

Computational Neuroscience: II

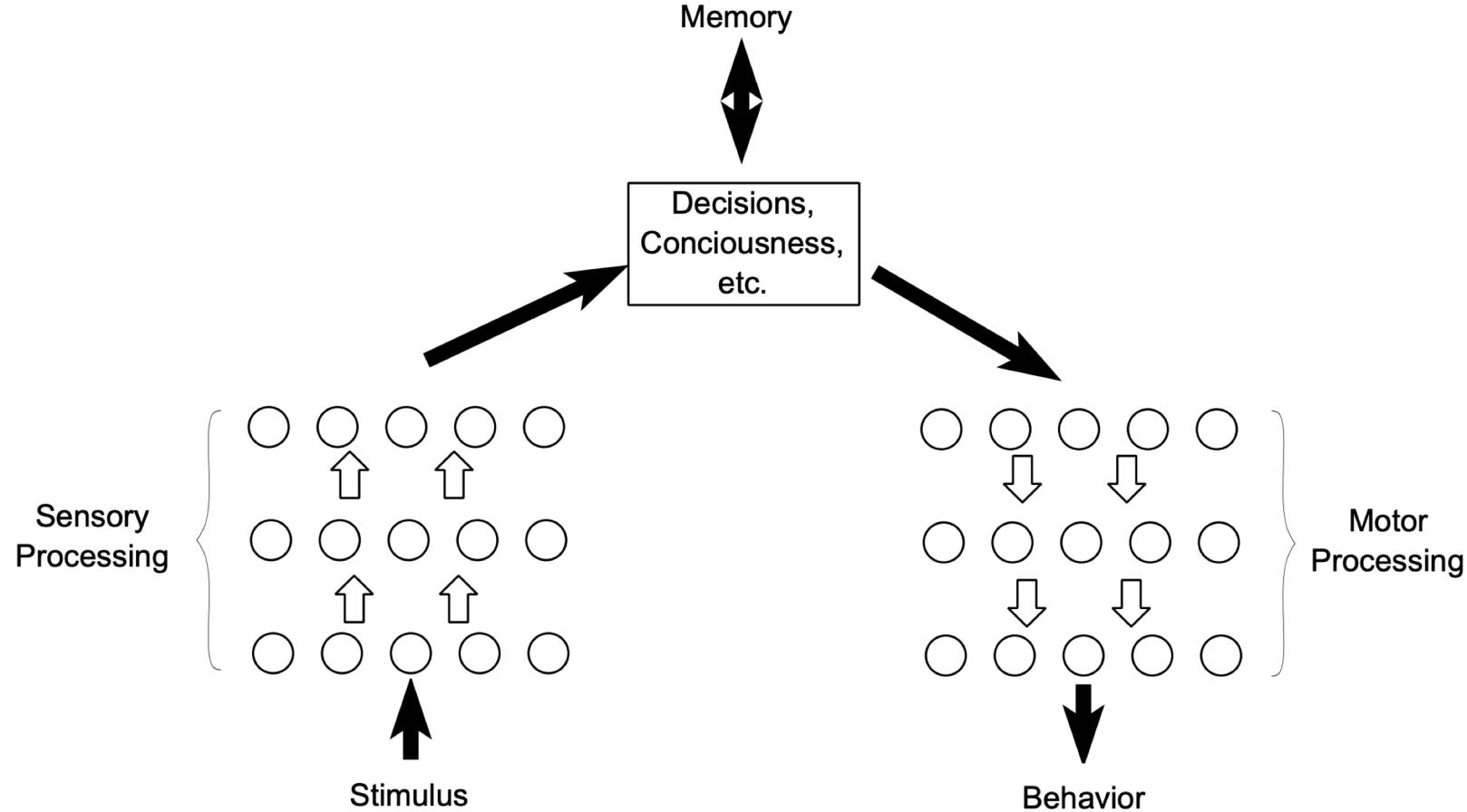
Lecture 4

Outline

- The dominant paradigm
- Plasticity in neuronal systems:
 - Hebbian rule
 - STDP
- Mathematical model of action potential generation: Hodgkin–Huxley model

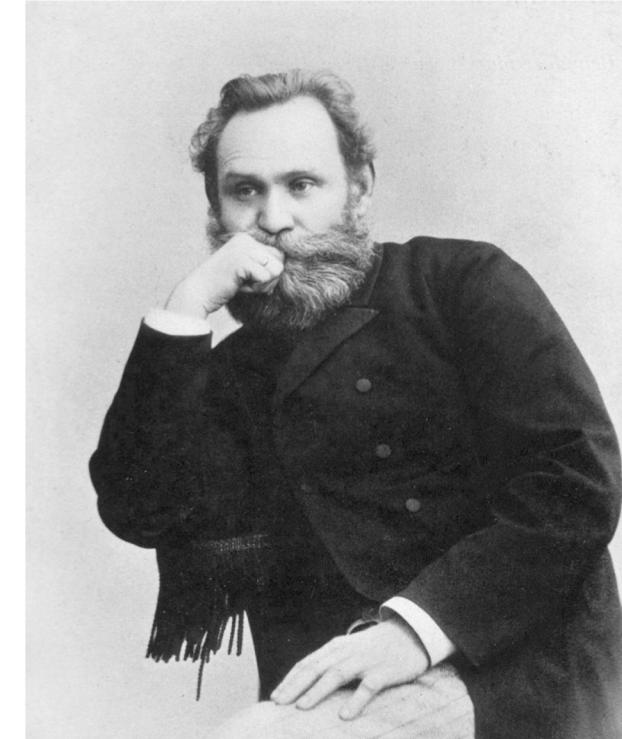
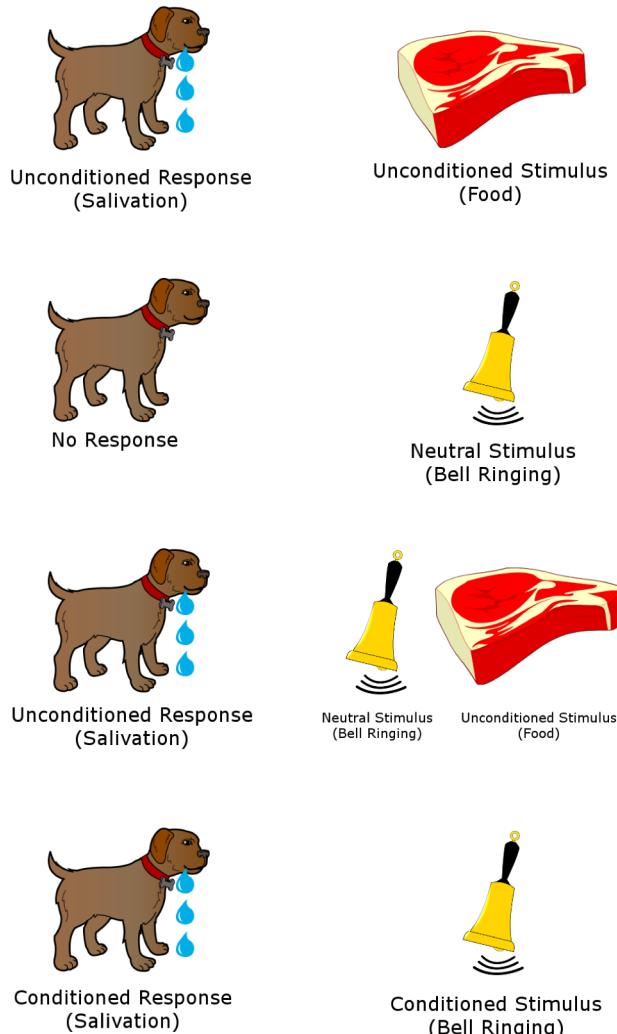
The dominant paradigm for thinking about brain function

- There is a particular view of brain function that is implicit in many discussions of neural coding.
- In this view, organisms are optimized to extract information presented to them by their environment and, based on this information, select behaviors that optimize their chance of survival.



Classical conditioning (also known as Pavlovian)

- Conditioning refers to a learning procedure in which a biologically potent stimulus (e.g. food) is paired with a previously neutral stimulus (e.g. a bell).
- It also refers to the learning process that results from this pairing, through which the neutral stimulus comes to elicit a response (e.g. salivation) that is usually similar to the one elicited by the potent stimulus.



1849-1936

Pavlov was awarded the Nobel Prize in Physiology or Medicine in 1904 for recognition of his work on the physiology of digestion, through which knowledge on vital aspects of the subject has been transformed and enlarged

The dominant paradigm for thinking about brain function

Information first enters the brain through sensory receptors.



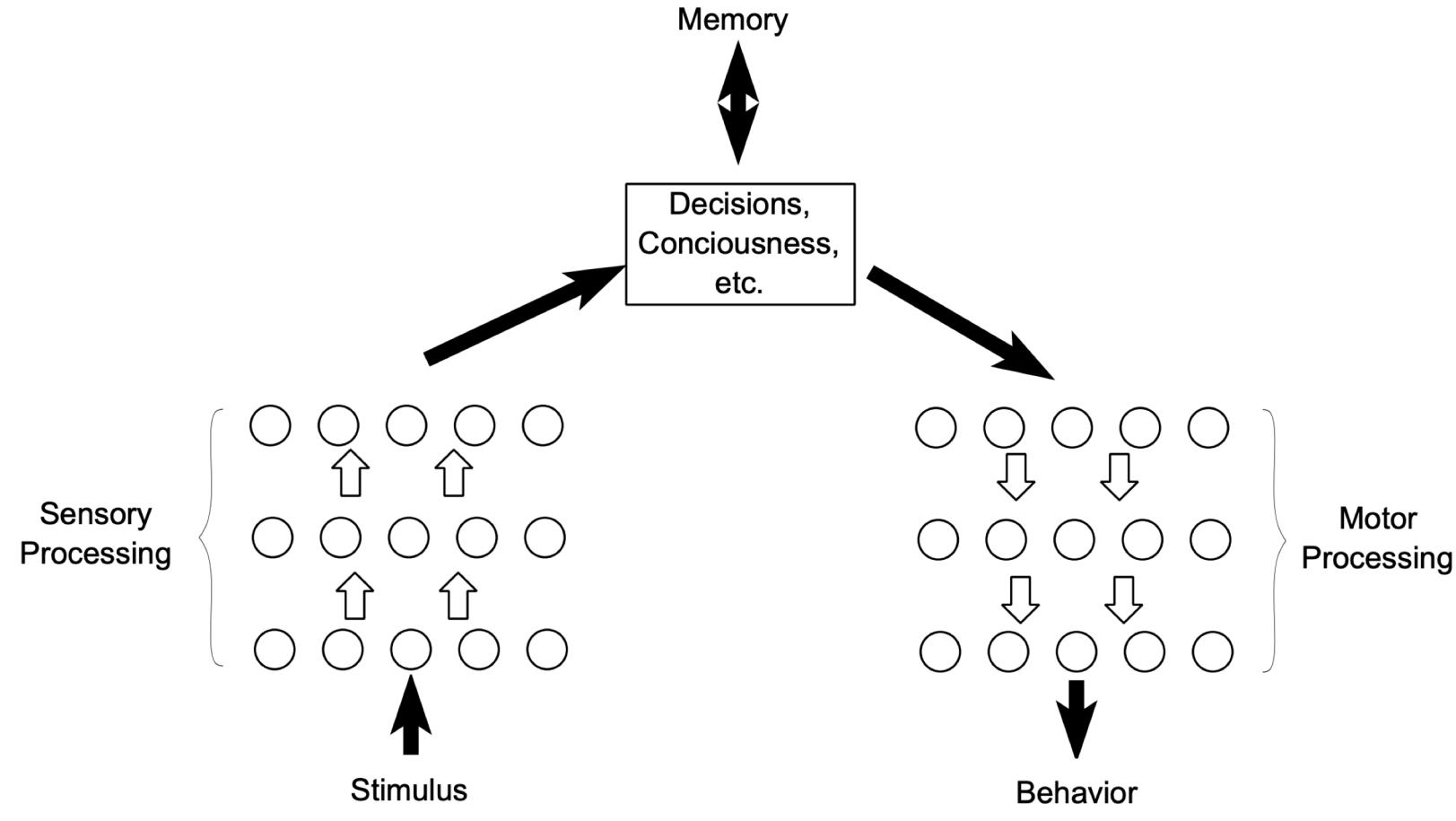
Information is extracted via a series of (sensory) processing stages.



