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A numerical analysis of a model of growth tumor

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Abstract

In this paper we study a free boundary problem modeling the growth of tumors. The model uses the conventional ideas of nutrient diffusion and consumption by the cells. We consider the radially symmetric case of this free boundary problem. We apply a spectral numerical method to the system of equations.

Keywords: Growth tumor; Spectral method

1. Introduction and preliminaries

A variety of PDE for tumor growth have been developed in the last decades. Some models are based on reaction–diffusion equations [4,5]. Other models include hyperbolic equations, we refer to [1–3,6]. In [3] the authors have studied a particular model with three cells populations: proliferating cells, quiescent cells and dead cells. This model includes densities P, Q, and D of proliferating,

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quiescent and dead (necrotic) cell respectively, and concentration C of nutrients (generally oxygen). These densities satisfy a system of nonlinear first order hyperbolic equations in the tumor, with tumor surface as a free boundary. The cells in different states are assumed to be mixed within the tumor, and to have the same size. They assumed that the tumor is uniformly packed with cells, so that

$$P + Q + D = \text{const} \equiv N.$$

Due to proliferation of cells and to removal of necrotic cells, there is a continuous movement of cells within the tumor and that the field velocity $\vec{v}$ satisfies the Darcy's law. They treat the tumor tissue as a porous medium, that is

$$\vec{v} = \nabla\sigma, \quad \sigma \text{ pressure.}$$

In this model they assume that

- $\overline{K}_Q(C)$ is increasing in C (rate of change from proliferating state to quiescent state).
- $\overline{K}_P(C)$ is decreasing in C (rate of change from quiescent state to proliferating state).
- $\overline{K}_D(C)$ is decreasing in C (quiescent cells become necrotic at a rate $\overline{K}_D(C)$).
- $\overline{K}_A(C)$ is decreasing in C (the death rate by apoptosis).
- $\overline{K}_B(C)$ is increasing in C (the proliferation rate).
- $\overline{K}_B(C) > \overline{K}_A(C)$.
- K_R is a positive constant (the rate of removal of dead cells).

The concentration C satisfies the next diffusion equation

$$\nabla^2 C - \lambda C = 0 \text{ en } \Omega(t) \ (\lambda > 0),$$
$$C = C_0 \text{ sobre } \partial\Omega(t),$$

where Ω is the tumor region at time t.

The densities P, Q and D satisfies the following system:

$$\frac{\partial P}{\partial t} + \operatorname{div}(Pv) = [\overline{K}_B(C) - \overline{K}_Q(C) - \overline{K}_A(C)]P + K_P(C)Q,$$

$$\frac{\partial Q}{\partial t} + \operatorname{div}(Qv) = \overline{K}_Q(C)P - [\overline{K}_P(C) + \overline{K}_D(C)]Q,$$

$$\frac{\partial D}{\partial t} + \operatorname{div}(Dv) = \overline{K}_A(C)P + \overline{K}_D(C)Q - \overline{K}_R D.$$

If we add the last equations then we obtain an equation for the pressure σ

$$N\nabla^2\sigma = \overline{K}_B(C)P - K_R D.$$

Now, we set

$$\bar{c} = C/C_0, \quad \bar{p} = P/N, \quad \bar{q} = Q/N,$$

we arrive at the following system of equations:

$$\begin{aligned}
&\nabla^2\bar{c} - \lambda\bar{c} = 0 \quad \text{in } \Omega(t),\\
&\bar{c} = 1 \quad \text{on } \partial\Omega(t),\\
&\frac{\partial\bar{p}}{\partial t} + \operatorname{div}(\bar{p}\nabla\sigma) = [K_B(\bar{c}) - K_Q(\bar{c}) - K_A(\bar{c})]\bar{p} + K_P(\bar{c})\bar{q} \quad \text{in } \Omega(t),\\
&\frac{\partial\bar{q}}{\partial t} + \operatorname{div}(\bar{q}\nabla\sigma) = K_Q(\bar{c})\bar{p} - [K_P(\bar{c}) - K_D(\bar{c})]\bar{q} \quad \text{in } \Omega(t),\\
&\nabla^2\sigma = -K_R + [K_B(\bar{c}) + K_R]\bar{p} + K_R\bar{q} \quad \text{in } \Omega(t),
\end{aligned}$$

where

$$K_i(\bar{c}) = \overline{K_i}(C_0\bar{c}) \quad \text{for } i = A, B, D, P, Q.$$

