

Simulation of Biological Neuronal Networks

Neuron Models

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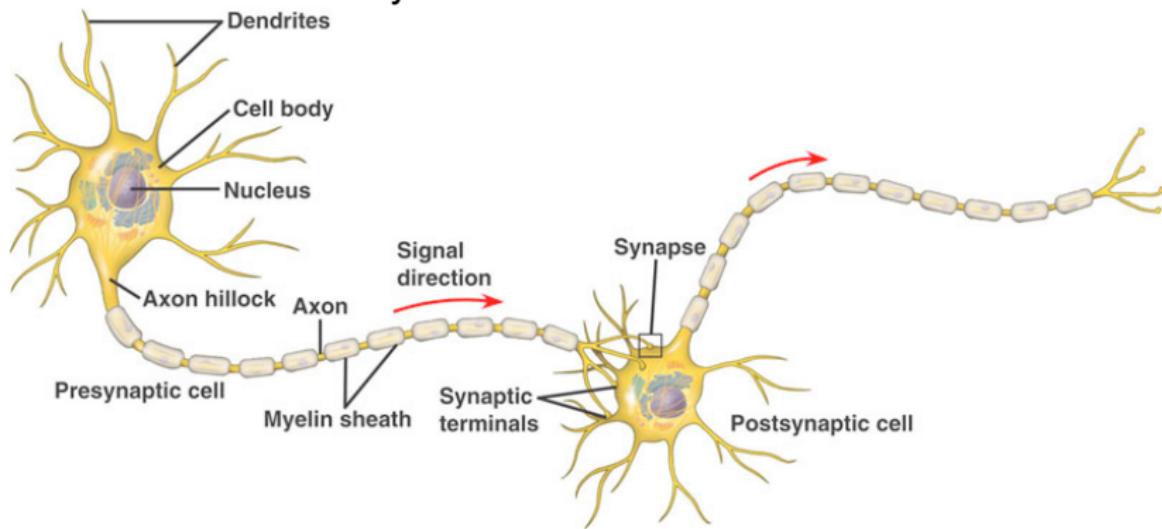
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some time July

The Neuron

All Neurons share key features:



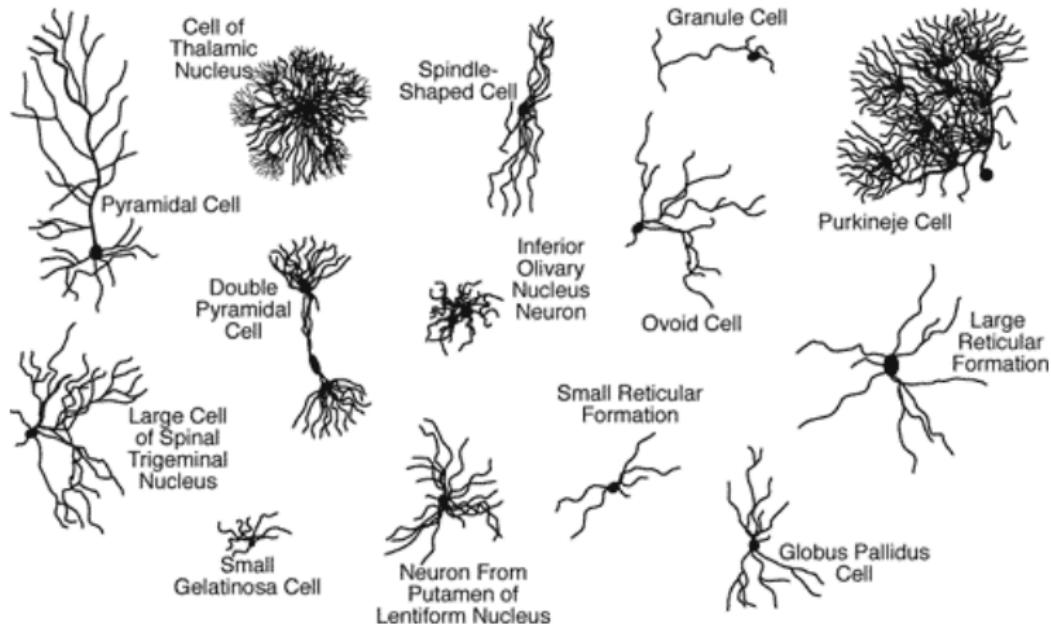
- ▶ input: dendrites ("belonging to the tree")
- ▶ integration: soma ("cell body")
- ▶ long range conduction: axon ("axis")
- ▶ output: synapse ("conjunction")

