

Semi-Analytical Solution for the Multicell Spheroid model for Vascular Tumor Growth

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Abstract: The homotopy analysis method is used to obtain semi-analytic solutions for the mathematical model describing a solid tumor growth in the initial a vascular stage of growth. During a vascular tumor growth, the balance between cell proliferation and cell loss determines whether the colony expands or progress. We focus on the chemical inhibition of mitosis within multicell spheroids. The main assumption of modeling the diffusion of a growth inhibitory factor (GIF) within a multicell spheroid and its possible effects on cell mitosis and proliferation.

Keywords: Homotopy analysis method, Tumor growth

1 Introduction

A vascular tumor growth models studied extensively in the last three decade, see for example, ([5], [7], [8]). Mathematical model for a vascular tumor growth and development that spans three distinct scales; cellular level, subcellular level, extracellular level, for more details see ([1]-[4]). Although, almost all studies reach similar conclusions that a vascular tumor can only grow up to a limited size, the saturation mechanisms that are assured in different models are not same ([5]-[6]), depending on nutrients concentration tumor cells are supposed to be in one of the three stages; proliferating, resting or dead. While the tumor expands, the nutrient concentration at the center falls below critical level. The cell proliferation rate will be decrease which causes a slow growth rate. Eventually, these interior cells can die off, creating what is known as a necrotic core. Although a significant progress in modeling tumor has been achieved by now, most of these models are based on numerical approach. Hence, an approach other than numerical approach such as semi-exact solutions is needed

Recently, some principles of the physics and It is known that approximate analytical method such as Homotopy Analysis Method(HAM) which advised by Shi-Jun Liao in ([15]-[18]) has been successfully applied to solve many types of nonlinear problems in science and

engineering by many authors, see ([1], [13], [14], and the references cited therein). The aim in this work is to employ HAM for establish an infinite series solutions for the mathematical model describing a solid tumor growth in the initial a vascular stage, for more details on the HAM method for linear and nonlinear differential equations, see([11]-[12]), [15], ([27]-[28]), and the references cited therein. We can pointed out here that , HAM contains the auxiliary parameter \hbar , which provides us with a simple way to adjust and control the convergence region of solution series[18], moreover, the approximate solutions can be obtained using a few number of iterations ([27]-[28]).

2 Basic idea of HAM

Consider the following general differential equation:

$$F(u(t)) = 0, \quad (1)$$

where F is a nonlinear operator, $u(t)$ is an unknown function. For simplicity, we ignore all boundary and initial conditions, which can be treated in the similar ways in [12], [15], [17].

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2.1 Zeroth-order deformation equation

Liao ([15]-[18]), constructed the so-called zeroth-order deformation equation

$$(1-q)L[\Phi(t;q) - u_0(t)] = q\hbar F[\Phi(t;q)], \quad (2)$$

where L is an auxiliary linear operator, $u_0(t)$ is an initial guess, \hbar is an auxiliary parameter and $q \in [0, 1]$ is the embedding parameter. Obviously, when $q = 0$ and $q = 1$, it holds, respectively

$$\Phi(t;0) = u_0(t), \quad \Phi(t;1) = u(t). \quad (3)$$

Thus, as q increasing from 0 to 1, the solution $\Phi(t;q)$ varies from $u_0(t)$ to $u(t)$. Expanding $\Phi(t;q)$ in Taylor series with respect to the embedding parameter q , one has

$$\Phi(t;q) = u_0(t) + \sum_{m=1}^{\infty} u_m(t)q^m, \quad (4)$$

where

$$u_m(t) = \frac{1}{m!} \left. \frac{\partial^m \Phi(t;q)}{\partial q^m} \right|_{q=0}. \quad (5)$$

