Modeling & Simulation Decisions

Анализ и предсказание динамики размера опухоли при НМРЛ методами нелинейного регрессионного моделирования со смешанными эффектами

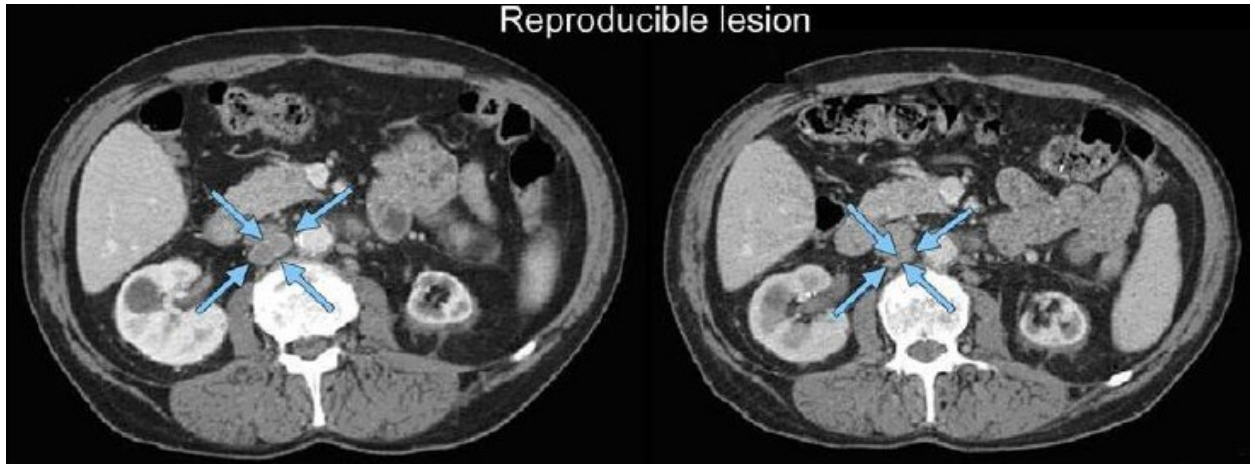
Мишина Анна, Кирилл Жуденков

1-3 ноября, 2022

XIV Конференция по математическим моделям и численным методам в биоматематике 2022

Tumor size assessment

Objective response and time to the development of disease progression are important endpoints in cancer clinical trials



RECIST (Response Evaluation Criteria in Solid Tumours)

The sum of the longest diameters (SLD) across target lesions.

Objective tumour response:

CR (Complete Response)	PR (Partial Response)	SD (Stable Disease)	PD (Progressive Disease)
Disappearance of all target lesions.	At least a 30% decrease in the sum of diameters of target lesions, taking as reference the baseline sum of diameters.	Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum diameters while on study.	At least a 20% increase in the sum of diameters of target lesions, taking as reference the smallest sum on study or an absolute increase of at least 5 mm or the appearance of one or more new lesions.

Eur J Cancer. 2009 Jan;45(2):228-47. doi: 10.1016/j.ejca.2008.10.026. PMID: 19097774., MRI figure is taken from this article

Objectives

The goal was to research and analyze different approaches to characterise tumor size dynamics using the SLD metric in order to find the model with the best descriptive and predictive power within the data under study. To rich the goal following objectives were established:

- to scope the literature for SLD biomarker models
- to qualify proposed models against selected training data and identify parameters
- to conduct diagnostics of qualified models
- to test models' predictions against validation data

Data under study

Phase III, randomized, double-blind study (ClinicalTrials.gov, identifier:NCT00364351) of patients with advanced NSCLC treated with Erlotinib, small molecule EGFR (epidermal growth factor receptor) inhibitor, was the source of SLD dynamics data in the present project.
The dataset was divided on training (n=300) and validation (n=116) sets.

