Model Reduction for Biochemical Systems: Computational Methods

Tom Snowden

Computational Reduction

- For high dimensional, complex models many of the analytical approaches to model reduction (discussed in the previous presentation) will be difficult to apply, as they often depend upon the researcher possessing high degree of model intuition.

- Instead it is common to seek computational algorithms for the application of model reduction in such settings.

- In this presentaton we discuss a range of such methods and demonstrate computational reduction via application to an example.

Presentation outline

- **How I define model reduction**
- Review of existing methods
- An example
- Linking with pharmacokinetics
- Conclusions

Chemical reaction network theory

Biochemical reaction networks are typically defined via systems of interacting chemical equations. Such networks can be expressed via three sets of information:

- An n dimensional set $\mathcal{S}$ representing the species in the network.
- A p dimensional set $\mathcal{C}$ representing the 'complexes' in the network.
- An m dimensional set $\mathcal{R} \subset \mathcal{C} \times \mathcal{C}$ representing the reations in the network.

Example:

$$2A \to D$$
$$A + B \rightleftarrows C \to D + B$$

$$\begin{aligned}\mathcal{S} &= \{A, B, C, D\}, \\ \mathcal{C} &= \{2A, C, D + B, A + B, D\}, \\ \mathcal{R} &= \{(2A, D), (A + B, C), \\ &\quad (C, A + B), (C, D + B)\}.\end{aligned}$$

Stoichiometric representation

Example:

$$2A \xrightarrow{k_1} D$$

$$A + B \underset{k_3}{\overset{k_2}{\rightleftarrows}} C \xrightarrow{k_4} D + B$$

$$N = \begin{bmatrix} -2 & -1 & 0 \\ 0 & -1 & 1 \\ 0 & 1 & -1 \\ 1 & 0 & 1 \end{bmatrix}$$

$$\boldsymbol{v} = \begin{bmatrix} k_1 x_1^2(t) \\ k_2 x_1(t) x_2(t) - k_3 x_3(t) \\ k_4 x_3(t) \end{bmatrix}$$

- It is common to describe the dynamics of such networks *en masse* via the Law of Mass Action.
- One common representation is via the product of a stoichiometry matrix N and a vector of reaction rates $\boldsymbol{v}(\boldsymbol{x}, \boldsymbol{p})$, such that

$$\dot{\boldsymbol{x}} = N\boldsymbol{v}(\boldsymbol{x}, \boldsymbol{p})$$

where $\boldsymbol{x}$ gives the time-varying molecular concentration of each of the species and $\boldsymbol{p}$ is a set of parameters.

Control theoretic representation

However, it is also common for certain applications to seek to represent such models in a control theoretic state-space representation, such that

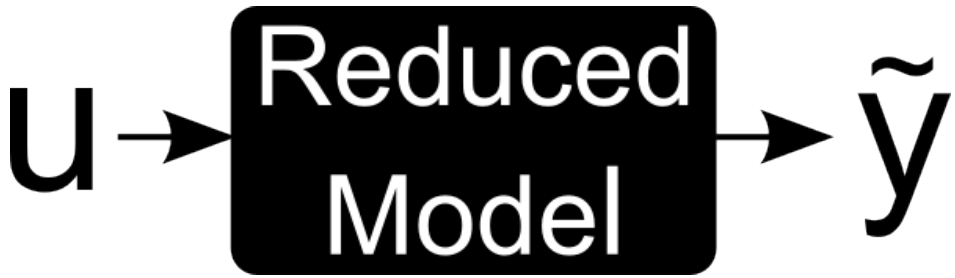
$$\dot{\boldsymbol{x}}(t) = \boldsymbol{f}(\boldsymbol{x}(t), \boldsymbol{p}) + \boldsymbol{g}(\boldsymbol{x}(t), \boldsymbol{p})\boldsymbol{u}(t),$$
$$\boldsymbol{y}(t) = \boldsymbol{h}(\boldsymbol{x}(t), \boldsymbol{p}),$$

with:

- $\boldsymbol{u}(t) \in \mathbb{R}^l$ representing inputs which can be interpreted in some way as controlling the system.
- $\boldsymbol{y}(t) \in \mathbb{R}^v$ representing combinations of the species that can be considered outputs.

Within the context of QSP, the inputs may represent the dose of a drug whilst the ouputs might represent the concentrations of species associated with some clinical response.

Definition of model reduction



$$\epsilon = \|\boldsymbol{y}(t) - \tilde{\boldsymbol{y}}(t)\|$$

Hence, I define a method of model reduction to be any method designed to give a system capable of **satisfactorily reproducing the input-output behaviour of the original model** (under some given metric of error) whilst producing a **reduction in the number of species $\mathcal{S}$, reactions $\mathcal{R}$, or complexes $\mathcal{C}$.**

Reducing systems biology models

Common disadvantages

1. **Stiffness:**
   $K = \frac{\lambda_{\max}(J_f(\boldsymbol{x}))}{\lambda_{\min}(J_f(\boldsymbol{x}))} \gg 1$
   Presents issues for numerical methods.
2. **Nonlinearity:** $\boldsymbol{f}(a\boldsymbol{x}) \neq a\boldsymbol{f}(\boldsymbol{x})$
   Presents issues for analytical methods.
3. **Conservation relations:**
   $\exists \Gamma \in \mathbb{R}^{\alpha \times n} : \ \Gamma \boldsymbol{x}(t) = \boldsymbol{x}_T, \ \forall t$
   Must be handled carefully to avoid violation.

Common advantages

1. **Asymptotic Stability:**
   $\lim_{t \to \infty} \|\boldsymbol{x}(t) - \boldsymbol{x}^*\| = 0$
   Enables a lot of theory.
2. **Conservation relations:**
   $\boldsymbol{x}_c = \boldsymbol{x}_T - \Gamma_c \boldsymbol{x}_i$
   Can be exploited to reduce system for 'free'.

Difficulty also arises from the wide range of aims associated with modelling in the field of systems biology. The best available reduced model necessarily depends upon what it will be used for.

Presentation outline

- How I define model reduction
- **Review of existing methods**
- An example
- Linking with pharmacokinetics
- Conclusions

Literature Review Introduction

The review limited itself to methods addressing deterministic systems of ODEs and which had seen application to models of biochemical reaction networks. Emphasis was placed on methods with published use since 2000.

This section begins by reviewing computational approaches for the application of conservation analysis.

It then moves on to reviewing model reduction methods, these are divided into 4 categories:

1. Time-scale exploitation methods;
2. Optimisation approaches and sensitivity analysis;
3. Lumping; and
4. Singular value decomposition (SVD) based methods.

Conservation relations

- α conservation relations imply that $\exists \Gamma \in \mathbb{R}^{\alpha \times n} : \ \Gamma \boldsymbol{x}(t) = \boldsymbol{x}_T, \ \forall t.$
- The conservation relations correspond to linear dependencies in the rows of the stoichiometry matrix N.
- It is possible to show[1] that $\Gamma = \text{Null}(N^T)$.
- A numerically stable method for obtaining this null-space for large systems is to employ QR factorisation via Householder reflections [2].

[1] Reder, J. Theor. Biol., 1988.
[2] Vallabhajosyula et al., Bioinformatics, 2006.

Time-Scale Exploitation Methods I

- This refers to any method that exploits the often large differences in reaction rates that can occur within a biochemical system.
- Typically such methods partition the system into fast and slow components - after some initial transient period those fast portions are assumed to be in equilibrium with respect to the remainder of the network.
- Such methods include singular perturbation approaches, ILDM, and CSP.

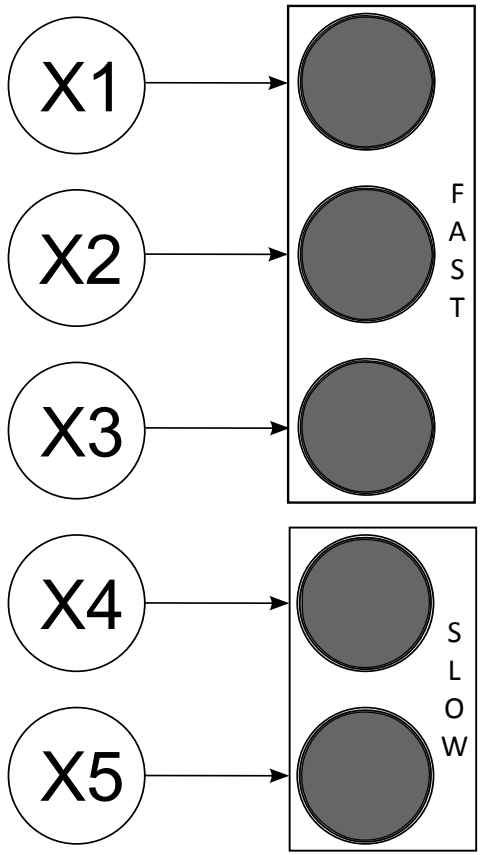


Figure: An example of model reduction via time-scale analysis

Time-Scale Exploitation Methods II

Singular Perturbation

If a system of ODEs can be expressed in the form

$$\dot{\boldsymbol{x}}(t) = \boldsymbol{f}(\boldsymbol{x}, z, t),$$
$$\delta \dot{z}(t) = \boldsymbol{g}(\boldsymbol{x}, z, t),$$

then as $\delta \to 0$ this system can be approximated by

$$\dot{\boldsymbol{x}}(t) = \boldsymbol{f}(\boldsymbol{x}, z, t),$$
$$z(t) = \phi(\boldsymbol{x}, t),$$

with $\phi(\boldsymbol{x}, t)$ a root of the equations $\boldsymbol{g}(\boldsymbol{x}, z, t) = 0$.

Species Partitioning

$$\begin{pmatrix} \dot{\boldsymbol{x}}_{\boldsymbol{s}} \\ \delta \dot{\boldsymbol{x}}_{\boldsymbol{f}} \end{pmatrix} = \begin{pmatrix} N_s \\ N_f \end{pmatrix} \boldsymbol{v}(\boldsymbol{x}_{\boldsymbol{s}}, \boldsymbol{x}_{\boldsymbol{f}}, \boldsymbol{p})$$

Reaction Partitioning

$$\dot{\boldsymbol{x}} = (N_s \; N_f) \begin{pmatrix} \boldsymbol{v}_{\boldsymbol{s}}(\boldsymbol{x}, \boldsymbol{p}) \\ \delta^{-1} \boldsymbol{v}_{\boldsymbol{f}}(\boldsymbol{x}, \boldsymbol{p}) \end{pmatrix}.$$

$\dot{\boldsymbol{x}}$ can then be decomposed into fast and slow contributions as a sum, such that $\dot{\boldsymbol{x}} = [\dot{\boldsymbol{x}}]_{\boldsymbol{s}} + [\dot{\boldsymbol{x}}]_{\boldsymbol{f}}$. Hence

$$[\dot{\boldsymbol{x}}(t)]_{\boldsymbol{s}} = N_s \boldsymbol{v}_{\boldsymbol{s}}(\boldsymbol{x}(t), \boldsymbol{p}),$$
$$0 = N_f \boldsymbol{v}_{\boldsymbol{f}}(\boldsymbol{x}(t), \boldsymbol{p}).$$

Time-Scale Exploitation Methods III

PROS:

- Species can maintain biological meaning.
- A large number of such methods exist in the literature.
- These methods are typically valid in the reduction of nonlinear systems.

