)} \right|.$$

Make the change of variables $\tan \theta = C(n - 1) / \sqrt{\beta_1 R}$ and apply the integral test to the infinite sum. Then

$$\left| \sum_{n=1}^{\infty} \frac{1}{1 + C^2(n - 1)^2 / (\beta_1 R)} \right| \leq \frac{\sqrt{\beta_1 R}}{C} \int_0^{\frac{\pi}{2}} \frac{\sec^2 \theta d\theta}{1 + \tan^2 \theta} = \frac{\pi \sqrt{\beta_1 R}}{2C}.$$

This implies that

$$\gamma_1 |S_1| \leq \frac{\gamma_1 M \pi}{2 |\operatorname{Re}(\lambda) + 1| C \sqrt{\beta_1 R}}.$$

Since $\gamma_1 = 3D_1 / (R\sigma)$ with $D_1 \beta_1$ finite, it follows that $\gamma_1 |S_1| = O(1/\sqrt{\beta_1})$ for low diffusivities and $\gamma_1 |S_1| = O(1/R)$ for large R . Thus, $\gamma_1 |S_1| \rightarrow 0$ as either $D_1 \rightarrow 0$ or $R \rightarrow \infty$. A similar argument shows that $\gamma_3 |S_2| \rightarrow 0$ as either $D_3 \rightarrow 0$ or $R \rightarrow \infty$. The conclusion of the lemma follows immediately.

The next part of the proof is to demonstrate that $|Q(\lambda)| \rightarrow 0$. The idea behind the proof is similar to Busenberg and Mahaffy [2] though the details are substantially more complex. For $\text{Re}(\lambda) \geq -\varepsilon$, the integrals following the characteristic equation are applied to (2.11). With this information the equation for $Q(\lambda)$ is written

$$\begin{aligned}
 Q(\lambda) &= \gamma_3 c_0 f'(w_1^s) \sum_{n=1}^{\infty} \frac{k \xi_n(R\sigma) \varepsilon_n}{\lambda + C_n} \\
 &\times \left(1 - (\lambda + 1)(\lambda + b_2) \sum_{n=0}^{\infty} \sum_{m=1}^{\infty} \frac{\delta_m^u \psi_n(R) \langle \phi_m, \psi_n \rangle}{(\lambda + A_m)(\lambda + B_n)} \right), \tag{3.2} \\
 &\equiv \gamma_3 c_0 f'(w_1^s) S_3 (1 - (\lambda + 1)(\lambda + b_2) S_4),
 \end{aligned}$$

where

$$\varepsilon_n = \langle D_3 \nabla^2 h, \xi_n(r) \rangle - (\lambda + b_3) \langle h, \xi_n(r) \rangle.$$

We divide our analysis into examining the factor $\gamma_3 c_0 f'(w_1^s)$, the infinite sum containing ε_n , and the factor containing the double infinite sum. Numerical studies show that each of the factors in $Q(\lambda)$ tends to zero as either $D_i \rightarrow 0$ or $R \rightarrow \infty$. Unfortunately, proving these facts is much harder. The analysis is divided into a close examination of each of the three factors.

The assumption on the function f given by (H1) implies that

$$f'(w) = -\frac{\rho K w^{\rho-1}}{(1 + K w^\rho)^2}.$$

The next lemma demonstrates that $f'(w_1^s) \rightarrow 0$ as either $D_i \rightarrow 0$ or $R \rightarrow \infty$.

LEMMA 3.2. Assume f satisfies (H1) and that w_1^s is the equilibrium solution for w_1 in (1.1). Then $f'(w_1^s) \rightarrow 0$ as $D_i \rightarrow 0$ or $R \rightarrow \infty$.

Proof. To demonstrate this result an estimate on w_1^s is needed. To find w_1^s , the time derivatives in (1.1) are set equal to zero. The result is a system of two algebraic equations and three boundary value problems. A summary of the details required to compute w_1^s is given in the appendix of Mahaffy, Jorgensen, and Vanderheyden [8]. The equilibrium value w_1^s is determined by the nonlinear equation

$$\begin{aligned}
 f(w_1^s) &= \left(\frac{(1 + \gamma_1 - \gamma_1 q_1 q_2)(q_3 - \alpha_2 R)[p_7 q_5 - p_5 q_7 + \alpha_3 R(q_7 - q_5)]}{q_2(q_3 q_6 + k R q_3 q_4 - \alpha_2 R q_6)(p_7 - p_5)} \right) w_1^s, \\
 &\equiv \widehat{M} w_1^s, \tag{3.3}
 \end{aligned}$$

where $\alpha_i^2 = b_i/D_i$, $i = 1, 2, 3$ ($b = 1$), and the constants q_i , $i = 1, \dots, 7$, p_5 , and p_7 are defined below. The unique positive solution to this equation is readily found using Newton's method. The constants q_i , $i = 1, \dots, 7$, p_5 , and p_7 are

given by the following formulae:

$$\begin{aligned}
 q_1 &= \frac{1}{R\sigma} \left(\cosh[\alpha_1 R(1 - \sigma)] - \frac{1}{\alpha_1 R} \sinh[\alpha_1 R(1 - \sigma)] \right), \\
 q_2 &= \frac{\beta_1 R^3 \sigma^2 \alpha_1}{a_1 \cosh[\alpha_1 R(1 - \sigma)] + a_2 \sinh[\alpha_1 R(1 - \sigma)]}, \\
 q_3 &= \frac{(\sinh[\alpha_2 R(1 - \sigma)] + \alpha_2 R\sigma \cosh[\alpha_2 R(1 - \sigma)])}{(\cosh[\alpha_2 R(1 - \sigma)] + \alpha_2 R\sigma \sinh[\alpha_2 R(1 - \sigma)])}, \\
 q_4 &= \frac{c_0}{D_2 \alpha_2} \left(\int_0^{R(1-\sigma)} \left(\frac{1}{\alpha_1 R} \sinh(\alpha_1 u) - \cosh(\alpha_1 u) \right) \sinh(\alpha_2 u) du \right. \\
 &\quad \left. + \alpha_2 R \int_0^{R(1-\sigma)} \left(\cosh(\alpha_1 u) - \frac{1}{\alpha_1 R} \sinh(\alpha_1 u) \right) \cosh(\alpha_2 u) du \right), \\
 p_5 &= \frac{((1 + \beta_3 R\sigma) \sinh[\alpha_3 R(1 - \sigma)] + \alpha_3 R\sigma \cosh[\alpha_3 R(1 - \sigma)])}{((1 + \beta_3 R\sigma) \cosh[\alpha_3 R(1 - \sigma)] + \alpha_3 R\sigma \sinh[\alpha_3 R(1 - \sigma)])}, \\
 q_5 &= \frac{\beta_3 R^2 \sigma^2}{((1 + \beta_3 R\sigma) \cosh[\alpha_3 R(1 - \sigma)] + \alpha_3 R\sigma \sinh[\alpha_3 R(1 - \sigma)])}, \\
 q_6 &= \frac{c_0 k}{D_2 \alpha_2} \int_0^{R(1-\sigma)} \left(R \cosh(\alpha_1 u) - \frac{1}{\alpha_1} \sinh(\alpha_1 u) \right) \sinh(\alpha_2 u) du, \\
 p_7 &= \frac{\sinh[\alpha_3 R(1 - \sigma)]}{\cosh[\alpha_3 R(1 - \sigma)]}, \\
 q_7 &= \frac{R\sigma(\gamma_3 + \hat{b}_3)}{\gamma_3 \cosh[\alpha_3 R(1 - \sigma)]},
 \end{aligned}$$

where $a_1 = R\alpha_1(1 + \beta_1 R\sigma - \sigma)$ and $a_2 = R^2\sigma\alpha_1 - 1 - \beta_1 R\sigma$.

To obtain an estimate of $f'(w_1^s)$, the value of w_1^s needs to be approximated. This is done by examining the coefficient \widehat{M} in (3.3) as $D_i \rightarrow 0$ or $R \rightarrow \infty$. Considering the first factor $(1 + \gamma_1 - \gamma_1 q_1 q_2)/q_2$ in \widehat{M} , we see

$$\frac{1 + \gamma_1 - \gamma_1 q_1 q_2}{q_2} = \frac{A_1 \cosh[\alpha_1 R(1 - \sigma)] + A_2 \sinh[\alpha_1 R(1 - \sigma)]}{\beta_1 R^3 \sigma^2 \alpha_1},$$

where

$$A_1 = R\alpha_1(1 + \beta_1 R\sigma - \sigma) + \gamma_1 R\alpha_1(1 - \sigma),$$

$$A_2 = (R^2\sigma\alpha_1 - 1 - \beta_1 R\sigma) + \gamma_1 (R^2\sigma\alpha_1 - 1).$$

As $D_1 \rightarrow 0$, recall $D_1\beta_1$ is finite and $\alpha_1 = \sqrt{1/D_1}$. Thus, the largest terms in both the numerator and the denominator have $\alpha_1\beta_1$, which is $O(\beta_1^{3/2})$. With this information we obtain the approximation that as $D_1 \rightarrow 0$,

$$\frac{1 + \gamma_1 - \gamma_1 q_1 q_2}{q_2} \simeq \frac{\cosh[\alpha_1 R(1 - \sigma)]}{R\sigma}.$$

In a similar manner by considering the highest-order terms in R and recalling the mass balance information that shows γ_1 is $O(1/R)$, we obtain that as $R \rightarrow \infty$,

$$\frac{1 + \gamma_1 - \gamma_1 q_1 q_2}{q_2} \simeq \frac{\beta_1 \cosh[\alpha_1 R(1 - \sigma)] + \sinh[\alpha_1 R(1 - \sigma)]}{\beta_1 R\sigma}. \tag{3.5}$$

