Model-Informed Drug Development

MIDD+

2021 Virtual Conference

Predicting optimal scheduling of drug combinations in lung cancer xenografts using a population PK/PD model

Pauline Traynard

SimulationsPlus
Cognigen | DILIsym Services | Lixoft

Introduction

Case study based on data published and modeled in:

- Imbs et al. (2018). Revisiting Bevacizumab + Cytotoxics Scheduling Using Mathematical Modeling: Proof of Concept Study in Experimental Non-Small Cell Lung Carcinoma. *CPT: PSP.*
- Schneider et al. (2019). Optimal Scheduling of Bevacizumab and Pemetrexed/Cisplatin Dosing in Non-Small Cell Lung Cancer. *CPT: PSP.*

Context:

- Bevacizumab-pemetrexed/cisplatin is a first-line therapeutic for advanced nonsquamous non-small cell lung cancer.
- **Bevacizumab potentiates** pemetrexed/cisplatin (**chemotherapy**) **cytotoxicity** by inducing transient tumor vasculature normalization.
- The increase in neoplasm vascular quality because of bevacizumab typically occurs within a **period of a few days after administration**.

Goal of the study:

Estimate the optimal gap between administration of bevacizumab and chemotherapy to reach full cytotoxicity activation

Workflow

Data exploration

- Longitudinal data from 77 xenografts
- Different dosing schedules

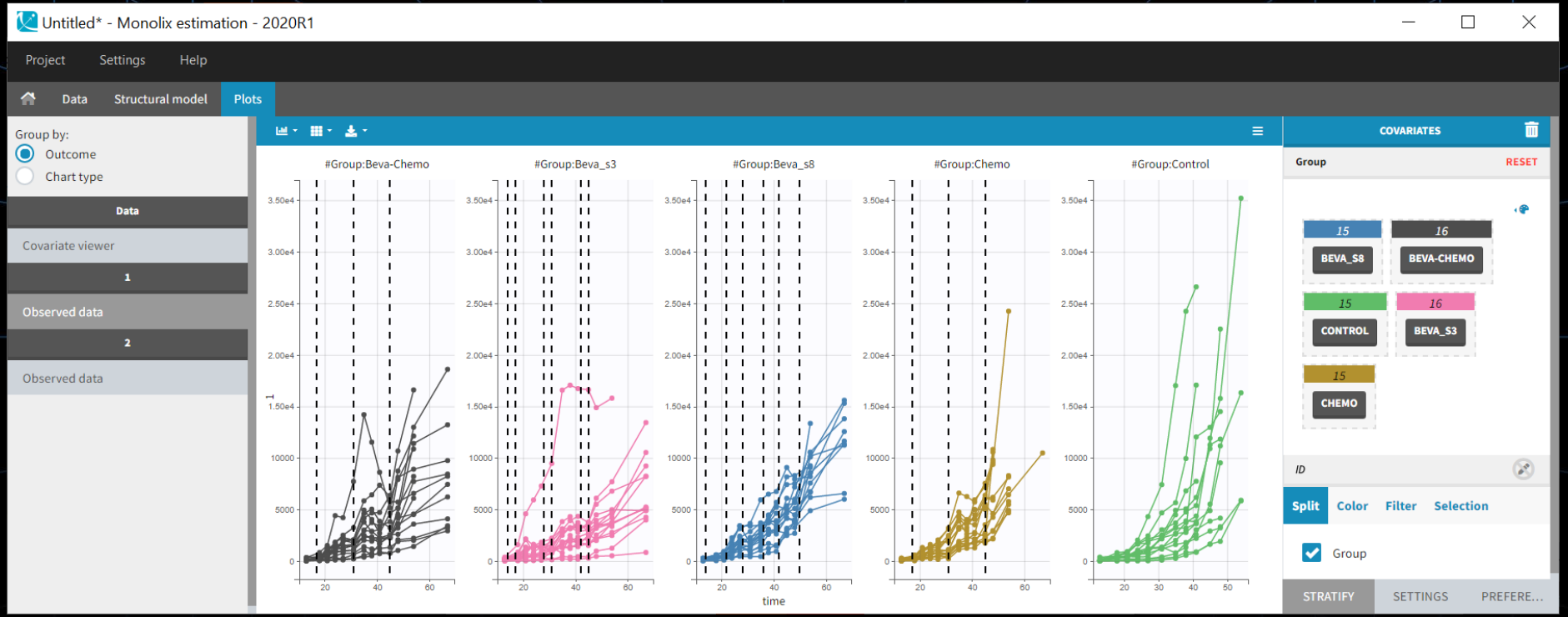
Population modeling in Monolix

- Stepwise development of a tumor growth inhibition model for combination therapy

