GRADING SHEET - MODELLING PROJECTS - 6.337

STUDENT NAME: Paul Dyck
PROJECT TITLE: Drug Dosage

GRAMMAR, SPELLING	5	dosage repeatedly misspelled.	4
DESCRIPTION OF PROBLEM	5	not bad but often convoluted. — did not help new.	5
IDENTIFICATION OF VARIABLES AND PARAMETERS	5		4
ASSUMPTIONS, INCLUDING REASONS AND DESCRIPTION	10		8
MATHEMATICAL ANALYSIS	20	sloppy notation, analysis incomplete	10
CONCLUSIONS AND SUGGESTIONS FOR IMPROVEMENT	5		3
EXAMPLE(S)	5	asthma! good	5
REFERENCES	5	none that I didn't give him.	5
ADDITIONAL COMMENTS: Copied (often almost verbatim) from Giordano & Weir.		TOTAL (OUT OF 60)	~~44~~ 49.

A Model for Drug Dosage

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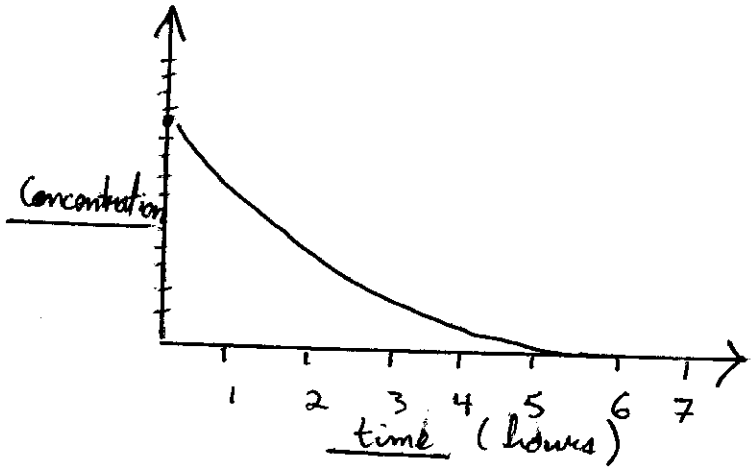
5713511

6.337 - Mathematical Modelling
Prof. T. Berry
Friday April 07, 2000

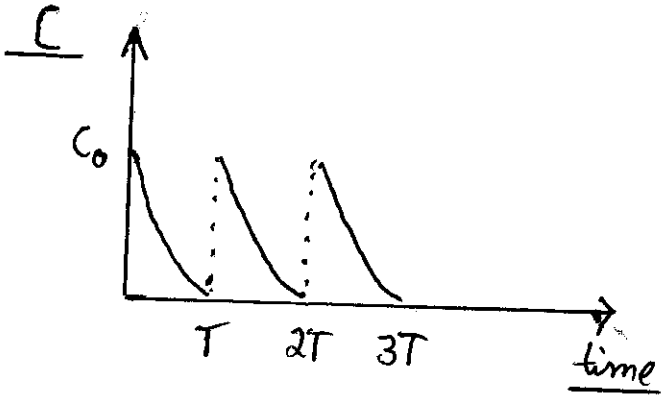
The question as to how large a dose of a drug we prescribe for a patient and how often we administer the drug is a question of great signifigance in the field of pharmacology. Most drugs have two levels which need to be considered. These are the level of "insignigance", and the level of danger. If you remain under the first the drug is essentially of no use, and if you go above the latter the drug could possibly be fatal to the patient

So we want to try to find out how we can vary the doses and the dosage schedule (time between doses) in order that the drug will be both effective and safe.

The concentration in the blood resulting from a single dose will normally decrease as time passes, as a result of the drug being eliminated from the body (see figure PD-1). However, we would like to see what will happen to the concentration of the drug in the blood as we repeat doses on a regular basis. If H is to denote the highest safe level and L the lowest level of the drug being effective, what we would like to do is administer an initial dose of C_0 with time T between doses so that the concentration of the drug in the bloodstream remains between these two levels during the duration of the interval T.



