

Mathematics and radiotherapy of tumors

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Abstract

The present work takes inspiration from the scientific degree plan of the Italian Ministry of Education and has a didactic and cultural character. It pursues three objectives: the first is to make young people understand the importance of mathematics in medicine; the second is to stimulate students to use mathematical tools to give rational answers in the therapeutic field, in particular in the treatment of some types of nodular tumors; the third is to inform people on the effectiveness of mathematical methods and their indispensability in the rigorous treatment of some human pathologies.

Using the experimental data about the development of a tumor, we move on to the analysis of the mathematical models able to allow a rational control of its behavior. The method we used in the development of this therapeutic process is essentially deterministic, even if some passages implicitly have a probabilistic nature.

Keywords: population, cells, tumor, carrying capacity, differential equation

2010 AMS subject classification: 92B08, 92D08, 34K02, 39A06, 62P07, 97D06. †

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1. Premise

Usually, when we talk about the therapeutic treatment of serious pathologies it is difficult to consider the contribution of mathematics and statistics to the success of the interventions. Most often it is thought that positive results correspond to the abilities and knowledge of the luminaries of surgery and medicine. This article aims to provide additional information: to demonstrate that applied mathematics (in particular statistics) offers indispensable tools for a rational approach to these therapies. The method we used in the development of this therapeutic process is essentially deterministic, although some passages implicitly provide a probabilistic reference; in particular, when the least squares principle is applied for the research of the theoretical model of interpolation. The basic hypothesis is that the deviations of the experimental values from the theoretical values of the model have a Normal distribution.

2. Mathematics as a measure of the world

The field in which Mathematics moves has become vast. Usually, it is divided into two major sectors: the pure and that applied mathematics. The first sector has a purely speculative nature and is concerned with a rigorous arrangement of the basic principles of the discipline; the second, instead, relates to the applications of mathematical methods to Natural Sciences, Medicine, Engineering and Economics. It is in this second sector that interesting applications can be found that can help man solve several technical-scientific problems. It is necessary, however, to warn this is only an exemplifying division. Actually, mathematics is a unitary whole and it is difficult to know where its theoretical part ends and its experimental soul begins and vice versa. Often, problems arise in an application environment that requires in-depth theoretical analysis. So, it is necessary to refer to an experience, to a useful operational path.

A wider approach, not only descriptive, to natural phenomena requires a considerable knowledge of the mathematics that allows:

- Their measurement (Analysis, Probability Calculus, Statistics);
- The study of their possible forms (Analysis, Geometry, Statistics);
- The coherent arrangement of the rules followed (Logic, Algebra).

All scientific methodologies require compliance with these three points.

3. Problem analysis

Biology is one of the sciences that is proving to be very ductile to use mathematical techniques for a rational response to problems. It enables, with

genetics good practices and good procedures to improve the lives of human beings. The mathematical fields that can be applied to Biology range from Combinatorial Calculus to Probability Calculus, to Geometry, to Statistics and they offer a vast set of procedures.

The problem I am presenting is, certainly, of undoubted effect. It is an efficient and effective treatment to counteract, and eventually block, the progress of a particular type of tumor: the glioblastoma. It is a nodular tumor that lurks in the brain tissues and soon leads to the death of the host (the patient). We start from an experimental model of the tumor nodule, which, growing in the laboratory, gives us a lot of biological and kinetic measures of its growth (Figure 1). In particular, we can determine the growth time, the number of the cells for each instant of time and the critical limit of their growth beyond which there is nothing left to do (for example, for the compression of the tissues or for metastasis). In the dynamics of the tumor, we also consider the necrosis of many of its cells for the lack of food and of oxygen. It is also necessary to know the clinical picture of the patient and his immune response.

After that, we analyze the mathematical models able to guarantee a rigorous control of the behavior of this type of tumor.

4. The choice of mathematical models

On the basis of what we previously analyzed, the process requires the selection of mathematical models, as the first approach, in order to quantitatively describe the natural growth of the tumor mass over time and to find a mathematical model that allows to give to the patient a therapy that increases his life expectancy compared to the natural one, starting from the observation of the neoplasm.

The mathematical models able to control the growth of biological populations are studied by that part of mathematics that is known as population dynamics [8]. When dealing with a problem of growth of biological populations, we take on known and tested standard models. Usually, any changes to be made to the models are arranged during the work, keeping the standard model used as fixed as possible. One of the most well-known growth models is that of Verhulst [8]. In our case, however, the Verhulst equation does not adapt well to describe the growth dynamics of the glioblastoma tumor cells. It has been observed, from previous studies, that the most suitable model to describe this growth is given by the differential equation of B. Gompertz.

