Parameter Sensitivities in a Multiscale model of Acetaminophen Metabolism: from Whole-body to Subcellular Reaction Kinetics

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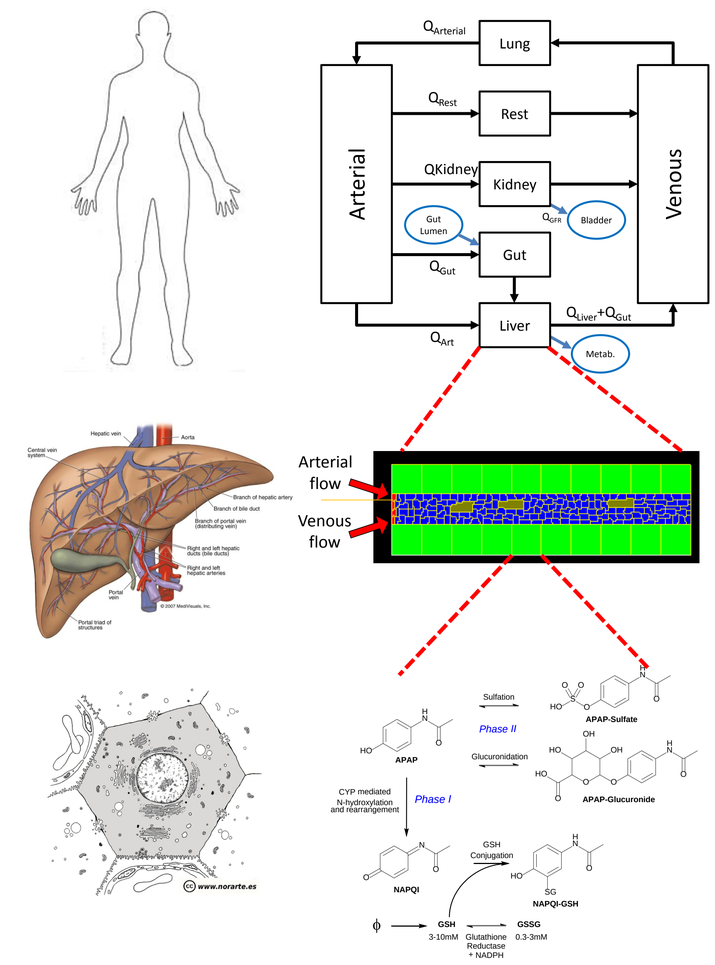
Introduction

Multiscale models of biological responses to therapeutic and toxic agents link models across a wide range of spatial and temporal scales. Often the mathematical and computational modalities vary between scales, which presents issues in parameterizing models and in understanding how changes in parameters at one scale affect responses at other scales. If one or more of the scales includes stochastic components then purely analytic approaches to sensitivity analysis are not possible. We have performed a broad ranging sensitivity analysis of a multiscale model of Acetaminophen (APAP) bioavailability that includes models of the whole-body (PBPK), a tissue level multi-cell model of blood flow and APAP uptake from the blood coupled with subcellular reaction kinetic models of Phase I and II metabolism of APAP and subsequent recycling of the metabolites back to the multicell and whole body levels. The quality of the model was judged based on the concordance between the predicted blood concentration versus time for APAP and its metabolites compared to human data. Parameter sensitivities were examined by first scanning the large set of parameters (37 total) one at a time. This initial scan suggested parameters that had the largest individual influence on the accuracy of the predicted blood levels. We then proceeded to a random sampling approach in which all parameters we changed simultaneously. Analysis of these simulations provided information on interactions between parameters at the three modeling scales. The parameter scan results indicated that the model has highly variable sensitivities to model parameters. The random sampling identified three parameter sets that were as good as or better than the initial reference model. Each of these sets were then examined in fixed-point sensitivity analysis.

