

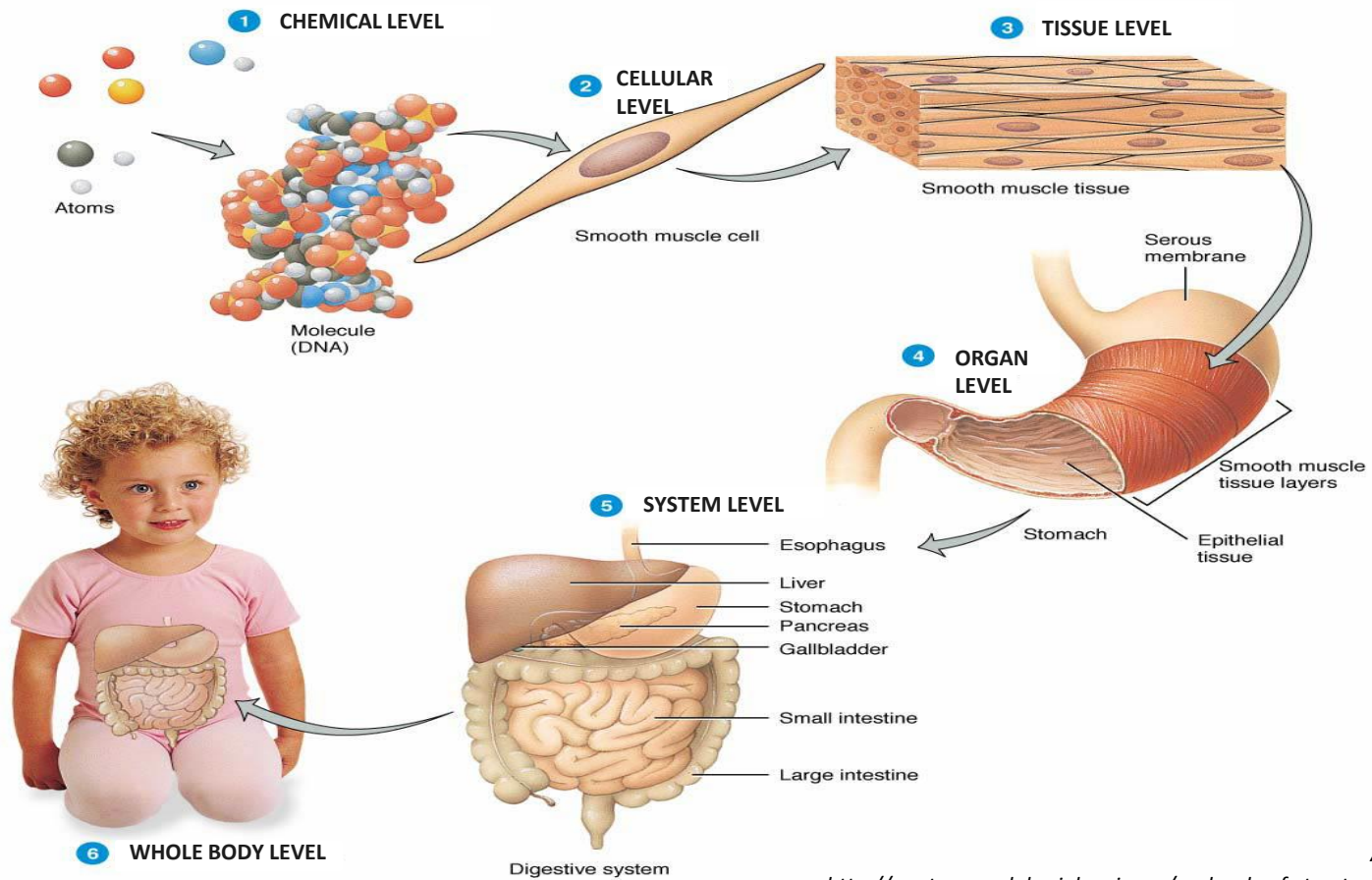
Automated proper lumping for simplification of systems models

