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Multifidelity approximate Bayesian computation

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Acknowledgements

- All the multifidelity ABC work was carried out by Dr Thomas Prescott.

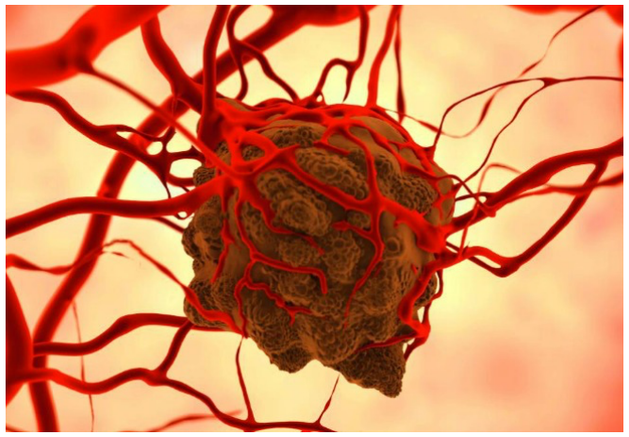
- References:

  - Multifidelity approximate Bayesian computation. *SIAM J. Uncertainty Quantification* 8(1):114-138 (2020). (also on arXiv)

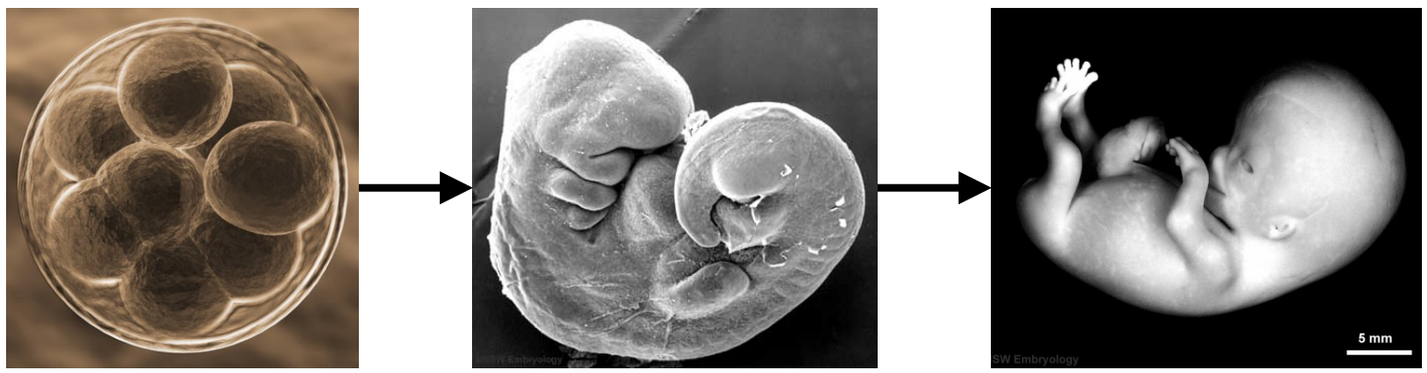
  - Multifidelity approximate Bayesian computation with sequential Monte Carlo parameter sampling. arXiv (2020).

Applied research focus

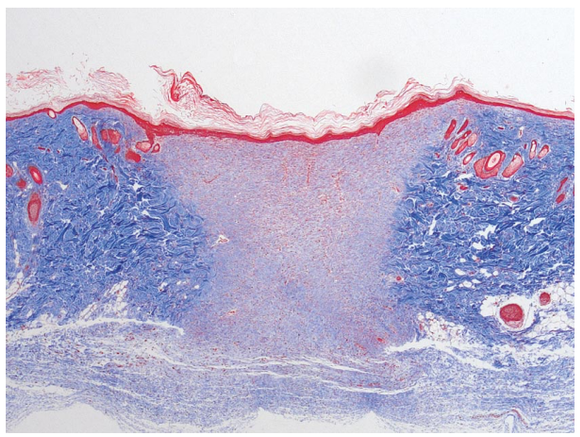
To understand the mechanisms driving collective cell motility, proliferation and death and their contributions to complex biological processes, such as those associated with development, disease and repair.



tumour growth



embryo development



wound healing

Goal: to interrogate multiplex quantitative data using validated and biologically realistic mathematical models.

Interdisciplinary methodology

Mathematical modelling computational simulations

Data analysis and model testing

improves

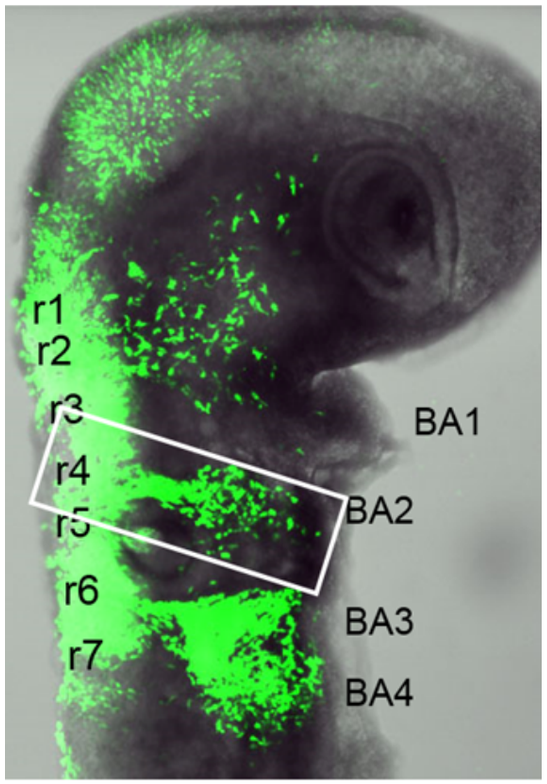
guides

Experiments: wildtype and perturbation

Neural crest invasion

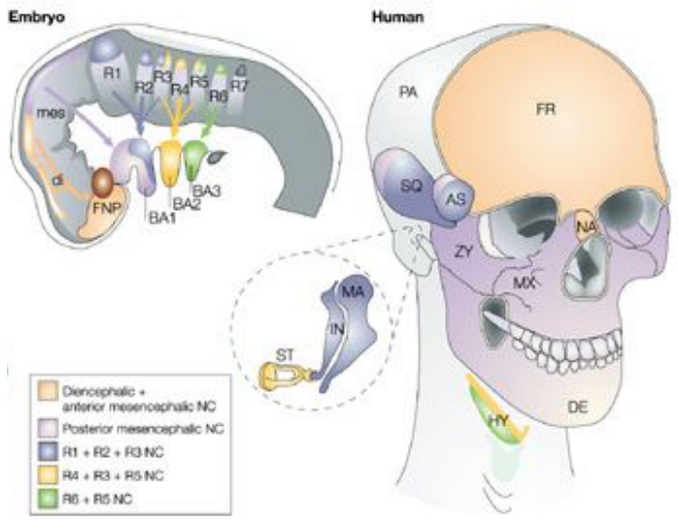
- Clinical need for a better understanding - failure results in significant morphological abnormalities.

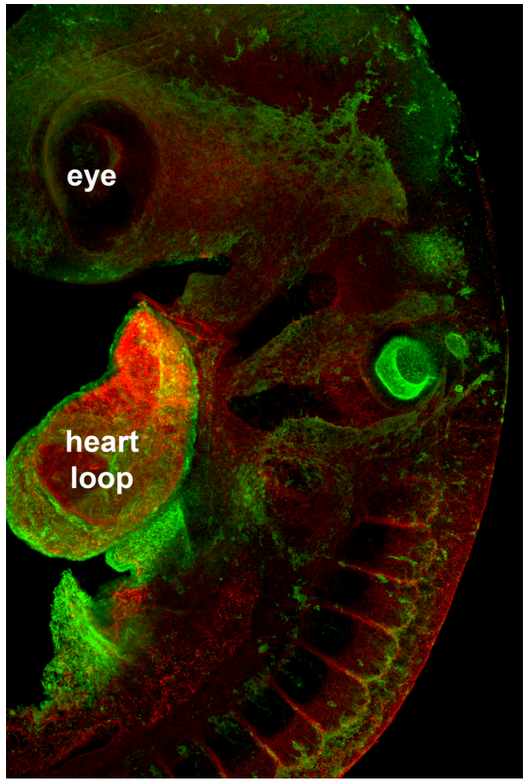
- Model system - diverse cell invasion mechanisms.



neural crest migratory streams

neural crest target sites





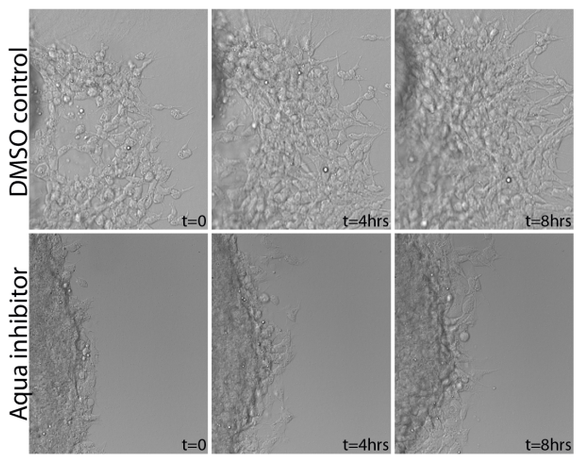
neural crest distribution

Schumacher, Baker *et al. Open Biol.* (2016).

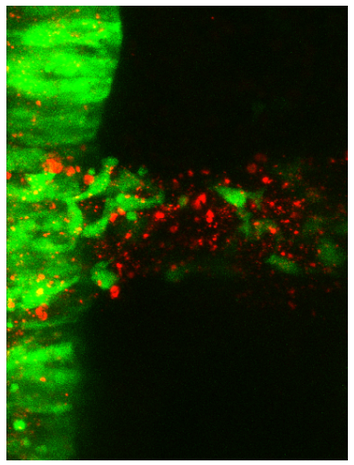
Neural crest invasion: mathematics?

- Combinatorially intractable experimentally.
  - Mechanistic models are the only solution.
- Translation from laboratory to clinic remains limited.
- Provide a bridge between *in vitro* and *in vivo*.

mechanistic model +



Validation *in vitro*

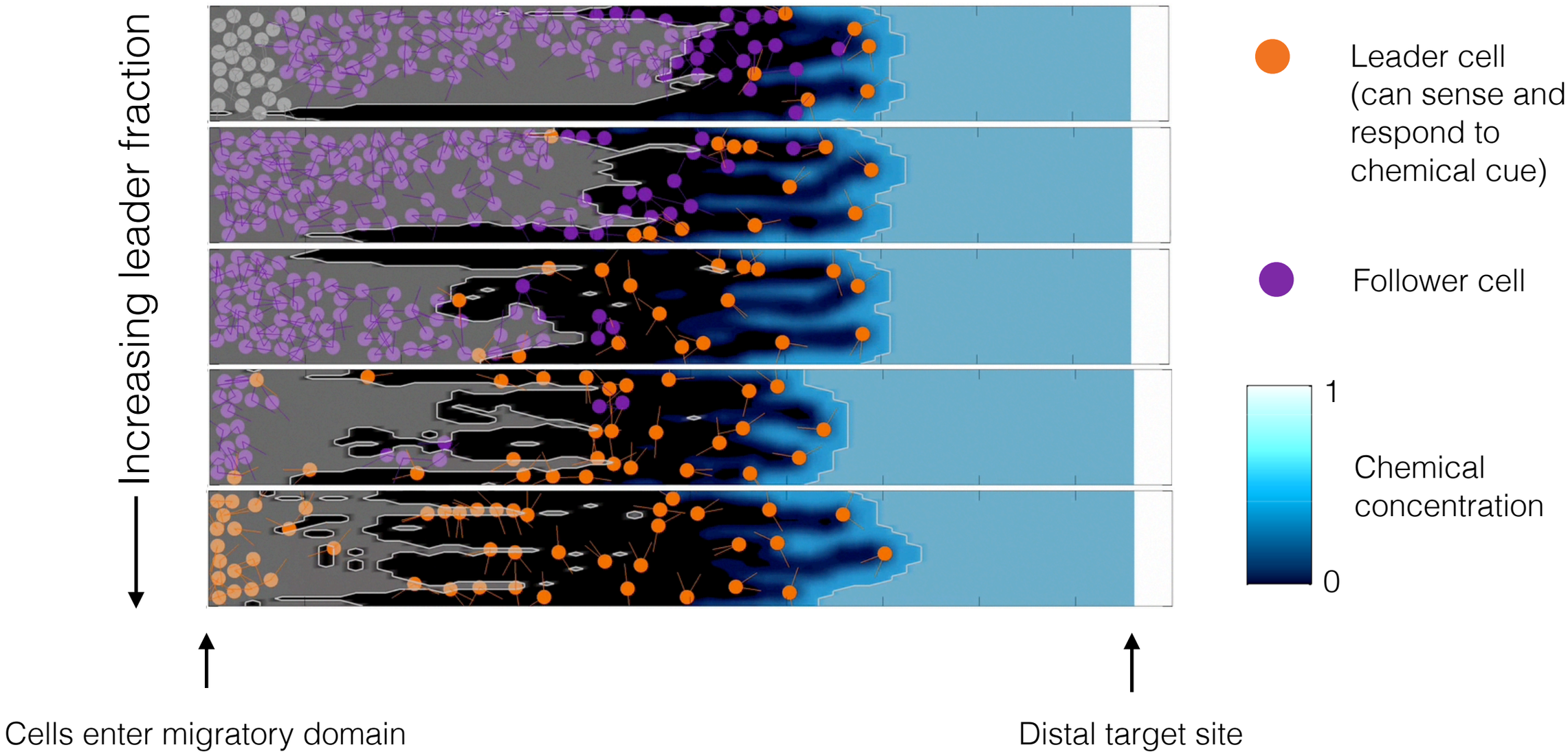


Bridge to *in vivo*

Schumacher, Baker *et al. Open Biol* (2016).

Neural crest invasion: recent work

- Population heterogeneity crucial for successful invasion.

