Compartment models for pharmacokinetics and event histories

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1. Constructing compartment models

2. Event histories

3. Pharmacokinetics

4. Comparison

1. Constructing compartment models

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

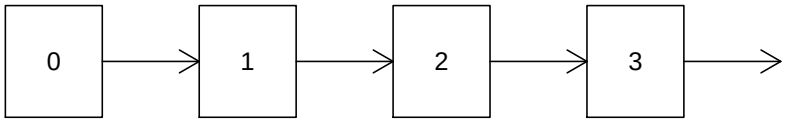
In chemistry, the compartments may be molecules between which atoms are moving.

In pharmacokinetics, they may be organs or tissues of the body.

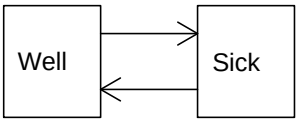
In event histories, they may be states of a patient.

Often, all potential movements among compartments will not be possible.

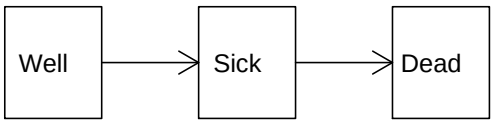
Recurrent events



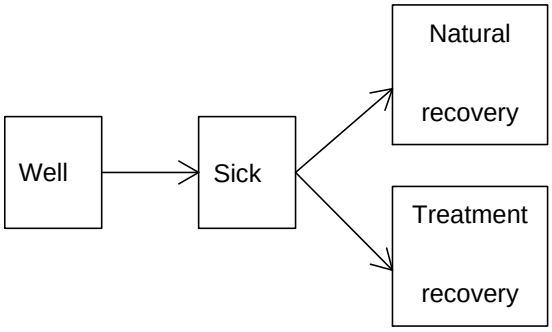
Alternating events



Progressive events



Alternative outcomes



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.

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

Unless these equations can be assumed to be linear, the problem may be intractable.

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:

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

Matrix exponentiation is defined by

$$\mathrm{e}^{\mathbf{A}t} = \mathbf{I} + \frac{\mathbf{A}t}{1!} + \frac{(\mathbf{A}t)^2}{2!} + \cdots$$

A preferable way to calculate the exponential is by spectral decomposition.

If **W** is a matrix with the eigenvectors of **A** as columns and **D** is a diagonal matrix containing the corresponding eigenvalues, then

$$\mathbf{A} = \mathbf{W}\mathbf{D}\mathbf{W}^{-1}$$

The exponential is then

$$\mathrm{e}^{\mathbf{A}t} = \mathbf{W}\mathrm{e}^{\mathbf{D}t}\mathbf{W}^{-1}$$

In simple cases, the differential equations can be solved analytically, but often only a numerical solution will be available.

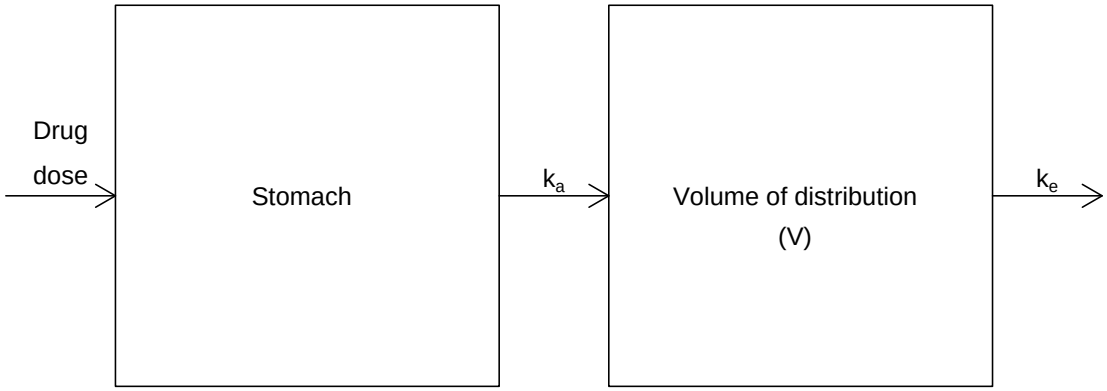
Generally, we may be interested in

- how the quantities of the elements in one or more of the compartments change over time (a marginal question) or

- the probable length of time an element stays in a given compartment (a conditional question).

