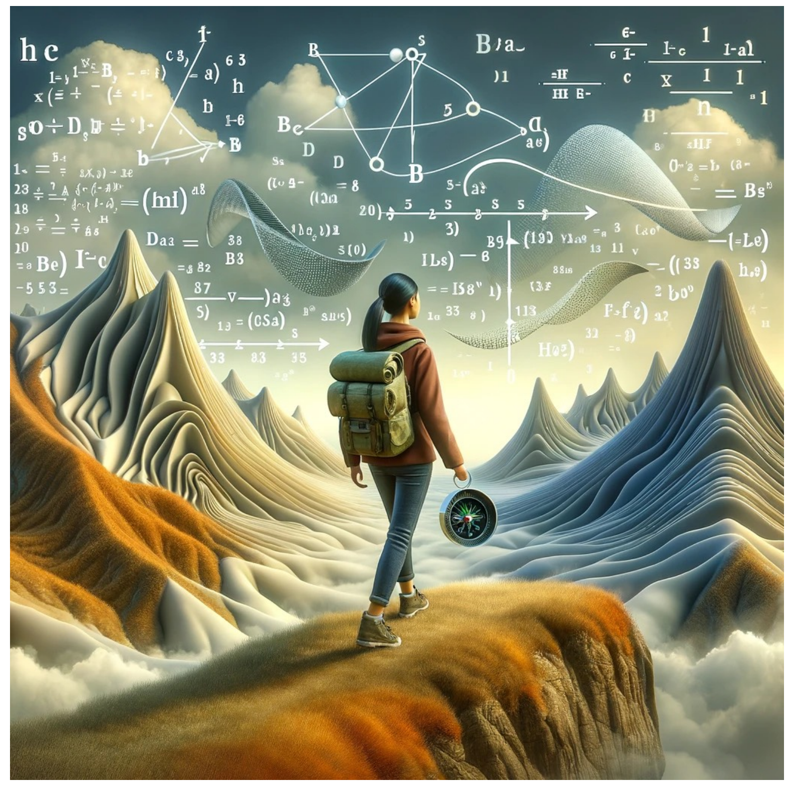
Simulation and inference in neuroscience



Lecture 6: Introduction to simulation-based inference

March 2025

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Cornelius Schröder

Michael Deistler

Manuel Glöckler

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- Some slides by Álvaro Tejero-Cantero

Computational Neuroscience and Machine Learning

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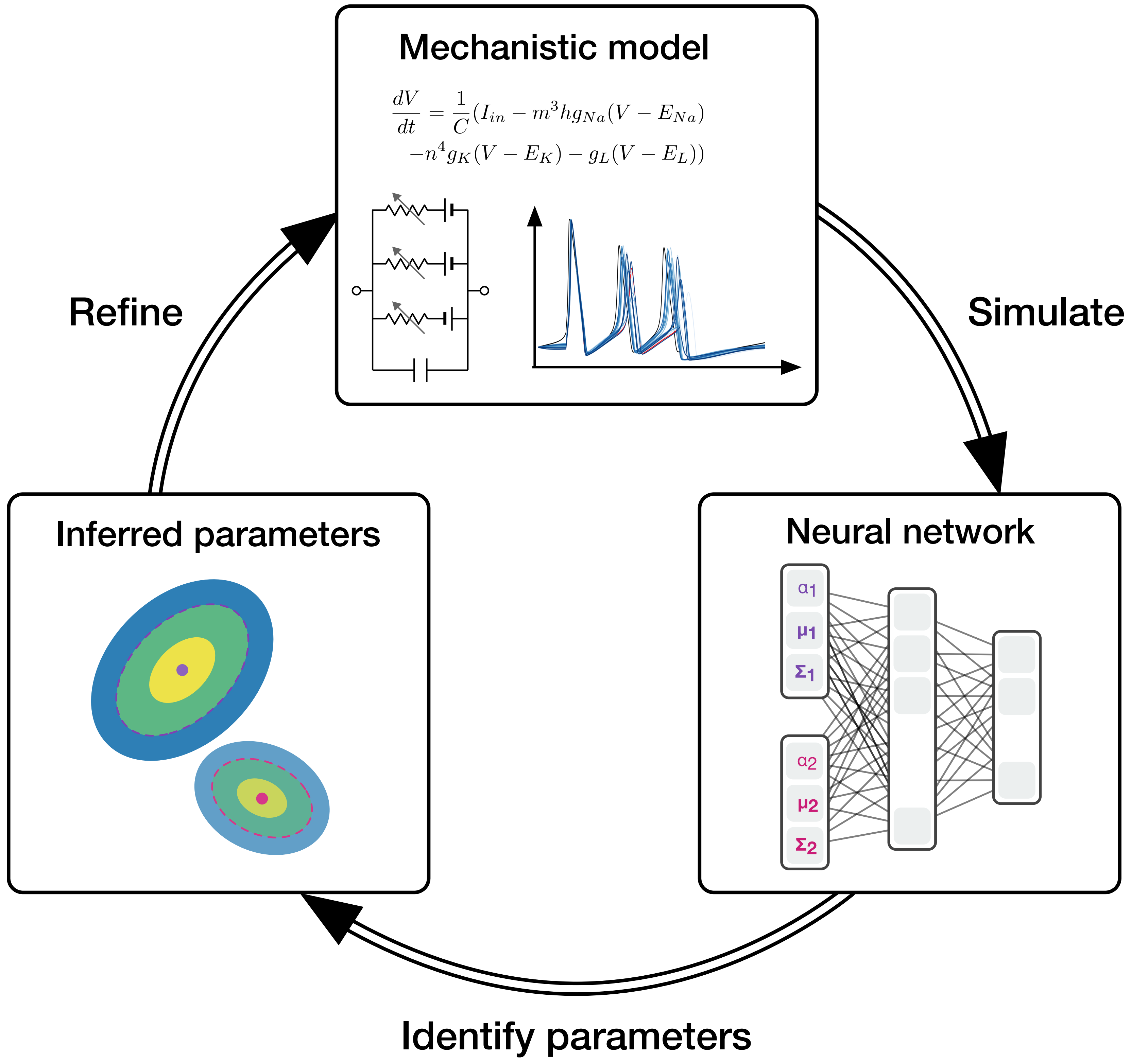
What my labs does

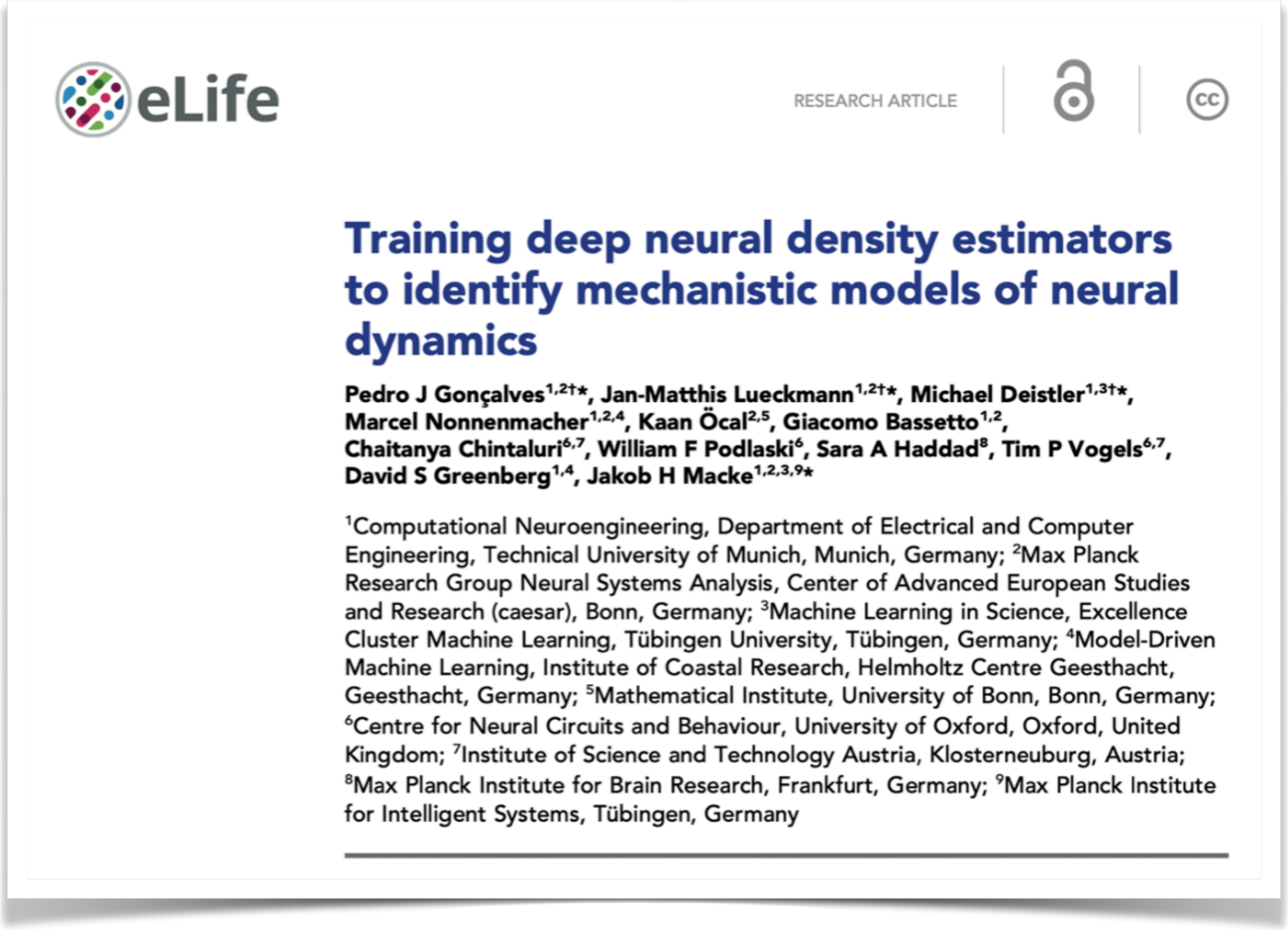
Scientific Modelling **Machine Learning**

How can we combine these two approaches
to build tools for data-driven scientific discovery?

