HERTIE INSTITUTE FOR AI IN BRAIN HEALTH

Lecture 3

The Hodgkin-Huxley model

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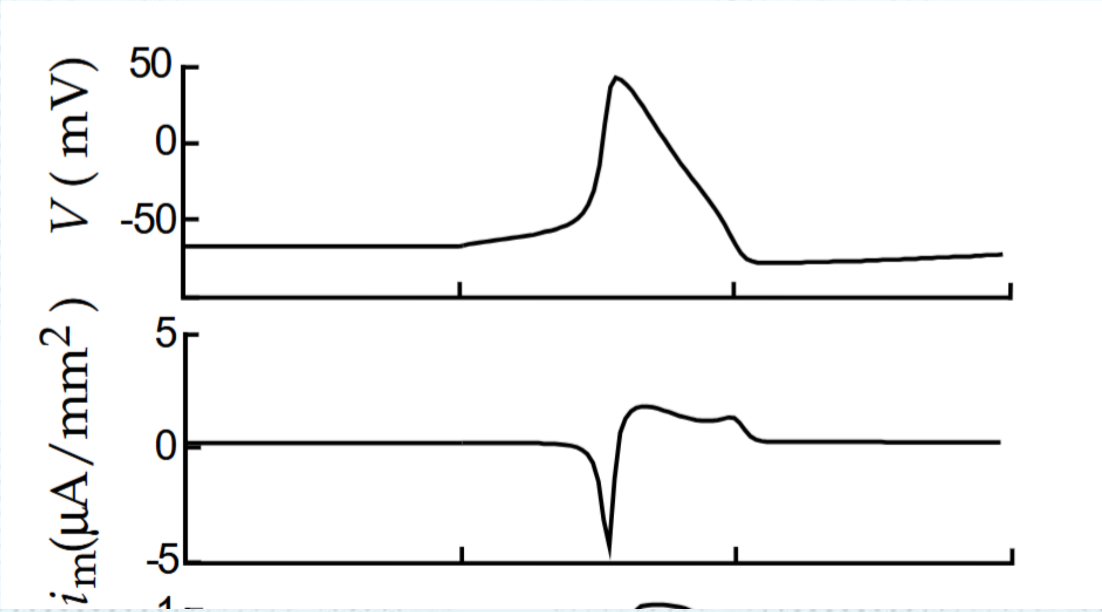
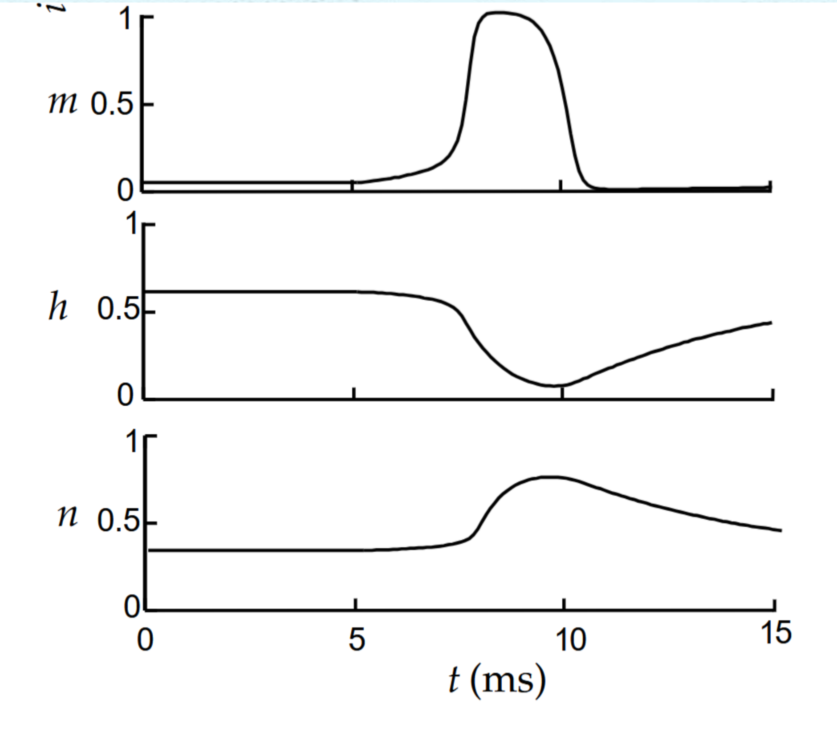
Dayan & Abbott, 2001

- Model of action potential generation

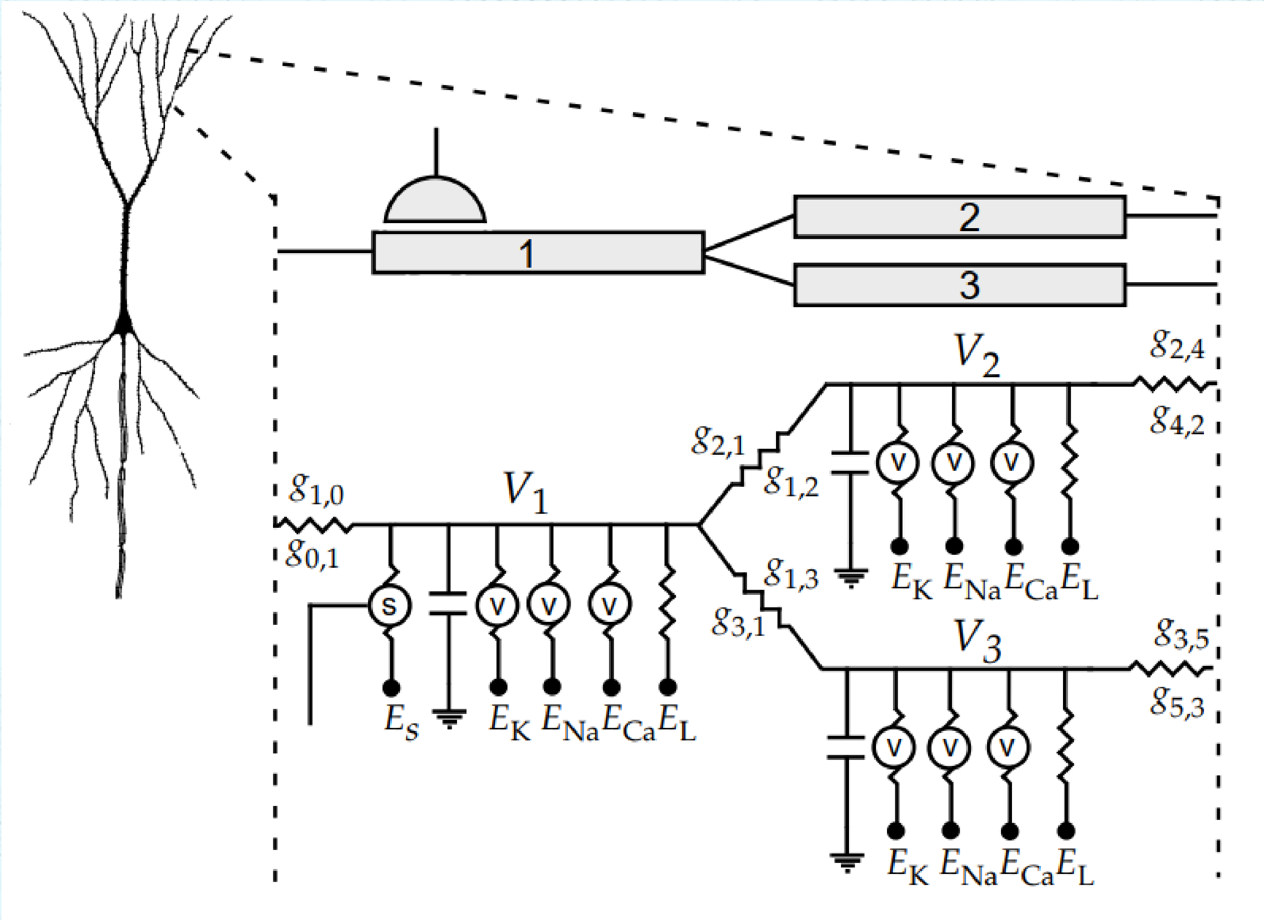
$$c_m \frac{dV}{dt} = -i_m + \frac{I_e}{A}\,.$$

$$i_m = \overline{g}_L(V - E_L) + \overline{g}_K n^4 (V - E_K) + \overline{g}_{Na} m^3 h (V - E_{Na})$$





Action potential propagation



Multicompartment models

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- Non-branching compartment:

Connections to neighbouring compartments

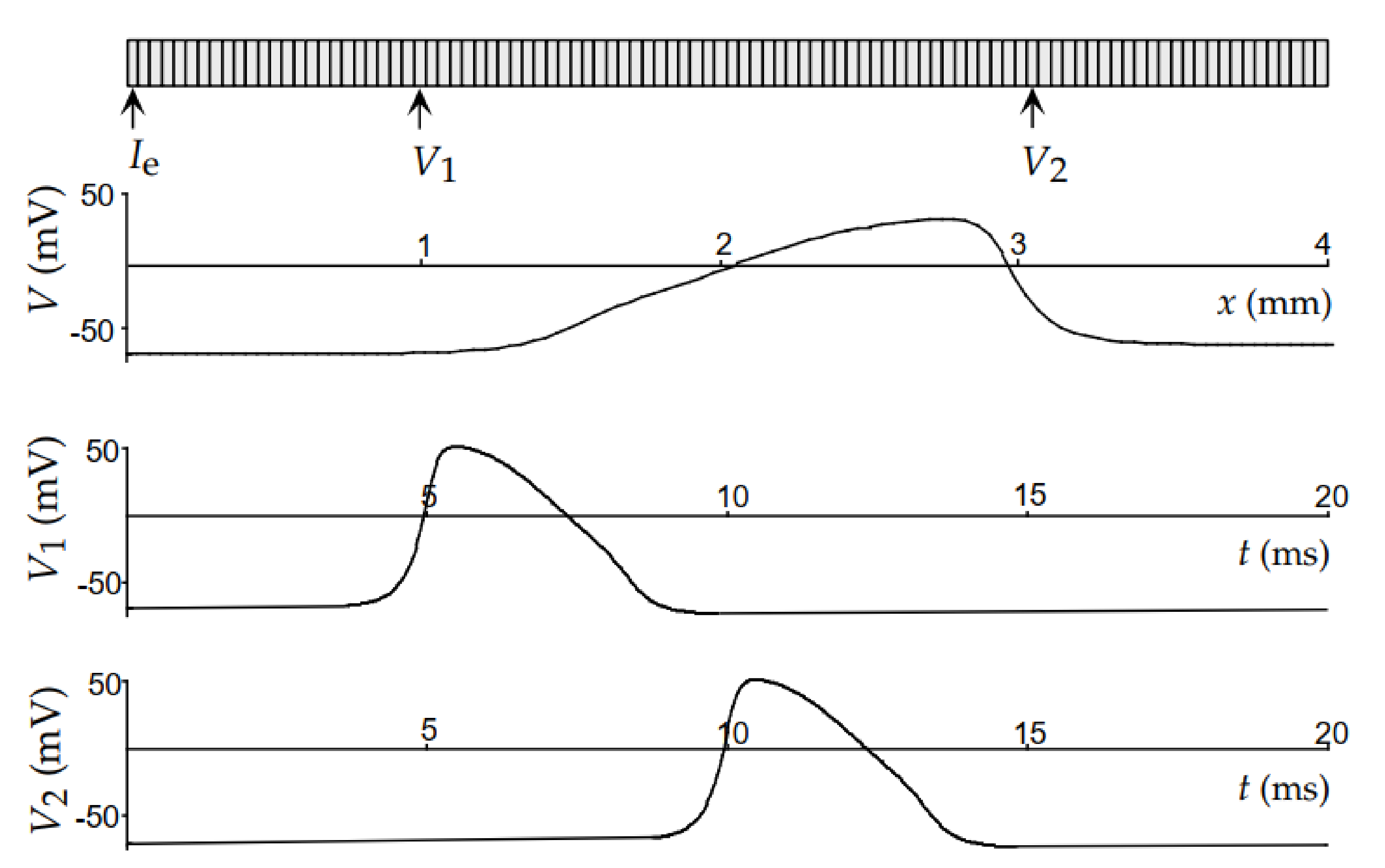
$$c_{\mathrm{m}} \frac{dV_{\mu}}{dt} = -i_{\mathrm{m}}^{\mu} + \frac{I_{\mathrm{e}}^{\mu}}{A_{\mu}} + g_{\mu,\mu+1}(V_{\mu+1} - V_{\mu}) + g_{\mu,\mu-1}(V_{\mu-1} - V_{\mu})$$

- Coupling constant:

$$g_{\mu,\mu'} = \frac{a_{\mu} a_{\mu'}^{2}}{r_{\mathrm{L}} L_{\mu} (L_{\mu} a_{\mu'}^{2} + L_{\mu'} a_{\mu}^{2})}$$

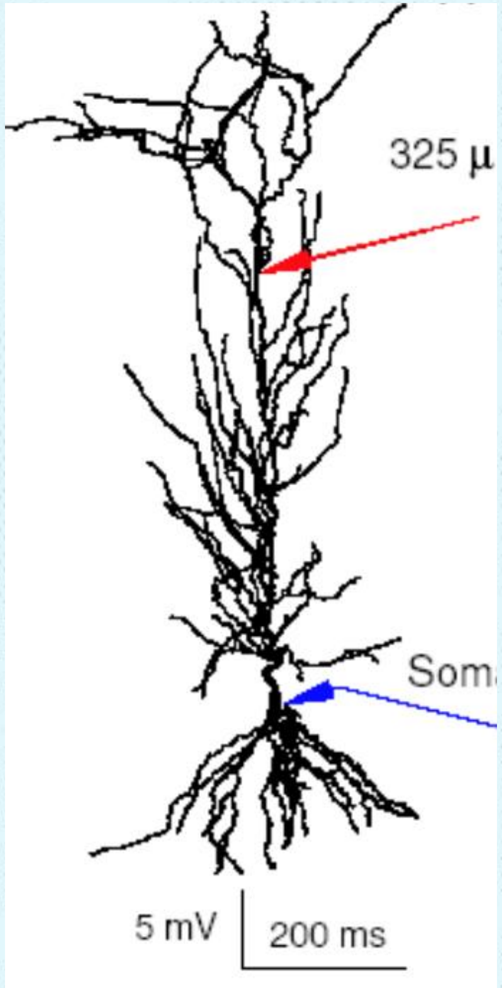
- Solving: Numerical integration!

