Modeling Astrocytes

Understanding the Models

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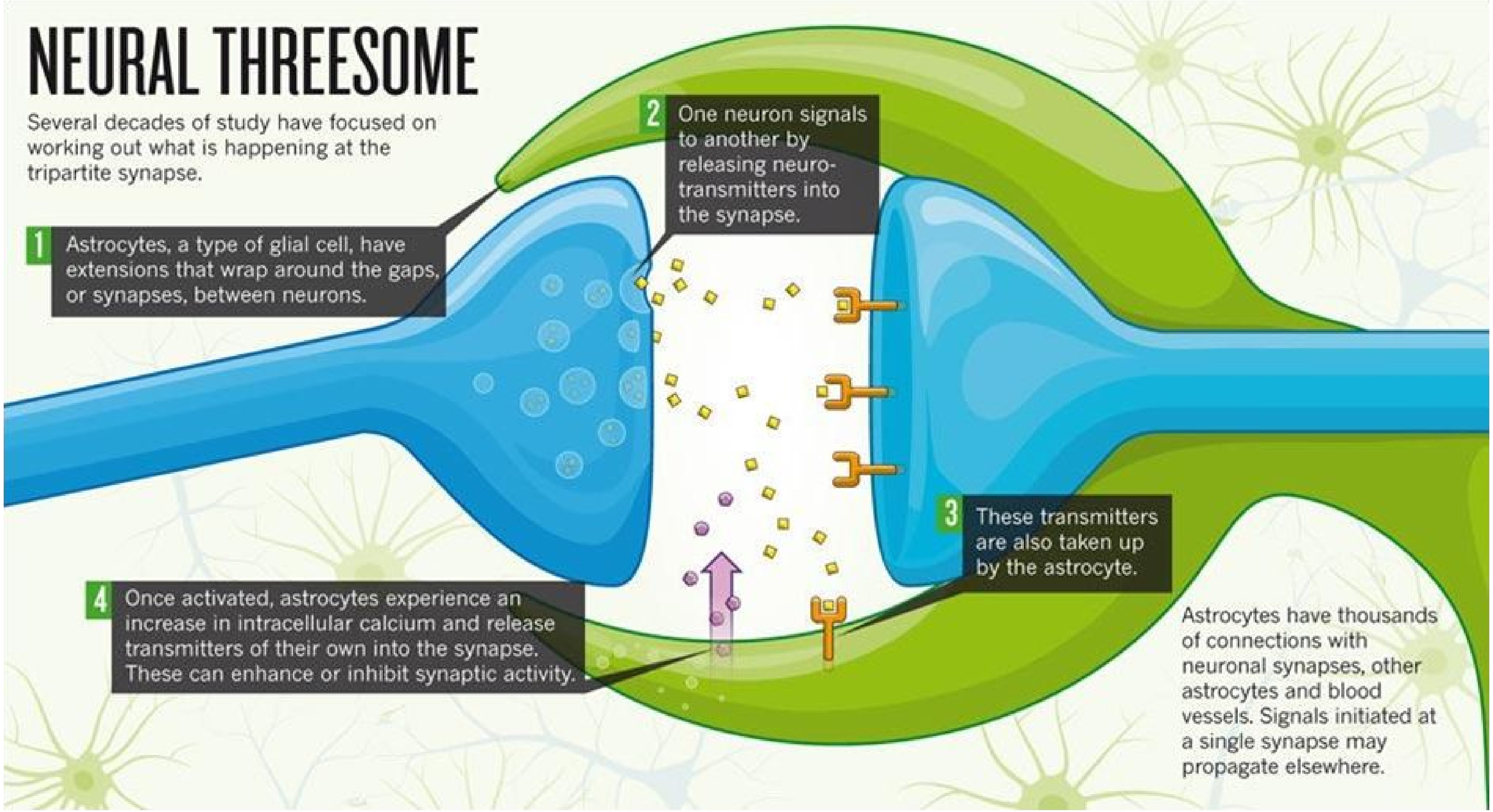
What am I doing?

