

A REACTION-DIFFUSION MODEL
FOR INTRACELLULAR CALCIUM

By

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ABSTRACT

Intracellular calcium ions (Ca^{2+}) play important roles in neurobiology by either triggering or modulating a large number of processes which are associated with nerve cell behaviour. In spite of this importance, it is very difficult experimentally to obtain quantitative information on the dynamics of intracellular calcium. For this reason, Connor and Nikolakopoulou [13] formulated a diffusion model based upon experimentally estimated parameters. They used this model to study the spatial distribution of calcium within the cytoplasm and the increases in the concentration of intracellular calcium ions that a given influx of calcium through the cell membrane can bring about. The mathematical model consists of a system of five reaction-diffusion equations which is treated as a two-point initial-boundary-value problem with constant initial states and nonlinear boundary conditions. Analytical results reveal that the system admits a unique spatially homogeneous stationary state which is asymptotically stable. A regular perturbation technique is used for constructing an approximate transient solution which possesses transition layers. A simplified comparison theorem for parabolic equations is used to provide analytical bounds on the approximate solution. Finally, a B-spline collocation code, called *PDECOL*, is used to supplement the analytical results to provide a detailed description of the calcium dynamics.

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CHEMICAL NOTATIONS

$[\cdot]$	concentration of a chemical
Arz	calcium indicator dye arsenazo III
$[\text{Arz}]$	total concentration of Arz
B^T	intrinsic buffer
$[B]$	total concentration of B
Ca^{2+}	calcium ions
$[\text{Ca}^{2+}]$	rest value of Ca^{2+} concentration
$[\text{Ca}^{2+}]^R$	intracellular concentration of Ca^{2+}
$[\text{Ca}^{2+}]^i$	extracellular concentration of Ca^{2+}
$[\text{Ca}^{2+}]^0$	
CaArz	complex formed by Ca^{2+} and Arz
CaB	complex formed by Ca^{2+} and B
D_i	diffusion coefficient, $i = 1, 2, 3$
k_i	reaction rate constant, $i = 1, 2, 3, 4$

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*This thesis is dedicated to
my parents.*

1. INTRODUCTION

In this thesis, the phrase *nonlinear diffusion equations* refers specifically to semilinear systems of second-order partial differential equations of the form

$$\partial \bar{u} / \partial t = D \Delta \bar{u} + \bar{F}(\bar{x}, t, \bar{u}, \nabla \bar{u}), \quad \bar{u} = (u_1, \dots, u_m). \quad (1.1)$$

Here $\bar{x} \in R^n$, $\Delta = \sum_{j=1}^n \partial^2 / \partial x_j^2$ is the Laplace operator in R^n , and the *diffusion matrix* D is diagonal¹ consisting of constant nonnegative elements² only.

Diffusion is a physical phenomenon by which matter is transported from one part of a system to another as a result of random molecular motions. Diffusion equations of type (1.1) with appropriate initial and boundary conditions are widely used as models for biological, ecological, and chemical systems. In most physical applications, the independent variables $\bar{x}$ and t represent positions in space and time, respectively. In the context of ecology, the components of $\bar{u}$ represent the population densities of various species, the term $D \Delta \bar{u}$ represents the rate of

¹In anisotropic media, e.g., crystals and textile fibres, in which the molecules have a preferential direction of orientation, D is generally not diagonal.

²In many systems, e.g., the interdiffusion of metals or the diffusion of organic vapours in high-polymer substances, D depends on the concentration of diffusing substances, $u_1, u_2, \dots$. In this case and also when the medium is not homogeneous so that D varies from point to point, the diffusion term in (1.1) becomes $\Delta D \bar{u}$, where D may be a function of $\bar{x}$ and $\bar{u}$.

change of the population densities at any given position and time due to random spatial migration, and the term $\bar{F}$ represents the interactions between various species such as reproduction processes or deaths. Various examples of biological and ecological diffusion models are given in [4,12].

In this thesis, we study a special case of equation (1.1) which models the dynamics of intracellular calcium ion concentration changes in one spatial dimension. Intracellular calcium either triggers or modulates a large number of processes which are associated with nerve cell behaviour. Some of these are muscle contraction, release of neural transmitter, and sensory cell transduction. The mathematical model [13] consists of a system of five nonlinear diffusion equations describing the evolution of the various ionic concentrations which are taken into account. The system of equations is of the form

$$\partial \bar{u} / \partial t = D \partial^2 \bar{u} / \partial x^2 + \bar{F}(\bar{u}), \quad (1.2)$$

where $\bar{u} = (u_1, u_2, u_3, u_4, u_5)$, $x \in [a, b]$, D is a diagonal matrix with constant positive entries d_i , and $\bar{F}$ is a quadratic polynomial in $\bar{u}$. The initial conditions are specific constants chosen to represent the equilibrium state of the system. The boundary conditions are of nonlinear Neumann type. Equations of type (1.2) with $\bar{F}$ polynomials in $u_1, u_2, \dots, u_5$ are sometimes known as *reaction-diffusion equations*.

Although (1.2) is a special case of (1.1), it includes two very important extreme cases :

i) $\bar{F} = 0, d_i > 0 :$

$$\frac{\partial u_i}{\partial t} = d_i \frac{\partial^2 u_i}{\partial x^2}, \quad i = 1, 2, \dots, 5. \quad (1.3)$$

Thus each equation is a scalar diffusion equation.

ii) $d_i = 0 :$

$$d\bar{u}/dt = \bar{F}(\bar{u}), \quad (1.4)$$

which is a system of kinetic equations associated with (1.2). Observe that even when $D \neq 0$, equation (1.4) is satisfied by x -independent solutions of (1.2).

The layout of this thesis is as follows. In Chapter 2 we introduce the mathematical model proposed by Connor and Nikolakopoulou [13] (CN) in their efforts to study the dynamics of intracellular calcium ion concentration changes in nerve cytoplasm¹ resulting from external influxes of calcium ions. Numerical solutions to the mathematical model are given in their paper. However, they have included no analytical results. It is our objective in this thesis to provide some analytical descriptions of the calcium dynamics and compare them with the numerical solutions.

In Chapter 3 we reformulate the CN model so that it is amenable to various mathematical analyses and in Chapter 4 we

¹Cytoplasm is characterized as a simple diffusion compartment containing an intrinsic buffer for Ca.

explore some of its mathematical properties. These properties are used in subsequent sections to facilitate the calculations of the steady-state solution and to establish its uniqueness and asymptotic stability. In Chapter 5, we use a regular perturbation technique to obtain an approximate small-time solution to the model equations so that we can make a quantitative statement about the transient behaviour of the calcium concentration. Moreover by utilising a *comparison* theorem, we provide analytical bounds on the exact solution. In Chapter 6 we present the numerical solutions to the problem and compare them with the experimental results given by Connor and Nikolakopoulou [13].

In Appendix A, we give a brief description of the numerical algorithm, *PDECOL*, which was used to solve the model equations and report some of the difficulties encountered in the numerical procedures. In Appendix B, we find an approximate solution to a linear second-order partial differential equation with nonlinear boundary conditions and the results are used to simplify the calculations for the transient solutions.

All computations leading to the numerical results presented in this paper were performed in double precision at the University of British Columbia Computing Center using an Amdahl V/8 Model 470 computer.

2. THE MATHEMATICAL MODEL

There is a considerable amount of evidence in the literature (Sandow [23], Jobsis & O'Connor [18], Ebashi & Endo [16]) to suggest that small transient changes in sarcoplasmic calcium concentration play a crucial part in the complex process of excitation-contraction coupling in skeletal muscle. It is thus of interest to know the precise sizes of these calcium changes that lead to the production of tension. Various experimental methods such as photometric [6], voltage clamp technique [1], and indicator dye absorbance [9] have been designed for this particular purpose. Among them, indicator methods have proven to be the most successful because of their sensitivity and ability to respond rapidly to concentration changes. However, such methods are imprecise as to the location of changes within the cytoplasm. Several reviews of the indicator techniques are given in [8] and [9].

Experimental results by Ahmed and Connor [2] using indicator techniques show that the internal calcium concentration ($[Ca^{2+}]$) changes are brought about either by a calcium influx from some extracellular reservoir or by the release of calcium ions from an internal source. However, the short time course of the calcium influx (on the order of ten milliseconds) and the small concentration changes of Ca^{2+} (in the micromolar range) together with the small volumes generally encountered with biological preparations make the problem of direct quantitative measurement of the Ca^{2+} transient a very difficult one.

In 1982 Connor and Nikolakopoulou performed experiments¹ on molluscan giant neurons using indicator dye absorbance in combination with a voltage clamp technique in an attempt to make a quantitative statement about the dynamics of intracellular calcium ion concentration changes. The experiments provided them with a great deal of qualitative information about calcium entry into the neurons but with little or no insight as to the spatial distribution of the Ca^{2+} within the cytoplasm. To add to their frustration, the experiment provided no information as to the magnitude of the perturbation in $[\text{Ca}^{2+}]$ that a given influx can bring about. In order to solve the puzzle, Connor and Nikolakopoulou formulated a one-dimensional² diffusion model based upon experimentally estimated³ parameters and what appear to be reasonable estimates for those parameters which they have not been able to measure.

Figure 1 indicates the structure of the CN diffusion model and shows that extracellular calcium ions, Ca_o , are loaded through the membrane for a period t^* ($\approx 100\text{msecs}$). As soon as the calcium ions enter the cell membrane, they are assumed to be instantaneously at local equilibrium with the intrinsic

¹Detailed descriptions of the experimental methods are given in Ahmed & Connor [1], Ahmed, et al. [2].

²It will soon be clear from the model equations that a more realistic model in 3-dimensions would be mathematically too complicated to handle.

³Experimental methods used in estimating the parameters of the model are described in [13].

buffer (B)¹, and the calcium indicator dye arsenazo III (Arz)². Initially, the two buffers (B and Arz) have uniform concentrations and thus the entry of calcium ions causes diffusional movement within the membrane.

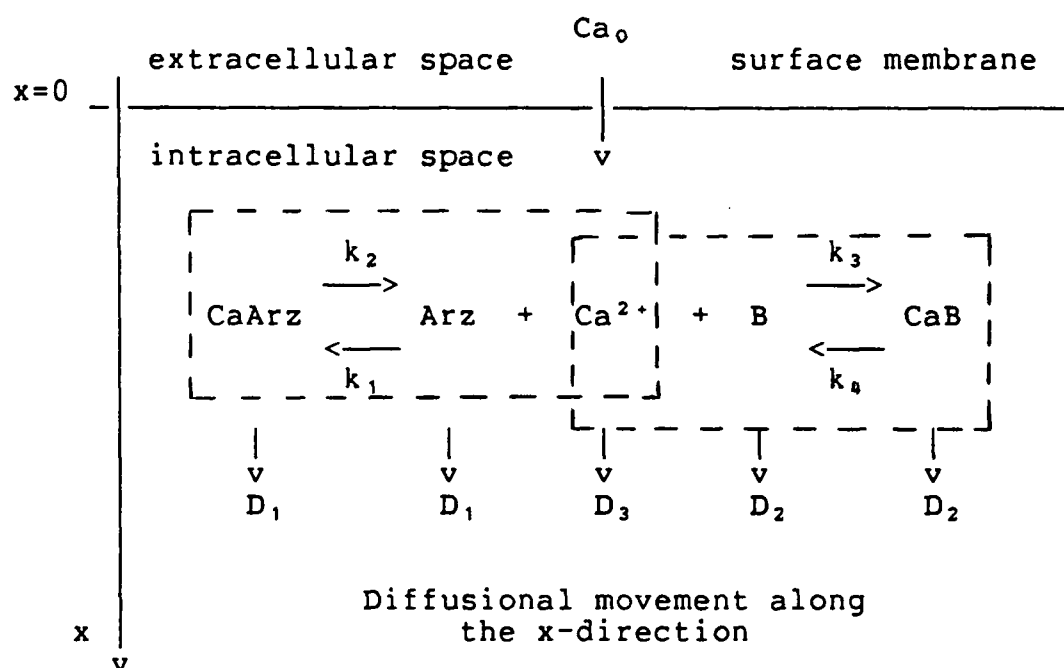


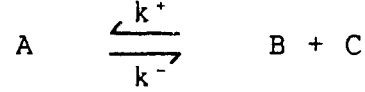
Figure 1 : Structure of diffusion model with local reactions.

Let $U_1(x,t)$, $U_2(x,t)$, $U_3(x,t)$, $U_4(x,t)$, and $U_5(x,t)$

¹An intrinsic buffer is an inherent substance in the solution that makes the degree of acidity (hydrogen ion concentration) resistant to change when an acid or base is added.

²The absorbance spectrum of the dye arsenazo III undergoes known changes when the dye forms a complex with calcium. These changes have been used in a number of studies to describe calcium movement levels in living cells. (See Baker, Hodgkin & Ridgway [5].)

represent the concentrations of CaArz , Arz , Ca^{2+} , B , and CaB , respectively. Recall from elementary chemistry that the *law of mass action* for a first-order chemical reaction between species A , B , and C ,



is given by

$$d[\text{A}]/dt = k^-[\text{B}][\text{C}] - k^+[\text{A}],$$

$$d[\text{B}]/dt = k^+[\text{A}] - k^-[\text{B}][\text{C}],$$

$$d[\text{C}]/dt = k^+[\text{A}] - k^-[\text{B}][\text{C}],$$

where $[\cdot]$ denotes the concentration of a chemical and where k^+ and k^- denote the forward and reverse reaction rate constants of chemical A , respectively.

Thus assuming a first-order reaction in an isotropic medium and ignoring spatial inhomogenities¹, we can apply the law of mass action and write down the kinetic equations plus the diffusion terms associated with our chemical model :

$$\partial U_1 / \partial t = D_1 \partial^2 U_1 / \partial x^2 + k_1 U_2 U_3 - k_2 U_1, \quad (2.1a)$$

$$\partial U_2 / \partial t = D_1 \partial^2 U_2 / \partial x^2 - k_1 U_2 U_3 + k_2 U_1, \quad (2.1b)$$

$$\partial U_3 / \partial t = D_3 \partial^2 U_3 / \partial x^2 - k_1 U_2 U_3 + k_2 U_1 - k_3 U_3 U_4 + k_4 U_5, \quad (2.1c)$$

$$\partial U_4 / \partial t = D_2 \partial^2 U_4 / \partial x^2 - k_3 U_3 U_4 + k_4 U_5, \quad (2.1d)$$

$$\partial U_5 / \partial t = D_2 \partial^2 U_5 / \partial x^2 + k_3 U_3 U_4 - k_4 U_5, \quad (2.1e)$$

where D_1 , D_2 , and D_3 are constant diffusion coefficients, and k_1 ,

¹These are reasonable assumptions to ensure that the diffusion matrix D is diagonal and constant.

k_2 , k_3 , and k_4 are the forward and reverse reaction rate constants as shown in Figure 1.