Based on this information, and perhaps information recalled from memory, the organism makes a decision to act.

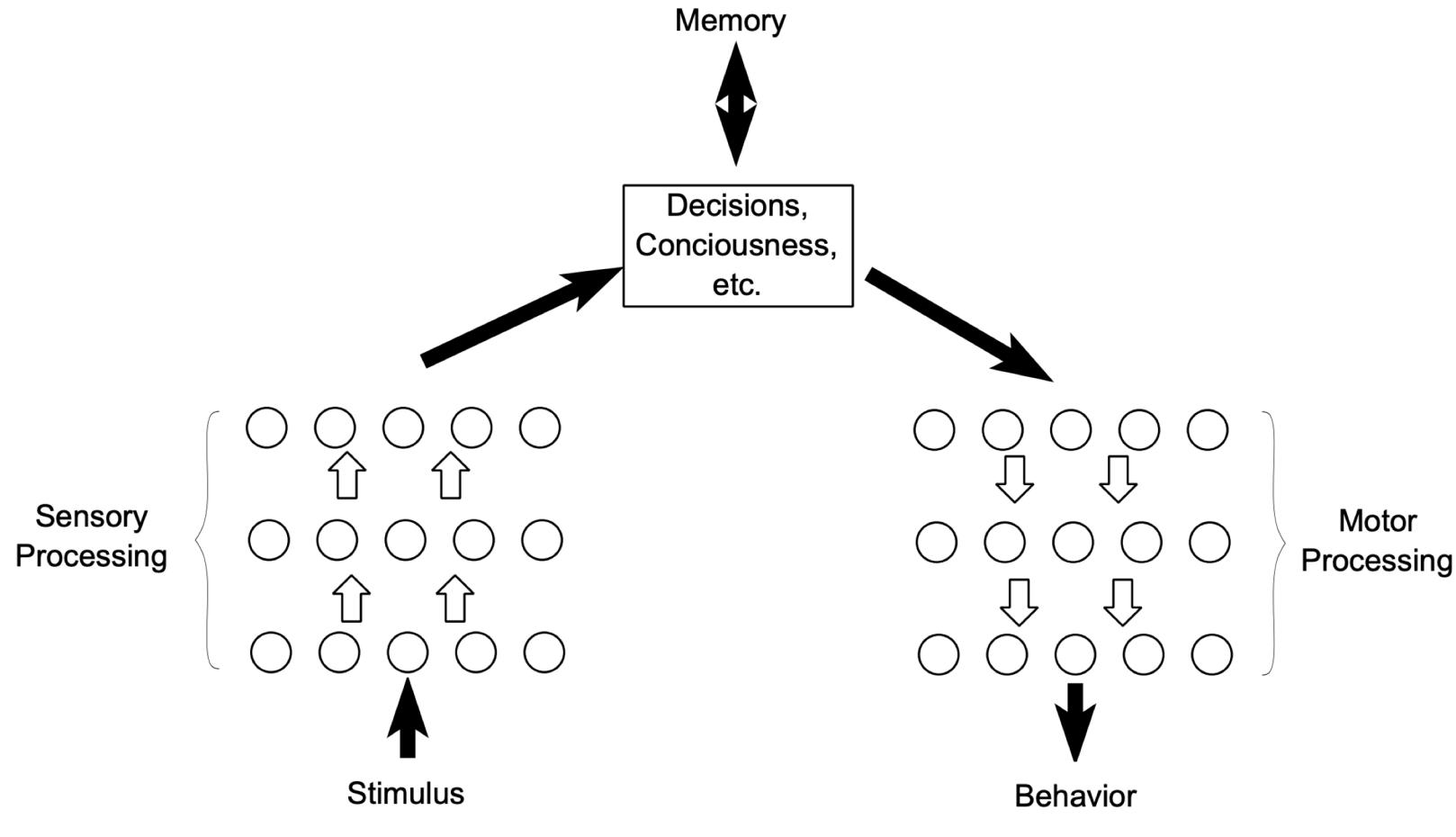


Finally, the details of an appropriate command are computed in another series of processing stages, eventually leading to behavior



Criticism of the dominant paradigm

- The strict stimulus-response paradigm has often been criticized as a much too passive view of an organisms role in the world
- Current trends toward “active perception.”: the motor end of the picture is fundamental – animals have evolved to act.
- Sensory input is of course important, but instead of looking to the world to determine the origin of behavior, perhaps one should view sensory stimuli as making adjustments to an animal’s ongoing behavioral repertoire.



The dominant paradigm for thinking about brain function

These issues touch on two of the basic dichotomies encountered while studying the brain:

- the degree to which behavior is innately specified versus learned
- the degree to which a given pattern of brain activity is driven by the external stimulus versus internal brain processes.

Synaptic plasticity

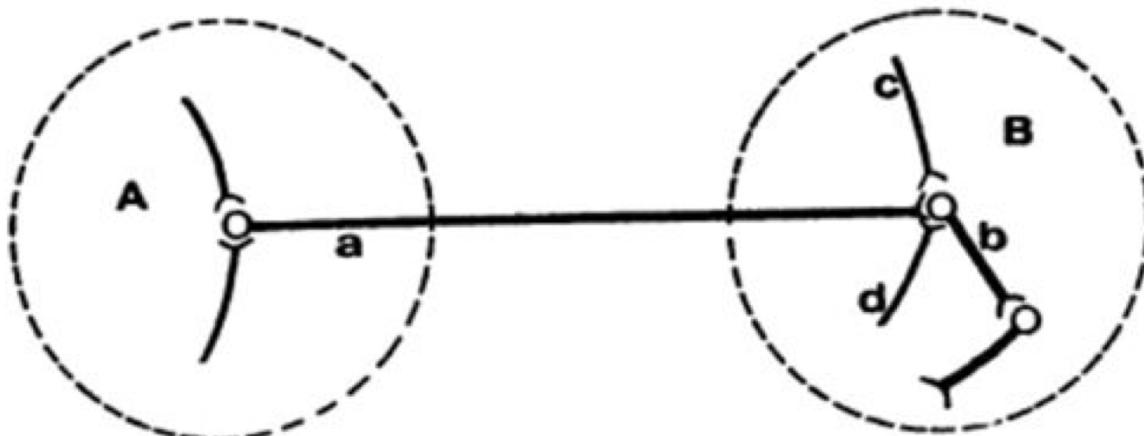
- Synaptic transmission can be changed by previous activity. These changes may result in either a decrease in the efficacy of the synapse, called depression, or an increase in efficacy, called potentiation.
- These changes can either be long-term or short-term. Forms of short-term plasticity include synaptic fatigue or depression and synaptic augmentation.
- Forms of long-term plasticity include long-term depression and long-term potentiation.

Hebbian rule

- Synapses increase their efficiency if the synapse persistently takes part in firing the postsynaptic target neuron
- Neurons that fire together, wire together



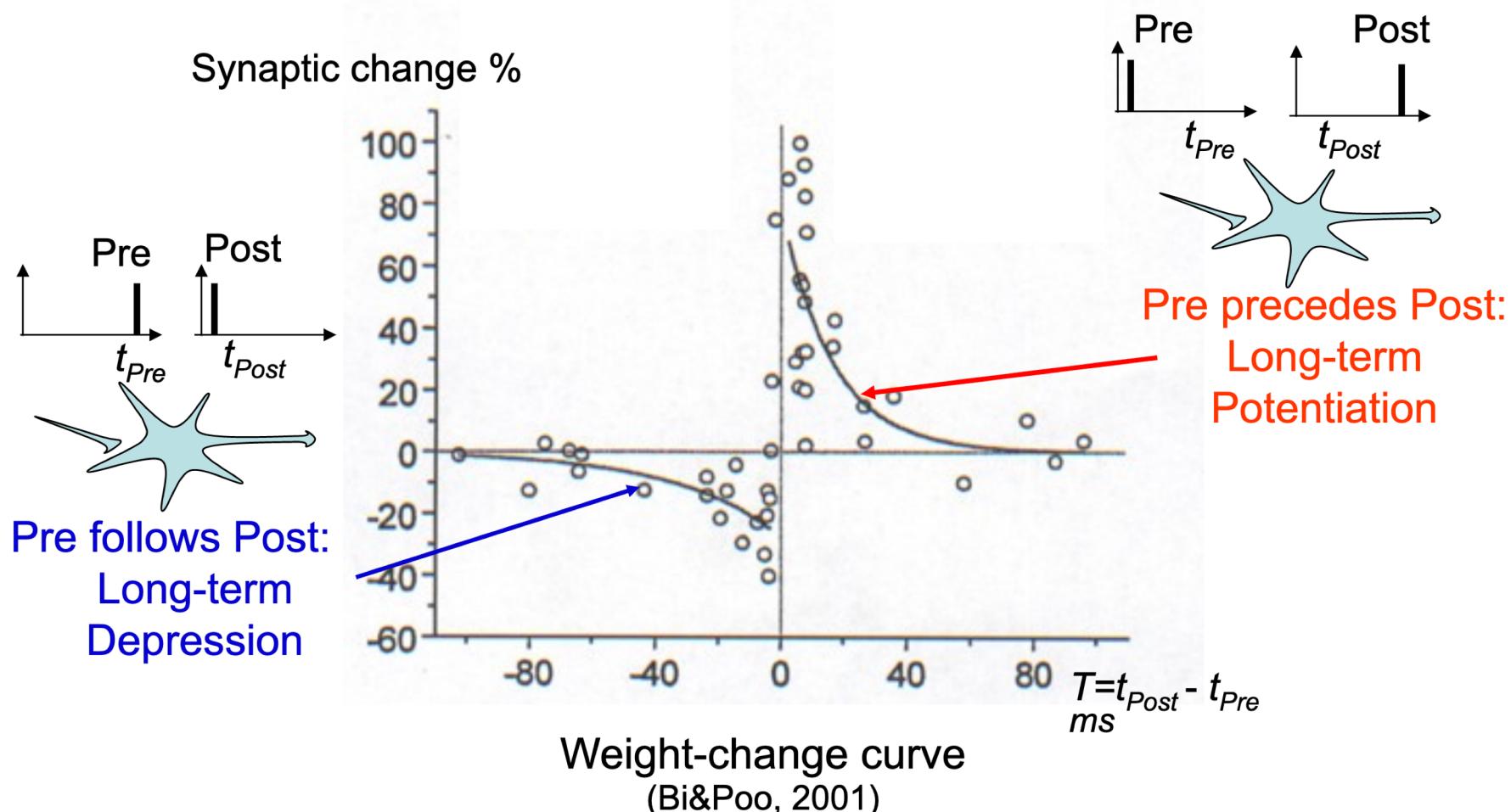
Donald O. Hebb (1905-1985)



