Lumping of compartments

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PAGE 2012

Model order reduction

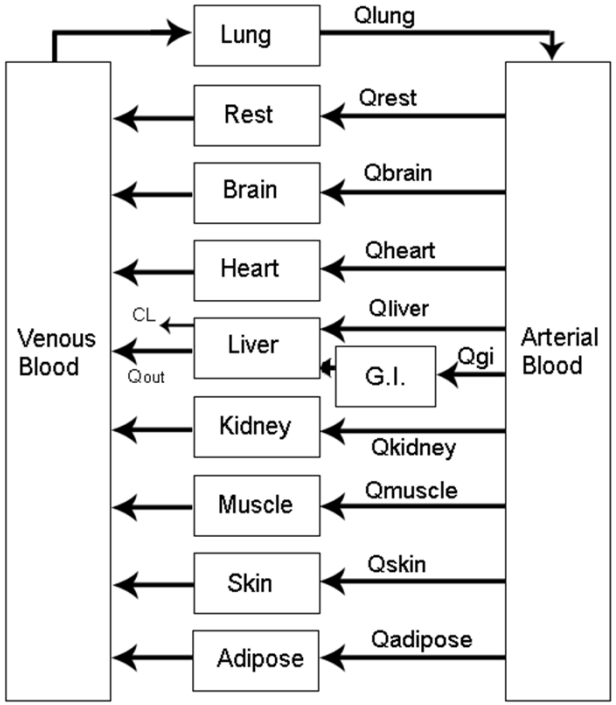
Starting from a large / complex mathematical model, Model Order Reduction provides a mathematical transformation such that a smaller in size system is produced but with effectively the same input – output behaviour

Several methods for model order reduction

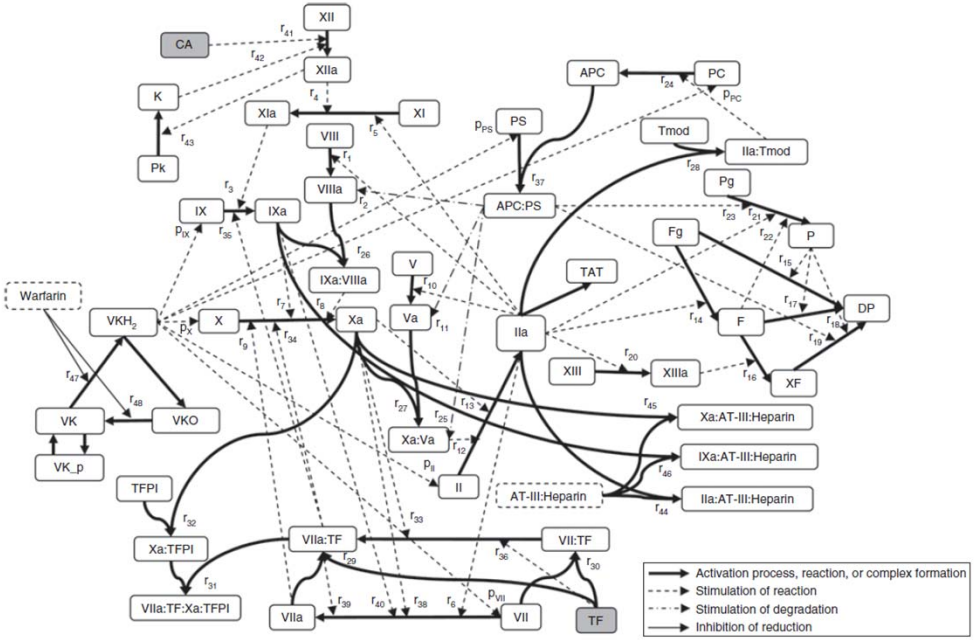
- Elimination of states
- Time scale separation
- Lumping (merging of states) 

Motivation / potential applications

In Pharmacokinetics
PBPK models



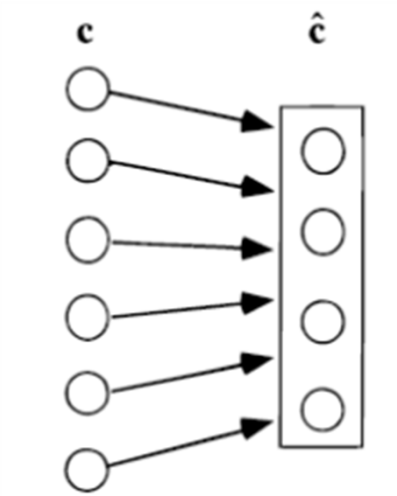
In Pharmacodynamics
Systems biology models



Lumping as a method for model order reduction

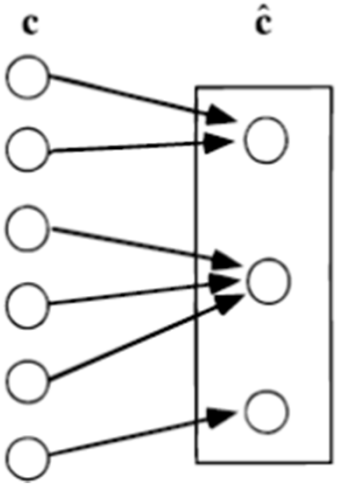
A formal way for model order reduction by merging together some of the system's states thus reducing its size.

Generalised lumping



The states of the reduced system are linear combinations (or even non linear functions) of the states of the original system.

Proper lumping



Each state of the original system is included only in one state of the reduced system, retaining physical meaning.

Dynamical systems

A dynamical system described by a set of ODEs is

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

Where y are the states of the system

The observables of the systems are given by a transformation of the states
we assume a linear transformation

$$\mathrm{C} = \mathrm{a} \cdot y$$

In a compartmental system the states are the amounts A
while the proportionality constants “a” relate the amounts to the observable concentrations and are:

$$\mathrm{a} = \begin{pmatrix} \mathrm{V}_1 & 0 & 0 \\ \vdots & \ddots & \vdots \\ 0 & \cdots & \mathrm{V}_2 \end{pmatrix}^{-1}$$

The lumping matrix M

A dynamical system

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

can be lumped such that

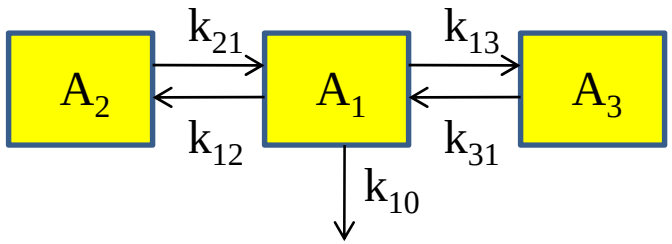
$$\hat{y} = My$$

where M is the **lumping matrix** consisting of **1**s and **0**s.

Then a new set of ODEs is produced

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

Lumping of a 3-compartment mammillary model to 2-compartment

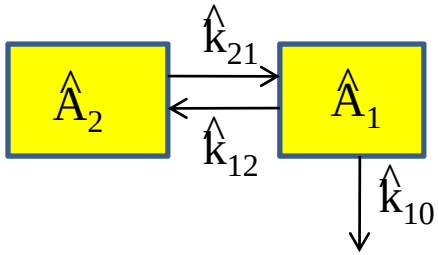


$$\frac{dA_1}{dt} = -(k_{12} + k_{13} + k_{10})A_1 + k_{21}A_2 + k_{31}A_3$$

$$\frac{dA_2}{dt} = k_{12}A_1 - k_{21}A_2$$

$$\frac{dA_3}{dt} = k_{13}A_1 - k_{31}A_3$$

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



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

Number of final states

Number of original states

$$\hat{A} = M \cdot A$$

$$\begin{pmatrix} \hat{A}_1 \\ \hat{A}_2 \end{pmatrix} = \begin{pmatrix} 1 & 0 & 0 \\ 0 & 1 & 1 \end{pmatrix} \begin{pmatrix} A_1 \\ A_2 \\ A_3 \end{pmatrix} = \begin{pmatrix} A_1 \\ A_2 + A_3 \end{pmatrix}$$

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

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

Note that for **proper lumping** there is only one “1” in each column because each of the original states contributes to one final state only

The inverse transformation

Apart from the lumping transformation

$$\hat{y} = My$$

We also have the inverse transformation

$$y = M^{+}\hat{y}$$

where M^{+} is the pseudo-inverse of M, such that $MM^{+}=I$.

