Seminar: Compartmental Modelling

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ES4A4 Biomedical Systems Modelling

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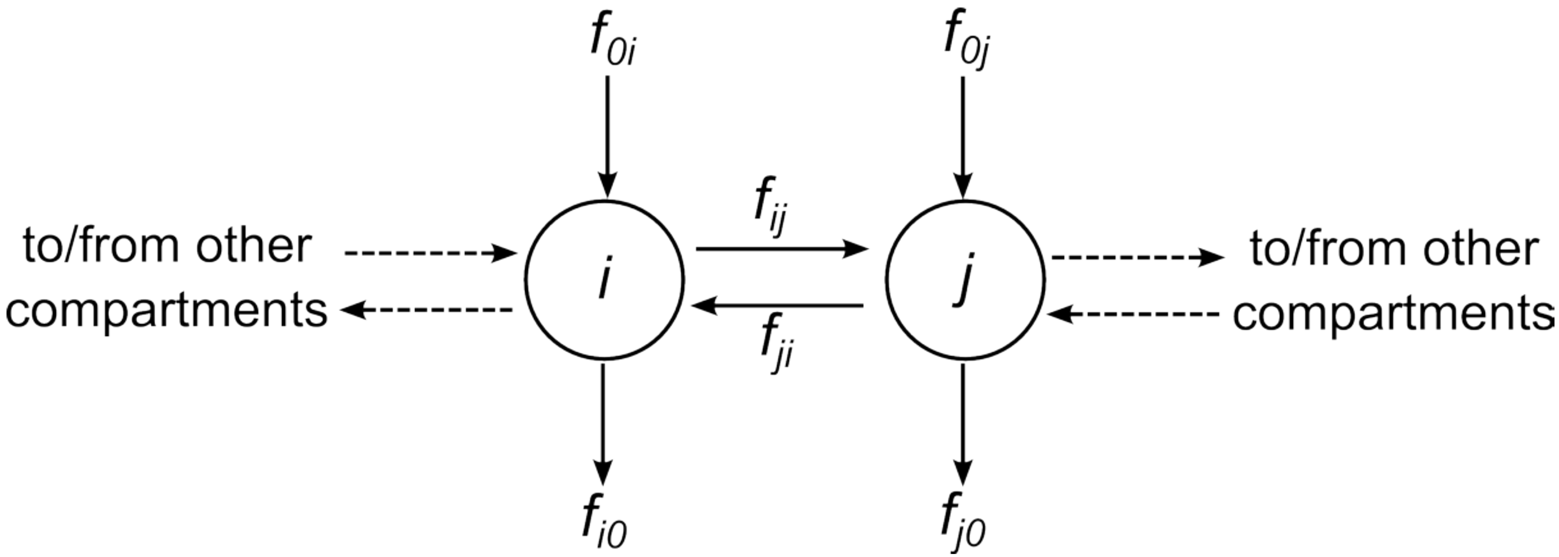
What are compartmental models?

- 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

$$\frac{\mathrm{d}q_i}{\mathrm{d}t} = \left[f_{0i} + \sum_{\substack{j=1 \\ j \neq i}}^{n} f_{ji} q_j \right] - \left[f_{i0} + \sum_{\substack{j=1 \\ j \neq i}}^{n} f_{ij} \right] q_i \quad \text{for } i = 1, 2, \ldots, n$$

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

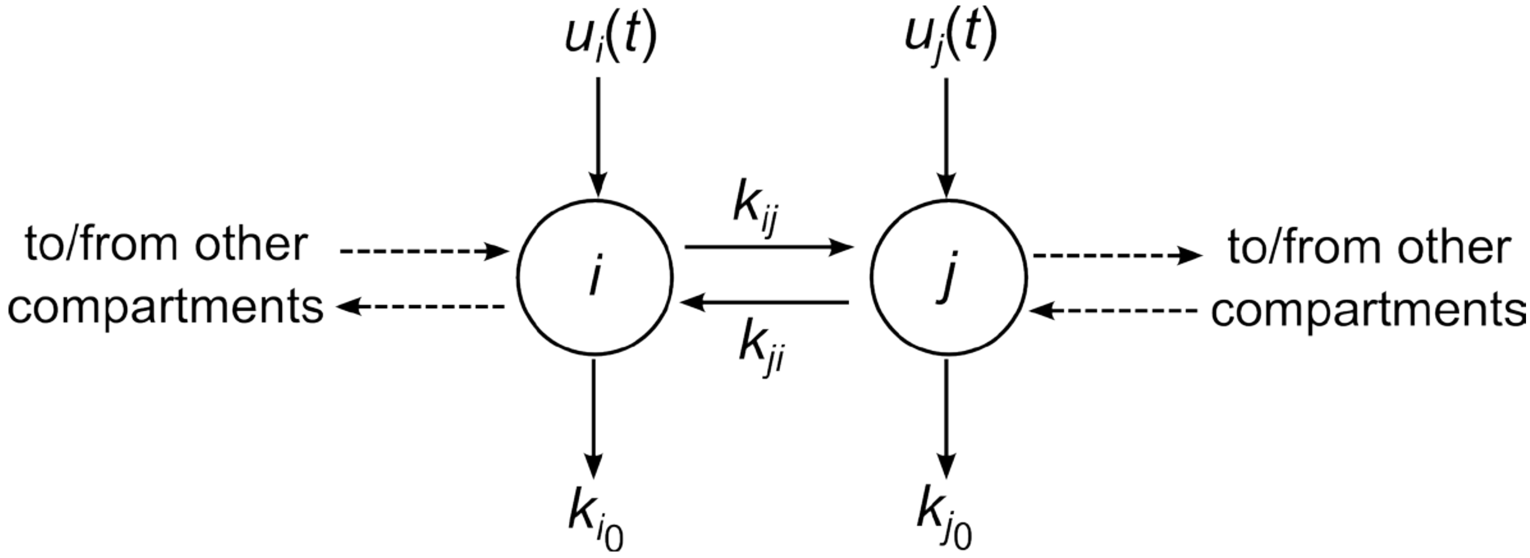
- Used extensively in:
  - Pharmacokinetics and Anaesthesia (drug kinetics)
  - Biomedicine/Biomedical Control (Tumour Targeting)
  - Chemical Reaction Systems (Enzyme Chains, Nuclear Reactors)
- Also:
  - Electrical Engineering (Lumped systems of transmission lines, filters, ladder networks)
  - Ecosystems (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:

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

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

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

- 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

  $\sum_{j=1}^{m} D_{ij}\delta\left(t - t_j\right)$ – repeated impulsive inputs of size D_{ij} at times t_j

- Pharmacokinetic Term

  input or intervention

  bolus injection of dose D_i

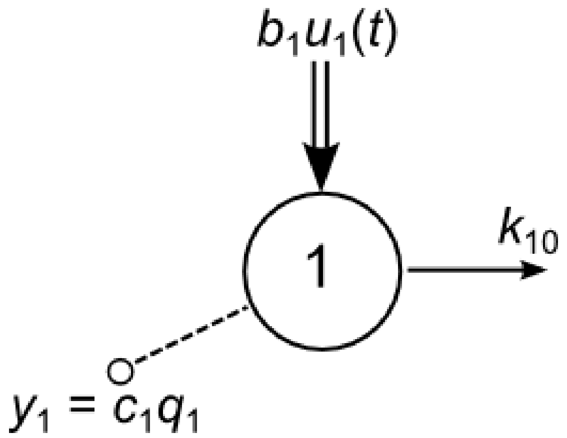
  constant infusion of drug, rate k_{0i} per unit of time

  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, $f_{ij}(\boldsymbol{q})q_i \geq 0$
- State space form:
  - can be written in form $\boldsymbol{q}' = \boldsymbol{F}(\boldsymbol{q})\boldsymbol{q} + \boldsymbol{I}$
  - $\boldsymbol{F}(\boldsymbol{q})$ 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

$$\dot{q}_1(t) = -k_{10}q_1(t) + b_1u_1(t)$$

with observation

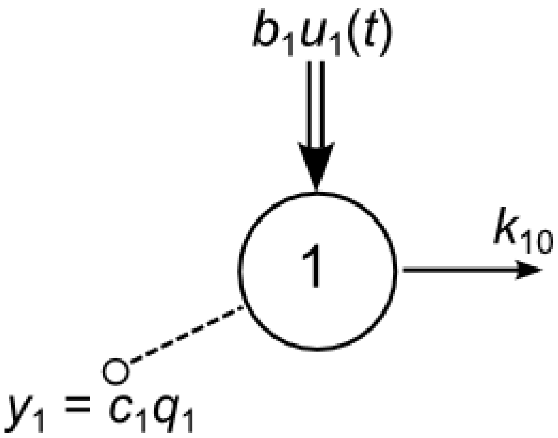
$$y_1(t) = c_1 q_1(t)$$

(c_1 is observation gain)

Example: One compartment model

- System equations

$$\dot{q}_1(t) = -k_{10}q_1(t) + b_1u_1(t)$$
$$y_1(t) = c_1 q_1(t)$$

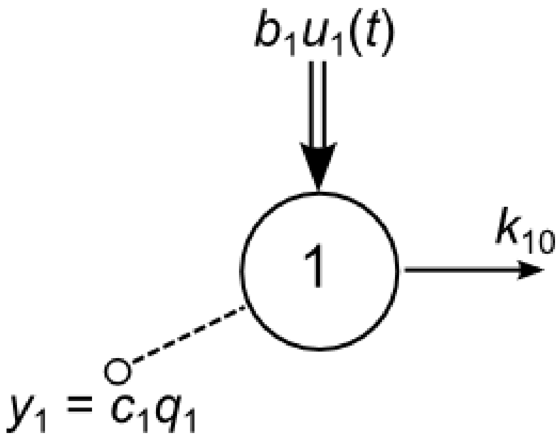


- Taking Laplace transforms and rearranging

$$G(s) = \frac{Y(s)}{U(s)} = \frac{c_1b_1}{s + k_{10}}$$

- the **transfer function** relating input to output

Example: One compartment model



- Transfer function:

$$G(s) = \frac{Y(s)}{U(s)} = \frac{b_1c_1}{s + k_{10}}$$

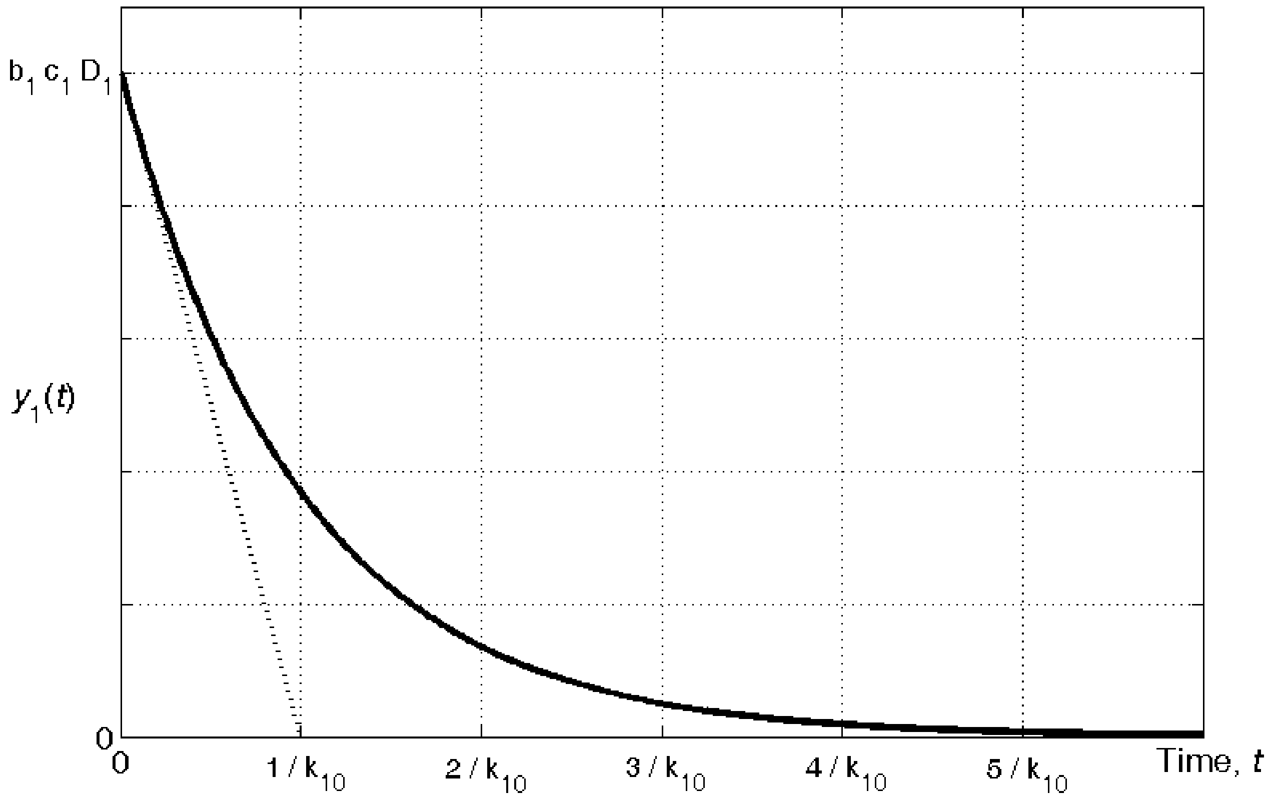
- Impulsive input, $u_1(t) = D_1\delta(t)$

