Automated proper lumping for simplification of systems models

Shan Pan

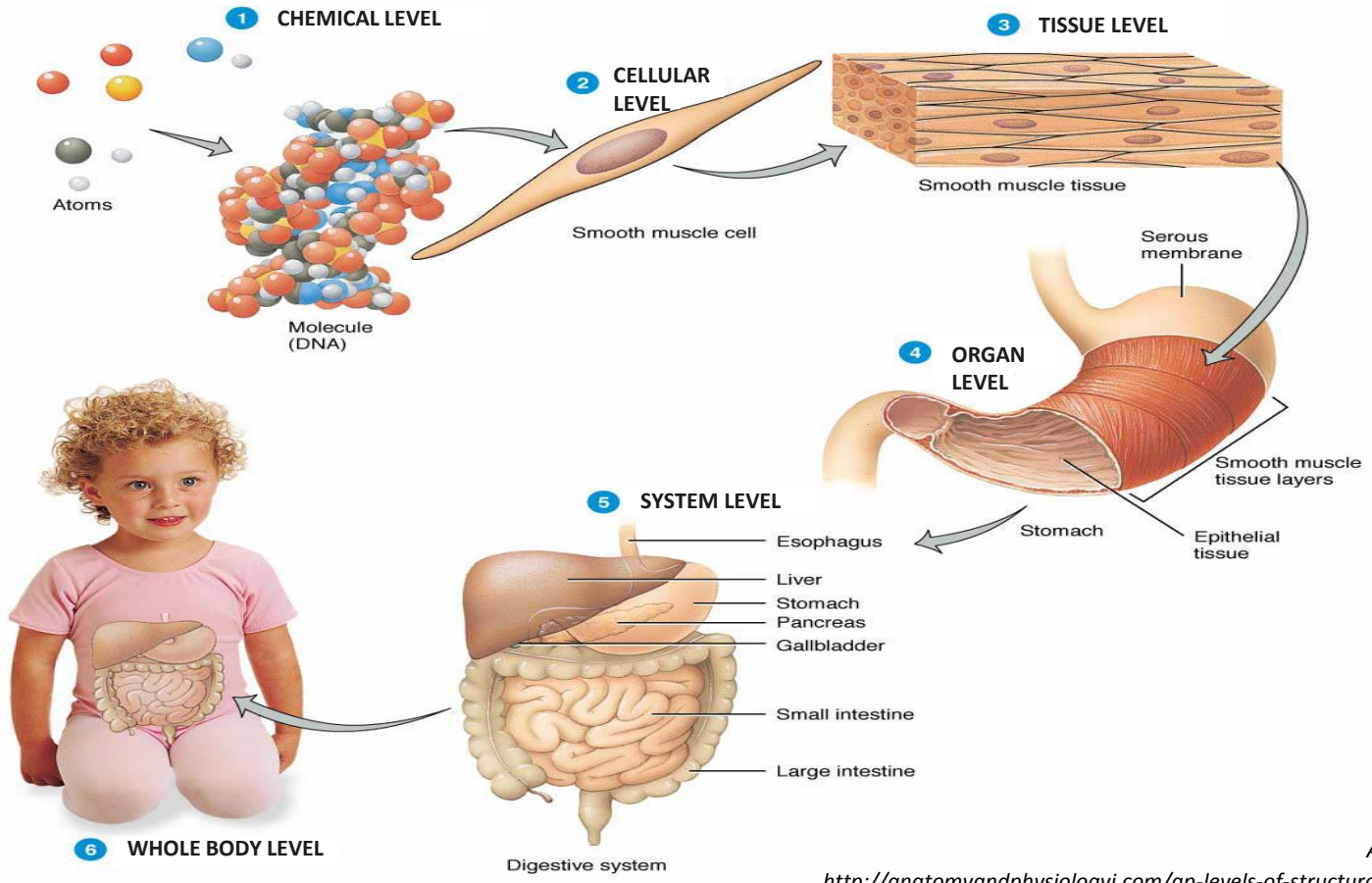
Stephen Duffull

School of Pharmacy, University of Otago, Dunedin, New Zealand

otago pharmacometrics

UNIVERSITY of OTAGO
Te Whare Wānanga o Otāgo
NEW ZEALAND

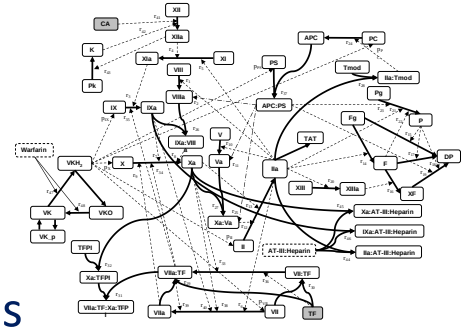
Human body is multi-scale

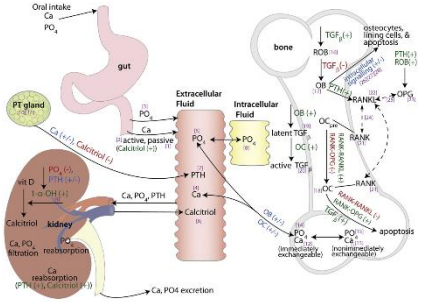


Adapted from:
http://anatomyandphysiologyi.com/ap-levels-of-structural-organization/

