



Computational Neurobiology

Lecture 4: Neuron models 2

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Syllabus

- Modeling channels
- Conductance-based models
- The cable equation
- Multi-compartment models



Modeling channels

- Motivation
- Types of channels and their properties
- Probabilistic description



Motivation

- Hodgkin-Huxley formalism describes voltage-dependent conductances arising from a large number of channels
- With the advent of single-channel studies, microscopic descriptions of the transitions between the conformational states of channel molecules have been developed
- Single-channel models have less limits than voltage-dependent only Hodgkin-Huxley formalism
- We can determine the function with detailed channel models



Types of channels

- Passive/Active classification (pumps, leakage)
- Gating classification (voltage-gated, ligand-gated, lipid-gated, etc)
- Ion types classification (chloride, potassium, sodium, calcium, proton, non-selective)
- Cellular localization classification (plasma membrane, intracellular: endoplasmic, mitochondria)
- Other (e.g. by the duration of their response to stimuli)



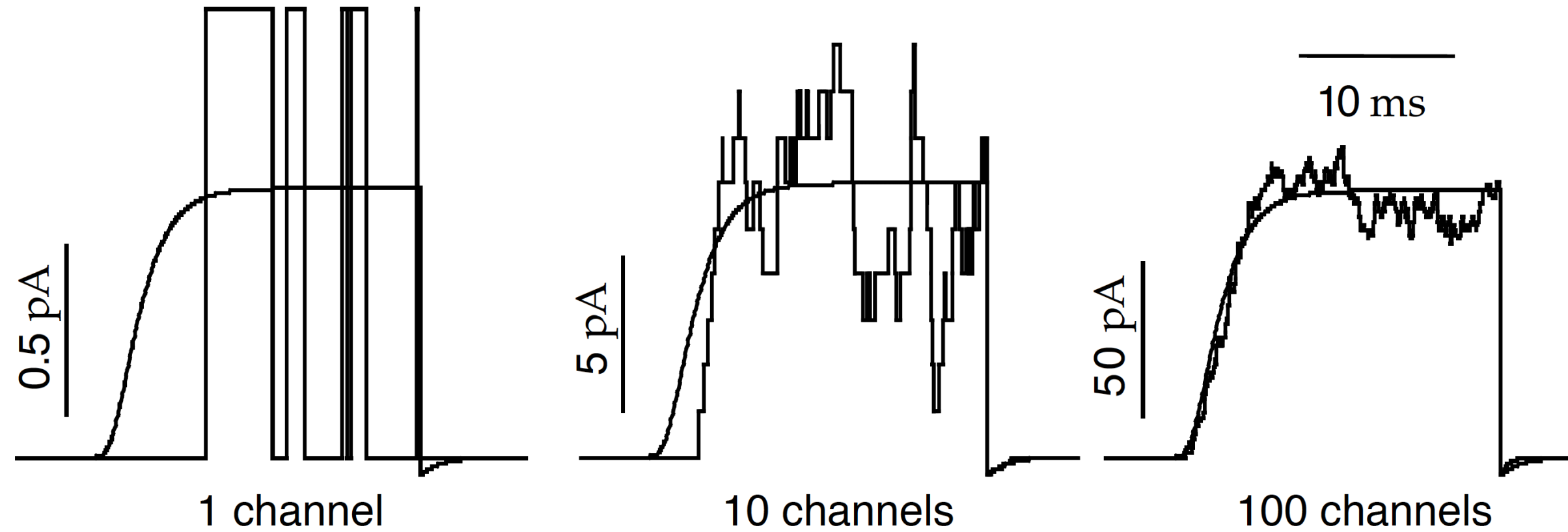
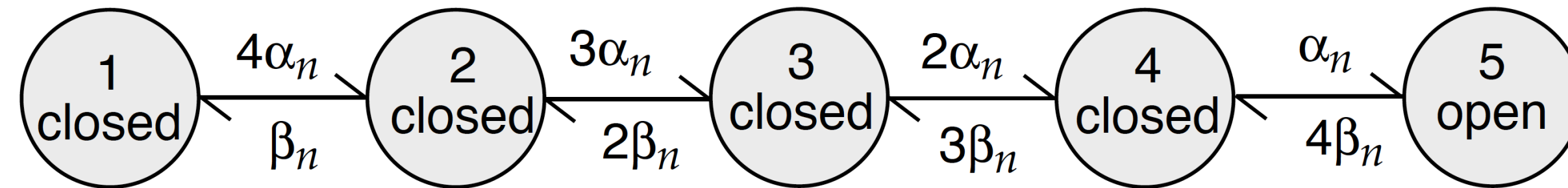
Ion channels properties

- High selectivity
- Controlled permeability
- Inactivation
- Blocking
- Plasticity



Channel state

- Models of single channels are based on state diagrams that indicate the possible conformational states that the channel can assume
- Typically, one of the states in the diagram is designated as open and ion-conducting, while the other states are nonconducting
- The current conducted by the channel is written as $\bar{g}P(V - E)$, where E is the reversal potential, \bar{g} is the single-channel open conductance, and P is 1 for the open state and 0 otherwise
- If the model is updated in short time steps of duration Δt , the probability that the channel makes a given transition during an update interval is the transition rate times Δt



A model of the delayed-rectifier K^+ channel



Probabilistic description

- We denote the probability that a channel is in state k by p_k , with $k = 1, 2, \dots, 5$
- The rate of change for a given p_k is equal to the probability per unit time of entry into state k from other states minus the rate for leaving state k
- The entry probability per unit time is the product of the appropriate transition rate times the probability that the state making the transition is occupied
- The probability per unit time for leaving is p_k times the sum of all the rates for possible transitions out of the state



Equations for the state probabilities

$$\text{Let } \dot{p} = \frac{dp}{dt}$$

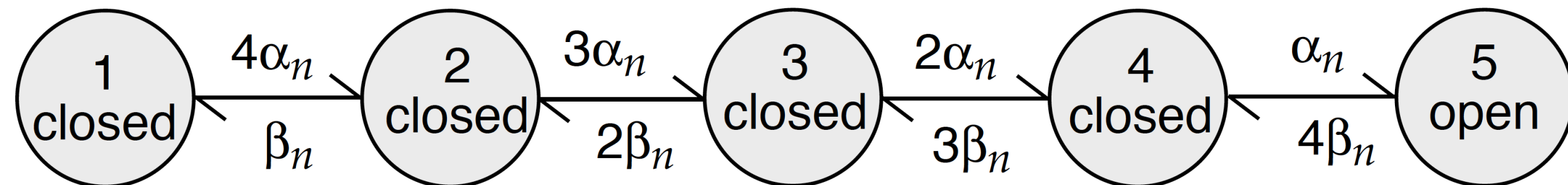
$$\dot{p}_1 = \beta_n p_2 - 4\alpha_n p_1$$

