On the Numerical Solution of Mathematical Models of Cancer Growth and Optimal Cancer Therapy

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Abstract: - In the recent years, much mathematical research has been observed in the description of tumors' growth, in the early detection of cancer and in the optimization of cancer treatment planning. In this paper, the Crank-Nicolson method is proposed for the solution of different mathematical models of carcinogenesis and cancer therapy and a Genetic-Algorithms-based method for the optimal cancer therapy is also presented. First we intend to provide the Crank-Nicolson for a tumor-immune system interaction, which describes the early dynamics of cancerous cells, competing with the immune system, potentially leading to either the elimination of tumoral cells or to the viability of a solid tumor. Secondly we provide the Crank-Nicolson method for the brain tumors and a Genetic-Algorithms-based method for the optimal cancer therapy for the brain tumors is also presented.

Keywords: - Mathematical Models, Cancer Growth, Partial Differential Equations, Genetic Algorithms, Optimal Control, Optimal Cancer Therapy

1 Introduction

Recently, many mathematical research papers have been published in the description of tumors' growth, in the early detection of cancer and in the optimization of cancer treatment planning. The mathematical models on these papers are based on mass conservation laws and on the reaction-diffusion process for cell densities and nutrient concentration within the tumor. (see [18]÷[57]).

The growth and control of cancers have been the subject of medical and scientific scrutiny for a very long time (see [18]÷[57]). Roughly speaking a tumor, like most cancerous cells originates from a single cell, that proliferates and effects its neighboring normal tissues. As the tumor cells become malignant they become more dangerous for the host. The mathematical description of the mechanism of tumor progression seems to be useful for the cancer diagnosis and treatment. The paper [56] contains a short presentations related to the

mathematical modeling of Cancer. The paper [56] introduces a tumor-immune system interaction, which describes the early dynamics of cancerous cells, competing with the immune system, potentially leading to either the elimination of tumoral cells or to the viability of a solid tumor. In the present paper we propose the solution of this model with the Crank-Nicolson method. Similarly, in this paper we propose the Crank-Nicolson method of the model for drug delivery to brain tumor of [57]. Finally, a Genetic-Algorithms-based method for the optimal cancer therapy for both models is also presented.

2 Mathematical Models

As one can see in [56], At their early stage of growth, solid tumors are avascular. They do not need a blood network, being small enough to get nutrients mainly by tissue diffusion. However, their needs are proportional to their -growing- volume, while the feeding is proportional to the surface in contact with the host tissue. So, they rapidly reach a critical size for which the supply by diffusion is no more enough to continue developing. Then, avascular tumors sometimes turn into a dormant phase during which the growth stops, as a result of balance between proliferation and apoptosis -death- of cancer cells. Tumors which do not enter dormancy need ways alternative to diffusion. It is now well known that solid tumors use vascular supply. Tumor-associated neovascularization allows the tumor cells to express their critical growth advantage as reported by Saaristo et al [54]. The process by which solid tumors develop a vascular network is called angiogenesis. Angiogenesis is a complex process, a complete description of which is outside the scope of the present paper. Readers interested in fundamental basics, particularly in view of mathematical modeling could refer to the well documented review paper by Mantzaris, Webb and Othmer [51]. Most if not all of the above contributions use mathematical models of nonlinear parabolic reaction-diffusion type. These models are based on equations which express balance or conservation laws of physical relevant quantities like as blood cells or extracellular matrix densities. The full dynamics of the tumor growth are determined starting from given initial conditions. So, we start with the model [40] and [56]:

$$\frac{\partial n}{\partial t} = \nabla \delta (\nabla n) - x \nabla \left(\frac{n}{k+c} \nabla c \right) - \rho \nabla (n \nabla f) \quad (1)$$

$$\frac{\partial f}{\partial t} = w\,n - \mu\,n\,f \quad (2)$$

$$\frac{\partial c}{\partial t} = -\lambda\,n\,c \quad (3)$$

where n is the density of the blood vessels, f is the density of the matrix tissue, c : concentration of angiogenic factors. As one can see the term $\nabla d_n \nabla n$ expresses the random motility, $x \nabla \left(\frac{n}{k+c} \nabla C \right)$ expresses the so-called chemotaxis and the term $\rho \nabla (n \nabla f)$ is the haptotaxis.