The pressure σ on the surface of the tumor is equal to the surface tension, that is

$$\sigma = \gamma\kappa \quad \text{on } \partial\Omega(t) \quad (\gamma > 0),$$

where κ is the mean curvature. The motion of the free boundary is given by the continuity equation

$$\vec{v}\cdot\vec{n} = V_n, \quad \text{or} \quad \frac{\partial\sigma}{\partial\vec{n}} = V_n \quad \text{on } \partial\Omega(t),$$

where $\vec{n}$ is the outward normal and V_n is the velocity of the free boundary of the free boundary in the outward normal direction. Given initial conditions

$$\Omega(0), \quad p(x,0), \quad q(x,0),$$

we would like to determine the family of domains $\Omega(t)$ and the functions $p(x,t)$, $q(x,t)$, $c(x,t)$ and $\sigma(x,t)$ satisfying the last system.

2. The radial model and its properties

We note that tumors grown in vitro are typically of spherical shape, which makes the study of radially symmetric solutions quite relevant. The radially symmetric case of the the general model is given by the following equations system:

$$\frac{1}{r^2}\frac{\partial}{\partial r}\left(r^2\frac{\partial\bar{c}}{\partial r}\right) = \lambda\bar{c} \quad (0 < r < R(t),\ t > 0),$$

$$\frac{\partial\bar{c}}{\partial r}(0,t) = 0, \quad \bar{c}(R(t),t) = 1 \quad (t > 0),$$

$$\frac{\partial \bar{p}}{\partial t} + \bar{u}\frac{\partial \bar{p}}{\partial r} = [K_B(\bar{c}) - K_Q(\bar{c}) - K_A(\bar{c})]\bar{p} + K_P(\bar{c})\bar{q} - [(K_B(\bar{c} + K_R)\bar{p} + K_R\bar{q} - K_R]\bar{p} \quad (0 \leqslant r \leqslant R(t),\ t > 0),$$

$$\frac{\partial \bar{q}}{\partial t} + \bar{u}\frac{\partial \bar{q}}{\partial r} = K_Q(\bar{c})\bar{p} - [K_P(\bar{c}) + K_D(\bar{c})]\bar{q} - [(K_B(\bar{c}) + K_R)\bar{p} + K_R\bar{q} - K_R]\bar{q} \quad (0 \leqslant r \leqslant R(t),\ t > 0),$$

$$\frac{1}{r^2}\frac{\partial}{\partial r}(r^2\bar{u}) = [K_B(\bar{c}) + K_R]\bar{p} + K_R\bar{q} - K_R,$$

$$\bar{u}(0,t) = 0 \quad (t > 0),$$

$$\frac{\mathrm{d}R(t)}{\mathrm{d}t} = \bar{u}(R(t),t) \quad (t > 0),$$

with initial data

$$R(0), \quad \bar{p}(r,0), \quad \bar{q}(r,0).$$

To transform the above free boundary problem in a problem with fixed boundary we first note that, for $R(t)$ given $\bar{c}(r,t)$ is given by

$$\bar{c}(r,t) = \frac{R(t)\sinh(\sqrt{\lambda}r)}{r\sinh(\sqrt{\lambda}R(t))} = c\left(\frac{r}{R(t)}, R(t)\right),$$

where

$$\frac{\partial p}{\partial t} + v\frac{\partial p}{\partial r} = [K_B(c) - K_Q(c) - K_A(c)]p + K_P(c)q - [(K_B(c) + K_R)p + K_Rq - K_R]p \quad (0 \leqslant r \leqslant 1,\ t > 0),$$

