

Models of genetic control by repression with time delays and spatial effects

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Abstract. Two models for cellular control by repression are developed in this paper. The models use standard theory from compartmental analysis and biochemical kinetics. The models include time delays to account for the processes of transcription and translation and diffusion to account for spatial effects in the cell. This consideration leads to a coupled system of reaction-diffusion equations with time delays. An analysis of the steady-state problem is given. Some results on the existence and uniqueness of a global solution and stability of the steady-state problem are summarized, and numerical simulations showing stability and periodicity are presented. A Hopf bifurcation result and a theorem on asymptotic stability are given for the limiting case of the models without diffusion.

Key words: Genetic control models — reaction — diffusion equations with delays

1. Introduction

Jacob and Monod [11] proposed that genes control certain biochemical pathways in cells, such as the biosynthesis of tryptophan, by a negative feedback mechanism or repression. Mathematical models for this biochemical control of the gene were first proposed by Goodwin [6, 7]. These Goodwin models of repression were derived from biochemical kinetics with certain standard velocity approximations. The resulting nonlinear mathematical model has been studied extensively [cf. 3, 6, 7, 8, 10, 18, 19, 23, 27, 28] and is given by the following system of ordinary differential equations:

$$\begin{aligned} \dot{x}_1(t) &= \frac{\sigma}{1 + k[x_n(t)]^\rho} - b_1 x_1(t) \\ x_i(t) &= c_i x_{i-1}(t) - b_i x_i(t), \quad i = 2, 3, \dots, n, \end{aligned} \tag{1.1}$$

where the σ , c_i 's, b_i 's, and k are kinetic constants and ρ is the Hill coefficient or order of repression. Many studies have analyzed (1.1) for asymptotic stability or

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existence of periodic solutions to determine whether this model could explain epigenetic oscillations. A summary of these results can be found in Othmer [19].

Goodwin [6] suggested that delays caused by transcription and translation could affect the stability of the system. The Goodwin model for repression with discrete delays is given by the following system of equations:

$$\begin{aligned} \dot{x}_1(t) &= \frac{\sigma}{1 + k[x_n(t - r_1)]^p} - b_1 x_1(t) \\ \dot{x}_i(t) &= c_i x_{i-1}(t - r_i) - b_i x_i(t), \quad i = 2, 3, \dots, n, \end{aligned} \tag{1.2}$$

where the r_i 's represent delays for transcription and translation. There have been numerous studies of the qualitative behavior of solutions of (1.2), [cf. 1, 2, 4, 9, 15, 17].

Goodwin [6] also suggested that the spatial effects and diffusion should be taken into account. There have been several papers that study the effects of modeling enzymes that are spatially dependent [cf. 12, 20, 25, 26]. Shymko and Glass [24] considered a model of repression where the processes of transcription and translation occurred at specific locations in an infinite one-dimensional domain. The processes of transcription and translation were modeled as if they were catalytic sites using a delta function. Thames and Elster [26] considered a repression model on the interval $[0, 1]$ with the processes of transcription and translation occurring at the two different boundaries. Neither of the above models took into account any time delays. Thames and Elster noted that the spatial separation needed to produce oscillations in a Goodwin model with diffusion alone is too great to be of importance in a cell.

We develop and analyze two models which incorporate both time delays and diffusion. The models are formulated using a combination of the biochemical techniques used to derive (1.2) and a division into compartments to account for spatial effects. A steady-state analysis is presented for the models, and some results on existence of global solutions and stability of steady-state solutions are given. The limiting case where the diffusion is considered insignificant is analyzed. For this case a Hopf bifurcation result and a global asymptotic stability theorem are presented.

2. Formulation of the mathematical models

As was noted in the previous section there are many references which have studied either delays or diffusion in models of repression. There are several fundamental questions about how delays and diffusion affect the qualitative behavior of the systems of differential equations governing the models. MacDonald [14] states that the process of diffusion can be modeled by the addition of a delay into the model. In this section we develop two models based on genetic repression which we believe will aid the understanding of the relative importance of diffusion and time delays. Similar models with differing production or decay terms could be developed for predator-prey interactions where the breeding habitats are separated and incubation or maturity times are taken into account. Also, the modeling of a hormonal control system, where the endocrine gland is

separated from the target organ, would have spatial effects, and time delays would arise from the time required for release of the hormones or for the time to affect the organ.

The first model considers repression of the gene by an endproduct produced at a distance from the gene. The Jacob-Monod theory of repression has only been shown for prokaryotic organisms. It has been proposed that a similar but more complicated control mechanism occurs for eukaryotes [5, 13]; however, experimental evidence on whether the more complicated mechanism is qualitatively similar to the Jacob-Monod theory has been inconclusive. If this theory of endproduct repression is applied to eukaryotic cells, then the above model would be appropriate as the DNA is separated from the cytoplasm by a nuclear membrane and translation occurs at the ribosomes bound to the endoplasmic reticulum in the cytoplasm. One compartment is the nucleus. The second compartment represents the cytoplasm where diffusion occurs but there are no reactions. We chose to model the reacting ribosomes as a distinct third compartment which is assumed to be a fixed distance from the nucleus. Another option would have been to have the reactions occurring as boundary conditions; however, a distinct compartment has advantages for studying the importance of diffusion. The third compartment may have very little volume if one considers diffusion important or on the other hand when diffusion is insignificant in the asymptotic limit it could incorporate the second compartment and reduce to a two compartment well-mixed model with only delays. For this three compartment model to be appropriate for a prokaryotic cell one would want to consider an enzyme at the cell membrane producing an endproduct which represses the gene in the center of the cell. The first and third compartments in this case are the reacting compartments which are for modeling purposes separated by artificial barriers rather than actual physical barriers.

The first model contains three interacting compartments (see Fig. 2.1). The first and third compartments are well-mixed compartments with differential delay equations governing the reactions. The second compartment connects the first and third, is non-reacting except for a term to account for decay of the chemical species, and allows diffusion to account for the spatial separation between the first and third compartments.

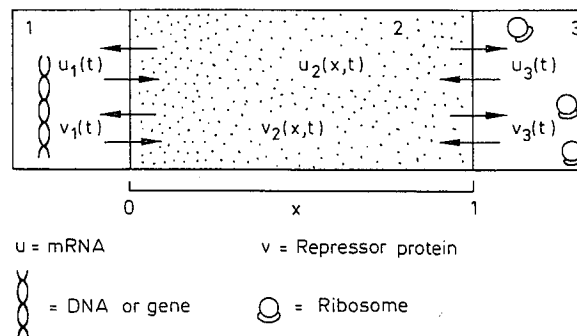
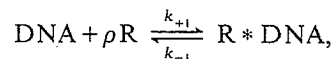
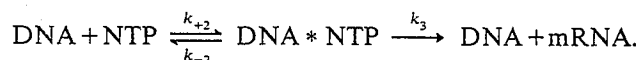


Fig. 2.1. Three compartment model: Compartment 1 is the nucleus of the cell. Compartment 2 is the cytoplasm and allows for diffusion. Compartment 3 is the endoplasmic reticulum or the cell wall unit distance from the nucleus

