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Cristina Vaghi. Combining Population Modeling and Bayesian Inference for Tumor Growth Prediction. SMB 2019 annual meeting, Jul 2019, Montreal, Canada. hal-02424592

HAL Id: hal-02424592

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Submitted on 27 Dec 2019

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Combining Population Modeling and Bayesian Inference for Tumor Growth Prediction

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SMB 2019
Montreal, July 22nd 2019



Motivations

- 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 [1].
- 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**.

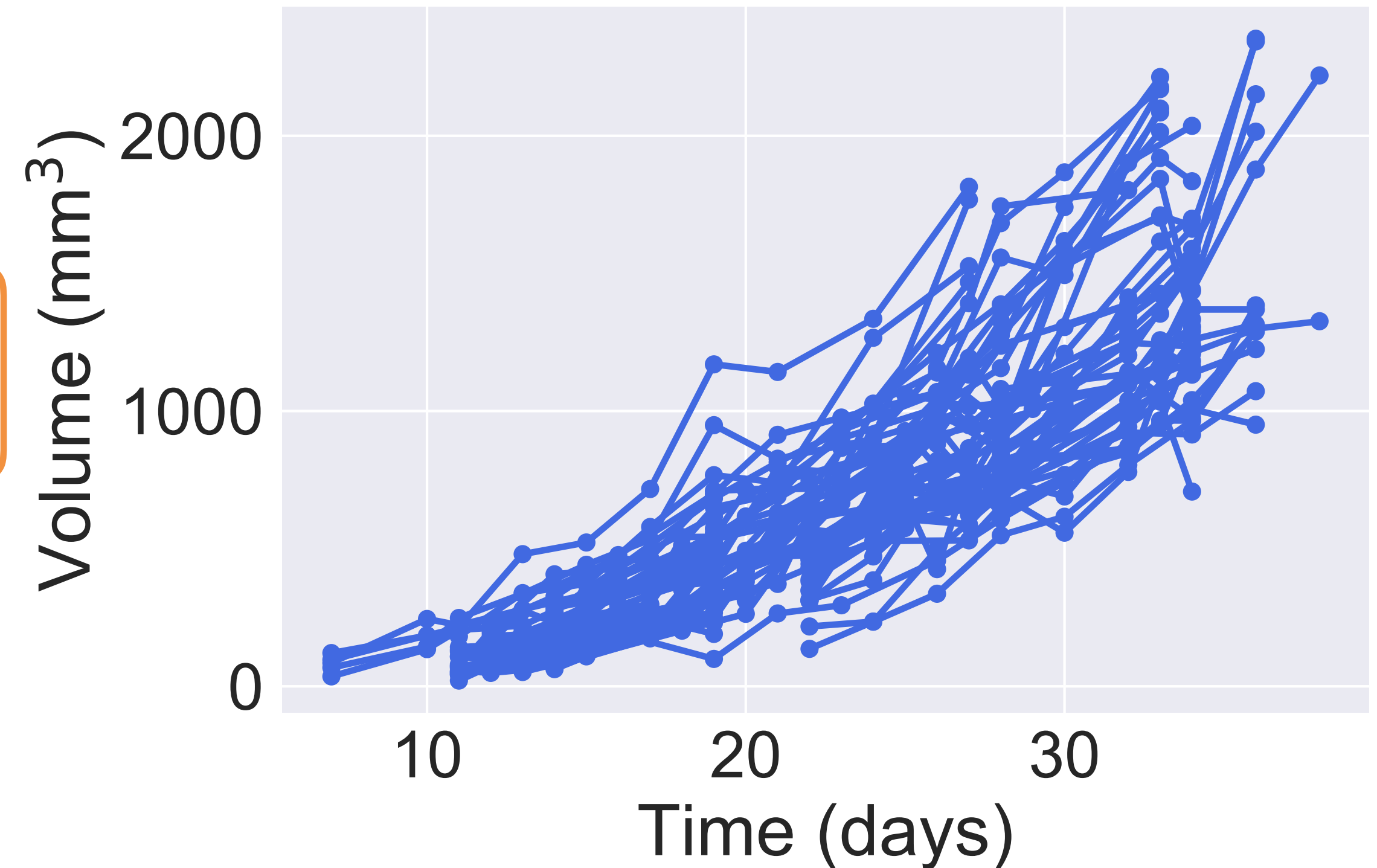
Outline

- Material and methods
 - ▶ Preclinical data
 - ▶ Tumor growth models
 - ▶ Nonlinear mixed effects modeling: population approach
 - ▶ Bayesian inference
- Results
 - ▶ Population analysis
 - ▶ The reduced Gompertz model
 - ▶ Backward prediction of the initiation time of the tumor
- Conclusions

Material and methods

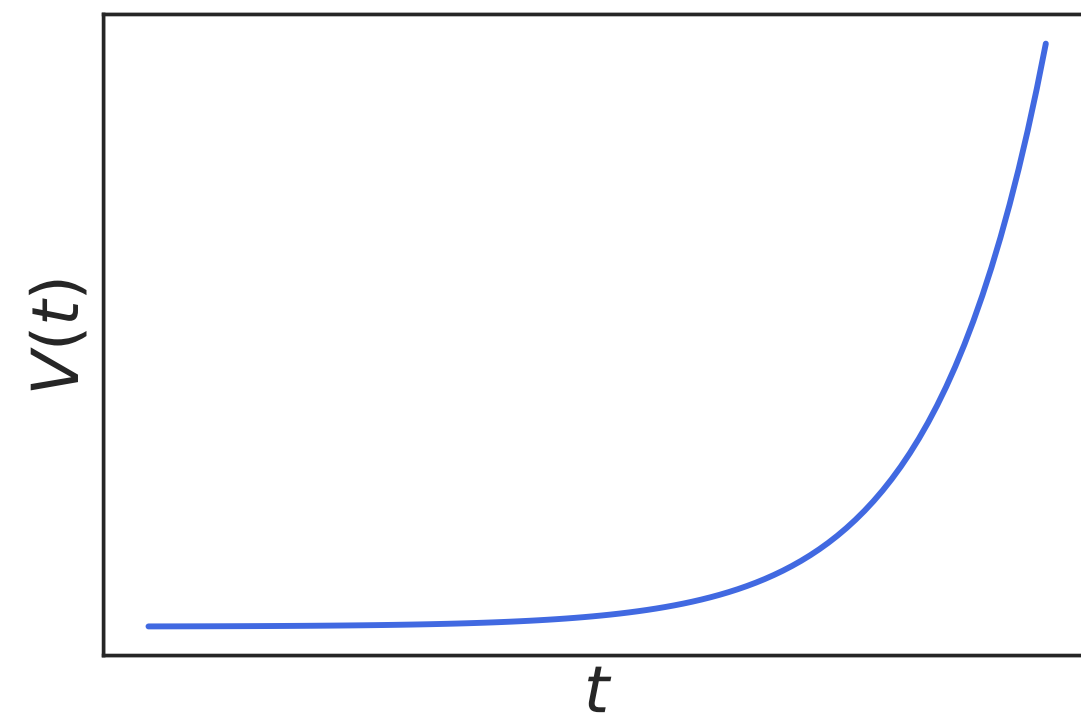
Data

- Preclinical data
- Longitudinal measurements of the primary tumor
- Three data sets:
 - ▶ Breast cancer (volume data): 66 individuals (J. Ebos et al., Roswell Cancer Park)
 - ▶ Breast cancer (fluorescence data): 8 individuals (A. Rodallec et al., SMARTc team)
 - ▶ Lung cancer (volume data): 20 individuals (S. Benzekry, C. Lamont, Center of Cancer and System Biology)



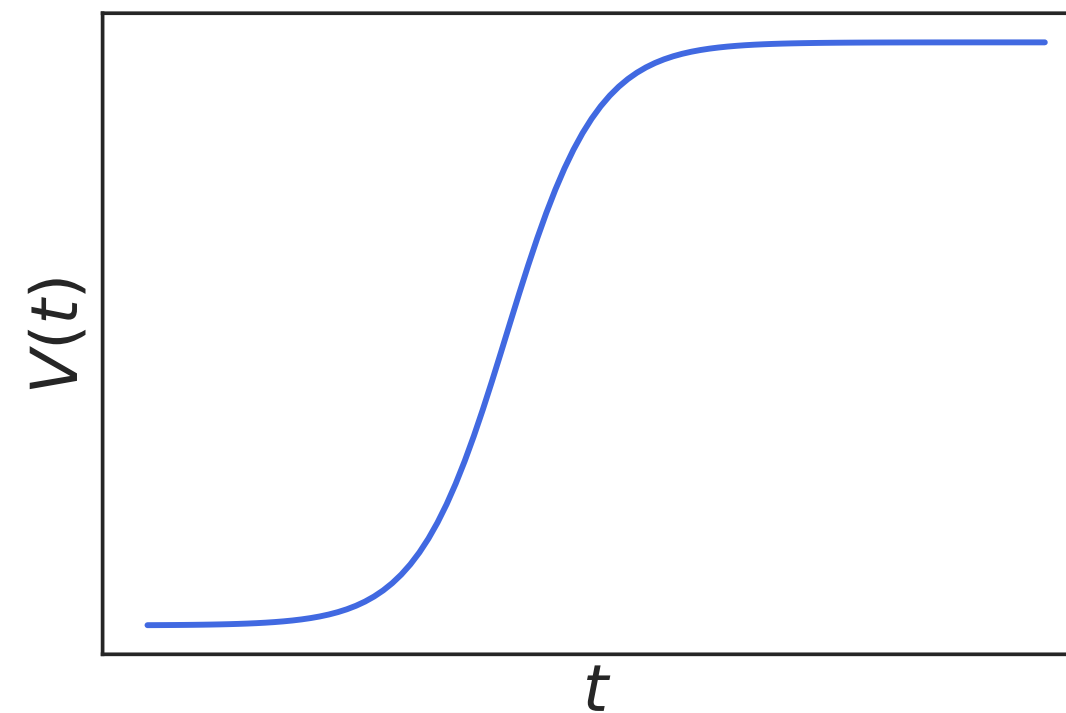
Material and methods

Tumor growth models



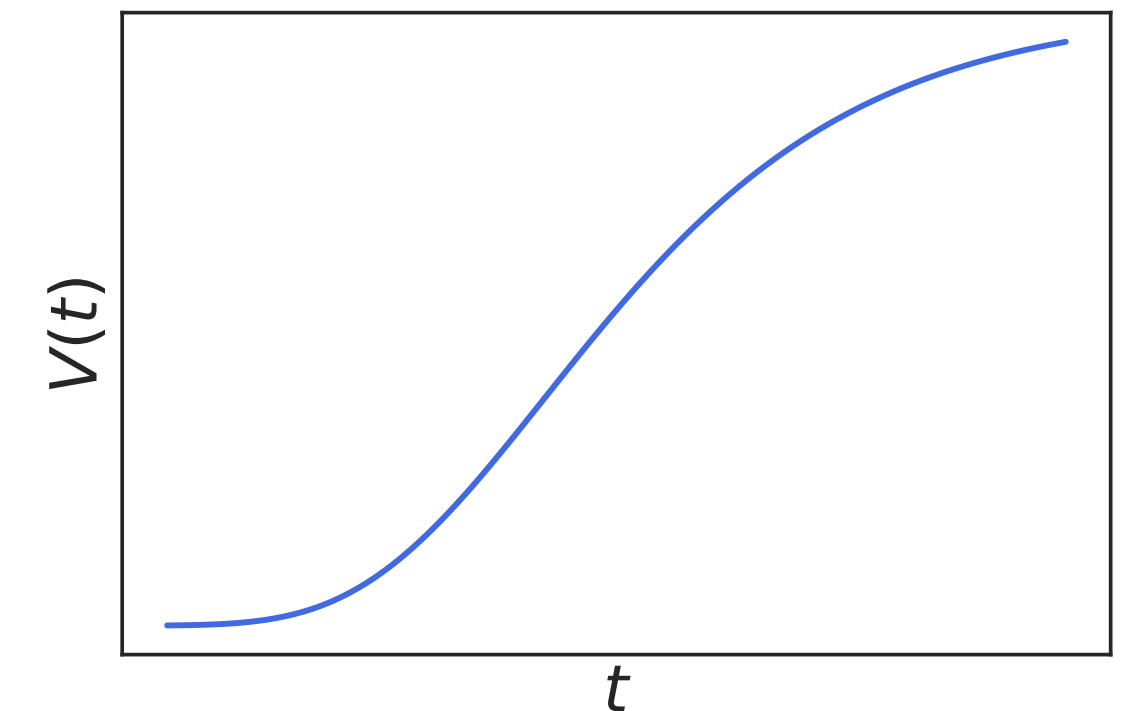
Exponential

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



Logistic

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



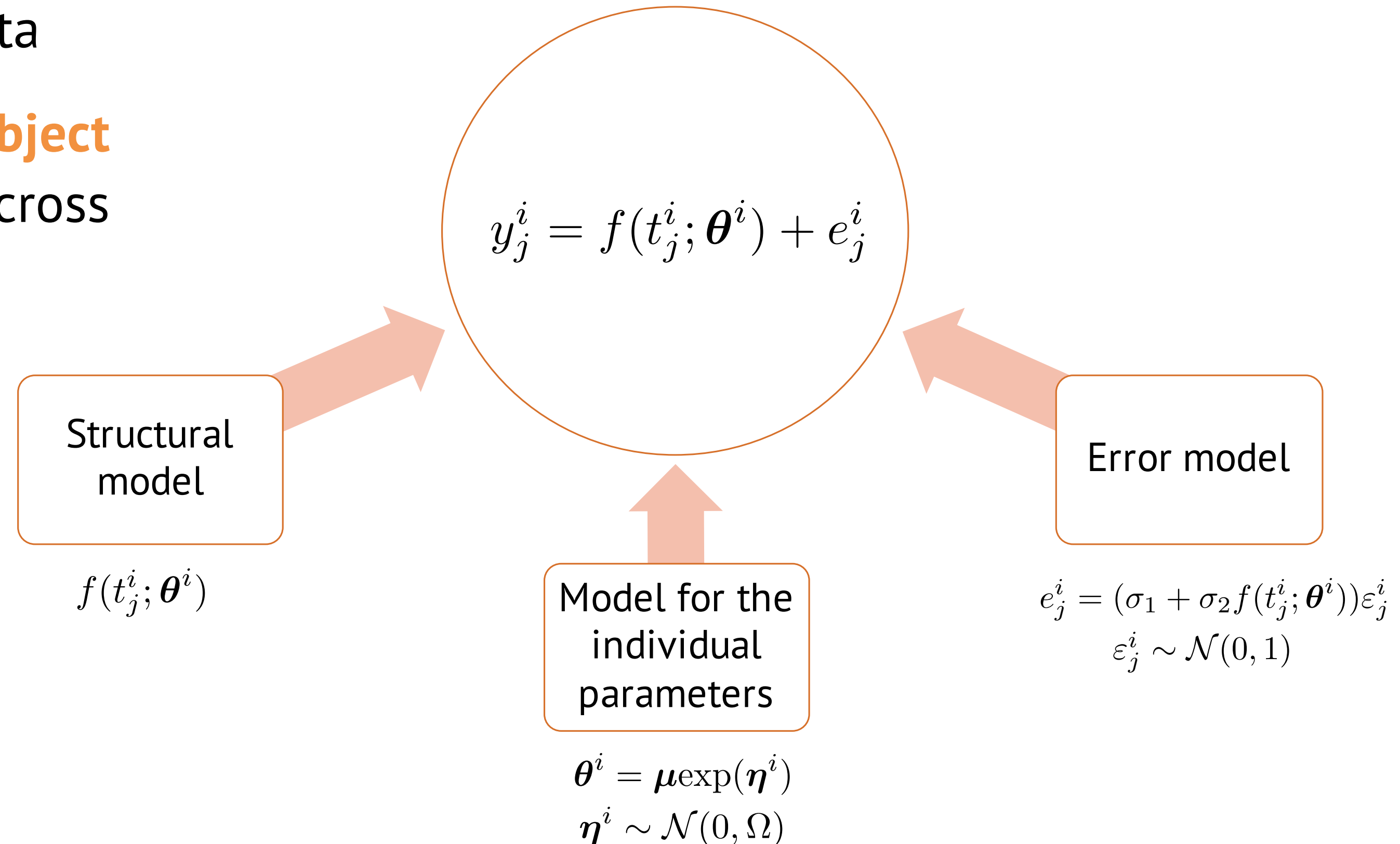
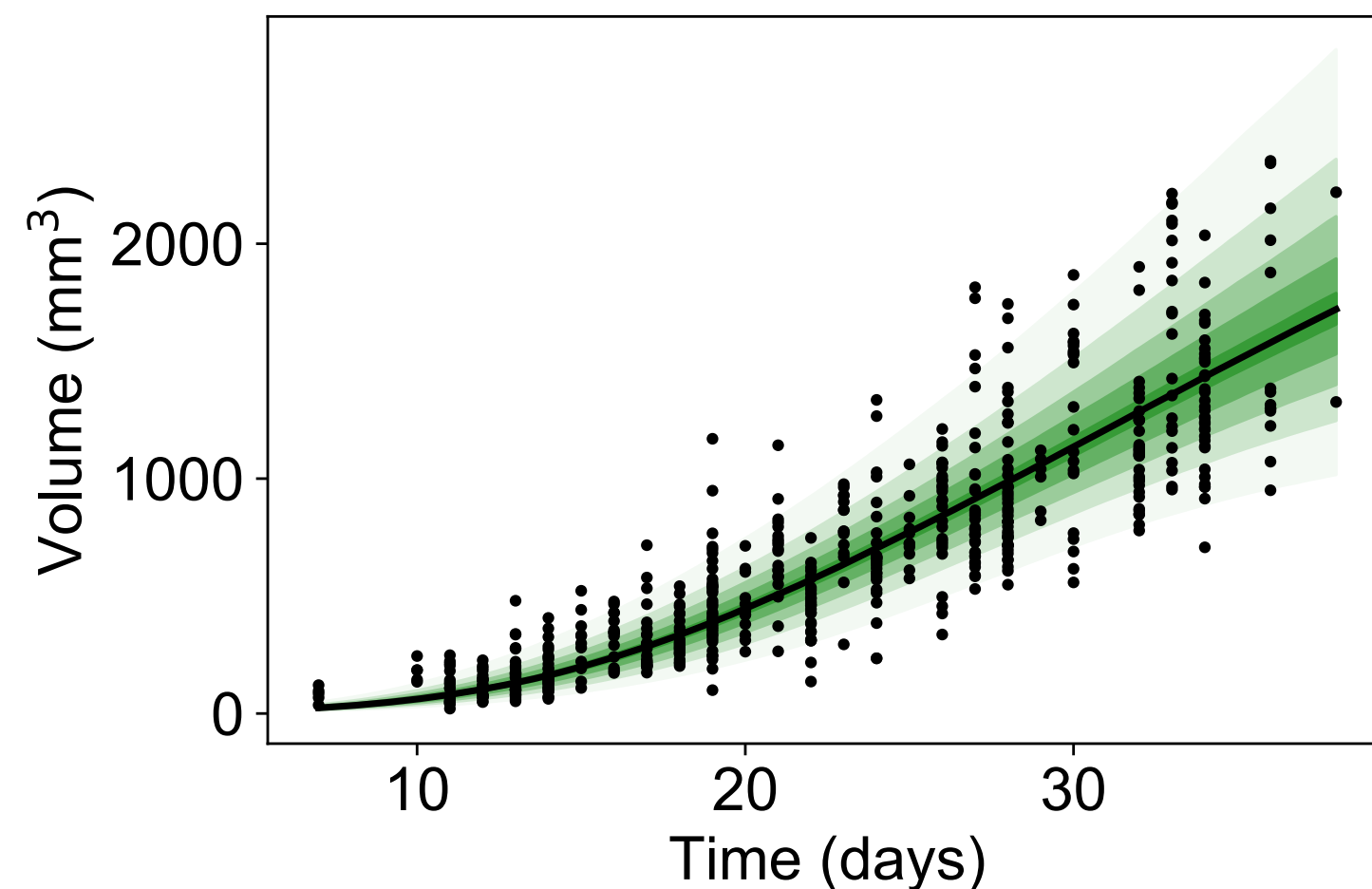
Gompertz

