UNIVERSITÄT BONN

HELMHOLTZ MUNICH

Amortized inference for pharmacological mixed-effects models with incomplete data

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JHS Add-On 8th Cohort First Meeting, Hamburg 2023-02-11

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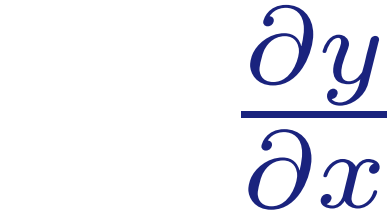
yannikschaelte.github.io/pres_npe_hjs_2023



mechanistic modeling

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

mechanistic modeling

- theory-driven
- interpretation
- testability

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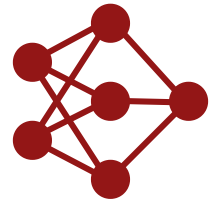

machine learning

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

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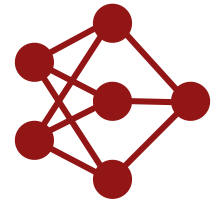

machine learning

- data-driven
- large data
- automation

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

mechanistic modeling

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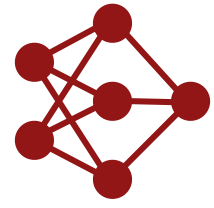
+



machine learning

- data-driven
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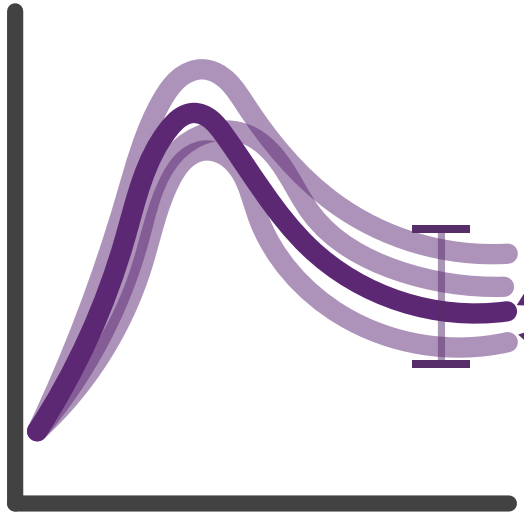
sciML

model-based data-efficient ML

MIXED-EFFECTS MODELING



fixed effects α

random effects β

MIXED-EFFECTS MODELING

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

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

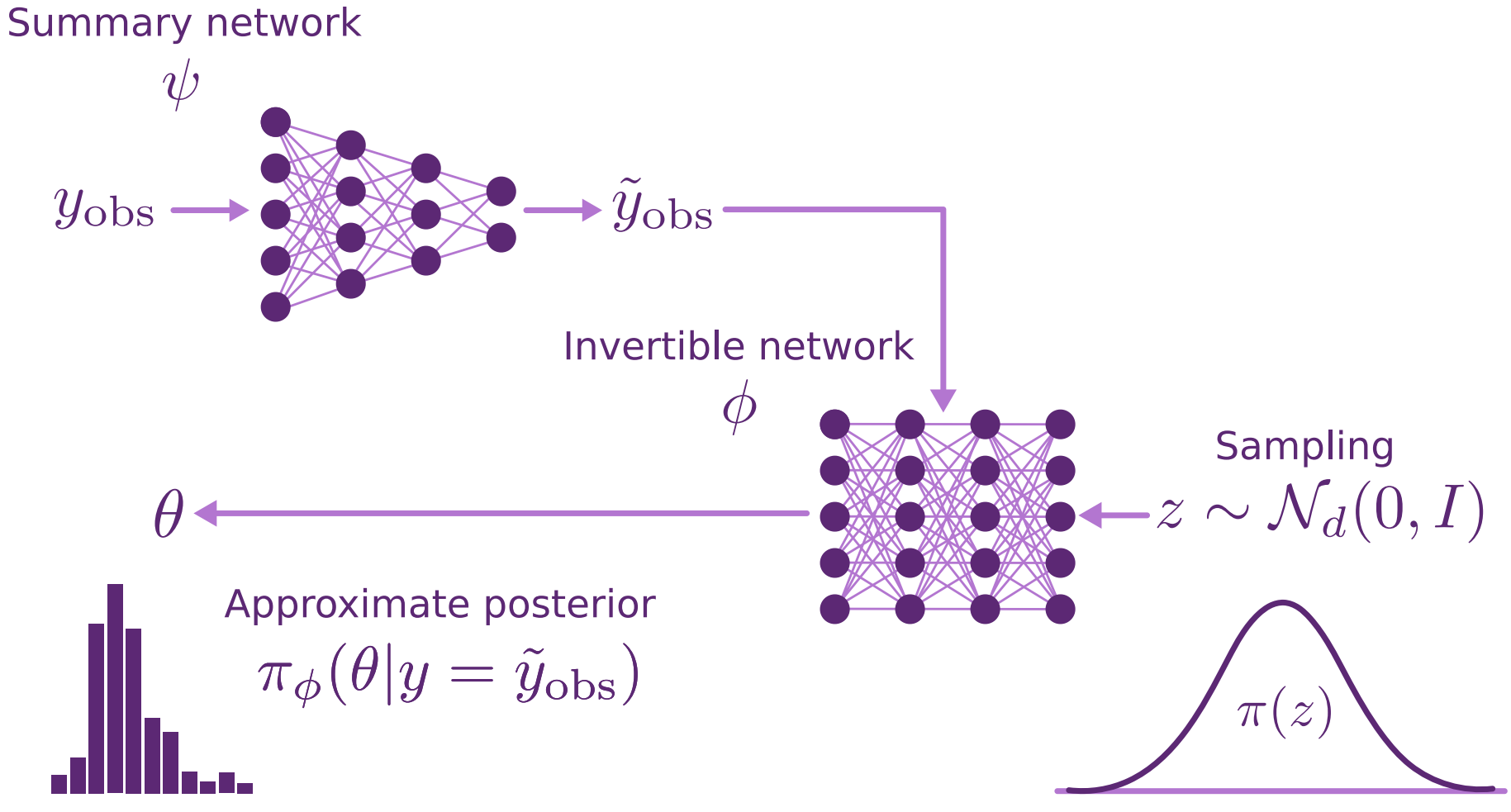
parameters: $\theta = A\alpha + B\beta, \quad \beta \sim \mathcal{N}(0, \Sigma)$

THE PROBLEM

THE PROBLEM

AMORTIZED INFERENCE VIA INVERTIBLE NEURAL NETWORKS

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



similar to: Radev et al., 2021

- parameter estimation requires repeatedly evaluating an integral

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

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OUR METHOD

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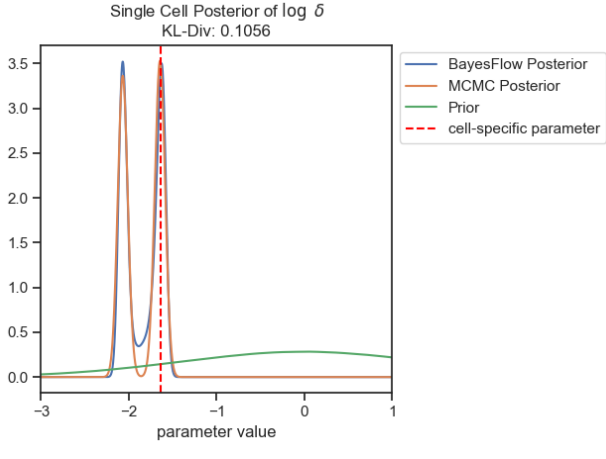
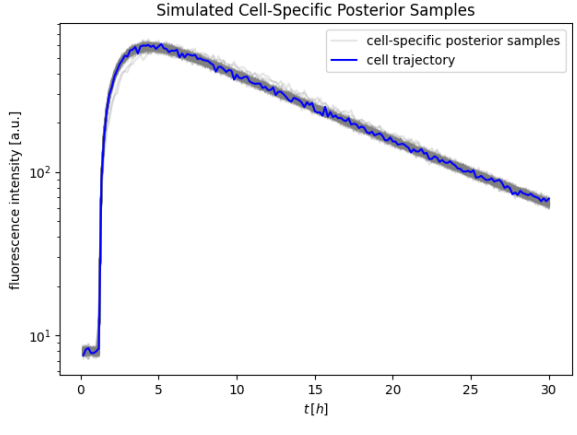
OUR METHOD

