BIO Web of Conferences **97**, 00118 (2024) https://doi.org/10.1051/bioconf/20249700118
ISCKU 2024

Comparative Study of Tumor Growth Based on Single Species Models

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Abstract

Although the ideal way to simulate tumour development is still unknown, mathematical models are often employed to forecast how cancer will advance and how treatments will be developed. Five alternative ordinary differential Equation (ODE) models of tumour development have been proposed: exponential, logistic, Allee effect, Gompertz, and Bertalanffy. The problem is no consensus exists on the best model for a given cancer type. Using a sample dataset, we compared how these quantities differ depending on the growth model chosen. Equations were developed to determine the largest possible size of the tumour and the least level of chemotherapy needed for suppressing the tumour.

INTRODUCTION

Because of its chronic nature, cancer is a significant source of mortality in addition to it being a financial strain on the healthcare system, the illness, and the many adverse consequences of therapies and surgeries [1, 2, 3]. Much work goes into this research. Enhancing the effectiveness of existing therapies [4] and creating novel therapeutic approaches [5, 6, 7], mathematical models will play a significant role when cancer therapy shifts to individualized care. The study aids in forecasting the tumor's temporal course and enhancing treatment plans [7, 8]. The applications of mathematical models are numerous. To support cancer research and treatment, models are used to understand the growth and development of cancer [9, 10]. They are used for personalization or optimization [11, 12, 13, 14, 15] to provide treatment plans, assess the effectiveness of novel therapeutics [16] or mixes of several interventions [17], [18], and provide information on the evolution of treatment resistance [19]. Although models have excellent potential to enhance the creation and use of cancer therapy, scientists will not be able to use this potential until they fully provide precise forecasts. The foundation of every study-related mathematical model tumor development is modelled in cancer therapy. The subject of this study is single-species tumor growth models. Numerous models have been suggested as tumor growth representations [20, 21], and they are often used to forecast the effectiveness of cancer therapies [22]. Regretfully, selecting a growth paradigm is often motivated by how simple math analysis is instead of whether it offers the most effective development approach to growth [20]. Scholars have adjusted many models for a limited amount of experimental data sets on the development of tumour in an effort to identify the "best" ODE growth model [23, 24, 25, 26]. Overall, the findings are ambiguous, arguing that selecting a growth model depends on the nature of the tumor [27, 25]. Thus, modelers are left with lack of direction while selecting a tumor growth model. Various scientists know that using the wrong model of growth might be troublesome [20] and cause variations in treatment success estimates [21] Nevertheless, no research has yet been conducted that compares and measures the variations in the model's predictions and how these Variations impact treatment result projections.

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The findings of analyzing several ODE growth models are presented in this study, along with an overview of how well they predict tumour development with and without treatment. In addition, we integrate the models with a sampling of experimental tumor development data sets, and depending on the growth model used, we discover a broad range of expected results.

Mathematical Modelling

In many cases, models considered here were first presented during the early days of research into tumor development when scientists were trying to establish equations that explain the expansion of cancer cells [1, 2, 3]. The models foretell tumor expansion by characterizing its volume (w) evolution. Table 1 displays the model equations [28] which are utilized during this investigation, and the models themselves are discussed in the following text. Adjusting the m, M, and r values allows one to provide a more precise description of a given data collection.

Table 1. ODE models of tumor growth

Model	Equation
Exponential	$w' = rw$
Logistic	$w' = rw(1 - \frac{w}{M})$
Gompertz	$w' = rw \ln\left(\frac{M}{w}\right)$
Bertalanffy	$w' = \alpha w^{\lambda} - \beta w$
Allee Effects	$w' = rw\left(1 - \frac{w}{M}\right)\left(1 - \frac{m}{w}\right)$

