Population modeling of tumor growth curves, the reduced Gompertz model and prediction of the age of a tumor

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BACKGROUND

- Few studies have modeled **tumor growth kinetics** with a population approach and across tumor types.
- The Gompertz model is a widely accepted model of tumor growth. Several studies have reported a strong **correlation** between the two parameters of the model.
- Prediction of the time from cancer initiation would have important clinical implications, such as the determination of invisible metastasis at diagnosis.

OBJECTIVES

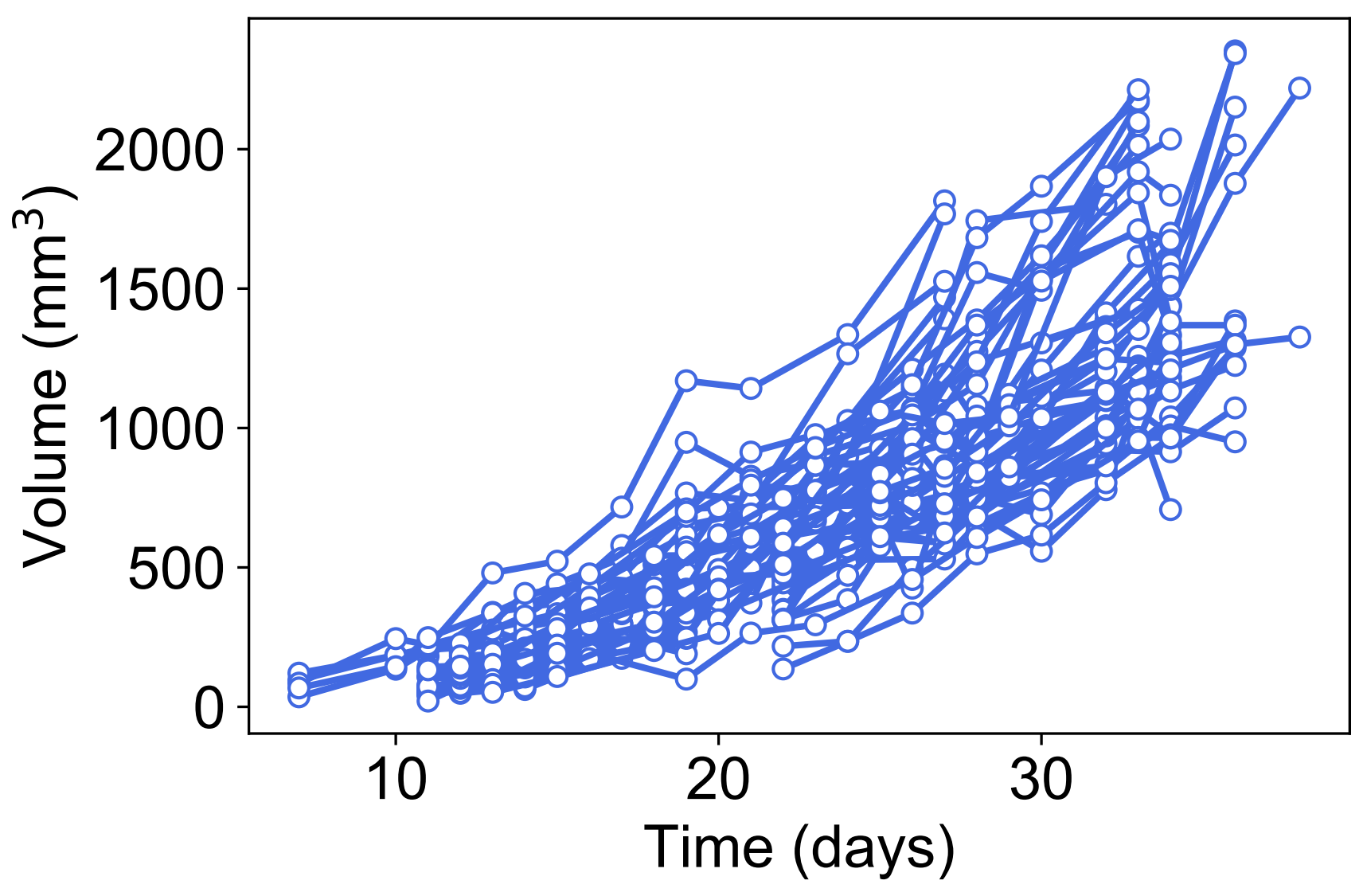
- Test the descriptive power of different tumor growth models within a population.
- Study the correlation between the parameters of the Gompertz model within a population and define a novel, simplified model: **the reduced Gompertz model**.
- Use the estimated population parameters to perform individual predictions of tumor initiation using **Bayesian inference**.

