QUANTITATIVE PHARMACOKINETICS

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Quantitative Pharmacokinetics

Modern medicine is one of the single, most influential aspects of life in the first world. The administration of therapeutic drugs is at least of indirect concern to almost everyone in our society; and we all tend to assume that the drugs we take will actually have the desired effect.

Pharmacokinetics is the study of the time course of drug distribution, metabolism, and excretion; a quantitative analysis of the dynamics of drug concentrations in the body. As a subject in the area of mathematical modelling, it is a merging of differential equations with pharmacology and biology. Pharmacokinetics is an attempt to describe mathematically how the concentration of a drug in the body varies with time. It has many obvious uses in a clinical context, most notably the determination of dosage regimens for optimal therapy.

It is a well known medical fact that numerous drugs have both a minimum effective level, below which they are not effective, and a maximum or toxic level, above which they are actually dangerous. The problem in terms of pharmacokinetics then is *to determine a safe but effective level of drug within the body throughout the length of therapy*.

1.1 ASSUMPTIONS

There are certain aspects that will impede us from the start. Namely, that the actual enzyme dynamics and physiology are beyond the scope of this paper. Also it is extremely difficult if not

impossible to attain relevant data right at the "action sites" where a given drug is having its effect. We will therefore assume right from the outset that **the magnitudes of both the desired response and toxicity are functions of indirectly measured drug concentrations.**

Drug absorption, distribution and excretion are most probably discrete events, but due to the "small" size and relative effect of those events, it seems reasonable to model them as continuous phenomenon.

Now, if we let C(t) represent the concentration of some drug at time t, then our problem becomes determining the form of this relation. In reality C as a function is tremendously complex, a more accurate description might be:

C (drug elimination rate, assimilation rate, dosage, blood volume, age, weight, sex, type and degree of illness, genetic structure, diet,....)

For our purposes, we will assume that the latter factors, beginning with blood volume, are all approximately constant and average.

1.2 MODELS

Let us begin with the logical observation that:

Rate of change of drug in the body	=	Rate of absorption	−	Rate of elimination [1]

(A)

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[1]Rowland, M. and Tozer, T.; Clinical Pharmacokinetics; (Lea and Febiger, Philadelphia, 1980); p.15. All references following this will be noted by the author's name in brackets, followed by a formal bibliographical reference.

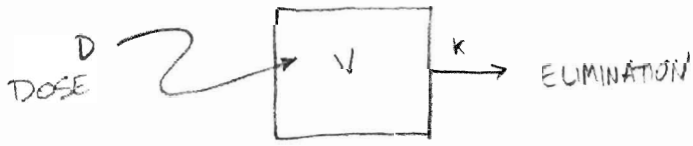
1.3 THE ONE COMPARTMENT OPEN MODEL

The simplest abstraction of the body in terms of pharmacokinetics is to depict the body as a single, kinematically homogeneous unit. This type of model is useful for analyzing drugs that distribute themselves rapidly throughout the body.

As stated earlier, we employ indirect testing to determine drug concentrations. We do not assume that concentrations are equal throughout all tissues and fluids in the body, but rather that **the rate of change of drug concentration in the plasma reflects the change in drug concentration in all body tissues and fluids.** In this sense, the blood and "action sites" can be viewed as a single or central compartment.

1.3.1 The One Compartment Open Model with Single Dose Bolus Intravenous injection

Schematically, this model can be viewed as the following:



Assumptions: (a) The body is represented by a single compartment with volume V.

(b) There is no distribution phase. A "spike" dose is injected into the central compartment via an I.V. and is distributed instantaneously at time t=0.

(c) Elimination from the body is said to be first order.

Elimination of drugs occurs via several pathways, for example urinary and biliary excretion, biotransformation in the liver, glomerular filtration and tubular secretion in the kidneys (Rowland 80). Plausibly, not all of these phenomenon are describable in terms of simple linear relationships. However, we will be assuming that they all can be approximated by linear functions. That is, we will be assuming that **the rate of elimination of drug from the body, at any time, is directly proportional to the amount of drug that is in the body at that time.** This is often described as first order elimination. If we let **A** denote the amount of drug in the body, and **t** time, then:

$$dA/dt = -kA \quad \text{where } k>0.$$

k is called the elimination rate constant and can be seen to represent the relative instantaneous rate of decrease in the amount of drug in the body. Separating and integrating we see that:

$$A=A_0e^{-kt} \qquad (1)$$

where A_o = initial amount or dose. Now if **C** = the concentration of drug in the body, we easily see that **C** is directly proportional to **A** and inversely proportional to **V** = volume so that: **C=A/V**. Thus equation (1) becomes:

$$C=C_0e^{-kt} \qquad (2)$$

where C_o = initial concentration. It should be noted that V, above, is not really a true volume in a strict sense of the word. V is most frequently called the apparent volume of distribution. As noted in the assumptions above, a drug in the central compartment

is not evenly distributed. Now, C=A/V implies A=CV is true only for uniformly distributed solutions; so calculations from concentrations of drugs in blood plasma can only yield apparent volumes, which will vary from drug to drug depending on their chemical properties.

Plotting C(t) we can see that drug levels decreases with time, as could be expected. As this is simply another application of Malthusian decay, no further analysis will be presented.

