6.337 MODELLING PROJECT

Administration of Drugs Problem

STELLA CHAN

DR. T. G. BERRY

April 7, 1997

DESCRIPTION OF PROBLEM

"Patients with asthma have constriction of the airways in the lungs and consequent difficulty in breathing out. This ailment can be alleviated by introducing the drug theophylline into the bloodstream. This is done by injecting another drug, aminophylline, which the body quickly converts to theophylline. Once present in the blood, however, the drug is steadily excreted from the body via the kidney." (Burghes 124)

"It is known from experiments that theophylline has hardly any therapeutic effect if its concentrations in the bloodstream is below 5 mg/l, and that concentration of above 20 mg/l are likely to be toxic." (Burghes 124). The questions that often arise are how much of a dosage to prescribe for a drug and how often the dosage should be administered, so that the concentration remains within the therapeutic range. In this case within the range of 5mg/l and 20mg/l.

When one knows the basic mathematical model that a drug follows after being given to a patient, the quantitative aspects of drug disposition may be followed over the time course of drug therapy by measurements of drug levels in suitable representative media.

In our problem, a drug is given by intravenous injection is rapidly dissolved in the body fluid. A pharmacokinetic model that would describe this situation would be a one-compartment model. If a known set of drug concentrations in the body were determined at various time intervals, then the volume of fluid in the body and the rate of drug elimination would be established.

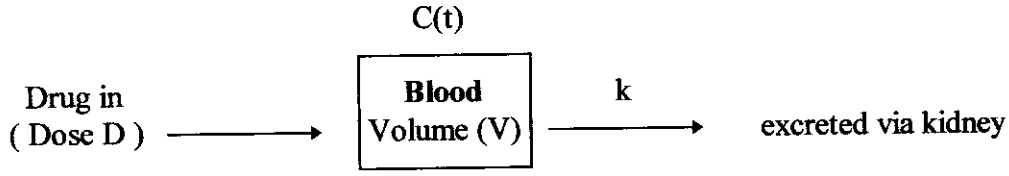
MATHEMATICAL ANALYSIS

D: Initial quantity = 300 mg	
C : Concentration, mg/l	**t : Time, hours**
10.0	1
7.0	3
5.0	5
3.5	7
2.5	9
2.0	11
1.5	13
1.0	15
0.7	17
0.5	19

- Experimental measurements obtained by injecting a known dose of theophylline into a patient, allowing time for it to diffuse throughout the bloodstream, and finding the drug concentration in blood samples taken at regular intervals. (Burghes 125).

One compartment model :

A drug is quickly injected into the bloodstream and rapidly distributes itself throughout the body.



Let C(t) = the concentration of drug in the blood at time t measured in mg/l.

C_0 = concentration of drug at time 0 measured in mg / l.

t = time measured in hours.

k = positive elimination constant measured in hr^{-1}.

D = dose of drug given measured in mg.

V = volume of distribution measured in liter.

Assumptions :

1. For the purpose of simplicity, we assume that the drug is injected directly into this compartment. And distributes itself instantaneously through the compartment. Thus, the concentration of drug at time 0 (C_0) can be calculated or, conversely if C_0 is known volume (V) can be calculated.
2. The rate at which the drug is removed by the kidney is proportional to the amount of drug in the body. This allows us to obtain a differential equation which describes the concentration C(t) any time t.
3. For the purpose of simplicity, the drug does not collect in organs and tissue and is eliminated through urine only so that the concentration of drug is constant throughout.
4. For the purpose of simplicity, "Body weight and blood volume are constants (say an average over some specific group)", (Weir 318) in which each particle present in it has an equal probability of exits.

In order to determine the mathematical relationship of this model, it is a good idea to plot the given set of data. From our data we obtain a graph (shown in Figure 1).

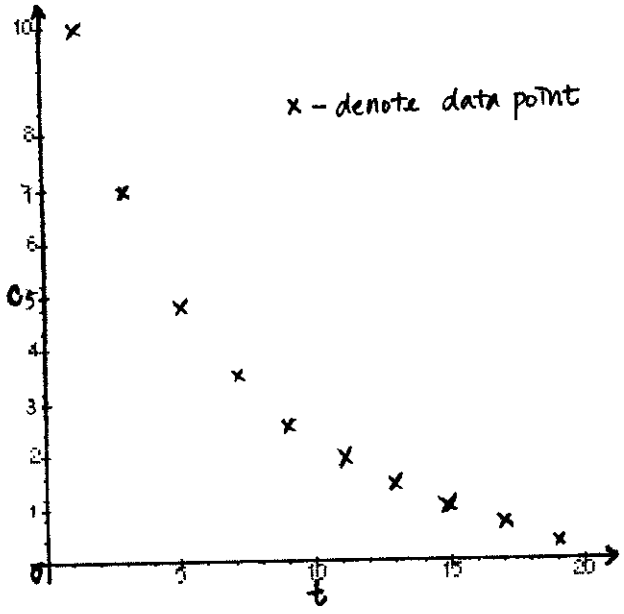


Figure 1.

Observations : For $t > 0$ and $C(t) > 0$, as t increases , C(t) tends to decrease at an ever decreasing rate, suggest that this data may be approximate by an exponential function of the form :

$$C(t) = M e^{-kt} \qquad (k > 0, M > 0)$$

By least - squares approximation methods, we obtain :

$$\ln C(t) = \ln M - kt$$
$$c = m - kt \qquad (\ln M = m, \text{ or } M = e^m)$$

which is a linear equation.

Therefore,
$$-(\sum t_i)^2 k + (\sum t_i) m = (\sum t_i) \ln C_i$$
$$-(\sum t_i) k + n m = \sum \ln C_i$$

Hence,
$$-1330 k + 100 m = 26.86585739$$
$$-100 k + 10 m = 8.075777018$$

Solving the above equation by using Maple V software (see Appendix), we obtain the unique solution :

$$k = 0.1633088265$$
$$m = 2.440665967$$

Thus, with the use of this logarithmic - based method of least - squares, we find that the best - fitting exponential function for the data is given by :

$$C(t) = M e^{-kt}$$
$$= e^m e^{-kt}$$
$$= 11.48068395 e^{-0.1633088265 t}$$

$C(t_i)$ calculated value	C_i	t_i
9.750876135	10.0	1
7.033887133	7.0	3
5.073961305	5.0	5
3.660150186	3.5	7
2.640284108	2.5	9
1.904594024	2.0	11
1.373896993	1.5	13
0.9910736476	1.0	15
0.7149203908	0.7	17
0.5157146156	0.5	19

- Approximate Calculated values, using the logarithmic - based least - squares method for an exponential approximating function, for the given data.

An exponential least-square fit is show in Figure 2.

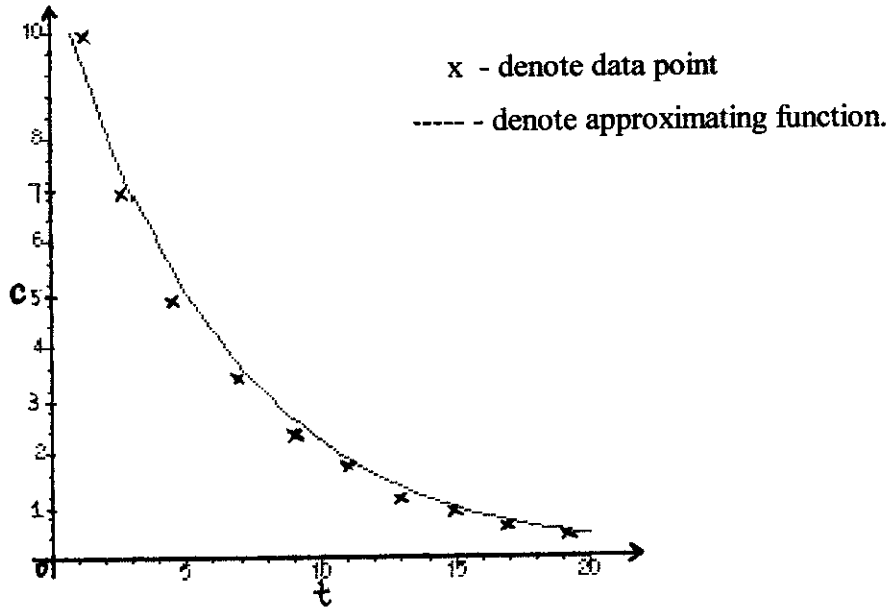


Figure 2.