Simulations in Simulx

- Predict optimal time gap for cytotoxicity activation

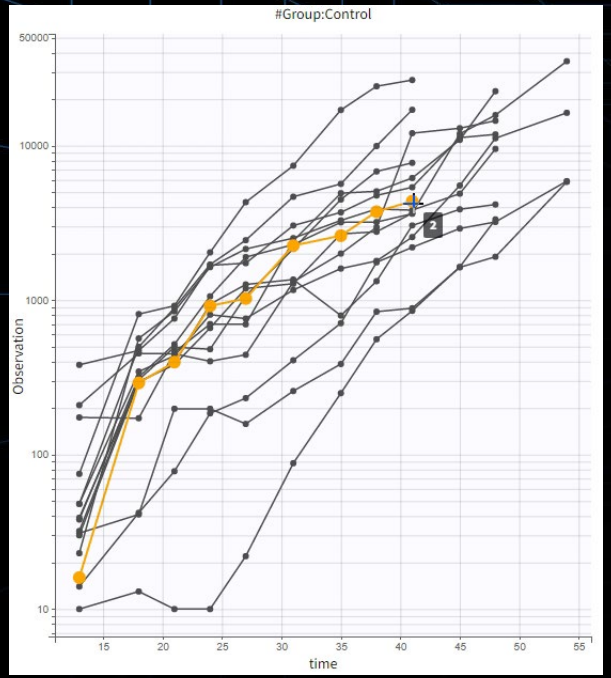
Data exploration



Bevacizumab and Chemo at the same time	Bevacizumab then Chemo after 3 days	Bevacizumab then Chemo after 8 days	Chemotherapy	Control group
n=15	n=16	n=15	n=15	n=15

Data exploration

Data for **control group** in log scale

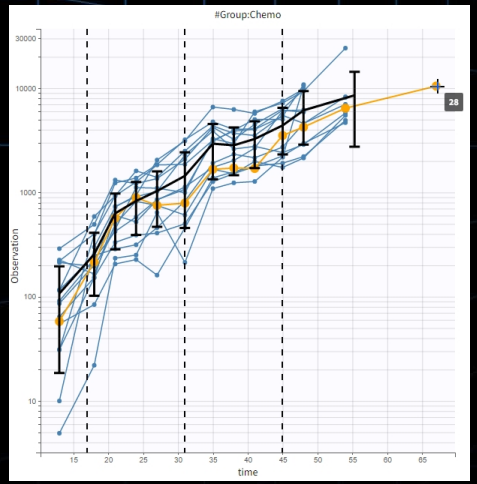


→ Choice of tumor growth model:

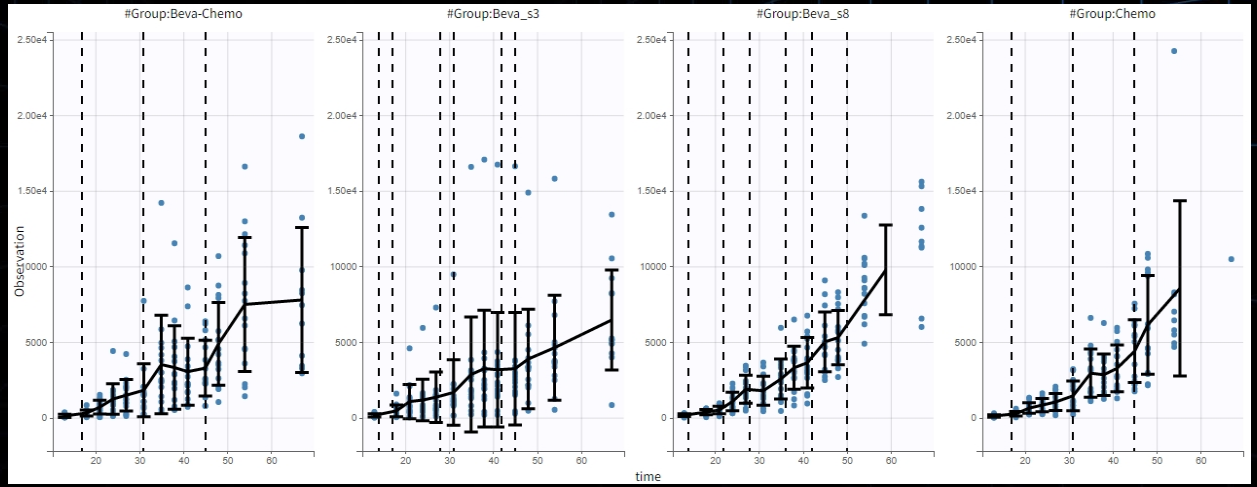
- Not exponential nor linear models
- No clear carrying capacity

