A Tutorial on Tackling High Dimensionality in QSP

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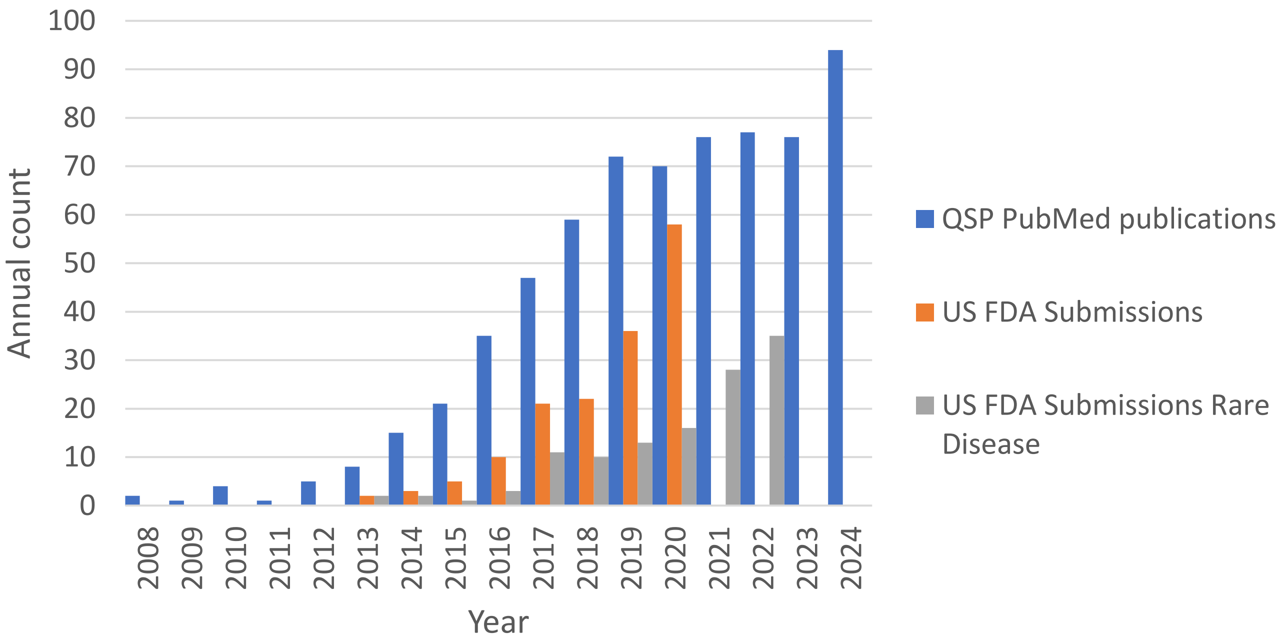
QSP's Evolving Role in Industry

Combined with Machine Learning Opens New Frontiers for Precision Medicine

Progression in the number of annual
QSP publications/supported FDA submissions#



Integrating multi-omics datasets with QSP

Omics

- Large-scale datasets capturing structure and function of bological system

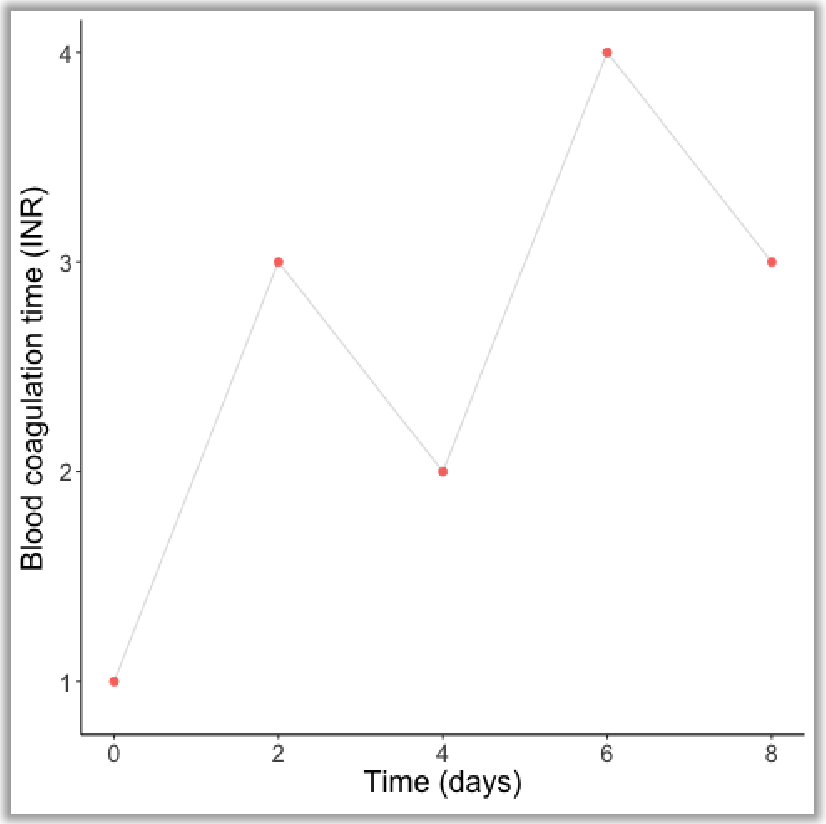
"Patient-specific multi-omics dataset when integrated with QSP models can improve the generation of virtual patient cohorts/digital twin with personalised pharmacokinetics and treatment effect that accurately represent real patients."[1]

Figure redrawn and combined from Cucurull-Sanchez, L. (2024). An industry perspective on current QSP trends in drug development. *Journal of Pharmacokinetics and Pharmacodynamics*, *51*(5). And Bai, J. P., Wang, J., Zhang, Y., Wang, L., & Jiang, X. (2023). Quantitative Systems Pharmacology for Rare Disease Drug Development. *Journal of Pharmaceutical Sciences*, *112*(9), 2313–2320.
[1] Arulraj, T., Wang, H., Ippolito, A., Zhang, S., Fertig, E. J., & Popel, A. S. (2024). Leveraging multi-omics data to empower quantitative systems pharmacology in immuno-oncology. *Briefings in Bioinformatics*, *25*(3).

