Development and calibration of tumor models

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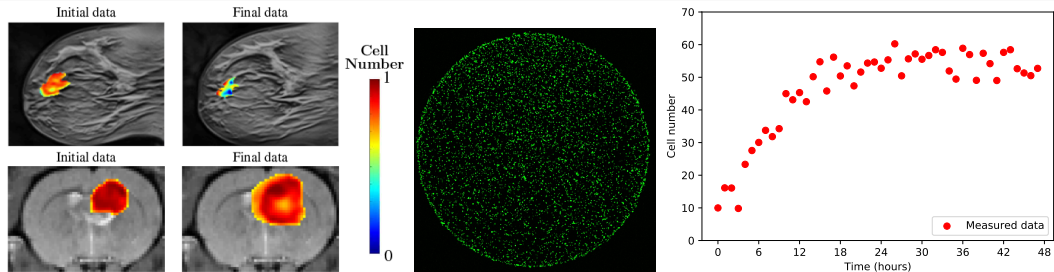THE CENTER FOR
COMPUTATIONAL
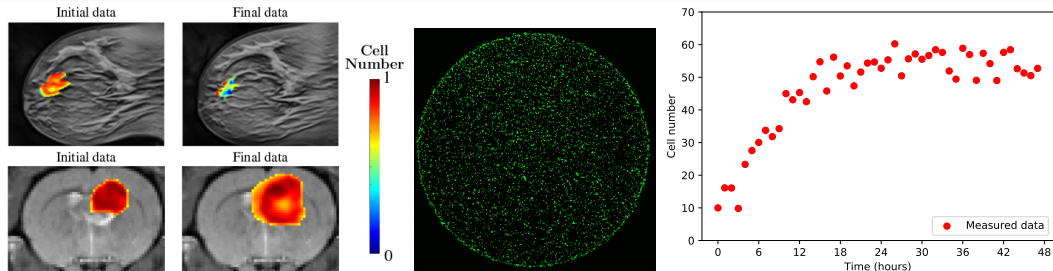ONCOLOGY

Model Calibration

- Calibration Theory:
  - Maximum Likelihood Estimation
  - Bayesian Approach
- EMCEE Python Library[1]

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[1]Foreman-Mackey, Daniel, et al. "emcee v3: A Python ensemble sampling toolkit for affine-invariant MCMC." arXiv preprint arXiv:1911.07688 (2019).
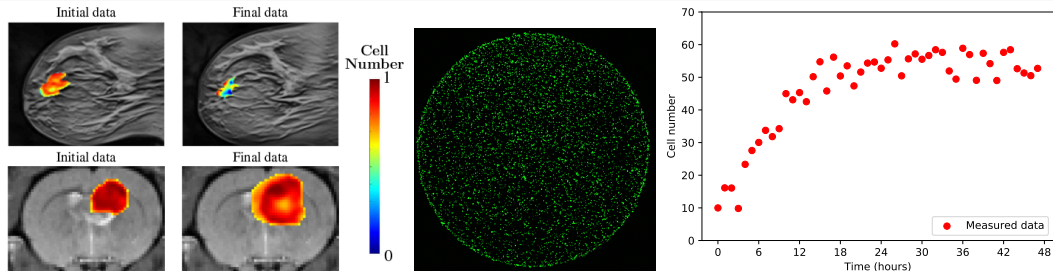
$$\frac{dN}{dt} = rN\left(1 - \frac{N}{K}\right),$$

- N: number of tumor cells;
- r: tumor growth rate;
- K: environment carrying capacity.

Initial data   Final data

Initial data   Final data

Cell Number

$$\frac{dN}{dt} = rN\left(1 - \frac{N}{K}\right),$$

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Model Calibration

It is done to adjust the selected model parameters, such as growth and death rates, to obtain the best fit between the model predicted responses and the available data.

Model calibration: frequentist and Bayesian statistics[2]

Frequentist and maximum likelihood approaches

- the probability of an event is the frequency with which the event is expected to be observed over infinite samples;
- the model parameters remain constant during the repeatable process;
- maximum likelihood approach: find the parameter that enables the model to deliver the best characterization of the true target distribution.

