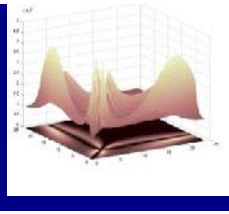


Simplification of a multi-scale systems coagulation model with an application to modelling PKPD data

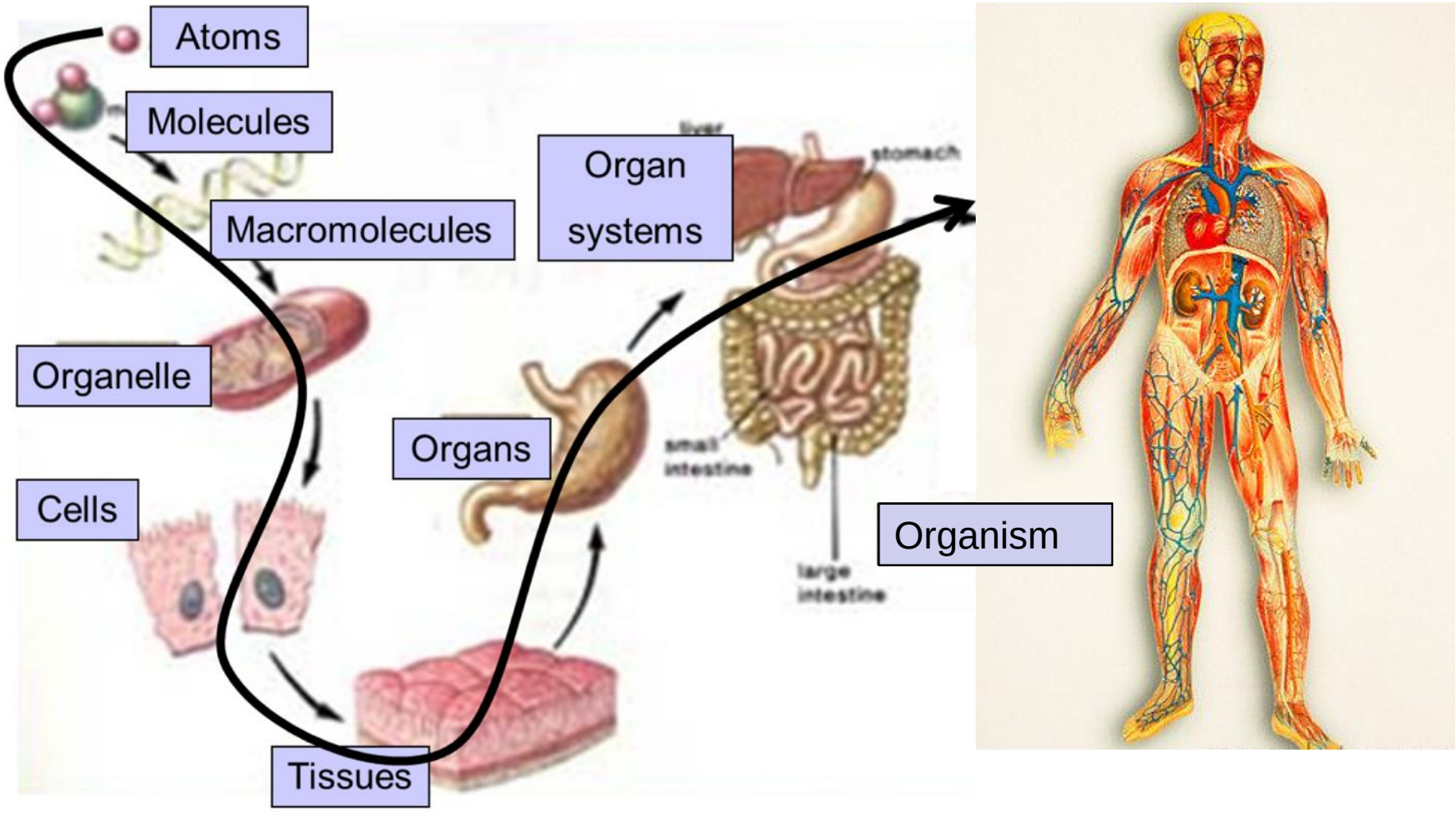
Abhishek Gulati[1], Geoffrey Isbister[2, 3], Stephen Duffull[1]

[1]School of Pharmacy, University of Otago, Dunedin, New Zealand

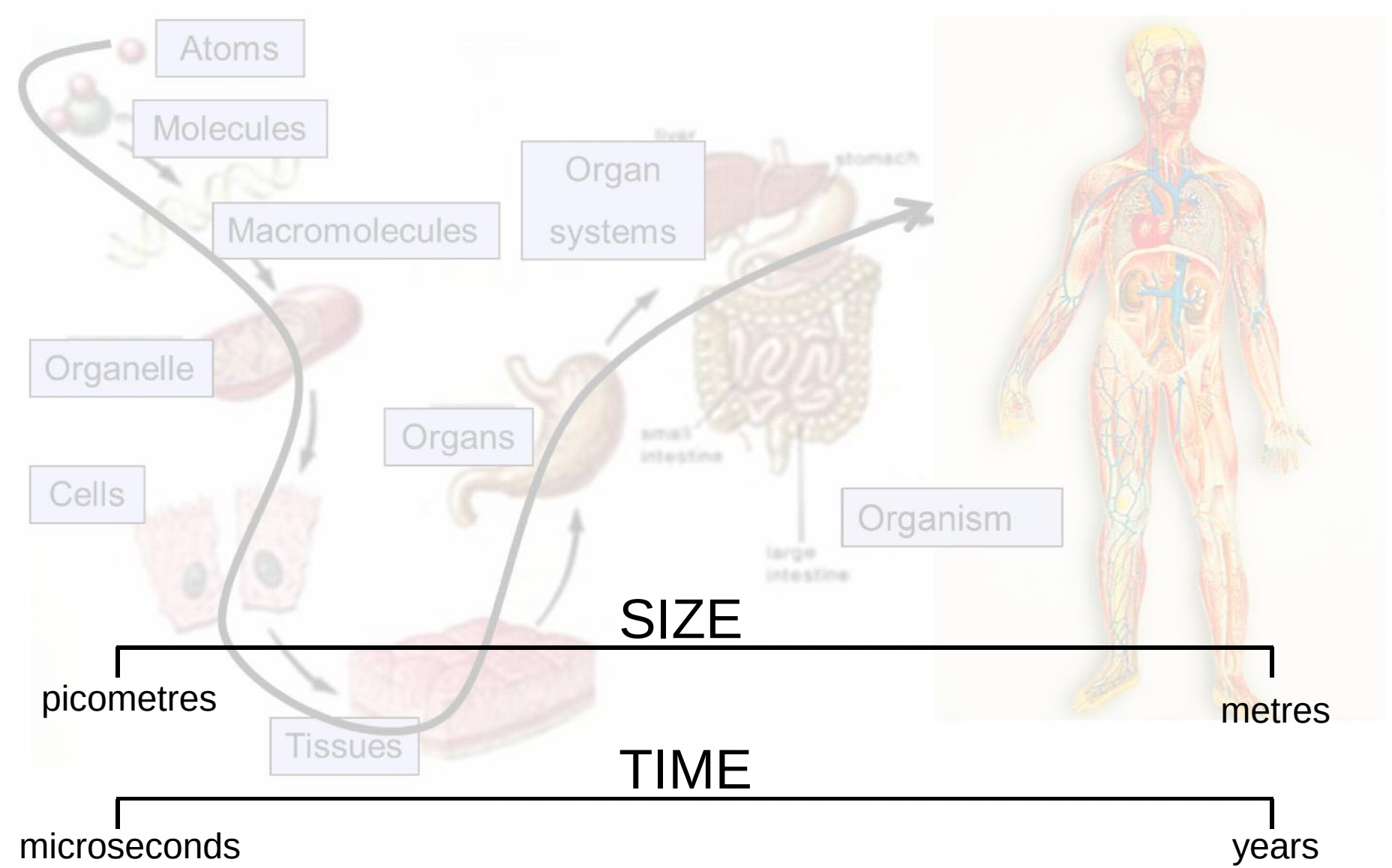
[2]Department of Clinical Toxicology and Pharmacology, Calvary Mater Newcastle, NSW, Australia

[3]School of Medicine and Public Health, University of Newcastle, NSW, Australia

Human body is complex



Multi-scale


Atoms
Molecules
Macromolecules
Organelle
Cells
Tissues
Organs
Organ systems
Organism
SIZE
picometres
metres
TIME
microseconds
years

Systems pharmacology

- Deals with mathematical models relating pharmacology of drug(s) in biological system(s)[1]
- Because of the complexity of the human body, the resulting models:
  - are highly non-linear systems
  - an arbitrarily small perturbation in the initial conditions may lead to significantly different future behaviour

⇩

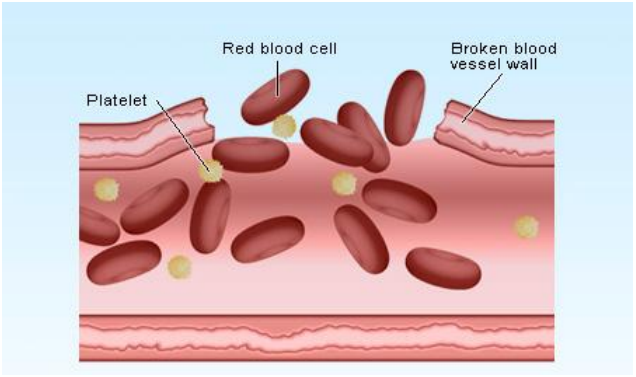
may make quantification of the output difficult to predict from the input

[1]Van der Graaf *et al* Future Med Chem 2009

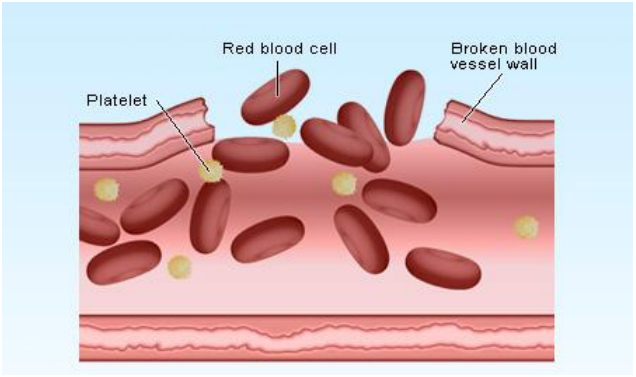
The systems pharmacology model used for this work describes the process of blood coagulation in the human body

