Simulation-based inference

Lecture 1: Introduction

January 2024

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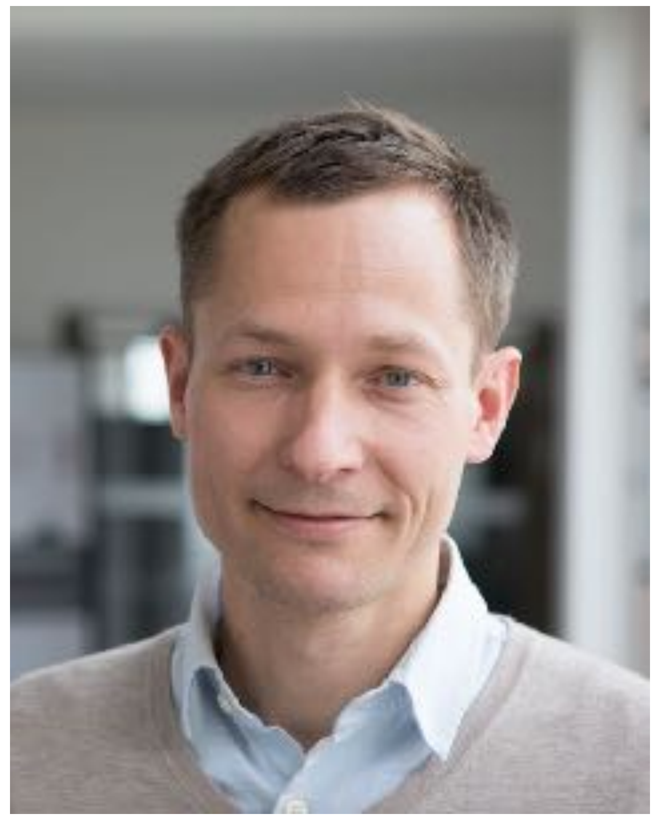
Machine Learning in Science
Excellence Cluster Machine Learning
Tübingen AI Center
Bernstein Center for. Comp. Neuroscience

Who we are ...



Jakob Macke

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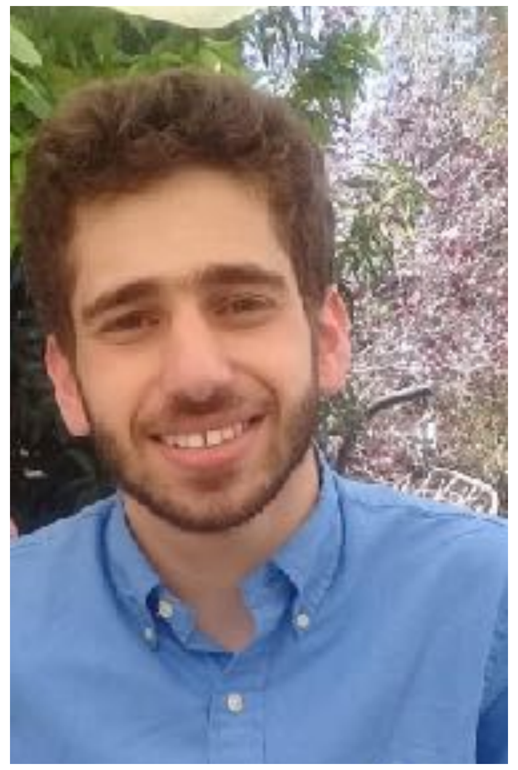


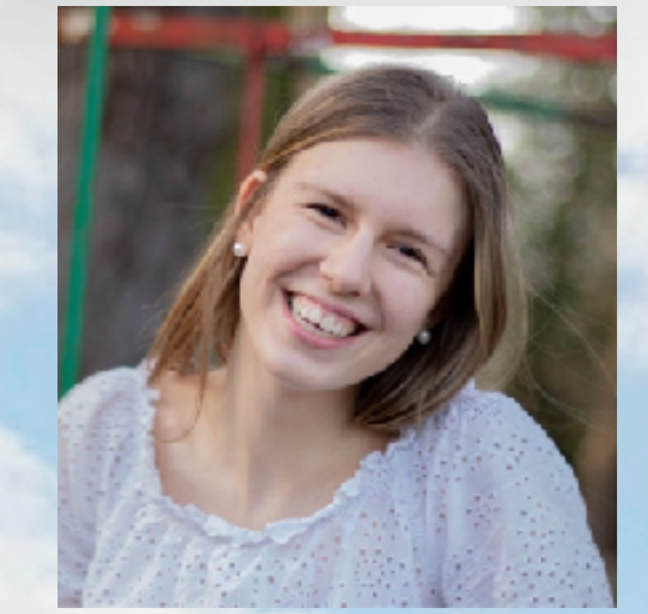
Guy Moss

Manuel Glöckler

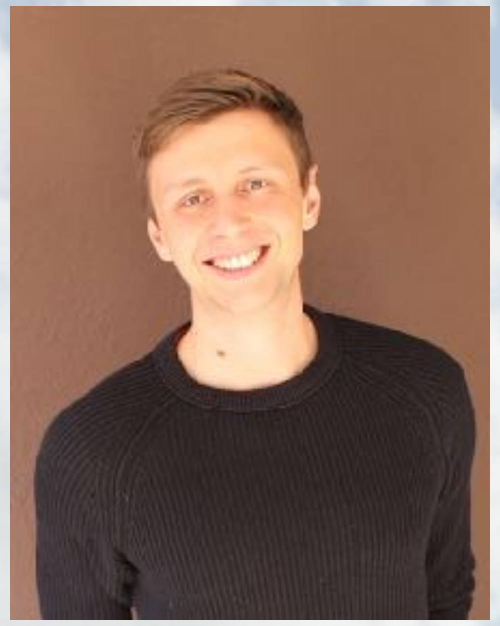
Machine Learning in Science

Computational Neuroscience and Machine Learning

Auguste
Schulz



Nastya
Krouglova



Michael
Deistler

Rachel
Rapp

Serkan
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nerf VIB KU LEUVEN imec

We are hiring students and postdocs!

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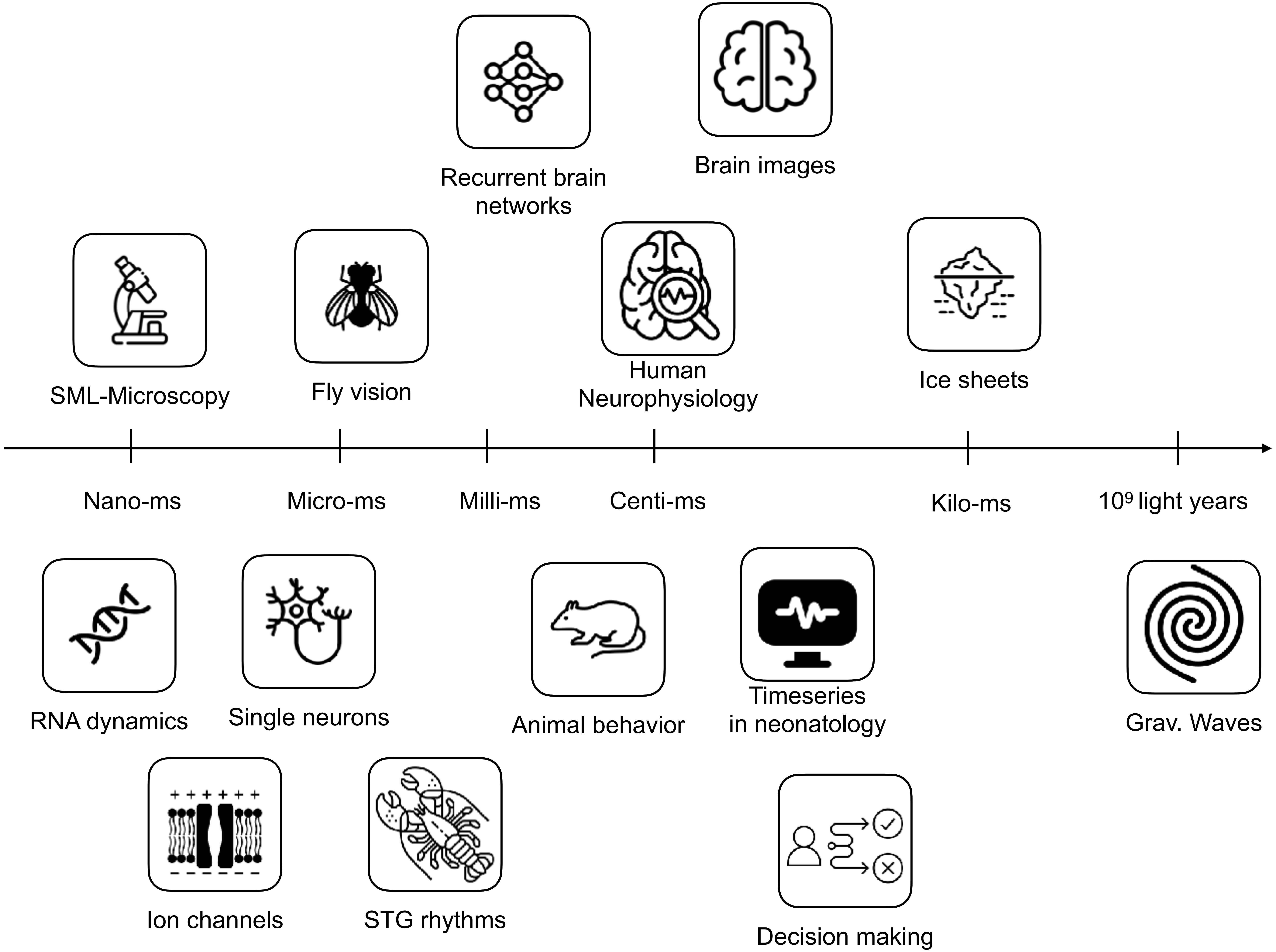
… and what we do (when not teaching)

Scientific Modelling **Machine Learning**

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

Applications: Focus on neuroscience


Recurrent brain networks
Brain images
SML-Microscopy
Fly vision
Human Neurophysiology
Ice sheets
Nano-ms
Micro-ms
Milli-ms
Centi-ms
Kilo-ms
10^9 light years
RNA dynamics
Single neurons
Animal behavior
Timeseries in neonatology
Grav. Waves
Ion channels
STG rhythms
Decision making