In the first compartment we have the following biochemical reactions occurring. DNA combines reversibly with ρ molecules of the repressor R to form an inactive complex according to the following reaction:



where the k_i 's are kinetic reaction rate constants. The free DNA combines with nucleotide triphosphates, NTP, in the process of transcription to form mRNA according to the following reaction:



In the above reactions it is assumed that the DNA is conserved and that the NTP's are in excess so that they can be treated as having a constant concentration. $\text{DNA} * \text{NTP}$ is the initiation complex for the process of transcription. Once the reaction begins it is assumed that it continues to completion. The equilibria are assumed to be fast so that a Michaelis-Menten velocity approximation can be made. If we assume a linear decay of the mRNA, then a differential equation for the production and decay of mRNA can be written for the first compartment in a similar manner to [3, 19, 28]. Let u_1 be the concentration of mRNA and v_1 be the concentration of the repressor in the first compartment, then

$$\frac{du_1(t)}{dt} = \frac{\sigma}{1 + k[v_1(t - r_1)]^\rho} - b_1 u_1(t) \quad (2.1)$$

where $\sigma = k_3 K_2 \text{DNA}_T [\text{NTP}] / (1 + K_2 [\text{NTP}])$, $K_2 = k_{+2} / k_{-2}$, and $k = k_{+1} / k_{-1} (1 + K_2 [\text{NTP}])$. DNA_T is the total concentration of DNA and $[\text{NTP}]$ is the concentration of NTP. The delay r_1 accounts for the transcription time needed in the transcription reaction. As the first compartment is well-mixed there is no spatial dependence for the variables u_1 and v_1 .

The other biochemical reaction or series of reactions occurs in the third compartment. As in the first compartment the third compartment is well-mixed and so there is no spatial dependence. In this compartment the mRNA is translated by the ribosomes to produce an endproduct. For simplicity we shall assume that this endproduct is the repressor protein though in fact it may undergo some other reactions. Let AA denote the amino acids needed to produce the translated protein and $\text{mRNA} * \text{AA}$ denotes the initiation complex for the process of translation. We assume that once translation starts it proceeds to completion according to the following reaction:



where R is the repressor protein. If we make similar assumptions and velocity approximations to the ones we made for the process of transcription, and if we assume a linear decay rate for the repressor protein, then a differential equation for the production and decay of R can be written for the third compartment in a similar manner to [3, 19]. Let u_3 be the concentration of the mRNA and v_3 be

the concentration of the repressor in the third compartment, then

$$\frac{dv_3(t)}{dt} = c_0 u_3(t - r_2) - b_2 v_3(t), \quad (2.2)$$

where $c_0 = k_5 K_4 [AA]$ and $K_4 = k_{+4}/k_{-4}$. $[AA]$ is the concentration of amino acids which are assumed to be in excess hence constant. The delay r_2 accounts for the translation time. The second compartment is separated from the first and third by "membranes" that allow substances to diffuse passively across them according to Fick's law. The membrane in this case is either an artificial barrier or a boundary layer that separates the reacting compartments of the model from the region where there is only diffusion or it could be a real membrane such as the nuclear membrane in eukarotic cells. As before u_i and v_i represent mRNA and repressor, respectively, in the i th compartment. If a_i 's are the membrane permeabilities and D_i 's are the coefficients of diffusion and if we assume a linear decay of the u_i 's and v_i 's, then the three compartment model is represented by the following system of equations:

$$\begin{aligned} \frac{du_1(t)}{dt} &= f(v_1(t - r_1)) - b_1 u_1(t) + a_1(u_2(0, t) - u_1(t)) \\ \frac{dv_1(t)}{dt} &= -b_2 v_1(t) + a_1(v_2(0, t) - v_1(t)), \\ \frac{\partial u_2(x, t)}{\partial t} &= D_1 \frac{\partial^2 u_2(x, t)}{\partial x^2} - b_1 u_2(x, t), \\ \frac{\partial v_2(x, t)}{\partial t} &= D_2 \frac{\partial^2 v_2(x, t)}{\partial x^2} - b_2 v_2(x, t), \\ \frac{du_3(t)}{dt} &= -b_1 u_3(t) + a_3(u_2(1, t) - u_3(t)), \\ \frac{dv_3(t)}{dt} &= c_0 u_3(t - r_2) - b_2 v_3(t) + a_3(v_2(1, t) - v_3(t)), \end{aligned} \quad (2.3)$$

with the boundary conditions

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

where f is the nonlinear production term in (2.1) and the β_i 's and β_i^* 's are constants associated with the permeability of the membrane.

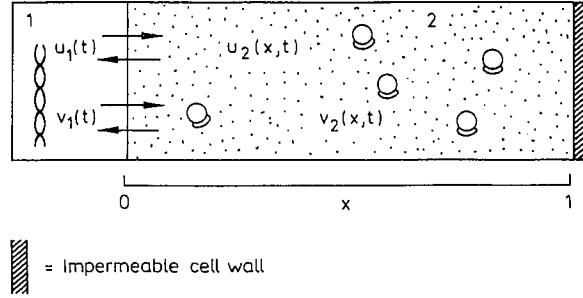


Fig. 2.2. Two compartment model: Compartment 1 is the nucleus as before. Compartment 2 is the cytoplasm with free ribosomes and again takes into account diffusion

A second model that is related to this first model contains only two compartments and accounts for translation occurring uniformly throughout the cytoplasm (see Fig. 2.2). The first compartment in this model is the same as in the previous model. The second compartment contains free ribosomes which translate the mRNA at varying distances from the gene. This means that the second compartment has both diffusion to account for spatial effects and delays for the time of translation. This model better describes the Jacob and Monod theory of repression for prokaryotic cells. We shall assume that the cell membrane (not the "membrane" between the first and second compartments) is impermeable to both mRNA and the repressor. With these assumptions we see that the two compartment model can be described by the following system of equations:

$$\begin{aligned}
 \frac{du_1(t)}{dt} &= f(v_1(t-r_1)) - b_1 u_1(t) + a_1(u_2(0,t) - u_1(t)) \\
 \frac{dv_1(t)}{dt} &= -b_2 v_1(t) + a_1(v_2(0,t) - v_1(t)), \\
 \frac{\partial u_2(x,t)}{\partial t} &= D_1 \frac{\partial^2 u_2(x,t)}{\partial x^2} - b_1 u_2(x,t), \\
 \frac{\partial v_2(x,t)}{\partial t} &= D_2 \frac{\partial^2 v_2(x,t)}{\partial x^2} + c_0 u_2(x,t-r_2) - b_2 v_2(x,t),
 \end{aligned} \tag{2.4}$$

with the boundary conditions

$$\begin{aligned}
 -\frac{\partial u_2(0,t)}{\partial x} &= \beta_1(u_1(t) - u_2(0,t)), \\
 -\frac{\partial v_2(0,t)}{\partial x} &= \beta_1^*(v_1(t) - v_2(0,t)), \\
 \frac{\partial u_2(1,t)}{\partial x} &= 0 \quad \text{and} \quad \frac{\partial v_2(1,t)}{\partial x} = 0.
 \end{aligned}$$

The description of the functions and constants for the first model of repression apply for this model of repression except now translation occurs throughout the second compartment instead of in a distinct third compartment. Hence the diffusion equations have delays in the equations, but the boundary conditions at $x=1$ are simple Neumann conditions. In both models the coupling effect is through the boundary conditions.

