The Hodgkin-Huxley Model: A Quick Historical Overview

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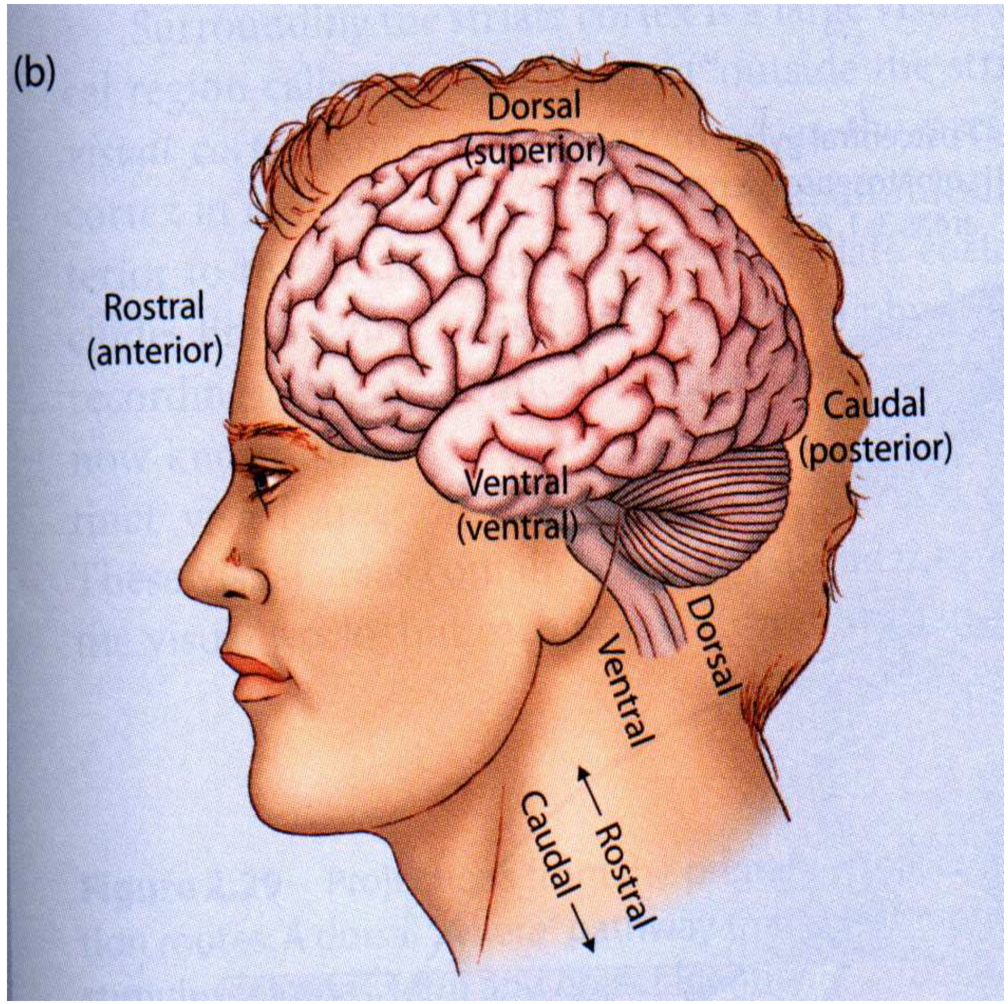
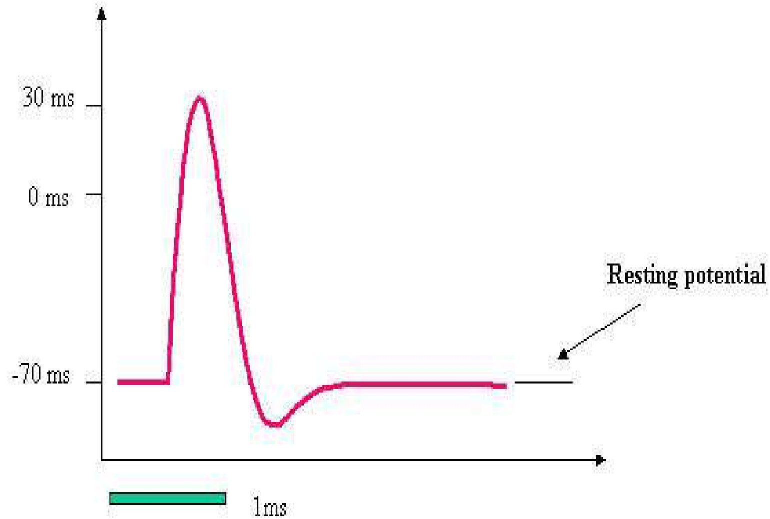
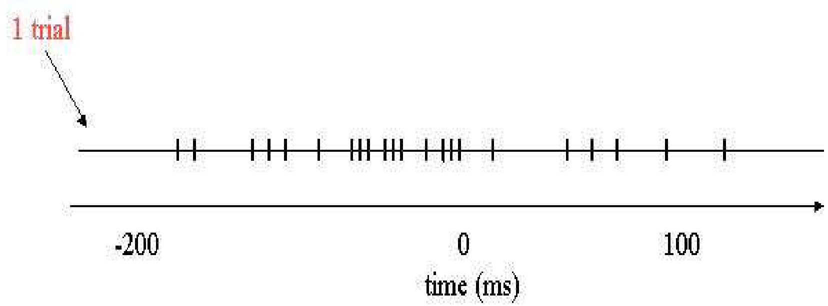