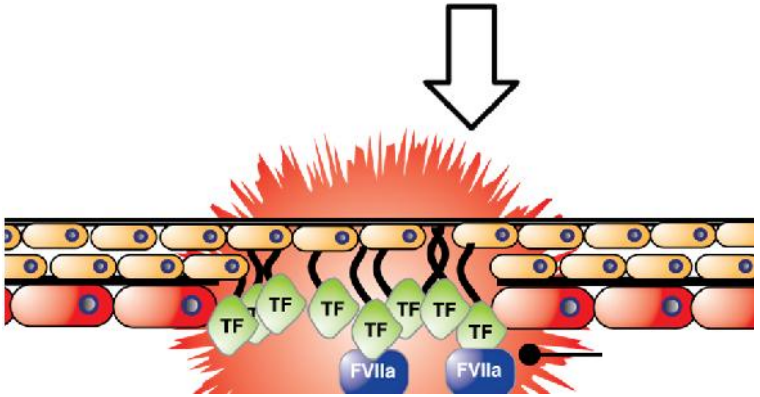
Blood coagulation

Blood coagulation

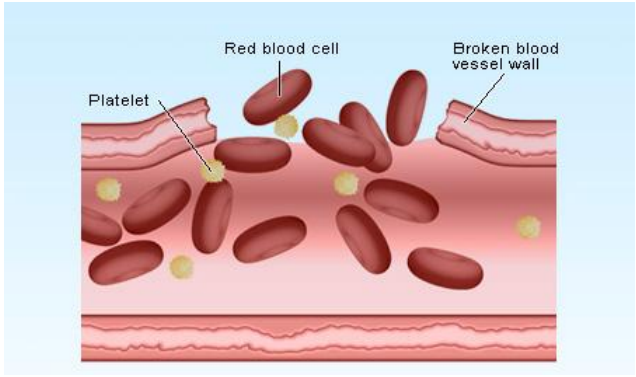


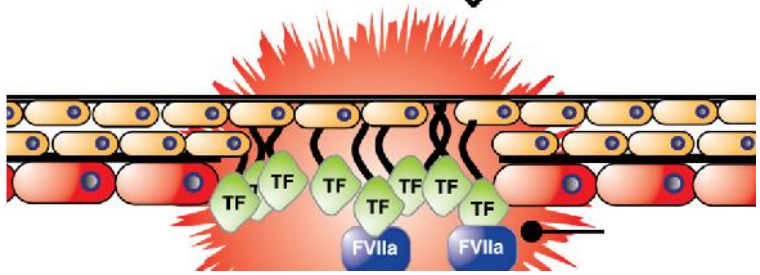
Blood coagulation

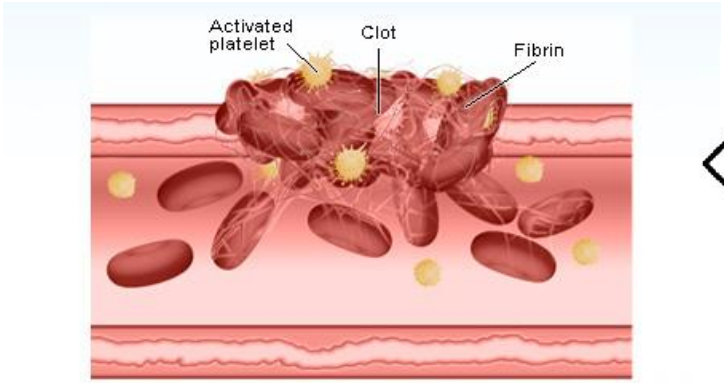




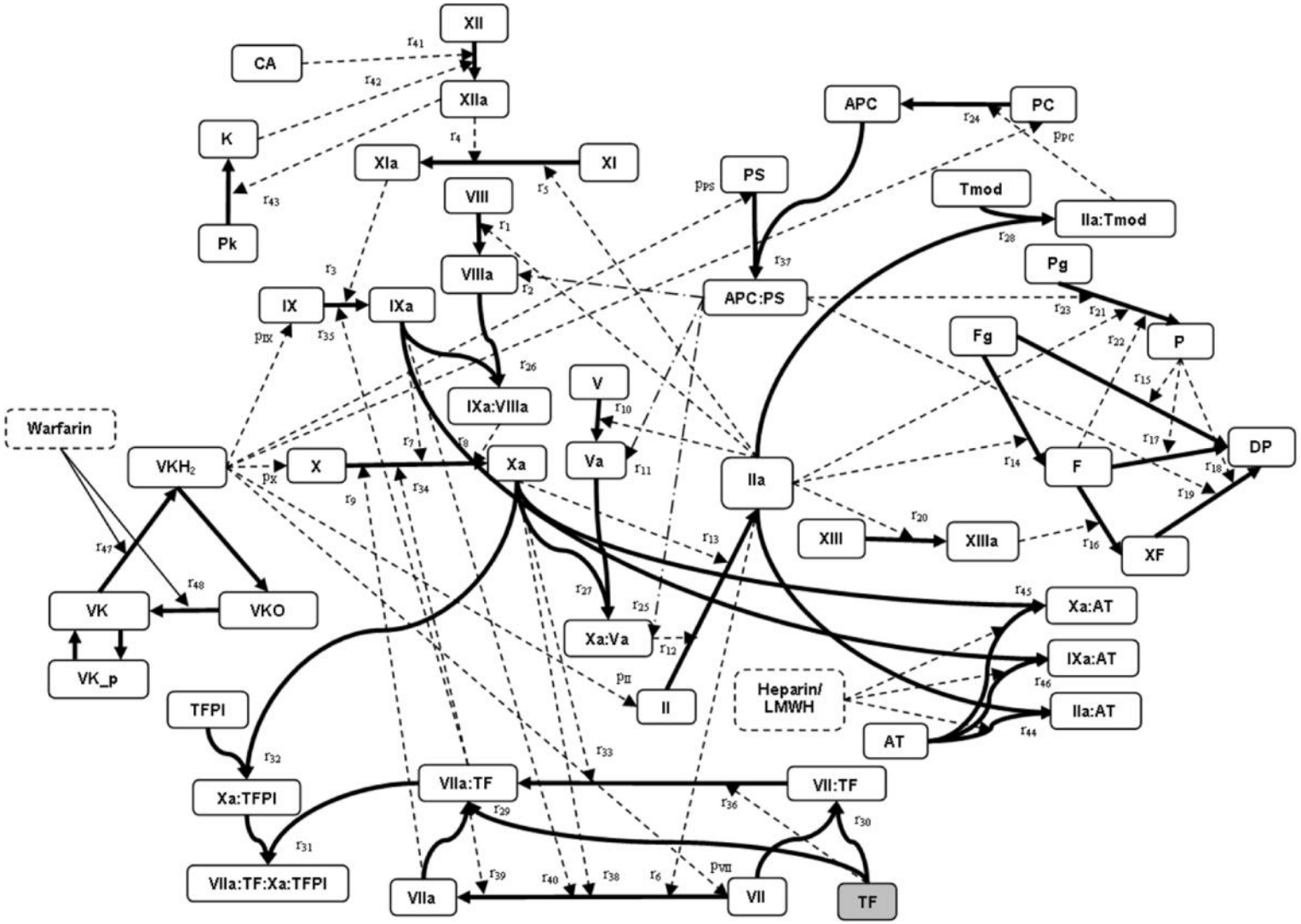
Blood coagulation





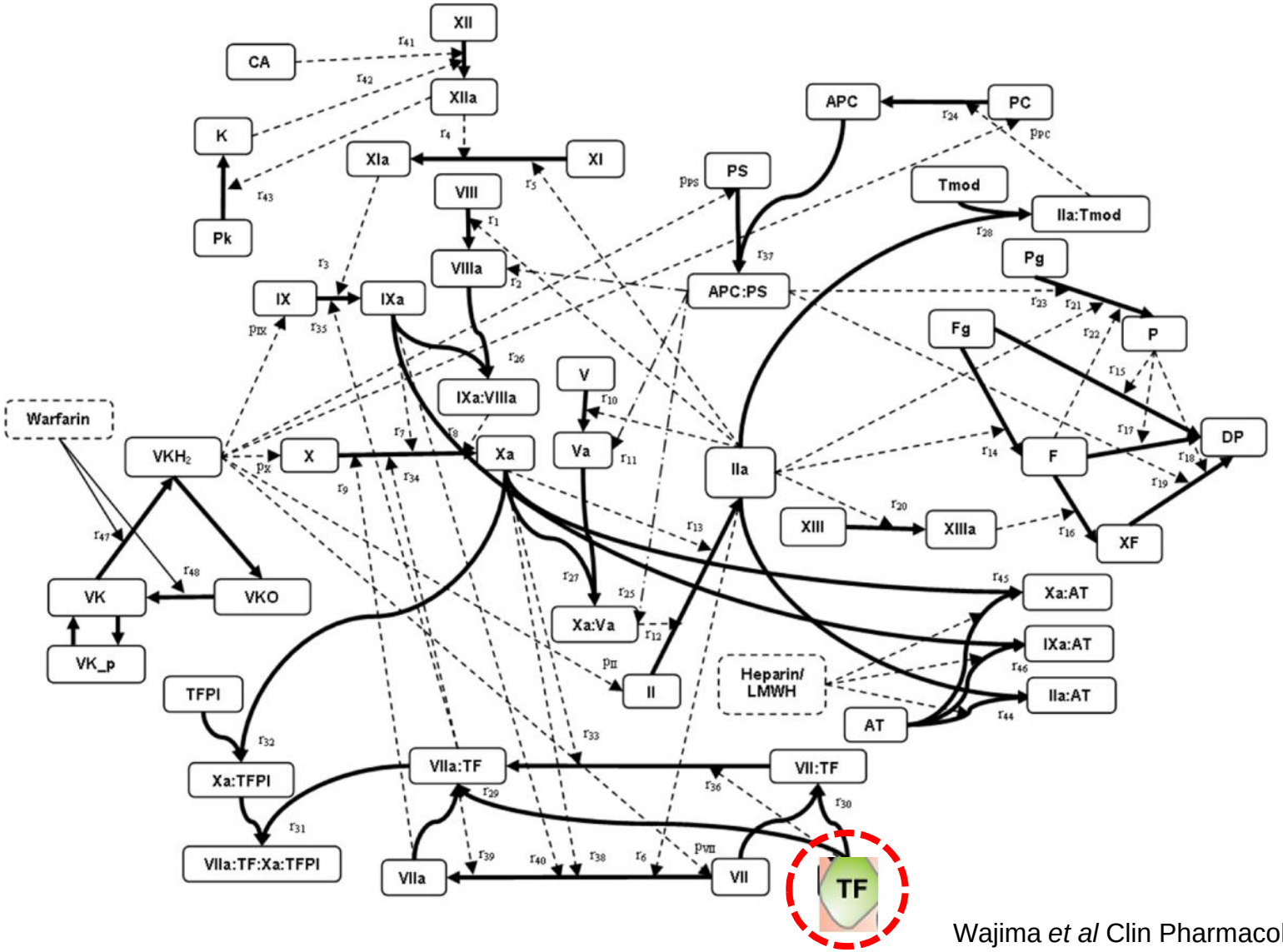