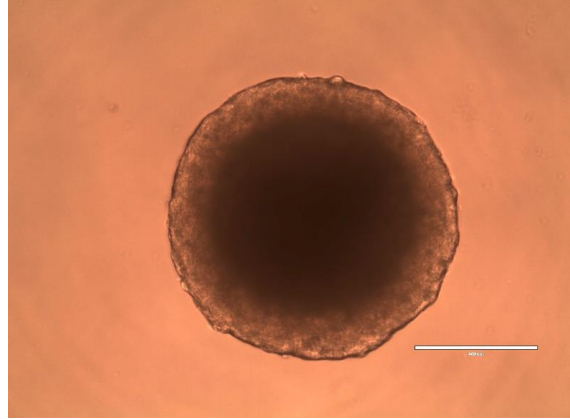


Figure 1. Photomicrograph of an experimental tumor nodule (tumor spheroid). The reference bar is 400 μm long. The central area of the nodule, darker and denser, is mainly formed by dead cells because of the poor availability of oxygen and the accumulation of toxic substances produced by the cells themselves with their metabolism, due to problems related to the diffusion of these molecules in the tissue. This area is generally referred to as the necrotic heart. Photo courtesy of Dr Roberto Chignola, Department of Biotechnology, University of Verona.

5. Gompertz model and tumor growth

This model can be expressed as a system of differential equations

$$\begin{cases} \frac{dX(t)}{dt} = kp(t) \cdot X(t) \\ \frac{dkp(t)}{dt} = -\beta \cdot kp(t) \end{cases} \quad (1)$$

or as a differential equation that includes both equations (2).

$$\frac{dX(t)}{dt} = \beta \cdot X(t) \cdot \text{Log} \left[\left(\frac{X(t)}{K} \right)^{-1} \right] \quad (2)$$

Model (2) derives from (1), as can be demonstrated.

We now present the parameters and variables of models (1) and (2). $X(t)$ is the number of tumor cells at time t ; K is the carrying capacity of the environment in which the tumor cells live and is equal to $K = \text{Max}(X(t))$: it represents the critical limit beyond which a tumor mass cannot go (otherwise would kill the host); $X(t)/K$ is the occupancy rate of the environment; $kp(t)$ is the time-dependent growth rate of the tumor cell population; β is a parameter that dampens the genetic growth of the population of individuals considered.

The differential equation (2) admits an integral curve in a closed form. It is given by:

$$X(t) = K \cdot e^{-C \cdot e^{-\beta \cdot t}} . \quad (3)$$

As shown, (3) depends on the parameters K , β , C .

The tumor has a mass whose volume is estimated on an experimental basis as follows:

$$Vol(t) = \frac{4}{3} \cdot \pi \cdot r_0^3 \quad , \quad r_0 = \frac{1}{2} \cdot \sqrt{d_{min} \cdot d_{max}} \quad , \quad (4)$$

where $Vol(t)$ is the volume of the tumor mass at time t , r_0 is the geometric mean of the two rays $d_{min}/2$ and $d_{max}/2$, where d_{min} and d_{max} are the minimum and the maximum of the diameters of the spheroid. Once the volume is known, taking into account that a tumor cell has a known size (usually estimated in $10^{-9} cm^3$), one can determine the number of cells in the nodule in the following way:

$$X(t) = Vol(t)/Vol_{cellula} . \quad (4bis)$$

$X(t)$ of (4bis) is a very large value and therefore not very useful for calculations. Since the volume of a cell is known and is constant, the size of the population of tumor cells is conveniently replaced by the volume of the tumor mass $Vol(t)$. Starting from this substitution, $X(t)$ becomes $Vol(t)$ and, considering the multiplicative constant ($1 / Vol_{cellula}$), is also the population numerosness.

It is now necessary to estimate the parameters of the model (3).