[2]Oden et al., Encyclopedia of Computational Mechanics Second Edition (2017)

Model calibration: frequentist and Bayesian statistics[2]

## Frequentist and maximum likelihood approaches

- the probability of an event is the frequency with which the event is expected to be observed over infinite samples;
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Bayesian approach

- transfers information from prior knowledge and observation data to the estimated parameter;
- the estimated parameter is regarded as a random variable, and the true parameter is merely a realization of the random variable.

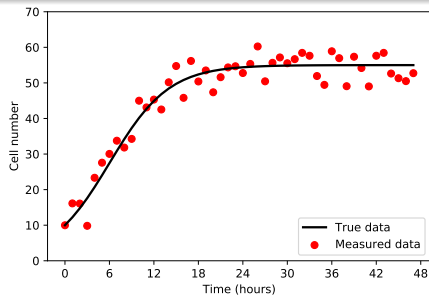[2]Oden et al., Encyclopedia of Computational Mechanics Second Edition (2017)
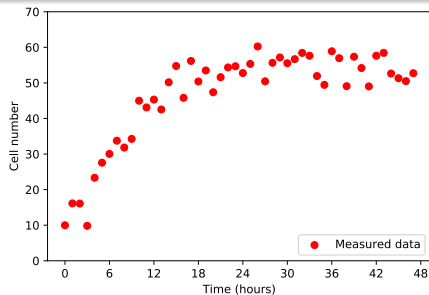
- **D**: measured data;

Mathematical model

$$\frac{dN}{dt} = rN\left(1 - \frac{N}{K}\right),$$

- $\boldsymbol{\theta}$: vector of model parameters, $\boldsymbol{\theta} = (r, K)$;
- r: tumor growth rate;
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- $\boldsymbol{Y}(\boldsymbol{\theta})$: model prediction;

Definitions

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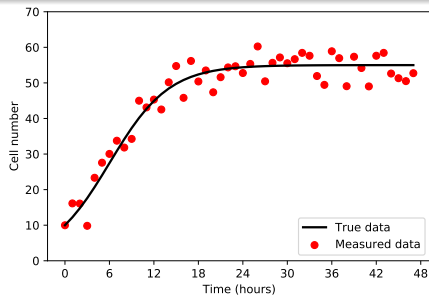
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- γ: model inadequacy.

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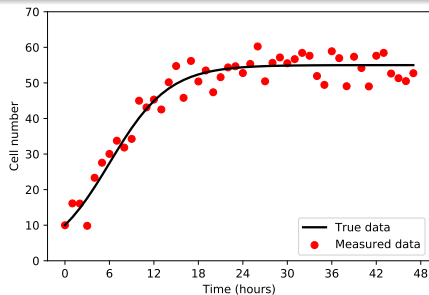
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Maximum likelihood estimation

Likelihood

The conditional probability that the data ($\boldsymbol{D}$) is observed for a given set of parameters ($\boldsymbol{\theta}$) is the likelihood $\pi(\boldsymbol{D}|\boldsymbol{\theta})$.

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Assuming:

1. the experimental noise is normally distributed ($\epsilon \sim \mathcal{N}(0_{N\times 1}, \sigma_{data}^2 \boldsymbol{I}_{N\times N})$);
2. the model inadequacy is normally distributed ($\boldsymbol{\gamma} \sim \mathcal{N}(0_{N\times 1}, \sigma_{model}^2 \boldsymbol{I}_{N\times N})$);
3. the variance of the total error (σ) is such as $\sigma^2 = \sigma_{data}^2 + \sigma_{model}^2$;
4. the data distribution as Gaussian;

Likelihood

The conditional probability that the data (D) is observed for a given set of parameters (θ) is the likelihood $\pi(D|\theta)$.