[It seems implicit in numerous books that this result was initially determined by a linear least squares fit to logarithmically transformed data some time around 1937. As every source I have encountered states these results with little justification, I will assume that this, and the apparent plausibility of the model, implies a reliable correlation between actual data and model predictions.]

1.3.2 The One Compartment Open Model with Multiple Dose Bolus I.V. Injection

The same assumptions hold as for the single dose case above, but now we are administering a dose of size D at t=0 and at regular time intervals T. Since it takes an infinite amount of time for a

drug to be excreted from the body, according to our model, repeated doses will result in an accumulation of drug. Suppose that due to our assumption of instantaneous distribution, a concentration C_o is present after the initial injection. After T hours have elapsed, a residual $R_1=C_oe^{-kT}$ remains in the central compartment. At this time, according to the scheme as outlined, a second injection is given and the concentration of drug immediately rises to $C_1=C_o + C_oe^{-kT}$. After T hours again, we have a residual $R_2 = C_1e^{-kT} = C_oe^{-kT}+C_oe^{-2kT}$. Clearly, $R_n=C_oe^{-kT}(1+r+r^2+r^3+...)$ where $r=e^{-kT}$, and R_n is the residual amount of drug in the central compartment after n periods of T hours have expired. But since $k>0$ and $T>0$, $e^{-kT}<1$ so the above series is simply a geometric one and:

$$R_n=\frac{C_0e^{-kT}(1-e^{-nkT})}{1-e^{-kT}} \qquad (3)$$

Also note that:

$$R=\lim_{n\to\infty}R_n=\frac{C_0e^{-kT}}{1=e^{-kT}}=\frac{C_0}{e^{kt}-1} \qquad (4)$$

Where R is seen to be the limiting value of the sequence of R_n's (Giordano, Wier 85).

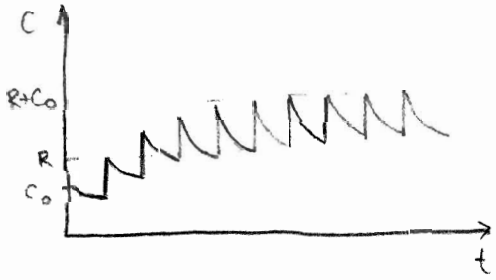
1.3.3 Determining Dosage Regimens

We easily see that, because R_1 must be positive and because all the R_n's are positively autocorrelated, all the residual concentrations must also be positive; so that if T is finite, there must (in theory) be some build-up of drug in the system and that

for all n, $0 < R_n < R$. But what effect does the magnitude of T have? From the form of equation (4) we see that if T is sufficiently long to make $e^{kT}-1$ large then, the residual concentration will be negligible.

Now suppose that the time T is short enough so that e^{kT} is not much greater than 1. As discussed earlier, the sequence of residuals will be strictly increasing. We know that as R_n becomes larger so does C_n and because **dC/dt=-kC** the loss of drug during T increases with C_n. Eventually, the drop in concentration after time T will become negligibly close to the amount of drug injected and the concentration of drug in the compartment will fluctuate between the two values $R + C_o$ and R.

Fig 3.



NOTICE HOW RATE OF LOSS INCREASES DURING THE FIRST FEW DOSING INTERVALS

As mentioned earlier, most drugs have minimum effective concentrations as well as toxic levels, and the main objective of pharmacokinetics is to determine a safe, but effective dosage regimen. If we let P^* be the concentration at which a certain drug becomes poisonous and E^* it's minimum effective level, then because of the inherent variability in these measurements, we can work with P and E which represent safe guidelines for P^* and E^*. For instance if P^* and E^* were analyzed to be normally distributed random variables then choose $P=P^*-2$(standard deviation of observed toxic

levels) and E similarly. Now if we let R=E and C_o+R=P, because these are the two values between which drug concentrations vary, we see that C_o=P-R. Substituting into (4) we get:

$$E=\frac{P-E}{e^{kT}-1}$$

Solving for T we get:

$$T = 1/k \ln(P/E)$$

where k,P and E are determined in reference to some particular drug. Note that a "loading dose", which will bring about a drug concentration P, may be administered initially and then be followed by subsequent doses, which result in concentration rises of P-E. If the time between doses is T as calculated above then this will describe a convenient, optimal regimen.

1.4 One Compartment Model with Continuous I.V. Infusion

In determining this model, we make the same assumptions as above, but now we are adding a continuous flow of drug into the central compartment at a constant rate over some time period. The main difference being there is no vertical rise in drug concentrations immediately after administration.

Let A = the amount of drug in the body
K = the first order elimination rate constant
R = the constant replenishment rate
ie) rate of infusion

then we can express the model as follows.

$$\frac{dA}{dt} = -kA + R$$ (due to simplicity, phase plane analysis will be neglected)

