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Robust numerical solutions of two singularly perturbed problems in mathematical biology [1]

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Abstract

In this paper, a numerical method is suggested for solving a mathematical model for the process of cell proliferation and maturation and a model for determining the expected time for the generation of action potentials in nerve cells by random synaptic inputs in the dendrites. Both these models give rise to singularly perturbed delay differential equations. The former is an initial value problem for a first order singularly perturbed delay partial differential equation, while the latter is a boundary value problem for a second order singularly perturbed delay differential equation. Numerical illustrations are provided.

Keywords: Singularly perturbed delay differential equations, boundary layers, finite difference schemes, Shishkin mesh.

1 Introduction

Singularly perturbed delay differential equations arise frequently in the modelling of biological dynamics [5], [2] and [8] and in a variety of models for

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physiological processes or diseases [10],[6] and [9]. As most of these differential equations exclude analytical solution, developing parameter uniform numerical methods to derive numerical approximations to the solution is an important area of research. Fitted operator methods [3] and fitted mesh methods [7] are robust and most popular numerical methods reported in the literature to solve these problems. Of these, fitted mesh methods are preferred because these methods resolve layers exhibited by the solutions of singularly perturbed differential and delay differential equations. In [1] and [5] two mathematical models arising in biology - (i) a mathematical model for the process of cell proliferation and maturation and (ii) a model for determining the expected time for the generation of action potentials in nerve cells by random synaptic inputs in dendrites - are considered and solved numerically. Here, in this paper, fitted mesh methods involving classical finite difference scheme on a piecewise uniform fitted mesh are suggested to solve these problems. Numerical illustrations are also presented.

2 Model Description- Model 1

The following model describes cell population dynamics in which there is simultaneous proliferation and maturation. In this model the dynamics of the density U of proliferating cells is described as a function of time t, the maturation variable x and the age a of these cells by the equation

$$\frac{\partial U}{\partial t} + \frac{\partial U}{\partial a} + \frac{\partial [V(x)U]}{\partial x} = -\gamma U \tag{1}$$

with the initial conditions

$$U(0,x,a) = \gamma(x,a) \text{ for } (x,a) \in [0,1] \times [0, \bar{\tau}_{max}) \tag{2}$$

$$\text{and } U(t,x,0) \equiv \mathcal{F}(u(t,x)) = 2\int_{\bar{\tau}_{min}}^{\bar{\tau}_{max}} f(\bar{\tau}) U(t,x,\bar{\tau}) d\bar{\tau} \tag{3}$$

where

$U(t,x,a)$	-	density of proliferating cells
$V(x)$	-	Velocity of maturation of the cells
γ	-	death rate of the cells
$\bar{\tau}$	-	age at cytokinesis of a cell
$u(t,x)$	-	total proliferating cells of a given maturation level

Further, $\bar{\tau}$ is not identical between cells, but is distributed with a density $f(\bar{\tau})$ and $0 < \bar{\tau}_{min} \leq \bar{\tau} \leq \bar{\tau}_{max} < \infty$. The range of the maturation variable is from $x = 0$ to $x = 1$. It is assumed that $V(x) = rx, r > 0$. Then equation (1) becomes

$$\frac{\partial U}{\partial t} + \frac{\partial U}{\partial a} + rx\frac{\partial U}{\partial x} = -[\gamma + r]U \tag{4}$$

with the same boundary conditions. Integrating the above equation over the age variable a gives

$$\frac{\partial u}{\partial t} + rx\frac{\partial u}{\partial x} = -[\gamma + r]u - \{U(t, x, \bar{\tau}_{max}) - U(t, x, 0)\} \tag{5}$$

The general solution of (4) in conjunction with boundary condition (3) gives

$$\frac{\partial u}{\partial t} + rx\frac{\partial u}{\partial x} = -[\gamma + r]u + \psi$$

where

$$\psi = \begin{cases} 2[\int_0^{\bar{\tau}_{max}} f(\bar{\tau})\Gamma(xe^{-rt}, \bar{\tau} - t)\, \mathrm{d}\bar{\tau} - \\ \qquad \Gamma(xe^{-rt}, \bar{\tau}_{max} - t)]e^{-(\gamma+r)t}, 0 \leq t \leq \bar{\tau}_{max} \\ 2\int_0^{\bar{\tau}_{max}} f(\bar{\tau})\mathcal{F}(u(t - \bar{\tau}, xe^{-r\bar{\tau}}))e^{\gamma+r}\bar{\tau}\mathrm{d}\bar{\tau} - \\ \quad \mathcal{F}(u(t - \bar{\tau}_{max}, xe^{-r\bar{\tau}_{max}}))e^{(\gamma+r)\bar{\tau}_{max}}, \bar{\tau}_{max} < t. \end{cases}$$

