Model simplification

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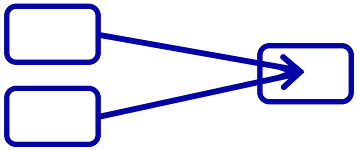
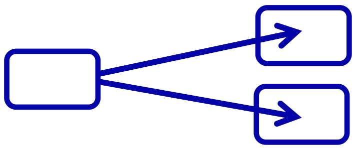
Proper lumping

- A way to simplify a model by merging together some of the model's states thus reducing its size.



- Complex system models can be simplified for data-driven PK/PD studies.
  - simpler structure yet physiological meaning retained
- We can also unlump:



Proper lumping

ODEs in original system

$$\frac{dy}{dt} = f(y)$$

y: $n \times 1$ vector of original states

can be lumped such that

$$\hat{y} = My$$

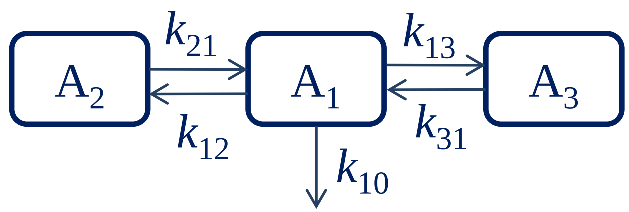
$\hat{y}$: $m \times 1$ vector of lumped states
M: lumping matrix

New set of ODEs

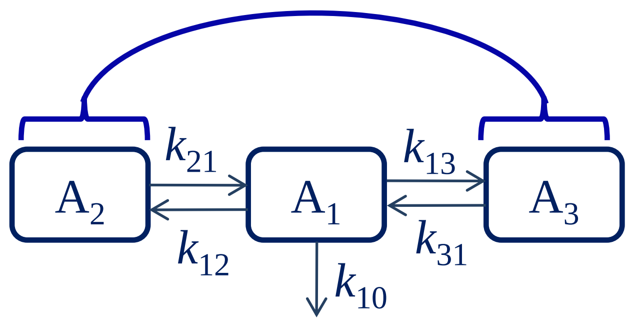
$$\frac{d\hat{y}}{dt} = \hat{f}(\hat{y})$$

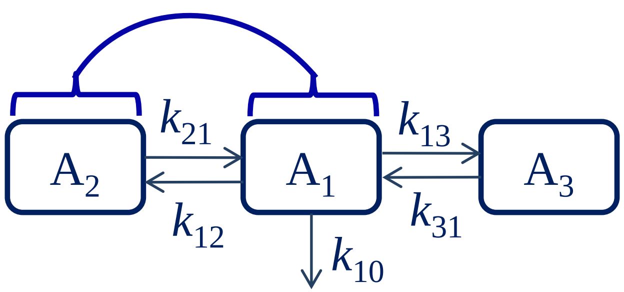
Example of lumping: 3-cpt to a 2-cpt model

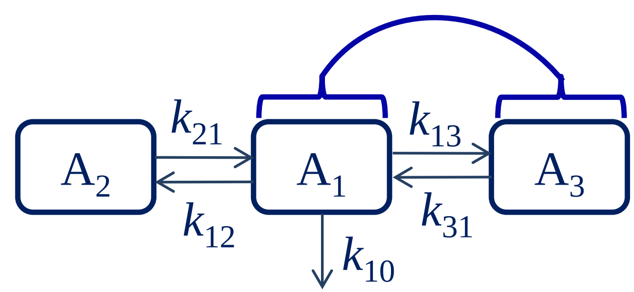
Original system



Ways of lumping

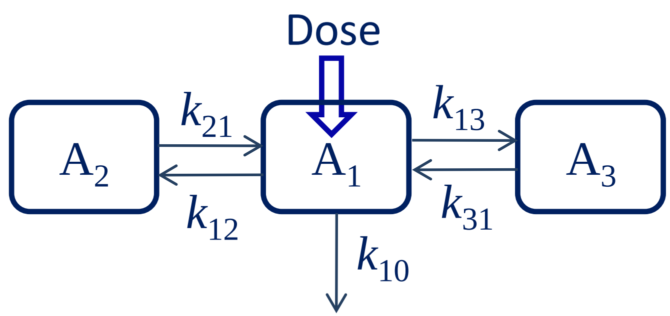






A 3-cpt model

Original system



ODEs

$$\frac{dA_1}{dt} = -(k_{12} + k_{13} + k_{10})A_1 + k_{21}A_2 + k_{31}A_3 \qquad A_{1(0)}=\text{Dose}$$