CONS:

- A system may not have a large enough time-scale seperation to justify reduction.
- What happens during the initial transient period may be of interest.
- If a slow/fast partitioning is not known a priori approaches for determining the most appropriate one can be computationally expensive.

Optimisation and Sensitivity Analysis Methods I

- Reduction can be expressed as an optimisation problem - i.e. obtain the lowest possible dimensional model (either in terms of species, reactions or complexes) for which a metric of error ϵ remains within an acceptable bound, such that $\epsilon < \epsilon_c$.
- Hence it is common to either:
  1. Seek to measure how 'sensitive' the constraint variable ϵ is to perturbations and use this to guide a reduction. Or;
  2. Employ an iterative optimisation procedure.

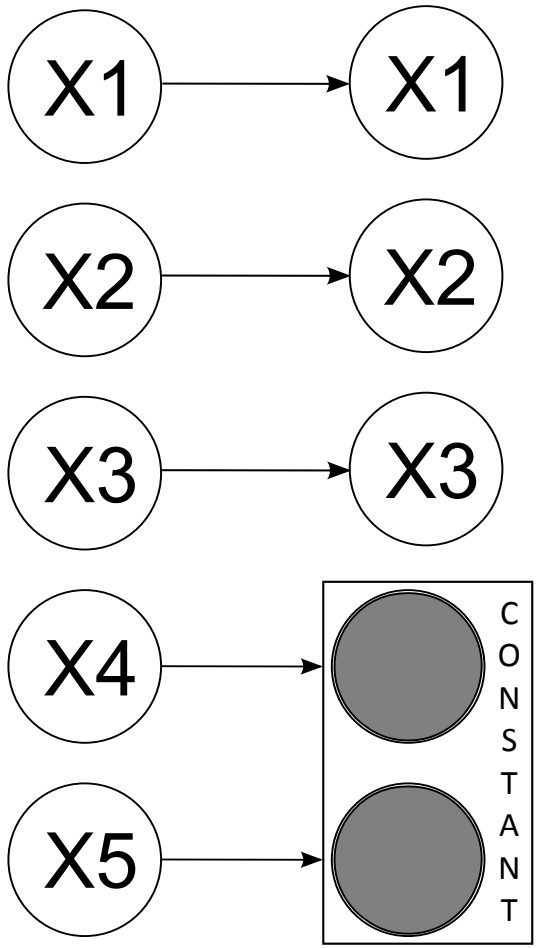
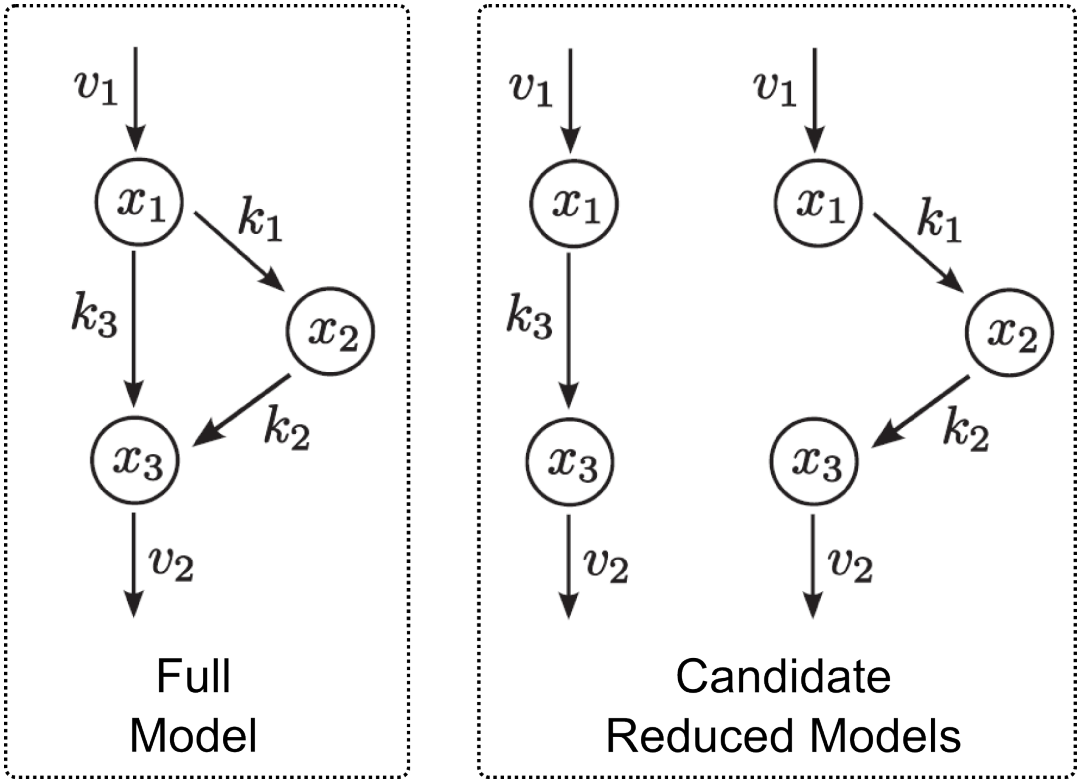


Figure: An example of model reduction via optimisation

Optimisation and Sensitivity Analysis Methods II

- A typical optimisation proceedure might involve 'switching off' of reactions or species.
- For example, kinetic parameters can be given switch variables,
- It is then an integer programming problem with these switches to determine a minimal reduced model constrained by an error bound [3].



[3] Maurya et al., IET Syst Biol., 2009.

Optimisation and Sensitivity Analysis Methods III

PROS:

- Species can maintain their biological meaning.
- The application of such methods can be highly algorithmic and computationally efficient (e.g. heuristic approaches such as genetic algorithms).
- Common procedures are implemented well in a number of software packages.

CONS:

- For very large systems performing a sufficeint search through the range of candidate solutions may be highly computationally expensive.
- Similarly, for sensitivity analysis convincingly searching the entire parameter space may be impossible.

Lumping Based Methods I

- Lumping is a classification that encompasses a range of methods.
- In particular it pertains to any method that constructs a reduced system with state-variables corresponding to subsets of the original species.
- These new states are referred to as 'lumped' variables.

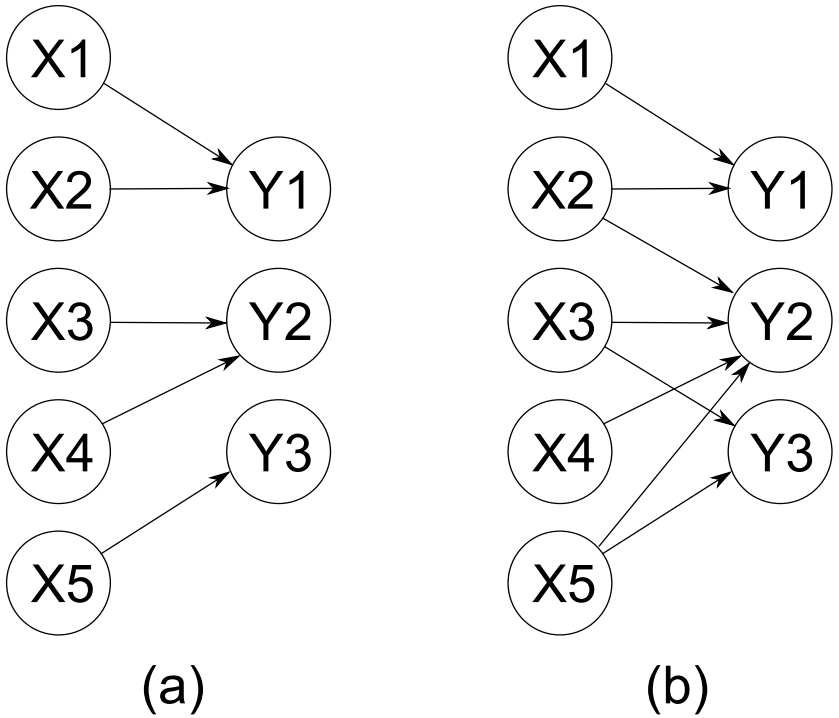


Figure: (a) Proper lumping - each of the original species corresponds to, at most, one of the lumped states. (b) Improper lumping - each of the original states can correspond to one or more of the lumped states.

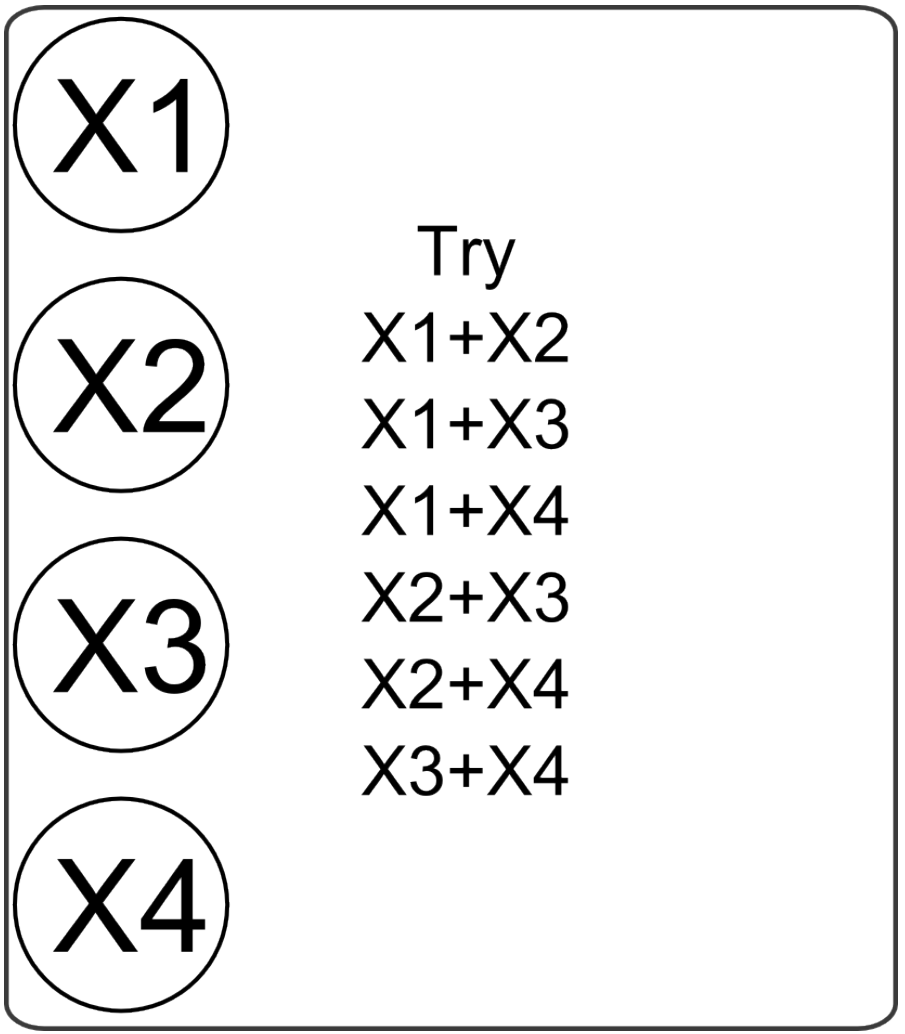
Lumping Based Methods II

Applying a lumping:

- A set of species can be reduced via some proper, linear lumping[4] $L \in \{0,1\}^{r \times n}$ giving a reduced set of species $\tilde{\boldsymbol{x}} \in \mathbb{R}^r$ where $\tilde{\boldsymbol{x}} = L\boldsymbol{x}$.
- Via the Galerkin projection we can obtain a reduced dynamical system of the form:

$$\dot{\tilde{\boldsymbol{x}}} = L\boldsymbol{f}(\bar{L}\tilde{\boldsymbol{x}}, \boldsymbol{p}) + L\boldsymbol{g}(\bar{L}\tilde{\boldsymbol{x}}, \boldsymbol{p})\boldsymbol{u}$$
$$\tilde{\boldsymbol{y}} = \boldsymbol{h}(\bar{L}\tilde{\boldsymbol{x}}, \boldsymbol{p}).$$

- Here $\bar{L}$ represents a generalised inverse of L such that $L\bar{L} = I_r$.



[4] Li & Rabitz, Chem. Eng. Sci., 1990.

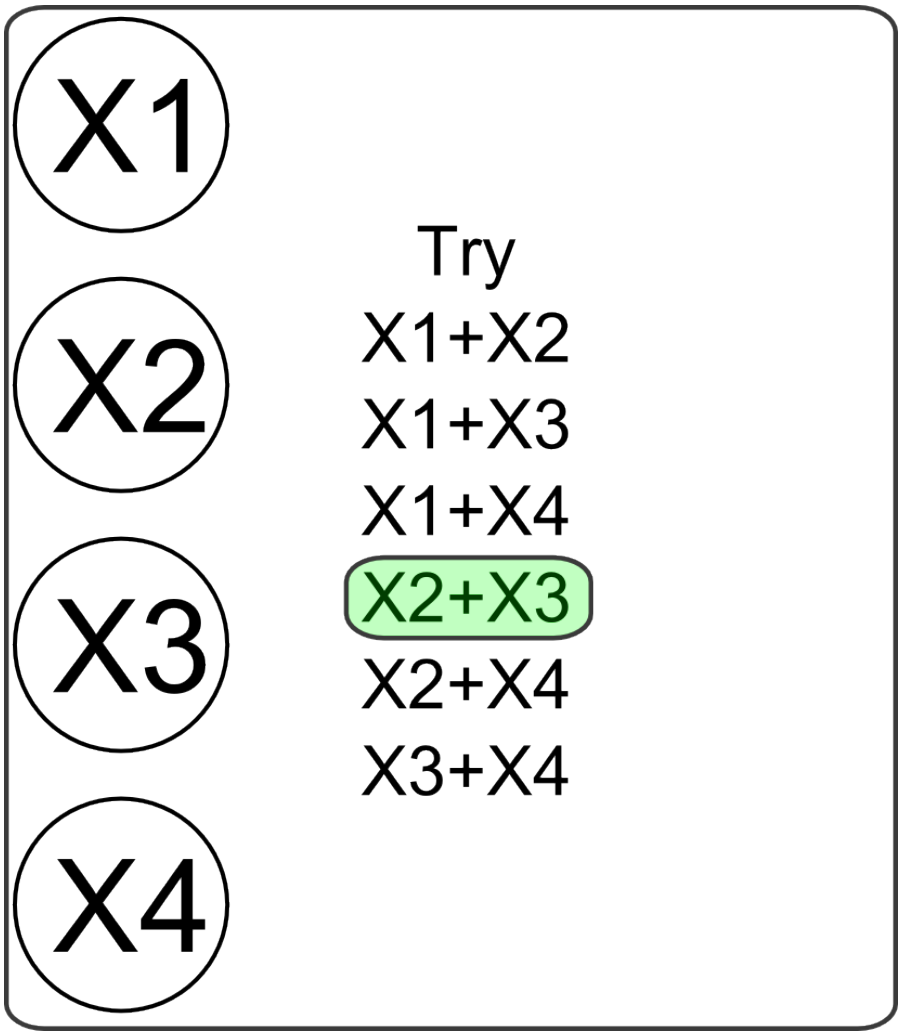
Lumping Based Methods II

Applying a lumping:

- A set of species can be reduced via some proper, linear lumping[4] $L \in \{0,1\}^{r \times n}$ giving a reduced set of species $\tilde{\boldsymbol{x}} \in \mathbb{R}^r$ where $\tilde{\boldsymbol{x}} = L\boldsymbol{x}$.
- Via the Galerkin projection we can obtain a reduced dynamical system of the form:

$$\dot{\tilde{\boldsymbol{x}}} = L\boldsymbol{f}(\bar{L}\tilde{\boldsymbol{x}}, \boldsymbol{p}) + L\boldsymbol{g}(\bar{L}\tilde{\boldsymbol{x}}, \boldsymbol{p})\boldsymbol{u}$$
$$\tilde{\boldsymbol{y}} = \boldsymbol{h}(\bar{L}\tilde{\boldsymbol{x}}, \boldsymbol{p}).$$

- Here $\bar{L}$ represents a generalised inverse of L such that $L\bar{L} = I_r$.



[4] Li & Rabitz, Chem. Eng. Sci., 1990.

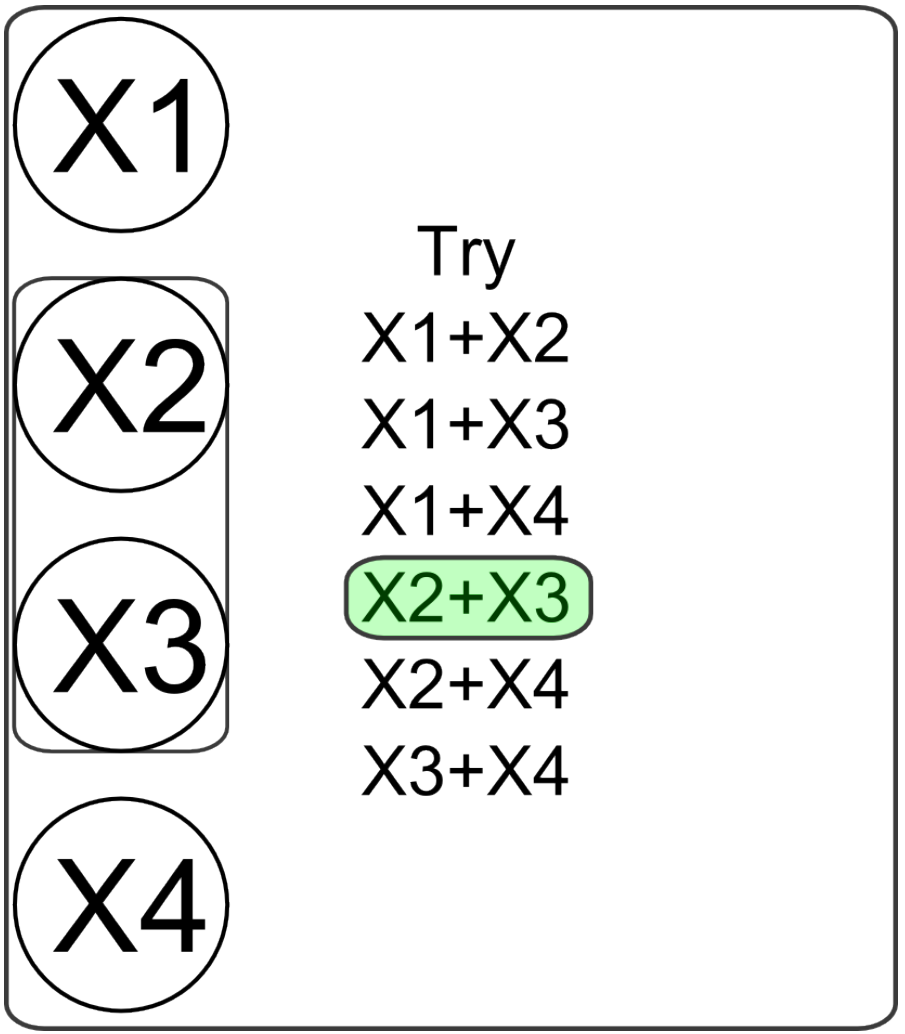
Lumping Based Methods II

Applying a lumping:

- A set of species can be reduced via some proper, linear lumping[4] $L \in \{0,1\}^{r \times n}$ giving a reduced set of species $\tilde{\boldsymbol{x}} \in \mathbb{R}^r$ where $\tilde{\boldsymbol{x}} = L\boldsymbol{x}$.
- Via the Galerkin projection we can obtain a reduced dynamical system of the form:

$$\dot{\tilde{\boldsymbol{x}}} = L\boldsymbol{f}(\bar{L}\tilde{\boldsymbol{x}}, \boldsymbol{p}) + L\boldsymbol{g}(\bar{L}\tilde{\boldsymbol{x}}, \boldsymbol{p})\boldsymbol{u}$$
$$\tilde{\boldsymbol{y}} = \boldsymbol{h}(\bar{L}\tilde{\boldsymbol{x}}, \boldsymbol{p}).$$

- Here $\bar{L}$ represents a generalised inverse of L such that $L\bar{L} = I_r$.



[4] Li & Rabitz, Chem. Eng. Sci., 1990.