Applications: Focus on neuroscience

Image credit: Ryan Garcia, Simons Foundation




eLife
RESEARCH ARTICLE

Training deep neural density estimators to identify mechanistic models of neural dynamics

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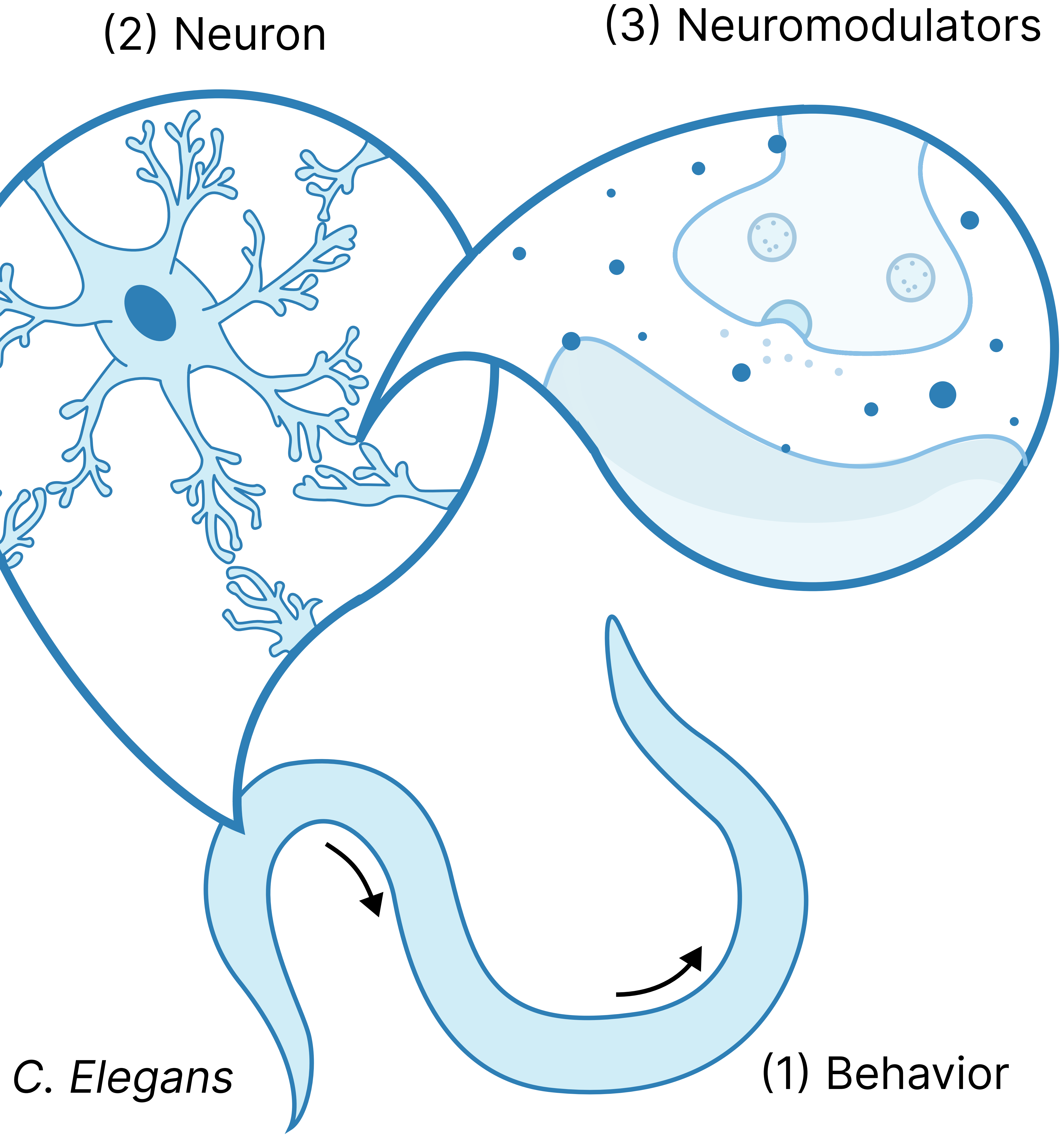
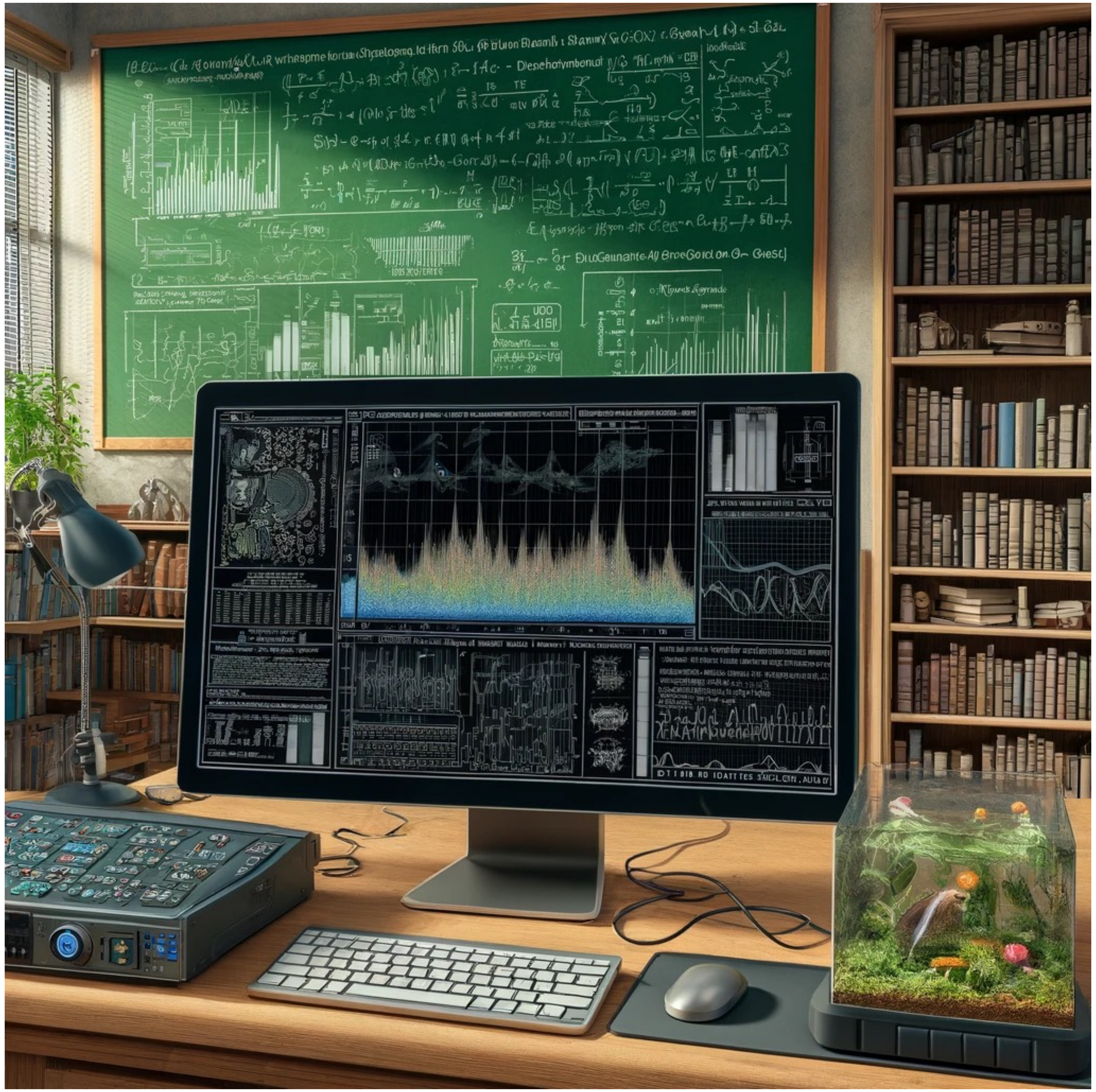
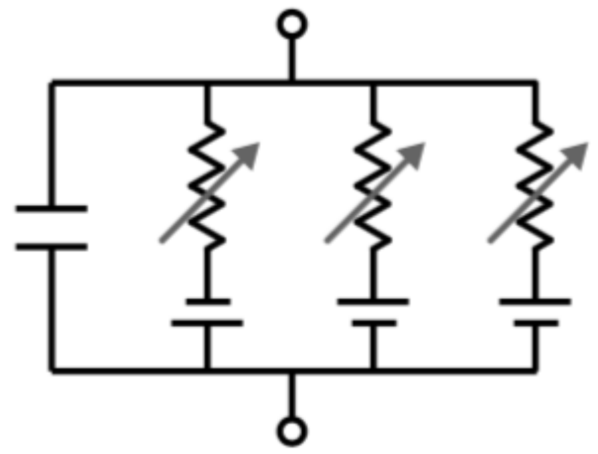