Consider now the influence of a drug. Let us denote d the concentration of the drug, then this system will be modifies as follows

$$\frac{\partial n}{\partial t} = \nabla \delta (\nabla n) - x \nabla \left(\frac{n}{k+c} \nabla c \right) - \rho \nabla (n \nabla f) - m_1 d\,n$$
$$(1.1)$$

$$\frac{\partial f}{\partial t} = w\,n - \mu\,n\,f - m_2\,d\,f$$
$$(1.2)$$

$$\frac{\partial c}{\partial t} = -\lambda\,n\,c - m_3\,d\,c$$
$$(1.3)$$

$$\frac{\partial d}{\partial t} = \nabla \varepsilon (\nabla d) - \varepsilon_2 d + u$$
$$(1.4)$$

$k, \delta, c, x, \rho, w, \mu, \lambda, m_1, m_2, m_3, \varepsilon, \varepsilon_2$ represent appropriate functions and u is the appropriate input for the **drug.**

In the therapy of angiogenesis the objective functional is taken to be a quadratic form of running and terminal costs

$$J(d) = \frac{1}{2}\int_0^{t_f} dt \int_V dv \left(r_1 n^2(v,t) + s\,(d-d_0)^2(v,t)\right)$$
$$+ \int_V dv \left(r_1 n^2(v,t_f) + s_2\, d^2(v,t_f)\right)$$

(4)

Our goal is to minimize the functional with respect to the drug input rate $d(v,t)$

$v = (x_1, x_2, x_3) \in \Re^3$ our space vector of $\Re^3$

and t is the time (t_f is the final time of our therapy). r_1, s, s_2 represent appropriate positive constants.

Before proceeding we consider that for the case of

$$\frac{\partial}{\partial x} a\left(\frac{\partial}{\partial x}\phi\right) \approx \frac{\partial}{\partial x} a\left(\frac{\phi_i - \phi_{i-1}}{h}\right)$$
$$\approx a_{i+1}\left(\frac{\phi_{i+1} - \phi_i}{h^2}\right) - a_i\left(\frac{\phi_i - \phi_{i-1}}{h^2}\right)$$
$$= \frac{a_{i+1}\phi_{i+1} - a_{i+1}\phi_i - a_i\phi_i + a_i\phi_{i-1}}{h^2}$$

Or

$$\frac{\partial}{\partial x} a\left(\frac{\partial}{\partial x}\phi\right) \approx \frac{\partial}{\partial x} a\left(\frac{\phi_{i+1} - \phi_i}{h}\right)$$
$$\approx a_i\left(\frac{\phi_{i+1} - \phi_i}{h^2}\right) - a_{i-1}\left(\frac{\phi_i - \phi_{i-1}}{h^2}\right)$$
$$= \frac{a_i\phi_{i+1} - a_i\phi_i - a_{i-1}\phi_i + a_{i-1}\phi_{i-1}}{h^2}$$

It can be easily seen that we can consider

$$\frac{\partial}{\partial x} a\left(\frac{\partial}{\partial x}\phi\right) \approx$$
$$\approx \frac{a_{i+1}\phi_{i+1} - 2a_i\phi_i + a_{i-1}\phi_{i-1}}{h^2}$$

and this is a realistic approximation in our problem for biological quantities.

