Model-Informed Drug Development

MIDD+

2021 Virtual Conference

Monika Twarogowska

Using a population PK/PD model developed on phase I to select the dose for Phase II: an example with an IgG1 mAb

SimulationsPlus

Cognigen | DILIsym Services | Lixoft

In cycling…

How 1% performance Improvements Led to Olympic Gold, Eben Harrell, Harvard Business Review", 2015

Winning strategy: SMALL improvements in ALL areas

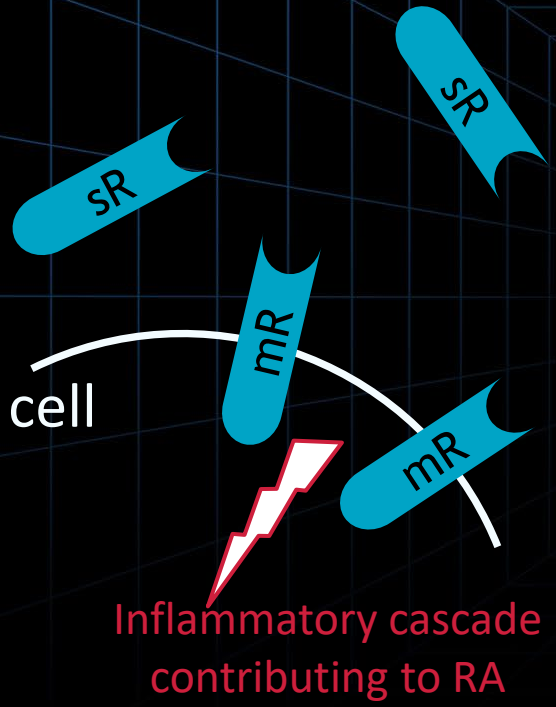
What about clinical trials?

Probability of Success

Chi Heem Wong, Kien Wei Siah, Andrew W Lo. “Estimation of clinical trial success rates and related parameters.” Biostatistics, 2019

	P1 to P2	P2 to P3	P3 to Approval	Overall
Oncology	57.6	32.7	35.3	3.4
Metabolic/Endocrinology	76.2	59.7	51.6	19.6
Cardiovascular	73.3	65.7	62.2	25.5
Central nervous system	73.2	51.9	51.1	15.0
Autoimmune/Inflammation	69.8	45.7	63.7	15.1
Genitourinary	68.7	57.1	66.5	21.6
Infectious Disease	70.1	58.3	75.3	25.2
Ophthalmology	87.1	60.7	74.9	32.6
Vaccines	76.8	58.2	85.4	33.4
Overall	66.4	48.6	59.0	13.8
Overall (excluding oncology)	73.0	55.7	63.6	20.9