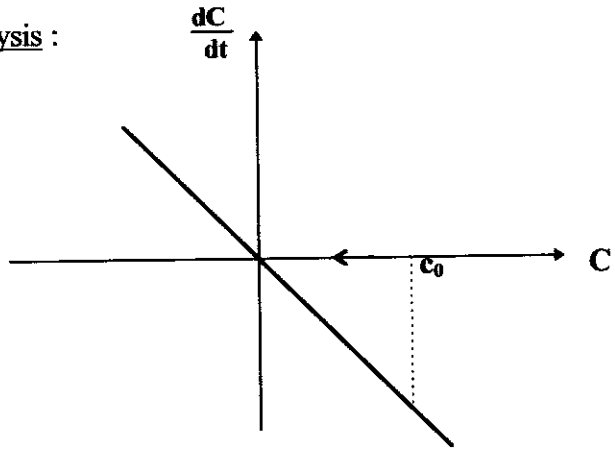
According to my assumption, the concentration of drug in the blood at time t is a differentiable function C(t) then,

$$\frac{dC}{dt} = -k\,C$$

For equilibrium : $\frac{dC}{dt} = 0 \quad \Rightarrow \quad k = 0$ (uninteresting)

or $C = 0$ which is equilibrium concentration

Phase plane analysis :



If we know the concentration at $t = 0$ is $C_0 > 0$.

Then the anticipated solutions is $\left.\frac{dC}{dt}\right|_0 < 0 \Rightarrow$ C decreasing, and as C decreasing, $\frac{dC}{dt}$ is increasing, and $\frac{dC}{dt}$ approaches 0. The graph will look like the one in Figure 3.

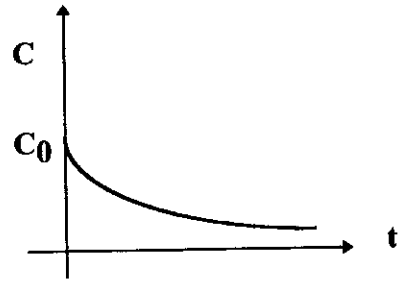


Figure 3.

Therefore, we suspect that $C(t) = C_0 e^{-kt}$. This also tells us that $C = 0$ is a stable equilibrium.

To verify our suspicion, we assume that C_0 is the concentration at $t = 0$, then we have the model with initial condition $C(0) = C_0$:

$$\frac{dC}{dt} = -k\,C \qquad , C(0) = C_0 \qquad (k > 0)$$

which is essentially Malthusian model of population decay.

Solve : $\frac{1}{C}\,dC = -k\,dt \qquad (k, C > 0)$

$$\ln|C| = -kt + C_1$$

$$C = e^{-kt + c_1}$$

$$C = D\,e^{-kt} \qquad (D = e^{c_1} > 0)$$

Solution : $C = C(t) = D\,e^{-kt}$

$$C(0) = C_0\,e^{-k(0)}$$

$$= D\,e^{0}$$

$$\Rightarrow \qquad D = C_0$$

Therefore, the solution of the model gives $C(t) = C_0\,e^{-kt}$ as anticipated. This equation allows us to calculate the expected amount of drug in the compartment at any time (t) when the dose and elimination constant are known.

However, repeated administration of a drug is usually necessary for effective therapy. Chronic administration generally results in an accumulation of the drug in the body, particularly "if the drug is administered at a fixed dose D and a fixed dosage-interval T, the amount of drug in the body will increase and then plateau to a mean plasma level which is higher than the peak concentration of drug in the blood obtained from the initial dose". (Shargel 231) When the second dose is given after a time interval shorter than the time required to eliminate the previous dose, drug accumulates in the body. However, if the second dose is given after a time interval longer than the time required to eliminate the

will never happen
governed by Math
law

previous dose, the drug will not accumulate. Here, we assume that early doses of drug do not affect the pharmacokinetics of subsequent doses.

Let R_i = the residual concentration of drug of the i^{th} interval, $i = 1.....n$

C_0 = the rising concentration resulting from each time a dose is administered regularly at fixed time interval of length T.

Suppose at time $t = 0$, the first dose is administered.

According to our model : $\frac{dC}{dt} = -k\,C \qquad (k > 0)$

$$\Rightarrow \quad C(t) = D\,e^{-kt} = D\,e^{-k(t-t_0)} \qquad \text{where } D = C(t_0)$$

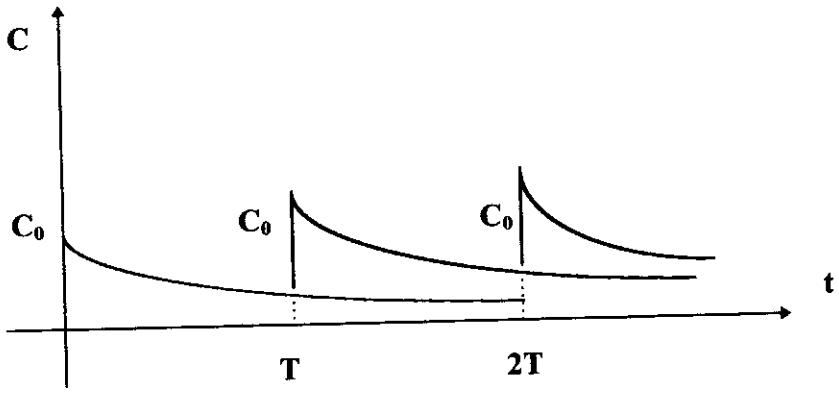


Figure 4. Possible effect of repeating equal dose

From Figure 4, we have :

$C_1 = C_0$ $\qquad$ $C_2 = R_1 + C_0$ $\qquad$ $C_3 = R_2 + C_0$

$C(t) = C_0\,e^{-kt}$ $\qquad$ $C(t) = (R_1 + C_0)\,e^{-k(t-T)}$ $\qquad$ $C(t) = (R_2 + C_0)\,e^{-k(t-2T)}$

$R_1 = C_0\,e^{-kT}$ $\qquad$ $R_2 = (R_1 + C_0)\,e^{-kT}$ $\qquad$ $R_3 = (R_2 + C_0)\,e^{-kT}$

$= C_0\,(1 + e^{-kT})\,e^{-kT}$ $\qquad$ $= (C_0 + C_0\,e^{-kT} + C_0\,e^{-2kT})\,e^{-kT}$

Proceeding in this way, we can easily obtain the following table :