Schematic of a model for blood coagulation



Wajima *et al* Clin Pharmacol Ther 2009

Schematic of a model for blood coagulation



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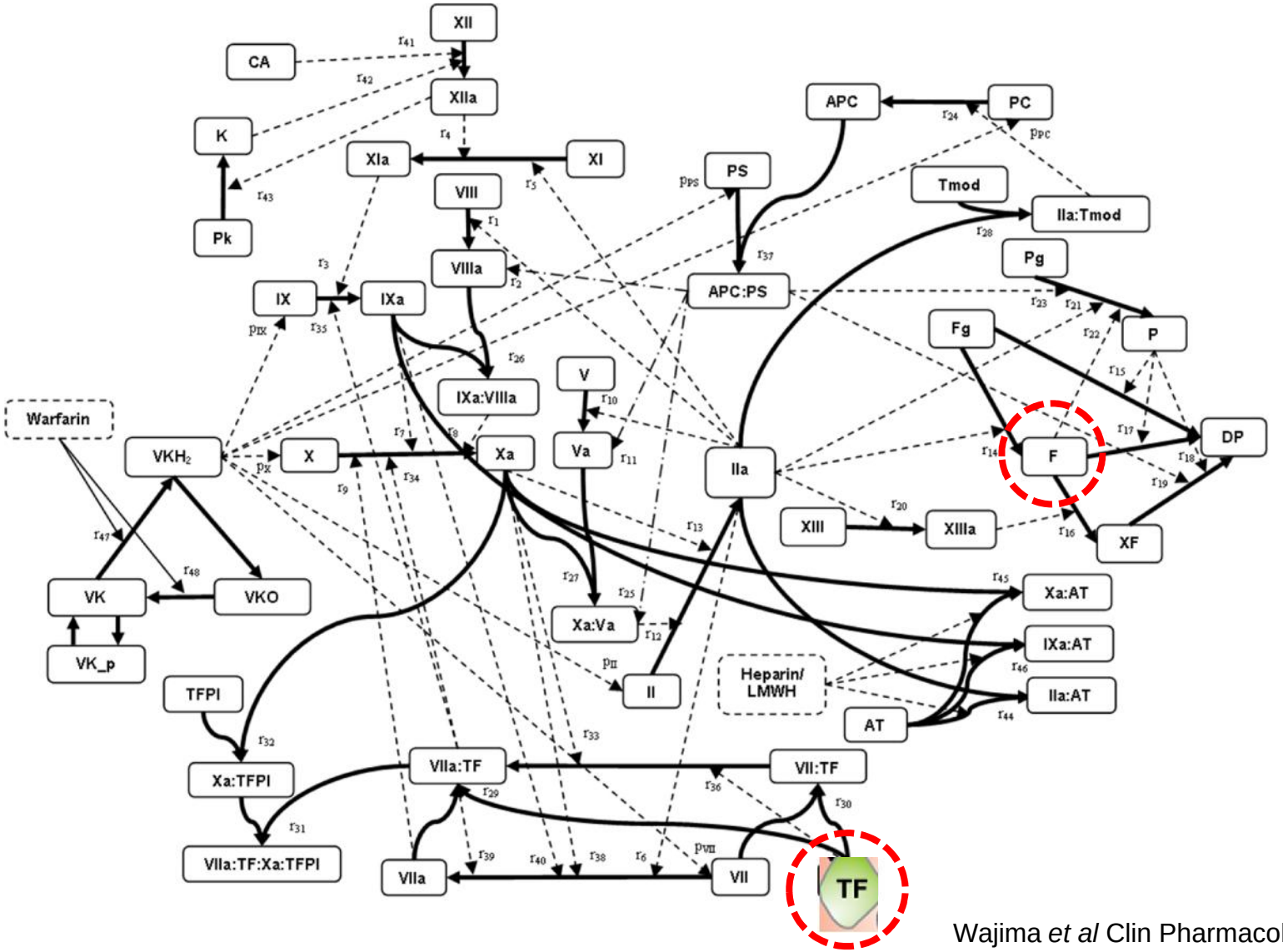

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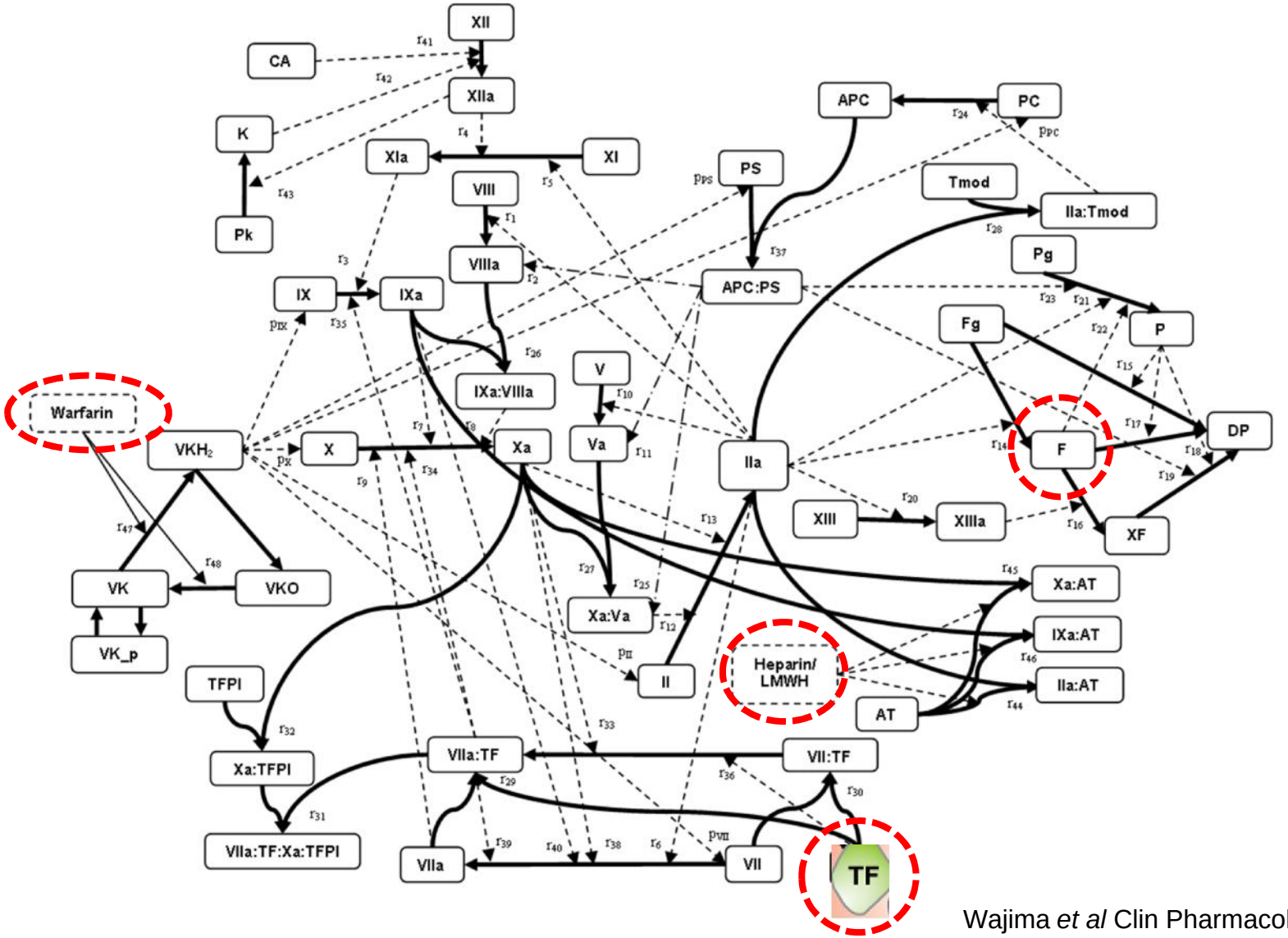
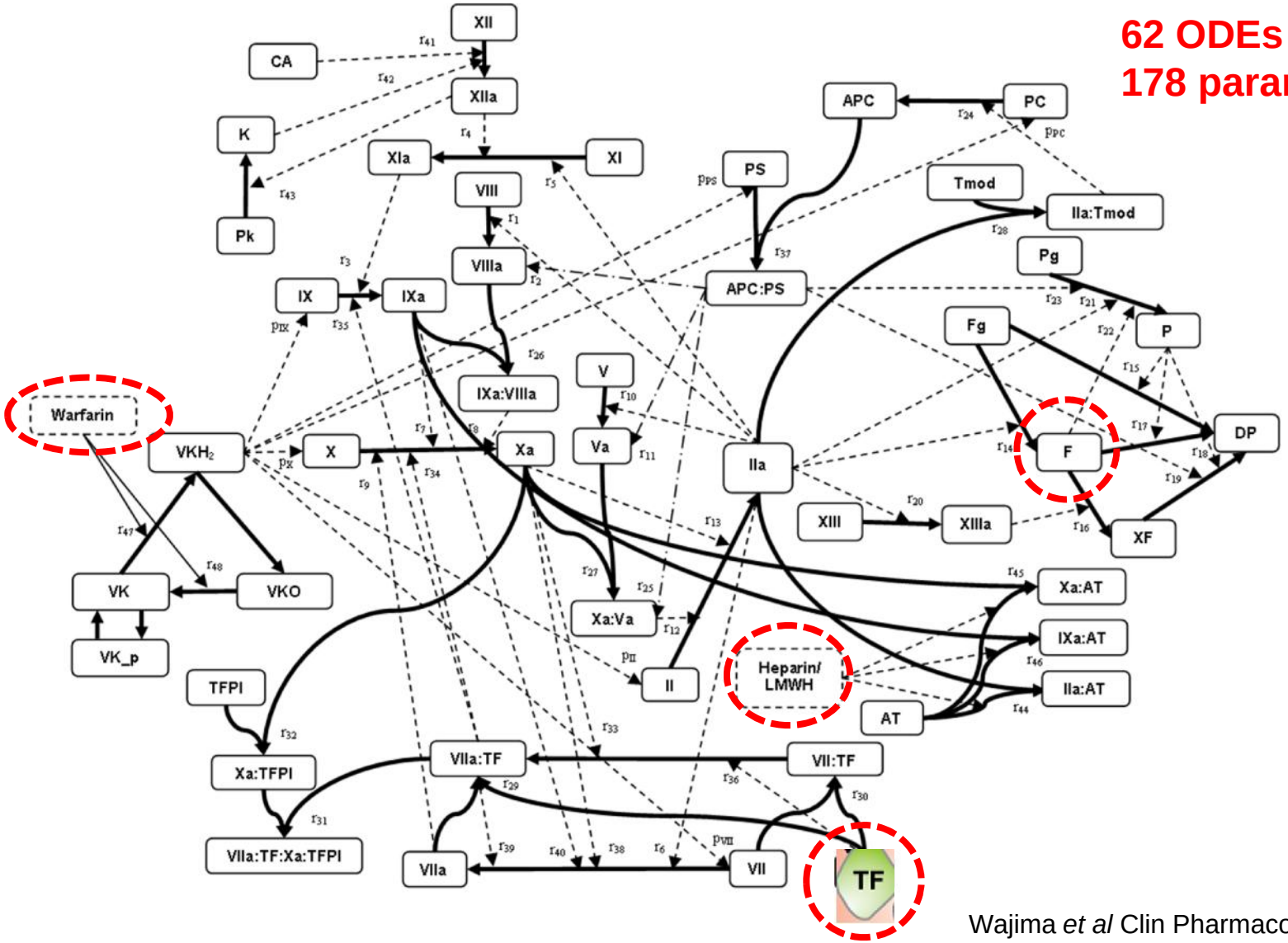


