Compartmental Modelling: Eigenvalues, Traps and Nonlinear Models

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More Compartmental Modelling

1. Linear (time-invariant) compartmental models
   - No inflows (homogeneous)
   - With inflows (inhomogeneous)
   - Four basic (sub)systems
2. Nonlinear compartmental models
   - Some Examples
   - Pseudo Steady State Approximation

Following definitions relate to compartmental model diagrams:

Definition

A compartmental model is strongly connected (SC) if, for any two compartments i and j, there exists a **path** from i to j, and a **path** from j to i.

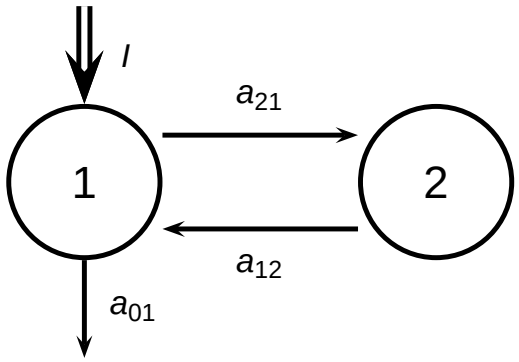
Definition

A compartmental model is outflow connected (OC) if there is a path from any compartment to a compartment with an outflow.

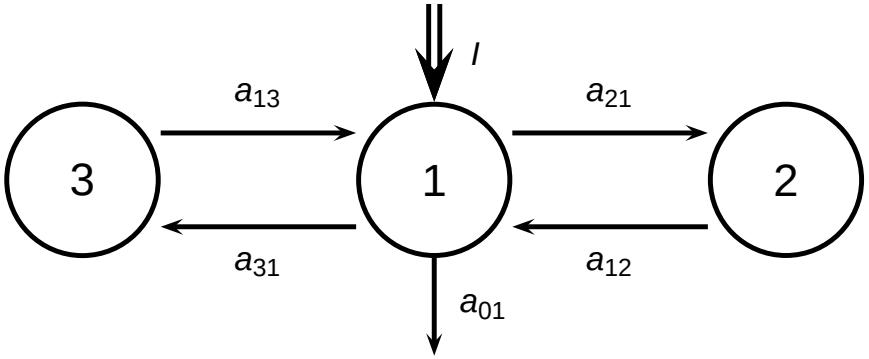
Definition

A trap is a subset of compartments that is outflow-closed and there are no transfers/paths to compartments outside of the trap.

Example 1 (Drug distribution, 2 compartments). Widely used in pharmacokinetics (PK) to analyse distribution of drug after injection into blood:

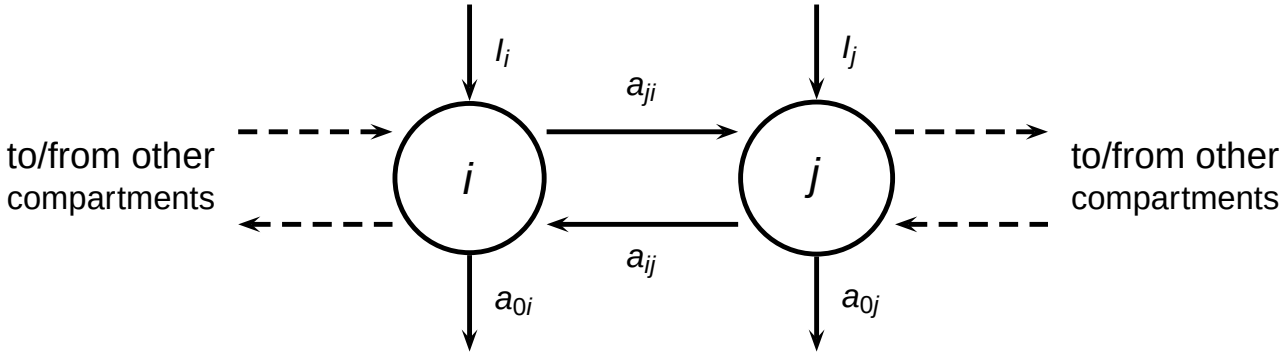


Example 2 (Drug distribution, 3 compartments). Also widely used in PK to analyse distribution of drug after injection into the blood:



Linear (time-invariant) compartmental models

General n compartment linear model



Since system linear: $f_{ij}(\boldsymbol{q}(t), t) = a_{ij}$, and

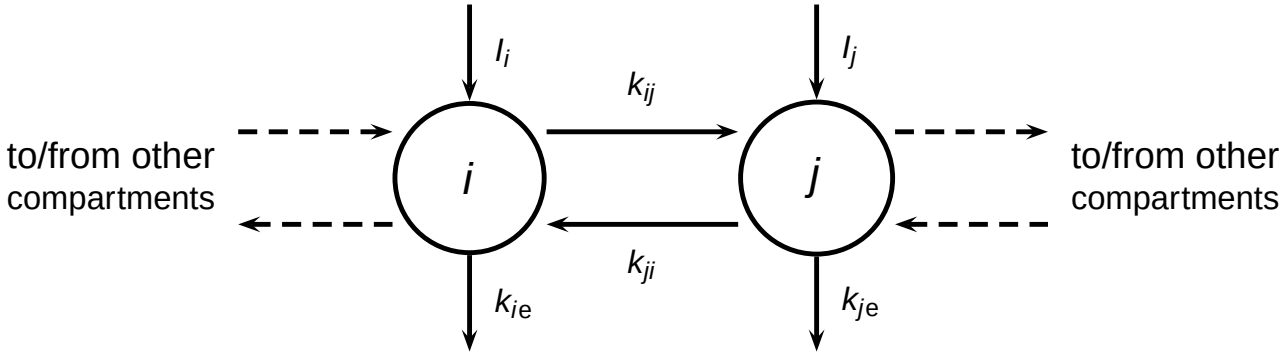
$$\dot{\boldsymbol{q}}(t) = \boldsymbol{A}\boldsymbol{q}(t) + \boldsymbol{I}(t) \tag{1}$$

where

$$\boldsymbol{q}(t) = \begin{pmatrix} q_1(t) \\ q_2(t) \\ \vdots \\ q_n(t) \end{pmatrix}, \ \boldsymbol{A} = \begin{pmatrix} a_{11} & a_{12} & \dots & a_{1n} \\ a_{21} & a_{22} & \dots & a_{2n} \\ \vdots & \vdots & \ddots & \vdots \\ a_{n1} & a_{n2} & \dots & a_{nn} \end{pmatrix} \quad a_{ii} = -\left(a_{0i} + \sum_{j \neq i} a_{ji}\right)$$

Constants a_{ij} are rate constants, with units $[T]^{-1}$; and for outflows, a_{0i}, called elimination rate constants.

General n compartment linear model



Since system linear: $f_{ij}(\boldsymbol{q}(t), t) = a_{ij} = k_{ji}$, and

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Constants k_{ji} are rate constants, with units $[T]^{-1}$; and for outflows, k_{ie}, called elimination rate constants.