Example: IgG1 mAb



Monoclonal anti-body (mAb)
developed as an
immunotherapy against
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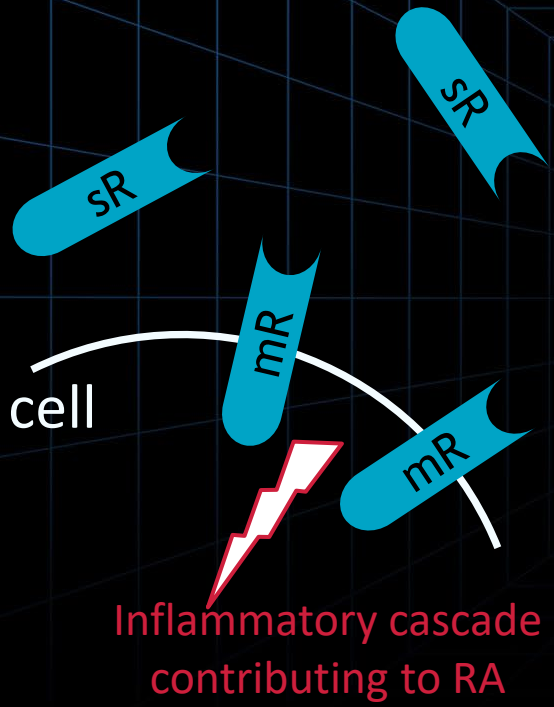
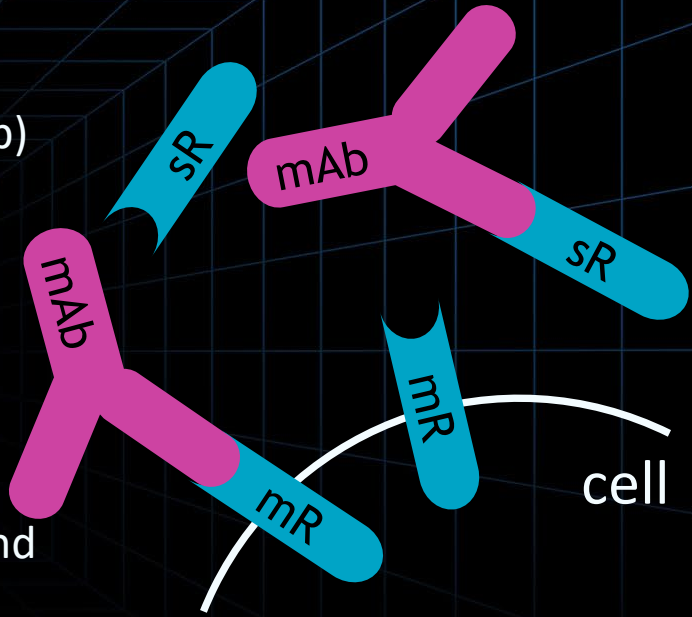
Example: IgG1 mAb



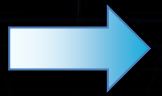
Monoclonal anti-body (mAb) developed as an immunotherapy against rheumatoid arthritis

mAb binds to soluble (sR) and membrane-bound (mR) receptors and blocks the inflammatory cascade



Phase I clinical trial: results

SAD on healthy and RA patients



- Safety up to 30 mg/kg
- Population PK/PD model

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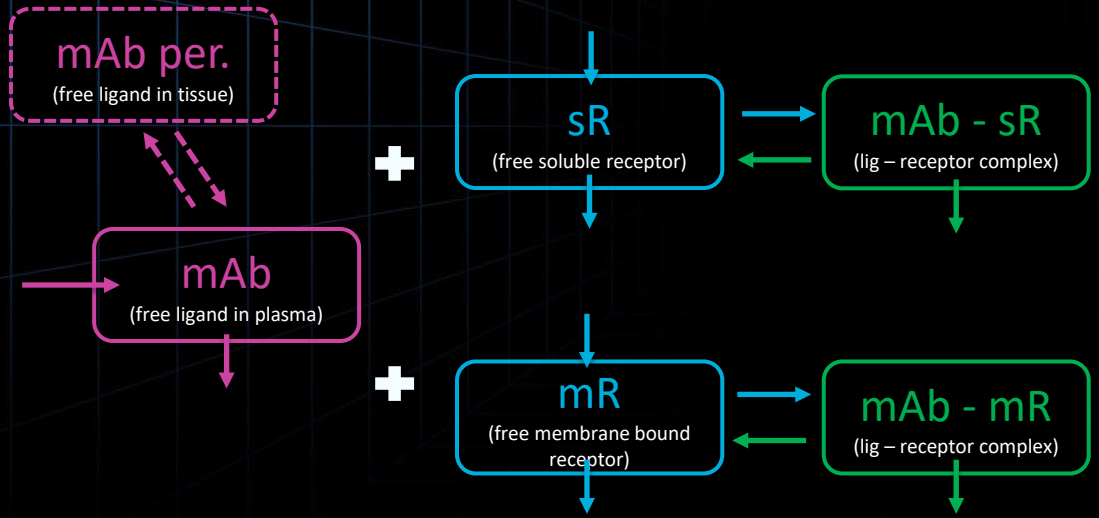