Therefore, a numerical scheme for the solution of (1.1), (1.2), (1.3) and (1.4) could be the following Crank-Nicolson numerical scheme:

1st **Finite Difference Equation:**

$$\frac{u_{i_1,i_2,i_3,j} - u_{i_1,i_2,i_3,j-1}}{k} =$$

$$\left(\frac{(\delta n)_{i_1+1,i_2,i_3,j} - 2(\delta n)_{i_1,i_2,i_3,j} + (\delta n)_{i_1-1,i_2,i_3,j}}{2h_1^2} + \right.$$

$$\left. \frac{(\delta n)_{i_1+1,i_2,i_3,j-1} - 2(\delta n)_{i_1,i_2,i_3,j-1} + (\delta n)_{i_1-1,i_2,i_3,j-1}}{2h_1^2}\right) +$$

$$\left(\frac{(\delta n)_{i_1,i_2+1,i_3,j} - 2(\delta n)_{i_1,i_2,i_3,j} + (\delta n)_{i_1,i_2-1,i_3,j}}{2h_2^2} + \right.$$

$$\left. \frac{(\delta n)_{i_1,i_2+1,i_3,j-1} - 2(\delta n)_{i_1,i_2,i_3,j-1} + (\delta n)_{i_1,i_2-1,i_3,j-1}}{2h_2^2}\right) +$$

$$\left(\frac{(\delta n)_{i_1,i_2,i_3+1,j} - 2(\delta n)_{i_1,i_2,i_3,j} + (\delta n)_{i_1,i_2,i_3-1,j}}{2h_3^2} + \right.$$

$$\left. \frac{(\delta n)_{i_1,i_2,i_3+1,j-1} - 2(\delta n)_{i_1,i_2,i_3,j-1} + (\delta n)_{i_1,i_2,i_3+1,j-1}}{2h_3^2}\right) +$$

$$\left(\frac{(x\frac{nc}{k+c})_{i_1+1,i_2,i_3,j} - 2(x\frac{nc}{k+c})_{i_1,i_2,i_3,j} + (x\frac{nc}{k+c})_{i_1-1,i_2,i_3,j}}{2h_1^2} + \right.$$

$$\frac{(x\frac{nc}{k+c})_{i_1+1,i_2,i_3,j-1} - 2(x\frac{nc}{k+c})_{i_1,i_2,i_3,j-1} + (x\frac{nc}{k+c})_{i_1-1,i_2,i_3,j-1}}{2h_1^2} \Bigg) +$$

$$\left(\frac{(x\frac{nc}{k+c})_{i_1,i_2+1,i_3,j} - 2(x\frac{nc}{k+c})_{i_1,i_2,i_3,j} + (x\frac{nc}{k+c})_{i_1,i_2-1,i_3,j}}{2h_2^2} + \right.$$

$$\frac{(x\frac{nc}{k+c})_{i_1,i_2+1,i_3,j-1} - 2(x\frac{nc}{k+c})_{i_1,i_2,i_3,j-1} + (x\frac{nc}{k+c})_{i_1,i_2-1,i_3,j-1}}{2h_2^2} \Bigg) +$$

$$\left(\frac{(x\frac{nc}{k+c})_{i_1,i_2,i_3+1,j} - 2(x\frac{nc}{k+c})_{i_1,i_2,i_3,j} + (x\frac{nc}{k+c})_{i_1,i_2,i_3-1,j}}{2h_3^2} + \right.$$

$$\frac{(x\frac{nc}{k+c})_{i_1,i_2,i_3+1,j-1} - 2(x\frac{nc}{k+c})_{i_1,i_2,i_3,j-1} + (x\frac{nc}{k+c})_{i_1,i_2,i_3-1,j-1}}{2h_3^2} \Bigg) +$$

$$\frac{(m_1 dn)_{i_1,i_2,i_3,j} + (m_1 dn)_{i_1,i_2,i_3,j-1}}{2}$$

(5.1)

2nd **Finite Difference Equation:**

$$\frac{f_{i_1,i_2,i_3,j} - f_{i_1,i_2,i_3,j-1}}{k} =$$

$$\frac{(wn - \mu n f - m_2 d f)_{i_1,i_2,i_3,j} + (wn - \mu n f - m_2 d f)_{i_1,i_2,i_3,j-1}}{2}$$

(5.2)