Outline

- ▶ Review of spatial structure and dynamics of a physiological neuron
- ▶ Modeling approaches: detail or abstraction?
- ▶ Representation of physiological neuron features in a point neuron model
- ▶ Advantages of the point neuron modeling approach
- ▶ Simulating a mathematical model
- ▶ Choosing a model

Spatial Structure

- ▶ There are uncountable different neuron types



based on drawings by Ramon y Cajal 1852-1934

Resting Potential

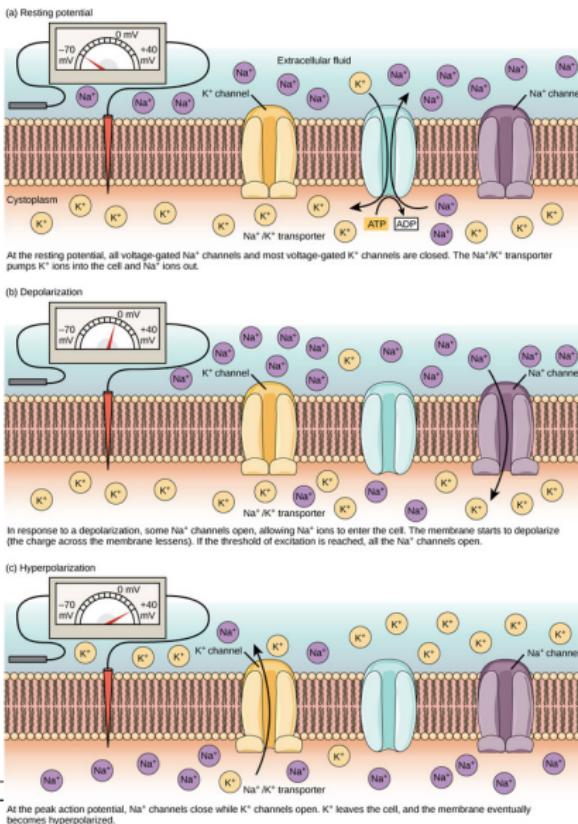
- ▶ neurons have a voltage called resting potential
- ▶ determined by concentration gradients and membrane permeability
- ▶ active ion pumps move 3 Na^+ , 2 K^+ ions to keep up gradients

▶ Nernst Potential:

$$E_{eq,K^+} = \frac{RT}{zF} \ln \frac{[K^+]_o}{[K^+]_i} =$$

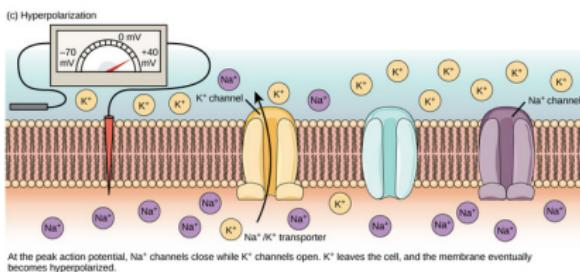
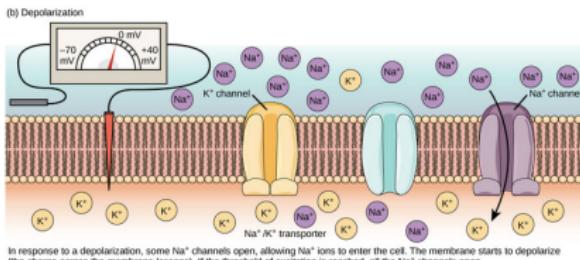
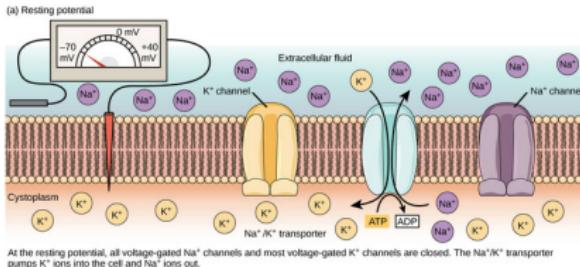
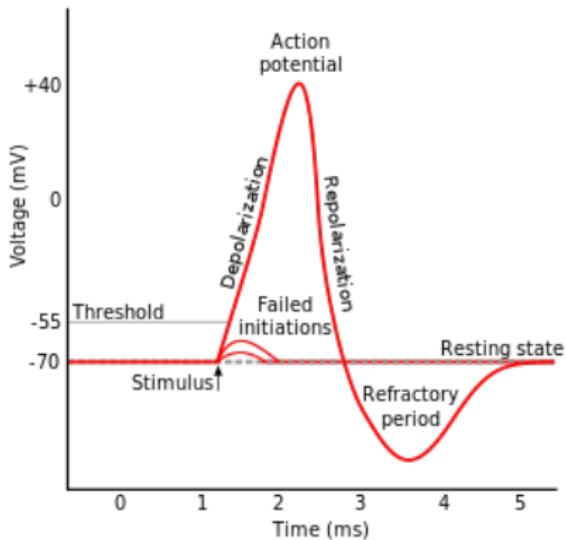
$$61.54 \text{ mV} \log \frac{[K^+]_o}{[K^+]_i}$$

▶ $E_m = \frac{g_K E_{eq,K^+} + g_{Na} E_{eq,Na} + g_{Cl^-} E_{eq,Cl^-}}{g_{K^+} + g_{Na^+} + g_{Cl^-}}$



Resting Potential

- In response to depolarization: Na^+ open, K^+ still closed
- At peak Action potential: Na^+ close, K^+ open
- Hyperpolarization: K^+ leads to overshoot



Essential features of neurons

- ▶ Connectivity/morphology
- ▶ Internal dynamics that integrate inputs
- ▶ generation of action potentials

If we want to investigate these features outside of experiments
we need to capture these features

Two main approaches

- ▶ detailed (biophysical) neuron models
- ▶ Reduced (abstract) neuron models

we will focus on the latter one specifically point neuron models

Detailed neuron models

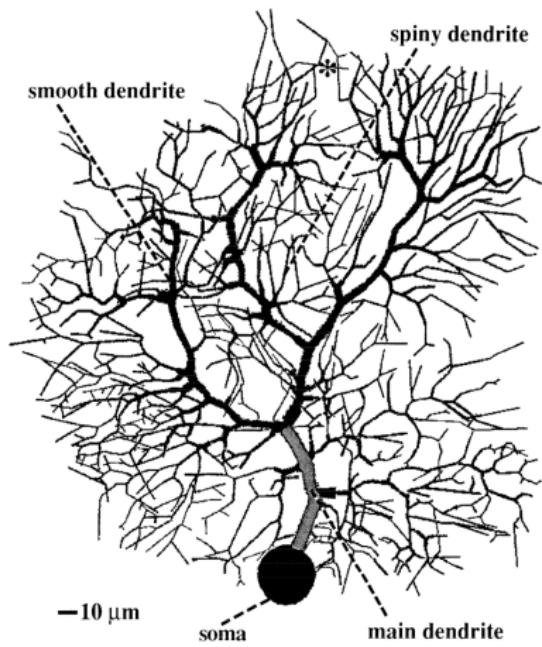
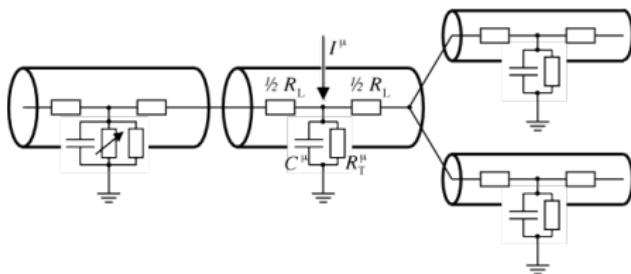