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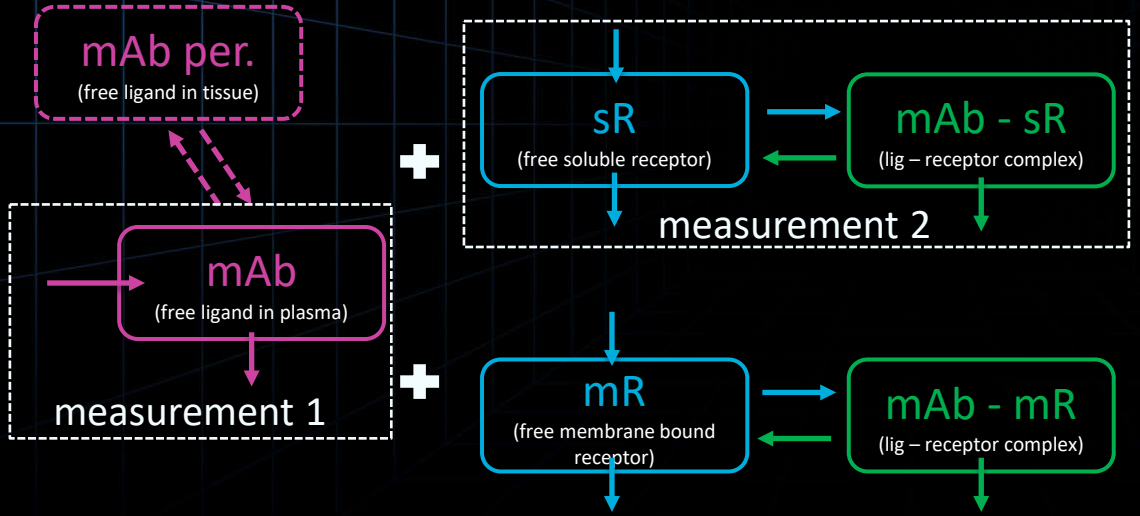

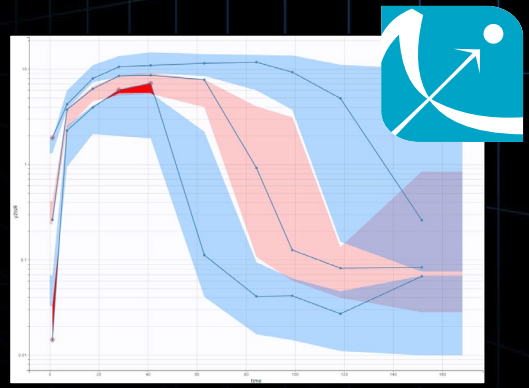

Total soluble receptor in RA patients

Next: dose selection for Phase II

Phase I
Single dose + Safety

Phase II
Multidose + Efficacy

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Which multidose regimens lead to *>90% inhibition* relative to baseline of the *membrane-bound receptor*?

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Is Simulx a “faster bike”?

Setting up a simulation

- Model
- Parameters estimates
- Covariates from dataset
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- New output element: 6 months observation, RR at trough
- New covariate element: RA patients

Setting up a simulation

Export the Monolix project to Simulx

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Simple & fast

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Live demo in Simulx

Export of a Monolix project to Simulx and definition of new elements

Exploration of dosing regimens

What is the membrane-bound receptor inhibition for various dosing regimens?

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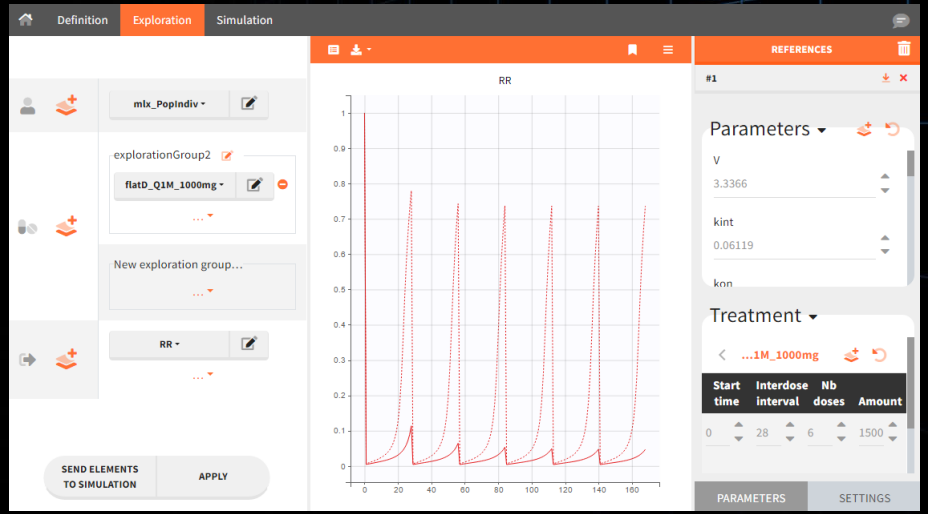
Interactive exploration