An illustration of the Hebbian rule and a small assembly of cells. Here, presynaptic cell **a**, along with afferents **c** and **d**, repeatedly and persistently drive the postsynaptic cell **b**, thus leading to a long-term increase in the connective strength between cells **a** and **b**.

Spike-timing dependent plasticity (STDP)

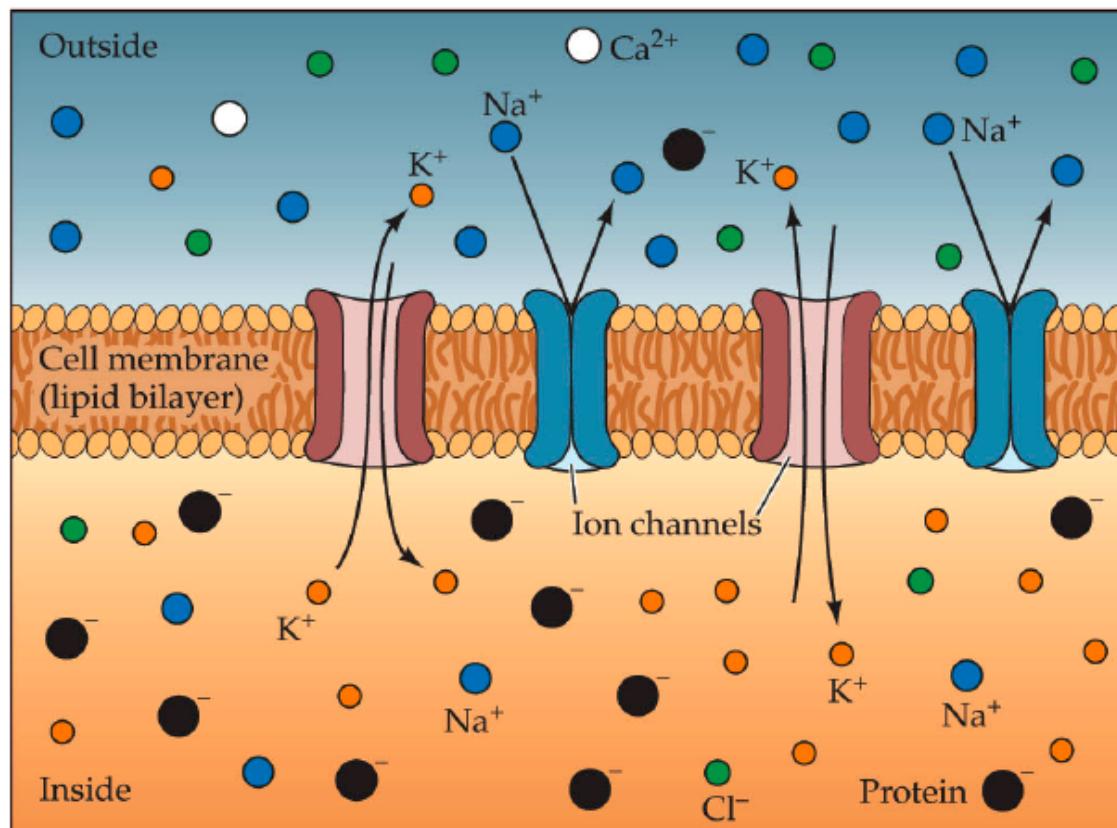
Weight changes depending on the degree of correlated firing



Mathematical models of neurons

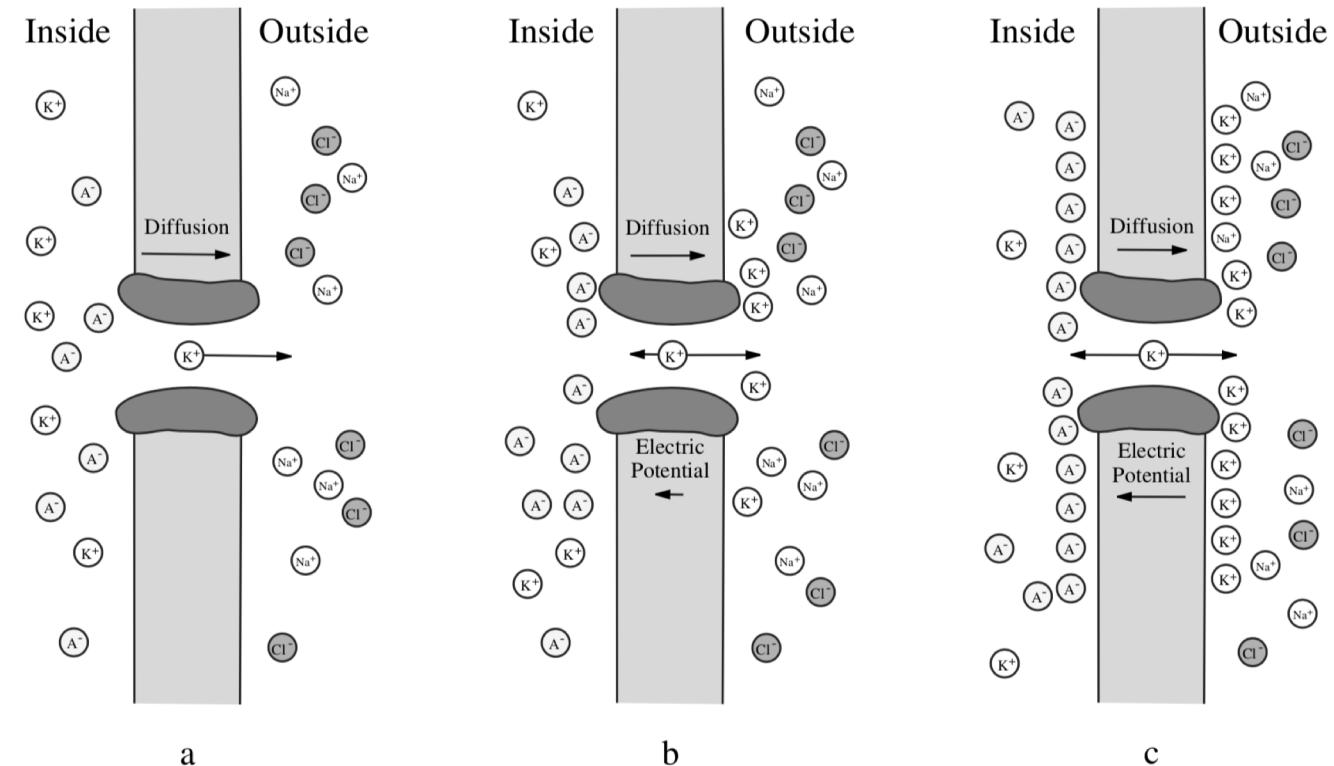
- Electrical activity in neurons is sustained and propagated via ionic currents through neuron membranes.
- Most of these transmembrane currents involve one of four ionic species: sodium (Na^+), potassium (K^+), calcium (Ca^{2+}), or chloride (Cl^-).
- The concentrations of these ions are different on the inside and the outside of a cell, which creates electrochemical gradients – the major driving forces of neural activity.

	Na^+	K^+	Cl^-	Ca^{2+}	Proteins
Outside cell	many	few	many	many	few
Inside cell	few	many	few	few	many



Equilibrium membrane potential

- There are two forces that drive each ion species through the membrane channel: concentration and electric potential gradients.
- The positive and negative charges accumulate on the opposite sides of the membrane surface, creating an electric potential gradient across the membrane – **membrane potential**.