MATERIAL AND METHODS

Preclinical data

The experimental data comprised three data sets:

- Breast data measured by volume (66 animals).
- Breast data measured by fluorescence (8 animals)
- Lung tumor measured by volume (20 animals)



Breast data measured by volume.

Tumor growth models[1]

Exponential

$$\begin{cases} \frac{dV}{dt} = \alpha V \\ V(t_I) = V_I \end{cases}$$

Logistic

$$\begin{cases} \frac{dV}{dt} = \alpha V \left(1 - \left(\frac{V}{K}\right)\right) \\ V(t_I) = V_I \end{cases}$$

Gompertz

$$\begin{cases} \frac{dV}{dt} = \left(\alpha - \beta \log\left(\frac{V}{V_{\text{inj}}}\right)\right) V \\ V(t_I) = V_I \end{cases}$$

Nonlinear mixed effects modeling[2]

$$\underbrace{y_j^i}_{\substack{\text{observation}\\ \text{of individual } i\\ \text{at time } t_j^i}} = \underbrace{f(t_j^i; \theta^i)}_{\text{structural model}} + \underbrace{e_j^i}_{\text{error model}}$$

$\theta^i = \mu \exp(\eta^i)$ $\eta^i \sim \mathcal{N}(0, \omega)$ μ fixed effects, η^i random effects

$e_j^i = (\sigma_1 + \sigma_2 f(t_j^i; \theta^i))\epsilon_j^i$ $\epsilon_j^i \sim \mathcal{N}(0, 1)$ combined error model

