PHARMACOLOGY MODELS

Introduction

Pharmacology models fall into two categories:

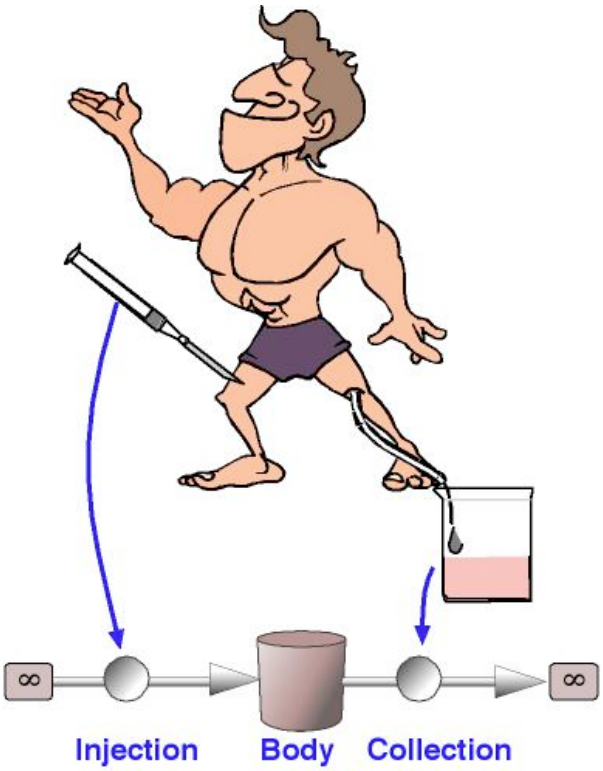
- ***Pharmacokinetic*** models predict the time dependence of a drug's concentration in the body fluids following it's administration.
- ***Pharmacodynamic*** models deal with the action of the drug once it reaches its target organ.

Although a complete model would incorporate both parts, each type is independently useful for different purposes.

In this first exercise we shall study a simple one compartment (one reservoir) pharmacokinetic model. This will suffice to introduce the general concepts of:

- steady state
- exponential response
- relaxation times
- the principle of superposition in linear systems,

as well as a number of Madonna features. Details of the model will depend on the specific drug. We begin with the simplest case, infusion of the biologically inert substance, inulin.



One Compartment Pharmacokinetics

Biological Background

Inulin is an inert polysaccharide that is infused into animals or humans to estimate the volume of extracellular fluids as well as the renal glomerular filtration rate (GFR). The GFR, a fundamental parameter for investigation and evaluation of kidney function is calculated from measurements of urinary flow and urinary and plasma concentrations. But, this calculation assumes that the plasma concentration of inulin remains constant during the time required to sample urinary flow rates and concentrations. This exercise estimates the time required for development of a steady state during an inulin infusion experiment. The model computes the level of inulin concentration in the plasma at any time in terms of the rates of infusion and excretion. It enables us to study and evaluate protocols for making these measurements.

