KYUNGPOOK Math. J. 48(2008), 395-410

A Chemotherapy-Diffusion Model for the Cancer Treatment and Initial Dose Control

Hamdy Ibrahim Abdel-Gawad
Department of Mathematics, Faculty of Science, Cairo University, Egypt
e-mail : hamdyig@yahoo.com

Khaled Mmohamed Saad
Department of Mathematics, Faculty of Science, Taiz University, Yemen
e-mail : khaledma_sd@hotmail.com

Abstract. A one site chemotherapy agent-diffusion model is proposed which accounts for diffusion of chemotherapy agent, normal and cancer cells. It is shown that, by controlling the initial conditions, consequently an initial dose of the chemotherapy agent, the system is guaranteed to evolute towards a target equilibrium state. Or, growth of the normal cells occurs against decay of the cancer cells. Effects of diffusion of chemotherapy-agent and cells are investigated through numerical computations of the concentrations in square and triangular cancer sites.

1. Introduction

It is known in cancer treatment that when a chemotherapy is injected into the body, the effective agent attack the cancer as well as the normal cells. One of the objectives of the research in chemotherapy is to synthesize an agent which maximizes the effect on cancer cells but minimizes side effects [1]. Mathematical and computer modeling may be deterministic in this area. Different computer and optimization models have been proposed [2], [3]. Mathematical models accounting for dynamical treatment have been recently proposed in [4], [5], [6].

A two-site-model with metastasis had been very recently proposed in [7]. Spreading of cancer from one site to an another one had been treated. The proposed model is described by a set of differential equations that admit a large number of possible equilibrium states. In the one site model with chemical treatment, numerous equilibrium points also exist. In fact this number depends on the dimension of the space of parameters which ,for example,is twelve for the one site model. An important point to illustrate is select appropriate initial conditions so that a target equilibrium state is attained. That is for a specific equilibrium state we search if there exist initial conditions in $\Re^6$ (or in $\Re^3$) for two (one) sites model where

Received January 11, 2007.
2000 Mathematics Subject Classification: 37K99.
Key words and phrases: Chemotherapy cancer treatment, a diffusion model, initial dose control, an approach to solutions of coupled diffusion equations.

the solution evolutes asymptotically towards this state.The objective beyond this is that how to control (select) an initial dose-value in order that the concentration of the normal cells grows and that one of the cancer cells decays. Furthermore the effect of diffusivity is investigated.

2. The one site-diffusion model

The model proposed here is based on the main equations proposed in [7] but accounts for the diffusion of chemotherapy agent and migration of, normal and cancer cells. It is more appropriate in cases of leukemia [8]. In what follows u and v are the concentrations of the normal and cancer cells while w designates the concentration of the chemotherapy agent. Thus the model is given, by accounting for diffusion,as

$$u_t = D_1 u_{xx} + \alpha_1 u(1 - \frac{u}{k_1}) - q_1 uv - \frac{p_1 uw}{a_1 + u} \tag{2.1}$$

$$v_t = D_2 v_{xx} + \alpha_2 v(1 - \frac{v}{k_2}) - q_2 uv - \frac{p_2 vw}{a_2 + v} \tag{2.2}$$

$$w_t = D_3 w_{xx} + \triangle - (\xi + \frac{c_1 u}{a_1 + u} + \frac{c_2 v}{a_2 + v})w \quad in \quad \Omega = (-\infty, \infty) \times (0, T) \tag{2.3}$$

In the equation (2.1–2.3) the indices 1 and 2 correspond to the normal and cancer cells respectively, α_i are the generation rates of cells, k_i are the carrying capacities, q_i are the competitions coefficients between u and v, p_i are the predation coefficients of w on u and v, a_i designate the speeds at which u and v reach the carrying capacities in the absence of competitions and predation, c_i are the combination rates of the chemotherapy agent, Δ is the continuous infusion rate of the chemotherapy agent while ξ is the washout rate.
In (2.1–2.3) D_i, $i = 1, 2, 3$ are the diffusion coefficients of the normal, cancer (cells) and of the chemotherapy agent respectively.
This model is subjected to some conditions on the relevant parameters. As, it is well known that cancer cells grow much faster than the normal cells so that we take $\alpha_2 \gg \alpha_1$. Also, it is assumed that the chemotherapy is more destructive on cancer than on normal cells so that $p_1 << p_2$.

3. Initial dose control

Here, we consider the homogeneous model which is obtained by setting $D_i = 0$ in the equations (2.1–2.3) to get

$$u_t = \alpha_1 u(1 - \frac{u}{k_1}) - q_1 uv - \frac{p_1 uw}{a_1 + u} \tag{3.1}$$

$$v_t = \alpha_2 v(1 - \frac{v}{k_2}) - q_2 uv - \frac{p_2 vw}{a_2 + v} \tag{3.2}$$

$$w_t = \triangle - (\xi + \frac{c_1 u}{a_1 + u} + \frac{c_2 v}{a_2 + v})w \tag{3.3}$$

