Seminar: Compartmental Modelling

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ES4A4 Biomedical Systems Modelling
What are compartmental models?

- Consist of finite number of compartments
  - homogeneous, well-mixed, lumped subsystems
  - kinetically the same
- Exchange with each other and environment
- Inter-compartment transfers represent flow of material
- Rate of change of quantity of material in each compartment described by first order ODE
  - principle of mass balance
General form of system equations

\[ \frac{dq_i}{dt} = f_{0i} + \sum_{j=1, j\neq i}^{n} f_{ji} q_j - f_{i0} - \sum_{j=1, j\neq i}^{n} f_{ij} q_i \quad \text{for } i = 1, 2, \ldots, n \]

where \( q_i \) denotes quantity in compartment \( i \)
\( f_{ij} \) denotes the flow rate coefficient from \( i \) to \( j \)
compartment 0 is external environment
Areas of application of compartmental models

- Used extensively in:
  - Pharmacokinetics and Anaesthesia (drug kinetics)
  - Biomedicine/Biomedical Control (Tumour Targeting)
  - Chemical Reaction Systems (Enzyme Chains, Nuclear Reactors)

- Also:
  - Electrical Engineering (Lumped systems of transmission lines, filters, ladder networks)
  - Ecosystems (Ecological Models)
  - Neural Computing (Neural Nets)
  - Process Industries (Black Box Models)
Linear (time-invariant) compartmental models

- Flow rates, $F_{ij} = f_{ij} q_i$
  - directly proportional to amount of material in donor compartment, $q_i$ (mathematically: $f_{ij} = k_{ij}$)
  - does not depend on any other amounts

- System equations:

$$
\frac{dq_i}{dt} = \sum_{j=1}^{n} k_{ji} q_j - \left( k_{i0} + \sum_{j=1}^{n} k_{ij} \right) q_i + u_i \quad \text{for } i = 1, 2, \ldots, n
$$

where inflow rate $f_{0i}$ has been written as an input/control function $u_i(t)$ – external source of material
• General form of system equations

\[
\begin{pmatrix}
\dot{q}_1 \\
\vdots \\
\dot{q}_n
\end{pmatrix} =
\begin{pmatrix}
-k_{10} - k_{12} - \cdots - k_{1n} & \cdots & k_{n1} \\
\vdots & & \vdots \\
-k_{n0} - k_{n1} - \cdots - k_{n(n-1)} & \cdots & -k_{nn}
\end{pmatrix}
\begin{pmatrix}
q_1 \\
\vdots \\
q_n
\end{pmatrix} +
\begin{pmatrix}
u_1 \\
\vdots \\
u_n
\end{pmatrix}
\]

• Perhaps an oversimplification, but does provide (in general) good description of responses of many systems when small perturbation (ie: input) is made to system previously in steady state
Common forms of input for pharmacokinetic models

- Mathematical Term
  \[ u_i(t) \]
  \[ D_i \delta(t) \] – impulsive input of size \( D_i \) at time \( t = 0 \)
  \[ k_{0i} \] – constant input of size \( k_{0i} \) per unit of time
  \[ \sum_{j=1}^{m} D_{ij} \delta(t - t_j) \] – repeated impulsive inputs of size \( D_{ij} \) at times \( t_j \)

- Pharmacokinetic Term
  input or intervention
  bolus injection of dose \( D_i \)
  constant infusion of drug, rate \( k_{0i} \) per unit of time
  repeated bolus injections of dose \( D_{ij} \) at times \( t_j \)
Rules for compartmental models

• General rules
  – amounts can’t be negative (positive system), $q_i \geq 0$
  – flows can’t be negative, $f_{ij}(q)q_i \geq 0$

• State space form:
  – can be written in form $q' = F(q)q + I$
  – $F(q)$ is compartmental matrix and satisfies
    ▪ sum of terms down column $i$ equals elimination from compartment $i$
    ▪ diagonal terms are outflows from respective compartments – so not positive
    ▪ off diagonal terms are inflows so not negative
Example: One compartment model

• Examples:
  – radioactive substance (decay)
  – systemic blood & perfused tissue

• System equations
  \[
  \dot{q}_1(t) = -k_1 q_1(t) + b_1 u_1(t)
  \]
  with observation
  \[
  y_1(t) = c_1 q_1(t)
  \]
  \((c_1 \text{ is observation gain})\)
Example: One compartment model