No inflows (homogeneous)

Spectral/modal analysis

In the absence of inflows linear compartmental model is:

$$\dot{\boldsymbol{q}}(t) = \boldsymbol{A}\boldsymbol{q}(t), \qquad \boldsymbol{q}(0) = \boldsymbol{q}_0. \tag{2}$$

If $\boldsymbol{A}$ has n distinct eigenvalues $\lambda_1, \lambda_2, \ldots, \lambda_n$ ($\boldsymbol{A}\boldsymbol{v}_i = \lambda_i \boldsymbol{v}_i$), then any sum of exponentials

$$\boldsymbol{q}(t) = \sum_{i=1}^{n} c_i \boldsymbol{v}_i \mathrm{e}^{\lambda_i t}$$

is a general solution of (2). The particular solution starts at $\boldsymbol{q}_0$, namely:

$$\boldsymbol{q}(0) = \sum_{i=1}^{n} c_i \boldsymbol{v}_i = \boldsymbol{q}_0.$$

Matrix exponential

We can also write the particular solution in terms of the initial state $\boldsymbol{q}(0)$ and the matrix exponential of $\boldsymbol{A}$:

$$\boldsymbol{q}(t) = \sum_{i=1}^{n} c_i \boldsymbol{v}_i \mathrm{e}^{\lambda_i t} = \mathrm{e}^{\boldsymbol{A}t} \boldsymbol{q}_0, \tag{3}$$

where

$$\mathrm{e}^{\boldsymbol{A}t} = \boldsymbol{I}_n + t\boldsymbol{A} + \frac{t^2}{2!}\boldsymbol{A}^2 + \cdots + \frac{t^r}{r!}\boldsymbol{A}^r + \cdots \quad .$$

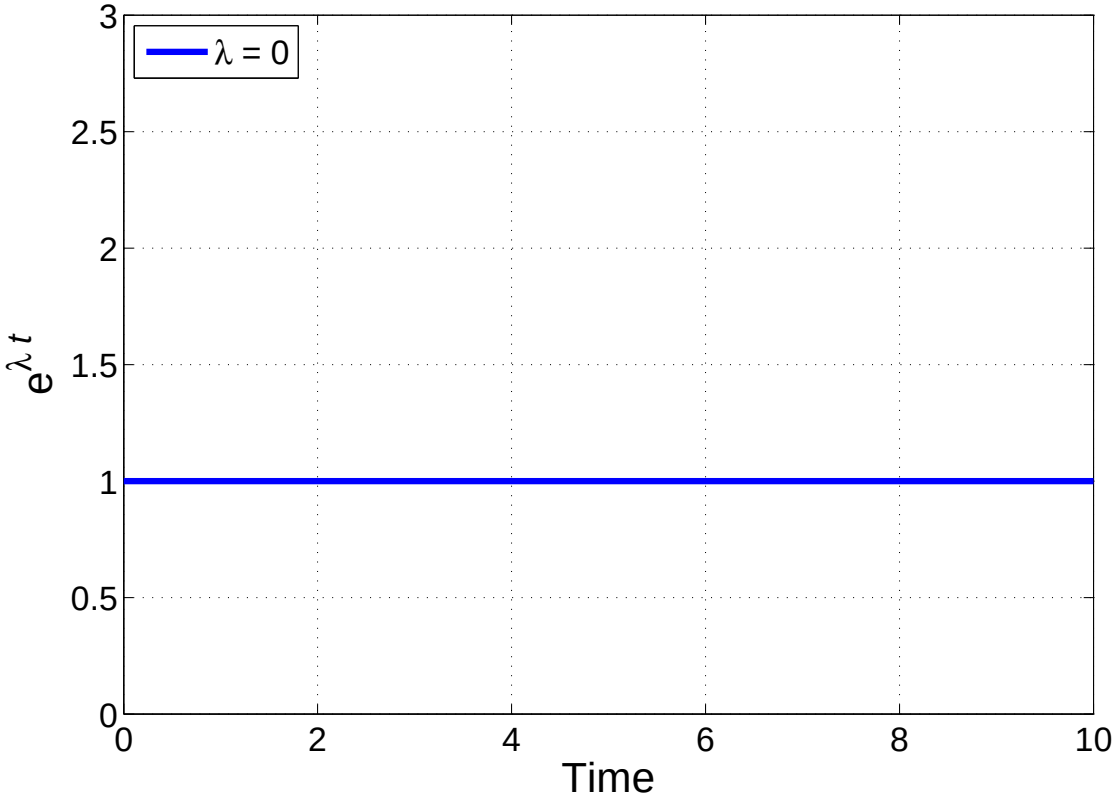
Eigenvalues of compartmental models (i.e., of $\boldsymbol{A}$) must satisfy:

- No eigenvalue can have a positive real part;
- There can be no purely imaginary eigenvalues;
- Model has a trap if and only if $\boldsymbol{A}$ has a zero eigenvalue.

Behaviour of exponentials

For a fixed λ consider behaviour of exponential term: $e^{\lambda t}$

$\lambda = 0$ gives constant term



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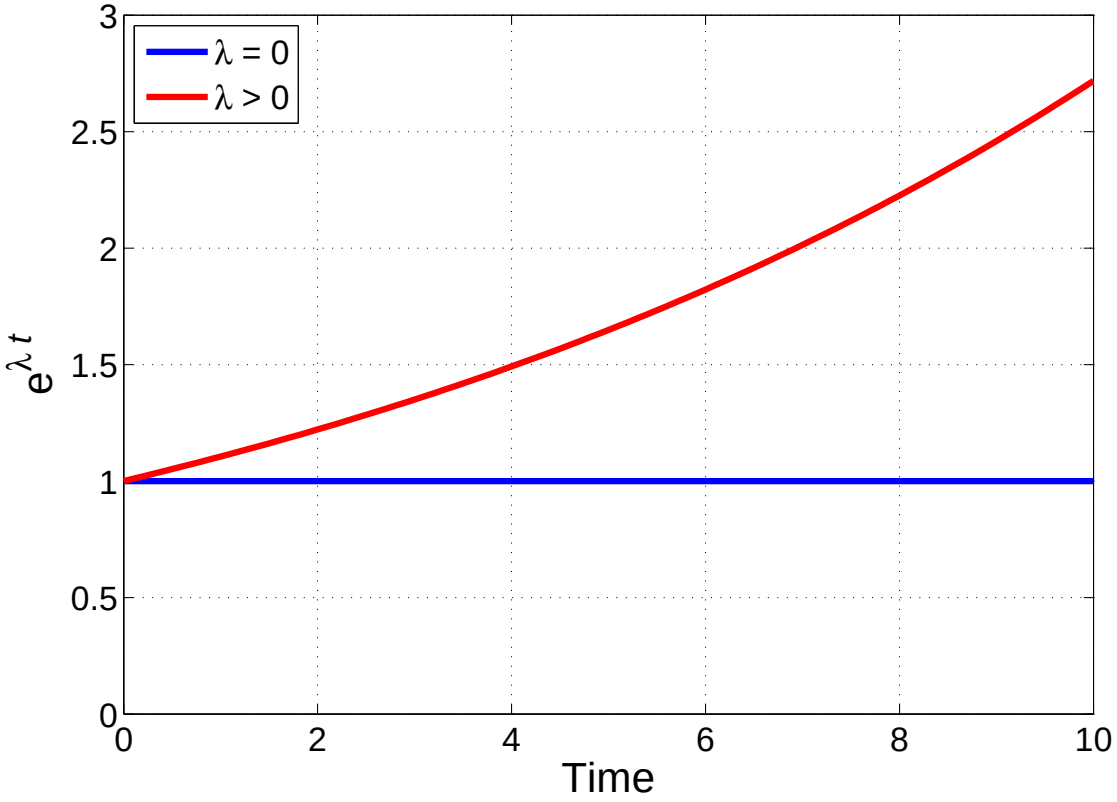

