

PHAR 7632 Chapter 2

Background Mathematical Material

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Student Objectives for this Chapter

After completing the material in this chapter each student should:-

- understand exponents and logarithms, algebraically and graphically
- be able to use linear (Cartesian) and semi-log graph paper for the representation of data
- be able to draw a 'best-fit' straight line through data on linear and semi-log graph paper
- understand and able to use spreadsheets
- understand differential and integral calculus
- be able to write differential equations given a compartmental modeling scheme as a diagram or description
- be able calculate the area under the plasma concentration *versus* time curve (AUC) using the linear trapezoidal rule

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Exponents

Definition:

$$N = b^x \text{ or } N = b^{\wedge}x \text{ or } N = b ** x$$

where N is the number, b is the base, often 10 but also [e \(= 2.7183... Napier's constant\)](#), and x is the exponent (or power term when an integer as in 10^2 is 10 to the power 2).

Note use of \wedge (common calculator or single line format) or $**$ (common computer language format)

With the same base, exponents can be added or subtracted

For example; $a^x \times a^y = a^{(x+y)}$ to perform multiplication

or

$a^x / a^y = a^{(x-y)}$ to perform division.

Some Example Calculations

a) $100 = 10^2 = 10^{\wedge}2 = 10**2$

b) $100 = e^{4.605} = e^{\wedge}4.605 = e**4.605$ where $e = 2.7183$!!!

c) $10 \times 100 = 10^1 \times 10^2 = 10^{1+2} = 10^3 = 1000$

d) $10 \times 100 = e^{2.303} \times e^{4.605} = e^{6.908} = 1000$ when the base is the same you can add exponents to multiply numbers

Subtract exponents to divide

e) $5.6/1.2 = e^{1.723} / e^{0.182} = e^{1.723 - 0.182} = e^{1.541} = 4.67$

Use your calculator to check this answer

In pharmacokinetics and the study of other rate processes we are interested in numbers expressed as a base 10 or e with a negative exponent. Exponential decay refers to the decrease in the value of the number as the negative exponent increases in magnitude. Exponential decay is illustrated in tabular form and graphical form in Table 2.2.1 and Figure 2.2.1, respectively.

Table 2.2.1

x	0.0	0.5	1.0	1.5	2.0	2.5	3.0
10^{-x}	1.000	0.316	0.100	0.032	0.010	0.003	0.001
e^{-x}	1.000	0.607	0.368	0.223	0.135	0.082	0.050

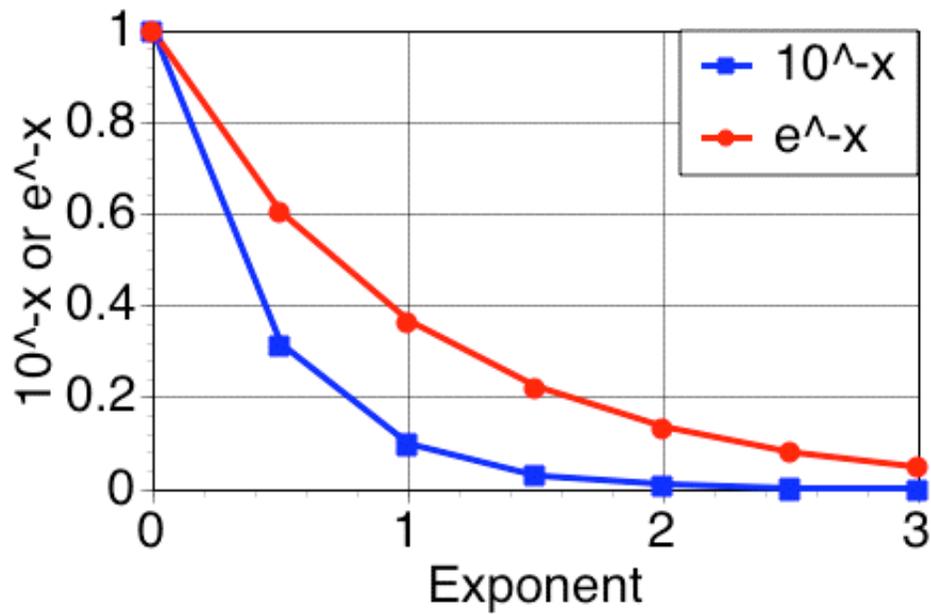


Figure 2.2.1 Linear plot of 10^{-x} or e^{-x} versus x

Click on the figure to view the Java Applet window

Try your own calculation

Calculator 2.2.1 Calculate 10^{-x} or e^{-x}

Enter your own values of x

Calculate

10^{-x} is:
 e^{-x} is:

References

- [Exponential function](#) at Wikipedia
- [Exponential function](#) at MathWorld
- Search for [Exponential function](#) at Goggle

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Logarithms

If $N = b^x$ then $x = \log_b N$

For example, $100 = 10^2$ thus $\log(100) = 2$ [base 10 assumed] or 100 is the antilog of 2.

These are called common logs (log). [Natural logs](#) (ln) use the base e (=2.7183). Note the use of log and ln to denote common or natural logarithms, respectively.

To convert from common log (base 10) to natural log (base e)

$$\text{use } 2.303 \times \log_{10}(N) = \ln_e(N)$$

$$\text{that is, } \ln(10) \times \log(N) = \ln(N)$$

$$\text{For example, } \ln(100) = 2.303 \times \log(100) = 2.303 \times 2 = 4.606$$

Common logs are often used with equilibrium equations and buffer or pH calculations. Logarithms to base e are often used in pharmacokinetics and other kinetic processes.

Before calculators, logarithms were used to multiply or divide numbers. The two numbers to be multiplied or divided would be converted to logarithms. For multiplication the logs are added and for division the logs are subtracted.

Examples:

$$\text{a) } 23.7 \times 56.4 = x$$

To find x take the natural log of both numbers, add and take the 'anti'-log (base e)

$$\ln(23.7) + \ln(56.4) = \ln(x)$$

$$3.1655 + 4.0325 = 7.1980 = \ln(x)$$

$$x = 1337$$

$$\text{or } 23.7 \times 56.4 = e^{3.1655} \times e^{4.0325} = e^{(3.1655 + 4.0325)} = e^{7.1980} = 1337$$

$$\text{b) } 6.75 / 14.7 = y$$

To find y take the common log of both numbers, subtract and take the 'anti'-log (base 10)

$$\log(6.75) - \log(14.7) = \log(y)$$

$$0.8293 - 1.1673 = -0.338 = \log(y)$$

$$y = 0.4592$$

If you can find a slide rule you will notice that the scale on the slide is proportional to \log of the number. By aligning numbers on the slide you can quickly add or subtract the length of each number and thus multiply or divide the numbers. When carefully preform the result can be quite accurate. Later we will look at semi-log graph paper. The y-axis on this paper also has a scale proportional to the \log of the number.