Systems models

- Systems models are multi-scale
  - Quantify the interaction between drug(s) and integrated system
  - Complex mathematical models
- Examples of systems models
  - Physiologically-based pharmacokinetic (PBPK) models
  - Systems pharmacology models, e.g.,
    - coagulation network: 62 states
    - bone remodelling and calcium homeostasis: 28 states





Wajima et al, Clin Pharmacol Ther 2009; 86(3):290-8
Peterson and Riggs, Bone 2010; 46(1):49-63

Systems models

- Application of systems models
  - PBPK models
    - Predict PK in humans before first-in-human studies
    - Extrapolate findings in special populations (e.g. paediatrics, the obese)
  - Systems pharmacology models
    - Test and identify drug targets in early discovery stage
    - Characterise influence of perturbed conditions on overall efficacy profile
- They are structurally complex and may need to be simplified

Why model simplification?

- These mechanism-driven models can be used to explore datasets
  - Better predictability and extrapolatability than empirical approach
  - Can be used as the basis of model development for estimation and optimisation
- Numeric problems with systems models
  - Large number of parameters
  - Unknown or uncertain parameter values
  - Identifiability issue during estimation (i.e. structural / deterministic)

Model simplification

- An existing technique to reduce a complex system into a simpler structure (i.e. reduced number of states and parameters)
  - Has long been investigated in chemical engineering
  - Model order reduction algorithms to transform system into fewer orders
  - Simpler structure yet similar input-output relationship

Model simplification

- Model simplification techniques
  - **Time-scale analysis**
    - Separate system into different time-scales (e.g. mAbs PBPK simplification)
    - Replace fast-scale with quasi-steady state (e.g. drug-receptor binding)
    - Fix slow-scale state with constant (e.g. constant in disease progression)
  - **Sensitivity analysis**
    - Determine and eliminate states insensitive to output of interest
  - **Lumping**
    - Merge states into reduced pseudo-states

Okino and Mavrovouniotis, Chem Rev 1998; 98(2):391-408
Elmeliegy et al, AAPS J 2014; 16(4):810-42

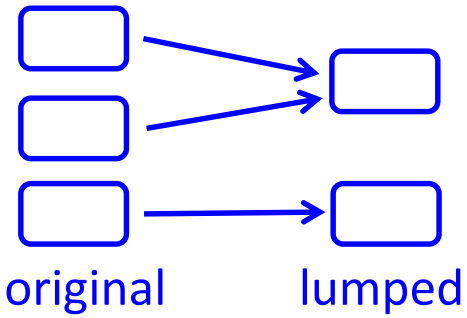
Model simplification

- Model simplification techniques
  - **Time-scale analysis**
    - Separate system into different time-scales (e.g. mAbs PBPK simplification)
    - Replace fast-scale with quasi-steady state (e.g. drug-receptor binding)
    - Fix slow-scale state with constant (e.g. constant in disease progression)
  - **Sensitivity analysis**
    - Determine and eliminate states insensitive to output of interest
  - **Lumping**
    - Merge states into reduced pseudo-states

Okino and Mavrovouniotis, Chem Rev 1998; 98(2):391-408
Elmeliegy et al, AAPS J 2014; 16(4):810-42

Proper lumping

- A special case of lumping that merges some of the states to only one pseudo-state

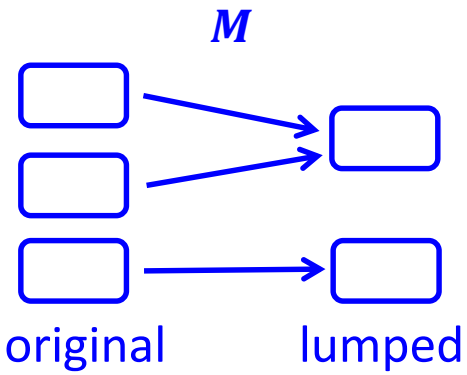


- Reduced states after proper lumping are able to retain the physical meaning as in the original system

Dokoumetzidis and Aarons, IET Syst Biol 2009; 3(1):40-51

Proper lumping

- A special case of lumping that merges some of the states to only one pseudo-state



- Reduced states after proper lumping are able to retain the physical meaning as in the original system

- Lumping matrix, M, transforms the states between original and reduced systems

Defining Lumping matrix

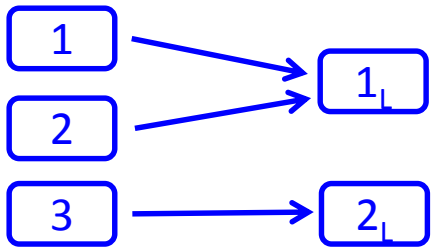
- The lumping matrix, M, is a $m \times n$ matrix of switches (0s and 1s) where $m \leq n$

- n is the number of states in the original system
  - n = 3 for the 3-state example

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

Lumping matrix

- Lumping matrix example: $M = \begin{bmatrix} 1 & 1 & 0 \\ 0 & 0 & 1 \end{bmatrix}$



original lumped

- For linear systems, proper lumping directly produces parameter values for lumped system with given M