We remark that this system is a three-components system. In which the number of possible equilibrium states may be less or equal eight ones. But here for realistic values, we confine ourselves to the case where $u \geq 0$ and $v \geq 0$. We aim here to predict initial conditions in order that the system evolutes towards a target equilibrium state. In chemotherapy cancer treatment, the objective is to attain a steady state where cancer cells are destructed completely and the number of normal ones is maximized. Here, we show that an appropriate choice of the initial conditions guarantees a specific equilibrium state to hold. We proceed by the following theorem concerning the two-component system that is when $w = 0$ in (3.1–3.3)

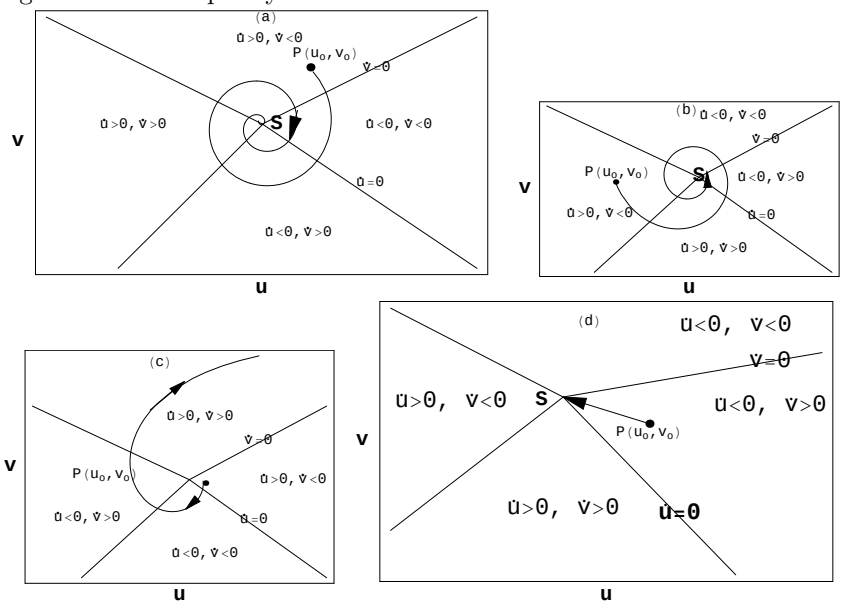
Theorem 3.1. *If $S = (u_e, v_e)$ is an equilibrium state which is a stable node for the two-component system, and $P = (u_o, v_o)$ is an initial condition such that $\dot{u}(0) > 0$ and $\dot{v}(0) < 0$ then S holds for $u_o < u_e$ and $v_o > v_e$.*

We sketch a proof to this theorem. As S is an equilibrium point then it holds for at least one initial values (u_o, v_o) which may satisfy the different permutations.

(a) $u_o > u_e, v_o > v_e$, (b)$u_o < u_e, v_o < v_e$, (c)$u_o > u_e, v_o < v_e$, and (d)$u_o < u_e, v_o > v_e$.

In any of the above four cases the assumption $\dot{u}(0) > 0$ and $\dot{v}(0) < 0$ is used. For simplicity it is shown diagrammatically (in figures 1a, b, c and d) that the cases $(i) - (iii)$ hold if S is a stable (unstable)spiral while the fourth one holds if S is a stable node.

In figure 1, the boundary curves (nullclines) between different regions are taken as straight lines for simplicity.



Figures 1 a, b, c and d. Illustrations of the different cases mentioned in Theorem (3.1). (a) Case of $u_o > u_e$ and $v_o > v_e$. (b) Case of $u_o < u_e$ and $v_o < v_e$. (c) Case of $u_o > u_e$ and $v_o < v_e$ (d) Case of $u_o < u_e$ and $v_o > v_e$. (u_e, v_e) is the conditions of the point S.

Now,we apply theorem 3.1 to the set of equations (3.1–3.3). We proceed to this by determining the equilibrium states and show that they are stable nodes. The equilibrium states are viewed in the $w = w_e$ plane, where w_e is obtained after setting the RHS of (3.3) equal zero and we get

$$w_e = \frac{\Delta}{\xi + \frac{c_1 u_e}{a_1 + u_e} + \frac{c_2 v_e}{a_2 + v_e}} \tag{3.4}$$

By substituting from w_e from (3.4) into (3.1) and (3.2), we find that the equilibrium points satisfy the equations

$$u_e(\alpha_1(1 - \frac{u_e}{k_1}) - q_1 v_e - \frac{p_1 \Delta}{(\xi(a_1 + u_e) + c_1 u_s + \frac{c_2 v_e (a_1 + u_e)}{a_2 + v_e})}) = 0 \tag{3.5}$$

$$v_e(\alpha_2(1 - \frac{u_e}{k_2}) - q_2 u_e - \frac{p_2 \Delta}{(\xi(a_2 + v_e) + c_2 v_e + \frac{c_1 u_e (a_2 + v_e)}{a_2 + u_e})}) = 0 \tag{3.6}$$

