What does pharmacokinetics model?

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1. Introduction

Pharmacokinetics (PK) is the study of the course of absorption, distribution, metabolism, and elimination of some substance in a living body.

Pharmaceutical companies use PK models for assessing tolerability, bioavailability, bioequivalence, and compliance.

Plasma drug levels often show a stronger relationship to clinical response (efficacious or toxic) than does dose level.

Therefore, it can act as an important surrogate endpoint.

PK is a valuable component in the determination of optimal (safe and effective) doses and dosing schedules.

In a Phase I study, a small number of healthy volunteers may be given a dose of a new drug.

Most often, a cross-over design is used, with individuals receiving different doses in various orders.

After administration of a given dose, blood samples are taken at frequent intervals to determine the profile of the concentration of the drug in the plasma.

In later phase studies, concentrations of the drug are measured at infrequent intervals on a large number of patients.

The former are data-rich studies whereas the latter are called population PK.

The process is often represented as passage through a series of ‘compartments’ in the body.

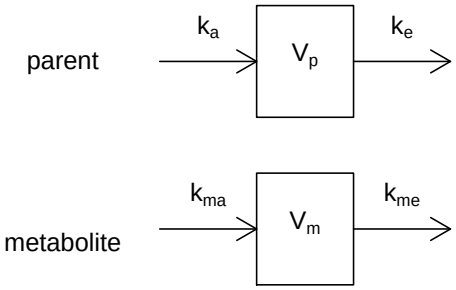
Usually absorption of a drug is more rapid than elimination.

Generally, the body transforms the drug into another form called the metabolite.

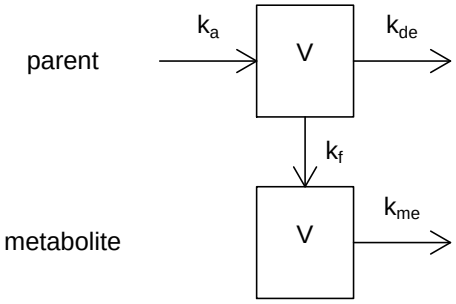
If the metabolite is active, it may be necessary to model it along with the parent drug.

There may be large inter-individual variability in all aspects of the passage of these substances through the body.

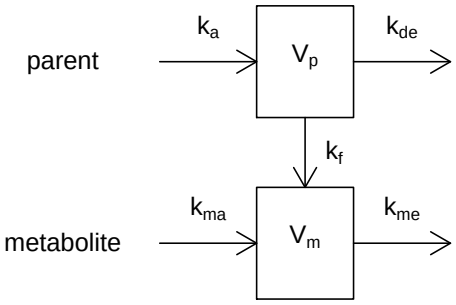
Model 1



Model 2



Model 3



2. Compartment models

Suppose that some sort of individual elements (atoms, molecules, ...) can move among a number of different states or compartments.

In pharmacokinetics, the compartments are organs or tissues of the body.

The dynamics of the system can be described by the *rates* or *intensities* with which the elements move among the compartments.

These rates will depend on a number of factors, especially the numbers of elements in the two compartments between which moves are made.

One way to describe such a process that moves from state to state (the compartments) is as a Markov chain.

Let $\boldsymbol{\pi}(t)$ be the vector of *marginal* probabilities of being in the various states at time t and

$\mathbf{A}$ be a matrix of *conditional transition intensities* such that

$$\mathbf{T} = \mathrm{e}^{\mathbf{A}}$$

where $\mathbf{T}$ is the transition matrix of conditional probabilities of changing among states in unit time.

Then,

$$\boldsymbol{\pi}^{\mathsf{T}}(t) = \boldsymbol{\pi}^{\mathsf{T}}(0)\mathrm{e}^{\mathbf{A}t}$$

This involves the following assumptions:

the process remains in each state i a strictly positive length of time

the sojourn times in each state have independent exponential distributions,

each with a different mean time in the state μ_i or intensity of leaving the state $k_i = 1/\mu_i$.

In certain stochastic systems, we cannot observe changes for individual elements but only in aggregation.

For example, in a chemical reaction, we cannot observe the changes of state of the participating atoms but only the total concentration of each reactant and product.

In the growth of a biological organism, we cannot observe the addition of individual proteins, or even of cells, but only the increase in weight or length.

In other words, records of change in such a system are averages of the stochastic changes of the components involved.

