Focusing on the essential dynamics of systems pharmacology models by exploiting an input-response characterisation

Jane Knöchel[1,2,4], **Charlotte Kloft**[3], **Wilhelm Huisinga**[1]

1. Computational Physiology Group, Institute of Mathematics, Universität Potsdam, Germany
2. PharMetrX Graduate Research Training Program, Freie Universität Berlin and Universität Potsdam, Germany
3. Department of Clinical Pharmacy and Biochemistry, Institute of Pharmacy, Freie Universität Berlin, Germany
4. Current address: AstraZeneca RD, Mölndal, Sweden

Motivation

Continuous insight into biological processes has led to the development of large-scale, mechanistic systems biology models of pharmacologically relevant networks. While these models are typically designed to study the impact of diverse stimuli or perturbations on multiple system variables, the focus in pharmacological research is often on a specific input, e.g., the dose of a drug, and a specific output related to the drug effect or response in terms of some surrogate marker. To study a chosen input-output pair, the complexity of the interactions as well as the size of the models hinders an easy access and understanding of the details of the input-output relationship.

Objectives:

1. **Introduction of a novel measure of importance for state variables**
2. **Reduction of systems pharmacology models to their essential functionality based on the introduced measure of importance**

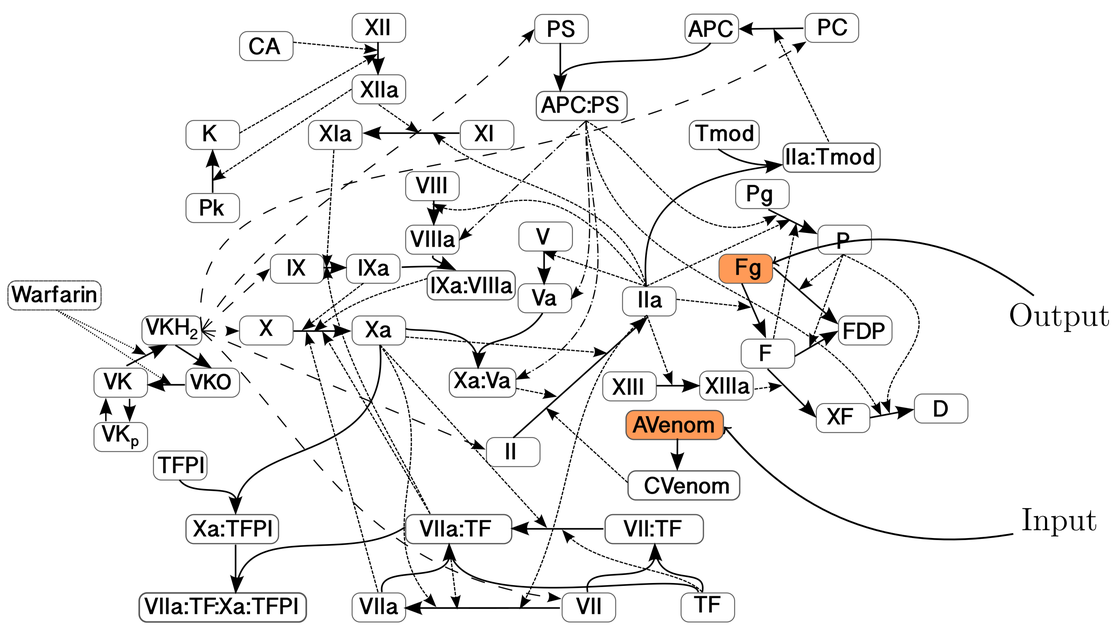
Methods

By considering the drug administration or some other entity as a model input u and the drug effect or some surrogate as the output y, 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 time-dependent state variables. The function f represents the systems pharmacology model of interest, and the function h maps the state vector $x(t)$ to the output $y(t)$ of interest.

We have chosen the blood coagulation network model [3, 1], in specific the brown snake venom-fibrinogen relationship, to illustrate our approach.



Results

Derivation of sensitivity based 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 $y_{\mathrm{ref}} = h(x_{\mathrm{ref}})$.

