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A mathematical model of a biosensor

S. JONES[1], B. JUMARHON[2], S. McKEE[3] and J.A. SCOTT[4]
[1] *Unilever Research, Colworth Laboratory, Colworth House, Sharnbrook, Bedford, U.K.*
[2] *School of Computing and Mathematical Sciences, Oxford Brookes University, Oxford, OX3 0BP, U.K.*
[3] *Department of Mathematics, Strathclyde University, 26 Richmond Street, Glasgow, Scotland, U.K.*
[4] *Rutherford Appleton Laboratory, Didcot, Oxon, U.K.*

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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 perturbation 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.

1. The biosensor device

An optical biosensor is a small device which uses optical principles quantitatively to convert chemical and biochemical concentrations, of interest in biology, into electrical signals. The sensor may also itself incorporate biological molecules, such as antibodies, to provide a transducing element that gives the desired specificity. The sensor to be considered here is a disposable type of immunosensor, the fluorescence capillary fill device. It consists of two pieces of plastic, separated by a narrow gap, as shown in schematic form in Fig. 1. The lower plate is coated with an immobilized layer of specific antibody and acts as an optical waveguide. One of the plates has a dissoluble reagent layer of antigen labelled with fluorescent dye. When a sample is presented to one end of the capillary fill device it is drawn into the gap by capillary action and dissolves the reagent. If the device is set up for competition assay, the fluorescently labelled antigen in the reagent will compete with simple antigen for the limited number of antibody binding sites on the waveguide solid face.

Since the reactions are reversible a steady state will be reached in which there are a certain proportion of labelled antigen/antibody complexes. If there were no antigen present in the sample all the labelled antigen would react with the specific antibody displaying, through the optical waveguide, a different signature. Metering of the sample and the reagent then becomes unnecessary provided the capillary gap is precise and there is accurate loading of the antibody and reagent during the device manufacture. A typical medical product based on this antigen/antibody technology is a particular kind of pregnancy kit. A full description of the fluorescent capillary fill device can be found in Badley *et al.* [1].

The primary interest is in the determination of the size of the device and the amount of specific antibody to be coated on the lower plate within a specified time. For this reason the labelled and unlabelled antigen will not be differentiated and will be considered to be one species X, which reacts with the labelled antibody Y, on the lower plate to produce a complex XY.

This paper outlines the model development. It provides an asymptotic solution for small time. This shows that the concentration of the complex (the substance resulting from the