6. Discretization and parameter estimation

The inevitable step to estimate the parameters of the model (2) or (3) with the least squares method is the discretization of the model. In practice, it consists to replacing the derivative with the incremental ratio and with the application of the finite difference operator first. Let $\Delta X_t = X_{t+1} - X_t$, from (2) we obtain:

$$\frac{\Delta X_t}{\Delta t} = \beta \cdot X_t \cdot \text{Log} \left[\left(\frac{X_t}{K} \right)^{-1} \right] , \quad (5)$$

where $\Delta t = 1$. With easy algebraic steps, we get to:

$$\frac{X_{t+1}}{X_t} = 1 + \beta \cdot \text{Log} \left(\frac{K}{X_t} \right) . \quad (6)$$

Equation (6) can be set in the following way:

$$\hat{Y}_t = A + B \cdot \text{Log}(X_t) , \quad (7)$$

where $\hat{Y}_t = X_{t+1}/X_t$, $A = 1 + \beta \cdot \text{Log}(K)$, $B = -\beta$.

Equation (7) is a linear model in the parameters. Thus we can apply the least squares method to estimate parameters A and B based on the experimental data in our possession. We obtain:

$$S(A, B) = \sum_{j=1}^n (Y_j - \hat{Y}_j)^2 = \sum_{j=1}^n (Y_j - A - B \cdot \text{Log}(X_t))^2. \quad (8)$$

Passing to the partial derivatives with respect to A and to B , setting them equal to zero and solving the system, we have:

$$\begin{pmatrix} n & \sum_{j=1}^n \text{Log}(X_j) \\ \sum_{j=1}^n \text{Log}(X_j) & \sum_{j=1}^n [\text{Log}(X_j)]^2 \end{pmatrix} \cdot \begin{pmatrix} A \\ B \end{pmatrix} = \begin{pmatrix} \sum_{j=1}^n Y_j \\ \sum_{j=1}^n Y_j \cdot \text{Log}(X_j) \end{pmatrix}. \quad (9)$$

In this case, it is not necessary to proceed to the calculation of the second derivatives since the Hessian is a positive semidefinite matrix and therefore the solutions of the system (9) give precisely the minimum of $S(A, B)$ [9].

Once we have found the values for A and B , β and K are easily obtained. It is then calculated X_t . For the calculation of the constant C in (3), the initial condition is taken into account: at time $t = 0$ we have $X(0) = K \cdot e^{-C}$, and hence we get $C = \text{Log}K - \text{Log}X(0)$.

7. Processing

To verify the validity of the method presented above, one uses the experimental measurements daily obtained with glioblastoma tumor nodules grown in laboratory (spheroids). The measures are relative to the variations of nodular size, taken for 77 days. We start, therefore, from the set W of the experimental data, where the first term of each pair represents the discrete time expressed in days of each observation and the second the volume of the tumor mass expressed in mm^3 :

$$\begin{aligned} W = & \{ \{0, 3.57\}, \{1, 7.37\}, \{2, 10.9025\}, \{3, 14.435\}, \{4, 21.5\}, \{5, 28.6\}, \\ & \{6, 37.14\}, \{7, 41.98\}, \{8, 52.89\}, \{9, 57.805\}, \{10, 62.72\}, \{11, 72.55\}, \\ & \{12, 88\}, \{13, 105.6\}, \{14, 96.5\}, \{15, 105.6\}, \{16, 116.05\}, \{17, 126.5\}, \\ & \{18, 147.4\}, \{19, 147.4\}, \{20, 185.2\}, \{21, 172\}, \{22, 199\}, \{23, 199\}, \\ & \{24, 199\}, \{25, 199\}, \{26, 213.6\}, \{27, 199\}, \{28, 199\}, \{29, 199\}, \{30, 199\}, \\ & \{31, 199\}, \{32, 199\}, \{33, 213.6\}, \{34, 199\}, \{35, 213.6\}, \{36, 206.5\}, \\ & \{37, 199.4\}, \{38, 193\}, \{39, 185.2\}, \{40, 199\}, \{41, 199\}, \{42, 213.6\}, \end{aligned}$$

{43, 213.6}, {44, 213.6}, {45, 213.6}, {46, 213.6}, {47, 185.2}, {48, 213.6},
 {49, 199}, {50, 213.6}, {51, 209.95}, {52, 206.3}, {53, 199}, {54, 199},
 {55, 213.6}, {56, 199}, {57, 199}, {58, 199}, {59, 199}, {60, 199},
 {61, 213.6}, {62, 185.2}, {63, 185.2}, {64, 185.2}, {65, 185.2}, {66, 185.2},
 {67, 213.6}, {68, 213.6}, {69, 199}, {70, 213.6}, {71, 203.2}, {72, 192.8}, {73,
 172}, {74, 199}, {75, 185.2}, {76, 199}, {77, 199}.