$$\frac{\partial q}{\partial t} + v\frac{\partial q}{\partial r} = K_Q(c)p - [K_P(c) + K_D(c)]q - [(K_B(c) + K_R)p + K_Rq - K_R]q \quad (0 \leqslant r \leqslant 1,\ t > 0),$$

$$v(r,t) = u(r,t) - ru(1,t) \quad (0 \leqslant r \leqslant 1,\ t > 0),$$

$$\frac{1}{r^2}\frac{\partial}{\partial r}(r^2u) = [K_B(c) + K_R]p + K_Rq - K_R \quad (0 \leqslant r \leqslant 1,\ t > 0),$$

$$u(0,t) = 0 \quad (t > 0),$$

$$\frac{\mathrm{d}R(t)}{\mathrm{d}t} = R(t)u(1,t) \quad (t > 0),$$

with initial data

$$R(0) = R_0, \quad p(r,0) = p_0(r), \quad q(r,0) = q_0(r),$$

where

$$R_0 > 0, \quad p_0(r) \geqslant 0, \quad q_0(r) \geqslant 0, \quad p_0(r) + q_0(r) \leqslant 1, \quad (0 \leqslant r \leqslant 1).$$

In [3] the authors show that the last system has a unique solution for $0 \leqslant r \leqslant 1$, $0 \leqslant t > \infty$, and it has the following properties:

1. $p(r,t) \geqslant 0$, $q(r,t) \geqslant 0$, $p(r,t) + q(r,t) \leqslant 1$,
2. $R_0 e^{-\frac{1}{3}K_R t} \leqslant R(t) \leqslant R_0 e^{\frac{1}{3}K_B(1)t}$,
3. $\lim_{t\to\infty} R(t) = \infty$ if $K_R = 0$,
4. $\delta_0 \leqslant R(t) \leqslant M$ for all $t \geqslant 0$ if $0 < K_R < \infty$.

3. The numerical method

Spectral methods are based in simple ideas of interpolation [7], we use these ideas for the numerical method. We give a description of our numerical scheme for the problem with fixed boundary. Let $r_i = \frac{i}{N+1}$ for $0 < i \leqslant N+1$ be a partition of the interval $[0,1]$ into subintervals $I_i = [r_i, r_{i+1}]$, of length $h = \frac{1}{N+1}$. First, we consider the following matrix:

$$D^r_{ij} = \frac{1}{a_j} \prod_{k=1}^{N+1} (r_i - r_k) = \frac{a_i}{a_j(r_i - r_j)} \quad (i \neq j)$$

and

$$D^r_{ii} = \sum_{k=1}^{N+1} (r_j - r_k)^{-1},$$

where

$$a_j = \prod_{k=1}^{N+1} (r_i - r_j).$$

We use the following notation

$$P = (P_j(t))_j = (p(r_j,t))_j,$$
$$Q = (Q_j(t))_j = (q(r_j,t))_j,$$
$$U = (U_j(t))_j = (u(r_j,t))_j,$$
$$V_j(t) = V_j(t) = U_j(t) - U_{N+1}(t),$$

where $(\cdot)_j$ is a vector with j components. We approximate

$$D^r P \approx \left(\frac{\partial p}{\partial r}(r_j,t)\right)_j,$$

$$D^r Q \approx \left(\frac{\partial q}{\partial r}(r_j,t)\right)_j.$$

Now, we consider the following approximations

$$\frac{\partial p}{\partial t}(r_j,t) + v(r_j,t)\frac{\partial p}{\partial r}(r_j,t) \approx \left[\frac{\mathrm{d}P}{\mathrm{d}t} + \mathrm{diag}(V_j)D^r P\right]_j,$$

where $[\cdot]_j$ denote the j-component of the vector $(\cdot)_j$.

