Divide and Conquer: Using SBML to represent both the whole body and subcellular scales in a liver-centric multiscale model

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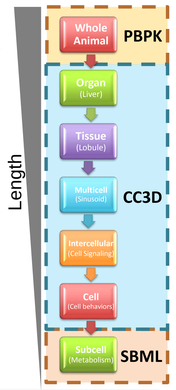
Introduction

Pharmacological and toxicological processes occur across a wide range of spatial and temporal scales and include multiple organ systems. A pharmacological model must include submodels that cover the multiple scales and tissues relevant to human pharmacology and toxicology. We have developed a liver-centered, mechanism based, multiscale in silico simulation framework for xenobiotic toxicity and metabolism that incorporates four key biological scales: (1) Population variation scale, (2) Physiologically-Based Pharmaco-kinetic (PBPK) whole body scale, (3) Tissue and multicell scale, and (4) Subcellular signaling and metabolic pathways scale. Our multiscale model focuses on the liver, a critical organ in many toxicological, pharmacological, normal and disease processes. We make extensive use of models written in SBML and couple multiple copies of two distinct SBML models to our multicell centered simulation. These SBML models represent the whole-body (PBPK) scale and the subcellular reaction kinetic (metabolic) scales. The use of SBML format for both the largest and smallest scales allows us to leverage existing models and modelling tools for these two different scales. In addition, the SBML models can be run as stand-alone models allowing us to refine the models individually using SBML tools for tasks such as model building, annotation and parameterization.

Design Goals for a Multiscale – Multimodal Model:

- Multiple spatial and temporal scales coupled to create a single composite multiscale model.
- Use standard model formats for each scale.
- Models at individual scales should be runnable on their own.



Biological Background: Acetaminophen (*APAP*, Paracetamol) is a widely used over the counter analgesic and fever reducer. APAP's therapeutic index (ratio of toxic dose to therapeutic dose) of ~10 is unusually low for an over the counter medication. APAP overdose results in rapid centrilobular necrosis of the liver, which can lead to death. APAP is a leading cause of acute liver failure in the Western world.[5]

References and Acknowledgements

1.http://www.nsf.gov/bfa/dias/policy/rcr.jsp
2.Wambaugh, J. & Shah, I. (2010), *PLoS Computational Biology* **6**.
3.http://sys-bio.org/.
4.http://www.compucell3d.org/
5.Gautam R, *et al.* (2012) *PLoS ONE* **7(9)**.
6.Andasari V, Roper RT, Swat MH, Chaplain MAJ (2012) *PLoS ONE* **7(3)**.
7.Critchley JAJH, *et al.* (2005) *Journal of Clinical Pharmacy and Therapeutics* 30: 179-84.

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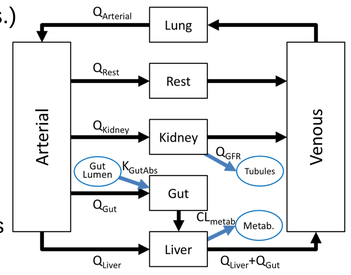
Whole-Body PBPK Model

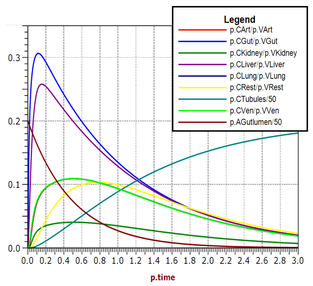
The whole-body PBPK model is based on published models.[2] The model was translated into SBML using SBW tools, particularly Jarnac and JDesigner.[3] (There is no standard for PBPK models.)

Biological Model (right): Compartment model for oral administration of APAP.

Mathematical Model: Compartment transfer ODEs used in the simulation are in SBML format.

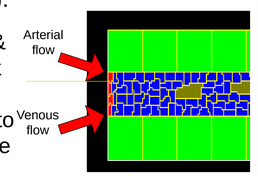


Standalone Run (right): Simulation results for the PBPK model in SBML for a 10g oral APAP dose simulated in Jarnac. The vertical axis is g/L and the time axis is hours.



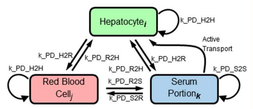
Multicell Sinusoid Model

A single liver sinusoid is modeled in Compucell3D (CC3D)[4]. The CC3D model describes the behavior of the cells and blood in the model. Blood is modeled as a mixture of serum portions and red blood cells (RBCs).

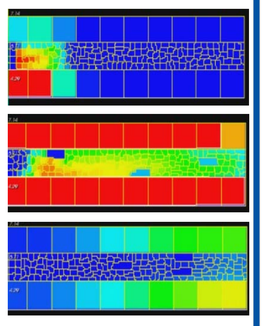


Biological Model: Hepatocytes (top & bottom), Red Blood Cells (RBCs, dark green), Serum Portions (blue), Blood "source" cells (red). Blood is forced into the model from the left and exits on the right.