Proper lumping with M

Original model: $\frac{dy}{dt} = K \cdot y$ — $\boldsymbol{y}$: *vector of original states,* $\boldsymbol{K}$: *original parameter matrix*

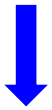
Lumped model: $\frac{d\hat{y}}{dt} = \hat{K} \cdot \hat{y}$ — $\hat{\boldsymbol{y}}$: *vector of lumped states,* $\hat{\boldsymbol{K}}$: *lumped parameter matrix*

Proper lumping with M

Original model: $\frac{dy}{dt} = K \cdot y$ — $\boldsymbol{y}$: *vector of original states,* $\boldsymbol{K}$: *original parameter matrix*

Lumped model: $\frac{d\hat{y}}{dt} = \hat{K} \cdot \hat{y}$ — $\hat{\boldsymbol{y}}$: *vector of lumped states,* $\hat{\boldsymbol{K}}$: *lumped parameter matrix*

Lumped states: $\hat{y} = M \cdot y$ — $\boldsymbol{M}$: *lumping matrix*



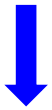
$y = M^{+} \cdot \hat{y}$ — $\boldsymbol{M}^{+}$: *Moore–Penrose pseudo-inverse of M*

Proper lumping with M

Original model: $\frac{dy}{dt} = K \cdot y$ — $\boldsymbol{y}$: *vector of original states,* $\boldsymbol{K}$: *original parameter matrix*

Lumped model: $\frac{d\hat{y}}{dt} = \hat{K} \cdot \hat{y}$ — $\hat{\boldsymbol{y}}$: *vector of lumped states,* $\hat{\boldsymbol{K}}$: *lumped parameter matrix*

Lumped states: $\hat{y} = M \cdot y$ — $\boldsymbol{M}$: *lumping matrix*



$y = M^{+} \cdot \hat{y}$ — $\boldsymbol{M}^{+}$: *Moore–Penrose pseudo-inverse of M*

From original to lumped model:

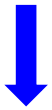
$$\frac{dy}{dt} = K \cdot y \longrightarrow M\,\frac{dy}{dt} = M \cdot K \cdot y$$

Proper lumping with M

Original model: $\frac{dy}{dt} = K \cdot y$ — $\boldsymbol{y}$: *vector of original states,* $\boldsymbol{K}$: *original parameter matrix*

Lumped model: $\frac{d\hat{y}}{dt} = \hat{K} \cdot \hat{y}$ — $\hat{\boldsymbol{y}}$: *vector of lumped states,* $\hat{\boldsymbol{K}}$: *lumped parameter matrix*

Lumped states: $\hat{y} = M \cdot y$ — $\boldsymbol{M}$: *lumping matrix*



$y = M^{+} \cdot \hat{y}$ — $\boldsymbol{M}^{+}$: *Moore–Penrose pseudo-inverse of M*

From original to lumped model:

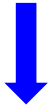
$$\frac{dy}{dt} = K \cdot y \longrightarrow M\,\frac{dy}{dt} = M \cdot K \cdot y \longrightarrow M\,\frac{dy}{dt} = M \cdot K \cdot M^{+}\hat{y}$$

Proper lumping with M

Original model: $\frac{dy}{dt} = K \cdot y$ — $\boldsymbol{y}$: *vector of original states,* $\boldsymbol{K}$: *original parameter matrix*

Lumped model: $\frac{d\hat{y}}{dt} = \hat{K} \cdot \hat{y}$ — $\hat{\boldsymbol{y}}$: *vector of lumped states,* $\hat{\boldsymbol{K}}$: *lumped parameter matrix*

Lumped states: $\hat{y} = M \cdot y$ — $\boldsymbol{M}$: *lumping matrix*



$y = M^{+} \cdot \hat{y}$ — $\boldsymbol{M}^{+}$: *Moore–Penrose pseudo-inverse of M*

From original to lumped model:

$$\frac{dy}{dt} = K \cdot y \longrightarrow M\,\frac{dy}{dt} = M \cdot K \cdot y \longrightarrow M\,\frac{dy}{dt} = M \cdot K \cdot M^{+}\hat{y} \longrightarrow \frac{d\hat{y}}{dt} = M \cdot K \cdot M^{+}\hat{y}$$

Proper lumping with M

Original model: $\frac{dy}{dt} = K \cdot y$ — $\boldsymbol{y}$: *vector of original states,* $\boldsymbol{K}$: *original parameter matrix*

Lumped model: $\frac{d\hat{y}}{dt} = \hat{K} \cdot \hat{y}$ — $\hat{\boldsymbol{y}}$: *vector of lumped states,* $\hat{\boldsymbol{K}}$: *lumped parameter matrix*

Lumped states: $\hat{y} = M \cdot y$ — $\boldsymbol{M}$: *lumping matrix*

$y = M^{+} \cdot \hat{y}$ — $\boldsymbol{M}^{+}$: *Moore–Penrose pseudo-inverse of M*

From original to lumped model:

$$\frac{dy}{dt} = K \cdot y \longrightarrow M\,\frac{dy}{dt} = M \cdot K \cdot y \longrightarrow M\,\frac{dy}{dt} = M \cdot K \cdot M^{+}\hat{y} \longrightarrow \frac{d\hat{y}}{dt} = M \cdot K \cdot M^{+}\hat{y}$$