(2) Neuron
(3) Neuromodulators
C. Elegans
(1) Behavior

6.1 Science and the role of simulators



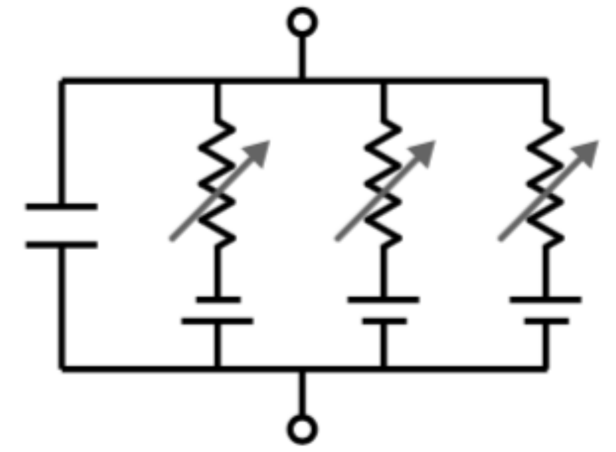
Mechanistic model

$$C_m \frac{dV}{dt} = \sum_c \bar{g}_c g_c [E_c - V] + I$$

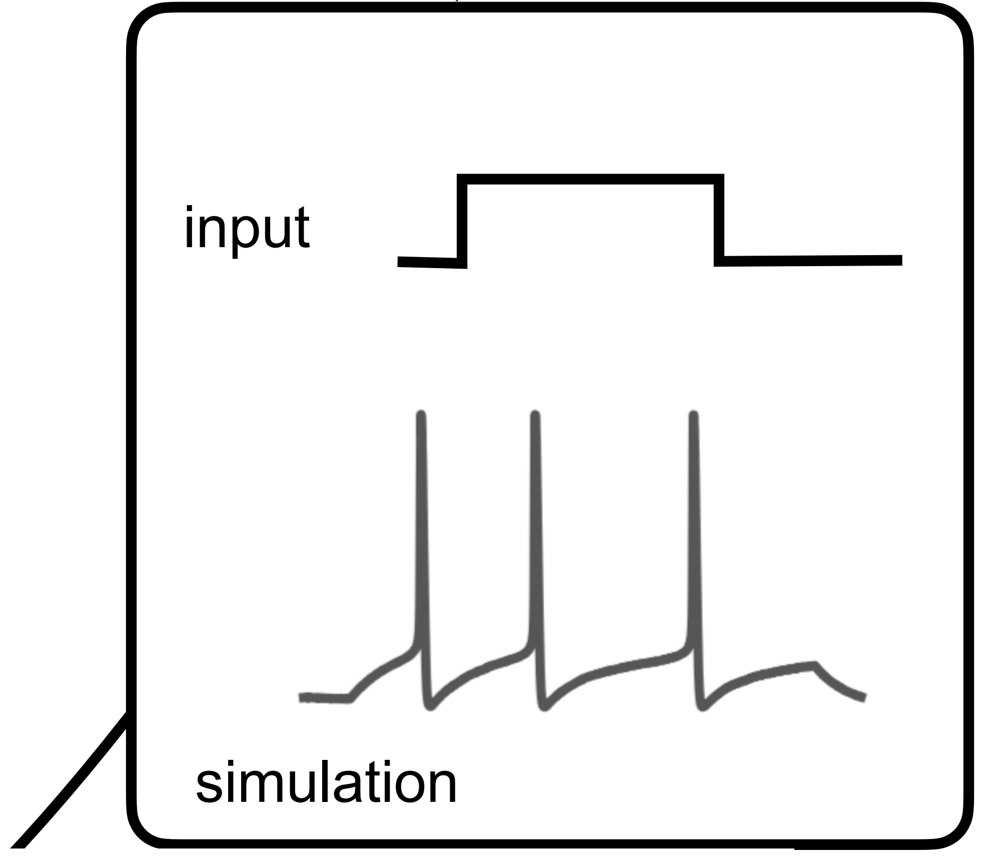


Mechanistic model

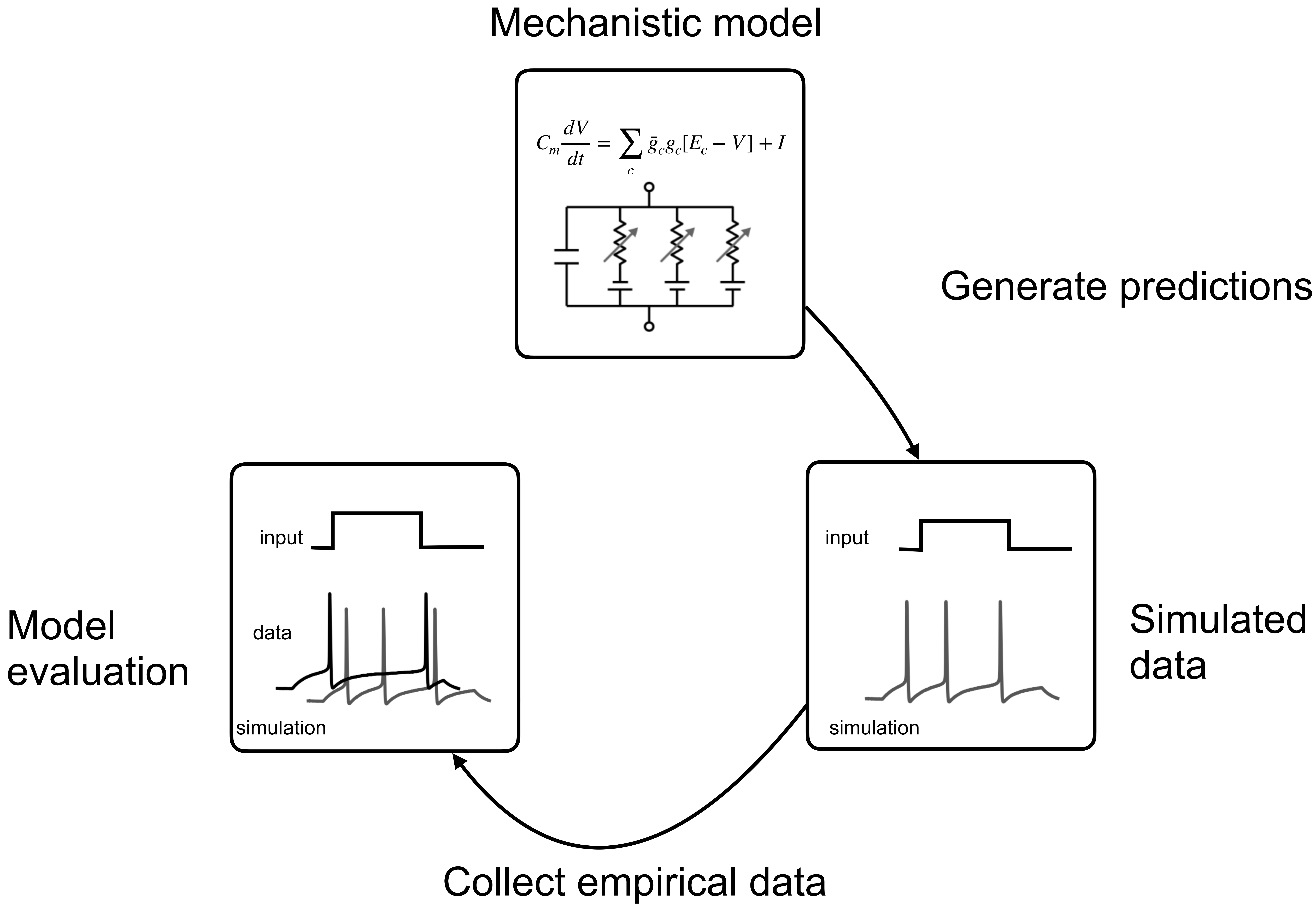
$$C_m \frac{dV}{dt} = \sum_c \bar{g}_c g_c [E_c - V] + I$$

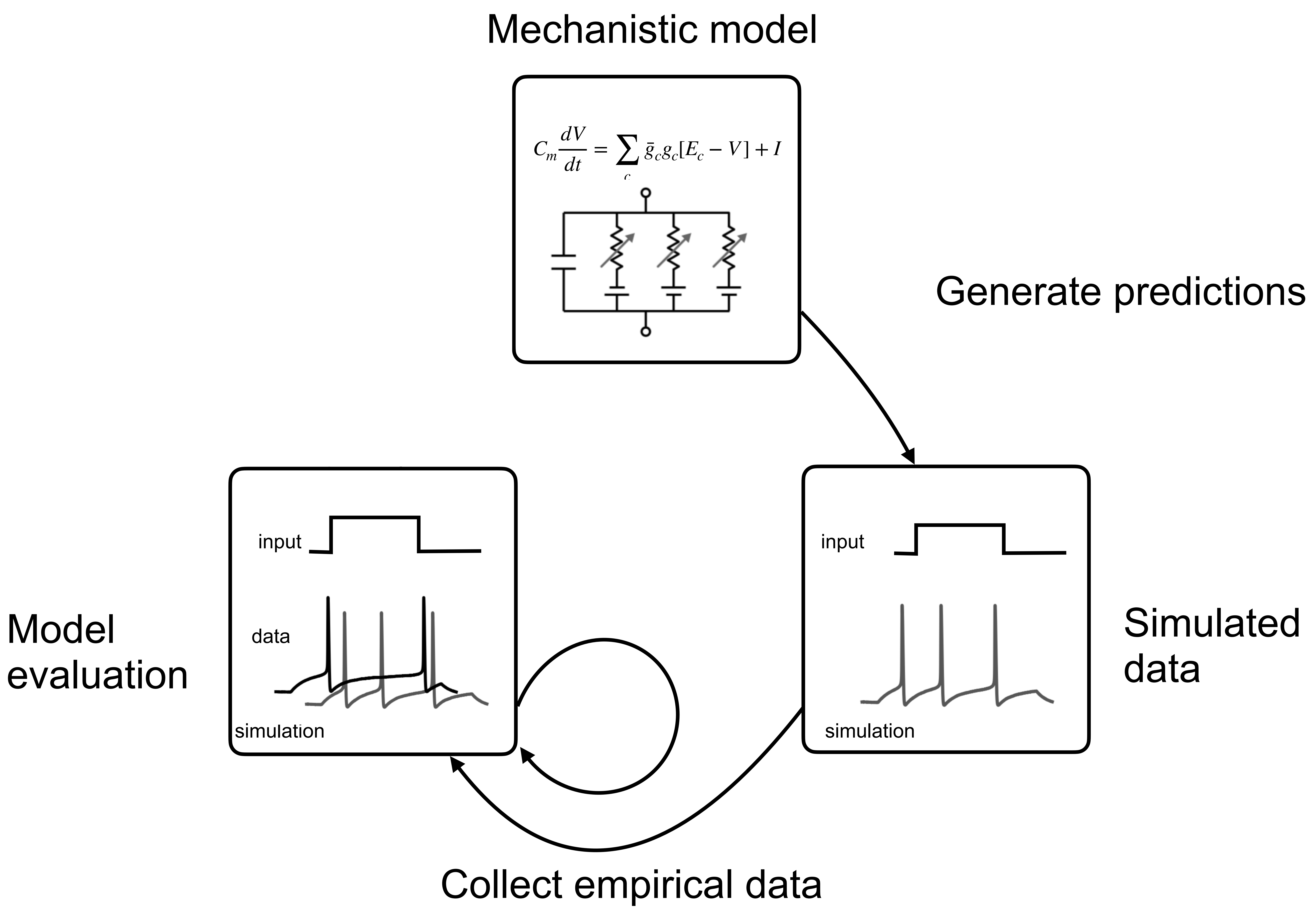


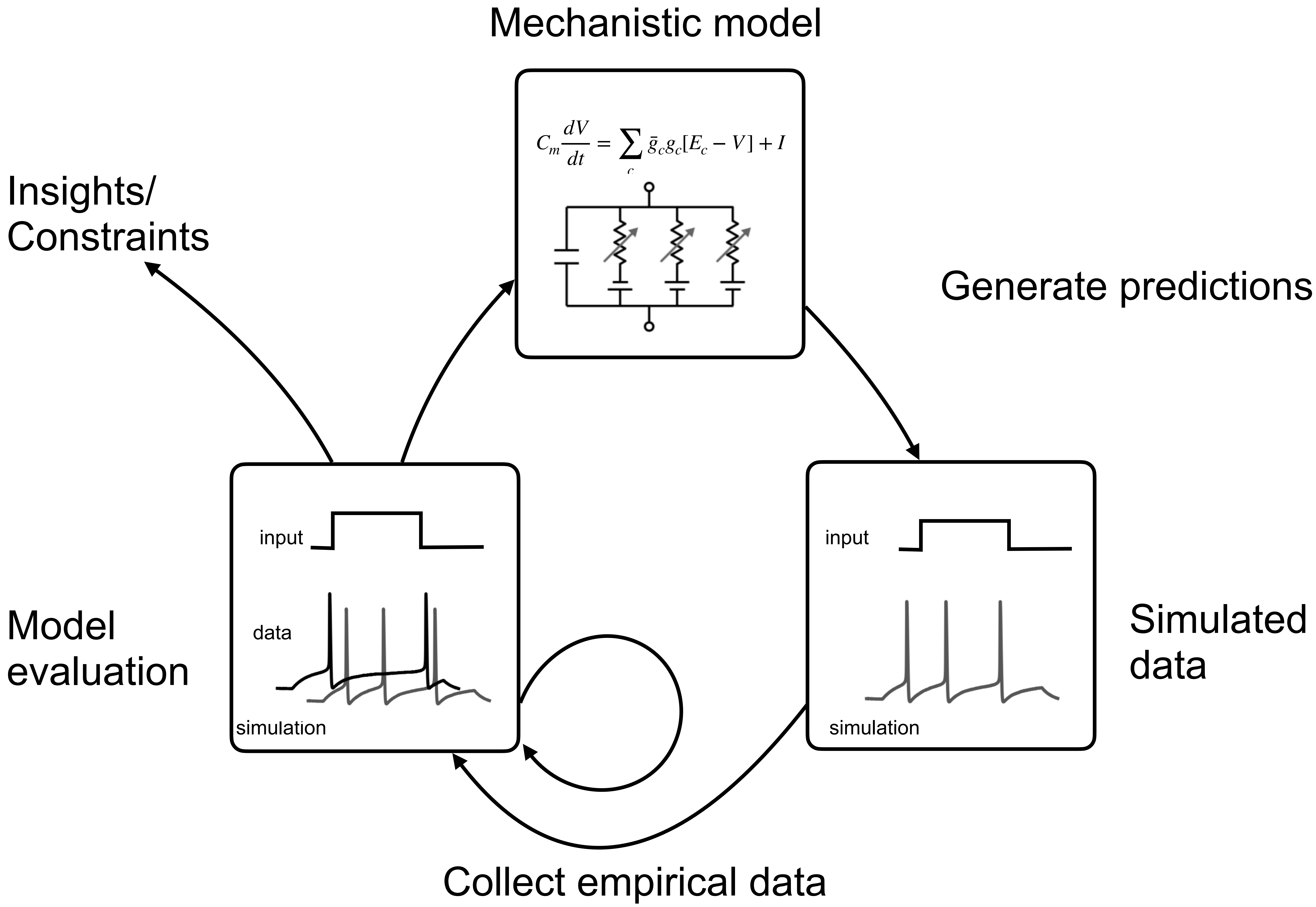
Generate predictions



Simulated data

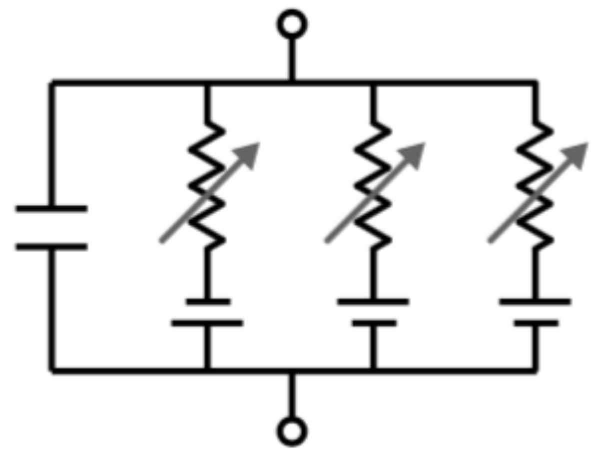

Mechanistic model
$C_m \frac{dV}{dt} = \sum_c \bar{g}_c g_c [E_c - V] + I$
Generate predictions
Simulated data
input
simulation
Collect empirical data
Model evaluation
input
data
simulation