Here, Γ is a continuous function.
When the distribution of ages at cytokinesis is sharply peaked, the density is approximated by a delta function, $f(\bar{\tau}) = \delta(\tau - \bar{\tau})$ with $\bar{\tau}_{max} = \tau > 0$, then

$$\frac{\partial u}{\partial t} + rx\frac{\partial u}{\partial x} = -[\gamma + r]u + \begin{cases} \Gamma(xe^{-rt}, \tau - t)e^{-(\gamma+r)t}, \\ \qquad 0 \leq t \leq \tau, \\ \mathcal{F}(u(t - \tau, xe^{-r\tau}))e^{(\gamma+r)\tau}, \\ \qquad \tau < t. \end{cases} \tag{6}$$

Taking the function $\mathcal{F}$ to be $\mathcal{F}(u) = u(1-u)$, $\delta = \gamma+r$, $\alpha = e^{-r\tau}$, $\lambda = e^{\gamma+r}\tau$ and an initial function $u(t', x') = \varphi(x')$ for $0 \leq t' \leq \tau$ and $0 \leq x' \leq 1$, (6) becomes

$$\frac{\partial u}{\partial t} + rx\frac{\partial u}{\partial x} = -\delta u + \lambda u(t - \tau, \alpha x)[1 - u(t - \tau, \alpha x)], \tau < t. \tag{7}$$

Thus when r is very small, i.e. when $0 < rx << 1$, and when $\tau = 1$, the given problem is an initial value problem for a first order, time-dependent, singularly perturbed delay-differential equation.

Motivated by the above model, the following numerical method is suggested to solve an initial value problem for a first order singularly perturbed delay differential equation of the form

$$\frac{\partial u}{\partial t} + \varepsilon \frac{\partial u}{\partial x} + a(x,t)u(x,t) + b(x,t)u(x,t-1) = f(x,t), \ (x,t) \in (0,2] \times (0,2] \tag{8}$$

with $u(x,t) = \phi(x,t), (x,t) \in [0,2] \times [-1,0]$

Motivation for the fitted mesh method:
The motivation to the construction of the numerical method comes from the nature of the solution of this problem (8). The solution exhibits initial layer at $x = 0$ because of the perturbation parameter ε occurring and due to the delay term present in the equation, the solution undergoes some additional changes, at $t = 1$, as the delay is big. The mesh is constructed in such a way that points are furnished inside the layers so as to know the behavior of the solution in the layer regions. Therefore, it is appropriate to have a mesh that has many points in the layer regions and less number of points in the outer regions. In other words, a piece-wise uniform mesh which is fine inside the layers and coarse outside the layers will serve the purpose.

3 Numerical Method

The Shishkin mesh that we suggest here is one such mesh that is suitable for the problem under consideration. This piece-wise uniform Shishkin mesh $\bar{\Omega}^{M,N}$ with $M \times N$ mesh intervals is defined as follows:
Let $\Omega_t^M = \{t_k\}_{k=1}^M$, $\Omega_x^N = \{x_j\}_{j=1}^N$, $\overline{\Omega}_t^M = \{t_k\}_{k=0}^M$, $\overline{\Omega}_x^N = \{x_j\}_{j=0}^N$, $\Omega^{M,N} = \Omega_t^M \times \Omega_x^N$, $\overline{\Omega}^{M,N} = \overline{\Omega}_t^M \times \overline{\Omega}_x^N$
The mesh $\overline{\Omega}_t^M$ is chosen to be a uniform mesh with M mesh-intervals on $[0,2]$, whereas, the mesh $\overline{\Omega}_x^N$ is chosen to be a piecewise-uniform mesh with N mesh-intervals on $[0,2]$ as follows:

The interval $[0,1]$ is divided into 2 sub-intervals $[0,\tau]$ and $(\tau,1]$ where,

$$\tau = \min\left\{\frac{1}{2}, \frac{\varepsilon}{\alpha}\ln N\right\}. \tag{9}$$

