Journal of Computer Science & Systems Biology

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

Research Article Open Access

Math Modeling of Cancer Angiogenesis and its Treatments

Abdellatif Bettayeb[1], **Ahlem Benzahi**[2] **and Cheima Belbezzouh**[2]

[1]*Department of General Studies, Jubail Industrial College, Kingdom of Saudi Arabia*

[2]*Department of Mathematics, Department of Mathematics, Mentouri University of Constantine, Algeria*

[*]**Corresponding author:** Abdellatif Bettayeb, Department of General Studies, Jubail Industrial College, Jubail Industrial City, Kingdom of Saudi Arabia, Tel: 00966560755963; E-mail: abdellatif.bettayeb@gmail.com, haloumabenz1995@gmail.com, belbezzouhchaima1995@gmail.com

Rec date: December 18, 2019; **Acc date:** February 17, 2020; **Pub date:** February 24, 2020

Abstract

This work is part of the general framework of the study of mathematical modeling of cancer and its treatment. The purpose of this article is to present and analyze the model of tumor angiogenesis, (second stage of cancer: formation of new blood vessels by a malignant tumor), then to describe models of associated therapies, such as: anti-angiogenesis treatments and chemotherapeutic treatments. And finally, to numerically illustrate these models and to compare between the two therapies using MATLAB.

Keywords: Cancer angiogenesis; Tumor angiogenesis; Chemotherapy; Radiotherapy; Immunotherapy

Introduction

What is cancer?

Cancer is a disease of the cell. A cancer cell is that can be modified. Usually these changes are repaired by the body. However, when the cell becomes cancerous, it loses its repair capabilities. It then begins to multiply and nit by forming a mass called a malignant tumor. Cancer cells tend to migrate to other parts of the body through the lymphatic vessels or blood vessels, and develop new tumors there, called metastasis. In this case, the cancer is said to be metastatic [1].

Some cancer treatments

Surgery: The goal of surgery is to completely remove the tumor.

Chemotherapy: Chemotherapy uses drugs to kill cancer cells. It aims to eliminate cancer cells wherever they are in the body, either by destroying them directly or by preventing them from multiplying. Chemotherapy works on all cancer cells, even those that could not be identified during examinations. Chemotherapy drugs can be administered in several ways: through injections into a vein, through the mouth, or through injections into the muscle [1].

Radiotherapy: Radiotherapy uses very powerful beams of energy, such as X-rays or protons, to kill cancer cells. Radiation therapy can come from a machine outside your body or be placed inside your body [2].

Immunotherapy: Immunotherapy, also called biological therapy, uses your body's immune system to fight cancer. It helps the immune system to see and attack cancer [2].

From tumor to mathematical model

Today mathematicians have applied the mathematical model to real situations (clinical cases). To do this, we must be able to estimate the many parameters involved in the model. Indeed, formulations based on partial differential equations (EDP), or ordinary differential equations (EDO), often involve very many coefficients. In addition, the various forms of cancer do not all have the same behavior. However, the vast majority of tumors are characterized erect by three stages of growth [3]:

- The avascular (non-vascularized) stage, where the tumor consumes the nutrients present in its immediate environment.
- The vascular stage, where the tumor will increase its supply of nutrients via the creation of a microvascular network. This process of creating new vessels is called angiogenesis.
- The metastatic stage, where the tumor spreads to the rest of the body. Cancer is then generalized and nit by threatening the functioning of many vital organs.

Modeling of Angiogenesis and Its Treatments

Model of angiogenesis of the tumor

We mainly considered formulations based on ODEs, which only describe the dynamics of cancer growth. In this context, the tumor growth model of Hahnfeldt et al. [4] is usually preferred. Indeed, the formulation of Hahnfeldt et al. is based on experimental observations. The tumor angiogenesis model according to Hahnfeldt et al. formalizes itself as follows. Let C(t) be the volume of the cancerous cells, and E(t) the volume of the endothelial cells (The endothelial cells are those that line the inside of the vessels. These are the cells that are in direct contact with the blood and that ensure the integrity of the vessels. In the capillaries, they form the small channels within which the circulating blood feeds the tissues that feed the tumor with oxygen and nutrients). The tumor angiogenetic evolution is described by the system following EDO [3]:

$$dC/dt=-\lambda_c C(t)\log[C(t)/E(t)],$$

$$dE/dt=bC(t)-dC(t)^{2/3}E(t) \quad \ldots\ldots\ldots\ldots\ldots(1)$$

With: λ_c the growth rate of the tumor, b the birth rate of vascular endothelial cells, d the endothelial cell death rate.