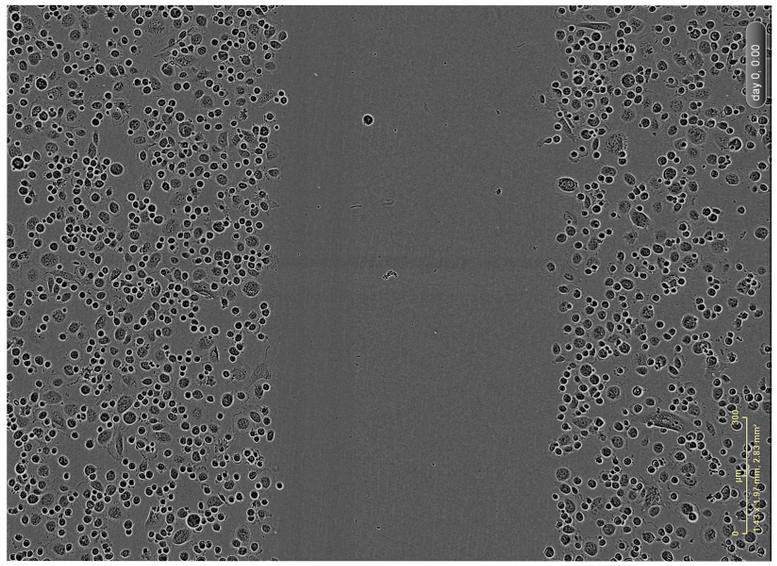


McLennan *et al. Development* (2012), *Dev. Biol.* (2015), *Development* (2015), *J. Cell. Biol.* (2017), Dyson, Maini and Baker, *Phys. Rev. E* (2012), Dyson and Baker, *J. Math. Biol.* (2015).

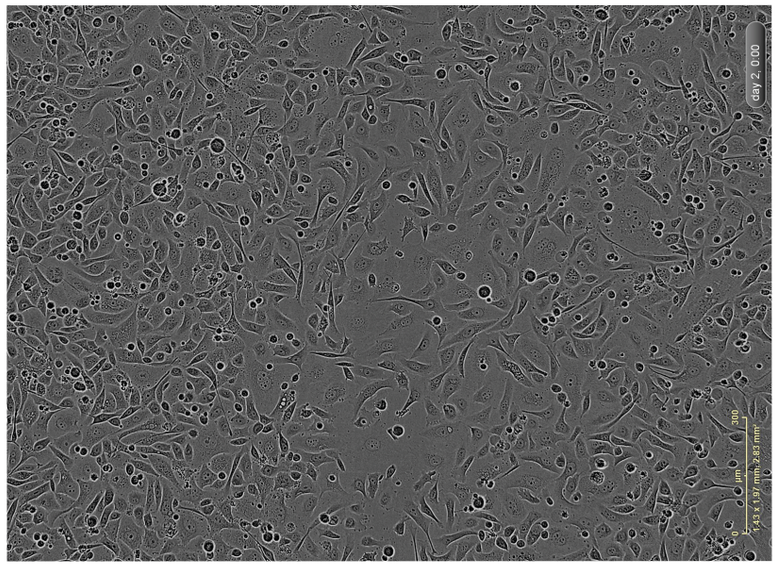
Example - *in silico* wound healing

- Use scratch (wound healing) assays to explore the importance of cell-cell pushing in cell invasion.

0 hours



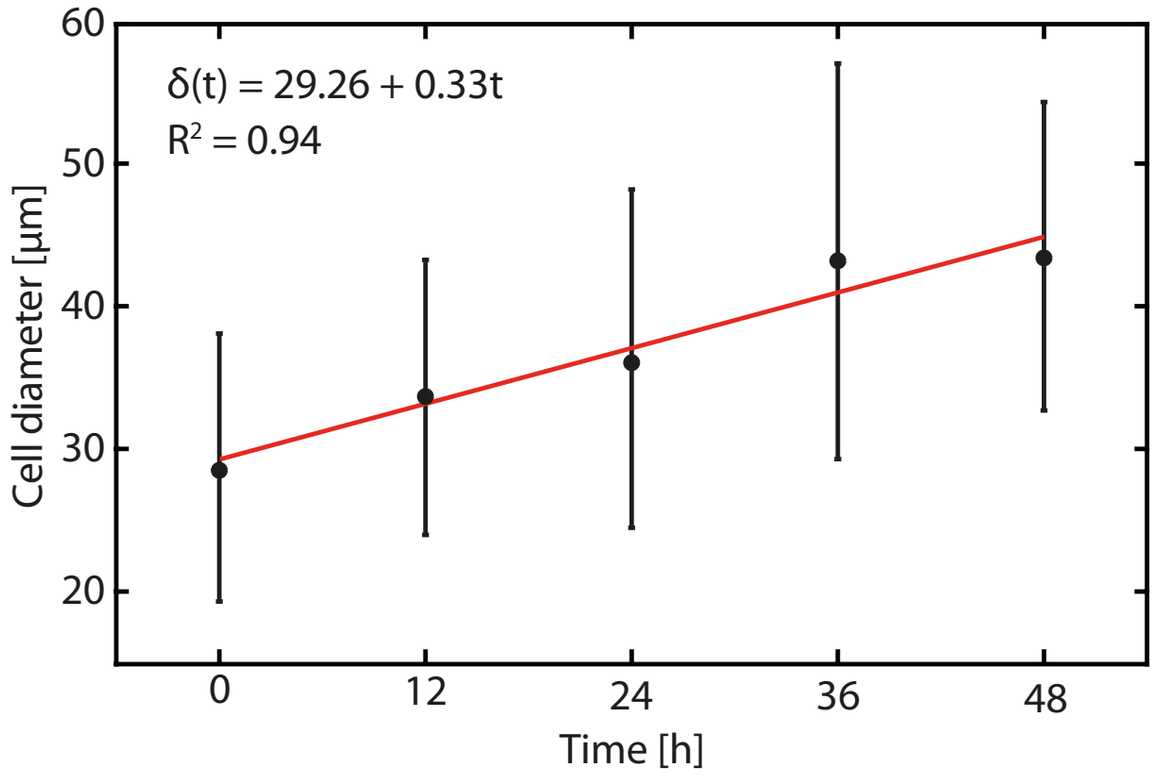
48 hours

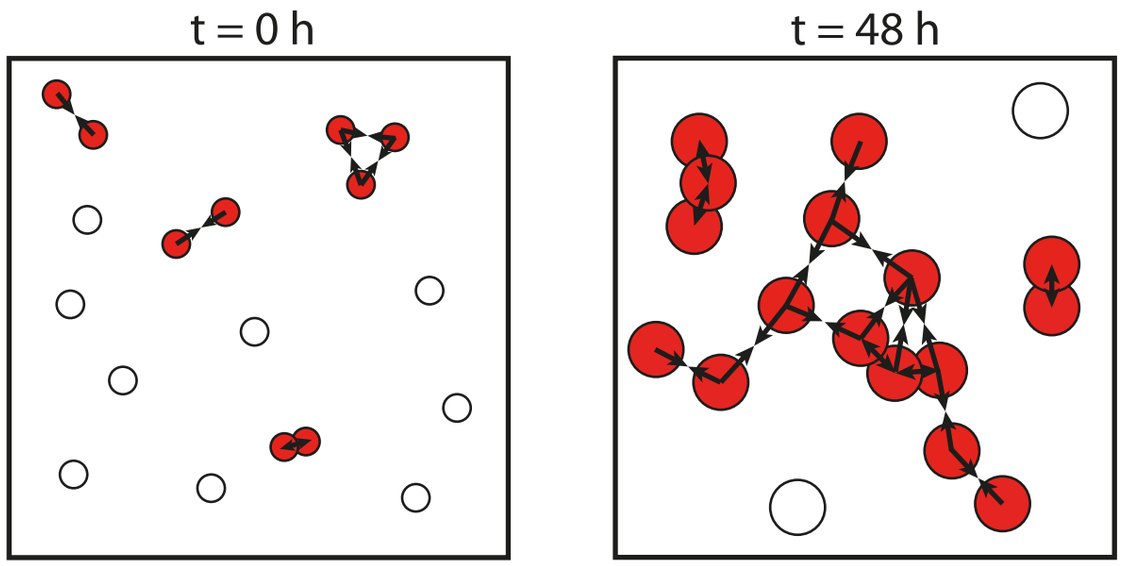


How much biological detail do we need to include to faithfully recapitulate biological observations?

Matsiaka *et al. Biomed. Phys. Eng. Exp.* (2018).

Example - *in silico* wound healing





- Consider a suite of agent-based models, with gradually increasing model complexity:

Position of cell i

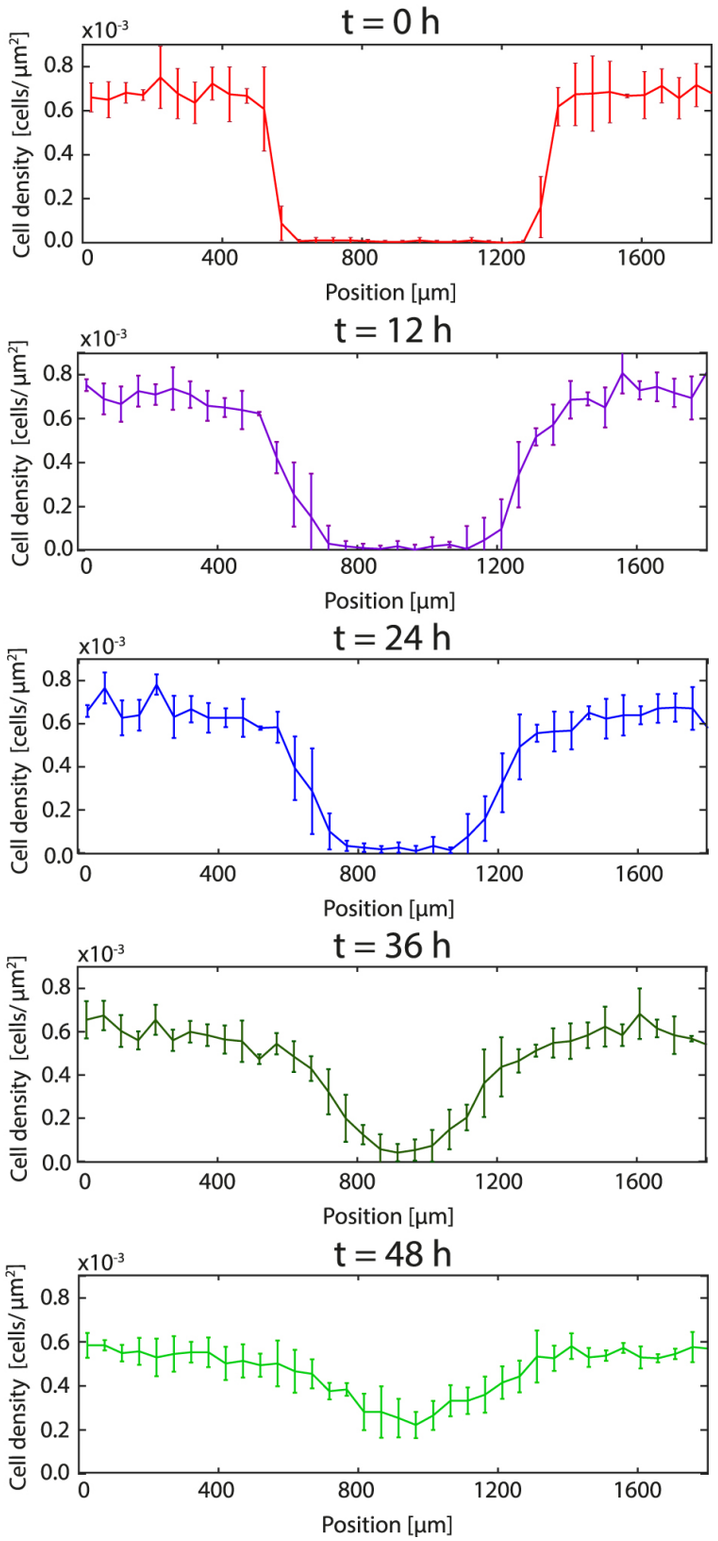
Random movements

$$\frac{\mathrm{d}}{\mathrm{d}t}x_i(t) = \sum_{i \neq j} F_{ij} + \xi_i$$

Pairwise interactions

Matsiaka *et al. Biomed. Phys. Eng. Exp.* (2018).

Example - *in silico* wound healing

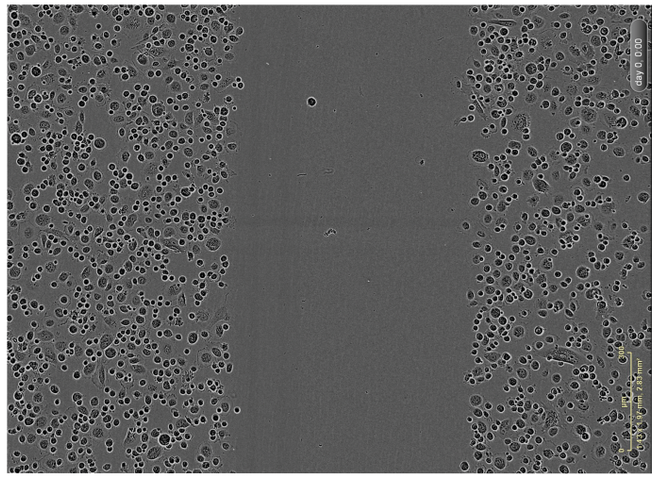


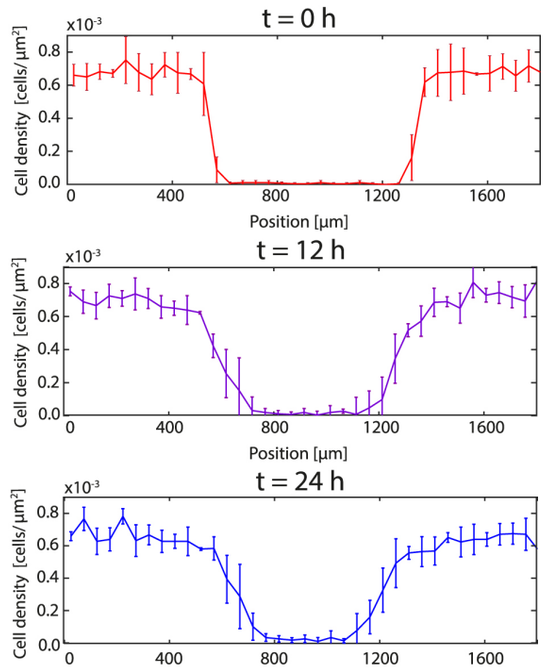
- Carried out model comparison, using these quantitative data.
- Neglecting finite size effects, together with intercellular forces (e.g. cell pushing), significantly reduces our ability to mimic and predict cell invasion speeds and profiles.

Matsiaka *et al. Biomed. Phys. Eng. Exp.* (2018).

The inverse problem

- Given quantitative data, can we estimate model parameters?