I	C_{i-1}	R_i
1	C_0	$C_0 e^{-kT}$
2	$C_0 (1 + e^{-kT})$	$C_0 (1 + e^{-kT}) e^{-kT}$
3	$C_0 + C_0 e^{-kT} + C_0 e^{-2kT}$	$(C_0 + C_0 e^{-kT} + C_0 e^{-2kT}) e^{-kT}$
.	.	.
.	.	.
.	.	.
n	$C_0(1 + e^{-kT} + e^{-2kT} + ... + e^{-(n-1)kT})$	$C_0 e^{-kT} + C_0 e^{-2kT} + ... + C_0 e^{-nkT} = C_{n-1} e^{-kT}$

According to the table :

$C_{n-1} = C_0(1 + e^{-kT} + e^{-2kT} + ... + e^{-(n-1)kT})$, which is a geometric series with $r = e^{-kT}$

we get, $$C_{n-1} = C_0 \left(\frac{1-e^{-nkT}}{1-e^{-kT}}\right) \qquad (1)$$

we can easily observe that, as n approaches infinity, e^{-nkT} approaches zero . Thus, the concentration never exceeds $C_M = C_0 \left(\frac{1}{1 - e^{-kT}}\right)$. (2)

From the table above, we also have : $R_n = C_{n-1} e^{-kT}$, therefore by equation **(1)**, we get :

$$R_n = C_0 e^{-kT} \left(\frac{1-e^{-nkT}}{1-e^{-kT}}\right) \qquad (3)$$

It is easy to verify that, $$R = \lim_{n \to \infty} Rn = \lim_{n \to \infty} \left[C_0 e^{-kT} \left(\frac{1-e^{-nkT}}{1-e^{-kT}}\right) \right]$$

$$= \frac{C_0 e^{-kT}}{1 - e^{-kT}}$$

$$= \frac{C_0}{e^{kT}-1} \qquad (4)$$

According to what we have so far, we observed the following relationship ;

$$C_0 + R = C_0 + \frac{C_0}{e^{kT} - 1}$$

$$= \frac{C_0(e^{kT}-1) + C_0}{e^{kT}-1}$$

$$= \frac{C_0(e^{kT})}{e^{kT}-1}$$

$$= \frac{C_0}{1-e^{-kT}}$$

$$= C_M \qquad (5)$$

"A meaningful way to examine what happens to the residual concentration **R** for different intervals T between doses is to look at **R** in comparison with C_0 , the change in concentration due to each dose." (Weir 320). $\frac{R}{C_0} = \frac{1}{e^{kT}-1}$

By observing the behavior of this ratio, one of 2 case could have happen. We could have no residual concentration from the previous dose, or the residual could exists at each time after the first dose of drug is taken.

First case : This ratio tell us that if T between doses is long enough to make $e^{kT} - 1$ sufficiently large then $\frac{R}{C_0}$ will be close to zero.

We know that R_n is positive since R_n is equal to $C_n e^{-kT}$, since C_n is greater than zero and exponential function never be negative. This implies that whenever

R is small the R_n s are even smaller. Therefore whenever T is long enough to make $e^{kT}-1$ sufficiently large, the residual concentration R is almost equal to zero. That is the dose administered is equal to that which had been eliminated. This is illustrated in Fig. 5.

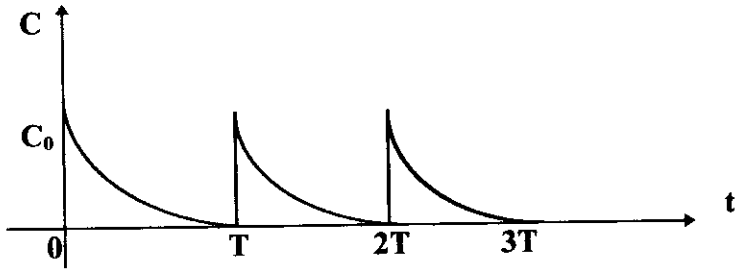


Figure 5. Drug concentration for long intervals between doses (Weir 321)

Second case : If the length of time T between doses is so short that e^{kT} is not very much larger than 1 then $\frac{R}{C_0}$ is significantly greater than 1. Since $R_n = C_{n-1}\, e^{-kT}$, therefore as R_n becomes larger, the concentration C_n after each dose becomes larger. That is to say that after each subsequent dose there is more drug within the patient than after the previous dose. Therefore, the administered dose is greater than the dose eliminated. However, there is a limit. Just as we showed that the concentration after each dose will never exceed $C_M = \frac{C_0}{1-e^{-kT}}$, and $C_0 + R = C_M$. This tells us that the concentration swings between C_M and R, never exceeding the one nor falling below the other. Therefore, once the body has reached this state, the dose administered is equal to that which had been eliminated. This is illustrated in Figure 6.

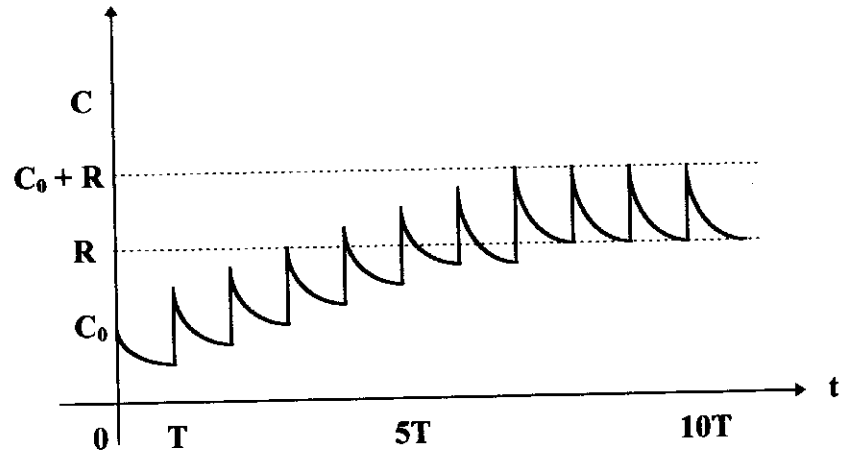


Figure 6. Buildup of drug concentration when the interval between doses is short.

Our problem is trying to decide the dose D mg and interval T in order to keep the concentration in the therapeutic range $5 \le C(t) \le 20$.

Clearly, we want $C_M = \frac{C_0}{1-e^{-kT}} = 20$. Thus, $C_0 = 20(1 - e^{-kT})$.

Therefore, to answer our question, we must find out what the parameter k is. We can do so by solving a linear equation. But first, let us make use of the following result : "Clinical experiment shows that the apparent volume of distribution (V liters) and the patient's weight (W kg) are connected by the simple relationship $V = \frac{1}{2} W$." (Burghes 125)

Suppose we have a 50 kg patient and our initial dose is D = 300 mg.

Then $V = \frac{1}{2} W \Rightarrow V = \frac{1}{2}(50) \Rightarrow V = 25$ liters ,

and, $C_0 = \frac{D}{V} \Rightarrow D = C_0 V \Rightarrow D = 25\ C_0$,

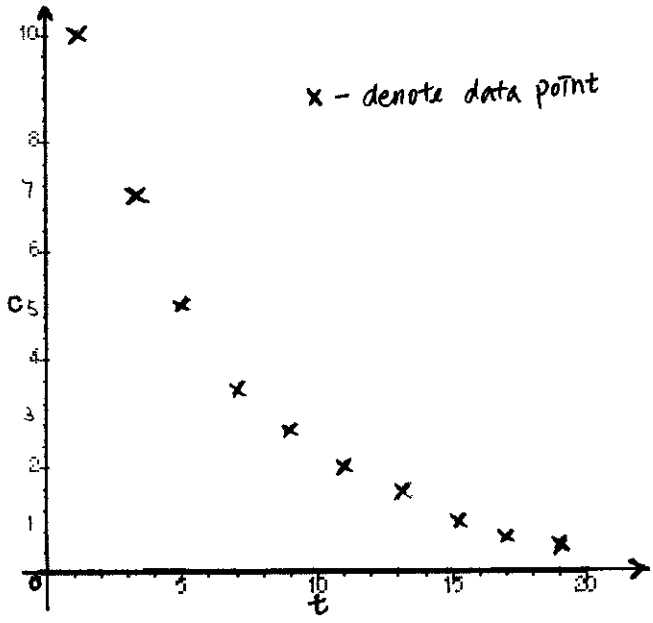
We have shown that : $C(t) = C_0 e^{-kT}$

$$\ln C(t) = \ln C_0 - kt$$

By solving this equation graphically,(see Fig 7. & Fig. 8.) we have :

(i) y-intercept : $\ln C_0 = 2.48490665 \Rightarrow C_0 = 12$ mg/l which satisfies with our initial dose = 300 mg (D = 25 (12) = 300).