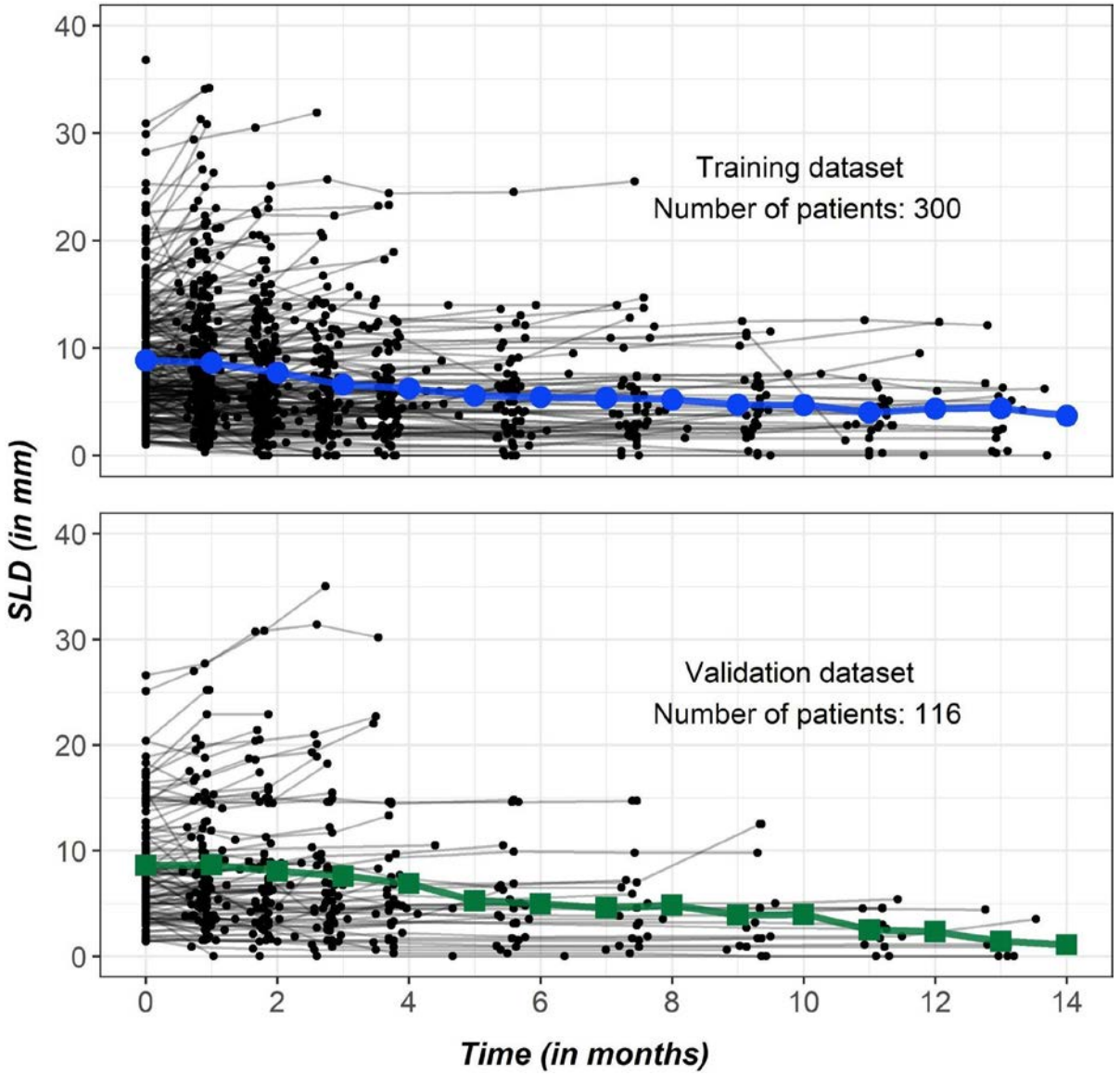


Fig. 1 Scatterplot of SLD observations. Blue and green lines represent the moving average values.

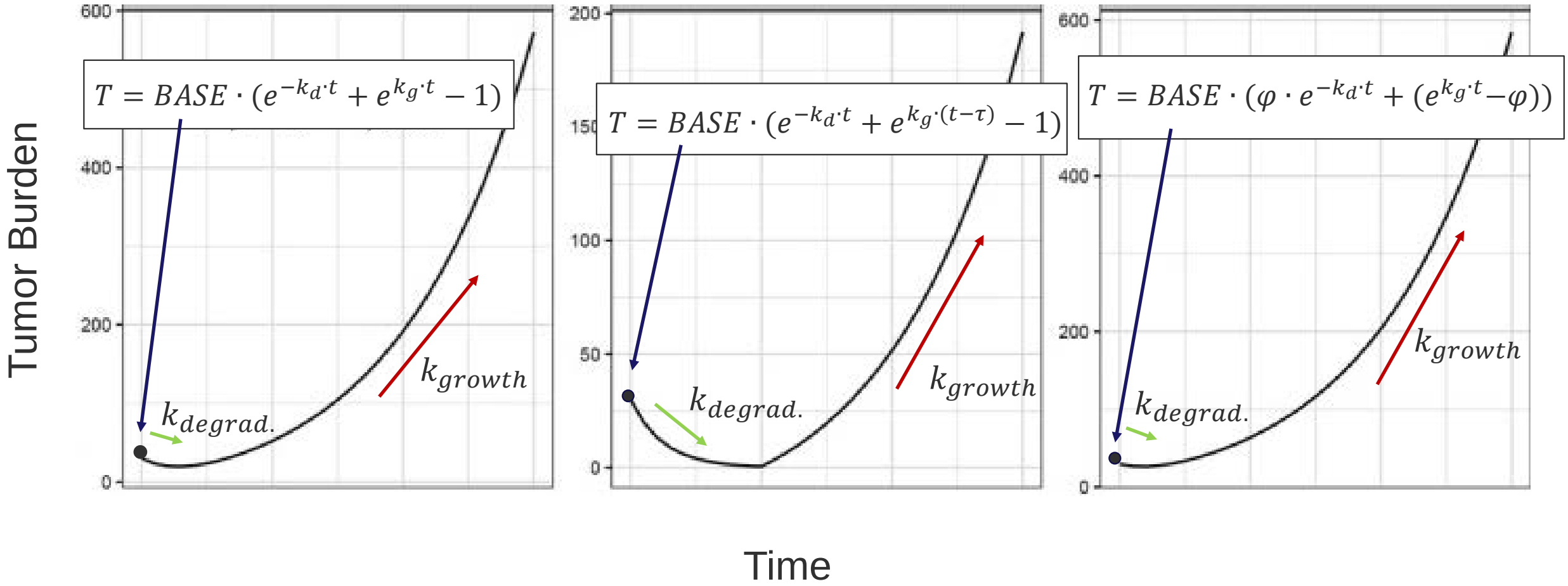
The source of dataset is Project Data Sphere

- Based on the published review of mathematical models for tumor dynamics the 6 models were chosen for investigation.
- 2 of the investigated models represented different empirical mechanisms of tumor resistance to treatment

Model	Peculiarities	Application
$SLD = (e^{-k_d \cdot t} + e^{k_g \cdot t} - 1) \cdot Base$	Two-phase bi-exponential model	PSA measurements, AI prostate cancer, chemotherapy; metastatic castration-resistant prostate carcinoma patients undergoing combination therapy; sum of perpendicular diameter measurements, RCC patients, bevacizumab treatment;
$SLD = (e^{-k_d \cdot t} + e^{k_g \cdot (t-\tau)} - 1) \cdot Base$	A parameter τ has been introduced to account for the delayed tumor regrowth	PSA measurements, AI prostate cancer, chemotherapy;
$SLD = (\varphi \cdot e^{-k_d \cdot t} + [e^{k_g \cdot t} - \varphi]) \cdot Base$	A parameter φ been introduced to differentiate the sensitive and resistant part of the tumor	Sum of the perpendicular diameters measurements, RCC patients, bevacizumab treatment
$SLD = Base \cdot e^{-A \cdot t} + B \cdot t$	Two-phase exponential-linear model	SLD measurements, NSCLC patients, 4 different targeted therapies; SLD measurements, NSCLC patients, 3 different chemotherapies;
$SLD = Base \cdot e^{-A \cdot t} + B \cdot t + C \cdot t^2$	Exponential-quadratic model	SLD measurements, RCCpatients, pazopanib treatment;
$SLD = Base \cdot e^{k_g \cdot t - (\frac{k_d}{\lambda}) \cdot (1 - e^{-\lambda \cdot t})}$	Tumor growth inhibition (TGI) model with parameter λ that accounts for drug resistance	SLD measurements, RCC/NSCLC/gastric cancer patients, targeted therapy/chemotherapy;