RESULTS

RESULTS

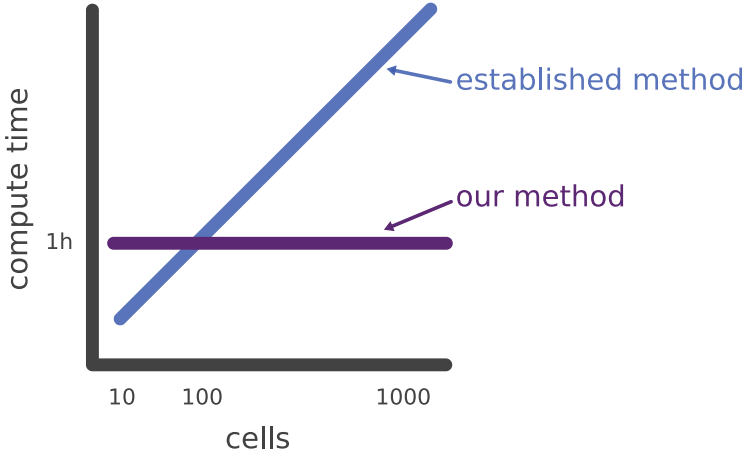
✓ NN **fits the posterior** well

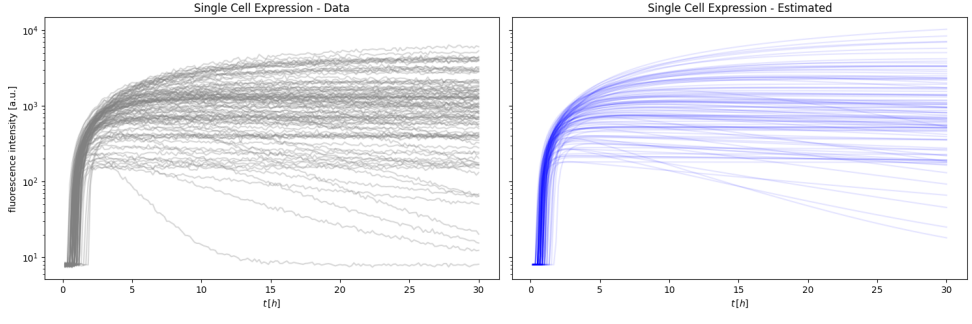




RESULTS

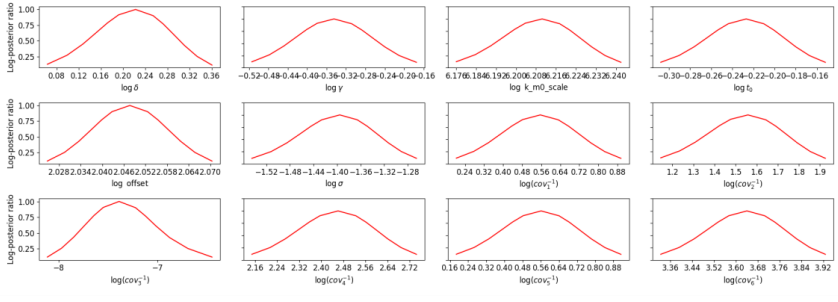
- ✓ NN **fits the posterior** well
- ✓ after training once $(1 - 2h)$, the optimization is **very fast** $(s - min)$

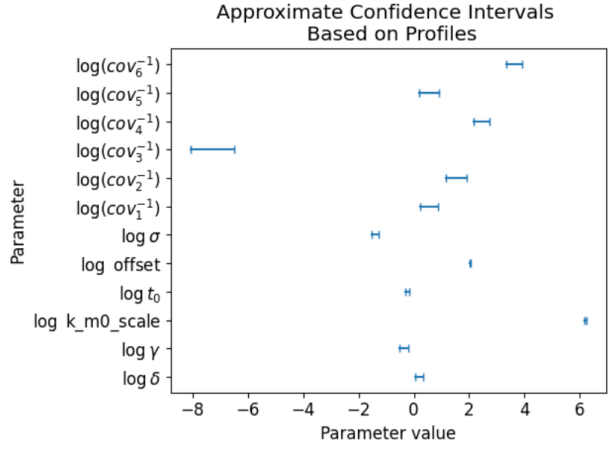




RESULTS

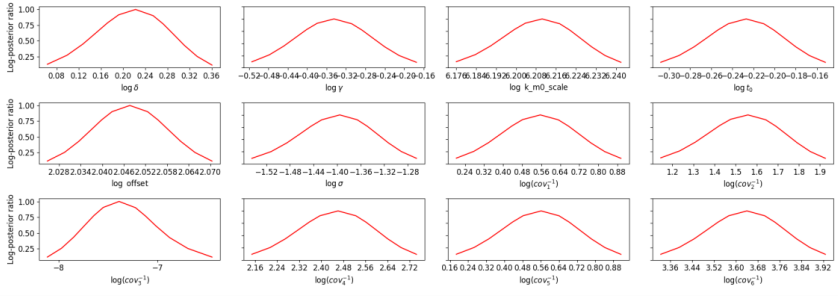
- ✓ NN **fits the posterior** well
- ✓ after training once $(1 - 2h)$, the optimization is **very fast** $(s - min)$
- ✓ even **uncertainty analysis** easily possible

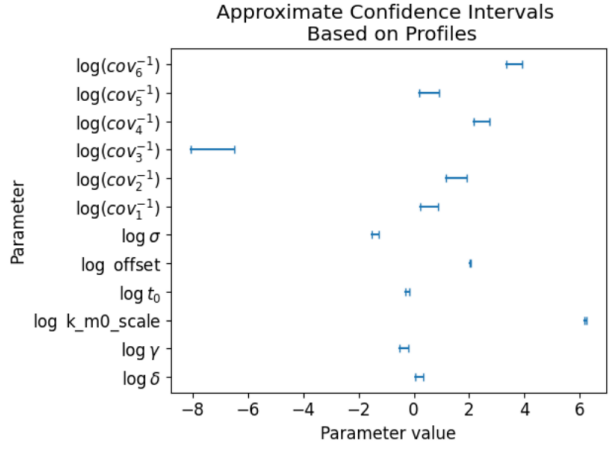




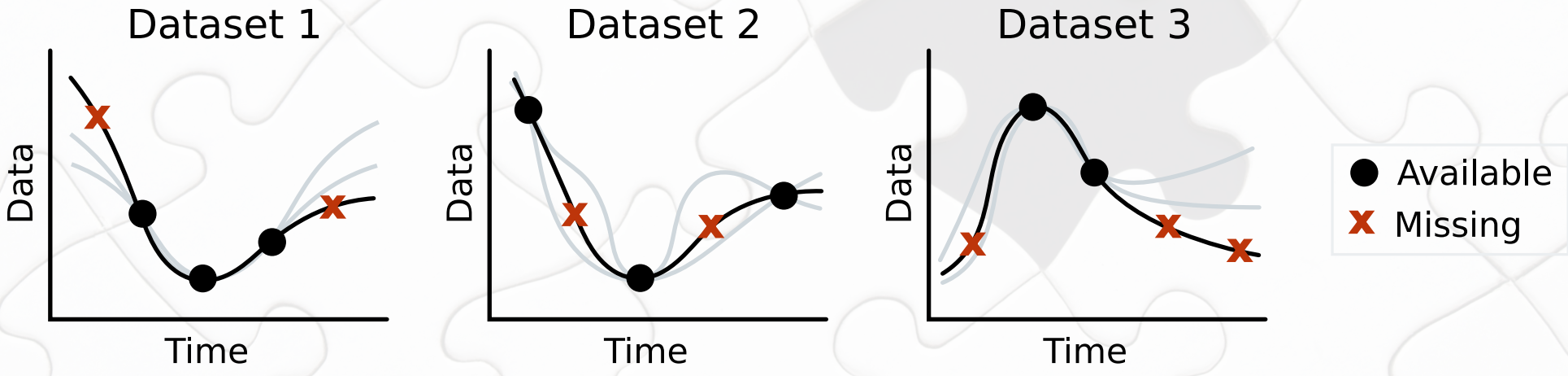
RESULTS

- ✓ NN **fits the posterior** well
- ✓ after training once $(1 - 2h)$, the optimization is **very fast** $(s - min)$
- ✓ even **uncertainty analysis** easily possible
- ✓ can handle multiple **experiment conditions**