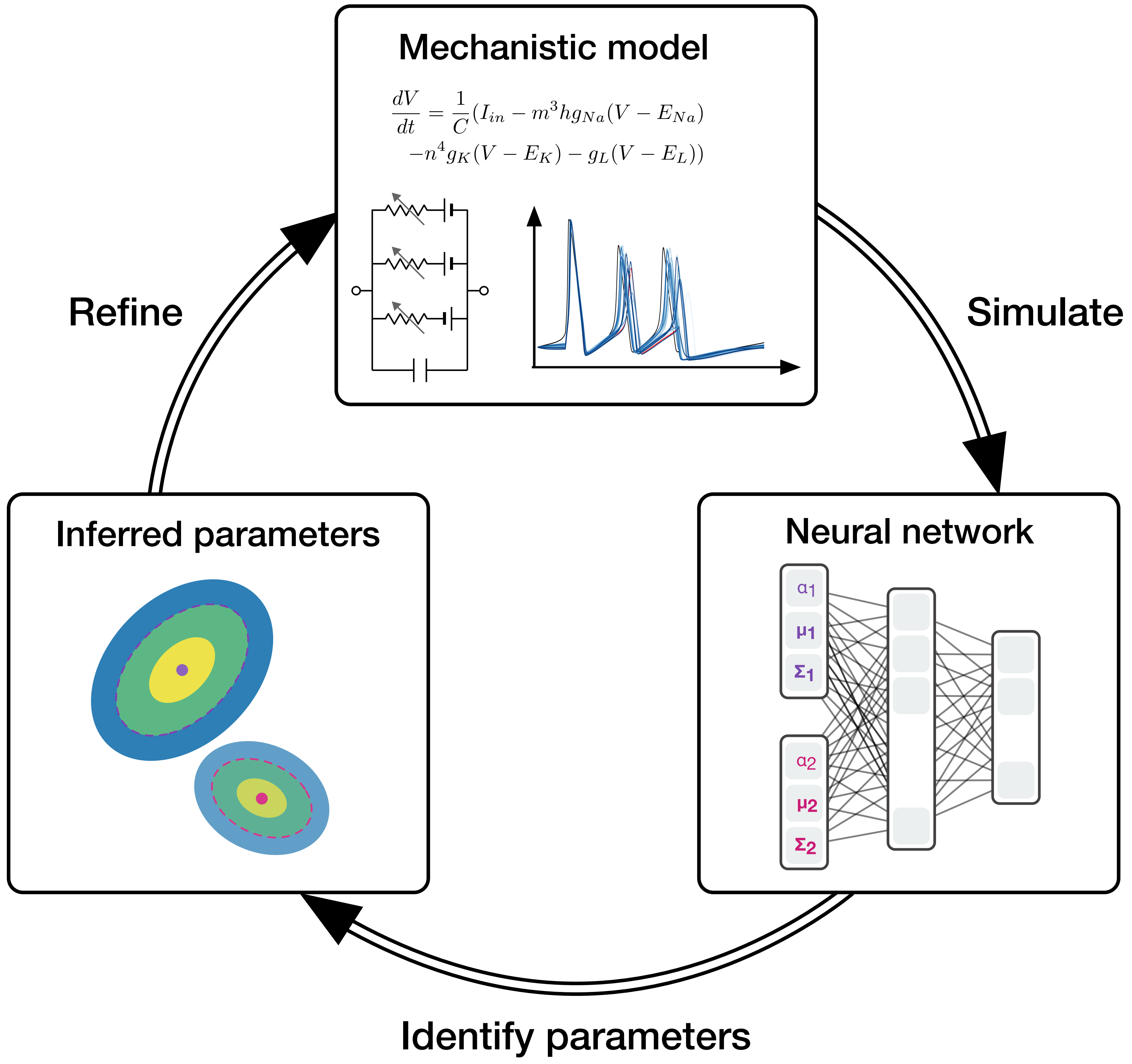
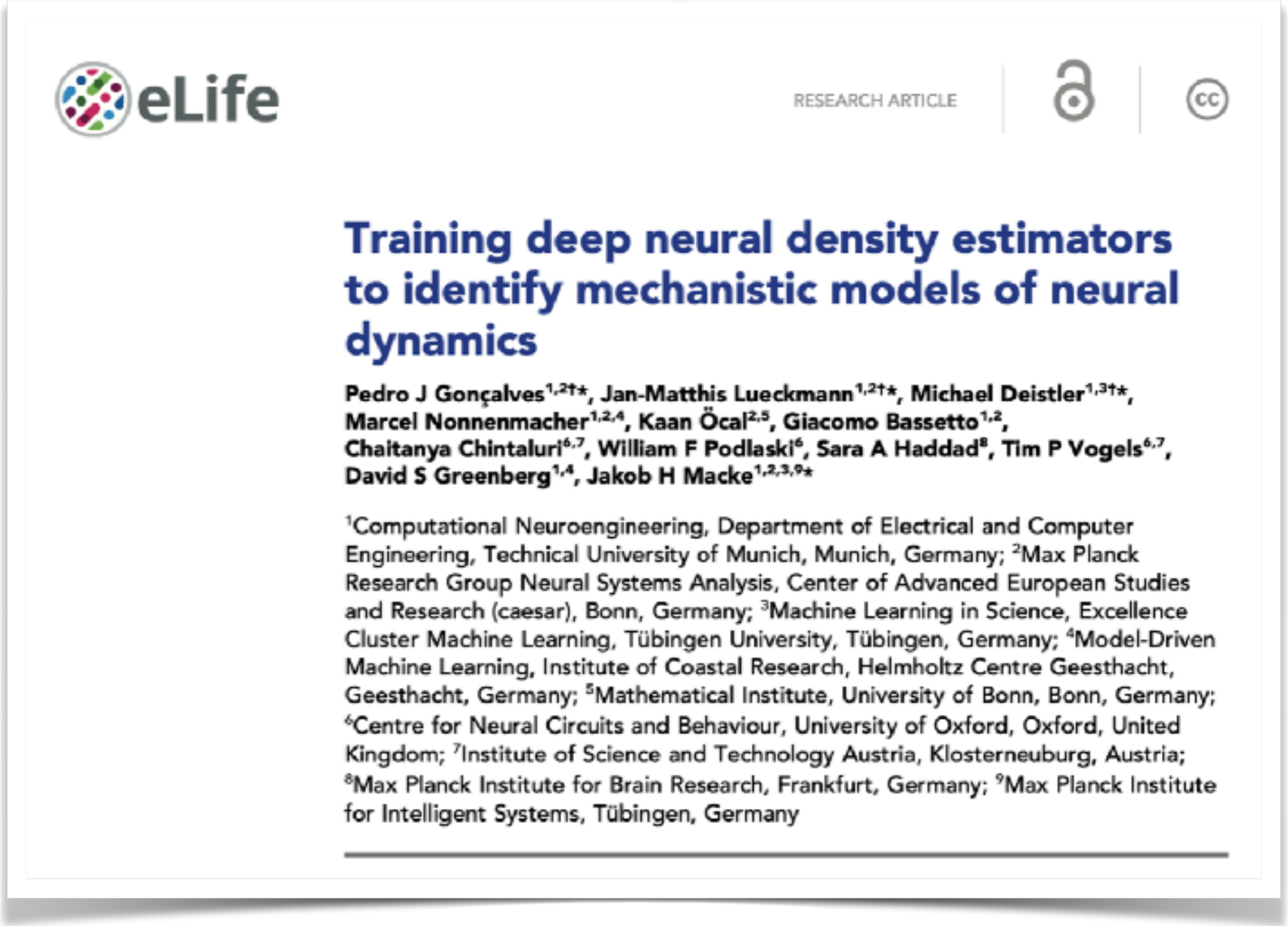


Image credit: Ryan Garcia, Simons Foundation



eLife

RESEARCH ARTICLE

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

Pedro J Gonçalves[1,2†*], Jan-Matthis Lueckmann[1,2†*], Michael Deistler[1,3†*], Marcel Nonnenmacher[1,2,4], Kaan Öcal[2,5], Giacomo Bassetto[1,2], Chaitanya Chintaluri[6,7], William F Podlaski[6], Sara A Haddad[8], Tim P Vogels[6,7], David S Greenberg[1,4], Jakob H Macke[1,2,3,9*]

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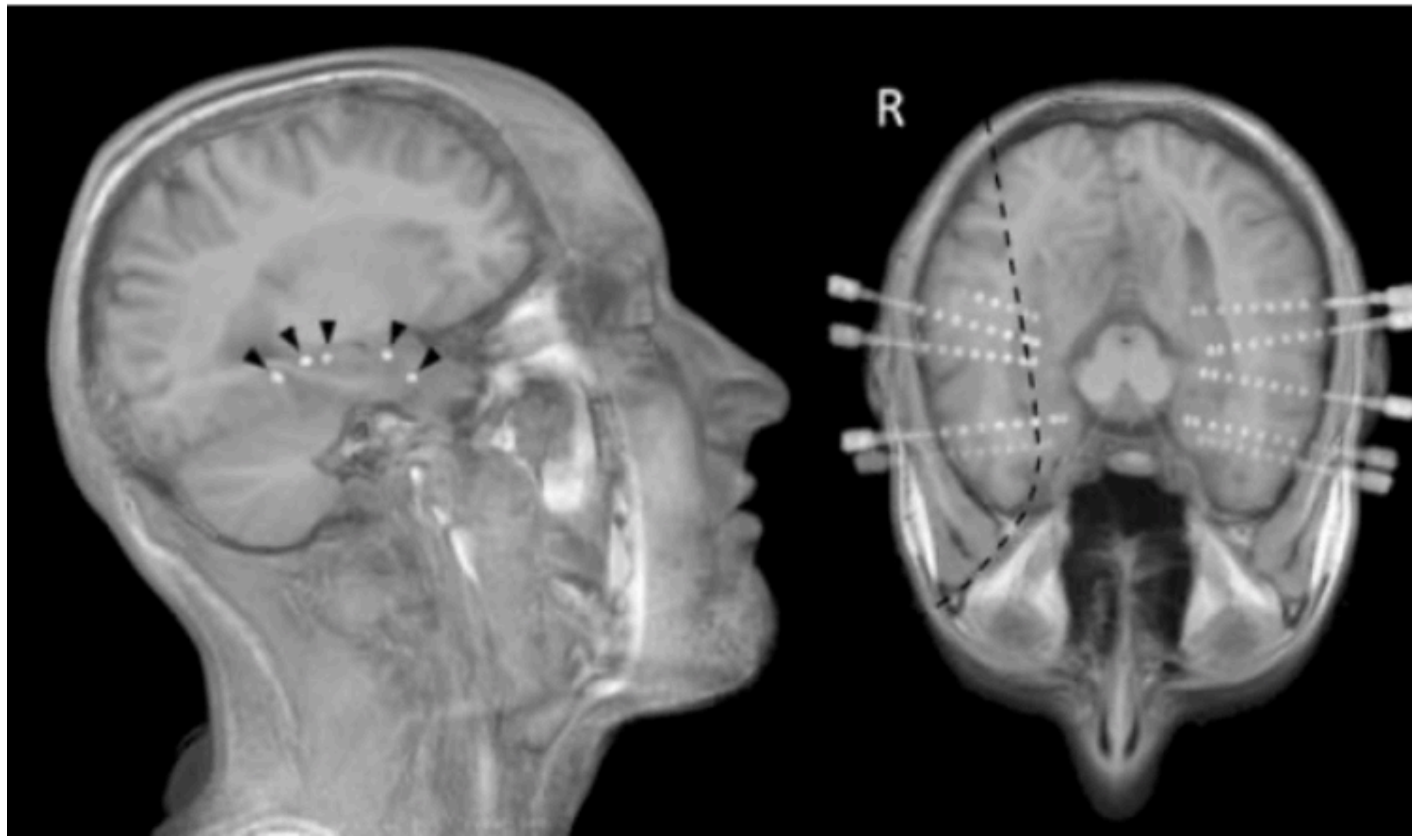
nature methods
ARTICLES
https://doi.org/10.1038/s41592-021-01236-x
Check for updates

Deep learning enables fast and dense single-molecule localization with high accuracy

Artur Speiser[1,2,3,4,12], Lucas-Raphael Müller[5,6,12], Philipp Hoess[5], Ulf Matti[5], Christopher J. Obara[7], Wesley R. Legant[8,9,10], Anna Kreshuk[5], Jakob H. Macke[1,2,3,11,13], Jonas Ries[5,13] and Srinivas C. Turaga[7,13] ✉

Images from Rezah Ershadi + Reinhard Drews

Image: Shutterstock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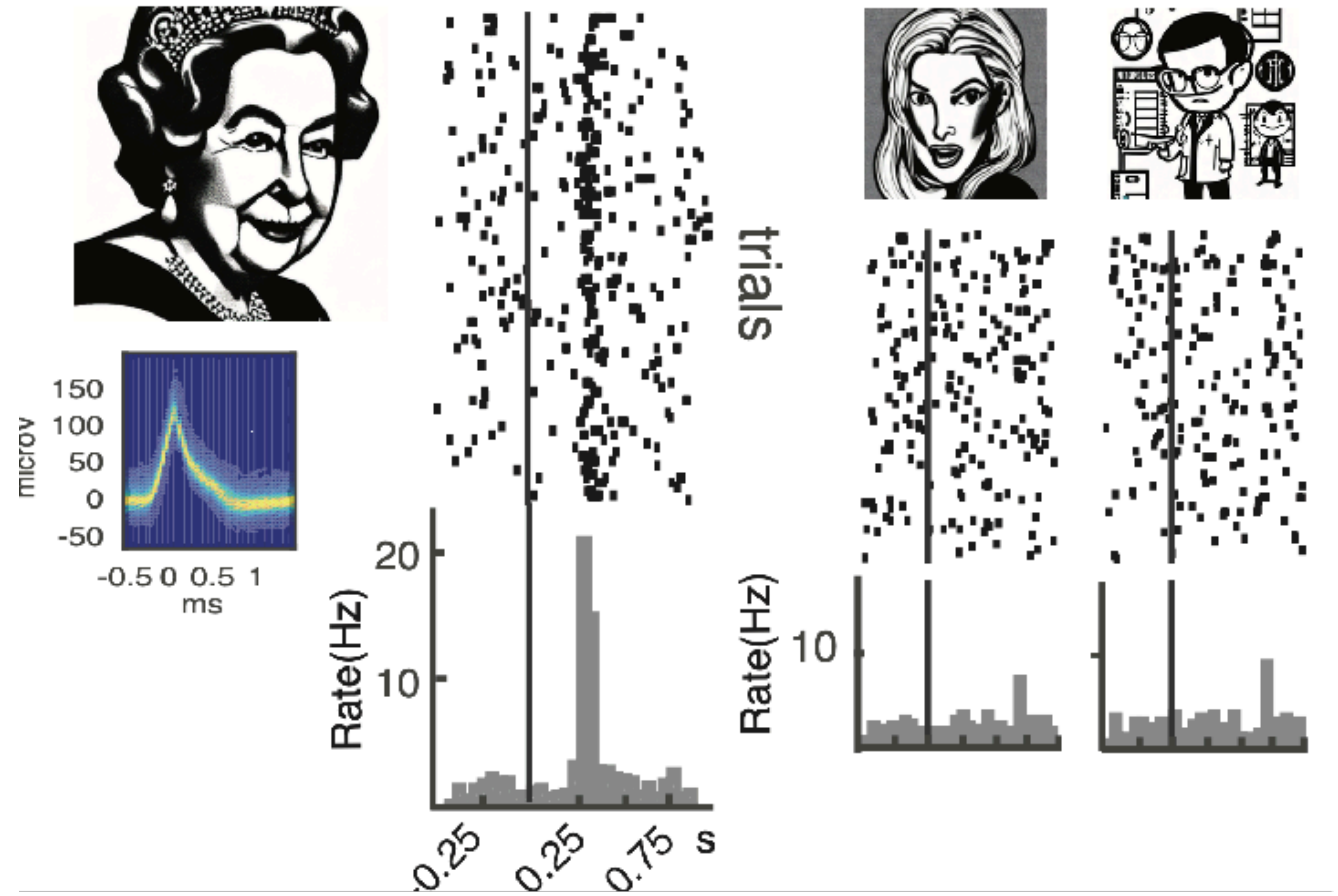
microv
150
100
50
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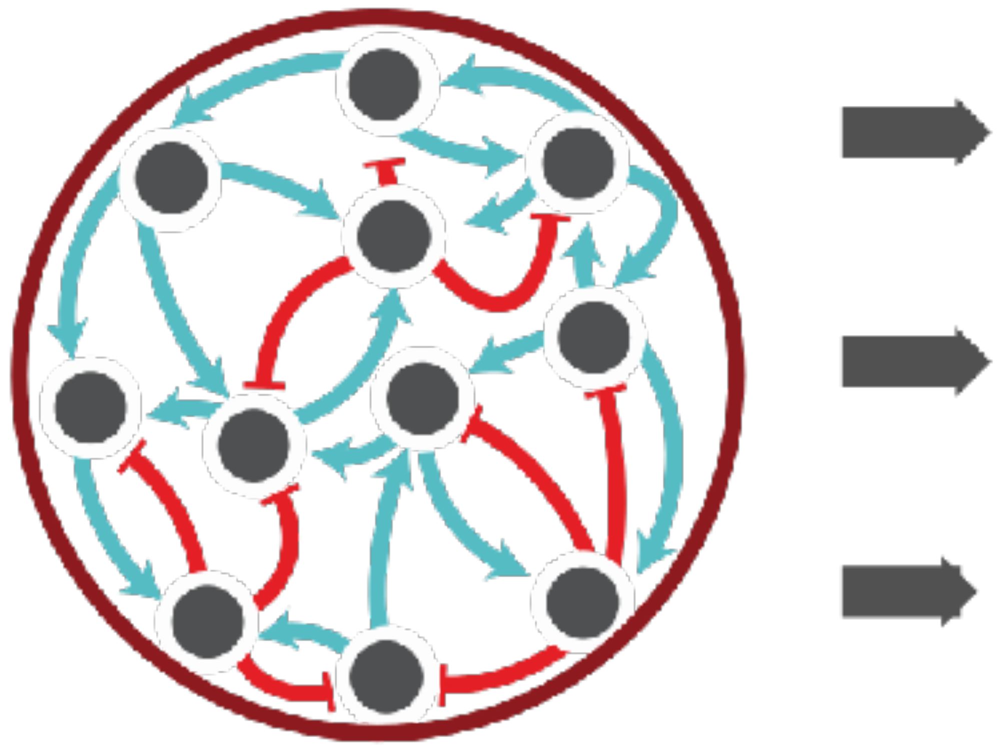
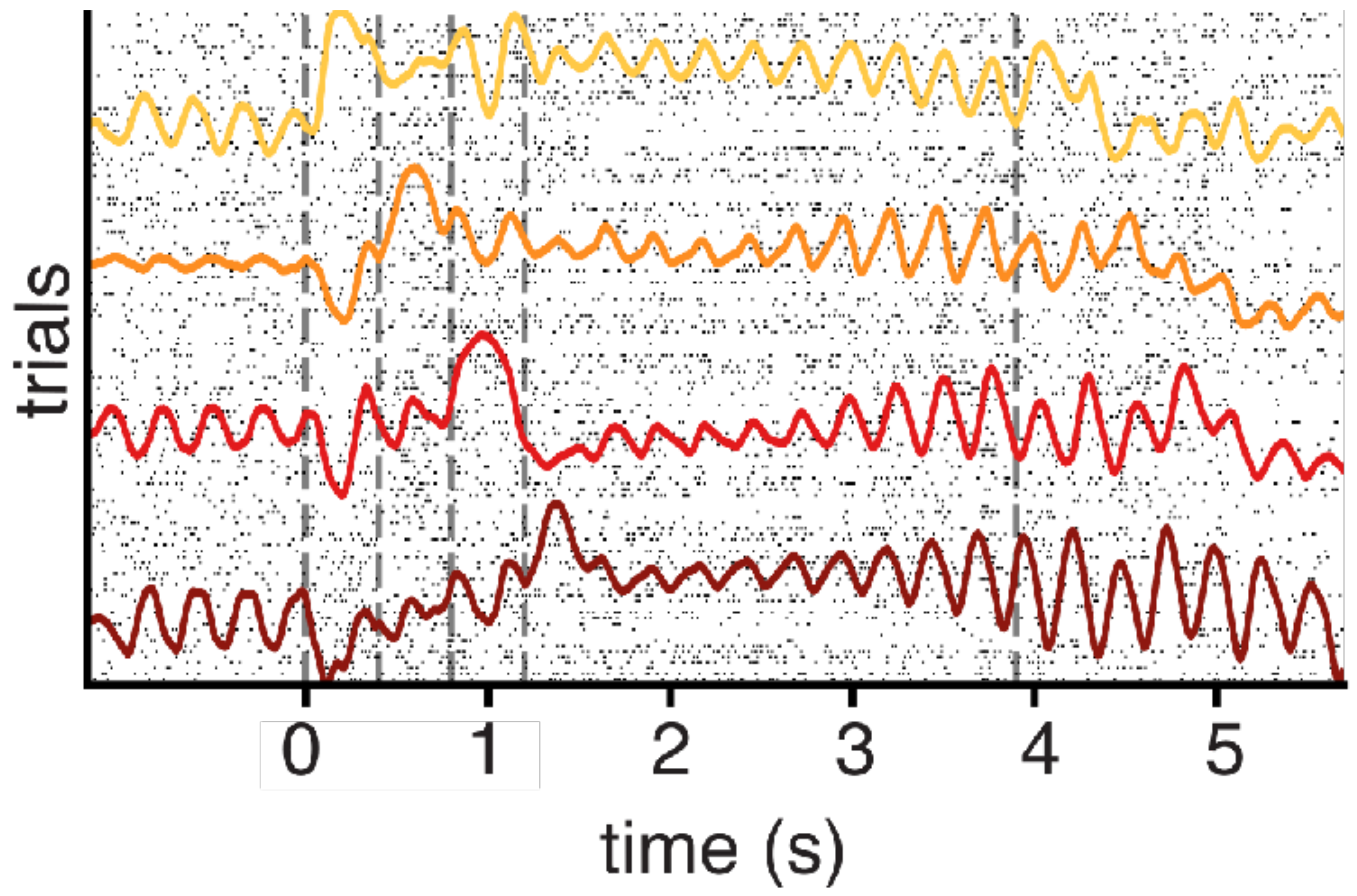
ms
Rate(Hz)
20
10
trials
0.25
0.25
0.75
s
Rate(Hz)
10

