Journal of Computer Science & Systems Biology

Bettayeb et al., J Comput Sci Syst Biol 2020, 13:1

Research Article Open Access

A Prediction Model of a Lung Tumor Growth and Chemotherapy Treatment: Equilibrium Points and Stability

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Rec date: December 11, 2019; **Acc date:** February 20, 2020; **Pub date:** March 02, 2020

Abstract

The purpose of this paper is to study the prediction model of tumor growth non-vascularized lung cancer (first stage of cancer) before and during chemotherapeutic treatment. This model will be represented by a differential equations system, which will describe, among other things, tumor volume and proliferating cells. Finally, all the numerical results presented in this paper have been implemented in Scilab.

Keywords: Tumor; Temporal model; Lung; Chemotherapy; Equilibrium; Stability

Introduction

Proliferation cells: These cancerous cells participate in the growth of the tumor by their incessant division, and they are able to use glucose from medium to ensure their energy far more easily than others cells.

Quiescent cells: They are old proliferating cells which suffer from a lack of nutrients. They are waiting to have enough energy at their disposal to become proliferating again.

Necrotic cells: They are quiescent cells that have died because of a lack of nutrients.

Hypoxia: It is the absence of oxygen in the environment.

Scanner: The scanner is a medical imaging method that measures the absorption of X-rays by the tissues. The apparatus consists of a ring in which the patient is placed. The scanner makes it possible to have 2D and 3D images with precision. It gives information on the geometry of the tumor and its size. The duration of the exam takes less than an hour.

Methods

The laws of tumor growth

The exponential law: To model tumor growth, the most appropriate way is to consider the growth rate of the tumor. In the first half of the 20th century, the analysis of observations experimental animal and human population data led to consider an exponential growth of the tumor. The evolution of the tumor is therefore given by the following dynamics [1,2]:

$$dC/dt=\lambda_C C(t) \quad \ldots\ldots\ldots(1)$$

Where C(t) represents the law of evolution of the quantity of cancerous cells; $C_0=C(t=0)$ is the initial quantity; and $\lambda_C \geq 0$ denotes the growth rate of the tumor. The solution of the equation (1) is given by:

$$C(t)=C_0 e^{\lambda_C t}$$

Using the data in Table 1, we obtain (Figure 1):

Model	Parameter	Unit	Value
Exponential	C_0	mm^3	13.2
	λ_C	day^{-1}	0.257
Logistic	λ_C	day^{-1}	0.502
	C_∞	mm^3	1297
Gompertz	λ_C	day^{-1}	0.742
	k	day^{-1}	0.0792

Table 1: Parameter values estimated from lung data adjustments.

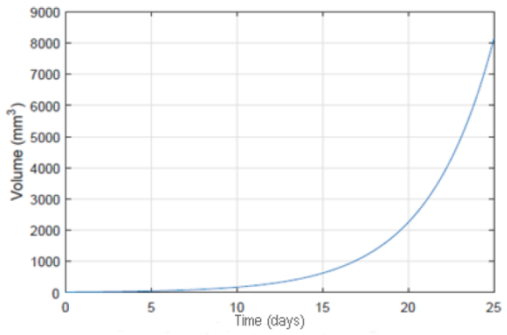

Figure 1: The evolution of the quantity of cancer cells according to the exponential law.

Tumor growth in this model is considered not limited by any factor. But the continuation of tumor growth is linked by mechanical and environmental constraints (problem of oxygen distribution, nutrients), so unlimited proliferation is impossible. These constraints are taken into account in the following models:

The logistic law: It was formulated for the first time by Verhulst in 1838 [3], as a means of describe the dynamics of the population with an intrinsic growth rate, whose size total is limited by a load capacity. The logistics equation presupposes that the growth rate decreases linearly with size. The Logistic growth model has been proposed [4]:

$$\frac{dC}{dt} = \lambda_C C\left(1 - \frac{C}{C_\infty}\right),$$

$C(0)=C_0$

Where $C_\infty=(t\to\infty)$ represents the tumor equilibrium state. Initially, the growth of the tumor is exponential with a rate λ_C, then, it converges to the equilibrium state C_∞. However, the logistics function does not correspond faithful to the experimental observations of the tumors evolution. The logistic law is an equation of type (Figure 2):