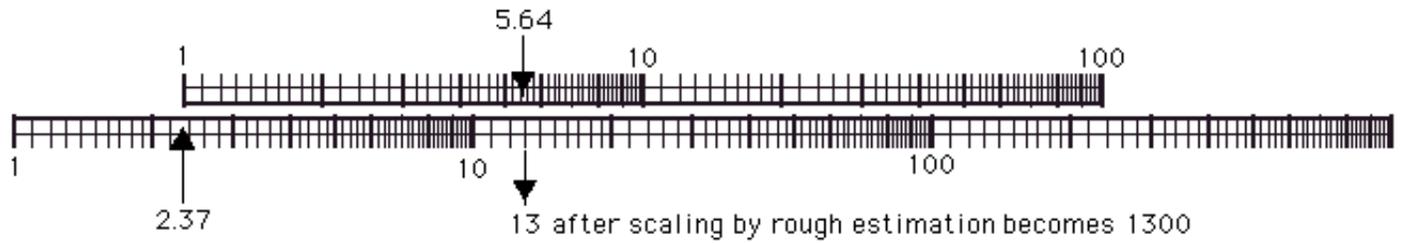


Figure 2.3.1 Illustrates the Similarity of Semi-Log Graph Paper and a Slide Rule

Figure 2.3.1 illustrates the multiplication of 23.7×56.4 using a slide rule to give approximately 1300. The decimal point is determined by rough estimation.

x	$\log_{10}x$	$\ln_e x$
0.5	-0.301	-0.693
1	0.0	0.0
5	0.699	1.609
10	1.0	2.303
50	1.699	3.913
100	2.0	4.605

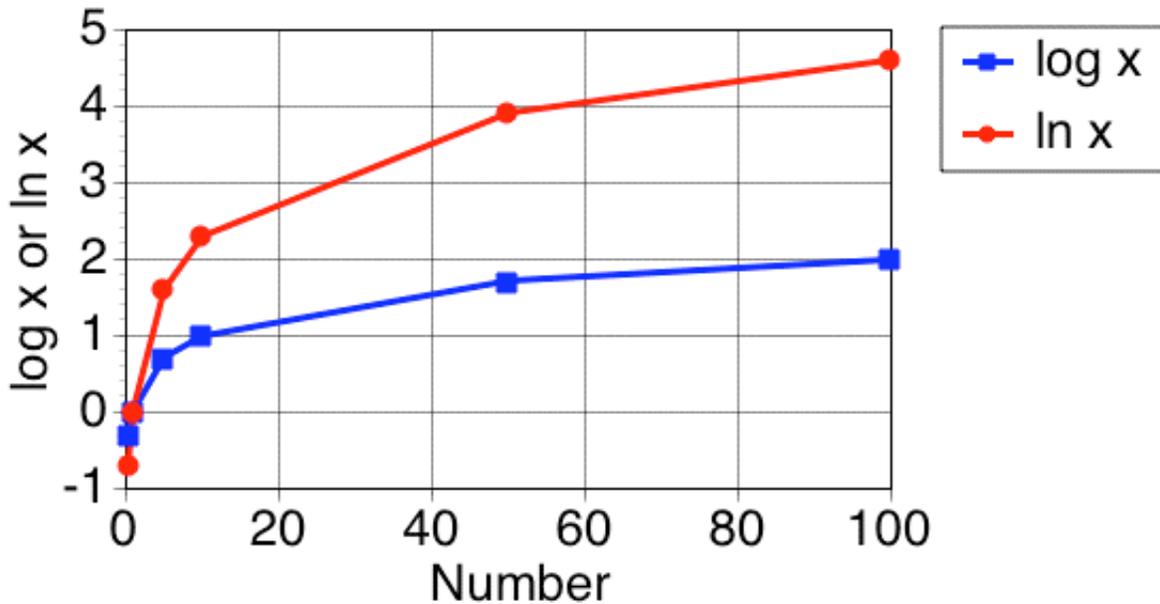


Figure 2.3.2 Plot of $\log x$ or $\ln x$ versus x

[Click on the figure to view the Java Applet window](#)

References

- [Logarithm](#) at Wikipedia
- Search for [Logarithm](#) at Goggle
- Search for [Slide Rule](#) at Goggle

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Graphing Data on Linear and Semi-Log Graph Paper

A very important part of pharmacokinetic analysis is the ability to graph data and interpret the resulting graphs. The graph can provide a useful picture of the data and provide an insight into the underlying mathematical model. Graphs should be drawn carefully. Straight lines should be straight --- use a ruler!!

Pharmacokinetic data involves models with rate processes. The most simple of these would be a single first order decline described with a single exponential term. We may use an equation such as: $C_p = 40 * \exp(-0.23*t)$ to describe drug concentrations after an IV bolus dose. These data are drawn in three graphs on this page. The first figure is a linear (or Cartesian) plot of the data *versus* time. Notice the smooth decline in concentration with time. The second figure is a plot of the natural log (ln) of the concentration values *versus* time. Now we get a straight line graph. You might try 'rearranging' the equation above to verify that a straight line is to be expected. The third graph is on different paper. This is semi-log graph paper. On this graph paper the scale on the y-axis is proportional to the log of the number not the number itself. Notice that the distance from 1 to 2 is the same as the distance from 2 to 4 or from 4 to 8. Again, we have a straight line but without the need to calculate the natural log of each number.

