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STUDENT VERSION
Exploring Tumor Growth Modeling

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STATEMENT

This is an INDIVIDUAL assignment. Your primary submission is a hard copy report that should **not exceed three (3) pages**. To support your primary report, you should include annotated and referenced appendices.

You should include any additional supporting graphs, equations, and computations in the appendices. If you think that your code is important, you may include it in an appendix, but you should ensure that it includes annotations describing what you are doing. If you think a computation or equation is important for the reader, then ensure it is in the report or appendices.

Ensure all work is logical, neat, and organized. Properly document any sources or assistance you receive. Doing the mathematics correctly is important, but it is also critical to be able to analyze and effectively communicate your mathematical results, as well as reflect on the relevance of your results in the real world.

Goals

1. Clearly communicate your mathematical model and solution methods in a written form.
2. Explore aspects of the problem from a different disciplinary perspective to supplement mathematical modeling.
3. Design and solve a mathematical model for a real world problem using differential equations.
4. Confront the ambiguity of problem solving and understand the necessity of making assumptions in formulating a mathematical model. Explore the impact these assumptions have on solutions.
5. Apply technology learned in the course to analyze and to solve a differential equations model. Develop an appreciation for how technology enhances your problem solving capabilities.

Helpful tools

1. Mathematical computation software.
2. Differential equations textbook.

BACKGROUND

Tumor growth has been investigated extensively for more than 60 years [1]. Normally, human cell repair and reproduction is achieved through a regulated cell division process. Lumps or tumors develop when cell division continues at an uncontrolled rate (Figure 1). There are many factors that contribute to tumor growth and development. This complex system of influencing factors can be simplified and represented as a mathematical model. Designing models helps researchers understand many issues surrounding tumors including evaluation of growth hypotheses, predicting patient prognosis, and determining the effectiveness of different therapies applied to combating tumor growth [5, 3, 2].

Experimental observation has revealed that the relative growth rate of a tumor decreases with time [1]. This observation implies a connection between the principles of tumor growth and general growth laws, which can be expressed as ordinary differential equations [4]. Many mathematical models have been studied to predict tumor growth, however, the most widely used are the **logistic model** and **Gompertz model** described below.

The **logistic model** is given by

$$\frac{dV_L}{dt} = r_L(1 - \frac{V_L}{K_L})V_L, \quad V_L(0) = V_{L0}, \tag{1}$$

where $V_L(t)$ is the tumor volume at time t, r_L is the growth rate constant of the tumor, K_L is the carrying capacity, and V_{L0} is the volume of the tumor at the time of initial observation, $t = 0$. The general logistic model solution is given by

$$V_L = \frac{V_{L0}K_L}{V_{L0} + (K_L - V_{L0})e^{-r_L t}}.$$

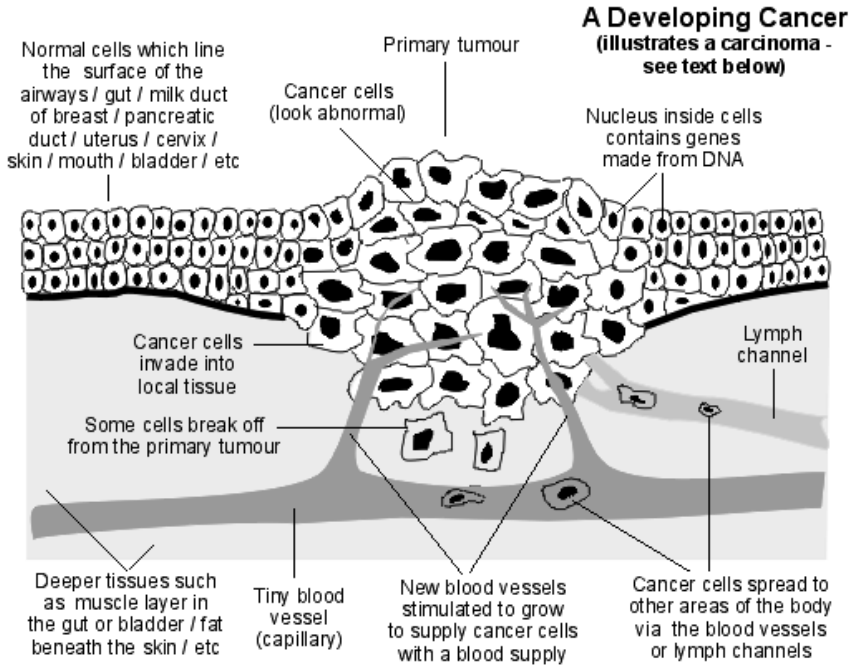

Figure 1. The development of a tumor [6].

The **Gompertz model** is given by

$$\frac{dV_G}{dt} = r_G \ln\left(\frac{K_G}{V_G}\right)V_G, \quad V_G(0) = V_{G0}, \tag{2}$$

where $V_G(t)$ is the tumor volume at time t, r_G is the growth rate constant of the tumor, K_G is the carrying capacity, and V_{G0} is the tumor volume at, $t = 0$.

Notice that both models are **autonomous** differential equations and so concepts introduced in your textbook may be useful to analyze solutions of each model. Table 1 displays data for a typical spheroid tumor growth over a 60 day period.

time (days)	0	10	20	30	40	50	60
volume (μm^3)	2.90×10^3	1.20×10^8	3.00×10^9	6.00×10^9	6.60×10^9	7.20×10^9	7.30×10^9

Table 1. Typical spheroid tumor growth over a 60 day period.

