A library of tumor growth and tumor growth inhibition models for the MonolixSuite

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Modular tumor growth (TG) and tumor growth inhibition (TGI) library

- New library integrated in MonolixSuite2020
- Large combination of common basic models and possible additional features from the literature
- Modular filters for easy selection
- Permits to test different hypotheses for the tumor growth kinetics and effect of a treatment
- Flexible treatment definition
- Includes shortcuts to some typical models from the literature
- Documented with guidelines to help choose an appropriate model

Shortcuts To Commonly Used Models

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

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		

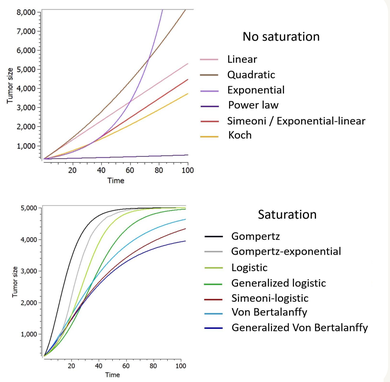
Killing Hypothesis	Dynamics	Resistance	Delay
Log-kill	First-order	Claret exponential	Signal distribution
Norton-Simon	Michaelis-Menten	Resistant cells	Cell distribution
	Michaelis-Menten Hill	None	None
	Exponential Kill		

Tumor growth models

Initial tumor size

The initial tumour size TS0 can be either be:
- a parameter to estimate
- a regressor to read from the dataset

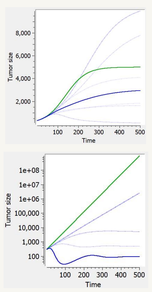
Kinetics of tumor growth



Tumor growth models available in the library are divided into two broad categories:
- Models able to capture the saturation as the tumor grows (via a carrying capacity or spontaneous decay)
- Models without saturation

Additional features

Additional features can be included to consider more complex tumor growth models:
- Dynamic carrying capacity due to *angiogenesis*
- *Immune dynamics* causing shrinkage or oscillations of tumor size



Examples tumor growth curves with diverse shapes caused by angiogenesis (top) or immune dynamics (bottom).

Green: tumor growth without additional feature

Blue: tumor growth with additional feature and different parameter values

Treatment effect

Killing hypothesis

Skipper-Schabel-Wilcox log-kill (LK):

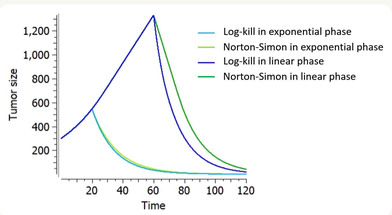
Treatment kills off fraction of tumor

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

Norton-Simon (NS):

Killing term proportional to growth rate

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

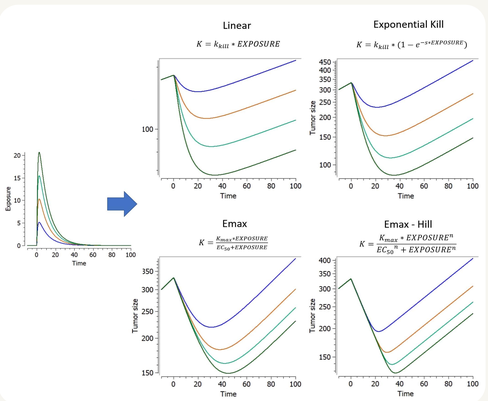


Comparison of LK and NS killing hypotheses

The tumor size follows an exponential-linear growth, and a constant treatment effect is applied either in the exponential phase (at t=20) or in the linear phase (at t=60) with linear kinetics.

→ NS inhibition depends on the growth rate while LK inhibition does not.

Dynamics of treatment effect



Comparison of the different treatment dynamics available in the library

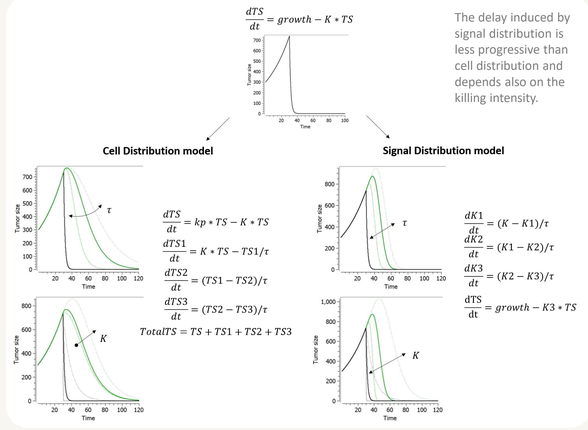
The tumor size follows an exponential-linear growth, and the treatment effect depends on the exposure as drug concentration following a single dose at time 0, with log-kill hypothesis.