Wajima *et al* Clin Pharmacol Ther 2009

Schematic of a model for blood coagulation

62 ODEs
178 parameters



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Applications of existing systems models

- Used for simulation purposes to answer “what-if” style questions
- Have not been used for estimation purposes

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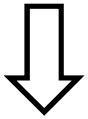


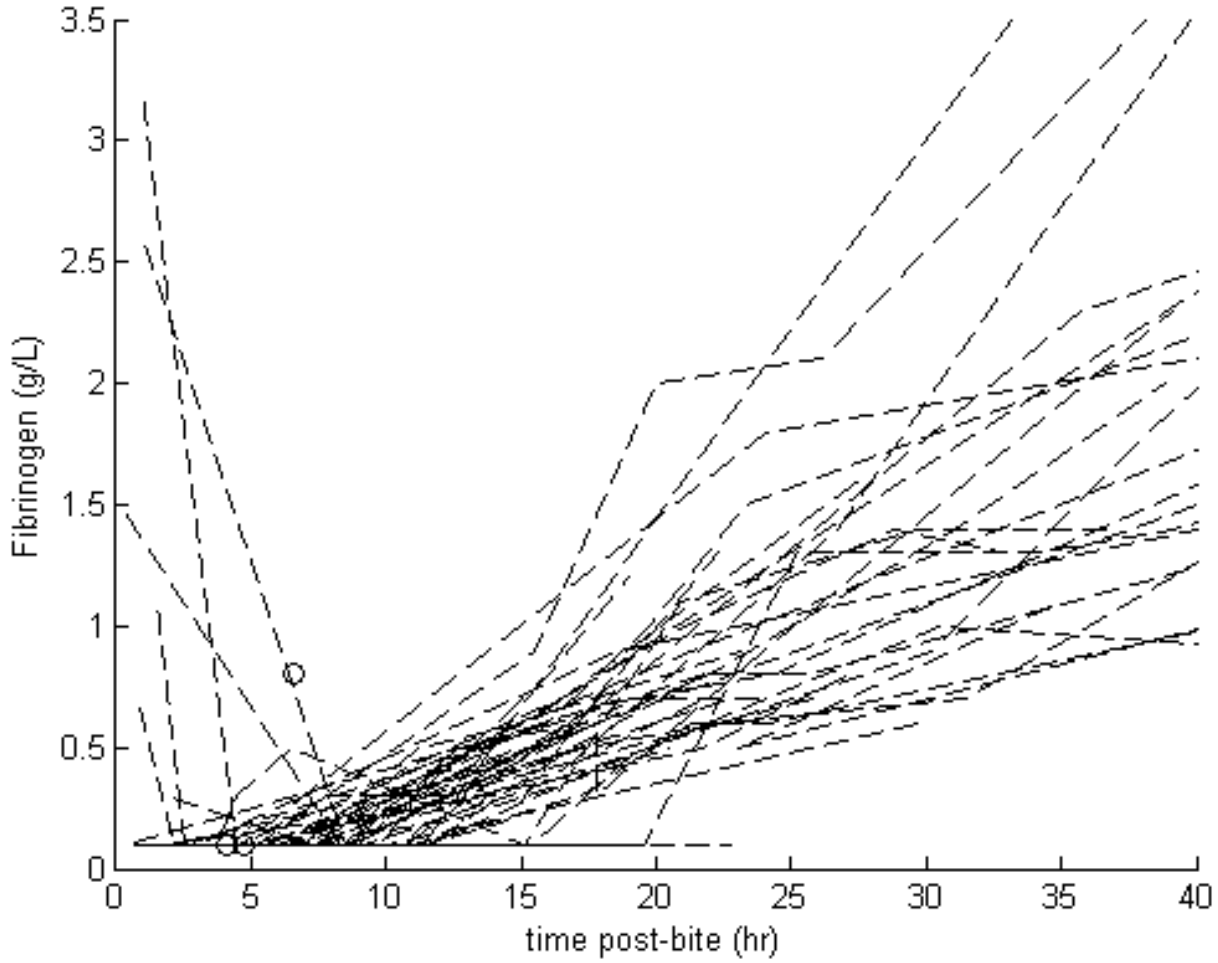
- Depending on the input-output data available, there may arise a need to simplify these models in order to reduce the number of equations as well as parameters
- The estimated parameters in that case would describe the relationship between the input and output being studied

Dataset from Australian Snakebite Project

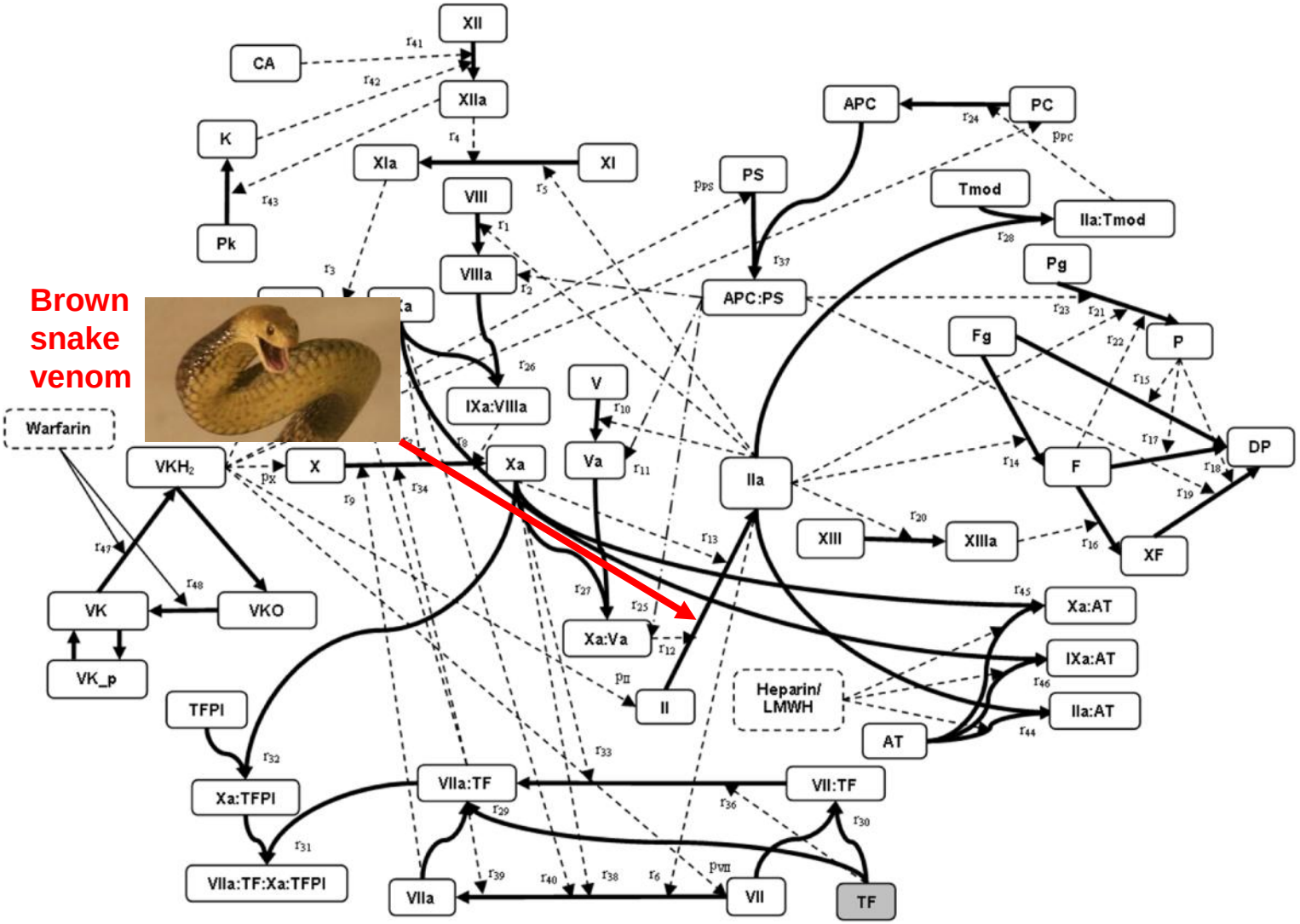
- 140 snakebite cases recruited from over 100 hospitals in Australia
- Data from bites from 8 different type of snakes
  - Brown snakes cause most number of snakebite deaths in Australia
  - 60 patients in the dataset were bitten by brown snake
- Concentration-time data for various clotting factors after snake bite
  - Including fibrinogen which is the clotting factor that is most affected

