Accelerating mechanistic inference via neural density estimation

Yannik Schaelte
AstraZeneca, Computational Pathology, 2023-05-16
Journal Club

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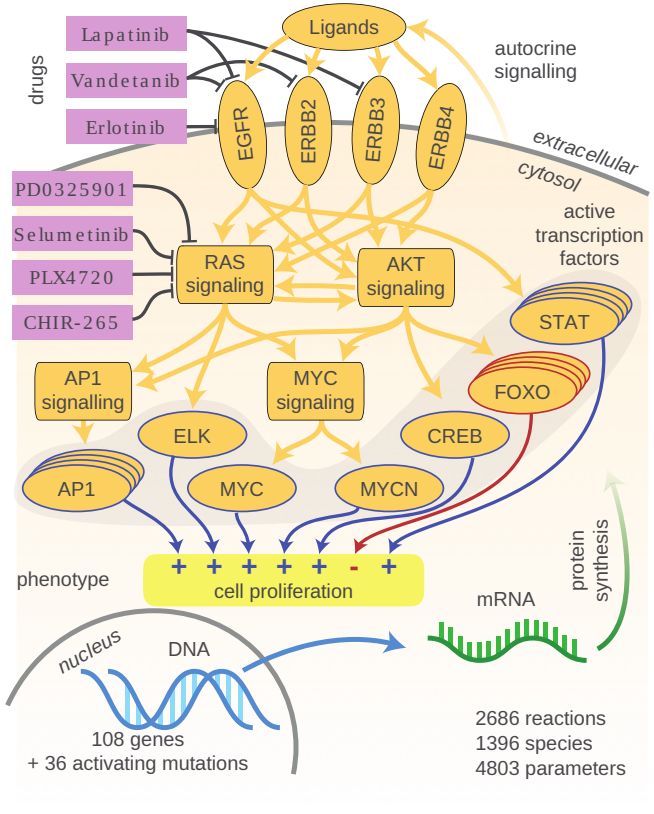
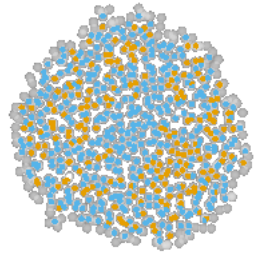
OVERVIEW

- Quantitative systems biology
- Amortized inference
- Missing data
- Mixed-effects modeling

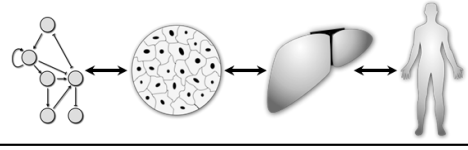
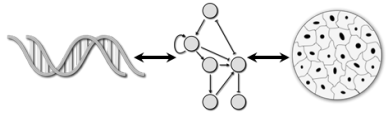
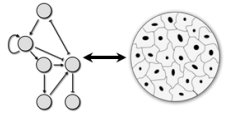
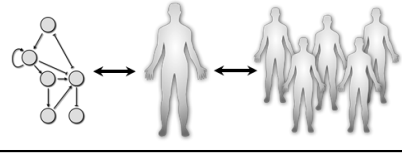
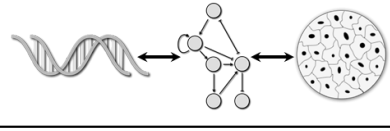
BIOLOGICAL PROCESSES ARE COMPLICATED





Fröhlich et al., Cell Systems, 2018, and Jagiella et al., Cell Systems, 2017

MODEL TYPES

		Boolean / Petri net models	Constraint-based models	Markov chain models	SDE models	ODE models	PDE models	Agent-based models	
whole-heart (tissue and fluid mechanics, signaling)		■				■	■		Hunter and Borg, *Nature Reviews Molecular Cell Biology*, 4(3):237-243, 2003
cancer growth (signaling, cell division and death, angiogenesis, tissue remodeling)					■		■	■	Anderson and Quaranta, *Nature Reviews Cancer*, 8(3):227-234. 2008
liver lobule (cell division and cell death, tissue mechanics)				■	■		■	■	Hoehme et al., *PNAS*, 107(23):10371-10376, 2010
glucose-insulin-glucagon regulation (blood and interstitial flow, organ uptake, signaling)						■	■	■	Schaller et al., *CPT: Pharmacometrics and Systems Pharmacology*, 2:e65, 2013
whole-cell (transcription, translation, DNA replication, metabolism, replication)		■	■	■		■		■	Karr et al., *Cell*, 150(2):389-401, 2012

based on Hasenauer et al., Coupl. Sys. 2015

THE INVERSE PROBLEM

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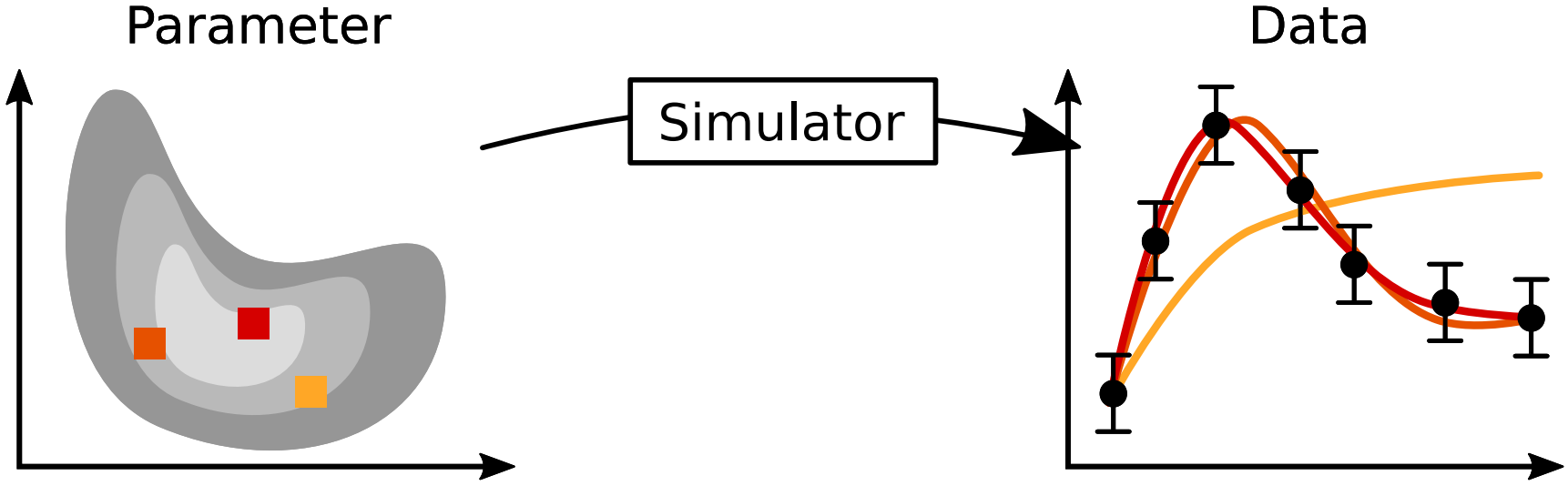

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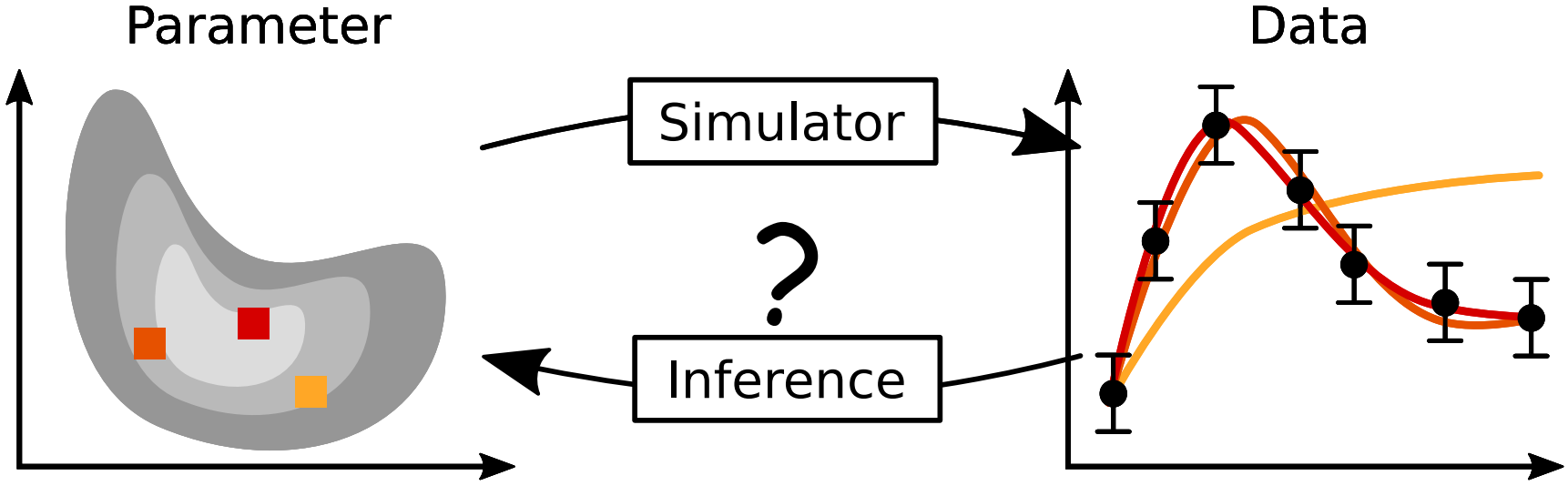

Efficient accurate and robust statistical inference for deterministic and stochastic models of biochemical systems

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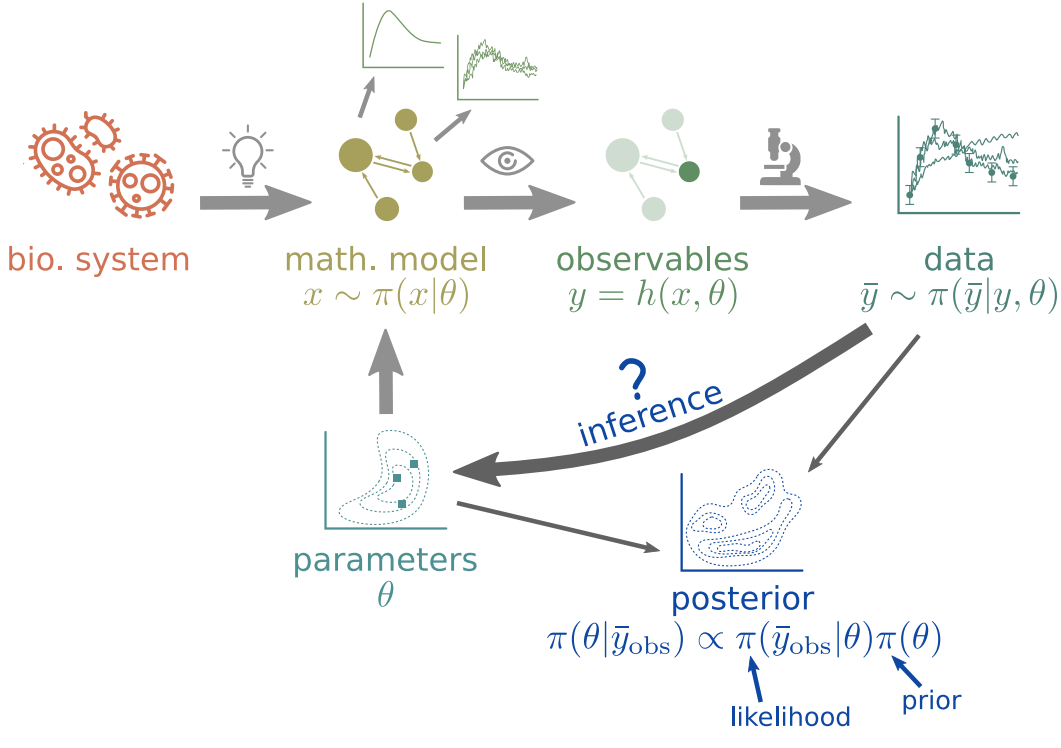
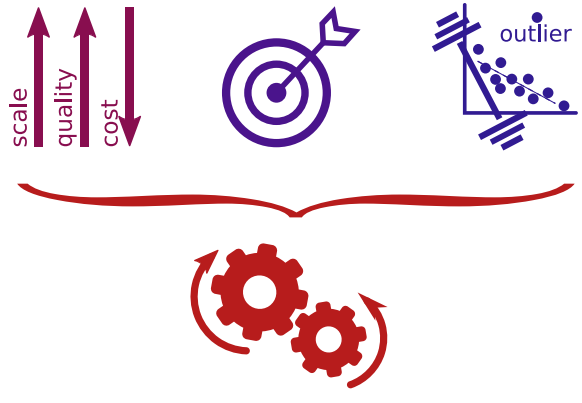




SOFTWARE

ODE simulation and sensitivity analysis

parameter inference: optimization, sampling, profiles, ...

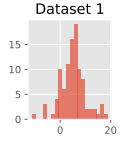
analysis of multi-scale multi-cellular models