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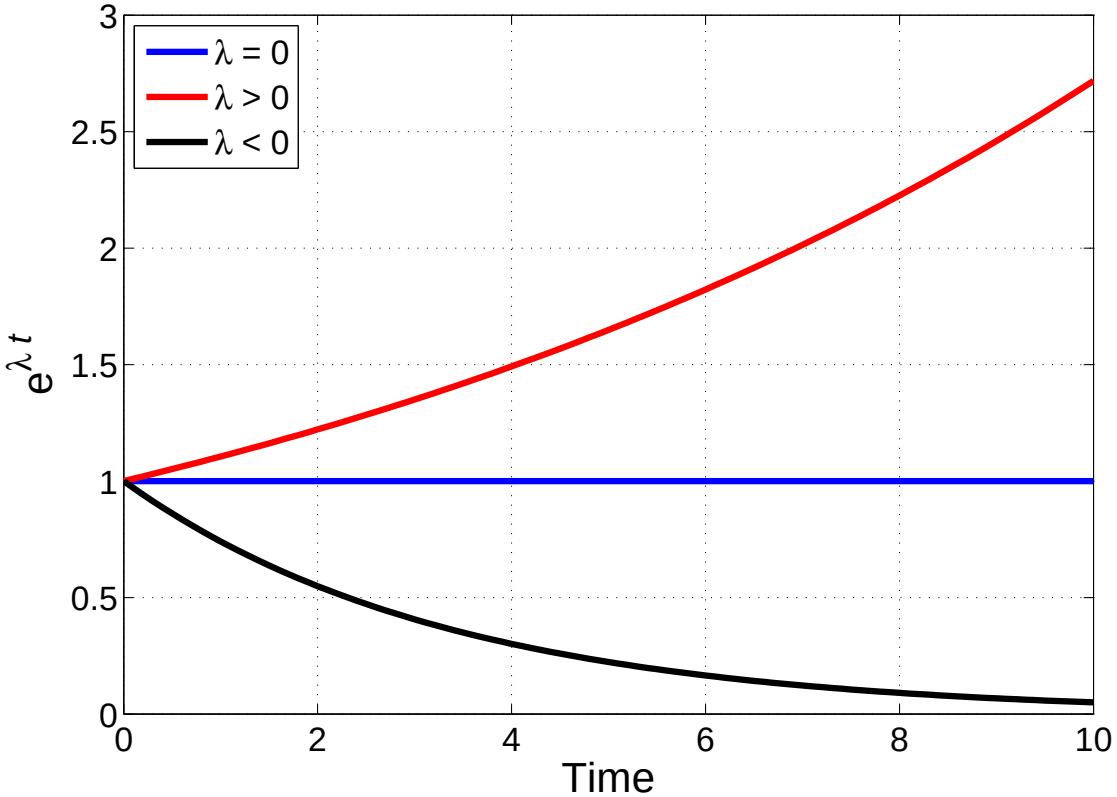
Half-life: τ

$$e^{\lambda\tau} = \frac{1}{2} \Rightarrow \tau = -\frac{1}{\lambda}\ln 2$$



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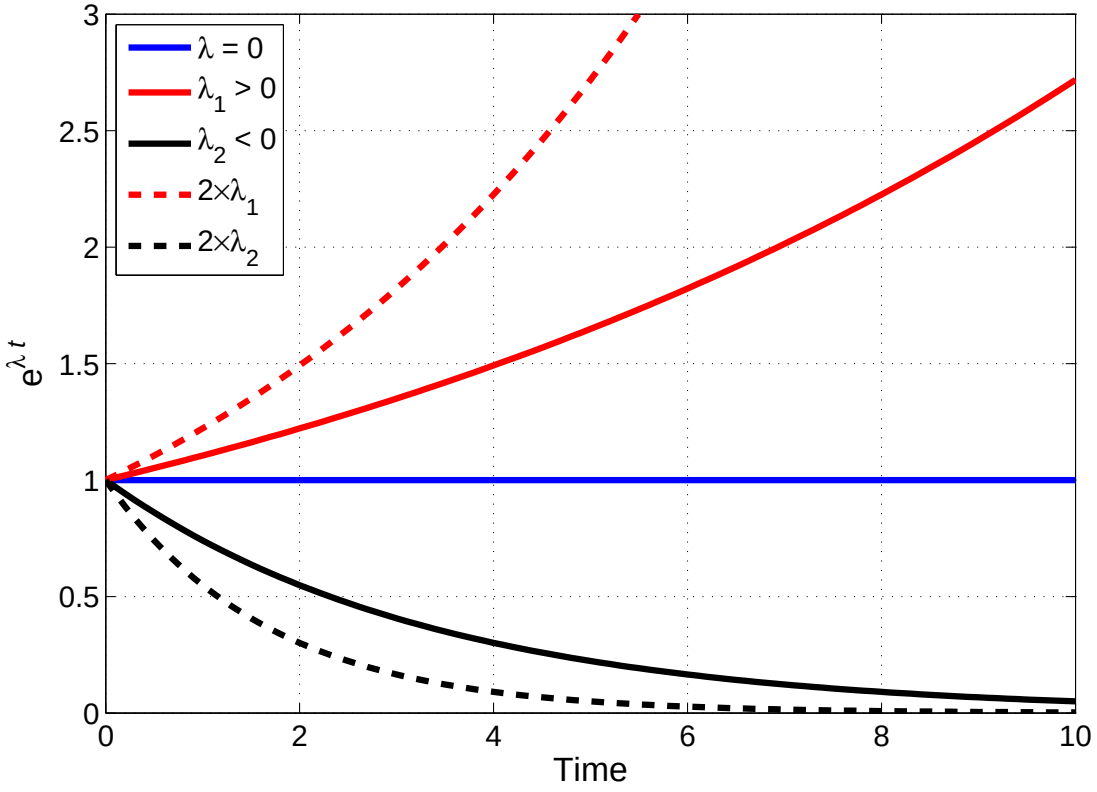
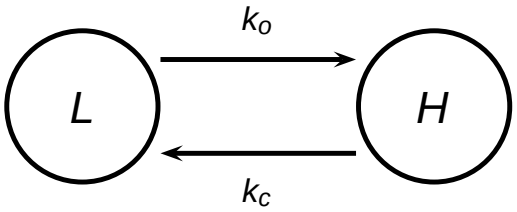