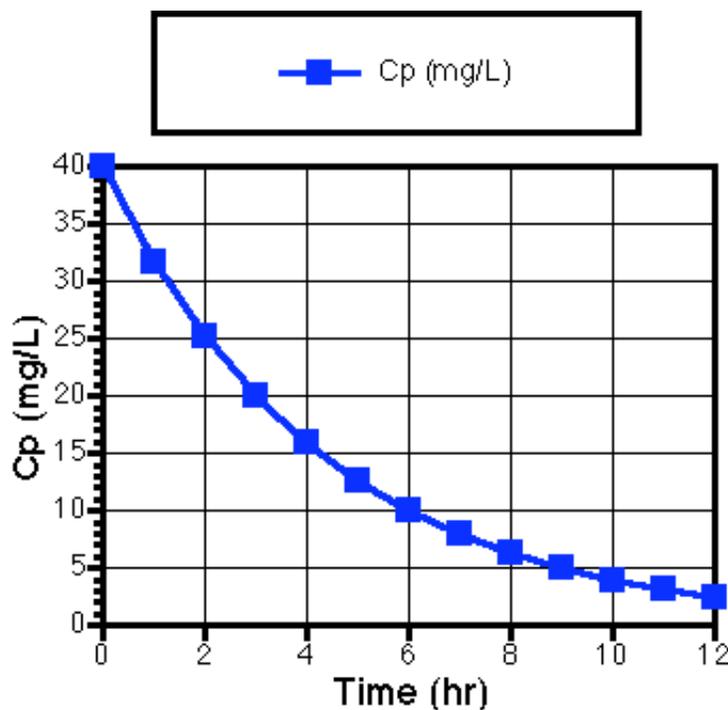


Figure 2.4.1. Linear Plot of Cp *versus* Time

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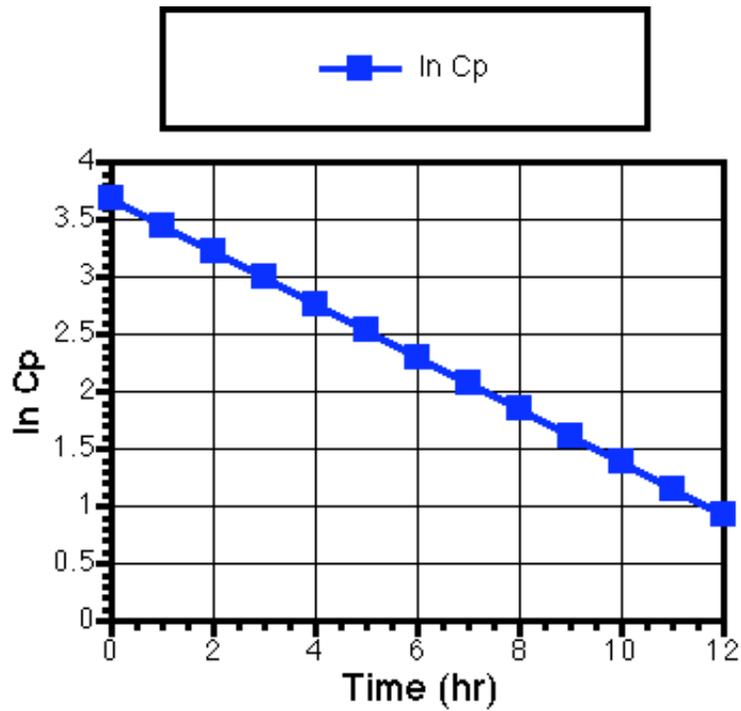


Figure 2.4.2. Linear Plot of $\ln(C_p)$ versus Time

[Click on the figure to view the Java Applet window](#)

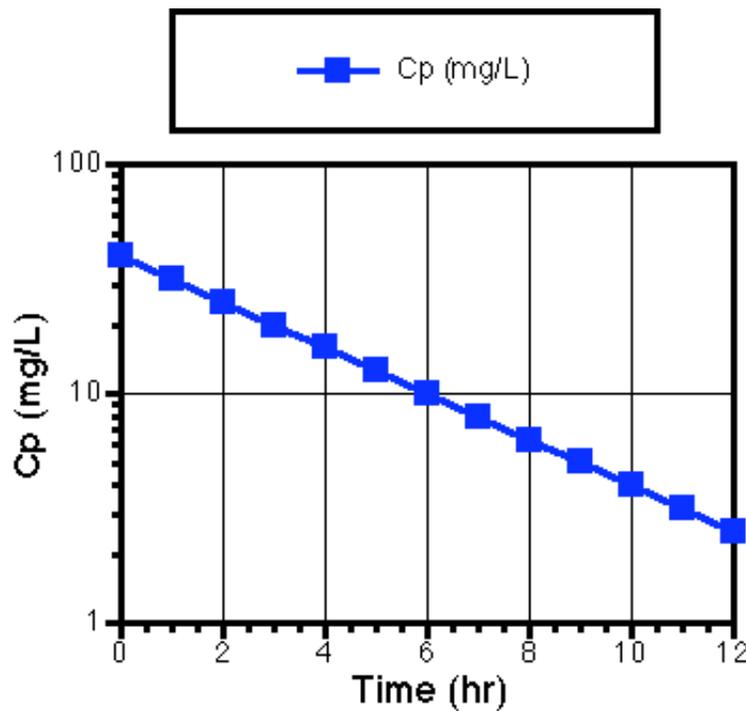


Figure 2.4.3. Semi-log Plot of C_p versus Time

[Click on the figure to view the Java Applet window](#)

For many calculations involving rate constants you will be determining the slope of these lines. The second and third graphs (Figure 2.4.2 and 2.4.3) are a lot easier to use in terms of calculating slopes than Figure 2.4.1, since they each represent a straight line. Later

we will revisit the equation for this line. Remember semi-log graph paper has a normal x- axis scaling but the y- axis scaling is proportional to the log of the number not the number itself. It saves you from taking the log of each number before you plot it. **Note: Once you take the log of a number you loose the units.**

Example use of semi-log graph paper: Plot the data, draw a line "through the data", and calculate the slope of the line.

Table 2.4.1 Example Cp versus Time Data					
Time (hr)	1	2	4	8	12
Cp (mg/L)	20	15	6.8	3.2	1.3

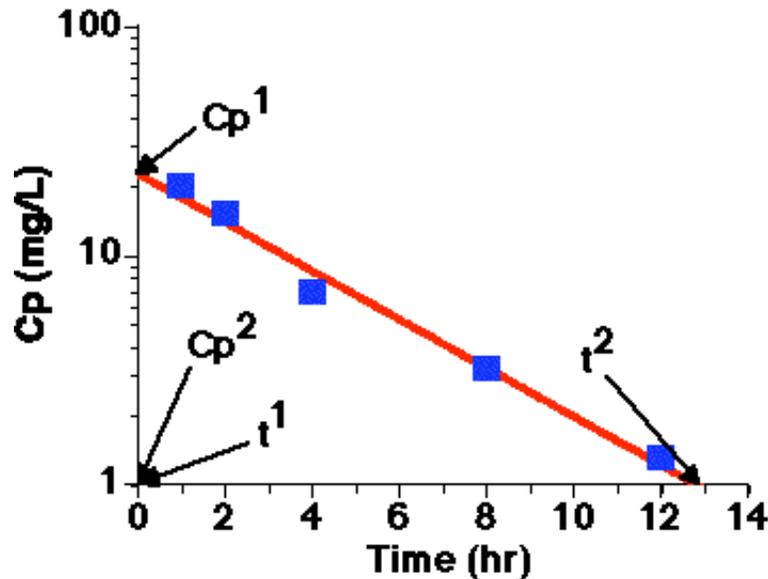


Figure 2.4.4. Semi-log Plot of Cp versus Time

A best-fit line is drawn through the data points and extended to the extremes of the graph paper (for better accuracy). Values for Cp_1 and Cp_2 are read from the y-axis and t_1 and t_2 values are read from the x-axis. These values can be used to estimate a value for the slope of the line and also the rate constant for the drug elimination. From the Y-axis the first point is 0, 22.8 and from the X-axis the second point is 12.8, 1 (in the format x-value, y-value). Always try to use the extremes of the line for the best accuracy.

From Figure 2.4.4	Value
Cp_1	22.8
Cp_2	1.0
t_1	0
t_2	12.8

The slope can be calculated using the equation:

$$\text{Slope} = \frac{\log(y_2) - \log(y_1)}{x_2 - x_1}$$

Equation 2.4.1 Slope of the line on a semi-log plot

This equation uses logarithms with base 10 for the calculation of slope.