The next part of the analysis requires a closer examination of the factor $q_3 q_6 + kRq_3 q_4 - \alpha_2 Rq_6$ in the denominator. In order to expand the integrals we consider the case where $\alpha_1 > \alpha_2$. The reader can verify that the other cases are similar. From the expressions for q_4 and q_6 , it follows that

$$\begin{aligned} & q_3 q_6 + kRq_3 q_4 - \alpha_2 Rq_6 \\ &= \frac{c_0 k R}{D_2 \alpha_1} \left[q_3 \int_0^{R(1-\sigma)} (\alpha_1 R \cosh(\alpha_1 u) \cosh(\alpha_2 u) - \sinh(\alpha_1 u) \cosh(\alpha_2 u)) du \right. \\ &\quad \left. - \int_0^{R(1-\sigma)} (\alpha_1 R \cosh(\alpha_1 u) \sinh(\alpha_2 u) - \sinh(\alpha_1 u) \sinh(\alpha_2 u)) du \right] \\ &= \frac{c_0 k R}{D_2 \alpha_1} \left[\alpha_1 R \left(q_3 \left(\frac{\sinh[(\alpha_1 + \alpha_2)R(1 - \sigma)]}{2(\alpha_1 + \alpha_2)} + \frac{\sinh[(\alpha_2 - \alpha_1)R(1 - \sigma)]}{2(\alpha_2 - \alpha_1)} \right) \right) \right. \\ &\quad \left. - \left(\frac{\cosh[(\alpha_1 + \alpha_2)R(1 - \sigma)]}{2(\alpha_1 + \alpha_2)} + \frac{\cosh[(\alpha_2 - \alpha_1)R(1 - \sigma)]}{2(\alpha_2 - \alpha_1)} - \frac{\alpha_2}{\alpha_2^2 - \alpha_1^2} \right) \right) \right] \\ &\quad - \left(q_3 \left(\frac{\cosh[(\alpha_1 + \alpha_2)R(1 - \sigma)]}{2(\alpha_1 + \alpha_2)} + \frac{\cosh[(\alpha_1 - \alpha_2)R(1 - \sigma)]}{2(\alpha_1 - \alpha_2)} - \frac{\alpha_1}{\alpha_1^2 - \alpha_2^2} \right) \right) \right. \\ &\quad \left. - \left(\frac{\sinh[(\alpha_1 + \alpha_2)R(1 - \sigma)]}{2(\alpha_1 + \alpha_2)} - \frac{\sinh[(\alpha_2 - \alpha_1)R(1 - \sigma)]}{2(\alpha_2 - \alpha_1)} \right) \right) \right]. \tag{3.6} \end{aligned}$$

From the definition of q_3 and since $\sinh[\alpha_2 R(1 - \sigma)] \rightarrow \cosh[\alpha_2 R(1 - \sigma)]$ as $D_2 \rightarrow 0$ or equivalently $\alpha_2 \rightarrow \infty$, it is clear that $\lim_{\alpha_2 \rightarrow \infty} q_3 = 1$, very rapidly. As $\alpha_1 \rightarrow \infty$ with $\alpha_1 > \alpha_2$, the first two lines in (3.6) contribute the most to the expression. However, $\sinh[(\alpha_1 + \alpha_2)R(1 - \sigma)] \rightarrow \cosh[(\alpha_1 + \alpha_2)R(1 - \sigma)]$ rapidly, leaving only the $\sinh[(\alpha_1 - \alpha_2)R(1 - \sigma)]$ and $\cosh[(\alpha_1 - \alpha_2)R(1 - \sigma)]$ terms. The latter is approximately equal to $\sinh[(\alpha_1 - \alpha_2)R(1 - \sigma)]$; hence we obtain the estimate

$$q_3 q_6 + kRq_3 q_4 - \alpha_2 Rq_6 \simeq \frac{c_0 k R^2 \sinh[(\alpha_1 - \alpha_2)R(1 - \sigma)]}{D_2(\alpha_1 - \alpha_2)}. \tag{3.7}$$

Next we consider the last factor in (3.3). From the definitions of these quantities, a straightforward calculation shows that the last factor is given by

$$\begin{aligned} & \frac{p_7 q_5 - p_5 q_7 + \alpha_3 R (q_7 - q_5)}{p_7 - p_5} \\ &= - \frac{((\gamma_3 + \hat{b}_3)(\alpha_3^2 R^2 \sigma - 1) - \hat{b}_3 \beta_3 R \sigma)}{\alpha_3 \gamma_3} \sinh[\alpha_3 R (1 - \sigma)] \\ & \quad - \frac{\alpha_3 R ((\gamma_3 + \hat{b}_3)(1 - \sigma) + \hat{b}_3 \beta_3 R \sigma)}{\alpha_3 \gamma_3} \cosh[\alpha_3 R (1 - \sigma)]. \end{aligned} \quad (3.8)$$

Recall that as $D_3 \rightarrow 0$, $\beta_3 \rightarrow \infty$ and $\alpha_3 = O(\beta_3^{1/2})$. Thus, the highest-order term in the numerator of (3.8) is $\alpha_3 \beta_3 \hat{b}_3 R^2 \sigma \cosh[\alpha_3 R (1 - \sigma)]$. This implies that

$$\frac{p_7 q_5 - p_5 q_7 + \alpha_3 R (q_7 - q_5)}{p_7 - p_5} \simeq - \frac{\beta_3 \hat{b}_3 R^2 \sigma}{\gamma_3} \cosh[\alpha_3 R (1 - \sigma)]. \quad (3.9)$$

Recall that $\gamma_3 = O(1/R)$. Using this information, one can easily verify that

$$\frac{p_7 q_5 - p_5 q_7 + \alpha_3 R (q_7 - q_5)}{p_7 - p_5} \simeq - \frac{\hat{b}_3 R^2 \sigma}{\gamma_3} (\alpha_3 \sinh[\alpha_3 R (1 - \sigma)] + \beta_3 \cosh[\alpha_3 R (1 - \sigma)]) \quad (3.10)$$

for large R .