Example: Topotecan Hydrolysis

Reversible hydrolysis of anti-cancer agent topotecan (TPT) can be modelled via a two-compartment model:



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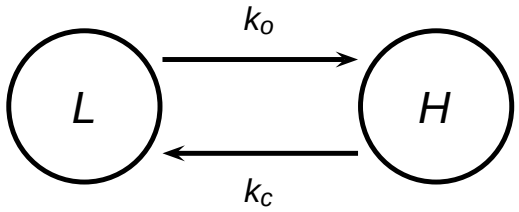

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$$\dot{q}_L(t) = -k_o q_L(t) + k_c q_H(t), \qquad q_L(0) = d$$
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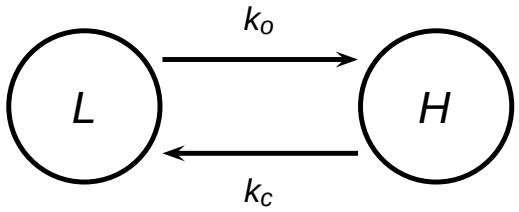

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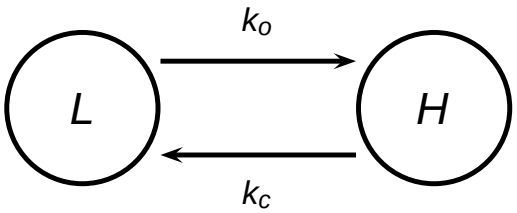

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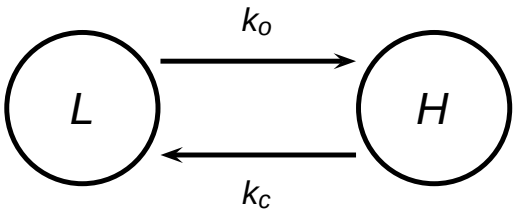

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$$\boldsymbol{A} = \begin{pmatrix} -k_o & k_c \\ k_o & -k_c \end{pmatrix} \qquad \det(\lambda \boldsymbol{I} - \boldsymbol{A}) = \lambda^2 + (k_o + k_c)\lambda$$

Eigenvalues: $\lambda = 0$, $\lambda = -(k_o + k_c)$

Eigenvectors: $(\lambda \boldsymbol{I} - \boldsymbol{A})\,\boldsymbol{v} = \boldsymbol{0}$

$$\begin{pmatrix} \lambda + k_o & -k_c \\ -k_o & \lambda + k_c \end{pmatrix} \begin{pmatrix} v_1 \\ v_2 \end{pmatrix} = \begin{pmatrix} 0 \\ 0 \end{pmatrix}$$

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Initial conditions:

$$\begin{pmatrix} d \\ 0 \end{pmatrix} = c_1 \begin{pmatrix} k_c \\ k_o \end{pmatrix} + c_2 \begin{pmatrix} 1 \\ -1 \end{pmatrix}$$

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Initial conditions:

$$\begin{pmatrix} d \\ 0 \end{pmatrix} = \frac{d}{k_c + k_o} \begin{pmatrix} k_c \\ k_o \end{pmatrix} + \frac{dk_o}{k_c + k_o} \begin{pmatrix} 1 \\ -1 \end{pmatrix}$$

Solution is

$$\begin{pmatrix} q_L(t) \\ q_H(t) \end{pmatrix} = c_1 \begin{pmatrix} k_c \\ k_o \end{pmatrix} \mathrm{e}^{0t} + c_2 \begin{pmatrix} 1 \\ -1 \end{pmatrix} \mathrm{e}^{-(k_o+k_c)t}$$

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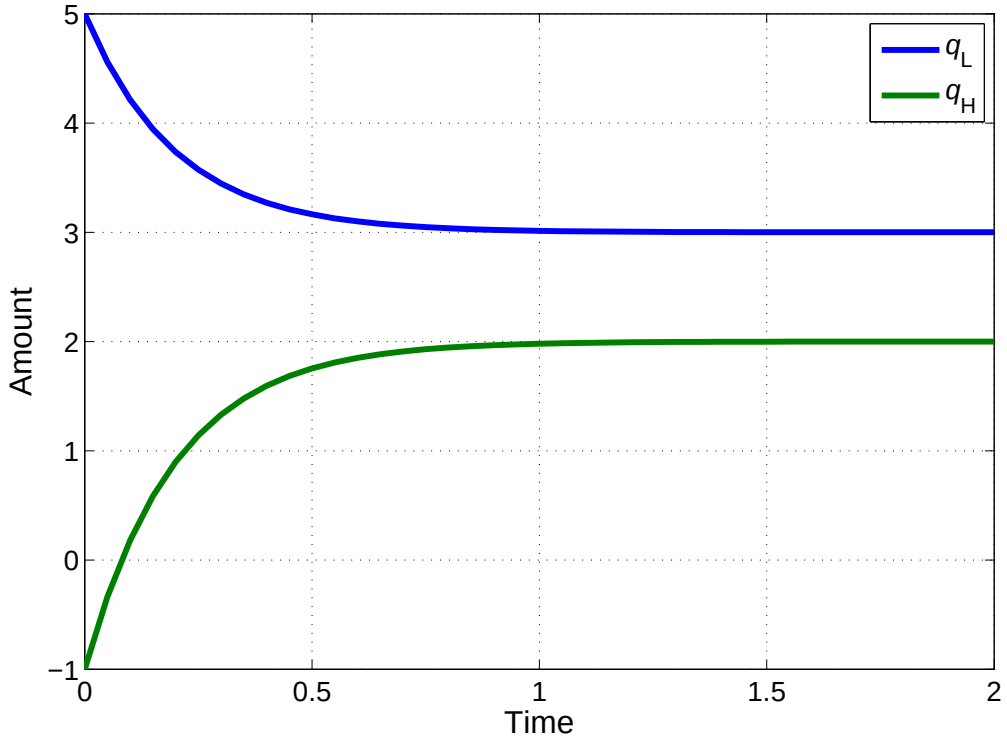
For example ($k_o = 2, k_c = 3, d = 5$)



With inflows (inhomogeneous)

General case

In the presence of inflows linear compartmental model given by:

$$\dot{\boldsymbol{q}}(t) = \boldsymbol{A}\boldsymbol{q}(t) + \boldsymbol{I}(t), \qquad \boldsymbol{q}(0) = \boldsymbol{q}_0, \tag{4}$$

and

$$\boldsymbol{q}(t) = \mathrm{e}^{\boldsymbol{A}t}\boldsymbol{q}_0 + \int_0^t \mathrm{e}^{\boldsymbol{A}(t-s)}\boldsymbol{I}(s)\,\mathrm{d}s.$$

Probably the most common forms for the inputs in pharmacokinetics:

- Impulsive input
- Constant infusion

Impulsive input

Also called bolus injection in applications; corresponds to giving specific amount, d, in a negligible amount of time at $t = \tau$.