3rd **Finite Difference Equation:**

$$\frac{f_{i_1,i_2,i_3,j} - f_{i_1,i_2,i_3,j-1}}{k} =$$

$$\frac{(-\lambda n c - m_3 d c)_{i_1,i_2,i_3,j} + (-\lambda n c - m_3 d c)_{i_1,i_2,i_3,j-1}}{2}$$

(5.3)

4th **Finite Difference Equation:**

$$\frac{d_{i_1,i_2,i_3,j} - d_{i_1,i_2,i_3,j-1}}{k} =$$

$$\left(\frac{(\varepsilon d)_{i_1+1,i_2,i_3,j} - 2(\varepsilon d)_{i_1,i_2,i_3,j} + (\varepsilon d)_{i_1-1,i_2,i_3,j}}{2h_1^2} + \right.$$

$$\frac{(\delta n)_{i_1+1,i_2,i_3,j-1} - 2(\delta n)_{i_1,i_2,i_3,j-1} + (\delta n)_{i_1-1,i_2,i_3,j-1}}{2h_1^2} \Bigg) +$$

$$\left(\frac{(\varepsilon d)_{i_1,i_2+1,i_3,j} - 2(\varepsilon d)_{i_1,i_2,i_3,j} + (\varepsilon d)_{i_1,i_2-1,i_3,j}}{2h_2^2} + \right.$$

$$\left(\frac{(\rho n f)_{i_1+1,i_2,i_3,j} - 2(\rho n f)_{i_1,i_2,i_3,j} + (\rho n f)_{i_1-1,i_2,i_3,j}}{2h_1^2} + \right.$$

$$\frac{(\rho n f)_{i_1+1,i_2,i_3,j-1} - 2(\rho n f)_{i_1,i_2,i_3,j-1} + (\rho n f)_{i_1-1,i_2,i_3,j-1}}{2h_1^2} \Bigg) +$$

$$\left(\frac{(\rho n f)_{i_1,i_2+1,i_3,j} - 2(\rho n f)_{i_1,i_2,i_3,j} + (\rho n f)_{i_1,i_2-1,i_3,j}}{2h_2^2} + \right.$$

$$\frac{(\rho n f)_{i_1,i_2+1,i_3,j-1} - 2(\rho n f)_{i_1,i_2,i_3,j-1} + (\rho n f)_{i_1,i_2-1,i_3,j-1}}{2h_2^2} \Bigg) +$$

$$\left(\frac{(\rho n f)_{i_1,i_2,i_3+1,j} - (\rho n f)_{i_1,i_2,i_3,j} + (\rho n f)_{i_1,i_2,i_3-1,j}}{2h_3^2} + \right.$$

$$\frac{(\rho n f)_{i_1,i_2,i_3+1,j-1} - 2(\rho n f)_{i_1,i_2,i_3,j-1} + (\rho n f)_{i_1,i_2,i_3-1,j-1}}{2h_3^2} \Bigg) +$$

$$\left.\frac{(\varepsilon d)_{i_1,i_2+1,i_3,j-1} - 2(\varepsilon d)_{i_1,i_2,i_3,j-1} + (\varepsilon d)_{i_1,i_2-1,i_3,j-1}}{2h_2^2}\right) +$$

$$\left(\frac{(\varepsilon d)_{i_1,i_2,i_3+1,j} - 2(\varepsilon d)_{i_1,i_2,i_3,j} + (\varepsilon d)_{i_1,i_2,i_3-1,j}}{2h_3^2} + \right.$$

$$\left.\frac{(\varepsilon d)_{i_1,i_2,i_3+1,j-1} - 2(\varepsilon d)_{i_1,i_2,i_3,j-1} + (\varepsilon d)_{i_1,i_2,i_3+1,j-1}}{2h_3^2}\right) +$$

$$\frac{(-\varepsilon_2 d + u)_{i_1,i_2,i_3,j} + (-\varepsilon_2 d + u)_{i_1,i_2,i_3,j-1}}{2}$$

(5.4)