Thus the slope of the line in Figure 2.4.4 is: $[\log(1.0) - \log(22.8)]/(12.8 - 0) = (0.000 - 1.358)/12.8 = -0.106 \text{ hr}^{-1}$

In the study of pharmacokinetics first order rate processes and rate constants are common. When the rate constant, k , is calculated from the slope drawn on a semi-log plot, k is found to equal to $-\text{slope} \cdot 2.303$ [Note $\ln(10) = 2.303$]. Thus, the rate constant is calculated as $-\text{slope} \times 2.303$. The calculation of k is easier with calculators (etc.) if you use **ln** (logarithm with base 'e') in the calculation. At the same time you can change the sign by calculating the numerator as $\ln(Cp_1) - \ln(Cp_2)$. Thus k can be calculated using the equation:

$$k = \frac{\ln(Cp_1) - \ln(Cp_2)}{t_2 - t_1}$$

Equation 2.4.2 Equation for estimating First Order Rate Constants

Thus $k = [\ln(22.8) - \ln(1.0)]/(12.8 - 0) = [3.127 - 0.000]/12.8 = 3.127/12.8 = 0.244 \text{ hr}^{-1}$

We can perform this calculation using a different approach. Remember when I was talking about using logarithms to do multiplication and division. We can use that approach to re-arrange Equation 2.4.2. Therefore instead of subtracting the two logarithms we can divide one by the other and take the log of the quotient.

$$k = \frac{\ln(Cp_1/Cp_2)}{t_2 - t_1}$$

Equation 2.4.3 Equation for estimating k

Thus $k = \ln(22.8/1.0)/(12.8 - 0) = \ln(22.8)/12.8 = 3.127/12.8 = 0.244 \text{ hr}^{-1}$

Although I prefer to use the approach in Equation 2.4.2 the advantage of the approach in Equation 2.4.3 is that you don't have to deal with a double negative when Cp_2 is less than one. For example, if Cp_1 and Cp_2 were 12.5 and 0.13 at 0 and 12 hours, respectively.

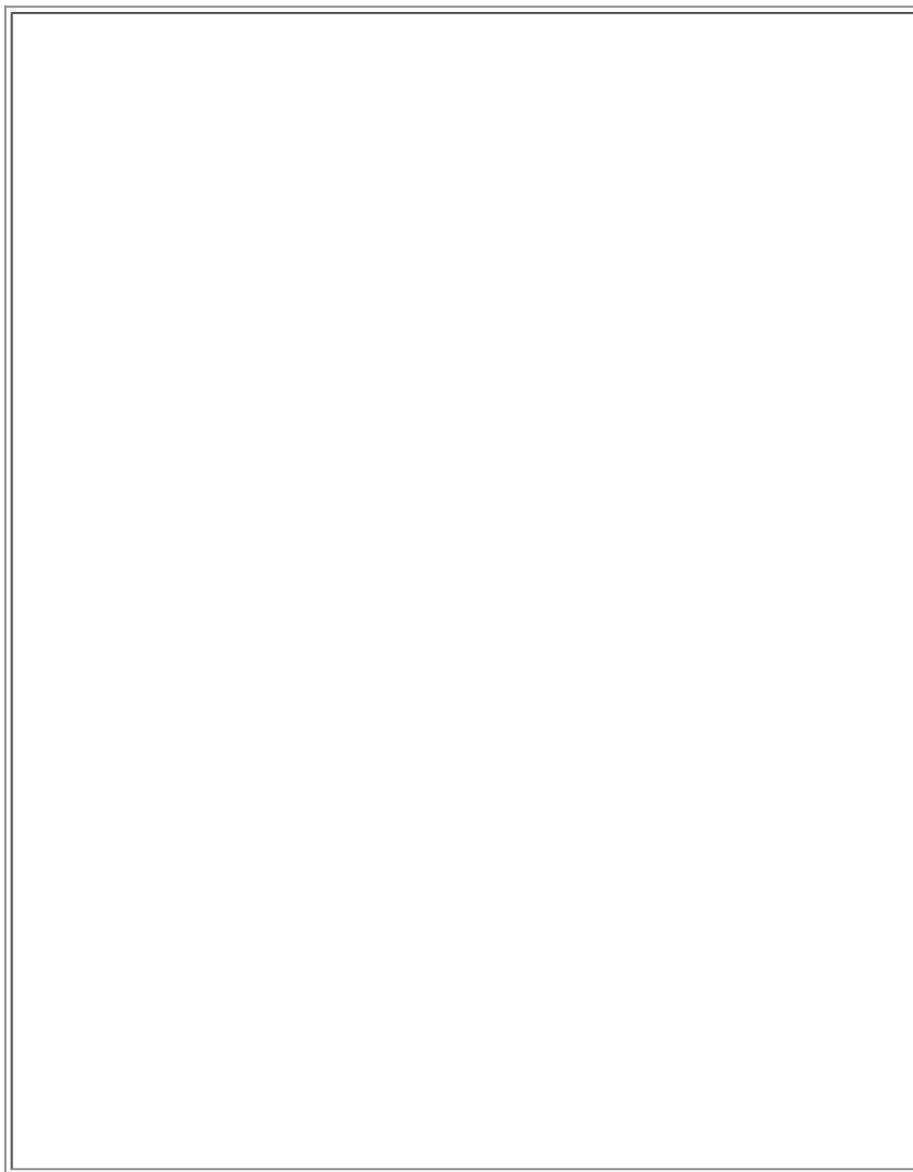
Using Equation 2.4.2 gives $k = [\ln(12.5) - \ln(0.13)]/12 = [2.526 - -2.040]/12 = [2.526 + 2.040]/12 = 4.566/12 = 0.381 \text{ hr}^{-1}$. Using Equation 2.4.3 gives $k = \ln(12.5/0.13)/12 = \ln(96.15)/12 = 4.566/12 = 0.381 \text{ hr}^{-1}$. Note, each approach gives the same answer.

Drawing a best-fit line through the Data

Drawing a line through the data doesn't mean through just two data points but through all the data points. Be especially careful about picking two adjacent data points. Sometimes the first and last point can work but the last point, the lowest concentration data point will probably be inaccurate. The best approach is to put the line through all the data. There should be points above and below the line.



Calculate k_{el} from the best-fit line



Practice and Assignments

Two exercises allowing you to draw straight lines through data on both linear and on semi-log graph paper.

[Linear Graph](#)

[Semi-log Graph](#)

Try them out if you need practice graphing data and calculating intercept and slope in these graphs.

Graph Paper Resources

Graph Paper in [Adobe Reader \(v5.0\)](#) - PDF Format. If you have Adobe Reader installed (or Preview in Mac OS X) clicking on the links below will provide the graph paper indicated.

- [Linear 7 x 9 inches](#)
- [Linear 18 x 22 cm](#)

- [Semi-log One Cycle](#)
- [Semi-log Two Cycle](#)
- [Semi-log Three Cycle](#)
- [Semi-log Four Cycle](#)
- [Semi-log Five Cycle](#)

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Using Spreadsheets

From [Visicalc™](#), to [Lotus 1-2-3™](#), to [Excel™](#), spreadsheets have provided powerful what-if capability to the personal computer user. Using a combination of numbers, labels, and formulas the user is able try out various equations and mathematical scenarios. The results of these calculations can be linked to graphical output in various forms of charts or graphs. The spreadsheet program, Excel™ is available for a number of platforms including the Macintosh™ and Windows™ operating systems.

A new spreadsheet document provides a sheet of cells. The user can enter either numbers, labels, or functions into each cell. Cells are designated by letter and number. For example, Cell 'A1' in the top left corner contains the text 'Chapter II'. Cells A8:A16 contain the numbers 0 through 8. Cell B8 could be completed by entering the formula '=(B\$3/B\$5)*EXP(-B\$4*A8)' which calculates Cp at time = 0.