Proper lumping with M

Original model: $\frac{dy}{dt} = K \cdot y$ — $\boldsymbol{y}$: *vector of original states,* $\boldsymbol{K}$: *original parameter matrix*

Lumped model: $\frac{d\hat{y}}{dt} = \hat{K} \cdot \hat{y}$ — $\hat{\boldsymbol{y}}$: *vector of lumped states,* $\hat{\boldsymbol{K}}$: *lumped parameter matrix*

Lumped states: $\hat{y} = M \cdot y$ — $\boldsymbol{M}$: *lumping matrix*

$y = M^{+} \cdot \hat{y}$ — $\boldsymbol{M}^{+}$: *Moore–Penrose pseudo-inverse of M*

From original to lumped model:

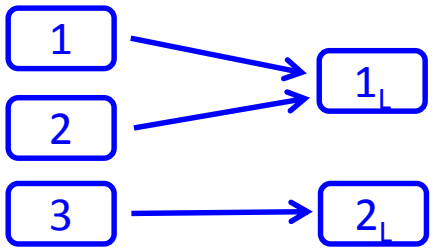
$$\frac{dy}{dt} = K \cdot y \longrightarrow M\,\frac{dy}{dt} = M \cdot K \cdot y \longrightarrow M\,\frac{dy}{dt} = M \cdot K \cdot M^{+}\hat{y} \longrightarrow \frac{d\hat{y}}{dt} = \overbrace{M \cdot K \cdot M^{+}}^{=\hat{K}}\hat{y}$$

otago pharmacometrics

UNIVERSITY of OTAGO
Te Whare Wānanga o Otāgo
NEW ZEALAND

Lumping matrix

- Lumping matrix example: $M = \begin{bmatrix} 1 & 1 & 0 \\ 0 & 0 & 1 \end{bmatrix}$

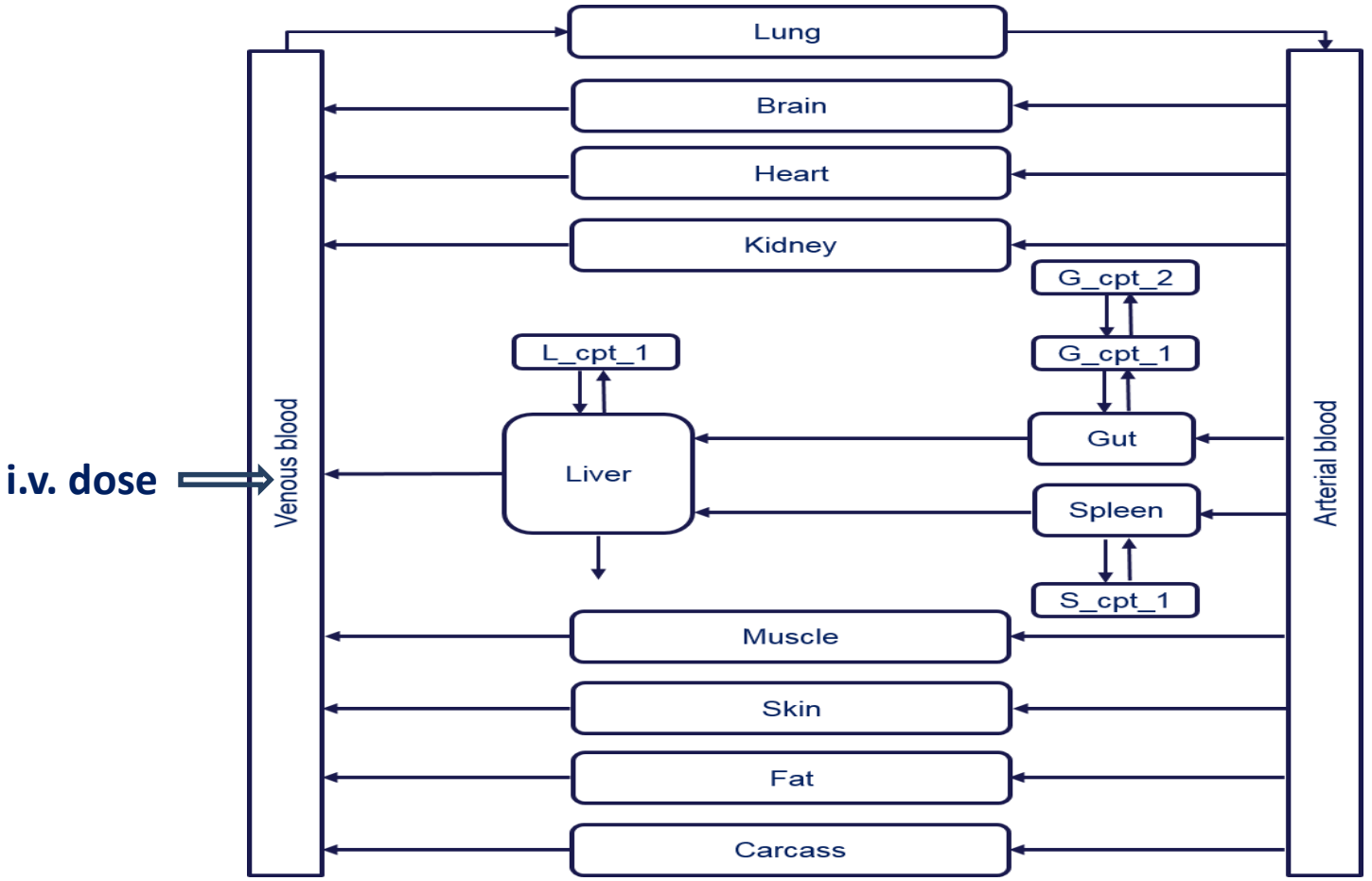


- Automated process is designed to search the M that satisfies a predefined criterion

