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A Mathematical Model of a Biosensor

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ABSTRACT

This paper is concerned with the modelling of the evolution of a chemical reaction within a small cell. Mathematically the problem consists of a heat equation with nonlinear boundary conditions. Through an integro-differential equation reformulation, an asymptotic result is derived, a pertubation solution is developed, and a modified product integration method is discussed. Finally, an alternative integral formulation is presented which acts as a check on the previous results and permits high accuracy numerical solutions.

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1. Introduction

The problem involves the modelling of the evolution of a chemical reaction within a small cell. A simple reversible reaction takes place between two reactants X and Y to produce XY. In the system of interest, one species, say Y, is immobilized on a side wall of the cell, and the other species X is dissolved in solution. The reaction takes place only on the side wall. The immobilized species Y is a specific binding agent for the dissolved species X. If a solution X is introduced to the cell at time $t = 0$, then as the reaction at the wall proceeds, an X concentration gradient develops, and X diffuses to the wall until equilibrium results. The aim of this study is to predict the concentration of the species X and the concentration of the complex XY at the reaction side wall as functions of time. The motivation for this work came from a study of a biosensor device (see, for example, Radley, Drake, Shanks, Smith, and Stephenson [16]), and a specific application is the use of this device as a pregnancy testing kit.

In Section 2 the model development is outlined. An asymptotic solution for small time is presented in Section 3. This shows that the concentration of the complex (the substance resulting from the chemical reaction of the antibody and the antigen) is not a smooth function of time and so indicates limitations on the direct use of finite differences. A pertubation solution is then developed using a non-dimensional parameter (the molar ratio–see Section 2). This proves to be an accurate representation for small values of this parameter and hence a useful check on the numerical results. Following Dixon[7], a numerical method is written down and a modification is suggested which is seen to overcome the loss of accuracy for small time. In Section 5 an alternative integral formulation is presented. This allows a derivation of further asymptotic results which are seen to agree with earlier results. For this formulation, high accuracy is achievable by subtracting out the singularities. Numerical results are given in Section 6.

2. The mathematical model

In this section the mathematical model of the reaction-diffusion process is developed.

The detail of the following modelling analysis can be found in Burgess, Dixon, Jones, and Thoma [4]. Let X denote the antigen concentration and Y denote the antibody concentration. The reaction is given as

$$X + Y \underset{k_{-1}}{\overset{k_1}{\rightleftarrows}} XY,$$

where k_1 and k_{-1} are the forward and backward reaction rates.

Let $[X]$ denote the concentration of X (in moles/m^3), $[Y]$ denote the concentration of Y (in moles/m^2) and $[XY]$ denote the concentration of XY (in moles/m^2). We require the following constants:

a_0 : initial Y concentration (moles/m^2),

c_0 : initial X concentration at the reaction side wall (moles/m^3),

d : edge of vessel to surface (m),

D : diffusion coefficient of X (m^2/s).

If we ignore edge effects we can neglect any diffusion in the y-direction and $[X]$ satisfies the diffusion equation

$$\frac{\partial[X]}{\partial t} = D\frac{\partial^2[X]}{\partial x^2}.$$

Also

$$\frac{\partial[X]}{\partial x} = 0 \quad \text{at} \quad x = 0.$$

Further $[X]_{t=0} = c_0$ since the concentration is assumed uniform initially.

We need, however, the boundary condition $\frac{\partial[X]}{\partial x}$ at $x = d$ on the antibody surface.

To facilitate the discussion let us introduce the notation:

$$u(x,t) \equiv \text{ concentration of } X \text{ ie } [X],$$

$$\gamma(t) \equiv \text{ concentration of } XY \text{ ie } [XY].$$

Now the law of mass action states

$$D\frac{\partial u}{\partial x}\,(d,t) = k_{-1}\gamma(t) - k_1 u(d,t)[Y],$$

where we have assumed that one molecule of X and one molecule of Y combine to give one molecule of the complex XY.

The initial concentration of Y is a_0. This will be depleted by the amount of X used up in the reaction. Therefore,

$$[Y](t) = a_0 - (c_0 d - \int_0^d u(x,t)\,dx).$$

Thus

$$\frac{\partial u}{\partial x}\,(d,t) = k_{-1}\gamma(t) - k_1 u(d,t)(a_0 - c_0 d + \int_0^d u(x,t)\,dx). \tag{2.1}$$

In addition, the conservation of the total number of species X, either in solution or bound in the complex XY is given by

$$\int_0^d u(x,t)\,dx + \gamma(t) = c_0 d. \tag{2.2}$$

Equations (2.1) and (2.2) together imply

$$D\frac{\partial u}{\partial x}\,(d,t) = k_{-1}\gamma(t) - k_1 u(d,t)(a_0 - \gamma(t)).$$

Summarising, a consistent model of the antibody-antigen reaction is

$$\frac{\partial u}{\partial t}\,(x,t) = D\frac{\partial^2 u}{\partial x^2}\,(x,t), \tag{2.3a}$$

subject to

$$u(x,0) = c_0, \tag{2.3b}$$

and the boundary conditions

$$\frac{\partial u}{\partial x}\,(0,t)=0, \tag{2.3c}$$

$$D\frac{\partial u}{\partial x}\,(d,t)=k_{-1}\gamma(t)-k_1 u(d,t)(a_0-\gamma(t)), \tag{2.3d}$$