likelihood-free inference for stochastic models

standard to specify estimation problems

definition of ODE problems in YAML and conversion to SBML

AMORTIZED INFERENCE


Dataset 1
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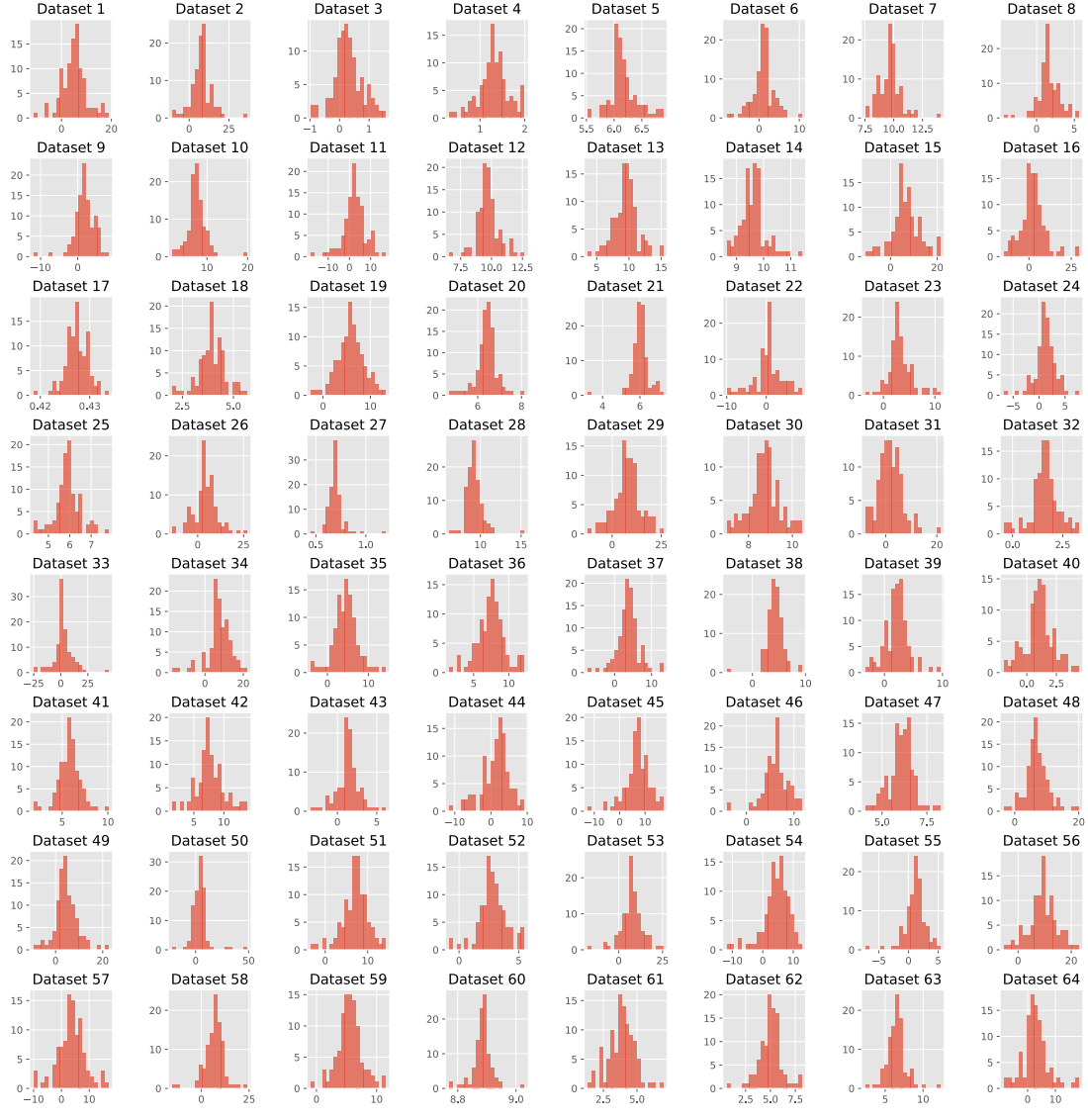
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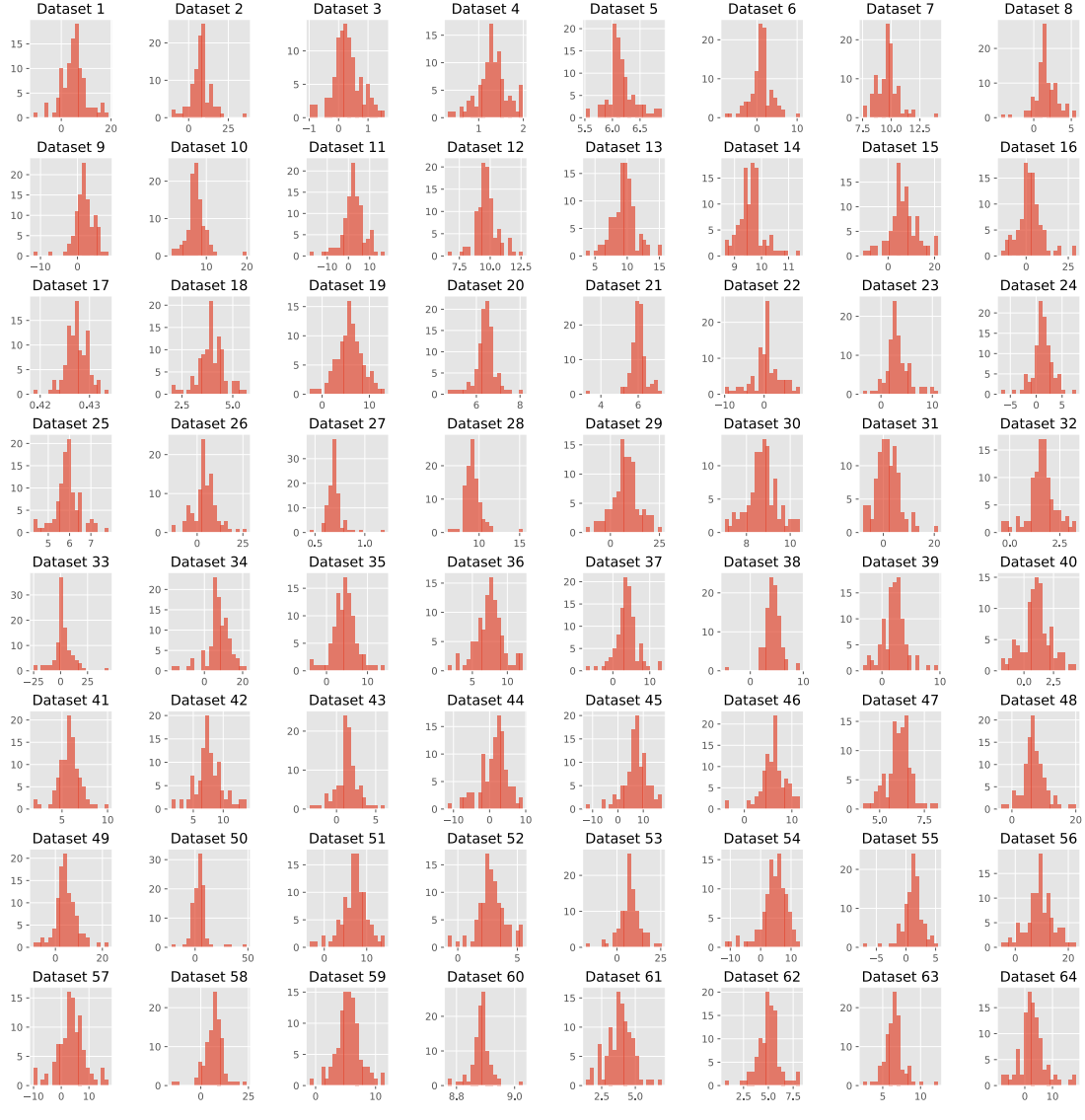

FITTING A MODEL TO MANY DATASETS?

IN BRIEF

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✗ Classical (simulation-based) parameter estimation is case-based + slow + approximate

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- ✗ What if we want to fit the same model to multiple datasets?

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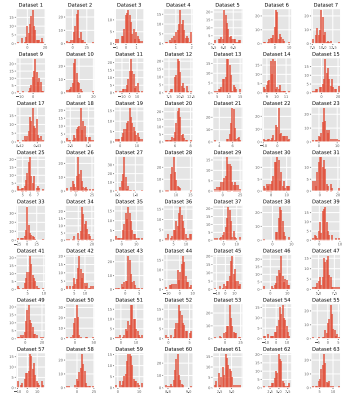

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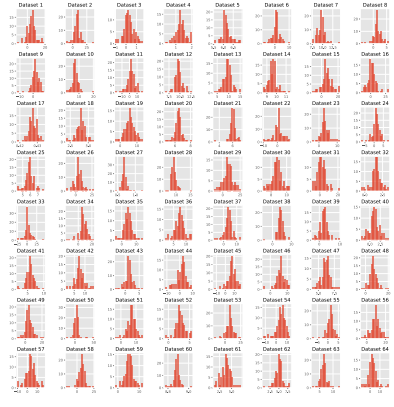

✓ Learn a global estimator for the probabilistic mapping from data to parameters

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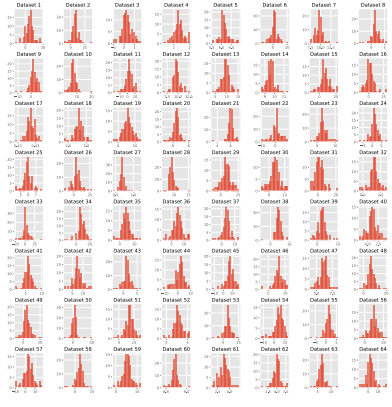

✓ Learn a global estimator for the probabilistic mapping from data to parameters

✓ Once trained, amortize inference on arbitrarily many datasets

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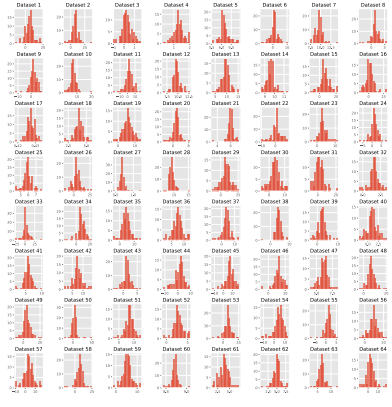


✓ Learn a global estimator for the probabilistic mapping from data to parameters

✓ Once trained, amortize inference on arbitrarily many datasets

✓ Embed data via summary statistics model

GENERATIVE MODELS

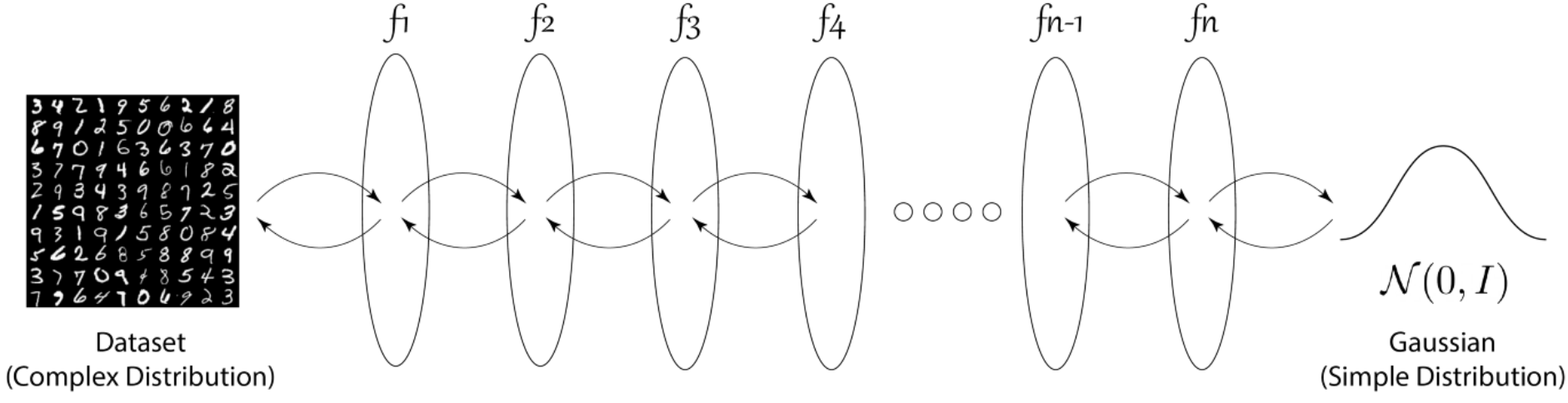
generate new data instances, $x \sim \pi(X|Y = y)$

from: Kingma et al., NeurIPS 2019

e.g.: GANs, VAEs, Flows

NORMALIZING FLOWS

generative models based on an invertible transformation



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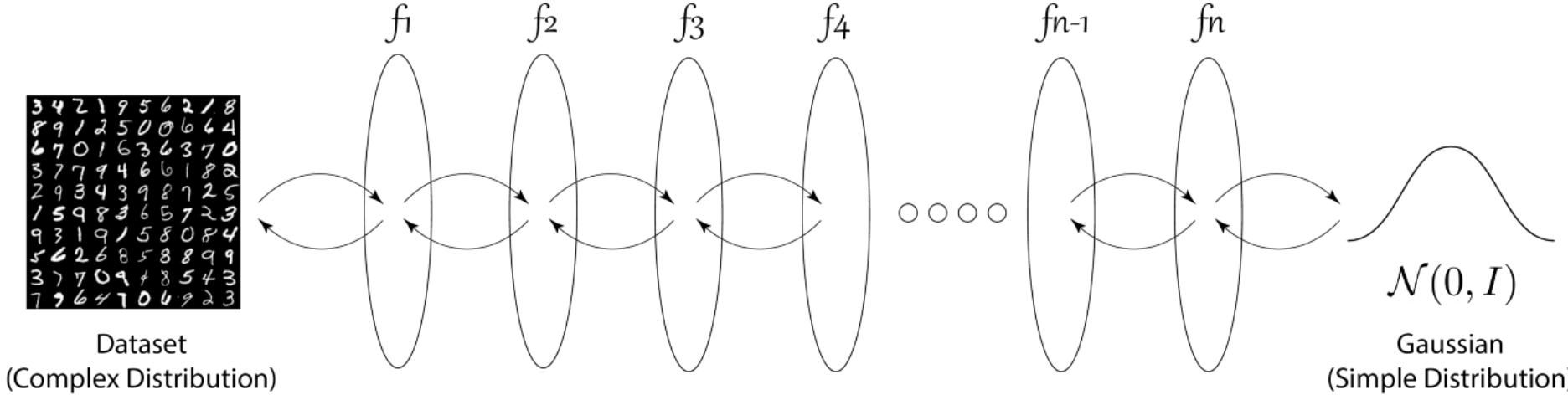

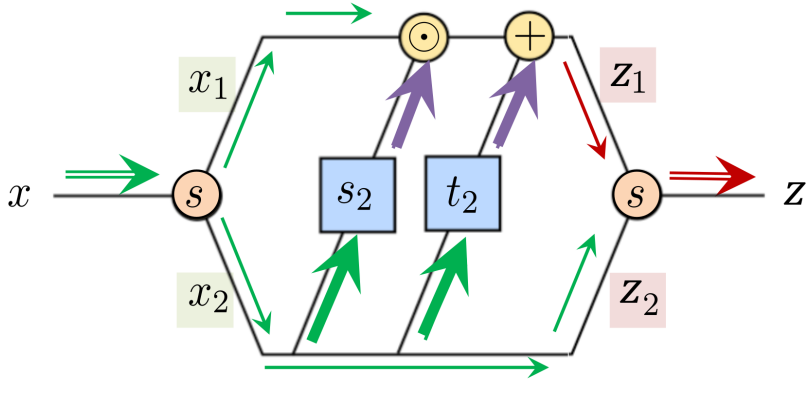

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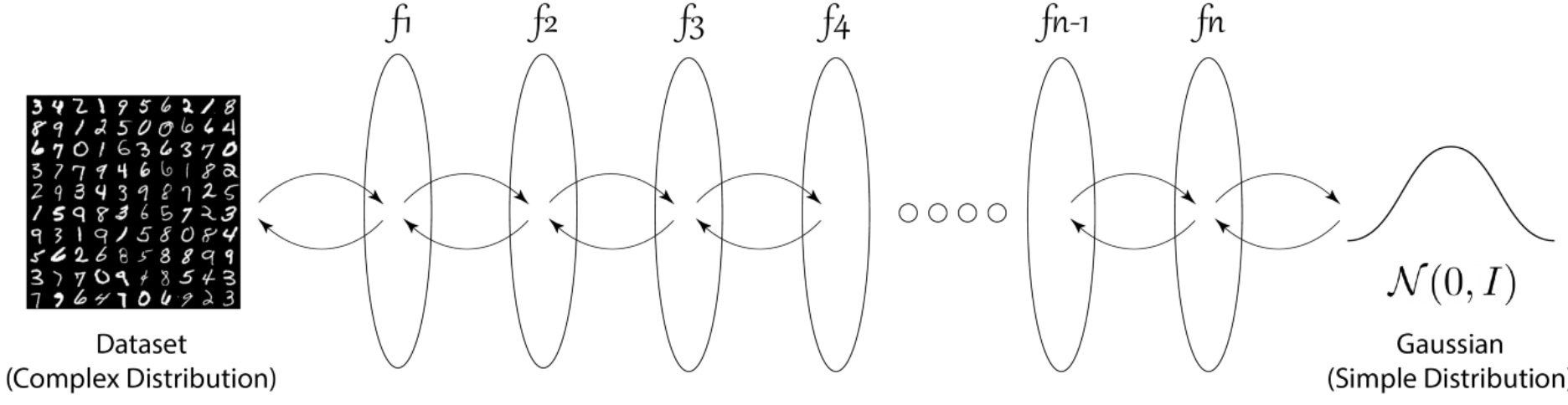