3. Analysis of the steady-state problems

In this section we consider the time-independent equations to the models given by (2.3) and (2.4). By setting the time derivatives in (2.3) equal to zero we have the following steady-state equations:

$$\begin{aligned}
 f(v_1^s) - (b_1 + a_1)u_1^s + a_1u_2^s(0) &= 0 \\
 (b_2 + a_1)v_1^s - a_1v_2^s(0) &= 0 \\
 \frac{d^2u_2^s(x)}{dx^2} - \delta_1^2u_2^s(x) &= 0 \\
 \frac{d^2v_2^s(x)}{dx^2} - \delta_2^2v_2^s(x) &= 0 \\
 (b_1 + a_3)u_3^s - a_3u_2^s(1) &= 0 \\
 c_0u_3^s - (b_2 + a_3)v_3^s + a_3v_2^s(1) &= 0
 \end{aligned} \tag{3.1a}$$

with the boundary conditions

$$\begin{aligned}
 -\frac{du_2^s(0)}{dx} &= \beta_1(u_1^s - u_2^s(0)) \\
 \frac{du_2^s(1)}{dx} &= \beta_2(u_3^s - u_2^s(1)) \\
 -\frac{dv_2^s(0)}{dx} &= \beta_1^*(v_1^s - v_2^s(0)) \\
 \frac{dv_2^s(1)}{dx} &= \beta_2^*(v_3^s - v_2^s(1))
 \end{aligned} \tag{3.1b}$$

where u_i^s and v_i^s denote the steady-state solutions and $\delta_i^2 = b_i/D_i$. With this notation the solutions to the second order ordinary differential equations in (3.1a) can be written as follows:

$$\begin{aligned}
 u_2^s(x) &= A_1 \cosh \delta_1 x + A_2 \sinh \delta_1 x \\
 v_2^s(x) &= B_1 \cosh \delta_2 x + B_2 \sinh \delta_2 x.
 \end{aligned} \tag{3.2}$$

By using (3.2) in (3.1) we are left with the following eight equations:

$$\begin{aligned}
a_1 A_1 &= (b_1 + a_1)u_1^s - \sigma / (1 + k(v_1^s)^\rho) \\
a_1 B_1 &= (b_2 + a_1)v_1^s \\
a_3(A_1 \cosh \delta_1 + A_2 \sinh \delta_1) &= (b_1 + a_3)u_3^s \\
a_3(B_1 \cosh \delta_2 + B_2 \sinh \delta_2) &= (b_2 + a_3)v_3^s - c_0 u_3^s \\
-\delta_1 A_2 &= \beta_1(u_1^s - A_1) \\
\delta_1(A_1 \sinh \delta_1 + A_2 \cosh \delta_1) &= \beta_2(u_3^s - (A_1 \cosh \delta_1 + A_2 \sinh \delta_1)) \\
-\delta_2 B_2 &= \beta_1^*(v_1^s - B_1) \\
\delta_2(B_1 \sinh \delta_2 + B_2 \cosh \delta_2) &= \beta_2^*(v_3^s - (B_1 \cosh \delta_2 + B_2 \sinh \delta_2))
\end{aligned} \tag{3.3}$$

with the eight unknowns u_1^s , v_1^s , u_3^s , v_3^s , A_1 , A_2 , B_1 , and B_2 . As only the first equation in (3.3) is nonlinear this system of equations can be solved. If we define the following positive constants that depend only on the parameters of the system (2.3):

$$\begin{aligned}
\varepsilon_1 &= \frac{b_2 \beta_1^*}{\delta_2 (b_2 + a_1)} \\
\varepsilon_2 &= \frac{b_1 \beta_2 \cosh \delta_1 + (b_1 + a_3) \delta_1 \sinh \delta_1}{b_1 \beta_2 \sinh \delta_1 + (b_1 + a_3) \delta_1 \cosh \delta_1} \\
\varepsilon_3 &= b_2 \beta_2^* (b_1 + a_3) (\cosh \delta_2 + \varepsilon_1 \sinh \delta_2) \\
&\quad + \delta_2 (b_1 + a_3) (b_2 + a_3) (\sinh \delta_2 + \varepsilon_1 \cosh \delta_2) \\
\varepsilon_4 &= \frac{\delta_1 (b_1 + a_3)}{(b_1 \beta_2 \sinh \delta_1 + (b_1 + a_3) \delta_1 \cosh \delta_1)} \\
\varepsilon_5 &= \frac{\varepsilon_3 (b_1 \beta_1 + (b_1 + a_1) \delta_1 \varepsilon_2)}{c_0 \beta_2^* a_3 \varepsilon_4} \\
\varepsilon_6 &= k(a_1 / (b_2 + a_1))^\rho,
\end{aligned}$$

then the nonlinear equation is of the form

$$\varepsilon_5 B_1 = \sigma \beta_1 / (1 + \varepsilon_6 B_1^\rho).$$

This equation has a unique positive solution B_1 .

In the derivation we find that $B_2 = \varepsilon_1 B_1$ which implies that there is a unique positive solution B_2 . Similarly $A_1 = \varepsilon_3 B_1 / c_0 a_3 \beta_2^*$ which implies there is a unique positive solution A_1 . Also $A_2 = -\varepsilon_2 A_1$ which gives a unique negative A_2 ; however, $A_1 \varepsilon_4 = A_1 (\cosh \delta_1 - \varepsilon_2 \sinh \delta_1) = A_1 \cosh \delta_1 + A_2 \sinh \delta_1 > 0$.

From (3.3) we can readily verify that $u_1^s > 0$, $u_3^s > 0$, $v_1^s > 0$, and $v_3^s > 0$. As $v_2^s(x)$ is monotone increasing and clearly $v_2^s(0) > 0$, it follows that $v_2^s(x) > 0$ for all $x \in [0, 1]$. To show there is a unique positive steady state it only remains to show that $u_2^s(x) > 0$ for all $x \in [0, 1]$. Clearly $u_2^s(0)$ and $u_2^s(1)$ are positive. Differen-

tiating u_2^s it can be shown that

$$\frac{d}{dx} u_2^s(x) = -\varepsilon_7 [b_1 \beta_1 \cosh \delta_1(1-x) + (b_1 + a_3) \delta_1 \sinh \delta_1(1-x)]$$

where $\varepsilon_7 = \delta_1 A_1 / [b_1 \beta_2 \sinh \delta_1 + (b_1 + a_3) \delta_1 \cosh \delta_1]$. Thus $d[u_2^s(x)]/dx < 0$ for $0 < x < 1$ which shows that $u_2^s(x)$ is monotone decreasing. As $u_2^s(1) > 0$, it follows that $u_2^s(x) > 0$ for all $x \in [0, 1]$.