The equations (3.5) and (3.6) are solved for v_e in terms of u_e as

$$v_e = \frac{-B_1 \pm \sqrt{B_1^2 - 4A_1 C_1}}{2A_1} \quad or \quad u_e = 0, \tag{3.7}$$

$$v_e = \frac{-B_2 \pm \sqrt{B_2^2 - 4A_2 C_2}}{2A_2} \quad or \quad v_e = 0, \tag{3.8}$$

$$\begin{aligned} A_1 &= \lambda k_1 q_1, \ B_1 = (u_e - k_1)\alpha_1 \lambda + k_1(\Delta p_1 + \mu q_1), \\ C_1 &= a_2(u_e \alpha_1 \mu + k_1(\Delta p_1 a_2 - \mu \alpha_1)) \end{aligned} \tag{3.9}$$

$$\begin{aligned} A_2 = \lambda \alpha_2, \ \ B_2 = (\mu \alpha_2 + \lambda k_2(u_e q_2 - \alpha_2)), \\ C_2 = k_2(\Delta(u_e + a_1)p_2 + \mu \alpha_2(u_e q_2 - \alpha_2)) \end{aligned} \tag{3.10}$$

where $\lambda = (a_1 + u_e)(\xi + c_2 + c_1))$, $\mu = a_2(\xi(a_1 + u_e) + c_1 u_e)$. The results (3.7–3.10) are displayed for a class of possible numerical data where they can be classified in figures 2 and 3. After these figures, we find that the equilibrium states are only stable nodes. After theorem and these figures, the following corollary holds.

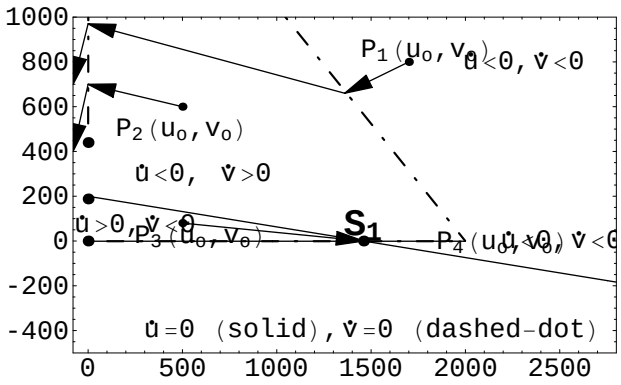


Figure 2. The equilibrium states for the parameter values $\alpha_1 = 1.5, \alpha_2 = 10, k_1 = 1460, k_2 = 2100, q_1 = 0.0075, q_2 = 0.005, p_1 = 0.0008, p_2 = 0.08, a_1 = 1, a_2 = 1, c_1 = 0.0024, c_2 = 0.24, \Delta = 2000; \zeta = 20$. The target equilibrium state in this case is $S_1 = (1459, 0, 0)$. (black circles) The other equilibrium states.

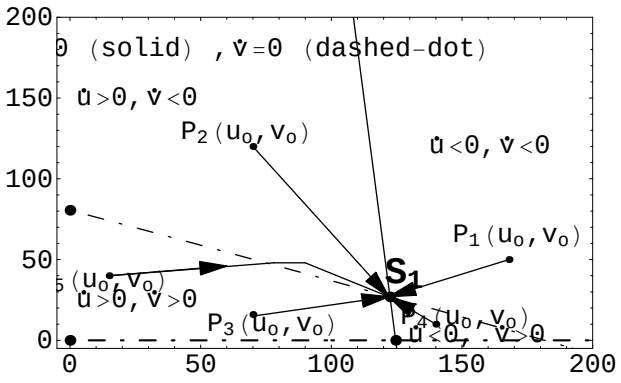


Figure 3. The equilibrium states for the parameter values $\alpha_1 = 13, \alpha_2 = 37, k_1 = 125, k_2 = 167, q_1 = 0.0084, q_2 = 0.08, p_1 = 0.0058, p_2 = 18, a_1 = 20, a_2 = 801, c_1 = 0.001, c_2 = 36, \Delta = 50000; \zeta = 50$. The target equilibrium state in this case is $S_1 = (122.5, 26.9, 0)$. (black circles) The other equilibrium states.

Corollary 3.2. *If the initial conditions* (u_o, v_o, w_o) *are taken such that* $\dot{u}(0) > 0$ *and* $\dot{v}(0) < 0$ *then the system (3.1–3.3) attains the sss given by* (u_e, v_e, w_e) *where* $u_e > u_o$, $v_e < v_o$. *Further* $w_e > w_o$ $(or w_e < w_o)$ *if* $\dot{w}(0) > 0$ $(or \dot{w}(0) < 0)$.

Finally it remains to determine the initial dose w_o which guarantees that $\dot{u} > 0$ and $\dot{v} < 0$. By solving these inequalities , we get

$$w_1(u_o, v_o) < w_o < w_2(u_o, v_o) \tag{3.11}$$

In (3.11) by omitting the subscript "o" and averaging over the domain $u_o < u < u_s$,

$v_s < v < v_o$, we get

$$\bar{w}_1 = \frac{1}{(u_e - u_o)(v_o - v_e)} \int_{v_e}^{v_o} \int_{u_o}^{u_e} w_1(u,v) du dv < w_o < \tag{3.12}$$
$$< \frac{1}{(u_e - u_o)(v_o - v_e)} \int_{v_e}^{v_o} \int_{u_o}^{u_e} w_2(u,v) du dv = \bar{w}_2$$

In the inequality (3.12) the values of $\bar{w}_1$ and $\bar{w}_2$ can be calculated for the data given in figures 2 and 3, and initial conditions are taken in the region where $\dot{u} > 0$ and $\dot{v} < 0$. These results are given by;

In Figure 2, if the initial values (u_0, v_0) are taken as $(1100, 0.5)$ then we find that $56.2322 < w_0 < 279291$.

