A novel measure of importance of state variables for model reduction: results for the blood coagulation network

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Motivation

An increasing understanding of complex processes in pharmacology has led to large-scale mechanistic models. These models, however, are not suitable for the analysis of sparse clinical data due to parameter identifiability issues. A potential solution is to reduce the complexity of the system using model reduction techniques. While many purely computational approaches exist, a quantity that gives insight into the model reduction process by quantifying the importance of a given state for the systems dynamic is still lacking.

Objective: Introduction of a novel measure of importance for nonlinear systems – the input-response indices

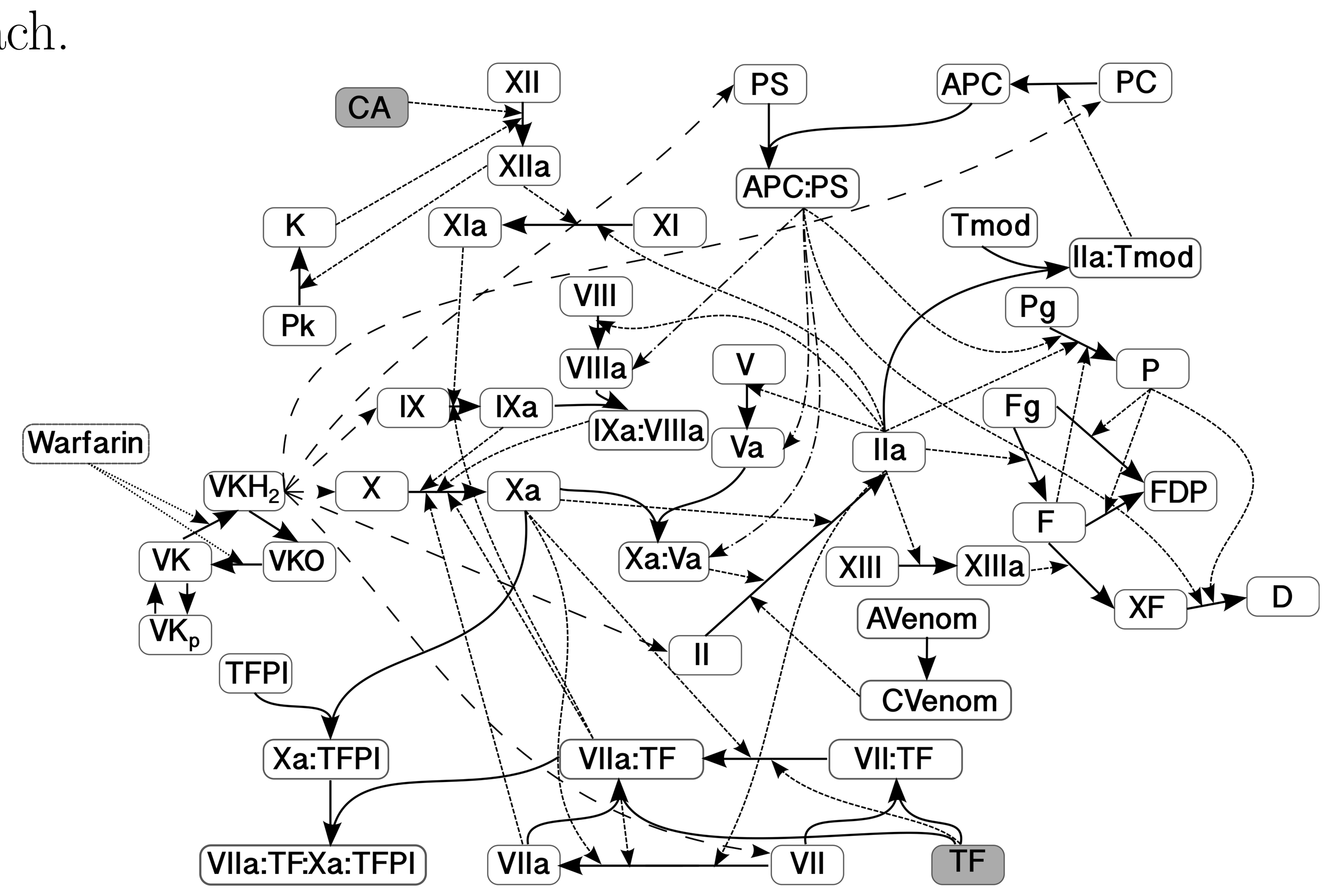
Methods

By considering the drug administration or some other entity as a model input u and the drug effect or some surrogate as the output, we obtained the following control-theoretical input-output problem setting.

$$\frac{\mathrm{d}x(t)}{\mathrm{d}t} = f\big(x(t)\big), \quad x(0) = x_0 + u$$
$$y(t) = h\big(x(t)\big)$$

where $x(t)$ are the states variables and t denotes time. The function f represents the systems pharmacology model of interest, and the function h extracts from the state vector $x(t)$ the output $y(t)$ of interest.