To find the steady-state solutions to the model given by (2.4), we again set the time derivatives equal to zero and obtain the following system of equations:

$$\begin{aligned} f(v_1^s) - (b_1 + a_1)u_1^s + a_1 u_2^s(0) &= 0 \\ (b_2 + a_1)v_1^s - a_1 v_2^s(0) &= 0 \\ \frac{d^2 u_2^s(x)}{dx^2} - \delta_1^2 u_2^s(x) &= 0 \\ \frac{d^2 v_2^s(x)}{dx^2} - \delta_2^2 v_2^s(x) &= -\gamma u_2^s(x) \end{aligned} \quad (3.4a)$$

with the boundary conditions

$$\begin{aligned} -\frac{du_2^s(0)}{dx} &= \beta_1 (u_1^s - u_2^s(0)) \\ -\frac{dv_2^s(0)}{dx} &= \beta_1^* (v_1^s - v_2^s(0)) \\ \frac{du_2^s(1)}{dx} &= \frac{dv_2^s(1)}{dx} = 0 \end{aligned} \quad (3.4b)$$

where $\gamma = c_0/D_2$ and u_i^s and v_i^s denote the steady-state solutions and $\delta_i^2 = b_i/D_i$. A solution to the second order equation for u_2^s in (3.4a) can be written as follows:

$$u_2^s(x) = A_1 \cosh \delta_1(1-x) + A_2 \sinh \delta_1(1-x).$$

The boundary condition $d[u_2^s(1)]/dx = 0$ implies that $A_2 = 0$, so it follows that

$$u_2^s(x) = A_1 \cosh \delta_1(1-x).$$

If $\delta_1 \neq \delta_2$, then we can use the solution $u_2^s(x)$ and the boundary condition $d[v_2^s(1)]/dx = 0$ to find the solution to the second order equation for v_2^s in (3.4a). This solution is given by

$$v_2^s(x) = B_1 \cosh \delta_2(1-x) - (\gamma A_1 / (\delta_1^2 - \delta_2^2)) \cosh \delta_1(1-x), \quad (3.5a)$$

where B_1 is a constant to be determined.

If $\delta_1 = \delta_2$, then with the solution $u_2^s(x)$ and the boundary condition $d[v_2^s(1)]/dx = 0$ the solution to the second order equation for v_2^s in (3.4a) satisfies:

$$v_2^s(x) = B_1 \cosh \delta_1(1-x) - (\gamma A_1 / 2\delta_1)(1-x) \sinh \delta_1(1-x). \quad (3.5b)$$

where B_1 is a constant to be determined.

With (3.5a) used in (3.4) the following equations are obtained:

$$\begin{aligned}
 f(v_1^s) - (b_1 + a_1)u_1^s + a_1 A_1 \cosh \delta_1 &= 0 \\
 (b_2 + a_1)v_1^s - a_1(B_1 \cosh \delta_2 - [\gamma A_1 / (\delta_1^2 - \delta_2^2)] \cosh \delta_1) &= 0 \\
 -A_1 \delta_1 \sinh \delta_1 &= \beta_1(A_1 \cosh \delta_1 - u_1^s) \\
 -B_1 \delta_2 \sinh \delta_2 + [\gamma A_1 / (\delta_1^2 - \delta_2^2)] \delta_1 \sinh \delta_1 \\
 &= \beta_1^*(B_1 \cosh \delta_2 - [\gamma A_1 / (\delta_1^2 - \delta_2^2)] \cosh \delta_1 - v_1^s)
 \end{aligned} \tag{3.6a}$$

and with (3.5b) the second and fourth equations in (3.6a) are replaced by

$$\begin{aligned}
 (b_2 + a_1)v_1^s - a_1(B_1 \cosh \delta_1 - [\gamma A_1 / 2\delta_1] \sinh \delta_1) &= 0 \\
 -B_1 \delta_1 \sinh \delta_1 + [\gamma A_1 / 2\delta_1](\delta_1 \cosh \delta_1 + \sinh \delta_1) \\
 &= \beta_1^*(B_1 \cosh \delta_1 - [\gamma A_1 / 2\delta_1] \sinh \delta_1)
 \end{aligned} \tag{3.6b}$$

The above equations contain the four unknowns A_1 , B_1 , u_1^s , and v_1^s .

For $\delta \neq \delta_2$ we can solve (3.6a). By defining the positive constants

$$\begin{aligned}
 \mu_1 &= \beta_1 \cosh \delta_1 + \delta_1 \sinh \delta_1 \\
 \mu_2 &= \beta_1^* \cosh \delta_2 + \delta_2 \sinh \delta_2 \\
 \mu_3 &= b_1 \mu_1 + a_1 \delta_1 \sinh \delta_1 \\
 \mu_4 &= b_2 \mu_2 + a_1 \delta_2 \sinh \delta_2 \\
 \mu_5 &= (\delta_1^2 - \delta_2^2) / (\delta_1 \sinh \delta_1 \cosh \delta_2 - \delta_2 \cosh \delta_1 \sinh \delta_1),
 \end{aligned}$$

we obtain

$$f(v_1^s) = \frac{\mu_3 \mu_4 \mu_5}{\beta_1 \gamma a_1} v_1^s.$$

As in the first model this equation has a unique positive solution v_1^s . In the derivation we find $A_1 = \mu_4 \mu_5 v_1^s / \gamma a_1$, $u_1^s = \mu_1 A_1 / \beta_1$, and $B_1 = (a_1 \delta_1 \sinh \delta_1 + b_2 (\delta_1 \sinh \delta_1 + \beta_1^* \cosh \delta_1)) v_1^s / a_1 (\delta_1 \sinh \delta_1 \cosh \delta_2 - \delta_2 \cosh \delta_1 \sinh \delta_2)$.

From the above information it is easily seen that $u_2^s(x)$ is positive, so it only remains to show that $v_2^s(x)$ is positive to obtain a unique positive steady-state solution to (2.4). However $v_2^s(0) = [1 + (b_2/a_1)]v_1^s$ and $d[v_2^s(x)]/dx \geq 0$ for $x \in [0, 1]$, thus $v_2^s(x) > 0$ for $x \in [0, 1]$.

For $\delta_1 = \delta_2$ we can solve for A_1 , B_1 , u_1^s , and v_1^s using the modifications in (3.6b) as stated above. A similar argument to the one presented for $\delta_1 \neq \delta_2$ gives a unique positive steady-state solution to (2.4), hence for any set of parameter values in (2.4) we obtain a unique positive steady-state solution u_1^s , v_1^s , $u_2^s(x)$, and $v_2^s(x)$.

