Continuous-infusion simulations in PBPK and QSP models reveal steady-state properties and rate-limiting steps.

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Intro

Many of the currently available model analysis tools have significant limitations as listed in Table 1. [1-3]. Here we explore extensions of the local sensitivity analysis to obtain an extensive, intuitive, and scalable sensitivity analysis for large-scale models.

Table 1: Overview of available model analysis methods

Method	Pros	Cons
Mathematical model analysis	• Comprehensive • Explicit assumptions	• Time + skill intensive • Only for small models • Not easy to interpret
Global sensitivity analysis	• Comprehensive • Easy to interpret	• Only relative parameter contributions • Sensitive to conditions
Local sensitivity analysis	• Easy to interpret • Allows specific predictions	• Time consuming • No combined parameter effects • Sensitive to conditions

Methods

The analysis toolbox presented here utilizes the standard sensitivity analysis spider plots as present in the esqlabsR package (v5.1.3) and the ospsuite package (v12.0.0) in R (v4.3.1). Simulation models were created using a whole-body Physiologically-Based Pharmacokinetic model (PK-Sim® v11.2) and extended in MoBi® (v11.2) to include TMDD or PD models. The created models were saved as .pkml files and analyzed in R using dedicated R code for the developed analysis toolbox.

Results

We developed a “repeated local sensitivity analysis spider plot”, a first extension of a single spider plot, by repeating the same analysis for various combinations of two other parameters that define relevant scenarios (Figure 1, Figure 4). The next step towards a comprehensive understanding of model behavior was the model modification with a continuous infusion to introduce a steady-state (Figure 1, 3). Finally, the output was normalized for the output of the neighboring compartment to identify the specific sensitivity for a single compartment (Figure 2, 3, 6).

Conclusion

As pointed out by Gabrielsson and Peletier[4], analyzing a system in a continuous infusion steady-state can provide significant insight into models with multiple nonlinearities, such as TMDD models. Here we provide such an analysis in a numerical sensitivity analysis framework. This framework allows the application of numerical steady-state analyses to large-scale PBPK or QSP models, as illustrated by the whole body PBPK and the PBPK-QSP examples. This analysis can be further normalized to provide insight into steady-state concentration ratios rather than absolute concentrations. Intermediary versions in between a single sensitivity analysis and a repeated normalized steady-state sensitivity analysis can be of additional value, such as the (normalized) repeated sensitivity analysis.

Acknowledgments

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References

[1] D. Lee, S. Nayak, S.W. Martin, A.C. Heatherington, P. Vicini, F. Hua, J. Thromb. Haemost. 14 (2016) 2430–2445. https://doi.org/10.1111/jth.13515.

[2] S. Bakshi, E. de Lange, P. van der Graaf, M. Danhof, L. Peletier, CPT Pharmacomet. Syst. Pharmacol. 5 (2016) 339–351. https://doi.org/10.1002/psp4.12098.

[3] L.A. Peletier, J. Gabrielsson, J. Pharmacokinet. Pharmacodyn. 39 (2012) 429–451. https://doi.org/10.1007/s10928-012-9260-6.

[4] J. Gabrielsson, L.A. Peletier, AAPS J. 19 (2017) 772–786. https://doi.org/10.1208/s12248-016-0031-y.

Continuous-infusion repeated sensitivity analysis for steady-state analysis and model characterization

From local sensitivity analysis to Continuous-Infusion Repeated Sensitivity Analysis (CIRSA)