Source: Gazzaniga, Michael.S, Ivry, R.B., Mangun, G.R.,Congnitive Neuroscience, page:49, W.W.Norton, 1998.


30 ms
0 ms
-70 ms
Resting potential
1ms


1 trial
-200
0
100
time (ms)

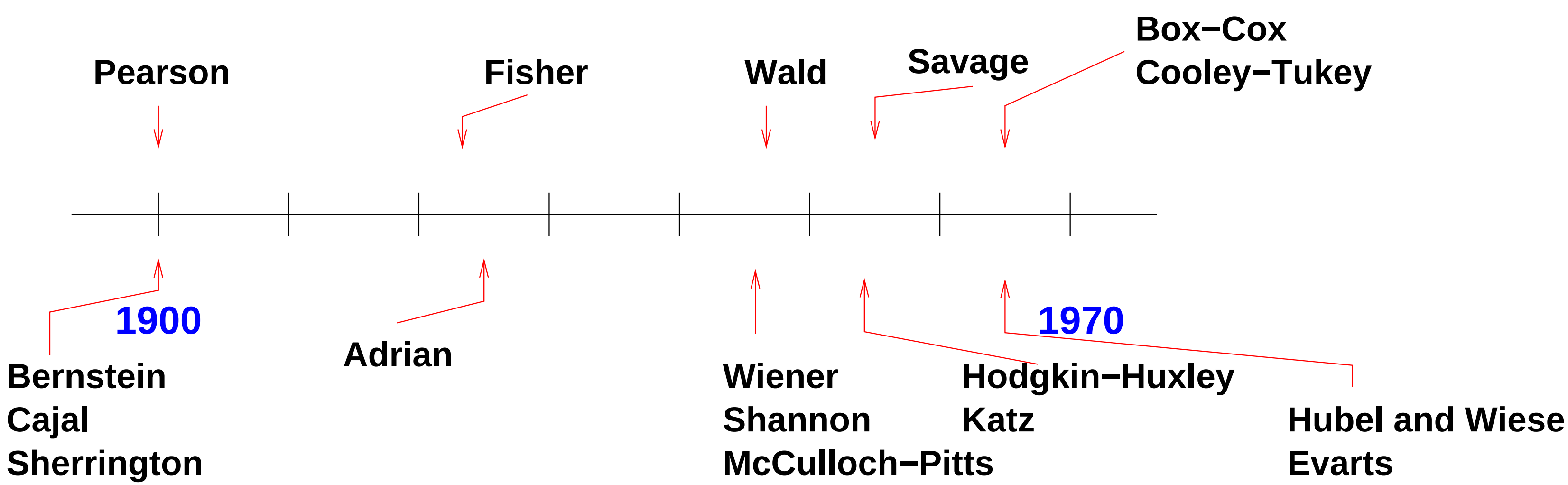
Action Potential and Spike Trains

The conception that information is conveyed by sequences of action potentials (spike trains) has resulted from more than 100 years of neurophysiological investigation.

It involves both the relation of action potentials to behavior, and an explicit, detailed understanding of how action potentials work. The latter is the triumph of the Hodgkin-Huxley model. I have broken the basic argument into 6 historical steps, of which the Hodgkin-Huxley model is the last.

Main References: Hille (1992) *Ionic Channels of Excitable Membranes*; Piccolino, M. (1998) Animal electricity and the birth of electrophysiology: The legacy of Luigi Galvani, *Brain Res. Bull.*, 46: 381-407.

Neuronal representation of information: Timeline relative to Statistics.