In particular, the tumor follows a Gompertzian function implying that its growth is saturates at a maximum volume.

Endothelial cell birth (b) and death (d) rates are mainly dependent on tumor type and patient.

Behavior of the solutions of the model

The calculation of equilibrium points: The system (1) always has the trivial equilibrium point $(C_*,E_*)=(0,0)$ (it is not acceptable because $\log(C_*/0)$ is undefined), then look for other equilibrium points.

From the system (1), the equilibrium state is obtained as follows: An equilibrium point of the system (1) is the point (C_*,E_*) that satisfies the system solution:

$dC/dt=-\lambda_c C_* \log(C_*/E_*)=0$,

$dE/dt=bC_*-dC_*^{2/3}E_*=0$ ……(2)

The resolution of the system (2) gives us this equilibrium point:

$A=[(b/d)^{3/2},(b/d)^{3/2}]$ ……(3)

The stability of the equilibrium point: To study stability, we have to:

Calculate the Jacobian of *f* at the point A, we obtain:

$$J = J_f(A) = \begin{bmatrix} -\lambda_c & \lambda_c \\ \frac{b}{3} & -b \end{bmatrix}$$

Let's now calculate the eigen values of the matrix J, we obtain:

$$\lambda_1 = \frac{-(\lambda_c + b) - \sqrt{\Delta}}{2} \text{ and } \lambda_2 = \frac{-(\lambda_c + b) + \sqrt{\Delta}}{2}$$

To study the sign of λ_1 and λ_2, we obtain that λ_1 and λ_2 are negative, so the point $A=(b/d)^{3/2}$ is an asymptotically stable equilibrium point.

Numerical simulation

The original model of the physiological data of Hahnfeldt et al. was initially established to describe the vascular stage of the tumor. The authors were able to validate their formulation after the observation of Lewis lung carcinoma on mice [4]. They then identified the parameters λ_c,b,d of their model from experimental data. The identified values are summarized in the following Table 1:

Parameters	Values [4]	Unit
λ_c	0.192/ln(10)	1/day
b	0.00873	1/(day mm^2)
d	5.85	1/day

Table 1: Parameters of tumor growth by angiogenesis according to the observations of Hahnfeldt et al. of a tumor in the mouse.

Figure 1 shows the evolution of tumor and endothelial volume growth for the vascular stage. The volume of the tumor increases along a Gompertzian curve and after 100 days it reaches the equilibrium value $C_*=E_*=17346.5$ mm^3 predicted by the equation (3).

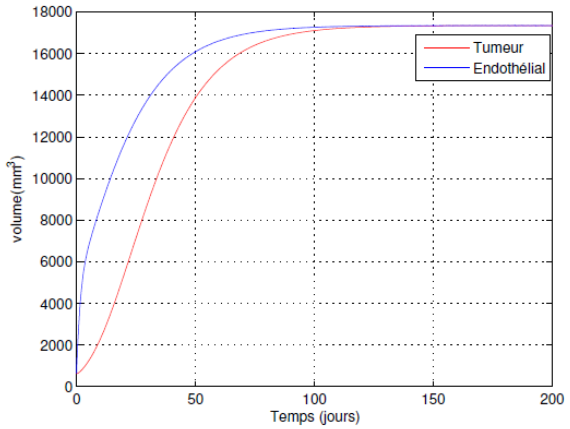
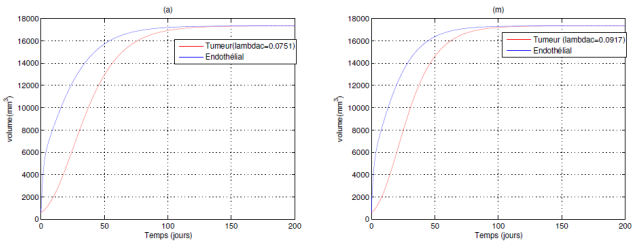


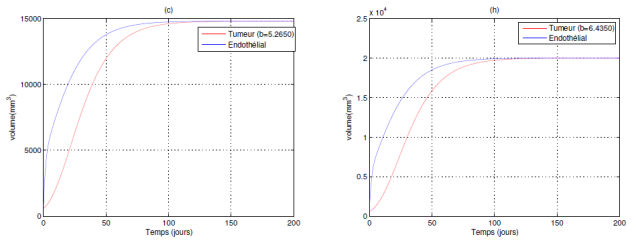
Figure 1: Evolution of tumor volumes and endothelial cells.