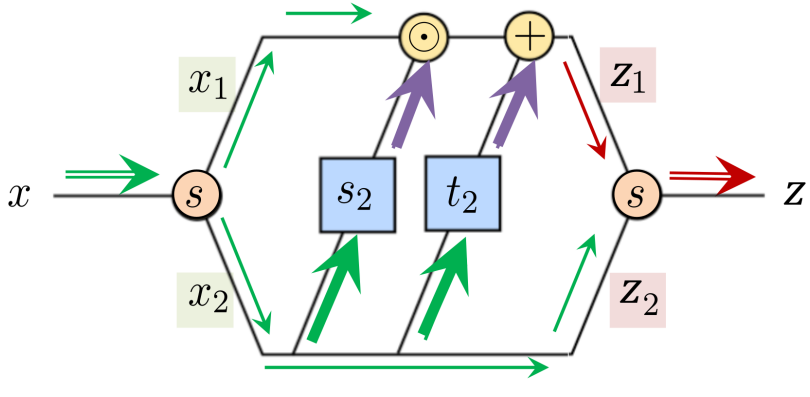

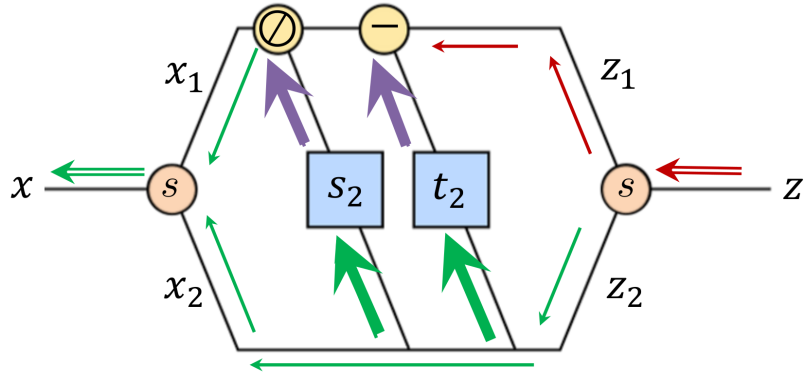

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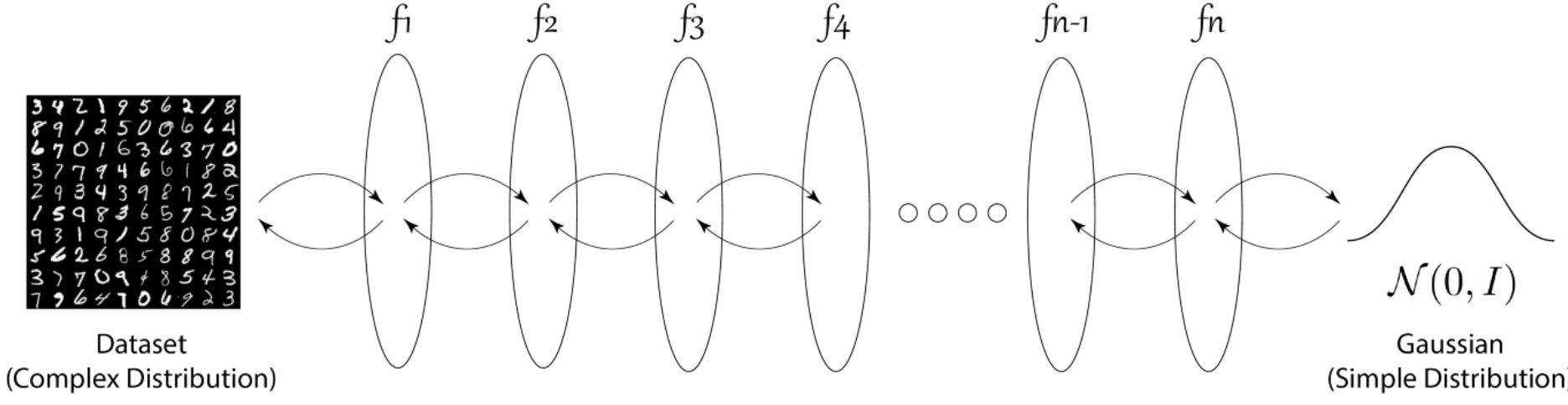
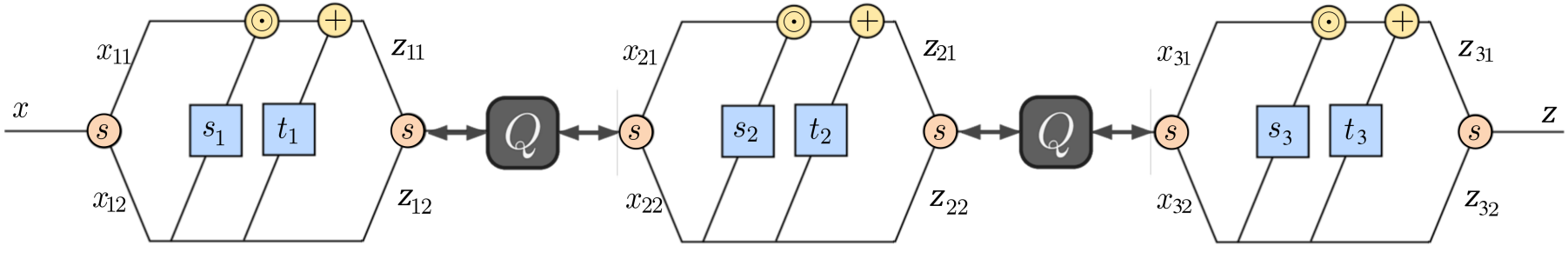


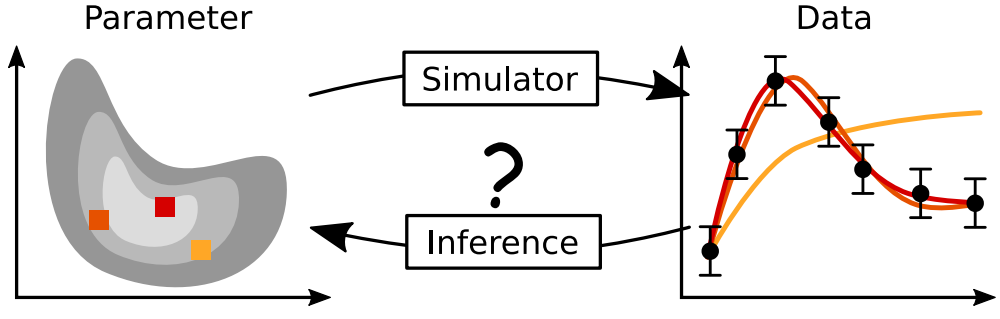


Let $z \sim \mathcal{N}(0, I)$ and $f : z \mapsto x$ bijective. Then via change of variable,s the pdf of $x = f(z)$ is given as

$$p_x(x) = p_z(f^{-1}(x)) \cdot |\det(\frac{df^{-1}}{dx}(x))|.$$

- in training, transform data points to simple distribution
- trained via negative log-likelihood
- afterwards, generate samples via $f^{-1}(z)$ with $z \sim \mathcal{N}(0, I)$

POSTERIOR LEARNING



- parameters θ
- observations x
- forward model $x \sim p(x|\theta) \Leftrightarrow x = g(\theta, \xi)$ with $\xi \sim p(\xi)$
- Bayesian posterior $p(\theta|x) \propto p(x|\theta)p(\theta)$

- aim: find a NF $p_\phi(\theta|x) \approx p(\theta|x) \, \forall \theta, x$

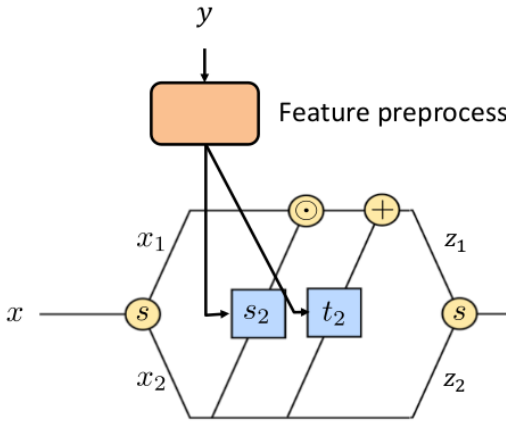
THE METHOD

Parameterize p_ϕ in terms of a cINN given via a bijective

$$f_\phi : \mathbb{R}^D \to \mathbb{R}^D, \quad \theta \mapsto z,$$

which implements a normalizing flow between θ and a Gaussian latent variable z,

$$\theta \sim p_\phi(\theta|x) \Leftrightarrow \phi = f_\phi^{-1}(z; x) \quad \text{with} \quad z \sim \mathcal{N}_D(z|0, I).$$



Seek neural network parameters $\hat{\phi}$ that minimize the KL divergence between true and approximate posterior $\forall x$

THE METHOD

$$\hat{\phi} = \arg\min_{\phi} \mathbb{E}_{p(x)}[\mathrm{KL}(p(\theta|x) \,||\, p_\phi(\theta|x))]$$

$$= \arg\max_{\phi} \iint p(x,\theta) \log p_\phi(\theta|x) dx d\theta$$

$$= \arg\max_{\phi} \iint p(x,\theta)(\log p(f_\phi(\theta; x)) + \log |\det \boldsymbol{J}_{f_\phi}|) dx d\theta$$

Approximate via Monte-Carlo sample:

$$\hat{\phi} = \arg\min_{\phi} \frac{1}{M} \sum_{m=1}^{M} (-\log p(f_\phi(\theta^{(m)}; x^{(m)})) - \log |\det \boldsymbol{J}_{f_\phi}^{(m)}|$$

$$= \arg\min_{\phi} \frac{1}{M} \sum_{m=1}^{M} \left(\frac{|f_\phi(\theta^{(m)}; x^{(m)})|_2^2}{2} - \log |\det \boldsymbol{J}_{f_\phi}^{(m)}| \right)$$

LEARN SUMMARY STATISTICS

If data $x_{1:N}$ are high-dimensional: Jointly learn a summary network $\tilde{x} = h_\psi(x_{1:N})$, giving the objective

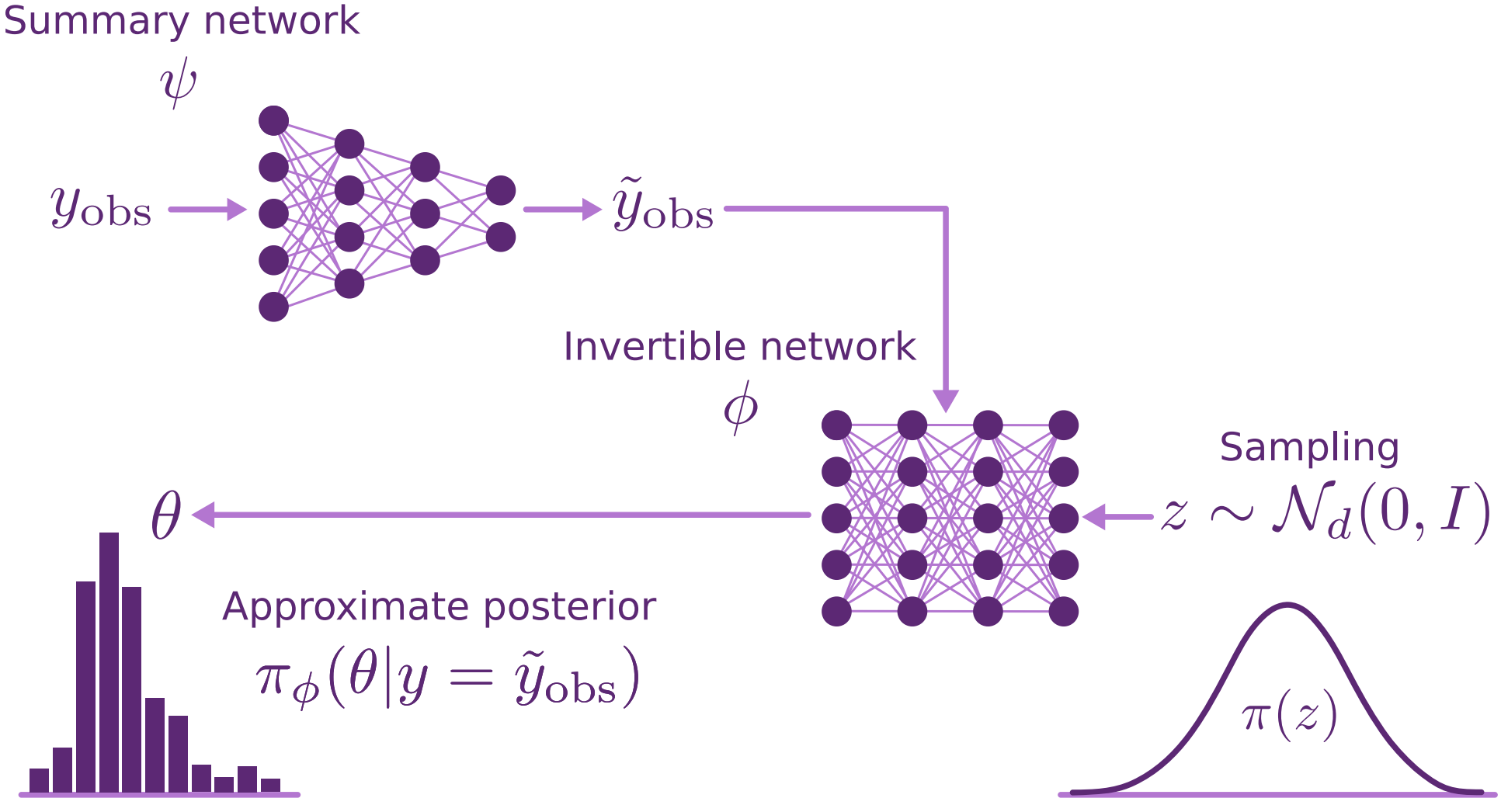
$$\hat{\phi}, \hat{\psi} = \arg\max_{\phi,\psi)} \mathbb{E}_{p(x,\theta,N)}[\log p_\phi(\theta | h_\psi(x_{1:N})]$$

with Monte-Carlo estimate

$$\hat{\phi}, \hat{\psi} = \arg\min_{\phi,\psi} \frac{1}{M} \sum_{m=1}^{M} \left(\frac{|f_\phi(\theta^{(m)}; h_\psi(x_{1:N}^{(m)})|_2^2}{2} - \log |\det(\boldsymbol{J}_{f_\phi}^{(m)})| \right)$$

AMORTIZED INFERENCE VIA INNS

you have to solve many similar problems? amortize the solution!



based on: Radev et al., 2021

TRAINING AND INFERENCE

Training phase:

- create plenty of synthetic data $(y_i, \theta_i) \sim \pi(y, \theta)$
- train a cINN in forward mode

Inference phase:

- sample many latent $z_i \sim \pi(z)$
- run cINN backwards, $\theta_i = g(z_i; y_{\text{obs}}) \sim \pi(\theta | y_{\text{obs}})$

✓ fast + accurate amortized simulation-based Bayesian inference

$$\frac{\partial y}{\partial x}$$

mechanistic modeling

$$\frac{\partial y}{\partial x}$$

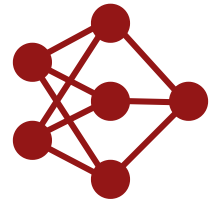
mechanistic modeling

- theory-driven
- interpretation
- testability

$$\frac{\partial y}{\partial x}$$

mechanistic modeling

- theory-driven
- interpretation
- testability

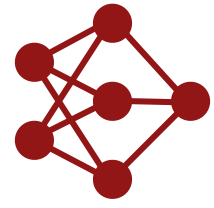


machine learning

$$\frac{\partial y}{\partial x}$$

mechanistic modeling

- theory-driven
- interpretation
- testability



machine learning

- data-driven
- large data
- automation

$$\frac{\partial y}{\partial x}$$

mechanistic modeling

- theory-driven
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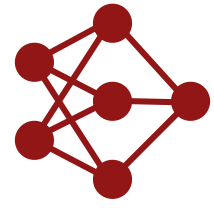

machine learning

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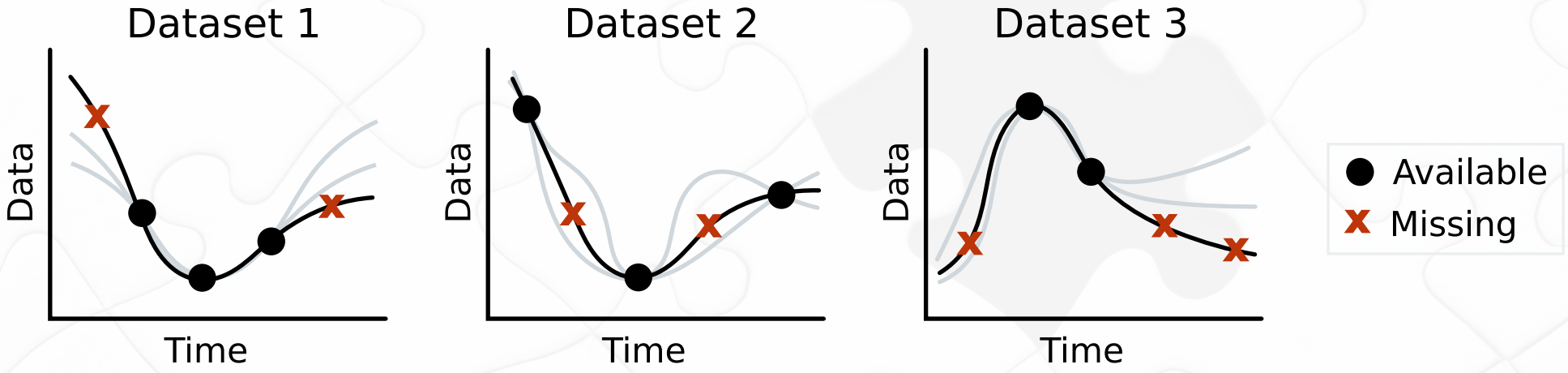
sciML

model-based data-efficient ML

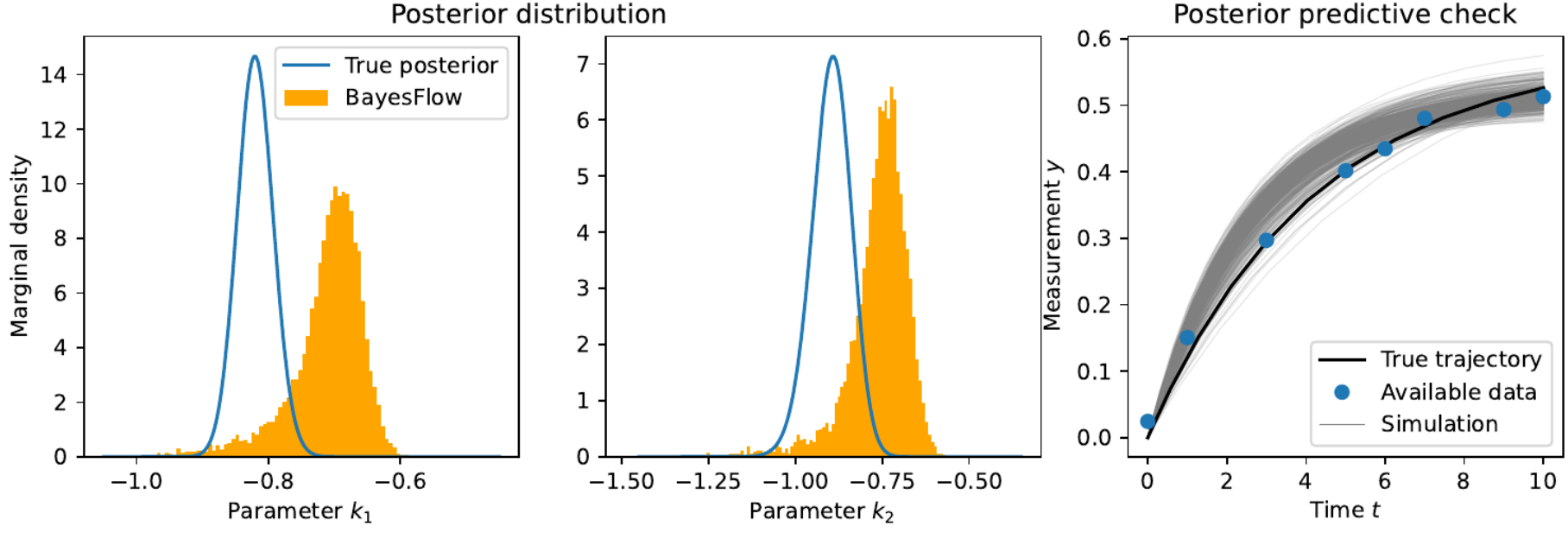
MISSING DATA

HOW TO HANDLE MISSING DATA IN AMORTIZED INFERENCE?