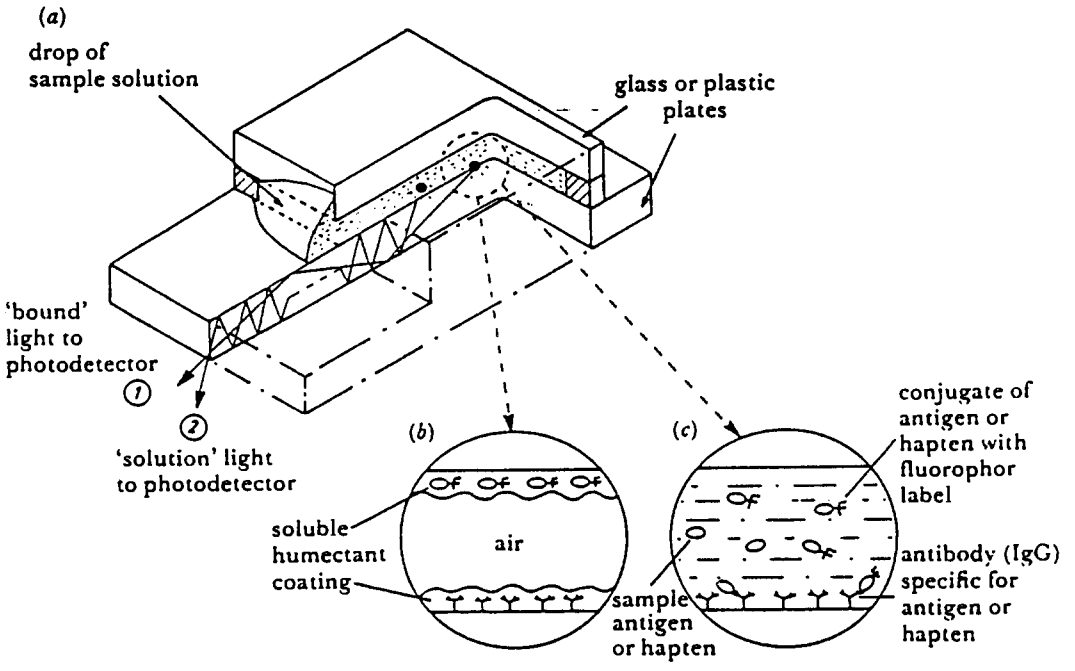

Fig. 1. Schematic diagram of the fluorescence capillary-fill device (FCFD) illustrating a competition immunoassay for a desired antigen or hapten. *(a)* Cutaway view of device showing construction and optical waveguiding principles. *(b)* Enlarged inset of gap in the empty device showing immobilized antibody layer on lower plate and dissoluble reagent layer on upper plate. *(c)* Enlarged inset of gap in the filled device showing competitive immunological binding of the desired antigen or hapten and its fluorescently labelled counterpart (the conjugate) to the limited number of antibody molecules. Sandwich-type immunoassays are also possible in this device.

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 perturbation 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 [2] a numerical method is written down and a modification is suggested which is seen to overcome the loss of accuracy for small time. Finally, 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.

2. The mathematical model

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

The details of the following modelling analysis can be found in Burgess *et al.* 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 X concentration (moles/m^3),
c_0: initial Y concentration at the reaction side wall (moles/m^2),
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 $[X]_{t=0} = a_0$ since the concentration is assumed uniform initially.

We need, however, the boundary condition $\partial[X]/\partial x$ at $x = d$ on the antibody surface. To facilitate the discussion let us introduce the notation:

$$u(x,t) \equiv \text{concentration of } X \text{ i.e. } [X],$$
$$\gamma(t) \equiv \text{concentration of } XY \text{ i.e. } [XY].$$

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 c_0. This will be depleted by the amount of X used up in the reaction. Therefore,

$$[Y](t) = c_0 - \left(a_0 d - \int_0^d u(x,t)\,\mathrm{d}x\right).$$

Thus

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

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

$$\int_0^d u(x,t)\,\mathrm{d}x + \gamma(t) = a_0 d. \tag{2.2}$$

Equations (2.1) and (2.2) together imply

$$D\frac{\partial u}{\partial x}(d,t) = k_{-1}\gamma(t) - k_1 u(d,t)(c_0 - \gamma(t)).$$

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

$$u(x,0) = a_0, \tag{2.3b}$$

and the boundary conditions

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

$$D\frac{\partial u}{\partial x}(d,t) = k_{-1}\gamma(t) - k_1 u(d,t)(c_0 - \gamma(t)), \tag{2.3d}$$

together with

$$\int_0^d u(x,t)\,\mathrm{d}x + \gamma(t) = a_0 d. \tag{2.3e}$$

By introducing the non-dimensional variables

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

and scaling the dependent variables

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

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

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

subject to

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

and

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

and

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

together with

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

where the primes have been omitted for clarity. The constant $m = c_0/(a_0 d)$ is the molar ratio, $L = k_{-1}/k_1 a_0$ is the reaction time scale ratio, and $E = (k_1 a_0 + k_{-1})d^2/D$ 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 perturbation for $\gamma(t;m)$ is derived for small m. Finally, a product Euler scheme due to Dixon [2] 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

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

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

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

Taking Laplace transforms of (2.4a) with respect to t, after some manipulation involving the convolution theorem (see Burgess *et al.* [3]), we obtain

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

where

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

Thus, using (3.1), we obtain

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

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

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

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 $0 < x < t$, $t > 0$ (see Burgess et al. [3]).

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

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

we obtain from (3.4), for small t,

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

which yields

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

Furthermore, since when $t \leqslant (1/\ln 2)$,

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

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

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

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 [2] using a different approach.

3.3. A PERTURBATION SOLUTION

We consider an analytic expansion of $\gamma(t) = \gamma(t;m)$ in powers 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

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

which leads, on noting that $\gamma^{(0)}(0) = 0$, 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 by $\exp(Et)$ on both sides of (3.13) gives

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

Since $\gamma^{(1)}(0) = 0$, 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, finally results in

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

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 [2].

