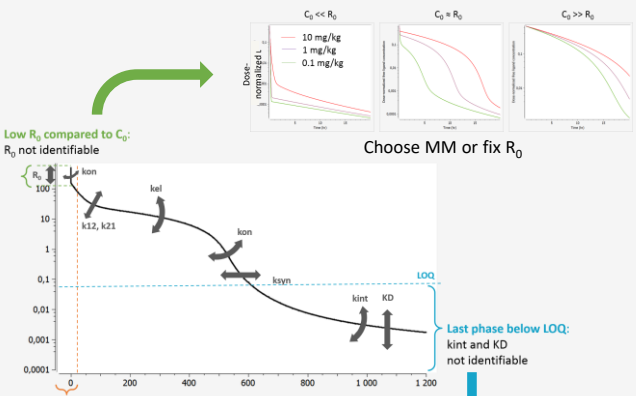
TMDD model development GUIDELINES

DO I NEED A TMDD MODEL?

- Type of molecule: biologics such as monoclonal anti-bodies, cytokines, growth factors, fusion proteins, antibody-small molecule drug conjugates or hormones
- NCA shows Vd, Cl, AUC/Dose or Cmax/Dose vary for different dose amounts or between first and subsequent doses
- Shape of the concentration-time curve
- Parameters of linear mixed-effect model vary with dose amount

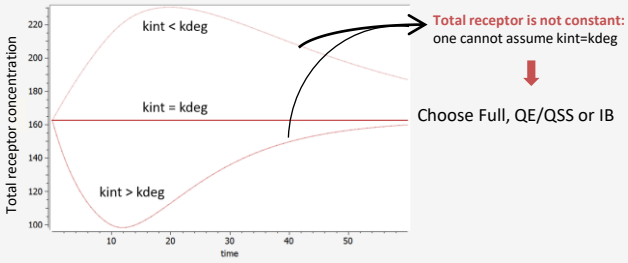
WHICH MODEL TO START WITH?

A) Only the free drug has been measured



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.



HOW TO SET THE INITIAL VALUES?

Best order to find the initial values using the "Check initial estimates":
V => Cl => Q (≈Cl) and V2 (≈V) => R0 (≈C0) => ksyn or Vm => KD or Km

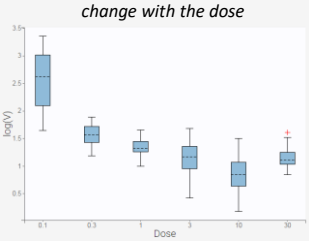
Parameter	Typical value	Parameter	Typical value
Dose	10-3000 nmol	kon	1-100 /nM/day
Cl, Q	0.24-1.4 L/day	koff	0.1-100 /day
V, V2	3-6 L	K_D	1-100 nM
ka	0.2-1.5 /day	ksyn	1-2 nM/day
kint (soluble target)	0.01-0.2 /day	kdeg	1-150 /day
kint (membrane target)	5-100 /day	R_0	0.001-10 nM

HOW TO DIAGNOSE THE MODEL?

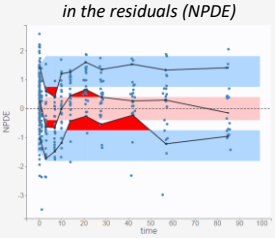
A) Examples of hints that the model is too simple

MM model has been fitted on a data set that requires a QE model.

The individual parameter values change with the dose



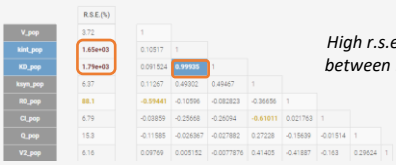
Trend over time in the residuals (NPDE)



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

QE model has been fitted on a data set that requires a MM model.



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

Tip: 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

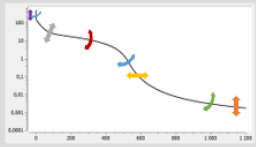
SimulationsPlus

Library of TMDD models for the MonolixSuite

SimulationsPlus

Full model

9: V, kel, kint, kon, K_D, ksyn, R_0, k12, k21



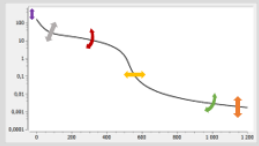
Rapid binding (kon & koff large)
kon → +∞

R_{tot} *constant (kint = kdeg)*
ksyn = R_0·*kint*

Irreversible binding (koff ≈ 0)
$K_D \rightarrow 0$

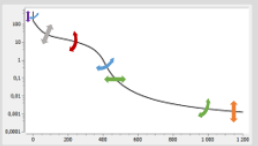
QE/QSS model

8: V, kel, kint, K_D, ksyn, R_0, k12, k21



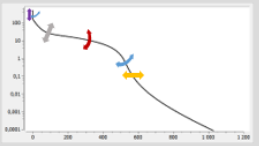
Constant Rtot model

8: V, kel, kint, kon, K_D, R_0, k12, k21



Irreversible binding (IB) model

8: V, kel, (kint), kon, ksyn, R_0, k12, k21



R_{tot} *constant (kint = kdeg)*
ksyn = R_0·*kint*

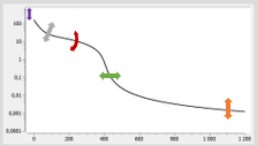
Rapid binding (kon & koff large)
kon → +∞

Irreversible binding (koff ≈ 0)
$K_D \rightarrow 0$

R_{tot} *constant (kint = kdeg)*
ksyn = R_0·*kint*

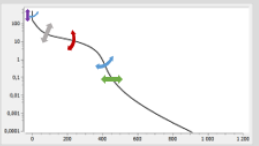
Wagner model

7: V, kel, kint, K_D, R_0, k12, k21



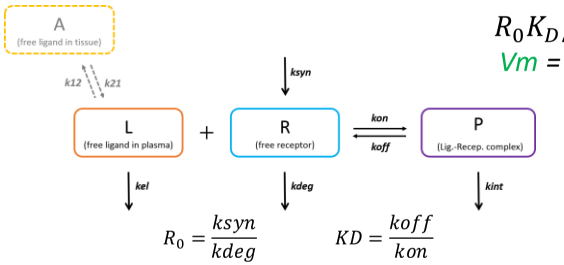
Const. Rtot + Irr. binding model

7: V, kel, kint, kon, R_0, k12, k21



$R_0 K_D/(L+K_D)^2 \ll 1$
Vm = R_0·*kint*, *Km* = K_D

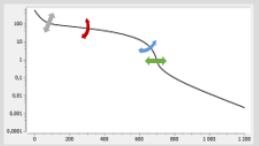
QSS on P
Vm = R_0·*kint*, *Km* = *kint*/*kon*



$R_0 = \frac{ksyn}{kdeg}$ $KD = \frac{koff}{kon}$

Michaelis-Menten (MM) model

6: V, kel, V_m, K_m, k12, k21



Learn more!