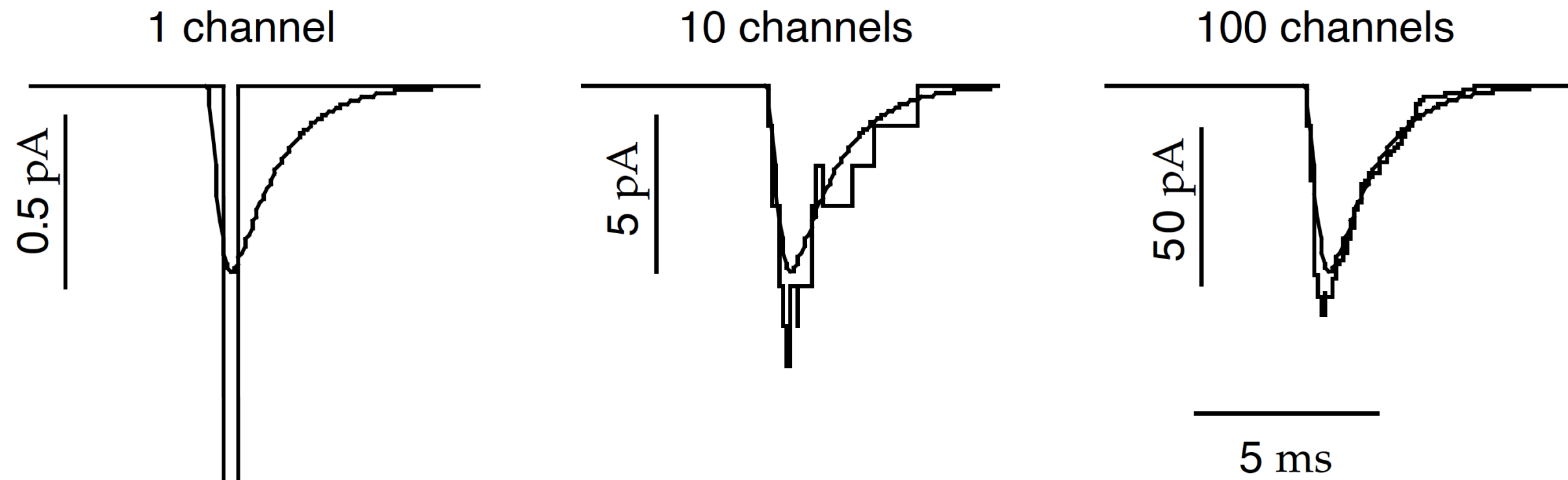
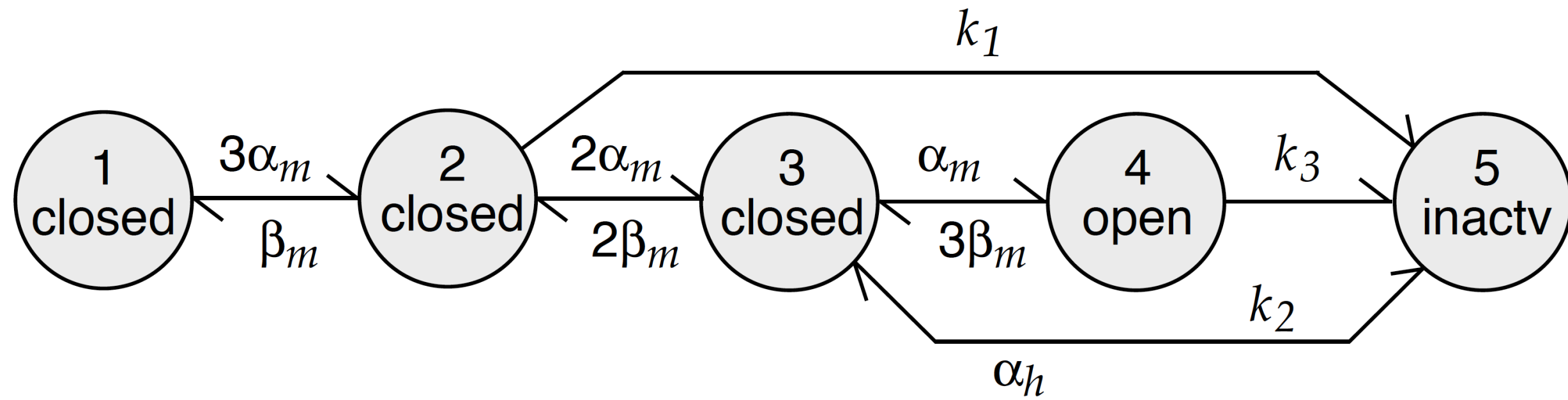
$$\dot{p}_2 = 4\alpha_n p_1 + 2\beta_n p_3 - (\beta_n + 3\alpha_n) p_2$$

$$\dot{p}_3 = 3\alpha_n p_2 + 3\beta_n p_4 - (2\beta_n + 2\alpha_n) p_3$$

$$\dot{p}_4 = 2\alpha_n p_3 + 4\beta_n p_5 - (3\beta_n + \alpha_n) p_4$$

$$\dot{p}_5 = \alpha_n p_4 - 4\beta_n p_5$$





A model of the fast Na^+ channel



Conductance-based models

- Levels of neuron modeling
- The Connor-Stevens model
- Postinhibitory rebound and bursting



Levels of neuron modeling

- In modeling neurons, we must deal with two types of complexity: **the intricate interplay of active conductances** and **the elaborate morphology**
- Choosing the most appropriate level of modeling requires a **careful assessment** of the experimental information available and a **clear understanding** of the research goals
- Oversimplified models can give misleading results, excessively detailed models can obscure interesting results beneath inessential and unconstrained complexity.



Gating functions

All the gating variables are determined by equations of the form:

$$\tau_z(V) \frac{dz}{dt} = z_\infty(V) - z, \text{ where}$$

z - a generic gating variable, the functions $\tau_z(V)$ and $z_\infty(V)$ are determined from experimental data

For some conductances, these are written in terms of the opening and closing rates $\alpha_z(V)$ and $\beta_z(V)$ as

$$\tau_z(V) = \frac{1}{\alpha_z(V) + \beta_z(V)}$$

$$z_\infty(V) = \frac{\alpha_z(V)}{\alpha_z(V) + \beta_z(V)}$$

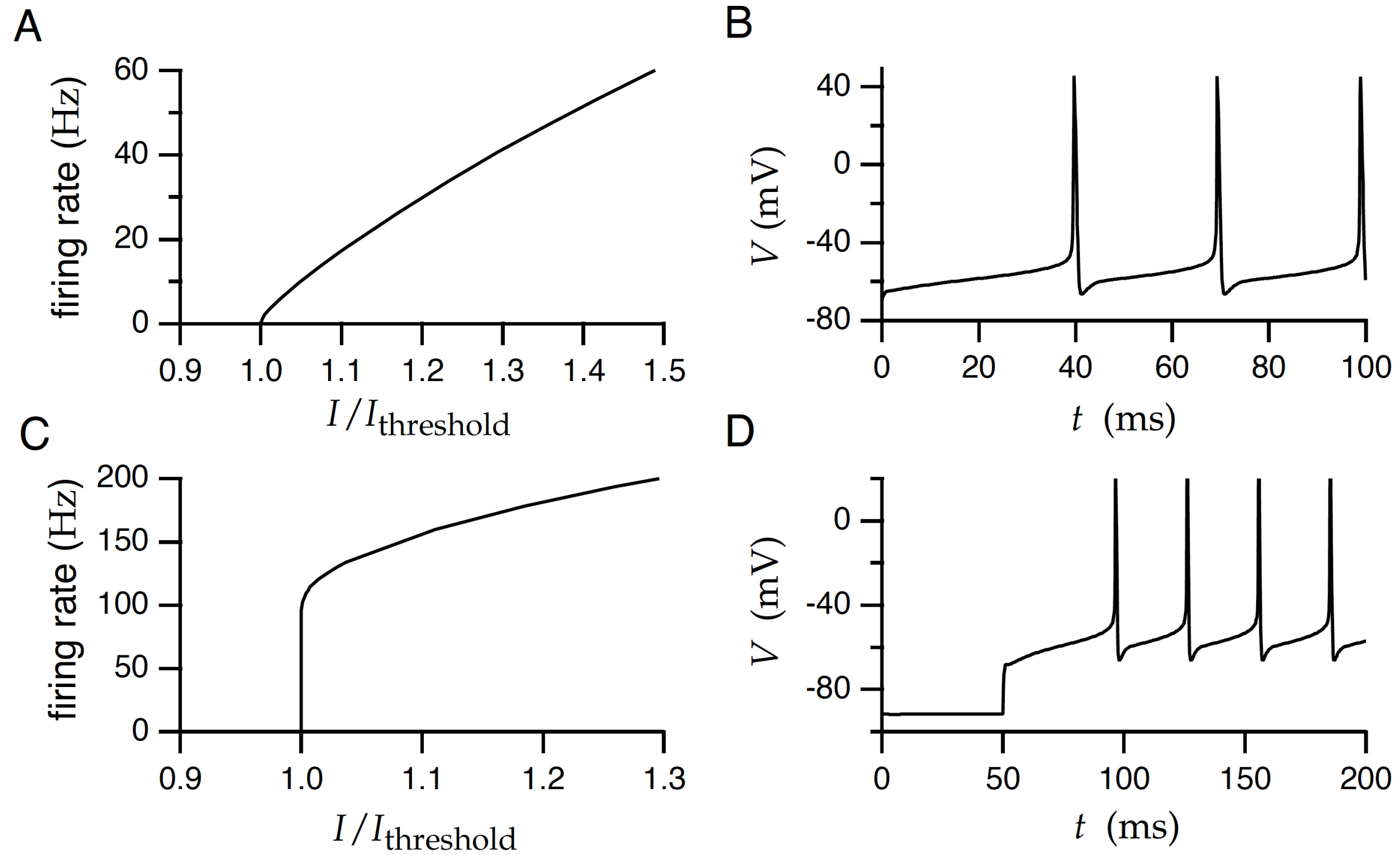


The Connor-Stevens model

- Provides an alternative description of action-potential generation
- Contains fast Na^+ , delayed rectifier K^+ , and leakage conductances
- Contains an extra K^+ conductance, called the A-current, that is transient

The membrane current:

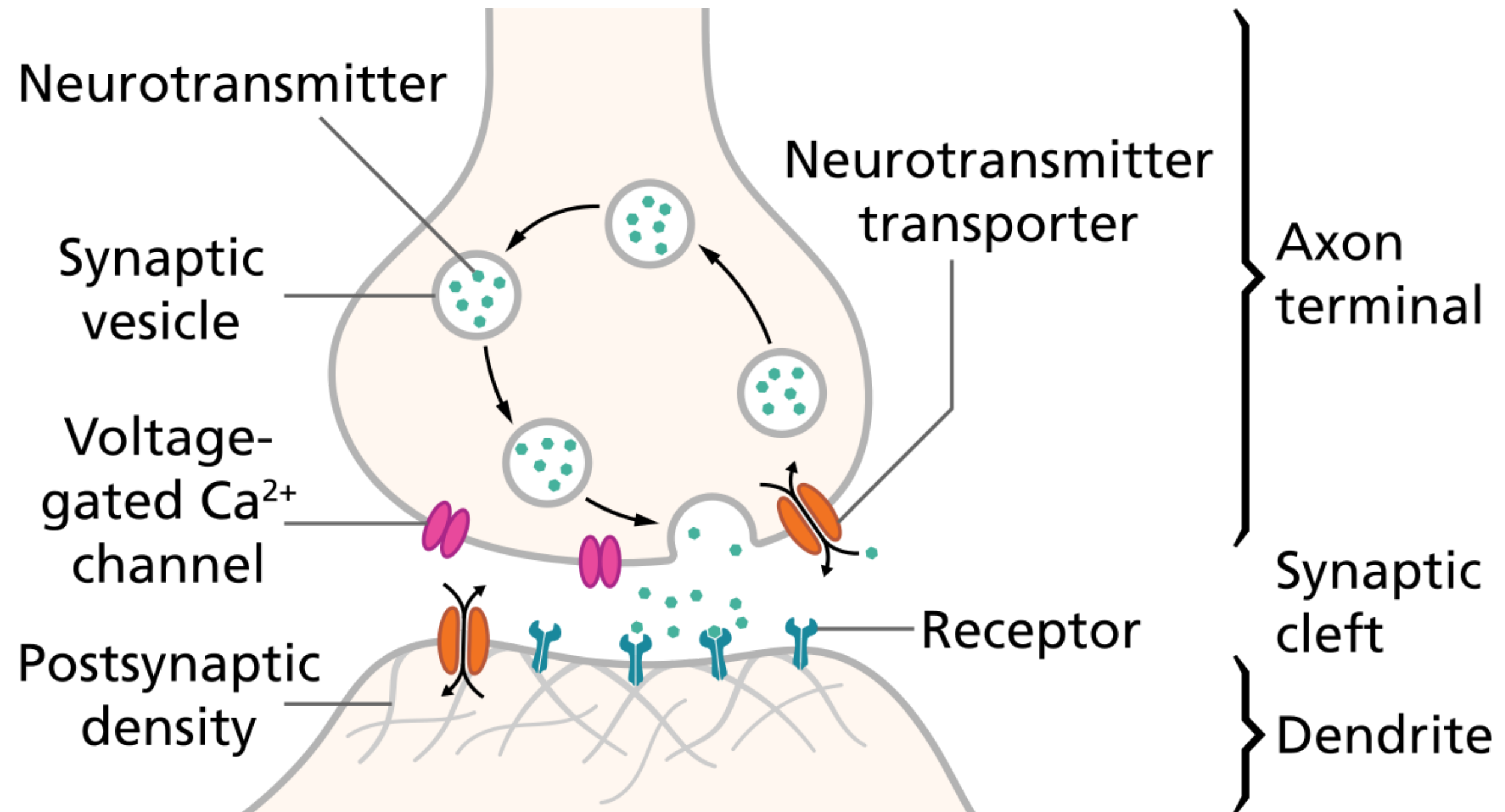
$$i_m = \bar{g}_L(V_m - E_L) + \bar{g}_{Na}m^3h(V_m - E_{Na}) + \bar{g}_Kn^4(V_m - E_K) + \bar{g}_Aa^3b(V_m - E_A)$$