• System equations
  \[ \dot{q}_1(t) = -k_{10}q_1(t) + b_1u_1(t) \]
  \[ y_1(t) = c_1 q_1(t) \]

• Taking Laplace transforms and rearranging
  \[ G(s) = \frac{Y(s)}{U(s)} = \frac{c_1b_1}{s + k_{10}} \]

• the **transfer function** relating input to output
Example: One compartment model

- **Transfer function:**
  \[ G(s) = \frac{Y(s)}{U(s)} = \frac{b_1 c_1}{s + k_{10}} \]

- **Impulsive input,** \( u_1(t) = D_1 \delta(t) \)
  \[ U(s) = D_1 \quad \Rightarrow \quad y_1(t) = b_1 c_1 D_1 e^{-k_{10}t} \]

- **Constant input,** \( u_1(t) = k_{01} \)
  \[ U(s) = \frac{k_{01}}{s} \quad \Rightarrow \quad y_1(t) = \frac{b_1 c_1 k_{01}}{k_{10}} \left( 1 - e^{-k_{10}t} \right) \]
Example: One compartment model

Observed impulse response of one compartment model
Example: One compartment model

Observed step (constant infusion) response of one compartment model
Example: One compartment model

Observed response of one compartment model with repeated bolus injections of size $D_1$ repeated at regular intervals of $T$
Example: Two compartment model

- System equations

\[ y_1 = c_1 q_1 \]

with observation

\[ c_1 \text{ is observation gain} \]
Example: Two compartment model

- System equations
  \[
  \dot{q}_1(t) = -(k_{10} + k_{12})q_1(t) + k_{21}q_2(t) + b_1u_1(t)
  \]
  \[
  \dot{q}_2(t) = k_{12}q_1(t) - (k_{20} + k_{21})q_2(t) + b_2u_2(t)
  \]
  with observation
  \[
  y_1(t) = c_1q_1(t), \quad y_2(t) = c_2q_2(t)
  \]
  \((c_i\text{ are observation gains})\)
Example: Two compartment model

- System equations
  \[ \dot{q}_1(t) = -(k_{10} + k_{12})q_1(t) + k_{21}q_2(t) + b_1u_1(t) \]
  \[ \dot{q}_2(t) = k_{12}q_1(t) - (k_{20} + k_{21})q_2(t) + b_2u_2(t) \]
  \[ y_1(t) = c_1q_1(t) \]
  \[ y_2(t) = c_2q_2(t) \]

- These can be rewritten in vector-matrix state-space form:
  \[ \dot{q}(t) = Aq(t) + Bu(t) \]
  \[ y(t) = Cq(t) \]

- for matrices \(A, B and C\); and so the Transfer Function is given by \(C (sI - A)^{-1} B\)
Example: Two compartment model

- **System equations**
  \[
  \dot{q}_1(t) = -(k_{10} + k_{12})q_1(t) + k_{21}q_2(t) + b_1u_1(t)
  \]
  \[
  \dot{q}_2(t) = k_{12}q_1(t) - (k_{20} + k_{21})q_2(t) + b_2u_2(t)
  \]

- **Note:**
  \[
  \begin{pmatrix}
  a_{11} & a_{12} \\
  a_{21} & a_{22}
  \end{pmatrix}
  \]
  \[
  \text{If } A = \begin{pmatrix}
  a_{11} & a_{12} \\
  a_{21} & a_{22}
  \end{pmatrix}
  \]
  then \(a_{11} = -(k_{10} + k_{12}), \quad a_{12} = k_{21}\)
  \(a_{21} = k_{12}, \quad a_{22} = -(k_{20} + k_{21})\)

- **So** \(a_{ij} = k_{ji} \quad (i \neq j)\) – off diagonal terms

- **Diagonal terms:** \(a_{ii} = -k_{i0} - \sum_{j=1, j \neq i}^{2} k_{ij}\)
Example: Two compartment model