Procedure

MODEL THE ACCUMULATION OF INULIN IN THE BODY FLUIDS

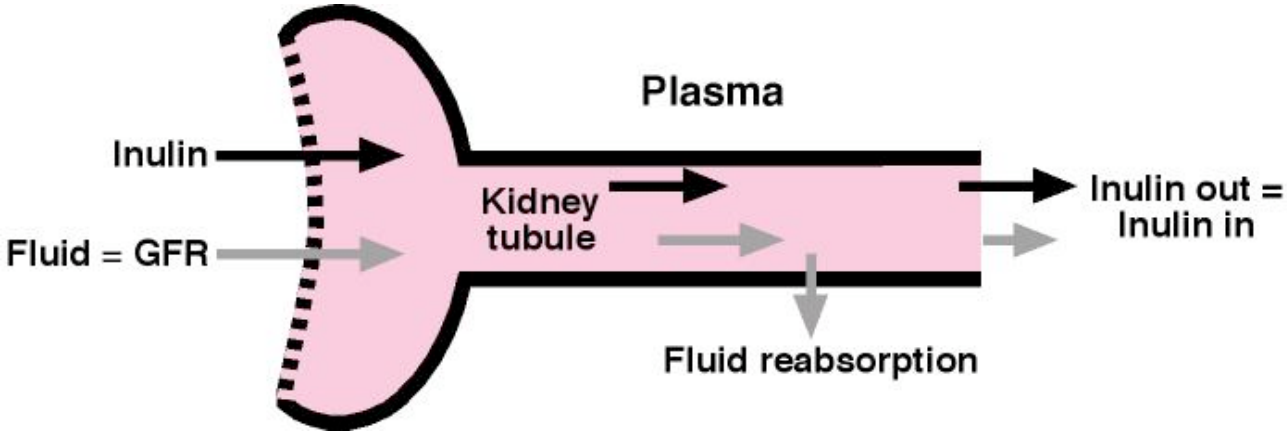
Let a single reservoir represent the *mass* (mg) of inulin in the body. We will assume that this mass is uniformly dissolved in the extracellular fluid which occupies approximately 20% of the body weight.

Inulin enters by an experimental infusion at a constant rate of 10 mg/min = 600mg/hr.

It leaves by an especially simple type of excretion. Unlike most other solutes and water, it is not recognized by the cells of the kidney so that the amount excreted equals the amount that filters into the kidney (see figure below). In other words, for inulin,

Excretion rate (mg/min.) = Entry rate by filtration

= ***Glomerular Filtration Rate*** (ml/min.) x *Concentration* (mg/ml).



We can approximate the *concentration* of inulin within the body fluids by dividing the mass by the extracellular *volume* (20% body weight = 0.20 x 70 kg) = 14 kg (14 L). (In practice, inulin concentration is obtained by chemical determination from the blood plasma.)

Construct a 1-compartment model using a reservoir for the total mass (mg) of inulin in the extracellular fluid. Use converters for (i) extracellular volume, (ii) concentration in the extracellular fluid (= concentration in plasma), and (iii) GFR = 120 ml/min = 7.2 L/hr. Run the model using time units in hours and volume units in liters. Answer the following questions:

1. What is the steady state value for plasma inulin concentration? (Plot concentration rather than mg inulin). How does this value change when the infusion rate doubles?
2. How long does it take the concentration of inulin to reach 50%, 63%, and 95% of its steady-state value? .

Simulate the time course of plasma inulin after the infusion is stopped. To do this it would be convenient to have a switch that would switch the infusion on and off at your discretion. This can be accomplished by using the Madonna function, **SQUAREPULSE(t, d);** this function provides a pulse of height 1 starting at time t with duration d. To implement the switch simply multiply your infusion rate by it. For example if you want an infusion of 600 mg/hr to turn on 6 min after the beginning of the experiment and to turn off 10 hr later, you would write

SQUAREPULSE(0.1, 10)*600

In the flow dialog.

How long does it take the concentration of inulin to decay to 50%, 37%, and 5% of its initial value? Compare the values with 2 above. How do these values change if you double the rate of infusion? Read these values from the graph and compare them to the theoretical expressions given in the Appendix.

Verify your solution: Compare the computer's numerical results with a theoretical exponential decay of inulin concentration shown in the **Appendix** to be

$$C_t = C_0 \exp((-g/v)\text{time})$$

Where:

C_t = inulin concentration at time t (hr.), g = glomerular filtration rate (ml/hr.)

v = extracellular volume [L], and

C_0 = the concentration at the time that the infusion was turned off. You can get this number from your graph (use the button), or you can assume that the system has reached a steady state and calculate it from the steady state condition (infusion rate = excretion rate = gC_0 so that $C_o = 600/7.2 = 83.3$ mg/L.