Possible dosing regimens:

- 1500 mg Q4W
- 2000 mg Q4W
- 1000 mg Q2W
- …



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Interactive exploration

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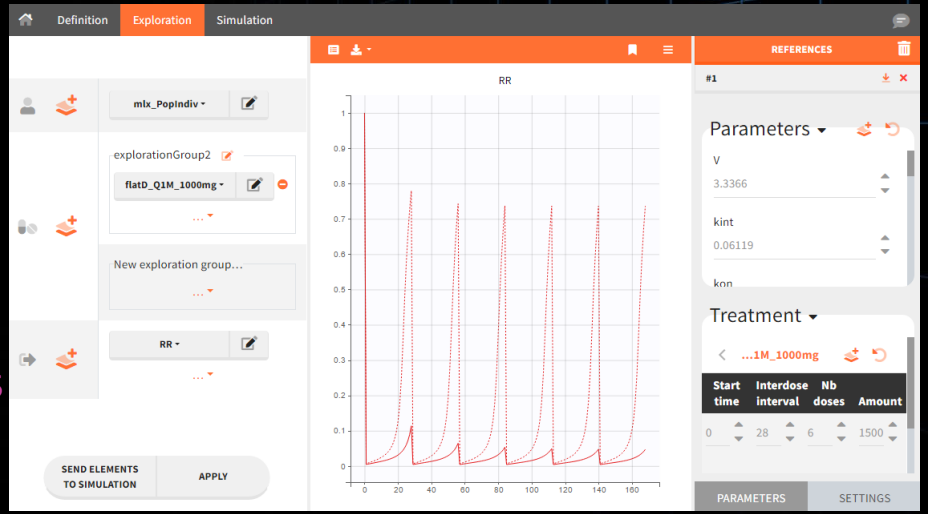
Investigate in a population of patients
20, 25 and 30 mg/kg Q4W



Live demo in Simulx

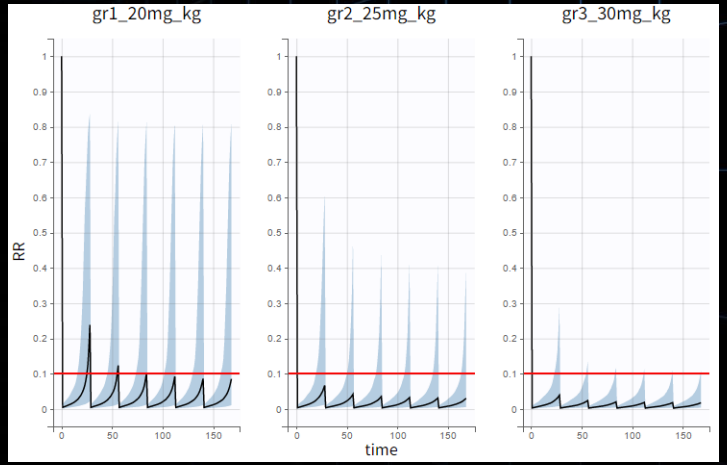
Simulation scenario having three groups with different dosing regimens

Simulation of treatment groups

Which dosing regimens look promising in a population of patients?