In figure 3 if $u_0 = 100$ and $v_0 = 2$ then, we find that $0 < w_0 < 486848$.

4. Solution of the diffusion-model

In the previous section, we analyzed the solution of the homogeneous model for the aim of inspecting the cases where chemotherapy of cancer treatment is effective. This was done through examining the initial conditions (u_0, v_0, w_0) which guarantee equilibrium value for v to be $v_e = 0$. Now, we analyze the solution of the equations (2.1-2.3)in the open rectangle $\Omega = (0, T) \times (-M, M)$in the xt-plane. As a qualitative behavior to the solution of these equations,we mention that in the absence of nonlinear terms ,the normal and cancer cells diffuse in space and they grow in time while the concentration of the chemotherapy agent decays with time. By taking into consideration of the nonlinear terms and if they can balance the linear ones locally (that is if there exists a region $\bar{\Omega} \subset \Omega$ where their contribution can balance that of the linear terms) then solutions stop growing (damping) with time. They start to propagate in space leading the onset of traveling waves at variant speeds.For great time values, permanent traveling waves PTW are generated that travel at a constant speed.

Here, we confine ourselves to take the initial conditions for the concentration of normal and cancer cells namely $u(x, 0)$ and $v(x, 0)$ to satisfy the conditions of theorem . That is, by taking the values $(u_o, v_o) = (\inf_x\ u(x,0), \sup_x\ v(x,0))$ satisfy $u_t(u_o, v_o) > 0$ and $v_t(u_o, v_o) < 0$ for $D_1 = D_2 = 0$ in (2.1) and (2.2).Together with the following inequalities , namely $\sup_x(v(x,0)) << \sup_x(u(x,0)),\ \sup_x(u(x,0)) >> 1$ and $\sup_x(w(x,0)) >> 1$ (in free units). Consequently, we shall have $v(x,t) << u(x,t),\ \ u(x,t) >> 1$ and $w(x,t) >> 1$ everywhere in Ω.

We derive approximate analytic solutions for (2.1–2.3)in the form of a rational function. We state that rational function approximations of solutions of PDE are currently appearing in the literature [13], [14].

The dynamics a reaction-diffusion system suggest that the system evolutes from the initial conditions towards an equilibrium point, passing probably by the traveling wave solution as a transient solution. By bearing this in mind we construct a rational function approximation to (2.1–2.3)in the following steps:

I: Inspecting a target equilibrium state, (u_s, v_s, w_s) after the equations (3.1-3.3) in view of the initial conditions.

II: The equations (2.1–2.3) are divided by $(u-u_e)^2 = \bar{u}^2$, $(v-v_e)^2 = \bar{v}^2$ and $(w-w_e)^2 = \bar{w}^2$ respectively and to get

$$\frac{u_t}{\bar{u}^2} = U, \quad \frac{v_t}{\bar{v}^2} = V, \quad \frac{w_t}{\bar{w}^2} = W, \tag{4.1}$$

where U, V and W are the right hand sides of (2.1–2.3) divided by $\bar{u}^2, \bar{v}^2$ and $\bar{w}^2$ respectively.

III: By integrating (4.1) formally,

we have for the first equation;

$$u(x,t) = u_e + \frac{(u(x,0)_- u_e)}{1-(u(x,0_- u_e)\int_0^t U dt_1} \tag{4.2}$$

$$U = \frac{(D_1 u_{xx} + \alpha_1 u(1-\frac{u}{k_1}) - q_1 uv - \frac{p_1 uw}{a_1+u})}{\bar{u}^2} \tag{4.3}$$

Similar equations hold for v and w. We note that the function U under the integral in (4.2) depends implicitly on t_1.

IV: In analogy to the fixed point iteration,we construct an iterative scheme after the formal solution given by (4.2-4.3)) as

$$u^{(n)} = u_e + \frac{(u(x,0)-u_e)}{1-(u(x,0)-u_e)\int_0^t U(u^{(n-1)}, v^{(n-1)}, w^{(n-1)})dt_1}, n \geq 1. \tag{4.4}$$

A similar iterative scheme is constructed for $v^{(n)}$,and $w^{(n)}$.

For $n=0$, we take $\bar{u}^{(0)}$, $\bar{v}^{(0)}$ and $w^{(0)}$ satisfy the diffusion equations

$$u_t^{(0)} = D_1 u_{xx}^{(0)}, \quad v_t^{(0)} = D_2 v_{xx}^{(0)}, \quad w_t^{(0)} = D_3 w_{xx}^{(0)}. \tag{4.5}$$

In applications, the solution given by (4.4) and (4.5) is truncated at the first, second or higher approximations.

Now, we prove that the sequences of solutions $\left\{u^{(n)}\right\}, \left\{v^{(n)}\right\}$ *and* $\left\{w^{(n)}\right\}$ converges uniformly to the exact solution of (2.1).