(ii) Slope : $k = 0.17$ / hr



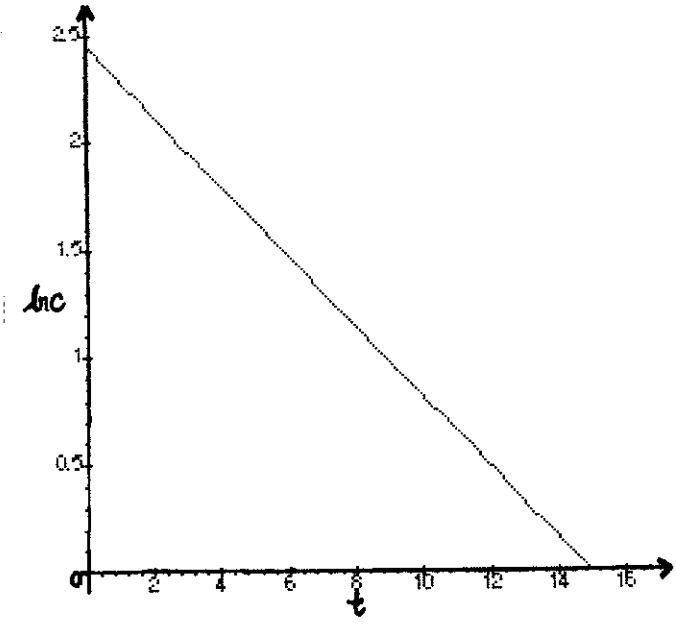


Figure 7. Graph of given data

Figure 8. Graph of lnC(t) vs. t.

Now, solve for C_0 , D and C(t) by using $C_0 = 20 (1 - e^{-kT})$ and k = 0.17.

For T = 1,

$$C_0 = 20 (1 - e^{-kT})$$
$$= 20 (1 - e^{-0.17})$$
$$\cong 3.1$$

Therefore, $D = 25 C_0 \Rightarrow D = 25 (3.1) \Rightarrow D \cong 78$

According to our model, we have;

$$C(t) = C_0\, e^{-kT} \quad \Rightarrow \quad C(1) = 3.1\,(e^{-0.17}) \quad \Rightarrow \quad C(1) \cong 2.6$$

For T = 2,

$$C_0 = 20\,(1 - e^{-kT})$$
$$= 20\,(1 - e^{-2\,(0.7)})$$
$$\cong 5.8$$

$$\therefore \; D = 25\, C_0 \quad \Rightarrow \quad D = 25\,(5.8) \quad \Rightarrow \quad D \cong 144$$

$$\therefore \; C(t) = C_0\, e^{-kT} \quad \Rightarrow \quad C(2) = 5.8\,(e^{-2\,(0.7)}) \quad \Rightarrow \quad C(1) \cong 4.1$$

Proceeding in this way, we get the following table :

T hours	D mg	C(t) mg/l
1	78	2.6
2	144	4.1
3	200	4.8
4	247	5.0
6	320	4.6
8	372	3.8
12	435	2.3
16	467	1.2
18	477	0.9
24	492	0.3

We now can easily see that if we choose T = 4 hours the concentration never leaves the therapeutic range. Therefore, for this particular problem, we should give a dose of 250 mg every 4 hours to the 50 kg patient, unless a concentration just less than 20 mg/l is preferable to one just greater than 5 mg/l, there is no point at all in giving a larger initial dose and smaller repeat doses.

When a drug is to be administered, it is desirable, for therapeutic reasons, to maintain optimum amounts of drug at target sites and, at the same time, minimize the total

dose to be administered so as to reduce the risk of side effects. Assume now that C_M and R are 'safe ' guidelines, where C_M is the tolerance concentration level, above which side effects might occur. If we have information on C_0 and C_M and given that $C_M > C_0$, we can find the minimum dosage time interval T which can be used , if the drug is to be used "safely for an indefinite amount of time."

We now want : $\lim_{n \to \infty} C_n \leq C_M \quad , \quad C_M > C_0$

$$\lim_{n \to \infty} C_n = \frac{C_0}{1-e^{-kT}} \leq C_M$$

$$= \frac{C_0}{1-e^{-kT}} \leq 20$$

$$C_0 \leq 20 (1 - e^{-kT})$$

$$-(\frac{C_0}{20} - 1) \geq e^{-kT}$$

$$\ln (1- \frac{C_0}{20}) \geq -kT$$

$$-\frac{1}{k} \ln (1- \frac{C_0}{20}) \leq T$$

$\therefore$ The minimum dosage time interval is $T_{min} = -\frac{1}{k} \ln (1- \frac{C_0}{20})$.

To verify this result, let's refer back to our example.

We have shown that we should give a dose of 250 mg every 4 hours to the patients. Therefore, for our 50 kg patient $C_0 = \frac{D}{V} = \frac{250}{25} = 10$ mg/l. Since $C_0 = 10$ is less than $C_M = 20$, when we apply this result to the formula, we have :

$$T_{min} = -\frac{1}{k} \ln\left(1 - \frac{C0}{20}\right)$$

$$= -\frac{1}{0.17} \ln\left(1 - \frac{10}{20}\right)$$

$$= -\frac{1}{0.17} \ln(0.5)$$

$$= 4.077$$

$$\cong 4 \text{ hours as anticipated.}$$

In conclusion, our model is quite useful in that it provides quantitatively for the prediction of concentration levels under varying condition for dose rates and gradual buildup can be avoided, if that is desirable. Since sub-optimal concentrations may induce resistance to the drug by the micro-organisms concerned, some antibiotics can have harmful effects until their concentration has surpassed a certain threshold. Therefore, our model for prescribing a safe and effective dosage of drug concentration appears to be a good one.

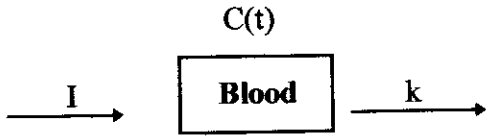
However, the assumption of an instantaneous rise in concentration whenever a drug is administered is the deficiency in the model. Some drugs are administered intravenously at a constant rate over an extended time period, and some are taken orally, which requires a finite time to diffuse into the blood stream and therefore, the assumption is not realistic for such a drug.