4. Existence and stability results for the three-compartment model

Existence and uniqueness as well as boundedness of solutions to the three-compartment model has been shown in [22]. The basic tool in obtaining these

results is the monotone method and the associated upper-lower solutions as in [21]. If we define the following differential operators:

$$\begin{aligned} L_1[u_1] &= u_1' + (a_1 + b_1)u_1 & \mathcal{L}_1[v_1] &= v_1' + (a_1 + b_2)v_1 \\ L_2[u_2] &= (u_2)_t - D_1(u_2)_{xx} + b_1u_2 & \mathcal{L}_2[v_2] &= (v_2)_t - D_2(v_2)_{xx} + b_2v_2 \\ L_3[u_3] &= u_3' + (a_3 + b_1)u_3 & \mathcal{L}_3[v_3] &= v_3' + (a_3 + b_2)v_3 \end{aligned}$$

and the boundary operators

$$\begin{aligned} B[u_2](0) &= -(u_2)_x(0, t) + \beta_1u_2(0, t) \\ B[u_2](1) &= (u_2)_x(1, t) + \beta_2u_2(1, t) \\ \mathcal{B}[v_2](0) &= -(v_2)_x(0, t) + \beta_1^*v_2(0, t) \\ \mathcal{B}[v_2](1) &= (v_2)_x(1, t) + \beta_2^*v_2(1, t), \end{aligned}$$

then we can define upper and lower solutions, $(\tilde{u}_i, \tilde{v}_i)$ and $(\underline{u}_i, \underline{v}_i)$, of (2.3) if they satisfy the differential inequalities

$$\begin{aligned} L_1[\tilde{u}_1] - a_1\tilde{u}_2(0, t) - f(p_1(t - r_1)) &\geq 0 \geq L_1[\underline{u}_1] - a_1\underline{u}_2(0, t) - f(\tilde{v}_1(t - r_1)) \\ \mathcal{L}_1[\tilde{v}_1] - a_1\tilde{v}_2(0, t) &\geq 0 \geq \mathcal{L}_1[\underline{v}_1] - a_1\underline{v}_2(0, t) \\ L_2[\tilde{u}_2] &\geq 0 \geq L_2[\underline{u}_2] \\ \mathcal{L}_2[\tilde{v}_2] &\geq 0 \geq \mathcal{L}_2[\underline{v}_2] \\ L_3[\tilde{u}_3] - a_3\tilde{u}_2(1, t) &\geq 0 \geq L_3[\underline{u}_3] - a_3\underline{u}_2(1, t) \\ \mathcal{L}_3[\tilde{v}_3] - a_3\tilde{v}_2(1, t) - c_0\tilde{u}_3(t - r_2) &\geq 0 \geq \mathcal{L}_3[\underline{v}_3] - a_3\underline{v}_2(1, t) - c_0\underline{u}_3(t - r_2), \end{aligned}$$

the boundary inequalities

$$\begin{aligned} B[\tilde{u}_2](0) - \beta_1\tilde{u}_1(t) &\geq 0 \geq B[\underline{u}_2](0) - \beta_1\underline{u}_1(t) \\ B[\tilde{u}_2](1) - \beta_2\tilde{u}_3(t) &\geq 0 \geq B[\underline{u}_2](1) - \beta_2\underline{u}_3(t) \\ \mathcal{B}[\tilde{v}_2](0) - \beta_1^*\tilde{v}_1(t) &\geq 0 \geq \mathcal{B}[\underline{v}_2](0) - \beta_1^*\underline{v}_1(t) \\ \mathcal{B}[\tilde{v}_2](1) - \beta_2^*\tilde{v}_3(t) &\geq 0 \geq \mathcal{B}[\underline{v}_2](1) - \beta_2^*\underline{v}_3(t), \end{aligned}$$

and the initial inequalities

$$\begin{aligned} \tilde{u}_1(0) &\geq \xi_1 \geq \underline{u}_1(0) & \tilde{v}_1(t) &\geq \eta_1(t) \geq \underline{v}_1(t), & t \in [-r_1, 0] \\ \tilde{u}_2(x, 0) &\geq \xi_2(x) \geq \underline{u}_2(x, 0), & \tilde{v}_2(x, 0) &\geq \eta_2(x) \geq \underline{v}_2(x, 0) \\ \tilde{u}_3(t) &\geq \xi_3(t) \geq \underline{u}_3(t), & \tilde{v}_3(0) &\geq \eta_3 \geq \underline{v}_3(0), & t \in [-r_2, 0]. \end{aligned}$$

With the above definitions we can establish an existence theorem for (2.3) by constructing monotone sequences $\{\tilde{u}_i^m\}$, $\{\tilde{v}_i^m\}$ and $\{\underline{u}_i^m\}$, $\{\underline{v}_i^m\}$ with $(\tilde{u}_i^0, \tilde{v}_i^0) = (\tilde{u}_i, \tilde{v}_i)$ and $(\underline{u}_i^0, \underline{v}_i^0) = (\underline{u}_i, \underline{v}_i)$. It has been shown in [22] that these sequences converge monotonically from above and below, respectively, to give a unique solution (u_i, v_i) with

$$(\underline{u}_i, \underline{v}_i) \leq (u_i, v_i) \leq (\tilde{u}_i, \tilde{v}_i).$$

In addition it is shown that there exist constants ρ_i and ρ_i^* such that

$$0 \leq u_i \leq \rho_i \quad \text{and} \quad 0 \leq v_i \leq \rho_i^*$$

for all $t > 0$ and $x \in [0, 1]$. Hence the time-dependent problem has a unique uniformly bounded solution. Details of these existence-comparison and boundedness proof can be found in [22].

A sufficient condition for the global asymptotic stability of the steady-state solution found in the previous section can be established by constructing some upper and lower solutions of (2.3) that exponentially approach the steady-state solution as $t \rightarrow \infty$. This global stability result is with respect to any nonnegative initial functions and is independent of the time delays r_1 and r_2 . The result is summarized by the following theorem:

Theorem 4.1. *Let (u_i^s, v_i^s) be a nonnegative steady-state solution of (2.3). If*

$$\sup_{v_i \geq 0} [-f'(v_i)] < b_1 b_2 / c_0$$

then for any nonnegative initial function (ξ_i, η_i) there exist positive constants M and ε , independent of the time delays r_1 and r_2 , such that the corresponding time-dependent solution (u_i, v_i) satisfies the relations

$$\begin{aligned} |u_i(t) - u_i^s| &\leq M e^{-\varepsilon t}, & |v_i(t) - v_i^s| &\leq M e^{-\varepsilon t}, & i = 1, 3, \\ |u_2(x, t) - u_2^s(x)| &\leq M e^{-\varepsilon t}, & |v_2(x, t) - v_2^s(x)| &\leq M e^{-\varepsilon t}, \end{aligned}$$

for all $t > 0$.

The proof of this theorem is based on the construction of a suitable pair of upper and lower solutions in the form

$$\begin{aligned} (\tilde{u}_i, \tilde{v}_i) &= (u_i^s + p(t), v_i^s + q(t)) \\ (\underline{u}_i, \underline{v}_i) &= (u_i^s - p^*(t), v_i^s - q^*(t)). \end{aligned}$$

In fact, it suffices to take $p(t) = p_0 e^{-\varepsilon t}$, $p^*(t) = p_0^* e^{-\varepsilon t}$, $q(t) = q_0 e^{-\varepsilon t}$, and $q^*(t) = q_0^* e^{-\varepsilon t}$ for some sufficiently large constants p_0 , p_0^* , q_0 and q_0^* and sufficiently small $\varepsilon > 0$. The existence comparison theorem then shows that all solutions of (2.3) tend to (u_i^s, v_i^s) as $t \rightarrow \infty$. Details of the argument can be found in [22].

It has been shown [cf. 17] that for (1.2) if

$$-f'(\bar{x}_n) < \left(\prod_{i=1}^n b_i \right) / \left(\prod_{i=2}^n c_i \right)$$

where \bar{x}_n is the equilibrium solution and f is the nonlinear function, then all solutions asymptotically approach the equilibrium solution. The result of Theorem 4.1 is similar (though weaker) to the results previously obtained for the Goodwin model with delays but not diffusion.