Thus, one way to construct a mechanistic model for a process of material moving through a system is

to divide that system into compartments;

to assume that the rate of flow of the substance between these obeys *first-order kinetics*.

The rate of transfer to a receiving or sink compartment is proportional to the concentration in the supply or source compartment.

Then, the differential equations are linear.

These are called the *mass balance equations*.

Thus, the rates can be described mathematically by one or more differential equations.

In the simple case, there are no inputs to the system after $t = 0$ when the process begins.

The system of linear differential equations will have the form

$$\frac{\mathrm{d}\boldsymbol{\mu}^{\mathsf{T}}(t)}{\mathrm{d}t} = \boldsymbol{\mu}^{\mathsf{T}}(t)\mathbf{A}$$

$\boldsymbol{\mu}(t)$ is a column vector of length P, the number of compartments.

A is a $P \times P$ transfer matrix containing rate constants of movement between states in the system.

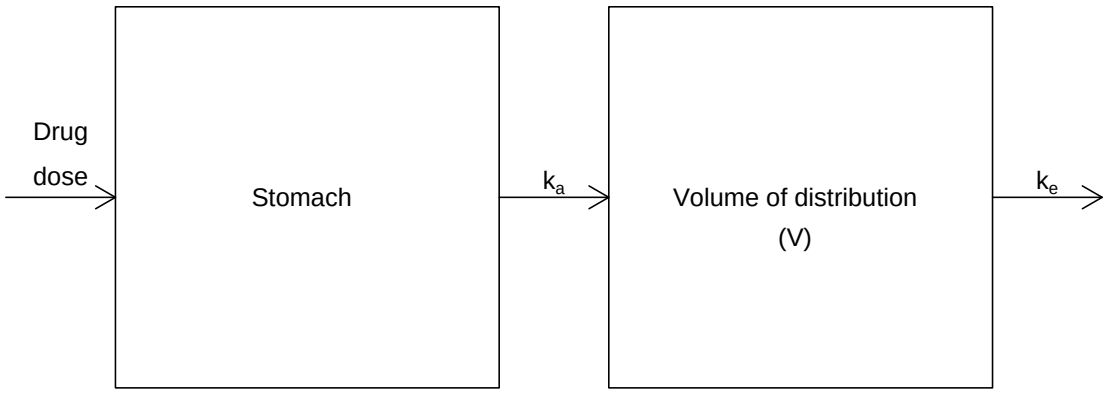
In direct analogy to the solution of one such equation, the general solution is

$$\boldsymbol{\mu}^{\mathsf{T}}(t) = \boldsymbol{\mu}^{\mathsf{T}}(0)\mathrm{e}^{\mathbf{A}t}$$

If there are inputs to the system over time, the function describing these, say $\mathbf{b}(t)$, must be included:

$$\boldsymbol{\mu}^{\mathsf{T}}(t) = \boldsymbol{\mu}^{\mathsf{T}}(0)\mathrm{e}^{\mathbf{A}t} + \int_0^t \mathbf{b}(u)\mathrm{e}^{\mathbf{A}(t-u)}\mathrm{d}u$$

Suppose that a substance is ingested at one point in time (not continuously over the study period).



The corresponding differential equations are

$$\frac{\mathrm{d}\mu_0(t)}{\mathrm{d}t} = -k_a\mu_0(t)$$

$$\frac{\mathrm{d}\mu_1(t)}{\mathrm{d}t} = k_a\mu_0(t) - k_e\mu_1(t)$$

μ_0 is the *mean* amount at the absorption site (often the stomach),

μ_1 is the *mean* of the concentration that interests us, usually measured in the blood,

k_a is the absorption rate at that site,

k_e the elimination rate at that site.

