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THE METHOD OF LINES FOR THE NUMERICAL SOLUTION OF A MATHEMATICAL MODEL IN THE INITIATION OF ANGIOGENESIS

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Abstract. In this paper we present the method of lines to obtain the numerical solution of a mathematical model for the roles of endothelial, pericyte and macrophage cells in the initiation of tumor angiogenesis. This method is an approach to the numerical solution of partial differential equations that involve a time variable t and a space variable x. We provide computer programs written in Matlab. Also, the stability analysis of the solutions is given, and the figures for endothelial, pericyte and macrophage cell movements in the capillary are presented for large times.

Keywords: Method of lines, stability, angiogenesis, capillary

AMS Subject Classification: 65M20, 34D20

1. Introduction

Angiogenesis is the main feature of the formation of new blood vessels. The abluminal surface of the capillaries is covered by a collageneous network intermingled with laminin which is called the basal lamina (BL). The BL is mainly formed by the Endothelial Cells (EC). In the neighborhood of BL, there are other cell types such as Pericyte Cells (PC) and Macrophage Cells (MC) [4].

In this paper we consider the following initial boundary-value problem originally presented in [4]:

$$\frac{\partial \eta}{\partial t} = D_1 \frac{\partial}{\partial x}\left(\eta \frac{\partial}{\partial x}\left(\ln \frac{\eta}{\tau_1}\right)\right),\ 0 < x < 1,\ 0 < t \leq T, \tag{1}$$

$$\frac{\partial \sigma}{\partial t} = D_2 \frac{\partial}{\partial x}\left(\sigma \frac{\partial}{\partial x}\left(\ln \frac{\sigma}{\tau_2}\right)\right),\ 0 < x < 1,\ 0 < t \leq T, \tag{2}$$

$$\frac{\partial m}{\partial t} = D_3 \frac{\partial}{\partial x}\left(m \frac{\partial}{\partial x}\left(\ln \frac{m}{\tau_3}\right)\right),\ 0 < x < 1,\ 0 < t \leq T, \tag{3}$$

where $\eta(x,t), \sigma(x,t)$ and $m(x,t)$ are the concentrations of EC, PC and MC, respectively, and τ_1, τ_2 and τ_3 are the transition probability functions of them. Also, D_1, D_2, D_3 are EC, PC and MC diffusion constants. We impose the initial conditions,

$$\eta(x,0) = 1, \quad \sigma(x,0) = 1, \quad m(x,0) = 1, \quad 0 < x < 1, \tag{4}$$

and the boundary conditions,

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$$D_1\eta\frac{\partial}{\partial x}\left(\ln\frac{\eta}{\tau_1}\right)\Big|_{x=0}=D_2\sigma\frac{\partial}{\partial x}\left(\ln\frac{\sigma}{\tau_2}\right)\Big|_{x=0}=D_3 m\frac{\partial}{\partial x}\left(\ln\frac{m}{\tau_3}\right)\Big|_{x=0}=0, \tag{5}$$

$$D_1\eta\frac{\partial}{\partial x}\left(\ln\frac{\eta}{\tau_1}\right)\Big|_{x=1}=D_2\sigma\frac{\partial}{\partial x}\left(\ln\frac{\sigma}{\tau_2}\right)\Big|_{x=1}=D_3 m\frac{\partial}{\partial x}\left(\ln\frac{m}{\tau_3}\right)\Big|_{x=1}=0. \tag{6}$$

As in [6,7], for numerical purposes we take the transition probability functions τ_1, τ_2 and τ_3 as follows:

$$\tau_1=f(x)=\left(\frac{\alpha_1+Ax^n(1-x)^n}{\alpha_2+Ax^n(1-x)^n}\right)^{\gamma_1}\left(\frac{\beta_1+1-Bx^n(1-x)^n}{\beta_2+1-Bx^n(1-x)^n}\right)^{\gamma_2}, \tag{7}$$

$$\tau_2=g(x)=\left(\frac{\alpha_3+1-Bx^n(1-x)^n}{\alpha_4+1-Bx^n(1-x)^n}\right)^{\gamma_3}, \tag{8}$$

$$\tau_3=r(x)=\left(\frac{\beta_3+Ax^n(1-x)^n}{\beta_4+Ax^n(1-x)^n}\right)^{\gamma_4}. \tag{9}$$

Here, n, A, B, α_i, β_i and γ_i $(i=1:4)$ are some positive constants which we take here to be the same as in [4]. The Authors of Ref.[4] have chosen the transition probability functions $f(x)$, $g(x)$ and $r(x)$ more complicated for biological reasons. But for simplicity, we take them as a function of x only.

2. Method

The method of lines (MOL) is a general way of viewing a partial differential equation (PDE) as a system of ordinary differential equations (ODE) [1-3,5,6,9-11]. The partial derivatives with respect to the space variables are discretized to obtain a system of ODEs in the time variable and then a suitable initial-value problem solver is used to solve this ODE system. This method has the broad applicability to physical and chemical systems modeled by PDEs [9]. Also, this method provides very accurate numerical solution for linear or nonlinear PDE' s in comparison with other existing methods [6]. As the number of lines increases, the accuracy of the MOL representation of the original system increases [5]. We now apply this method to our problem given by Eqs.(1)-(6).

We proceed uniform grid,

$W=\{(x_i,t_j): x_i=(i-1)h,\ t_j=(j-1)k,\ i=1:M,\ j=1:N,\ h=1/(M-1),\ k=1/(N-1)\}$ and obtain a difference scheme for the problem in Eqs.(1)-(6). Eqs.(1)-(3) can be written as follows:

$$\eta_t=D_1\left(\eta_{xx}-(\eta F)_x\right), \tag{10}$$

$$\sigma_t=D_2\left(\sigma_{xx}-(\sigma G)_x\right), \tag{11}$$

$$m_t=D_1\left(m_{xx}-(mH)_x\right), \tag{12}$$

where $F=\dfrac{f'(x)}{f(x)}$, $G=\dfrac{g'(x)}{g(x)}$ and $H=\dfrac{r'(x)}{r(x)}$.

