Statistical methods for mechanistic models in neuroscience

Likelihood-Free Inference Workshop, Flatiron Institute

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Computational Neuroengineering (Jakob Macke)

March 18th, 2019

Technical University of Munich
caesar
center of advanced european studies and research

Mechanistic models vs. statistical/ML models

Hodgkin-Huxley model

Multi-compartmental model

Conductance-based LIF

Balanced networks

Biophysical network simulations

Generalized linear models

Deep neural networks

RNNs

Maximum entropy models

Gaussian Process Factor Analysis

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Often optimised for a given function

RNNs

Can be directly fit to data

Design respects statistical convenience

Gaussian Process Factor Analysis

Mechanistic models vs. statistical/ML models

Hodgkin-Huxley model

Designed with mechanistic principles

Often have biophysical parameters

Balanced networks

Hard to fit to data

Biophysical networks simulations

Generalized linear models

Often optimised for a given function

RNNs

Can be directly fit to data

Design respects statistical convenience

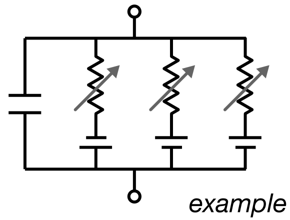
Gaussian Process Factor Analysis

How can we make statistical inference tractable for mechanistic models?

How can we find parameters that are consistent with data and prior knowledge?

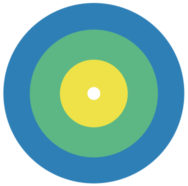
Goal: Bayesian inference for mechanistic models

forward model

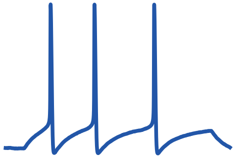


example

prior over parameters

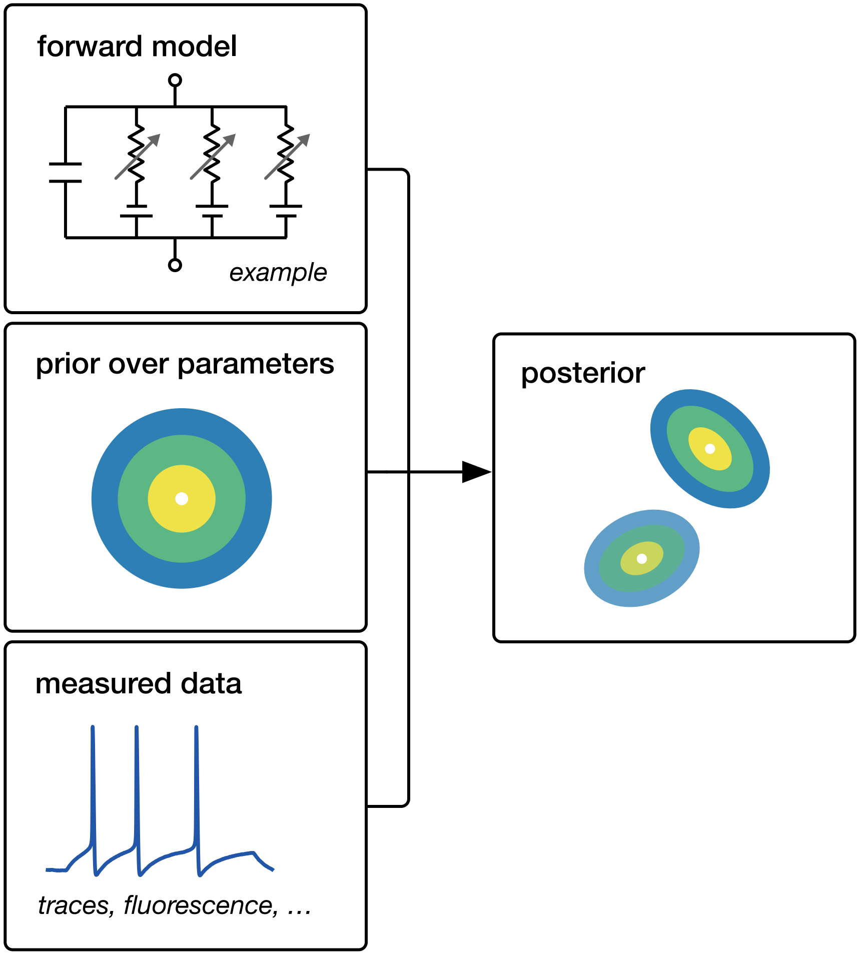


measured data

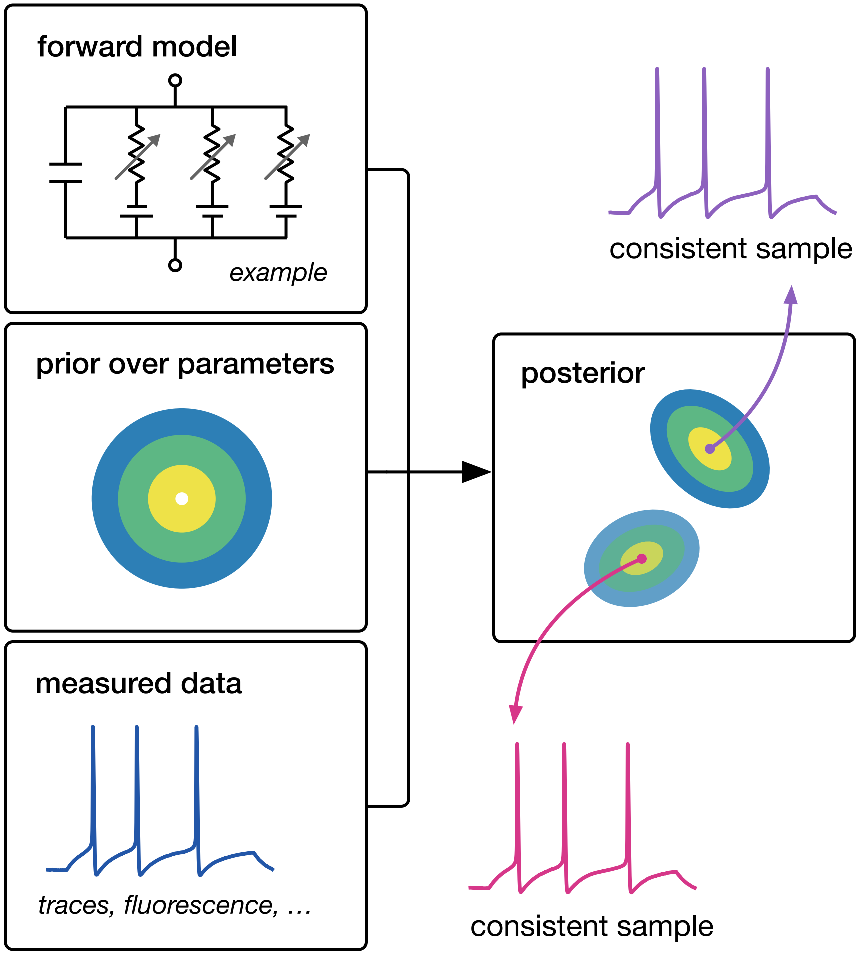


traces, fluorescence, …

Goal: Bayesian inference for mechanistic models



Goal: Bayesian inference for mechanistic models



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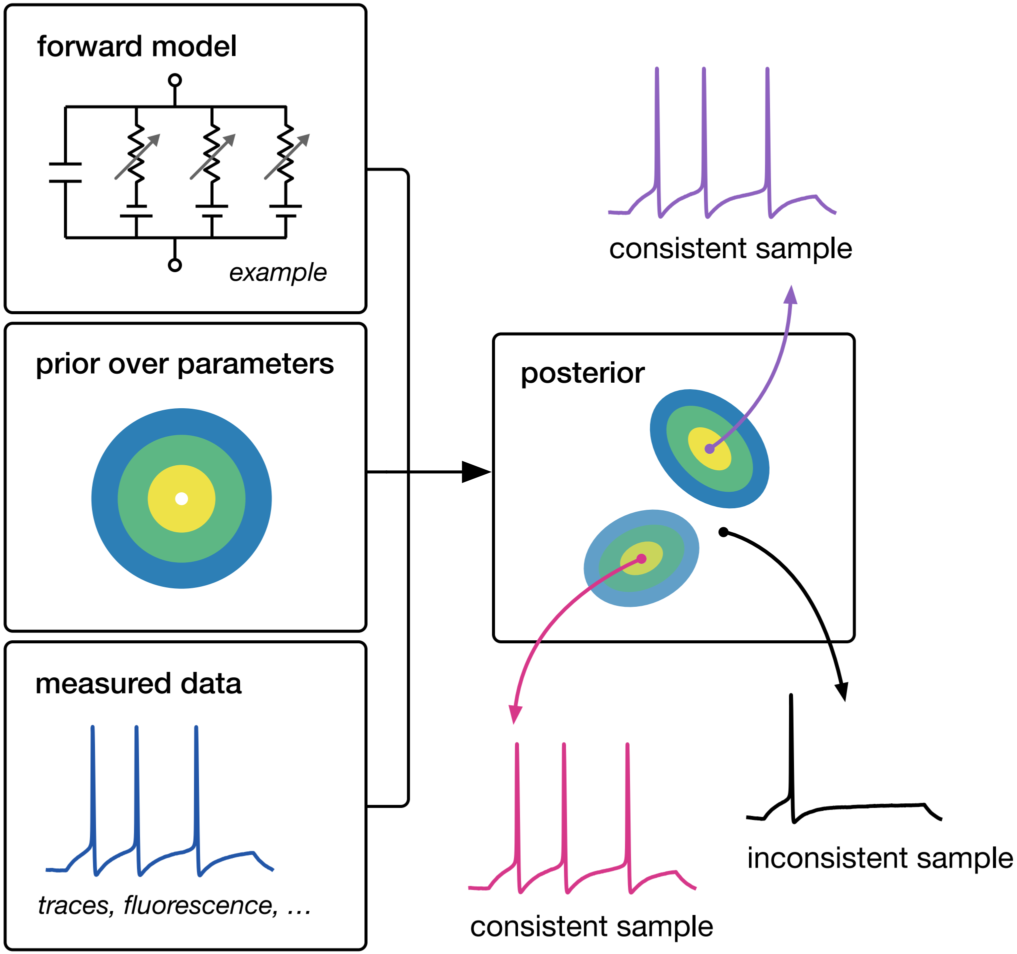


Nobel Prize in Physiology or Medicine 1963

"for their discoveries concerning the ionic mechanisms involved in excitation and inhibition in the peripheral and central portions of the nerve cell membrane."

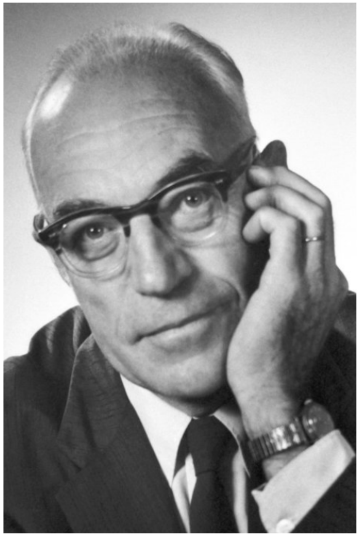


Photo from the Nobel Foundation archive.

Sir John Carew Eccles

Prize share: 1/3

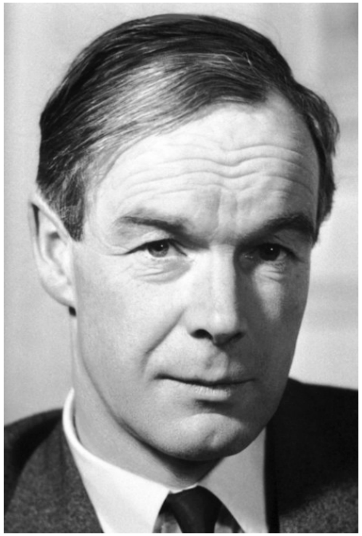


Photo from the Nobel Foundation archive.

Alan Lloyd Hodgkin

Prize share: 1/3

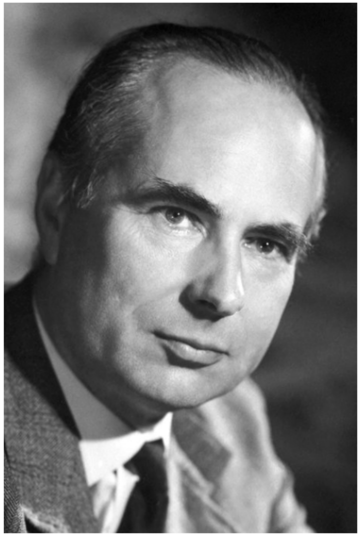


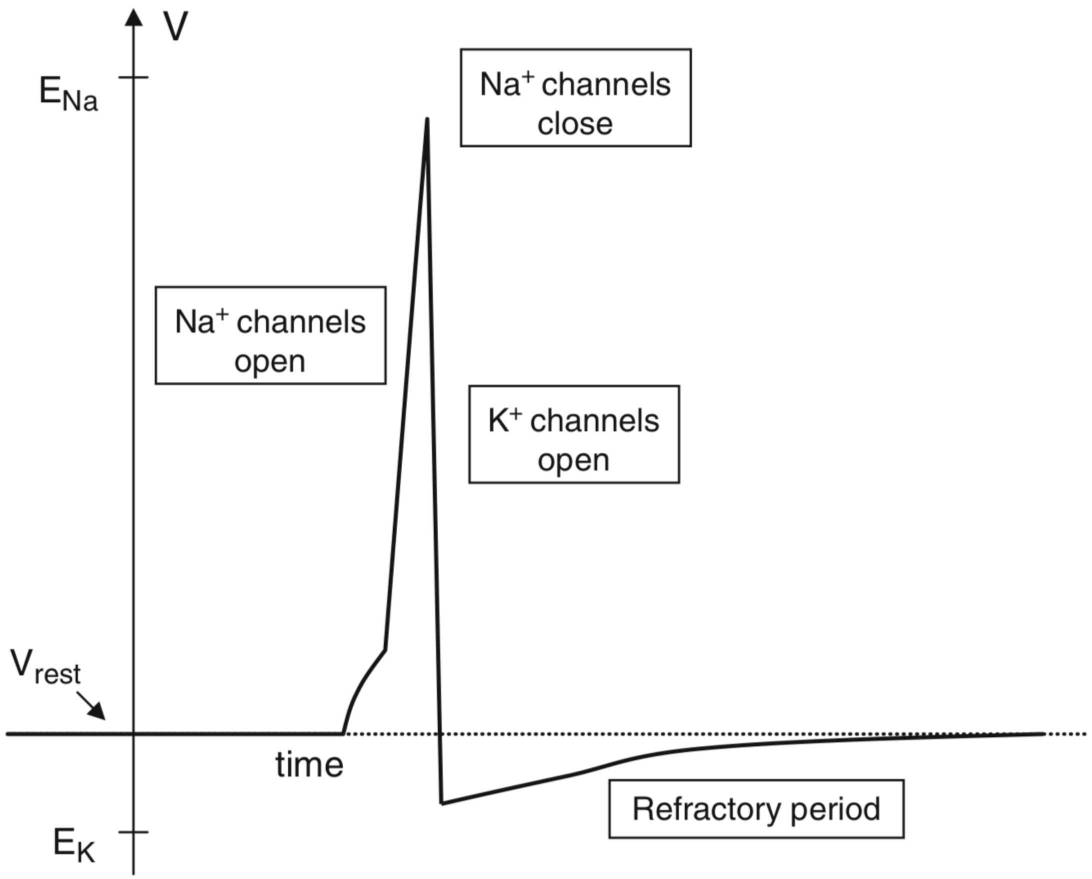
Photo from the Nobel Foundation archive.

Andrew Fielding Huxley

Prize share: 1/3

The Nobel Prize in Physiology or Medicine 1963. NobelPrize.org. Nobel Media AB 2019.
https://www.nobelprize.org/prizes/medicine/1963/summary/

Action potential



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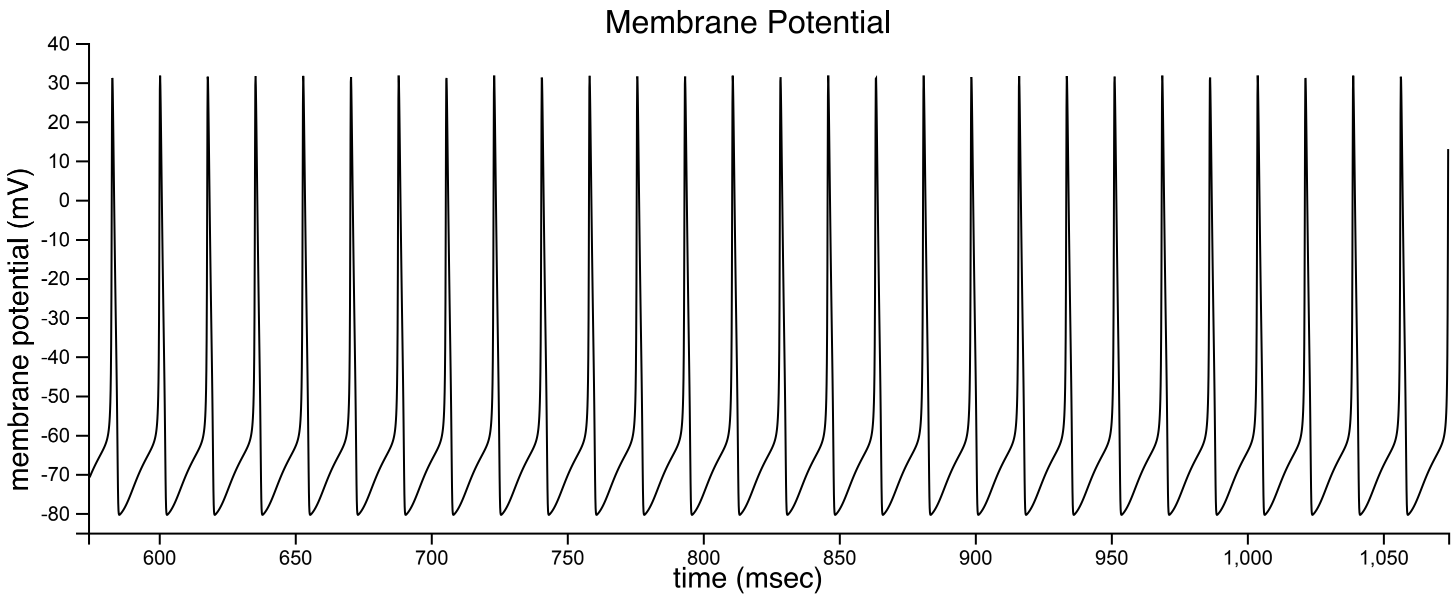
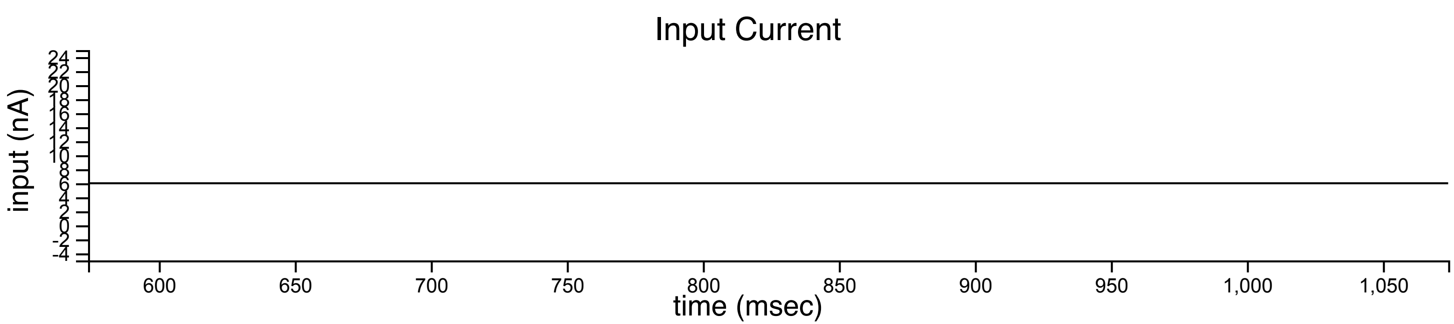
Ermentrout, G. Bard, and David H. Terman. Mathematical Foundations of Neuroscience. Vol. 35. Interdisciplinary Applied Mathematics. New York, NY: Springer New York, 2010. https://doi.org/10.1007/978-0-387-87708-2.