Application example: fentanyl PBPK model

- Fentanyl is a potent synthetic opioid
- Small molecule and highly lipophilic
  - readily distribute into body tissues
- Administration routes: intravenous, transdermal, oral …
- Intravenous fentanyl is commonly used for anaesthesia during surgery and pain management before or after surgery

Fentanyl PBPK model



17 states
Linear system

Björkman et al, J Pharmacokinetic Biopharm 1994; 22(5):381-410

otago pharmacometrics

UNIVERSITY of OTAGO
Te Whare Wānanga o Otāgo
NEW ZEALAND

Simplification of fentanyl PBPK model

- Inputs for simplifying fentanyl PBPK model
  - i.v. infusion of 11 µg/kg over 5 minutes
  - Parameter matrix
  - Arterial concentration as measurement of interest
- Proper lumping as the simplification technique
  - Arterial state unlumped

Lumping matrix in fentanyl PBPK model

- Original lumping matrix

$$M = I_n; \quad n = \text{number of states in original model}$$

- Simplification started from fully lumped matrix

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

Parameter matrix in fentanyl PBPK model

$$
K = \begin{bmatrix}
-Qcad/Vven & 0 & KTbra*Vbra/Vven & KThea*Vhea/Vven & KTkid*Vkid/Vven & KTliv*Vliv/Vven & KTmus*Vmus/Vven & KTski*Vski/Vven & \cdots \\
Qcad/Vart & -Qcad/Vart & 0 & 0 & 0 & 0 & 0 & 0 & \cdots \\
0 & Qbra/Vbra & -KTbra & 0 & 0 & 0 & 0 & 0 & \cdots \\
0 & Qhea/Vhea & 0 & -KThea & 0 & 0 & 0 & 0 & \cdots \\
0 & Qkid/Vkid & 0 & 0 & -KTkid & 0 & 0 & 0 & \cdots \\
0 & 0 & 0 & 0 & 0 & Loss\_liver & 0 & 0 & \cdots \\
0 & Qmus/Vmus & 0 & 0 & 0 & 0 & -KTmus & 0 & \cdots \\
0 & Qski/Vski & 0 & 0 & 0 & 0 & 0 & -KTski & \cdots \\
0 & Qfat/Vfat & 0 & 0 & 0 & 0 & 0 & 0 & \cdots \\
0 & Qcar/Vcar & 0 & 0 & 0 & 0 & 0 & 0 & \cdots \\
0 & Qsint/Vgut\_1 & 0 & 0 & 0 & 0 & 0 & 0 & \cdots \\
0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & \cdots \\
0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & \cdots \\
0 & Qpas/Vpas\_1 & 0 & 0 & 0 & 0 & 0 & 0 & \cdots \\
0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & \cdots \\
0 & 0 & 0 & 0 & 0 & CL12\_hep/Vhep\_2 & 0 & 0 & \cdots
\end{bmatrix}
$$