$[dY/dt(x)]=a(x)Y(x)+b(x)Y(x)^n$

By using Bernoulli's method this problem is reduced to a following linear problem:

$dZ/dt=[-\lambda_C Z(t)+(\lambda_C/C_\infty)]$ .....(2)

With: $Z(t)=C(t)^{-1}$

The resolution of linear equation (3) gives:

$Z(t)=[(1+C_1 C_\infty e^{-\lambda_c t})/C_\infty]$

Where C_1 is a constant.

So the general solution of problem (3) is:

$$C(t) = \frac{C_\infty C_0 e^{\lambda_C t}}{C_\infty + C_0 e^{\lambda_C t} - 1}$$

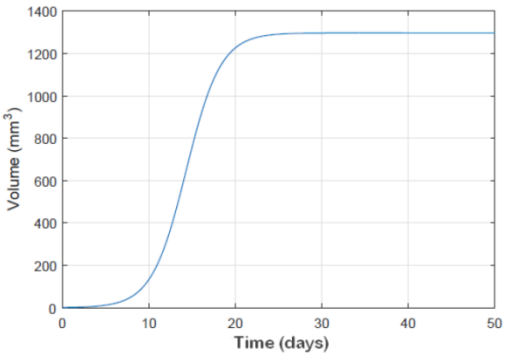

Figure 2: The evolution of the cancer cells quantity according to the logistic law (Table 1).

The law of Gompertz: In the 1960s, Laird et al. succeeded in fitting experimental tumor growth data using a Gompertz function. The Gompertzian evolution of the tumor is then described by the following dynamics [4,5] (Figure 3):

$dC/dt=\lambda_C Ce^{-kt}$ .....(3)

Where k is a positive constant. The equation (3) is an ordinary differential equation of the first order which admits the following solution with $C(0)=C_0$:

$$C(t) = C_0 e^{\frac{\lambda_C}{k}\left(1 - e^{-kt}\right)}$$

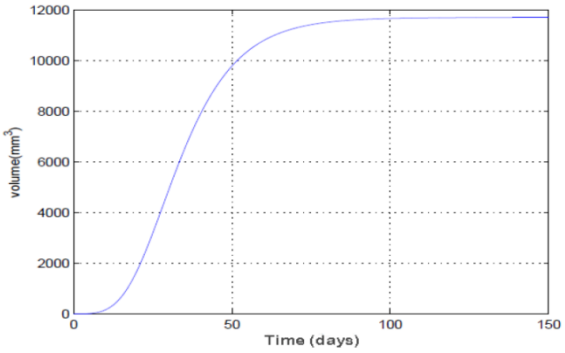

Figure 3: The evolution of the amount of cancer cells according to the Gompertian law (Table 2) [6].

τ0	4
τ1	5.0000007
τ2	6.0000071

Table 2: Treatment dates [7].

Tumor Growth Model (Temporal Model)

The authors set up a model based on a system of ODE (Ordinary Differential Equations) to describe the evolution of tumor volume over time (model of growth and activity of a non-vascularized tumor). This model does not take into account the spatial aspects of the tumor but calculates the amount of oxygen (or other nutrients) available inside the tumor. They considered only two types of cells: proliferating and quiescent (which are assumed to have the same behavior as necrotic cells) [7].

We note:

P: The proportion of proliferating cells in the tumor ($P\in[0;1]$).

V: The total volume of the tumor (the amount of proliferating cells in the tumor is therefore equal to PV).

Q: The proportion of quiescent cells in the tumor ($Q\in[0;1]$, assuming the confusion of the quiescent cells and the necrotic ones, we have: 1=P+Q).

C: The amount of nutrients available in the tumor.(This si a concentration; it does not take into account the problems of difision and distribution. This constant concentration is assumed to be 1 in healthy tissues).