Analysis of the Hahnfeldt et al. growth model

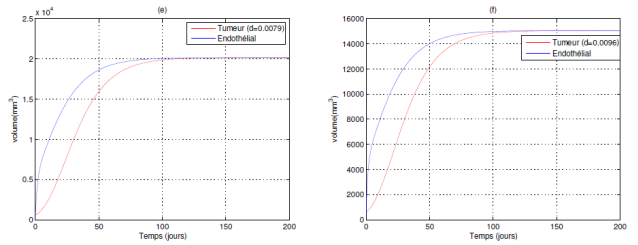
In this part, we vary the parameters of the Hahnfeldt et al. from the previous table. The results obtained are illustrated on the curves of Figure 2. In the first place, the growth rate of the tumor λ_c as in Figures 2a and 2m only moderately affects the time that puts the tumor to reach its state of equilibrium. As expected, a change in the birth and death rates of "b" induces a change in the equilibrium state of tumor and endothelial cell volumes as in Figures 2c, 2h, 2e and 2f. In practice, the mortality rate d hardly varies. On the other hand, the birth rate b evolves according to the stage of the tumor. Finally, a good knowledge, and a good control of the birth rate, is really necessary for the description of the growth model of the tumor [3].



Figures 2a and 2m: Analysis of tumor and endothelial volume growth as a function of tumor growth rate (a): λc=0:0751, (m): λc=0:0917; of birth rate b.



Figures 2c and 2h: Analysis of tumor and endothelial volume growth as a function of tumor growth rate (c): b=5.2650, (h): b=6.4350; and mortality d.



Figures 2e and 2f: Analysis of tumor and endothelial volume growth as a function of tumor growth rate (e): d=0.0079, (f): d=0.0096 mortality d.

Finally, without any intervention on the tumor, it will evolve from one stage to another (i.e., from an avascular stage, then vascular, to then spread into metastases), while continuing to grow and invade healthy tissue in the vicinity of the tumor. It is therefore important to act quickly, using the most appropriate therapy according to the state of development of the tumor, and the state of health of the patient.

Modeling anti-angiogenesis treatment

Anti-angiogenesis treatment is a special form of chemotherapy. It is applied to limit the growth of the tumor, reducing its vascularity, and therefore its nutrient intake. Therefore, for such treatment, only the growth of endothelial cells will be limited by an anti-angiogenic agent, such as endostatin, whose plasma concentration is denoted $\delta_a(t)$. The formulation of an anti-angiogenesis treatment according to the tumor growth model considered can thus be expressed by the following EDO system [4]:

$$dC/dt=-\lambda_c C(t)\log[C(t)/E(t)],$$

$$dE/dt=[bC(t)-dC(t)^{2/3}E(t)]-[k_a\delta_a(t)E(t)],$$

$$d\delta_a/dt=\mu-\lambda_\delta\delta_a(t) \quad \ldots\ldots\ldots\ldots..(3)$$

With k_a the parameter defining the efficacy of the anti-angiogenic agent that inhibits vascularization of the tumor.

Behavior of the solutions of the model

The calculation of equilibrium points:

With the same previous way we will calculate the equilibrium points we obtain:

The trivial equilibrium point $(C_*,E_*)=(0,0)$ which is not acceptable and the second is the following:

$$B=[(b-k_{aa}/d)^{3/2},(b-k_{aa}/d)^{3/2}] \quad \ldots\ldots\ldots\ldots(5)$$

The stability of the equilibrium point: We will follow the same previous steps and after the Jacobian calculus at point B and calculate the eigenvalues of the Jacobian matrix we deduced that, the point $B=[(b-k_{aa}/d)^{3/2},(b-k_{aa}/d)^{3/2}]$ is an asymptotically stable equilibrium point.