There are infinite matrices with this property but we choose the Moore–Penrose pseudo-inverse which is the most commonly used

It is can be calculated numerically and is readily available in various software packages e.g.:

MATLAB	**`pinv()`**
Mathematica	**`PseudoInverse[]`**
S-Plus/R	**`ginv()`**

Back to lumping the 3-compartment model to 2-compartment

$$M = \begin{pmatrix} 1 & 0 & 0 \\ 0 & 1 & 1 \end{pmatrix} \qquad M^{+} = \begin{pmatrix} 1 & 0 \\ 0 & 1/2 \\ 0 & 1/2 \end{pmatrix}$$

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

$$A = M^{+}\hat{A}$$

$$\begin{pmatrix} A_1 \\ A_2 \\ A_3 \end{pmatrix} = \begin{pmatrix} 1 & 0 \\ 0 & 1/2 \\ 0 & 1/2 \end{pmatrix} \begin{pmatrix} \hat{A}_1 \\ \hat{A}_2 \end{pmatrix} = \begin{pmatrix} \hat{A}_1 \\ \hat{A}_2/2 \\ \hat{A}_2/2 \end{pmatrix}$$

One can go back to the original configuration
but will not get back the original information
Compression is “lossy”

Main lumping formula for the linear system

$$\frac{dy}{dt} = K \cdot y \quad \xrightarrow{M} \quad \frac{d\hat{y}}{dt} = \hat{K} \cdot \hat{y}$$

what is $\hat{K}$?

Multiply both sides by M $\quad M\frac{dy}{dt} = M \cdot K \cdot y$

Replace $\quad y = M^{+}\hat{y} \quad M\frac{dy}{dt} = M \cdot K \cdot M^{+}\hat{y}$

But $\quad M\frac{dy}{dt} = \frac{d\hat{y}}{dt}$

So finally $\quad \frac{d\hat{y}}{dt} = M \cdot K \cdot M^{+}\hat{y}$ $= \hat{K}$

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

A LUMPING ANALYSIS IN MONOMOLECULAR REACTION SYSTEMS

Analysis of the Exactly Lumpable System

JAMES WEI AND JAMES C. W. KUO

Research Department, Central Research Division, Mobil Research and Development Corp., Princeton, N.J. 08540

Wei J, Kuo JCW. A lumping analysis in monomolecular reaction systems - Analysis of exactly lumpable system. Industrial & Engineering Chemistry Fundamentals 8 (1): 114, **1969**

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DOI: 10.1007/s10928-005-0054-y

Lumping in Pharmacokinetics

Céline Brochot,[1,*] János Tóth,[2] and Frédéric Y. Bois[1]

Received May 17, 2005—Final August 2, 2005

Back to lumping the 3-compartment model to 2-compartment

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

$$M = \begin{pmatrix} 1 & 0 & 0 \\ 0 & 1 & 1 \end{pmatrix} \qquad M^{+} = \begin{pmatrix} 1 & 0 \\ 0 & 1/2 \\ 0 & 1/2 \end{pmatrix}$$