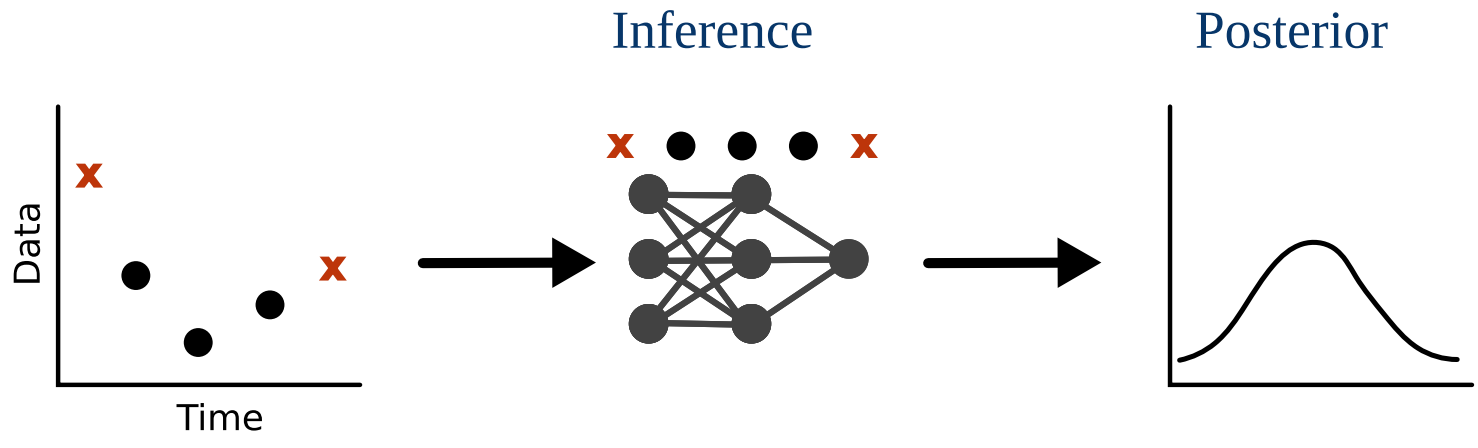
HOW TO HANDLE MISSING DATA IN AMORTIZED INFERENCE?

PROBLEM: INN CANNOT INTERPRET THE DATA



(besides iid + time-series data of heterogeneous length)

CAN WE JUST IMPUTE MISSING VALUES?



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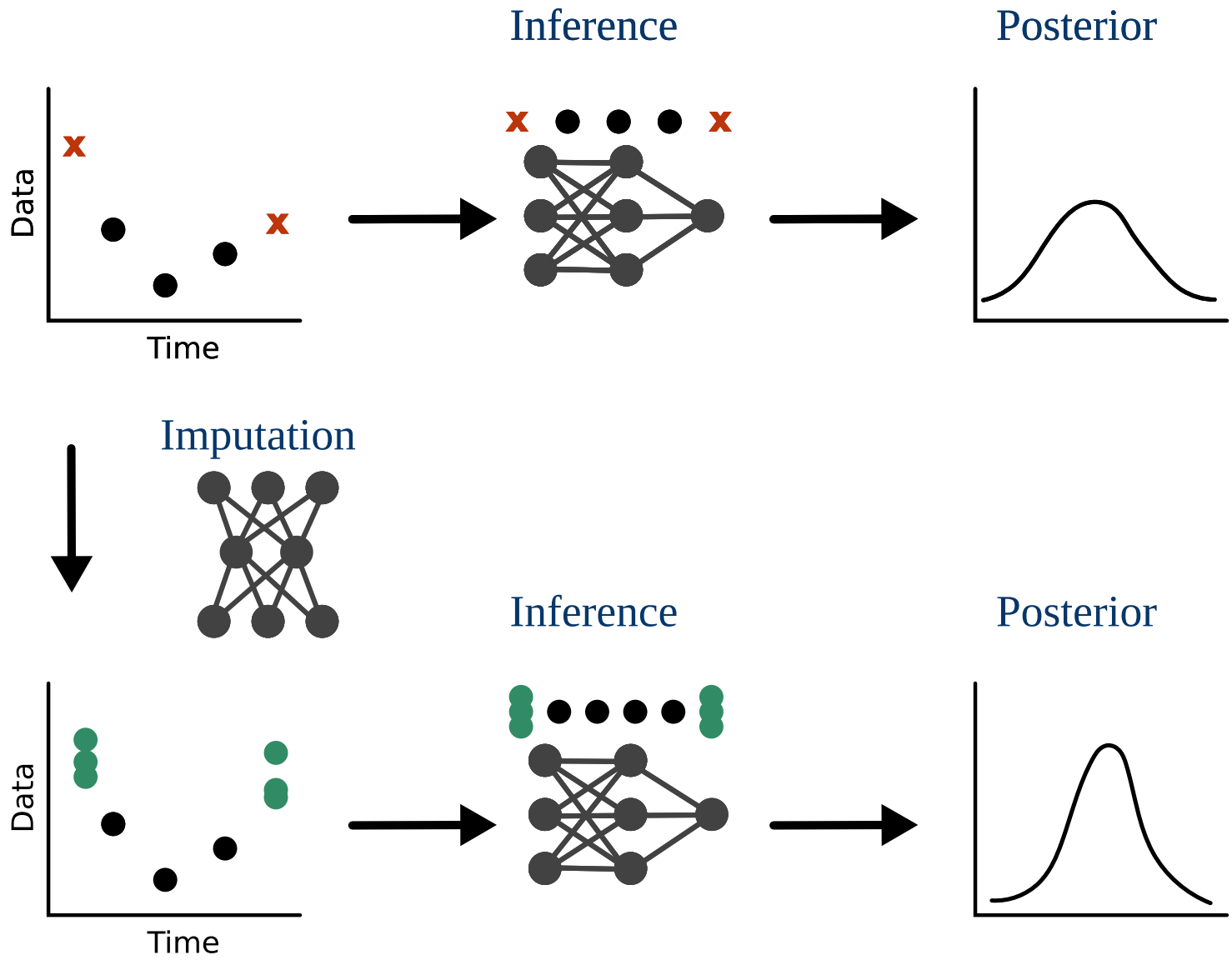
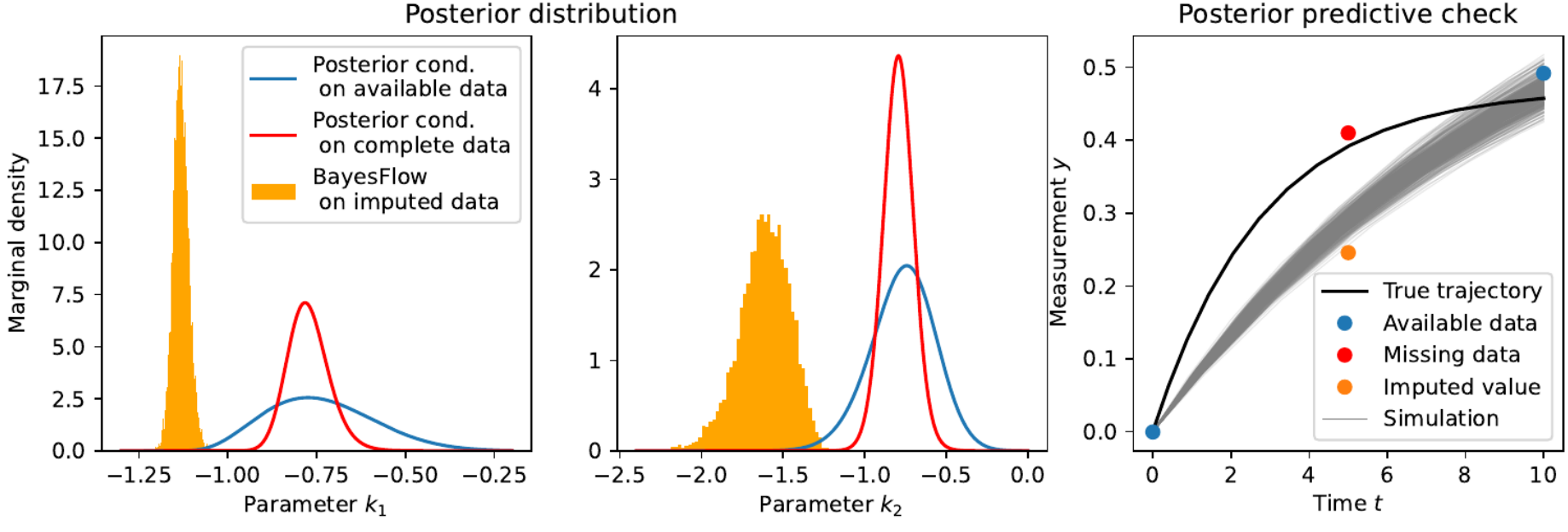


INAPPROPRIATE IMPUTATION CAN LEAD TO BIASED RESULTS



THERE ARE NO FREE DATA

Imputation means that instead of working with available data x, we try to reconstruct the full data $\bar{x}$, and estimate parameter probabilities $\pi(\theta|\bar{x})$ instead of $\pi(\theta|x)$. However, the true full data are unknown, therefore we need to take uncertainty in $\bar{x}$ into account, considering a full distribution of values $\pi(\bar{x}|x)$.

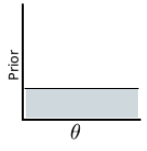
We must either make up a distribution (introducing a bias), or use a faithful approximation $p(\bar{x}|x) = \pi(\bar{x}|x)$ where $\pi(\bar{x}|x)\pi(x) = \pi(\bar{x}, x)$.

However, if we integrate out over all possible realizations of full data, we obtain $\int \pi(\theta|\bar{x})\pi(\bar{x}|x)d\bar{x} = \pi(\theta|x)$ (or similarly $\pi(\theta|x, \tau)$).

TLDR: With correct uncertainty quantification (which is hard), we just recover the same posterior.

ENCODE MISSING DATA

Training phase



Sample from prior
$\theta \sim \pi(\theta)$

Sample simulated full data
$x \sim \pi(x|\theta)$

Example

$x = \begin{bmatrix} 1.8 & 0.9 & 0.1 & 3.3 & 4.1 \end{bmatrix}$

Sample missing entries
$\tau \sim \pi(\tau)$

$\tau = \begin{bmatrix} 1 & 0 & 1 & 1 & 0 \end{bmatrix}$

Simulated incomplete data
$x_{\text{avai}} = x \odot \tau + \text{NA} \cdot (1 - \tau)$

$x_{\text{avai}} = \begin{bmatrix} 1.8 & \text{NA} & 0.1 & 3.3 & \text{NA} \end{bmatrix}$

Encode missing data
$x_{\text{aug}} = x_{\text{aug}}(x_{\text{avai}})$

$x_{\text{aug}} = \begin{bmatrix} 1.8 & -1.0 & 0.1 & 3.3 & -1.0 \\ 1 & 0 & 1 & 1 & 0 \end{bmatrix}$

Train BayesFlow networks

loss, gradient

Missingness encoding

Insert *c*

$x_{\text{aug}} = \begin{bmatrix} 1.8 & -1.0 & 0.1 & 3.3 & -1.0 \end{bmatrix}$

Augment by 0/1

$x_{\text{aug}} = \begin{bmatrix} 1.8 & -1.0 & 0.1 & 3.3 & -1.0 \\ 1 & 0 & 1 & 1 & 0 \end{bmatrix}$

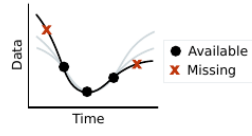
Time labels

$x_{\text{aug}} = \begin{bmatrix} 1.8 & 0.1 & 3.3 \\ 1 & 3 & 4 \end{bmatrix}$

Inference phase

Experiment

Example



Incomplete data
$x^{\text{obs}}_{\text{avai}}$

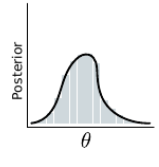
$x^{\text{obs}}_{\text{avai}} = \begin{bmatrix} \text{NA} & 3.9 & 2.5 & 3.4 & \text{NA} \end{bmatrix}$

Encode missing data
$x^{\text{obs}}_{\text{aug}} = x_{\text{aug}}(x^{\text{obs}}_{\text{avai}})$

$x^{\text{obs}}_{\text{aug}} = \begin{bmatrix} -1.0 & 3.9 & 2.5 & 3.4 & -1.0 \\ 0 & 1 & 1 & 1 & 0 \end{bmatrix}$

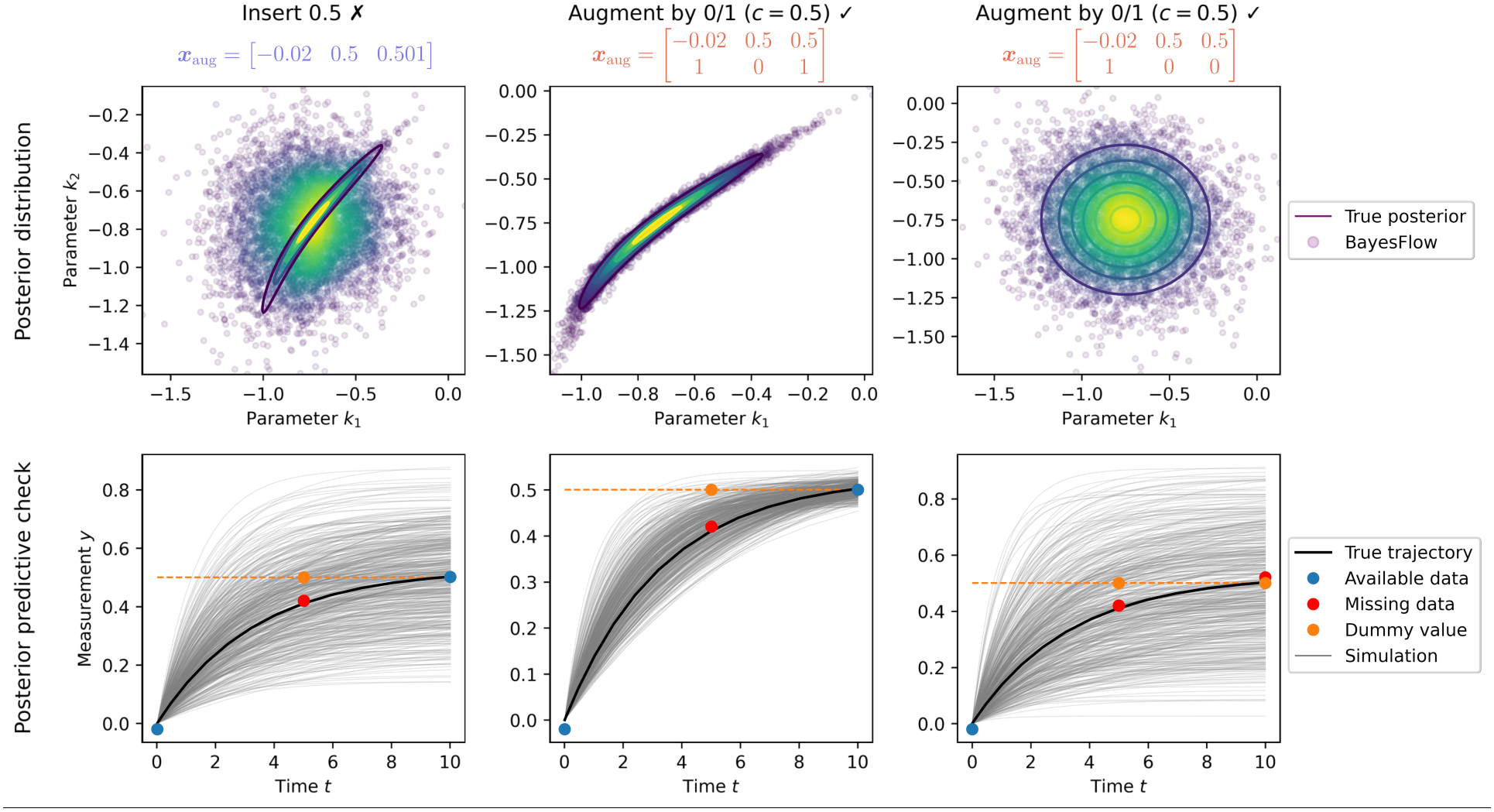
Sample from BayesFlow
$\theta \sim \pi(\theta|x^{\text{obs}}_{\text{avai}})$