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

Material and methods

Nonlinear mixed effects modeling

- Statistical framework to study longitudinal data
- The goal is to understand the **intra-subject process** of tumor growth and its **variability** across the individuals



Material and methods

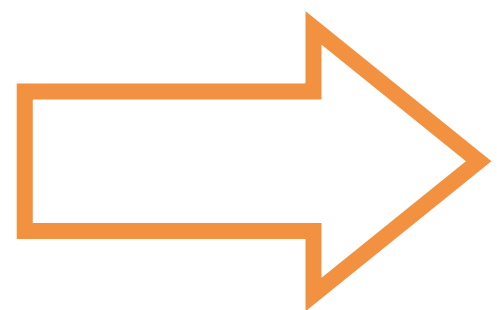
Bayesian inference

$$\underbrace{p(\boldsymbol{\theta}^j | \mathbf{y}^j; \phi)}_{\text{posterior distribution}} = \underbrace{p(\boldsymbol{\theta}^j; \phi)}_{\text{prior distribution}} \underbrace{p(\mathbf{y}^j | \boldsymbol{\theta}^j; \phi)}_{\text{likelihood}}$$

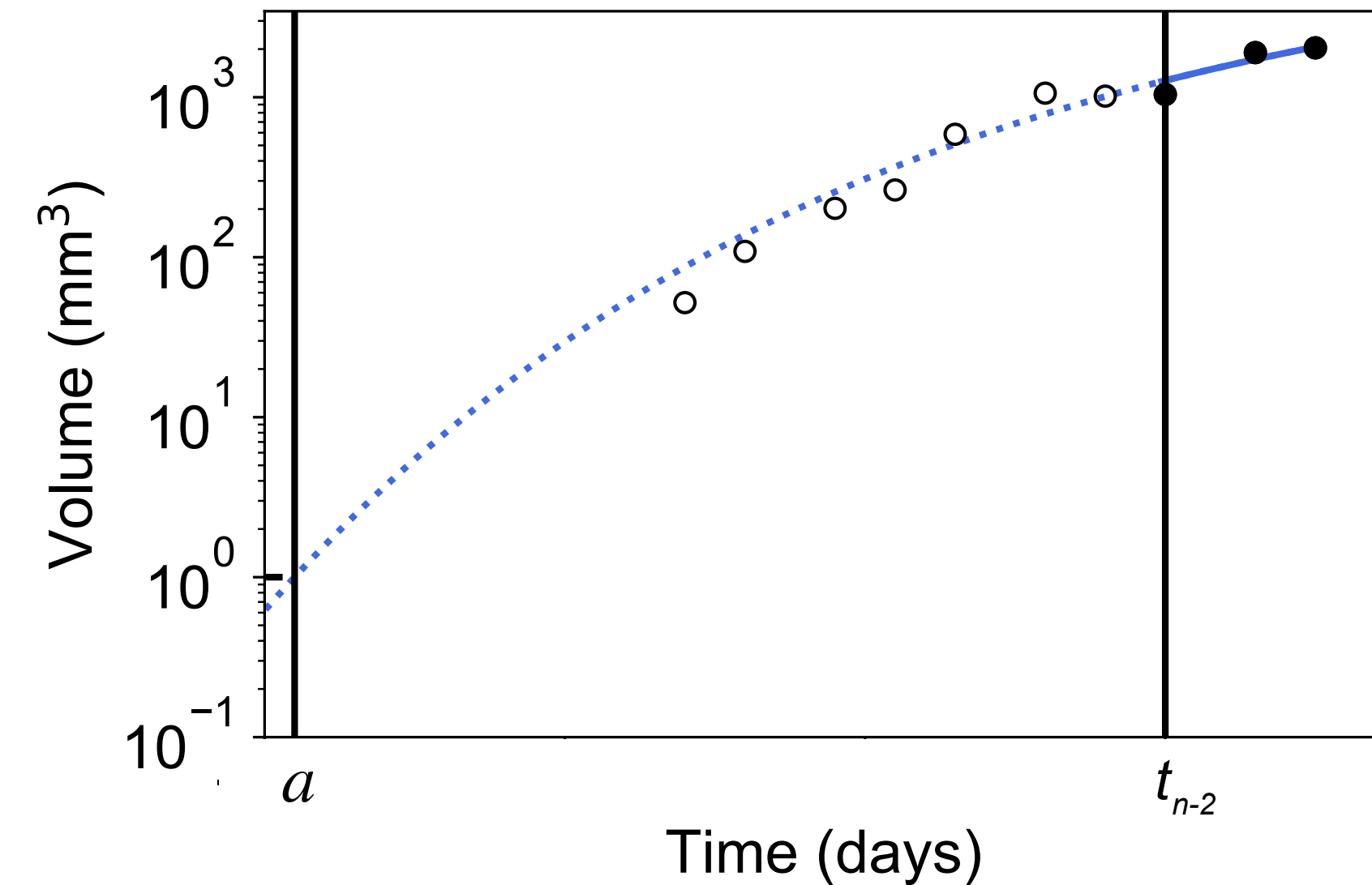
Algorithm:

- Draw a realization from the posterior distribution

- Compute $a_{pred}^{(l)i} = f^{-1}(V_{inj}; \boldsymbol{\theta}^{(l)i}), l = 1, \dots, L$