$$\frac{dA_2}{dt} = k_{12}A_1 - k_{21}A_2 \qquad A_{2(0)}=0$$

$$\frac{dA_3}{dt} = k_{13}A_1 - k_{31}A_3 \qquad A_{3(0)}=0$$

Lumping of a 3-cpt model to a 2-cpt model

ODEs

$$\frac{dA_1}{dt} = -(k_{12} + k_{13} + k_{10})A_1 + k_{21}A_2 + k_{31}A_3 \qquad A_{1(0)}=\text{Dose}$$

$$\frac{dA_2}{dt} = k_{12}A_1 - k_{21}A_2 \qquad A_{2(0)}=0$$

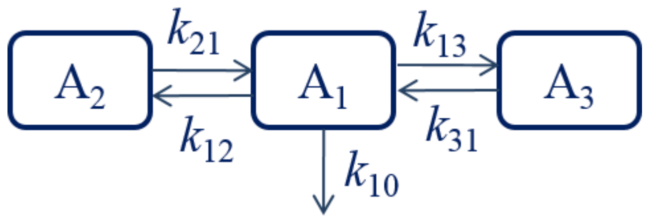
$$\frac{dA_3}{dt} = k_{13}A_1 - k_{31}A_3 \qquad A_{3(0)}=0$$

Can be written in matrix exponential form

$$\frac{dA}{dt} = f(A) = K \cdot A$$

$$K = \begin{bmatrix} -(k_{12} + k_{13} + k_{10}) & k_{21} & k_{31} \\ k_{12} & -k_{21} & 0 \\ k_{13} & 0 & -k_{31} \end{bmatrix} \qquad A = \begin{bmatrix} A_1 \\ A_2 \\ A_3 \end{bmatrix}$$

Defining the K matrix



- How mass transfer is written

$$K = \begin{bmatrix} all\ losses\ from\ A_1 & transfer\ A_2 \rightarrow A_1 & transfer\ A_3 \rightarrow A_1 \\ transfer\ A_1 \rightarrow A_2 & all\ losses\ from\ A_2 & transfer\ A_3 \rightarrow A_2 \\ transfer\ A_1 \rightarrow A_3 & transfer\ A_2 \rightarrow A_3 & all\ losses\ from\ A_3 \end{bmatrix}$$

- Mass transfer matrix of rate constants

$$K = \begin{bmatrix} -(k_{12} + k_{13} + k_{10}) & k_{21} & k_{31} \\ k_{12} & -k_{21} & 0 \\ k_{13} & 0 & -k_{31} \end{bmatrix}$$

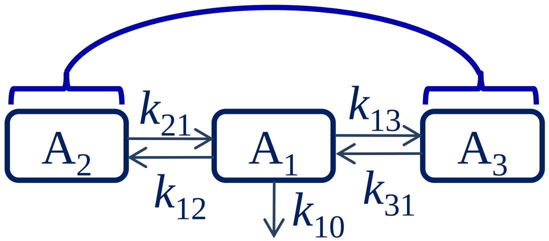
Defining the M matrix

- The lumping matrix M is a $m \times n$ matrix of switches (0s and 1s) where $m \leq n$

- n is the number of states in the full model
  - n = 3 for the 3 cpt model example

- m is the number of states in the lumped model
  - m = 2 for lumping the 3cpt model to be a 2 cpt model
  - All lumped states are shown as 1s in the same row

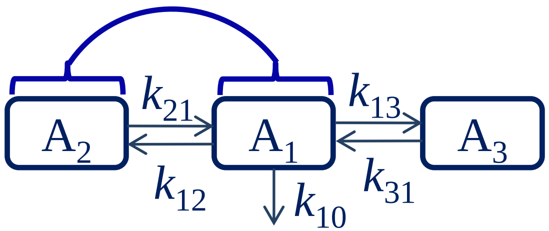
M matrix for lumping a 3-cpt model



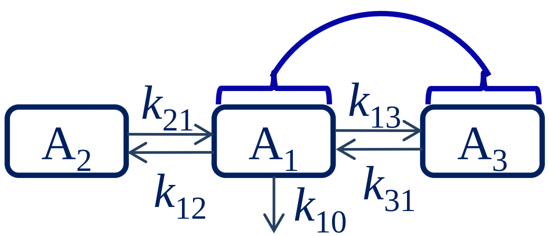
$$M = \begin{bmatrix} 1 & 0 & 0 \\ 0 & 1 & 1 \end{bmatrix}$$