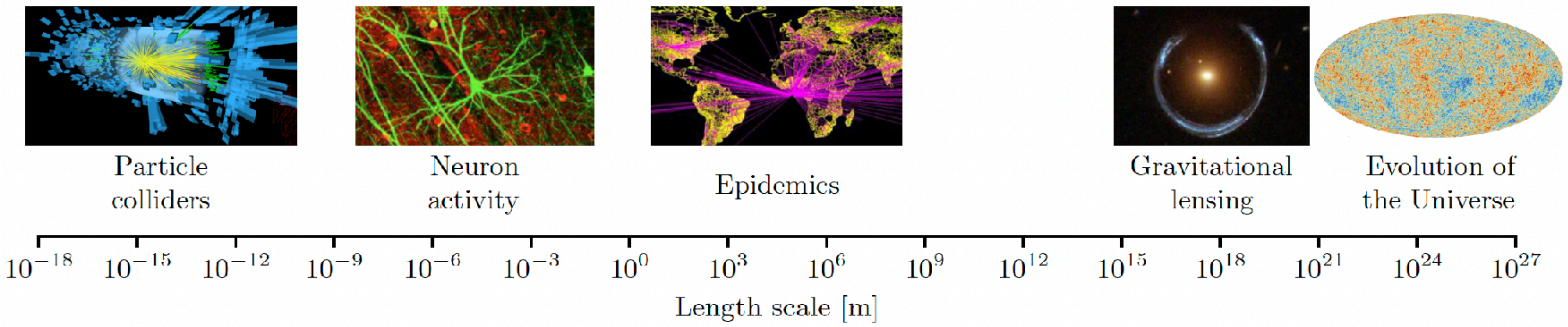



trials
0
1
2
3
4
5
time (s)

1.1 Simulators

Some slides by Álvaro Tejero-Cantero

Models defined as simulators are everywhere



- Astrophysics: simulate formation of galaxies, stars, or planets
- Neuroscience: simulate neural network dynamics
- Epidemiology: simulate spread of an infectious disease
- Different communities use different names for simulator-based models: generative models, implicit models, stochastic simulation models, probabilistic programs…

But what is a simulator? Why do we need it?

- Making models/simulators is part of the scientific method:
  1. models reproduce (only) some aspects of reality, they are similar to something that exists;
  2. when mathematically formalized, they enable quantitative, testable hypotheses.

- Model functionalities:
  1. prediction — to support decisions;
  2. understanding — to select interventions.

- The structure that does not change is the model:
  1. the malleable part are parameters;
  2. parameters are 'tuned' based on observations.

Simulators come in all sorts of flavors

- Simulator as numerical solver for an explicit model (e.g., Ordinary differential Equations) — based on discretization.
- Simulator as defined by code, i.e., an implicit model built from individual interaction rules (e.g., Cellular Automata).
- Anything in-between.
- Continuous vs. discrete, dynamic vs. steady-state, deterministic vs. stochastic...

We are particularly interested in stochastic simulators

- Stochastic modelling is more general than deterministic modelling, although typically harder to simulate and analyse.

- Often, stochasticity is used for modelling processes that lack mechanistic hypotheses.
- The process itself can be stochastic, e.g., decay in a nucleus.

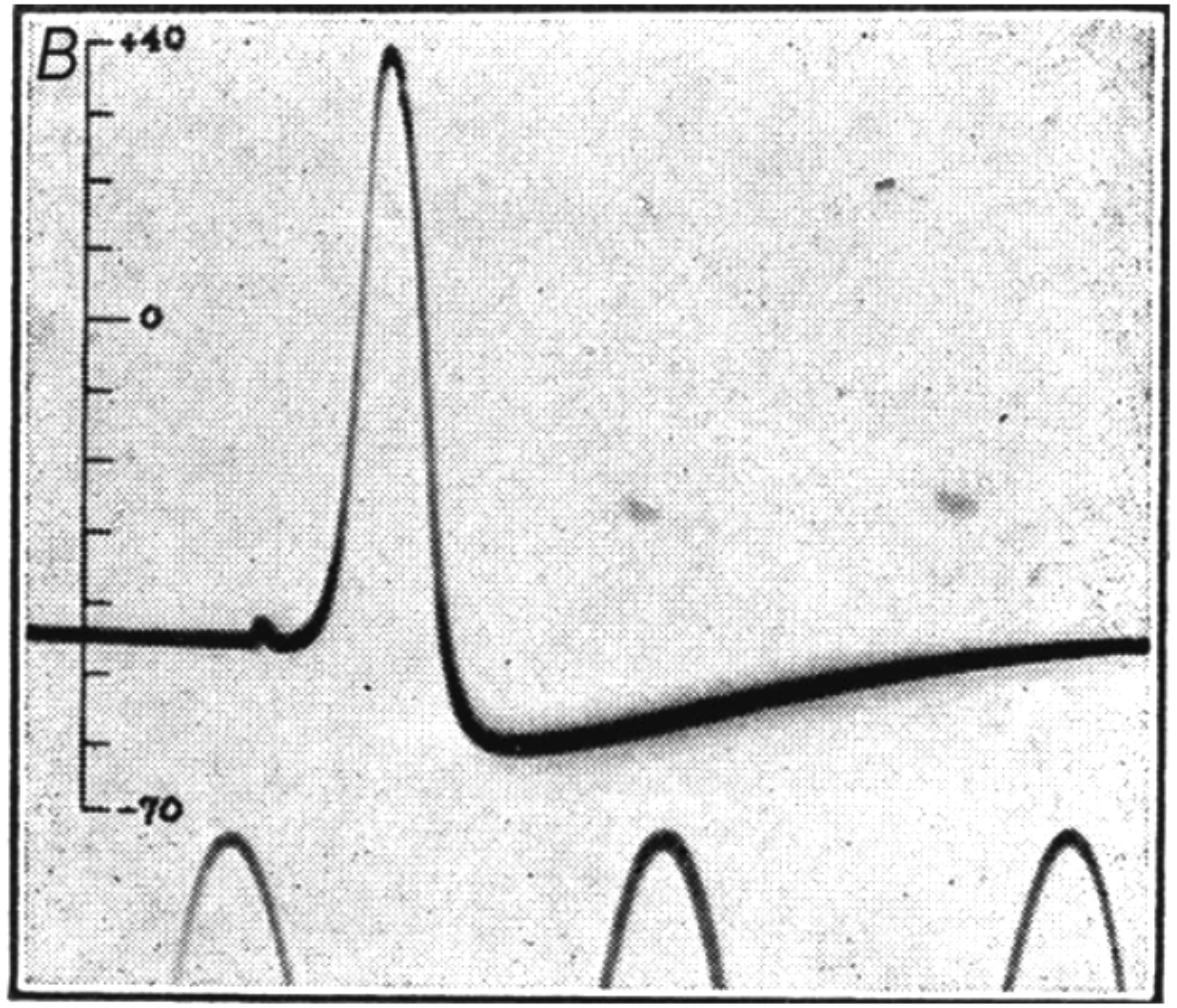
- Some sources of stochasticity: unobserved latent variables, instrument noise, numerical approximations.

- Outputs must be stochastic themselves - random variables: probabilities!

1.2 Three example simulators

1.3.1 A famous neuroscience model: The Hodgkin-Huxley equations

How do neurons generate action potentials?