k-fold cross validation

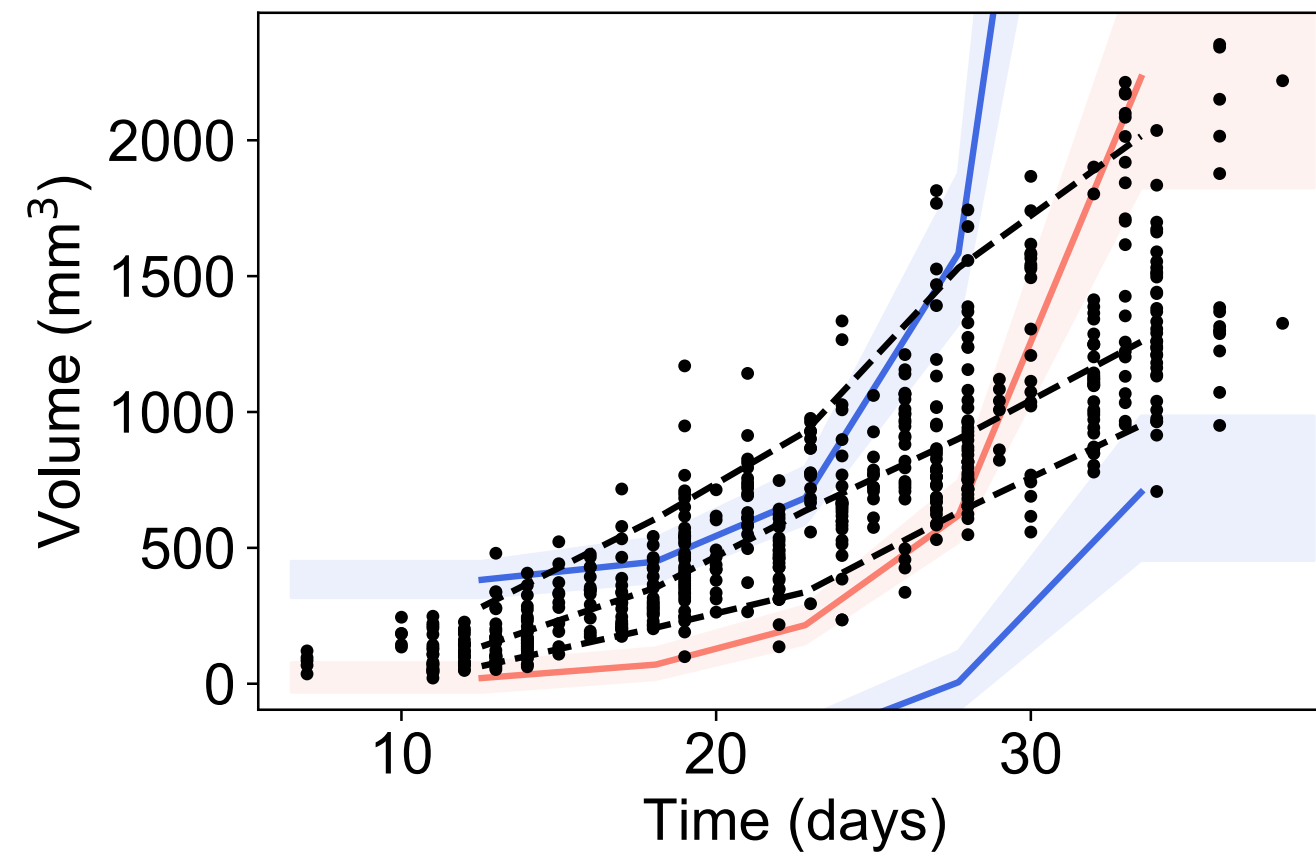


$$\text{err}^i = \frac{a_{pred}^i - a^i}{a^i}$$

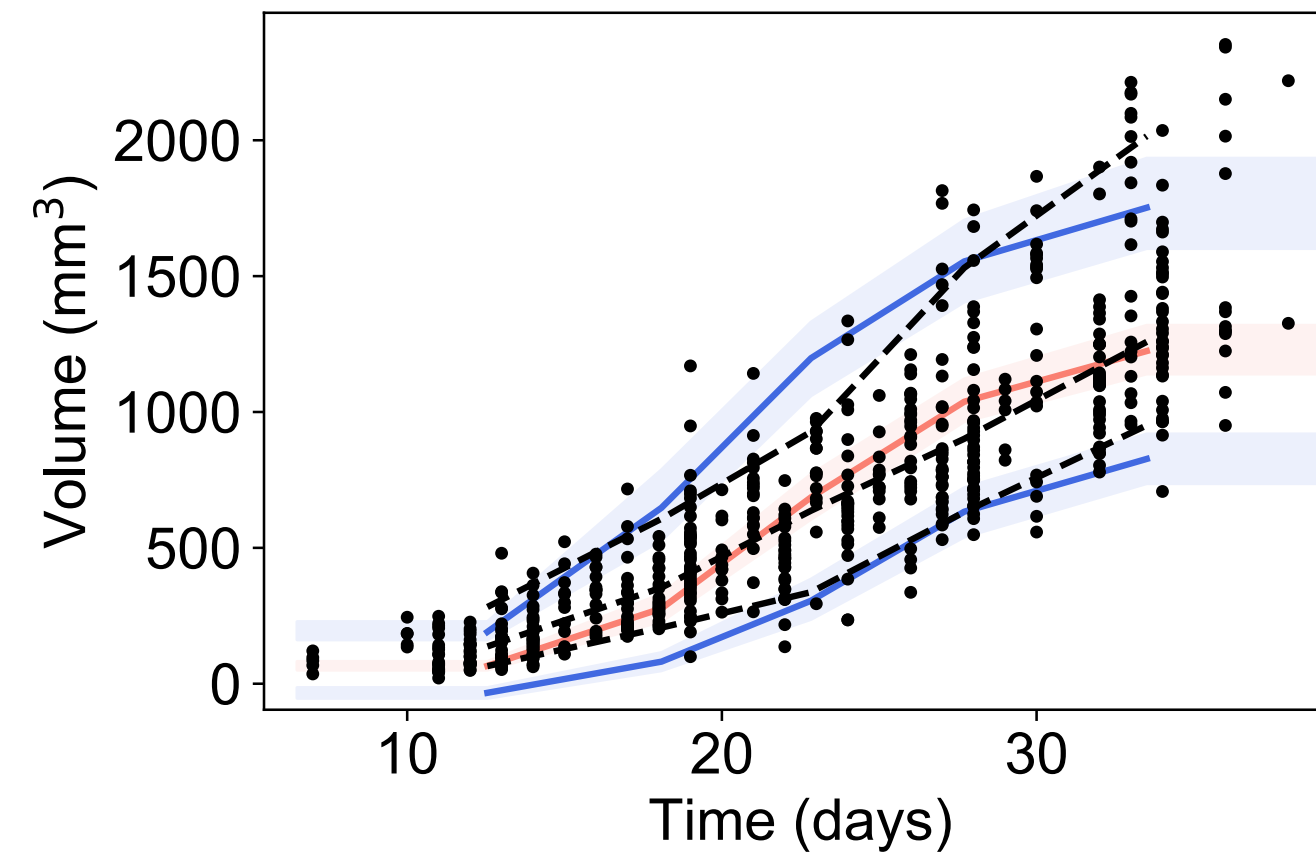
Results

Population analysis

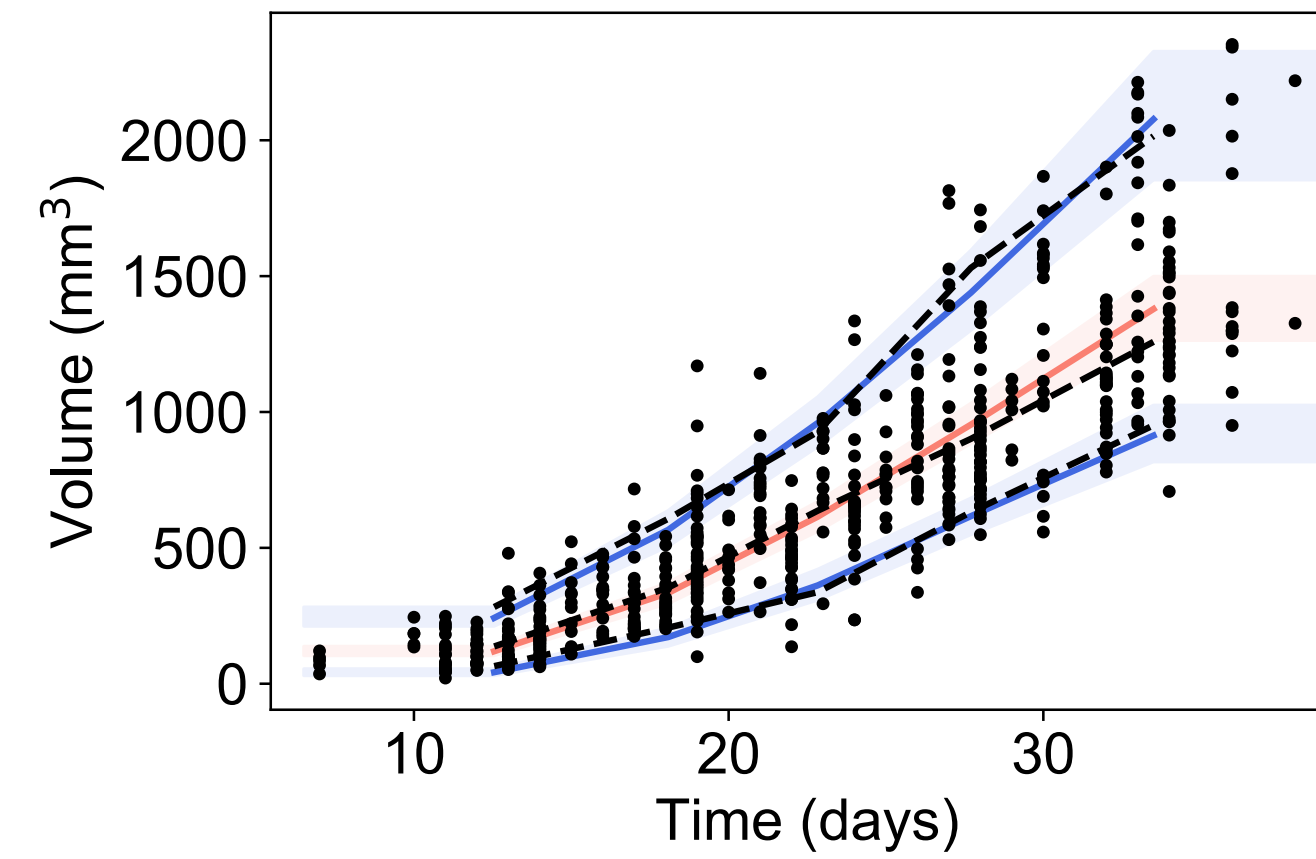
Exponential



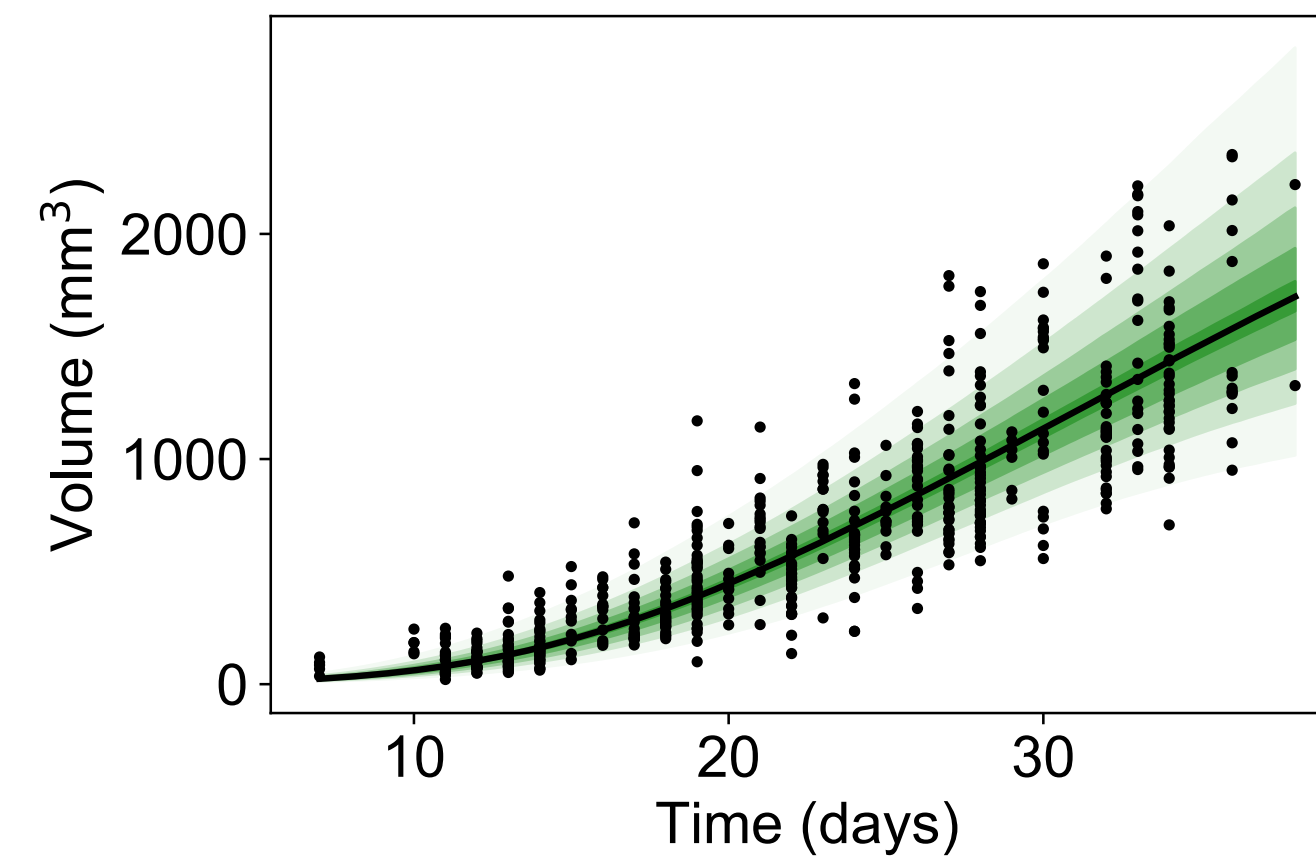
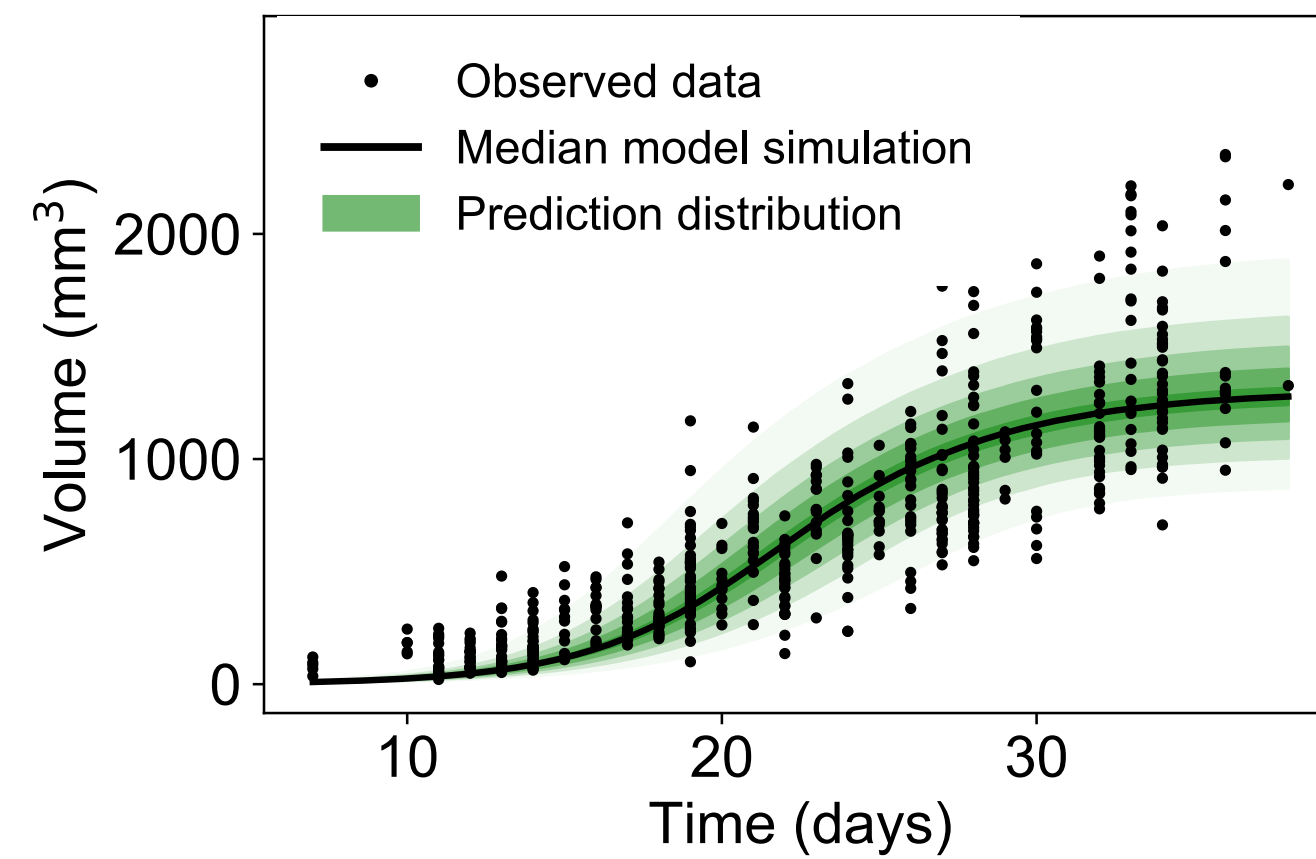
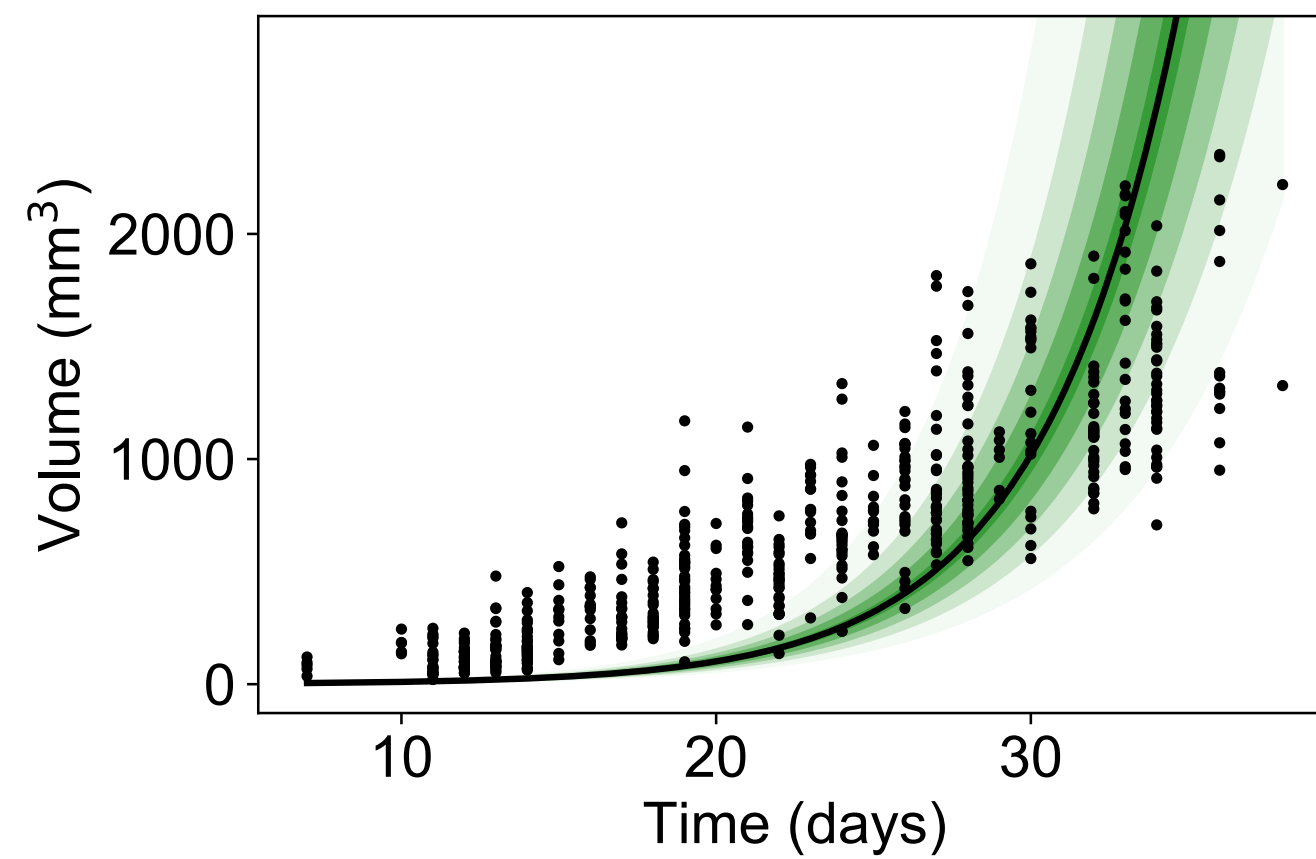
Logistic



Gompertz



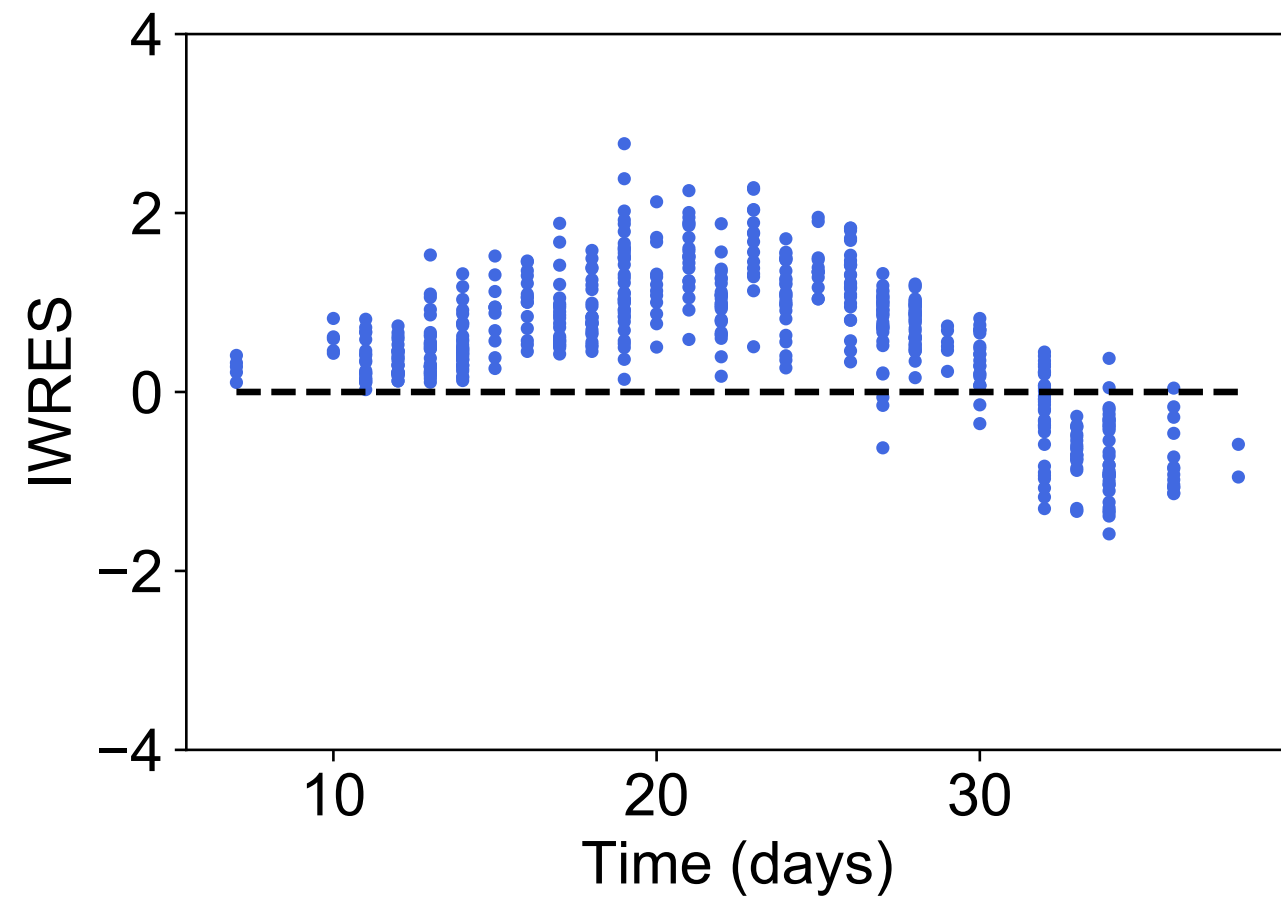
- Predicted median 50%
- Predicted median 10% and 90%
- - - Empirical percentiles
- P.I. 50%
- P.I. 10% and 90%
- Data