$k, R > 0$

$$\frac{dA}{-kA+R} = dt$$

$$\therefore \quad \frac{\ln|-kA+R|}{-k} = t + C_1$$

$$\ln|-kA+R| = -kt + C_2 \qquad C_2 = -kC_1$$

$$|-kA+R| = L e^{-kt} \qquad L = e^{C_2} > 0$$

$$A = \frac{\pm L e^{-kt} - R}{-k}$$

$$A = R/k \pm L/k\, e^{-kt}$$

now applying the initial conditions

$A(0) = 0$,

$$0 = R/k \pm L/k\, e^{0}$$

$$R \pm L = 0$$

but $R > 0$, $L > 0$ so

$$L = R$$

and

$$A = R/k\,(1 - e^{-kt}) \qquad \text{NB } A(t) > 0 \text{ since } 1 < e^{-kt} < 0 \text{ for } t > 0$$

so

$$C(t) = R/VK\,(1 - e^{-kt})$$

where $C(t)$ represents the concentration of drug

V = the apparent volume of distribution

NB $\lim_{t\to\infty} C(t) = \lim_{t\to\infty} R/VK\,(1 - e^{-kt}) = R/VK$

after infusion stops, the drug concentration undergoes only first order elimination. So follows the model

$$C(t) = C_{max}\, e^{-kt}$$ where C_{max} is the maximum concentration attained during infusion

2. continued on

2.1 THE TWO COMPARTMENT MODEL

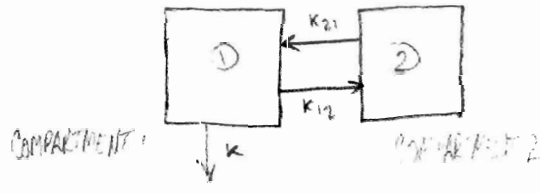
The preceding models assumed that the body reacted as a single, kinetically homogeneous unit. This assumption, however useful, is not necessarily valid for all types of drugs since we know empirically that the body is composed of a heterogeneous group of tissues. For example, many different types of tissues can each have a different affinity for different drug molecules and correspondingly, a different rate of equilibration with them. The blood and highly perfused tissues such as the liver and kidneys will have an administered drug distributed within themselves much faster than other tissues such as the bones and cartilage. In theory then, an accurate compartmental model ought to have a separate rate constant for each possible tissue wherein the drug is being distributed, ie.) a separate compartment for each tissue. Clearly though, this approach has little merit given the number of different tissues in the body, and the fact that any tissue may have radically different affinities for various drugs. However, tissues having similar characteristics may be grouped together, vastly simplifying the compartmental approach.

The simplest of these approaches is to divide the body into two groups: the central compartment, which is assumed to have instantaneous drug distribution characteristics, and the peripheral compartment which equilibrates more slowly (these are often referred to as compartments 1 and 2 respectively). Note that this classification is arbitrary, and no attempt should be made to

identify various organs with specific compartments. It is even possible to have a portion of a single organ residing simultaneously in two compartments; the only distinction made between compartments is the rate of drug distribution within that compartment. (Niazi 80)

The postulation of this kind of model was determined by sampled drug concentration data from the blood. Mono exponential curves provided a poor fit to the sampled time course distribution of many drugs while multi exponentials fit the data much better.

If we assume an instantaneous distribution in the first compartment and first order transfers between compartments along with first order elimination, then the simplest model looks like:



where $k, K_{ij} > 0$; k_{ij} represents transfer constant from compartment i to compartment j

Here, all of the elimination from both metabolism and excretion occurs in the central compartment. Using (A) we can describe this model as

$$dC_1/dt = -(K_{12}+k)C_1 + K_{21}C_2$$

$$dC_2/dt = K_{12}C_1 - K_{21}C_2$$

where C_j represents the drug concentration in compartment j

A little more discussion as to the nature of the two compartments & their interaction would be useful. Why does elimination occur from only one compartment?

Phase Plane Analysis

we have that $dC_1/dt = -(K_{12}+K)C_1 + K_{21}C_2$ $\quad K_{12}, K_{21}, K > 0$

$dC_2/dt = K_{12}C_1 - K_{21}C_2$

the system is in equilibrium when $dC_1/dt = dC_2/dt = 0$

Clearly, the origin is an equilibrium point. Now,

$dC_1/dt = -(K_{12}+K)C_1 + K_{21}C_2 = 0$

$\Leftrightarrow \quad (K_{12}+K)C_1 = K_{21}C_2$

$C_2 = \frac{(K_{12}+K)}{K_{21}} C_1$ is a nullcline of the system

and

$dC_2/dt = K_{12}C_1 - K_{21}C_2 = 0$

$\Leftrightarrow \quad K_{12}C_1 = K_{21}C_2$

$C_2 = K_{12}/K_{21}\, C_1$ is the other nullcline

so when

$C_1 = 0$ and $C_2 > 0$ then $dC_1/dt > 0$, $dC_2/dt < 0$

$C_2 = 0$ and $C_1 > 0$ then $dC_1/dt < 0$, $dC_2/dt > 0$

and

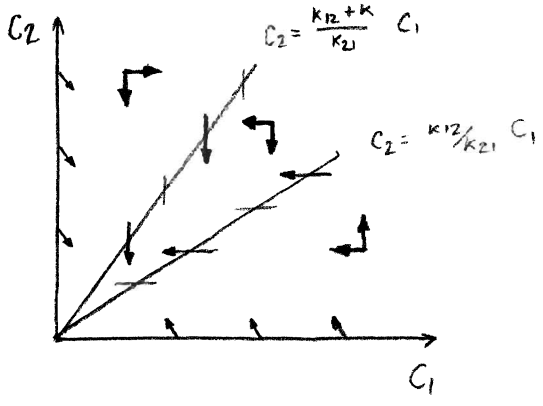
$C_1 > 0$; $0 < C_2 < K_{12}/K_{21}\, C_1 \Rightarrow 0 < K_{21}C_2 < K_{12}C_1 \Rightarrow dC_1/dt < 0$, $dC_2/dt > 0$

$C_1 > 0$; $C_2 > \frac{K_{12}+K}{K_{21}} C_1 \Rightarrow K_{21}C_2 > (K_{12}+K)C_1 \Rightarrow dC_1/dt > 0$, $dC_2/dt < 0$

$C_1, C_2 > 0$; $K_{12}/K_{21}\, C_1 < C_2 < \frac{K_{12}+K}{K_{21}} C_1 \Rightarrow K_{12}C_1 < K_{21}C_2 < (K_{12}+K)C_1$

$\Rightarrow dC_1/dt < 0$, $dC_2/dt < 0$

Combining this information on a $C_1 C_2$ plane that supresses time we can get a qualatative feel for the solutions of the model.



