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STUDENT VERSION

Modeling Cancer Growth with Differential Equations

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STATEMENT

Cancer is approaching heart disease as the leading cause of death in the United States [1]. Knowledge of tumor growth is important in cancer screening planning and treatment. Effective models of tumor growth not only help researchers understand the dynamics of cancer growth and evaluate screening strategies, but they also enable clinicians to predict the efficacy of cancer therapies and optimize treatment protocols.

In this project, you will investigate classical models for cancer growth and make predictions about the cancer growth based on the models. These models can be used to evaluate how the predictions of tumor growth change when chemotherapy or other treatments are introduced, such as, how does the maximum tumor size change? What is the minimum effective concentration of the medical drug needed to halt the tumor growth? Analysis and data fitting may be carried out to assess the models' ability to predict future growth of tumors and shed some light on the development of resistance to cancer treatment. In this lab activity you will begin to explore some of these questions, most notably you will learn about different models for cancer tumor growth and you will compare and contrast the models to determine which is the most appropriate to fit the data.

PART 1. Exponential Model

The growth of cancer can be modeled through a differential equation by examining the change of tumor volume $V(t)$ as a function of time t. A simple exponential model describes the early stages of tumor growth, where the growth is proportional to the tumor population. Cells divide and create two daughter cells at a constant rate that is independent of tumor size. This model is given by the differential equation below. The exponential model was first applied to cancer growth in 1956 [2]. The differential equation is

$$V' = aV \tag{1}$$

for proportionality constant $a > 0$.

(a) What is a solution to this differential equation?

$$V(t) = \_\_\_\_\_$$

(b) The *tumor doubling time* is defined as the time it takes for the volume to double the initial size. The tumor doubling time is introduced to measure how fast a tumor grows and to quantify the growth rate. Find the doubling time in terms of a. Show your work.

(c) The exponential model predicts *early* growth well. Explain using your function from part (a) why this model and its solution is unrealistic as $t \to \infty$.

What's the problem? The exponential model uses a differential equation in the form

$$V' = (\text{ growth rate })$$

However, depletion of nutrients inside the body and cell death is not incorporated into this model.

PART 2. Von Bertalanffy Model

In this section we will investigate an alternative model using a differential equation in the format

$$V' = (\text{ growth rate }) - (\text{ death rate }). \tag{2}$$

The Bertalanffy model balances synthesis and destruction of tumor cells [3]. This model assumes that growth is proportional to the surface area, since nutrients enter through the surface of the

cells. Remember that volume is measured in units of (length)^3 and surface area is measured in units of (length)^2. This model uses a 2/3 power in order to convert volume into surface area, up to a multiplicative constant. This leads to a **growth rate term of** $aV^{2/3}$ where $a > 0$ is a proportionality constant. The model also assumes that the death rate is proportional the tumor volume. This leads to a **death rate term of** bV for proportionality constant $b > 0$.

(a) Using the format of (2) above, what is the differential equation here?

This model is also known as the surface rule model. It has been successfully applied to describe human tumor growth in tumor research studies.

(b) The solution to the above differential equation is

$$V(t) = \left[\frac{a}{b} + Ce^{-bt/3}\right]^3.$$

where C is an arbitrary constant. Show the work to *verify* that $V(t)$ solves the differential equation. Remember, you will do this by (i) calculating V', and separately (ii) calculating the right side of the differential equation, and then (iii) verifying they are equal.

(c) Determine the maximum tumor size by finding $\lim_{t\to\infty} V(t)$. Explain why this model is more realistic than the exponential model. Note: your limit result will be in terms of a and b.

PART 3. Gompertz Model

The Gompertz model is yet another model that can be used for tumor growth. This model was created by Benjamin Gompertz in 1825 to explain human mortality graphs and to determine the value of life insurances [5]. It was later applied to organism growth a hundred years later! Rather than using a growth rate and a death rate like the previous model, the Gompertz model takes a different approach. This model uses *an exponentially decaying* growth rate, and it achieves this by using two different differential equations which are then combined together (as we will see below). The Gompertz model has been successfully used to model breast and lung cancer growth.

This model begins with a pair of differential equations

$$V' = rV \text{ and } r' = -br \tag{3}$$

where $V(t)$ represents the volume as a function of time t and $r(t)$ represents the variable growth rate that is also a function of time t. The value $b > 0$ is a proportionality constant.

(a) What is a solution for the second differential equation, for the growth rate function $r(t)$?

(b) Using the $r(t)$ function, what is the new revised differential equation for V?

(c) The solution to the differential equation is $V(t) = Ce^{\left(-\frac{1}{b}e^{-bt}\right)}$. where C is an arbitrary constant. Show the work to *verify* that $V(t)$ solves the differential equation in part (b). Remember to calculate both sides of the differential equation independently, then show they are equal.