Posterior approximation
$\{\theta_l\}_{l=1}^{L}$

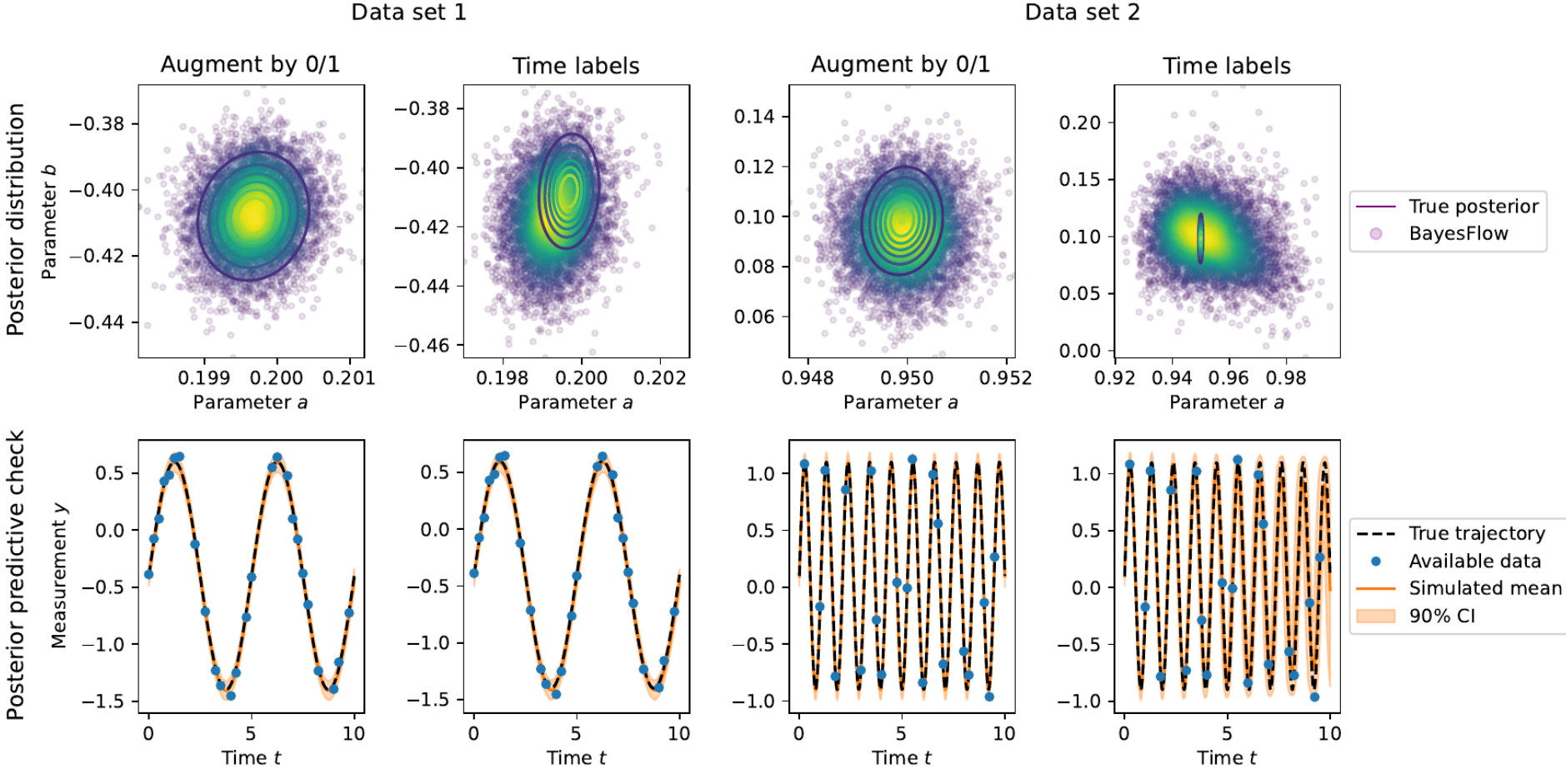


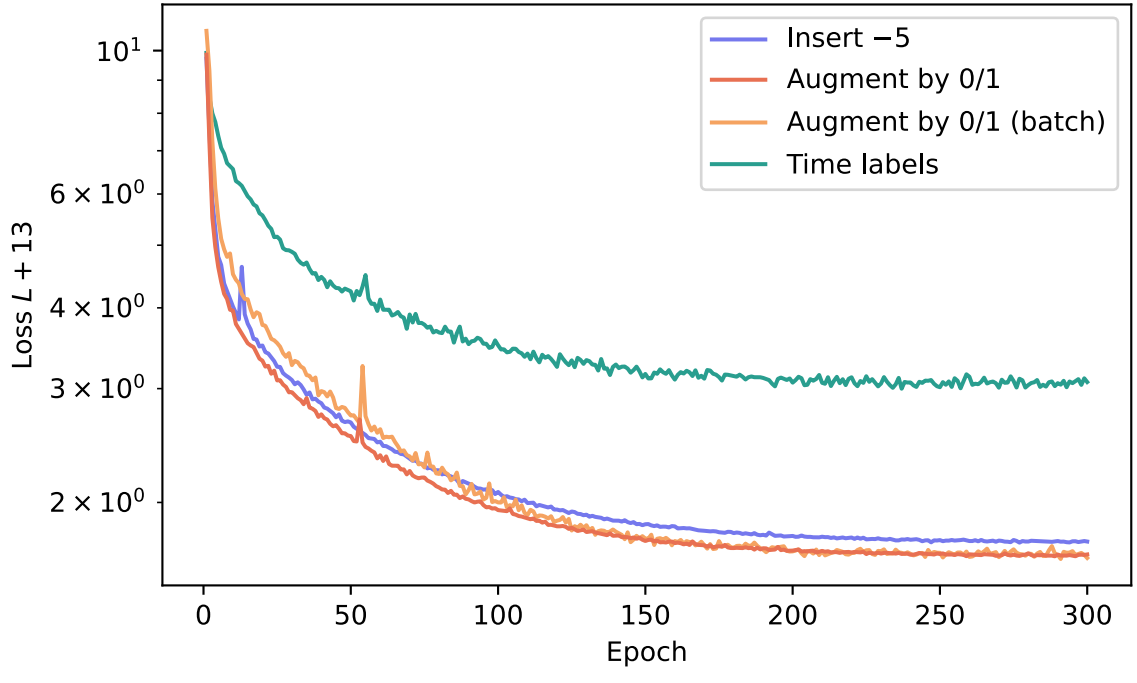
ALL APPROACHES PERFORM WELL ON SIMPLE TEST PROBLEM

BINARY INDICATOR AUGMENTATION MORE ROBUST FOR AMBIGUOUS FILL-IN VALUES

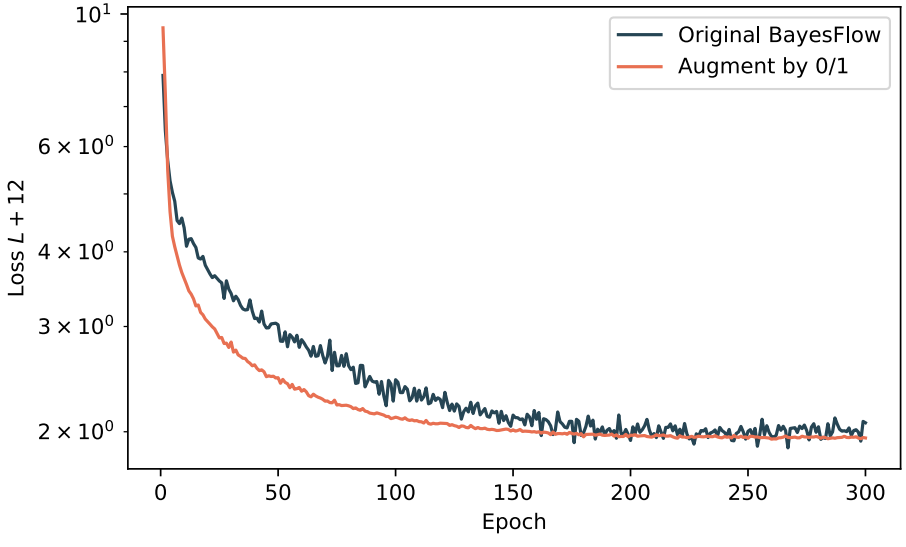


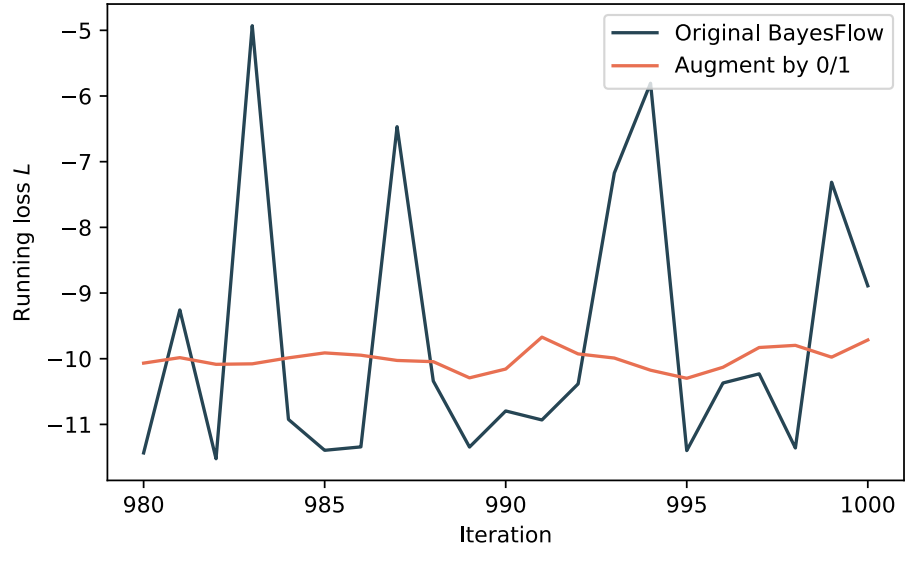
POSITIONAL ENCODING NOT ROBUST ON OSCILLATORY DATA




Insert −5
Augment by 0/1
Augment by 0/1 (batch)
Time labels
10^1
6×10^0
4×10^0
3×10^0
2×10^0
Loss $L + 13$
0
50
100
150
200
250
300
Epoch

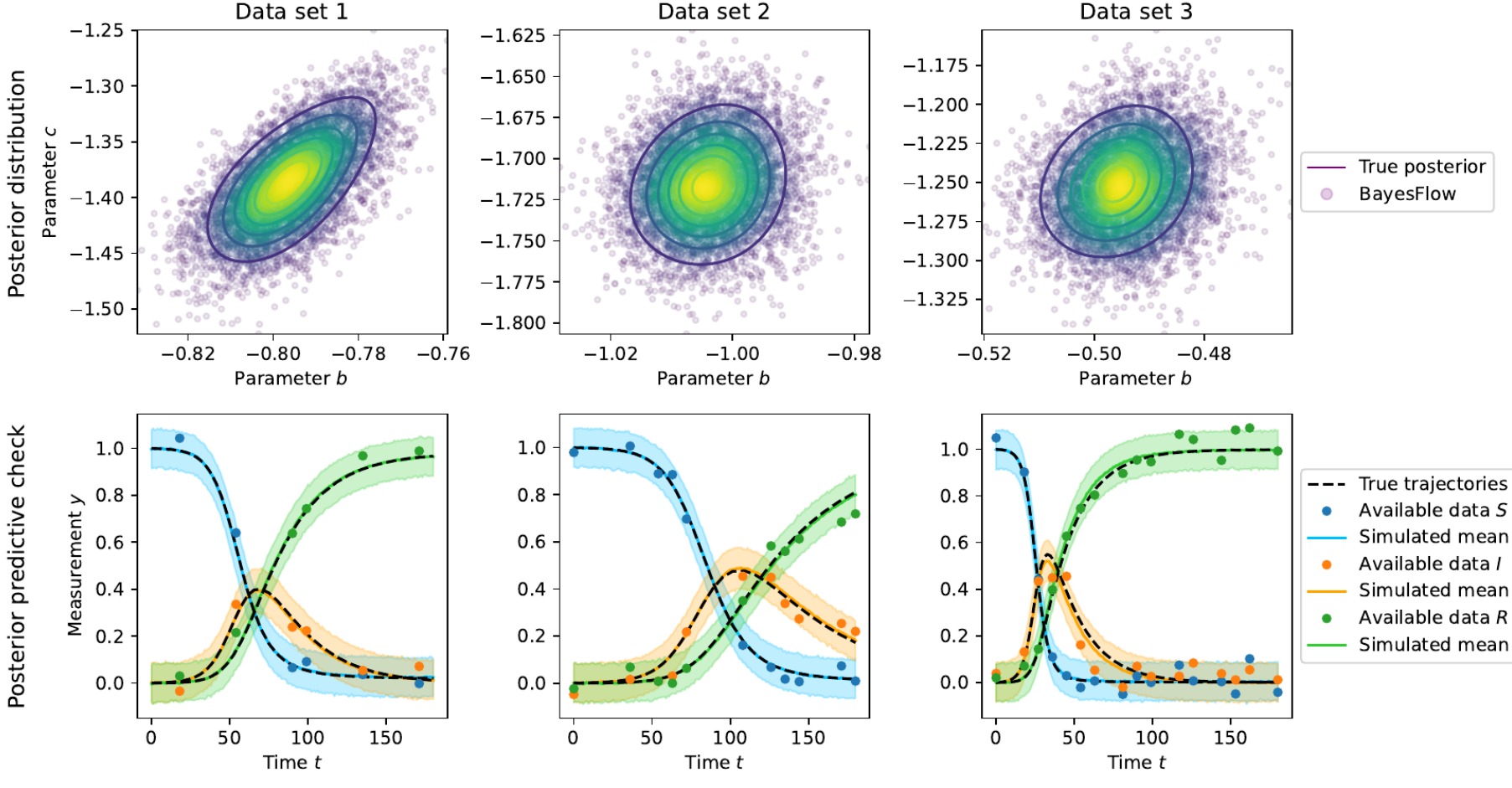
VARIABLE DATASET SIZE AS A SPECIAL CASE OF MISSING DATA



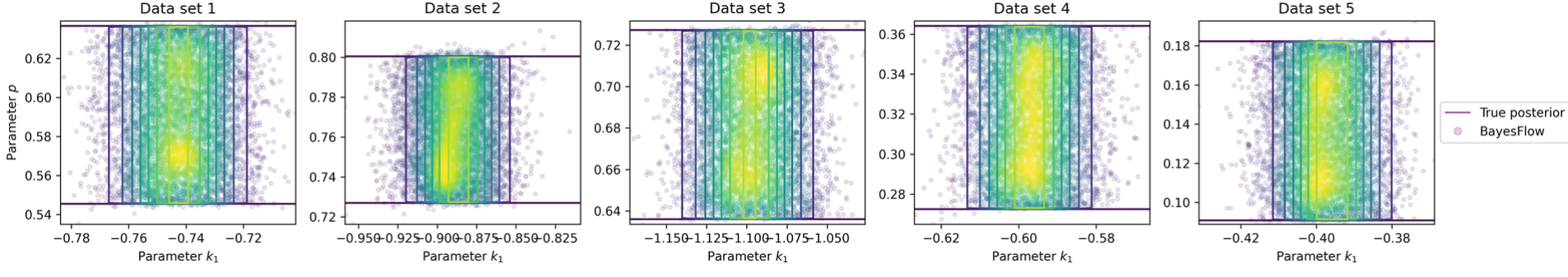


Augment by 0/1 improves performance due to better cost function approximation with individual-specific missingness