Numerical simulations of the model (2.3) indicate that our estimates in Theorem 4.1 are conservative. Figure 4.1 was obtained by an integration scheme which coupled a fourth-order method for delay differential equations to an implicit finite difference scheme. The following parameter values were used: $\sigma = c_0 = 1$,

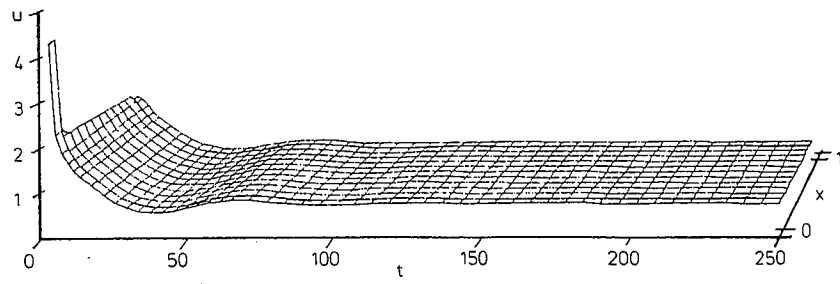


Fig. 4.1a. The surface representing the concentration $u(x, t)$ and showing asymptotic stability

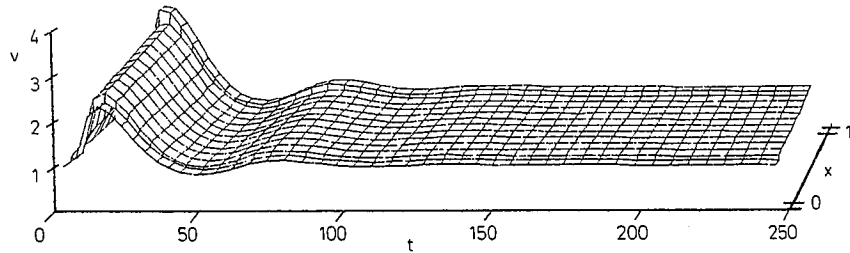


Fig. 4.1b. The surface representing the concentration $v(x, t)$ and showing asymptotic stability

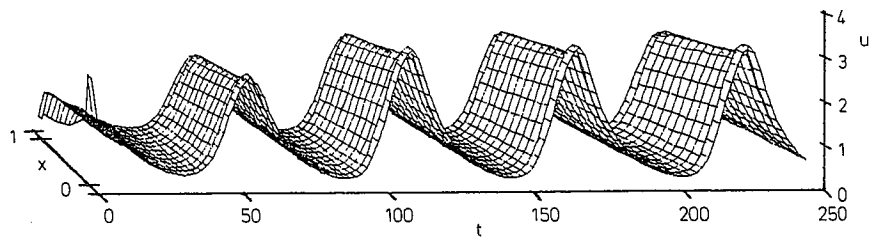


Fig. 4.2a. The surface representing the concentration of $u(x, t)$ and showing oscillatory behavior

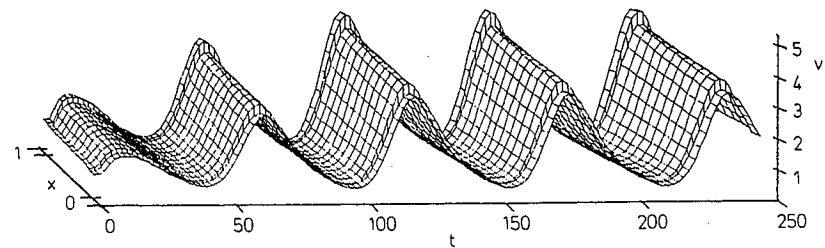


Fig. 4.2b. The surface representing the concentration $v(x, t)$ and showing oscillatory behavior

$b_1 = 0.1$, $b_2 = 0.2$, $D_1 = D_2 = 4$, $a_1 = a_3 = 10$, $k = 2$, $r_1 = 10$, $r_2 = 2$, and $\rho = 1$. The data were generated by an APL program on the Claremont Graduate School VAX/780 with stepsizes $\Delta t = 0.05$, $\Delta x = 0.1$. The data were transformed into the 3-dimensional surfaces shown with the help of graphics routines of MATHLIB from the Department of Mathematics at Harvey Mudd College. With the above parameter values the condition of Theorem 4.1 is violated; however, the numerical simulation clearly indicates asymptotic stability of the system of equations (2.3). Note that in Fig. 4.1 and 4.2 the first and third compartment concentrations are shown just outside the 0 and 1 endpoints of the x -axis respectively.

By a simple change of the Hill coefficient ρ to $\rho = 4$ we no longer have asymptotic stability. Figure 4.2 shows this particular case where all other parameters are as above. In both figures the initial data were near the equilibrium except for a perturbation from the equilibrium in the u_1 component (shown by the sharp spike in each graph of u). In Fig. 4.2 the system appears to generate self-sustained stable periodic solutions with a period of approximately 58. Hence numerically we see that the model (2.3) can generate the same types of behavior as observed in the Goodwin model with delays (1.2). More work is needed to see what are the relative effects of diffusion and time delays.

5. Analysis of the models without diffusion

Though the principle reason for the above models is to allow a comparative study of the effects of diffusion and delays, a first approximation for the above models would be to ignore the effects of diffusion. The time for a particular chemical species to diffuse across a cell is relatively short compared to the times for either transcription or translation. If we use this assumption and still consider the nucleus separate from the cytoplasm, we have the following two-compartment model which is equivalent to (2.3) without the non-reacting diffusion compartment or (2.4) without diffusion:

$$\begin{aligned} \dot{u}_1(t) &= f(v_1(t-r_1)) + a_1 u_2(t) - (b_1 + a_1) u_1(t), \\ \dot{v}_1(t) &= a_2 v_2(t) - (b_2 + a_2) v_1(t), \\ \dot{u}_2(t) &= a_3 u_1(t) - (b_1 + a_3) u_2(t), \\ \dot{v}_2(t) &= c_0 u_2(t-r_2) + a_4 v_1(t) - (b_2 + a_4) v_2(t), \end{aligned} \tag{5.1}$$

where f and b_i are as before and we allow different permeabilities a_i . By transforming $v_i(t+r_2) \rightarrow v_i(t)$ the above system of equations reduces to a system of delay differential equations with only one delay in the nonlinear function or equivalently $r_2 = 0$.

System (5.1) can be shown to have a unique equilibrium $(\bar{u}_1, \bar{v}_1, \bar{u}_2, \bar{v}_2)^T$, where \bar{v}_1 satisfies the equation $f(\bar{v}_1) = B_1 B_2 \bar{v}_1 / c_0$ or equivalently

$$k B_1 B_2 \bar{v}_1^{\rho+1} + B_1 B_2 \bar{v}_1 - \sigma c_0 = 0, \tag{5.2}$$

where $B_1 = (b_1^2 + a_1 b_1 + a_3 b_1) / a_3$ and $B_2 = (b_2^2 + a_2 b_2 + a_4 b_2) / a_2$. With \bar{v}_1 , we obtain $\bar{v}_2 = (b_2 + a_2) \bar{v}_1 / a_2$, $\bar{u}_2 = B_2 \bar{v}_1 / c_0$, and $\bar{u}_1 = (b_1 + a_3) \bar{u}_2 / a_3$.