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

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

$\hat{k}_{12} = k_{12} + k_{13}$

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

exact when $k_{12}=k_{13}$ and $k_{21}=k_{31}$

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

$$\hat{k}_{12} = k_{12} + k_{13}$$

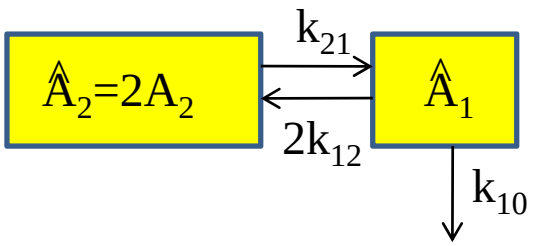
$$\hat{k}_{21} = (k_{21}+k_{31})/2$$

when $k_{12}=k_{13}$ and $k_{21}=k_{31}$

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

$$\hat{k}_{12} = 2k_{12}$$

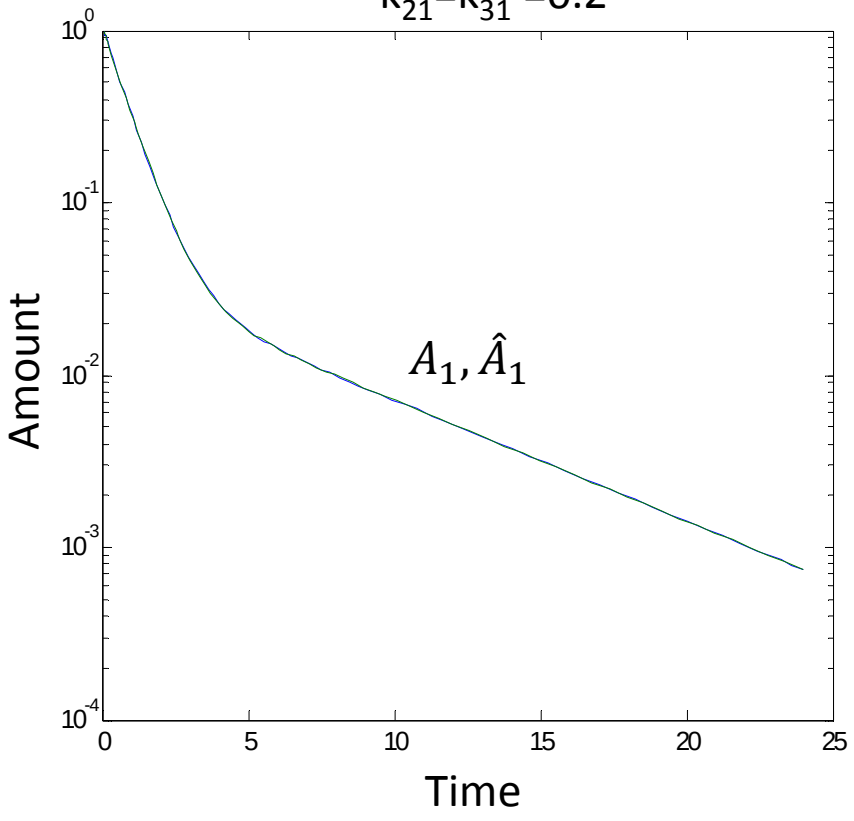
$$\hat{k}_{21} = k_{21}$$



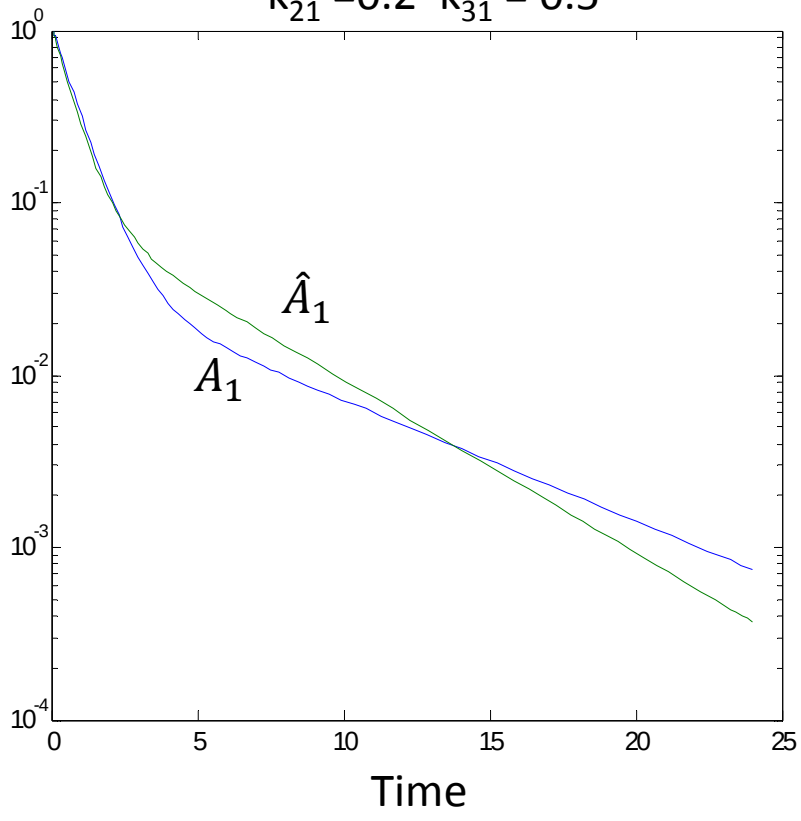
$$\hat{V}_1 = V_1$$

$$\hat{V}_2 = V_2 + V_3$$

k_{10}= 1
k_{12}=k_{13} =0.1
k_{21}=k_{31} =0.2

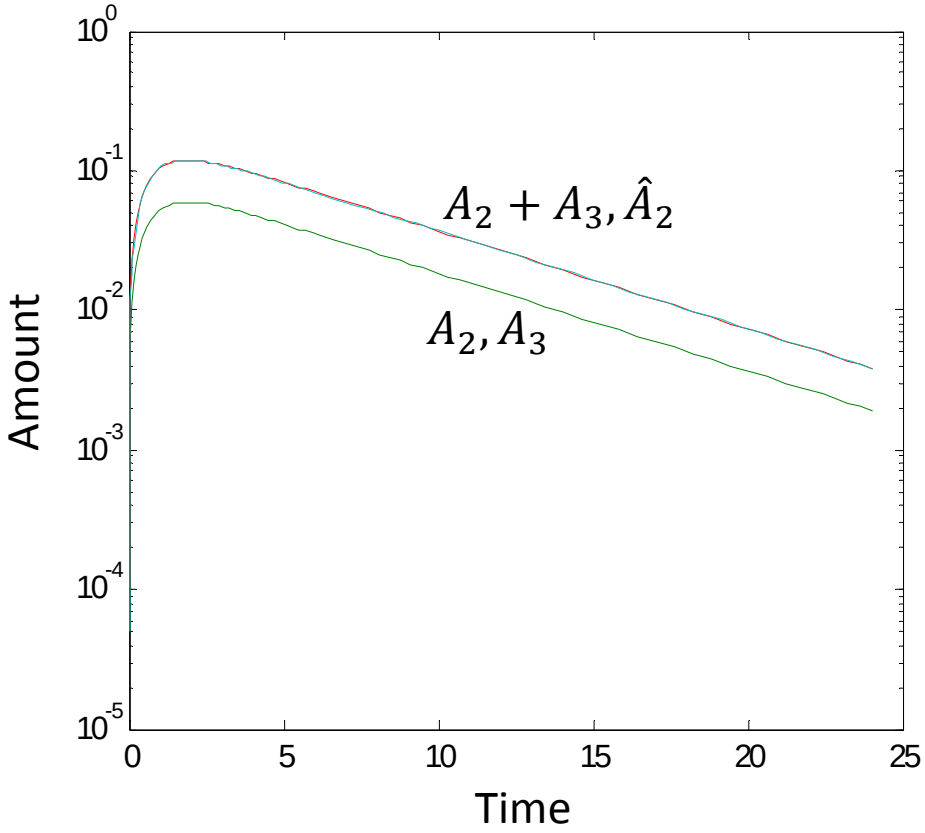


k_{10}= 1
k_{12} =0.1 k_{13} = 0.3
k_{21} =0.2 k_{31} = 0.5

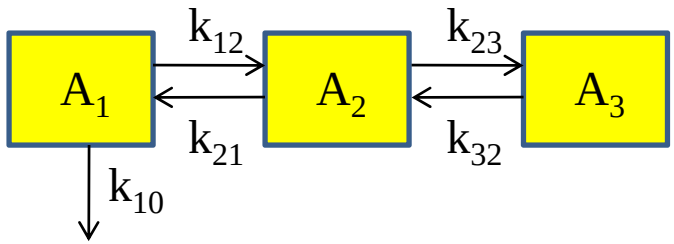


Lumping scheme is good locally in the parameter space

k_{10}= 1
k_{12}=k_{13} =0.1
k_{21}=k_{31} =0.2



Lumping of a 3-compartment catenary model to 2-compartment



$$K = \begin{pmatrix} -(k_{12}+k_{10}) & k_{21} & 0 \\ k_{12} & -(k_{21}+k_{23}) & k_{32} \\ 0 & k_{23} & -k_{32} \end{pmatrix}$$

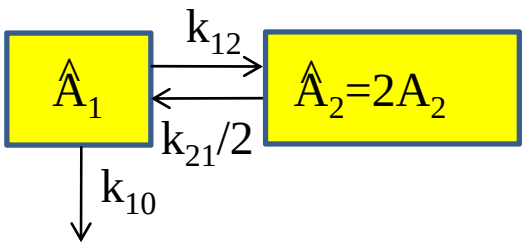
$$M = \begin{pmatrix} 1 & 0 & 0 \\ 0 & 1 & 1 \end{pmatrix} \qquad M^{+} = \begin{pmatrix} 1 & 0 \\ 0 & 1/2 \\ 0 & 1/2 \end{pmatrix}$$

$$\widehat{K} = MKM^{+} = \begin{pmatrix} -(k_{12}+k_{10}) & \frac{k_{21}}{2} \\ k_{12} & -\frac{k_{21}}{2} \end{pmatrix}$$

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

$$\hat{k}_{12} = k_{12}$$

$$\hat{k}_{21} = k_{21}/2$$

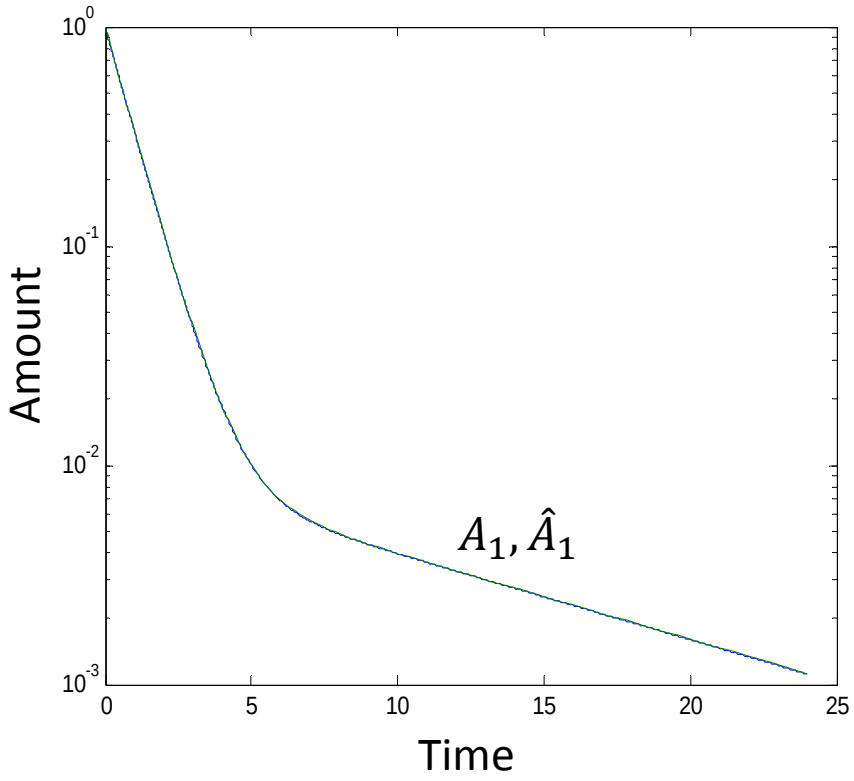


exact when k_{23} and k_{32} are very large such that A_2 and A_3 equilibrate instantly