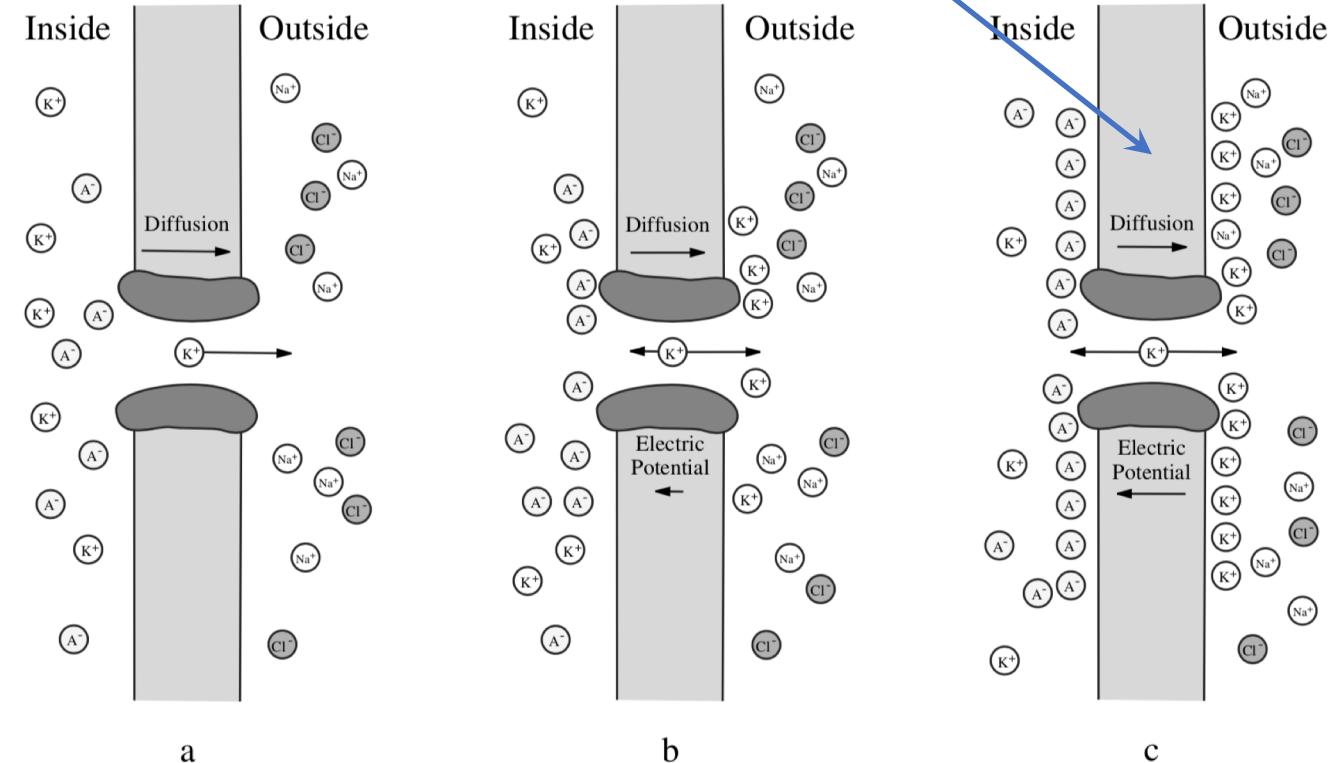


Diffusion of K^+ ions down the concentration gradient through the membrane (a) creates an electric potential force pointing in the opposite direction (b) until the diffusion and electrical forces counter each other (c).

Capacitor with capacitance C
($C \approx 1.0 \mu\text{F}/\text{cm}^2$ in the squid axon)

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Nernst Potential

- The value of an equilibrium potential depends on the ionic species, and it is given by the Nernst equation

$$E_{\text{ion}} = \frac{RT}{zF} \ln \frac{[\text{Ion}]_{\text{out}}}{[\text{Ion}]_{\text{in}}}$$

$$E_{\text{ion}} \approx 62 \log \frac{[\text{Ion}]_{\text{out}}}{[\text{Ion}]_{\text{in}}} \quad (\text{mV})$$
$$T = 310^\circ\text{K} (37^\circ\text{C})$$

$[\text{Ion}]_{\text{in}}$ and $[\text{Ion}]_{\text{out}}$ are concentrations of the ions inside and outside the cell, respectively;

R is the universal gas constant ($8.315 \text{ mJ/(K}^\circ\cdot\text{Mol})$);

T is temperature in degrees Kelvin ($K^\circ = 273.16 + C^\circ$);

F is Faraday's constant (96.480 coulombs/Mol),

z is the valence of the ion (z=1 for Na^+ and K^+ ; z=-1 for Cl^- ; and z=2 for Ca^{2+}).

Ionic Currents and Conductances

- V is the membrane potential
- E_{Na} , E_{Ca} , E_K , E_{Cl} are the Nernst equilibrium potentials
- When the membrane potential equals the equilibrium potential, for example E_K , the K^+ current, denoted as I_K , is zero.
- K^+ current is proportional to the difference of potentials (Ohm law)

$$I_K = g_K (V - E_K)$$

- g_K is the K^+ conductance and $(V - E_K)$ is the K^+ driving force

$$I_{Na} = g_{Na} (V - E_{Na}) , \quad I_{Ca} = g_{Ca} (V - E_{Ca}) , \quad I_{Cl} = g_{Cl} (V - E_{Cl})$$

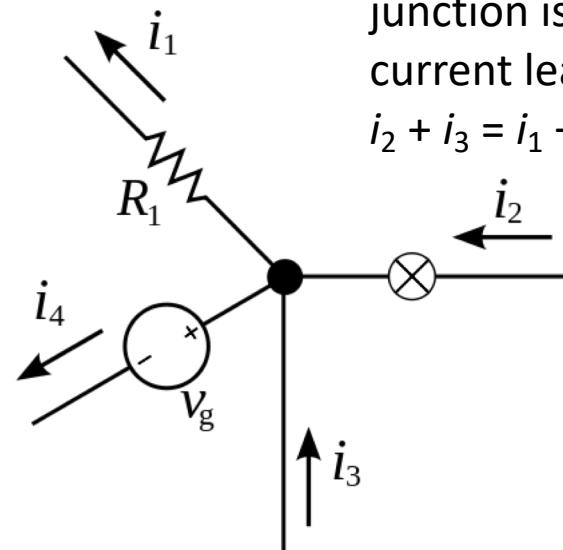
Kirchhoff's circuit laws

- **First Law:** the sum of currents flowing into that node is equal to the sum of currents flowing out of that node

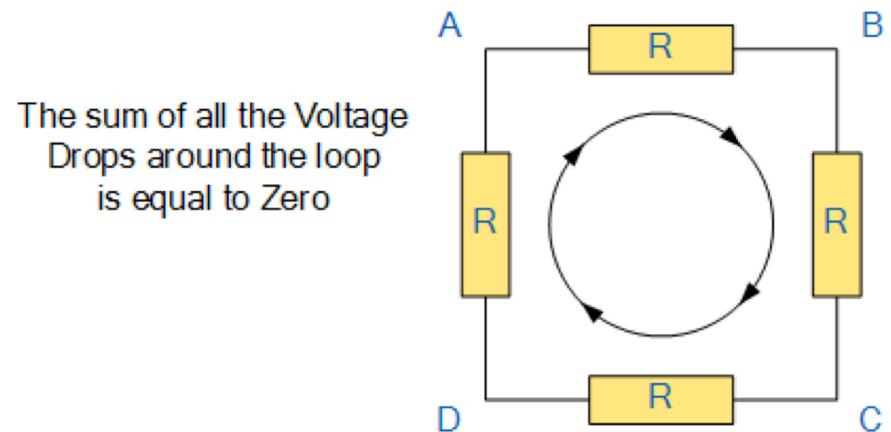
$$\sum_{k=1}^N i_k = 0$$

- **Second Law:** the directed sum of the potential differences (voltages) around any closed loop is zero

$$\sum_{k=1}^N V_k = 0$$

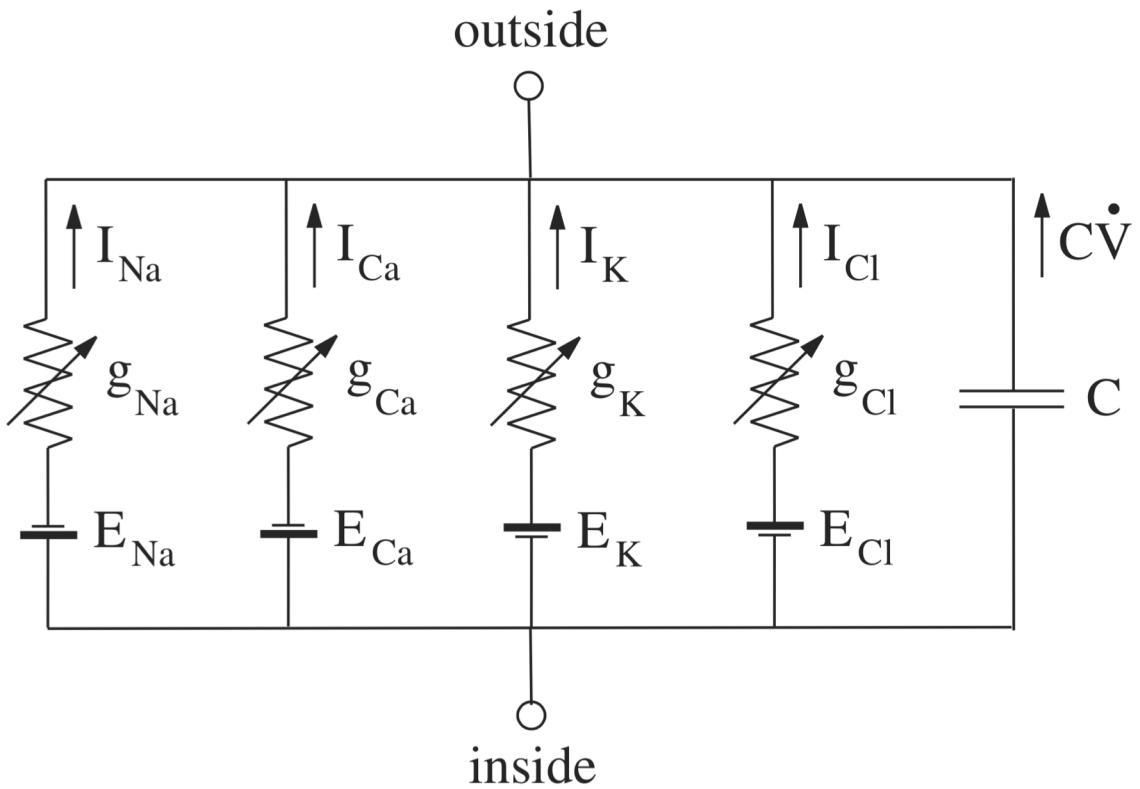


The current entering any junction is equal to the current leaving that junction.
 $i_2 + i_3 = i_1 + i_4$



$$V_{AB} + V_{BC} + V_{CD} + V_{DA} = 0$$

Equivalent circuit representation of a patch of cell membrane



$$I = C\dot{V} + I_{\text{Na}} + I_{\text{Ca}} + I_{\text{K}} + I_{\text{Cl}}$$

$\dot{V} = dV/dt$ is the derivative of the voltage variable V with respect to time t .

