Radboud University

IGSSE TUM International Graduate School of Science and Engineering

Bayesian calibration and comparison of models of tumour cell dynamics

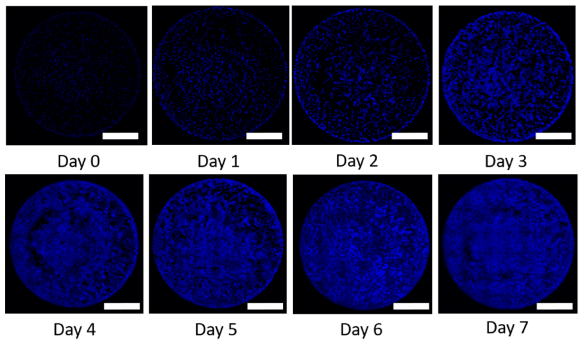
Laura Scarabosio

joint with S. Schönfeld and C. Kuttler (TU Munich),
A. Ozkan (Harvard) and M. N. Rylander (UT Austin)

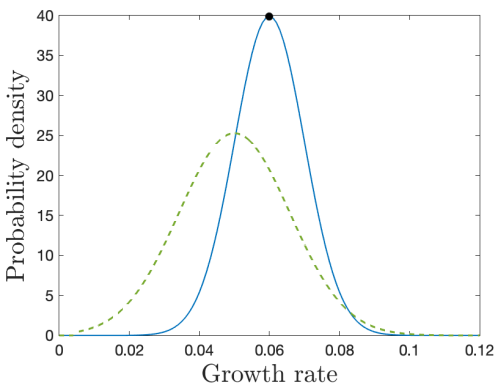
General Mathematics Colloquium
VU Amsterdam, 30.11.2022

The predictive estimation process

Data



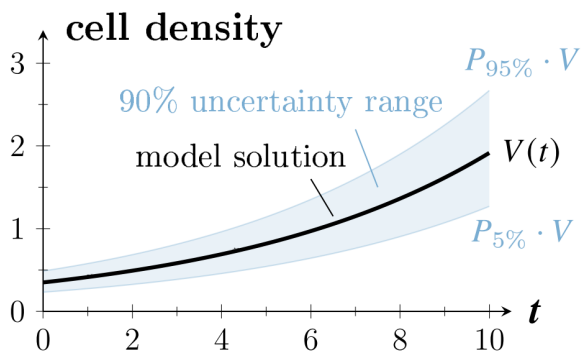
Uncertain parameter



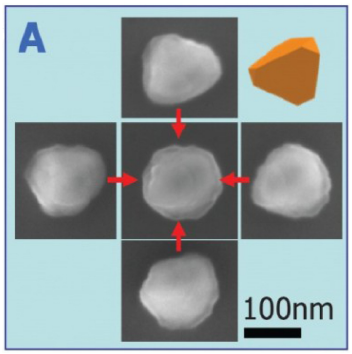
Models

Model

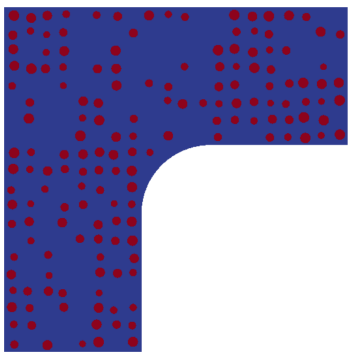
Prediction



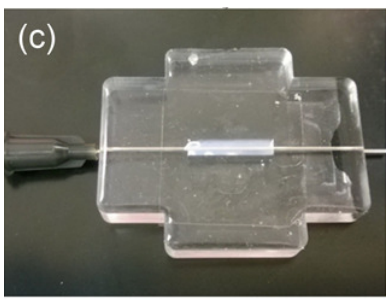
Main research interests



Shape uncertainty in acoustic scattering



Random multiscale materials



Predicting tumor growth

The team

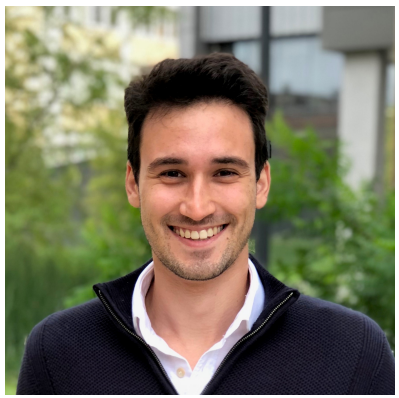
Christina Kuttler

Laura Scarabosio

Sabrina Schönfeld

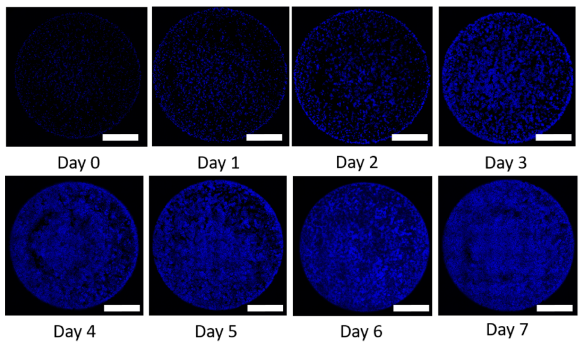
Marissa N. Rylander

Alican Ozkan

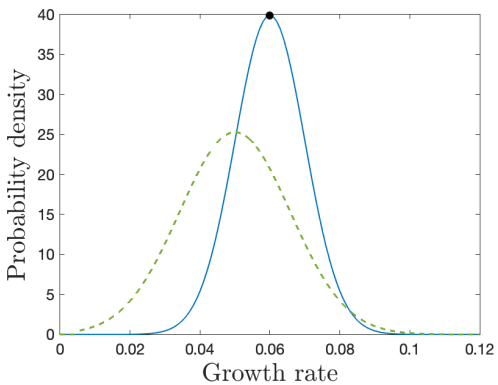


The inverse problem

Data



Uncertain parameter



Models

We need:

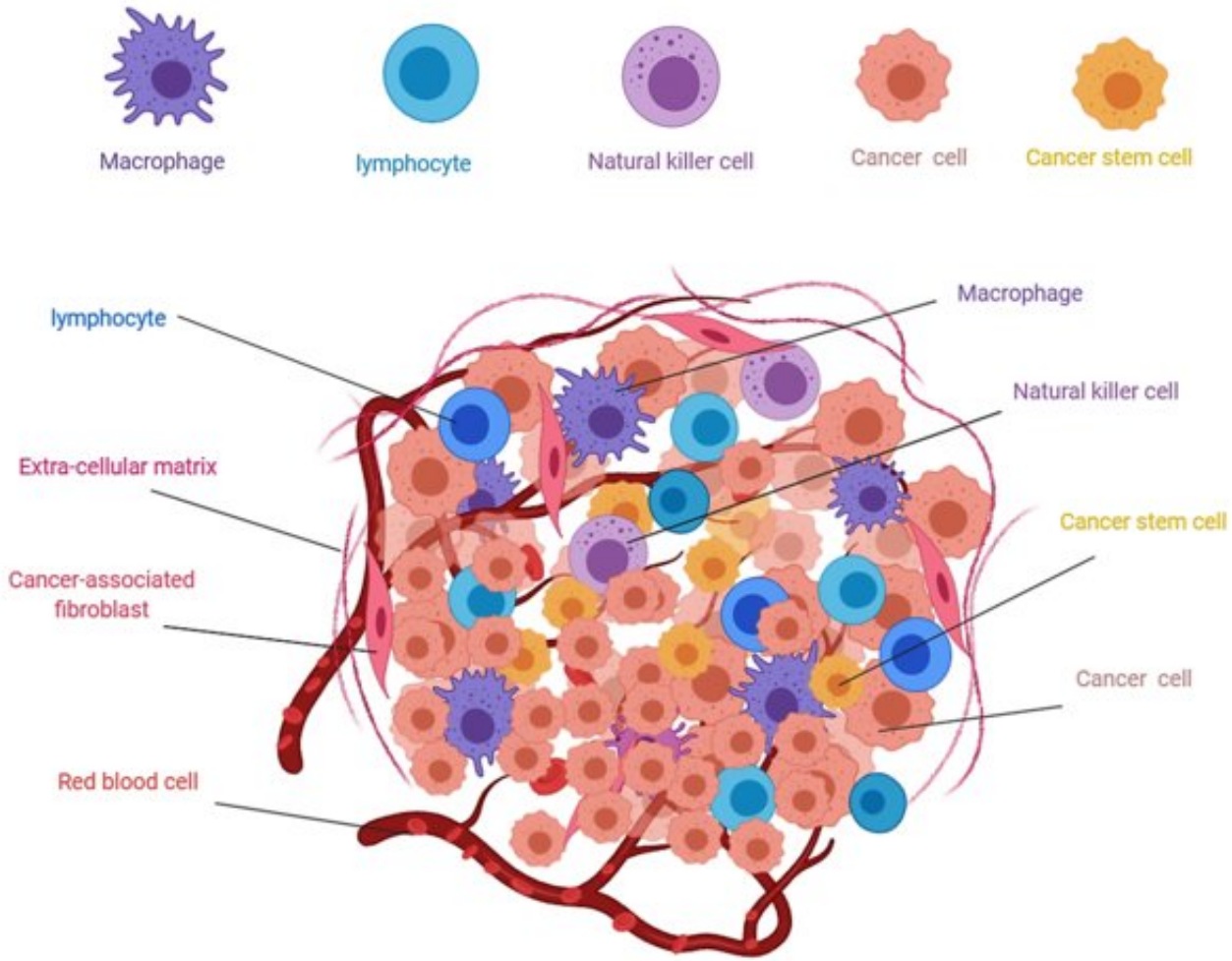
The model(s)

The data

The learning algorithm

The model

The tumour microenvironment (TME)



Hassan, Seno, *Cells* (2020).

Modeling the influence of TME on viable cells

Assumption: spatial homogeneity.

$\eta : [0, T] \to [0, 1]$ **environmental stress level**

Optimal growth conditions ($\eta \equiv 0$)

$$\dot{V}(t) = \beta V(t) \left(1 - \left(\frac{V(t)}{K}\right)^m\right) - \lambda V(t)$$

Most inexpedient conditions ($\eta \equiv 1$)

$$\dot{V}(t) = -(\lambda + \lambda_{\text{ind}}) V(t)$$

Varying conditions

$$\dot{V}(t) = (1 - \eta(t))\beta V(t) \left(1 - \left(\frac{V(t)}{K}\right)^m\right) - (\lambda + \eta(t)\lambda_{\text{ind}}) V(t)$$

Modeling the environmental stress level

Environmental factors: $\boldsymbol{E} = (E_1, \ldots, E_n)$

Influence functions: $\delta_j^{\pm} : \boldsymbol{E} \mapsto \delta_j^{\pm}(\boldsymbol{E}) \in [0,1]$, for $j = 1, \ldots, n$

Sensitivity rates: $\alpha_j^{\pm},\ j = 1, \ldots, n$

$$\dot{\eta}(t) = \underbrace{\left(\sum_{j=1}^{n} \alpha_j^{-} \delta_j^{-}(\boldsymbol{E}(t))\right)(1 - \eta(t))}_{\text{increasing stress level}} - \underbrace{\left(\sum_{j=1}^{n} \alpha_j^{+} \delta_j^{+}(\boldsymbol{E}(t))\right)\eta(t)}_{\text{recovery from stress}}$$