Diffusion model: RBCs and Serum Portions carry a chemical "load" of APAP that diffuses into / out of the serum, RBCs and Hepatocytes. Transfer requires, and is scaled by, contact.



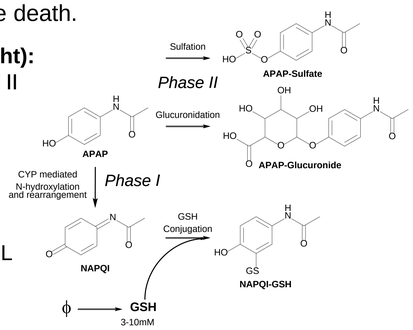
Standalone Run: Three time points of the CC3D model of an input pulse of APAP in the venous flow into the model sinusoid. Cells and serum portions are colored by the amount of APAP. The top image shows the pulse entering the portal end of the sinusoid. The middle and bottom images show the peak pulse and the washout period after the end of the input pulse.



Sub-Cellular RK Model

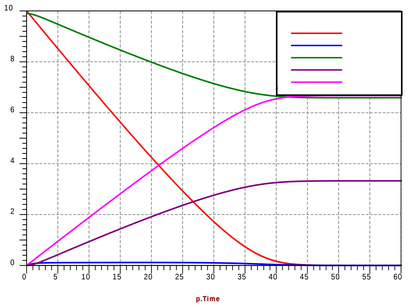
APAP is extensively metabolized in the liver in both Phase I and Phase II reactions. At high APAP doses significant depletion of hepatocyte Glutathione (GSH) levels occurs leading to hepatocyte death.

Biological Model (right): Simplified phase I and II metabolism of APAP.



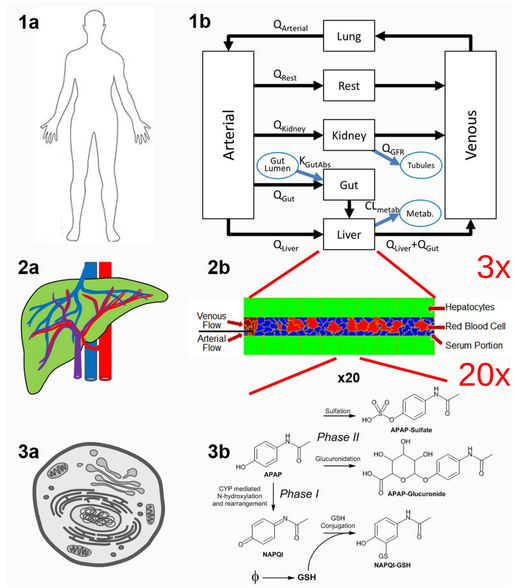
Math Model: Reaction kinetic (RK) ODEs used in the simulation are in SBML format.

Standalone Run (right): Simulation results for the reaction kinetic model, for a single Hepatocyte, in Jarnac. In this sim the GSH conjugation reaction has been disabled. The vertical axis is mM and the time axis is seconds.



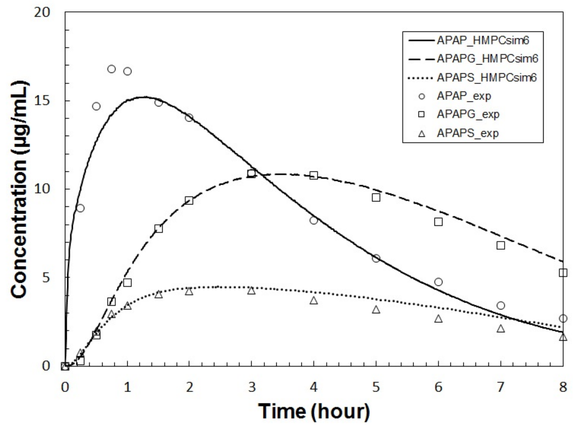
Complete Multiscale Model

The complete model uses CC3D as the controller.[6] CC3D implements the multicellular model (2b), time steps the subcellular SBML (3b) and whole body PBPK SBML models (1b).



Biological Model (below left): Linking the PBPK, multicell and subcell models. The PBPK model is repeated for APAP, APAPG and APAPS. The RK model is repeated 20x,once for each of the hepatocytes.

Simulation Results (below): Plasma concentrations versus time for APAP and metabolites simulated with the complete multiscale model using the best parameter set. Open symbols are *in vivo* averages from nine subjects given a 1.4g oral dose of APAP.[7]



Population Simulation (below): Population variability based on 839 simulated individuals. The population was generated by assuming that for each in silico individual, each parameter was within a truncated normal distribution with coefficient of variation of 25% around the base parameter set. Comparison of the average response (closed symbols) of the simulated population with the simulated individual from the population that deviates the most from the population average (open symbols).