Day 3: Therapeutic Range

INS 099 Summer 2007
Data Analysis

Data Analysis

The table below contains pharmacokinetic information for Bloxidone, an alternative to Progen. Suppose that a 60-kg, 20-year-old male patient is injected (intravenously) with 1500 mg of Bloxidone. Assuming that a typical adult has ~36 mL of plasma per kg of mass, the initial plasma concentration for this patient will be ~690 mg/L.

1. How long will the 1500-mg dose be effective?
2. If you increase the dosage, the drug will remain effective for a longer time. What is the longest possible time that this dose can be effective? Use a diagram or graph to illustrate this scenario.

Property	Progen	Bloxidone
Half-life, $t_{1/2}$ (hrs)	6.6	4.2
Time constant, τ (hrs)		
Effective Level, *EL* (mg/L)	295	87
Toxic Level, *TL* (mg/L)	2100	982

Homework

1. Suppose that you were on the dosing schedule described in the tutorial, but you accidentally took Progen instead of Bloxidone. Would you be ok? Explain why by using a graph and one or two sentences.
2. A pharmaceutical company decides to sell pills containing 1200 mg of Bloxidone. If you take these pills on the four-step dosing schedule above, how much should you weigh (at least)?

Dosing Schedule

1. A dosing schedule is specified by:
    a. dose, D
    b. period of dosing, T
2. Concentration function $c(t)$ depends on parameters:
    a. dose, D
    b. period of dosing, T
    c. mass, m
    d. half-life, $t_{1/2}$
    e. absorption time, t_0
3. Constraints:
    a. concentration can't exceed toxic level ($c < TL$)
    b. concentration should be above therapeutic level ($c > EL$)
    c. dosing period T should be convenient for the patient ($T \neq 1.2$ hrs)

Half-Life

Definition:

$$y\left(t_{1/2}\right) = \tfrac{1}{2}\, y\left(0\right)$$

Relation to time constant τ:

$$y_0 e^{-\frac{t_{1/2}}{\tau}} = \tfrac{1}{2}\, y_0$$

$$\frac{t_{1/2}}{\tau} = \ln(2) \approx 0.693$$

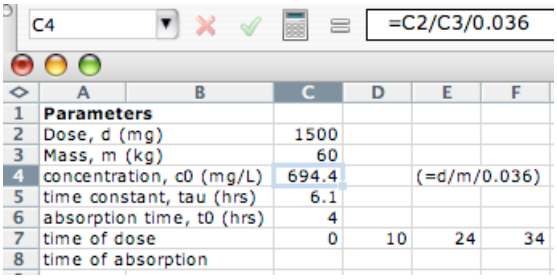
Tutorial: Four-Step Dosing Schedule

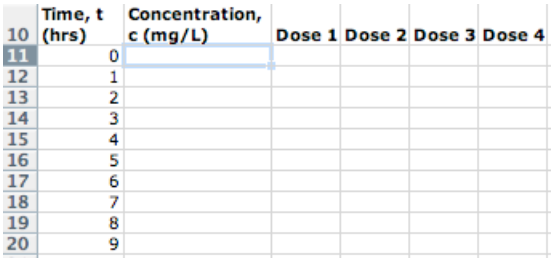
To make a drug effective for a longer time — without poisoning your patient — you can repeat the dose at regular intervals. You must still be careful about prescribing the dose, however, because of a phenomenon known as the "accumulation effect." In the next two tutorials, we'll develop a model of the accumulation effect and use this model to find safe and effective doses for patients. The first tutorial starts with a simple, four-step dosing schedule.

You will prescribe a certain amount of Bloxidone (d) for the patient to take orally *four times*: one dose of d after breakfast (8:00a) and another dose of d after dinner (6:00p), and then two doses on the next day at the same times. The absorption time for Bloxidone is 4 hours.

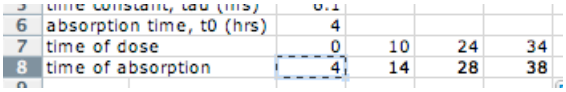
1. You'd like the Bloxidone to last as long as possible. What should d be?
2. Using this dose, how long (after the initial absorption) will the Bloxidone be effective?
3. Prepare a plot of plasma concentration versus time.