Example: Hodgkin-Huxley model

input current (nA): 6





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Simulator by Jack Terwilliger

http://jackterwilliger.com/biological-neural-networks-part-i-spiking-neurons/

Example: Hodgkin-Huxley model

$$c_{\mathrm{M}} \frac{\mathrm{d}V}{\mathrm{d}t} = -\bar{g}_{\mathrm{Na}} m^3 h (V - E_{\mathrm{Na}}) - \bar{g}_{\mathrm{K}} n^4 (V - E_{\mathrm{K}}) - \bar{g}_{\mathrm{L}} (V - E_{\mathrm{L}}),$$

Hodgkin, A. L., & Huxley, A. F. (1952). A quantitative description of membrane current and its application to conduction and excitation in nerve. J Physiol, 117(4).

Example: Hodgkin-Huxley model

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$$C \underset{\beta(V)}{\overset{\alpha(V)}{\rightleftharpoons}} O$$

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$$C \underset{\beta(V)}{\overset{\alpha(V)}{\rightleftharpoons}} O$$

$$\begin{aligned}
\frac{\mathrm{d}n}{\mathrm{d}t} &= \phi[\alpha_n(V)(1-n) - \beta_n(V)n], \\
\frac{\mathrm{d}m}{\mathrm{d}t} &= \phi[\alpha_m(V)(1-m) - \beta_m(V)m], \\
\frac{\mathrm{d}h}{\mathrm{d}t} &= \phi[\alpha_h(V)(1-h) - \beta_h(V)h].
\end{aligned}$$

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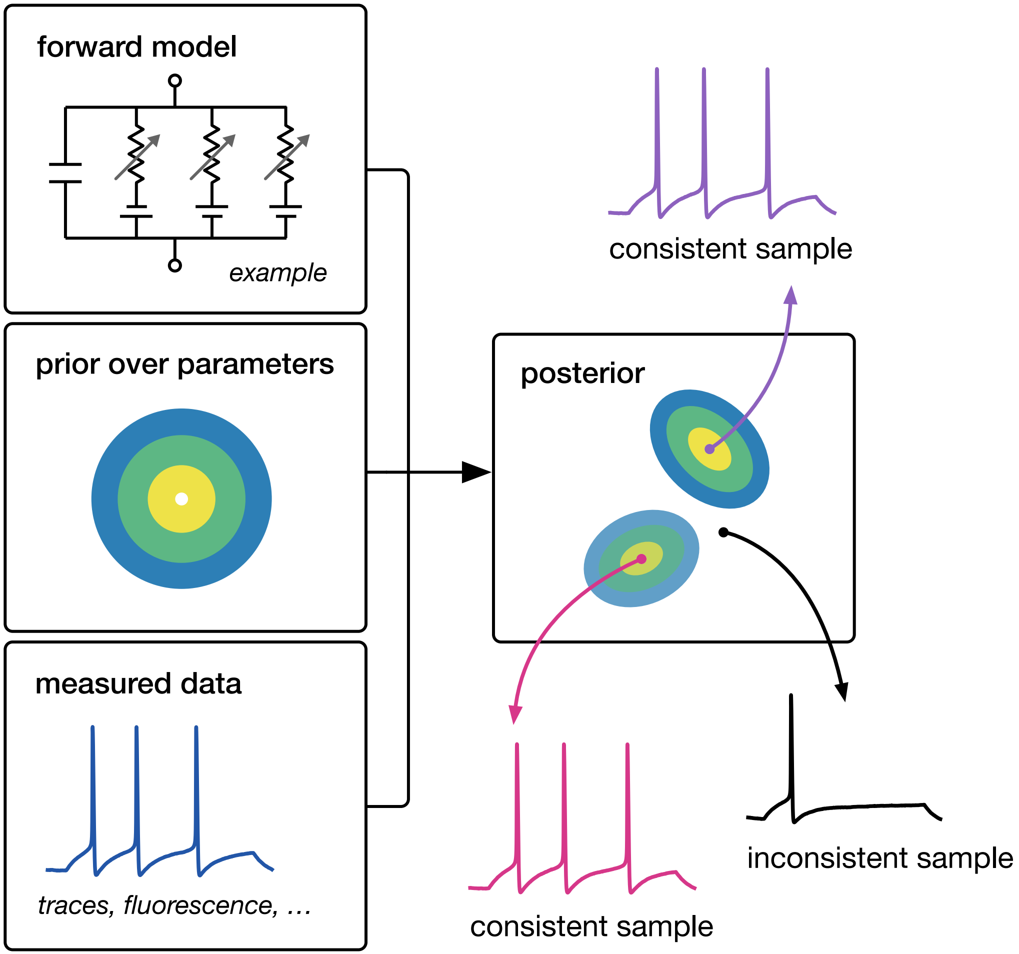
Hodgkin, A. L., & Huxley, A. F. (1952). A quantitative description of membrane current and its application to conduction and excitation in nerve. J Physiol, 117(4).

Goal: Bayesian inference for mechanistic models



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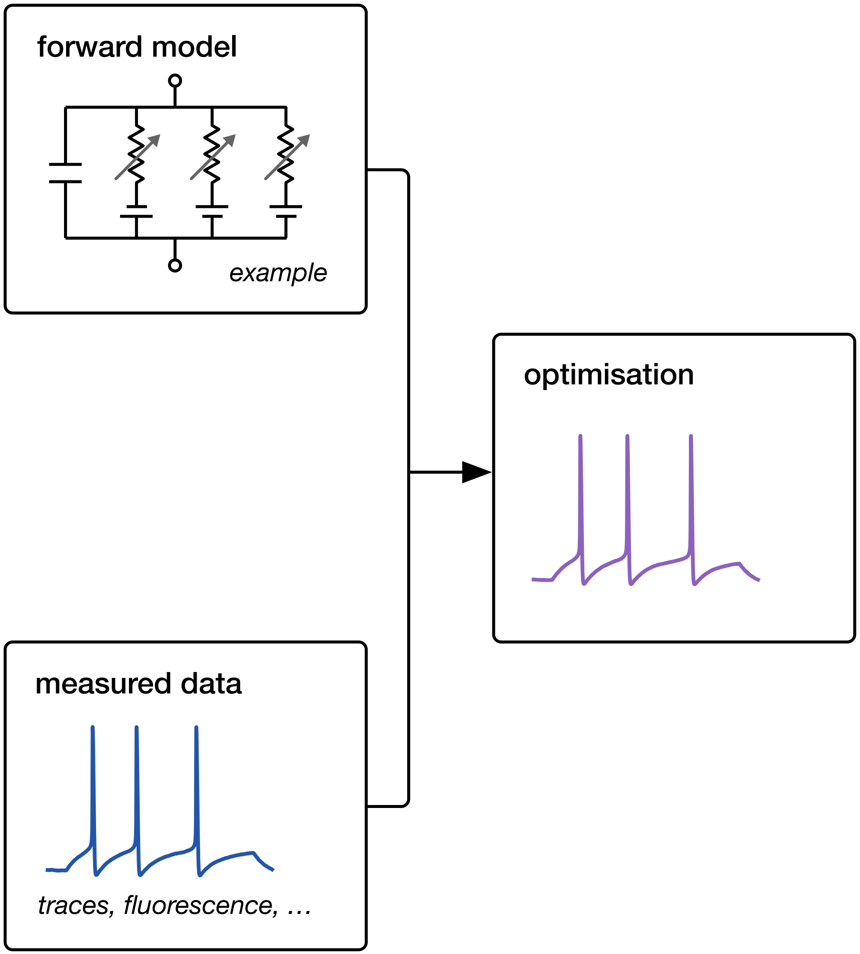

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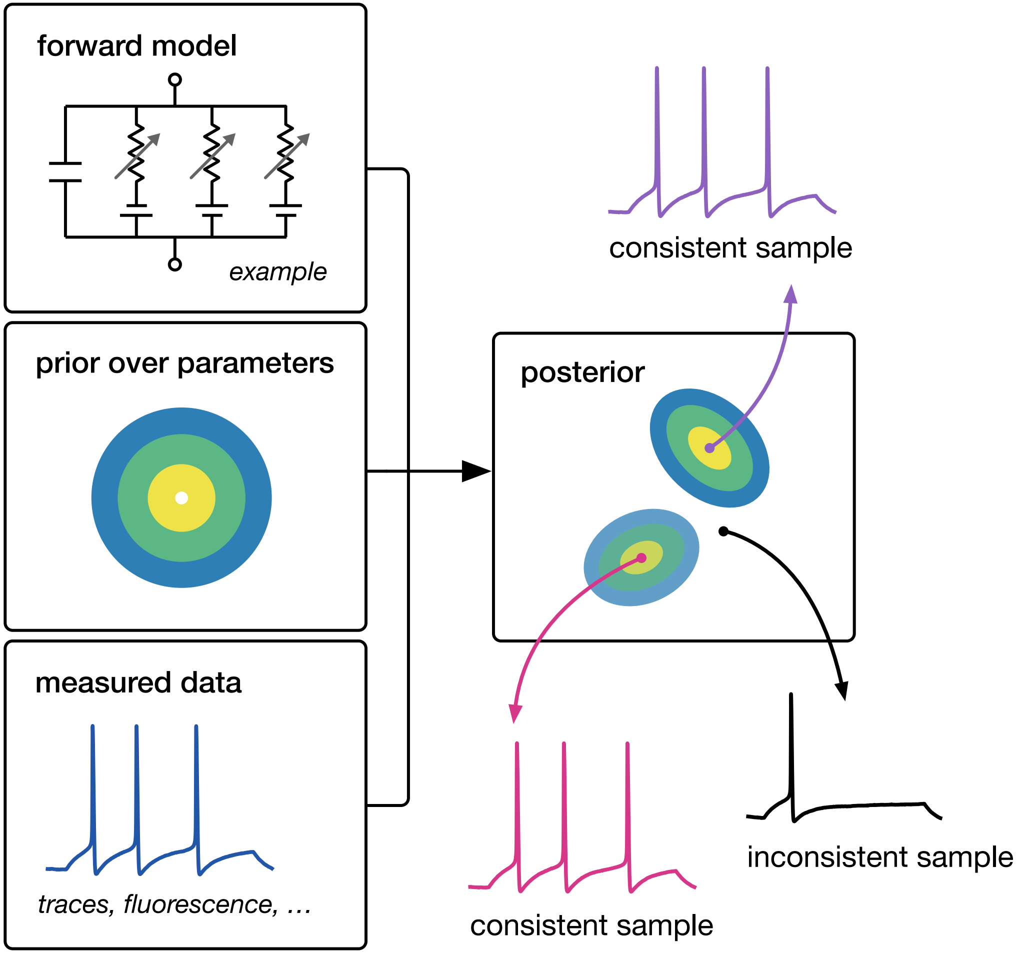

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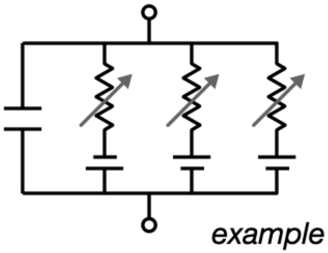
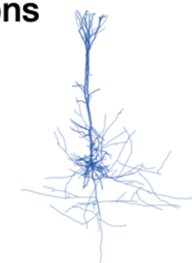
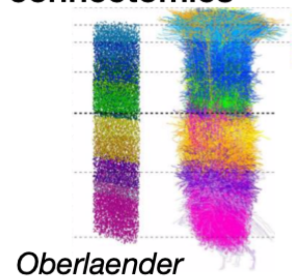


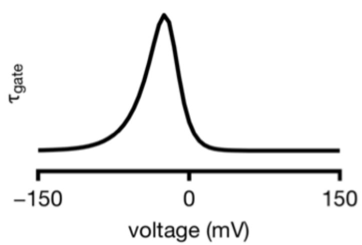
multi-compartmental neurons



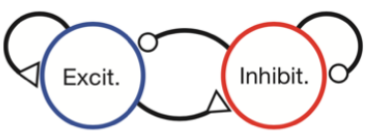
connectomics



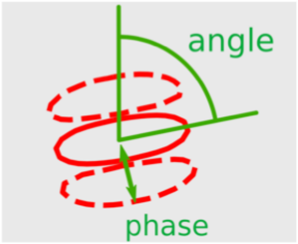
ion-channel kinetics



spiking networks



receptive field models



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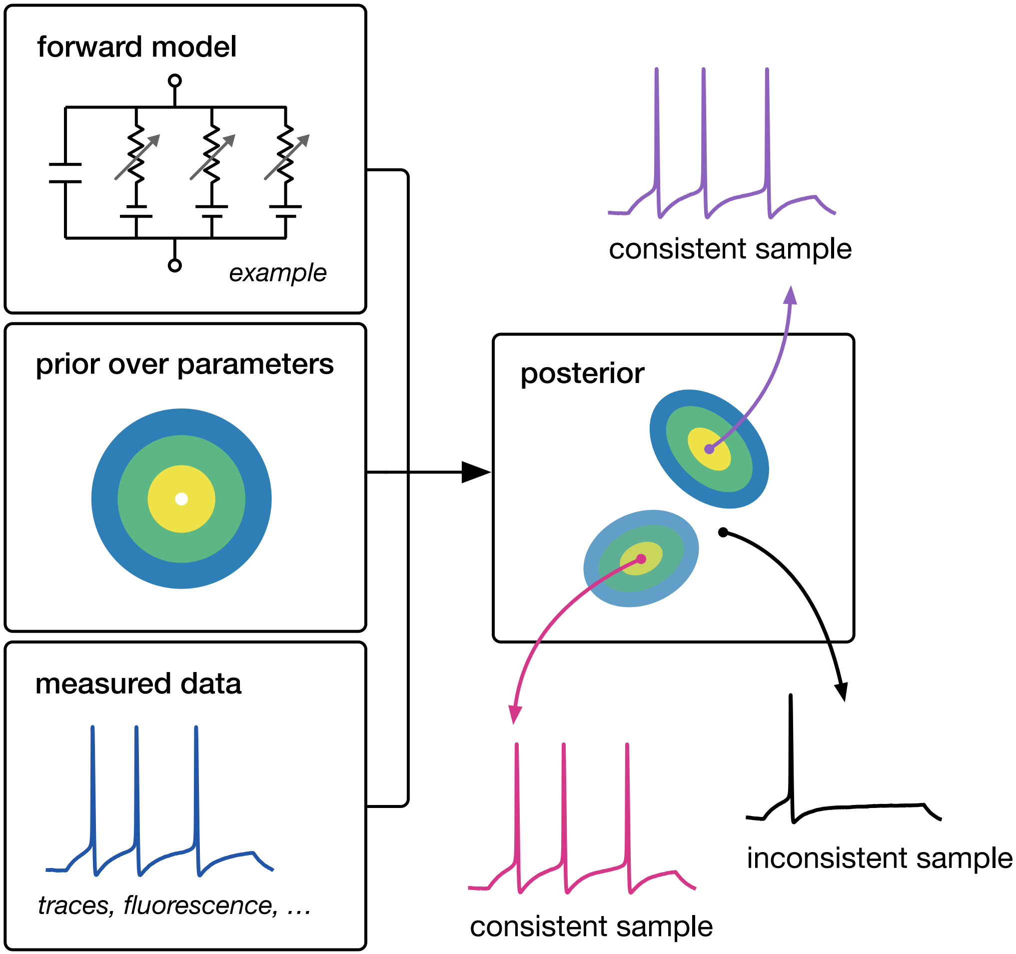

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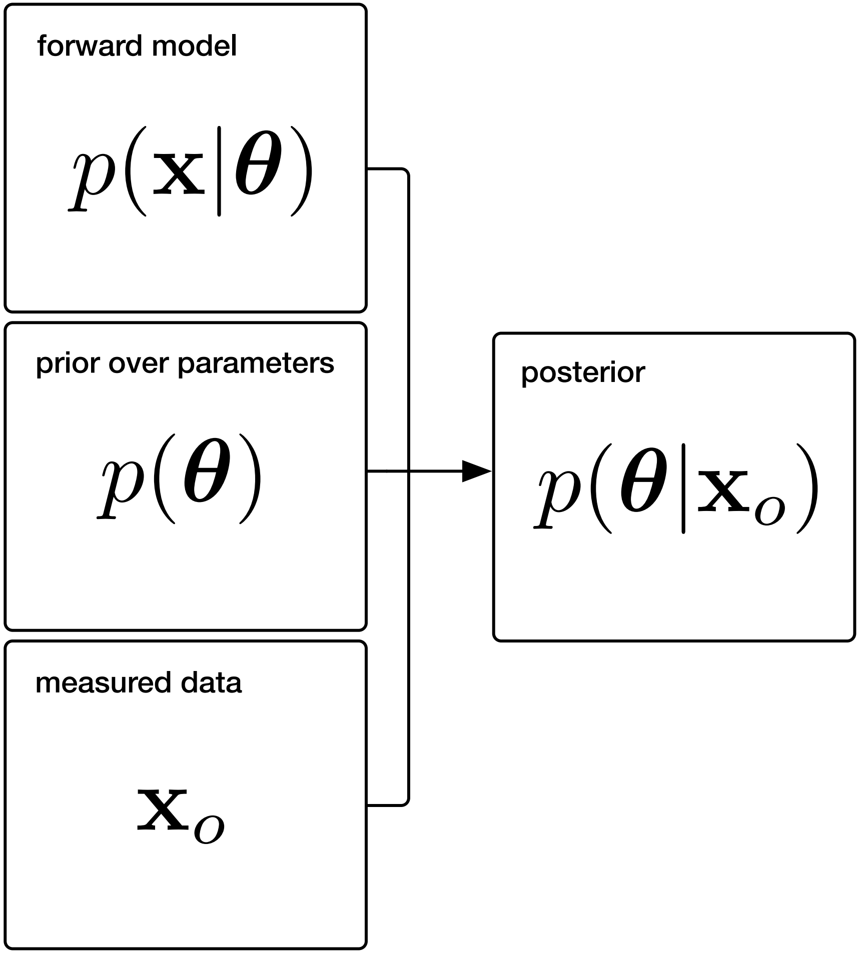

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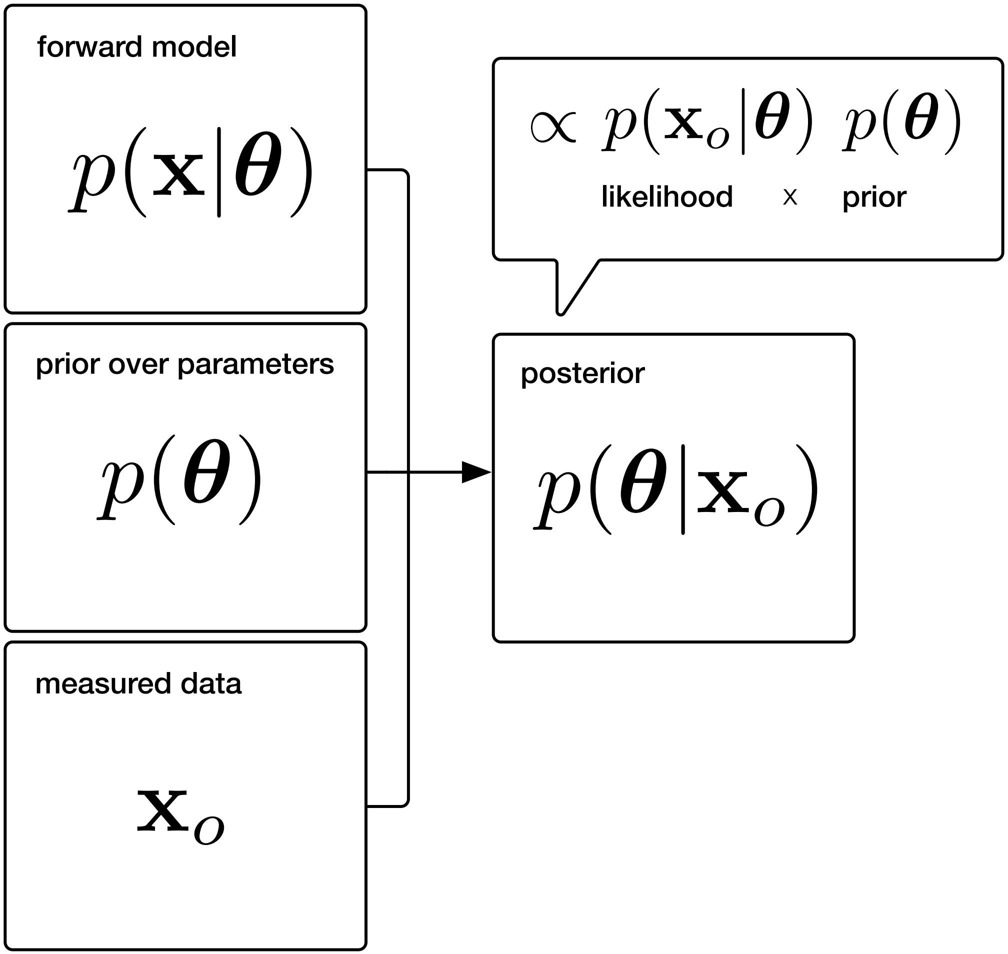