Data exploration

Data for **Chemo** group: treatment effect is small, and seems delayed

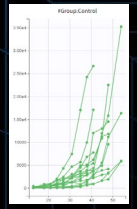


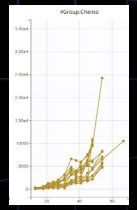
Data for **all groups except Control**: bevacizumab seems to make a difference with concomitant administration and 3-days gap, but not with 8-days gap

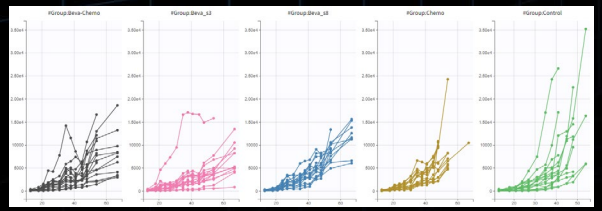


Development of a tumor growth inhibition model for combination therapy with Monolix

Modeling workflow

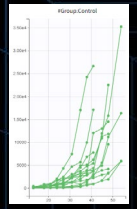


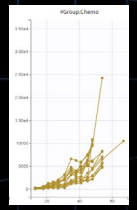


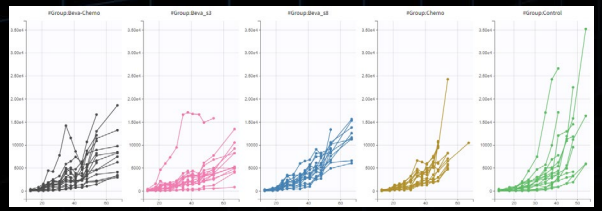


1. Tumor growth model estimated on **Control group**
2. Tumor growth inhibition model for chemotherapy estimated on **Chemo group**
3. Tumor growth inhibition model for combination of chemotherapy and bevacizumab estimated on **all groups**