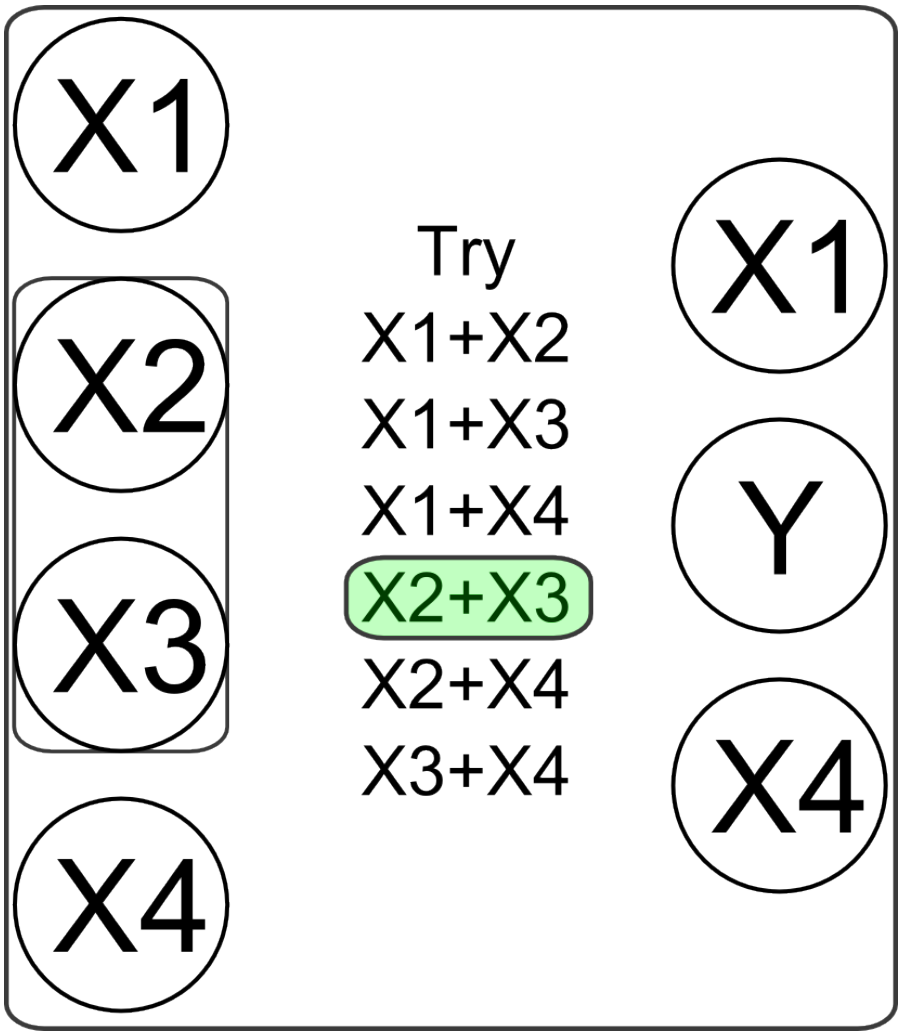
Lumping Based Methods II

Applying a lumping:

- A set of species can be reduced via some proper, linear lumping[4] $L \in \{0,1\}^{r \times n}$ giving a reduced set of species $\tilde{\boldsymbol{x}} \in \mathbb{R}^r$ where $\tilde{\boldsymbol{x}} = L\boldsymbol{x}$.
- Via the Galerkin projection we can obtain a reduced dynamical system of the form:

$$\dot{\tilde{\boldsymbol{x}}} = L\boldsymbol{f}(\bar{L}\tilde{\boldsymbol{x}}, \boldsymbol{p}) + L\boldsymbol{g}(\bar{L}\tilde{\boldsymbol{x}}, \boldsymbol{p})\boldsymbol{u}$$
$$\tilde{\boldsymbol{y}} = \boldsymbol{h}(\bar{L}\tilde{\boldsymbol{x}}, \boldsymbol{p}).$$

- Here $\bar{L}$ represents a generalised inverse of L such that $L\bar{L} = I_r$.



[4] Li & Rabitz, Chem. Eng. Sci., 1990.

Lumping Based Methods II

Applying a lumping:

- A set of species can be reduced via some proper, linear lumping[4] $L \in \{0,1\}^{r \times n}$ giving a reduced set of species $\tilde{\boldsymbol{x}} \in \mathbb{R}^r$ where $\tilde{\boldsymbol{x}} = L\boldsymbol{x}$.
- Via the Galerkin projection we can obtain a reduced dynamical system of the form:

$$\dot{\tilde{\boldsymbol{x}}} = L\boldsymbol{f}(\bar{L}\tilde{\boldsymbol{x}}, \boldsymbol{p}) + L\boldsymbol{g}(\bar{L}\tilde{\boldsymbol{x}}, \boldsymbol{p})\boldsymbol{u}$$
$$\tilde{\boldsymbol{y}} = \boldsymbol{h}(\bar{L}\tilde{\boldsymbol{x}}, \boldsymbol{p}).$$

- Here $\bar{L}$ represents a generalised inverse of L such that $L\bar{L} = I_r$.

[4] Li & Rabitz, Chem. Eng. Sci., 1990.

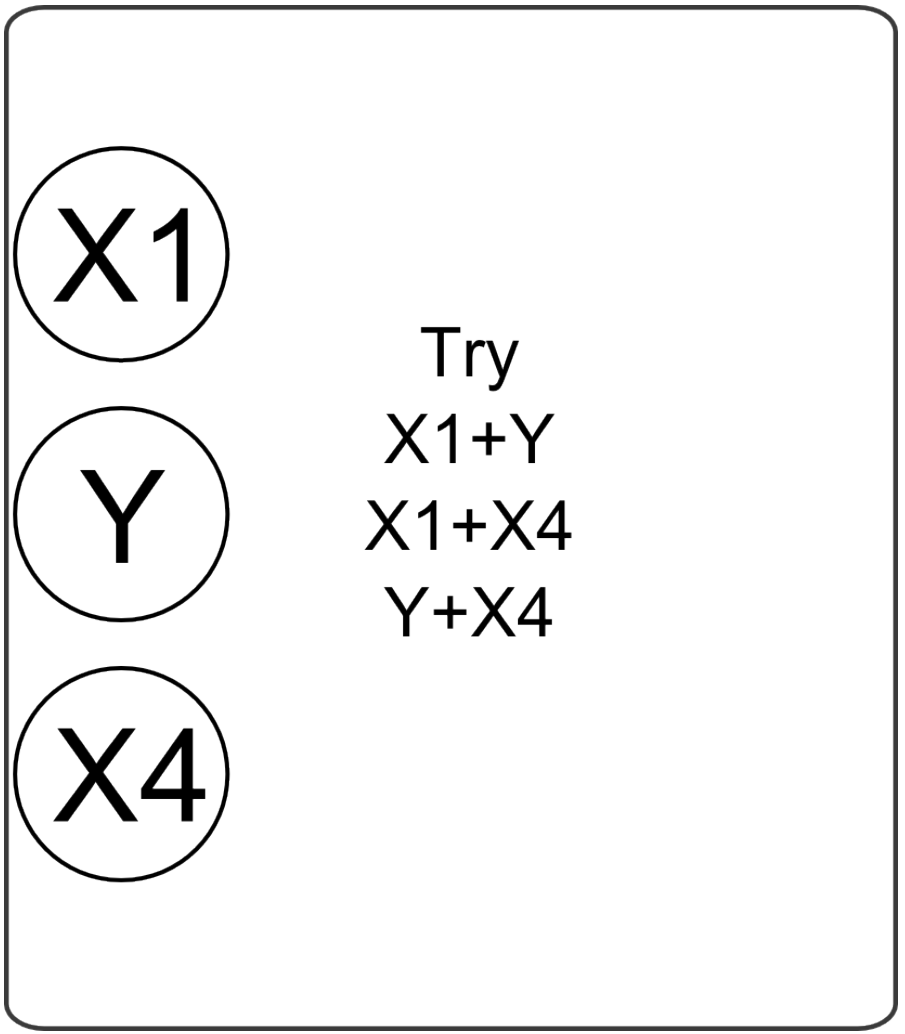
Lumping Based Methods II

Applying a lumping:

- A set of species can be reduced via some proper, linear lumping[4] $L \in \{0,1\}^{r \times n}$ giving a reduced set of species $\tilde{\boldsymbol{x}} \in \mathbb{R}^r$ where $\tilde{\boldsymbol{x}} = L\boldsymbol{x}$.
- Via the Galerkin projection we can obtain a reduced dynamical system of the form:

$$\dot{\tilde{\boldsymbol{x}}} = L\boldsymbol{f}(\bar{L}\tilde{\boldsymbol{x}}, \boldsymbol{p}) + L\boldsymbol{g}(\bar{L}\tilde{\boldsymbol{x}}, \boldsymbol{p})\boldsymbol{u}$$
$$\tilde{\boldsymbol{y}} = \boldsymbol{h}(\bar{L}\tilde{\boldsymbol{x}}, \boldsymbol{p}).$$

- Here $\bar{L}$ represents a generalised inverse of L such that $L\bar{L} = I_r$.



[4] Li & Rabitz, Chem. Eng. Sci., 1990.

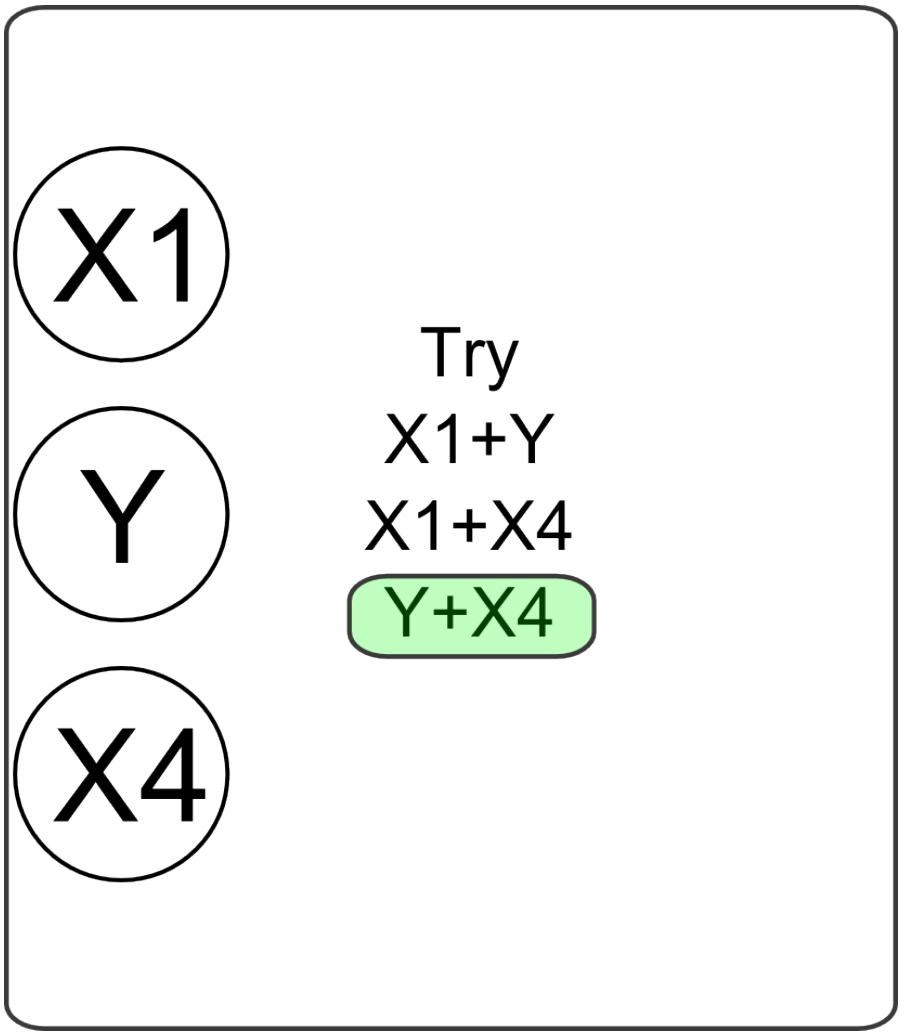
Lumping Based Methods II

Applying a lumping:

- A set of species can be reduced via some proper, linear lumping[4] $L \in \{0,1\}^{r \times n}$ giving a reduced set of species $\tilde{x} \in \mathbb{R}^r$ where $\tilde{x} = Lx$.
- Via the Galerkin projection we can obtain a reduced dynamical system of the form:

$$\dot{\tilde{x}} = Lf(\bar{L}\tilde{x}, p) + Lg(\bar{L}\tilde{x}, p)u$$
$$\tilde{y} = h(\bar{L}\tilde{x}, p).$$

- Here $\bar{L}$ represents a generalised inverse of L such that $L\bar{L} = I_r$.