You can plot the theoretical curve by defining a Madonna Formula (C_t) with the exponential decay equation (use TIME for "t" and EXP(·) for the exponential)

To see the correspondence between the two curves, it would be helpful to superimpose them. In your current graph the model curve is too complex; it contains the acquisition of inulin (during the first 10.1 hours) as well as the decay that follows after the infusion is stopped. To eliminate the acquisition portion, set the infusion rate = 0 and the initial value of the total mass (i.e. in the reservoir) $= C_o v = 83.3 \times 14 = 1166$ mg.

3. Verify that a plot of the log of concentrations during this exponential decline yields a straight line. You can do this by changing the scales of the Y (conc) axis from linear to logarithmic: Double click on the Y axis. Choose the *Scales* tab and check the *Log* box for the *Left Y Axis*. The graph should change into a straight line. This is a common test for an exponential process. (A similar test can be applied to the acquisition curve, but it requires a few more manipulations of the data—see the **Appendix**.)

4. Verify that a correct Time Constant can be obtained by taking the (negative) reciprocal of the slope of the line.

5. Since our model is *linear*, the response to *any* input (infusion) function can be used to predict the response to any other input. We illustrate this with an example by showing that:

IF input (infusion) S1 results in output (response) R1

AND input (infusion) S2 results in output (response) R2

THEN an input (S1+S2) will result in output (R1+R2)

Thus, if you double the input to a linear system the output doubles. Once you know one response you know all responses!

6. Is the constant infusion method a practical procedure? Can you improve on it? How about a booster shot at the beginning? To simulate a "shot" use the **PULSE** function.. This built-in function will deliver pulses at desired intervals. The format for **PULSE** is:

PULSE (volume, first pulse, interval)

where

volume = size of the pulse (mg inulin/booster shot)

first pulse = time of first pulse (0 or 1 hr)

interval = the time between pulses (to give only 1 shot use a time interval > the length of the simulation).

IMPROVING THE MODEL

1. List several ways in which your model is deficient. Can you think of ways to improve it?
2. Construct a two compartment model: Plasma and Interstitial Space

   In the original model we assumed instantaneous distribution of inulin throughout the entire extracellular volume (plasma compartment + interstitial space). Actually, substances are infused into the plasma and then diffuse across the capillary membrane into the interstitial space. The inulin will equilibrate at a rate that is proportional to the concentration gradient between these two compartments (plasma and interstitial space). The rate of exchange (mg/min.) is given by

   $$\textit{Flow across membrane} = k(C_p - C_i) \qquad (1)$$

   where k is a transfer constant and C_p and C_i are plasma and interstitial concentrations, respectively.
3. Continue the inulin infusion problem, but now simulate a simple sudden injection of inulin into the plasma. Assume that the inulin distributes instantly in the entire plasma compartment (volume = 3000 ml) and then leaks into the other extracellular compartment (interstitial spaces, volume = 11,000 ml).
4. Try 3 different runs with **k** = 10, 70, and 500 ml/min. Plot the concentrations in both compartments on the same graph. Select **Batch Runs** from the pull down menu. Choose k as the variable of interest and then specify the maximum and minimum values. Click the **Geometric Series** button and then **OK**.
5. Try using **Define Sliders** from the pull down menu to manipulate k. This will let you investigate the results of changing a variable instantaneously. Ask for help.

Dosage regimens

Biological Background

Unlike inulin, drugs are not inert. They are absorbed on plasma proteins, dissolve in fatty tissue, they are metabolized, and they have biological effects- some desirable, some not. A common problem is to determine a dosage regimen that will produce extracellular fluid concentrations that are sufficiently high to produce the desired effect, but low enough to avoid toxic reactions. These complications are taken into account by the following general definitions which are used extensively in the pharmacology literature:

1. Volume of distribution, ***Vd***, is an empirical volume defined by

$$Vd = \textit{amount of drug in body}/\ Cp \qquad (2)$$

Where Cp is the plasma concentration. It is used to compute how much drug must be added to the body to obtain a given Cp (neglecting drug dissipation by metabolism, excretion etc.) Vd accounts for drug bound to proteins and other structures, and for the fact that the drug may not be evenly dispersed throughout the body. Its units are volume units (e.g. liters)