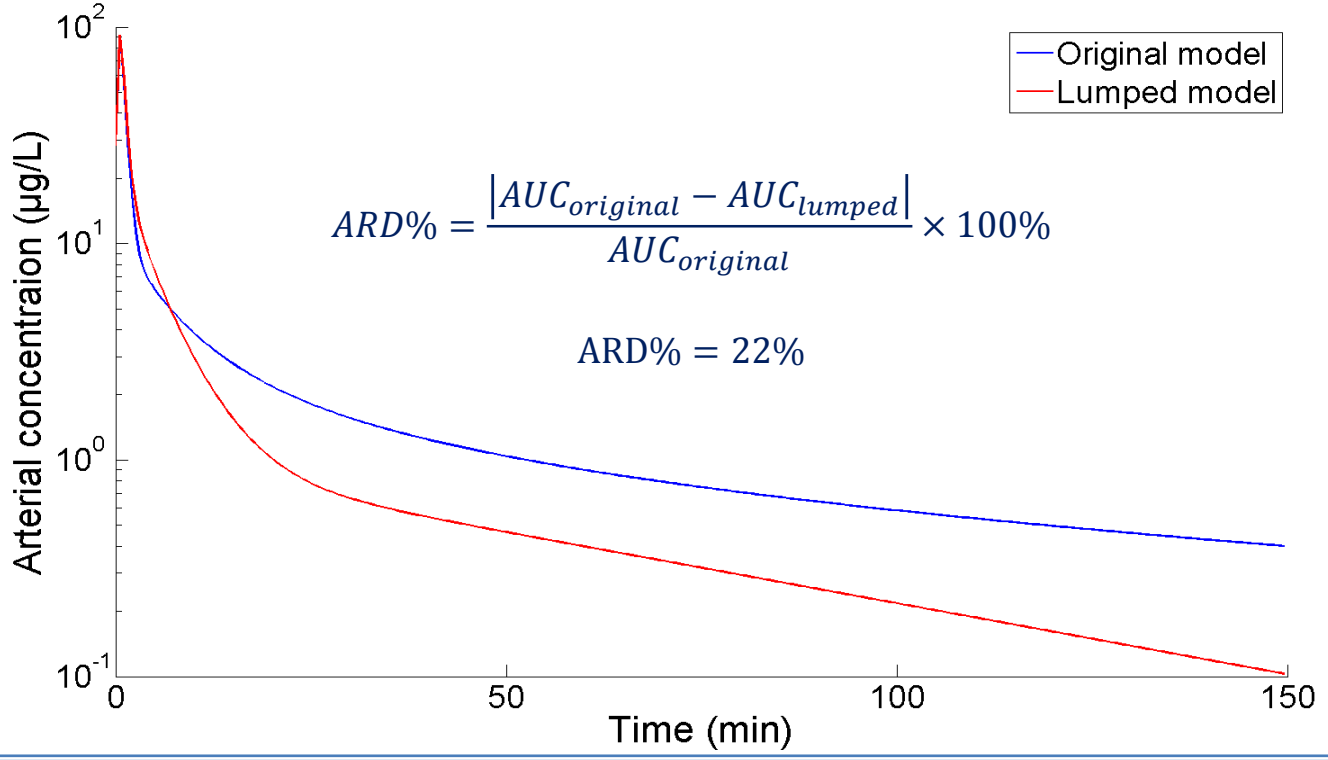
$$
\begin{bmatrix}
KTfat*Vfat/Vven & KTcar*Vcar/Vven & 0 & 0 & 0 & 0 & 0 & 0 \\
0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\
0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\
0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\
0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\
0 & 0 & S11\_to\_Liver & 0 & 0 & S14\_to\_Liver & 0 & S16\_to\_Liver \\
0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\
0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\
-KTfat & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\
0 & -KTcar & 0 & 0 & 0 & 0 & 0 & 0 \\
0 & 0 & Loss\_gut\_1 & CL21\_gut/Vgut\_1 & 0 & 0 & 0 & 0 \\
0 & 0 & CL12\_gut/Vgut\_2 & Loss\_gut\_2 & CL32\_gut/Vgut\_2 & 0 & 0 & 0 \\
0 & 0 & 0 & CL23\_gut/Vgut\_3 & -CL32\_gut/Vgut\_3 & 0 & 0 & 0 \\
0 & 0 & 0 & 0 & 0 & Loss\_pas\_1 & CL21\_pas/Vpas\_1 & 0 \\
0 & 0 & 0 & 0 & 0 & CL12\_pas/Vpas\_2 & -CL21\_pas/Vpas\_2 & 0 \\
0 & 0 & 0 & 0 & 0 & 0 & 0 & -CL21\_hep/Vhep\_2];
\end{bmatrix}
$$