Modeling workflow







1. Tumor growth model estimated on **Control group**

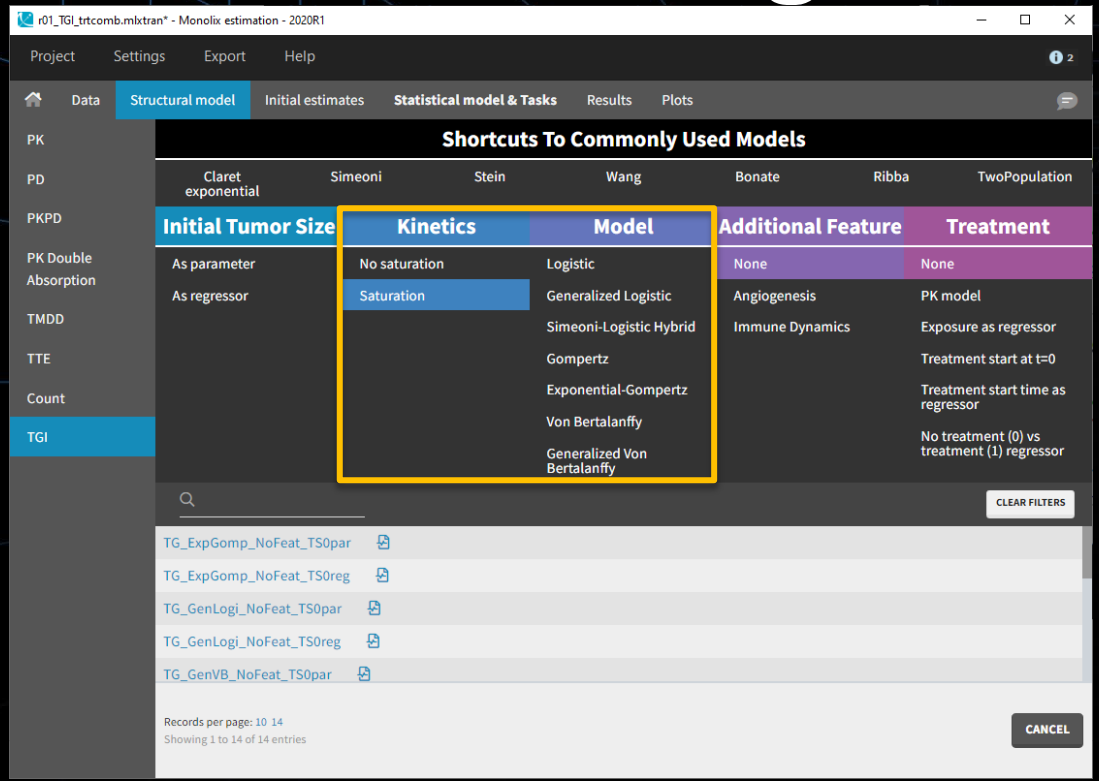
   ↓ *Use last estimates*

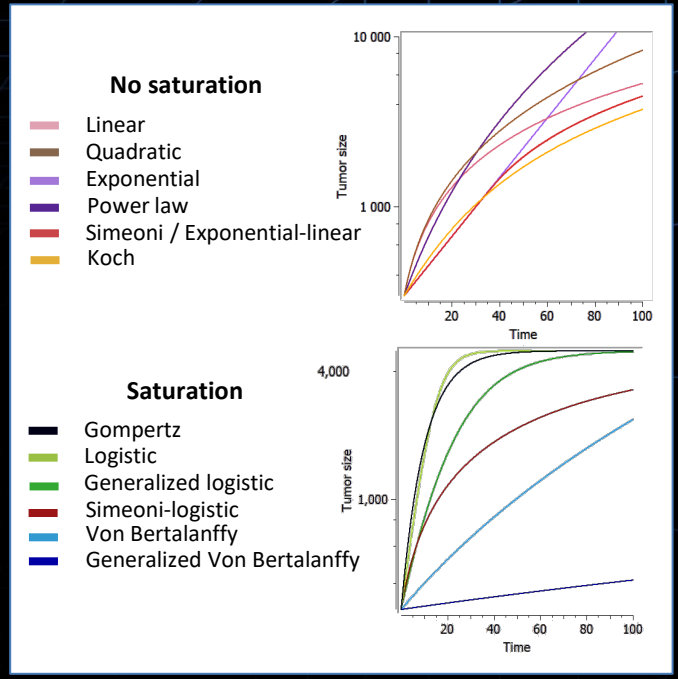
2. Tumor growth inhibition model for chemotherapy estimated on **Chemo group**

   ↓ *Use last estimates*

3. Tumor growth inhibition model for combination of chemotherapy and bevacizumab estimated on **all groups**

Tumor growth model





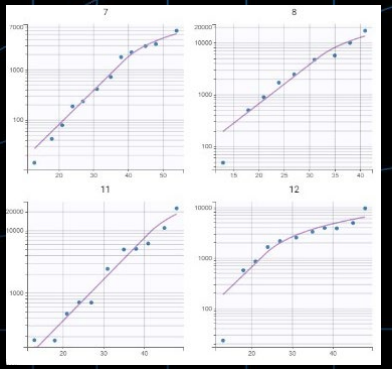
→ The TGI library makes it easy to test different hypotheses…

Tumor growth model

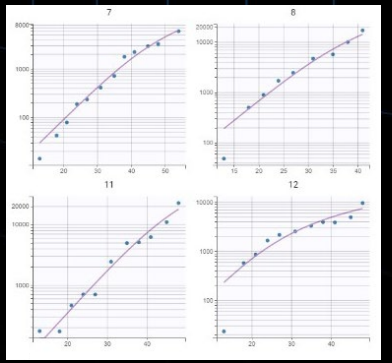
… and compare them in Sycomore

Project name All | None	Hierarchy Add all | Clean	Actions	Rating	-2*LL (Lin)	-2*LL (IS)	BICc (Lin)	BICc (IS)	Structural model	Observation model	Individual model
r01_explin					2452.91		2486.37	TG_ExponentialLinear.txt	y1: comb1	TS0 kp kpl
r02_Simeoni					2453.14		2486.61	TG_Simeoni.txt	y1: comb1	TS0 kp kpl psi
r09_Koch					2454.38		2487.85	TG_Koch.txt	y1: comb1	TS0 kp kpl
r03_logis					2459.86		2493.33	TG_Logistic.txt	y1: comb1	TS0 kp TSmax
r06_SimeoLogis					2452.97		2494.22	TG_Hybrid.txt	y1: comb1	TS0 kp kpl psi TSmax
r04_Gomp					2465.95		2499.42	TG_GompertzTSmax.txt	y1: comb1	TS0 beta TSmax
r05_genLogis					2458.89		2500.13	TG_GenLogistic.txt	y1: comb1	TS0 kp TSmax gamma
r08_GenVonBertalanffy					2466.74		2507.99	TG_GenVonBertalanffy.txt	y1: comb1	TS0 kp kd gamma
r07_VonBertalanffy					2578.32		2611.79	TG_VonBertalanffy.txt	y1: comb1	TS0 kp kd

