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Gompertz Model: Resolution and Analysis for Tumors

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Abstract.
It is called cancer a wide range of diseases that has in common an unusual cells proliferation of the organism itself. This uncontrolled proliferation provokes the formation of a cellular mass named tumor. In order to enable the tumor develop beyond a given volume it needs to develop the capacity to promote the growth of new blood vases towards itself. Those new vases will proportionate the blood irrigation of the tumor, supplying its needs of nutrition and oxygenation. If this vascularization does not happen, the tumor`s cells enters in degeneration and necrosis. The formation process of these new blood vases is called angiogenesis or neovascularization. The main objective of this paper is to use the Gompertz equation in order to study the development of blood irrigated solid tumors, using parameters defined in some important bibliographic references about the mathematical modelling of this biological phenomenon. Thus, It is showed a simple introduction of the Gompertz Equation history, its detailed resolution, and also the analysis of its equilibrium conditions, using important parameters of the tumors evolution, related to the growth rate and also to the maximum number of tumor`s cells that the organism can stand. As results, it was obtained the possibility of better understand the development behavior of a tumor mass, even modeling the standard behavior of sigmoidal growth. In addition to that, it was verified that this research can be used as support for observation and understanding of the practical application of differentials equations on teaching and on research in graduation and post-graduation of several areas.

Key words: Gompertz equation, mathematical modeling, growth tumor.

1 Introduction

As we have mentioned in the abstract, it is called cancer a wide range of diseases that have in common the unusual cell proliferation of the organism itself, i.e., the cells begins to proliferate, regardless the organism necessity (Vitria, 1997). This uncontrolled widespread provokes the formation of a cell mass named tumor, which, accordingly with its characteristics, structure and clinical proprieties, is classified as benign or malignant, and if it is malignant, usually receives the name of cancer. In the cancers, this uncontrolled and not wished proliferation provokes changes in the original function of the tissue where it is located, promoting health problems to the hostage. The tumor, in order to develop beyond a given volume, needs to develop the capacity to promote the growth of new blood vases towards itself, irrigating it and supplying therefore its necessities of nutrition and oxygenation. In case this vascularization does not happen, the tumor‘s cells enters in degeneration and necrosis. The formation process of these new blood vases is named angiogenesis or neovascularization. In this work, we will consider a tissue with cancer, where the angiogenesis has already occurred, because the initial population of cells that we will use is considerably big for a benign tumor. We will use the Gompertz equation, that is an Ordinary Differential Equation (O.D.E) that shapes mathematically the population growth, in order to study the development of solids tumor, considering that, previously, we will do a detailed mathematical resolution and we will grasp the meaning of each one of its parameters.

The Gompertz equation was developed by the Jewish mathematician Benjamin Gompertz when in 1938 he used it to describe the growth of solid tumors assuming that the growth rate of tumors diminishes in a non-linear way when its mass increases. In this paper, we will use, to make the calculations easier, that this rate r is invariable. Therefore, we will consider, like one of ours references (Boyce, 2005), and by doing some changes that this equation is as following:

$$\frac{dN}{dt} = rN \ln\left(\frac{K}{N}\right), \tag{1}$$

where

- $N = N(t)$ is the population of tumor cells.
- r is the constant intrinsic growth of cells, with $r > 0$.
- K is the carrying capacity of the tumor, that is, the maximum size that it can achieve with the available nutrients (Sachs, 2001).

It is known that solid tumors have reduced growth in the beginning of its formation and also the bigger they get, lesser they grow. What we will see, afterwards, which is described by equation 1, explaining the reason by which the Gompertz equation is widely used in modeling the growth of solid tumors.

Although the carrying capacity, K, of a tumor be intimately related with quantity of tumors cells, $N(t)$, in the instant t, we will consider, that a tumor has a limit for cell quantity that cannot be overtaken and that this value is 10^{13} cells (Spencer, 2004).