$$\frac{\partial q}{\partial t}(r_j,t) + v(r_j,t)\frac{\partial q}{\partial r}(r_j,t) \approx \left[\frac{\mathrm{d}Q}{\mathrm{d}t} + \mathrm{diag}(V_j)D^r Q\right]_j,$$

$$\frac{1}{r^2}\frac{\partial}{\partial r}(r^2 u)(r_j,t) \approx \left[\mathrm{diag}\left(\frac{1}{r_k^2}\right)D^r r_j^2 U\right]_j.$$

We remark that $K_i(c) = K_i(r,R)$ for $i = A,B,P,Q,D$.

We define the following matrices:

$$M_1(R) = \mathrm{diag}(K_B(r_j,R) - K_Q(r_j,R) - K_A(r_j,R)),$$
$$M_2(R) = \mathrm{diag}(K_P(r_j,R)),$$
$$M_3(R) = \mathrm{diag}(K_B(r_j,R) + K_R),$$
$$M_4(R) = \mathrm{diag}(K_Q(r_j,R)),$$
$$M_5(R) = \mathrm{diag}(K_P(r_j,R) + K_D(r_j,R)),$$

and the following vectors:

$$P^2(t) = (P_j^2(t))_j,$$
$$Q^2(t) = (Q_j^2(t))_j,$$
$$P.Q(t) = (P_j(t)Q_j(t))_j,$$
$$r^2 U(t) = (r_j^2 U_j(t))_j,$$
$$\mathbf{1} = (1)_j.$$

We have the following approximations

$$\frac{\mathrm{d}P}{\mathrm{d}t} + \mathrm{diag}(V_j)D^r P = M_1 P + M_2 Q - M_3 P^2 - K_R PQ + K_R P,$$
$$\frac{\mathrm{d}Q}{\mathrm{d}t} + \mathrm{diag}(V_j)D^r Q = M_4 P - M_5 Q - M_3 PQ - K_R Q^2 - K_R Q,$$

$$\operatorname{diag}\left(\frac{1}{r_k^2}\right) D^r r^2 U = M_3 P + K_R Q - K_R \mathbf{1},$$

$$U = \operatorname{diag}\left(\frac{1}{r_j^2}\right) (D^r)^{-1} \operatorname{diag}(r_k^2)(M_3 P + K_R Q - K_R \mathbf{1}).$$

From the last equation, we can obtain the vector U as function of the P, Q and R. Then we can express $\operatorname{diag}(V_j)$ as function of P, Q, and R we obtain the following system of ordinary differential equations

$$\frac{\mathrm{d}P}{\mathrm{d}t} = \mathscr{F}_1(R, P, Q),$$
$$\frac{\mathrm{d}Q}{\mathrm{d}t} = \mathscr{F}_2(R, P, Q),$$
$$\frac{\mathrm{d}R}{\mathrm{d}t} = \mathscr{F}_3(R, P, Q),$$

with initial conditions

$$P(0) = (p(r_j, 0))_j = (p_0(r_j))_j,$$
$$Q(0) = (q(r_j, 0))_j = (q_0(r_j))_j,$$
$$R(0) = R_0.$$

If we define $W = [P \quad Q \quad R]^{\mathrm{t}}$ then we can use the following notation

$$\frac{\mathrm{d}\mathscr{W}}{\mathrm{d}t} = \mathscr{F}(\mathscr{W}),$$
$$\mathscr{W}(0) = \mathscr{W}_0.$$

This system can be resolved by means the standard numerical methods for the ordinary differential equations.

4. Numerical examples

From [6], in this section we set the following values for the parameters of the problem:

1. $R(0) = 3$,
2. $\lambda = 0.05$,
3. $K_A(c) = 0$,
4. $K_P(c) = 0.05c$,
5. $K_Q(c) = -0.05(c + 1)$,
6. $K_D(c) = -c + 1$,
7. $K_B(c) = c$.

