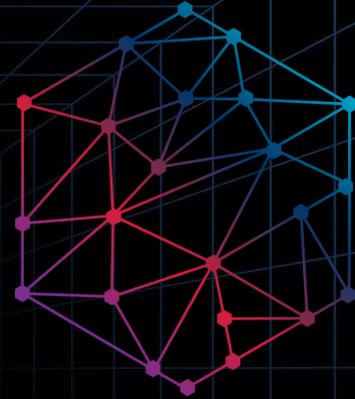


Model-Informed Drug Development

MIDD+

2021 Virtual Conference



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



Pauline Traynard

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

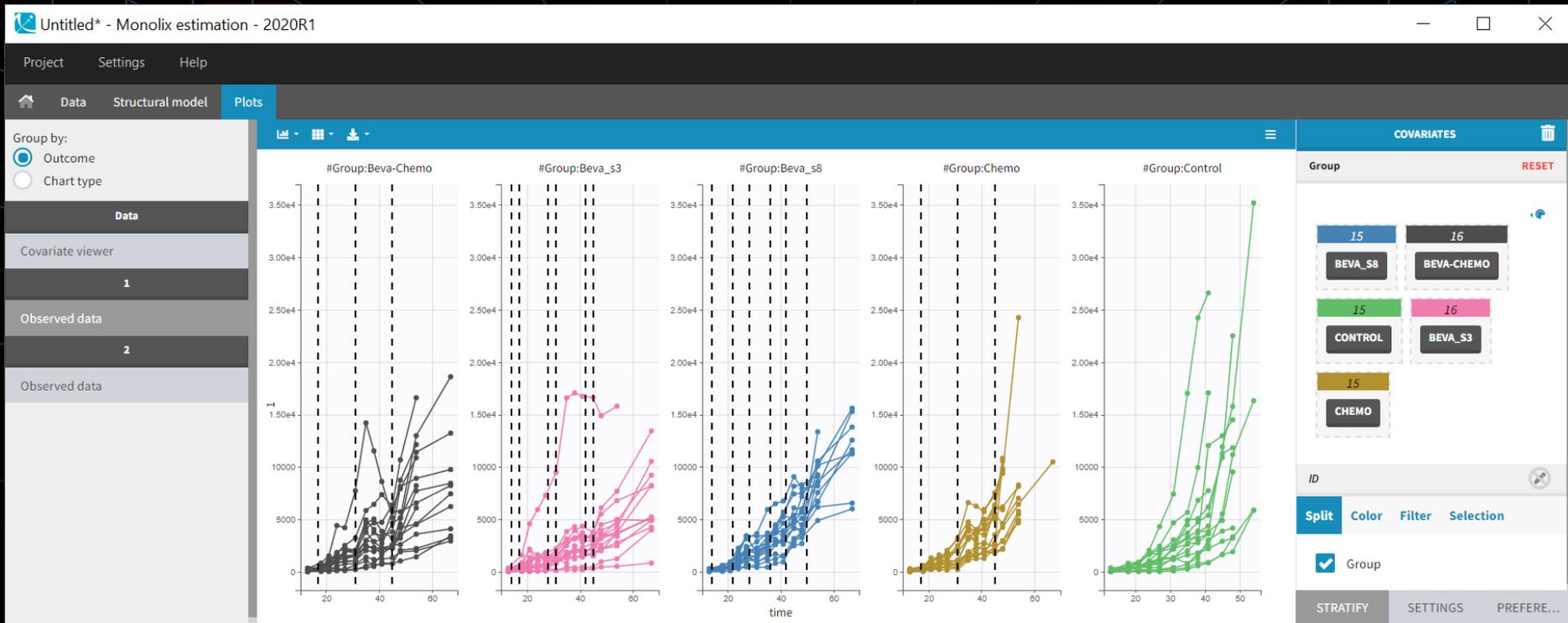


Simulations in Simulx

- Predict optimal time gap for cytotoxicity activation



Data exploration



**Bevacizumab
and Chemo at
the same time**
n=15

**Bevacizumab
then Chemo
after 3 days**
n=16

**Bevacizumab
then Chemo