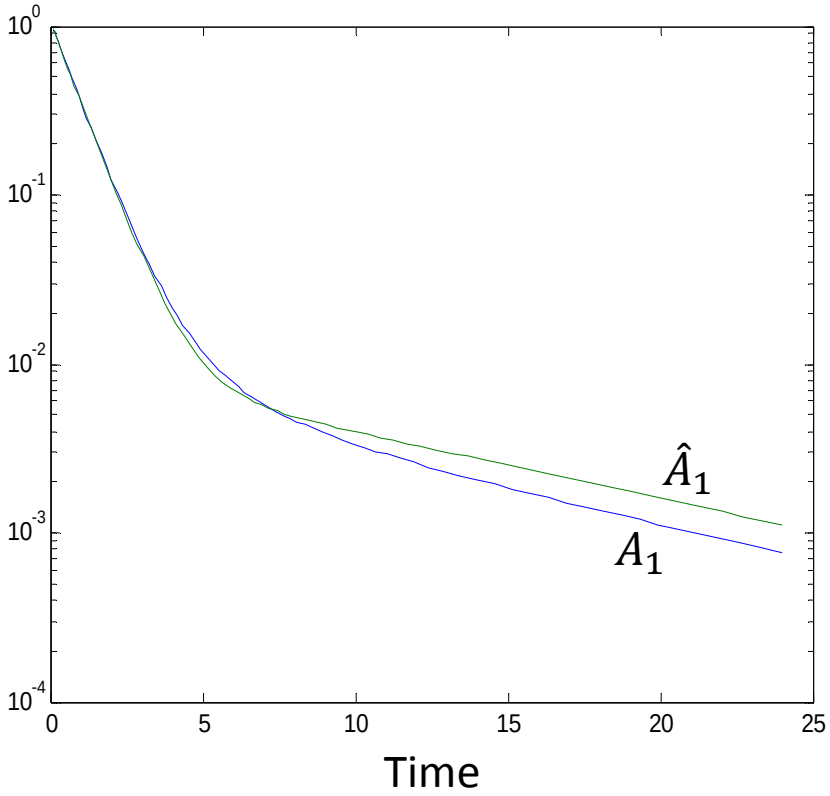
$$\hat{V}_1 = V_1$$

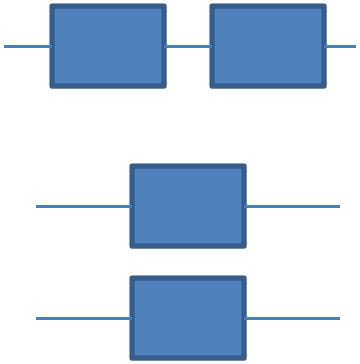
$$\hat{V}_2 = V_2 + V_3$$

k_{10}= 1
k_{12} =0.1 k_{23} = 100
k_{21} =0.2 k_{32} = 100



k_{10}= 1
k_{12} =0.1 k_{23} = 0.3
k_{21} =0.2 k_{32} = 0.5





Compartments in series can be lumped when they equilibrate fast

Compartments in parallel can be lumped when they have similar times scales

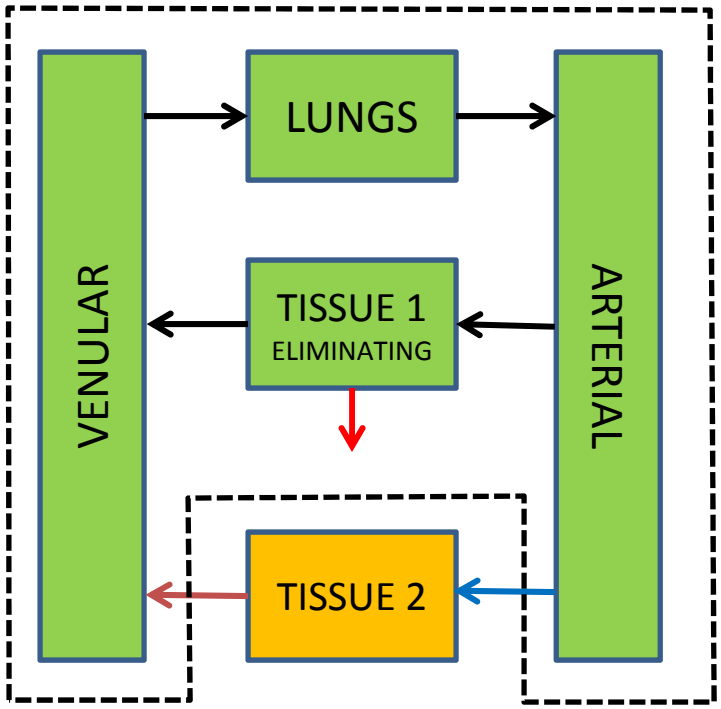
Journal of Pharmacokinetics and Biopharmaceutics, Vol. 26, No. 1, 1998

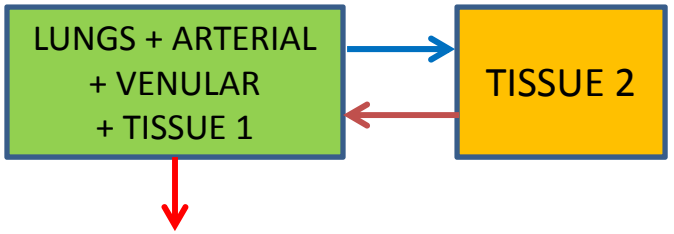
Lumping of Whole-Body Physiologically Based Pharmacokinetic Models

Ivan A. Nestorov,[1,2,5] Leon J. Aarons,[2,3] Philip A. Arundel,[4] and Malcolm Rowland[2,3]

Received October 7, 1997—Final March 13, 1998

Lumping of a PBPK model to 2-compartment





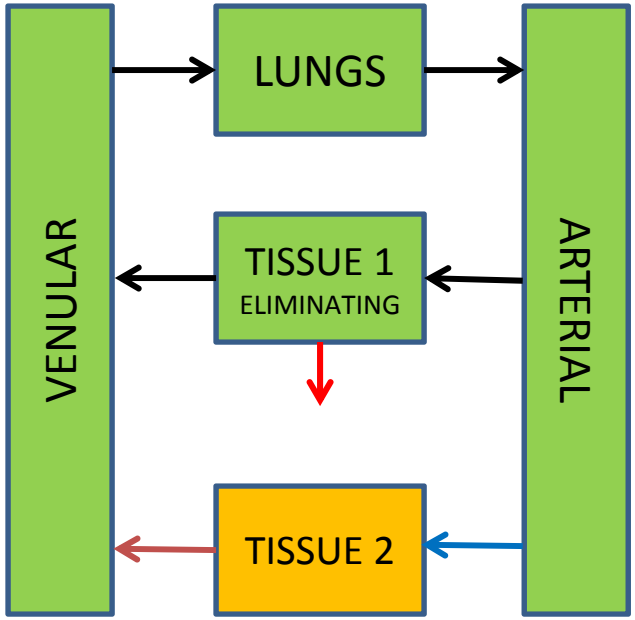
Tissue 1 $$V_1 \frac{dC_1}{dt} = Q_1 \left(C_A - \frac{C_1}{K_{p1}} \right) - CL \frac{C_1}{K_{p1}}$$

Tissue 2 $$V_2 \frac{dC_2}{dt} = Q_2 \left(C_A - \frac{C_2}{K_{p2}} \right)$$

Arterial $$V_A \frac{dC_A}{dt} = Q_L \frac{C_L}{K_{pL}} - Q_1 \frac{C_A}{K_{pA}} - Q_2 \frac{C_A}{K_{pA}}$$

Venular $$V_V \frac{dC_V}{dt} = Q_1 \frac{C_1}{K_{p1}} - Q_2 \frac{C_2}{K_{p2}} - Q_L C_V$$

Lungs $$V_L \frac{dC_L}{dt} = Q_L \left(C_V - \frac{C_L}{K_{pL}} \right)$$



$$k_{A1} = \frac{Q_1}{V_A}$$

$$k_{A2} = \frac{Q_2}{V_A}$$

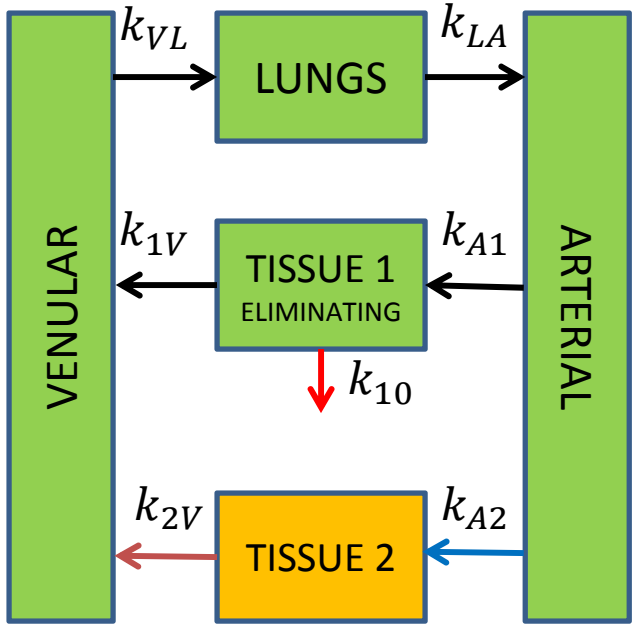
$$k_{1V} = \frac{Q_1}{V_1 K_{p1}}$$

$$k_{2V} = \frac{Q_2}{V_2 K_{p2}}$$

$$k_{VL} = \frac{Q_L}{V_V}$$

$$k_{LA} = \frac{Q_L}{V_L K_{pL}}$$

$$k_{10} = \frac{CL}{V_1 K_{p1}}$$



$$\frac{dA}{dt} = KA \qquad A = \begin{pmatrix} A_1 \\ A_2 \\ A_A \\ A_V \\ A_L \end{pmatrix}$$

$$K = \begin{pmatrix} -k_{1V} - k_{10} & 0 & k_{A1} & 0 & 0 \\ 0 & -k_{2V} & k_{A2} & 0 & 0 \\ 0 & 0 & -k_{A1} - k_{A2} & 0 & k_{LA} \\ k_{1V} & k_{2V} & 0 & -k_{VL} & 0 \\ 0 & 0 & 0 & k_{VL} & -k_{LA} \end{pmatrix}$$