At $t = \tau = 0$ easiest to include in initial conditions:

$$\boldsymbol{q}(0) = \boldsymbol{q}_0 + \boldsymbol{d},$$

and treat as homogeneous.

If at $t = \tau \neq 0$ treat as homogeneous model for $0 \leq t < \tau$ such that $\boldsymbol{q}_\tau = \boldsymbol{q}(\tau)$; and then as homogeneous model for $T = t - \tau \geq 0$ starting at

$$\boldsymbol{q}(\tau) = \boldsymbol{q}_\tau + \boldsymbol{d}.$$

Multiple impulsive inputs (at times τ_i) handled similarly:

$$\boldsymbol{q}(\tau_{i+1}) = \boldsymbol{q}_{\tau_i} + \boldsymbol{d}_i.$$

Scalar example: Single input

Consider a single compartment model subject to an impulsive input of size d at time $t = \tau$. For $0 \leq t < \tau$ we have

$$\dot{q}(t) = -aq(t), \quad q(0) = q_0 \qquad \Longrightarrow \quad q(t) = q_0 \mathrm{e}^{-at}.$$

Then for $t \geq \tau$:

$$\dot{q}(t) = -aq(t), \quad q(\tau) = q_0 \mathrm{e}^{-a\tau} + d$$
$$\Longrightarrow \quad q(t) = \left(q_0 \mathrm{e}^{-a\tau} + d\right) \mathrm{e}^{-a(t-\tau)}.$$

Hence the full general solution is given by:

$$q(t) = \begin{cases} q_0 \mathrm{e}^{-at} & 0 \leq t < \tau \\ q_0 \mathrm{e}^{-at} + d\mathrm{e}^{-a(t-\tau)} & t \geq \tau \end{cases}.$$

Scalar example: Multiple inputs

For multiple impulsive inputs, of size d_i at time τ_i ($i = 1 \ldots m$), it can be shown that the general solution is given by:

$$q(t) = \begin{cases} q_0 \mathrm{e}^{-at} & 0 \leq t < \tau_1 \\ q_0 \mathrm{e}^{-at} + d_1 \mathrm{e}^{-a(t-\tau_1)} & \tau_1 \leq t < \tau_2 \\ q_0 \mathrm{e}^{-at} + d_1 \mathrm{e}^{-a(t-\tau_1)} + d_2 \mathrm{e}^{-a(t-\tau_2)} & \tau_2 \leq t < \tau_3 \\ \vdots & \\ q_0 \mathrm{e}^{-at} + \sum_{i=1}^{m} d_i \mathrm{e}^{-a(t-\tau_i)} & \tau_m \leq t. \end{cases}$$

i.e., sum of the homogeneous model starting from $\boldsymbol{q}_0$ and the sum of the **impulse responses** for the inputs.

Constant input

Solution with constant infusion at a certain rate, ie $\boldsymbol{u}(t) = \boldsymbol{d}$:

$$\dot{\boldsymbol{q}}(t) = \boldsymbol{A}\boldsymbol{q}(t) + \boldsymbol{d} \qquad \Longrightarrow \qquad \boldsymbol{q}(t) = \mathrm{e}^{\boldsymbol{A}t}\boldsymbol{q}_0 + \int_0^t \mathrm{e}^{\boldsymbol{A}(t-s)}\boldsymbol{d}\ \mathrm{d}s.$$

Suppose eigenvalues λ_i of $\boldsymbol{A}$ are distinct. Then there are constants $c_{11}, \ldots, c_{1n}$ and $c_{21}, \ldots, c_{2n}$ such that

$$\boldsymbol{q}_0 = \sum_{i=1}^{n} c_{1i}\boldsymbol{v}_i \quad \text{and} \quad \boldsymbol{d} = \sum_{i=1}^{n} c_{2i}\boldsymbol{v}_i,$$

where $\boldsymbol{v}_i$ are eigenvectors corresponding to λ_i. Then solution of compartmental model with constant input is given by:

$$\boldsymbol{q}(t) = \left(\sum_{i=1}^{n} c_{1i}\boldsymbol{v}_i \mathrm{e}^{\lambda_i t}\right) + \int_0^t \left(\sum_{i=1}^{n} c_{2i}\boldsymbol{v}_i \mathrm{e}^{\lambda_i (t-s)}\right) \mathrm{d}s$$

Constant input

Solution with constant infusion at a certain rate, ie $\boldsymbol{u}(t) = \boldsymbol{d}$:

$$\dot{\boldsymbol{q}}(t) = \boldsymbol{A}\boldsymbol{q}(t) + \boldsymbol{d} \qquad \Longrightarrow \qquad \boldsymbol{q}(t) = \mathrm{e}^{\boldsymbol{A}t}\boldsymbol{q}_0 + \int_0^t \mathrm{e}^{\boldsymbol{A}(t-s)}\boldsymbol{d}\ \mathrm{d}s.$$

Suppose eigenvalues λ_i of $\boldsymbol{A}$ are distinct. Then there are constants $c_{11}, \ldots, c_{1n}$ and $c_{21}, \ldots, c_{2n}$ such that

$$\boldsymbol{q}_0 = \sum_{i=1}^{n} c_{1i}\boldsymbol{v}_i \quad \text{and} \quad \boldsymbol{d} = \sum_{i=1}^{n} c_{2i}\boldsymbol{v}_i,$$

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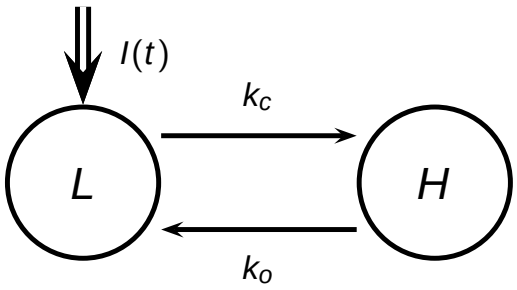
$$\boldsymbol{q}(t) = \sum_{i=1}^{n} \left(\left(c_{1i} + \frac{c_{2i}}{\lambda_i} \right) \boldsymbol{v}_i \mathrm{e}^{\lambda_i t} - \frac{c_{2i}}{\lambda_i}\boldsymbol{v}_i \right).$$

Example: Topotecan Hydrolysis

Now suppose active form of TPT added as continuous infusion:



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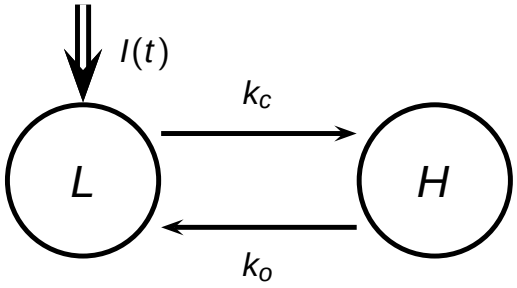

