Automated model reduction for pharmacology models

J. Cisneros[1], J. Feigelman[2], and D. Lu[2]

[1] *University of Washington, Seattle, WA 98195*
[2] *Genentech, Inc., South San Fransisco, CA 94080*

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

[1] A. Dokoumetzidis and L. Aarons. Proper lumping in systems biology models. *IET Systems Biology*, 3(1):40–51, 2009.

[2] C. Hasegawa and S. B. Duffull. Automated scale reduction of nonlinear qsp models with an illustrative application to a bone biology system. *CPT Pharmacometrics Syst. Pharmacol.*, 7:562–572, 2018.

[3] C. Hasegawa and S. B. Duffull. Selection and qualification of simplified qsp models when using model order reduction techniques. *The AAPS Journal*, 20(2):1–11, 2018.

[4] S. Ledesma, G. Avina, and R. Sanchez. Practical considerations for simulated annealing implementation. In C. M. Tan, editor, *Simulated Annealing*, chapter 20. IntechOpen, Rijeka, 2008.

[5] S. Pan and S. B. Duffull. Automated proper lumping for simplification of linear physiologically based pharmacokinetic systems. *J Pharmacokinet Pharmacodyn*, 46:361–370, 2019.

[6] T. J. Snowden, P. H. van der Graaf, and M. J. Tindall. A combined model reduction algorithm for controlled biochemical systems. *BMC Systems Biology*, 11(17):1–18, 2017.

[7] T. J. Snowden, P. H. van der Graaf, and M. J. Tindall. Methods of model reduction for large-scale biological systems: a survey of current methods and trends. *Bull. Math. Biol.*, 79(7):1449–1486, 2017.

[8] T. J. Snowden, P. H. van der Graaf, and M. J. Tindall. Model reduction in mathematical pharmacology: integration, reduction, and linking of pbpk and systems biology models. *J Pharmacokinetics and Pharmacodynamics*, 45:537–555, 2018.