From (9) we get: $A = 1.93967$, $\beta \cong 0.18076$, $K \cong 180.991 \text{ mm}^3$, $X_0 \cong 3.57 \text{ mm}^3$, $C \cong 3.92588$.

It, therefore, turns out to be

$$\hat{X}(t) = 180.991 \cdot e^{-3.92588 \cdot e^{-0.18076 \cdot t}} \quad (10)$$

It is not linear and therefore the goodness of fit is measured by the following fit index (which is a particular coefficient of variation):

$$I_2 = \frac{1}{M(\hat{X})} \cdot \sqrt{\frac{\sum_{j=1}^n (X_j - \hat{X}_j)^2}{n}}, \quad (11)$$

where X_j are the second terms of the data pairs W , \hat{X}_j are the theoretical results of the application of (10), M is the average of the theoretical values \hat{X}_j and n is the sample size.

In our case the value is $I_2 \cong 0.147582$.

The value of I_2 seems acceptable; moreover, given the difficulty of data collection, we can be satisfied with this approach even if, according to the international standard, a value lower than 0.1 should be recommended [10].

We now present the graph of the theoretical model and the distribution of experimental data around it (Figure 2).

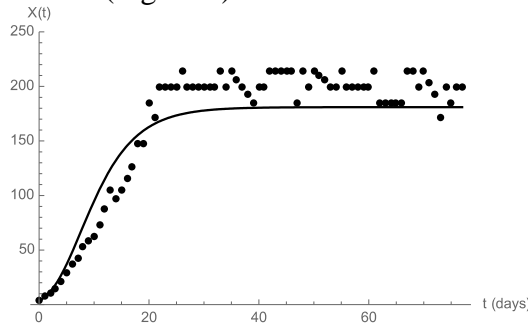


Figure 2. On the t-axis there is time in days, on the ordinates there is the volume of tumor.

Calculating the second derivative of (10) and placing it equal to zero, we obtain the inflection point [7]. It is equal to (7.56578 days, 66.5829 mm^3). We have thus finished studying the Gompertz model applied to our experimental

data. Let us now turn to the study of the optimal therapy to be applied to the nodule to control its growth.

8. The radiobiological treatment of tumor

The goal of radiological treatment of the cancer is to reduce its mass by killing its cells, without simultaneously damaging healthy cells. Radiotherapies aim to achieve this goal. This treatment, however, is rather dangerous since, in the irradiation of the tumor mass, healthy tissue cells are unfortunately also affected. In short, the following problem must be addressed: how much minimum radiant dose should be given to the patient to maximize the number of cancer cells killed with minimal damage to healthy cells? To answer this question, we need to address some preliminary aspects on the subject.

We have shown that the Gompertz model is valid in the interpretation of the dynamics of the tumor mass of an experimental nodule of glioblastoma. At this point we apply the model also to evaluate the dynamic behavior of the same tumor in a patient.

Before tackling the preliminaries, we consider that $X_0 = K \cdot e^{-c}$ and we put it in (3), obtaining the following formula (algebraic steps are simple and are omitted):

$$X(t) = X_0 \cdot e^{\frac{\alpha_0}{\beta} \cdot (1 - e^{-\beta t})}, \quad (12)$$

where $\alpha_0/\beta = C$, the parameter α_0 assumes the meaning of instantaneous spheroid growth rate at time $t = 0$ and β is a generic factor that deaden the tumour growth. From (12) it is confirmed that

$$\text{Max}[X(t)] = \lim_{t \rightarrow +\infty} X_0 \cdot e^{\frac{\alpha_0}{\beta} \cdot (1 - e^{-\beta t})} = X_0 \cdot e^{\frac{\alpha_0}{\beta}} = K. \quad (13)$$

Equation (13) represents a constraint on the growth of the spheroid. On the basis of a consolidated case series, it is believed that the maximum volume of the tumour borne by a patient can reach 25 cm^3 , after which the effects are devastating and lead to the death of the guest in a short time. Then from (13) we have:

$$\begin{aligned} \text{Log}(K) &= \text{Log}(X_0) + \frac{\alpha_0}{\beta}, \\ \frac{\alpha_0}{\beta} &= \text{Log}\left(\frac{K}{X_0}\right) \cong \text{Log}\left(\frac{25 \text{ cm}^3}{10^{-9} \text{ cm}^3}\right) \cong 23.94, \end{aligned} \quad (14)$$

where X_0 in this case corresponds to the volume in cm^3 of a tumor cell at the beginning of the process; that is $X_0 = \text{Vol}_{cellula}$.