Solution given by:

$$\boldsymbol{q}(t) = c_{11}\boldsymbol{v}_1 e^{\lambda_1 t} + c_{12}\boldsymbol{v}_2 e^{\lambda_2 t} + \int_0^t \left(c_{21}\boldsymbol{v}_1 e^{\lambda_1 (t-s)} + c_{22}\boldsymbol{v}_2 e^{\lambda_2 (t-s)} \right) \, ds$$

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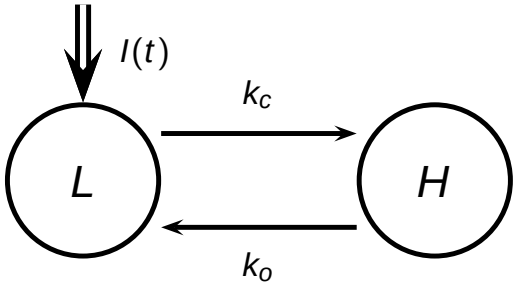

Solution given by:

$$\boldsymbol{q}(t) = \int_0^t \left(c_{21}\boldsymbol{v}_1 \mathrm{e}^{\lambda_1(t-s)} + c_{22}\boldsymbol{v}_2 \mathrm{e}^{\lambda_2(t-s)} \right) \mathrm{d}s$$

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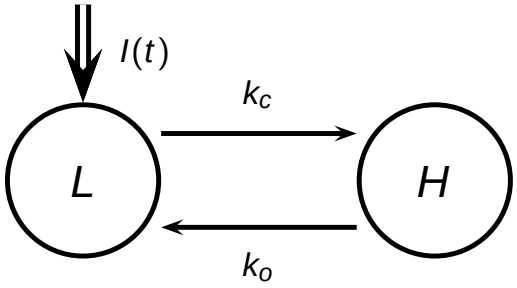

Solution given by:

$$\boldsymbol{q}(t) = \int_0^t \left(c_{21}\boldsymbol{v}_1 + c_{22}\boldsymbol{v}_2 \mathrm{e}^{\lambda_2(t-s)} \right) \mathrm{d}s$$

Example: Topotecan Hydrolysis

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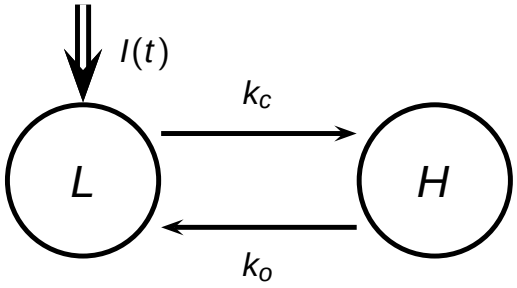

Solution given by:

$$\boldsymbol{q}(t) = c_{21}\begin{pmatrix} k_c \\ k_o \end{pmatrix} t + c_{22}\begin{pmatrix} 1 \\ -1 \end{pmatrix}\left(\frac{1}{k_o + k_c} - \frac{1}{k_o + k_c}\mathrm{e}^{-(k_o+k_c)t}\right)$$

Example: Topotecan Hydrolysis

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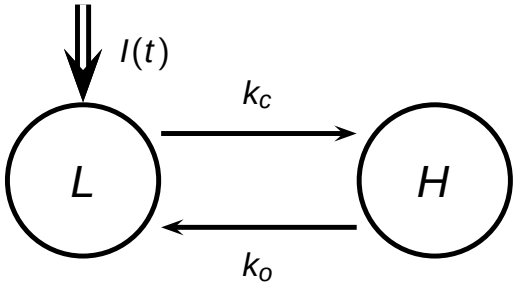

Solution given by:

$$\boldsymbol{q}(t) = \frac{d}{k_c + k_o}\left[\begin{pmatrix} k_c \\ k_o \end{pmatrix} t + \frac{1}{k_o + k_c}\begin{pmatrix} k_o \\ -k_o \end{pmatrix}\left(1 - \mathrm{e}^{-(k_o+k_c)t}\right)\right]$$

Example: Topotecan Hydrolysis

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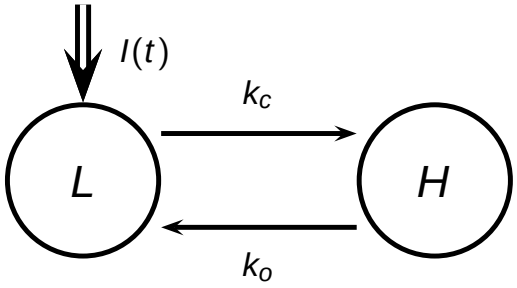

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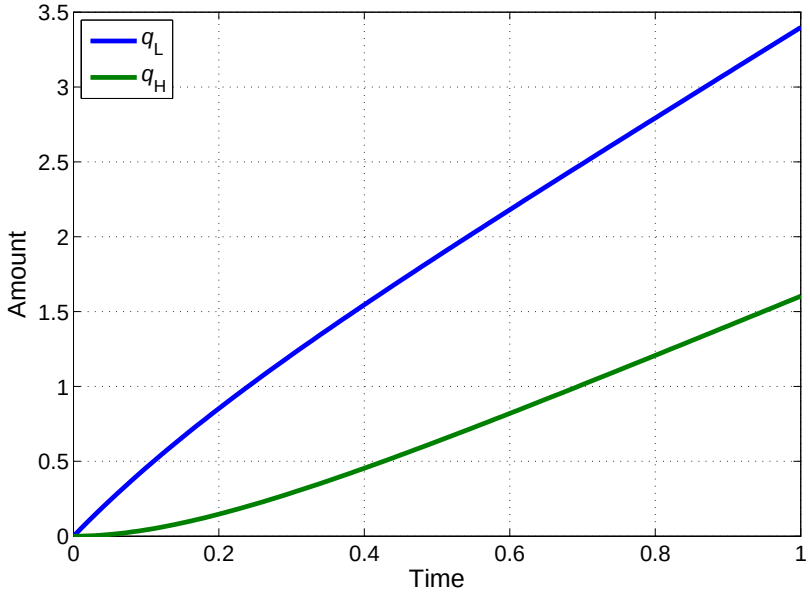
For example: $k_o = 2, k_c = 3, d = 5$



Four basic (sub)systems

Linear compartmental models can be decomposed into isolated subsystems of four types:

NIO(OC) Systems with no inflows, but at least one outflow (**NIO**); in addition, they are outflow-connected (**OC**).

Asymptotic behaviour: All compartments decay to 0 exponentially: **0** only steady state (& asymptotically stable)

IO(OC) Systems with inflows (**IO**) & outflow-connected (**OC**).

For constant input $\boldsymbol{u}(t) \equiv \boldsymbol{d}$, system approaches non-zero steady state:

$$\boldsymbol{q} = -\boldsymbol{A}^{-1}\boldsymbol{d},$$

and if eigenvalues of $\boldsymbol{A}$ are distinct, then:

$$\boldsymbol{q}(t) = \sum_{i=1}^{n} \left(\left(c_{1i} + \frac{c_{2i}}{\lambda_i} \right) \boldsymbol{v}_i \mathrm{e}^{\lambda_i t} - \frac{c_{2i}}{\lambda_i} \boldsymbol{v}_i \right) \longrightarrow -\sum_{i=1}^{n} \left(\frac{c_{2i}}{\lambda_i} \boldsymbol{v}_i \right)$$

NINO(SC) Systems with no inflows & no outflows (**NINO**), but strongly connected (**SC**); they are themselves traps.