Multiscale Model

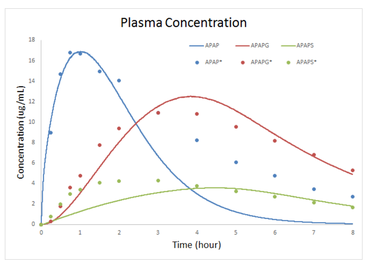


Whole-Body Model (*PBPK*): The whole-body Physiologically Based Pharmaco-Kinetic (*PBPK*) model is based on published models.[1,2] The model was translated into SBML using SBW tools, particularly Jarnac and JDesigner.[3] The PBPK model is for an oral dose of 1g APAP in a 70Kg human male. Replicates of the PBPK/SBML model are used to model APAP and the APAP-Sulfate and APAP-Glucuronide metabolites.

Multi-cell Liver Sinusoid Model (*CC3D*): A single liver sinusoid is modeled in CC3D (Compucell3D)[4]. CC3D models the behavior of the cells, blood and diffusion of APAP. Blood is modeled as a mixture of serum portions and red blood cells (*RBC*s). Hepatocytes (top & bottom), Red Blood Cells (RBCs, dark green), Serum Portions (blue), and Blood "source" cells (red) make up the model. Blood is forced into the model from the left (periportal) and exits on the right (central vein). RBCs and Serum Portions carry APAP that diffuses into / out of the serum, RBCs and Hepatocytes.

Hepatocyte Sub-cellular Metabolic Model (*SC*): APAP is extensively metabolized in the liver in both Phase I and Phase II reactions. RK (reaction kinetic) model of Phase I and II metabolism of APAP leading to APAP sulfate and glucuronide conjugates and CyP450 mediated oxidation of APAP to NAPQI, which subsequently reacts with cellular glutathione (GSH).

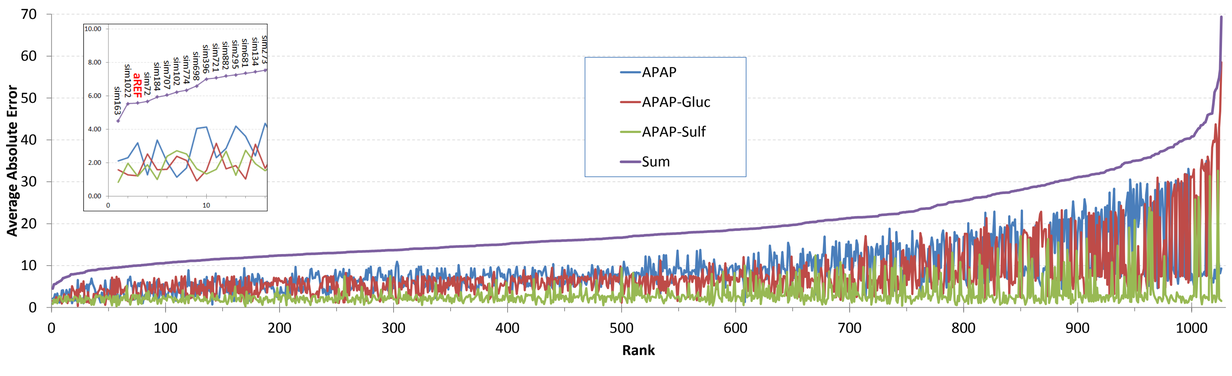
Reference Calibration: The complete multi-scale model uses CC3D as the "marshaling point".[5] CC3D runs the multi-cellular model, time steps the sub-cellular SBML and whole body PBPK/SBML models, and transfers values between scales. Zonation of the CyP450 is imposed on the SC model by the CC3D model. As a reference data set we used published human ADME data for blood levels following a 1g oral dose of APAP.



Adsorption, Distribution, Metabolism and Excretion (*ADME*) data (points), along with the reference model output (lines), for an oral 1g dose of APAP in humans.