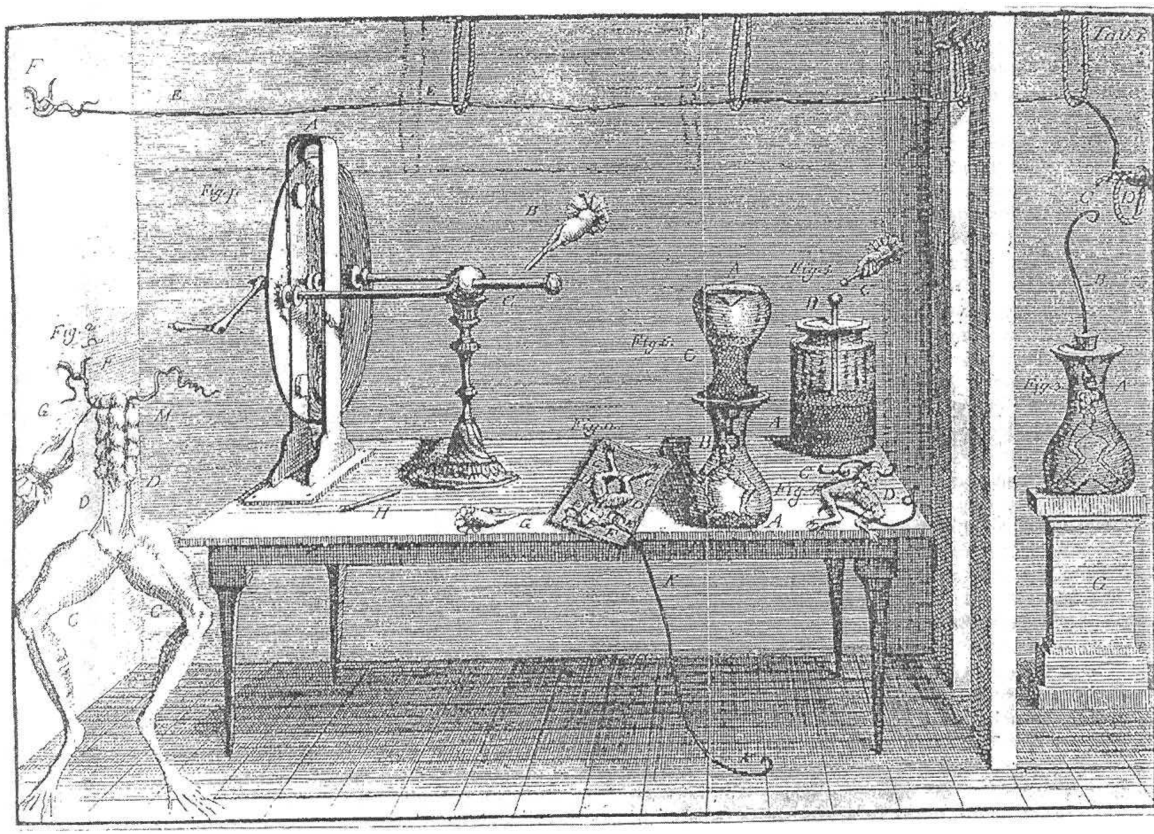


Minimum Background on Circuits

Q=Charge
C=Capacitance
V=Voltage=E
I=Current
g=Conductance=1/Resistance=1/R

$$
\begin{aligned}
Q(t) &= CV(t) \\
I(t) &= \frac{dQ}{dt} \\
C\frac{dV}{dt} &= I(t) \qquad (1) \\
I &= \frac{V}{R} \\
I(t) &= g(t)V(t) \qquad (2)
\end{aligned}
$$

1. Signals are transmitted electrically (Galvani, 1791).

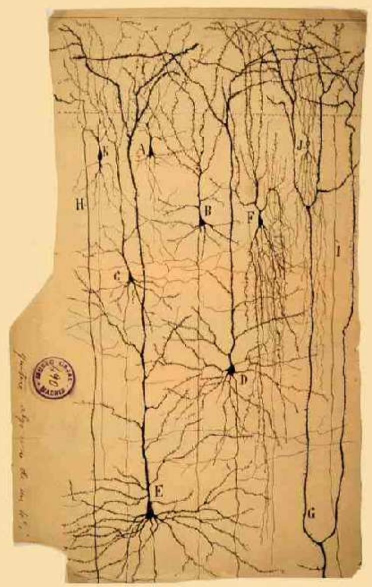


1. Signals are transmitted electrically.

- Volterra disputed Galvani’s interpretation and, in trying to prove him wrong, invented the battery (the “Voltaic pile”).
- In the mid-1800s Matteucci, and then Du Bois-Reymond, reported an increase in current in a pile of frog thighs in proportion to the number of thighs in the pile.
- In the mid-1800s von Helmholtz, then Bernstein measured the speed of propagation of the nervous impulse. Bernstein also carefully matched the speed of the impulse with the speed of the electrical field and showed the duration of the field at any location to be roughly 1 millisecond.

  But a puzzle emerged: why was the propagation of “animal electricity” many orders of magnitude slower than that of other electrical fields?