Action potential propagation



Example 1: CA1 pyramidal cell

- Goal: understand dendritic integration in pyramidal cells
- Experiments are very difficult, replace real cells with model
- 21 types of ion channels + synapses
- Data source: primary literature on ion channels, synapses, channel densities
- Models inference: Hand-tuning!



Poirazi et al. 2003

Example 1: CA1 pyramidal cell

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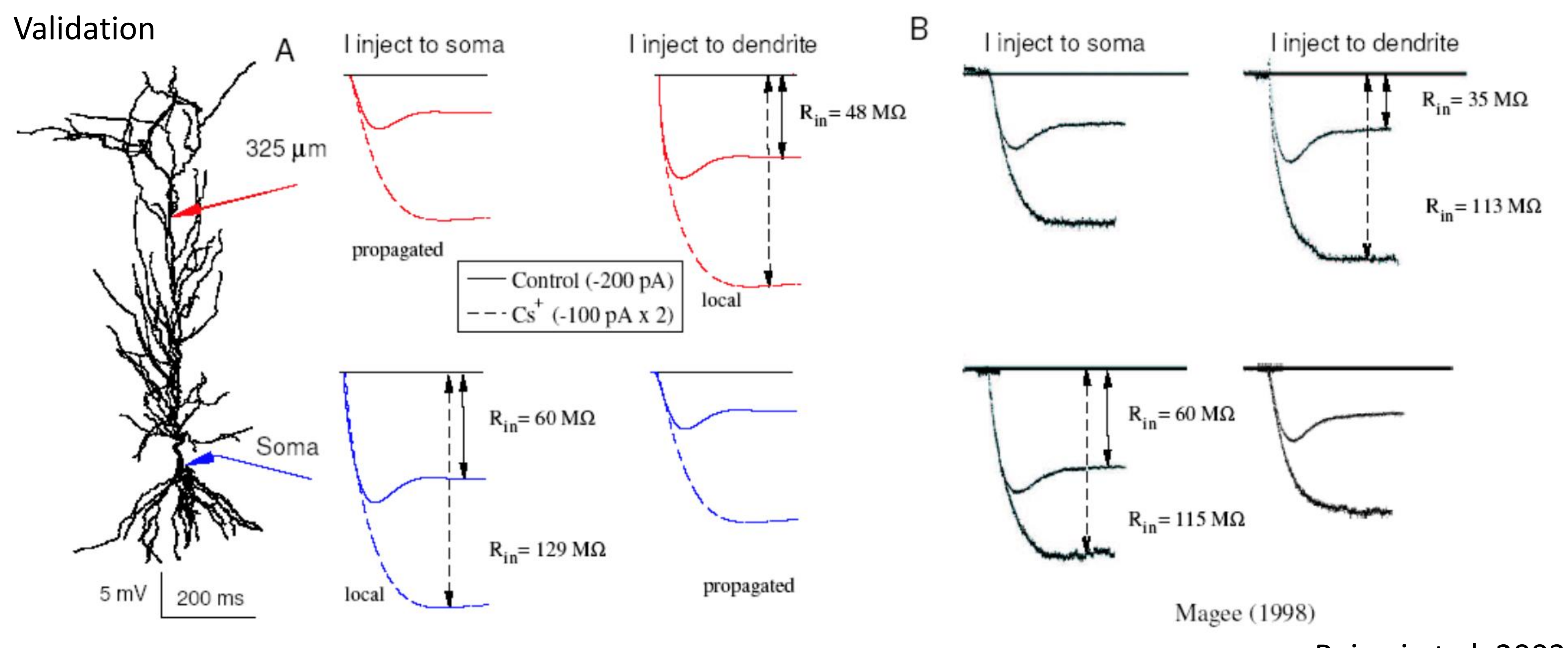
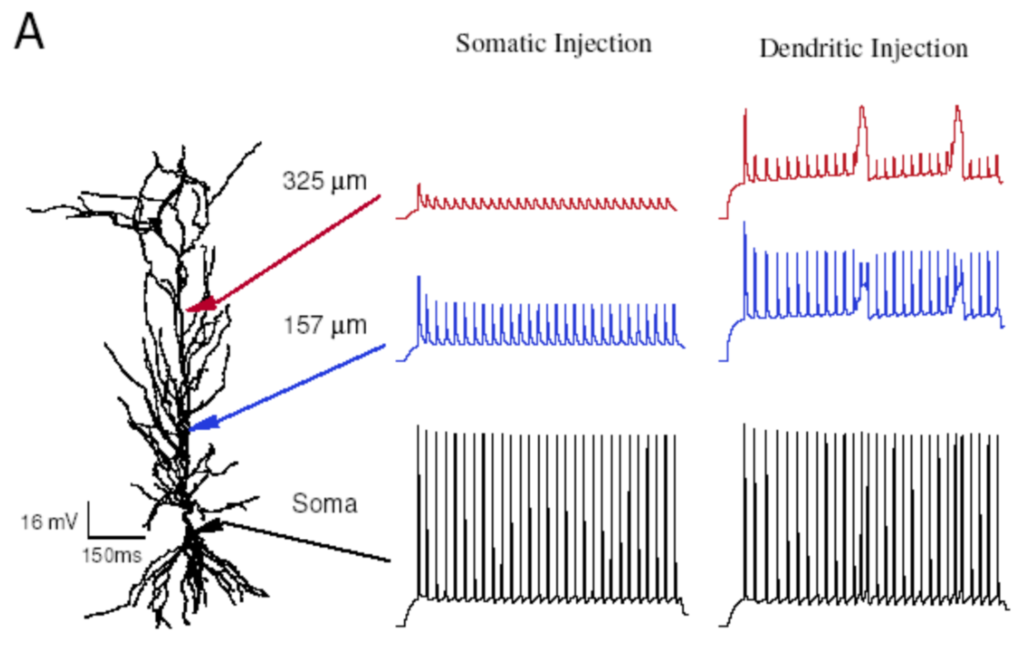
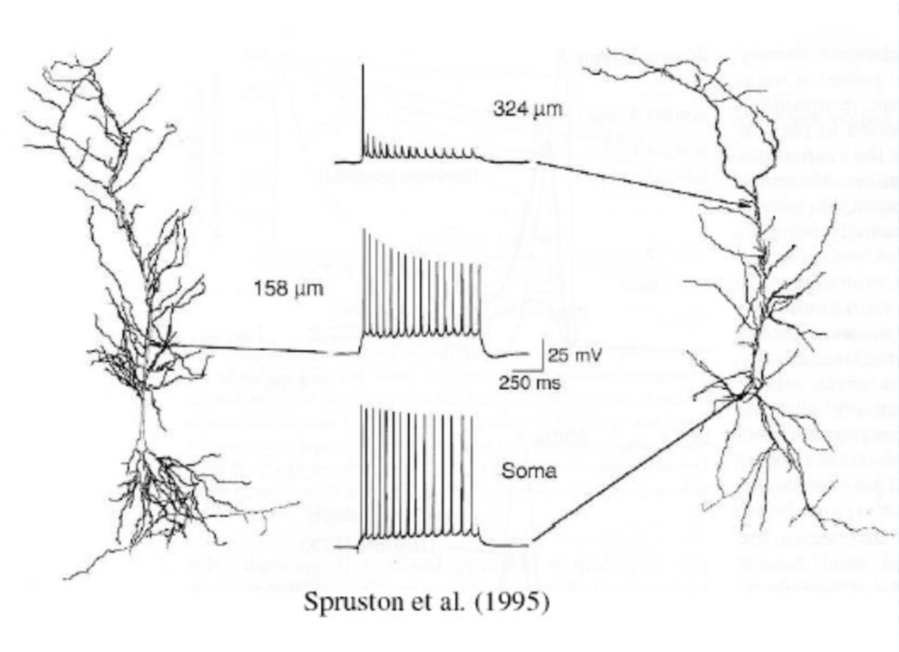


Poirazi et al. 2003

Example 1: CA1 pyramidal cell

Validation

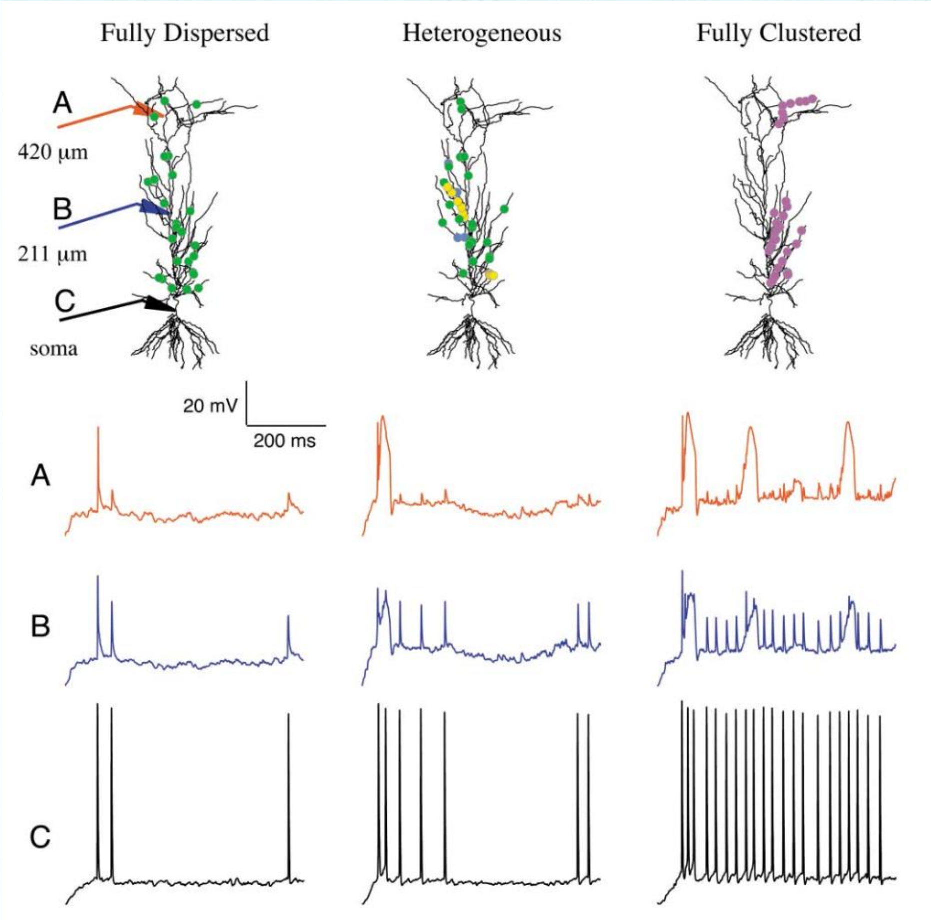




Poirazi et al. 2003

Example 1: CA1 pyramidal cell

- Placement of inputs affects propagation through the cell even with identical total input
- Dispersed: Minimal effect
- Clustered: Activates dendritic calcium spikes and leads to effective propagation



