LIXOFT

Simulation of first-in-human using an allometrically scaled population mechanistic TMDD model

A step-by-step example with the MonolixSuite

Géraldine Ayral

Introduction

- First-in-human: what dose to choose to elicit the desired effect (efficacy), without causing harm (safety)?
- Translation of the preclinical information to human clinical trials is challenging.
- Scaling of the 'No Adverse Effect Level' dose based on body-weight or BSA has proven its limits, especially for biologics.
- Model-based prediction of the human PK is valuable for the first-in-human dose selection

Can we accurately predict the human PK using a model fitted on preclinical data?

Starting point

1521-0103/12/3413-702–708$25.00
THE JOURNAL OF PHARMACOLOGY AND EXPERIMENTAL THERAPEUTICS
Copyright © 2012 by The American Society for Pharmacology and Experimental Therapeutics
JPET 341:702–708, 2012

Vol. 341, No. 3
191999/3770786

A Model-Based Approach to Predicting the Human Pharmacokinetics of a Monoclonal Antibody Exhibiting Target-Mediated Drug Disposition

Kenneth T. Luu, Simon Bergqvist, Enhong Chen, Dana Hu-Lowe, and Eugenia Kraynov

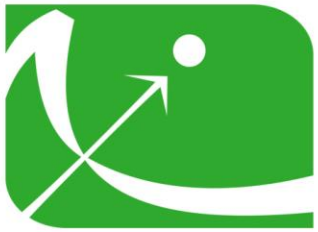
Clinical Pharmacology-Oncology Business Unit (K.T.L.), Oncology-Biochemistry & Primary Screening (S.B.), Oncology-Translational Research (E.C., D.H.-L.), and Pharmacokinetics, Dynamics and Metabolism (E.K.), Pfizer Global Research and Development, La Jolla, California

Received January 15, 2012; accepted March 12, 2012

- PF-03446962, an IgG2 antibody directed against human ALK1 receptor
- ALK1 is a cell surface type I receptor of the TGFß receptor family expressed on endothelial cells as well as various solid tumors
- ALK1 has been proposed as an antiangiogenic target that complements the antivascular endothelial growth factor therapy

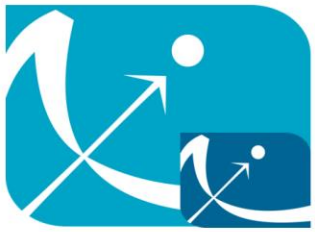
MonolixSuite

LIXOFT



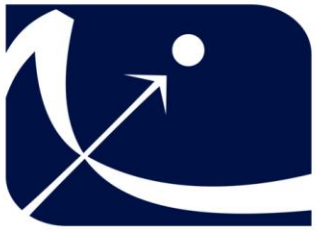
PKanalix

NCA and CA analysis



Monolix

Estimation, diagnosis, and run management

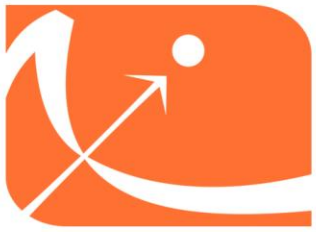


Mlxplore

Model exploration

Datxplore

Data exploration

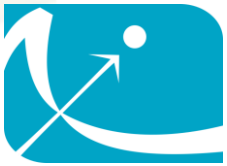


Simulx

Simulations

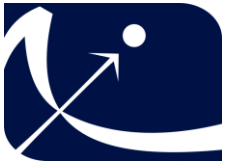
Agenda

1: visualize the monkey PK data at hand with Datxplore



2: develop a popPK model to capture the monkey data with Monolix

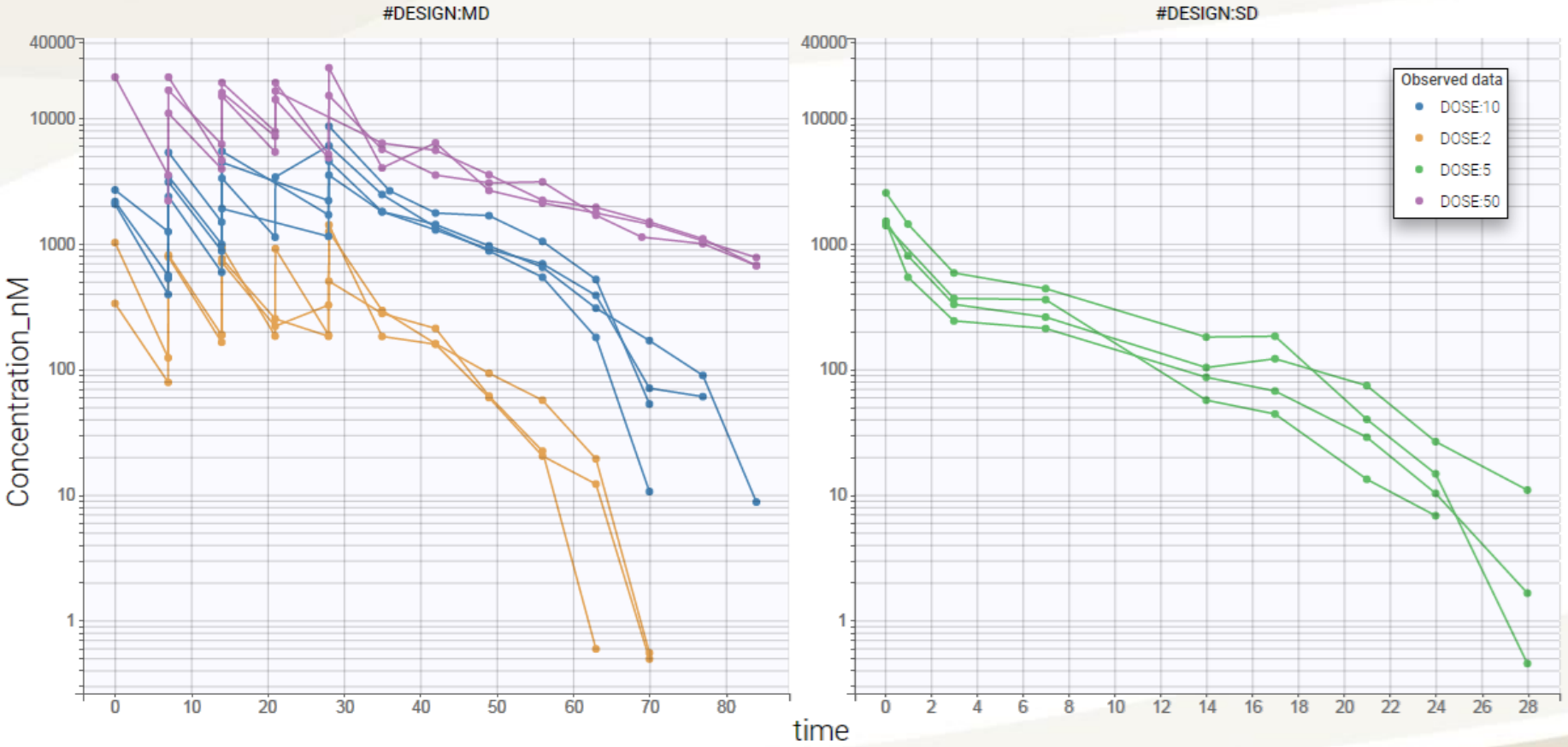
3: scale, and predict the human PK for various doses with Simulx



4: check the influence of the parameter scaling choices with Mlxplore

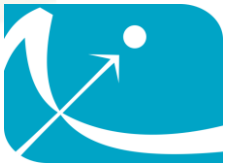
Datxplore: data visualization

Preclinical monkey data extracted from Luu et al.



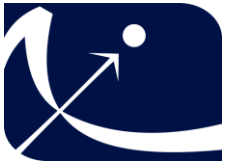
Agenda

1: visualize the monkey PK data at hand with Datxplore



2: develop a popPK model to capture the monkey data with Monolix

3: scale, and predict the human PK for various doses with Simulx

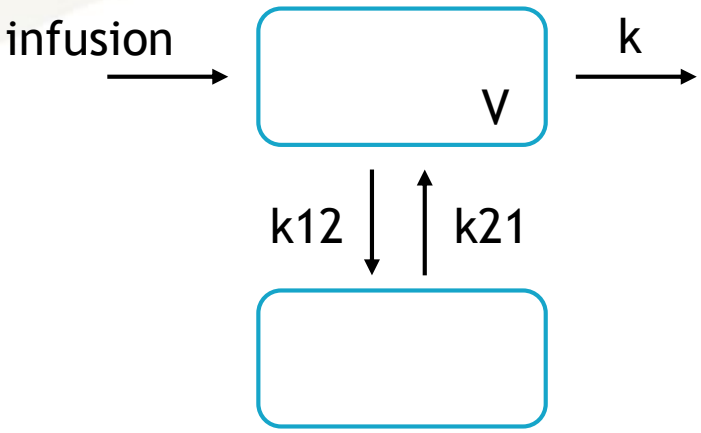


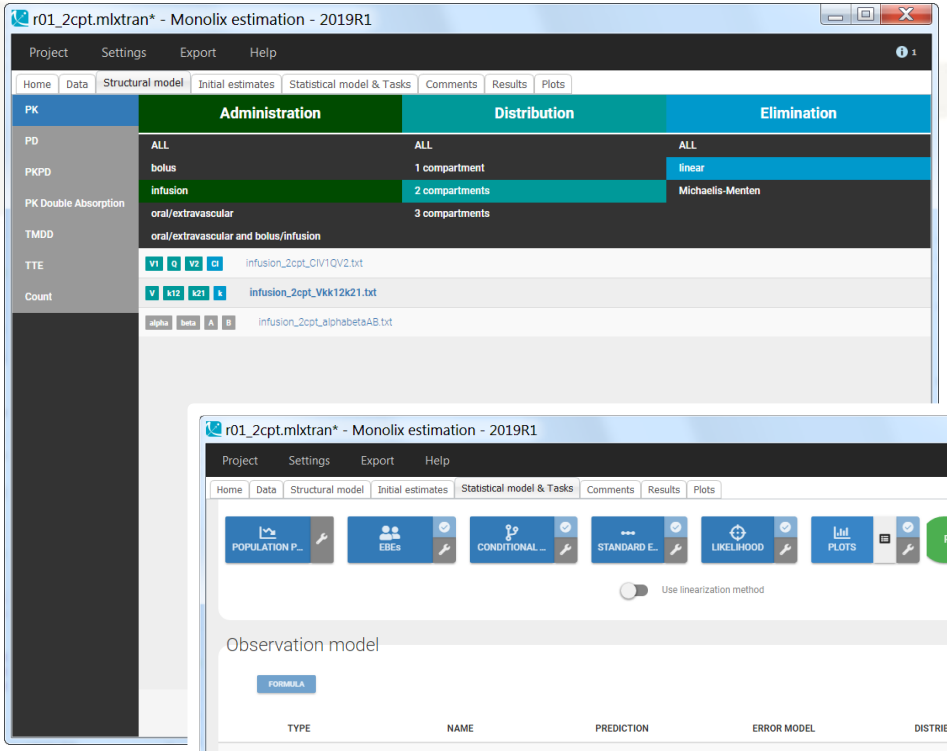
4: check the influence of the parameter scaling choices with Mlxplore