First modification; **Constant intravenous infusion** :

From our previous study of the one-compartment model, we know that the differential equation to be satisfied is :

$$\frac{dC}{dt} = -kC$$

Modifying the model to incorporate a constant infusion rate I measured in appropriate units (say mg/hr), we obtain :



$$\frac{dC}{dt} = -kC + I \qquad (k > 0, I > 0)$$

For equilibrium : $\frac{dC}{dt} = 0 \quad \Rightarrow \quad \frac{I}{K} = 0$

or $C = 0$ (which is equilibrium concentration)

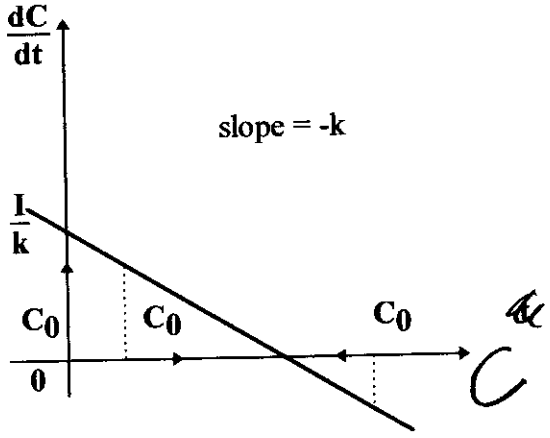
Phase plane analysis : when $C_0 = 0$ then $\frac{dC}{dt} = I$

$$\frac{dC}{dt} = -kC + I = I$$

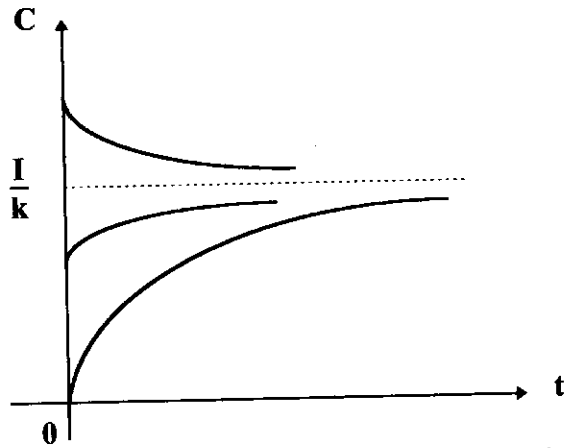
$$\Rightarrow \quad -kC = 0$$

$$\Rightarrow \quad C = 0$$

or $k = 0$ (uninteresting)



Anticipated solution :



◆ a rough sketch of the concentrations as a function of time.

This shows that $C = 0$ is an unstable equilibrium and $C = \frac{I}{k}$ is a stable equilibrium. We will verify our anticipation by solving the differential equation.

Solve : $\frac{dC}{dt} = -kC + I \qquad (k > 0, I > 0)$

$$\frac{1}{-kC + I}\, dC = dt$$

$$-\frac{1}{k} \ln | -kC + I | = t + C_1$$

$$| -kC + I | = e^{-kt + C_2}$$

$$| -kC + I | = De^{-kt} \qquad (D = e^{C_2} > 0)$$

$$-kC + I = L e^{-kt} \qquad (L = +/-D \neq 0)$$

Solutions : $C(t) = \frac{Le^{-kt} - I}{-k}$

$$= \frac{I}{k} - \frac{L}{k} e^{-kt} \qquad (6)$$

Equation 6 has shown us that during infusion at a constant rate, the drug concentration at any time (t) can be calculated if the infusion rate (I), and elimination constant (k) are known.

Observations : We observed that e^{-kt} is a negative exponential and $k > 0$, therefore

(i) $-\frac{L}{k} > 0$ if $L < 0$ and

(ii) $-\frac{L}{k} < 0$ if $L > 0$

If an initial injection of size $C_0 > \frac{I}{k}$ is given, then C(t) will approach $\frac{I}{k}$ from above, otherwise C(t) approaches $\frac{I}{k}$ from below as anticipated.

We can easily verify that as t approaches ∞, the concentration of the drug in the blood at time t approaches $\frac{I}{k}$.

Let us assume that C_0 is the concentration at $t = 0$, we obtain :

$$\frac{dC}{dt} = -kC + I \quad , \quad C(0) = 0$$

Apply the initial condition to equation (6) $C(t) = \frac{I}{k} - \frac{L}{k} e^{-k(t)}$

we get : $C(0) = \frac{I}{k} - \frac{L}{k} e^{-k(0)}$

$$= \frac{I}{k} - \frac{L}{k}$$

$$\frac{L}{k} = \frac{I}{k} - C(0)$$

We already know that $C_\infty = \lim_{n \to \infty} C(t) = \frac{I}{k}$ (7)

hence, $\frac{L}{k} = C_\infty - C(0)$ (8)

Apply equation (7) and (8) to our solution $C(t) = \frac{I}{k} - \frac{L}{k} e^{-kt}$, upon rearrangement expression we obtain the following :

$$C(t) = C_\infty - [\, C_\infty - C(0) \,] e^{-kt}$$

$$C_\infty - C(t) = [\, C_\infty - C(0) \,] e^{-kt}$$

Good

This equation states that the difference between the equilibrium concentration C_∞ and any instantaneous drug concentration in blood we choose to look at in time t (C(t)) declines exponentially as a function of time with the same rate constant, k, which governed the first order excretion of that drug. Because this function is first order, its rate is essentially identical to the first order process for drug elimination that was already described (in equation : $C = C_0 e^{-kt}$). Because the exponent has only a rate constant and a time parameter, the rate of approach to equilibrium concentration is independent of dose. As a result, an increase in the dose rate results in a proportional change to the equilibrium concentration of drug ($C_\infty = \frac{I}{k}$) but does not affect the time it takes to reach the equilibrium concentration.

The loading dose of a drug is used to obtain the equilibrium concentrations as rapidly as possible. Therefore, if proper loading dose D is given, followed by an

intravenous infusion, equilibrium drug concentration in the blood are obtained immediately and maintained.

Obviously, the parameter needed is that of the desired equilibrium concentration of drug in the blood, C_{∞} , then we can calculate the amount of drug in the body under the equilibrium conditions.

Let D = the amount of drug in the body under the equilibrium condition. (mg)

V = the volume of distribution. (liters)

k = positive rate constant for elimination of drug from the body. (hr^{-1})

C_{∞} = equilibrium concentration of drug in the blood. (mg/l)

I = constant infusion rate. (mg/hr)

Let us make use of the relationship $\frac{D}{V} = C$ that we have indicated before. This gives $D = C_{\infty} V$.

We have shown that $C_{\infty} = \frac{I}{k}$ where k and I are both positive constant, therefore C_{∞} is also a constant, and hence its rate of change is zero. That is, the rate in equals the rate out. Since "the total clearance is related to the product of the volume of distribution and the elimination" (Gladtke 24), so we have clearance = V k. This gives us $\mathbf{I = k C_{\infty} V}$ (mg / hr)

As we indicated before, when a drug is to be administered it is desirable to maintain the concentration of drug in the blood within the maximum tolerance level $\mathbf{C_{Max}}$ and the minimum effective level $\mathbf{C_{Min}}$. Usually, the infusion rate is adjusted to maintain the therapeutic level.

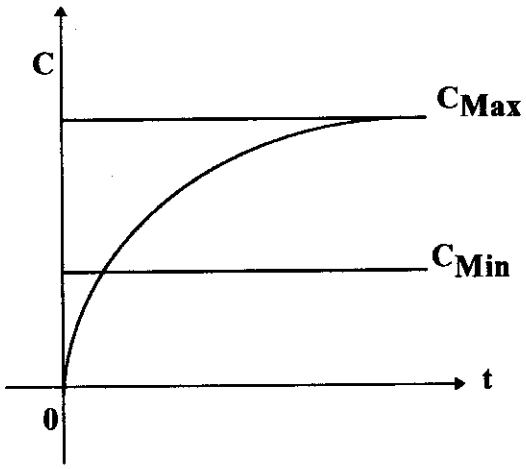


Figure 9.