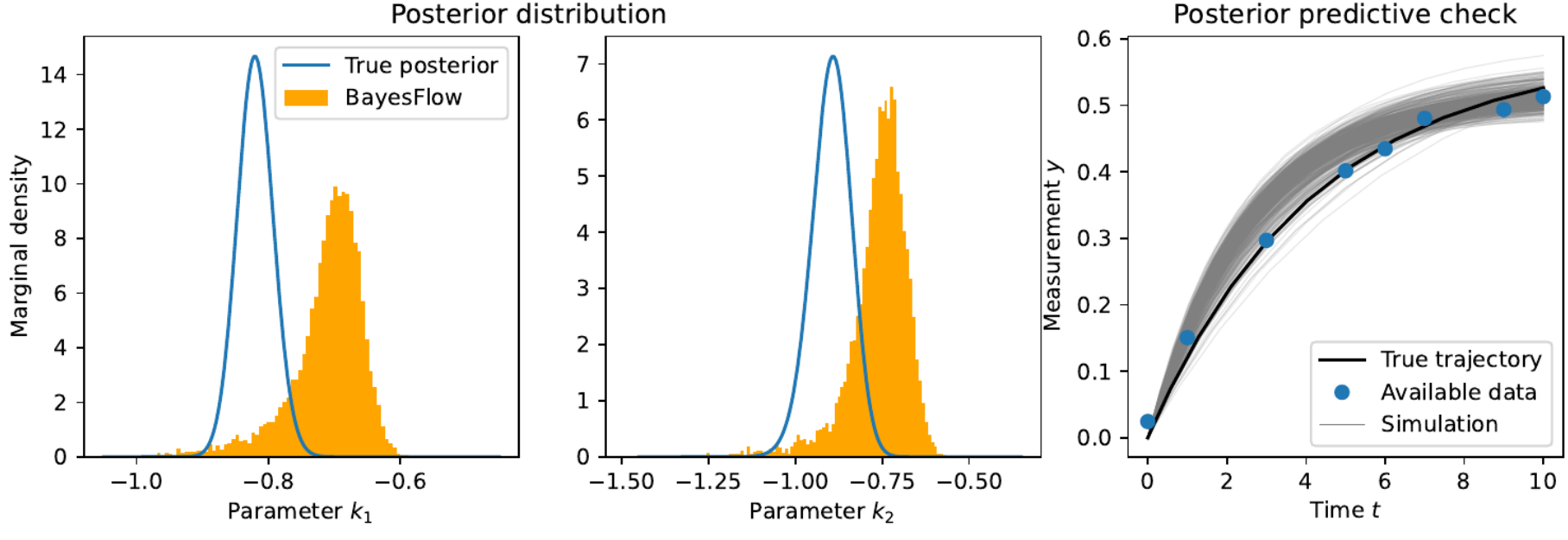


HOW TO HANDLE MISSING DATA IN AMORTIZED INFERENCE?



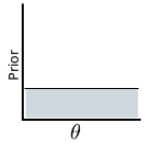
HOW TO HANDLE MISSING DATA IN AMORTIZED INFERENCE?

PROBLEM: BAYESFLOW CANNOT INTERPRET THE DATA



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

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

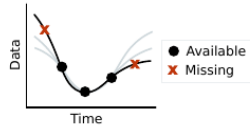
Time labels

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

Inference phase

Experiment

Example



Incomplete data
$x_{\text{avai}}^{\text{obs}}$

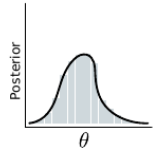
$x_{\text{avai}}^{\text{obs}} = \begin{bmatrix} \text{NA} & 3.9 & 2.5 & 3.4 & \text{NA} \end{bmatrix}$

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

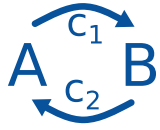
$x_{\text{aug}}^{\text{obs}} = \begin{bmatrix} -1.0 & 3.9 & 2.5 & 3.4 & -1.0 \\ 0 & 1 & 1 & 1 & 0 \end{bmatrix}$

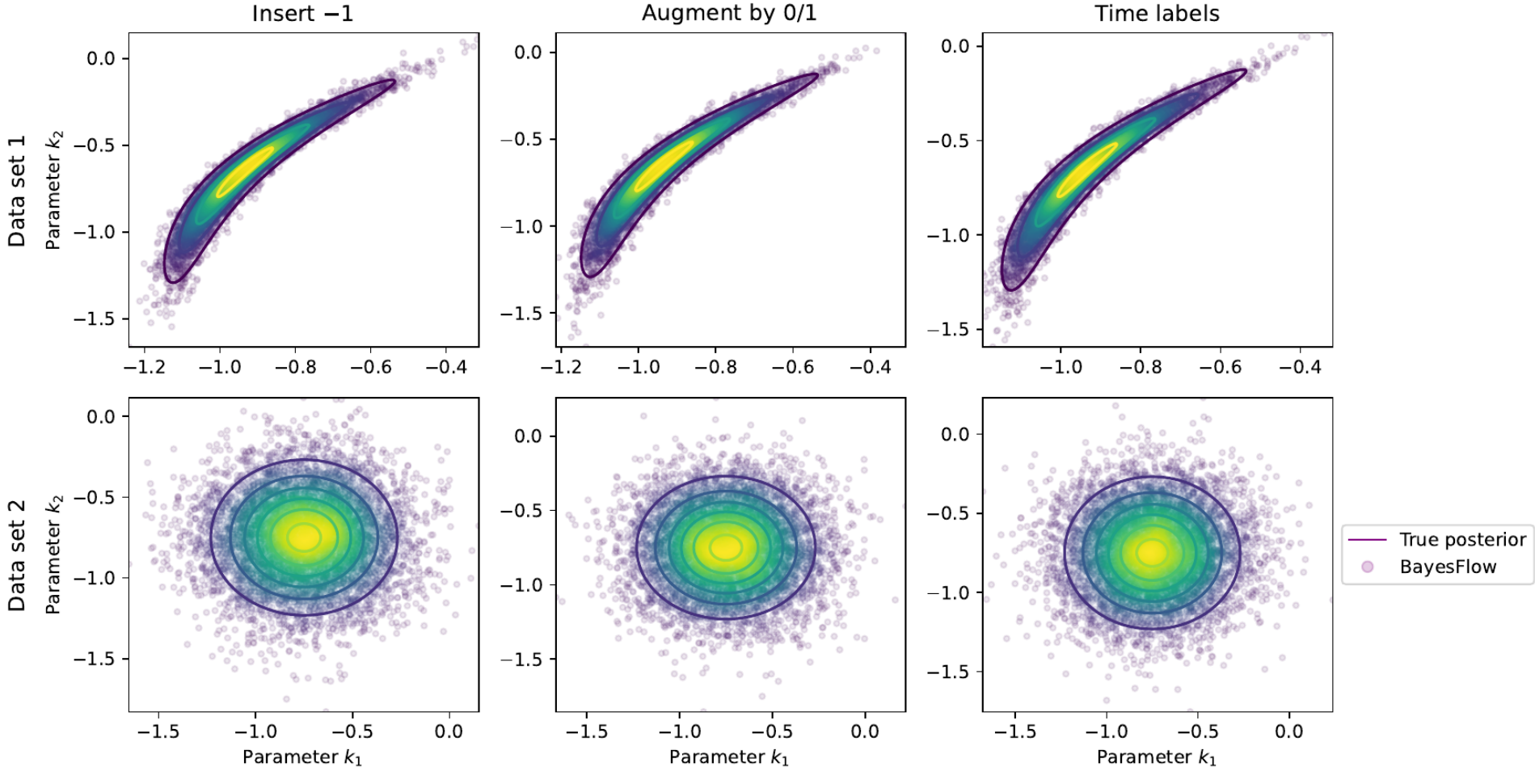
Sample from BayesFlow
$\theta \sim \pi(\theta|x_{\text{avai}}^{\text{obs}})$