2. Nerves are made up of individual neurons (the “neuron doctrine”; Cajal, 1886).



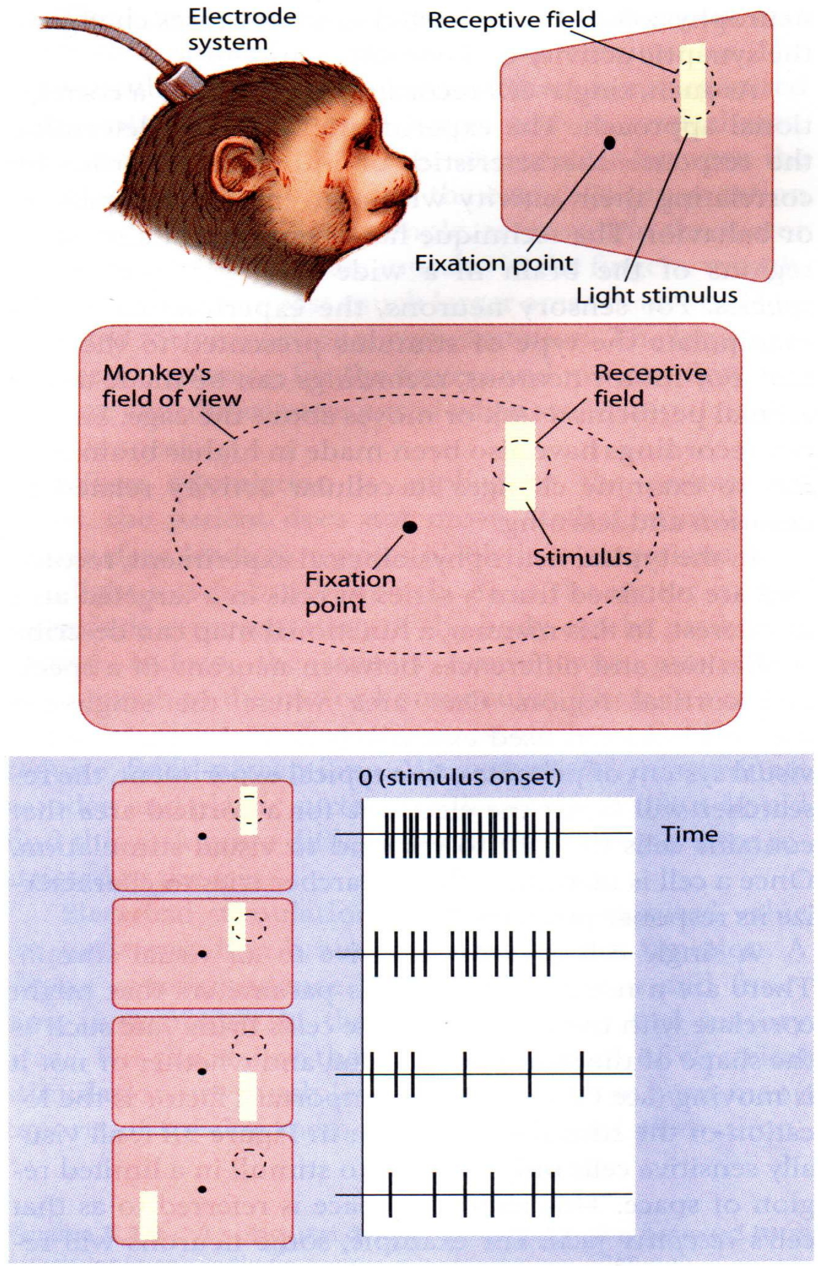
"First, second and third layers of the precentral gyrus of the cerebrum of a child of one month. A, B, C, small pyramidal cells; D, E, medium pyramidal cells; F, bitufted cells; G, dendritic shaft emanating from a large fourth layer pyramidal cell; H, I, thin dendritic shafts of cells of the fifth and sixth layers; J, small bitufted cells; K, fusiform cell with a long axon. Modified from a photograph taken from the original (13.5X24 cm). Drawn on sheet/paper. P.Y. 1904. S.R. y Cajal Institute - CSIC - Madrid, Spain.

3. Signals are transmitted from one neuron to another across synapses (Sherrington, 1897).

4. Action potentials are not graded in intensity; they are “all or nothing” (Adrian, 1926).

5. Substantial information is contained in the neuronal firing rate (Adrian, 1926; Hubel and Wiesel, 1962; Evarts, 1966).