- Parameter inference using a Bayesian framework:

$$\mathbb{P}\left(\boldsymbol{\theta} \,|\, \mathcal{D}\right) \propto \mathbb{P}\left(\mathcal{D} \,|\, \boldsymbol{\theta}\right) \mathbb{P}\left(\boldsymbol{\theta}\right)$$

- For the models we consider, the likelihood is intractable…

Approximate Bayesian computation

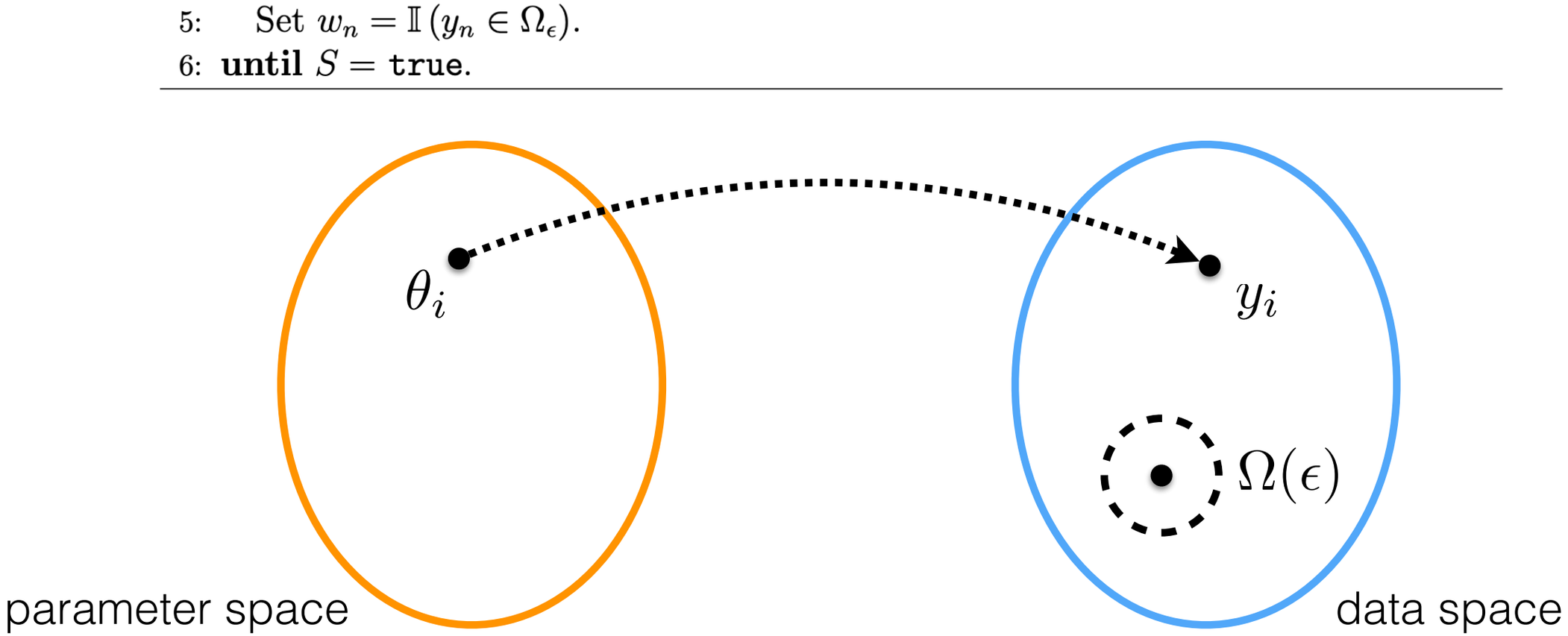
- Estimate the posterior using repeated forward simulation:

Algorithm 1 Rejection sampling ABC (ABC-RS)

Input: Data y_{obs} and neighbourhood Ω_ϵ; model $f(\cdot \mid \theta)$; prior π; sample index $n = 0$; stopping criterion S.

Output: Weighted sample $\{\theta_n, w_n\}_{n=1}^{N}$.

1: **repeat**
2: Increment $n \leftarrow n + 1$.
3: Generate $\theta_n \sim \pi(\cdot)$.
4: Simulate $y_n \sim f(\cdot \mid \theta_n)$.
5: Set $w_n = \mathbb{I}(y_n \in \Omega_\epsilon)$.
6: **until** $S =$ `true`.



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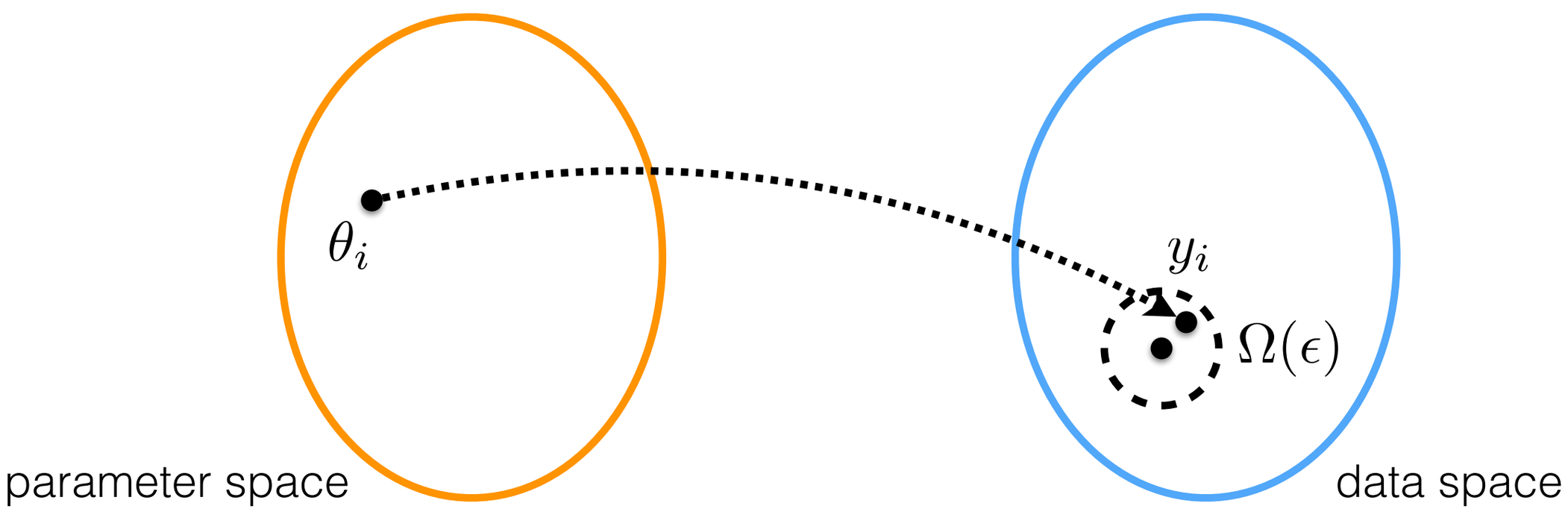


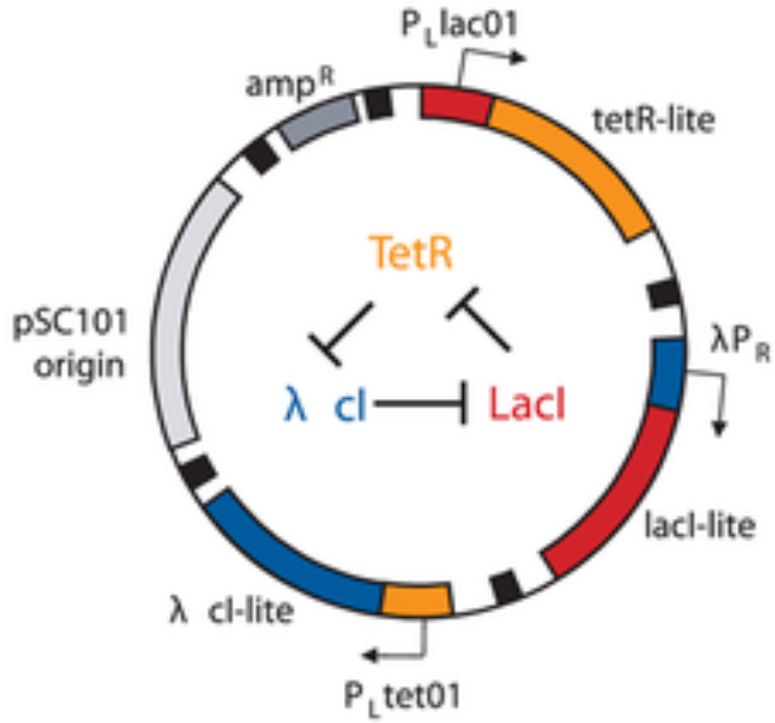
Example - repressilator model

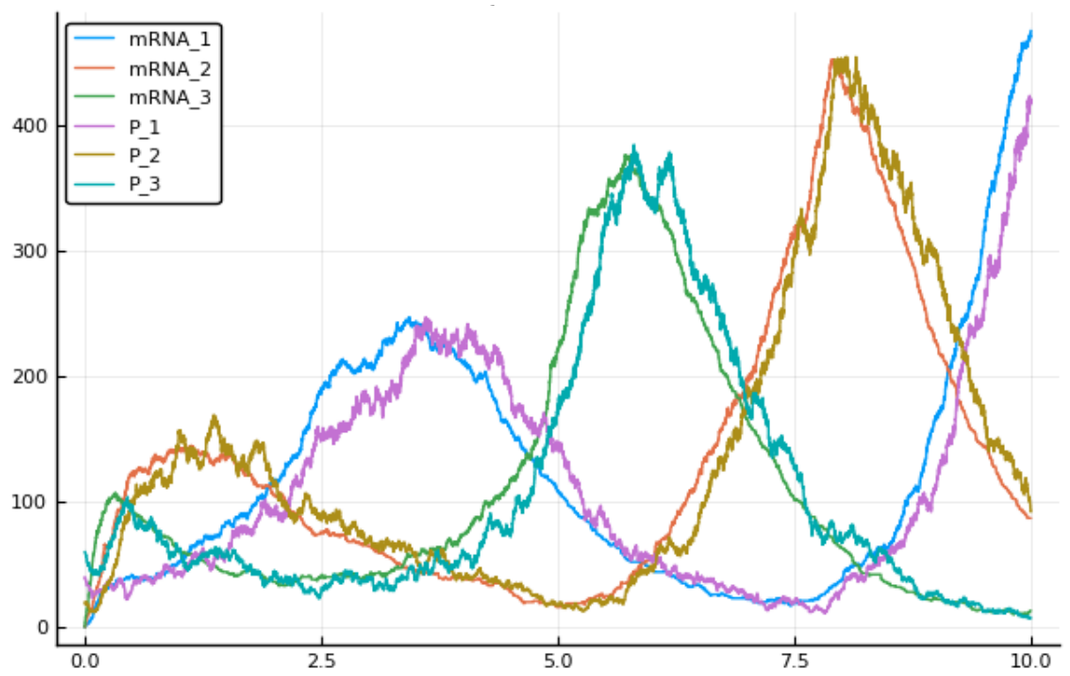
$$\xrightarrow{\alpha_0+\alpha f(p_j)} \quad m_i \xrightarrow{1} \emptyset \qquad \text{for } (i,j) = (1,3),\ (2,1), \text{ and } (3,2)$$

$$m_i \xrightarrow{\beta} m_i + p_i \qquad \text{for } i = 1,2,3$$

$$p_i \xrightarrow{\beta} \emptyset \qquad \text{for } i = 1,2,3$$

$$f(p) = \frac{K_h^n}{(K_h^n + p^n)}$$





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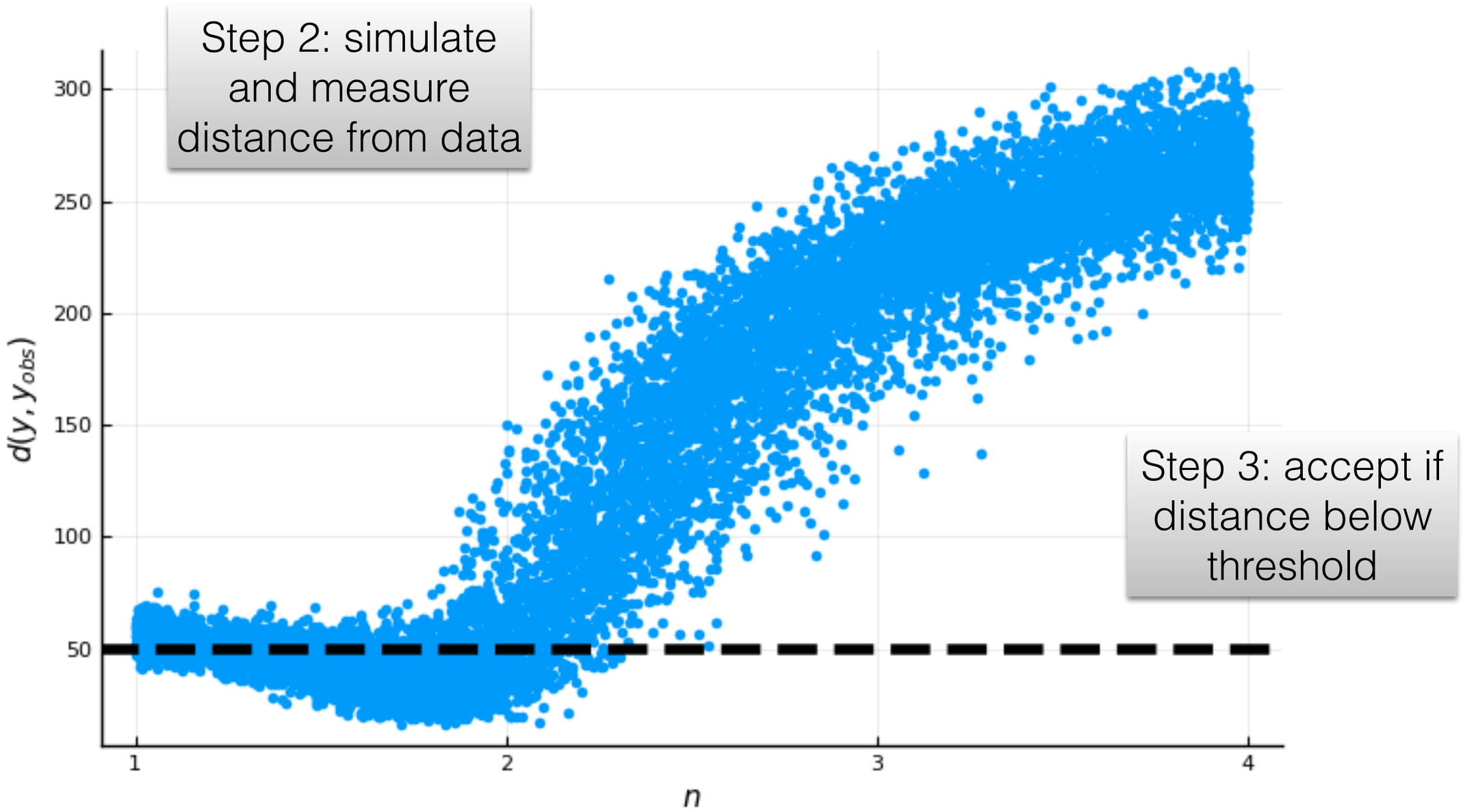