Analysis of the model of anti-angiogenesis treatments

From the experimental observations, the authors identified the following values for the parameters of the model PK-PD [3] part for the Endostatin administration. Endostatin is a type of cytokine produced by the cells of the immune system. It's a vector therapeutically used in anti-angiogenic treatments: $k_a=0.66/(day.conc)$, $\lambda_{delta}=1.7/day$, $\lambda_c=[0.192/\ln(10)]$ (1/day), b=5.85 (1/day), $d=8.73\times10^3$ $[1/(day.mm^2)]$.

Figures 3 and 4 simulate the anti-angiogenesis treatment of a tumor with an initial volume of $C_0=300$ mm^3, and for a volume of cells endothelial cells of $E=300$ mm^3, treated with continuous (e.g., intravenous) administration of $\mu=20$ conc/day of endostatin. This simulation corresponds to the experiments carried out by Hahnfeldt et al.

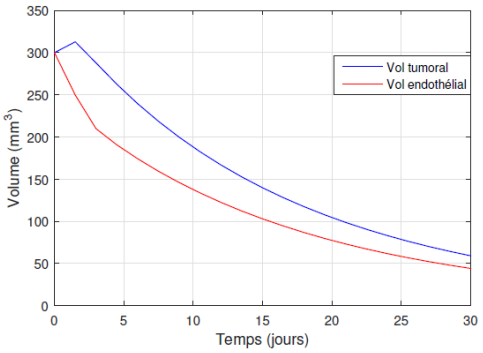


Figure 3: Anti-angiogenesis treatment of cancer: simulation of the evolution of tumor volume and endothelial cells.

As we can see the volume of endothelial cells begins to decrease, thus limiting the nutrient supply to the tumor. As a result, the volume of it decreases and becomes almost negligible. This result shows the interest of anti-angiogenesis treatments to limit the development of cancers. It is important to note that the simulation results obtained by the EDO (4) system coincide perfectly with the experimental observations of Hahnfeldt et al. [4], represented in the Figures 3 and 4. However, we can also observe on the curve of Figure 4 that the concentration of endostatin remains important.

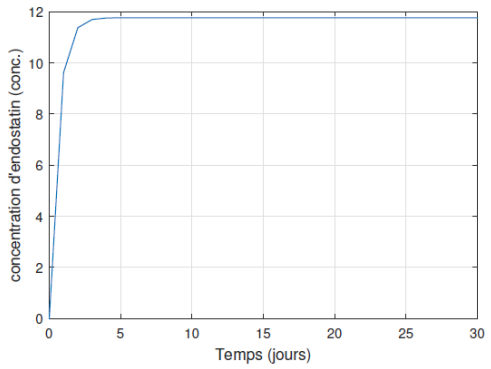


Figure 4: The concentration of the anti-angiogenic agent (here endostatin).

Modeling of chemotherapeutic treatment

Chemotherapy is one of the major categories of cancer treatment that uses chemicals. Generally, the chemotherapeutic agents use one or more cytotoxic agents (such as doxorubicin) to kill cells that behave like tumor cells (e.g., those that divide rapidly). To model the effect of a cytotoxic chemotherapeutic agent concentration $\delta_x(t)$ on the growth of a tumor, the following approximation is considered [5]:

$dC/dt=[-\lambda_c C(t)\log\{C(t)/E(t)\}-k_{cx}C(t)\delta_x(t)]$,

$dE/dt=[bC(t)-dC(t)^{2/3}E(t)]-[k_{ex}E(t)\delta_x(t)]$,

$\delta_x/dt=\mu-\lambda_\delta\delta_x(t)$ …….. (6)

With k_{cx} and k_{ex} the parameters of the PD model. In particular, the case where $k_{ex}=0$ means that the cytotoxic drug has no effects on the endothelial cells.