We used the blood coagulation network model [3, 2] to illustrate our approach.



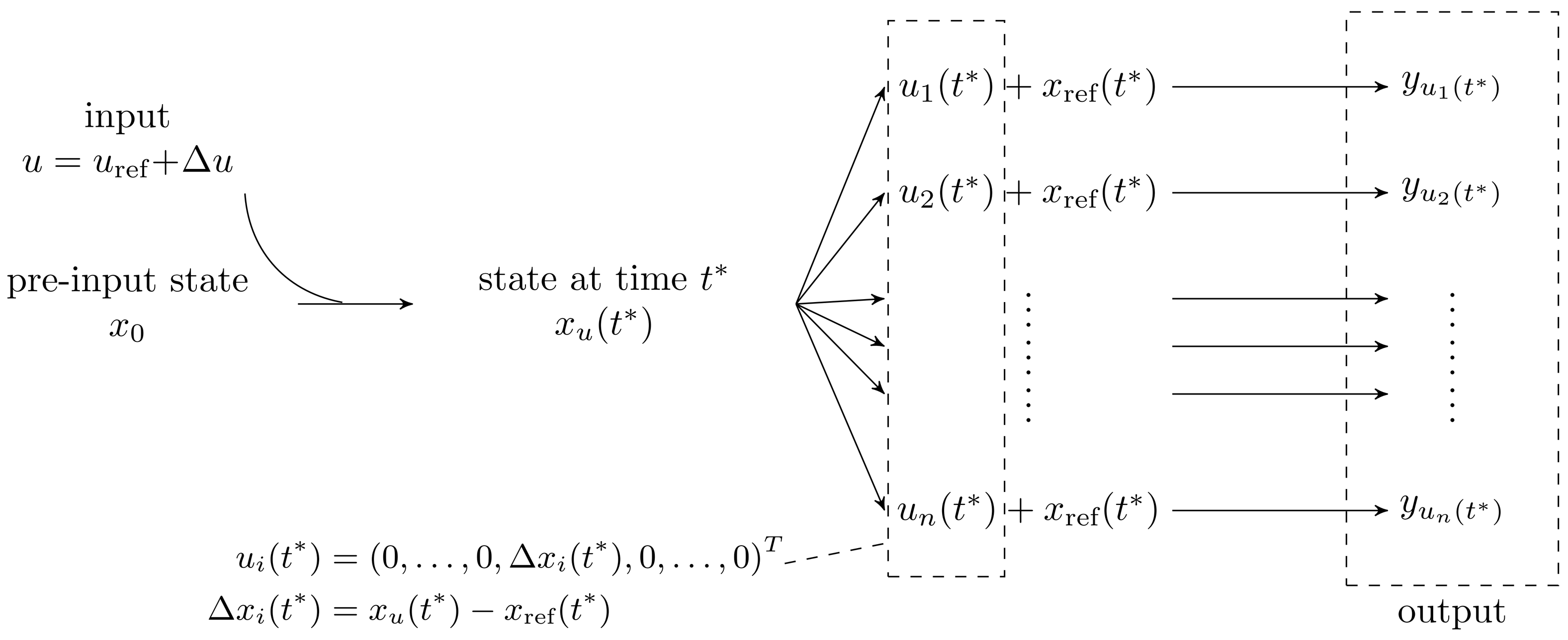
Results

Derivation of input-response indices

We aim to introduce a measure that quantifies the importance of a given state x_i for the input-response relationship relative to a reference trajectory x_{ref} and reference output $y_{\text{ref}} = h(x_{\text{ref}})$.

The input-response indices are based on two constituents that characterise

1) to what extent the input has an impact on the state x_i at some time $t^* \in [0, t_{\text{end}}]$ ('How does the input affect a state?')
2) to what extent variations in x_i impact the output y on the remaining time interval $[t^*, t_{\text{end}}]$ ('How does a state impact the output?')



Definition of the input-response index

The **input-response index** ir_i of the ith state at time t^* is defined by:

$$\text{ir}_i(t^*) = \left(\frac{1}{N} \sum_{\Delta u \in \mathcal{U}} \frac{1}{Z_u} \int_{t^*}^{t_{\text{end}}} \left| y_{u_i(t^*)}(t) - y_{\text{ref}}(t) \right|^2 \mathrm{d}t \right)^{\frac{1}{2}},$$

where Z_u denotes a normalisation constant and N the number of initial perturbations of the reference input.