The system (exponentially) approaches a steady state $\boldsymbol{q}^* = (q_1^*, \ldots, q_n^*)^\mathsf{T}$, such that

$$\dot{\boldsymbol{q}}^* = \boldsymbol{A}\boldsymbol{q}^* = \boldsymbol{0}.$$

Since there are no inflows or outflows the total amount in the system remains constant, $A_0 = \sum_{i=1}^n q_i^*$ say.

Use this to replace equation for first compartment to get:

$$\boldsymbol{H}\boldsymbol{q}^* = \boldsymbol{M} = (A_0, 0, \ldots, 0)^\mathsf{T}$$

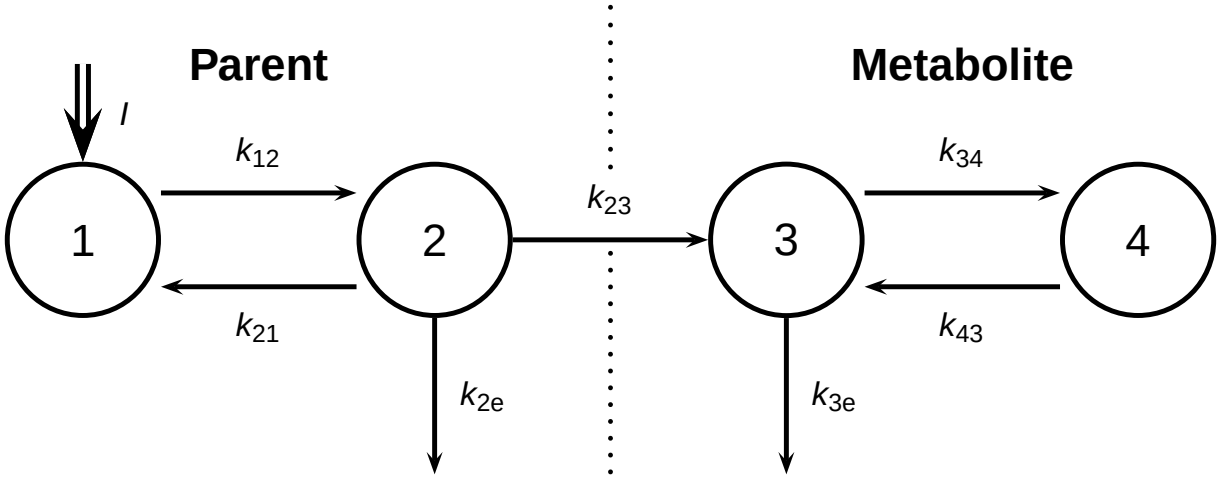
where $\boldsymbol{H}$ is nonsingular. The steady state is then given by

$$\boldsymbol{q}^* = \boldsymbol{H}^{-1}\boldsymbol{M}.$$

INO(SC) Systems with inflows & no outflows (**INO**), & strongly connected (**SC**). Unless inflow is bounded system continues to grow.

If inflow is bounded system approaches steady state of NINO(SC) case, with total amount equal to initial amount in system plus total inflow.

Example (Parent-Metabolite Model for Bromosulphthalein).



Nonlinear compartmental models

Nonlinear compartmental models

Transfers between compartments can depend on

- time
- vector of rate constants $\boldsymbol{k}$
- amounts in the compartments

so that rate of change of amount in compartment i is

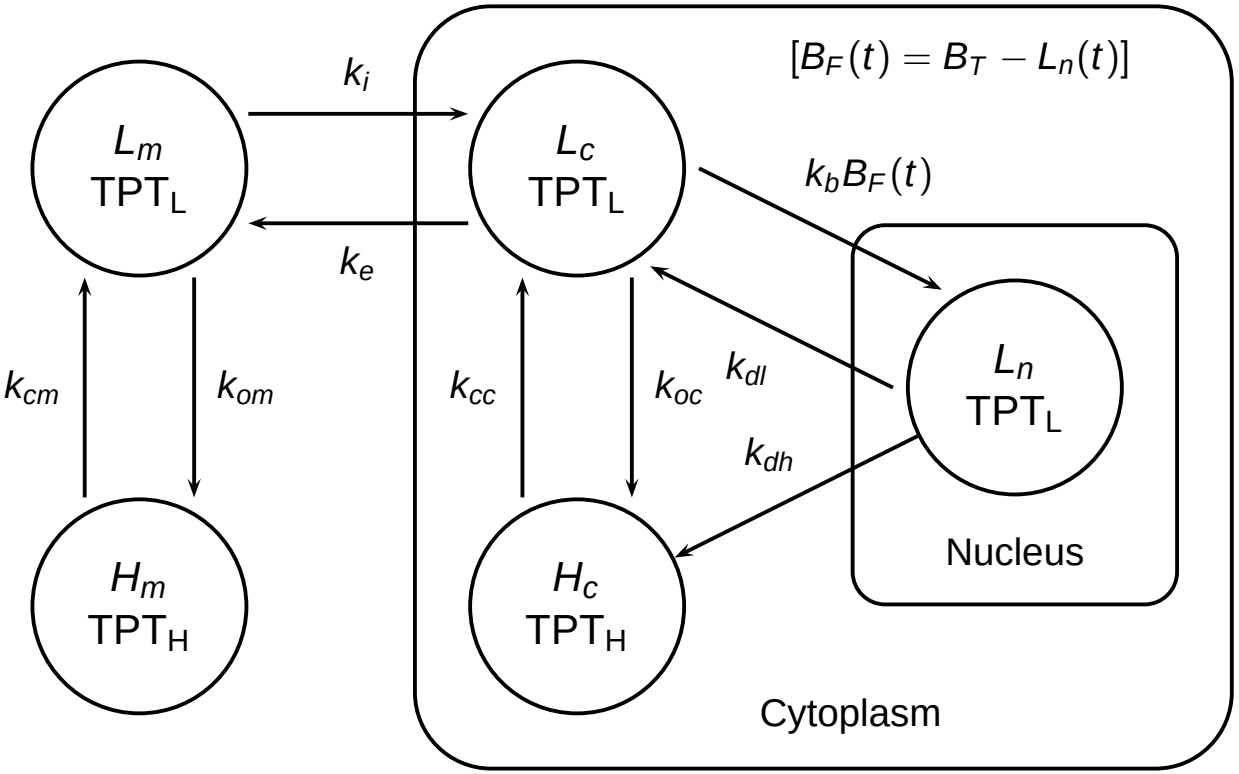
$$\dot{q}_i(t) = I_i(t) + \sum_{j=1}^{n} f_{ij}(\boldsymbol{q}(t), \boldsymbol{k}, t)\, q_j(t). \tag{5}$$

where

$$f_{ii}(\boldsymbol{q}(t), \boldsymbol{k}, t) = -\left(f_{0i}(\boldsymbol{q}(t), \boldsymbol{k}, t) + \sum_{\substack{j=1 \\ j \neq i}}^{n} f_{ji}(\boldsymbol{q}(t), \boldsymbol{k}, t) \right)$$