We suppose the solutions of Eqs.(10)-(12) $\eta(x,t)$, $\sigma(x,t)$ and $m(x,t)$ can be approximated by η_i, σ_i and m_i, respectively, and use the standart difference equations for the first and the second derivatives of these variables. Therefore, by discretizing the right handside of Eqs.(10)-(12) we obtain the following system of ODE's:

$$\frac{d\eta_i}{dt}=D_1\left(\frac{\eta_{i+1}-2\eta_i+\eta_{i-1}}{h^2}-\frac{\eta_{i+1}F_{i+1}-\eta_{i-1}F_{i-1}}{2h}\right), \tag{13}$$

$$\frac{d\sigma_i}{dt} = D_2\left(\frac{\sigma_{i+1} - 2\sigma_i + \sigma_{i-1}}{h^2} - \frac{\sigma_{i+1}G_{i+1} - \sigma_{i-1}G_{i-1}}{2h}\right), \tag{14}$$

$$\frac{dm_i}{dt} = D_3\left(\frac{m_{i+1} - 2m_i + m_{i-1}}{h^2} - \frac{m_{i+1}H_{i+1} - m_{i-1}H_{i-1}}{2h}\right). \tag{15}$$

The initial conditions in Eq.(4) and boundary conditions in Eqs.(5)-(6) now become:
$\eta_i = 1$, $\sigma_i = 1$, $m_i = 1$, $1 < i < M$, $t = 0$, (16)

$$D_1\left(\frac{\partial \eta_1}{\partial x} - \eta_1 F_1\right) = 0, \text{ for } t > 0, \tag{17}$$

$$D_1\left(\frac{\partial \eta_M}{\partial x} - \eta_M F_M\right) = 0, \text{ for } t > 0, \tag{18}$$

$$D_2\left(\frac{\partial \sigma_1}{\partial x} - \sigma_1 G_1\right) = 0, \text{ for } t > 0, \tag{19}$$

$$D_2\left(\frac{\partial \sigma_M}{\partial x} - \sigma_M G_M\right) = 0, \text{ for } t > 0, \tag{20}$$

$$D_3\left(\frac{\partial m_1}{\partial x} - m_1 H_1\right) = 0, \text{ for } t > 0, \tag{21}$$

$$D_3\left(\frac{\partial m_M}{\partial x} - m_M H_M\right) = 0, \text{ for } t > 0. \tag{22}$$

Using the central difference for the boundary conditions in Eqs.(17)-(22) and taking into account Eqs.(13)-(15), we obtain the following system of ODE's:

$$\frac{d\eta_1}{dt} = D_1\left(\frac{2\eta_2 - 2(1 + hF_1)\eta_1}{h^2} - \frac{\eta_2 F_2 - (\eta_2 - 2h\eta_1 F_1)F_0}{2h}\right), \tag{23}$$

$$\frac{d\eta_i}{dt} = D_1\left(\frac{\eta_{i+1} - 2\eta_i + \eta_{i-1}}{h^2} - \frac{\eta_{i+1}F_{i+1} - \eta_{i-1}F_{i-1}}{2h}\right), \ 1 < i < M, \tag{24}$$

$$\frac{d\eta_M}{dt} = D_1\left(\frac{2\eta_{M-1} - 2(1 - hF_M)\eta_M}{h^2} - \frac{(\eta_{M-1} + 2h\eta_M F_M)F_{M+1} - \eta_{M-1}F_{M-1}}{2h}\right), \tag{25}$$

$$\frac{d\sigma_1}{dt} = D_2\left(\frac{2\sigma_2 - 2(1 + hG_1)\sigma_1}{h^2} - \frac{\sigma_2 G_2 - (\sigma_2 - 2h\sigma_1 G_1)G_0}{2h}\right), \tag{26}$$

$$\frac{d\sigma_i}{dt} = D_2\left(\frac{\sigma_{i+1} - 2\sigma_i + \sigma_{i-1}}{h^2} - \frac{\sigma_{i+1}G_{i+1} - \sigma_{i-1}G_{i-1}}{2h}\right), \ 1 < i < M, \tag{27}$$

$$\frac{d\sigma_M}{dt} = D_2\left(\frac{2\sigma_{M-1} - 2(1 - hG_M)\sigma_M}{h^2} - \frac{(\sigma_{M-1} + 2h\sigma_M G_M)G_{M+1} - \sigma_{M-1}G_{M-1}}{2h}\right), \tag{28}$$

$$\frac{dm_1}{dt} = D_3\left(\frac{2m_2 - 2(1 + hH_1)m_1}{h^2} - \frac{m_2 H_2 - (m_2 - 2hm_1 H_1)H_0}{2h}\right), \tag{29}$$

$$\frac{dm_i}{dt} = D_3\left(\frac{m_{i+1} - 2m_i + m_{i-1}}{h^2} - \frac{m_{i+1}H_{i+1} - m_{i-1}H_{i-1}}{2h}\right), \ 1 < i < M, \tag{30}$$

$$\frac{dm_M}{dt} = D_3\left(\frac{2m_{M-1} - 2(1 - hH_M)m_M}{h^2} - \frac{(m_{M-1} + 2hm_M H_M)H_{M+1} - m_{M-1}H_{M-1}}{2h}\right). \tag{31}$$

3. Stability of the solutions

We let

$$\mathbf{x} = [\eta_1 \ \cdots \ \eta_i \ \cdots \ \eta_M \ \sigma_1 \ \cdots \ \sigma_i \ \cdots \ \sigma_M \ m_1 \ \cdots \ m_i \ \cdots \ m_M]^T \tag{32}$$

and

$$\mathbf{f(x)} = \begin{bmatrix} D_1\left(\frac{2\eta_2-2(1+hF_1)\eta_1}{h^2} - \frac{\eta_2 F_2-(\eta_2-2h\eta_1F_1)F_0}{2h}\right) \\ \vdots \\ D_1\left(\frac{\eta_{i+1}-2\eta_i+\eta_{i-1}}{h^2} - \frac{\eta_{i+1}F_{i+1}-\eta_{i-1}F_{i-1}}{2h}\right) \\ \vdots \\ D_1\left(\frac{2\eta_{M-1}-2(1-hF_M)\eta_M}{h^2} - \frac{(\eta_{M-1}+2h\eta_M F_M)F_{M+1}-\eta_{M-1}F_{M-1}}{2h}\right) \\ D_2\left(\frac{2\sigma_2-2(1+hG_1)\sigma_1}{h^2} - \frac{\sigma_2 G_2-(\sigma_2-2h\sigma_1G_1)G_0}{2h}\right) \\ \vdots \\ D_2\left(\frac{\sigma_{i+1}-2\sigma_i+\sigma_{i-1}}{h^2} - \frac{\sigma_{i+1}G_{i+1}-\sigma_{i-1}G_{i-1}}{2h}\right) \\ \vdots \\ D_2\left(\frac{2\sigma_{M-1}-2(1-hG_M)\sigma_M}{h^2} - \frac{(\sigma_{M-1}+2h\sigma_M G_M)G_{M+1}-\sigma_{M-1}G_{M-1}}{2h}\right) \\ D_3\left(\frac{2m_2-2(1+hH_1)m_1}{h^2} - \frac{m_2 H_2-(m_2-2hm_1H_1)H_0}{2h}\right) \\ \vdots \\ D_3\left(\frac{m_{i+1}-2m_i+m_{i-1}}{h^2} - \frac{m_{i+1}H_{i+1}-m_{i-1}H_{i-1}}{2h}\right) \\ \vdots \\ D_3\left(\frac{2m_{M-1}-2(1-hH_M)m_M}{h^2} - \frac{(m_{M-1}+2hm_M H_M)H_{M+1}-m_{M-1}H_{M-1}}{2h}\right) \end{bmatrix}, \tag{33}$$

