# Methods and tools for multiscale modelling in Systems Pharmacology: a review

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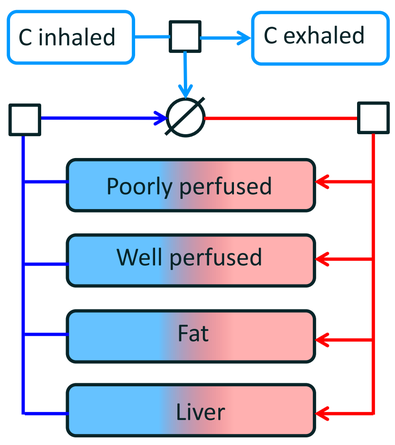
BACKGROUND. Systems Pharmacology aims to quantitatively study the dynamic interactions between drugs and biological systems by integrating models and data at different scales, to understand how the behaviour of individual constituents (modelled, e.g., via biological networks) and the behaviour of the whole system (modelled, e.g., via PBPK models) mutually interact. The objective of this work is to present and discuss: how models at different scales can be coupled; the types of data that can be used; the tools supporting the implementation; the practical research and drug development studies the models were built for.

METHODOLOGY AND TOOLS. From literature three main methods for coupling PBPK models and biological networks were identified:

## Combination of PBPK and networks ODEs

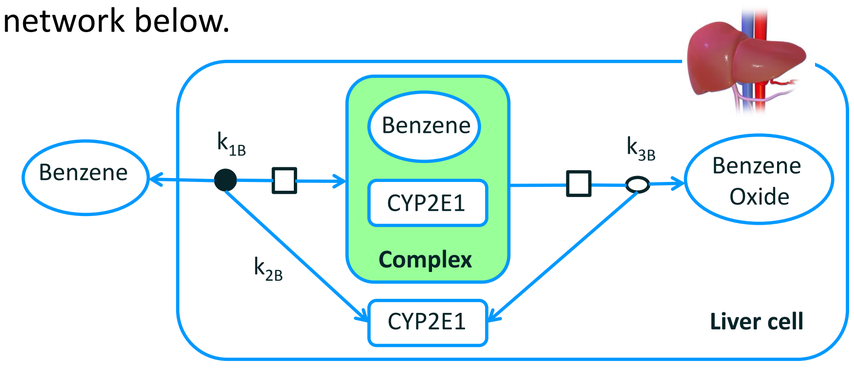
PBPK and network models are both represented by ODEs and the connection is provided by network exchange rates affecting the PBPK concentrations [F.Y. Bois, 2009].




As an illustrative example, a simple generic PBPK rat model considering absorption, transport and excretion of benzene is shown [S. Cheng,2011]. Here, only inhalation is modelled.

$$\frac{dQ_i}{dt} = F_i\left(C_{art} - \frac{Q_i}{V_i P_i}\right)$$

The metabolism of the substance is described by the network below.



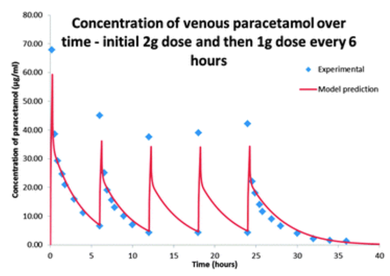

The mass-balance equations of the network are coupled with the PBPK model:

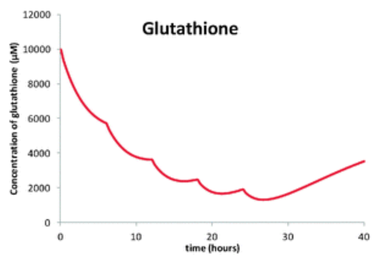
$$\frac{dB_{liver}}{dt} = B_{in} + F_i\left(B_{C_{art}} - B_{C_{outliver}}\right) + \\ - k_{1B} V_{liver}[CYP2E1][B] + k_{2B}[Complex_{CYP2E1-B}]$$

**Example of application:**

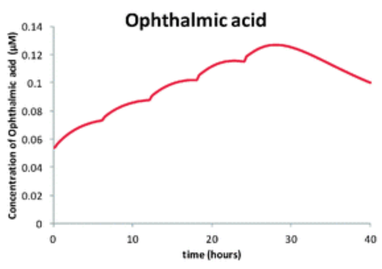
A joint PBPK model, including paracetamol PK combined with a network of GSH homeostasis, was developed to study candidate biomarkers of liver toxicity [S. Geenen, 2010].