together with

$$\int_0^d u(x,t)\,dx+\gamma(t)=c_0 d. \tag{2.3e}$$

By introducing the non-dimensional variables

$$x'=x/d,\quad t'=(D/d^2)t,$$

and scaling the dependent variables

$$u'(x',t')=u(x,t)/c_0,\quad \gamma'(t')=\gamma(t)/a_0,$$

it is not difficult to see that (2.3) can be rewritten as

$$\frac{\partial u}{\partial t}=\frac{\partial^2 u}{\partial x^2}, \tag{2.4a}$$

subject to

$$u(x,0)=1, \tag{2.4b}$$

and

$$\frac{\partial u}{\partial x}\,(0,t)=0, \tag{2.4c}$$

and

$$\frac{\partial u}{\partial x}\,(1,t)=\frac{Em}{1+L}\left(L\gamma(t)-\big(1-\gamma(t)\big)u(1,t)\right), \tag{2.4d}$$

together with

$$m\gamma(t)+\int_0^1 u(x,t)\,dx=1, \tag{2.4e}$$

where the 'primes' have been omitted for clarity. The constant $m=a_0/c_o d$ is the molar ratio, $L=k_{-1}/k_1c_0$ is the reaction time scale ratio, and $E=(k_1c_0+k_{-1})d^2/D$ is the diffusion reaction time scale ratio.

3. An integro-differential equation formulation and analytic and numerical solutions

In this section, a Volterra integro-differential equation is formulated for $\gamma(t)$. Using this formulation an asymptotic solution of $\gamma(t)$ for small t is obtained. Treating γ as both a function of t and the molar ratio m, a regular pertubation for $\gamma(t, m)$ is derived for small m. Finally, a product Euler scheme due to Dixon[7] is presented and a modified version, which is designed to cope with the low order convergence of Dixon's scheme near $t = 0$, is proposed.

3.1 Reformulation as an integro-differential equation

Differentiating (2.4e) with respect to time we obtain

$$m \frac{d\gamma}{dt}(t) + \int_0^1 \frac{\partial u}{\partial t}(x,t)\,dx = 0,$$

and using (2.4a) and (2.4c) gives

$$-m \frac{d\gamma}{dt}(t) = \frac{\partial u}{\partial x}(1,t). \tag{3.1}$$

Taking Laplace transforms of (2.4a) with respect to t, after some manipulation involving the convolution theorem, we obtain

$$u(1,t) = 1 + \int_0^t k(t-s)\frac{\partial u}{\partial x}(1,s)\,ds,$$

where

$$k(t) = \frac{1}{\sqrt{\pi t}}\left(1 + 2\sum_{n=1}^{\infty}\exp(-\frac{n^2}{t})\right). \tag{3.2}$$

Thus, using (3.1), we obtain (see Burgess et al.[4])

$$u(1,t) = 1 - m\int_0^t k(t-s)\frac{d\gamma}{ds}(s)\,ds. \tag{3.3}$$

Using (3.1) and (3.3) in equation (2.4d) yields

$$\frac{d\gamma}{dt}(t) = C - E\gamma(t) - Cm(1-\gamma(t))\int_0^t k(t-s)\frac{d\gamma}{ds}(s)ds. \tag{3.4}$$

where

$$C = \frac{E}{1+L}, \tag{3.5}$$

with initial condition $\gamma(0) = 0$.

Once γ is known, equation (3.3) may be used to obtain u on the boundary $x = 1$, and thus (2.4a) may be solved using (2.4b), (2.4c) and the value of $u(1,t)$ to determine u in the interior $0 < x < 1,\ t > 0$ (see Burgess et al.[4]).

3.2. An asymptotic solution

In this subsection we consider the behaviour of $\gamma(t)$ for small t.

Noting that when t is small,

$$\gamma(t) = o(1),$$

and

$$\int_0^t \frac{d\gamma}{ds}(s)k(t-s)ds = o(1),$$

we obtain from (3.4), for small t,

$$\frac{d\gamma}{dt}(t) = C + o(1), \tag{3.6}$$

which yields

$$\gamma(t) = Ct + o(t). \tag{3.7}$$

Furthermore, since when $t \ll \frac{1}{4\ln 2}$,

$$\sum_{n=1}^{\infty} \exp(-\frac{n^2}{t}) \le \sum_{n=1}^{\infty} \exp(-\frac{n}{t}) \le \frac{\exp(-\frac{1}{t})}{1-\exp(-\frac{1}{t})} \le 2\exp(-\frac{1}{t}) = o(1),$$

we have from (3.4), (3.6) and (3.7),

$$\begin{aligned} \frac{d\gamma}{dt}(t) &= C - Cm(1+O(t)) \int_0^t \frac{1+o(1)}{\sqrt{\pi}\sqrt{t-s}}(C+o(1))ds + O(t) \\ &= C - \frac{2C^2m}{\sqrt{\pi}}t^{\frac{1}{2}} + O(t), \end{aligned}$$

which admits

$$\gamma(t) = Ct - \frac{4C^2m}{3\sqrt{\pi}}t^{\frac{3}{2}} + O(t^2). \tag{3.8}$$

This asymptotic expansion has also been derived by Dixon[7] using a different approach.

3.3. A perturbation solution

We consider an analytic expansion of $\gamma(t) = \gamma(t;m)$ as a function of the molar ratio m.