9. Some notions of radiobiology

Often only possible therapy in the treatment of tumors is the radiotherapy, especially when the tumor involves important tissues of the human body or is located in places of difficult surgical access. From a clinical point of view, radiotherapy is an indispensable treatment even when it is considered necessary to intervene with more invasive therapies such as surgery and chemotherapy. Currently, biomedical research is further progressing with promising studies on the interaction between tumor cells and subatomic particles obtained with appropriate accelerators. At the moment encouraging results have been achieved, but the journey is still long. The treatment of tumor masses with radiation has the purpose of inducing massive molecular damage to the diseased cells so as to lead them to death. The decisive problem is to avoid as far as possible damage to healthy cells when one intervenes on sick cells. The damage induced by radiotherapy treatment depends on the intensity of the radiant dose. There are international indications that establish the effects of any radiation therapy. The radiant dose is expressed in Gray (Gy), which corresponds to the energy of 1 joule absorbed by 1 kg of biological tissue. Moreover, this basic unit must be multiplied by a suitable parameter that allows to take into account the effect on biological tissues of different nature of this radiant dose (RBE = Relative Biological Effectiveness). Finally, the product between Gy and RBE gives the equivalent biological dose to be administered, which is measured in Sievert (Sv). It should be considered that for radiations of clinical interest, radiation γ [4], we consider RBE = 1 and Gy = Sv. Table 1 highlights from a descriptive point of view the effects on human beings of exposure to radiant doses of different degrees of intensity [5].

Dose (Sv)	Effects
(0.05 - 0.2]	No symptoms, but risk of DNA mutations
(0.2 - 0.5]	Temporary drop in red blood cells
(0.5 - 1]	Drop in immune system cells and risk of infection
(1 - 2]	Immunodepression, nausea and vomiting. Mortality of 10% at 30 days from exposure
(2 - 3]	Severe immunodepression, nausea and vomiting 1-6 hours after exposure. Latency phase of 7-14 days after which symptoms appear such as hair loss. Mortality of 35% at 30 days from exposure
(3 - 4]	Bleeding of the mouth and urinary tract. Mortality of 50% at 30 days from exposure
(4 - 6]	Mortality of 60% at 30 days from exposure. Female infertility. The convalescence lasts from a few months to a year
(6 - 10]	Complete injury of the bone marrow (the organ that produces red blood cells and all cells of the immune system). Symptoms appear between 15 and 30 minutes after exposure and mortality is 100% at 14 days after exposure

(10 – 50]	Immediate nausea, bleeding from the gastrointestinal tract and diarrhea, coma and death within 7 days. No medical intervention is possible
(50 – 80]	Immediate coma. Death occurs in a few hours due to the collapse of the nervous system
> 80	Exposure to these doses occurred in two circumstances. Both subjects died within 49 hours of the accident

Table 1: Effects of radiation on human beings

10. The modeling of therapy

At this point, we must find a therapeutic process that allows us to stop the growth of the tumor or, even better, to reduce its mass to extinction. The model should take into account the disposition of the cells within the tumor mass, their microenvironment and the toxic effects induced on the healthy tissues of the surrounding cells and any other factor that may inform about the dynamics of the tumor. Studies conducted so far in various research institutes around the world have led to confirm, as an acceptable model to be considered in the treatment of tumors with radiant dose, the following one:

$$\widehat{SF}(D) = e^{-a \cdot D - b \cdot D^2}, \quad (15)$$

where \widehat{SF} is the survival rate, a and b are two arbitrary parameters and D is the radiant dose. We must estimate the parameters a and b of the model as a function of the experimental data. Even in this case we linearize the model and apply the least squares method.