The derivative arises because it takes time to charge the membrane.

$$C\dot{V} = I - I_{\text{Na}} - I_{\text{Ca}} - I_{\text{K}} - I_{\text{Cl}}$$

$$C\dot{V} = I - g_{\text{Na}}(V - E_{\text{Na}}) - g_{\text{Ca}}(V - E_{\text{Ca}}) - g_{\text{K}}(V - E_{\text{K}}) - g_{\text{Cl}}(V - E_{\text{Cl}})$$

Resting Membrane Potential

The value of the membrane potential at which all inward and outward currents balance each other so that the net membrane current is zero corresponds to the resting membrane potential

$$I = 0 \quad \dot{V} = 0$$

Resting Membrane Potential

$$I = 0 \quad \dot{V} = 0$$

$$C\dot{V} = I - g_{\text{Na}}(V - E_{\text{Na}}) - g_{\text{Ca}}(V - E_{\text{Ca}}) - g_{\text{K}}(V - E_{\text{K}}) - g_{\text{Cl}}(V - E_{\text{Cl}})$$

Resting Membrane Potential

$$I = 0 \quad \dot{V} = 0$$

~~$$\dot{V} = I - g_{\text{Na}}(V - E_{\text{Na}}) - g_{\text{Ca}}(V - E_{\text{Ca}}) - g_{\text{K}}(V - E_{\text{K}}) - g_{\text{Cl}}(V - E_{\text{Cl}})$$~~

$$V_{\text{rest}} = \frac{g_{\text{Na}}E_{\text{Na}} + g_{\text{Ca}}E_{\text{Ca}} + g_{\text{K}}E_{\text{K}} + g_{\text{Cl}}E_{\text{Cl}}}{g_{\text{Na}} + g_{\text{Ca}} + g_{\text{K}} + g_{\text{Cl}}}$$

Resting Membrane Potential

$$I = 0 \quad \dot{V} = 0$$

$$C\dot{V} = I - g_{\text{Na}}(V - E_{\text{Na}}) - g_{\text{Ca}}(V - E_{\text{Ca}}) - g_{\text{K}}(V - E_{\text{K}}) - g_{\text{Cl}}(V - E_{\text{Cl}})$$

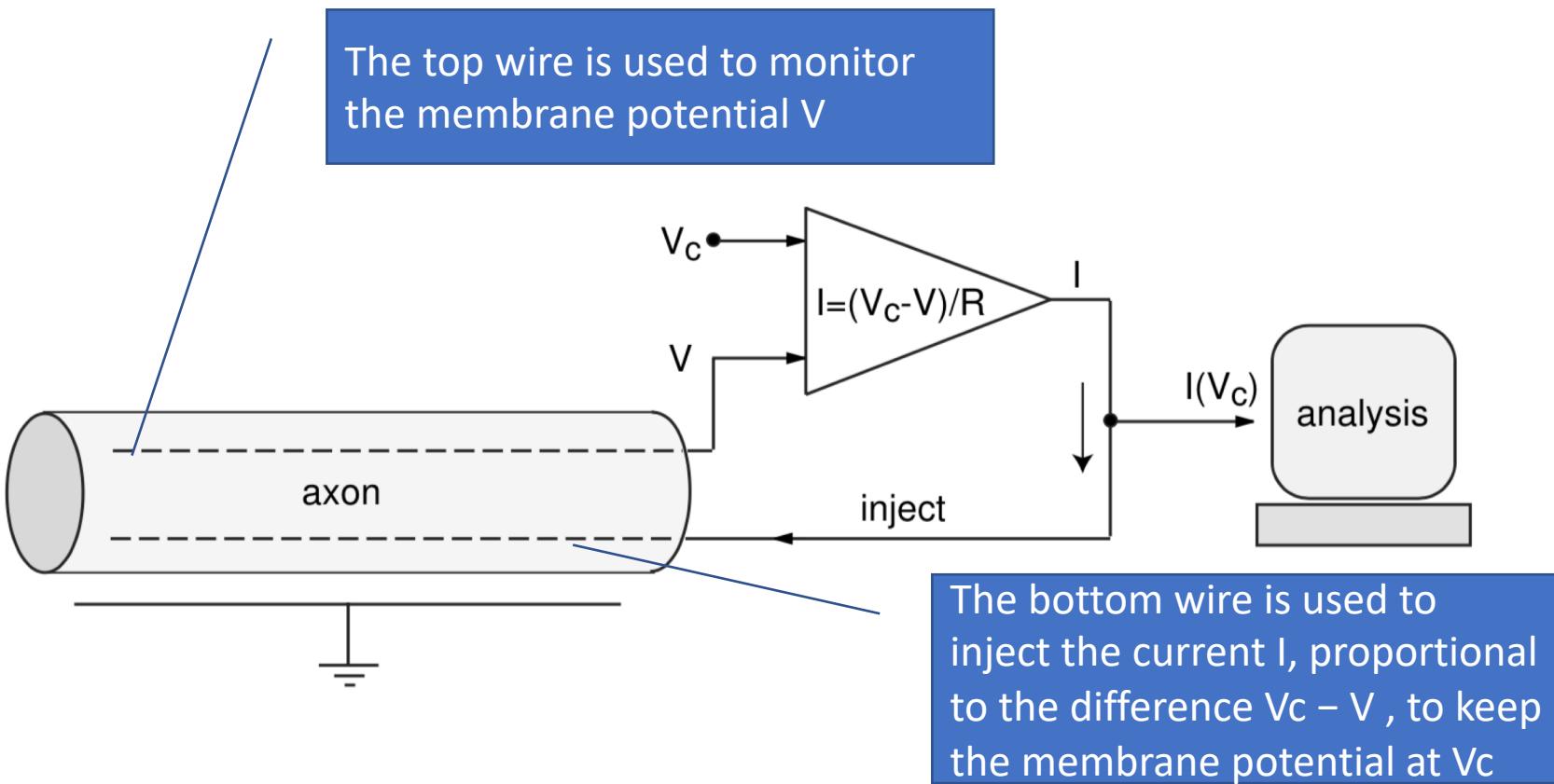


$$C\dot{V} = I - g_{\text{inp}}(V - V_{\text{rest}})$$

$$g_{\text{inp}} = g_{\text{Na}} + g_{\text{Ca}} + g_{\text{K}} + g_{\text{Cl}}$$

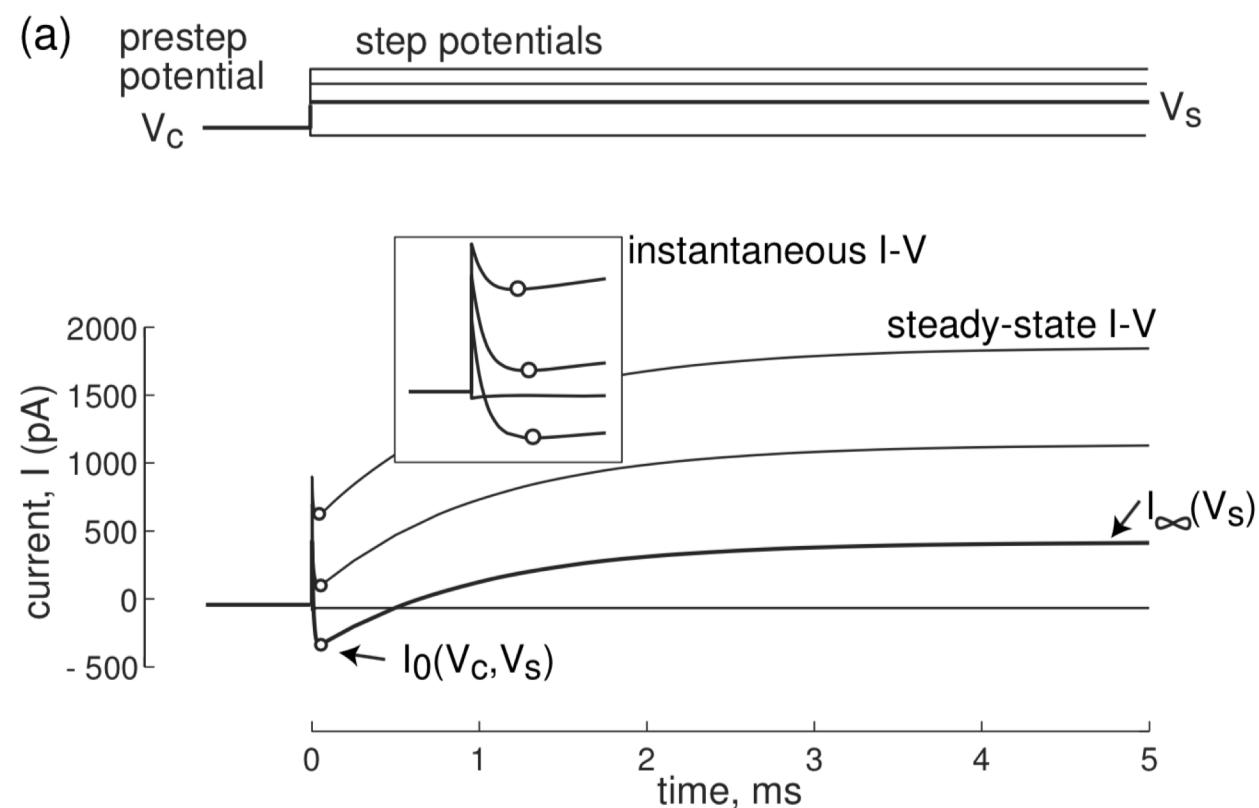
the total membrane conductance, called input conductance

Voltage-clamp experiment



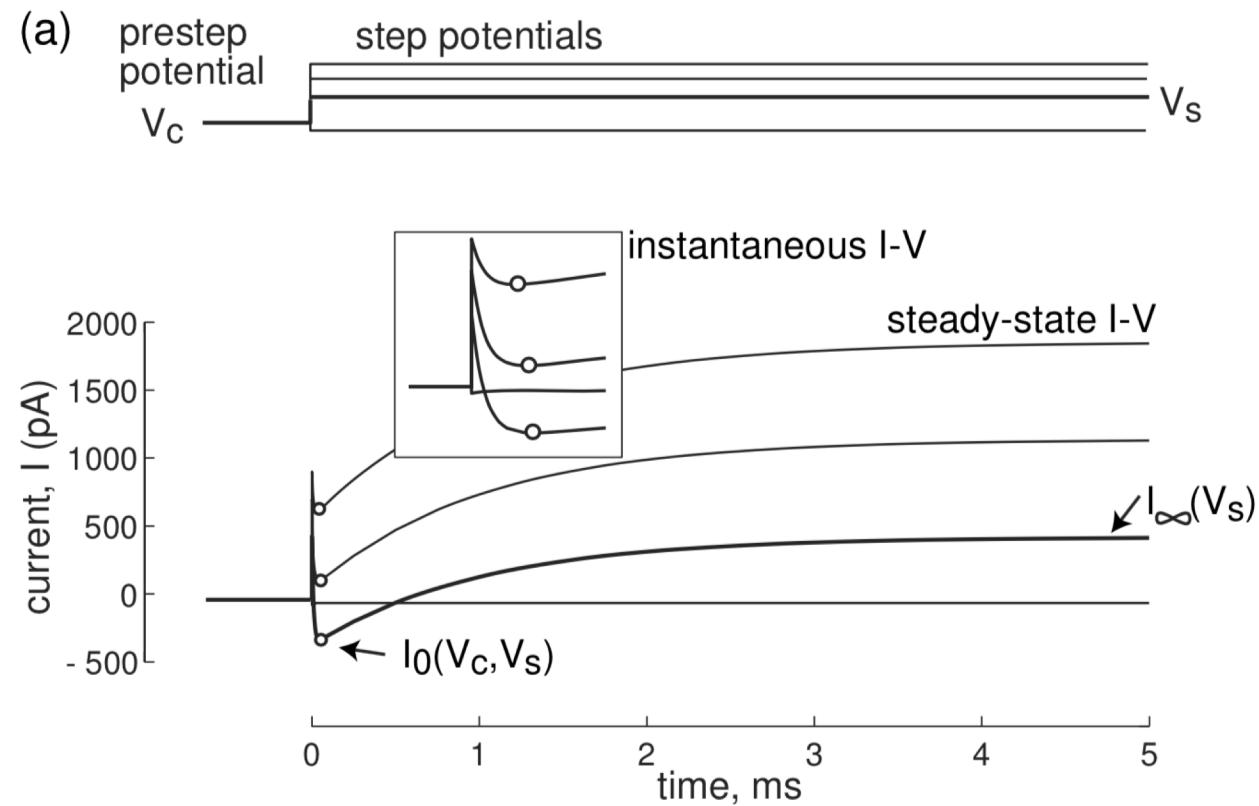
Voltage-clamp experiment to measure instantaneous and steady-state I-V relation

- The membrane potential is held at a certain resting value V_c and then reset to a new value V_s
- The injected membrane current needed to stabilize the potential at the new value is a function of time, the pre-step holding potential V_c , and the step potential V_s .