For small m, let

$$\gamma(t;m) = \gamma^{(0)}(t) + m\gamma^{(1)}(t) + O(m^2). \tag{3.9}$$

Inserting (3.9) into (3.4) and omitting the o(1) terms results in

$$\frac{d\gamma^{(0)}}{dt}(t) = C - E\gamma^{(0)}(t), \tag{3.10}$$

which leads to the zero order approximation of γ

$$\gamma^{(0)}(t) = \frac{1}{1+L}(1 - e^{-Et}). \tag{3.11}$$

Similarly, balancing the $O(m)$ terms in (3.4) we have

$$\frac{d\gamma^{(1)}}{dt}(t) = -E\gamma^{(1)}(t) - C(1-\gamma^{(0)}(t)) \int_0^t k(t-s)\frac{d\gamma^{(0)}}{ds}(s)ds, \tag{3.12}$$

which reduces to

$$\frac{d\gamma^{(1)}}{dt}(t) = -E\,\gamma^{(1)}(t) - C^2\left\{1 - \frac{1}{1+L}(1-\exp(-Et))\right\}\int_0^t \exp(-Es)k(t-s)\,ds. \tag{3.13}$$

Multiplying $\exp(Et)$ on both sides of (3.13) gives

$$\frac{d}{dt}\left(\gamma^{(1)}(t)\exp(Et)\right) = -\frac{C^2}{1+L}(1+\exp(Et))\int_0^t \exp(-Es)\,k(t-s)\,ds. \tag{3.14}$$

Since $\gamma(0) = 0$ and (3.11) shows $\gamma^{(0)}(0) = 0$, we must have

$$\gamma^{(1)}(0) = 0.$$

Thus we can integrate both sides of (3.14) to obtain

$$\gamma^{(1)}(t) = -\frac{C^2}{1+L}\exp(-Et)\int_0^t\int_0^{t'}(\exp(Et')\,L+1)\exp(-Es)\,k(t'-s)\,ds\,dt'. \tag{3.15}$$

Changing the order of integration in (3.15) followed by the transformation

$$t' = u + s$$

and again changing the order of integration results in

$$\gamma^{(1)}(t) = -\frac{C^2}{1+L}\exp(-Et)\int_0^t k(u)\int_0^{t-u}(\exp(-Es)+L\exp(Eu))\,ds\,du$$

$$= -\frac{C}{(1+L)^2}\exp(-Et)\int_0^t k(u)\left(1-\exp(-E(t-u))+LE(t-u)\exp(Eu)\right)du. \tag{3.16}$$

The right hand side of (3.16) can be evaluated by numerical quadrature using the trapezoidal rule or Simpson's rule, with the truncated expression for $k(u)$ discussed in Section 3.4 and Dixon[7].

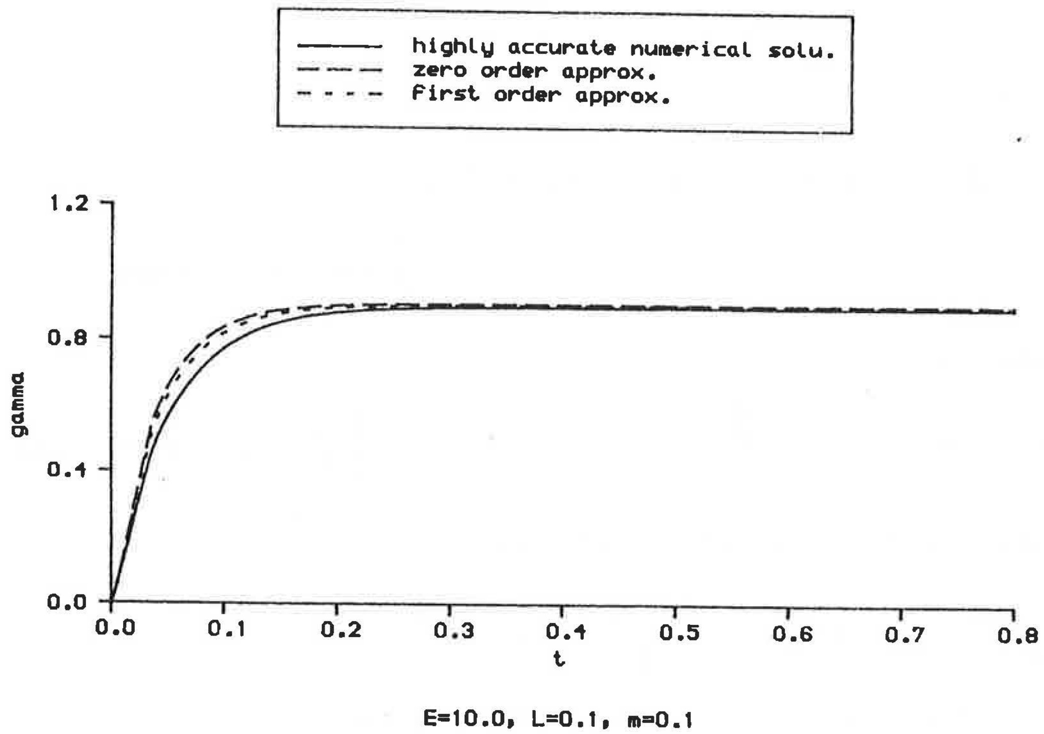

Figure 1

Figures 1 and 2 compare the numerical results obtained using the expansion (3.9) (here zero order and first order approximations refer to $\gamma^{(0)}(t)$ and $\gamma^{(0)}(t)+m\gamma^{(1)}(t)$, respectively) and the highly accurate solutions obtained by using the convergent product integration scheme of Dixon[7] (see also Subsection 3.4) with a very small time step.