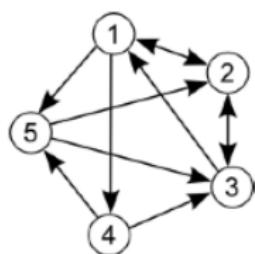
FIG. 1. Morphology of the Purkinje cell model (*cell 1* of Rapp et al. 1993). The 3 zones with different channel densities (Table 2) are marked as soma (black), main dendrite (dark gray), and the rest of the dendrites (black). Dashed lines: recording sites displayed in Figs 3–7. Asterisk: recording site for Figs. 12 and 13.



- ▶ Reconstruct neuron morphology from images
- ▶ decompose into compartments (between branches)
- ▶ define/fit/tune properties of individual compartments
- ▶ Simulate in e.g. Neuron

Detailed neuron models

Morphology is reduced to a directed graph:



directed graph

from →

	to →	1	2	3	4	5
from ↓	0	1	0	1	1	
	1	0	1	0	0	
	1	1	0	0	0	
	0	0	1	0	1	
	0	1	0	1	0	

connectivity matrix

1	2	3	4	5
2	1	1	3	2
4	3	2	5	3
5				

adjacency list

(or any network)

Connectivity matrix can be updated to include connection weight

Why all this complexity?

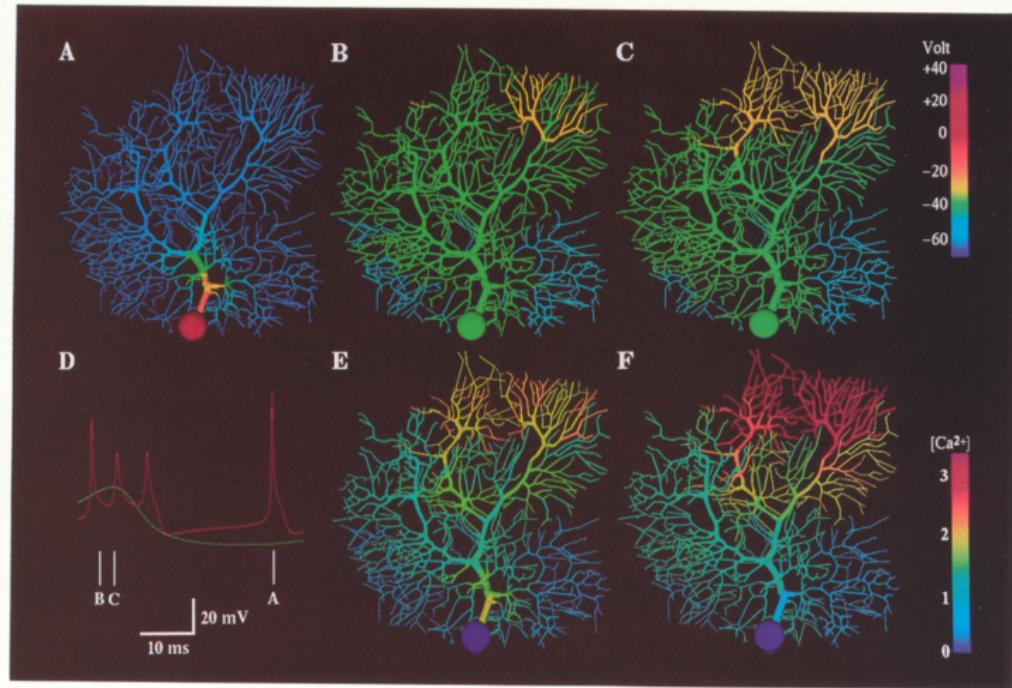
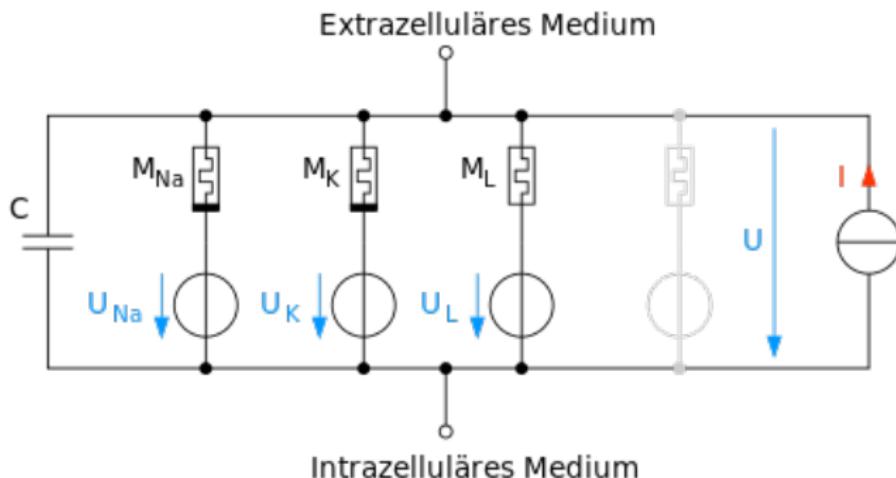