Exponential Model

Cells divide consistently into the early phases of tumor development, producing two daughter cells simultaneously. Therefore, the exponential model [29] in which growth is proportionate to population, provides an appropriate representation of the early phases of cancer development. The tumor growth rate is a proportionality constant. This model operated well at forecasting early development and was widely used in the first investigation of tumor growth curves [2,3]. Angiogenesis and nutrient deprivation are known to play a role in its failure at later stages [20, 25]. the formatted Equation can be representations :

$$\frac{dw}{dt} = rw \quad ,(1)$$

where $w(0) = w_0$ is the initial condition that represents items, $\frac{dw}{dt}$ is the derivative concerning time, r is the growth rate or reproduction rate, and w is the number of cancerous cells at a given time for a particular being in a given environment. It is a fundamental value that reflects the interest rate. The exponential differential equation based on equation (1) has an analytical solution of[28]

$$w(t) = w_0 e^{rt} \quad ,(2)$$

Progression of tumor development during the duration of the experiment.

Logistic Model

Pierre Francois Verhulst developed the logistic equation[30]. A population's expansion subject to M's carrying capacity is modeled here. The logistic Equation posits that the growth rate is constant up to the carrying capacity and then drops linearly with size until it reaches zero. The following is a representation of the logistic equation:

$$\frac{dw}{dt} = rw\left(1 - \frac{w}{M}\right) = \frac{rw(M-w)}{M} \quad ,(3)$$

The condition representing M represents a species' carrying capacity in a certain habitat and is a fundamental value that signifies the intrinsic growth rate. Equation 3's t logistic differential equation has the following analytical solution[28]

$$w(t) = \frac{Mw_0}{w_0+(M-w_0)e^{-rt}} \quad ,(4)$$

Gompertz Model

In 1825, Benjamin Gompertz developed the Gompertz model to interpret mortality rates [39]. This model is a logistic model variant in which the inflection point is offset from the center of the sigmoidal curve. Later, the curve was used to represent the expansion of complete organisms [31]. In recent times, it has been the best match for developing breast and lung cancers [32]. The following is a representation of the Gompertz differential equation:

$$\frac{dw}{dt} = rw \ln\left(\frac{M}{w}\right) \quad ,(5)$$

In Eq. (5),$w(0) = w_0$, M and r are Initial conditions, carrying capacity, and intrinsic growth rate, respectively, as in Eq. (2). The Gompertz differential equations based on equation 5 have an analytical solution of[28]

$$W(t) = M\left(\frac{M}{w_0}e^{-rt}\right)^{-1} \quad ,(6)$$

Allee effect Model

Tumor cells change their characteristics in response to their surroundings [33]. One well-known example is the so-called "go-or-grow mechanism," which describes the capacity of tumor cells to alternate between proliferative and migratory phenotypes. How this specific phenotypic flexibility influences total tumor development is unknown, however, to deal with this, we developed as well as examined a mathematical model for spatiotemporal tumour dynamics in which distinct reactions to local cell density mediate the go-or-grow dichotomy. Two different dynamic regimes were identified according to our findings. Regardless of the starting size, any tumor cell population will eventually endure if cell motility rises with local cell density.

Conversely, an Allee effect arises if cell motility decreases with local cell density, ultimately extinguishing any group of tumors less than a particular threshold in size. These findings imply that tactics targeted at impeding migration—such as augmenting contact inhibition—should be investigated as potential substitutes for those primarily concerned with limiting tumor growth. The Allee effect differential Equation can be represented.

$$\frac{dw}{dt} = rw\left(1 - \frac{w}{M}\right)\left(1 - \frac{m}{w}\right) \quad ,(7)$$

Where w is the population size, r is the rate of increase, M is the carrying capacity, and m is the threshold point. The Allee effect differential equation based on Equation (7) has an analytical solution of[33]

$$w(t) = \frac{m(M-w_0)+M(w_0-m)e^{\left(\frac{M-m}{M}\right)rt}}{M-w_0+(w_0-m)e^{\left(\frac{M-m}{M}\right)rt}} \quad , (8)$$