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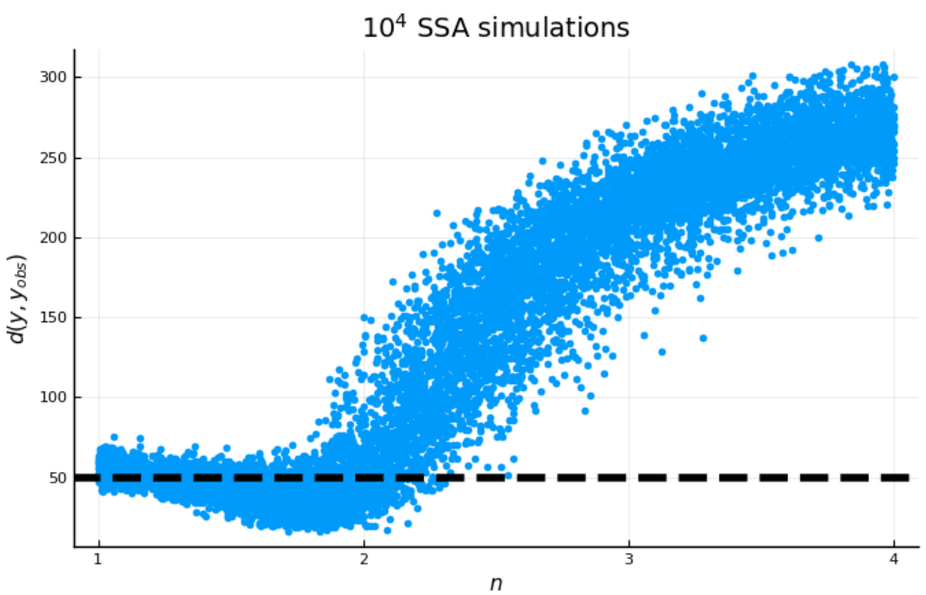
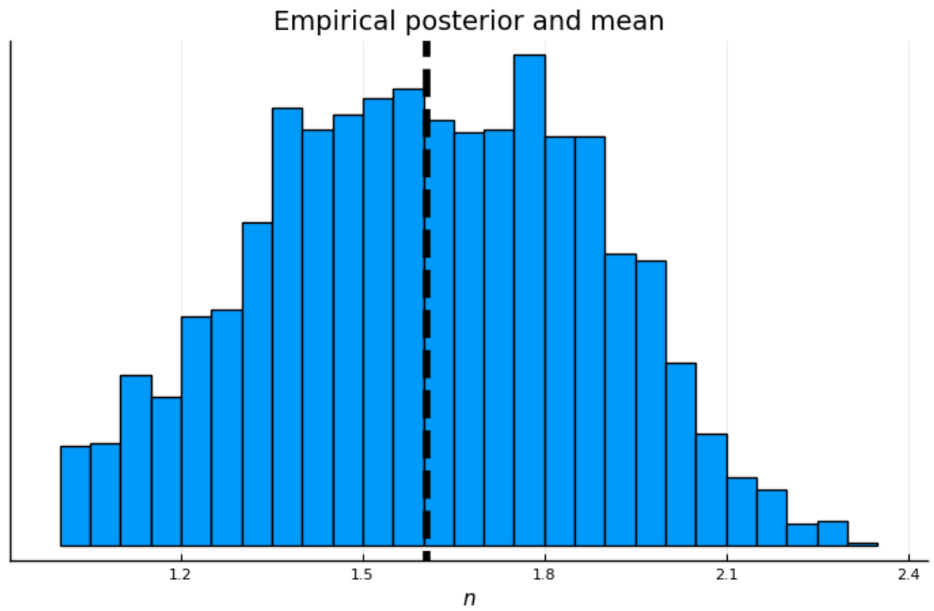
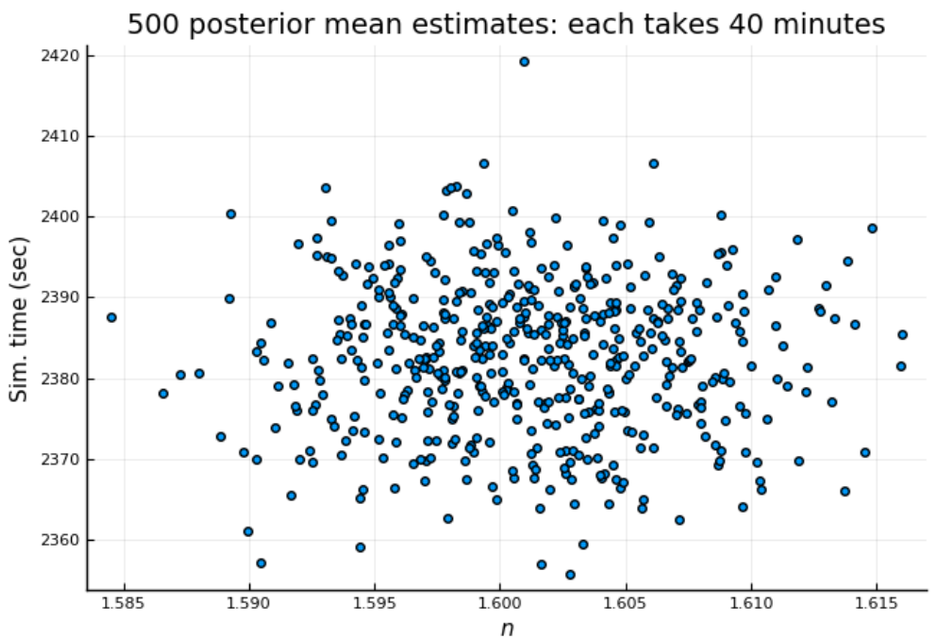




- Bottleneck - repeated simulation of the model.
- Trade off between simulation time and variance.

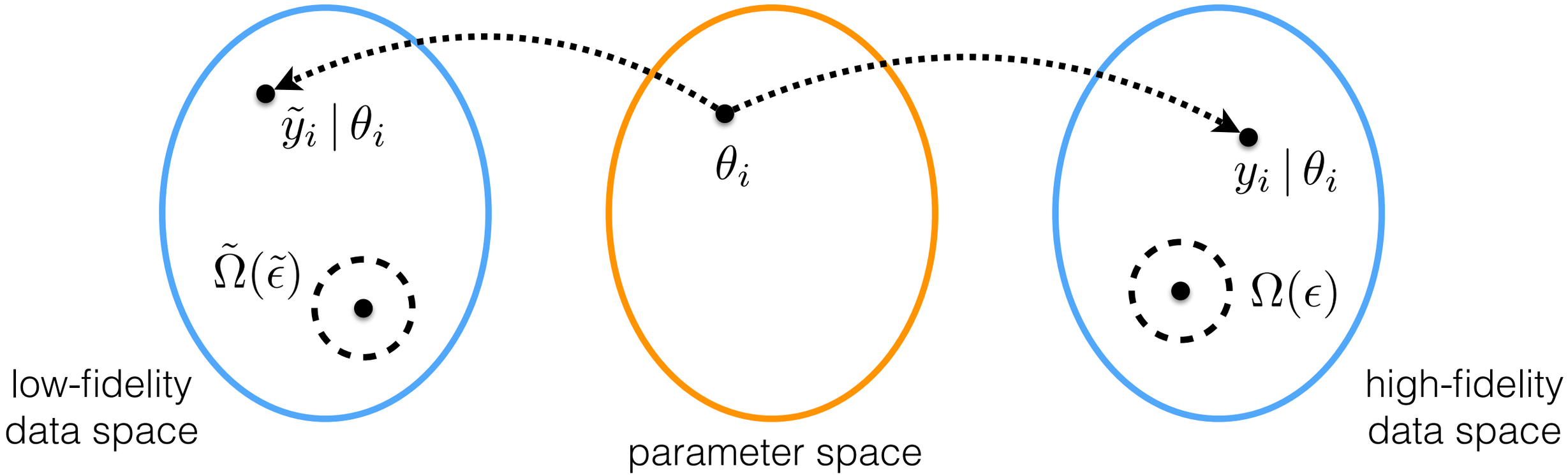


Increasing the efficiency of ABC

- Use a more intelligent exploration of parameter space.
  - Importance sampling, sequential Monte Carlo *etc.*
- Make the weight (accept / reject) less expensive to calculate.
  - Make simulations less expensive.
- Reduce model dimension, use a surrogate or approximate model, simulate over a shorter time interval, use coarser discretisation of space / time *etc.*

Aim of this talk: to demonstrate that we can do both at once, whilst maintaining accuracy.

Multifidelity ABC: the idea



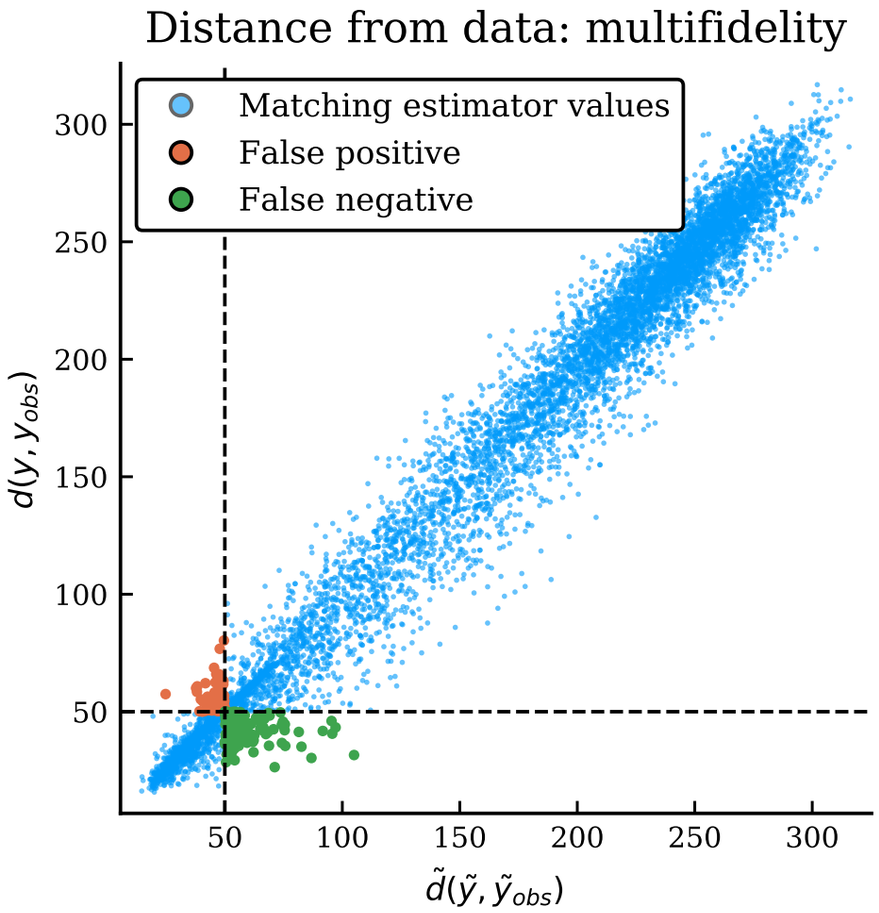
Each model requires a distance function, data and acceptance threshold e.g.

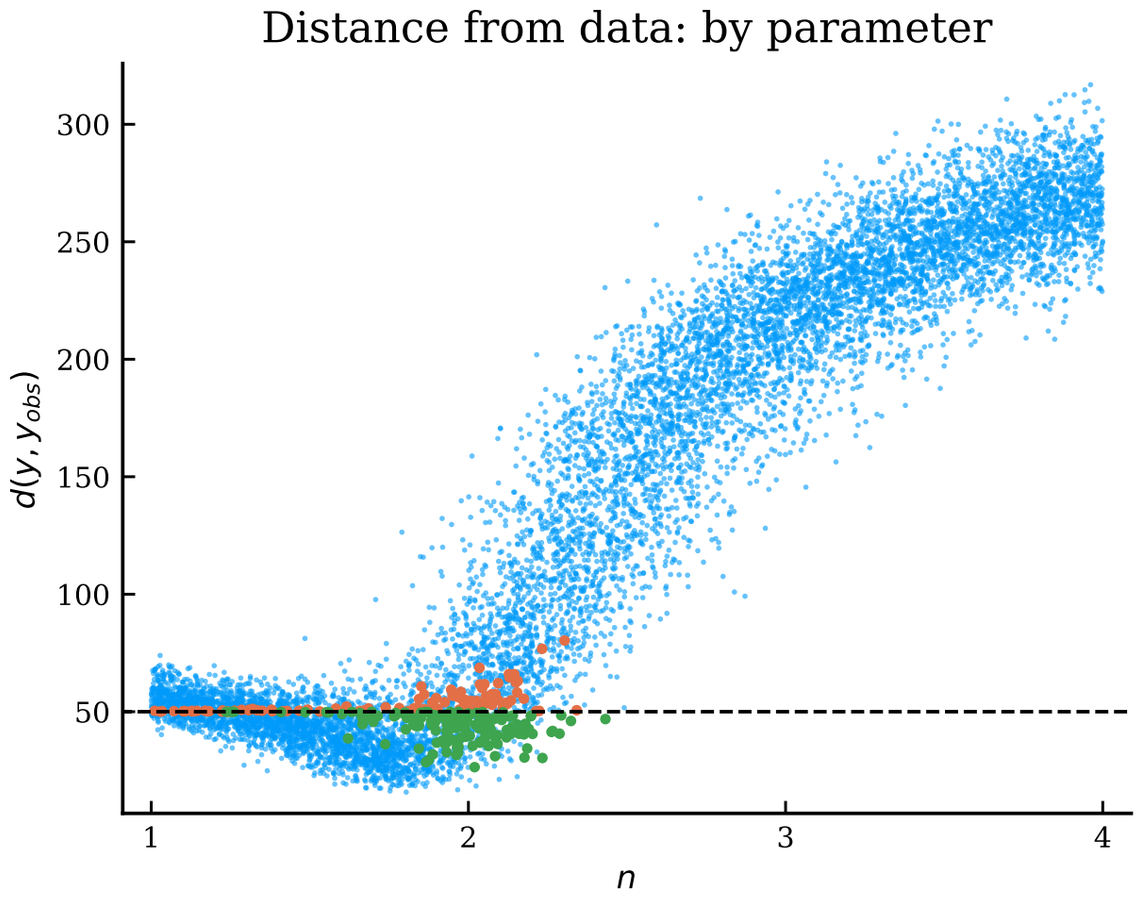
$$\Omega_\epsilon(d, y_{\text{obs}}) = \{y \in \mathcal{Y} \mid d(y, y_{\text{obs}}) < \epsilon\}$$

Multifidelity ABC: the problem

- How to combine the outputs of the two models, so that the result is unbiased weights?