1. Open a new file in Excel. To set up our model in Excel, start by defining the parameters of this schedule. Note that one of the parameters, concentration, is defined by an equation that depends on two other parameters, since c_0 = d / (plasma volume) = d / m / (plasma volume per body mass). The "time of dose" entries in row 7 define the dosing schedule.



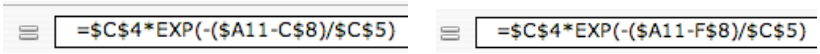


2. Note that row 8 is left blank, except for the label "time of absorption." I will explain this later.
3. Define column headings as in the upper left image. Cells A11:A111 contain time points every hour for 100 hours. The "concentration" column will contain our model's prediction.
4. The other four columns will calculate the concentration of each dose *by itself*. We assume that each dose simply adds on to the previous dose, so the total concentration function $c(t)$ should be a sum of the four individual "dose" functions. We will do this sum at the end.
5. Each dose is absorbed at a different time, so we will use row 8 to define the time shift of each dose function. Define an equation that calculates the time of absorption from the time of dose and the absorption time.

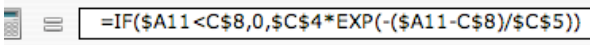


6. Click on cell C11 and use our model equation to define the 1st dose function:

$\text{Dose}(t) = c_0 e^{-\frac{(t-t_{abs})}{\tau}}$. Note that the time shift is t_{abs}, not t_0, because the time lag is *different* for each dose function. Pay attention to the "$": some go in front of letters, some in front of numbers, and some in front of both. Check your equation with the left image below.



7. Copy this equation and fill to the right. Cell F11 should look like the right image above.
8. Highlight the four cells and fill *down*.
9. You now have four columns of numbers predicted from our model above. Unfortunately, each column predicts a non-zero plasma concentration even for time points *before the lag time*. In order to make these time points 0, we will use the *conditional* function.
10. Modify the equation in C11 to read:

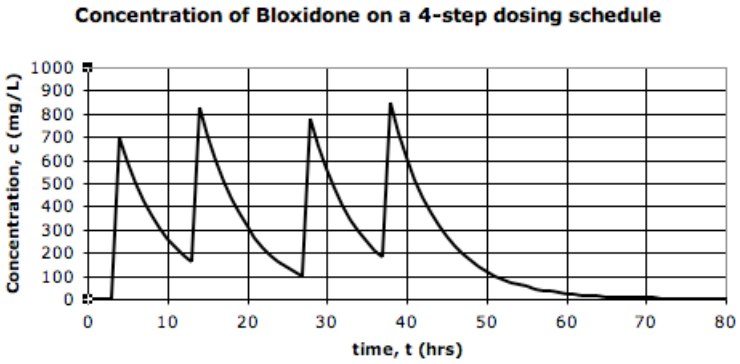


The IF function takes the form "IF(*logical test*, *value if true, value if false*)". The ***logical test*** in this case is "$A11<C$8" and it asks whether t is less than the time of absorption for this dose. If it is, then it hasn't been absorbed, so c should be 0 — this is the ***value if true***. Once we get to row 15, the logical test will no longer be true, so the C15 will instead take on the ***value if false***, which is the equation we originally defined.

11. Fill this equation down the rest of column C. Then select the column and fill right to the other three columns. You should see that the initial cells in each column are 0, and only take on a value after they reach the time of absorption (t_{abs}) for the corresponding dose.

10	Time, t (hrs)	Concentration, c (mg/L)	Dose 1	Dose 2	Dose 3	Dose 4
11	0		0	0	0	0
12	1		0	0	0	0
13	2		0	0	0	0
14	3		0	0	0	0
15	4		694.4	0	0	0
16	5		589.4	0	0	0
17	6		500.3	0	0	0
18	7		424.7	0	0	0
19	8		360.5	0	0	0
20	9		306	0	0	0
21	10		259.7	0	0	0

12. In B11, define an equation that adds up the four doses in row 11. The SUM function works well. Then, fill the equation down the rest of column B.
13. Plot concentration versus time. You should see the concentration spiking in 4 places, with exponential decay in between. The interesting thing is the second spike is higher than the first.



14. Change the dose parameter d. Adjust it until the second spike is below 982 mg/L. This happens with d=1775 mg (for a 60 kg patient). Using this maximum dose, you can visually inspect the graph to see that the concentration falls below the effective level (87 mg/L) at t=53 hrs. The time of effectiveness is therefore 53–4 hrs = 49 hrs.