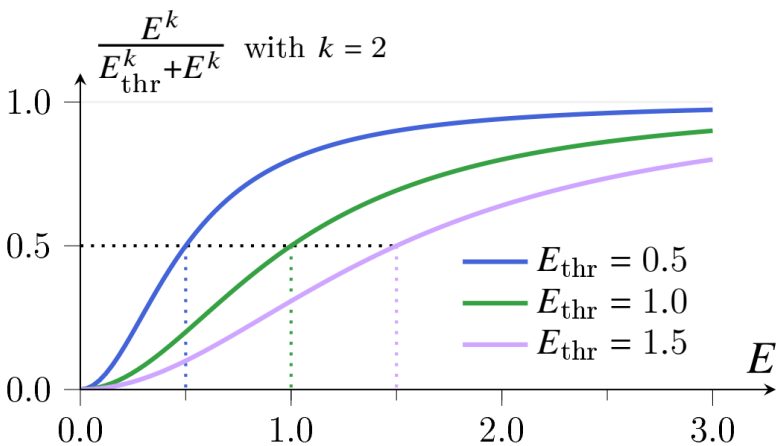
$$\eta(0) = \eta_0 \in [0,1]$$

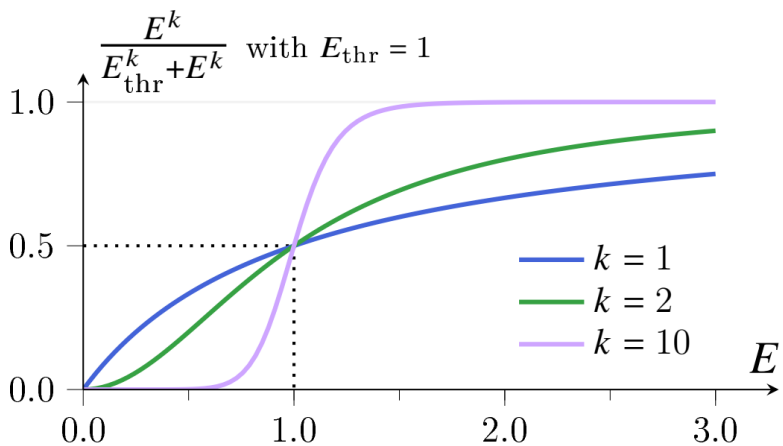
Choice of the influence functions

Beneficial factor: $\delta_j^+(\boldsymbol{E}) = \mathcal{H}(\boldsymbol{E}_{-j}, E_j)$

Harmful factor: $\delta_j^-(\boldsymbol{E}) = \mathcal{H}(\boldsymbol{E}_{-j}, E_j)$

$$\mathcal{H} : (\boldsymbol{E}_*, E) \mapsto \frac{E^k}{E_{\text{thr}}(\boldsymbol{E}_*)^k + E^k}, \quad k > 1$$





Application: nutrient deprivation

$$E_1(t) = N(t) \equiv N_0 \in [0, 1]$$

Assumption: same reaction to beneficial and harmful nutrient conditions:

$$\alpha_1^+ = \alpha_1^- = \alpha, \quad \delta_1^-(N_0) = 1 - \delta_1^+(N_0)$$

$$\dot{V}(t) = (1 - \eta(t))\beta V(t)\left(1 - \left(\frac{V(t)}{K}\right)^m\right) - (\lambda + \eta(t)\lambda_{\text{ind}})V(t)$$

$$\dot{\eta}(t) = \alpha\left(1 - \frac{N_0^2}{{N_{\text{thr}}}^2 + N_0^2}\right)(1 - \eta(t)) - \alpha\frac{N_0^2}{{N_{\text{thr}}}^2 + N_0^2}\eta(t)$$

$$V(0) = V_0, \ \eta(0) = \eta_0$$

Application: nutrient deprivation at steady state

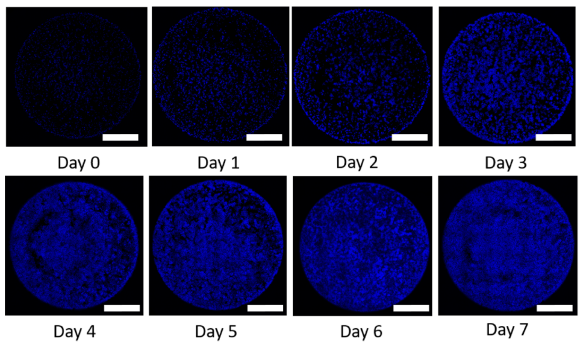
If changes in environmental stress level happen at much faster time scale:

$$\dot{V}(t) = \delta_1^+(N_0)\beta V(t)\left(1 - \left(\frac{V(t)}{K}\right)^m\right) - (\lambda + \delta_1^-(N_0)\lambda_{\text{ind}})V(t)$$

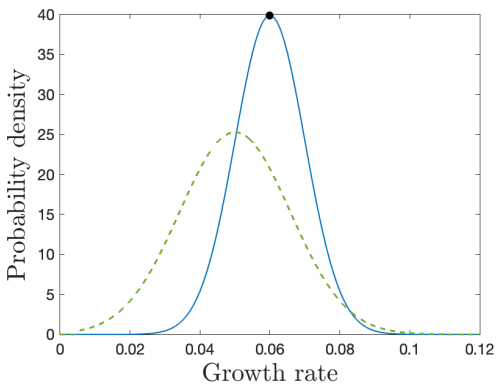
$$V(0) = V_0$$

The inverse problem

Data



Uncertain parameter



Models

We need:

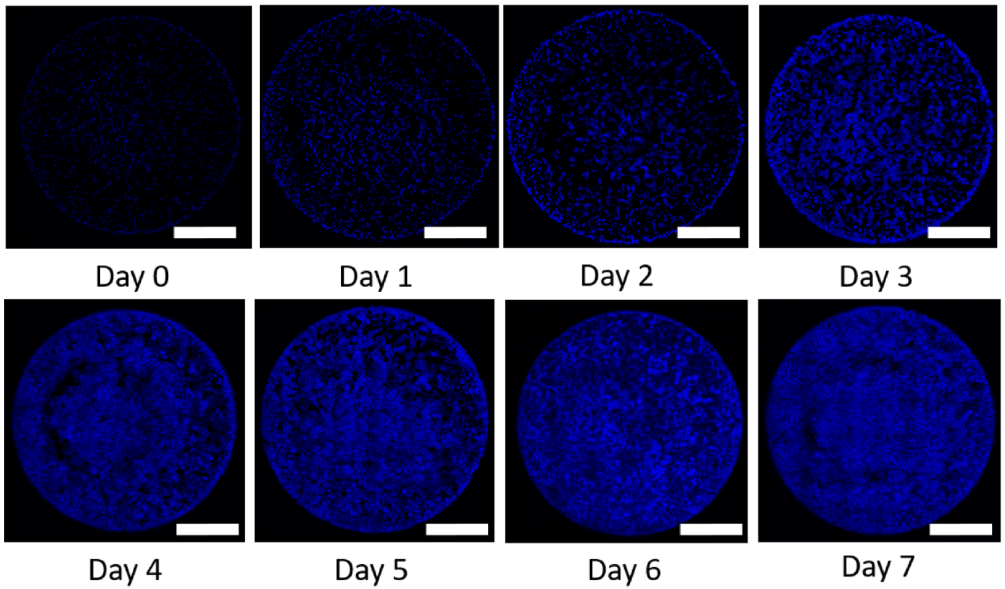
The model(s) ✓

The data

The learning algorithm

The data

Measurements



Lima et al., *Scientific reports* (2018)

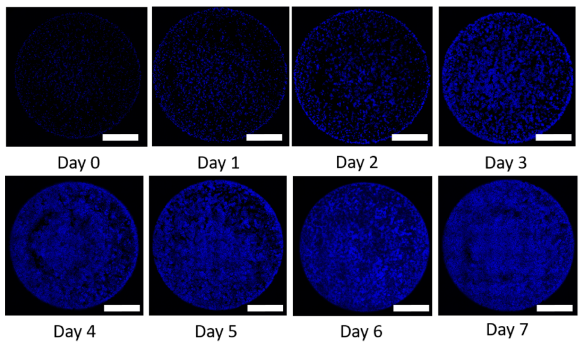
$I(t) \propto V(t)$

Different **initial conditions** (V_0) and **nutrient levels** (N_0)

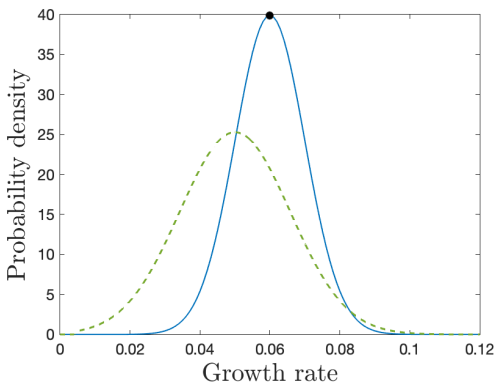
Four replicates per measurement

The inverse problem

Data



Uncertain parameter



Models

We need:

The model(s) ✓

The data ✓

The learning algorithm

The learning algorithm

The Bayesian inverse problem

$\vartheta \in \Theta \subseteq \mathbb{R}^d$	**parameters**
$\mathcal{I} = (I_i)_{i=1}^M \in \mathbb{R}^M$	**measurements**
$(\mathcal{G}_i)_{i=1}^M$	**forward operator**

$$I_i = \mathcal{G}_i(\vartheta)\varepsilon_i, \quad i = 1, \ldots, M$$

The inverse problem is usually **ill-posed**

Bayesian approach: **probability distribution** rather than point estimate

Bayes' rule

$$\text{posterior} = \frac{\text{likelihood} \cdot \text{prior}}{\text{model evidence}}$$

$$\pi(\vartheta|\mathcal{I}) = \frac{L(\mathcal{I}|\vartheta) \cdot \pi_0(\vartheta)}{Z}$$

Our Bayesian inverse problem

$$I_i = \mathcal{G}_i(\vartheta)\varepsilon_i, \quad i = 1, \dots, M$$

Assuming $\varepsilon_i \sim \Gamma\left(\frac{1}{\sigma^2}, \frac{1}{\sigma^2}\right)$ i.i.d.

we obtain the likelihood $L(\mathcal{I}|\vartheta) \propto \prod_{i=1}^{M} \left(\frac{I_i}{\mathcal{G}_i(\vartheta)}\right)^{\frac{1}{\sigma^2}-1} \exp\left(-\frac{1}{\sigma^2}\frac{I_i}{\mathcal{G}_i(\vartheta)}\right)$

where $\mathcal{G}_i(\vartheta) = nV_i(\vartheta)$ and V_i solves the ODE

Sampling with Sequential Monte Carlo: idea

Why Sequential Monte Carlo?

- **Efficient** for dynamical systems and time series data
- **No restrictions** on distributions and class of problems
- More **robust** than MCMC for multimodal distributions

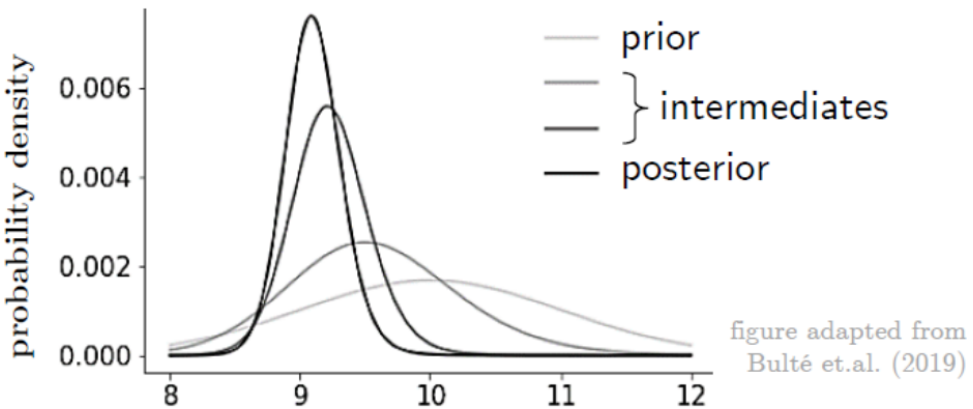


figure adapted from Bulté et.al. (2019)