- Understand the most detailed biological Astrocyte models
- Identify the relevant dynamical properties
- Construct a simpler model which exhibits the same dynamical behavior
- Go Big - Put as many together as will fit on the HPC

The Tripartite Synapse



The Tripartite Synapse

- Why the Tripartite Synapse?
  - "One of the most significant challenges in neuroscience is to identify the cellular and molecular processes that underlie learning and memory formation" *(Lynch, 2004)*
  - **Plasticity** - "Refers to changes in neural pathways and synapses which are due to changes in behavior, environment, neural processes, thinking, emotions, as well as changes resulting from bodily injury." *(Pascual-Leone, 2011)*
  - **"Astrocytes play crucial roles in the control of Hebbian plasticity" (Fellin, 2009)**

The Model

- A Mathematical Model of Tripartite Synapse: Astrocyte Induced Synaptic Plasticity (Tewari, 2012)

- Their model is an aggregation of pre-existing models

A) Pre-synaptic action potential train was generated using the HH model (Hodgkin & Huxley, 1952)

B) Ca2+ concentration elevation in the pre-synaptic bouton incorporating fast (using single protein properties (Erler et al., 2004)) and slow (using modified Li- Rinzel model (Li & Rinzel, 1994)) Ca2+ influx.

The Model

C) Glutamate release in the synaptic cleft as a two step process (using Bollman et al., (2000) for Ca2+ binding to synaptic vesicle sensor and, Tsodyks & Markram (1999) for synaptic vesicle fusion and recycling).

D) Glutamate modulated enhancement of astrocytic Ca2+ (using astrocyte specific G-Chi model (De Pitta et al., 2009)).

E) Glutamate mediated excitatory post-synaptic current (using Destexhe et al (1999)) and potential (using Tsodyks & Markram (1997)).

F) Extra-synaptic glutamate elevation is also modeled as a two- step process (using modified Bertram model (Bertram et al., 1996) to fit Synaptic- Like Micro-vesicle (SLMV) release probability determined recently (Malarkey & Parpura, 2011) and, Tsodyks & Markram (1997) for SLMV fusion and recycling).