Mechanistic model
$C_m \frac{dV}{dt} = \sum_c \bar{g}_c g_c [E_c - V] + I$
Generate predictions
input
simulation
Simulated data
Collect empirical data
Model evaluation
input
data
simulation


Mechanistic model
$C_m \frac{dV}{dt} = \sum_c \bar{g}_c g_c [E_c - V] + I$
Insights/ Constraints
Generate predictions
input
data
simulation
Model evaluation
input
simulation
Simulated data
Collect empirical data

Mechanistic model

$$C_m \frac{dV}{dt} = \sum_c \bar{g}_c g_c [E_c - V] + I$$



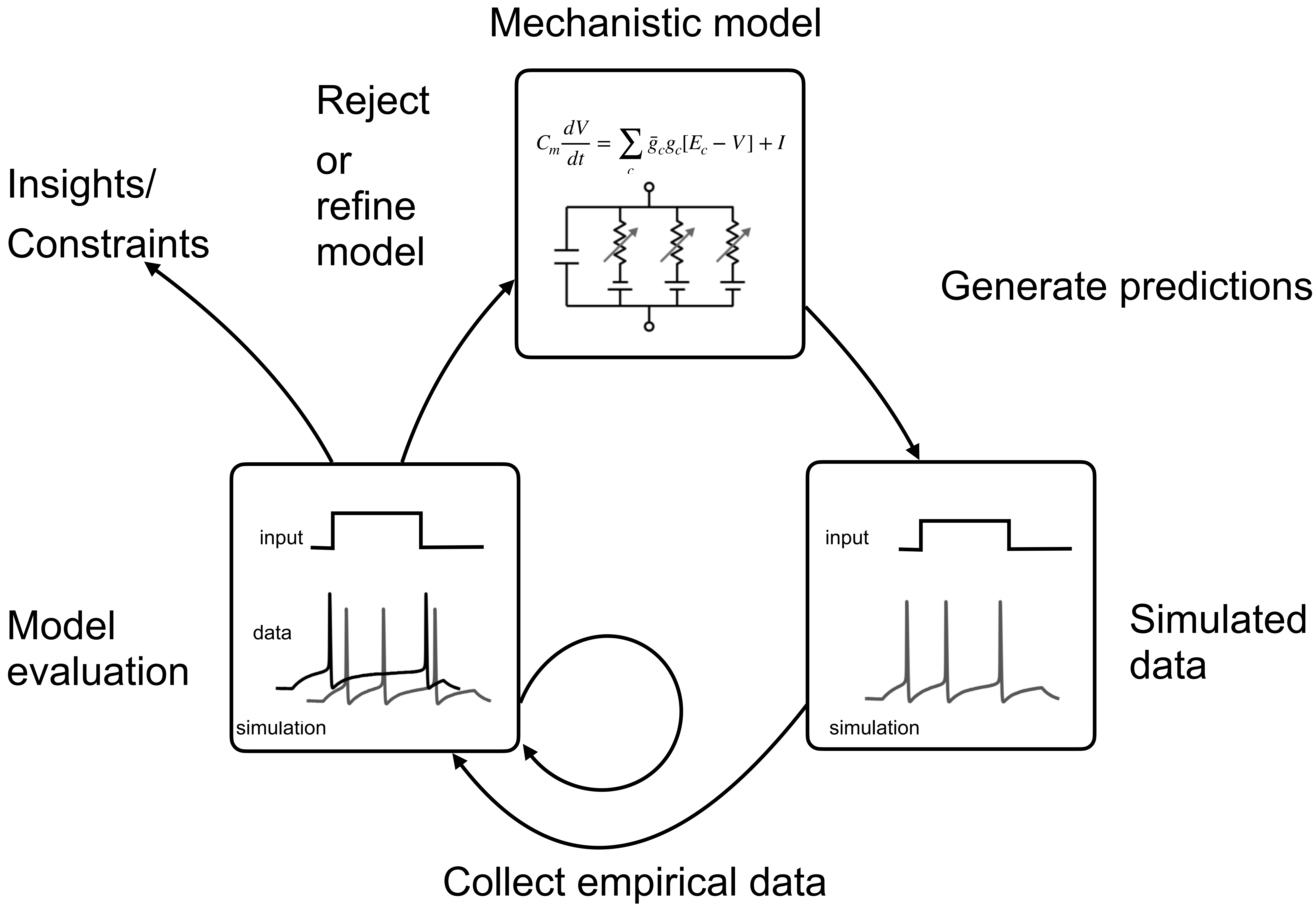
Mechanistic Models

- Goal: Understanding
- built from assumptions about mechanisms
- knowledge of (e.g.) dynamics
- interpretable parameters
- often hard to fit to data

Machine Learning

- Goal: Performance
- built with computation and generalization in mind
- data + inductive bias
- often no direct interpretation
- designed to fit data

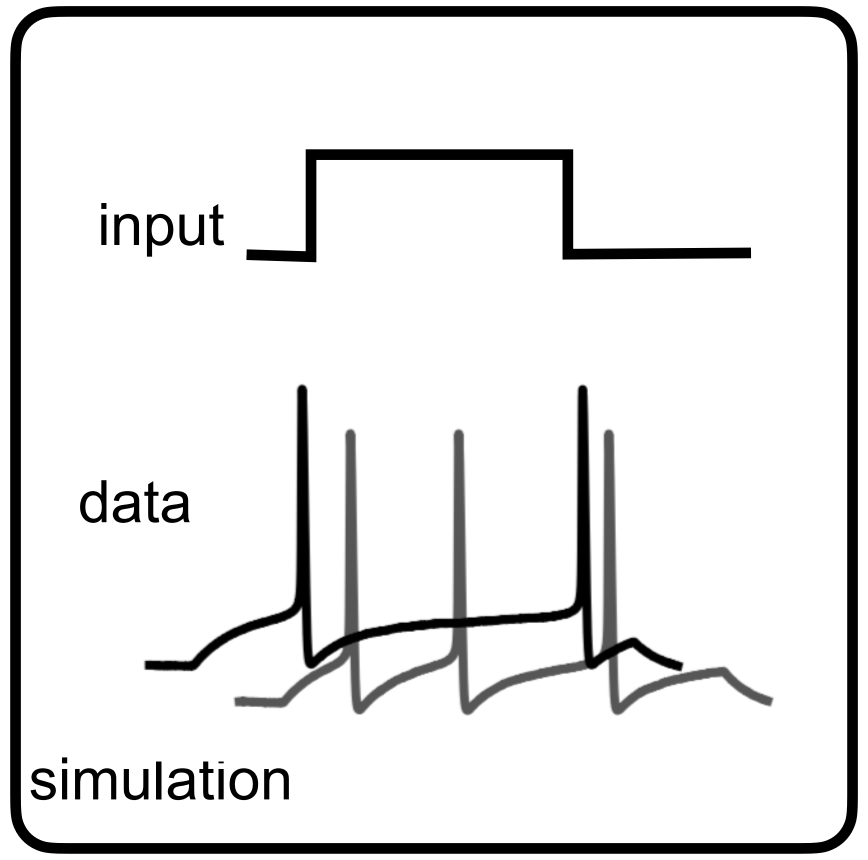
Goal: Combine strengths of both approaches to build tools for data-driven science.


Mechanistic model
$C_m \frac{dV}{dt} = \sum_c \bar{g}_c g_c [E_c - V] + I$
Reject
or
refine
model
Insights/
Constraints
Generate predictions
input
data
simulation
Model
evaluation
input
simulation
Simulated
data
Collect empirical data

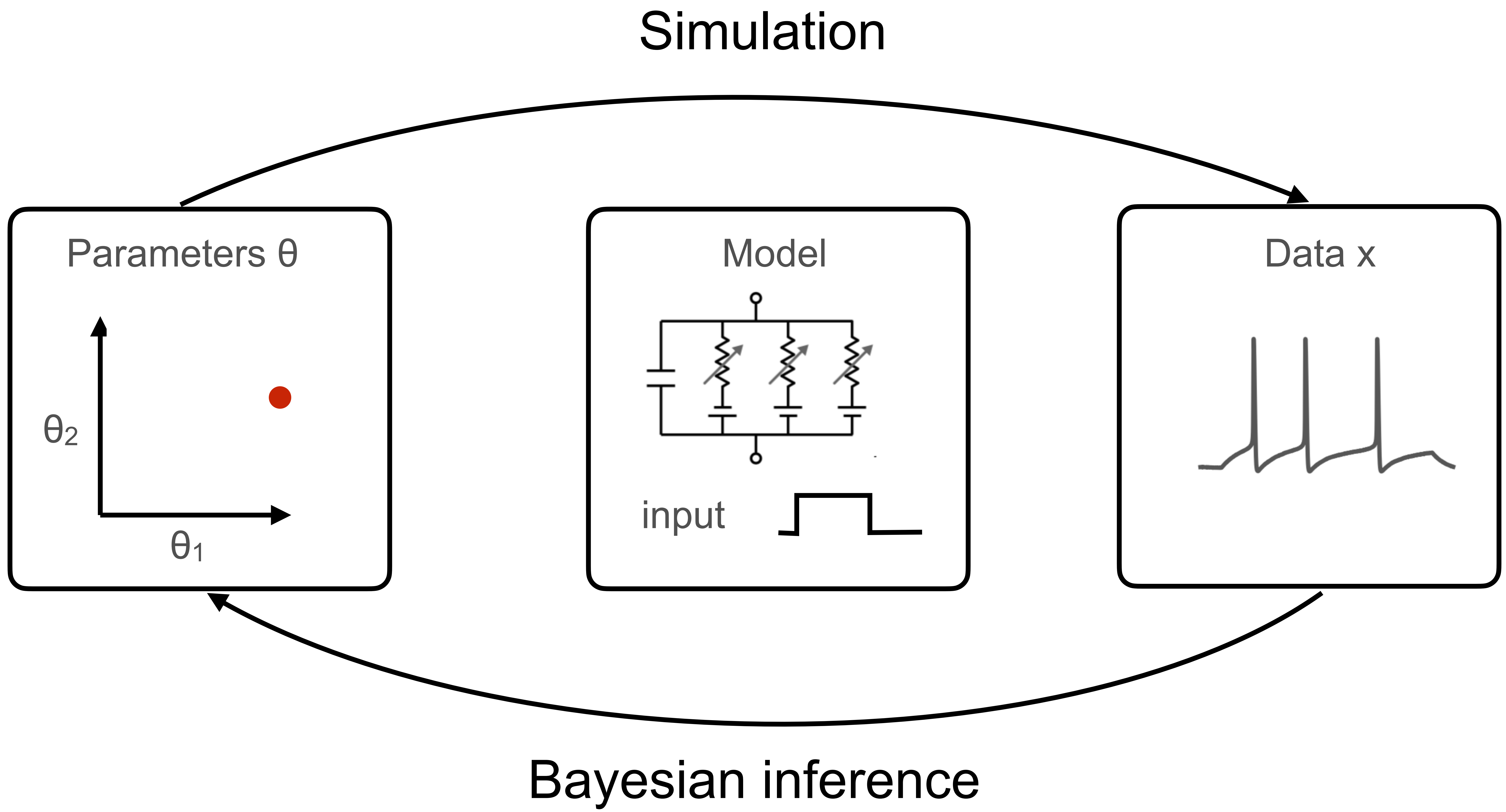
Key question: Which parameters of a mechanistic model are compatible with the data?