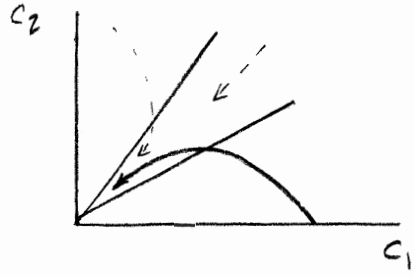
gives the direction elements in the phase plane

where ↖↓ denotes C_1 is decreasing while C_2 increases

↓↘ denotes C_1 and C_2 are decreasing

↘↑ denotes C_2 decreasing and C_1 increasing

thus we can anticipate trajectories of the form:



the dotted trajectories are mathematically feasible, but because bolus I.V. injection directly into compartment 2 is impossible, they are not physically plausible.

NB: the origin is the only equilibrium point and is seen to be stable.

also $dC_2/dC_1 = \dfrac{k_{12}C_1 - k_{21}C_2}{(-k_{12}-k)C_1 + k_{21}C_2} = \dfrac{aC_1 - bC_2}{-(a+k)C_1 + bC_2}$ where $a = k_{12}$ $b = k_{21}$ for simplicity

$$d^2C_2/dC_1^2 = \frac{\left(-(a+k)C_1 + k_{21}C_2\right)\left(aC_1' - bC_2'\right) - \left(aC_1 - bC_2\right)\left(-(a+k)C_1' + bC_2'\right)}{\left(-(a+k)C_1 + bC_2\right)^2}$$

d^2C_2/dC_1^2 is undefined if $C_1 = C_2 = 0$ or $C_2 = \dfrac{a+k}{b} C_1$

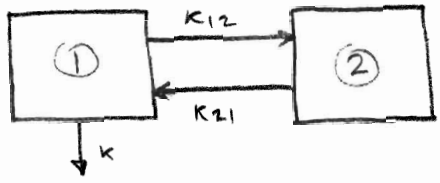
$= \dfrac{k_{12}+k}{k_{21}} C_1$ a nullcline

and $$d^2C_2/dC_1^2 = b\,\frac{\left(a(C_1'C_2 - C_1C_2')\right) + (a+k)(C_1C_2' - C_1'C_2)}{\left(-(a+k)C_1 + bC_2\right)^2}$$

$d^2C_2/dC_1^2 = 0$ if $C_1 = C_2 = 0$

so (0,0) is the only possible inflection point, however, we are only concerned with positive concentrations

again, graphically we can view the 2 compartement model with elimination through the central compartement as:



where K_{12} represents the first order rate constant for transfer from compartment ① to compartment ②, K_{21} is defined analagously, and K represents the first order elimination rate constant from compartment ①.

We can view this scheme as the following coupled system

$$\dot{C}_1(t) = K_{21}\, C_2(t) - (K_{12} + K)\, C_1(t)$$
$$\dot{C}_2(t) = K_{12}\, C_1(t) - K_{21}\, C_2(t) \qquad \text{where } K_{ij}, K > 0.$$

or more concisely as

$$\begin{bmatrix} \dot{C}_1 \\ \dot{C}_2 \end{bmatrix} = \begin{bmatrix} -(K_{12}+K) & K_{21} \\ K_{12} & -K_{21} \end{bmatrix} \begin{bmatrix} C_1 \\ C_2 \end{bmatrix} \iff \underset{\sim}{\dot{C}} = \underset{\sim}{B}\,\underset{\sim}{C} \qquad (1)$$

where C_1 denotes drug concentration in compartment 1, C_2 denotes drug concentration in compartment 2 and $\dot{C}_i = dC_i/dt$. Assuming a sol'n of the form $[C_1 \;\; C_2]^T = [A_1 e^{\lambda t} \;\; A_2 e^{\lambda t}]^T$ we find

$$0 = \begin{vmatrix} -(K_{12}+K) - \lambda & K_{21} \\ K_{12} & -K_{21} - \lambda \end{vmatrix} = \begin{vmatrix} (-a-k) - \lambda & b \\ a & -b - \lambda \end{vmatrix} \quad \text{where } a = K_{12},\; b = K_{21}$$