[4] Li & Rabitz, Chem. Eng. Sci., 1990.

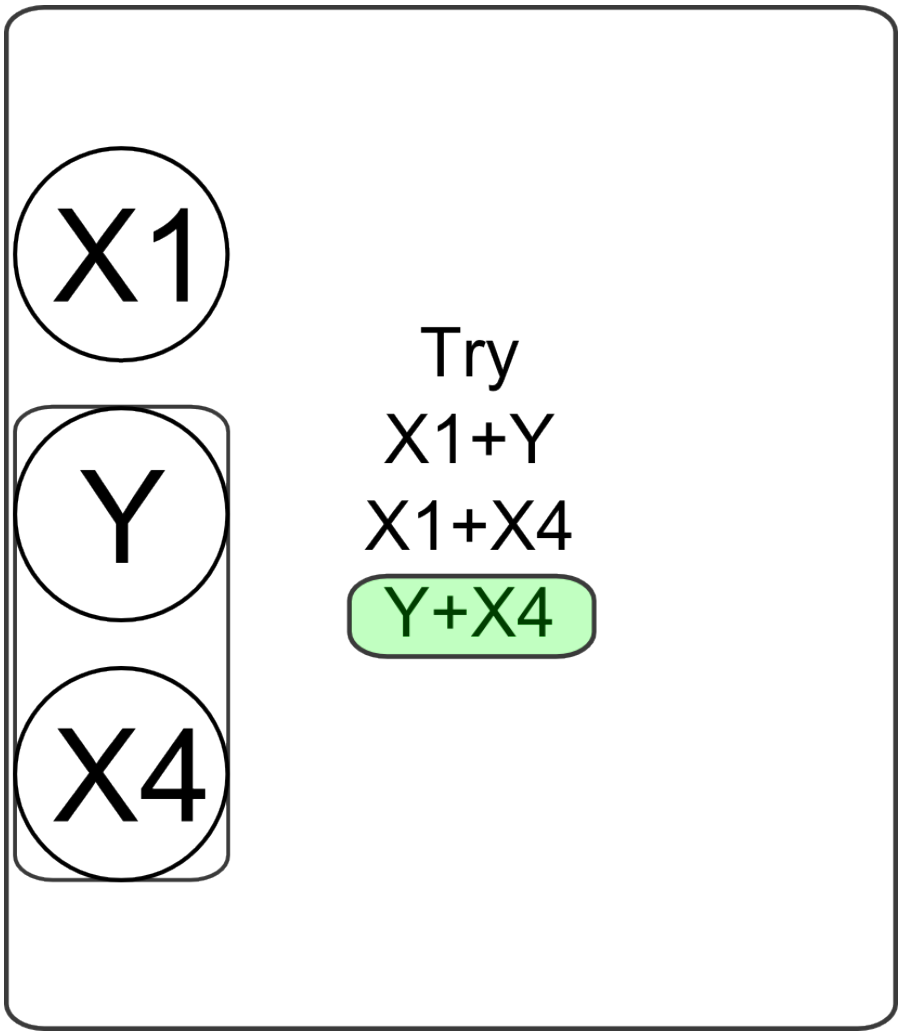
Lumping Based Methods II

Applying a lumping:

- A set of species can be reduced via some proper, linear lumping[4] $L \in \{0,1\}^{r \times n}$ giving a reduced set of species $\tilde{\boldsymbol{x}} \in \mathbb{R}^r$ where $\tilde{\boldsymbol{x}} = L\boldsymbol{x}$.
- Via the Galerkin projection we can obtain a reduced dynamical system of the form:

$$\dot{\tilde{\boldsymbol{x}}} = L\boldsymbol{f}(\bar{L}\tilde{\boldsymbol{x}}, \boldsymbol{p}) + L\boldsymbol{g}(\bar{L}\tilde{\boldsymbol{x}}, \boldsymbol{p})\boldsymbol{u}$$
$$\tilde{\boldsymbol{y}} = \boldsymbol{h}(\bar{L}\tilde{\boldsymbol{x}}, \boldsymbol{p}).$$

- Here $\bar{L}$ represents a generalised inverse of L such that $L\bar{L} = I_r$.



[4] Li & Rabitz, Chem. Eng. Sci., 1990.

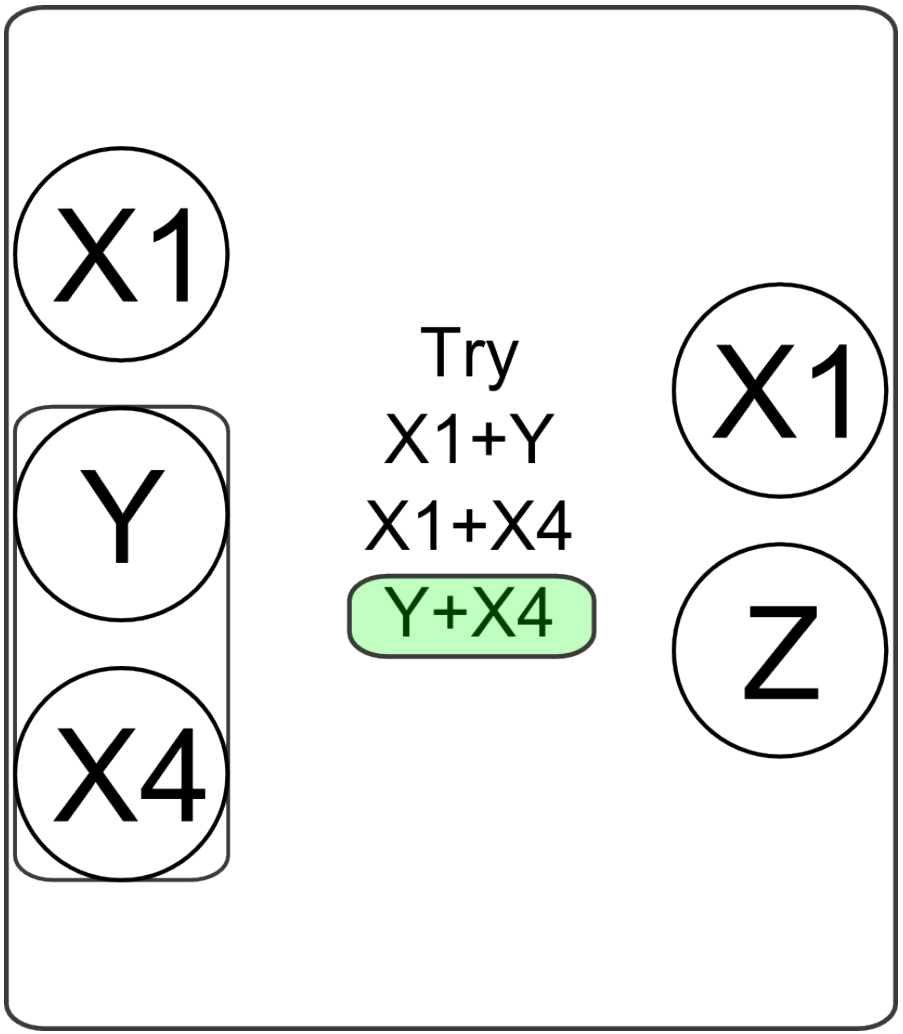
Lumping Based Methods II

Applying a lumping:

- A set of species can be reduced via some proper, linear lumping[4] $L \in \{0,1\}^{r \times n}$ giving a reduced set of species $\tilde{\boldsymbol{x}} \in \mathbb{R}^r$ where $\tilde{\boldsymbol{x}} = L\boldsymbol{x}$.
- Via the Galerkin projection we can obtain a reduced dynamical system of the form:

$$\dot{\tilde{\boldsymbol{x}}} = L\boldsymbol{f}(\bar{L}\tilde{\boldsymbol{x}}, \boldsymbol{p}) + L\boldsymbol{g}(\bar{L}\tilde{\boldsymbol{x}}, \boldsymbol{p})\boldsymbol{u}$$
$$\tilde{\boldsymbol{y}} = \boldsymbol{h}(\bar{L}\tilde{\boldsymbol{x}}, \boldsymbol{p}).$$

- Here $\bar{L}$ represents a generalised inverse of L such that $L\bar{L} = I_r$.



[4] Li & Rabitz, Chem. Eng. Sci., 1990.

Lumping Based Methods III

PROS:

- Lumping is a common method in the reduction of chemical kinetics - quite a large range of literature exists.
- Algorithmic approaches that can be implemented computationally exist.
- Lumped variables can be chosen to be biological meaningful such that the reduced model maintins some degree of biological intuitiveness.

CONS:

- Many of the procedures in the literature are highly computationally expensive for large systems.
- Most methods in the literature pertain to linear, proper lumping - better reduction is likely to be achieved by nonlinear and/or improper lumping techniques, but this may lead to loss of biological meaning.

Singular Value Decomposition Based Approaches I

- These methods are based upon the signular value decomposition (SVD).
- Crucially, via Eckart-Young-Mirsky theorem[5] the SVD provides a way to approximate a matrix via one of lower rank.
- The most commonly applied such method is balanced truncation.