Cells with formulas can be copied (down for example) and thus values for Cp at other times can be quickly calculated. Notice the use of '\$' to designate absolute cell references. When copied down these references stay the same and refer to the same cell, e.g. B3 = Dose. The reference A8 however is relative and changes for each cell to refer to the relative time in the 'A' column.

Once the formulas are entered changes to parameter values will be quickly reflected by new values in the appropriate cells.

A simple spreadsheet illustrating these and other spreadsheet facilities is illustrated in Figure 2.5.1.

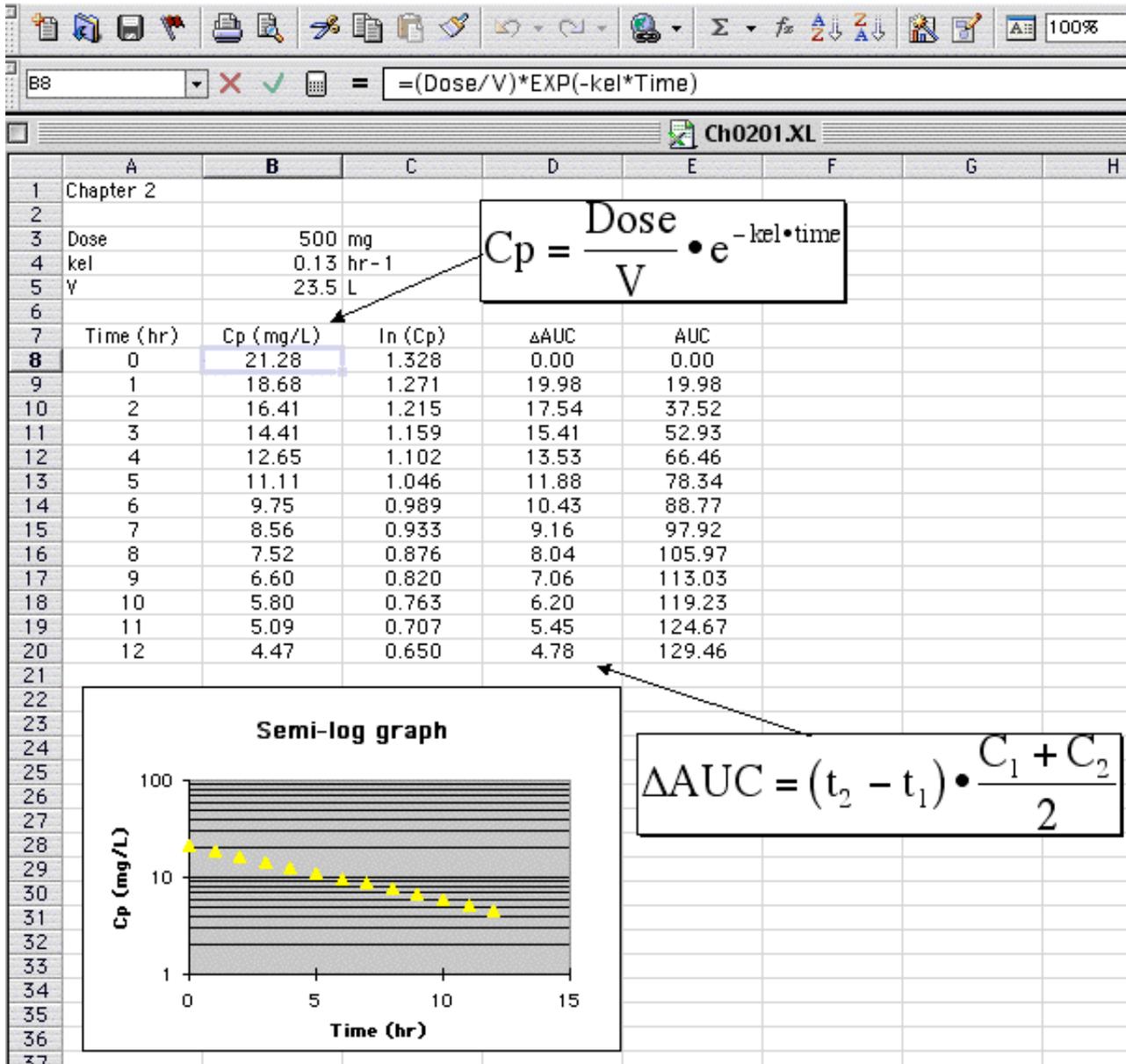


Figure 2.5.1 Example Excel™ Spreadsheet

Click on the figure to download the Excel™ Spreadsheet.
 With your browser set in the Helper section with .xls of type application/vnd.ms-excel this file will open in Excel™ (;-) maybe

If you have a problem downloading this Excel™ file it may help to download the file to your hard drive and open it manually with Excel™. Notice the equation in the formula bar.

Excel™ will be used to illustrate a number of calculations. Each "cell" of the spreadsheet may contain a number or a formula. Changes in the numbers are quickly reflected in calculation cells. Check out the on-line help or User Manuals for more information.

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Calculus

Differential Calculus

Pharmacokinetics is the study of the rate of drug absorption and disposition in the body. Thus differential calculus is an important stepping stone in the development of many of the equations used. These differential equations can be integrated using a variety of techniques including [Laplace transforms](#). However, in this course we won't be doing these integrations.

Differential calculus is involved with the study of rates of processes. The calculus part comes in when we look at these processes in detail, that is, during small time intervals.

We may say that at time zero a patient has a concentration of 25 mg/L of a drug in plasma and at time 24 hours the concentration is 5 mg/L. That may be interesting in its self, but it doesn't give us any idea of the concentration between 0 and 24 hours, or after 24 hours. Using differential calculus we are able to develop equations to look at the process during the small time intervals that make up the total time interval of 0 to 24 hours. Then we can calculate concentrations at any time after the dose is given.

In many cases the rate of elimination of a drug can be described as being dependent on or proportional to the amount of drug remaining to be eliminated. That is, the process obeys first order kinetics. This can be illustrated by Figure 2.6.1.

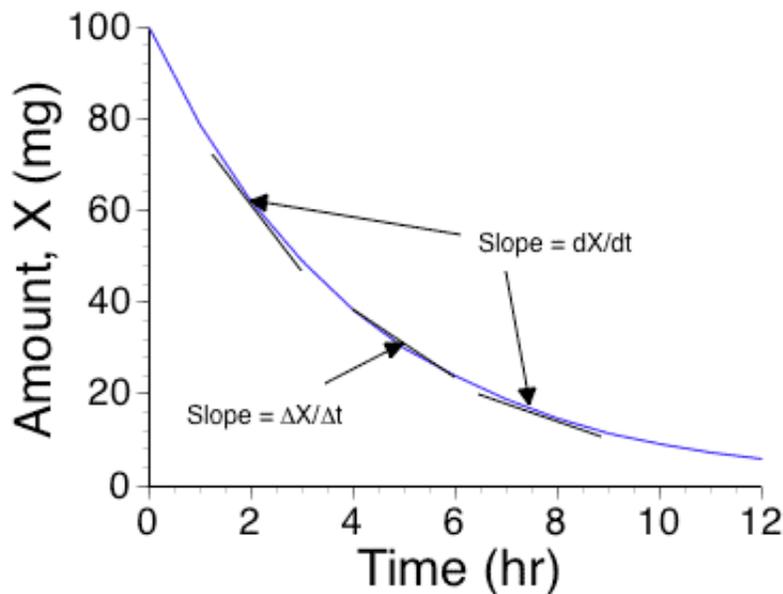


Figure 2.6.1 Linear plot of Amount, X, versus Time

This can be described mathematically using Equation 2.6.1.