after 8 days**
n=15

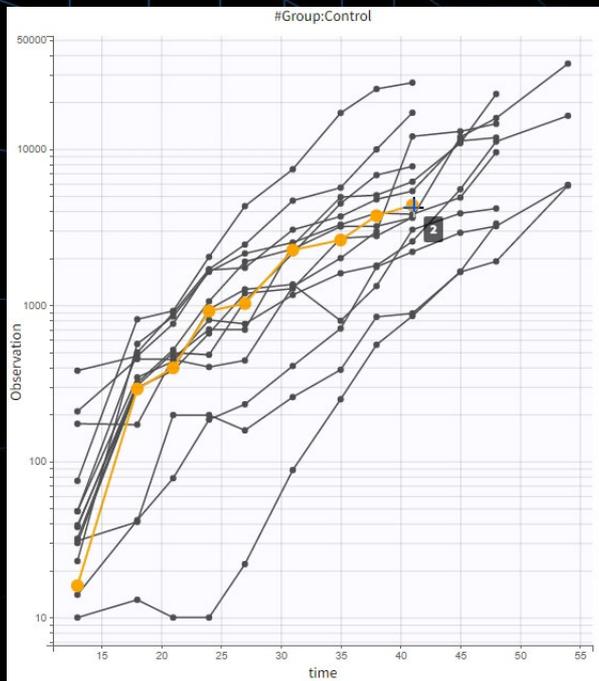
Chemotherapy
n=15

Control group
n=15



Data exploration

Data for control group in log scale



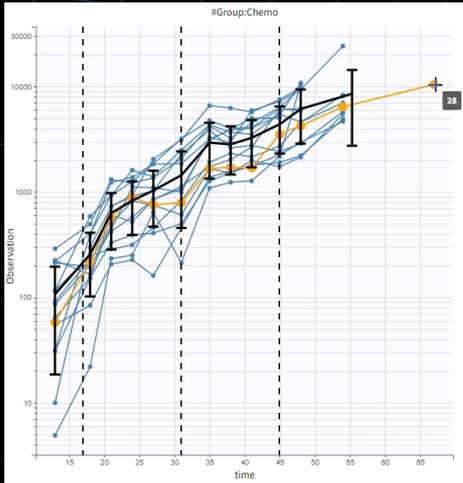
→ Choice of tumor growth model:

- Not exponential nor linear models
- No clear carrying capacity

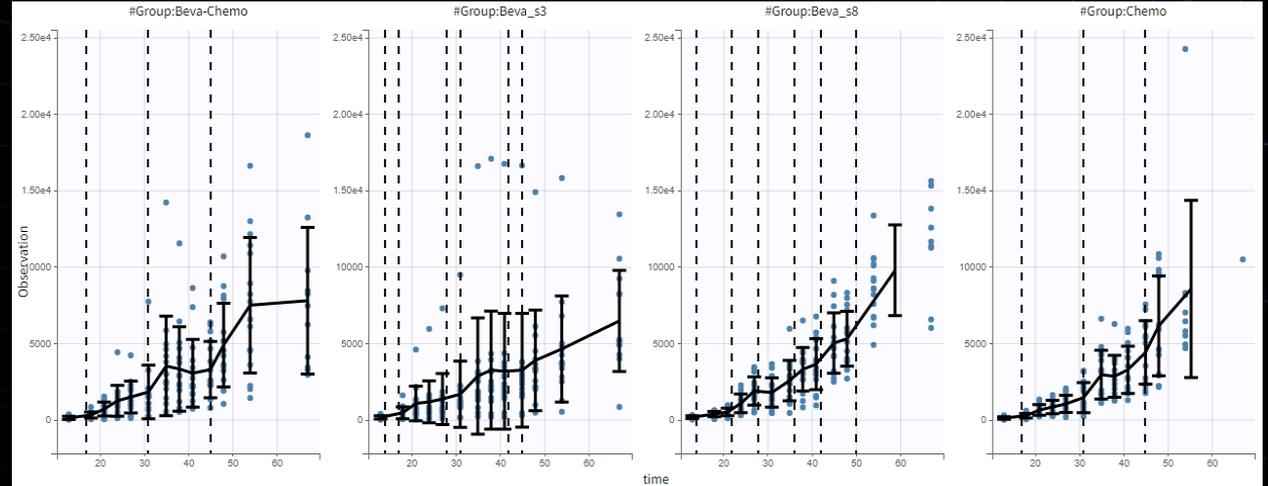


Data exploration

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

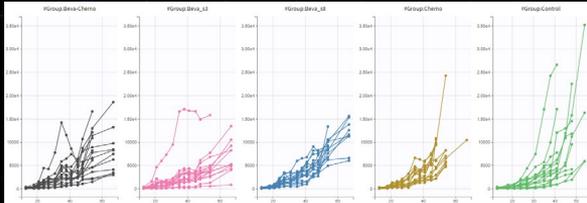
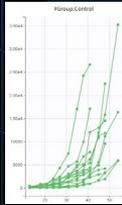