Exponential-linear



Koch



→ The exponential-linear (or Simeoni) model with a sharp switch between exponential and linear phases gives the best results

Tumor growth inhibition model

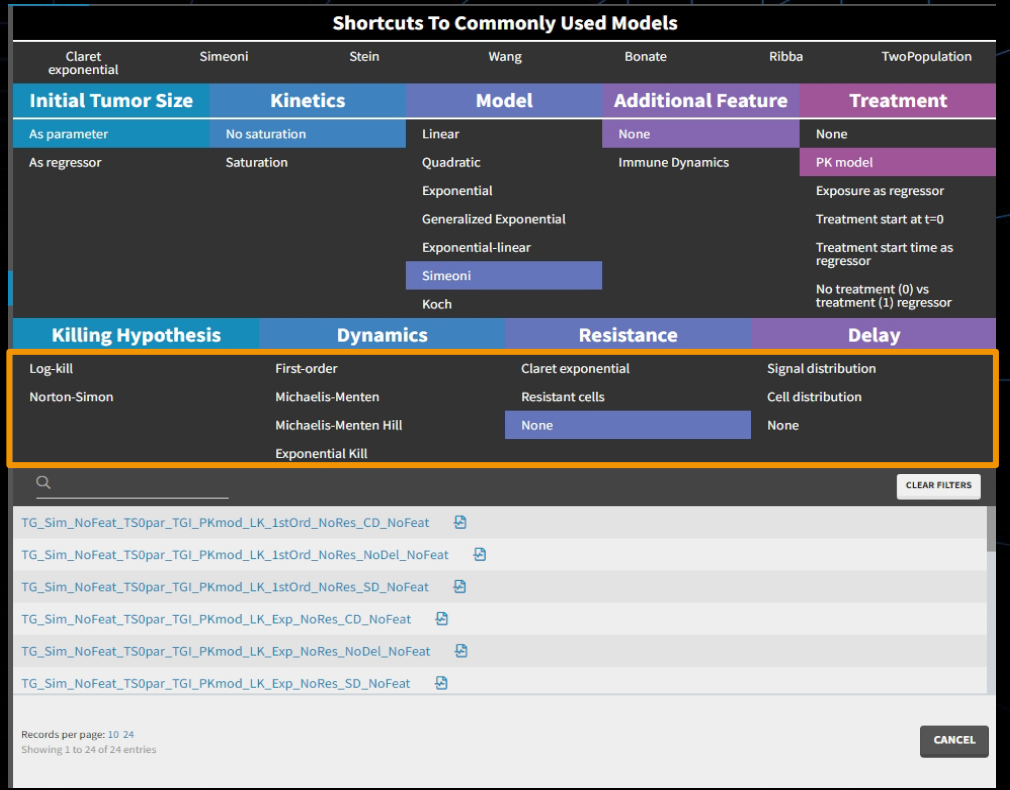
Possible inhibition model for the effect of chemotherapy:

Killing hypothesis:
- Log-kill
- Norton-Simon

Dynamics:
- First-order
- Michaelis-Menten
- Hill
- Exponential

Delay:
- Cell distribution
- Signal distribution

➔ 16 combinations



Final model

```
[LONGITUDINAL]
input = {TS0, kge, kgl, psi, kkill, tau, V, k}

PK:

EXPOSURE = pkmodel(V,k)

EQUATION:
odeType=stiff

;initial conditions of the model:

t_0=0
TS_0=TS0
K1_0=0
K2_0=0
K3_0=0

;model description:

K = (kkill*EXPOSURE)
ddt_K1 = (K-K1)/tau
ddt_K2 = (K1-K2)/tau
ddt_K3 = (K2-K3)/tau

ddt_TS = (kge*TS/(1+(kge/kgl*max(0,TS))^psi)^(1/psi))*(1-K3)

OUTPUT:
output = {TS}
```

Best model from the library:
Simeoni tumor growth with Norton-Simon linear killing and signal distribution