The parameters K_R and the functions $p_0(r)$ and $q_0(r)$ will be different in the examples. We set 10 points for the discretization of the interval [0, 1]. A Runge–Kutta method is used by integrate the ordinary differential equations.

Example 1. In this example, we consider several values for parameter K_R, we remark that

$$\lim_{t\to\infty} R(t) = \infty \quad \text{if } K_R = 0,$$

we set $p_0(r) = 0.3$ and $q_0(r) = 0.6$.

From Fig. 1 we can see that the solution is increasing with respect to K_R.

Example 2. Now $p_0(r) = \sin(\pi x/2(N-1))$ where $N = 10$ the number of points in [0, 1] for the discretization.

In Figs. 2 and 3 we show the behavior of the densities for different times.

Example 3. In the last example, the parameters are the same in Example 1, with $K_R = 1$. We remember that

$$R_0 e^{-\frac{1}{3}K_R t} \leqslant R(t) \leqslant R_0 e^{\frac{1}{3}K_B(1)t},$$

Fig. 4 shows that the analytic bounds are preserved by the numerical solution.

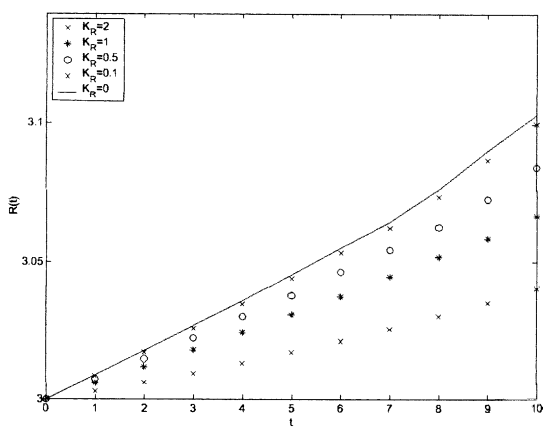

Fig. 1. $R(t)$ for several values of K_R.

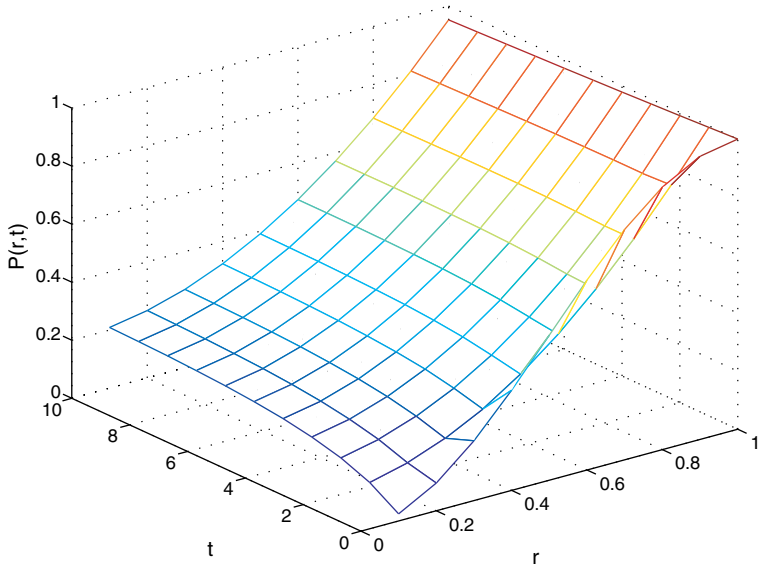

Fig. 2. $P(r,t)$ for different times.