[ineffectual substitutions such as the above only facilitate easier algebraic manipulations without subscripts]

$$= (-a-k-\lambda)(-b-\lambda) - ab = 0$$

$$= (-a-k)(-b) - \lambda(-a-k) + \lambda b + \lambda^2 - ab = 0$$

$$ab + bk + \lambda a + \lambda k + \lambda b + \lambda^2 - ab = 0$$

$$\lambda^2 + \lambda(a+b+k) + bk = 0$$

$$\lambda = \tfrac{1}{2}\left[-(a+b+k) \pm \sqrt{(a+b+k)^2 - 4bk}\right]$$

$$\therefore \lambda = \tfrac{1}{2}\left[-(k_{12}+k_{21}+k) \pm \sqrt{(k_{12}+k_{21}+k)^2 - 4k_{21}k}\right]$$

are the roots of the characteristic equation

Note: we can show that these must be real roots by considering the discriminant of the above expression

$$(k_{12}+k_{21}+k)^2 - 4k_{21}k$$

$$= k_{12}^2 + k_{21}^2 + k^2 + 2k_{12}k_{21} + 2k_{12}k + 2k_{21}k - 4k_{21}k$$

$$= k_{12}^2 + k_{21}^2 + k^2 + 2k_{12}k_{21} + 2k_{12}k - 2k_{21}k$$

$$= k_{21}^2 - 2k_{21}k + k^2 + k_{12}^2 + 2k_{12}k_{21} + 2k_{12}k$$

$$= (k_{21}-k)^2 + k_{12}^2 + 2k_{12}k_{21} + 2k_{12}k$$

> 0 since $k_{12}, k_{21}, k > 0$

Continuing, let $\lambda_1 = \tfrac{1}{2}\left[-(k_{12}+k_{21}+k) - \sqrt{(k_{12}+k_{21}+k)^2 - 4k_{21}k}\right] = -\alpha$ *

$\lambda_2 = \tfrac{1}{2}\left[-(k_{12}+k_{21}+k) + \sqrt{(k_{12}+k_{21}+k)^2 - 4k_{21}k}\right] = -\beta$

Then $\begin{bmatrix} A_1 \\ A_2 \end{bmatrix} = \underset{\sim}{A}$ should satisfy $\left(\underset{\sim}{B} - \lambda \underset{\sim}{I}\right)\underset{\sim}{A} = \underset{\sim}{0}$ for both λ

If $\lambda = -\alpha$

$$\begin{bmatrix} -(k_{12}+k) + \alpha & k_{21} \\ k_{12} & -k_{21} + \alpha \end{bmatrix} \begin{bmatrix} A_1 \\ A_2 \end{bmatrix} = \underset{\sim}{0}$$

$$\Leftrightarrow (\alpha - k_{12} - k)A_1 + k_{21}A_2 = 0 \quad \text{——— (1)}$$

$$k_{12}A_1 + (\alpha - k_{21})A_2 = 0 \quad \text{——— (2)}$$

from (2) we know:

$$A_2 = \frac{-k_{12}}{\alpha - k_{21}} A_1$$

so choose $A_1 = 1$ then $A_2 = \frac{k_{12}}{k_{21} - \alpha}$ and

* Note: by inspection we see that these roots are negative. So by Theorem 1, Ch. 9.2 DERREK and GROSSMAN, $(0,0)$ is an asymptotically stable soln as predicted in the phase plane analysis

$\begin{pmatrix} 1 \\ \frac{K_{12}}{K_{21}-\alpha} \end{pmatrix} e^{-\alpha t}$ is a soln

and similarly we can see that

II $\begin{pmatrix} 1 \\ \frac{K_{12}}{K_{21}-\beta} \end{pmatrix} e^{-\beta t}$ is also a soln to the system

$\therefore$ the general solution is $\mathcal{L} = \phi \begin{pmatrix} 1 \\ \frac{K_{12}}{K_{21}-\alpha} \end{pmatrix} e^{-\alpha t} + \theta \begin{pmatrix} 1 \\ \frac{K_{12}}{K_{21}-\beta} \end{pmatrix} e^{-\beta t}$

where θ, ϕ are arbitrary.

Now applying the initial conditions $C_1(0) = D$, $C_2(0) = 0$ where $D > 0$ is the initial Dose administered gives

$$C_1(0) = \phi e^{-\alpha(0)} + \theta e^{-\beta(0)} = D$$
$$C_2(0) = \phi \left(\frac{K_{12}}{K_{21}-\alpha}\right) e^{-\alpha(0)} + \theta \left(\frac{K_{12}}{K_{21}-\beta}\right) e^{-\beta(0)} = 0$$

$$\phi + \theta = D \quad \text{——————} \quad (3)$$
$$\phi \left(\frac{K_{12}}{K_{21}-\alpha}\right) + \theta \left(\frac{K_{12}}{K_{21}-\beta}\right) = 0 \quad \text{——————} \quad (4)$$

now $\phi = D - \theta$ from (3), substituting into (4) gives

$$(D-\theta)\left(\frac{K_{12}}{K_{21}-\alpha}\right) + \theta\left(\frac{K_{12}}{K_{21}-\beta}\right) = 0$$

$$\frac{D K_{12}}{K_{21}-\alpha} - \frac{\theta K_{12}}{K_{21}-\alpha} + \frac{\theta K_{12}}{K_{21}-\beta} = 0$$

$$\theta \left(\frac{K_{12}(\beta-\alpha)}{(K_{21}-\alpha)(K_{21}-\beta)} \right) = -\frac{D K_{12}}{K_{21}-\alpha}$$