C_{hyp}: The minimum concentration of nutrients to allow a cell to divide (hyp is for hypoxia). The amount of nutrients available in the tumor is directly related to how the cell divides, i.e., P because we do not consider space variables. The authors assume that if $C>C_{hyp}$, then cell division occurs normally and otherwise it does not occur at all. To describe this behavior, the first idea is to use a function of Heavyside (it is a function defined from $\mathbb{R}$ to the interval [0;1] and which is worth 0 if x<0 and 1 if no [8]).

In fact, it is more efficient for numerical calculations to pose a sort of regularized Heavyside, noted below.

Tumor growth is described by the following ODE system [7]:

$$\left\{\begin{array}{l}\frac{dV}{dt}=\gamma PV,\\ \frac{dP}{dt}=\gamma P(1-\mathrm{P})-(1-\gamma)\mathrm{P},\\ \frac{dC}{dt}=(1-\mathrm{C})(\frac{V}{V_0})^{\frac{2}{3}}-\alpha PC,\\ \gamma=\frac{1+\tanh(10(\mathrm{C}-\mathrm{C}_{hyp}))}{2}\end{array}\right\}\ldots\ldots\ldots(4)$$

The first line shows that the volume has an exponential growth if there are enough nutrients and remains constant in case of hypoxia (the absence of oxygen in the medium). On the second line, the right-hand side can be seen as the sum of a logistic term for cell division (γP(1−P)) and a term that refers to the passage in quiescent ((1−γ)P). The equation for C is composed of a production term proportional to the outer surface of the tumor and consumption by proliferating cells. V_0 is a characteristic term and a parameter. The quantity Q does not appear in the system because it is simply deduced from P by Q=1-P [7].

Behavior of the model solutions

Calculation of equilibrium points: An equilibrium point of (5) is the point (V, P, C) that is satisfied the solution of the system:

$$\left\{\begin{array}{l}\frac{dV}{dt}=\gamma PV=0,\\ \frac{dP}{dt}=\gamma P(1-\mathrm{P})-(1-\gamma)\mathrm{P}=0,\\ \frac{dC}{dt}=(1-\mathrm{C})(\frac{V}{V_0})^{\frac{2}{3}}-\alpha PC=0,\\ \gamma=\frac{1+\tanh(10(\mathrm{C}-\mathrm{C}_{hyp}))}{2}\end{array}\right\}\ldots\ldots\ldots(5)$$

Let's start with the resolution of the system (5):

We have:

dV/dt=0 ⇒ γPV=0 .....(6)
dP/dt=0 ⇒ γ P(1-P)-(1- γ) P=0 ……..(7)
dC/dt=0 ⇒ (1-C) $(V/V_0)^{2/3}$-αPC=0 ……..(8)

- If V=0 and P=0: then (0,0,C) is an equilibrium point with C∈[0;1].

From equation (6) we have: γ=0 or P=0 or V=0, but $\gamma \neq 0$, because if we assume the opposite:

γ=[1+tanh{10(C-C_{hyp})}/2]=0

We get:

$$\tanh(10(C-C_{hyp}))=\frac{e^{10(C-C_{hyp})}-e^{-10(C-C_{hyp})}}{e^{10(C-C_{hyp})}+e^{-10(C-C_{hyp})}}=-1$$

So: e^{10}(C-C_{hyp})=-$e^{10(C-C_{hyp})}$ This is impossible. Then $\gamma \neq 0$.

- If P=0 and V ≠ 0, we obtain from the equation (8) that C=1 or V=0, since V ≠ 0 then C=1.

Hence (V,0,1) is an equilibrium point, (it is acceptable because we have P+Q=1 (P=0, then Q=1, so there are quiescent cells from where V∈$\mathbb{R}_*^+$.)).