where $2 \leq i \leq M-1$. Then, by Eqs.(23)-(31) one has the following autonomous system of ordinary differential equations:

$$\dot{\mathbf{x}} = \mathbf{f(x)}, \quad t \geq 0. \tag{34}$$

We now let

$$\eta(x,t) = 1 + \eta^*(x,t), \qquad \sigma(x,t) = 1 + \sigma^*(x,t), \qquad m(x,t) = 1 + m^*(x,t), \tag{35}$$

and assume that $F'(x) \approx 0$, $G'(x) \approx 0$, $H'(x) \approx 0$ for small x. These assumptions are reasonable (see Figures (1)-(3)). Therefore, Eqs.(10)-(15) and Eqs.(17)-(31) stay the same in the variables with the asterisks except the initial conditions in Eq.(16) now become

$$\eta_i^* = 0,\ \sigma_i^* = 0,\ m_i^* = 0,\ 1 < i < M,\ t = 0. \tag{36}$$

For simplicity we drop all of the asterisks. Therefore, we now solve Eqs.(23)-(31) with the initial conditions in Eq.(36).

It is now clear to see that the only steady-state solution to Eqs.(23)-(31) is the vector $c = (0 \cdots 0 \ 0 \cdots 0 \ 0 \cdots 0)^T$ of length $3M$. Let A, B and C be the matrices of first order partial derivatives of $\mathbf{f(x)}$ with respect to the variables η_i, σ_i and m_i $(1 \leq i \leq M)$, respectively, evaluated at c. Therefore, the matrices A, B and C become

$$A = \begin{bmatrix} -D_1(\frac{2(1+hF_1)}{h^2} + F_1F_0) & D_1(\frac{2}{h^2} - \frac{F_2}{2h} + \frac{F_0}{2h}) & 0 & \cdots & 0 \\ D_1(\frac{1}{h^2} + \frac{F_1}{2h}) & -\frac{2D_1}{h^2} & D_1(\frac{1}{h^2} - \frac{F_3}{2h}) & & \vdots \\ 0 & \ddots & \ddots & \ddots & 0 \\ \vdots & & D_1(\frac{1}{h^2} + \frac{F_{M-2}}{2h}) & -\frac{2D_1}{h^2} & D_1(\frac{1}{h^2} - \frac{F_M}{2h}) \\ 0 & \cdots & 0 & 0 & D_1(\frac{2hF_M-2}{h^2} - F_MF_{M+1}) \end{bmatrix}$$

$$B = \begin{bmatrix} -D_2(\frac{2(1+hG_1)}{h^2} + G_1G_0) & D_2(\frac{2}{h^2} - \frac{G_2}{2h} + \frac{G_0}{2h}) & 0 & \cdots & 0 \\ D_2(\frac{1}{h^2} + \frac{G_1}{2h}) & -\frac{2D_2}{h^2} & D_2(\frac{1}{h^2} - \frac{G_3}{2h}) & & \vdots \\ 0 & \ddots & \ddots & \ddots & 0 \\ \vdots & & D_2(\frac{1}{h^2} + \frac{G_{M-2}}{2h}) & -\frac{2D_2}{h^2} & D_2(\frac{1}{h^2} - \frac{G_M}{2h}) \\ 0 & \cdots & 0 & 0 & D_2(\frac{2hG_M-2}{h^2} - G_MG_{M+1}) \end{bmatrix}$$

$$C = \begin{bmatrix} -D_3(\frac{2(1+hH_1)}{h^2} + H_1H_0) & D_3(\frac{2}{h^2} - \frac{H_2}{2h} + \frac{H_0}{2h}) & 0 & \cdots & 0 \\ D_3(\frac{1}{h^2} + \frac{H_1}{2h}) & -\frac{2D_3}{h^2} & D_3(\frac{1}{h^2} - \frac{H_3}{2h}) & & \vdots \\ 0 & \ddots & \ddots & \ddots & 0 \\ \vdots & & D_3(\frac{1}{h^2} + \frac{H_{M-2}}{2h}) & -\frac{2D_3}{h^2} & D_3(\frac{1}{h^2} - \frac{H_M}{2h}) \\ 0 & \cdots & 0 & 0 & D_3(\frac{2hH_M-2}{h^2} - H_MH_{M+1}) \end{bmatrix}$$

We let

$$S = \begin{bmatrix} A & & \mathbf{O} \\ & B & \\ \mathbf{O} & & C \end{bmatrix}$$

where $\mathbf{O}$ is the zero matrix. It is well known that the determinant of the matrix S is the product of the determinants of the matrices A, B and C. Therefore, the eigenvalues of S consists of the set of eigenvalues of A, B and C. We know that every solution of the system of equations given by Eqs.(23)-(31) is stable if all the eigenvalues of S have negative real part and unstable if at least one eigenvalue of S has positive real part [12].

In the following section we solve the system in Eqs.(23)-(31) with the initial conditions in Eq.(36) by using an ordinary differential equation solver which is built up in Matlab, and discuss the stability (or unstability) of the solutions of the system by determining the signs of the real parts of the eigenvalues of the matrix S for some values of M.

4. Numerical experiments

First, we solve the system in Eqs.(23)-(31) by the method of lines. For numerical purposes we take the following constants and parameters from [4,6,7]. $D_1 = D_2 = D_3 = 0.00025, \alpha_1 = 0.1, \alpha_2 = 2, \alpha_3 = 0.15, \alpha_4 = 1, \beta_1 = 10, \beta_2 = 0.1, \beta_3 = 0.5, \beta_4 = 1, \gamma_1 = 1, \gamma_2 = 1, \gamma_3 = 1, \gamma_4 = 1, n = 16, A = 28 \times 10^7, B = 0.22 \times 10^9$. We first code the input data as global variables and we code the system Eqs.(23)-(31) as a m-file called "fparabolic". Then, we use the form [t,y]=ode45('fparabolic', tspan, init) to obtain the solution. Here, "ode45" is an ODE solver which is built up in Matlab, "fparabolic" is a function m file we have just described above, "tspan" is the desired time vector which we want the solution for, and "init" is the initial condition vector. Also, "t" is the same as tspan and "y" is the solution vector of the system. The first M elements of y give EC concentration, the second M elements of y give PC concentration and the third M elements of y give MC concentration (see Section 5.1 for Matlab codes). These concentrations are shown in Figs. 4-7, respectively. Furthermore, the importance of these concentrations in the initiation of angiogenesis is explained in Conclusions.

