Validation and refinement of the large molecule biodistribution model in PK-Sim®.

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Intro

The predictive performance of the PK-Sim large molecule biodistribution model has been publicly evaluated on a dataset from 8 different molecules, of which 6 were monoclonal antibodies, one was a domain antibody of 25 kDa, and one was the 5.5 kDa protein inulin.[1] Novel modalities like scFv, F(ab), nanobodies, and affibodies have not been included, and only non-residualizing labels were used in this dataset.

We aimed to increase the variety of the data used for biodistribution validation and refinement by using a larger dataset, including more therapeutic modalities and both residualizing and non-residualizing radiolabels.

Methods

Simulation models were created using the large molecule model in PK-Sim® v12.0, including the two-pore distribution model shown in Figure 1, and were extended with renal clearance, organ-specific endosomal clearance compartments, and a residualizing radiolabel observer in MoBi® (v12.0). Data were collected from the literature and included 35 different molecules with biodistribution data for mice, rats, and monkeys. The dataset for non-residualizing labels included data for 4 mAbs, 4 Fabs, a nanobody, a diabody, two affibodies, and a scFv. The normalized continuous-infusion repeated sensitivity analysis was run in R using the esqlabsR package. Parameter identifications were performed in MoBi using the Levenberg-Marquardt algorithm.

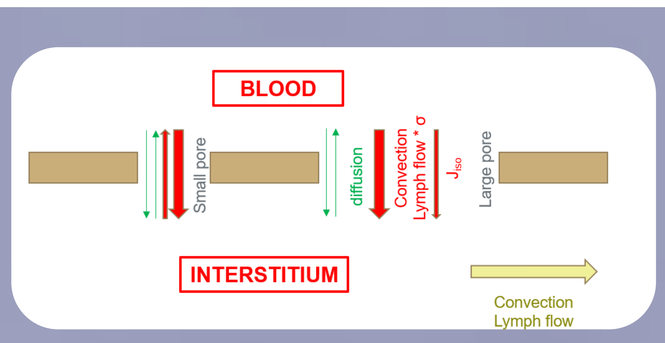

Figure 1: Schematic representation of the two-pore model as applied in the PK-Sim large molecule model. Large molecules distribute between plasma and interstitial space through bidirectional diffusion through both pores, and mainly monodirectional convection from plasma to interstitial space, and as lymph flow back to the central circulation.

Results

Here we present the first results, focusing on the non-residualizing radiolabel biodistribution data. Firstly, a repeated sensitivity analysis showed that the plasma/whole-organ ratio depends more on molecular size compared to FcRn affinity, and is sensitive mainly to the interstitial fraction and the vascular fraction in organs with a more leaky vasculature, like liver, and organs with a more tight vasculature, like muscle (Figure 2). A size-dependent sensitivity was also observed in muscle for the large-pore radius and the fluid recirculation flow. With these results, the interstitial fraction and vascular fraction were estimated in 4 organs for which rich data were available in our dataset (Table 1). In addition to the system-specific parameters, compound-specific parameters were estimated to describe clearance and distribution volume/kg by estimating the administered dose and the FcRn affinity for monoclonal antibodies, and the renal clearance for the other modalities. Finally, we compared the Goodness-Of-Fit for the optimized model with the default model. Firstly, the total error, as determined by the log-scaled residuals, went down from 5.1 to 4.5, indicating a relevant improvement in the overall fit. Furthermore, the default model showed a slightly stronger trend in the residuals over time compared to the optimized model (Figure 3).

Conclusion

In this study, we have successfully expanded the validation of the biodistribution of large molecules for new modalities, including nanobodies, fabs, affibodies, diabodies and scFvs. While the default model already performed well to describe the plasma to organ ratios in 4 main organs, it could be further improved by estimating the interstitial and vascular fractions in each organ.

