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STUDENT VERSION

Introduction to Systems of ODEs: Tumor Growth

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STATEMENT

How do cancerous tumors evolve in size over time? In general, tumor cells are characterized by their fast division (and hence quick proliferation). In this way, tumor volume may exhibit exponential growth early in its evolution. However, tumors cannot grow forever without bound. There are many factors that may limit a tumor's ability to grow beyond a certain point, including limited resources in terms of nutrients and space. When a tumor reaches this point where it can grow no further without additional resources, we say that it has reached its *carrying capacity*.

In a clinical setting, it is of utmost importance that clinicians understand how a cancerous tumor may change over time, so that they can design an appropriate treatment regimen. Mathematical modeling can play a role here; we can use our knowledge of how tumors evolve biologically to express their growth dynamics mathematically and make predictions about what a tumor may look like at some point in the future. Models for tumor growth in the literature range in complexity from a single differential equation to systems of tens of equations with hundreds of parameters [2]. In this activity, we'll investigate several models for describing the evolution of a solid tumor over time, using what we've learned about ordinary differential equations.

Part 1: A Single ODE Model

Our first goal is to build a simple model that will describe how the volume of a tumor changes over time in the absence of any form of treatment. We'll begin with a simplifying assumption: assume that the tumor is a homogeneous mass comprised only of viable (i.e. proliferating) cells.

(a) Using your intuition and our description of basic tumor mechanics above, sketch a graph depicting the general shape of the curve of tumor size over time you would expect to observe, with time on the x-axis and volume on the y-axis. Identify any equilibria that you would expect to be present. Discuss your graph with a partner, and justify your choices using biological reasoning.

(b) The following table gives a set of simulated data describing tumor volume, V (mm^3), as a function of time, t (days), for a tumor growing in vitro (i.e. in a culture dish) in a laboratory setting.

Day	0	4	8	12	16	20	24	28	32	36	40	44
Vol.	0.020	0.118	0.350	0.540	0.599	0.661	0.662	0.662	0.662	0.662	0.662	0.662

Table 1. Tumor volume (mm^3) reported over a period of 44 days for a tumor growing in vitro in a laboratory setting. Data is simulated using the cellular automaton model described in [1].

Plot the data and compare the shape of the resulting curve to your sketch from part (a). Develop a differential equation to describe the change in tumor volume over time, dV/dt. Make sure to check that your chosen ODE contains the equilibria that you identified in part (a).

(c) Solve your ODE using an appropriate method from class. Use your data and/or a graphing tool like Desmos to estimate the values of any unknowns so that your model provides a reasonable estimate of the data.

(d) Using your model solution and estimated parameter values from (c), evaluate your model at each day for which data is available, and complete Table 2 to evaluate the overall error in your model. (Note: the SSE, or *error sum of squares*, is a natural method for quantifying model error. We measure the deviations of the model from the data at each point, square them all so that they all contribute positively to the final error calculation, and sum them all together to obtain a final quantity that summarizes the accuracy of the fit.)

Part 2: A More Complex Model

In Part 1, we made a very large assumption; namely, that all cells in the tumor are viable and proliferating. In actuality, there is a great deal of heterogeneity in a tumor mass. For one, as a tumor grows, cells in the center of the mass are unable to receive nutrients as effectively as those on the outside due to a limited vasculature system (the system of blood vessels that connects a tumor to its outside environment). These cells may undergo natural cell death as a result, in essence forming a necrotic (dead) core at the center of the tumor. This core still contributes to the overall volume of the tumor, but these cells are no longer proliferating. Our simple model from Part 1 may no longer be adequate to represent the biological complexity of our situation! Our goal now becomes to develop a more complex model that can track both the viable and necrotic cell populations.

Day	**Actual Volume**	**Estimated Volume**	**(Actual - Estimated)^2**
0	0.020		
4	0.118		
8	0.350		
12	0.540		
16	0.599		
20	0.661		
24	0.662		
28	0.662		
32	0.662		
36	0.662		
40	0.662		
44	0.662		
		Sum of Squared Errors (SSE):	

Table 2. Sum of squares computation for assessing model fit to provided data.

(a) In the following table, data is provided from a simulation where a significant portion of the tumor is necrotic tissue. Using this data set, try fitting your model from Part 1 to this new data set by adjusting the values of any unknowns accordingly.

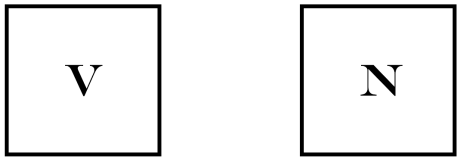
Day	0	4	8	12	16	20	24	28	32	36	40	44
Vol.	0.020	0.129	0.402	0.729	1.134	1.512	1.833	2.149	2.396	2.526	2.661	2.689

Table 3. Tumor volume (mm^3) reported over a period of 44 days for a tumor growing in vitro in a laboratory setting with a large necrotic core. Data is simulated using the cellular automaton model described in [1].

(b) Assess the fit of your model to this new data set both visually and computationally by analyzing the graphical fit and computing the SSE as done in Part 1. How does this fit to this second data set compare to your fit in Part 1? Write a few sentences explaining why we are unable to achieve such a close fit to this second data set.

(c) In order to account for both viable and necrotic cells, we need to create a *system of ODEs* capable of tracking both cell types. We can do this using *compartment modeling*. Below, we diagram our system by including a compartment for each of our cell populations, V for viable and N for necrotic. Complete the diagram by drawing arrows between compartments that describe how cells move through the system. (Hint: When we work with compartment diagrams, we think of "input-output". What is entering each compartment? What is exiting? When something exits one compartment, where does it go? How does each compartment

depend on the other? Consider the mechanisms by which cells may both enter and exit each compartment, and label each of your arrows with the corresponding terms that you'll use in your model.)



(d) Use your compartment diagram from (c) to develop a system of two ODEs: one for dV/dt (representing viable cells) and one for dN/dt (representing necrotic cells). Discuss your system with a partner and assign biological meaning to each of your parameter values. Prepare a short explanation of your model to share out to the full class.

REFERENCES

[1] Kannan, P., M. Paczkowski, A. Miar, *et al*. 2019. Radiation resistant cancer cells enhance the survival and resistance of sensitive cells in prostate spheroids. *bioRxiv*. doi: 10.1101/564724.

[2] Yin, A., D.J.A.R. Moes, J.G.C. van Hasselt, J.J. Swen, H.-J. Guchelaar. 2019. A Review of Mathematical Models for Tumor Dynamics and Treatment Resistance Evolution of Solid Tumors. *CPT: Pharmacometrics Syst. Pharmacol*. 8(10): 720-737.