Then,

$$\mathbf{A} = \begin{pmatrix} -k_a & k_a \\ 0 & -k_e \end{pmatrix}$$

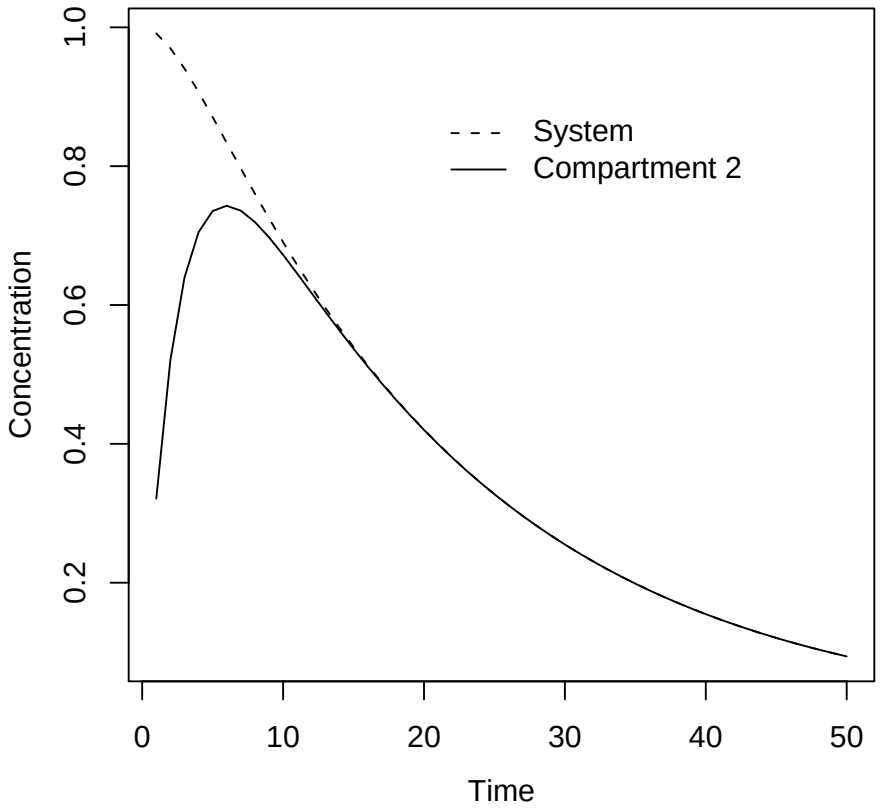
We can set the initial condition to $\boldsymbol{\mu}(0) = (d, 0)^{\mathsf{T}}$, where a dose of size d is the input to the first compartment.

When solving the above differential equations, we shall be interested in the second element of $\boldsymbol{\mu}(t)$, the amount in the second compartment.

For given, fixed values of the parameters, this can be calculated numerically using the equation involving matrix exponentiation.

Suppose that $k_a = 0.4$, $k_e = 0.05$, and $d = 1$.

The curves of total concentration in the system and of concentration in the second compartment are



In fact, in this example, numerical exponentiation of the transfer matrix is not necessary.

The differential equations can be solved analytically.

The resulting function of time for the compartment of interest is

$$\mu_1(t) = \frac{dk_a}{(k_a - k_e)} \left(\mathrm{e}^{-k_e t} - \mathrm{e}^{-k_a t} \right)$$

a nonlinear function in the parameters k_a and k_e.

This commonly used function is called the open, first-order, one-compartment model.

It describes how the average number of molecules in the compartment of interest changes over time.

However, the total dose x may not be absorbed into the blood.

Then, the function becomes

$$\mu(t) = \frac{dk_a}{V(k_a - k_e)} \left(\mathrm{e}^{-k_e t} - \mathrm{e}^{-k_a t} \right)$$

where the additional nonlinear parameter V is a proportionality constant, called the apparent volume of distribution.