Answer: Bayesian inference!

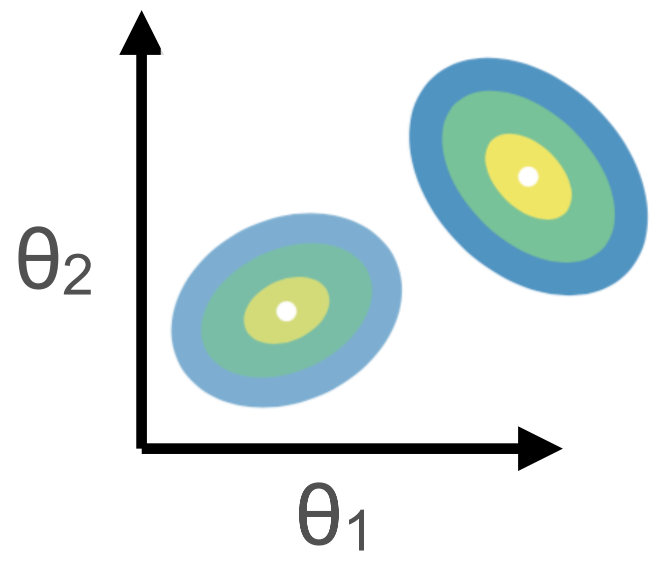
Model evaluation



Bayesian inference finds model-parameters which are consistent with data and prior knowledge



$$p(\theta \mid x) \propto p(x \mid \theta)\pi(\theta)$$



$$p(\theta \mid x) \propto p(x \mid \theta)\pi(\theta)$$

posterior: hard to compute

likelihood: often not tractable

For many mechanistic models, we can **simulate x**, but we cannot (easily) evaluate the likelihood **p(x|θ)**.

Models often defined through **black-box** simulators.

➡ A solution: simulation-based inference!

6.2 An intuitive first approach: Approximate Bayesian Computation

based on tutorial by Wilkinson 2016

Approximate Bayesian Computation

- ABC algorithms are a collection of methods used for performing inference on simulators:
  1. They do not require explicit knowledge of the likelihood function
  2. Inference is done using simulations from the model (they are ‘likelihood-free’)

- ABC methods are popular in biological disciplines, particularly genetics:
  1. Simple to implement
  2. Intuitive
  3. Embarrassingly parallelizable

Rejection Approximate Bayesian Computation. Rejection ABC

Rejection Algorithm

for $n = 1 \ldots N$ **do**
  sample $\boldsymbol{\theta}_n \sim p(\boldsymbol{\theta})$
  accept $\boldsymbol{\theta}_n$ with probability $p(\mathbf{x}_o|\boldsymbol{\theta}_n)$

Accepted θ are draws from the posterior distribution $p(\theta \mid x_o)$.

If the likelihood $p(x_o \mid \theta)$ is unknown:

'Mechanical' Rejection Algorithm

for $n = 1 \ldots N$ **do**
  sample $\boldsymbol{\theta}_n \sim p(\boldsymbol{\theta})$
  simulate $\mathbf{x}_n$ from model (equivalently, sample $\mathbf{x}_n \sim p(\mathbf{x}|\boldsymbol{\theta}_n)$)

Rejection Approximate Bayesian Computation. Rejection ABC

If $p(x_o)$ is small (or x_o continuous), we will rarely accept any θ. Instead, there is an approximate version:

Uniform Rejection Algorithm

for $n = 1 \ldots N$ **do**
  sample $\boldsymbol{\theta}_n \sim p(\boldsymbol{\theta})$
  sample $\mathbf{x}_n \sim p(\mathbf{x}|\boldsymbol{\theta}_n)$
  accept $\boldsymbol{\theta}_n$ if $\rho(\mathbf{x}_n, \mathbf{x}_o) \leq \epsilon$

ϵ reflects the tension between computability and accuracy:

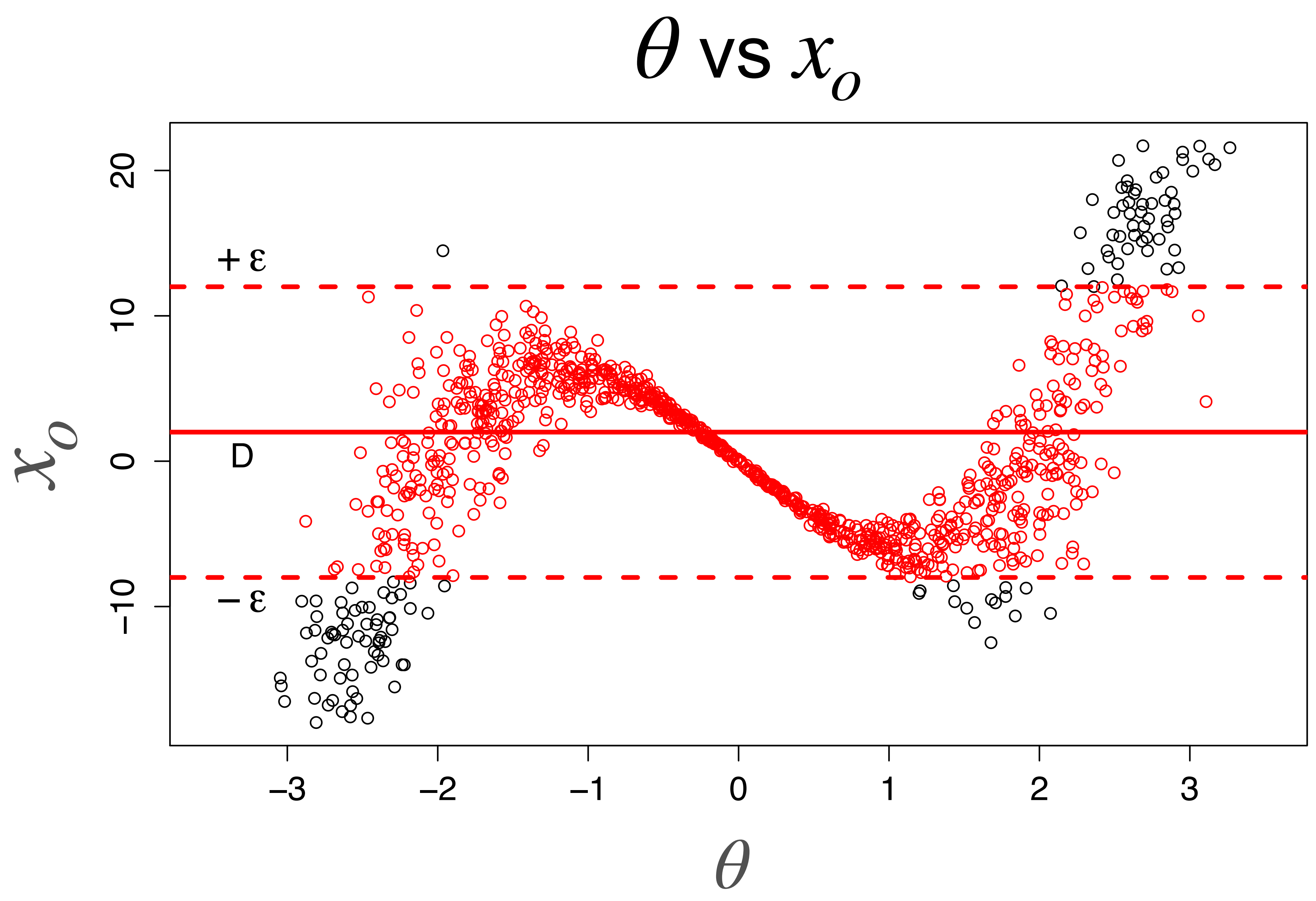
- As $\epsilon \rightarrow \infty$, we get observations from the prior $p(\theta)$.
- If $\epsilon = 0$, we generate observations from $p(\theta \,|\, x_o)$.

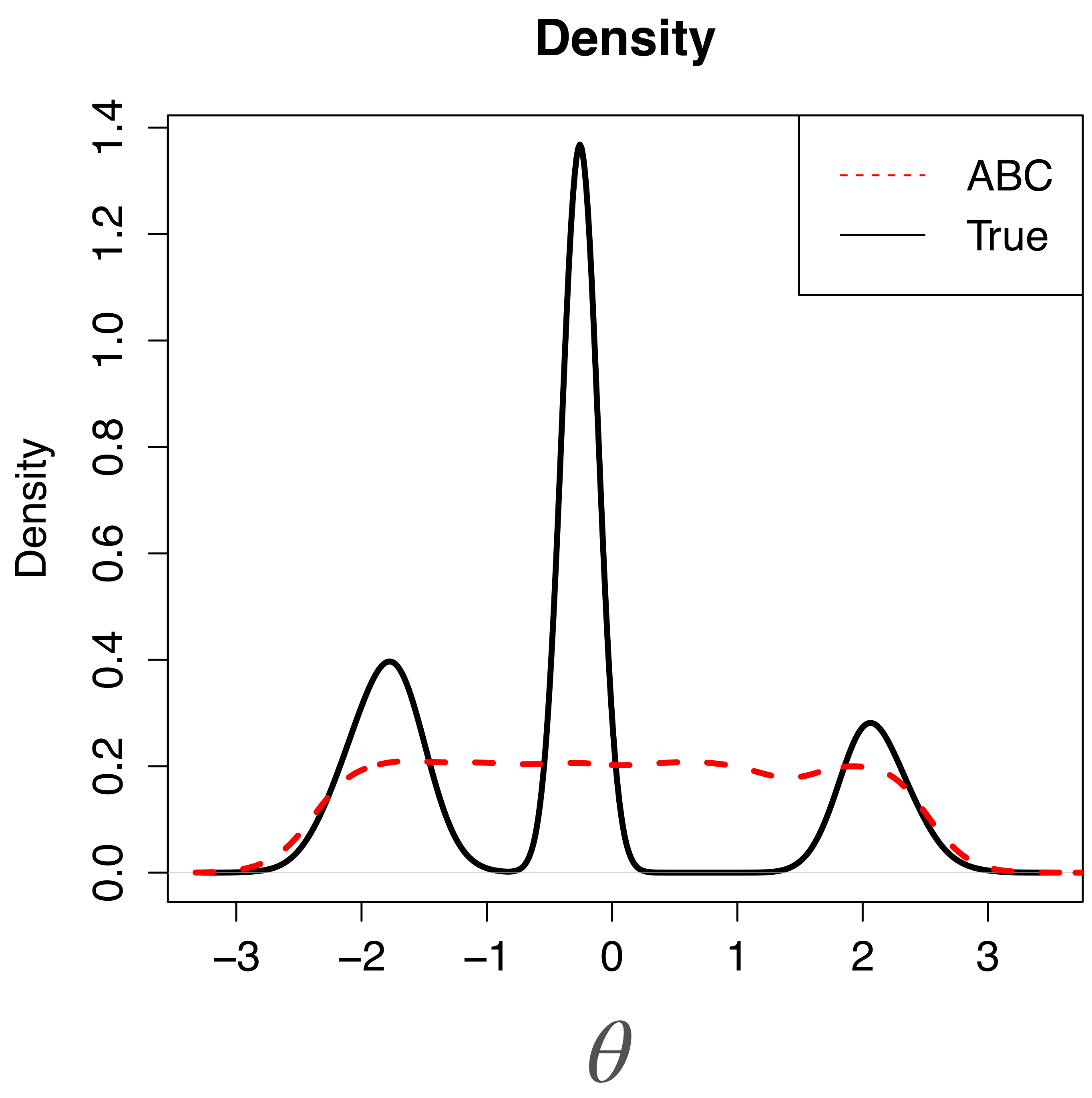
An example

$$\theta \sim \mathcal{U}[-10,10], x \sim \mathcal{N}(2(\theta+1)\theta(\theta-2), 0.1+\theta^2)$$