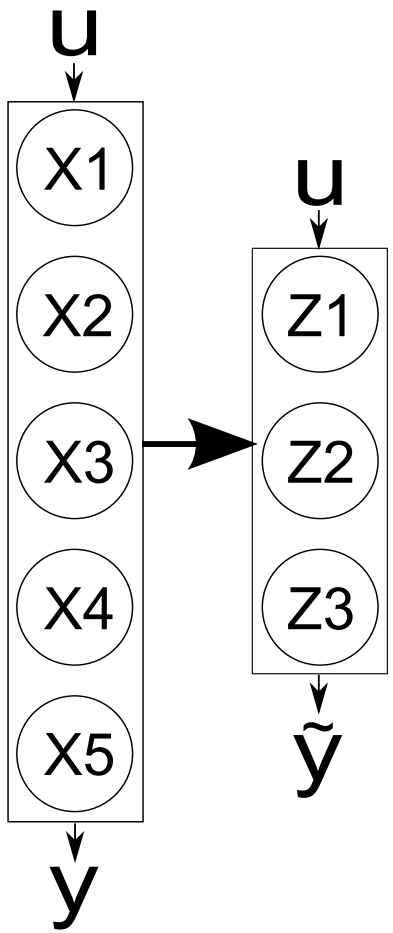


Figure: Balanced truncation reduces a model whilst seeking to preserve the input-output relationship

Singular Value Decomposition Based Approaches II

- Linear balanced truncation is typically applied to linear systems of the form

$$\dot{\boldsymbol{x}} = A\boldsymbol{x} + B\boldsymbol{u},$$
$$\boldsymbol{y} = C\tilde{\boldsymbol{x}}.$$

- It requires the computation of two matrices $\mathcal{P}$ and $\mathcal{Q}$:
  1. The controllability Gramian $\mathcal{P}$ provides information on how the state-variables $\boldsymbol{x}$ respond to perturbations in inputs $\boldsymbol{u}$.
  2. The observability Gramian $\mathcal{Q}$ provides information on how the outputs $\boldsymbol{y}$ respond to perturbations in the state-variables $\boldsymbol{x}$.

Balanced truncation done quick

1. Perform Cholesky factorisation of both gramians

$$\mathcal{P} = L^T L,\ \mathcal{Q} = R^T R.$$

2. Take SVD of matrix LR^T to obtain

$$LR^T = (U_1\ U_2)\begin{pmatrix} \Sigma_1 & 0 \\ 0 & \Sigma_2 \end{pmatrix}\begin{pmatrix} V_1^T \\ V_2^T \end{pmatrix}$$

Where U_1 is an $n \times r$ matrix, Σ_1 is an $r \times r$ diagonal matrix and V_1^T is a $r \times n$ matrix.

3. Set

$$T_1 = \Sigma_1^{-\frac{1}{2}} V_1^T R,\ S_1 = L^T U_1 \Sigma_1^{-\frac{1}{2}}.$$

4. Finally

$$\dot{\tilde{\boldsymbol{x}}} = T_1 A S_1 \tilde{\boldsymbol{x}} + T_1 B \boldsymbol{u},$$
$$\tilde{\boldsymbol{y}} = C S_1 \tilde{\boldsymbol{x}}.$$

Singular Value Decomposition Based Approaches II

PROS:

- Control theoretic description fits neatly with the idea of systems pharmacology (i.e. the drug controlling subcellular processes).
- They are highly algorithmic methods - can potentially be automated in a straightforward manner.
- An a priori error bound can be obtained.

CONS:

- Transformed/reduced states no longer have biological meaning - only inputs and outputs preserve their meaning.
- Standard approach only exists for linear models - but generalisations for nonlinear systems do exist.
- For large systems, empirical balanced truncation can be highly computational expensive.

Miscellaneous Methods

A number of other methods, with a limited publication record, do exist including:

- Motif replacment methods;
- Methods for reduction of combinatorial complexity;
- Complex reduction; and
- Publications addressing general reduction heuristics.

Conclusions of Literature Review I

This literature review enabled several specific conclusions:

- There is no 'one-size-fits-all' method of model reduction.
- Whilst many of these methods can be highly automated, the onus is on the modeller to choose the correct tool for the task.
- Consider what the reduced model will be used for to judge which method is most appropriate.

Conclusions of Literature Review II

	Suitable for very high dimensional systems	Suitable for stiff systems	Nonlinear systems	Preserves species meanings
Coordinate preserving timescale methods	-	✓	✓	✓
Coordinate transforming timescale methods	-	-	✓	X
Sensitivity analysis	-	-	-	✓
Optimisation approaches	✓	✓	✓	✓
Lumping	✓	✓	✓	-
Balanced truncation	✓	-	-	X

Presentation outline

- How I define model reduction
- Review of existing methods
- **An example**
- Linking with pharmacokinetics
- Conclusions

Aims

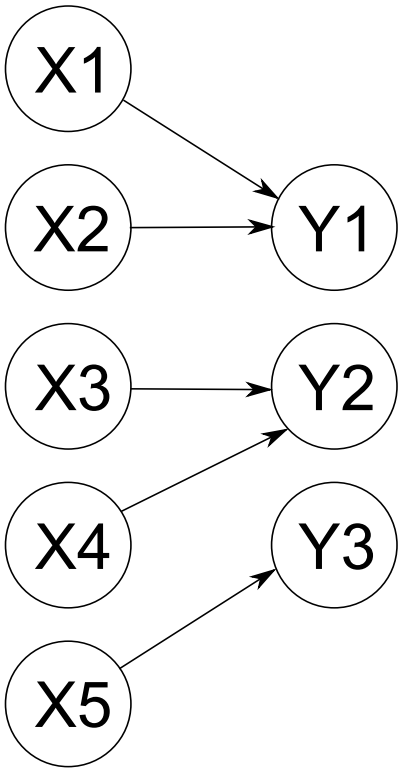


Figure: An example of a proper lumping

This section introduces a computational model reduction algorithm developed during my PhD.

Three existing methods are brought together in this approach:

- Conservation analysis.
- Proper lumping.
- Empirical balanced truncation.

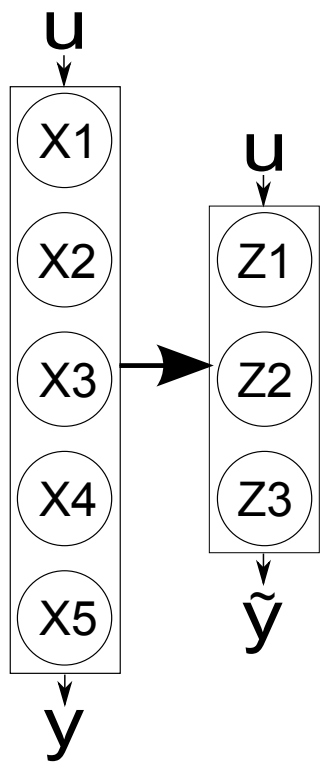
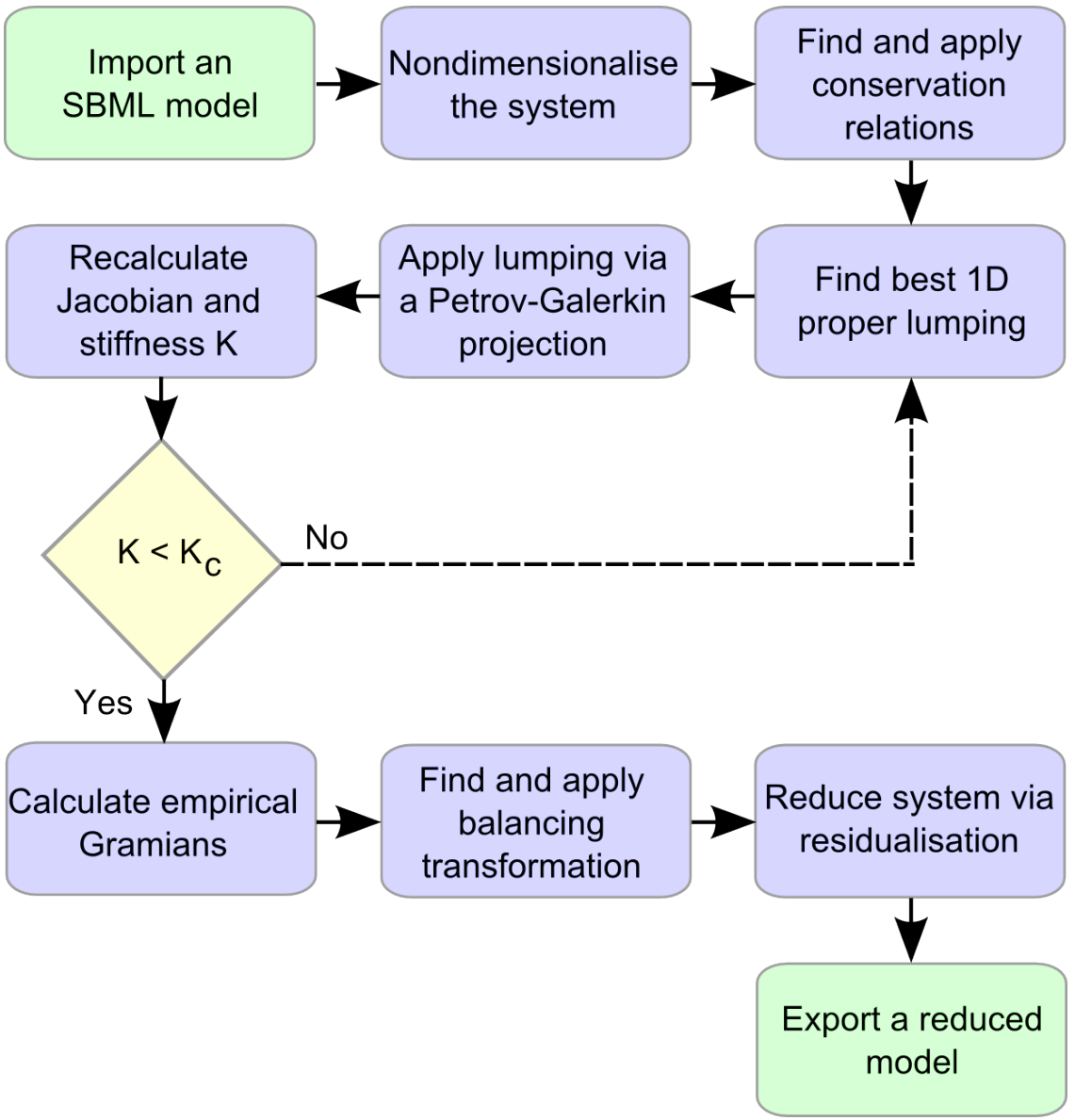


Figure: Schematic outline of Balanced Truncation - the method focuses on preserving the input-output relationship of the system.

Combined model reduction algorithm

Given this context, we have developed the an algorithm for model reduction which combines previously existing methods in a novel way. The following schematic outlines its operation:



Combined method justification

The core justification of the combined reduction algorithm is the use of proper lumping as a preconditioner for the application of empirical balanced truncation.

- Empirical balanced truncation (EBT) should, in theory, produce more accurate reduced networks than proper lumping.
- In practice, EBT often fails for highly stiff systems.
- Proper lumping, however, will tend to sum together those state-variables that interact on faster timescales than their neighbours.
- Hence the reduced model will often contain a smaller range of timescales and be less stiff with each additional dimension eliminated.

