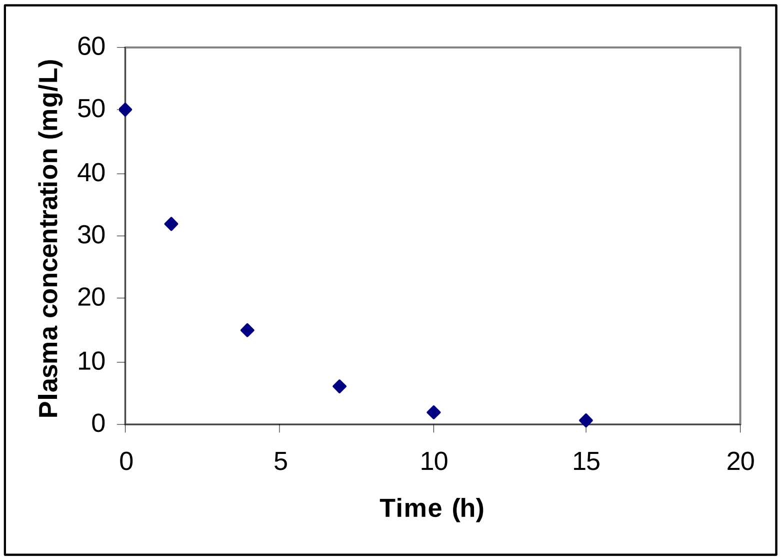
PHA 5127 Fall 2007
Case Study #1

#1) *Patient H.G. was given 1000mg drug X as an i.v. bolus. Determined plasma concentration-time profiles are listed in the table below.*

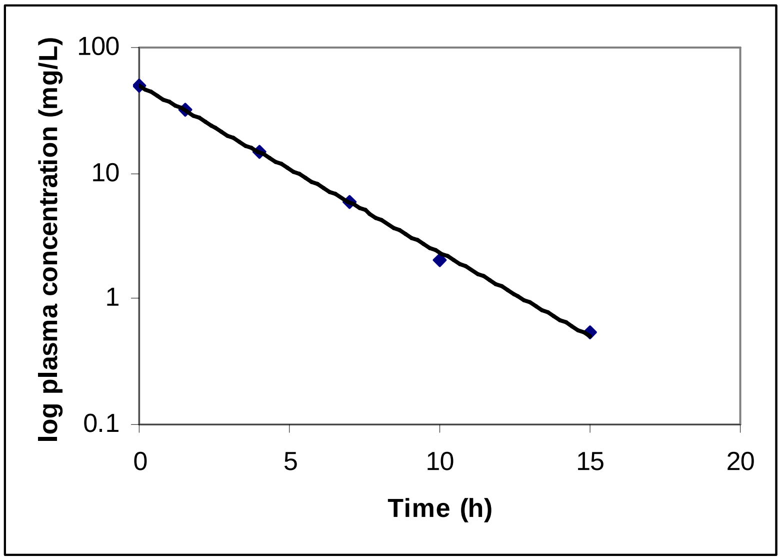
time (h)	Plasma concentration (mg/L)
0	50
1.5	32
4	15
7	6
10	2.5
15	0.5

a) Determine whether the drug follows a **zero-** or a **first-order** elimination process!

One way to address this question is to graph the data on both a linear and a semi-log scale.



If all points were on a straight line on a linear scale that would indicate zero-order kinetics. This is not what we have here, so let's check the data plotted on a semi-log scale.



The data points line up almost perfectly on a straight line when we plot the data on a semi-log scale. → first-order kinetics

b) Calculate the elimination rate constant (k_e)!

$$k_e = \frac{\Delta y}{\Delta x} = \frac{\ln C_1 - \ln C_2}{t_2 - t_1} = \frac{\ln\left(\frac{C_1}{C_2}\right)}{t_2 - t_1} = \frac{\ln\left(\frac{50}{15}\right)}{4h - 0h} = 0.3h^{-1}$$

c) Calculate $AUC_{0\rightarrow\infty}$!

Use the trapezoidal rule to calculate the area under the curve from time zero to the last time point ($AUC_{0\rightarrow last}$). The general formula to calculate the area of a trapezoid is:

$$AUC_{1\rightarrow 2} = \frac{C_1 + C_2}{2} * (t_2 - t_1)$$

Therefore,

$$AUC_{0\rightarrow last} = \begin{pmatrix} \frac{50+32}{2}*(1.5-0) + \frac{32+15}{2}*(4-1.5) + \frac{15+6}{2}*(7-4) + \\ + \frac{6+2.5}{2}*(10-7) + \frac{2.5+0.5}{2}*(15-10) \end{pmatrix} \frac{mg\cdot h}{L} =$$

$$= (41*1.5 + 23.5*2.5 + 10.5*3 + 4.25*3 + 1.5*5 = 61.5 + 58.75 + 31.5 + 12.75 + 7.5)\frac{mg\cdot h}{L} =$$

$$= 172\frac{mg\cdot h}{L}$$

In order to calculate the area under the curve from the last time point to infinity ($AUC_{last\rightarrow inf}$), we need to divide last given concentration (C_{last}) by the elimination rate constant (k_e).

$$AUC_{last\to\inf} = \frac{C_{last}}{k_e} = \frac{0.5\frac{mg}{L}}{0.3h^{-1}} = 1.67\frac{mg\cdot h}{L}$$

Let's finally calculate $AUC_{0\to\inf}$.

$$AUC_{0\to\inf} = AUC_{0\to last} + AUC_{last\to\inf} = 172\frac{mg\cdot h}{L} + 1.67\frac{mg\cdot h}{L} = 173.67\frac{mg\cdot h}{L}$$

d) Can you predict what the concentration of drug X after two half-lives will be?

$$t_{1/2} = \frac{\ln 2}{k_e} = \frac{0.693}{0.3h^{-1}} = 2.31h$$

$$\to 2\cdot t_{1/2} = 2\cdot 2.31h = 4.62h$$

$$C(t) = C_0\cdot e^{-k_e\cdot t}$$

$$\to C(2\cdot t_{1/2}) = C_0\cdot e^{-k_e\cdot 2\cdot t_{1/2}} = 50\frac{mg}{L}\cdot e^{(-0.3h^{-1}\cdot 4.62h)} = 12.5\frac{mg}{L}$$

Alternatively: Recall the definition of half-life. In one half-life, $C_{t1/2} = 0.5*C_t$
Accordingly two half-lives are:

$$C_{2t1/2} = 0.5\cdot 0.5\cdot C_t = 0.25\cdot C_t = 0.25\cdot 50\frac{mg}{L} = 12.5\frac{mg}{L}$$

#2) *Which of the following statements best describes a zero or a first order process?*

a) The same amount of drug is eliminated during a given time interval.

Zero-order

b) The same fraction of drug is eliminated during a given time interval.

First-order

c) Given a one-compartment body-model, a concentration vs. time profile after an i.v. bolus shows a straight line on a linear scale.

Zero-order

d) Given a one-compartment body-model, a concentration vs. time profile after an i.v. bolus shows a straight line on a semi-log scale.

First-order