Final model

```
[LONGITUDINAL]
input = {TS0, kge, kgl, psi, kkill, tau, delta, Tlag}

PK:
;=======bevacizumab
ka_b            = 2.6875
k_b             = 0.1143
Vd_b            = 2.3800

compartment(cmt = 1, concentration = C_bev, volume = Vd_b)
oral(adm = 1, cmt = 1, ka = ka_b, Tlag)
elimination(cmt = 1, k = k_b)

;=======cisplatin
ka_cis          = 66.5421
k_cis           = 0.2868
Vd_cis          = 65.1131
compartment(cmt = 2, concentration = C_cis, volume = Vd_cis)
oral(adm = 2, cmt = 2, ka = ka_cis)
elimination(cmt = 2, k = k_cis)

;=======pemetrexed
ka_pem          = 28.6
k_pem           = 2.1328
Vd_pem          = 102.7673
compartment(cmt = 3, concentration = C_pem, volume = Vd_pem)
oral(adm = 3, cmt = 3, ka = ka_pem)
elimination(cmt = 3, k = k_pem)

EXPOSURE = C_cis + C_pem
```

```
EQUATION:
odeType=stiff

;initial conditions of the model:

t_0=0
TS_0=TS0
K1_0=0
K2_0=0
K3_0=0

;model description:

K = (kkill*EXPOSURE)*(1+delta*C_bev)
ddt_K1 = (K-K1)/tau
ddt_K2 = (K1-K2)/tau
ddt_K3 = (K2-K3)/tau

ddt_TS = (kge*TS/(1+(kge/kgl*max(0,TS))^psi)^(1/psi))*(1-K3)

OUTPUT:
output = {TS}
```

Best model from the library:
Simeoni tumor growth with Norton-Simon linear killing and signal distribution

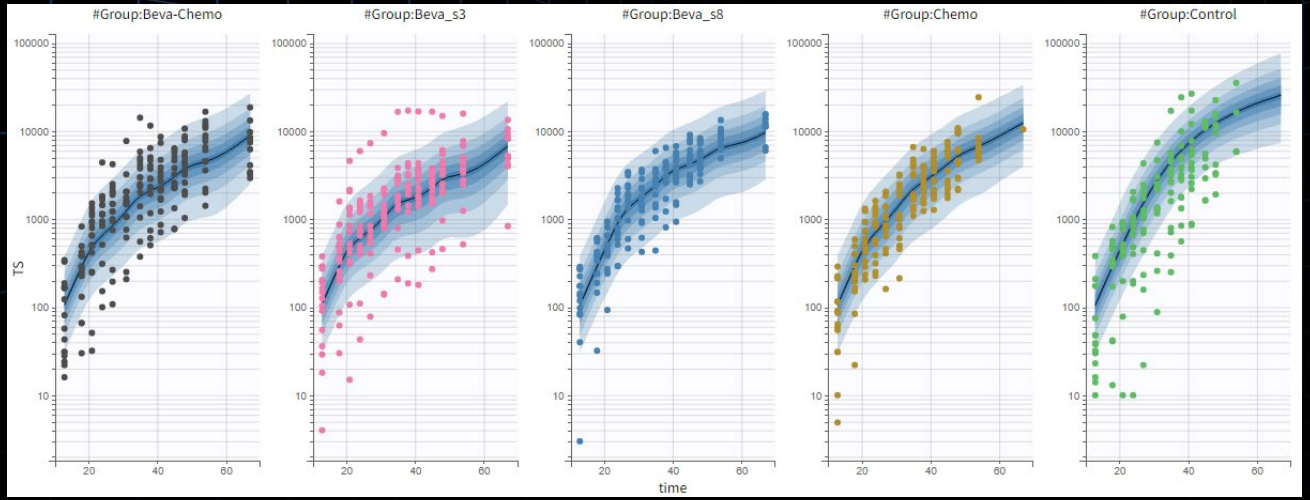
Extension of the model:

1. PK model combining cisplatin and pemetrexed
2. PK model for bevacizumab and new effect: activation of killing with delay

Final model

Results:

- Inter-individual variability was removed on several parameters
- Correlation group with eta_kge, eta_kgl, eta_TS0
- Good RSEs



Prediction distributions in Monolix

	STOCH. APPROX.	
	S.E.	R.S.E.(%)
Fixed Effects		
TS0_pop	7.68	16.5
kge_pop	0.19	3.83
kgl_pop	640.3	13.6
kkill_pop	501.23	4.24
tau_pop	3.52	2.33
delta_pop	3.63	6.92
Tlag_pop	0.33	4.75
Standard Deviation of the Random Effects		
omega_TS0	1.15	10.8
omega_kge	0.28	10.8
omega_kgl	0.87	12.8
omega_kkill	0.19	16.2
Correlations		
corr_kge_TS0	-0.76	7.69
corr_kgl_TS0	0.62	16.3
corr_kgl_kge	-0.66	14.1
Error Model Parameters		
a	34.97	14.9
b	0.23	3.99