$$\frac{dX}{dt} = -k \cdot X$$

Equation 2.6.1. Rate of Change of X with Time

where k is a proportionality constant we call a rate constant and X is the amount remaining to be eliminated. Note the use of the symbol 'd' to represent a very small increment in X or t . Thus dX/dt represents the slope of the line (or rate of change) over a small region of the curved line, see Figure 2.6.1. When data are collected at discrete times such as 4 and 6 hours the larger change in X and t can be represented by $\Delta X/\Delta t$ as shown in Figure 2.6.1. Note the slope changes as the value of X (y-axis) changes.

$$\frac{dX}{dt} = \text{the RATE of elimination}$$

Equation 2.6.2. Rate of Elimination

Integration of Equation 2.6.1 (and other differential equations) provides the integrated equations such as Equation 2.6.3.

$$X = X_0 \cdot e^{-k_{el} \cdot t}$$

Equation 2.6.3. Integrated Equation. X versus Time

Equation 2.6.3 is the resulting integrated equation. We will talk more of these equations during the semester.

What we have done is convert the equation for rate of change of X versus time into an equation for X versus time. A differential equation is converted into an integrated equation. (Compare Equation 2.6.1 and Equation 2.6.3).

We will work with both differential and integrated equations in this course.

Integral Calculus

Differentiation is the reverse of integration. With differentiation breaking a process down to look at the instantaneous process, integration sums up the information from small time intervals to give a total result over a larger time period.

Another example of integration is the calculation of the area under the plasma concentration versus time curve. Later we shall learn that this summation or integration process can be used to evaluate dosage forms, that is it can be used as a measure of dosage form performance.

In the section above we converted from the rate of change equation to an equation for X . We can also go further and get an area under the curve, which is a further integration.

Another example is the progression from distance, to speed (the rate of change of distance), to acceleration (the rate of change of speed).

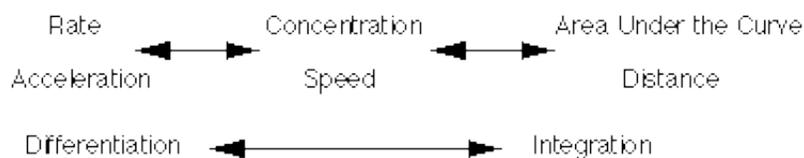


Figure 2.6.1 Relationship between Rate and Integral

References

- [Derivative](#) at Wikipedia
- Search for [Differential calculus](#) at Goggle
- [Integral](#) at Wikipedia
- Search for [Integral calculus](#) at Goggle

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Writing Differential Equations

Rate processes in the field of pharmacokinetics are usually limited to first order, zero order and occasionally Michaelis-Menten kinetics. Linear pharmacokinetic systems consist of first order disposition processes and bolus doses, first order or zero order absorption rate processes. These rate processes can be described mathematically.

First Order Equation
$$\frac{dX_1}{dt} = -k_1 \cdot X_1$$

Each first order rate process ("arrow") is described by a first order rate constant (k_1) and the amount or concentration remaining to be transferred (X_1).

Zero Order Equation
$$\frac{dX_1}{dt} = -k_0$$

Zero order rate processes are described by the rate constant alone. Amount or concentration to the zero power is 1.

Michaelis Menten Equation
$$\frac{dX_1}{dt} = -\frac{V_m \cdot X_1}{K_m + X_1}$$

The Michaelis Menten process is somewhat more complicated with a maximum rate (velocity, V_m) and a Michaelis constant (K_m) and the amount or concentration remaining.

The full differential equation for any component of a pharmacokinetic model can be constructed by adding an equation segment for each arrow in the pharmacokinetic model. The rules for each segment:

1. Direction of the arrow
 - If the arrow goes into the component the equation segment is positive
 - If the arrow leaves the component the equation segment is negative.
2. Type of rate process
 - If the rate process is first order multiply the (first order) rate constant by the amount or concentration of drug in the component at the tail of the arrow.
 - If the process is zero order just enter the rate constant.
 - For a Michaelis Menten processes include the amount or concentration of drug in the component at the tail of the arrow in the Michaelis-Menten equation.

An example

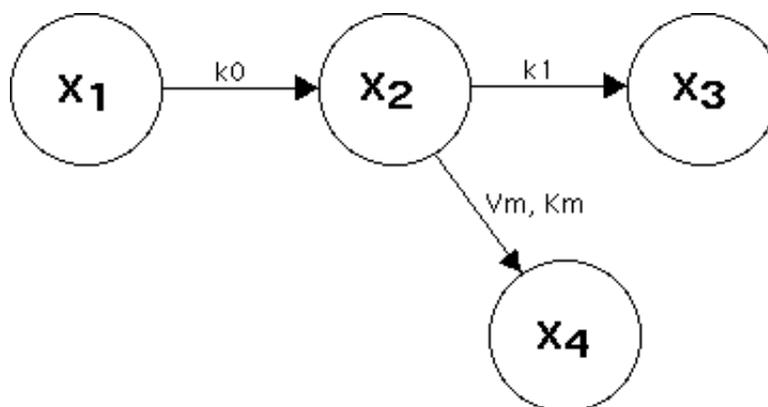


Figure 2.7.1 An example pharmacokinetic model with zero order, first order and Michaelis Menten processes.

In Figure 2.7.1 the rate process from one to two is zero order. The process from two to three is first order and the process from two to four follows Michaelis-Menten kinetics. We can now systematically write the differential equations for each component of the model.

- **Component 1** There is one arrow leading out of component one so the rate process is negative. This process is zero order so we just write the rate constant. The equation for this component is:

$$\frac{dX_1}{dt} = -k_0$$

- **Component 2** This component is more of a challenge. There are three arrows connected with this component. One arrow leads to the compartment so this equation segment is positive. The other two arrows lead away from the component and these equation segments are negative. Starting with the zero order process provides a positive k_0 to the differential equation. The first order process is developed as the rate constant multiplied by the amount remaining in component 2. This is negative and is $-k_1 \times X_2$. The final segment is the Michaelis Menten process from component 2 to component 4. This is also negative and is described as $-V_m \times X_2 / (K_m + X_2)$. The total differential equation for this component is:

$$\frac{dX_2}{dt} = k_0 - k_1 \cdot X_2 - \frac{V_m \cdot X_2}{K_m + X_2}$$

- **Component 3** OK; downhill from here. Now we have one arrow going to this component from component 2, thus the equation segment is positive. The rate process is first order so we multiply the rate constant by the amount remaining in the component at the tail of the arrow, component 2. The equation is:

$$\frac{dX_3}{dt} = k_1 \cdot X_2$$

- **Component 4** The fourth component is also described with one equation segment. The arrow leads to this component so the segment is positive. The rate process is a Michaelis Menten process. The equation for this component is:

$$\frac{dX_4}{dt} = \frac{V_m \cdot X_2}{K_m + X_2}$$

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PHAR 7632 Chapter 2

Background Mathematical Material

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Area under the plasma concentration time curve (AUC)

The area under the plasma (serum, or blood) concentration *versus* time curve (AUC) has an number of important uses in toxicology, biopharmaceutics and pharmacokinetics.