Bertalanffy Model

Ludwig Bertalanffy devised the Bertalanffy equation as a model for organism development [34]. This model implies that tumor volume decreases with cell death, and growth occurs proportionally to the surface area. This model was the most accurate in describing how tumors develop in humans [23]. The Bertalanffy differential Equation can be represented as follows

$$\frac{dw}{dt} = \alpha w^{\lambda} - \beta w \quad ,(9)$$

where α and ß may be seen as the birth and death rates per capita, Let $\lambda = \frac{2}{3}$, $W(0) = w_0$ demonstrates the initial condition, $\frac{dw}{dt}$ is the derivative concerning time, r is the growth rate or reproduction rate, and W is the total number of tumour cells present in a given environment at a specific time for a particular organism. It is a fundamental value that stands for the rate of intrinsic development. The exponential differential equation based on Equation 1 has an analytical solution of [35]

$$w(t) = \left[\frac{\alpha}{\beta} - \left(\frac{\alpha}{\beta} - w_0^{\left(1-\frac{2}{3}\right)}\right) e^{-(1-\lambda)\beta t}\right]^{\frac{1}{1-\frac{2}{3}}}, \quad \lambda \neq 1, \quad (10)$$ [35].

Methods and Estimations

Our objective is to compare the results of several models. We tend to focus on short-term forecasts, but looking at a model's projections for the far future is instructive. To this end, we determine the long-term predictions of each model by locating their respective fixed points in the corresponding equations. In addition, using the model equation, we decided the growth rate. We then obtained the analytical solution for each model by replacing the carrying capacity and growth rate data. Using Equation 16, we identified the error squares. Subsequently, we used MATLAB R2023a to minimize the error and obtain enhanced precision in the carrying capacity and growth rate estimations. This allowed us to get a more accurate solution and improve the quality of the graph. We were approximating the actual data. Ultimately, we assessed the magnitude of the sum square residual and determined that the model with the smallest value was the most suitable for representing the data extracted from [19] using the accessible data mining application WebPlotDigitizer. Table 2 presents the changes in tumor volume over time. The fitting process involved minimizing the sum of square residual values. The $SSR = \sum_I (X_I - m_i)^2$, where m(i) is the simultaneously predicted model value, and X (I) is the experimental data point. The optimal choice is the model with the minimum SSR to predict tumor size.

Table 2. Data used for tumor volume changes over time

Time(days)	0	13	20	32	42	55	65	75	85	88	95	98	107	115	120
Tumor size in mm^3	250	255	550	575	576	800	1050	1250	1750	2000	2550	2750	3000	3500	4000

ESTIMATION OF PARAMETERS VALUES

The carrying capacity, represented as M, was estimated at 4000 for the exponential, logistic, Gompertz, Allee effect, and Bertalanffy models.

A. Estimation of the Exponential model parameters

In order to estimate the growth rate of the exponential model's parameter, we use Equation (1) to find the growth rate at any time. t_i.

$$r_i = \frac{1}{w_i} * \frac{dw}{dt}\Big|_{t=i} \quad ,(11)$$

where $w_i = w(t_i), i = 0,1, \dots, N$ and $r = \frac{\sum_{i=1}^{N} r_i}{N}$, where N=15 (the number of samples).

Using equation 11 along with the data we are able to estimate the exponential model's intrinsic growth rate is r= 0.033109.

B. Estimation of the logistics model parameters

We use Equation (3) to estimate the growth rate of the logistic models such that,

$$r_i = \frac{1}{w_i\left(1-\frac{w_i}{M}\right)} * \frac{dw}{dt}\Big|_{t=i} \quad ,(12)$$

where $w_i = w(t_i), i = 0,1,\dots,N$ and $r = \frac{\sum_{i=1}^{N} r_i}{N}$, where N=15 (the number of samples).
Using equation 12 along with the data we are able to estimate the intrinsic growth rate of the logistic model, which is r=0.022828.

C. Estimation of the Gompertz model parameters

The intrinsic growth rate based on equation 5 can be conveyed using the following.

$$r_i = \frac{1}{w_i \ln\left(\frac{M}{w_i}\right)} * \frac{dw}{dt}\Big|_{t=i} \quad ,(13)$$

where $w_i = w(t_i), i = 0,1,\dots,N$ and $r = \frac{\sum_{i=1}^{N} r_i}{N}$, where N=15 (the number of samples).
Using equation 13 along with the data we are able to estimate the Gompertz model's intrinsic growth rate is r=0.045126.