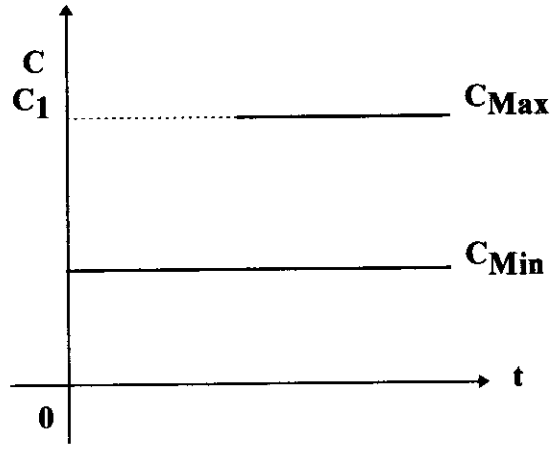


Figure 10.

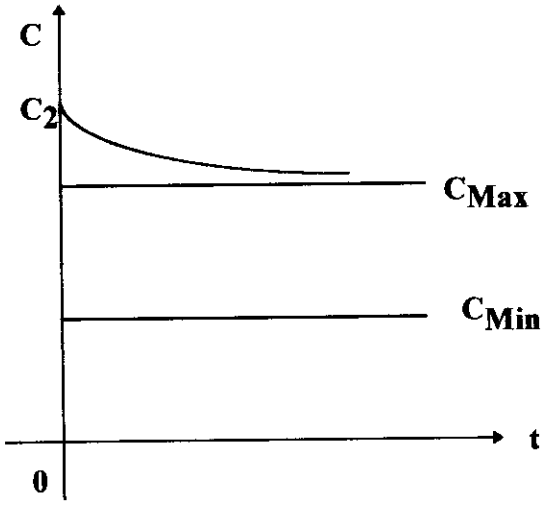


Figure 11.

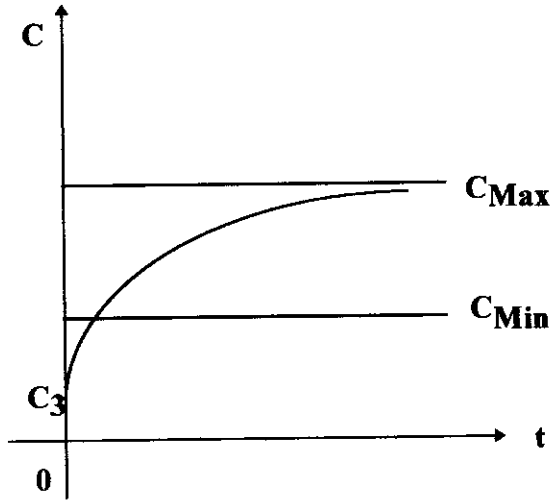


Figure 12.

As we can see in Figure 9, if there is no loading dose are given at the start of a constant-rate infusion, the drug is infused alone and the amount rises until it reach C_{Max} .

In Figure 10, the loading dose of C_1 immediately attains and the infusion rate thereafter maintain the maximum tolerance level C_{Max} .

In Figure 11, the loading dose of C_2 is excessive. Now, because the rate of loss is initially greater than the rate of infusion, the concentration of drug in the body falls.

This fall continues until C_{Max} is reached. Since C_{Max} is our maximum tolerance level, the loading dose in this case is likely to bring side effect to the patients.

In Figure 12, the loading dose of C_3 is below C_{Min}. Because the rate of infusion now exceeds the rate of drug elimination, the concentration of drug in the body continuously rises until C_{Max} is reached.

As we illustrated in the previous graphs, we conclude that specific steady state concentrations can be readily achieved by selecting appropriate drug dose rates.

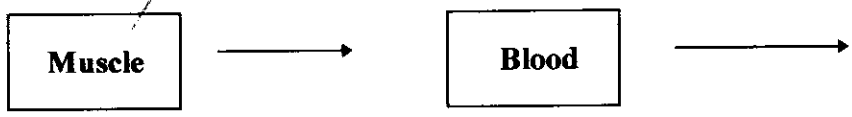
Therefore, if we want to achieve and maintain an adequate concentration rapidly, we probably should give a suitable amount of dose at the start and calculate in such a way that we will obtain a concentration - time curve similar to the one in Figure 10.

The one-compartment model discussed above assumes that elimination can occur from all compartments and that drugs can enter all areas of the body with equally ease. But in reality, this is not always valid; "many tissues cannot excrete directly and excretion takes place mainly from the blood". (Gibson 185). A refinement can be added to account for this in form of a non-excreting compartment (muscle compartment). As we indicated before, homogeneous distribution of the drug within a given compartment is assumed.

Second modification ; **Orally administered drug** :

Let's consider the two-compartment model that describes the blood concentration - time curve for simultaneous invasion and elimination.

Suppose we have :



Let M = the amount of drug from the muscle (mg).

B = the amount of drug from the blood (mg).

k_1 = positive transfer (invasion) constant between the muscle and blood compartment (hr^{-1}).

k_2 = positive elimination constant (represent excretion) (hr^{-1}).

D = dose given at time t (mg).

In this two-compartment model, we assume that the reactions are irreversible and the "substance" deposited in the muscle leaves the site of administration at the rate proportional to the concentration there. If we assume that M_0 is the amount of drug in the muscle compartment at t = 0, which is the same as the dose D mg given, and B_0 is the amount of drug in the blood compartment at t = 0, which is zero to start with, then we obtain the following model :

$$\frac{dM}{dt} = -k_1 M \qquad M_0 = D \qquad (9)$$

$$\frac{dB}{dt} = k_1 M - k_2 B \qquad B_0 = 0 \qquad (k_1, k_2 > 0) \qquad (10)$$

Solve : For equation (9), we have shown that the solution of this type is :

$$M(t) = M_0 e^{-k_1 t}$$

$$\therefore = De^{-k_1 t} \qquad (11)$$

substitute (11) into equation (10), we get :

$$\frac{dB}{dt} = k_1 M - k_2 B$$

$$\frac{dB}{dt} = k_1 De^{-k_1 t} - k_2$$

$$\frac{dB}{dt} + k_2 B = k_1 De^{-k_1 t}$$

$$\therefore P(t) = \int_0^t k_2 \, dt = k_2 t \qquad \text{then}$$

$$e^{P(t)} = e^{k_2 t} \qquad \text{and} \qquad e^{-P(t)} = e^{-k_2 t}$$

$$\therefore \int_0^t e^{P(t)} q(t) \, dt = \int_0^t e^{k_2 t} k_1 De^{-k_1 t} \, dt$$

$$= k_1 D \int_0^t e^{(k_2 - k_1)t} \, dt$$

$$= \frac{k_1 D}{k_2 - k_1} \left(e^{(k_2 - k_1)t} - 1 \right)$$

$$\therefore B(t) = e^{-k_2 t} \left[\frac{k_1 D}{k_2 - k_1} \left(e^{(k_2 - k_1)t} - 1 \right) \right]$$

$$= \frac{k_1 D}{k_2 - k_1} (e^{-k_1 t} - e^{-k_2 t}) \qquad (12)$$

Equation (12) is made up of the difference between the terms $\frac{k_1 D}{k_2 - k_1} e^{-k_1 t}$ and $\frac{k_1 D}{k_2 - k_1} e^{-k_2 t}$. If we draw these two curves separately on the same graph we obtain Figure 13 in which the value of B(t) is given by the difference of curve(1) and curve(2). Therefore, if we know the values of k_1 , k_2 and the injected dose D, we can obtain B(t) exclusively. Furthermore, we can also see that the value of B(t) starts from zero, reaches a maximum and finally approaches zero. The rough sketch of equation (12) is illustrated in Figure 14.

