LIXOFT

A SIMULATIONS PLUS COMPANY

TUMOR GROWTH INHIBITION MODELING

Webinar, 9 March 2021

Agenda

- Presentation of the models in the TGI library available in Monolix and Simulx
- Example 1: Combination therapy in lung cancer xenografts
- Example 2: PSA in metastatic Castration-Resistant Prostate Cancer treated with chemotherapy

TGI library

LIXOFT
A SIMULATIONS PLUS COMPANY

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		

LIXOFT

A SIMULATIONS PLUS COMPANY

Common tumor growth models

Common tumor growth models

Tumor growth models without saturation:

- Linear
- Quadratic
- Exponential
- Generalized exponential
- Exponential-linear
- Simeoni
- Koch

Tumor growth models with saturation:

- Logistic
- Generalized logistic
- Hybrid Simeoni-logistic
- Gompertz
- Gompertz-exponential
- Von Bertalanffy
- Generalized Von Bertalanffy

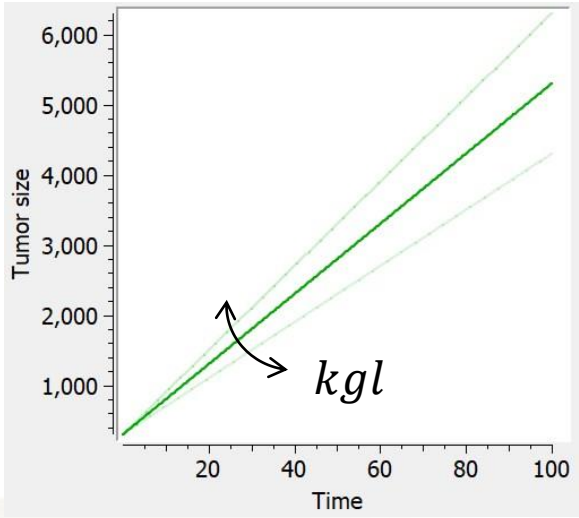
Tumor growth models

Linear model:

- constant zero-order growth rate

$$\frac{dTS}{dt} = kgl \quad \Leftrightarrow \quad TS = kgl * t + TS0$$

$$TS(t = 0) = TS0$$



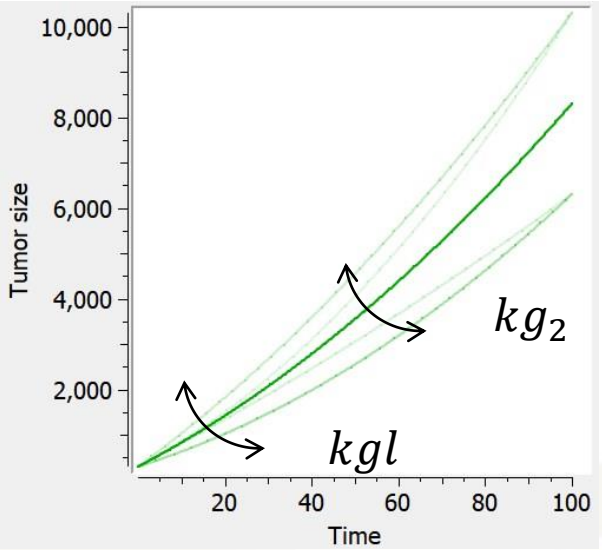
Tumor growth models

Quadratic model:

- combines linear and quadratic growth rates

$$\frac{dTS}{dt} = kgl + 2kg_2 * t \quad \Leftrightarrow \quad TS = kgl * t + kg_2 * t^2 + TS0$$

$$TS(t = 0) = TS0$$



Tumor growth models

Exponential model:

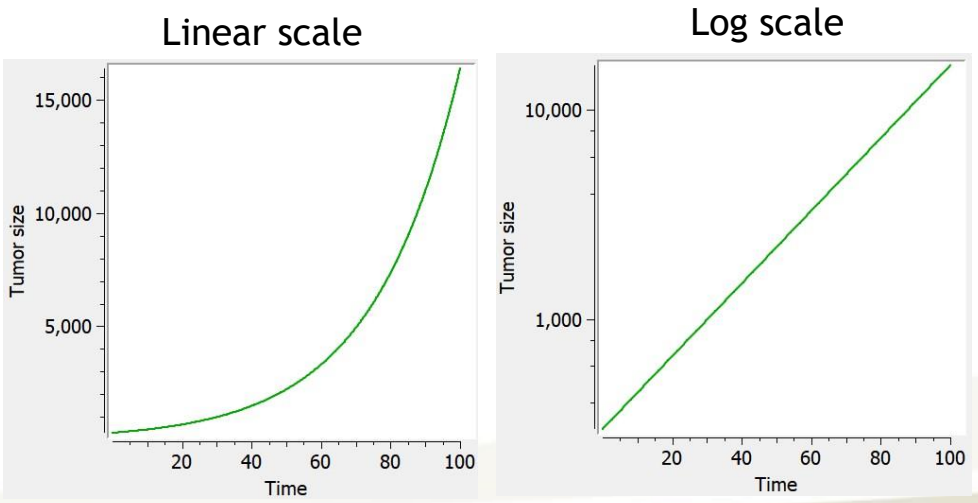
- assumes that the growth rate of a tumor is proportional to tumor burden (first-order growth)

$$\frac{dTS}{dt} = kge * TS$$

$$TS(t = 0) = TS0$$

$$\Leftrightarrow$$

$$TS = TS0 * e^{kge*t}$$



Tumor growth models

Generalized exponential model (power law):

- assumes that the growth rate of a tumor is proportional to tumor burden (first-order growth)

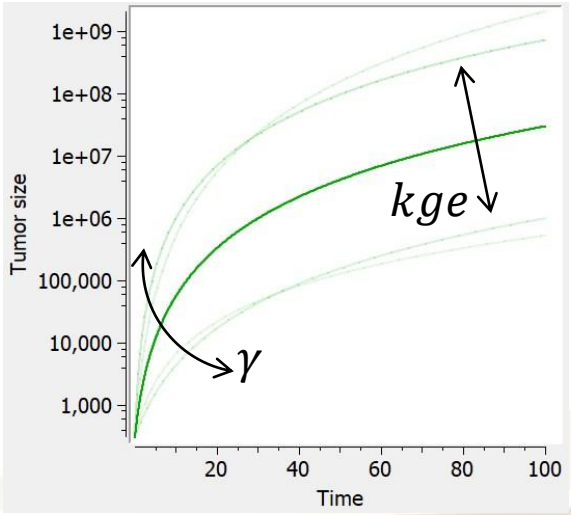
$$\frac{dTS}{dt} = kge * TS^{\gamma}$$

$$TS(t=0) = TS0$$

$$\Leftrightarrow$$

$$TS = [kge(1-\gamma)t + TS0^{1-\gamma}]^{\frac{1}{1-\gamma}}$$

Log scale



Tumor growth models

Exponential-linear model:

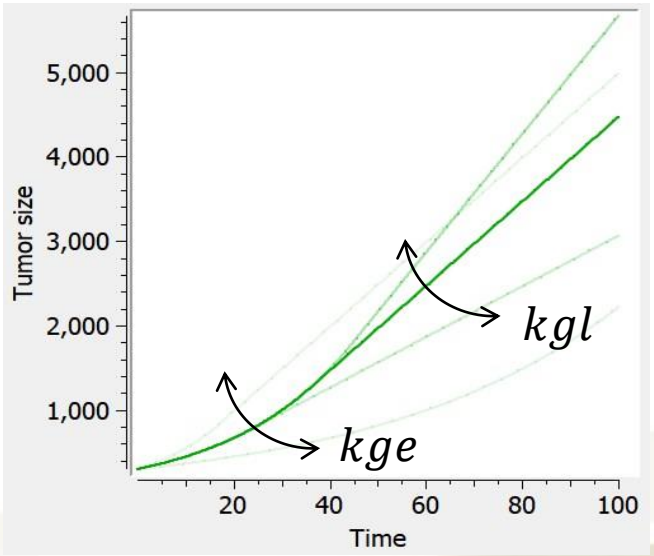
- assumes that the growth rate of a tumor is proportional to tumor burden (first-order growth)

$$\frac{dTS}{dt} = \begin{cases} kge * TS, & t \leq \tau \\ kgl, & t > \tau \end{cases} \quad \Leftrightarrow \quad TS = \begin{cases} TS0 * e^{(kge*t)}, & t \leq \tau \\ kgl * (t - \tau) + TS0 * e^{kge*\tau}, & t > \tau \end{cases}$$
$$TS(t = 0) = TS0$$

$$\tau = \frac{1}{kge} ln\left(\frac{kgl}{kg * TSO}\right)$$

- At t= τ, $TS = \frac{kgl}{kge}$
- The transition time can not be computed if the model is combined with a treatment effect or an additional feature

Linear scale



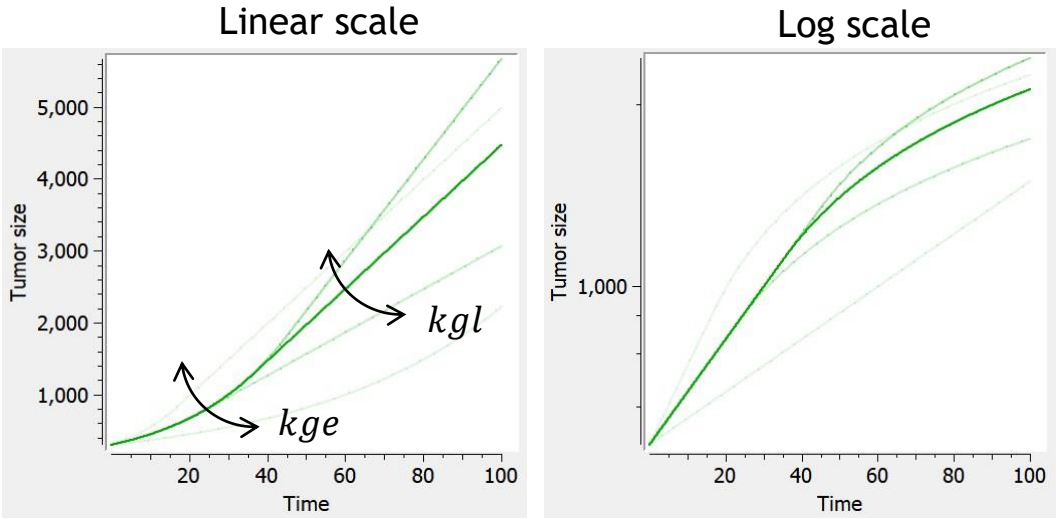
Tumor growth models

Simeoni model:

- approximates the exponential-linear model with a single differential equation

$$\frac{dTS}{dt} = \frac{kge * TS}{\left[1 + \left(\frac{kge}{kgl} * TS\right)^{\psi}\right]^{1/\psi}}$$

$$TS(t = 0) = TS0$$



- ψ should be fixed to a high value (20 for example) for a sharp switch from the first-order to the zero-order growth
- Differentiable even when combined with any type of treatment effect

[Simeoni et al. (2004). *Cancer Research*, *64*(3), 1094–1101.]

Tumor growth models

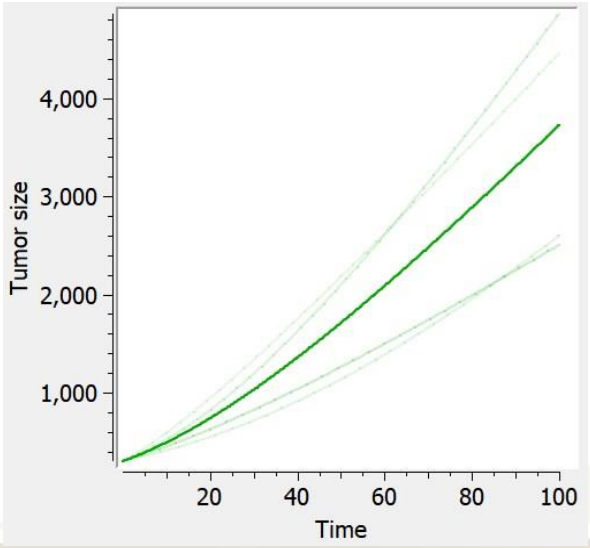
Koch model:

- assumes a smooth transition between exponential and linear growth phase

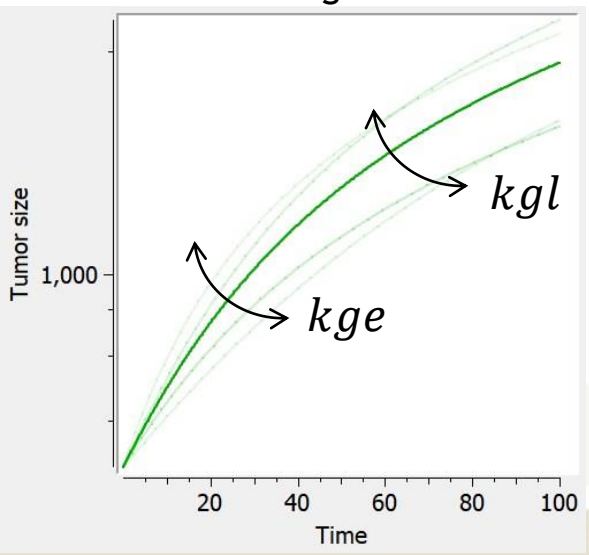
$$\frac{dTS}{dt} = \frac{2kge * kgl * TS}{kgl + 2kge * TS} \quad \Leftrightarrow \quad TS = TS0e^{2kge\left(t+\frac{1}{kgl}(TS0-TS)\right)}$$

$$TS(t=0) = TS0$$

Linear scale



Log scale



[Koch, G. et al. (2009). *Journal of Pharmacokinetics and Pharmacodynamics*, *36*(2), 179–197.]

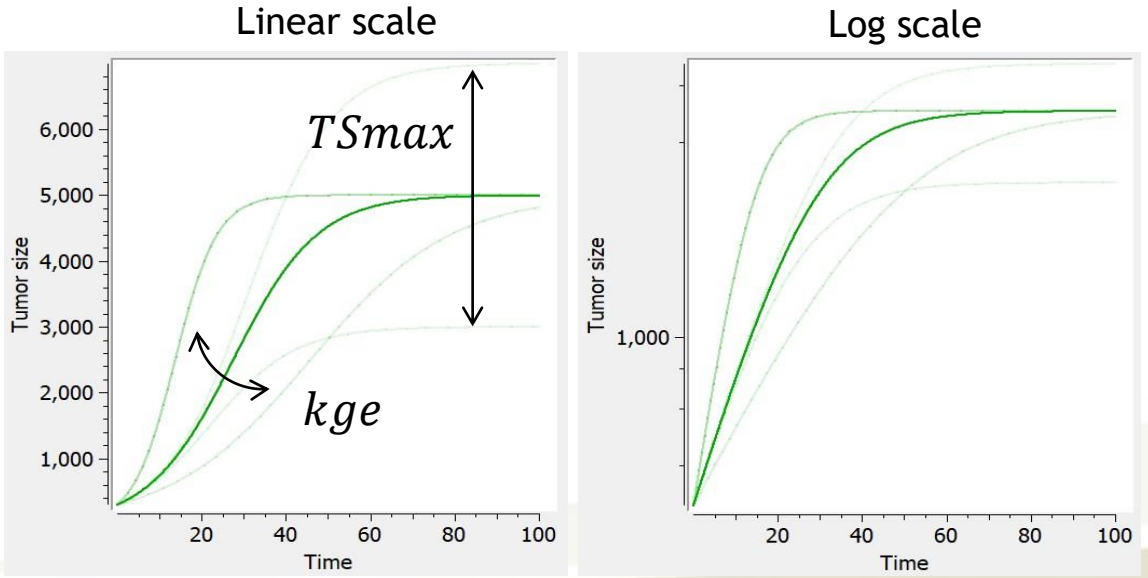
Tumor growth models

Logistic model:

- assumes an exponential growth rate which decelerates linearly with respect to the tumor size.

$$\frac{dTS}{dt} = kge * TS\left(1 - \frac{TS}{TS_{max}}\right) \quad \Leftrightarrow \quad TS = \frac{TS_{max} * TS0}{TS0 + (TS_{max} - TS0) * e^{-kge*t}}$$

$$TS(t = 0) = TS0$$



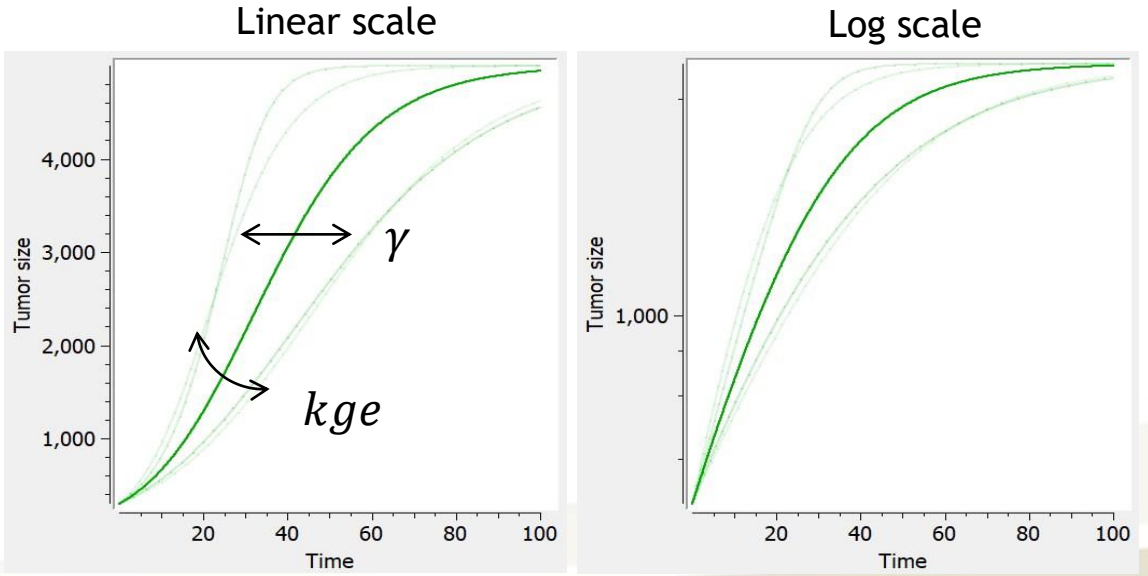
Tumor growth models

Generalized logistic model:

- assumes an exponential growth rate kg which decelerates linearly with respect to the tumor size.

$$\frac{dTS}{dt} = kge * TS\left(1 - \left(\frac{TS}{TS_{max}}\right)^{\gamma}\right) \Leftrightarrow TS = \frac{TS_{max} * TS0}{[TS0^{\gamma} + ({TS_{max}}^{\gamma} - TS0^{\gamma}) * e^{-kge*\gamma*t}]^{\frac{1}{\gamma}}}$$

$$TS(t = 0) = TS0$$



Tumor growth models

Gompertz model:

- assumes an exponential decay of the relative growth rate

$$\frac{dTS}{dt} = \alpha e^{-\beta * t} * TS \quad \Leftrightarrow \quad TS = TS0 * e^{\frac{\boldsymbol{a}}{\beta}\left(1-e^{-\beta * t}\right)}$$

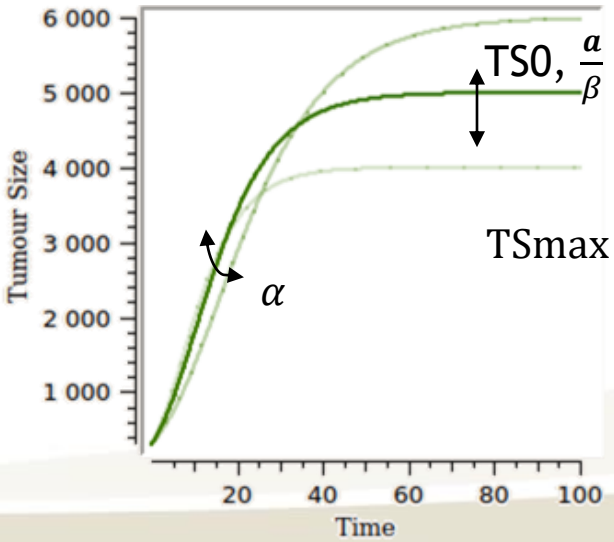
$$TS(t=0) = TS0$$

$$\Updownarrow$$

$$\frac{dTS}{dt} = \left(\alpha - \beta \ln\left(\frac{TS}{TS0}\right)\right) * TS$$

$$TS(t=0) = TS0$$

Linear scale



$$TSmax = TS0 * e^{\frac{\boldsymbol{a}}{\beta}}$$

Tumor growth models

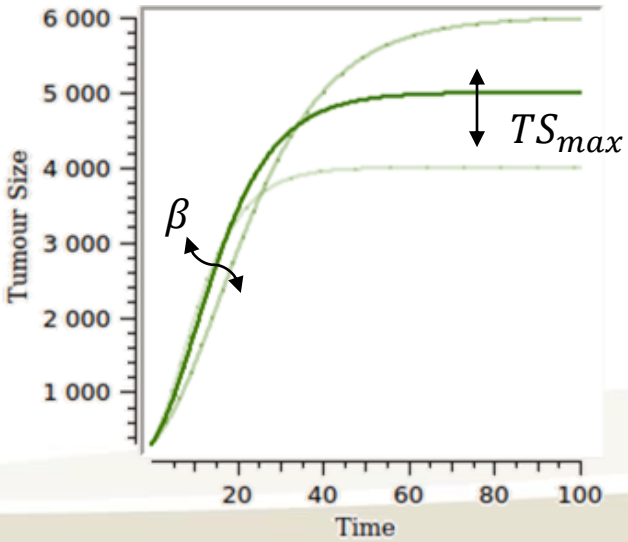
Gompertz model:

- assumes an exponential decay of the relative growth rate

$$\frac{dTS}{dt} = TS * \beta * ln\left(\frac{TS_{max}}{TS}\right) \quad \Leftrightarrow \quad TS = TS_{max} * e^{e^{-\beta * t} * \ln\left(\frac{TS0}{TS_{max}}\right)}$$

$$TS(t = 0) = TS0$$

Linear scale



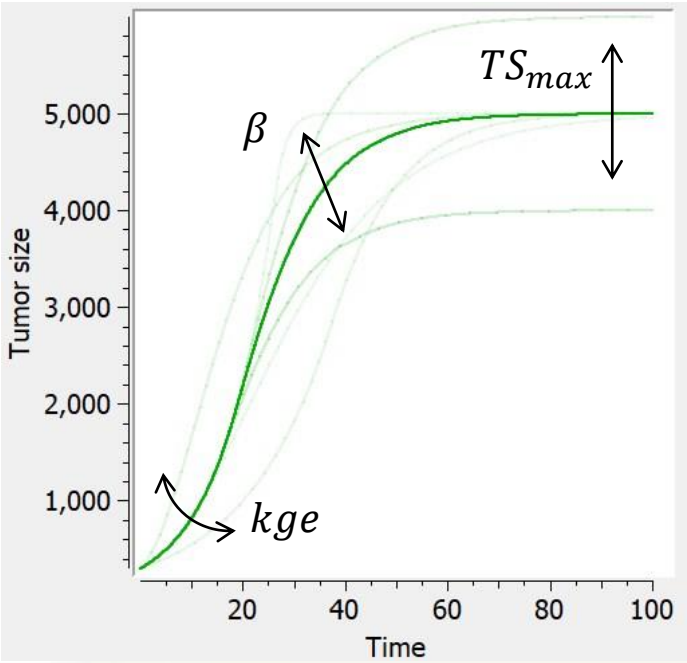
Tumor growth models

Exponential-Gompertz model:

- assumes that the tumor follows at first an exponential growth, and is then akin to a Gompertz model once the nutrients start to go scarce

$$\frac{dTS}{dt} = \min\left(kge * TS, \beta * TS * \ln\left(\frac{TS_{max}}{TS}\right)\right)$$

$$TS(t=0) = TS0$$



[Wheldon TE. Mathematical models in cancer research. Bristol: Hilger; 1988]

Tumor growth models

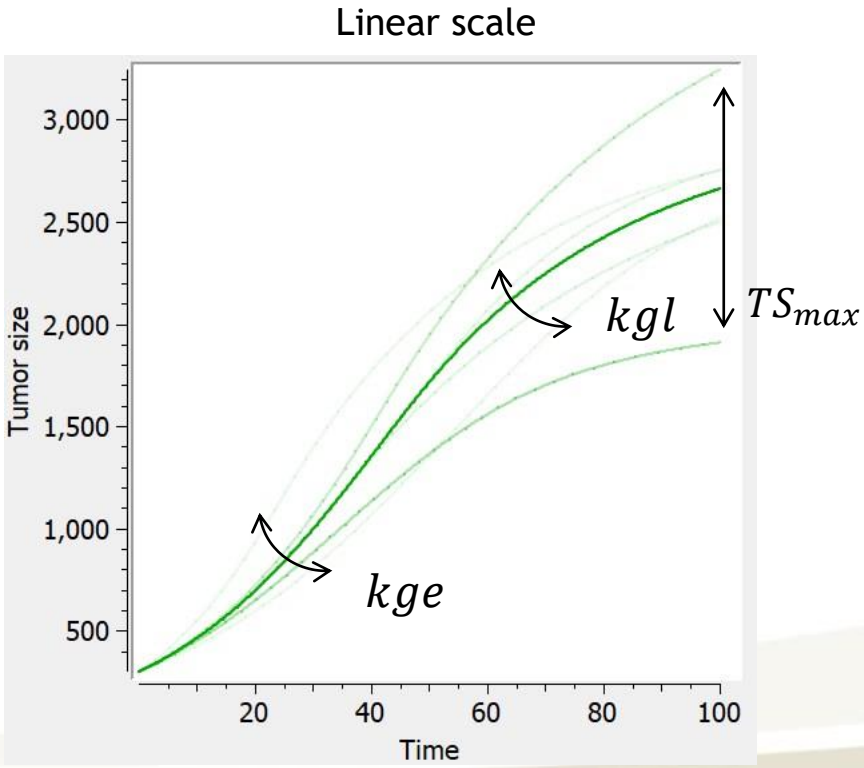
Hybrid Simeoni-logistic model:

- Hybrid model derived from the Simeoni model that combines exponential, linear and logistic growth.

$$\frac{dTS}{dt} = \frac{kge * TS * \left(1 - \frac{TS}{TS_{max}}\right)}{\left[1 + \left(\frac{kge}{kgl} * TS\right)^{\psi}\right]^{1/\psi}},$$

$$TS(t = 0) = TS0$$

- ψ should be fixed to a high value (20 for example)



[Haddish-Berhane et al., 2013]

Tumor growth models

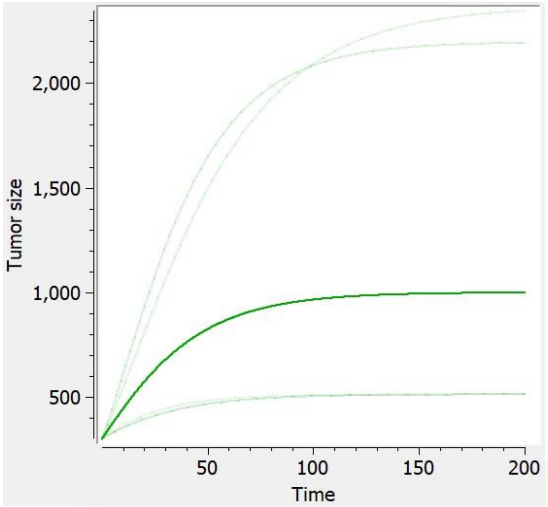
Von Bertalanffy model:

- Model based on balance equations of metabolic processes. The growth is proportional to the surface of the tumor and is limited with a loss term.

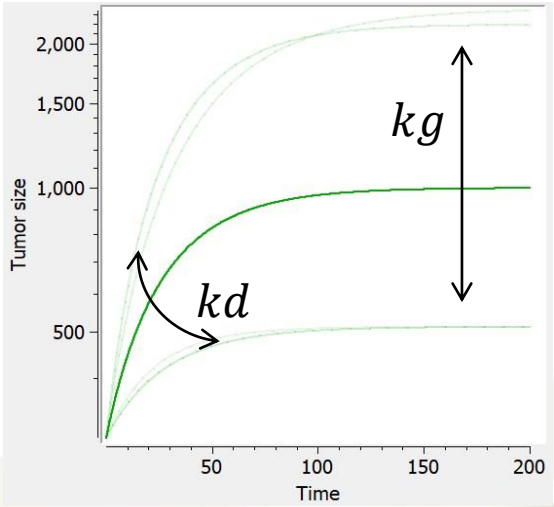
$$\frac{dTS}{dt} = kg * TS^{2/3} - kd * TS \quad \Leftrightarrow \quad TS = \left[\frac{kg}{kd} + \left(TS0^{1/3} - \frac{kg}{kd}\right) * e^{-\frac{1}{3}*kd*t}\right]^3$$

$$TS(t = 0) = TS0$$

Linear scale



Log scale



[Von Bertalanffy, 1957]

Tumor growth models

Von Bertalanffy model:

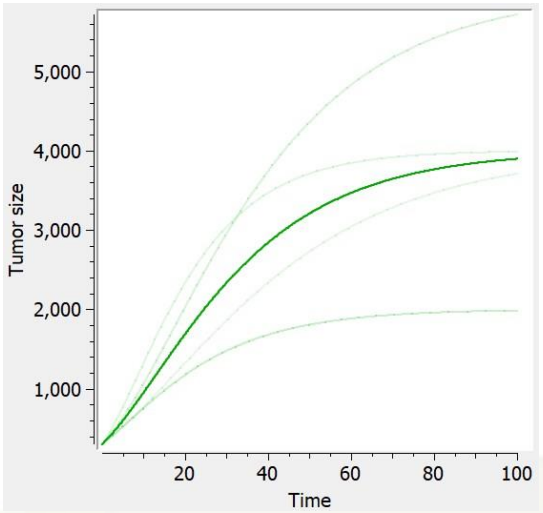
- Model based on balance equations of metabolic processes. The growth is proportional to the surface of the tumor and is limited with a loss term.

$$\frac{dTS}{dt} = kg * TS^{2/3} - kd * TS \quad \Leftrightarrow \quad TS = \left[\frac{kg}{kd} + \left(TS0^{1/3} - \frac{kg}{kd}\right) * e^{-\frac{1}{3}*kd*t}\right]^3$$

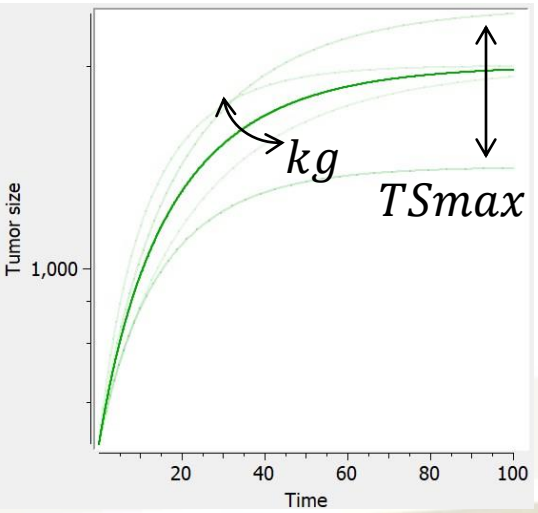
$$TS(t=0) = TS0$$

$$kd = \frac{kg}{TSmax^{\frac{1}{3}}}$$

Linear scale



Log scale



[Von Bertalanffy, 1957]

Tumor growth models

Generalized Von Bertalanffy model:

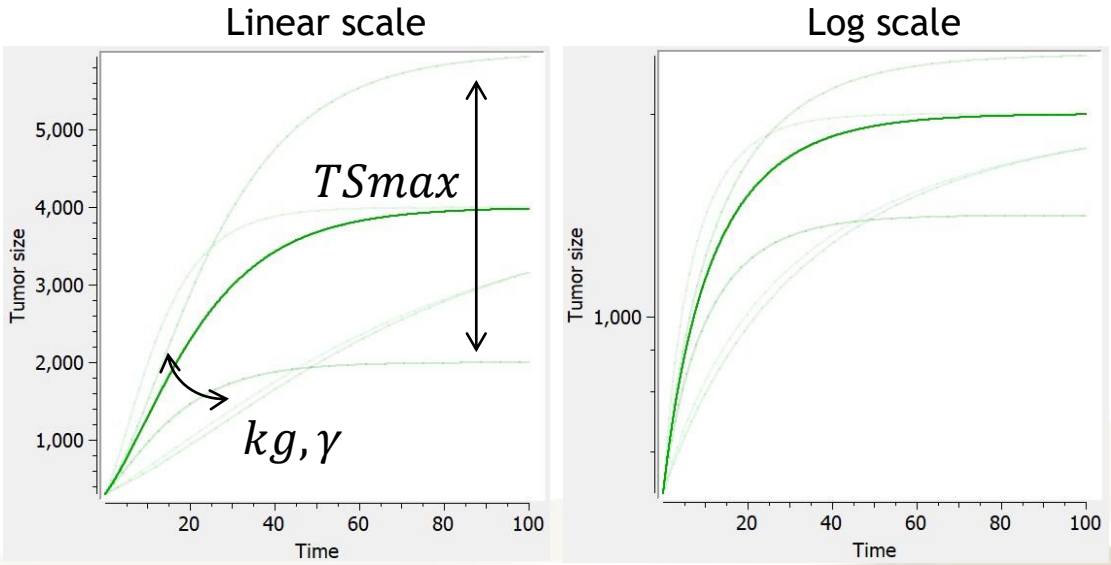
- Generalization to a power law growth

$$\frac{dTS}{dt} = kp * TS^{\gamma} - kd * TS \quad \Leftrightarrow \quad TS = \left[\frac{kp}{kd} + \left(TS0^{1-\gamma} - \frac{kp}{kd}\right) * e^{-(1-\gamma)*kd*t}\right]^{\frac{1}{1-\gamma}}$$

$$0 \leq \gamma \leq 1$$

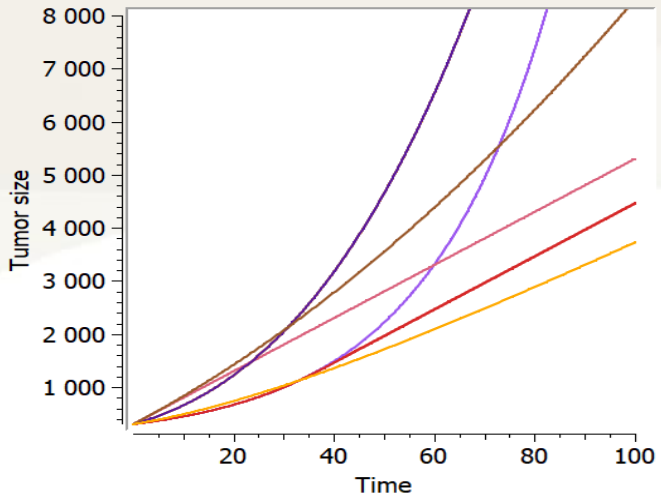
$$TS(t=0) = TS0$$

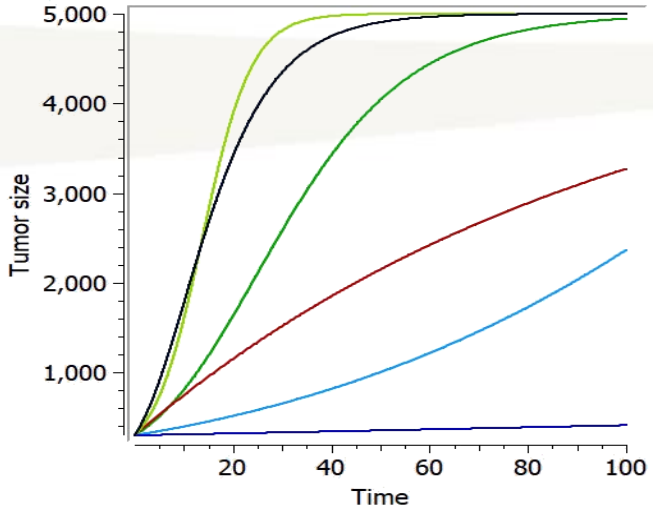
$$kd = \frac{kg}{TSmax^{(1-\gamma)}}$$



[Von Bertalanffy, 1957]

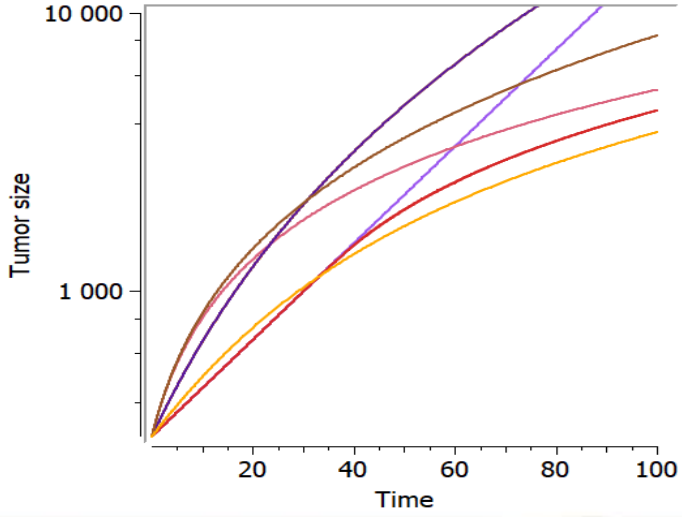
Common tumor growth models

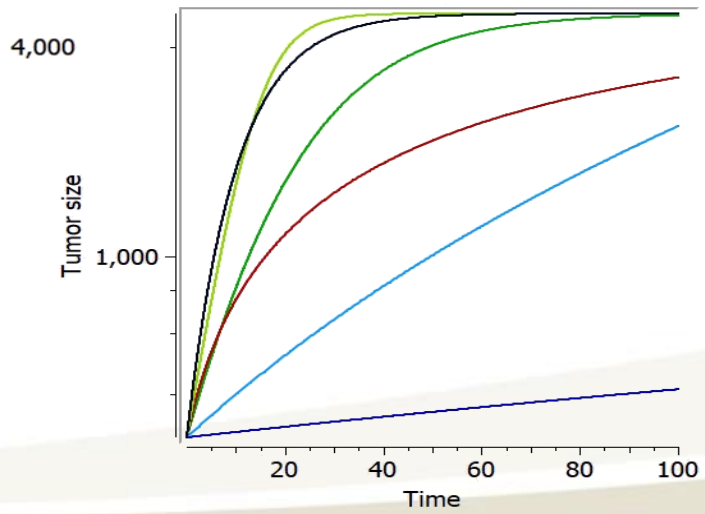




No saturation

- Linear
- Quadratic
- Exponential
- Power law
- Simeoni / Exponential-linear
- Koch





Saturation

- Gompertz
- Logistic
- Generalized logistic
- Simeoni-logistic
- Von Bertalanffy
- Generalized Von Bertalanffy

Additional TG features

Initial Tumor Size	Kinetics	Model	Additional Feature	Treatment
As parameter	No saturation	Logistic	None	None
As regressor	Saturation	Generalized Logistic	Angiogenesis	PK model
		Simeoni-Logistic Hybrid	Immune Dynamics	Exposure as regressor
		Gompertz		Treatment start at t=0
		Exponential-Gompertz		Treatment start time as regressor
		Von Bertalanffy		No treatment (0) vs treatment (1) regressor
		Generalized Von Bertalanffy		

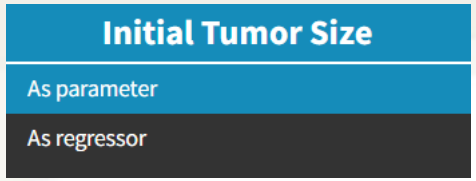
LIXOFT

A SIMULATIONS PLUS COMPANY

Different ways to encode the treatment and initial tumor size

Encoding initial tumor size

- TS0 as parameter



TS0 in input list

```
[LONGITUDINAL]
input = {kge, kkill, TS0}

EQUATION:
odeType=stiff

if t<0
  dTS = kge*TS
else
  dTS = kge*TS - kkill*TS
end

TS_0=TS0
ddt_TS = dTS

OUTPUT:
output = {TS}
```

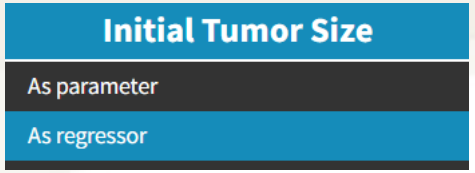
TS0 not in data

ID	TIME	Y
1	-45	98
1	-20	150
1	0	.
1	12	112

- TS0 is not TS at time 0 but at the initial integration time: the time of first dose or observation for each individual
- If t_0=0 is in the model, TS0 is TS at time 0, and TS=TS0 for all negative times

Encoding initial tumor size

- TS0 as regressor



TS0 in input list

```
[LONGITUDINAL]
input = {kge, kkill, TS0}
TS0 = {use = regressor}
EQUATION:
odeType=stiff

if t<0
  dTS = kge*TS
else
  dTS = kge*TS - kkill*TS
end

TS_0=TS0
ddt_TS = dTS

OUTPUT:
output = {TS}
```

TS0 in data

ID	TIME	Y	TS0
1	-45	98	98
1	-20	150	.
1	0	.	.
1	12	112	.

- TS0 is not TS at time 0 but at the initial integration time: the time of first dose or observation for each individual
- If t_0=0 is in the model, TS0 is TS at time 0, and TS=0 for all negative times

Encoding treatments

- Joint model for drug concentration and tumor size

Treatment
None
PK model
Exposure as regressor
Treatment start at t=0
Treatment start time as regressor
No treatment (0) vs treatment (1) regressor

PK model in structural model

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

PK:
Cc = pkmodel(V, k)

EQUATION:
odeType=stiff

TS_0=TS0

ddt_TS = kge*TS - kkill*Cc*TS

OUTPUT:
output = {TS}
```

Amounts and dosing times in dataset

ID	TIME	AMT	Y
1	-45	.	98
1	-20	.	150
1	0	0.02	.
1	12	.	112

- Possible if dosing information is available
- PK parameters can be estimated if PK data is available, or fixed to literature values
- High computation cost in case of dense doses over a large treatment period → not recommended for modeling

Encoding treatments

- Exposure read as regressor

Treatment
None
PK model
Exposure as regressor
Treatment start at t=0
Treatment start time as regressor
No treatment (0) vs treatment (1) regressor

EXPOSURE regressor in structural model

```
[LONGITUDINAL]
input = {TS0, EXPOSURE, kge, kkill}
EXPOSURE = {use=regressor}

EQUATION:
odeType=stiff

TS_0=TS0

ddt_TS = kge*TS - kkill*EXPOSURE*TS

OUTPUT:
output = {TS}
```

EXPOSURE in dataset

ID	TIME	EXP	Y
1	-45	0	98
1	-20	0	150
1	0	0.02	.
1	12	0.02	112

- EXPOSURE can come from PK concentration, AUC, Cmax, etc…
- EXPOSURE can be time-varying
- Carried-forward interpolation is used
- Not necessary to use the same names in data and model

Encoding treatments

- Exposure read as regressor

Treatment
None
PK model
Exposure as regressor
Treatment start at t=0
Treatment start time as regressor
No treatment (0) vs treatment (1) regressor

EXPOSURE regressor in structural model

```
[LONGITUDINAL]
input = {TS0, EXPOSURE, kge, kkill}
EXPOSURE = {use=regressor}

EQUATION:
odeType=stiff

TS_0=TS0

ddt_TS = kge*TS - kkill*EXPOSURE*TS

OUTPUT:
output = {TS}
```

EXPOSURE in dataset

ID	TIME	EXP	Y
1	-45	0	98
1	-20	.	150
1	0	0.02	.
1	12	.	112

- EXPOSURE can come from PK concentration, AUC, Cmax, etc…
- EXPOSURE can be time-varying
- Carried-forward interpolation is used
- Not necessary to use the same names in data and model

Encoding treatments

- Constant treatment at time 0

Treatment
None
PK model
Exposure as regressor
Treatment start at t=0
Treatment start time as regressor
No treatment (0) vs treatment (1) regressor

If/else in model to apply treatment after time 0

```
[LONGITUDINAL]
input = {TS0, kge, kkill}

EQUATION:
odeType=stiff

if t<0
  dTS = kge*TS
else
  dTS = kge*TS - kkill*TS
end

TS_0=TS0
ddt_TS = dTS

OUTPUT:
output = {TS}
```

No treatment information in dataset

ID	TIME	Y
1	-45	98
1	-20	150
1	0	.
1	12	112

- It is not possible to define an ODE directly in the if/else statement: an intermediate variable should be used

Encoding treatments

- Constant treatment at time T read as regressor

Treatment
None
PK model
Exposure as regressor
Treatment start at t=0
Treatment start time as regressor
No treatment (0) vs treatment (1) regressor

If/else in model to apply treatment after time T

```
[LONGITUDINAL]
input = {TS0 , kge, kkill, T}
T = {use = regressor}
EQUATION:
odeType=stiff

if t<T
  dTS = kge*TS
else
  dTS = kge*TS - kkill*TS
end

TS_0=TS0
ddt_TS = dTS

OUTPUT:
output = {TS}
```

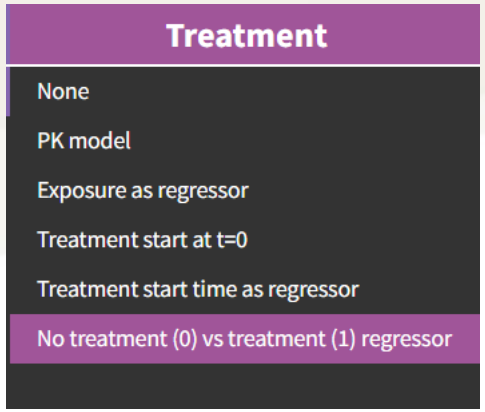
T in dataset

ID	TIME	Y	T
1	-45	98	5
1	-20	150	5
1	0	.	5
1	12	112	5

- It is not possible to define an ODE directly in the if/else statement: an intermediate variable should be used

Encoding treatments

- Treatment or not as regressor 0/1



If/else in model to apply treatment or not depending on the arm