Example 2: Direction selectivity in the retina

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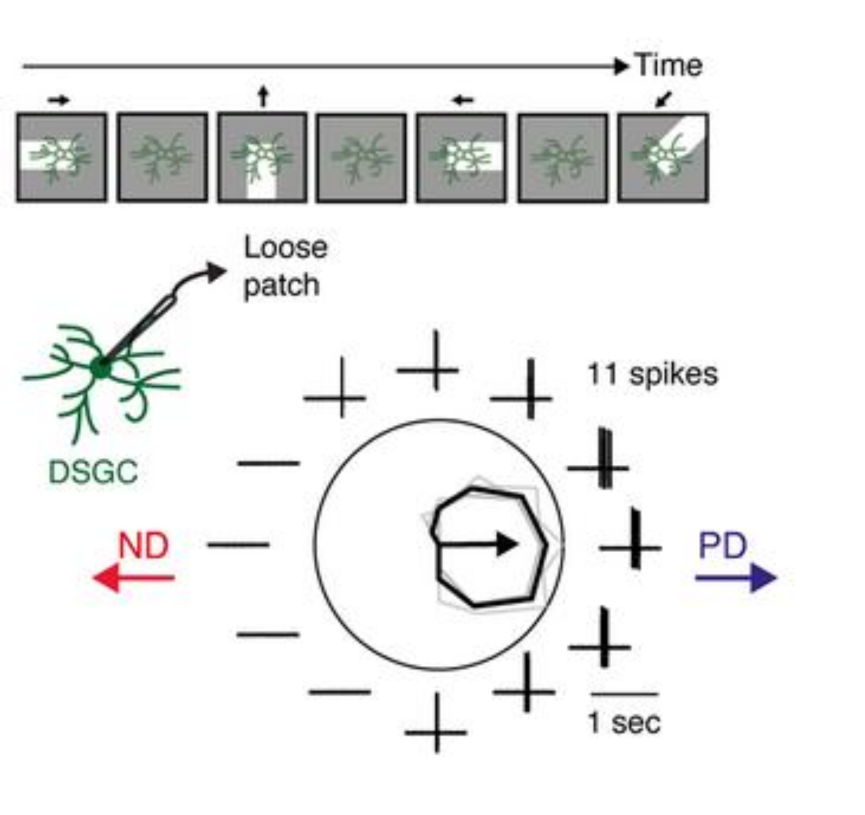
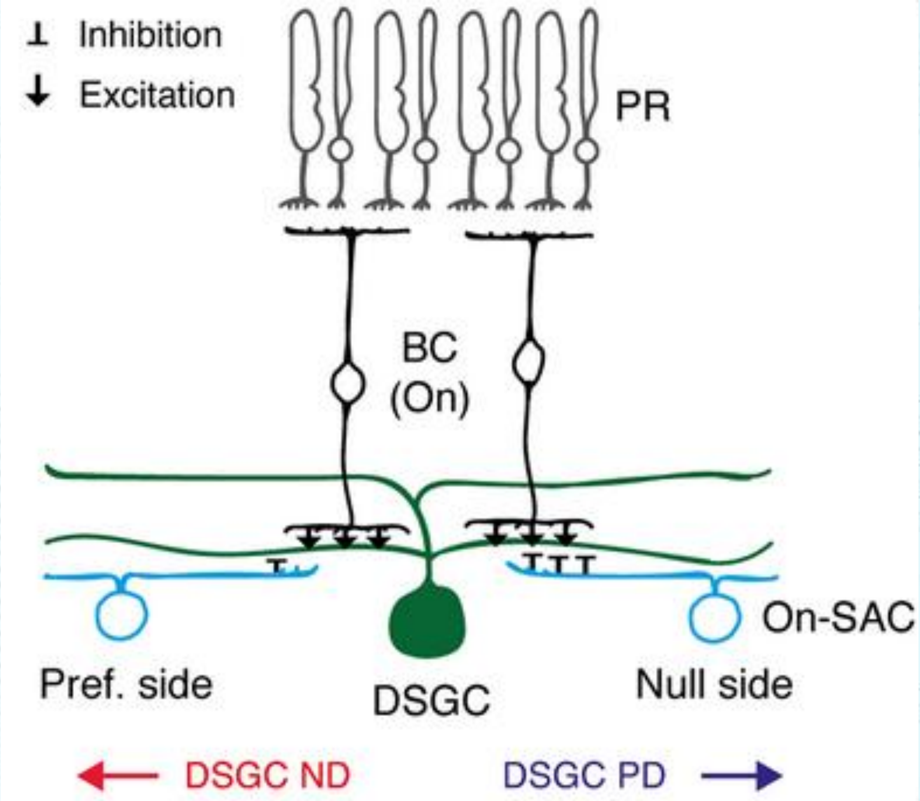
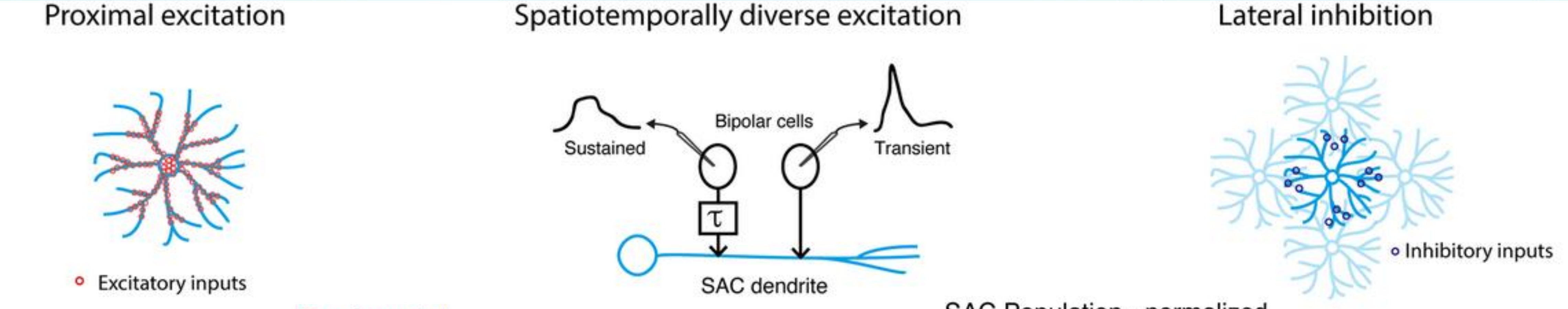


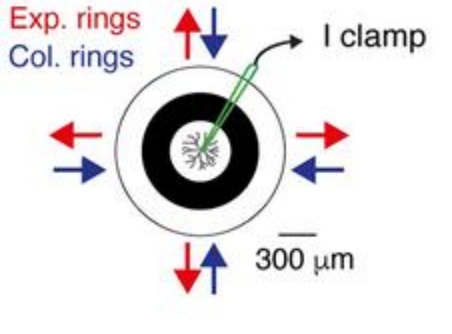


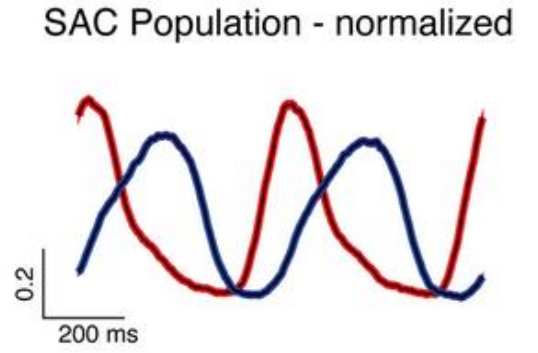
Ezra-Tsur et al. 2021

Example 2:
Direction selectivity in the retina

Goal: uncover mechanism underlying direction selectivity & role of starburst amacrine cells







Ezra-Tsur et al. 2021

Example 2:
Direction selectivity in the retina

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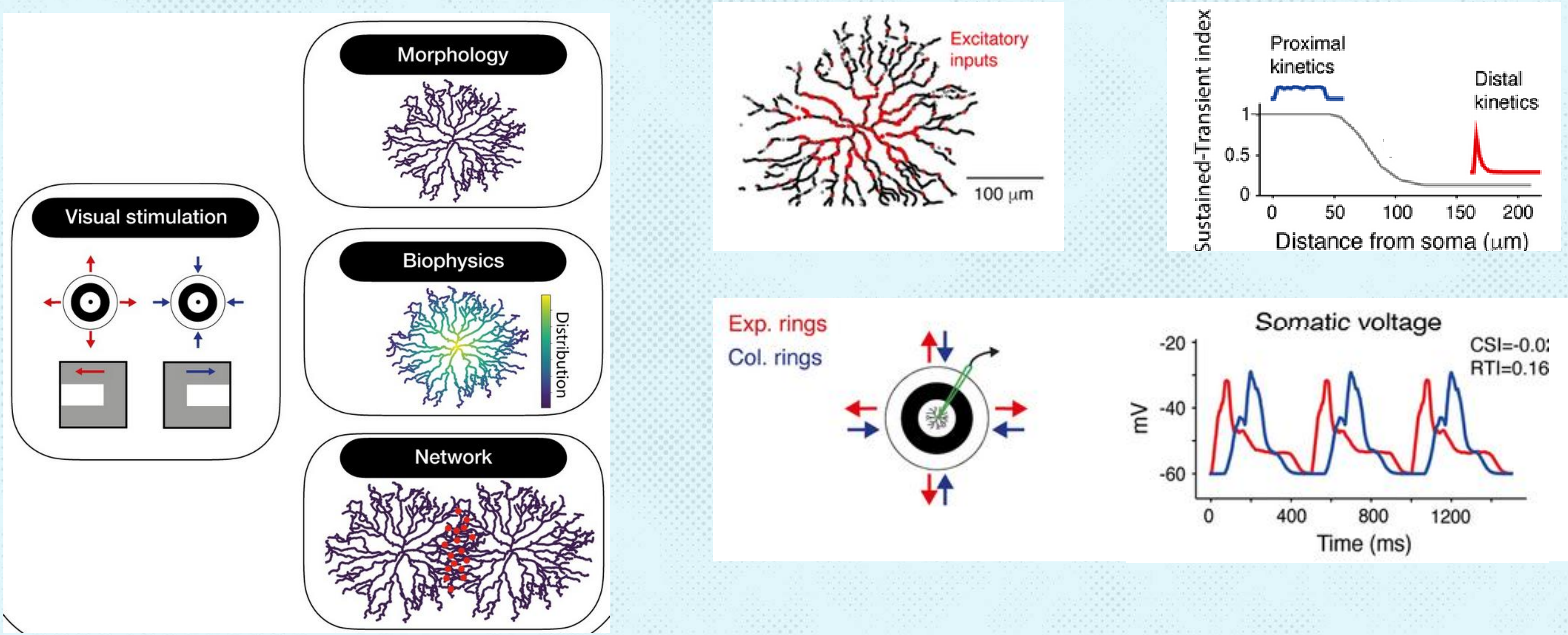

Ezra-Tsur et al. 2021

Example 2:
Direction selectivity in the retina

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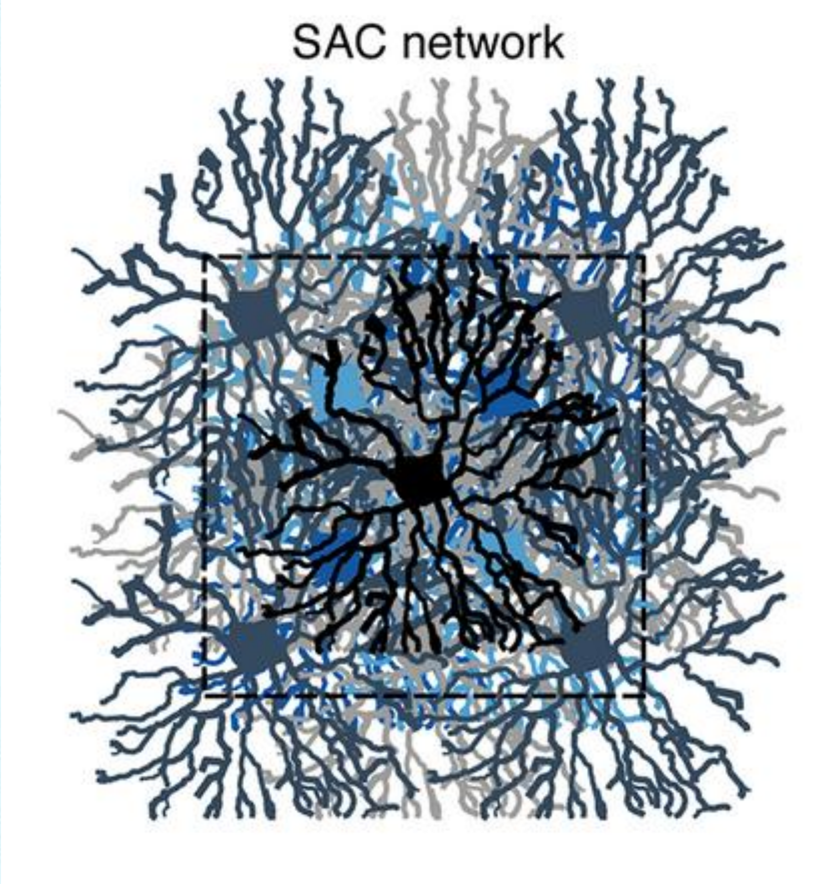
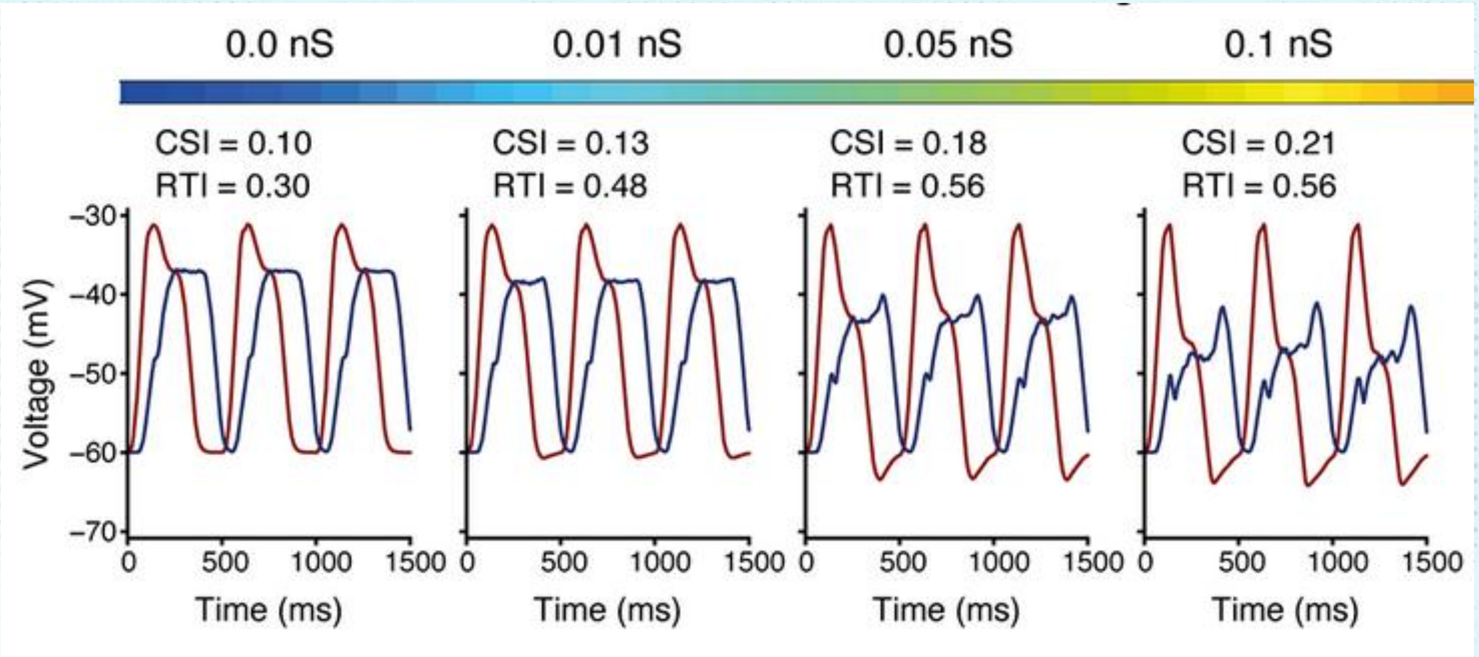
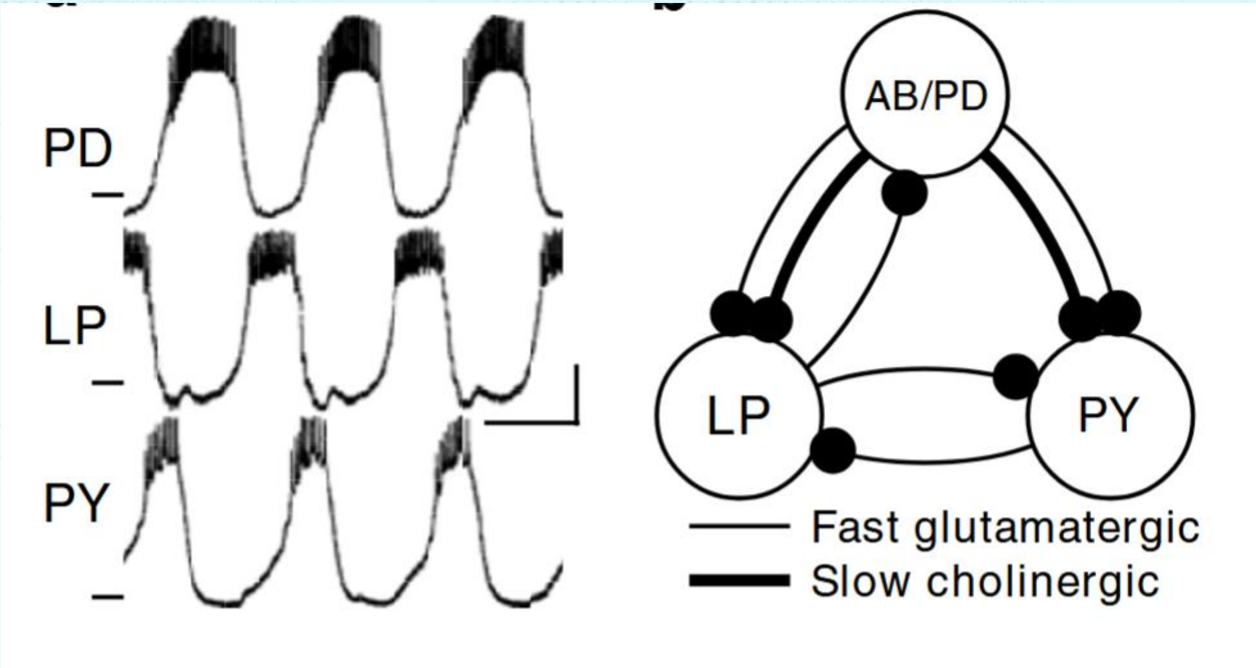