D. Estimation of the Allee effect model parameters

To calculate the growth rate of the parameter of the AIIee effect, we can use Equation (7).

$$r_i = \frac{1}{w_i\left(1-\frac{w_0}{M}\right)\left(1-\frac{m}{w_i}\right)} * \frac{dw}{dt}\Big|_{t=i} \quad ,(14)$$

where $w_i = w(t_i), i = 0,1,\dots,N$and $r = \frac{\sum_{i=1}^{N} r_i}{N}$, where N=15 (the number of samples).
Using equation 14 along with the data we are able to estimate the AIIee effect model's intrinsic growth rate as r= 0.04990273.

E. Estimation of the Von Bertalanffy Model parameters

To estimate the growth rate parameter of the von Bertalanffy, we can use Equation (9) and

$$r_i = \frac{1}{w_i^{\frac{2}{3}}-\frac{w_i}{M}} * \frac{dw}{dt}\Big|_{t=i} \quad ,(15)$$

where $w_i = w(t_i), i = 0,1,\dots,N$ and $r = \frac{\sum_{i=1}^{N} r_i}{N}$, where N=15 (the number of samples).
Using equation 15 along with the data we are able to estimate the von Bertalanffy model's intrinsic growth rate r= 0.000188244.

LEAST SQUARE APPROACH

We then minimize using the least squares method. The best-estimated parameters, r and M, are derived using the below function.

$$S(r, M) = \sum_{i=1}^{N}(w(t_i) - \widehat{w_i}) \quad ,(16)$$

$w(t_i)$ is the model's estimated number of infections at the time t_i, i =1,2,…., N by solving the differential equations as in Equations (3) and (5), where N is the total number of days from day 1 to day 120 and $\widehat{w_i}$It is the actual number intended. Therefore, the new (best estimated) values are $r = 0.0651144397262978$ and M= 4000 for the logistic model and r = 0.02533, M = 5464 for the Gompertz, and r= 0.29911998856184, M = 4214.09508897029, for the von Bertalanffy mode. Utilizing MATLAB 2023b, we have the MATLAB code changed in order to solve the logistic model, Gompertz model, and the von Bertalanffy in equations (3), (5), and (9). This effort resulted in several significant outcomes when we analyzed cancer data using the Gompertz model, logistic regression, exponential regression, von Bertalanffy, and Allee effect. Here is a summary of our findings: This effort resulted in several significant outcomes when we analyzed actual cancer data using the Gompertz model, logistic regression, Von Bertalanffy, exponential regression, and Allee effect. Tables 3 and 4 highlight the parameters along with the values that were allocated to them in the simulations and the sum square residual values.

Table 3. Models parameters before and after the least square method

Before using the least squares method					
Parameters	Exponential	Logistic Model	Gompertz	Allee effect	Von Bertalanffy
r value	0.033109	0.022828	0.045126	0.049903	0.000188244
M	4000	4000	4000	4000	4000
SSR	133754783.3	7509636.24	35811734.1	528352.564	37198029
After using the least squares method					
r value	0.033109	0.0651144397262978	0.02533	0.049903	0.29911998856184
M	4000	4000	5464	4000	4214.09508897029
SSR	133754783.3	29081933.73	893826.0914	528352.564	367275.9909

A. Exponential Model

The following figure show the solution of the exponential model for equation 2, where the intrinsic growth rate is r is illustrated. The logistic model's solution at r=0.033109 is shown in Figure 1 prior to the use of the least squares approach.

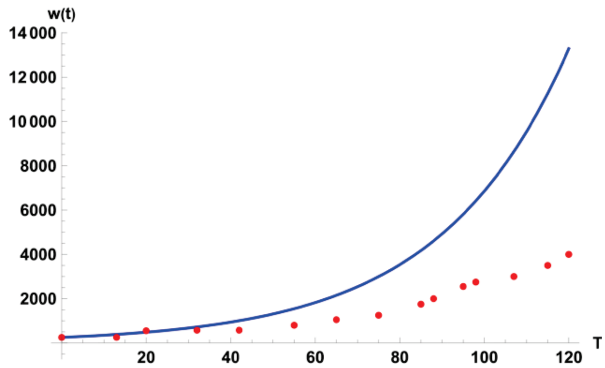

Fig. 1. Estimates the exponential model as in Equation 2 prior to using the least squares method, with an intrinsic growth rate r= 0.033109.

