COLIN PHIPPS, University of Waterloo

Parameter identifiability and sensitivity in large molecule PBPK models

One of the primary utilities of physiologically-based pharmacokinetic (PBPK) models is to perform interspecies (e.g. human from animal), or intraspecies (e.g. child from adult) prediction. In many cases the model prediction task is estimating an output of interest, such as the area under the curve (AUC) or the maximum concentration (Cmax), in a specific model compartment or organ (e.g. blood, brain, liver). Ensuring accurate prediction of these outputs in populations where little to no data exists, as is the case in pediatrics or in certain disease states (e.g. renally-impaired), is imperative. During this talk, I will outline a workflow for identifying potential issues that can be encountered during PBPK model prediction using the example of a large molecule model. Unlike the perfusion-limited and permeability-limited frameworks that have been established for small molecules, there remain a number of issues that pervade large molecule models. Once the differential equation system has been mechanistically established there are various parameters related to this process that vary in each organ (e.g. transvascular fluid flow and lymphatic uptake rates) and depend on molecular properties (e.g. vascular and lymphatic reflection coefficients). Estimating these parameters from existing data is challenging due to parameter sensitivity and identifiability issues. If a relatively uncertain model parameter is not identifiable then confidence in the model could be weakened. In this case we will evaluate whether various outputs of interest for the pediatric model are sensitive to non-identifiable parameters in the adult model. If so, model reformulation or further experimentation may be required.