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A Mathematical Model of Chemotherapy for Tumor Treatment

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Abstract

Consider a model that represents the procedure for tumor treatment, which consists tumor cell energy and specific dose of Adriamycin. The tumor cell energy depends upon tumor cell density and the Adriamycin is a specific drug that works against tumor cell energy. We modeled the problem in the form of partial differential equations for the tumor cells density, tumor cell energy and the effect of Adriamycin. The result of this work suggests that the tumor cell energy decrease by the effect of Adriamycin, if tumor cell energy decreases then the size of tumor reduce.

Introduction

The energy in all cells originates from the energy of the sun's light quanta, which is convicted by photosynthetic plants into cellular molecules. These plants are used as food sources by various microorganisms and animals. Life is an energy process. It takes energy to operate muscles, extract wastes, make a new cell, heal wounds, even to think. It's in an organism's cells where all this energy is spent. In some cells, as much as a half of a cells energy output is used to transfer molecules across the cell membrane. Cell movements require energy and thousands of energy-hungry chemical reactions go on in every living cell, every second, every day. The casual agents are certain chemicals, radiation, and viruses that behave as mutagens by acting at the level of DNA. However, it has also been proved that cancer is a genetic disease

caused by multiple mutations within the DNA of cells. The researchers [3] have discovered that an apparently nontoxic cellular "energy blockers" can eradicate large liver tumors grown, in rats. Liver cancer usually isn't detected in people until it's difficult or impossible to treat, and many other aggressive cancers spread to the liver, so we need more treatment options.

Martin et. al. [1] a quadruple drug combination consisting of a triple-drug combination of N-(phosphonacetyl)-L-aspartate (PALA) + 6-methylmercaptopurine riboside (MMPR) + 6-amino-nicotinamide (6-AN), designed to primarily deplete cellular energy in tumor cells, + Adriamycin (Adria) yielded significantly enhanced anticancer activity (i.e., tumor regressions) over that produced by either Adria alone at maximum tolerated dose (MTD) or by the triple-drug combination, against large, spontaneous, autochthonous murine breast tumors. Adriamycin is a type of antibiotic used specifically in the treatment of cancer. It interferes with the multiplication of cancer cells and slows or stops their growth and spread in the body. Stolfi et. al. [2] this report describes a highly active chemotherapeutic drug combination. This quadruple drug combination, administered on a 10-11-day schedule, produced an impressive partial tumor regression rate of 67% of large, spontaneous, autochthonous, murine breast tumors and a tumor regression rate of 74% of first-passage transplants of the spontaneous breast tumors.

Chemotherapy uses powerful drugs to kill cancer cells, control their growth, or relieve pain symptoms. Chemotherapy may involve one drug, or a combination of two or more drugs, depending on the type of cancer and its rate of progression. Chemotherapy can be used in combination with other treatments such as surgery or radiation, to make sure all cancer cells have been eliminated. Adriamycin (Doxorubicin) an active medicine against many cancers, is one of the order chemotherapy drugs, having been in use of decades. Adriamycin is clear, orange-red powder or liquid, which is administrated intravenously only. It is most commonly used in treatment of all cancers (Breast, Stomach, Lymphomas etc.). Adriamycin is chemotherapy drug that interrupts the cell cycle, effectively cell growth. Adriamycin degrades rapidly in solution; a fluorometric method was developed to determine the precise dose use in treatments. But Adriamycin also has more serious side effects that limit the amount you can safely take. At a certain level, Adriamycin increases the risk of heart damage. The Adriamycin works by impairing DNA synthesis, a crucial feature of cell division, and this is able to target rapidly dividing cells. Adriamycin is a very serious anticancer medication with definite potential to do great harm as well as great good. It used alone or in combination with other chemotherapy drugs. O'Brian [8] concluded that Doxil appears to be as effective as Adriamycin for treating women with metastatic breast cancer. Doxil was less likely to cause heart problems, less of white blood cells, vomiting, and hair loss.