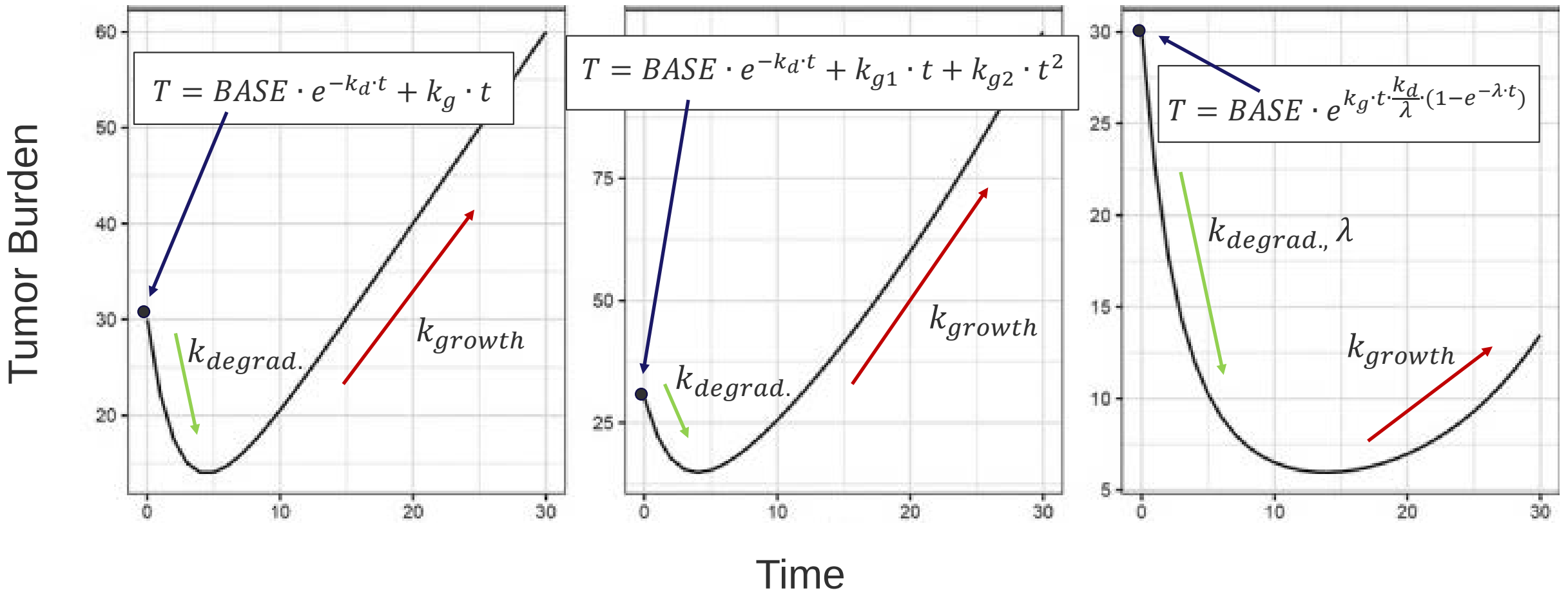
CPT Pharmacometrics Syst Pharmacol. 2019 Oct;8(10):720-737. doi: 10.1002/psp4.12450.

Models under investigation



CPT Pharmacometrics Syst Pharmacol. 2019 Oct;8(10):720-737. doi: 10.1002/psp4.12450. Epub 2019 Aug 9. PMID: 31250989

Models under investigation



CPT Pharmacometrics Syst Pharmacol. 2019 Oct;8(10):720-737. doi: 10.1002/psp4.12450. Epub 2019 Aug 9. PMID: 31250989

