Integrating Target Mediated Drug Disposition (TMDD) into a minimal physiologically based modelling framework: evaluation of different quasi-steady-state approximations

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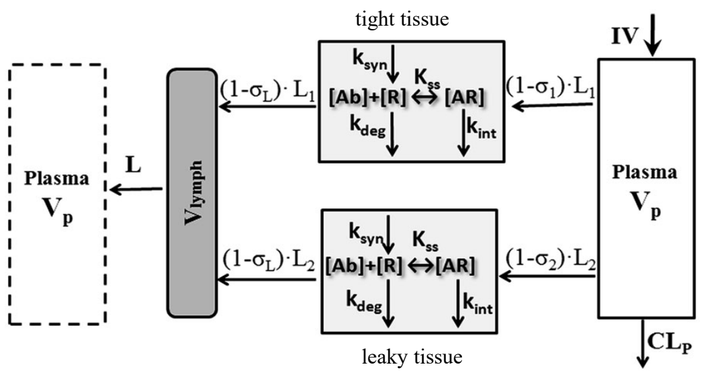
Background

Minimal physiologically based pharmacokinetic (mPBPK) models provide a simple and sensible approach that incorporates physiological elements into PK analysis. With this modelling concept, a second-generation mPBPK model was developed with specific accommodations for the unique PK properties of monoclonal antibodies (mAb) [1]; in [2] the target-binding process approximated by a quasi-steady-state model was also incorporated. The aim of this work is to evaluate the impact of different approximations on plasma and tissue concentration profiles generated with mPBPK-TMDD models and to understand how informative is plasma PK about binding processes occurring in periphery.

Methods

The full minimal PBPK model: the model structure, published by Cao and Jusko [1], with binding occurring in either leaky or tight tissue was considered (see Figure 1).



Param	Unit	Value	Sensitivity analysis range	
			Min	Max
σ1	-	0.99	0.715	0.99
σ2	-	0.712	0.25	0.75
CLp	ml/h/kg	0.128	0.01	1
Kss	nM	1.31	0.965	20
ksyn	nM/h	0.172	-	-
kdeg	10^{-2}/h	1.21	-	-
kint	10^{-2}/h	0.624	0.06	6
KD	nM	0.963	0.1	1.30
kon	1/nM/h	0.018	-	-
koff	1/h	0.017	-	-

Figure 1: Second-generation minimal-PBPK model structure for monoclonal antibody with target-mediated drug disposition in interstitial fluid. The plasma compartment in the left box represents the venous plasma as in full PBPK models, but is not applied in the present model [1].

Table 1: MPBPK parameter values used in the simulations and parameter ranges for the sensitivity analysis.

Simulations: Simulation of the full model was performed using mPBPK model parameters estimated in [1]. Additionally a plausible value of KD was assigned, with binding parameters kon and koff obtained as derived ones (see Table 1).

Simulations were also performed adding progressively three different approximations to the full model:

A- Binding process at quasi-steady state (as in [2])

B- Receptor concentration at quasi-steady state [3]

C- Free antibody tissue concentration at quasi-steady-state [3].

Simulations were performed at two dose levels administered intravenously: 1 and 5 mg/kg. Samples were simulated every 5 hours up to 84 days.

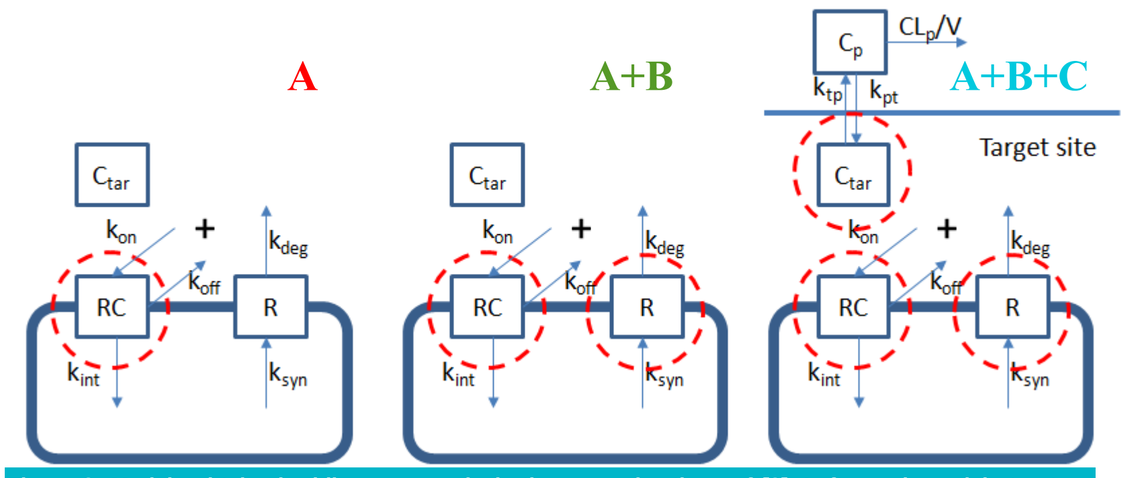


Figure 2: Models obtained adding progressively the approximations of [3]. Left panel: model structure with approximation A; central panel: model structure with approximations A and B; model structure with approximations A, B and C. The red dashed circles indicate the variable at quasi steady state.