Then, on each of these sub-intervals a uniform mesh with $\frac{N}{4}$ mesh points is placed. This τ is called a transition point separating the two uniform meshes. Similarly, the interval $(1,2]$ is also divided into 2 sub-intervals $(1, 1+\tau]$, $(1+\tau, 2]$ using the same transition point τ. In particular, when the transition point τ takes on its lefthand value, the Shishkin mesh $\overline{\Omega}^N$ becomes a classical uniform mesh on the interval $[0,2]$. On this mesh, the discrete problem corresponding to (8) is defined as follows: For any $(x_j, t_k) \in \bar{\Omega}^{M,N}$,

$$\begin{aligned} D_t^- U(x_j,t_k) + \varepsilon D_x^- U(x_j,t_k) + a(x_j,t_k)U(x_j,t_k) + b(x_j,t_k)U(x_j,t_k-1) \\ = f(x_j,t_k) \end{aligned} \tag{10}$$

$u(x,t) = \phi(x,t)$ for $(x,t) \in [0,2] \times [-1,0]$

4 Numerical Illustration

Consider the related initial value problem (IVP)

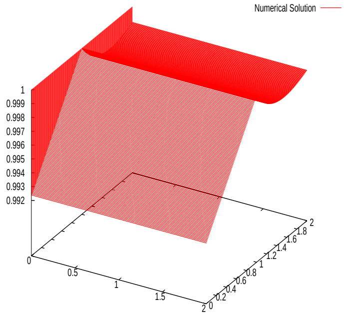
$$\begin{aligned} \frac{\partial u}{\partial t} + \varepsilon\frac{\partial u}{\partial x} + 2u(x,t) - u(x,t-1) = -1,\ (x,t) \in (0,2] \times (0,2] \\ u(x,t) = 1 + t \ \text{ for } (x,t) \in [0,2] \times [-1,0] \end{aligned}$$

This IVP is solved by the numerical method suggested in the previous section. Due to the presence of the perturbation parameter ε, an initial layer of width $O(\varepsilon)$ is exhibited by the solution at $x = 0$. And, due to the presence of the delay term, a change in the solution profile is observed at $t = 1$. The numerical results are plotted in Figure 1.

Observations:

The numerical results display a boundary layer at $x = 0$ and an interior layer along the line $t = 1$. Further, it is observed that for a given time, as the value of the maturation variable increases from 0, the total proliferating cells decrease rapidly and after a critical value ($O(\varepsilon)$), it becomes almost a constant. Also, as time increases for a given maturation level, the total proliferating cells increase till $t = 1$ and then decrease slowly.

Figure 1: Solution Profile-$\varepsilon = 0.0001$; N=512; M=128



5 Model 2: Problems of small delay

Motivation for problems of small delay:
According to Lange in [5], the determination of the expected time for the generation of action potentials in nerve cells by random synaptic inputs in the dendrites can be modeled as a first-exit time problem known as Stein's model which aims at deriving quantitative, experimentally testable predictions about neuronal behavior under natural conditions.

Further, from [5], it is observed that the inputs are distributed as a Poisson process with exponential decay between the inputs. If, in addition, there are inputs that can be modeled as a Wiener process with variance parameter σ and drift parameter μ, then the problem for the expected first-exit time y, given the initial membrane potential $x \in (x_1, x_2)$, can be formulated as a general boundary-value problem for the linear second-order differential-difference equation

$$\frac{\sigma^2}{2} y''(x) + (\mu - x)y'(x) + \lambda_E y(x + a_E) + \lambda_I y(x - a_I) - (\lambda_E + \lambda_I)y(x) = -1 \tag{11}$$

where the values $x = x_1$ and $x = x_2$ correspond to the inhibitory reversal potential and to the threshold value of membrane potential for action potential generation respectively. The first order derivative term $-xy'$ corresponds to exponential decay between synaptic inputs. The undifferentiated terms correspond to excitatory and inhibitory synaptic inputs modeled as Poisson processes with mean rates λ_E and λ_I, respectively and produce jumps in the membrane potential of amounts a_E and $-a_I$ respectively, which are small quantities and could depend on voltage. The boundary condition is $y(x) = 0, x \notin (x_1, x_2)$.

In particular, when the mean rate $\lambda_E = 0$, the problem is reduced to a simpler delay-differential equation,

$$\frac{\sigma^2}{2} y''(x) + (\mu - x)y'(x) + \lambda_I y(x - a_I) - \lambda_I y(x) = -1. \tag{12}$$

Motivated by this biological problem, boundary value problems for singularly perturbed delay differential equations were investigated in [5]. The solutions of such equations were analysed and matched aysmptotic expansions of the solutions of modified versions of singularly perturbed ordinary differential equations were presented.