Understanding inter-individual variability of response

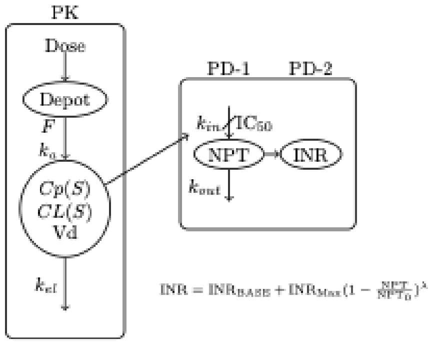
Statistical analysis of clinical data

The data

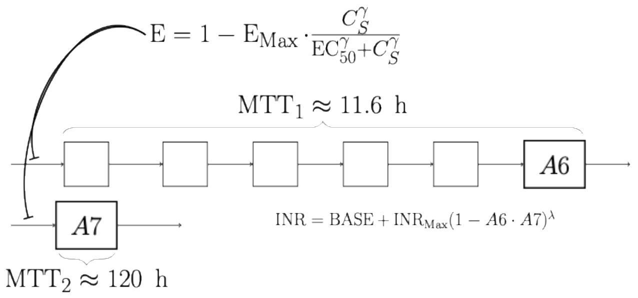


Data-driven sparse models

Model 1[1]



Model 2[2]



- Identify influencing factors (covariates) e.g. age, bodyweight or others

However, every dataset results in different data-driven sparse model.
Which model to choose for the next analysis?

[1] Hamberg, a-K., Dahl, M.-L., Barban, M., Scordo, M. G., Wadelius, M., Pengo, V., … Jonsson, E. N. (2007). A PK-PD model for predicting the impact of age, CYP2C9, and VKORC1 genotype on individualization of warfarin therapy. *Clinical Pharmacology and Therapeutics*, *81*(4), 529–538. https://doi.org/10.1038/sj.clpt.6100084

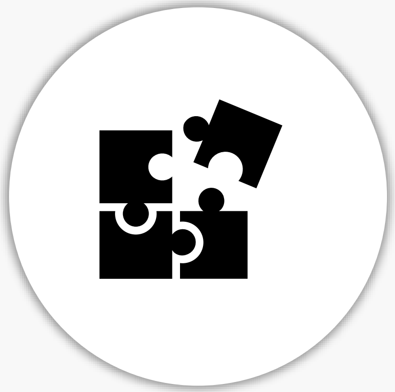
[2] The Pitfalls of Warfarin Dosing Using Different Pharmacodynamic Models: A Comparison of Two Different Warfarin Pharmacodynamic Models With Divergent Results. (n.d.), 1–30.

Aim:
Leverage the knowledge in systems pharmacology models in statistical analysis

Leveraging the knowledge in system pharmacology models

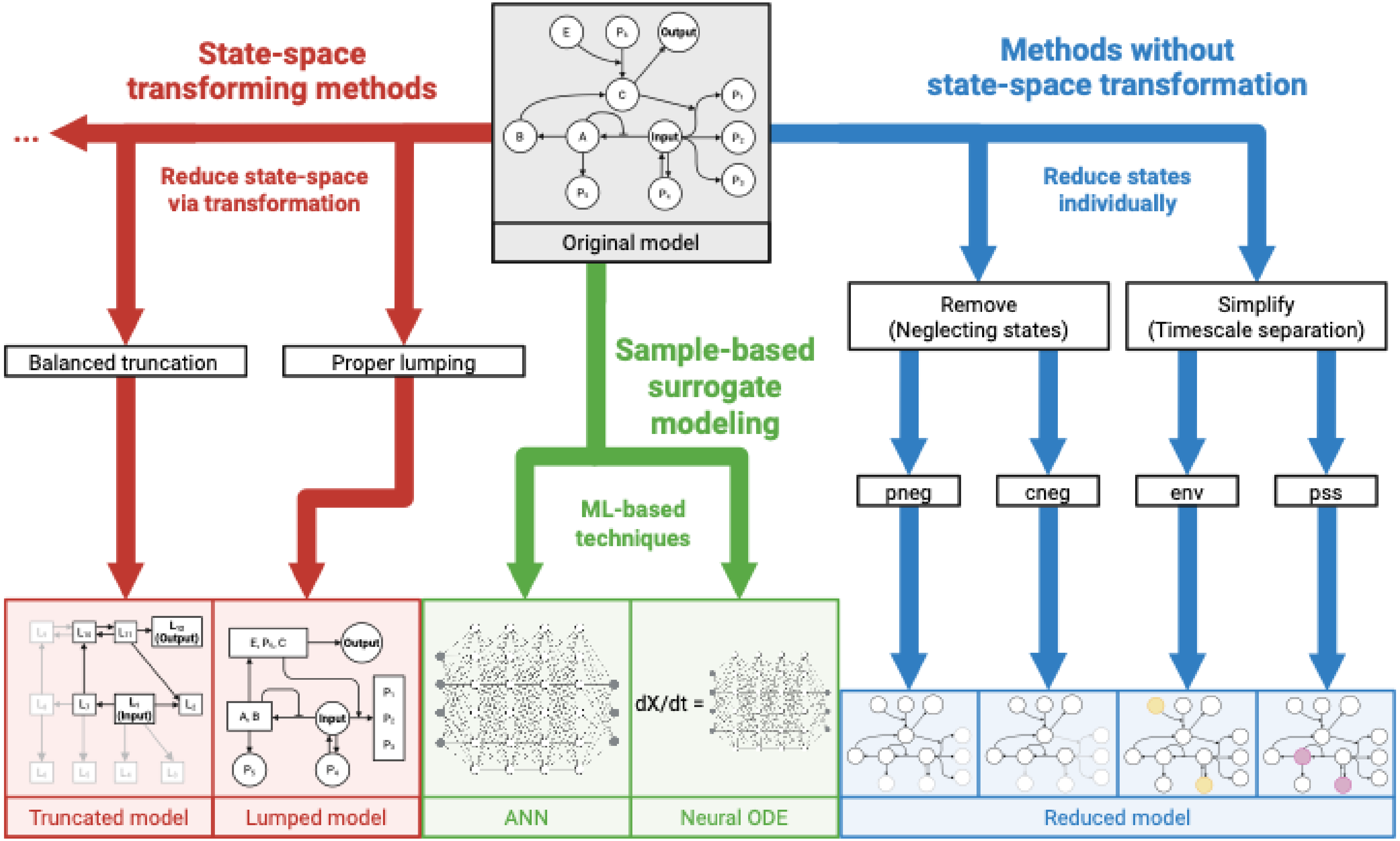
Knowledge on covariates included in system pharmacology model