Final estimates

Simulations in Simulx

Simulations in Simulx

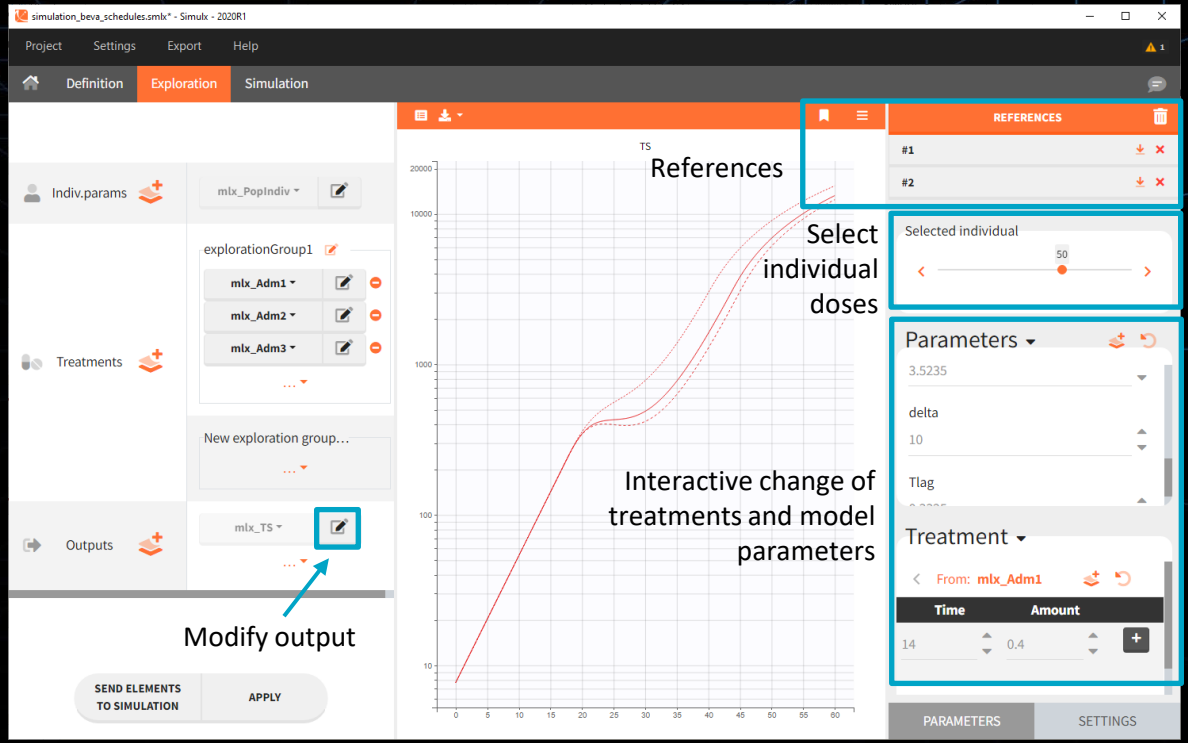
Question to answer by simulation:

What is the **optimal delay** between bevacizumab administration and chemotherapy?

Simulations in Simulx

First interactive exploration

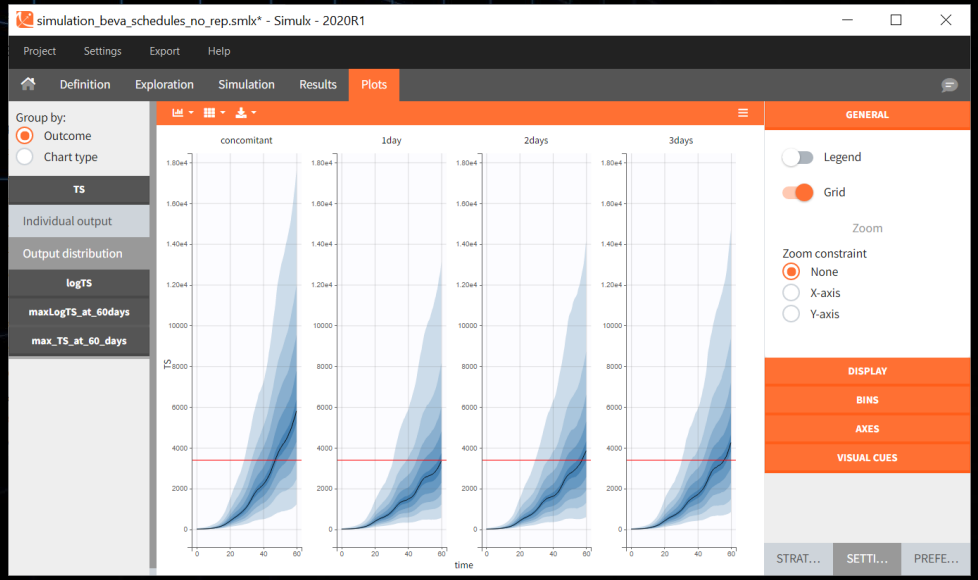
→ 1-2 days gap seems to be optimal for typical individual