Motivated by the works of Lange, in this paper, we consider a related singularly perturbed boundary value problem of the form

$$-\varepsilon u''(x) + a(x)u(x) + b(x)u(x - \delta(\varepsilon)) = f(x), x \in (0, 1) \tag{13}$$

$$u(x) = \phi(x), x \in [-\delta(\varepsilon), 0],\ u(1) = u_1 \tag{14}$$

where $\delta(\varepsilon) = k\varepsilon$, $k = O(1)$ and suggest a iterative fitted mesh method to solve the same.

It is found that, when the shift $\delta(\varepsilon)$ is very small, there is insignificant or no change in the boundary layers. When the shift $\delta(\varepsilon)$ is small, there are moderate layers at $x = \delta(\varepsilon)$ but well contained in the layer at $x = 0$ that results in simply broadening the layer at $x = 0$.

It is important to note that as $\delta(\varepsilon)$ is so small, on any fitted mesh on $[0, 1], x_j - \delta(\varepsilon) \neq x_k$ for any x_j, x_k of the mesh. Hence with an initial approximation 0 for $\delta(\varepsilon)$, the resulting boundary value problem is solved. To arrive at the solution of the original problem, an iterative method is adopted. Taking into consideration the fact that the layers are broadened by $O(\delta(\varepsilon))$ at $\delta(\varepsilon)$, the iterative method is applied on a Shishkin mesh which captures this behavior. Precisely, it consists of fine mesh portions near $x = 0$ and $x = 1$ and a coarse mesh potion away form the boundaries.

6 Description of the Numerical Method

The discrete problem corresponding to (13), (14), defined on a piecewise uniform Shishkin mesh $\bar{\Omega}^N$, is defined as follows:

$$-\varepsilon\delta^2 U_n(x_j) + (a(x_j) + b(x_j))U_n(x_j) = f(x_j) + b(x_j)(U_{n-1}(x_j) - U_{n-1}(x_j - \delta(\varepsilon))),$$
$$1 \le j \le N-1$$
$$U(x_0) = \phi(x_0); U(x_N) = u(1)$$

where $x_j \in \bar{\Omega}^N = \{x_j\}_{j=0}^N$ with

$$x_j = x_0 + jh_1,\ \ 0 \le j \le \frac{N}{8},\ x_{\frac{N}{8}+j} = \delta(\varepsilon) + jh_2,\ \ 1 \le j \le \frac{N}{8}$$
$$x_{\frac{N}{4}+j} = \tau + jh_3,\ \ 1 \le j \le \frac{N}{2},\ x_{\frac{3N}{4}+j} = (1-\tau) + jh_4,\ \ 1 \le j \le \frac{N}{4}$$
$$\text{and}\ \ h_1 = \frac{\delta(\varepsilon)}{\frac{N}{8}}\ \ ,\ \ h_2 = \frac{(\tau - \delta(\varepsilon))}{\frac{N}{8}}, h_3 = \frac{(1-2\tau)}{\frac{N}{2}}\ \ ,\ \ h_4 = \frac{\tau}{\frac{N}{4}}$$
$$\tau = \min(\frac{1}{2}, \sqrt{\varepsilon/\alpha}\ln(N)), (a(x) + b(x)) > \alpha > 0.$$

Here, U_0 is the initial approximation for $u(x)$ obtained by putting $\delta(\varepsilon) = 0$ and solving the resulting reaction-diffusion problem by the method suggested in [4]. Fixing an error tolerance TOL, the iterations are carried out until the required accuracy is attained.