The Tripartite Synapse

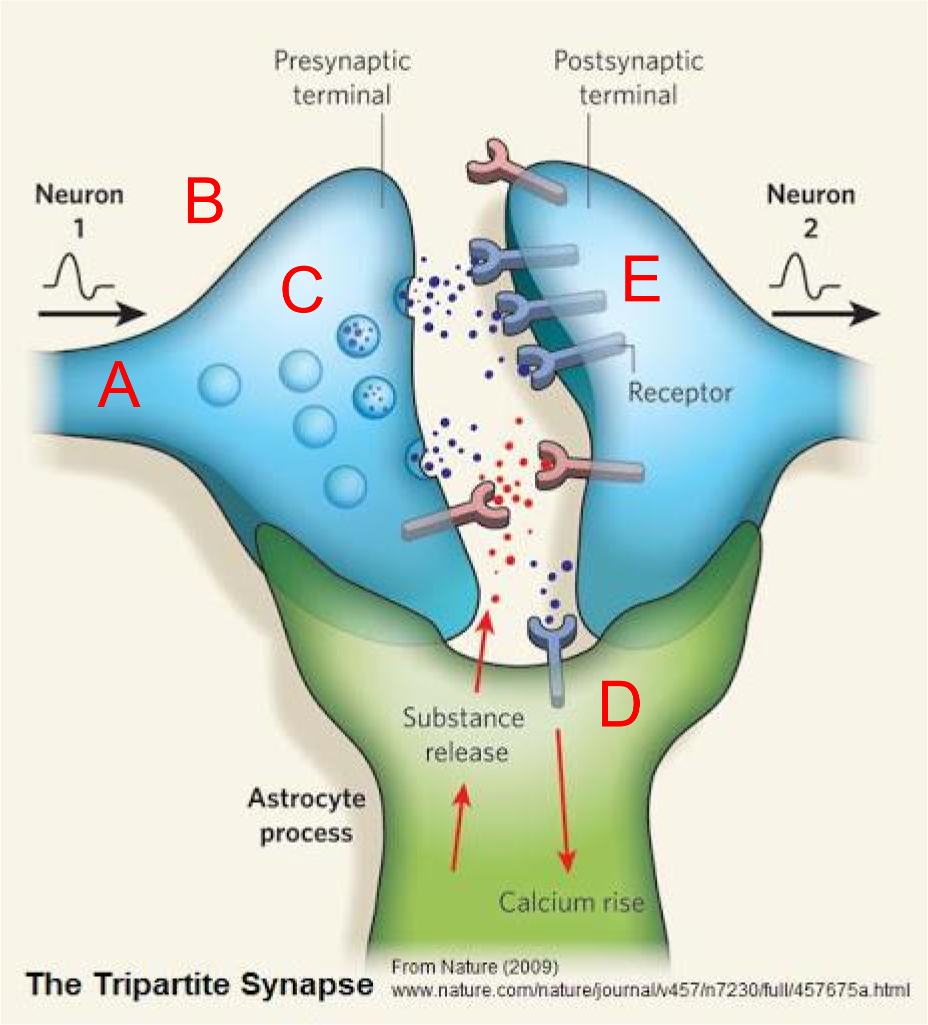
A) The arriving action potential

B) Calcium ion influx

C) Calcium binds to vesicles, vesicles bind to membrane, neurotransmitter is released

D) Neurotransmitters cause calcium rise in astrocyte, astrocyte release more neurotransmitter