$$U(s) = D_1 \quad \Rightarrow \quad y_1(t) = b_1c_1D_1\,\mathrm{e}^{-k_{10}t}$$

- Constant input, $u_1(t) = k_{01}$

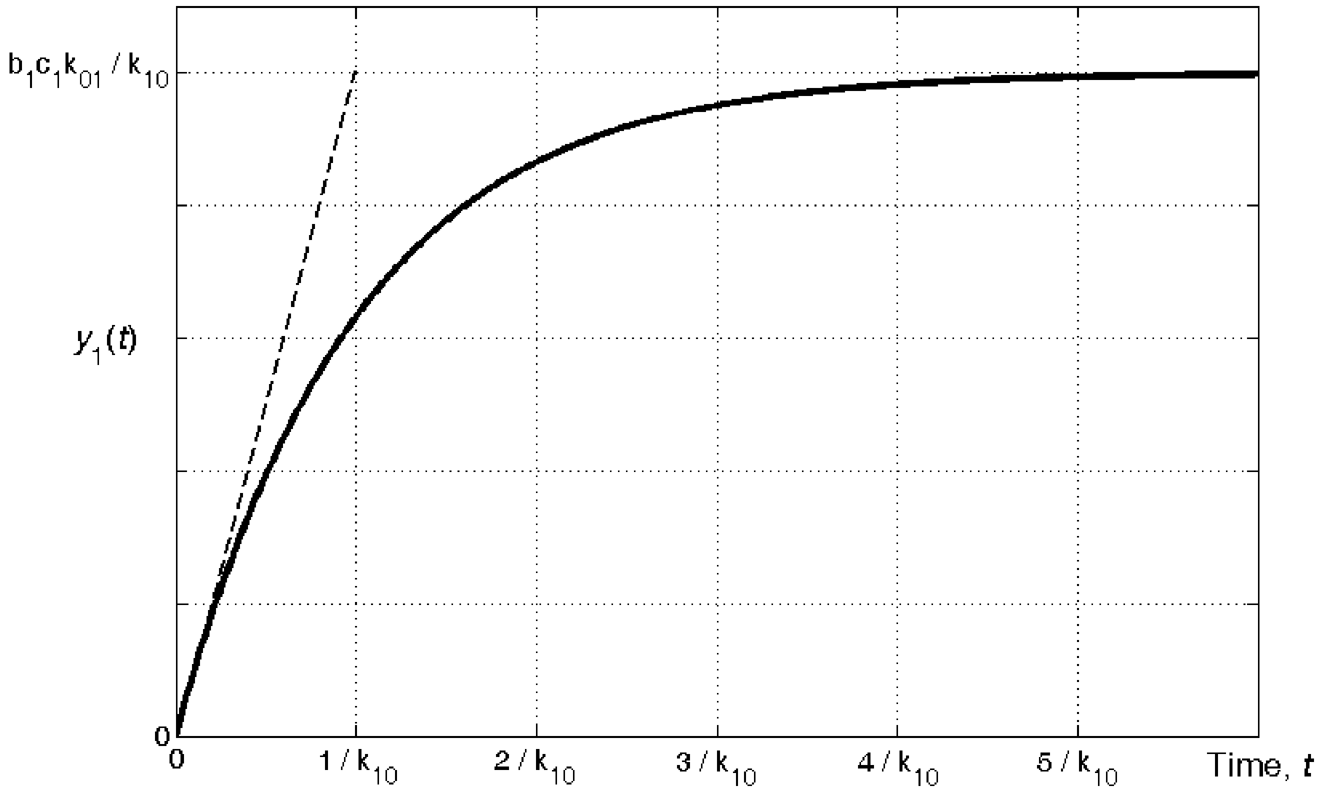
$$U(s) = \frac{k_{01}}{s} \quad \Rightarrow \quad y_1(t) = \frac{b_1c_1k_{01}}{k_{10}}\left(1 - \mathrm{e}^{-k_{10}t}\right)$$