Assume that the auxiliary linear operator, the initial guess and the auxiliary parameter \hbar are selected such that the series (4) is convergent at $q = 1$, then at $q = 1$ and by (20), the series (4) becomes

$$u(t) = u_0(t) + \sum_{m=1}^{\infty} u_m(t). \quad (6)$$

2.2 The m th-order deformation equation

Define the vector

$$\mathbf{u}_n(t) = [u_0(t), u_1(t), \dots, u_n(t)]. \quad (7)$$

Differentiating equation (2) m times with respect to the embedding parameter q , then setting $q = 0$ and dividing them by $m!$, finally using (5), we have the so-called m th-order deformation equations

$$L[u_m(t) - \delta_m u_{m-1}(t)] = \hbar \mathfrak{R}_m(\mathbf{u}_{m-1}), \quad (8)$$

where

$$\mathfrak{R}_m(\mathbf{u}_{m-1}) = \frac{1}{(m-1)!} \left. \frac{\partial^{m-1} F[\Phi(t;q)]}{\partial q^{m-1}} \right|_{q=0}, \quad (9)$$

and

$$\delta_m = \begin{cases} 0, & m \leq 1; \\ 1, & m > 1. \end{cases} \quad (10)$$

3 Mathematical formulation

We formulate this model in mathematical equation which describe the diffusion, production and degradation of the growth inhibitory factor GIF ([6], [7]) within the spheroid, It can be written as,

$$\frac{\partial C}{\partial t} = D\nabla^2 C + f(C) + \lambda S(r) \quad (11)$$

where $C = C(r, t)$ is the concentration of GIF within the spheroid occupying the region R^3 and λ is the inhibitor production rate (molecules per unit volume per second). Shymko and Glass [22], and Adam [2] use the function $f(C) = -\gamma C$, where γ is the depletion rate or decay constant, various forms for the source function $S(r)$ have been used. In the original model in [22], the GIF is assumed to be produced at a constant rate throughout the tissue, yielding the uniform source function[7]:

$$S(r) = \begin{cases} 1 - \frac{r^2}{R^2}, & 0 \leq r \leq R; \\ 0, & r > R. \end{cases} \quad (12)$$

Then the model will be,

$$\frac{\partial C}{\partial t} = D\nabla^2 C - \gamma C + \lambda S(r), \quad r \in \Omega, \quad (13)$$

$$\frac{\partial C}{\partial r} = 0, \quad r = 0, \quad (14)$$

$$D(r) \frac{\partial C}{\partial r} + PC = 0 \quad \text{on} \quad \partial\Omega, \quad P > 0, \quad (15)$$

$$C(r, 0) = 0, \quad r \in \Omega. \quad (16)$$

Initially, we assume that production of GIF is via the uniform source function $S(r)$. Considering the spherical geometry described in the introduction and assuming radial symmetry, the above system reduces to

$$\frac{\partial C}{\partial t} = \frac{1}{r^2} \frac{\partial}{\partial r} (r^2 D \frac{\partial C}{\partial r}) - \gamma C + \lambda S(r), \quad r \leq R, \quad (17)$$

$$\frac{\partial C}{\partial r} = 0, \quad r = 0, \quad (18)$$

$$D(r) \frac{\partial C}{\partial r} + PC = 0 \quad \text{on} \quad r = R, \quad P > 0, \quad (19)$$

$$C(r, 0) = 0, \quad r = R^3. \quad (20)$$

Before continuing with an analysis of the above system, it is appropriate to recast them in terms of dimensionless variables. Denoting by R and t , the radius of the spheroid GIF concentration and as reference time. The system now becomes, upon dropping the tildes for notational convenience,

$$\frac{\partial C}{\partial t} = \frac{1}{r^2} \frac{\partial}{\partial r} (r^2 D \frac{\partial C}{\partial r}) - B^2 C + aB^2(1 - r^2), \quad r \leq R, \quad (21)$$

$$\frac{\partial C}{\partial r} = 0, \quad r = 0, \quad (22)$$

$$D(r) \frac{\partial C}{\partial r} + PC = 0 \quad \text{on } r = R, \quad P > 0, \quad (23)$$

$$C(r, 0) = 0, \quad r = R^3, \quad (24)$$

where $B = kR$, $k^2 = \frac{\gamma}{D}$, $a = \frac{\lambda}{\gamma\theta}$ and $\eta = \frac{\gamma D^{1/2}}{P}$. With this non-dimensionlisation, we see that once the parameters for a particular spheroid are determined, the only undetermined parameter is the radius R . the solutions to the above equation can therefore be monitored for different size of spheroids R . Let $r = x$ and using the transformation

$$u(x, t) = xC(x, t). \quad (25)$$

Then,

$$\begin{aligned} \frac{\partial u}{\partial x} &= C + x \frac{\partial C}{\partial x}, \\ \frac{\partial^2 u}{\partial x^2} &= 2 \frac{\partial C}{\partial x} + x \frac{\partial^2 C}{\partial x^2}, \\ \frac{\partial u}{\partial t} &= x \frac{\partial C}{\partial t}. \end{aligned} \quad (26)$$