Parameter Searches

To refine the multiscale model we generated 1025 parameter sets in which 37 of the model's parameters were random chosen from a Log-normal distribution ranging from 0.03 to 30 times the parameter's initial estimates. From these 1025 simulations (below), and using the sum of the absolute residuals for the predicted serum levels vs. time for APAP and the two main metabolites as the metric, we identified just four simulations (below right) that give reasonable reproductions of the ADME blood data. Analysis of the full set of simulations indicates extensive interactions between parameters both within a model scale and across scales (data not shown).



Fixed-point Parameter Sensitivities

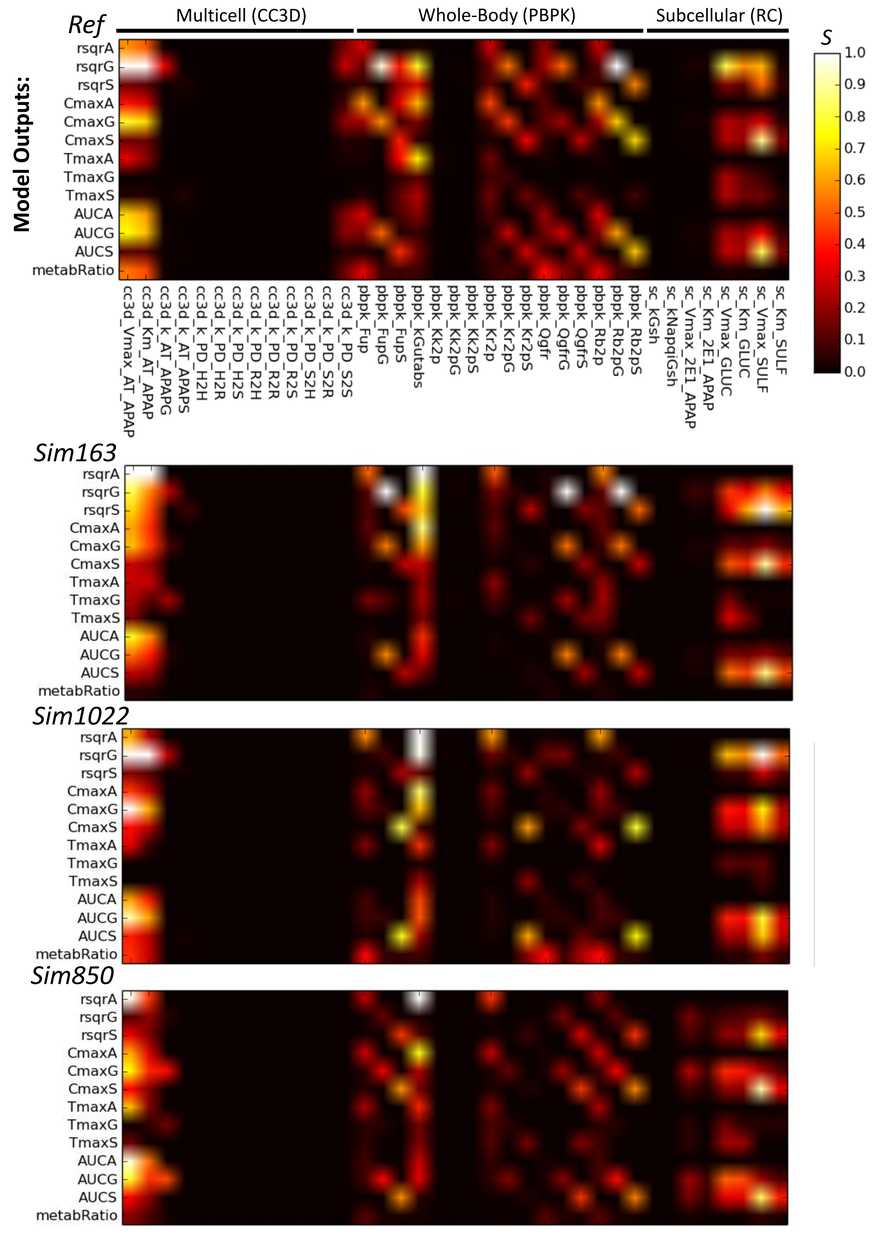
Using the four best models located in the parameter search we determined the fixed-point parameter sensitivities for the 9 *in vivo* measurables (plus 3 derived measurables) versus the 37 model parameters (tested at +/-25% of the reference value). The figures below show the sensitivities (S) versus parameters (the Jacobian Matrixes) for these four models.