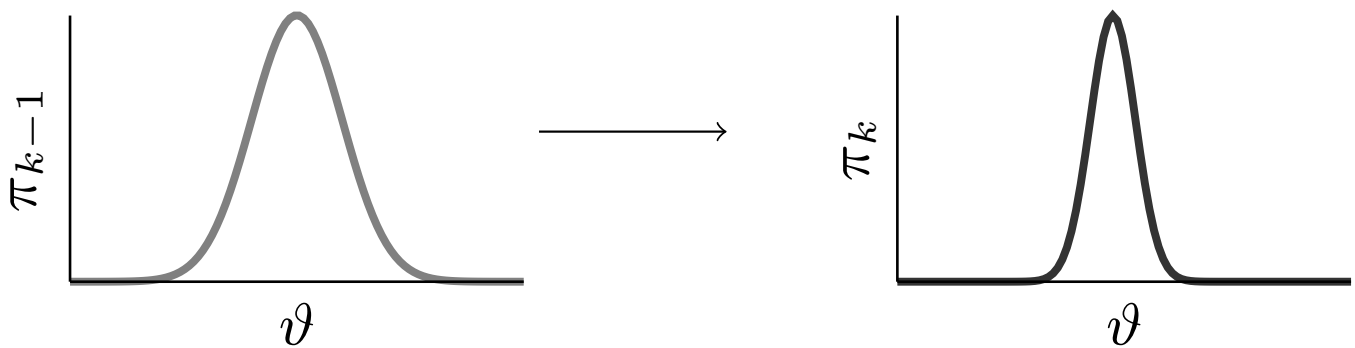
Given $\mathcal{I}_1 \subset \mathcal{I}_2 \subset \ldots \subset \mathcal{I}_K = \mathcal{I}$

$$\pi_k(\vartheta|\mathcal{I}_k) = \frac{1}{Z_k} L(\mathcal{I}_k|\vartheta)\pi_0(\vartheta), \text{ i.e. } \pi_k(\vartheta|\mathcal{I}_k) = \frac{1}{Z_k^*} L(\mathcal{I}_k \setminus \mathcal{I}_{k-1}|\vartheta)\pi_{k-1}(\vartheta|\mathcal{I}_{k-1})$$

Sampling with Sequential Monte Carlo: algorithm

$$\pi_k(\vartheta|\mathcal{I}_k) \approx \sum_{p=1}^{P} W_p^k \delta_{\vartheta_p}(\vartheta)$$

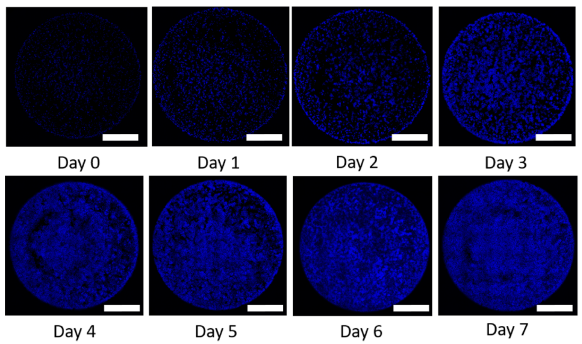
At each iteration:



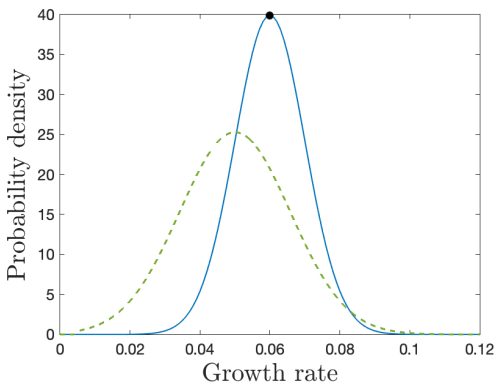
1. **Reweight**
2. **Resample** (if needed)
3. **Perturb**

The inverse problem

Data



Uncertain parameter



Models

We need:

The model(s) ✓

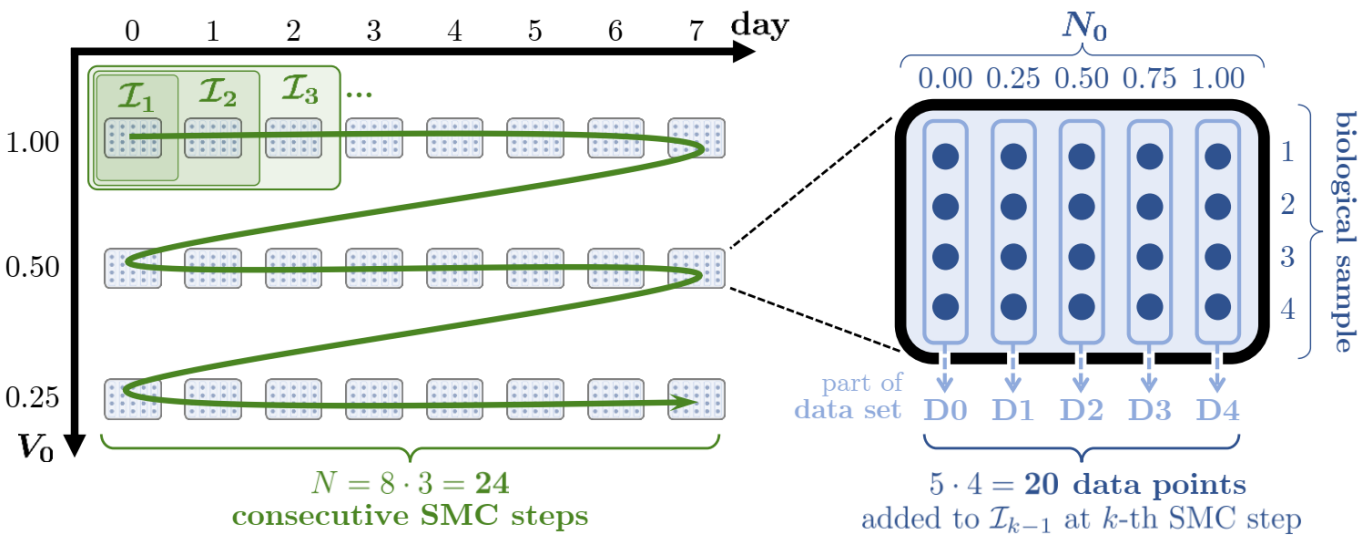
The data ✓

The learning algorithm ✓

Results

Data sets and data ordering

Data set	Nutrition (in % FBS)	Duration (in days)	Initial values in the models V_0	N_0	η_0
D0	0.0	7	1.00, 0.50, 0.25	0.00	0.00
D1	2.5	7	1.00, 0.50, 0.25	0.25	0.00
D2	5.0	7	1.00, 0.50, 0.25	0.50	0.00
D3	7.5	7	1.00, 0.50, 0.25	0.75	0.00
D4	10.0	7	1.00, 0.50, 0.25	1.00	0.00
DV	10.0	21	1.00, 0.50, 0.25, 0.10, 0.05	1.00	0.00



Posterior estimates

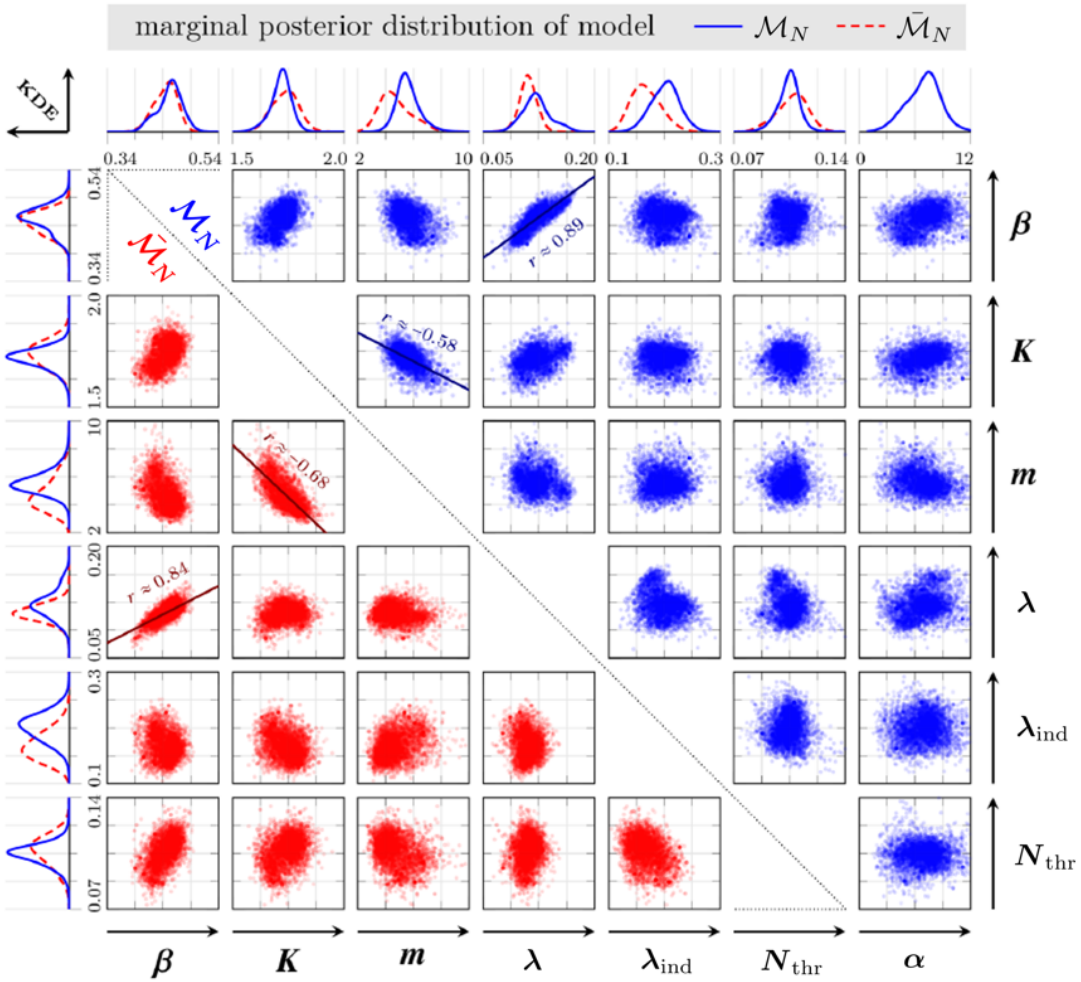
Averages

Model	β	λ	λ_{ind}	α
$\mathcal{M}_N$	0.437 ± 0.002	0.106 ± 0.002	0.196 ± 0.001	6.930 ± 0.213
$\bar{\mathcal{M}}_N$	0.435 ± 0.004	0.103 ± 0.003	0.186 ± 0.003	
	K	m	N_{thr}	
$\mathcal{M}_N$	1.731 ± 0.008	5.315 ± 0.247	0.106 ± 0.001	
$\bar{\mathcal{M}}_N$	1.740 ± 0.011	4.731 ± 0.198	0.104 ± 0.001	