Acknowledgements

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References

[1] C. Niederalt, L. Kuepfer, J. Solodenko, T. Eissing, H.-U. Siegmund, M. Block, S. Willmann, J. Lippert, A generic whole body physiologically based pharmacokinetic model for therapeutic proteins in PK-Sim, J. Pharmacokinet. Pharmacodyn. 45 (2018) 235–257. https://doi.org/10.1007/s10928-017-9559-4.

Continuous-Infusion Repeated Sensitivity Analysis, model validation and parameter optimization

Continuous-Infusion Repeated Sensitivity Analysis (CIRSA) of the default PK-Sim® large-molecule model.

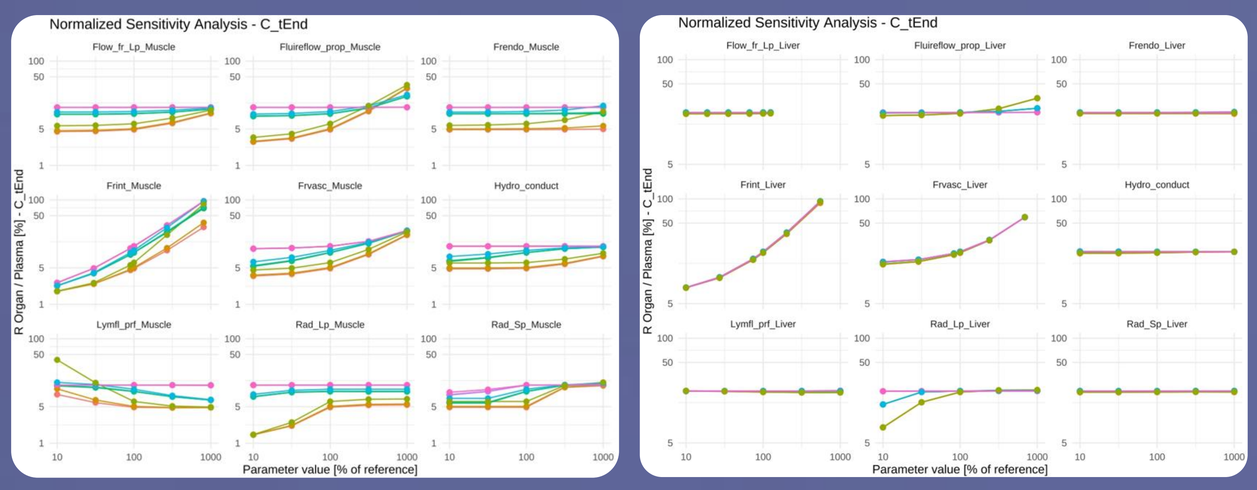

Figure 2: Continuous-Infusion Repeated Sensitivity Analysis (CIRSA) of the default PK-Sim® large-molecule model. Each point represents the final simulated concentration ratio between plasma and the whole organ in a simulation with continuous infusion of the drug in plasma. The parameter indicated on 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).

Parameter optimization and model comparison

Table 1: Parameter value estimation with the default values from the PK-Sim large molecule model, optimized system-specific values after parameter identification and the % change of the optimized value compared to the default value

Parameter	Default value	Optimized value ± 95% CI	% change
Fraction interstial Liver	0.16	0.13 +- 0.06	19
Fraction vascular Liver	0.12	0.17 +- 0.09	42
Fraction interstitial Lung	0.19	0.08 +- 0.12	58
Fraction vascular Lung	0.63	0.41 +- 0.09	35
Fraction interstitial Muscle	0.12	0.05 +-0.02	58
Fraction vascular Muscle	0.03	0.05 +- 0.01	67
Fraction interstitial Spleen	0.15	0.12 +- 0.08	20
Fraction vascular Spleen	0.28	0.14 +- 0.12	50