Combining the results in (3.4), (3.7), and (3.9) for small diffusivities, we find the quantity \widehat{M} in (3.3) is approximated by

$$\widehat{M} \simeq \frac{D_2 \alpha_2 (\alpha_1 - \alpha_2) \beta_3 \hat{b}_3 \cosh[\alpha_1 R (1 - \sigma)] \cosh[\alpha_3 R (1 - \sigma)]}{k c_0 \gamma_3 \sinh[(\alpha_1 - \alpha_2) R (1 - \sigma)]}. \quad (3.11)$$

From the information that $D_i \beta_i$ and $D_3 k$ are fixed finite numbers and α_i are $O(\beta_i^{1/2})$ for $i = 1, 2, 3$, the asymptotic behavior of (3.11) as $D_i \rightarrow 0$ depends on the behavior of the hyperbolic trigonometric functions. Thus, it is clear that $\lim_{D_i \rightarrow 0} \widehat{M} = \infty$.

From the results in (3.5), (3.7), and (3.10) for large radii, R , the following approximation is found for \widehat{M} :

$$\begin{aligned} \widehat{M} &\simeq \frac{D_2 \alpha_2 (\alpha_1 - \alpha_2) \hat{b}_3 (\beta_1 \cosh[\alpha_1 R (1 - \sigma)] + \sinh[\alpha_1 R (1 - \sigma)])}{k c_0 \gamma_3 \beta_1 \sinh[(\alpha_1 - \alpha_2) R (1 - \sigma)]} \\ &\quad \times (\alpha_3 \sinh[\alpha_3 R (1 - \sigma)] + \beta_3 \cosh[\alpha_3 R (1 - \sigma)]). \end{aligned} \quad (3.12)$$

Again it is the behavior of the hyperbolic trigonometric function that determines the behavior of \widehat{M} as $R \rightarrow \infty$. Thus, we find that $\lim_{R \rightarrow \infty} \widehat{M} = \infty$.

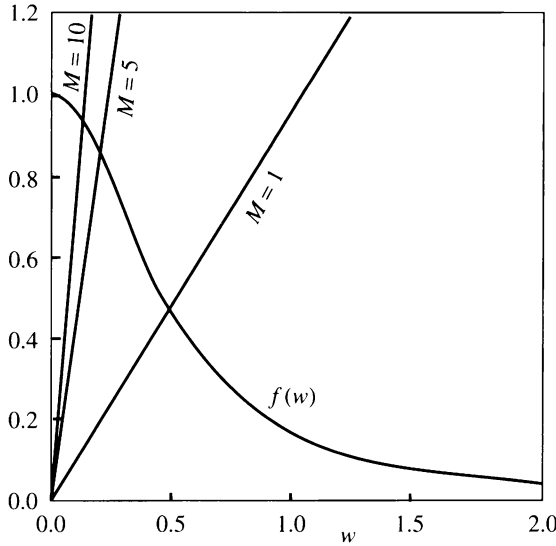


FIG. 3.2. The intersection of the curve $f(w)$ with the line $\widehat{M}x$ determines w_1^s . This graph shows that $w_1^s \rightarrow 0$ as $\widehat{M}x \rightarrow \infty$.

By definition \widehat{M} is the slope of the line on the right-hand side of (3.3). The nonlinear function on the left-hand side is fixed, so the intersection of these two curves occurs at lower values w_1^s with increasing \widehat{M} . From Fig. 3.2, it is clear that as $\widehat{M} \rightarrow \infty$ the equilibrium value $w_1^s \rightarrow 0$. In fact for large values of \widehat{M} it can be shown that a doubling of \widehat{M} results in almost a halving of w_1^s . For $\rho > 1$ the formula for $f'(w_1^s)$ shows that $\lim_{w_1^s \rightarrow 0} f'(w_1^s) \rightarrow 0$. This completes the proof of Lemma 3.2.

The next step in the analysis is to examine the factor S_3 in (3.2). The following lemma shows that this quantity is bounded for either small diffusivities or large R .

LEMMA 3.3. Consider the first infinite sum, S_3 , in (3.2). S_3 is bounded as either $D_i \rightarrow 0$ or $R \rightarrow \infty$.

Proof. To establish this result a complete expansion of the terms in S_3 is needed. From Mahaffy, Jorgensen, and Vanderheyden [8], we have

$$\frac{k\check{\xi}_n(R\sigma)\varepsilon_n}{\lambda + C_n} = -2Rk \left(\frac{\sigma(\omega_n^2 + 1)(2 - \beta_3 R\sigma)}{\omega_n^2(1 - \sigma)G_{\text{nor}}(\omega_n, \beta_3)} + \frac{(\lambda + b_3)[(\omega_n^2(1 - \sigma) - 2\sigma) - 2D_3\omega_n^2\sigma/R^2]H(n)}{(\lambda + C_n)\omega_n^2(1 - \sigma)G_{\text{nor}}(\omega_n, \beta_3)} \right), \tag{3.13}$$

where

$$H(n) = (-1)^{n-1} \sqrt{(\omega_n^2 + 1)(\omega_n^2\sigma^2 + 1 + 2\beta_3 R\sigma + \beta_3^2 R^2\sigma^2)}.$$