$$\rho(x, x_o) = |x - x_o|, x_o = 2$$

Rejection ABC. $\epsilon = 10$





$$\theta \sim \mathcal{U}[-10,10],\, x \sim \mathcal{N}(2(\theta+1)\theta(\theta-2), 0.1+\theta^2)$$

$$\rho(x, x_o) = |x - x_o|,\, x_o = 2$$

image from Wilkinson 2016 tutorial

Rejection ABC. $\epsilon = 7.5$

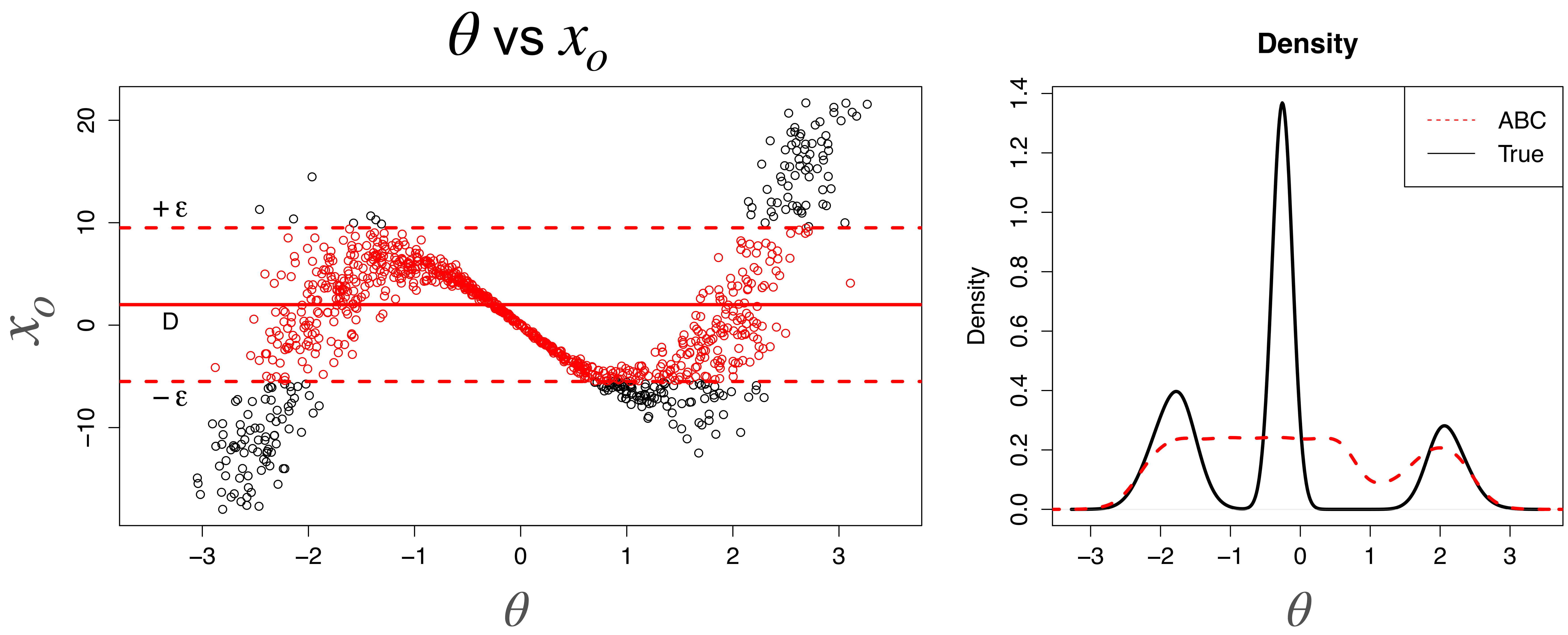
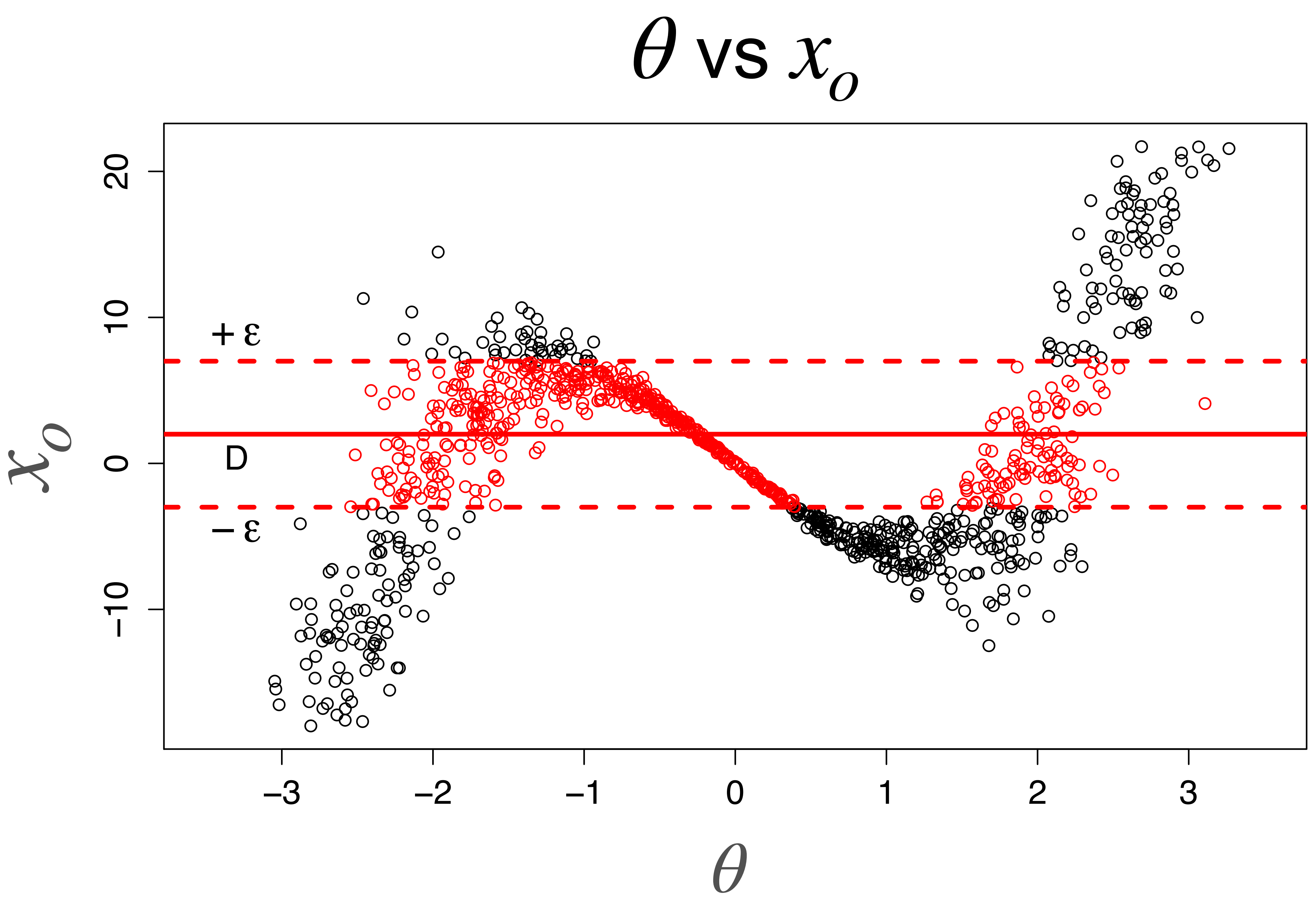