Second, we test the signs of the real parts of the eigenvalues of the matrix S for the system in Eqs.(23)-(31) (see Section 5.2 for the construction of the matrix S in Matlab). We do this by assuming $F'(x) \approx 0$, $G'(x) \approx 0$, $H'(x) \approx 0$ for small x, and taking $M = 21, 23, 25, 27, 29, 31, 41$, and 45, respectively. When $M = 21, 23, 25, 27, 29, 31$ we observe that the real parts of the eigenvalues of S are negative (see Table 1), and thus all of the solutions of our system are stable for large time levels [12]. Figs. 4-6 are some snapshots taken at $t = 10, 110, 210, 310, 410, 510, 610$ and $t = 710$. This is a strong evidence that all of the solutions of our system are stable for all time levels. But, when $M = 41$ and $M = 45$ we see that the real parts of two of the eigenvalues of S are positive (see Table 1), which means that every solution of our system is unstable. As it is clear from the Fig.7 that the stability changes to unstability around $t = 589$. As users may remember the ODE solver "ode45" which is built up in Matlab chooses its time step "k" automatically. One of the reason we get unstability for $M = 45$ as time increases may be the violation of the CFL condition

$$\frac{D_i k}{h^2} \leq \frac{1}{2}, \quad (i = 1, 2, 3),$$

where D_i are the diffusion constants and $h = 1/(M-1)$. As M increases one has to take k very small to meet the CFL condition since D_i are fixed constants. Therefore, the CFL condition is a severe restriction on time step.

The other reason for the unstability for $M = 45$ case could be the rounding errors in our computations. Although rounding errors can excite an unstability, more often it is discretisation errors that do so.

Fig.7 would have looked the same even if the computations had been carried out by using stiff ODE solvers built up in Matlab such as ode15s, ode23s.

Of course, a fully implicit or the Crank-Nicolson method can be used to address the unstability for most of the problems in PDEs. Although there is no restriction on time step for both methods, they require more work at each time step. Especially the Crank-Nicolson method is unconditionally stable.

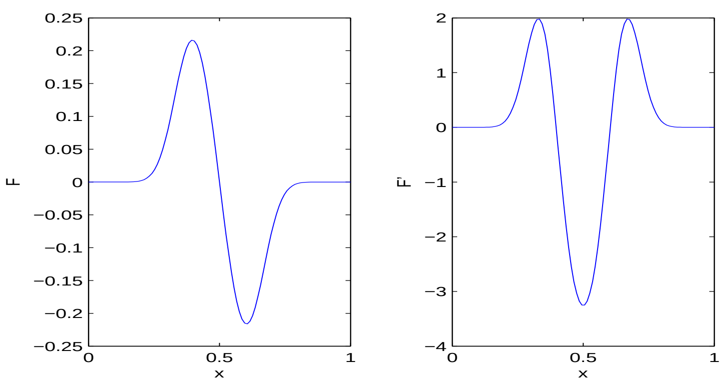

FIGURE 1. $F(x) = \frac{f'(x)}{f(x)}$ and $F'(x)$.

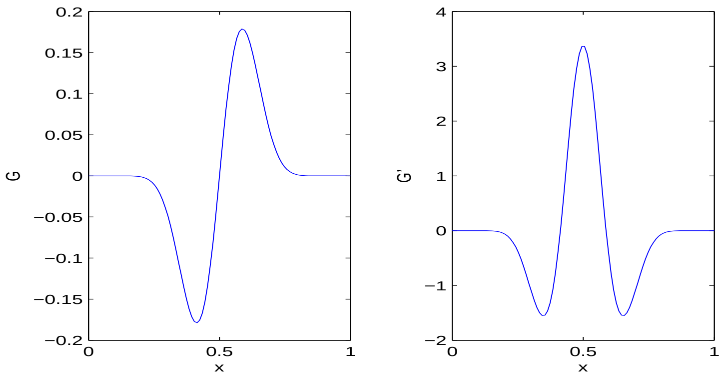

FIGURE 2. $G(x) = \frac{g'(x)}{g(x)}$ and $G'(x)$.

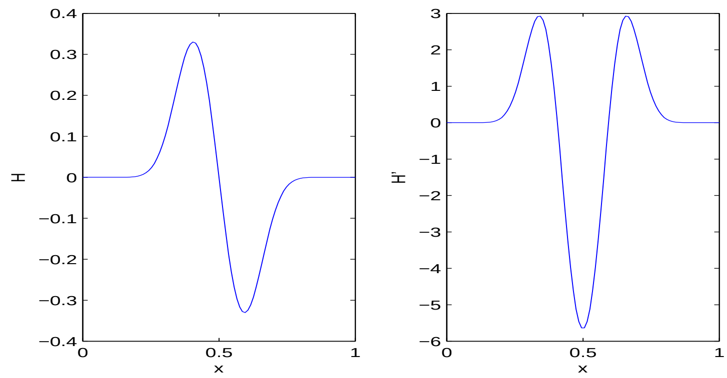

FIGURE 3. $H(x) = \frac{r'(x)}{r(x)}$ and $H'(x)$.

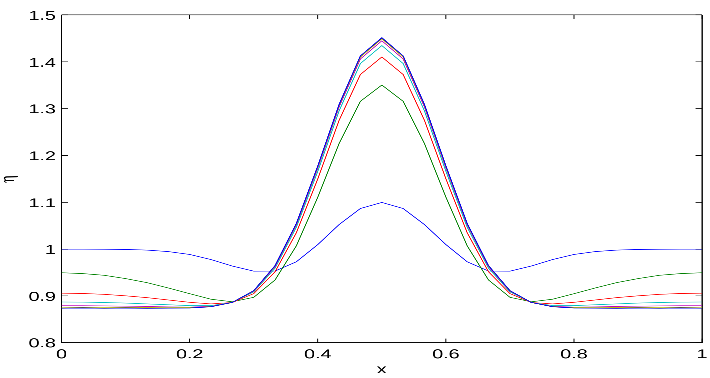

FIGURE 4. EC Concentration $\eta(x, t)$ with $M = 31$.