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

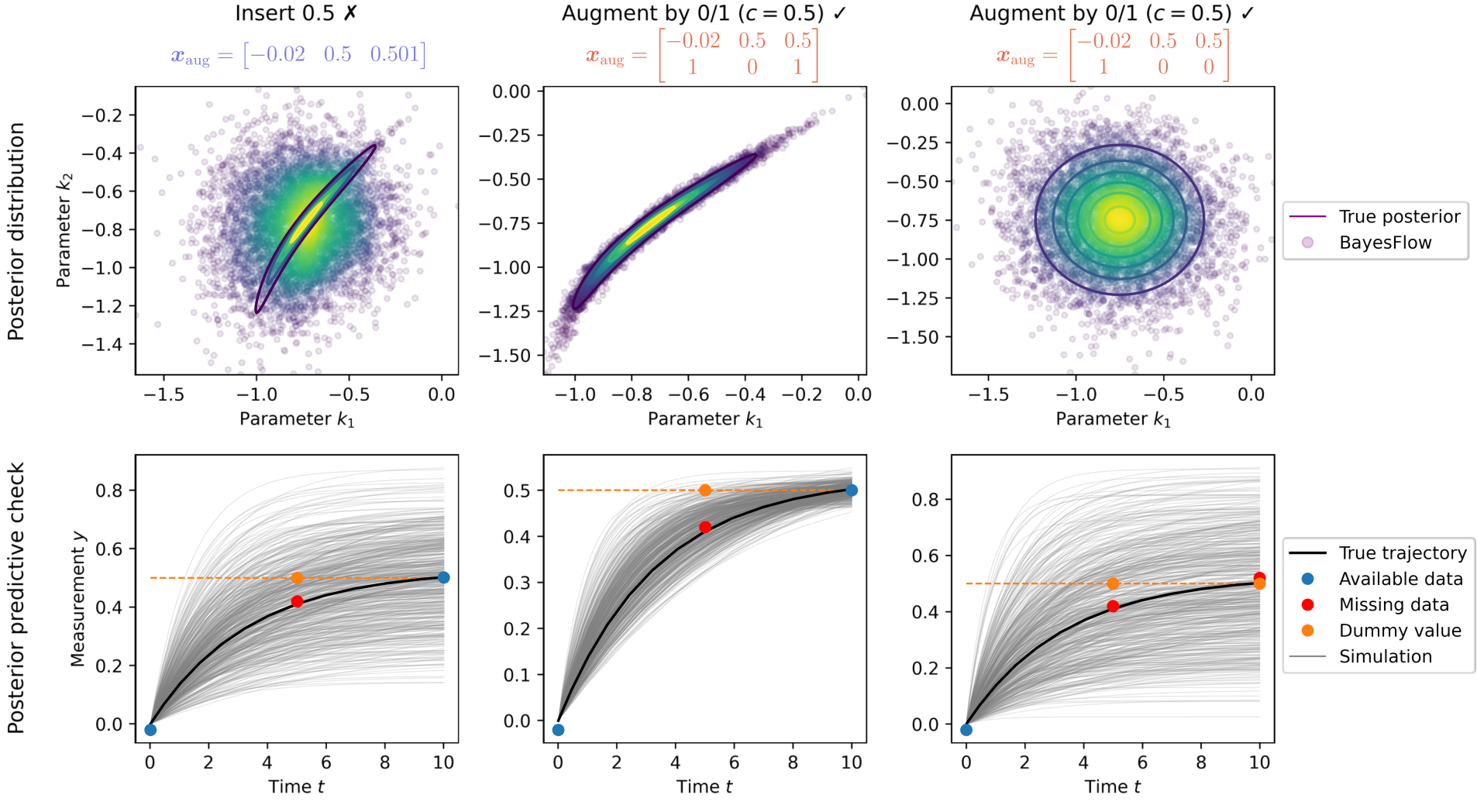


All approaches perform well on simple test problem

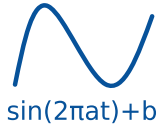


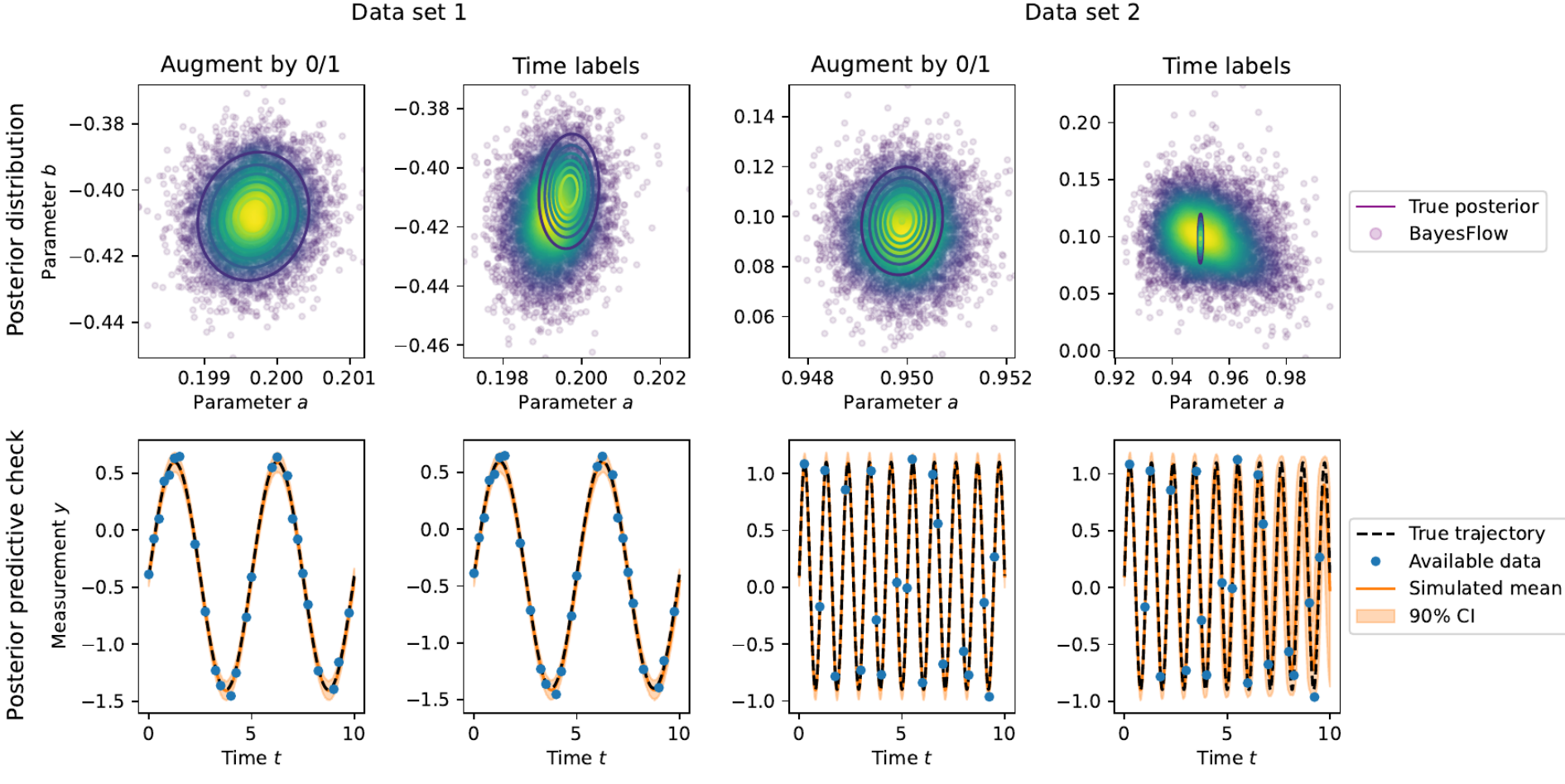


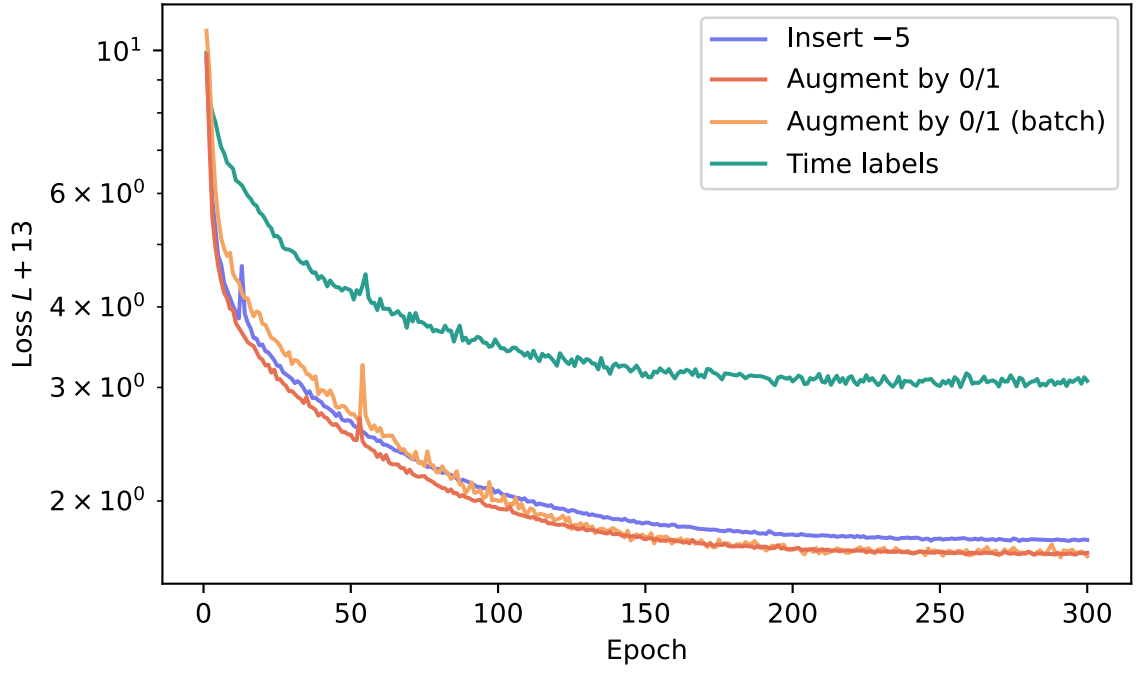
Binary indicator augmentation more robust for ambiguous fill-in values



