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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 several classical models for cancer growth and examine the behaviors of these equations and their solutions through qualitative techniques. Furthermore, you will 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 drug needed? 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.

1 Modeling scenarios

The growth of cancer can be modeled through first-order ordinary differential equations by examining the change of tumor volume V over time t, given an initial volume $V(0) = V_0$. This initial condition is used in the following models. The parameters in the models are positive.

1.1 Exponential growth

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. The model is given by (1). This model was first applied to cancer growth in 1956 [2].

$$\frac{dV}{dt} = aV \tag{1}$$

The tumor doubling time is introduced to measure how fast a tumor grows and quantify the growth rate,

$$DT = \frac{\ln 2}{a}.$$

The exponential model predicts early growth well. However, with depletion of nutrients and cell death, exponential growth is not valid for the long-term growth of solid tumors. Thus we investigate several alternative models below.

Exercise 1. Solve (1) for tumor volume $V(t)$. Determine the maximum tumor size.

1.2 Power law

A generalization of the exponential model is described by the power-law equation (2), introduced by Mendelsohn in 1963 [9].

$$\frac{dV}{dt} = aV^b \tag{2}$$

Exercise 2. Solve (2) for tumor volume $V(t)$ for $b < 1$. Determine the maximum tumor size.

1.3 Von Bertalanffy

The Bertalanffy model balances synthesis and destruction [3]. Assume that growth is proportional to surface area, since nutrient enters through the surface, and that death is proportional the tumor size. The model is given by (3), also known as the surface rule model.

$$\frac{dV}{dt} = aV^{2/3} - bV \tag{3}$$

This model has been successfully applied to describe human tumor growth.

Exercise 3. The exact solution of (3) is given below. Determine the maximum tumor size.

$$V(t) = \left[\frac{a}{b} + \left(V_0^{1/3} - \frac{a}{b}\right) e^{-bt/3}\right]^3.$$

1.4 Logistic

The logistic model of population growth was first published by Pierre Verhulst in 1845 [11]. The model assumes a linear decrease of the relative growth rate with population size. The maximum size is limited by a carrying capacity K.

$$\frac{dV}{dt} = aV\left(1 - \frac{V}{K}\right) \tag{4}$$

Exercise 4. Solve (4) for tumor volume $V(t)$ for $a = 1$ and $K = 1$. Determine the maximum tumor size.

1.5 Gompertz

The Gompertz model was created by Benjamin Gompertz in 1825 to explain human mortality curves and determine the value of life insurances [5]. It was applied to organism growth a hundred years later. The Gompertz model exhibits an exponential decay of the growth rate. It has been successfully used to model breast and lung cancer growth.

$$\frac{dV}{dt} = r(t)V(t), \quad \frac{dr}{dt} = -br(t) \tag{5}$$

From the above equations, we have

$$\frac{d}{dt}\ln V = \frac{1}{V}\frac{dV}{dt} = r(t) = -\frac{1}{b}\frac{dr}{dt}.$$

Thus,

$$\ln V = \frac{-r(t) + a}{b} \quad \text{for some constant } a.$$

Solving for $r(t)$ leads to $r(t) = a - b\ln V$. Substituting this into (5) we obtain an alternative and more popular form of the Gompertz model.

$$\frac{dV}{dt} = V(a - b\ln V) \tag{6}$$

Exercise 5. Rewrite (5) as $dV/dt = ke^{-bt}V$. Solve it for tumor volume $V(t)$. Determine the maximum tumor size.

1.6 Modeling summary

In the case of multicellular tumor spheroids, cancer growth follows a sigmoid curve with three phases: initial exponential growth, linear growth, and plateau. The Bertalanffy, logistic, and Gompertz models reflect the sigmoid nature of growth. They are summarized in Figure 1, originating from the generalized two-parameter model of growth for biological systems [7]. Note that these models are autonomous differential equations.

2 Model fitting and analysis

In the second part of this activity, you will fit models to real cancer data to predict the best fit model for tumor growth. The fitting is performed by minimizing the sum of squared residuals (SSR) or normalized mean square error (NMSE). The NMSE is independent of measurement units and scale. A value of NMSE close to zero indicates a good fit of the model.

$$SSR = \sum_i (y_i - \hat{y}_i)^2 \tag{7}$$

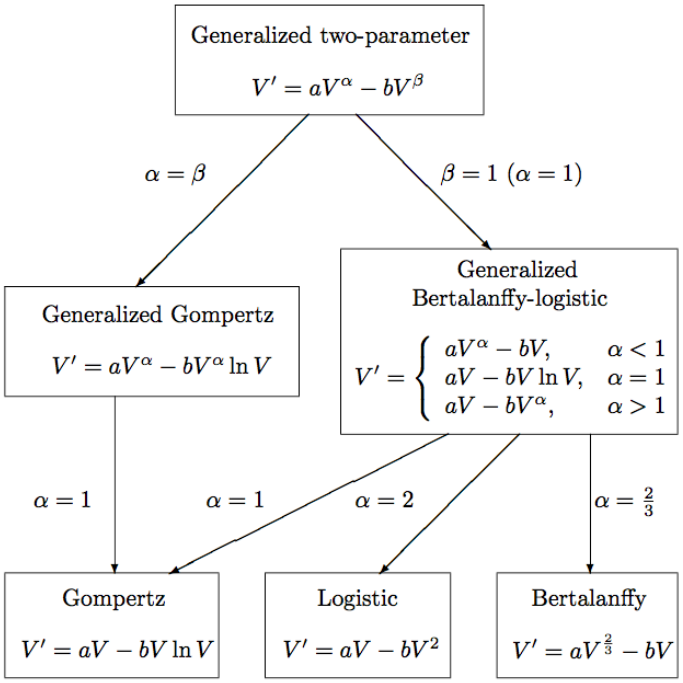

Figure 1. Nesting scheme for empirical models of growth [7].