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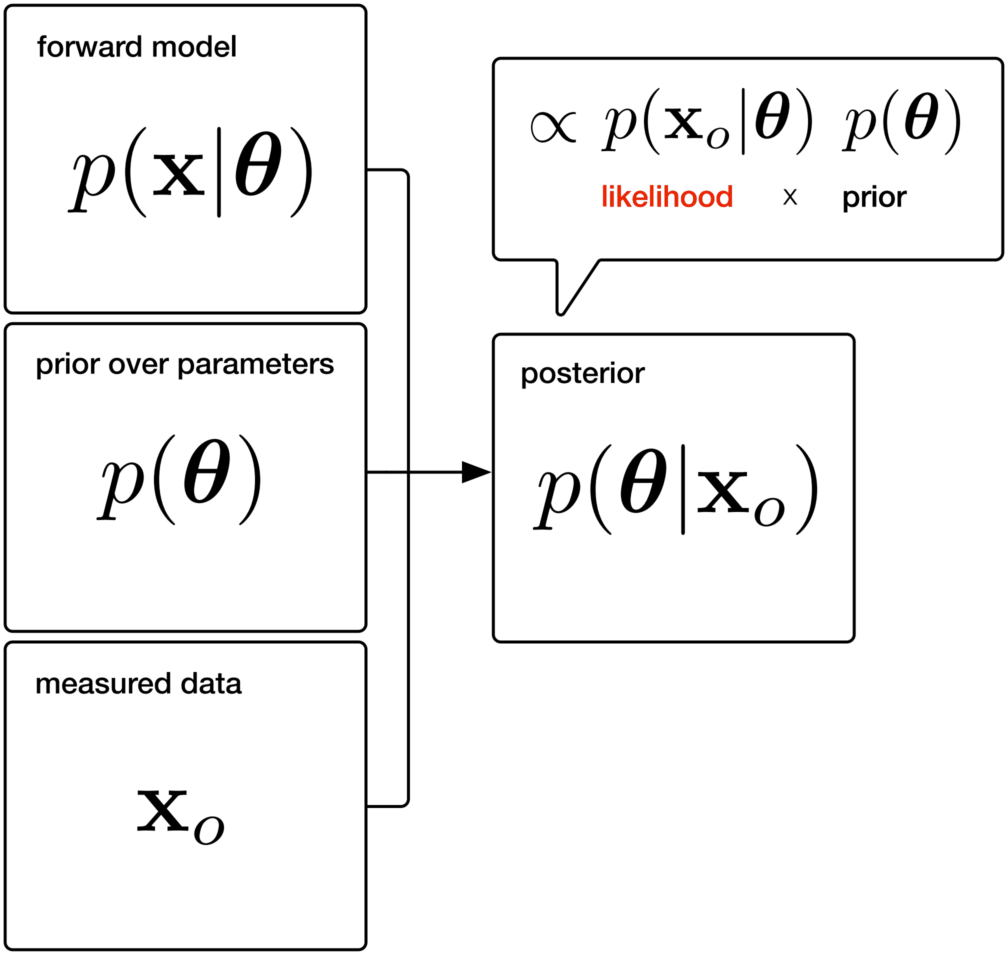

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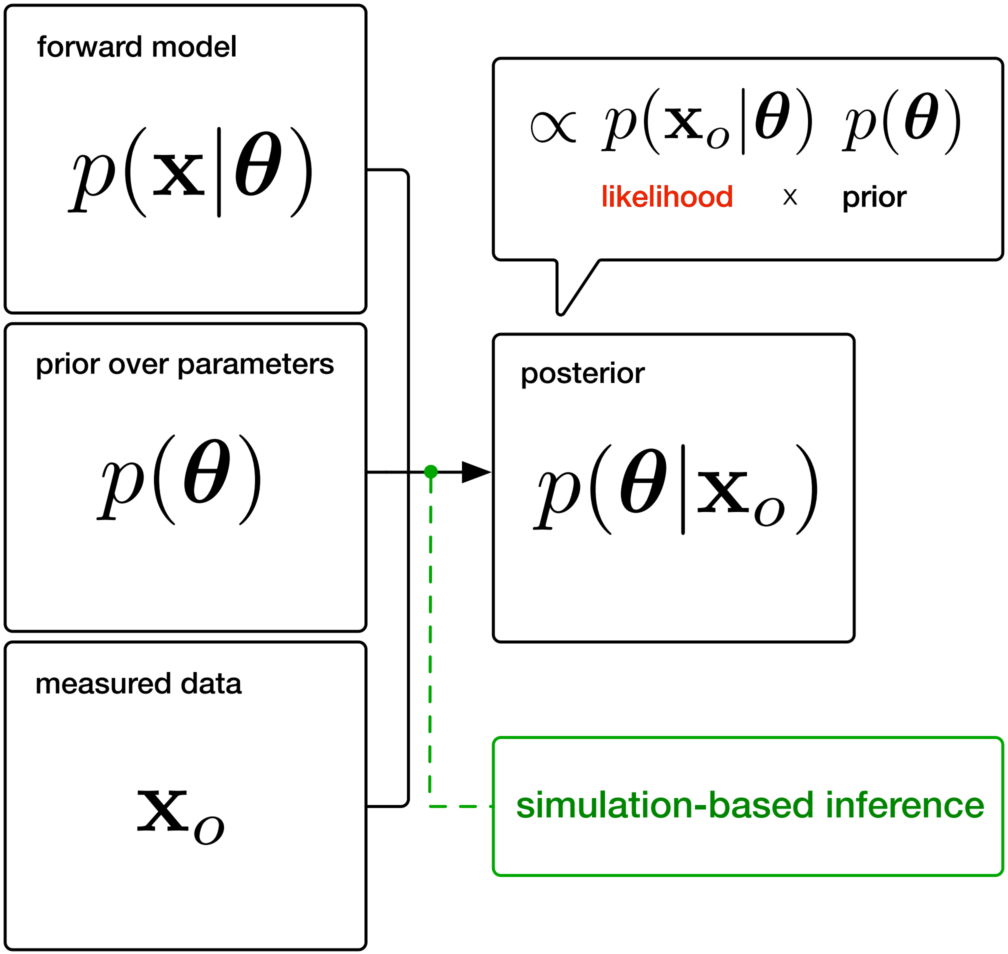
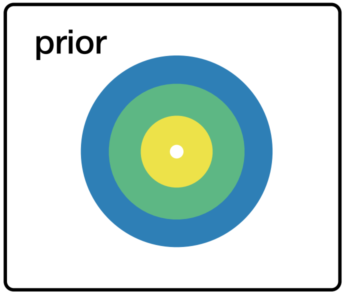


Learning the posterior

Simple algorithm:

Simulation-based inference by density estimation

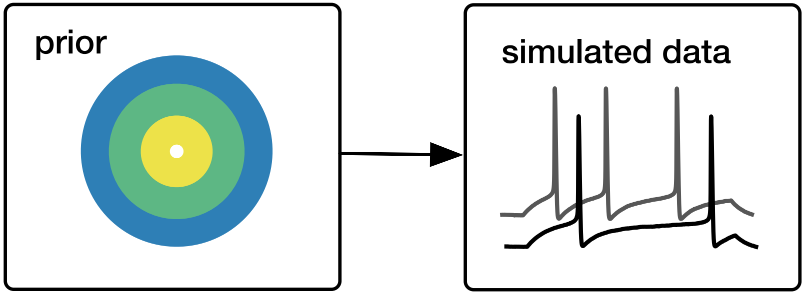
$$\boldsymbol{\theta}_{1:N} \sim p(\boldsymbol{\theta})$$



Simple algorithm:

Simulation-based inference by density estimation

$\boldsymbol{\theta}_{1:N} \sim p(\boldsymbol{\theta})$ $\qquad$ $\mathbf{x}_{1:N} \sim p(\mathbf{x}|\boldsymbol{\theta}_{1:N})$



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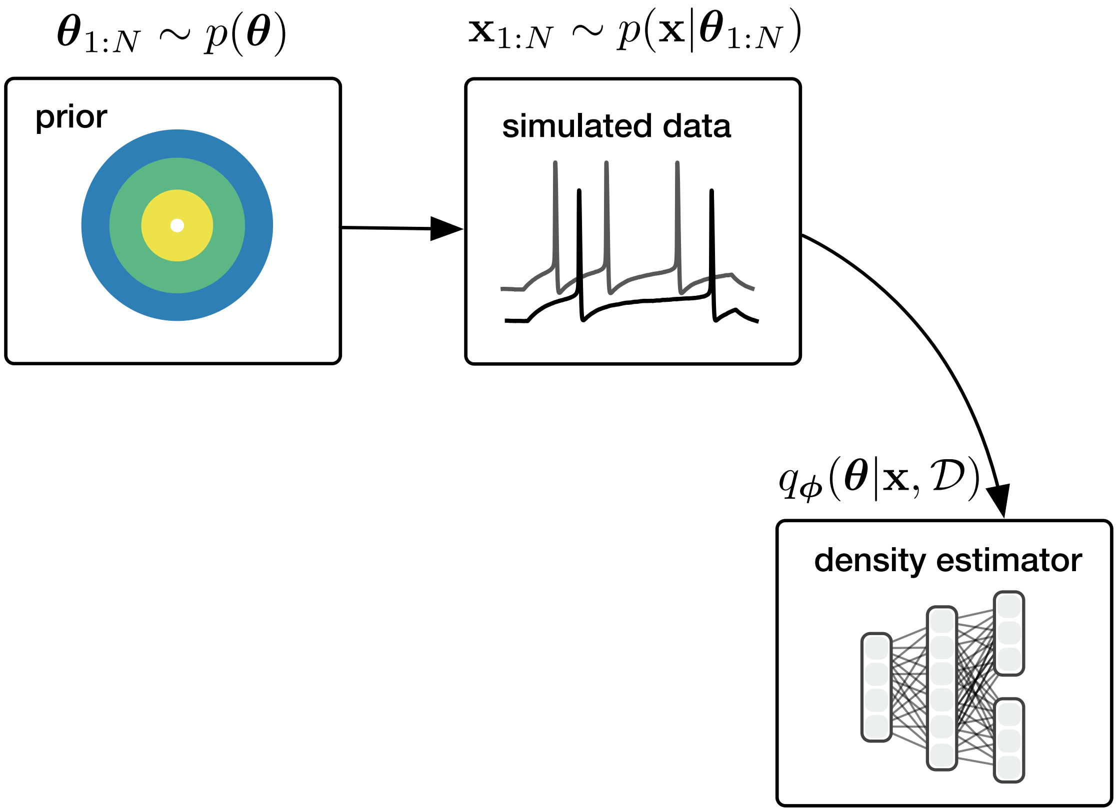
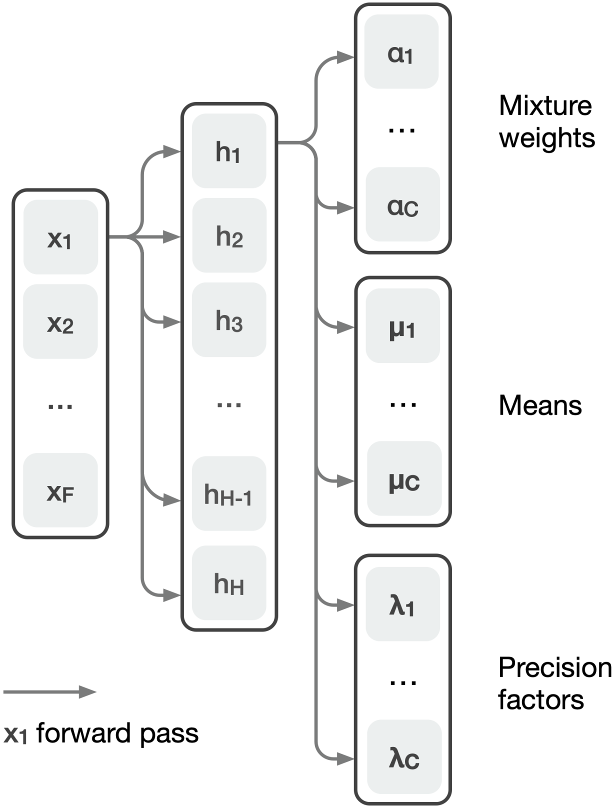


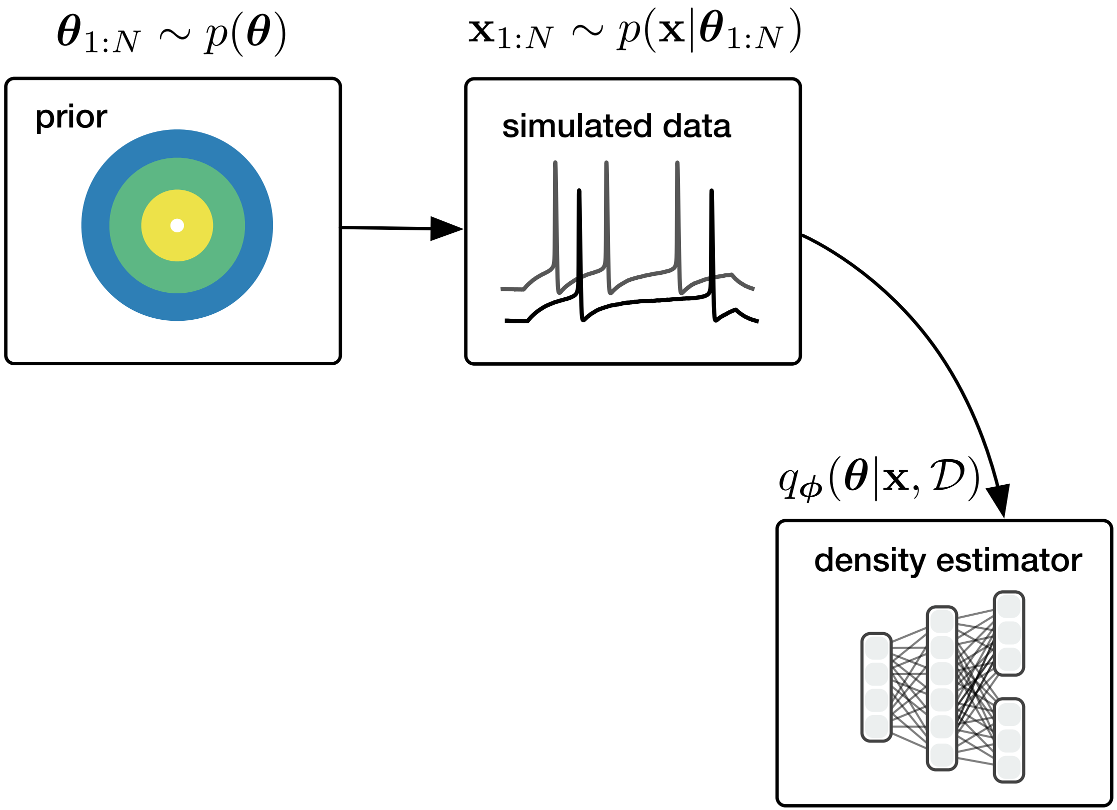
Mixture density network

$$q_\phi(\theta|x) = \sum_c \alpha_c(x)\mathcal{N}(\theta|\mu_c(x), \Sigma_c(x))$$

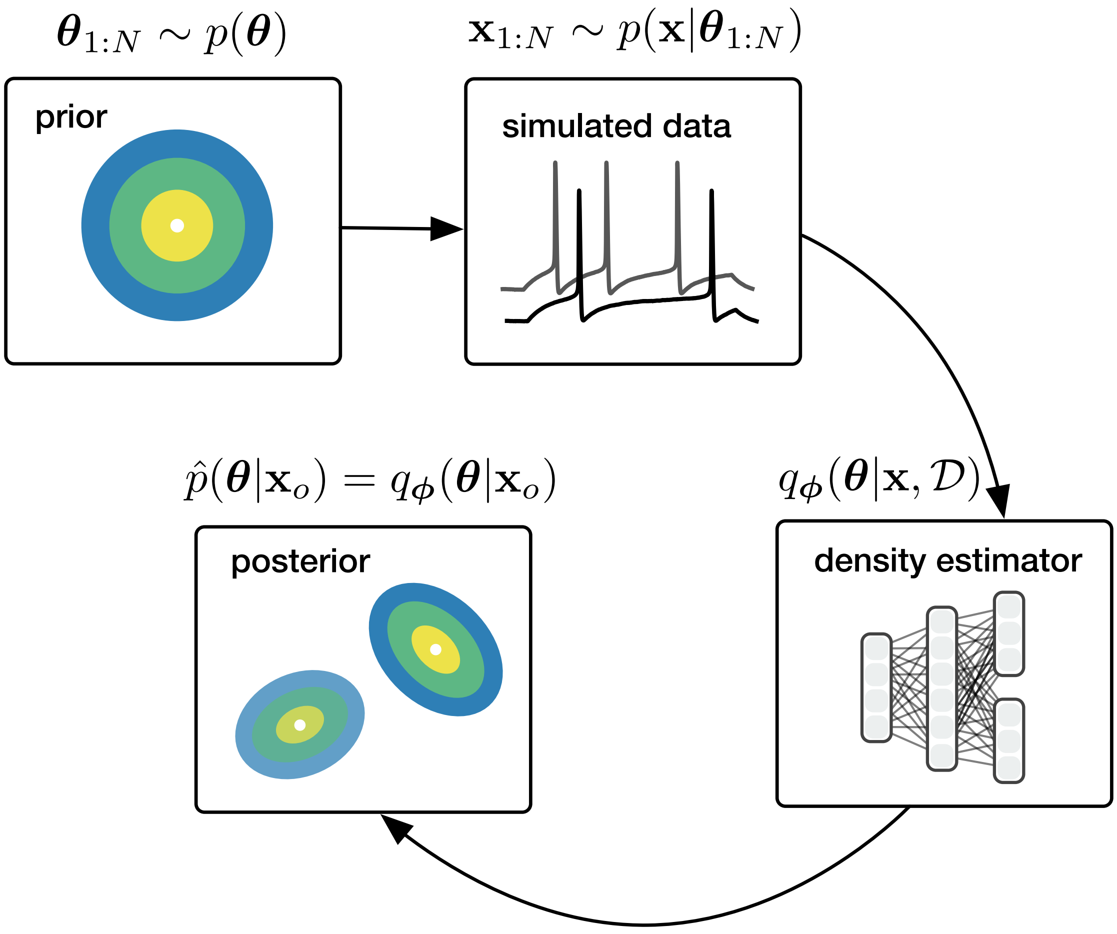


Simple algorithm:

Simulation-based inference by density estimation



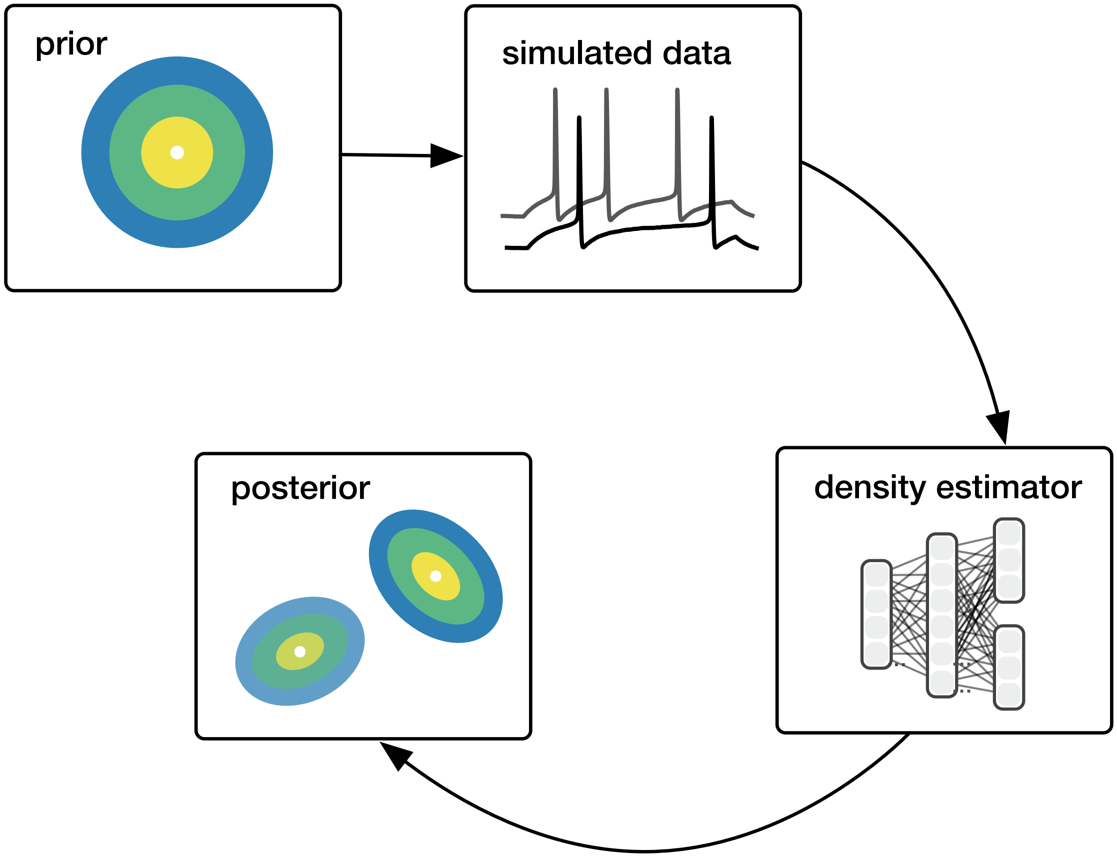
Simple algorithm:
Simulation-based inference by density estimation



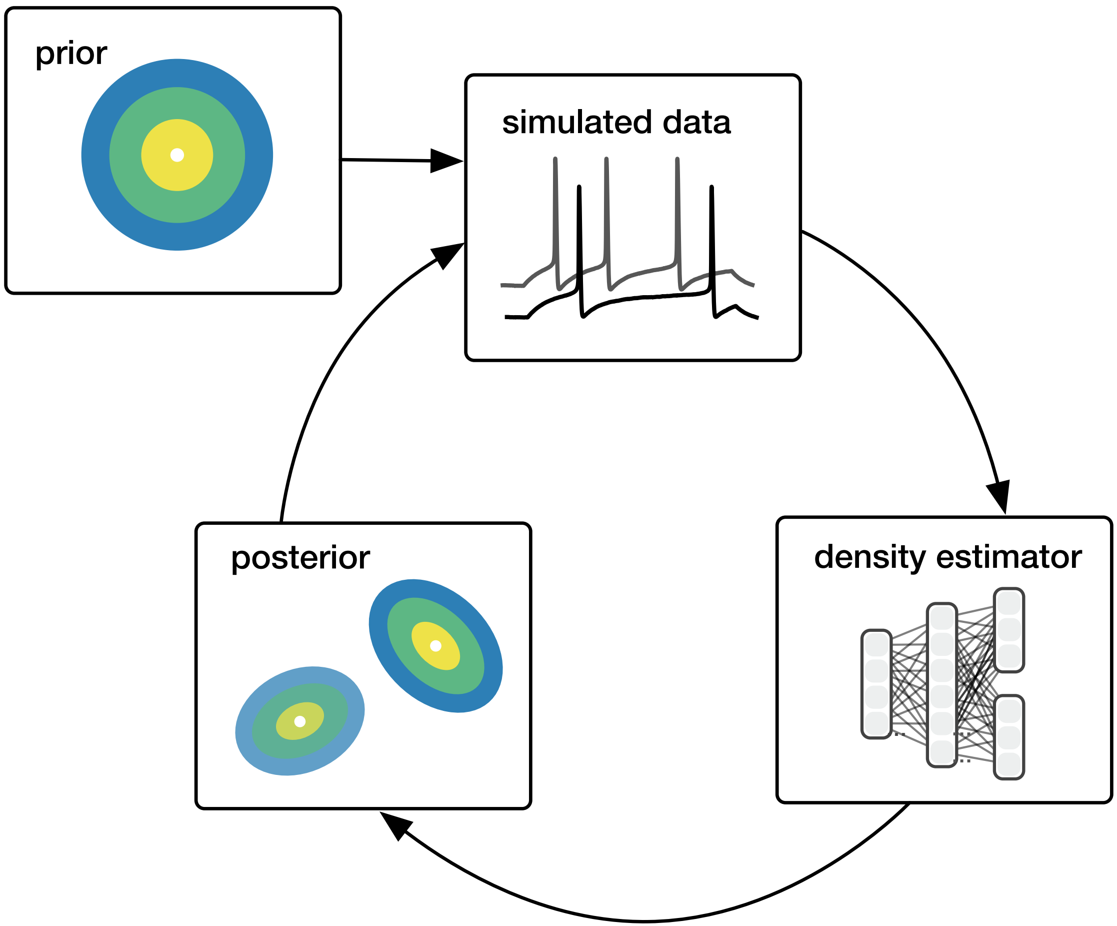
We got limited computational budget for running simulations.

How can we be efficient in the # of simulations?

Simple algorithm:
Simulation-based inference by density estimation



Sequential algorithm:
Simulation-based inference by density estimation



1) How do we correct for using a proposal distribution $\tilde{p}(\theta)$?

SNPE: Sequential Neural Posterior Estimation

$$\mathcal{L}(\phi) = -\frac{1}{N}\sum_n \frac{p(\theta_n)}{\tilde{p}(\theta_n)} \log q_\phi(\theta_n | x_n)$$

- correct for proposal distribution in the loss function

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Lueckmann*, J.-M., Goncalves*, P. J., Bassetto, G., Öcal, K., Nonnenmacher, M., & Macke, J. H. (2017). Flexible statistical inference for mechanistic models of neural dynamics.
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Papamakarios, G., & Murray, I. (2016). Fast ϵ-free inference of simulation models with bayesian conditional density estimation.
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SNPE: Sequential Neural Posterior Estimation

$$\mathcal{L}(\phi) = -\frac{1}{N}\sum_{n} \frac{p(\theta_n)}{\tilde{p}(\theta_n)} \log q_\phi(\theta_n | x_n)$$

- correct for proposal distribution in the loss function
- previous work: post-hoc analytical correction (Papamarkarios & Murray, 2016), which can lead to can lead to numerical issues in practice

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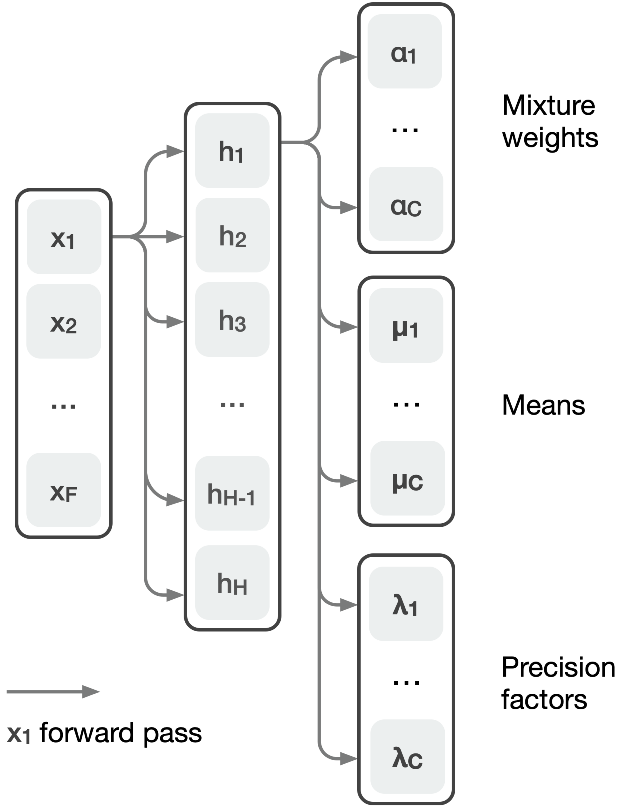
2) How do we update the density estimator with new training data?

Mixture density network

$$q_\phi(\theta|x) = \sum_c \alpha_c(x)\mathcal{N}(\theta|\mu_c(x), \Sigma_c(x))$$



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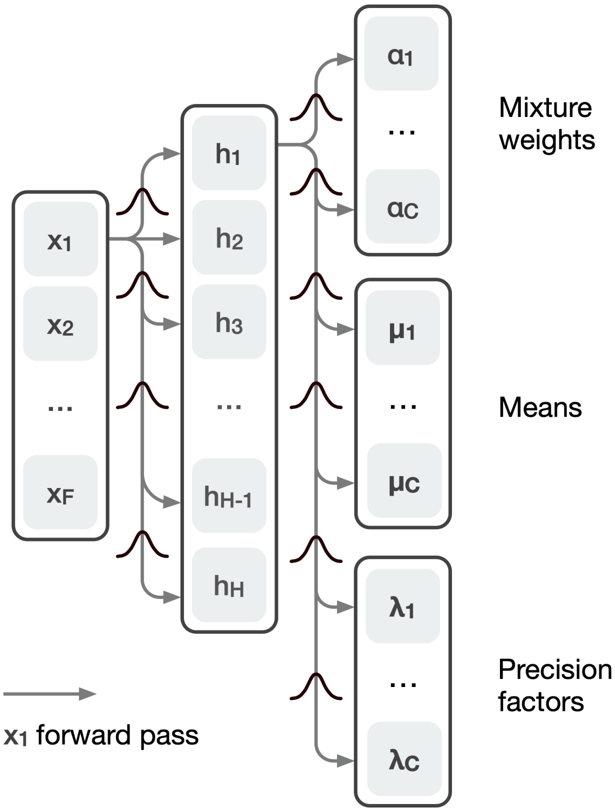
Bayesian Mixture density network

Assume distribution over network weights: $\pi_\phi(w) = \mathcal{N}(w|\phi_m; \phi_s^2)$.



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Bayesian Mixture density network

Assume distribution over network weights: $\pi_\phi(w) = \mathcal{N}(w|\phi_m; \phi_s^2)$.

Training via variational inference:

$$
\begin{aligned}
\phi^* &= \arg\min_\phi D_{KL}(\pi_\phi(\mathbf{w})||p(\mathbf{w}|\mathcal{D})) \\
&= \arg\min_\phi \int \pi_\phi(\mathbf{w}) \log \frac{\pi_\phi(\mathbf{w})}{p(\mathbf{w})p(\mathcal{D}|\mathbf{w})} d\mathbf{w} \\
&= \arg\min_\phi -\left\langle \log p(\mathcal{D}|\mathbf{w}) \right\rangle_{\pi_\phi(\mathbf{w})} + D_{KL}(\pi_\phi(\mathbf{w})||p(\mathbf{w}))
\end{aligned}
$$

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SNPE: Sequential Neural Posterior Estimation

$$\mathcal{L}(\phi^{(r)}) = -\frac{1}{N}\sum_n \frac{p(\theta_n)}{\tilde{p}^{(r)}(\theta_n)} \Big\langle \log q_w(\theta_n|x_n) \Big\rangle_{\pi_{\phi^{(r)}}(w)} + \frac{1}{N}\mathrm{KL}\left(\pi_{\phi^{(r)}}(w) || \pi_{\phi^{(r-1)}}(w)\right)$$

- KL-term acts as a regularizer: Keeps weights close to previous round

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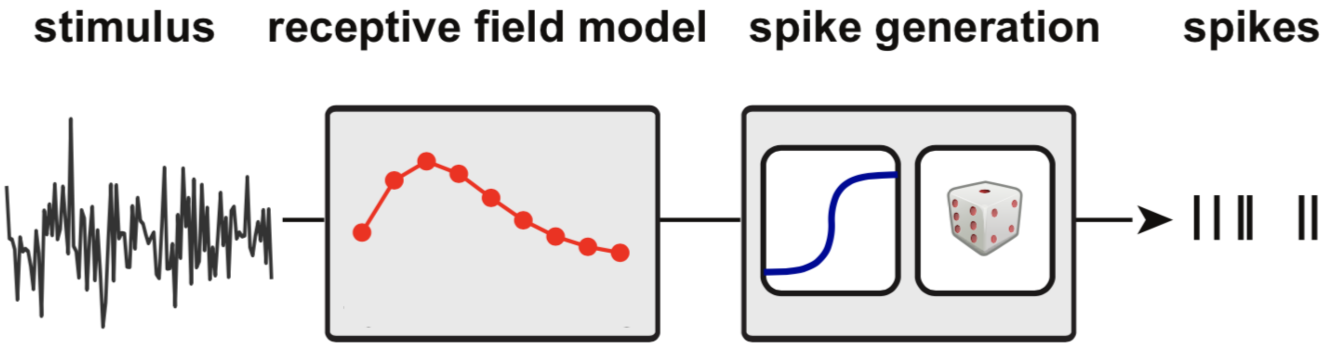
Bernoulli GLM (Generalised linear model)



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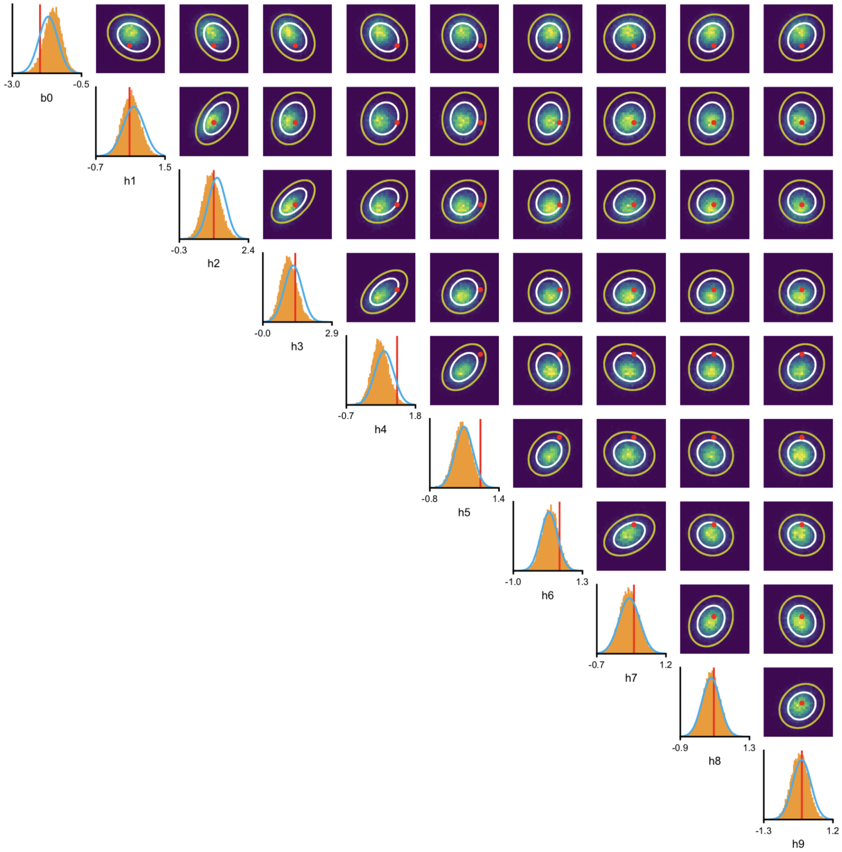
Bernoulli GLM

Posterior: Space of parameters consistent with prior and data



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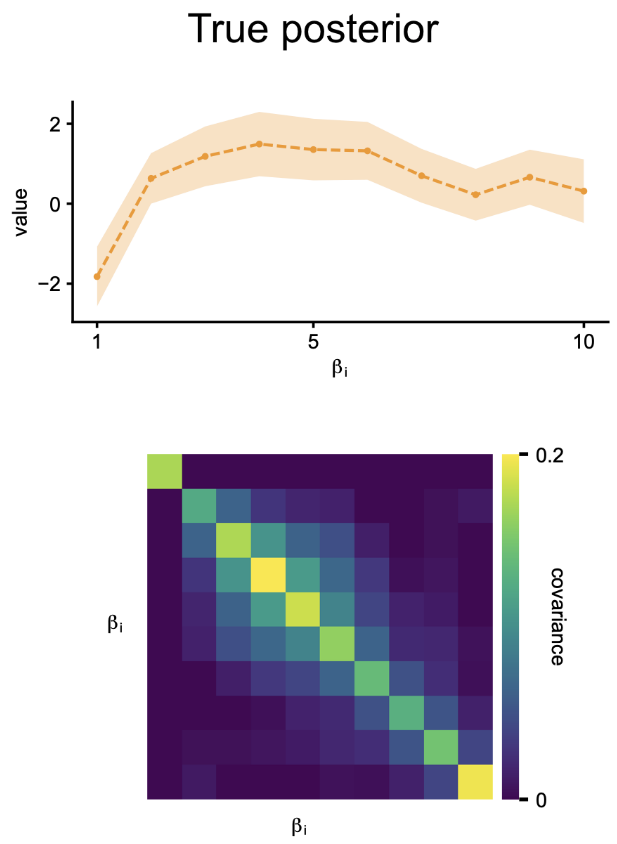
Bernoulli GLM



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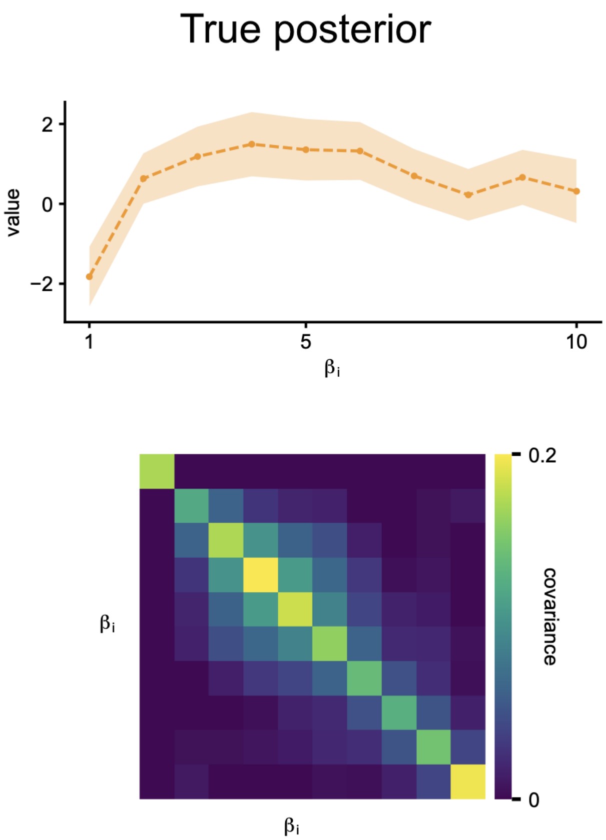