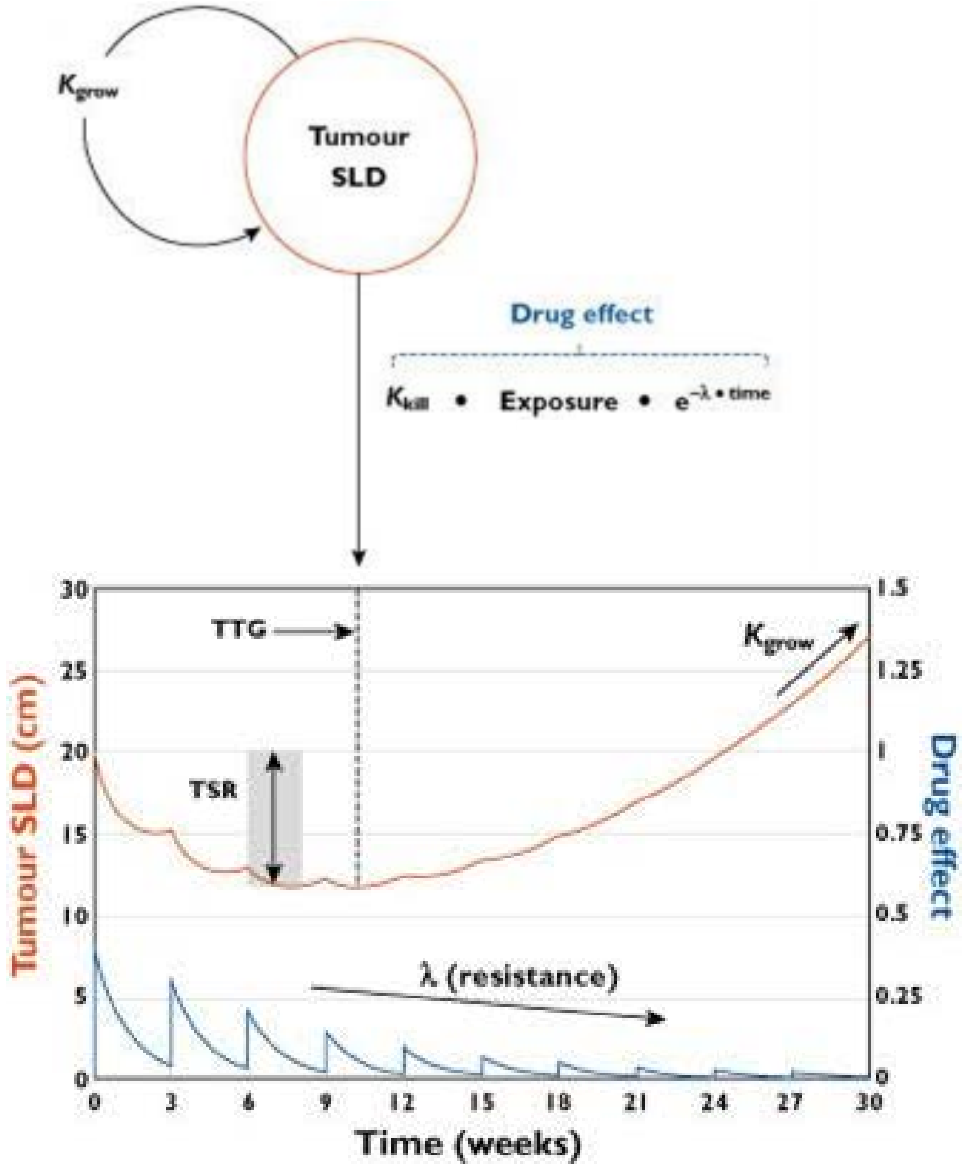
Tumor growth inhibition (TGI) model

$$SLD = Base \cdot e^{k_g \cdot t - (\frac{k_d}{\lambda}) \cdot (1 - e^{-\lambda \cdot t})}$$

The model is described by the differential equation below:

$$\begin{cases} \frac{d\,SLD(t)}{dt} = k_g \cdot SLD(t) - k_d \cdot Exposure(t) \cdot SLD(t) \\ k_d(t) = k_{d,0} \cdot e^{-\lambda \cdot t} \\ SLD(0) = Base \end{cases}$$

We will use the simplified version of the introduced TGI model where Exposure(t) is constant and equal to 1.



Br J Clin Pharmacol. 2015 Jan;79(1):56-71. doi: 10.1111/bcp.12258.

Pipeline

Qualification → Diagnostics → Validation

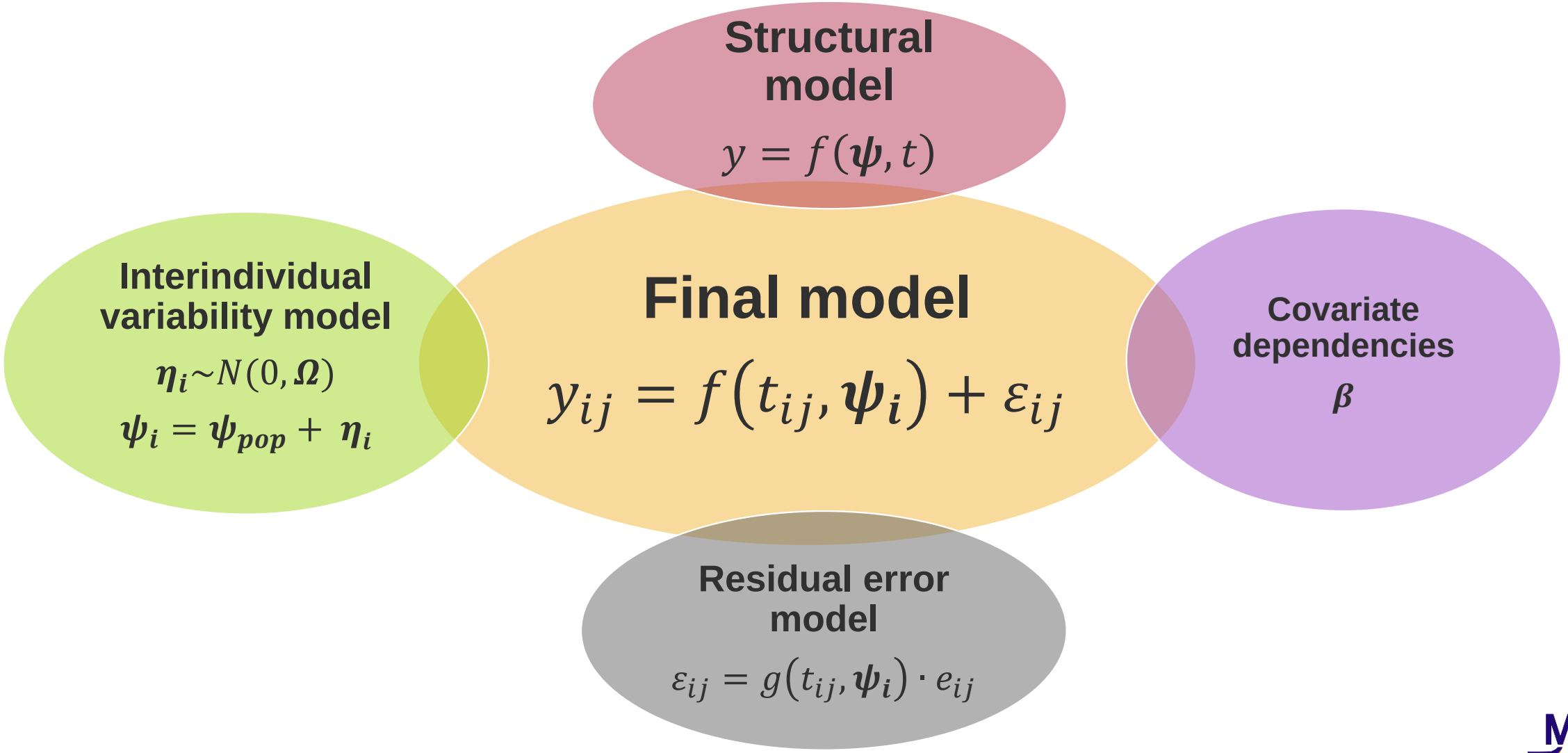
For models' parameters estimation Monolix Suite 2020 R1 modeling software controlled from the R programming environment was used

Qualified models were selected based on a set of criteria: successful convergence, RSE < 50%, optimal AIC, adequate diagnostic plots