Prediction of individual tumor age

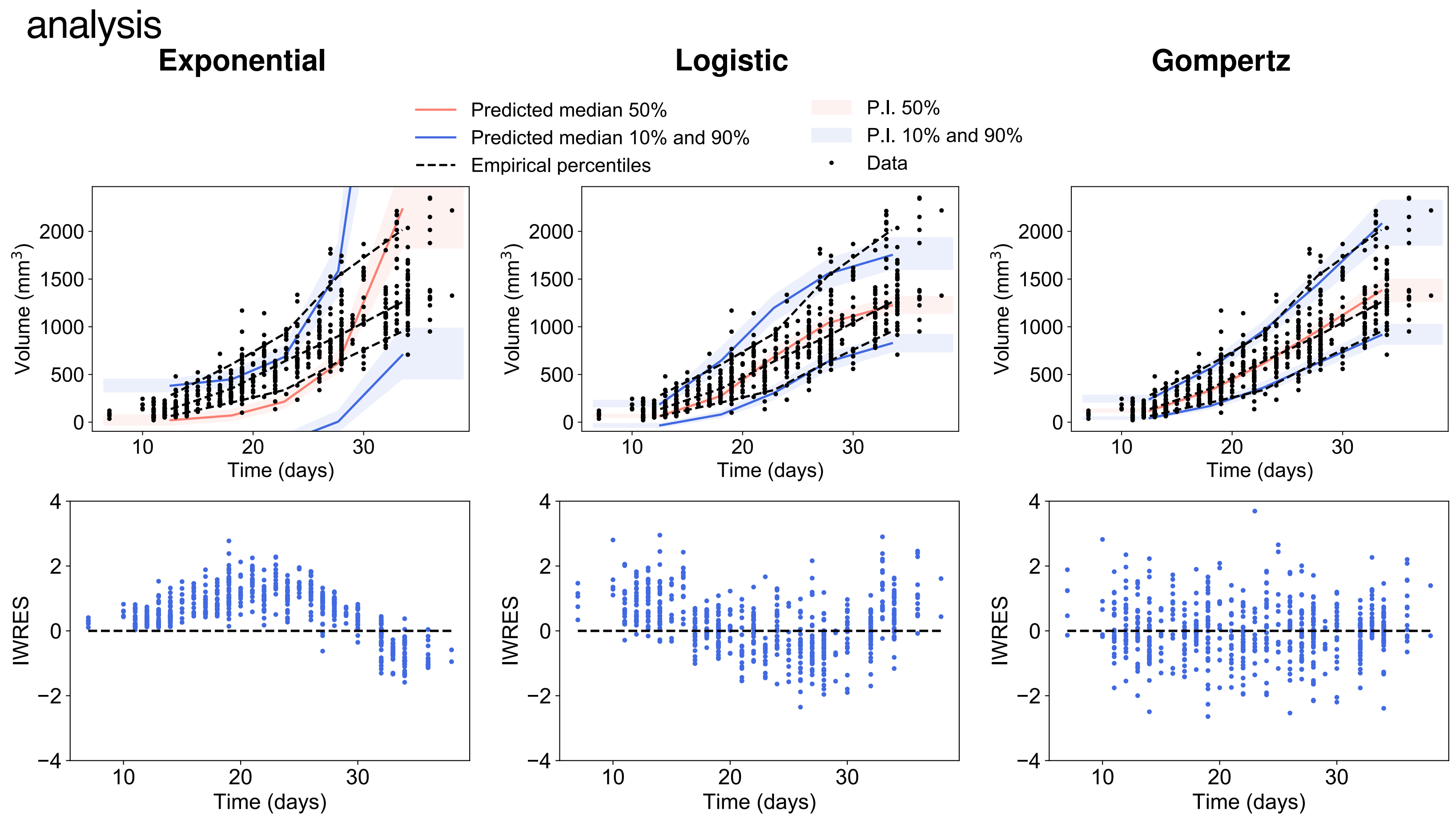
The tumor age $\hat{a}^i$ of the individual i was determined taking into account only the last three measurements. It was found according to $f\left(\hat{a}^i, \hat{\theta}^i\right) = V_{\text{inj}}$, where V_{inj} was the volume of injected cells and $\hat{\theta}^i$ was estimated by:

- Likelihood maximization (LM)
- Bayesian inference[3]: the population parameter distribution was considered as prior information. k-fold cross validation was performed (leave-one-out strategy).

RESULTS

Population analysis

- The optimal fits of the Exponential and Logistic models were unable to give appropriate description of the data
- The Gompertz model demonstrated excellent goodness-of-fit in all the experimental systems that we investigated
- Correlation between the individual parameters of the Gompertz model was observed in our analysis