Dose (Gy)	SF		Dose (Gy)	SF
0.0000	1.0000		5.5036	0.19609
0.53957	0.87780		6.0072	0.18372
1.0072	0.84048		6.5108	0.14785
1.5468	0.73778		7.0144	0.11642
2.0144	0.78746		7.5180	0.097850
2.5180	0.62009		7.9856	0.073780
3.0216	0.55627		8.4892	0.058100
3.5252	0.46753		8.9928	0.043800
3.9928	0.36816		9.4964	0.036020
4.5324	0.33752		10.000	0.033750
5.0360	0.26007		10.504	0.026010

Table n. 2: Numerical data relating to the graph in figure 3, further on

11. Assumptions for the radiotherapy

When we face the problem of finding the relationship between a dynamic model of natural growth of a tumor and its radio-therapeutic treatment, collateral effects inevitably arise that create states other than those we would have liked to encounter. The complete modeling of a radiotherapy treatment requires the consideration of numerous variables that influence the interaction between tumor cells and radiant doses. For this reason, as a first approximation, we put some valid hypotheses to simplify the method. The choice of the hypotheses useful for the simplification of an effective model for the treatment of a tumor is in any case indispensable every time the control of the final results is desired. If we consider the analysis of the problem from a mathematical point of view, it is necessary to think about the implication of having to replace differential equations, defined in the continuous, with equivalent equations defined in the discrete. At this point we present the list of the necessary hypotheses to get on with the analysis of the process.

Assumption 1: The Gompertz model is a good representation of the growth dynamic of a tumor mass, starting from a first degenerated cell up to asymptotically reaching a volume of 25 cm^3 . Thus, it is possible to simulate tumor growth using the equations (1), (2) and (3).

Assumption 2: A solid tumor, in general, consists of proliferating cells P , quiescent cells Q and dead cells U . The number of total cells N at time t is therefore given by

$$N(t) = P(t) + Q(t) + U(t). \quad (16)$$

Table 3 and Figure 5 refer only to proliferating cells since ionizing radiations are much less effective if directed against quiescent cells.

Assumption 3: In a solid tumor, on an experimental basis, it is possible to state that the number of quiescent and dead cells becomes significant with respect to the total of cells at the inflection point of the Gompertz curve (3) and (12).

Assumption 4: Radiation therapy has instantaneous effects, causing the immediate death of the cancer cells. These effects should at least be faster than the growth of tumor cells. This avoids a detailed kinetic analysis of the toxicity of radiation.

Assumption 5: After undergoing radiotherapy treatment, the tumor grows with the same dynamic modalities that preceded the treatment. It is a common convention in scientific treatises; however, there are also different points of view on this matter [6].

Assumption 6: The maximum dose in a single treatment is 3 Gy. You can also perform multiple treatments if and only if they are repeated at 24-hour intervals. It is not possible, however, to exceed 65 Gy. This assumption is

indicated by the radiotherapeutic protocols followed in the therapy of some tumors. The 3 Gy dose allows healthy tissues affected by radiation to recover from damage.

Assumption 7: We assume the existence of two critical thresholds in the treatment phase: 1) if after treatment a tumor falls below 1 mm^3 , then we consider a therapy to be successful; 2) if, on the other hand, the volume increases beyond the dimension corresponding to the inflection point of the Gompertz curve, the therapy must be considered as failed. In practice, nothing justifies this assumption from a clinical or biological point of view and yet we accept it as work hypothesis.

Based on these hypotheses, we can proceed with the estimation of the model parameters (15) and with the application of the programmed therapy.

12. Procedure for a rational therapy

The method we will use for the treatment of glioblastoma, meets the following two objectives:

- 1) Check if there is a relationship between the effectiveness of the radiotherapy treatment used and the rate of tumor growth.
- 2) In case of an affirmative answer to the first objective, find a specific treatment protocol that allows to optimize the relationship between the benefits of the therapy and the costs due to the induction of toxic effects; in concrete terms, it is necessary to find the minimum amount of radiation to be used with the maximum destructive effect of cancer cells.

We start with the estimation of the parameters of the model (15) using the well-known method of least squares and, also in this case, evaluating the goodness of fit with index I_2 (11). The model (15) must be linearized:

$$\text{Log}[\widehat{SF}(D)] = -a \cdot D - b \cdot D^2 \quad (17)$$

and applying the least squares method we have:

$$\begin{aligned} S(a, b) &= \sum_{j=1}^n \left(\text{Log}(SF(D_j)) - \text{Log}(\widehat{SF}(D_j)) \right)^2 = \\ &= \sum_{j=1}^n \left(\text{Log}(SF(D_j)) + a \cdot D + b \cdot D^2 \right)^2. \end{aligned}$$