More recent work on the mathematical models of the tumor growth are, Ward and King [11] consider the effect of cellular material as well, mainly because it is very simple to construct an analogous model to that of Ward and King [10] for monolayer cultures, so that a direct comparison of the effect of drugs on the two types culture can be made the approach used in this model of Ward & King [11], which assumes a source of cellular material outside a 3-dimensional monolayer case. Anderson et.

al.[12] works to examine fluid flow through the theoretical network structures. In order to achieve this we make use of flow modeling tools and techniques from the fluid of petroleum engineering. We discuss the realistic analysis of energy in appendix.

Our model

Mathematically, for an untreated tumor the work equation may be reasonably quantified by a single partial differential equation

$$\frac{\partial c}{\partial t} = \nabla . J + \lambda c \tag{1}$$

in which c(x,t) designates the tumor cell density and λ denotes the cell proliferation rate. Where $J = D\nabla\mu(c)$, the gradient of the potential μ produces a flux J is proportional to $\nabla\mu$. The D is Fickian diffusion coefficient represent the active motility of tumor cells, which in this derivation may depend on x, t and c. The tumor spread is assumed to be spherically symmetric in this model, and x measures the distance from the center.

$$\frac{\partial c}{\partial t} = \nabla . [D\nabla\mu(c)] + \lambda c \tag{2}$$

We associate with a spatial distribution of cells, an energy density n(c), which is an internal energy per unit volume of an evolving spatial pattern so that the total energy N(c) in a volume is given by

$$N(c) = \int_V n(c)dx \tag{3}$$

The small variation in energy δN, which is the work done in small variety states by an amount δc, is the variation derivative, $\delta N/\delta c$ which define a potential $\mu(c)$. Therefore

$$\mu(c) = \frac{\delta N}{\delta c} = n'(c) \text{ (Because } \delta c \to 0) \tag{4}$$

The internal energy density is usual quadrate with $n(c) = c^2/2$. In this context, we see that tumor cell energy depend on tumor cell density thus we get $\mu(c) = c$. Thus, we choose the following functional form for tumor cell c as discussed by in Burgess et al.[7]. We set:

$$c(x,T) = \frac{N_0 e^{\lambda(t_0+T)} e^{-x^2/4Dt_0}}{8(\pi D t_0)^{3/2}} \tag{5}$$

We find the initial and boundary condition for the Adriamycin resistance tumor cell density is determined as

$c = c_0(x)$ at t=0

$c = c_{\max.}$ at x=0

$c = c_*$ at x=1

Now we introduce the dose of Adriamycin bind with cells and it can prevent to repair of DNA. We can use Adriamycin against repair of DNA of tumor cells, the term α is the effect of Adriamycin on tumor. We get

$$\frac{\partial c}{\partial t} = \nabla.(D\nabla c) + \lambda c - \alpha c \qquad (6)$$

Numerical result

The parameters

D tumor diffusion coefficient	54×10^{-4} mm^2/h
λ net proliferation rate	50.4×10^{-5} /h
N_0 initial size of tumor at point of source	1.19×10^{6} cells
t_0 time to grow from point source to presentation	1.18×10^{4} h

To solve the partial differential equation, we use the Matlab *6.0*, a partial differential equation solver. In this result, we see that the tumor cell density is going to decrease as well as the effect of Adriamycin is increases. It shows that if tumor cell density decreases with the effect of Adriamycin then tumor cell energy decreases with the dose of Adriamycin because tumor cell energy is depend upon the tumor cell density.

