Mechanistic lumping of linear PBPK models

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Background & Objectives

(Approximate) proper lumping of linear systems

- Given: linear system of n ODEs
$$X' = AX$$
- Proper lumping $X_\mathrm{L} = MX$ via lumping matrix M
⇒ approximate system of $k < n$ lumped ODEs
$$X_\mathrm{L}' = MAM^\dagger X_\mathrm{L}$$
- Reconstruction $M^\dagger X_\mathrm{L} \approx X$ via pseudoinverse $M^\dagger$
⇒ not uniquely determined

Pharmacokinetics literature for choice of $M^\dagger$

- Moore-Penrose pseudoinverse [1-3] ⇒ not mechanistic
- Based on $\mathrm{diag}(A)$ eigendecomposition [4] ⇒ implicit
- Derived from lumping conditions [5,6]
⇒ mechanistic, but limited to specific systems

Objectives

- Generalize lumping conditions to stable linear systems
- Efficient implementation of automated calculation

Methods: Reconstruction via lumping conditions

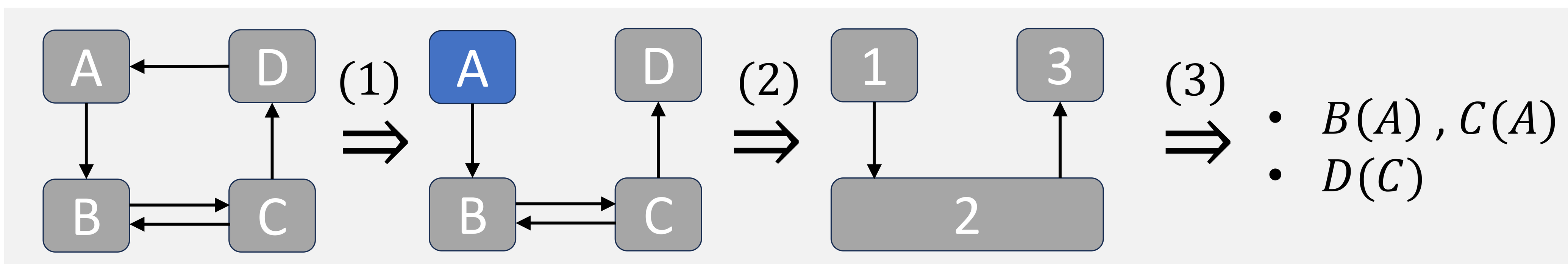
Formalization (requirement: A invertible)

- Quasi-steady-state (QSS) w.r.t. reference state $r \in \{1, \dots, n\}$
$A_{-r,-r}X_{-r} + A_{r,-r}X_r = 0 \Rightarrow$ weights $w_i = \frac{X_i}{X_r}$
- Weighted least-squares reconstruction ($W = \mathrm{diag}(w)$):
$$\hat{y} = \underset{z}{\mathrm{argmin}}\{\, \|z\|_{W^{-1}} : Mz = My\}$$
- Optimal reconstruction: $\hat{y} = M^\dagger M y$ with
$$M^\dagger = WM^\mathrm{T}(MWM^\mathrm{T})^{-1}$$

Algorithmic realization

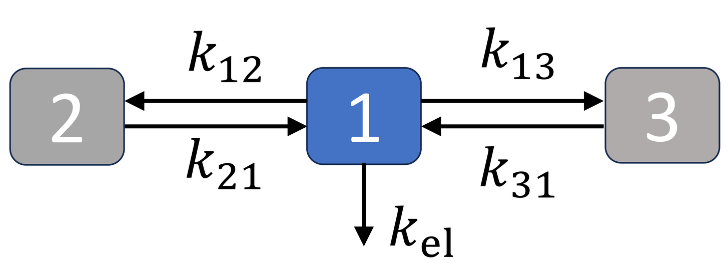
Graph-based implementation exploiting sparse connectivity of typical PBPK model topologies [7]:

(1) Choose reference state ⇒ prune graph (cut incoming edges)
(2) Construct condensation graph [8]
(3) Topological traversal; compute local QSS



Results: mechanistic lumping of different model structures

Three-state model

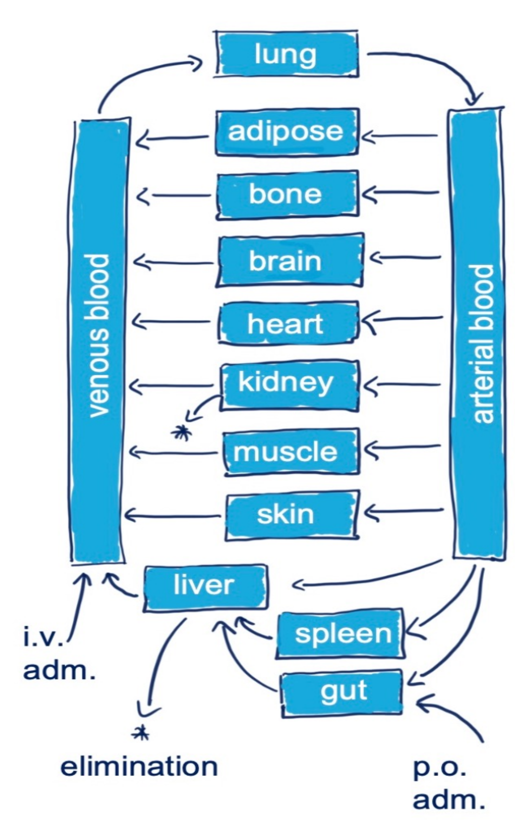


Underlying linear system:
$$A = \begin{pmatrix} -k_\mathrm{el} - k_{12} - k_{13} & k_{21} & k_{31} \\ k_{12} & -k_{21} & 0 \\ k_{13} & 0 & -k_{31} \end{pmatrix}$$

Assumed lumping scheme:
$$M = \begin{pmatrix} 1 & 0 & 0 \\ 0 & 1 & 1 \end{pmatrix} \Rightarrow M_\alpha^\dagger = \begin{pmatrix} 1 & 0 \\ 0 & \alpha \\ 0 & 1-\alpha \end{pmatrix}$$

QSS w.r.t. reference state $r = 1$:
$$\Rightarrow w = \begin{pmatrix} 1 \\ K_2 \\ K_3 \end{pmatrix} \text{ with } K_2 = \frac{k_{12}}{k_{21}}, K_3 = \frac{k_{13}}{k_{31}}$$
$$\Rightarrow M^\dagger = \begin{pmatrix} 1 & 0 \\ 0 & \frac{K_2}{K_2+K_3} \\ 0 & \frac{K_3}{K_2+K_3} \end{pmatrix} \neq \begin{pmatrix} 1 & 0 \\ 0 & \frac{1}{2} \\ 0 & \frac{1}{2} \end{pmatrix}$$
(Moore-Penrose pseudoinverse)

Well-stirred model



⇒ reproduced results from [5]
- Non-eliminating organs
$$w_\mathrm{org} = \frac{V_\mathrm{org}K_\mathrm{org}}{V_\mathrm{ven}}$$
- Liver
$$w_\mathrm{liv} = \frac{V_\mathrm{liv}K_\mathrm{liv}}{V_\mathrm{liv}} \cdot \frac{Q_\mathrm{liv}}{Q_\mathrm{liv} + \mathrm{CL}}$$

Conclusion & Outlook

- Method extended successfully (theory & implementation)
- Complexity is due to diffusive, not convective processes
- Open challenges:
  - General handling of first-pass effect
  - Several reference states

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