Behavior of the solutions of the model

The calculation of equilibrium points: With the same previous way we will calculate the equilibrium points we obtain:

The trivial equilibrium point $(C^*,E^*)=(0,0)$ which is not acceptable and the second is the following:

$$M=\left[\left(\frac{be^{\frac{-k_{cx}\delta_x}{\lambda_c}}-k_{ex}\delta_x}{d}\right)^{\frac{3}{2}},\left(\frac{be^{\frac{-k_{cx}\delta_x}{\lambda_c}}-k_{ex}\delta_x}{d}\right)^{\frac{3}{2}}e^{\frac{k_{cx}\delta_x}{\lambda_c}}\right] \quad .....(7)$$

The stability of the equilibrium point: We will follow the same previous steps and after the Jacobian calculus at point B and calculate the eigenvalues of the Jacobian matrix we deduced that, the point is an asymptotically stable equilibrium point.

$$M=\left[\left(\frac{be^{\frac{-k_{cx}\delta_x}{\lambda_c}}-k_{ex}\delta_x}{d}\right)^{\frac{3}{2}},\left(\frac{be^{\frac{-k_{cx}\delta_x}{\lambda_c}}-k_{ex}\delta_x}{d}\right)^{\frac{3}{2}}e^{\frac{k_{cx}\delta_x}{\lambda_c}}\right]$$

Analysis of the model of chemotherapeutic treatments

Unlike the previous model of inhibition of angiogenesis, to our knowledge, the literature does not propose any experimental data for PK-PD model parameters [3] Onofrio and al. have proposed the following values [5]: $k_{cx}=0.1$ conc/day and $k_{ex}=0.1$ conc/day, while exploiting the data proposed by Hahnfeldt et al. [4].

The Figure 5 illustrates a chemotherapeutic treatment of a tumor of an initial volume of $C_0=300$ mm^3 and a volume of endothelial cells of $E_0=300$ mm^3.

The tumor is treated with continuous administration of a cytotoxic substance of $\mu=3$ conc/day (such as doxorubicin, daunorubicin, vincristine, etc.). It has been found that in less than 5 days, the volume of the tumor decreases rapidly, and can be considered eliminated. Indeed, the cytotoxic agent will act directly on the cells of the tumor to destroy them. However, the curve of Figure 5b shows that the concentration of the cytotoxic agent remains very important. This vector will thus not only attack the cells of the tumor, but also healthy cells. To limit the impact on the latter, the drug dose must be established judiciously [6].

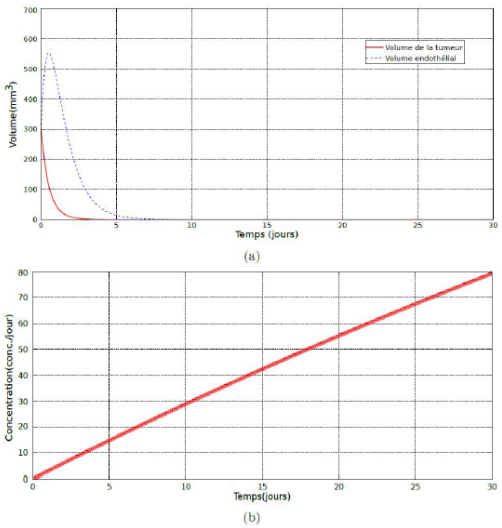


Figure 5: Simulation of a chemotherapeutic treatment of cancer with (a) the volume of the tumor and endothelial cells; and (b) evolution of the concentration of the cytotoxic agent (e.g., doxorubicin) [4].

Conclusion

These results illustrate that despite the downsides of chemotherapy, it remains more effective than anti-angiogenic treatment in eradicating cancer. But despite the positives of chemotherapy, it greatly affects human health, and this is why researchers are constantly thinking to avoid resorting to it, by developing other treatments that are more effective and less harmful to the human body. Perhaps with recent studies, researchers may reach to get rid of chemotherapy and its side effects from the way of immunotherapy.

References

1. Institut National du Cancer Service (2008) Comprendre la chimiothérapie. Réédition Actualisée.
2. Mayo Clinic (2019) Cancer treatment, USA.
3. Lyès M (2016) Modeling and ordering magnetic microbots for targeted cancer treatment. pp: 35-51.
4. Hahnfeldt P, Panigrahy D, Folkman J, Hlatky L (1999) Tumor development under angiogenic signaling: a dynamical theory of tumor growth, treatment response, and postvascular dormancy. Cancer Res 59: 4770-4775.
5. D'Onofrio A, Ledzewicz U, Maurer H, Schättler H (2009) On optimal delivery of combination therapy for tumors. Math Biosci 222: 13-26.
6. Verhulst PF (1838) Notice on the law that the population follows in its growth. Math Phys 10: 113-126.