Variances

Model	β	λ	λ_{ind}	α
$\mathcal{M}_N$	0.010 ± 0.002	0.009 ± 0.002	0.012 ± 0.002	3.211 ± 0.251
$\bar{\mathcal{M}}_N$	0.007 ± 0.001	0.006 ± 0.001	0.010 ± 0.002	
	K	m	N_{thr}	
$\mathcal{M}_N$	0.033 ± 0.006	1.071 ± 0.149	0.004 ± 0.001	
$\bar{\mathcal{M}}_N$	0.028 ± 0.005	0.751 ± 0.065	0.004 ± 0.001	

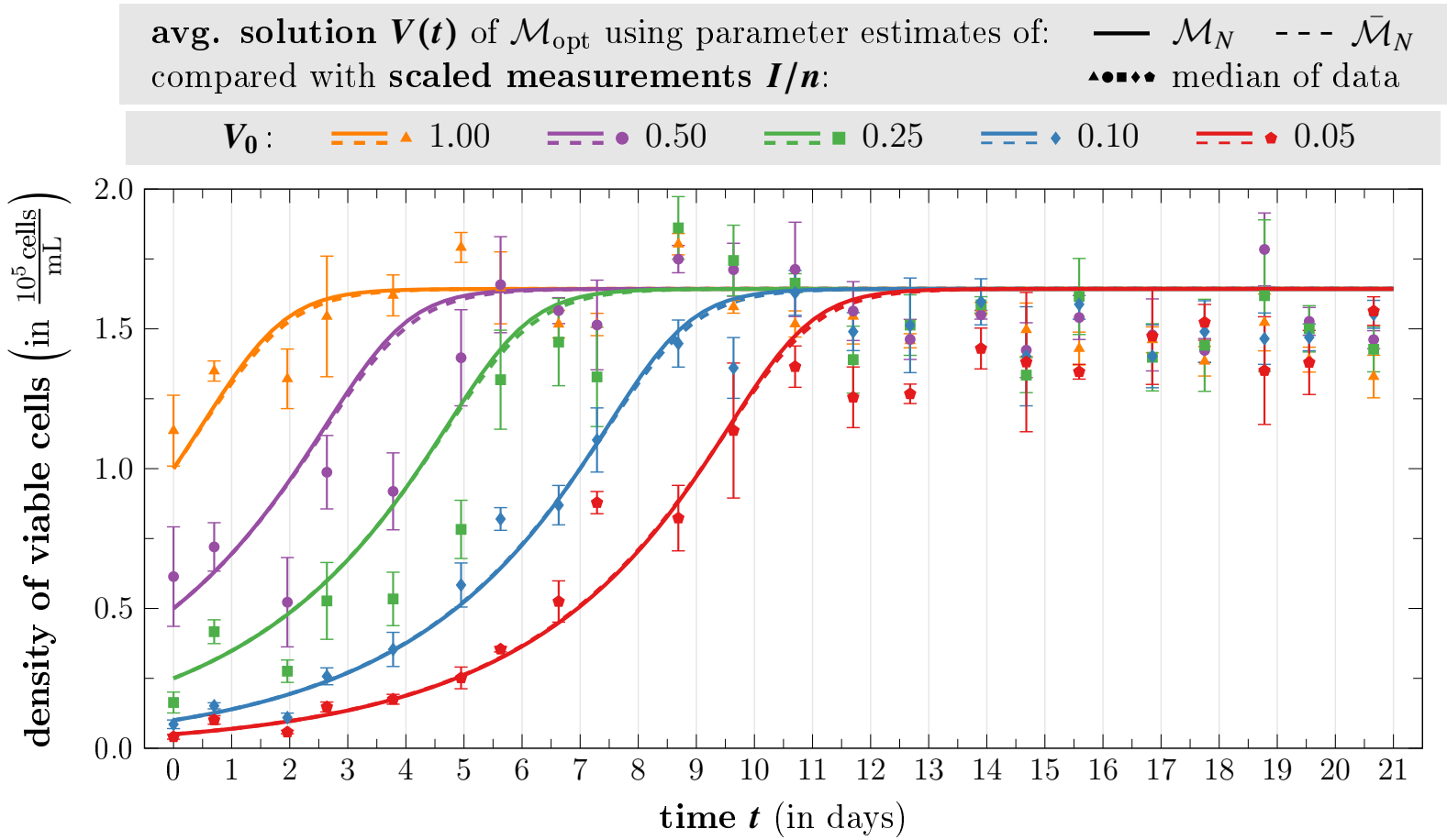
Parameter correlations



Remark: $\beta^* = \beta - \lambda$ "net" growth rate

$K^* = K(1 - \lambda/\beta)^{1/m}$ "net" carrying capacity

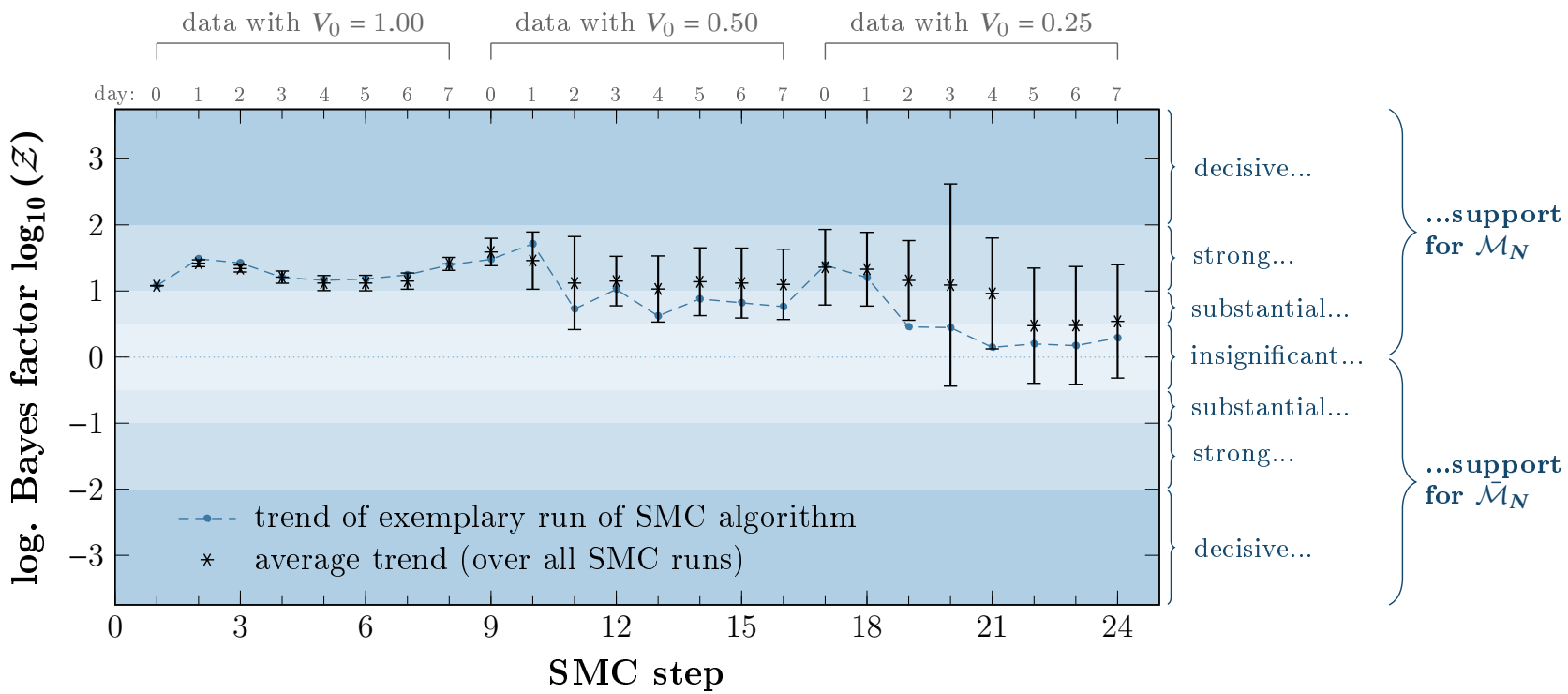
Model validation



Model comparison

Reminder: $\text{posterior} = \dfrac{\text{likelihood} \cdot \text{prior}}{\text{model evidence}}$

Bayes factor: $\mathcal{Z} = \dfrac{Z^{\mathcal{M}_N}}{Z^{\bar{\mathcal{M}}_N}}$

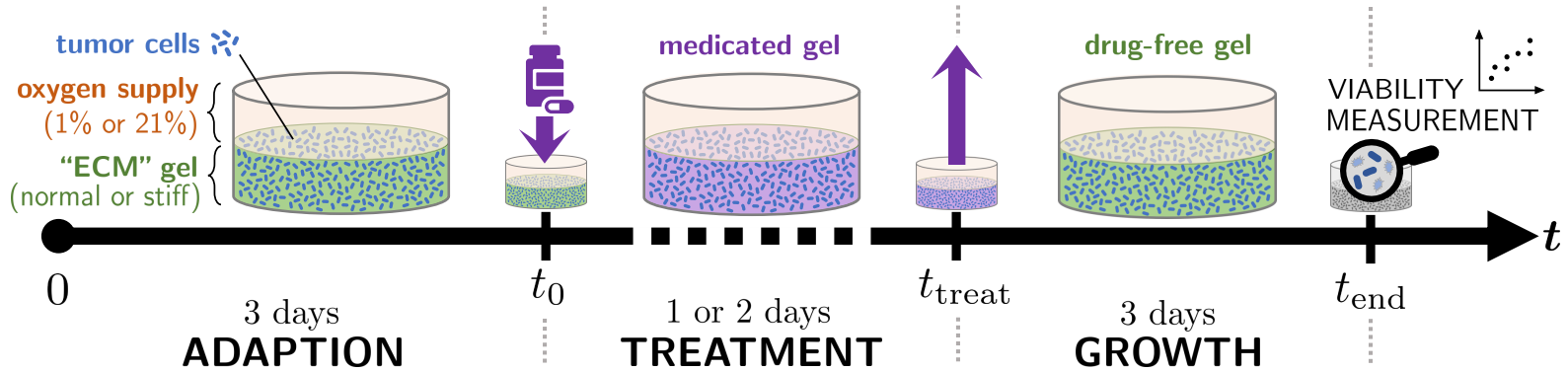


Conclusions

- The **environmental stress level** allows to **model systematically** the influence of many factors on tumour growth
- **Sequential Monte Carlo** allows for **efficient calibration** with ordered data and **model comparison**
- Calibrated models show **good fit** to data
- **Parameter calibrations** offer additional **biological insight**
- Calibrations results show that the new model is at least **plausible** as the standard one

Work in progress...

Influence of oxygen supply and ECM stiffness



Four environmental factors:

E_1 = doxorubicin concentration
E_2 = sorafenib concentration
E_3 = "hypoxia level"
E_4 = "cirrhosis level"

References

Schönfeld S, Ozkan A, Scarabosio L, Rylander MN, Kuttler C. *Environmental stress level to model tumor cell growth and survival*. MBE 2022;19(6):5509-5545.

Lima, E. A. B. F. et al. (2018). *Calibration of multi-parameter models of avascular tumor growth using time resolved microscopy data*. Scientific reports, 8(1), 1-17.

Bulté, M., Latz, J., Ullmann, E. (2020). *A practical example for the non-linear Bayesian filtering of model parameters*. In Quantification of Uncertainty: Improving Efficiency and Technology (pp. 241-272).

Zhou, Y., Johansen, A. M., Aston, J. A. (2016). *Toward automatic model comparison: an adaptive sequential Monte Carlo approach*. Journal of Computational and Graphical Statistics, 25(3), 701-726.