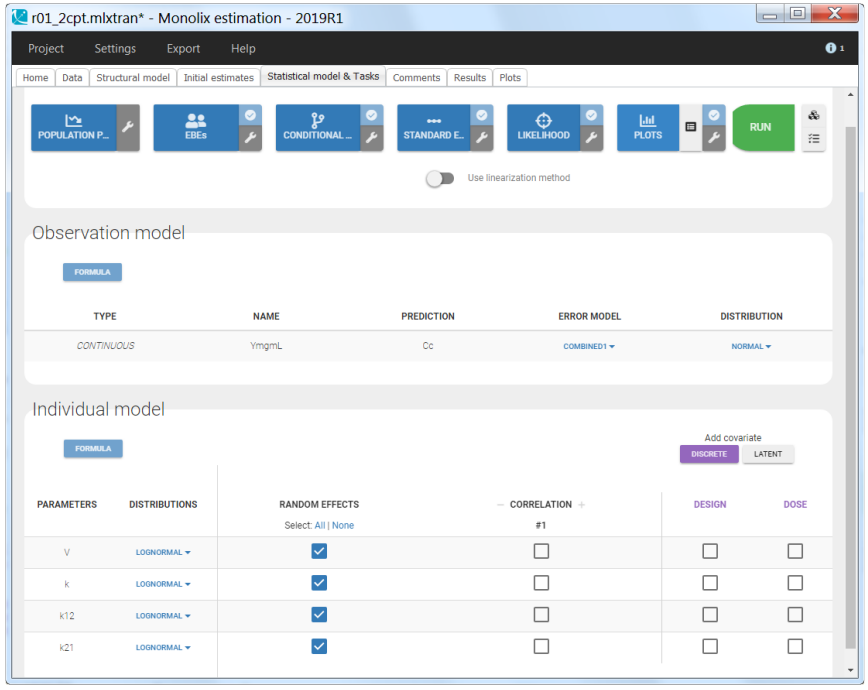
Monolix: parameter estimation

LIXOFT

2-compartment model



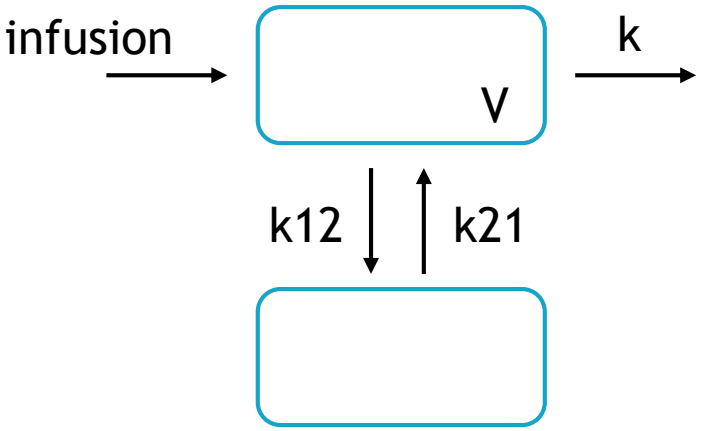




Monolix: parameter estimation

LIXOFT

2-compartment model

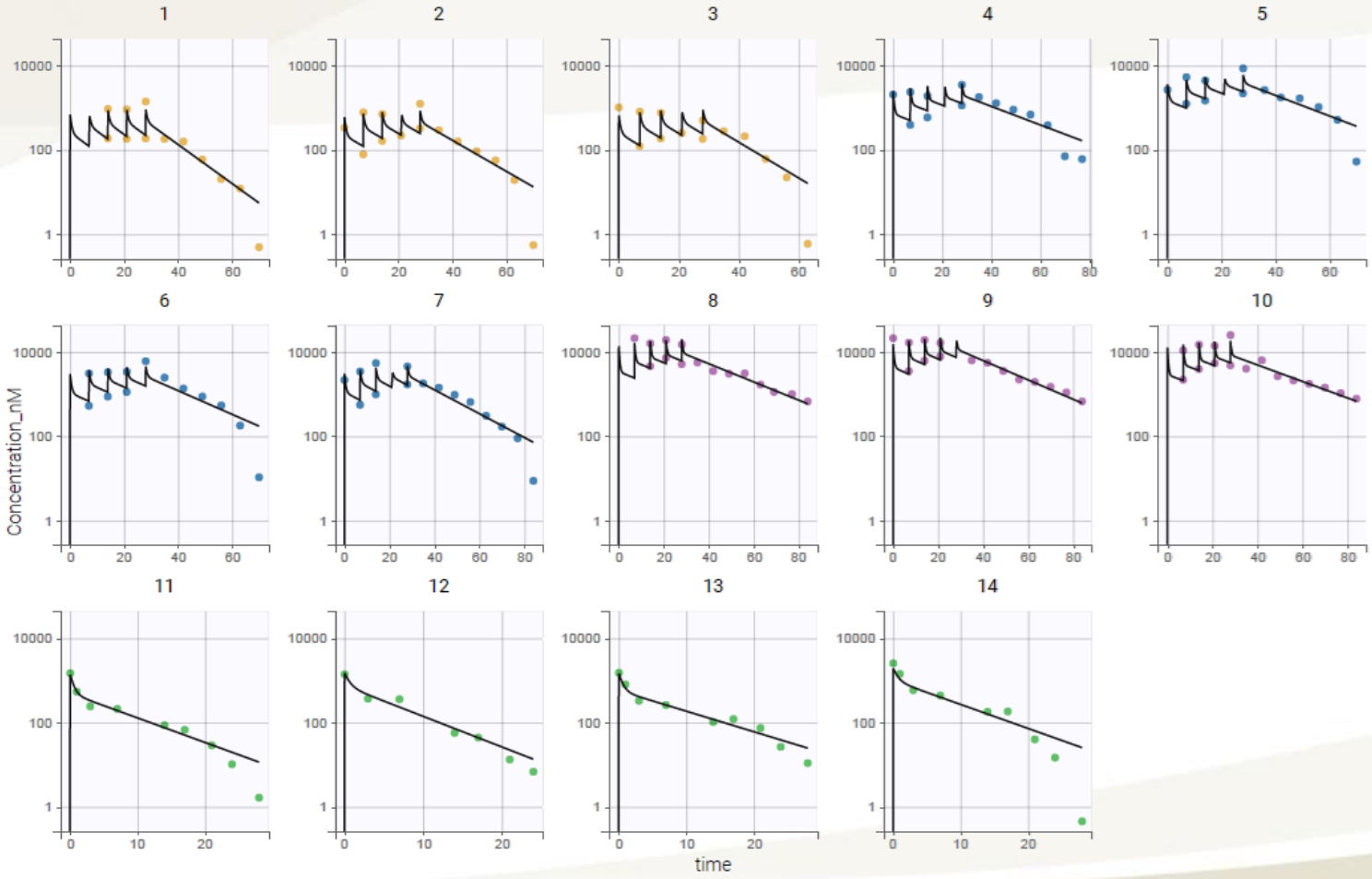


	Value	CV
V/F	22.0 mL/kg	15.8%
k	0.214 /day	27.4%
k12	1.15 /day	49.1%
k21	0.786 /day	23.0%

Monolix: parameter estimation

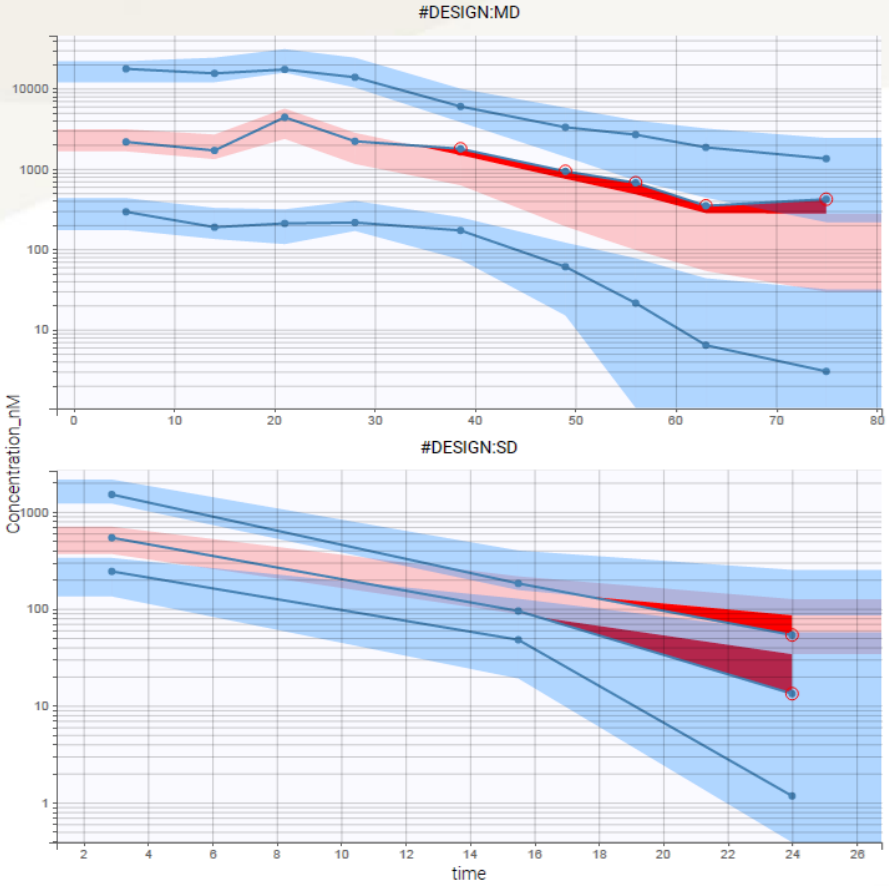
LIXOFT

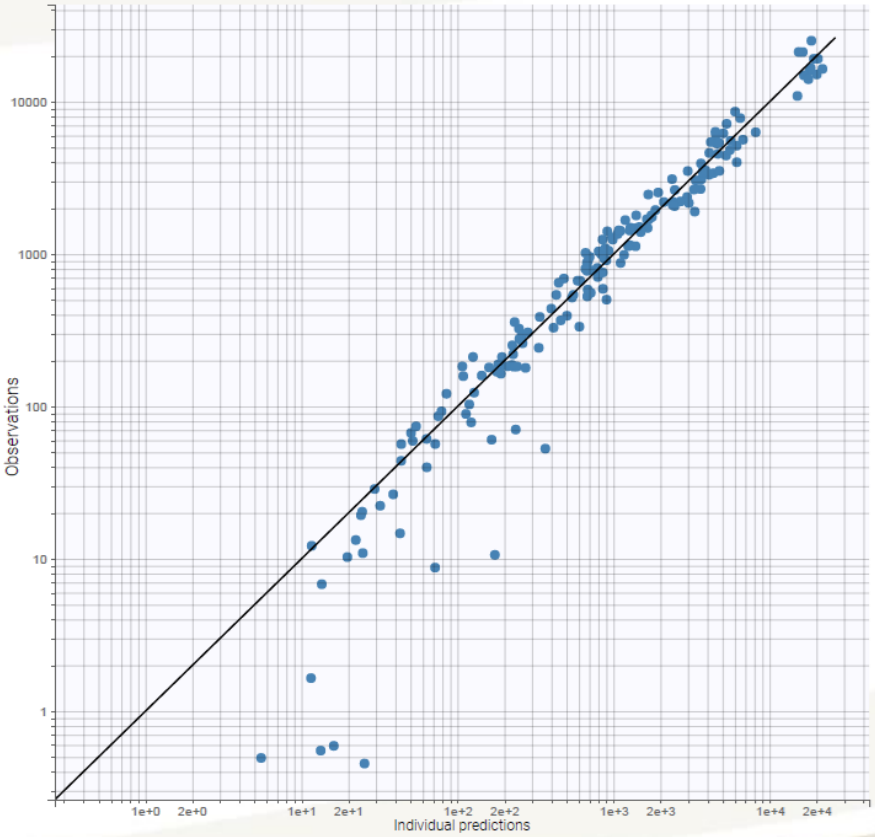
2-compartment model



Monolix: parameter estimation

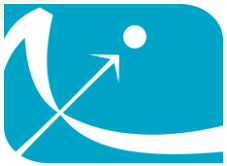
2-compartment model





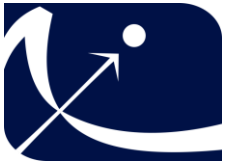
Agenda

1: visualize the monkey PK data at hand with Datxplore



2: develop a popPK model to capture the monkey data with Monolix

3: scale, and predict the human PK for various doses with Simulx



4: check the influence of the parameter scaling choices with Mlxplore

Simulx: parameter scaling

	Monkey	CV				Human	CV
V/F	22.0 mL/kg	15.2%	=>	Fixed to typical value for IgGs	=>	40 mL/kg	15.2%
k	0.214 /day	27.2%	=>	Allometric scaling $k_h = k_m \left(\frac{70}{4}\right)^{-0.25}$	=>	0.105 /day	27.2%
k12	1.15 /day	54.3%	=>	Allometric scaling $k_{12,h} = k_{12,m} \left(\frac{70}{4}\right)^{-0.25}$	=>	0.560 /day	54.3%
k21	0.786 /day	20.0%	=>	Allometric scaling $k_{21,h} = k_{21,m} \left(\frac{70}{4}\right)^{-0.25}$	=>	0.384 /day	20.0%