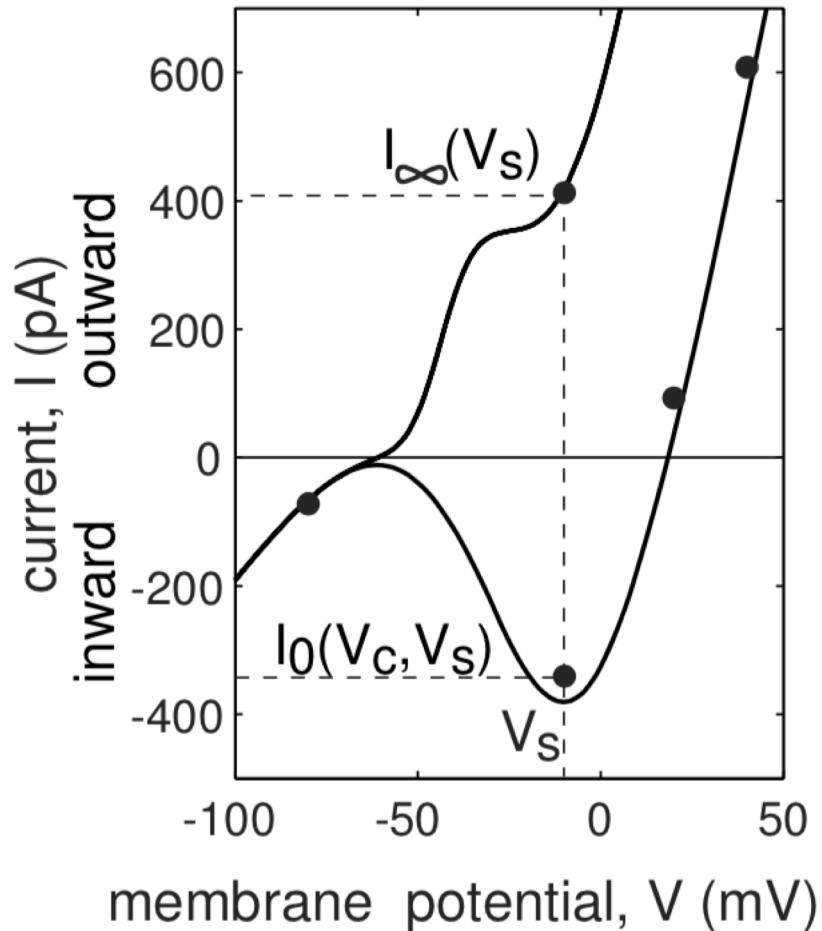
Voltage-clamp experiment to measure instantaneous and steady-state I-V relation

- First, the current jumps to a new value to accommodate the instantaneous voltage change from V_c to V_s on the value $g_{inp}(V_s - V_c)$
- Then, time- and voltage-dependent processes start to occur and the current decreases and then increases



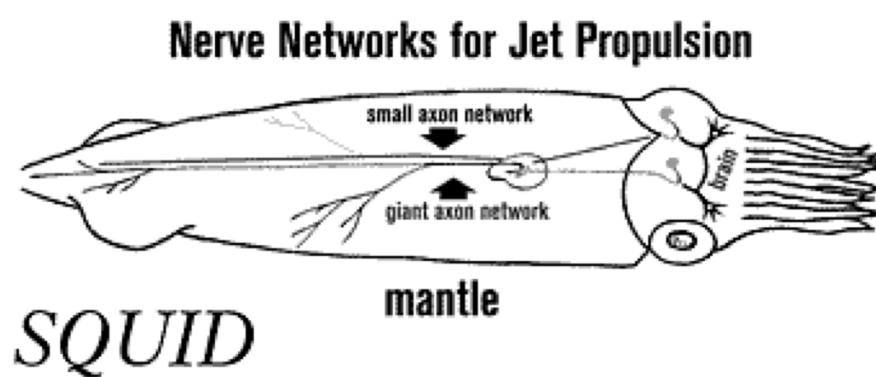
Instantaneous and steady-state I-V relation

- Both I-V relations provide invaluable quantitative information about the currents operating on fast and slow time scales, and both are useful in building mathematical models of neurons.



Hodgkin–Huxley model

Alan Hodgkin and Andrew Huxley developed a mathematical model to explain the behavior of nerve cells in a squid giant axon in 1952. Their model is based on the description of ionic mechanisms underlying the initiation and propagation of action potentials in the squid giant axon.

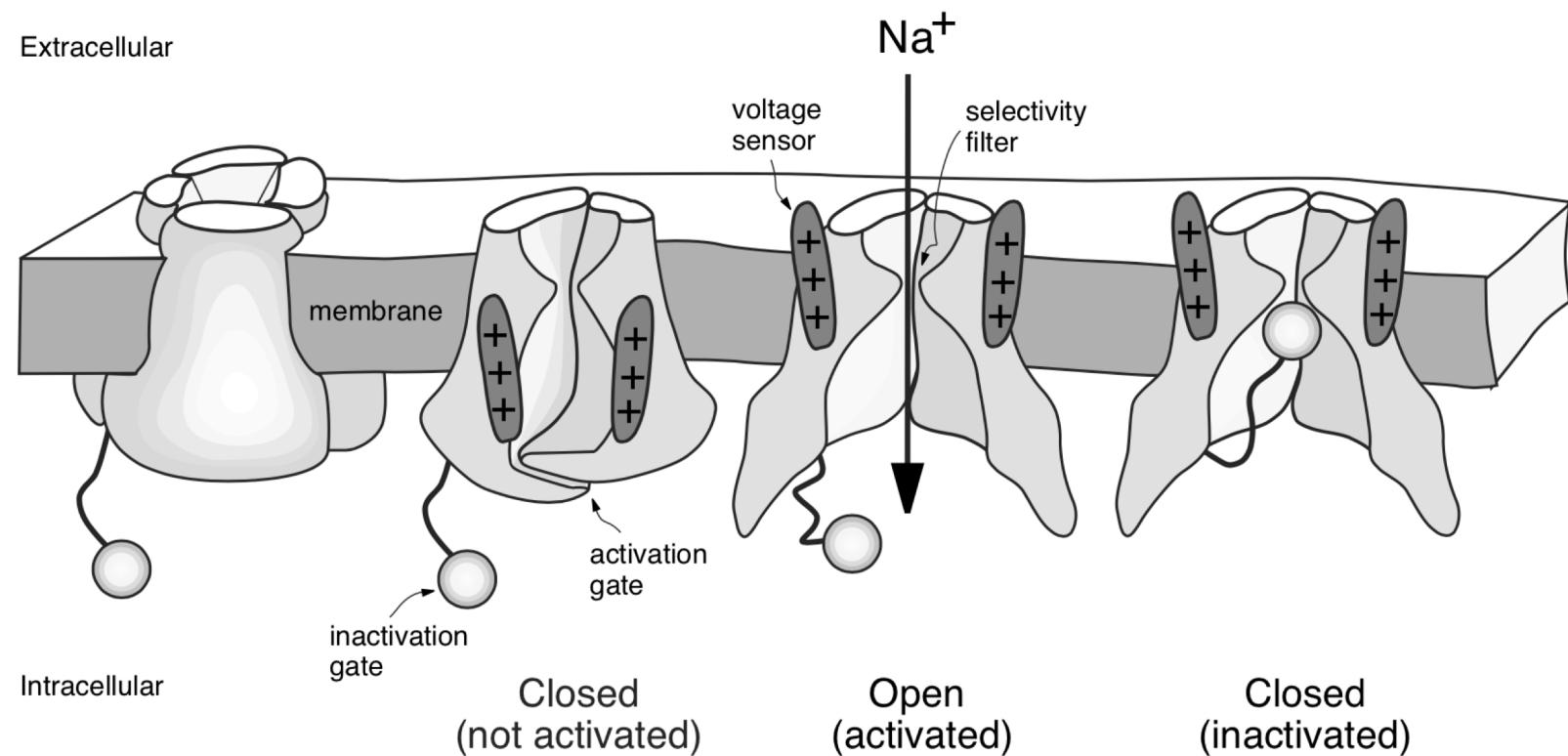


Alan Hodgkin (right) and Andrew Huxley (left) in their Plymouth Marine Lab in 1949

The squid giant axon is the very large (up to 1.5 mm in diameter; typically around 0.5 mm) axon that controls part of the water jet propulsion system in squid.