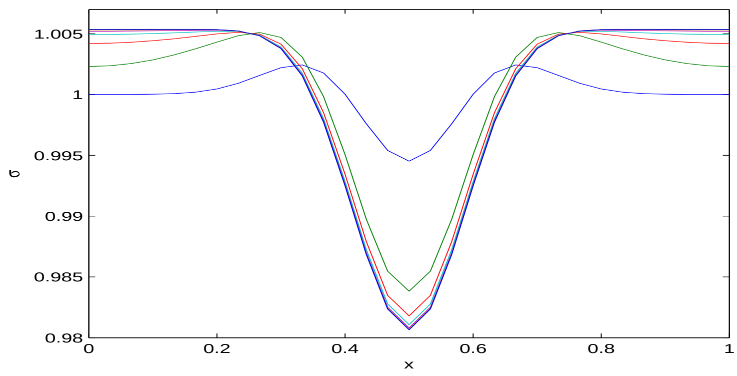

FIGURE 5. PC Concentration $\sigma(x,t)$ with $M = 31$.

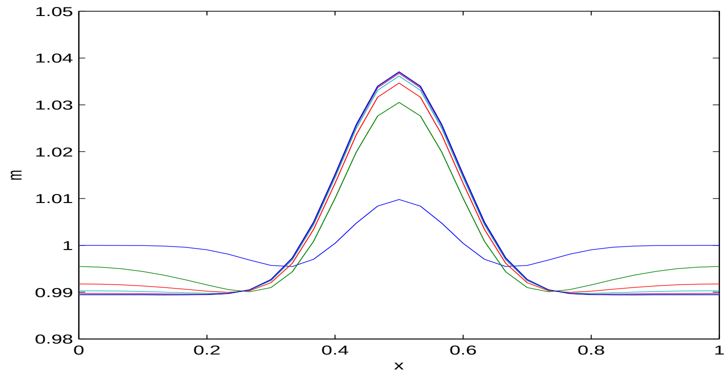

FIGURE 6. MC Concentration $m(x,t)$ with $M = 31$.

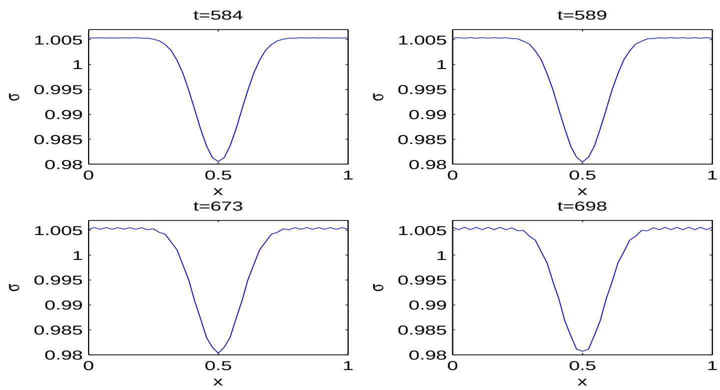

FIGURE 7. PC Concentration $\sigma(x,t)$ with $M = 45$.

M=21	M=23	M=25	M=27	M=29	M=31	M=41	M=45
-0.2000	-0.2420	-0.2880	-0.3380	-0.3920	-0.4500	-0.8000	-0.9680
-0.2000	-0.2420	-0.2880	-0.3380	-0.3920	-0.4500	-0.8000	-0.9680
-0.2000	-0.2420	-0.2880	-0.3380	-0.3920	-0.4500	-0.8000	-0.9680
-0.2000	-0.2420	-0.2880	-0.3380	-0.3920	-0.4500	-0.8000	-0.9680
-0.2000	-0.2420	-0.2880	-0.3380	-0.3920	-0.4500	-0.8000	-0.9680
-0.2000	-0.2420	-0.2880	-0.3380	-0.3920	-0.4500	-0.8000	-0.9680
-0.2000	-0.2420	-0.2880	-0.3380	-0.3920	-0.4500	-0.8000	-0.9680
-0.2000	-0.2420	-0.2880	-0.3380	-0.3920	-0.4500	-0.8000	-0.9680
-0.2000	-0.2420	-0.2880	-0.3380	-0.3920	-0.4500	-0.8000	-0.9680
-0.2000	-0.2420	-0.2880	-0.3380	-0.3920	-0.4500	-0.8000	-0.9680
-0.2000	-0.2420	-0.2880	-0.3380	-0.3920	-0.4500	-0.8000	-0.9680
-0.2000	-0.2420	-0.2880	-0.3380	-0.3920	-0.4500	-0.8000	-0.9680
-0.2000	-0.2420	-0.2880	-0.3380	-0.3920	-0.4500	-0.8000	-0.9680
-0.2000	-0.2420	-0.2880	-0.3380	-0.3920	-0.4500	-0.8000	-0.9680
-0.2000	-0.2420	-0.2880	-0.3380	-0.3920	-0.4500	-0.8000	-0.9680
-0.2000	-0.2420	-0.2880	-0.3380	-0.3920	-0.4500	-0.8000	-0.9680
-0.2000	-0.2420	-0.2880	-0.3380	-0.3920	-0.4500	-0.8000	-0.9680
-0.2000	-0.2420	-0.2880	-0.3380	-0.3920	-0.4500	-0.8000	-0.9680
-0.2000	-0.2420	-0.2880	-0.3380	-0.3920	-0.4500	-0.8000	-0.9680
-0.0000	-0.2420	-0.2880	-0.3380	-0.3920	-0.4500	-0.8000	-0.9680
-0.0030	-0.2420	-0.2880	-0.3380	-0.3920	-0.4500	-0.8000	-0.9680
-0.0087	-0.4840	-0.2880	-0.3380	-0.3920	-0.4500	-0.8000	-0.9680
-0.0231	-0.4810	-0.2880	-0.3380	-0.3920	-0.4500	-0.8000	-0.9680
-0.0379	-0.4753	-0.0000	-0.3380	-0.3920	-0.4500	-0.8000	-0.9680
-0.0827	-0.4608	-0.0030	-0.3380	-0.3920	-0.4500	-0.8000	-0.9680
-0.0587	-0.4459	-0.0087	-0.6760	-0.3920	-0.4500	-0.8000	-0.9680
-0.1092	-0.4247	-0.0233	-0.6730	-0.3920	-0.4500	-0.8000	-0.9680
-0.1383	-0.4002	-0.0383	-0.6673	-0.0000	-0.4500	-0.8000	-0.9680
-0.1687	-0.3728	-0.0597	-0.6527	-0.0030	-0.4500	-0.8000	-0.9680
-0.2313	-0.3425	-0.1127	-0.0000	-0.0234	-0.9000	-0.8000	-0.9680
-0.4000	-0.3101	-0.0846	-0.0030	-0.0385	-0.8970	-0.8000	-0.9680
-0.3970	-0.2764	-0.1441	-0.0087	-0.0858	-0.8766	-0.8000	-0.9680
-0.3913	-0.0000	-0.1779	-0.6376	-0.1149	-0.8614	-0.8000	-0.9680
-0.3769	-0.0030	-0.2135	-0.0600	-0.1477	-0.0000	-0.8000	-0.9680
-0.3621	-0.0087	-0.2504	-0.0384	-0.7840	-0.0030	-0.8000	-0.9680
-0.2617	-0.0232	-0.3256	-0.0853	-0.7810	-0.0234	-0.8000	-0.9680
-0.2908	-0.0381	-0.3625	-0.6160	-0.7606	-0.0386	-0.8000	-0.9680
-0.3173	-0.0593	-0.5760	-0.1139	-0.7753	-0.8395	-0.8000	-0.9680
-0.3413	-0.0838	-0.5730	-0.3787	-0.7455	-0.4970	-0.8000	-0.9680
-0.0586	-0.1112	-0.5673	-0.2973	-0.2220	-0.4030	-1.6000	-0.9680
-0.3414	-0.1415	-0.5527	-0.5907	-0.2626	-0.6330	-1.5970	-0.9680
-0.2000	-0.1739	-0.5377	-0.1461	-0.5214	-0.5890	-1.5913	-0.9680
-0.0000	-0.2076	-0.3981	-0.2572	-0.5620	-0.2670	-1.5765	-0.9680
-0.0025	-0.4131	-0.5163	-0.4188	-0.6982	-0.3110	-1.5611	-1.9360