Example: Topotecan kinetics

Only active form TPT_L binds to nuclear DNA target & so important to monitor activity of drug from injection to target

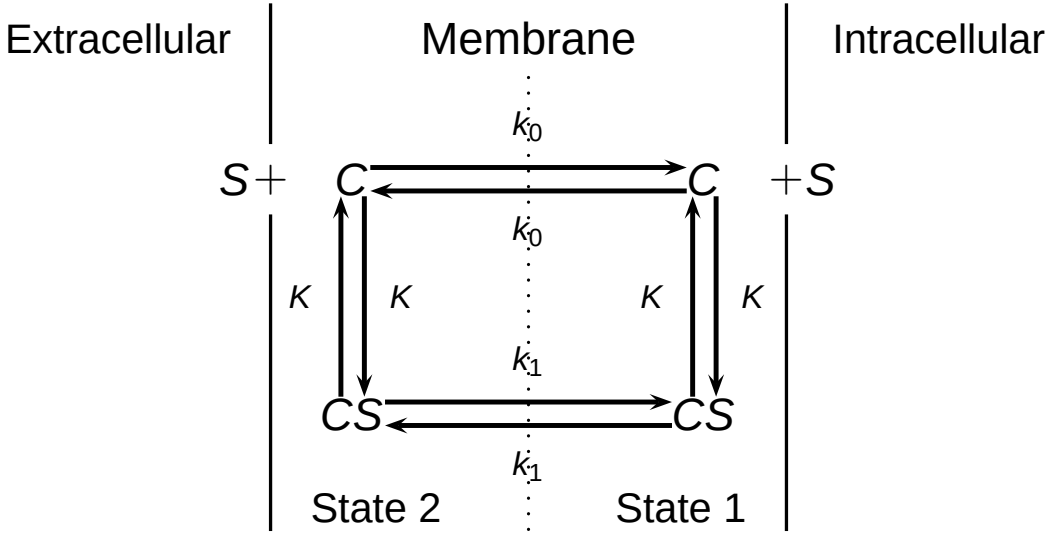


Dose consists of bolus input of active drug administered into extracellular medium.

Example: Facilitated Diffusion

Facilitated diffusion is one of simplest mechanisms for transporting material across cell membrane.

Eg: consider entry of glucose into red blood cells:



Could assume reactions very fast compared with transfer of substrate across membrane; ie in equilibrium (a pseudo-steady state assumption/approximation).

Steady states

Consider nonlinear compartmental model:

$$\dot{q}_i(t) = I_i(t) + \sum_{j=1}^{n} f_{ij}(\boldsymbol{q}(t), \boldsymbol{k}, t)\, q_j(t). \tag{6}$$

Steady states

Consider nonlinear compartmental model:

$$\dot{\boldsymbol{q}}(t) = \boldsymbol{F}(\boldsymbol{q}(t), \boldsymbol{k}, t)\boldsymbol{q}(t) + \boldsymbol{I}(t) = \boldsymbol{f}(\boldsymbol{q}(t), \boldsymbol{k}, t) + \boldsymbol{I}(t) \qquad (6)$$

where $\boldsymbol{F}$ is *compartmental matrix* of f_{ij}

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where $\boldsymbol{F}$ is *compartmental matrix* of f_{ij}

Definition

An equilibrium state or steady state $\hat{\boldsymbol{q}}$ for (6), with corresponding *steady state inflow* $\hat{\boldsymbol{I}}$, occurs if and only if

$$\boldsymbol{0} = \dot{\hat{\boldsymbol{q}}}(t) = \boldsymbol{f}(\hat{\boldsymbol{q}}(t), \boldsymbol{k}, t) + \hat{\boldsymbol{I}}(t).$$

Linearisation: Stability

Consider small perturbations: $\boldsymbol{q} = \hat{\boldsymbol{q}} + \overline{\boldsymbol{q}}$ and $\boldsymbol{I} = \hat{\boldsymbol{I}} + \overline{\boldsymbol{I}}$

$$\dot{\boldsymbol{q}}(t) = \boldsymbol{f}(\boldsymbol{q}(t), \boldsymbol{k}, t) + \boldsymbol{I}(t)$$

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Consider small perturbations: $\boldsymbol{q} = \hat{\boldsymbol{q}} + \overline{\boldsymbol{q}}$ and $\boldsymbol{I} = \hat{\boldsymbol{I}} + \overline{\boldsymbol{I}}$

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We can write $\boldsymbol{f}$ as:

$$\boldsymbol{f}(\hat{\boldsymbol{q}} + \overline{\boldsymbol{q}}(t), \boldsymbol{k}, t) = \boldsymbol{f}(\hat{\boldsymbol{q}}, \boldsymbol{k}, t) + \boldsymbol{A}\overline{\boldsymbol{q}}(t) + \ldots$$

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Eigenvalues of $\boldsymbol{A}$ determine stability of steady state

Pseudo Steady State Approximation

Consider an enzyme mediated reaction:

$$S + E \underset{k_{-1}}{\overset{k_1}{\rightleftharpoons}} ES \xrightarrow{k_2} E + P.$$

Let x_S denote concentration of S, x_P conc. of P, x_E conc. of E & x_C conc. of intermediate (ES). Applying law of mass action corresponding state-space model is:

$$\begin{aligned}
\dot{x}_S &= -k_1 x_S x_E + k_{-1} x_C \\
\dot{x}_P &= k_2 x_C \\
\dot{x}_E &= -k_1 x_S x_E + (k_{-1} + k_2)\, x_C \\
\dot{x}_C &= -\dot{x}_E = k_1 x_S x_E - (k_{-1} + k_2)\, x_C.
\end{aligned}$$

Note that these equations are not in compartmental form.

Quasi Steady State Assumption

Conservation Law:

$$\dot{x}_C + \dot{x}_E = 0 \qquad \Longrightarrow \qquad x_E = e_0 - x_C$$

so we can eliminate a variable (x_E).

Suppose that enzyme bit of reaction "fast" compared to overall reaction:

$$\dot{x}_C = 0 = k_1 x_S x_E - (k_{-1} + k_2)\, x_C$$

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$$\Longrightarrow \quad x_C = \frac{e_0 k_1 x_S}{k_{-1} + k_2 + k_1 x_S} = \frac{e_0 x_S}{K_M + x_S}$$

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where $K_M = (k_{-1} + k_2)/k_1$, let $V_M = e_0 k_2$:

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where $K_M = (k_{-1} + k_2)/k_1$, let $V_M = e_0 k_2$:

$$-\dot{x}_P = \dot{x}_S = -\frac{V_M x_S}{K_M + x_S}$$