ERK Activation Model

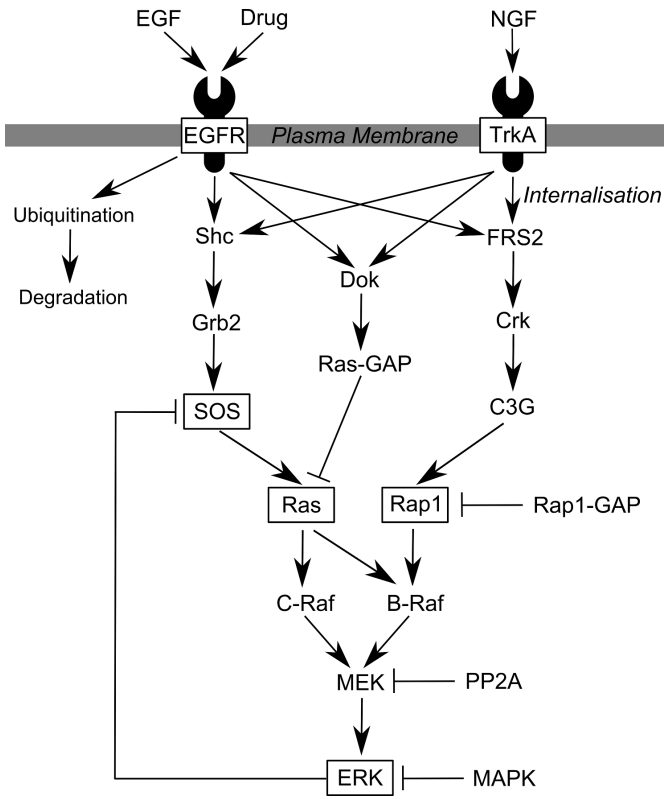


Figure: Block schematic overview of EGF and NGF dependent ERK signalling network[7]. Model consists of 150 reactions and 99 species. There are 23 conservation relations in this system enabling the model to be reduced to 76 states.

[6] Sasagawa et al., Nat. Cell Biol., 2005.

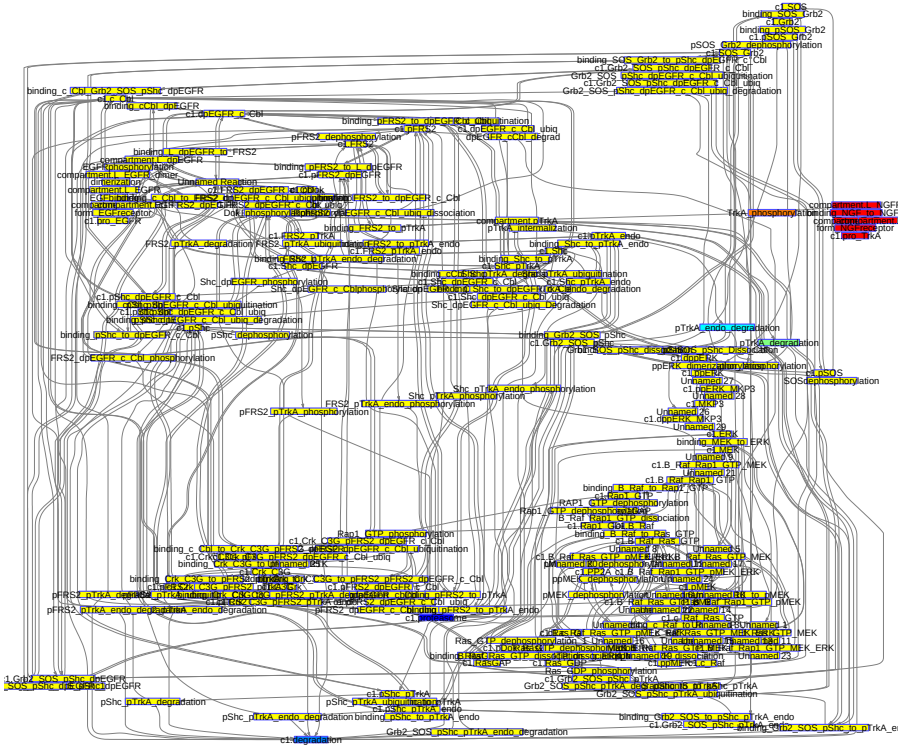


Figure: Full ERK activation pathway model in petri-net form

ERK Activation Reduction Results I

Dimension	EBT Error	Lumping Error	Stiffness	Combined Error
75	0.76%	$\approx 0\%^*$	42658	–
50	#	0.01%	42633	–
25	#	0.52%	10664	–
15	#	1.26%	7934	–
14	#	2.21%	7934	–
13	#	2.29%	7934	–
12	#	1.21%	1591	–
11	#	3.07%	236	–
10	#	6.02%	264	2.84%
9	#	10.96%	211	4.02%
8	#	13.12%	43	4.32%
7	#	14.18%	42	4.77%
6	#	29.53%	44	13.08%

Results for the reduction of the 99 dimensional Erk-activation model. '#' implies Matlab could not simulate this reduction using ode15s due to numerical error. '-' implies the error at this point was equal to the lumping error.

ERK Activation Reduction Results II

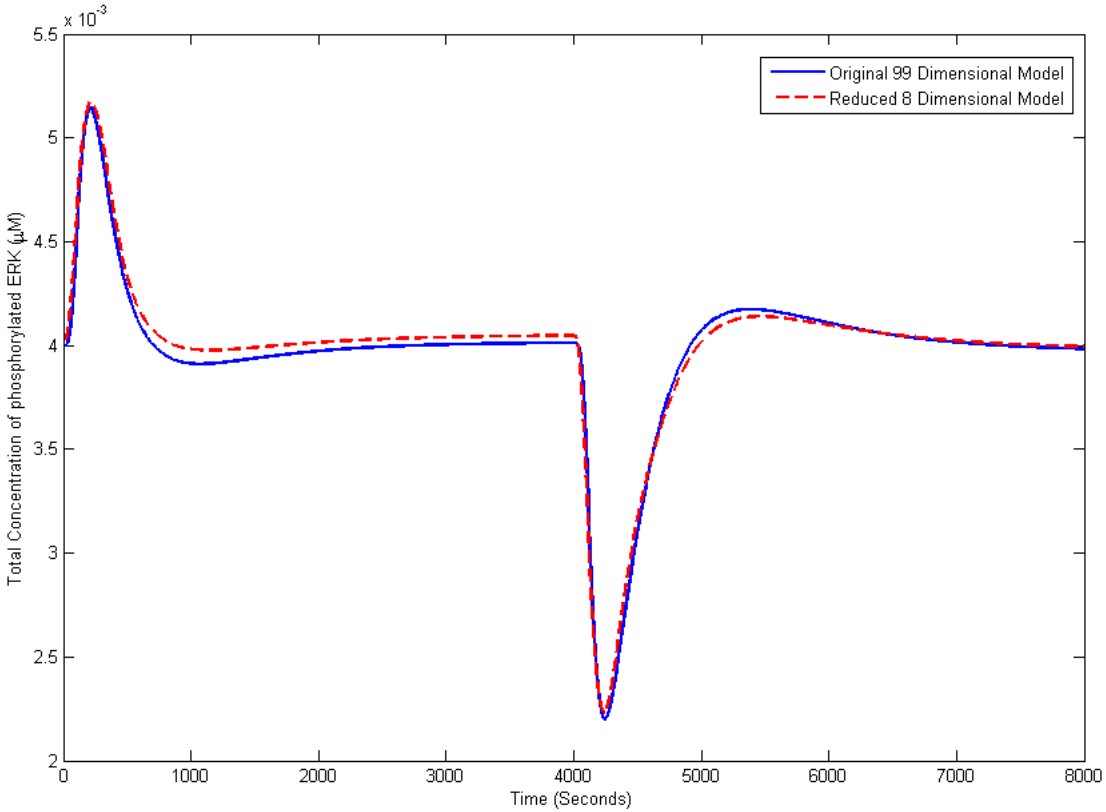


Figure: Simulated results for the output of the original 99-dimensional ERK activation model vs the reduced 8 dimensional model. This plot emphasises the fact that the reduced model is designed to remain valid for any reasonable change in input. The system starts by being affected by an agonist that increases the rate of EGF binding by 25% for over an hour (4000 seconds), at this point the input flips to an antagonist decreasing the rate of EGF binding by 25% and runs for the same time period (an additional 4000 seconds). At any given time point the error between the original and reduced model exceeds no more than 5%.

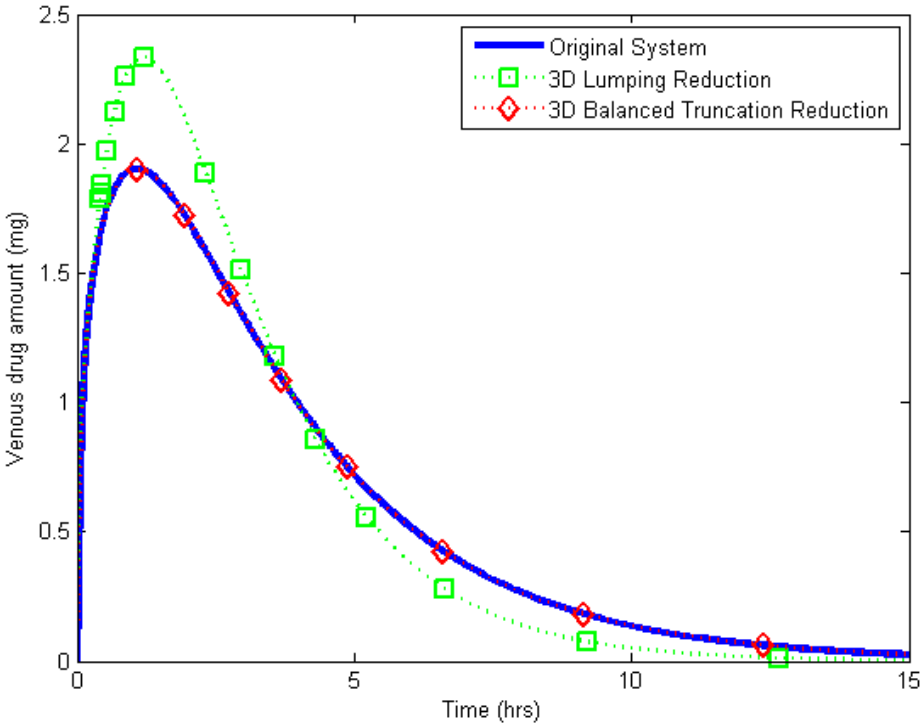
Presentation outline

- How I define model reduction
- Review of existing methods
- An example
- **Linking with pharmacokinetics**
- Conclusions