2 Resolution of the Gompertz equation

Considering that the Gompertz is and differential equation, we have, then, as a principle, only a relation that give us a variation rate of the tumors cells population as the time goes by. But, of course it would be great, if we had conditions, with this equation, to determine the one which describes exactly the tumor cells population as the time goes by, and not its variation. Well, it is enough, that we manage to solve the equation 1, to determine the equation we look for. In order to do this, we can do a replacement of variables, considering that:

$$v = \ln\left(\frac{N}{K}\right). \tag{2}$$

If we apply the exponential function on both sides of the equation 2, we obtain:

$$e^v = \frac{N}{K}.$$

Multiplying the above equation for K we can obtain that

$$N(t) = K \cdot e^v. \tag{3}$$

Using the chain rule to derive the equation 3, we conclude that:

$$\frac{dN}{dt} = Ke^v \cdot \frac{dv}{dt}. \tag{4}$$

Taking the equation 3 in equation 4 we can write

$$\frac{dN}{dt} = N \cdot \frac{dv}{dt}. \tag{5}$$

Of course, equation 2 can be written as

$$v = -\ln\left(\frac{K}{N}\right). \tag{6}$$

We can, also, replace 6 to 1 and obtain a new relation for it, as follows:

$$\frac{dN}{dt} = -v \cdot r \cdot N. \tag{7}$$

We can then match the equations 5 and 7 to find

$$\frac{dv}{dt} + r \cdot v = 0. \tag{8}$$

Let us now solve the equation 8 by the method of integrating factor, noting that it is given by $\mu(t) = e^{rt}$. Multiplying the equation 8 by the integrating factor, $\mu(t)$ we obtain:

$$\frac{dv}{dt} \cdot e^{rt} + r \cdot v \cdot e^{rt} = 0 \quad \Rightarrow \quad \frac{d}{dt}\,(v \cdot e^{rt}) = 0 \quad \Rightarrow \quad v \cdot e^{rt} = c,$$

where *c* is an arbitrary constant. Thus, we have the general solution of the equation 8 is

$$v = ce^{-rt}. \tag{9}$$

Just now, that equals the equations 2 and 9, to find that

$$\ln\left(\frac{N}{K}\right) = c \cdot e^{-rt} \quad \Rightarrow \quad \frac{N}{K} = e^{c \cdot e^{-rt}},$$

which means that we can say that the function $N(t)$, which represents the tumor cell population is given by

$$N(t) = K \cdot e^{c \cdot e^{-rt}}. \tag{10}$$

Once solved the Gompertz equation, we can think in considering an initial condition, that points out which one was the population of tumor cells in the beginning of the analysis in a way that we have a IVP (Initial Value Problem), i.e., one differential equation associated to an initial condition. Be then, the initial condition $N(0) = n_0$. Applying this condition to the equation 10, we find:

$$K \cdot e^{c \cdot e^{-r \cdot 0}} = n_0 \quad \Rightarrow \quad e^{c} = \frac{n_0}{K}.$$

Thus

$$c = \ln\left(\frac{n_0}{K}\right). \tag{11}$$

Therefore, the initial value problem of which associated deferential equation is the Gompertz equation, has got as solution the following time function:

$$N(t) = K \cdot e^{-e^{rt} \cdot \ln\left(\frac{n_0}{K}\right)}. \tag{12}$$

In possession of the Gompertz equation and its analytical solution considering a given population, we can do the study based on populations of tumor cells.

3 Analysis for tumors

Considering that, as the angiogenesis development, the tumor cell population, $N(t)$, tends to increase more and more, it is clear that it tends to approximate to the carrying capacity, *K*, of the tumor. So, we can write:

$$\lim_{t \to \infty} N(t) = K. \tag{13}$$

From the equation 1, we verify easily that the tumor cells population only stops growing, when the tumor reaches its carrying capacity, because, in this case, we have $\ln 1 = 0$, and this implies that the population variation be null.