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Human body is multi-scale



Adapted from:
<http://anatomyandphysiology.com/ap-levels-of-structural-organization/>

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

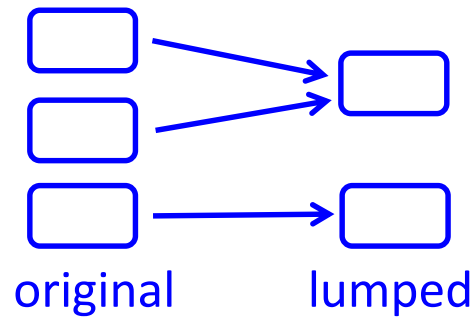
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Proper lumping

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

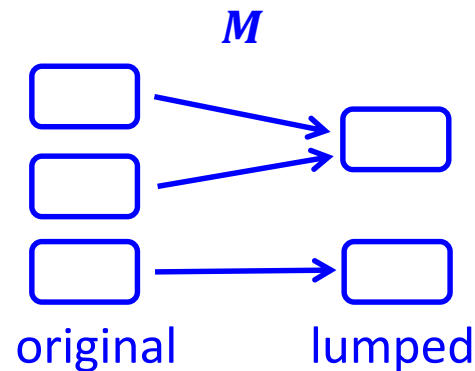


- Reduced states after proper lumping are able to retain the physical meaning as in the original system

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

Proper lumping

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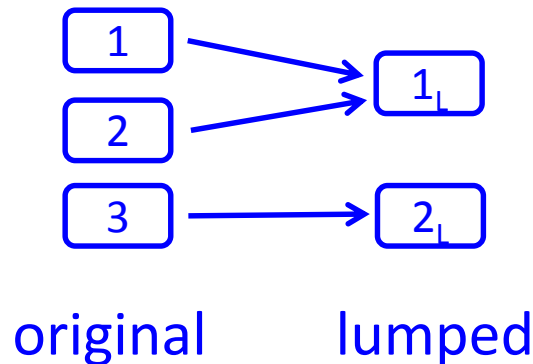
- Reduced states after proper lumping are able to retain the physical meaning as in the original system
- Lumping matrix, M , transforms the states between original and reduced systems

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



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

Proper lumping with M

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

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

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



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

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From original to lumped model:

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

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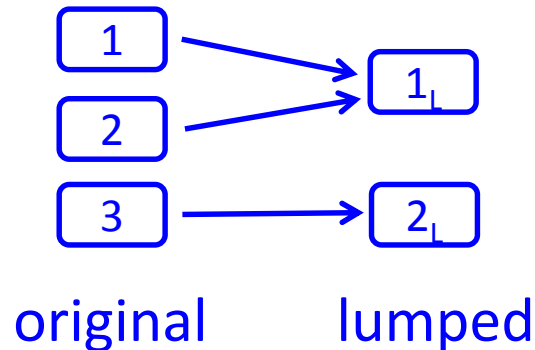
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Lumping matrix