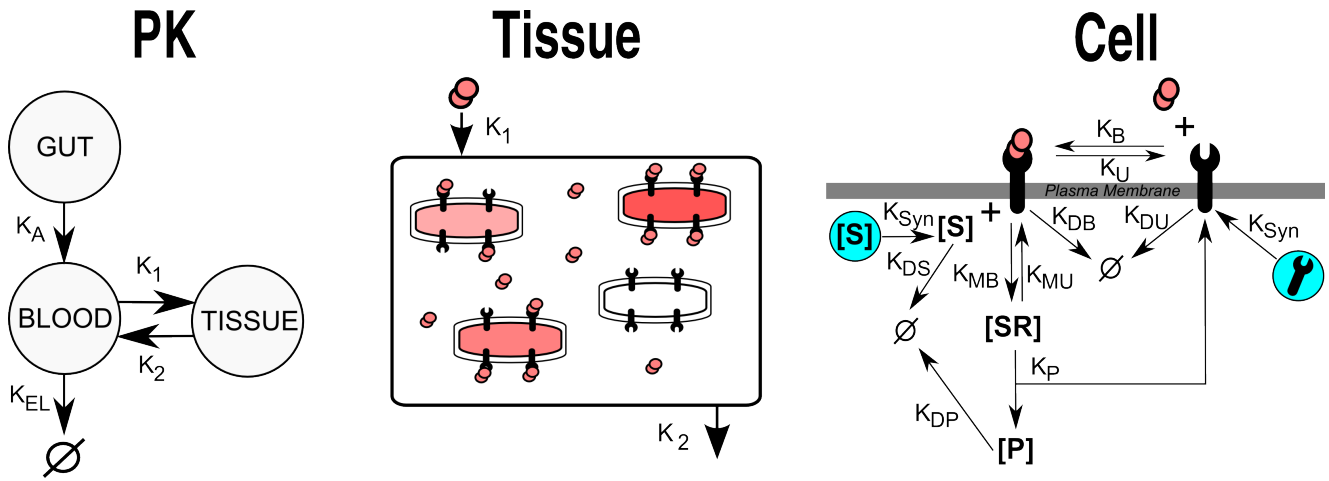
Reducing PBPK models I

- In this section we explore the application of model reduction methods to models of pharmacokinetics.
- Pharmacokinetic models are typically linear which enables more accurate reduction as compared with, typically nonlinear, models of biochemical reaction networks.
- A brief study of applying model reduction methods to physilogically based pharmacokinetic models was underaken.
- The PBPK system we chose to employ was a deterministic, linear, 16-dimensional, compartmental model.

Reducing PBPK models II



Analysis was made of both lumping and standard balanced truncation as a means for the reduction this system. Balanced truncation was found to give the best results

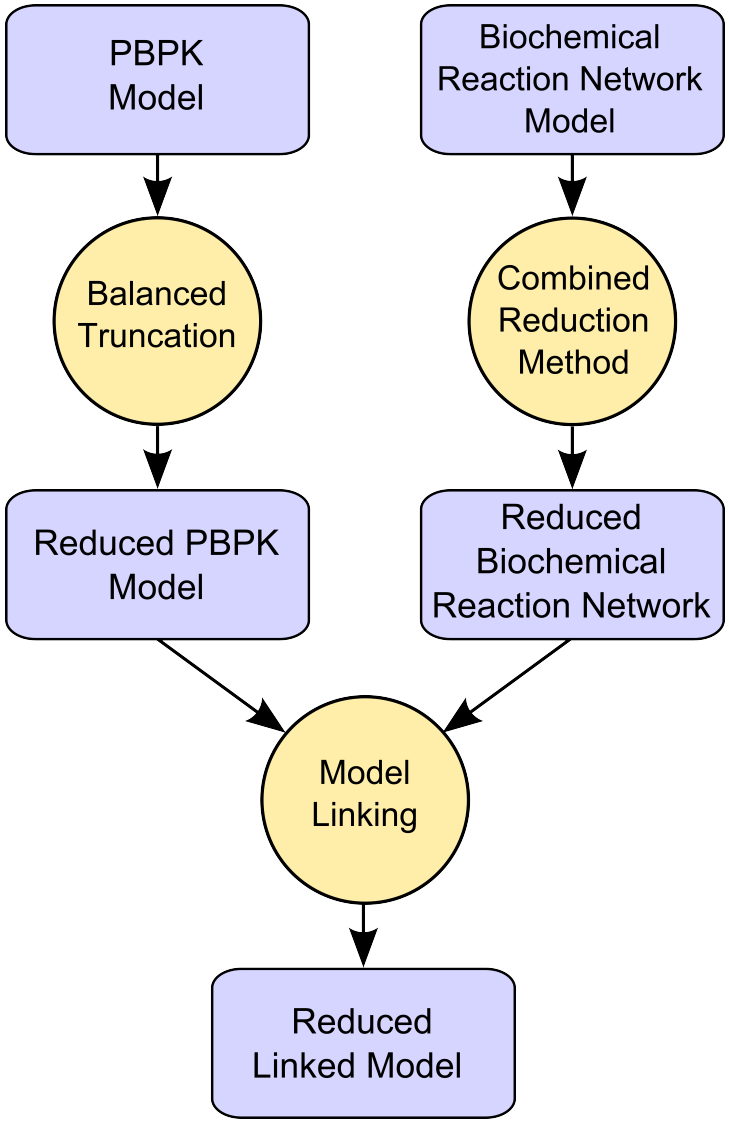


Questions include:

- Should spatial inhomogeneity in diffusion be explicitly accounted for?
- What is the cumulative effect of the cellular response?
- Should different cell types (e.g. diseased and healthy) and their differences in drug affinity be accounted for?

Linking II

- We made the simplifying assumption that the tissue effects were accounted for by the PBPK model and that the cells/receptors were homogeneously distributed in the relevant tissue compartment.
- Hence they are partially decoupled and can be reduced separately as in the schematic given on the right.



Linking Results: ERK activation

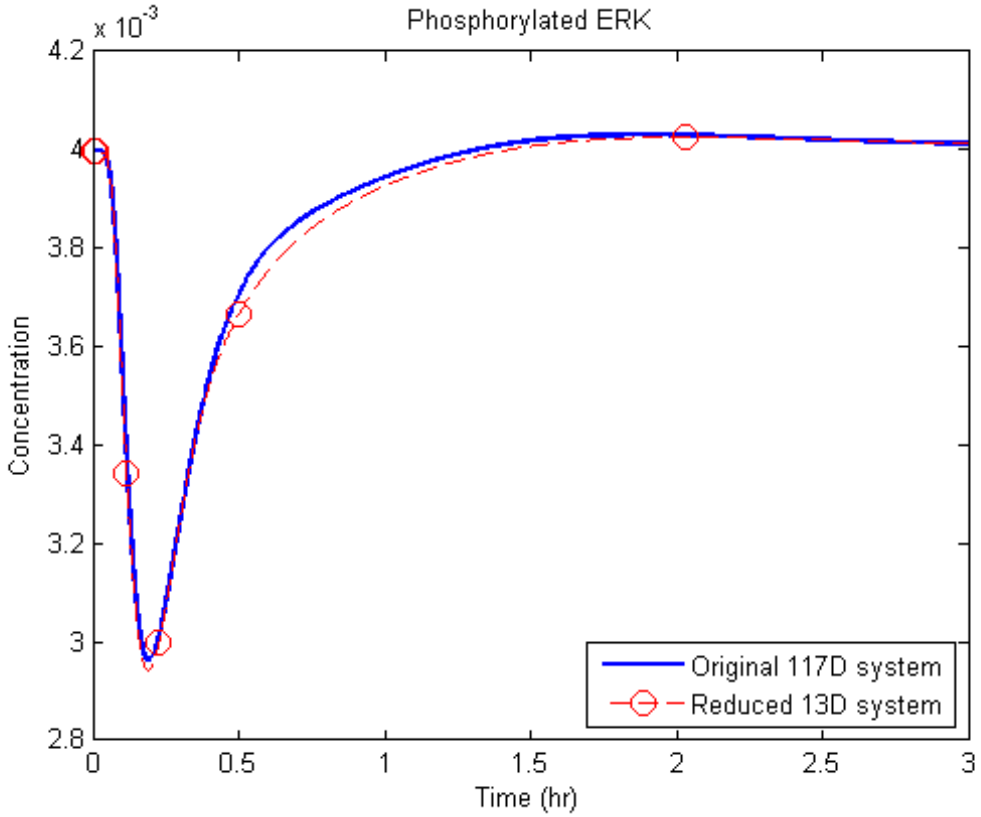


Figure: Linking the 10 dimensional reduced version of the ERK activation model obtained under the combined model reduction algorithm with a 3 dimensional reduced version of the PBPK model obtained via balanced truncation yields the results above. In comparison to a linked version of the original model, the reduced version maintains a 3% error bound.

Presentation outline

- How I define model reduction
- Review of existing methods
- An example
- Linking with pharmacokinetics
- **Conclusions**

Conclusions

We have hopefully demonstrated that model reduction methods can produce significant simplifications in a system whilst retaining a high degree of accuracy.

The literature review shows that a wide range of such methods currently exist.

The aims of such reduction might include seeking to speed up simulation time, obtaining a model of an appropriate scope relative to the avilable data, or trying to analyse which components of a model are most responsible for driving the dynamical behaviour of interest.

Crucially, the optimal reduction method is deeply dependent upon your research question!

Thank you for listening.

Acknowledgments

- Thank you to Pfizer and EPSRC for their financial support throughout the PhD.
- Thank you to Marcus Tindall and Piet van der Graaf for their supervision throughout the project.

APPENDIX

Petrov-Galerkin Projection

- System trajectories can often be well approximated in a lower dimensional subspace $\mathcal{S}$: $\dim(\mathcal{S}) = r$.
- Select a test basis $B \in \mathbb{R}^{n \times r}$ of $\mathcal{S}$, such that $\boldsymbol{x}(t) \approx B\tilde{\boldsymbol{x}}(t)$ with $\tilde{\boldsymbol{x}}(t) \in \mathbb{R}^r$ represents our reduced state vector.
- Hence, $B\dot{\tilde{\boldsymbol{x}}}(t) = \boldsymbol{f}\left(B\tilde{\boldsymbol{x}}(t), \boldsymbol{p}, \boldsymbol{u}(t)\right) + \boldsymbol{r}(t)$ where $\boldsymbol{r}(t)$ represents the residual incurred via our approximation.
- Constrain the residual to be orthogonal to a subspace $\mathcal{C}$ with an associated test basis $C \in \mathbb{R}^{n \times r}$ such that $C^T\boldsymbol{r}(t) \approx 0$.
- Therefore we left multiply by C^T to obtain $C^T B\dot{\tilde{\boldsymbol{x}}}(t) = C^T\boldsymbol{f}\left(B\tilde{\boldsymbol{x}}(t), \boldsymbol{p}, \boldsymbol{u}(t)\right)$
- Assuming $C^T B$ is non-singular we can obtain

$$\dot{\tilde{\boldsymbol{x}}}(t) = \left(C^T B\right)^{-1} C^T\boldsymbol{f}\left(B\tilde{\boldsymbol{x}}(t), \boldsymbol{p}, \boldsymbol{u}(t)\right)$$
$$\tilde{\boldsymbol{y}} = \boldsymbol{g}\left(B\tilde{\boldsymbol{x}}(t), \boldsymbol{p}\right)$$

- If $B = C$ this is a special case known as a Galerkin projection.