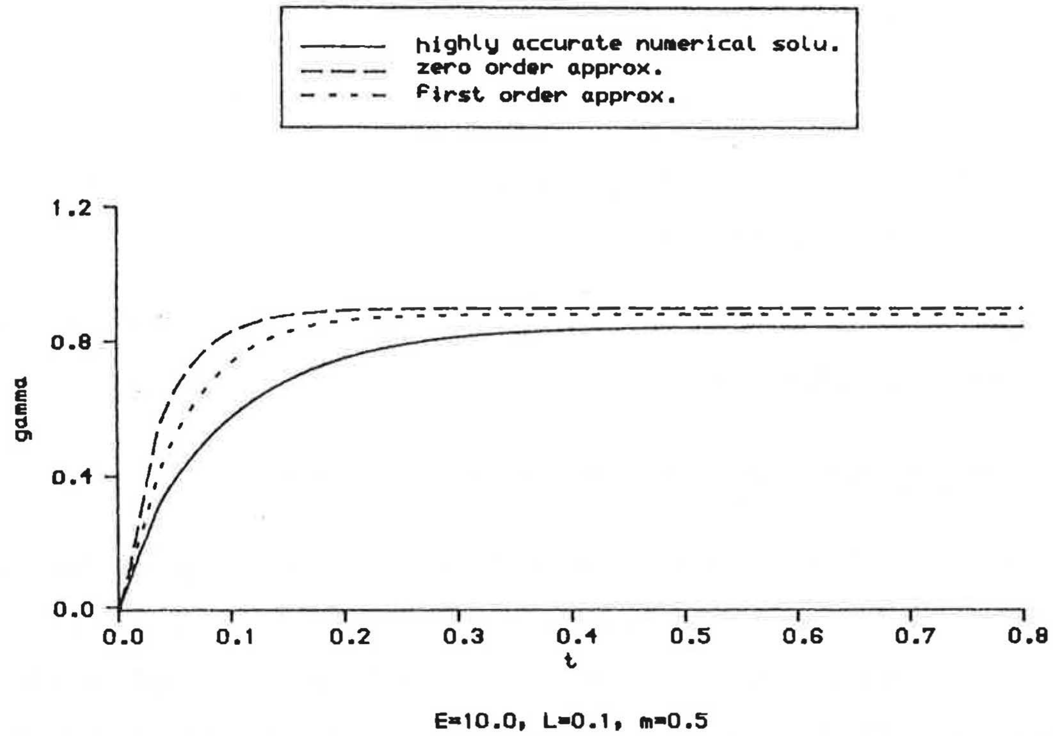

Figure 2

For $m < 1$, it appears from the graphical results that (3.9) provides a qualitatively correct approximation to $\gamma(t)$. Further evidence that the pertubation solution is qualitatively and quantitively correct is given by asymptotic results. We know (Jumarhon and McKee[11]) that

$$\lim_{t \to \infty} \gamma(t) = \frac{1}{m}(1 - \phi^*),$$

where

$$\phi^* = \frac{1}{2}\left(1 - m - L + \sqrt{(1 - m - L)^2 + 4L}\right).$$

However, it is not difficult to show that

$$\phi^* = 1 - \frac{m}{1 + L} + o(m),$$

giving

$$\lim_{t \to \infty} \gamma(t) = \frac{1}{1 + L} + o(1).$$

But

$$\gamma^{(0)}(t) = \frac{1}{1+L}(1 - e^{-Et})$$

and thus

$$\lim_{t\to\infty} \gamma^{(0)}(t) = \frac{1}{1+L}.$$

This shows that at least the $O(1)$ approximation of the pertubation solution tends, in the limit as $t \to \infty$, to the correct asymptotic value.

Furthermore, $\gamma^{(0)}(t)$ is obviously monotonic increasing and this agrees with the fact that $\gamma(t)$ is monotonic increasing (see [11]).

3.4. A product integration method and its modification

Before attempting to derive a numerical method two observations may be made: firstly, by differentiating (3.8) it can be seen that $\gamma(t)$ does not have a bounded second derivative at $t = 0$; secondly, for a method to be of practical use the infinite kernel given by (3.2) must be truncated. The first observation implies that the direct use of product integration schemes cannot produce high order accuracy; the second suggests the following truncation:

$$k_l(t) = \frac{1}{\sqrt{\pi t}} \left(1 + 2 \sum_{n=1}^{l} \exp(-\frac{n^2}{t}) \right).$$

Following Dixon[7],

$$|k(t) - k_l(t)| < 1 - \Phi(l\sqrt{\frac{2}{t}}), \tag{3.17}$$

where $\Phi(z)$ is a normal function; tables of $\Phi(z)$ may be found, for example, in Abramowitz and Stegun[1]. For given T and $\epsilon > 0$, l is chosen so that

$$|k(t) - k_l(t)| < \epsilon \quad \text{for all} \quad t \in [0, T].$$

It follows that l is chosen such that

$$\Phi(l\sqrt{\frac{2}{T}}) > 1 - \epsilon.$$

The numerical method which will now be proposed for equation (3.3) will be of product integration type. For details, see Dixon[7] where a convergence analysis of the method is presented.

Let $t_i = ih$, $i = 0(1)N$, $Nh = T$; γ_i and u_i will denote approximations to $\gamma(t_i)$ and $u(1,t_i)$ respectively. Using the approximation $\frac{1}{h}(\gamma_i - \gamma_{i-1})$ for $\gamma'(t_i)$, the product Euler method for the integral, and replacing $1-\gamma(t_i)$ with $1-\gamma_{i-1}$, an explicit product integration scheme for (3.4) can be obtained (see Dixon[7]),

$$\gamma_0 = 0,$$

$$\frac{\gamma_i - \gamma_{i-1}}{h} = C - E\gamma_i - \frac{Cm}{\sqrt{\pi}}(1-\gamma_{i-1})h\sum_{j=0}^{i-1}\alpha(i-j)\left(\frac{\gamma_{j+1}-\gamma_j}{h}\right), i = 1(1)N, \tag{3.18}$$

where the quadrature weights $\alpha(i-j)$ are given by

$$\alpha(i-j) = \frac{1}{h}\left\{1 + 2\sum_{n=1}^{l}\exp\left(\frac{-n^2}{t_i - t_j}\right)\right\}\int_{t_j}^{t_j+1}\frac{ds}{\sqrt{t_i - s}},$$

$$j = 0(1)i-1,\ i = 1(1)N.$$

Discretising (3.3) in a similar way gives

$$u_i = 1 - \frac{m}{\sqrt{\pi}}h\sum_{j=0}^{i-1}\alpha(i-j)\left(\frac{\gamma_{j+1}-\gamma_j}{h}\right), i = 1(1)N.$$

The numerical scheme (3.18) yields a global convergence of order $\frac{1}{2}$ due to the $t^{\frac{3}{2}}$ term in the expansion of $\gamma(t)$ for small t (equation (3.8)).

