

SYSTEMS BIOLOGY PBPK MODELING OF METABOLIC INTERACTIONS

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Abstract

We demonstrate the capabilities of new integrated approach and software tools to facilitate the development of systems biology models of interactions in metabolic networks.

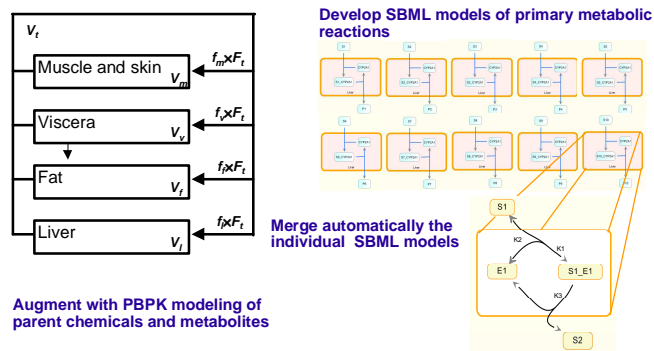
We proceed by automatically merging and coupling metabolic pathways SBML models for individual chemicals to a template physiologically based pharmacokinetic (PBPK) model, using GNU MCSim. The reaction network and transport model generated is very efficient and can simulate the interactions between a theoretically unlimited number of substances, at the body and organ or tissue levels. By using a fine-grain description of reactions, development time increases only linearly with the number of substances considered, while the number of possible interactions increases exponentially. In contrast, traditional approaches using K_i values consider only first order interactions and their complexity increases quadratically with the number of substances.

An example of application to the prediction of the joint kinetics of a set of 100 arbitrary chemicals or drugs (and their metabolites) is given. The qualitative and quantitative behaviour of the pathway network is analysed using Monte-Carlo simulations.

The integrative approach to interaction modelling is efficient and can be extended beyond metabolic interactions. It applies to drug-drug interactions or to generic chemicals substances. It relies on the availability of specific data on the rate constants of individual reactions. Such data can be obtained through specifically designed enzyme kinetics experiments, or through computational chemistry modelling of enzymatic reactions. We are currently exploring both approaches.

Methods

Concepts

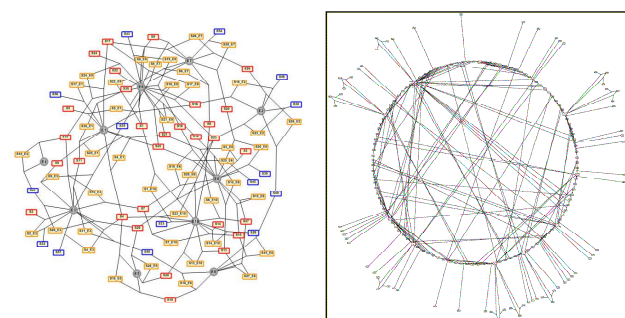


Software

All simulations have been performed with GNU MCSim version 5.3.1

Results

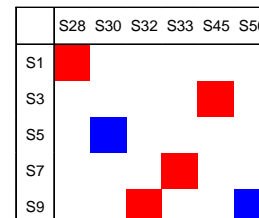
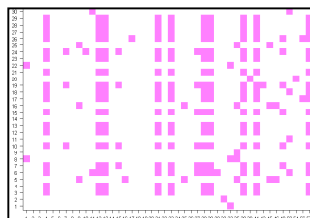
Analysis of random metabolic networks



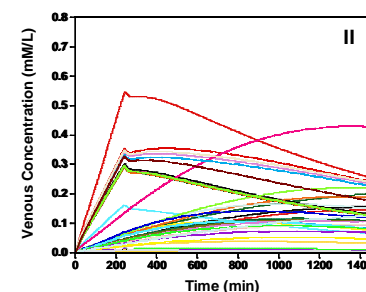
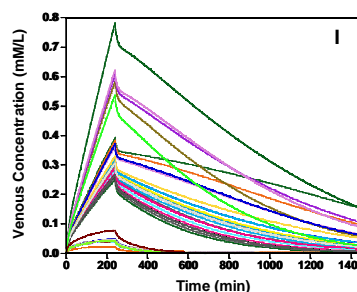
Simulating real-life networks: from 30 parents and 15 metabolites (A) to 50 parents and 150 metabolites (B). The associated PBPK models are not figured here.

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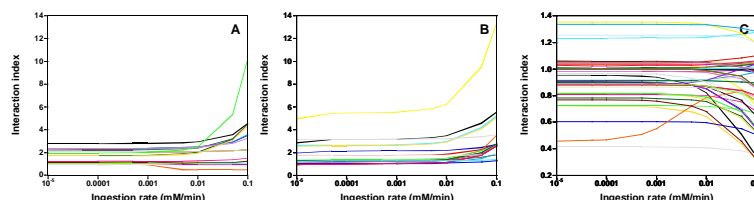
Extent of interactions



Theoretical versus significant interactions (as assessed by Monte-Carlo simulations of network A)



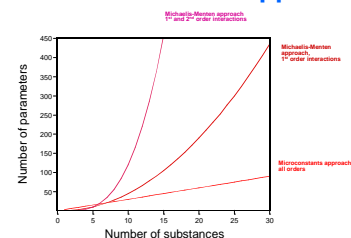
Time course of the concentration of each substance (I: administered parent substances; II: pure metabolites) when substances are administered together. Differences between profiles are entirely due to network B structure and metabolic interactions



Predicted interaction ratios for various groups of substances of network B, 24 hr after the start of 4 hr of joint exposure to a mixture of all parent substances.

Quantitative advantage of a micro-constants' approach

$$\begin{cases} \frac{dS}{dt} = -K_1 \times S \times E + K_2 \times ES \\ \frac{dE}{dt} = -K_1 \times S \times E + (K_2 + K_3) \times ES \\ \frac{dES}{dt} = K_1 \times S \times E - (K_2 + K_3) \times ES \\ \frac{dP}{dt} = K_3 \times ES \end{cases}$$



Micro-constants can be obtained from simple extension of standard enzyme kinetics assays