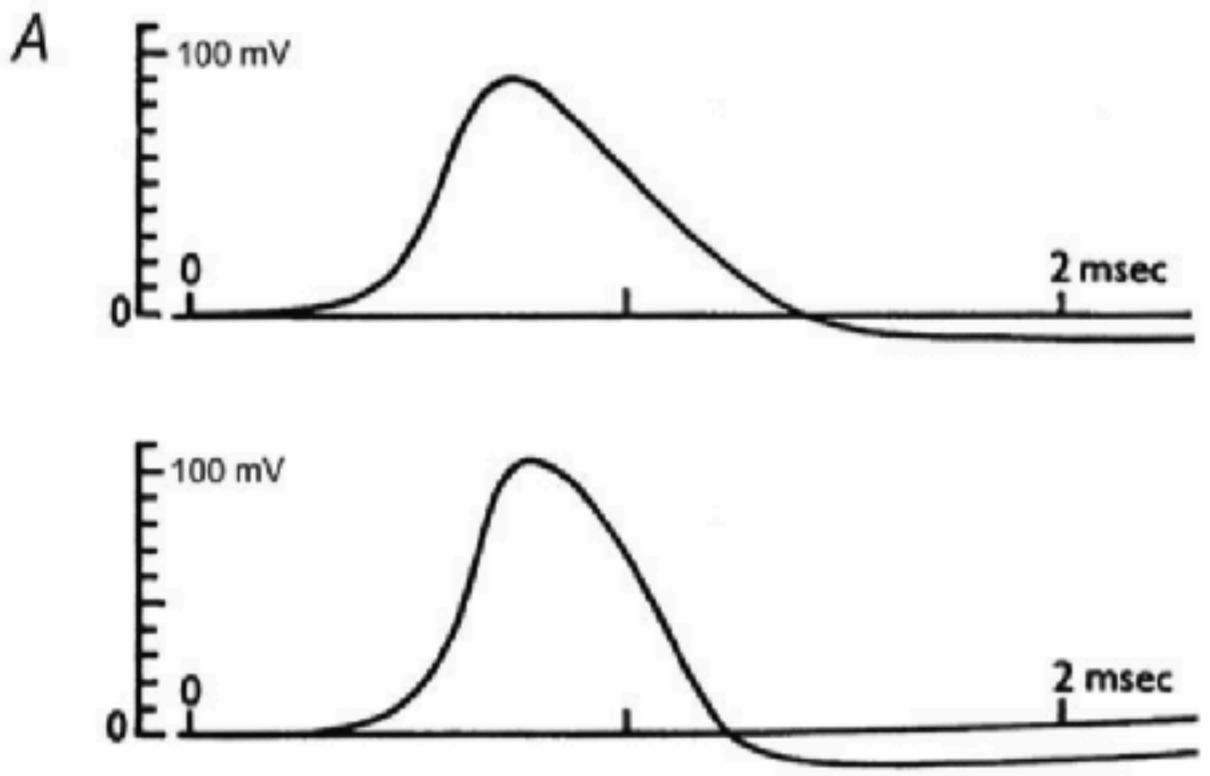


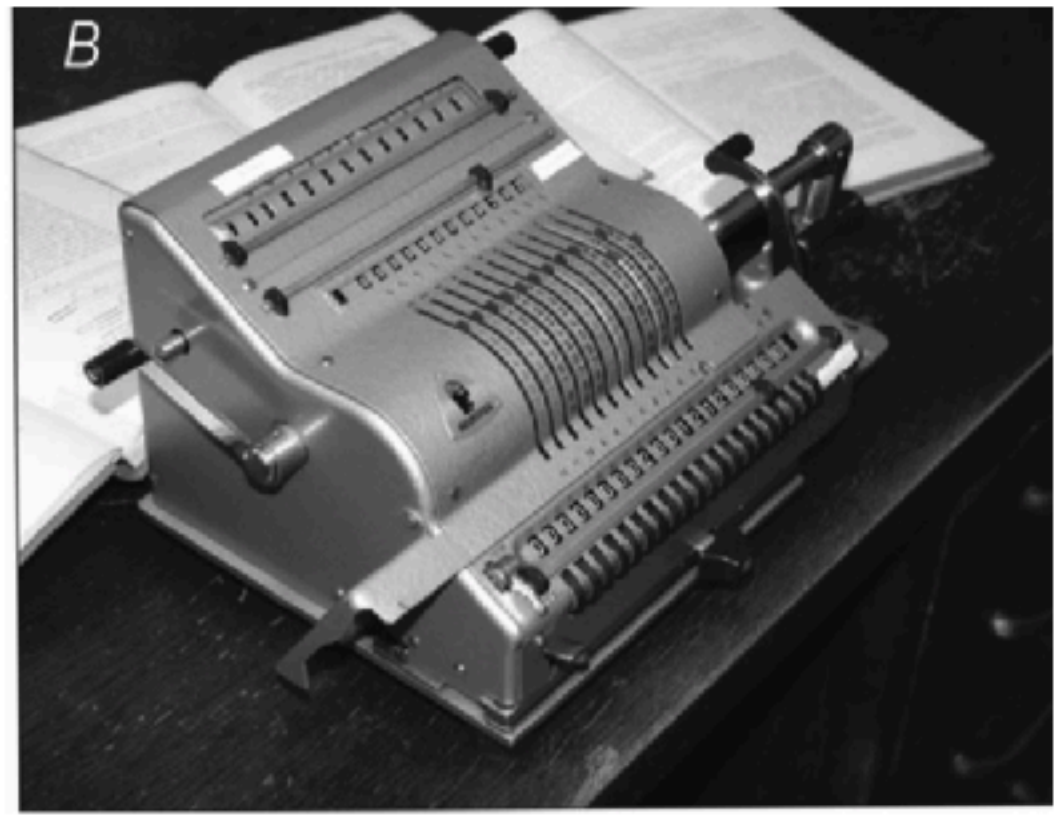
Nobel Prize 1963, images Schwiening 2010

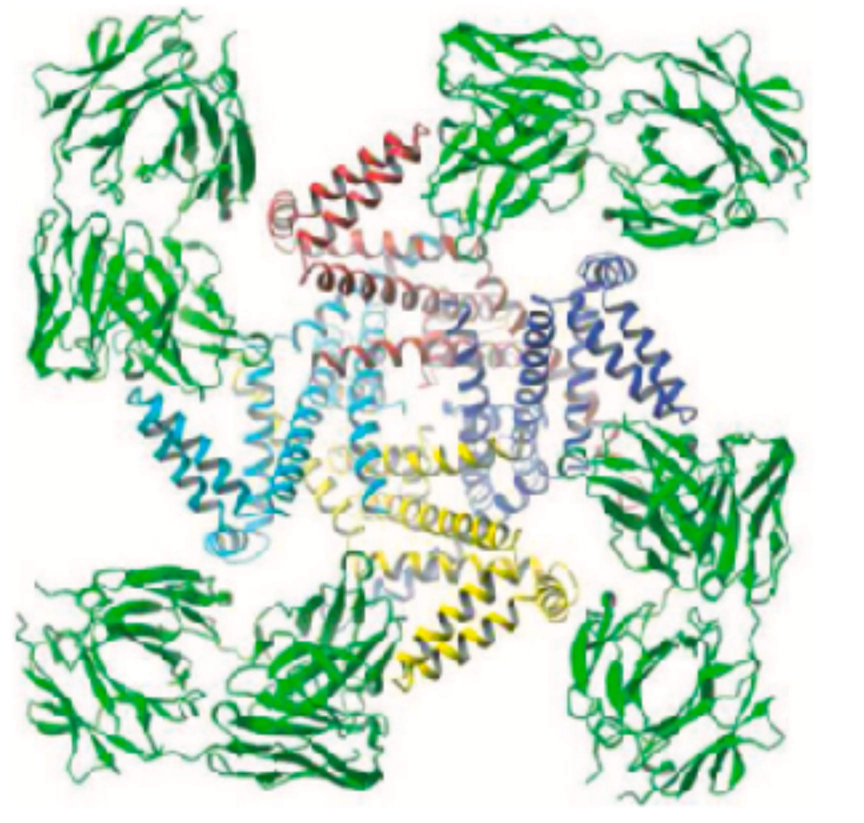
1.3.1 A famous neuroscience model: The Hodgkin-Huxley equations

Differential equations relating voltage to underlying ion-channel kinetics

$$C_m \frac{dV}{dt} = g_{\text{leak}}(E_{\text{leak}} - V) + \bar{g}_{\text{Na}} m^3 h (E_{\text{Na}} - V) + \bar{g}_{\text{K}} \boxed{n^4} (E_{\text{K}} - V) + \bar{g}_M p (E_{\text{K}} - V) + I_{\text{inj}}$$







- Equations (derived from squid) are applicable to (e.g.) humans
- Hypotheses about ion-channels

  MacKinnon Nobel Prize Chemistry 2003

1.3.2 Lotka-Volterra prey-predator model

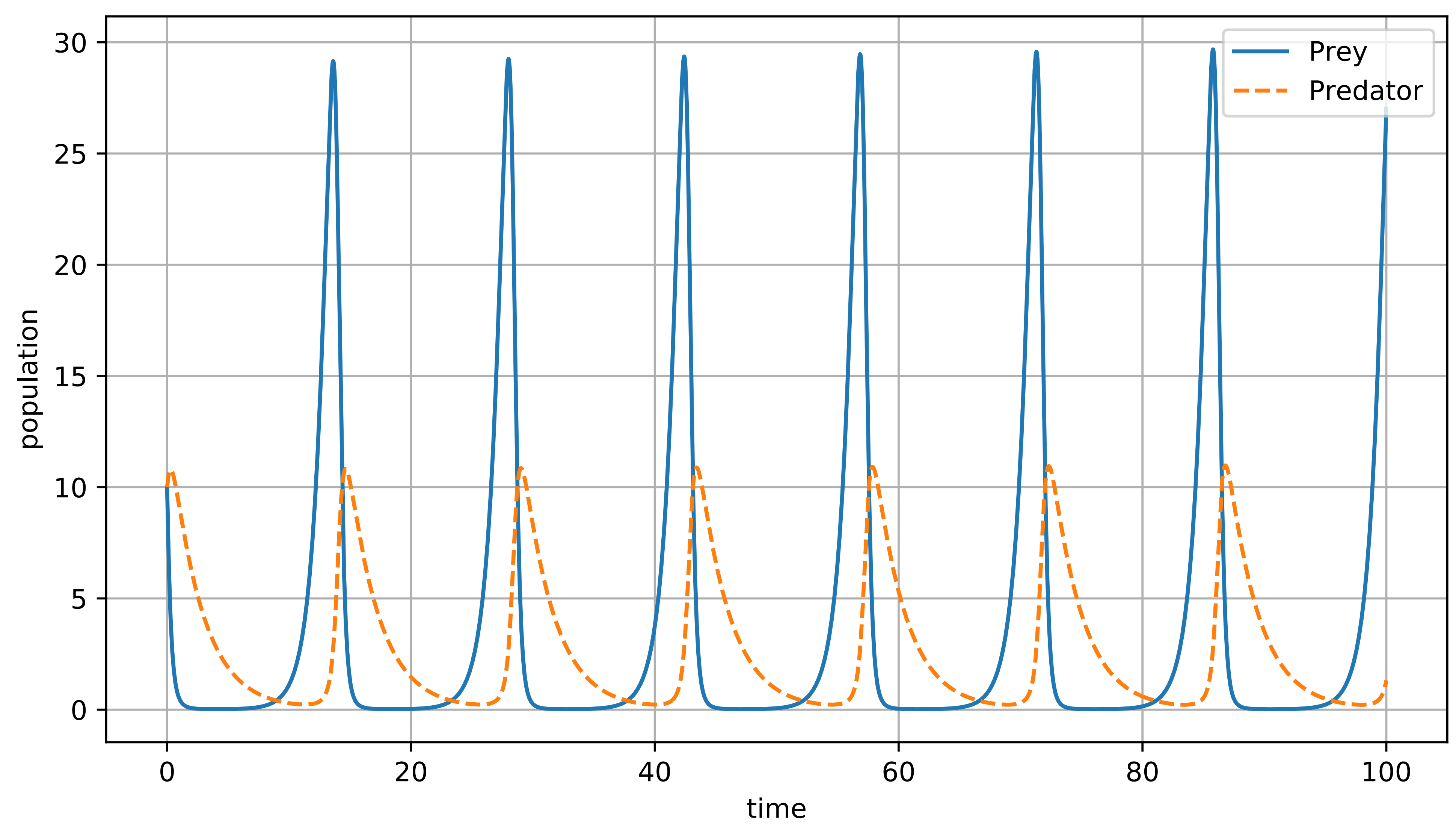
- Model of interaction between a prey and a predator (e.g., rabbit and fox):

$$\frac{dx}{dt} = \alpha x - \beta xy$$

$$\frac{dy}{dt} = \delta xy - \gamma y$$

x and y are the population densities of prey and predator, respectively.

- Applications in ecology, economics…



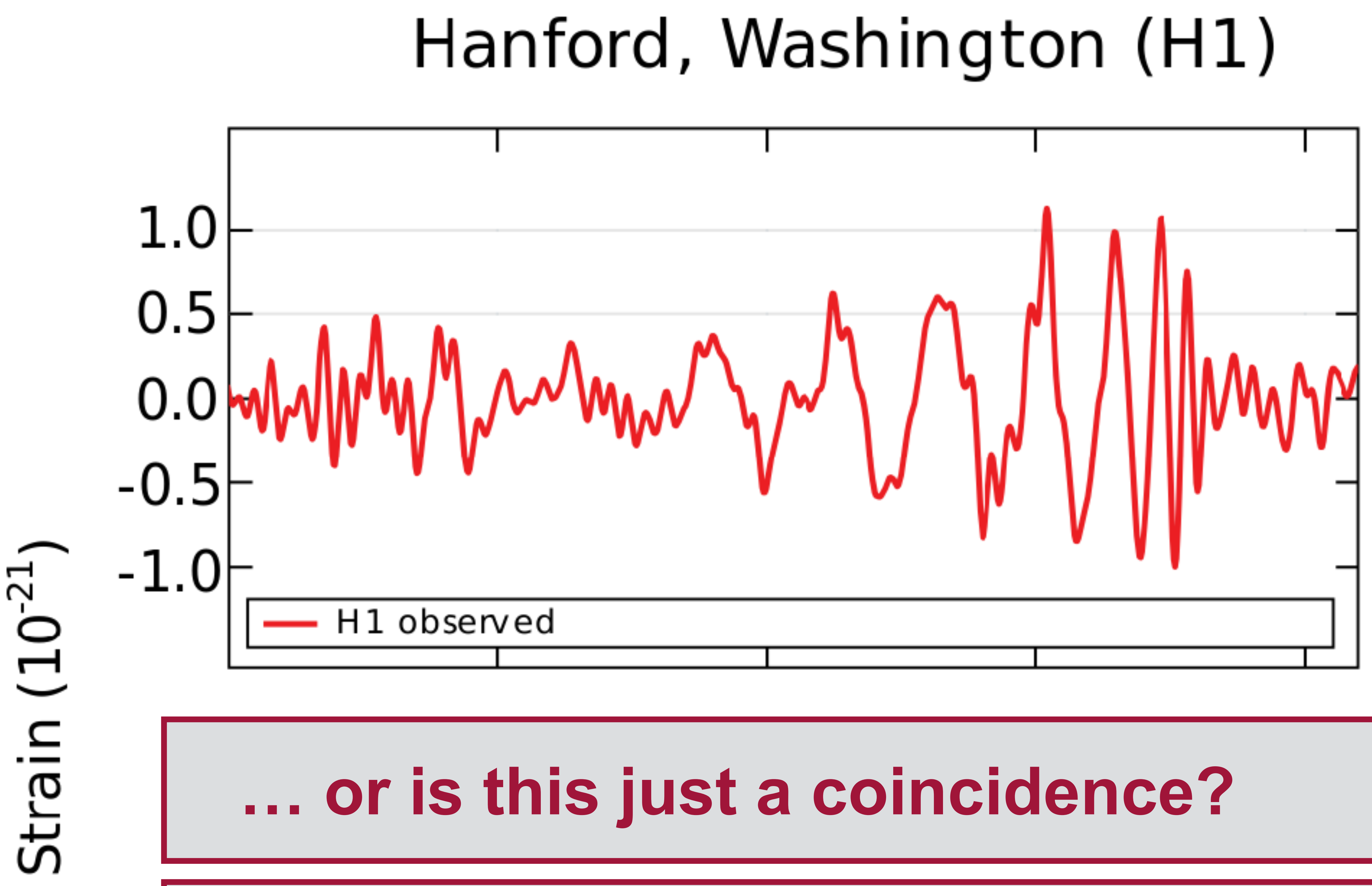
en.wikipedia.org/wiki/Lotka–Volterra_equations