25 and 30 mg/kg Q4W

Immediate feedback



RR output distribution with the 90% inhibition threshold line

Simulation of treatment groups

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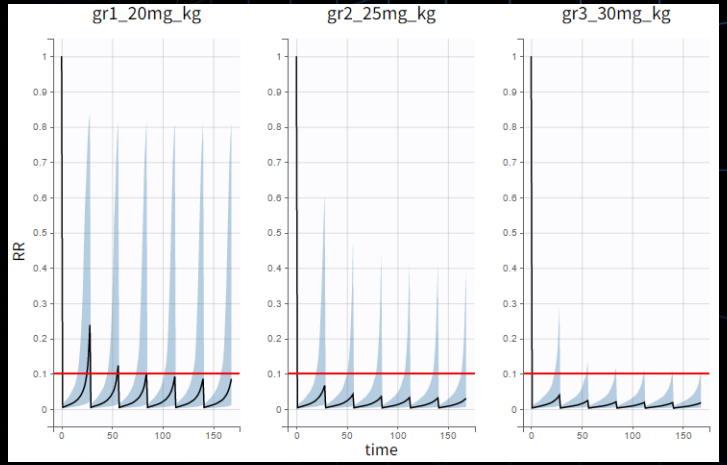
Immediate feedback

25 and 30 mg/kg Q4W

⬇

Quantify the results using the efficacy target:
RR at trough < 0.1



RR output distribution with the 90% inhibition threshold line

Efficacy target

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Built - in
post - processing

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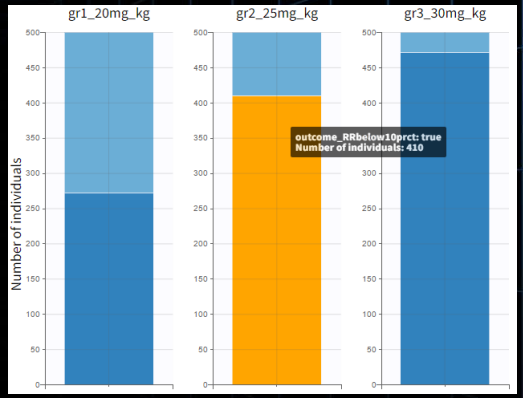
Outcome (calculated for each individual) distribution



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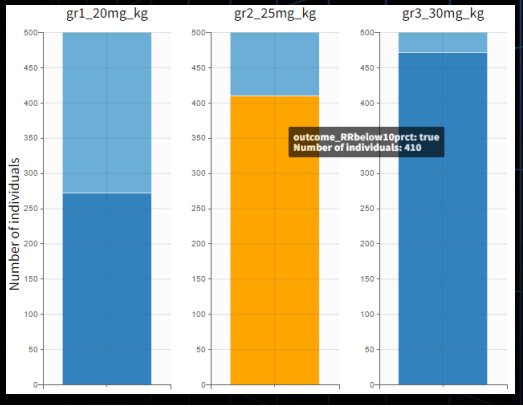