Example: One compartment model



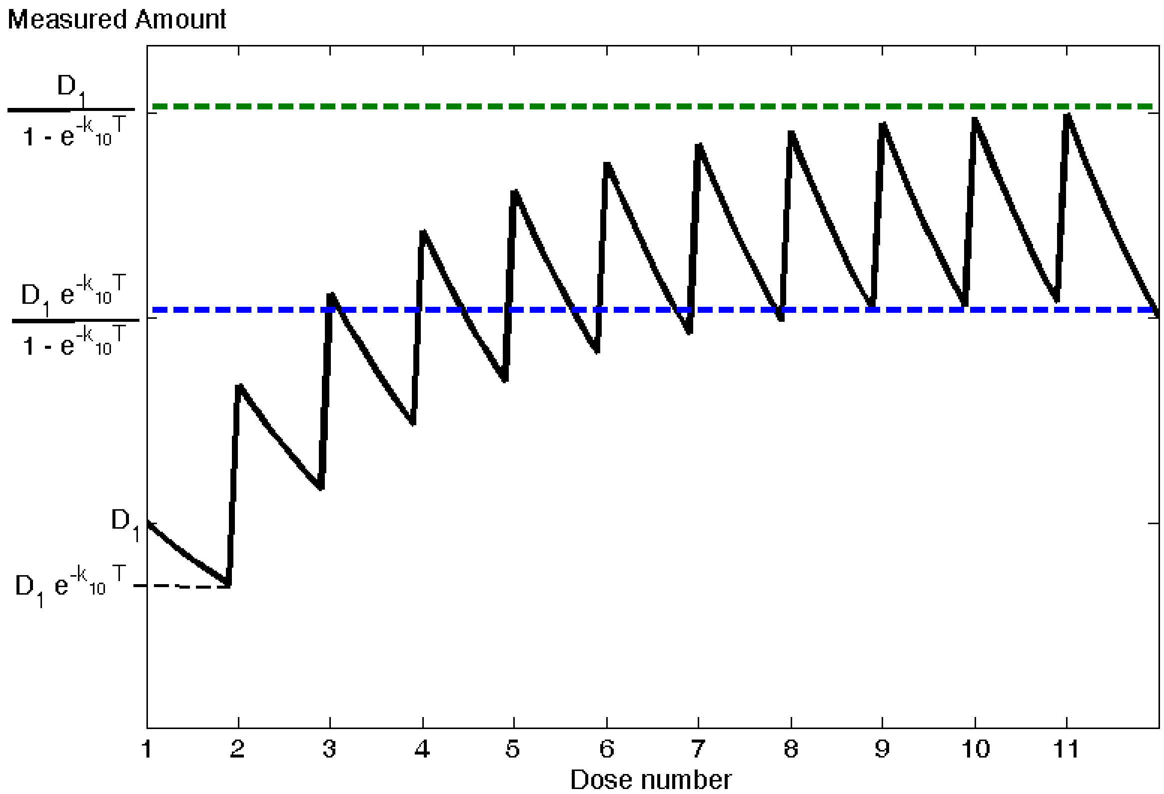
Observed impulse response of one compartment model

Example: One compartment model



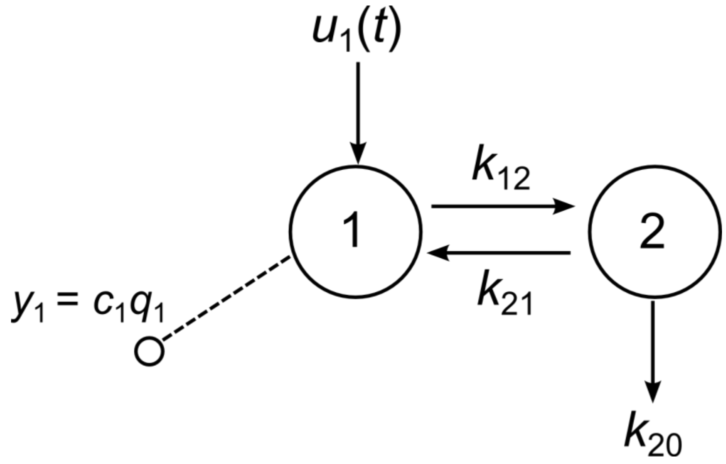
Observed step (constant infusion) response of one compartment model

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

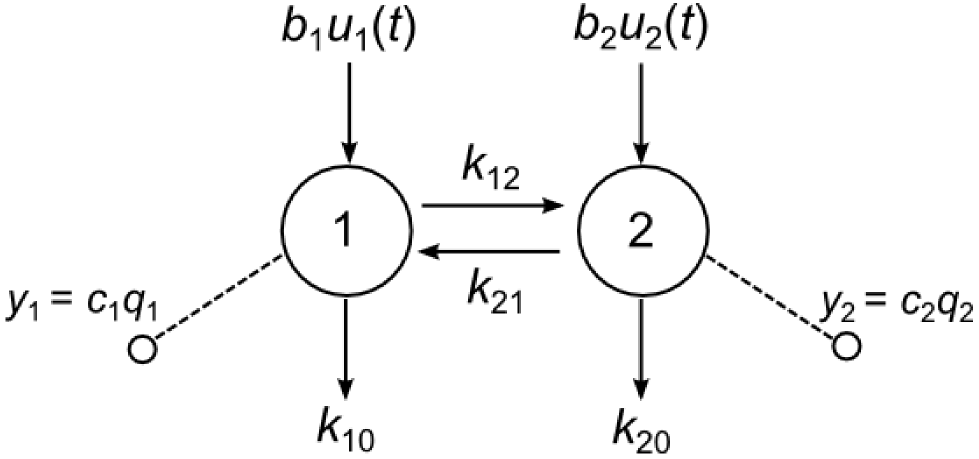
?????

with observation

?????

(c_1 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

$$y_1(t) = c_1 q_1(t), \quad y_2(t) = c_2 q_2(t)$$

(c_i are observation gains)

Example: Two compartment model

- System equations

$$\dot{q}_1(t) = -(k_{10} + k_{12})q_1(t) + k_{21}q_2(t) + b_1u_1(t)$$
$$\dot{q}_2(t) = k_{12}q_1(t) - (k_{20} + k_{21})q_2(t) + b_2u_2(t)$$
$$y_1(t) = c_1 q_1(t)$$
$$y_2(t) = c_2 q_2(t)$$

- These can be rewritten in vector-matrix state-space form:

$$\dot{\boldsymbol{q}}(t) = \boldsymbol{A}\boldsymbol{q}(t) + \boldsymbol{B}\boldsymbol{u}(t)$$
$$\boldsymbol{y}(t) = \boldsymbol{C}\boldsymbol{q}(t)$$

- for matrices ***A***, ***B*** and ***C***; and so the Transfer Function is given by $\boldsymbol{C}\,(s\boldsymbol{I} - \boldsymbol{A})^{-1}\,\boldsymbol{B}$

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:

If $\boldsymbol{A} = \begin{pmatrix} a_{11} & a_{12} \\ a_{21} & a_{22} \end{pmatrix}$

then $a_{11} = -(k_{10} + k_{12}), \quad a_{12} = k_{21}$

$a_{21} = k_{12}, \quad a_{22} = -(k_{20} + k_{21})$

- So $a_{ij} = k_{ji}$ ($i \neq j$) – 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 $u_2(t) = 0$)

$$y_1(t) = b_1 c_1 D_1 \left(\frac{\lambda_1 - a_{22}}{\lambda_1 - \lambda_2} e^{\lambda_1 t} + \frac{a_{22} - \lambda_2}{\lambda_1 - \lambda_2} e^{\lambda_2 t} \right)$$

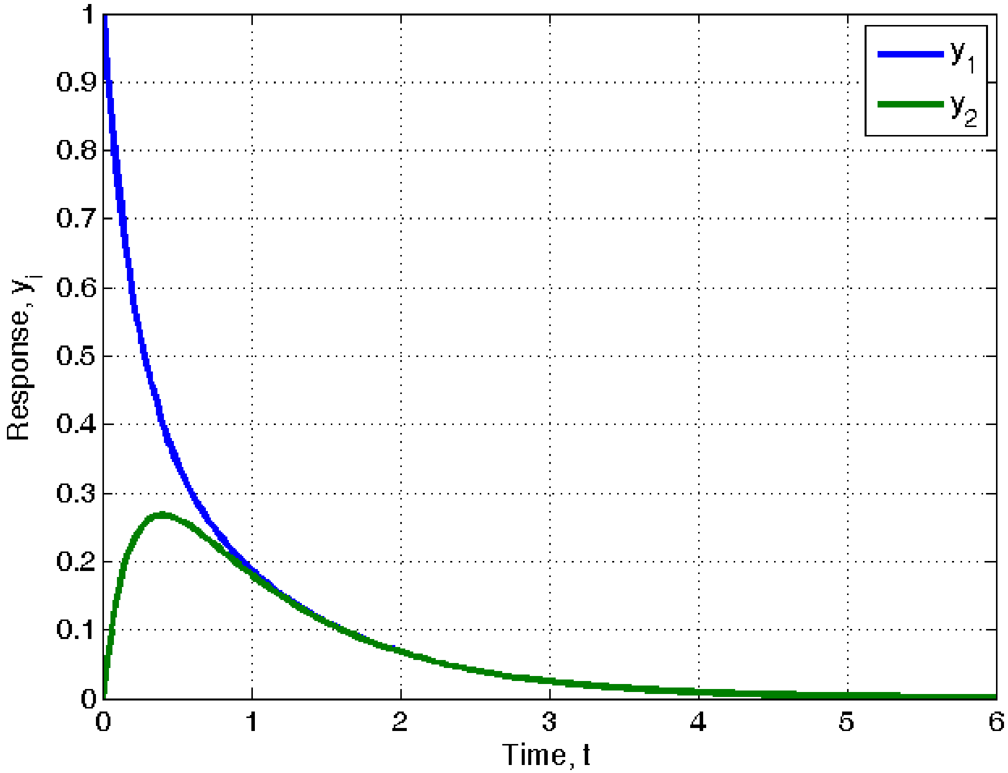
$$y_2(t) = \frac{a_{21} b_1 c_1 D_1}{\lambda_1 - \lambda_2} \left(e^{\lambda_1 t} - e^{\lambda_2 t} \right)$$

- **Constant infusion**
  - Suppose $u_1(t) = k_{01}$ (and $u_2(t) = 0$)

$$y_1(t) = b_1 c_1 k_{01} \left(\frac{\lambda_1 - a_{22}}{\lambda_1 (\lambda_1 - \lambda_2)} e^{\lambda_1 t} + \frac{a_{22} - \lambda_2}{\lambda_2 (\lambda_1 - \lambda_2)} e^{\lambda_2 t} - \frac{a_{22}}{\lambda_1 \lambda_2} \right)$$

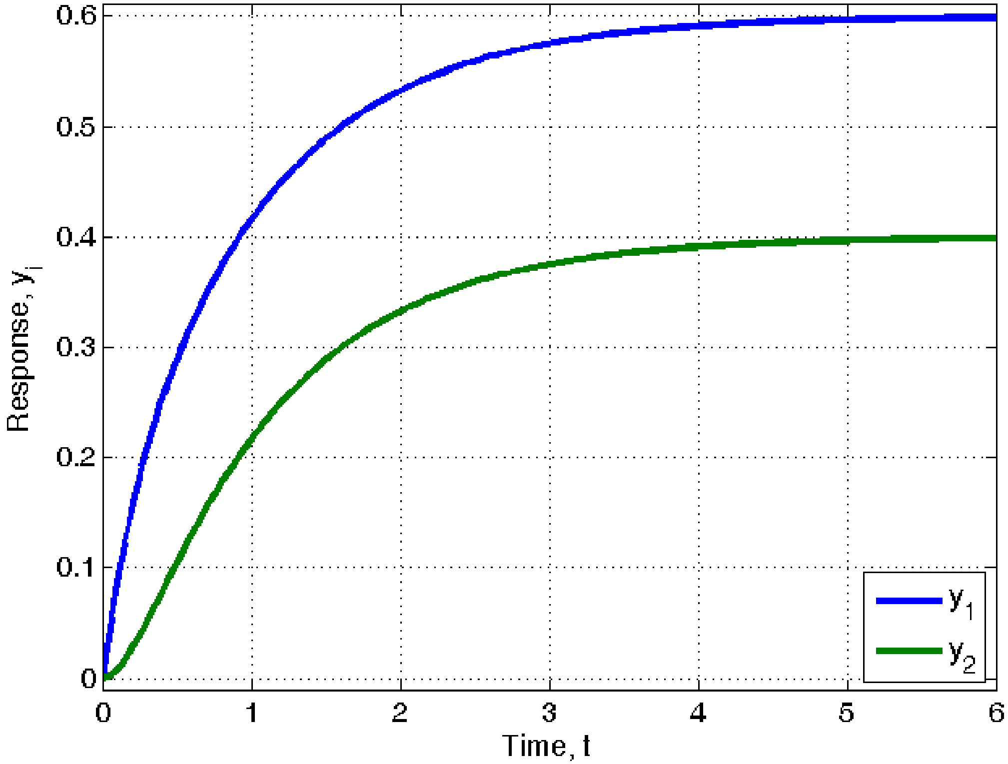
$$y_2(t) = a_{21} b_1 c_1 k_{01} \left(\frac{1}{\lambda_1 (\lambda_1 - \lambda_2)} e^{\lambda_1 t} - \frac{1}{\lambda_2 (\lambda_1 - \lambda_2)} e^{\lambda_2 t} + \frac{1}{\lambda_1 \lambda_2} \right)$$