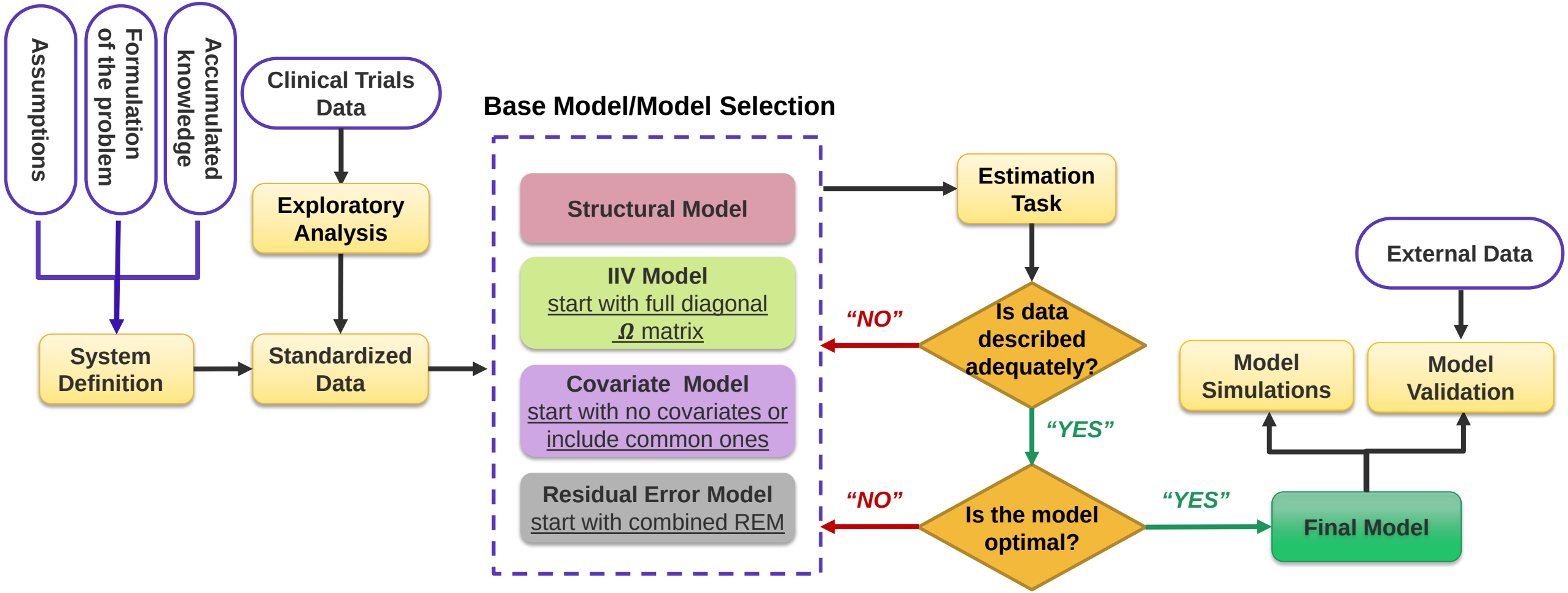
Model predictive performance was assessed in an external validation procedure where longitudinal SLD profiles were sampled from posterior distribution for truncated validation data.

The performance was assessed by Visual Predictive Check plots (VPC)

Mixed-Effects Models



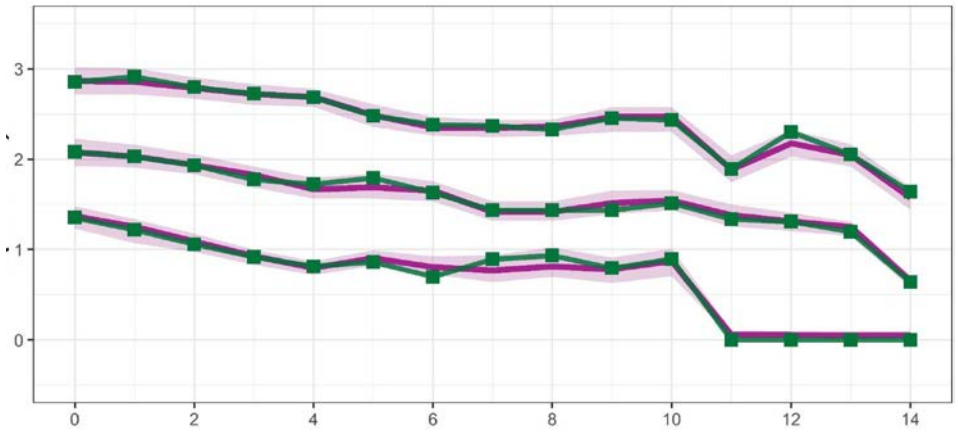
Population Pharmacometric Modeling Workflow



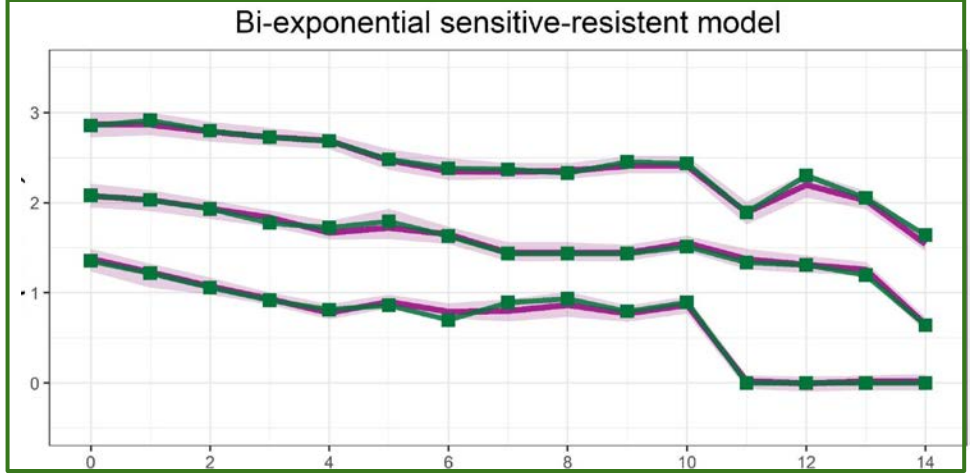
Investigation of models

Model	The optimal combination of parameters	AIC
$SLD = (e^{-k_d \cdot t} + e^{k_g \cdot t} - 1) \cdot Base$	EM: constant Corr.: $Base$, k_d	-55.6
$SLD = (e^{-k_d \cdot t} + e^{k_g \cdot (t-\tau)} - 1) \cdot Base$	EM: constant Corr.: $(Base, k_g)$ &(k_d, τ)	-60.19
$SLD = (\varphi \cdot e^{-k_d \cdot t} + [e^{k_g \cdot t} - \varphi]) \cdot Base$	EM: constant Corr.: $Base$, φ, k_d	-140.8
$SLD = Base \cdot e^{-A \cdot t} + B \cdot t$	EM: constant Corr.: $Base$, k_g	-56.3
$SLD = Base \cdot e^{-A \cdot t} + B \cdot t + C \cdot t^2$	EM: constant Corr.: $Base$, C	-25.76
$SLD = Base \cdot e^{k_g \cdot t - (\frac{k_d}{\lambda}) \cdot (1 - e^{-\lambda \cdot t})}$	EM: constant Corr.: $Base$, k_d	-114.8