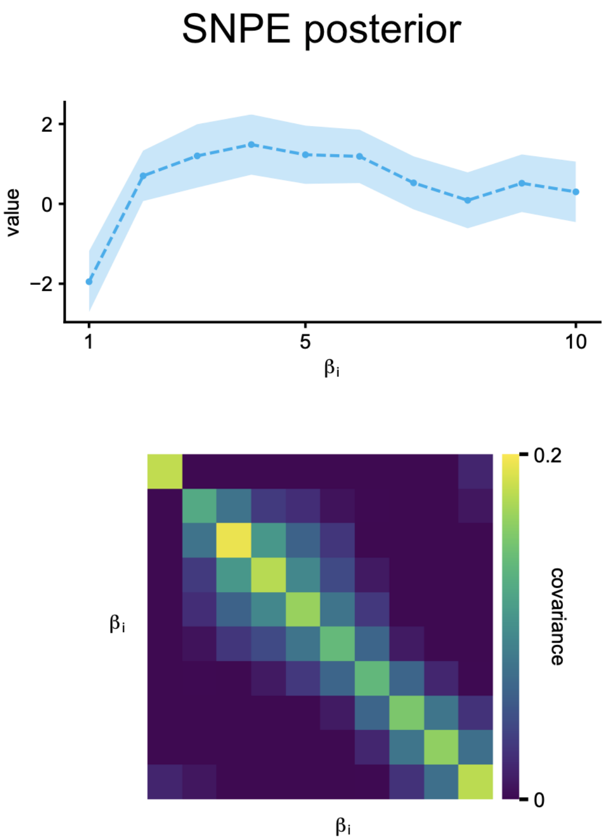

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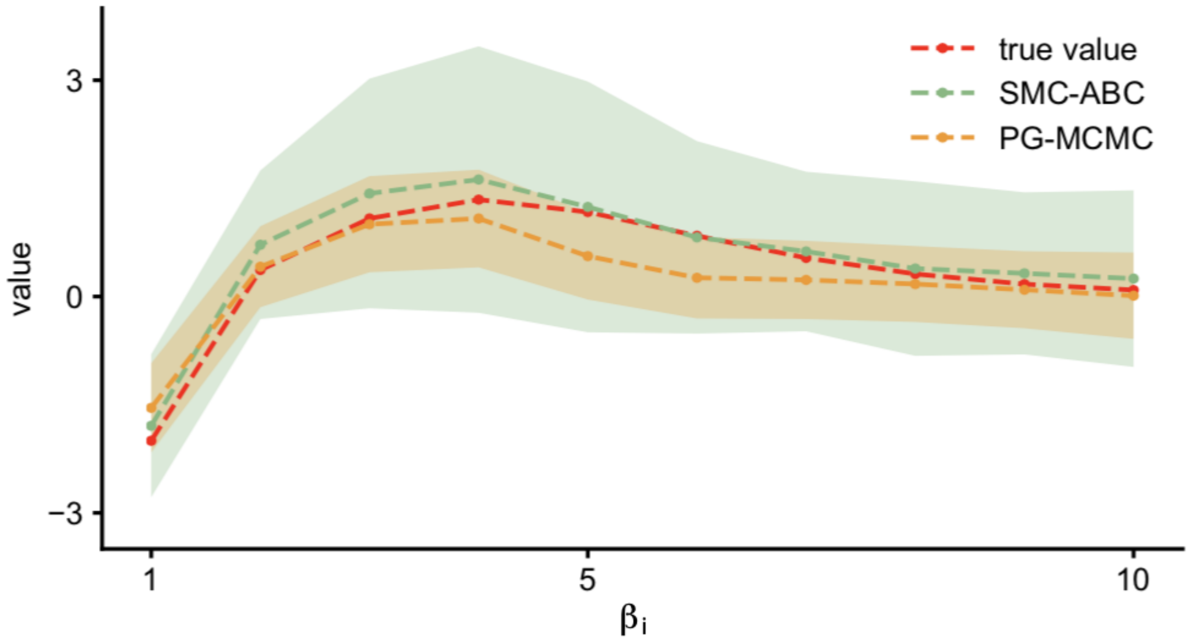
Bernoulli GLM

SMC-ABC needs significantly more simulations



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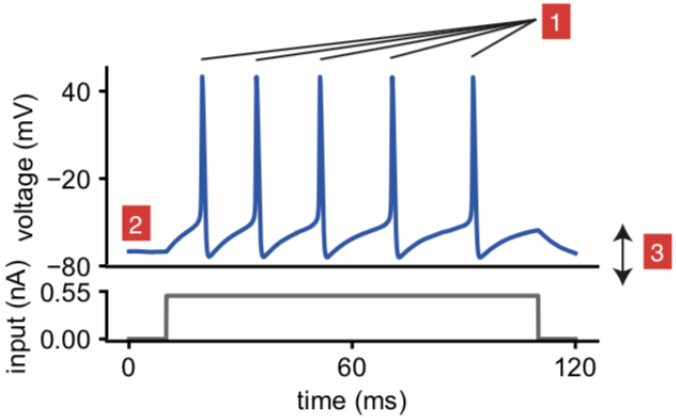
Hodgkin-Huxley

original data (simulated)



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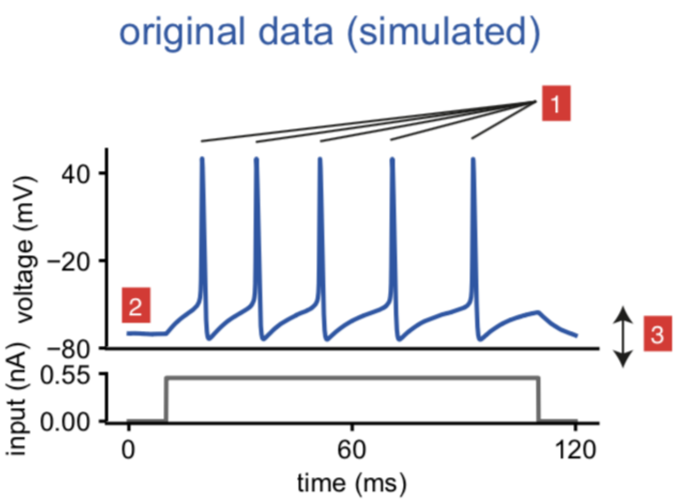
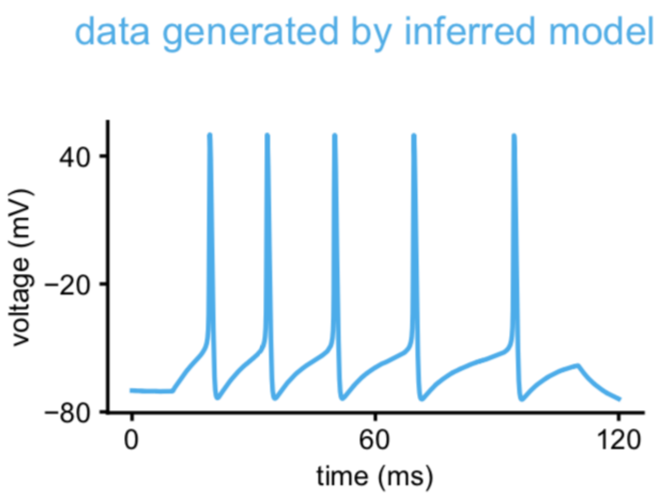
Lueckmann*, J.-M., Goncalves*, P. J., Bassetto, G., Öcal, K., Nonnenmacher, M., & Macke, J. H. (2017). Flexible statistical inference for mechanistic models of neural dynamics. In Advances in Neural Information Processing Systems 30 (pp. 1289–1299). Curran Associates, Inc.

Hodgkin-Huxley





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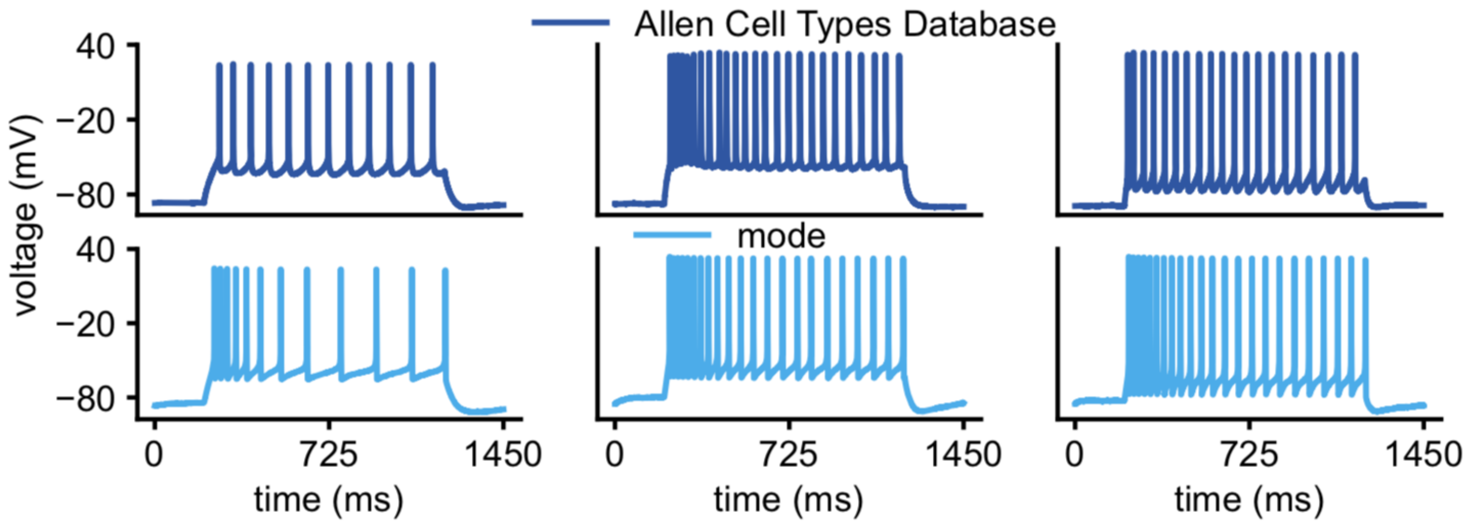
Lueckmann*, J.-M., Goncalves*, P. J., Bassetto, G., Öcal, K., Nonnenmacher, M., & Macke, J. H. (2017). Flexible statistical inference for mechanistic models of neural dynamics. In Advances in Neural Information Processing Systems 30 (pp. 1289–1299). Curran Associates, Inc.

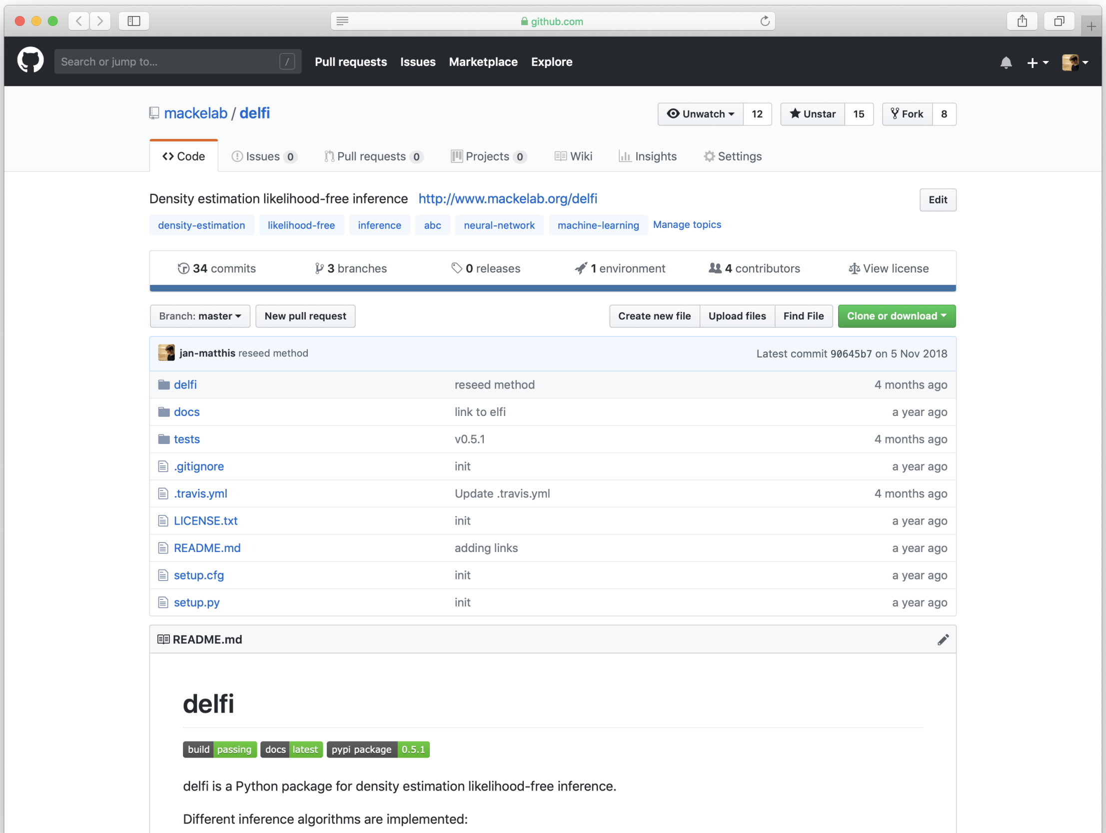
Hodgkin-Huxley



Lueckmann*, J.-M., Goncalves*, P. J., Bassetto, G., Öcal, K., Nonnenmacher, M., & Macke, J. H. (2017). Flexible statistical inference for mechanistic models of neural dynamics. In Advances in Neural Information Processing Systems 30 (pp. 1289–1299). Curran Associates, Inc.

... there's more

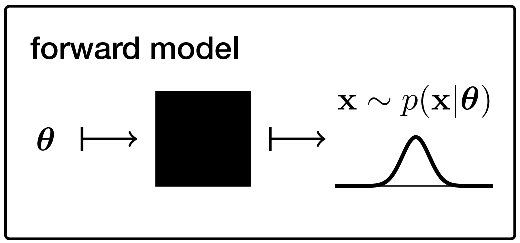
- No need for hand-crafted summary statistics
- Avoiding regions of bad parameters



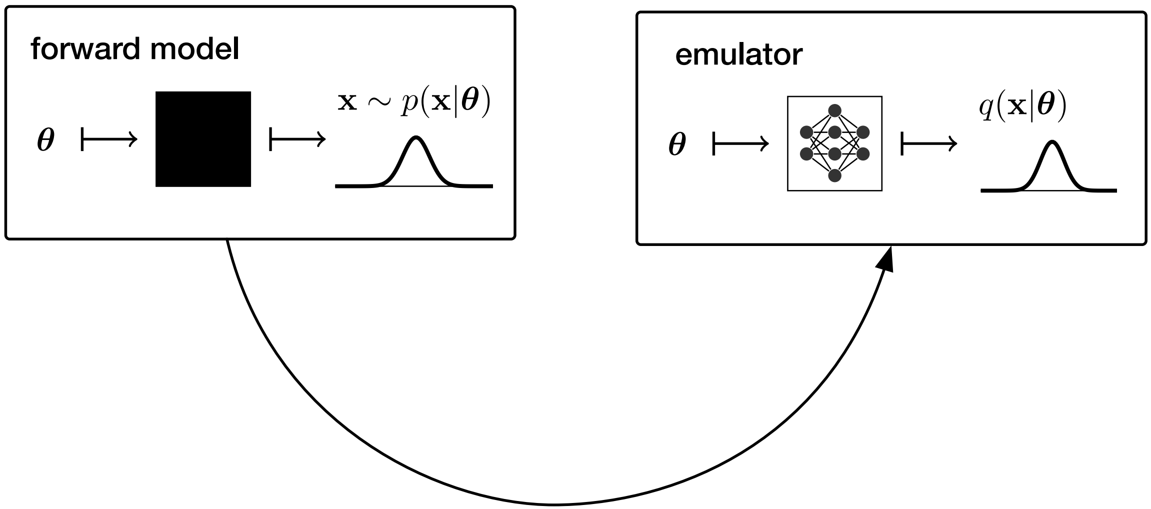
Lueckmann*, J.-M., Goncalves*, P. J., Bassetto, G., Öcal, K., Nonnenmacher, M., & Macke, J. H. (2017). Flexible statistical inference for mechanistic models of neural dynamics. In Advances in Neural Information Processing Systems 30 (pp. 1289–1299). Curran Associates, Inc.

Learning the likelihood

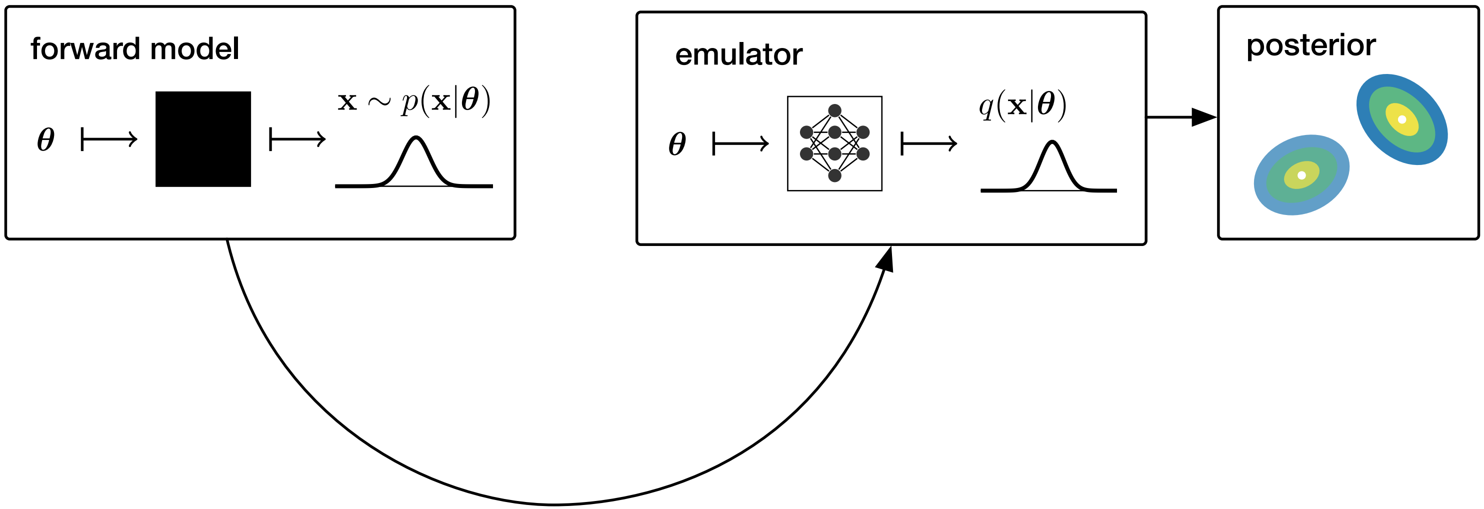
General approach



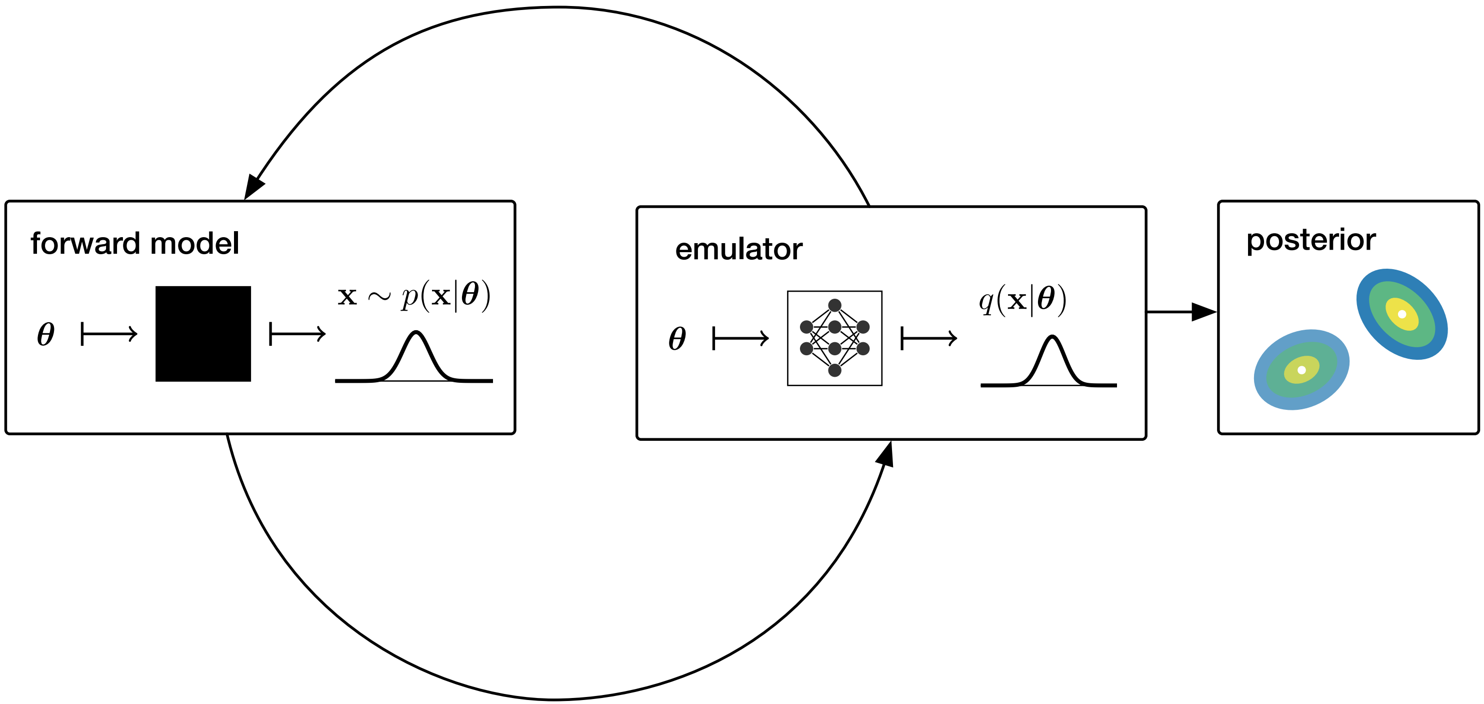
General approach



General approach



Sequential approach



Lueckmann, J.-M., Bassetto, G., Karaletsos, T., & Macke, J. H. (2018). Likelihood-free inference with emulator networks. In AABI 2018, PMLR volume 96.