It is clear from the chemistry of our physical model that $[Arz]$ and $[B]$ in the system are conserved at each x and for all $t \geq 0$; we shall denote these concentrations by $[Arz]_T$ and $[B]_T$, respectively. But moreover, since the initial distribution is uniform and since U_1 and U_2 have the same diffusion coefficient, we have

$$[Arz]_T = U_1(x,t) + U_2(x,t), \quad (2.2a)$$

for $t \geq 0$ and all x . Alternatively, (2.2a) can be derived by adding equations (2.1a) and (2.1b) giving

$$\partial(U_1+U_2)/\partial t = D_1 \partial^2(U_1+U_2)/\partial x^2.$$

Now since there is no flux contribution from U_1 and U_2 at the boundaries and since (2.2a) holds at $t = 0$, it holds for all $t \geq 0$. Similarly

$$[B]_T = U_4(x,t) + U_5(x,t). \quad (2.2b)$$

Thus equations (2.2a)-(2.2b) allow us to eliminate two of the five equations in (2.1a-e). We choose to eliminate U_2 and U_4 since they correspond to the concentrations of the buffers and hence are of less interest. The reduced system becomes

$$\begin{aligned} \partial U_1 / \partial t &= D_1 \partial^2 U_1 / \partial x^2 + k_1([Arz]_T - U_1)U_3 - k_2 U_1, \\ \partial U_3 / \partial t &= D_3 \partial^2 U_3 / \partial x^2 - k_1([Arz]_T - U_1)U_3 + k_2 U_1 \\ &\quad - k_3([B]_T - U_5)U_3 + k_4 U_5, \\ \partial U_5 / \partial t &= D_2 \partial^2 U_5 / \partial x^2 + k_3([B]_T - U_5)U_3 - k_4 U_5. \end{aligned} \quad (2.3)$$

In order to completely specify the problem, we must impose appropriate initial and boundary conditions to (2.3). To this end observe that the system is initially at equilibrium and thus the initial conditions can be obtained by simply setting the kinetic terms to zero, giving

$$U_1(x,0) = k_1 U_3(x,0) [Arz]_T / (k_2 + k_1 U_3(x,0)) \mu M/l,$$

$$U_3(x,0) = [Ca^{2+}]_R \mu M/l$$

$$U_5(x,0) = k_3 U_3(x,0) [B]_T / (k_4 + k_3 U_3(x,0)) \mu M/l, \quad (2.4)$$

where $[Ca^{2+}]_R$ denotes the initial rest value of calcium ion concentration and $\mu M/l$ stands for micromolars per liter.

The boundary conditions must take into account the influx of Ca^{2+} at $x = 0$. By Fick's law [15], we have

$$\partial U_3(0,t)/\partial x = I_{Ca} / (zFD_3),$$

where I_{Ca} = calcium current, z = valence of $Ca^{2+} = 2$,

F = faraday constant (96500 coulombs/mole).

From Ohm's Law

$$I_{Ca} = g_{Ca} V,$$

where g_{Ca} = conductance of membrane,

V = net driving potential on Ca^{2+}

$$= E_m - E_{Ca},$$

where E_m is the membrane potential and E_{Ca} is the Nernst

potential for Ca^{2+} [21] given by

$$E_{\text{Ca}} = (2.303RT/zF) \log_{10} [\text{Ca}^{2+}]_0 / [\text{Ca}^{2+}]_i \text{ Volts,}$$

where R = universal gas constant (8.31 joules/mole/ $^{\circ}\text{K}$),

T = temperature in $^{\circ}\text{K}$,

$[\text{Ca}^{2+}]_0$ = the extracellular concentration of Ca^{2+} ,

$[\text{Ca}^{2+}]_i$ = the intracellular concentration of Ca^{2+} .

Thus assuming a temperature of 18°C , the Nernst potential for Ca^{2+} is

$$E_{\text{Ca}} = 29 \log_{10} [\text{Ca}^{2+}]_0 / [\text{Ca}^{2+}]_i \text{ mVolts.}$$

Finally, since all other fluxes are zero at the boundaries, the appropriate boundary conditions for our problem are

$$\partial U_1(0,t)/\partial x = 0 = \partial U_1(L,t)/\partial x,$$

$$\partial U_5(0,t)/\partial x = 0 = \partial U_5(L,t)/\partial x,$$

$$\partial U_3(0,t)/\partial x = (g_{\text{Ca}}/zFD_3)(E_m - 29 \log_{10} [\text{Ca}^{2+}]_0/U_3(0,t)) \mu\text{M/lm},$$

$$\partial U_3(L,t)/\partial x = 0,$$

where L represents the radius of a neuron. For the purpose of mathematical calculations, we can choose L sufficiently large so that during the entire loading period t^* , the influx at the boundary ($x = 0$) does not induce concentration changes near the center of the neuron. In Table 1, we summarize the parameter values used by Connor and Nikolakopoulou's [13] in their diffusion model.

Numerical results published in Connor and Nikolakopoulou's paper [13] indicate that the proposed model gives a good account to the true qualitative behaviour of calcium dynamics. However,

the paper contains no mathematical analysis of the model equations. It is our intention to adopt the model and use it to give some analytical descriptions of calcium dynamics.

Table 1 : Parameter Values used in Diffusion Model

(Taken from Connor and Nikolakopoulou [13])

Cytoplasmic and Indicator Parameters :

$$\begin{aligned} [\text{Arz}]_T &= 300 \mu\text{M/l}, & [\text{B}]_T &= 200 \mu\text{M/l}, \\ D_1 &= 0.06 \mu\text{m}^2/\text{msec}, & D_2 &= 0.01 \mu\text{m}^2/\text{msec}, \\ D_3 &= 0.2 \mu\text{m}^2/\text{msec}, & k_1 &= 0.025 \text{ l}/\mu\text{Mmsec}, \\ k_2 &= 1.0/\text{msec}, & k_3 &= 1.0 \text{ l}/\mu\text{Mmsec}, \\ k_4 &= 1.0/\text{msec}. \end{aligned}$$

Parameter Values used for Calcium Influx :

$$\begin{aligned} [\text{Ca}]_0 &= 10000 \mu\text{M/l}, & [\text{Ca}]_R &= 0.1 \mu\text{M/l}, \\ F &= 96500 \text{ coulombs/M}, & g_{\text{Ca}} &= 8.6 \times 10^{-4} \text{ mhos/cm}^2, \\ E_m &= 10 \text{ mVolts}, & z &= 2. \end{aligned}$$

Control Parameters :

$$t^* = 100 \text{ msec}, \quad L = 30 \mu\text{m}.$$

Dimensions of the Variables :

$$\begin{aligned} [x] &= \mu\text{m}, & [t] &= \text{msec}, \\ [U_1] &= [U_2] = [U_3] = [U_4] = [U_5] = \mu\text{M/l}. \end{aligned}$$

3. MATHEMATICAL FORMULATION

Exact solutions to differential equations are rare in practice because of nonlinearities, inhomogeneities, and general boundary conditions. As a result, solutions are approximated using analytical techniques, numerical techniques, or combinations of both. In this and the next two chapters, we shall concentrate on analytical techniques, which when combined with the numerical solution discussed in Chapter 6, give a thorough description of the behaviour of the model equations (2.3)-(2.5).

Our first step in solving the present problem is to nondimensionalize the governing equations (2.3)-(2.5); for it is only in dimensionless form that we can compare the order of magnitude of the different variables and parameters of the system and thus be able to identify the important ones. For our problem the diffusion coefficients satisfy $D_3 \gg D_2 > D_1$ and thus U_3 diffuses faster than U_1 and U_5 . Moreover since the system is initially at equilibrium (i.e., the forward and backward reactions are in balance), the diffusion process of U_3 will, at least in early stages of development, dominate the entire reaction-diffusion process. Thus we rescale the governing equation of U_3 so that the $\partial/\partial t$ and $\partial^2/\partial x^2$ terms are of the same order. In view of (2.2a)-(2.2b), the other two dependent variables U_1 and U_5 can be made dimensionless by normalizing with respect to $[B]_T$ and $[Arz]_T$, respectively. The independent time variable t can be made dimensionless by using $\sqrt{k_2 k_4}$ which has the convenient value of 1. The dimensionless independent variable

corresponding to x is now determined. In summary we have introduced the following dimensionless independent variables, x' and t' , and the dimensionless dependent variables U , V and W :

$$\begin{aligned} t' &= \sqrt{(k_2 k_4)} t, & x' &= x/D, \\ U &= U_1/[Arz]_T, & V &= kU_3, \\ W &= U_5/[B]_T, & & \end{aligned} \quad (3.1a)$$

where

$$D = \sqrt{D_3/V(k_2 k_4)}, \quad k = \sqrt{(k_1 k_3/k_2 k_4)}.$$

Dimensionless parameters are

$$\begin{aligned} a_1 &= \sqrt{(k_1/k_3)}, & a_2 &= \sqrt{(k_2/k_4)}, \\ D_{13} &= D_1/D_3, & D_{23} &= D_2/D_3, \\ \delta &= k_2/(a_2 k_1 [Arz]_T), & \epsilon &= k_4 a_2 / (k_3 [B]_T). \end{aligned} \quad (3.1b)$$

After dropping the primes, equations (2.3)-(2.5) become

$$\begin{aligned} \partial U / \partial t &= D_{13} \partial^2 U / \partial x^2 + f(U, V), \\ \partial V / \partial t &= \partial^2 V / \partial x^2 + g(U, V, W), \\ \partial W / \partial t &= D_{23} \partial^2 W / \partial x^2 + h(V, W), \end{aligned} \quad (3.2)$$

where

$$\begin{aligned} f(U, V) &= a_1(1-U)V - a_2 U, \\ h(V, W) &= (1-W)V/a_1 - W/a_2, \\ g(U, V, W) &= -[(1/(\delta a_1))f(U, V) + (a_1/\epsilon)h(V, W)], \end{aligned}$$

subject to the boundary conditions for $t \geq 0$,

$$\begin{aligned} \partial U(0, t) / \partial x &= \partial W(0, t) / \partial x = 0, \\ \partial U(L, t) / \partial x &= \partial V(L, t) / \partial x = \partial W(L, t) / \partial x = 0, \end{aligned}$$

$$\partial V(0,t)/\partial x = \begin{cases} A + B \ln V(0,t), & 0 < t \leq t^*, \\ 0, & t > t^*, \end{cases} \quad (3.3)$$

where

$$A = \zeta [E - (29/\ln 10) \ln(k[Ca]_0)],$$

$$B = 29 \zeta^m / \ln 10,$$

$$\zeta = (10^7 g / z F D_3) k D,$$

and initial conditions on $0 < x < L$,

$$\begin{aligned} U(x,0) &= U_0 = V_0 / (a_2/a_1 + V_0), \\ V(x,0) &= V_0 = 0.1k, \\ W(x,0) &= W_0 = V_0 / (a_1/a_2 + V_0). \end{aligned} \quad (3.4)$$

Hence the present problem depends on six parameters, a_1 , a_2 , ϵ , δ , D_{13} , and D_{23} . For the set of parameter values given in Table 1, $0 < \epsilon \ll \delta \ll 1$. Thus since ϵ and δ are small we can use them as perturbation parameters to obtain an approximate solution to the problem (see Chapter 5). In the special case when $\epsilon = 0$, the solution to (3.2) subject to initial condition (3.4) is simply

$$U(x,t) = U_0, \quad V(x,t) = V_0, \quad W(x,t) = W_0.$$

Note that if V_0 is chosen such that $\ln V_0 = -A/B$, the boundary conditions reduce to homogeneous Neumann types at $t = 0$. In other words, the reactions are in a steady state and the concentration level of each chemical will remain at its rest value. Henceforth we assume that $\ln V_0 \neq -A/B$ and work with the dimensionless equations (3.2)-(3.4) which we shall refer to as system (P). Using the set of parameter values given in Table 1,

we can calculate the dimensionless parameter values from equations (3.1a-b), (3.3) and (3.4). The results are summarized in Table 2.

Table 2 : Values of the dimensionless parameters

$a_1 = 0.1581,$	$a_2 = 1.0000,$
$D_{13} = 0.300,$	$D_{23} = 0.050,$
$\epsilon = 0.0050,$	$\delta = 0.1333,$
$D = 0.4472,$	$k = 0.1581,$
$A = -1.30398,$	$B = 0.19842,$
$U_0 = 0.00249,$	$V_0 = 0.01581,$
$W_0 = 0.09091.$	

In Chapter 5 we shall rescale the initial values U_0 , V_0 , and W_0 to $O(1)$ before using a regular perturbation technique to obtain an approximation to the initial transient solution. We shall, however, first investigate some mathematical properties of system (P).

4. MATHEMATICAL PROPERTIES

In the analysis of a given problem, it is always useful to first exploit the special structures of that problem, e.g., symmetry. These special structures often facilitate calculations and, more importantly, provide greater intuition and understanding of the problem. In this Chapter, we shall examine some mathematical properties of system (P) [equations (3.2)-(3.4)]. These properties are useful for our analyses in later chapters.

Property 1 : Special features of the kinetic terms

The vector-valued function $\bar{F} = (f, g, h)$ possesses two special features which will greatly simplify our later analyses. Before stating them, we need the following definitions :

1. A vector-valued function $\bar{G}(\bar{u})$ is said to be *quasi-monotone nondecreasing* in $\bar{u}$ if each G_i is nondecreasing in u_j , for $j \neq i$.

2. For any given $V \geq 0$, define the set

$$T(V) = \{(U, V, W) : U = a_1 V / [a_2 + a_1 V], W = a_2 V / [a_1 + a_2 V]\}.$$

The two special features of $\bar{F}$ are :

S1 : $\bar{F}$ is quasi-monotone nondecreasing in $\bar{u} = (U, V, W)$.

S2 : $\bar{F}(U, V, W) = (f(U, V), g(U, V, W), h(V, W)) = \bar{0}$,

for all $V \geq 0$ and $(U, V, W) \in T(V)$.

S1 can be verified directly by differentiating $\bar{F}$ with

respect to $\bar{u}$ and noting that both U and W must lie between 0 and 1 (cf. Property 3). To prove S2, we simply set $f(U,V) = 0 = h(V,W)$. S2 states that our chemical system has a continuum of equilibrium states and in the special case when $V = V_0$, it reduces to the statement that the chemical system is initially at equilibrium.

Property 2 : Conservation Law

As in the case of many physical systems, the solution to system (P) is governed by a conservation law. To show this observe from equation (3.2) that

$$\begin{aligned} & (1/\delta a_1)\partial U/\partial t + \partial V/\partial t + (a_1/\epsilon)\partial W/\partial t \\ &= (D_{13}/\delta a_1)\partial^2 U/\partial x^2 + \partial^2 V/\partial x^2 + (D_{23}a_1/\epsilon)\partial^2 W/\partial x^2. \end{aligned} \quad (4.1)$$

Integrating both sides of equation (4.1) with respect to x from 0 to L and using boundary conditions (3.3) we have

$$\int_0^L \partial z/\partial t \, dx = -\partial V(0,t)/\partial x, \quad (4.2)$$

where $z(x,t) = U/(\delta a_1) + V + (a_1/\epsilon)W$. Integrating equation (4.2) with respect to t , we have

$$\int_0^L [z(x,t) - z(x,0)] \, dx = \begin{cases} \beta(t), & t \leq t^*, \\ \beta(t^*), & t \geq t^*. \end{cases} \quad (4.3)$$

where

$$\beta(t) = -\int_0^t \partial V(0,s)/\partial x \, ds. \quad (4.4)$$

Equation (4.3) is the conservation law governing system (P). Observe that since $[Ca^{2+}]$ is loaded into the system, $\partial V/(0,t)/\partial x < 0$ for $0 < t \leq t^*$, and hence $\beta(t)$ is positive and strictly increasing for $0 < t \leq t^*$.