Number of final states in lumped model m = 2

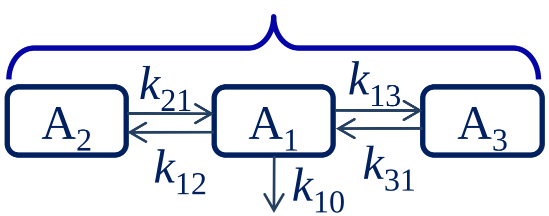
Number of original states in original model n = 3



$$M = \begin{bmatrix} 1 & 1 & 0 \\ 0 & 0 & 1 \end{bmatrix}$$

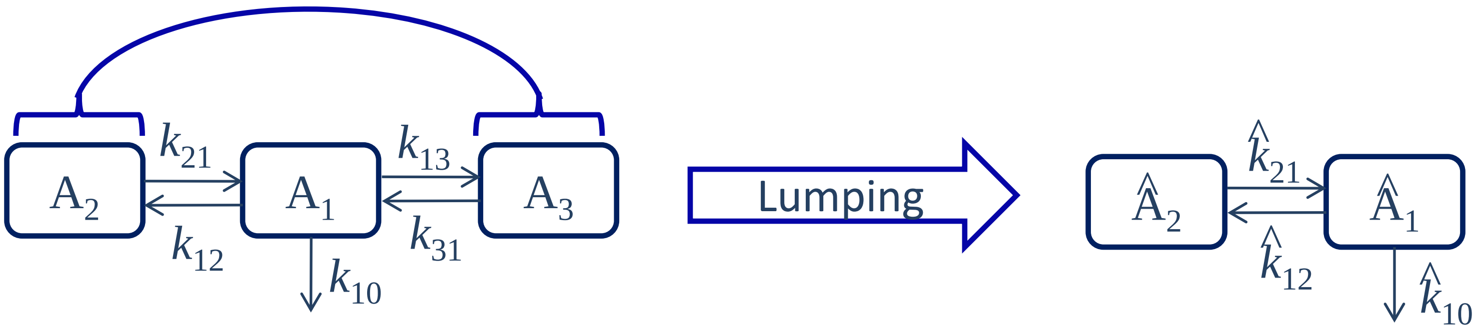


$$M = \begin{bmatrix} 1 & 0 & 1 \\ 0 & 1 & 0 \end{bmatrix}$$



$$M = \begin{bmatrix} 1 & 1 & 1 \end{bmatrix}$$

Defining the M matrix



$$y = \begin{bmatrix} A_1 \\ A_2 \\ A_3 \end{bmatrix} \qquad \hat{y} = My \qquad \hat{y} = \begin{bmatrix} \hat{A}_1 \\ \hat{A}_2 \end{bmatrix}$$

$$M = \begin{bmatrix} 1 & 0 & 0 \\ 0 & 1 & 1 \end{bmatrix}$$

When $M = I_n$ then $\hat{y} = y$ as $\hat{y} = I_n \cdot y$

$I_n = \begin{bmatrix} 1 & 0 & 0 \\ 0 & 1 & 0 \\ 0 & 0 & 1 \end{bmatrix}$ for $n = 3$ in this case

Inverse of the M matrix

Apart from the lumping transformation $\hat{y} = My$

We also have the inverse transformation $y = M^{+}\hat{y}$

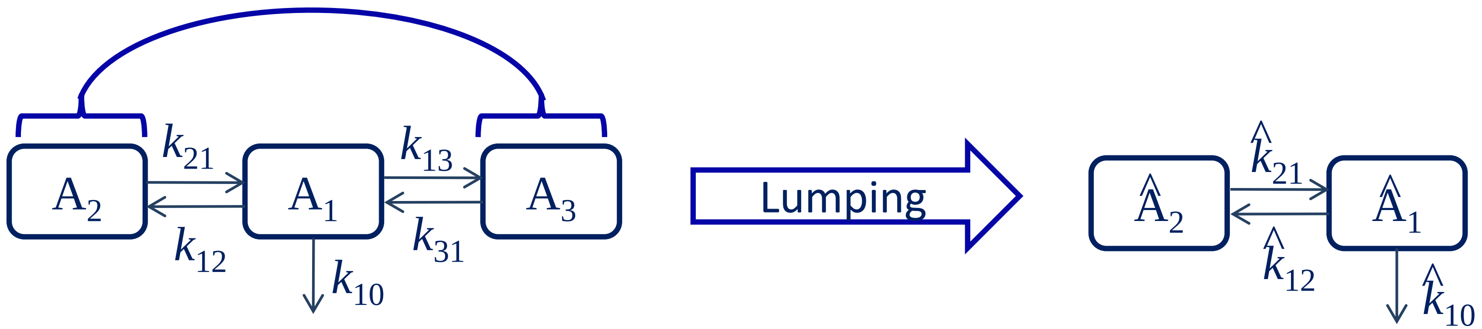
M^{+} is the inverse / pseudo-inverse of M such that $MM^{+} = I_m$

$$\begin{bmatrix} 2 & 0 \\ 0 & 2 \end{bmatrix} \begin{bmatrix} 1/2 & 0 \\ 0 & 1/2 \end{bmatrix} = \begin{bmatrix} 1 & 0 \\ 0 & 1 \end{bmatrix} \quad \text{and} \quad \begin{bmatrix} 1 & 0 & 0 \\ 0 & 1 & 1 \end{bmatrix} \begin{bmatrix} 1 & 0 \\ 0 & 1/2 \\ 0 & 1/2 \end{bmatrix} = \begin{bmatrix} 1 & 0 \\ 0 & 1 \end{bmatrix}$$