E) Neurotransmitters bind to receptors on postsynaptic terminal

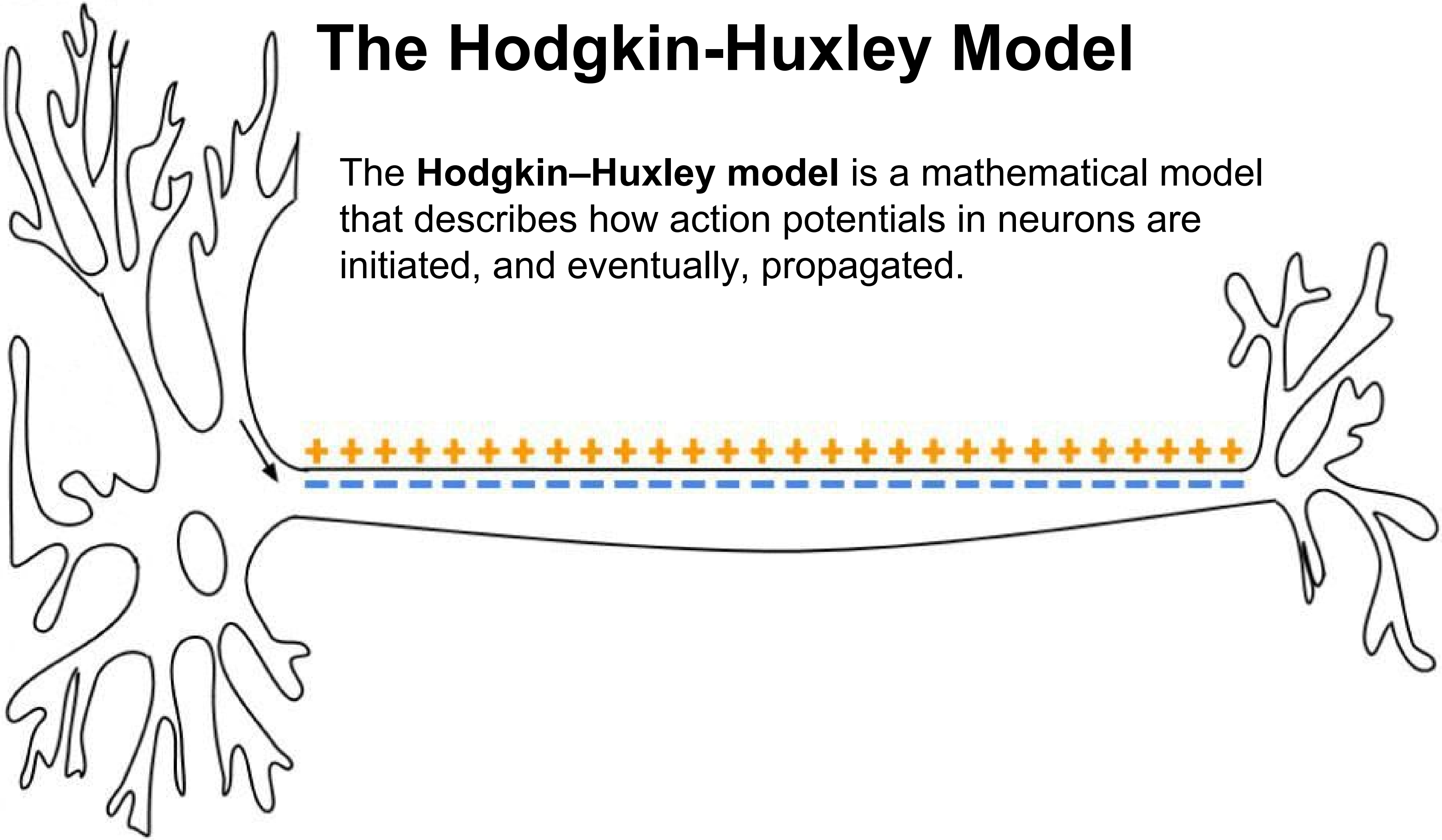


This is a lot of Modeling...

- Study one model at a time
- Start by understanding the process with pictures
- Conceptually model the behavior
- Turn the conceptual model into mathematics
- Begin with the Hodgkin-Huxley model

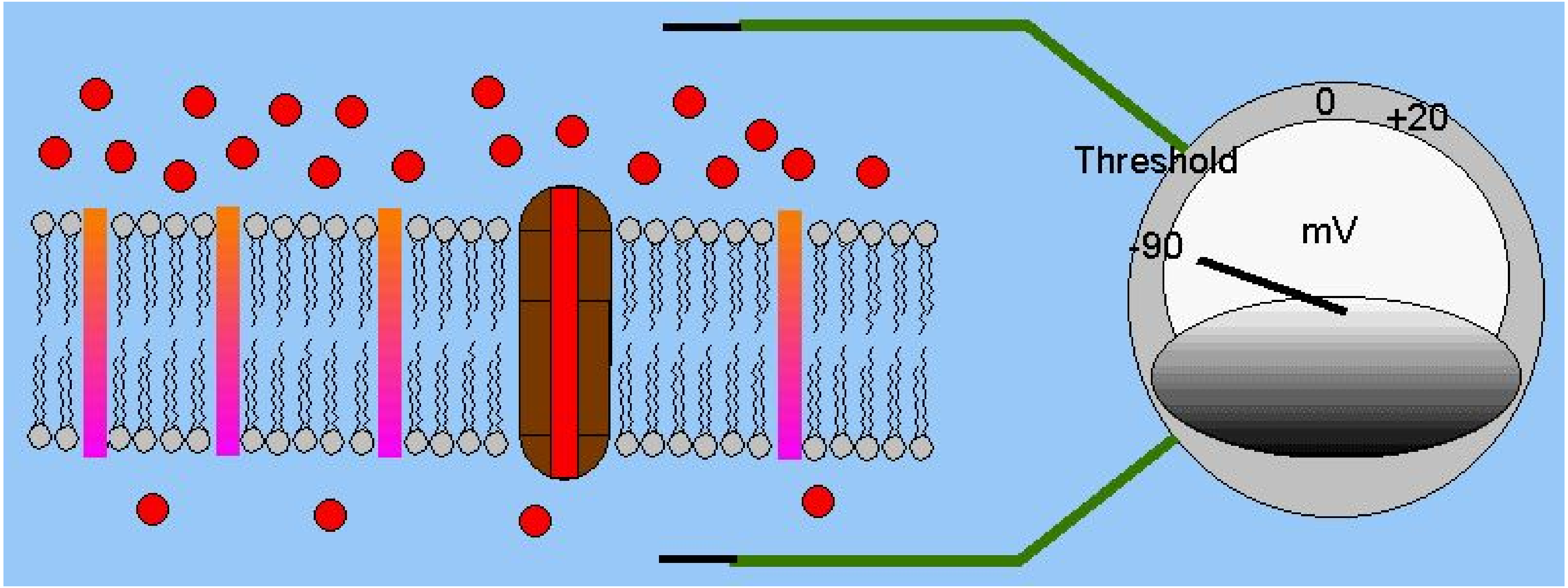
The Hodgkin-Huxley Model

The **Hodgkin–Huxley model** is a mathematical model that describes how action potentials in neurons are initiated, and eventually, propagated.



