Guidelines to efficiently choose and diagnose target-mediated drug disposition models

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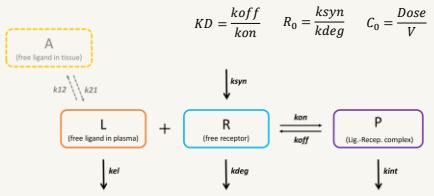
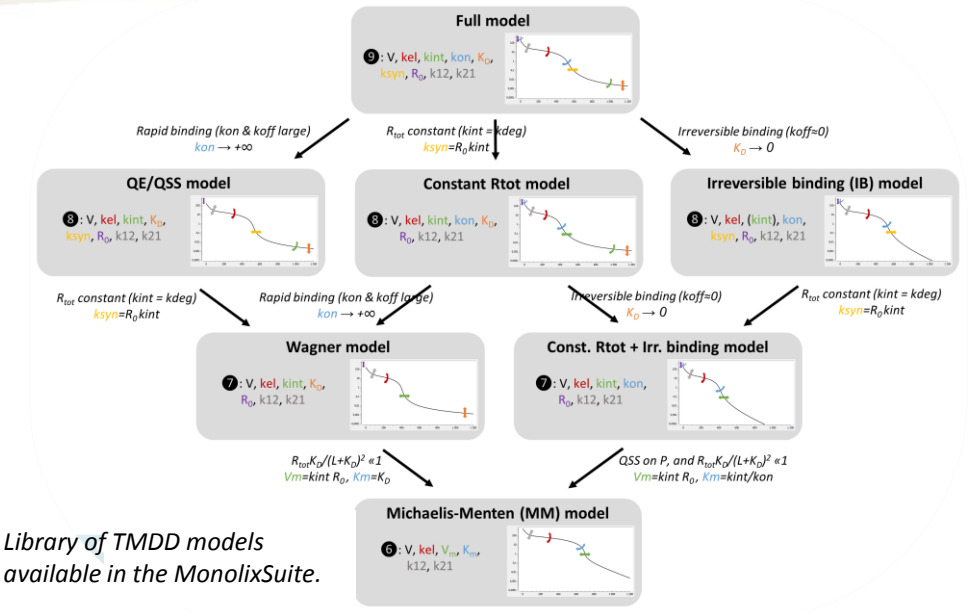
Introduction



A large variety of TMDD models have been proposed in the literature, corresponding to different modeling assumptions. Yet, it is often difficult to decide which TMDD approximation is the most appropriate for a given data set. We present guidelines to choose an appropriate model in a minimal number of iterations, using both a priori information and a posteriori diagnostic plots.

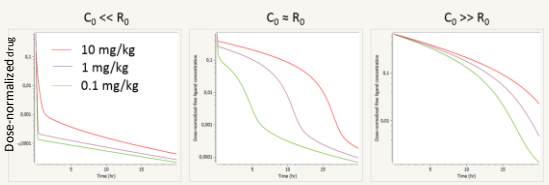


Library of TMDD models available in the MonolixSuite.

Choosing a first model

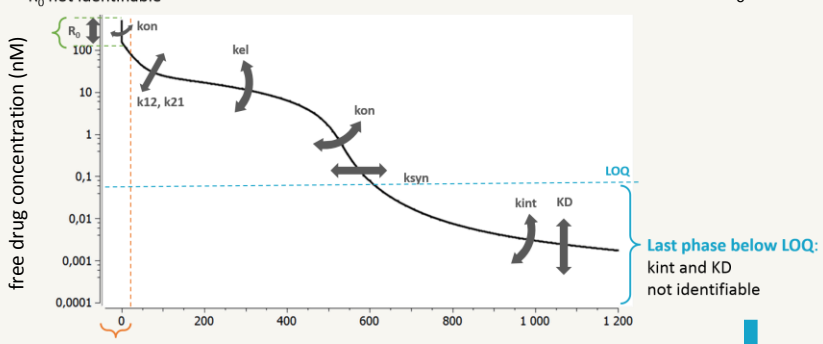
A) Only the free drug has been measured

The scheme below shows how the shape of the free drug concentration informs about non-identifiable parameters and thus the appropriate TMDD models.