Firing of action potentials in the Connor-Stevens model



Ca^{2+} role in transmission



Neurotransmission scheme in chemical synapse

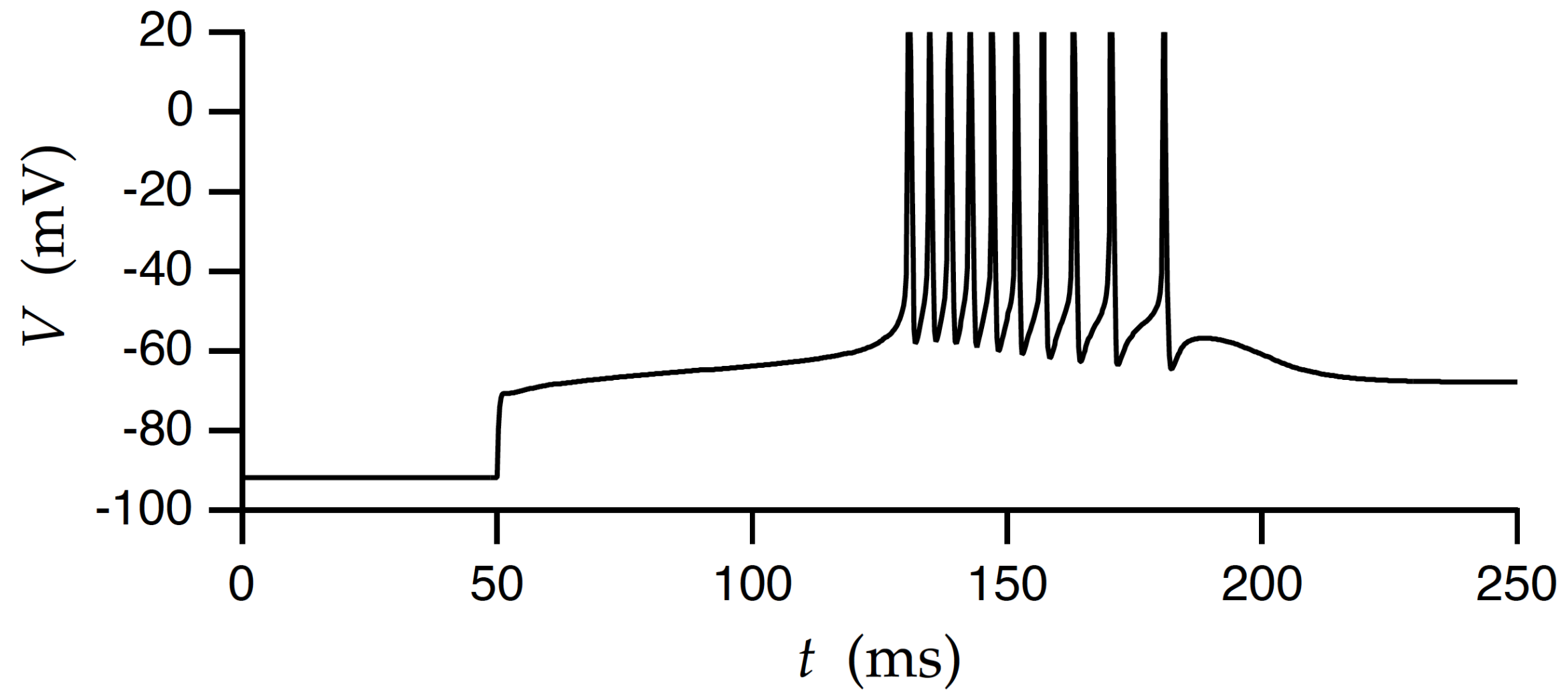


Postinhibitory rebound and bursting

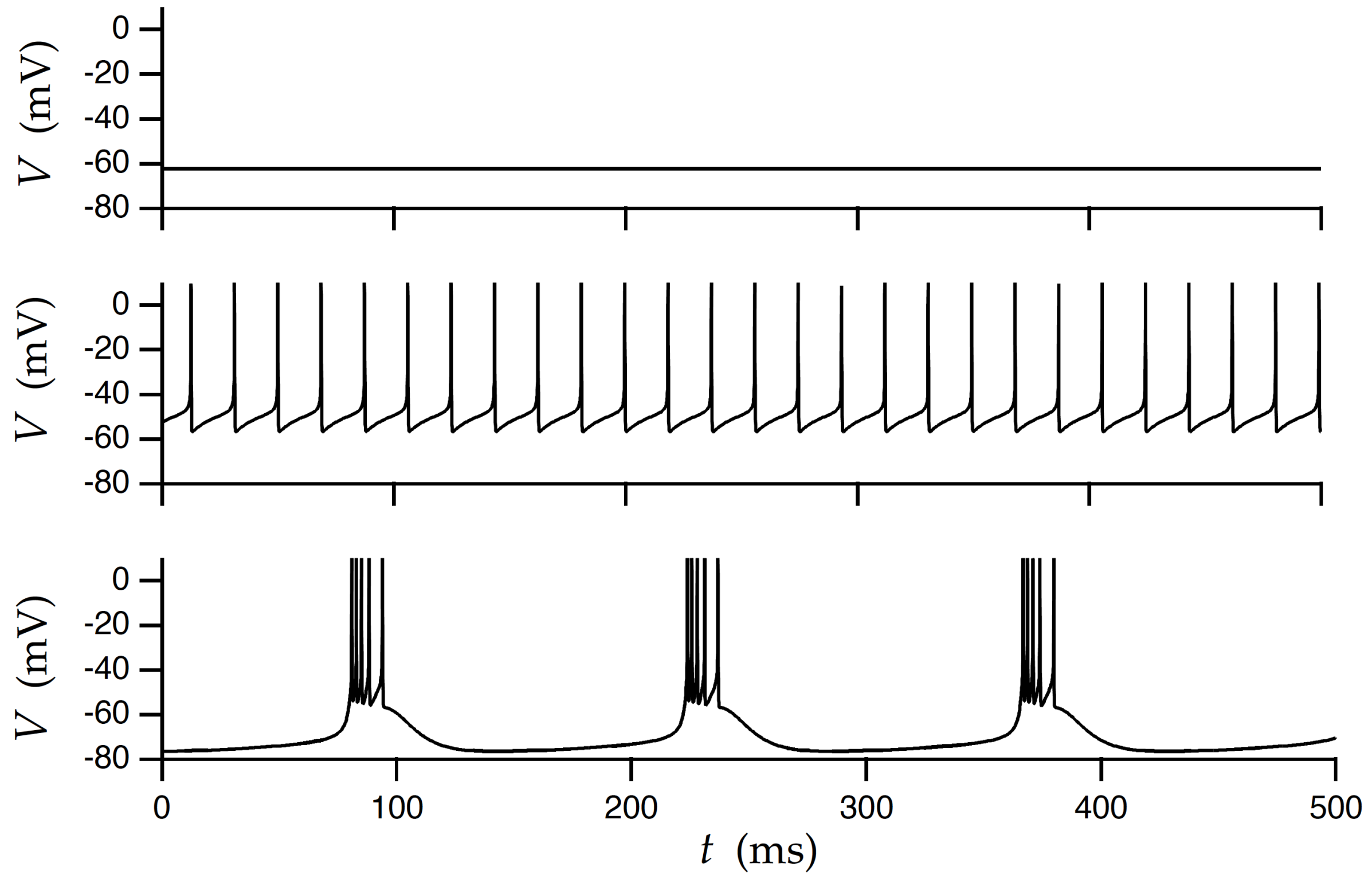
- Connor-Stevens model neuron can be extended by including a transient Ca^{2+} conductance
- Model (Huguenard and McCormick; 1992) based on data from thalamic relay cells
- Several different Ca^{2+} conductances (L, T, N and P types) are commonly expressed in neuronal membranes

The membrane current:

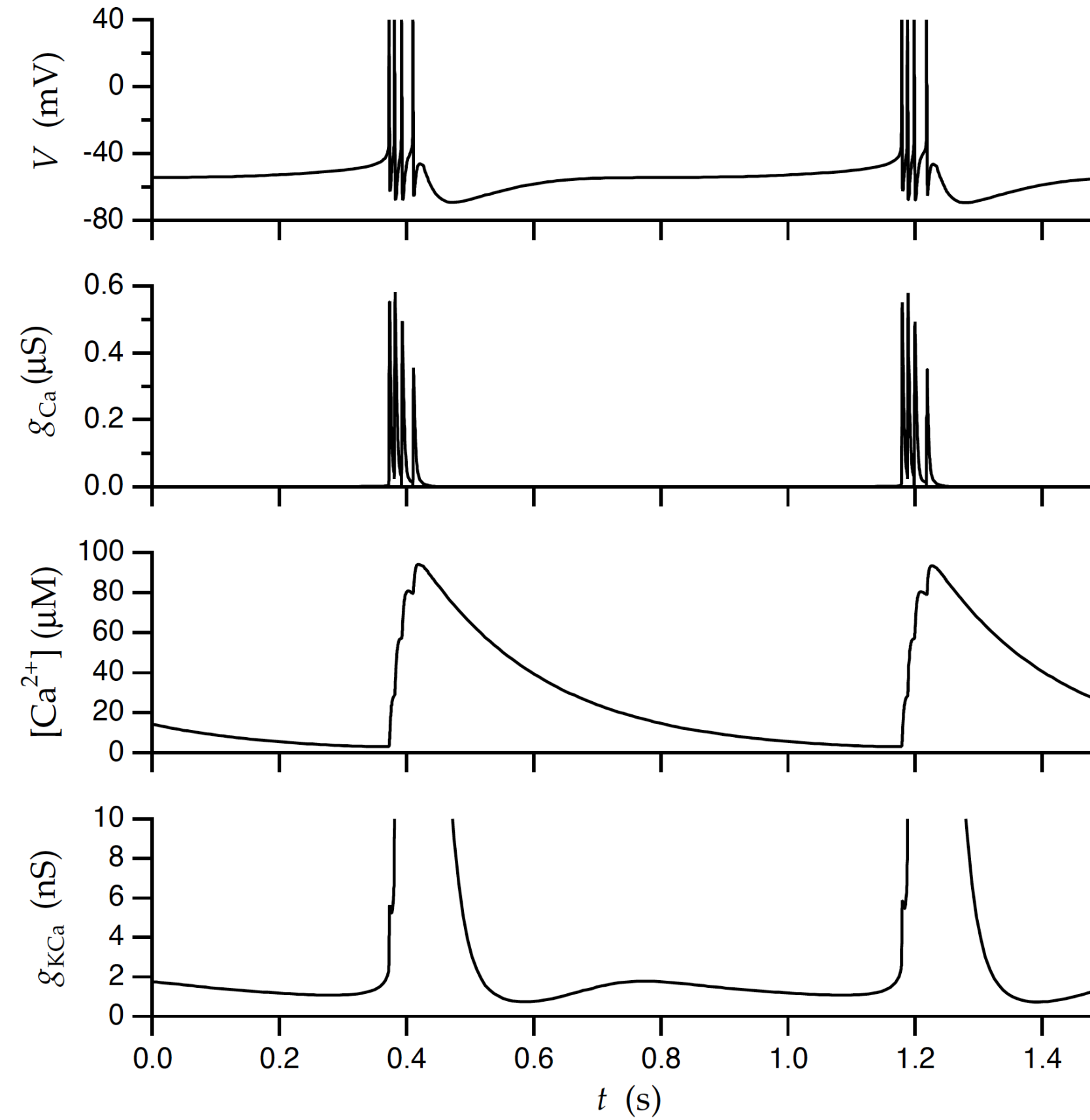
$$i_{CaT} = \bar{g}_{CaT} M^2 H(V_m - E_L)$$