Example: Two compartment model



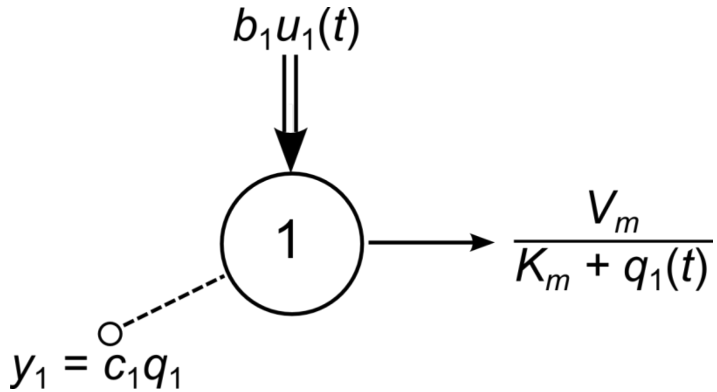
Observed response of two compartment model with impulsive input to compartment 1 (***impulse response***)

Example: Two compartment model



Observed response of two compartment model with constant input to compartment 1 (***step response***)

Example: One compartment nonlinear model

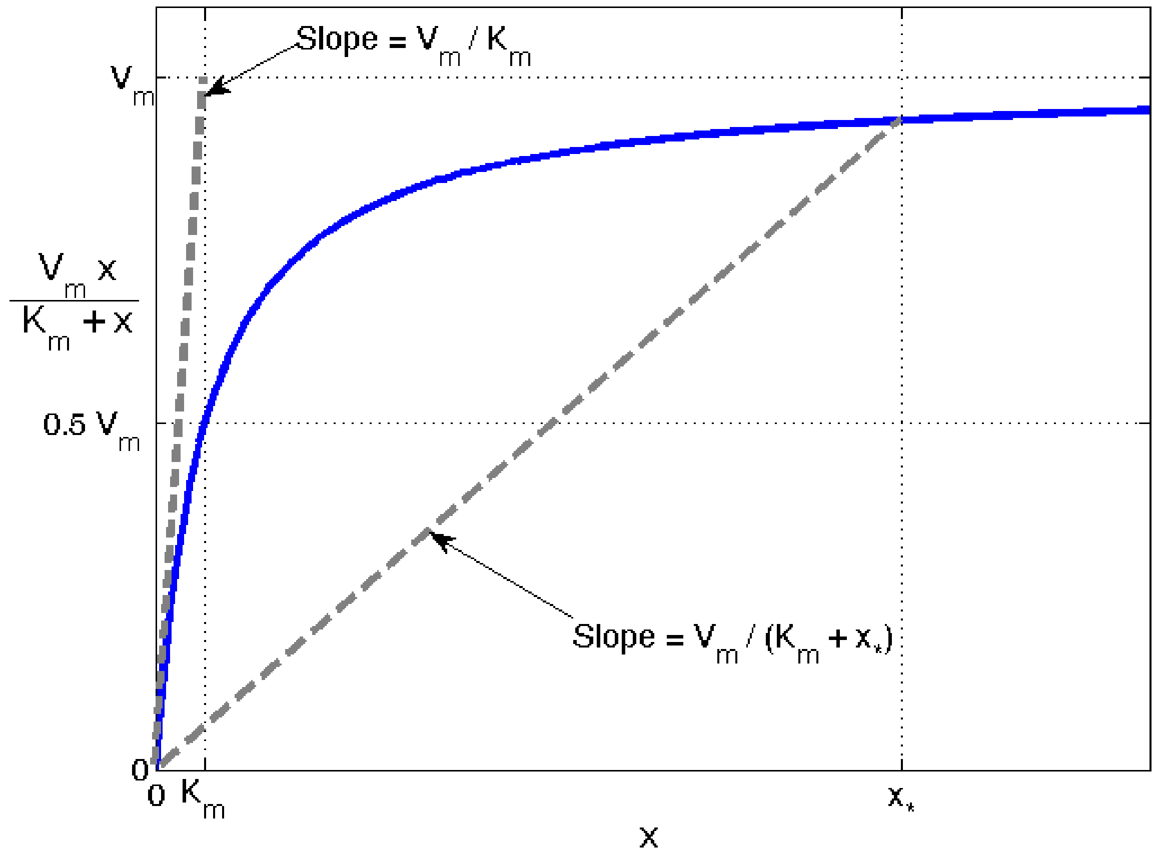


- System equation

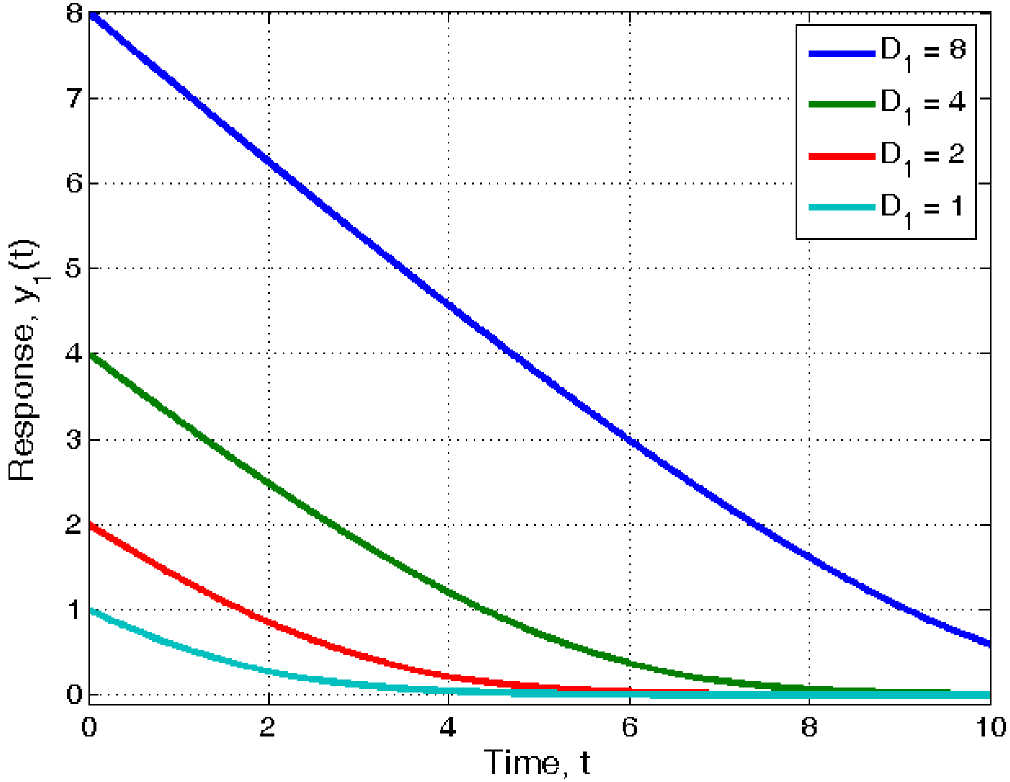
$$\dot{q}_1(t) = -\frac{V_m q_1(t)}{K_m + q_1(t)} + b_1 u_1(t), \quad q_1(0) = 0$$