7 Numerical Illustration

To illustrate the method the following boundary value problem for a singularly perturbed delay differential equation is considered. The above numerical method is applied and the results are presented in figures which show the broadening of the boundary layer by the small shift $\delta(\varepsilon)$. Estimating the error committed will be considered in a future work. The analysis for systems of small-delay differential equations seems to be more complicated than that for systems of big-delay differential equations. Consider the boundary value problem

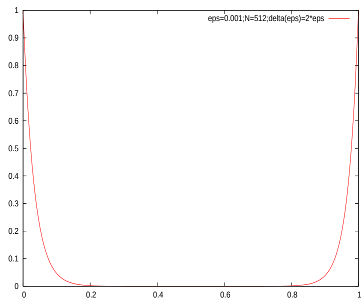
$$-\varepsilon u''(x) + 2u(x) - u(x - \delta(\varepsilon)) = 0, x \in (0,1), u(x) = 1 \text{ for } x \in [-1,0] \text{ and } u(1) = 1.$$

We solve this problem for $\varepsilon = 0.001$ using the above numerical method with $N = 512$ for the following two cases:

(a) **Very small shift** - When the shift is very small (i.e., $\delta(\varepsilon) = 2\varepsilon$ or $\delta(\varepsilon) = 5\varepsilon$), insignificant or no change in the layer profile is observed. Figures 2 and 3 are presented to show that the behavior of the solution with reference to the layers are the same in these two cases.

Observation:
It is observed that in this case, the expected time for the generation of action potential decreases rapidly for the initial values of the membrane potential, remain constant for its intermediate values and increases rapidly for the values of the membrane potential near 1.

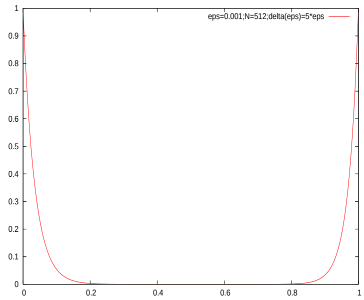
Figure 2: Solution Profile-u for $\varepsilon = 0.001$; N=512; $\delta(\varepsilon) = 2 * \varepsilon$



(b) **Small shift** - When the shift is small ($\delta(\varepsilon) = 50\varepsilon$ or $\delta(\varepsilon) = 100\varepsilon$), significant change occurs in the behavior of the solution. The boundary layer at the initial point gets broadened at $x = \delta(\varepsilon)$. The result is shown in figure 4, a detail of which is presented in figure 5 for $\delta(\varepsilon) = 100\varepsilon$. Figures 6 and 7 present the same for $\delta(\varepsilon) = 50\varepsilon$.

Observation:
In this case, the expected time for the generation of action potential decreases rapidly for the initial values of the membrane potential and when

Figure 3: Solution Profile-u for $\varepsilon = 0.001$; N=512; $\delta(\varepsilon) = 5 * \varepsilon$



the membrane potential takes the value $\delta(\varepsilon)$, the expected time increases suddenly and then it decreases. It remains constant for the intermediate values of the membrane potential and increases rapidly for the values of the membrane potential near 1.

Figure 4: Solution Profile-u for $\varepsilon = 0.001$; N=512; $\delta(\varepsilon) = 100 * \varepsilon$

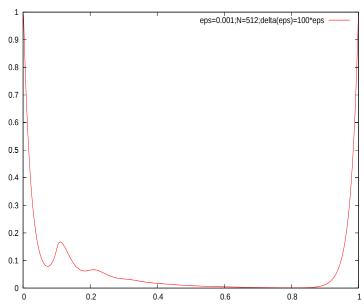


Figure 5: Detail of Fig. 4 near $x = 0$

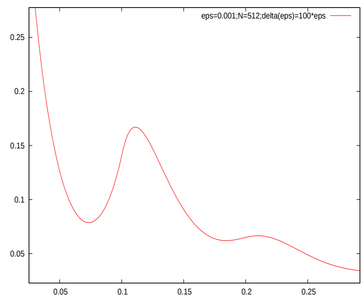


Figure 6: Solution Profile-u for $\varepsilon = 0.001$; N=512; $\delta(\varepsilon) = 50 * \varepsilon$

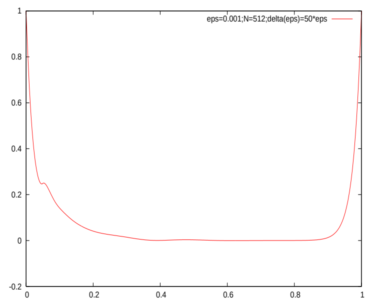
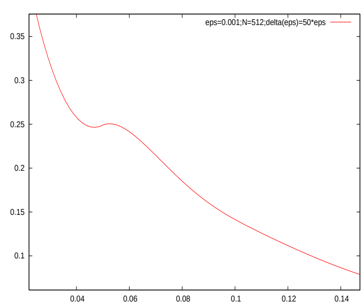


Figure 7: Detail of Fig. 6 near $x = 0$



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