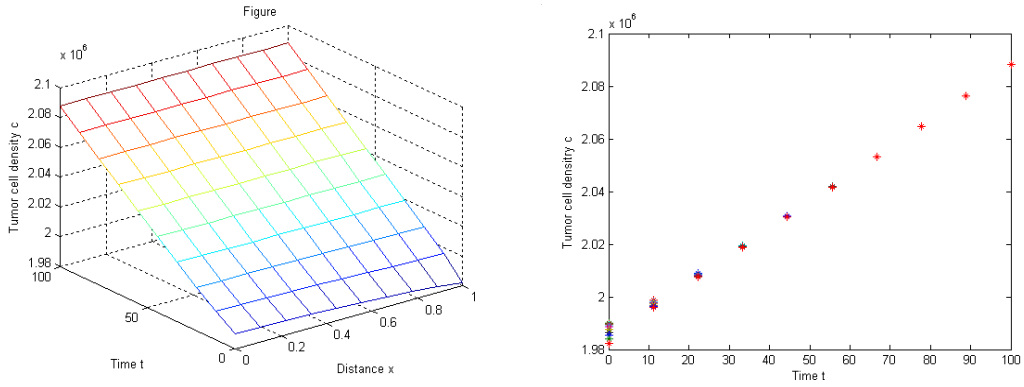


Figure 1: (a) showing the tumor cell density without effect of adriamycin and distance (0 to 1mm) from the center of the tumor and time (0-100h), (b) showing the tumor cell density with time

We show the 3D and 2D representation in the above figure 1. The figure 1 shows the surface plot tumor cell density with respect to time T and radius x. We consider the time 0 to 100 h and radius 0 to 1 mm. We analyzed the growth of tumor cell density in above figure shows the initially, tumor cell density is 1.99×10^{6} *cells* at center of tumor and 1.98×10^{6} *cells* at the boundary of the tumor. After the 100h the tumor cell density is almost same at the center and boundary of the tumor, without the effect of adriamycin. The figure shows at initially max. at the center of tumor but it is less at the boundary.

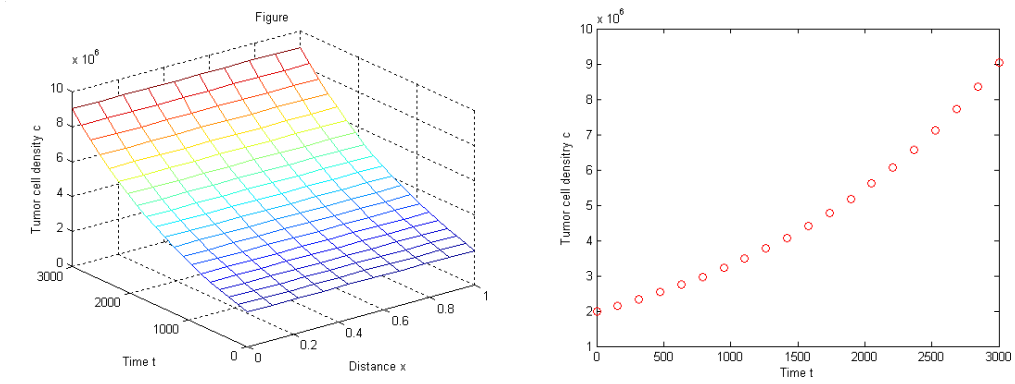
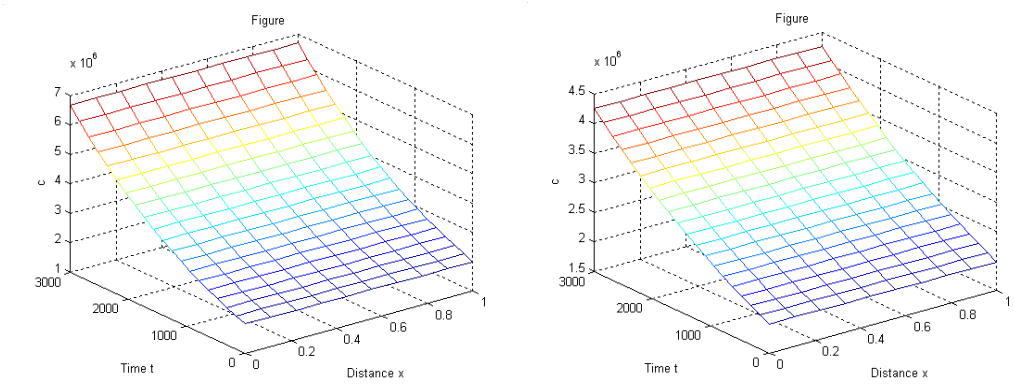