Simulx: human PK prediction

LIXOFT

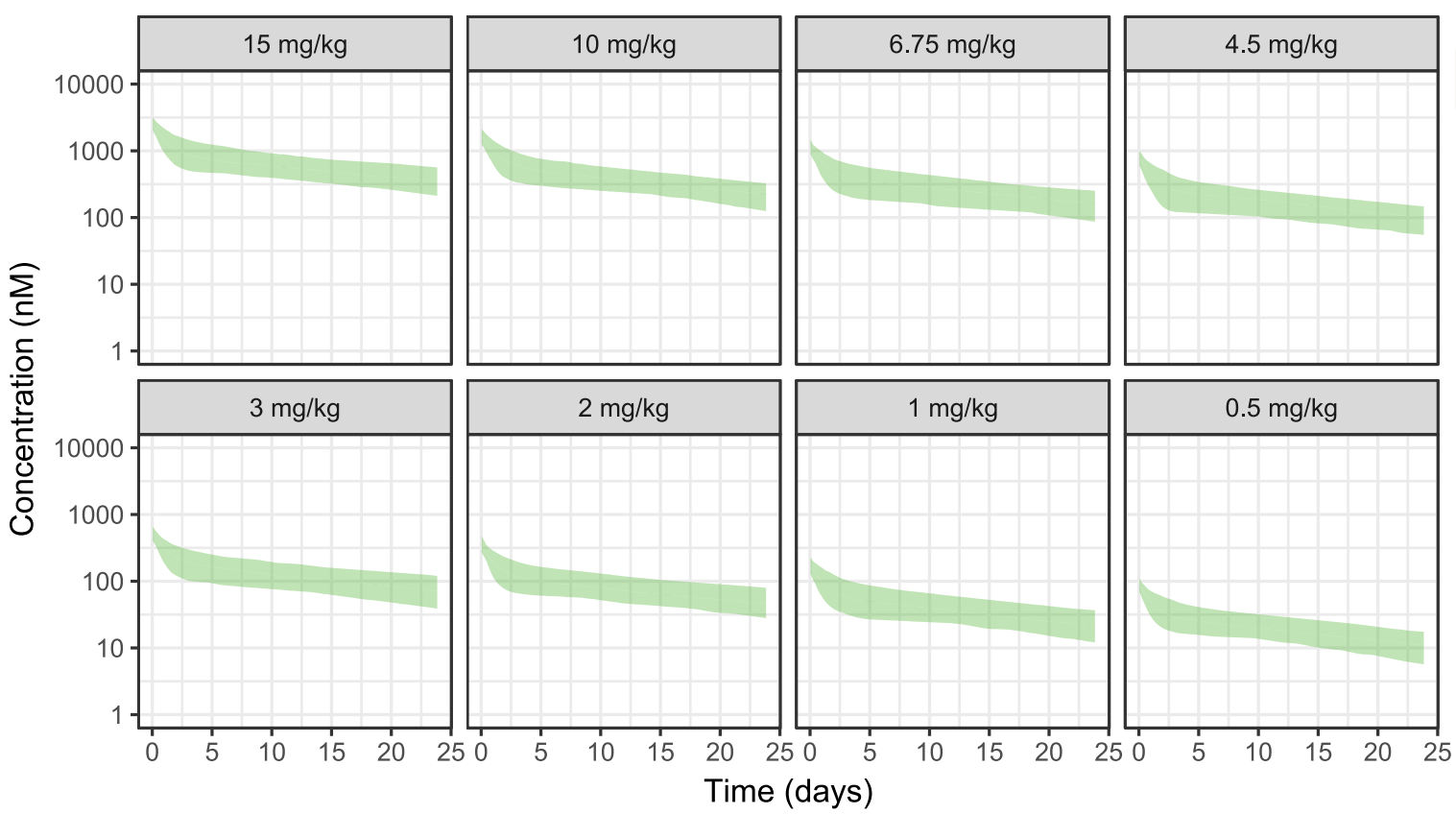
```
# define new treatments
N <- 100
g1 <- list(size=N, treatment=list(amount=15  *1e6/144.1, time=0, tinf=0.0416))
g2 <- list(size=N, treatment=list(amount=10  *1e6/144.1, time=0, tinf=0.0416))
g3 <- list(size=N, treatment=list(amount=6.75*1e6/144.1, time=0, tinf=0.0416))
g4 <- list(size=N, treatment=list(amount=4.5 *1e6/144.1, time=0, tinf=0.0416))
g5 <- list(size=N, treatment=list(amount=3   *1e6/144.1, time=0, tinf=0.0416))
g6 <- list(size=N, treatment=list(amount=2   *1e6/144.1, time=0, tinf=0.0416))
g7 <- list(size=N, treatment=list(amount=1   *1e6/144.1, time=0, tinf=0.0416))
g8 <- list(size=N, treatment=list(amount=0.5 *1e6/144.1, time=0, tinf=0.0416))

# read estimated population parameters
paramDF <- read.csv(file='../monolix/r01_2cpt/populationParameters.txt', header = T)
popparam <- setNames(paramDF$value, paramDF$parameter)
# do allometric scalling
popparam['V_pop']   <- 40 # mL/kg
popparam['k_pop']   <- popparam['k_pop']   *(70/4)^(-0.25)
popparam['k12_pop'] <- popparam['k12_pop'] *(70/4)^(-0.25)
popparam['k21_pop'] <- popparam['k21_pop'] *(70/4)^(-0.25)

# define output
out <- list(name='Cc', time=seq(0.0416,24,by=0.2))

# run simulation
res1 <- simulx(project = "../monolix/r01_2cpt.mlxtran",
               parameter = popparam,
               output = out,
               group = list(g1,g2,g3,g4,g5,g6,g7,g8))
```

Simulx: human PK prediction

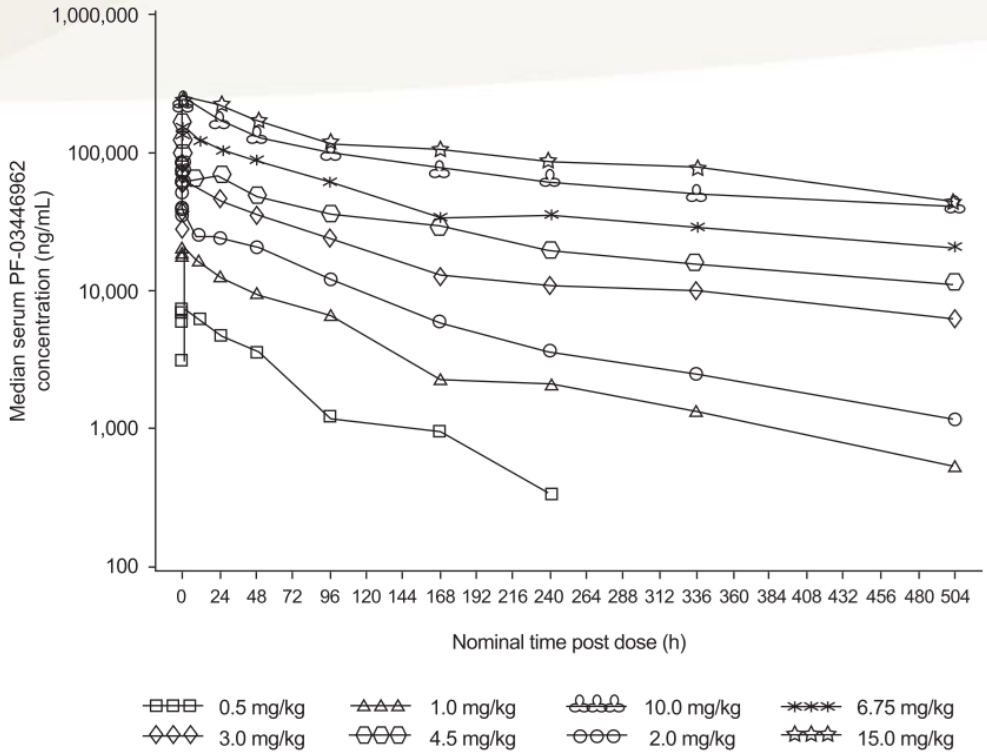


Do the predictions really reflect the PK in humans?

Simulx: human PK prediction

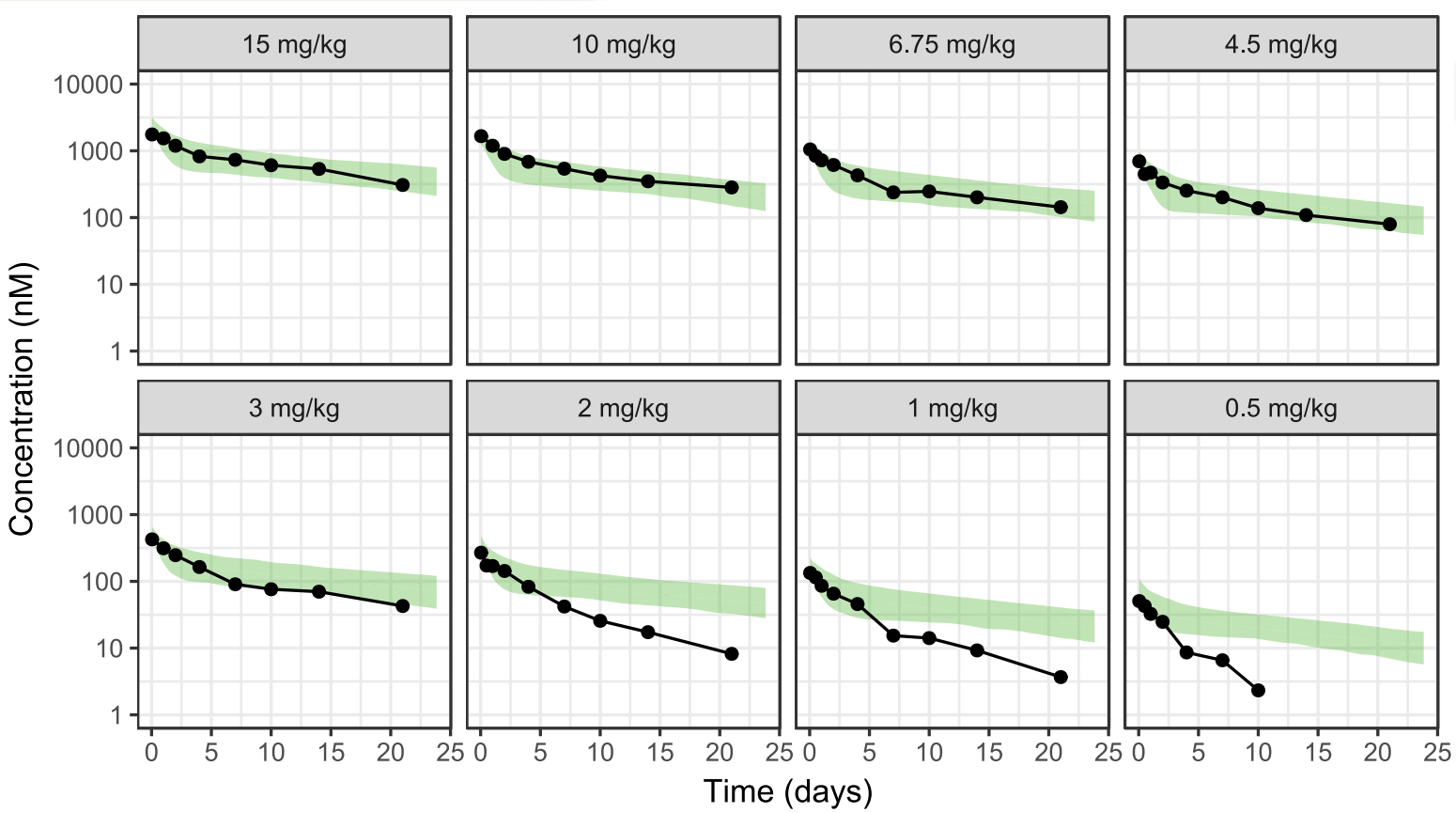
LIXOFT

Human phase I PK data



Goff LW et al. (2016) **A Phase I Study of the Anti-Activin Receptor-Like Kinase 1 (ALK-1) Monoclonal Antibody PF-03446962 in Patients with Advanced Solid Tumors**. *Clinical Cancer Research*, 22(9), 2146–2154.