1.3.3 Collision of two black holes

Image Credit: SXS project


LIGO Hanford

1.3.3 Did LIGO detect a merger of two black holes?

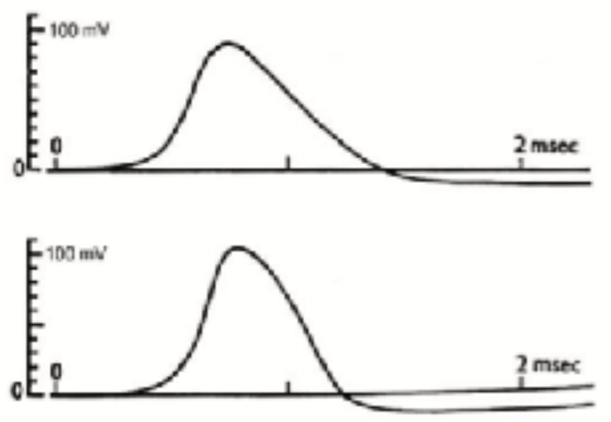


… or is this just a coincidence?

Lesson: (Prior) scientific knowledge can be extremely useful for data-interpretation

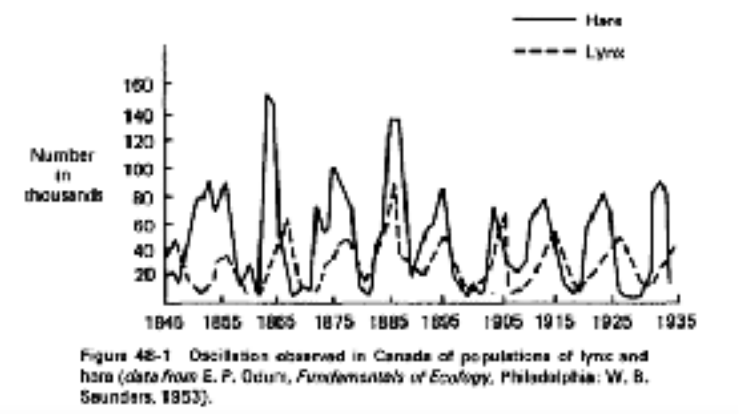
Mechanistic models and simulations play a central role across natural sciences

Neurophysiology



fig; Schwiening 2003

Population Dynamics



fig; Saunders 1953

Psychophysics of Decision Making

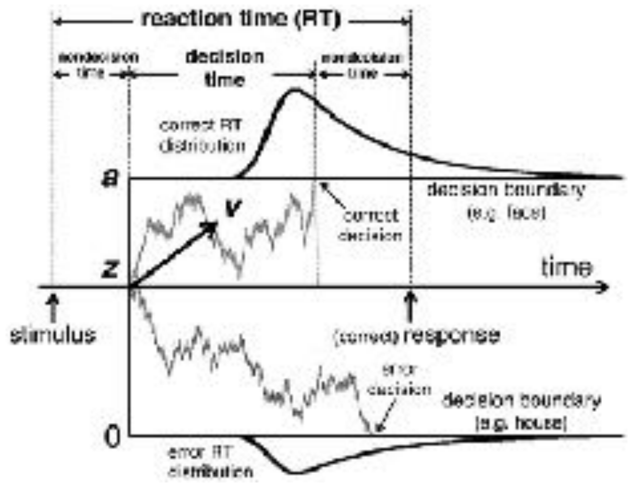


fig: Murata 2014

Particle Physics

$$
\begin{aligned}
\mathcal{L}_{SM} = \; & \underbrace{\frac{1}{4}\mathbf{W}_{\mu\nu}\cdot\mathbf{W}^{\mu\nu} - \frac{1}{4}B_{\mu\nu}B^{\mu\nu} - \frac{1}{4}G^a_{\mu\nu}G^{\mu\nu}_a}_{\text{kinetic energies and self-interactions of the gauge bosons}} \\
& + \underbrace{\bar{L}\gamma^\mu\left(i\partial_\mu - \frac{1}{2}g\tau\cdot\mathbf{W}_\mu - \frac{1}{2}g'YB_\mu\right)L + \bar{R}\gamma^\mu\left(i\partial_\mu - \frac{1}{2}g'YB_\mu\right)R}_{\text{kinetic energies and electroweak interactions of fermions}} \\
& + \underbrace{\frac{1}{2}\left|\left(i\partial_\mu - \frac{1}{2}g\tau\cdot\mathbf{W}_\mu - \frac{1}{2}g'YB_\mu\right)\phi\right|^2 - V(\phi)}_{W^\pm, Z, \gamma \text{ and Higgs masses and couplings}} \\
& + \underbrace{g''(\bar{q}\gamma^\mu T_a q)G^a_\mu}_{\text{interactions between quarks and gluons}} + \underbrace{(G_1\bar{L}\phi R + G_2\bar{L}\phi_c R + h.c.)}_{\text{fermion masses and couplings to Higgs}}
\end{aligned}
$$

fig: Cranmer 2017

Systems Biology

$$\dot{S} = \alpha - \gamma SI - dS, \qquad (3.10a)$$

$$\dot{I} = \gamma SI - vI - dI, \qquad (3.10b)$$

$$\dot{R} = vI - dR, \qquad (3.10c)$$

fig; Toni 20018

Cosmology

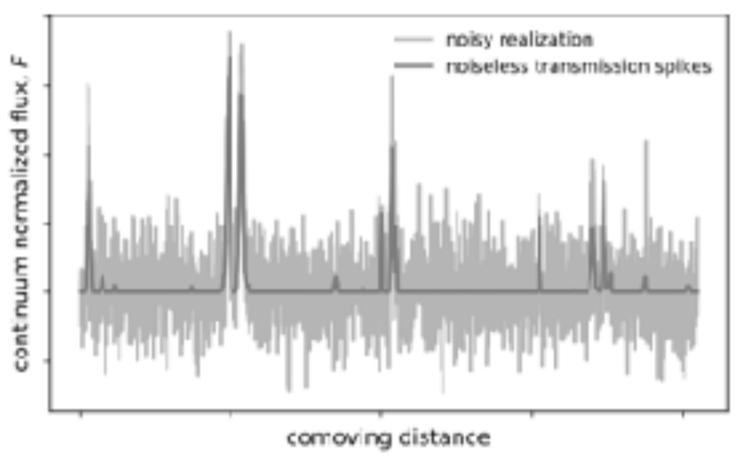


fig: Walting 2018

Molecular Dynamics

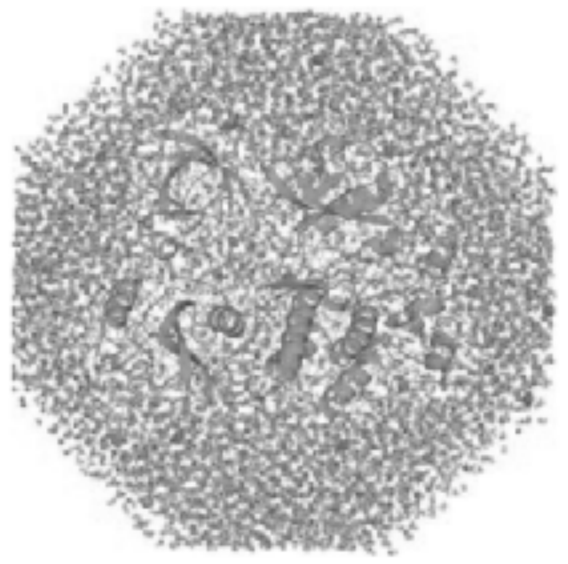


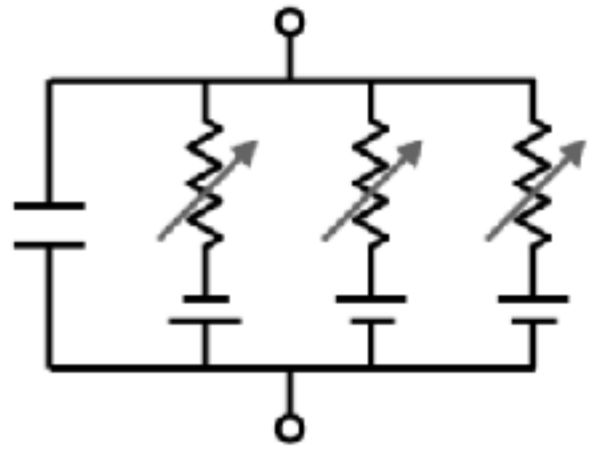
fig: Karplus 2005

...

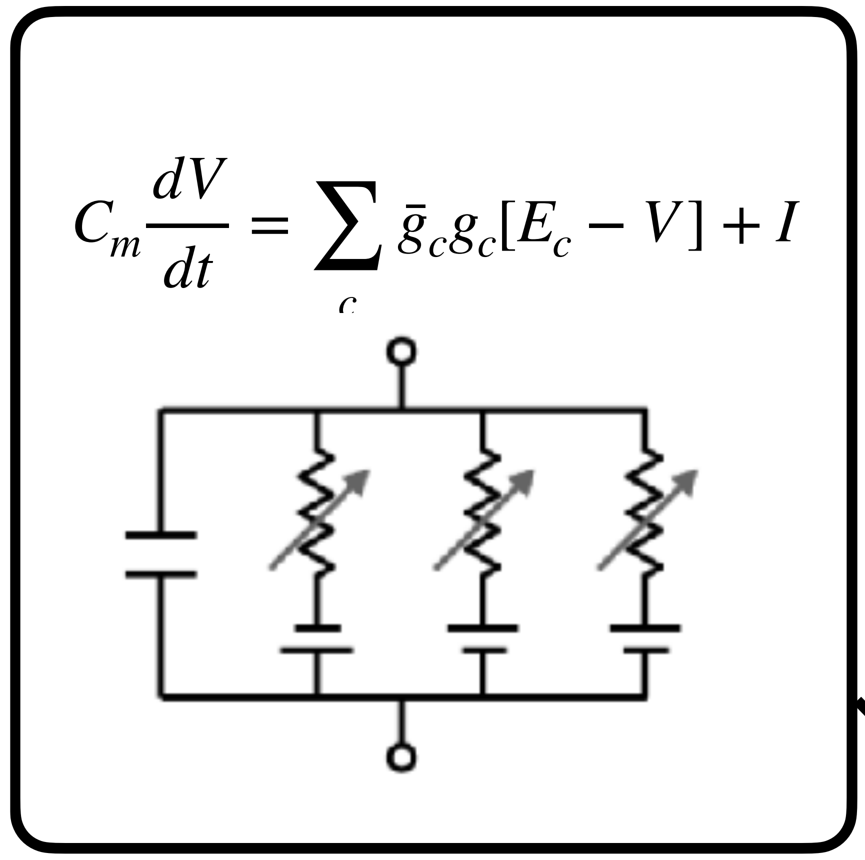
1.3 Science and the role of simulators

Mechanistic model

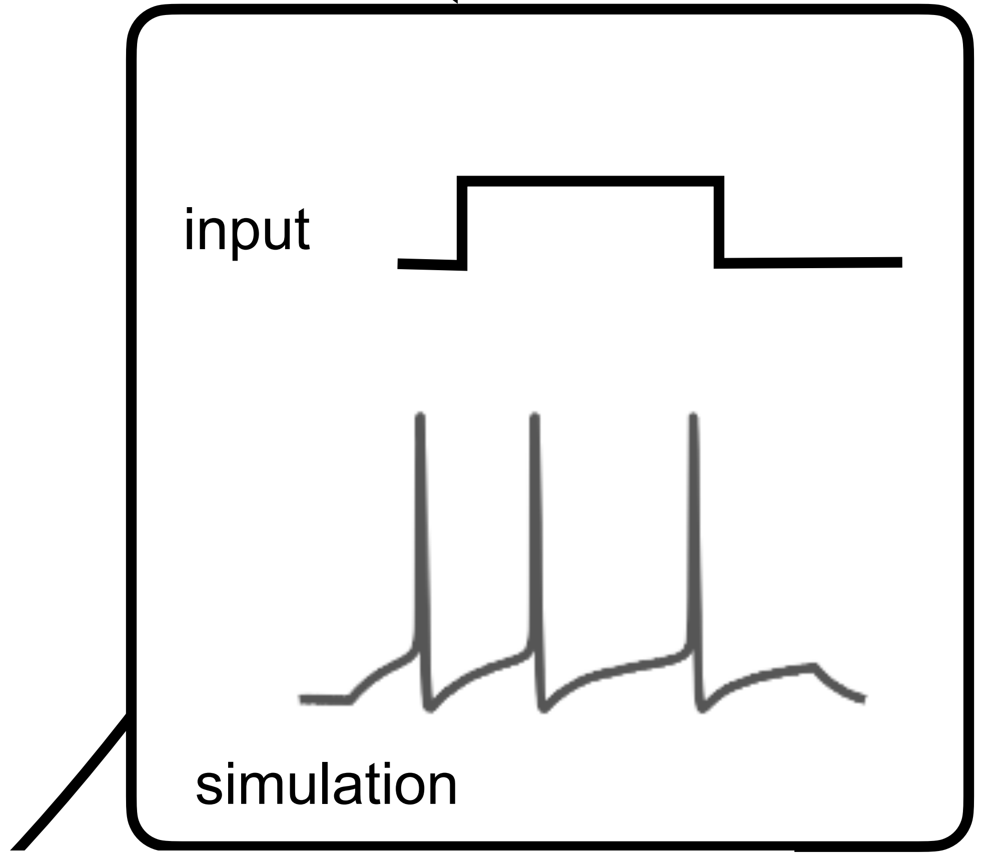
$$C_m \frac{dV}{dt} = \sum_c \bar{g}_c g_c [E_c - V] + I$$