- **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

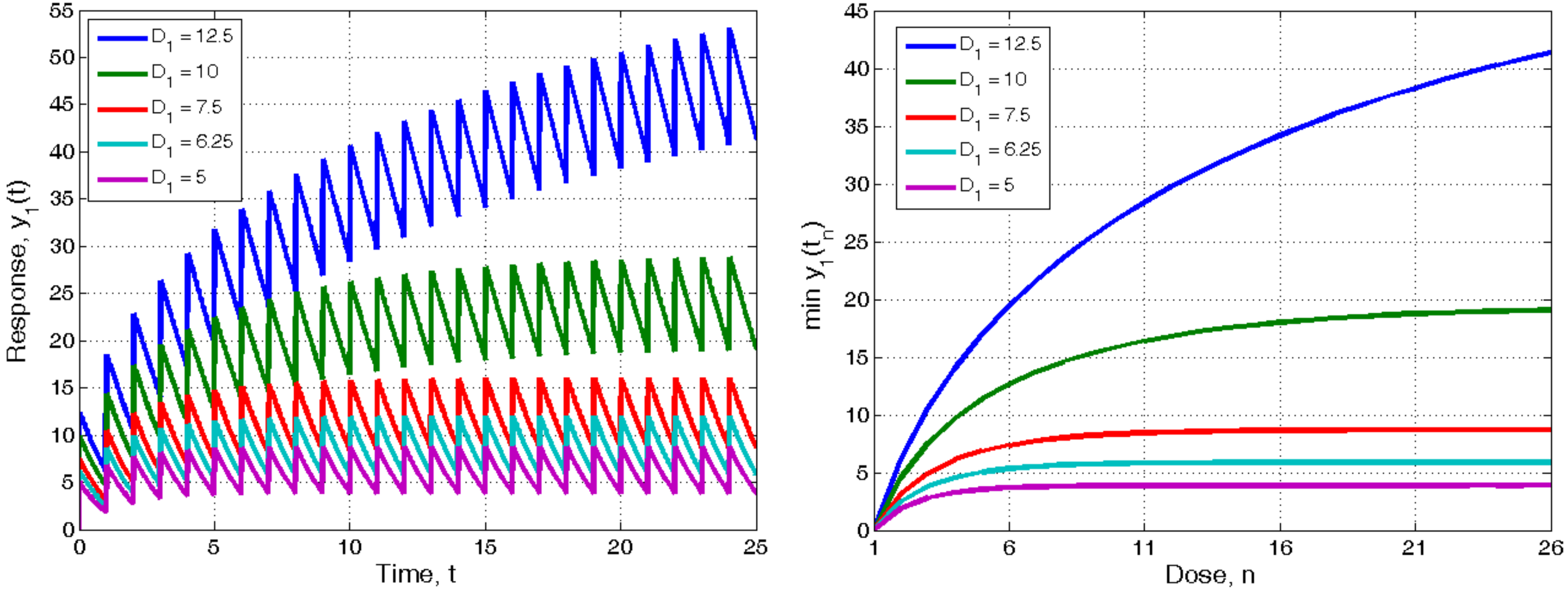


Input response under nonlinear elimination



Impulse response of one compartment nonlinear model with varying input ($K_m = V_m = b_1 = c_1 = 1$)