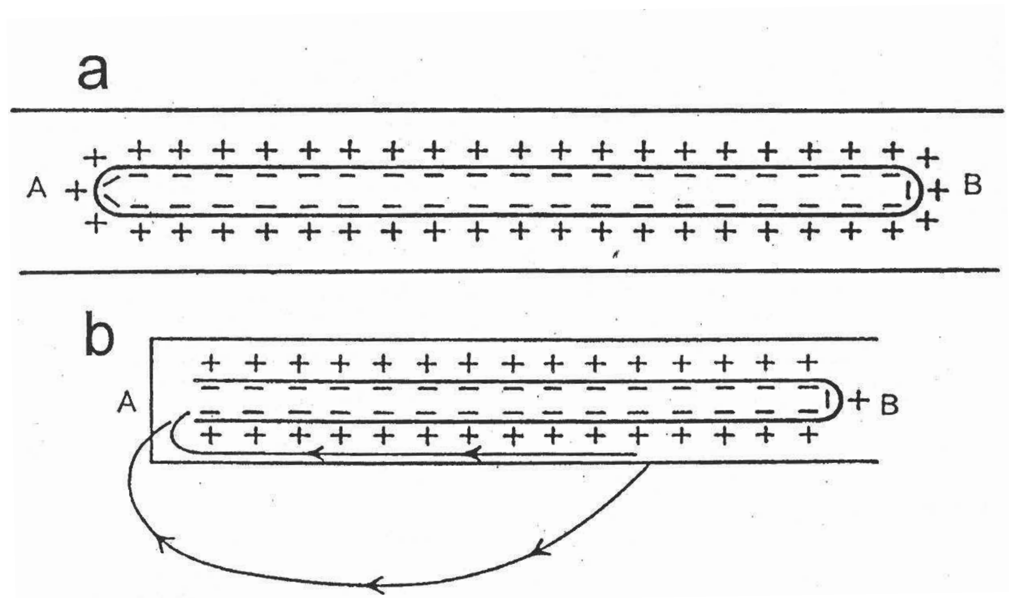
Textbook depiction: A neuron responds to a relevant stimulus, or contributes to the production of an action, by increasing its firing rate. (next slide)


Electrode system
Receptive field
Fixation point
Light stimulus
Monkey's field of view
Receptive field
Stimulus
Fixation point
0 (stimulus onset)
Time

6. Action potentials result from the flow of ions across excitable membranes.

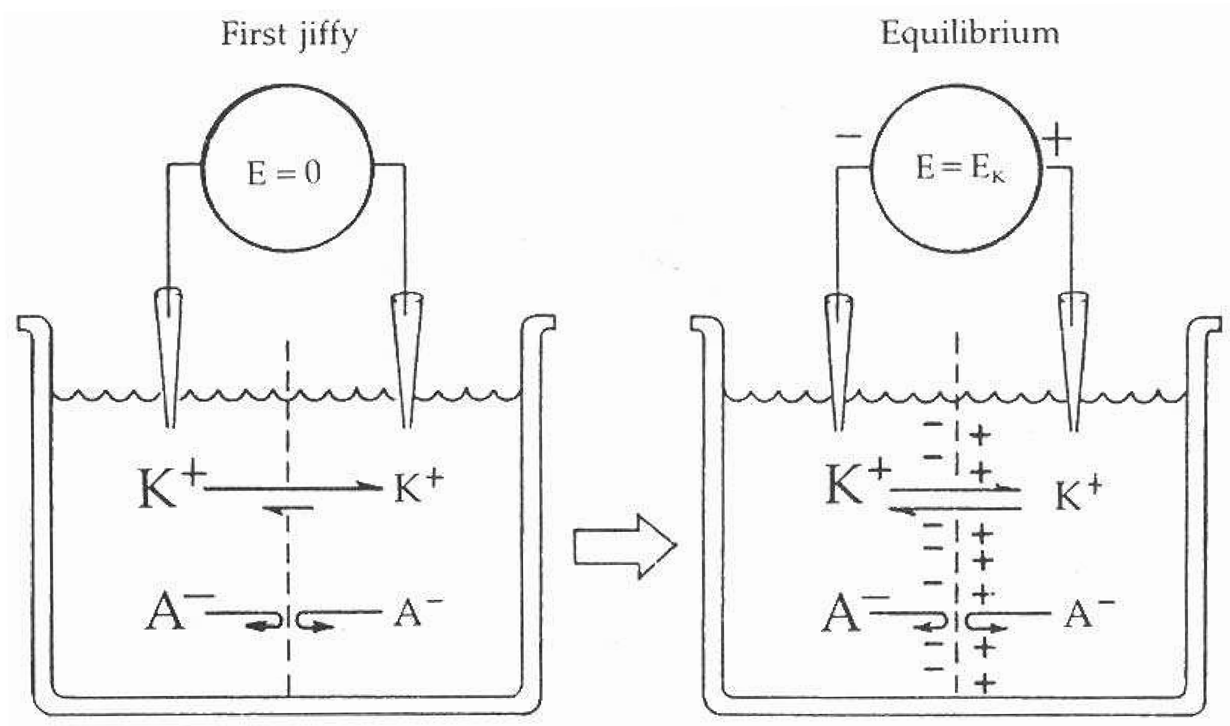
- Membranes can be electrically excitable (Bernstein, 1902; based on Nernst, 1888).
- Ion channels gate the flow of ions across membranes (Cole and Curtis, 1939).
- Sodium ions (in addition to potassium ions) are involved in action potential generation (Hodgkin and Katz, 1949).
- Hodgkin and Huxley (1952): Action potential generation may be described quantitatively using
  - voltage-current-capacitance relationships, and
  - voltage-dependent conductances of distinct ions.