A burst of action potentials due to rebound from hyperpolarization



Three activity modes of a model thalamic neuron



Periodic bursting in a model STG (stomatogastric ganglion) neuron



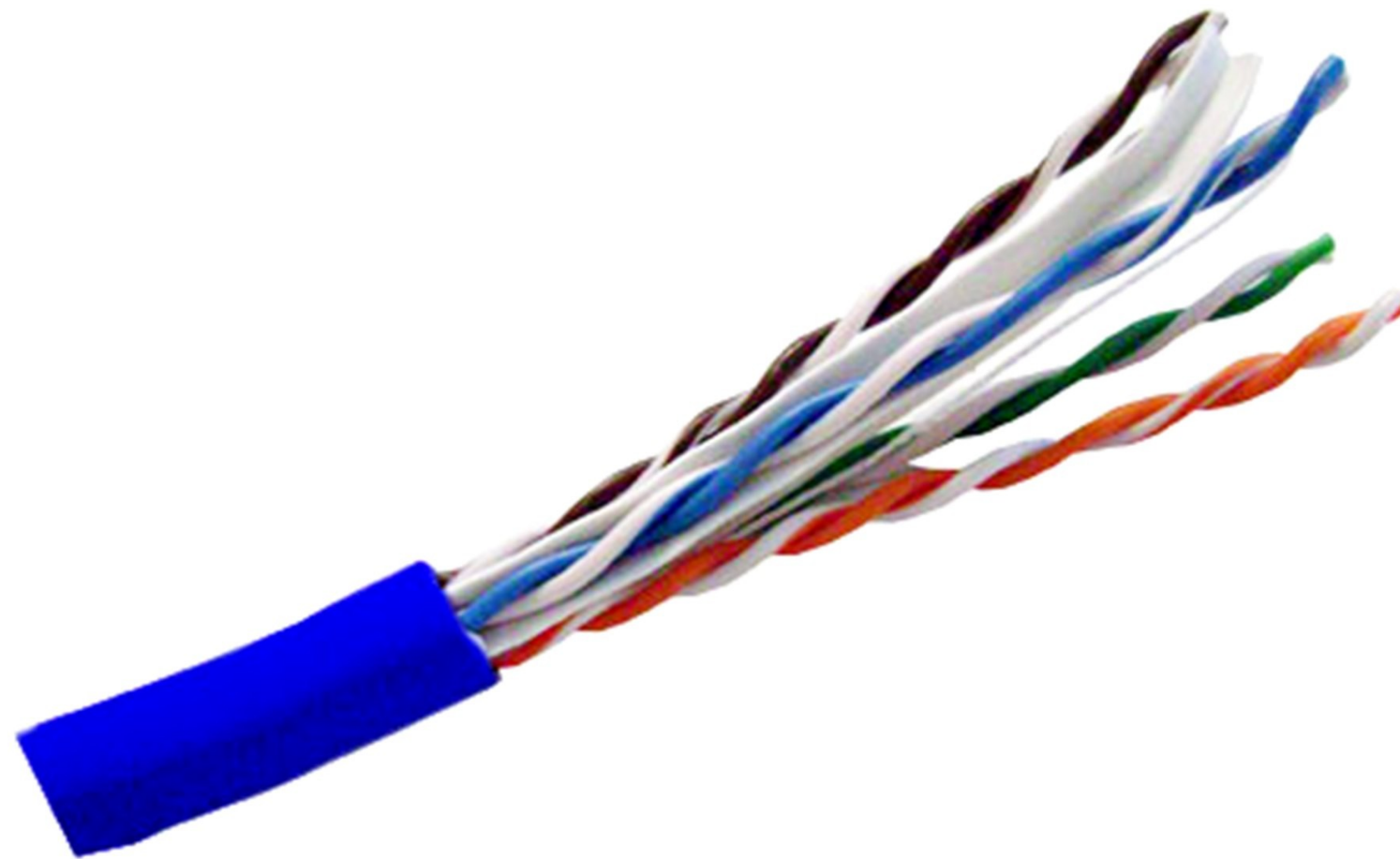
Kabal??? theory





Cable! theory

- Motivation
- Dendrite as a cable
- Cable equation



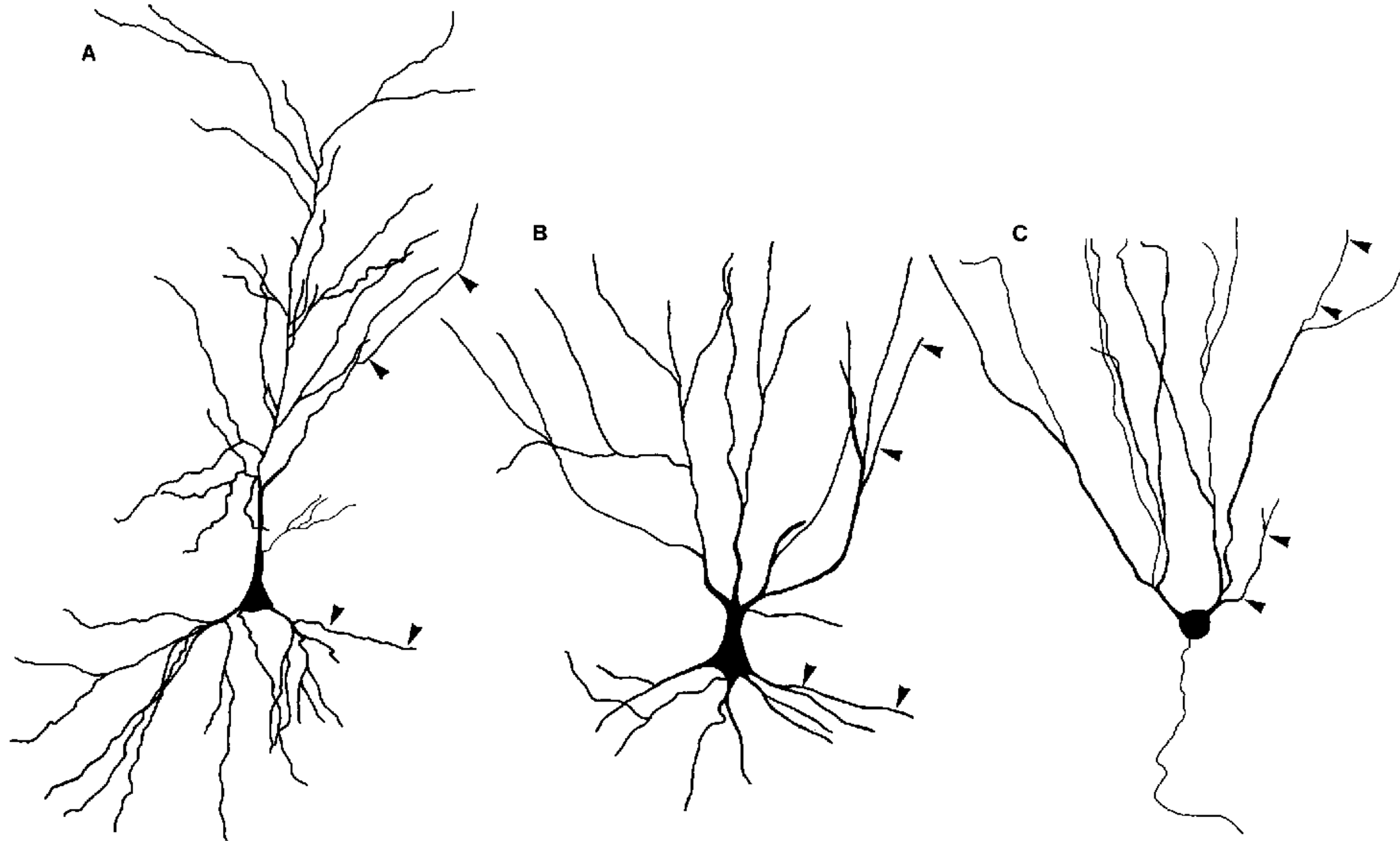


Motivation

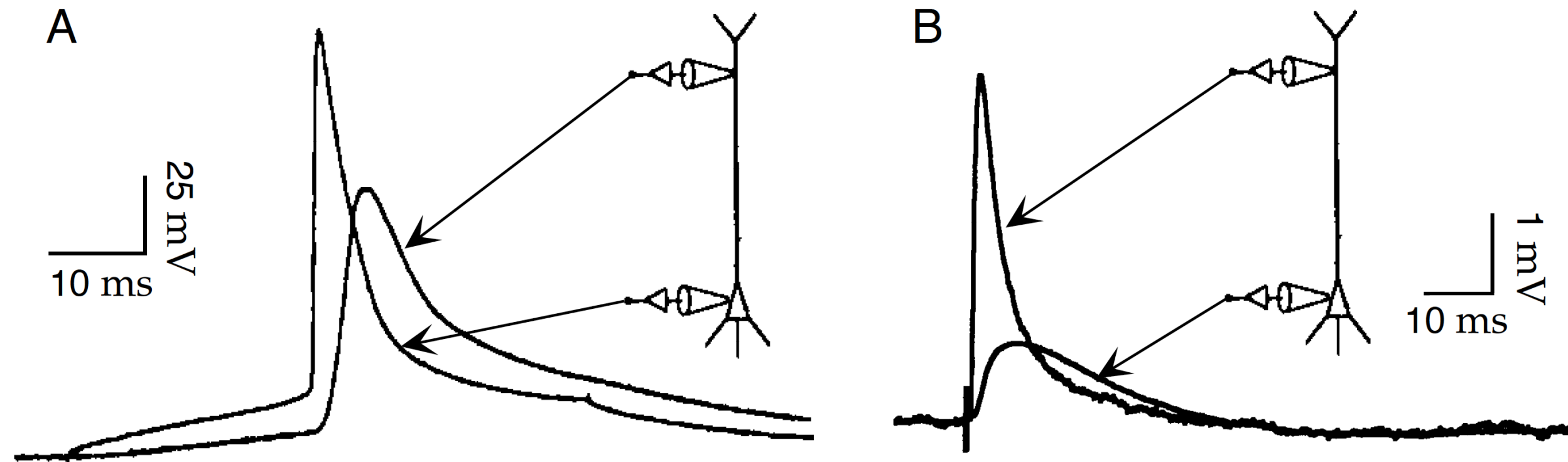
- Single-compartment models describe the membrane potential over an entire neuron with a single variable V
- Membrane potentials can vary considerably over the surface of the cell membrane: long and narrow processes, or rapidly changing membrane potentials
- The attenuation and delay within a neuron are most severe when electrical signals travel down the long, narrow, cablelike structures of dendritic or axonal branches
- Dendritic and axonal cables are typically narrow enough that variations of the potential in the radial or axial directions are negligible compared to longitudinal variations



Pyramidal neurons example



CA1 pyramidal cell (A), CA3 pyramidal cell (B), and dentate gyrus granule cell (C). Elizabeth Gould, Catherine S Woolley DOI:10.1523/jneurosci.10-04-01286.1990