```
[LONGITUDINAL]
input = {TS0, kge, kkill, Trt}
Trt = {use = regressor}
EQUATION:
odeType=stiff

if Trt ==0
  dTS = kge*TS
else
  dTS = kge*TS - kkill*TS
end

TS_0=TS0
ddt_TS = dTS

OUTPUT:
output = {TS}
```

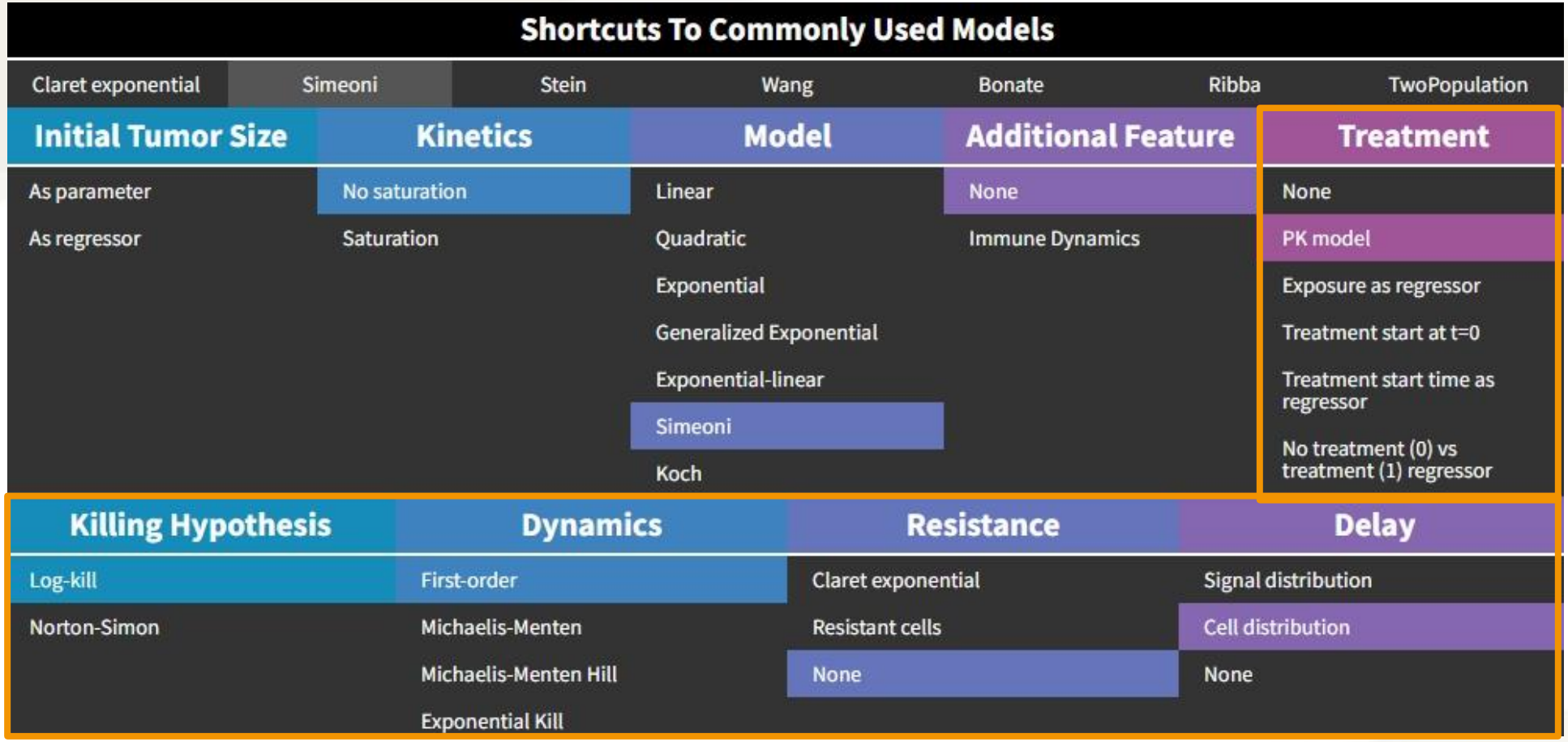
Treatment arm in dataset

ID	TIME	Y	TrtArm
1	-45	98	1
1	-20	150	1
1	0	.	1
1	12	112	1

- The regressor must be a number
- If the regressor names in the model and the data do not match, the mapping is done by order

Encoding treatments

LIXOFT
A SIMULATIONS PLUS COMPANY

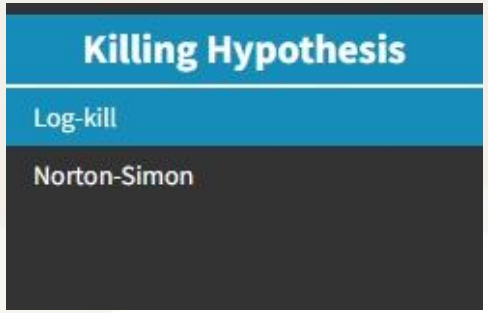


LIXOFT

A SIMULATIONS PLUS COMPANY

Common tumor growth inhibition models

Tumor killing hypothesis



Skipper-Schabel-Wilcox log-kill hypothesis:

$$\frac{dTS}{dt} = growth - K * TS$$

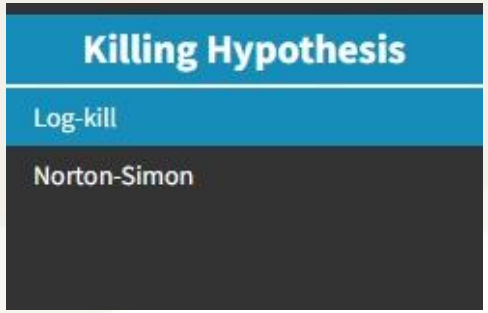
Norton-Simon killing hypothesis:

$$\frac{dTS}{dt} = growth * (1 - K)$$

K = killing of tumor cells

[R. Simon and R. Norton: The Norton-Simon hypothesis: designing more effective and less toxic chemotherapeutic regimens, Nature Clinical Practice Oncology 3(8) (2006), 406-407.]

Tumor killing hypothesis



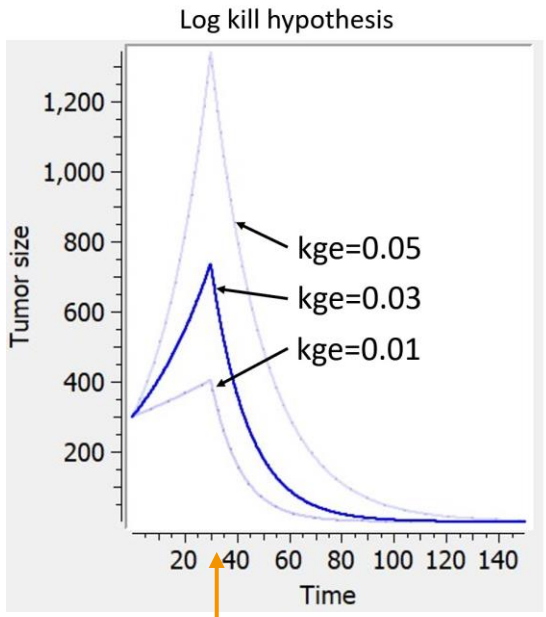
Skipper-Schabel-Wilcox log-kill hypothesis:

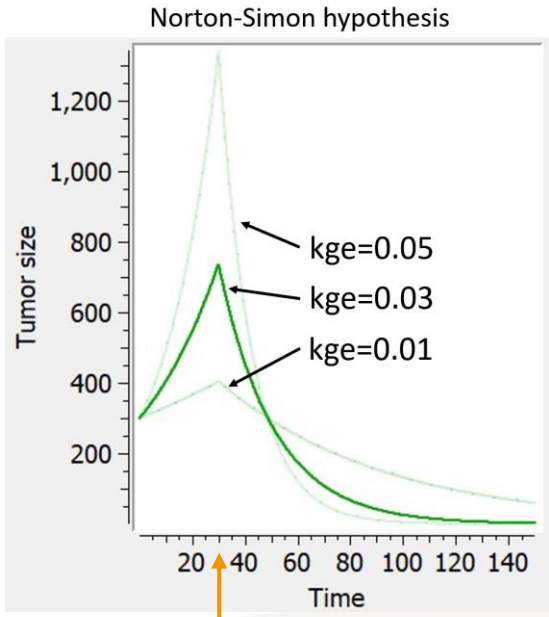
$$\frac{dTS}{dt} = growth - K * TS$$

Norton-Simon killing hypothesis:

$$\frac{dTS}{dt} = growth * (1 - K)$$

With exponential growth and constant K:





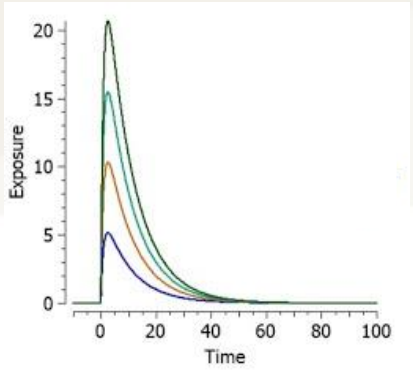
The inhibition from the Norton-Simon model depends on the growth rate

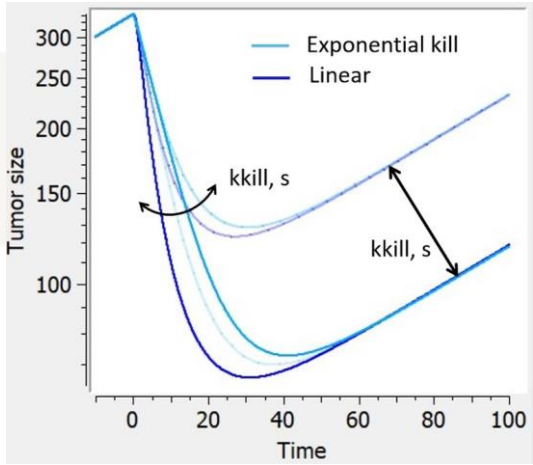
Exposure-dependent killing kinetics

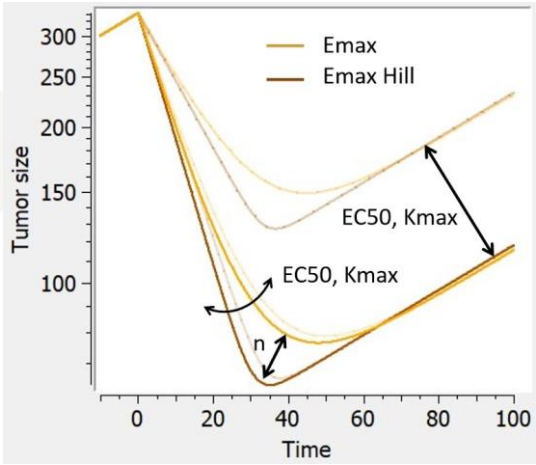
LIXOFT
A SIMULATIONS PLUS COMPANY

Dynamics

- First-order
- Michaelis-Menten
- Michaelis-Menten Hill
- Exponential Kill

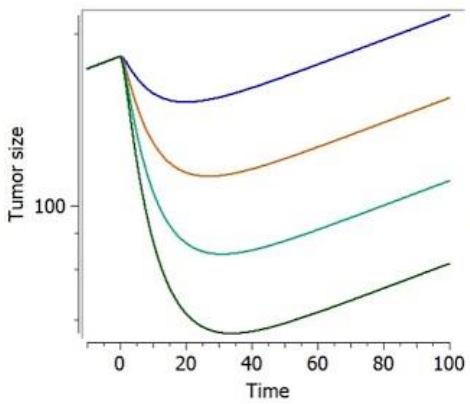






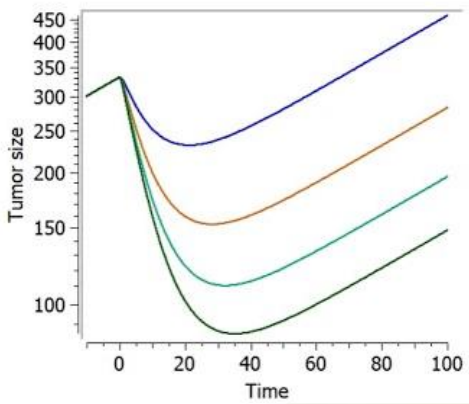
Linear

$K = k_{kill} * EXPOSURE$



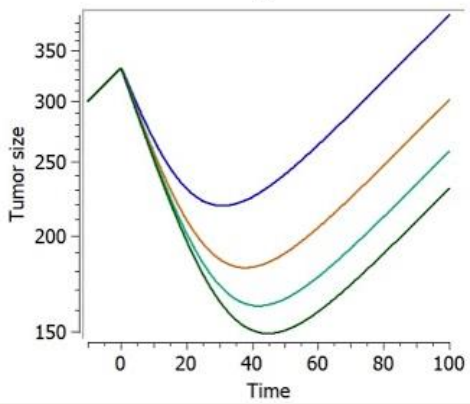
Exponential Kill

$K = k_{kill} * (1 - e^{-s*EXPOSURE})$



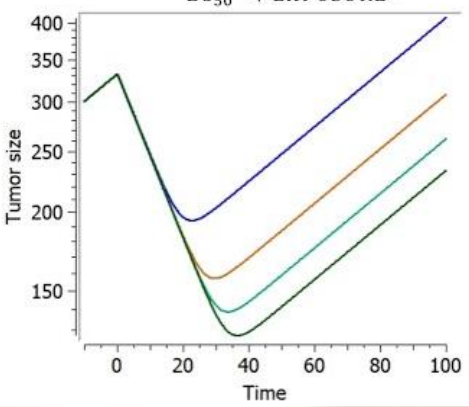
Emax

$K = \frac{K_{max}*EXPOSURE}{EC_{50}+EXPOSURE}$



Emax - Hill

$K = \frac{K_{max} * EXPOSURE^n}{EC_{50}{}^n + EXPOSURE^n}$



LIXOFT

A SIMULATIONS PLUS COMPANY

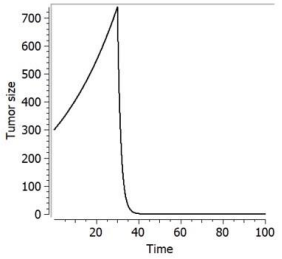
Delay in tumor growth inhibition

Delay for treatment effect

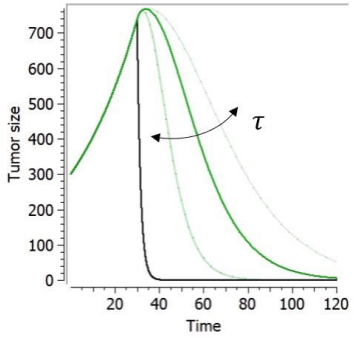
Delay

- Signal distribution
- Cell distribution
- None

$$\frac{dTS}{dt} = growth - K * TS$$



Cell Distribution model



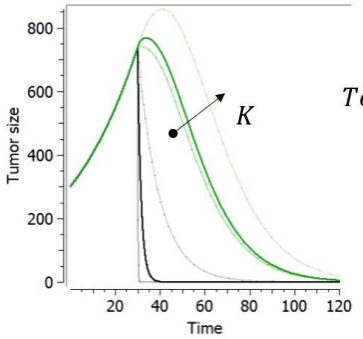
$$\frac{dTS}{dt} = kp * TS - K * TS$$

$$\frac{dTS1}{dt} = K * TS - TS1/\tau$$

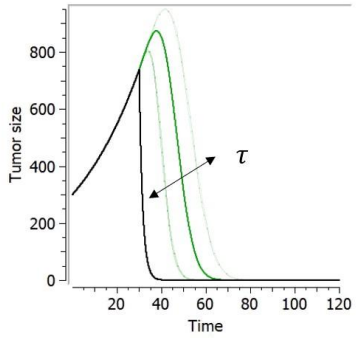
$$\frac{dTS2}{dt} = (TS1 - TS2)/\tau$$

$$\frac{dTS3}{dt} = (TS2 - TS3)/\tau$$

$$TotalTS = TS + TS1 + TS2 + TS3$$



Signal Distribution model

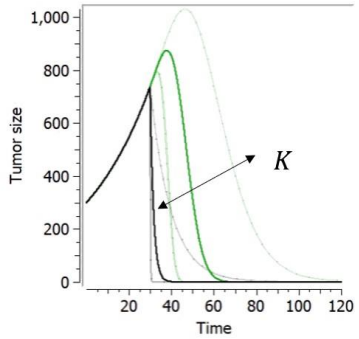


$$\frac{dK1}{dt} = (K - K1)/\tau$$

$$\frac{dK2}{dt} = (K1 - K2)/\tau$$

$$\frac{dK3}{dt} = (K2 - K3)/\tau$$

$$\frac{\mathrm{dTS}}{\mathrm{dt}} = growth - K3 * TS$$



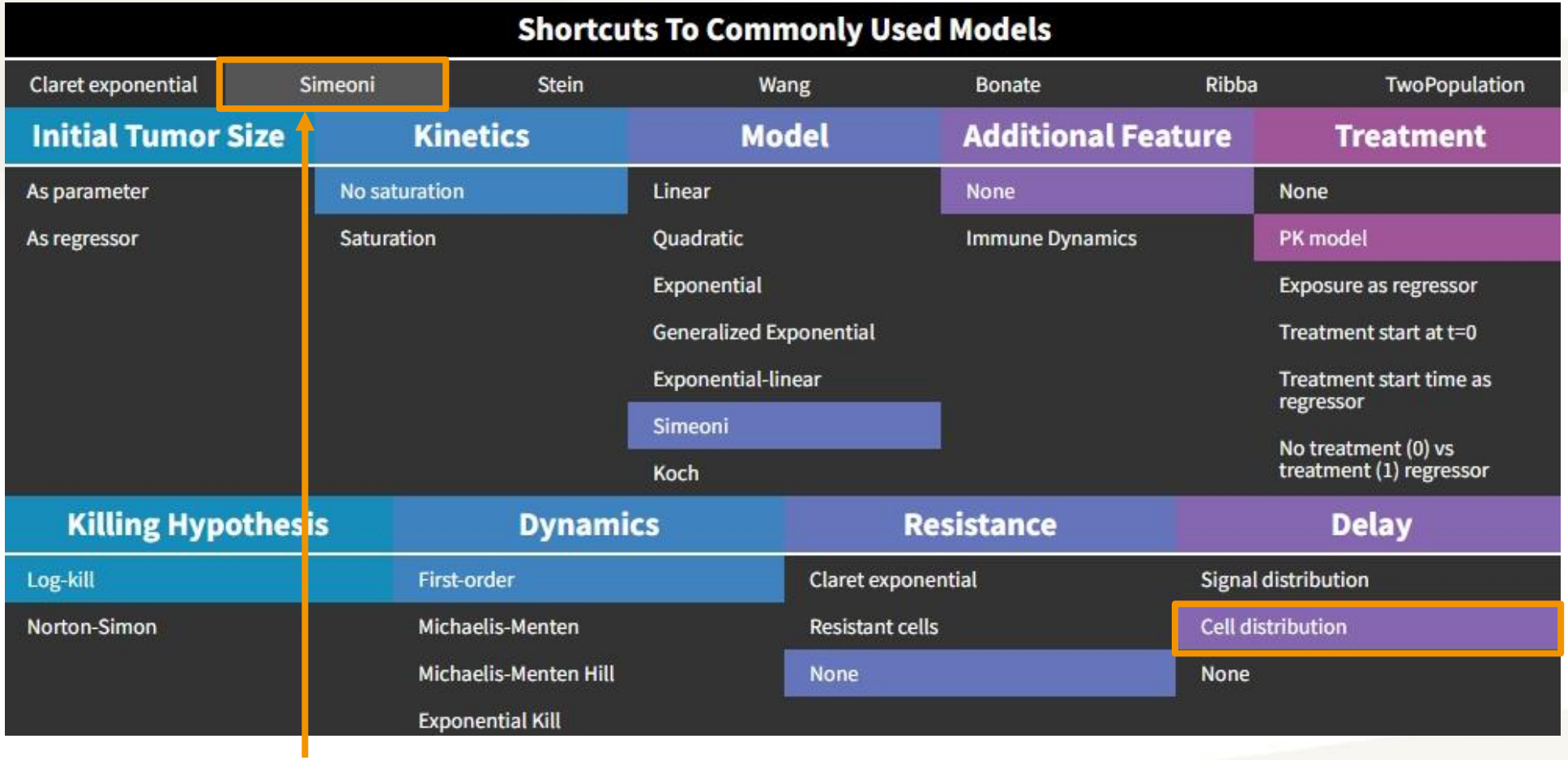
Cell distribution:

- The treatment effect is visible from the start but attenuated by the delay
- The model garantees a minimal delay independently on the strenght of the treatment effect

Signal distribution:

- The delay depends strongly on the signal intensity

Delay in Simeoni model



Shortcut to Simeoni model (TGI)

[Simeoni (2004)]

LIXOFT

A SIMULATIONS PLUS COMPANY

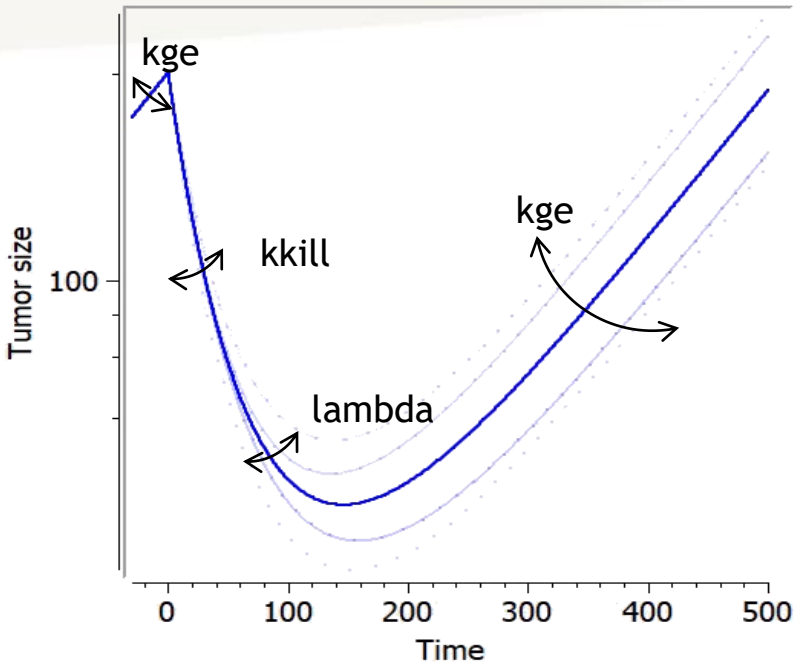
Common resistance models

Resistance: Claret model

Claret model

$$t < 0;\ \frac{dTS}{dt} = kge * TS$$

$$t \geq 0;\ \frac{dTS}{dt} = kge * TS - kkill * e^{-\lambda t} * TS$$



ANALYTICAL SOLUTION:

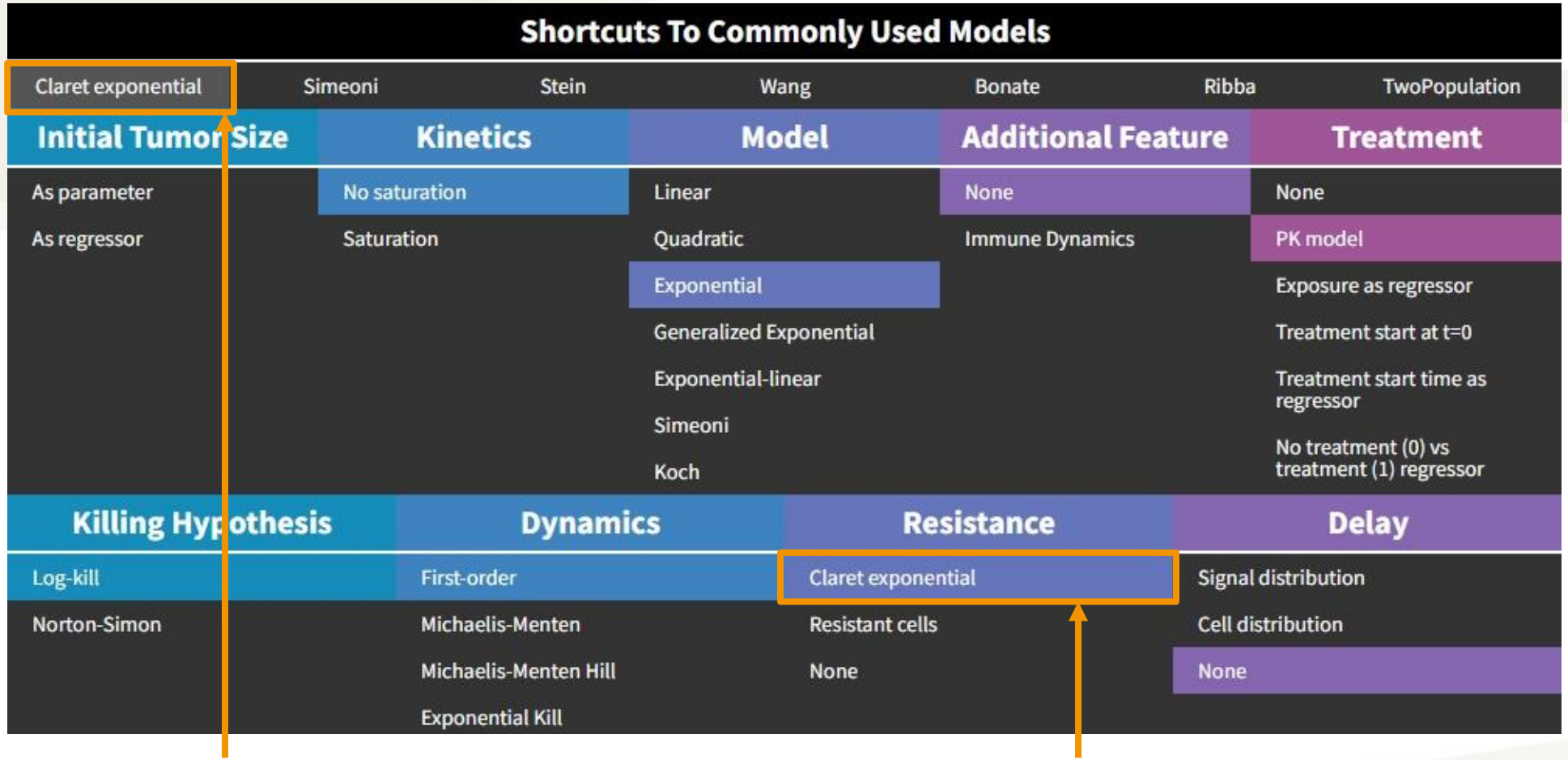
$$t < 0;\ TS = TS0 * e^{kge*t}$$

$$t \geq 0;\ TS = TS0 * e^{kge*t - \frac{kkill}{\lambda}(1-e^{-\lambda*t})}$$

⇒ With the analytical solution, TS0 is the tumor size at time 0

[Claret et al. (2009)]

Resistance: Claret model



Shortcut to exponential Claret with analytical solution

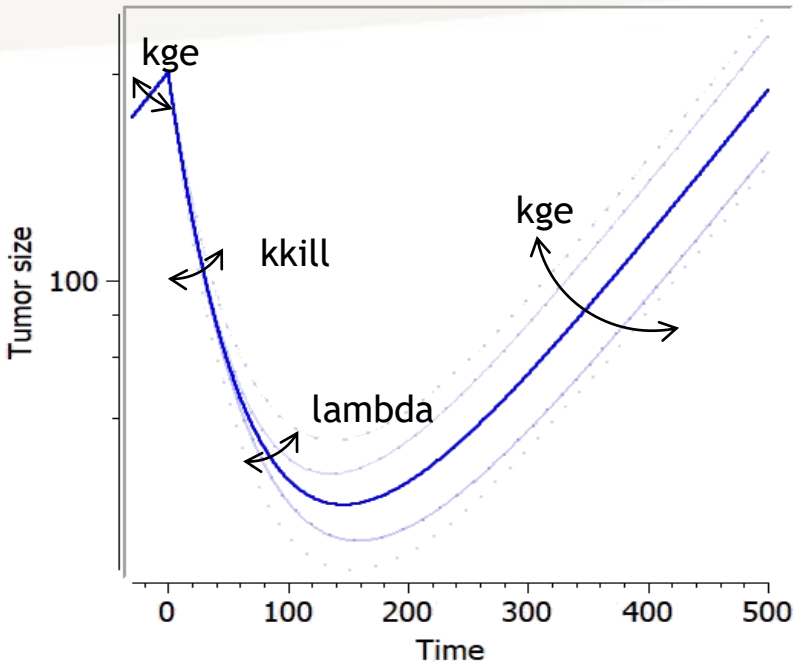
Resistance module

[Claret et al. (2009)]

Resistance: Claret model

$$K' = K * e^{-\lambda * t}$$

- accounts for the loss of drug-induced decay over time due to declining efficacy of the drug
- λ – resistance parameter

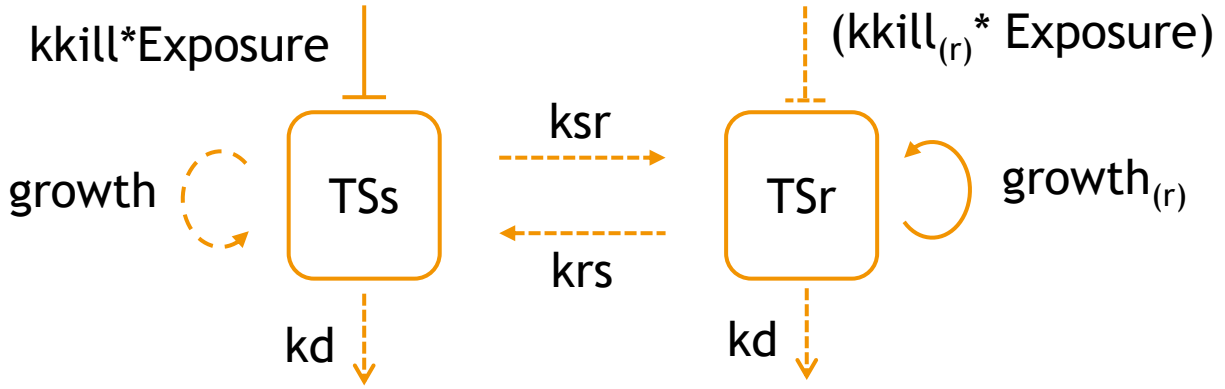


[Claret et al. (2009)]

Resistant population of tumor cells

- This model assumes that a fraction of the tumor is resistant to the treatment, thus being killed with a smaller rate than the sensitive part of the tumor.

- Several possible variants:



- Redundant properties in some conditions:
  - Initial fraction of resistant cells <-> Transfer of sensitive cells to resistant cells
  - Killing of resistant cells <-> Transfer of resistant cells to sensitive cells
  - Killing of resistant cells <-> Different growth for resistant cells

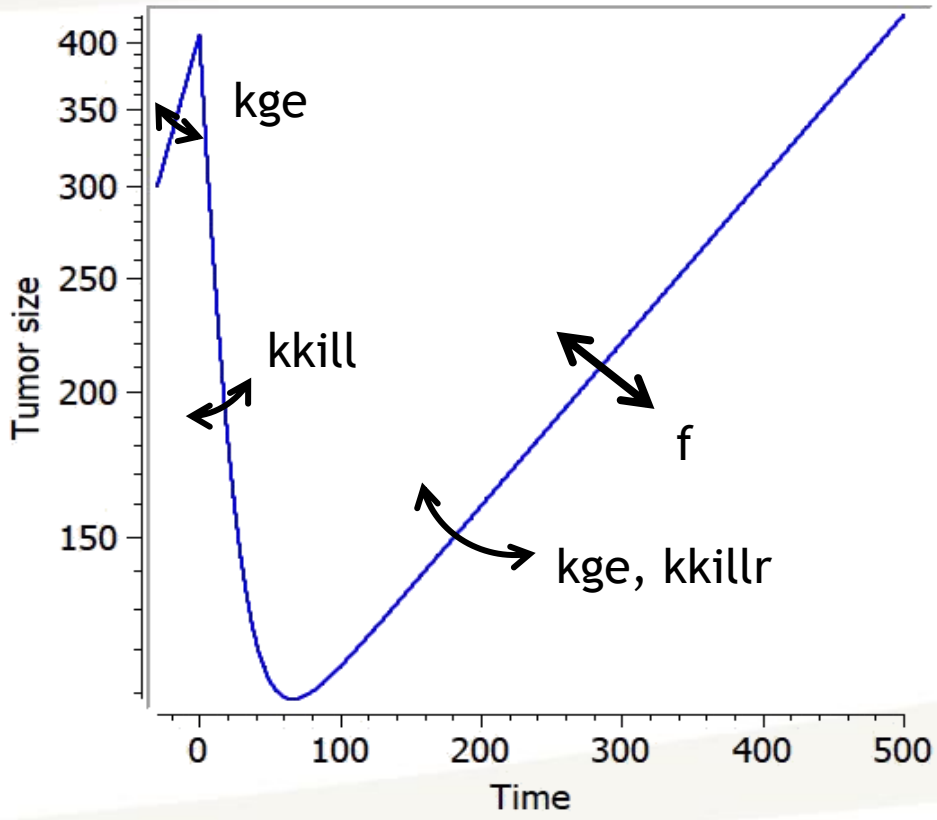
Resistant population of tumor cells

Model with initial fraction of resistant cells

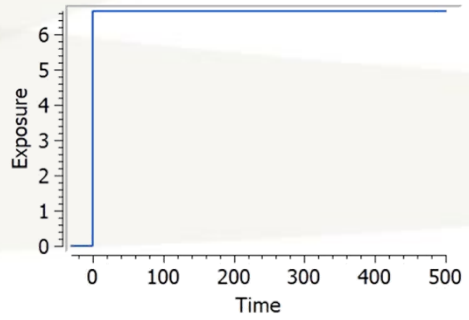
TS_0=(1-f)*TS0
TSr_0=f*TS0

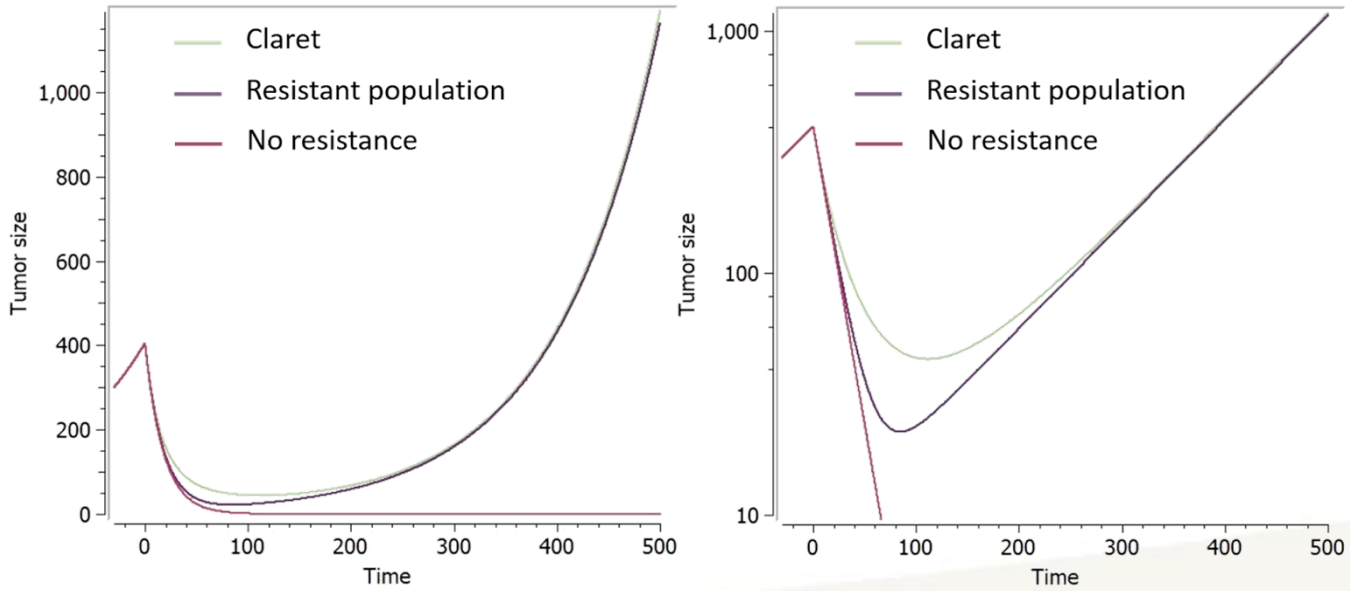
ddt_TS = (kge*TSs)-kkill * EXPOSURE*TS
ddt_TSr = (kge*TSr)- kkillr * EXPOSURE*TS

TotalTS = TS+TSr



Comparing resistance models





Common models from literature

Evolutionary model (two populations)

$$\frac{dTS_s}{dt} = -K * EXPOSURE * TS_s,$$

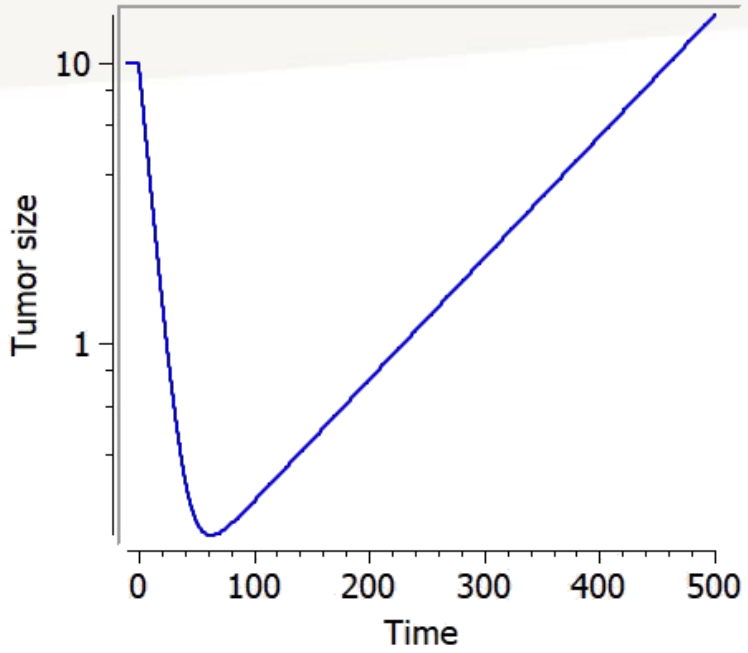
$$\frac{dTS_r}{dt} = kge * TS_r,$$

$$TS_s(t=0) = TS0 * (1-f)$$
$$TS_r(t=0) = TS0 * f$$

$$TS = TS_s + TS_r$$

ANALYTICAL SOLUTION for constant exposure

$$TS = TS0 * (f * e^{kp*t} + (1-f) * e^{-k*EXPOSURE*t})$$



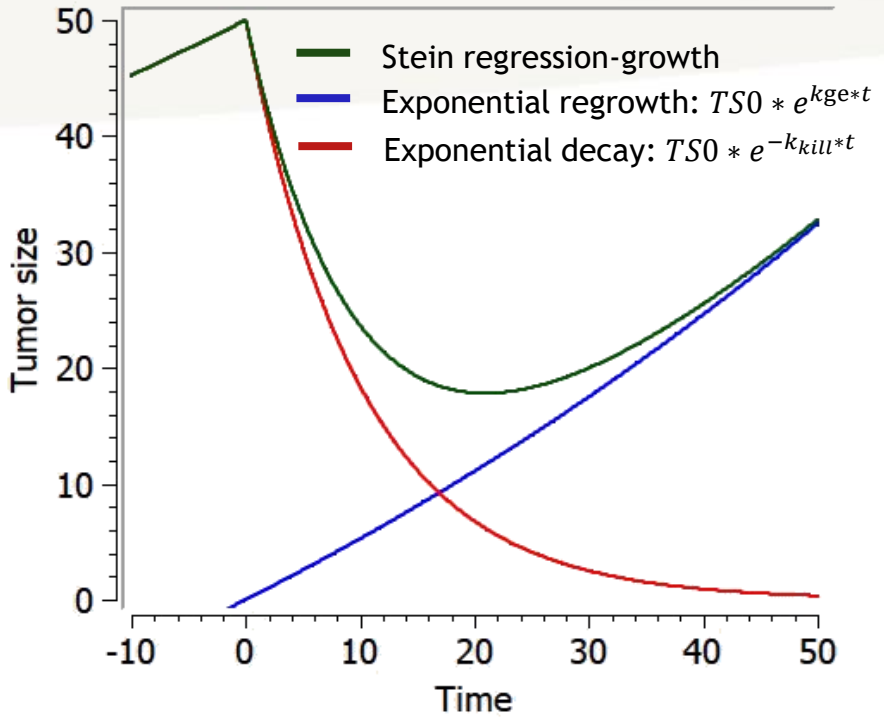
Shortcuts To Commonly Used Models						
Claret exponential	Simeoni	Stein	Wang	Bonate	Ribba	TwoPopulation

Common models from literature

Stein regression-growth model

$$t < 0;\ TS = TS0 * e^{kge*t}$$

$$t \geq 0;\ TS = TS0 * (e^{-k_{kill}*t} + e^{kge*t} - 1)$$



Shortcuts To Commonly Used Models

Claret exponential | Simeoni | **Stein** | Wang | Bonate | Ribba | TwoPopulation

[Stein et al. (2011))

Common models from literature

Ribba model

$$\frac{dP}{dt} = kp * P\left(1 - \frac{TotalTS}{TS_{max}}\right) + k_{QpP} * Q_p - k_{PQ} * P - K * ke * EXPOSURE * P$$

$$\frac{dQ}{dt} = t_{PQ} * P - k_Q * ke * EXPOSURE * Q$$

$$\frac{dQ_p}{dt} = k_Q * ke * EXPOSURE * Q - k_{QpP} * Q_p - kd * Q_p$$

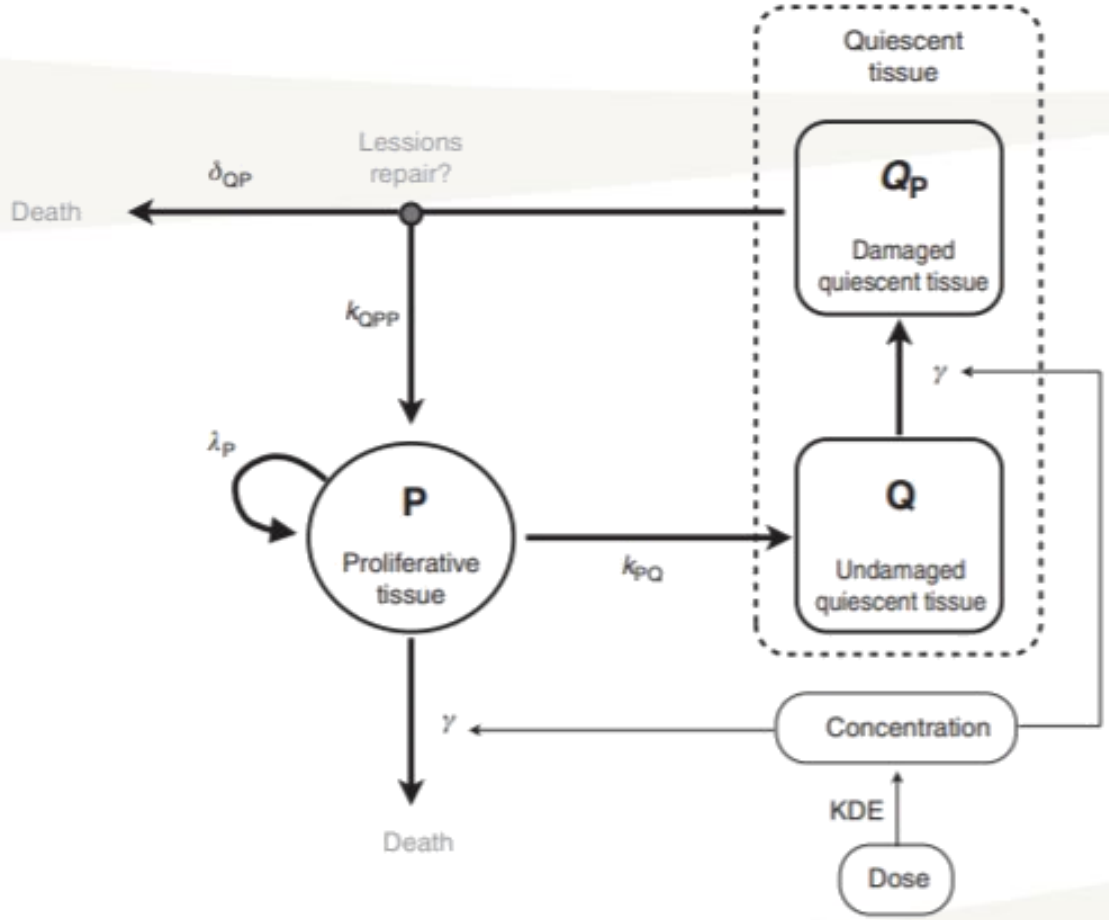
$$\frac{dEXPOSURE}{dt} = -ke * EXPOSURE$$

$$P(t = 0) = P0$$

$$Q(t = 0) = Q0$$

$$Q_p(t = 0) = 0$$

$$TotalTS = P + Q + Q_p$$



Shortcuts To Commonly Used Models

Claret exponential	Simeoni	Stein	Wang	Bonate	Ribba	TwoPopulation

[Ribba et al. (2012)]

LIXOFT

A SIMULATIONS PLUS COMPANY

Good practices for model definition in Monolix

Tumor growth models

- Model with analytical solution
  - Example: exponential-linear

