A simulation study to investigate the identifiability of parameters in a minimal PBPK model structure with target binding

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Objectives

To use simulations for investigating the ability to estimate the parameters of a minimal physiologically based pharmacokinetic (PBPK) model structure with target binding.

Methods

A **minimal PBPK** model of target engagement was constructed to represent localized inflammation [1].

Most organs were lumped into either **tight** or **leaky** compartments, while a third compartment was constructed to understand target binding in a **diseased tissue**.

Target was assumed to be primarily synthesized in the interstitial space (ISF) of the diseased tissue (50%), but also, at a lesser extent in plasma (12.5%) and the ISF of other tissues (tight 25%, leaky 12.5%), eliminated systemically from the plasma space, and distribute in the tissues through lymphatics, both uptake and recycling.

The drug distributes into the compartments and binds to the target in all compartments, while it is eliminated from plasma.

The drug-target complex can distribute among the compartments and is eliminated from plasma.

The parameters to be estimated were:

- Drug and complex plasma clearance
- Target plasma half-life and initial plasma concentration
- Binding parameters.

Two scenarios about the target half-life were considered:

Scenario A: A short half-life (30 minutes)

Scenario B: A longer half-life (6 hours)

The identifiability of the parameters was examined by two methods:

Method EST: By simulating concentration time profiles with the model and attempting to estimate the desired parameters. The relative bias (RBIAS) and the standard errors (RSE) of the estimates were calculated in order to assess the accuracy and the precision of the estimation.

Method FIM: By evaluating the Fisher Information Matrix (FIM) for the true parameter values and calculating the RSEs of the parameters.

Two datasets were used:

(a) with two outputs, i.e. total drug and total target in plasma,

(b) with three outputs, i.e. same as in (a) plus the complex in plasma.

Further scenarios in the investigation included three levels of residual error added to the simulated values, 5%, 10%, while the FIM method was applied also with 20% error. Furthermore fixing binding parameters was considered. All options that were considered in the simulation study are summarized in Table 1.

Model structure is shown in the Scheme on the right. Main model parameter values are shown in Table 2. All simulations were carried out in MATLAB. The model was constructed using an “Ubiquity” Perl script [2].

Table 1. Summary of the entire simulation study. All simulations were carried out for both scenarios A and B. The selected results shown in Tables 3 and 4 are indicated with orange colour.

Outputs	Parameters to estimate	Residual error (cv)				
		5%		10%		20%
Three outputs	all	FIM	EST	FIM	EST	FIM
	fixed kon	FIM	EST	FIM	EST	FIM
	fixed kon, KD	FIM	EST	FIM	EST	FIM
Two outputs	all	FIM	EST	FIM	EST	FIM
	fixed kon	FIM	EST	FIM	EST	FIM
	fixed kon, KD	FIM	EST	FIM	EST	FIM