FIG. 10. False color representation of membrane potential and Ca^{2+} concentration in the complete model during a 2.0-nA current injection in the soma. *A*: membrane potential distribution during a somatic action potential. *B*: membrane potential distribution at the beginning of a dendritic spike. *C*: membrane potential distribution 1.6 ms later, when the dendritic spike had peaked. *D*: somatic (red) and dendritic (green) recordings with the times when images *A-C* were taken indicated. *E*: submembrane Ca^{2+} concentration at same time as *B*. *F*: submembrane Ca^{2+} concentration at same time as *C*. Note the nonlinear voltage scale, which is expanded between -60 and -20 mV.

Some effects like dendritic spikes or backpropagation need morphology

Point Neuron Models: dynamics

- ▶ Membrane potential is driven by external and ionic current:
 $I_e = C_m \frac{dV_m}{dt} + I_c$
- ▶ Current is determined by Ion flow through channels:
- ▶ $I_c = -\bar{g}_K n^4(V_m - V_K) - \bar{g}_{Na} m^3 h(V_m - V_{Na}) - \bar{g}_l(V_m - V_l)$,
 1. $\frac{dn}{dt} = \alpha_n(V_m)(1 - n) - \beta_n(V_m)n$
 2. $\frac{dm}{dt} = \alpha_m(V_m)(1 - m) - \beta_m(V_m)m$
 3. $\frac{dh}{dt} = \alpha_h(V_m)(1 - h) - \beta_h(V_m)h$



Point Neuron Models: dynamics

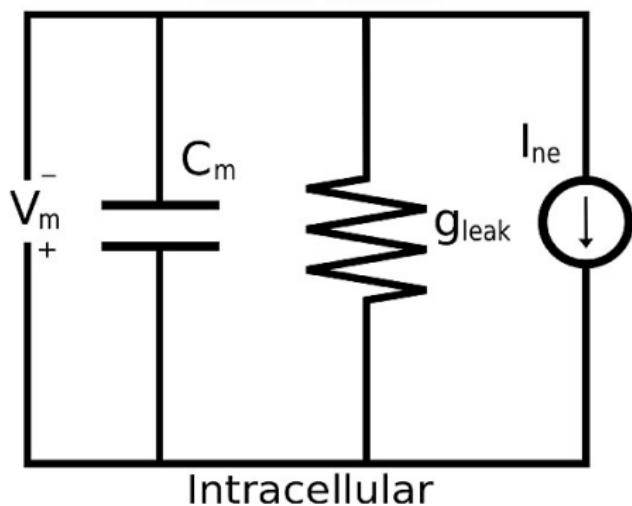
- ▶ From Kirchhoff's law:

$$C_m \frac{dV_m}{dt} = \frac{V_m}{R} + I_{ext}$$

- ▶ Threshold behaviour

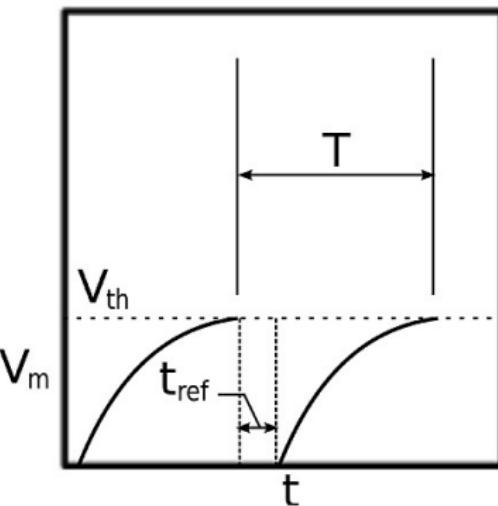
$$V_m > \Theta \rightarrow V_m = V_{rest}$$

Extracellular

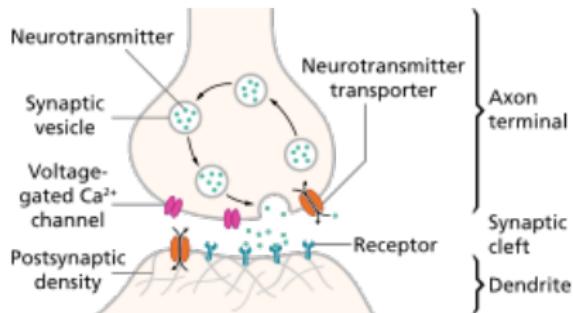


Additional simplifications:

- ▶ linear subthreshold integration
- ▶ time invariant parameters



Synaptic transmission: COBA vs. CUBA



- ▶ COBA i.e. change in conductance
- ▶ CUBA i.e. current flow irrespective of membrane potential
- ▶ can be positive (glutamate) or negative (GABA)

- ▶ Ionotropic or metabotropic,
- ▶ Ionotropic: ion channel is activated
- ▶ Metabotropic: activates G-protein, activates secondary messenger, which activates something else
- ▶ may or may not result in current flow, can also change synaptic plasticity