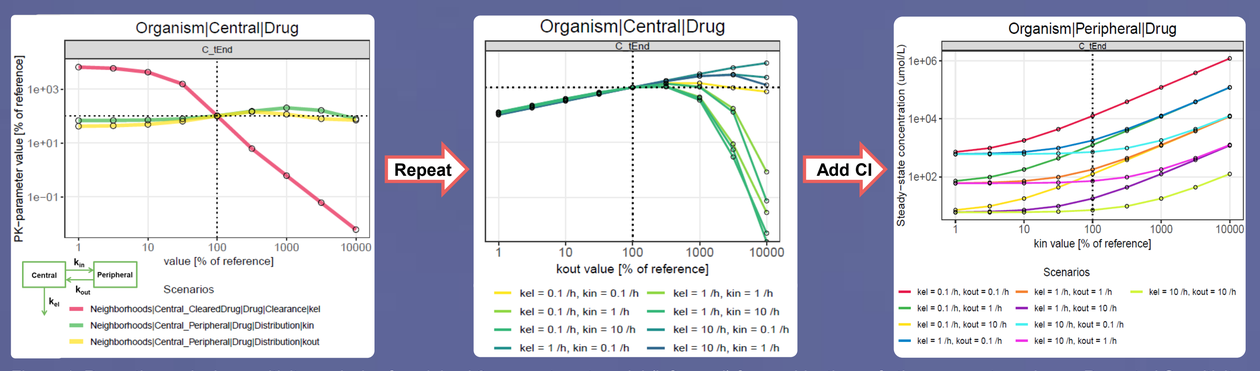
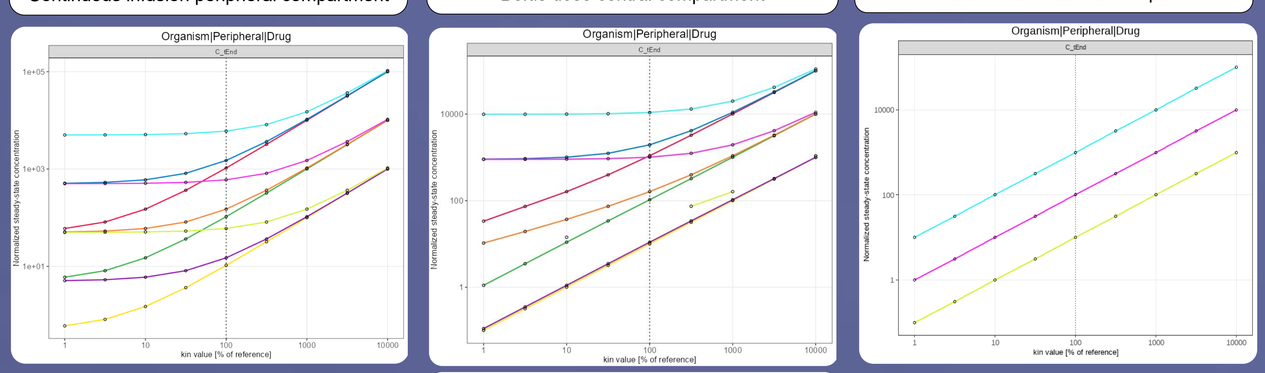


Figure 1: Repeating a single sensitivity analysis of a minimal 2-compartment model (left panel) for combinations of other parameters gives a Repeated Sensitivity Analysis (RSA, middle panel). Replacing the bolus dose by a continuous infusion and increasing simulation time to ensure steady-state yields a Continuous-Infusion Repeated Sensitivity Analysis(CIRSA, right panel). Reference values for kin, kout, and kel are 1/h.

Continuous-infusion analysis of the two-compartment model reveals two steady-states that are both relevant for bolus dose conditions