By paralleling the work in the proof of Lemma 3.1, which shows that $\mu_1^2(1 - \sigma) - \sigma$ is bounded away from zero, we can show that $\omega_1^2(1 - \sigma) - \sigma$ is similarly bounded

away from zero. Define

$$M_1 = \frac{\omega_1^2 + 1}{\omega_1^2(1 - \sigma) - \sigma}.$$

It is clear that for $n \geq 2$, $M_1 > (\omega_n^2 + 1)/(\omega_n^2(1 - \sigma) - \sigma)$. Assume that either D_3 is sufficiently small or R is sufficiently large so that $\beta_3 R \sigma > 2$; then the following bound on the first term in (3.13) is obtained:

$$\left| \frac{2Rk\sigma(\omega_n^2 + 1)(2 - \beta_3 R \sigma)}{\omega_n^2(1 - \sigma)G_{\text{nor}}(\omega_n, \beta_3)} \right| < \frac{2k\sigma^2 M_1}{\omega_n^2(1 - \sigma)\beta_3}. \tag{3.14}$$

The degree of ω_n in the numerator of the next term in (3.13) is higher than it is in the first term; thus, a different approach is required in the analysis. A straightforward computation shows that

$$\frac{d}{d\omega_n} \left[\frac{|H(n)|}{G_{\text{nor}}(\omega_n, \beta_3)} \right] < 0, \quad \omega_n > 0.$$

It is clear that $H(1)/G_{\text{nor}}(\omega_1, \beta_3)$ is $O(1/(\beta_3 R))$. The remaining factor

$$\frac{(\lambda + b_3)[(\omega_n^2(1 - \sigma) - 2\sigma) - 2D_3\omega_n^2\sigma/R^2]H(n)}{(\lambda + C_n)\omega_n^2(1 - \sigma)G_{\text{nor}}(\omega_n, \beta_3)},$$

which has magnitude less than one, can be divided into real and imaginary parts. In this expression, $|\lambda + b_3|/|\lambda + C_n|$ is clearly decreasing as ω_n increases, and the quantity $(1 - \sigma - 2D_3\sigma/R^2)/(1 - \sigma) \simeq 1$ for D_3 small or R large. It follows that the absolute values of the real and imaginary parts of the second term in (3.13) are monotonically decreasing as n increases. However, $H(n)$ alternates in sign, which implies by the alternating series test that

$$\left| \sum_{n=1}^{\infty} \frac{(\lambda + b_3)[(\omega_n^2(1 - \sigma) - 2\sigma) - 2D_3\omega_n^2\sigma/R^2]H(n)}{(\lambda + C_n)\omega_n^2(1 - \sigma)G_{\text{nor}}(\omega_n, \beta_3)} \right| < \frac{M_2}{\beta_3 R}, \tag{3.15}$$

where $M_2/(\beta_3 R)$ bounds the magnitude of the first term of the series.

With the estimates given in (3.14) and (3.15), the magnitude of the infinite sum, S_3 , in (3.2) can be analyzed. The following inequality follows from these estimates:

$$\left| \sum_{n=1}^{\infty} \frac{k\xi_n(R\sigma)\varepsilon_n}{\lambda + C_n} \right| < \sum_{n=1}^{\infty} \frac{2k\sigma^2 M_1}{\omega_n^2(1 - \sigma)\beta_3} + \frac{2kM_2}{\beta_3}. \tag{3.16}$$

As $\omega_n(1 - \sigma) > (n - 1)\pi$ and since $\omega_1^2(1 - \sigma)$ is bounded away from zero, the comparison test can be used to show that the infinite sum on the right-hand side of (3.16) converges absolutely. The mass balance relationships seen in Mahaffy, Jorgensen, and Vanderheyden [8] show that k is proportional to β_3 and that each of these quantities varies inversely with D_3 . This shows that S_3 is bounded, which completes the proof of Lemma 3.3. In fact, the above estimate is very conservative. Numerical studies show S_3 tends rapidly to zero as either $D_3 \rightarrow 0$ or $R \rightarrow \infty$.

The final step in the analysis is the examination of the last factor in (3.2), $(1 - (\lambda + 1)(\lambda + b_2)S_4)$, which contains the double sum. The following lemma shows that this quantity is bounded for either small diffusivities or large R .

LEMMA 3.4. Consider the term $(1 - (\lambda + 1)(\lambda + b_2)S_4)$ in (3.2). With $\text{Re}(\lambda) \geq -\varepsilon$, this term is bounded as either $D_i \rightarrow 0$ or $R \rightarrow \infty$.

Proof. As $\langle \phi_m, \psi_0 \rangle \psi_0(R) = 3\delta_m^u / (R^3(1 - \sigma^3))$, S_4 can be written

$$S_4 = \sum_{m=1}^{\infty} \frac{3(\delta_m^u)^2}{R^3(1 - \sigma^3)(\lambda + A_m)(\lambda + b_2)} + \sum_{n=1}^{\infty} \sum_{m=1}^{\infty} \frac{\delta_m^u \langle \phi_m, \psi_n \rangle \psi_n(R)}{(\lambda + A_m)(\lambda + B_n)}. \tag{3.17}$$