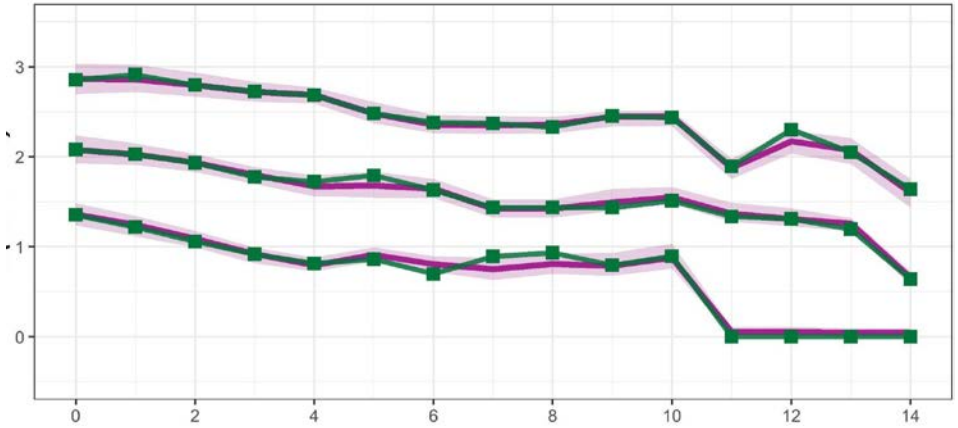
Bi-exponential model



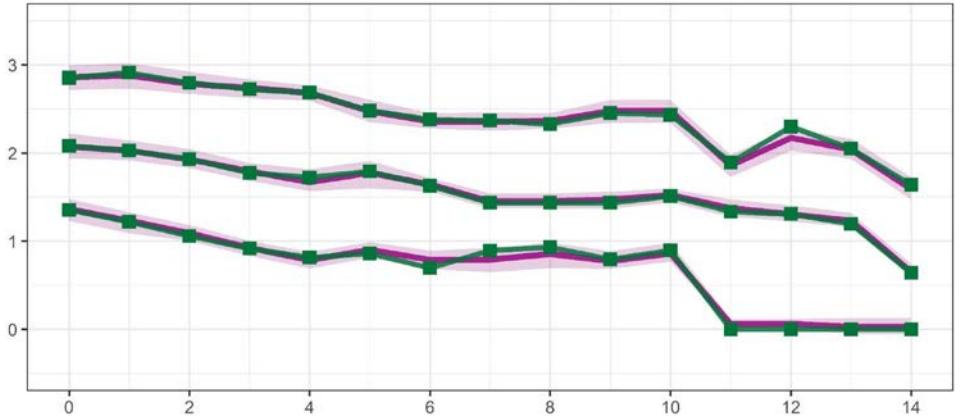
Bi-exponential sensitive-resistent model



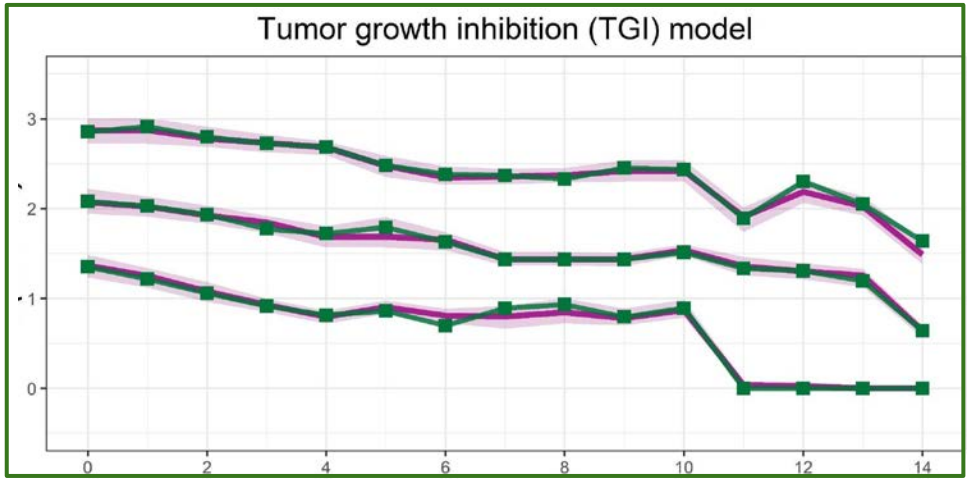
Exponential-linear model



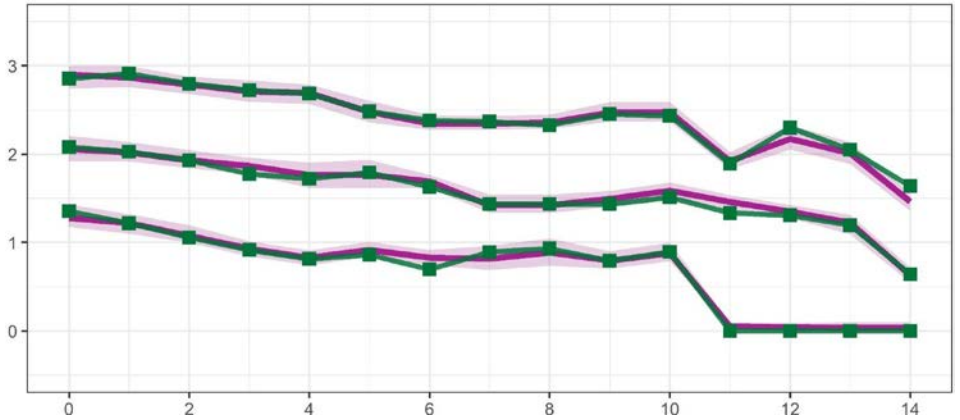
Bi-exponential model with delayed tumor regrowth