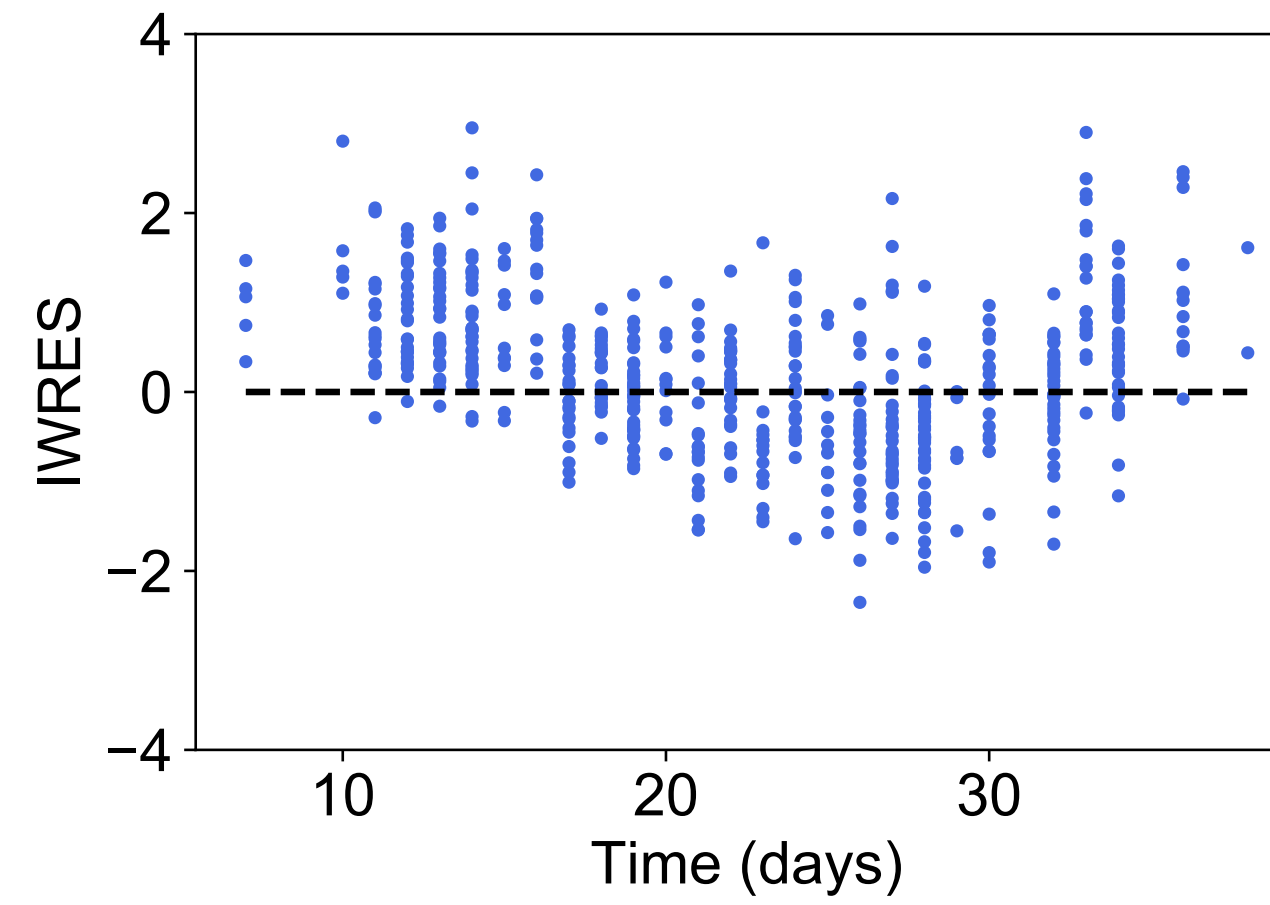
Results

Population analysis

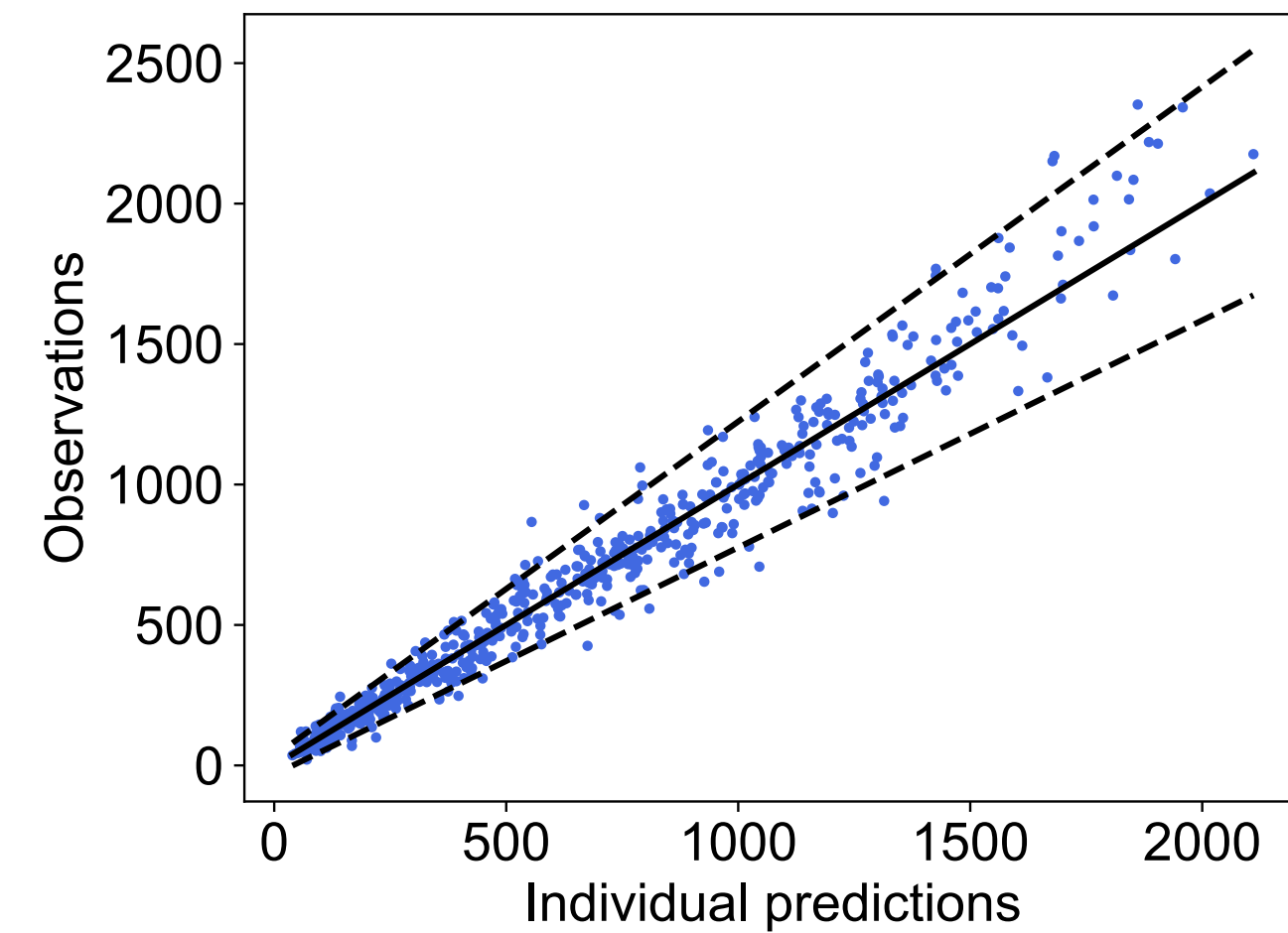
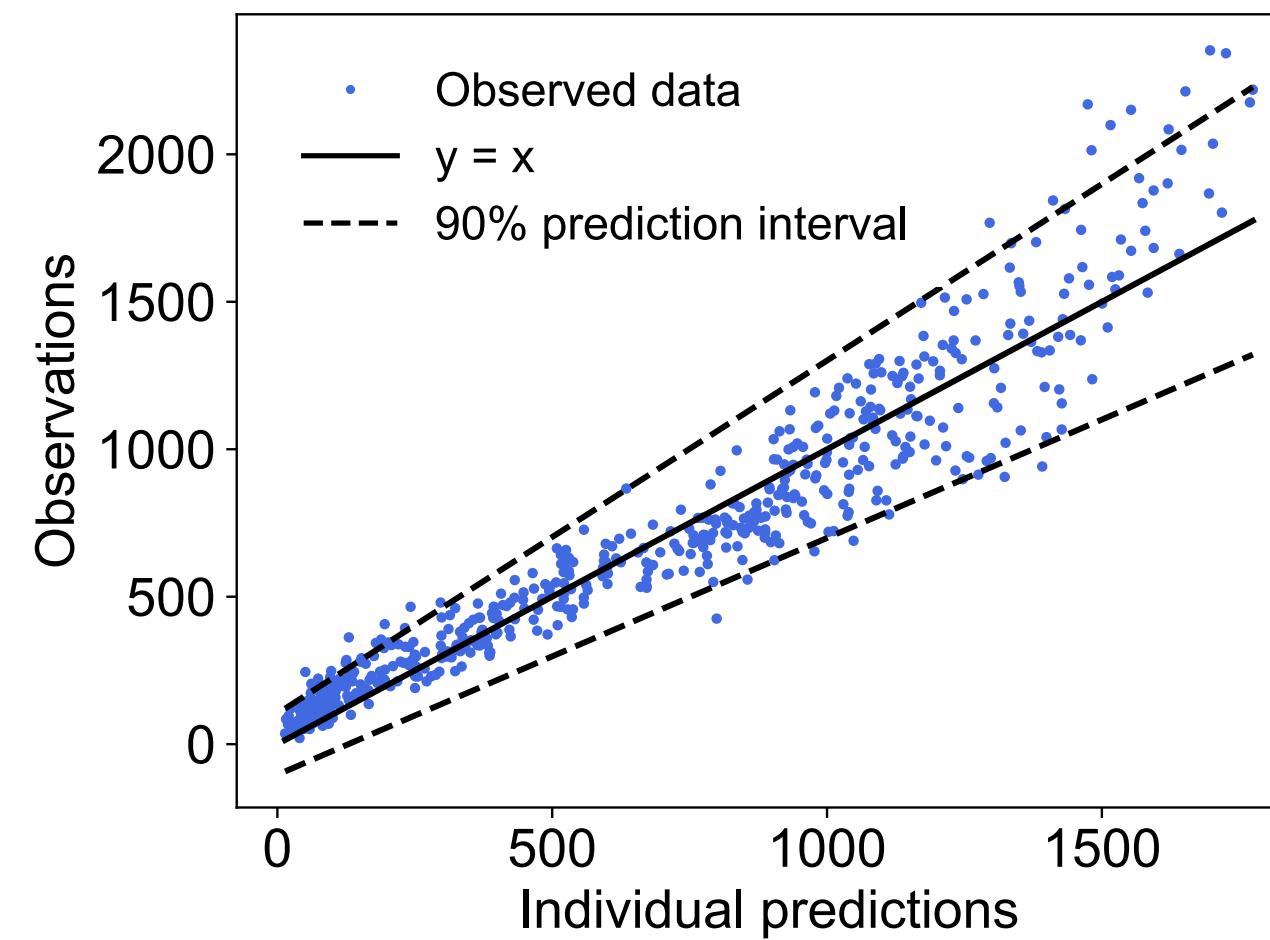
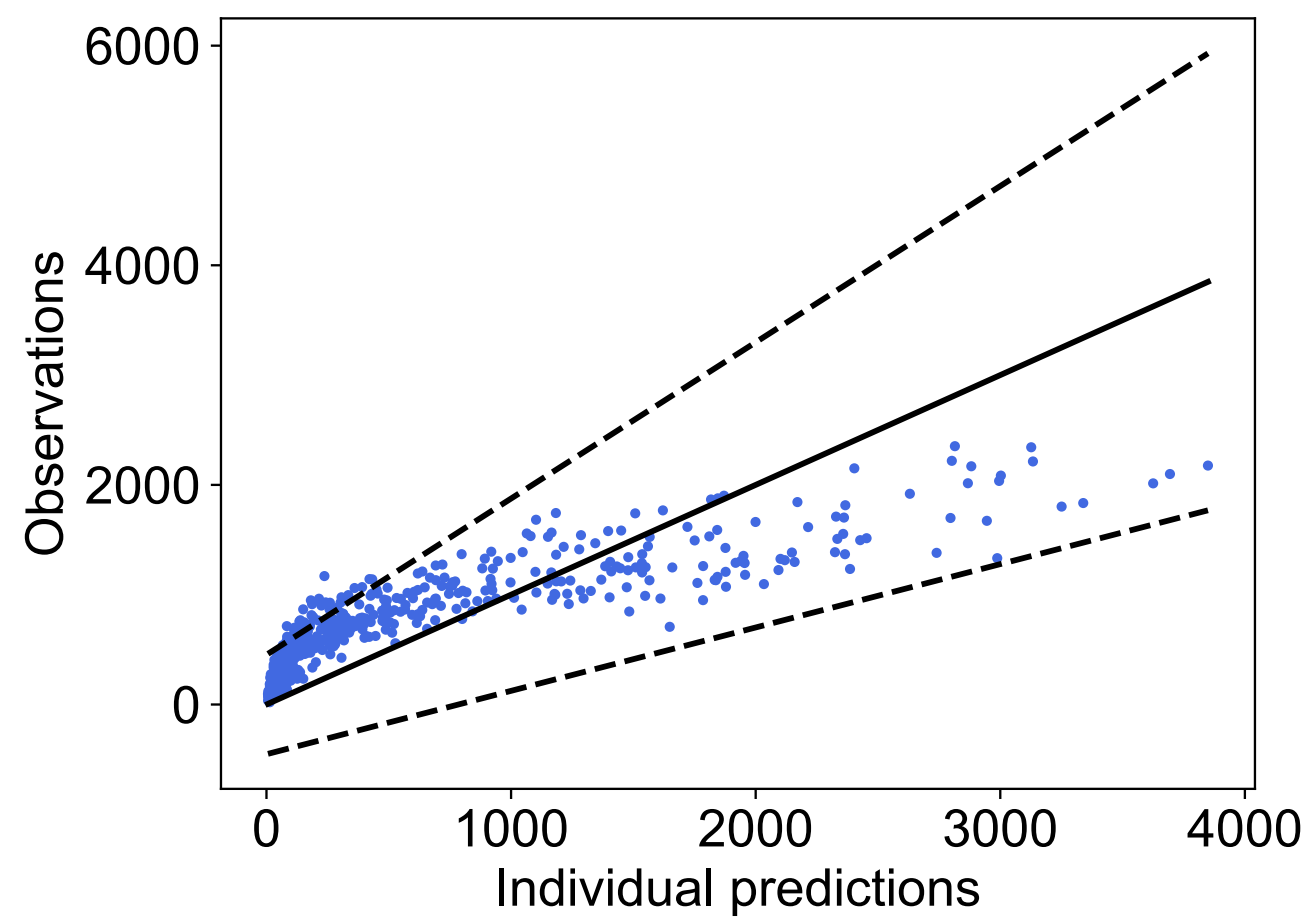
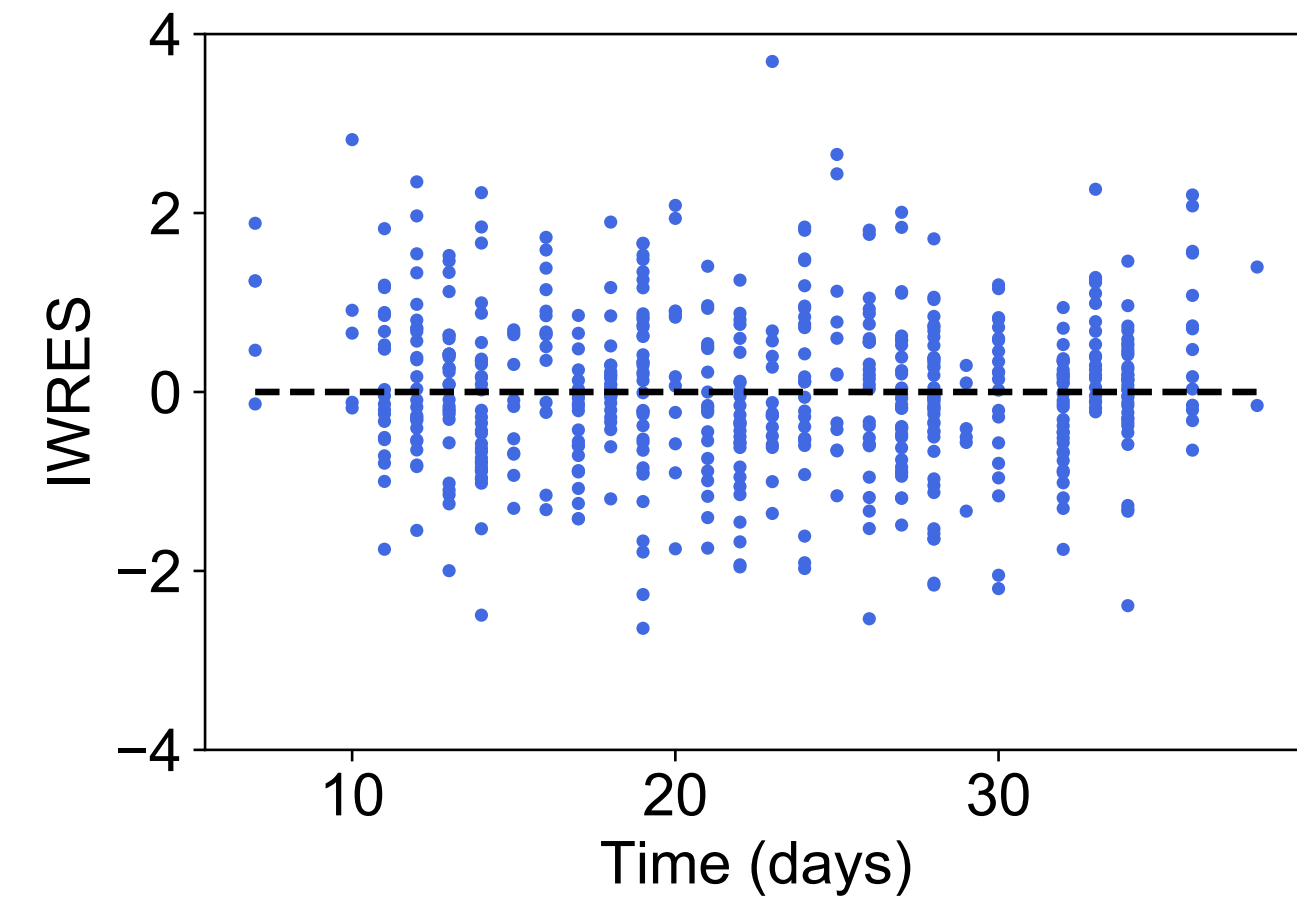
Exponential