image from Wilkinson 2016 tutorial

Rejection ABC. $\epsilon = 5$



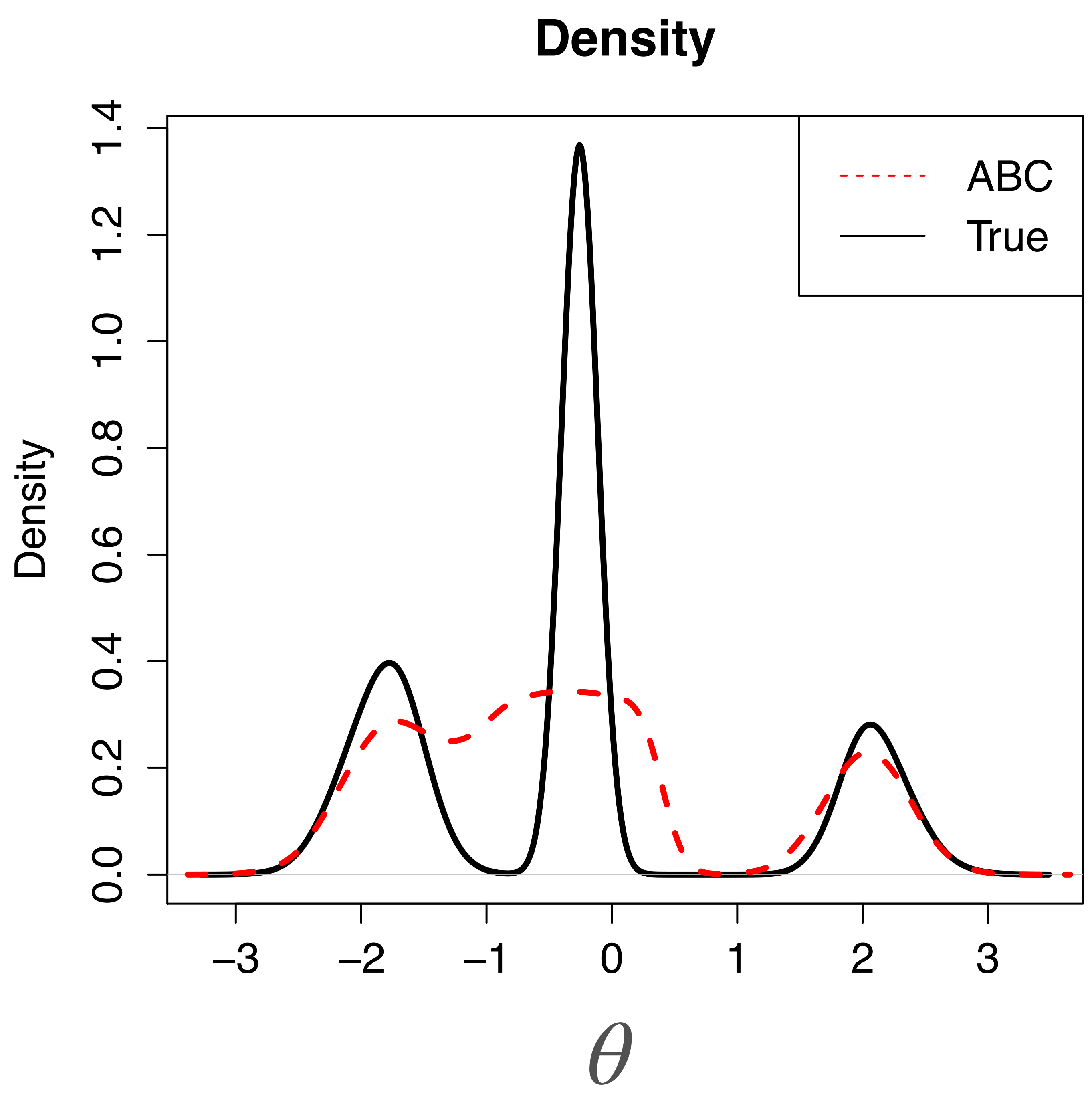


image from Wilkinson 2016 tutorial

Rejection ABC. $\epsilon = 2.5$

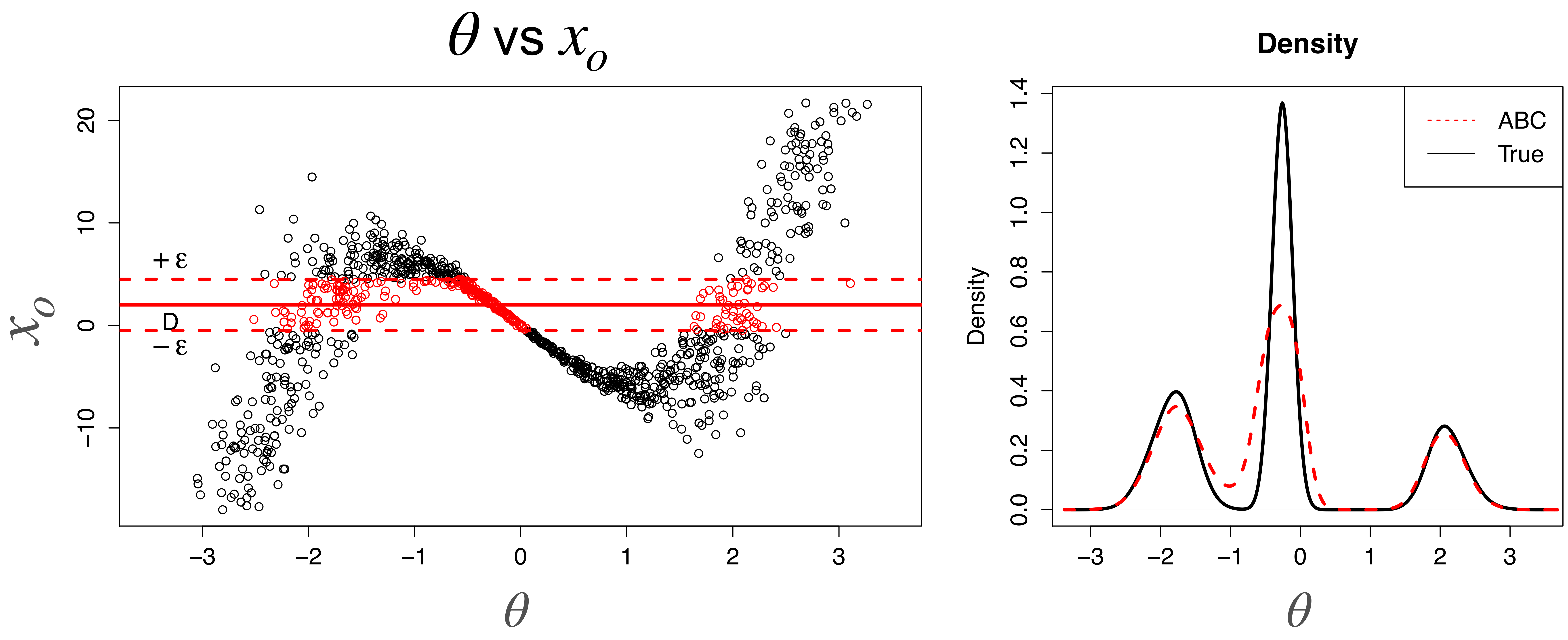


image from Wilkinson 2016 tutorial

Rejection ABC. $\epsilon = 1$

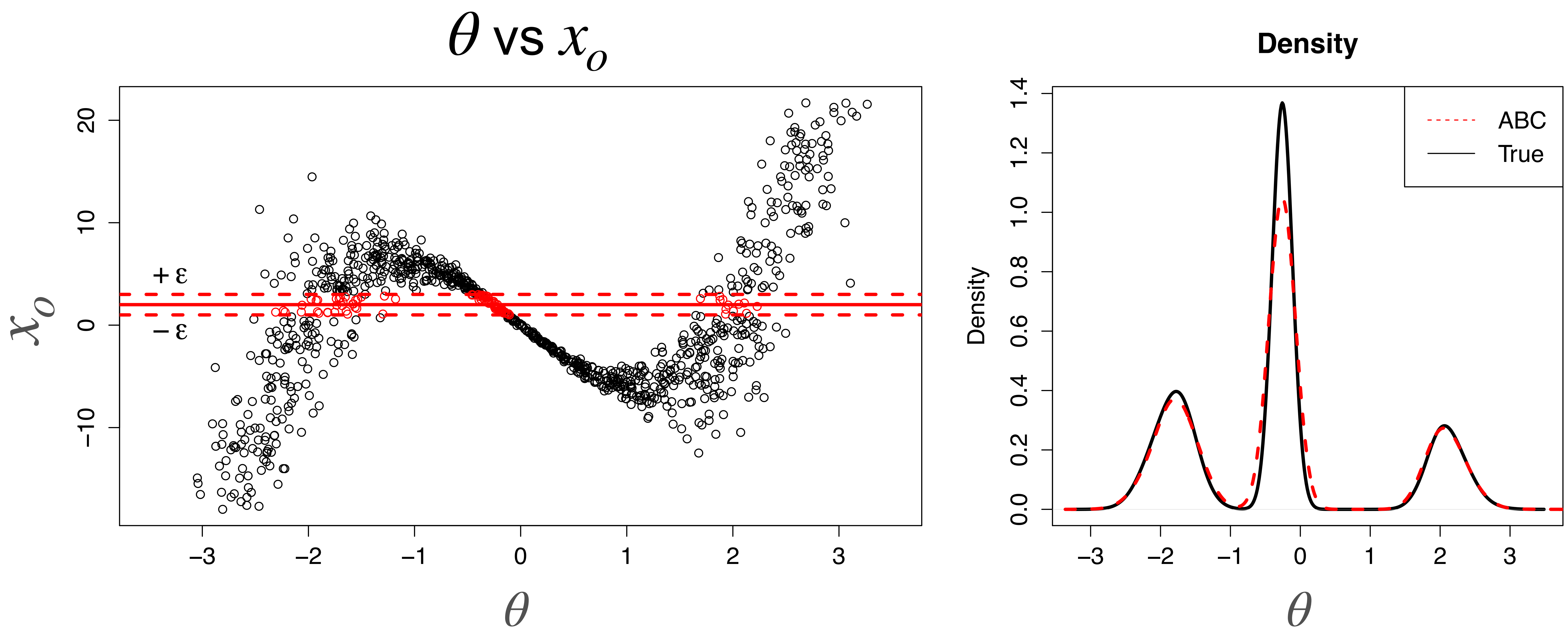


image from Wilkinson 2016 tutorial

Rejection ABC

If the data are too high dimensional, we never observe simulations that are 'close' to the measured data - curse of dimensionality.

Reduce the dimensionality using summary statistics $S(x_o)$.

Approximate Rejection Algorithm With Summaries

for $n = 1 \ldots N$ **do**
- sample $\boldsymbol{\theta}_n \sim p(\boldsymbol{\theta})$
- sample $\mathbf{x}_n \sim p(\mathbf{x}|\boldsymbol{\theta}_n)$
- accept $\boldsymbol{\theta}_n$ if $\rho(S(\mathbf{x}_n), S(\mathbf{x}_o)) \leq \epsilon$

Key challenges for ABC

Accuracy in ABC is determined by:

1. Tolerance ϵ, which controls the 'ABC error'
   - there are more efficient algorithms that allow us to use small ϵ
   - constrained by how much computation we can do. Rules out expensive simulators

2. Summary statistic $S(x_o)$, which controls 'information loss'
   - inference is based on $p(\theta \,|\, S(x_o))$ rather than $p(\theta \,|\, x_o)$
   - expert-knowledge and machine-learning tools can be used to find informative summaries

Some last comments about ABC

- Can we get more accurate and efficient algorithms (scaling to more parameters and summary statistics)?

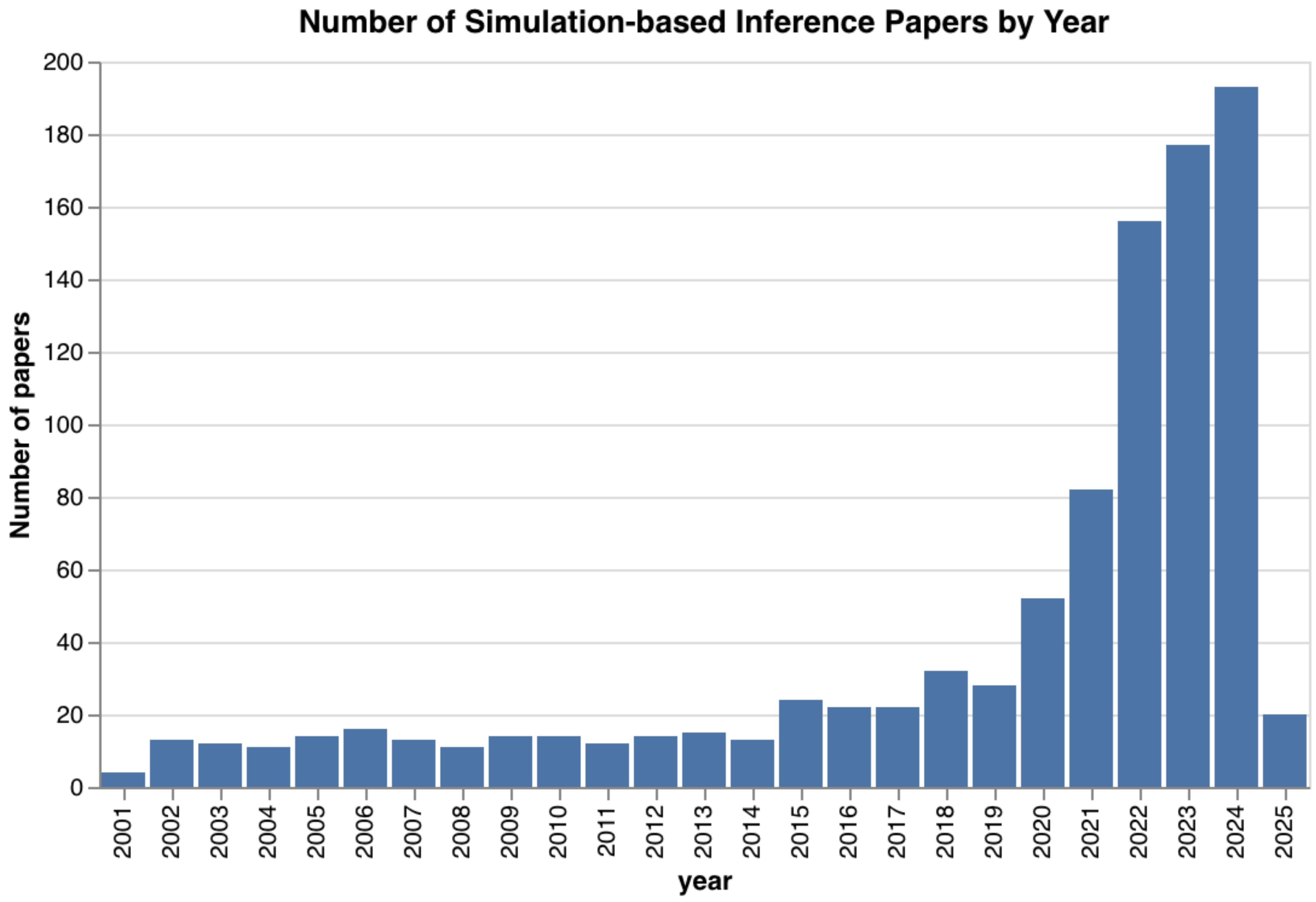
- How to choose summary statistics?