Isbister *et al* J Thromb Haemost 2010

Fibrinogen recovery after brown snake bite



Snake venoms and coagulation



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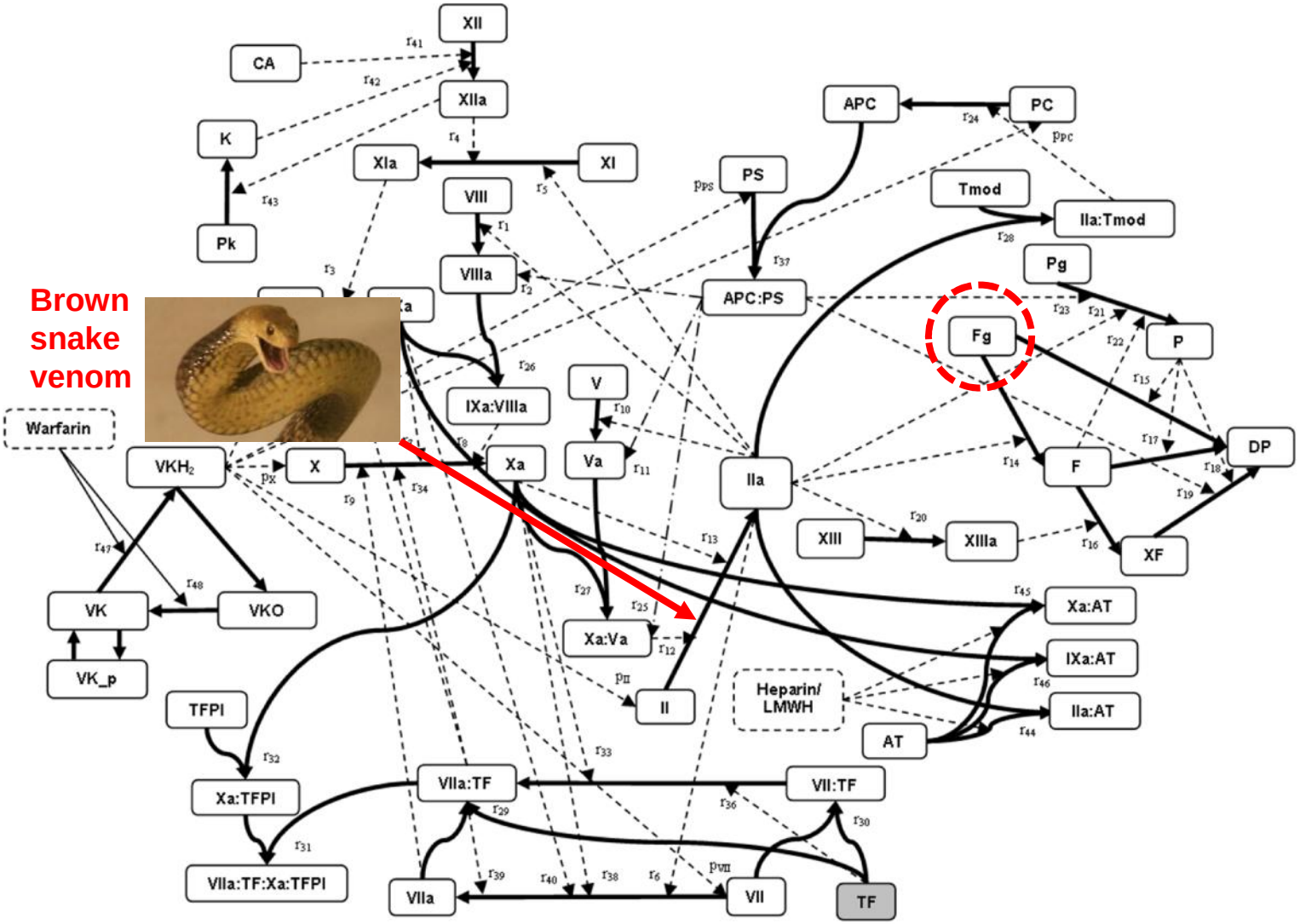

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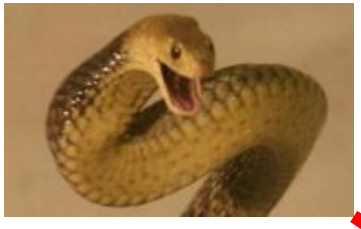
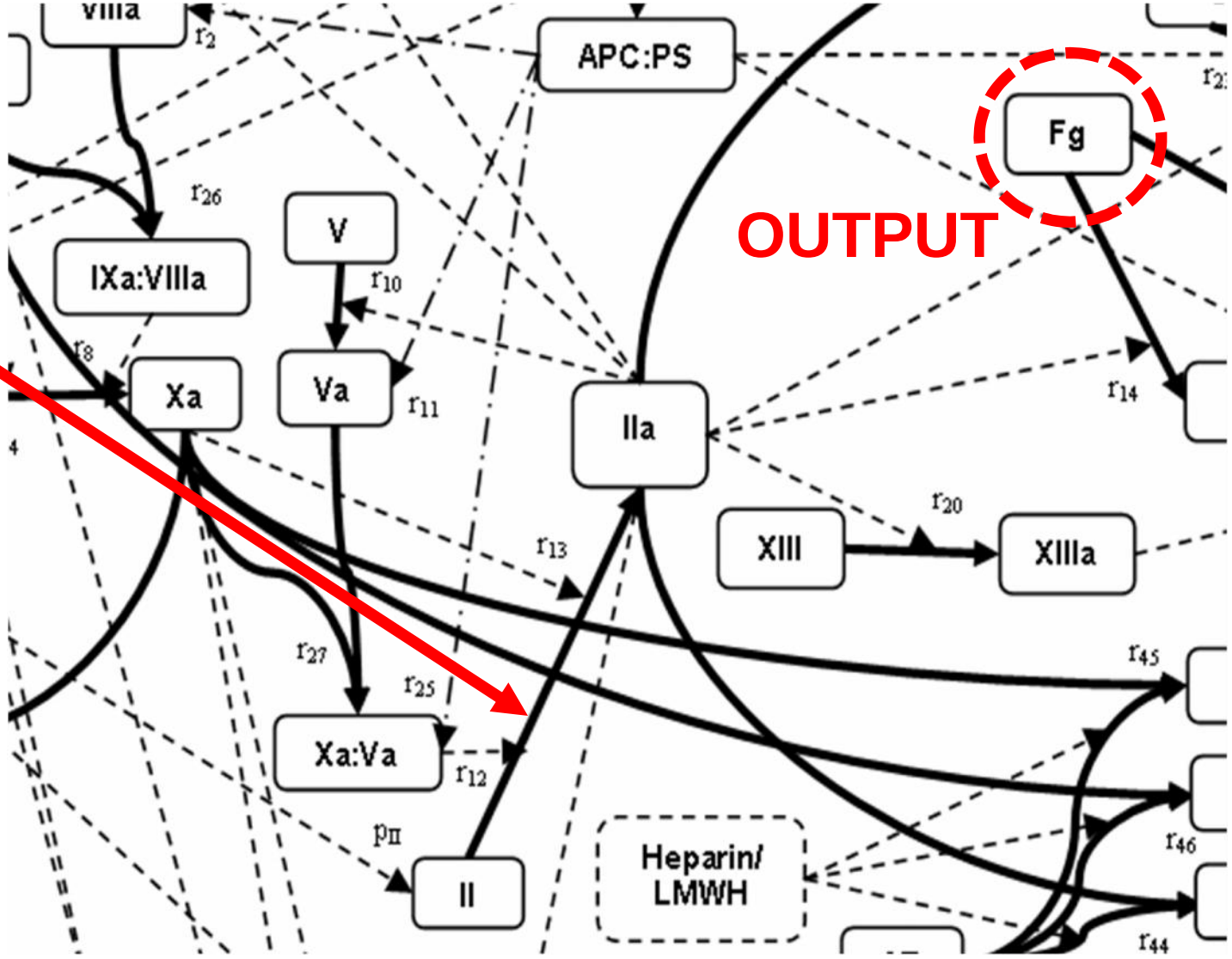


INPUT



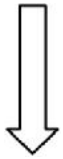
Aim and specific objectives

Aim: To explore a simplification of a coagulation systems pharmacology model for use in modelling brown snake venom-fibrinogen concentration-time data

Specific objectives:

1. To create a simplified model that mechanistically aligns with the coagulation systems pharmacology model
2. To extract the simplified model
3. To assess structural identifiability of the simplified model
4. To develop a population PKPD model for fibrinogen

Systems pharmacology model



Proper lumping
Model extraction

Input-output model

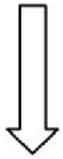
Structural Identifiability Analysis

Identifiable input-output model

Modelling

Population model

Systems pharmacology model



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Proper lumping

- A formal way of simplifying a model by merging together some of the model's states thus reducing its size

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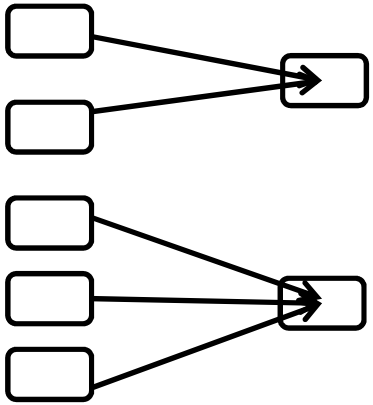

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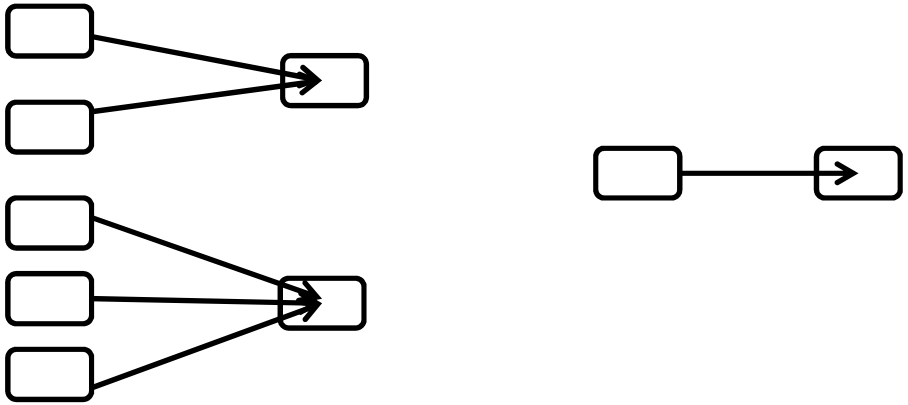

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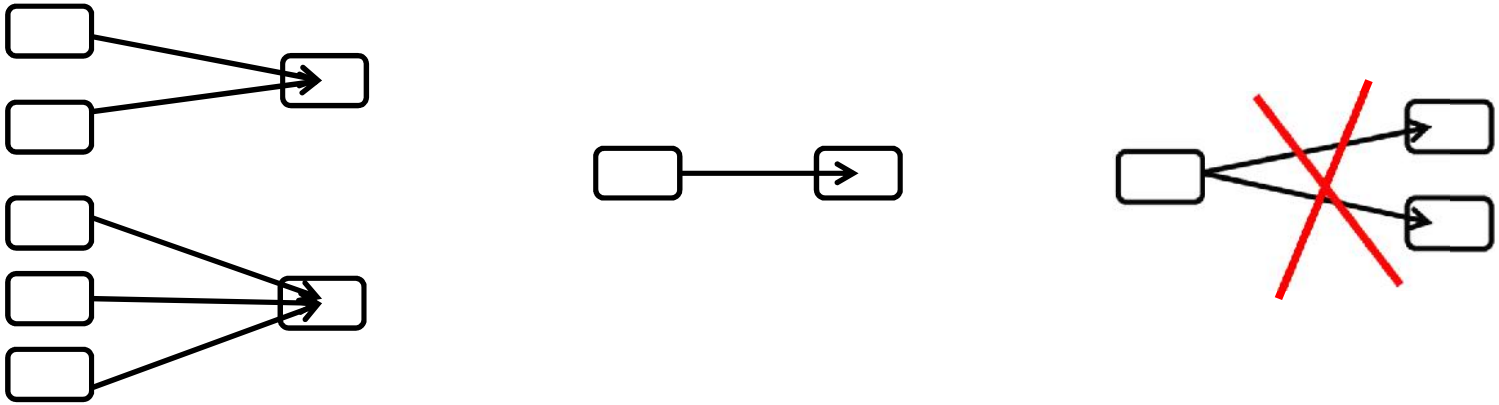