2. Clearance, CL, is also an empirical constant. It relates the concentration to the rate of elimination from the body. By definition

$$CL = \textit{the rate of elimination}/Cp \qquad (3)$$

Clearance accounts for elimination due to metabolism as well as excretion. It's unis are volume/time (e.g. liters/hour). In the case of inulin the only route for elimination is through glomerular filtration; i.e.

$$\textit{the rate of elimination of inulin} = GFR*Cp \quad (4)$$

Substituting this rate into (2) shows that for inulin GFR = CL_{inulin} . (In practice the rae of elimination is easily measured by the rate of appearance of inulin in the urine,)

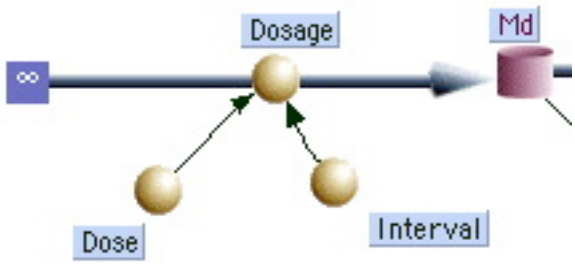
These two items, Vd and CL, are very useful because their values for virtually any common drug are listed in tables found in both textbooks and handbooks of Pharmacology.

We illustrate these considerations in the following example of the pharmacokinetics of theophylline. Theophylline. a common ingredient in tea, is a bronchodilator. It is used clinically to dilate the air passages and relieve the symptoms of chronic asthma. It is effective at plasma concentrations of 10 -20 mg/L . Concentrations beyond 20 mg are considered toxic. Our problem is to develop a dose schedule that will maintain a steady concentration within the effective range and will not spill over beyond the toxic limits.

Procedure

The theophylline clearance , CL, = 2.88 L/hr , while its volume of distribution, Vd, = 35 L.[1] Use this data to change your inulin model to a model for theophylline.

Begin by opening the inulin model and saving it with a new title. Change the labels so that GFR is replaced by CL, and extracellular volume is replaced by Vd, and infusion by Dosage. Include converters for the magnitude of the dose and the interval between doses.



Use Dosage = PULSE(Dose, Interval) in the dialog.

You now have a generic one compartment model that will apply to thousands of drugs whose parameters are tabulated in standard references.

Assume the theophyline is administered by repeated injections. Use the Pulse function to simulate different practical regimens i.e. 1, 2, 3,and 4 times per day. Set the Interval and vary the Dose (using *Slider* or *Batch Runs*) .

Two Compartments

Most drugs, including theophylline, are not injected directly into the veins. They are given orally; passing first into the GI tract and then into then into the circulation. To simulate oral administration, add an additional compartment, labeled GI, between the Dosage inflow and the Md (mass of drug) compartment. You will also need a new flow representing absorption (labeled Abs) between the Md and GI compartments. Set

$$Abs = k_{abs}*GI \quad (5)$$

where k_{abs} is an absorption coefficient. Set k_{abs} = 1 and run the model. Experiments with theophylline show that its plasma concentration reaches a peak value in about 2 hours following oral ingestion. Use a slider to adjust the value of k_{abs} so that the peak value in the model will appear at an appropriate time. Again, find the best dose to use at different dosage regimens (1, 2, 3,and 4 times per day).

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[1] Katzung, B. G. (1998). *Basic and Clinical Pharmacology* Appleton & Lange, Stamford CT USA.

Pharmacodynamics

Receptors

Drugs and hormones, C, bind to receptors; but there are only a limited number of receptors.