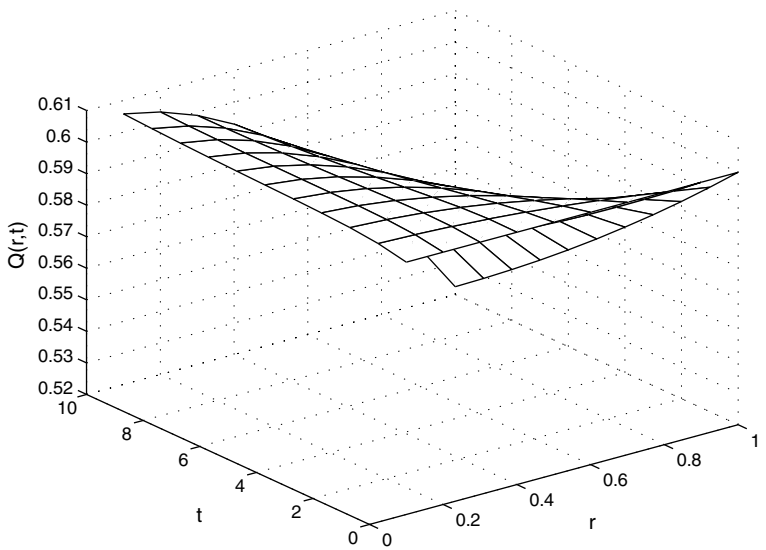

Fig. 3. $Q(r,t)$ for different times.

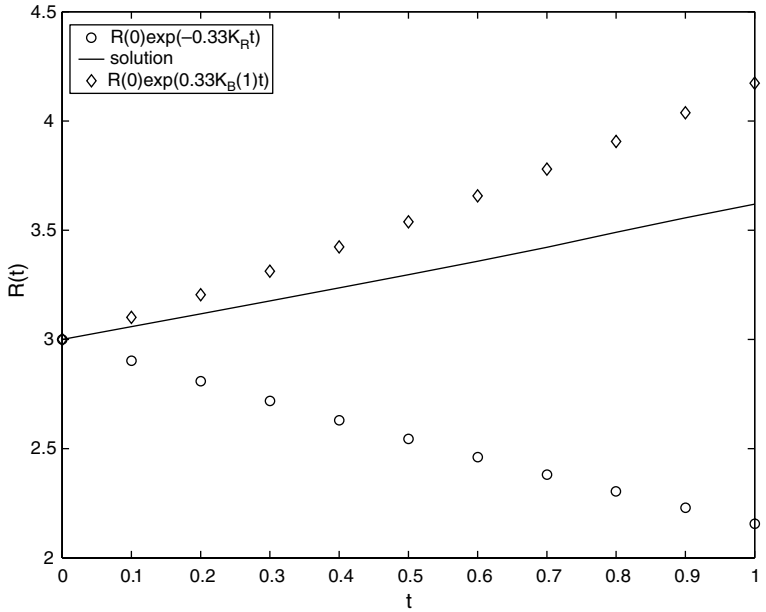

Fig. 4. $R(t)$, lower and upper bounds.

5. Conclusion

In this paper we have investigated the numerical solution of a model of tumor growth. An special approach of transforming a PDE system into a ODE system has been adopted, this approach is based in simple ideas of interpolation. The analytic properties of the solution are preserved for the numerical method.

References

[1] S. Cui, A. Friedman, Analysis of a mathematical model of the effect of inhibitors on the growth of tumors, Math Biosci. 164 (2000) 103–137.
[2] S. Cui, A. Friedman, Analysis of a mathematical model of the growth of necrotic tumors, J. Math. Anal. Appl. 255 (2001) 636–677.
[3] S. Cui, A. Friedman, A hyperbolic free boundary problem modeling tumor growth, Interf. Free Bound. 5 (2003) 159–181.
[4] J.A. Adam, A simplified mathematical model of tumor growth, Math. Biosci. 81 (1986) 224–229.
[5] H. Byrne, M. Chaplain, Free boundary value problems associated with growth and development of multicellular spheroids, Eur. J. Appl. Math. 8 (1997) 639–658.
[6] G. Pettet, C. Please, M. Tindall, D. McElwain, The migration of cells in multicell tumor spheroids, Bull. Math. Biol. 63 (2001) 231–257.
[7] L. Trefethen, Spectral Methods in Matlab, SIAM, Philadelphia, PA, 2000.