- If V=0 and P≠0, we obtain from the equation (8) that C=0 since P≠0 and α≠0, From equation (7) we have: P=(2γ-1)/γ

Hence [0,(2γ−1)/γ,0] is an equilibrium point, it is not acceptable because:

If C=0, then γ=[1+tanh(-10C_{hyp})/2] and

$$P=\frac{2\gamma-1}{\gamma}=\frac{2\tanh(-10C_{hyp})}{1+\tanh(-10C_{hyp})}=\frac{2\frac{\sinh(-10C_{hyp})}{\cosh(-10C_{hyp})}}{1+\frac{\sinh(-10C_{hyp})}{\cosh(-10C_{hyp})}}$$

$$-\frac{2\frac{e^{-10C_{hyp}}-e^{10C_{hyp}}}{e^{-10C_{hyp}}+e^{10C_{hyp}}}}{1+\frac{e^{-10C_{hyp}}-e^{10C_{hyp}}}{e^{-10C_{hyp}}+e^{10C_{hyp}}}}=\frac{e^{-10C_{hyp}}-e^{10C_{hyp}}}{e^{-10C_{hyp}}}$$

Since: $e^{-10C_{hyp}}$-$e^{10C_{hyp}}$<0 ……(9)

$e^{-10C_{hyp}}$>0 ……(10)

From (9) and (10) we obtain P<0 (this is impossible because P is the proportion of proliferating cells: 0 ≤ P ≤ 1.

So, [0,(2γ−1)/γ,0] is not an equilibrium point.

Stability of equilibrium points

The stability of an equilibrium point determines whether the equilibrium state approaches or not as the time increases. If we start from a point that is not a point of equilibrium, our values of V, P and C will change until they are equal to the point of stable equilibrium. A point of equilibrium is unstable if V, P and C will never reach this point, they will never be equal at this point of equilibrium [7]. To study the stability of a point of equilibrium, Theorem 1.1.2 is applied as follows:

f(V,P,C)=(f_1(V,P,C),f_2(V,P,C),f_3(V,P,C))

With f_1(V,P,C)=γPC, f_2(V,P,C)=γP(1-P)-(1-γ)P, f_3(V,P,C)= (1-C)$(V/V_0)^{2/3}$-αPC.

$$J_f(V,P,C)=\begin{pmatrix}\frac{\partial f_1(V,P,C)}{\partial V} & \frac{\partial f_1(V,P,C)}{\partial P} & \frac{\partial f_1(V,P,C)}{\partial C}\\ \frac{\partial f_2(V,P,C)}{\partial V} & \frac{\partial f_2(V,P,C)}{\partial P} & \frac{\partial f_2(V,P,C)}{\partial C}\\ \frac{\partial f_3(V,P,C)}{\partial V} & \frac{\partial f_3(V,P,C)}{\partial P} & \frac{\partial f_3(V,P,C)}{\partial C}\end{pmatrix}$$

$$= \begin{pmatrix} \gamma P & \gamma V & PVW \\ 0 & -2\gamma P + 2\gamma - 1 & -WP^2 + 2WP \\ \frac{2}{3}\frac{1-C}{(V_0)^{\frac{2}{3}}}(V)^{\frac{-1}{3}} & -\alpha C & -\alpha P - \left(\frac{V}{V_0}\right)^{\frac{2}{3}} \end{pmatrix}$$

With: $W=(5\text{-}5(\tanh^2(10(C-C_{hyp})))$

The stability of the point (0, 0, C): Note that the trivial equilibrium point (0,0,C) with $C \in [0;1]$ gives an indefinite case, because if we replace it in the Jacobian the $V^{-1/3}=0^{-1/3}$, then we cannot conclude anything.

The stability of the point (V, 0, 1): Let's calculate the Jacobian at the point (V,0,1), we obtain:

$$J = J_f(V,0,1) = \begin{pmatrix} 0 & \frac{1+\tanh(10-10C_{hyp})}{2}V & 0 \\ 0 & \tanh(10-10C_{hyp}) & 0 \\ 0 & -\alpha & -\left(\frac{V}{V_0}\right)^{\frac{2}{3}} \end{pmatrix}$$

Let's now calculate the eigenvalues of the matrix J:

The eigenvalues of the matrix J are the scalars such as:

Then:

det (J−λI)=0

$$\begin{vmatrix} -\lambda & \frac{1+\tanh(10-10C_{hyp})}{2}V & 0 \\ 0 & \tanh(10-10C_{hyp})-\lambda & 0 \\ 0 & -\alpha & -\left(\frac{V}{V_0}\right)^{\frac{2}{3}}-\lambda \end{vmatrix} = 0$$