Leverage knowledge to derive theoretically-justified effective models including relevant covariates



Full complexity not relevant – rather need to identify important parts

Method Selection for Reduced Models: Which Approach Yields the Desired Outcome?



No clear guidance exists on which MOR methods suit specific scenarios or how to combine them effectively.

Index Analysis:
Understanding what is important

Journal of Pharmacokinetics and Pharmacodynamics
https://doi.org/10.1007/s10928-017-9561-x

ORIGINAL PAPER

CrossMark

Understanding and reducing complex systems pharmacology models based on a novel input–response index

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

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PLOS COMPUTATIONAL BIOLOGY

RESEARCH ARTICLE

Index analysis: An approach to understand signal transduction with application to the EGFR signalling pathway

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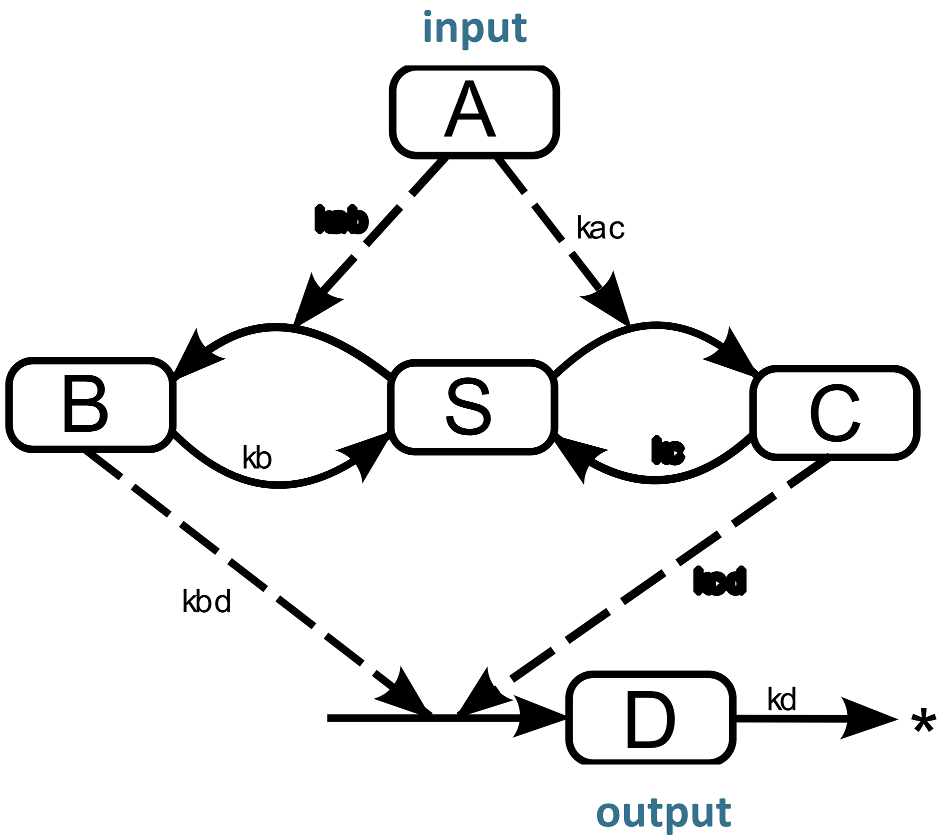
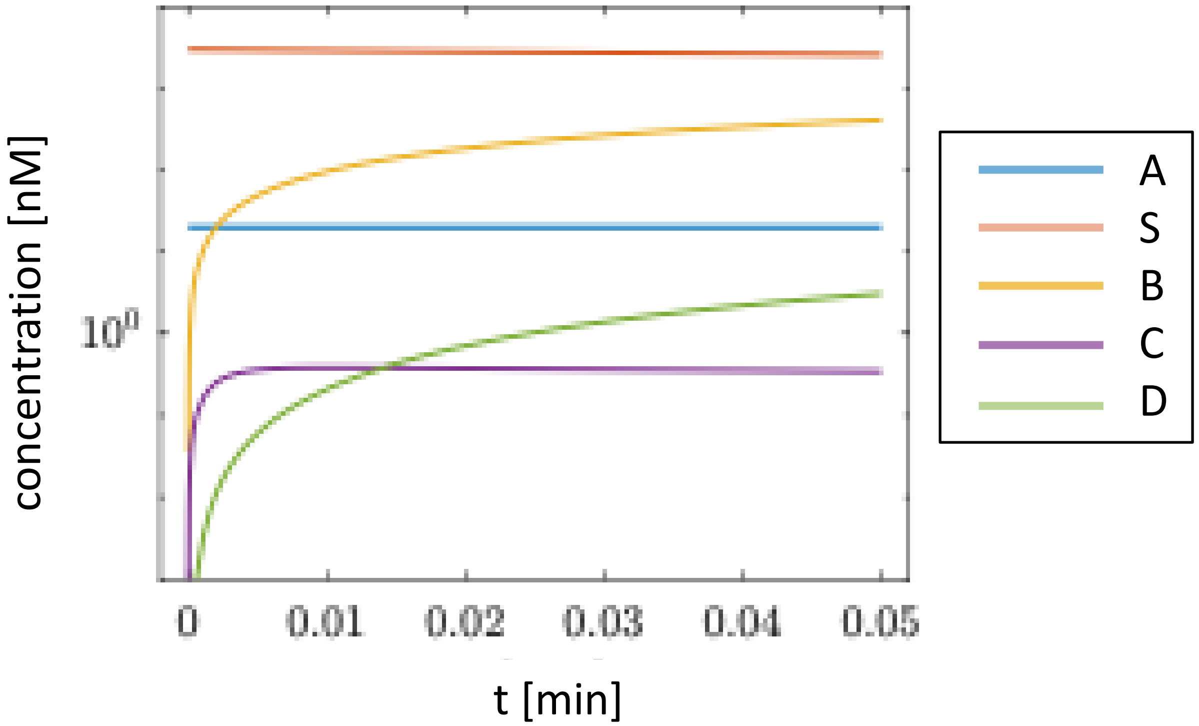
Index Analysis-guided model order reduction