otago pharmacometrics

UNIVERSITY of OTAGO
Te Whare Wānanga o Otāgo
NEW ZEALAND

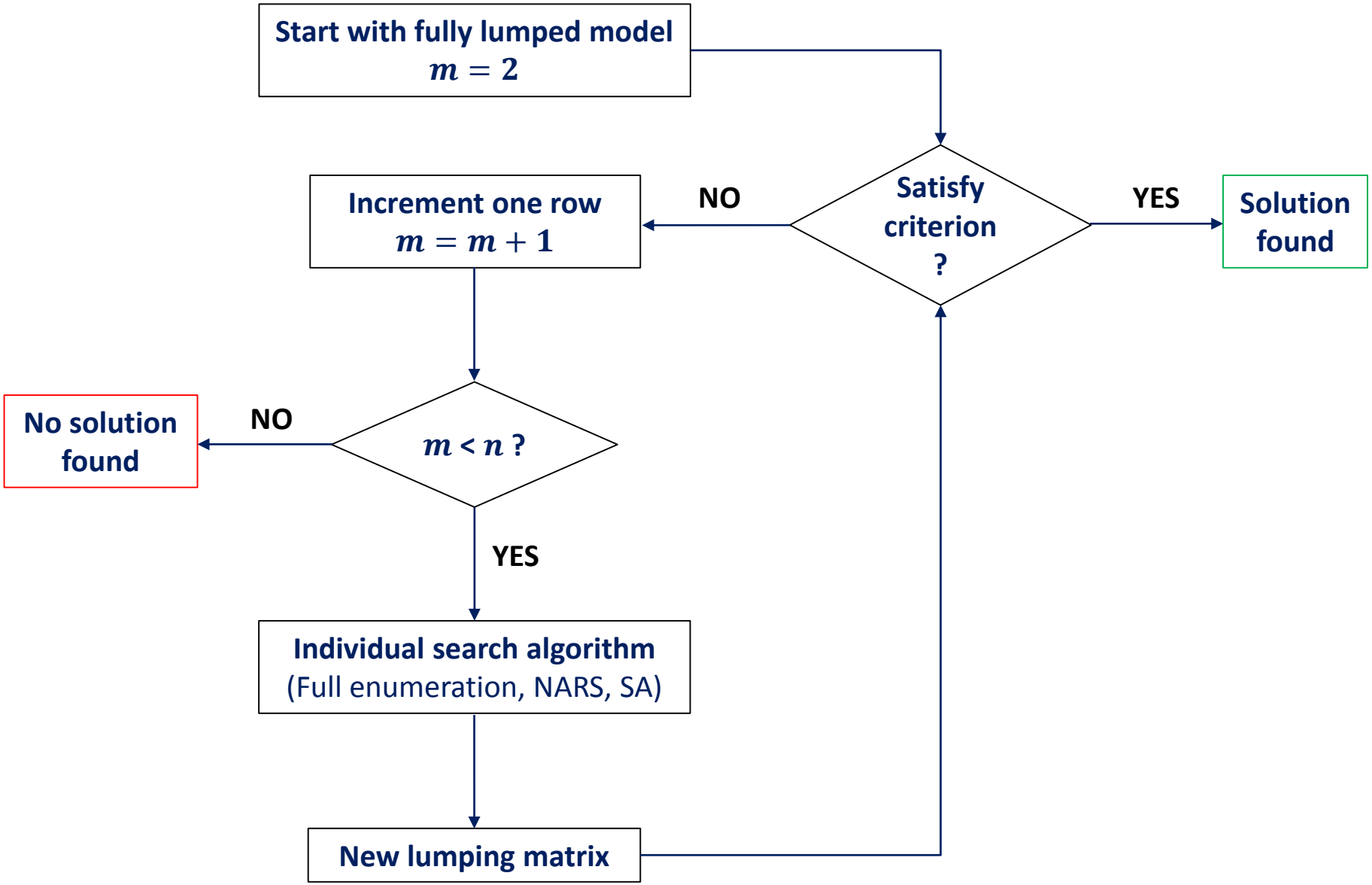
Acceptance criterion

- Absolute relative difference (ARD%) in total area under concentration-time curve (AUC)



Automated proper lumping

- Acceptance criterion
  - ARD% <= 0.002% in fentanyl PBPK example
  - Least number of rows in lumped model
- Constrained lumping
  - Output state unlumped during search
- Software
  - MATLAB® (version R2013b)


Start with fully lumped model
$m = 2$
Satisfy criterion ?
NO
Increment one row
$m = m + 1$
YES
Solution found
$m < n$?
NO
No solution found
YES
Individual search algorithm
(Full enumeration, NARS, SA)
New lumping matrix

Automated proper lumping

- Individual search algorithm of M matrix
  - Full enumeration
  - Non-adaptive random search (NARS)
  - Simulated annealing (SA)

Automated proper lumping

- Full enumeration
  - Exhaustive search all M matrices

Automated proper lumping

- Non-adaptive random search (NARS)
  - Randomly construct M matrices
  - Number of samples: 10 – 1,000,000 per increment

Automated proper lumping

- Simulated annealing (SA)
  - Annealing in metallurgy (slow cooling)
  - Temperature-regulated probability of accepting solutions
  - Minimize ARD%

Simplification of fentanyl PBPK model

- Full enumeration
  - A 4-state lumped model found after 40 minutes

Simplification of fentanyl PBPK model

- Non-adaptive random search (NARS)

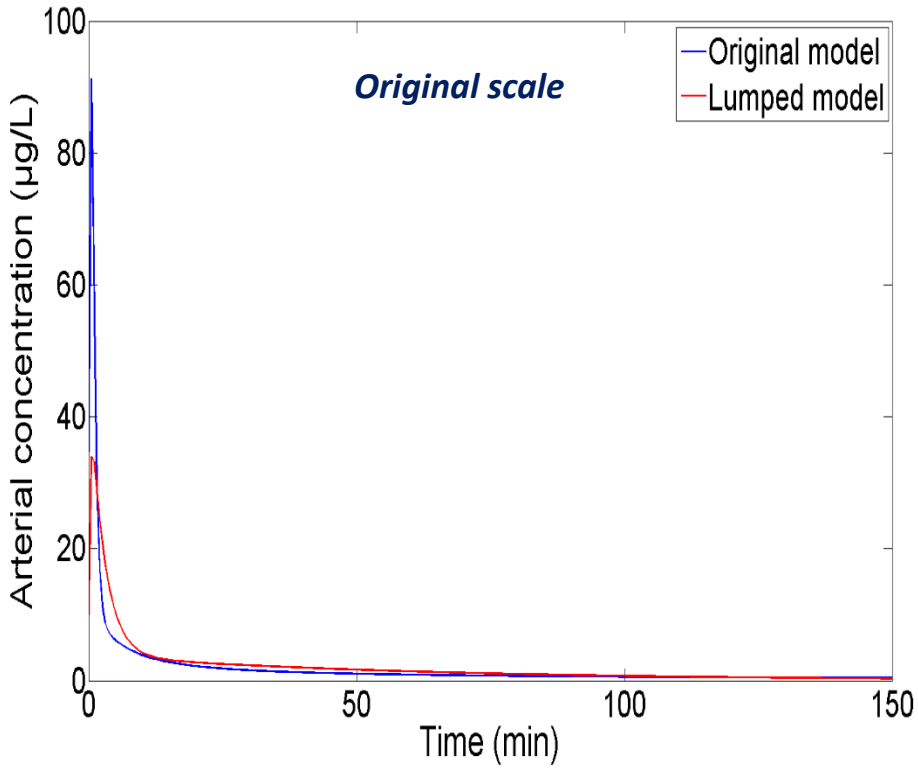
No. of samples	No. of lumped states	Time cost (min)
10	-	-
100	-	-
1,000	14	0.25
10,000	6	1
100,000	5	5
1,000,000	4	30