6A. The “membrane hypothesis.”



Nernst Equation:

$$\Delta V = \frac{RT}{ZF} \log \frac{[ion]_o}{[ion]_i}$$


First jiffy
E = 0
K+
K+
A−
A−
Equilibrium
E = E_K
K+
K+
A−
A−

$\phi(x)$ = Concentration

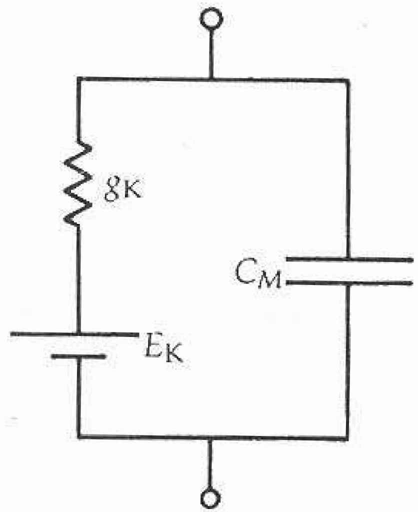
Consider current flowing from x to $x + dx$

current due to concentration gradient $\propto d\phi = \frac{d\phi}{dx} dx$

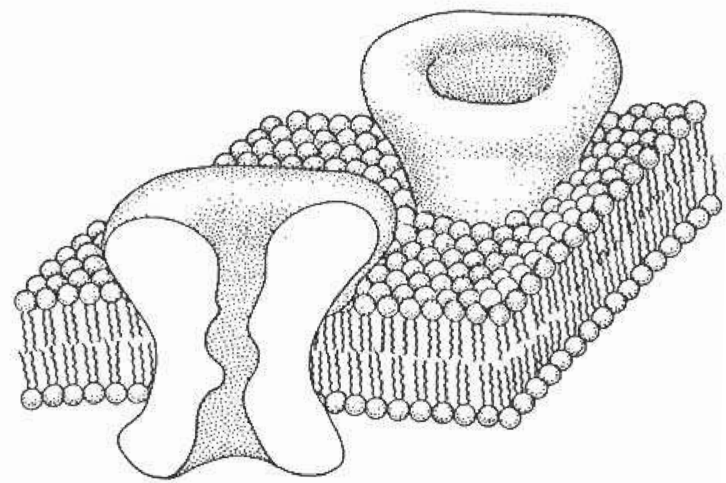
current due to electrical potential gradient $\propto \phi(x) dV = \phi(x) \frac{dV}{dx} dx$

Equating these, dividing by $\phi(x)$, and integrating gives

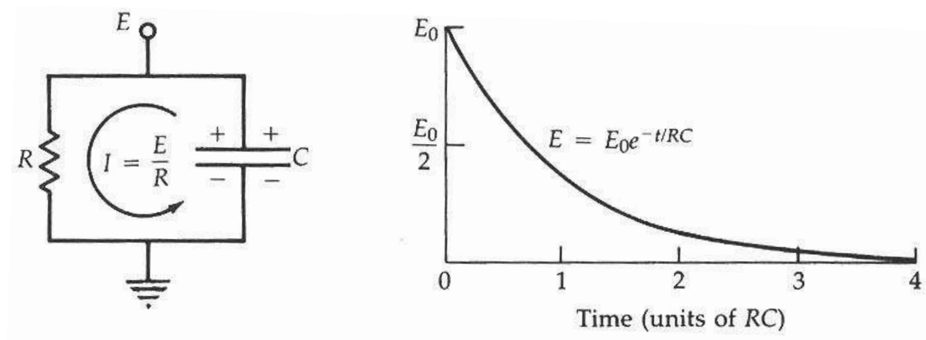
$$V(x_2) - V(x_1) \propto \log \frac{\phi(x_2)}{\phi(x_1)}$$