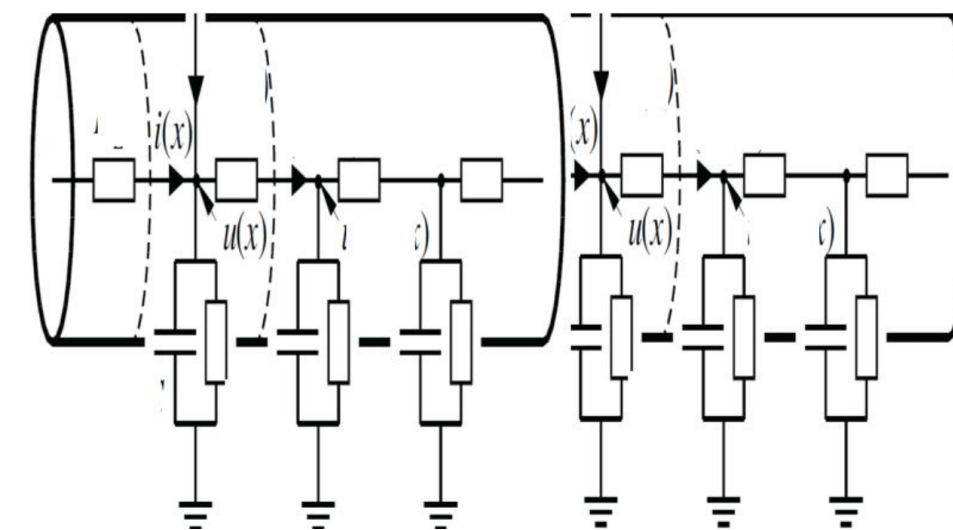
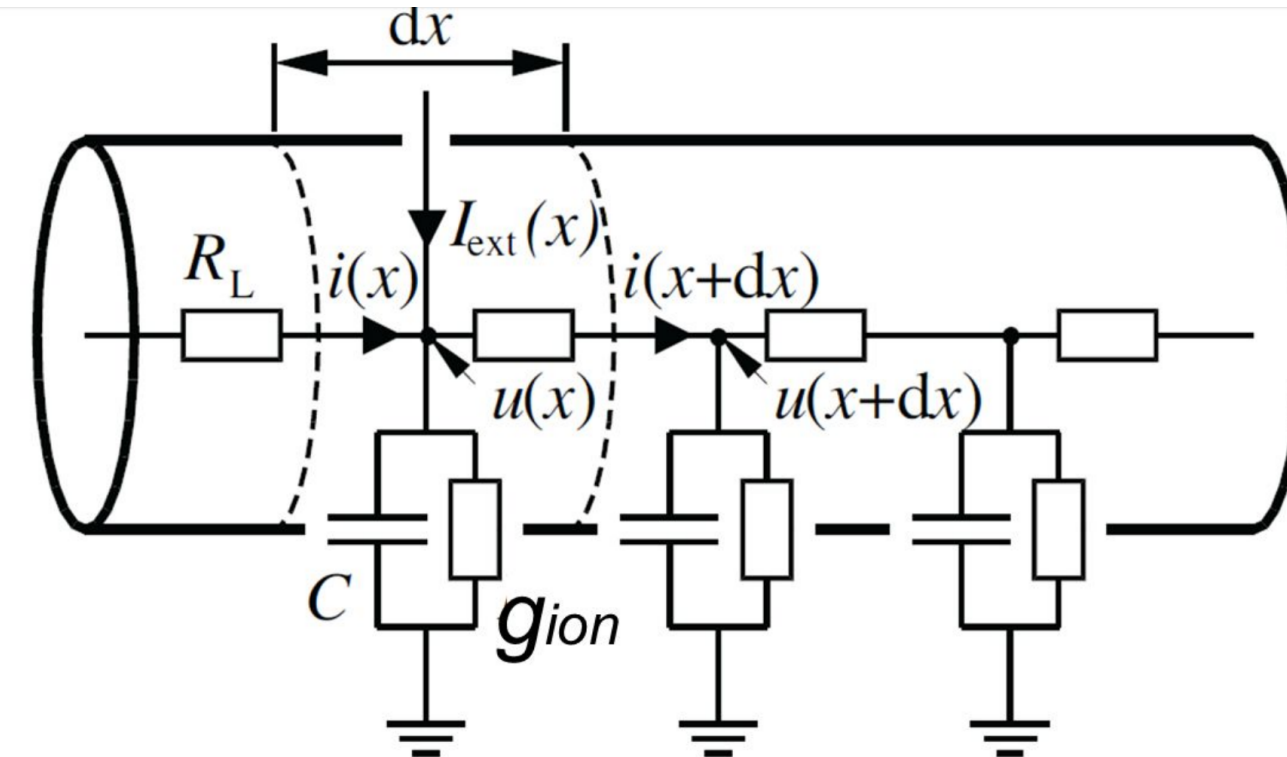
Simultaneous intracellular recordings from the soma and apical dendrite of cortical pyramidal neurons in slice preparations



Spatial discretization

$$R_L = r_L dx$$

$$C = c dx$$



$$I_{ion} = i_{ion} dx$$

$$I^{ext} = i^{ext} dx$$



Dendrites as a cable

$$I(t, x) = I_c(t, x) + \sum_{ions} I_{ion}(t, x) = C \frac{dV(t, x)}{dt} + \sum_{ions} I_{ion}(t, x) - \text{current}$$

$$I(t, x) = I^{ext}(t, x) + I_l(t, x) - I_l(t, x + dx) = I^{ext}(t, x) + \frac{V(t, x - dx) - V(t, x)}{R_L},$$
$$- \frac{V(t, x) - V(t, x + dx)}{R_L}$$

where

I^{ext} - external current, I_l - longitudinal current, R_L - longitudinal resistance, V - membrane potential

$$I^{ext}(t, x) + \frac{V(t, x - dx) - 2V(t, x) + V(t, x + dx)}{R_L} = C \frac{dV(t, x)}{dt} + \sum_{ions} I_{ion}(t, x)$$



Cable equation

$$I^{ext}(t, x) + \frac{V(t, x - dx) - 2V(t, x) + V(t, x + dx)}{R_L} = C \frac{dV(t, x)}{dt} + \sum_{ions} I_{ion}(t, x)$$

$$I^{ext}(t, x) + \frac{V(t, x - dx) - 2V(t, x) + V(t, x + dx)}{r_L dx} = c \cdot dx \frac{dV(t, x)}{dt} +$$

$$\sum_{ions} i_{ion}(t, x) dx$$

Lets take $\lim_{dx \rightarrow 0}$

$$\frac{\delta^2 V}{\delta x^2} = cr_L \frac{\delta V}{\delta t} + r_L \sum_{ions} i_{ion} - r_L i^{ext} \text{ - cable equation}$$



Multi-compartment models

- Motivation and main principle
- Neuron structure approximation
- Multi-compartment models
- Unmyelinated/myelinated axon