Theorem 4.1. *If $u(x,0)$, $v(x,0)$ and $w(x,0)$ are piece-wise smooth functions then the above sequences of solutions converge uniformly on in any compact domain in Ω.*

Proof. The assumption on the initial conditions is taken as in case of solution of the

linear diffusion equation. A proof that this condition holds also for the solution of the equation $u_t = u_{xx} + f(u)$ to exist had been carried out in [16](see also [12], [15]). This condition holds here as the iteration is based on the solution of the equations in (4.5).The convergence is proved in the maximum norm.
We consider the sequence $\left\{u^{(n)}\right\}$ where for n=1,

$$u^{(1)} = u_e + \frac{(u^{(0)} - u_e)}{1 - (u^{(0)} - u_e)\int_0^t U^{(0)} dt_1} \tag{4.6}$$

$$U^{(0)} = \frac{\alpha_1 u^{(0)} \left[(1 - \frac{u^{(0)}}{k_1}) - q_1 v^{(0)} - \frac{p_1 w^{(0)}}{a_1 + u^{(0)}}\right]}{(u^{(0)} - u_e)^2} \tag{4.7}$$

In the equations (4.6) and (4.7) we have $u^{(0)}(x,t) < u_e$ for $t \geq t_o$. By bearing in mind that we are working in the domain where the terms the square brackets are positive ($u_t > 0$), then the denominator in the RHS of (4.6) is strictly positive for $T > t \geq t_o > 0$.Consequently we have

$$|u^{(1)} - u^{(o)}| < (u^{(0)} - u_e)^2 | \int_0^t U^{(0)} dt_1 | \tag{4.8}$$

In $\Omega \times D$, where D is an open parallelepiped in the uvw space, the function $U^{(0)}$ is differentiable there.By applying the mean value theorem for multi-variables on $U^{(0)}$ and the boundedness of $u^(o)$, we get

$$|u^{(1)} - u^{(o)}| < K_1 t \tag{4.9}$$

Now, as $u^{(0)}$, the solution of the first equation in (4.2), belongs to the space S_∞; the space of infinitely differentiable and rapidly decreasing functions for large x, we have

$$|u_{xx}^{(1)} - u_{xx}^{(o)}| < M_1 t \tag{4.10}$$

Similar equations hold for the variables $vandw$. By induction, we can prove that

$$|u^{(n)} - u^{(n-1)}| < K_n t^n/n!, |u_{xx}^{(n)} - u_{xx}^{(n-1)}| < M_n t^n/n! \tag{4.11}$$

By taking $K = MaxK_i, M = MaxM_i$ and by using the identity

$$u^n - u = u_o - u + \sum_{i=1}^{i=n} (u^i - u^{i-1}) \tag{4.12}$$

we have

$$|u^{(n)} - u| < Kt^n/n! \leq KT_o^n/n! < \epsilon_1, n > N_1, T_o < T \tag{4.13}$$

$$|u_{xx}^{(n)} - u_{xx}| < Mt^n/n! \leq MT_o^n/n! < \epsilon_2, n > N_2 \tag{4.14}$$

Consequently the sequence u_n converges uniformly in any closed domain. Similar statements hold for v_n and w_n. □

In what follows, we carry out numerical computations of solutions of the set of equations (2.1–2.3) for two problems, namely for square and triangular cancer sites. Calculations are based on evaluating the first approximation for the concentration of normal and cancer cells and for the chemical agent namely, $u^{(1)}$, $v^{(1)}$ and $w^{(1)}$.

5. Numerical Computation

a. A square site

For a square site, we shall assume that cancer cells are concentrated in a square site of size L, while outside this site the concentration takes the value of the sss which is zero or otherwise. A similar initial concentration for the normal cells is taken appropriately. While for that of the chemotherapy agent is taken as a constant everywhere. Thus, we have

$$v(x,0) = \begin{cases} v_o, & |x| < L \\ 0, & |x| \geq L \end{cases}, \tag{5.1}$$

$$u(x,0) = \begin{cases} u_o, & |x| < L \\ u_e, & |x| \geq L \end{cases}, \tag{5.2}$$

$$u(x,0) = \begin{cases} w_o, & |x| < mL \\ 0, & |x| \geq mL, \quad m > 1 \end{cases}, \tag{5.3}$$

The boundary conditions are taken at $x = \pm\infty$ as $u = u_s$, $v = 0$ and $w(-\infty, t) = w(\infty, t)$. We mention that the initial conditions u_o, v_o and w_o are taken to satisfy $u_t(u_o, v_o, w_o) > 0$, $v_t(u_o, v_o, w_o) < 0$ while $w_t(u_o, v_o, w_o)$ is taken positive or negative (cf. figures 4 and 5).
Also w_o is taken to satisfy cases where solutions tends asymptotically to stable equilibrium states. The parameter values taken in figures 2 and 3 are reconsidered here.