```
[LONGITUDINAL]
input = {TS0, kge, kgl}

EQUATION:

TransitionTime = 1/kge*log(kgl/(kge*TS0))

if t<TransitionTime
  TS = TS0*exp(kge*t)
else
  TS = kgl*(t-TransitionTime)+TS0*exp(kge*TransitionTime)
end

OUTPUT:
output = {TS}
```

Tumor growth models

- Model with analytical solution
  - Example: exponential-linear

```
[LONGITUDINAL]
input = {TS0, kge, kgl}

EQUATION:

TransitionTime = 1/kge*log(kgl/(kge*TS0))

if t<TransitionTime
  TS = min(1e12, TS0*exp(kge*t))
else
  TS = min(1e12, kgl*(t-TransitionTime)+TS0*exp(kge*TransitionTime))
end

OUTPUT:
output = {TS}
```

Saturation to avoid infinitely large values

Tumor growth models

- Model based on ODE system
  - Example: Simeoni

```
[LONGITUDINAL]
input = {TS0, kge, kgl, psi}

EQUATION:
odeType=stiff
;defining initial conditions of the model:
;t_0=0
TS_0=TS0

;model description:
if TS < 1e12
   dTS = (kge*TS/(1+(kge/kgl*max(0,TS))^psi)^(1/psi))
else
  dTS = 0
end
ddt_TS = dTS

OUTPUT:
output = {TS}
```

Saturation to avoid infinitely large values

Tumor growth models

- Model based on ODE system
  - Example: Simeoni

```
[LONGITUDINAL]
input = {TS0, kge, kgl, psi}

EQUATION:
odeType=stiff
;defining initial conditions of the model:
;t_0=0
TS_0=TS0

;model description:
if TS < 1e12
   dTS = (kge*TS/(1+(kge/kgl*max(0,TS))^psi)^(1/psi))
else
  dTS = 0
end
ddt_TS = dTS