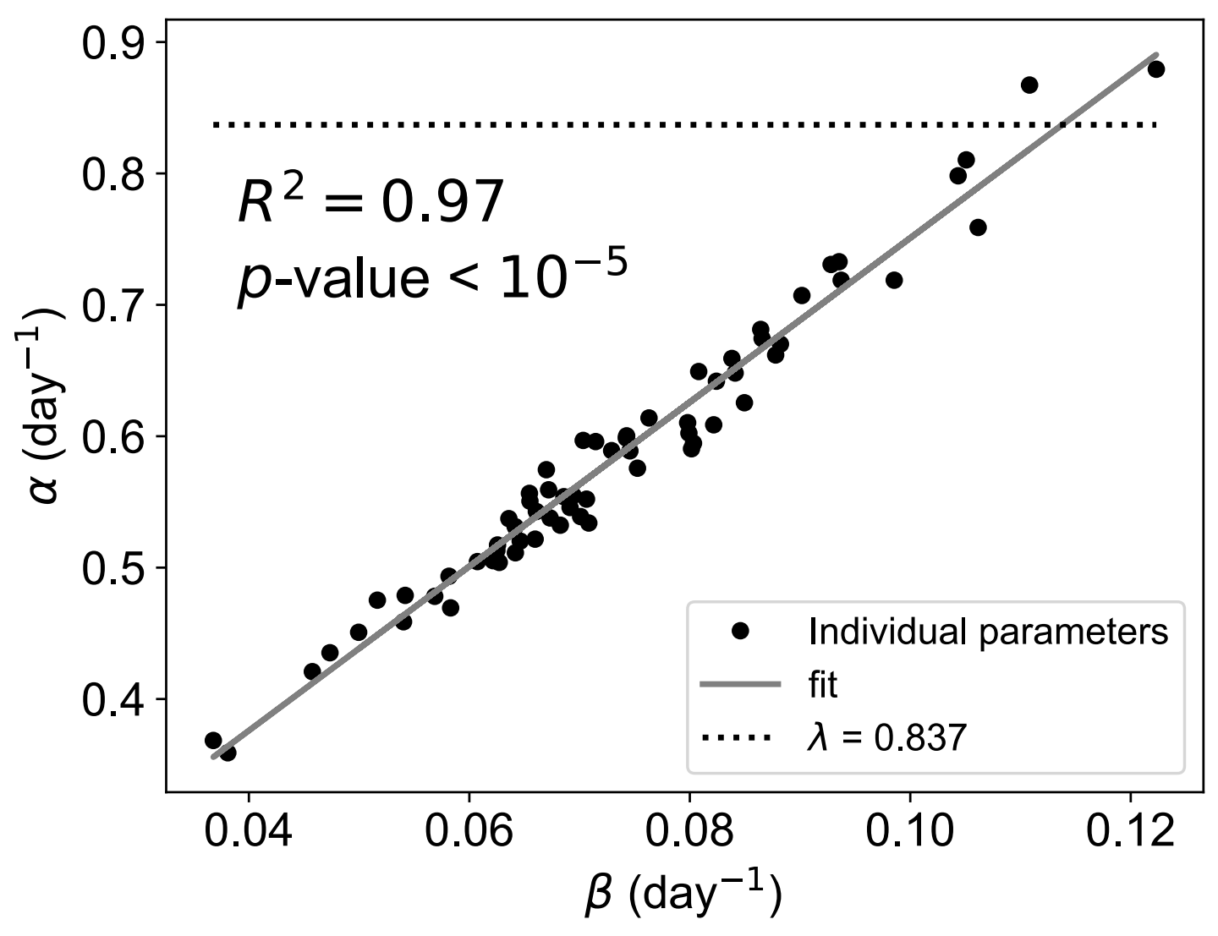
VPCs and scatterplot of the individual weighted residuals (IWRES) of the different tumor growth models (breast, volume).