As an example, consider a model often used in pharmacokinetics.

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,

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

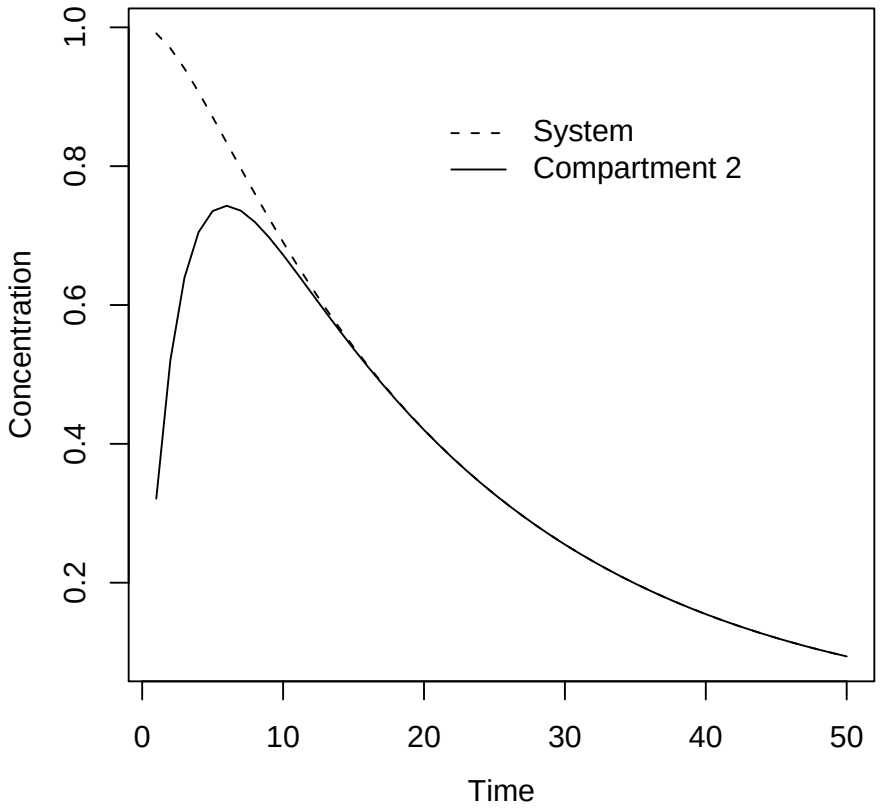
We can set the initial condition to $\boldsymbol{\mu}(0) = (x, 0)^{\mathsf{T}}$, where a dose of size x is the input to the first compartment.

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 $x = 1$.

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 nonlinear function for the compartment of interest is

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

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

The first compartment does not appear in the final function.

Recurrent events:

$$\begin{pmatrix} -\lambda_{1|0} & \lambda_{1|0} & 0 & 0 & \cdots \\ 0 & -\lambda_{2|1} & \lambda_{2|1} & 0 & \cdots \\ 0 & 0 & -\lambda_{3|2} & \lambda_{3|2} & \cdots \\ \vdots & \vdots & \vdots & \vdots & \ddots \end{pmatrix}$$

Alternating events:

$$\begin{pmatrix} -\lambda_{2|1} & \lambda_{2|1} \\ \lambda_{1|2} & -\lambda_{1|2} \end{pmatrix}$$

Progressive events:

$$\begin{pmatrix} -\lambda_{2|1} & \lambda_{2|1} & 0 \\ 0 & -\lambda_{3|2} & \lambda_{3|2} \\ 0 & 0 & 0 \end{pmatrix}$$

Alternative outcomes:

$$\begin{pmatrix} -\lambda_{2|1} & \lambda_{2|1} & 0 & 0 \\ 0 & -\lambda_{3|2} - \lambda_{4|2} & \lambda_{3|2} & \lambda_{4|2} \\ 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 \end{pmatrix}$$

2. Event histories

A Markov chain describes a process that moves from state to state (the compartments).

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

$\mathbf{T}$ be the transition matrix of *conditional* probabilities of changing among states.