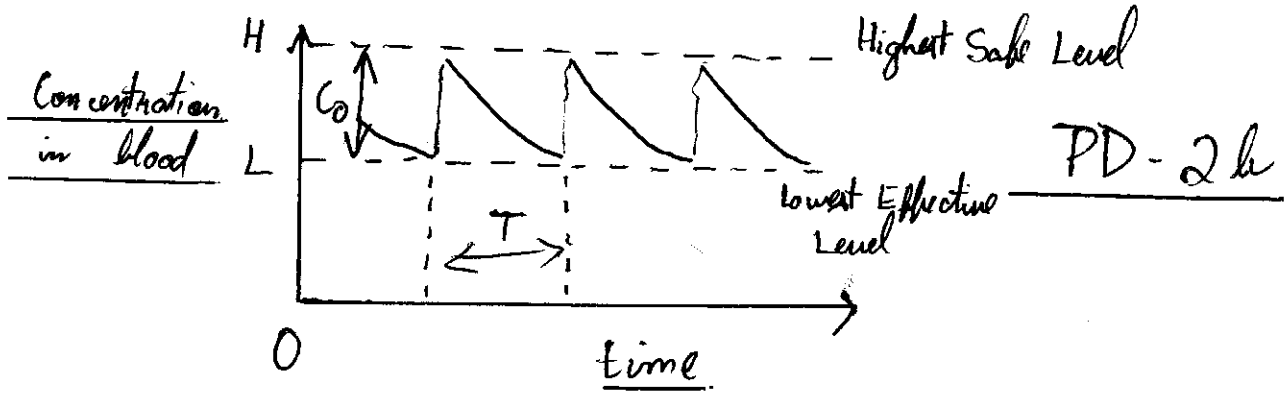
PD - 1



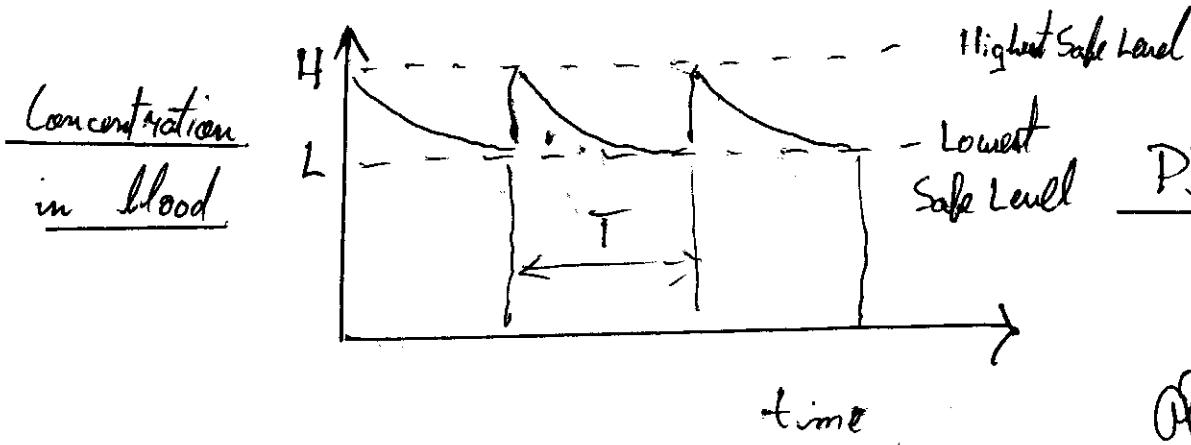
PD - 2a

graph not very representative 2

We will now look at a number of ways in which the drugs might be administered. In Figure PD-2a. the gap between subsequent doses is large enough that there is essentially no buildup of the drug in the body. To put it another way , the "residual concentration" from prior doses is for all practical purposes zero. Alternatively, in Figure PD-2b. the gap or interval between doses relative to the amount administered and the decay rate of drug-concentration is of the nature that there is a residual concentration existing each time the drug is administered after the first dose. Moreover, this residual level appears to be approaching a limit as can be seen in the graph. Our concern will be to determine if this is the case, and if so what is this limit. What we ultimately want to do when we prescribe drugs is to determine the amount per dose and also the time interval between doses so that the lower level L is reached quickly and after that the concentration is maintained between the lowest level L and the highest level H as we see in Figure PD-3. To start we will determine the residual level, which is dependant upon our assumptions for the drug assimilation rate into the bloodstream, and the rate of decay after assimilation..



PD - 2b



PD - 3

again this graph is not very representative

So that we may be able to solve the problem, let's now consider the factors that determine the concentration C(t) of the drug in the bloodstream at any given time t. Beginning with

C(t) = f(decay rate, assimilation rate, dosage amount, doseage interval,...)

and various other factors including body weight and blood volume. To simplify our assumptions, we will assume that body weight and blood volume are constants (for an average over a specific age group), and that concentration level is the most important or critical factor in determining the effect of a drug.

Now we would like to come up with some complementary or sub-models for decay and assimilation rates.

Let's now look at the elimination of the drug from the bloodstream. In all likelihood this would be a discrete phenomenon at a microscopic level, but we will approximate it by a continuous function. After all when is the last time you saw a molecule of medication. Clinical experiments (slightly more reliable than high school and university lab experiments) have shown that the decrease in the concentration of a drug in the bloodstream will be in proportion to the concentration of the drug in the bloodstream. In mathematical language, this assumption means if we are to claim the concentration of a drug in the bloodstream at time t is a differentiable function C(t), we will have

$$C'(t) = -kC'(t) \qquad \text{(SM-1)}$$

Here k is a positive constant, called the elimination constant of the drug. C'(t) is negative as we would expect if we Are talking about a decreasing concentration of the drug. Normally the quantities in Eqn. SM-1 are measured as follows: the time is given in hours, C(t) is milligrams per milliliter of blood (mg/ml), C'(t) is mg/(ml*hr), and k is 1/hr.

Let us now assume that the concentrations H and L can be determined by means of experiment for a given population for instance an age group. (This will be elaborated on later.). We will now set the drug concentration for a single dose at the following level:

$C_0 = H - L$

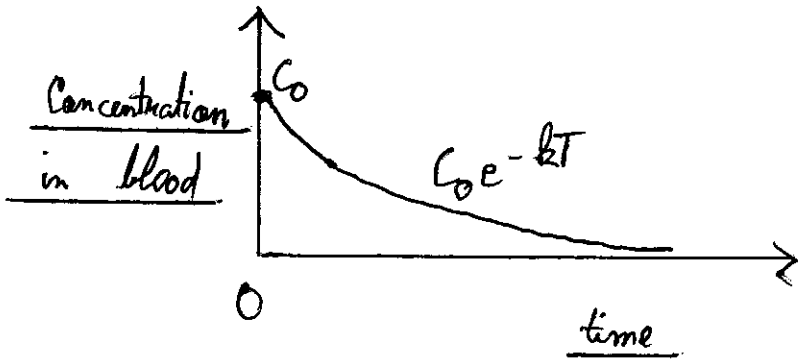
If we make the assumption that C is the concentration at $t = 0$, then we have the following model:

$$\frac{dC}{dt} = -kC, \qquad C(0) = C_0 \qquad \text{(SM-3)}$$

These variables can be seperated in Eqn. SM-3 and the model solved in the same way as for a Malthusian model of population growth. The solution to this model is

$$C(t) = C_0 e^{-kt} \qquad \text{(SM-4)}$$

To obtain the concentration at time $t > 0$, multiply the initial concentration C_0 (when $t = 0$) by e^{-kt}. The graph of C(t) looks like the graph of Figure PD-4.



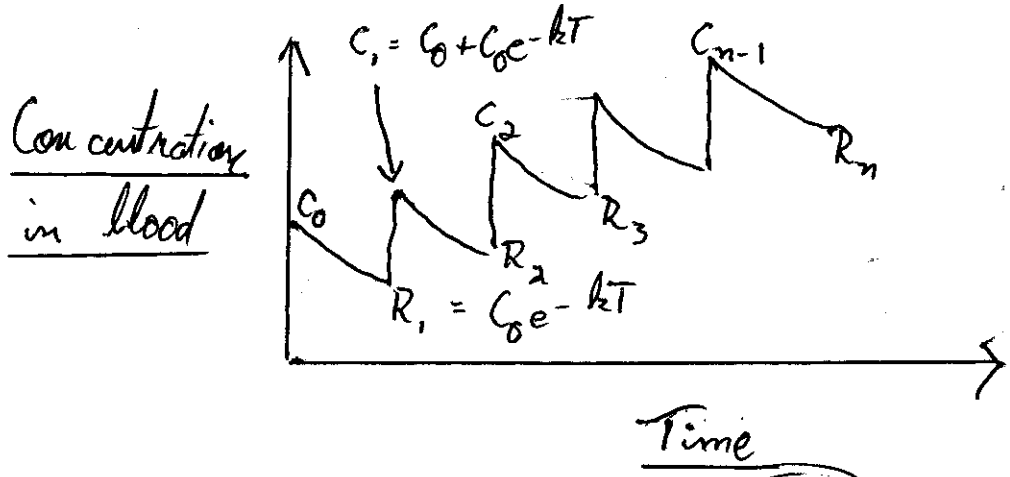
PD-4

Having made the assumption in regards to how drug concentration decreases with time, let's look at how the concentration increases again with time when drugs are given to the patient. We assume that when a drug is taken, it is distributed so quickly throughout the blood that the graph will be vertical for practical purposes. In other words we assume an immediate rise in the concentration of the drug whenever the drug is given. Clearly this won't likely be as valid an assumption for an oral drug such as Tylenol or perhaps Jolly Ranchers. We are thinking more along the lines of a drug that would be injected directly into the bloodstream. We want to see how

the drug will accumulate in the bloodstream with doses that are repeated.

Consider what will happen to the concentration C(t) when a dose that is capabable of raising the concentration by C_0 mg/ml each time it is given is administered at regular fixed time intervals of duration or length T.

Let the first dose be administered at time t = 0. In accordance with our model Eqn. SM-4, after T hours have elapsed, the remainder or residual $R_1 = C_0 e^{-kT}$ will remain in the blood at which point the second dose will be administered. As a result of our assumption in regards to the drug concentration which we discussed prior, the level of concentration instantaneously rises to $C_1 = C_0 + C_0 e^{-kT}$. After T hours pass again, the residual $R_2 = C_1 e^{-kT} = C_0 e^{-kT} + C_0 e^{-2kT}$ remains in the blood. This type of accumulation of the drug in the blood is depicted in the graph in Figure PD-5 below.



PD-5

Now, we need to find a formula for the nth residual R . If we let C_{i-1} be the concentration at the outset of the ith interval and R_i the residual concentration at the end of it, we can easily obtain table PD-6 that follows.

PD-6

i	C_{i-1}	R_i
1	C_0 — multiply by e^{-kT} →	$C_0 e^{-kT}$
2	$C_0 + C_0 e^{-kT}$ ← add C_0	$C_0 e^{-kT} + C_0 e^{-2kT}$
3	$C_0 + C_0 e^{-kT} + C_0 e^{-2kT}$	$C_0 e^{-kT} + C_0 e^{-2kT} + C_0 e^{-3kT}$
⋮	⋮	⋮
n		$C_0 e^{-kT} + \cdots + C_0 e^{-nkT}$

From the table we have :

$$R_n = C_0 e^{-kT} + C_0 e^{-2kT} + \cdots + C_0 e^{-nkT} \qquad \text{SM-5}$$

$$= C_0 e^{-kT} (1 + r + r^2 + \cdots + r^{n-1})$$

where algebraically we can verify (letting $r = e^{-kT}$) that

$$1 + r + r^2 + \cdots + r^{n-1} = \frac{1 - r^n}{1 - r}$$

so substitution for r gives the result :

$$R_n = \frac{C_0 e^{-kT} (1 - e^{-nkT})}{1 - e^{-kT}} \qquad \text{SM-6}$$

It is clear that as n becomes very large the number e^{-nkT} is very nearly 0. As a result, the sequence of the remainders or R `s has a limiting value which is approached. We will call this limiting value R.

$$R = \lim_{n \to \infty} R_n = \frac{C_0 e^{-kT}}{1 - e^{-kT}}$$

or,

$$R = \frac{C_0}{e^{kT} - 1} \qquad \text{SM-7}$$

In summary, if a dose is capable of raising the concentration by C_0 mg/ml and is repeated at intervals of T Hours, then the limiting value R of the residual is given by formula SM-7. The number k in this formula is

the elimination constant of the drug.