Toxicology AUC can be used as a measure of drug exposure. It is derived from drug concentration and time so it gives a measure how much - how long a drug stays in a body. A long, low concentration exposure may be as important as shorter but higher concentration. Haber's law propose exposure $k = C \times t$ (Fritz Haber, 1868-1934) where k is essentially AUC. Some drugs are dosed using AUC to quantitate the maximum tolerated exposure (AUC Dosing). The efficacy of some antibiotics are related to AUC/MIC, thus maintaining a concentration above a minimum inhibitory concentration (MIC) is more important than peak concentrations.

Biopharmaceutics The AUC measured after administration of a drug product is an important parameter in the comparison of drug products. Studies can be performed whereby different drug products may be given to a panel of subject on separate equations. These [bioequivalency or bioavailability studies](#) can be analyzed by comparing AUC values.

Pharmacokinetics Drug AUC values can be used to determine other pharmacokinetic parameters, such as clearance or bioavailability, F . Similar techniques can be used to calculate area under the [first moment curve \(AUMC\) and thus mean resident times \(MRT\)](#).

Calculation of AUC using the Trapezoidal Rule

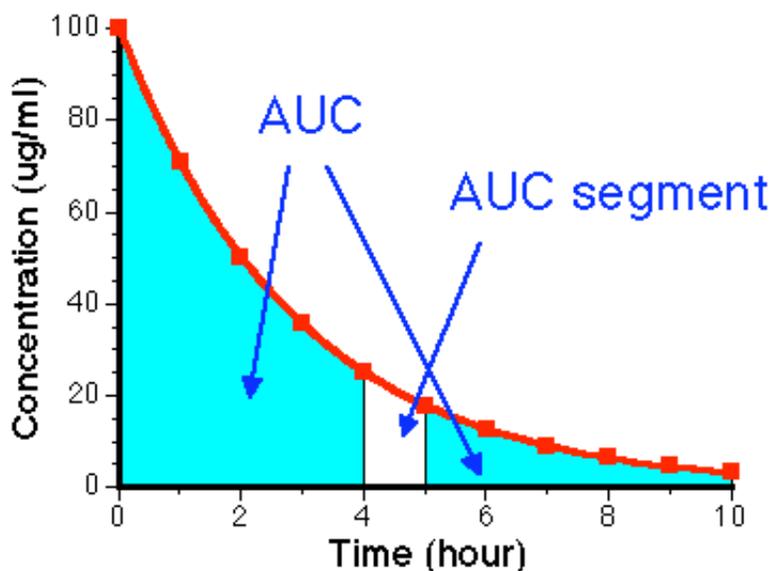


Figure 2.8.1. Linear Plot of C_p *versus* Time showing AUC and AUC segment

The area under the plasma concentration time curve (AUC) is very useful for calculating the relative efficiency of different drug products (We'll talk about this later, see [Chapter 9](#)). It can used to calculate the total body clearance (CL) and the apparent volume of distribution.

If we have a smooth line for concentration *versus* time or an equation for C_p *versus* time from a pharmacokinetic model we could slice the area into vertical segments. Each segment would be very thin, Δt and in extreme dt , in width (much smaller than the segment in Fig 2.8.1). The total AUC is calculated by adding these segments together. In calculus this would be the integral. Each very narrow segment has an area = $C_p \cdot dt$. Thus the total area (AUC) is given by Equation 2.8.1:

$$AUC = \int_{t=0}^{t=\infty} C_{p_t} \cdot dt$$

Equation 2.8.1. Total AUC calculated from Very Narrow Segment

Moving ahead a little to Chapter 4 the integrated equation for plasma concentration as a function of time is:

$$C_{p_t} = C_{p_0} \cdot e^{-kel \cdot t} = \frac{Dose}{V} \cdot e^{-kel \cdot t}$$

Equation 2.8.2. C_p *versus* Time after an IV Bolus dose

This is essentially the same as the integrated equation we demonstrated for amount of drug remaining (which can be derived using Laplace transforms). The difference here is the use of V , apparent volume of distribution, to convert amount into concentration. We can substitute this equation for C_{p_t} into Equation 2.8.1 to derive an analytical equation for AUC:

$$AUC = \int_{t=0}^{t=\infty} \frac{Dose}{V} \cdot e^{-kel \cdot t} \cdot dt = \frac{Dose}{V} \cdot \int_{t=0}^{t=\infty} e^{-kel \cdot t} \cdot dt$$

Equation 2.8.3. AUC calculated as the integral of C_p *versus* time

From Math Tables we would find that:

$$\int_{t=t_1}^{t=t_2} e^{-a \cdot t} \cdot dt = \left[\frac{e^{-a \cdot t}}{-a} \right]_{t=t_1}^{t=t_2} = \frac{e^{-a \cdot t_2}}{-a} - \frac{e^{-a \cdot t_1}}{-a}$$

With $a = kel$ (in Equation 2.8.3), $t_1 = 0$, and $t_2 = \infty$,

At $t = 0$, $e^{-kel \cdot t} = 1$ and at $t = \infty$, $e^{-kel \cdot t} = 0$

Therefore:

$$AUC_{0-\infty} = \frac{Dose}{V} \cdot \left[\frac{e^{-kel \cdot \infty}}{-kel} - \frac{e^{-kel \cdot 0}}{-kel} \right] = \frac{Dose}{V} \cdot \left[0 - \frac{1}{-kel} \right]$$

or

$$AUC_{0-\infty} = \frac{Dose}{V \cdot kel} = \frac{C_{p_0}}{kel}$$

Equation 2.8.4. AUC Calculated from Concentration and kel

This is analytical integration (exact solution, given exact values for V and kel)

Note: For $t = 0$ to ∞ , $AUC = C_{p0}/k_{el}$. With $t = t$ to ∞ , AUC is calculated as C_{p_t}/k_{el} . We will use this result further down on this page

That is:

$$AUC_{t-\infty} = \frac{\text{Dose}}{V} \cdot \left[\frac{e^{-k_{el} \cdot \infty}}{-k_{el}} - \frac{e^{-k_{el} \cdot t}}{-k_{el}} \right] = \frac{\text{Dose}}{V} \cdot \left[0 - \frac{e^{-k_{el} \cdot t}}{-k_{el}} \right]$$

or

$$AUC_{t-\infty} = \frac{\text{Dose} \cdot e^{-k_{el} \cdot t}}{V \cdot k_{el}} = \frac{C_{p_t}}{k_{el}}$$

Rearranging Equation 2.8.4 to solve for V gives:

$$V = \text{Dose}/(\text{AUC} \cdot k_{el})$$

Equation 2.8.5. Volume of Distribution Calculated from Dose, AUC and kel

We could use Equation 2.8.4 to calculate the AUC value if we knew DOSE, kel, and V but usually we don't do this. We can calculate AUC directly from the C_p versus time data. We need to use a different approach. The simplest, most common approach is a numerical approximation method called the **trapezoidal rule**.