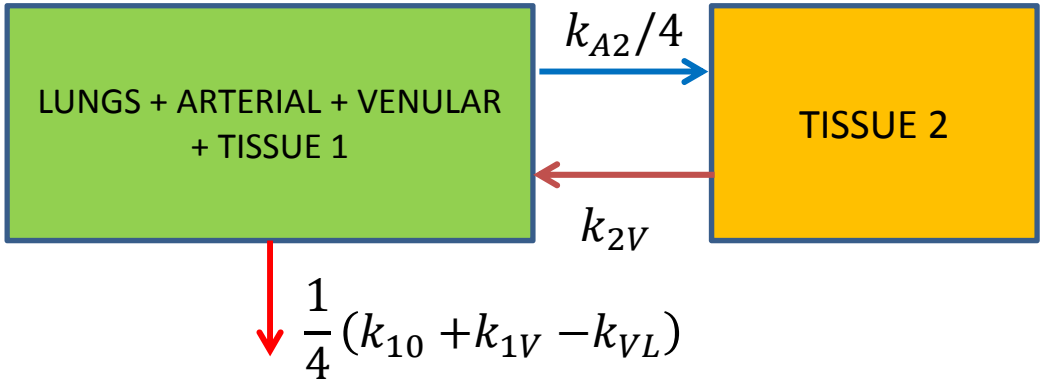
Lumping matrix:

Inverse of M:

$$A = \begin{pmatrix} A_1 \\ A_2 \\ A_A \\ A_V \\ A_L \end{pmatrix} \qquad M = \begin{pmatrix} 1 & 0 & 1 & 1 & 1 \\ 0 & 1 & 0 & 0 & 0 \end{pmatrix} \qquad M^{+} = \begin{pmatrix} 1/4 & 0 \\ 0 & 1 \\ 1/4 & 0 \\ 1/4 & 0 \\ 1/4 & 0 \end{pmatrix}$$

$$\widehat{K} = MKM^{+} = \begin{pmatrix} \frac{1}{4}(k_{VL} - k_{A2} - k_{1V} - k_{10}) & k_{2V} \\ \frac{k_{A2}}{4} & -k_{2V} \end{pmatrix}$$

$$\frac{d\hat{A}}{dt} = \widehat{K}\hat{A}$$



$k_{A1} = k_{1V} = k_{VL} = k_{LA} = 10$

$k_{10} = 0.1$

$k_{A2} = k_{2V} = 0$

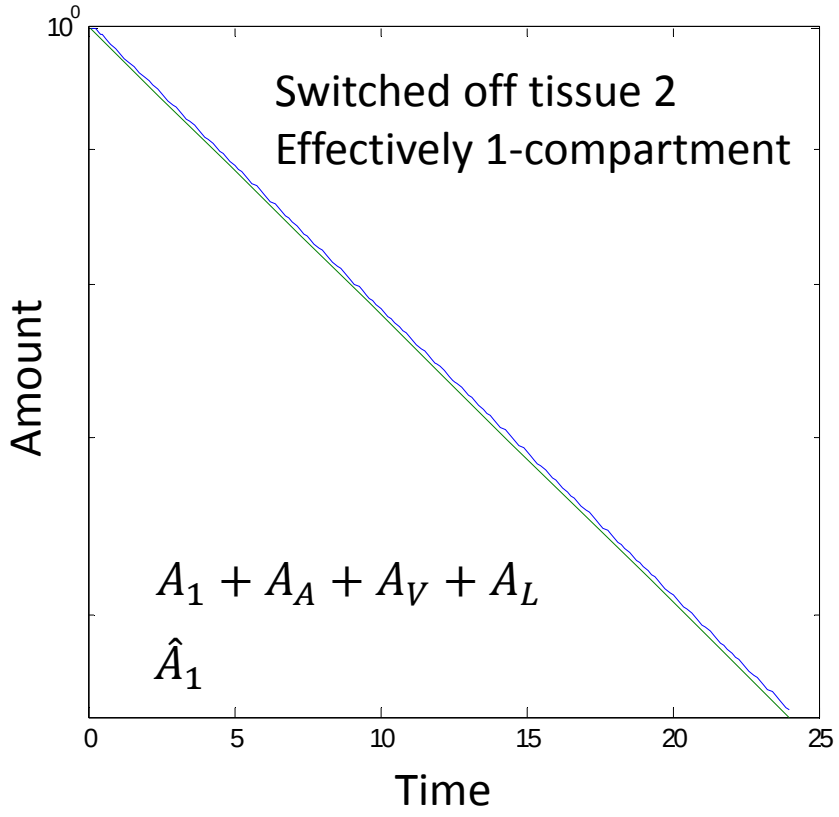
Fast distribution
Slow elimination

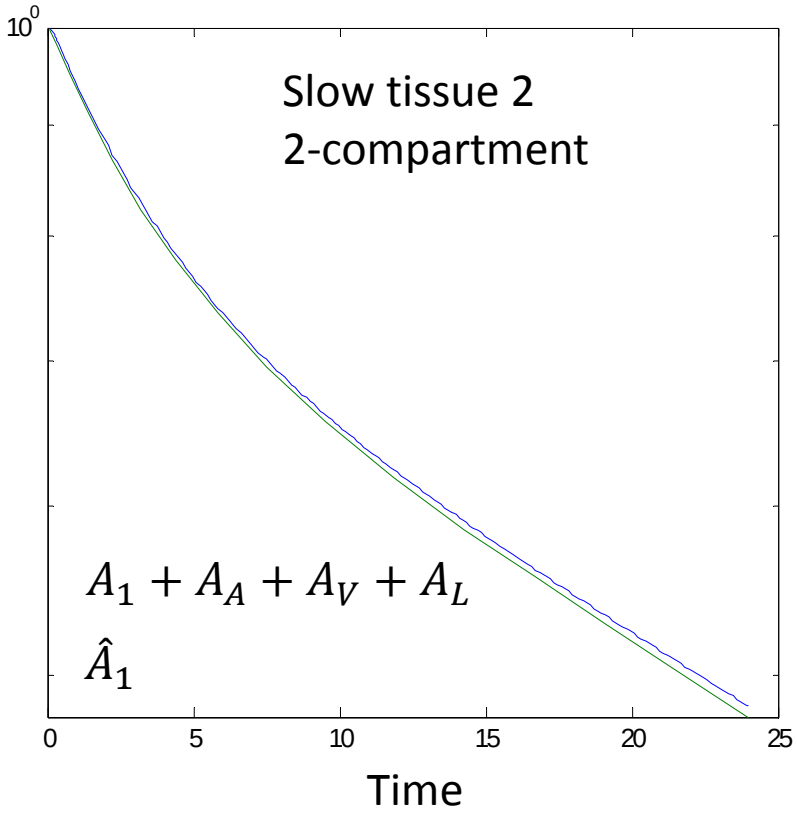
off ← Tissue 2 → slow

$k_{A1} = k_{1V} = k_{VL} = k_{LA} = 10$

$k_{10} = 0.1$

$k_{A2} = k_{2V} = 0.2$





J Pharmacokinet Pharmacodyn (2010) 37:365–405
DOI 10.1007/s10928-010-9165-1

Lumping of physiologically-based pharmacokinetic models and a mechanistic derivation of classical compartmental models

Sabine Pilari · Wilhelm Huisinga

The main lumping formula for nonlinear systems

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

And the lumping matrix **M** such that $\hat{y} = My$

we need to determine $\hat{f}(\hat{y})$ such that $\frac{d\hat{y}}{dt} = \hat{f}(\hat{y})$

$$\frac{dy}{dt} = f(y) \longrightarrow M\frac{dy}{dt} = Mf(y) \longrightarrow \frac{d\hat{y}}{dt} = Mf\ (M^{+}\hat{y})$$

($y = M^{+}\hat{y}$ substituted into $f(y)$)

$$\boxed{\hat{f}(\hat{y}) = Mf\ (M^{+}\hat{y})}$$

special case of a **linear model** where $f(y) = Ky$

$$\hat{f}(\hat{y}) = \hat{K}\hat{y} = MKM^{+}\hat{y} \longrightarrow \hat{K} = MKM^{+}$$

Chemical Engineering Science, Vol. 44, No. 6, pp. 1413–1430, 1989.
Printed in Great Britain.