Moore–Penrose pseudo-inverse in various software packages:

MATLAB/Freemat	*pinv()*
Mathematica	*PseudoInverse[]*
R	*ginv()*

Lumping of a 3-cpt model to a 2-cpt model



$$M = \left.\underbrace{\begin{bmatrix}1 & 0 & 0\\ 0 & 1 & 1\end{bmatrix}}_{\text{Number of original states (original model)}}\right\}\text{Number of final states (lumped model)}$$

$$\hat{A} = M \cdot A \longrightarrow \begin{bmatrix}\hat{A}_1\\ \hat{A}_2\end{bmatrix} = \begin{bmatrix}1 & 0 & 0\\ 0 & 1 & 1\end{bmatrix}\begin{bmatrix}A_1\\ A_2\\ A_3\end{bmatrix}$$

$$\therefore\ \hat{A}_1 = A_1$$

$$\hat{A}_2 = A_2 + A_3$$

Parameter values for the lumped model

We have seen that $\hat{y} = My$ $\quad y = M^{+}\hat{y}$ (slide 3 & 11)

ODEs in lumped states

$$\frac{d\hat{y}}{dt} = M \cdot f(y) \quad \text{and } f(y) = K \cdot y \quad \text{(slide 6)}$$

$$= M \cdot K \cdot y$$

$$= \underline{M \cdot K \cdot M^{+}}\hat{y}$$

also $\frac{d\hat{y}}{dt} = \hat{f}(\hat{y}) = \underline{\hat{K}} \cdot \hat{y}$ (slide 3)

so $\boxed{\hat{K} = M \cdot K \cdot M^{+}}$

Defining $\hat{K}$

$$\boxed{\hat{K} = M \cdot K \cdot M^{+}}$$

$$M = \begin{bmatrix} 1 & 0 & 0 \\ 0 & 1 & 1 \end{bmatrix} \quad K = \begin{bmatrix} -(k_{12} + k_{13} + k_{10}) & k_{21} & k_{31} \\ k_{12} & -k_{21} & 0 \\ k_{13} & 0 & -k_{31} \end{bmatrix} \quad M^{+} = \begin{bmatrix} 1 & 0 \\ 0 & 1/2 \\ 0 & 1/2 \end{bmatrix}$$

Matrix operations to define $\hat{\mathrm{K}}$

$$\boxed{\hat{K} = M \cdot K \cdot M^{+}}$$

$$M = \begin{bmatrix} 1 & 0 & 0 \\ 0 & 1 & 1 \end{bmatrix} \qquad K = \begin{bmatrix} -(k_{12} + k_{13} + k_{10}) & k_{21} & k_{31} \\ k_{12} & -k_{21} & 0 \\ k_{13} & 0 & -k_{31} \end{bmatrix} \qquad M^{+} = \begin{bmatrix} 1 & 0 \\ 0 & 1/2 \\ 0 & 1/2 \end{bmatrix}$$

Matrix dimensions $\Rightarrow$ 2x3 3x3 3x2

2x2 matrix

Lumping to produce $\hat{K}$

$$\boxed{\hat{K} = M \cdot K \cdot M^{+}}$$

$$M = \begin{bmatrix} 1 & 0 & 0 \\ 0 & 1 & 1 \end{bmatrix} \qquad K = \begin{bmatrix} -(k_{12}+k_{13}+k_{10}) & k_{21} & k_{31} \\ k_{12} & -k_{21} & 0 \\ k_{13} & 0 & -k_{31} \end{bmatrix} \qquad M^{+} = \begin{bmatrix} 1 & 0 \\ 0 & 1/2 \\ 0 & 1/2 \end{bmatrix}$$

Matrix dimensions → 2x3 3x3 3x2

2x2 matrix

$$MM^{+} = \begin{bmatrix} 1 & 0 \\ 0 & 1 \end{bmatrix}$$

$$\hat{K} = \begin{bmatrix} -(k_{12}+k_{13}+k_{10}) & \dfrac{k_{21}+k_{31}}{2} \\ k_{12}+k_{13} & -\dfrac{k_{21}+k_{31}}{2} \end{bmatrix}$$

$\hat{k}_{10} = k_{10}$

$\hat{k}_{12} = k_{12} + k_{13}$ → special case: when $k_{21} = k_{31}$

$\hat{k}_{21} = (k_{21}+k_{31})/2$