Methods of coping with nonsmoothness of solutions of Volterra integral equations have been studied by many authors, for example, Brunner[2,3], who suggested nonpolynomial spline collocation, and by Norbury and Stuart[15] who studied the idea of applying an algebraic transformation to the variables of the integrands. Here we use the technique of subtracting out singularities, which was introduced by Eggermont[8] in a numerical example.

To obtain a scheme of order one convergence, consider the following identity,

$$(\gamma(t) + \frac{4C^2m}{3\sqrt{\pi}}t^{\frac{3}{2}})' - \frac{2C^2m}{\sqrt{\pi}}t^{\frac{1}{2}} = \gamma'(t),$$

and note from (3.8) that $\gamma(t) + \frac{4C^2m}{3\sqrt{\pi}}t^{\frac{3}{2}}$ is twice continuously differentiable. Let

$$\mu_{n+1} = \frac{1}{h}(\gamma_{n+1} + \frac{4C^2m}{3\sqrt{\pi}}t_{n+1}^{\frac{3}{2}} - \gamma_n - \frac{4C^2m}{3\sqrt{\pi}}t_n^{\frac{3}{2}}), \qquad n = 0(1)N-1.$$

Thus by replacing the left hand side of (3.18) with $\mu_i - \frac{2C^2 m}{\sqrt{\pi}} t_i^{\frac{1}{2}}$, and replacing the expression $\alpha(i-j)\frac{\gamma_{j+1}-\gamma_j}{h}$ in the right hand side of (3.18) with

$$\nu(i,j) = \alpha(i-j)\mu_{j+1} - \frac{2C^2 m}{\sqrt{\pi}} \beta(i,j)$$

where

$$\beta(i,j) = \frac{1}{h}\left\{1 + 2\sum_{n=1}^{l} \exp\left(\frac{-n^2}{t_i - t_j}\right)\right\} \int_{t_j}^{t_{j+1}} \frac{s^{\frac{1}{2}}}{\sqrt{t_i - s}} ds, \quad j = 0(1)i-1, \ i = 1(1)N,$$

we obtain a numerical scheme with order one convergence,

$$\begin{aligned} &\gamma_0 = 0, \\ &\mu_i - \frac{2C^2 m}{\sqrt{\pi}} t_i^{\frac{1}{2}} = C - E\gamma_i - \frac{Cm}{\sqrt{\pi}}(1-\gamma_{i-1})h \sum_{j=0}^{i-1} \nu(i,j), \quad i = 1(1)N. \end{aligned} \tag{3.19}$$

Obviously (3.19) allows an explicit solution of γ_i ($i = 1(1)N$). Similarly we have an order one approximation for $u(1, t_i)$

$$u_i = 1 - \frac{m}{\sqrt{\pi}} h \sum_{j=0}^{i-1} \nu(i,j), \quad i = 1(1)N.$$

4. An alternative integral formulation and high order numerical solutions

In this section, an equivalent system of Volterra integral equations is obtained for the initial-boundary value problem (2.4). Using this integral formulation, high order product integration schemes are derived.

4.1. A Volterra integral formulation

In this subsection we develop an alternative integral formulation which allows us to construct arbitary high order schemes by subtracting out the singularities.

Modifying the results of Cannon[6], Jumarhon and McKee[11] have shown that for piecewise continuous g, H_1 and continuous H_2, the solution of the following problem

$$\frac{\partial V}{\partial t} = \frac{\partial^2 V}{\partial x^2}, \qquad 0 < x < 1, \quad t > 0 \tag{4.1a}$$

$$V(x,0) = g(x), \qquad 0 < x < 1, \tag{4.1b}$$

$$\frac{\partial V}{\partial x}(0,t) = H_1(t), \qquad t > 0, \tag{4.1c}$$

$$\frac{\partial V}{\partial x}(1,t) = H_2(t, V(1,t), \int_0^1 V(x,t)\,dx), \qquad t > 0, \tag{4.1d}$$

can be written as

$$\begin{aligned} V(x,t) =& w(x,t) - 2\int_0^t \theta(x, t-s)\ H_1(s)\,ds \\ &+ 2\int_0^t \theta(x-1, t-s)\ H_2(s, \eta_1(s), \eta_2(s))\,ds \end{aligned} \tag{4.2}$$

where $\eta_1(t) = V(1,t)$ and $\eta_2(t) = \int_0^1 V(x,t)dx$ are piecewise-continuous solutions of the following system of Volterra integral equations,

$$\begin{aligned} \eta_1(t) =& w(1,t) - 2\int_0^t \theta(1, t-s)\ H_1(s)\,ds \\ &+ 2\int_0^t \theta(0, t-s)\ H_2(s, \eta_1(s), \eta_2(s))\,ds, \end{aligned} \tag{4.3a}$$

$$\begin{aligned} \eta_2(t) =& \int_0^1 w(x,t)\,dx - \int_0^t H_1(s)\,ds \\ &+ \int_0^t H_2(s, \eta_1(s), \eta_2(s))\,ds, \end{aligned} \tag{4.3b}$$

with

$$w(x,t) = \int_0^1 \{\theta(x-z,t) + \theta(x+z,t)\}\ g(z)\,dz, \tag{4.4}$$

and

$$\theta(x,t) = \frac{1}{\sqrt{4\pi t}} \sum_{n=-\infty}^{+\infty} \exp\left(-\frac{(x+2n)^2}{4t}\right). \tag{4.5}$$