Index	Type	Purpose	Interpretation
Ir/nir	**Input-response**	**Assess dynamic importance of state**	**How relevant is a state for the input-output relationship?**
Env, Pss	State classificiation	Classification based on time scale seperation	Can we simplify this state by an algebraic equation?
Pneg, Cneg	State classification	Classification of states with negligible impact on the output	Can this state be ignored?

Case Examples

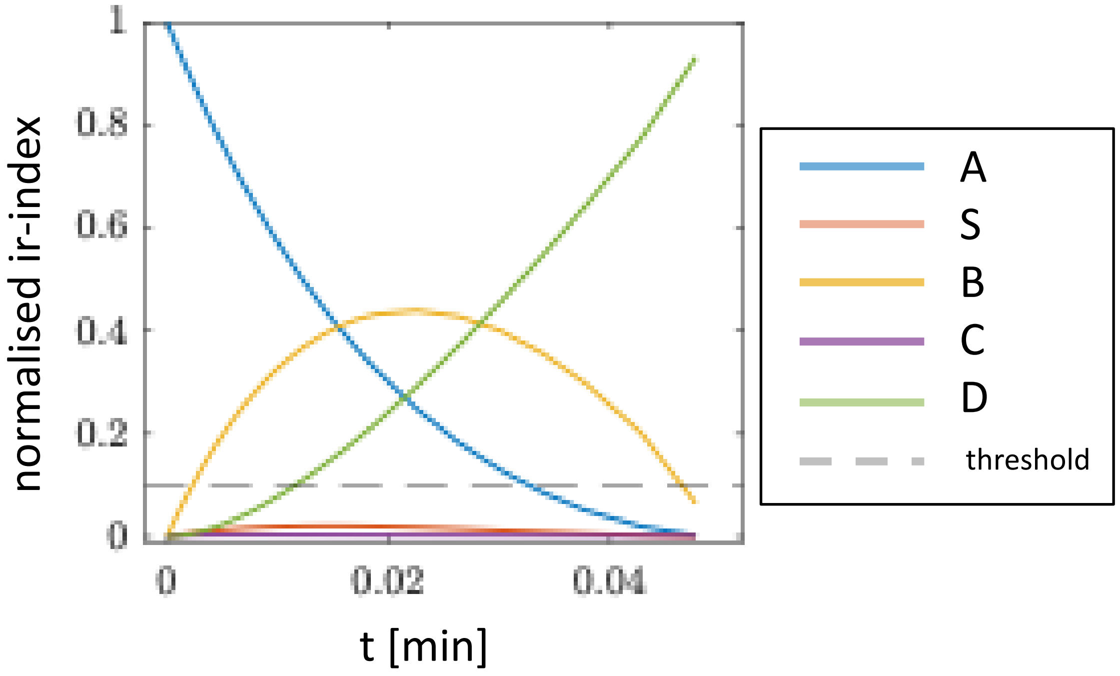
Small example – parallel pathways



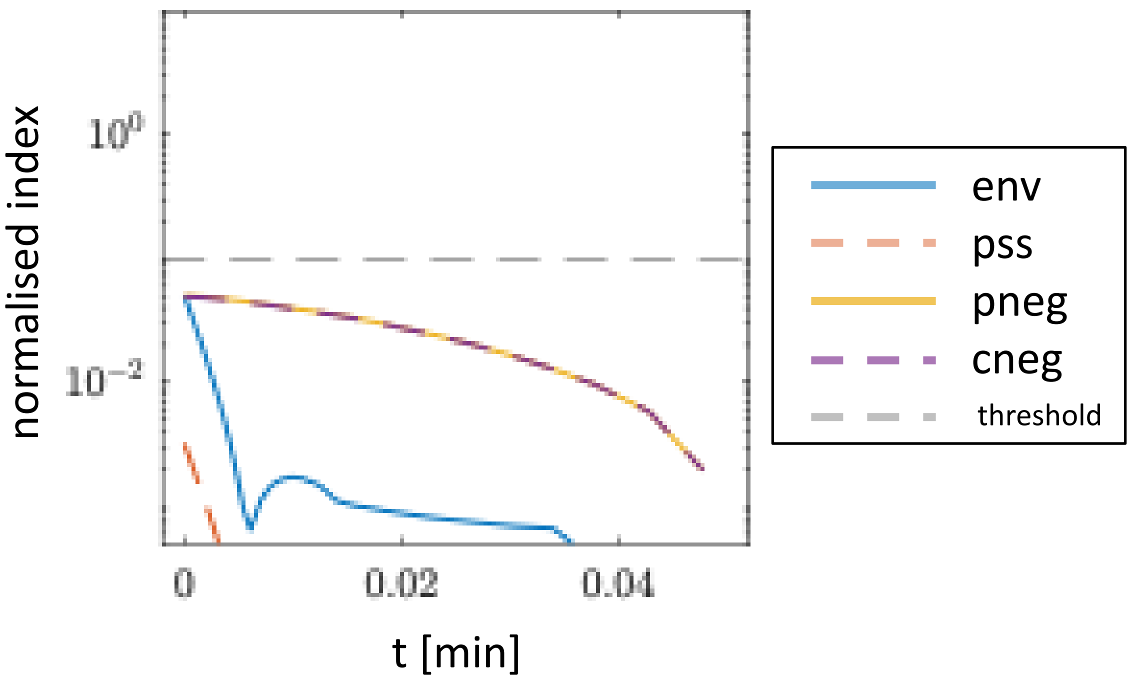


Indices reveal appropriate reduction method

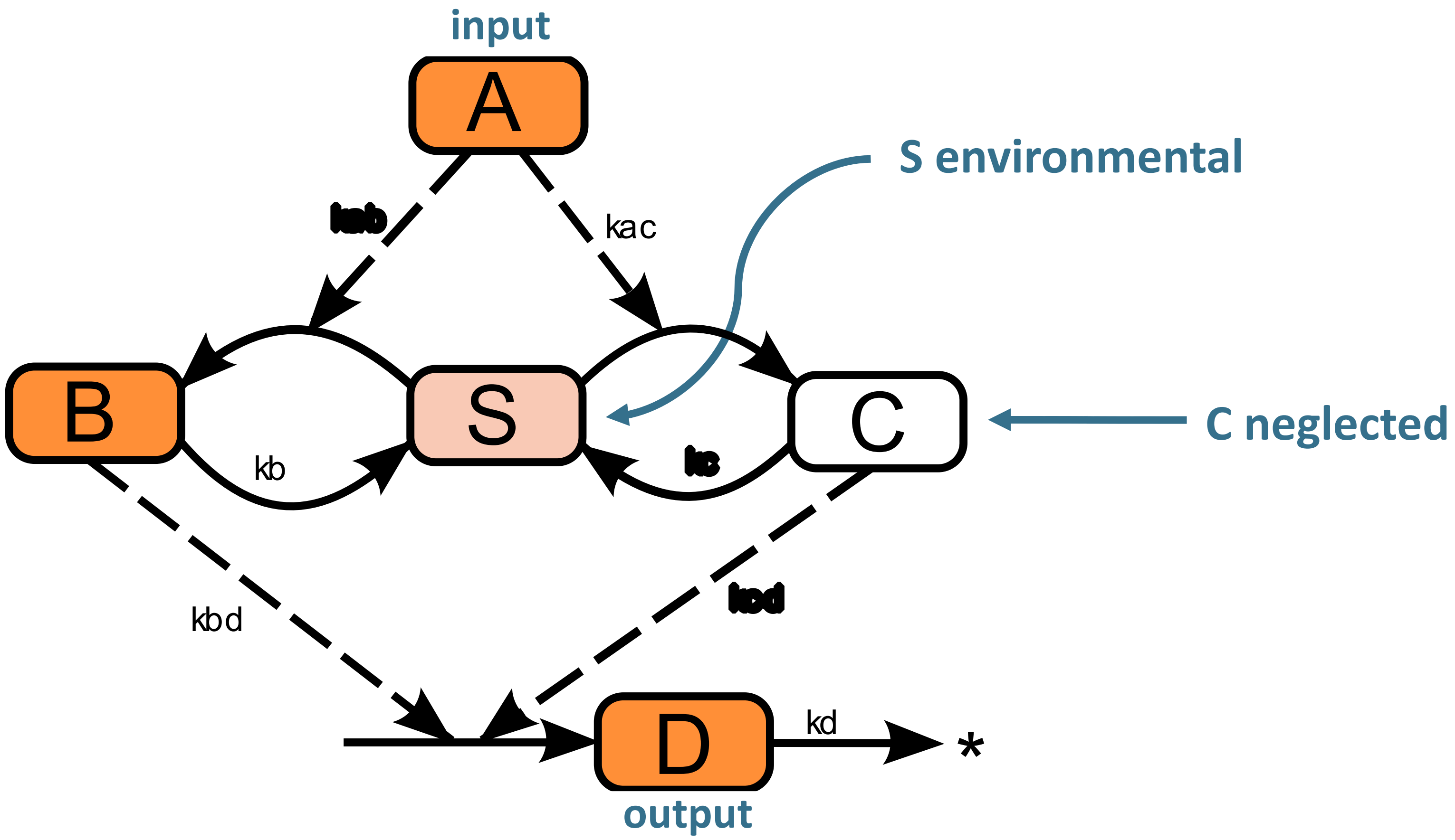
