From Macro to Micro Dosimetry, Pharmacology and Toxicity: A multiscale modeling framework of Xenobiotics using open source tools.

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Pharmacological and toxicological processes occur across a wide range of scales and include multiple organ systems. A true Systems Biology pharmacological model must include submodels that cover multiple scales and multiple tissues relevant to human medicine and toxicology. We describe a multiscale modeling framework for xenobiotic pharmacology, metabolism and toxicity that incorporates ADME and PBPK whole body representations, tissue level (multicell) behaviors and subcellular signaling and metabolic pathways. At the ADME/PBPK level we represent uptake, distribution and excretion of a xenobiotic. At the multicell level we model tissue level behaviors such as cell proliferation and death. At the subcellular level we represent signaling, metabolic and gene expression processes. The models at each of these three scales communicate with the model(s) at higher or lower scales.

We link existing open source tools into an aggregate model and avoided building a single monolithic tool. This approach allows us to leverage not only preexisting tools but also preexisting models at the individual scales. We implement PBPK whole body models as Systems Biology Markup Language (SBML) models, multicell and tissue scale as CompuCell3D (CC3D) models and subcellular signaling, metabolism and gene expression models as SBML. Copies of the subcellular SBML models are embedded into each of the cells in the CC3D model. In turn, the CC3D model is a compartment (tissue) in the whole body PBPK model. CC3D uses the SBML ODE Solver Library (SOSlib) for solving systems of ODEs. CC3D controls the models at the higher and lower scales since both the whole body and subcellular models are expressed in SBML, which can be controlled by CC3D. The individual models at each of the three scales can generally be run as a standalone (single scale) model. This facilitates validation at the individual scales and makes it easy to incorporate preexisting single scale models developed by others.

As an example of linking these existing tools and models, from the whole body to the subcellular, we present a model of Acetaminophen ADME, pharmacological action and liver toxicity.