

Cancer Cell Kinetics

Learning Objectives

After completion of this module, the student will be able to

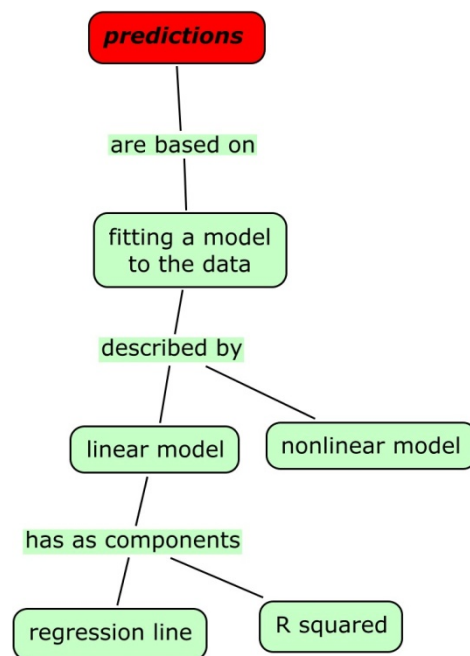
1. build a data-driven phenomenological model of tumor growth with a minimal number of parameters
2. make predictions about the kinetic behavior of a tumor based on a mathematical model
3. define growth rate and exponential growth
4. develop a differential equations describing tumor growth
5. use **WolframAlpha** to solve algebraic equations and take limits

Knowledge and Skills

1. continuous time population models
2. fitting a straight line to data
3. doubling time of an exponentially growing population
4. growth rate and exponential growth

Prerequisites

1. Volume of a sphere
2. straight lines
3. natural logarithm, exponential function
4. graphing in EXCEL
5. Logarithmic transformation
6. fitting a straight line to data points in EXCEL and displaying the equation



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Background

Death rates for many diseases have plummeted over the last 50 years. Yet cancer death rates have remained essentially the same despite billions of dollars spent on research.

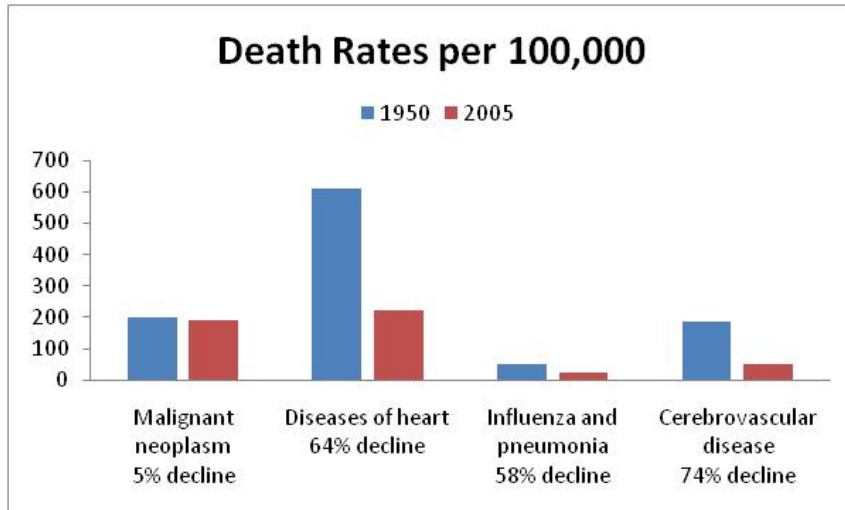


Figure 1: Death rates for selected diseases in the U.S. in 1950 and 2005 adjusted for the size and the age of the population (Source: National Center for Health Statistics and New York Times)

Research has led to improved treatments but once the cancer has spread beyond the primary tumor, survival rates tend to be low. An important aspect of cancer treatment is understanding the growth and spread of tumors. The following investigations shed some light on the kinetics of tumors.

Background Reading

Friberg, S. and S. Mattson. 1997. On the growth rates of human malignant tumors: Implications for medical decision making. *Journal of Surgical oncology* 65: 284-297

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Case Study

A patient seen at the Universitäts-Frauenklinik, Heidelberg (Germany), presented with a case of breast cancer¹. Repeated mammograms demonstrated the growth of the (untreated) tumor over time. The following data show the measurements of tumor size. Three different radiologists read the mammogram and measured the diameter of the tumor (in mm).