So:

$(-\lambda)(\tanh(10\text{-}10_{hyp}\text{-}\lambda)(-(V/V_0)^{2/3}\text{-}\lambda)=0$

Finally we have: $\lambda_1=0$,

Where, $\lambda_2= \tanh(10\text{-}10C_{hyp})>0$. (Because if:

$$\tanh(10-10C_{hyp}) = \frac{e^{10(C-C_{hyp})} - e^{-10(C-C_{hyp})}}{e^{10(C-C_{hyp})} + e^{-10(C-C_{hyp})}} < 0.$$

Then $e^{10(C-C_{hyp})}<-e^{10(C-C_{hyp})}$, this is impossible).

And: $\lambda_3=-(V/V_0)^{2/3}<0$ (because $V>0$ and $V_0>0$). Hence

the point (V,0,1) is an unstable equilibrium point.

The existence of model solutions

The local existence of the solutions of the system (2.5) is given by the Cauchy Lipschitz theorem, if we succeed in obtaining that P and C are bounded, we will have the global existence.

Proposition 3.1: [9] (P and V properties). Let γ be a real function such as $\gamma \in C^\infty([0,+\infty[)$ and: $\forall t \geq 0$, $\gamma(t) \in [0;1]$.

Let now $P_0 \in [0;1]$ et (P,V) such as: $V(0)=1, P(0)=P_0$

$\forall t \geq 0$:

$dV/dt=\gamma PV$,

$dP/dt=(2\gamma\text{-}1)P\text{-}\gamma P^2$ ….. (11)

Then, there exists a unique pair $(P,V) \in C^\infty([0,+\infty[$ solution of (5). In addition, P and V verify: $\forall t>0$, $V(t) \geq 1$; $P(t) \in [0;1]$.

Proof: see [7].

Proposition 3.2: [7] (properties of C). Let $\propto$ be a positive parameter and P, V two functions $C^\infty([0,+\infty])$ such as:

$\forall t \geq 0$, $V(t) \geq 1$; $P(t) \in [0;1]$.

Let $C_0 \in [0;1]$ and C such as:

$C(0)=C_0$

$dC/dt=(1-C)(V/V_0)^{2/3}$- PC

Then, C exists and is unique in C^1 ($[0,+\infty[$ and verifes:

$\forall t>0$, $C(t) \in [0;1]$.

Proof: see [7].

Adding Treatment

We modeled the growth of a non-vascularized lung tumor in the absence of treatment. The only cause of a decrease in the amount of proliferating cells was thus the case where the tumor was in a state of hypoxia. However, cases in which no treatment is undertaken to treat the tumor are quite rare. So we will add a term in our equation to simulate chemotherapy [10]. This is simply a term that decreases the amount of proliferating cells in the tumor. We will consider that chemotherapy consists of several injections, on dates t_i and quantities of f_i product. The quantity of product present in the organism has an exponential decay in $1_{t > t_i} e^{-\lambda(t-t_i)}$. (This hypothesis is false: chemotherapy is eliminated very quickly in the body, but its effects are long-lasting in the body because certain types of cells take a long time to regenerate. side effects of chemotherapy that have an exponential decay. For obvious reasons of patient health, one cannot restart the treatment as long as these effects are not largely passed) [7].

It is considered that the total of the injection will not be able to exceed a quantity f_{max} of product, even if modifying the coefficient which gives the force of action of the chemotherapy on the proliferating cells, one can take $f_{max}=1$, [7]. Let

$$\sum_i f_i \leq 1.$$

We consider here that the parameters of our problem are known (that is, we have already determined the parameters that come into play in the growth of the tumor without treatment and we consider that the treatment does not change these parameters) and that we only have to determine the optimal moments and the ideal doses for injection [7].