Figures 2 and 3 compare the results obtained using the expansion (3.9) (in Figs. 2 and 3, zero order and first order approximations refer to $\gamma^{(0)}(t)$ and $\gamma^{(0)}(t) + m\gamma^{(1)}(t)$ respectively) and the accurate solutions obtained by using the proven convergent product integration scheme (see next subsection and Dixon [2]) with a very small time step.

For the case $m = 0.1$ Fig. 2 shows reasonable agreement between the various sets of results, as might be expected. However, for $m = 0.5$ the agreement is rather poor. It may be noted that $\gamma^{(0)}(t)$, $\gamma^{(0)}(t) + m\gamma^{(1)}(t)$ and the numerical solution approach different constant values as $t \to \infty$. But we know from Jumarhon and McKee [4] that

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

where

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

It is not difficult to show that

$$\phi^* = 1 - \frac{m}{1+L} + \frac{2Lm^2}{(1+L)^4} + O(m^3)$$

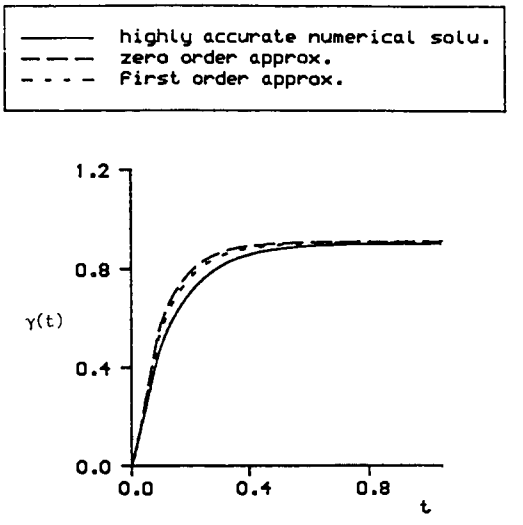

Fig. 2. $L = 0.1$, $E = 10.0$ $m = 0.1$.

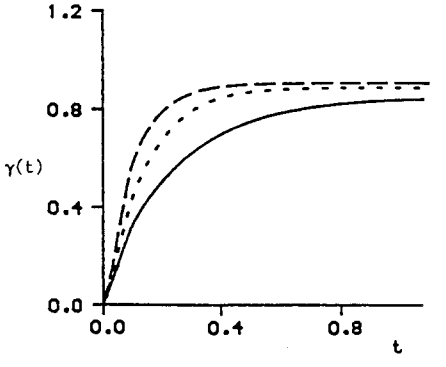

Fig. 3. $L = 0.1$, $E = 10.0$ $m = 0.5$.

giving

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

so that we may write

$$\lim_{t\to\infty} \gamma(t) = \lim_{t\to\infty} \gamma^{(0)}(t) + \lim_{t\to\infty} \gamma^{(1)}(t) + O(m^2)$$

with

$$\lim_{t\to\infty} \gamma^{(0)}(t) = \frac{1}{1+L} \quad \text{and} \quad \lim_{t\to\infty} \gamma^{(1)}(t) = -\frac{2L}{(1+L)^4}.$$

Since $\gamma^{(0)}(t) = 1/(1+L)(1-e^{-Et})$ this shows that at least the $O(1)$ approximation of the perturbation solution trends, in the limit as $t \to \infty$, to the correct asymptotic value.

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:

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

Following Dixon [2],

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

where $\Phi(z)$ is a normal function; tables of $\Phi(z)$ may be found, for example, in Abramowitz and Stegun [5]. 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

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

The numerical method which will now be proposed for equation (3.3) will be of product integration type. For details, see Dixon [2] where a convergence analysis of the method is presented.

Let $t_i = ih$, $i = 0, 1, \ldots, N$, $Nh = T$; γ_i and u_i will denote approximations to $\gamma(t_i)$ and $u(1, t_i)$ respectively. Using the approximation $(\gamma_i - \gamma_i)/h$ 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 [2]),

$$\begin{aligned} \gamma_0 &= 0, \\ \frac{\gamma_i - \gamma_{i-1}}{h} &= C - E\gamma_i - \frac{Cm}{\sqrt{\pi}}(1 - \gamma_{i-1})h\sum_{j=0}^{i-1} \alpha(i-j)\left(\frac{\gamma_{j+1} - \gamma_j}{h}\right), \\ & \qquad i = 1, 2, \ldots, N, \end{aligned} \tag{3.18}$$