Input-response indices for the PT test: Impact of the input on the resulting reduced model

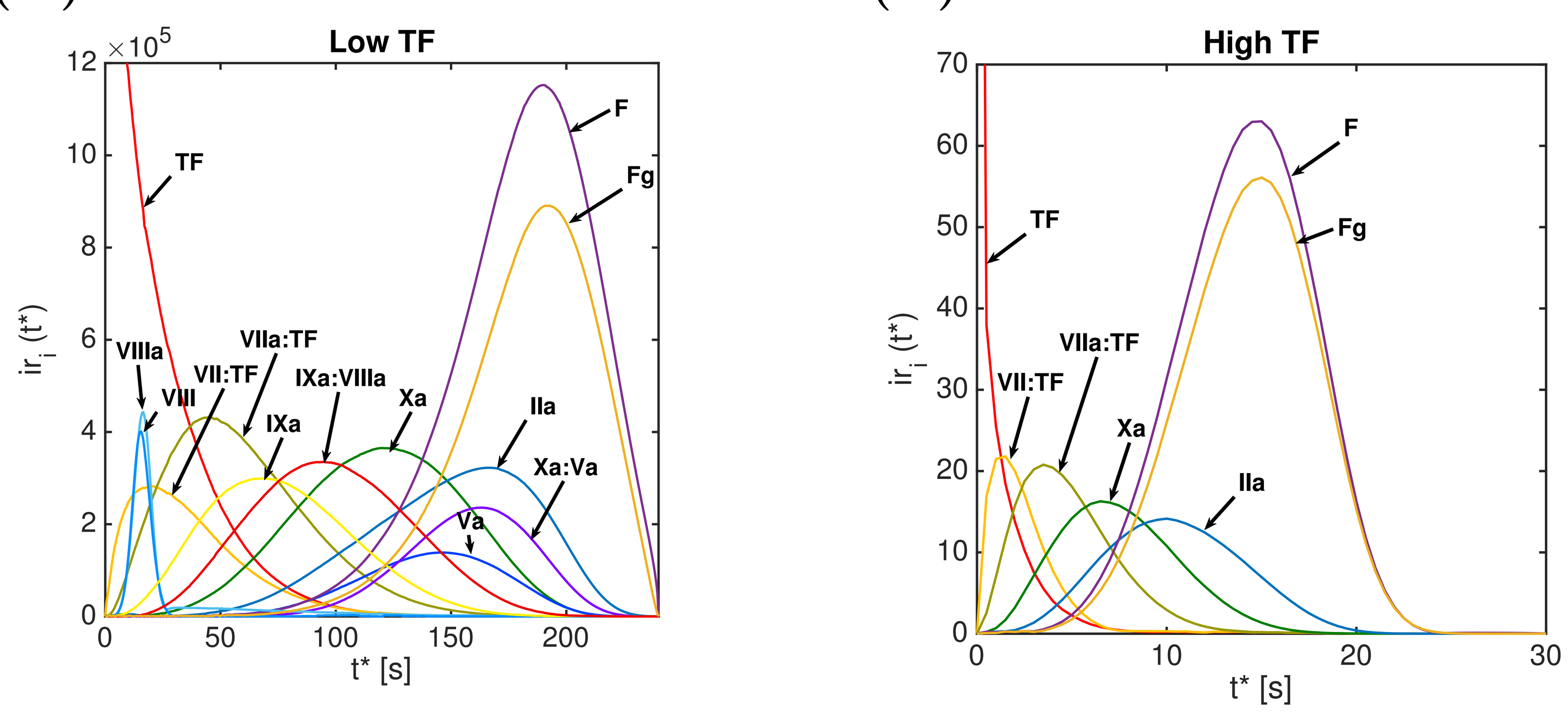
The prothrombin time (PT) test is an *in vitro* test quantifying the activity of the extrinsic pathway initiated by the addition of the tissue factor (TF).