Now, we can solve via PC the system of **1st , 2nd, 3rd and 4th Finite Difference Equation:**
i.e. (5.1), (5.2) ,(5.3), (5.4)

In the therapy of angiogenesis, we have to find the appropriate input for the drug in order to minimize

$$J(d) = \frac{1}{2}\int_0^{t_f} dt \int_V dv\,(r_1 n^2(v,t) + s\,(u-u_0)^2(v,t)$$

$$+ \int_V dv\,(r_1 n^2(v,t_f) + s_2\,d^2(v,t_f))$$

(4)

Our goal is to minimize this functional with respect to the drug input rate $d(v,t)$

$v = (x_1, x_2, x_3) \in \Re^3$ our space vector of $\Re^3$

and t is the time (t_f is the final time of our therapy). r_1, s, s_2 represent appropriate positive constants.

What we must do is to find the appropriate input Before proceeding in the solution of the problem, some background on GA (Genetic Algorithms).

Fitness function is the objective function we want to minimize.

Population size specifies how many individuals there are in each generation. We can use various Fitness Scaling Options (rank, proportional, top, shift linear, etc), as well as various Selection Options (like Stochastic uniform, Remainder, Uniform, Roulette, Tournament). Fitness Scaling Options: We can use scaling functions. A Scaling function specifies the function that performs the scaling. A scaling function converts raw fitness scores returned by the fitness function to values in a range that is suitable for the selection function.

We have the following options:
Rank Scaling Option: scales the raw scores based on the rank of each individual, rather than its score. The rank of an individual is its position in the sorted scores. The rank of the fittest individual is 1, the next fittest is 2 and so on. Rank fitness scaling removes the effect of the spread of the raw scores.
Proportional Scaling Option: The Proportional Scaling makes the expectation proportional to the raw fitness score. This strategy has weaknesses when raw scores are not in a "good" range.
Top Scaling Option: The Top Scaling scales the individuals with the highest fitness values equally.

Shift linear Scaling Option: The shift linear scaling option scales the raw scores so that the expectation of the fittest individual is equal to a constant, which you can specify as Maximum survival rate, multiplied by the average score.
We can have also option in our Reproduction in order to determine how the genetic algorithm creates children at each new generation.
For example,
Elite Counter specifies the number of individuals that are guaranteed to survive to the next generation.
Crossover combines two individuals, or parents, to form a new individual, or child, for the next generation.
Crossover fraction specifies the fraction of the next generation, other than elite individuals, that are produced by crossover.
Scattered Crossover: Scattered Crossover creates a random binary vector. It then selects

the genes where the vector is a 1 from the first parent, and the genes where the vector is a 0 from the second parent, and combines the genes to form the child.

Mutation: Mutation makes small random changes in the individuals in the population, which provide genetic diversity and enable the GA to search a broader space. Gaussian Mutation: We call that the Mutation is Gaussian if the Mutation adds a random number to each vector entry of an individual. This random number is taken from a Gaussian distribution centered on zero. The variance of this distribution can be controlled with two parameters. The Scale parameter determines the variance at the first generation. The Shrink parameter controls how variance shrinks as generations go by. If the Shrink parameter is 0, the variance is constant. If the Shrink parameter is 1, the variance shrinks to 0 linearly as the last generation is reached.

Migration is the movement of individuals between subpopulations (the best individuals from one subpopulation replace the worst individuals in another subpopulation). We can control how migration occurs by the following three parameters.

Direction of Migration: Migration can take place in one direction or two. In the so-called "Forward migration" the nth subpopulation migrates into the (n+1)'th subpopulation. while in the so-called "Both directions Migration", the nth subpopulation migrates into both the (n-1)th and the (n+1)th subpopulation. Migration wraps at the ends of the subpopulations. That is, the last subpopulation migrates into the first, and the first may migrate into the last. To prevent wrapping, specify a subpopulation of size zero.