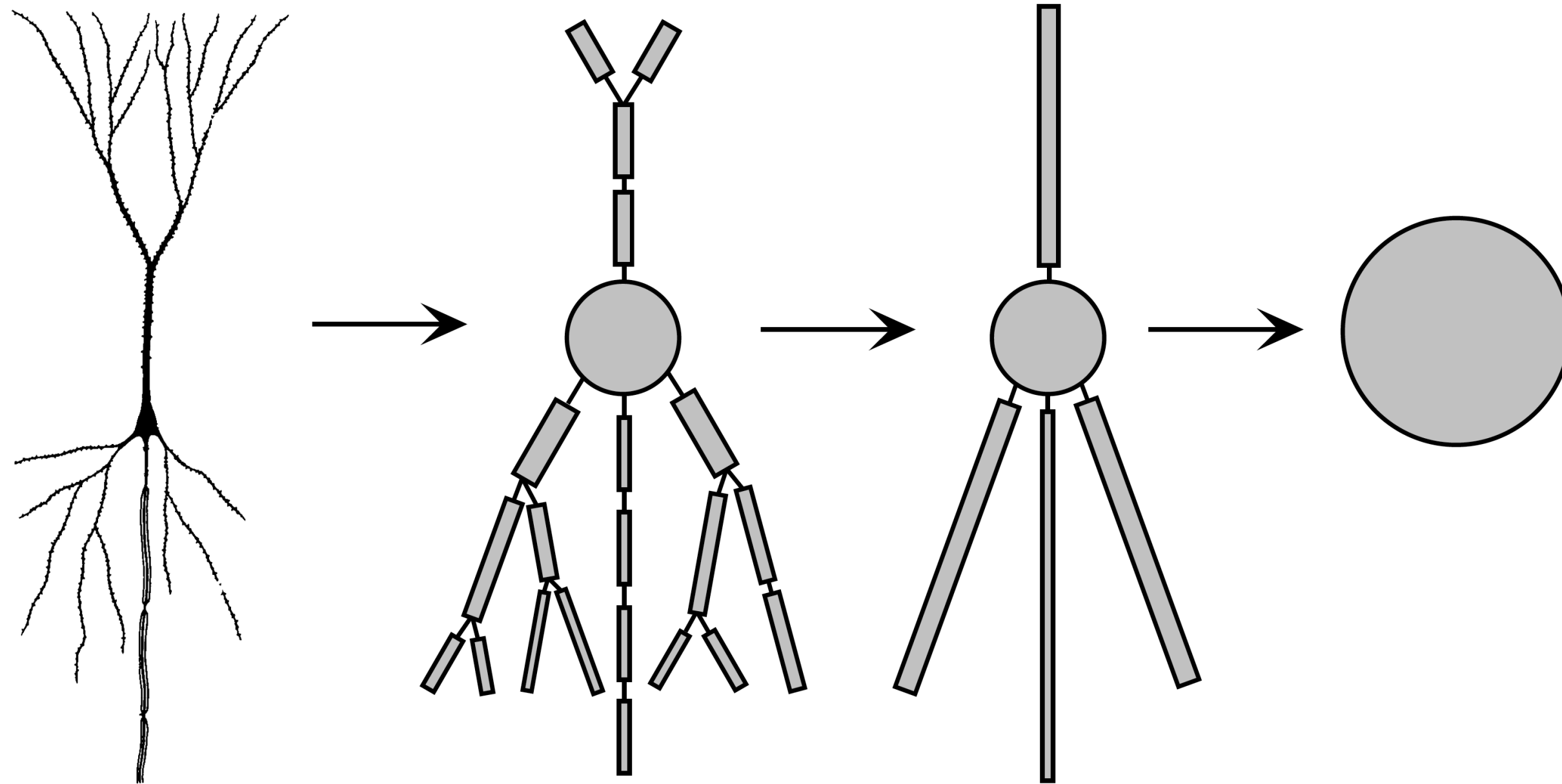


Motivation and main principle

- The cable equation can be solved analytically only in relatively simple cases
- When the complexities of real membrane conductances are included, the membrane potential must be computed numerically
- Split the modeled neuron into separate compartments, and approximating the continuous membrane potential $V(x, t)$ by a discrete set of values
- Each compartment is small enough so that there is negligible variation of the membrane potential across it



Neuron structure approximation



A sequence of approximations of the structure of a neuron. The neuron is represented by a variable number of discrete compartments, each representing a region that is described by a single membrane potential.



Membrane potential in multi-compartment models

For a nonbranching cable, each compartment is coupled to two neighbors and the equations for the membrane potentials of the compartments are

$$c_m \frac{dV_\mu}{dt} = -i_m^\mu + \frac{I_e^\mu}{A_\mu} + g_{\mu,\mu+1}(V_{\mu+1} - V_\mu) + g_{\mu,\mu-1}(V_{\mu-1} - V_\mu), \text{ where}$$

V_μ - membrane potential of compartment μ

I_e^μ - total electrode current

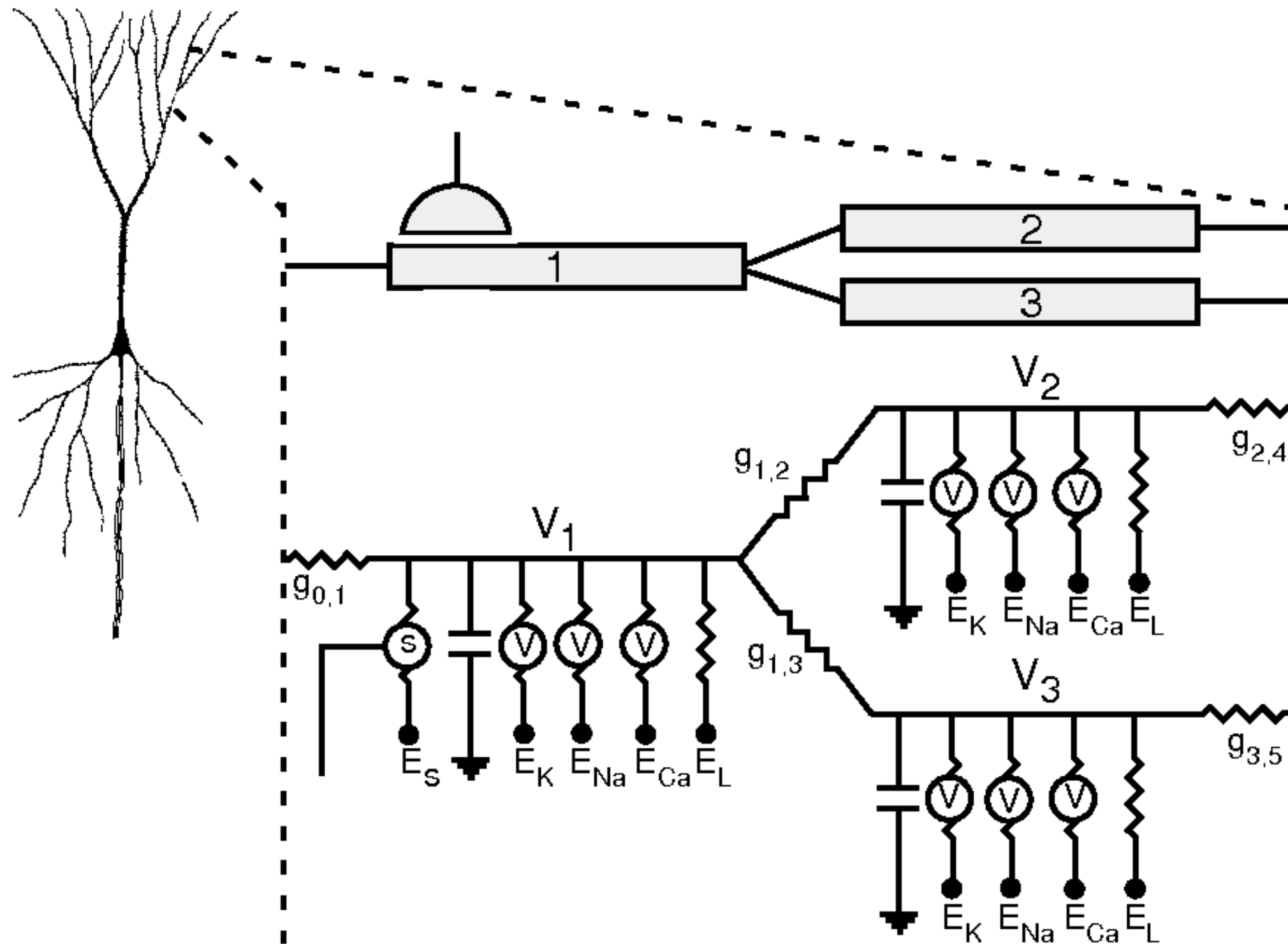
A_μ - compartment surface area

$g_{\mu,\mu'}$ determines the resistive coupling from neighboring compartment μ' to compartment μ is determined by computing the current due to Ohm's law.

Single term for each end of a cable. Three terms for branches.



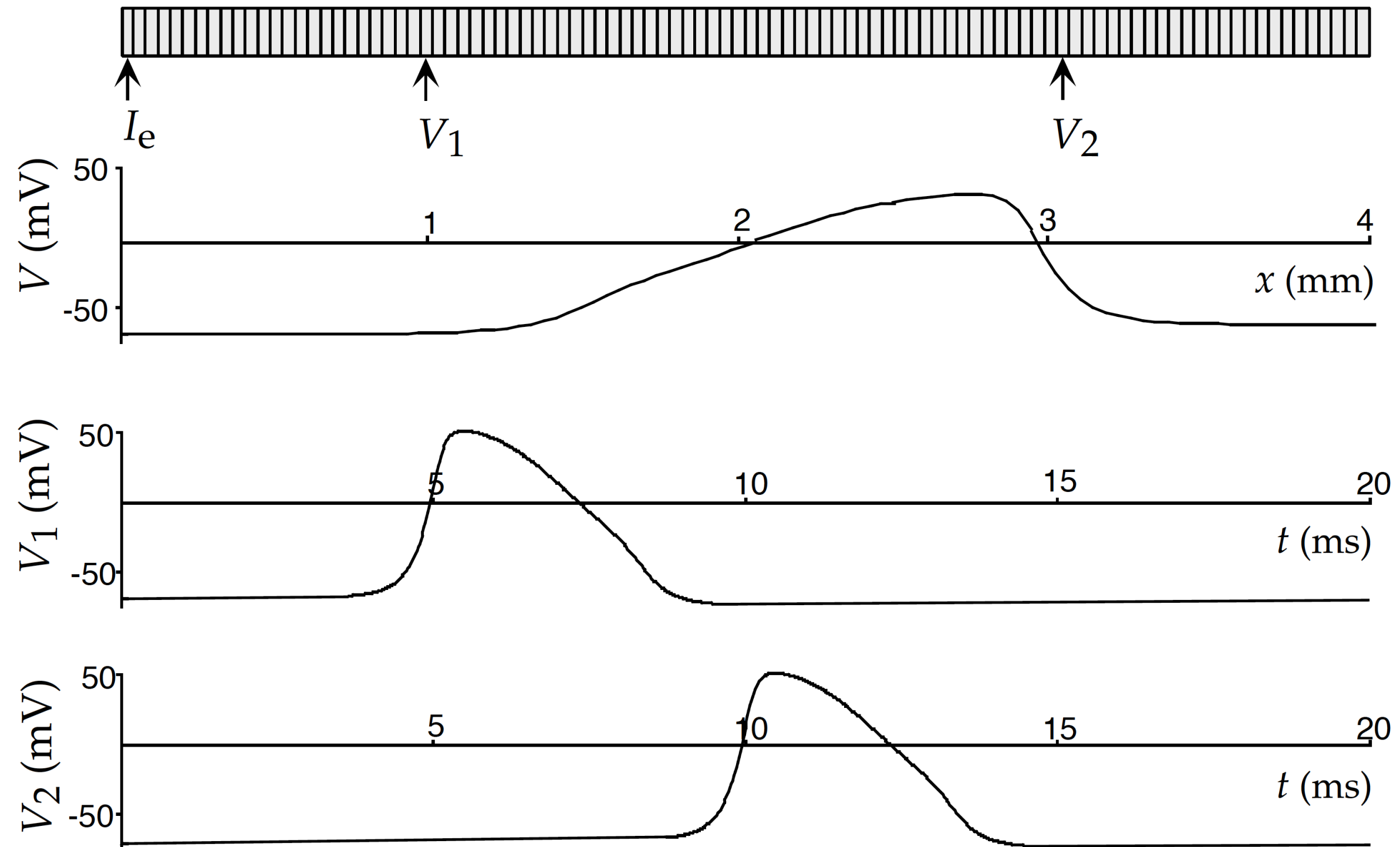
Multi-compartment models



A multi-compartment model of a neuron. The expanded region shows three compartments at a branch point where a single cable splits into two.