OUTPUT:
output = {TS}
```

Saturation to avoid mathematically undefined situations

Tumor growth models

- Model based on ODE system
  - Example: Simeoni

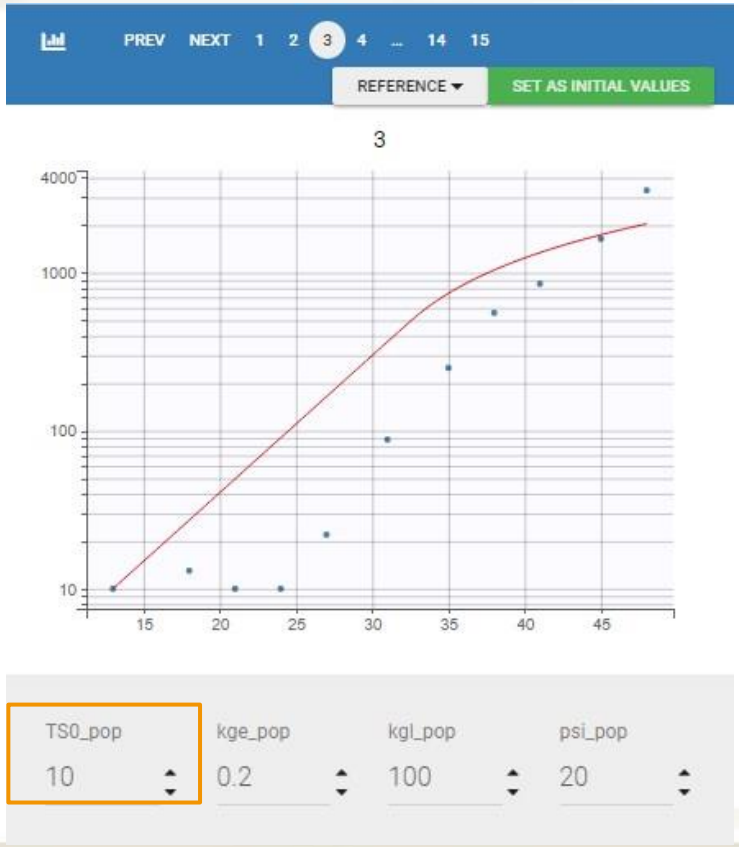
```
[LONGITUDINAL]
input = {TS0, kge, kgl, psi}

EQUATION:
odeType=stiff
;defining initial conditions of the model:
;t_0=0
TS_0=TS0

;model description:
if TS < 1e12
   dTS = (kge*TS/(1+(kge/kgl*max(0,TS))^psi)^(1/psi))
else
  dTS = 0
end
ddt_TS = dTS

OUTPUT:
output = {TS}
```

- Initial integration time
- Can be negative
- *Default value if not indicated*: time of first dose or observation, vary between individuals
- Initial conditions such as TS_0 are values at that time

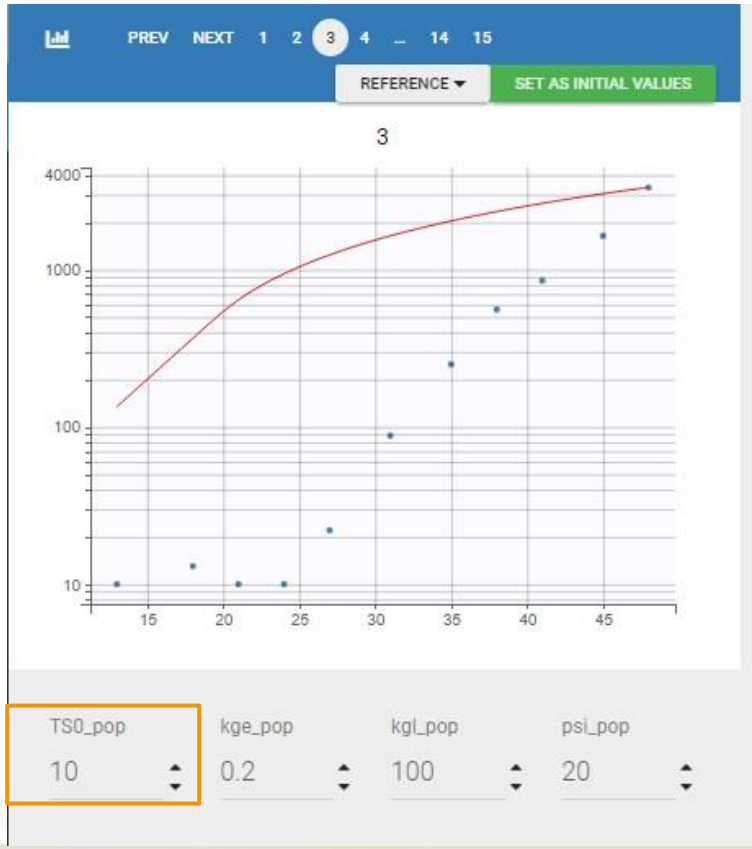
Tumor growth models

- Model based on ODE system
  - Example: Simeoni

Without t_0 = 0



With t_0 = 0



LIXOFT

A SIMULATIONS PLUS COMPANY

Combination therapy in lung cancer xenografts

Example 1

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 activation

Introduction: lung cancer dataset

Dataset overview:

- 77 xenografts of initially 120000 H460 Luc+ dTomato+ cells, tracked with fluorescence

Measurements:

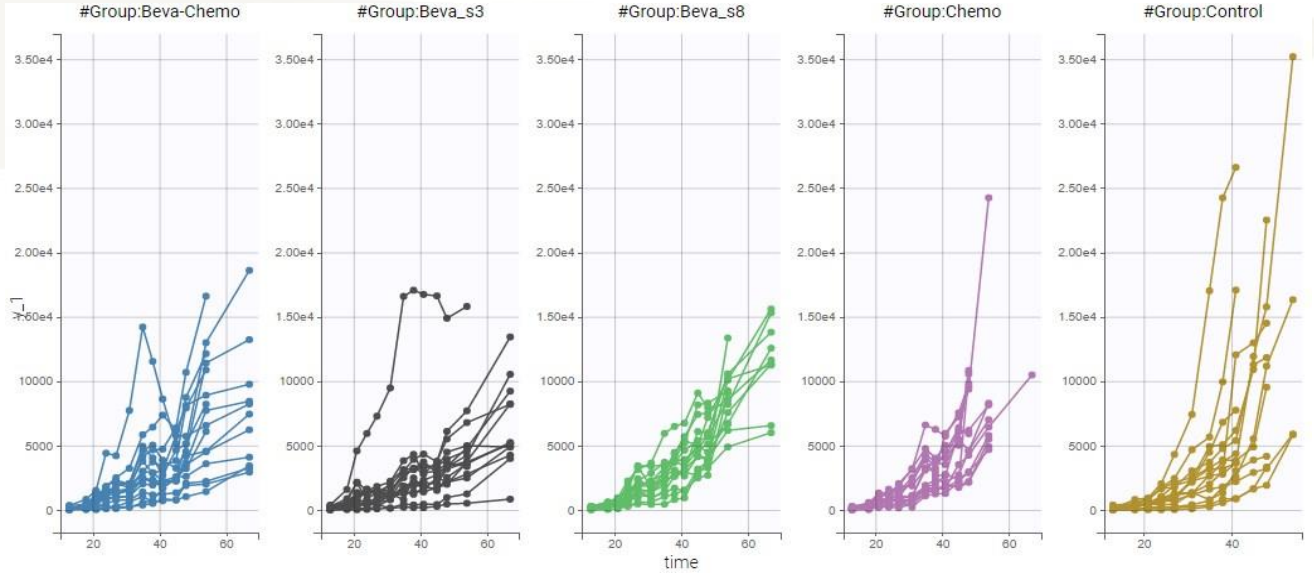
- OBSID = 1 - tumor size (relative fluorescence unit)
- OBSID = 2 - survival

Treatments:

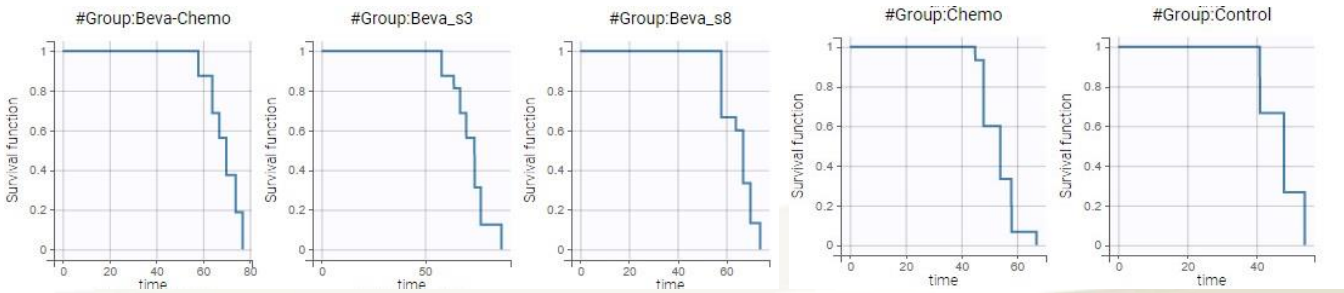
- 3 drugs, each given 3 times every 2 weeks

- 5 treatment arms:
  - Control (n=15)
  - Chemo (n=15) = pemetrexed + cisplatin
  - Beva-Chemo: Bevacizumab and Chemo at the same time (n=15)
  - Beva_s3: Bevacizumab then Chemo after 3 days (n=16)
  - Beva_s8: Bevacizumab then Chemo after 8 days (n=15)

Tumor size

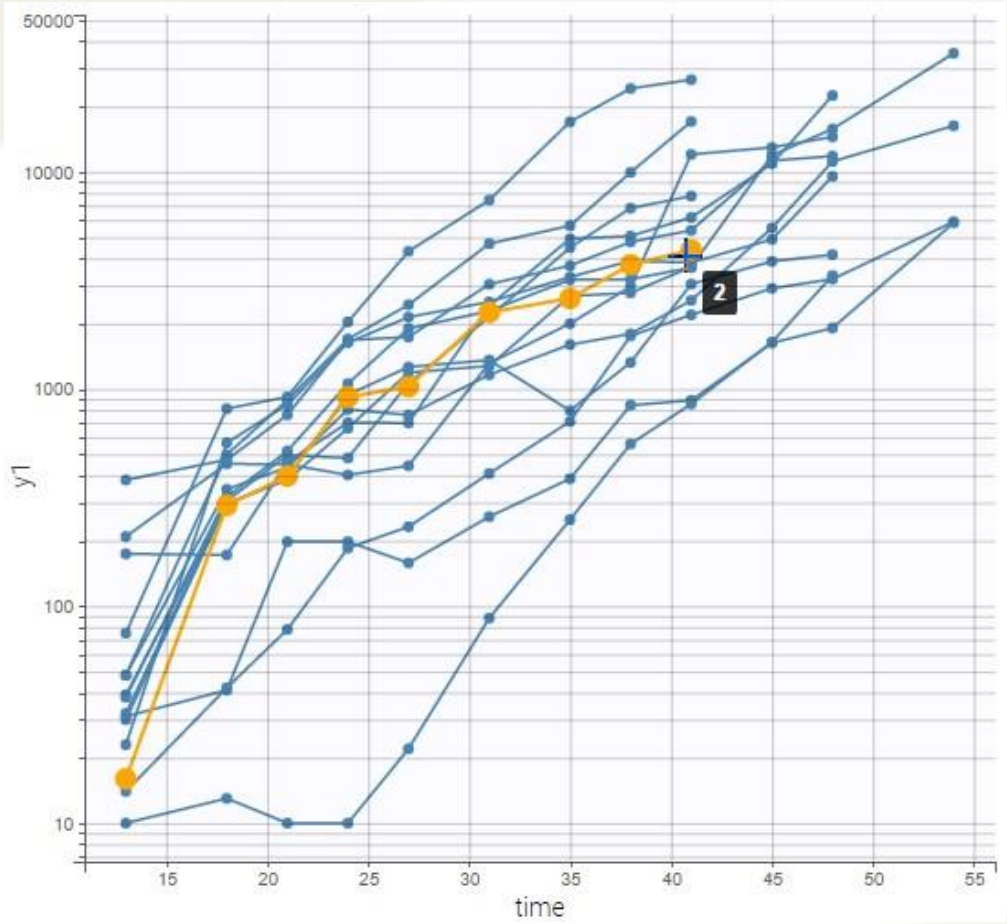


Survival



Tumor growth models

Data for control group in log scale



⇒ Which tumor growth model?

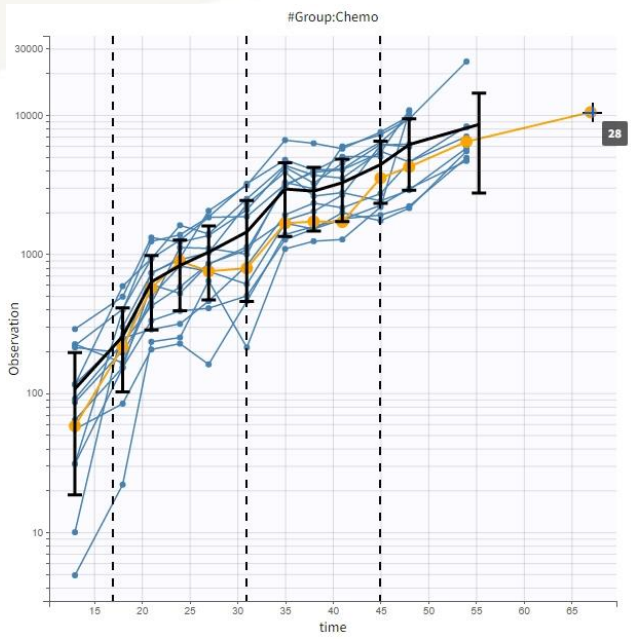
Data for control group in log scale

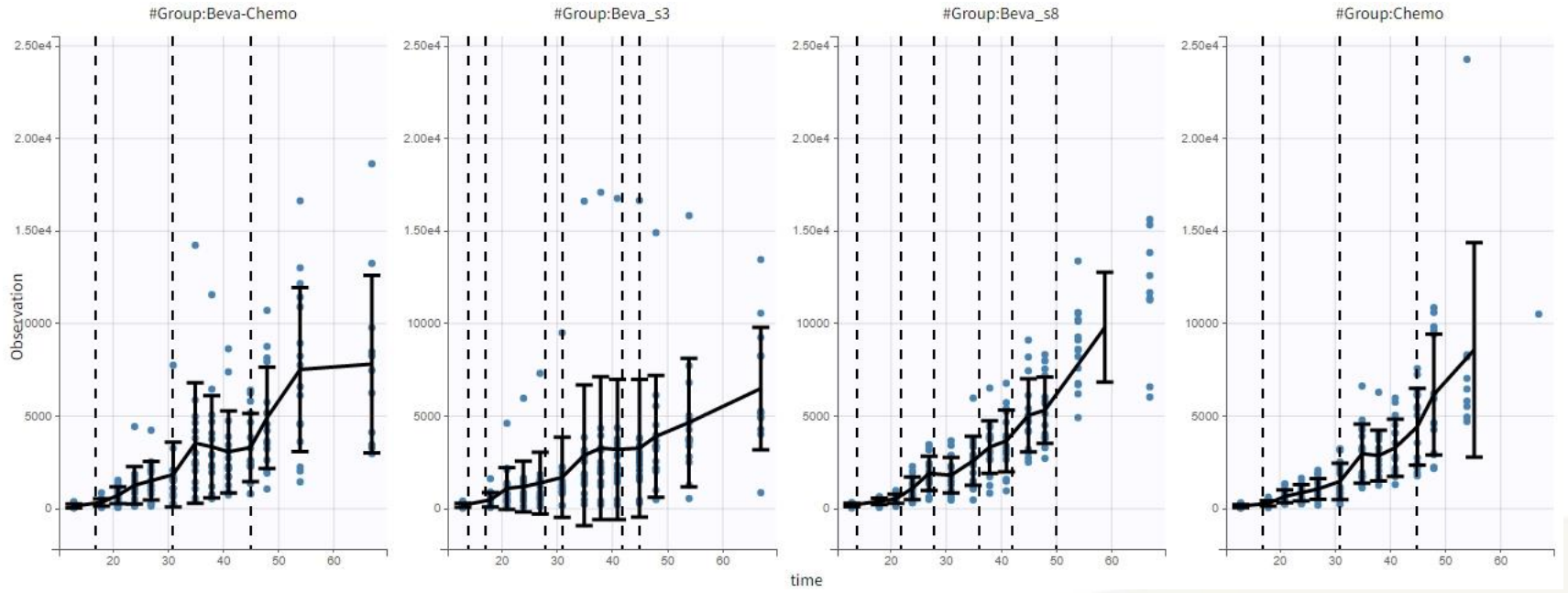
- Not exponential nor linear models
- No clear carrying capacity

Tumor growth inhibition data

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

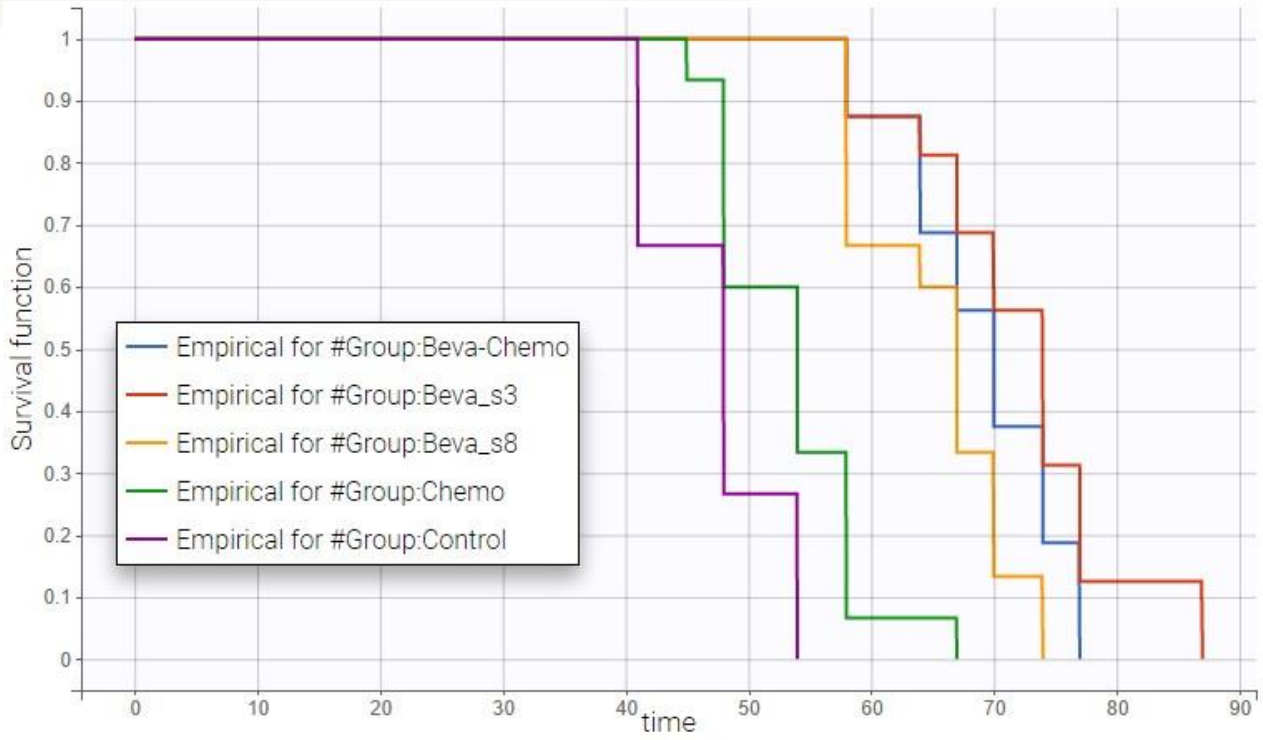




Survival data

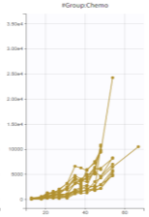
LIXOFT
A SIMULATIONS PLUS COMPANY

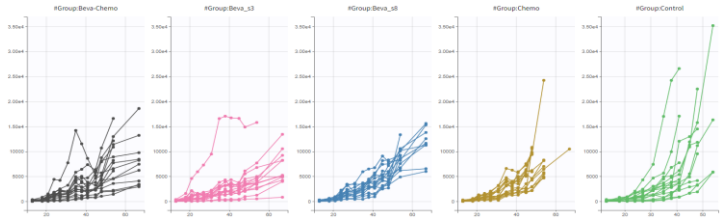
Survival data split by Group

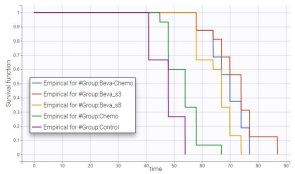


Modeling workflow

The modeling workflow can be done in 4 steps:







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 chemotherapy combined with bevacizumab estimated on all groups

Use last estimates

4. Joint model tumor size and survival

Step 1: Tumor growth models

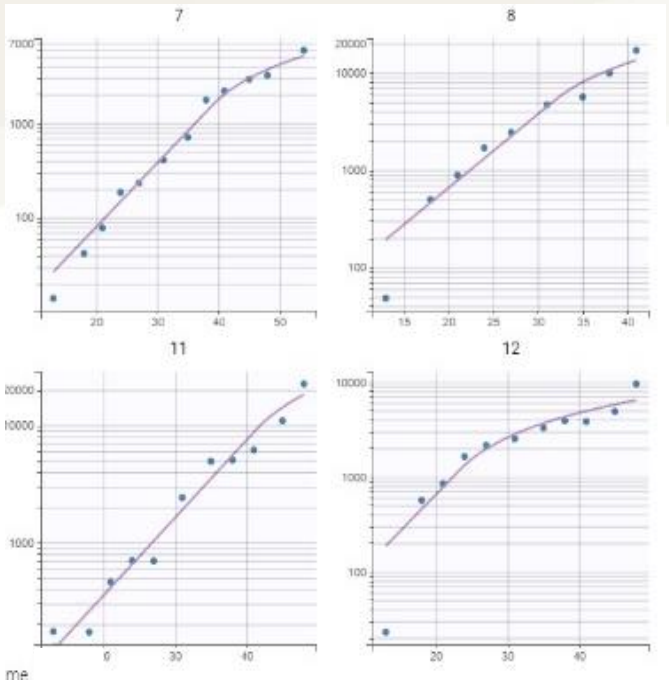
LIXOFT
A SIMULATIONS PLUS COMPANY

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
r02_Simeoni					2453.02		2486.49	*lib: TG_Sim_NoFeat_TS0par.txt*	**Observation:** comb1	TS0 kge kgl
r01_explin					2453.24		2486.71	*lib: TG_ExpLin_NoFeat_TS0par.txt*	**Observation:** comb1	TS0 kge kgl
r03_Koch					2454.47		2487.93	*lib: TG_Koch_NoFeat_TS0par.txt*	**Observation:** comb1	TS0 kge kgl
r04_logis					2459.94		2493.41	*lib: TG_Logi_NoFeat_TS0par.txt*	**Observation:** comb1	TS0 kge TSmax
r05_SimeoLogis					2453.06		2494.31	*lib: TG_SimLogi_NoFeat_TS0par.txt*	**Observation:** comb1	TS0 kge kgl TSmax
r07_expGomp					2459.97		2501.22	*lib: TG_ExpGomp_NoFeat_TS0par.txt*	**Observation:** comb1	TS0 kge beta TSmax
r06_Gomp					2467.9		2501.37	*lib: TG_Gomp_NoFeat_TS0par.txt*	**Observation:** comb1	TS0 beta TSmax
r09_genVonBertalanffy					2468.85		2510.09	*lib: TG_GenVB_NoFeat_TS0par.txt*	**Observation:** comb1	TS0 kg kd gamma
r08_vonBertalanffy					2709.81		2743.72	*lib: TG_VB_NoFeat_TS0par.txt*	**Observation:** comb1	TS0 kg kd

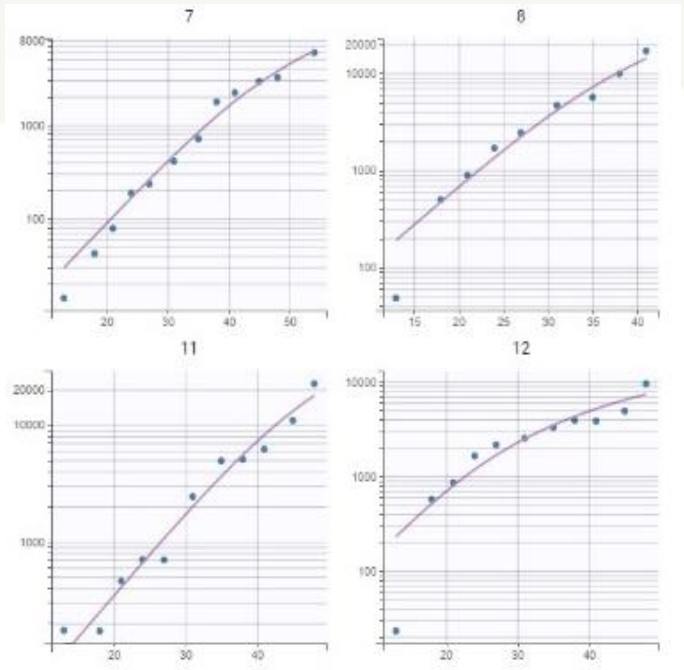
Step 1: Tumor growth models

LIXOFT
A SIMULATIONS PLUS COMPANY

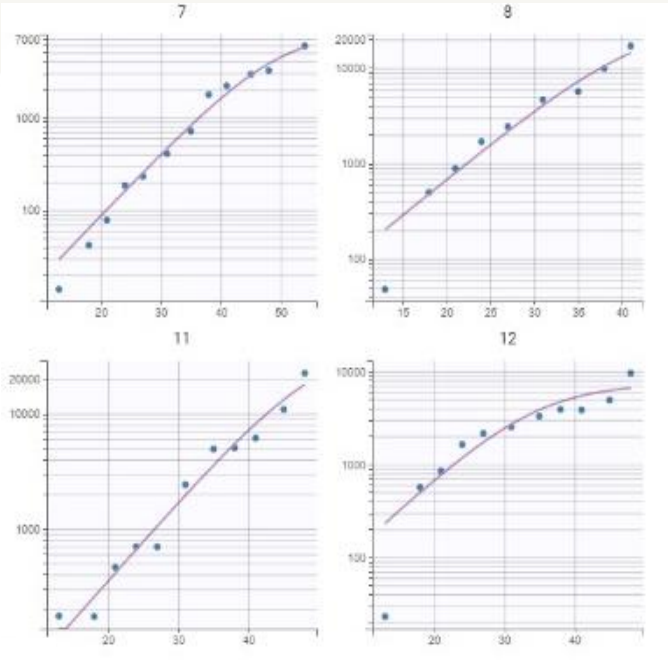
Exponential-linear



Koch



Logistic



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

Step 2: TGI

LIXOFT
A SIMULATIONS PLUS COMPANY

Possible inhibition model for the effect of chemotherapy:

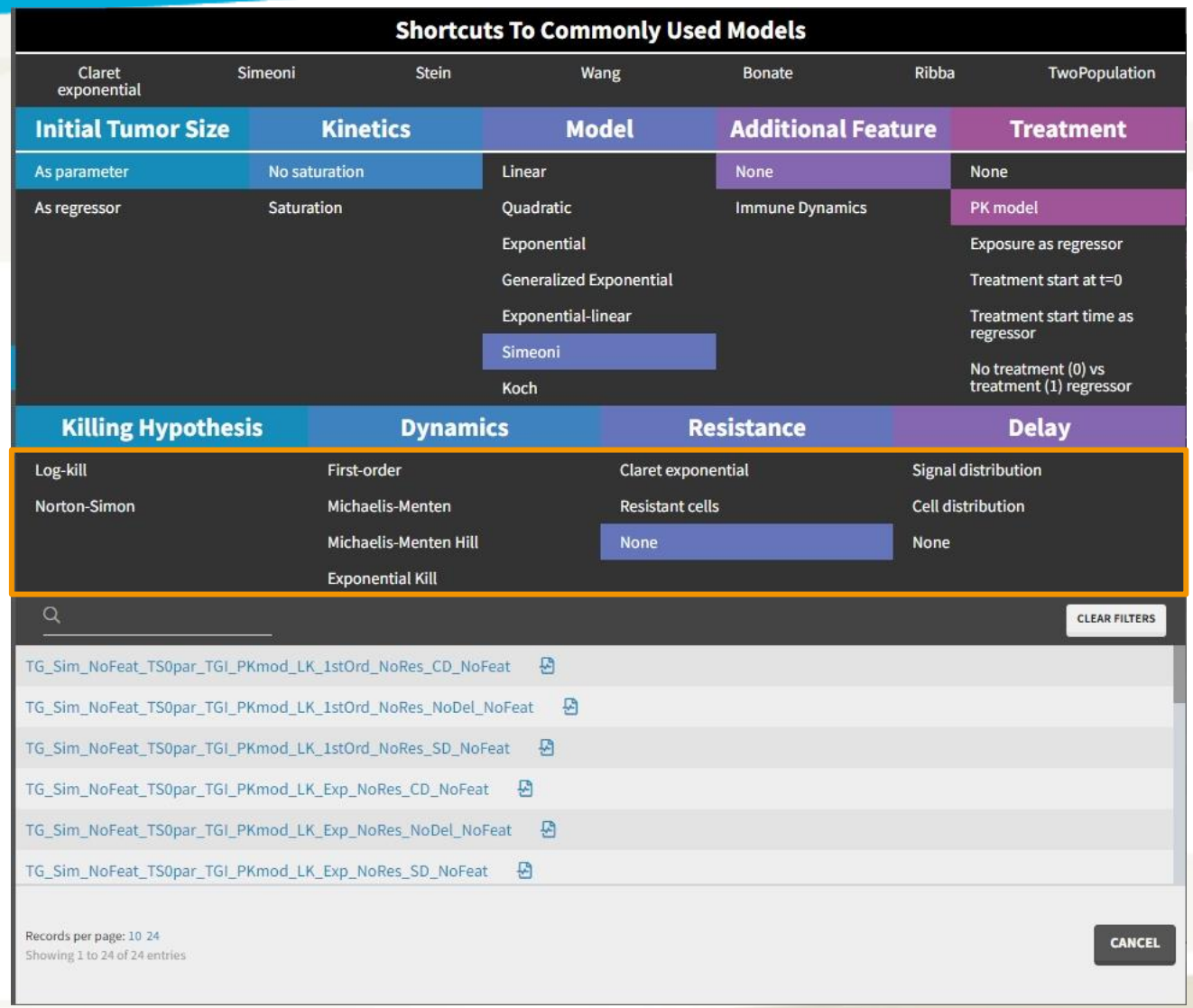
Killing hypothesis:
- Log-kill
- Norton-Simon

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

Delay:
- Cell distribution
- Signal distribution

➔ 16 combinations

➔ The library allows to easily test different hypotheses



Step 2: TGI