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The model

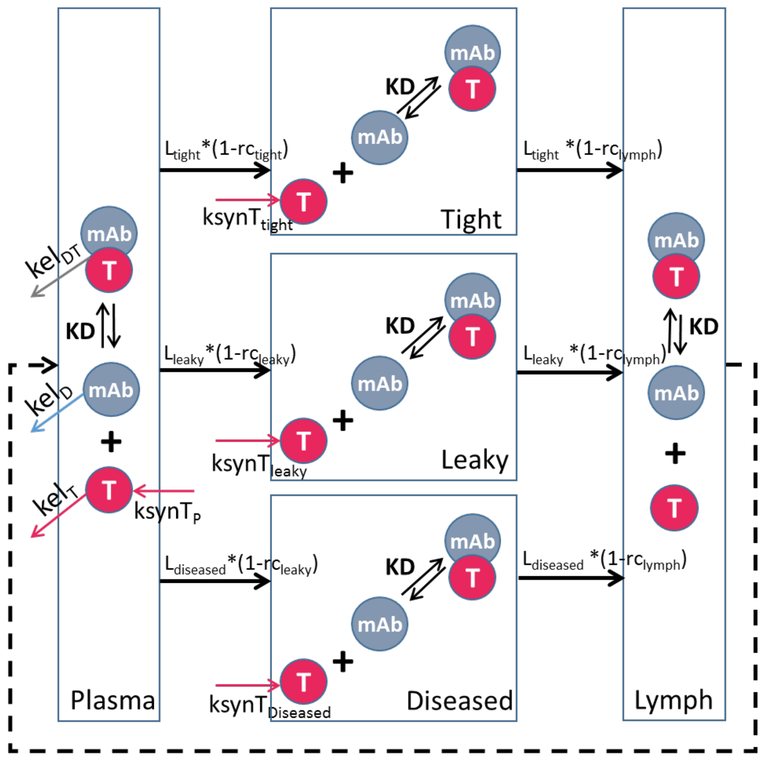

Table 2. Model key parameters

Parameters	Value	unit
Dose	2333	nmoles
CL drug plasma	0.31	L/day
C_{init} target plsm.	0.05	ng/ml
$t_{1/2}$ target	30	min
KD	0.04	nM
Kon	3	1/nM/day
Koff	0.12	1/day
MW drug	150	KDA
MW target (IL13)	16	KDA
Kel target	33.27	1/day
Ksyn target total	0.322	nmole/day
Kel complex	0.1	1/day
Refl. coef. tight	0.9	
Refl. coef. leaky	0.7	
Lymph flow total	3	L/day
F lymph fl. tight	0.33	
F lymph fl. Leaky	0.42	
F lymph fl. dis.	0.25	

Results

The two methods EST and FIM produced similar results, i.e. low RBIAS of EST corresponded to low RSEs in FIM and vice versa.

For **Scenario A**, drug clearance was estimated with high precision (RSE<2%, RBIAS <1%), target parameters (RSE<20%, RBIAS <5%) and complex clearance (RSE<23%, RBIAS < 17%) were reasonably estimated but binding parameters were not (RSE>48%, RBIAS <130%).

The three outputs gave better results than two outputs, especially for target affinity parameters and complex clearance. Indicative results are shown in Table 3 (two outputs) and Table 4 (three outputs)

Generally, similar results were drawn for **scenario B** (long target half-life, results not shown).

Table 3. Results for **two outputs** and **residual error of 10%**

	All parameters estimated				Fixed binding parameters			
		Simulation		FIM		Simulation		FIM
	Estimated parameter	RBIAS %	RSE %	RSE %	Estimated parameter	RBIAS %	RSE %	RSE %
CL drug plasma	yes	-0.81	0.82	0.94	yes	-1.02	0.80	0.87
C_{init} target plasma	yes	-2.16	6.23	8.69	yes	-5.37	6.29	8.10
$t_{1/2}$ target	yes	2.05	8.32	11.04	yes	0.30	7.75	10.03
Kon	yes	-77.35	68.60	134.83	no	-	-	-
KD	yes	137.29	30.31	74.78	no	-	-	-
CL complex plasma	yes	-17.25	11.38	15.65	yes	-5.96	5.79	7.34

Table 4. Results for **three outputs** and **residual error of 10%**

	All parameters estimated				Fixed binding parameters			
		Simulation		FIM		Simulation		FIM
	Estimated parameter	RBIAS %	RSE %	RSE %	Estimated parameter	RBIAS %	RSE %	RSE %
CL drug plasma	yes	-1.06	0.794547	0.89	yes	-1.28	0.79	0.85
C_{init} target plasma	yes	-1.02	6.37	7.90	yes	-3.40	6.06	6.98
$t_{1/2}$ target	yes	-2.07	7.66	9.67	yes	-3.44	7.28	8.35
Kon	yes	-67.95	67.18	97.93	no	-	-	-
KD	yes	82.49	32.10	54.83	no	-	-	-
CL complex plasma	yes	-5.93	7.85	11.37	yes	0.53	4.71	5.25

Conclusions

In a minimal PBPK model structure including target binding, most parameters except the binding parameters can be estimated reasonably, when data of total drug and total target in plasma are available. When total complex in plasma data are available, estimates of binding parameters and complex clearance improve.

References

1. Cao Y, Jusko WJ. Incorporating target-mediated drug disposition in a minimal physiologically-based pharmacokinetic model for monoclonal antibodies. J Pharmacokinet Pharmacodyn. 2014 Aug;41(4):375-87.
2. Harrold JM, Abraham AK. Ubiquity: a framework for physiological/mechanism-based pharmacokinetic/pharmacodynamic model development and deployment. J Pharmacokinet Pharmacodyn. 2014 Apr;41(2):141-51.