Compartmental modeling

This is a very short summary of the notes from my two-hour lecture. These notes were not originally meant to be distributed, and so they are far from being complete. A comprehensive introduction to compartmental modeling can be found for example in the book *Compartmental Analysis in Biology and Medicine* by J. A. Jacquez (Elsevier, Amsterdam, 1972).

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The basic definition and a couple of examples

**Definition:** A compartment is a kinetically homogeneous amount of some material.

**Example:** The basic model is a well-stirred tank of volume $V$ with an influx $q_{in}$ and out-flux $q_{out}$ as in figure 1; then the right half of the same figure shows a graphical abstraction, the pictorial idea of a compartment.

![Figure 1: A compartmental model](image1)

**Example:** One of the most important applications of compartmental modeling is in pharmacokinetics. Figure 2 shows a typical example, where the body is modeled with two compartments: one for the blood and one for all tissue in the body. The drug enters the blood either intravenously or orally, and is then transferred from the blood to the remaining part of the body, and reversely, or somehow leaves the body.

![Figure 2: A pharmacokinetic model](image2)
Example: Figure 3 shows a less typical example. We consider a chemical reaction:

\[ A + B \xrightarrow{v_1} AB \xleftarrow{v_2} \]

The concentrations are denoted

\[ x_1 = [A] \]
\[ x_2 = [B] \]
\[ x_3 = [AB] \]

and typically the reaction rates are given by

\[ v_1 = k_1 x_1 x_2 \]
\[ v_2 = k_2 x_3 \]

Representations of compartmental models

The representation of a compartmental model as a collection of boxes (or circles) and arrows may be called a connectivity diagram. An alternative is to use a directed graph, as in figure 3. The arrows are then the directed edges, which connect the nodes.

Some vocabulary:

- A directed graph is complete if all pairs of nodes, \( x_i, x_j \) are connected in at least one direction, i.e. either \( x_i \rightarrow x_j \) or \( x_j \rightarrow x_i \).
- A directed graph is symmetric if whenever there is an edge \( x_i \rightarrow x_j \), there is also the edge \( x_j \rightarrow x_i \).
- A path from node \( x_i \) to node \( x_j \) is a sequence of edges \( x_i \rightarrow x_{k_1} \rightarrow \cdots \rightarrow x_{k_N} \rightarrow x_j \)
- A node \( x_i \) is reachable from \( x_j \) if there is a path from \( x_i \) to \( x_j \).
- A graph is strongly connected if for any pair of nodes \( x_i, x_j \), there is a path from \( x_i \) to \( x_j \).
**Example:** The following graph (figure 5) is not strongly connected. However, the subgraphs which consist of the encircled nodes and edges are. These subgraphs are called the strong components of the graph. Sometimes it is useful to consider a simplified graph that is obtained by replacing the strong components by a single node. This is called condensation by strong components, and is illustrated in the figure.

![Figure 5: A directed graph which is connected but not strongly connected. The strong components are indicated by circles.](image)

**The adjacency matrix and the reachability matrix**

Consider the following graph:

![Figure 6: A directed graph with five nodes](image)

For a graph with $N$ nodes, $x_1, ..., x_N$, the adjacency matrix is a matrix $A = \{a_{ij}\}$ with 0 on the diagonal, and the entry $a_{ij} = 1$ if there is an edge from $x_i$ to $x_j$ and $a_{ij} = 0$ otherwise. The reachability matrix is a matrix $R = \{r_{ij}\}$ with 1 on the diagonal, and the entry $r_{ij} = 1$ if there is a path from $x_i$ to $x_j$ and $a_{ij} = 0$ otherwise. For the example in figure 6 we have

$$
\begin{align*}
A &= \begin{pmatrix}
0 & 1 & 1 & 0 & 0 \\
1 & 0 & 1 & 0 & 0 \\
0 & 0 & 0 & 1 & 1 \\
0 & 0 & 1 & 0 & 0 \\
0 & 0 & 0 & 1 & 0 \\
\end{pmatrix} \\
\text{and} \\
R &= \begin{pmatrix}
1 & 1 & 1 & 1 \\
1 & 1 & 1 & 1 \\
0 & 0 & 1 & 1 \\
0 & 0 & 1 & 1 \\
0 & 0 & 1 & 1 \\
\end{pmatrix}
\end{align*}
$$

One can show that

$$
R = I + A + A^2 + ... + A^{N-1}
$$
Two special types of compartmental models

A catenary system is one where all compartments are connected in a chain, with only one input compartment and one output compartment. A mamillary system is one which has one central compartment, that may have an input and an output, and a number of compartments that are connected only to the central compartment.