Development of a tumor growth inhibition model for combination therapy with Monolix



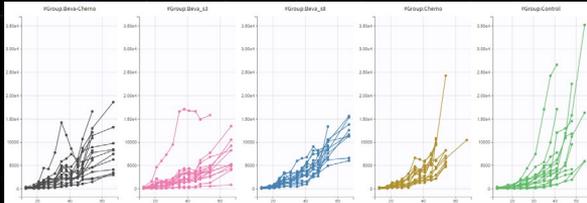
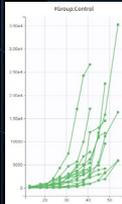
Modeling workflow



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**

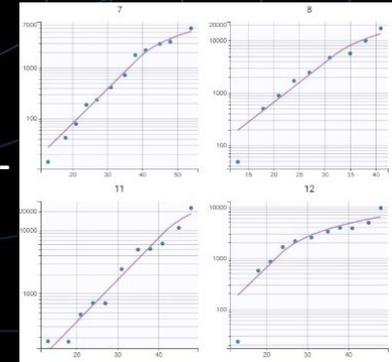


Tumor growth model

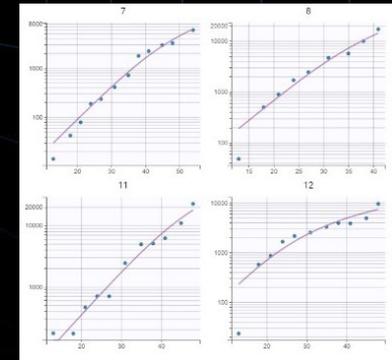
... and compare them in Sycomore

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_ExponentialLinea r.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_GompertzTSma x.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_GenVonBertalanf fy.txt	y1: comb1	TS0 kp kd gamma
r07_VonBertalanffy	+	✕ 📄 🔄 🗑️	★★★★		2578.32		2611.79	TG_VonBertalanffy.tx t	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

Shortcuts To Commonly Used Models						
Claret exponential	Simeoni	Stein	Wang	Bonate	Ribba	TwoPopulation
Initial Tumor Size	Kinetics	Model	Additional Feature	Treatment		
As parameter	No saturation	Linear	None	None		
As regressor	Saturation	Quadratic	Immune Dynamics	PK model		
		Exponential		Exposure as regressor		
		Generalized Exponential		Treatment start at t=0		
		Exponential-linear		Treatment start time as regressor		
		Simeoni		No treatment (0) vs treatment (1) regressor		
		Koch				
Killing Hypothesis	Dynamics	Resistance	Delay			
Log-kill	First-order	Claret exponential	Signal distribution			
Norton-Simon	Michaelis-Menten	Resistant cells	Cell distribution			
	Michaelis-Menten Hill	None	None			
	Exponential Kill					

Search	CLEAR FILTERS
TG_Sim_NoFeat_TS0par_TGI_PKmod_LK_1stOrd_NoRes_CD_NoFeat	
TG_Sim_NoFeat_TS0par_TGI_PKmod_LK_1stOrd_NoRes_NoDel_NoFeat	
TG_Sim_NoFeat_TS0par_TGI_PKmod_LK_1stOrd_NoRes_SD_NoFeat	
TG_Sim_NoFeat_TS0par_TGI_PKmod_LK_Exp_NoRes_CD_NoFeat	
TG_Sim_NoFeat_TS0par_TGI_PKmod_LK_Exp_NoRes_NoDel_NoFeat	
TG_Sim_NoFeat_TS0par_TGI_PKmod_LK_Exp_NoRes_SD_NoFeat	

Records per page: 10 24
Showing 1 to 24 of 24 entries

CANCEL



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:

$$K = (kkill * EXPOSURE) * (1 + \text{delta} * C_{bev})$$
$$ddt_K1 = (K - K1) / \tau$$
$$ddt_K2 = (K1 - K2) / \tau$$
$$ddt_K3 = (K2 - K3) / \tau$$
$$ddt_TS = (kge * TS / (1 + (kge / kgl * \max(0, TS))^{\psi}))^{1/\psi} * (1 - K3)$$