```
[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

Step 2: TGI

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

PK:

;=======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)
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}
```

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

Step 3: Combination therapy

LIXOFT
A SIMULATIONS PLUS COMPANY

```
[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}
```

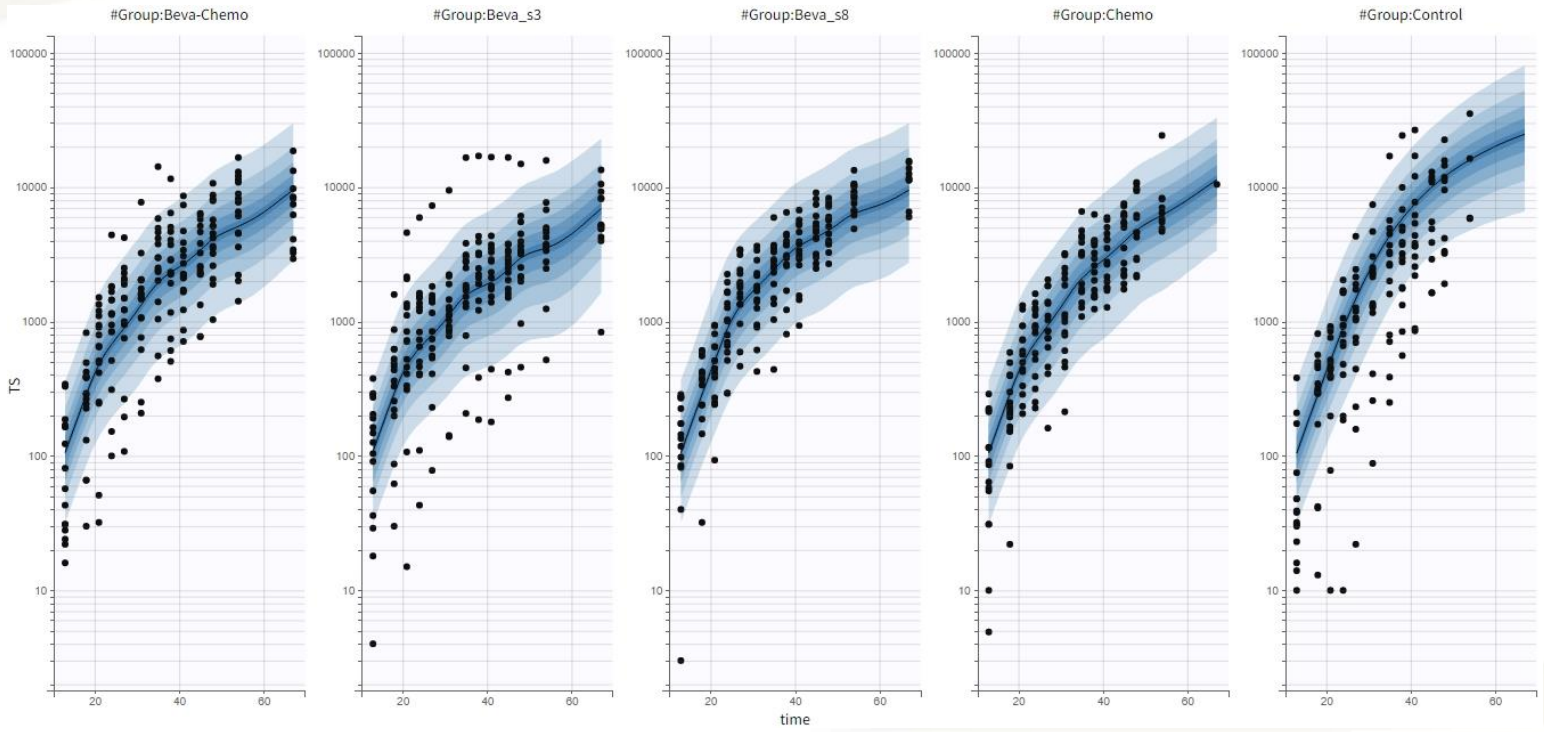
Model from the library:
Simeoni tumor growth with Norton-Simon linear killing and signal distribution

Extension of the model:

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

Step 3: Combination therapy

- The final project is given in: starting_material/2_TGI/r01_trtcomb.mlxtran
- **Inter-individual variability was removed on several parameters**
- Correlation group with eta_kge, eta_kgl, eta_TS0
- Good RSEs



	VALUE	STOCH. APPROX. S.E.	STOCH. APPROX. R.S.E.(%)
Fixed Effects			
TS0_pop	7.72	1.3	16.8
kge_pop	0.19	0.0076	3.91
kgl_pop	620.03	89.61	14.5
kkill_pop	535.76	23.8	4.44
tau_pop	3.77	0.13	3.31
delta_pop	2.58	0.12	4.77
Tlag_pop	0.83	0.011	1.31
Standard Deviation of the Random Effects			
omega_TS0	1.1	0.13	12.1
omega_kge	0.27	0.028	10.3
omega_kgl	0.92	0.13	13.8
omega_kkill	0.18	0.028	15.1
Correlations			
corr_kge_TS0	-0.76	0.056	7.40
corr_kgl_TS0	0.62	0.096	15.5
corr_kgl_kge	-0.63	0.098	15.6
Error Model Parameters			
a	42.45	6.13	14.4
b	0.23	0.0094	4.13

Step 4: joint TGI-TTE model

Survival model: delayed Weibull after TS reaches a threshold TSth

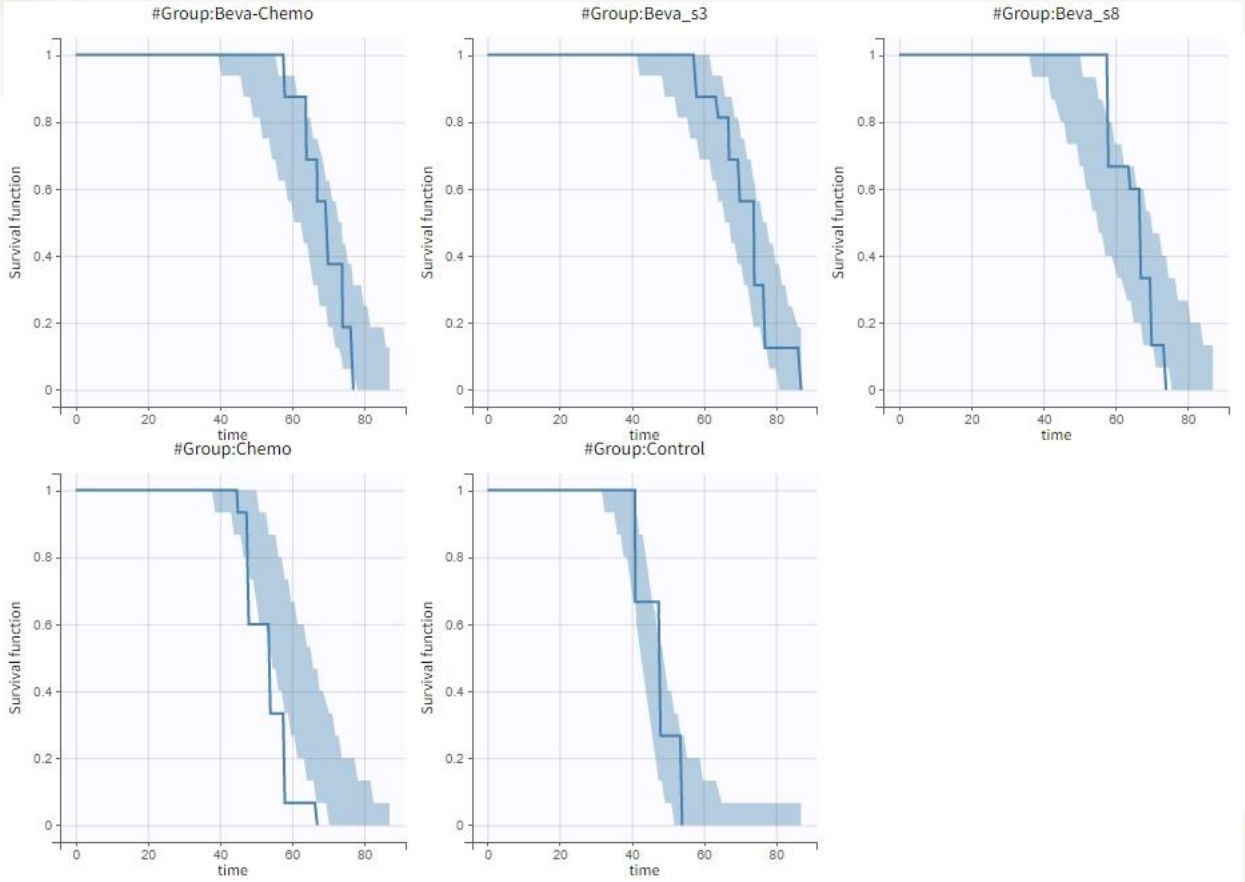
```
...
; computing time when TS>TSth
TimeTSth_0  = 0
if TS < TSth
  xTime = 1
else
  xTime = 0
end
ddt_TimeTSth = xTime

; hazard
if TS < TSth
 h = 0
else
 h = p/Te * max(1e-6,(t-TimeTSth)/Te)^(p-1)
end

OBSERVATION:
Survival = {type = event, hazard = h, maxEventNumber = 1}
...
```

Definition of hazard function with time

Definition of single exactly observed random event

Step 4: joint TGI-TTE model

TTE VPC split by group



LIXOFT

A SIMULATIONS PLUS COMPANY

PSA in metastatic Castration-Resistant Prostate Cancer treated with chemotherapy

Example 2

Introduction: PSA + survival dataset

- Published in:
  - Desmée, S. et al. (2017). Using the SAEM algorithm for mechanistic joint models characterizing the relationship between nonlinear PSA kinetics and survival in prostate cancer patients. *Biometrics*, 73(1), 305–312.
  - Data from the control arm of phase 3 clinical trial VENICE
- Dataset overview:
  - 400 men with metastatic Castration-Resistant Prostate Cancer (mCRPC)
  - treated with docetaxel and prednisone (first-line reference chemotherapy)
- Observations:
  - PSA concentration
  - Death or censoring time

Data set

ID	TIME	Y	CENS	YTYPE	TSOreg	TIME_ENDtr_reg	TIME_ENDtr	maxTime	AMT
2002	-43	14.2	0	1	14.2	328	328	670	.
2002	-2	14.83	0	1	.	328	328	670	.
2002	0	0	0	2	.	328	328	670	.
2002	0	.	.	.	.	328	328	670	0
2002	21	18.55	0	1	.	328	328	670	.
2002	42	14.8	0	1	.	328	328	670	.
2002	111	2.52	0	1	.	328	328	670	.
2002	196	0.49	0	1	.	328	328	670	.
2002	238	0.22	0	1	.	328	328	670	.
2002	327	0.12	0	1	.	328	328	670	.
2002	328	.	.	.	.	328	328	670	0
2002	411	0.1	1	1	.	328	328	670	.
2002	670	0.1	1	1	.	328	328	670	.
2002	677	0	0	2	.	328	328	670	.

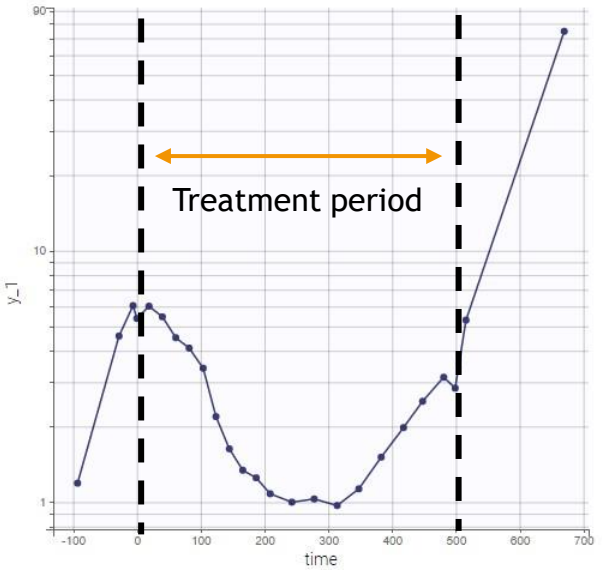
LOQ

Regressors

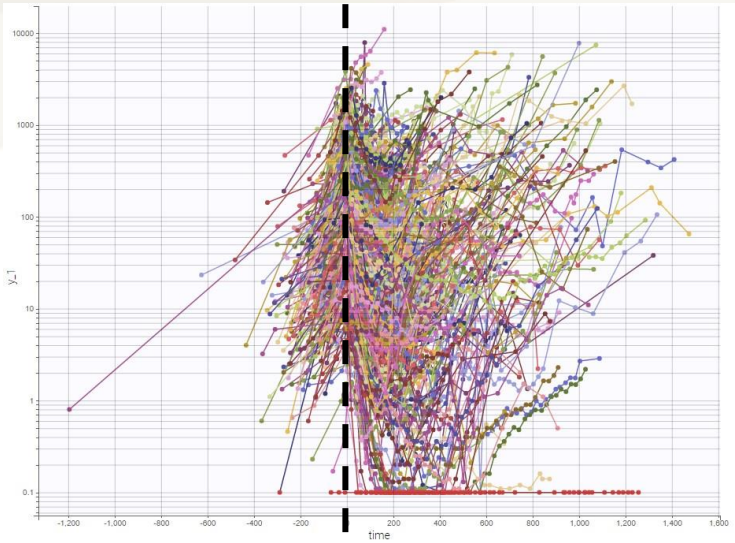
1 = PSA concentration
→ marker of tumor size
2 = death

Covariates for stratification

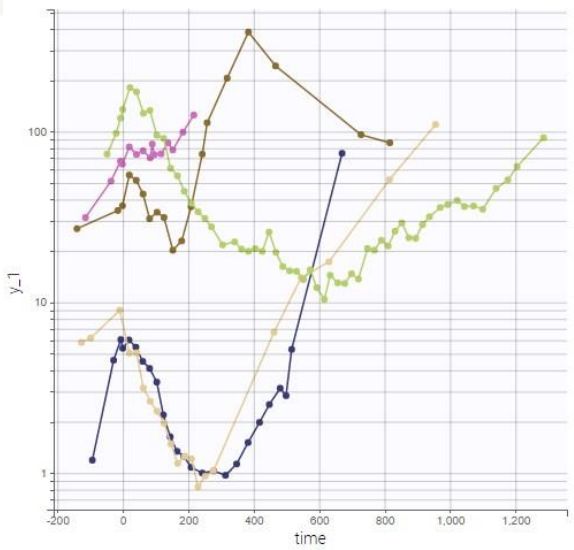
Dummy doses to visualize start and end of treatment

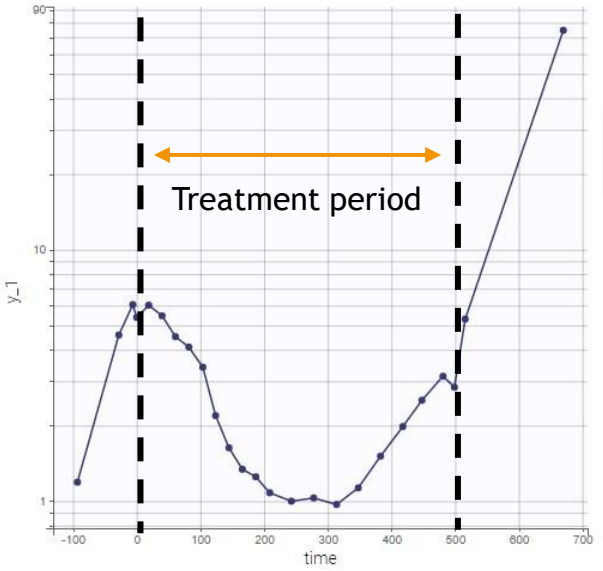


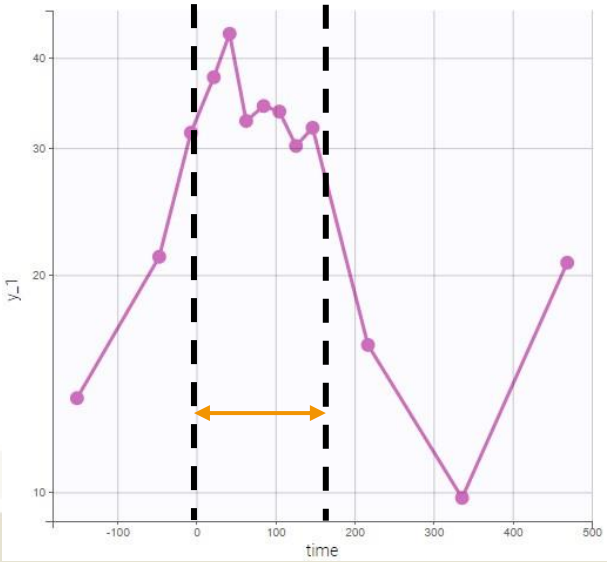
Introduction: PSA + survival dataset



Time=0: Start of treatment







⇒ TGI data shows emergence of resistance

TGI model with Claret resistance