Logistic

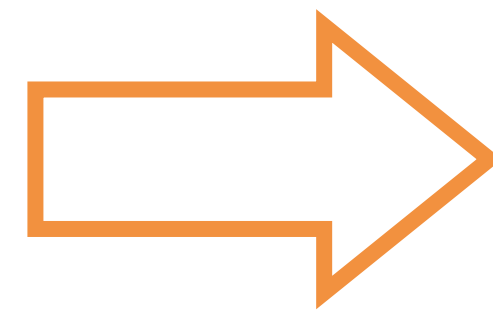
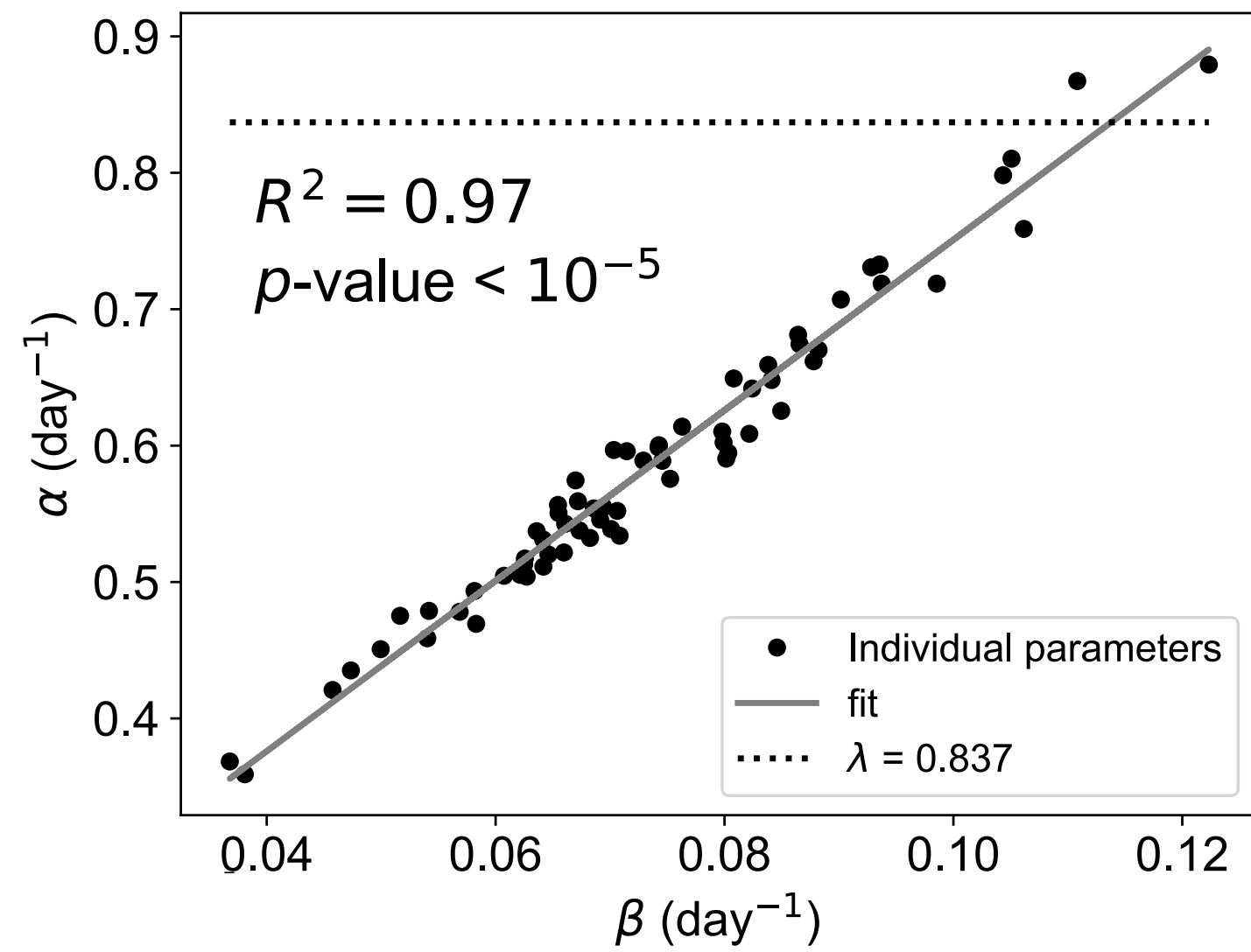


Gompertz

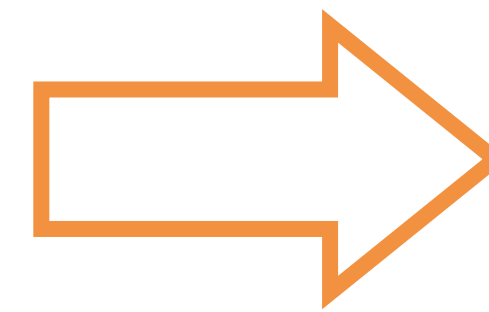


Results

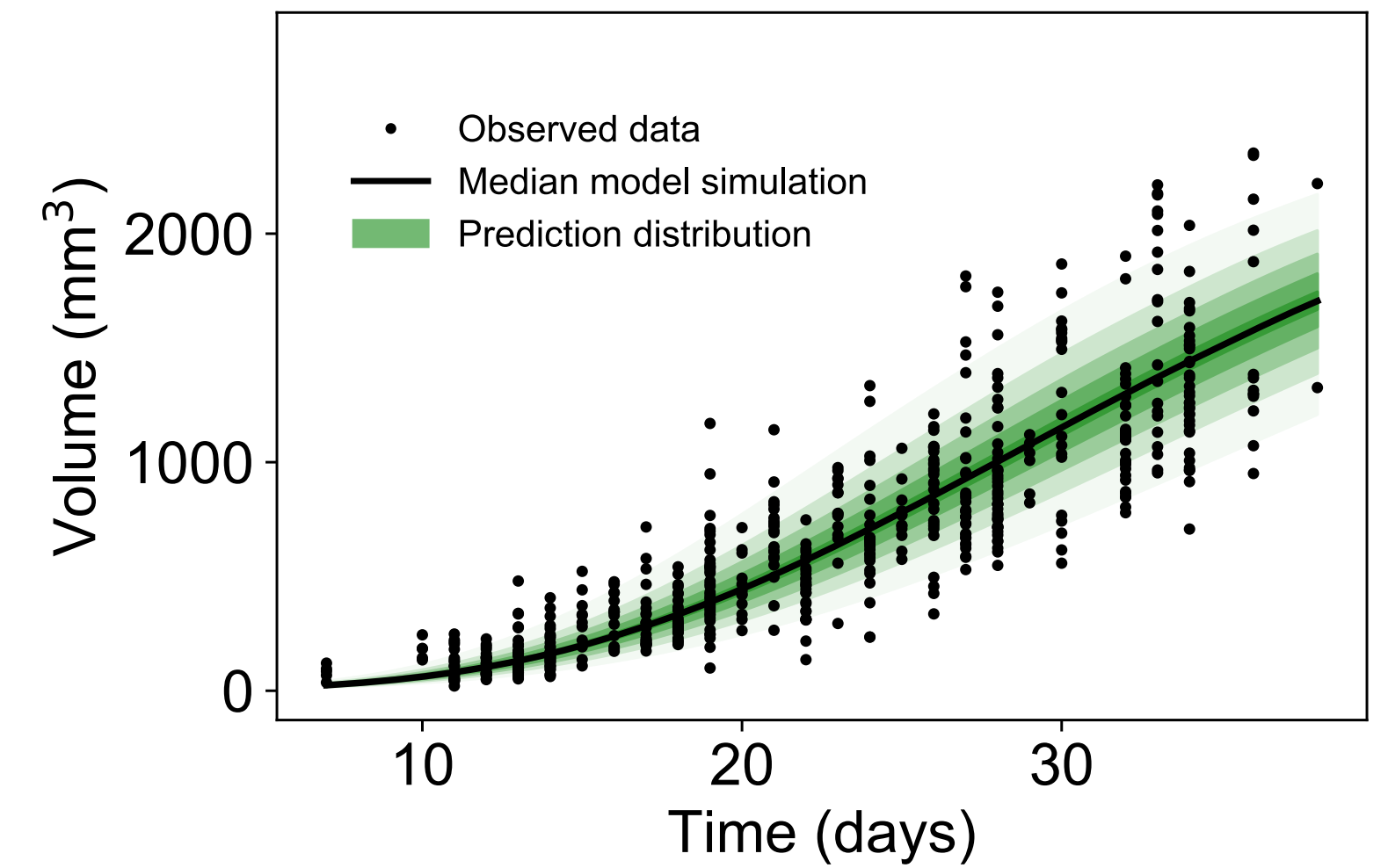
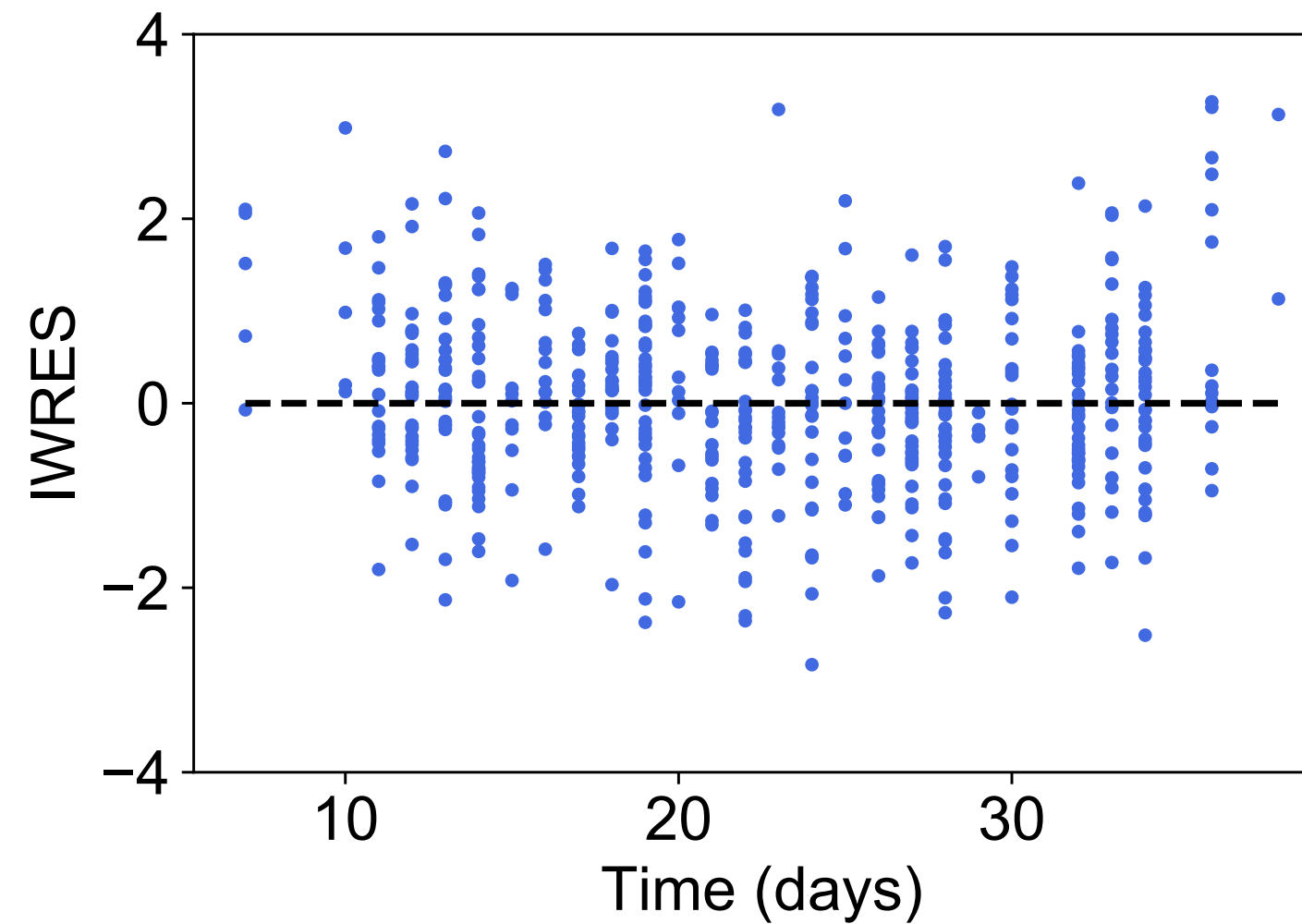
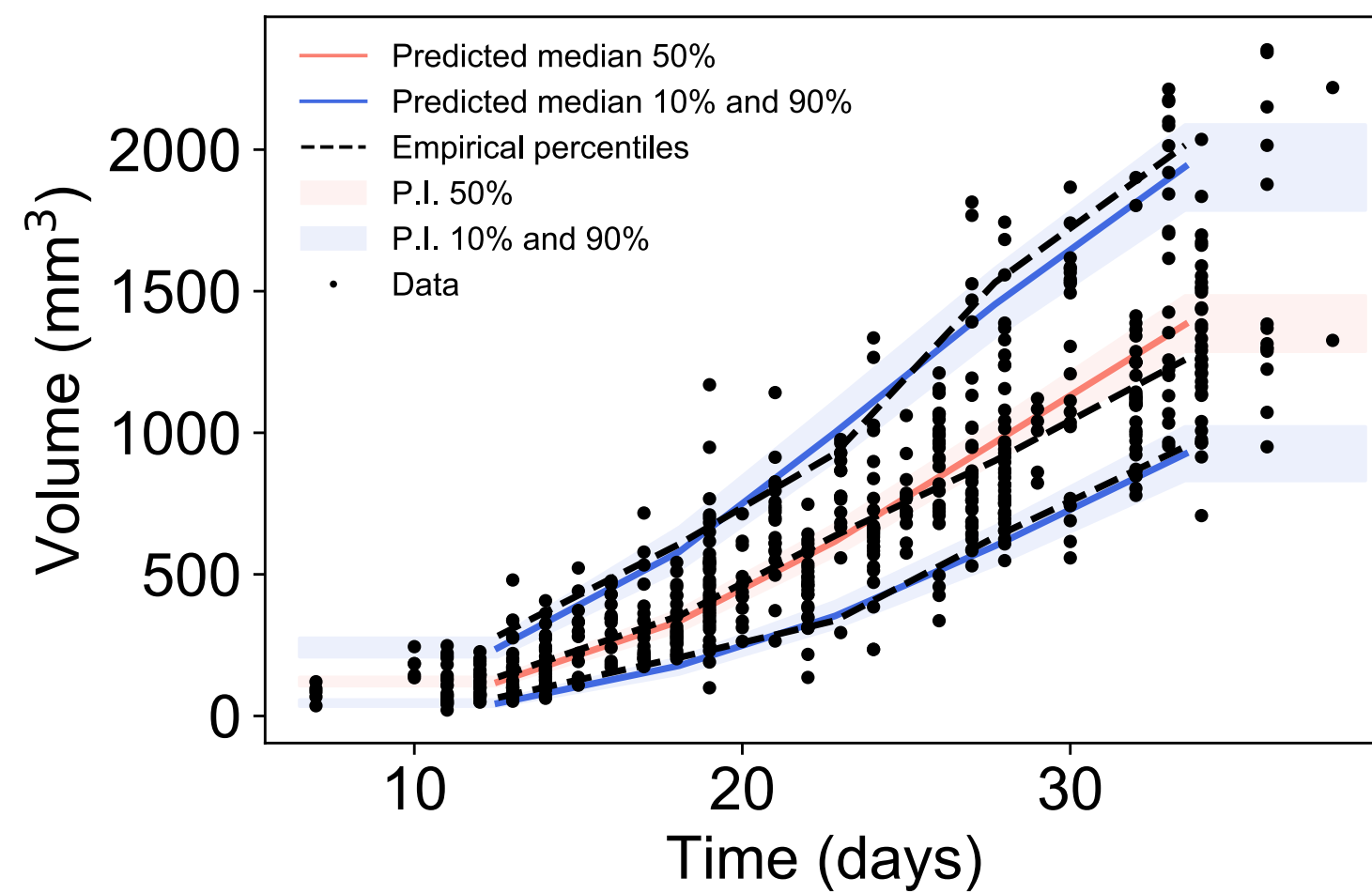
The reduced Gompertz model