Now, by re-writing the boundary conditions (2.4d) and (2.4e) as

$$\begin{aligned} \frac{\partial u}{\partial x}(1,t) &= F\left(u(1,t), \int_0^1 u(x,t)\,dx\right) \\ &= C\left[L - (m-1)u(1,t) - L\int_0^1 u(x,t)\,dx - u(1,t)\int_0^1 u(x,t)\,dx\right]. \end{aligned} \tag{4.6}$$

and using a result from Jumarhon and McKee[11],

$$\int_0^1 \{\theta(x+z,t)+\theta(x-z,t)\}dz = 1,$$

the solution of the initial-boundary value problem (2.4) can be written as

$$u(x,t) = 1 + 2\int_0^t \theta(x-1,t-s)\ F(\phi_1(s),\phi_2(s))\,ds, \tag{4.7}$$

where $\phi_1(t) = u(1,t)$ and $\phi_2(t) = \int_0^1 u(x,t)dx$ are piecewise-continuous solutions of

$$\phi_1(t) = 1 + \int_0^t k(t-s)\ F(\phi_1(s),\phi_2(s))\,ds, \tag{4.8a}$$

$$\phi_2(t) = 1 + \int_0^t F(\phi_1(s),\phi_2(s))\,ds, \tag{4.8b}$$

where $k(t)$ is as defined in (3.2). The system (4.8) is a coupled system of Volterra integral equations of the second kind, with (4.8a) having an unbounded but integrable kernel. The proof of the existence and uniqueness of the solution of the system of Volterra integral equations (4.8) on $[0,\infty)$ is given in [11] thus establishing the existence and uniqueness of the solution of the initial-boundary value problem (2.4) on $[0,\infty)$.

4.2. High accuracy numerical methods

Miller and Feldstein[14] and more recently Lubich[13] studied the structure of solutions of systems of Abel-Volterra integral equations of the second kind. The weakly singular kernel of (4.8a) suggests that we might apply the same argument as Lubich[13] to show that (4.8) has the asymptotic solution

$$\phi_1(t) = 1 + a_1 t^{1/2} + a_2 t + \ldots \tag{4.9a}$$

$$\phi_2(t) = 1 + b_1 t^{1/2} + b_2 t + \ldots \tag{4.9b}$$

near $t = 0$. Replacing $\phi_1(t), \phi_2(t)$ in (4.8) by (4.9) gives the expressions

$$\phi_1(t) = 1 - \frac{2Cm}{\sqrt{\pi}}\ t^{1/2} + C^2m^2t + \frac{4C^2m}{3\sqrt{\pi}}\ (1+L-Cm^2)\ t^{3/2} + O(t^2), \tag{4.10a}$$

$$\phi_2(t) = 1 - Cmt + \frac{4C^2m^2}{3\sqrt{\pi}}\ t^{3/2} + O(t^2). \tag{4.10b}$$

The expansion (4.10b) confirms the asymptotic solution (3.8), since $\phi_2(t) = 1 - m\gamma(t)$ by definition. The following asymptotic result

$$\lim_{t\to\infty}\phi_1(t) = \lim_{t\to\infty}\phi_2(t) = \frac{1}{2}\{1 - m - L + \sqrt{(1-m-L)^2 + 4L}\}$$

is derived in [11].

Intuitively one might apply the trapezoidal product integration method to numerically solve (4.8). But (4.10) shows that $F(\phi_1(t), \phi_2(t))$ has a weak singularity $t^{1/2}$ at $t = 0$, which will give rise to a loss of accuracy. Here, we again use the technique of subtracting out singularities to obtain high order schemes.

For $t > 0$, define $\kappa(t) = \frac{1}{\sqrt{\pi}}(1 + 2\sum_{n=1}^{\infty}\exp(-\frac{n^2}{t}))$. This is clearly a bounded function.

Now consider the following system for $q = 1, 2$,

$$\phi_1(t) = f_1^{(q)}(t) + \int_0^t \frac{G_1^{(q)}(t, s, \phi_1(s), \phi_2(s))}{\sqrt{t-s}}ds, \tag{4.11a}$$

$$\phi_2(t) = f_2^{(q)}(t) + \int_0^t G_2^{(q)}(t, s, \phi_1(s), \phi_2(s))ds, \tag{4.11b}$$

with

$$G_1^{(q)}(t, s, \phi_1(s), \phi_2(s)) = \kappa(t-s)(F(\phi_1(s), \phi_2(s)) + g^{(q)}(s)), \tag{4.12a}$$

$$G_2^{(q)}(t, s, \phi_1(s), \phi_2(s)) = F(\phi_1(s), \phi_2(s)) + g^{(q)}(s), \tag{4.12b}$$

$$f_1^{(q)}(t) = 1 - \int_0^t \kappa(t-s)\frac{g^{(q)}(s)}{\sqrt{t-s}}ds, \tag{4.12c}$$

$$f_2^{(q)}(t) = 1 - \int_0^t g^{(q)}(s)ds, \tag{4.12d}$$

where

$$g^{(1)}(s) = -\frac{2}{\sqrt{\pi}}C^2m^2s^{\frac{1}{2}}, \tag{4.13a}$$

$$g^{(2)}(s) = -\frac{2}{\sqrt{\pi}}C^2m^2s^{\frac{1}{2}} - \frac{4}{3\sqrt{\pi}}C^3m^2(Cm^2 - 2L - 7/2)s^{\frac{3}{2}}. \tag{4.13b}$$

Simple calculations show that both (4.11) and (4.12) with (4.13a), and (4.11) and (4.12) with (4.13b) are equivalent to the system (4.8); furthermore, $G_1^{(q)}(t,s,\phi_1(s),\phi_2(s))$ and $G_2^{(q)}(t,s,\phi_1(s),\phi_2(s))(q=1,2)$ are q times continuously differentiable with respect to s.