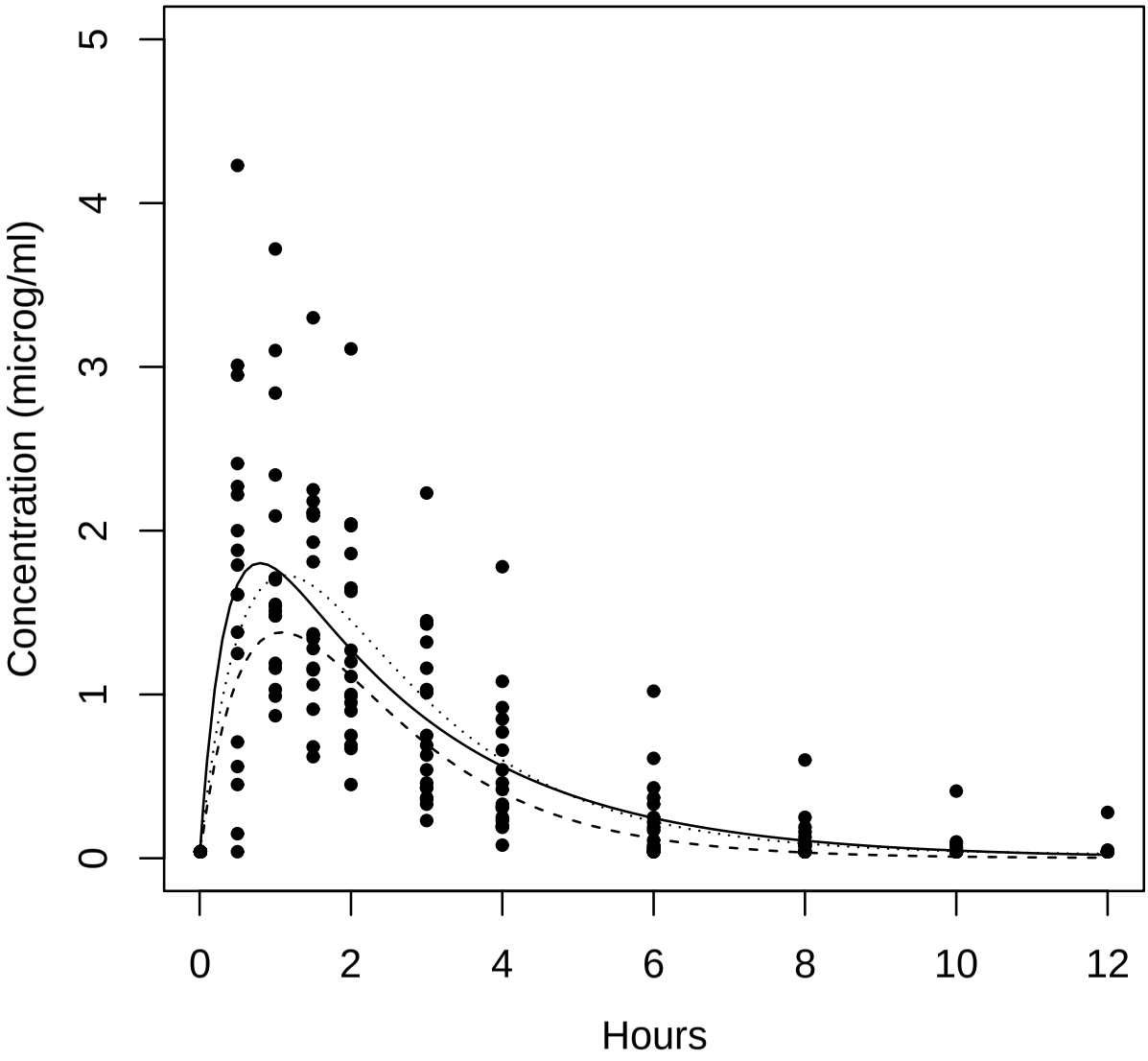
3. Stochastic variability

However, a second level of stochastic variability is usually also present in PK measurements, resulting from random external influences to the system:

changes in food supply, stress, and so on, to the biological organism.

Thus, changes at the level of the individual components can only be modelled as a mean function, with variation about it arising from the second level.

The probability distribution of elements in a compartment over time is used as a nonlinear regression curve.