- How to deal with expensive simulators?

- Many, many ABC algorithms (SMC-ABC, Regression-ABC, GP-ABC, Hamiltonian-ABC…)

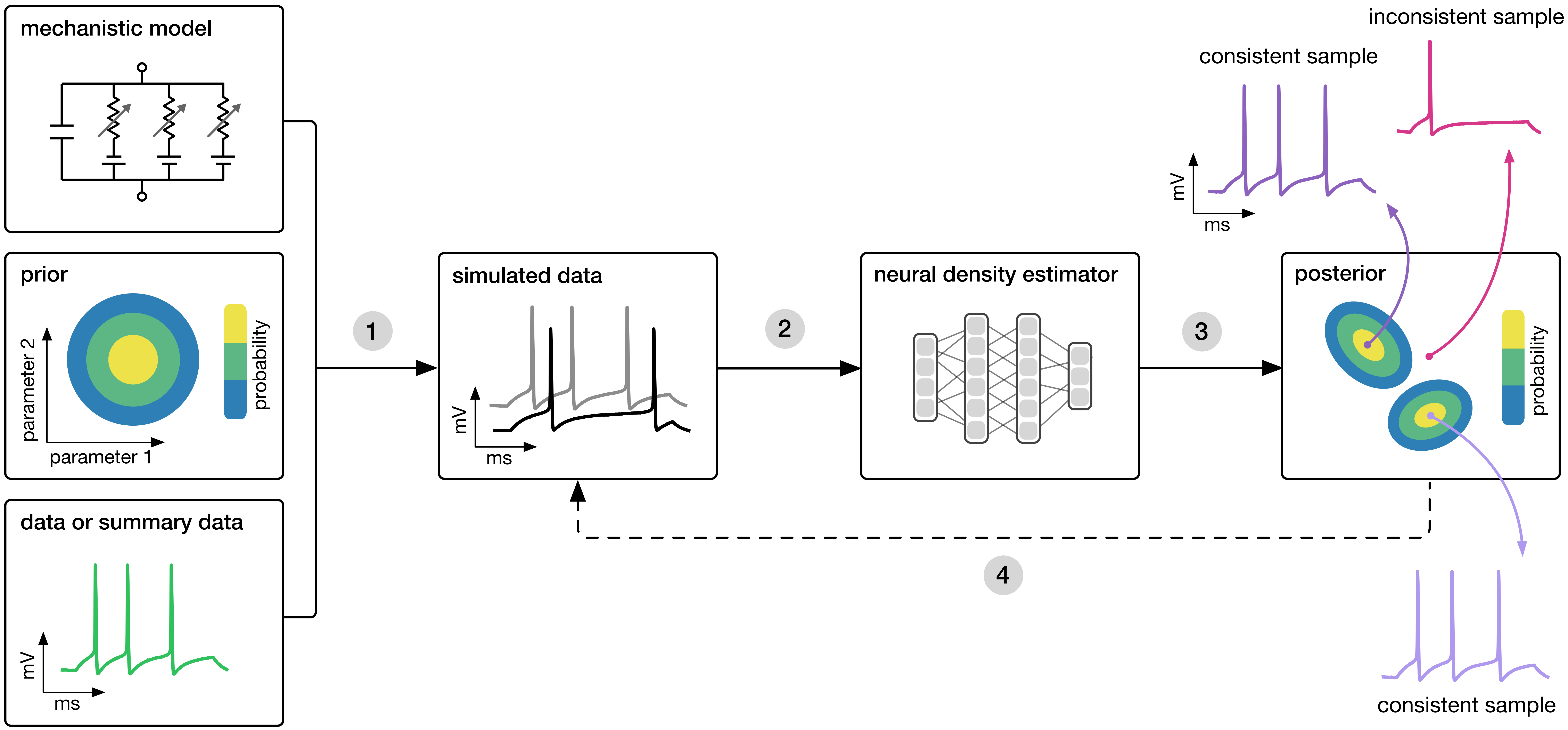
6.3 Can we do better? Simulation-based inference with neural networks

Simulation-based inference is rapidly expanding thanks to recent developments in (probabilistic) deep learning



https://simulation-based-inference.org/

Teaser: train neural networks to identify data-compatible models



Some general aims of the next two weeks

- An appreciation of how simulators and data can be combined to generate insights.
- Probability theory as the mathematical language for performing inference.
- An overview of how the latest advances in machine learning (in particular, neural networks) can be used for Bayesian inference.

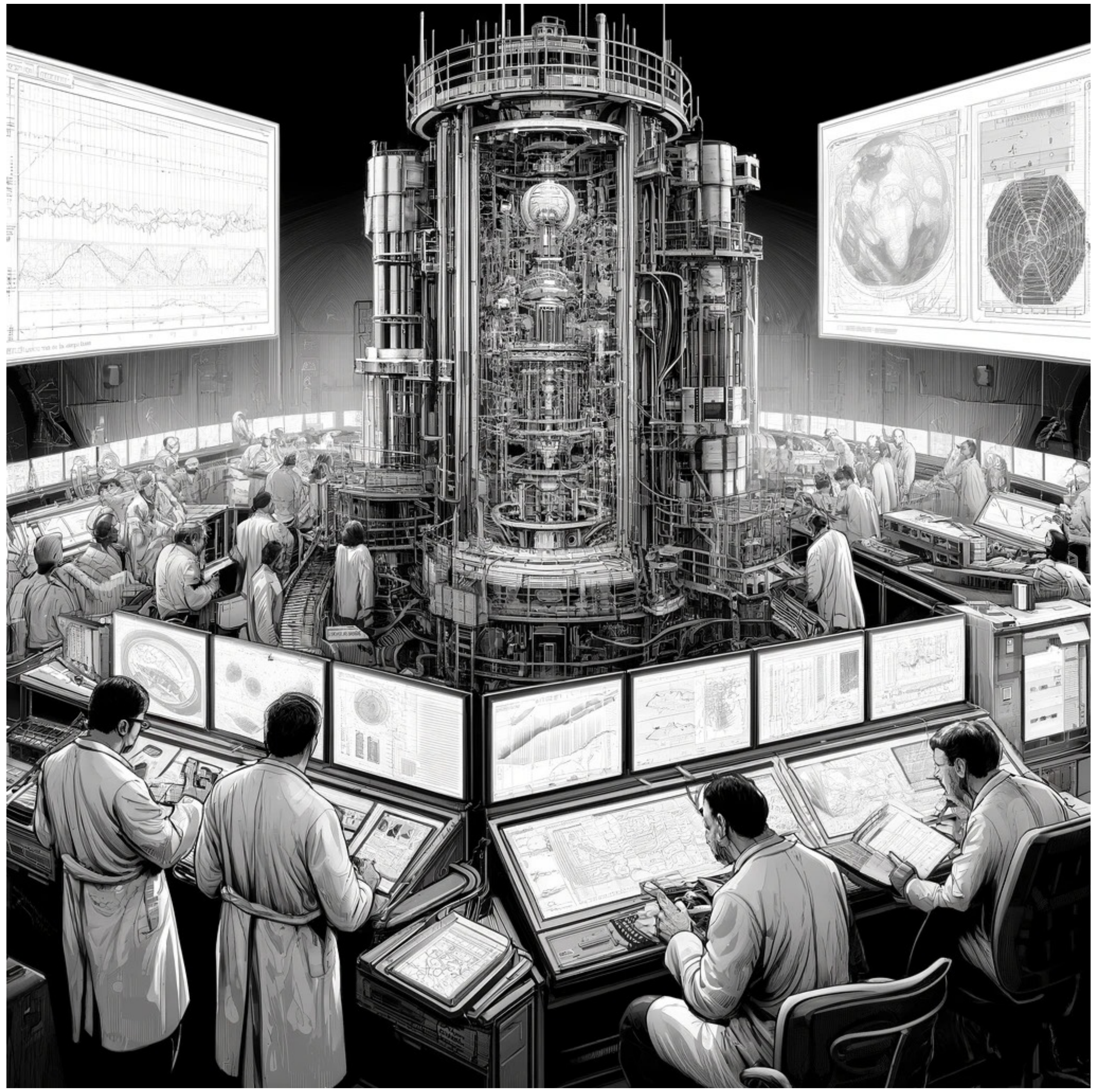
Course Outline for the next two weeks

- Week 2: ABC, neural density estimation, NPE, normalising flows, advanced topics in SBI
- Week 3: SBI hands-on tutorial, project work

6.4 Organisational matters

Communication

- To communicate with us, email pedro.goncalves@kuleuven.be, jonas.beck@uni-tuebingen.de
- We will provide all lecture material on GitHub (https://github.com/berenslab/AIMS2025-NeuroSimInf).



Evaluation

- Exam this Friday: you will have 30min to answer pen and paper questions.
- Project evaluation on Thursday 20.
- Final grade will be an average of the weekly grades.

Simulation-based inference: How to go from simulator and data to insight?

Lecture 6: Introduction

- For mechanistic insights, we need to combine mechanistic models and data.
- Probability theory as a framework for reasoning with data, and quantifying our uncertainty about it.
- How can we make *causal* statements from data?

- **Simulation-based inference: a toolkit for making sense of the real world with simulations**

Simulation-based inference: How to go from simulator and data to insight?

Lecture 6: Introduction

- ABC-based methods are popular methods for doing simulation-based inference.
- ABC is typically simple to implement, intuitive and embarrassingly parallelizable.
- But, ABC does not scale well with the number of parameters to infer or with the dimensionality of the summary statistics.

Further reading on ABC

- Turner, Brandon M., and Trisha Van Zandt. "A tutorial on approximate Bayesian computation." Journal of Mathematical Psychology 56.2 (2012): 69-85.

- Lintusaari, Jarno, et al. "Fundamentals and recent developments in approximate Bayesian computation." Systematic biology 66.1 (2017): e66-e82.

- ABC Tutorial (video): https://cds.cern.ch/record/2067048