We evaluate the first approximations namely $u^{(1)}$, $v^{(1)}$ and $w^{(1)}$ which are given by

$$u^{(1)} = u_e + \frac{(u^{(0)} - u_e)}{1 - (u^{(0)} - u_e)\int_0^t \frac{u^{(0)}\alpha_1(1 - \frac{u^{(0)}}{k_1}) - q_1 v^{(0)} - \frac{p_1 w^{(0)}}{a_1 + u^{(0)}}}{(u^{(0)} - u_e)^2}} dt_1 \tag{5.4}$$

$$v^{(1)} = v_e + \frac{(v^{(0)} - v_e)}{1 - (v^{(0)} - v_e)\int_0^t \frac{v^{(0)}\alpha_1(1 - \frac{v^{(0)}}{k_1}) - q_1 u^{(0)} - \frac{p_1 w^{(0)}}{a_1 + v^{(0)}}}{(v^{(0)} - v_e)^2}} dt_1 \tag{5.5}$$

$$w^{(1)} = w_e + \frac{(w^{(0)} - w_e)}{1 - (w^{(0)} - w_e)\int_0^t \frac{\xi w^{(0)} + \Delta - (\frac{c_1 u^{(0)}}{a_1 + u^{(0)}} + \frac{c_2 v^{(0)}}{a_2 + v^{(0)}}) w^{(0)}}{(w^{(0)} - w_e)^2}} dt_1 \tag{5.6}$$

where $u^{(0)}$, $v^{(0)}$ and $w^{(0)}$ are solutions of the equations (5.15) and are given by

$$u^{(0)} \equiv u^{(0)}(x,t) = u_e + (u_o - u_e) f_1 \tag{5.7}$$

$$v^{(0)} \equiv v^{(0)}(x,t) = v_o f_2 \tag{5.8}$$

$$w^{(0)} \equiv w^{(0)}(x,t) = \tilde{f}_3 w_o, \tag{5.9}$$

$$f_i = \frac{1}{2}\left[erf\left(\frac{L-x}{2\sqrt{D_i t}}\right) + erf\left(\frac{L+x}{2\sqrt{D_i t}}\right)\right], \tilde{f}_i = f_i(mL). \tag{5.10}$$

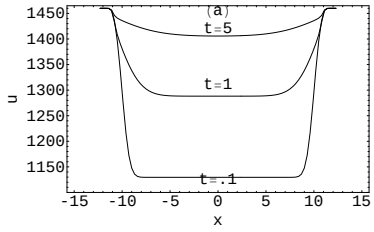
Hereafter, we shall take $m = 2$.

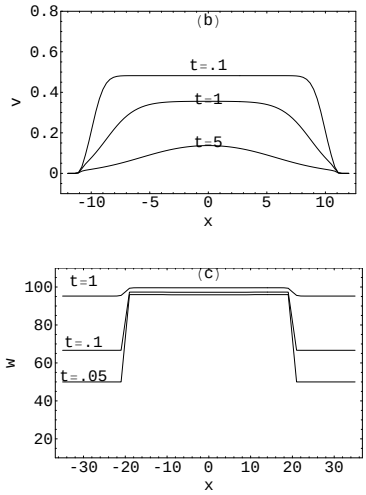
Numerical results for the concentrations of the chemotherapy agent, normal and cancer cells are carried out after (5.4–5.6) and they are shown in figures 4 a, b and c.

For the initial values $(u_o, v_o, w_o) = (1100, 0.5, 92)$ and for parameter values mentioned in the legend of Figure 2. In figures 5 a, b and c the initial values are taken $(u_o, v_o, w_o) = (110, 1100, 800)$ and parameter values are taken after the legend of Figure 3. Further parameters are included in the legends.

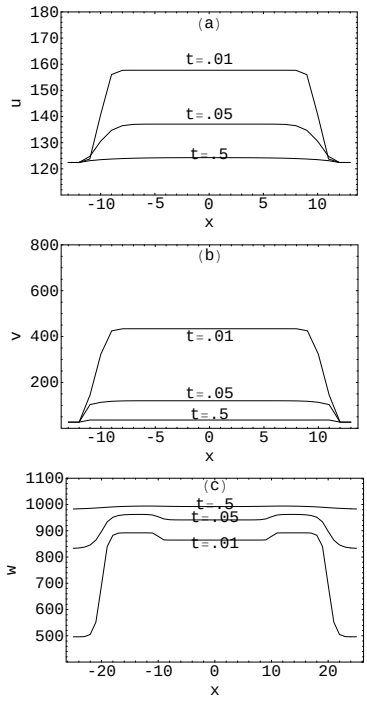
After these figures, we find that for small time values diffusion effects manifest through enlarging the range of initial conditions . For later times, predation terms due to the chemical agent handle diffusion effects. This holds in the concentrations of the normal and cancer cells.

Researches are carried out to design an intelligent chemotherapy agent to attack directly the cancer site leaving other sites free from the agent.





Figures 4 a, b and c. The concentration of the normal and cancer cells and of the chemotherapy agent are displayed against x for different values of t. The parameter values are taken as $\alpha_1 = 1.5, \alpha_2 = 10, k_1 = 1460; k_2 = 2100, q_1 = .0075, q_2 = 0.005, p_1 = 0.0008, p_2 = 0.08, a_1 = 1, a_2 = 1, c_1 = 0.0024, c_2 = 0.24, \Delta = 2000; \zeta := 20; D_1 = 2, D_2 = 4; D_3 = .5, L = 10, u_o = 1100, v_o = 0.5, w_o = 92, u_s = 1459.950, v_s = 0, w_s = 99.988$.