In Section 4.1 we shall show that the steady-state solution to system (P) is spatially homogeneous and in such case (4.3) simplifies to

$$z(x, \infty) = z(x, 0) + \beta(t^*)/L. \quad (4.5)$$

Equation (4.5) states that the total equilibrium concentration of the chemicals is the sum of the total initial concentration plus the total amount of $[Ca^{2+}]$ injected into the system. We shall see in subsequent sections that equations (4.3)-(4.5) play key roles in establishing the uniqueness and stability of the equilibrium solution.

Property 3 : Invariant Region

From the chemistry of the system, one would conjecture that U , V , and W are bounded functions of x and t . In particular, it is clear from (2.2a-b) and (3.1a) that U and W must lie between 0 and 1. We shall now give a mathematical statement of our conjecture which relies on the concept of an *invariant region* originally introduced by Chueh, Conley, and Smoller [11].

An invariant region Σ is a subset of the phase space (i.e. (U, V, W) space) such that if the values of the solution of the PDE are contained in the region for some value of t , e.g., the initial conditions, then the solution remains in the region for

all later times. We shall show that an invariant region to system (P) is given by

$$\Sigma = \{ (U, V, W) : 0 \leq U_0 \leq U \leq U_m \leq 1, 0 \leq V_0 \leq V \leq V_m < \infty, \\ 0 \leq W_0 \leq W \leq W_m \leq 1 \}, \quad (4.6)$$

where $(U_m, V_m, W_m) \in T(V_m)$ and V_m is a finite upper bound of V to be determined.

Since the second spatial derivative is always nonnegative (nonpositive) at a minimum (maximum), by the closing remark in Section 2 of [14], it suffices to show that $\bar{F}$ does not point out of Σ , i.e.,

$$\begin{aligned} (1) \quad & f(U_0, V) \geq 0, \quad f(U_m, V) \leq 0; \\ (2) \quad & g(U, V_0, W) \geq 0, \quad g(U, V_m, W) \leq 0, \\ (3) \quad & h(V, W_0) \geq 0, \quad h(V, W_m) \leq 0; \end{aligned}$$

hold for all $(U, V, W) \in \Sigma$. To this end observe that

$f(U_0, V) = f(U_0, V_0) + a_1(1-U_0)(V-V_0) = a_1(1-U_0)(V-V_0) \geq 0$,
and $f(U_m, V) = f(U_m, V_m) + a_1(1-U_m)(V-V_m) = a_1(1-U_m)(V-V_m) \leq 0$,
since by S2 $f(U_0, V_0) = 0 = f(U_m, V_m)$. The proof for (3) is similar. To prove (2) simply observe that

$$\begin{aligned} & g(U, V_0, W) \geq g(U_0, V_0, W_0) = 0, \\ \text{and} \quad & g(U, V_m, W) \leq g(U_m, V_m, W_m) = 0, \end{aligned}$$

where we have again applied S2 in obtaining the right-hand equality. In Chapter 5 we shall obtain an analytical estimate for V_m .

4.1 EXISTENCE AND UNIQUENESS OF THE STEADY STATE

In this thesis, a vector $\bar{u}$ is defined as a *steady-state* solution to a system of PDEs iff $\bar{u}$ is a time independent solution to the PDEs satisfying the boundary conditions¹. For a general system of reaction-diffusion equations, two questions concerning the steady-state of the system arise naturally. First, does there exist a unique steady-state solution? Second, which steady-state solutions are stable? In this section we shall answer the first question and show that for all positive parameter values a_1 , a_2 , δ and ϵ , system (P) has a unique steady-state value. In the next section we show that the steady-state solution is asymptotically stable.

Before proving the main result, we shall use the concept of invariant region developed in Chapter 4 (Property 3) and state a lemma which is a direct consequence of a theorem proved by Conway, Hoff, and Smoller (Theorem 3.1 in [14]).

Lemma

Let $\bar{u} = (u_1, \dots, u_m)$, $\bar{v} = (v_1, \dots, v_m)$, $m \geq 1$, $x \in I = [a, b]$, and D be a diagonal matrix with positive entries d_i . Let (S) and (S') denote the problems

¹We have excluded the steady oscillatory solution in our definition.

$$\begin{aligned}
 (S) \quad & \left\{ \begin{aligned} \partial \bar{u} / \partial t &= D \partial^2 \bar{u} / \partial x^2 + \bar{F}(\bar{u}) \\ \bar{u}(x, t_0) &= \bar{u}_0(x), & x \in I, \\ \partial \bar{u}(x, t) / \partial x &= 0, & x \in \partial I, t \geq t_0. \end{aligned} \right. \\
 (S') \quad & \left\{ \begin{aligned} d\bar{v} / dt &= \bar{F}(\bar{v}), \\ \bar{v}(t_0) &= [\int_a^b \bar{u}_0(x) dx] / (b-a). \end{aligned} \right.
 \end{aligned}$$

Finally let σ denote the quantity

$$\sigma = d\lambda - M$$

where $d = \min_i \{d_i\}$,

$\lambda =$ smallest positive eigenvalue of $-d^2/dx^2$ on I subject to homogeneous Neumann boundary conditions

$$= \pi / (b-a),$$

$$M = \max \{ |d\bar{F}(\bar{u})| : \bar{u} \in \Sigma \},$$

where Σ is the invariant region defined by equation (4.6), and the quantity $|d\bar{F}(\bar{u})|$ denotes the determinant of the Jacobian matrix with entries $\partial F_i / \partial u_j$. Now if $\bar{u}_0(x) \in \Sigma$ for all $x \in I$, and $\sigma > 0$, then

$$\bar{u}(x, t) \rightarrow \bar{v}(t)$$

uniformly and exponentially for all $x \in I$ as $t \rightarrow \infty$.

The above lemma states that the solution to problem (S) can be approximated arbitrarily closely by the solution to the related kinetic system (S') if t is sufficiently large. In other words, when $\sigma > 0$, the large time behaviour of the solution to system (S) is determined only by the reaction mechanism $\bar{F}(\bar{u})$.

In view of the above lemma, we make the following proposition :

Proposition I :

All solutions to system (P) decay exponentially to a constant steady-state solution for any $(U_0, V_0, W_0) \in \Sigma$.

Proof :

For $t > t^*$, the nonlinear boundary condition to system (P) reduces to the homogeneous Neumann condition. By assumption, $(U_0, V_0, W_0) \in \Sigma$ and it follows from Property 3 that $(U(x, t^*), V(x, t^*), W(x, t^*)) \in \Sigma$. Hence the quantities

$$u_0(t^*) = \int_0^L U(x, t^*) dx / L,$$

$$v_0(t^*) = \int_0^L V(x, t^*) dx / L,$$

$$w_0(t^*) = \int_0^L W(x, t^*) dx / L,$$

also belong to Σ since they merely correspond to the spatial averages of $U(x, t^*)$, $V(x, t^*)$, and $W(x, t^*)$, respectively. Thus if we choose $u_0(t^*)$, $v_0(t^*)$, and $w_0(t^*)$ as the initial conditions to the related kinetic system for $t \geq t^*$, then by our lemma, we need only to show that $\sigma > 0$ and that the steady-state solution to the related kinetic system is a constant. We calculate

$$|d\bar{F}| = \begin{vmatrix} -a & a_1 b & 0 \\ a/(\delta a_1) & -b/\delta - c/\epsilon & (a_1/\epsilon)d \\ 0 & c/a_1 & -d \end{vmatrix}$$

where $a = a_1 V + a_2$, $b = (1-U)$,

$c = (1-W)$, $d = V/a_1 + 1/a_2$.

Observe that the second row is a linear combination of the first and third rows and thus $|d\bar{F}| = 0$ for all (U, V, W) and all parameter values a_1 , a_2 , δ , and ϵ . Hence¹

$$\sigma = d\lambda > 0.$$

Next we shall show that the steady-state solution to the related kinetic system is a constant. Let

$$\bar{z}(t) = (U - U_c, V - V_c, W - W_c)^T$$

denote the deviation from the critical point (U_c, V_c, W_c) of the kinetic system. By Theorem (9.2) of [7], it suffices to consider only the linearized form of the kinetic system about (U_c, V_c, W_c) ,

$$\bar{z}'(t) = A_0 \bar{z}(t),$$

and show that all eigenvalues of the linearized matrix A_0 are either zero or have negative real parts. Clearly A_0 is the same

¹One can interpret the condition that σ be positive to mean that the minimum rate of diffusion in the spatial domain is large relative to the maximum rate of reaction.

as the Jacobian matrix $d\bar{F}$ with (U,V,W) replaced by (U^c, V^c, W^c) in the definition of a, b, c , and d . We shall show in Section 4.2 (Property 4, with $n = 0$) that one eigenvalue of A_0 is zero and the other two eigenvalues have negative real parts. Thus the steady-state solution to the related kinetic system is a constant and this completes the proof.

We now turn to finding the steady-state solution (U^s, V^s, W^s) of system (P). By Proposition I, (U^s, V^s, W^s) are independent of x , hence they must satisfy

$$f(U^s, V^s) = 0 = h(V^s, W^s)$$

or equivalently,

$$U^s = a_1 V^s / [a_2 + a_1 V^s], \quad (4.1-1)$$

$$W^s = a_2 V^s / [a_1 + a_2 V^s]. \quad (4.1-2)$$

Moreover, (U^s, V^s, W^s) satisfies the conservation equation (4.5),

$$U^s / (a_1 \delta) + V^s + (a_1 / \epsilon) W^s = \xi, \quad (4.1-3)$$

where

$$\xi = U_0 / (a_1 \delta) + V_0 + (a_1 / \epsilon) W_0 + \beta(t^*) / L \quad (4.1-4)$$

and $\beta(t^*)$ is defined by equation (4.4). Using equations (4.1-1)-(4.1-3) we can prove the following proposition :

Proposition II :

For all positive parameter values a_1, a_2, δ , and ϵ , the steady-state solution to system (P) is unique.

Proof :

Observe that equations (4.1-1)-(4.1-2) define a monotonically increasing curve in a 3-dimensional space with V_s as a parameter ranging from 0 to infinity (see Figure 2). Thus the curve intersects the plane defined by equation (4.1-3) at precisely one point, (U_s, V_s, W_s) , and this completes the proof.

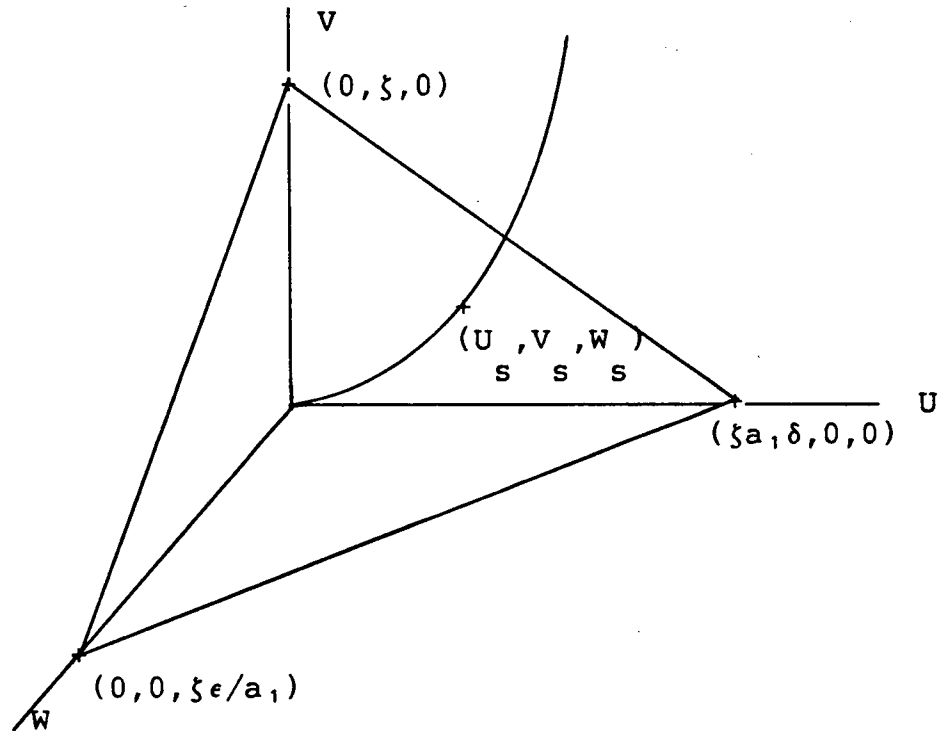


Figure 2 : Geometrical illustration of the uniqueness of the steady-state solution.

In order to find the steady-state value (U_s, V_s, W_s) , we substitute equations (4.1-1)-(4.1-2) into (4.1-3) and we see that V_s must satisfy the cubic equation

$$V_s^3 + \kappa_1 V_s^2 + \kappa_2 V_s - \xi = 0, \quad (4.1-5)$$

where $\kappa_1 = a_1/\epsilon + 1/(\delta a_1) + (a_1/a_2 + a_2/a_1) - \zeta$,
 $\kappa_2 = 1 + 1/(\delta a_2) + a_2/\epsilon - \zeta(a_1/a_2 + a_2/a_1)$.

By Proposition II, (4.1-5) has a unique positive real root. Using formulas from a standard table [25], we obtain

$$V_s = \kappa_1/3 + A_1 + A_2, \quad (4.1-6)$$

where

$$A_1^3 = -p/2 + \sqrt{p^2/4 + q^3/27}, \quad A_2^3 = -p/2 - \sqrt{p^2/4 + q^3/27},$$

and where¹

$$p = [2\kappa_1^3 - 9\kappa_1\kappa_2 + 27\zeta]/27, \quad q = [3\kappa_2 - \kappa_1^2]/3.$$

The values of U_s and W_s can now be obtained from equations (4.1-1)-(4.1-2). For the set of parameter values shown in Table 2, the steady-state value is

$$U_s = 0.00711, \quad V_s = 0.04525, \quad W_s = 0.22249.$$

In passing we remark that due to the complexity of the coefficients κ_1 and κ_2 , it is difficult to prove Proposition II directly from using equation (4.1-5) and this illustrates the importance of geometrical ideas in mathematics. We shall now turn to study the stability of the steady-state solution.

¹Note that since (4.1-5) has a unique positive real root, the expression $p^2/4 + q^3/27 > 0$.

4.2 ASYMPTOTIC STABILITY OF THE STEADY-STATE

We shall begin by giving a formal definition of stability. Let $\bar{y}_s(x)$ be a steady-state solution to a system of PDEs of type (1.2) with initial condition $\bar{y}_0(x, t_0)$ and appropriate boundary conditions. Let $|\cdot|$ denote the usual Euclidean norm. The steady-state $\bar{y}_s(x)$ is said to be stable if given any $\epsilon > 0$, there exists a δ such that

$$|\bar{y}_0(x, t_0) - \bar{y}_s(x)| < \delta \Rightarrow |\bar{y}(x, t) - \bar{y}_s(x)| < \epsilon,$$

for all $t \geq t_0$. If in addition

$$|\bar{y}(x, t) - \bar{y}_s(x)| \rightarrow 0 \text{ as } t \rightarrow \infty,$$

then the steady-state $\bar{y}_s(x)$ is asymptotically stable.

Intrinsically, it is easier to prove instability than it is to establish stability. For to establish stability we have to show that every sufficiently small perturbation dies away, whereas instability will be demonstrated if we can show that one sufficiently small perturbation away from the steady-state will grow with time. Sufficient conditions for instability are given by Amundson [3] and Jackson [17].