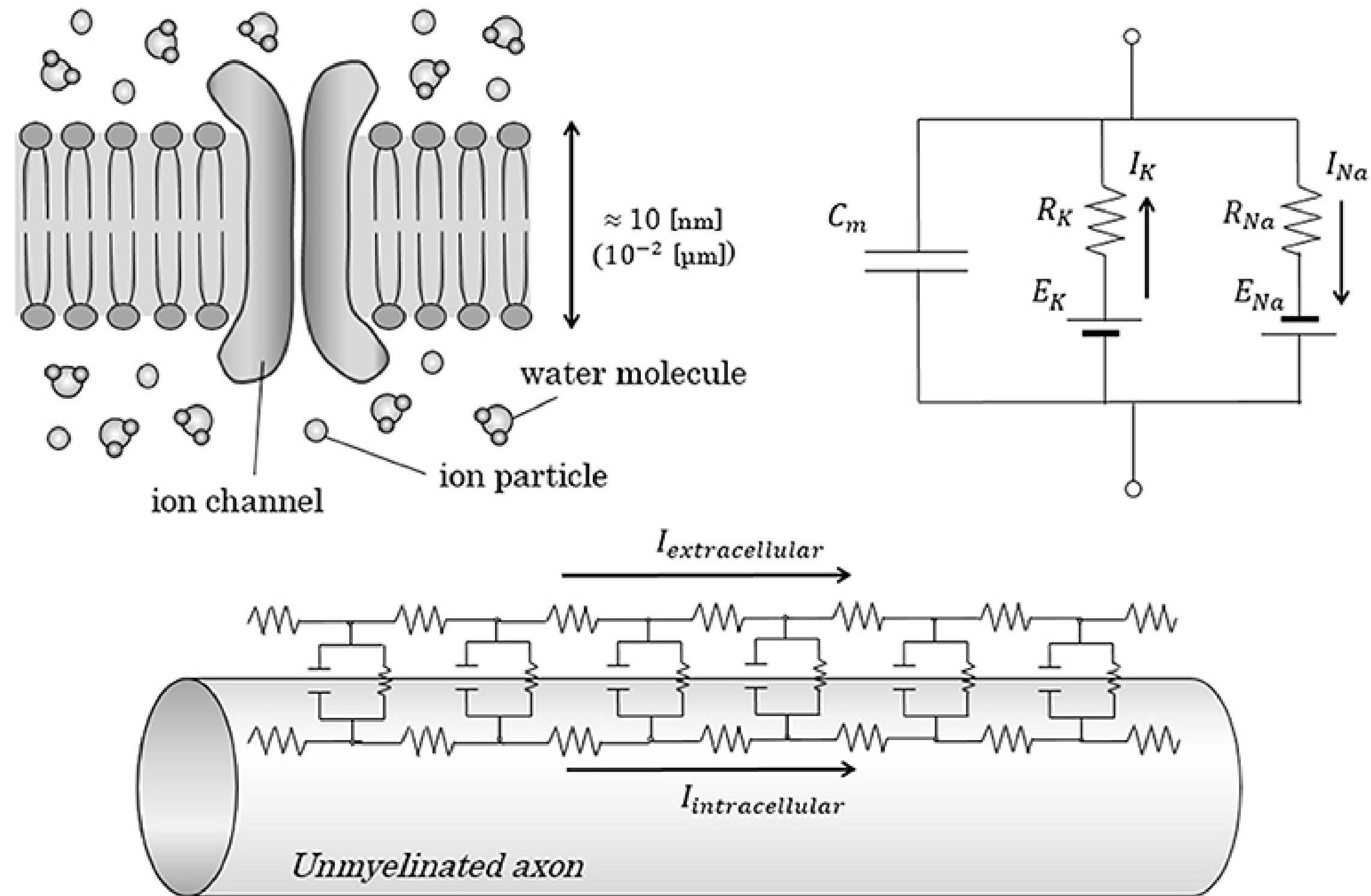
Action-potential propagation



Propagation of an action potential along a multi-compartment model axon

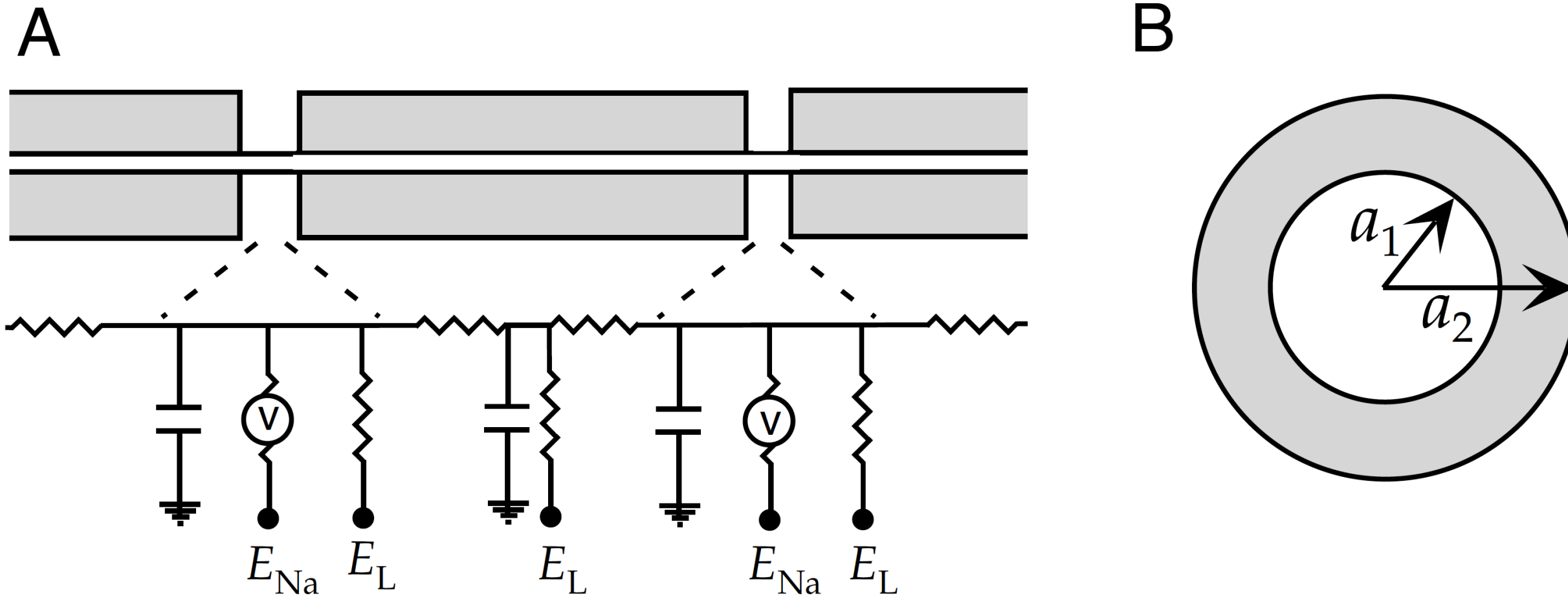


Action-potential propagation along an unmyelinated axon





Action-potential propagation along a myelinated axon



The capacitance of a myelinated cylinder of length L :

$$\frac{1}{C_m} = \frac{1}{c_m 2\pi d_m L} \int_{a_1}^{a_2} \frac{da}{a} = \frac{\ln(a_1/a_2)}{c_m 2\pi d_m L}$$



Hay et al. (2011) model

Morphological reconstruction

- Branching points
- 200 compartments
- Spatial distribution of ion currents

Sodium currents (2 types)

- $I_{Na,transient}$ - HH-type (inactivating)
- I_{NaP} - persistent (non-inactivating)

Calcium currents (2 types and calcium pump)

Potassium currents (3 types, includes I_M)

Unspecific current