Assume that the biological effect E is proportional to the number of occupied receptors, and that the Drug and receptors are in quasi equilibrium. Then

$$E = Emax*C / (C50 + C) \quad (6)$$

where Emax is the maximal effect and C50 is the dissociation constant the drug receptor action

1. Plot families of curves of E as a function of C with Emax = 100 and C50 as the variable parameter. Verify that C50 is the concentration where E = Emax/2. Pharmacologists like to view these curves on a semi-log plot (log C). Select *Axis Settings* under the *Graph* menu to obtain a dialog with a check box that will implement a log scale on the x-axis. Try it - you now have a Dose-Response curve as usually presented in the literature.
2. Plot families of curves of E as a function of C with C50 = 5 and Emax as the variable parameter. Verify that Emax is the maximum value

Bacterial Populations

Using N to represent the number of bacteria, use the following data to model its population:

- Initial number of bacteria = 100,000 = 1E5
- Rate of bacterial production = 1.6*N/hr
- Rate of bacterial death = kd*N/hr
- kd = 5E-5
- Run the model over a 24 hour period.

Effect of an Antibiotic on the Population

Assume that the antibiotic acts by killing the bacteria (rather than inhibiting its production), and that the "effect" E as given by equation 4 represents the kill rate per bacterium. Then the antibiotic kill rate for the whole colony will be E*N. Use the following data to simulate the response of the population:

Emax = 2 /hr C50 = 3 mg/L C= 0 to 20 mg/L

Try using a log plot on the y axis.

Combining Pharmacokinetic and Pharmacodynamic Models

Use the following data to change your pharmacokinetic theophylline model to an appropriate model for *amoxicillin* (a *penicillin*):

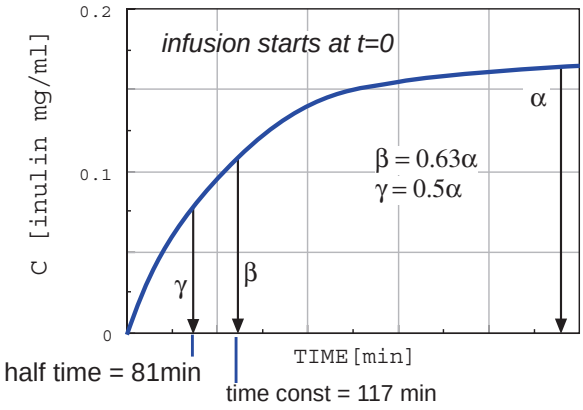
Vd = 15 L

CL = 10.8

Now hook this model up to the previous one (*Effect of an Antibiotic on the Population*) to simulate dosage regimens in vivo. They are coupled through C. The pharmacokinetic model computes the time dependence of C that is fed into the pharmacodynamic model. Begin with oral doses of say 200 mg and find regimens that will work.

This all assumes that there is no spontaneous recovery from the infection. A further elaboration on the model would be to develop a primitive model of the immune response and incorporate it into the model. This would allow the introduction of mutant bacterial populations.

Appendix:
The Exponential Response



Infusion starts

The mathematical solution to the inulin infusion problem is

$$c_t = \frac{in}{g}\left(1 - e^{\frac{-g}{v}t}\right) \qquad (1)$$

where

1. c_t = inulin concentration at time t (min.)
2. in = infusion rate (mg/min.)
3. g = glomerular filtration rate
4. (ml/min.)
5. v = extracellular vol.

Steady state

When $t = 0$, the exponential term approaches 1 and c_t is zero.

As t ----> ∞, the exponential term goes to zero so that c_t approaches a steady state value

$$c_t = \frac{in}{g}$$

We can verify this by noting that a steady state (i.e. one where c_t is constant) will only occur when *inflow = outflow*

$$in = gc\tau.$$

Time constant

In most problems dealing with exponential functions of time, it is a great convenience to introduce a new constant called the *time constant*, denoted by *t*, which allows us to write the exponential in the form

$$e^{-\frac{t}{\tau}}.$$

In our problem, we let

$$\tau = \frac{v}{g} \qquad (2)$$

and rewrite (1) as

$$c_t = \frac{in}{g}\left(1 - e^{\frac{-t}{\tau}}\right) \qquad (3)$$

When $t = \tau$,

$$c_t = \frac{in}{g}(1 - e^{-1}) = \frac{in}{g}(1 - .37)$$
$$= 0.63\frac{in}{g}$$

When $t = 3\tau$,

$$c_t = \frac{in}{g}(1 - e^{-3}) = \frac{in}{g}(1 - .05)$$
$$= 0.95\frac{in}{g}$$

and the system has gone 95% of the way to its final destination.