```
[LONGITUDINAL]
input = {TS0, kge, kkill, lambda}
TS0 = {use=regressor}


EQUATION:
odeType=stiff

TS_0=TS0

K = kkill*exp(-lambda*t)

TSsat = min(TS,1e9)
if t<0; before treatment (kkill = 0)
  TSDynamics = kge*TSsat
else ; during treatment
  TSDynamics = kge*TSsat-K*TS
end

ddt_TS = TSDynamics

OUTPUT:
output = {TS}
```

Model from library:

- Exponential growth and log-kill treatment effect
- No fixed initial time
- TS0 read as regressor
- Treatment effect applied after time 0

TGI model with Claret resistance

```
[LONGITUDINAL]
input = {TS0, TimeEndTrt, kge, kkill, lambda}
TS0 = {use=regressor}
TimeEndTrt = {use=regressor}

EQUATION:
odeType=stiff

TS_0=TS0

K = kkill*exp(-lambda*t)

TSsat = min(TS,1e9)
if t<0 | t>TimeEndTrt ; before and after treatment (kkill = 0)
  TSDynamics = kge*TSsat
else ; during treatment
  TSDynamics = kge*TSsat-K*TS
end

ddt_TS = TSDynamics

OUTPUT:
output = {TS}
```

Model from library:

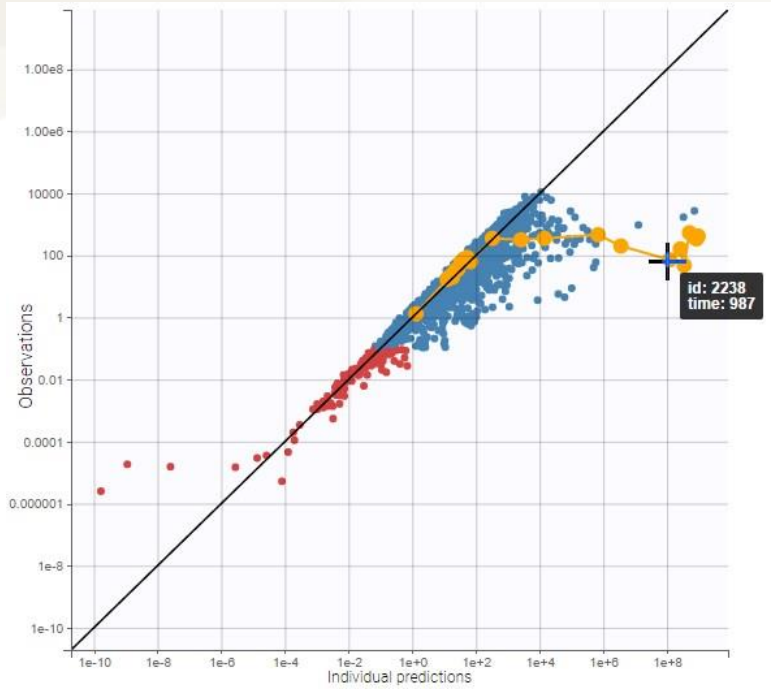
- Exponential growth and log-kill treatment effect
- No fixed initial time
- TS0 read as regressor
- Treatment effect applied after time 0

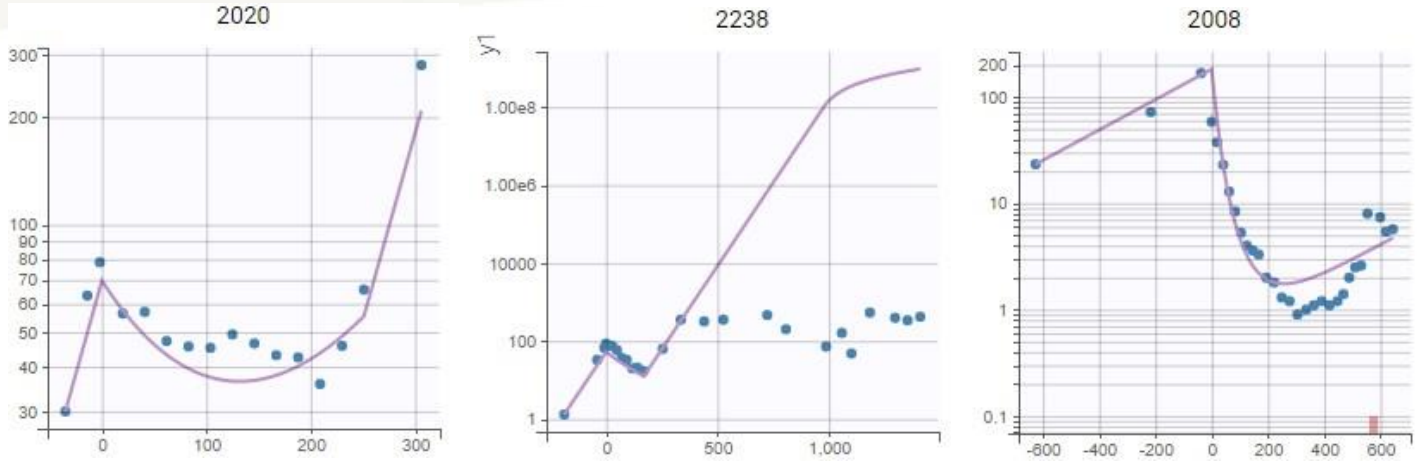
Customization of the model:

- TimeEndTrt read as regressor
- Treatment effect applied between time 0 and TimeEndTrt

TGI model with Claret resistance

Result for exponential tumor growth and log-kill





➔ Need for a maximal tumor size

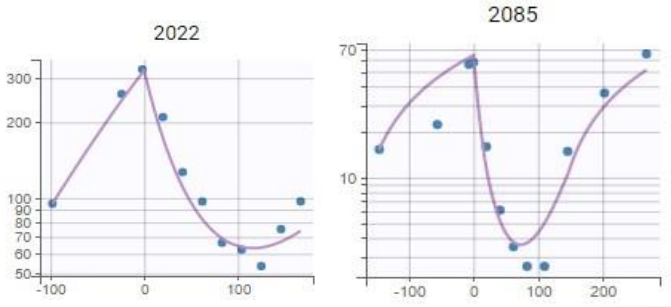
➔ After comparing several options, the **Simeoni-logistic** function gives the best result

TGI model with Claret resistance

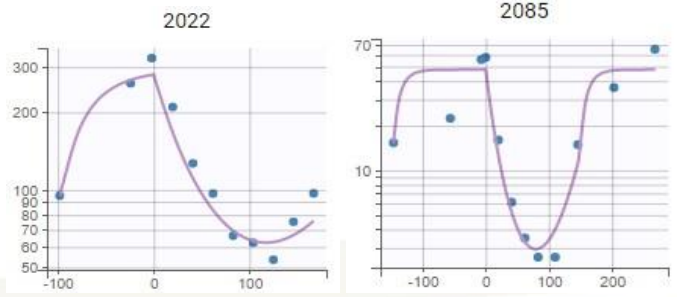
Comparing Norton-Simon and log-kill treatment effects → LK gives the best results

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
TGSimeoniLogis_LK_lin_Claret					52734.51		52826.06	TG_SimeoLogis_TGI_LK_lin_ClaretExp.txt	y1: comb1	kge kgl psi TSmax kkill lambda
TGSimeoniLogis_NS_Claret					53101.54		53207.88	TG_SimeoLogis_TGI_NS_ClaretExp.txt	y1: comb1	kge kgl psi TSmax kkill lambda kd

Log-kill



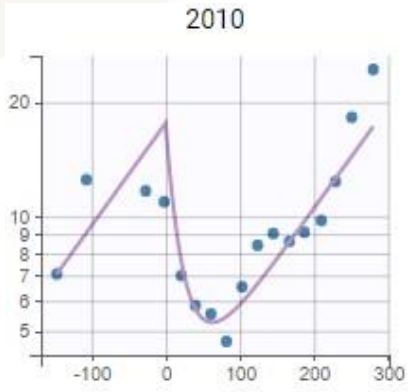
Norton-Simon



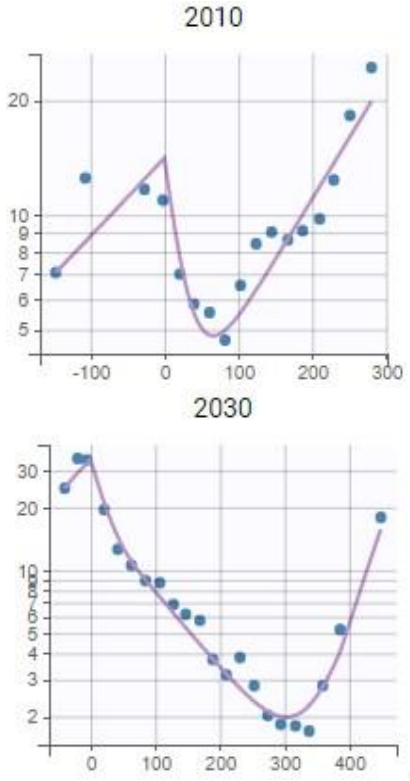
Comparing different hypotheses

Comparing resistance models:
→ two population model than Claret resistance

Claret

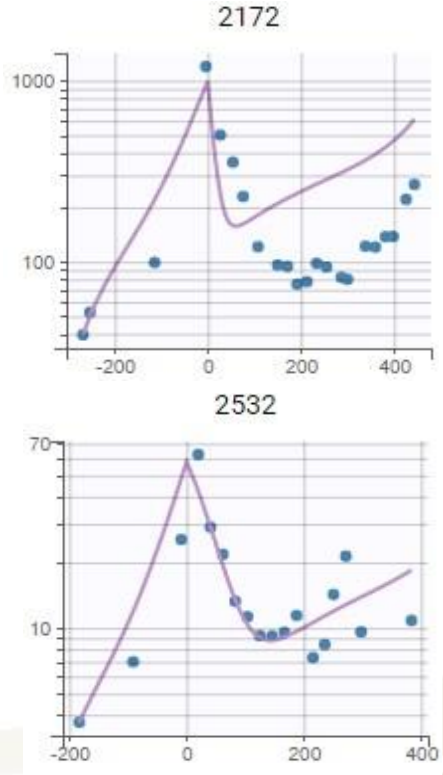


2 pop

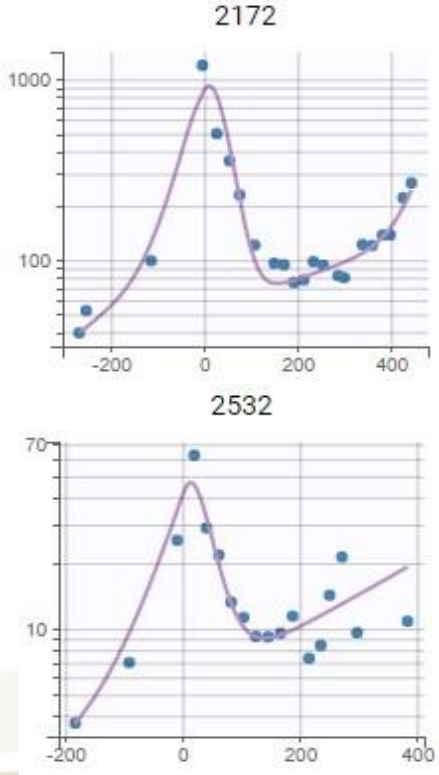


Comparing delays:
→ Cell distribution gives better results than signal distribution

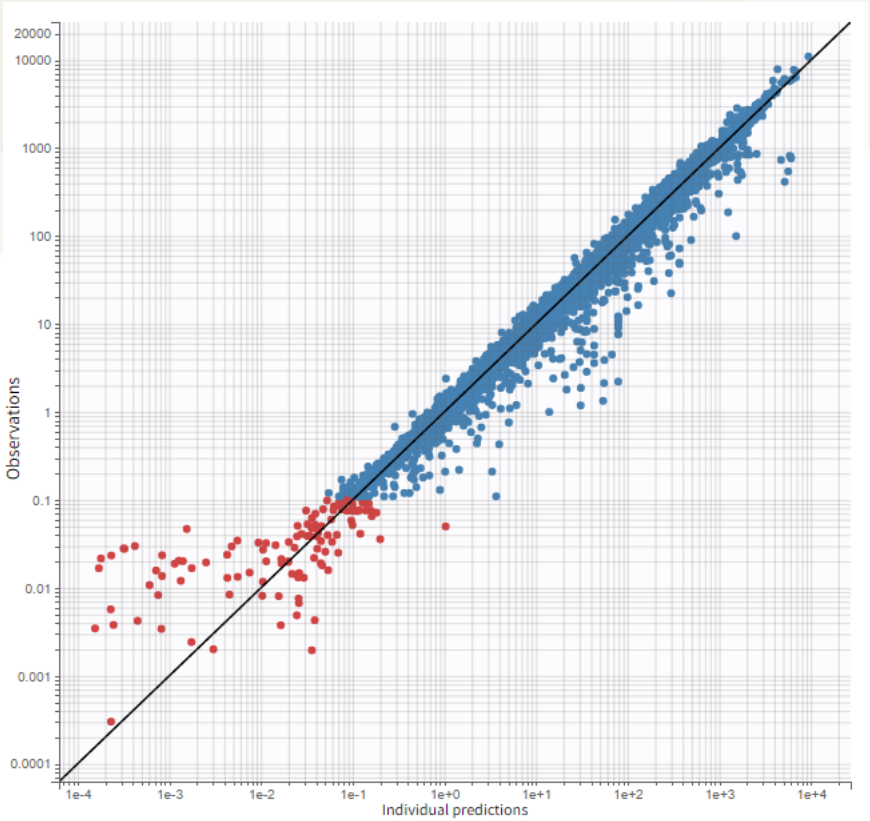
Signal distribution

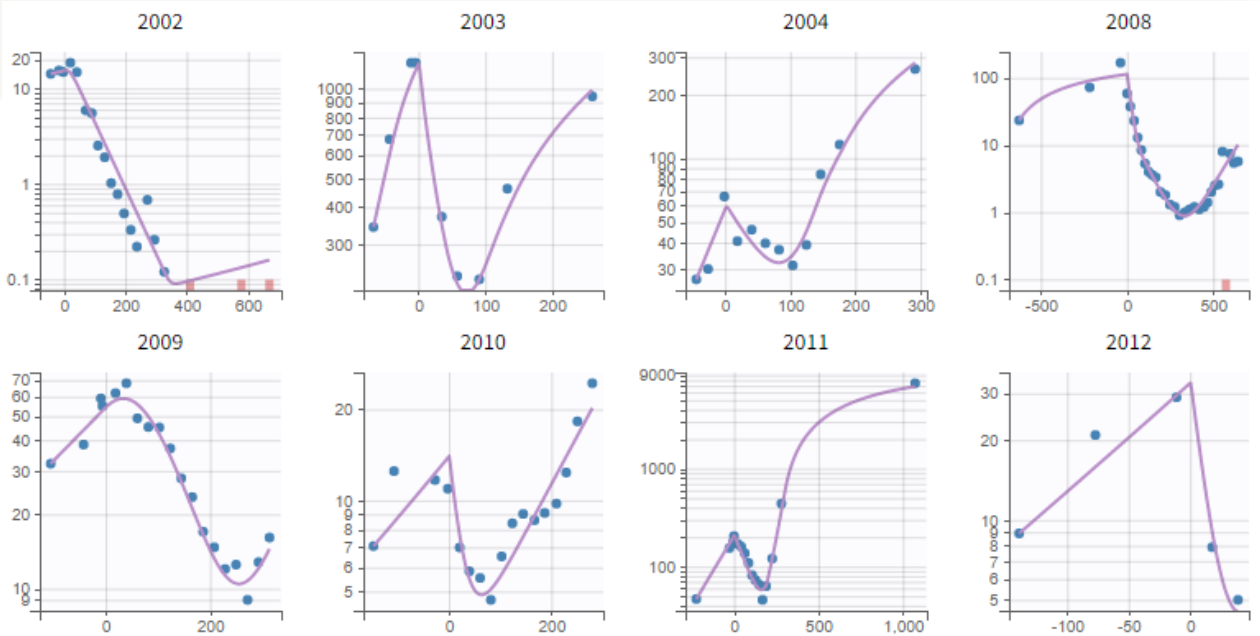


Cell distribution



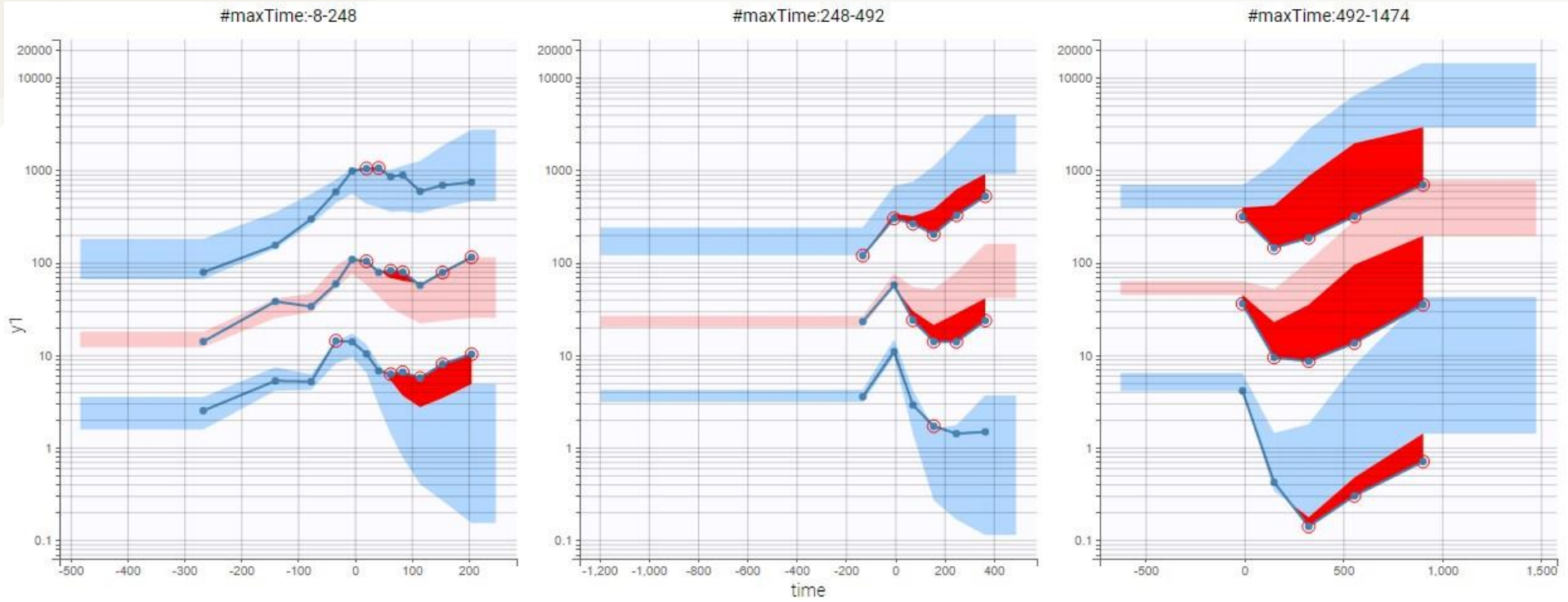
Final model


Observations
Individual predictions


2002
2003
2004
2008
2009
2010
2011
2012

VPC bias

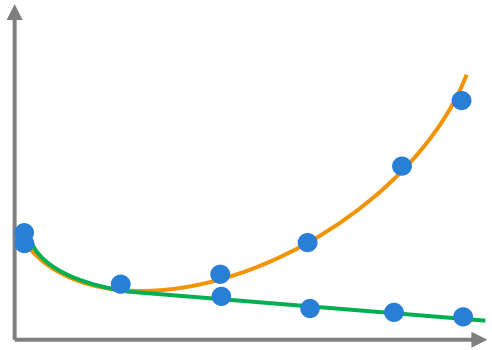
VPC split by maximal time of observation



⇒ Under-prediction for small maxTime and over-prediction for large maxTime might be a VPC dias due to non-random dropout

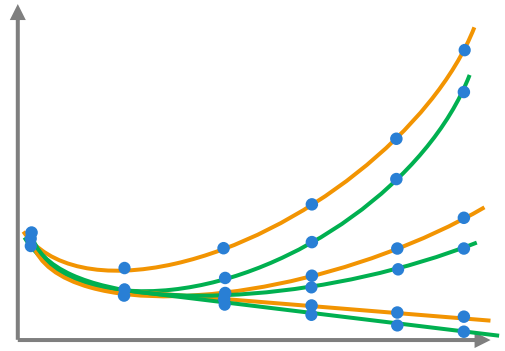
Dropout and VPC

Tumor progression without dropout



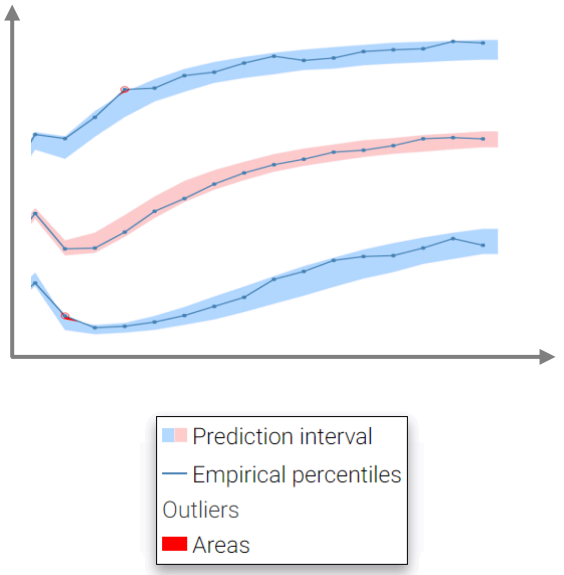
Empirical percentiles

Simulations for VPC



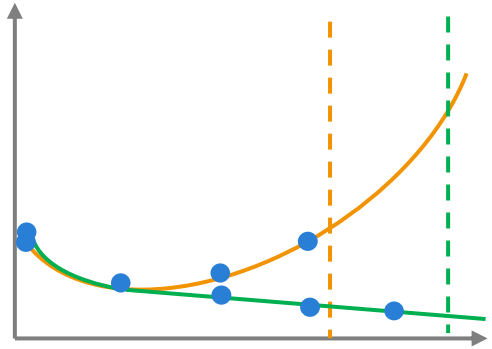
Prediction intervals

VPC



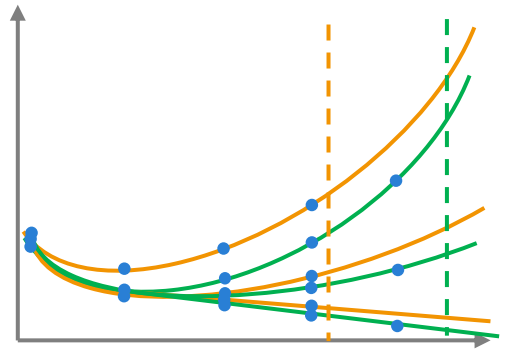
Dropout and VPC

Tumor progression with dropout



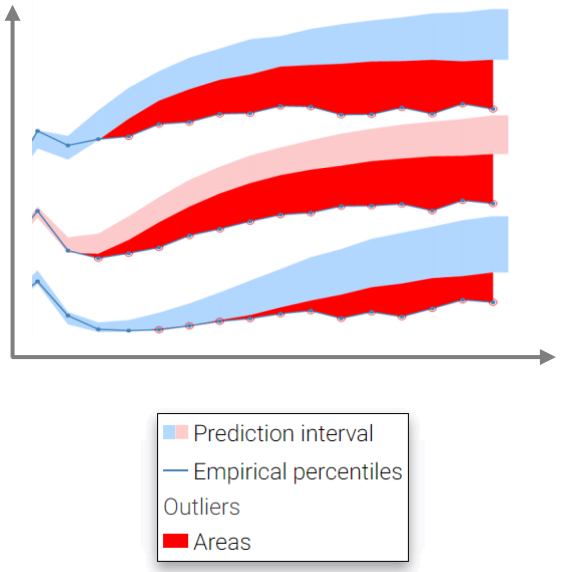
Empirical percentiles

Simulations for VPC



Prediction intervals

VPC



LIXOFT

A SIMULATIONS PLUS COMPANY

Q & A

LIXOFT

A SIMULATIONS PLUS COMPANY

Additional tumor growth features

Additional TG features

LIXOFT
A SIMULATIONS PLUS COMPANY

Initial Tumor Size	Kinetics	Model	Additional Feature	Treatment
As parameter	No saturation	Logistic	None	None
As regressor	Saturation	Generalized Logistic	Angiogenesis	PK model
		Simeoni-Logistic Hybrid	Immune Dynamics	Exposure as regressor
		Gompertz		Treatment start at t=0
		Exponential-Gompertz		Treatment start time as regressor
		Von Bertalanffy		No treatment (0) vs treatment (1) regressor
		Generalized Von Bertalanffy		

Additional TG features

Logistic growth with dynamic TSmax due to angiogenesis

$$\frac{dTS}{dt} = kp * TS\left(1 - \frac{TS}{TS_{max}}\right)$$

$$TS(t=0) = TS0$$

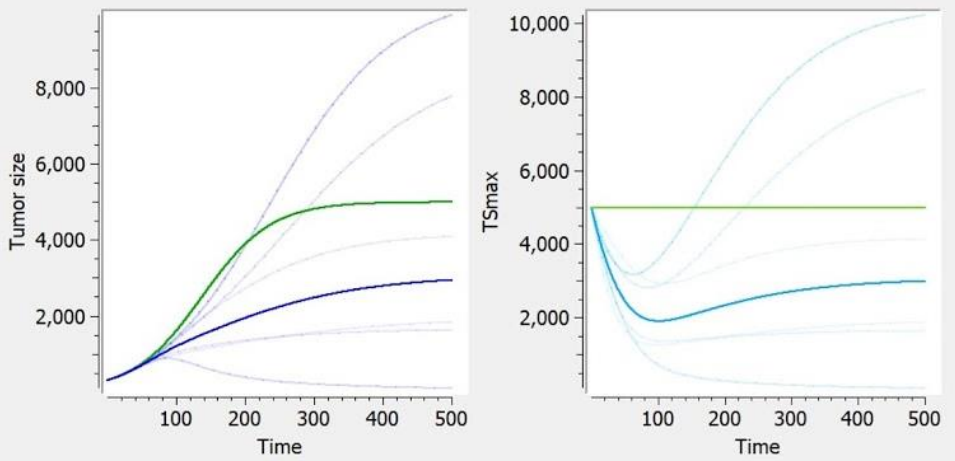
$$\frac{dTS_{max}}{dt} = kp_v * TS - \kappa * TS_{max} - kd_v * TS_{max} * TS^{\frac{2}{3}}$$

$$TS_{max}(t=0) = TS_{max}0$$

Stimulatory capacity of the tumor upon the vasculature via angiogenic factors

Intrinsic loss rate

Endogenous inhibition of previously generated vasculature by inhibition of endothelial cell proliferation, via inhibitors released through the tumor surface



[Hahnfeldt et al (1999)]

Additional TG features

Exponential growth with immune dynamics model

$$\frac{dTS}{dt} = kp * TS - c * I * TS$$

$$\frac{dI}{dt} = kp_i - kd_i * I + g * \frac{TS}{h + TS} * I - p * I * TS$$

$$kp_i = kd_i * I0$$

Killing of tumor cells by effector immune cells

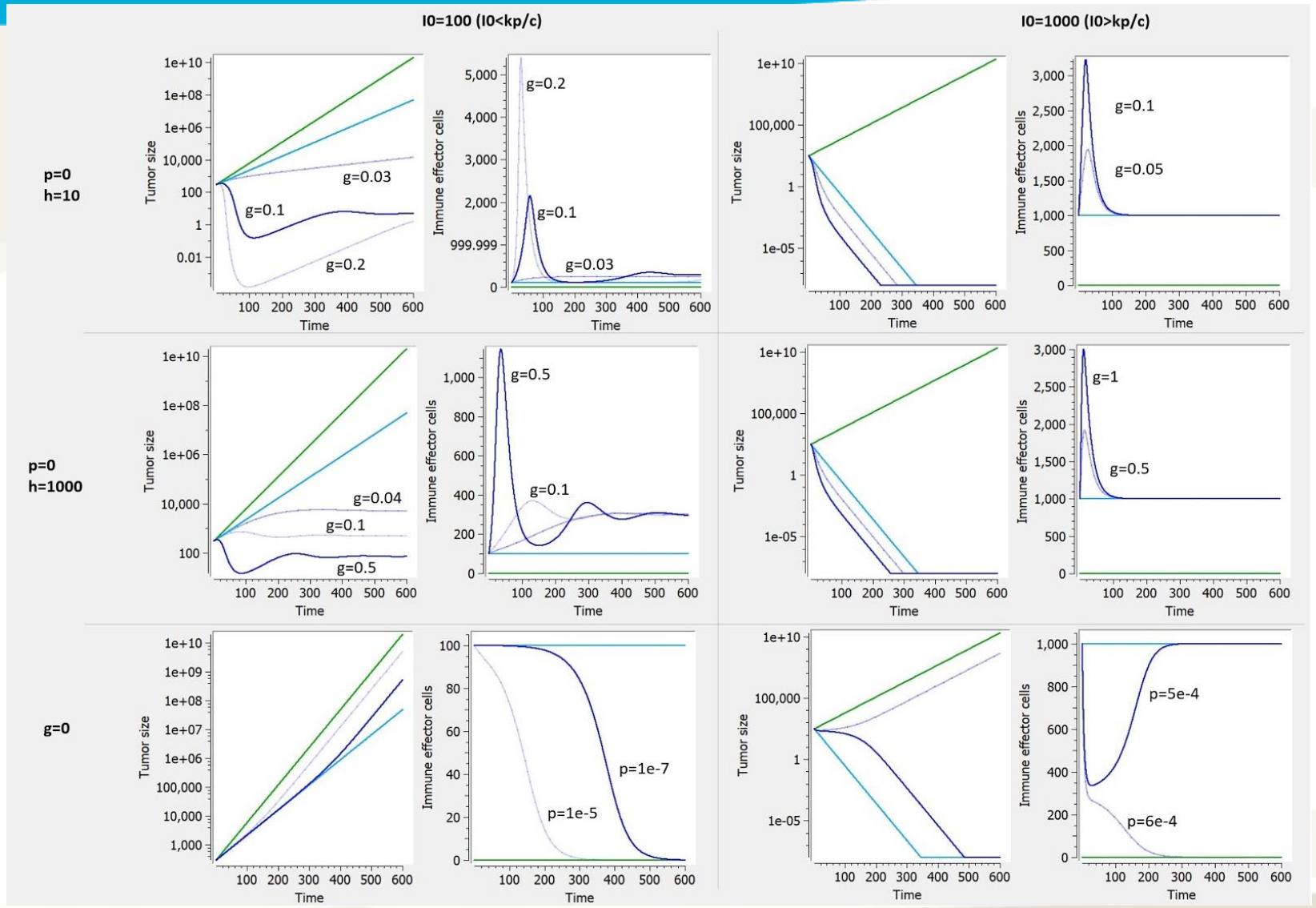
Constant source rate and death proportional to the population of effector cells

Effector cells are recruited by tumor cells through a Michaelis-Menten term

Effector cells are inactivated through contact with tumor cells according to a mass-action dynamic

[de Pillis et al. (2006)]

Additional TG features



Tumor growth
- Exponential rate: kp
- Exponential rate: kp-c*I0
- With immune dynamics model

[de Pillis et al. (2006)]

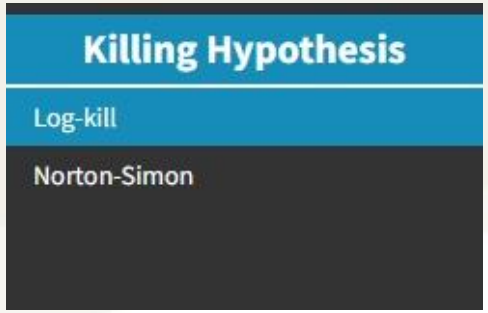
Tumor growth models

- Model based on ODE system
  - Example: Simeoni