Tumor growth inhibition (TGI) model

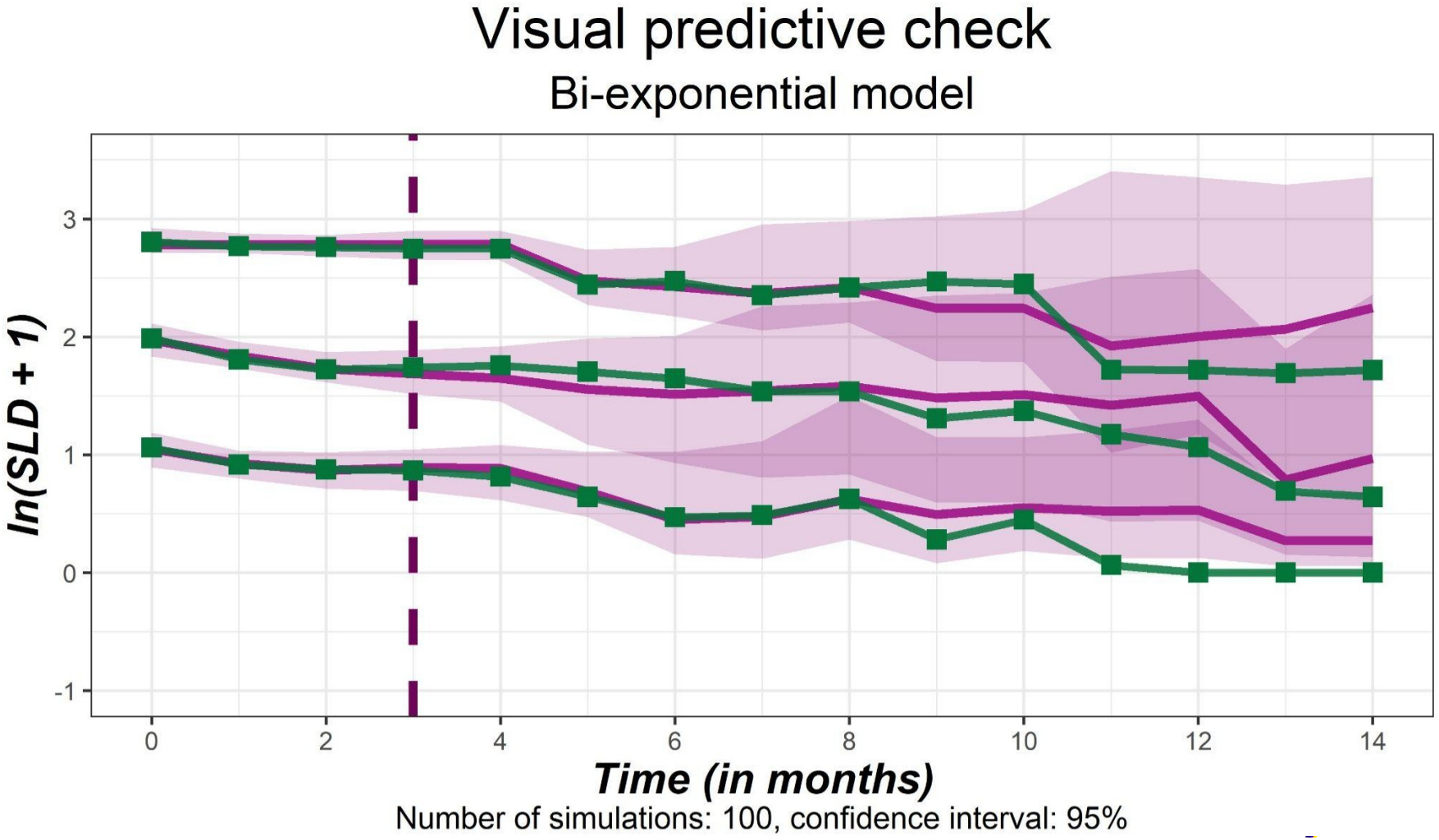


Exponential-quadratic model



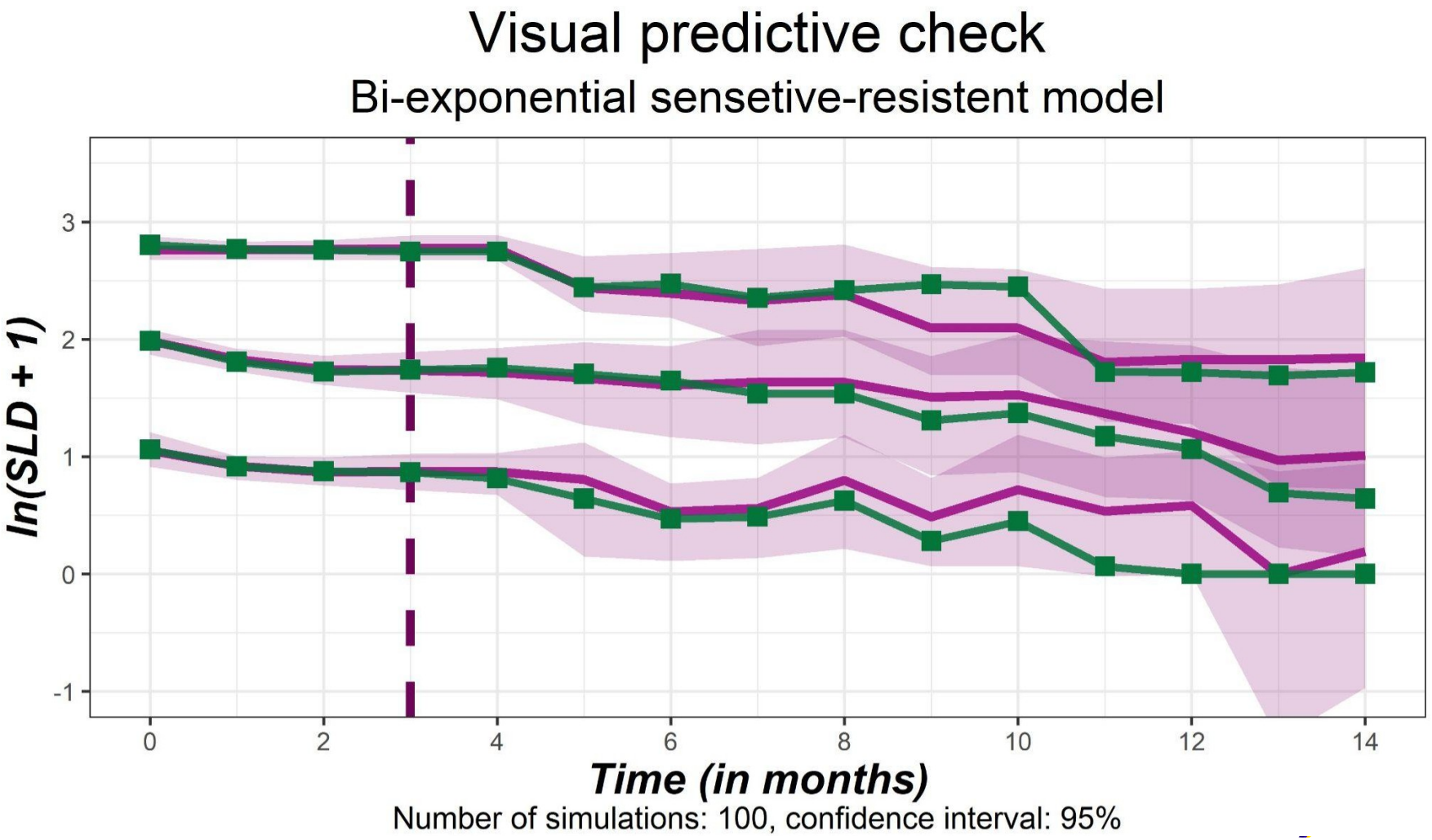
Bi-exponential model

Parameter	Value	RSE (in %)
Base	7.16	4.02
k_d	0.0125	23.3
k_g	0.0228	17
Corr. Base vs k_d	-0.33	25
Error rate const.	0.109	2.8



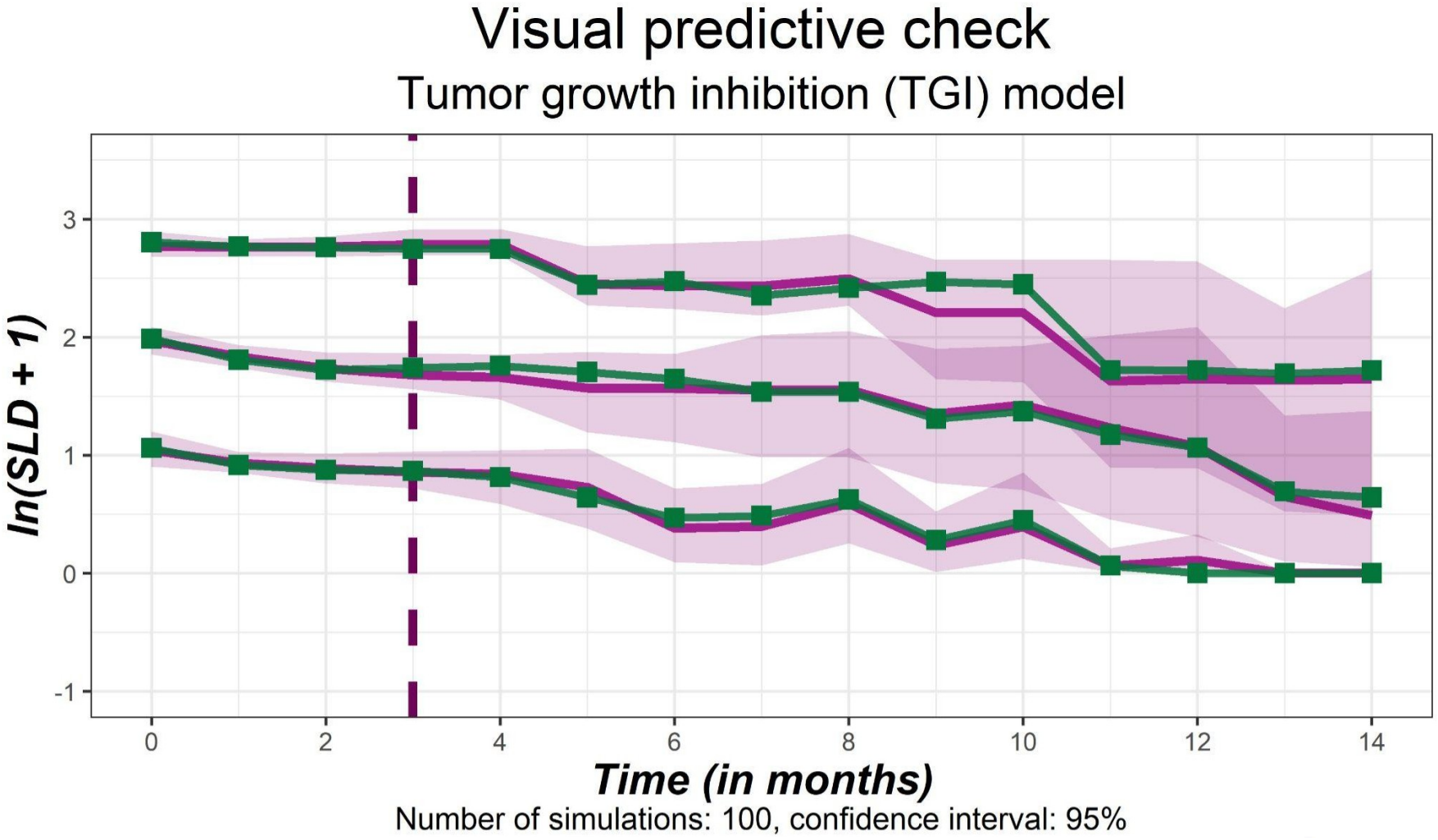
Bi-exponential sensitive-resistant model

Parameter	Value	RSE (in %)
Base	7.29	3.93
k_d	0.0093	42.7
k_g	0.0175	20.2
φ	0.84	15
Corr. Base vs k_d	-0.504	14.7
Corr. φ vs k_d	-0.584	24.3
Corr. Base vs φ	0.429	23.4
Error rate const.	0.099	2.92



TGI model

Parameter	Value	RSE (in %)
Base	7.23	3.98
k_d	0.07	28.2
k_g	0.023	17.4
λ	2.14	47.8
Corr. Base vs k_d	-0.38	25.9
Error rate const.	0.1	2.72



Conclusions

- Different modeling approaches to assess and predict longitudinal tumor size in NSCLC were investigated in this analysis.
- Traditional bi-exponential empirical model expressed high performance in the description of selected NSCLC data. However, bi-exponential sensitive-resistant and TGI models were capable of more efficient description.
- Given the considered clinical study data, the highest predictive performance was achieved by the TGI longitudinal model of SLD.

M&S Modeling & Simulation Decisions