SCALES TO COMPLEX DYNAMICS



ABLE TO UNRAVEL PARAMETER-DEPENDENT MISSINGNESS



MIXED-EFFECTS MODELS

MIXED-EFFECTS MODELING

MIXED-EFFECTS MODELING

dynamical model: $\dot{x} = f(x, \theta)$

observables: $y = h(x, \theta) + \varepsilon$

parameters: $\theta = A\alpha + B\beta, \quad \beta \sim \mathrm{N}(0, \Sigma)$

PROBLEM

- **estimate parameters:** maximize over α and Σ the likelihood of data y_{obs}, marginalized over random effects β,

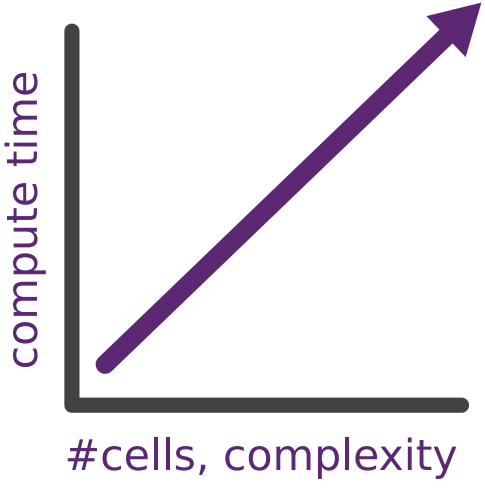
$$\pi(y_{\text{obs}}|\alpha, \Sigma) = \prod_i \int \pi(y_i|\theta)\pi(\theta|\alpha, \Sigma)d\theta$$

PROBLEM

- **estimate parameters:** maximize over α and Σ the likelihood of data y_{obs}, marginalized over random effects β,

$$\pi(y_{\text{obs}} \mid \alpha, \Sigma) = \prod_i \int \pi(y_i \mid \theta)\pi(\theta \mid \alpha, \Sigma)d\theta$$

- **problem: evaluating these (high-dim) integrals is challenging**, especially with many individuals



AN AMORTIZED APPROACH

AN AMORTIZED APPROACH

- **idea:** rewrite in terms of an **individual-specific posterior:**

$$\pi(y_{\text{obs}} \mid \alpha, \Sigma) = \prod_i \pi(y_i) \int \pi(\theta \mid y_i) \frac{\pi(\theta \mid \alpha, \Sigma)}{\pi(\theta)} d\theta$$

$$= \prod_i \pi(y_i) \mathrm{E}_{\theta \sim \pi(\theta \mid y_i)} \left[\frac{\pi(\theta \mid \alpha, \Sigma)}{\pi(\theta)} \right]$$

AN AMORTIZED APPROACH

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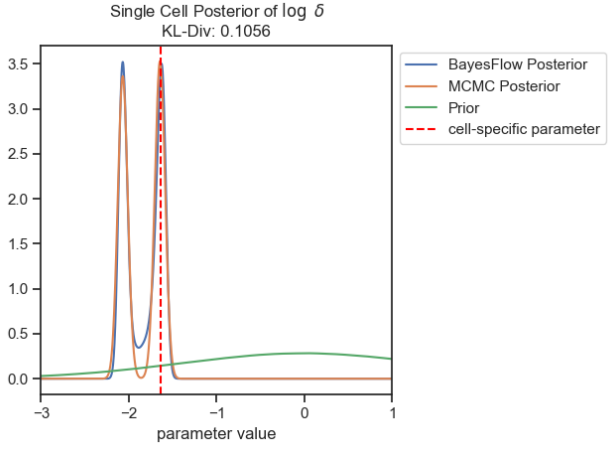
$$= \prod_i \pi(y_i) \mathrm{E}_{\theta \sim \pi(\theta \mid y_i)} \left[\frac{\pi(\theta \mid \alpha, \Sigma)}{\pi(\theta)} \right]$$

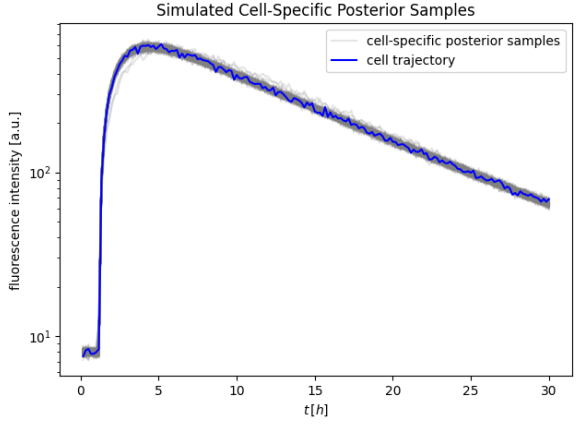
- ... and approximate the posterior using a **neural density estimator** trained on synthetic data!

EVALUATION

✓ INN **fits the posterior** well
✓ after training once (h), the optimization is **very fast** ($s - min$)
✓ allows to **easily test hypotheses**
✓ allows considering **stochastic models**
✓ even **uncertainty analysis** easily possible

EVALUATION





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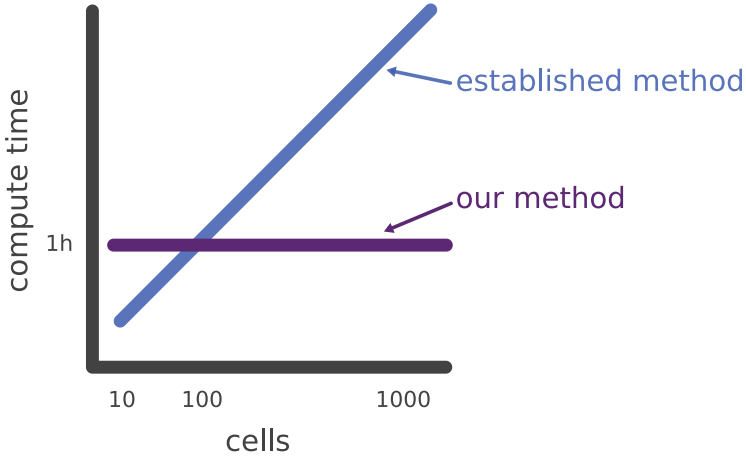

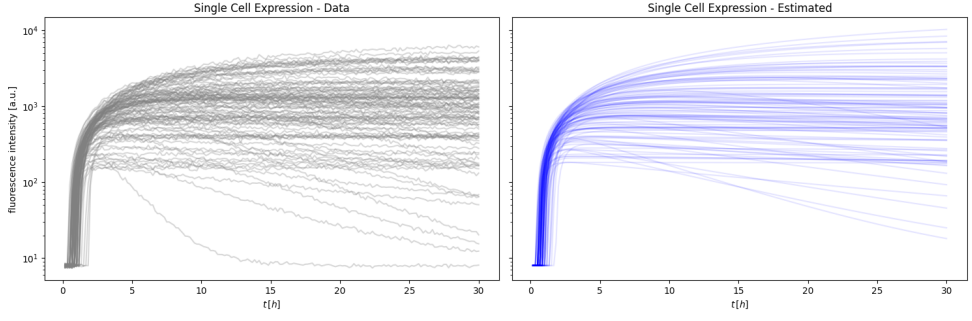

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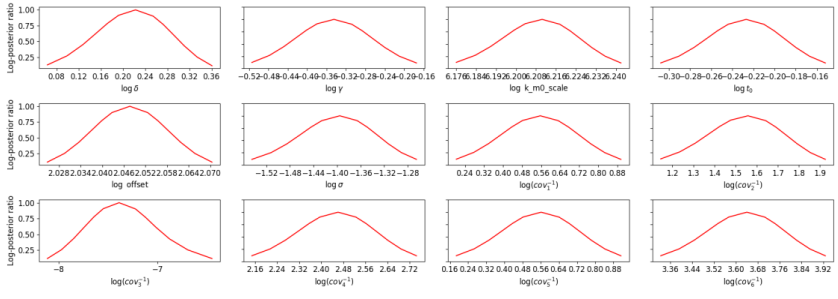

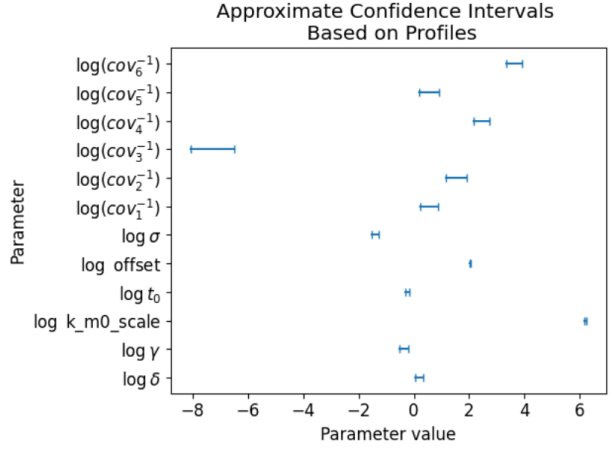

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OUTLOOK

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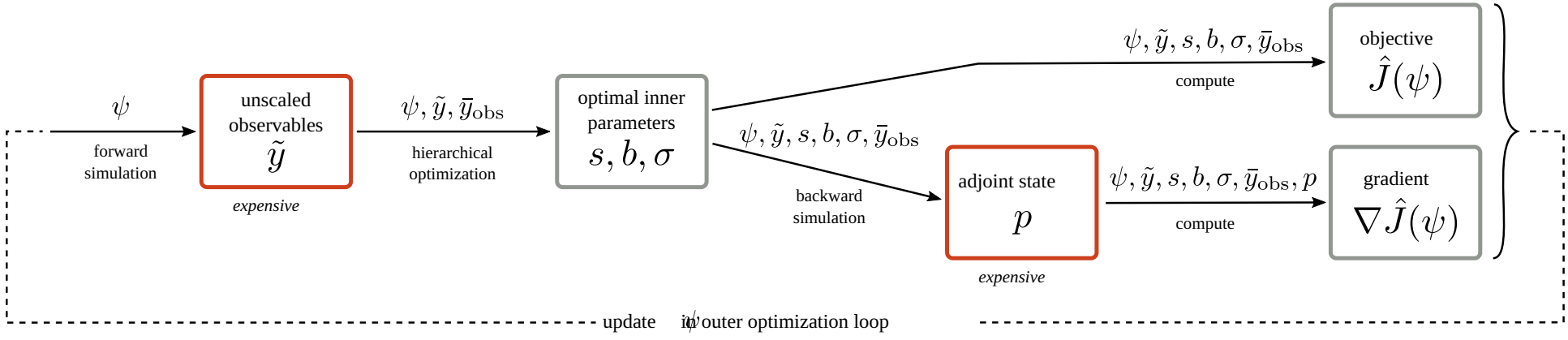
- applications in pharmacology and single-cell biology
- mechanistic insights to inform drug therapy
- combine with equation learning
- integrate image and tabular data in one framework
- large-scale modeling
- federated learning
- software


THANKS! QUESTIONS?
yannik-schaelte
@yannik_schaelte
yannikschaelte

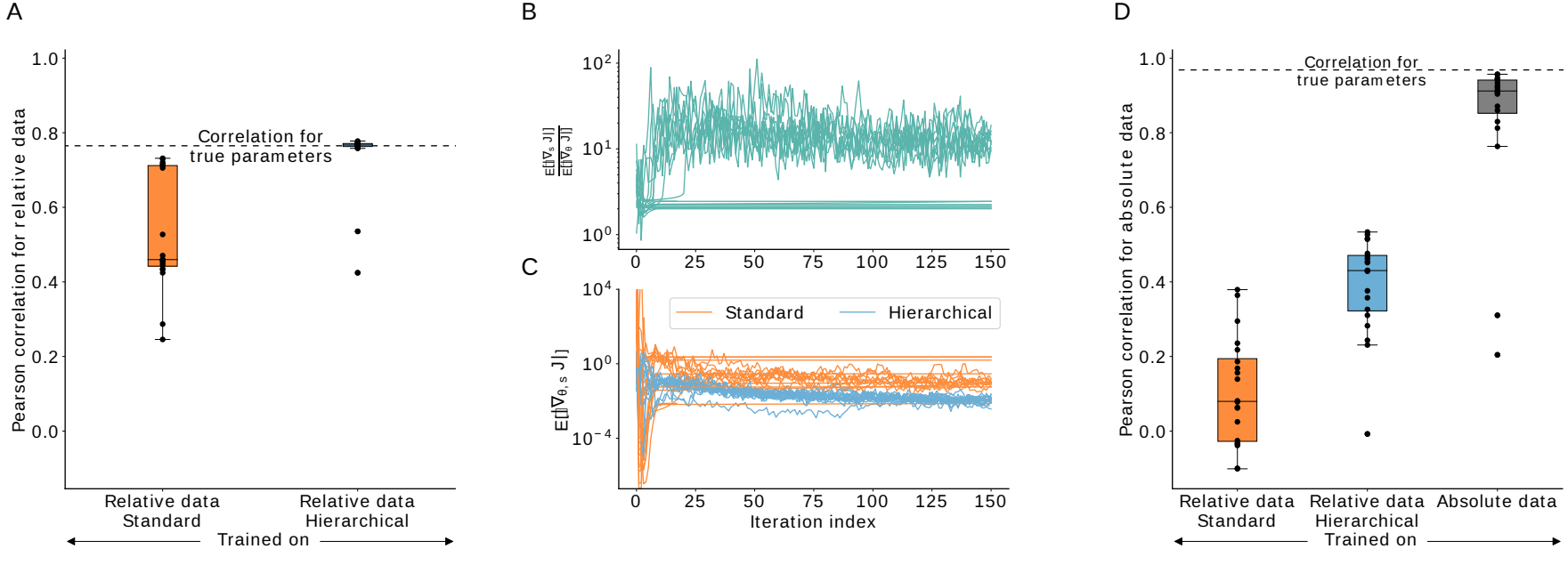
BACKUP

ILLUSTRATION OF ADJOINT-HIERARCHICAL EVALUATION SCHEME



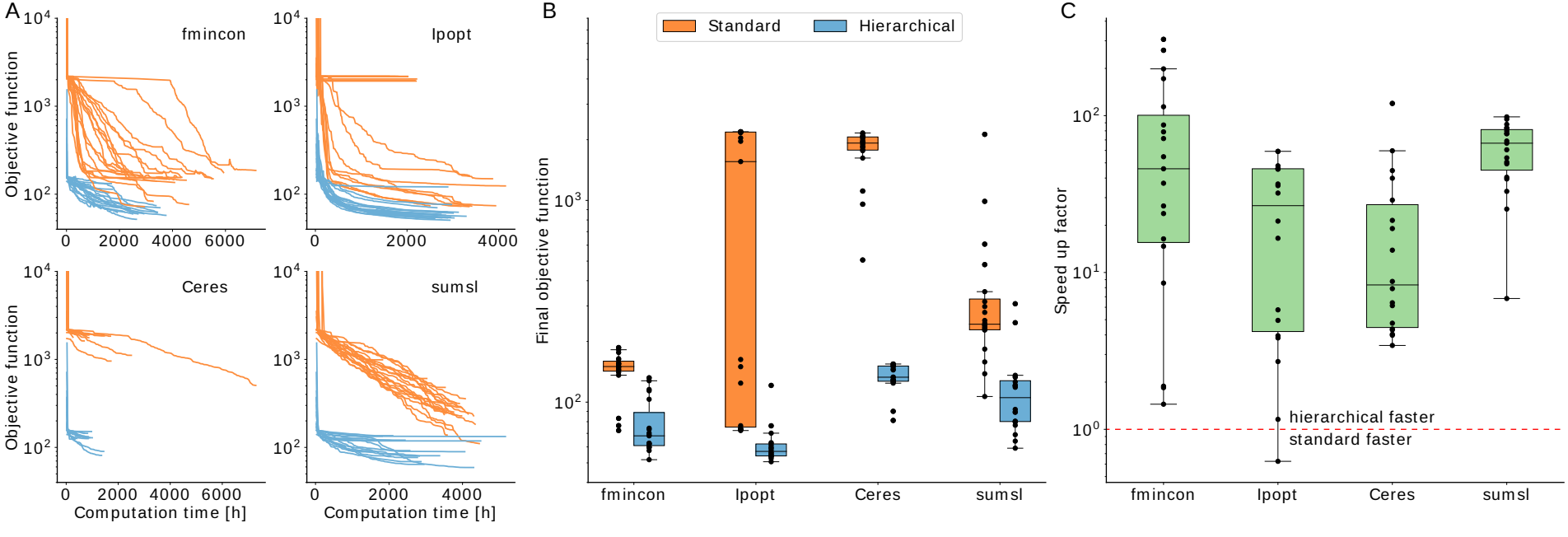
from: Schmiester, Schälte et al., Bioinformatics 2020