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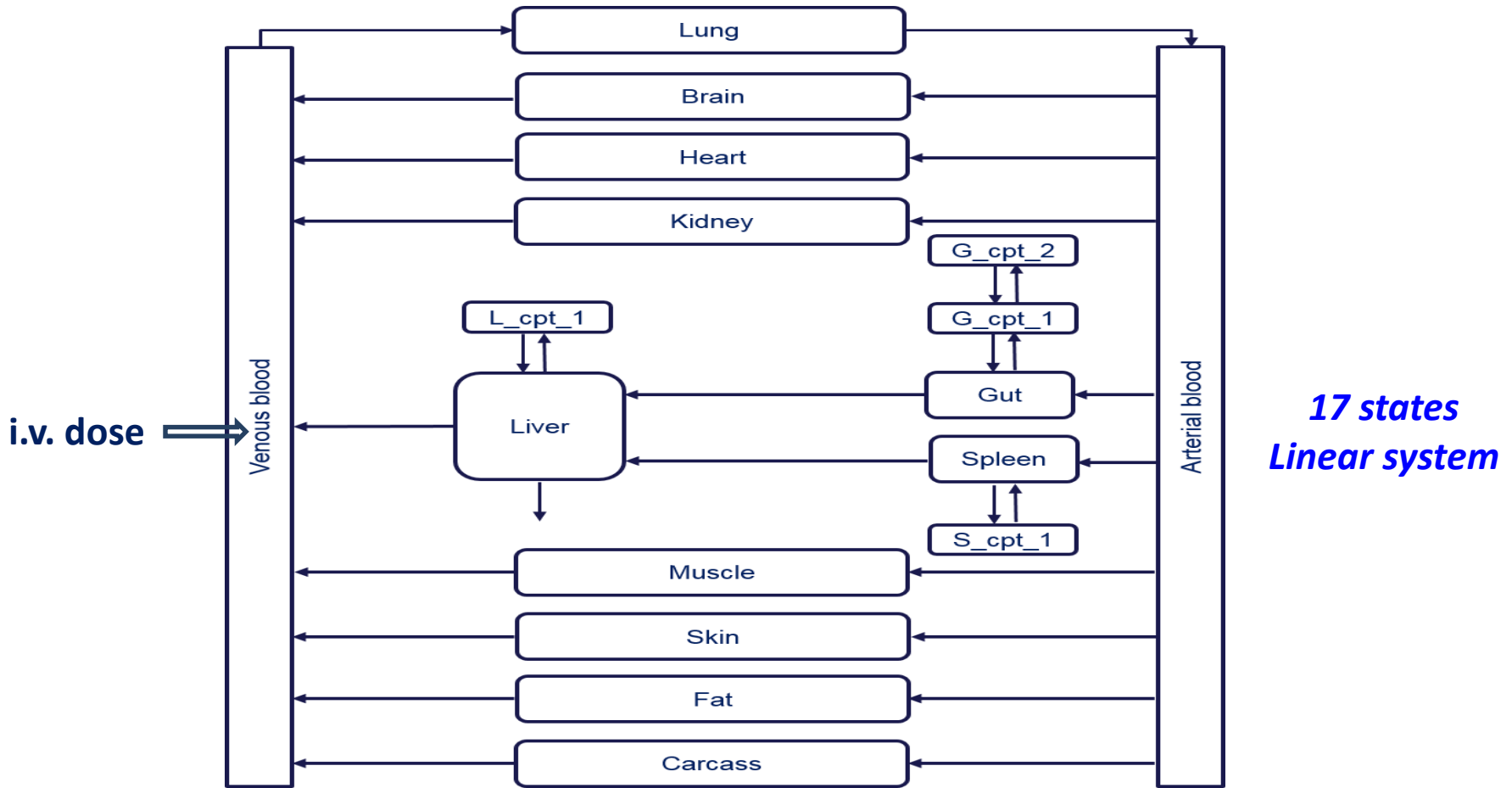


- Automated process is designed to search the M that satisfies a predefined criterion

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



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

Simplification of fentanyl PBPK model

- Inputs for simplifying fentanyl PBPK model
 - i.v. infusion of 11 $\mu\text{g}/\text{kg}$ 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