Substitute (25)-(26) into(21), we claim

$$\frac{\partial u}{\partial t} = D \frac{\partial^2 u}{\partial x^2} - B^2 u + aB^2 x(1 - x^2), \quad (27)$$

subject to the initial conditions $u(x, 0) = 0$.

4 Method of solution

In this section, we apply HAM to obtain the approximate solution to the problem of vascular tumor growth. Consider above eqn(27).

$$\frac{\partial u}{\partial t} = D \frac{\partial^2 u}{\partial x^2} - B^2 u + aB^2 x(1 - x^2),$$

with initial conditions $u(x, 0) = 0$. By means of homotopy analysis method we choose the linear operator

$$L[\varphi(x, t; q)] = \frac{\partial \varphi(x, t; q)}{\partial t}, \quad (28)$$

where the operator L satisfies the relation $L[c] = 0$ for some arbitrary constant c also we define the non-linear operator as

$$N(\varphi(x, t; q)) = \frac{\partial \varphi(x, t; q)}{\partial t} - D \frac{\partial^2 \varphi(x, t; q)}{\partial x^2} \quad (29)$$

$$+ B^2 \varphi(x, t; q) - aB^2 x(1 - x^2), \quad (30)$$

we can construct the zeroth-order deformation equation in the form

$$(1 - q)L[\varphi(x, t; q) - u_0(x, t)] = q\hbar N(\varphi(x, t; q)). \quad (31)$$

Obviously when $q = 0$ and $q = 1$, we obtain $\varphi(x, t; 0) = u_0(x, t), \quad \varphi(x, t; 1) = u(x, t)$.

Therefore, as the embedding parameter q increases from 0 to 1, $\varphi(x, t; q)$ varies from the initial guess $u_0(x, t)$ to the solution $u(x, t)$. Expanding $\varphi(x, t; q)$ in Taylor series with respect to q

$$\varphi(x, t; q) = u_0(x, t) + \sum_{m=1}^{\infty} q^m u_m(x, t), \quad (32)$$

where

$$u_m(x, t) = \frac{1}{m!} \frac{\partial^m \varphi(x, t; q)}{\partial q^m} \Big|_{q=0}. \quad (33)$$

Now, we define the vector $u(x, t) = [u_0(x, t), u_1(x, t), \dots]$. The m th-order deformation equation is

$$L[u_m(x, t) - \delta_m u_{m-1}(x, t)] = \hbar R_m(\vec{u}_{m-1}), \quad (34)$$

with initial conditions $u_m(x, 0) = 0$, where

$$R_m(\vec{u}_{m-1}) = \frac{\partial u_{m-1}(x, t)}{\partial t} - D \frac{\partial^2 u_{m-1}(x, t)}{\partial x^2} \quad (35)$$

$$+ B^2 u_{m-1}(x, t) - aB^2 x(1 - x^2). \quad (36)$$

Now, the solution of the m th-order deformation equation becomes

$$u_m(x, t) = \delta_m u_{m-1}(x, t) + \hbar \int_0^t R_m(\vec{u}_{m-1}) dt, \quad (37)$$

then the approximate solution will take the following

$$u(x, t) = u_0(x, t) + u_1(x, t) + \dots \quad (38)$$

5 Existence and Convergence of HAM

To investigate the influence of \hbar on the convergence of the solution series given by HAM, we first plot the so-called \hbar -curve of $u(x, t)$. According to the \hbar -curve, it is easy to discover the valid region of \hbar at $-1.5 \leq \hbar \leq 2$ (see figure 1).