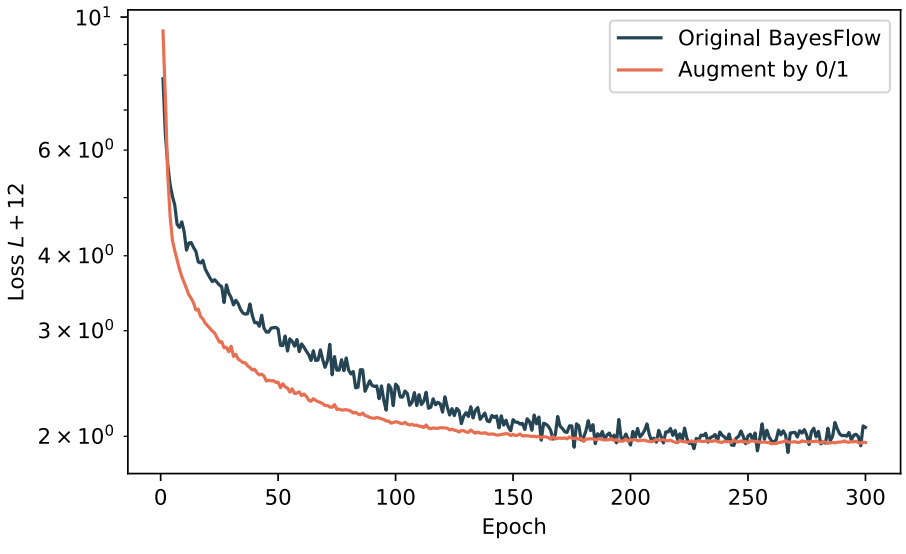
Time labels encoding performs not robustly in case of oscillatory data

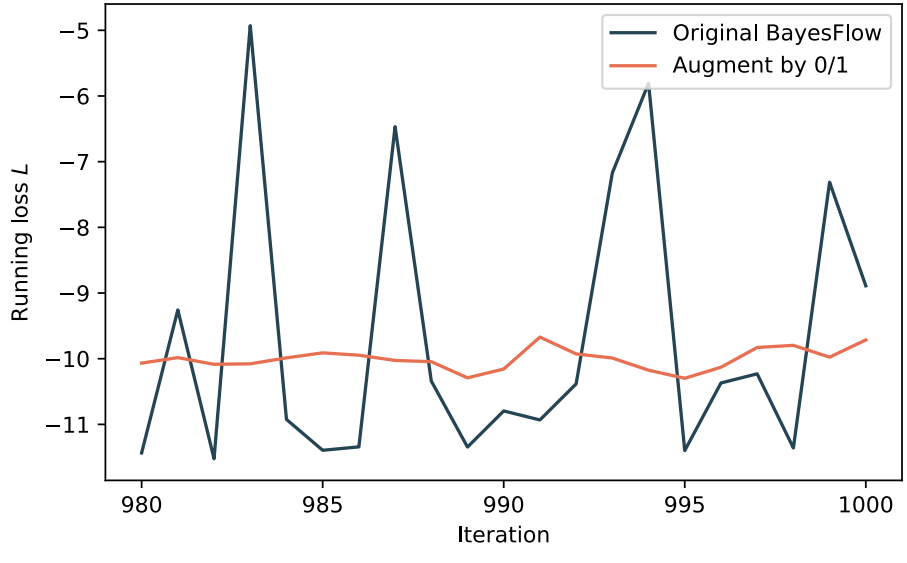





Insert −5
Augment by 0/1
Augment by 0/1 (batch)
Time labels
10^1
6×10^0
4×10^0
3×10^0
2×10^0
Loss $L + 13$
0
50
100
150
200
250
300
Epoch