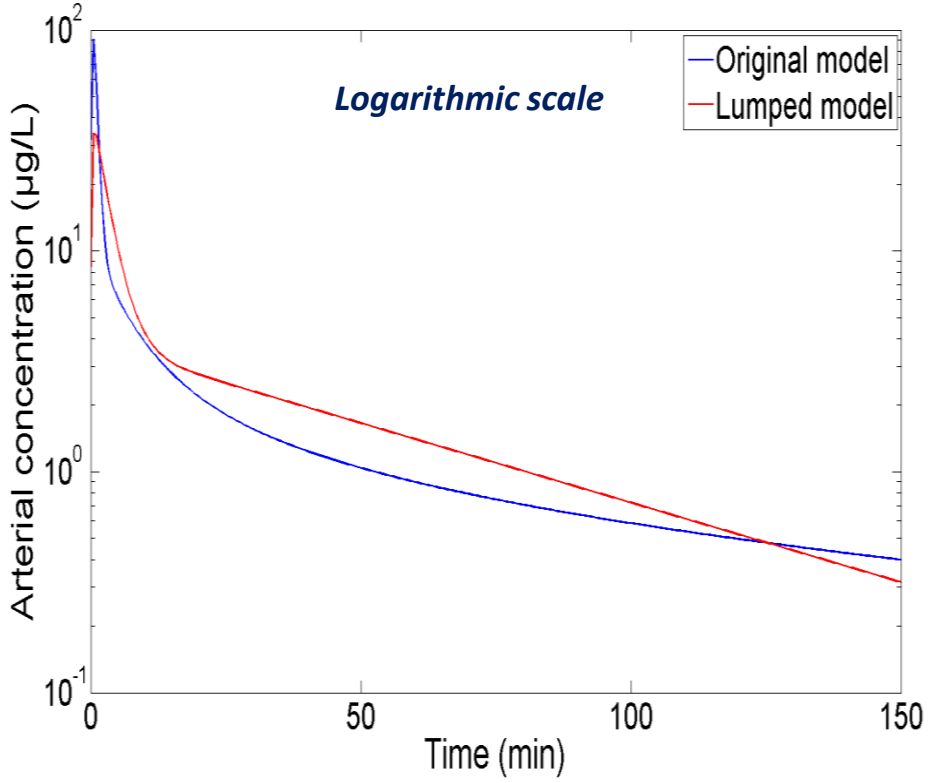
Simplification of fentanyl PBPK model

- Simulated annealing (SA)
  - A 4-state lumped model found after 3 minutes
  - Stable after various test runs

Simulation of fentanyl arterial concentrations

- Fentanyl arterial concentrations in *original* and *lumped* models





otago pharmacometrics

UNIVERSITY of OTAGO
Te Whare Wānanga o Otāgo
NEW ZEALAND

Discussion - application

- We have demonstrated automated simplification process using a fentanyl PBPK model
  - Proper lumping technique
  - Constrained on output state of interest
  - Different algorithms for automation
- Potential uses of simplified model structure
  - Population PKPD modelling (e.g. Fibrinogen PKPD modelling)
  - Optimal design (e.g. Methotrexate PK sampling)
  - ...

Gulati et al, CPT Pharmacometrics Syst Pharmacol 2014; 3:e90
Pan et al, 2015 (to be submitted)

Discussion – search algorithms

- The surface of the criterion is spiky & without obvious continuous gradients over the M-matrix
  - In some cases there was a million-fold difference in the criterion for two neighbouring lumping matrices (i.e. exchanging a 0 for a 1) and in others only a 10% change
- Full enumeration does not scale well for large-scale problems
  - e.g. 5-state search took 2 months for the fentanyl PBPK example

Discussion – search algorithms

- Non-adaptive random search
  - Requires a large number of samples for a 4-state lumped solution
  - Unlikely to scale well for large-scale problems
- Exchange algorithm (results not shown)
  - Was not stable due to local minima
- Simulated annealing
  - Worked well in this example
  - Has the capacity to escape from local minima

Conclusion

- Methods for automated model simplification represent large-scale combinatorial search problems
- It is expected that these methods will have significant potential benefits for those using multi-scale models
  - Simulated annealing may work well for general applications
  - More efficient algorithms may be required for large-scale systems (e.g. >50 states)

Acknowledgements

- University of Otago Postgraduate Scholarship
- School of Pharmacy
- Otago Pharmacometrics Group

otago pharmacometrics

UNIVERSITY of OTAGO
Te Whare Wānanga o Otāgo
NEW ZEALAND