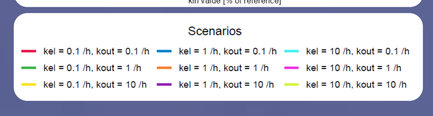
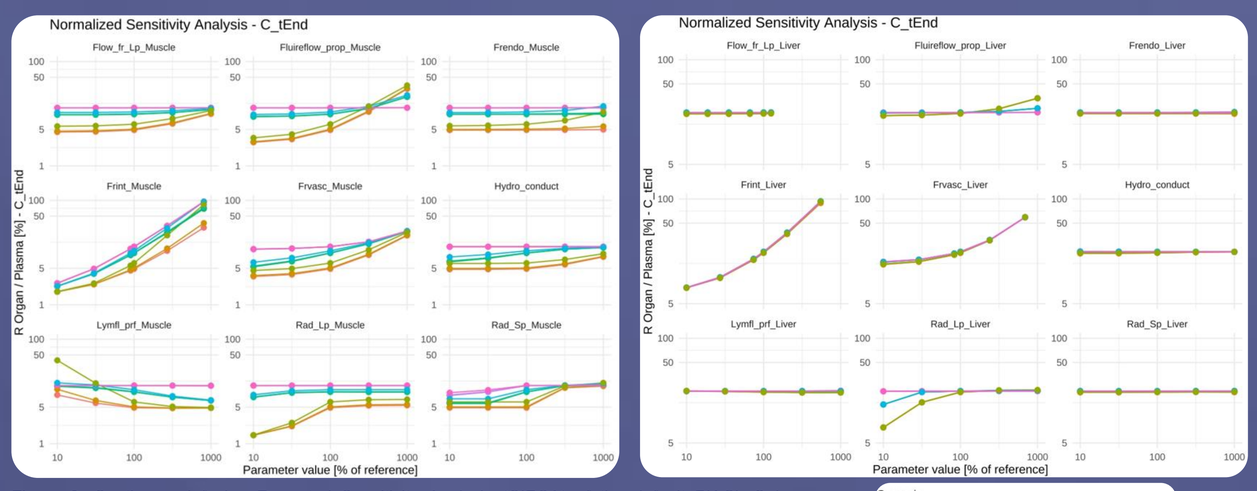


Figure 2: Normalized Continuous-Infusion Repeated Sensitivity Analysis of a minimal 2-compartment model. Reference values for kin, kout, and kel are 1/h. For normalization, concentrations in the peripheral compartment are divided by concentrations in the central compartment.

Application to the default PK-Sim two-pore model



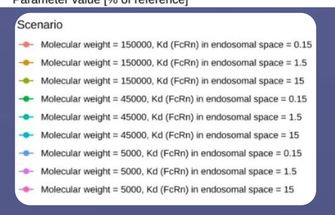
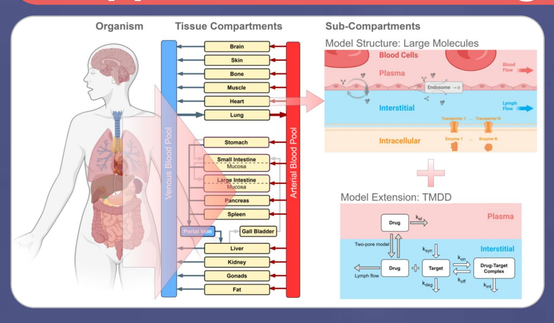


Figure 3: Continuous-Infusion Repeated Sensitivity Analysis (CIRSA) of the default PK-Sim® large-molecule model. Each point represents the final simulated concentration ratio between plasma and the whole organ in a simulation with continuous infusion of the drug in plasma. The parameter indicated on top of each panel is varied over a ten-fold range up and down for each combination of molecular weight and endosomal FcRn affinity listed in the legend. The left panel shows the muscle concentrations, and the right panel shows the liver concentrations. Parameter abbreviations refer to the following parameter names, from top left to bottom right: Flow fraction via large pores, Fluid recirculation flow proportionality factor, Fraction endosomal, Fraction interstitial, Fraction vascular, Hydraulic conductivity, Lymph flow proportionality factor, Radius (large pores), Radius (small pores).

Application to an integrated MoBi PBPK-TMDD model



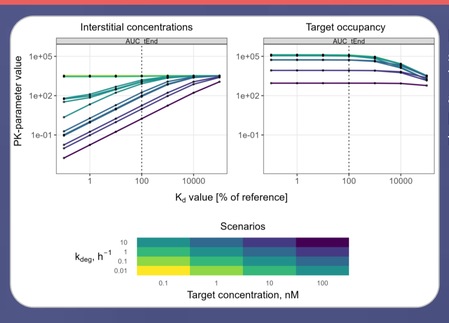


Figure 4: Repeated sensitivity analysis of a Tissue TMDD model with a single IV dose of an IgG. The reference value for Kd is 1 nM.