Additionally, best fit curves were obtained for models (1) & (2) resulting in the optimal parameter values: $r_L = .721$ per day, $K_L = 6.77 \times 10^9$ μm^3, $r_G = .141$ per day and $K_G = 7.23 \times 10^9$ μm^3.

Figure 2 illustrates the spheroid growth process for a tumor for the first 20 days.

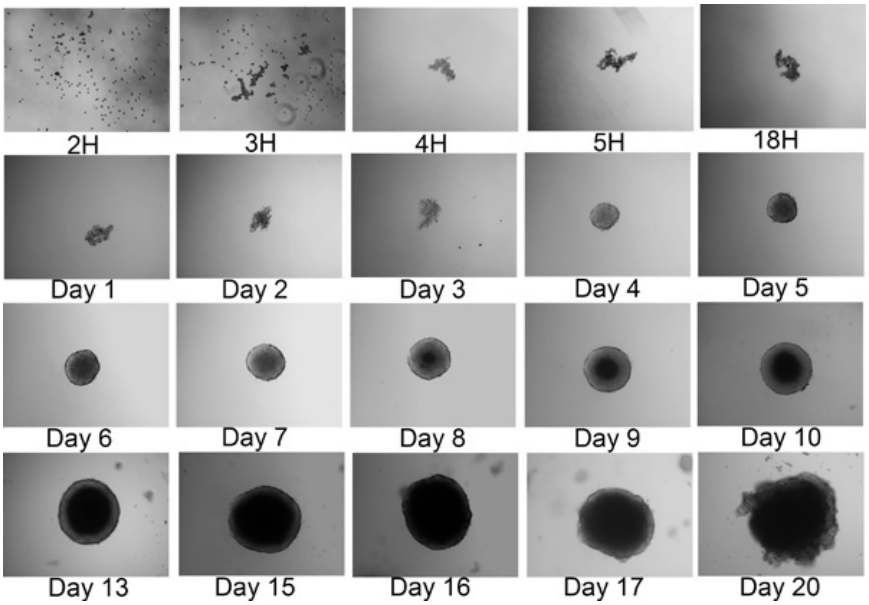

Figure 2. Example of Spheroid Growth [7].

TASK: TUMOR GROWTH MODEL EVALUATION AND COMPARISON

Conduct an analysis of the Gompertz model (2) and provide a comparison of it to the logistic model using the data provided in Table 1. Address the following questions in your report:

1. Find the solution to the Gompertz model.
2. Discuss at least two assumptions that are both reasonable and necessary to model tumor growth with the Gompertz model.
3. Plot the graph of $V_L(t)$ & $V_G(t)$ verses t for $0 \leq t \leq 60$ (with the given parameter values) along with the data provided in Table 1. Properly label the graph. Qualitatively comment on the similarities and differences of the two solution curves.
4. Plot the graph of $f(V_G) = r_G \ln(K_G/V_G)V_G$ versus V_G, find the critical point(s) and label each as *asymptotically stable* (attractor), *unstable* (repeller), or *semi-stable*. What does it mean to be asymptotically *stable*, *unstable*, or *semi-stable* within the context of tumor growth?
5. For $0 \leq V_G \leq K_G$, determine where V_G versus t is *concave up* and where it is *concave down*. Comment on the dynamics of the tumor growth associated within each interval.
6. Conduct a goodness-of-fit test of the logistic and Gompertz models using the data provided in Table 1. One method is to complete a sum of square errors (SSE) analysis. A SSE can be computed by summing the square of each error in the model's predicted values at $t =$ 0, 10, 20, 30, 40, 50 and 60 days. Which is the better model? Why?
7. Suppose $V(\tau) = 3\times10^9$ μm^3 is the tumor size for which cancer treatments (such as immunother-

apy and chemotherapy) are unlikely to bring about a successful outcome. Use the logistic *and* Gompertz models to solve for time τ. Which value of τ do you think is more accurate? Why?

8. The logistic model is typically used to to model population growth. Per (unit) population growth rate (PPGR) measures the growth one person contributes. By re-arranging the logistic equation we can express (1) as the per (unit) tumor volume growth rate (PVGR) as a function of V_L, which is
$$PVGR(V_L) = \frac{1}{V_L}\frac{dV_L}{dt} = r_L(1 - \frac{V_L}{K_L}). \tag{3}$$
What does PVGR measure as it applies to our tumor growth logistic model?

9. Rearrange (2) to find $PVGR(V_G)$. For the logistic and Gompertz models respectively, find the following:
(i) $\lim_{V_L \to 0} PVGR(V_L)$ (ii) $\lim_{V_L \to K_L} PVGR(V_L)$
(iii) $\lim_{V_G \to 0} PVGR(V_G)$ (iv) $\lim_{V_G \to K_G} PVGR(V_G)$

10. Compare and contrast the behavior of the PVGR of these models. Provide a final recommendation as to which model is better for modeling tumor growth.

REFERENCES

[1] Benzekry, Sbastien *et al*. 2014. Classical mathematical models for description and prediction of experimental tumor growth. *PLOS computational biology*. 10.8: 1-19.

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