OUTPUT:

output = {TS}



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

Extension of the model:

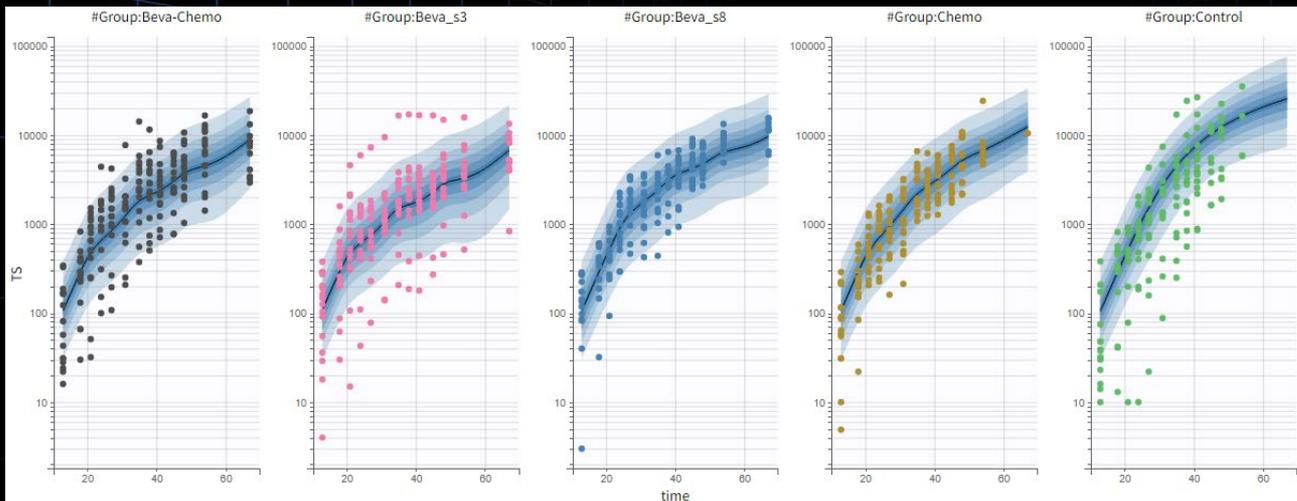
1. PK model combining cisplatin and pemetrexed
2. PK model for bevacizumab and new effect: activation of killing with delay



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	1.26	16.5
kge_pop	0.19	0.0074	3.83
kgl_pop	640.3	86.8	13.6
kkill_pop	501.23	21.24	4.24
tau_pop	3.52	0.082	2.33
delta_pop	3.63	0.25	6.92
Tlag_pop	0.33	0.016	4.75

Standard Deviation of the Random Effects

omega_TS0	1.15	0.12	10.8
omega_kge	0.28	0.03	10.8
omega_kgl	0.87	0.11	12.8
omega_kkill	0.19	0.031	16.2

Correlations

corr_kge_TS0	-0.76	0.059	7.69
corr_kgl_TS0	0.62	0.1	16.3
corr_kgl_kge	-0.66	0.093	14.1

Error Model Parameters

a	34.97	5.22	14.9
b	0.23	0.0093	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

The screenshot displays the Simulx software interface. The main window is titled "simulation_beve_schedules.mlx" and shows a simulation in progress. The interface is divided into several sections:

- Left Panel:** Contains "Indiv.params" (mlx_PopIndiv), "Treatments" (mlx_Adm1, mlx_Adm2, mlx_Adm3), and "Outputs" (mlx_TS). A blue box highlights the "mlx_TS" output, with an arrow pointing to the "Modify output" button below it.
- Center Panel:** A graph titled "References" showing a red curve on a semi-logarithmic scale (y-axis from 10 to 20000, x-axis from 0 to 60). The curve shows an initial rise, a plateau, and a second rise. A blue box highlights the graph area with the text "Interactive change of treatments and model parameters".
- Right Panel:** Contains a "REFERENCES" table with two entries (#1 and #2), a "Selected individual" slider set to 50, and a "Parameters" section with values for "3.5235", "delta" (10), and "Tlag". Below this is a "Treatment" dropdown set to "From: mlx_Adm1" and a table with columns "Time" and "Amount".

Buttons at the bottom include "SEND ELEMENTS TO SIMULATION" and "APPLY".