CONVERGENCE OF STANDARD AND HIERARCHICAL OPTIMIZATION



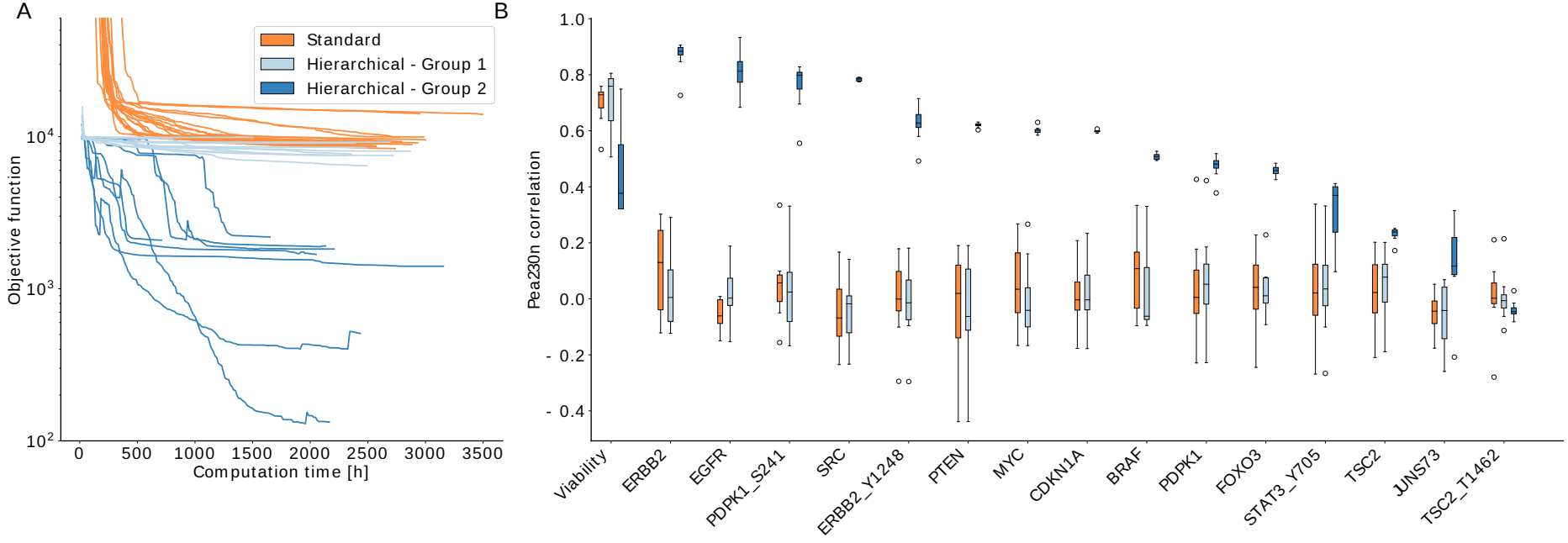
from: Schmiester, Schälte et al., Bioinformatics 2020

COMPUTATIONAL EFFICIENCY OF STANDARD AND HIERARCHICAL OPTIMIZATION



from: Schmiester, Schälte et al., Bioinformatics 2020

INTEGRATION OF HETEROGENEOUS DATA USING HIERARCHICAL OPTIMIZATION



from: Schmiester, Schälte et al., Bioinformatics 2020

pyABC

github.com/icb-dcm/pyabc

Klinger et al., Bioinformatics 2018 and Schälte et al., JOSS 2022

```python
# specify problem and parallelization
abc = ABCSMC(model, prior, distance, sampler)
# pass data
abc.new(db, data)
# run it
abc.run()
```

flexible

modular
configure
extend

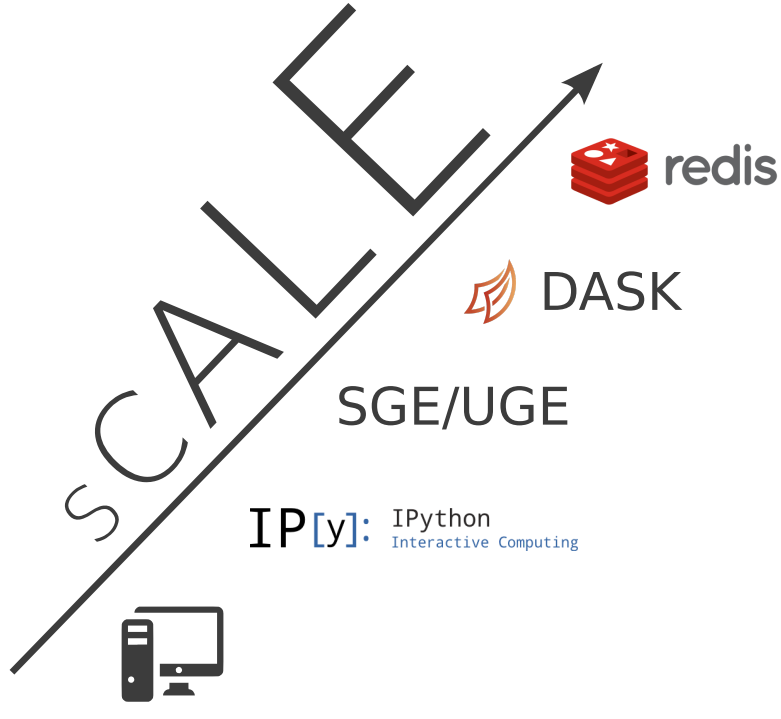
user-friendly

documented
self-tuning
robust

scalable

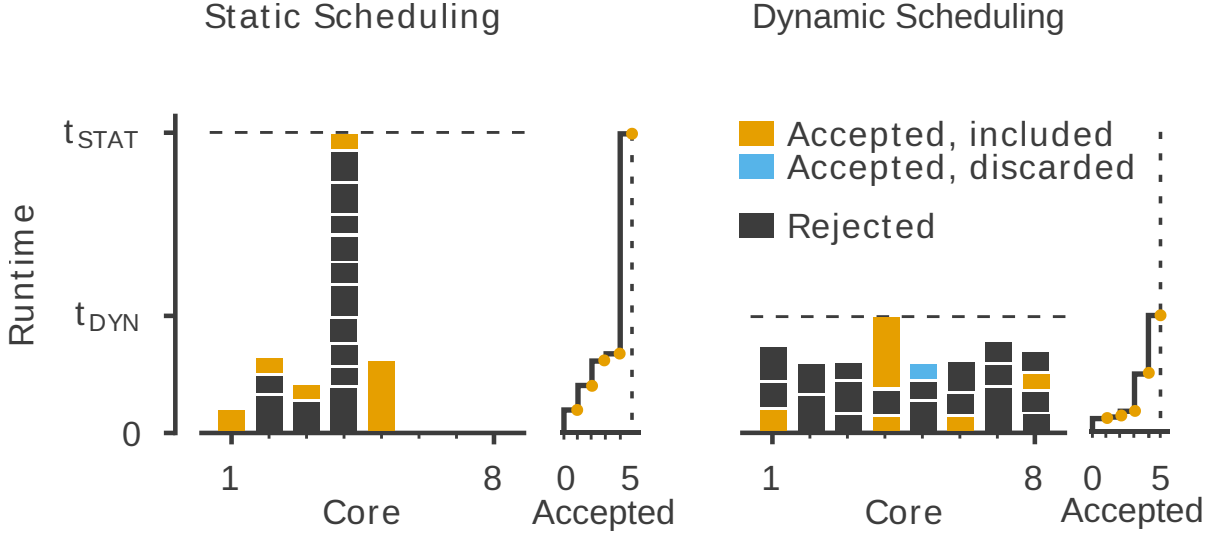
1 to 1,000s cores
efficient
tested

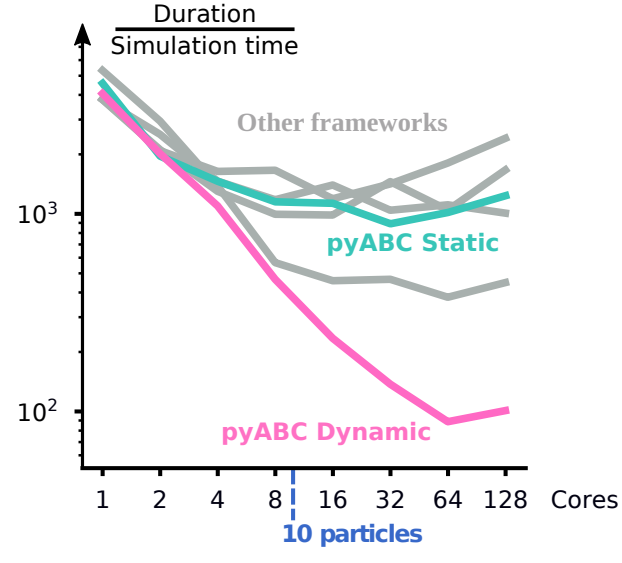
PARALLEL BACKENDS: 1 TO 1,000S CORES



PARALLELIZATION STRATEGIES

Klinger et al., CMSB Proceedings 2017

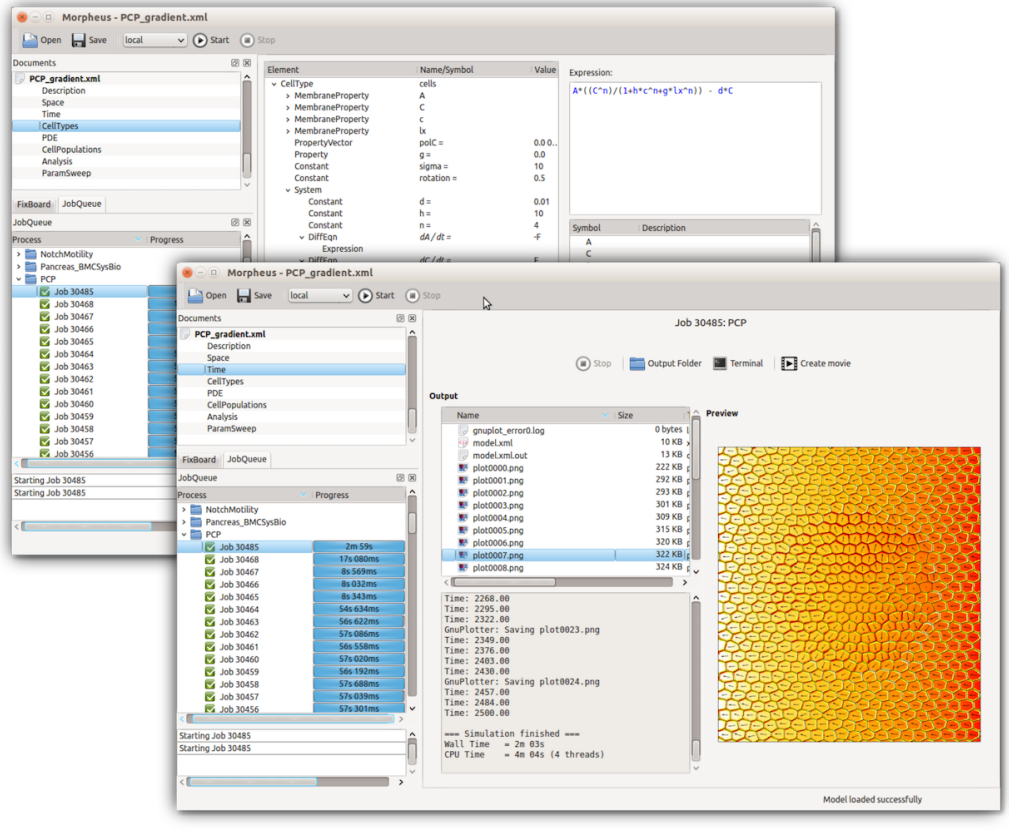




FitMultiCell

fitmulticell.gitlab.io

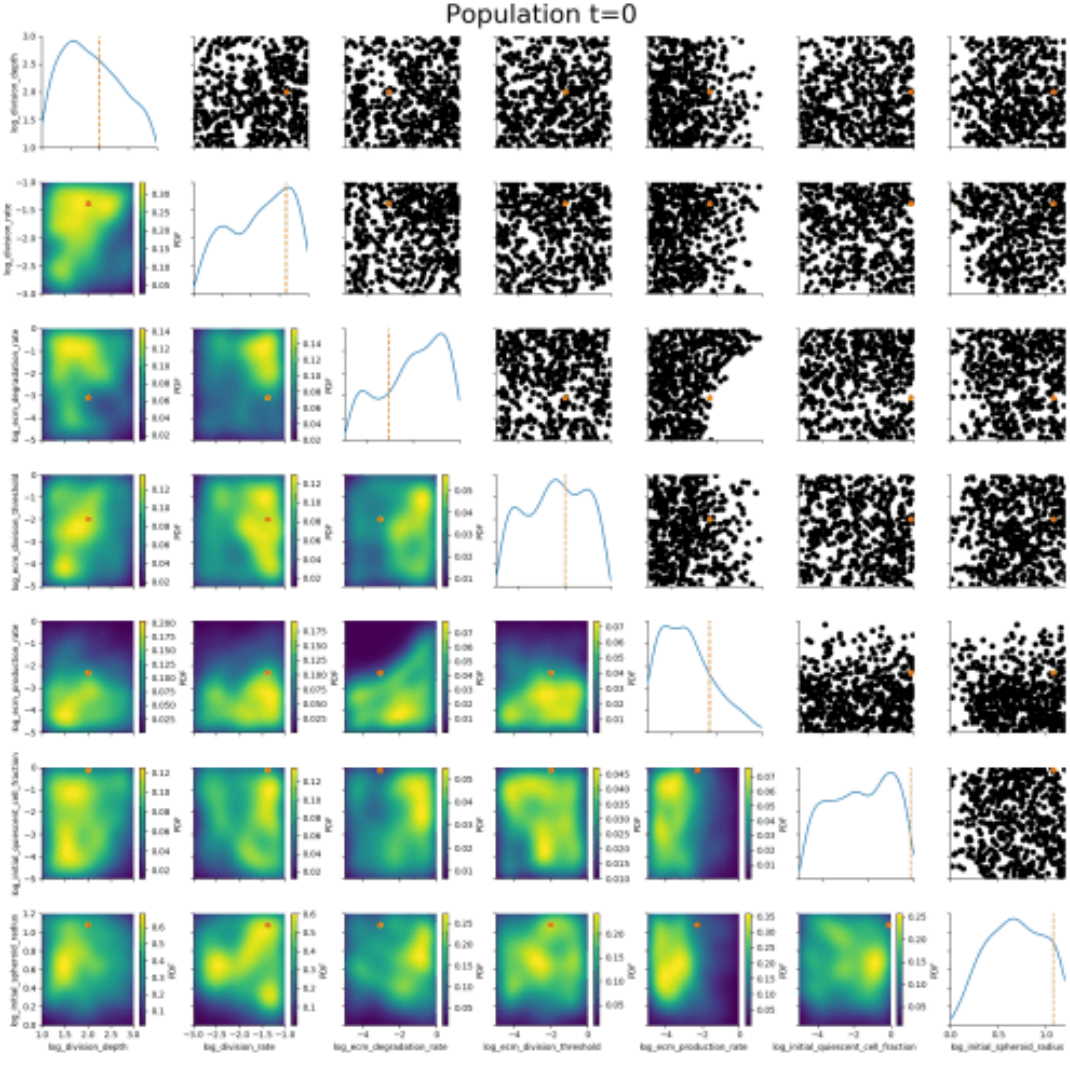
a platform for modeling, simulation and inference for multi-scale multi-cellular