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

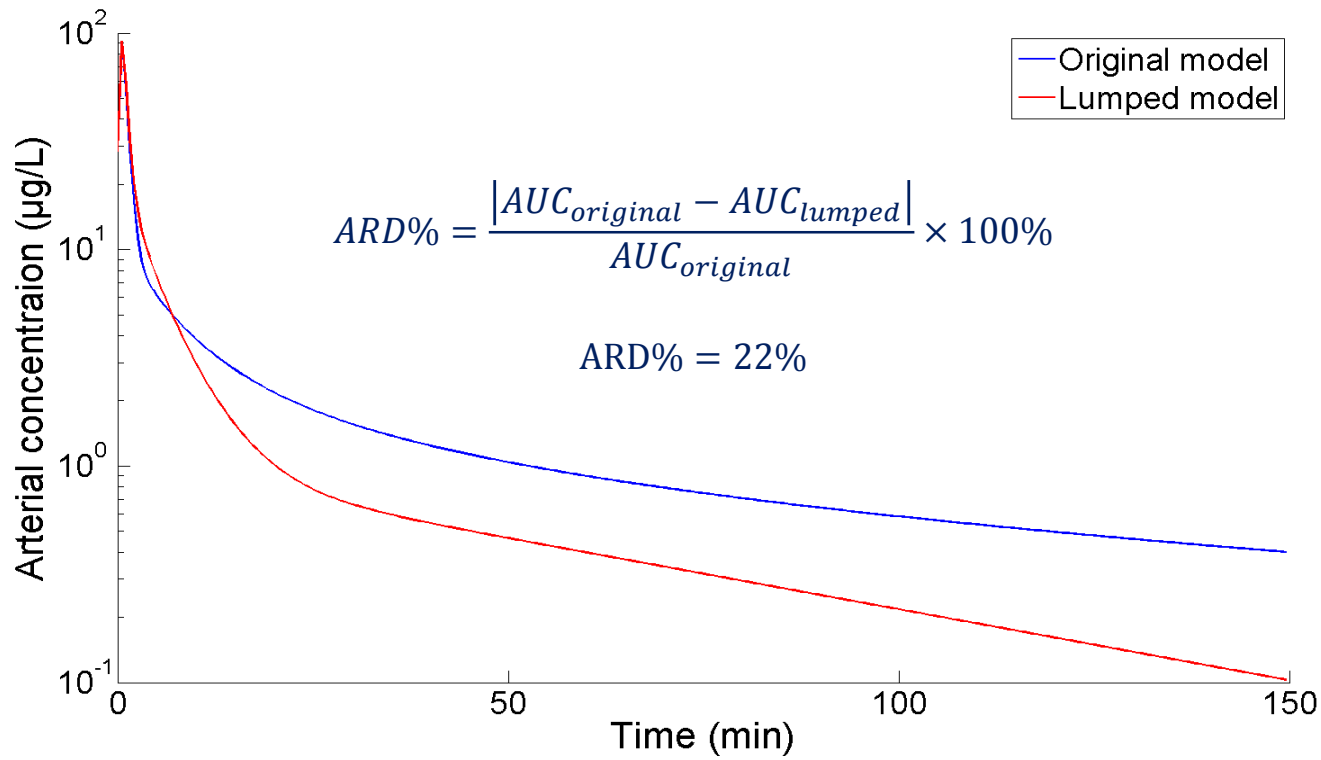
Parameter matrix in fentanyl PBPK model

K = [-Qcad/Vven	0	KTbra*Vbra/Vven	KThea*Vhea/Vven	KTkid*Vkid/Vven	KTliv*Vliv/Vven	KTmus*Vmus/Vven	KTski*Vski/Vven	...
Qcad/Vart	-Qcad/Vart	0	0	0	0	0	0	...
0	Qbra/Vbra	-KTbra	0	0	0	0	0	...
0	Qhea/Vhea	0	-KThea	0	0	0	0	...
0	Qkid/Vkid	0	0	-KTkid	0	0	0	...
0	0	0	0	0	Loss_liver	0	0	...
0	Qmus/Vmus	0	0	0	0	-KTmus	0	...
0	Qski/Vski	0	0	0	0	0	-KTski	...
0	Qfat/Vfat	0	0	0	0	0	0	...
0	Qcar/Vcar	0	0	0	0	0	0	...
0	Qsint/Vgut_1	0	0	0	0	0	0	...
0	0	0	0	0	0	0	0	...
0	0	0	0	0	0	0	0	...
0	Qpas/Vpas_1	0	0	0	0	0	0	...
0	0	0	0	0	0	0	0	...
0	0	0	0	0	CL12_hep/Vhep_2	0	0	...