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3. the variance of the total error (σ) is such as $\sigma^2 = \sigma_{data}^2 + \sigma_{model}^2$;
4. the data distribution as Gaussian;

$$\pi(D|\theta) = \prod_{i=1}^{N_t} \frac{1}{\sqrt{2\pi\sigma^2}} e^{-\frac{(D_i - Y_i(\theta))^2}{2\sigma^2}},$$
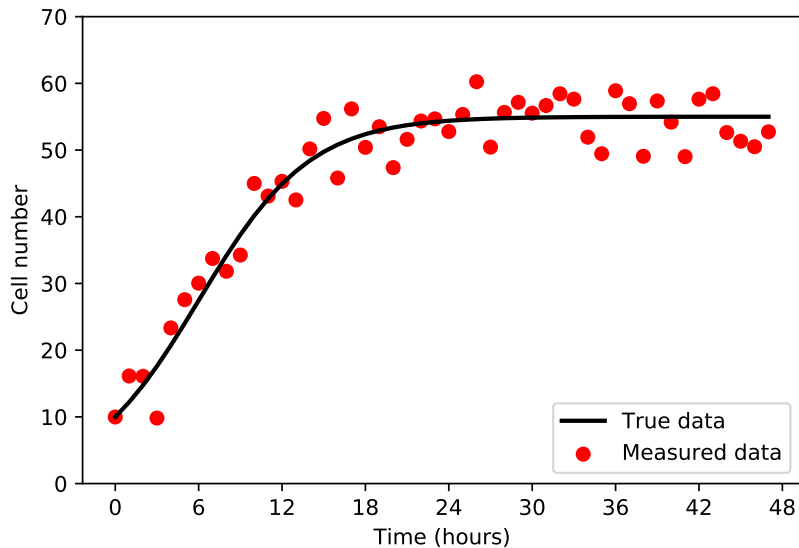
- N_t: the number of data points.

Find $\hat{\boldsymbol{\theta}} \in \Theta$, where Θ is the parameter space, that maximize the likelihood.
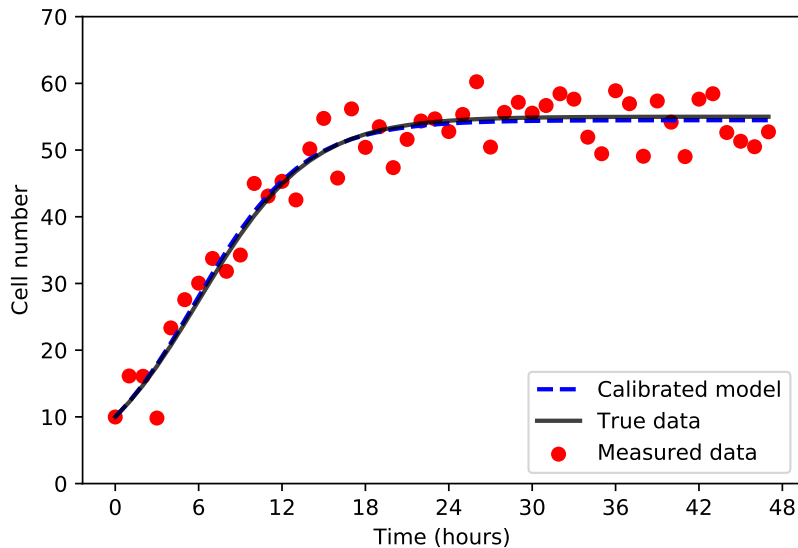
It is customary to work with the more manageable log-likelihood function.

$$
\begin{aligned}
\hat{\boldsymbol{\theta}} &= \operatorname*{argmax}_{\boldsymbol{\theta} \in \Theta} [\log \pi(\boldsymbol{D}|\boldsymbol{\theta})]; \\
&= \operatorname*{argmax}_{\boldsymbol{\theta} \in \Theta} \left[-\frac{N_t}{2} \log(2\pi) - \frac{N_t}{2} \log(\sigma^2) - \sum_{i=1}^{N_t} \frac{1}{2} \frac{(D_i - Y_i(\boldsymbol{\theta}))^2}{2\sigma^2} \right].
\end{aligned}
$$