We use four terms in evaluating the approximate solution,

$$u_0(x, t) = aB^2 \hbar x(1 - x^2)t, \quad (39)$$

$$u_1(x, t) = -aB^2 \hbar^2 x(3D + \frac{B^2}{2}(1 - x^2))t^2 - (1 - x^2)t, \quad (40)$$

$$u_2(x, t) = aB^4 \hbar^3 x(2D + \frac{B^2}{6}(1 - x^2))t^3, \quad (41)$$

$$u_3(x, t) = -a \frac{B^6}{4} \hbar^4 (3D + \frac{B^2}{6}(1 - x^2))t^4. \quad (42)$$

It is noted that our approximate solutions converge at $(-2 \leq \hbar \leq 2)$ see figure 1. Figures 2 and 3 show the results for HAM for various values of R , which show the development of a spheroid from its early stages of growth

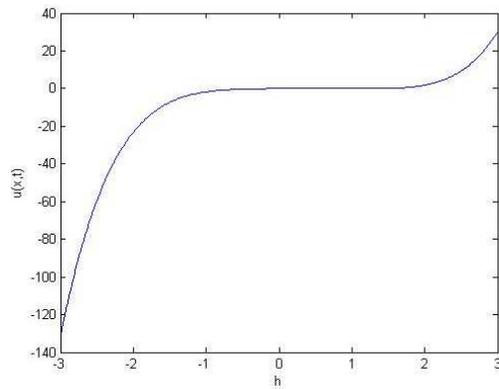


Fig. 1: \hbar curve of GIF at $t = 10$, $a = 76.764$, $D = 5 \times 10^{-7}$, $R = 0.02$, $\gamma = 5 \times 10^{-5}$.

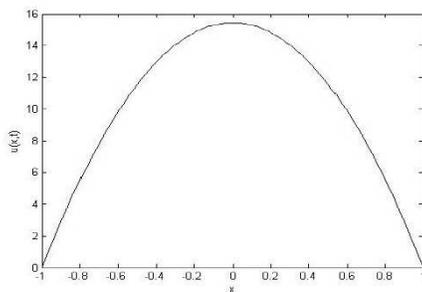


Fig. 2: Approximate solution of GIF for $\hbar = -1.5$, $t = 10$, $a = 76.764$, $D = 5 \times 10^{-7}$, $R = 0.02$, $\gamma = 5 \times 10^{-5}$.

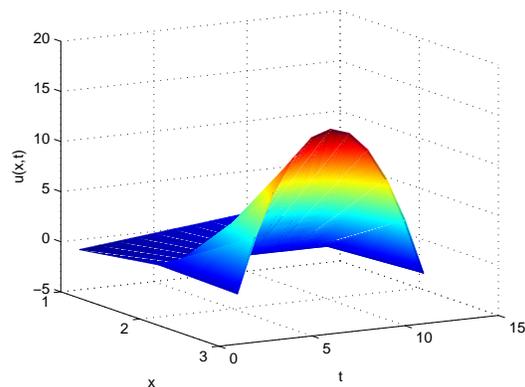


Fig. 3: Approximate solution of GIF in 3D for $\hbar = -1.5$, $a = 76.764$, $D = 5 \times 10^{-7}$, $R = 0.02$, $\gamma = 5 \times 10^{-5}$.

to its diffusion - limited size of a stable radius of 0.2 cm. Our results in agreement with [7] where the threshold value for the GIF concentration is $C = 1$. Thus if the concentration of GIF is greater than 1 in any region within the spheroid, then mitosis will be inhibited (necrotic core) to be distinguished. Fig 1 shows that the model predicts that the onset of necrosis occurs in the center of spheroids are ($C = 1$ at $r = 0$).

6 Conclusions

In this work, HAM is adapted to obtain series solutions with a high degree of accuracy for the nonlinear mathematical model describing a solid tumor growth in the initial a vascular stage of growth. No discretizations, linearization, small perturbations or restrictive assumption are needed when we apply this method.

It may be concluded that this methodology is very powerful and efficient technique in finding semi-exact solutions for wide classes of problems. It is also worth noting to point out that the advantage of this methodology shows a fast convergence of the solutions by means of the auxiliary parameter \hbar . We can conclude that HAM is easy to apply for both linear or nonlinear differential systems.

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