In this section, however, we shall use the linearization technique¹ to establish the asymptotic stability of (U_s, V_s, W_s)

¹Justification of the linearization technique for establishing stability is discussed by Krasnosel'skii [19].

found in the previous section. The linearized form of the governing equations is

$$\begin{aligned}\partial u / \partial t &= D_{13} \partial^2 u / \partial x^2 - au + a_1 bv, \\ \partial v / \partial t &= \partial^2 v / \partial x^2 + au / (a_1 \delta) - (b / \delta + c / \epsilon) v + (da_1 / \epsilon) w, \\ \partial w / \partial t &= D_{23} \partial^2 w / \partial x^2 + (c / a_1) v - dw,\end{aligned}\quad (4.2-1)$$

where

$$\begin{aligned}a &= a_1 V_s + a_2, & b &= (1 - U_s), \\ c &= (1 - W_s), & d &= (V_s / a_1 + 1 / a_2),\end{aligned}$$

and where (u, v, w) are deviations from (U_s, V_s, W_s) , i.e.,

$$u = U - U_s, \quad v = V - V_s, \quad w = W - W_s.$$

Moreover for every given steady-state value satisfying (4.5), it is easy to deduce from (4.3) that the deviation must satisfy the integral equation

$$\int_0^L [u(x, t) / (a_1 \delta) + v(x, t) + (a_1 / \epsilon) w(x, t)] dx = 0. \quad (4.2-2)$$

Since the system of equations (4.2-1) is linear and has constant coefficients, its solution can be found by separation of variables. Moreover, for $t > t^*$, the nonlinear boundary conditions (3.3) reduce to the homogeneous Neumann type and hence we write

$$\begin{aligned}u(x, t) &= \sum_{n=0}^{\infty} u_n(t) \cos(\omega_n x), & v(x, t) &= \sum_{n=0}^{\infty} v_n(t) \cos(\omega_n x), \\ w(x, t) &= \sum_{n=0}^{\infty} w_n(t) \cos(\omega_n x),\end{aligned}\quad (4.2-3)$$

where

$$\omega_n = n\pi/L, \quad n = 0, 1, 2, \dots$$

Substituting equation (4.2-3) into (4.2-1) we obtain a system of ordinary-differential equations

$$\bar{z}'_n(t) = A_n \bar{z}_n(t), \quad (4.2-4)$$

where $\bar{z}_n(t) = (u_n(t), v_n(t), w_n(t))^T$ and

$$A_n = \begin{bmatrix} -(D_{13}\omega_n^2 + a) & a_1 b & 0 \\ a/(\delta a_1) & -(\omega_n^2 + b/\delta + c/\epsilon) & da_1/\epsilon \\ 0 & c/a_1 & -(D_{23}\omega_n^2 + d) \end{bmatrix}$$

We shall first establish the following property of matrix A_n .

Property 4 :

For all positive parameter values a_1 , a_2 , δ , and ϵ , all the eigenvalues of matrix A_n have negative real parts for $n > 0$. When $n = 0$, one of the eigenvalues is zero and the other two eigenvalues have negative real parts.

Proof :

To find the eigenvalues of A_n we set

$$f(\lambda) = |\lambda I - A_n| = \lambda^3 + a\lambda^2 + \beta\lambda + \gamma = 0, \quad (4.2-5)$$

where I is the 3×3 identity matrix and

$$\alpha = (1 + D_{13} + D_{23})\omega^2 + (a + b/\delta + c/\epsilon + d),$$

$$\begin{aligned} \beta = & (D_{13} + D_{13}D_{23} + D_{23})\omega^4 \\ & + [(b/\delta + c/\epsilon + d)D_{13} + (a + b/\delta + c/\epsilon)D_{23} + (a + d)]\omega^2 \\ & + [ac/\epsilon + ad + bd/\delta], \end{aligned}$$

$$\begin{aligned} \gamma = & D_{13}D_{23}\omega^6 + [dD_{13} + (b/\delta + c/\epsilon)D_{13}D_{23} + aD_{23}]\omega^4 \\ & + [(bd/\delta)D_{13} + ad + (ac/\epsilon)D_{23}]\omega^2. \end{aligned}$$

Observe that since a , b , c , and d are all positive, so are α , β , and γ . When $n = 0$, we have $\gamma = 0$ and the required result follows immediately since α and β are positive. For $n > 0$, observe that

$$f(0) = \gamma > 0, \quad \text{and} \quad f(-a) = \gamma - a\beta < 0.$$

Thus there exists a negative real number λ_1 , $-a < \lambda_1 < 0$, such that

$$f(\lambda_1) = 0.$$

Dividing equation (4.2-5) by its factor $(\lambda - \lambda_1)$, we see that the other two roots must satisfy the quadratic equation

$$\lambda^2 + (a + \lambda_1)\lambda + [\beta + \lambda_1(a + \lambda_1)] = 0.$$

Now since $a + \lambda_1 > 0$, the roots to the quadratic must have negative real parts and this completes the proof.

According to the standard theory of linear stability [7], Property 4 states that for $n > 0$, the system of ordinary differential equations (4.2-4) is stable and the solution $\bar{z}_n(t) = \exp(A_n t) \rightarrow 0$ as $t \rightarrow \infty$. For $n = 0$, (4.2-4) is neutrally

stable and the solution $\bar{z}_0(t) = \exp(A_0 t)$ is bounded.

Using the above result we can prove the following proposition about the stability of system (P).

Proposition III :

For all positive parameter values a_1, a_2, δ , and ϵ , the unique steady-state solution (U_s, V_s, W_s) is asymptotically stable.

Proof :

It suffices to show that the deviation (u, v, w) tends to zero in the steady-state. By Property 4 the steady-state value can be obtained by merely solving

$$\bar{z}_0'(t) = A_0 \bar{z}_0(t)$$

and letting $t \rightarrow \infty$. The solution is

$$\begin{aligned} u(x, \infty) &= u_0(\infty) = (a_1 b/a) \mu, \\ v(x, \infty) &= v_0(\infty) = \mu, \\ w(x, \infty) &= w_0(\infty) = (c/da_1) \mu, \end{aligned} \quad (4.2-6)$$

where μ is some constant depending on the initial condition as well as the parameters a_1, a_2, δ , and ϵ . Since $u(x, \infty)$, $v(x, \infty)$ and $w(x, \infty)$ are independent of x , the integral equation (4.2-2) reduces to the algebraic equation

$$u_0(\infty)/(a_1 \delta) + v_0(\infty) + (a_1/\epsilon) w_0(\infty) = 0. \quad (4.2-7)$$

Combining equations (4.2-6) and (4.2-7) we deduce that

$$u(x, \infty) = v(x, \infty) = w(x, \infty) = 0$$

and this completes the proof.

5. SOME FEATURES OF THE TRANSIENT BEHAVIOUR

One of our main objectives in formulating the mathematical model (P) is to provide qualitative and quantitative information about the behaviour of the initial transient changes of Ca^{2+} . In this chapter we shall approximate the transient solution via a regular perturbation approach. Moreover, we shall use a comparison theorem to obtain analytical upper and lower bounds on the exact solution.

We mentioned in Section 4.1 that during the initial transient state, the diffusion rate of system (P) is very rapid compared with its reaction rate. Thus before carrying out the perturbation analysis, we shall rescale our variables so that the diffusion terms are of dominant order. To this end we introduce the stretching variables¹

$$\begin{aligned}\xi &= \sqrt{(\delta/\epsilon^2)}x, & \tau &= (\delta/\epsilon^2)t, \\ u(\xi, \tau) &= U/(\epsilon/\delta)^2, & v(\xi, \tau) &= V/(\epsilon/\delta), & w(\xi, \tau) &= W/(\epsilon/\delta).\end{aligned}$$

In (ξ, τ) space, system (P) becomes

$$\begin{aligned}\partial u / \partial \tau &= D_{13} \partial^2 u / \partial \xi^2 + (\epsilon/\delta)[\delta a_1 v] - (\epsilon/\delta)^2[\delta a_2 u] \\ &\quad + (\epsilon/\delta)^3[\delta a_1 uv], \\ \partial v / \partial \tau &= \partial^2 v / \partial \xi^2 + (\epsilon/\delta)[a_1 w / a_2 - v] \\ &\quad + (\epsilon/\delta)^2[a_2 u / a_1 - v(1-w)] + (\epsilon/\delta)^3[uv],\end{aligned}$$

¹The new dependent variables are chosen such that the initial conditions are of $O(1)$.

$$\begin{aligned} \partial w / \partial \tau = D_{23} \partial^2 w / \partial \xi^2 + (\epsilon / \delta)^2 [\delta(v/a_1 - w/a_2)] \\ - (\epsilon / \delta)^3 [\delta w v / a_1], \end{aligned} \quad (5.1)$$

with initial conditions

$$u(\xi, 0) = u_0, \quad v(\xi, 0) = v_0, \quad w(\xi, 0) = w_0, \quad (5.2)$$

where

$$u_0 = U_0 / (\epsilon / \delta)^2, \quad v_0 = V_0 / (\epsilon / \delta), \quad w_0 = W_0 / (\epsilon / \delta).$$

The boundary conditions are

$$\begin{aligned} \partial u(0, \tau) / \partial \xi = \partial u(L', \tau) / \partial \xi = \partial w(0, \tau) / \partial \xi = \partial w(L', \tau) / \partial \xi = 0, \\ \partial v(L', \tau) / \partial \xi = 0, \quad \partial v(0, \tau) / \partial \xi = A' + B' \ln v(0, \tau), \end{aligned} \quad (5.3)$$

where $A' = \sqrt{\delta}(A + B \ln(\epsilon / \delta))$, $B' = \sqrt{\delta}B$, $L' = \sqrt{(\delta / \epsilon^2)}L$.

It is clear from (5.1) that (ϵ / δ) is a natural choice as a perturbation parameter. For the set of parameter values shown in Table 2, ϵ / δ has a value of 0.0375.

In order to obtain an approximate transient solution to system (P), we consider a regular expansion of the form

$$\begin{aligned} u(\xi, \tau) &= u^0(\xi, \tau) + (\epsilon / \delta) u^1(\xi, \tau) + (\epsilon / \delta)^2 u^2(\xi, \tau) + \dots \\ v(\xi, \tau) &= v^0(\xi, \tau) + (\epsilon / \delta) v^1(\xi, \tau) + (\epsilon / \delta)^2 v^2(\xi, \tau) + \dots \\ w(\xi, \tau) &= w^0(\xi, \tau) + (\epsilon / \delta) w^1(\xi, \tau) + (\epsilon / \delta)^2 w^2(\xi, \tau) + \dots \end{aligned} \quad (5.4)$$

The nonlinear boundary condition on $v(\xi, \tau)$ becomes

$$\begin{aligned} A' + B' \ln v(0, \tau) &= A' + B' \ln v^0(0, \tau) + (\epsilon / \delta) [B' / v^0(0, \tau)] v^1(0, \tau) \\ &+ O((\epsilon / \delta)^2). \end{aligned}$$

Our objective is to obtain the first-order correction terms in the expansion (5.4). Substituting equation (5.4) into (5.1) and collecting terms of the same order gives

$$\begin{aligned} O((\epsilon/\delta)^0) : \quad & \partial u^0 / \partial \tau = D_{13} \partial^2 u^0 / \partial \xi^2, \\ & \partial v^0 / \partial \tau = \partial^2 v^0 / \partial \xi^2, \\ & \partial w^0 / \partial \tau = D_{23} \partial^2 w^0 / \partial \xi^2, \end{aligned} \quad (5.5)$$

with initial and boundary conditions

$$\begin{aligned} u^0(\xi, 0) &= u_0, \quad v^0(\xi, 0) = v_0, \quad w^0(\xi, 0) = w_0, \\ \partial u^0(0, \tau) / \partial \xi &= \partial u^0(L', \tau) / \partial \xi = \partial w^0(0, \tau) / \partial \xi = \partial w^0(L', \tau) / \partial \xi = 0, \\ \partial v^0(L', \tau) / \partial \xi &= 0, \quad \partial v^0(0, \tau) / \partial \xi = A' + B' \ln v^0(0, \tau). \end{aligned} \quad (5.6)$$

Thus the zeroth-order equations¹ to our nonlinear system are linear uncoupled heat equations with nonlinear boundary condition on $v^0(\xi, \tau)$. In view of the initial and boundary conditions, the solutions to $u^0(\xi, \tau)$ and $w^0(\xi, \tau)$ can be obtained by inspection as

$$u^0(\xi, \tau) = u_0, \quad w^0(\xi, \tau) = w_0. \quad (5.7)$$

However, because of the nonlinear boundary condition, the exact solution to $v^0(\xi, \tau)$ cannot be obtained analytically. Moreover, linearization of the boundary condition is not fruitful since $v^0(\xi, \tau)$ changes rapidly near $\tau = 0$. Thus, $v^0(\xi, \tau)$ is calculated numerically using an algorithm called PDECOL (see

¹On physical grounds, the zeroth-order solution corresponds to an approximate solution of the system when the diffusion rate is rapid relative to the reaction rate.

Appendix A for a detail discussion).

We shall proceed to obtain correction terms for u , v , and w . The first-order governing equations are

$$O((\epsilon/\delta)) : \quad \partial u^1/\partial \tau = D_{13} \partial^2 u^1/\partial \xi^2 + \delta a_1 v^0, \quad (5.8a)$$

$$\partial v^1/\partial \tau = \partial^2 v^1/\partial \xi^2 + (a_1 w^0/a_2 - v^0), \quad (5.8b)$$

$$\partial w^1/\partial \tau = D_{23} \partial^2 w^1/\partial \xi^2, \quad (5.8c)$$

with initial and boundary conditions

$$\begin{aligned} u^1(\xi, 0) &= 0, \quad v^1(\xi, 0) = 0, \quad w^1(\xi, 0) = 0, \\ \partial u^1(0, \tau)/\partial \xi &= \partial u^1(L', \tau)/\partial \xi = \partial w^1(0, \tau)/\partial \xi = \partial w^1(L', \tau)/\partial \xi = 0, \\ \partial v^1(L', \tau)/\partial \xi &= 0, \quad \partial v^1(0, \tau)/\partial \xi = [B'/v^0(0, \tau)]v^1(0, \tau). \end{aligned} \quad (5.9)$$

An inspection of the initial and boundary conditions on w^1 reveals that

$$w^1(\xi, \tau) = 0. \quad (5.10)$$

Thus in order to obtain a correction term for $w(\xi, \tau)$, we must consider the $O((\epsilon/\delta)^2)$ equation and we have

$$O((\epsilon/\delta)^2) : \quad \partial w^2/\partial \tau = D_{23} \partial^2 w^2/\partial \xi^2 + \delta[v^0/a_1 - w^0/a_2], \quad (5.11)$$

with initial and boundary conditions

$$w^2(\xi, 0) = 0, \quad \partial w^2(0, \tau)/\partial \xi = 0 = \partial w^2(L', \tau)/\partial \xi. \quad (5.12)$$

Equations (5.8a) and (5.11) are precisely of the form given in Appendix B with $a = 0$. The solutions are

$$u^1(\xi, \tau) = \sum_{n=0}^{\infty} u_n(\tau) \cos \lambda_n (\xi - L'), \quad (5.13a)$$

$$w^2(\xi, \tau) = \sum_{n=0}^{\infty} w_n(\tau) \cos \lambda_n (\xi - L') - (\delta w_0 / a_2) \tau, \quad (5.13b)$$

where $\lambda_n = n\pi/L'$,

$$u_n(\tau) = [\delta a_1] \int_0^{\tau} q_n(s) \exp(-D_{13} \lambda_n^2 (\tau - s)) ds,$$

$$w_n(\tau) = [\delta/a_1] \int_0^{\tau} q_n(s) \exp(-D_{23} \lambda_n^2 (\tau - s)) ds,$$

for $n = 0, 1, 2, \dots$ and where

$$q_0(s) = (1/L') \int_0^{L'} v^0(\xi, s) d\xi,$$

$$q_n(s) = (2/L') \int_0^{L'} v^0(\xi, s) \cos \lambda_n (\xi - L') d\xi, \quad n \geq 1.$$

Since $v^0(\xi, \tau)$ is known from the zeroth-order calculation, $q_n(s)$ can be obtained by direct numerical integration.