Input: initial TF concentration
Output: fibrin concentration

The reference systems were chosen to be the dynamics of the PT test with

Scenario	initial TF conc.	time interval
low TF (Fig. A)	5pM	[0,240s]
high TF (Fig. B)	100nM	[0,30s]

(A) **(B)**

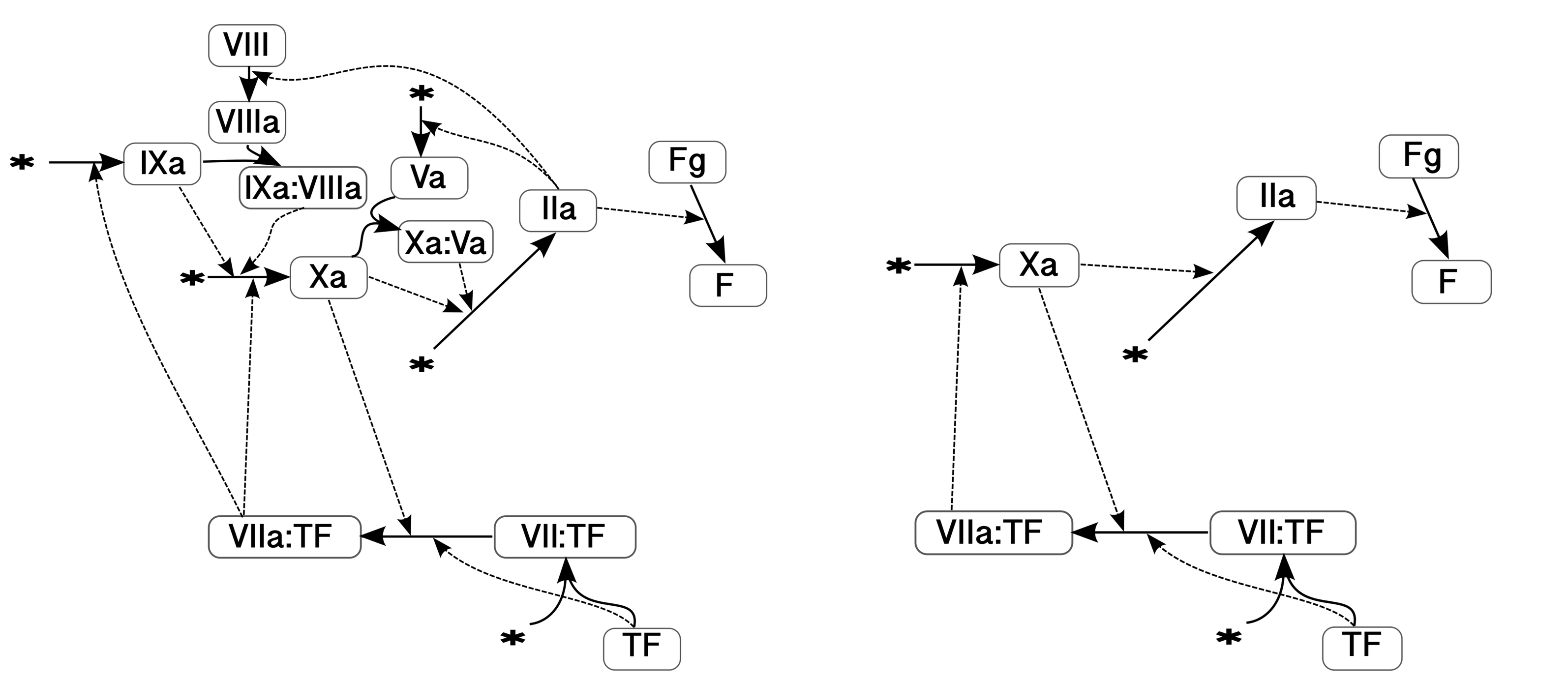


Reduced models based on input-response indices

A first automated model reduction technique:

i) compute input-response indices ir_i
ii) test all states recursively for elimination in the order of increasing maximal ir_i value by considering them as
   - **environmental states:** considered to be constant in time and identical to their initial value **or**
   - **negligible states:** considered unimportant and set to be constant zero, thereby neglected in the model.

(A) Low TF **(B) High TF**



The results confirmed findings in [1] that the low TF but not the high TF PT test is sensitive to detecting genetic deficiencies of factor VIII and IX. The original model with 62 states was reduced to 13 state model for low TF (Fig. A) and 8 state model for the high TF (Fig. B).

Conclusion

The novel measure of importance is a powerful tool for model reduction of nonlinear models that provides further insight into the system dynamics.

Literature

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[2] A. Gulati, G. K. Isbister, and S. B. Duffull. Scale reduction of a systems coagulation model with an application to modeling pharmacokinetic-pharmacodynamic data. *CPT: pharmacometrics & systems pharmacology*, 3(October 2013):e90, Jan. 2014.
[3] T. Wajima, G. Isbister, and S. Duffull. A Comprehensive Model for the Humoral Coagulation Network in Humans. *Journal of Clinical Pharmacology and Therapeutics*, 86:290–298, 2009.

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