The reduced Gompertz model

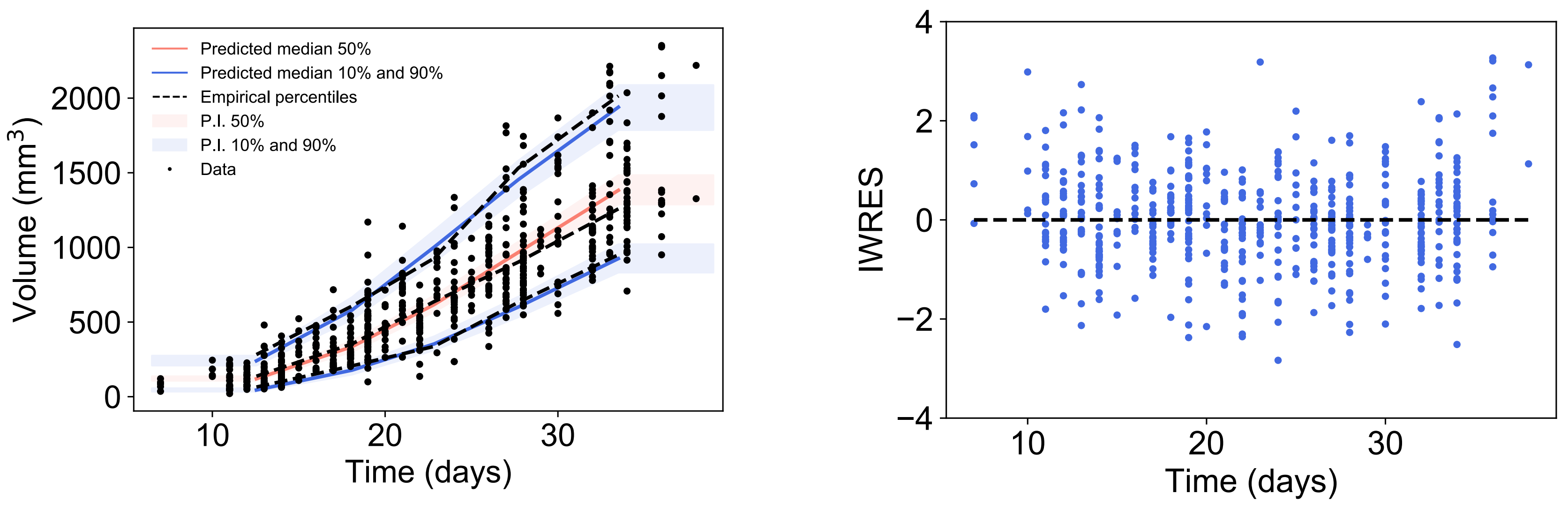
We considered $\alpha^i = k\beta^i$, where k could be a characteristic constant of tumor growth within a given animal model.

$$\begin{cases} \frac{dV}{dt} = \left(k\beta^i - \beta^i \log\left(\frac{V}{V_{\text{inj}}}\right)\right) V \\ V(t_I) = V_I \end{cases}$$

