Day 2: Pharmacokinetics

INS 099 Summer 2007
Data Analysis

Data Analysis

The first tab in your spreadsheet, named "Plasma Assay," contains two columns of data. These data were collected from a 37-year-old, 72-kg, female patient who took 1500 mg of Progen orally. A lab technician collected blood samples every hour and analyzed the concentration of Progen in the blood. The technician stopped collecting blood after 8 hours.

1. Predict the plasma concentration of Progen in the 16th hour.
2. Assuming that only blood plasma (and no other tissues) absorbs Progen, what is the volume of plasma in this patient? *Note: Adults average 5 L of blood, but you can't assume that all of that volume is made of plasma.*

Rate Laws

Rate equation for the change in y per unit of time: $\frac{dy}{dt} = ky$

Dependence of concentration over time: $y(t) = y(t_0)e^{k(t-t_0)}$, where k is the rate constant and t_0 is the lag time. If there is no lag time, then set $t_0 = 0$.

Exercise

Some foods and drugs can bind to the cytochrome enzymes that break down drug molecules. When this happens, most of the enzyme molecules stop working, and your body eliminates the drug more slowly.

The drug information for Progen warns you not to drink alcohol when you're on Progen, because alcohol slows down the rate of Progen elimination by a factor of 3.4.

1. Write two equations to describe Progen elimination.
2. Prepare a graph with two plots of Progen concentration versus time: (a) one without alcohol, and (b) one with alcohol. Assume the same patient as in the tutorial.
3. Predict the plasma concentration of Progen, taken with alcohol, in the 16th hour.

Homework

Stained glass has color because it contains ions that selectively absorb some of the light passing through it. These ions are very dilute and they are spread evenly throughout the glass. Whenever an incoming photon collides with an ion, the photon is absorbed. The more ions there are in the glass, the more collisions and absorption there will be, so the amount of light passing through is less. By comparing the number of photons entering the glass (N_{in}) with the number of photons passing through (N_{out}), you can measure the concentration of ions (c) in a pane of stained glass.

Thanks to modern optical detectors, measuring N_{in} and N_{out} are easy. But what is the dependence of N_{out} on ion concentration c? We can predict this dependence using a geometric model of photon absorption. Think of a glass plate, with thickness d, as made of many, thin layers stacked together, each one at a different position x. When a beam of light hits the first layer (x=0), the number of photons absorbed is proportional to (a) the number of photons entering the layer, and (b) the concentration of ions in this layer. The remaining photons then enter the second layer. Again, the same proportionality applies, but now the number absorbed is slightly smaller, because there were fewer photons hitting the second layer to begin with. This process repeats all the way through the glass, until the light exits the last layer.

At each imaginary layer, the number of photons N decreases by the amount:

$$\frac{dN}{dx} = -\sigma c N$$

In this equation, σ is called the "optical cross-section" (although it has other names), and it depends only on the type of ion absorbing the light. The equation above is *not* a rate equation because there's no time variable, but it has the *form* of a rate equation, so the same mathematical operations apply.

1. Write an equation that relates N_{out} to N_{in}, c, d, and σ. **Before you go on to the rest of this problem, check your equation with me or with your TA, because you need it for part 2.** Also, write an equation to calculate the *transmission* T of a glass plate, which is defined as:

2. The optical cross-section of Cr(III) ions in glass is 1.7×10^{-19} cm^2/ion. Suppose you have three different kinds of chromium-stained red glass containing: (a) 1.5×10^{18} ions/cm^3, (b) 4.0×10^{18} ions/cm^3, and (c) 15×10^{18} ions/cm^3. You can also get plates of four different thicknesses: 0.5 cm, 1.0 cm, 1.5 cm, and 2.0 cm.

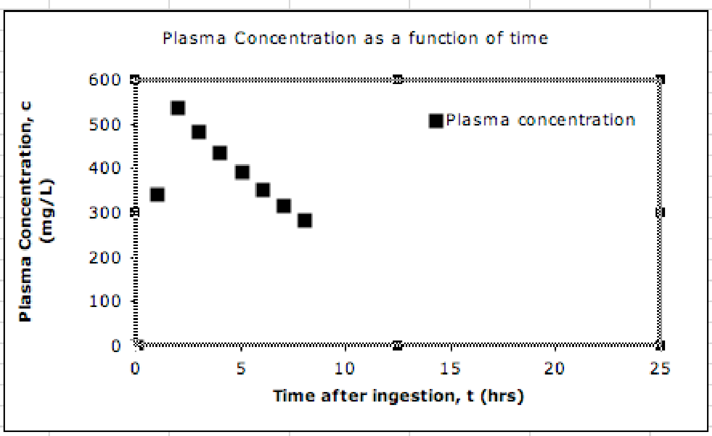
   Prepare a graph with three plots, with each plot showing the dependence of transmission on plate thickness for a different concentration of Cr(III) ions. List transmission values in a table.