$$\alpha^i = k\beta^i$$



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



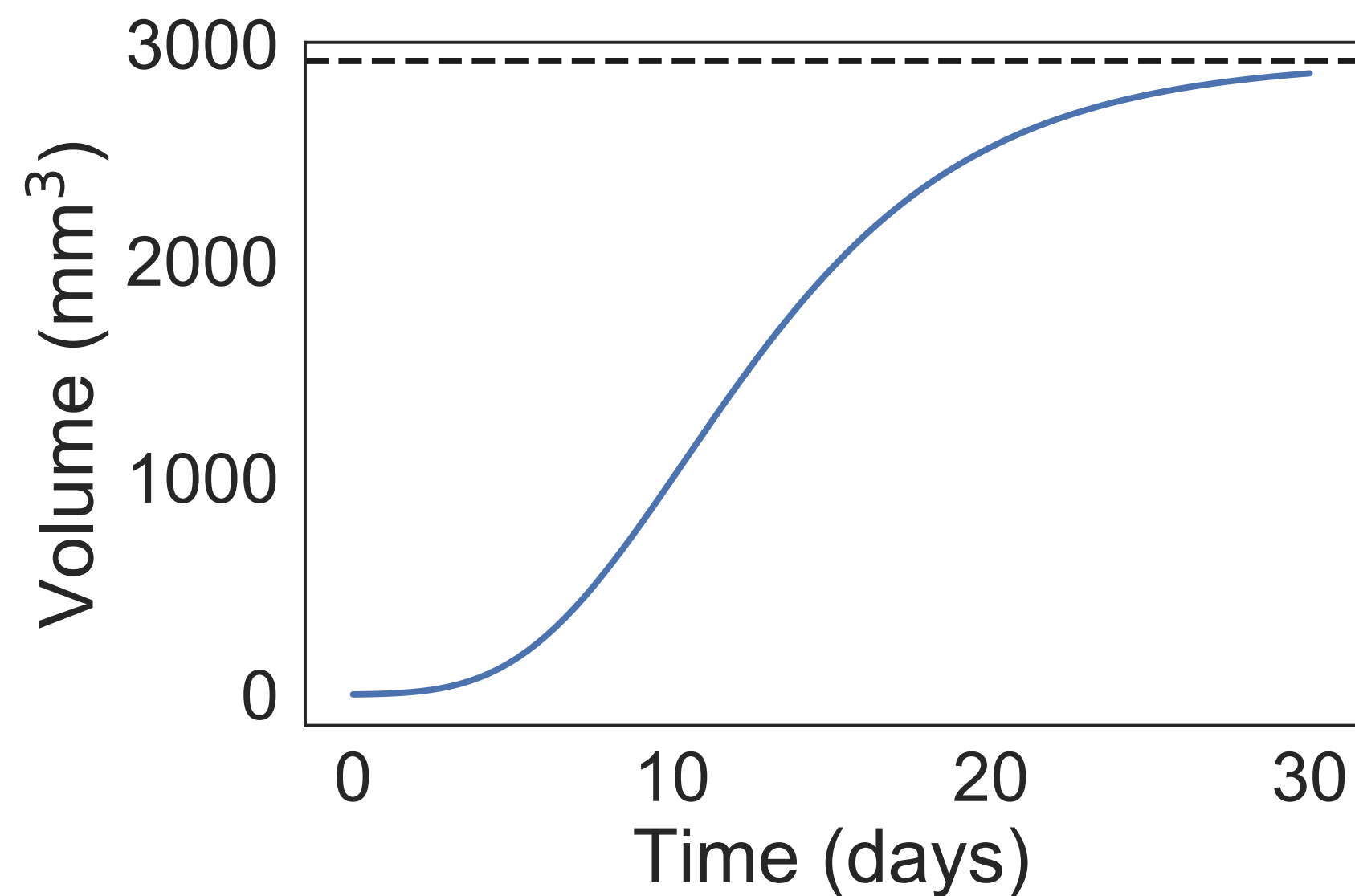
Results

The reduced Gompertz model: biological interpretation

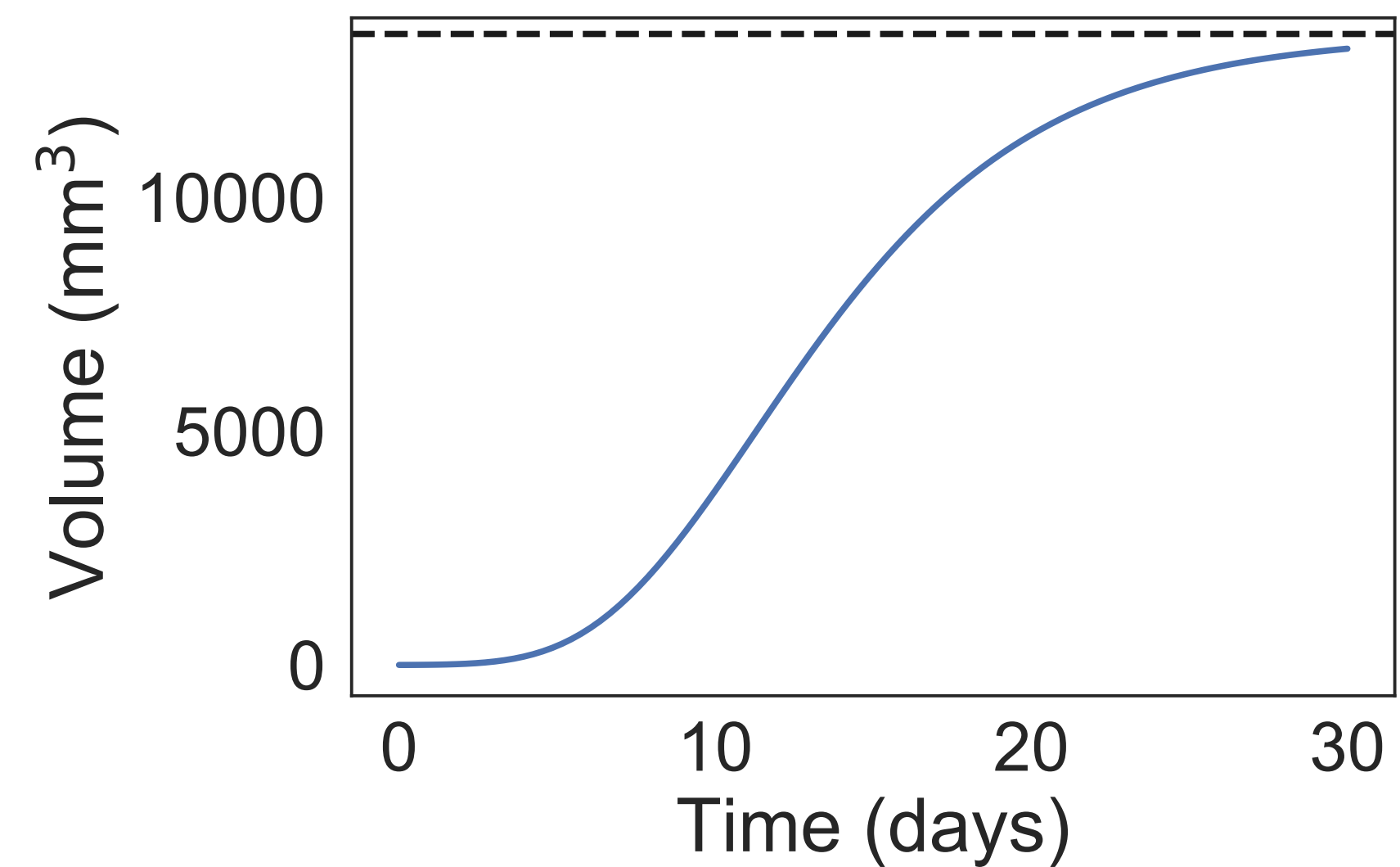
$$K^i = V_{inj} e^{\frac{\alpha^i}{\beta^i}} \simeq V_{inj} e^k \quad \forall i.$$

Constant maximal tumor size within a tumor type in a given species

Breast cancer



Lung cancer



Results

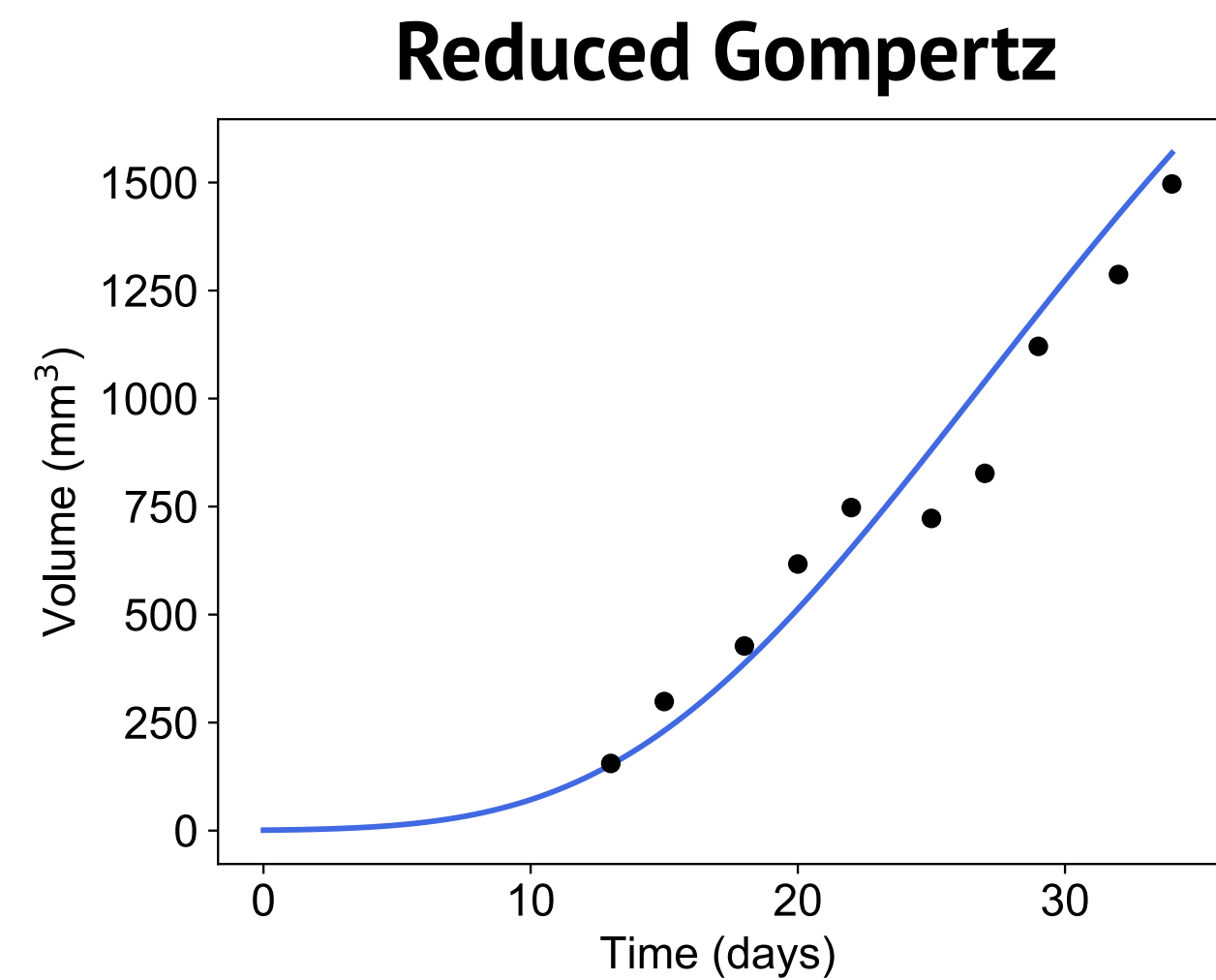
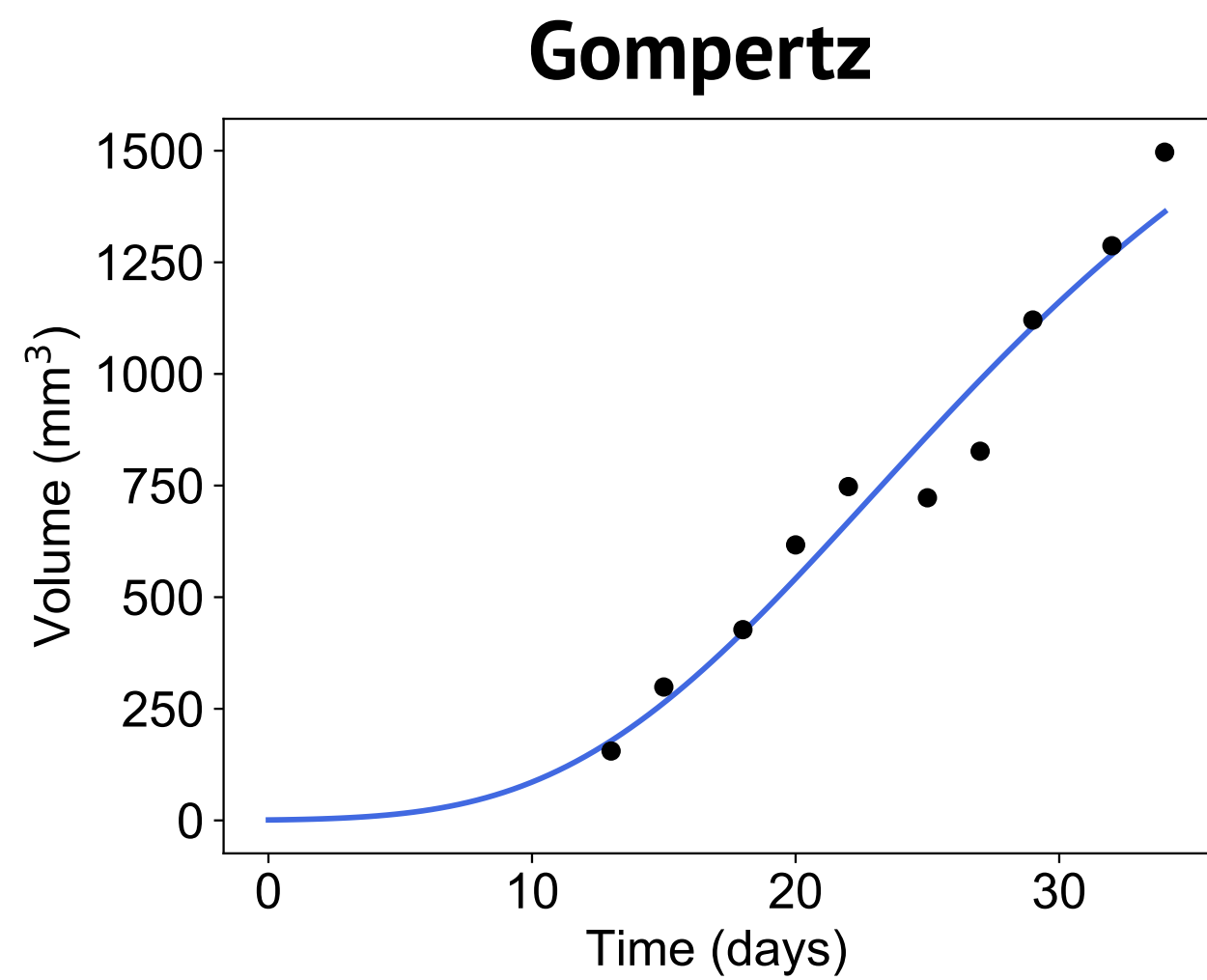
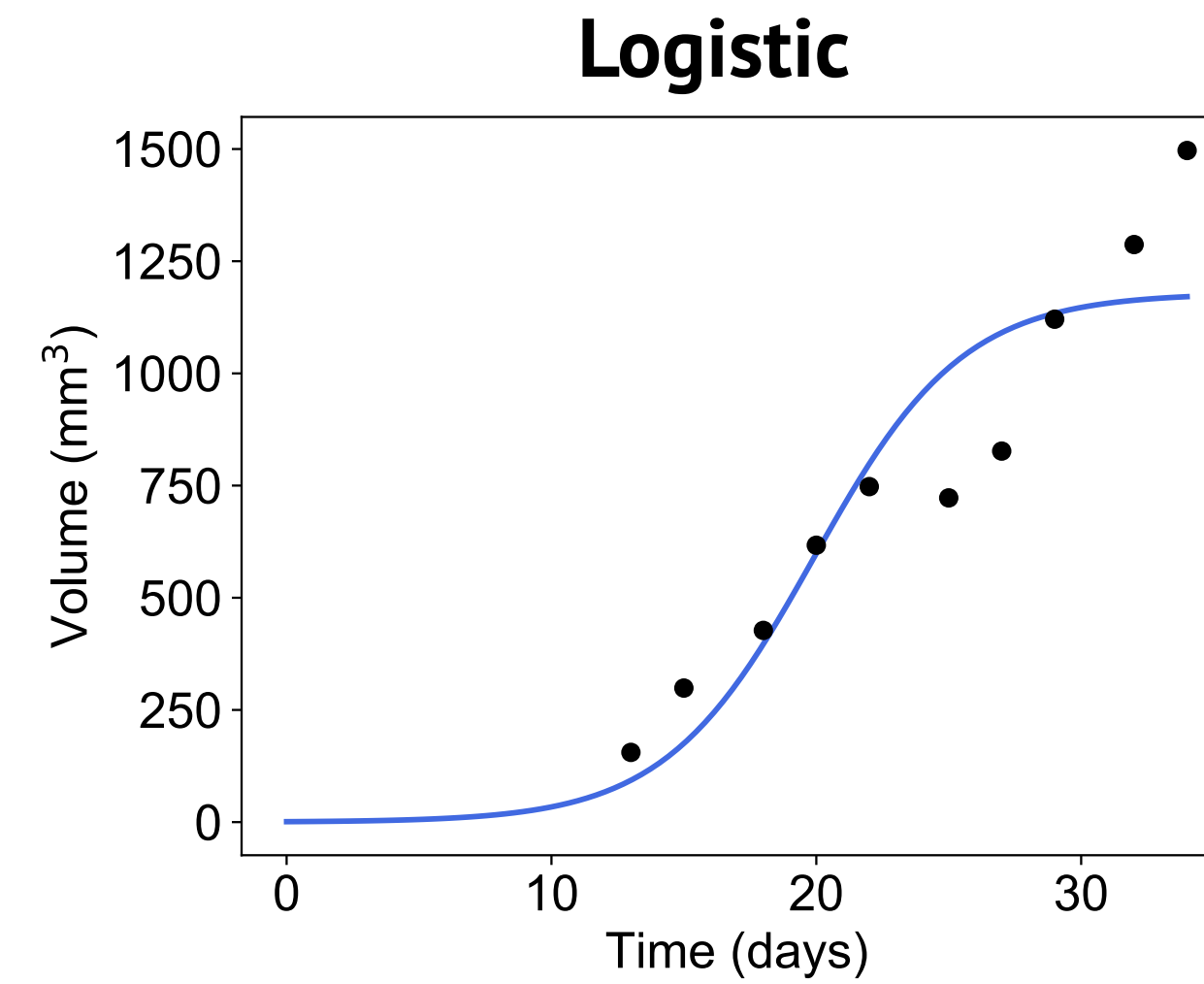
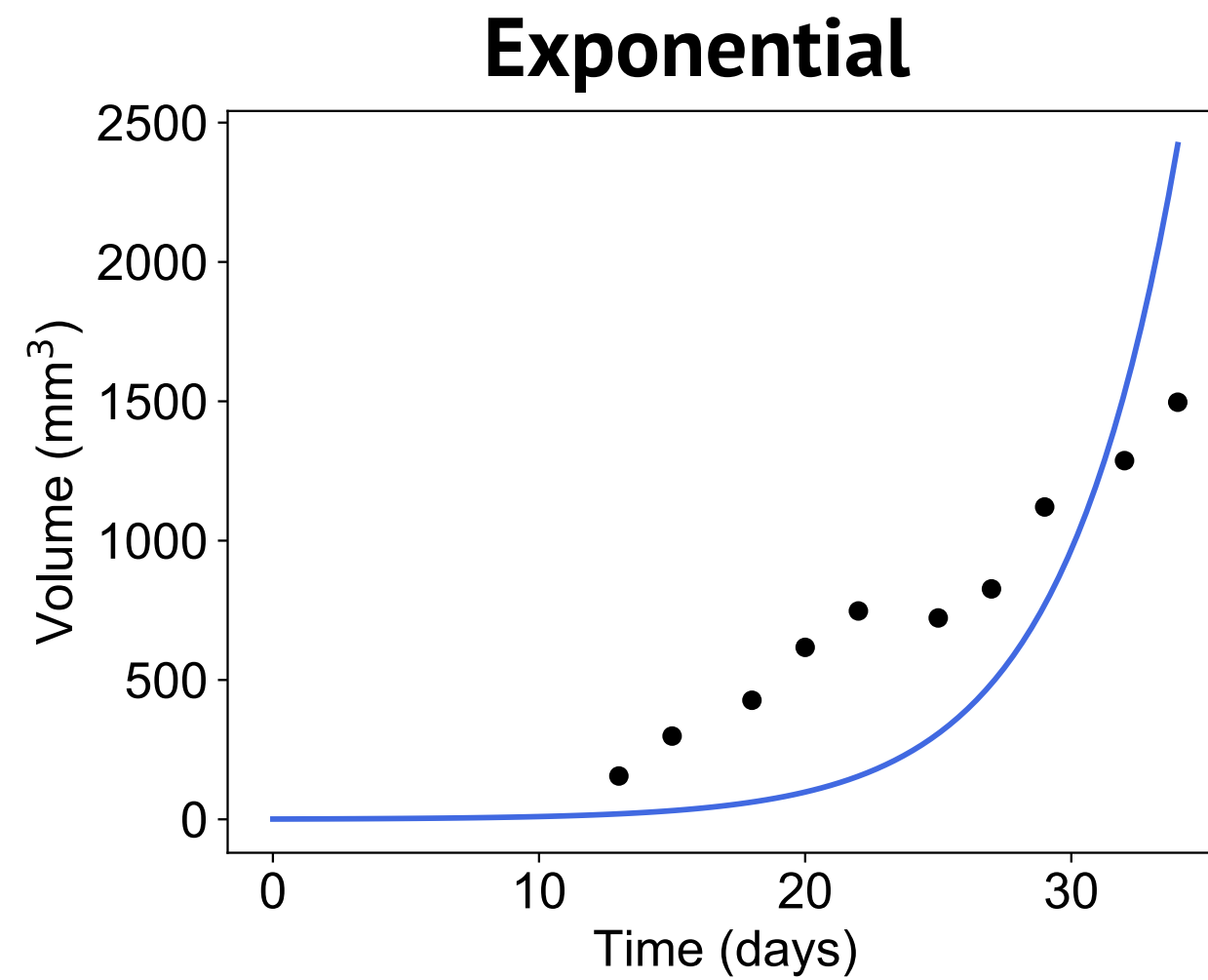
Population analysis