• Impulsive input
  – Suppose $u_1(t) = D_1 \delta(t)$ (and $u_2(t) = 0$)
    $$y_1(t) = b_1 c_1 D_1 \left( \frac{\lambda_1 - a_{22}}{\lambda_1 - \lambda_2} e^{\lambda_1 t} + \frac{a_{22} - \lambda_2}{\lambda_1 - \lambda_2} e^{\lambda_2 t} \right)$$
    $$y_2(t) = \frac{a_{21} b_1 c_1 D_1}{\lambda_1 - \lambda_2} \left( e^{\lambda_1 t} - e^{\lambda_2 t} \right)$$

• Constant infusion
  – Suppose $u_1(t) = k_{01}$ (and $u_2(t) = 0$)
    $$y_1(t) = b_1 c_1 k_{01} \left( \frac{\lambda_1 - a_{22}}{\lambda_1 (\lambda_1 - \lambda_2)} e^{\lambda_1 t} + \frac{a_{22} - \lambda_2}{\lambda_2 (\lambda_1 - \lambda_2)} e^{\lambda_2 t} - \frac{a_{22}}{\lambda_1 \lambda_2} \right)$$
    $$y_2(t) = a_{21} b_1 c_1 k_{01} \left( \frac{1}{\lambda_1 (\lambda_1 - \lambda_2)} e^{\lambda_1 t} - \frac{1}{\lambda_2 (\lambda_1 - \lambda_2)} e^{\lambda_2 t} + \frac{1}{\lambda_1 \lambda_2} \right)$$
Example: Two compartment model

Observed response of two compartment model with impulsive input to compartment 1 (impulse response)
Example: Two compartment model

Observed response of two compartment model with constant input to compartment 1 (*step response*)
Example: One compartment nonlinear model

- System equation
  \[ \dot{q}_1(t) = -\frac{V_m q_1(t)}{K_m + q_1(t)} + b_1 u_1(t), \quad q_1(0) = 0 \]

- **Note:** Elimination (Michaelis-Menten) saturates
- **Impulsive input:** \( u_1(t) = D_1 \delta(t) \), treat as \( q_1(0^+) = D_1 \)
- No explicit analytical solution for \( q_1(t) \)
Michaelis-Menten saturation curve

\[
\frac{V_m \cdot x}{K_m + x}
\]

\[
V_m = \text{Slope} = \frac{V_m}{K_m}
\]

\[
0.5 V_m = \text{Slope} = \frac{V_m}{K_m + x_0}
\]
Input response under nonlinear elimination

Impulse response of one compartment nonlinear model with varying input \((K_m = V_m = b_1 = c_1 = 1)\)
Repeated impulsive inputs under nonlinear elimination

Response to repeated impulsive inputs at regular intervals of 1 time unit with varying input \((K_m = 12, V_m = 15, b_1 = c_1 = 1)\)

(adapted from K. Godfrey. *Compartmental Models and their Applications*, 1983)
Model for Tumour Targeting

- Circles represent states.
- Arrows with single-headed arrows represent linear transitions.
- Arrows with double-headed arrows represent chemical reactions (e.g., A + B ↔ C).
- The equations for the transitions are:
  - $k_1$, $k_2$, $k_3$, $k_4$, $k_5$, $k_6$, $k_7$

### States:
- 1: Injected dose
- 2: Environment
- 3, 4, 5, 6, 3, 5, 3, 6: Various intermediate states

### Equations:
- $k_1$ transition from injected dose to environment
- $k_2$, $k_3$, $k_4$, $k_5$, $k_6$ transitions between states
- $k_7$ transition from environment to injected dose

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Other important considerations

• Identifiability of unknown system parameters
  – Given postulated system model, values for some of parameters (e.g., rate constants) may not be known
  – Identifiability is a theoretical analysis of whether these parameters may be uniquely determined from perfect input/output data
    ▪ Linear systems – relatively straightforward
    ▪ Nonlinear systems – fewer methods, complex

• Parameter estimation (the real situation)
Other important considerations

• Parameter estimation (the *real situation*)
  – It may be necessary/instructive to actually calculate estimates for unknown parameter values for postulated model from real data (actual measurements/observations)
  – Generally performed using computer packages which employ linear/nonlinear regression techniques
  – Practical problems for Pharmacokinetic Models:
    ▪ Few Data Points (eg blood samples)
    ▪ Inaccuracy of Measurement – method of collection (eg urine samples)
    ▪ Measurement Noise