Simulx: human PK prediction



Small doses not properly predicted…
=> Try a TMDD model

Agenda

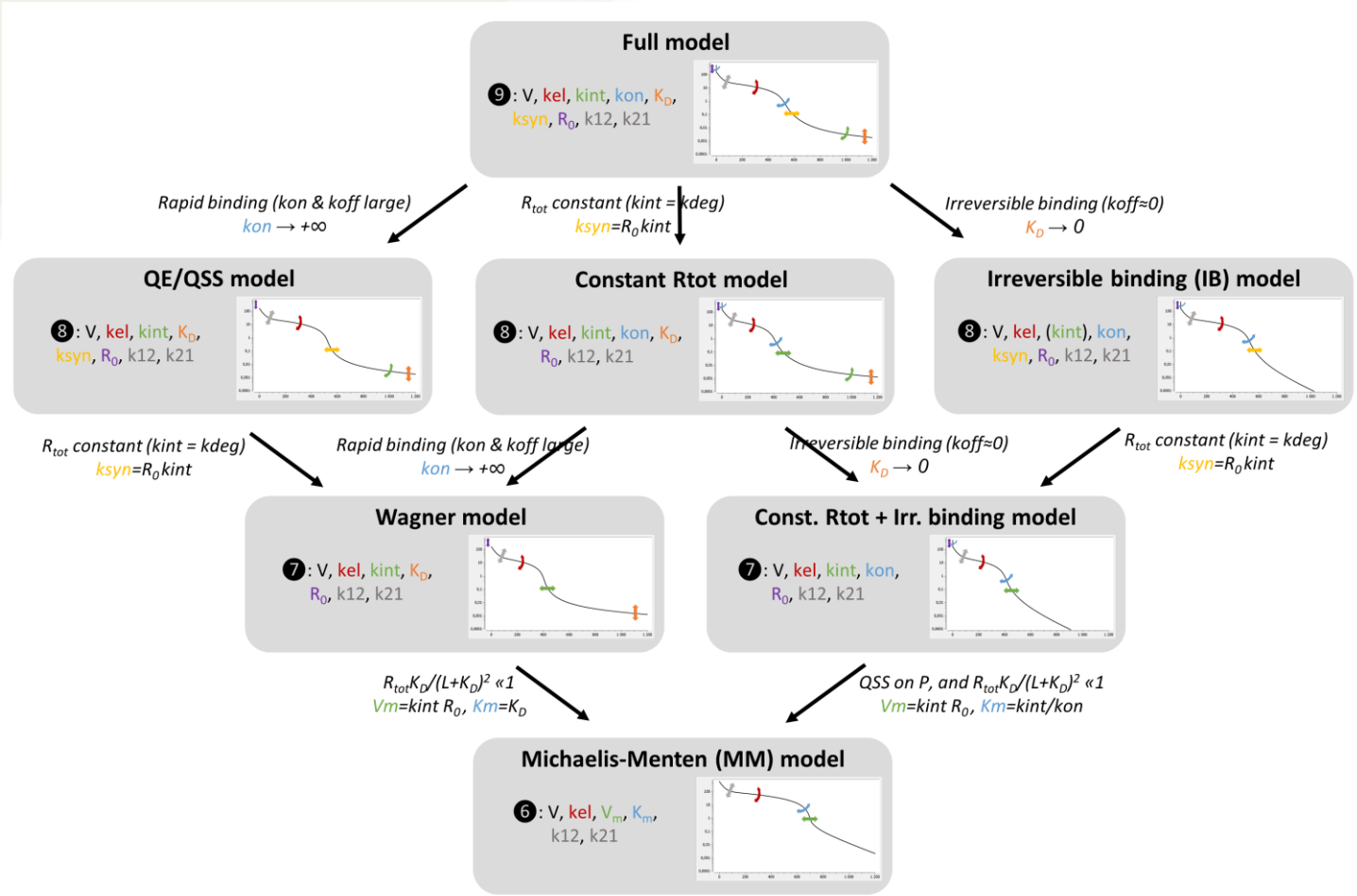
1: visualize the monkey PK data at hand with Datxplore

2: develop a popPK model to capture the monkey data with Monolix

3: scale, and predict the human PK for various doses with Simulx

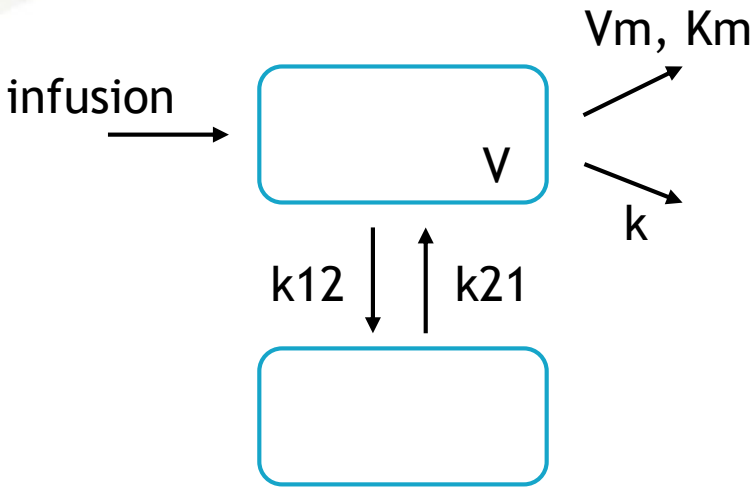
4: check the influence of the parameter scaling choices with Mlxplore

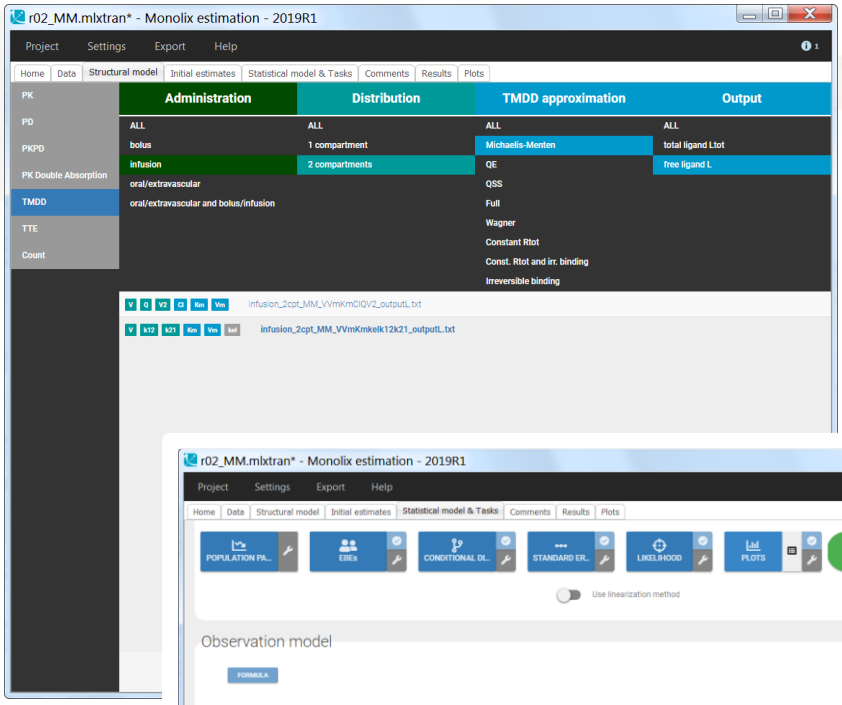
Monolix: TMDD library

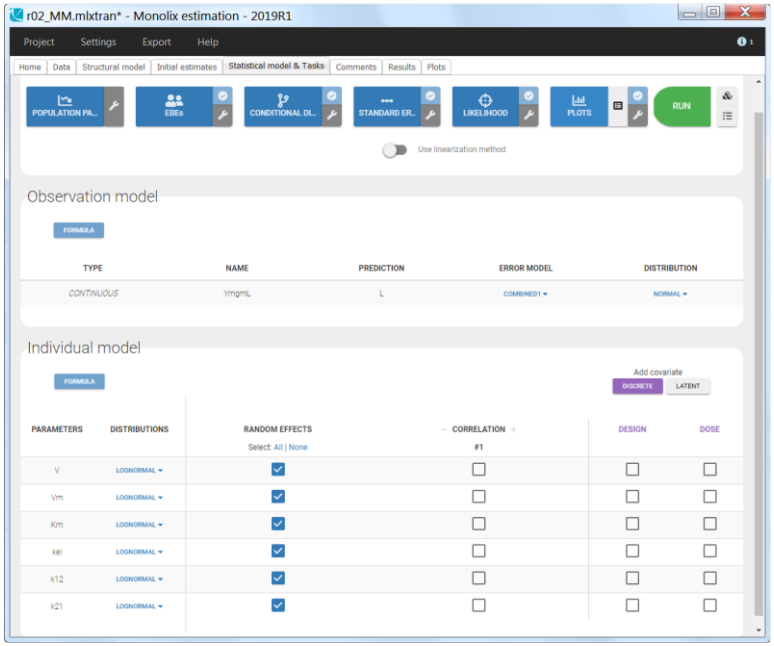


Monolix: parameter estimation

TMDD Michaelis-Menten model



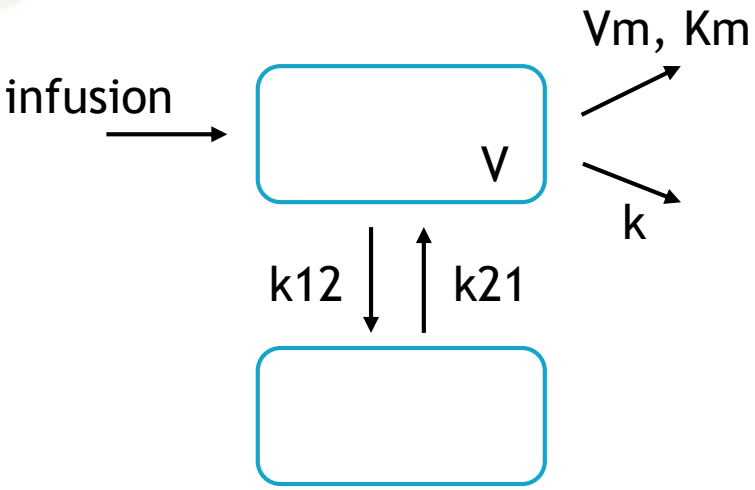




Monolix: parameter estimation

LIXOFT

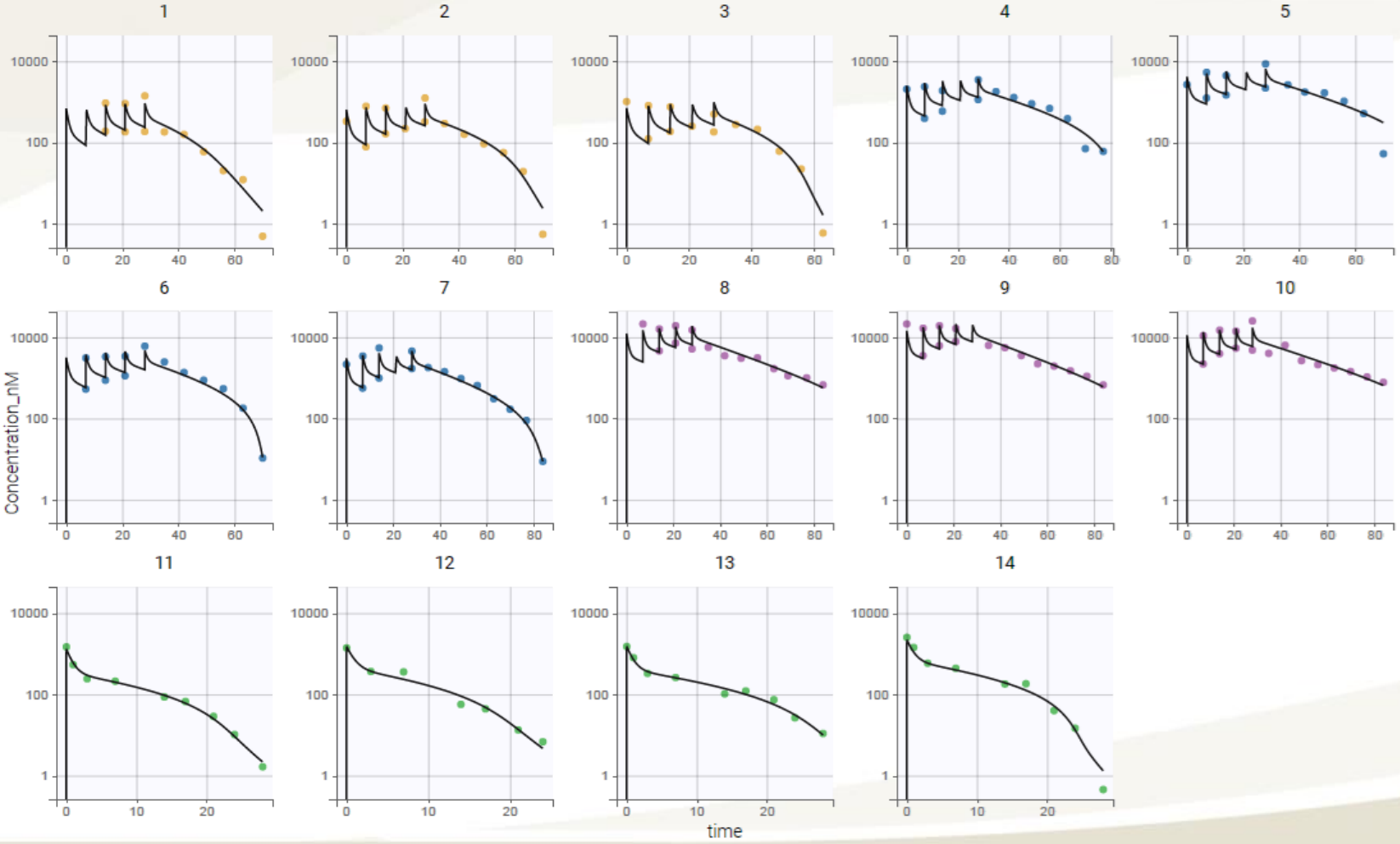
TMDD Michaelis-Menten model



	Value	CV
V/F	22.1 mL/kg	20.1%
k	0.141 /day	9.2%
k12	0.765 /day	10.8%
k21	0.393 /day	12.6%
Vm	34.7 nM/day	31.9%
Km	12.3 nM	79.6%