Some more definitions

- An outflow corresponds to a compartment with which has an arrow leaving the system. In a graph representation, one usually adds a node that corresponds to the outside.
- A compartmental system is outflow connected if from every compartment (node) there is a path to a compartment with an outflow.
- A compartment A is structurally influenced by a compartment C if it can reached from C (see figure 9).
A compartment B may be *rate influenced* by a compartment C if the a transfer rate $v_{BA}$ depends on the content of compartment C.

A subsystem that is *outflow closed*, i.e., there is no path leading to a compartment that has an outflow, is called a *trap*.

If a trap does not contain any traps in itself, it is called a *simple trap*.

**The differential equation**

The rate of transfer into and out from a compartment are usually defined as in figure 10 below. This means that

- The rate of input into compartment number $i$ is denoted $I_i$.
- The rate of outflow from a compartment to the outside of the compartmental system is denoted $F_{0i}$. The sum of all outflows is often called *clearance*.
- The rate of flow from compartment $i$ to compartment $j$ is denoted $F_{ji}$. N.B. The order of the indices is opposite to the one often used to describe a Markov chain!

The units used to define the transfer rates should be *amount of material / unit of time*, and typically these rates depend on both the concentration and on time. In particular the transfer rates from a compartment is usually described in terms of the *fractional transfer rate*, which gives the *fraction* of the material contained in compartment $i$ that leaves the compartment in a unit of time. The unit is then $\text{time}^{-1}$.
If we write
- \( q_i \) for the amount of material in compartment \( i \)
- \( f_{ij} \) the fractional transfer rate from compartment \( i \) to \( j \)

we may write a system of differential equation for the amount of material in each compartment:

\[
\frac{dq_i}{dt} = \sum_{i \neq j} (F_{ij} - F_{ji}) + I_i - F_{0i}q_i
\]

The system is said to be \textit{linear} if the fractional transfer rates and the input rates are independent of the \( q_j \).

To simplify notation, we may write

\[
q = \begin{pmatrix} q_1 \\ q_2 \\ \vdots \\ q_N \end{pmatrix} \quad \text{and} \quad f = \begin{pmatrix} f_{11} & f_{12} & \cdots & f_{1N} \\ f_{21} & f_{22} & \cdots & f_{2N} \\ \vdots & \vdots & \ddots & \vdots \\ f_{N1} & f_{N2} & \cdots & f_{NN} \end{pmatrix},
\]

where the diagonal elements are defined as

\[
f_{ii} = -f_{0i} - \sum_{j \neq i} f_{ji}.
\]

The system of differential equations is then

\[
\frac{dq}{dt} = f q + I. \tag{1}
\]

The matrix \( f \) and the vector \( I \) may in general depend on both \( q \) and \( t \), and often also on a set of parameters:

\[
f = f(t, q, p) \quad \text{and} \quad I = I(t, q, p)
\]

The coefficients of \( f \) satisfy
1. \( f_{ij} \geq 0 \) for \( i \neq j \).
2. \( f_{ii} \leq -\sum_{j \neq i} f_{ji} \)

Any matrix satisfying these to criteria is called a \textit{compartmental matrix}, and a differential equation as in equation (1) is called a \textit{compartmental system}.
Two examples

Infectious diseases

Here we consider a population consisting of individuals that are either susceptible to be infected, infected (in this case, that are sick, it may happen that individuals carry an infection, and may infect others without being sick themselves), and finally, individuals who have recovered from the infection, but are immune. Denoting these different categories by $X$, $Y$ and $Z$, we may draw the following compartmental model:

![Figure 11: A model for an infectious disease](image)