For β_1 and R sufficiently large, Lemma 3.1 provides the estimates $\mu_1 \simeq \sqrt{3\sigma}$ and $\mu_m > (m - 1)\pi / (1 - \sigma)$. With this information, the following bounds can be found:

$$\begin{aligned} \frac{\beta_1^2 R^2 (1 + \mu_m^2)}{G_{\text{nor}}(\mu_m, \beta_1)} &\leq \frac{\beta_1^2 R^2 (1 + \mu_1^2)}{G_{\text{nor}}(\mu_1, \beta_1)} < \frac{1 + \mu_1^2}{\sigma^2(\mu_1^2(1 - \sigma) - \sigma)} \\ &\simeq \frac{(1 + 3\sigma)(1 - \sigma)}{\sigma^3(2 + \sigma)}, \quad m = 1, 2, \dots \end{aligned}$$

Thus, for β_1 and R sufficiently large and $\text{Re}(\lambda) > -\varepsilon$, the first infinite sum in (3.17) satisfies

$$\begin{aligned} &\left| \sum_{m=1}^{\infty} \frac{3(\delta_m^u)^2}{R^3(1 - \sigma^3)(\lambda + A_m)(\lambda + b_2)} \right| \\ &= \frac{6\sigma^4}{(1 - \sigma^3)} \left| \sum_{m=1}^{\infty} \frac{\beta_1^2 R^2 (1 + \mu_m^2)}{\mu_m^2 G_{\text{nor}}(\mu_m, \beta_1)(\lambda + A_m)(\lambda + b_2)} \right| \\ &< \frac{6\sigma^2(1 + \mu_1^2)}{(1 - \sigma^3)(\mu_1^2(1 - \sigma) - \sigma)|\lambda + A_1||\lambda + b_2|} \sum_{m=1}^{\infty} \frac{1}{\mu_m^2}, \end{aligned} \tag{3.18}$$

which is bounded.

The remaining double sum in (3.17) requires special treatment. A direct computation shows that

$$\delta_m^u \langle \phi_m, \psi_n \rangle \psi_n(R) = \frac{4\beta_1^2 R^2 \sigma^4 \nu_n^2 (\mu_m^2 + 1) (-1)^n \sqrt{(\nu_n^2 + 1)(\nu_n^2 \sigma^2 + 1)}}{(\mu_m^2 - \nu_n^2) G_{\text{nor}}(\mu_m, \beta_1) G_{\text{nor}}(\nu_n, 0)}. \tag{3.19}$$

When $m = n$, μ_m and ν_n are separated by less than $\pi / (2(1 - \sigma))$. When $m \neq n$, the separation of μ_m and ν_n is approximately an integer multiple of $\pi / (1 - \sigma)$.

Begin with the analysis of the terms where $n = m$. Let $\mu_m = \nu_m + \varepsilon_m$. By applying (2.4) to (2.3) with the above substitution, we obtain the following implicit expression for ε_m :

$$\begin{aligned} &\cos(\nu_m(1 - \sigma)) \left[(\nu_m \beta_1 R \sigma + \varepsilon_m(1 - \sigma + \beta_1 R \sigma)) \cos(\varepsilon_m(1 - \sigma)) \right. \\ &\quad \left. - (\nu_m^2 + 1 + \beta_1 R \sigma + 2\varepsilon_m + \varepsilon_m^2) \sin(\varepsilon_m(1 - \sigma)) \right] \\ &= \sin(\nu_m(1 - \sigma)) \left[(\nu_m + \varepsilon_m)(1 - \sigma + \beta_1 R \sigma) \sin(\varepsilon_m(1 - \sigma)) \right. \\ &\quad \left. + (\beta_1 R \sigma + 2\varepsilon_m + \varepsilon_m^2) \cos(\varepsilon_m(1 - \sigma)) \right]. \end{aligned} \tag{3.20}$$

For $\nu_m \simeq (m - 1)\pi / (1 - \sigma) \geq \beta_1 R \sigma \gg \varepsilon_m$, (3.20) yields

$$\varepsilon_m \simeq \frac{\beta_1 R \sigma}{(1 - \sigma)[\nu_m + \beta_1 R \sigma]}.$$

For $\nu_m \gg \beta_1 R\sigma$ (or large m), this estimate gives

$$\varepsilon_m \simeq \frac{\beta_1 R\sigma}{(m-1)\pi},$$

which implies that $\mu_m^2 - \nu_m^2 \rightarrow 2\beta_1 R\sigma/(1-\sigma)$ as $m \rightarrow \infty$. For small m , the estimate in (3.20) cannot be used to determine the difference between μ_m and ν_m . However, for β_1 bounded away from zero, it is easy to see that $\mu_m^2 - \nu_m^2$ remains bounded away from zero for all $m \geq 1$. In fact, $\mu_m^2 - \nu_m^2$ increases with increasing m .

The analysis of equation (3.19) continues by separating the factors that depend on ν_n and those that depend on μ_m and β_1 . For ν_n , we examine

$$\frac{\nu_n^2 \sqrt{(\nu_n^2 + 1)(\nu_n^2 \sigma^2 + 1)}}{G_{\text{nor}}(\nu_n, 0)} = \frac{\sqrt{(\nu_n^2 + 1)(\nu_n^2 \sigma^2 + 1)}}{(1 - \sigma)(1 + \sigma + \sigma^2 + \nu_n^2 \sigma^2)}, \tag{3.21}$$

which tends to $1/(\sigma(1 - \sigma))$ as $n \rightarrow \infty$. The factor given by

$$\frac{\beta_1^2 R^2 (\mu_m^2 + 1)}{G_{\text{nor}}(\mu_m, \beta_1)} < \frac{\beta_1^2 R^2 (\mu_m^2 + 1)}{[\mu_m^2 (1 - \sigma) - \sigma](\mu_m^2 + \beta_1^2 R^2)}, \tag{3.22}$$

clearly decreases to zero as $m \rightarrow \infty$. By differentiating this quantity with respect to μ_m , one can easily show that it is monotonically decreasing to zero.