(d) Determine the maximum tumor size by finding $\lim_{t\to\infty} V(t)$. Explain why this model is more realistic than the exponential model. Note: your limit result will be in terms of C and/or b.

PART 4. Models summary

In addition to the Von Bertalanffy and Gompertz models, there is a larger scheme of other models summarized in Figure 1. These models all originate from a generalized two-parameter model of growth for biological systems involving constants $a, b > 0$ depending on various powers of V labeled as α and β [7].

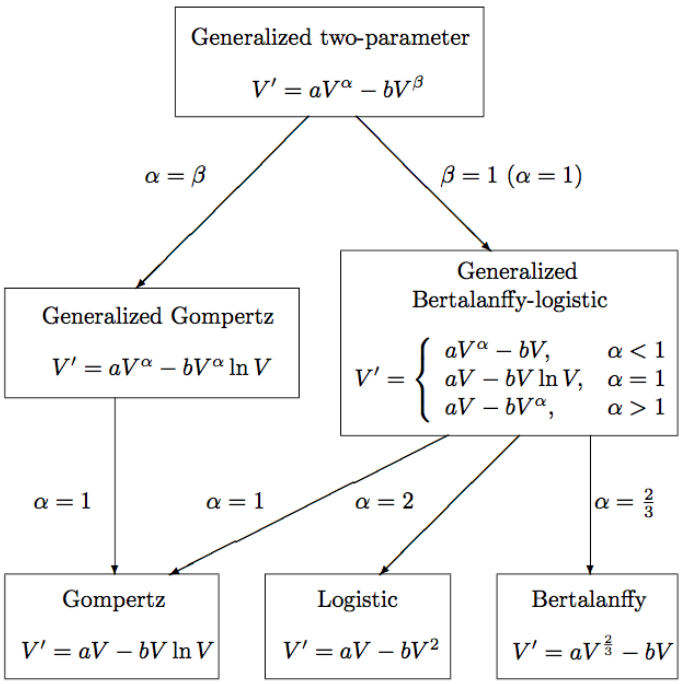

Figure 1. Nesting scheme for empirical models of growth [7].

These other models could be explored another time, for today we will stick to just the Von Bertalanffy and Gompertz models!

PART 5. Model fitting and analysis

In the case of multicellular tumor spheroids, cancer growth follows a sigmoid curve shown below in Figure 2 with three phases: initial exponential growth, linear growth, and plateau. Both the Von Bertalanffy and the Gompertz models reflect the sigmoid nature of growth!

In the next part of this activity, you will fit the Von Bertalanffy and Gompertz models to real cancer data to predict the best fit model for tumor growth. The fitting will be performed using

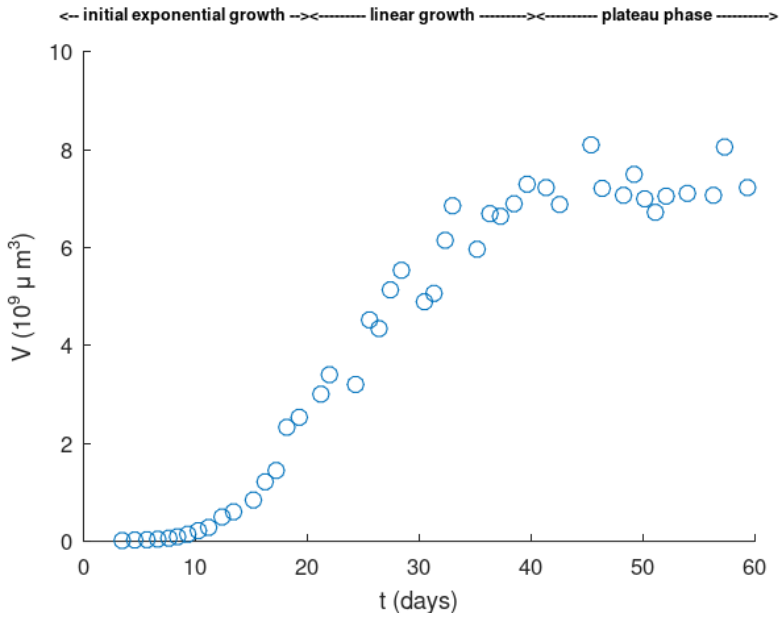

Figure 2. Nesting scheme for empirical models of growth [7].