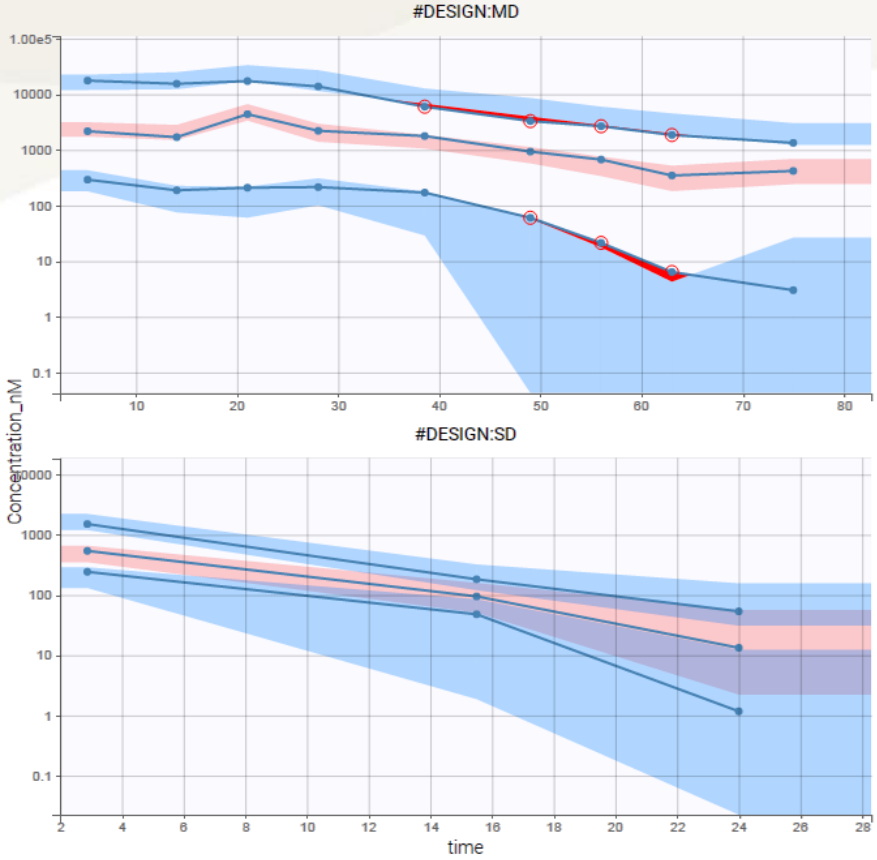
Monolix: parameter estimation

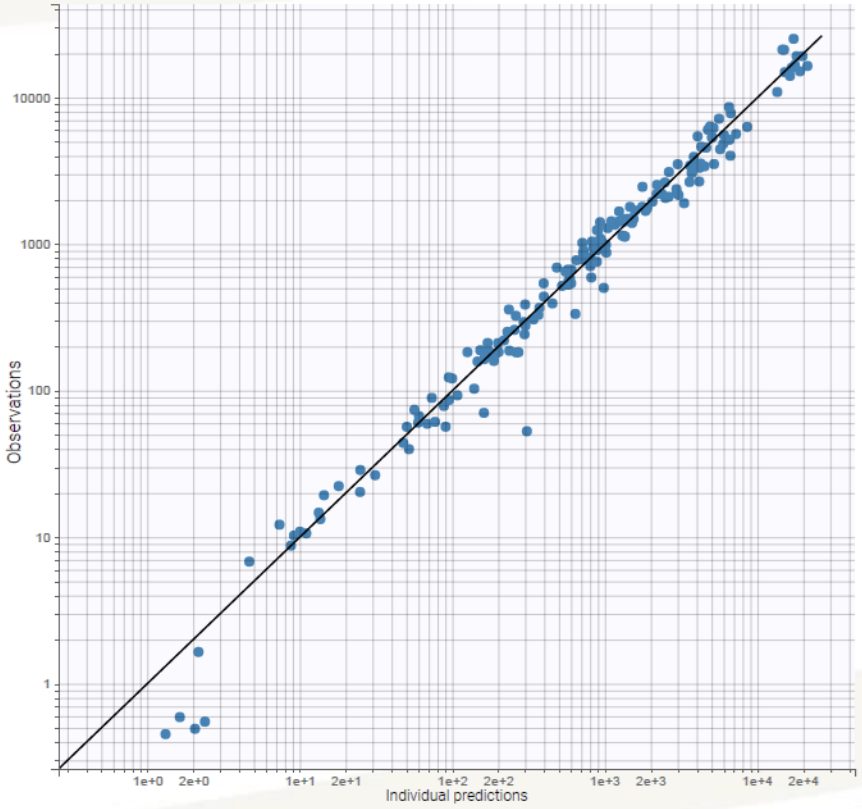
TMDD Michaelis-Menten model



Monolix: parameter estimation

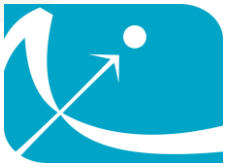
TMDD Michaelis-Menten model





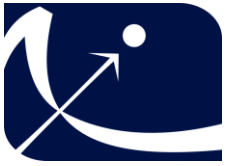
Agenda

1: visualize the monkey PK data at hand with Datxplore



2: develop a popPK model to capture the monkey data with Monolix

3: scale, and predict the human PK for various doses with Simulx

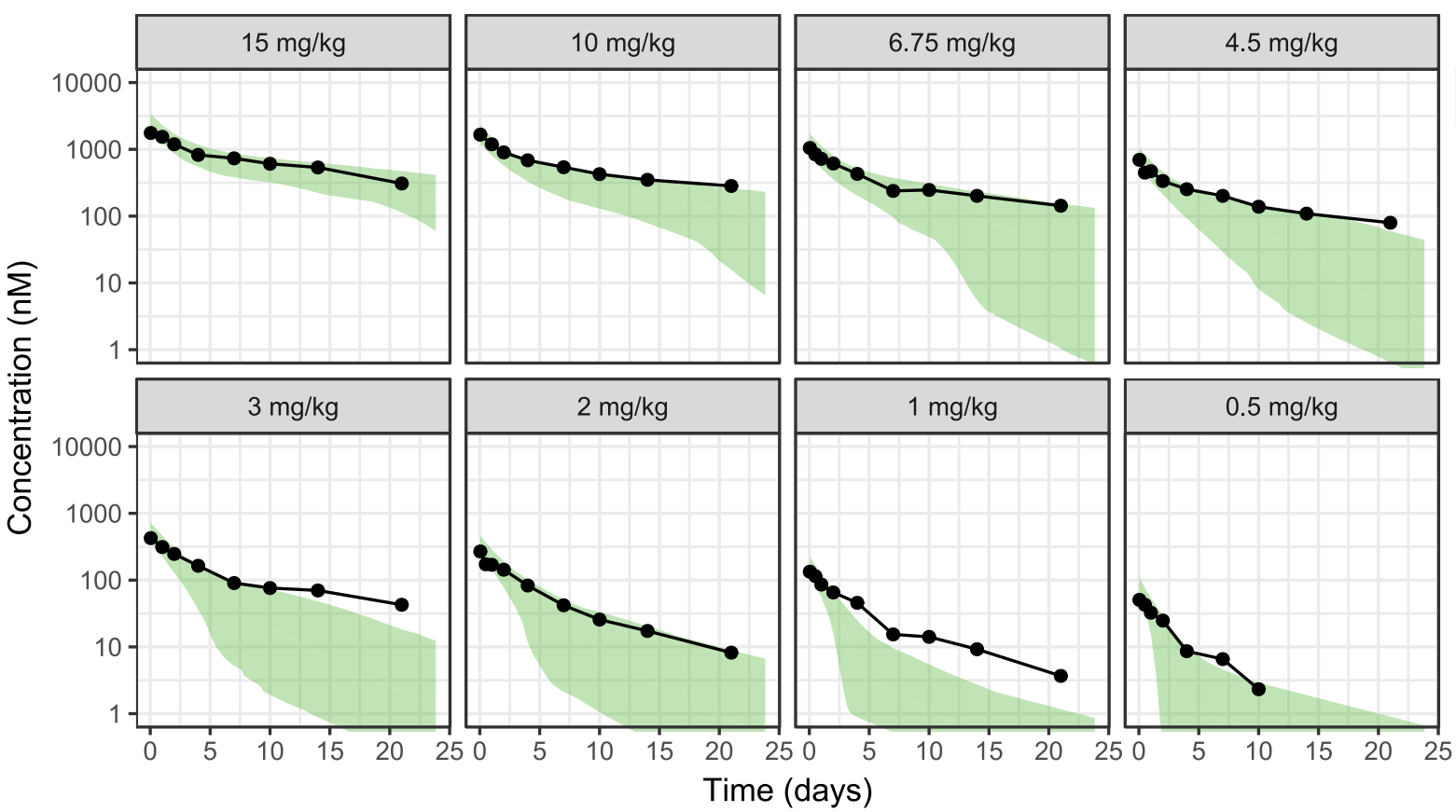


4: check the influence of the parameter scaling choices with Mlxplore

Simulx: parameter scaling

	Monkey	CV				Human	CV
V/F	22.1 mL/kg	20.1%	=>	Fixed to typical value for IgGs	=>	40 mL/kg	20.1%
k	0.141 /day	9.2%	=>	Allometric scaling $k_h = k_m \left(\frac{70}{4}\right)^{-0.25}$	=>	0.069 /day	9.2%
k12	0.765 /day	10.8%	=>	Allometric scaling $k_{12h} = k_{12,m} \left(\frac{70}{4}\right)^{-0.25}$	=>	0.374 /day	10.8%
k21	0.393 /day	12.6%	=>	Allometric scaling $k_{21,h} = k_{21,m} \left(\frac{70}{4}\right)^{-0.25}$	=>	0.192 /day	12.6%
Vm	34.7 nM/day	31.9%	=>	Assumed identical	=>	34.7 nM/day	31.9%
Km	12.3 nM	79.6%	=>	Assumed identical	=>	12.3 nM	79.6%