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

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

$$j = 0, 1, \ldots, i-1, \quad i = 1, 2, \ldots, N.$$

Discretising (3.3) in a similar way gives

$$u_i = 1 - \frac{m}{\sqrt{\pi}} h \sum_{j=0}^{i-1} \alpha(i-j)\left(\frac{\gamma_{j+1} - \gamma_j}{h}\right), \quad i = 1, 2, \ldots, N.$$

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

Methods of coping with nonsmoothness of solutions of Volterra integral equations have been studied by many authors, for example, Brunner [6], who suggested nonpolynomial spline collocation, and by Norbury and Stuart [7] 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,

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

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

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

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

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

where

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

$$j = 0, 1, \ldots, i-1, \quad i = 1, 2, \ldots, N,$$

we obtain a numerical scheme with order one convergence,

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

Obviously (3.19) allows an explicit solution of γ_i $(i = 1, 2, \ldots, N)$. Similarly we have an order one approximation for $u(1, t_i)$

$$u_i = 1 - \frac{m}{\sqrt{\pi}}h\sum_{j=0}^{i-1}\nu(i,j), \quad i = 1, 2, \ldots, N.$$

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 arbitrary high order schemes by subtracting out the singularities.

Modifying the results of Cannon [9], Jumarhon and McKee [4] have shown that for piecewise-continuous g, H_1 and continuous H_2, the solution of the following problem

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

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

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

$$\frac{\partial V}{\partial x}(1,t) = H_2\left(t, V(1,t), \int_0^t V(x,t)\,\mathrm{d}x\right), \quad t > 0, \tag{4.1d}$$

can be written as

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

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

$$\eta_1(t) \;=\; w(1,t) - 2\int_0^t \theta(1,t-s)H_1(s)\,\mathrm{d}s + 2\int_0^t \theta(0,t-s)H_2(s,\eta_1(s),\eta_2(s))\,\mathrm{d}s, \tag{4.3a}$$

$$\eta_2(t) \;=\; \int_0^1 w(x,t)\,\mathrm{d}x - \int_0^t H_1(s)\,\mathrm{d}s + \int_0^t H_2(s,\eta_1(s),\eta_2(s))\,\mathrm{d}s, \tag{4.3b}$$

with

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

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

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

and using the results from Jumarhon and McKee [4],

$$\int_0^1 \{\theta(x+z,t)+\theta(x-z,t)\}\,\mathrm{d}z = 1, \qquad \int_0^1 \theta(x-1,t)\,\mathrm{d}x = \tfrac{1}{2},$$

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

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

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

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

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

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 [4] 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

Recently, Lubich [10] 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 [10] to show that (4.8) has the asymptotic solution

$$\phi_1(t) = 1 + a_1 t^{1/2} + a_2 t + \cdots, \quad \phi_2(t) = 1 + b_1 t^{1/2} + b_2 t + \cdots, \tag{4.9}$$

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

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

is derived in [4].

Intuitively one might directly 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 of $O(t^{1/2})$ 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

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

This is clearly a bounded function.

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

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

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

with

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

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

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

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

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 $\phi_1(t_i)$, $\phi_2(t_i)$ $(i = 0, 1, \ldots, N)$. Then we have the following system of product integration schemes

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

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

$$\phi_1^0 = 1, \quad \phi_2^0 = 1, \quad i = 1, 2, \ldots, N, \tag{4.14c}$$

where

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

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

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

$$\alpha_{ij}^{(1)} = \int_{t_j}^{t_{j+1}} \frac{\mathrm{d}s}{\sqrt{t_i - s}}, \quad j = 0, 1, \ldots, i-1, \quad i = 1, 2, \ldots, N, \tag{4.15a}$$

$$\alpha_{ii}^{(1)} = \beta_{ii}^{(1)} = 0, \qquad i = 1, 2, \ldots, N, \tag{4.15b}$$

$$\beta_{ij}^{(1)} = h, \qquad j = 0, 1, \ldots, i-1, \quad i = 1, 2, \ldots, N, \tag{4.15c}$$

we obtain the explicit product Euler scheme, while when

$$\alpha_{ij}^{(1)} = \int_{t_{j-1}}^{t_j} \frac{\mathrm{d}s}{\sqrt{t_i - s}}, \qquad j = 0, 1, \ldots, i-1, \quad i = 1, 2, \ldots, N, \tag{4.16a}$$