Besides that, we observe that when the tumor cells population tends to zero, its rate of variation in function of the time also tends to zero, then

$$If\ N(t) \to 0, then\ \frac{dN}{dt} \to 0.$$

To better understand the Gompertz equation, we will do, now, an analysis more detailed of it, aiming to find its extremes values and classify, in case it exists, its equilibrium solution.

In order to do it, initially, we will find the critical points of this equation, that if they exists, well occur when

$$\frac{d}{dt}\left[r \cdot N \cdot \ln\left(\frac{K}{N}\right)\right] = 0.$$

Then

$$r\left[\frac{dN}{dt} \cdot \ln\left(\frac{K}{N}\right) + N \cdot \frac{d}{dt}\ln\left(\frac{K}{N}\right)\right] = 0 \tag{14}$$

As in this paper we are considering that the carrying capacity, *K*, is a constant, we can conclude that

$$\ln\left(\frac{K}{N}\right) = \ln\left(K \cdot \frac{1}{N}\right) = \ln K + \ln\left(\frac{1}{N}\right).$$

What allows us to guarantee that:

$$\frac{d}{dt}\ln\left(\frac{K}{N}\right) = -\frac{dN/dt}{N}. \tag{15}$$

Replacing, now, the equation 15 for the equation 14, we find that:

$$r\left[\frac{dN}{dt} \cdot \ln\left(\frac{K}{N}\right) - \frac{dN}{dt}\right] = 0 \quad \Rightarrow \quad \ln\left(\frac{K}{N}\right) = 1 \quad \Rightarrow \quad \frac{K}{N} = e.$$

Therefore, there is only one critical point for the Gompertz equation, and it is described by the equation 16:

$$N = \frac{K}{e}. \tag{16}$$

Making the necessary calculations, we verify that the second derivate of the equation 1 applied on the critical point, that we have just determined, has a negative value, and because of it, we conclude that this point is the only one of maximum point of this function and, thus, global maximum, V_{max}, that corresponds to the biggest rate of the population $N(t)$ variation, which will be given by:

$$V_{max} = r \cdot \frac{K}{e}. \tag{17}$$

Considering the main research works related to the development of tumor that we have checked for the elaboration of this paper [Domingues, 2010; Sachs, 2001; Spencer, 2004), we used the following parameters values for the Gompertz equation:

r	*K*	*N(0)*
0,0060	10^{13}	10^{9}

Table 1 Parameters used for construction of the Gompertz curve.

With the parameters described on the Table 1 and using the computational algebra system Maple 13, we plot the Gompertz curve, represented by the graphic N x $\frac{dN}{dt}$ of the bellow figure:

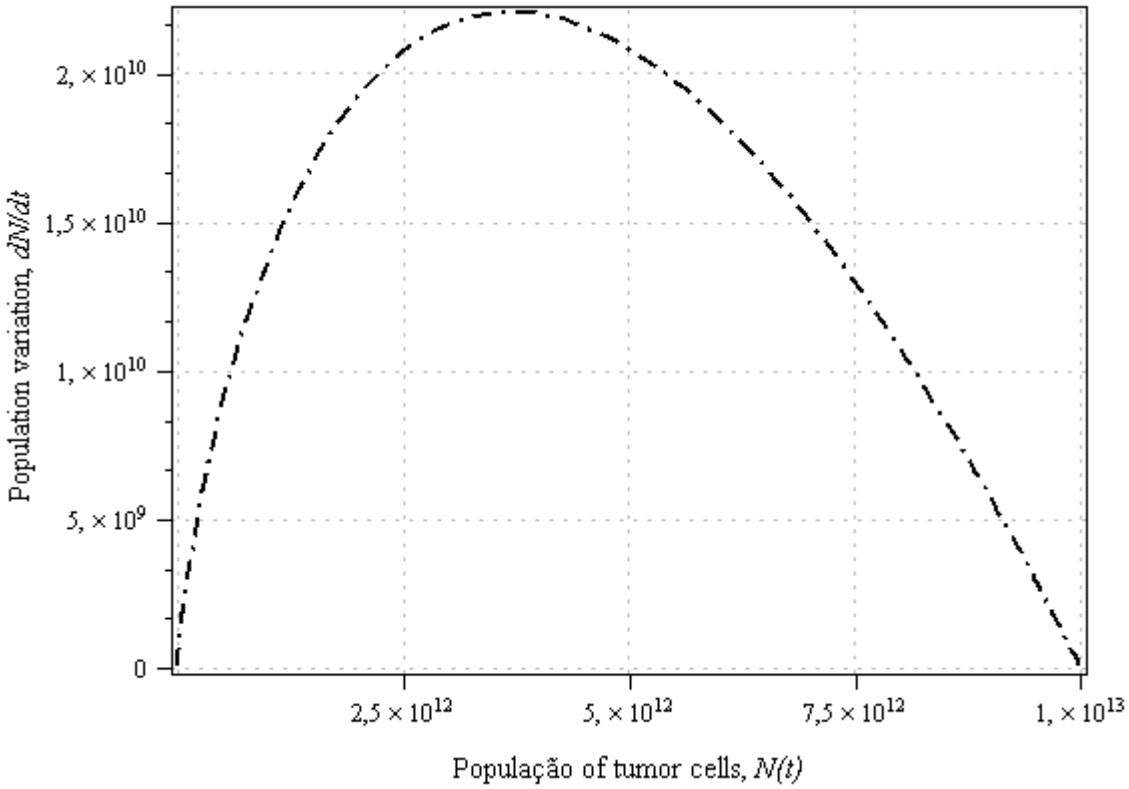


Figure 1: Graphic N x $\frac{dN}{dt}$, where the observable change in $\frac{dN}{dt}$ as N increases.

Looking at the graphic of the Figure 1, we perceive clearly that the variation rate of the tumor cell population grows until $N = K/e$ and, from that point on, decreases until zero. We understand that this decay decrease is due to the competition for nutrients and oxygen which from the maximum point on becomes too big, doing that the tumor gets its growth rate continuously diminished. Besides that, it is clear that when the variation rate nulls itself, means that the population of tumor cells enters in equilibrium, i.e., it maintains itself constant and, as we have already analytically predicted this equilibrium happens exactly when $N(t) = K$. Being so, we have that the tumor has a growth more speeded up for a period and that from $N = K/e$ and this growth has velocity slowed down, until it nulls itself and the tumor stops developing.

Doing the analysis of the graphic of the Figure 1 and using the test of second derivate we can conclude that the concavity of the curve that represents $N(t)$ is turned up on the interval $(0, K/e)$ and, turned down on the interval $(K/e\,, K)$. Besides that, as $N(t)$ tends to K when t increases, we have that the horizontal straight line $N(t) = K$ is asymptote of the graphic of $N(t)$ versus t and, that the maximum point, $N(t) = K/e$, is the point of inflexion of the graphic curve. So, the graphic t x N is as following:

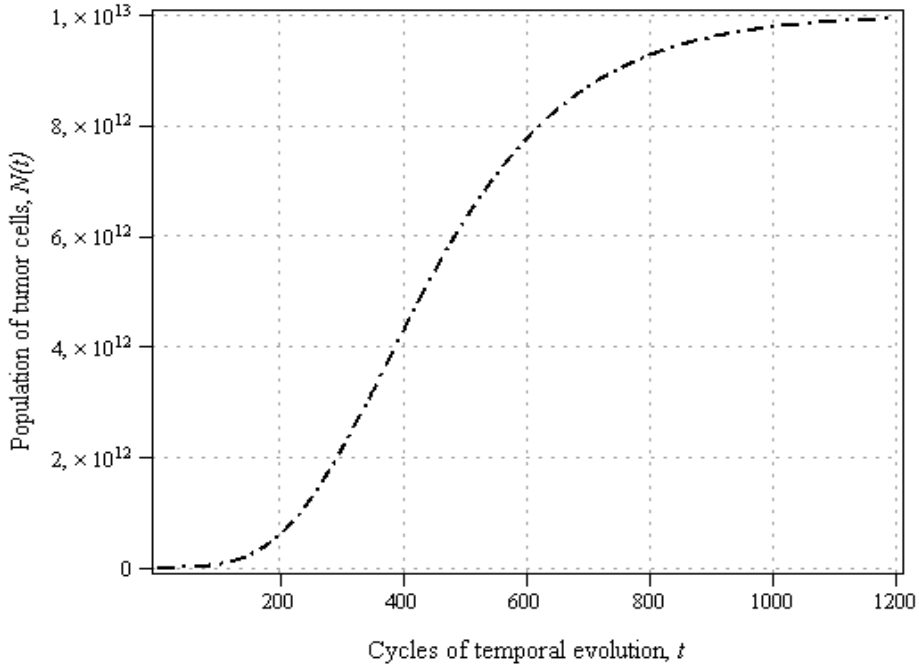
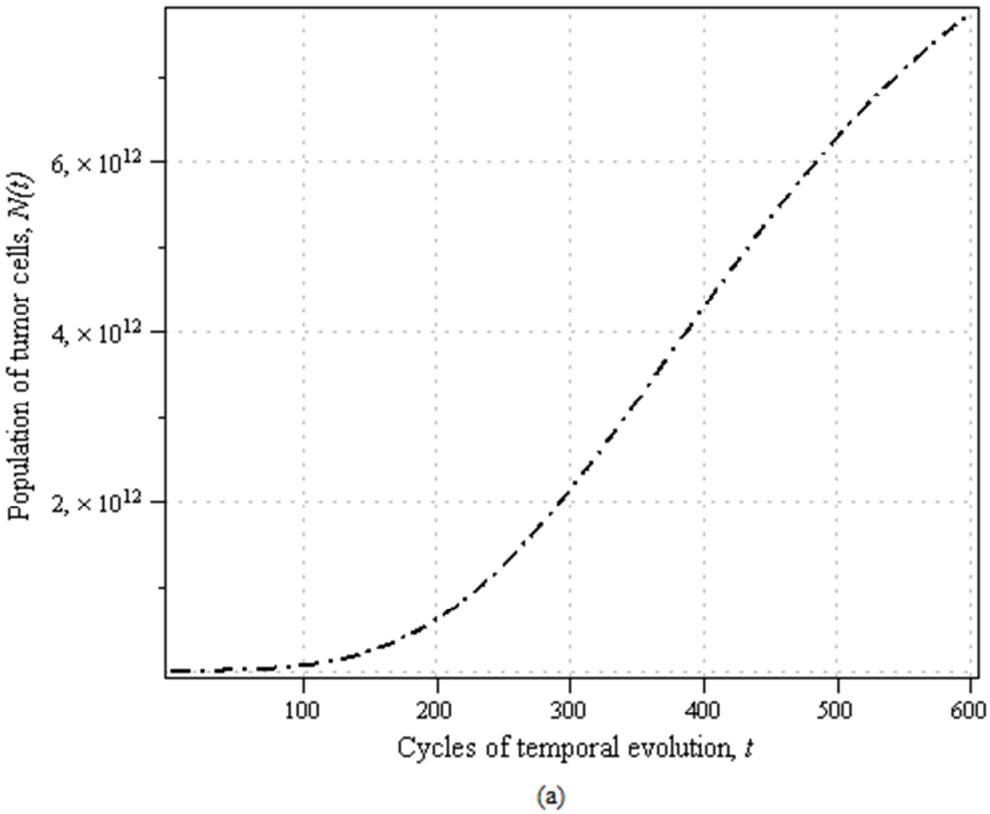


Figure 2: Graphic t x N, where it is seen that the tumor cells population tends to the equilibrium solution that occurs exactly on the value $K = 1,0 \times 10^{13}$, which is the carrying capacity of the tumor.