From the above information with $m = n$ and $\text{Re}(\lambda) > -\varepsilon$, the alternating series test can be applied to the series

$$\sum_{m=1}^{\infty} \frac{\delta_m^2 \langle \phi_m, \psi_m \rangle \psi_m(R)}{|\lambda + A_m| |\lambda + B_m|}$$

to show convergence. In fact, from the monotonicity of the terms, this sum must be less than the first term in the sum. For β_1 and R bounded away from zero, one can easily find a bound on this first term.

Next we examine the terms where $m = n + k$ for k a nonzero integer and $m, n \geq 1$. For sake of definiteness, consider the case when $k \geq 1$ and $n = 1, 2, \dots$. The other case where $k \leq -1$ and $m = 1, 2, \dots$ is handled similarly. Assume that k is fixed and use (3.19) to examine

$$\sum_{n=1}^{\infty} \frac{\delta_{n+k}^u \langle \phi_{n+k}, \psi_n \rangle \psi_n(R)}{|\lambda + A_{n+k}| |\lambda + B_n|}. \tag{3.23}$$

As stated before the eigenvalues μ_{n+k} and ν_n are separated by approximately $k\pi/(1 - \sigma)$ and $\nu_n \simeq n\pi/(1 - \sigma)$, which implies that $(\mu_{n+k}^2 - \nu_n^2) \simeq (2n + k)k\pi^2/(1 - \sigma)^2$. The information on the factors given in (3.21) and (3.22) still applies in these cases, so again we can apply the alternating series test along the sums for each k .

Thus, for k fixed, each of the infinite sums in (3.23) is bounded by the first term. A total bound can be found by summing over k the first terms, i.e.,

$$\sum_{k=1}^{\infty} \frac{\delta_{1+k}^u \langle \phi_{1+k}, \psi_1 \rangle \psi_1(R)}{|\lambda + A_{1+k}| |\lambda + B_1|}. \tag{3.24}$$

Since $(\mu_{1+k}^2 - \nu_1^2) \simeq (2+k)k\pi^2/(1-\sigma)^2$ and since the factor (3.22) with $m = k + 1$ decreases with increasing k , (3.24) is absolutely convergent with a bound independent of D_i and R .

As stated before, the remaining terms of the double sum can be handled in a similar fashion; that is, the double sum,

$$\left| \sum_{m=1}^{\infty} \sum_{n>m}^{\infty} \frac{\delta_m^u \langle \phi_m, \psi_n \rangle \psi_n(R)}{|\lambda + A_m| |\lambda + B_n|} \right| < \sum_{k=1}^{\infty} \frac{|\delta_1^u \langle \phi_1, \psi_{k+1} \rangle \psi_{k+1}(R)|}{|\lambda + A_1| |\lambda + B_{k+1}|},$$

converges absolutely. Thus, S_4 has a bound independent of D_i and R , and the lemma is established. In fact, the computer studies indicate that the double sum converges to zero.

Now Lemma 3.1 shows that $|P(\lambda)|$ is bounded, while Lemmas 3.2–3.4 taken together show that $|Q(\lambda)| \rightarrow 0$ as $R \rightarrow \infty$ or $D_i \rightarrow 0$, $i = 1, 2, 3$ for $\text{Re}(\lambda) > -\epsilon$. Thus, there are no solutions to (2.9) with $\text{Re}(\lambda) > -\epsilon$ under the conditions of either Theorem 2.1 or Theorem 2.2. This proves the stability results of these theorems. Note that as $k \rightarrow 0$, (2.11) shows that $|Q(\lambda)| \rightarrow 0$. The proof of Theorem 2.3 follows immediately by a similar argument.

4. Discussion. This study furthers the analysis of the model developed by Mahaffy, Jorgensen, and Vanderheyden [8]. The two-compartment model represents a cell that uses negative feedback or repression to control the production of a protein or permease that mediates transport of some nutrient or other substance across the cell membrane. At sufficiently high concentrations, the nutrient (perhaps with another protein) binds to the operator region of the gene used to produce the permease and represses the transcription process. This lowers the concentration of the permease, which in turn lowers the concentration of the nutrient. Related repression models have been shown to exhibit oscillatory behavior. (See [1, 2, 4, 6, 12, 13, 14].)

Mathematically, this study shows how some reaction diffusion models with time delays can be reduced to an analysis of a system of delay differential equations and linear Volterra equations that have only exponentially damped spatial dependence. Thus, the structure of certain models that may include diffusion have their behavior controlled by the time varying part of the equations. This allows analysis by classical techniques for time varying systems of equations, i.e., analysis of a characteristic equation. From our analysis we have in effect shown how the diffusion operator can act as a time delay, though it is significantly more complicated than adding a simple time delay to the original system of equations.