From Table PD-6 the concentration C_{n-1} at the beginning of the nth interval is given by

$$C_{n-1} = C_0 + R_{n-1} \qquad \text{SM-8}$$

If the desired dosage level must approach the highest safe level as pictured in Figure PD-3, then

We want C_{n-1} to approach H as n becomes large. That is,

$$H = \lim_{n \to \infty} C_{n-1} = \lim_{n \to \infty} (C_0 + R_{n-1}) = C_0 + R$$

Combining this result with $C_0 = H - L$ gives us

$$R = L \qquad \text{SM-9}$$

Another way of looking at what happens to the residual concentration R for different intervals T between doses, is to look at the ratio of R / C_0. This is a dimensionless ratio given by

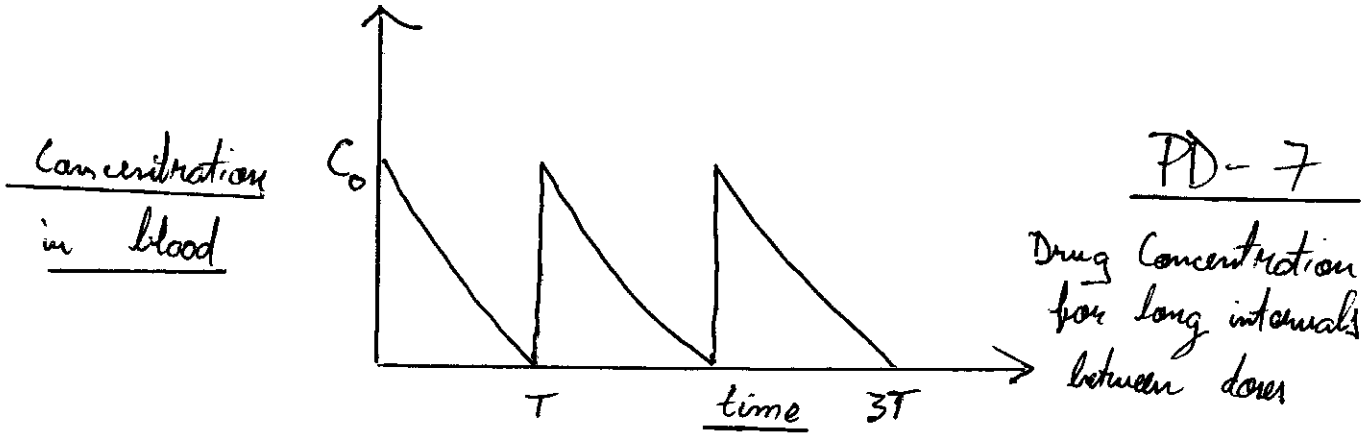
$$\frac{R}{C_0} = \frac{1}{e^{kT} - 1} \qquad \text{SM-10}$$

Equation SM-10 says R/C_0 will be close to 0 whenever T (time between doses) is long enough to make $e^{kT} - 1$ sufficiently large. We can see from Table PD-6 that each intermediate value of R_n is obtained from the previous R_{n-1} by adding the positive quantity $C_0 e^{-nkT}$. This means that all the R_n's are positive, because R_1 is positive. It also means that R is larger than each of the R_n's. To put it another way

$$0 < R_n < R$$

for all n.

This implies that for drug dosage whenever R is small, the R_n's are even smaller. In particular, when T is long enough to make $e^{kT} - 1$ significantly large, the remaining or residual concentration from each dose is effectively non-existant. Basically, each dose of the drug can be regarded as an independent dose. The graph of this would look as follows in Figure PD-7



PD-7

Drug Concentration for long intervals between doses

Alternatively, we can have a situation where the time interval between doses is so short that e^{kT} is not only slightly larger than 1, so that R/C_0 is significantly larger than 1. As R_n becomes larger, the concentration C_n after each dose becomes larger. The loss during the time period after each dose increases with larger C_n from Eqn. SM-3 (C decreases proportionally to the amount of C that is present). Eventually, the drop in concentration after each dose becomes for all intents and purposes the same as the rise in concentration C due to each dose. When this situation occurs (the loss in concentration being equal to the gain), the concentration will alternate between R at the end of each dosage period and $R + C_0$ at the start of each period. This situation is represented in Figure PD-8.