We shall now turn to the discussion of $v^1(\xi, \tau)$. By Lemma 1 of Appendix B, provided that

$$|\Delta[B'/v^0(0, \tau)]/[B'/(v^0(0, \tau))]| \ll 1,$$

or equivalently

$$|[v^0(0, \tau + \Delta\tau) - v^0(0, \tau)]/v^0(0, \tau)| \ll 1, \quad (*)$$

then $v^1(\xi, \tau)$ is approximately given by

$$v^1(\xi, \tau) = \sum_{n=1}^{\infty} v_n(\tau) \cos \lambda_n (\xi - L'), \quad (5.14)$$

where λ_n satisfies the transcendental equation

$$\lambda_n \sin \lambda_n L' - [B'/v^0(0, \tau)] \cos \lambda_n L' = 0, \quad (5.15)$$

and

$$v_n(\tau) = \int_0^\tau p_n(s) \exp(-\lambda_n^2(\tau-s)) ds,$$

with

$$p_n(s) = \left[\int_0^{L'} (a_1 w^0/a_2 - v^0(\xi, s)) \cos \lambda_n (\xi - L') d\xi \right] / c_n,$$

and where

$$c_n = \{L' + [B'/v^0(0, \tau)] \cos^2 \lambda_n L' / \lambda_n^2\} / 2,$$

for $n = 1, 2, \dots$

In order to ensure that condition (*) holds we divide the interval $[0, \tau]$ into m subintervals

$$0 = \tau_0 < \tau_1 < \dots < \tau_m = \tau,$$

so that

$$v_n(\tau) = \sum_{k=1}^m \int_{\tau_{k-1}}^{\tau_k} p_n(s) \exp(-\lambda_n^2(\tau-s)) ds.$$

For each subinterval $\tau_{k-1} < \tau < \tau_k$, we approximate $v^0(0, \tau)$ by $v^0(0, \tau_{k-1})$ and generate a new set of $\{\lambda_n\}$ via equation (5.15). Thus by choosing m sufficiently large, condition(*) is satisfied.

In summary the approximate transient solutions obtained from the perturbation method are

$$\begin{aligned} u(\xi, \tau) &= u_0 + (\epsilon/\delta) u^1(\xi, \tau) + O((\epsilon/\delta)^2), \\ v(\xi, \tau) &= v^0(\xi, \tau) + (\epsilon/\delta) v^1(\xi, \tau) + O((\epsilon/\delta)^2), \\ w(\xi, \tau) &= w_0 + (\epsilon/\delta)^2 w^2(\xi, \tau) + O((\epsilon/\delta)^3). \end{aligned} \quad (5.16)$$

In terms of U , V and W , the perturbation solutions are

$$U(\xi, \tau) = U_0 + (\epsilon/\delta)^3 u^1(\xi, \tau) + O((\epsilon/\delta)^4), \quad (5.17a)$$

$$V(\xi, \tau) = V^0(\xi, \tau) + (\epsilon/\delta)^2 v^1(\xi, \tau) + O((\epsilon/\delta)^3), \quad (5.17b)$$

$$W(\xi, \tau) = W_0 + (\epsilon/\delta)^3 w^2(\xi, \tau) + O((\epsilon/\delta)^4), \quad (5.17c)$$

where $V^0(\xi, \tau) = (\epsilon/\delta)v^0(\xi, \tau)$. Thus our perturbation solutions are good up to $O((\epsilon/\delta)^2)$ for V and $O((\epsilon/\delta)^3)$ for U and W . For values¹ of $t \leq 10^{-3}$ ($t = \tau(\epsilon^2/\delta)$), equations (5.17a-c) provide good approximations to the initial transient behaviour of system (P). In Figures (3a-b) we compare the exact solution of $V(\xi, \tau)$ with the perturbation solutions for $t = 10^{-3}$ and 10^{-2} . We have omitted plotting the $U(\xi, \tau)$ and $W(\xi, \tau)$ solutions since for values of $t < 10^{-2}$, the deviations from the initial state, U_0 and W_0 , are negligible.

Our perturbation analysis is unsatisfactory in the sense that we are not able to obtain an analytical solution² for $V^0(\xi, \tau)$. Moreover for values of $t > 10^{-3}$, the perturbation solutions (5.17a-c) begin to deviate from the exact solutions and they no longer provide any qualitative information of the true solutions. Thus one would at least like to find good analytical bounds which will give us quantitative information on the exact solutions. The following version of the comparison theorem [10] for parabolic equations suits our situation.

¹The value $t = 10^{-3}$ corresponds to 1 μsec in physical units.

²However the computing time for solving $V^0(\xi, \tau)$ is less than half the computing time for solving the full system of PDEs.

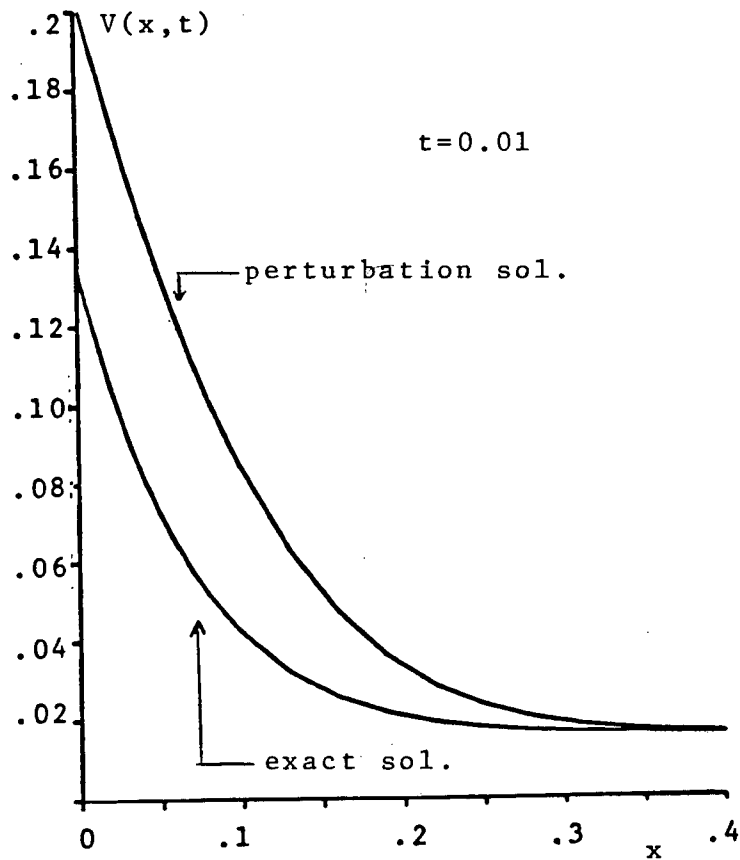
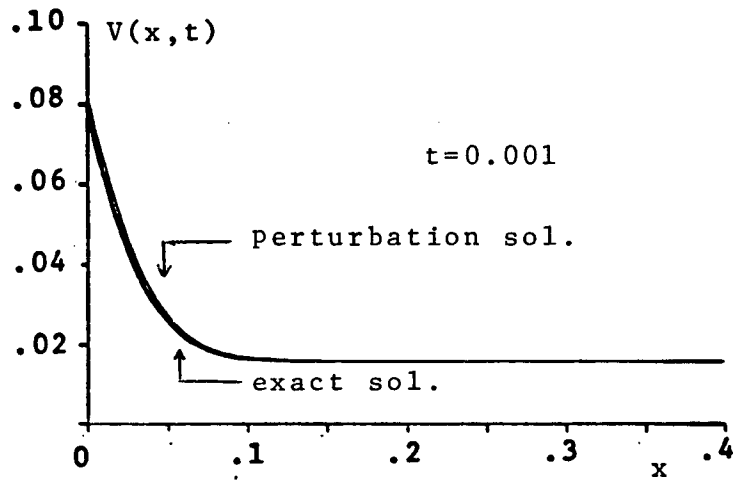


Figure 3a-b : Comparison between the exact solution of V with the perturbation solution for $t = 0.001, 0.01$.

Comparison Theorem

Consider the system of parabolic equations of type (1.2)

$$\partial \bar{v} / \partial t = D \partial^2 \bar{v} / \partial x^2 + \bar{G}(\bar{v}),$$

$$\partial \bar{u} / \partial t = D \partial^2 \bar{u} / \partial x^2 + \bar{F}(\bar{u}),$$

defined for $x \in I = [a, b]$, $t > 0$ with prescribed initial conditions and Neumann boundary conditions. Assume

- i) $\bar{F}(\bar{u})$ is quasi-monotone nondecreasing in $\bar{u}$,
- ii) $\bar{G}(\cdot) \geq \bar{F}(\cdot)$,
- iii) $\bar{v}(x, 0) \geq \bar{u}(x, 0)$, $x \in I = [a, b]$,
- iv) $\partial \bar{v}(x, t) / \partial n \geq \partial \bar{u}(x, t) / \partial n$, $x \in \partial I$, $t > 0$,

where $\partial / \partial n$ denotes outward directional derivative on ∂I . Then

$$\bar{v}(x, t) \geq \bar{u}(x, t), \quad \text{for } x \in I, t \geq 0,$$

for any continuous solutions $\bar{u}(x, t)$ and $\bar{v}(x, t)$.

Thus provided that condition (i) is satisfied, the above theorem allows us to calculate an upper bound for $\bar{u}$ by replacing the kinetic term, the initial condition, and the normal derivatives by any convenient differentiable functions subject to conditions (ii)-(iv).

We shall use the above theorem to find analytical bounds for U , V , and W . In particular we are interested in finding good bounds during the initial transient state. By Property 3 of Chapter 4, we know that U_0 , V_0 , and W_0 are lower bounds for U , V , and W , respectively. Moreover our perturbation solutions indicate

that for small t , they are good lower bounds. Thus we shall merely concentrate on finding analytical upper bounds. The following upper bounds for f , g , and h are easy to establish :

$$f(U,V) \leq a_1(1-U_0)(V - V_0) = \bar{f}, \quad (5.19a)$$

$$g(U,V,W) \leq a_2/(\delta a_1) + a_1/(\epsilon a_2) = \bar{g}, \quad (5.19c)$$

$$h(V,W) \leq (1-W_0)(V - V_0)/a_1 = \bar{h}, \quad (5.19b)$$

where V_m is a finite upper bound on V to be determined.

We shall temporarily assume that V_m is known and prove the following proposition :

Proposition V :

A pointwise upper bound $(\bar{U}, \bar{V}, \bar{W})$ for (U, V, W) is given by

$$\bar{U}(x,t) = U_0 + \bar{f}t, \quad (5.20a)$$

$$\bar{W}(x,t) = W_0 + \bar{h}t, \quad (5.20b)$$

$$\bar{V}(x,t) = V_0 + \bar{g}t + V^*(x,t), \quad (5.20c)$$

where

$$\begin{aligned} V^*(x,t) = 2\beta\sqrt{t} \{ & \sum_{k=-\infty}^{\infty} (1/\sqrt{\pi}) \exp(-(x-2kL)^2/4t) - \sum_{k=1}^{\infty} P[(2kL-x)/2\sqrt{t}] \\ & - \sum_{k=0}^{\infty} P[(x+2kL)/2\sqrt{t}] \}, \end{aligned} \quad (5.21)$$

where $\beta = -(A + B \ln V_0)$, $P(z) = z \operatorname{erfc}(z)$ and $\operatorname{erfc}(x)$ is the complementary error function,

$$\operatorname{erfc}(x) = 2/\sqrt{\pi} \int_x^{\infty} \exp(-a^2) da.$$

Proof :

By Property 1 of Chapter 4, $\bar{F} = (f, g, h)$ is quasi-monotone nondecreasing in $\bar{u} = (U, V, W)$. Thus condition (i) of our comparison theorem is satisfied and an upper bound to system (P) can be obtained by solving the system of equations

$$\partial \bar{U} / \partial t = D_{1,3} \partial^2 \bar{U} / \partial x^2 + \bar{f}, \quad (5.22a)$$

$$\partial \bar{V} / \partial t = \partial^2 \bar{V} / \partial x^2 + \bar{g}, \quad (5.22b)$$

$$\partial \bar{W} / \partial t = D_{2,3} \partial^2 \bar{W} / \partial x^2 + \bar{h}, \quad (5.22c)$$

with initial conditions on $0 < x < L$,

$$\bar{U}(x, 0) = U_0, \quad \bar{V}(x, 0) = V_0, \quad \bar{W}(x, 0) = W_0, \quad (5.23)$$

and boundary conditions for $t > 0$,

$$\begin{aligned} \partial \bar{U} / \partial x(0, t) = 0 = \partial \bar{U} / \partial x(L, t), \quad \partial \bar{W} / \partial x(0, t) = 0 = \partial \bar{W} / \partial x(L, t), \\ \partial \bar{V} / \partial x(0, t) = -\beta, \quad \partial \bar{V} / \partial x(L, t) = 0. \end{aligned} \quad (5.24)$$

Observe that we have kept the same initial conditions and have simply replaced the kinetic terms by their respective upper bounds. Now since

$$\partial \bar{V} / \partial x(0, t) = -\beta = A + B \ln V_0 \leq A + B \ln V(0, t) = \partial V / \partial x(0, t),$$

all conditions of the theorem are satisfied. The solutions for $\bar{U}$ and $\bar{W}$ can be obtained by inspection as

$$\bar{U}(x, t) = U_0 + \bar{f}t, \quad \bar{W}(x, t) = W_0 + \bar{h}t.$$

To solve for $\bar{V}(x, t)$ we consider the transformation

$$v^*(x, t) = \bar{V} - V_0 - \bar{g}t. \quad (5.25)$$

Substituting (5.25) into (5.21b) we have

$$\partial V^*/\partial t = \partial^2 V^*/\partial x^2, \quad (5.26)$$

subject to initial condition on $0 < x < L$,

$$V^*(x, 0) = 0, \quad (5.27)$$

and boundary conditions for $t > 0$,

$$\partial V^*/\partial x(0, t) = -\beta, \quad \partial V^*/\partial x(L, t) = 0. \quad (5.28)$$

We shall solve (5.26) using the Laplace transform. Taking the transform on both sides of (5.26) and using initial condition (5.27) we have

$$d^2 v^*/dx^2 - s v^* = 0, \quad (5.29)$$

where $v^*(x, s) = \mathcal{L}\{V^*(x, t)\}$. The boundary conditions are

$$dv^*(0, s)/dx = -\beta/s, \quad dv^*(L, s)/dx = 0. \quad (5.30)$$

Solving (5.29) subject to conditions (5.30) gives

$$v^*(x, s) = (\beta/\sqrt{s^3}) [\cosh \sqrt{s}(x-L)/\sinh \sqrt{s}L]. \quad (5.31)$$

Since we are interested in the solution for small t , we expand (5.31) for large s and we get

$$v^*(x, s) = (\beta/\sqrt{s^3}) \left\{ \sum_{k=1}^{\infty} \exp(-\sqrt{s}(2kL-x)) + \sum_{k=0}^{\infty} \exp(-\sqrt{s}(x+2kL)) \right\}. \quad (5.32)$$

Using a standard transform table [25], we can invert (5.32) term by term and we obtain (5.21) as desired.