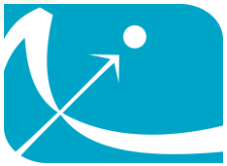
Simulx: human PK prediction



Human PK is underpredicted…
=> Try a more mechanistic TMDD model

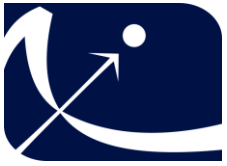
Agenda

1: visualize the monkey PK data at hand with Datxplore



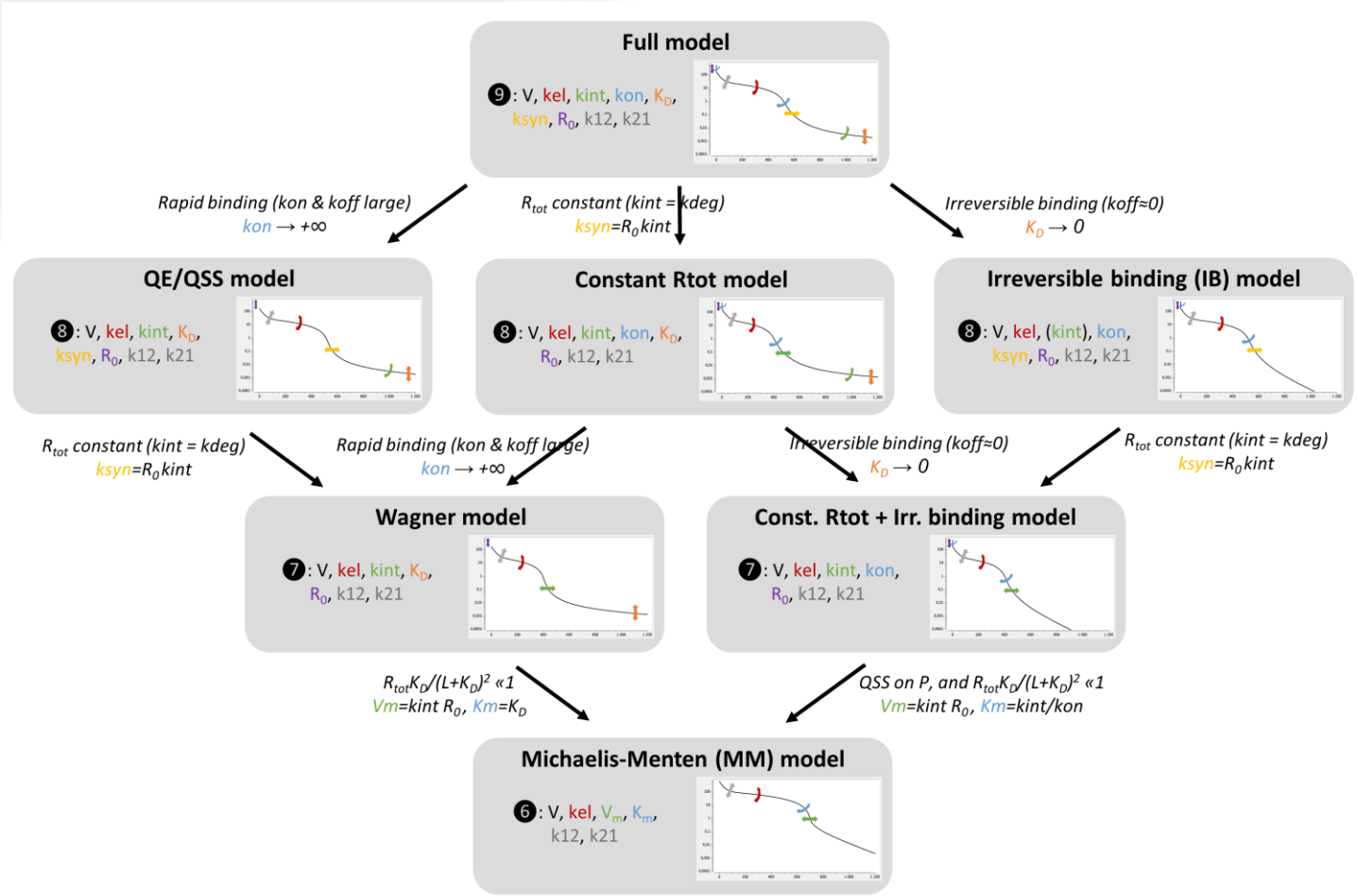
2: develop a popPK model to capture the monkey data with Monolix

3: scale, and predict the human PK for various doses with Simulx



4: check the influence of the parameter scaling choices with Mlxplore

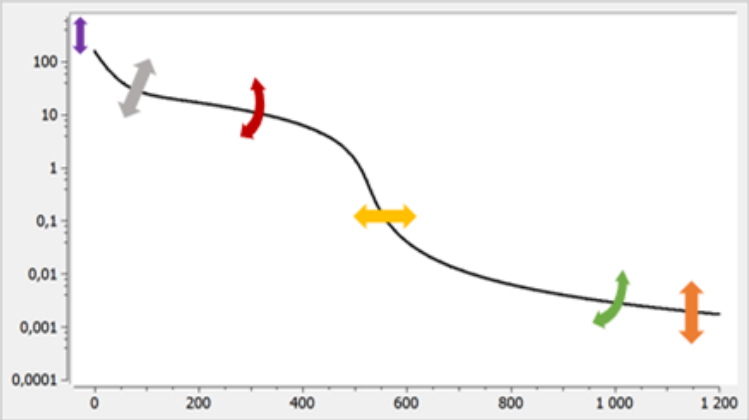
Monolix: TMDD library



Monolix: TMDD library

QE/QSS model

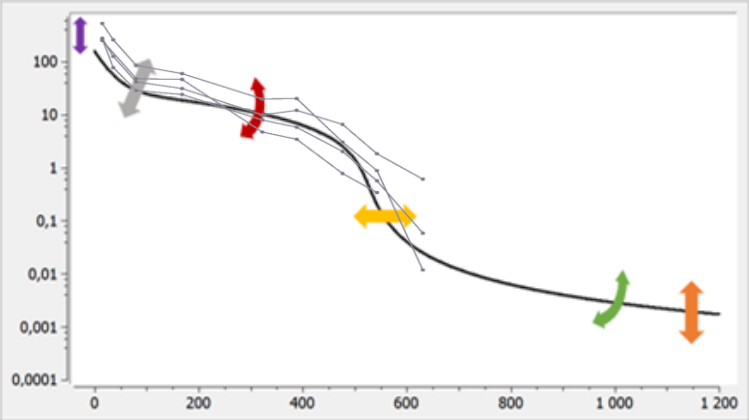
8 : V, kel, kint, K_D, ksyn, R_0, k12, k21



Monolix: TMDD library

QE/QSS model

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

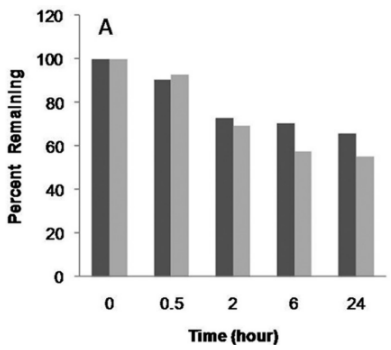


Monolix: experimental

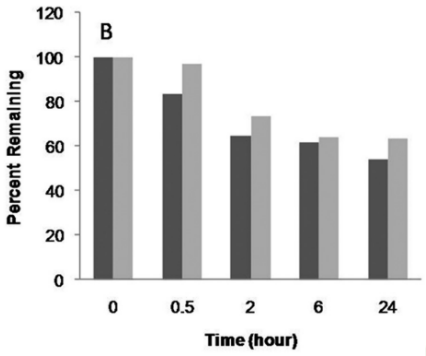
	Monkey	Human	Experiment
kint	14 /day	18 /day	internalization via FACS
KD	2.4 nM	2.9 nM	surface plasmon resonance
kdeg	?	5 /day	decay via RNA expression

Percentage of mAb-ALK1 complex remaining on cell surface over time as quantified from FACS data

Monkey

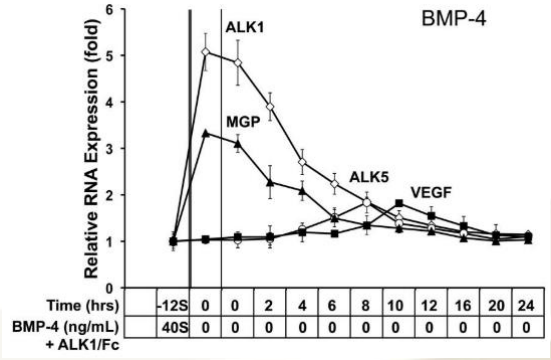


Human



Expression of ALK1 by real-time PCR after treatment with BMP-4

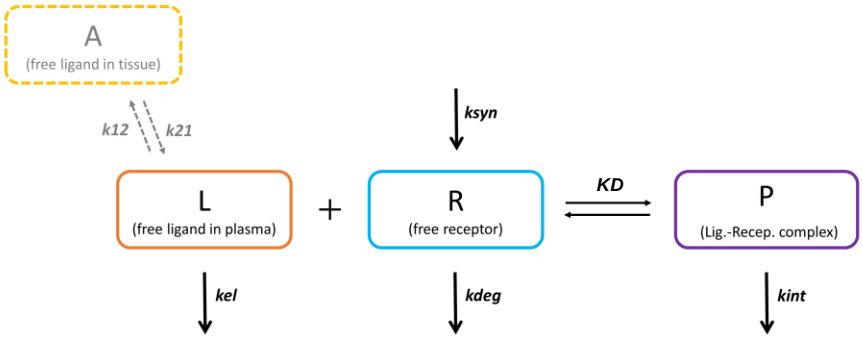
Human

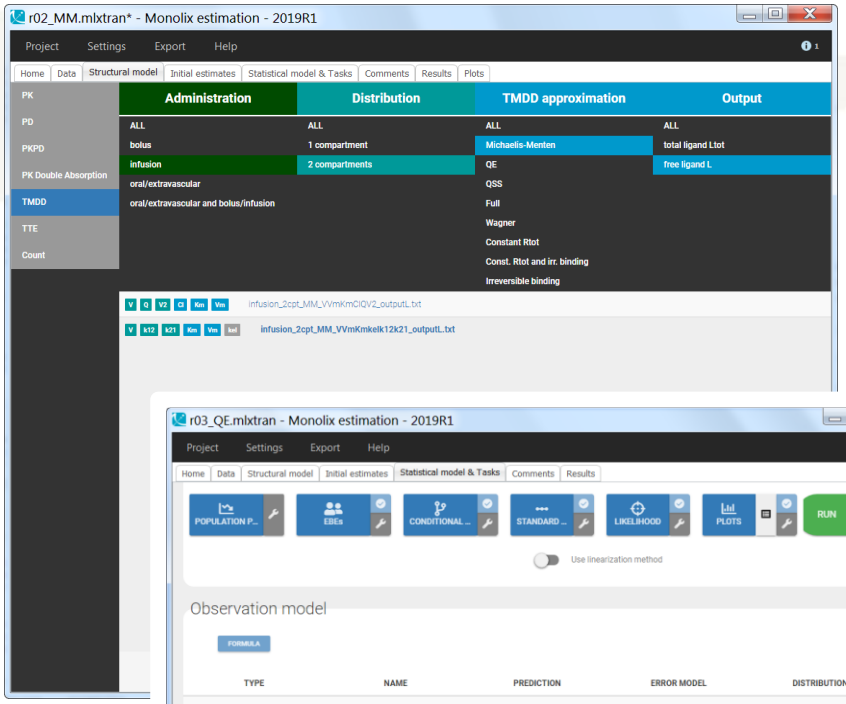


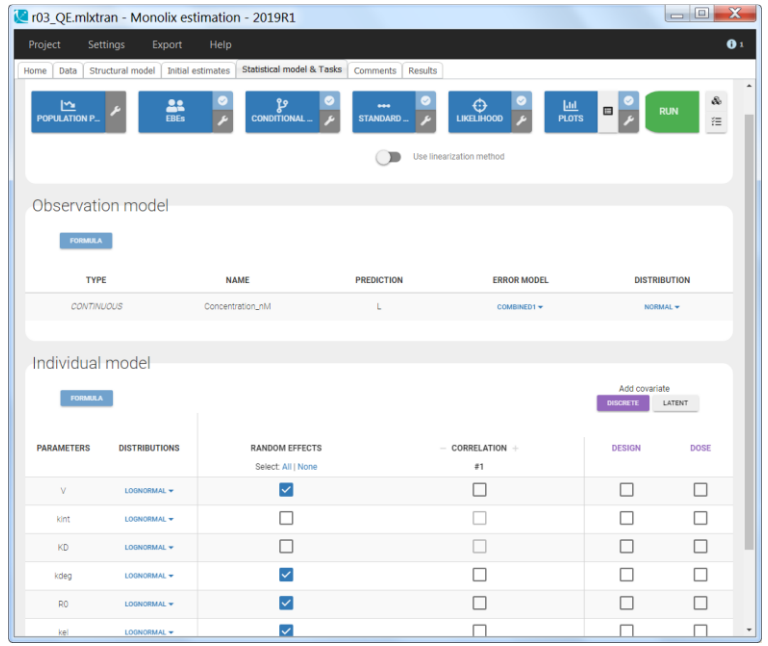
Shao E.S et al. (2009). *Vascular Biology*, *114*(10), 2197–2206.