$$NMSE = \frac{\sum_i (y_i - \hat{y}_i)^2}{\sum_i y_i^2} \tag{8}$$

The y_i's are tumor volume measurements at time points t_i; the $\hat{y}_i$'s are tumor volume estimates predicted by the model at the same time points.

2.1 Fibroblast tumor cell

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.

Evaluate the models and perform the following tasks.

1. **The best model for cancer growth.**
   Consider the three models $V' = f(V)$: **Bertalanffy**, **logistic**, and **Gompertz**. Use model equations given in Figure 1. Note that $K = a/b$ for logistic model. Find the optimal values of parameters a and b by minimizing the NMSE. Which model best describes the cancer growth? You may use Excel "Solver" function or Matlab or any other software of your choice.

   Hint: In Excel, the model estimate can be evaluated using Euler's method to numerically solve the differential equations:

$$V_i = V_{i-1} + f(V_{i-1}) \cdot (t_i - t_{i-1}), \quad i = 1, 2, \ldots, 45\,. \tag{9}$$

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

A helpful guide to Excel "Solver" function is provided in [4].

2. The **optimal parameter values** and NMSE obtained from above are:

$$\begin{array}{lllll} \textbf{Bertalanffy} & a = 0.4340, & b = 0.2158, & NMSE = 0.0089 \\ \textbf{Logistic} & a = 0.3389, & b = 0.0489, & NMSE = 0.0138 \\ \textbf{Gompertz} & a = 0.2375, & b = 0.1179, & NMSE = 0.0049 \end{array}$$

The Gompertz model gives the best fit to the tumor growth data with an NMSE of 0.49%.

   (a) Find the equilibria of the three models using these values. Plot the three growth rate functions $f(V)$ in one graph. Label graph including proper units.

   (b) Sketch the phase line for each model. Identify the types of equilibria (sink, source, node) and their stabilities.

   (c) Hand sketch the slope fields and solution graphs in separate planes.

   (d) In Excel, or Matlab, or other softwares, plot the data measurements given in Table 1 and three model fitting curves (9) in one graph. Label your graph including proper units.

   (e) Describe the behavior of the solutions.

3. **Prediction of cancer growth.**
   Repeat the task in Problem 1, but only use the first third of the data to find the optimal values of a and b. How well do the models predict cancer growth? Which model best predicts cancer growth? Assess the difference in model predictions. You may compute the NMSE and plot the solution graphs. Can the model prediction be improved with more data (such as half of the data)? How much improvement can we see?

4. **With cancer treatments** (e.g., chemotherapy, immunotherapy, or drug treatment).
   The prediction will be affected when cancer treatment is added to 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 model equation for some constant drug supply c [10].

(a) What is the maximum tumor volume for all five models with cancer treatment? Do not plug in the parameter values. Express your answers in terms of a, b, c. (Hint: You don't need to solve the differential equations. You may find the equilibria and use stability analysis.)

(b) What is the minimum amount of drug needed to eradicate the tumor in each model? (i.e. to achieve a negative initial growth rate of the tumor.) Express your answers in terms of a, b, c, V_0. Can the tumor be eradicated?

2.2 Mouse skin carcinogenesis

The second dataset provided in Table 2 is taken from mice tumors that arise in situ from normal skin as a result of chemical mutagenesis, and develop naturally in the context of a full immune system, thus more closely resembling the complexity and dynamics of tumorigenesis *in vivo* [6]. It consists of 24 measurements during the time period of 11 weeks.

t (days)	**V** (mm^3)	**t** (days)	**V** (mm^3)	**t** (days)	**V** (mm^3)	**t** (days)	**V** (mm^3)
0	1.0410	21	35.1929	42	87.7625	62	407.5250
3	4.3156	24	32.3758	45	98.7135	65	303.3899
7	2.8523	28	36.9683	49	131.8011	69	393.7301
10	4.1246	31	62.4162	52	147.4074	72	337.5277
14	5.9634	35	135.3351	56	267.1758	76	376.4903
17	8.2353	38	137.0422	59	421.1538	78	395.8532

Table 2. Mouse tumor CM.37 T.1

Perform the same tasks as in problems 1 & 2 in Sec. 2.1. The optimal fit values and NMSE are found below. Which model gives the best fit? Is it the same or different? If different, what are possible reasons? Examine and compare the two dataset plots. Has the second dataset reached the third phase, *i.e.*, plateau?

Bertalanffy	$a = 0.4947,$	$b = 0.0465,$	$NMSE = 0.0514$
Logistic	$a = 0.1402,$	$b = 0.000357,$	$NMSE = 0.0388$
Gompertz	$a = 0.2619,$	$b = 0.0413,$	$NMSE = 0.0463$

3 Conclusions

Write a paragraph summarizing your analysis, findings, and recommendations.

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