Sensitivity analysis The sensitivity analysis was performed for all four models on the following parameters: σ1, σ2, CLp, Kss, Kint and KD. The parameter ranges used for these parameters are reported in Table 1.

Model estimation: The full model and the model with approximation A were fitted in different situations:

- with binding in leaky tissue or in tight tissue adding data from tissue compartments (total drug concentration or total receptor concentration)
- with different NONMEM estimation methods
- with different sampling schemes

Drug related parameters (see Table 1) were estimated, while volumes and flow rate parameters were fixed to typical physiological values.

Software. Model simulations and sensitivity analysis were implemented in Mlxtran, the model coding language used by Monolix, MlxPlore and Simulix. The Mlxtran code is run from R (version 3.1.2) by calling the Simulx function of the R package mlxR.

Model estimations were performed with NONMEM 7.3.

Results

Simulations with binding in the leaky tissue

- Model A generates the closest profiles to the full mPBPK model in plasma and target site for both compound and receptor variables, free and total (see Figure 3).
- Model A+B deviates from the full model mainly in the receptor concentration profiles (see Figure 3).
- Model A+B+C systematically deviates from the full mPBPK for both drug and target concentrations (see Figure 3).

Simulations with binding in the tight tissue

•All approximation models after a transient period of 3 or 4 weeks overlap with the full mPBPK model (plots not shown). This was predictable for the plasma drug concentration profiles: binding in tight compartment does not affect the PK in plasma.

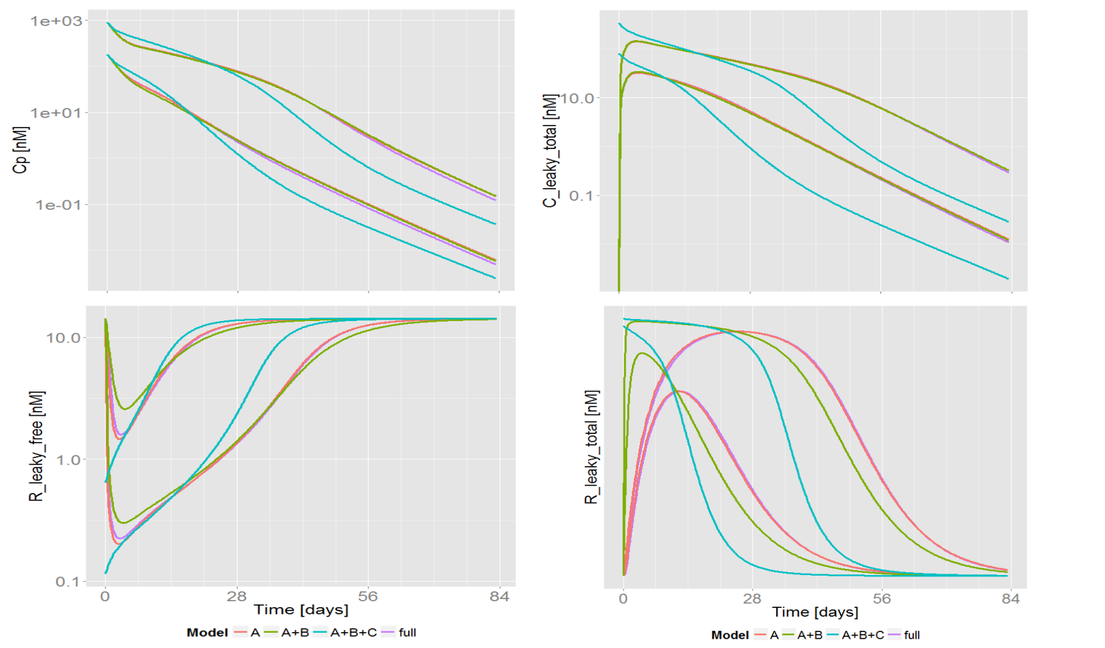


Figure 3: Simulations of the two IV doses, with binding in the leaky tissue with full model (orchid) and approximations of the binding process (Indian red), binding process and target turnover (olive), binding process, receptor turnover and drug concentration at the target site (sea green). Upper left panel: free drug concentration in plasma. Upper right panel: total drug concentration in leaky tissue. Lower left panel: free receptor concentration in leaky tissue. Lower right panel: total receptor concentration in leaky tissue.

Sensitivity analysis for binding in leaky tissue: As regards the plasma drug concentration, it appears that the change in KD (equal to the ratio koff/kon) does not affect significantly the shape of the profiles obtained with the different models, while the change in the other parameters tested (CLp for example) has a significant impact at both doses (see Figure 4).