$$\frac{dN}{dt} = rN\left(1 - \frac{N}{K}\right),$$

$r = 0.25$
$K = 59.14$

Bayesian approach

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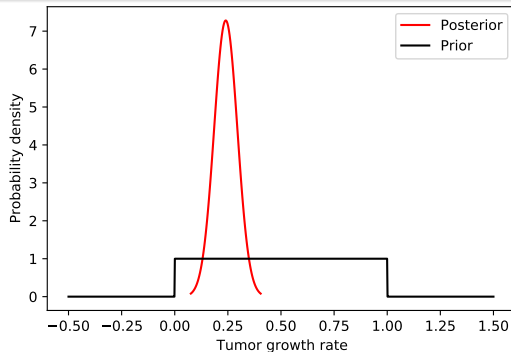
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Converting to probability densities π, if A represents the parameter $\boldsymbol{\theta}$ of a model, and B the observational data $\boldsymbol{D}$:

$$\underbrace{\pi(\boldsymbol{\theta}|\boldsymbol{D})}_{\text{posterior}} = \frac{\overbrace{\pi(\boldsymbol{D}|\boldsymbol{\theta})}^{\text{likelihood}}\overbrace{\pi(\boldsymbol{\theta})}^{\text{prior}}}{\underbrace{\pi(\boldsymbol{D})}_{\text{evidence}}}; \qquad \pi(\boldsymbol{D}) = \int_{\Theta} \pi(\boldsymbol{D}|\boldsymbol{\theta})\pi(\boldsymbol{\theta})\,\mathrm{d}\theta$$

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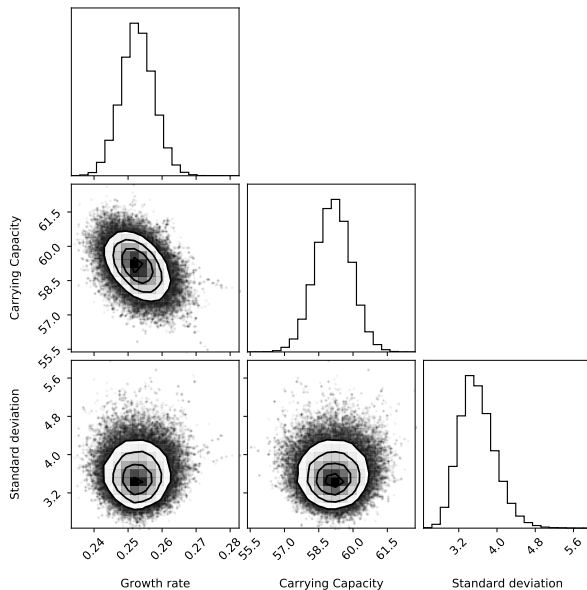$$P(A|B)P(B) = P(B|A)P(A);$$
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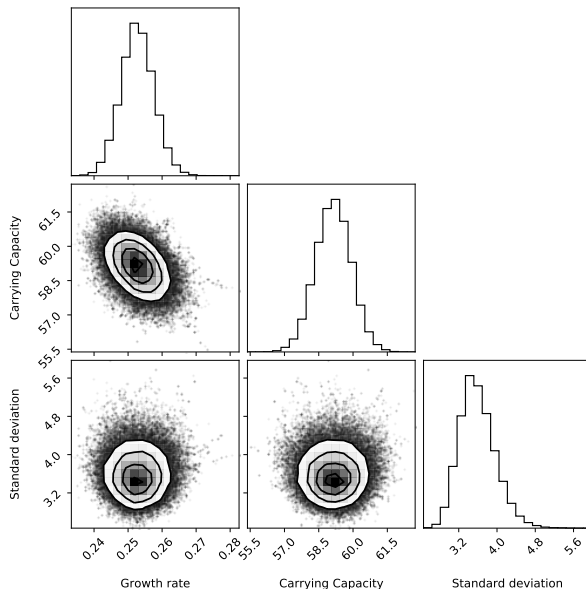
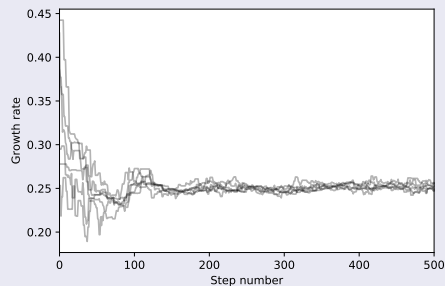## Markov Chain Monte Carlo:

Markov Chain Monte Carlo methods draw samples where the next sample is dependent on the existing sample, called a Markov Chain.