An interesting feature of the infinite series representation of $V^*(x,t)$ is that it converges rapidly for small t . To see this recall that the asymptotic expression for $\text{erfc}(x)$ is

$$\text{erfc}(x) = (1/\sqrt{\pi})\exp(-x^2)[1/x - 1/2x^3 + O(1/x^5)] \quad \text{as } x \rightarrow +\infty.$$

Using the above expansion it is easy to deduce that

$$\begin{aligned} V^*(x,t) = \beta\sqrt{t}/\pi \left\{ \sum_{k=-\infty}^{\infty} \exp(-(x-2kL)^2/4t) / [(x-2kL)^2/4t] \right. \\ \left. + O([(2kL-x)/2\sqrt{t}]^{-5}) \right\} \quad \text{as } [(2kL-x)/2\sqrt{t}] \rightarrow +\infty. \end{aligned} \quad (5.33)$$

For values of $t < 0.1$, it is only necessary to calculate the $k = 0, \pm 1$ terms to obtain sufficient accuracy for $V^*(x,t)$.

It is clear from (5.33) that for small t , the contribution of V^* in (5.20c) is small¹ compared with $V_0 + \bar{g}t$. Thus for values of $t < 1$, we shall neglect the V^* term in (5.20c) and we have

$$V_m(t) = \bar{V}(x,t) = V_0 + \bar{g}t, \quad x \in [0,L], \quad 0 \leq t < 1.$$

Thus for small t , the bounds $(\bar{U}, \bar{V}, \bar{W})$ are independent of x . Using the set of parameter values given in Table 1, we summarize in Table 3 the true maximum values of (U, V, W) which occur at $x = 0$ together with their respective upper bounds for $t = 0.001$, 0.01 , and 0.1 .

¹Numerical calculations indicate that for values of $t < 1.0$, the contribution from V^* is negligible.

	$t = 0.001$	$t = 0.01$	$t = 0.1$
Max $U(x,t)$ x	0.00250	0.00258	0.00314
$\bar{U}$	0.00250	0.00374	0.12719
Max $V(x,t)$ x	0.07776	0.13423	0.14558
$\bar{V}$	0.09488	0.80651	7.92283
Max $W(x,t)$ x	0.09111	0.09514	0.12851
$\bar{W}$	0.09136	0.13638	4.63752

Table 3 : Summary of the true maximum values of (U,V,W) together with their respective upper bounds.

It is clear from Table 3 that as t increases the bounds deviate further and further away from the exact solutions and hence they are not very useful for large values of t . This is due mainly to the rough estimate we used in calculating $\bar{f}$, $\bar{g}$, and $\bar{h}$ in equations (5.19a-c). Our present analysis, however, provides us with an idea of the relative maximum amplitude of U , V , and W . We shall now turn to discuss the numerical results of system (P).

6. NUMERICAL SOLUTION

In the area of chemically reacting systems, nonlinearity is more the rule than the exception, and accordingly analytical solutions are rare. We were "fortunate" to obtain analytical results for the steady-state and the initial transient behaviour of system (P). However for intermediate values of t , analytical results for system (P) are beyond our reach and we must resort to numerical techniques.

In order to give a complete description of the calcium dynamics, we use the parameter values in Table 1 and solve the full system of equations (3.2)-(3.4) using PDECOL. Figures (4a-c) show the concentration profiles of U, V, and W ($[CaArz]$, $[Ca^{2+}]$, and $[CaB]$) in their original physical units during a 0.1 second (t^*) loading period. It is clear from the figures that the concentrations of $CaArz$, Ca^{2+} , and CaB rise to their respective maxima¹ at $t = t^*$ and as Ca^{2+} influx continues, the front of CaB and $CaArz$ moves away from the surface membrane (or into the cell).

In Figures (5a-c) we show that after the pulse stops ($t > t^*$), diffusion proceeds carrying Ca^{2+} and the complexes further into the cell which permits a spatial redistribution of Ca^{2+} inside the cytoplasm. The concentrations

¹At the same time, the intrinsic buffer concentrations Arz and B decrease according to equations (2.2a) and (2.2b), respectively.

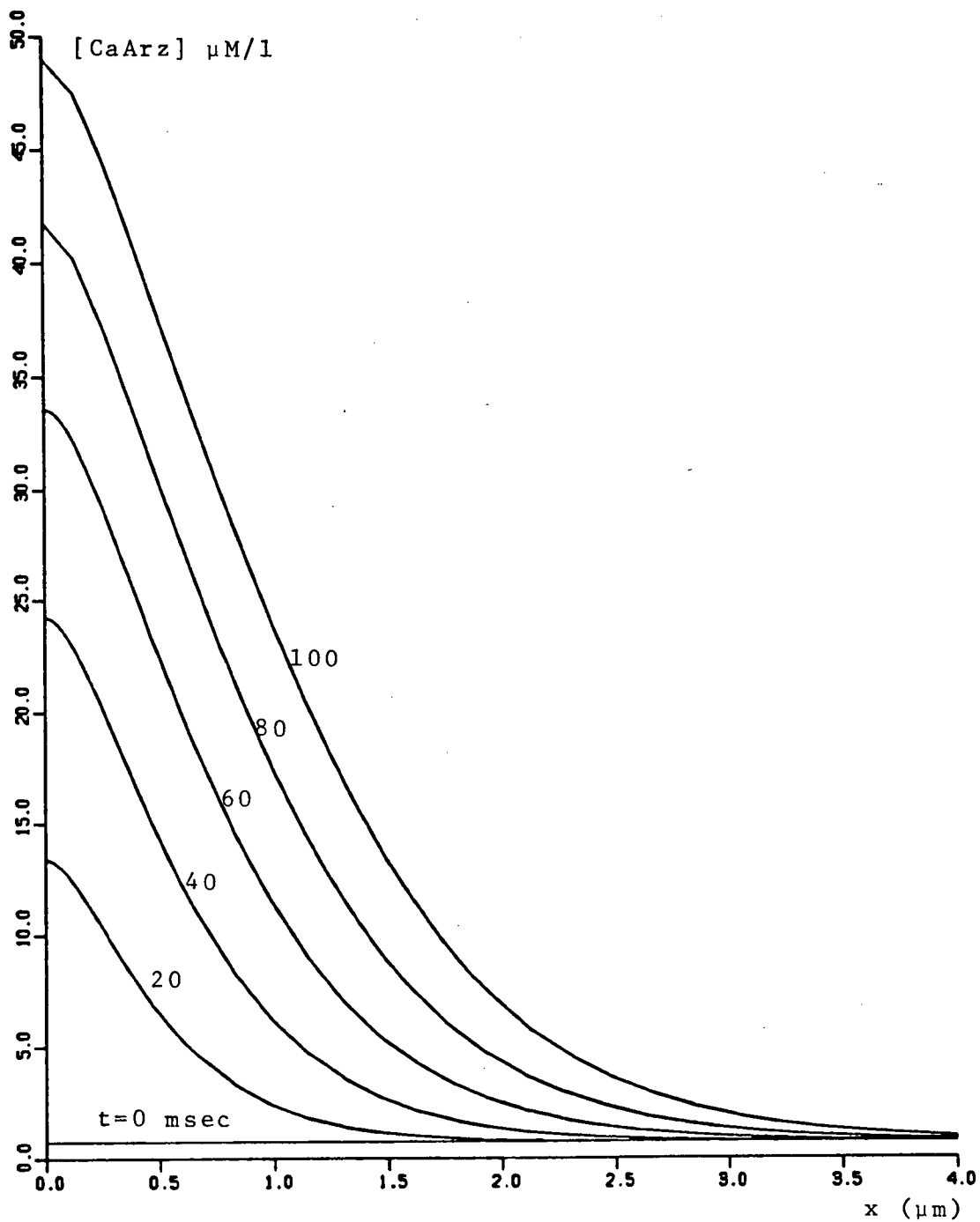


Figure 4a : Concentration profiles of CaArz during a 0.1 second loading period.

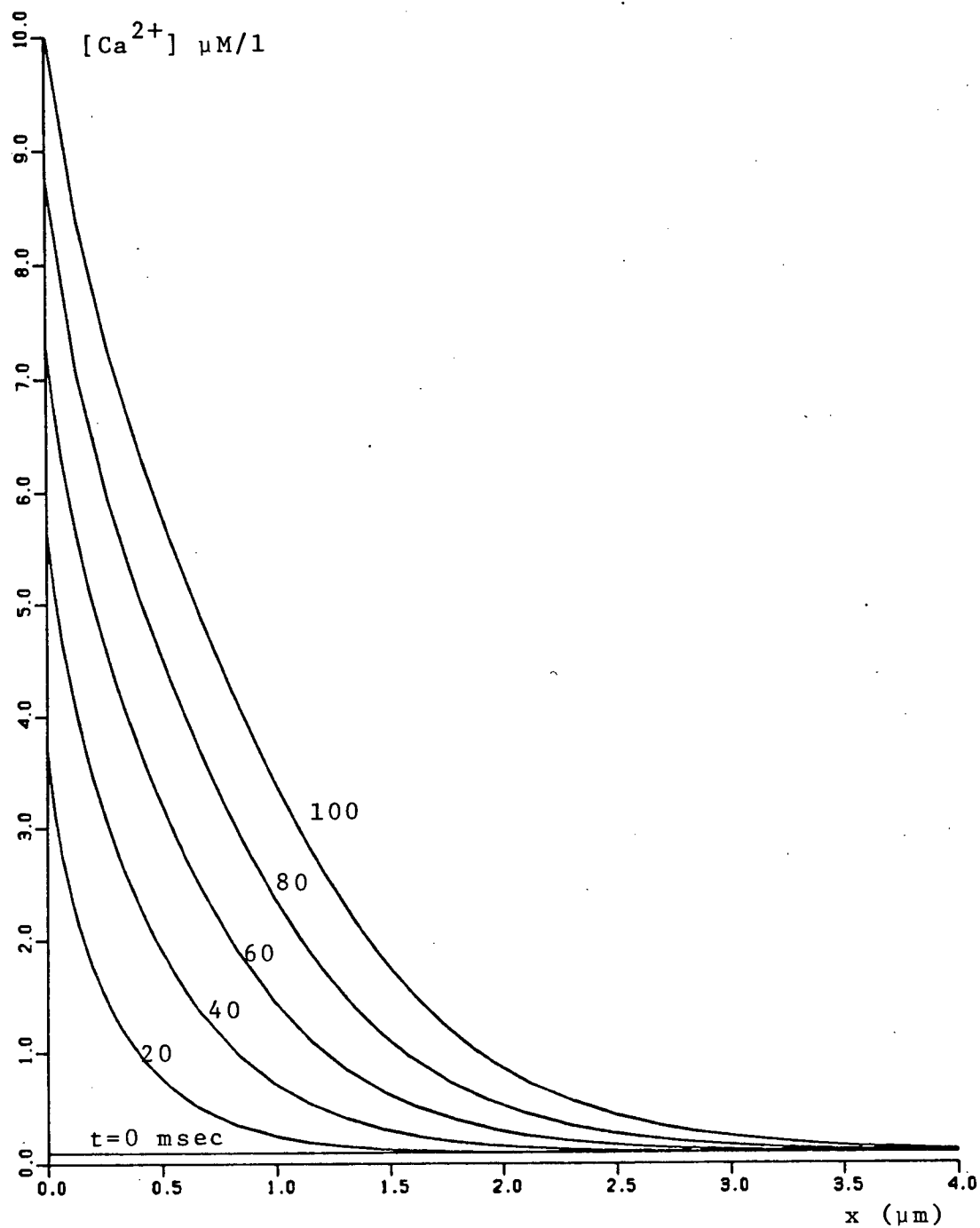


Figure 4b : Concentration profiles of Ca^{2+} during a 0.1 second loading period.

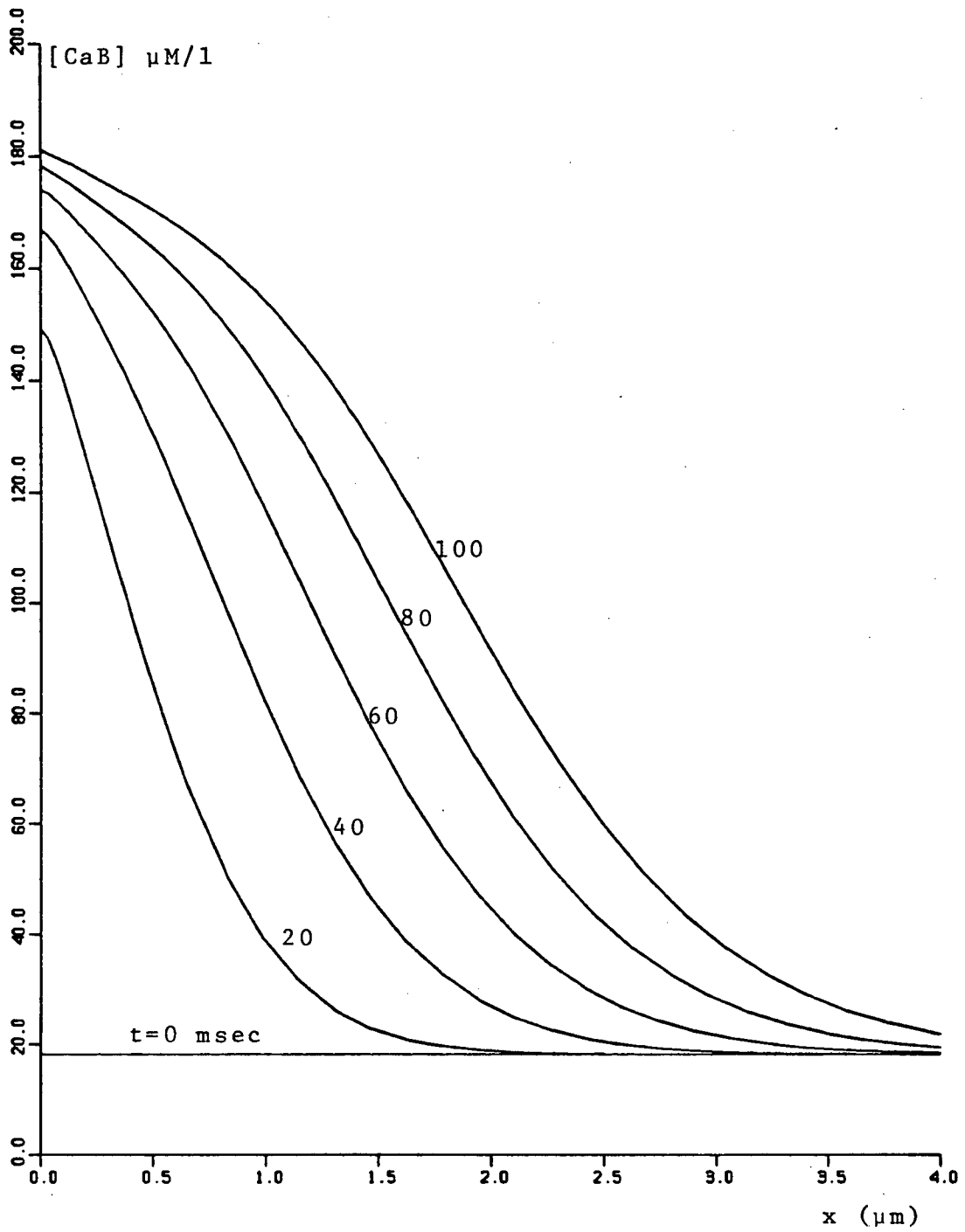


Figure 4c : Concentration profiles of CaB during a 0.1 second loading period.