- How can we make this process efficient?





Multifidelity ABC: the algorithm

- Attempt to make an “early decision” using the low-fidelity model, and “sometimes” check that decision using the high-fidelity model.

- Decision to check is made uniformly at random, with probability $\alpha(\tilde{y}, \theta_n)$.

  - Here, we will take a simple approach, assuming

$$\alpha(\tilde{y}, \theta_n) = \eta_1 \mathbb{I}(\tilde{y} \in \tilde{\Omega}(\tilde{\epsilon})) + \eta_2 \mathbb{I}(\tilde{y} \notin \tilde{\Omega}(\tilde{\epsilon}))$$

- We also assume, for simplicity,

$$\tilde{\mathcal{Y}} = \mathcal{Y} \qquad \tilde{y}_{\text{obs}} = y_{\text{obs}} \qquad \tilde{d} = d \qquad \tilde{\epsilon} = \epsilon$$

$$\implies \quad \tilde{\Omega}_{\tilde{\epsilon}} = \Omega_{\epsilon}$$

Multifidelity ABC: the algorithm

Algorithm 4 Rejection sampling multifidelity ABC (MF-ABC-RS)

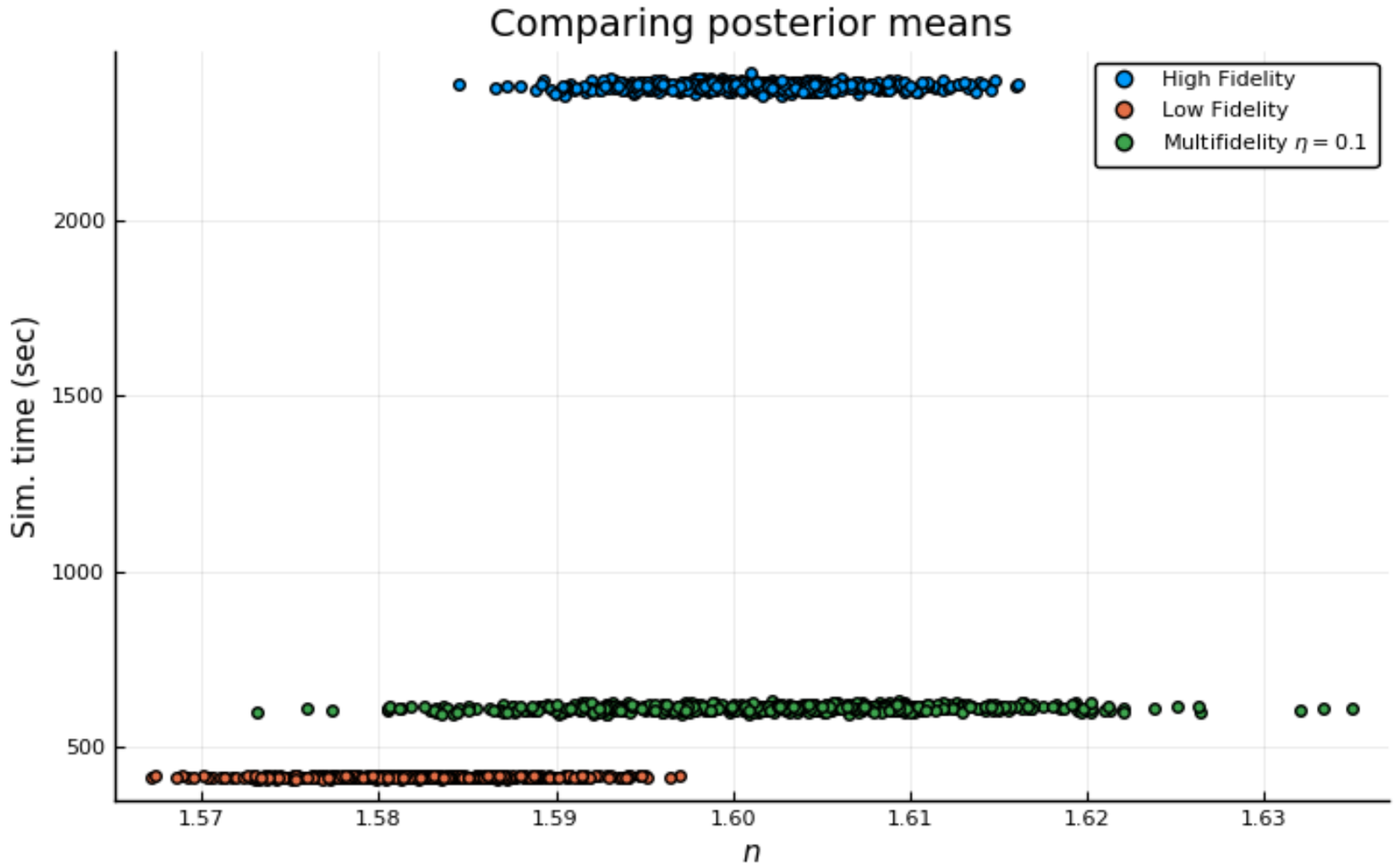
Input: Data y_{obs} and neighbourhood Ω_ϵ; prior π; models $\tilde{f}(\cdot \mid \theta)$, $f(\cdot \mid \tilde{y}, \theta)$; continuation probability function $\alpha = \alpha(\tilde{y}, \theta)$; sample index $n = 0$; stopping condition S.

Output: Weighted sample $\{\theta_n, w_n\}_{n=1}^N$.

repeat
  Increment $n \leftarrow n + 1$.
  Generate $\theta_n \sim \pi(\cdot)$.
  Simulate $\tilde{y}_n \sim \tilde{f}(\cdot \mid \theta_n)$.
  Set $w_n = \mathbb{I}(\tilde{y}_n \in \Omega_\epsilon)$.
  Generate $u_n \sim \text{Uniform}(0, 1)$.
  if $u_n < \alpha(\tilde{y}_n, \theta_n)$ **then**
    Simulate $y_n \sim f(\cdot \mid \tilde{y}_n, \theta_n)$.
    Update $w_n \leftarrow w_n + [\mathbb{I}(y \in \Omega_\epsilon) - w_n] / \alpha(\tilde{y}_n, \theta_n)$.
  end if
until $S =$ `true`.

Multifidelity ABC: results

- For non-zero continuation probability, the weighted sample has the correct distribution, the ABC approximation to the posterior induced by the high-fidelity model.



Multifidelity ABC: efficiency

- Effective sample size:

$$\mathrm{ESS} = \frac{\left(\sum_n w_n\right)^2}{\sum_n w_n^2}.$$

- Observed efficiency - defined as the effective number of samples per time unit:

$$\frac{\mathrm{ESS}}{T_{\mathrm{total}}} = \frac{\left(\sum_n w_n\right)^2}{\left(\sum_n w_n^2\right)\left(\sum_n T_n\right)}$$

- Theoretical efficiency:

$$\psi = \frac{\mathbb{E}(w)^2}{\mathbb{E}(w^2)\mathbb{E}(T)}$$

Optimal continuation probabilities

- Theoretical efficiency can be written

$$\psi(\eta_1, \eta_2) = \frac{\mathbb{E}(w)^2}{\mathbb{E}(w^2)\mathbb{E}(T)} = \frac{Z^2}{\phi(\eta_1, \eta_2)}$$

where

$$\phi(\eta_1, \eta_2) = \left(W + \left(\frac{1}{\eta_1} - 1\right) W_{\mathrm{fp}} + \left(\frac{1}{\eta_2} - 1\right) W_{\mathrm{fn}}\right) \times \left(\bar{T}_{\mathrm{lo}} + \eta_1 \bar{T}_{\mathrm{hi,p}} + \eta_2 \bar{T}_{\mathrm{hi,n}}\right)$$

probability of false positive

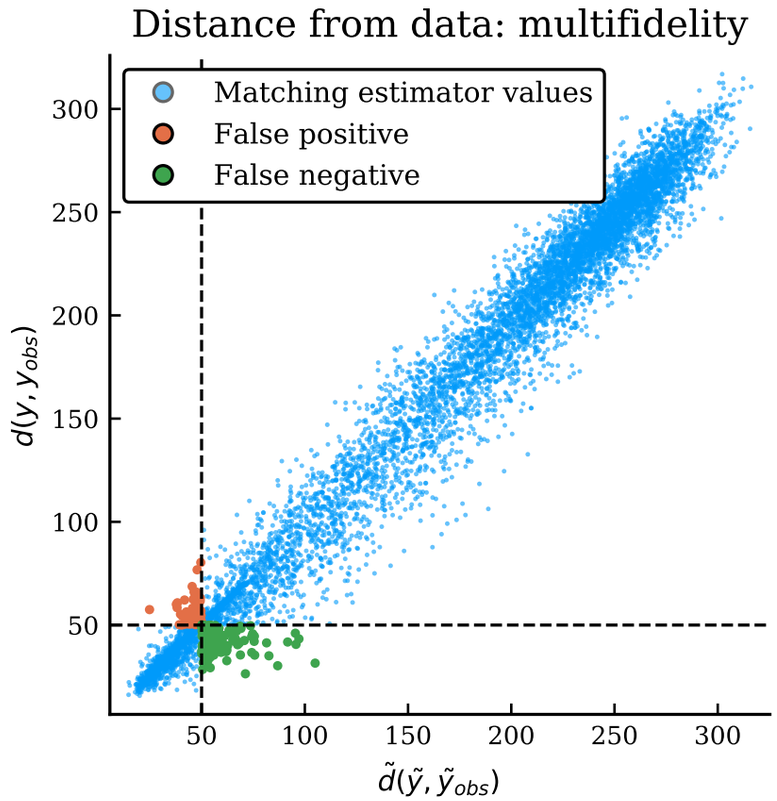
probability of false negative

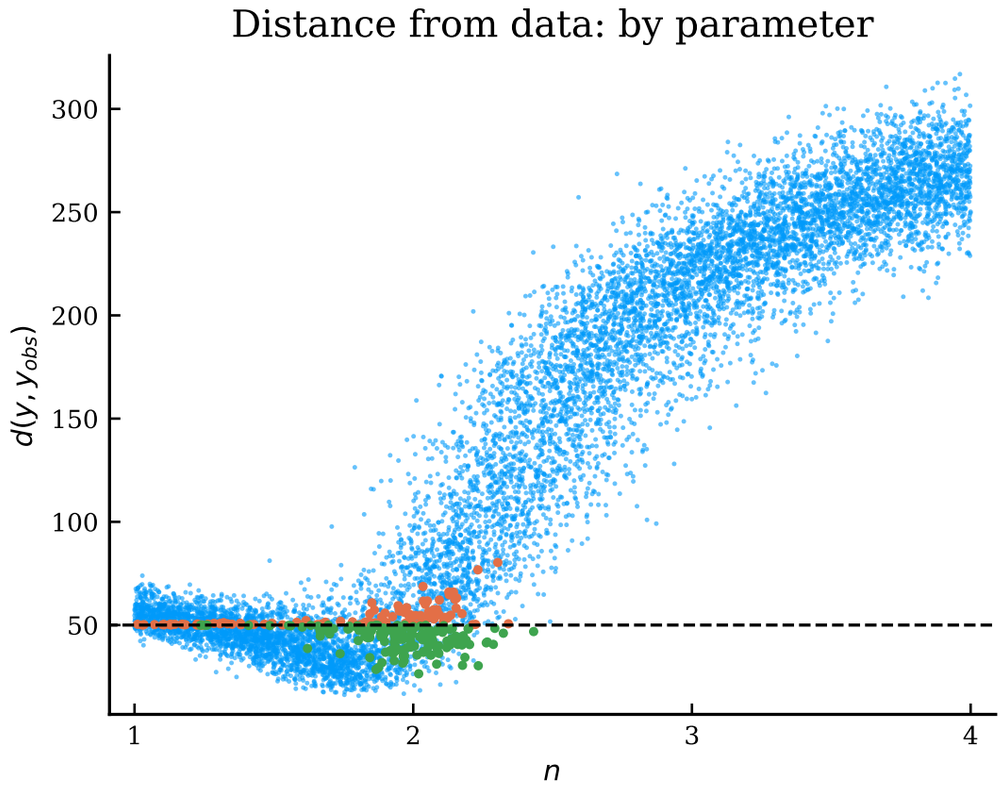
average simulation time for low-fidelity model

average simulation time for high-fidelity model given low-fidelity models close/far