0009–2509/89 53.00 + 0.00

A GENERAL ANALYSIS OF EXACT LUMPING IN CHEMICAL KINETICS

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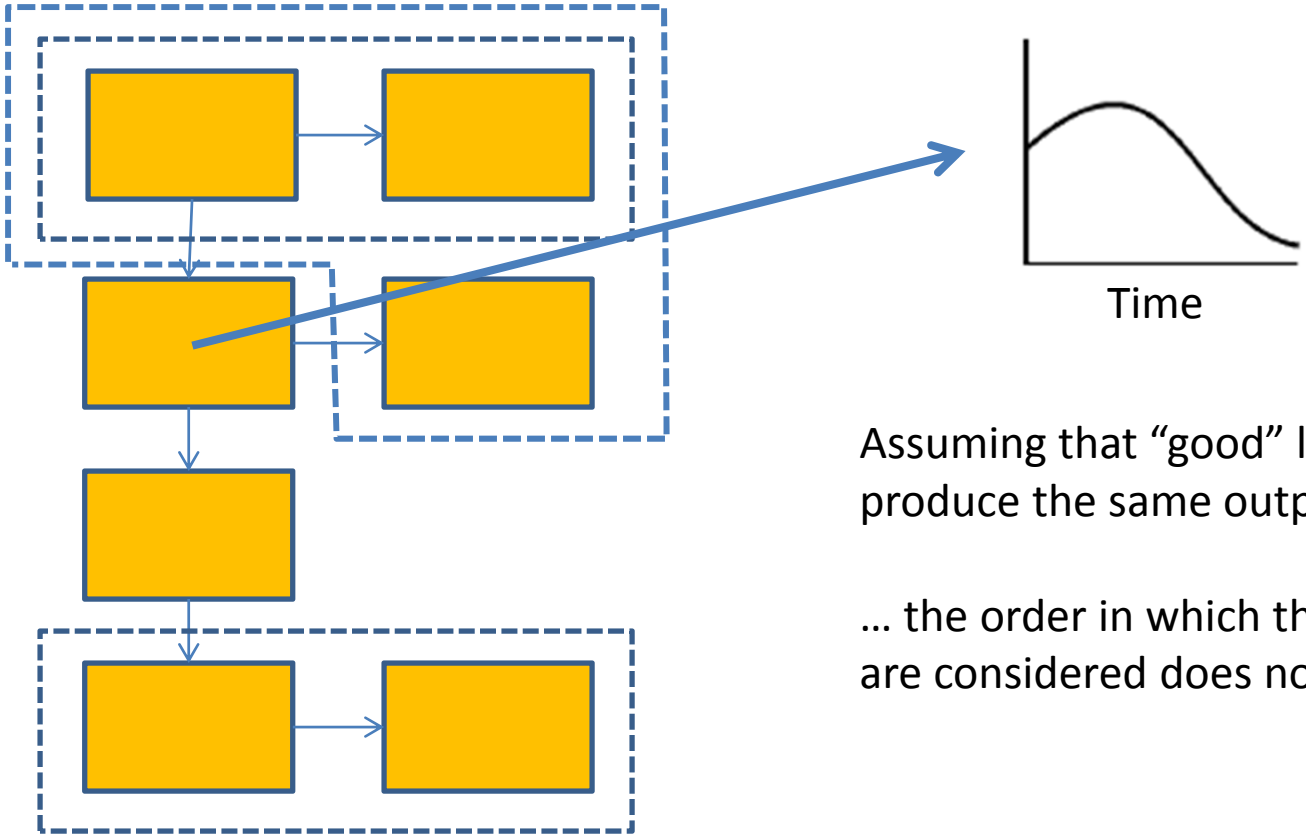
Department of Chemistry, Princeton University, Princeton, NJ 08540, U.S.A.

(*Received* 29 *September* 1987; *accepted* 12 *September* 1988)

A useful property



Assuming that “good” lumped models produce the same output…

… the order in which the lumps are considered does not matter

Automatic lumping algorithm outline
Search for optimal M: Try them all

1. Consider an initial list of all lumpable pairs of states

2. Consider all the combinations of these for the desired size of reduced system

3. For each combination construct the appropriate lumping matrix M

4. Solve numerically the lumped model using the formula $\hat{f}(\hat{y}) = Mf\ (M^{+}\hat{y})$

5. Compare the profile to the profile of the original model (already available) using an objective function

6. Repeat the procedure for all combinations and find the lumping scheme with the smallest objective function.

Problem: Combinatorial explosion

Assume that the model is of dimension **n** and any state can be lumped with any other state (co constraints at all).

Then there are **n(n-1)/2** pairs of states that may be lumped, which means that to lump the model by one we need to make **n(n-1)/2** function calls.

But if we want to reduce the system by **k** then the possible combinations are

binomial coefficient: $$\binom{n(n-1)/2}{k} = \frac{(n(n-1)/2)!}{k!\,(n(n-1)/2-k)!}$$

For example for **n=30** and **k=20** we have about **10^{34}** combinations

Automatic lumping algorithm outline
Search for optimal M: Try one at a time

1. Consider an initial list of all lumpable pairs of states
2. Consider all the combinations of these for size of reduced system n-1
3. For each combination construct the appropriate lumping matrix M
4. Solve numerically the lumped model using the formula $\hat{f}(\hat{y}) = Mf\ (M^{+}\hat{y})$
5. Compare the profile to the profile of the original model (already available) using an objective function
6. Repeat the procedure for all combinations and find the lumping scheme with the smallest objective function. (**Inner loop: parallelizable**)
7. Go to step 2 and repeat until desired dimension of the reduce systems is reached (**outer loop**)

This is going to cost us less than $\frac{1}{6}k(k^2 - 2kn + 2n^2 - 1)$ function calls, for example for **n=30** and **k=20** its **4330** combinations instead of $\mathbf{10^{34}}$.

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Proper lumping in systems biology models

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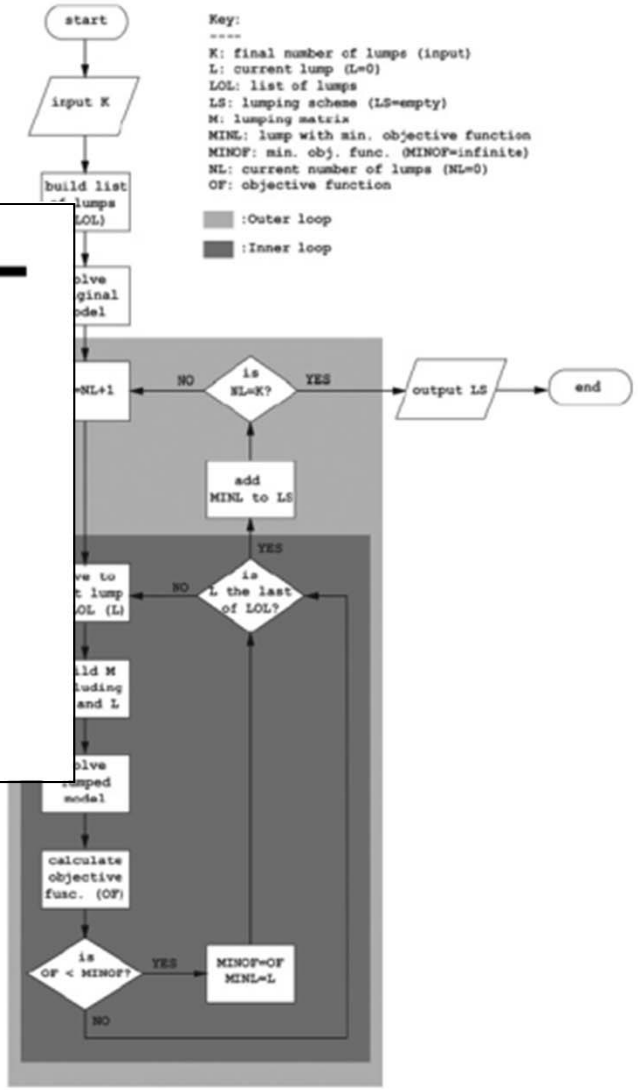


Objective function

Sum of squares of the distances of all the states of the reduced and the original model, normalised.

$$d = \sum_{i=1}^{\hat{n}} \int_{0}^{T} \left(\frac{y_i - \hat{y}_i}{\max y_i} \right)^2 dt$$

This is only indicative. Alternative objective functions that do feature matching or any appropriate similarity criterion.