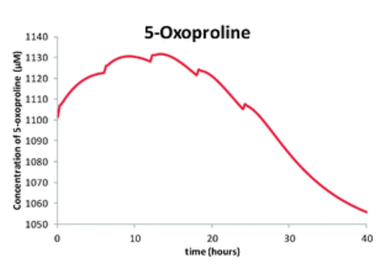
- Some parameters are derived from literature, while others are estimated. The PBPK model well describes paracetamol concentration in plasma.




- Ophthalmic acid and 5-oxoproline were evaluated as biomarkers to monitor GSH depletion toxicity.

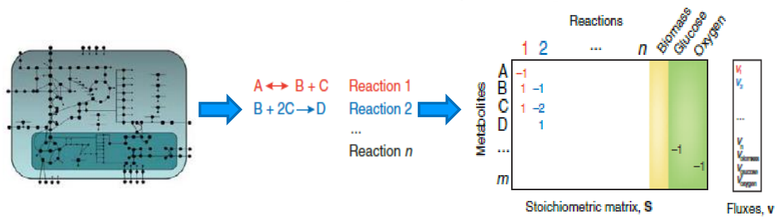


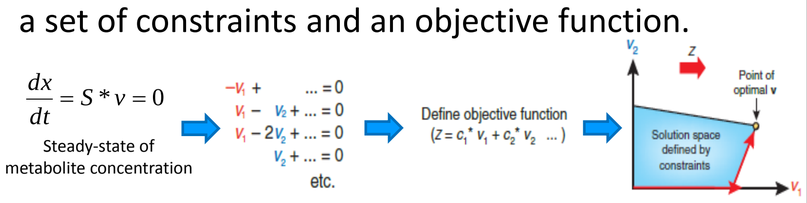

**Tools:** GNU Operating System (Sponsored by the Free Software Foundation) · COPASI · SBML.org

## Coupling with dynamic Flux Balance Analysis

Metabolites, reactions and fluxes in a metabolic network are represented by a stoichiometric matrix and a vector of fluxes [D. Orth, 2010].

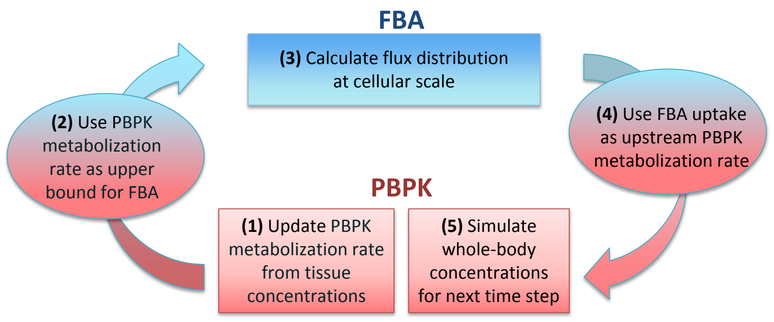



Flux Balance Analysis (FBA) is a mathematical approach for calculating the unknown fluxes given a set of constraints and an objective function.



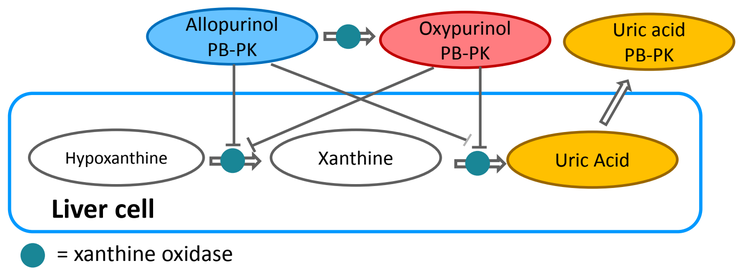

### Feed-forward or feed-back coupling

The PBPK model, represented by ODEs, can be coupled to the network via dynamic FBA by feed-forward (steps 1-3) or feed-back (steps 1-5) approach [M. Krauss, 2012].

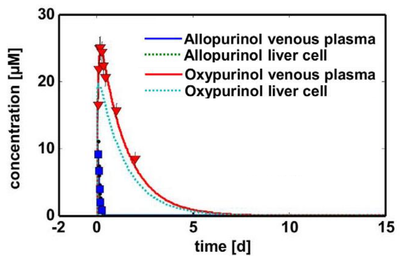


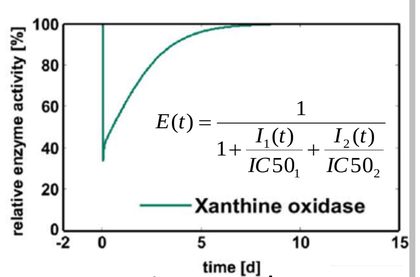

**Example of application:**

A multiscale PK/PD model is developed to study the therapeutic effect of allopurinol in the treatment of hyperuricemia [M. Krauss, 2012].