The linearization of (5.1) with $r_2=0$ about the equilibrium can be written

$$\begin{bmatrix} \dot{u}_1(t) \\ \dot{v}_1(t) \\ \dot{u}_2(t) \\ \dot{v}_2(t) \end{bmatrix} = \begin{bmatrix} -(a_1+b_1) & 0 & a_1 & 0 \\ 0 & -(a_2+b_2) & 0 & a_2 \\ a_3 & 0 & -(a_3+b_1) & 0 \\ 0 & a_4 & c_0 & -(a_4+b_2) \end{bmatrix} \begin{bmatrix} u_1(t) \\ v_1(t) \\ u_2(t) \\ v_2(t) \end{bmatrix} \\ + \begin{bmatrix} 0 & f'(\bar{v}_1) & 0 & 0 \\ 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 \end{bmatrix} \begin{bmatrix} u_1(t-r_1) \\ v_1(t-r_1) \\ u_2(t-r_1) \\ v_2(t-r_1) \end{bmatrix}.$$

The characteristic equation for this linear system can be written as

$$(\lambda + b_1)(\lambda + b_2)(\lambda + b_1 + a_1 + a_3)(\lambda + b_2 + a_2 + a_4) - c_0 a_2 a_3 f'(\bar{v}_1) e^{-\lambda r_1} = 0. \quad (5.4)$$

This is precisely the form of the exponential polynomial analyzed in Theorem 1 of Mahaffy [16]. Let $P(\lambda) = (\lambda + b_1)(\lambda + b_2)(\lambda + b_1 + a_1 + a_3)(\lambda + b_2 + a_2 + a_4)$ and $\alpha = -c_0 a_2 a_3 f'(\bar{v}_1)$, (Note: $\alpha > 0$).

Theorem 5.1. *If $b_1 b_2 (b_1 + a_1 + a_3)(b_2 + a_2 + a_4) < \alpha$, then there exists a delay r_0 such that for all $r_1 > r_0$, (5.3) has at least two roots with $\text{Re } \lambda > 0$. If either $b_1 b_2 (b_1 + a_1 + a_3)(b_2 + a_2 + a_4) > \alpha$ or $0 \leq r_1 < r_0$, then all solutions of (5.4) have $\text{Re } \lambda < 0$. Moreover, the critical value r_0 where the Hopf bifurcation occurs is given by*

$$r_0 = \frac{\pi + \arg P(-iv^*)}{\nu^*},$$

where $\nu^* > 0$ solves $|P(-\nu^*)| = \alpha$.

Theorem 5.1 gives a method for obtaining an r_0 where the eigenvalues for the linear system (5.3) cross the imaginary axis with respect to the parameter r_1 , the delay. Near r_0 the nonlinear system (5.1) has small amplitude periodic solutions.

Because the nonlinearity $f(v_1)$ is a decreasing function in v_1 , one can use differential inequalities to show that all positive solutions remain bounded. By continuing the differential inequality arguments in a manner similar to Banks and Mahaffy [3, 4] one can obtain the following global asymptotic stability theorem for (5.1):

Theorem 5.2. *Given any non-negative initial data for the system of differential equations (5.1), then if the equation*

$$B_1 B_2 y (1 + ky^\rho)^\rho + k B_1 B_2 (\sigma c_0 / B_1 B_2)^\rho y - c_0 \sigma (1 + ky^\rho)^\rho = 0 \quad (5.5)$$

has a unique positive solution $y = \bar{v}_1$, then any solution of (5.1) asymptotically approaches the equilibrium solution independent of the delays.

The proof of this theorem is given in the appendix. The proof uses contracting invariant regions which provide asymptotic bounds for the solution of (5.1). When (5.5) has a unique positive solution, then asymptotically the invariant

region reduces to the equilibrium point, giving the global stability result of Theorem 5.2. One immediate corollary is given by the following:

Corollary 5.1. *In (5.1) if $\rho = 1$, then all solutions with non-negative initial data asymptotically approach the equilibrium solution.*

The proof of this follows from the fact that Eq. (5.5) reduces to Eq. (5.2) in this case.

Appendix: Proof of Theorem 5.2

A technique similar to the one found in Banks and Mahaffy [3, 4] can be used to obtain the asymptotic stability result in Theorem 5.2. It is easily seen that if non-negative initial data are used in (5.1), then for all $t > 0$ the solution remains non-negative. Define $z = a_3 u_1 + a_1 u_2$, then (5.1) implies

$$\dot{z}(t) = a_3 f(v_1(t-r_1)) - b_1 z(t).$$

As $v_1(t) \geq 0$, for $t \geq -r_1$ and taking $f(x) = \sigma/[1+kx^\rho]$ we see that $\dot{z}(t) \leq a_3 \sigma - b_1 z(t)$ which implies $z(t) \leq (a_3 \sigma / b_1) + [z(0) - a_3 \sigma / b_1] \exp(-b_1 t)$. Choosing $0 < \varepsilon_1^0 < 1$, there exists a $t_1^0 > 0$ such that

$$z(t) \leq (a_3 \sigma / b_1) + a_3 \varepsilon_1^0 \quad \text{for } t \geq t_1^0.$$

As $u_2(t) \geq 0$, we see that

$$u_1(t) \leq z(t) / a_3 \leq \bar{U}_1^0 = (\sigma / b_1) + \varepsilon_1^0 \quad \text{for } t \geq t_1^0.$$

Now we use this upper bound on $u_1(t)$ to see that $\dot{u}_2(t) \leq a_3 \bar{U}_1^0 - (b_1 + a_3) u_2(t)$. In a similar manner to the one above we may choose $0 < \varepsilon_2^0 < \varepsilon_1^0$, then there exists a $t_2^0 \geq t_1^0$ such that

$$u_2(t) \leq \bar{U}_2^0 = \frac{a_3 \bar{U}_1^0}{b_1 + a_3} + \varepsilon_2^0 \quad \text{for } t \geq t_2^0.$$

Let $y = a_4 v_1 + a_2 v_2$, then $\dot{y}(t) = a_2 c_0 u_2(t-r_2) - b_2 y(t)$. Choosing $0 < \varepsilon_3^0 < \varepsilon_2^0$, there exists a $t_3^0 \geq t_2^0 + r_2$ such that

$$y(t) \leq (a_2 c_0 \bar{U}_2^0 / b_2) + a_2 \varepsilon_3^0 \quad \text{for } t \geq t_3^0.$$

As $v_1(t) \geq 0$, we see that

$$v_2(t) \leq y(t) / a_2 \leq \bar{V}_2^0 = (c_0 \bar{U}_2^0 / b_2) + \varepsilon_3^0 \quad \text{for } t \geq t_3^0.$$

Then as before we choose an $\varepsilon_4^0 < \varepsilon_3^0$, such that

$$v_1(t) \leq \bar{V}_1^0 = \frac{a_2 \bar{V}_2^0}{b_2 + a_2} + \varepsilon_4^0, \quad t \geq t_4^0,$$

for some $t_4^0 \geq t_3^0$.