Monolix: parameter estimation

TMDD QE model



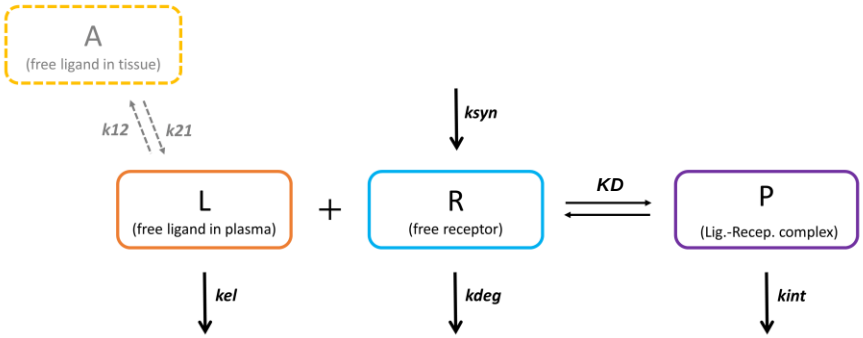




Monolix: parameter estimation

LIXOFT

TMDD quasi-equilibrium model

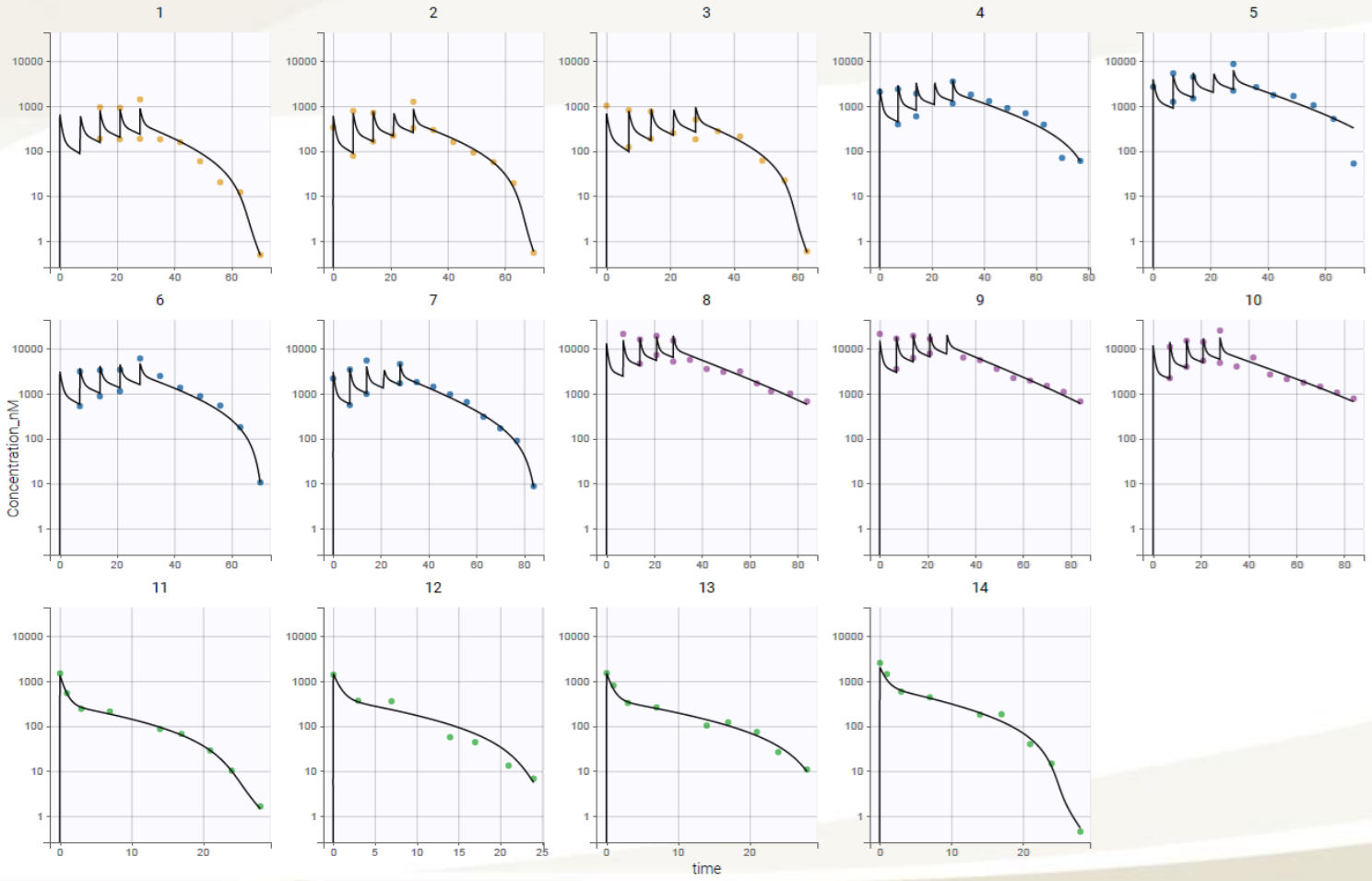


	Value	CV
V/F	22.2 mL/kg	17.3%
k	0.153 /day	14.7%
k12	0.846 /day	20.4%
k21	0.424 /day	15.6%
R0	1.27 nM	30.1%
kint	14 /day (fixed)	-
kdeg	20.1 /day	37.3%
KD	2.4 nM (fixed)	-