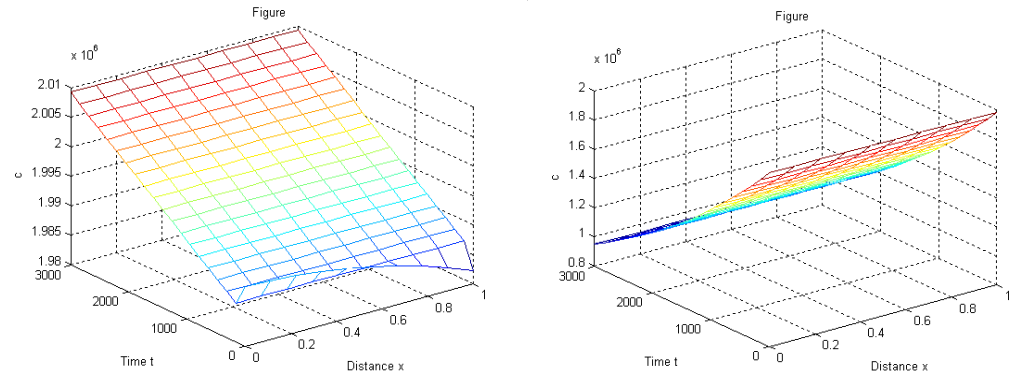
Figure 2: (a) showing the tumor cell density without effect of adriamycin and distance (0 to 1mm) from the center of the tumor and time (0-3000h), (b) showing the tumor cell density with time

The figure 2 shows the surface plot tumor cell density with respect to time T and radius x form equation 1.0. We consider the time 0 to 3000 h and radius 0 to 1 mm. We analyzed the growth of tumor cell density in above figure shows the initially, tumor cell density is 1.99×10^{6} *cells* at initially. After the 3000 *h* the tumor cell density is almost same at the center and boundary of the tumor, in which the effect of Adriamycin is neglected ($\alpha = 0$).



Figures 3 and 4: showing the tumor cell density with the effect of dose Adriamycin $\alpha = 0.0001/h$ and $\alpha = 0.00025/h$ distance (0 to 1mm) from the center of the tumor and time (0-3000h) respectively.

Figure 3 shows the tumor cell density is 1.99×10^6 *cells* at initially and after the treatment of 3000h it increases up to 6.75×10^6 *cells,* in which the effect of Adriamycin is $\alpha = 0.0001/h$. Figure 4 shows, after the treatment the tumor cell density is 4.2×10^6 *cells*, in which the effect of Adriamycin is $\alpha = 0.010/h$.



Figures 5 and 6: showing the tumor cell density with the effect of dose Adriamycin $\alpha = 0.0005$/h and $\alpha = 0.00075$/h distance (0 to 1mm) from the center of the tumor and time (0-3000h) respectively.

Figure 5 shows, after the treatment the tumor cell density is 2.01×10^6 *cells,* in which the effect of Adriamycin is $\alpha = 0.0005/h$. Figure *6* shows, after the treatment the tumor cell density is 0.99×10^6 *cells,* in which the effect of Adriamycin is $\alpha = 0.00075/h$. The numerical prediction of

our model it possible to compared the mechanisms involved in the appearance of spatio-temporal homogeneities detected in tumor cell culture. We assume that at initially the tumor cell density is same in different effect of the dose of Adriamycin.