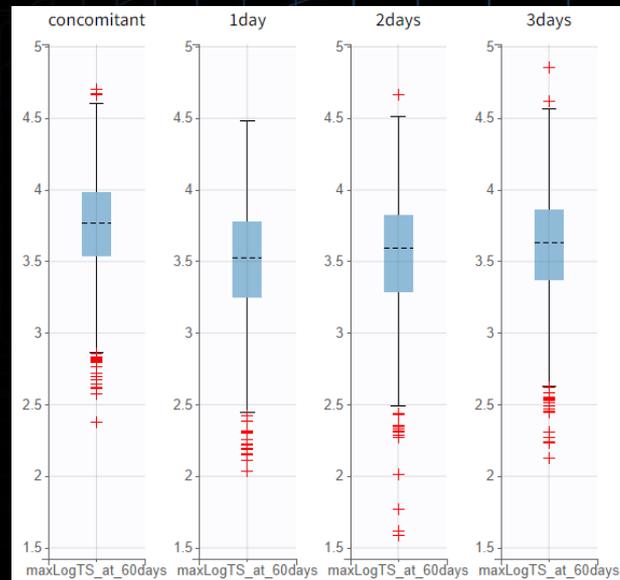
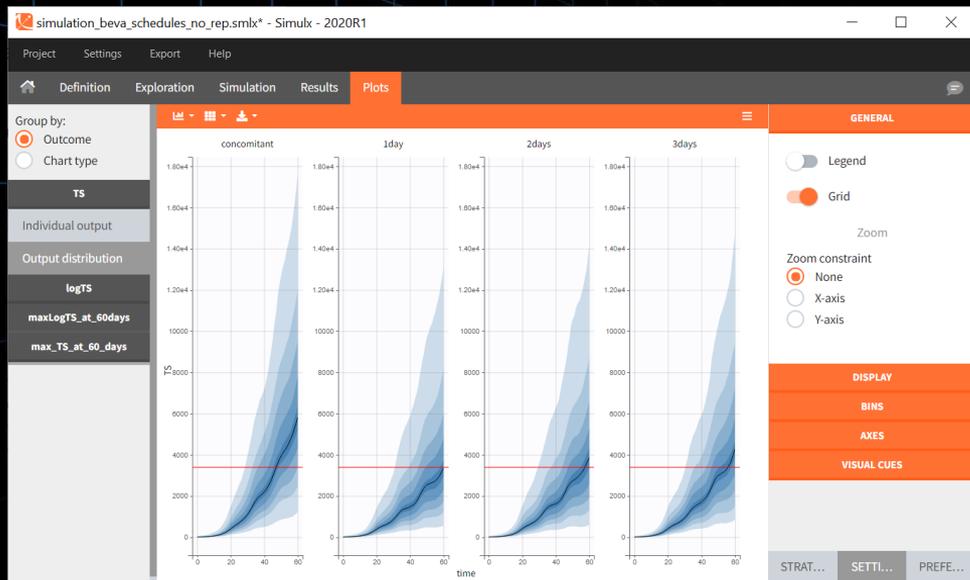
Simulations in Simulx



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")

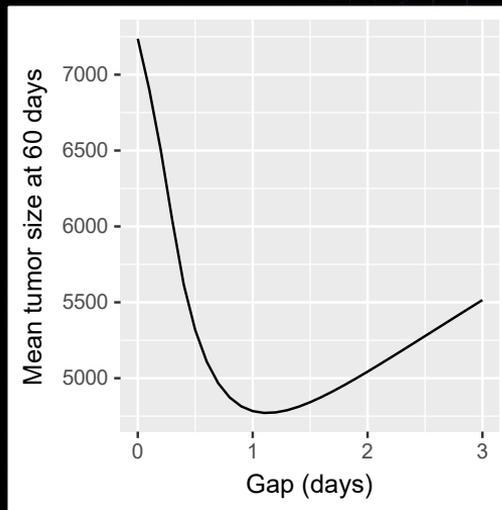
time_gaps <- seq(0,3,by=0.1)

for(gap in time_gaps) {

  loadProject(projectFile ="simulationsTGI.smlx")

  trtref <- getTreatmentElements()$`3doses_beve`
  dosing_times <- trtref$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.

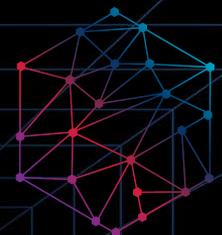
Q & A

Questions & Answers

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