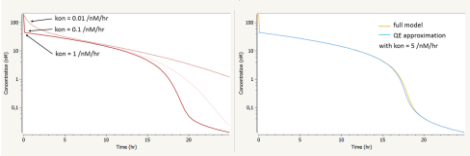
Choose MM or fix R_0

Low R_0 compared to C_0:
R_0 not identifiable

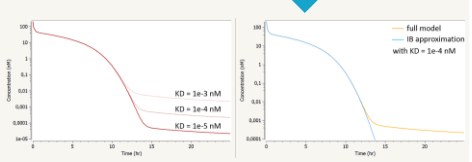


Last phase below LOQ:
kint and KD
not identifiable

No data at very early time points:
kon not identifiable



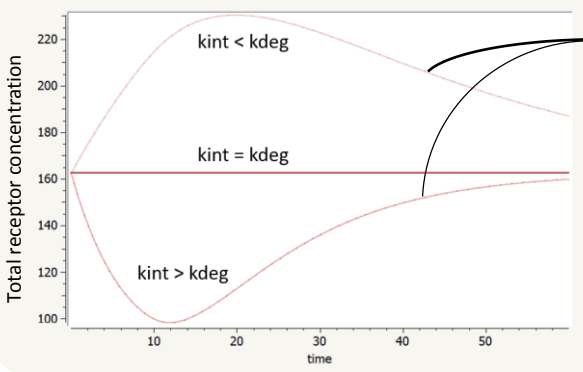
Choose QE/QSS, Wagner, or MM



Choose IB, const. Rtot + IB, or MM

B) The free drug and the total receptor have been measured

The shape of the total receptor concentration indicates if models assuming Rtot constant can be used. If not, it indicates if kint is larger or smaller than kdeg.



Total receptor is not constant:
one cannot assume kint=kdeg

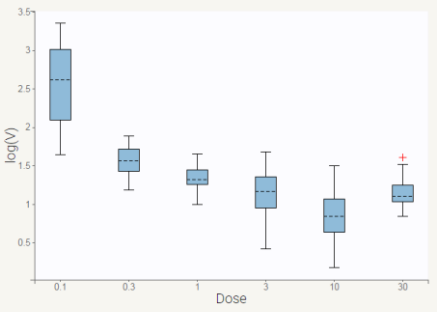
Choose Full, QE/QSS or IB

Diagnosing/improving the model

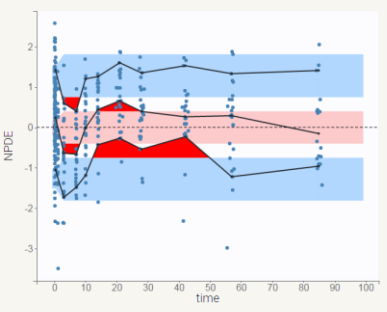
A) Examples of hints that the model is too simple

In this example, a MM model has been fitted on a data set that requires a QE model.

The individual parameter values change with the dose



Trend over time in the residuals (NPDE)



Tip: encode the dose group as categorical covariates in the data set to be able to split/color/filter by dose group

B) Examples of hints that the model is too complex

In this example, a QE model has been fitted on a data set that requires a MM model.

	R.S.E.(%)						
V_pop	3.72	1					
kint_pop	1.65e+03	0.10517	1				
KD_pop	1.79e+03	0.091524	0.99935	1			
ksyn_pop	6.37	0.11267	0.49302	0.49467	1		
R0_pop	88.1	-0.59441	-0.10596	-0.082823	-0.36656	1	
Cl_pop	6.79	-0.03859	-0.25668	-0.26094	-0.61011	0.021763	1
Q_pop	15.3	-0.11585	-0.026367	-0.027882	0.27228	-0.15639	-0.01514	1
V2_pop	6.16	0.09769	0.005152	-0.0077876	0.41405	-0.41887	-0.163	0.29624	1

High r.s.e and high correlation between kint_pop and KD_pop

Options to reduce the model complexity:

- use a simpler TMDD model
- remove the inter-individual variability on the parameters difficult to estimate
- fix the unidentifiable parameters

Available online

- Full case study with downloadable material
- Detailed description of all TMDD models
- Table of typical parameter values