Let ϕ_1^i, ϕ_2^i denote the approximate solutions of $\phi_1(t_i), \phi_2(t_i)$ (($i=0(1)N$). Then we have the following system of product integration schemes

$$\phi_1^i = I_i^{(q)} + \sum_{j=0}^{i} \alpha_{ij}^{(q)} \tilde{G}_1^{(q)}(t_i, t_j, \phi_1^j, \phi_2^j), \tag{4.14a}$$

$$\phi_2^i = f_2^{(q)}(t_i) + \sum_{j=0}^{i} \beta_{ij}^{(q)} G_2^{(q)}(t_i, t_j, \phi_1^j, \phi_2^j), \tag{4.14b}$$

$$\phi_1^0 = 1, \quad \phi_2^0 = 1, \tag{4.14c}$$

$$i = 1(1)N,$$

where

$$\tilde{G}_1^{(q)}(t_i, t_j, \phi_1^j, \phi_2^j) = \kappa_l(t_{i-j})(F(\phi_1^j, \phi_2^j) + g^{(q)}(t_j)),$$

and

$$\kappa_l(t) = \frac{1}{\sqrt{\pi}}(1 + 2\sum_{n=1}^{l} \exp(-\frac{n^2}{t}))$$

(l is again chosen according to the accuracy required), and $I_i^{(q)}$ is an approximation of $f_1^{(q)}(t_i)$ obtained by using product integration schemes consistent with that used in the system (4.14). The calculation of $I_i^{(q)}$ involves polynomial interpolation of $k_l(t_i - s)$, and analytical quadrature of the expression $s^{p+\frac{1}{2}}(t-s)^{-\frac{1}{2}}$ ($p = 0,1,2$) over $[t_j, t_{j+1}]$. In (4.14), when

$$\alpha_{ij}^{(1)} = \int_{t_j}^{t_j+1} \frac{ds}{\sqrt{t_i - s}}, \; j = 0(1)i-1, \; i = 1(1)N, \tag{4.15a}$$

$$\alpha_{ii}^{(1)} = \beta_{ii}^{(1)} = 0, \qquad i = 1(1)N, \tag{4.15b}$$

$$\beta_{ij}^{(1)} = h, \qquad j = 0(1)i-1, \; i = 1(1)N, \tag{4.15c}$$

we obtain the explicit product Euler scheme, while when

$$\alpha_{ij}^{(1)} = \int_{t_{j-1}}^{t_j} \frac{ds}{\sqrt{t_i - s}}, \; j = 0(1)i-1, \; i = 1(1)N, \tag{4.16a}$$

$$\alpha_{i0}^{(1)} = \beta_{i0}^{(1)} = 0, \qquad i = 1(1)N, \tag{4.16b}$$

$$\beta_{ij}^{(1)} = h, \qquad j = 0(1)i-1, \; i = 1(1)N, \tag{4.16c}$$

we obtain the implicit product Euler scheme, and when

$$\alpha_{i0}^{(2)} = \frac{1}{h}\int_0^h \frac{h-s}{\sqrt{t_i - s}}ds, \quad i = 1(1)N, \tag{4.17a}$$

$$\alpha_{ij}^{(2)} = \frac{1}{h}\int_{t_{j-1}}^{t_j} \frac{s-t_{j-1}}{\sqrt{t_i - s}}ds + \frac{1}{h}\int_{t_j}^{t_j+1} \frac{t_{j+1}-s}{\sqrt{t_i - s}}ds, \; j = 0(1)i-1, \; i = 1(1)N, \tag{4.17b}$$

$$\alpha_{ii}^{(2)} = \frac{1}{h}\int_{t_{i-1}}^{t_i} \frac{s-t_{i-1}}{\sqrt{t_i - s}}, \quad i = 1(1)N, \tag{4.17c}$$

$$\beta_{i0}^{(2)} = \beta_{ii}^{(2)} = h/2, \qquad i = 1(1)N, \tag{4.17d}$$

$$\beta_{ij}^{(2)} = h, \qquad j = 0(1)i-1, \; i = 1(1)N, \tag{4.17e}$$

we obtain the product trapezoidal scheme. For implicit schemes, a system of two nonlinear equations is required to be solved iteratively using Newton's method at every time step. By subtracting off more terms in the asymptotic expansions it is straightforward to construct product integration schemes with third order and fourth order convergence rates.

Once approximations to $\phi_1(t)$ and $\phi_2(t)$ have been completed on the interval $[0,T]$, approximations to $u(x,t)$ may be found from (4.7) by replacing $\theta(x,t)$ with the truncated series

$$\theta_l(x,t) = \frac{1}{\sqrt{4\pi t}} \sum_{n=-l}^{l} \exp\left(-\frac{(x+2n)^2}{4t}\right).$$

An estimate similar to (3.17) exists for $\theta(x,t) - \theta_l(x,t)$ (see Jumarhon et al.[9]).

Convergence proofs for the numerical schemes (4.14) are not entirely straightforward since F is nonlinear and does not satisfy a global Lipschitz condition, so the standard techniques for proving the convergence of product integration methods for Abel-Volterra type equations (see, e.g., Cameron and McKee [5]) could not be employed directly. Detailed convergence proofs for the numerical schemes presented in this section can be found in Jumarhon and McKee[10].