Fixed effects



Correlation of the Gompertz parameters

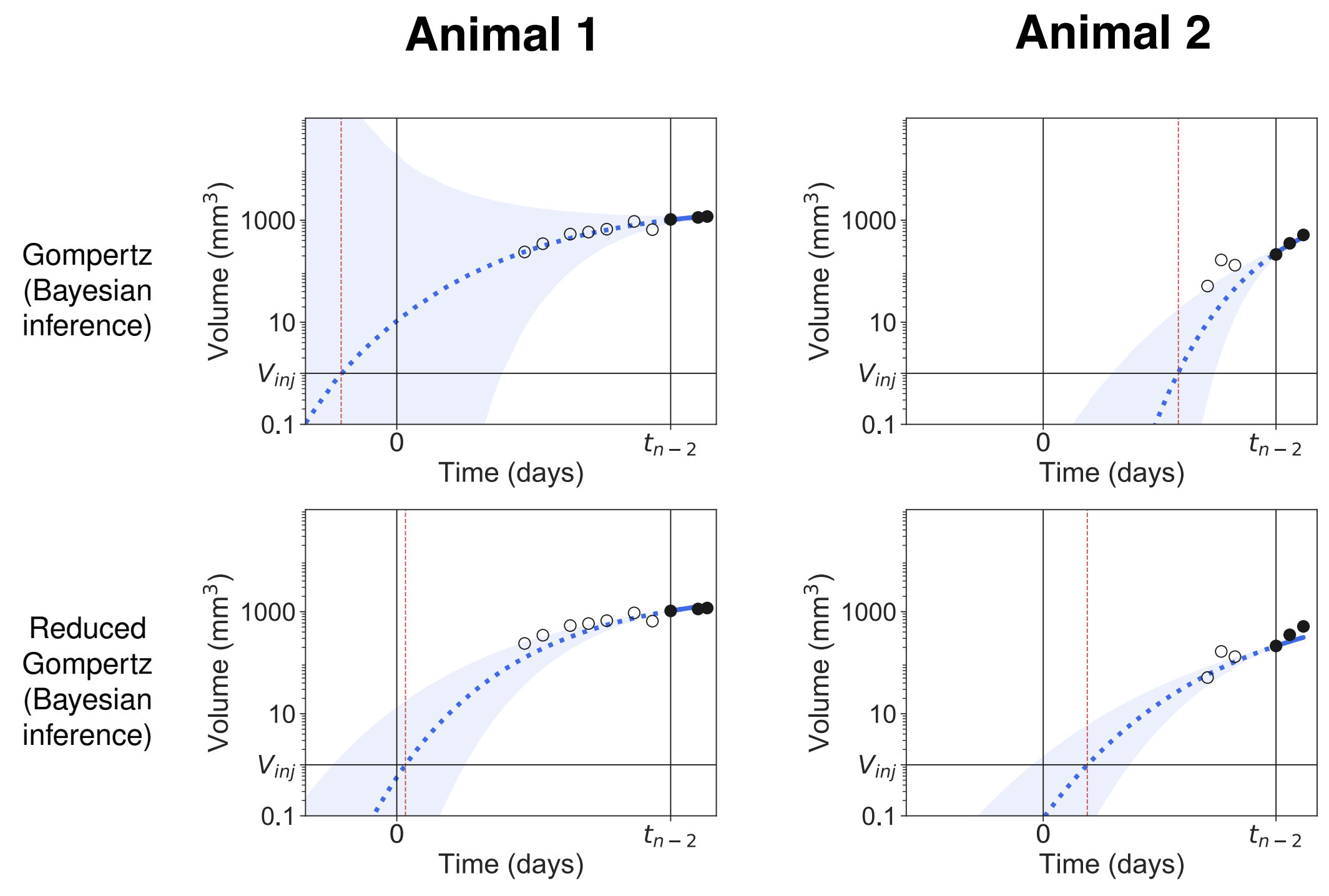


VPC and scatterplot of the individual weighted residuals (IWRES) of the reduced Gompertz model (breast, volume).

Prediction of individual tumor age

- Thanks to its simplicity, the **reduced Gompertz model showed superior predictive power**.
- Drastic improvements were observed when leveraging population priors using Bayesian inference, both in terms of **accuracy** and **precision**.

Two examples of individual tumor age predictions (breast, volume). →



Accuracy and precision of methods for prediction of the age of experimental tumors of the three data sets.
Reported are the means and standard errors (in parenthesis) ↓

Cell line	Model	Method	Accuracy (%)	Precision (days)
Breast, volume	Reduced Gompertz	Bayesian	12.1 (1.02)	15.2 (0.503)
	Reduced Gompertz	LM	74.1 (11.6)	186 (52.8)
	Gompertz	Bayesian	19.6 (1.77)	40.1 (1.94)
	Gompertz	LM	205 (55.4)	-
Lung, volume	Reduced Gompertz	Bayesian	9.4 (1.57)	7.34 (0.33)
	Reduced Gompertz	LM	66.1 (31)	81.6 (71.7)
	Gompertz	Bayesian	19.6 (2.99)	18.2 (2.38)
	Gompertz	LM	175 (69.6)	-
Breast, fluorescence	Reduced Gompertz	Bayesian	12.3 (2.9)	23.6 (5.15)
	Reduced Gompertz	LM	91.7 (21.1)	368 (223)
	Gompertz	Bayesian	13.5 (3.5)	45.4 (4.43)
	Gompertz	LM	236 (150)	-

CONCLUSIONS AND PERSPECTIVES

- The Gompertz model described well tumor growth kinetics.
- The combination of **nonlinear mixed effects modelling and Bayesian inference** allowed to have reliable predictions of individual tumor age.
- The reduced Gompertz model fitted well the data and improved predictions in terms of accuracy and precision.
- The method proposed herein remains **to be extended to clinical data**. Personalized estimations of the age of a given patient's tumor would yield important epidemiological insights and could also be informative in routine clinical practice.

References

1. Benzekry S. et al., Classical Mathematical Models for Description and Prediction of Experimental Tumor Growth. PLoS Comput Biol. (2014)
2. Monolix Version 2018R2. Lixoft SAS (2018)
3. Carpenter B. et al., Stan: A Probabilistic Programming Language. J Stat Softw. (2017)