Monolix: parameter estimation

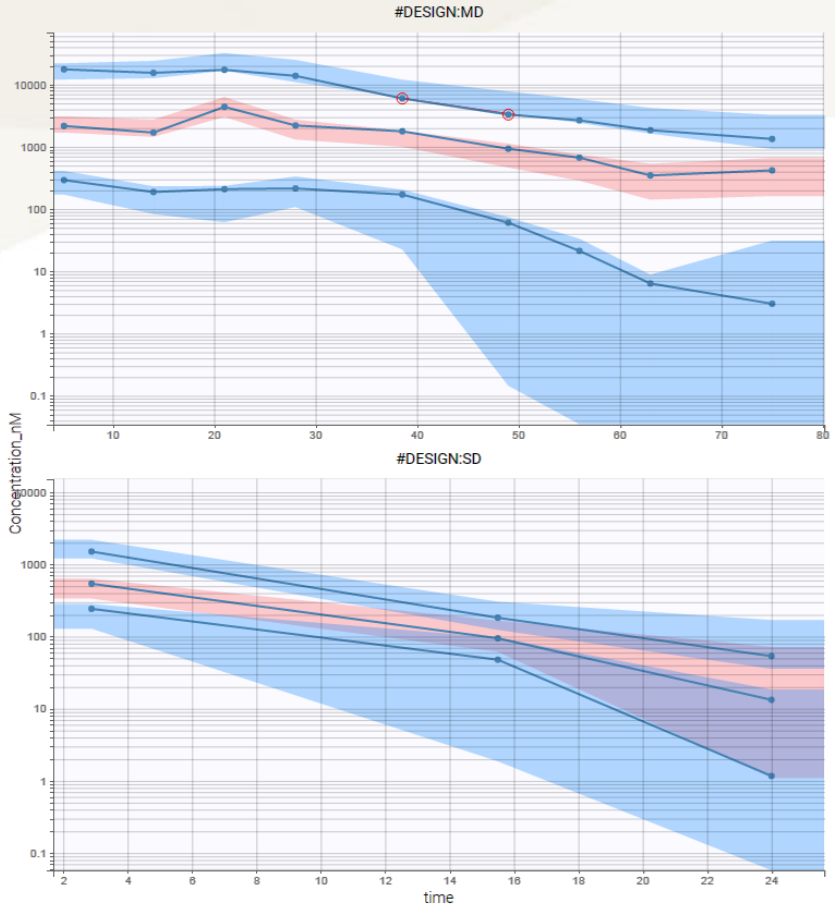
LIXOFT

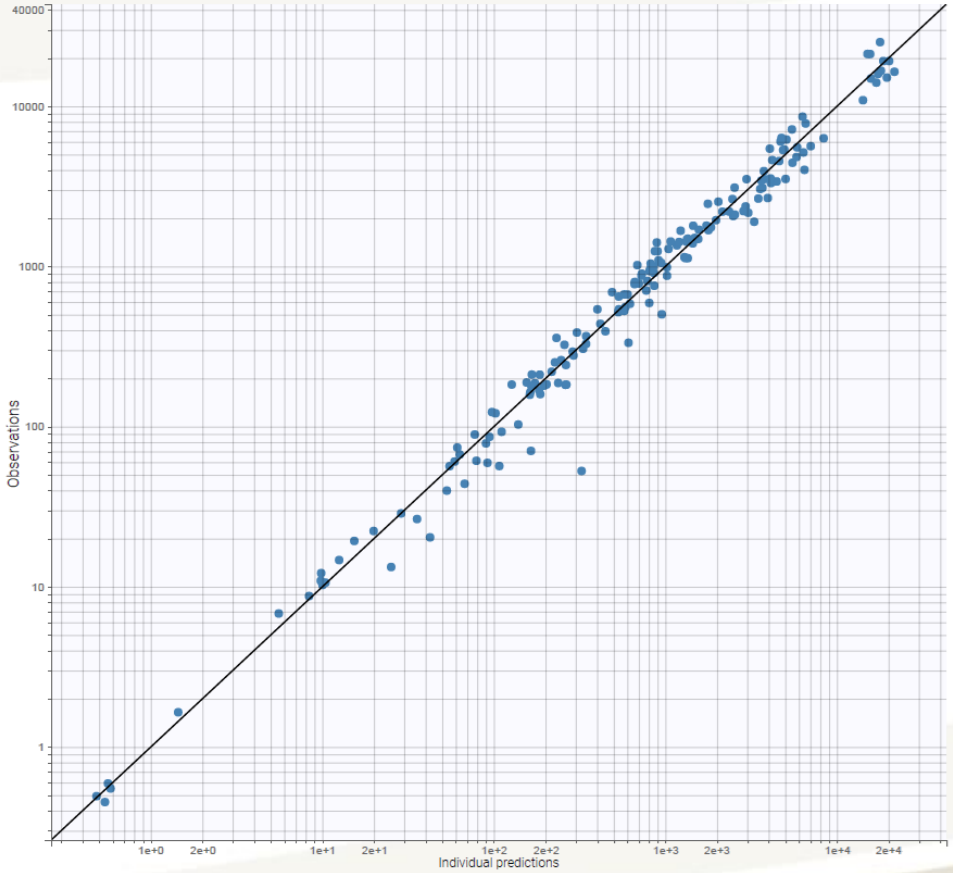
TMDD quasi-equilibrium model



Monolix: parameter estimation

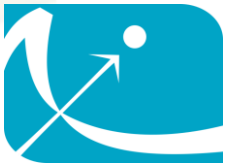
TMDD quasi-equilibrium model





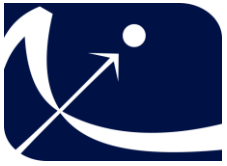
Agenda

1: visualize the monkey PK data at hand with Datxplore



2: develop a popPK model to capture the monkey data with Monolix

3: scale, and predict the human PK for various doses with Simulx

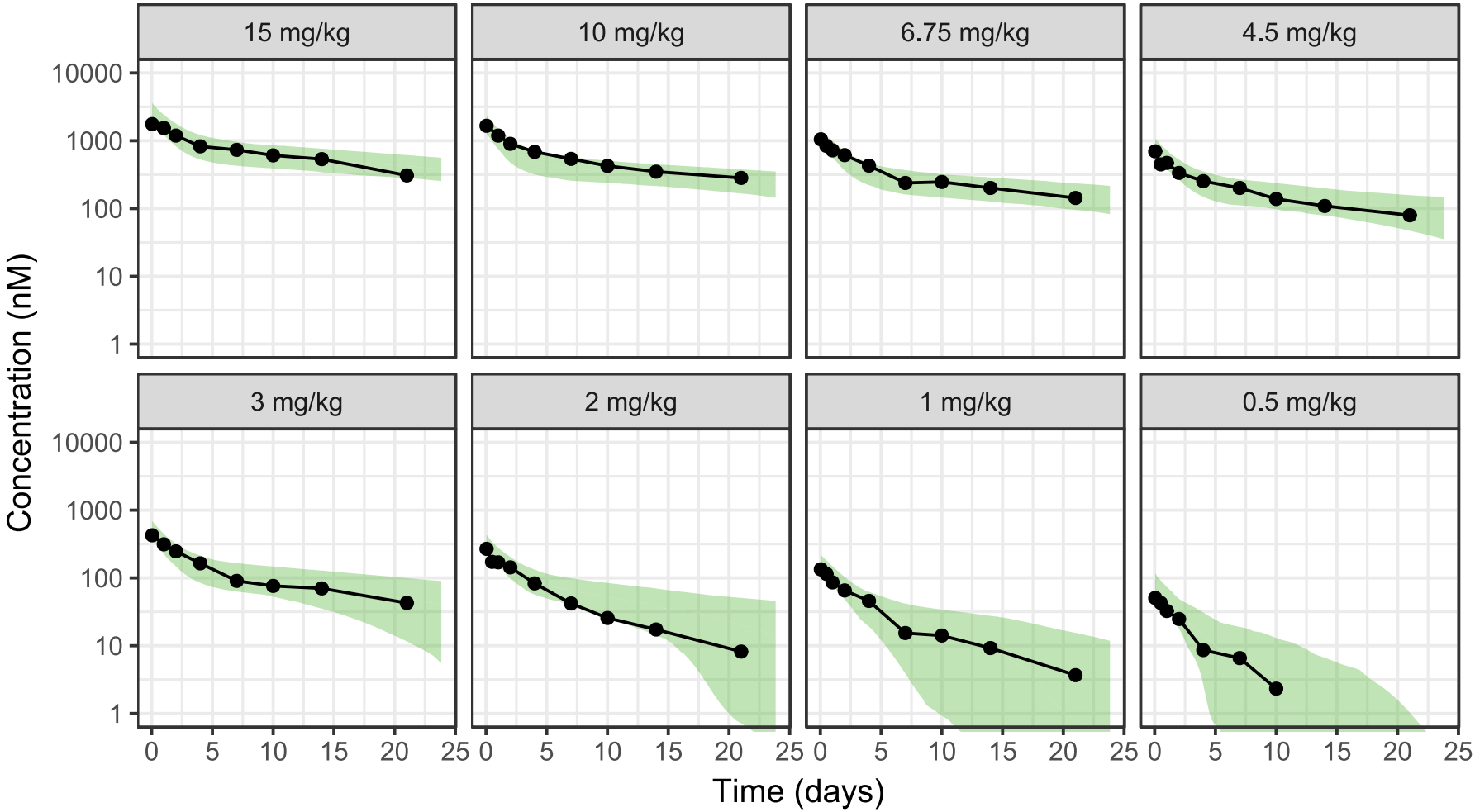


4: check the influence of the parameter scaling choices with Mlxplore

Simulx: parameter scaling

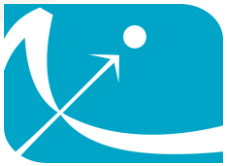
	Monkey	CV				Human	CV
V/F	22.2 mL/kg	17.3%	=>	Fixed to typical value for IgGs	=>	40 mL/kg	17.3%
k	0.153 /day	14.7%	=>	Allometric scaling $k_h = k_m \left(\frac{70}{4}\right)^{-0.25}$	=>	0.075 /day	14.7%
k12	0.846 /day	20.4%	=>	Allometric scaling $k_{12h} = k_{12,m} \left(\frac{70}{4}\right)^{-0.25}$	=>	0.413 /day	20.4%
k21	0.424 /day	15.6%	=>	Allometric scaling $k_{21,h} = k_{21,m} \left(\frac{70}{4}\right)^{-0.25}$	=>	0.207 /day	15.6%
R0	1.27 nM	30.1%	=>	Assumed identical	=>	1.27 nM	30.1%
kint	14 /day	-	=>	Fixed to experimental value	=>	18 /day	-
kdeg	20.1 /day	37.3%	=>	Fixed to experimental value	=>	5 /day	37.3%
KD	2.4 nM	-	=>	Fixed to experimental value	=>	2.9 nM	-

Simulx: human PK prediction



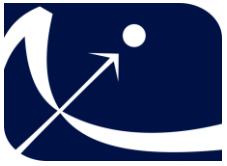
Agenda

1: visualize the monkey PK data at hand with Datxplore



2: develop a popPK model to capture the monkey data with Monolix

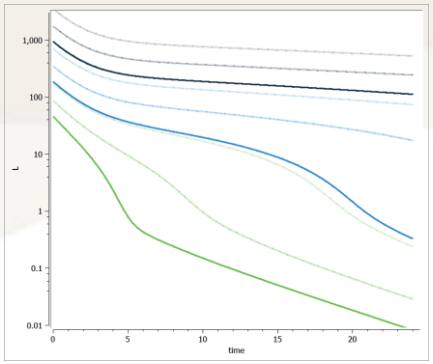
3: scale, and predict the human PK for various doses with Simulx



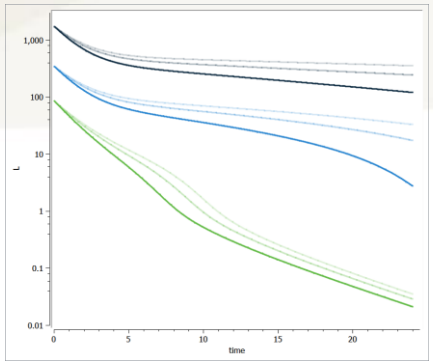
4: check the influence of the parameter scaling choices with Mlxplore

Mlxplore: sensitivity analysis

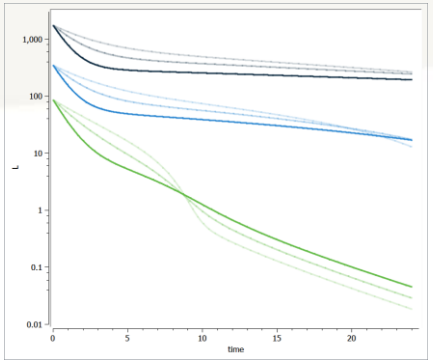
V



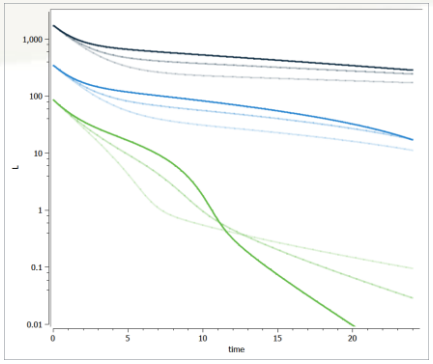
k



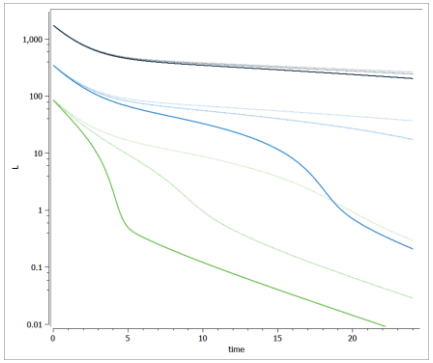
k12



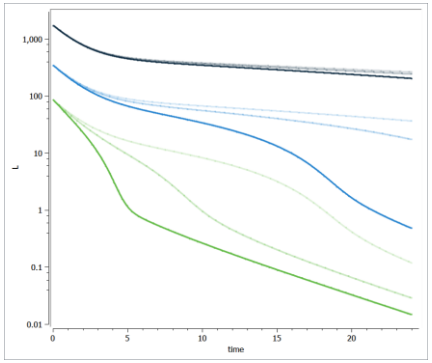
k21



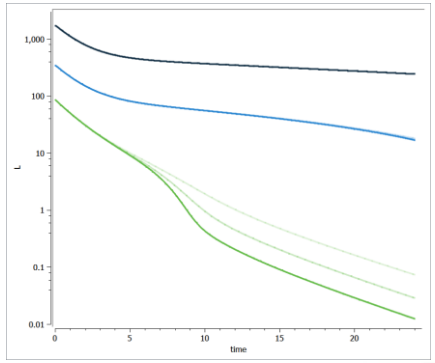
R0



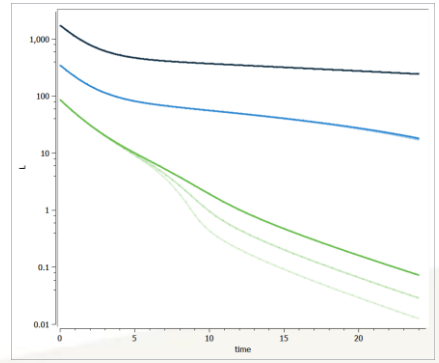
kdeg



kint



KD



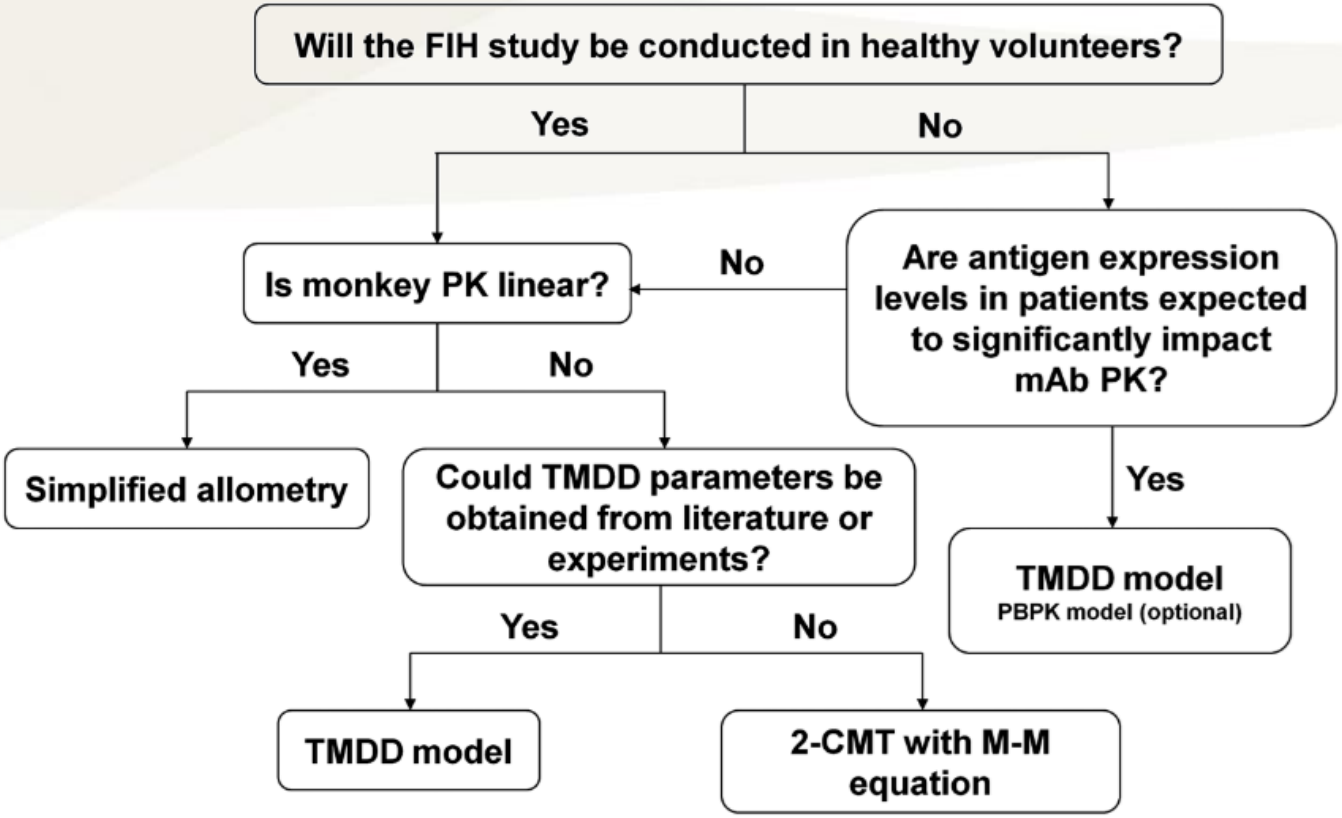
Overview

	2-cpt model	TMDD MM	TMDD QE with exp. value
Captures monkey PK	≈ (BIC=2474)	✓ (BIC=2397)	✓ (BIC=2398)
Prediction of high doses (linear PK range)	✓	✓	✓
Prediction of low doses (nonlinear PK range)	✗	✗	✓

The choice of the model depends on the goal.

Which model to choose to predict the human PK (blindly)?

Guidelines



Wang J., Iyer S., Fielder P. J., Davis J. D., & Deng R. (2016). **Projecting human pharmacokinetics of monoclonal antibodies from nonclinical data: comparative evaluation of prediction approaches in early drug development**. *Biopharmaceutics & Drug Disposition*, *37*(2), 51–65.

Conclusion

- PF-03446962 example:
  - A mechanistic TMDD model with:
    - linear PK parameters allometrically scaled based on preclinical monkey PK data
    - TMDD parameters fixed to experimentally measured values

  successfully predicts the human PK.

  - This model can be used to simulate target occupancy (or extended to other relevant PD) to guide the choice of the first-in-human dose.

- Tools:

  The MonolixSuite permits an efficient modeling & simulation workflow.