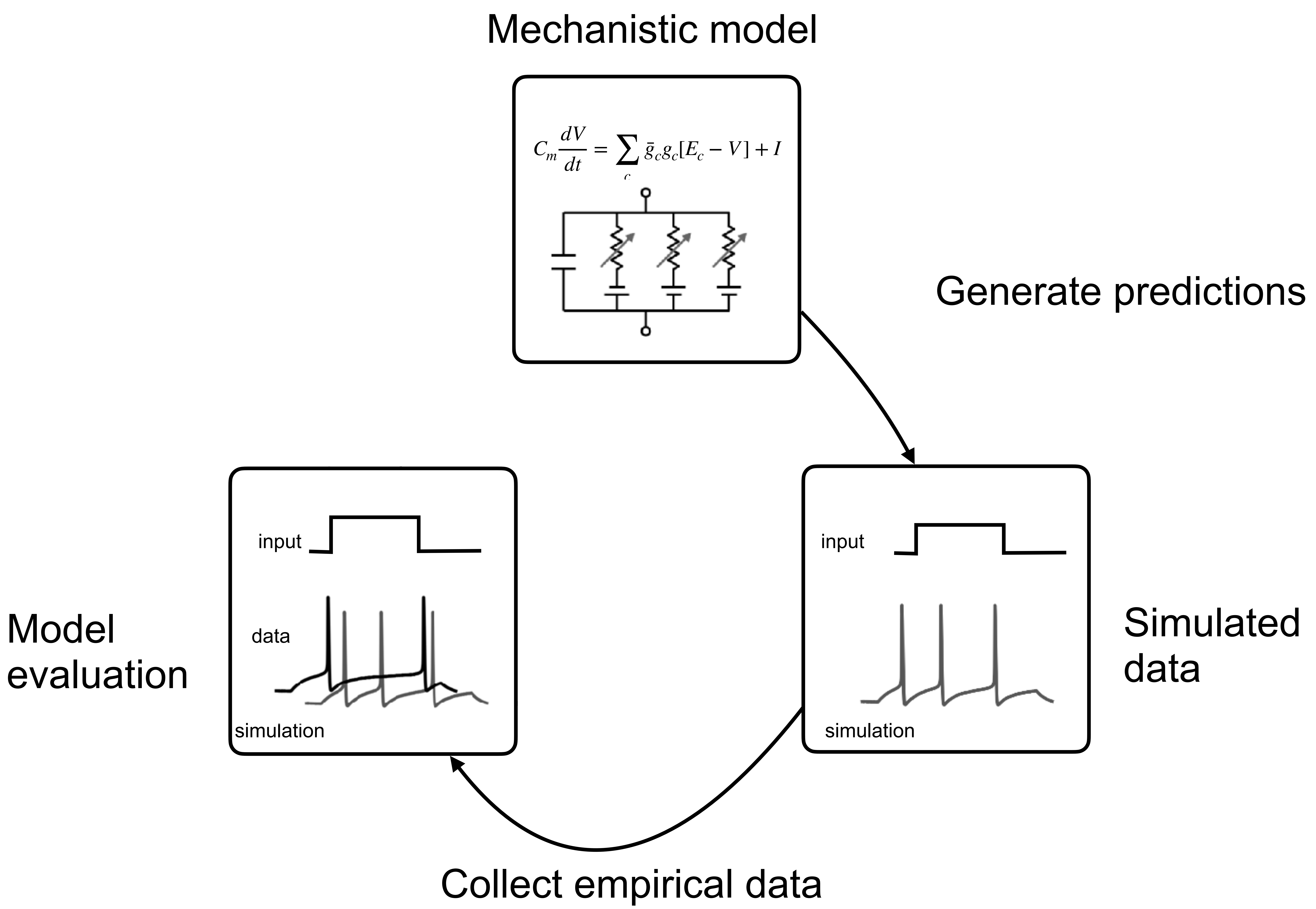
Mechanistic model

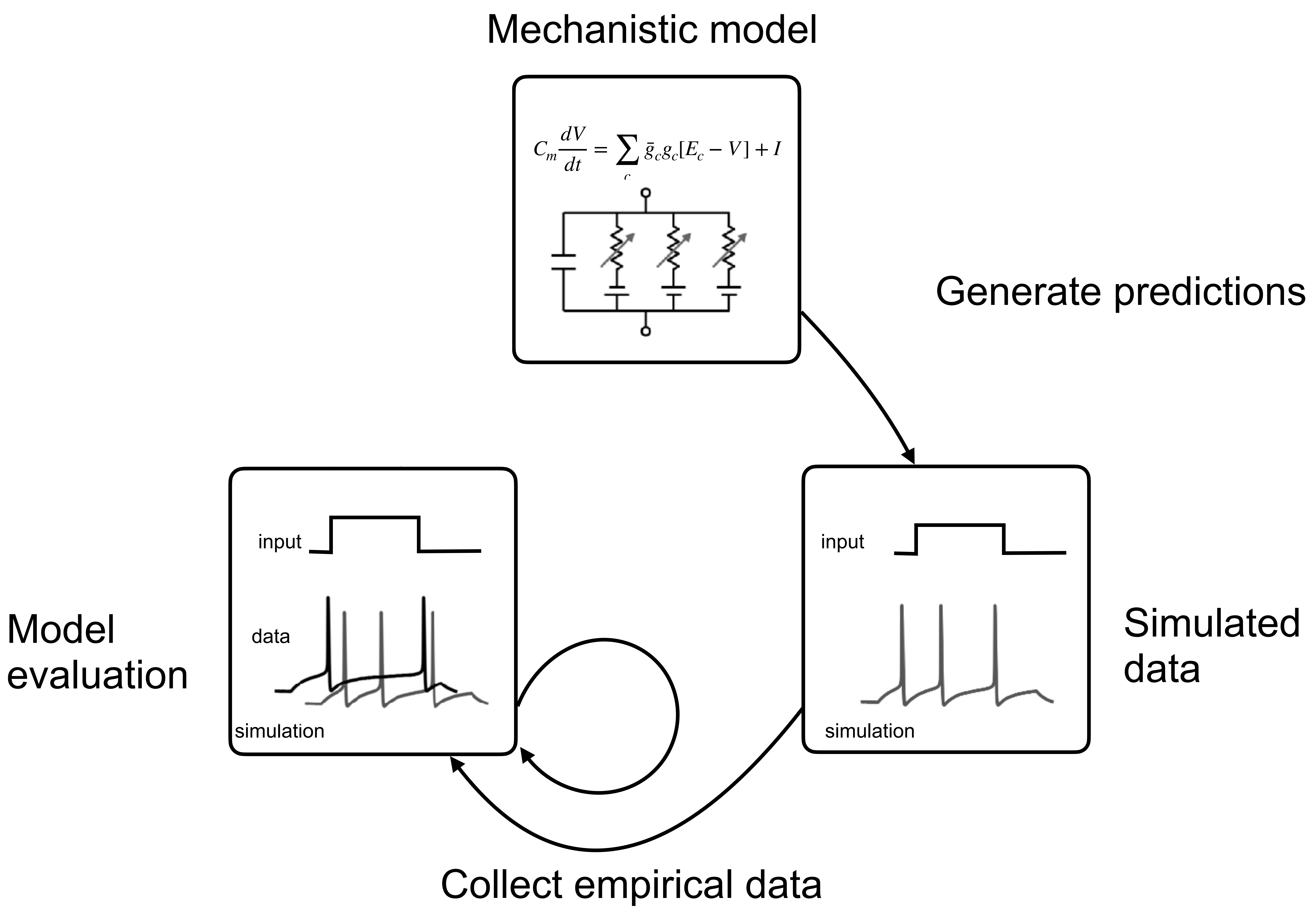


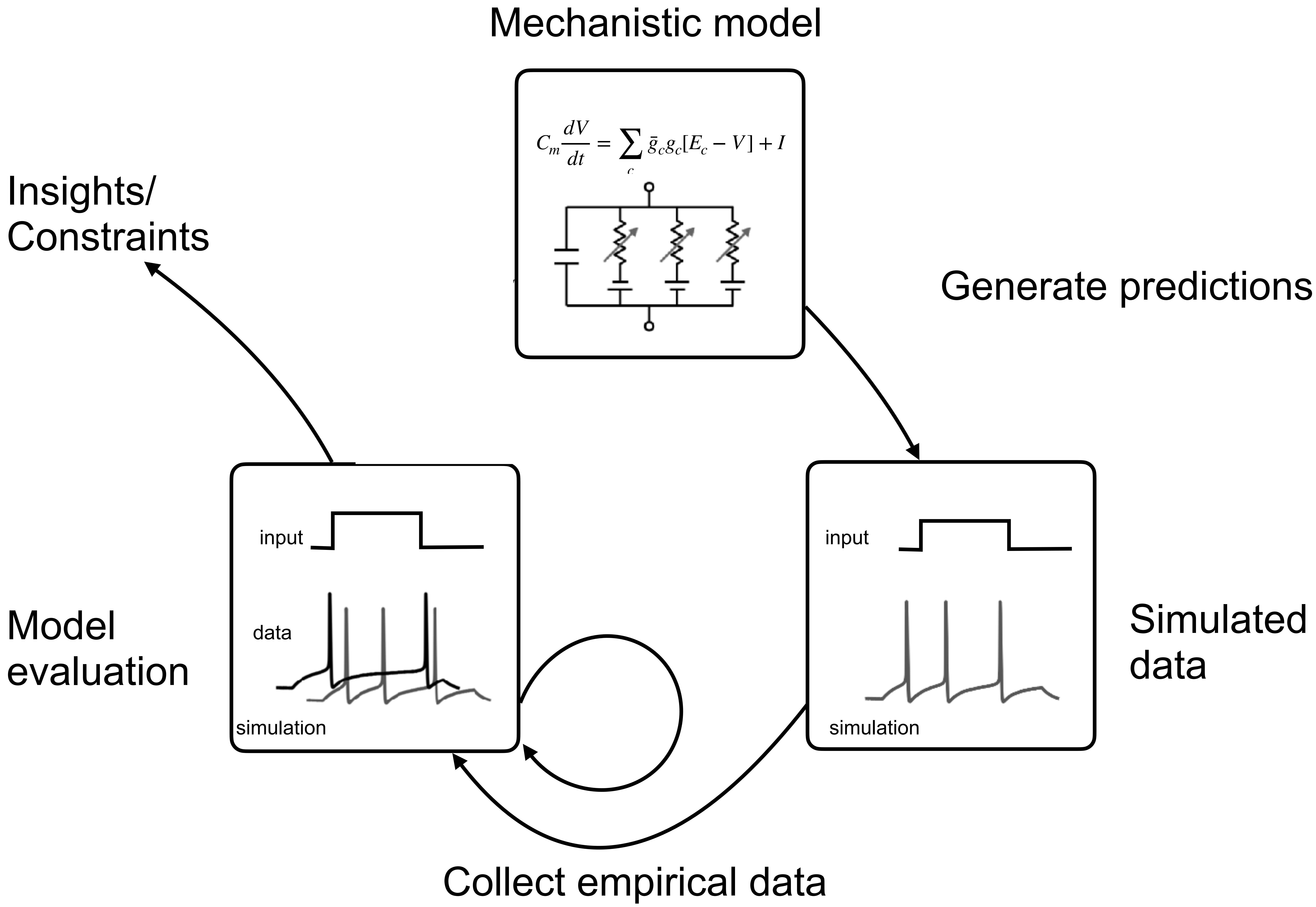
Generate predictions



Simulated data

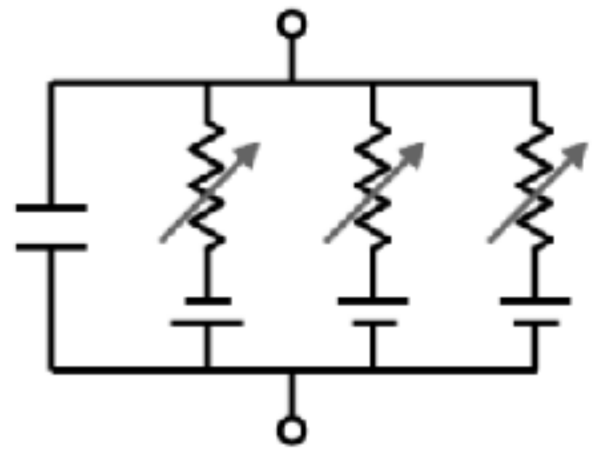

Mechanistic model
$$C_m \frac{dV}{dt} = \sum_c \bar{g}_c g_c [E_c - V] + I$$
Generate predictions
input
simulation
Simulated data
Collect empirical data
input
data
simulation
Model evaluation


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
input
data
simulation
Model evaluation