Considering that treatment consists of three injections and that the amount of chemotherapy in an organism decreases exponentially over time, our system equation becomes [7]:

$$\left\{\begin{array}{l}\dfrac{dV}{dt}=\gamma PV,\\ \dfrac{dP}{dt}=\gamma P(1-\mathrm{P})-(1-\gamma)\,\mathrm{P}-\beta\sum_{i=0}^{2}1_{t>t_i}\,f_i e^{-\lambda(\mathrm{t}-\mathrm{t}_i)}P,\\ \dfrac{dC}{dt}=(1-\mathrm{C})\left(\dfrac{V}{V_0}\right)^{\frac{2}{3}}-\alpha PC,\\ \gamma=\dfrac{1+\tanh(10(\mathrm{C}-\mathrm{C}_{hyp}))}{2}\end{array}\right\}$$

$$J_f(V,P,C)=\begin{pmatrix}\gamma P & \gamma V & PVW\\ 0 & -2\gamma P+2\gamma-1-\beta\sum_{i=0}^{2}1_{t>t_i}f_i e^{-\lambda(t-t_i)}P & -WP^2+2WP\\ \dfrac{2}{3}\dfrac{1-C}{(V_0)^{\frac{2}{3}}}(V)^{\frac{-1}{3}} & -\alpha C & -\alpha P-\left(\dfrac{V}{V_0}\right)^{\frac{2}{3}}\end{pmatrix},$$

.....(12)

Where, λ is a parameter.

The first injection is carried out at a fixed time t_0 and with a known amount f_0 of drug. We want to determine the dates of injections 1 and 2 and the amount of product f_1 to be injected at time t_1.

Behavior of Model Solutions (12)

With the same procedure (already done above), we will calculate and study the stability of the system equilibrium points (13).

Calculation of equilibrium points

In the same previous way we obtain the three following equilibrium points: The trivial equilibrium point (0, 0, C) with C∈[0;1],(,0,1) with V>0 and

$$(0,2-(\frac{1+\beta\sum_{i=0}^{2}1_{t>t_i}f_i e^{-\lambda(t-t_i)}}{\gamma}),0)$$

Stability of equilibrium points

Let's compute the Jacobian of f:

Let's put:

X=(V,P,C), f(X) =[f_1(X),f_2(X),f_3(X)]

Such as:

f_1(V,P,C)=γPC,

$$f_2(V,P,C)=\gamma P(1-P)-(1-\gamma)P-\beta\sum_{i=0}^{2}1_{t>t_i}f_i e^{-\lambda(t-t_i)}P,$$

f_3(V,P,C)=(1-C)(V/V_0)$^{2/3}$- PC.

With: W=(5−5[tanh^2{10(C−C_{hyp})}])

The stability of the point (0,0,C): For the point (0,0,C) with C∈[0;1] we cannot conclude anything about its stability. (See more above).

The stability of the point (0,2-(1+Σ$^2_{i=0}$1$_{t>ti}$f$_i$e$^{-λ(t-ti)}$/),1): Note that this equilibrium point gives an indefinite case, because if we replace it in the Jacobian we obtain $V^{-1/3}=0^{-1/3}$, then it is not an equilibrium point.

The stability of the point (V,0,1) with V>0: With the same method that we adopted above (by substituting the point (V,0,1) in the Jacobian and by calculating the eigenvalues of this matrix) we obtain three eigenvalues:

$λ_1$=0, $λ_2$=[tanh(10-10C_{hyp})-Σ$^2_{i=0}$1$_{t>ti}$f$_i$e$^{-λ(t-ti)}$]>0, and $λ_3$=-(V/V_0)2/3<0 (because V>0 and V_0>0)

Hence the point (, 0, 1) is an unstable equilibrium point.

Numerical Simulation

To fully understand these models, we will illustrate the result of the problems (2.5) and (2.13) on the same Figure 4, using the SCILAB software. For a fast-growing (exponential) tumor the algorithm advises giving the maximum doses of treatment at the smallest possible time intervals. For example for the tumor of Figure 4, we considered that the treatment could only take place between the instants t=4 and t=10. The algorithm advises us the dates of treatment and the chemotherapy following quantities [7] (Tables 3-5):

φ0	**0.3**
φ1	0.3939344
φ2	0.3060656

Table 3: Quantities of chemotherapy injected [7].