Model	-2LL	AIC	BIC
Gompertz	7128	7142	7157
Reduced Gompertz	7259	7269	7280
Logistic	7584	7596	7609
Exponential	8652	8660	8669

Model	Parameter	Unit	Fixed effects	CV (%)	R.S.E. (%)
Gompertz	α	day ⁻¹	0.573	34.73	2.56
	β	day ⁻¹	0.0705	391.49	3.61
	σ	-	[19.1, 0.12]		[18.3, 7.36]
Reduced Gompertz	β	day ⁻¹	0.0725	180.69	1.91
	k	-	7.98	0	0.363
	σ	-	[13.9, 0.183]		[22.3, 5.17]
Logistic	α	day ⁻¹	0.324	42.90	1.88
	K	mm ³	1332	0.02	4.39
	σ	-	[57.2, 0.136]		[9.8, 8.74]
Exponential	α	day ⁻¹	0.229	34.98	1.35
	σ	-	[283, 0.254]		[6.06, 14.3]

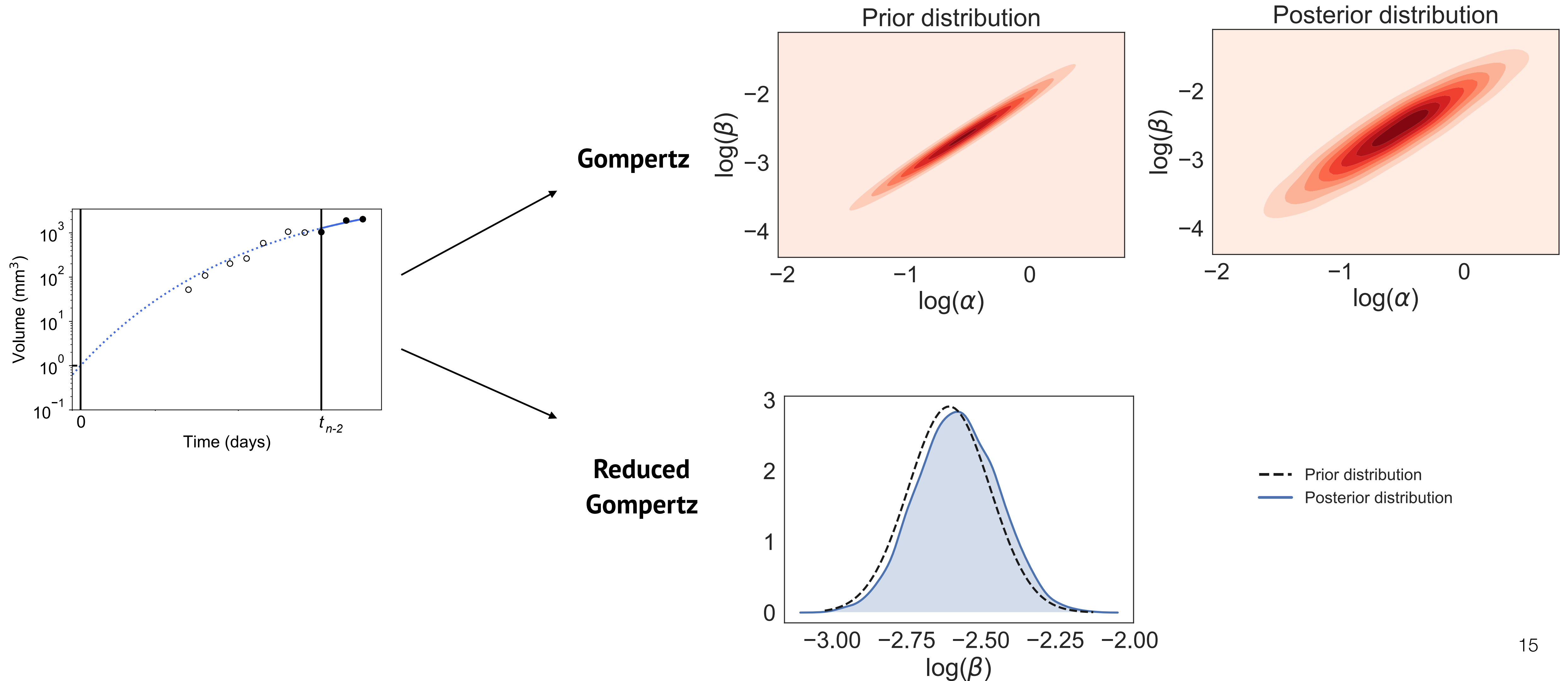
Results

Population analysis: example of individual fits



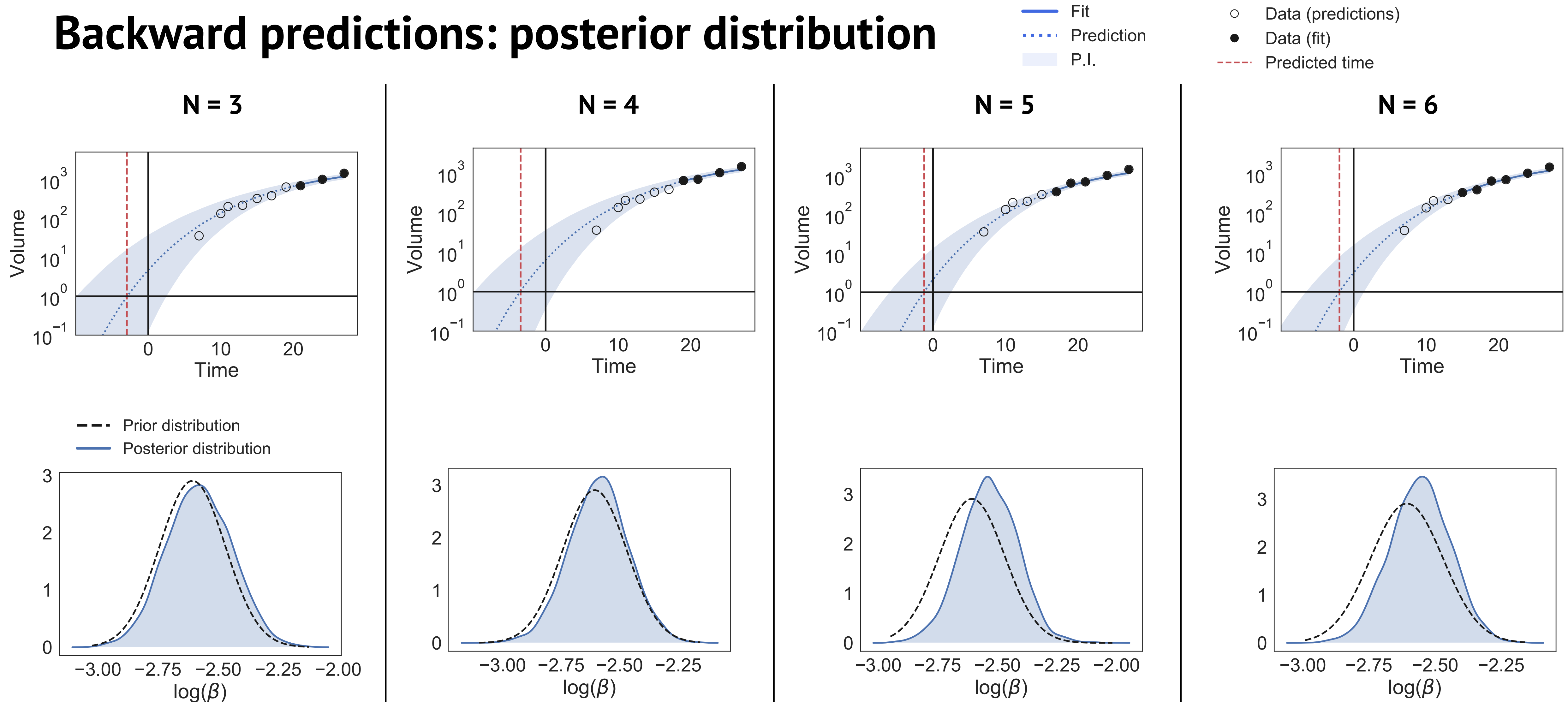
Results

Backward predictions: posterior distribution



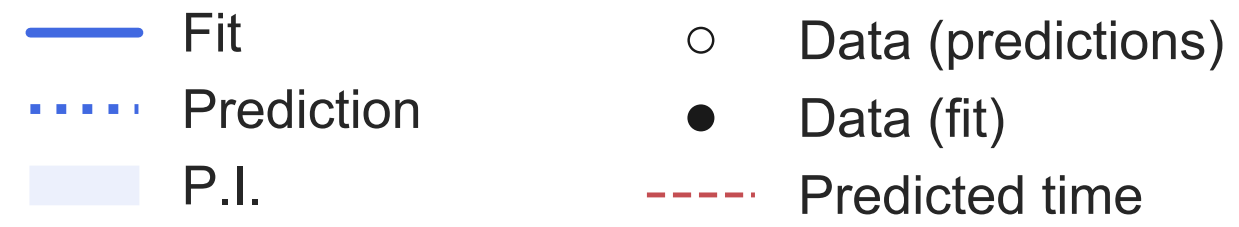
Results

Backward predictions: posterior distribution

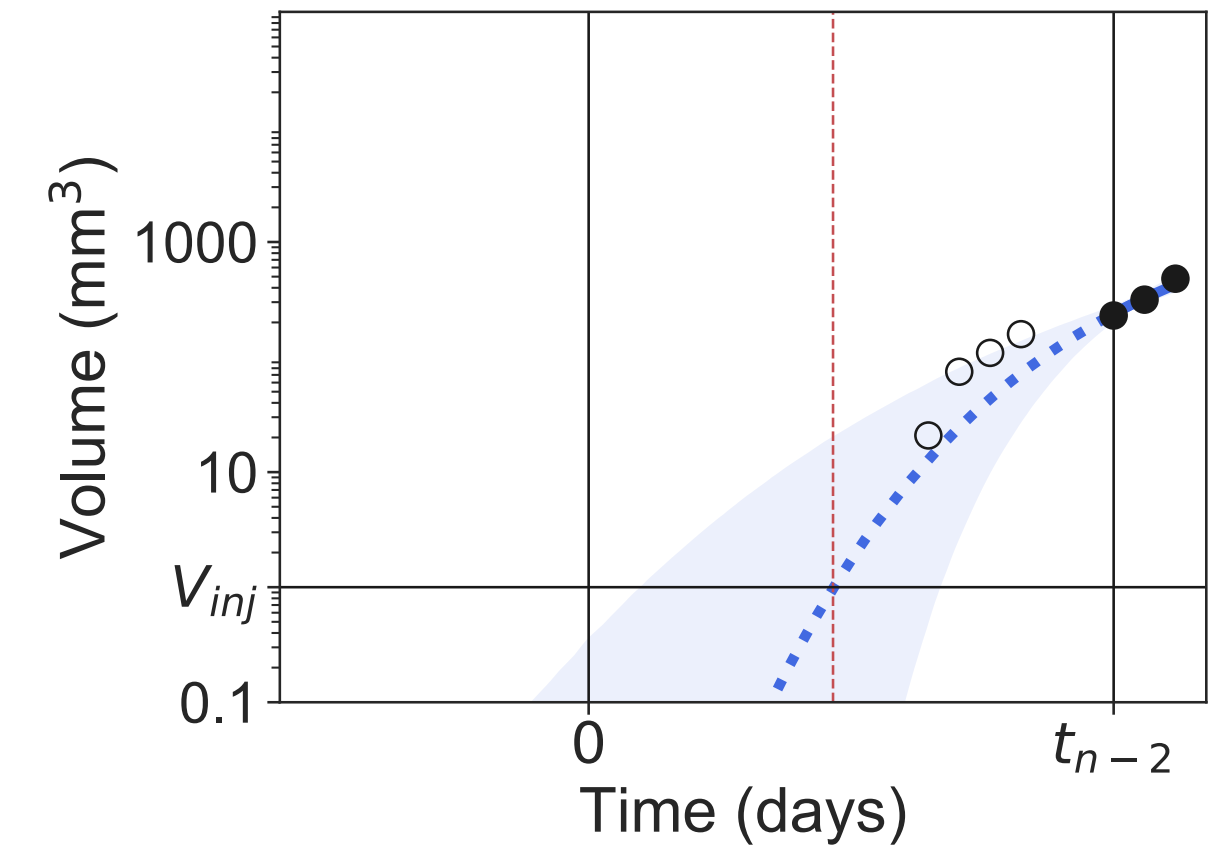
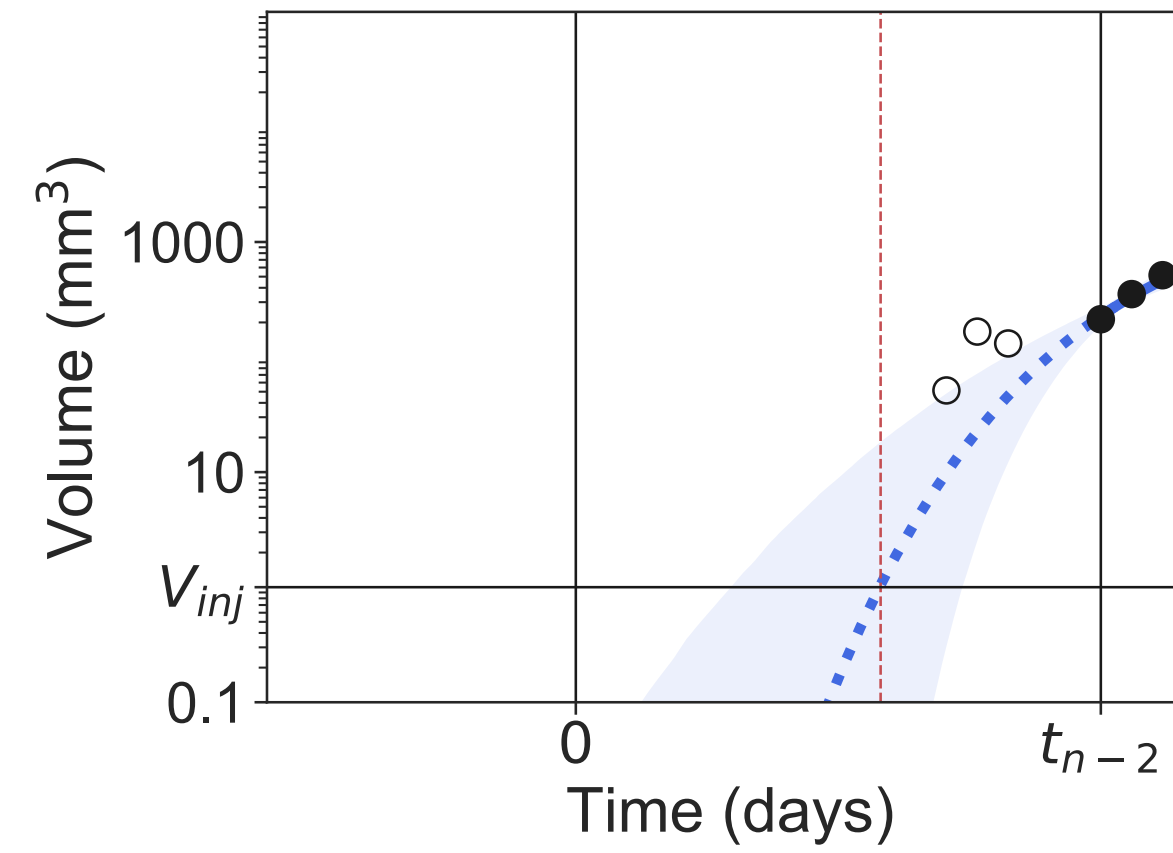
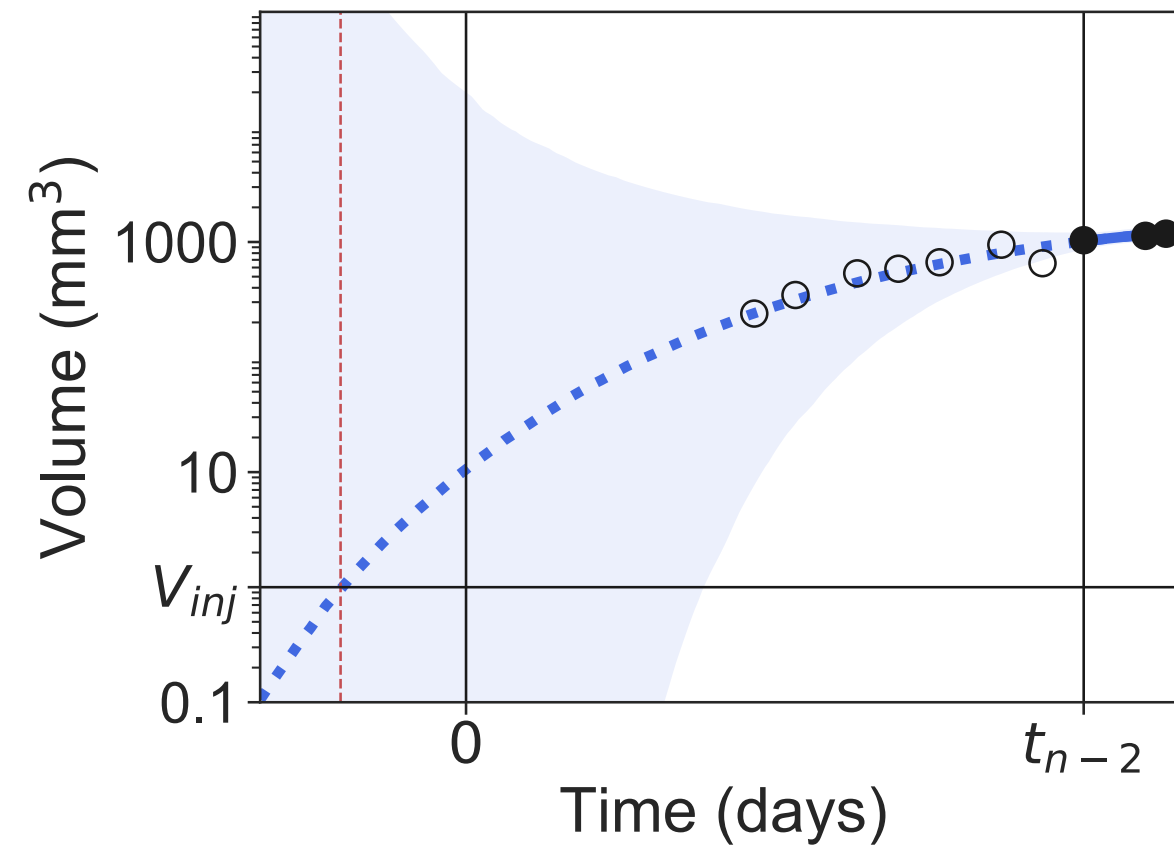


Results

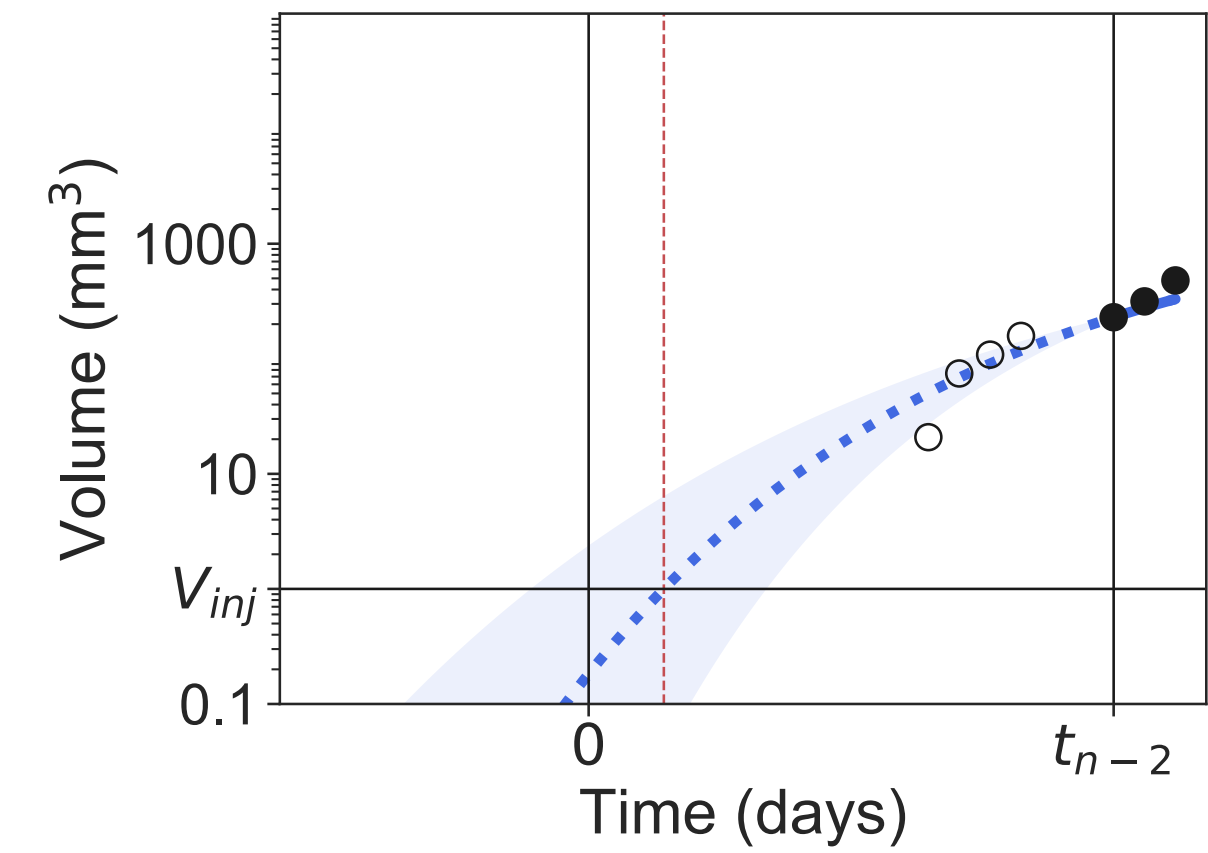
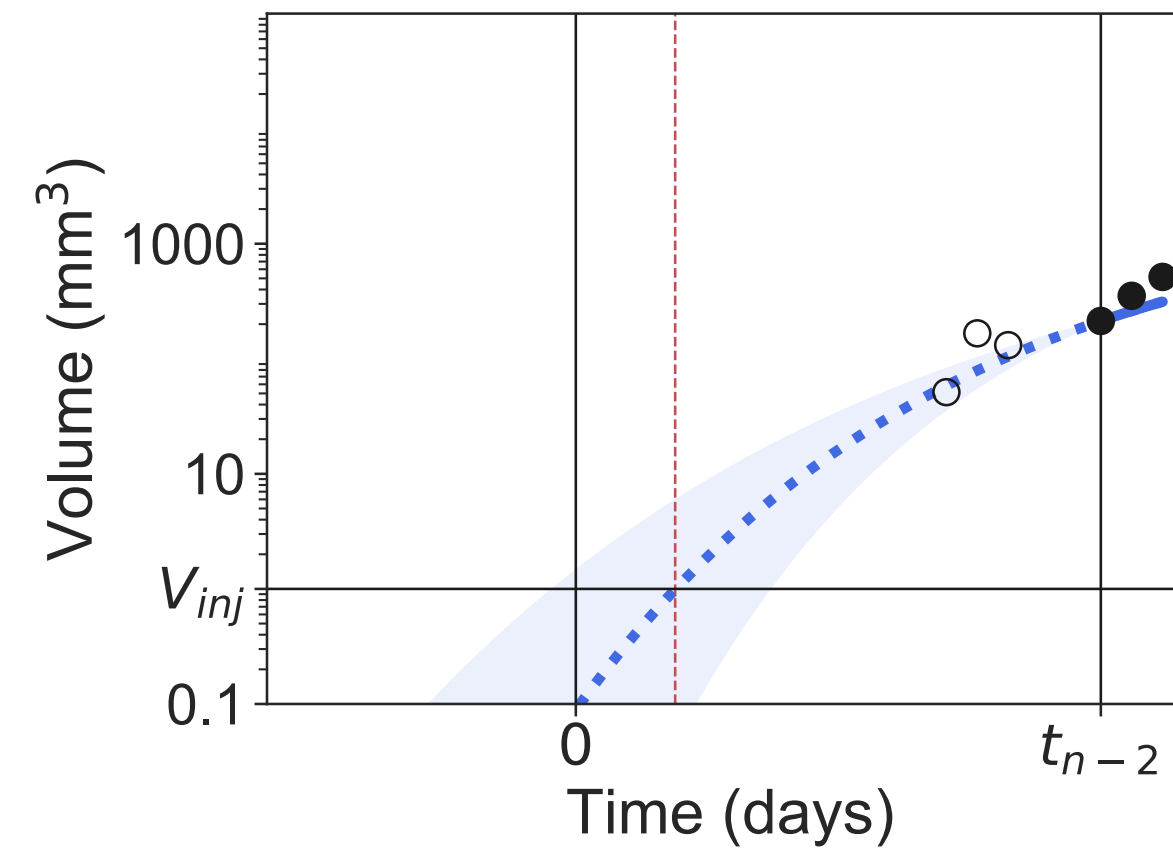
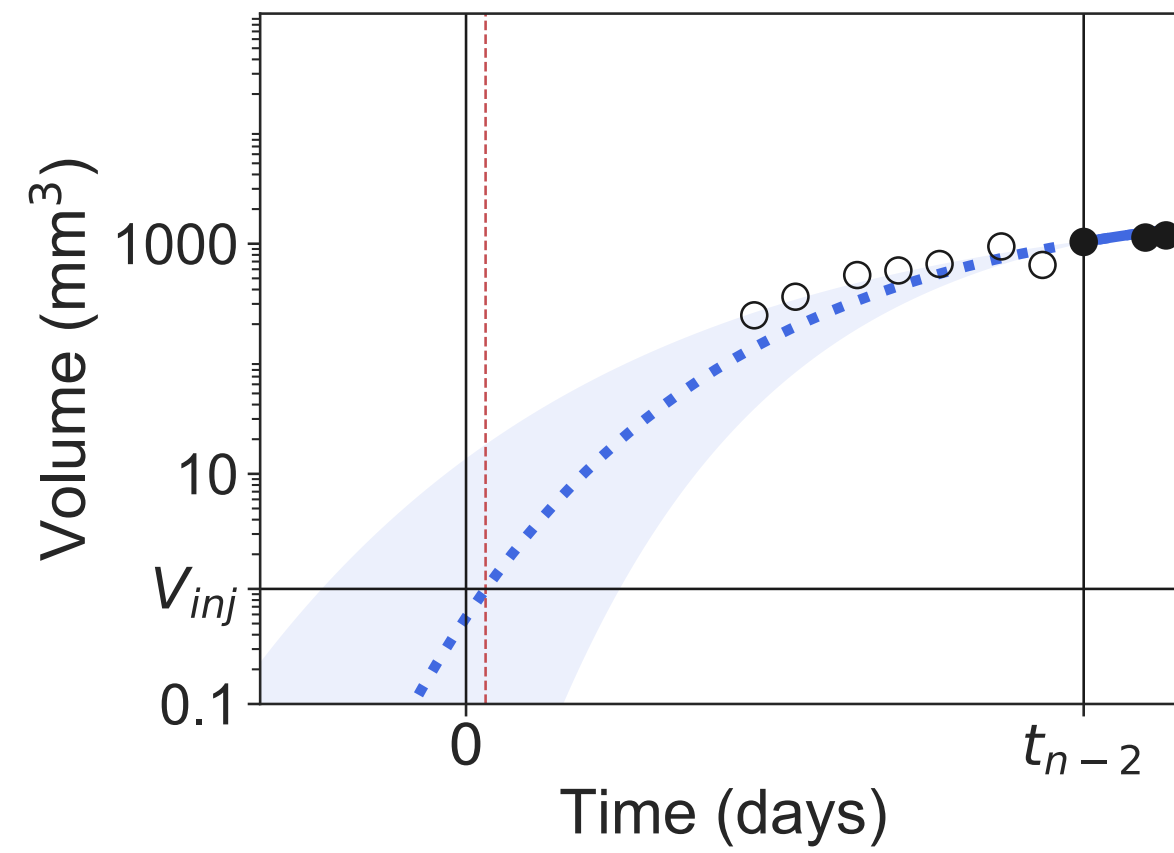
Backward predictions



Gompertz
(Bayesian inference)



Reduced Gompertz
(Bayesian inference)



Results

Backward predictions

- Reduced Gompertz >> Gompertz