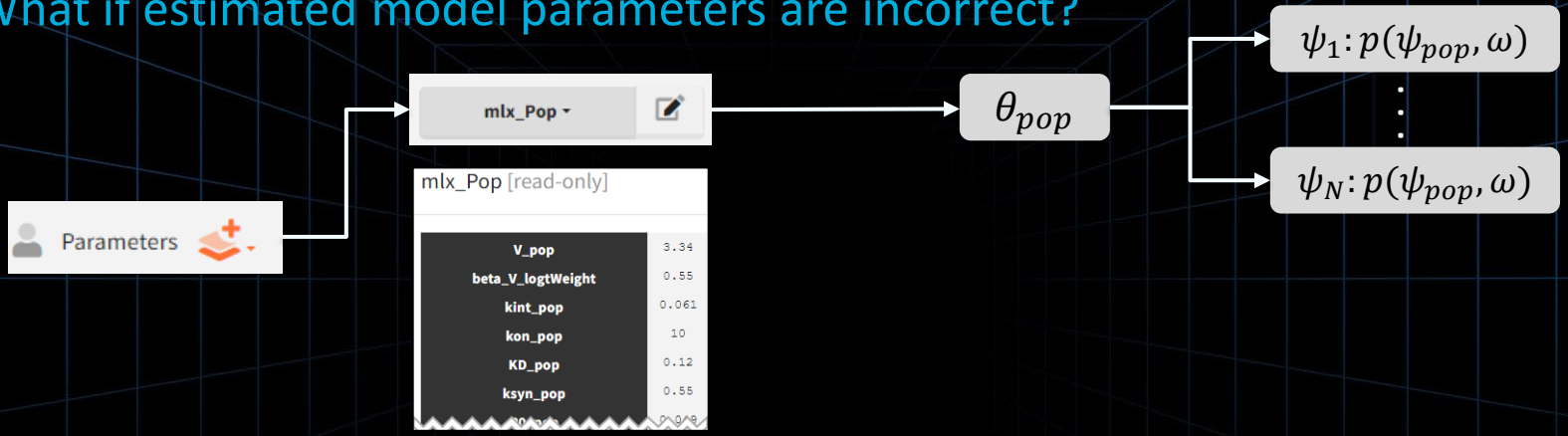
Built - in post - processing

Endpoint results

gr1_20mg_kg		gr2_25mg_kg		gr3_30mg_kg	
percentTrue	totalTrue	percentTrue	totalTrue	percentTrue	totalTrue
54.4	272	82	410	94.2	471

Uncertainty

What if estimated model parameters are incorrect?



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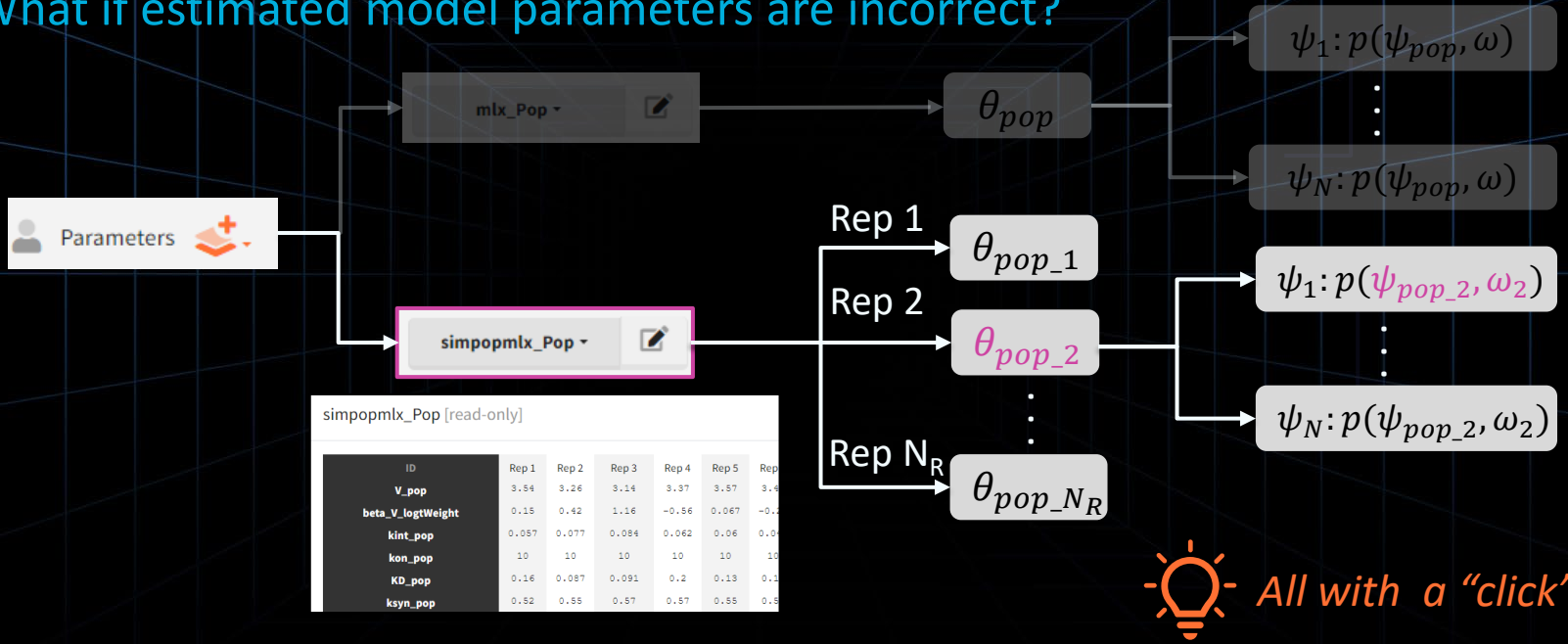