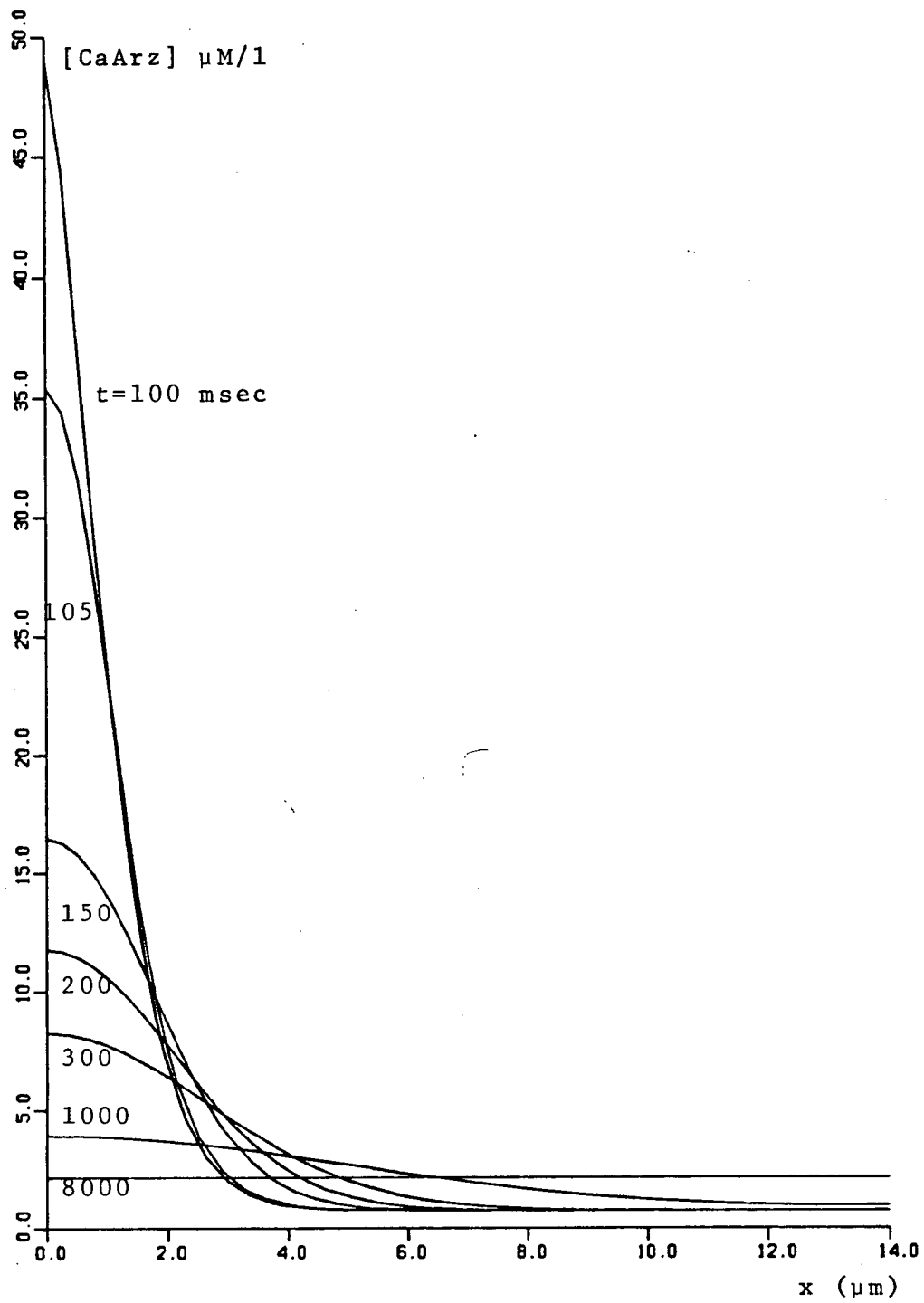


Figure 5a : Concentration profiles of CaArz after influx.

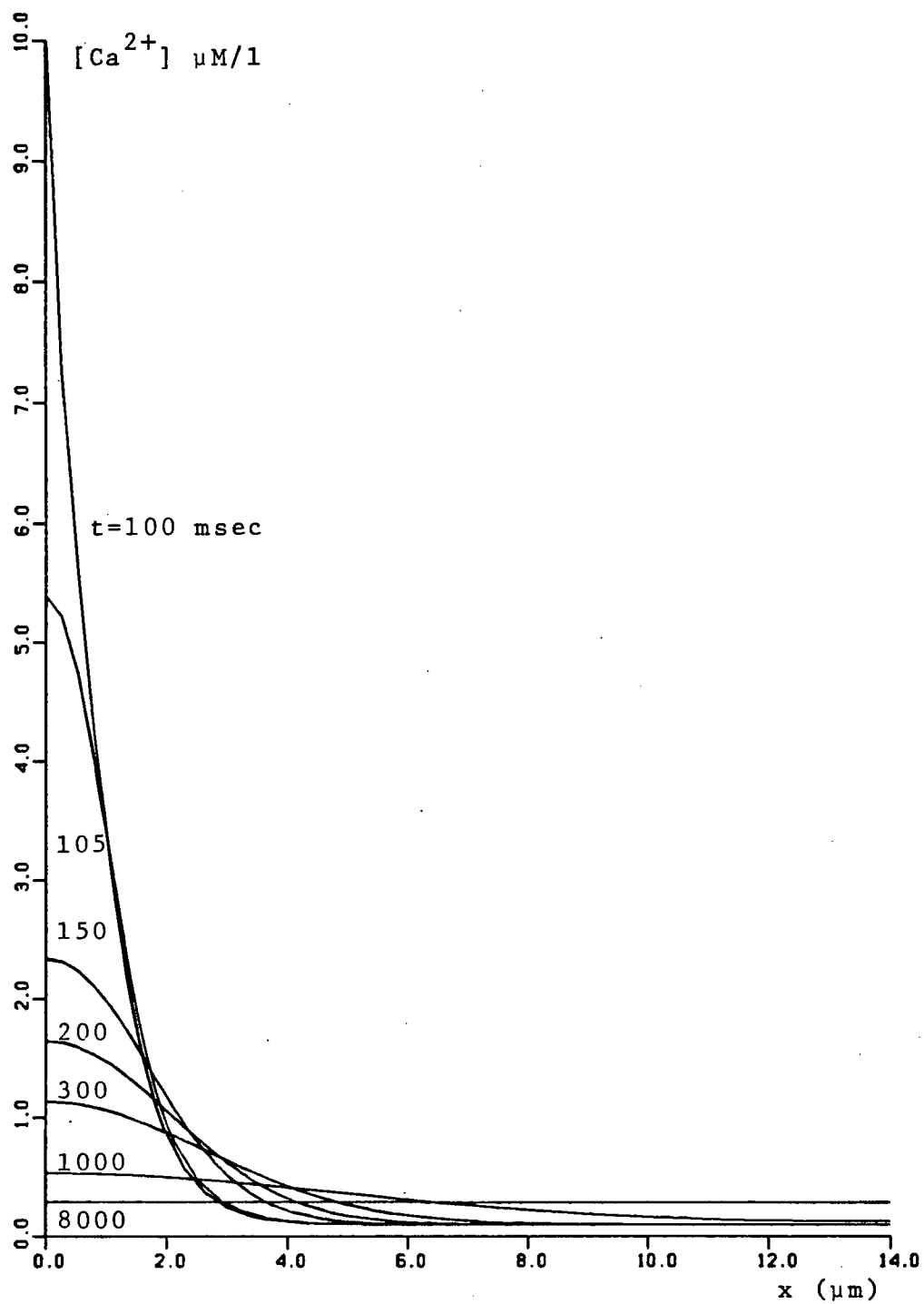


Figure 5b : Concentration profiles of Ca^{2+} after influx.

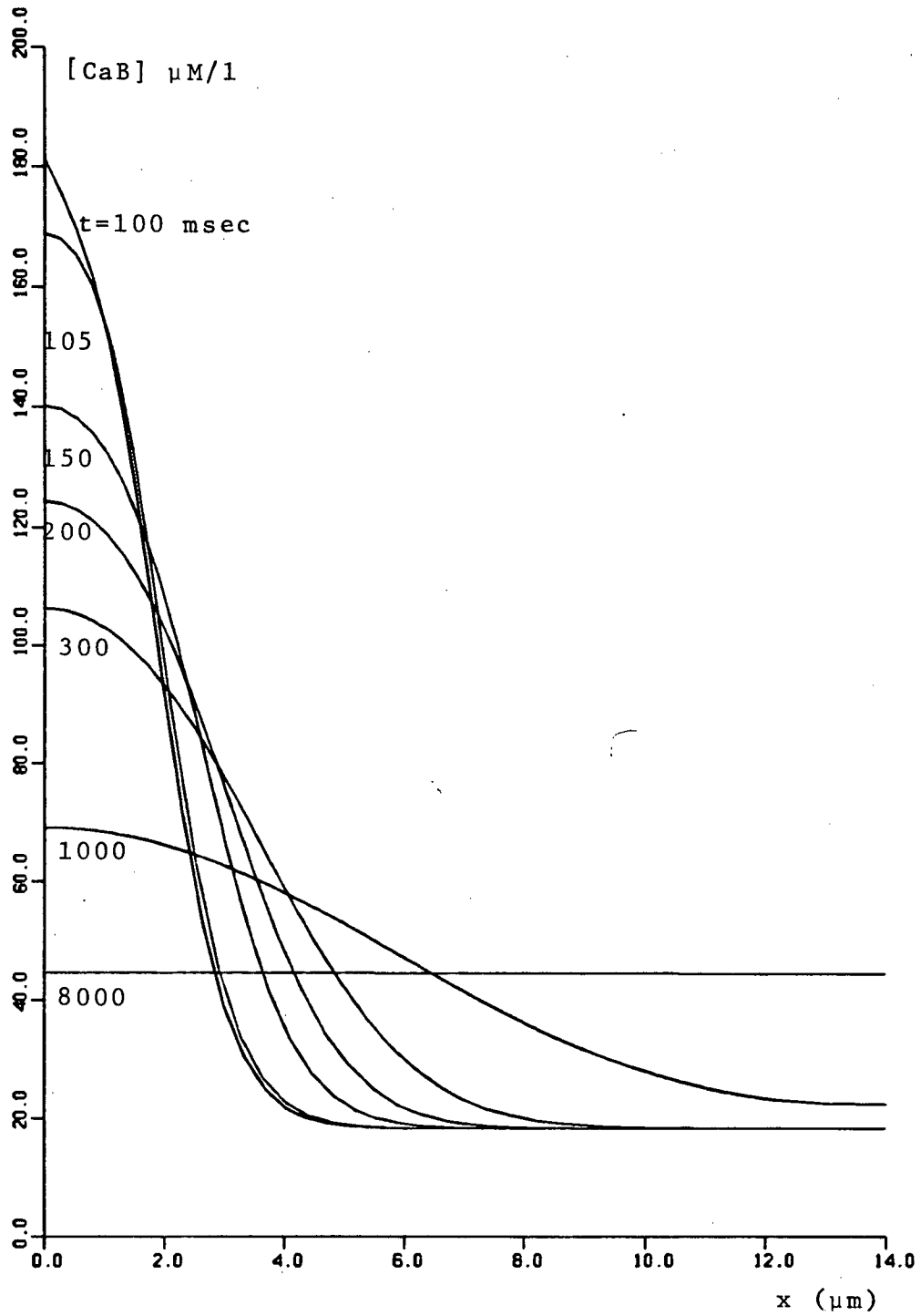


Figure 5c : Concentration profiles of CaB after influx.

of the Ca^{2+} and the complexes steadily approach their respective equilibrium values and the recovery time is approximately 8 seconds. Using the set of parameter values given in Table 1, we summarize in Table 4 the initial, maximum, and steady-state concentration levels of CaArz, Ca^{2+} , and CaB.

	t secs	[CaArz] $\mu\text{M}/\text{l}$	[Ca^{2+}] $\mu\text{M}/\text{l}$	[CaB] $\mu\text{M}/\text{l}$
Initial state	0.0	0.7482	0.1000	18.1818
Maximum value	0.1	49.0101	10.0776	181.1472
Steady-state value	8.0	2.1413	0.2876	44.6679

Table 4 : Summary of the initial, maximum, and steady-state concentration levels of CaArz, Ca^{2+} , and CaB.

Finally we remark that our numerical results are identical to those given by Connor and Nikolakopoulou. (See Figures 5A-B and Figure 7 of their paper [13].) As mentioned in their paper, the numerical results do not only give a good qualitative account of the calcium dynamics, but quantitatively, they are within 50% of the experimental values. Possible changes in the model parameters which give better experimental-computational agreement are also discussed in their paper.

7. CONCLUSION

In this thesis we analyse a diffusion model which arises in neurobiology describing the dynamics of intracellular calcium ion concentration changes due to diffusion and to buffering in nerve cytoplasm. The model was originally formulated by Connor and Nikolakopoulou [13] in an effort to answer some quantitative questions including the spatial distribution of calcium within the cytoplasm and the increase in intracellular $[Ca^{2+}]$ that a given influx can bring about. The model consists of a system of five reaction-diffusion equations describing the evolution of the various ionic concentration changes which are taken into account. The influx of calcium ions through the nerve cell membrane results in nonlinear boundary conditions which make analytical solution unobtainable.

Through simple mathematical manipulations, we reduced the model to a system of three reaction-diffusion equations and we found that the system possesses some interesting mathematical properties such as a conservation law and an invariant region. The conservation law plays a key role in establishing the uniqueness and asymptotic stability of the steady-state which was shown to be spatially homogeneous and an analytical expression for the steady-state value is given. On the other hand, the invariant region simply confirms the chemical law that the concentration levels of the complexes at all times must be greater than the initial concentration levels but less than the initial concentration levels plus the total amount loaded into

the system.

Further examination of the equations reveals that the system possesses two small parameters, ϵ and δ , whose presence allows us to construct an approximation to the initial transient solution using a regular perturbation technique. However, because of the nonlinear boundary conditions, we were not able to find an analytical approximation to the initial transient solution which is valid for a longer period of time. To this end, a simplified comparison theorem was used to provide rough bounds on the exact solutions.

In order to give a complete description of the calcium dynamics, a B-spline collocation code, called PDECOL, is used to solve the full system of equations. The results are identical to those given by Connor and Nikolakopoulou [13]. However we believe that our numerical scheme is more efficient than the POST algorithm used in [13].

In closing, we note that our analytical results in this thesis have provided greater understanding and insight into the mechanisms of diffusion, kinetics, and sequestration of calcium in nerve cells.