M=21	M=23	M=25	M=27	M=29	M=31	M=41	M=45
-0.0097	-0.0709	-0.4319	-0.5299	-0.3481	-0.0605	-1.5389	-1.9330
-0.0219	-0.2420	-0.4633	-0.4578	-0.4359	-0.6749	-1.5125	-1.9273
-0.0381	-0.0000	-0.4914	-0.5621	-0.1835	-0.2251	-1.4820	-1.9125
-0.0586	-0.0025	-0.0844	-0.1810	-0.0602	-0.7510	-1.4471	-1.8971
-0.0824	-0.0097	-0.2880	-0.2182	-0.6005	-0.7843	-1.4082	-1.8748
-0.1092	-0.0220	-0.4916	-0.4950	-0.0087	-0.1490	-1.3194	-1.8482
-0.1382	-0.0384	-0.5760	-0.0233	-0.6363	-0.1157	-1.1061	-1.8175
-0.1687	-0.0591	-0.5735	-0.5770	-0.7238	-0.8138	-1.1631	-1.7822
-0.2000	-0.0835	-0.5663	-0.3380	-0.3048	-0.0862	-1.0472	-1.7428
-0.2313	-0.1112	-0.5540	-0.0990	-0.4792	-0.3565	-0.9251	-1.6994
-0.2618	-0.1415	-0.5375	-0.6760	-0.6691	-0.5435	-0.8628	-1.6018
-0.2908	-0.1738	-0.5165	-0.6735	-0.6692	-0.1856	0.0000	-1.5480
-0.3176	-0.2076	-0.4916	-0.6663	-0.3920	-0.7144	-0.0030	-1.4912
-0.4000	-0.2420	-0.4633	-0.6539	-0.1148	-0.0087	-0.4939	-1.4318
-0.3975	-0.2764	-0.4320	-0.6373	-0.7840	-0.8913	-0.5528	-1.3701
-0.3903	-0.3102	-0.3982	-0.6162	-0.7815	-0.7682	-0.4369	-1.3062
-0.3781	-0.3425	-0.3625	-0.5910	-0.7743	-0.1318	-0.0087	-1.2407
-0.3619	-0.3728	-0.3256	-0.5621	-0.7619	-0.4500	-0.0611	-1.1737
-0.3414	-0.4840	-0.2880	-0.4579	-0.7452	-0.9000	-0.0389	-1.1057
	-0.4815	-0.2504	-0.4189	-0.7239	-0.8975	-1.2701	-1.0370
	-0.4743	-0.2135	-0.4951	-0.6985	-0.8903	-0.0875	-0.8990
	-0.4620	-0.1778	-0.3787	-0.0000	-0.8779	-0.6749	-0.8303
	-0.4456	-0.1440	-0.2973	-0.6692	-0.8612	-0.3821	-0.7623
	-0.4005	-0.1127	-0.2571	-0.4359	-0.8397	-1.3656	-0.6953
	-0.4249	-0.0000	-0.2181	-0.6364	-0.8141	-0.1918	-0.6298
		-0.0025	-0.1809	-0.5621	-0.7511	-0.1180	-0.5659
		-0.0097	-0.1139	-0.5215	-0.7145	-0.1529	-0.5042
		-0.0220	-0.0000	-0.4792	-0.7844	-1.2179	0.0000
		-0.0385	-0.0025	-0.3481	-0.0000	-0.0235	-0.0030
		-0.0595	-0.0850	-0.3048	-0.6330	-0.2806	-0.0087
		-0.0844	-0.0097	-0.2219	-0.4970	-0.7372	-0.0235
			-0.0387	-0.2625	-0.5436	-0.9867	-0.0389
			-0.0598	-0.6006	-0.4030	-0.6133	-0.0612
			-0.5300	-0.1148	-0.3564	-0.3299	-0.0878
			-0.0221	-0.0097	-0.6750	-0.2344	-0.1185
			-0.1460	-0.0221	-0.2670	-1.3657	-0.1538
			-0.3380	-0.0601	-0.5891	-0.8000	-0.1932
				-0.1476	-0.1855	-0.2343	-0.4448
				-0.0855	-0.0221	-1.6000	-0.2366
				-0.1834	-0.0097	-1.5975	-0.3880
				-0.0388	-0.3109	-1.5903	-0.3342
				-0.0025	-0.0859	-1.5778	-1.6524
				-0.3920	-0.2250	-1.5609	-0.2836
					-0.1489	-1.5391	-1.6525
					-0.0603	-1.5128	-0.9680
					-0.0025	-1.4821	-0.2835