Acquisition rules:

1. Learning local emulators

- Maximum variance in approximate posterior
- Takes into account measured data x_o
- Good approximation of $p(x|\theta)$ by q around x_o

$$\begin{aligned}\boldsymbol{\theta}^* &= \arg\max_{\boldsymbol{\theta}} \mathbb{V}_{\phi|\mathcal{D}}[\tilde{p}(\boldsymbol{\theta}|\mathbf{x}_o, \boldsymbol{\phi})] \\ &= \arg\max_{\boldsymbol{\theta}} p(\boldsymbol{\theta})^2 \, \mathbb{V}_{\phi|\mathcal{D}}[\hat{\mathcal{L}}(\boldsymbol{\theta})] \\ &= \arg\max_{\boldsymbol{\theta}} \log p(\boldsymbol{\theta}) + \log \sqrt{\mathbb{V}_{\phi|\mathcal{D}}[\hat{\mathcal{L}}(\boldsymbol{\theta})]}.\end{aligned}$$

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2. Learning global emulators

- Bayesian Active Learning by Disagreement
- Does not take account particular x_o
- Good approximation of $p(x|\theta)$ by q for all x

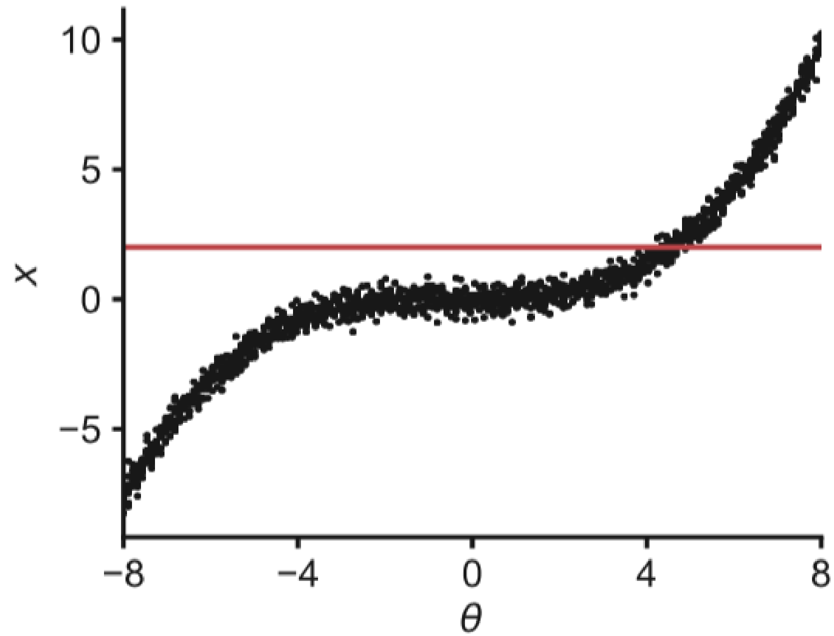
$$\begin{aligned}\boldsymbol{\theta}^* &= \arg\max_{\boldsymbol{\theta}} \mathbb{I}[\mathbf{x}, \boldsymbol{\phi}|\boldsymbol{\theta}, \mathcal{D}] \\ &= \arg\max_{\boldsymbol{\theta}} \underbrace{\mathbb{H}[\mathbf{x}|\boldsymbol{\theta}, \mathcal{D}]}_{\text{entropy}} - \underbrace{\mathbb{E}_{\phi|\mathcal{D}}\left[\mathbb{H}[\mathbf{x}|\boldsymbol{\theta}, \boldsymbol{\phi}]\right]}_{\text{expected conditional entropy}}\end{aligned}$$

Lueckmann, J.-M., Bassetto, G., Karaletsos, T., & Macke, J. H. (2018). Likelihood-free inference with emulator networks. In AABI 2018, PMLR volume 96.

Houlsby, N., Huszár, F., Ghahramani, Z., & Lengyel, M. (2011). Bayesian active learning for classification and preference learning. ArXiv:1112.5745 [Cs, Stat]

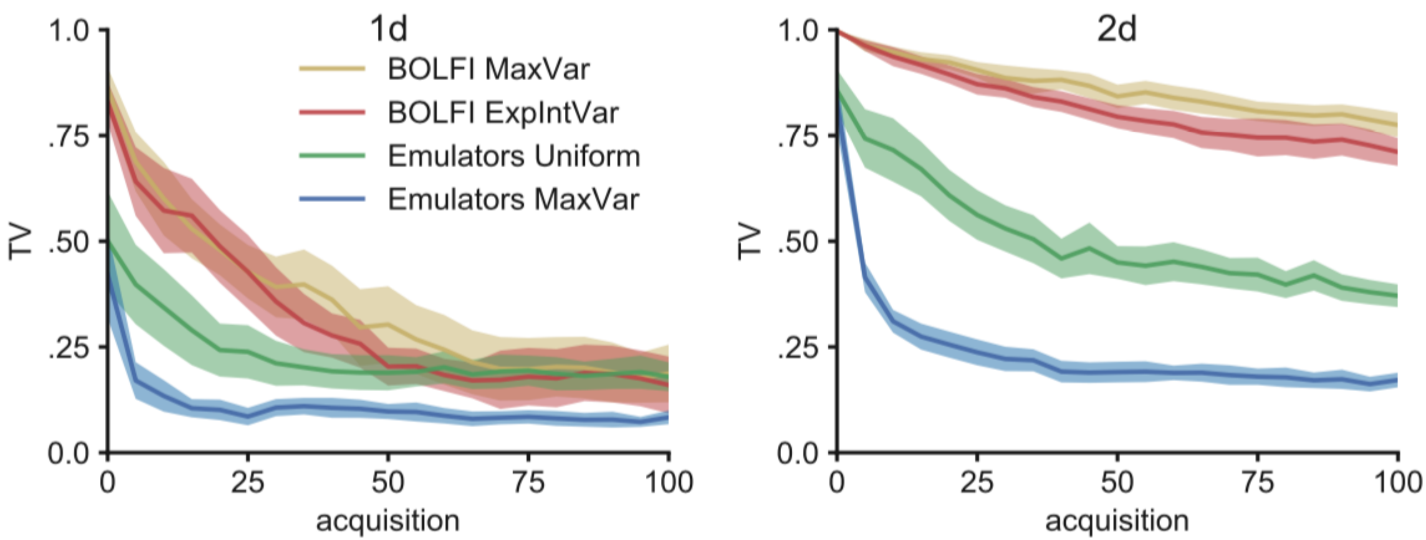
Local emulators: Comparison to BOLFI

BOLFI: Bayesian Optimization for Likelihood-Free Inference



Lueckmann, J.-M., Bassetto, G., Karaletsos, T., & Macke, J. H. (2018). Likelihood-free inference with emulator networks. In AABI 2018, PMLR volume 96.

Local emulators: Comparison to BOLFI



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Lueckmann, J.-M., Bassetto, G., Karaletsos, T., & Macke, J. H. (2018). Likelihood-free inference with emulator networks. In AABI 2018, PMLR volume 96.

Local emulators: Sequential neural likelihood

Sequential Neural Likelihood: Fast Likelihood-free Inference with Autoregressive Flows

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Abstract

We present Sequential Neural Likelihood (SNL), a new method for Bayesian inference in simulator models, where the likelihood is intractable but simulating data from the model is possible. SNL trains an autoregressive flow on simulated data in order to learn a model of the likelihood in the region of high posterior density. A sequential training procedure guides simulations and reduces simulation cost by orders of magnitude. We show that SNL is more robust, more accurate and requires less tuning than related state-of-the-art methods which target the posterior, and discuss diagnostics for assessing calibration, convergence and goodness-of-fit.

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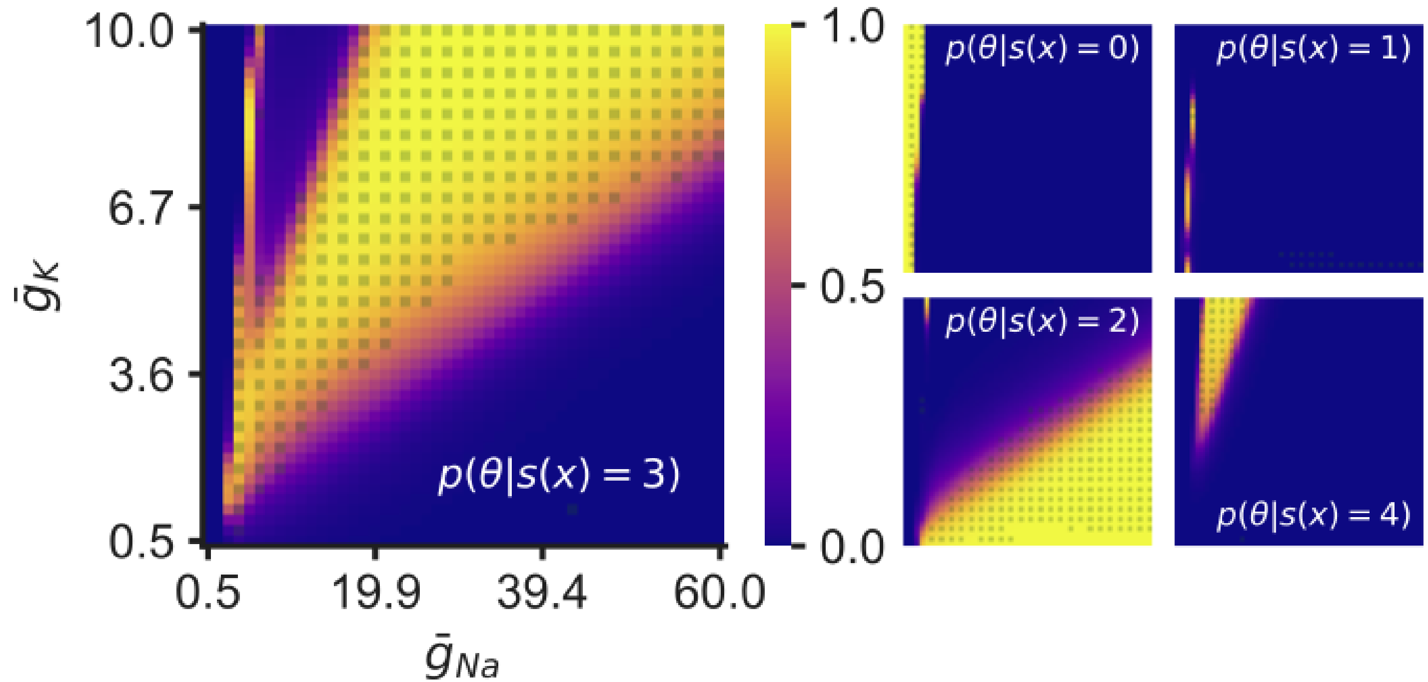
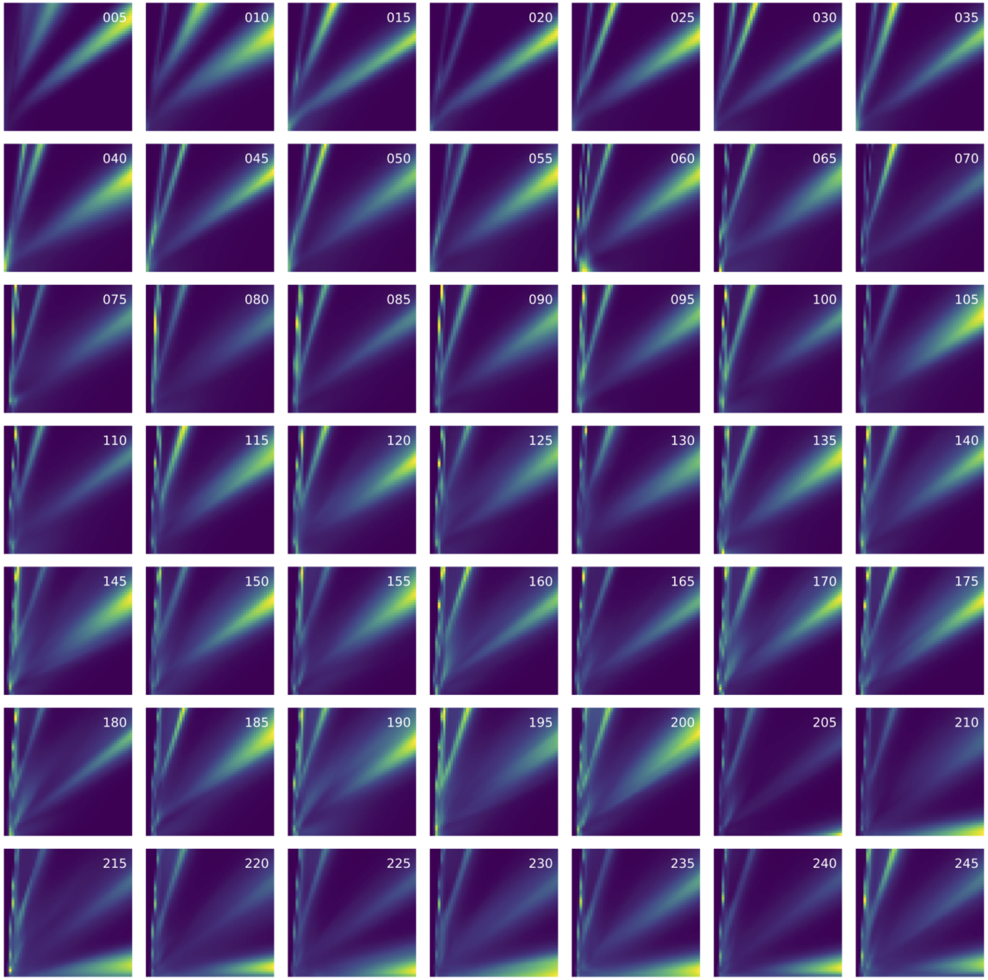
Papamakarios, G., Sterratt, D. C., & Murray, I. (2019). Sequential neural likelihood: fast likelihood-free inference with autoregressive flows. In AISTATS 2019, PMLR volume 89.

Global emulators: Hodgkin-Huxley



Lueckmann, J.-M., Bassetto, G., Karaletsos, T., & Macke, J. H. (2018). Likelihood-free inference with emulator networks. In AABI 2018, PMLR volume 96.

Global emulators: Hodgkin-Huxley



Lueckmann, J.-M., Bassetto, G., Karaletsos, T., & Macke, J. H. (2018). Likelihood-free inference with emulator networks. In AABI 2018, PMLR volume 96.

Applications

Applications

Channelomics

Collaboration with Tim Vogels' group

Theoretical and Computational Neuroscience

Tim Vogels

William Podlaski

Chaitanya Chintaluri

UNIVERSITY OF
OXFORD

Centre
for Neural
Circuits and
Behaviour

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TOOLS AND RESOURCES

Mapping the function of neuronal ion channels in model and experiment

William F Podlaski[1,2*†], Alexander Seeholzer[3,4,5†], Lukas N Groschner[1,2], Gero Miesenböck[1,2], Rajnish Ranjan[6], Tim P Vogels[1,2]

[1]Centre for Neural Circuits and Behaviour, University of Oxford, Oxford, United Kingdom; [2]Department of Physiology, Anatomy and Genetics, University of Oxford, Oxford, United Kingdom; [3]School of Computer and Communication Sciences, École Polytechnique Fédérale de Lausanne, Lausanne, Switzerland; [4]School of Life Sciences, Ecole Polytechnique Federale de Lausanne, Lausanne, Switzerland; [5]Brain Mind Institute, Ecole Polytechnique Federale de Lausanne, Lausanne, Switzerland; [6]Blue Brain Project, École Polytechnique Fédérale de Lausanne, Geneva, Switzerland

Abstract Ion channel models are the building blocks of computational neuron models. Their biological fidelity is therefore crucial for the interpretation of simulations. However, the number of published models, and the lack of standardization, make the comparison of ion channel models with one another and with experimental data difficult. Here, we present a framework for the automated large-scale classification of ion channel models. Using annotated metadata and responses to a set of voltage-clamp protocols, we assigned 2378 models of voltage- and calcium-gated ion channels coded in *NEURON* to 211 clusters. The *IonChannelGenealogy* (ICGenealogy) web interface provides an interactive resource for the categorization of new and existing models and experimental recordings. It enables quantitative comparisons of simulated and/or measured ion channel kinetics, and facilitates field-wide standardization of experimentally-constrained modeling.

DOI: 10.7554/eLife.22152.001

***For correspondence:** william.podlaski@cncb.ox.ac.uk

†These authors contributed equally to this work

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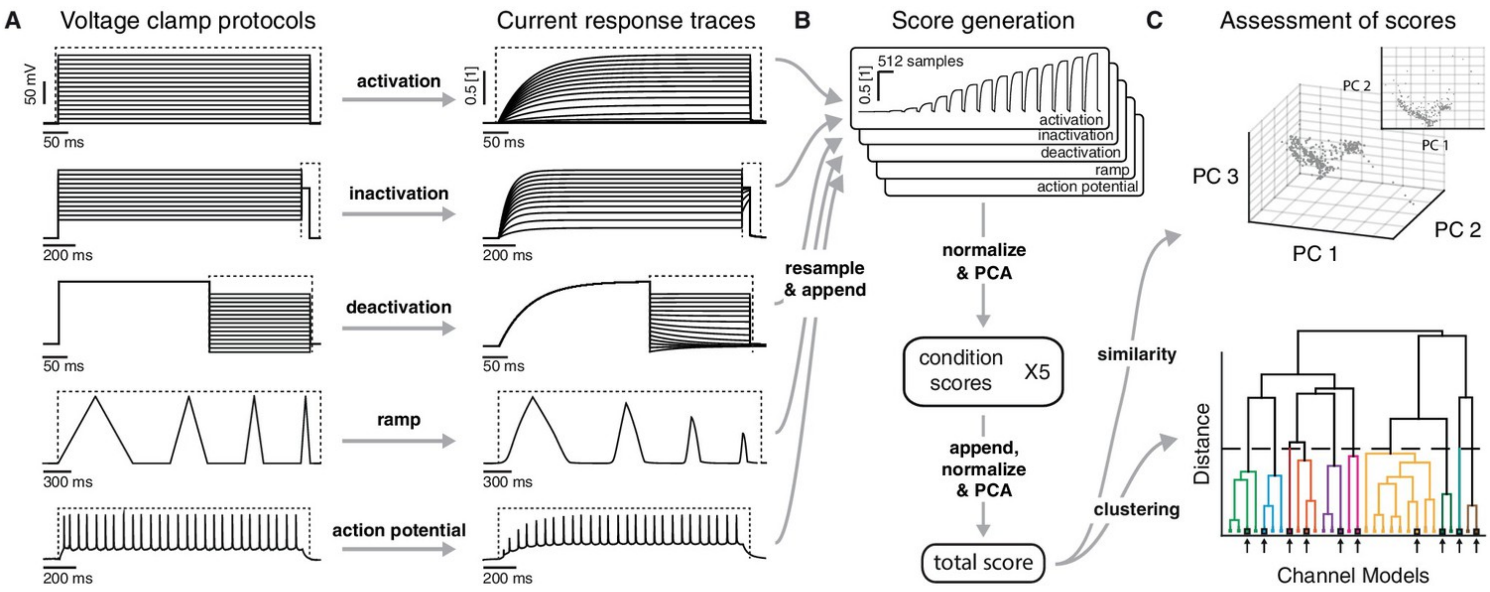
Podlaski, W. F., Seeholzer, A., Groschner, L. N., Miesenböck, G., Ranjan, R., & Vogels, T. P. (2017). Mapping the function of neuronal ion channels in model and experiment. ELife, 6, e22152. https://doi.org/10.7554/eLife.22152