(A) EQUIVALENT CIRCUIT

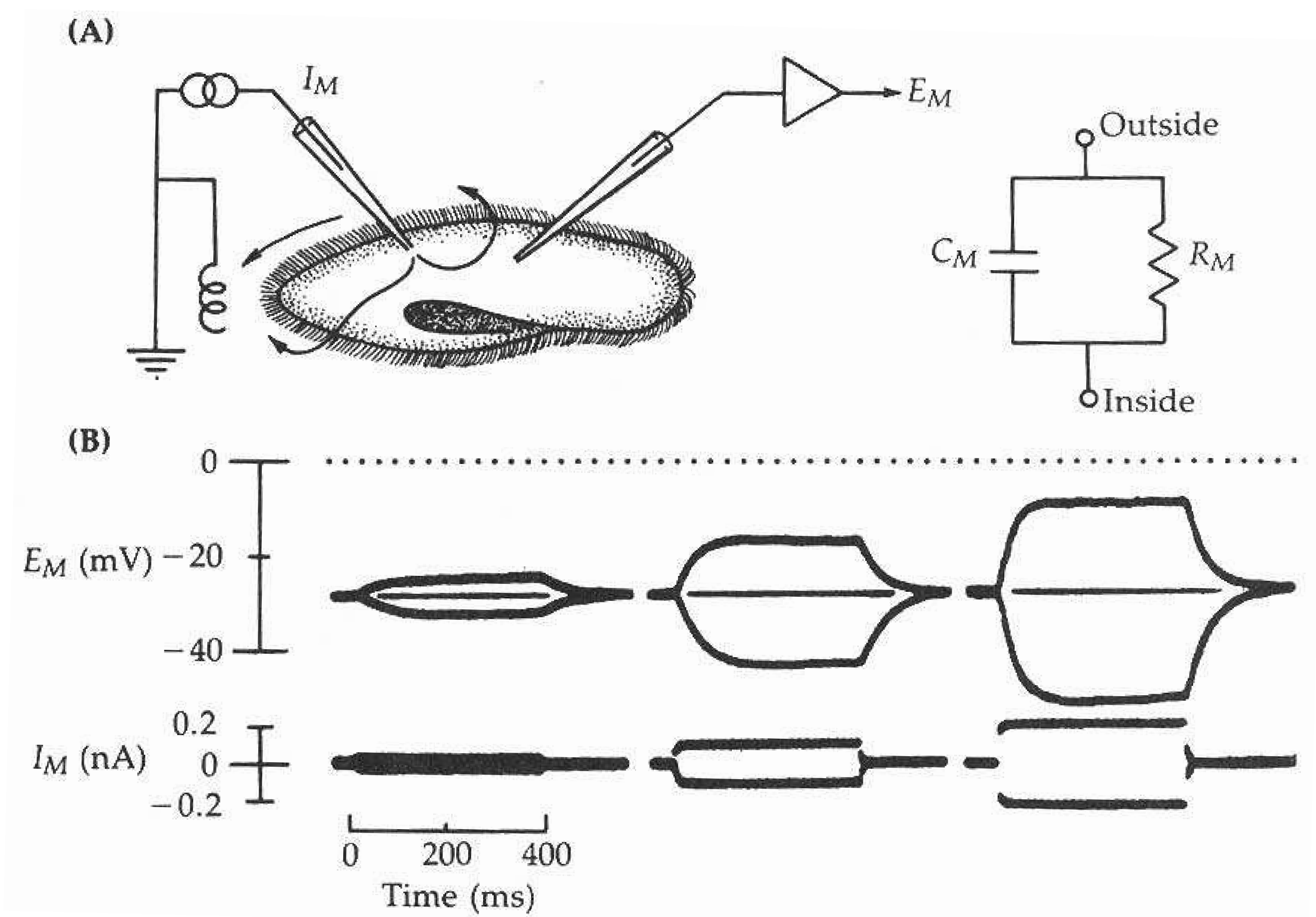


(B) INTERPRETATION

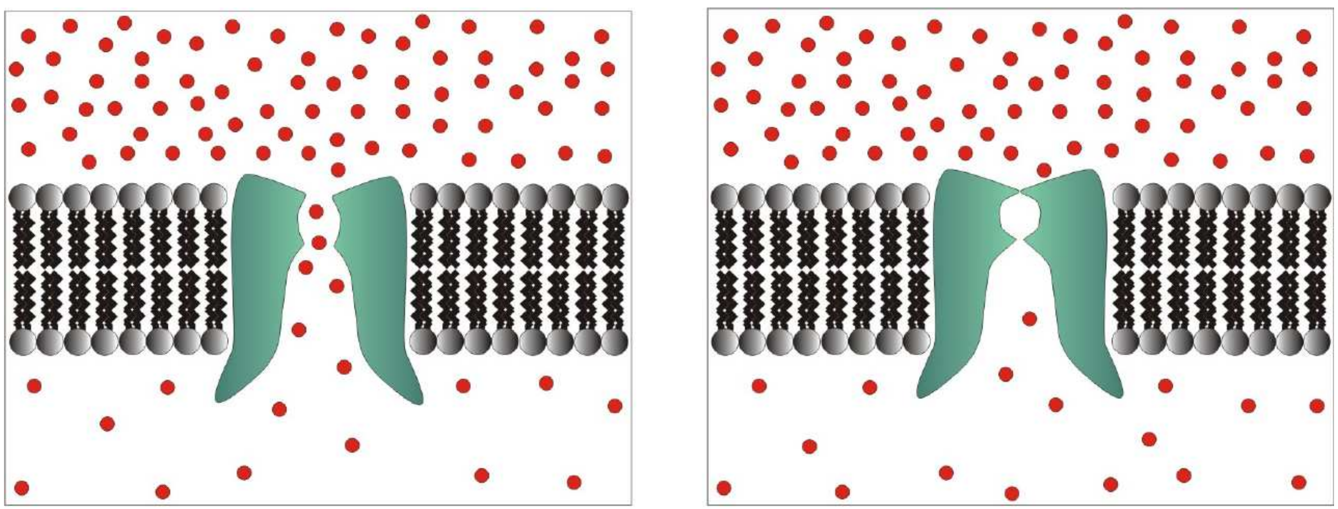


(A) CIRCUIT (B) TIME COURSE OF DISCHARGE

$$\frac{dV}{dt} = -\frac{V}{CR}$$

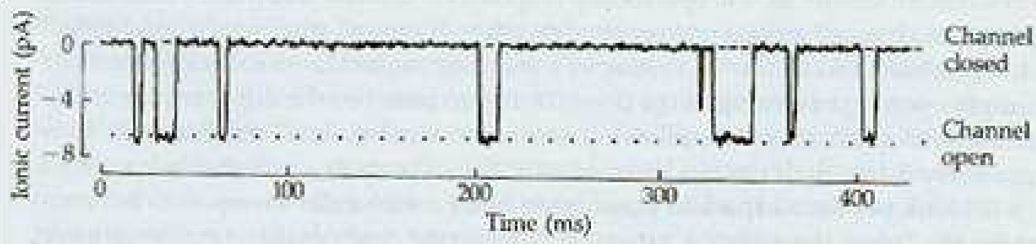

(A)
I_M
E_M
Outside
C_M
R_M
Inside
(B)
0
E_M (mV) −20
−40
0.2
I_M (nA) 0