$$\alpha_{i0}^{(1)} = \beta_{i0}^{(1)} = 0, \qquad i = 1, 2, \ldots, N, \tag{4.16b}$$

$$\beta_{ij}^{(1)} = h, \qquad j = 0, 1, \ldots, i-1, \quad i = 1, 2, \ldots, N, \tag{4.16c}$$

we obtain the implicit product Euler scheme, and when

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

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

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

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

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

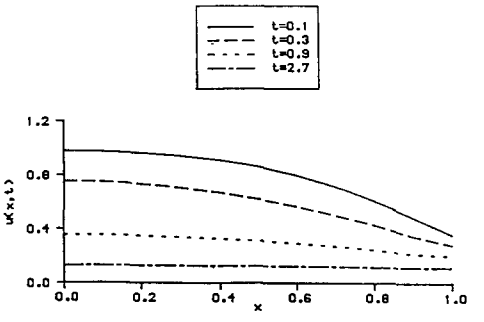

Fig. 4. $L = 0.01$, $E = 5.0$ $m = 1.0$.

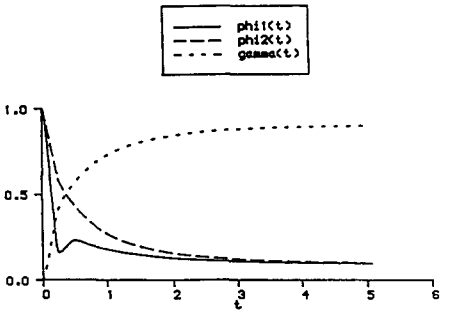

Fig. 5. $L = 0.01$, $E = 5.0$ $m = 1.0$.

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 Jumharon et al. [11]).

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 [12]) could not be employed directly. Detailed convergence proofs for the numerical schemes presented in this section can be found in Jumharon and McKee [13].

5. Numerical computations

The numerical methods discussed in this paper were employed to compute $u(x,t)$ against x and $\phi_1(t) = u(1,t)$, $\phi_2(t) = \int_0^1 u(x,t)\,dx$ and $\gamma(t) = [xy](t)$ against t. These are displayed

respectively in Figs. 4 and 5. Figure 4 shows $u(x,t)$ to be a monotonic decreasing function of time apparently uniform in x. However, Fig. 5 shows that this is not so at $x = 1$. We observe here initially a rapid decrease in the concentration of the antigen until a point where the reaction briefly becomes diffusion dominated before decreasing again to its asymptotic value. We note, however, that the total concentration of antigen (i.e. $\int_0^1 u(x,t)\,\mathrm{d}x$) is monotonic decreasing with time; in contrast we note that the concentration of the complex is monotonic increasing with time.

Computations have also been performed confirming the asymptotic results given in Section 3.3; and the convergence rates of the various numerical methods given in this paper have been verified.

6. Concluding remarks

This paper has been concerned with the modelling of a chemical reaction within a small cell. A reaction-diffusion system was constructed, nondimensionalised and, through the use of Laplace transforms, reduced to an integro-differential equation. Asymptotic results for both a small and large time were given; a regular perturbation solution was derived; and a numerical method was discussed at length. In addition, an alternative integral formulation using the ideas of Cannon was formulated and numerical methods for its solution were set out.

These mathematical techniques were used to facilitate the design of a specific antibody/antigen product: a pregnancy testing kit. If a particular antigen was present in the urine (the bulk fluid in the cell) then the chemical reaction of the labelled antibody would, (through a biosensor) produce a signature which would manifest itself as the colour blue. The bioscientists were anxious that the product should provide a signature in reasonable time and consequently needed some indication of the size of the cell (i.e. d) and the amount of specific antibody to afix to the 'side wall' – in this case a dip stick. The results of this paper quickly answered these questions, thus saving a large amount of experimental analysis. For instance, from Fig. 5 we note that the asymptotic value of the complex is attained when (nondimensional) time is approximately equal to 3. Thus $t \simeq 3(d^2/D)$ is the time required for the woman to wait until the dip stick has turned blue. Marketing deemed that this should be no more than ten minutes: this immediately determined the size of the device.

The point of this paper was not simply to relate a case study, but rather to provide a number of mathematical tools, namely asymptotic analysis techniques, perturbation methods and numerical schemes, for mathematically orientated bioscientists and engineers interested in developing other (possibly very different) products based on this antibody/antigen technology.

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