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
Insights/ Constraints

Mechanistic model

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



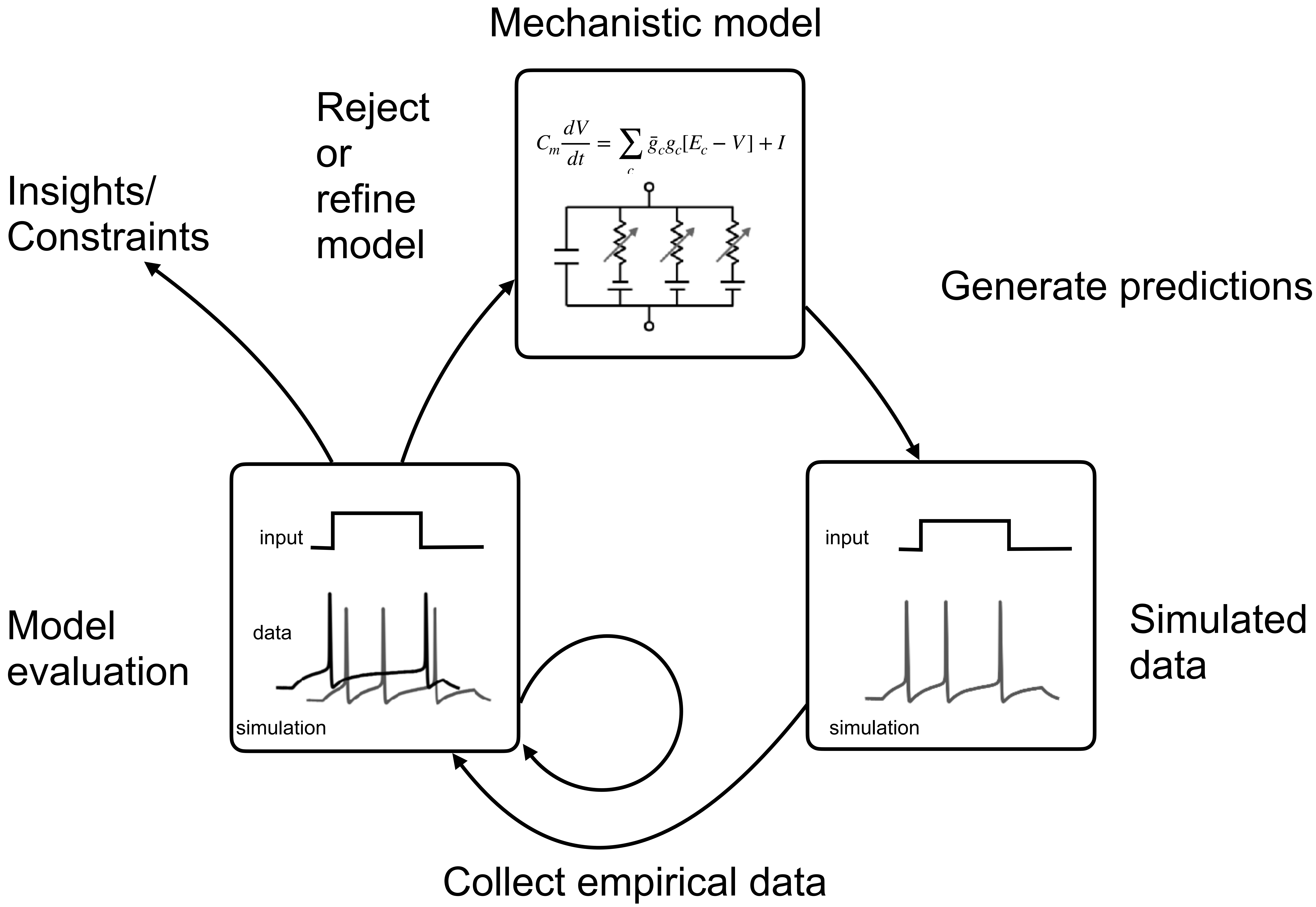
Mechanistic Models

- 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

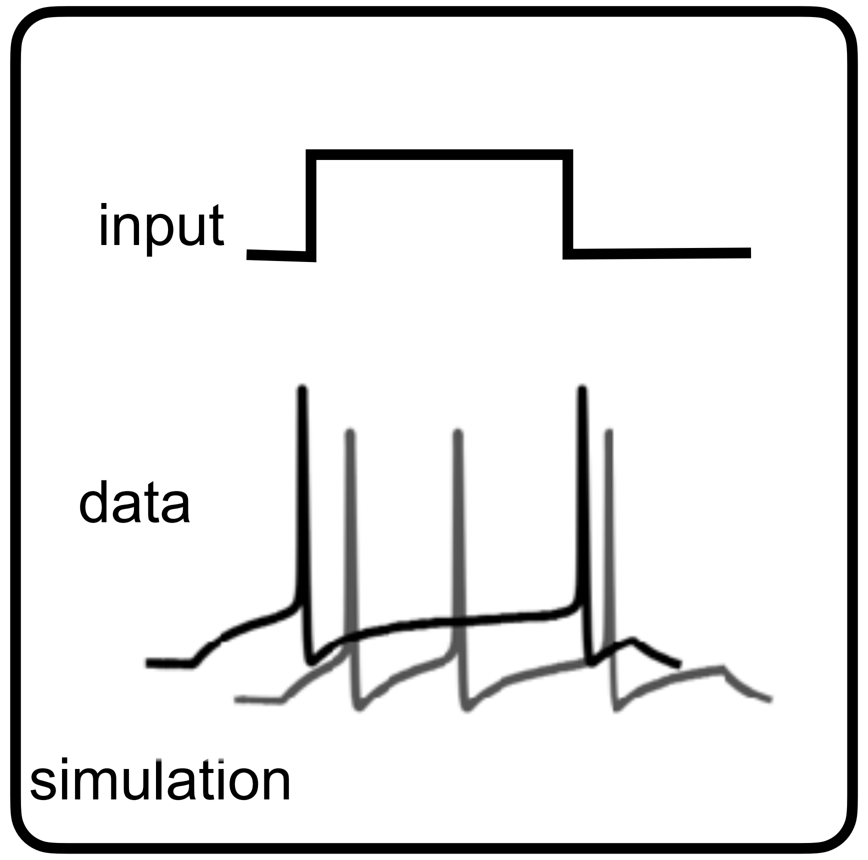
Goal: Combine strengths of both approaches to build tools for data-driven science.


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

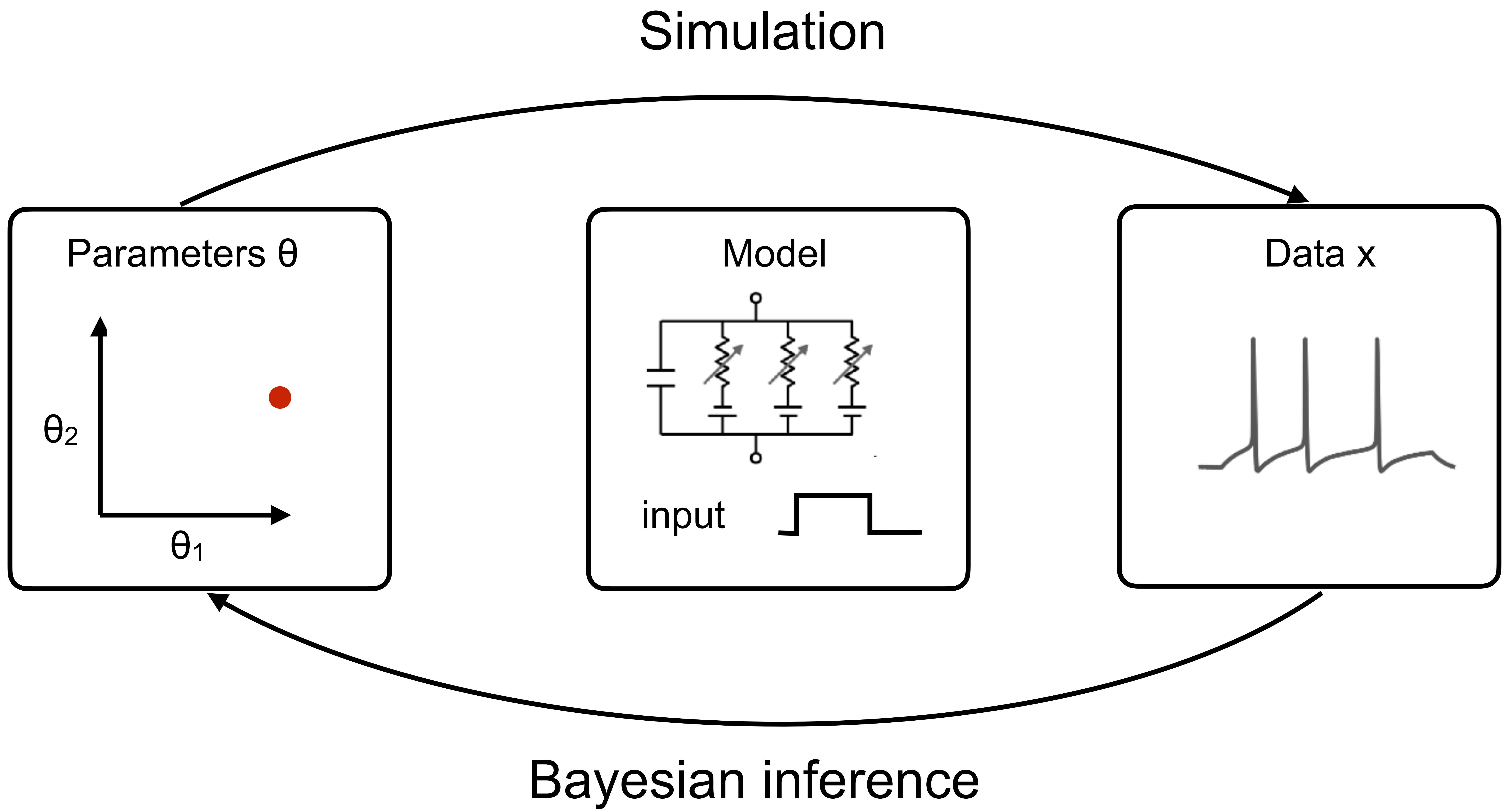
Key question: Which parameters of a mechanistic model are compatible with the data?

Answer: Bayesian inference!

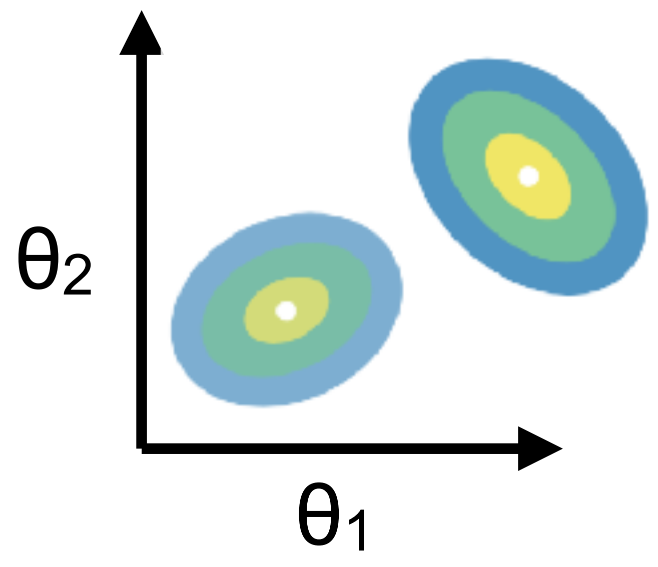
Model evaluation



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

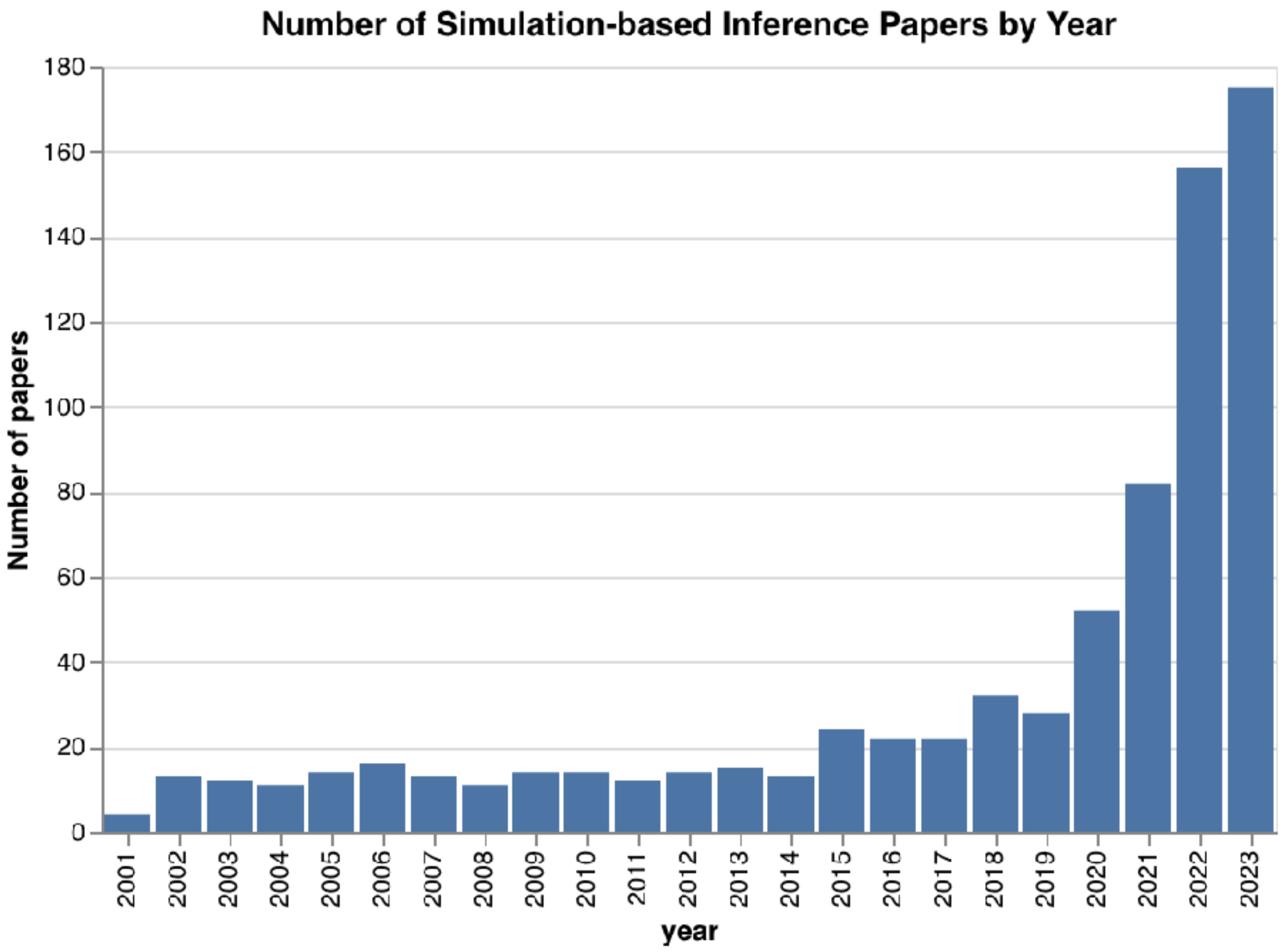
For many mechanistic models, we can **simulate x**, but we cannot (easily) evaluate the likelihood **p(x|θ)**.