Fraction of Migration is the number of the individuals that we move between the subpopulations. So, Fraction of Migration is the fraction of the smaller of the two subpopulations that moves. If individuals migrate from a subpopulation of 50 individuals into a population of 100 individuals and Fraction is 0.1, 5 individuals (0.1 * 50) migrate. Individuals that migrate from one subpopulation to another are copied. They are not removed from the source subpopulation.

Interval of Migration counts how many generations pass between migrations.

After this preparation, we are ready to solve the

the mimization of

$$J(d) = \frac{1}{2} \int_0^{t_f} dt \int_V dv \, (r_1 n^2(v,t) + s \, (u - u_0)^2(v,t)$$

$$+ \int_V dv \, (r_1 n^2(v,t_f) + s_2 \, d^2(v,t_f)$$

We propose the following algorithm

Consider $u_{i_1,i_2,i_3,j} = \sum_{\kappa=0}^{MT} U * \delta(j - \kappa * T)$

Where the discrete delta function:
$$\delta(n) = \begin{cases} 1 & \text{for } n = 0 \\ 0 & \text{otherwise} \end{cases}$$

i.e. we consider that we grant the drug at a the time moments $0, T, 2T, ..., MT$ at constant and uniform doses U. So, we have only two unknowns: the dose U and our integer T.

With these two unknowns we construct our chromosome - vector x and

Population type:
Double Vector Population size: 30
Creation function: Uniform
Fitness scaling: Rank
Selection function: roulette
Reproduction: 6 – Crossover fraction 0.8
Mutation: Gaussian – Scale 1.0,
Shrink 1.0
Crossover: Scattered
Migration: Both – fraction 0.2, interval: 20
Stopping criteria: 50 generations

For every member of the population we run the

the Finite Differences System of (5.1), (5.2),(5.3), (5.4) and we compute $J(d)$. Then by applying our GA finally we find the optimum U and T.

Similarly consider the model of [57] with the notation of [57] we have:

$$\frac{\partial n_1}{\partial t} = \nabla^2(D_1 n_1) + a_1 n_1 g_1(n_1) - (a_{1,2}n_2 + \kappa_{1,3}c)\,n_1$$

$$\frac{\partial n_2}{\partial t} = \nabla^2(D_2 n_2) + a_2 n_2 g_2(n_2) - (a_{2,1}n_1 + \kappa_{2,3}c)\,n_2$$

$$\frac{\partial c_2}{\partial t} = \nabla^2(D_3 c) + a_3 c g_3(c) + u$$

n_1 is assumed to be the density of the tumor cells in the brain n_2 is the density of the normal cells. Other details can be found in [57]. Therefore, a numerical scheme for the solution of the previous 3 equations could be the following Crank-Nicolson numerical scheme:

$$\frac{(n_1)_{i_1,i_2,i_3,j} - (n_1)_{i_1,i_2,i_3,j-1}}{k} =$$

$$\left(\frac{(D_1n_1)_{i_1+1,i_2,i_3,j} - 2(D_1n_1)_{i_1,i_2,i_3,j} + (D_1n_1)_{i_1-1,i_2,i_3,j}}{2h_1^2} + \right.$$

$$\left. \frac{(D_1n_1)_{i_1+1,i_2,i_3,j-1} - 2(D_1n_1)_{i_1,i_2,i_3,j-1} + (D_1n_1)_{i_1-1,i_2,i_3,j-1}}{2h_1^2} \right) +$$

$$\left(\frac{(D_1n_1)_{i_1,i_2+1,i_3,j} - 2(D_1n_1)_{i_1,i_2,i_3,j} + (D_1n_1)_{i_1,i_2-1,i_3,j}}{2h_2^2} + \right.$$

$$\left. \frac{(D_1n_1)_{i_1,i_2+1,i_3,j-1} - 2(D_1n_1)_{i_1,i_2,i_3,j-1} + (D_1n_1)_{i_1,i_2-1,i_3,j-1}}{2h_2^2} \right) +$$