Ezra-Tsur et al. 2021

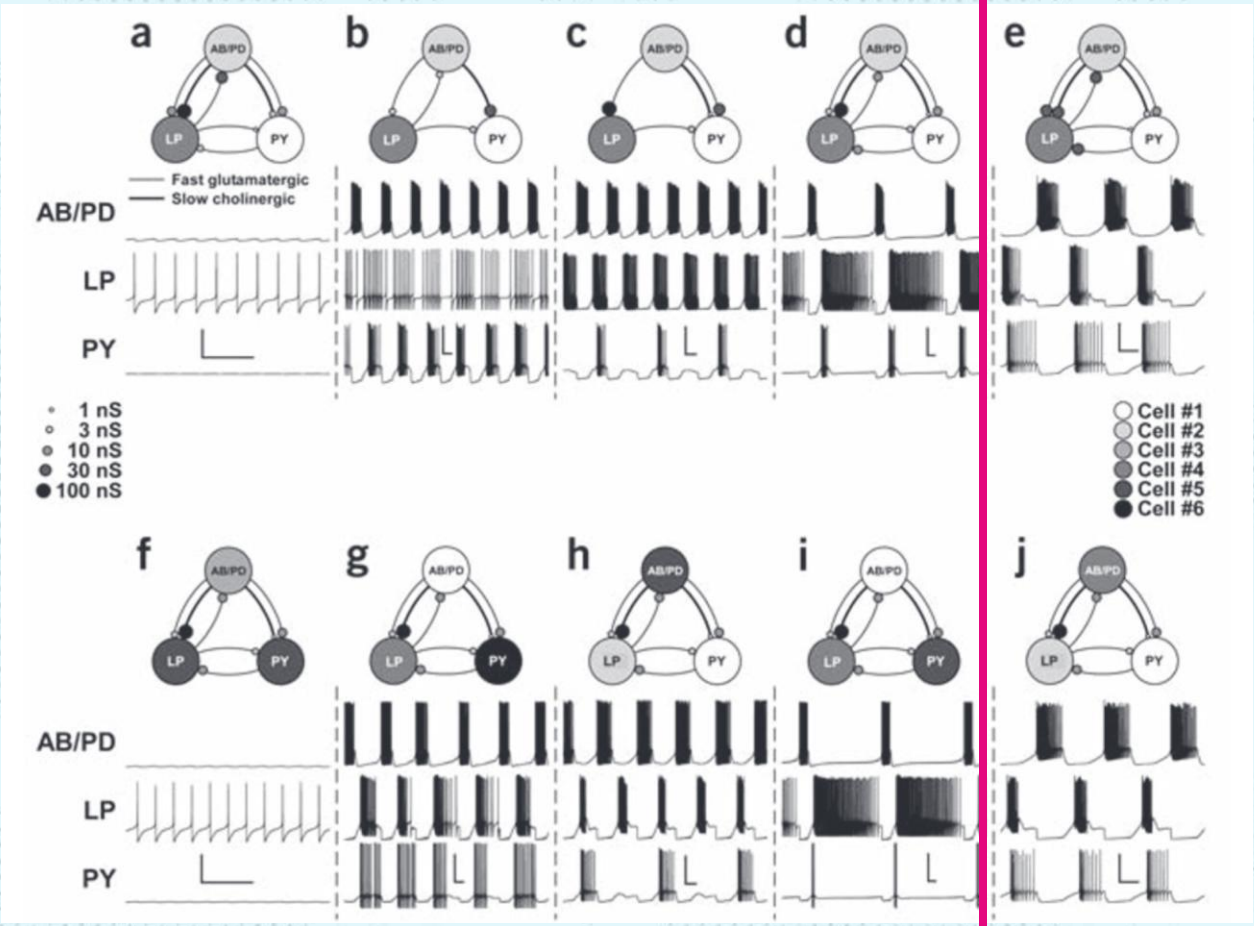
Example 3: STG circuit

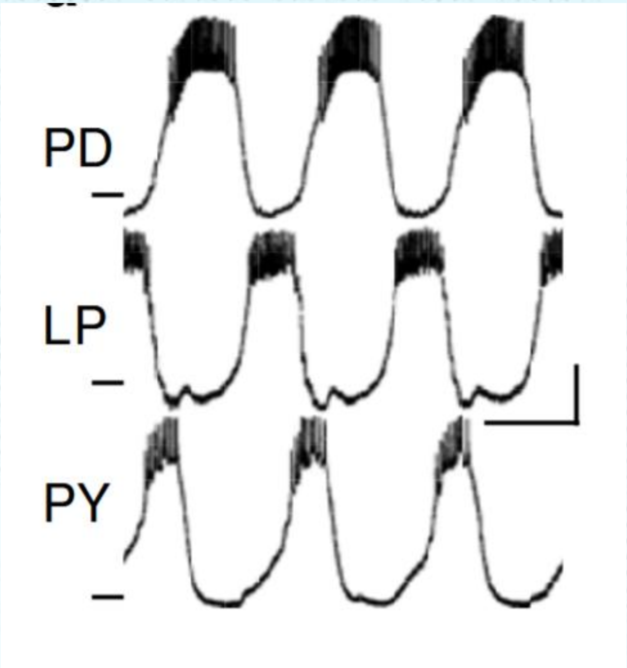
- Stomatogastric ganglion of crabs
- 3 neurons: LP, PY and PD
- Rhythmic network
- 7 synapses