Tutorial

You know how to fit an exponential model to your data, but least-squares fitting is not the only practical use for a model. Another technique is *numerical simulation*, which allows you to see what a model predicts about the future. This technique is especially useful for complex processes, but we'll start out with the simple, exponential decay problem. Our goal in this tutorial is to set up Excel to simulate exponential decay when you give it specific parameters. Once the model is in place, we can adjust the parameters to make the model fit the data.

When you are finished with the tutorial, please summarize these conventions in a list, discuss them with your group, and put together a combined list. I expect you to follow these conventions in all homework assignments and exams.

1. Make sure you have the spreadsheet open and the data is displayed. Select the menu command "`Insert > Chart…`" to bring up the "Chart Wizard" dialog, and select the "XY (Scatter)" type of graph.
2. Now define the Chart's source data by adding a series. Define the "X values" using all the time points, including the ones that have no plasma concentration data (all the way up to 22 hours). Do the same for the Y values, and include even the empty cells with no data.
3. Define the *x* and *y* axes appropriately. For the *x* axis, use a descriptive label, like "Time after ingestion." Leave the legend in place, because we will need it later.
4. In the last dialog, tell Excel to place the graph in the current spreadsheet, *not* in a separate window. Adjust the appearance of your graph if you like. Your graph should look like this:



The *x* axis goes all the way to 25 hours, even though you have no data in half of that range! This is okay, because eventually we want to make predictions for these later times.

5. In this example, our model is a delayed exponential:

, where *A* is the initial concentration, τ(tau) is the decay time, and t_0 is the delay time.

6. At the top of the spreadsheet, insert 5 rows and type in the names of the parameters, along with some values. You'll have to guess by looking at the data and knowing how the exponential function depends on parameters. For example, the initial concentration looks like it's about 550 mg/L.

	A	B	C	D
1	Parameters			
2		Initial concentration, A (mg/L)		550
3		Decay time, tau (hrs)		10
4		Absorption time, t0 (hrs)		2

7. In the third column, type a new column heading "Model (mg/L)."

8. Two cells underneath the heading (for the 2nd hour), type "=" to start defining an equation. You can either type it in or click on cells to reference the appropriate cells. If you click on cells, the equation will look something like this:

	A	B	C	D
1	Parameters			
2		Initial concentration, A (mg/L)		550
3		Decay time, tau (hrs)		10
4		Absorption time, t0 (hrs)		2
5				
6				
7	Time of Assay (hrs)	Plasma Concentration (mg/L)	Model (mg/L)	
8	0	0		
9	1	344		
10	2	538	=D2*exp(-(A10-D4)/D3)	
11	3	485		

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   This equation is wrong. To see why, use the "Fill > Down" command to copy the equation to the cell below. Excel replaces D2 with D3, but we don't want it to! To stop Excel from doing this, place a "$" in front of the "D" and the "2" to get "D2." Repeat for all references to the *parameter cells* ("A10" shouldn't be changed in this example). See the image above right. The dollar sign tells Excel not to change the cell reference as it fills down.

9. Use "Fill > Down" to calculate the prediction of this equation for 2–22 hours.

10. Let's graph this prediction so we can judge it visually. Click on the chart and select the menu command "Chart > Source Data." Add a new series that plots the model prediction, and define it using the first and third column of values. The model points will now overlap the data.

11. Adjust the first two parameters to get the model to match the data as closely as you can. Keep the third parameter, absorption time, to 2 hrs. You should get $A = 540$ mg/L and $\tau = 9.5$ hrs.

12. Now you have the parameters you need to predict the plasma concentration at any time. By filling in these numbers for the parameters in your exponential equation, you can predict the plasma concentration for an arbitrary time. Of course, for the 9th through 22nd hours, the predictions are already listed in the spreadsheet.

	Time of Assay (hrs)	Plasma Concentration (mg/L)	Model (mg/L)
8	0	0	
9	1	344	
10	2	538	540
11	3	485	486
12	4	436	437
13	5	393	394
14	6	353	354
15	7	318	319
16	8	286	287
17	9		258
18	10		233
19	11		209
20	12		188
21	13		170
22	14		153
23	15		137
24	16		124
25	17		111