$$\theta \frac{(\beta-\alpha)}{(K_{21}-\beta)} = -D$$

$$\theta = D\left(\frac{K_{21}-\beta}{\alpha-\beta}\right)$$

$\therefore \phi = D - \theta = D - D\frac{(K_{21}-\beta)}{(\alpha-\beta)} = \frac{D(\alpha-K_{21})}{\alpha-\beta}$

so the model becomes:

$$C_1(t) = \frac{D(\alpha - K_{21})}{\alpha - \beta} e^{-\alpha t} + \frac{D(K_{21} - \beta)}{\alpha - \beta} e^{-\beta t}$$

$$C_2(t) = \frac{D(\alpha - K_{21})}{\alpha - \beta}\left(\frac{K_{12}}{K_{21} - \alpha}\right) e^{-\alpha t} + \frac{D(K_{21} - \beta)}{\alpha - \beta}\left(\frac{K_{12}}{K_{21} - \beta}\right) e^{-\beta t}$$

where $D > 0$ is the initial Dose,

$K_{ij} > 0$ represent first order transfer constants from compartment i to j

$K > 0$ represents first order excretion constant

$$\alpha = \tfrac{1}{2}\left((K_{12} + K_{21} + K) + \sqrt{(K_{12} + K_{21} - K)^2 - 4K_{21}K}\right)$$

$$\beta = \tfrac{1}{2}\left((K_{12} + K_{21} + K) - \sqrt{(K_{12} + K_{21} + K)^2 - 4K_{21}K}\right).$$

(Decreasing functions as expected)

However, since this model assumes excretion only from compartment one, we are only concerned with $C_1(t)$ in a practical setting.

Because the liver & kidneys are the most important organs in terms of drug excretion and because they are both so highly perfused with blood (an indicator of the function of excretion) the previous model seems plausible. However, it also seems plausible that for some drugs, either direct excretion or "effective excretion" through metabolism, elimination may also occur in the second compartment.

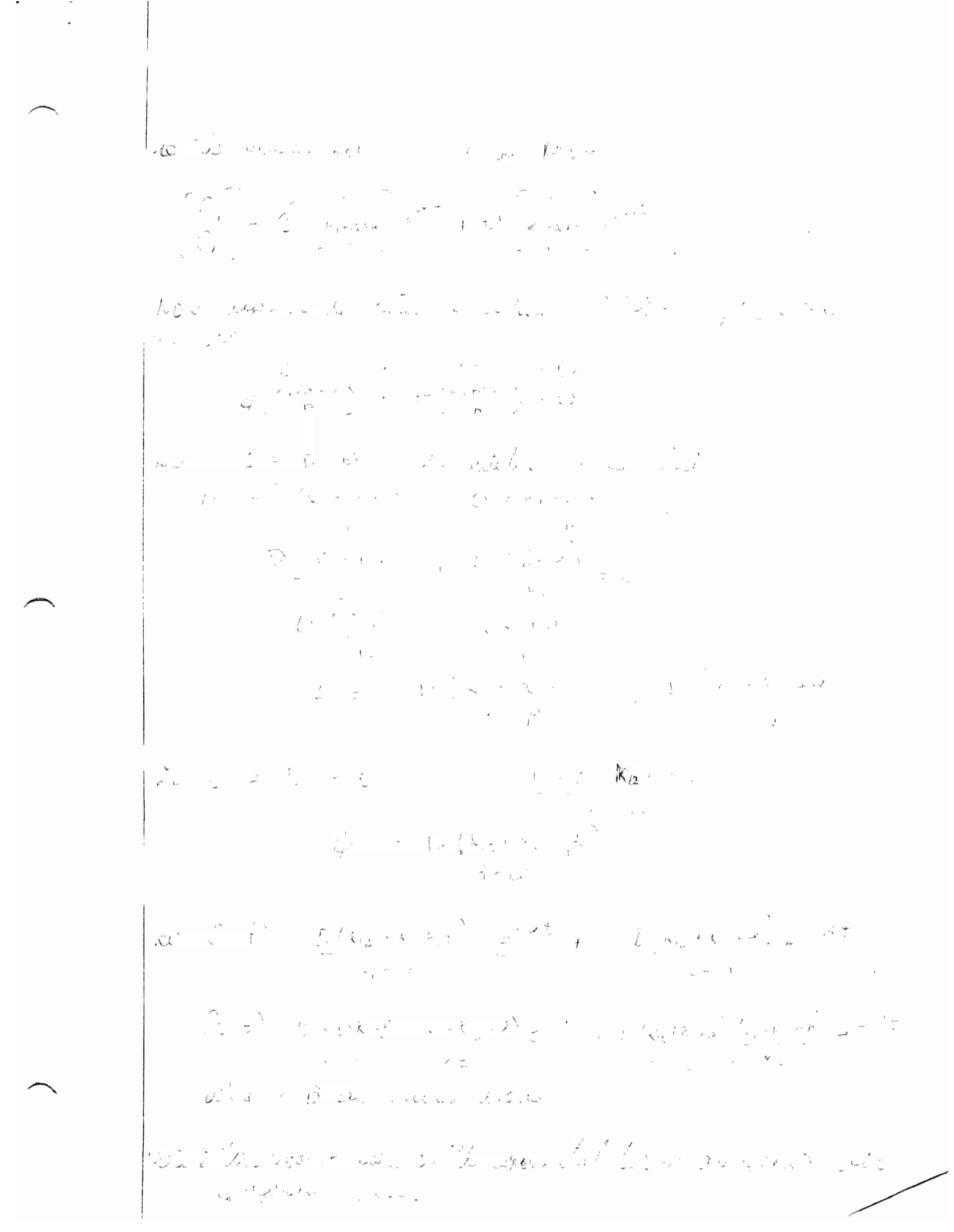
THE TWO COMPARTMENT OPEN MODEL WITH ELIMINATION FROM BOTH COMPARTMENTS

Because of the similarity to the previous model, Phase Plane Analysis will not be done here.