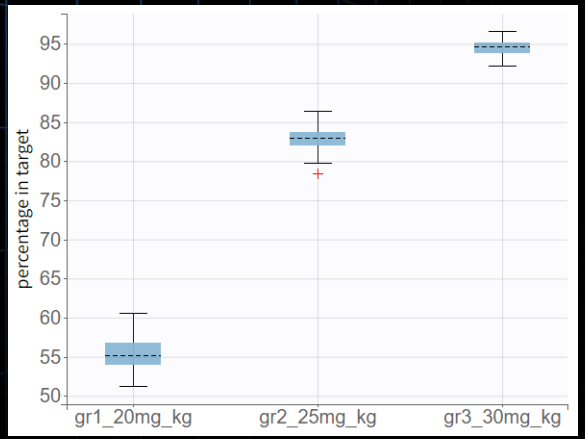
ID	Rep 1	Rep 2	Rep 3	Rep 4	Rep 5	Rep
V_pop	3.54	3.26	3.14	3.37	3.57	3.4
beta_V_logtWeight	0.15	0.42	1.16	-0.56	0.067	-0.1
kint_pop	0.057	0.077	0.084	0.062	0.06	0.0
kon_pop	10	10	10	10	10	10
KD_pop	0.16	0.087	0.091	0.2	0.13	0.1
ksyn_pop	0.52	0.55	0.57	0.57	0.55	0.5

Live demo in Simulx

Simulation of replicates and uncertainty of the endpoint

Phase II dosing regimen

Dosing of 30 mg/kg Q4W could guarantee >90% inhibition of membrane-bound receptor for 9 in 10 individuals



Endpoint (% in target) distribution

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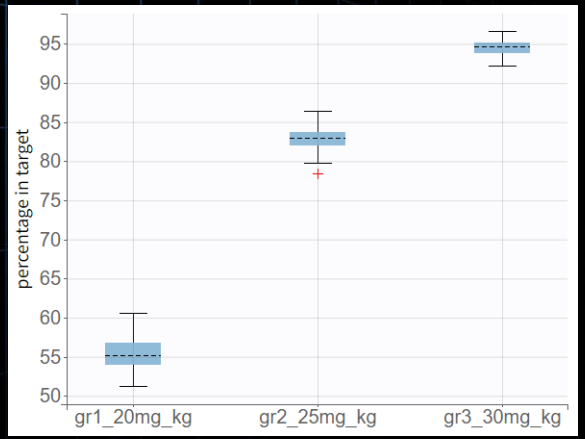

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But…what if

- weight distribution is different?
- patients have reduced clearance due to the renal impairment?
- we start with a loading dose?
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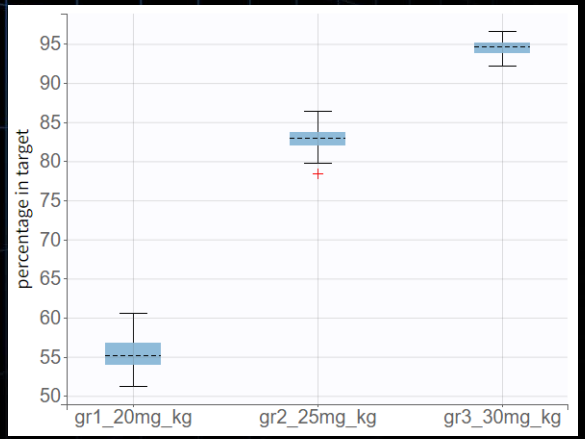

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Go faster and win with Simulx

Q&A

Questions & Answers

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