Figures 5 a, b and c. The concentration of the normal and cancer cells and of the chemotherapy agent are displayed against x for different values of t. The other parameter values are taken as $\alpha_1 = 13, \alpha_2 = 37, k_1 = 125; k_2 = 167, q_1 = .084, q_2 = 0.08, p_1 = 0.0058, p_2 = 18, a_1 = 20, a_2 = 801, c_1 = 0.001, c_2 = 36, \Delta = 50000; \zeta := 50; D_1 = 20, D_2 = 10; D_3 = 30, L = 10, u_o = 110, v_o = 1100, w_o = 800, u_s = 122.65, v_s = 26.44, w_s = 967.89.$

In this case instead of considering a more flat initial concentration for the chemical agent, we use the initial condition

$$w(x,0) = \begin{cases} w_o, & |x| < L \\ 0, & |x| \geq L \end{cases}, \tag{5.11}$$

$$w^{(0)}(x,t) = w_o f_3 \tag{5.12}$$

where f_i are given by (5.10). By using the same initial value $w_o = 92$ as in Figure 4; numerical results are carried out and they show no relevant change in the concentrations of the normal and cancer cells. So that they shall not be produced here. Practically the relaxation time, the effective time required for the system to evolute from the initial state reaching asymptotically the equilibrium point, is the same. But if the initial dose is increased namely $w_o = 110$, we find that the relaxation time is remarkably decreased. (see figure 6)

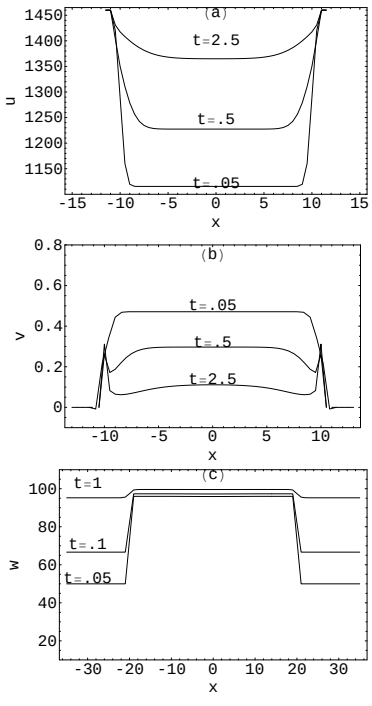


Figure 6 a, b and c. The concentrations of the normal and cancer cells and the chemotherapy agent are displayed against x for different values of t . The other parameter values are taken as in figures 6 but $w(x,0) = 0$ for $x < -L$ or $x > L$ and $w(x,0) = wo = 110$ for $-L < x < L$.

b. A triangular site.

In this case, initial conditions for the concentrations of the normal and cancer cells may be taken as

$$u(x,0) = \begin{cases} u_o \dfrac{|x|}{L}, & |x| < L \\ u_e, & |x| \geq L \end{cases}, \tag{5.13}$$

$$v(x,0) = \begin{cases} v_o(1 - \dfrac{|x|}{L}), & |x| < L \\ 0, & |x| \geq L \end{cases}, \tag{5.14}$$

$$w(x,0) = \begin{cases} w_o, & |x| < mL \\ 0, & |x| \geq mL, \quad m > 1 \end{cases}, \tag{5.15}$$

The boundary conditions are taken the same as before. In this case the solutions of the equations (5.18) are given by

$$u^{(0)}(x,t) = u_e(1 - f_1) - h_1 - g_1 \tag{5.16}$$

$$v^{(0)}(x,t) = v_o f_2 + h_2 + g_2 \tag{5.17}$$

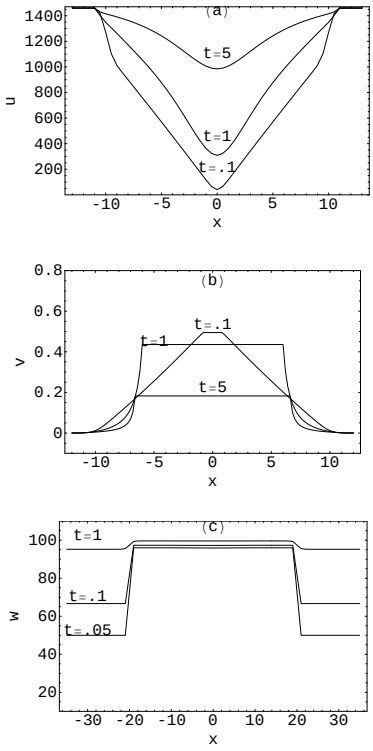
$$w^{(0)}(x,t) = w_o \tilde{f_3}, \tag{5.18}$$

where

$$h_i = \frac{x}{2L}\left(-erf\left(\frac{L-x}{2\sqrt{D_i t}}\right) + erf\left(\frac{L+x}{2\sqrt{D_i t}}\right) - 2erf\left(\frac{x}{2\sqrt{D_i t}}\right)\right), \tag{5.19}$$

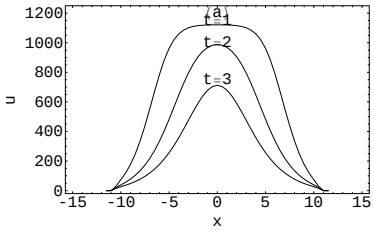
$$g_i = \left(e^{-\frac{(L-x)^2}{4D_i t}} + e^{-\frac{(L+x)^2}{4D_i t}} - 2e^{\frac{-x^2}{4D_i t}}\right)\sqrt{\frac{D_i t}{\pi L^2}}, \tag{5.20}$$