Enlarging specifics excerpts on the Figure 2, such as, the excerpts between the cycles of timing evolution which goes from 0 to 600 and from 0 to 40, Figures 3 (a) and (b), respectively, we can analyze more clearly some proprieties of the Gompertz Equation considering the parameters that we are using for the analysis. On the figure we perceive that the concavity of the curve is changed when $N = K/e \approx 3{,}68 \times 10^{12}$, part (a), and also, that the cell evolution begins exactly on the initial population of tumor cells, (b), i.e., 10^9.



(a)

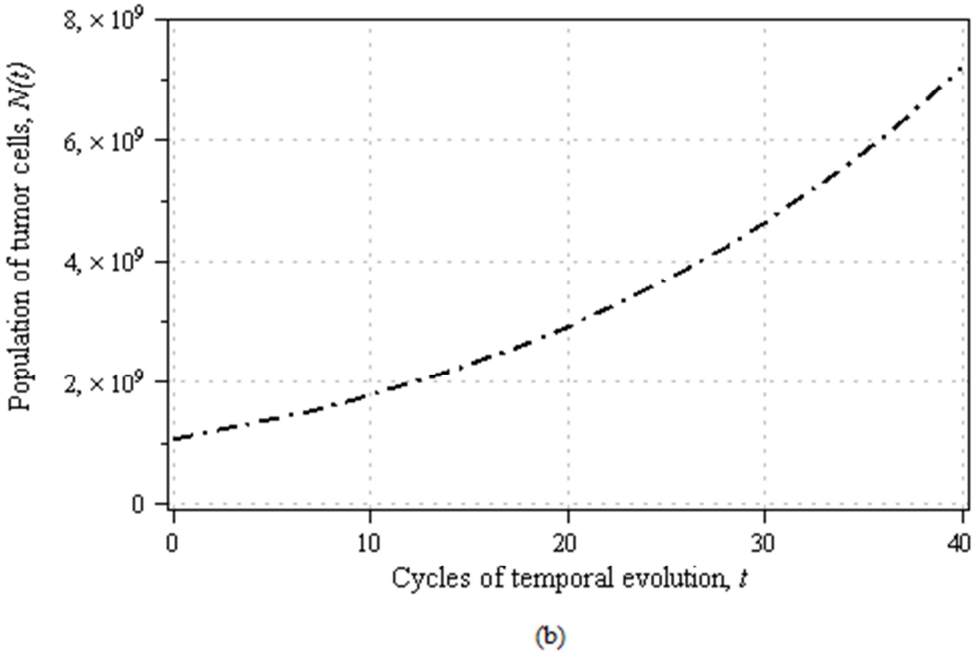


Figure 3: Enlargement of specifics excerpts of Figure 2 for an analysis more detailed of some proprieties of the Gompertz equation.

When we do variation only on the initial condition, i.e., change the value of n_0, we obtain the following behavior of tumor cells population:

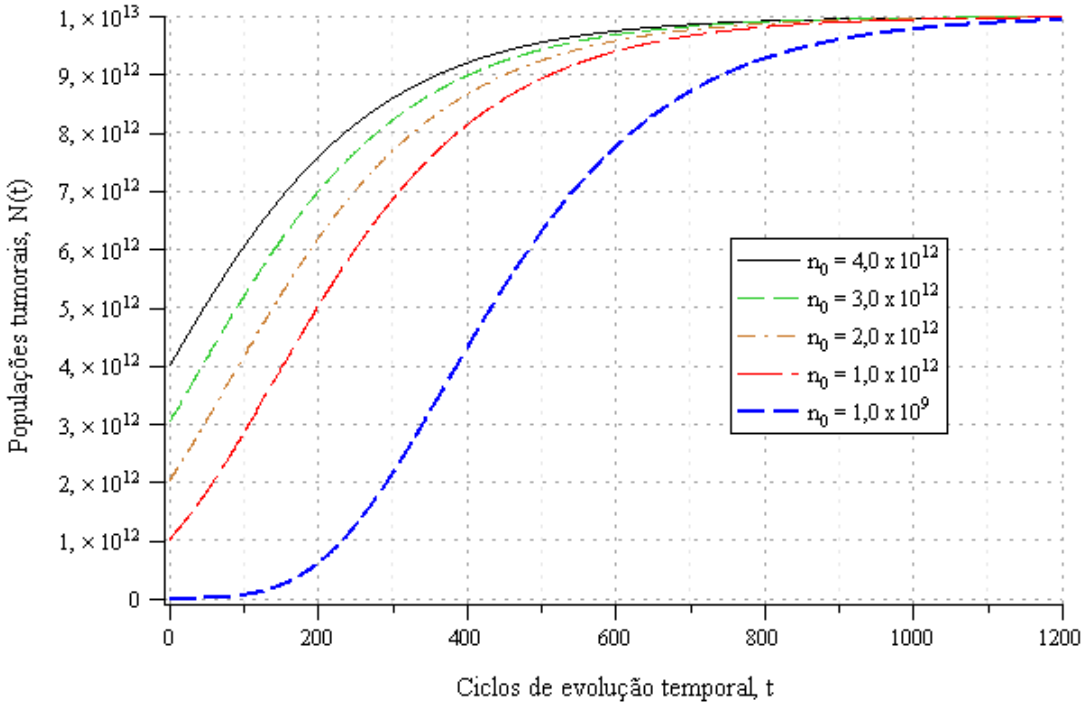


Figure 4: Behavior of Gompertz Equation solution, when varies the initial condition.

We, thus, see that the population below the equilibrium solution tends to K the more the timing evolution cycles, t, increases. It means that, if the populations of tumor cells are below the value K, it tends to grow towards this value. If we also consider, for any reason, that for some reason the tumor cell population that exceeded the value set for the carrying capacity, it also tends to this value, i.e., as K is the maximum amount that can reach the tumor if for some reason occur $N(t) > K$,

has been that with the passage of time $N(t) \to K$. Thus, we may assume that K is a stable equilibrium solution of the equation 1.

Obviously, we are analyzing the growth of tumor tissue, without considering the effect of treatments against this tumor. Being so, it is to expect that with this consideration of treatment technique, as chemotherapy or specific medication, the population equilibrium of tumor cells be reached quite before the carrying capacity, K, of the tumor or then, that this population diminishes drastically due the action of those techniques - we came out with those conclusions on our work entitled "Análise do Modelo de Gompertz no crescimento de tumores sólidos e inserção de um fator de tratamento" (Domingues, 2011).

4 Conclusions

Through this paper, we can better understand the Gompertz equation, which is little studied (or not even commented) on the introductory courses of Differential Equations, through its resolution in a simple and well detailed way and, also we can understand how, in fact, it can be used to describe the evolution of certain kinds of populations, in this particular case, of tumor cells of a solid tumor, considering its behavior since known scientific literature parameters which happens to be a innovating differential in our work. The proposed model is accordingly with the biological reality to the scenario of when the blood irrigation of tumors happens, it will have oxygen and nutrient supply, being able to develop in a uncontrolled way, and because of it is that the mathematical conclusion was that the tumor cells population, $N(t)$, when t is equal to the carrying capacity K of the tumor. In this way, we hope that this paper fits as a didactic method of support for teaching Differential Equation on the level of graduation and post-graduation, that allows to base others research works of application on Math and on Biology, as, for example, the insertion and analysis of the results of the treatment factors on Gompertz model and, that also helps the professionals of the biologic or medical fields on the understanding of the usage of mathematical models for description the evolution of tumor populations.

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