Comparing Detailed vs. abstract

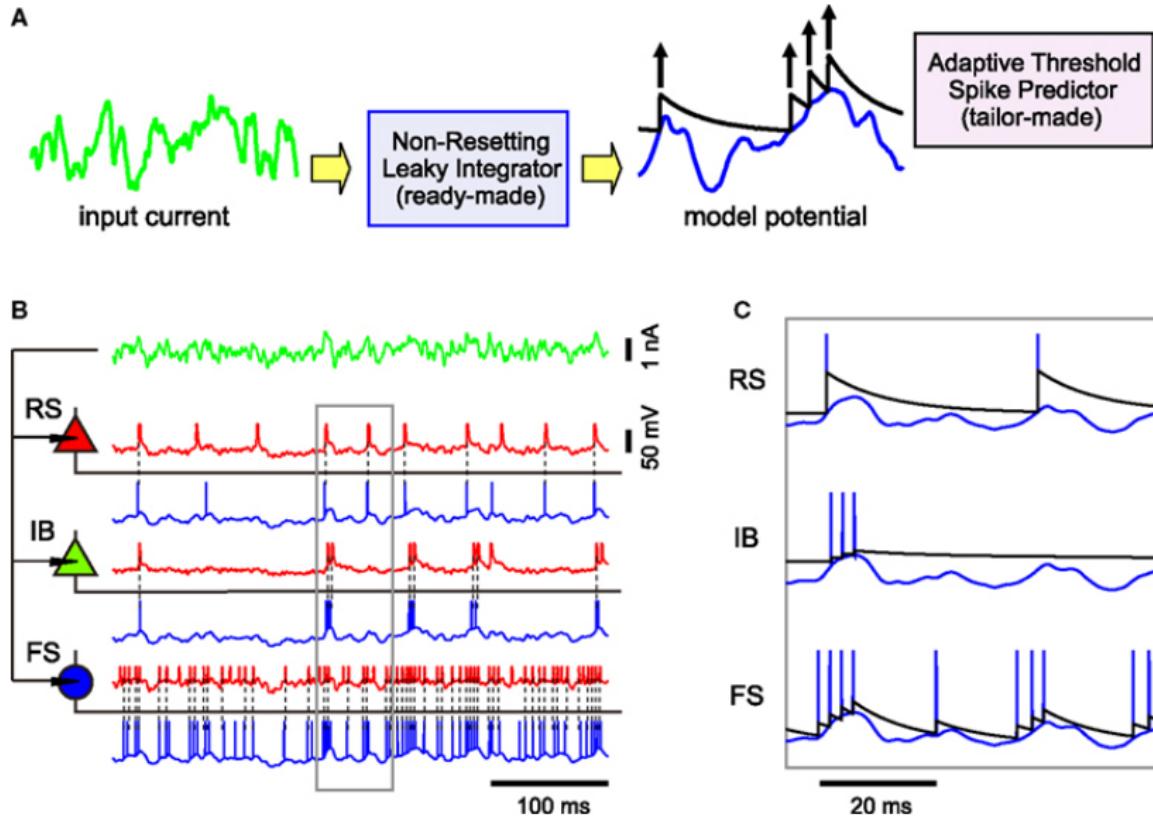
- ▶ Detailed neuron models:
 - ▶ Have physical extent
 - ▶ Give a good approximation of the electrical properties of a physiological neuron
 - ▶ Can be made arbitrarily complex
- ▶ Point neuron models:
 - ▶ Have no physical extent
 - ▶ Represent the dynamics in an extremely reduced fashion
 - ▶ Are very simple

Why would anyone want to use a point neuron model?

Comparing Detailed vs. abstract

- ▶ Much less initial investment
- ▶ Analysis, some models might be analytically tractable
- ▶ Network simulation
- ▶ Not as bad an approximation as one might think

Not that bad



Kobayashi et al. 2009, Izhikevich 2004

Not that bad



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SUB NAVIGATION

- DIADEM
- Spike Time Prediction

2009

Challenge A

Submissions

Challenge B

Challenge C

Challenge D

2007

2008

CHALLENGE A

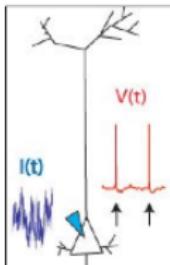
Predict the spike timing of a regular spiking L5 pyramidal cell responding to in-vivo-like current injection.

Experimental Methods

The experiments were performed by Thomas Berger and Richard Naud in the laboratory of Henry Markram at the EPFL. A 14-day-old Wistar rat was decapitated and its brain was quickly transferred to a slicing chamber filled with iced artificial cerebrospinal fluid (ACSF). 300 mm thick slices of the primary somatosensory neocortex were prepared using a HR2 vibratome (Sigmann Elektronik, Heidelberg, Germany). Slices were incubated at 36°C for 45 min and left at room temperature until recording. The ACSF contained (in mM): 125 NaCl, 2.5 KCl, 25 D-glucose, 25 NaHCO₃, 1.25 NaH₂PO₄, 2 CaCl₂, and 1 MgCl₂.