Prinz et al. 2004

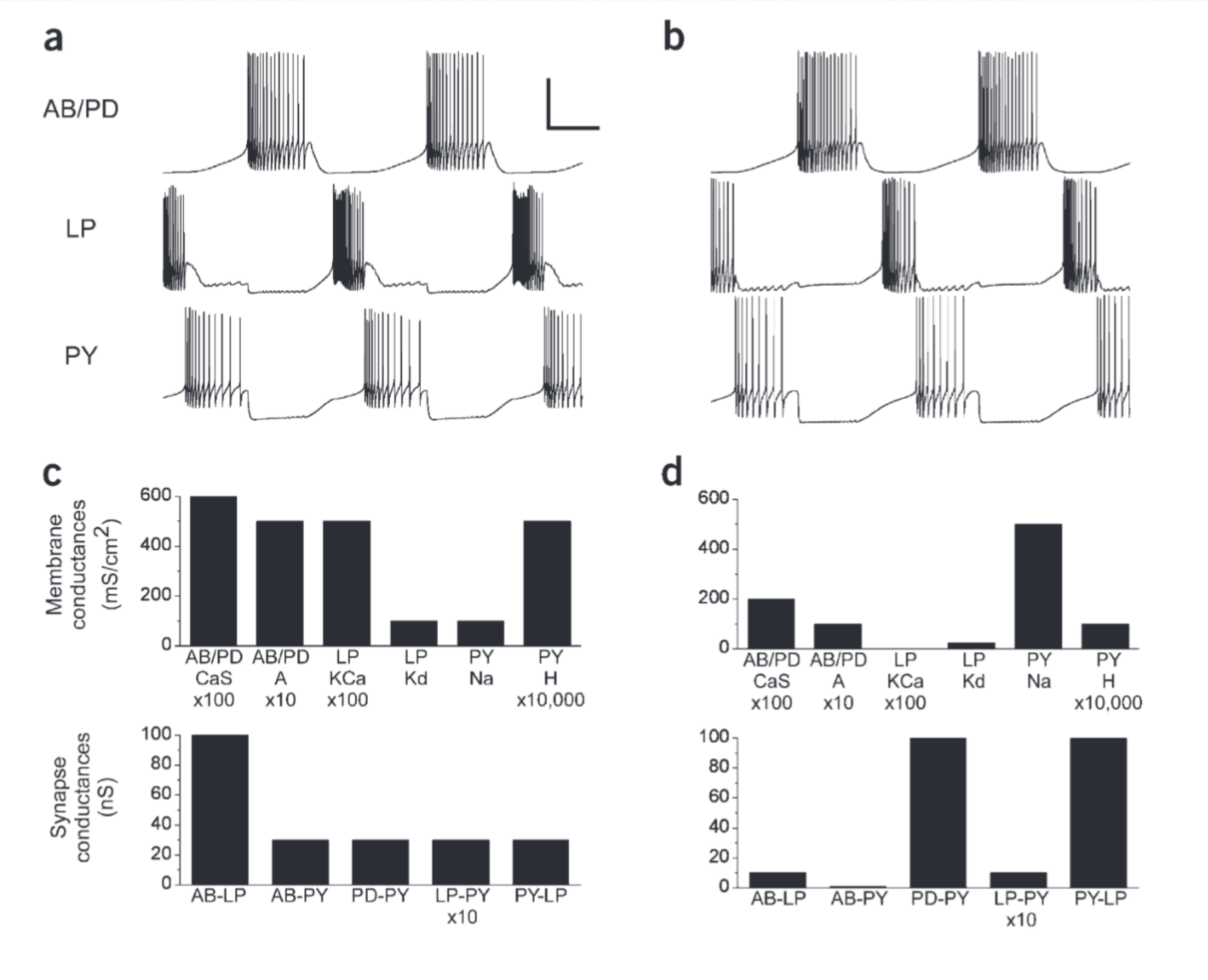
Example 3: STG circuit





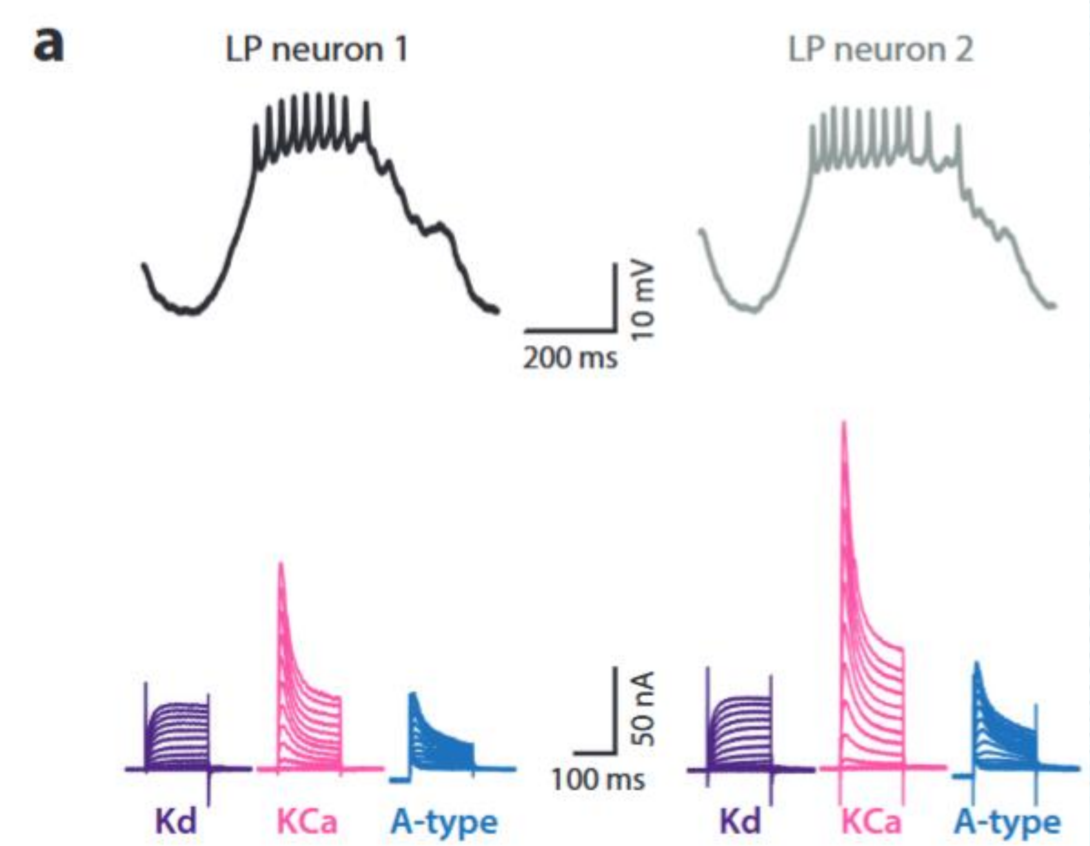
Prinz et al. 2004

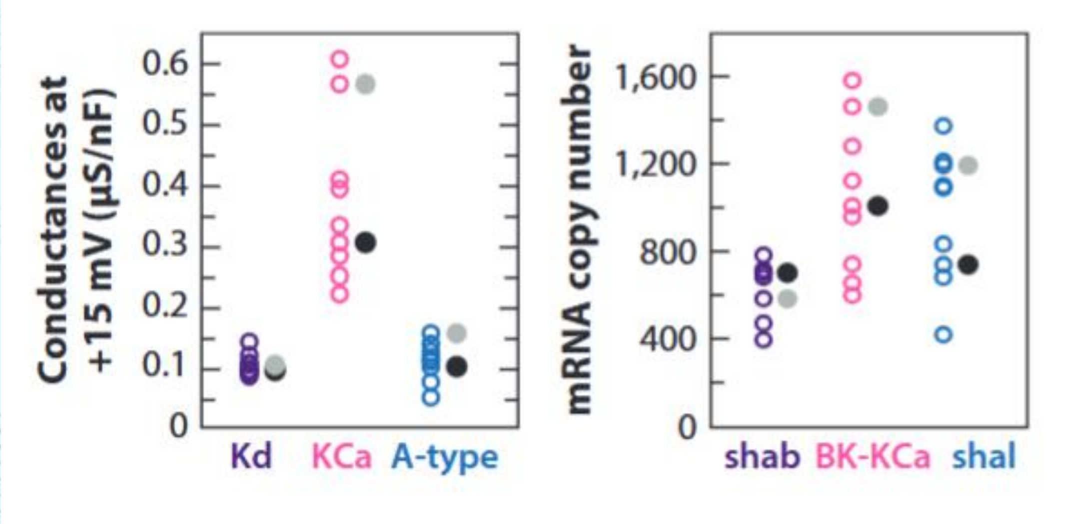
Example 3: STG circuit



Prinz et al. 2004

Example 3: STG circuit





Goaillard & Marder 2021

Simulating cellular models with Forward Euler

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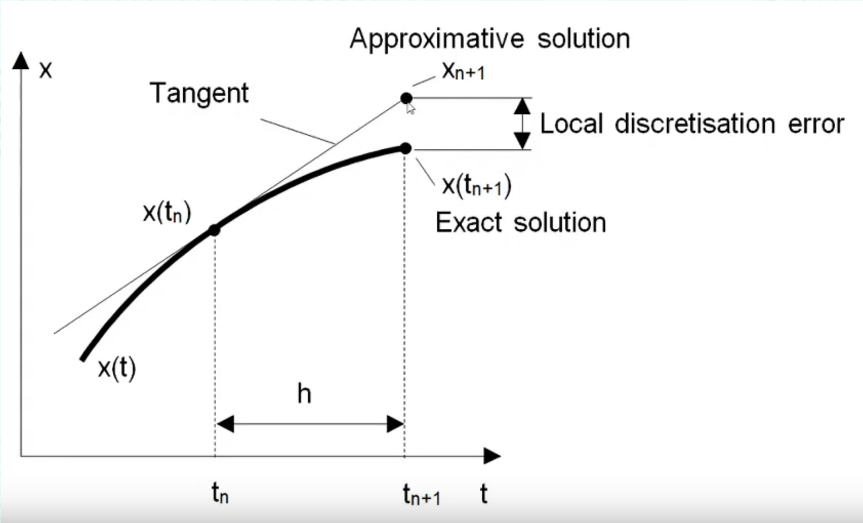
$$c_{\mathrm{m}} \frac{dV}{dt} = -i_{\mathrm{m}} + \frac{I_{\mathrm{e}}}{A} \,.$$

- Define initial time t_0 and time step Δt $\rightarrow$ solution grid: $t_n = n \cdot \Delta t$
- Compute discrete approximation to left hand side

$$c_m \frac{dV(t_n)}{dt} = c_m \frac{V(t_{n+1}) - V(t_n)}{\Delta t} = -i_m(t_n) + \frac{I_e(t_n)}{A}$$

$$V(t_{n+1}) = V(t_n) - \frac{i_m(t_n)\Delta t}{c_m} + \frac{I_e(t_n)\Delta t}{A c_m}$$

- Approximation error is large for multicompartment models



https://www.youtube.com/watch?v=rjeSqqHowTg

Software solutions

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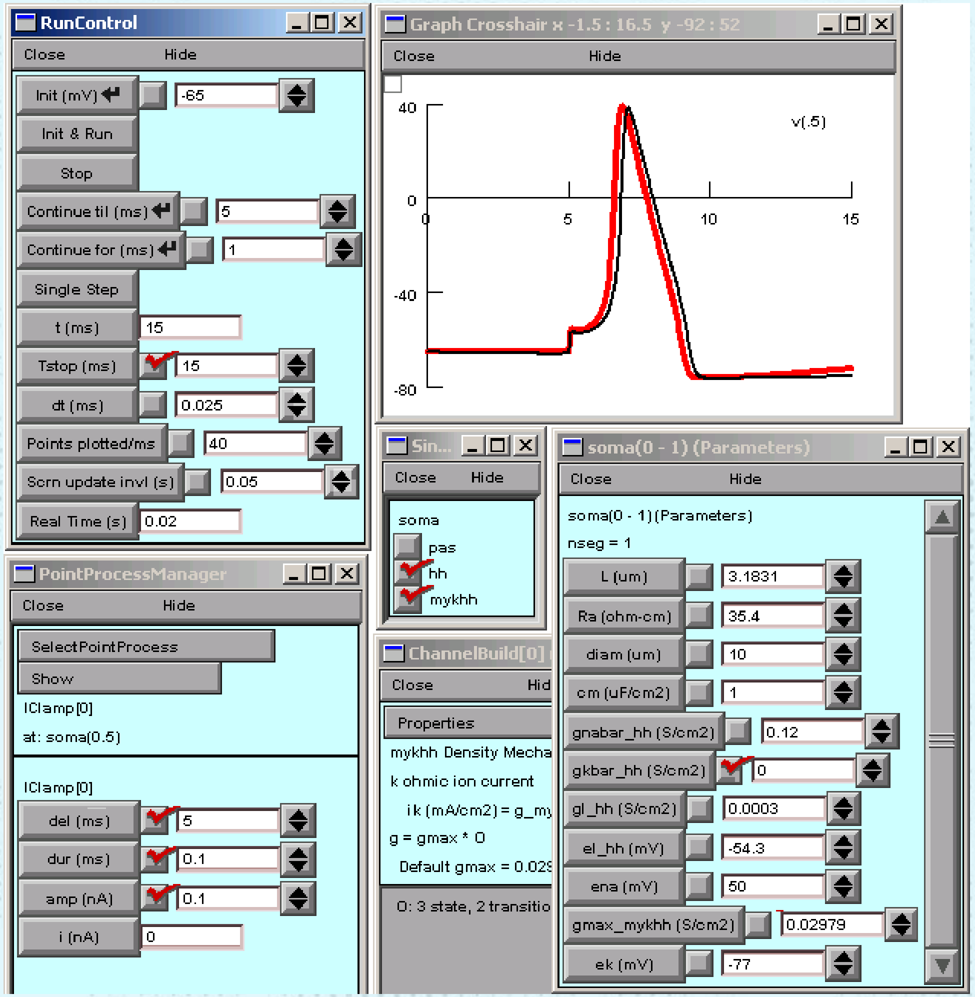
- Specialized software solutions exist for simulation of multicompartment models

- Classic simulator: NEURON

- >2000 papers



Issues with classic simulators

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Int J Biomed Comput, 24 (1989) 55—68 55
Elsevier Scientific Publishers Ireland Ltd.

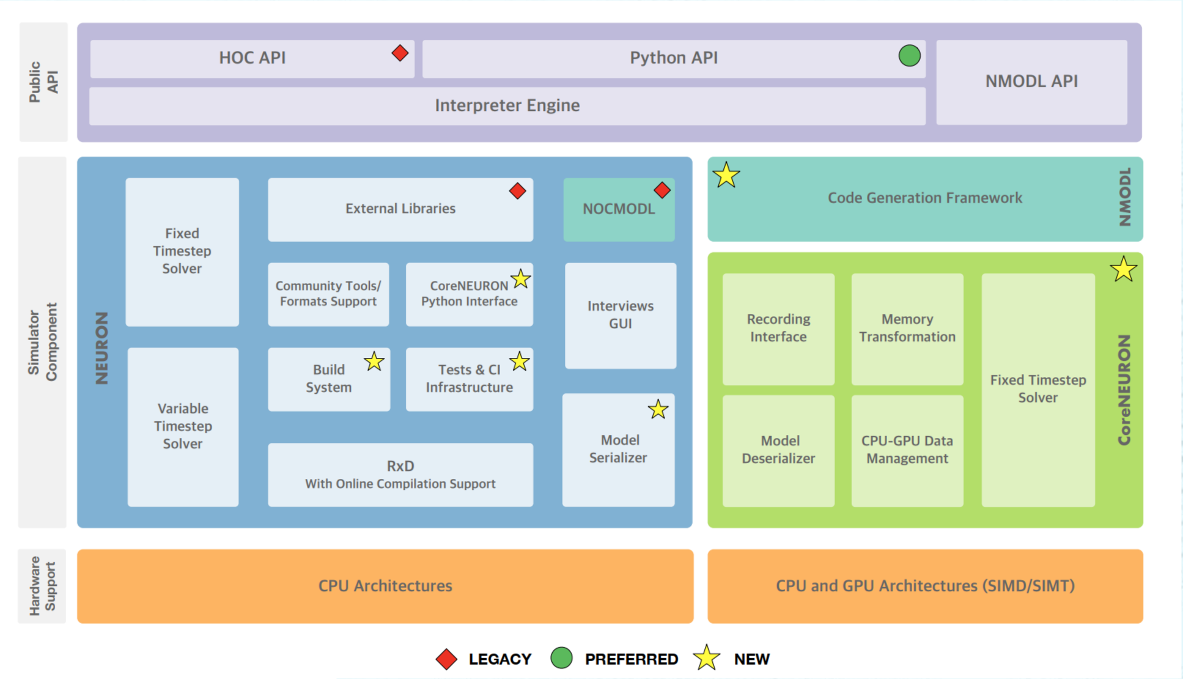
A PROGRAM FOR SIMULATION OF NERVE EQUATIONS WITH BRANCHING GEOMETRIES

MICHAEL HINES

Department of Neurobiology, Duke University Medical Center, Durham, NC 27710 (U.S.A.)

(Received September 7th, 1988)
(Accepted December 6th, 1988)

In the mid 1970s we began to carry out our simulations by
equation subroutines written in *FORTRAN* with a *FOCAL* int
*CAL*culator — a line oriented interpreter similar to *BASIC* for
Corporation minicomputers). We were astonished at the increas
this simulation methodology over the time consuming edit, comp
— much less effort was required to create a casual or explorato
gram to control the simulation. Unfortunately, since the interpreter portion of the cable program was written in Assembler (and therefore not portable to other machines) and since the program was limited to non-branching cables with Hodgkin-Huxley membrane kinetics, the program was unsuitable for general use outside our lab.