```
[LONGITUDINAL]
input = {TS0, kge, kgl, psi}

EQUATION:
odeType=stiff

;defining initial conditions of the model:
t_0=0
TS_0=TS0

;model description:
ddt_TS = (kge*TS/(1+(kge/kgl*TS)^psi)^(1/psi))

OUTPUT:
output = {TS}
```

Statement to use the stiff ODE solver.
Default ODE solver: non-stiff

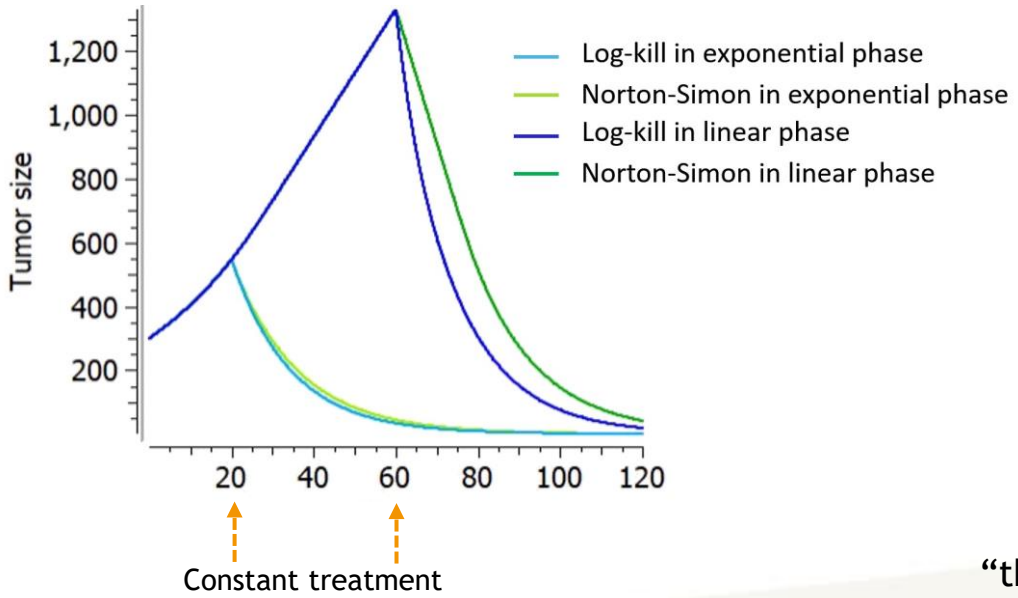
Tumor killing hypothesis



Skipper-Schabel-Wilcox log-kill hypothesis:

$$\frac{dTS}{dt} = growth - K * TS$$

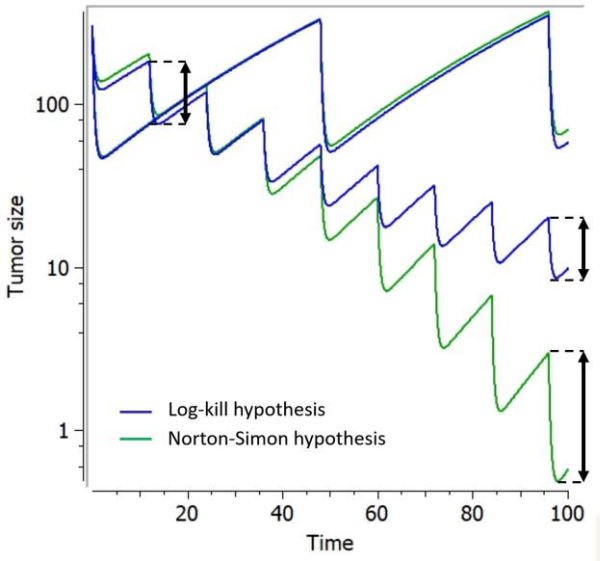
With exponential-linear growth:



Norton-Simon killing hypothesis:

$$\frac{dTS}{dt} = growth * (1 - K)$$

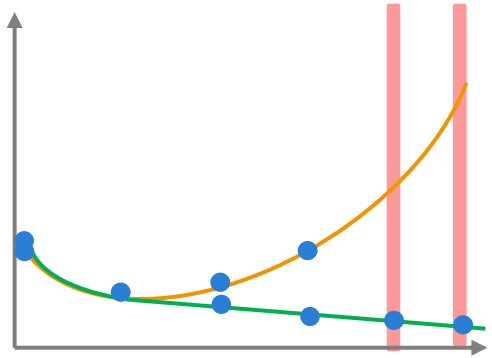
With a Gompertz growth and multiple doses:



"the chance of eradicating the tumor is maximized by delivering the most effective dose level of drug over as short a time as possible"

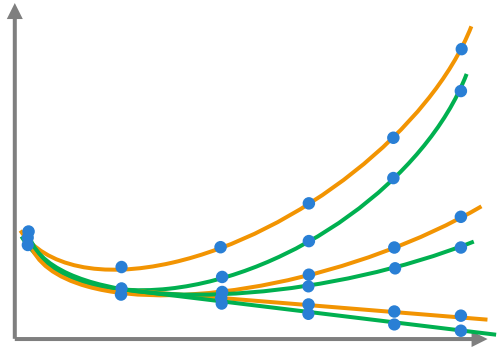
Dropout and VPC

Tumor progression with dropout and censored observations



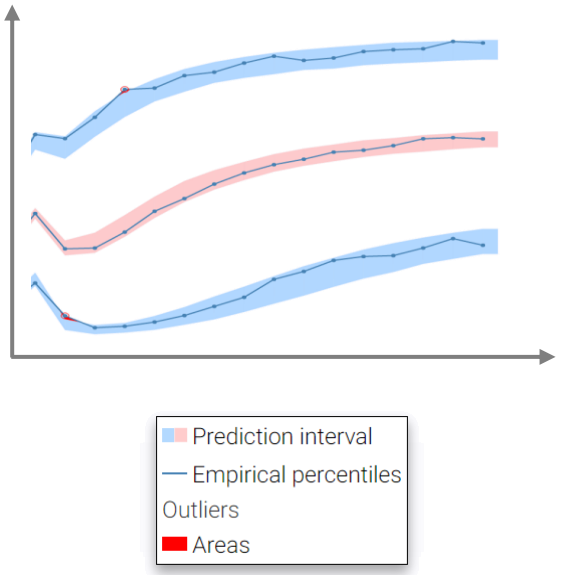
Empirical percentiles

Simulations for VPC



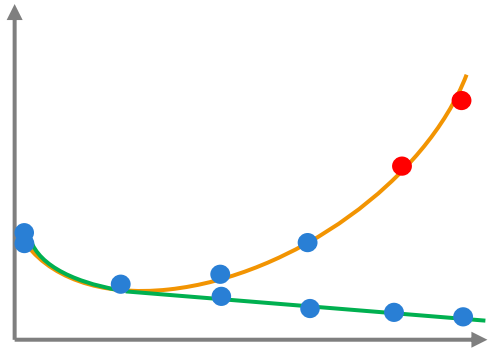
Prediction intervals

VPC



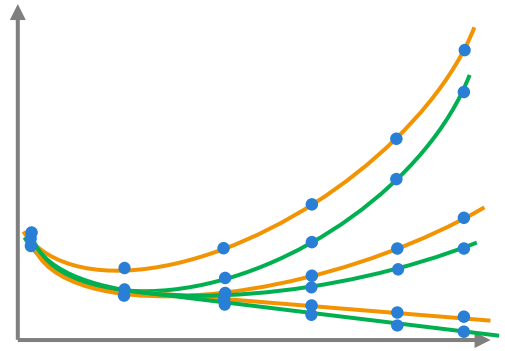
Dropout and VPC

Tumor progression with dropout and censored observations



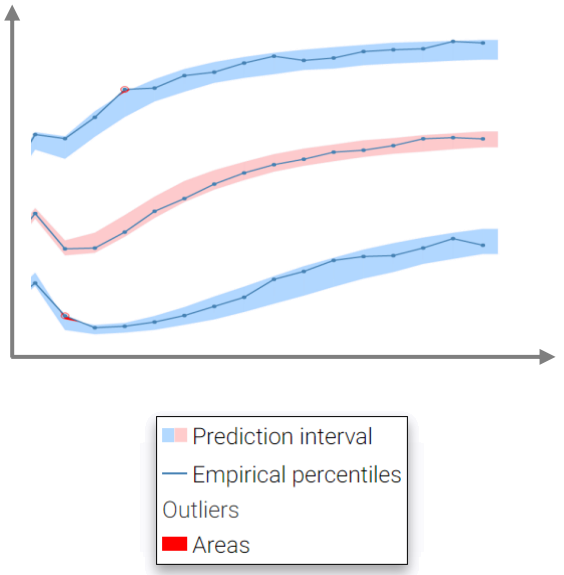
Empirical percentiles

Simulations for VPC



Prediction intervals

VPC



Simulated censored observations are sampled from the conditional distribution: $p(y_{BLQ}|y_{nonBLQ}, \hat{\psi}, \hat{\theta})$

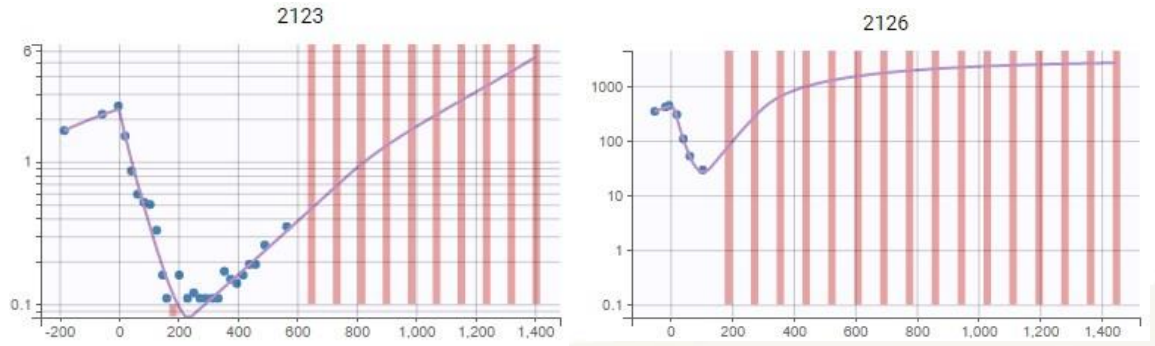
VPC correction for censored observations

Adding censored observations until time 1500 for all ids:

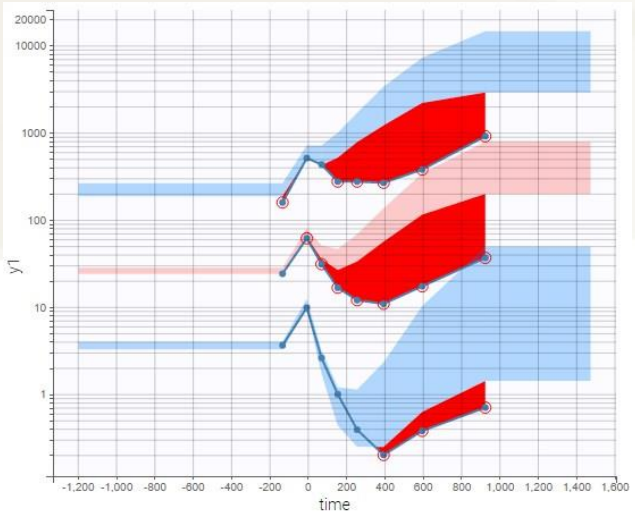
TIME	OBSERVATION	CENSORING	OBSERVATION ID
TIME	Y	CENS	YTYPE
460	0.19	0	1
491	0.26	0	1
565	0.35	0	1
734	0	0	2
649	0.1	-1	1
733	0.1	-1	1
817	0.1	-1	1

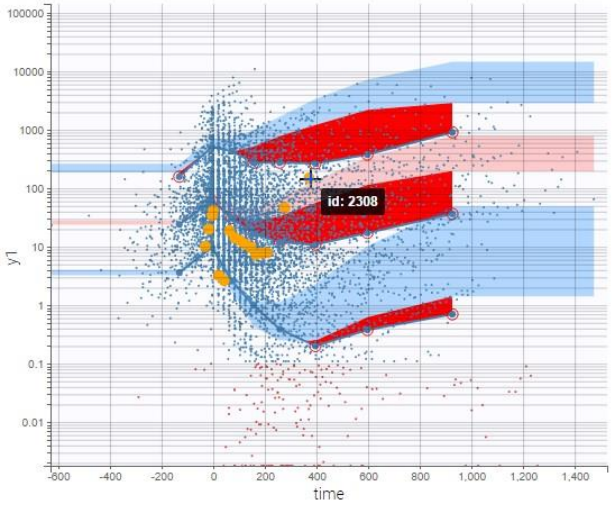
Dropout

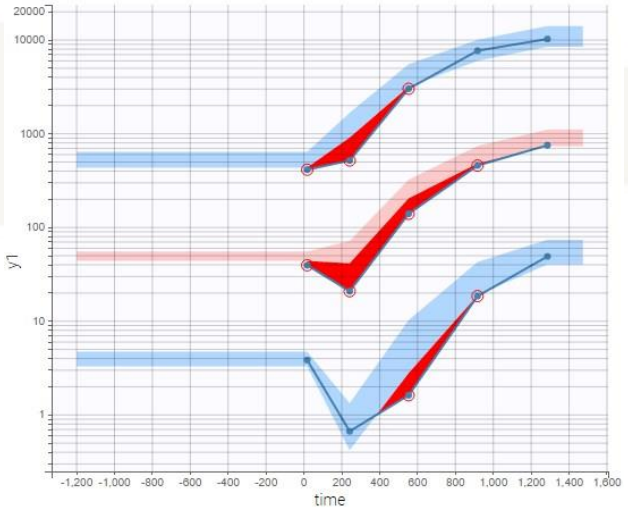
Censored observations added after dropout

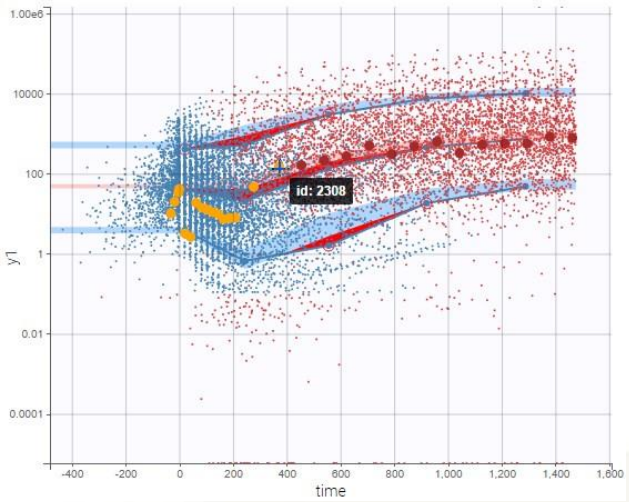


VPC correction for censored observations









⇒ Empirical percentiles take into account missing times via simulated observations (based on the model)