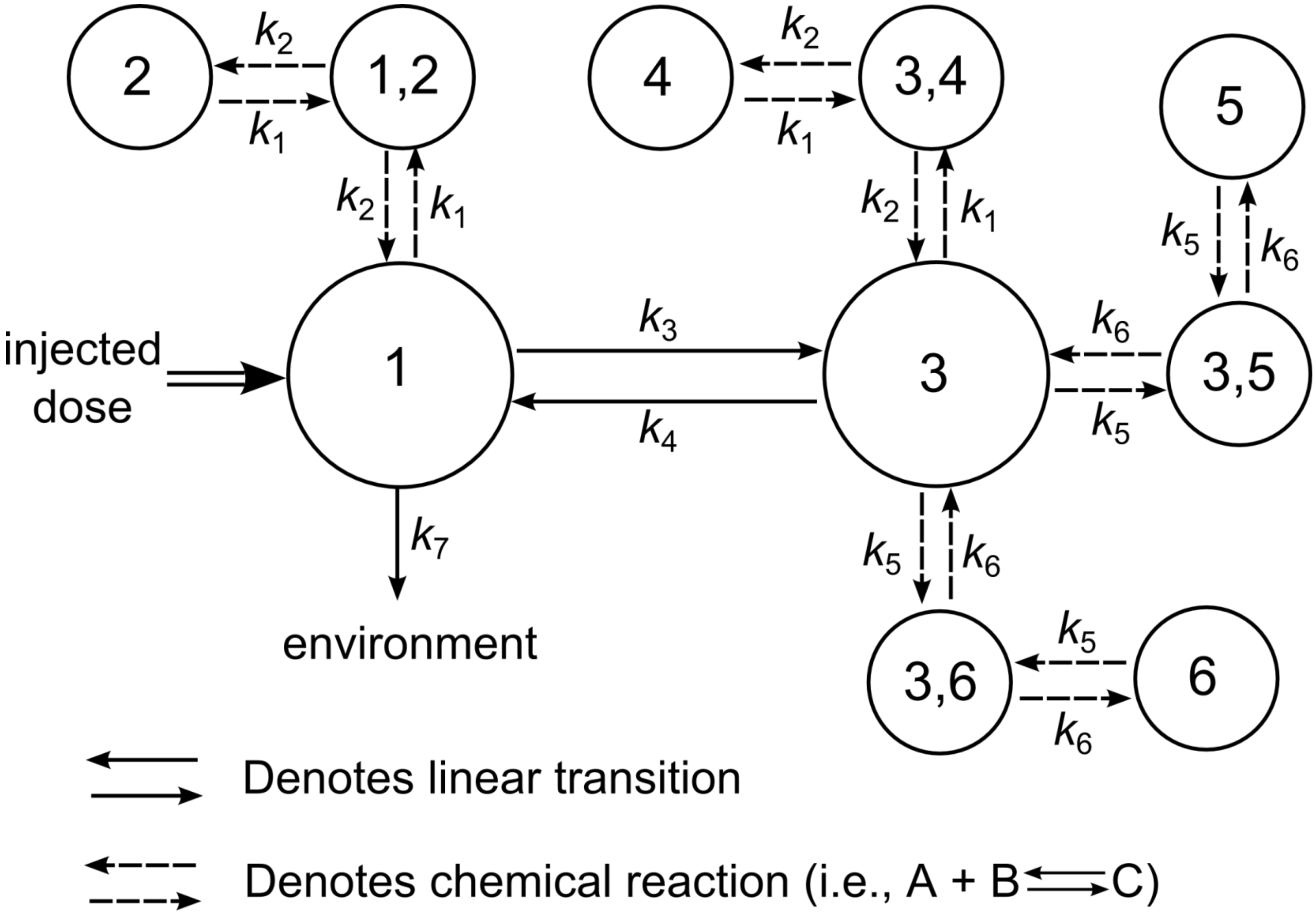
Repeated impulsive inputs under nonlinear elimination



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

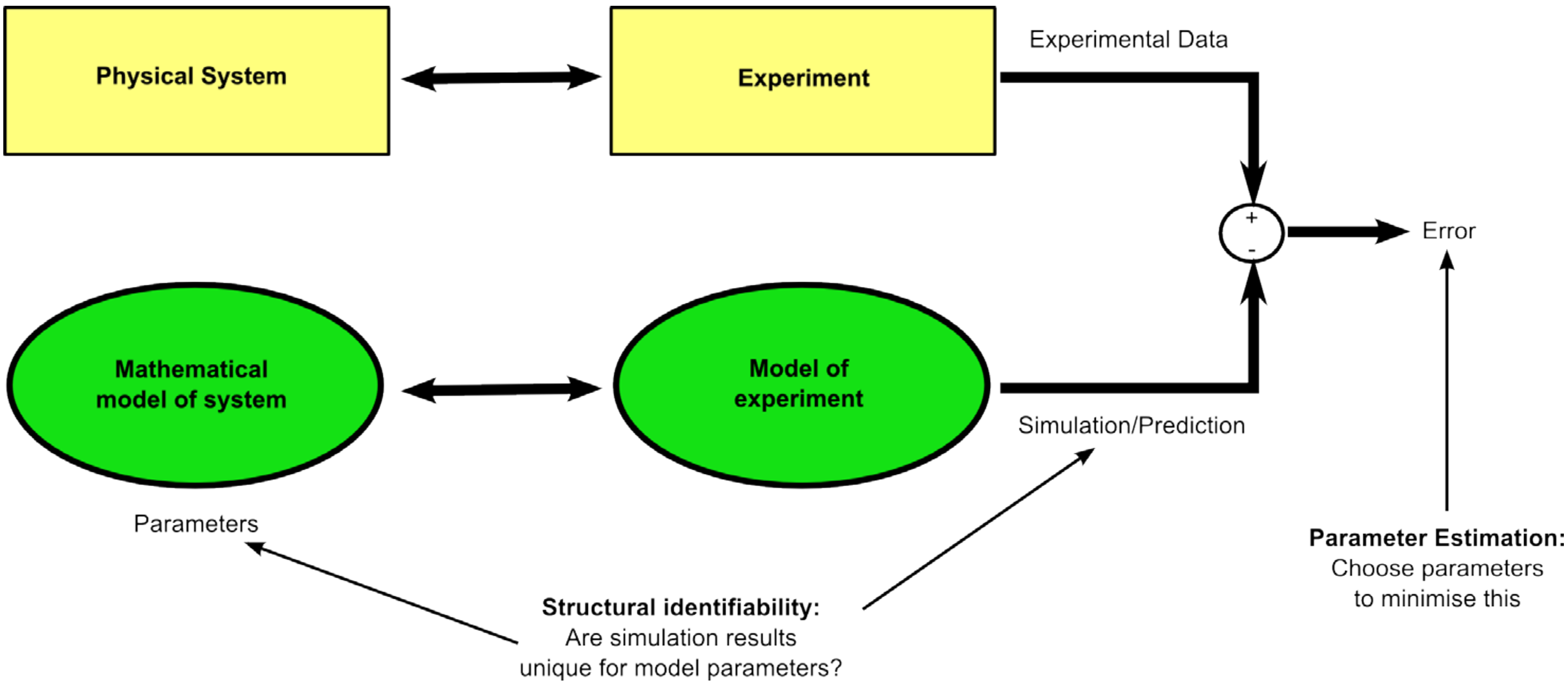


Other important considerations

- Identifiability of unknown system parameters
  - Given postulated system model, values for some of parameters (eg 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


Physical System
Experiment
Experimental Data
+
-
Error
Mathematical model of system
Model of experiment
Simulation/Prediction
Parameters
Structural identifiability:
Are simulation results unique for model parameters?
Parameter Estimation:
Choose parameters to minimise this