Then,

$$\boldsymbol{\pi}^{\mathsf{T}}(t+1) = \boldsymbol{\pi}^{\mathsf{T}}(t)\mathbf{T}$$

and

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

where t is an integer.

For a Markov chain in continuous time, $\mathbf{T}$ is replaced by a matrix $\mathbf{\Lambda}$ of *transition intensities* such that

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

so that

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

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 $\lambda_i = 1/\mu_i$.

If the state is absorbing, the mean duration is infinite and $\lambda_i = 0$.

The matrix $\mathbf{\Lambda}$ contains the conditional transition intensities $\lambda_{j|i}$ of moving from state i to state $j \neq i$.

The diagonal element is set equal to $-\lambda_i$ where

$$\lambda_i = \sum_{j \neq i} \lambda_{j|i}$$

so that the sum of each row is zero.

The corresponding matrix of transition probabilities for a given time interval Δt can be obtained by matrix exponentiation:

$$\mathbf{T}_{\Delta t} = \mathrm{e}^{\mathbf{\Lambda} \Delta t}$$

Modelling involves allowing the conditional intensities $\lambda_{j|i}$ to depend on covariates.

Advantages:

- Simple to estimate.

- Missing values and dropouts easily handled (add compartments).

Disadvantages:

- Unrealistic constant intensity (exponential distribution) assumption of random movement among states.

Possible extensions:

- semi-Markov models where the conditional intensities depend on time;
- variation in intensities among individuals (frailty);
- time-varying random external influences;
- nonlinear differential equations.

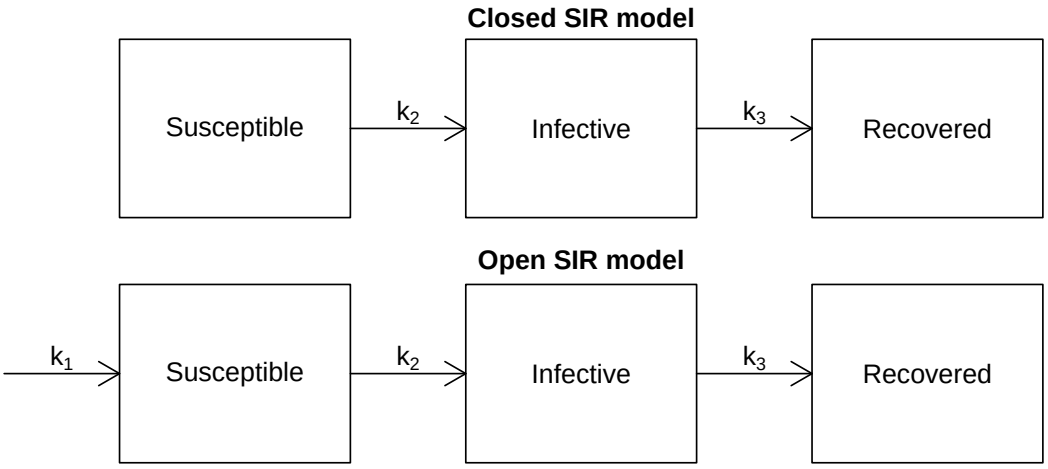
Consider the example of people who may contract a nonfatal infectious disease that confers immunity upon recovery.

We can then divide a given population into three distinct categories:

1. susceptibles (S) who can catch the disease;

2. infectives (I) who have the disease and are contagious so that they can transmit it;

3. recovered (R), who have had the disease and are now immune.



Assumptions:

- the rate (k_2) of exit from the susceptible category and entry to the infective category is proportional to the present numbers of infectives and susceptibles;

- the rate (k_3) of exit from the infective category and entry to the recovered category is proportional to the present number of infectives;

- each category of people is uniformly mixed so that every pair of individuals has the same probability of meeting; and

- the population is of constant size.

Then, the model can be defined by the nonlinear differential equations

$$\begin{aligned} \frac{\mathrm{d}S(t)}{\mathrm{d}t} &= -k_2 S(t) I(t) \\ \frac{\mathrm{d}I(t)}{\mathrm{d}t} &= k_2 S(t) I(t) - k_3 I(t) \\ \frac{\mathrm{d}R(t)}{\mathrm{d}t} &= k_3 I(t) \end{aligned}$$

with initial conditions $S(0) = S_0 > 0$, $I(0) = I_0 > 0$, and $R(0) = 0$.