$$\left(\frac{(D_1n_1)_{i_1,i_2,i_3+1,j} - 2(D_1n_1)_{i_1,i_2,i_3,j} + (D_1n_1)_{i_1,i_2,i_3-1,j}}{2h_3^2} + \right.$$

$$\left. \frac{(D_1n_1)_{i_1,i_2,i_3+1,j-1} - 2(D_1n_1)_{i_1,i_2,i_3,j-1} + (D_1n_1)_{i_1,i_2,i_3+1,j-1}}{2h_3^2} \right) +$$

$$\frac{\left(a_1 n_1 g_1(n_1) - (a_{1,2}n_2 + \kappa_{1,3}c)\,n_1\right)_{i_1,i_2,i_3,j} + \left(a_1 n_1 g_1(n_1) - (a_{1,2}n_2 + \kappa_{1,3}c)\,n_1\right)_{i_1,i_2,i_3,j-1}}{2}$$

$$(6.1)$$

$$\frac{(n_2)_{i_1,i_2,i_3,j} - (n_2)_{i_1,i_2,i_3,j-1}}{k} =$$

$$\left(\frac{(D_2n_2)_{i_1+1,i_2,i_3,j} - 2(D_2n_{21})_{i_1,i_2,i_3,j} + (D_2n_2)_{i_1-1,i_2,i_3,j}}{2h_1^2} + \right.$$

$$\left. \frac{(D_2n_2)_{i_1+1,i_2,i_3,j-1} - 2(D_2n_2)_{i_1,i_2,i_3,j-1} + (D_2n_2)_{i_1-1,i_2,i_3,j-1}}{2h_1^2} \right) +$$

$$\left(\frac{(D_2n_2)_{i_1,i_2+1,i_3,j} - 2(D_2n_2)_{i_1,i_2,i_3,j} + (D_2n_2)_{i_1,i_2-1,i_3,j}}{2h_2^2} + \right.$$

$$\left. \frac{(D_2n_2)_{i_1,i_2+1,i_3,j-1} - 2(D_2n_2)_{i_1,i_2,i_3,j-1} + (D_2n_2)_{i_1,i_2-1,i_3,j-1}}{2h_2^2} \right) +$$

$$\left(\frac{(D_2n_2)_{i_1,i_2,i_3+1,j} - 2(D_2n_2)_{i_1,i_2,i_3,j} + (D_2n_2)_{i_1,i_2,i_3-1,j}}{2h_3^2} + \right.$$

$$\left. \frac{(D_2n_2)_{i_1,i_2,i_3+1,j-1} - 2(D_2n_2)_{i_1,i_2,i_3,j-1} + (D_2n_2)_{i_1,i_2,i_3+1,j-1}}{2h_3^2} \right) +$$

$$\frac{\left(a_2 n_2 g_2(n_2) - (a_{2,1}n_1 + \kappa_{2,3}c)\,n_2\right)_{i_1,i_2,i_3,j} + \left(a_2 n_2 g_2(n_2) - (a_{2,1}n_1 + \kappa_{2,3}c)\,n_2\right)_{i_1,i_2,i_3,j-1}}{2}$$

$$(6.2)$$

$$\frac{c_{i_1,i_2,i_3,j} - c_{i_1,i_2,i_3,j-1}}{k} =$$

$$\left(\frac{(D_3c)_{i_1+1,i_2,i_3,j} - 2(D_3c)_{i_1,i_2,i_3,j} + (D_3c)_{i_1-1,i_2,i_3,j}}{2h_1^2} + \right.$$

$$\left. \frac{(D_3c)_{i_1+1,i_2,i_3,j-1} - 2(D_3c)_{i_1,i_2,i_3,j-1} + (D_3c)_{i_1-1,i_2,i_3,j-1}}{2h_1^2} \right) +$$

$$\left(\frac{(D_3c)_{i_1,i_2+1,i_3,j} - 2(D_3c)_{i_1,i_2,i_3,j} + (D_3c)_{i_1,i_2-1,i_3,j}}{2h_2^2} + \right.$$