No.	Date	Diameter [mm]		
		D1	D2	D3
1	06/26/69	4	4	4
2	11/27/69	5	4	6
3	11/24/70	7	8	9
4	07/06/71	11	12	14
5	08/17/73	29	33	31
6	09/18/73	32	36	34

Building a Model

We will use the data to build a model of tumor growth that relates the volume of the tumor to time (measured in days). This will allow us to predict when the tumor started to grow and when it will reach a size that is lethal to the patient.

Size of a tumor

To build the model, we will make some simplifying assumptions:

1. the shape of a tumor is a sphere
2. a tumor is a solid mass of tumor cells
3. a tumor cell is a sphere with diameter $d = 10\mu\text{m}$
4. 1g of tumor cells corresponds to 10^9 cells

Recall that the volume of a sphere of radius r is $\frac{4}{3}\pi r^3$. The radius of a sphere r and its diameter d are related with $d = 2r$. With this information at hand, we can calculate the number of cells of a tumor and its weight based on its diameter.

¹ D. v. Fournier, E. Weber, W. Hoeffken, M. Bauer, F. Kubli, and V. Barth. 1980. Growth rate of 147 mammary carcinoma. *Cancer* 8: 2198-2207.

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a tumor with diameter D has volume $V_T = \frac{4}{3}\pi\left(\frac{D}{2}\right)^3$

a tumor cell with diameter d has volume $V_C = \frac{4}{3}\pi\left(\frac{d}{2}\right)^3$

Since the tumor is a solid mass of tumor cells, the number of tumor cells of diameter d in a tumor of diameter D is

$$(1) \quad \text{Number of tumor cells} = \frac{V_T}{V_C} = \frac{\frac{4}{3}\pi\left(\frac{D}{2}\right)^3}{\frac{4}{3}\pi\left(\frac{d}{2}\right)^3} = \left(\frac{D}{d}\right)^3$$

Since 10^9 tumor cells weigh 1g, the weight of a tumor is

$$(2) \quad \text{weight of tumor} = \text{number of cells} \frac{1\text{g}}{10^9 \text{ cells}}$$

In-class Activity 1

In the spreadsheet under tab *Patient 1*, calculate for each set of measurements (a) the average diameter for the tumor of the patient (Column G), (b) the volume of the tumor based on the average diameter (Column H), (c) the number of cells of the tumor (Column I), and (d) the weight of the tumor (Column J).

Kinetic Model

A kinetic model of tumor growth may relate the number of cells of a tumor to time. The patient data and our calculations in In-class Activity 1 provide data to build such a model.

In-class Activity 2

In the spreadsheet (tab *Patient 1*), the date of each observation is listed. Set the time of the first observation equal to 0 and calculate the number of days since the first observation for each of the subsequent observations (Column C). Excel can calculate the number of days between dates by simply subtracting one date from another. Plot the number of cells (Column I) as a function of time (Column C).

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Transform the vertical axis logarithmically. What type of curve would be a good fit for the data points on this semi-log graph? What does this imply for the functional relationship between the two variables (number of cells and time)?

Tumor Model

Kinetic Model ctd.

In In-class Activity 2, we observed that the data points fall on a straight line when plotted on a semi-log graph, which indicates that the relationship between the number of tumor cells and time can be described by an exponential function.

In-class Activity 3

Use the Trendline option in Excel to fit an exponential function to the data and display the equation on the graph. The equation is of the form

$$(3) \quad N(t) = ae^{ct}$$

where t corresponds to time and $N(t)$ corresponds to number of tumor cells at time t . What are the values of the two parameters a and c ?

In-class Activity 4

(a) A number of studies have shown that a primary tumor starts from a single cell. Use the model equation to predict the date when the tumor started.

(b) Tumors can be detected by palpitation when their size is about 10^7 to 10^9 cells. Tumors become lethal when their size is about 10^{12} to 10^{13} cells. This size is called the lethal burden. Based on the model equation, determine when the tumor was detectable and when the tumor reached the lethal burden?

Doubling Time

An important quantity that characterizes exponential growth is doubling time. This is the time it takes a population size to double in size. We denote the doubling time by T_2 . The doubling time satisfies the following equation:

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$$(4) \quad N(T_2) = 2N(0)$$

We will show that doubling time does not depend on the size of the population when the population is growing exponentially. Combining Equations (3) and (4), we can calculate the doubling time:

$$\begin{aligned} ae^{cT_2} &= 2a \\ e^{cT_2} &= 2 \\ cT_2 &= \ln 2 \\ T_2 &= \frac{\ln 2}{c} \end{aligned}$$

You can also use [WolframAlpha](#) to solve an equation of the form $e^{cx} = 2$. Enter “solve $e^{(c*x)}-2=0$ for x ” into the search engine and click on the equality sign. Click on “Show steps” and you will find that $x = \frac{\log 2}{c}$. Note that $\log(x)$ denotes the natural logarithm. With $x = T_2$, you see that this is the same answer as above. The screenshot below shows the result.