Input-response indices



State classification indices of C



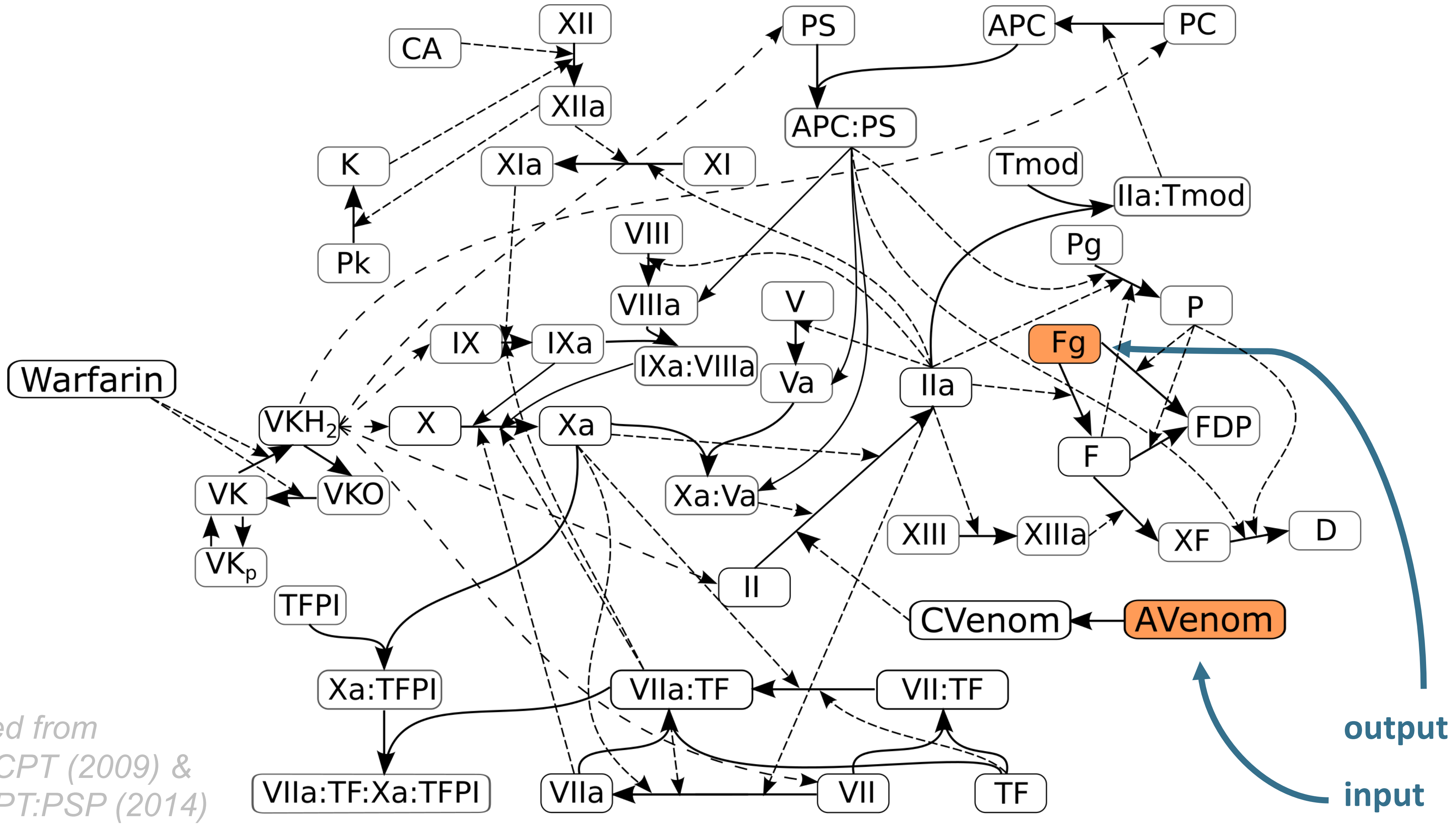
Indices guide the model order reduction



orange – dynamical states; light orange – environmental states; white – neglected states

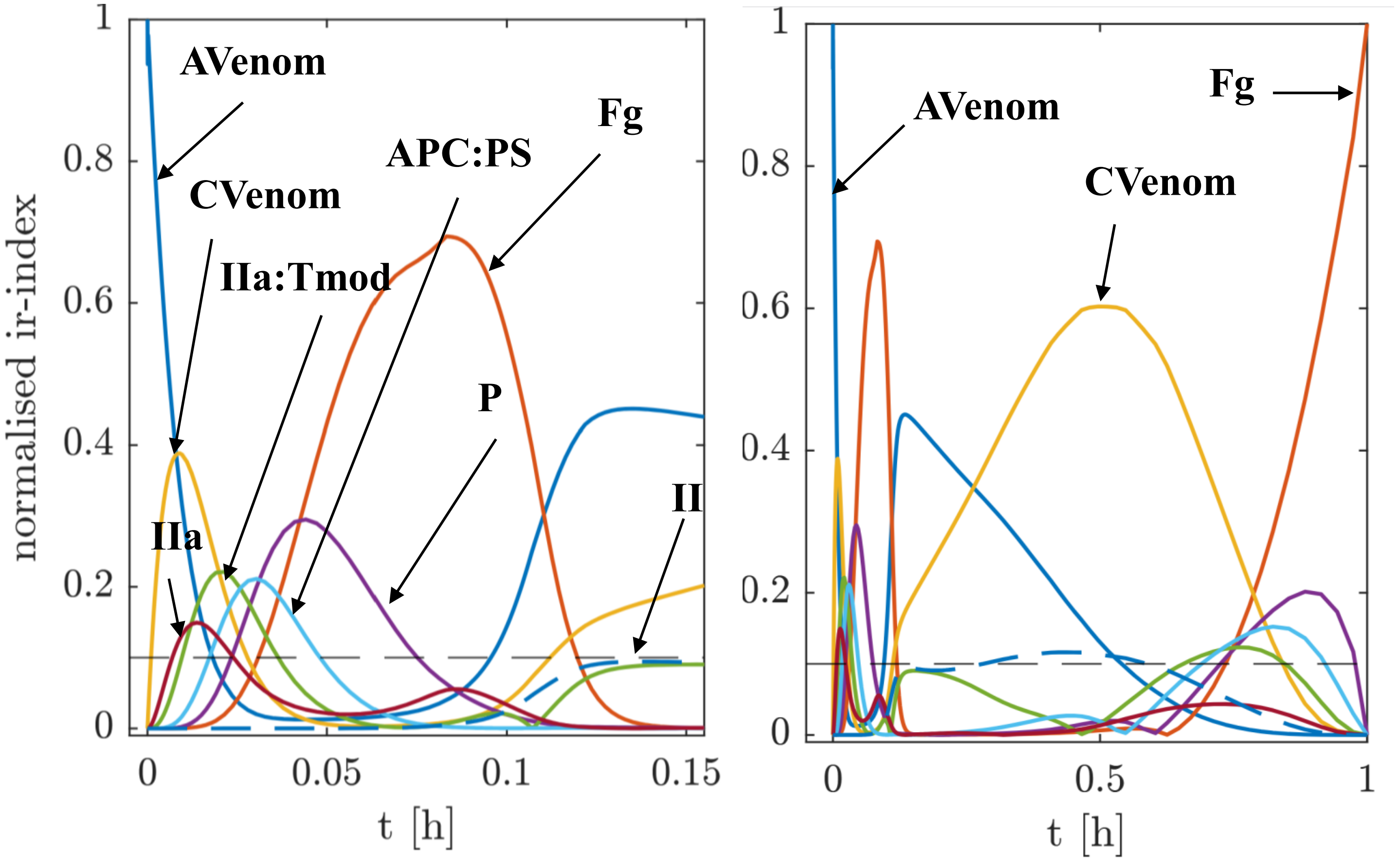
Large-scale QSP model – the blood coagulation network