$$\left.\frac{(D_3c)_{i_1,i_2+1,i_3,j-1} - 2(D_3c)_{i_1,i_2,i_3,j-1} + (D_3c)_{i_1,i_2-1,i_3,j-1}}{2h_2^2}\right) +$$

$$\left(\frac{(D_3c)_{i_1,i_2,i_3+1,j} - 2(D_3c)_{i_1,i_2,i_3,j} + (D_3c)_{i_1,i_2,i_3-1,j}}{2h_3^2} + \right.$$

$$\left.\frac{(D_3c)_{i_1,i_2,i_3+1,j-1} - 2(D_3c)_{i_1,i_2,i_3,j-1} + (D_3c)_{i_1,i_2,i_3+1,j-1}}{2h_3^2}\right) +$$

$$\frac{(a_3cg_3(c)+u)_{i_1,i_2,i_3,j} + (a_3cg_3(c)+u_2)_{i_1,i_2,i_3,j-1}}{2}$$

where u is the input

After this preparation, we are ready to solve the

the mimization of

$$J(d) = \frac{1}{2}\int_0^{t_f} dt \int_V dv\,(r_1 n_1{}^2(v,t) + s\,(u-u_0)^2(v,t)$$
$$+ \int_V dv\,(q_1 n_1{}^2(v,t_f) + s_2\,c^2(v,t_f))$$

We propose the following algorithm

Consider $u_{i_1,i_2,i_3,j} = \sum_{\kappa=0}^{MT} U * \delta(j - \kappa * T)$

Where the discrete delta function:

$$\delta(n) = \begin{cases} 1 & for\ \ n = 0 \\ 0 & otherwise \end{cases}$$

i.e. we consider that we grant the drug at a the time moments $0, T, 2T, ..., MT$ at constant and uniform doses U. So, we have only two unknowns: the dose U and our integer T.

With these two unknowns we construct our chromosome - vector x and
Population type:
Double Vector Population size: 30
Creation function: Uniform
Fitness scaling: Rank
Selection function: roulette
Reproduction: 6 – Crossover fraction 0.8
Mutation: Gaussian – Scale 1.0,
Shrink 1.0
Crossover: Scattered
Migration: Both – fraction 0.2, interval: 20
Stopping criteria: 50 generations

For every member of the population we run the

the Finite Differences System of (5.1), (5.2),(5.3), (5.4) and we compute $J(d)$. Then by applying our GA finally we find the optimum U and T and roughly speaking our results agree with the following results of [57].
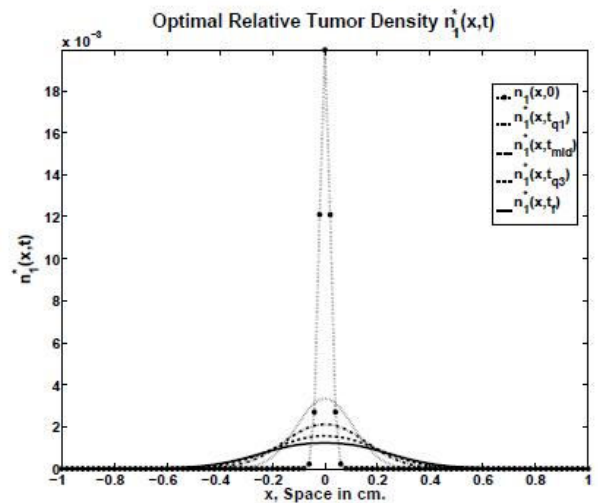
Tumor density versus the one-dimensional spatial coordinate x with time t at the rounded quartile values {0, tq1=0.25tf , tmid=0.5tf , tq3=0.75tf , tf}, where tf = 5 days. The targeted tumor density rapidly decays in this simulated 5 day trial. The Figure is from [57]

3 Conclusion

The Crank-Nicolson numerical scheme has been proposed for the solution of different mathematical models of cancer frowth and a Genetic-Algorithms-based method for the optimal cancer therapy is also briefly outlined.

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