Multifidelity ABC: efficiency

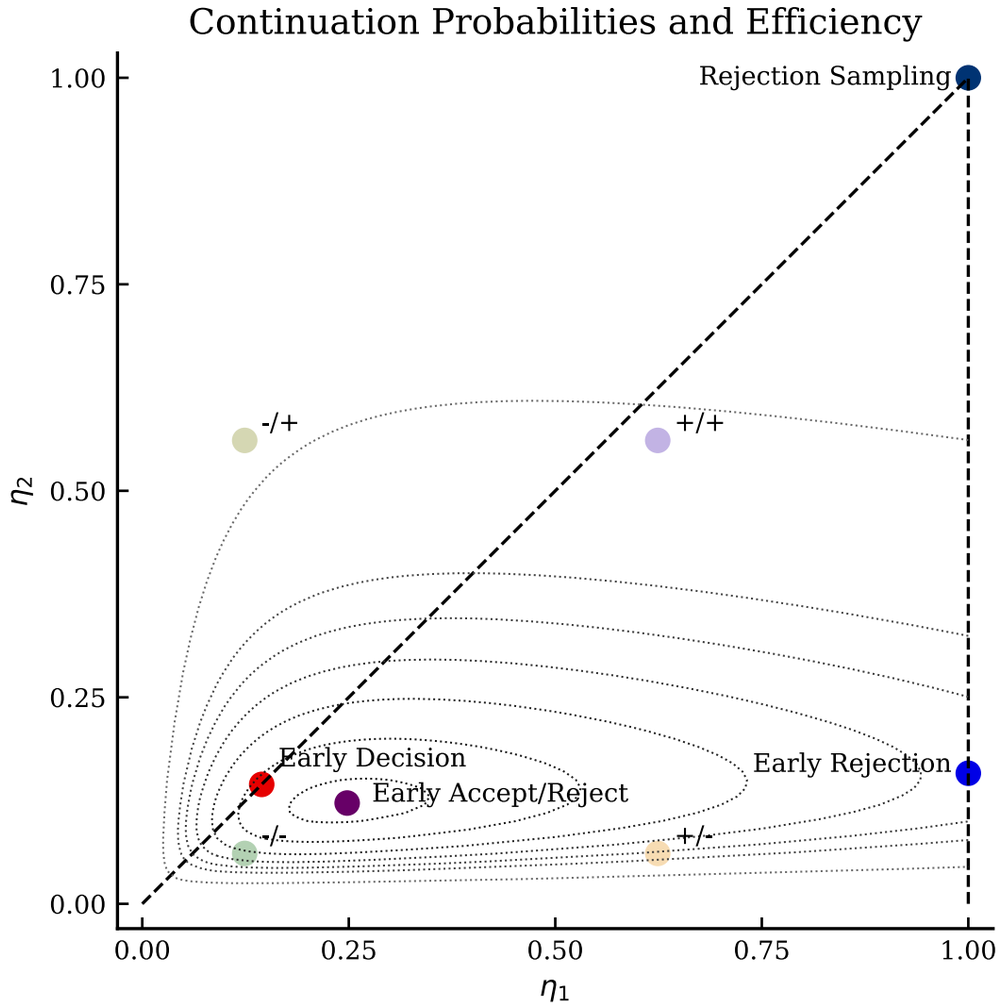
- Derive analytical expressions for the optimal continuation probabilities, given estimates of these quantities.
  - In practice: adapt the continuation probabilities “on the fly”, as samples are generated…

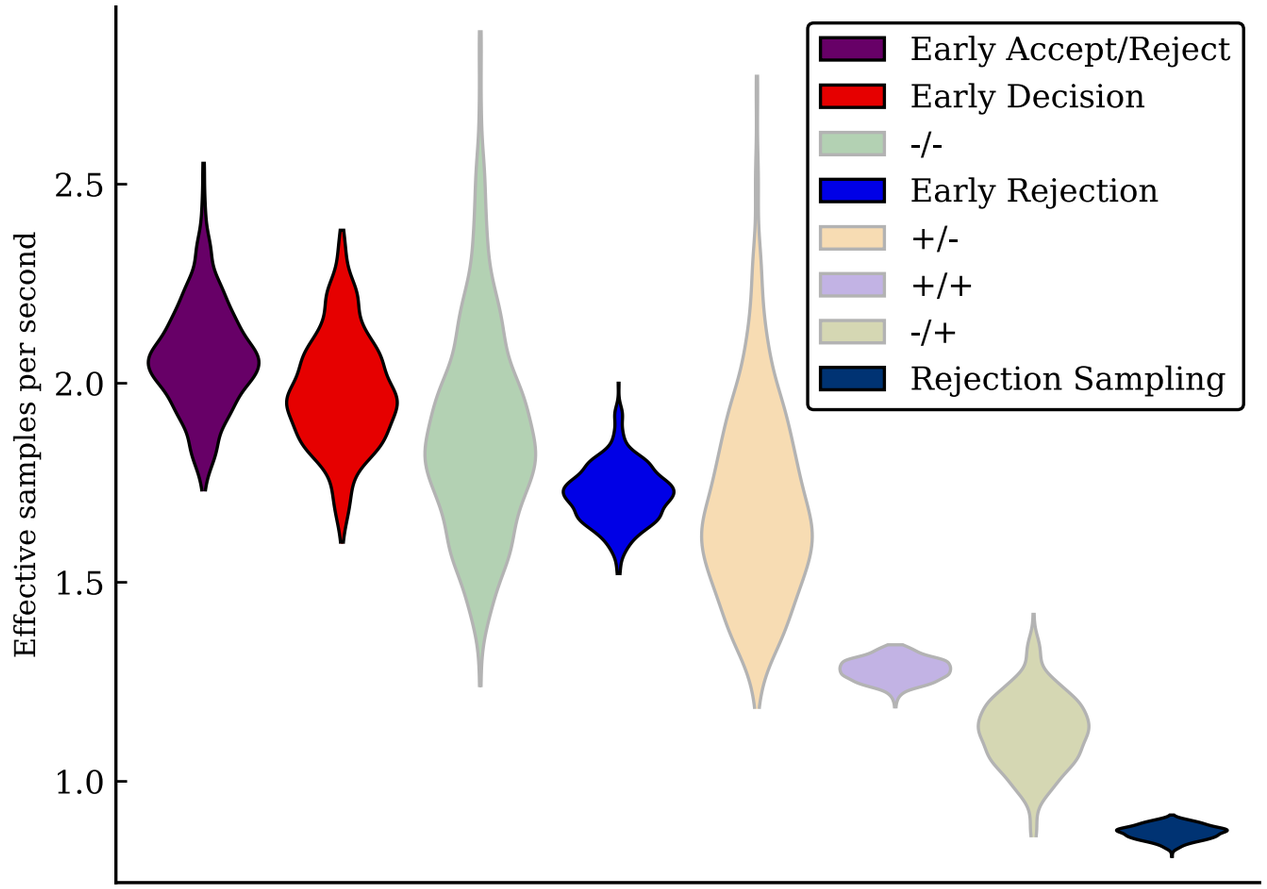




Multifidelity ABC: results

- Comparing results for a range of continuation probabilities:





Multifidelity ABC: conclusions

- Multifidelity ABC can provide time savings, through the combined use of high- and low-fidelity models.

- Can “learn” optimal continuation probabilities as the algorithm proceeds, separately controlling rates of checking early acceptance and early rejection.

- Rates of false positives and negatives can be reduced by generating the high-fidelity model output conditional on the low-fidelity model output.

    - Enables smaller continuation probabilities and hence simulation cost.

Multifidelity ABC: the algorithm

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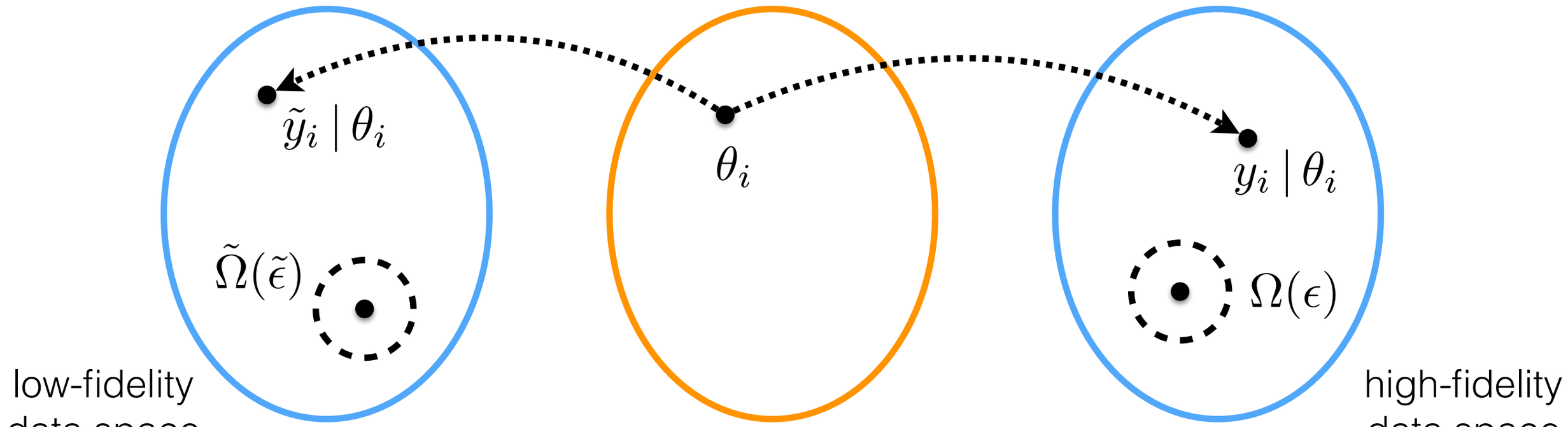
    Simulate $y_n \sim f(\cdot \mid \tilde{y}_n, \theta_n)$.
    Update $w_n \leftarrow w_n + [\mathbb{I}(y \in \Omega_\epsilon) - w_n] / \alpha(\tilde{y}_n, \theta_n)$.
  end if
until $S =$ `true`.

Coupling between models

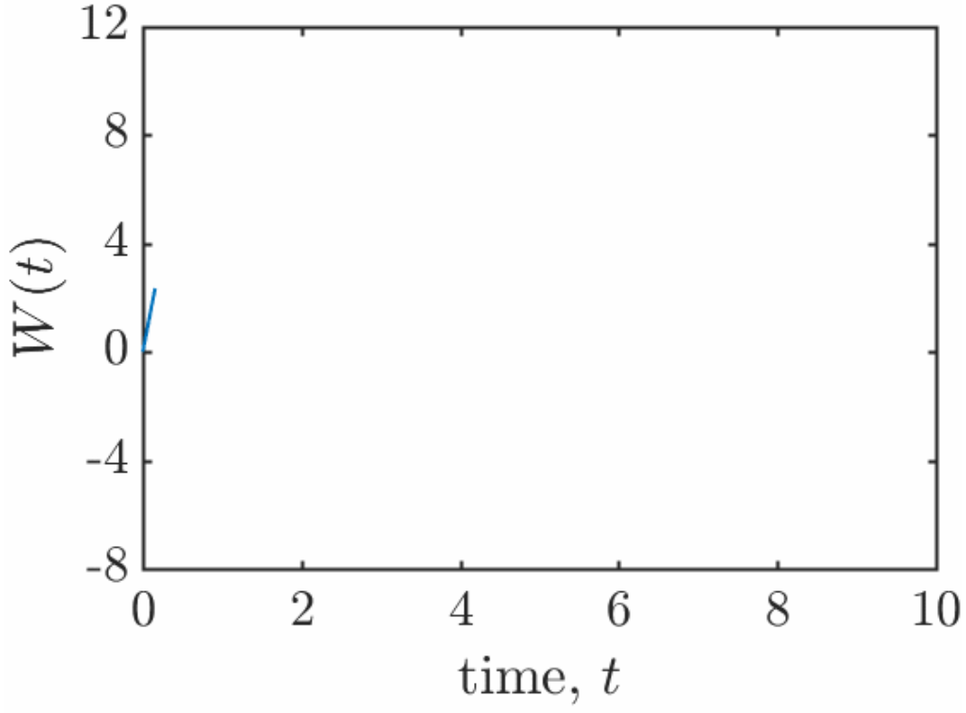


- Generating data from the high-fidelity model, conditional on the output of the low-fidelity model.
  - Drive down the rates of false positives and false negatives.
  - Approach heavily dependent on the choice of low-fidelity model.

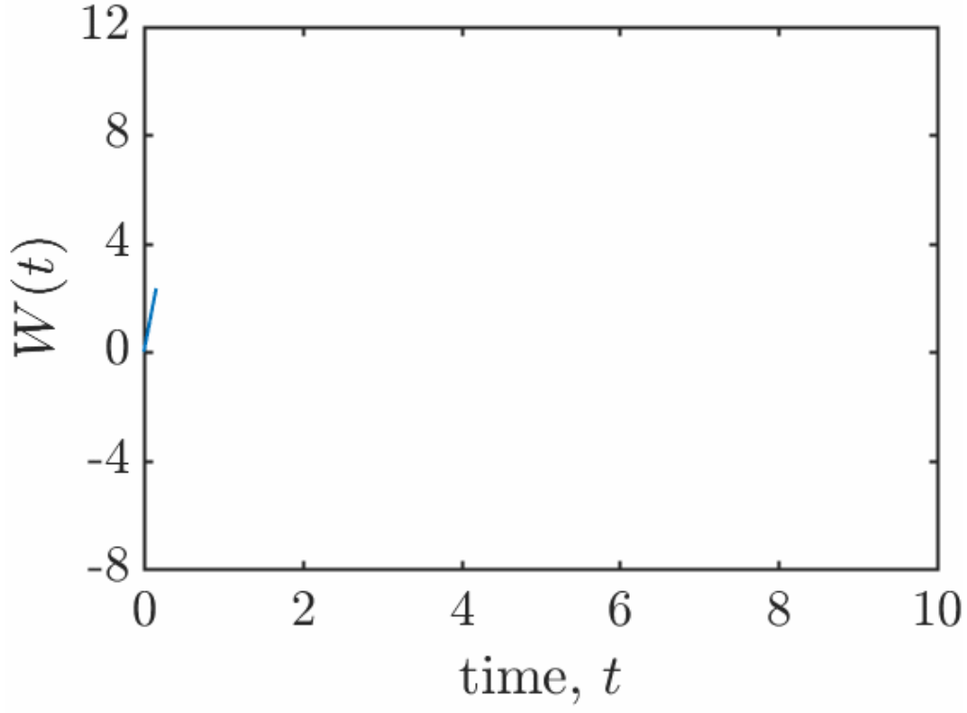
Example: common noise input stream

$$\hat{X}(t+\tau) = \hat{X}(t) + r\hat{X}(t)\tau + \sigma\hat{X}(t)\sqrt{\tau}\xi, \qquad \hat{X}(0) = 1, \qquad \xi \sim \mathcal{N}(0,1).$$

Use the same Brownian path for generation of the high- and low-fidelity simulations:



Uncoupled paths



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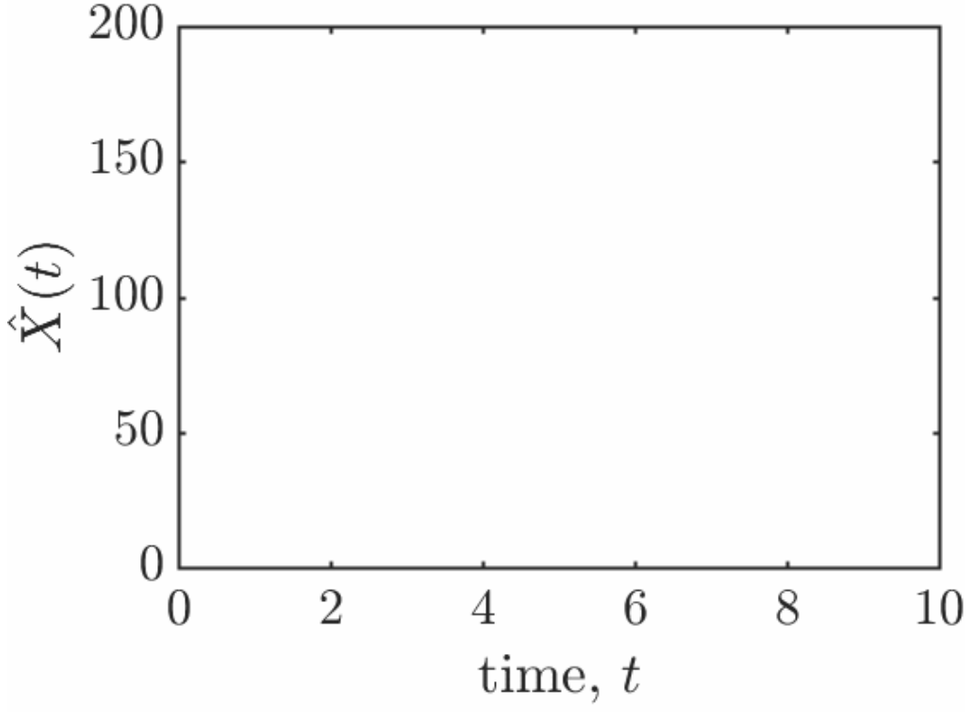
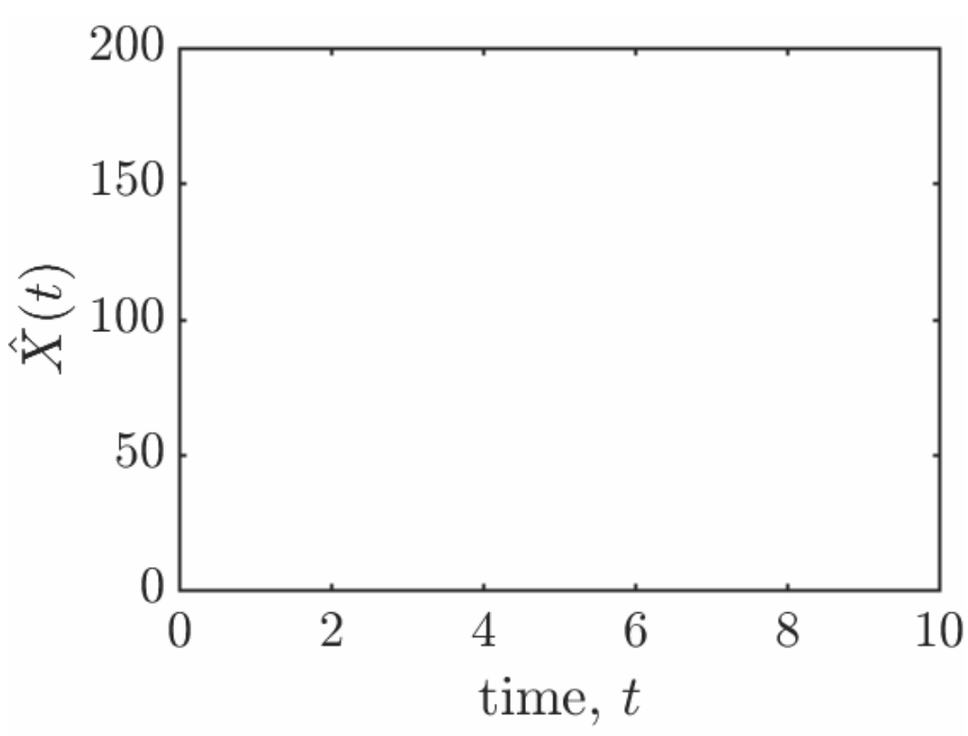


Uncoupled paths



Coupled paths

Can we combine these multifidelity ideas with other ideas for increasing the efficiency of ABC?

ABC sequential Monte Carlo

- ABC-SMC uses a sequence of importance distributions to gradually increase accuracy of the posterior.

- For a sequence of thresholds $\epsilon_1 > \epsilon_2 > \cdots > \epsilon_T$:

– for $t = 1, \ldots, T-1$:
  – generate $\left\{w_i^{(t)}, \theta_i^{(t)}\right\}_{i=1}^{N_t}$ using importance distribution $\hat{q}_t$ and $\Omega(\epsilon_t)$;
  – define the next importance distribution, $\hat{q}_{t+1}(\theta)$, proportional to

$$q_{t+1}(\theta) = \begin{cases} \sum_{i=1}^{N_t} w_i^{(t)} K_t(\theta \,|\, \theta_i^{(t)}) \Big/ \sum_{m=1}^{N_t} w_m^{(t)} & \pi(\theta) > 0 \\ 0 & \text{else;} \end{cases}$$

– generate $\left\{w_i^{(T)}, \theta_i^{(T)}\right\}_{i=1}^{N_T}$ using importance distribution $\hat{q}_T$ and $\Omega(\epsilon_T)$.

Towards SMC: importance sampling

- First, need to integrate importance sampling into the multifidelity ABC framework:

Algorithm 5 Multifidelity ABC importance sampling (MF-ABC-IS)

Input: Data y_{obs} and neighbourhood Ω_ϵ; prior π; models $\tilde{f}(\cdot \mid \theta)$, $f(\cdot \mid \tilde{y}, \theta)$; continuation probability function $\alpha = \alpha(\tilde{y}, \theta)$; sample index $n = 0$; importance distribution $\hat{q}$ pr

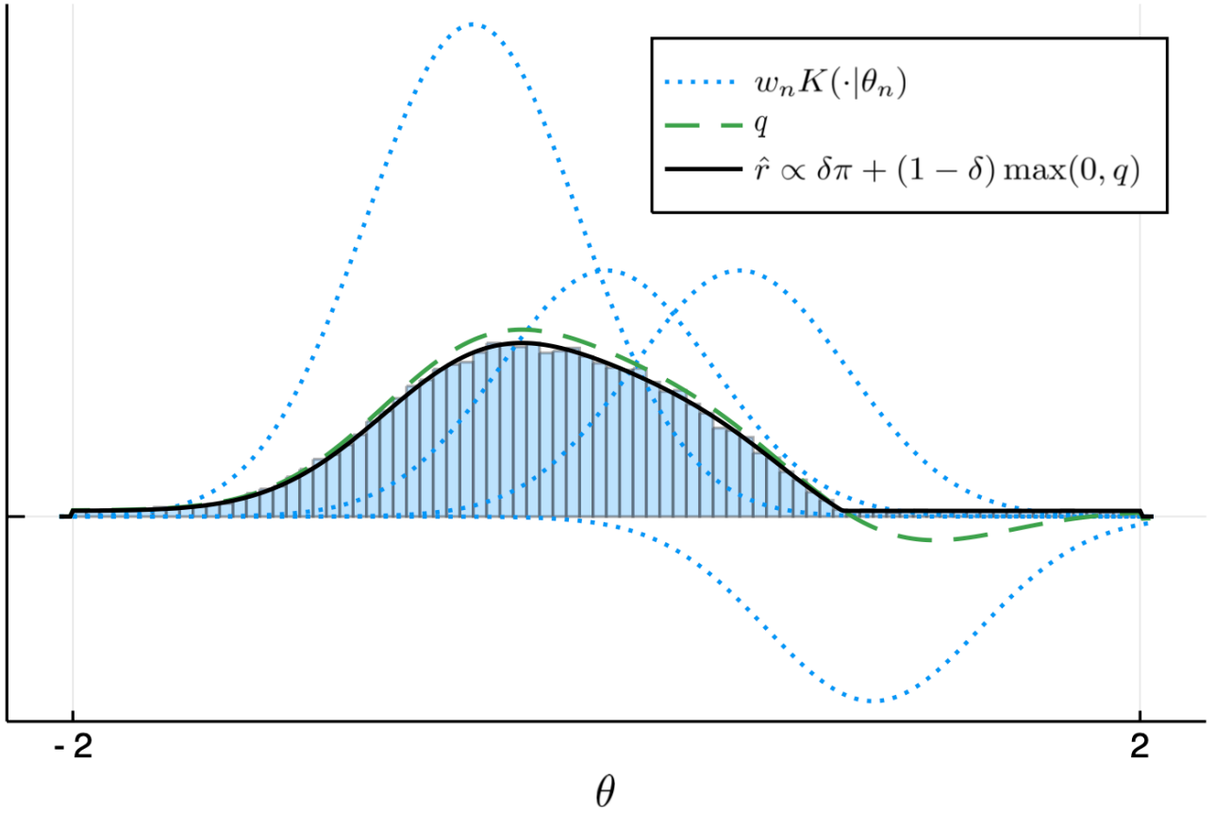
Output

1: **repe**
2: In
3: Ge
4: Si
5: Se
6: Generate $u_n \sim \text{Uniform}(0, 1)$.
7: **if** $u_n < \alpha(\tilde{y}_n, \theta_n)$ **then**
8: Simulate $y_n \sim f(\cdot \mid \tilde{y}_n, \theta_n)$.
9: Update $w_n \leftarrow w_n + \left[\mathbb{I}(y_n \in \Omega_\epsilon) - w_n\right] / \alpha(\tilde{y}_n, \theta_n)$.
10: **end if**
11: Update $w_n \leftarrow \left[\pi(\theta_n)/q(\theta_n)\right] w_n$.
12: **until** $S = \texttt{true}$.

For SMC: how do we sample from the importance distribution, given the weights that result from multifidelity ABC can be negative?

Towards multifidelity SMC-ABC

- Use defensive importance sampling, first defining a new (non-negative) importance distribution.



- Estimate continuation probabilities for each generation “on the fly”, using information from the previous generations.

MF ABC SMC in action

- Kuramoto oscillator network:

$$\dot{\phi}_i = \omega_i + \frac{K}{M}\sum_{j=1}^{M}\sin\left(\phi_j - \phi_i\right)$$

angular velocities drawn from Cauchy distribution
median - ω_0
dispersion - γ

- Low-fidelity model - based on tracking Daido order parameters:

$$Z_n(t) = \frac{1}{M}\sum_{j=1}^{M}\exp(in\phi_j)$$

assume $Z_n(t) = Z_1(t)^n$

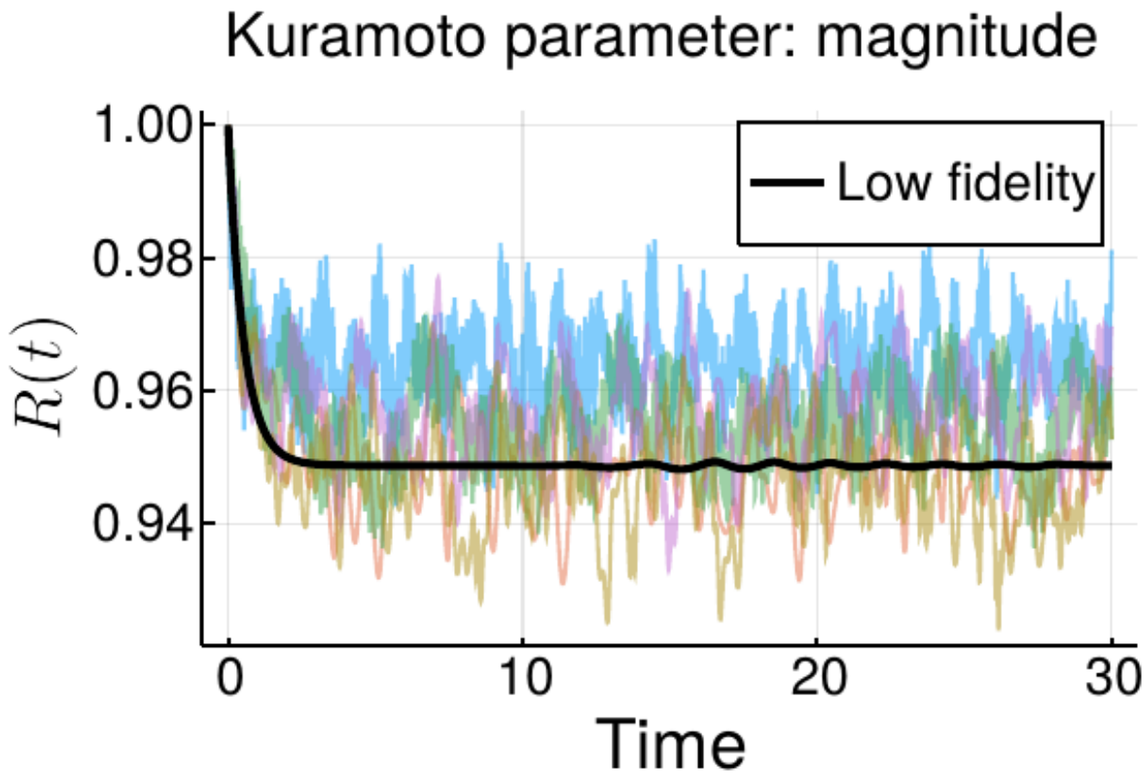
to get

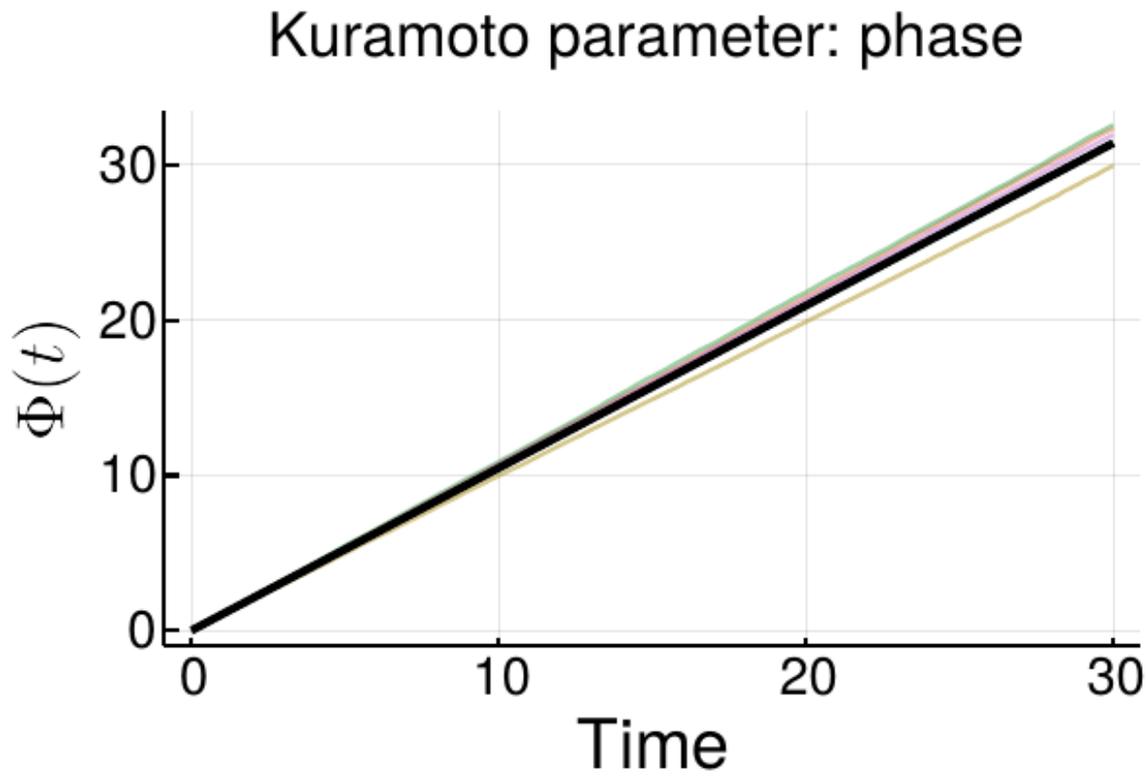
$$\dot{\tilde{R}} = \left(\frac{K}{2} - \gamma\right)\tilde{R} - \frac{K}{2}\tilde{R}^3 \qquad \text{(magnitude)}$$