Not all the models are affected in the same way by the change in parameters.

The observations provided by this analysis help in detecting the most critical parameters to identify from only plasma data.

(Results for the sensitivity analysis performed on the models with binding in tight tissue not reported)

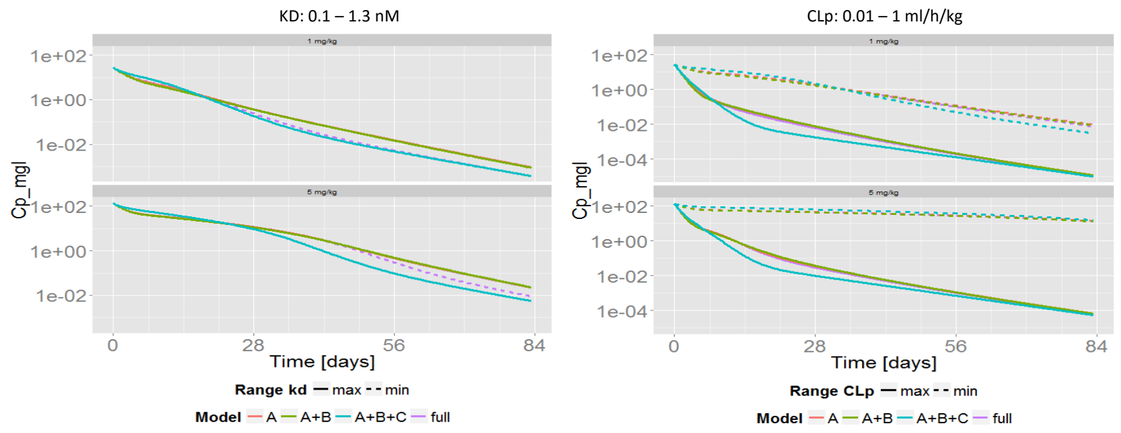


Figure 4: Plasma drug concentrations obtained with the four models varying KD (left panel) and CLp (right panel) from its minimum (dashed line) to its maximum (solid line). Upper panels: simulations at 1 mg/kg; lower panels: simulations at 5 mg/kg.

Model estimation: Both full model and model A showed identifiability issues, especially as far as binding and receptor parameters are concerned. The results of the identification are extremely sensitive to the amount of data provided, to the noise in the data and to the initial values (see Figure 5).

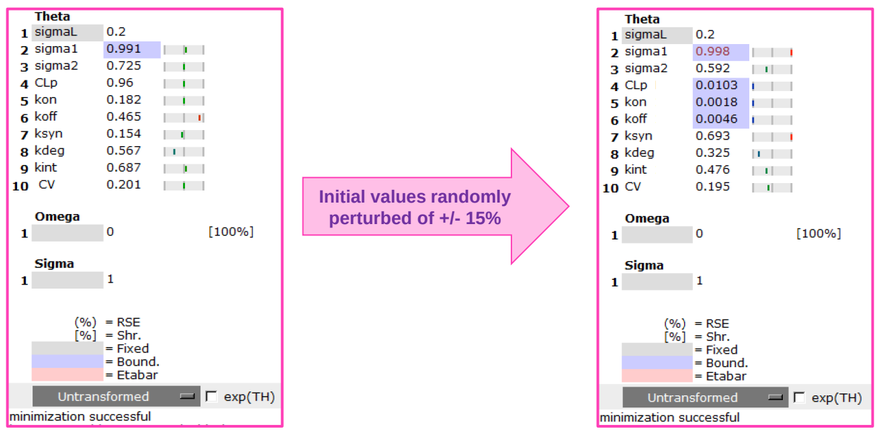


Figure 5: Identification test for the full mPBPK-TMDD model with binding in the leaky tissue with a realistic sampling scheme and initial values equal to the true values in Table 1 (left panel, CLp is reported in L/h), or to the true values randomly perturbed of +/-15% (right panel).

Conclusions

- **Simulations:** If the binding occurs in leaky tissue, approximation A generates the closest profiles to the full model.
- **Sensitivity analysis:** Plasma drug concentration profiles obtained with the four models are not equally sensitive to the change in different parameters. Some of them do not affect the shape of the observable data.
- **Model estimation:** Both tested models, full and A, showed identifiability issues in the various scenarios experimented.

References

1. Cao Y, Balthasar JP, Jusko WJ (2013). Second-generation minimal physiologically-based pharmacokinetic model for monoclonal antibodies. J Pharmacokinet Pharmacodyn 40(5): 597-607.
2. Cao Y, Jusko WJ (2014). Incorporating target-mediated drug disposition in a minimal physiologically-based pharmacokinetic model for monoclonal antibodies. J Pharmacokinet Pharmacodyn 41(4): 375-387.
3. Grimm HP (2009). Gaining insights into the consequences of target-mediated drug disposition of monoclonal antibodies using quasi-steady-state approximations. J Pharmacokinet Pharmacodyn 36(5): 407–420.

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