Hodgkin-Huxley gate model of membrane channels

- When the gating particles are sensitive to the membrane potential, the channels are said to be voltage-gated.
- The gates are divided into two types: those that activate or open the channels, and those that inactivate or close them



Hodgkin-Huxley gate model of membrane channels

- The proportion of open channels in a large population is $p = m^a h^b$

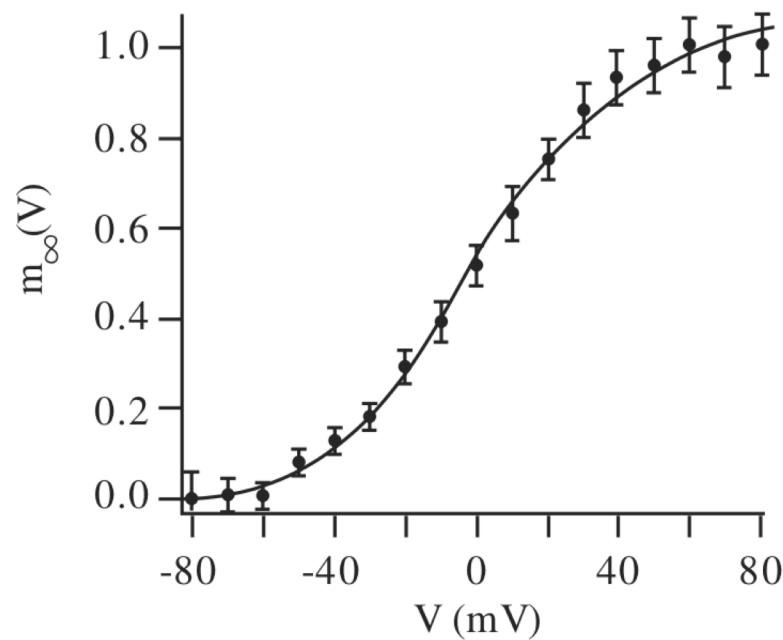
Here m is the probability of an activation gate being in the open, h is the probability of an inactivation gate being in the open state, a is the number of activation gates and b is the number of inactivation gates per channel

- The channels can be partially ($0 < m < 1$) or completely activated ($m = 1$); not activated or deactivated ($m = 0$); inactivated ($h = 0$); released from inactivation or deinactivated ($h = 1$).
- Some channels do not have inactivation gates ($b = 0$). Such channels do not inactivate, and they result in persistent currents. In contrast, channels that do inactivate result in transient currents

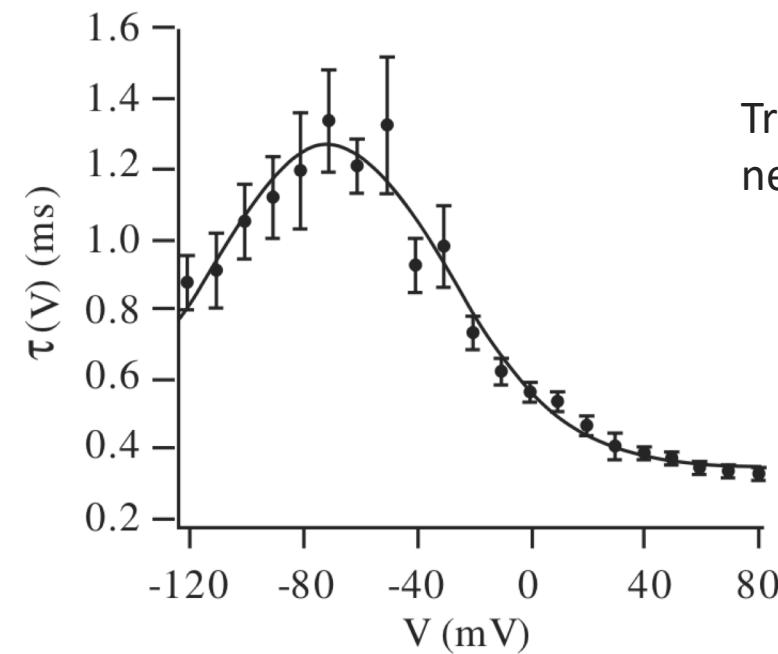
Activation of Persistent Currents

$$\dot{m} = (m_\infty(V) - m)/\tau(V)$$

the voltage-sensitive steady-state activation function



the time constant function



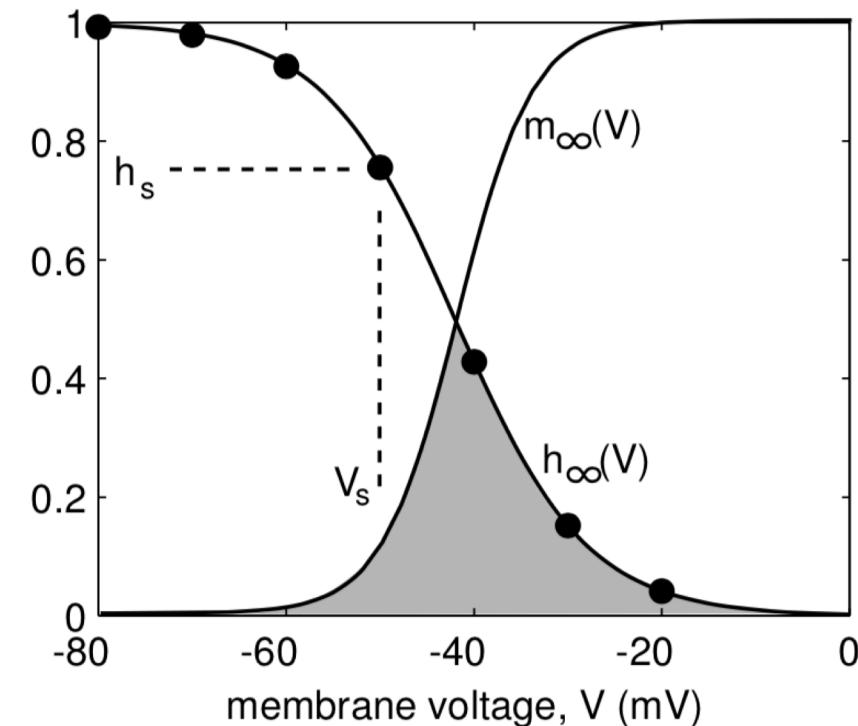
Transient K⁺ current in layer 5 neocortical pyramidal neurons

Activation of Transient Currents

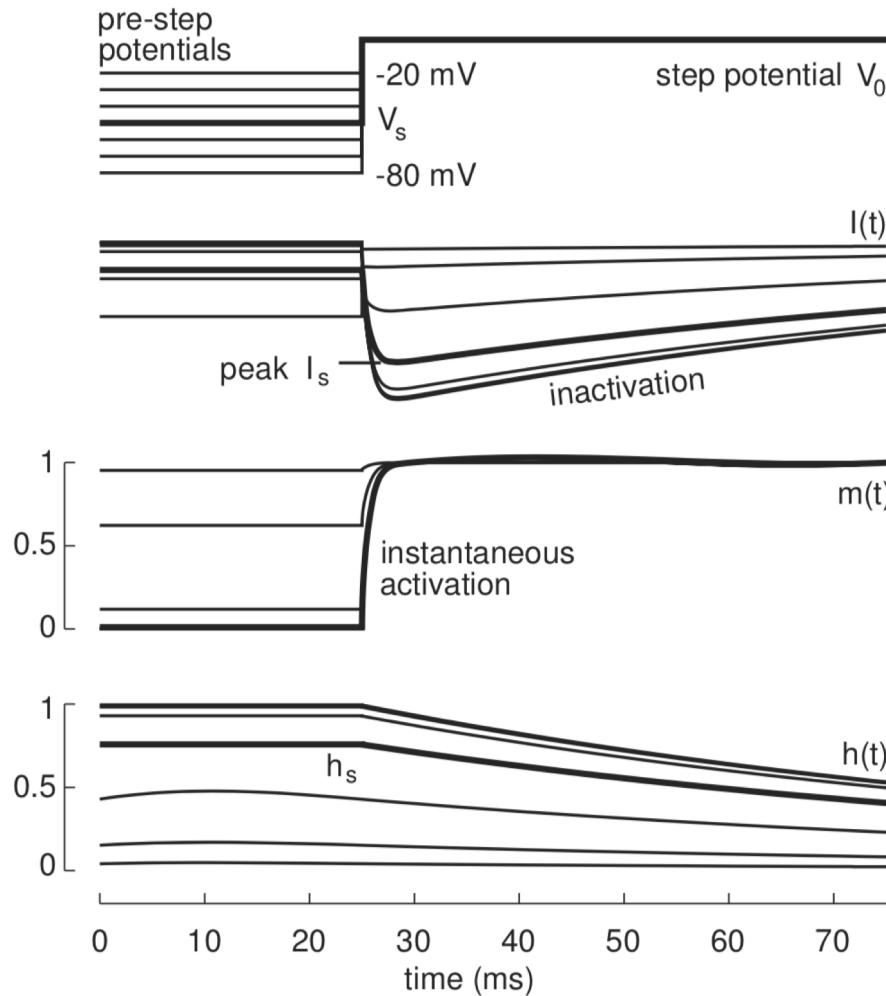
$$\dot{h} = (h_\infty(V) - h)/\tau(V)$$

the voltage-sensitive steady-state activation and inactivation function of the persistent and transient Na^+ current in Purkinje cells

Overlap (shaded region) produces a noticeable, persistent “window” current.



Dynamics of the current (I), activation (m), and inactivation (h) variables in the voltage-clamp experiment



Hodgkin-Huxley Equations

Hodgkin and Huxley (1952) determined that the squid axon carries three major currents:

- voltage-gated persistent K⁺ current with four activation gates (resulting in the term n^4 in the equation below, where n is the activation variable for K⁺);
- voltage-gated transient Na⁺ current with three activation gates and one inactivation gate (the term m^3h below),
- Ohmic leak current, I_L , which is carried mostly by Cl⁻ ions.

Hodgkin-Huxley Equations

$$C \dot{V} = I - \overbrace{\bar{g}_K n^4 (V - E_K)}^{I_K} - \overbrace{\bar{g}_{Na} m^3 h (V - E_{Na})}^{I_{Na}} - \overbrace{g_L (V - E_L)}^{I_L}$$