Application to a default PK-Sim small molecule model

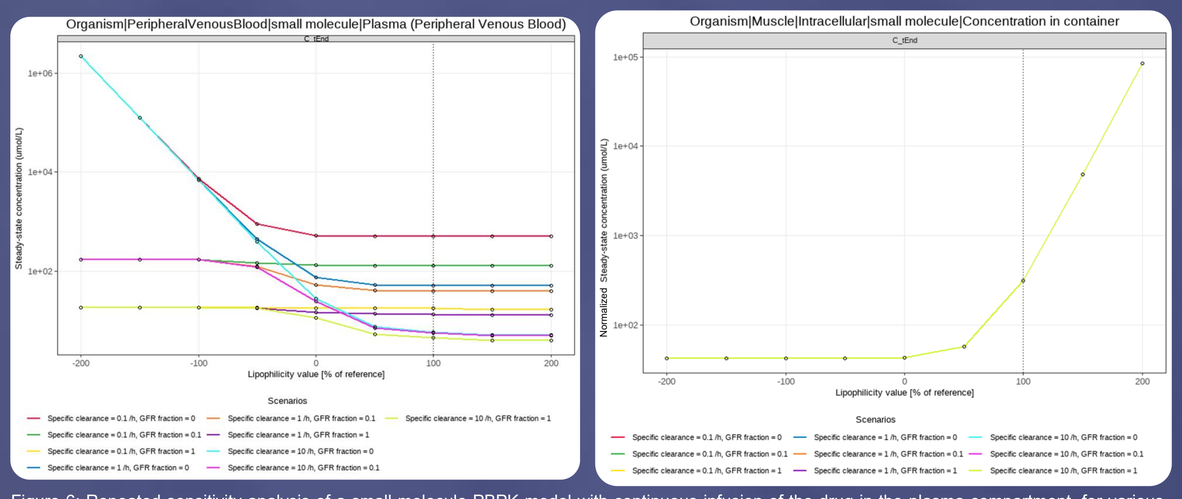


Figure 6: Repeated sensitivity analysis of a small molecule PBPK model with continuous infusion of the drug in the plasma compartment, for various parameter value combinations. The reference value for lipophilicity is 1. For normalization, the Muscle intracellular concentrations were divided by the plasma concentration.

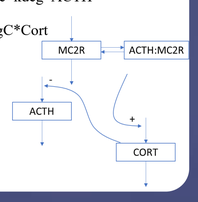
Application to an integrated MoBi PBPK-QSP model

Corticosterone and ACTH are in a feedback loop trough MC2R binding:

$$\frac{dACTH}{dt} = \text{kdegA} * \left(\frac{Cortbase}{Cort}\right)^{Corteffect} * \text{ACTHbase} - \text{kdeg} * \text{ACTH}$$

$$\frac{dCort}{dt} = \text{kdegC} * \frac{Emax * ROnorm^{\gamma}}{EC50^{\gamma} + ROnorm^{\gamma}} * \text{Cortbase} - \text{kdegC} * \text{Cort}$$

$$\text{ROnorm} = \frac{\text{ACTH:MCR2}}{\text{MCR2base}}$$



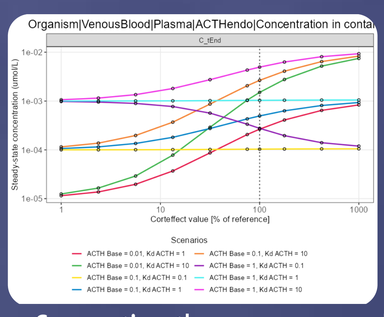


Figure 5: Continuous-Infusion Repeated Sensitivity Analysis of a QSP model of ACTH/Corticosterone feedback for understanding of its steady-state behaviour. The reference value for the “Corteffect” parameter is 1.

Modeling Scaling Coding

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