B. Logistic Model

The following figure illustrates the logistic model result for Equation (4), in which the carrying capacity M and the intrinsic growth rate r are shown. The logistic model's solution using the least squares method is presented in Figure 2, where M= 4000 and r=0.0651144397262978.

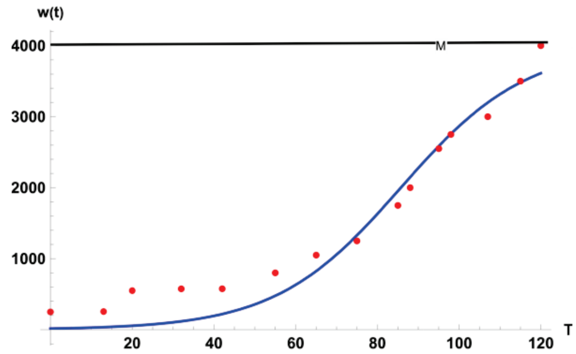

Fig. 2. Estimating the logistic model using equation 4 prior to applying the least square approach, having carrying capacity M=4000 and intrinsic growth rate r=0.0651144397262978.

C. Gompertz Model

The Gompertz model solution, as indicated by equation six, is depicted in the following illustration, within which carrying capacity is M and intrinsic growth rate is r. The Gompertz model solution is shown in Figure3. After using the least squares approach, the Gompertz model solution is presented with r=0.02533 and M=5464.

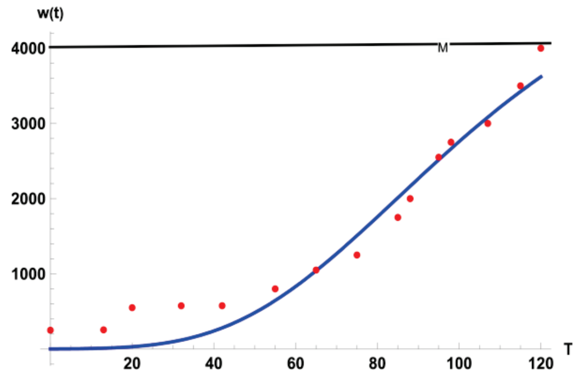

Fig. 3. Gompertz model estimations, based on Equation six, given intrinsic growth rate r=0.02533 and carrying capacity M=5464, following the least squares approach.

D. Allee effect

The following illustrations demonstrate the Allee effect model result according to Equation 8, where the threshold points are the carrying capacity M and m and the intrinsic growth rate r. The Figure 4 shows the logistic model solution for r = 0.049903, M = 4000, and m = 4000, prior to utilizing the least squares approach.

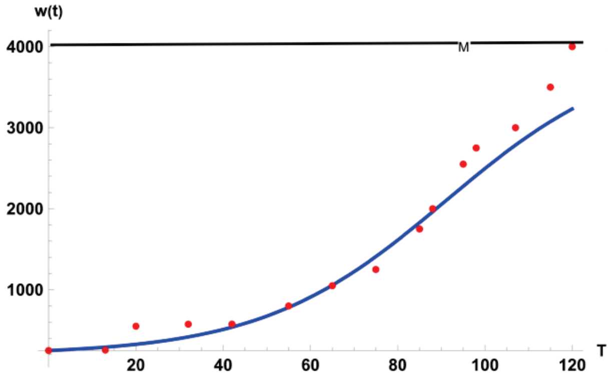

Fig. 4. Estimating the Allee effect model based on equation 8, after using the least square method, and having an intrinsic growth rate of r=0.049903 and carrying capacity of M= 4000 in addition to a threshold point of m=200.