In the appendix it is shown that the time constant is equal to the mean residence time (in this case the average time an inulin molecule spends in the body.)

Half time

To solve for the half time, $\tau_{1/2}$, (i.e. the time for the system to go 50% of the way to its final destination), set

$$t = t_{1/2} \qquad \text{and} \qquad c_t = \frac{1}{2}\frac{in}{g}$$

and use Eq. (3) to arrive at

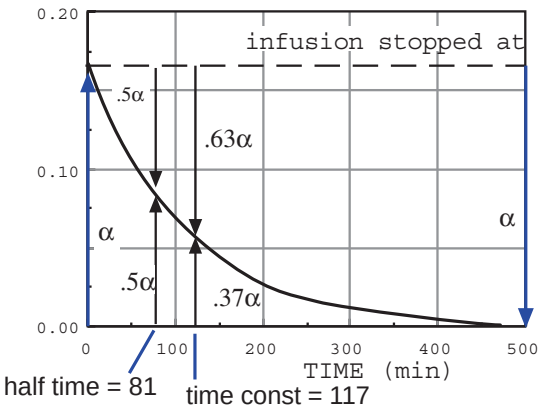
$$\frac{1}{2}\frac{in}{g} = \frac{in}{g}\left(1 - e^{\frac{-t_{1/2}}{\tau}}\right)$$

solving for $t_{1/2}$

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

$$\log_e \frac{1}{2} = \log_e e^{\frac{-t_{1/2}}{\tau}} = -\frac{t_{1/2}}{\tau}$$

$$t_{1/2} = 0.69\ \tau$$



Infusion stops

When the infusion stops c_t will decay exponentially. Suppose $c_t = c_o$ when the infusion stops. Then, counting time from this point on, the future of c_t is given by (see appendix)

$$c_t = c_o\, e^{\frac{-g}{v}t} = c_o\, e^{\frac{-t}{\tau}}$$

The same remarks hold for time constants and half times as before because in both cases the time dependence is all contained in the same exponential term. (Use the same arguments to prove it.)

Things to know about time constants

1. When $t = \tau$

the system has gone to 63% of its final destination.

2. When $t = 3\tau$

the system --> 95% of its final destination i.e. it is nearly complete.

3. mean residence time = time constant

4. When $t = t_{1/2}$, the system --> 50% of its final destination.

5. $t_{1/2} = 0.69\ \tau$

6. If some variable, call it y, has a time const = t, then the rate of decay (outflow) is given by y/t , in our example by

$$\frac{c_t}{\tau} = \frac{c_t}{\frac{v}{g}} = \frac{gc_t}{v}$$

Semi-Log Plots

Expressions containing a single exponential term occur commonly in physiology. In our case starting and stopping the infusion both led to single exponentials:

$$c_t = \frac{in}{g}\left(1 - e^{\frac{-t}{\tau}}\right) \qquad (4)$$

and

$$c_t = c_o\, e^{\frac{-t}{\tau}} \qquad (5)$$

A semi-log plot is a simple test for data that can be represented as a single exponential of the form

$$y_t = y_o\, e^{\frac{-t}{\tau}} \qquad (6)$$

Letting $c = y$, shows that (5) and (6) are the same form. To cast (4) into this form Subtract in/g from both sides of (4) and let $y = (in/g - ct)$ and $yo = in/g$.

$$\frac{in}{g} - c_t = y_t = \frac{in}{g}e^{\frac{-t}{\tau}} = y_0 e^{\frac{-t}{\tau}}$$

So dealing with (6) covers both cases (4) and (5).