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

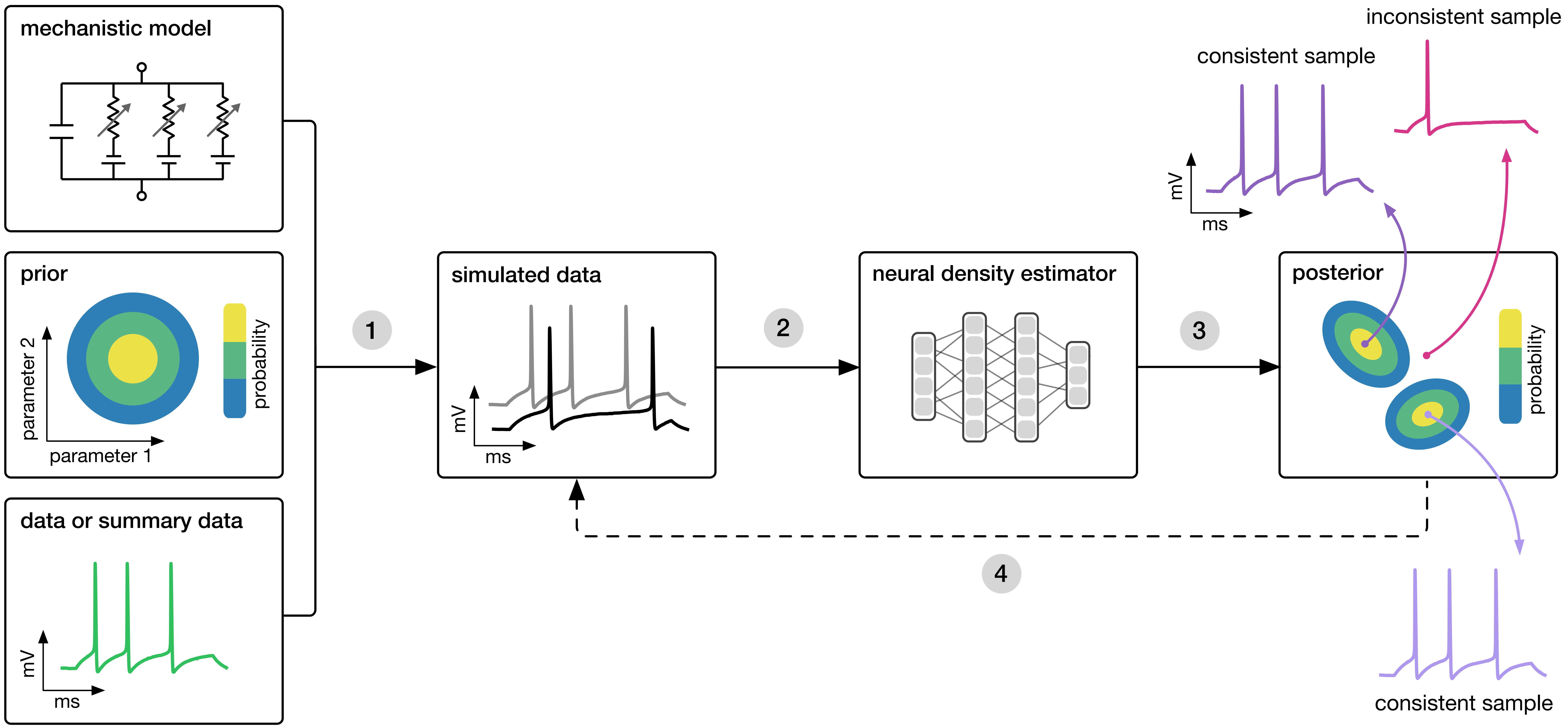
➡ A solution: simulation-based inference!

1.4 What is Simulation-based inference?

Simulation-based inference is a rapidly expanding sub-field of machine learning



Teaser: one solution is to train neural networks to identify data-compatible models



Some general aims of the course

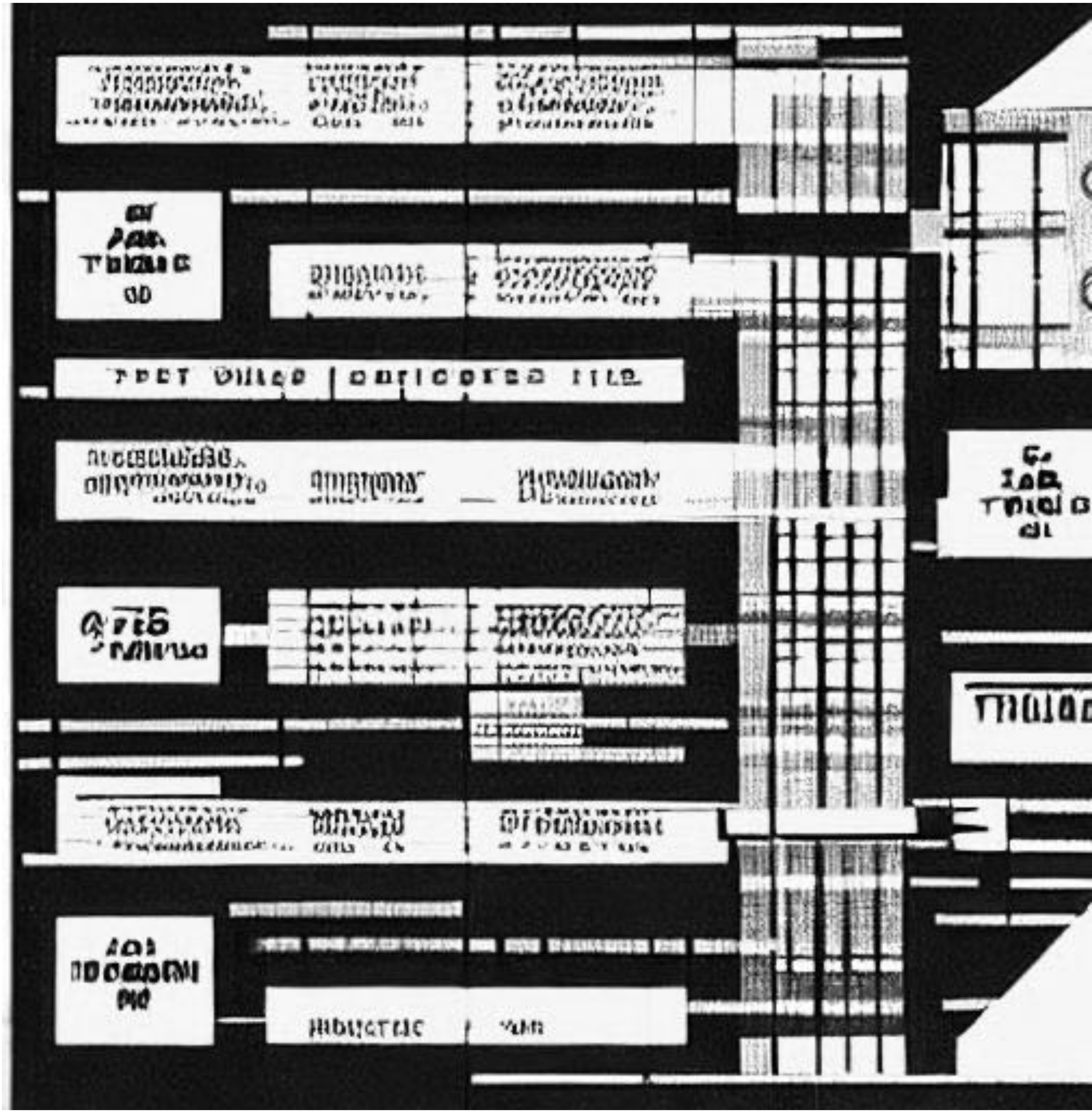
- An appreciation of how simulators and data can be combined to generate insights.
- Probability theory as the mathematical language for performing inference.
- An overview of how the latest advances in machine learning (in particular, neural networks) can be used for Bayesian inference.

Course Outline

- Week 1: Introduction, ABC, and conditional density estimation
- Week 2: Neural density estimation and Normalising flows
- Week 3: Advanced topics and applications

1.3 Organisational matters

How this thing is (hopefully) gonna work

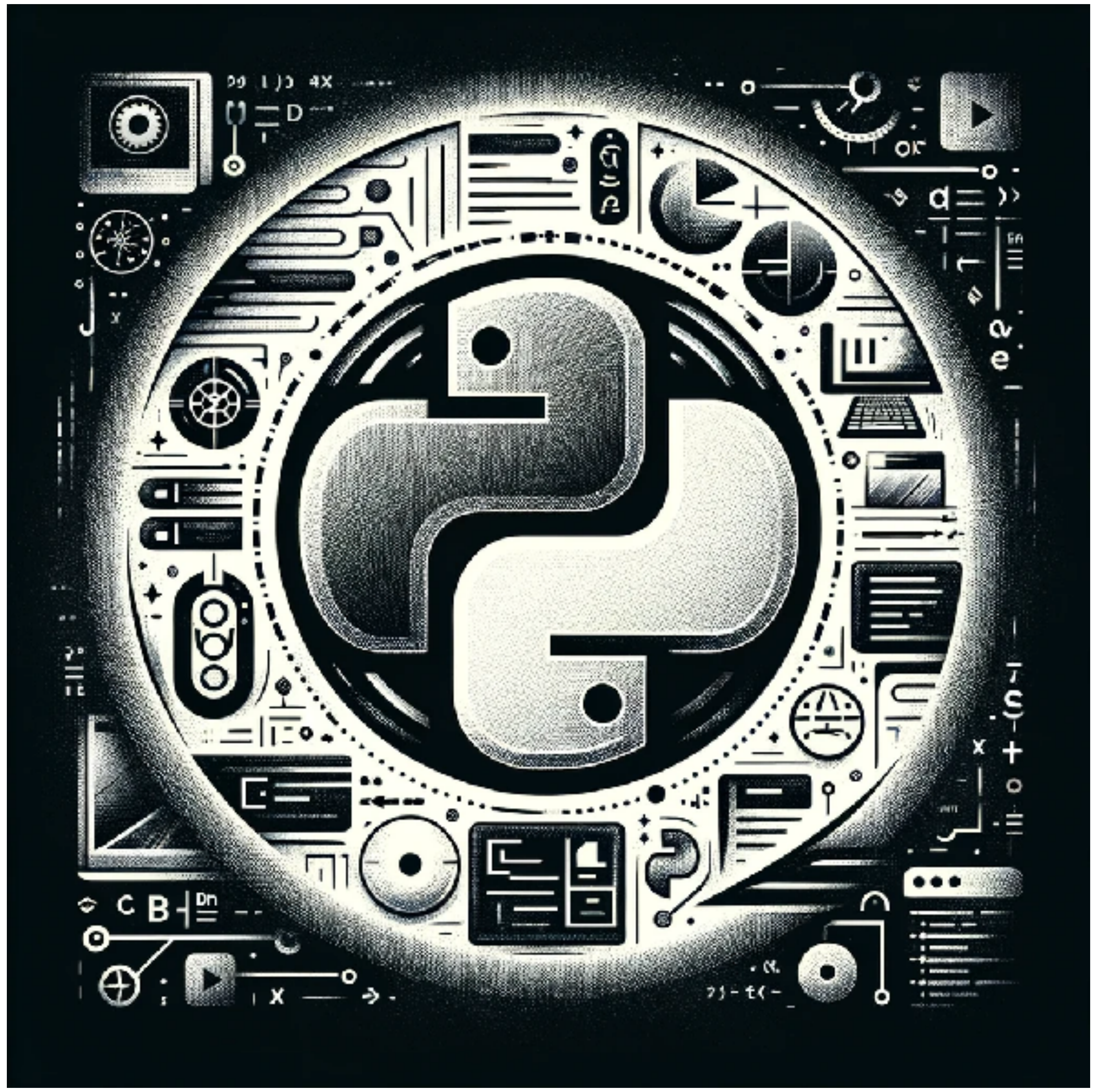


Communication

- To communicate with us, email cornelius.schroeder@uni-tuebingen.de, jakob.macke@uni-tuebingen.de, pedro.goncalves@nerf.be
- We will provide all lecture material on GitHub (https://github.com/mackelab/sbi_AIMS).
- Found a cool scientific question involving a simulator: **Do share with the class!**
- We might discuss the example in lecture!

Python

- Our codebase is Python.
- Required Python packages are pre-installed in the workstations.
- In order to work on your laptops, you need to install the packages in the yml file at https://github.com/mackelab/sbi_AIMS
- Many of the classes will include hands-on Python sessions.



The Exams

- Exams will happen every Friday: 3 exams.
- You will have 30min to answer pen and paper questions.
- We will decide soon whether there will also be some coding exercises.
- Final grade will be an average of the exam-grades.

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

Lecture 1: 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**

1.4 Anonymous mini-test (30 min)