The above function assumes that there is **equal interest** in all states of the model. This is unlikely, so **weights** can be introduced to favour the **most interesting** states.

Constraints

It is reasonable to introduce constraints

Exclude specific combinations or consider only specific combinations,
e.g. taken from the stoichiometry matrix of the system.

Force states of particular interest to be left unlumped

These are determined by a matrix
(in graph theory terminology an **incidence matrix** or **adjacency matrix**):

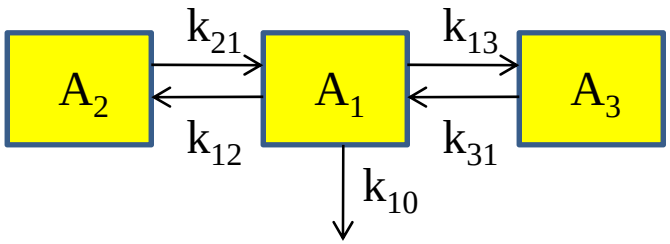
	A	B	C	D	E	F	G	H	I	J
A										
B	1									
C	1	1								
D	1	1	1							
E	1	1	1	1						
F	1	1	1	1	1					
G	1	1	1	1	1	1				
H	1	1	1	1	1	1	1			
I	1	1	1	1	1	1	1	1		
J	1	1	1	1	1	1	1	1	1	

Locality

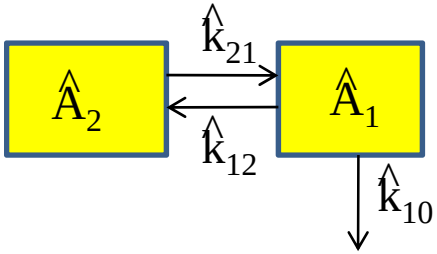
All model reduction techniques produce results which are **valid only locally** in the parameters space.

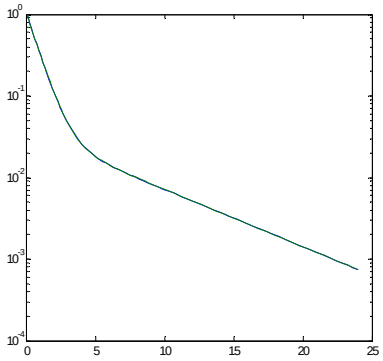
This means that are good only for a specific set of parameter values.

As in the 3-compartment example the lumping is meaningful only when the rate constants are similar or ideally equal.



when $k_{12}=k_{13}$ and $k_{21}=k_{31}$





Incorporation of uncertainty

But in most cases in biological networks parameter values are uncertain

To address this problem a **Bayesian objective function** may be considered that incorporates parameter uncertainty and averages over prior parameter distributions.

A Bayesian objective function may look like this:

$$d_{Bayes} = \int_{prior} (P(\theta)d)d\theta$$

where d is a value of a local objective function.

In this case the lumped model is not the optimal one for any parameter set but it the optimal one on average, given the parameter distributions

J Pharmacokinet Pharmacodyn (2009) 36:613–628
DOI 10.1007/s10928-009-9141-9

A method for robust model order reduction in pharmacokinetics

Aristides Dokoumetzidis · Leon Aarons

Application to a coagulation model for warfarin and enoxaparin
Preliminary results by Abhishek Gulati
(Steve Duffull's PhD student in Otago)

A Comprehensive Model for the Humoral Coagulation Network in Humans

T Wajima[1,2], GK Isbister[3,4] and SB Duffull[1]

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Pharm Res (2012) 29:225–235
DOI 10.1007/s11095-011-0537-z

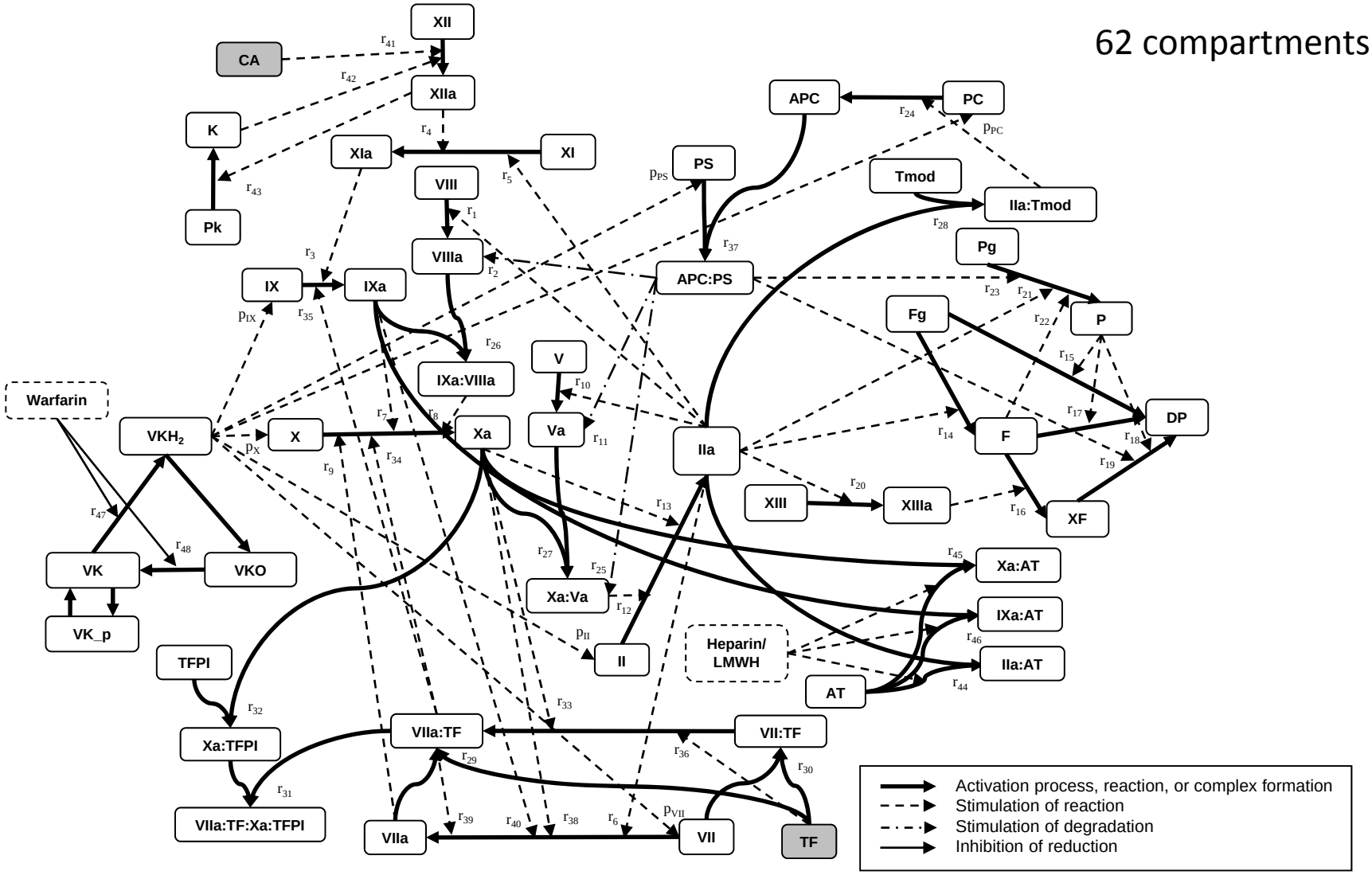
RESEARCH PAPER

Development and Evaluation of a Prototype of a Novel Clotting Time Test to Monitor Enoxaparin