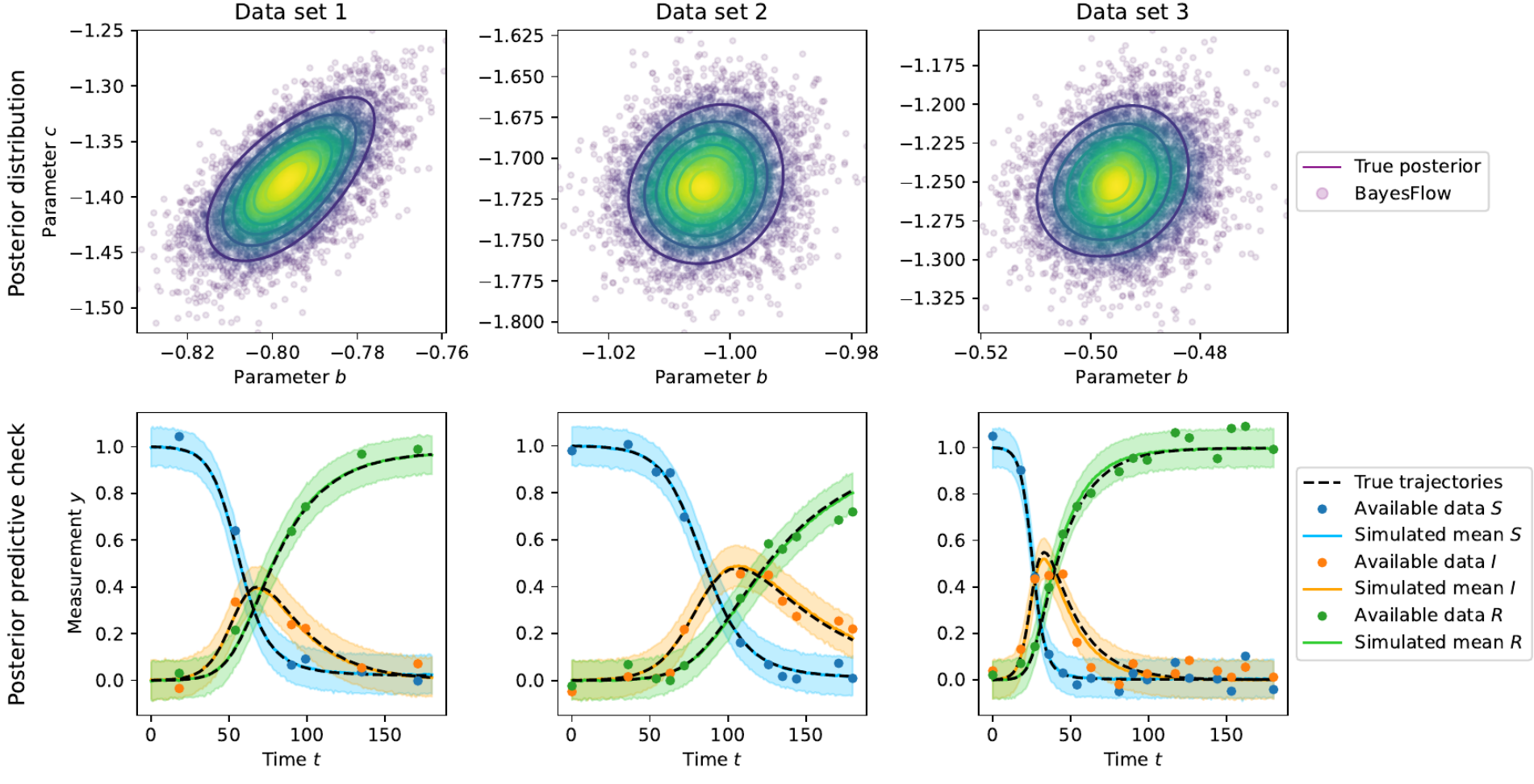
Variable dataset size as a special case of missing data



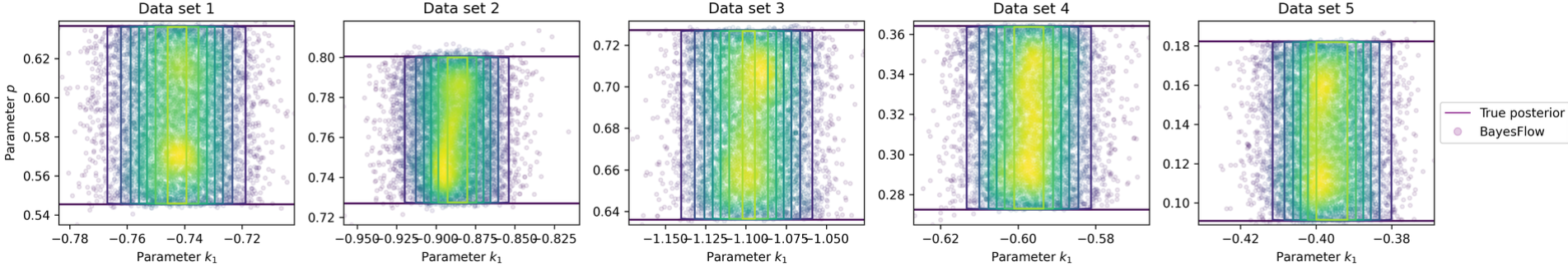


Augment by 0/1 improves performance due to better cost function approximation with individual-specific missingness

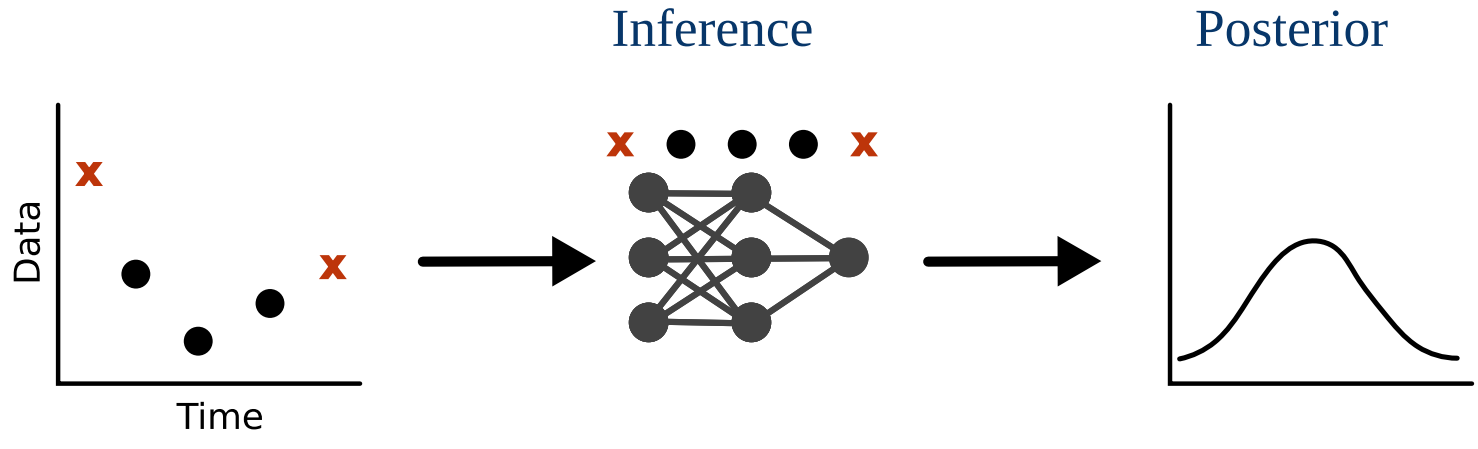
Scales to more complex inference problems



Able to unravel parameter-dependent missingness



CAN WE JUST IMPUTE MISSING VALUES?