A linear range of dose amounts has been applied in order to exhibit the linear and non-linear relationships between exposure and treatment effect.

Delay & resistance

Delay of treatment effect

A delay in either the treatment effect (signal distribution model) or cell death (cell distribution model) may be added via transit compartments.



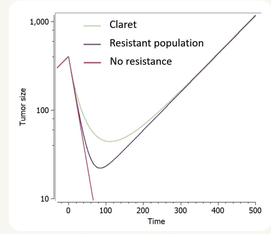
The delay induced by signal distribution is less progressive than cell distribution and depends also on the killing intensity.

Emergence of resistance

Claret resistance model

- simple phenomenological model
- accounts for the loss of drug-induced decay over time due to declining efficacy of the drug

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



The Claret model exhibits a more progressive onset of resistance.

Initial fraction of resistant cells

- a resistant fraction of the tumor is killed with a smaller rate than the sensitive part of the tumor

Model with log-kill hypothesis:

$$\begin{cases} TS_S(t_0) = (1-f) * TS0 \\ TS_R(t_0) = f * TS0 \\ \frac{dTS_S}{dt} = growth - TS_s * K_{TSs} \\ \frac{dTS_r}{dt} = growth - TS_r * K_{TSr} \end{cases}$$

Model with Norton-Simon hypothesis:

$$\begin{cases} TS_S(t_0) = (1-f) * TS0 \\ TS_R(t_0) = f * TS0 \\ \frac{dTS_S}{dt} = growth * (1 - K_{TSs}) \\ \frac{dTS_r}{dt} = growth * (1 - K_{TSr}) \end{cases}$$

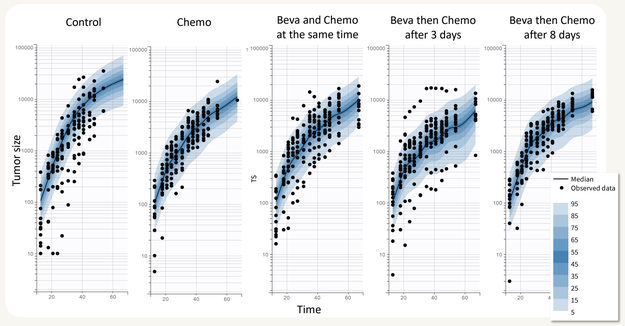
Case studies

We modeled two real datasets with models from the TGI library. The library allows to easily test different hypotheses and identify the most appropriate model.

Drug combinations in lung cancer xenografts

Dataset overview:
- Data published in [Imbs et al. (2018), *PSP*]
- 77 xenografts
- Measurements: tumor size (relative fluorescence unit)
- 5 treatment arms:
  - Control
  - Chemo
  - Bevacizumab and Chemo at the same time
  - Bevacizumab then Chemo after 3 days
  - Bevacizumab then Chemo after 8 days

Model from library :
- Tumor growth function: Simeoni
- Treatment effect: linear Norton-Simon killing
- Delay for treatment effect: signal distribution
- Extended model to take into account effect of bevacizumab: activation of killing after a lag time

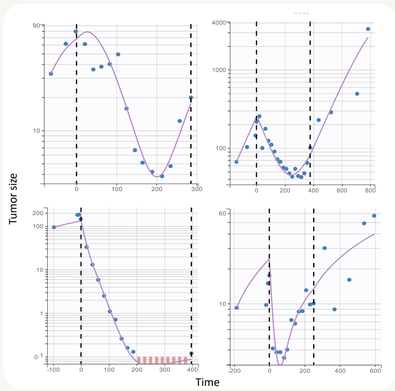


Blue: prediction distribution based on the model. Black: Observed data.

PSA kinetics in prostate cancer patients

Dataset overview:
- Data published in [Desmée et al. (2017), *Biometrics*]
- Data from the control arm of phase 3 clinical trial VENICE
- Measurements: PSA concentration
- 400 men with metastatic Castration-Resistant Prostate Cancer
- Treatment: first-line reference chemotherapy

Model from library:
- Tumor growth function: Simeoni
- Treatment effect: linear log-kill killing
- Delay for treatment effect: cell distribution
- Resistance: fraction of resistant tumor cells



Individual fits from 4 representative subjects. The effect of the treatment is constant between the two dashed lines.