Take the natural log of both sides of (6)

$$\log_e y_t = \log_e y_o\, e^{\frac{-t}{\tau}}$$

$$= \log_e y_o + \log_e e^{\frac{-t}{\tau}}$$

or

$$\log_e y_t = \log_e y_o + \frac{-t}{\tau}$$

This last expression shows that plotting ***loge****(yt)* vs *t* should give a straight line with slope = *1/t* . To illustrate take two different time points *t1* and *t2*

$$\log_e y_{t_1} = \log_e y_o + \frac{-t_1}{\tau} \qquad (7)$$

$$\ln y_{t_2} = \ln y_o + \frac{-t_2}{\tau} \qquad (8)$$

Subtract (8) from (7)

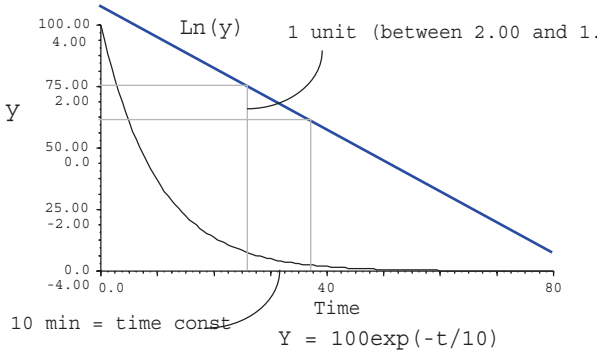
$$\ln y_{t_1} - \ln y_{t_2} = \frac{t_2}{\tau} - \frac{t_1}{\tau}$$

or solving for t,

$$\tau = \frac{t_2 - t_1}{\ln y_{t_1} - \ln y_{t_2}} \qquad (9)$$

Note that if we deliberately two pick points on the straight line where *ln(yt1) - ln(yt2) = 1* then the expression for t is particularly convenient *t = t2 - t1*

This is illustrated on the following graph where an exponential with time constant = 10 min. is plotted. Both y and *ln(y)* are plotted and the time const is extracted using the above equation.



Derivation of Exponential Response

Let::

in = infusion rate of inulin (mg/min.)

Out = excretion rate for inulin (mg/min.)

n = no. of mg of inulin in extra-cellular space (mg)

then

$$\frac{dn}{dt} = in - Out \qquad (1)$$

In this simulation, inulin in the plasma and interstitial space is assumed to exchange rapidly so that for practical purposes they are in equilibrium.... plasma conc = interstitial space conc = extracellular space conc.

Let

c = conc. of inulin in extra-cell. space (mg/ml)

g = glomerular filtration rate (ml/min.)

then *Out* = *gc* and (1) becomes

$$\frac{dn}{dt} = in - gc \qquad \textbf{(2)}$$

To eliminate *n, let*

v = volume of extra-cellular space (ml),

and note that c = n/v so that

$$\frac{dc}{dt} = \frac{1}{v}\frac{dn}{dt} \qquad \textbf{(3)}$$

and using eqns. **(2)** and **(3)** together

$$\frac{dc}{dt} = \frac{in}{v} - \frac{g}{v}c \qquad \textbf{(4)}$$

To solve (4) make the substitution

$$x \equiv \frac{in}{v} - \frac{g}{v}c \qquad \textbf{(5)}$$

so that using both (4) and (5)

$$\frac{dx}{dt} = -\frac{g}{v}\frac{dc}{dt} = -\frac{g}{v}x \quad , \qquad \textbf{(6)}$$