Concentration (microg/ml)
0
1
2
3
4
5
0
2
4
6
8
10
12
Hours

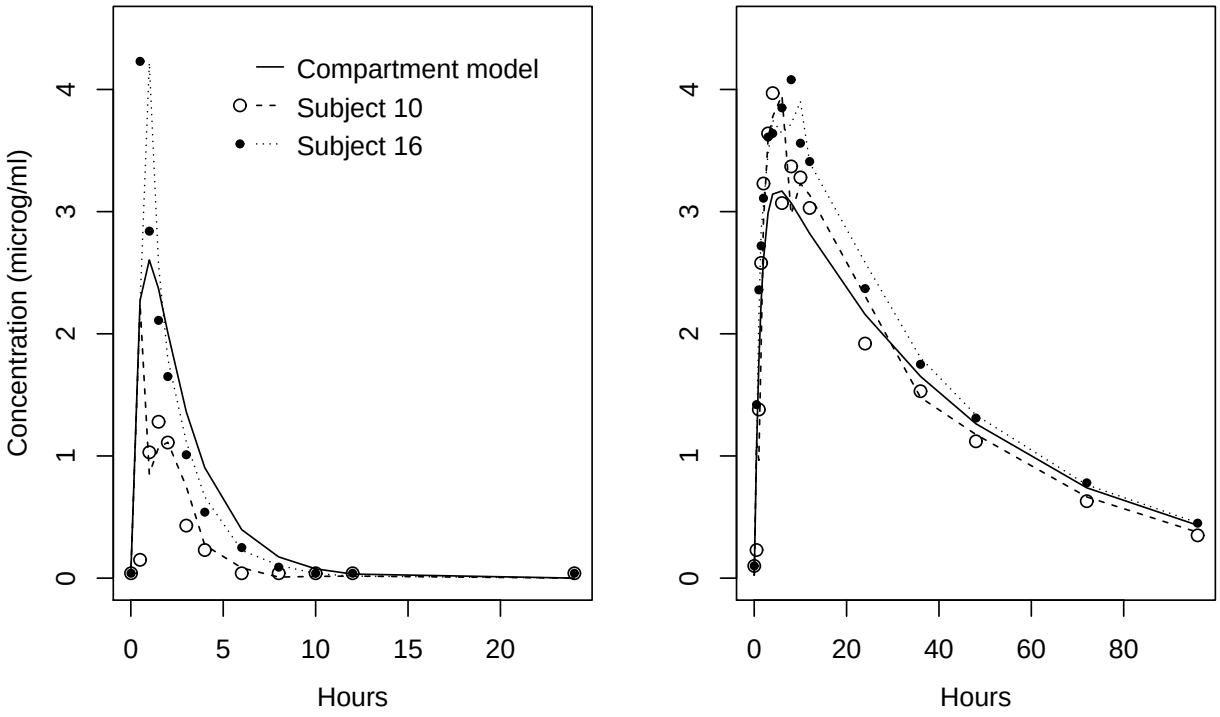
Stochastic variability about the mean will involve:

1. skew, with a few large values;

2. nonconstant dispersion;

3. dependence among observations on the same individual.

Traditionally, these are handled by a log normal distribution with random effects for the nonlinear parameters.


Compartment model
Subject 10
Subject 16
Concentration (microg/ml)
0
1
2
3
4
0
5
10
15
20
Hours
0
20
40
60
80
Hours

Skewed distributions

Empirically, the gamma distribution generally fits better than the log normal (criterion: AIC).

A useful possibility is the generalised gamma distribution

$$f(y_t; \mu_t, \phi_t, \lambda) = \frac{\lambda \phi_t^{\phi_t} y_t^{\phi_t \lambda - 1} \mathrm{e}^{-\phi_t (y_t/\mu_t)^{\lambda}}}{\mu_t^{\phi_t \lambda} \Gamma(\phi_t)}$$

When $\lambda = 1$, this yields a gamma distribution, when $\phi_t = 1$, a Weibull distribution, and when $\lambda \to \infty$, a log normal distribution.

Nonconstant dispersion

Usually, the dispersion (variance) is assumed to be a function of the mean:

$$\phi(t) = \sigma^2 \mu(t)^\kappa$$

where κ is often set to 2.

This implies that the unknown parameters (k_a, k_e, V above) are estimated simultaneously in this equation and in the mean equation.

A preferable approach is to allow $\phi(t)$ to be a separate function with its own parameters.

The dispersion parameter of the gamma distribution is a function of the coefficient of variation.

This parameter is of more interest to pharmacokineticists than the variance.

Dependence

Random effects only allow *static* differences among subjects.

They are necessary if inadequate covariates are available to describe differences in the parameters (k_a, k_e, V above) among individuals.

However, dynamic variation from the regression curve is usually also present.

At a given time point, suppose that the observed concentration for individual i is y_{it}.

The deviation from the overall curve, or a residual, will be $y_{it} - \mu_t$.

The concentration for that individual at the next observation point can be predicted by

$$\widehat{y}_{i,t+1} = \mu_{t+1} + \rho^{\Delta t}(y_{it} - \mu_t)$$

where $0 < \rho < 1$ is an unknown parameter and Δt is the time between the two observations.

4. Conclusions

PK claims to provide *mechanistic* models explaining the flow of a substance through the body.

However, the compartment models are applied as a black box without close examination of the underlying stochastic assumptions.

Differential equations are solved and applied deterministically, with randomness reduced to 'measurement error' and static individual differences.

Modelling questions:

1. What compartments are required (which Markov chain model)?

2. Which distribution adequately describes random external influences?

3. What rate constants vary among individuals (covariates or 'frailty')?

4. In what way is the process influenced by unknown internal and external factors over time?