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

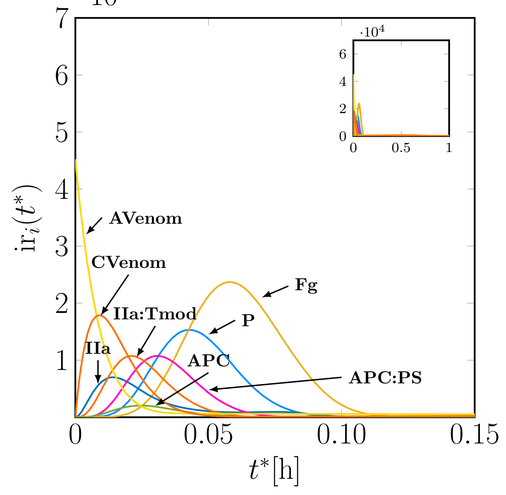
1) to what extent the input has an impact on the state x_i at some time $t^* \in [0, t_{\mathrm{end}}]$ ('How does the input affect a state?')
   Characterised by $\partial \left[\Phi^{t^*,0} x\right]_i / \partial x_j \Big|_{x=x_0}$
2) to what extent variations in x_i impact the output y on the remaining time interval $[t^*, t_{\mathrm{end}}]$ ('How does a state impact the output?')
   Characterised by $\partial \left[\Phi^{t,t^*} x\right]_o / \partial x_i \Big|_{x=x_{\mathrm{ref}}(t^*)}$

Definition of the input-response index

The **input-response index** ir_i of the ith state at time t^* is then defined as the product of two sensitivity coefficients:

$$\mathrm{ir}_i^2(t^*) = \int_{t^*}^{t_{\mathrm{end}}} \left(\mathcal{S}_{o,i}(t, t^*)\right)^2 dt \cdot \mathcal{S}_{i,j}(t^*, 0)^2 \text{ with } \mathcal{S}_{i,j}(t, s) = \frac{\partial \left[\Phi^{t,s} x\right]_i}{\partial x_j}\Big|_{x=x_{\mathrm{ref}}(s)}$$

Input-response indices of the brown snake venom-fibrinogen system during the first hour after envenomation

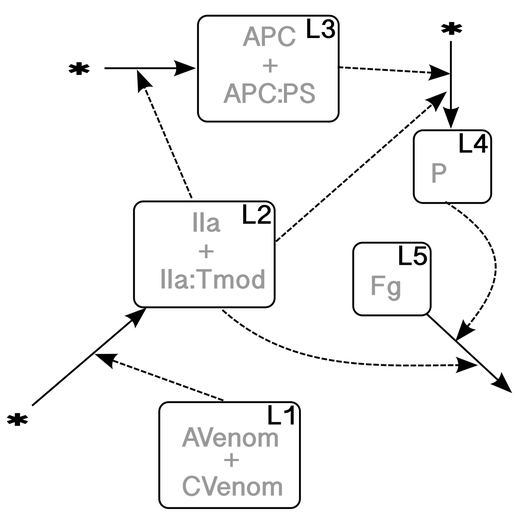


- insight into coordinate action of state variables → most relevant path is elucidated
- indices dependent on initial state (important feature)
- different factors are only relevant during certain time windows

Two-step automated model reduction technique based on input-response indices

i) 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.

ii) apply proper lumping technique of the remaining reduced model

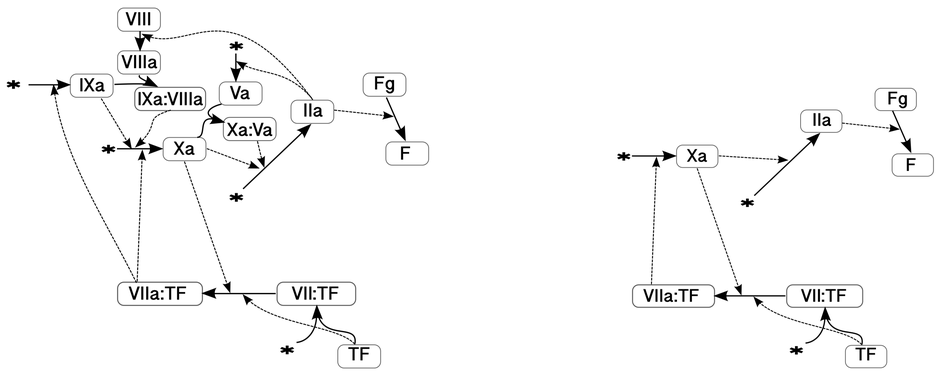


- reduction from 62 state variables to 8 state variables in first step
- finally reduction to 5 state variable model [2]
- no manual post-processing required/no parameter adjustment (as in [1])
- clear gain in understanding of the system
- provides ordering of state variables

Informative dependence of reduced model on reference state & input

Example: PT test (input: TF, output: F)

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



Conclusion

The input-response indices are a powerful tool for a very efficient model order reduction and thus an important step towards translating insight of the biological process, incorporated in detailed systems pharmacology models, to the population analysis of clinical data.

Literature

[1] 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.

[2] J. Knöchel, C. Kloft, and W. Huisinga. Understanding and reducing complex systems pharmacology models based on a novel input-response index. *Journal of Pharmacokinetics and Pharmacodynamics*, 45:139–157, 2018.

[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.

Contact: Jane Knöchel jknoechel@uni-potsdam.de, Wilhelm Huisinga huisinga@uni-potsdam.de