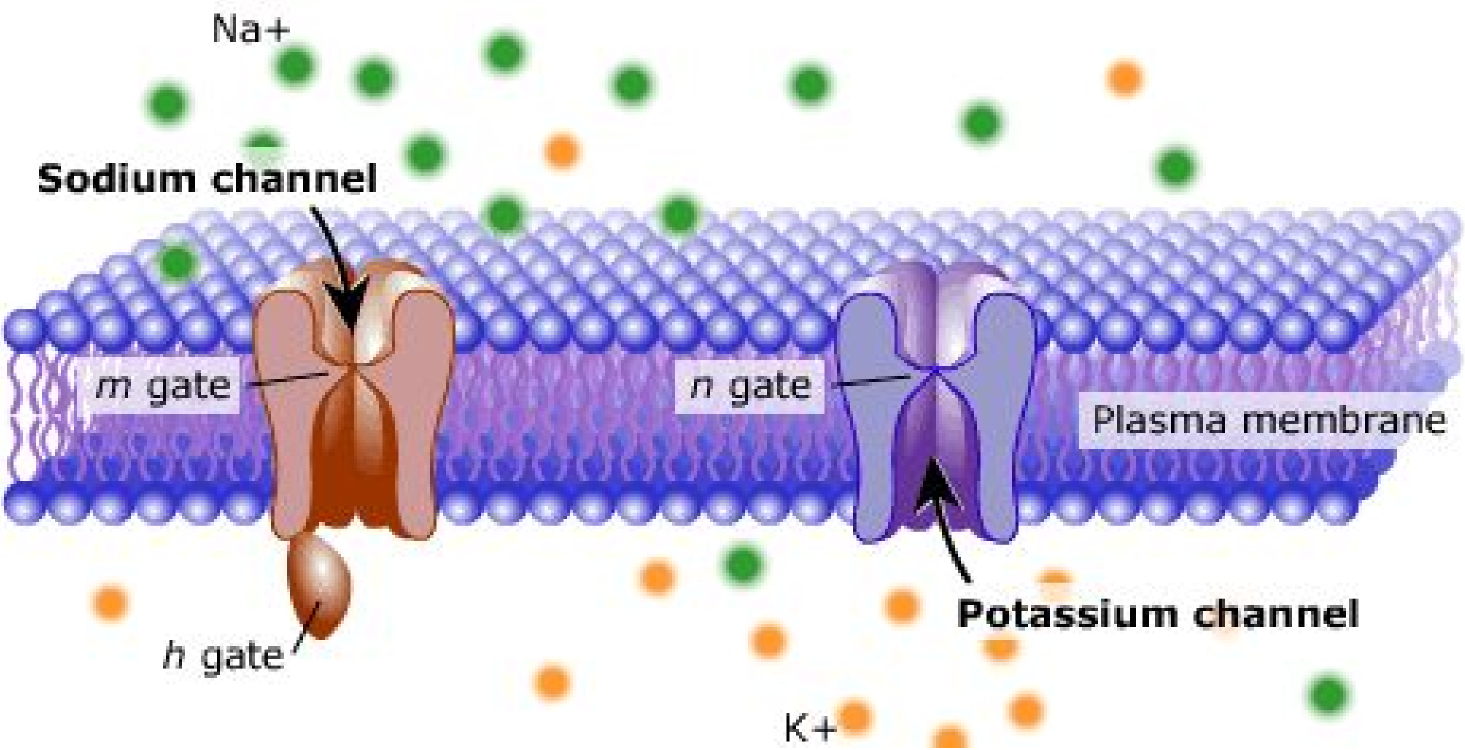
The Hodgkin-Huxley Model

The ions flow across the membrane, into the cell, depolarizing it. Then they quickly flow back across the membrane, out of the cell, hyperpolarizing it.