the link **https://www.desmos.com/calculator/ybmshqjqew** with the nonlinear regression calculator provided at this link. The suitability of the model is determined by the R^2-value, which represents the fraction of the variation of the data that is predicted by the model equation. The R^2 value is determined by

$$R^2 = 1 - \frac{SS_{res}}{SS_{tot}}.$$

This equation is composed of two sums of squares (denoted by SS) calculated as follows. The first is called the **sum of the squares of the residuals** and corresponds to the forrmula

$$SS_{res} = (y_1 - f_1)^2 + (y_2 - f_2)^2 + (y_3 - f_3)^2 + \cdots$$

where $y_1, y_2, y_3, \ldots$ represent the observed data values and $f_1, f_2, f_3, \ldots$ represent the corresponding model's function values. The **total sum of squares** corresponds to the formula

$$SS_{tot} = (y_1 - \overline{y})^2 + (y_2 - \overline{y})^2 + (y_3 - \overline{y})^2 + \cdots$$

where $\overline{y}$ represents the average of the observed data. The closer the R^2 value is to 1 the more percentage of the variation in the data is predicted by the model.

The dataset provided in Table 1 is taken from the Chinese hamster V79 fibroblast tumor cell line [8]. It consists of 45 measurements of volumes ($10^9 \mu m^3$) during the time period of 60 days.

Perform the following tasks to evaluate and analyze the models.

(a) Using the Von Bertalanffy model equation in PART 2 (b), assume that the initial volume of the tumor is equal to zero and determine C in terms of a and b. Once you have an expression for

t (days)	**V** ($10^9 \mu m^3$)	**t**	**V**	**t**	**V**	**t**	**V**	**t**	**V**
3.46	0.0158	12.39	0.4977	24.33	3.2046	35.20	5.9668	48.29	7.0694
4.58	0.0264	13.42	0.6033	25.58	4.5241	36.34	6.6945	49.24	7.4971
5.67	0.0326	15.19	0.8441	26.43	4.3459	37.29	6.6395	50.19	6.9974
6.64	0.0445	16.24	1.2163	27.44	5.1374	38.50	6.8971	51.14	6.7219
7.63	0.0646	17.23	1.4470	28.43	5.5376	39.67	7.2966	52.10	7.0523
8.41	0.0933	18.18	2.3298	30.49	4.8946	41.37	7.2268	54.00	7.1095
9.32	0.1454	19.29	2.5342	31.34	5.0660	42.58	6.8815	56.33	7.0694
10.27	0.2183	21.23	3.0064	32.34	6.1494	45.39	8.0993	57.33	8.0562
11.19	0.2842	21.99	3.4044	33.00	6.8548	46.38	7.2112	59.38	7.2268

Table 1. Chinese hamster V79 fibroblast tumor

C state the function $V(t)$ using your new C-expression. Show your work.

(b) Using the Gompertz model equation in PART 3 (b) explain why you cannot assume the initial volume of the tumor is equal to zero for this model equation. What problem would occur with the model equation? What difficulty would you find if you tried to solve for C? Explain and show your work. Using your result from this part we must include the C letter in the Gompertz model.

The best model for cancer growth.

(c) Notice that the C-letters are missing from the model equations in the online calculator **https://www.desmos.com/calculator/ybmshqjqew**. Using your result from part (a) above type the C expression into the calculator (in terms of a and b) into the Von Bertalanffy equation in the correct spot. Using your result from part (b) keep the C letter in the Gormpertz formula and type it into the online calculator in the correct spot. NOTE: You should also double check that all your data points are typed into the table!

(i) What parameters best fit the **Von Bertalanffy** model?

$a =$ _____ $b =$ _____

(ii) What parameters best fit the **Gompertz** model?

$C =$ _____ $b =$ _____

(iii) Which model best describes the cancer growth? Fully explain your answer using the R^2 values.

Maximum tumor growth for each model.

(d) Using your a and b values from above, what is the maximum tumor volume size for the Von Bertalanffy model?

(e) Using your C and b values from above, what is the maximum tumor volume size for the Gompertz model?

Modeling cancer treatments (e.g., chemotherapy, immunotherapy, or drug treatment)
(f) The predictions of these models will be different when the effects of cancer treatment is added into the model. It is important to examine this effect because the cancer growth model is often used as a basis for assessing the efficacy of cancer treatments. We model a simple implementation of a cancer treatment by subtracting cV from each volume rate equation where c represents some constant drug supply [10].

(i) What would be the new differential equations for both models after incorporating the effects of the cancer treatments? Show your answer for both Von Bertalanffy and Gompertz models.

(ii) Give a brief narrative description of how you would analyze these new differential equations. What process would you follow to find the best fit parameters? What other analysis can you think of doing for these cancer models? What additional research questions could you potentially investigate based on these new models? NOTE: This is more about the process of brainstorming than "being right". Express your replies in clearly written complete sentences.

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