If the population is not closed so that susceptibles are born or can immigrate at the constant rate k_1, the first equation becomes

$$\frac{\mathrm{d}S(t)}{\mathrm{d}t} = k_1 - k_2 S(t) I(t)$$

3. Pharmacokinetics

Individuals following a stochastic process can move through a number of different states in an event history.

Similar procedures can be used to describe the quantity (particles) of some material that moves through the different parts (the states) of a system.

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.

Such a system can generally be described by rates of change among compartments.

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*.

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

changes in pressure or temperature of a chemical reaction, changes in food supply, stress, and so on, to a 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.

Simple models are progressive.

For the open, first-order, one-compartment model,

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

is the nonlinear regression function.

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

Hence, V, called the apparent volume of distribution, is included as an extra parameter, a proportionality constant.

Modelling questions:

1. What compartments are required?

2. Which distribution adequately describes random external influences?

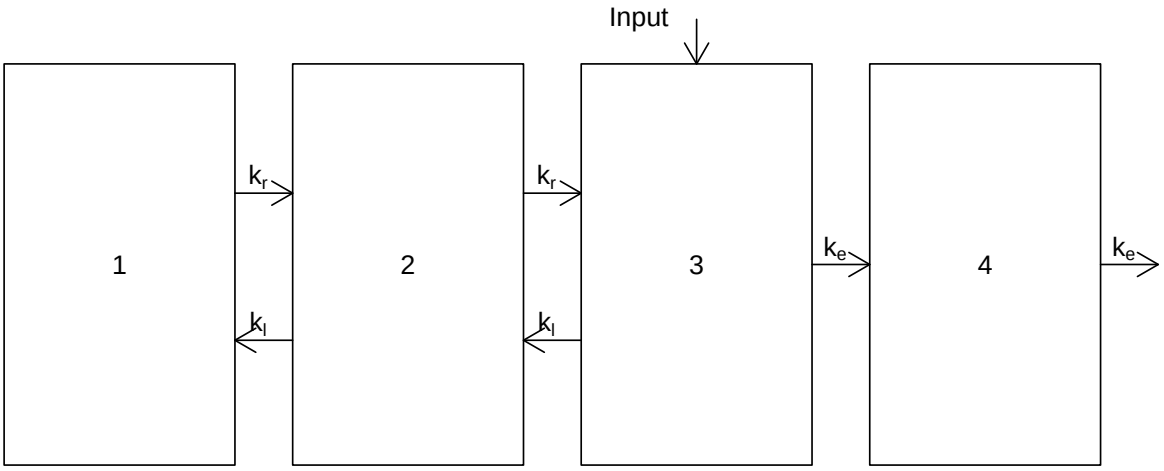
3. What rate constants vary among individuals (‘frailty’)?

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

When only one compartment is studied, an arbitrary set of additional compartments can be added to the system to modify the characteristics of the one of interest.

Consider a series of compartments where input occurs to one of the last compartments in the series.

Output only occurs by passing through the compartments to the right and out the last compartment, all with rates k_e.



Elimination through the compartments to the right of input corresponds to a gamma-distributed clearance time.

The dispersion parameter equals the number of elimination compartments, including the input compartment.

However, some of the material can also move through the compartments to the left of the input, one compartment at a time.

This is a random walk with reflecting barrier at compartment 1.

The rates are k_l to the left and k_r to the right (drift if $k_l \neq k_r$; generally, $k_l < k_r$).

A large number of compartments to the left of input indicates a delay in elimination.

The random walk describes retention of the material.

With a large number of random walk compartments, this approximates a diffusion process.

Thus, the model has two components: diffusion within the site of input and gamma-distributed clearance from that site.

The transfer matrix will be

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

and $\boldsymbol{\mu}(0) = (0, 0, x, 0)^{\mathsf{T}}$ for an input dose of x.

The number of parameters to estimate in this model does not change with the number of compartments.

4. Comparison

	Event history	Pharmacokinetics
Level	Individual	'Ecological'
Modelling	Conditional	Marginal
External disturbance	No	Yes
Realistic assumptions	Not usually	Yes