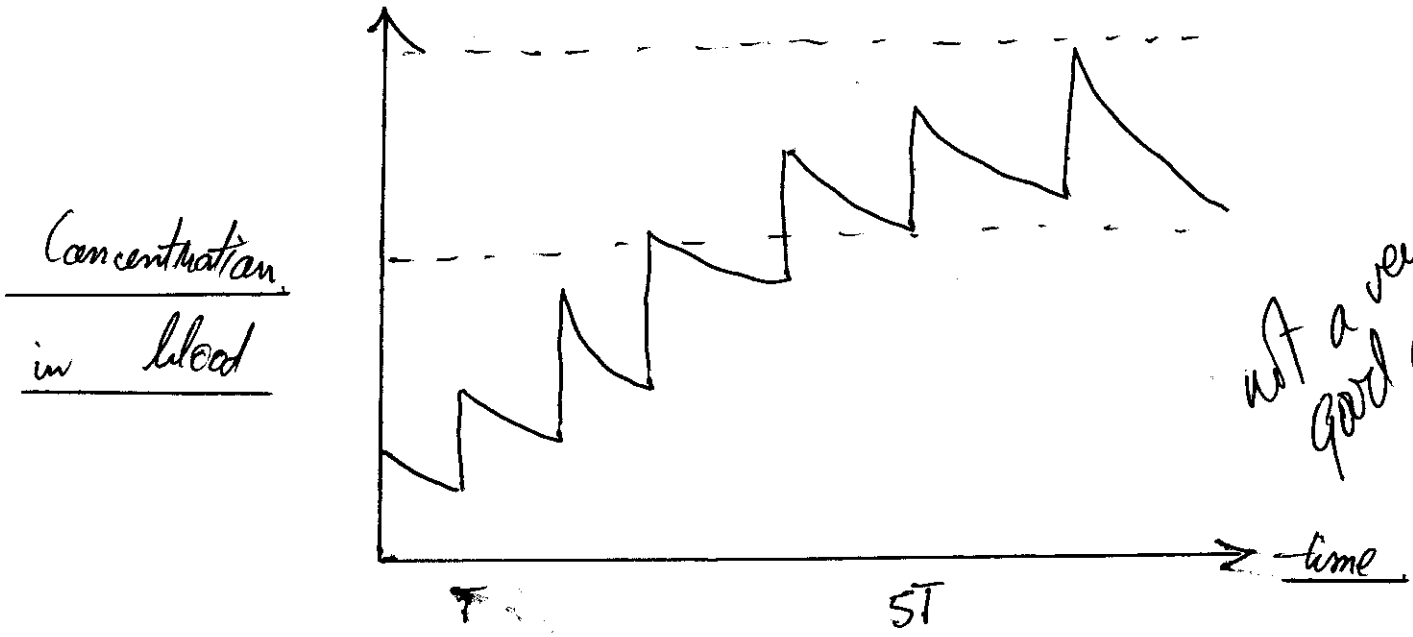
Suppose we have a drug that is not effective below the concentration L and is harmful above some higher concentration H, as discussed earlier. Let us assume now that L and H are "safe" guidelines in order that a person would not suffer a major overdose if the drug concentration rises slightly above H, and that we do not need to begin an accumulation process if the drug falls slightly below L. For the convenience of the patient we might choose to adopt the strategy of maximizing the time between drug doses by setting R = L and $C = H - L$, as we have indicated before. Substitution of R = L and $C_0 = H - L$ in Eqn. SM-7 gives us

$$L = \frac{H - L}{e^{kT} - 1}$$

We can solve this equation for e^{kT} to obtain

$$e^{kT} = H / L$$

PD-8



not a very good graph

Buildup of Drug Concentration when the interval between doses is short.

Taking the logarithm of both sides of this equation and dividing the result by k gives the desired dose schedule.

$$T = \frac{1}{k} \ln \frac{H}{L} \qquad \text{SM-11}$$

To reach an effective level in a rapid manner, one could initiate the medication with a primary or "loading dose", that will give us an immediate blood concentration of H mg/ml. This medication can then be administered every $T = (1/k) \ln (H/L)$ hours by a dose that raises the concentration by $C_o = H - L$ mg/ml.

Our model for administering a safe and effective dose of drug concentration seems to be a reasonable one. It is consistent with the common medical practice of giving a large dose at the outset and smaller doses following this. The model is also based on the assumption that the decrease in the concentration of the drug in the bloodstream is in proportion to the concentration itself, which has been verified clinically. The model also provides us with a quantitative way to predict the concentration levels under varying circumstances for dose rates, using Equation SM-7. Therefore, the drug may be tested to determine experimentally the minimum effective level and the highest safe level within safe guidelines to allow for possible oversights in the modelling process. After this we can use formulas SM-2 and SM-11 to prescribe a safe and effective doseage of the drug (assuming the loading dose is significantly larger than subsequent doses of C_o). As a result our model proves to be a useful one.

Now we'll look at a few examples of how this model might be used in practice.

H=eL

Say we know that k = 0.05 / hr. and the highest level that is a safe concentration is e times the lowest level that is safe and effective for the drug in question. We can then find the time between successive doses that will allow us safe but effective concentrations.

$$\frac{1}{k} \ln\left(\frac{e \cdot L}{L}\right) = \frac{1}{k} \ln e = \frac{1}{k} = \frac{1}{0.05} = 20 \text{ hours.}$$

Perhaps in this instance we know the "fatal" concentration , or the "ineffective" concentration we can easily determine the appropriate dosage. We simply multiply e times L to get H or divide H by e to get L. We can then subtact L from H and find C_0

Next we might want to answer how long our drug in question will remain effective.

We'll look at an instance where k = 0.02 / hr. and the smallest level of effectiveness is 0.03 mg. / ml. Now consider a dose that produces a concentration of 0.1 mg. / ml.

$$C_0 = 0.1 = H - L$$

$$H = 0.1 + 0.03$$

$$= 0.13 \text{ (mg. / ml.)}$$

Therefore $T = \frac{1}{0.02} \ln\left(\frac{0.13}{0.03}\right) \approx 73$ hours

Perhaps it is not only ineffective but dangerous if the level of the drug falls below a certain level. What we would like to do is determine a scheme which is convenient for the patient, and more importantly insures their safety.