Voltage-clamp protocols for the quantitative analysis of ion channel models



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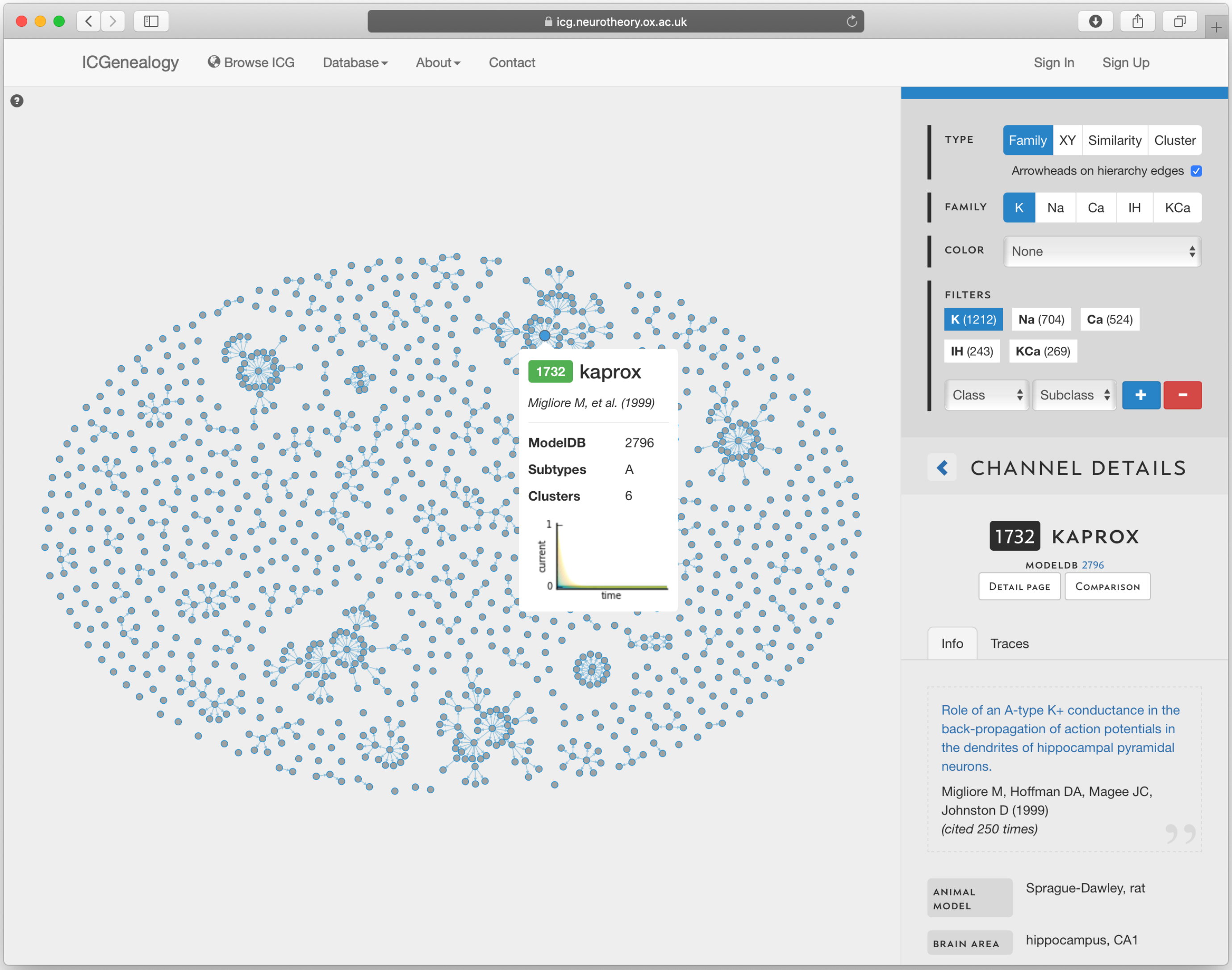
Podlaski, W. F., Seeholzer, A., Groschner, L. N., Miesenböck, G., Ranjan, R., & Vogels, T. P. (2017). Mapping the function of neuronal ion channels in model and experiment. ELife, 6, e22152. https://doi.org/10.7554/eLife.22152



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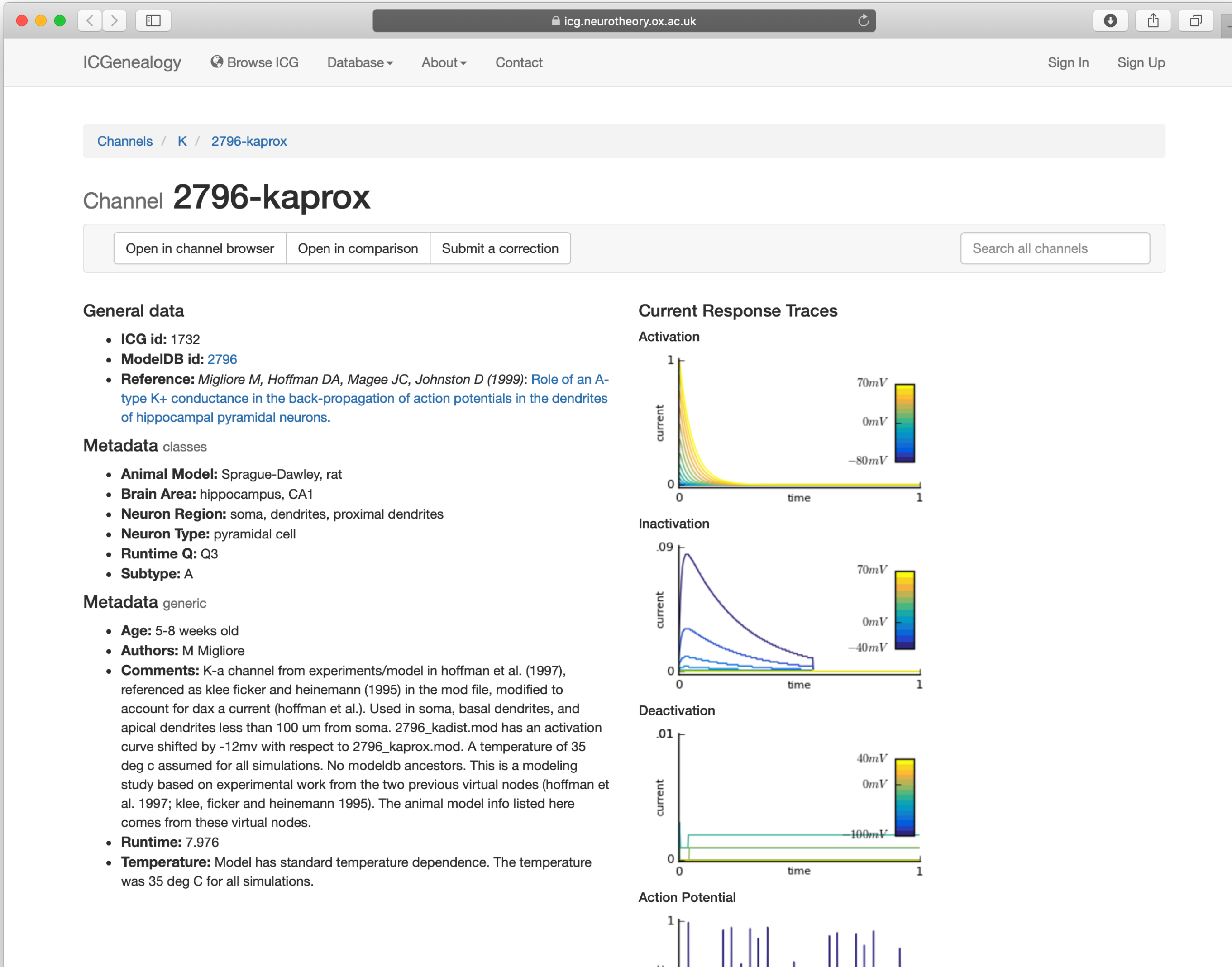
https://channelomics.neurotheory.ox.ac.uk/



icg.neurotheory.ox.ac.uk

ICGenealogy | Browse ICG | Database | About | Contact | Sign In | Sign Up

Channels / K / 2796-kaprox

Channel **2796-kaprox**

Open in channel browser | Open in comparison | Submit a correction | Search all channels

General data

- **ICG id:** 1732
- **ModelDB id:** 2796
- **Reference:** *Migliore M, Hoffman DA, Magee JC, Johnston D (1999)*: Role of an A-type K+ conductance in the back-propagation of action potentials in the dendrites of hippocampal pyramidal neurons.

Metadata classes

- **Animal Model:** Sprague-Dawley, rat
- **Brain Area:** hippocampus, CA1
- **Neuron Region:** soma, dendrites, proximal dendrites
- **Neuron Type:** pyramidal cell
- **Runtime Q:** Q3
- **Subtype:** A

Metadata generic

- **Age:** 5-8 weeks old
- **Authors:** M Migliore
- **Comments:** K-a channel from experiments/model in hoffman et al. (1997), referenced as klee ficker and heinemann (1995) in the mod file, modified to account for dax a current (hoffman et al.). Used in soma, basal dendrites, and apical dendrites less than 100 um from soma. 2796_kadist.mod has an activation curve shifted by -12mv with respect to 2796_kaprox.mod. A temperature of 35 deg c assumed for all simulations. No modeldb ancestors. This is a modeling study based on experimental work from the two previous virtual nodes (hoffman et al. 1997; klee, ficker and heinemann 1995). The animal model info listed here comes from these virtual nodes.
- **Runtime:** 7.976
- **Temperature:** Model has standard temperature dependence. The temperature was 35 deg C for all simulations.

Current Response Traces

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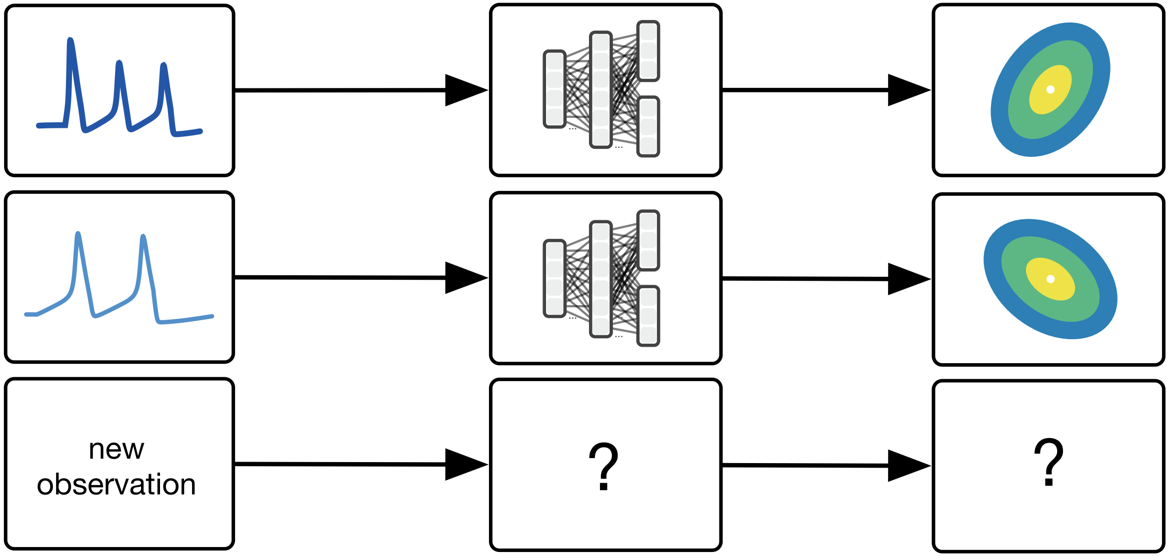
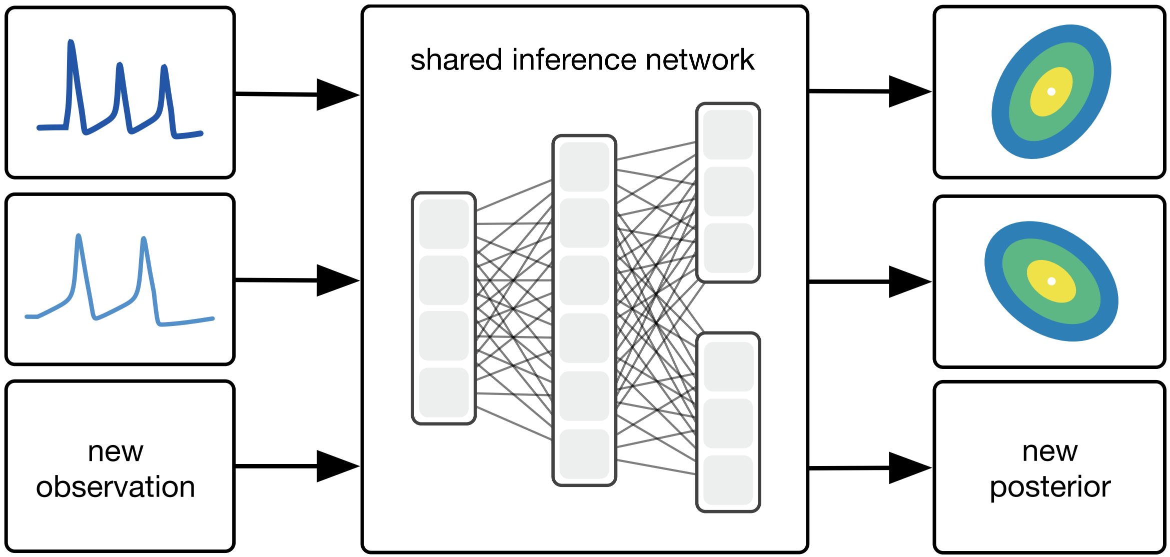
https://channelomics.neurotheory.ox.ac.uk/