$$\dot{\tilde{\Phi}} = \omega_0 \qquad \text{(phase)}$$

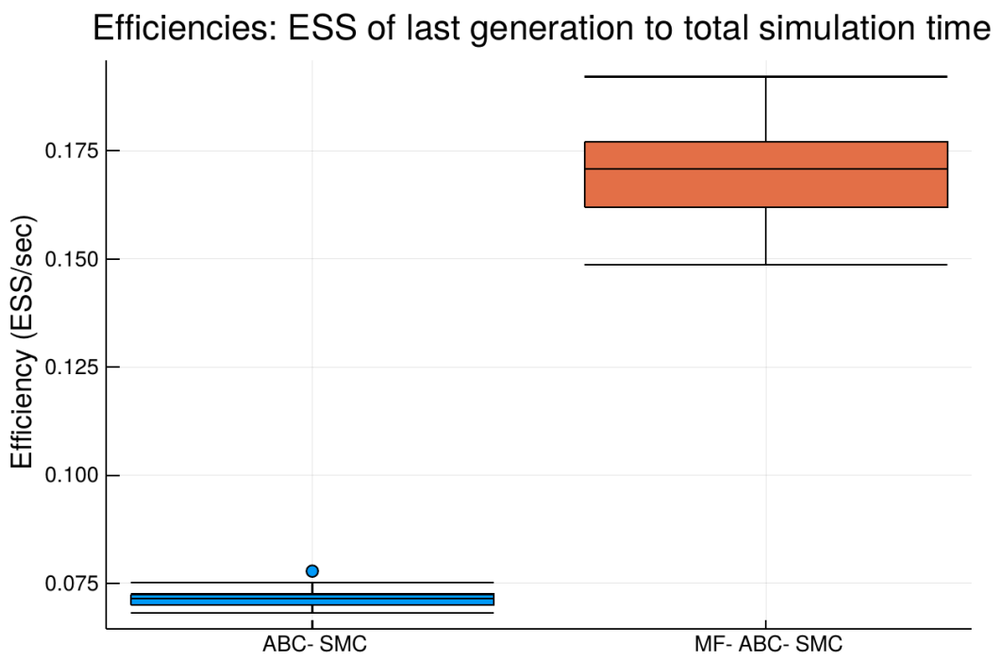
MF ABC SMC in action

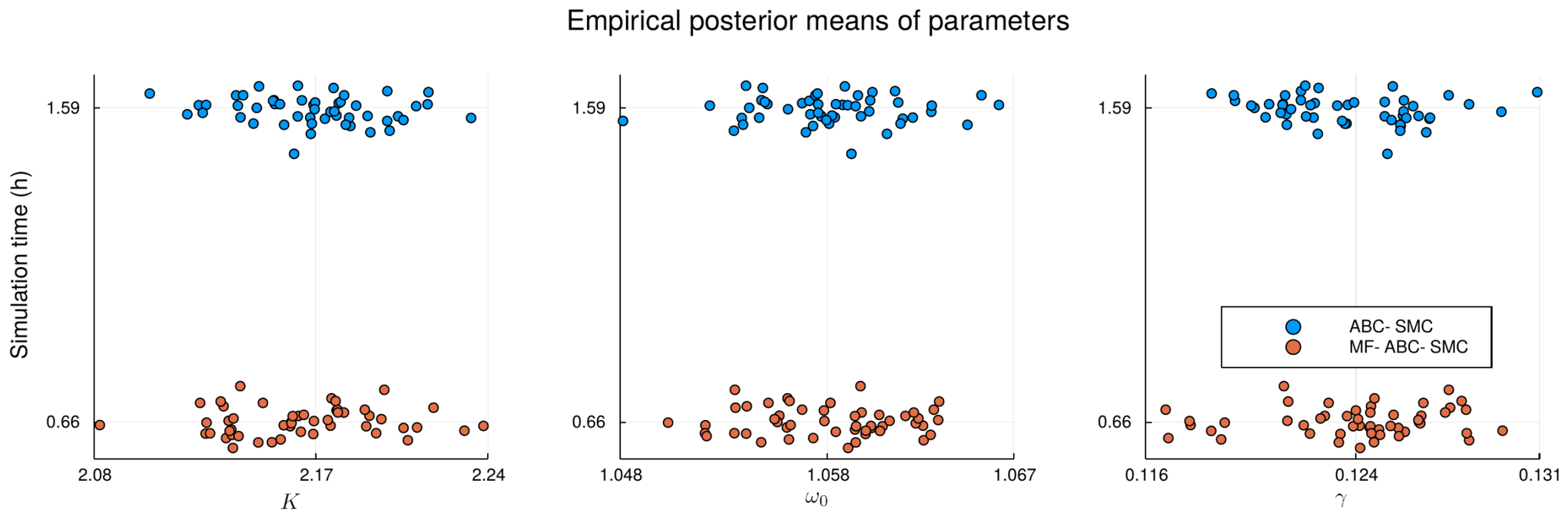
- Typical simulation output:





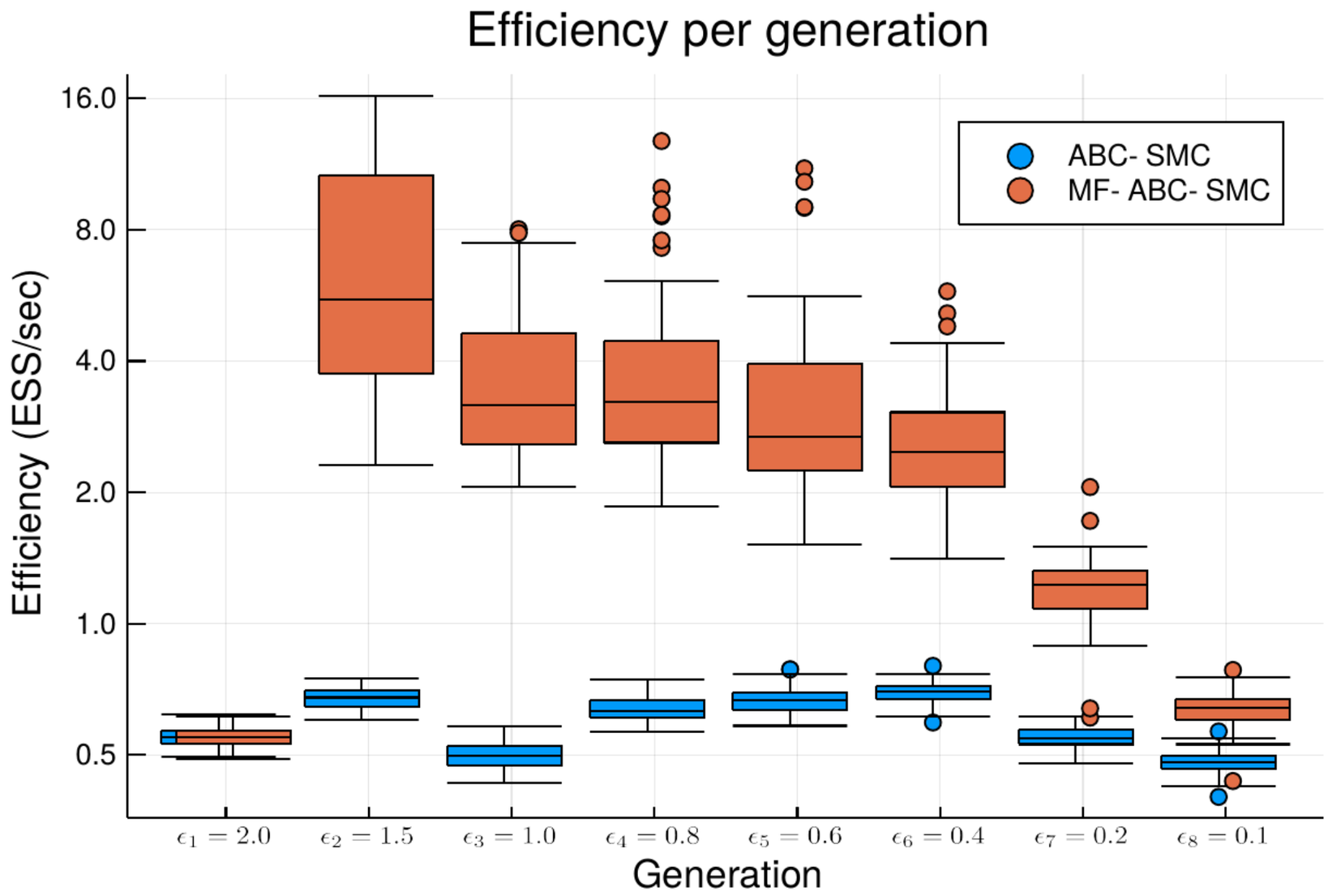
MF ABC SMC in action



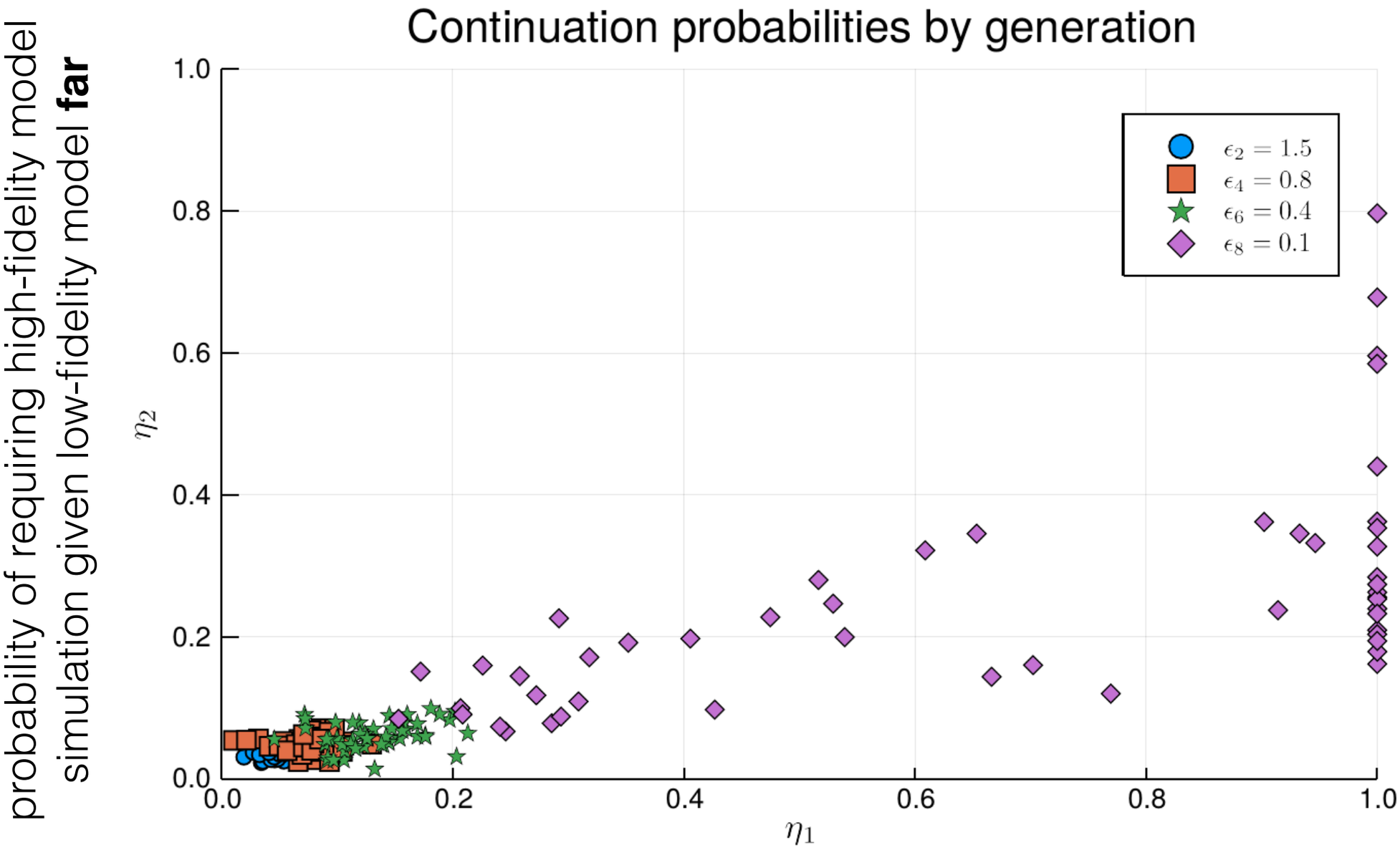


Towards multifidelity SMC-ABC

- Stopping criterion at each generation: $\mathrm{ESS} \geq 400$.



Towards multifidelity SMC-ABC



Summary

- Demonstrated that it is possible to incorporate both multifidelity and SMC approaches in generating the ABC posterior.
    - Can choose the sequence of acceptance thresholds adaptively, e.g. to maintain efficiency across generations.
- Many open questions remain, including:
    - How best to design and estimation continuation probabilities?
    - How to use multiple low-fidelity models?
    - How to chose optimal perturbation kernels?

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