Brown snake envenomation



Picture adopted from Wajima et al, CPT (2009) & Gulati et al, CPT:PSP (2014)

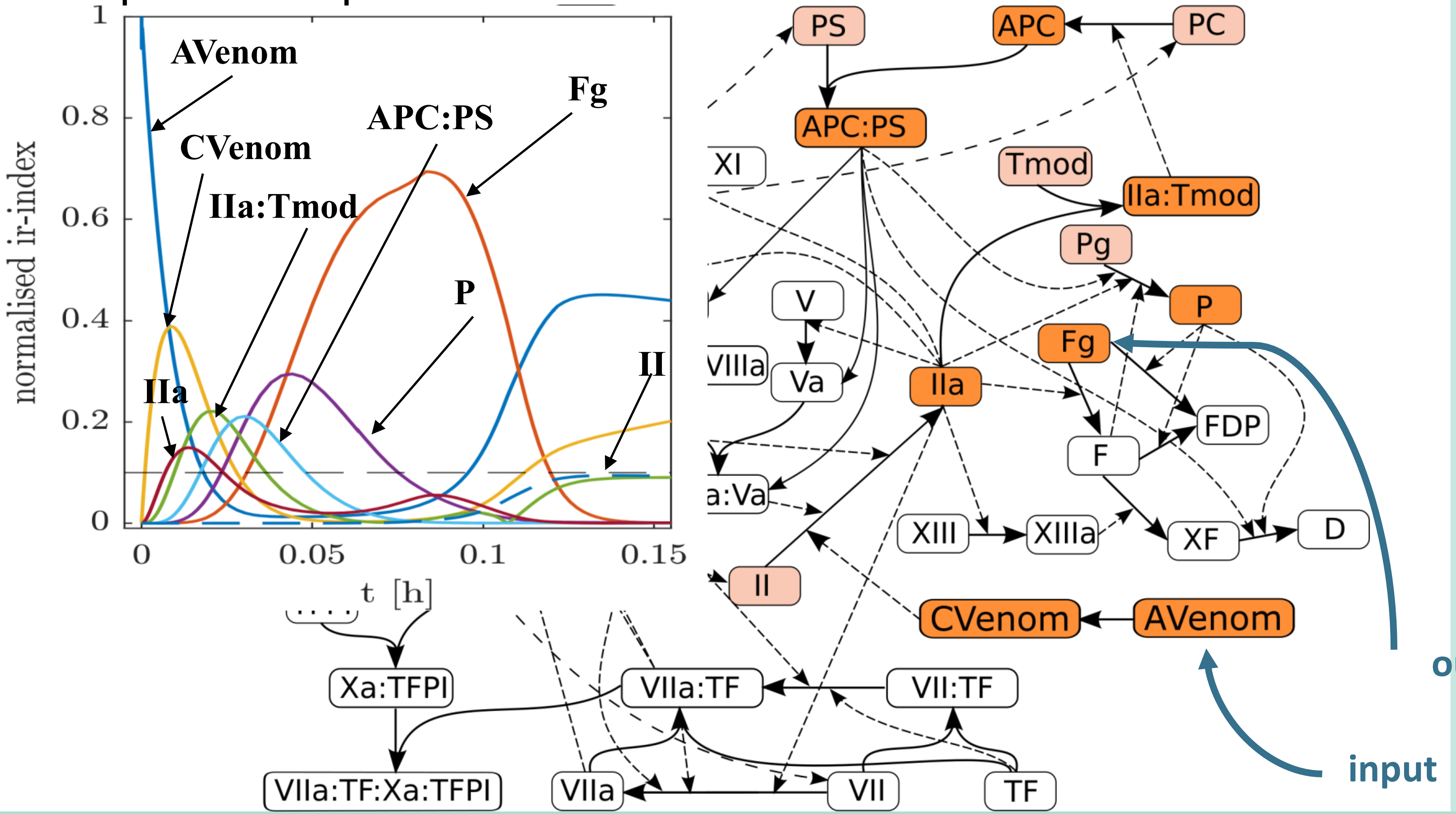
The input-response indices in action
Brown snake venom effect on Fibrinogen



Demonstrates how the signal moves through the network!

Let's combine this with the graphical illustration of the model!