Calculating the partial derivatives of $S(a, b)$ with refer to a and to b , we obtain the system

$$\begin{cases} \left(\sum_{j=1}^n D_j^2\right) \cdot a + \left(\sum_{j=1}^n D_j^3\right) \cdot b = -\sum_{j=1}^n D_j \cdot \text{Log}[SF(D_j)] \\ \left(\sum_{j=1}^n D_j^3\right) \cdot a + \left(\sum_{j=1}^n D_j^4\right) \cdot b = -\sum_{j=1}^n D_j^2 \cdot \text{Log}[SF(D_j)] \end{cases} \quad (18)$$

Considering the data in Table 2 and solving (18) with refer to a and b we obtain:

$$a \cong 0.124275; b \cong 0.0264028.$$

The model adapted to the data in table 2 is, therefore:

$$\widehat{SF}(D) \cong e^{-0.124275 D - 0.0264028 D^2} \quad (19)$$

Using the coefficient of variation:

$$I_{2,SF} = \frac{1}{M(\widehat{SF}(D))} \cdot \sqrt{\frac{\sum_{j=1}^n (SF(D_j) - \widehat{SF}(D_j))^2}{n}} \quad (20)$$

and taking into account both the data in table 2, and the theoretical values calculated with (19), we get the goodness of fit: $I_{2,SF} \cong 0.0998765$. This value shows that our approach is good. Figure 3 presents both the trend of experimental data and the interpolated model.

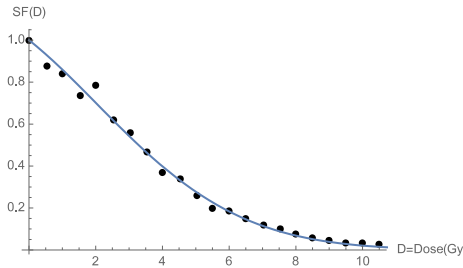


Figure 3: the graph shows the link between the radiant dose and the fraction of surviving individuals (19). The points represent, in Cartesian coordinates, the data of table 2. We put on the D -axis the radiant dose, on the ordinate axis the survival rate $SF(D)$.

13. Research of the inflection point

At this point, it is necessary to start the therapy taking into account what has resulted from these preliminary procedures. We consider again the model (10) and figure 3. Furthermore, on the basis of the assumption 3, the most effective radiotherapy treatment is the one which begins at the inflection point of the Gompertz curve.

We consider the model (12):

$$\hat{X}(t) = X_0 \cdot e^{\frac{\alpha_0}{\beta} (1 - e^{-\beta t})}, \quad (21)$$

and taking into account that a cancer cell has a volume of 10^{-9} cm^3 and that $\beta = 0.016$ we have:

$$\hat{X}(t) = 10^{-9} \cdot e^{23.9421 (1 - e^{-0.016 t})}. \quad (22)$$

Calculating the second derivative of $X(t)$ and setting it equal to zero we get the inflection point (198.477 days, 9.19654 cm^3) [7]. We note that this result is different from that obtained using the model (10). Here, in fact, the parameters of the Gompertz model are changed, which are now imposed not by the experimental data of the single experimental nodule (which in our case led to the model (10)), but by a different operating standard that requires both a start from a single tumor cell, whose volume is fixed at 10^{-9} cm^3 , and from a critical maximum limit of tumor expansion equal to $K \cong 25 \text{ cm}^3$. Figure 4 presents the function with the flex point.

At this point the radiant doses should be applied at intervals that allow the patient's average life to be maximized. The first simulation (Fig. 4) considers a single-dose therapy to hit the tumor mass with a single dose of radiation (from 1 to 3 Gy with intervals of 0.4). Starting at the time of the cancer diagnosis observation, when the tumor mass can vary from a minimum of 0.0050 cm^3 to a maximum marked by the flex point, we have to measure the effect of the therapy on the cancer using the delay time of its growth. This time corresponds to the one that the tumor mass needs, after having been treated with radiotherapy, to return to the mass it had before the treatment was carried out. Methods and procedures are reported in [2]. In the last two graphs we report two other simulations in which, with respect to the protocol for the search for an optimal result, two different outcomes are observed. In figure 5, the result is not satisfactory; instead, in figure 6 the protocol gives a favorable outcome and the mass of the glioblastoma is reduced below the desired minimum threshold.

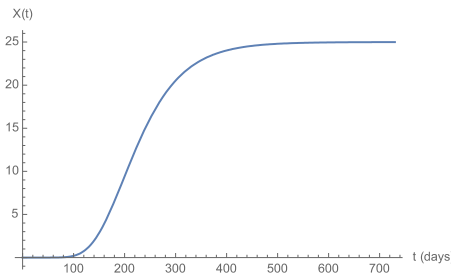


Figure 4. Gompertz curve (22) related to the investigated tumor. The inflection point is (198.477 days, 9.19654 cm^3). On the t -axis there is the time in *days* and on the ordinate axis the tumor volume in cm^3 .