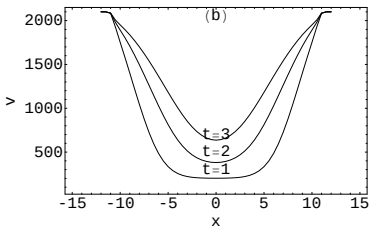
and f_i are given by (5.10). Numerical results for the first approximations given by (5.4–5.6) are carried out. They are shown in figures 7 a, b and c for the same parameter values given in figure 2.



Figures 7 a, b and c. The concentrations of the normal and cancer cells and of the chemotherapy agent are displayed against x for different values of t. The other parameter values are taken as in figures 4 but in a triangular site.

After figures 4-7, we find that no traveling wave generation occurs which confirms the predations of theorem 5. We think that in the present model, predation by the chemical agent blocks generation of these waves. To justify this statement, numerical computations are carried out in the absence of the chemotherapy agent by setting $w = \Delta = 0$ in (2.1–2.3). The results are shown in figures 8 a and b where they show the generation of traveling waves propagating at speed $\approx \dfrac{\Delta x}{\Delta t} \approx 2$ for the normal cells and at speed $\approx \dfrac{\Delta x}{\Delta t} \approx 2$ for the cancer cells.





Figures 8 a and b. The concentrations of the normal and cancer cells in the absence of the chemical agent for $\alpha_1 = 1.5, \alpha_1 = 10, k_1 = 1460, k_2 = 2100, q_1 = .0075, q_2 = 0.005, D_1 = 2, D_2 = 4, L = 10, u_o = 1200, v_o = 45, u_s = 0, v_s = 2100$. These figures show generation of traveling waves.

6. Conclusions

In a chemotherapy cancer treatment, a target equilibrium state is relevant to be attained. The bounds for the initial dose of the chemotherapy agent which is required to attain a state of no cancer cell present are determined. It has been found that diffusion effects are relevant for small time values and no generation of traveling waves occurs. We think that in chemotherapy models of cancer treatment, predation by the chemical agent blocks generation of these waves.While in the absence of the chemical agent traveling waves are generated. These statements are confirmed by the numerical results of solutions of the proposed diffusion model.

References

[1] R. T. Dorr, and D. D. Hoff, *Cancer chemotherapy Handbook Appeleton and Lange*,Connecticut(1994).

[2] J. M. Murray, *Optimal drug regimens in cancer chemotherapy for single drugs that block progression through the cell cycle*, Math. Biosci, **123**(1994), 183-193.

[3] A. Y. Yukovler and S. H. Molgavekar Guest Editors, *Modeling and data analysis in cancer studies*, Special Issue of Math. and Comput. Modeling, **33**(2001), 12-13.

[4] J. A. Sherratt, *Cellular growth control and traveling waves of cancer*, SIAM J. Appl. Math., **53(6)**(1993), 1713-1730.

[5] J. A. Adam, *A simplified mathematical model of tumor*,Math. Biosci, **81**(1986), 229-244.

[6] J. A. Adam, *A Mathematical model of tumor growth III. Comparison with experiment*, Math. Biosci, **86**(1987), 213-227.

[7] S. T. R. Pinho, H. I. Freed man and F. A. Nani, *Chemotherapy model for the treatment of cancer with metastasis*, Math. and Comput. Modeling, **36**(2002), 773-803.

[8] A. T. Look, *On congenic transcription factors in the acute human leukimias*, Science, **278**(1997), 1059-1064.

[9] J. A. Leach, J. H. Merkin and S. K. Scott, *An analysis of a two-cell coupled nonlinear chemical oscillator* Dyn. and Stability of Systems, **6(4)**(1991), 341-366.

[10] N. F. Briton, *Reaction- Diffusion Equations and their Applications to Biology*, Academic, New York(1986).

[11] J. D. Murray, *Mathematical Biology*, Second Edition. Springer Verlag(1993).

[12] H. I. Abdel-Gawad and K. M. Saad, *On the behaviour of solutions of a two-cell cubic autocatalator reaction model*, Proc. Aust. Math Soc., **ANZIAMJ44(E)**(2002), 1-32.

[13] H. N. Ismail and E. M. Elbarbary, *Restrictive Pade approximation and parabolic partial differential equations*, Int. J. Comput. Math., **66**(1998), 343.

[14] H. N. Ismail, E. M. Elbarbary, and A. A. Elbietar, *Approximation for the solution of the schrodinger equation*, Int. J. Comput. Math., **79(5)**(2002), 603.

[15] H. I. Abdel-Gawad and A. M. Elshrae, *An approach to solutions of coupled semilinear partial differential equations with applications*, Math. Meth. Appl. Sci., **23**(2000), 845-864.

[16] H. Poorkarimi and J. Wiener, *Bounded solutions of nonlinear parabolic equations with time delay*, Electronic J. of Differential Equations, **Conference 02**(1999), 87-91