Somatic recordings were performed at 33-35°C with a Axopatch 200B amplifier (Molecular Devices, Union City, CA) in the current clamp mode. Voltage traces were filtered with a 24 kHz Bessel filter. The amplifier was connected to a ITC-18 acquisition board (Instrutech Co, Port Washington, NY), which was in turn connected to a PC or Macintosh running a custom written routine under IgorPro (WaveMetrics, Portland, OR). Patch pipettes were pulled with a Flaming/Brown micropipette puller P-97 (Sutter Instruments Co, Novato, CA) and had an initial resistance of <4MΩ. Pipettes were filled with intracellular solution (ICS) containing (in mM): 110 potassium gluconate, 10 KCl, 4 ATP-Mg, 10 Na-Phosphocreatine, 0.3 Na-GTP, 10 Hepes, 30 Mannitol, and 8 Biocytin. Chemicals were provided by SIGMA or MERCK. The liquid junction potential between the ACSF and the ICS was around 12 mV and not corrected for.

The current-clamp stimulus has two parts. The first part is 17.5 seconds of various stimulus waveforms frequently used to calibrate neuron models. It consists of a series of four step current with a duration of 2 seconds and an inter-step rest time of two seconds (one hyperpolarizing and 3 depolarizing steps). The steps are followed by an injection of white noise of two seconds. The white noise injection can be used to remove the artifact.



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CHALLENGE A
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CHALLENGE B
DATA SET
Epileptic Time Prediction

2019

Challenge A
Submissions
Challenge B
Challenge C
Challenge D
2017
2018

CHALLENGE A
Predict the spike timing of a regular spiking L5 pyramidal cell responding to in-vivo-like current injection.

Experimental Methods

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Somatic recordings were performed at 33–35°C with a Axopatch 200B amplifier (Molecular Devices, Union City, CA) in the current-clamp mode. Voltage traces were filtered with a 2–4 kHz Bessel filter. The amplifier was connected to a TFC-18 acquisition board (IntanTech Co., Port Washington, NY), which was in turn connected to a 16-bit 100 MHz digital-to-analog converter (D/A converter, National Instruments, Portland, OR). Input ground was patch pipette ground/Brown indifferent electrode (part P-07 (Gitter Instruments Co., Novato, CA) and had an input resistance of > 4 MΩ. Pipettes were filled with intracellular solution (ICS) containing (in mM): 110 potassium chloride, 10 KCl, 4 ATP-Mg, 10 Na₂Phosphocreatine, 0.3 Na₂-GTP, 10 Hepes, 30 Mannitol, and 0 D-glucose. Chemicals were provided by SVVMA or MERCK. The liquid junction potential between the ACSF and the ICS was around 12 mV and not corrected for.

The current-clamp stimulus has two parts. The first part is 17.5 seconds of various stimulus waveforms frequently used to stimulate neurons models. It consists of a series of four step current with a duration of 2 seconds and an inter-step rest time of less seconds (one Hyperpolarizing and 3 depolarizing steps). The second part follows the last one and consists of a series of two spikes. The whole noise waveform can be used in neurons that self-tun-

A graph showing the membrane potential (Vt) and current (I(t)) over time. The membrane potential Vt shows a series of sharp upward spikes. The current I(t) shows a corresponding series of downward deflections, indicating the flow of current during each spike. The graph illustrates the relationship between the applied current and the resulting firing of the neuron.

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CHALLENGE A

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DIB NAVIGATION

- Challenge A**
- Challenge B**
- Challenge C**
- Challenge D**
- 2017
- 2018

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The current-clamp stimulus has two parts. The first part is 17.5 seconds of no-voltage stimulus waveform, frequently used to calibrate neuron models. It consists of a series of four step current with a duration of 2 seconds and an inter-step rest time of two seconds (one hyperpolarizing and three depolarizing steps). The second part is 1000ms of an injection of a single noise of 100 nanovolts. This single noise injection can be used in neurons that self-rectify.

◀ ▶ ▲ ▼ □ ▢ ▤ ▥ ▦ ▨ ▩

Not that bad

- ▶ Point neurons won all challenges in all years, despite behaviorally relevant incentives
- ▶ The MAT2 model (Kobayashi et al., 2009) only has one dynamic variable more than the standard leaky IaF model
- ▶ The arbitrary complexity of biophysical neuron models makes them a parameter fitting nightmare
- ▶ Save complexity for when you really need it