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];

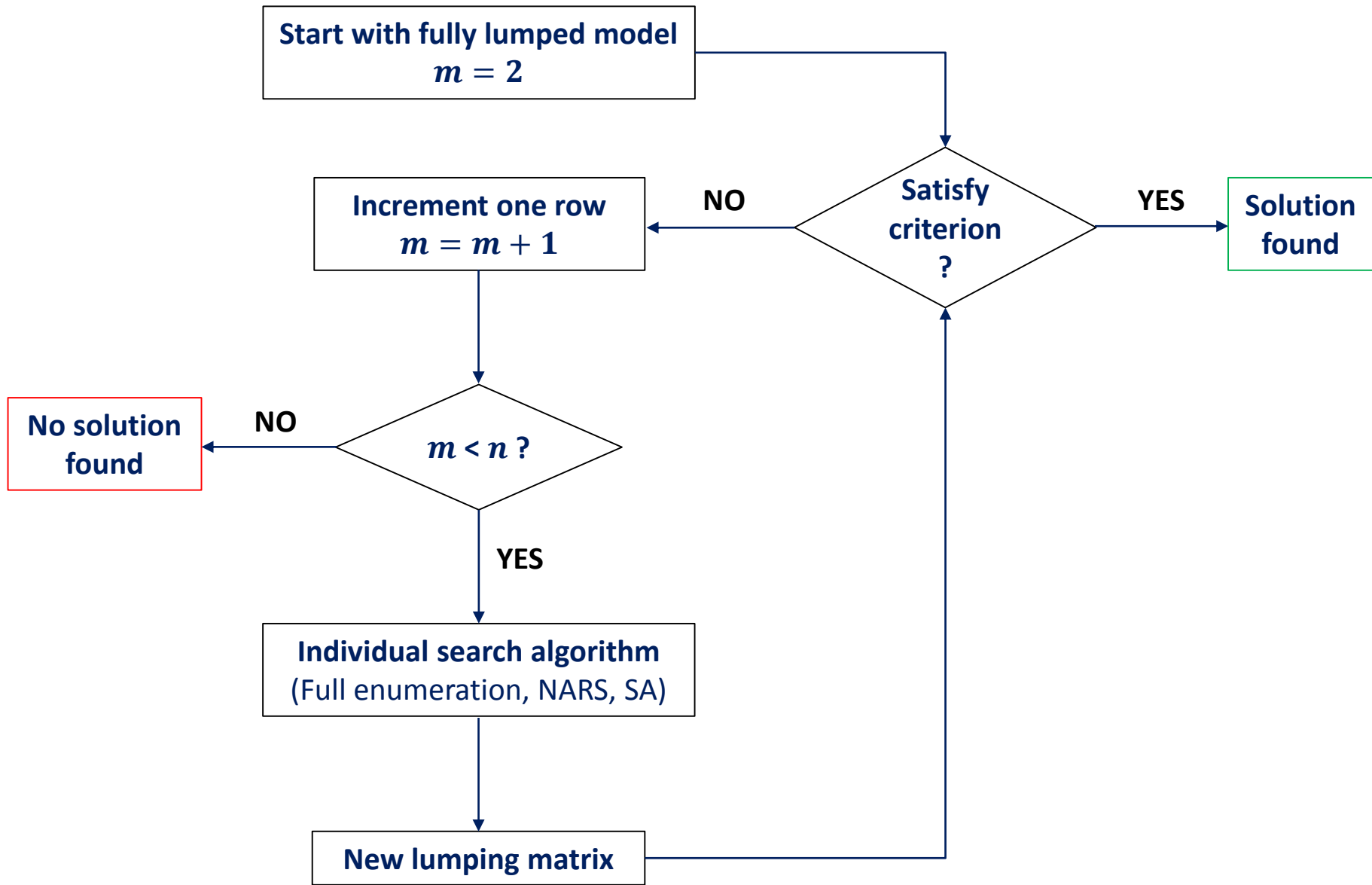
Acceptance criterion

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



Automated proper lumping

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



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)