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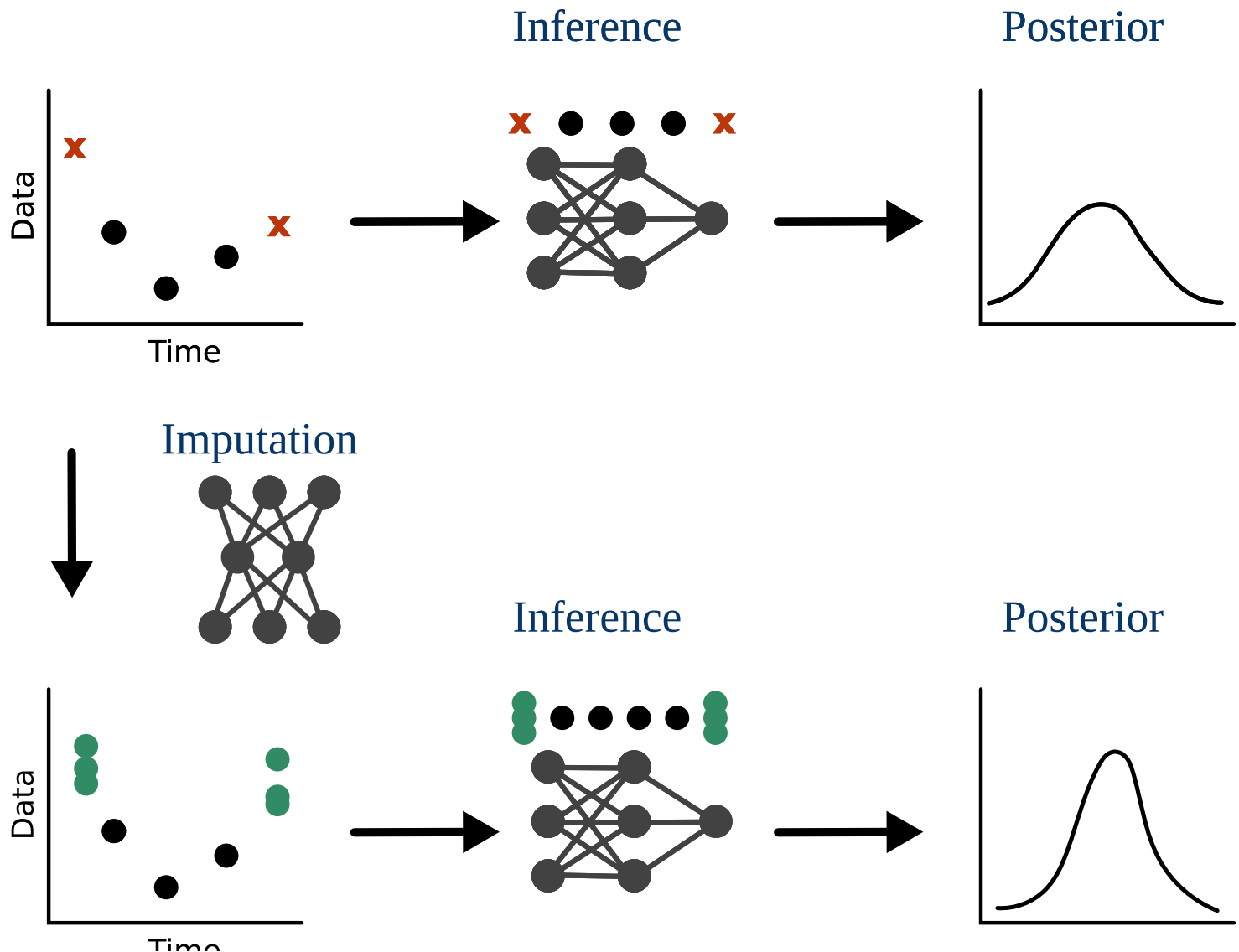
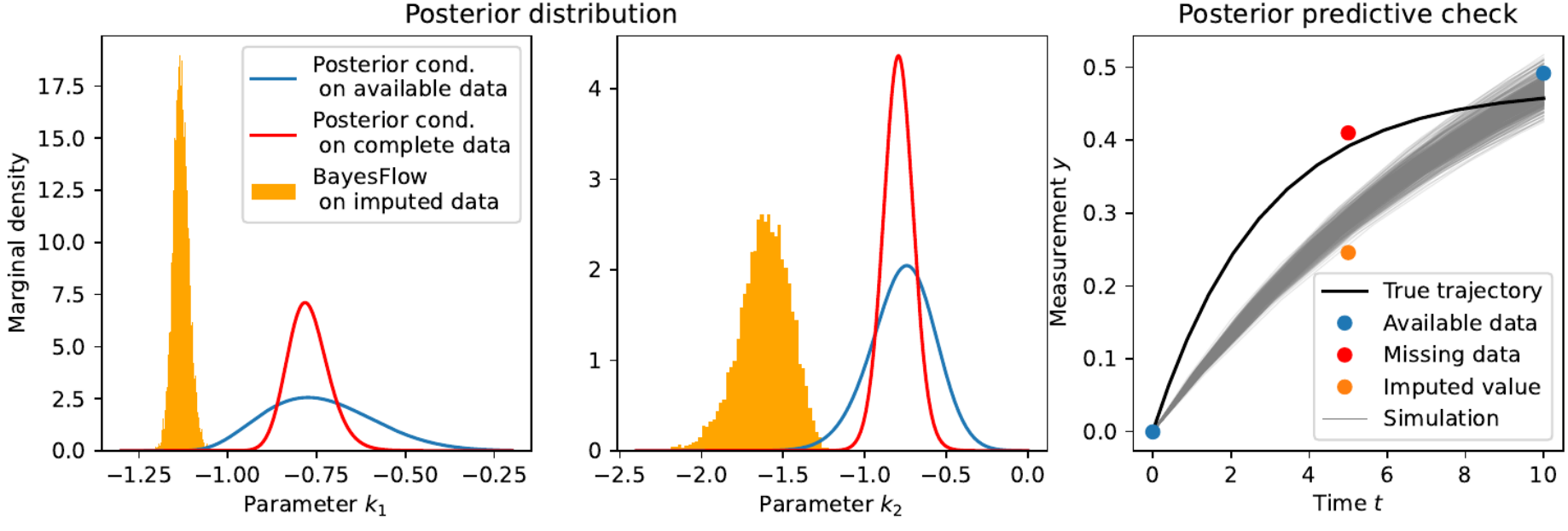


Inappropriate imputation can lead to biased results



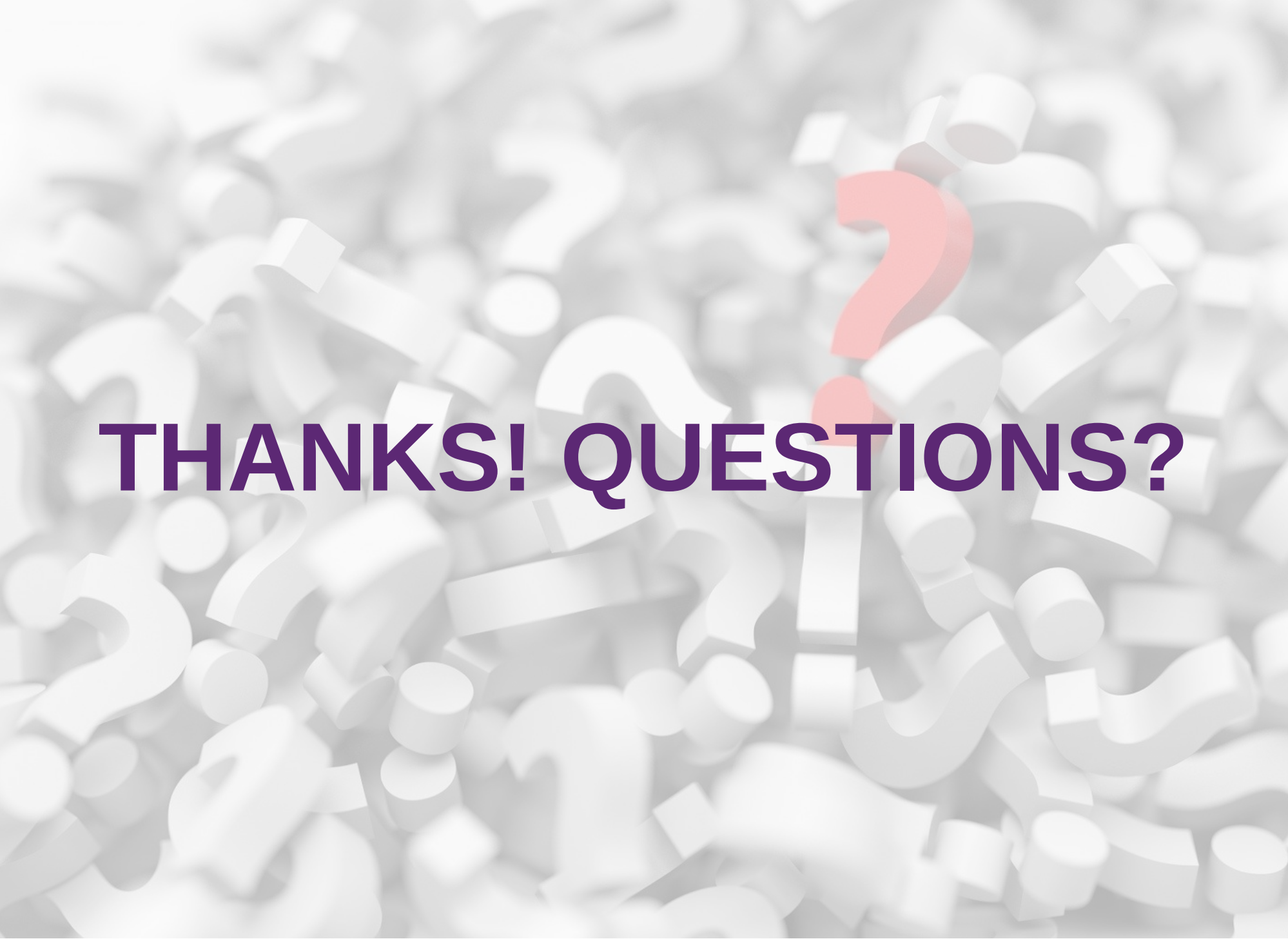
THERE ARE NO FREE DATA

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 $\pi(\bar{x}|x)$.