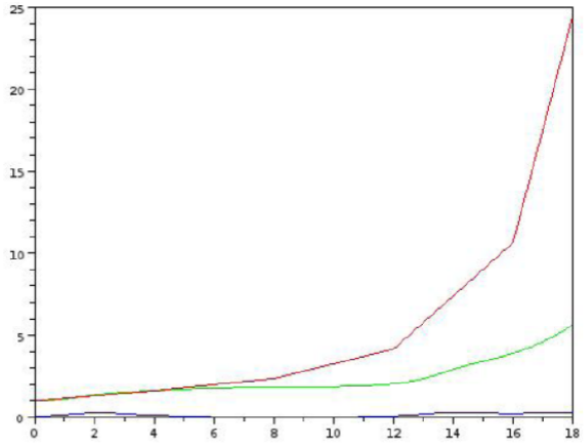

Figure 4: In red, the V without treatment, in green the V with treatment and in blue PV with treatment.

This modifies the growth of the tumor as shown in Figure 4. On the other hand, for a tumor with growth slowed by a tray, the algorithm advises well to wait the end of the tray to give the last two injections [7]:

τ0	**4**
τ1	6.0077193
τ2	8.0023693

Table 4: Treatment dates [7].

φ0	**0.3**
φ1	0.4627891
φ2	0.2372109

Table 5: Maximum doses of treatment each time [7].

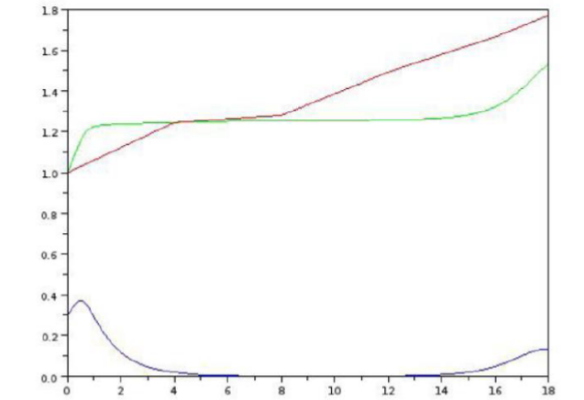

Figure 5: In red, the V without treatment, in green the V with treatment and in blue PV with treatment [7].

Discussion

According to Figure 4, we note that the tumor volume without treatment gradually increases from an initial volume V_0=1 at t=0 to V=25 at t=18 with an exponential growth (Note that the quantity of proliferating cells in the tumor grows from t=0 to t=3). But during the first chemotherapy injection f_0=0.3 at t=4, we notice that the volume increases slowly then it becomes constant (The proliferating cells begin to disappear). After t=12, the tumor volume is still growing until V=6 at t=18, and the proliferating cells begin to multiply again.

From Figure 5, we note that the tumor volume with treatment is increased from an initial volume V_0=1 at t=0 to V=1.2 at t=1 and that the quantity of proliferating cells in the tumor also grows from t=0 to t=1. During the first chemotherapeutic injection f_0=0.3 at t=4, the volume becomes constant from t=1 to t=15 (add other injections), and at the same time, the curve of the quantity of proliferating cells in the tumor decreases and then vanishes from t=1 to t=15. Note that after t=15, the tumor volume begins to grow again until it reaches V=1.5 at t=18 (the same behavior of proliferating cells).

From these experiments, it is deduced that chemotherapy is not very effective in getting rid of the tumor, but only to minimize its size and slow down its growth.

Conclusion

In this paper, we presented a temporal mathematical model which represents firstly the growth of a non-vascularized pulmonary tumor with a study of the stability of this model and secondly we studied the same model in the presence of chemotherapeutic treatment, and for that we have to add a term in our equation to simulate the chemotherapy, this one is simply presented as a term which decreases the quantity of proliferating cells in the tumor, and also we study the stability in this case.

After, a comparison was made between the evolution of the growth of this tumor before and during the treatment which in the figures shows that chemotherapy is not very effective in definitively rid the tumor, but just to minimize its size and slow its growth. Lung cancer starts in the cells of the lung. The tumor cancerous (malignant) is a group of cancer cells that can invade and destroy the neighboring tissue. It can also spread (metastasize) to other parts of the body.

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