We can easily see from the form of the equations that the phase plane is qualitatively the same with shifted nullclines. There are nine cases: $K_{12} > K_{21}$ and $K_1 > K_2$, $K_{12} > K_{21}$ and $K_1 = K_2$, $K_{12} > K_{21}$ and $K_1 < K_2$, and similarly for $K_{12} = K_{21}$ and $K_{12} < K_{21}$. Because of this tediousness and the fact that linear systems of this type are solvable, we proceed to the analysis.

(these all variables are defined later)

$-2K_{2b} + 4K_{2b}$



The similarity of the previous two cases suggests that the same technique can be applied to any of these so called Mammillary models with any number of compartments or arrangment of transfers and excretions. I emphasize suggests for the only way to prove that any Mammilary model can be represented by a set of multi-exponential relations is to show that all roots of all possible characteristic polynomials are real, distinct and negative. Of course, this cannot be shown analytically for polynomials of greater degree than a quartic. And I was not able to determine any abstract pattern relating the characteristic polynomials of all Mammillary models, which may have made this task possible.

It should also be noted that the preceding models dealt with concentrations directly. Because it is unlikely that both compartments will have the same volume of distribution the quantities listed as concentrations ought to have represented amounts so as not to include the effect of dilution due to different Volumes. The mathematical analysis on amounts would be identical therefore there is no need for distress. To obtain True Concentration functions, the preceding relations ought to have been divided by their respective volumes of distributions [I would have remedied this if I had done all the work on a word processor]

INTERACTING DRUGS

Often patients receive several drugs at a time. There could be several reasons for this. The multiple Treatment may just be effective, there may be multiple symptoms etc. So clearly it is advantageous to be able to specify how any interactions between drugs are relevant to their time course distribution.

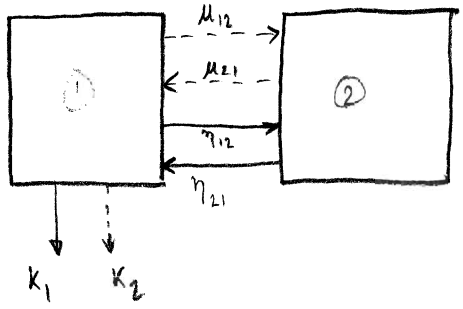
The most common explanation for altered distribution in a drug interaction is displacement. Displacement is the reduction in binding of a drug to a macromolecule caused by competition of another drug (ROWLAND 59)

If we were to assume that both drugs obeyed a 2 compartment analysis with excretion from the central compartment and that the presence of both drugs only had influence on the excretion rate, not the transfer rate, then we could propose the following model:

> Each rate of change of drug amounts ought to be "penalized" a quantity proportional to the amount of the other drug.

[Admittedly, this is not the best modification, but more complicated modifications lead to systems of non linear equations the solutions of which are beyond the scope of this paper]

Graphically we can see the problem as follows



where K_1 = elimination const. for Drug 1
K_2 = " " " 2
μ_{ij} = transfer const for Drug 2
η_{ij} = " " " 1
$K_i, \mu_{ij}, \eta_{ij} > 0$.

Let X_{11} denote the amount of Drug 1 in compartment 1
X_{12} " 1 " 2
X_{21} " 2 " 1
X_{22} " 2 " 2

$$dX_{11}/dt = -(K_2 + \mu_{12})X_{11} + \mu_{21}X_{12} + \eta X_{21}$$
$$dX_{12}/dt = \mu_{12}X_{11} - \mu_{21}X_{12}$$
$$dX_{21}/dt = \eta X_{11} - (K_1 + \eta_{12})X_{21} + \eta_{21}X_{22}$$
$$dX_{22}/dt = \eta_{12}X_{21} - \eta_{21}X_{22}$$

the characteristic polynomial of this system can be found by finding

$$0 = \begin{vmatrix} a & b & c & 0 \\ d & e & 0 & 0 \\ f & 0 & g & h \\ 0 & 0 & i & j \end{vmatrix}$$

where $a = -(K_2+\mu_{12}) - \lambda$ $b = \mu_{21}$ $c = \eta$
$d = \mu_{12}$ $e = -\mu_{21} - \lambda$, $f = \eta$
$g = -(K_1+\eta_{12}) - \lambda$, $h = \eta_{21}$
$i = \eta_{12}$, $j = -\eta_{21} - \lambda$

$$= a\begin{vmatrix} e & 0 & 0 \\ 0 & g & h \\ 0 & i & j \end{vmatrix} - d\begin{vmatrix} b & c & 0 \\ 0 & g & h \\ 0 & i & j \end{vmatrix} + f\begin{vmatrix} b & c & 0 \\ e & 0 & 0 \\ 0 & i & j \end{vmatrix}$$