- PBPK models for allopurinol, oxypurinol and uric acid were built using physiological information and plasma concentration data.
- Feedback coupling was used to study the effect of drug on xanthine oxidase in the hepatic metabolic network. Maximization of uric acid production was considered as objective function.



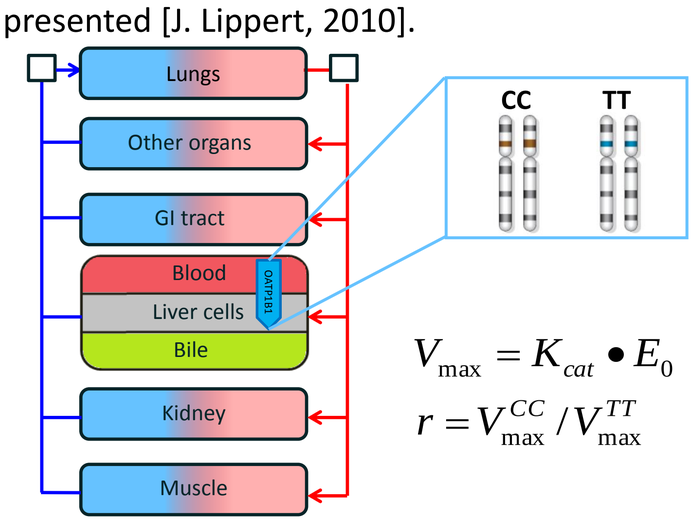




- Model evaluation: comparison between simulation of uric acid and venous plasma concentration after a single dose of allopurinol.

**Tools:** PK-Sim · MoBi · SBML.org

## Integration of genic information as covariate in PBPK models parameters

Genic information is included as a covariate for tissue-specific transporter-activity. Here an example relative to SNP in OATP1B1 transporter is presented [J. Lippert, 2010].



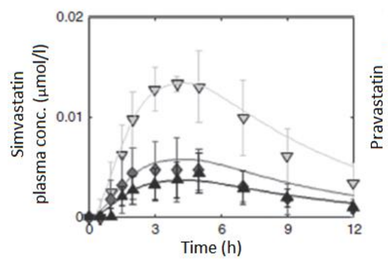

$$V_{max} = K_{cat} \bullet E_0$$

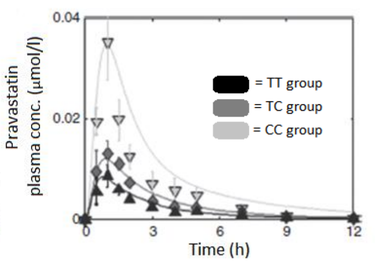
$$r = V_{max}^{CC} / V_{max}^{TT}$$

**Example of application:**

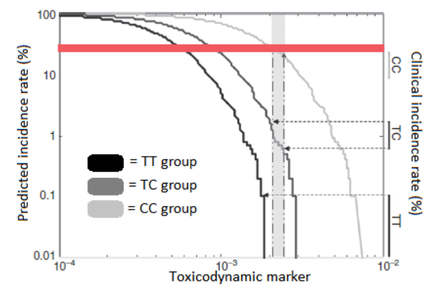
A PBPK model representing ADME genes involved in simvastatin and pravastatin metabolism to predict the risk of myopathy in individuals with specific genotype was developed [J. Lippert, 2010].

- PBPK models for simvastatin and pravastatin were built for the reference homozygous TT genotype using plasma data.
- PBPK models for the CC genotype were built based on the TT models by adjusting OATP1B1 transporter activity. PBPK model for the CT genotype uses the average of the transporter activities.




- Safety risk was evaluated to forecast the incidence rate in the CC subgroup population given the incidence rate of TT and TC subpopulations.




**Tools:** PK-Sim · MoBi

| | ODEs | FBA | Covariate |
|---|---|---|---|
| ✓ | • Mechanistic approach<br>• Traditional solving methods | • Mechanistic approach<br>• Enables genome-scale models<br>• Easy estimation of network parameters | • Easy implementation<br>• Inclusion of genetic information |
| ✗ | • Need for parameter values and rescaling<br>• Large-scale networks implementation | • Jointly solving of ODEs and FBA | • Non-mechanistic at cellular level |

CONCLUSIONS.

- The PBPK-network combination with ODEs is the most widely used approach.
- Computational tools have been proposed to facilitate model coupling for the ODE and covariate approaches; databases, e.g., BioModels Database (EBI), JWS and SABIO-RK, are available to retrieve networks and their parameters.
- Multiscale modelling is a major challenge in Systems Pharmacology, for which guidelines are still missing. Efficient integration of heterogeneous data, including genetic information, will greatly improve our knowledge of the mechanisms underlying complex diseases and drive new approaches for drug discovery.