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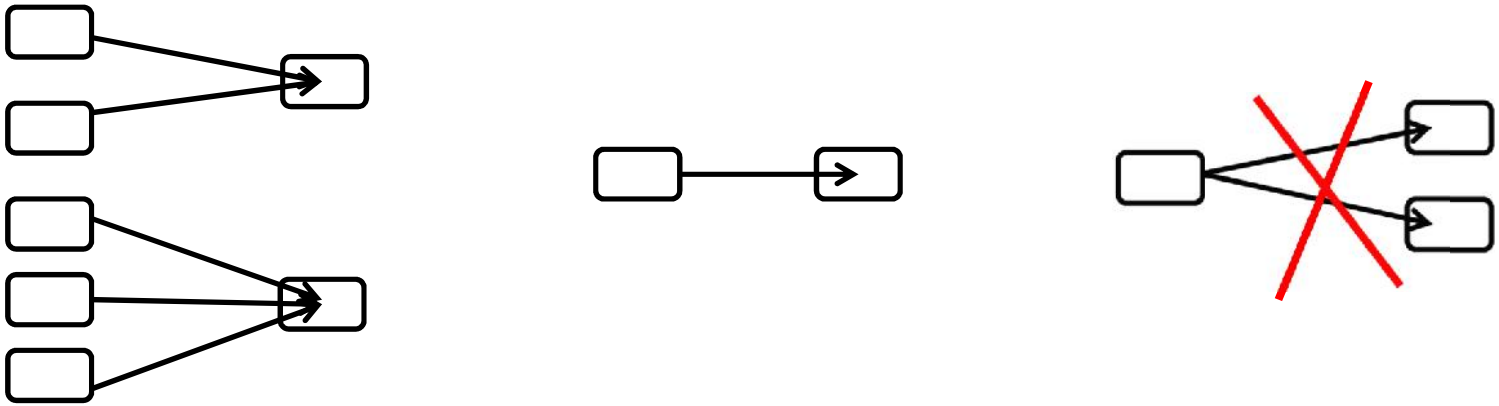

- Some constraints on the choices of states being lumped may be required
- In this work, venom and fibrinogen states were kept unlumped

Proper lumping

- Use of a method by Dokoumetzidis and Aarons[1]:

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

A lumping matrix $\mathbf{M}$ consisting of 0s and 1s and of dimension $n_L \times n$ is used to transform the vector of states of dimension $n \times 1$ to a vector of lumped states of dimension $n_L \times 1$ such that:

$$\mathbf{y_L} = \mathbf{M}\mathbf{y}$$

Inverse transformation: $\mathbf{y} = \mathbf{M}^{+}\mathbf{y_L}$

($\mathbf{M}^{+}$ = Moore-Penrose pseudo inverse of $\mathbf{M}$)

$$\mathbf{y} = \mathbf{M}^{+}\mathbf{y_L}$$

$$\downarrow$$

$$\frac{d\mathbf{y}}{dt} = f(\mathbf{y}) \rightarrow \mathbf{M}\frac{d\mathbf{y}}{dt} = \mathbf{M}f(\mathbf{y}) \rightarrow \frac{d\mathbf{y_L}}{dt} = \mathbf{M}f\left(\mathbf{M}^{+}\mathbf{y_L}\right)$$

[1]Dokoumetzidis & Aarons *IET Syst Biol* 2009

Proper lumping

Linear system	Non-linear system
Lumping formula gives parameter values of the reduced model	Lumping formula does not give parameter values of the reduced model

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Lumping formula gives parameter values of the reduced model	Lumping formula does not give parameter values of the reduced model

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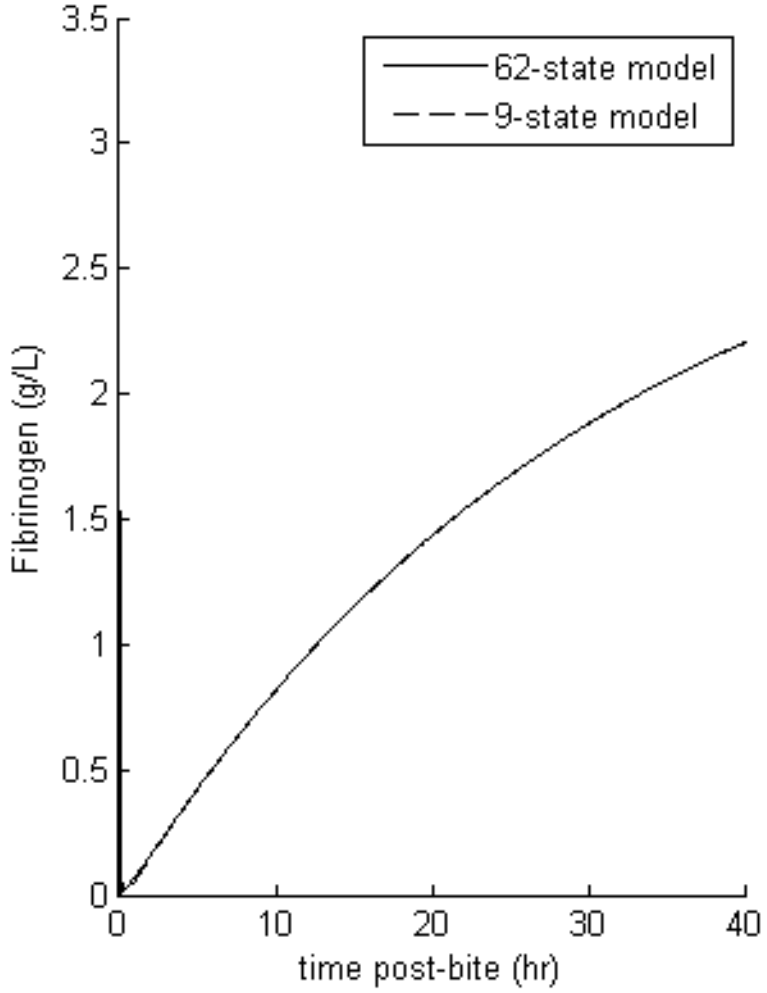
Initially, the initial conditions given by the lumping formula and the parameters of the original system were used to simplify the 62-state model

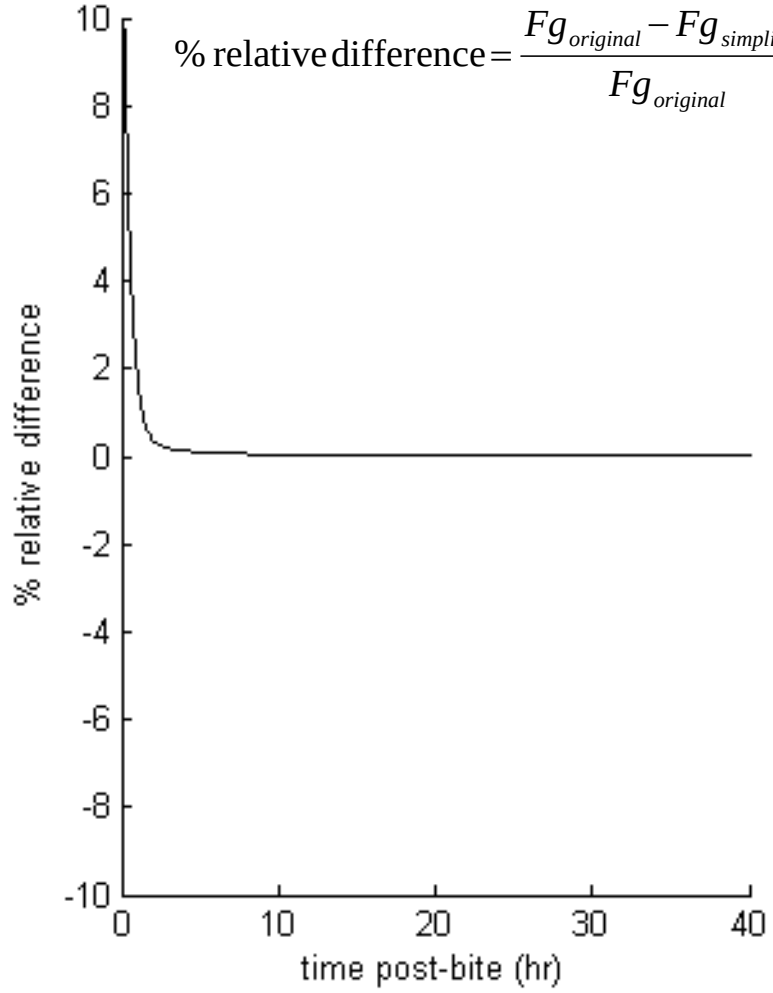
9-State model

# state in the lumped model	States	Initial conditions (nM)	Corresponding states of the original model
1L	Venom absorption state	$C_{1L}(0)=0.0075$	28
2L	Venom plasma state	$C_{2L}(0)=0$	62
3L	Fibrinogen	$C_{3L}(0)=8900$	14
4L	IIa	$C_{4L}(0)=0$	7
5L	Xa:Va	$C_{5L}(0)=0$	5
6L	Lumped state 1	$C_{6L}(0)=5600$	1, 6, 15, 17, 18, 19, 20, 24, 29, 31, 32, 33, 34, 45, 54, 55, 56
7L	Lumped state 2	$C_{7L}(0)=0.10$	2, 4, 9, 10, 13, 25, 27, 46, 52
8L	Lumped state 3	$C_{8L}(0)=2300$	3, 12, 22, 26, 40, 41, 42, 47, 51, 53
9L	Lumped state 4	$C_{9L}(0)=0.70$	8, 11, 16, 21, 23, 30, 35, 36, 37, 38, 39, 43, 44, 48, 49, 50, 57, 58, 59, 60, 61

Performance of the 9-state model



$$\%\ \text{relative difference} = \frac{Fg_{original} - Fg_{simplified}}{Fg_{original}} \times 100$$