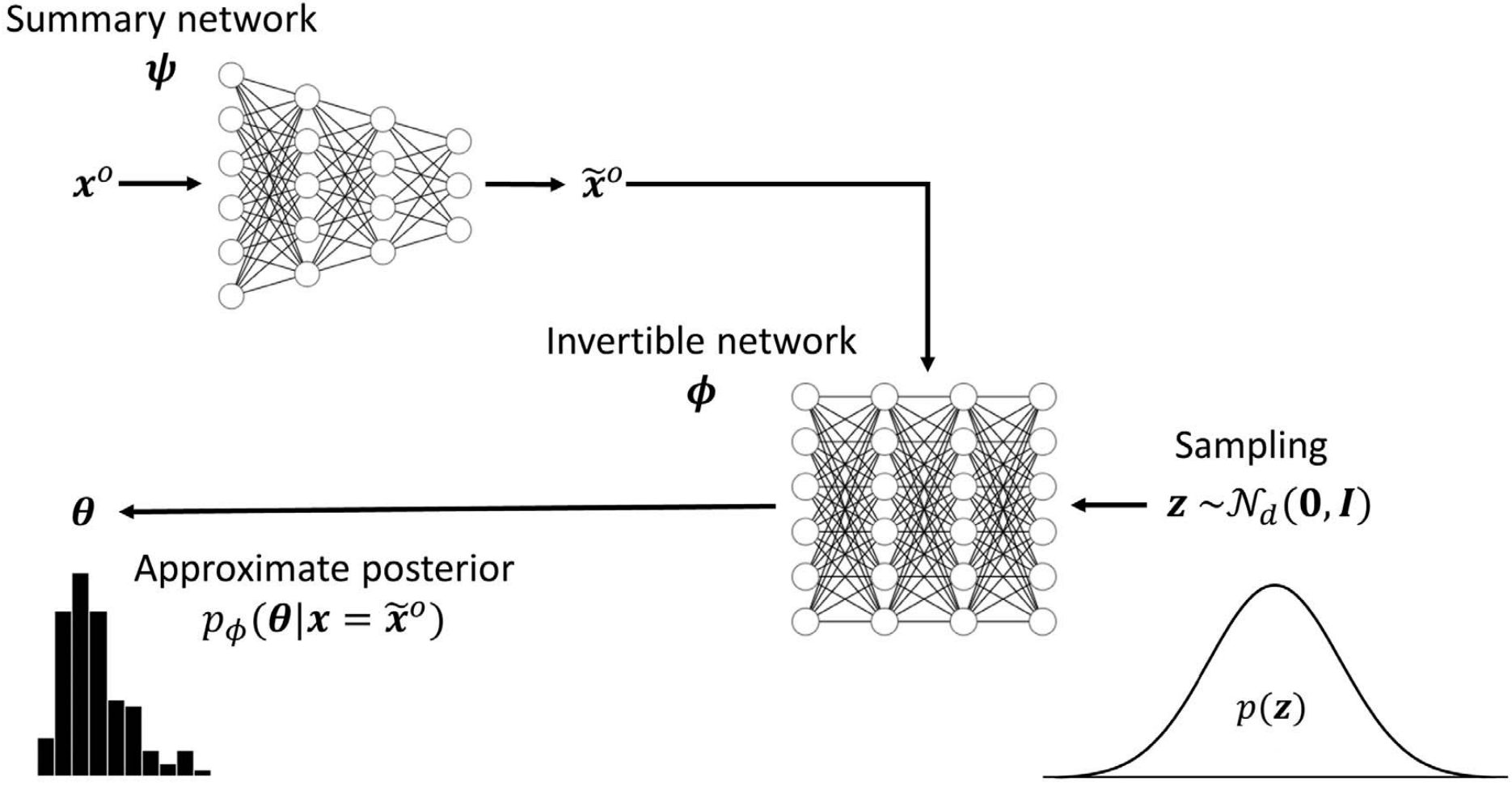
We must either make up a distribution (introducing a bias), or use a faithful approximation $p(\bar{x}|x) = \pi(\bar{x}|x)$ where $\pi(\bar{x}|x)\pi(x) = \pi(\bar{x}, x)$.

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: When doing uncertainty quantification properly, we just recover the same posterior.


THANKS! QUESTIONS?

BAYESFLOW



from: Radev et al, IEEE Transactions on Neural Networks 2020

THE PROBLEM

- Classical simulation-based inference is case-based + slow + ε-approximate
- What if we want to fit the same model to multiple datasets?

THE IDEA

- Learn a global estimator for the probabilistic mapping $y \mapsto \theta$ via cINNs
- Once trained, amortize inference on arbitrarily many datasets
- Embed data via summary statistics model

GENERATIVE MODELS

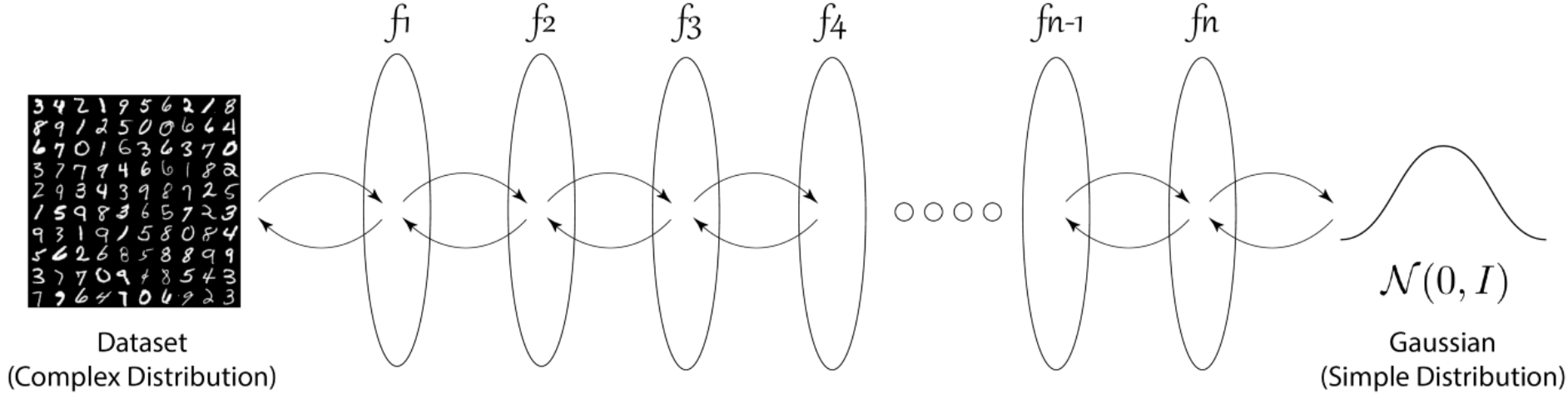
generate new data instances, $x \sim \pi(X|Y = y)$

from: Kingma et al, NeurIPS 2019

e.g.: GANs, VAEs, Flows

NORMALIZING FLOWS

generative models based on an invertible transformation



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

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

THE PROBLEM

- forward model $x_i \sim p(x|\theta) \Leftrightarrow x_i = g(\theta, \xi_i)$ with $\xi_i \sim p(\xi)$
- Bayesian inference $p(\theta|x_{1:N}) \propto p(x_{1:N}|\theta)p(\theta)$
- aim: train an invertible neural network that approximates the true posterior $p_\phi(\theta|x) \approx p(\theta|x)\ \forall \theta, x$

THE METHOD

Goal: Approximate the true posterior $p_\phi(\theta|x) \approx p(\theta|x)\ \forall \theta, x.$

Parameterize p_ϕ in terms of a cINN given via a bijective $f_\phi : \mathbb{R}^D \to \mathbb{R}^D, \theta \mapsto z$, 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 $\forall x$, giving the objective ...

THE METHOD

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

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

$$= \arg\max_{\phi} \iint p(x,\theta)(\log p(f_\phi(\theta;x)) + \log|\det J_{f_\phi}|)dxd\theta$$

Approximate via Monte-Carlo sample:

SUMMARY STATISTICS LEARNING

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

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

Learning 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 Bayesian inference