Jaxley – a modern simulator for biophysically detailed neurons

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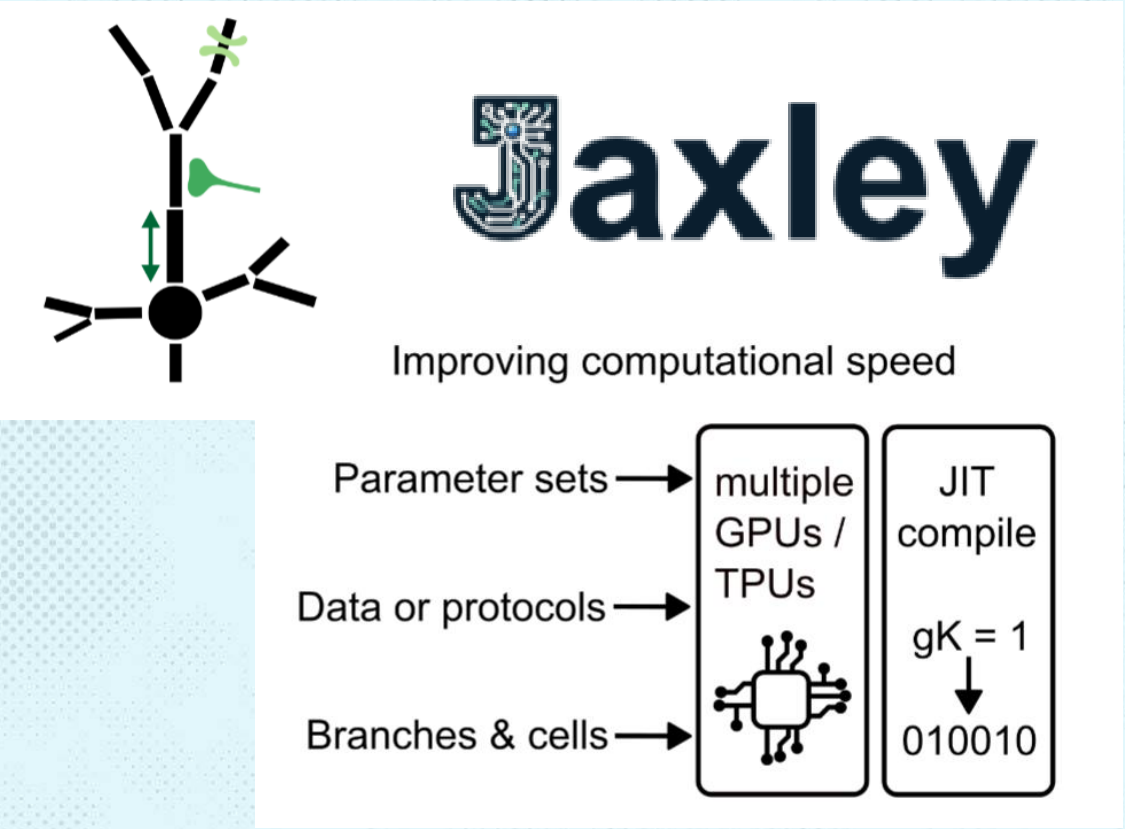
- Based on jax, a deep learning framework
- Native GPU support
- Speeds up simulation through native parallelization



Jaxley

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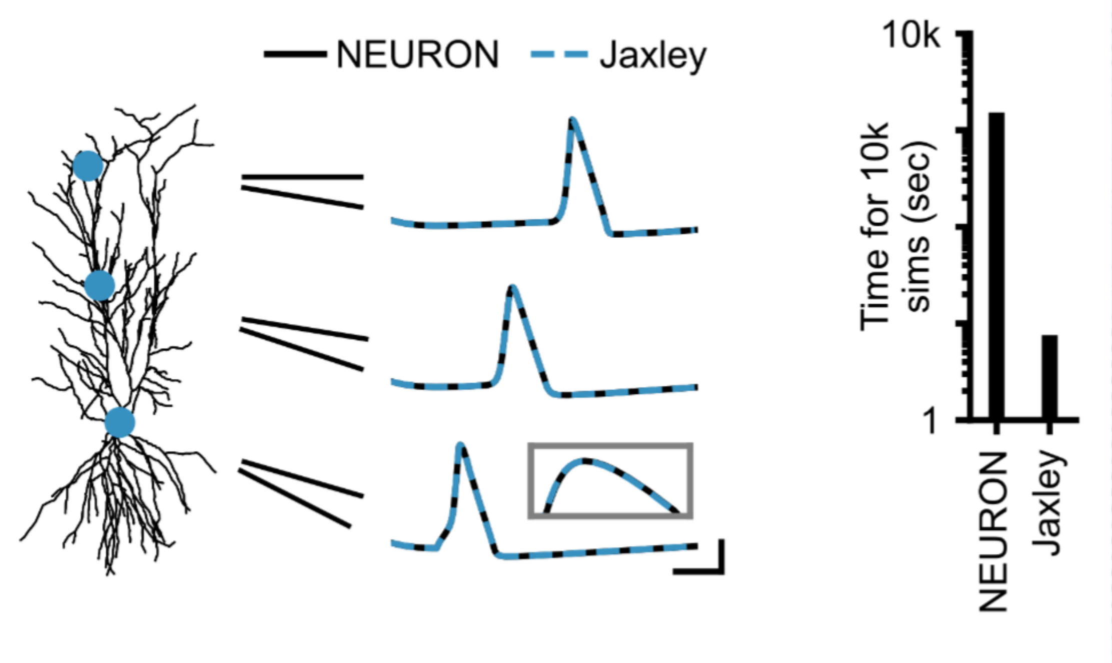
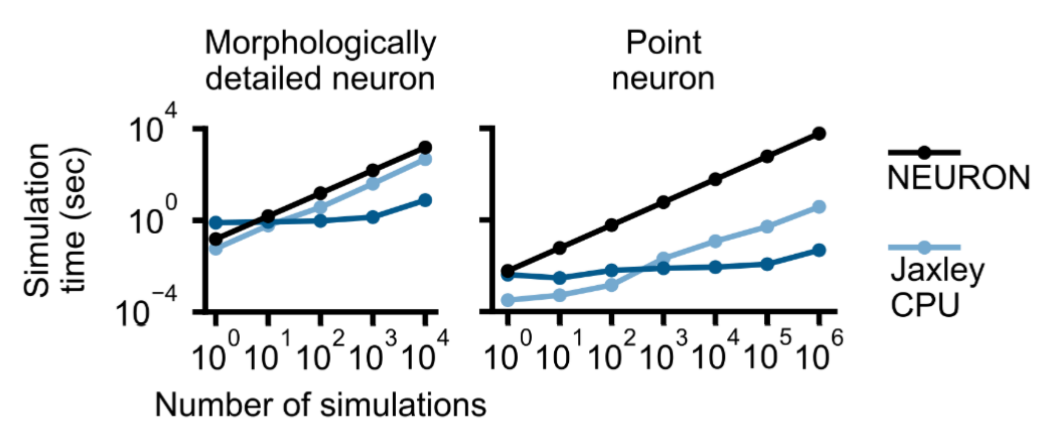
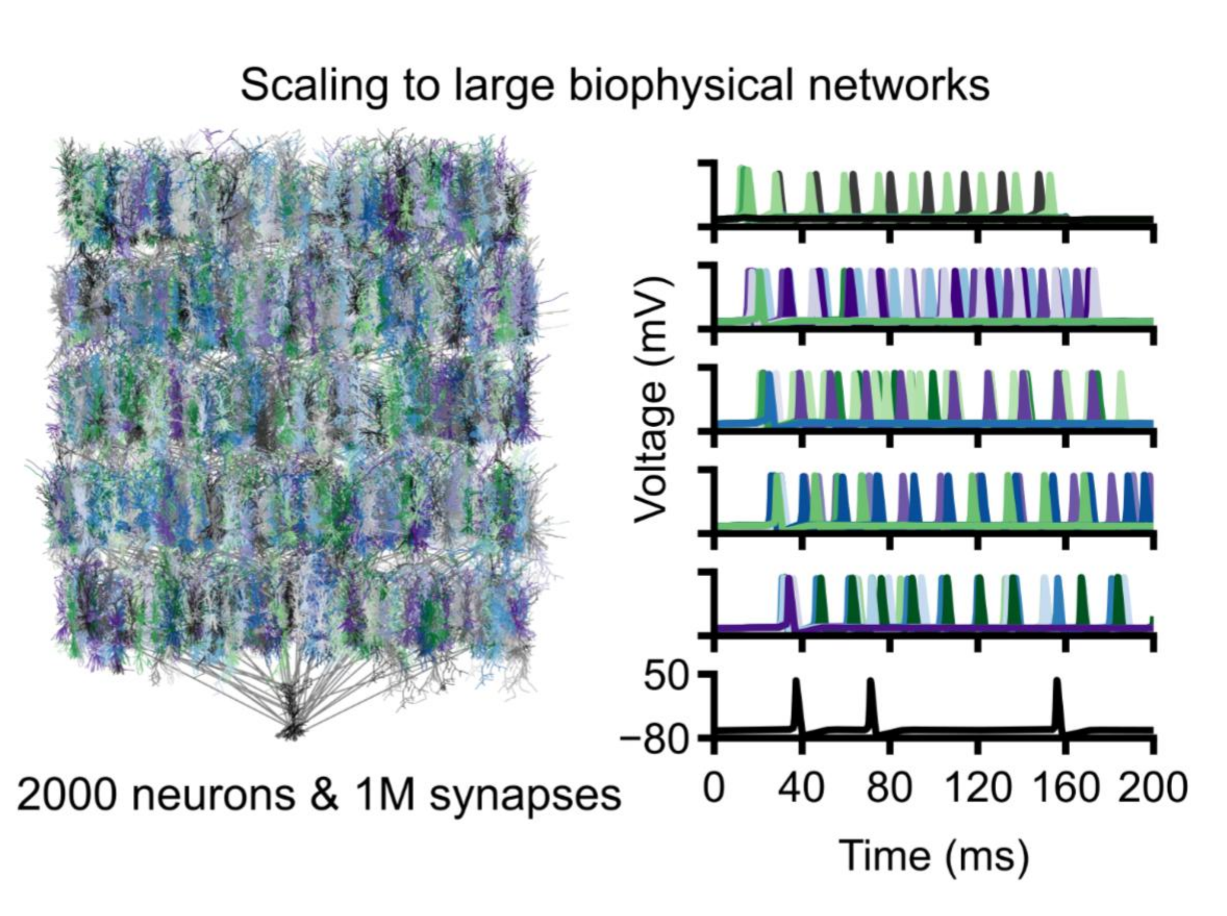