When compared to the work of Busenberg and Mahaffy [2] on a repression model with diffusion and time delays, the stability results presented here required substantially more effort. The principal difference in the models in these studies is the mixed boundary condition for transport of the nutrient across the cell membrane. This added complexity does not make the numerical studies or the comparison to a well-mixed model at high diffusivities substantially harder, as seen in [8]. The increased difficulty in obtaining the stability results suggests that the analysis done for this model may not extend to related models with additional complexities. Since Theorems 2.1 and 2.2 can be interpreted physically as having the decay processes

dominate the diffusion, one might expect that some other approach may give a more general stability result.

From an extension of the method described in Mahaffy [7], the characteristic equation (2.9) can be studied numerically to determine where a supercritical Hopf bifurcation occurs as the time delay, T , is varied. Mahaffy, Jorgensen, and Vanderheyden [8] have generated a series of bifurcation curves that show how the region of stability changes as the parameters D_i , R , or k vary. Their study shows that for high diffusivities, D_i , the region of stability matches that of a corresponding well-mixed model. As the diffusivities decrease, the critical delay, T , necessary for a Hopf bifurcation decreases. This supports the heuristic notion that diffusion acts like a delay, at least for intermediate values of the diffusivities. For very small diffusivities, the numerical studies support Theorem 2.1 showing the critical delay tending to infinity. The physical interpretation of this result is that the molecular motion through the cell is slowed to where the delay processes predominate. One open problem suggested by the numerical studies that has not been answered analytically is how one can determine which values of the diffusivities are most destabilizing.

The numerical study of Mahaffy, Jorgensen, and Vanderheyden [8] shows that the critical delay at the Hopf bifurcation increases as the cell radius increases. Theorem 2.2 shows that there is some finite cell that guarantees that (1.1) is locally stable. Physically, this implies that when the cell gets too large the biochemical species must diffuse too far to react, so the decay processes once again predominate. The numerical studies for this model have only shown this bifurcation curve to be monotonic; however, Busenberg and Mahaffy [3] produced parameter values where a related repression model becomes less stable as the cell size increases for small cell radii. In a result that our Theorem 2.2 parallels, they proved that when the cell is sufficiently large, the repression model is locally stable.

Perhaps the most interesting result from this model is the observation that (1.1) becomes more unstable as the external concentration of the nutrient is increased or, equivalently, k increases. Theorem 2.3 shows that (1.1) is always locally stable when this external concentration is sufficiently low; however, the numerical studies show that the critical delay for a Hopf bifurcation decreases as k increases. If this external nutrient was a morphogen, then our results show that for very low concentrations the model is locally stable. As the concentration in the environment increases, the model undergoes a Hopf bifurcation (as the critical delay is fixed for biological reasons). With the Hopf bifurcation the intracellular concentration of the morphogen begins to oscillate, which could signal to the cell that it should alter its response to the environment. This is one aspect of morphogenesis.

REFERENCES

- [1] S. N. Busenberg and J. M. Mahaffy, *Interaction of spatial diffusion and delays in models of genetic control by repression*, *J. Math. Biol.* **22**, 313–333 (1985)
- [2] S. N. Busenberg and J. M. Mahaffy, *The effects of dimension and size for a compartmental model of repression*, *SIAM J. Appl. Math.* **48**, 882–903 (1988)
- [3] S. N. Busenberg and J. M. Mahaffy, *A compartmental reaction-diffusion cell cycle model*, *Computers Math. Appl.* **18**, 883–892 (1989)

- [4] B. C. Goodwin, *Oscillatory behavior of enzymatic control processes*, Adv. Enzyme Reg. **3**, 425–439 (1965)
- [5] M. D. Lundrigan and R. J. Kadner, *Nucleotide sequence of the gene for the ferrienterochelin receptor FepA in Escherichia coli*, J. Biol. Chem. **261**, 10797–10801 (1980)
- [6] J. M. Mahaffy, *Periodic solutions for certain protein synthesis models*, J. Math. Anal. Appl. **74**, 72–105 (1980)
- [7] J. M. Mahaffy, *A test for stability of linear differential delay equations*, Quart. Appl. Math. **40**, 193–202 (1982)
- [8] J. M. Mahaffy, D. A. Jorgensen, and R. L. Vanderheyden, *Oscillations in a model of repression with external control*, to appear in J. Theoret. Biol.
- [9] J. M. Mahaffy and C. V. Pao, *Models of genetic control by repression with time delays and spatial effects*, J. Math. Biol. **20**, 39–58 (1984)
- [10] J. B. Neilands, *Microbial iron compounds*, Ann. Rev. Biochem. **50**, 715–731 (1981)
- [11] J. B. Neilands, *Microbial envelope proteins related to iron*, Ann. Rev. Microbiol. **36**, 285–309 (1982)
- [12] H. G. Othmer, *The qualitative dynamics of a class of biochemical control circuits*, J. Math. Biol. **3**, 53–78 (1976)
- [13] P. E. Rapp, *Mathematical techniques for study of oscillations in biochemical control loops*, Bull. Inst. Math. Appl. **12**, 11–20 (1976)
- [14] J. J. Tyson and H. G. Othmer, *The dynamics of feedback control circuits in biochemical pathways*, Progress in Theoretical Biology, R. Rosen and F. M. Snell, eds., Academic Press, New York, 1978.