Further simplification of the 9-state model

- Only possible by adjusting values of relevant parameter(s)
- Value of a single parameter was adjusted using trial and error
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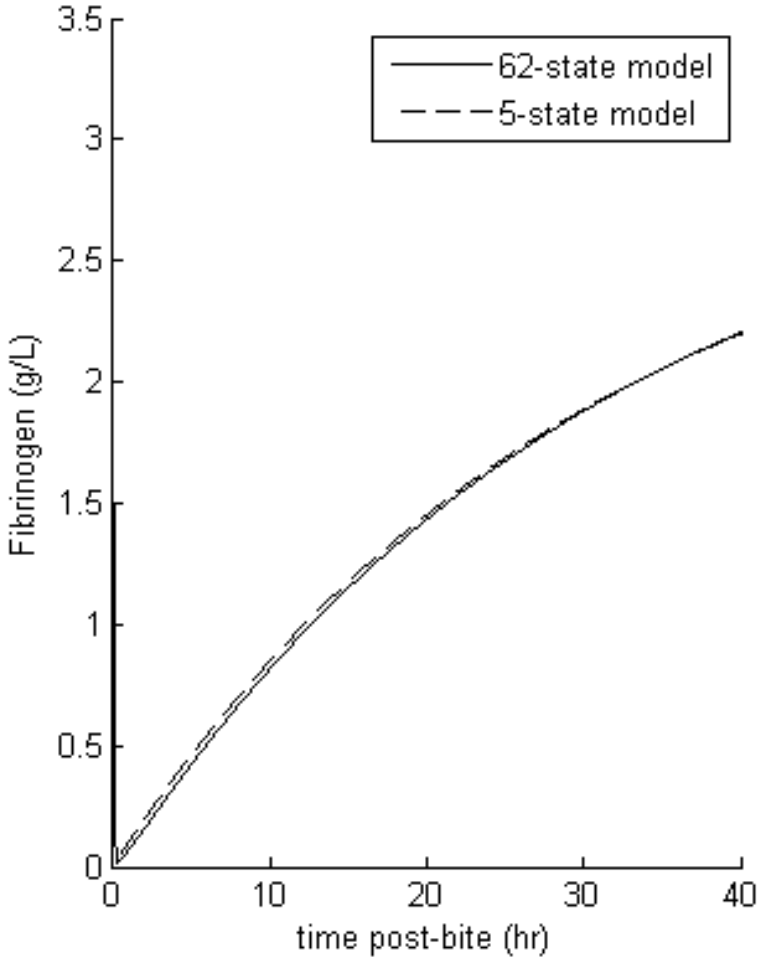
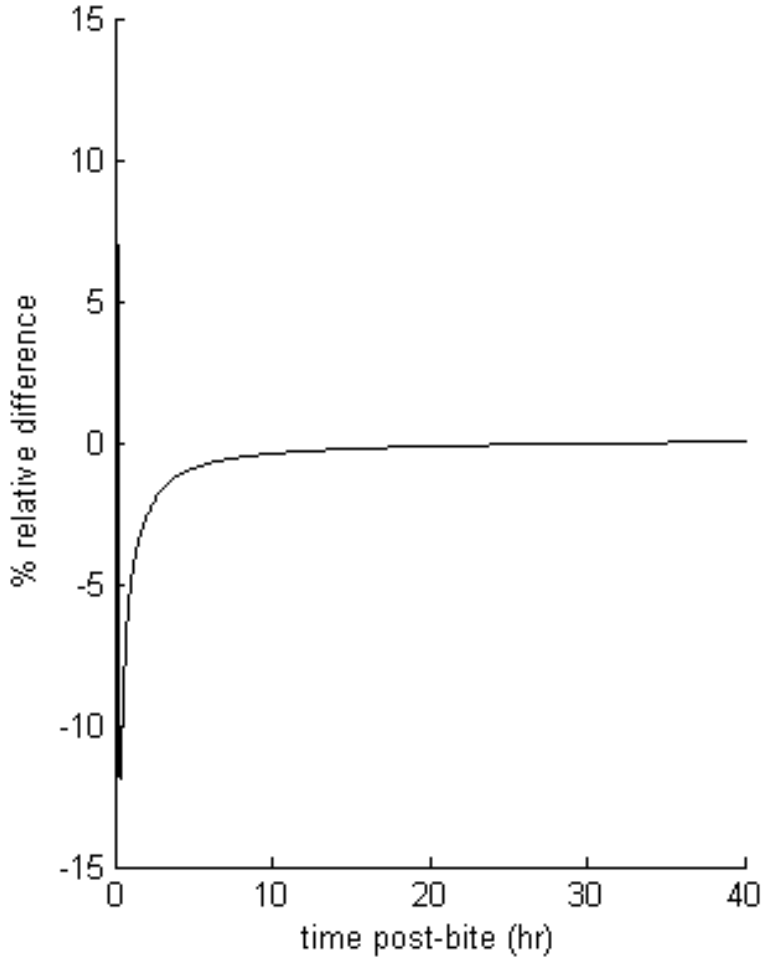
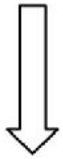
5L	Lumped state	$C_{5L}(0)=7900$	1, 2, 3, 4, 5, 6, 8, 9, 10, 11, 12, 13, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, 40, 41, 42, 43, 44, 45, 46, 47, 48, 49, 50, 51, 52, 53, 54, 55, 56, 57, 58, 59, 60, 61

Performance of the 5-state model





Systems pharmacology model



Proper lumping
Model extraction

Input-output model

Structural Identifiability Analysis

Identifiable input-output model

Modelling

Population model

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- ODEs of the unlumped states were written by eliminating the reactions that did not have any influence on the fibrinogen profile
- ODEs of the lumped states had to be explicitly written as if they had been unlumped states
- The clotting factor that was most relevant to the brown snake venom-fibrinogen relationship represented its respective lumped state

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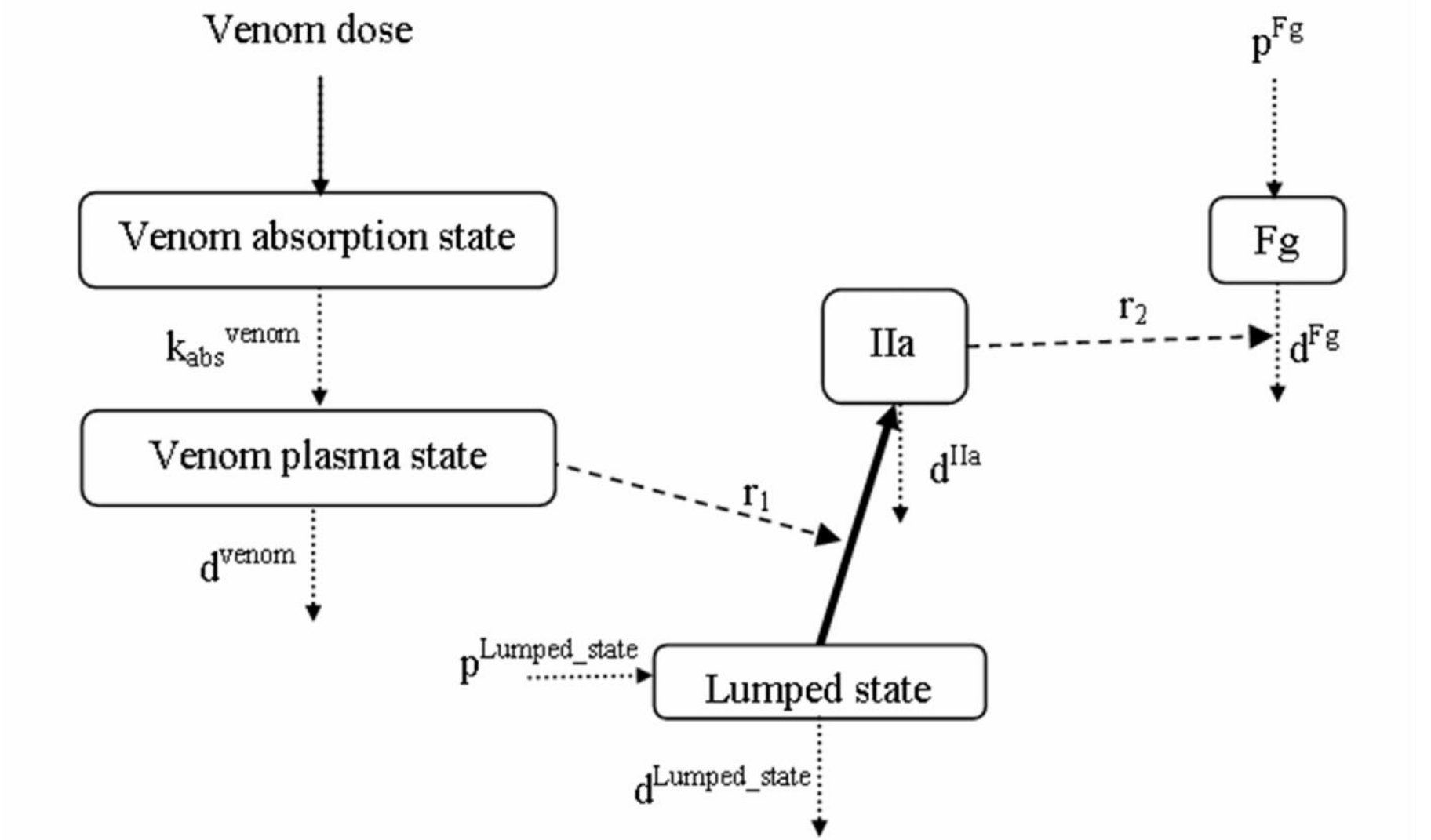
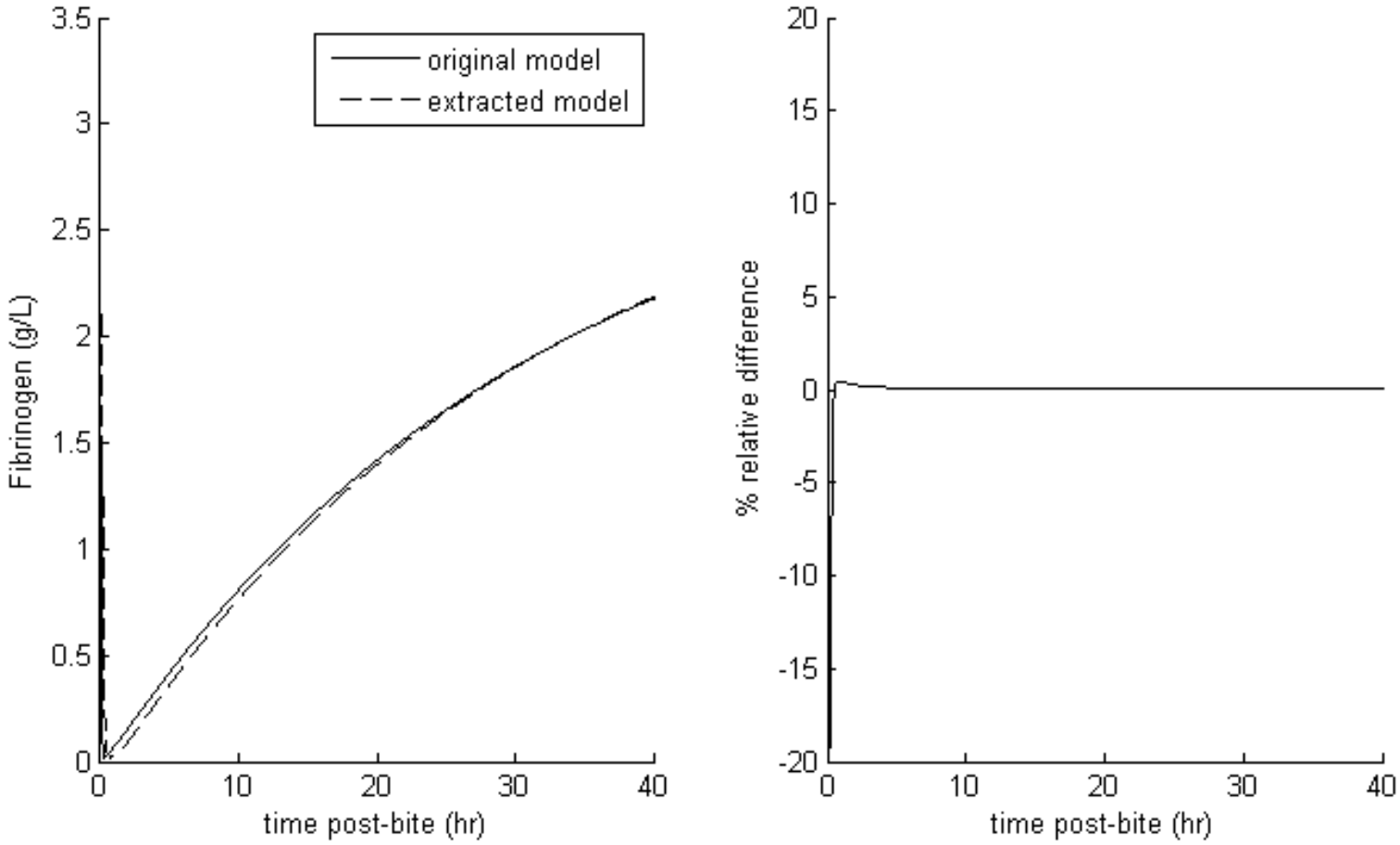
⇩

