Automated model reduction for pharmacology models

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Quantitative systems pharmacology (QSP) and physiologically-based PK (PBPK) models are often too complex for population analysis in a clinical setting [5]. Developing an automatic and robust workflow for model reduction may help fill this gap [2, 6, 7, 8]. We constructed a computational pipeline in MATLAB that loads SimBiology models and allows users to define constraints (species of interest). We symbolically prepare nonlinear models to avoid linearizations and associated errors. Reduced-order models are automatically determined for a given model through proper lumping, where simulated annealing searches for the best lumping matrices for a given model order and a selection criterion determines the best reduced model [1, 3, 4]. This pipeline is applied to reduce the number of species and parameters, either separately or together. Then, the robustness of the selected reduced model is assessed at various doses and parameter values. The pipeline was applied to several nonlinear models, where predefined species of interest from the reduced models minimally deviated from the full models. Most notably, one model is reduced from 14 to 12 species and 38 to 22 parameters, while another is reduced from 17 to 11 species and 33 to 7 parameters. Our novel approach allows for automatic reduction of several types of models, while retaining high accuracy. The simplified models will be better suited for future population analyses.

References