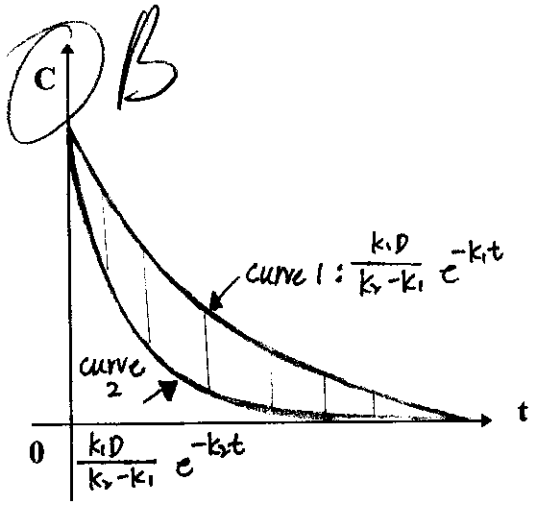


Figure 13.

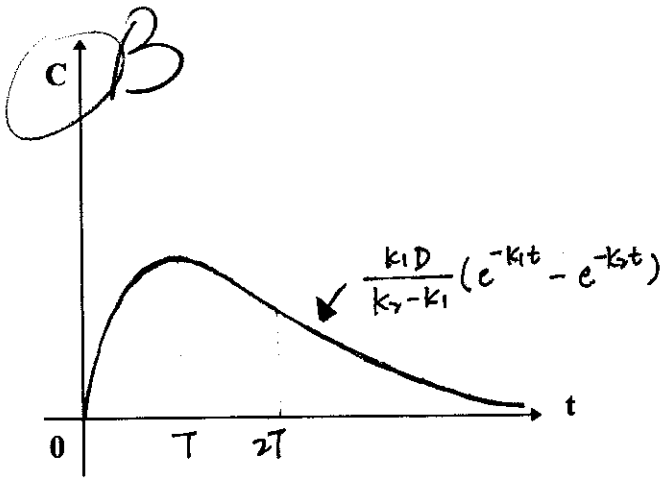


Figure 14.

Therefore, the rough sketch of this pair of linear system will then be the like the one in Figure 15.

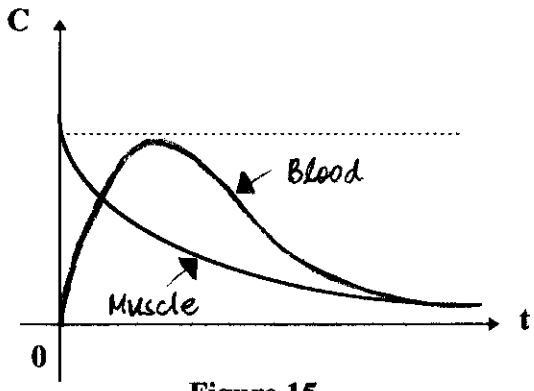
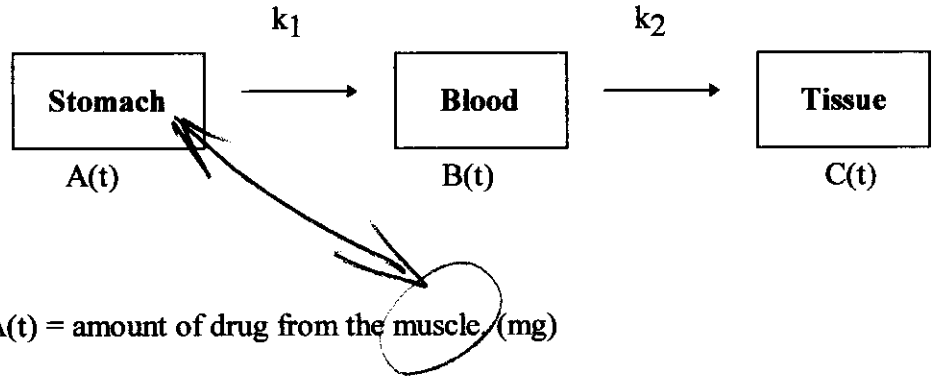


Figure 15.

For the *orally administered drug*, we often deal with the multi-compartment model, let us consider the simplify three compartment model ;

Suppose we have :



Let A(t) = amount of drug from the muscle. (mg)

B(t) = amount of drug from the blood. (mg)

C(t) = amount of drug from the tissue. (mg)

k_1 = positive transfer (invasion rate) constant between the stomach and blood compartment. (hr^{-1})

k_2 = positive elimination constant . (hr^{-1})

D = dose given at time t. (mg)

As we indicated in the two-compartment model, in this system of three compartments in series it is also assume to result in irreversible reactions. Therefore, if the system is administered in a known amount of dose at a constant rate through the first compartment, after a certain interval of time, an equilibrium state will be reached in each of the successive compartments because the amount of drug in will be equal to the amount of drug out. If we assume that C_0 is the amount of drug in the tissue compartment at t = 0, we obtain the following system of differential equation :

$$\frac{dA}{dt} = -k_1 A \qquad A_0 = D \qquad (k_1, k_2 > 0) \qquad (13)$$

$$\frac{dB}{dt} = k_1 A - k_2 B \qquad B_0 = 0 \qquad (14)$$

$$\frac{dC}{dt} = k_2 B \qquad C_0 = 0 \qquad (15)$$

Solve : According to equation (9) and (10), we have ;

$$A(t) = A_0 e^{-k_1 t} = D e^{-k_1 t} \qquad (16)$$

$$B(t) = \frac{k_1 D}{k_2 - k_1}(e^{-k_1 t} - e^{-k_2 t}) \qquad (17)$$

Substitute equation (16) and (17) back into equation (15), we get :

$$\frac{dC}{dt} = k_2 B$$

$$\frac{dC}{dt} = \frac{k_1 k_2 D}{k_2 - k_1}(e^{-k_1 t} - e^{-k_2 t})$$

$$C = \frac{k_1 k_2 D}{k_2 - k_1} \int_0^t (e^{-k_1 t} - e^{-k_2 t})\, dt$$

$$= \frac{k_1 k_2 D}{k_2 - k_1} \left(e^{-k_1 t} - e^{-k_2 t} \right) \qquad (18)$$

Therefore, we suspect that the graph of equation (18) will look like the one in equation (12). Since $k_2 > 0$, the numerator of equation (18) which is $k_1 k_2 D \left(e^{-k_1 t} - e^{-k_2 t} \right)$ is always greater than the numerator of equation (12). Hence, equation (18) should have a larger maximum point than equation (12) has. The rough sketch of equation (18) is illustrated in Figure 16

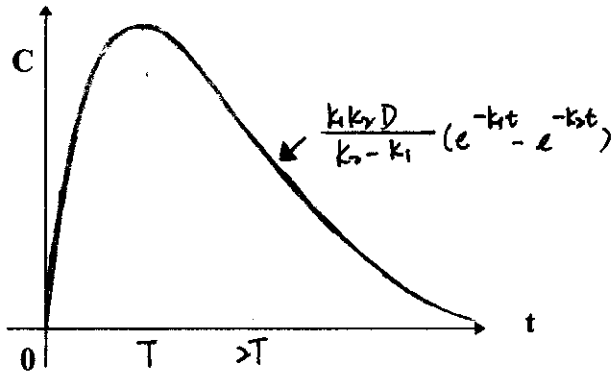


Figure 16.