Resulted in reduction of number of parameters to 11 compared to 178 in the original model

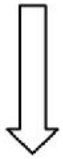
Input-output (or extracted) model



Performance of the extracted model



Systems pharmacology model



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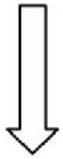

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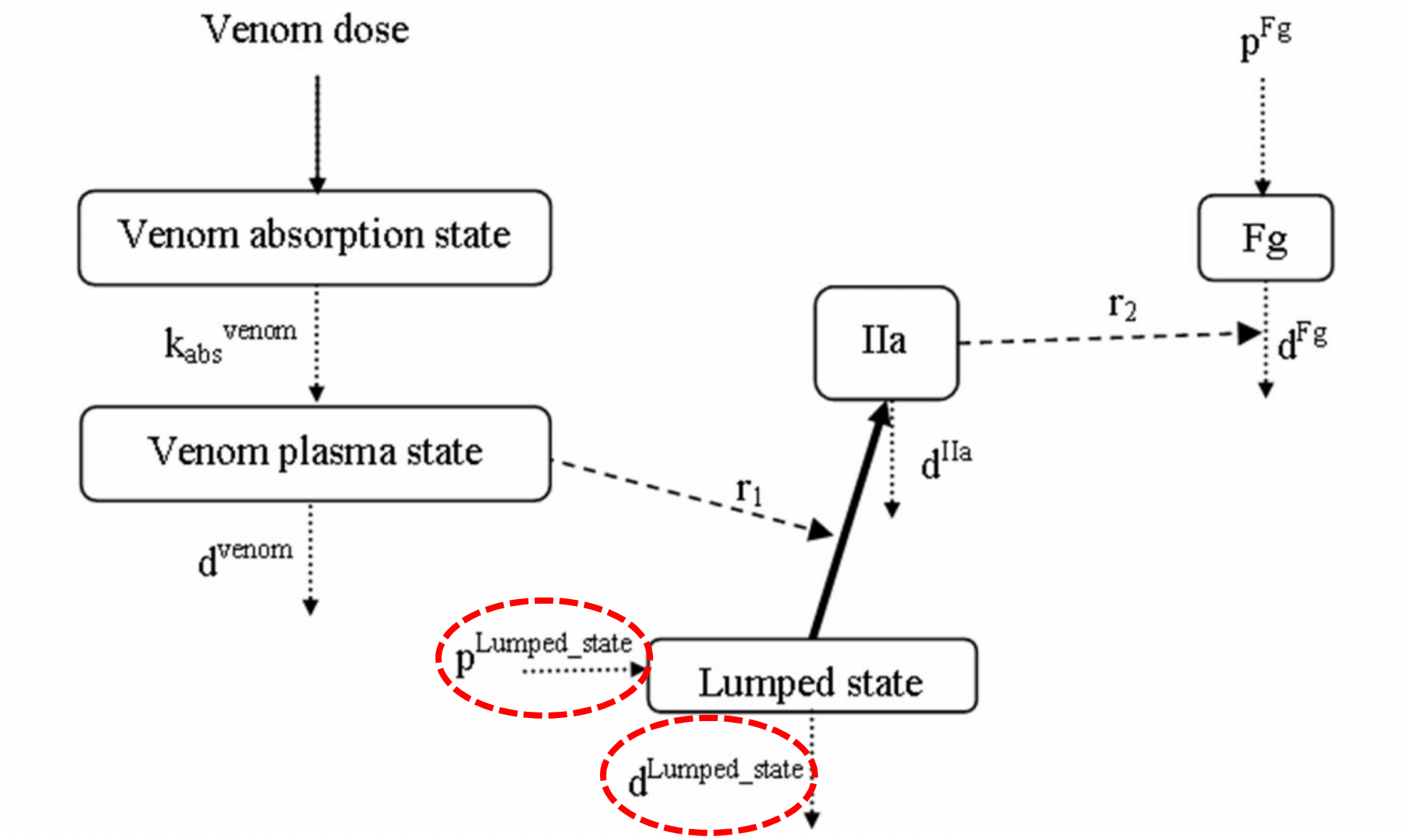
Structural Identifiability Analysis

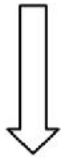
- Initial attempt with Differential Algebra for Identifiability of Systems (DAISY) was unsuccessful
- Use of a Information Theoretic Approach[1]:

[1]Shivva *et al* CPT:PSP 2013

Identifiable input-output model



Systems pharmacology model



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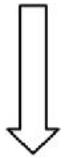

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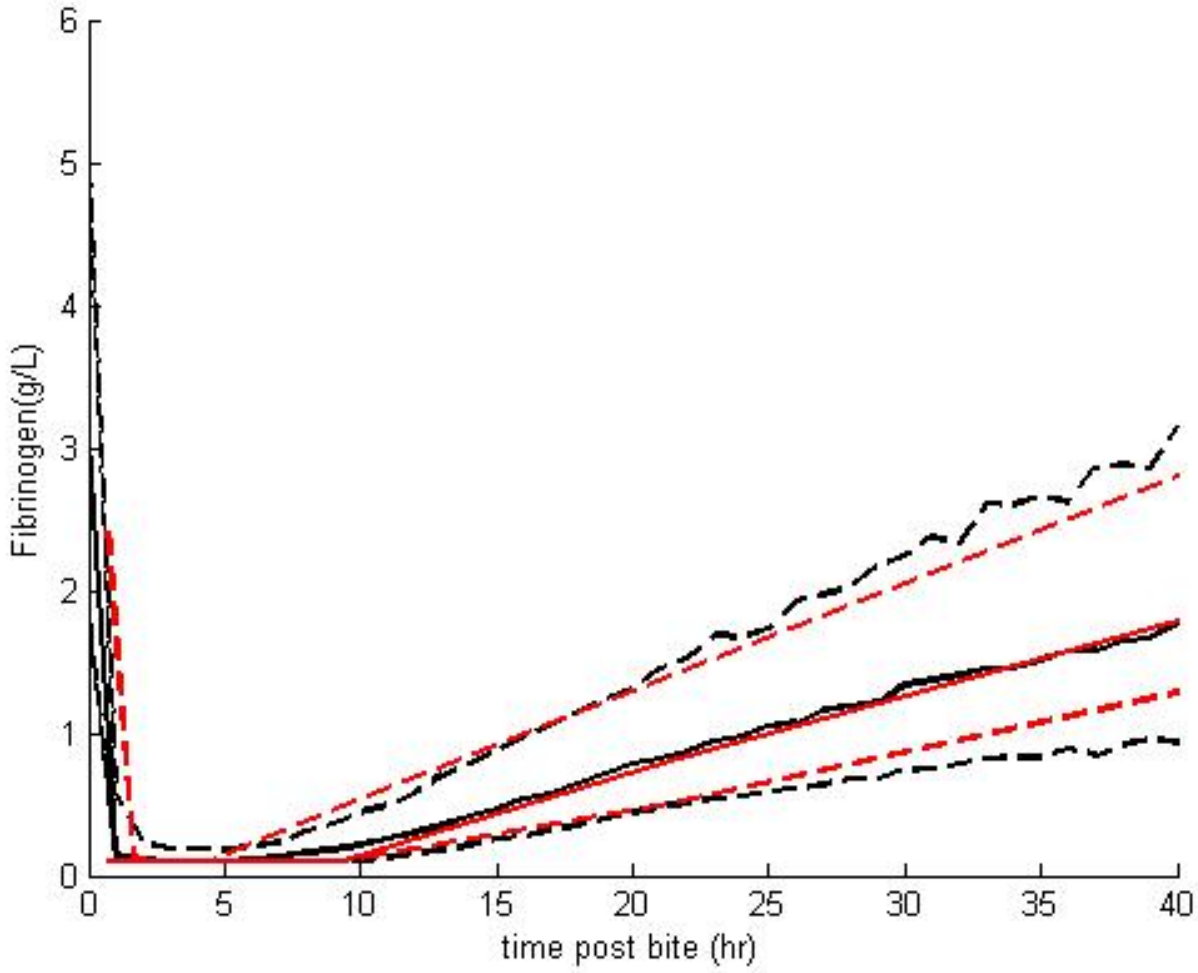
Population model

Modelling venom-fibrinogen data

- Use of a full population approach to analyse the data using NONMEM v7.2
- Identifiable input-output model was taken as the structural model; no further changes were made to the structure of the model
- Unidentifiable parameters were fixed
- BSV was considered for identifiable parameters
- A visual predictive check was used to evaluate the final model

Fibrinogen recovery after brown snake bite



Fibrinogen recovery after brown snake bite

- Half-life of fibrinogen = 1.5 days
- Half-life of brown snake venom = 1 hour

refers to the activator in the venom affecting coagulation and not to the venom as a whole

Discussion

- A complex coagulation model was able to be simplified using proper lumping
- The simplified model retained a clear interpretation of the input-output relationship as seen with the original model
- The parameters of the simplified model that could be estimated precisely were able to be identified using structural identifiability analysis

Discussion

- The model simplification technique used in this study:
  - can be applied to other input-output relationships, e.g. warfarin to INR
  - can be used with other systems pharmacology models (e.g. diabetes models) in order to obtain a simplified mechanistically driven model that can be used as the basis for rapid model building for analysis of new clinical studies

- The technique will need to be automated to consider the possible combinations

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