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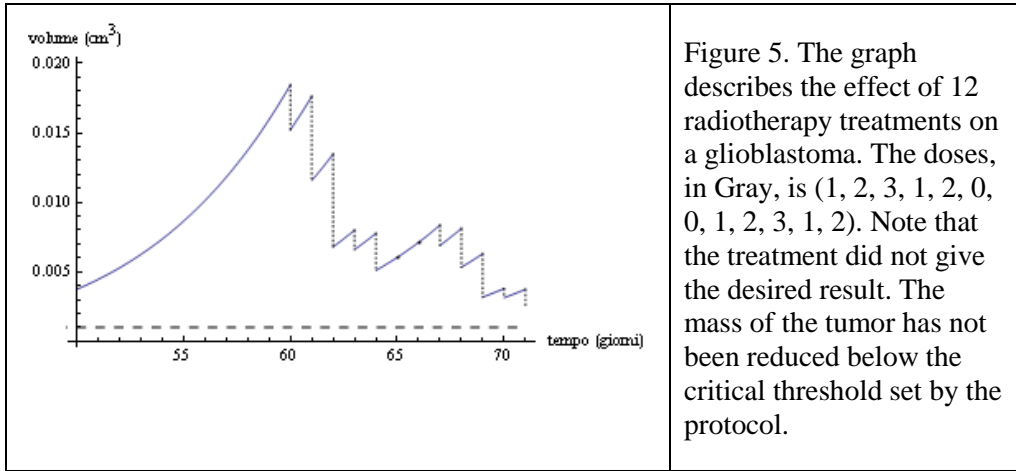


Figure 5. The graph describes the effect of 12 radiotherapy treatments on a glioblastoma. The doses, in Gray, is (1, 2, 3, 1, 2, 0, 0, 1, 2, 3, 1, 2). Note that the treatment did not give the desired result. The mass of the tumor has not been reduced below the critical threshold set by the protocol.

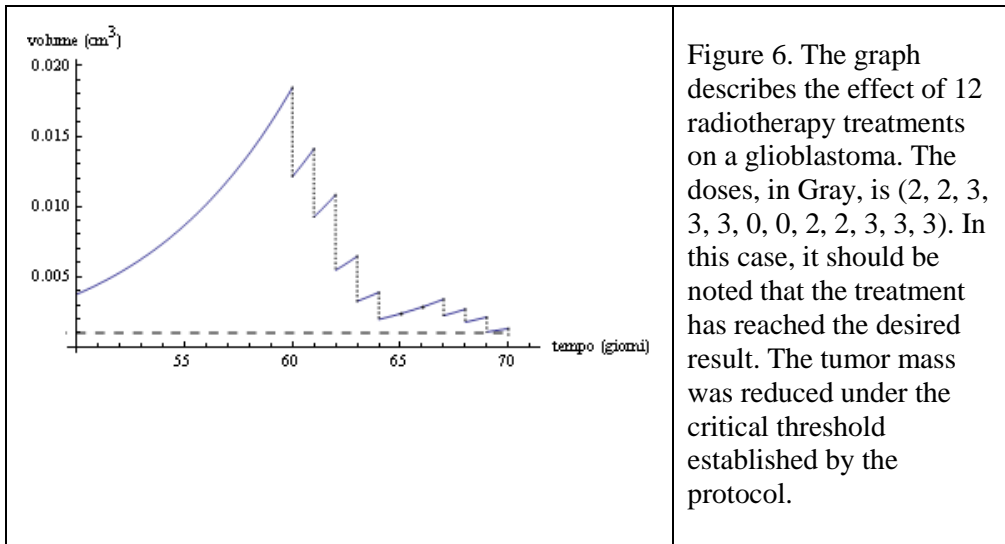


Figure 6. The graph describes the effect of 12 radiotherapy treatments on a glioblastoma. The doses, in Gray, is (2, 2, 3, 3, 3, 0, 0, 2, 2, 3, 3, 3). In this case, it should be noted that the treatment has reached the desired result. The tumor mass was reduced under the critical threshold established by the protocol.

Each cusp corresponds to the flex point of the various curves that sequentially describe the progression of tumor growth after each treatment.

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