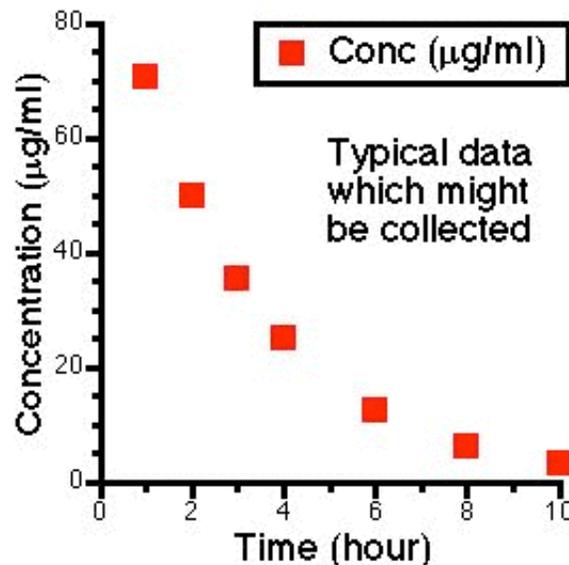


Figure 2.8.2. Linear Plot of C_p versus Time showing Typical Data Points

We can calculate the AUC of each segment if we consider the segments to be trapezoids. [Four sided figure with two parallel sides].

The area of each segment can be calculated by multiplying the average concentration by the segment width. For the segment from C_{p_2} to C_{p_3} :

$$\text{For example: } AUC_{2-3} = \frac{C_{p_2} + C_{p_3}}{2} \cdot (t_3 - t_2)$$

This segment is illustrated in Fig 2.8.3 below.

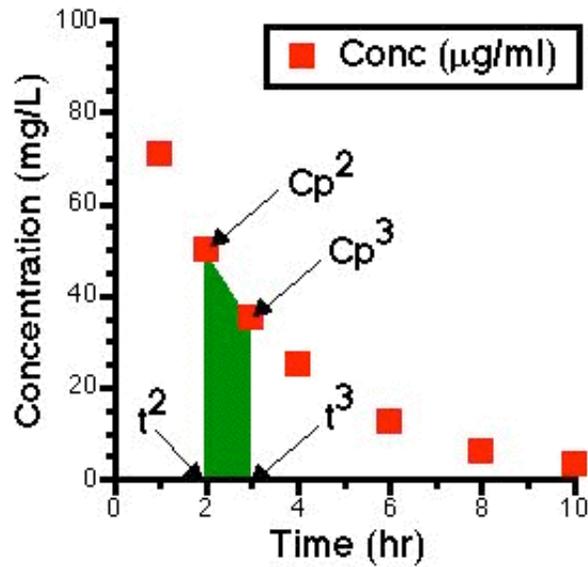


Figure 2.8.3. Linear Plot of C_p versus Time showing One Trapezoid

The area from the first to last data point can then be calculated by adding the areas together.

$$AUC_{1-n} = \sum \left\{ \frac{C_{p1} + C_{p2}}{2} \cdot (t_2 - t_1) \right\} + \left\{ \frac{C_{p2} + C_{p3}}{2} \cdot (t_3 - t_2) \right\} + \dots$$

Equation 2.8.6 AUC from C_p 1 to C_p n

Note: Summation of data point information (non-calculus)

This gives:

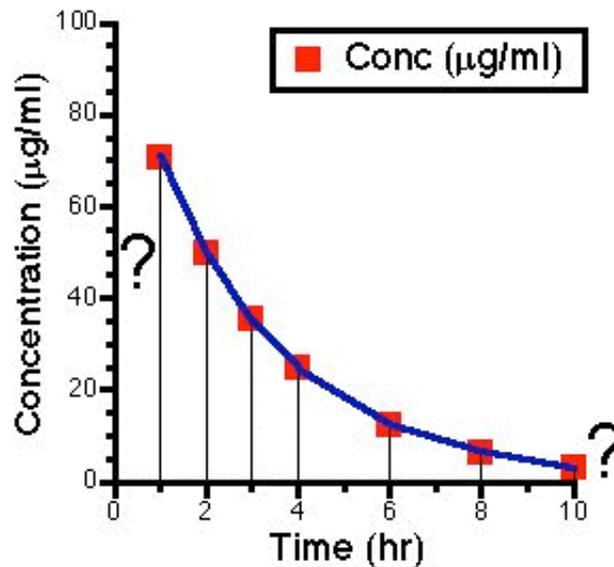


Figure 2.8.4. Linear plot of Cp versus time showing areas from data 1 to data n

To finish this calculation we have two more areas to consider. The first and the last segments.

After a rapid IV bolus, the first segment can be calculated after determining the zero plasma concentration Cp^0 by extrapolation.

Thus

$$AUC_{0-1} = \left\{ \frac{Cp_0 + Cp_1}{2} \cdot (t_1) \right\}$$

Equation 2.8.7 AUC from Cp 0 to Cp 1

If we assume that the last data points follow a single exponential decline (a straight line on semi-log graph paper) the final segment can be calculated from the equation above from t_{last} to infinity:

$$AUC_{t_{last} - \infty} = \int_{t=t_{last}}^{t=\infty} Cp \cdot dt = \frac{Cp_{last}}{kel}$$

Equation 2.8.8 AUC from t_{last} to infinity

Thus the total AUC can be calculated as:

$$\begin{aligned} AUC_{0-\infty} &= AUC_{0-1} + AUC_{1-last} + AUC_{last-\infty} \\ &= \frac{Cp_0 + Cp_1}{2} \cdot t_1 + \frac{Cp_1 + Cp_2}{2} \cdot (t_2 - t_1) \\ &\quad + \frac{Cp_2 + Cp_3}{2} \cdot (t_3 - t_2) + \dots + \frac{Cp_{last}}{kel} \end{aligned}$$

Equation 2.8.9 Total AUC from time zero to infinity

Time (hr)	Concentration (mg/L)	Δ AUC	AUC (mg.hr/L)
0	100*		
1	71	85.5	85.5
2	50	60.5	146.0
3	35	42.5	188.5
4	25	30.0	218.5
6	12	37.0	255.5
8	6.2	18.2	273.7
10	3.1	9.3	283.0
Total		8.9**	291.9

* Extrapolated value ** Calculated as Cp_{last}/kel

Other methods have been described by Yeh and Kwan (Yeh, K.C. and Kwan, K.C. 1978 "A comparison of numerical integrating algorithms by trapezoidal Lagrange and spline approximation", *J. Pharmacokin. Biopharm.*, **6**, 79-98) and Purves (Purves, R.D. 1992 "Optimum numerical integration methods for estimation of area under the curve (AUC) and area under the moment curve (AUMC)", *J. Pharmacokin. Biopharm.*, **20**, 211-226).

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References

- AUC has been discussed on [the PharmPK listserv](#)

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