Understanding Signal Propagation and Key Molecular Players via Input-Response Index



Reduced model:
8 dynamical,
5 environmental
state variables

50 state variables
neglected

orange – dynamical states; light orange – environmental states; white – neglected states

Theoretical Models for Optimizing Warfarin Therapy

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ARTICLE

Deriving mechanism-based pharmacodynamic models by reducing quantitative systems pharmacology models: An application to warfarin

Undine Falkenhagen[1,2] | Jane Knöchel[1] | Charlotte Kloft[3] | Wilhelm Huisinga[1]

ARTICLE

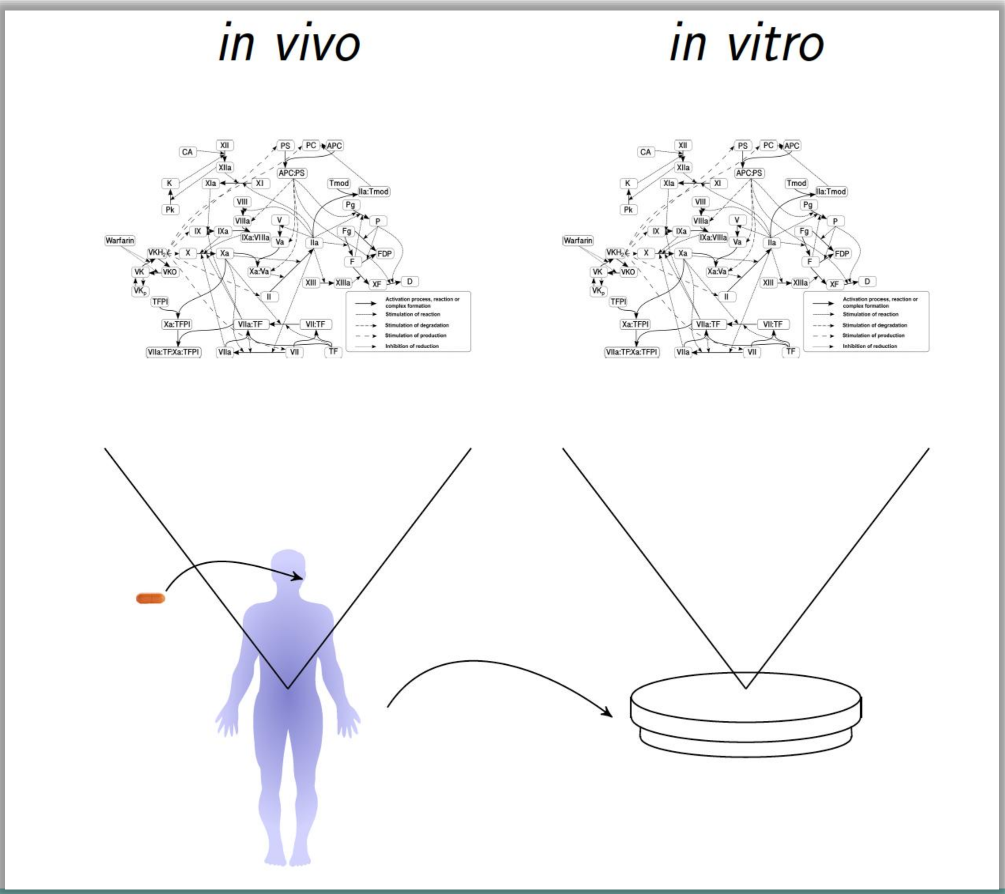
Leveraging QSP Models for MIPD: A Case Study for Warfarin/INR

Undine Falkenhagen[1,2], Larisa H. Cavallari[3], Julio D. Duarte[3], Charlotte Kloft[4], Stephan Schmidt[5] and Wilhelm Huisinga[2,*]

Warfarin dosing remains challenging due to substantial inter-individual variability, which can lead to unsafe or ineffective therapy with standard dosing. Model-informed precision dosing (MIPD) can help individualize warfarin dosing, requiring the selection of a suitable model. For models developed from clinical data, the dependence on the

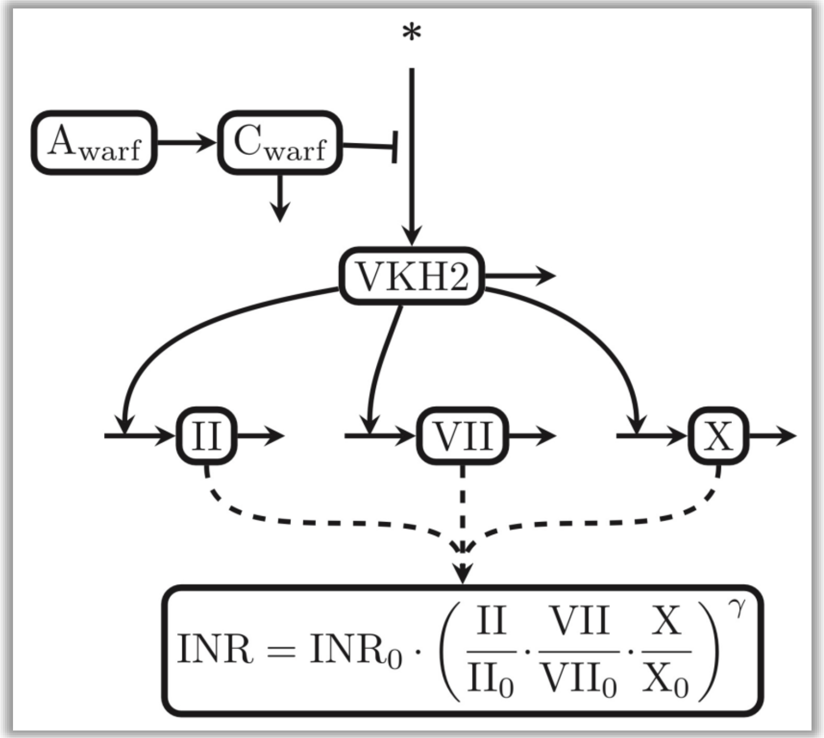
Resulting Theoretical Model Size Allows Statistical Analysis of Clinical Data

Modelling Warfarin Therapy (2x60 ODEs)



MOR

Theoretically justified models



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