Abhishek Gulati • James M. Faed • Geoffrey K. Isbister • Stephen B. Duffull

Original Coagulation Model

62 compartments



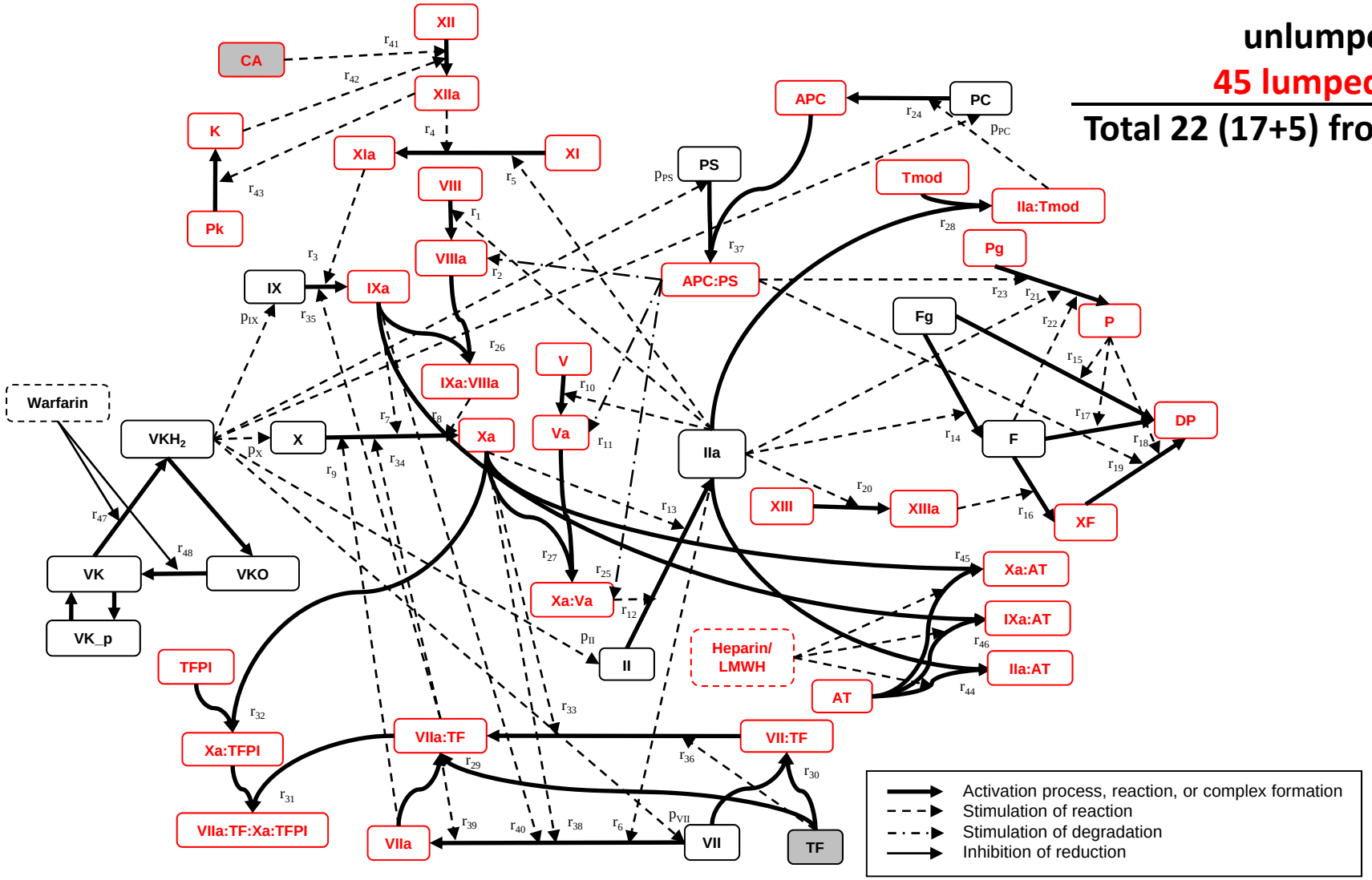
Gulati et al, *Pharm Res* (2012)

Lumped Coagulation Model

unlumped 17

45 lumped to 5

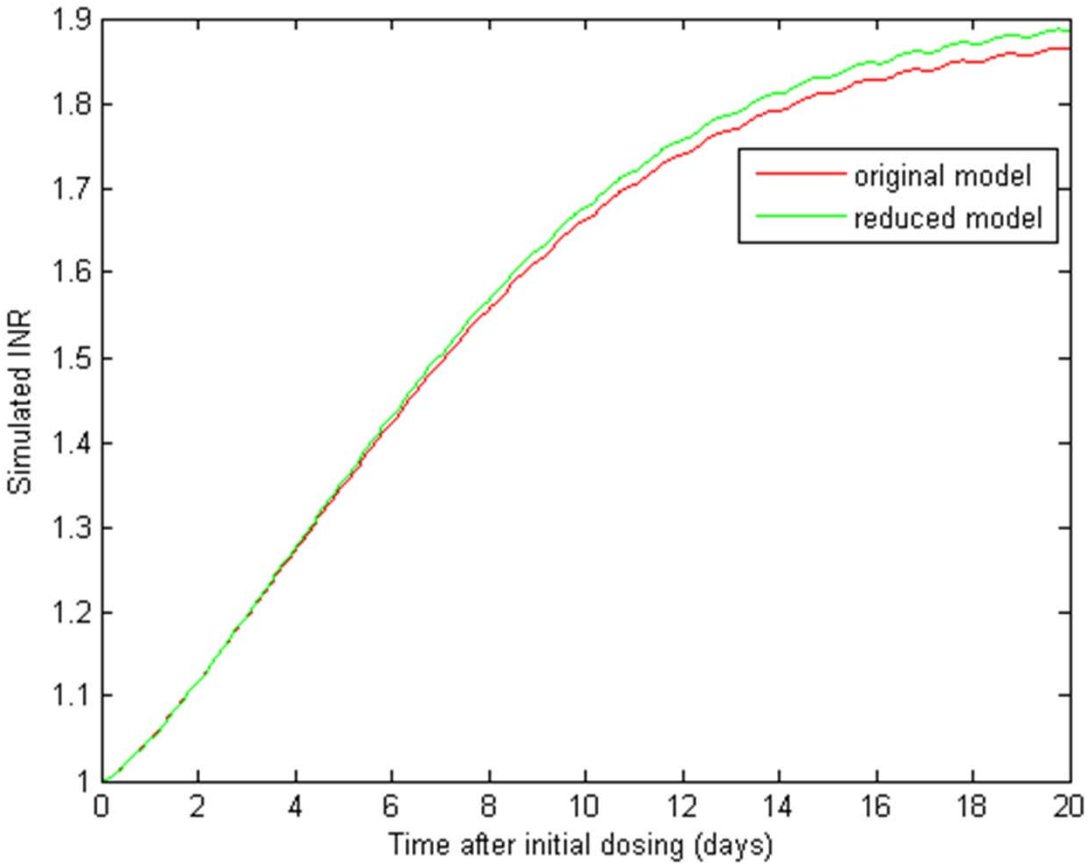
Total 22 (17+5) from 62



Lumped Coagulation Model

Lumped 1	Lumped 2	Lumped 3	Lumped 4	Lumped 5	Cmpts 6 to 22 (unlumped)
APC	XI	XF	Taipan	Tiger absorption	warfarin absorption
Tmod	XIa	D-dimers	delay taipan 1	Tiger plasma	warfarin plasma
IIa:Tmod	XII	FDPs	delay taipan 2	Xa	VK
APC:PS	XIIa		XaVa		VKH2
LMWH absorption	Pk		brown snake absorption		VKO
LMWH central	K		brown snake plasma		Vkperi
LMWH peripheral	TAT				II
UFH	ATIII				VII
kaolin	XIII				IX
V	XIIIa				X
Va	plasminogen				PC
VIIa	plasmin				PS
VII-TF					fibrinogen
VIIa-TF					fibrin
TFPI					integral fibrin
Xa-TFPI					IIa
VIIa-TF-Xa-TFPI					TF
VIII					
VIIIa					
IXa					
IXaVIIIa					

Comparison of original and lumped models



Simulated time course of INR following warfarin therapy (4 mg once daily)

Conclusions

Lumping can be a useful technique to reduce the size of a system

Automation is possible but it is important to select carefully the criteria and the constrains

Main drawback is locality and one should check for robustness depending on the scope (speed, controller, identification, etc)

Thank you for your attention

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