$$\dot{n} = (n_\infty(V) - n)/\tau_n(V),$$

$$\dot{m} = (m_\infty(V) - m)/\tau_m(V),$$

$$\dot{h} = (h_\infty(V) - h)/\tau_h(V),$$

$$n_\infty = \alpha_n / (\alpha_n + \beta_n),$$

$$m_\infty = \alpha_m / (\alpha_m + \beta_m),$$

$$h_\infty = \alpha_h / (\alpha_h + \beta_h),$$

$$\tau_n = 1 / (\alpha_n + \beta_n),$$

$$\tau_m = 1 / (\alpha_m + \beta_m),$$

$$\tau_h = 1 / (\alpha_h + \beta_h)$$

$$\alpha_n(V) = 0.01 \frac{10 - V}{\exp(\frac{10 - V}{10}) - 1},$$

$$\beta_n(V) = 0.125 \exp\left(\frac{-V}{80}\right),$$

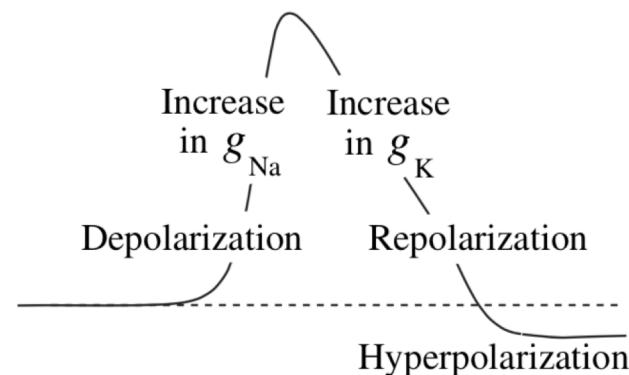
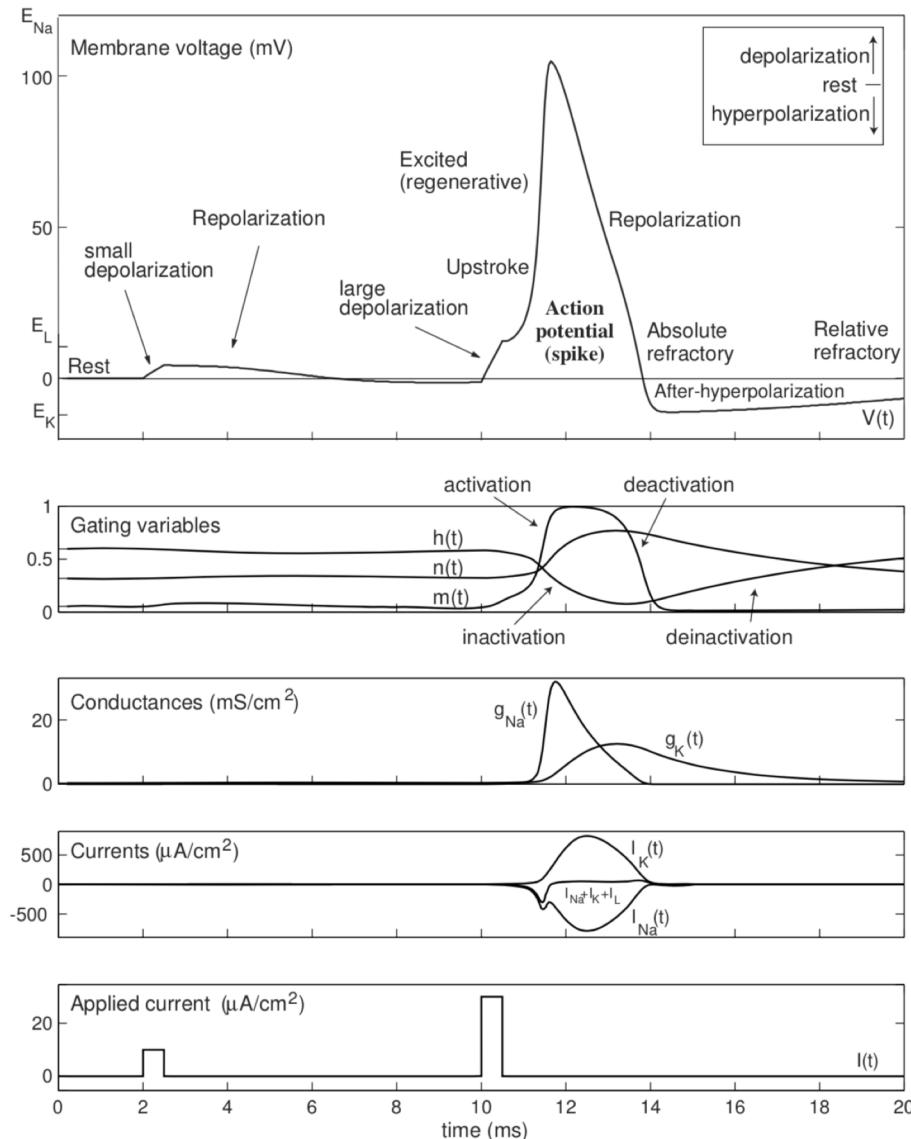
$$\alpha_m(V) = 0.1 \frac{25 - V}{\exp(\frac{25 - V}{10}) - 1},$$

$$\beta_m(V) = 4 \exp\left(\frac{-V}{18}\right),$$

$$\alpha_h(V) = 0.07 \exp\left(\frac{-V}{20}\right),$$

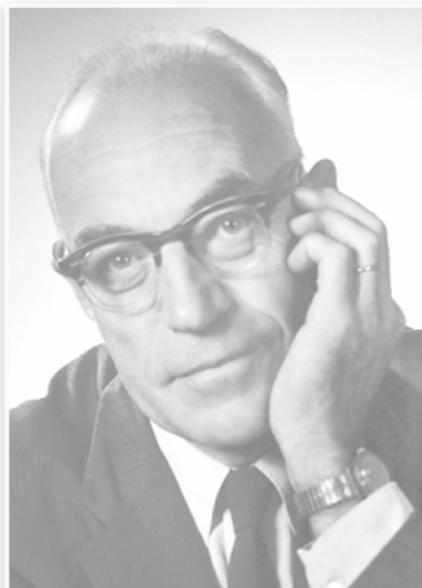
$$\beta_h(V) = \frac{1}{\exp(\frac{30 - V}{10}) + 1}.$$

Action potential in the Hodgkin-Huxley model

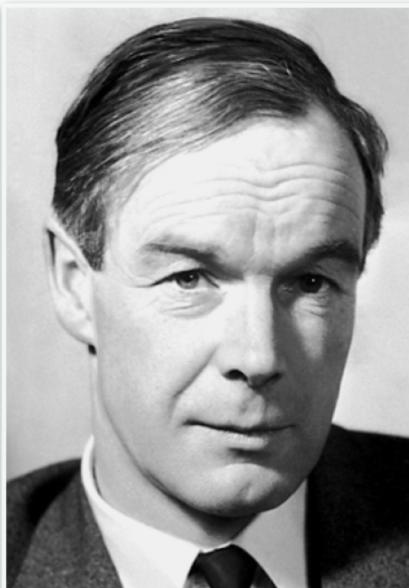


The Hodgkin & Huxley model (1952)

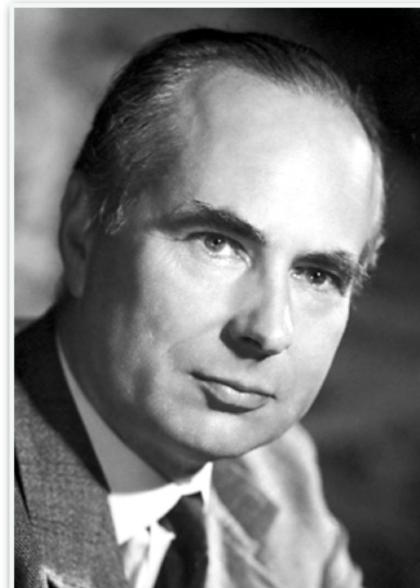
- The Nobel prize was awarded to both men a decade later in 1963. The field of computational neuroscience was launched. More than 60 years later, the Hodgkin-Huxley model is still a reference.



J.C. Eccles



A.L. Hodgkin



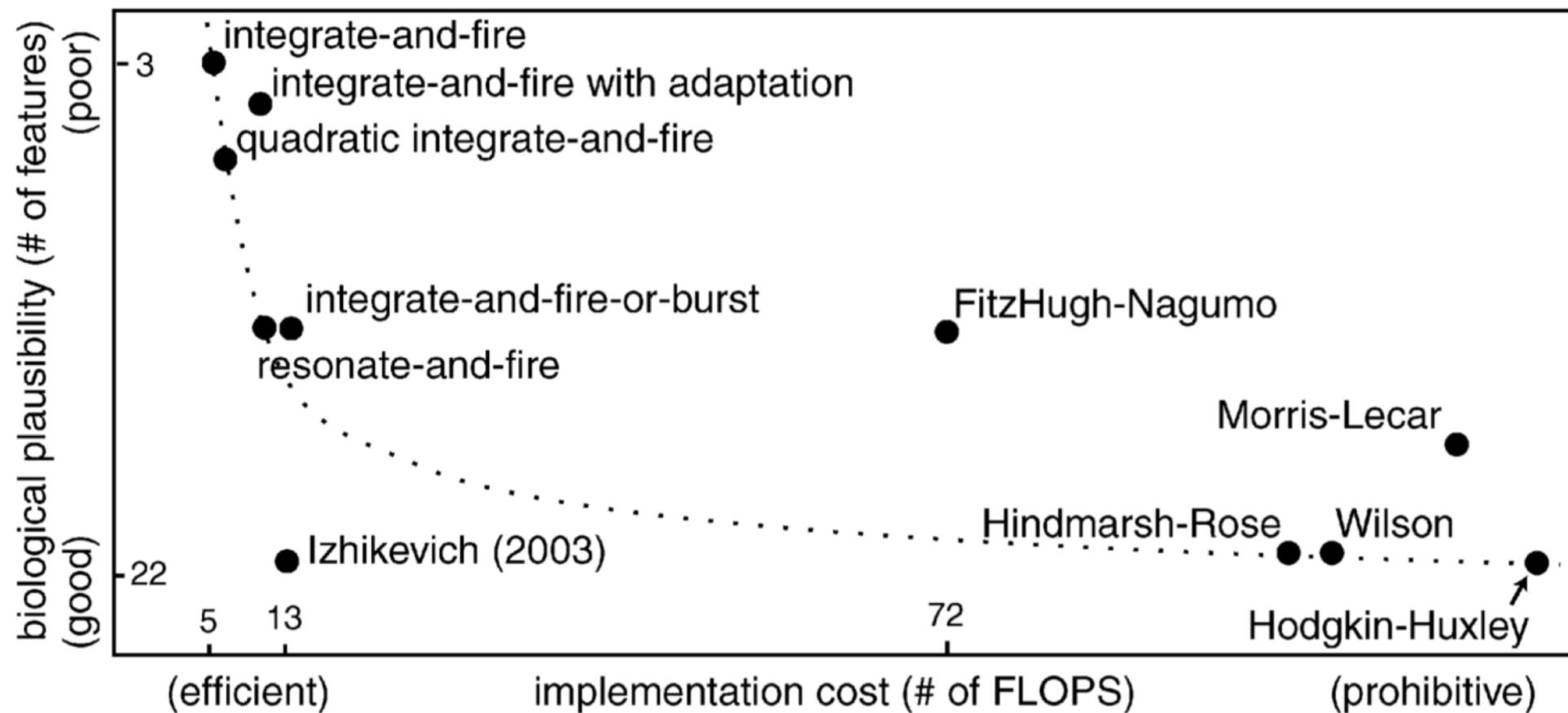
A. Huxley

Reduced models are simpler

- The behavior of high-dimensional nonlinear differential equations is difficult to visualize and even more difficult to analyze.
- The four-dimensional model of Hodgkin-Huxley can be reduced to two dimensions under the assumption that the m-dynamics is fast as compared to h, and n, and that the latter two evolve on the same time scale.
- Even if conductance-based models are the simplest possible biophysical representation of an excitable cell and can be reduced to simpler model, they remain difficult to analyse (and simulate) due to their intrinsic complexity.
- For this reason, simple threshold-based discrete models have been developed and are highly popular for studying neural coding, memory, and network dynamics.

Which model for what purpose ?

- It depends on what you're trying to achieve...



Attention!!!

Next lecture, the first test will be held...