M=21	M=23	M=25	M=27	M=29	M=31	M=41	M=45
					-0.1156	-1.4472	0.0000
					-0.0388	-1.3657	-0.0025
					-0.4500	-1.3196	-0.0097
						-1.2702	-0.0222
						-1.1632	-0.0391
						-0.8628	-0.0610
						-0.9251	-0.0875
						-1.1061	-0.1184
						-0.7372	-0.1537
						-0.9868	-0.1931
						-0.6749	-0.2364
						0.0000	-0.2835
						-0.6132	-0.3341
						-0.4939	-0.3879
						-0.4368	-0.4447
						-0.0025	-0.5041
						-0.3298	-0.5659
						-0.1179	-0.6297
						-0.0391	-0.6953
						-0.0222	-0.7622
						-0.1528	-0.8302
						-0.2804	-0.8989
						-0.2343	-0.9680
						-0.0872	-1.0371
						-1.0472	-1.1058
						-1.2180	-1.1738
						-0.5528	-1.2407
						-0.0609	-1.3063
						-0.3820	-1.3701
						-1.4083	-1.4319
						-0.0097	-1.4913
						-0.1917	-1.5481
						-0.8000	-1.6019
							-1.9360
							-1.9335
							-1.9263
							-1.9138
							-1.8969
							-1.8750
							-1.8485
							-1.8176
							-1.7823
							-1.7429
							-1.6996
							-1.6525

Table 1: Real Parts of the Eigenvalues of the Matrix S for some Values of M

5. Conclusions

In this paper we have presented the MOL for the numerical solution of a mathematical model for the roles of EC, PC and MC in the initiation of tumor angiogenesis. This method does not require large computer memory, and avoids linearization and physically unrealistic assumptions. As the number of lines increases, the accuracy of the MOL representation increases. This method is also applicable to non-linear systems of PDEs. In Figs. 4-6, we have plotted the EC, PC and MC concentrations for large times. Notice that pericyte aggregation in the opening in the capillary wall is low where the EC and MC concentrations are high and conversely. In particular, the maximum of PC density is higher closer to the wall of the forming capillary than is the maximum of EC density [4]. These are consistent with the observations of [8] that the PC closely regulate the development of the forming channel.

We have also showed that when $M = 21, 23, 25, 27, 29, 31$ all of the solutions of our system obtained from the discretisation of the space variable x are stable. This a strong evidence that all of the solutions are stable for all time levels as it is clear from the Figs. 4-6. To show the stability of the solutions, we have obtained (in Table 1) the negativity of the real parts of the eigenvalues of the matrix (namely S) consisting of the first order partial derivatives of the discretised vectoral function with respect to the unknown variables, evaluated at a constant steady state solution.

When we increase M we have faced that the real parts of two of the eigenvalues of the matrix S are positive, which means that every solution of our system is unstable. For example, when $M = 45$ the stability changes to unstability around $t = 589$ as it is clear from the Fig. 7, which may be caused by the violation of the CFL condition.

We have also presented our Matlab codes in the Appendix A and B below, which may enlighten young researchers to learn one of the numerical methods to solve PDEs or systems of PDEs.