Goal: Rapidly infer channel parameters from current responses

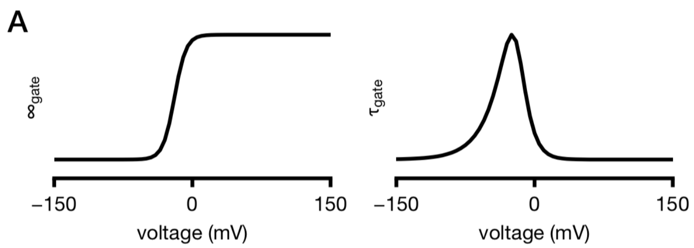
Standard inference scheme



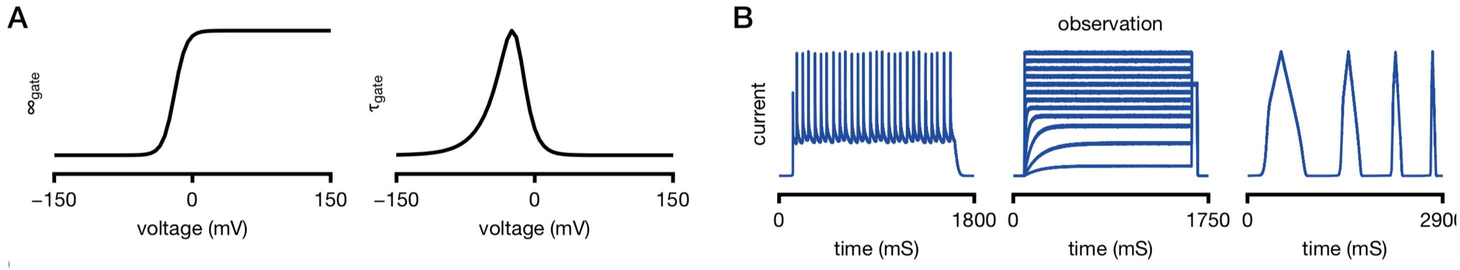
Amortized inference



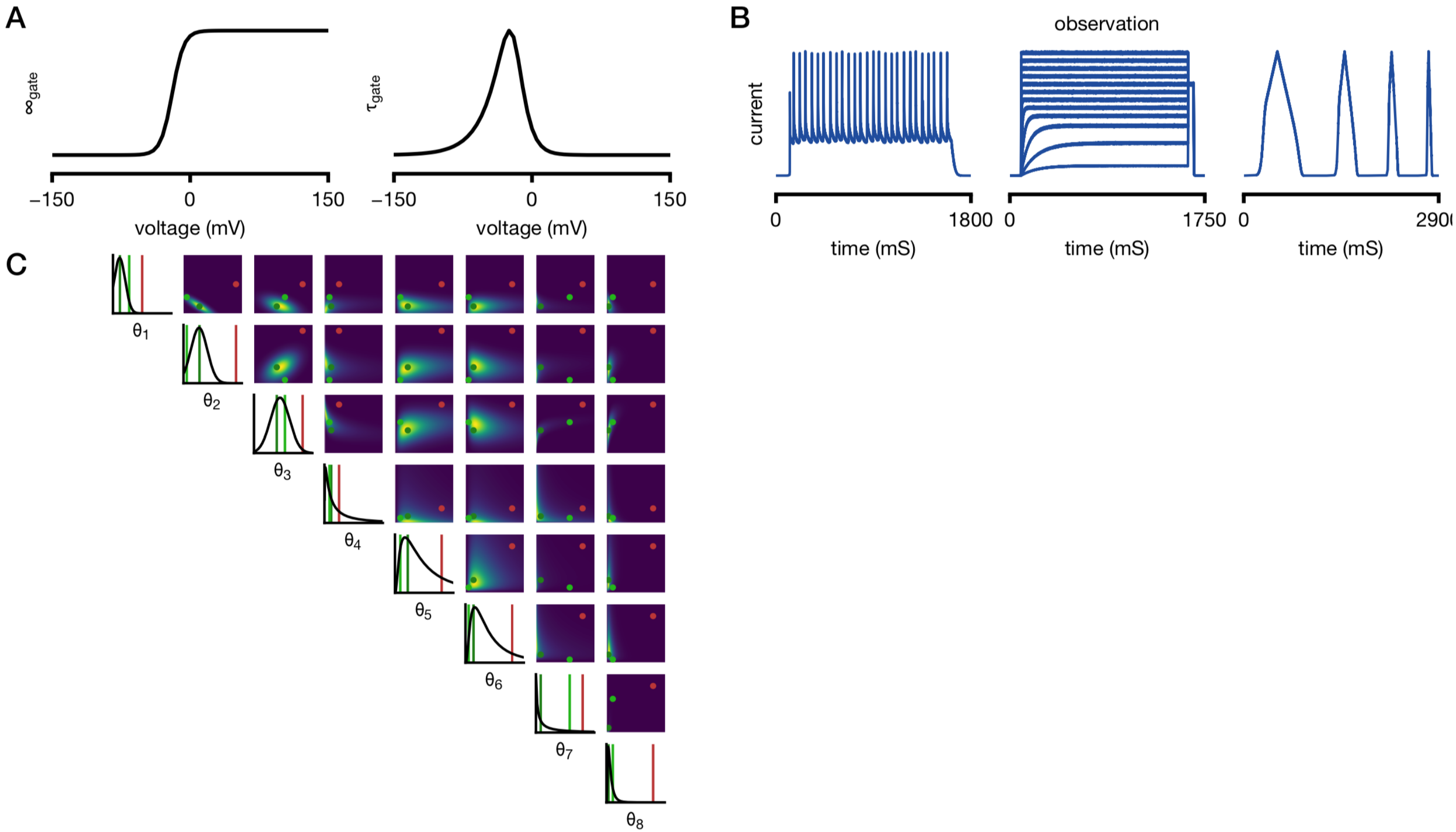
Amortized inference on ion channels



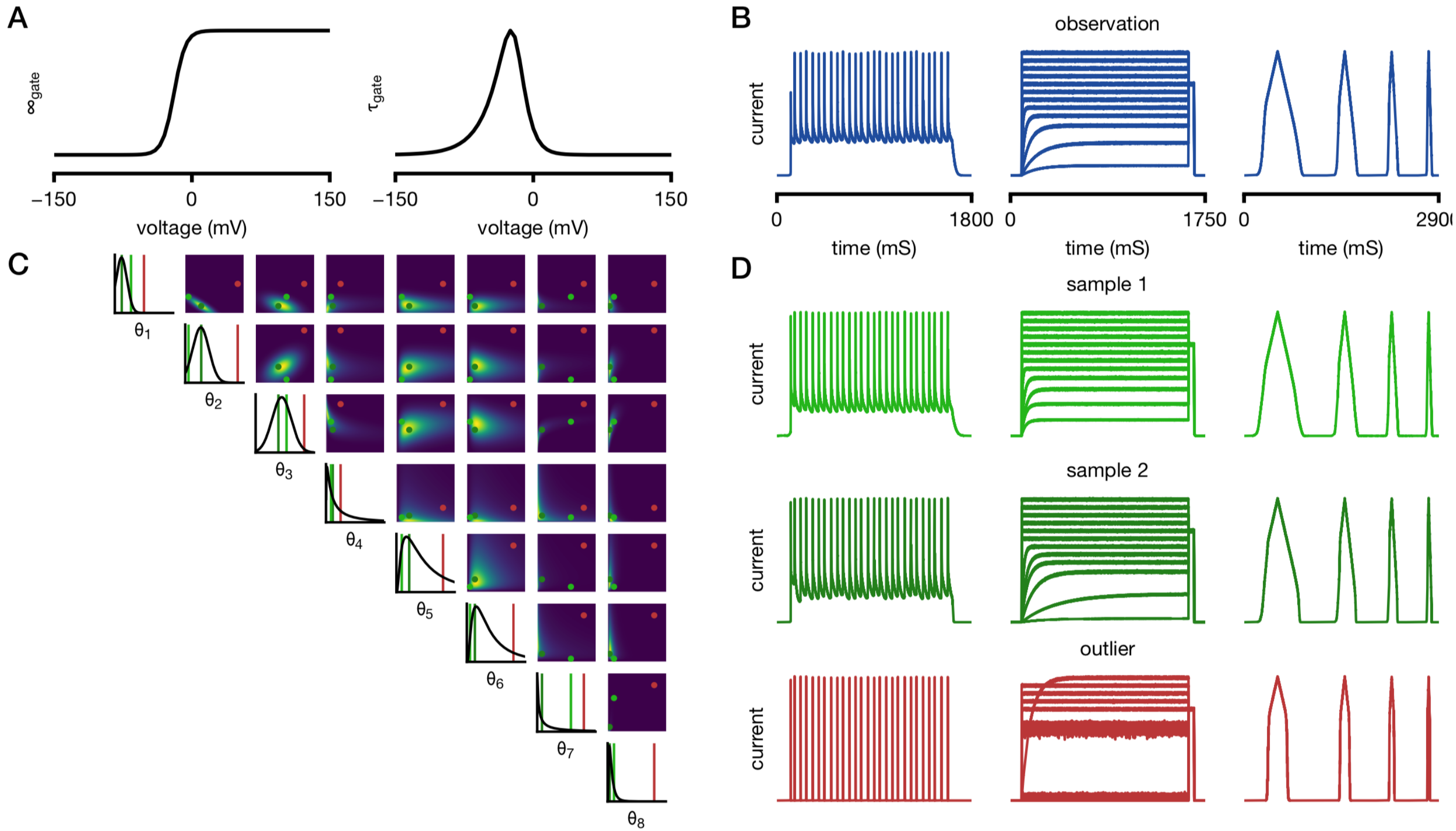
Amortized inference on ion channels



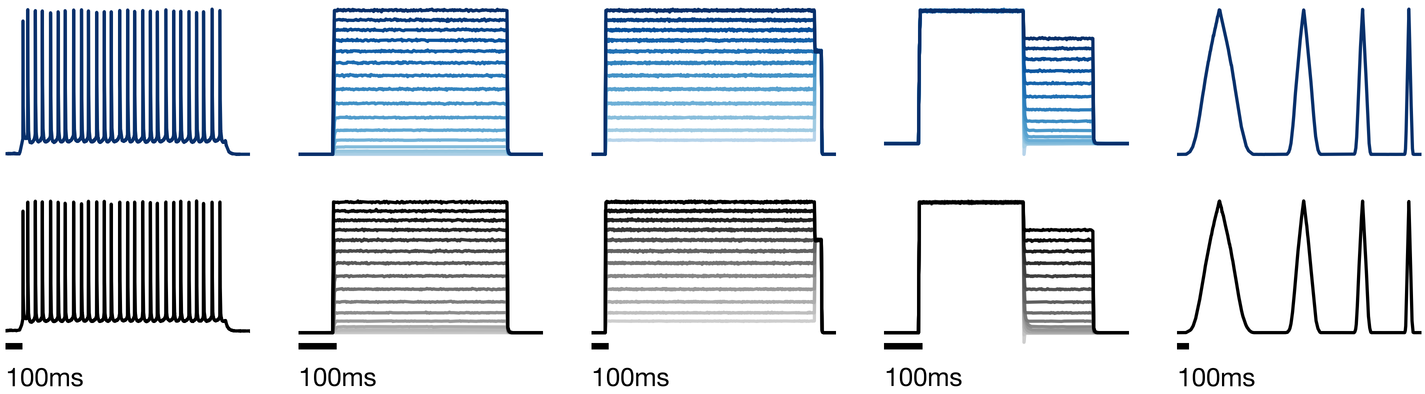
Amortized inference on ion channels



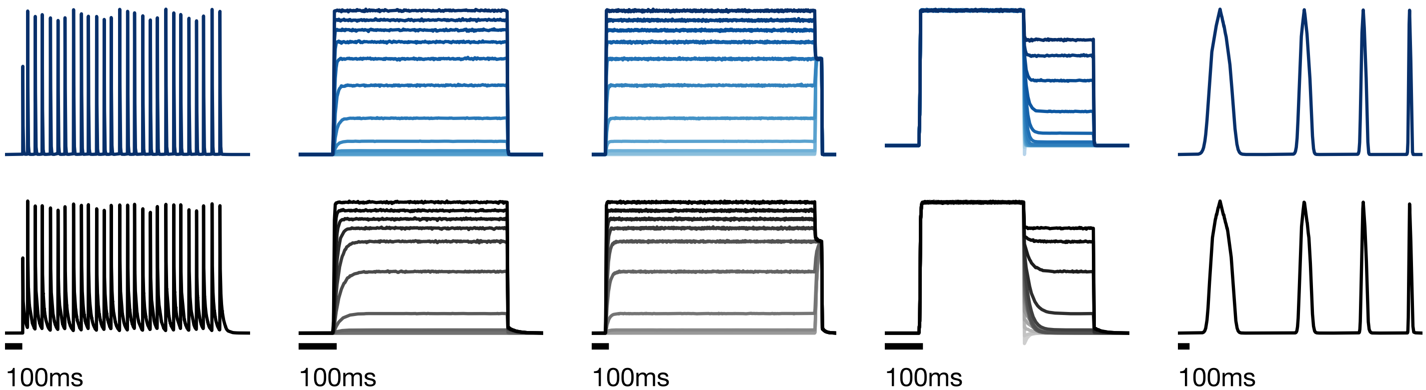
Amortized inference on ion channels



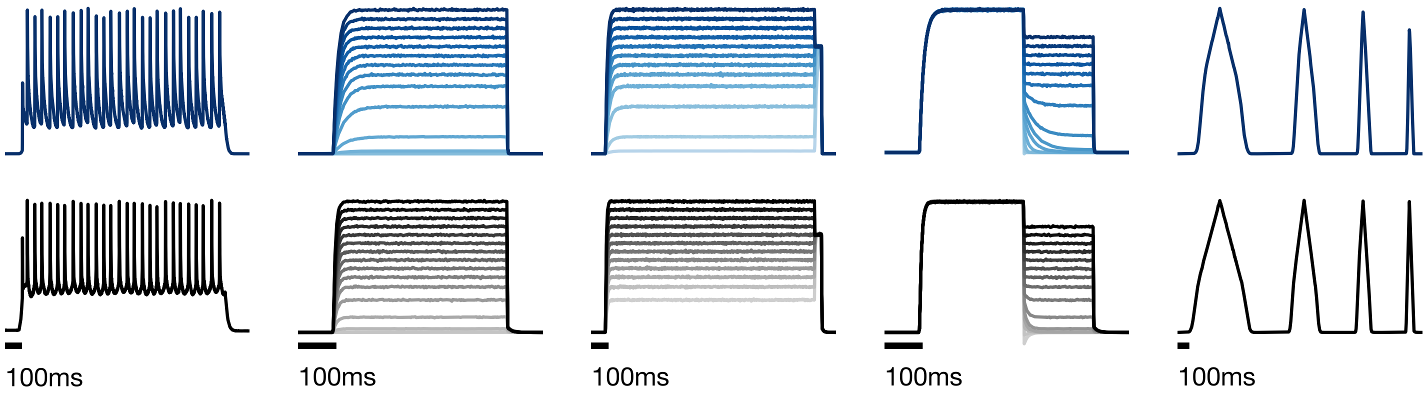
Channel 48332_kpkjslow · L_2-error 0.05



Channel 153280_ch_Kdrp · L_2-error 0.24

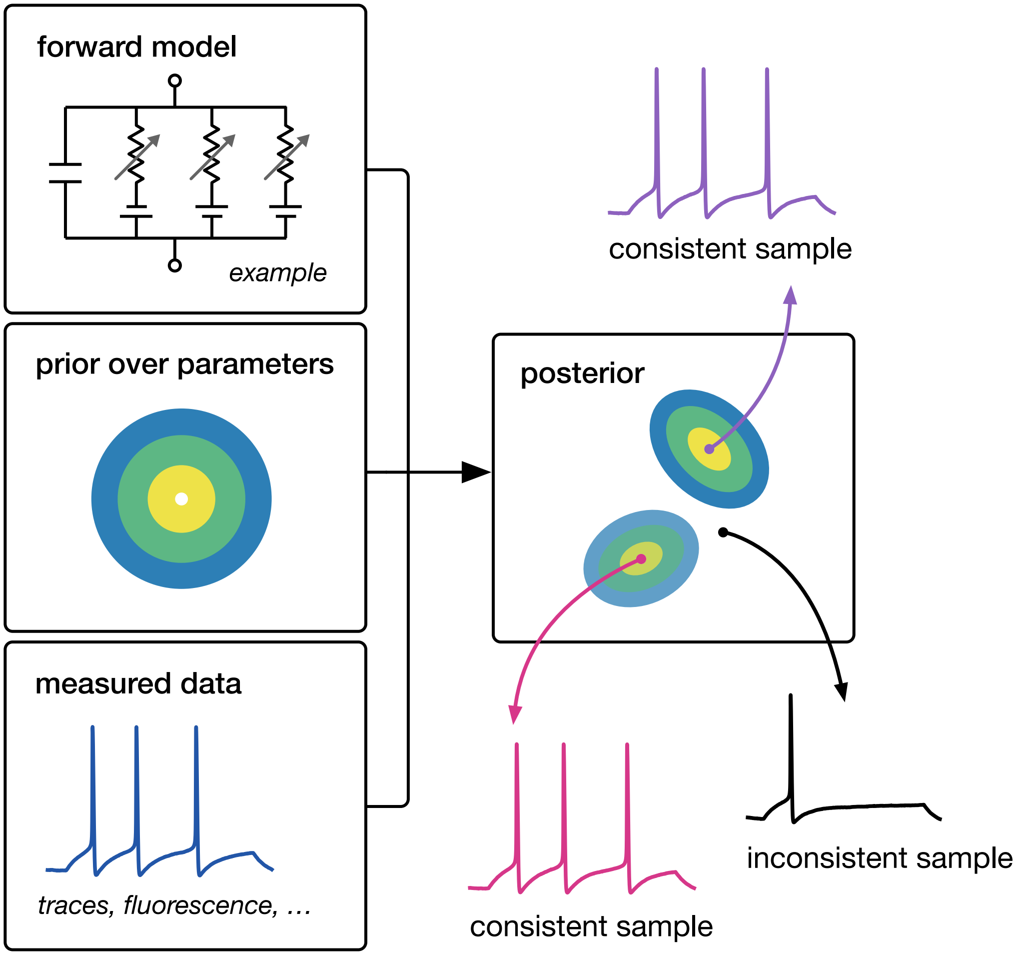


Channel 45539_km · L_2-error 0.49



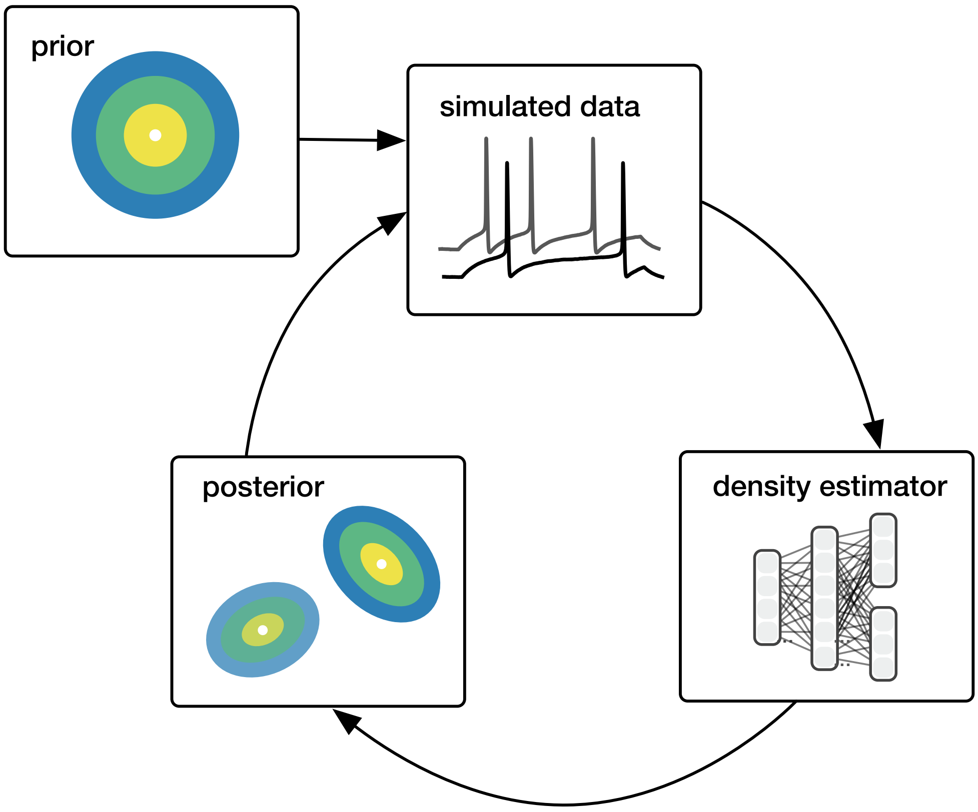
Summary

Goal: Bayesian inference for mechanistic models



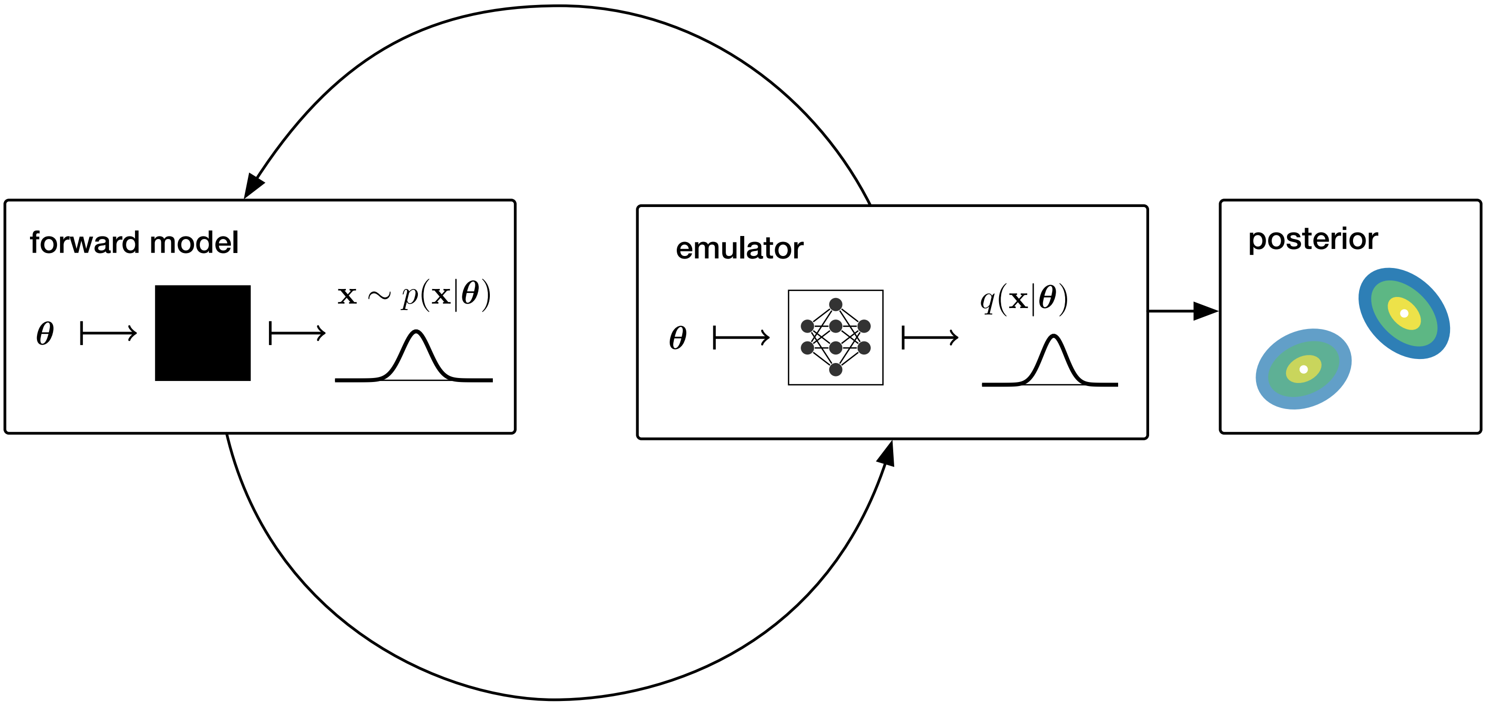
Approach 1: Sequential simulation-based inference

Learn posterior: $x \rightarrow \theta$



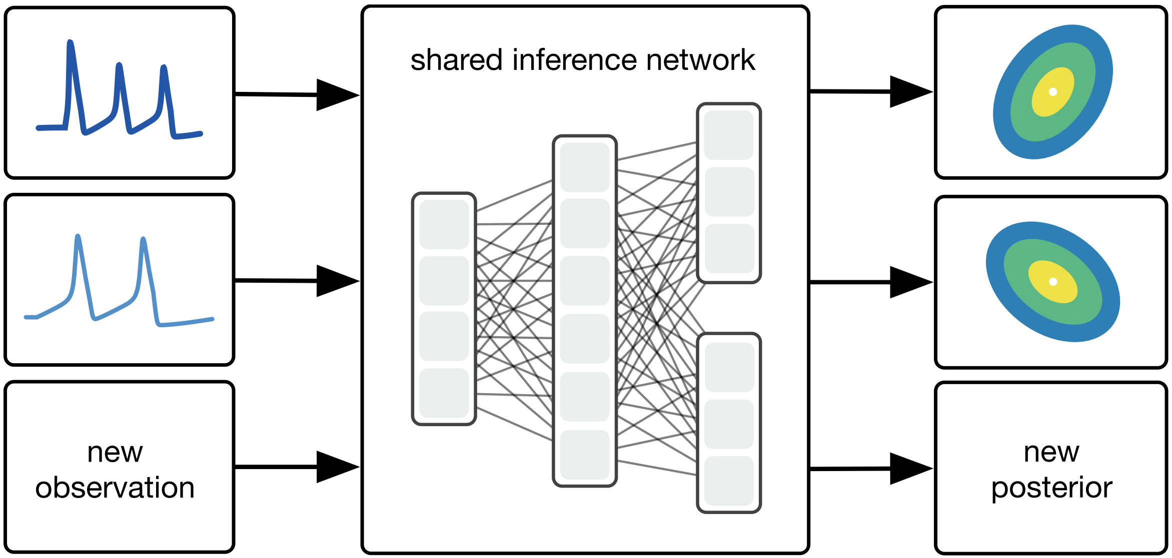
Approach 2: Sequential simulation-based inference

Learn likelihood: $\theta \to x$



Amortized inference

Applied to channelomics



Thank you!


Jakob Macke


Pedro Gonçalves


Giacomo Bassetto


Marcel Nonnenmacher

Thank you!

Jakob Macke

Pedro Gonçalves

Giacomo Bassetto

Marcel Nonnenmacher

Theofanis Karaletsos

Tim Vogels

William Podlaski

Chaitanya Chintaluri

Thank you!

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William Podlaski

Chaitanya Chintaluri

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