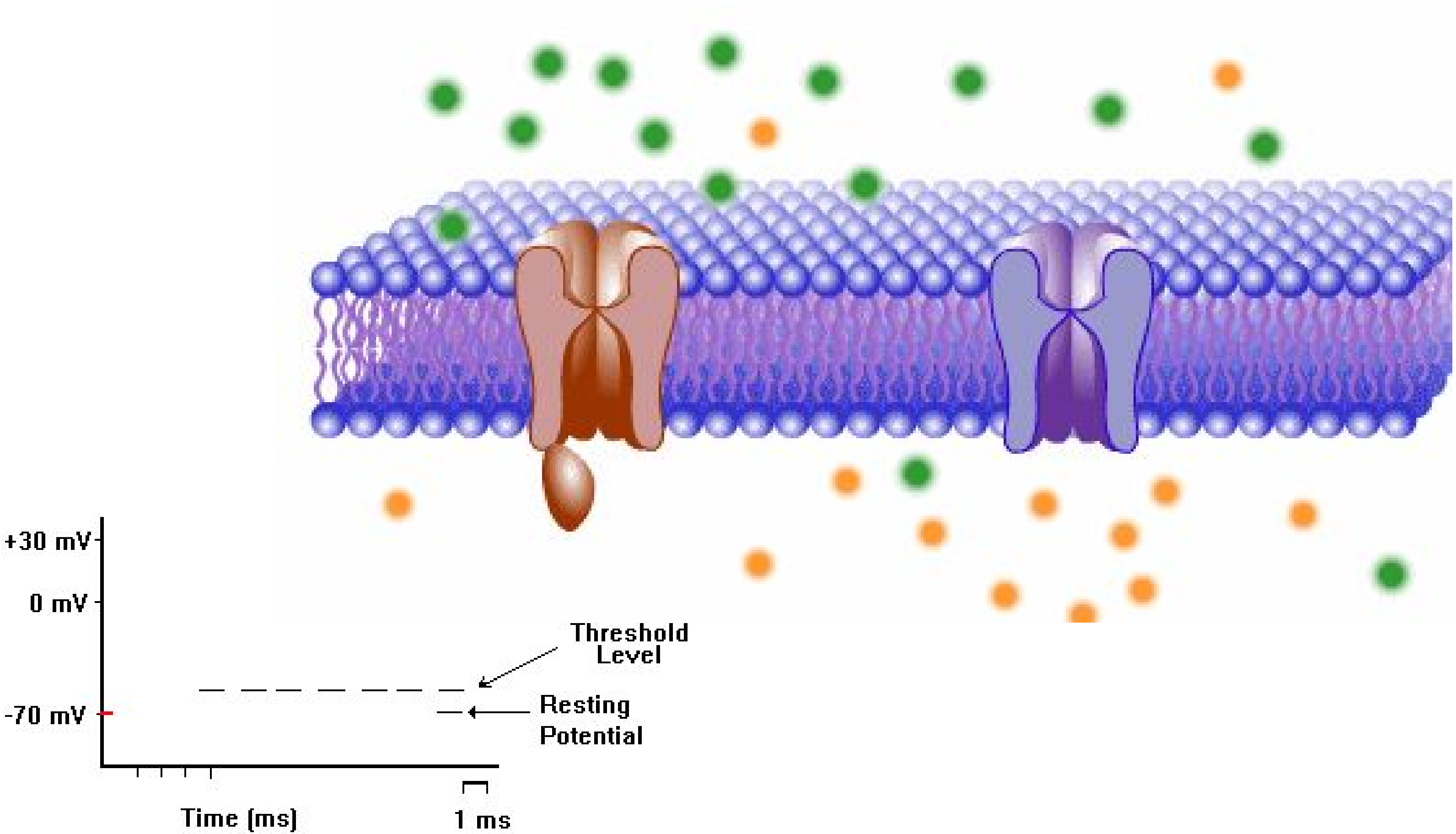


The Hodgkin-Huxley Model

Channel Gating during an action potential

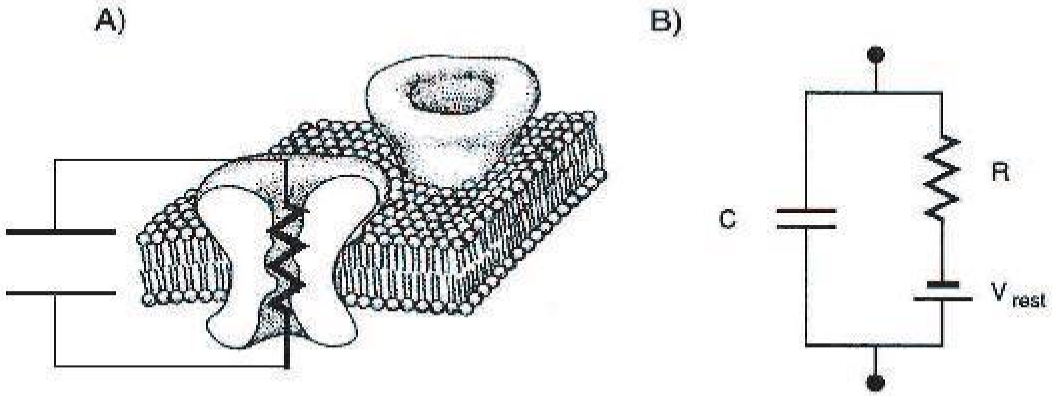


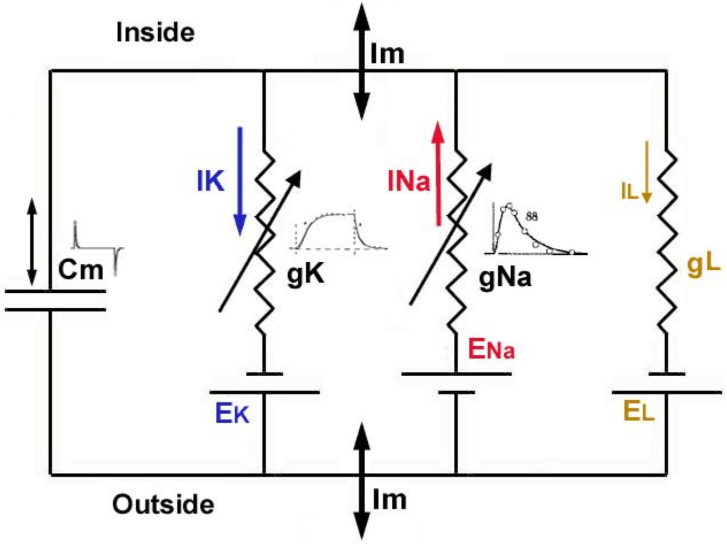
The Hodgkin-Huxley Model



The Hodgkin-Huxley Model

- Each part of the cell is approximated as a component in an electrical circuit.
- The standard equations modeling circuits are then applied to the cell.





The Hodgkin-Huxley Model

- The current flowing through the lipid-bilayer is

$$I_c = C_m \frac{\mathrm{d}V_m}{\mathrm{d}t}$$

- The current through a given ion channel is

$$I_i = g_i(V_m - V_i)$$

- Total current through the membrane is given by

$$I = C_m \frac{\mathrm{d}V_m}{\mathrm{d}t} + g_K(V_m - V_K) + g_{Na}(V_m - V_{Na}) + g_l(V_m - V_l),$$

The Hodgkin-Huxley Model

- It is a set of nonlinear differential equations that approximates the neuron's electrical characteristics.

$$I = C_m \frac{\mathrm{d}V_m}{\mathrm{d}t} + \bar{g}_K n^4 (V_m - V_K) + \bar{g}_{Na} m^3 h (V_m - V_{Na}) + \bar{g}_l (V_m - V_l),$$

$$\frac{dn}{dt} = \alpha_n(V_m)(1-n) - \beta_n(V_m)n$$

$$\frac{dm}{dt} = \alpha_m(V_m)(1-m) - \beta_m(V_m)m$$

$$\frac{dh}{dt} = \alpha_h(V_m)(1-h) - \beta_h(V_m)h$$

Where...

$$\alpha_p(V_m) = p_\infty(V_m)/\tau_p$$
$$\beta_p(V_m) = (1 - p_\infty(V_m))/\tau_p$$