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APPENDIX A : DISCUSSION OF THE NUMERICAL ALGORITHM - PDECOL

The UBC library program, PDECOL, is used to solve the full system of equations (3.2)-(3.4). PDECOL is a general purpose program for numerically solving systems of partial differential equations in one spatial dimension. The class of problems which PDECOL can solve must have the following structure :

$$\partial \bar{u} / \partial t = \bar{F}(x, t, \bar{u}, \partial \bar{u} / \partial x, \partial^2 \bar{u} / \partial x^2), \quad (\text{A.1})$$

where $\bar{u} = (u_1, \dots, u_n)$, $\bar{F} = (f_1, \dots, f_n)$, $x \in I = [a, b]$ and $t \geq t_0$. The boundary conditions must have the form

$$\bar{B}(\bar{u}, \partial \bar{u} / \partial x) = \bar{Z}(t), \quad x \in \partial I, \quad t > t_0, \quad (\text{A.2})$$

where $\bar{B} = (b_1, \dots, b_n)$ and $\bar{Z} = (z_1, \dots, z_n)$. The initial conditions on $a \leq x \leq b$ are

$$\bar{u}(x, t_0) = \bar{g}(x), \quad (\text{A.3})$$

where $\bar{g} = (g_1, \dots, g_n)$.

The initial conditions must be consistent with the boundary conditions, i.e.,

$$\bar{B}(\bar{g}, \partial \bar{g} / \partial x) = \bar{Z}(t_0), \quad x \in \partial I. \quad (\text{A.4})$$

Finally all functions must be continuous in t and piecewise continuous in x .

Given a system of PDEs of the above structure, PDECOL solves the system using time discretization and collocation spatial

discretization techniques¹. For simplicity, we shall set $n = 1$ and outline the solution procedures used by PDECOL. For more detailed information we refer the reader to [22].

PDECOL Algorithm

The algorithm requires the user to specify a spatial mesh $(x_1, \dots, x_N)$ on $[a, b]$ such that

$$a = x_1 < x_2 < \dots < x_N = b.$$

Associated with each interval in the mesh are the polynomials $p_i(x)$, $i = 1, \dots, N-1$, which form a piecewise polynomial space that is used to compute the approximate solution. The user must specify k , the order of the polynomials ($k = \text{the polynomial degree} + 1$) and the number of continuity conditions (NCC) to be imposed on the polynomial pieces across the mesh points x_i . The recommended choices are $k = 6$ and $NCC = 2$ so that the approximate solution which is made up of separate fifth-degree polynomial pieces and the first derivative of the approximate solution are both continuous across the mesh points and hence on the entire interval $[a, b]$. The dimension of the linear polynomial space (i.e., the total number of degrees of freedom) over $[a, b]$ is therefore

$$m = k(N-1) - NCC(N-2).$$

¹Theoretical results [20] suggest that the collocation method provides more reliable results than a straightforward finite-difference method.

In PDECOL a B-spline basis consisting of m known piecewise polynomial functions $\theta_i(x)$ are used to span the polynomial space. This basis has the property that for any $x \in [a,b]$, at most k of the $\theta_i(x)$ have nonzero values. This property results in a banded matrix which leads to efficient numerical computation. For a given value of t , the algorithm assumes an approximate solution of the form

$$U(x,t) = \sum_{i=1}^m c_i(t) \theta_i(x),$$

where the coefficients $c_i(t)$, $i = 1, \dots, m$, are determined by a spatial collocation technique. The collocation technique requires $U(x,t)$ to satisfy the system of PDEs and the boundary conditions at a set of m collocation points. The collocation points, ξ_j , are selected automatically by PDECOL such that

$$a = \xi_1 < \xi_2 < \dots < \xi_m = b.$$

Hence for each $j = 1, \dots, m$,

$$u(\xi_j, t) = U(\xi_j, t) = \sum_{i=1}^m c_i(t) \theta_i(\xi_j), \quad (\text{A.5})$$

where u is the exact solution to the PDE. Substituting equation (A.5) into (A.1) we obtain a system of time dependent ordinary differential equations

$$\sum_{i=1}^m \theta_i(\xi_j) \frac{\partial c_i(t)}{\partial t} = F(\xi_j, t, U(\xi_j, t), \frac{\partial U(\xi_j, t)}{\partial x}, \frac{\partial^2 U(\xi_j, t)}{\partial x^2}), \quad (\text{A.6})$$

subject to the initial conditions

$$\sum_{i=1}^m c_i(t_0) \theta_i(\xi_j) = g(\xi_j). \quad (\text{A.7})$$

Equations (A.6)-(A.7) must be satisfied for $j = 2, \dots, m-1$. At the boundaries, special collocation equations are formed to account for the boundary conditions. Thus we have transformed a single PDE into a system of ordinary differential equations which can be solved by integrating with respect to the time variable.

The present algorithm possesses three desirable features. First of all, there are no limits on the number of PDEs to be solved. Secondly, the solution procedures applied to the system of time dependent ordinary differential equations (A.6)-(A.7) are very efficient since the choice of the B-spline basis results in a banded $m \times m$ matrix of maximum bandwidth $[2n(k-1)-1]$. Thirdly, PDECOL allows the user to restart integration from the previous termination time rather than to repeat the entire run. This is particularly convenient and economical since the length of time to reach the equilibrium state is not known a priori.

Despite all of the above desirable features, PDECOL suffers from one major drawback¹, namely, the consistency condition (A.4) must be satisfied by the PDEs in order to invoke PDECOL correctly. This is a severe restriction since in applications

¹Through private conversations with Carolyn Moore and Tom Nicol, both of whom are numerical analysts at the UBC Computer Center, we are unaware of any other collocation method which will automatically handle the inconsistency situation.

where an impulse or an influx is introduced into the system at the boundaries at $t = t_0^+$, the consistency requirement on the PDEs is often violated.

In our case the initial and boundary conditions on $V(x,t)$ are

$$\begin{aligned} V(x,0) &= V_0, \\ \partial V(0,t)/\partial x &= \begin{cases} A + B \ln V(0,t), & 0 < t \leq t^*, \\ 0, & t > t^*. \end{cases} \end{aligned}$$

Now since $\ln V_0 \neq -A/B$,

$$\partial V(x,0)/\partial x \neq \partial V(0,t)/\partial x \quad \text{at } (x,t) = (0,0),$$

and thus the consistency condition is not satisfied. Moreover, we observe that $\partial V(0,t)/\partial x$ is not continuous at $t = t^*$.

In order to overcome our present numerical difficulty, we introduced a trapezoidal-shaped function

$$H(t) = 1/2 [\tanh(\gamma(t-t')) - \tanh(\gamma(t-t''))]$$

where we have chosen

$$\gamma = 10^{16}, \quad t' = 10^{-14}, \quad t'' = t^* - t'.$$

The above parameter values are chosen such that

$$\begin{aligned} H(0) &\approx 0 \approx H(t^*), & H(t') &\approx 1/2 \approx H(t''), \\ H(t) &\approx 1, & 2t' < t < t^* - 2t', \end{aligned}$$

where the " $\approx$ " sign indicates an error of less than 10^{-40} . A sketch of $H(t)$ is shown in Figure 6.

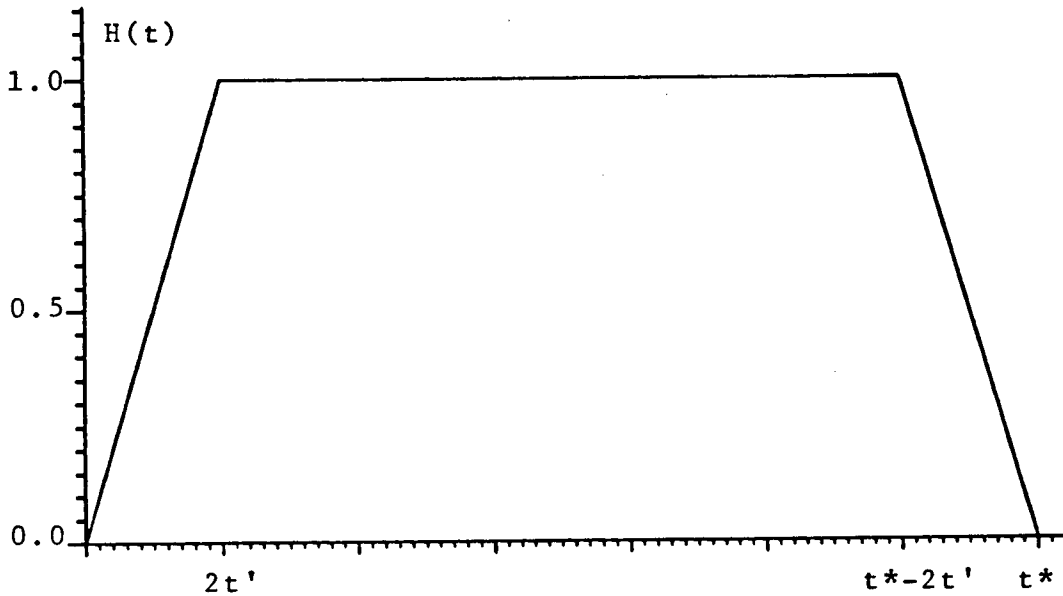


Figure 6 : Sketch of the trapezoidal-shaped function $H(t)$.

To overcome our numerical difficulty, we can reformulate our boundary conditions as

$$\partial V(0,t)/\partial x = \begin{cases} [A + B \ln V(0,t)]H(t), & 0 < t \leq t^*, \\ 0, & t > t^*. \end{cases}$$

Now since $H(0) = 0 = H(t^*)$, the consistency condition is satisfied and $\partial V(0,t)/\partial x$ is continuous everywhere. Although the above method is formulated to suit our particular situation, it is clear that the method can be modified and adapted to other similar situations as well.

We shall devote the remainder of this Appendix to discuss the numerical accuracy of PDECOL. There are mainly two sources of error in the approximate solution generated by PDECOL. The first is due to the time discretization method and the second is due to

the collocation spatial discretization technique. PDECOL controls the time discretization error by selecting a stepsize below the user's specification. However, it has no control over the spatial discretization errors.

Theoretical results in [20] indicate that the maximum error between the exact solution and the approximate solution generated by PDECOL is proportional to h^k , where

$$h = \max_i |x_i - x_{i-1}|.$$

Moreover the maximum error¹ between the j th derivatives of the exact solution and that of the approximate solution is proportional to h^{k-j} . Our system of reaction-diffusion equations involves second order spatial derivatives and hence the maximum error is of the order h^{k-2} .

¹In practice one should choose a variable spatial mesh so that more mesh points are inserted near the region where the solution changes rapidly.

Appendix B : AN APPROXIMATION TO A SECOND-ORDER PDE

In this appendix we shall find an approximate solution to the linear second-order partial differential equation

$$\partial z / \partial t = a \partial^2 z / \partial x^2 + b w(x, t) \quad (\text{B.1})$$

with initial condition on $0 < x < L$

$$z(x, 0) = 0, \quad (\text{B.2})$$

and boundary conditions

$$\partial z(0, t) / \partial x - a(t) z(0, t) = 0, \quad \partial z(L, t) / \partial x = 0, \quad (\text{B.3})$$

and where $a(t)$ and $w(x, t)$ are known functions and a, b are given constants.

We shall temporarily set $a(t) = a = \text{constant}$ and seek a solution to (B.1)-(B.3) of the form

$$z(x, t) = \sum_{n=1}^{\infty} T_n(t) \cos \lambda_n (x-L). \quad (\text{B.4})$$

In order to satisfy the boundary conditions, λ_n must satisfy the transcendental equation

$$\lambda_n \sin \lambda_n L - a \cos \lambda_n L = 0, \quad (\text{B.5})$$

for $n = 1, 2, \dots$ with $0 \leq \lambda_1 < \lambda_2 < \lambda_3 < \dots$. We expand

$$w(x, t) = \sum_{n=1}^{\infty} w_n(t) \cos \lambda_n (x-L) \quad (\text{B.6})$$

where

$$w_n(t) = \begin{cases} \frac{1}{K} \int_0^L w(x,t) \cos \lambda_n (x-L) dx, & \lambda_n \neq 0, \\ \frac{1}{L} \int_0^L w(x,t) dx, & \lambda_n = 0, \end{cases}$$

for $n = 1, 2, \dots$ and where $K = [L + a \cos^2 \lambda_n L / \lambda_n^2] / 2$. (Note : $\lambda_1 = 0$ iff $a = 0$.) Substituting equations (B.4) and (B.6) into (B.1)-(B.2) and solving yields

$$T_n(t) = b \int_0^t w_n(s) \exp(-a \lambda_n^2 (t-s)) ds. \quad (B.7)$$

Thus for constant a , a solution to the partial differential equation (B.1)-(B.3) is given by (B.4) with $T_n(t)$ defined by (B.7).

The following lemma extends the above result for general $a(t)$.

Lemma 1 : Let $a(t) > 0$ be continuous and differentiable. Provided that

$$|\Delta a / a| = |[a(t+\Delta t) - a(t)] / a(t)| \ll 1,$$

then (B.4) is an arbitrarily good approximation to the exact solution of the partial differential equation (B.1)-(B.3).

Proof : It suffices to show that

$$|\Delta \lambda_n / \lambda_n| = |[\lambda_n(t+\Delta t) - \lambda_n(t)] / \lambda_n(t)| < |\Delta a / a|,$$

for all $n \geq 1$ so that the roots $\{\lambda_n\}$ to the transcendental

equation are approximately constant and hence equations (B.4)-(B.7) hold.

We set $a = a(t)$, $\lambda_n = \lambda_n(t)$ and differentiate (B.5) with respect to t giving

$$\frac{\lambda'_n(t)}{\lambda_n} = \{1/G(\lambda_n, a)\} a'(t)/a,$$

or
$$\left| \frac{\lambda'_n(t)}{\lambda_n} \right| = \left| \{1/G(\lambda_n, a)\} a'(t)/a \right|$$

where $G(\lambda_n, a) = 1 + aL + \lambda_n^2 L/a$.

Now

$$\min_a |G(\lambda_n, a)| = |G(\lambda_n, \lambda_n)| = |1 + 2\lambda_n L|.$$

Thus

$$\left| \frac{\Delta \lambda_n}{\lambda_n} \right| \leq [1/(1 + 2\lambda_n L)] |\Delta a/a| < |\Delta a/a|$$

for all $n \geq 1$ as desired.

The key step in solving the partial differential equation (B.1)-(B.3) lies in finding the roots of the transcendental equation (B.5). Numerical schemes will be more efficient if we can give an approximate location of the roots. The next lemma serves this purpose.

Lemma 2 : Let

$$\beta_n = n\pi/L, \quad n = 0, 1, 2, \dots$$

denote the roots to (B.5) with $a = 0$. For a small positive perturbation Δa , the roots to (B.5) are approximately given by

$$\lambda_1 \approx \sqrt{(\Delta a/L)}, \quad \lambda_n \approx \beta_{n-1} + \Delta a/((n-1)\pi), \quad n > 1.$$

Proof : Let $\xi_n = \lambda_n L$ and replace a by Δa in (B.5). It is easy to deduce from equation (B.5) that

$$\tan \xi_n = \tan(\xi_n - (n-1)\pi) = \Delta a L / \xi_n,$$

and thus

$$\xi_n - (n-1)\pi = \tan^{-1}(\Delta a L / \xi_n) \approx (\Delta a L / \xi_n)$$

for $|\Delta a L / \xi_n| \ll 1$. The last approximation is justified since the perturbation Δa is assumed to be small and $|\Delta a L / \xi_n|$ decreases as n increases. Thus for $n = 1$,

$$\xi_1 \approx (\Delta a L / \xi_1), \quad \text{or} \quad \lambda_1 \approx \sqrt{(\Delta a / L)},$$

and for $n > 1$,

$$\xi_n \approx (n-1)\pi + (\Delta a L / \xi_n) \quad \text{or} \quad \lambda_n \approx \beta_{n-1} + \Delta a / ((n-1)\pi)$$

as required.