Default and optimized model comparison

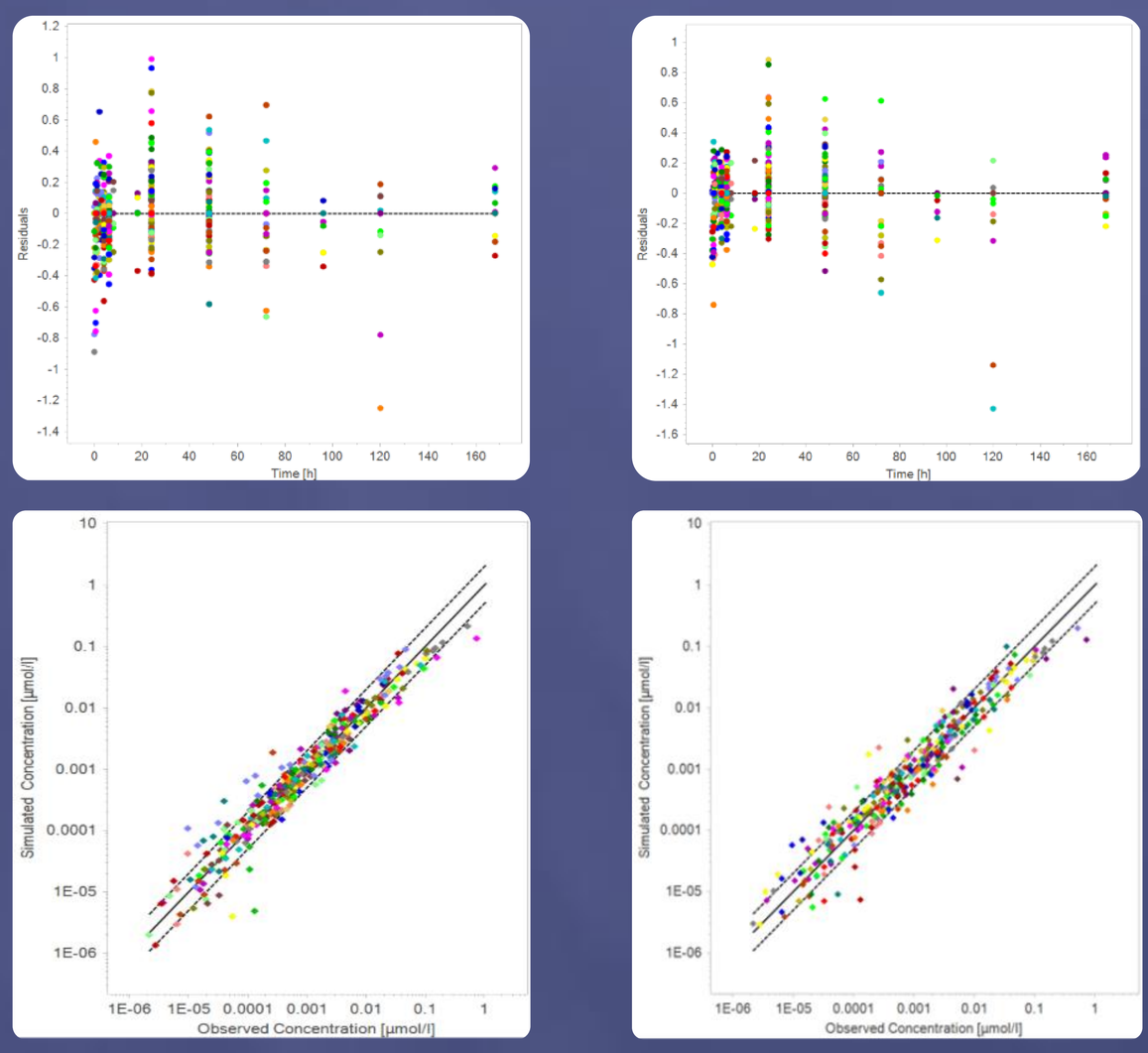

Figure 3: Goodness-Of-Fit plots with residuals versus time in the upper panels, and observed versus predicted in the lower panels. Left panels show the default models, where only drug-specific properties were fitted, while right panels show the optimized models. The diagonal lines in the lower panels represent a two-fold deviation from the line of identity.

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