We'll look at the example where H = 2 mg. / ml., L = 0.5 mg. / ml., and k = 0.02 / hr. Using Formula SM-2 we have

$$48 = \frac{1}{0.02} \ln\left(\frac{H}{L}\right)$$

Simplifying and solving for the ratio of H / L we have 2.61 = (H / L). If we divide the maximum loading dosage of 2 by this ratio of 2.61 we can obtain a corresponding concentration level for L. This dosage concentration is 0.77. Now we form the difference of H – L (C_0)

This gives us a value of 1.23 mg. / ml. Hence we conclude that in order for the patient's convenience they Take an initial dose of 2 mg. / ml. and thereafter take a dose of 1.23 mg. / ml. every 48 hours.

Let's now look at one final example. Patients with asthma have constriction of the airways in the lungs and as a result difficulty breathing out. This condition can be relieved by introducing the drug theophylline into the bloodstream. This is accomplished by injecting the drug aminophylline, which the body quickly converts to theophylline. Once present in the blood the drug is steadily excreted from the body via the kidneys. In other words unless there is a restoration of the drug aminophylline, the concentration of theophylline will fall.

It is known however from experimental evidence that theophylline has hardly any therapeutic effect if it's concentration is below 5 mg. / l. , and that concentrations of above 20 mg. / l. are likely to be toxic. So we are faced with a situation where we want to maintain the level of theophylline in the bloodstream between 5 mg. / l. and 20 mg. / l.

Measurements from experiments can be obtained by injecting a known dose of theophylline into a patient allowing time for it to diffuse through the bloodstream, and find the various concentration levels in blood samples taken at regular time intervals. We will know the initial quantity put into the bloodstream and the concentration at various later times, but it isn't possible to know these two values at the same time. The data that follows is from such an experiment.

Initial Quantity = 300 mg.

Concentration, mg ./ l	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

Another observation made from experiment is that the apparent volume of distribution (V litres) and the patient's weight (W kg.) are related by the straightforward relationship $V = 0.5 \cdot W$. Thus the dose needed to achieve a required initial theophylline concentration can be inferred from the patient's weight alone : the dose in mg. D to obtain a 12 mg. / l concentration in a 50 kg. Patient is obtained from

$$(D / V) = 12 ,$$

so that

$$D = 12\,V = 6\,W = 300 \text{ mg.}$$

So, now we have some data and it's pretty much a safe bet that we might learn something about the nature of how our drug is absorbed by plotting the data on a graph. We have the figure EXPONENTIAL (see least squares appendix) named this way because it reminds us of an exponential curve.

When we re-plot the data as ln C vs. time our gut feeling or hunch is confirmed (see figure STRAIGHT in least squares appendix)We now expect that all of our analysis will yield something of the nature $C(t) = C_0 e^{-kt}$. To validate this theoretically we note thatthe drug is removed by the kidneys at a rate proportional to the amount present. Thus if Y(t) is the amount of drug present at time t, then

$$dy/dt = -kY(t).$$

We also know, however, that the amount of drug and the concentration are connected via the apparent volume :

$$C(t) = Y(t) / V.$$

Therefore $dc/dt = -kC(t)$, giving us

$$C(t) = C_0 e^{-kt} \text{ as expected.}$$

To tidy all of this up and complete this stage of analysis, we need to determine what our parameters are for C_0 and K. The linear graph STRAIGHT, is ln C(t) vs. time. We of course have the equation of this straight line being

$$\ln C(t) = \ln C_0 - K t.,$$

so the intercept on the graph is $\ln C_0$ and the slope is -K.

Now it's pretty clear that the next question you're going to ask is "So big-shot tell me now how you find those parameters. I like that attitude because it shows that you're using ~~you're~~ your head, and just so you're satisfied I will say that the method we will use is least-squares (I will leave the explanation of least-squares for another day). The important thing is that we now have values for our parameters. These are :

C_o = 12 mg. / l, and K = 0.17 / hr.

and it agrees well with the data we have obtained from our patient of 50 kg.

As we discussed earlier we can use this information to decide on the appropriate dose and dosage schedule. Using this time H as our limit for R we have a limit that tends to the value of $C_o / (1 - e^{-kt})$.

Well this has all become rather mathematical, so why don't we try to bring this discussion back down to earth (Sure that phrase was straight from the book but I liked it so much I thought it had to be used.). We're going to decide on the dose D and the interval T to keep the drug in the effective and safe range of :

$$5 \leq C(t) \leq 20$$

For our patient (50 kg) we already have K = 0.17 / hr. , and it seems obvious that we need our limit of $C_o / (1 - e^{-kt})$ to be 20 mg. / ml. Therefore we have $C = 20 (1 - e^{-kt})$, and we can choose convenient values of T and obtain our corresponding dose $D = 25 C_o$ (remembering V = 0.5 W and (D / V) = C(t)). This results in the following table, where the concentration just before the second dose is also listed.

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

We now are able to observe that when we choose T = 4 hours the concentration never leaves the desired range of effectiveness. As a result in this case unless a higher concentration level near 20 mg./ l is preferred to one that is just above 5 mg. / l , there is no reason to give a large initial dose and smaller doses thereafter. We will therefore give a dose of 250 mg. every 4 hours.