Multiply both sides of (6) by dt,

$$x = -\frac{g}{v}xdt \quad ,$$

then divide by x, and integrate

$$\int_{x_o}^{x_t}\frac{dx}{x} = -\frac{g}{v}\int_{0}^{t}dt$$

$$\ln(x_t) - \ln(x_o) = \ln\left(\frac{x_t}{x_o}\right) = -\frac{g}{v}t$$

taking the exponential of both sides

$$\frac{x_t}{x_o} = e^{\frac{-g}{v}t}, \qquad or \qquad x_t = x_o e^{\frac{-g}{v}t}$$

where

x_O = value of x at time $t=0$

x_t = value of x at any time t

Letting

$c_O =$ c at time $t = 0$

$c_t =$ c at any time t

we use definition (5) to eliminate x in favor of c and arrive at

$$c_t = \frac{in}{g} - \left[\frac{in}{g} - c_o\right]e^{\frac{-g}{v}t} \qquad \textbf{(7)}$$

In our problem, when we began infusing at $t=0$ there was no inulin in the body so $c_O = 0$, and

$$c_t = \frac{in}{g}\left(1 - e^{\frac{-g}{v}t}\right) \quad .$$

After a certain amount of time elapses we shut the infusion off so that from this point on $in = 0$. If we agree to set our stop watch back to zero at this point and start counting time all over again, we wil have begun our new time regime with a certain non zero concentration, i.e. c_O is now whatever the value of c was when we stopped the infusion . Eq **(7)** becomes

$$c_t = c_o e^{\frac{-g}{v}t}$$

For simple exponential mean residence time = time constant

Begin with a simple example to calculate the average time molecule X spends in body. Suppose at time t=0 there were only 6 X molecules, three were eliminated on day 1, two on day 2 and one on day 3. Then the average time, t_{ave}, spent in the body would be

$$t_{ave} = \frac{1+1+1+2+2+3}{6}$$
$$= \frac{3\times 1 + 2\times 2 + 3}{6} = 1.66 \quad days$$

In other words if n_i = the number of molecules that leave at time t_i, then the average time a molecule spends in the body is given by

$$t_{ave} = \frac{n_1 t_1 + n_2 t_2 + \ldots}{n_1 + n_2 + \ldots}$$
$$= \frac{\sum_i n_i t_i}{\sum_i n_i} = \frac{\sum_i n_i t_i}{N_0} \qquad \textbf{(1)}$$

where N_O is the total number of molecules at $t=0$.

In our more general problem we count time continuously. We begin with N_O molecules at $t=0$, and the number N_t at any subsequent time is given by

$$N_t = N_0 e^{-\frac{t}{\tau}}$$

the number that leave in any time interval between t and $t+dt$ (i.e. their "age" or the duration they stay in the body lies between t

and $t+dt$) is given by $-dN_t$, (The minus sign occurs because we are counting the number of molecules that leave the body for the environment - each time the environment gains one, the body loses one)

$$-dN_t = -\frac{dN_t}{dt}dt = \frac{1}{\tau}N_0 e^{-\frac{t}{\tau}}$$

Using this result together with our formula **(1)** for averaging we have

$$t_{ave} = \frac{1}{N_0}\sum_{t=0}^{\infty}(-dN_t)\,t = \sum_{t=0}^{\infty}\left(\frac{1}{\tau}e^{-\frac{t}{\tau}}\right)t\,dt$$

As dt gets smaller and smaller, the summation approaches an integral

$$t_{ave} = \int_0^{\infty}\left(\frac{1}{\tau}e^{-\frac{t}{\tau}}\right)t\,dt = \int_0^{\infty} e^{-\left(\frac{t}{\tau}\right)}\left(\frac{t}{\tau}\right)dt$$

Multiplying and dividing the last expression by t (which is a constant) allows us to write

$$t_{ave} = \tau\int_0^{\infty} e^{-\left(\frac{t}{\tau}\right)}\left(\frac{t}{\tau}\right)\left(\frac{dt}{\tau}\right) \qquad \textbf{(2)}$$

Standard integral tables show that

$$\int_0^{\infty} e^{-x}x\,dx = 1$$

Letting $x = \frac{t}{\tau}$, $dx = \frac{dt}{\tau}$, we use this formula in **(2)** to see that

$$t_{ave} = \tau$$