Here $u$ denotes the rate of (non-infected) individuals entering the population, and $\alpha$, $\beta$ and $\gamma$ denote the fractional transfer coefficients. By $\mu$ we mean the mortality rate; in this case susceptible and infected individuals have the same mortality rate, which may not be realistic, at least for dangerous infections. It is reasonable to assume that the infection rate is proportional to the fraction of infected individuals, so

$$\beta = \frac{\lambda y}{x + y + z}$$

The dynamics of this particular disease can then be expressed by a system of three coupled differential equations:

$$\frac{dx}{dt} = u - \mu x - \frac{\lambda y}{x + y + z} x + \alpha z$$

$$\frac{dy}{dt} = \frac{\lambda y}{x + y + z} x - \gamma y - \lambda y$$

$$\frac{dz}{dt} = \gamma y - \alpha z$$

You should check for yourself that this is indeed a compartmental system.

An enzyme reaction

This is a typical reaction that involves a substrate $S$, a product $P$, the enzyme $E$ that catalyses the reaction, and the intermediary complex $ES$. The reaction can be written

$$S + E \xrightarrow{k_1} AB \xrightarrow{k_3} P + E$$

We denote the concentrations of the different substances as follows:

$$x_1 = [S] \quad x_2 = [S]$$

$$y_1 = [E] \quad y_2 = [ES]$$

$$x_3 = [\text{ES}]$$
where $x_3$ is the concentration of $S$ bound in the complex with the enzyme. The total amounts of the substances is obtained by multiplying the concentrations by the volume $V$:

$$
q_1 = x_1 V, \quad q_2 = x_2 V, \quad q_3 = x_3 V
$$

$$
q_4 = y_1 V, \quad q_5 = y_2 V.
$$

Here it is natural to consider a compartment system as illustrated in figure 12.

![Figure 12: A compartmental model for an enzyme reaction](image)

Of course the different concentrations are not independent, and the system can be fully described by a system of three ordinary differential equations:

$$
\frac{dx_1}{dt} = -k_1 y_1 x_1 + k_2 y_2
$$

$$
\frac{dx_2}{dt} = k_3 y_2 x_1 - k_4 y_1 x_2
$$

$$
\frac{dy_2}{dt} = k_1 x_1 y_1 - (k_2 + k_3)y_2 + k_4 x_2 y_1
$$

**Tracer experiments**

The last couple of pages concern the possibility of determining the state of the system by experiment. The model is again the well stirred tank, and we suppose that it is in a stationary state, which means that the in and out flows as well as the quantity kept in the tank are constant. If it is not possible to directly measure the flux rates, is it possible to design an experiment to find the values anyway?

A very common procedure is by the introduction of a tracer. In the tank we can think of introducing a small quantity of a different substance $X$ into the tank. As the content of the tank is replaced, the concentration of the added substance will decrease, and by measuring its concentration in the tank, it is in fact possible to determine both the volume $V$ and the fluxes. Figure 13 illustrates the situation.

We denote the concentration $[X]$ by $Q(t)$, so that $Q(t) = X(t)/V$. Then the initial concentration $Q(0) = X(0)/V$, and if we assume that we know the quantity $X(0)$ of substance that was injected into the tank, we can already compute $V$. In practice one measures a time series of concentrations, according to figure 14.

The measured data should now be compared with the theoretical concentrations for a given set of parameters. The total amount of substance in the tank is described by

$$
\frac{dX(t)}{dt} = -Q(t)q_2 = -\frac{q_2}{V} X(t)
$$
and dividing by $V$ gives the same equation for the concentration, which then evolves according to

$$Q(t) = Q(0)e^{-\frac{q_2}{V}t}.$$  

In figure 14 both the theoretical curve and the experimental data are plotted. The most common way of estimating the parameters is by minimizing

$$S(V, q_2) = \frac{(\tilde{Q}_1 - Q(t_1))^2}{\sigma^2_1} + \frac{(\tilde{Q}_2 - Q(t_2))^2}{\sigma^2_2} + \ldots + \frac{(\tilde{Q}_N - Q(t_N))^2}{\sigma^2_N},$$

(in the figure, there are $N = 4$ measurements). The $\sigma^2_i$ describe the size of the errors in measurements. If the errors are normally distributed, and the $\sigma^2_i$ are estimators of the variance in the errors, then minimizing $S(V, q_2)$ is equivalent to finding $V$ and $q_2$ by the principle of maximum likelihood.