One deficiency in this model is the assumption that the drug is instantaneously diffused in the bloodstream. This could however be dealt with although it would become a more complex and involved problem.

Least Squares Appendix

Least Squares performed using Matlab.

```
Commands to get started: intro, demo, help help
Commands for more information: help, whatsnew, info, subscribe

» X=[1 10; 3 7; 5 5; 7 3.5; 9 2.5; 11 2; 13 1.5; 15 1; 17 7; 19 .5]

X =

    1.0000   10.0000
    3.0000    7.0000
    5.0000    5.0000
    7.0000    3.5000
    9.0000    2.5000
   11.0000    2.0000
   13.0000    1.5000
   15.0000    1.0000
   17.0000    7.0000
   19.0000    0.5000

» plot (X(:,1),exp (12.657)*exp(-0.173*X(:,1)))
» hold on
» plot(X(:,1),X(:,2),'x')
» t = X(:,1);
» t

t =

     1
     3
     5
     7
     9
    11
    13
    15
    17
    19

» A = [sum(t.^2) sum(t); sum(t) length(t)]

A =

        1330         100
         100          10

» y = log(X(:,2))

y =

    2.3026
    1.9459
    1.6094
    1.2528
    0.9163
    0.6931
    0.4055
         0
    1.9459
   -0.6931

» B = [sum(t.*y); sum(y)]

B =

   66.0098
   10.3784

» S = A\B

S =
```

```
    1.0000   10.0000
    3.0000    7.0000
    5.0000    5.0000
    7.0000    3.5000
    9.0000    2.5000
   11.0000    2.0000
   13.0000    1.5000
   15.0000    1.0000
   17.0000    7.0000
   19.0000    0.5000


X =

    1.0000   10.0000
    3.0000    7.0000
    5.0000    5.0000
    7.0000    3.5000
    9.0000    2.5000
   11.0000    2.0000
   13.0000    1.5000
   15.0000    1.0000
   17.0000    0.7000
   19.0000    0.5000

» y = log(X(:,2))

y =

    2.3026
    1.9459
    1.6094
    1.2528
    0.9163
    0.6931
    0.4055
         0
   -0.3567
   -0.6931

» B = [sum(t.*y); sum(y)]

B =

   26.8659
    8.0758

» S = A\B

S =

   -0.1633
    2.4407

» clf
» plot(t, S(1)*t + S(2))
```