Next we iterate to find a new set of lower bounds. As $u_2(t) \geq 0$ and $v_1(t) \leq \bar{V}_1^0$ for $t \geq t_4^0$, then

$$\dot{u}_1(t) \geq \frac{\sigma}{1+k(\bar{V}_1^0)^\rho} - (b_1 + a_1) u_1(t).$$

Choose $0 < \delta_1^1 < \min\{\frac{1}{2}, \varepsilon_4^0\}$ and such that $U_1^1 = [\sigma / (b_1 + a_1)(1+k(\bar{V}_1^0)^\rho)] - \delta_1^1 > 0$, then there exists an $s_1^1 \geq t_4^0 + r_1$ such that

$$u_1(t) \geq U_1^1 \quad \text{for } t \geq s_1^1.$$

Similarly the new lower bounds for $u_2(t)$, $v_2(t)$, and $v_1(t)$ in that order can be found.

At the $i+1$ st iterate we choose $0 < \delta_1^{i+1} < \min\{1/(i+2), \varepsilon_4^i\}$ and such that

$$U_1^{i+1} = \frac{1}{(b_1 + a_1)} \left(\frac{\sigma}{1+k(\bar{V}_1^i)^\rho} + a_1 U_2^i \right) - \delta_1^{i+1} \geq U_1^i,$$

then there exists an $s_1^{i+1} \geq t_4^i + r_1$ such that $u_1(t) \geq U_1^{i+1}$ for $t \geq s_1^{i+1}$. Similarly we choose $0 < \delta_2^{i+1} < \delta_1^{i+1}$ such that

$$U_2^{i+1} \equiv \frac{a_3}{(b_1 + a_3)} U_1^{i+1} - \delta_2^{i+1},$$

then there exists an $s_2^{i+1} \geq s_1^{i+1}$ such that $u_2(t) \geq U_2^{i+1}$ for $t \geq s_2^{i+1}$. Continuing this process we choose $0 < \delta_4^{i+1} < \delta_3^{i+1} < \delta_2^{i+1}$ and obtain times $s_4^{i+1} \geq s_3^{i+1} \geq s_2^{i+1} + r_2$ such that

$$v_2(t) \geq Y_2^{i+1} \equiv \frac{1}{(b_2 + a_4)} (c_0 U_2^{i+1} + a_4 Y_1^i) - \delta_3^{i+1} \geq Y_2^i \quad \text{for } t \geq s_3^{i+1}$$

and

$$v_1(t) \geq Y_1^{i+1} \equiv \frac{1}{(b_2 + a_2)} Y_2^{i+1} - \delta_4^{i+1} \geq Y_1^i \quad \text{for } t \geq s_4^{i+1}.$$

We now form the $i+1$ st iterate for the upper bounds. As before we choose $0 < \varepsilon_4^{i+1} < \varepsilon_3^{i+1} < \varepsilon_2^{i+1} < \varepsilon_1^{i+1} < \delta_4^{i+1}$, then there exists $t_4^{i+1} \geq t_3^{i+1} \geq t_2^{i+1} + r_2 \geq t_1^{i+1} + r_2 \geq s_4^{i+1} + r_2 + r_1$ such that

$$u_1(t) \leq \bar{U}_1^{i+1} \equiv \frac{1}{(b_1 + a_1)} \left(\frac{\sigma}{1 + k(Y_1^{i+1})^\rho} + a_1 \bar{U}_2^i \right) + \varepsilon_1^{i+1} \leq \bar{U}_1^i \quad \text{for } t \geq t_1^{i+1}$$

$$u_2(t) \leq \bar{U}_2^{i+1} \equiv \frac{a_3}{(b_1 + a_3)} \bar{U}_1^{i+1} + \varepsilon_2^{i+1} \leq \bar{U}_2^i \quad \text{for } t \geq t_2^{i+1}$$

$$v_2(t) \leq \bar{V}_2^{i+1} \equiv \frac{1}{(b_2 + a_4)} (c_0 \bar{U}_2^{i+1} + a_4 \bar{V}_1^i) + \varepsilon_3^{i+1} \leq \bar{V}_2^i \quad \text{for } t \geq t_3^{i+1}$$

$$v_1(t) \leq \bar{V}_1^{i+1} \equiv \frac{a_2}{(b_2 + a_2)} \bar{V}_2^{i+1} + \varepsilon_4^{i+1} \leq \bar{V}_1^i \quad \text{for } t \geq t_4^{i+1}.$$

By the choice of ε_j^i and δ_j^i with $\lim_{i \rightarrow \infty} \varepsilon_j^i = \lim_{i \rightarrow \infty} \delta_j^i = 0$ we have the monotonically nondecreasing sequences $\{U_j^i\}_{i=1}^\infty$ and $\{Y_j^i\}_{i=1}^\infty$, $j = 1, 2$ and the monotonically nonincreasing sequences $\{\bar{U}_j^i\}_{i=0}^\infty$ and $\{\bar{V}_j^i\}_{i=0}^\infty$, $j = 1, 2$, which each approach a limit, so

$$\lim_{i \rightarrow \infty} U_j^i = U_j^* \quad \text{and} \quad \lim_{i \rightarrow \infty} V_j^i = V_j^*,$$

where U represents either U or \bar{U} and similarly for V .

Note that at the i th iterate we have the following invariant region:

$$U_j^i \leq u_j(t) \leq \bar{U}_j^i \quad \text{and} \quad Y_j^i \leq v_j(t) \leq \bar{V}_j^i \quad \text{for } t \geq t_4^i, \quad j = 1, 2$$

which gives asymptotic bounds for all solutions. In the limit as $t \rightarrow \infty$, $\varepsilon_j^i \rightarrow 0$ and $\delta_j^i \rightarrow 0$, thus we have

$$\begin{aligned} \frac{\sigma}{1 + k(Y_1^*)^\rho} &= (b_1 + a_1) \bar{U}_1^* - a_1 \bar{U}_2^* \\ &= \left[\frac{(b_1 + a_1)(b_1 + a_3)}{a_3} - a_1 \right] \bar{U}_2^* = B_1 \bar{U}_2^* \\ &= \frac{B_1}{c_0} [(b_2 + a_4) \bar{V}_2^* - a_4 \bar{V}_1^*] \\ &= (B_1 B_2 / c_0) \bar{V}_1^*. \end{aligned}$$

By symmetry we have

$$\frac{\sigma}{1 + k(\bar{V}_1^*)^\rho} = (B_1 B_2 / c_0) Y_1^*.$$

Let $y = Y_1^*$ or \bar{V}_1^* , then combining the above equations we have

$$\frac{\sigma}{1 + k \left[\frac{c_0 \sigma / B_1 B_2}{1 + ky^p} \right]^p} = (B_1 B_2 / c_0) y,$$

which is equivalent to equation (5.5). Thus if (5.5) has a unique solution \bar{v}_1 , then $Y_1^* = \bar{v}_1 = \bar{V}_1^*$. This implies that asymptotically

$$\lim_{t \rightarrow \infty} v_1(t) = \bar{v}_1,$$

as $v_1(t)$ must lie between the upper and lower bounds which converge to the equilibrium solution. Clearly, $u_1(t)$, $u_2(t)$ and $v_2(t)$ also converge to the equilibrium solution.

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