models

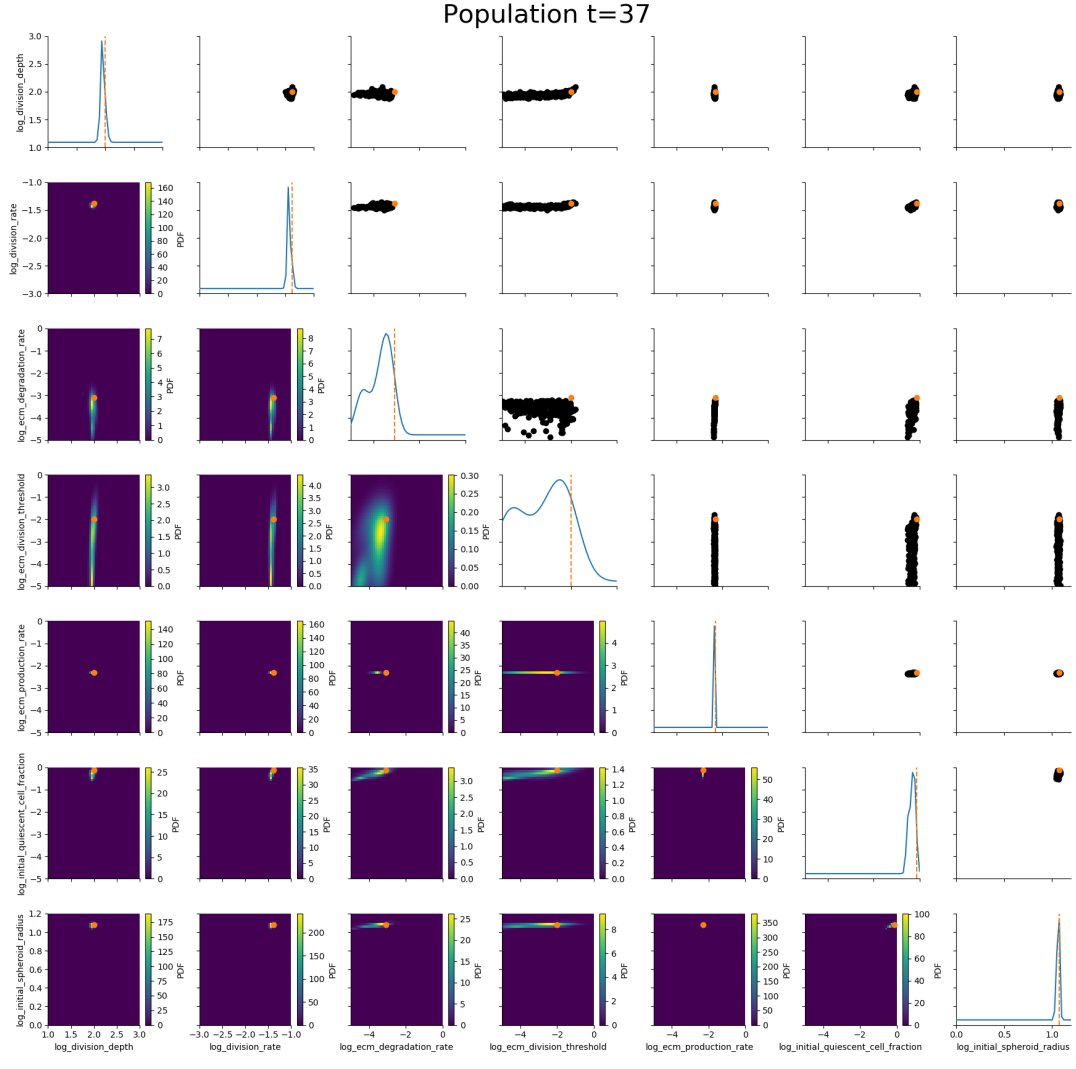
Starruß et al., Bioinformatics 2014; Alamoudi et al., NIC Proc. 2022; Alamoudi et al., bioRxiv 2023

APPLICATION EXAMPLE



ABC worked where many other methods had failed.

APPLICATION EXAMPLE



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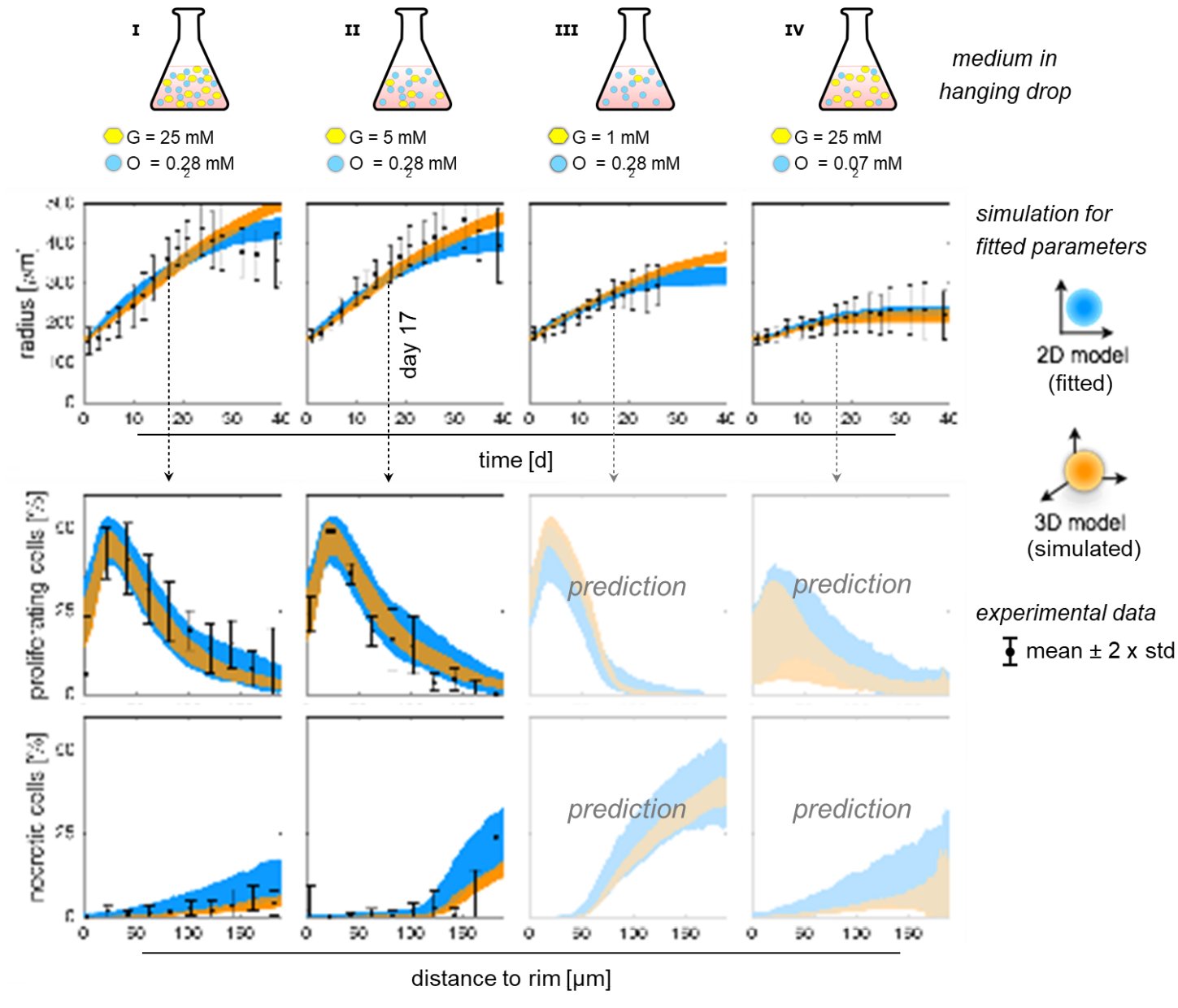
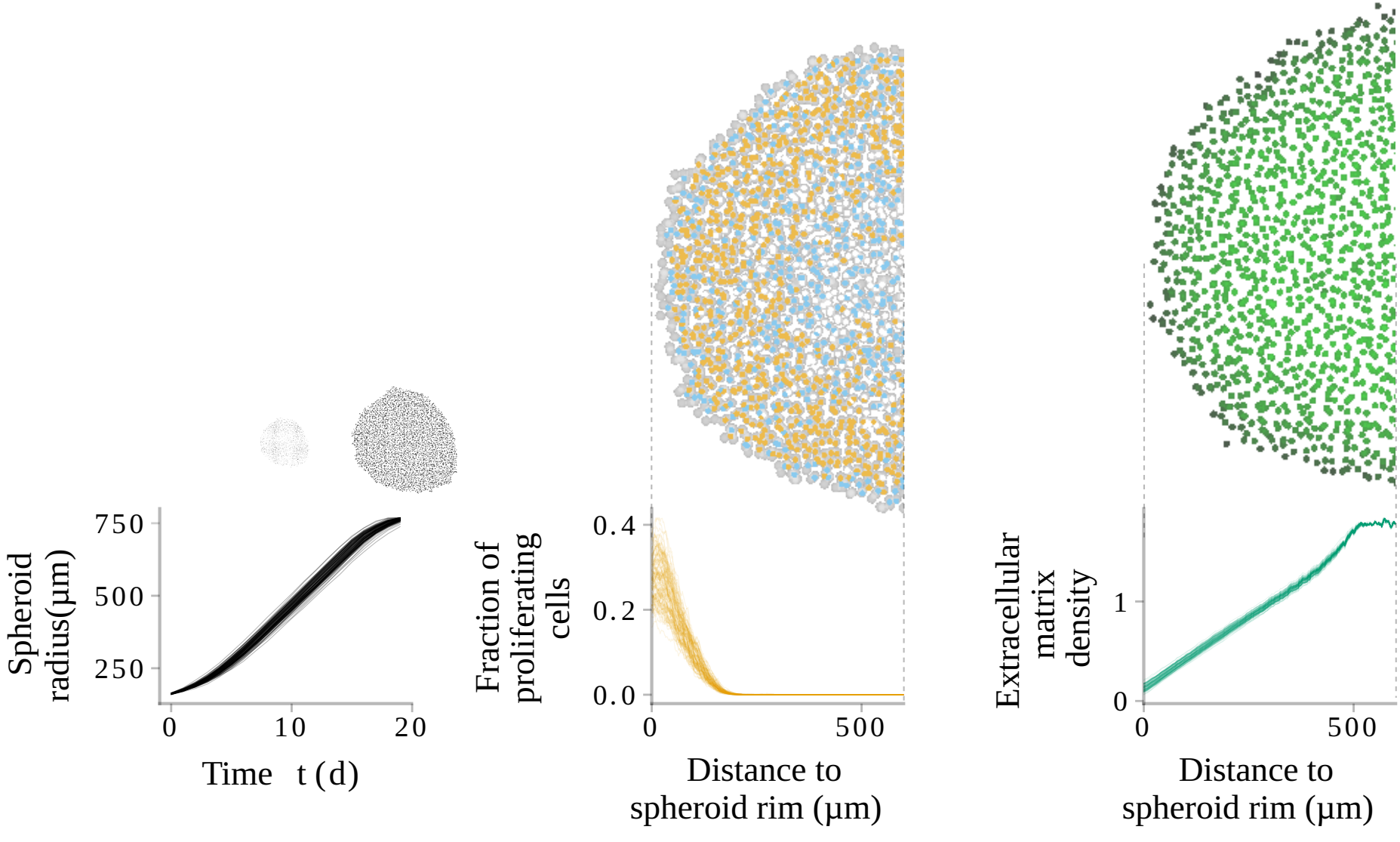
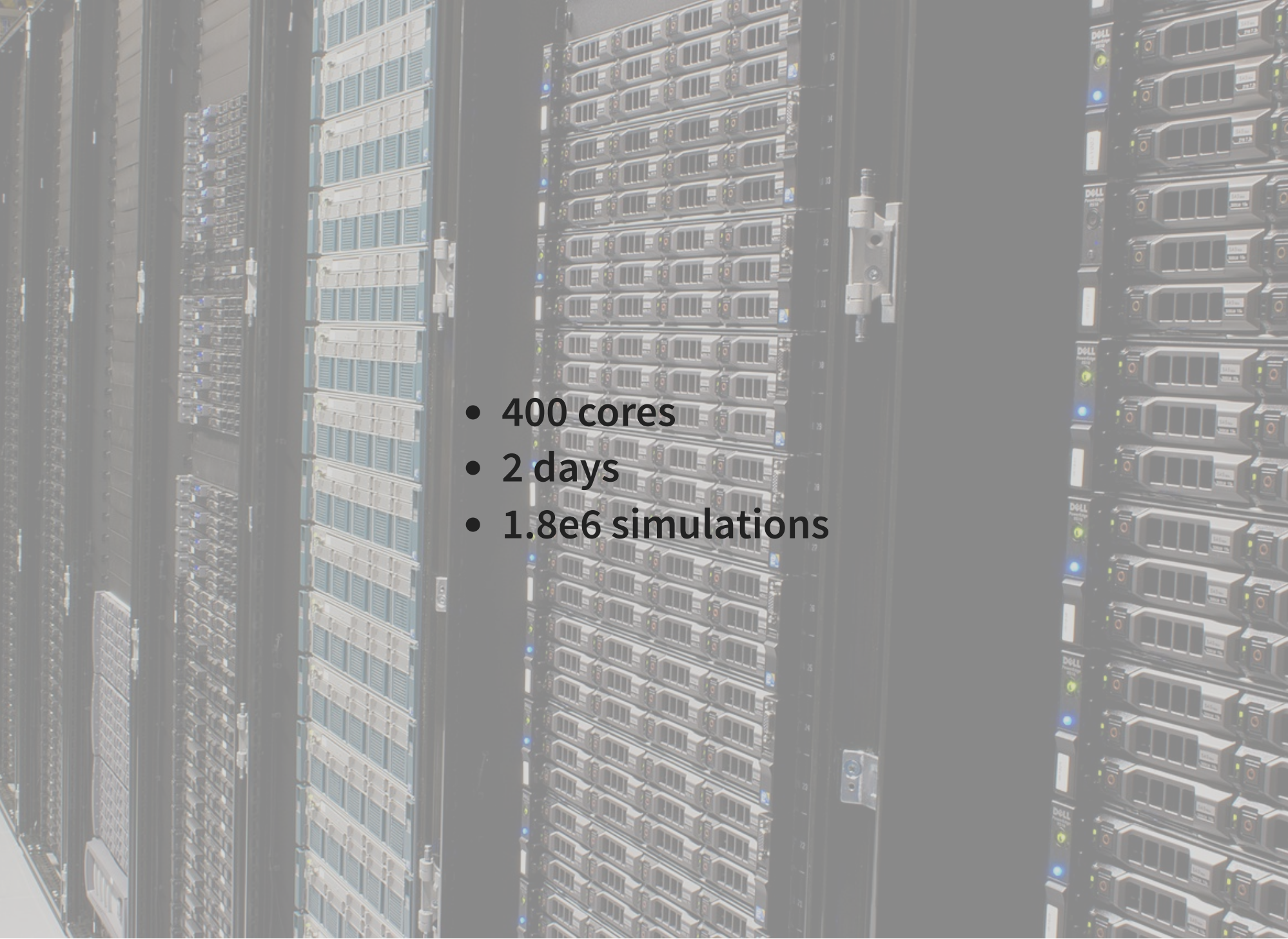


Uncertainty-aware predictions, easy data integration.

DEFINE SUMMARY STATISTICS





- 400 cores
- 2 days
- 1.8e6 simulations

THEOREM (EXACT INFERENCE)

Using the **modified kernel** with $c > \pi(\bar{y}_{\text{obs}}|y, \theta)\ \forall y, \theta$, we sample from the **true posterior**

$$\pi_{\text{ABC}}(\theta|\bar{y}_{\text{obs}}) = \pi(\theta|\bar{y}_{\text{obs}}) \propto \int \pi(\bar{y}_{\text{obs}}|y, \theta)p(y|\theta)\, dy \cdot \pi(\theta)$$

assuming **noisy data** $\bar{y}_{\text{obs}} \sim \pi(\bar{y}|y, \theta)$.

- non-trivial **noise** allows to do **exact likelihood-free** inference
- applicable to **stochastic models**
- **parameterized noise** model

THEOREM (OPTIMAL SUMMARY STATISTICS)

[...] Given $\lambda : \mathbb{R}^{n_\theta} \to \mathbb{R}^{n_\lambda}$ such that $\mathbb{E}_{\pi(\theta)}[|\lambda(\theta)|] < \infty$, define **summary statistics as the conditional expectation**

$$s(y) := \mathbb{E}[\lambda(\Theta)|Y = y] = \int \lambda(\theta)\pi(\theta|y)d\theta.$$

Then, it holds $\left\|\mathbb{E}_{\pi_{\mathrm{ABC},\varepsilon}}[\lambda(\Theta)|s(y_{\mathrm{obs}})] - s(y_{\mathrm{obs}})\right\| \leq \varepsilon$, and therefore

$$\lim_{\varepsilon \to 0} \mathbb{E}_{\pi_{\mathrm{ABC},\varepsilon}}[\lambda(\Theta)|s(y_{\mathrm{obs}})] = \mathbb{E}[\lambda(\Theta)|Y = y_{\mathrm{obs}}].$$

In practice: Train regression model $s : y \mapsto \lambda(\theta) = (\theta^1, \ldots, \theta^k)$.

SCALE-NORMALIZING AND OUTLIER-ROBUST ADAPTIVE DISTANCES