$$S = \frac{|\partial Out_{Param^+}| + |\partial Out_{Param^-}|}{2}$$

In the CC3D model the Vmax and Km values are for active transport, using Michaelis-Menten kinetics, of APAP into the hepatocytes from the blood. The PD values are first order rate constants for passive diffusion transfer between compartment types where S, H and R refer to serum, hepatocytes and RBCs, respectively.

In the PBPK model Fup is fraction unbound in the blood for the indicated species. "Kk" values are first order transfer rate constants and "Kr" values are partition ratios. Qgfr values are the kidney glomerular filtration rate for the indicated species. "Rb" values are partition coeffi-cients between blood and plasma for the indicated species.

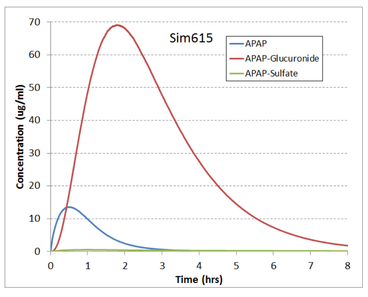
In the RC model the Vmax and Km values are Michaelis-Menten constants giving rise to the named product. APAP, APAPG and APAPS are APAP and the APAP glucuronide and sulfate, respectively. kGsh is the rate of synthesis of GSH and kNapqiGsh is the first order rate constant for the reaction of NAPQI with GSH.

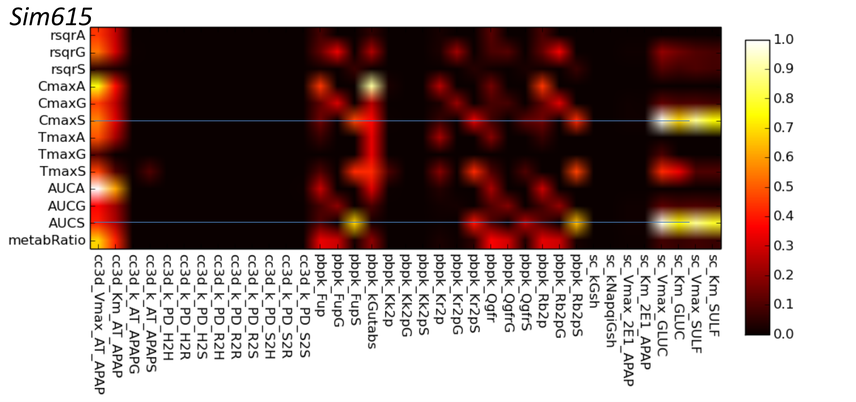


Though there is some variability in parameter sensitivities depending on the parameter set, overall these four models respond very similarly to their parameters. A more rigorous analysis of the fixed-point sensitivities is in progress.

Divergent Fixed-point Sensitivities

Examining other simulation results from the 1025 parameter scans identified many parameter sets that could represent the ADME profile of hypothetical compounds being processed by the ADME framework of this model. These "hypotheticals" present an opportunity to examine how the multiscale model's sensitivity changes as a function of a range of chemical, biological and model parameters. Below is the fixed-point sensitivity analysis for one such model that has a significantly different ADME profile (below left) compared to APAP. Surprisingly, this different ADME profile has a similar parameter sensitivity profile. The parameters that have significantly different sensitivities (compared to the four models above) are those that most directly impact the production of APAP-sulphate, which this parameter set produces very little of.





References

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3. The Systems Biology Workbench, including Jarnac, is available at http://sys-bio.org/.
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This research was funded by the US EPA (R835001) and the NIH (GM077138), which is gratefully acknowledged.