$$= ae(gj - ch) - db(gj - ih) + f\left(b\begin{vmatrix} 0 & 0 \\ i & j \end{vmatrix} - e\begin{vmatrix} c & 0 \\ i & j \end{vmatrix}\right)$$
$$= ae(gj - ih) - db(gj - ih) - fecj = 0$$

$$(ae - db)(gj - ih) - fecj$$

$$\Leftrightarrow \Big[\big(-(K_2+\mu_{12})-\lambda\big)\big(-\mu_{21}-\lambda\big) - \mu_{21}\mu_{12}\Big]\Big[\big(-(K_1+\eta_{12})-\lambda\big)\big(-\eta_{21}-\lambda\big) - \eta_{12}\eta_{21}\Big] - \big((m)(-\mu_{12}-\lambda)(+n)(-\eta_{21}-\lambda)\big) = 0$$

$$= \Big[(K_2+\mu_{12})\mu_{21} + (K_2+\mu_{12})\lambda + \mu_{21}\lambda + \lambda^2 - \mu_{21}\mu_{12}\Big]\Big[(K_1+\eta_{12})\eta_{21} + (K_1+\eta_{12})\lambda + \eta_{21}\lambda + \lambda^2 - \eta_{12}\eta_{21}\Big] + mn\left(\mu_{12}\eta_{21} + \lambda(\mu_{12}+\eta_{21}) + \lambda^2\right)$$

$$= \left[K_2\mu_{21} + \lambda(K_2+\mu_{12}+\mu_{21}) + \lambda^2\right]\left[K_1\eta_{21} + \lambda(K_1+\eta_{12}+\eta_{21}) + \lambda^2\right] - mn\left(\mu_{12}\eta_{21} + \lambda(\mu_{12}+\eta_{21}) + \lambda^2\right)$$

$$= \lambda^4 + \lambda^3\left(K_2+\mu_{12}+\mu_{21}+K_1+\eta_{12}+\eta_{21}\right) + \lambda^2\Big((K_2+\mu_{12}+\mu_{21})(K_1+\eta_{12}+\eta_{21}) + K_2\mu_{21} + K_1\eta_{21}\Big) + \lambda\Big((K_2\mu_{21})(K_2+\mu_{12}+\mu_{21}) + (K_1\eta_{21})(K_2+\mu_{12}+\mu_{21})\Big) + K_2\mu_{21}K_1\eta_{21} - mn\left(\mu_{12}\eta_{21} + \lambda(\mu_{12}+\eta_{21}) + \lambda^2\right)$$

$$= \lambda^4 + \lambda^3\left[K_2+\mu_{12}+\mu_{21}+K_1+\eta_{12}+\eta_{21}\right] + \lambda^2\left[(K_2+\mu_{12}+\mu_{21})(K_1+\eta_{12}+\eta_{21}) + K_2\mu_{21} + K_1\eta_{21} - mn\right] + \lambda\left[(K_2\mu_{21})(K_2+\mu_{12}+\mu_{21}) + (K_1\eta_{21})(K_2+\mu_{12}+\mu_{21}) - mn\mu_{12} - mn\eta_{21}\right] + \left[K_2\mu_{21}K_1\eta_{21} - mn\mu_{12}\eta_{21}\right] = 0$$

These eigenvalues are solvable analytically, but are very messy. We must show that these eigenvalues are either real or complex or a combination there of, for the format of the solution depends on it. Obviously this is not an easy task. One could estimate the above constants through least squares

and then solve the remainder of the problem numerically. However I have no access to relevant data so will not.

However if we assume that all the eigenvalues are real then by the similarity to the solution methods in preceding models we may conclude that this interaction is describable in terms of a quad exponential function, instead of the bi exponential function associated with the two compartment model. This new model could then provide otherwise unavailable information relative to dosage regimens.

CONCLUSIONS

Earlier, simpler models allowed us to specify concentration equations explicitly. As expected, they predicted decreasing concentrations with respect to time; and in the two compartment case a distributive phase which eventually declines towards zero. Clearly, if a particular drug matches the respective assumptions in one of the previous models, then knowing the concentration time course of that drug implicitly describes the optimal regimen. We can evaluate toxicity and minimum effective levels experimentally, goodness of fit tests can be performed on these models and clinically useful predictions made with them.

The last model could have implied either oscilatory or a higher number of exponentials in order to describe drug time courses. In either case, the model provides clinically useful information.

So again if therapeutic response is a function of drug time course distributions then knowing the explicit form of a function predicting drug concentrations implicitly defines an optimal therapy.

SUGGESTED IMPROVEMENTS / DIFFICULTIES

Clearly, the largest improvement that could be made to any of the previous models would be a relaxation of the first order transfer and elimination rate assumption. As noted earlier, these phenomenon are almost surely non linear in nature & so ought to be modeled as such.

The Mammilary approach treats each compartment as a kinetically homogeneous unit. This too is almost certainly not the case. It is possible to have region of the body whose drug time course is independent of $C(t)$ as described above. If this region had a sufficiently small capacity for a particular drug, it would go unnoticed in the compartmental analysis. But this region could also have a strong affinity for that small fraction of the dose and so on repeated dosing, you could attain an undetected toxic level in that region. Indeed, some drugs do not fit any Mammilary models making the claim of kinetically homogeneous pools even more dubious

More frequent and intensive sampling right after administration tends to yield data that must be described by equations containing more exponential terms. Thus the compartmental model required depends in part on the experimental design (GIBALDI 82)

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