According to our solutions, we should have a sketch for our "direct linear cascade system" that like the one illustrated in Figure 17.

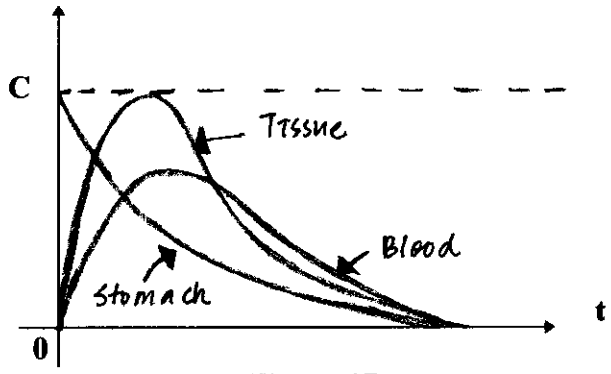


Figure 17

In conclusion, we have indicated before that many drugs are given in a multiple-dosage regimen (through any route of administration) for prolonged therapeutic activity. It is necessary to adjust the dosage of the drugs and the time interval between doses so that the desired concentration of drug in the blood will fall into the therapeutic range.

Thus far, our model is quite manageable. Multi-compartment is often used in defined, physiologically identifiable compartments. In concept it tends toward larger, more complicated mathematical models that will predict tissue concentrations within specific organs. Although this is more physiologically defined, model parameters becomes harder to estimate accurately. Therefore, it provides little information to help us to decide the size of dose that will results in effective drug therapy. Thus, our simple model approach seems to give us the information we needed to better understand the kinetic behaviour of a specific drug within the body.

APPENDIX

```
> with(linalg):
Warning, new definition for norm
Warning, new definition for trace
> n:= 10;
```

$$n := 10$$

```
> x:= ([1,3,5,7,9,11,13,15,17,19]);
```

$$x := [1, 3, 5, 7, 9, 11, 13, 15, 17, 19]$$

```
> y:=([10.0,7.0,5.0,3.5,2.5,2.0,1.5,1.0,0.7,0.5]);
```

$$y := [10.0, 7.0, 5.0, 3.5, 2.5, 2.0, 1.5, 1.0, .7, .5]$$

```
> x1:=sum(x[k],k=1..n):
> x2:=sum(x[k]^2,k=1..n):
> y1:=sum(ln(y[k]),k=1..n):
> xy:=sum(x[k]*ln(y[k]),k=1..n):
> A:= matrix(2,2,[x2,x1,x1,n]);
```

$$A := \begin{bmatrix} 1330 & 100 \\ 100 & 10 \end{bmatrix}$$

```
> b:=vector([xy,y1]);
```

$$b := [26.86585739, 8.075777018]$$

```
> c:=linsolve(A,b);
```

$$c := [-.1633088265, 2.440665967]$$

```
> f:= x-> c[1]*x + c[2];
```

$$f := x \rightarrow c_1 x + c_2$$

```
> Y:= vector(n,k -> f(x[k]));
```

$$Y := [2.277357141, 1.950739488, 1.624121835, 1.297504181, .970886528, .644268875, .317651222, -.008966431, -.335584084, -.662201737]$$

```
> m:'m';
```

$$m$$

```
> for m from 1 to n
> do
> evalf(exp(Y[m])),evalf(y[m]),evalf(x[m]):
> od;
```

$$9.750876135, 10.0, 1.$$
$$7.033887133, 7.0, 3.$$
$$5.073961305, 5.0, 5.$$
$$3.660150186, 3.5, 7.$$
$$2.640284108, 2.5, 9.$$
$$1.904594024, 2.0, 11.$$
$$1.373896993, 1.5, 13.$$
$$.9910736476, 1.0, 15.$$
$$.7149203908, .7, 17.$$
$$.5157146156, .5, 19.$$

```
> residual:=sum((y[k] - exp(Y[k]))^2, k=1..n);
```

$$residual := .1395625413$$

```
>
```

REFERENCE

1. Anderson, David H., "*Lectures Notes in Biomathematics; Vol. 50, Compartmental Modeling and Tracer Kinetics*," Managing Editor: Levin S., New York: Springer-Verlag Berlin, Heidelberg, 1983.

2. Burghes, D. et. al., "*Applying Mathematics; A First Course in Mathematical Modeling*," Ellis Horwood, 1982. pp. 124-129.

3. Clark, Wesley G., Brater, D. Craig, Johnston, Alice R., "*Goth's medical pharmacology*," 13th Edition, St. Louis : Mosby - Year Book, 1992. pp.24 - 31

4. Cullen, M. R., "*Liner Models in Biology, Linear Systems Analysis With Biological Applications*," England: Ellis Horwood, 1985. pp. 109-144.

5. Curry Stephen H., "*Drug disposition and pharmacokinetics*," London : Blackwell Scientific, 1974. pp. 124 - 147.

6. Eisen, Martin M., "*Mathematical Methods and Models in the Biological Sciences*," Prentice Hall, 1988.

7. Gibson G, Gordon, Skett, Paul, "*Introduction to drug metabolism*," 2nd Edition, Great Britain : Chapman and Hall, 1994. pp. 180-213.

8. Gladtke, E., Von Hattingberg, H. M., "*Pharmacokinetics An Introduction*," New York: Springer-Verlag, Berlin, Heidelberg, 1979.

9. Graig, Charles R., Stitzel, Robert E., "*Modern pharmacology*," 3rd Edition, Boston : Little, Brown and company, 1990. pp. 68-81.

10. Jones, D. S., Sleeman, B. D., " *Differential Equations and Mathematical Biology*," London: George Allen & Unwin, 1983. pp. 3-5.

11. Leah, Edelstein-Keshet, "*Mathematical Models in Biology*," The Random House, 1988.

12. "*Lecture Notes in Biomathematics; Vol. 11, Mathematical Models in Medicine, Workshop, Mainz, March 1976*," Edited by Berger J., Buhler W., Repges R., and Tautu P., New York: Springer-Verlag, Berlin, Heidelberg, 1976. pp. 159-243.

13. Notari Robert E., "*Biopharmaceutics and Pharmacokinetics An Introduction*," 2nd Edition, Revised & Expanded, New York: Marcel Derker, 1975.

14. "*Pharmacology*," Edited by Theoharis C. Theoharides, 1st Edition, Boston : Little, Brown and company, 1992 pp. 12-43.

15. Rescigno Aldo, Segre Giorgio, " *Drug and Tracer kinetics*," London : Blackwell Scientific, 1974. pp. 124-147.

16. Rogers, H. J., Spector, R. G., Trounce, J. R., " *A Text Book of Clinical Pharmacology*," London : Hodder and stoughton, 1981. pp. 1-25.

17. Rowland Malcolom, Tozer, Thomas N., " *Clinical Pharmacokinetics : Concepts and Applications*," 2nd Edition, Philadelphia : Lea and Febiger, 1989. pp. 63-90.

18. Shargel Leon, Yu, Andrew B. C., "*Applied Biopharmaceutics and Pharmacokinetics*," 2nd Edition, Sydney : Appleton - Century -Crofts, 1985. pp. 37-55, 213-237.

19. Simon William, "*Mathematical Techniques for Physiology and Medicine*," London: Academic Press, 1972. pp. 23-39, 84-97, 194-208.

20. Smith, Cedric M., Reynard, Alan M., "*Text Book of Pharmacology*," Philadelphia : W. B. Saunderrs, 1992. pp.59-71.

21. Weir, Maurice D., "*A First Course in Mathematical Modeling*," California: Brooks/Cole Publishing, Monterey, 1985. pp. 316-322.