Jaxley

Simulation:
21 s



Adjusting parameters

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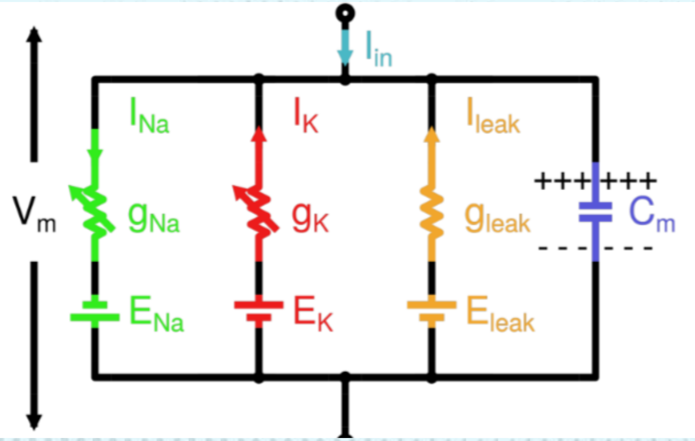
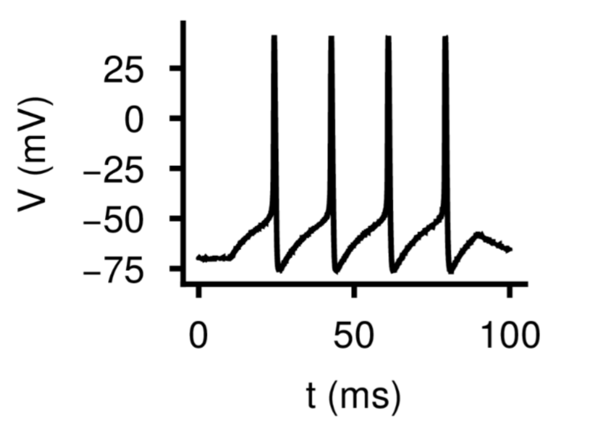
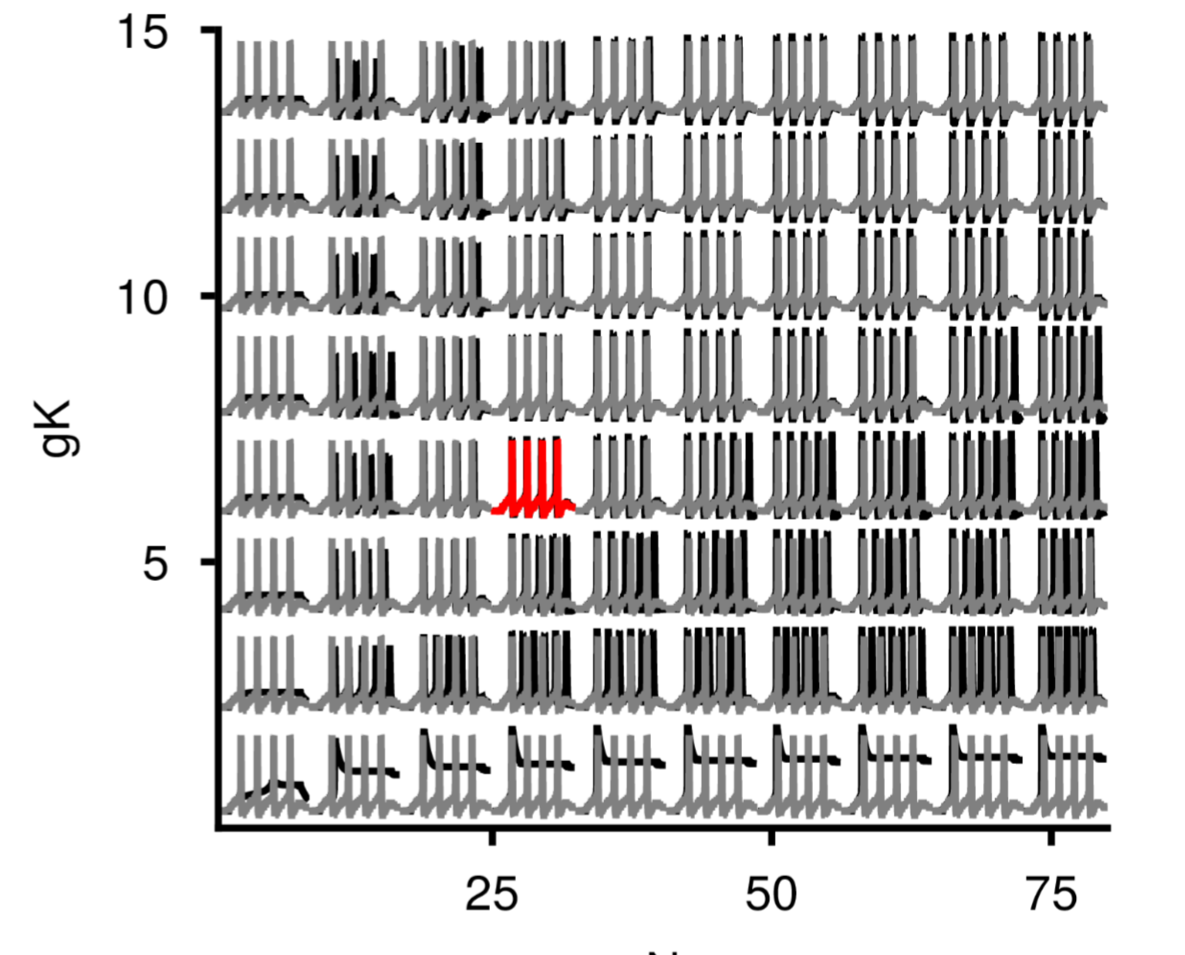
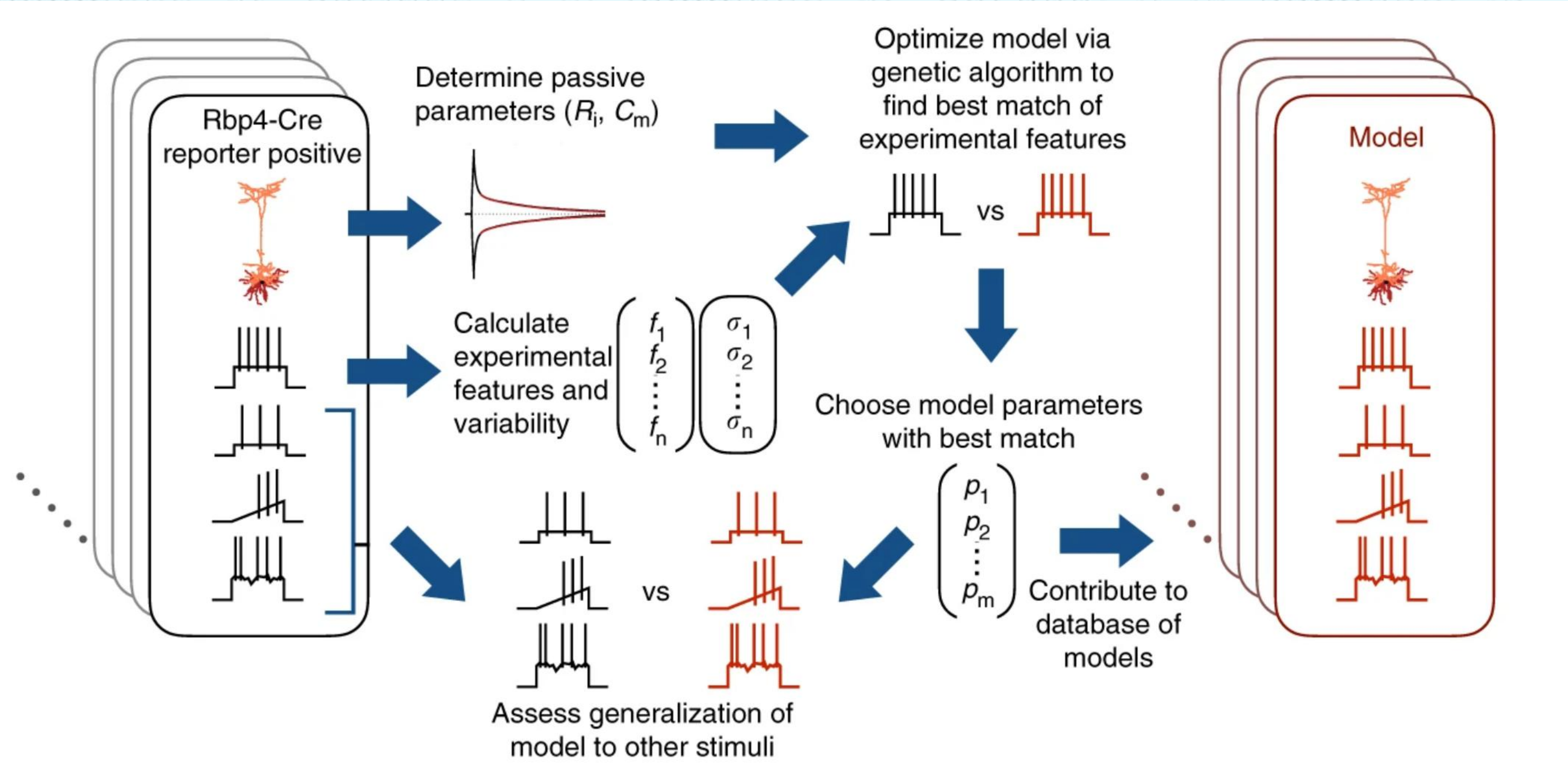






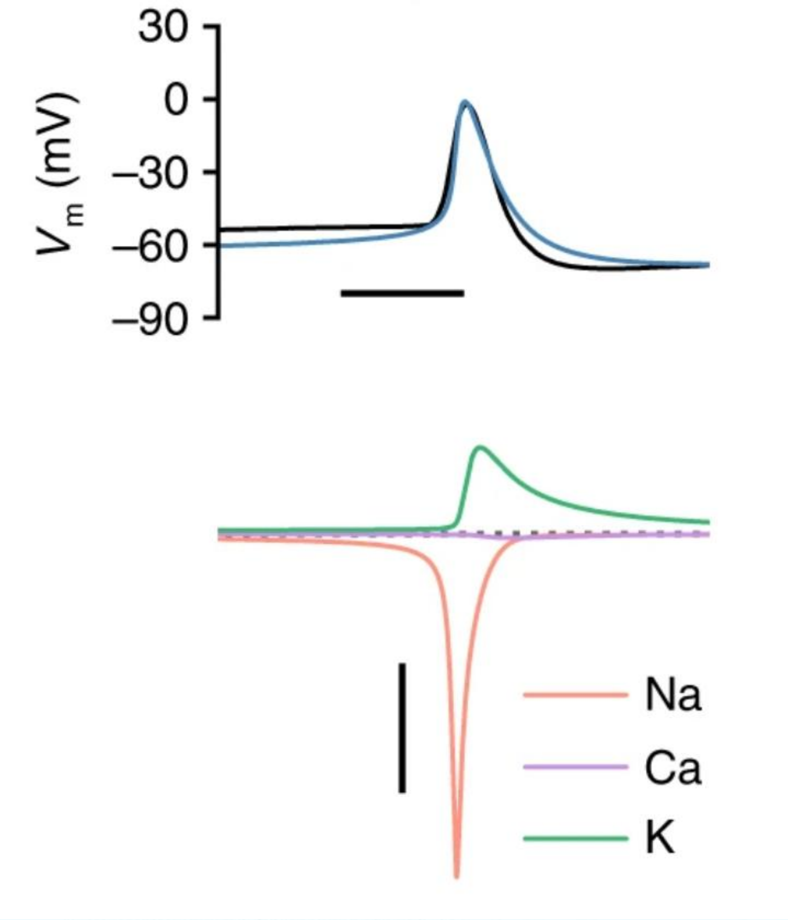
Beck et al. 2024

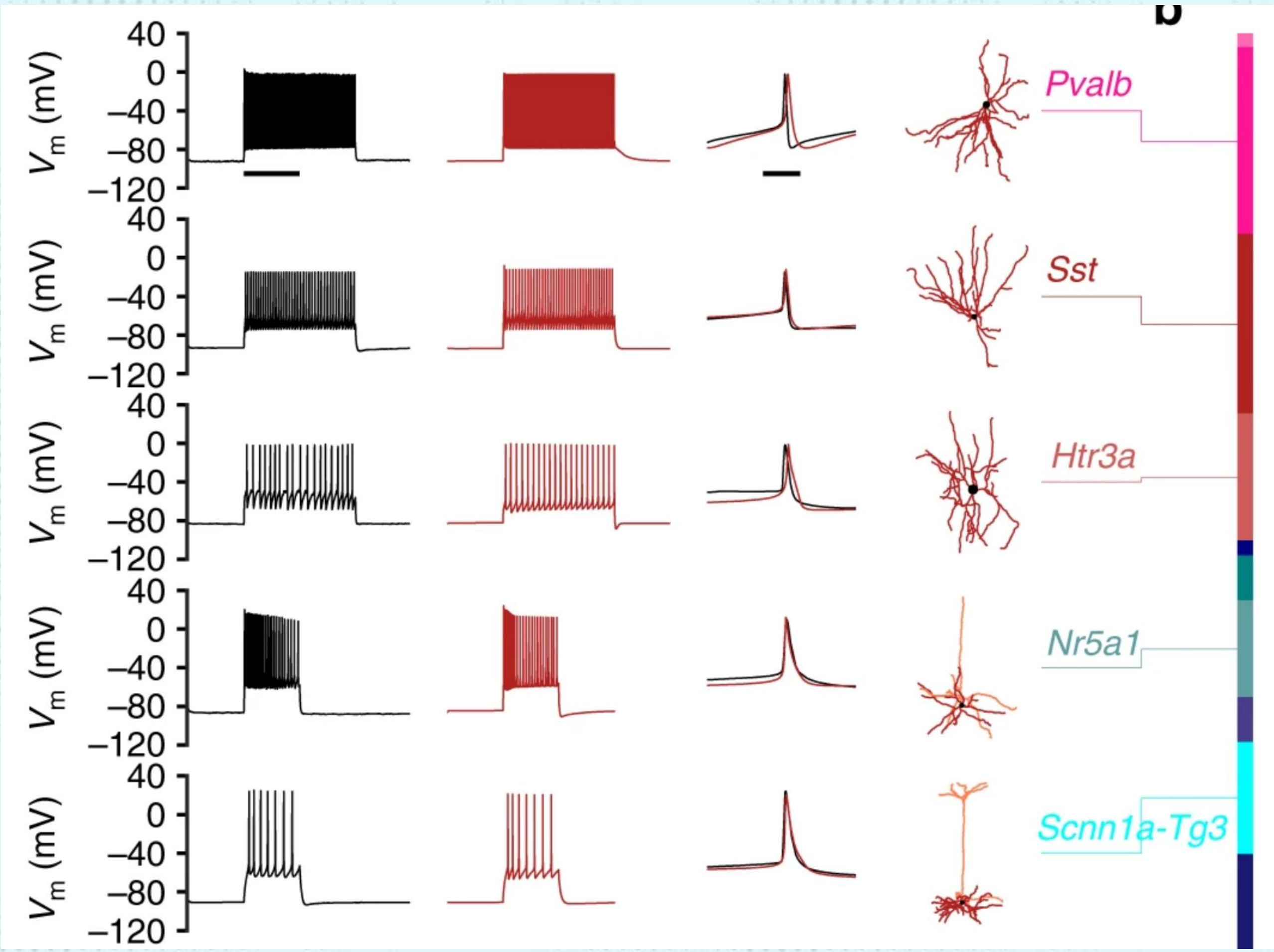
Adjusting parameters with genetic algorithms