Unlike the logistic and Gompertz models, using the least squares technique is unnecessary to obtain new intrinsic growth rates and carrying capacity values. The Allee effect model is best suited to represent experimental cancer data accurately before finding SSR.

E. Von Bertalanffy

The von Bertalanffy model result based on equation 9, where the intrinsic growth rate r and the carrying capacity M, are illustrated below. Figure 5 depicts the result of the Bertalanffy model using the least square approach, where r= 0.29911998856184 and M= 4214.09508897029.

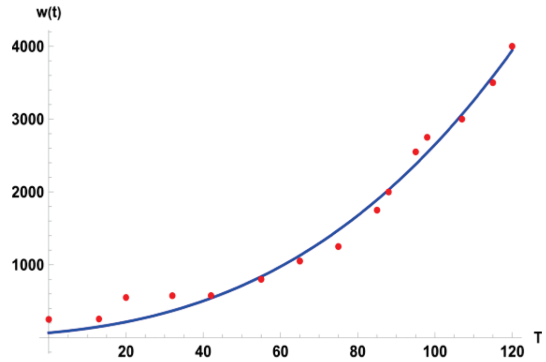

Fig. 5. The estimation for the number of infections using the von Bertalanffy model, based on equation nine, using the least squares method, and having intrinsic growth rate r=0.29911998856184 and carrying capacity M=4214.09508897029.

Discussion

We used Wolfram Mathematica 13.2 to represent the data for the five models as this software could be used for numerical computations. We drew the five models mentioned above using the Mathematica program and MATLAB and Figure 6 shows the data comparison between models and which model is the best compared to other models. It can be seen that the exponential growth is the least appropriate model to be used in representing tumour development as the model is far different from the true values. The rest of the models are far more logical to represent tumour development as they all are close to the true data values. The true data goes up to 120 days, whereas the models go up to 200. Comparing the 4 models, we determine that the Bertalanffy model is the most accurate model to represent the size of the tumour. Therefore, the extrapolation of the Bertalanffy is the most accurate which would be useful to use in predicting how the tumour would develop in the future. We expect the tumour to increase according to this model when the tumour size increases.

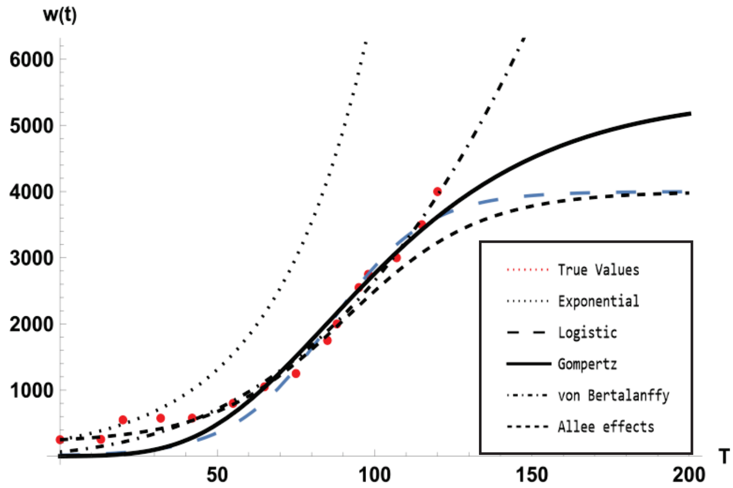

Fig. 6. Plot all five models with accurate data.

CONCLUSION

We analyzed the growth rate of five different models and determined their carrying capacity. We entered the values of the analytical solution and calculated the least squares value for each model. The exponential model had a value of 133,754,783.3, the logistic model had a value of 7,509,636.237, the Gompertz model had a value of 35,811,734.1 the Allee effect had a value of 528,352.5639, and von Bertalanffy had a value 37,198,029.46. In addition, we adjusted the growth rate figures for logistics, the Gompertz model, and Von Bertalanffy using MATLAB R2023a. As a result, Logistics is now at 29081933.73, Gompertz is now at 893826.0914, and von Bertalanffy is now at 367275.9909. Therefore, we determined that the von Bertalanffy model was the optimal representation of our data because it had the smallest least squares value.

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