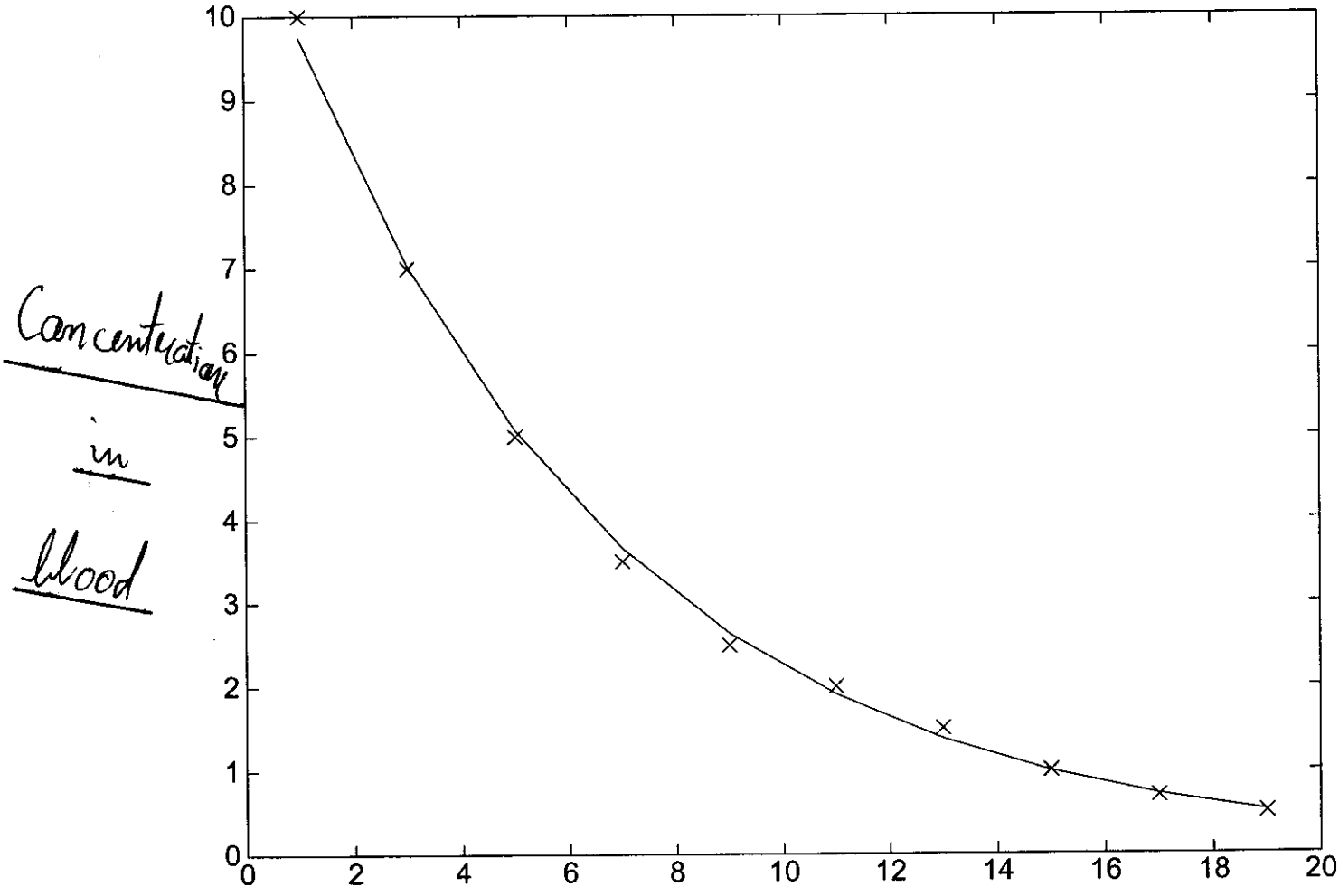
$K \simeq .17$

$\ln C_0 \simeq 12$

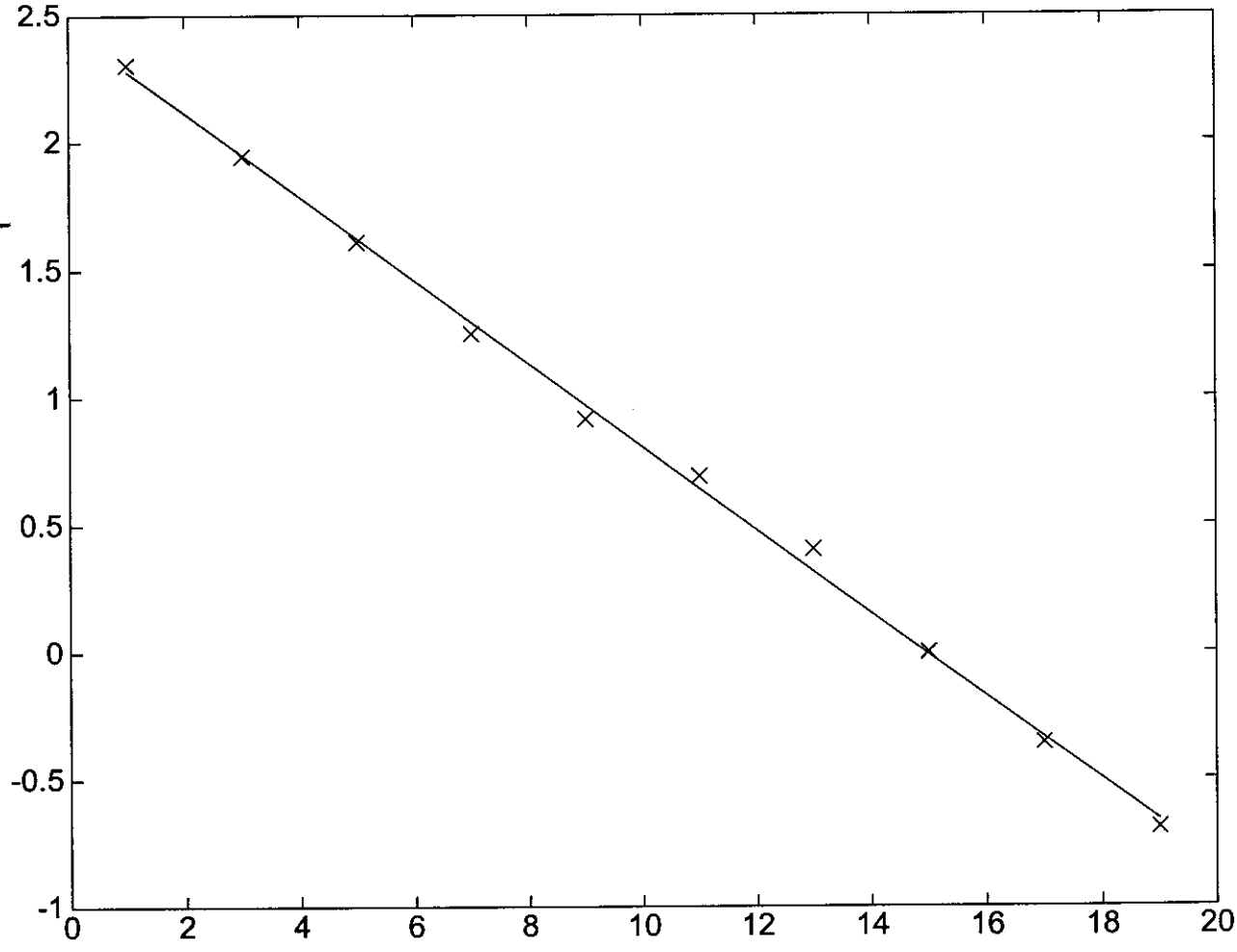
```
» plot(t, S(1)*t + S(2))
» figure(3);
» plot(t, exp(S(2))*exp(S(1)*t)
??? p(S(2))*exp(S(1)*t)
```

```
» plot(t, exp(S(2))*exp(S(1)*t))
» hold on;
» plot(t, X(:,2), 'x');
```

EXPONENTIAL



STRAIGHT



ln C(t)

Time (hours)

C(t) - denotes concentration

Bibliography

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2. D.N. Burghes, D. Huntley, J. McDonald; Applying Mathematics a course in mathematical modelling; pp. 124 - 129; Ellis Horwood Limited © 1982