Conclusions

An enzyme (Adenosine Triphoshate ATP) provides chemical energy for the cell, ATP release energy by releasing a phosphoric acid radical. Then, energy derived from the cellular nutrient causes the acceptor molecule and phosphoric acid to recombine to form new ATP. The entire process continues over and over again. Without that energy, blood vessels cannot grow to the site of a tumor, and without the nutrient supply in blood, tumors cannot grow larger than a pinhead.

In this paper our aim to develop a modeling framework for studying avascular tumor growth with the effect of dose of the adriamycin. We solve the equation numerically in this case. Throughout the paper, our philosophy when modeling has been to use the simplest functional forms that capture the physical phenomena that we are aiming to describe. Our model does not account the behavior of dead tumor cells, we except that a dead cell phase. The numerical simulation mainly involved the study of the effects on tumor cell survival of the dimensionless parameter α, which encapsulates the extent of penetration of the drug. The simulation emphasize that drug penetration is a crucial factor in determining drug effectiveness. The growth of tumor in a spherical shape has been examined in order to describe the initial stages. We have introduced a tumor cell energy model and used tumor cell density with the effect of Adriamycin to describe the movement of tumor cells. In section 3 the numerical results suggest that the tumor cell density decreases with the effect of adriamycin. We have observed for different values of effect of adriamycin. The tumor cell energy decreases with the effect of Adriamycin because tumor cell energy fully depends on the tumor cell density.

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Appendix: Realistic Energy Analysis

So we suppose a more realistic energy functional, which is chosen as to be constant under reflection $(x_i \to -x_i)$ and rotations $(x_i \to x_j)$, as

$$N(c) = \int_V \left[n(c) + k_1 \nabla^2 c + k_2 (\nabla c)^2 + ... \right] dx \tag{6}$$

If k is the function of c, then we are using Green's theorem

$$\int_V k_1 \nabla^2 c dx + \int_V \nabla k_1 . \nabla n dx = \int_S k_1 \frac{\partial c}{\partial L} ds \tag{7}$$

Where L is representing the outward normal to the surface S which encloses V and we suppose that k_1 depend on c so that $\nabla k_1 = k_1'(c) \nabla c$. From the equation (10)

$$\int_V k_1 \nabla^2 c dx = -\int_V k_1' (\nabla n)^2 dx + \int_S k_1 \frac{\partial c}{\partial L} ds \tag{8}$$

Because we are not considering the effects at the external boundary, therefore we can choose the bounding surface S such that $\partial c / \partial L = 0$ on S; that is zero flux at the boundary. Therefore equation (9) for the energy functional in spatially heterogeneous situation becomes

$$N(c) = \int_V \left[n(c) + \frac{k}{2} (\nabla c)^2 + ... \right] dx \tag{9}$$

Where

$$\frac{k}{2} = -k_1'(c) + k_2$$

in a spatially homogeneous situation the energy density n(c) with the other terms which depends on the neighboring spatial density variations.

Now we get the potential μ is obtained from equation (12) the energy functional as the form

$$\mu = \mu(c, \nabla c) = \frac{\delta N(c)}{\delta c} = -k \nabla^2 c + n'(c) \tag{10}$$

To find the value of $\delta N(c) / \delta c$, we are using the calculus of variations and taking k as a constant. Now the flux is

$$J = \overline{D} \nabla \mu(c, \nabla c).$$

The equation (1) will become

$$\frac{\partial c}{\partial t} = \nabla.[\overline{D}\nabla\mu(c,\nabla c)] + \lambda c \tag{11}$$

form equation (13), we get

$$\begin{aligned}\frac{\partial c}{\partial t} &= \overline{D}\nabla^2[\nabla^2 c + n'(c)] + \lambda c \\ &= k\overline{D}\nabla^4 c + \overline{D}\nabla.[n''(c)\nabla c] + \lambda c\end{aligned} \tag{12}$$

A basic assumption about $n(c)$ is that it can involve only even powers of c since the energy density cannot depend on the sign of energy density.