Gouwens et al. 2018

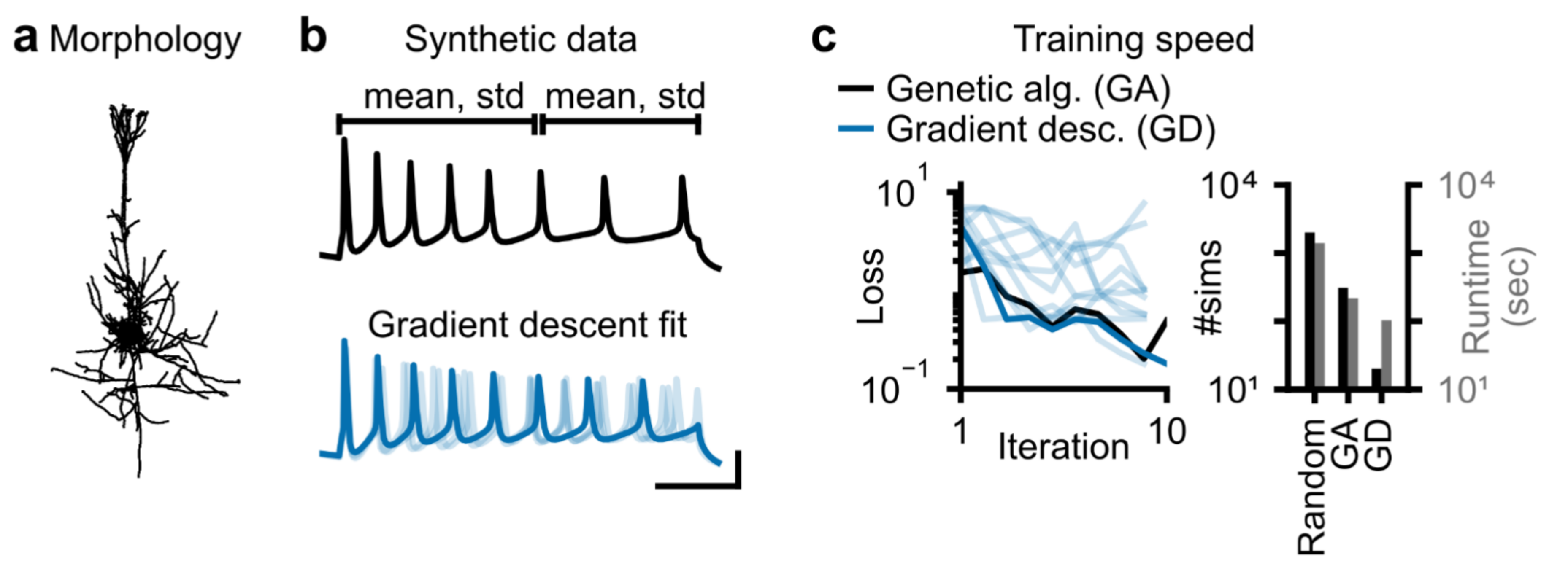
Adjusting parameters with genetic algorithms





Adjusting parameters with gradient descent

- Idea: Use auto-diff functionality of jax to get gradients!



Deistler et al. 2025

Allows to train biophysical models for ML tasks!

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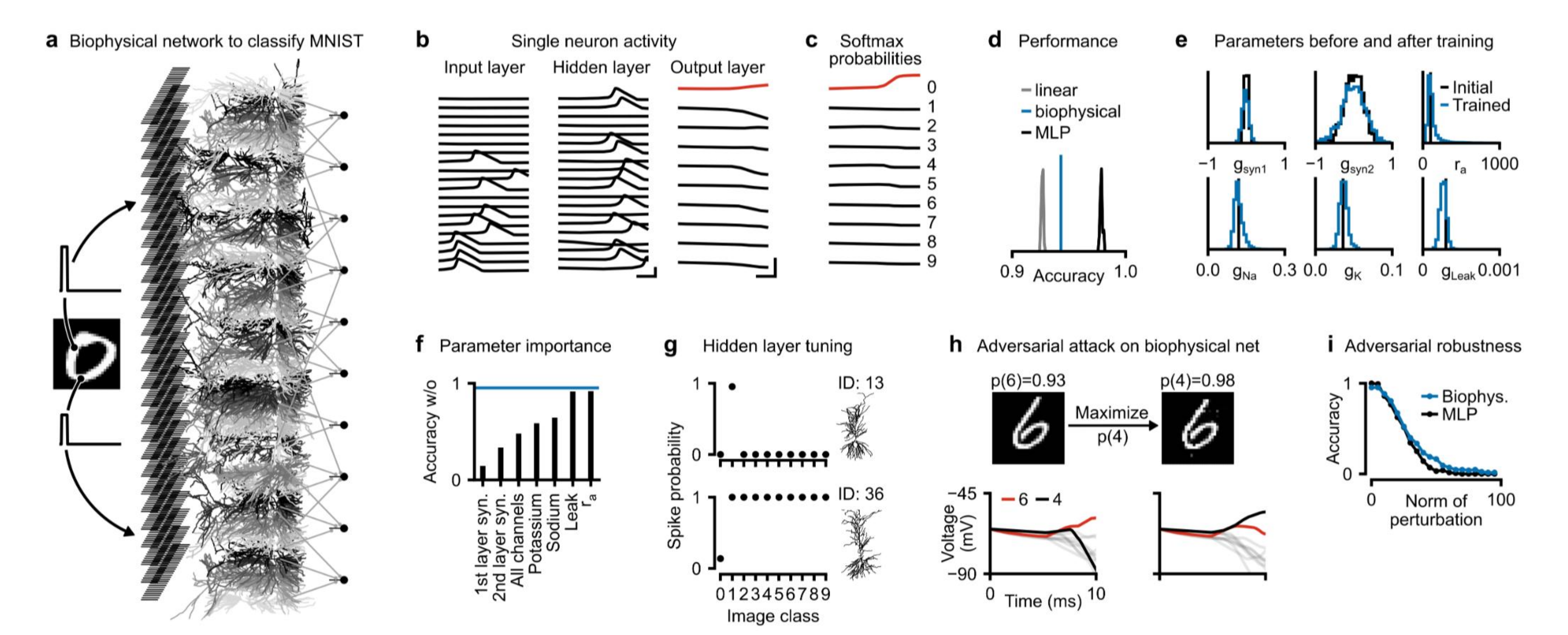
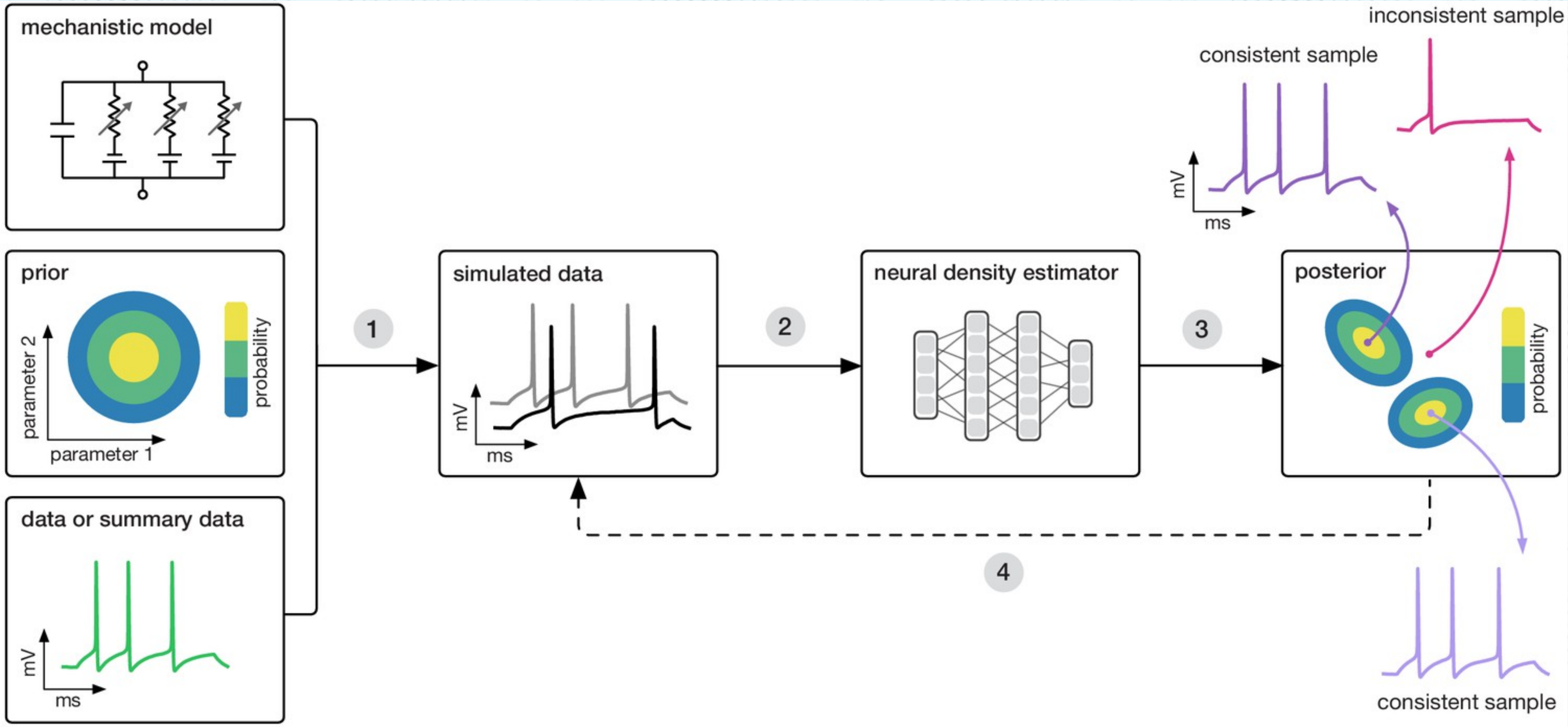


Adjusting parameters with simulation-based inference



Goncalves et al. 2020

SBI allows to identify multiple solutions

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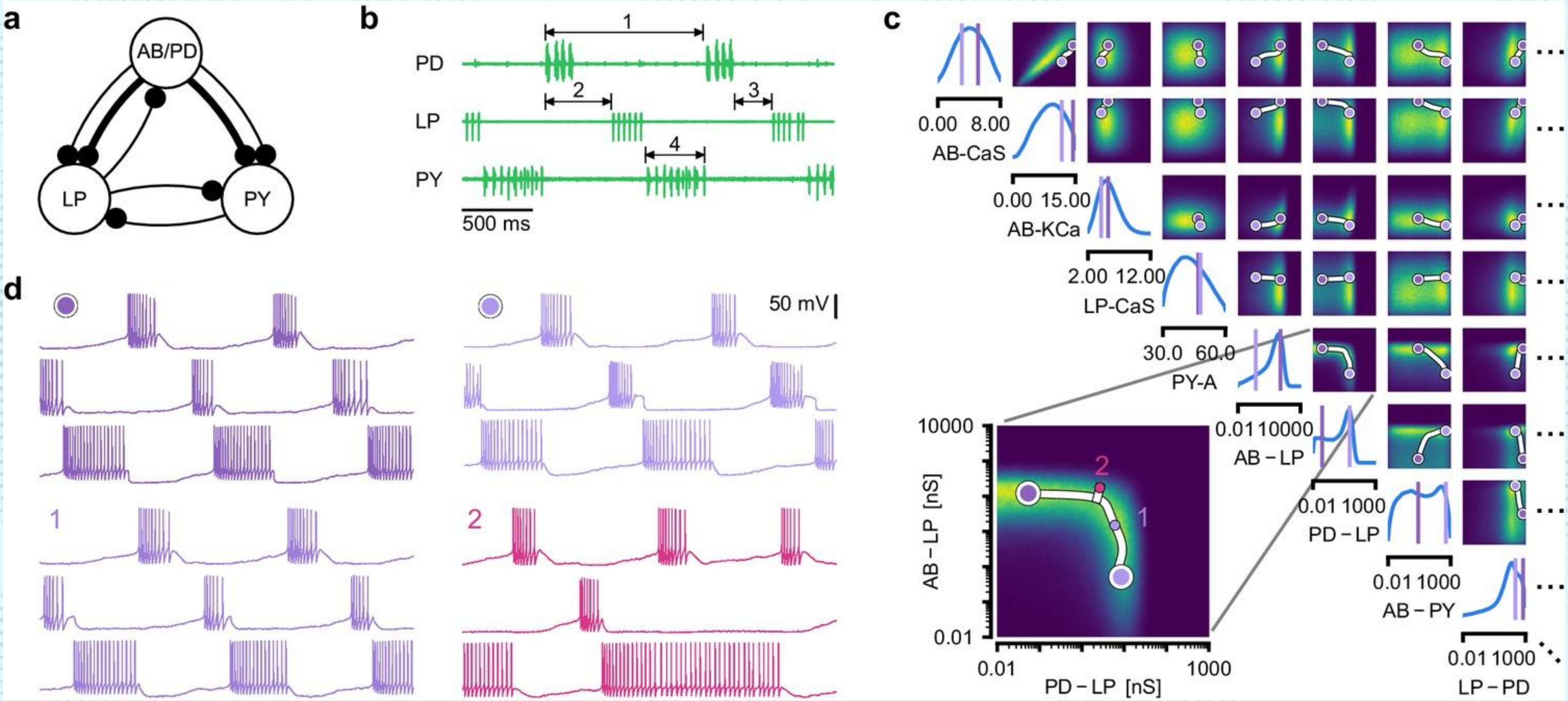

Recap

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- Roles of models in science
- Passive neuron membranes
  - Equilibrium potential of important ions
  - RC circuit model – equation, response to step stimulus
- Active neuron membranes
  - Action potentials – time course, phases, involved ions
  - Hodgkin-Huxley model – equation, time course, ion channels
- Forward Euler integration
- Parameter estimation – algorithms