6. Appendix A

Matlab codes for the method of lines

```
%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%
function z=fparabolic(t,w)
global h M
alpha1=0.1; alpha2=2; alpha3=0.15; alpha4=1; beta1=10; beta2=0.1; beta3=0.5; beta4=1;
gama1=1;
gama2=1; gama3=1; gama4=1; D1=0.00025; D2=0.00025; D3=0.00025; n=16;
A=28*10^7; B=0.22*10^9;
eta=w(1:M); sigma=w(M+1:2*M); m=w(2*M+1:3*M);
h=1./(M-1);
%%%%%%%%%%%%%% F,G,H functions%%%%%%%%%%%%%%
for i=1:M
x(i)=(i-1)*h; % the vector x
end
F0=gama1*(alpha2-alpha1)*A*n*(-h-h^2)^(n-1)*(1+2*h)/...
((alpha1+A*(-h-h^2)^n)*(alpha2+A*(-h-h^2)^n))+...
gama2*(beta1-beta2)*B*n*(-h-h^2)^(n-1)*(1+2*h)/...
((beta1+1-B*(-h-h^2)^n)*(beta2+1-B*(-h-h^2)^n));          % F(x) at x=0
G0=gama3*(alpha3-alpha4)*B*n*(-h-h^2)^(n-1)*(1+2*h)/...
((alpha3+1-B*(-h-h^2)^n)*(alpha4+1-B*(-h-h^2)^n));          % G(x) at x=0
H0=gama4*(beta4-beta3)*A*n*(-h-h^2)^(n-1)*(1+2*h)/...
((beta3+A*(-h-h^2)^n)*(beta4+A*(-h-h^2)^n));          % H(x) at x=0
for i=1:M
F(i)=gama1*(alpha2-alpha1)*A*n*(x(i)-x(i)^2)^(n-1)*(1-2*x(i))/...
((alpha1+A*(x(i)-x(i)^2)^n)*(alpha2+A*(x(i)-x(i)^2)^n))+...
```

```
gama2*(beta1-beta2)*B*n*(x(i)-x(i)^2)^(n-1)*(1-2*x(i))/...
((beta1+1-B*(x(i)-x(i)^2)^n)*(beta2+1-B*(x(i)-x(i)^2)^n)); % F(x) in the interval 0<x<1
G(i)=gama3*(alpha3-alpha4)*A*n*(x(i)-x(i)^2)^(n-1)*(1-2*x(i))/...
((alpha3+1-A*(x(i)-x(i)^2)^n)*(alpha4+1-A*(x(i)-x(i)^2)^n)); % G(x) in the interval 0<x<1
H(i)=gama4*(beta4-beta3)*B*n*(x(i)-x(i)^2)^(n-1)*(1-2*x(i))/...
((beta3+B*(x(i)-x(i)^2)^n)*(beta4+B*(x(i)-x(i)^2)^n)); % H(x) in the interval 0<x<1
end
F(M+1)=gama1*(alpha2-alpha1)*A*n*(M*h-(M*h)^2)^(n-1)*(1-2*M*h)/...
((alpha1+A*(M*h-(M*h)^2)^n)*(alpha2+A*(M*h-(M*h)^2)^n))+...
gama2*(beta1-beta2)*B*n*(M*h-(M*h)^2)^(n-1)*(1-2*M*h)/...
((beta1+1-B*(M*h-(M*h)^2)^n)*(beta2+1-B*(M*h-(M*h)^2)^n)); % F(x) at x=1
G(M+1)=gama3*(alpha3-alpha4)*A*n*(M*h-(M*h)^2)^(n-1)*(1-2*M*h)/...
((alpha3+1-A*(M*h-(M*h)^2)^n)*(alpha4+1-A*(M*h-(M*h)^2)^n)); % G(x) at x=1
H(M+1)=gama4*(beta4-beta3)*B*n*(M*h-(M*h)^2)^(n-1)*(1-2*M*h)/...
((beta3+B*(M*h-(M*h)^2)^n)*(beta4+B*(M*h-(M*h)^2)^n)); % H(x) at x=1
%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%
z(1)=D1*((2*eta(2)-2*eta(1)-2*h*eta(1)*F(1))/h^2-...
(eta(2)*F(2)-(eta(2)-2*h*eta(1)*F(1))*F0)/(2*h)); % gives Eq. (23)
z(M+1)=D2*((2*sigma(2)-2*sigma(1)-2*h*sigma(1)*G(1))/h^2-...
(sigma(2)*G(2)-(sigma(2)-2*h*sigma(1)*G(1))*G0)/(2*h)); % gives Eq. (26)
z(2*M+1)=D3*((2*m(2)-2*m(1)-2*h*m(1)*H(1))/h^2-...
(m(2)*H(2)-(m(2)-2*h*m(1)*H(1))*H0)/(2*h)); % gives Eq. (29)
for i=2:M-1;
z(i)=D1*((eta(i+1)-2*eta(i)+eta(i-1))/h^2-...
(eta(i+1)*F(i+1)-eta(i-1)*F(i-1))/(2*h)); % gives Eq. (24)
z(M+i)=D2*((sigma(i+1)-2*sigma(i)+sigma(i-1))/h^2-...
(sigma(i+1)*G(i+1)-sigma(i-1)*G(i-1))/(2*h)); % gives Eq. (27)
z(2*M+i)=D3*((m(i+1)-2*m(i)+m(i-1))/h^2-...
(m(i+1)*H(i+1)-m(i-1)*H(i-1))/(2*h)); % gives Eq. (30)
end
z(M)=D1*((2*h*eta(M)*F(M)-2*eta(M)+2*eta(M-1))/h^2-...
((eta(M-1)+2*h*F(M)*eta(M))*F(M+1)-eta(M-1)*F(M-1))/(2*h)); % gives Eq. (25)
z(2*M)=D2*((2*h*sigma(M)*G(M)-2*sigma(M)+2*sigma(M-1))/h^2-...
((sigma(M-1)+2*h*G(M)*sigma(M))*G(M+1)-sigma(M-1)*G(M-1))/(2*h)); % gives Eq. (28)
z(3*M)=D3*((2*h*m(M)*H(M)-2*m(M)+2*m(M-1))/h^2-...
((m(M-1)+2*h*H(M)*m(M))*H(M+1)-m(M-1)*H(M-1))/(2*h)); % gives Eq. (31)
z=z';
%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%
clc;clear all; global h M;
h=1/(M-1); %M=31,45
tf=751;% final time
x=linspace(0,1,M);
tspan=0:1:751;
for i=1:M;
eta0(i)=1;sigma0(i)=1;m0(i)=1;
end
```

```
init=[eta0 sigma0 m0];
init=init';
[t,y]=ode45('fparabolic',tspan,init);          % solver that is built up in Matlab
eta=y(:,1:M); sigma=y(:,M+1:2*M); m=y(:,2*M+1:3*M);
  figure;        % gives Fig.4
plot(x,eta(11:100:750,:)); xlabel('x'); ylabel('η');
figure;        % gives Fig.5
plot(x,sigma(11:100:750,:));axis([0 1 0.98 1.007]); xlabel('x'); ylabel('σ');
figure;       % gives Fig.6
plot(x,m(11:100:750,:));
xlabel('x'); ylabel('m')
figure;        % gives Fig.7
tt=[585 590 674 699];
for i=1:4
subplot(2,2,i); plot(x,sigma(tt(i),:));axis([0 1 0.98 1.007]); xlabel('x'); ylabel('σ');
title(['t=',num2str(tt(i)-1)]);
end
```

7. Appendix B

Matlab codes for the construction of the stability matrix S

```
%%%%%%%%%%%%%%%%%% S matrix%%%%%%%%%%%%%%%%%%%%%%%
% All of the constants and functions in the following code are the same as in chapter
5.1.
S=zeros(3*M,3*M);
S(1,1)=-D1*(2*(1+h*F(1))/h^2+F0*F(1));
S(1,2)=D1*(2/h^2-F(2)/(2*h)+F0/(2*h));
for i=2:M-1
S(i,i-1)=D1*(1/h^2+F(i-1)/(2*h));
S(i,i)=-2*D1/h^2;
S(i,i+1)=D1*(1/h^2-F(i+1)/(2*h));
end
S(M,M-1)=D1*(2/h^2+F(M-1)/(2*h)-F(M+1)/(2*h));
S(M,M)=D1*((2*h*F(M)-2)/h^2-F(M)*F(M+1));
S(M+1,M+1)=-D2*(2*(1+h*G(1))/h^2+G0*G(1));
S(M+1,M+2)=D2*(2/h^2-G(2)/(2*h)+G0/(2*h));
for i=2:M-1
S(M+i,M+i-1)=D2*(1/h^2+G(i-1)/(2*h));
S(M+i,M+i)=-2*D2/h^2;
S(M+i,M+i-1)=D2*(1/h^2-G(i+1)/(2*h));
end
S(2*M,2*M-1)=D2*(2/h^2+G(M-1)/(2*h)-G(M+1)/(2*h));
S(2*M,2*M)=D2*((2*h*G(M)-2)/h^2-G(M)*G(M+1));
S(2*M+1,2*M+1)=-D3*(2*(1+h*H(1))/h^2+H0*H(1));
S(2*M+1,2*M+2)=D3*(2/h^2-H(2)/(2*h)+H0/(2*h));
for i=2:M-1
S(2*M+i,2*M+i-1)=D3*(1/h^2+H(i-1)/(2*h));
S(2*M+i,2*M+i)=-2*D3/h^2;
S(2*M+i,2*M+i+1)=D3*(1/h^2-H(i+1)/(2*h));
end
```

```
S(3*M,3*M-1)=D3*(2/h^2+H(M-1)/(2*h)-H(M+1)/(2*h));
S(3*M,3*M)=D3*((2*h*H(M)-2)/h^2-H(M)*H(M+1));
S;                %The Matrix S
D=real(eig(S));          %The Real Parts of the Matrix S
```

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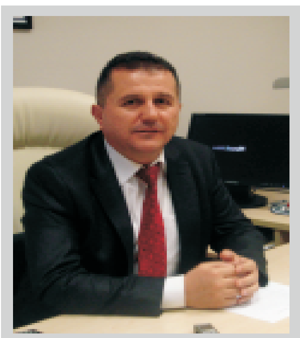

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