Figure 1: Screenshot

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In-class Activity 5

Calculate the doubling time for the tumor of the patient based on the kinetic model for tumor cell numbers.

Group Project: Summative Assessment

Assume for this activity that a tumor has 10^9 cells at the time of detection and 10^{13} cells at the time it reaches the lethal burden. Find an equation that relates doubling time for tumor cell numbers of an exponentially growing tumor to (a) time to detection and (b) time to lethal burden. (c) Based on your findings in (a), calculate the time to detection and time to lethal burden for the following cancers

Primary	Doubling Time (days)	Number of Cases
Malignant Melanoma	48	10
Colon	109	10
	116	25
Kidney	66	5
	132	8
Thyroid, anaplastic	29	7

Data Source: Table III in Friberg and Mattson (1997)

Friberg and Mattson (1997) write that “when a malignant tumor is detected, it has already existed for at least half of its lifespan.” Calculate the fraction of time a tumor spends before detection and the fraction of time a tumor spends between detection and reaching the lethal burden. Do these two quantities depend on the type of tumor?

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The following requires Calculus:

Understanding the Dynamics of Exponential Growth

Exponential growth of a population is often referred to as unrestricted growth. The reason for this is that exponential growth results if each cell divides after a fixed time interval, independent of all other cells. Exponential growth is equivalent to a constant relative growth rate. For a mathematical formulation of this statement, denote the size of the population at time t by $N(t)$. The change in population size in the interval $[t, t+h]$ is

$$\Delta N = N(t+h) - N(t)$$

The **average growth rate** during this time interval of length h is then

$$\frac{\Delta N}{\Delta t} = \frac{N(t+h) - N(t)}{h}$$

To define the **(instantaneous) growth rate** of the population, we take smaller and smaller time intervals. Mathematically, this means that we take the limit as h tends to 0. This is the derivative of the function $N(t)$ at time t , denoted by

$$\frac{dN}{dt} = \lim_{h \rightarrow 0} \frac{N(t+h) - N(t)}{h}$$

The **relative growth rate** is defined as

$$\frac{1}{N(t)} \frac{dN}{dt} = \lim_{h \rightarrow 0} \frac{1}{N(t)} \frac{N(t+h) - N(t)}{h}$$

In-class Activity 6

Use the exponential model of tumor growth to calculate the **relative average growth rate**

$$\frac{1}{N(t)} \frac{N(t+h) - N(t)}{h}$$

for $h = 1, 0.1, 0.01, \text{ and } 0.001$. Logarithmically transform the horizontal axis. Based on what you see, what value does the relative average growth rate approach as h becomes smaller?

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Let's calculate the average relative growth rate for $N(t) = ae^{ct}$:

$$\begin{aligned}\frac{1}{N(t)} \frac{N(t+h) - N(t)}{h} &= \frac{1}{ae^{ct}} \frac{ae^{c(t+h)} - ae^{ct}}{h} \\ &= \frac{1}{ae^{ct}} \frac{ae^{ct}(ae^{ch} - 1)}{h} = \frac{e^{ch} - 1}{h}\end{aligned}$$

The final expression does not depend on t . We denote it by $g(h)$:

$$g(h) = \frac{e^{ch} - 1}{h}$$

Use [WolframAlpha](#) to show that

$$\lim_{h \rightarrow 0} \frac{e^{ch} - 1}{h} = c$$

(Enter: "find limit $(e^{c \cdot h} - 1)/h$ as h to 0") This agrees with the limit for the cancer model we found in In-class Activity 6.

It follows that exponential growth can be described by the following equation

$$\frac{1}{N} \frac{dN}{dt} = c$$

This equation can be written as

$$(5) \quad \frac{dN}{dt} - cN = 0$$

Equation (5) is an example of a first-order differential equation since the highest order derivative that occurs in this equation is of order 1. These types of equations are studied in detail in calculus. The solution of this differential equation with $N(0) = a$ is $N(t) = ae^{ct}$.

We summarize: A constant relative growth rate leads to exponential growth.

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