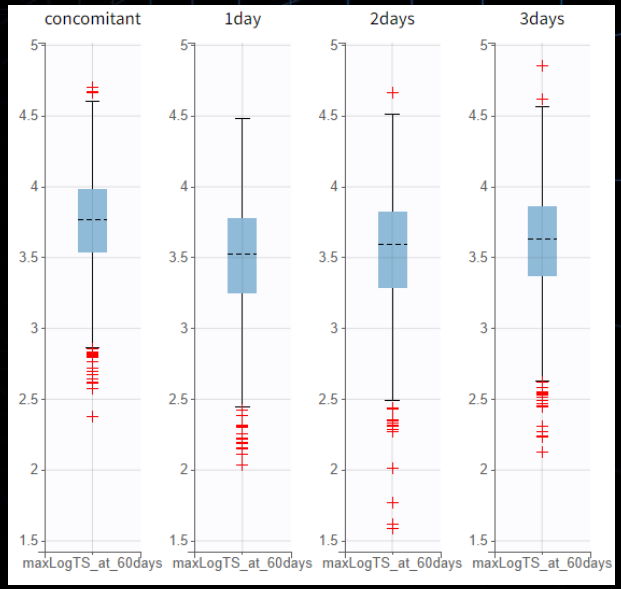


Simulations in Simulx

Simulation on large populations for several gaps

Post-processing for quantitative results

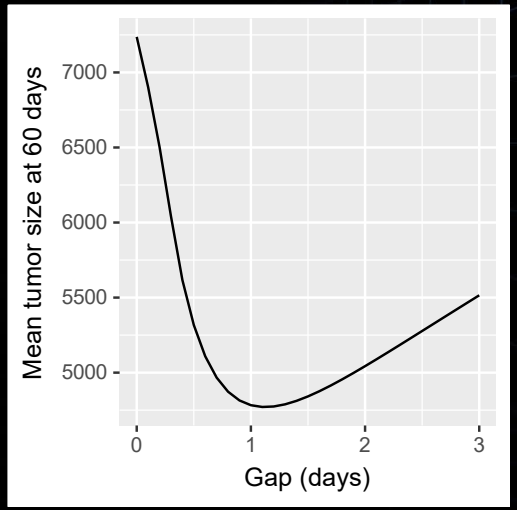




Finding optimal gap

Repeat simulation for different time gaps with LixoftConnectors (R functions calling Simulx)

```
library(lixoftConnectors)
initializeLixoftConnectors(software="simulx")

time_gaps <- seq(0,3,by=0.1)

for(gap in time_gaps){

  loadProject(projectFile ="simulationsTGI.smlx")

  trtref <- getTreatmentElements()$`3doses_beva`
  dosing_times <- trtref$data
  dosing_times$time <- c(17,31,45) - gap
  defineTreatmentElement(name="newbeva",
                         element = list(data=dosing_times))
  setGroupElement("shared", c("3doses_cis",
                              "3doses_pem",
                              "newbeva"))

  runSimulation()
  sim <- getSimulationResults()$res$TS
  …
}
```



Results:

- Gap yielding smallest mean TS at 60 days = 1.1 days
- Efficacy loss in scheduling a greater gap than optimal is much less than the efficacy loss in scheduling a shorter gap

Conclusion

- Estimation of a population model of tumor dynamics in response to combination of bevacizumab and pemetrexed-cisplatin chemotherapy.
- Simulations show that 1.1 days-gap gives a smaller tumor size at 60 days, and that the efficacy loss in scheduling a greater gap than optimal is much less than the efficacy loss in scheduling a shorter gap.
- **Next step**: extrapolation of the model to human could be used to predict optimal dosing schedule in human.

Q&A

Questions & Answers

Model-Informed Drug Development

MIDD+

2021 Virtual Conference

Learn More! www.simulations-plus.com

SimulationsPlus

Cognigen | DILIsym Services | Lixoft