5. Numerical examples

In this section we present some numerical results. The results are for the case $E = 0.2$, $L = 0.01$, $m = 1.0$. The number of terms l in the truncated kernel was taken to be 8, which assures an accuracy of at least 10^{-11} for $k(t)$ on $(0,1]$. All the results were computed using double precision FORTRAN. In Tables 1 and 2, approximate values of $\gamma(0.05)$ and $\gamma(0.5)$ are presented using both Dixon's scheme and the modified Dixon's scheme. In Tables 3, 4, and 5 approximate values of $\gamma(0.05)$, $u(1,0.05)$ and $\gamma(0.5)$, $u(1,0.5)$ are given using the explicit and implicit product Euler schemes and the product trapezoidal scheme. Stepsizes $h = \frac{1}{40}, \frac{1}{80}$, and $\frac{1}{160}$ are used and the differences between the approximate solutions for consecutive values of h are also presented. These differences (denoted by Δ in the tables) indicate convergence of order 1 for the Dixon scheme, the modified Dixon scheme, and the explicit and implicit Euler product integration schemes, and convergence of order two for the trapezoidal product integration method (Aitken's method (see Linz[12]) is used to check the approximate convergence rates). Other numerical experiments show that the Dixon scheme converges slower then the modified Dixon scheme near the origin. The essential difference between the Dixon scheme and the modified Dixon scheme is that, whereas the former exhibits order one convergence on $[\delta, T]$(where $\delta \in (0,T)$), the latter is convergent of order one on $[0,T]$.

Table 1. Dixon scheme

h, Δ	$\gamma(0.05)$	$\gamma(0.5)$
$h = \frac{1}{40}$	0.009428	0.08524
Δ	5.0D-5	2.4D-4
$h = \frac{1}{80}$	0.009478	0.08548
Δ	2.7D-5	1.2D-4
$h = \frac{1}{160}$	0.009505	0.08560

Table 2. The modified Dixon scheme

h, Δ	$\gamma(0.05)$	$\gamma(0.5)$
$h = \frac{1}{40}$	0.0095174	0.085548
Δ	9.1D-6	8.7D-5
$h = \frac{1}{80}$	0.0095265	0.085634
Δ	4.6D-6	4.3D-5
$h = \frac{1}{160}$	0.0095310	0.085677

Table 3. The explicit Euler scheme

h, Δ	$u(1, 0.05)$	$\gamma(0.05)$	$u(1, 0.5)$	$\gamma(0.5)$
$h = \frac{1}{40}$	0.952130	0.0095527	0.86062	0.085823
Δ	5.5D-5	-8.7D-6	3.9D-4	-5.2D-5
$h = \frac{1}{80}$	0.952185	0.0095440	0.86101	0.085771
Δ	2.6D-5	-4.2D-6	1.9D-4	-2.6D-5
$h = \frac{1}{160}$	0.952211	0.0095398	0.86120	0.085745

Table 4. The implicit Euler scheme

h, Δ	$u(1, 0.05)$	$\gamma(0.05)$	$u(1, 0.5)$	$\gamma(0.5)$
$h = \frac{1}{40}$	0.952294	0.0095192	0.86208	0.085616
Δ	-2.7D-5	8.2D-6	-3.4D-4	5.2D-5
$h = \frac{1}{80}$	0.952267	0.0095274	0.86174	0.085668
Δ	-1.5D-5	4.1D-6	-1.8D-4	2.6D-5
$h = \frac{1}{160}$	0.952252	0.0095315	0.86156	0.085694

Table 5. The trapezoidal product integration scheme

h, Δ	$u(1, 0.05)$	$\gamma(0.05)$	$u(1, 0.5)$	$\gamma(0.5)$
$h = \frac{1}{40}$	0.952234084	0.0095356151	0.8613728	0.08571871
Δ	-4.7D-8	1.1D-8	7.8D-6	7.5D-7
$h = \frac{1}{80}$	0.952234037	0.0095356259	0.8613806	0.08571946
Δ	-1.2D-8	2.8D-9	1.9D-6	1.9D-7
$h = \frac{1}{160}$	0.952234025	0.0095356287	0.8613825	0.08571965

Other numerical experiments show that the technique of subtracting out the singularities is not so effective for large C (for example, $C > 10$). The reason for this is that (4.12) and (4.13) involve high order powers of C. So, for large C, we recommend the direct application of product integration schemes to the system of integral equations (4.8), i.e, for $q = 1, 2$, let

$$f_1^{(q)}(t) = 1,$$

$$f_2^{(q)}(t) = 1,$$

$$\tilde{G}_1^{(q)}(t, s, \phi_1(s), \phi_2(s)) = \kappa_l(t - s)F(\phi_1(s), \phi_2(s)),$$

and

$$G_2^{(q)}(t, s, \phi_1(s), \phi_2(s)) = F(\phi_1(s), \phi_2(s))$$

in (4.14).

6. Concluding remarks

In this paper, the modelling of a reaction-diffusion process in a small cell was carried out. Mathematically, the problem consisted of a heat equation and nonlinear boundary conditions. Through a Volterra integro-differential equation reformulation, a pertubation solution was developed, and an asymptotic result for small time was derived. This asymptotic result indicated the limitations on the direct use of product integration methods. The product Euler scheme developed by Dixon[7] was introduced, and a modification was presented which was seen to overcome the loss of accuracy for small t. Finally, an alternative integral equation formulation was given which permited higher order numerical solutions.

From a practical viewpoint the model of this paper has proved to be a valuable aid to the rapid development of several medical products involving antibody-antigen technology.

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