- Bayesian inference >> likelihood maximization (LM)

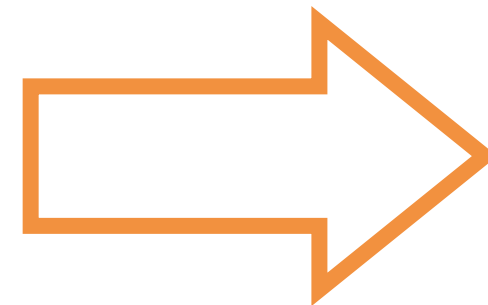
Model	Method	Accuracy (%)	Precision (days)
Reduced Gompertz	Bayesian	12.1 (1.02)	15.2 (0.503)
Reduced Gompertz	LM	74.1 (11.6)	186 (52.8)
Gompertz	Bayesian	19.6 (1.77)	40.1 (1.94)
Gompertz	LM	205 (55.4)	-

Conclusions

- The Gompertz model described well tumor growth kinetics while the Exponential and the Logistic showed inferior predictive power.
- We proposed a novel **reduced Gompertz model** with only one individual parameter.
- The combination of **nonlinear mixed effects modelling and Bayesian inference** allowed to have reliable predictions of individual tumor age.
- The method proposed herein remains **to be extended to clinical data**: it would yield important epidemiological insights and could also be informative in routine clinical practice for prediction of metastatic extent.

Thank you for your attention!

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A reduced Gompertz model for predicting tumor age using a population approach

 C. Vaghi,  A. Rodallec,  R. Fanciullino,  J. Ciccolini,  J. Mochel,  M. Mastri,  C. Pognard,  J. ML Ebos,  S. Benzekry

doi: <https://doi.org/10.1101/670869>