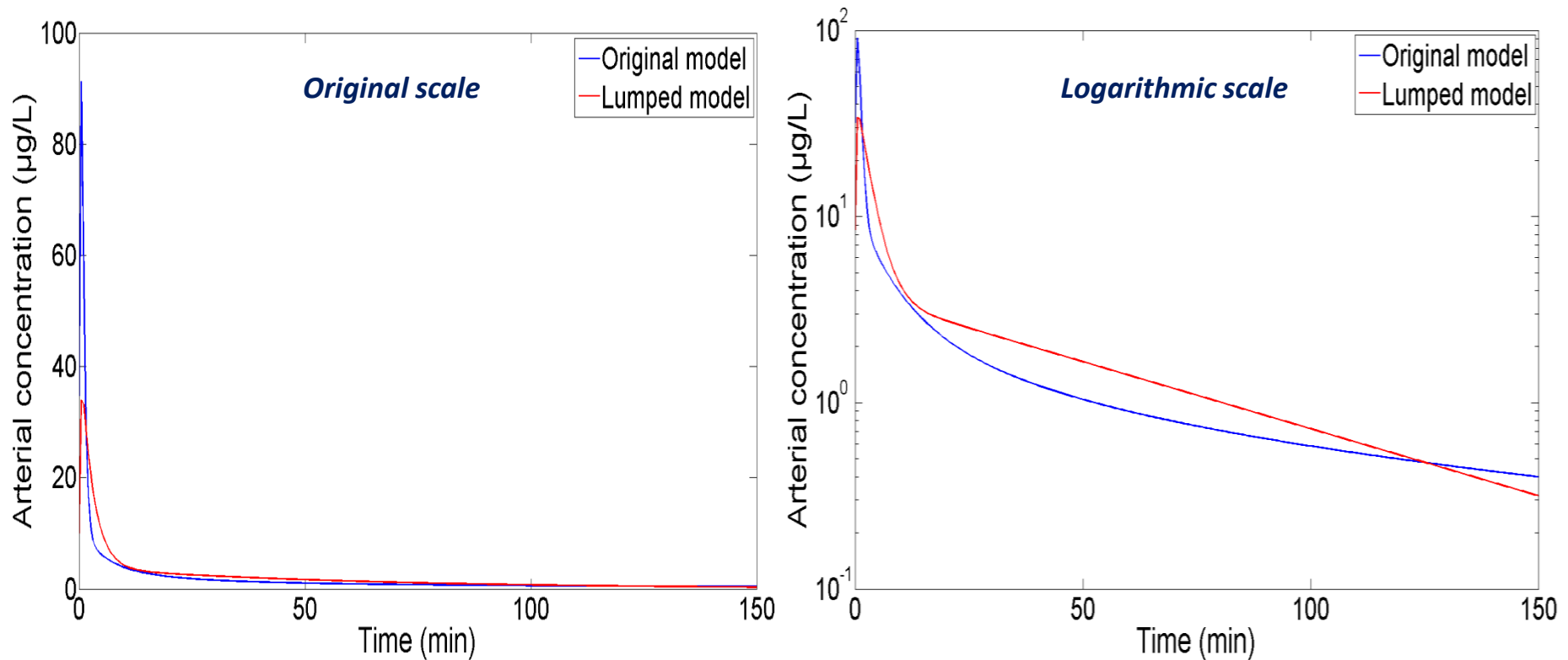
No. of samples	No. of lumped states	Time cost (min)
10	-	-
100	-	-
1,000	14	0.25
10,000	6	1
100,000	5	5
1,000,000	4	30

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



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