−0.2
0 200 400
Time (ms)

6B. Ion channels



Open Closed

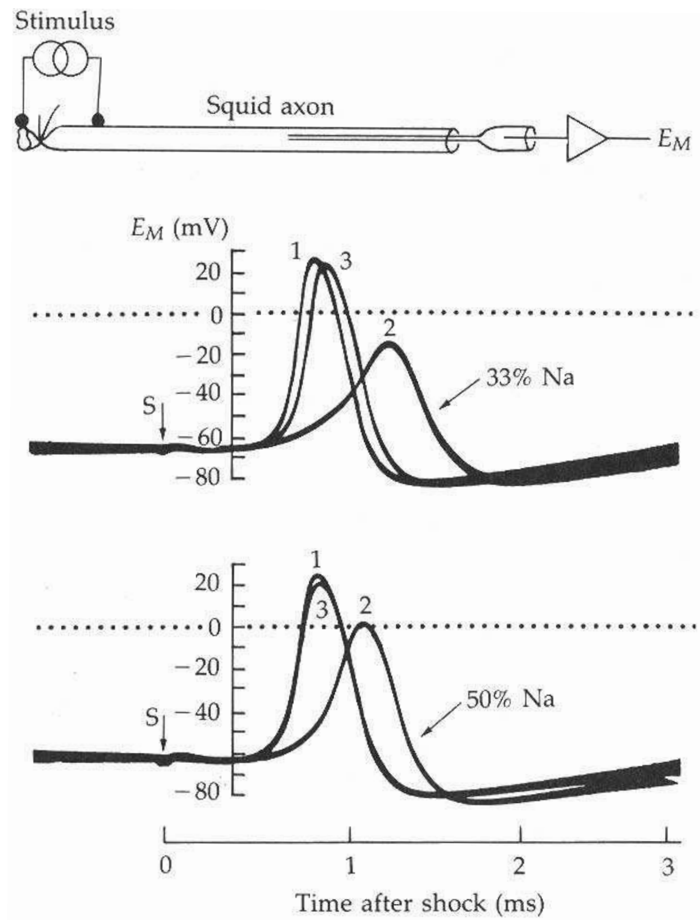
6B. Ion channel gating



1 OPEN–SHUT GATING OF AN IONIC CHANNEL

Ionic current flowing across a tiny patch of excitable membrane showing eight brief openings (downward current deflections) of single ionic channels. The membrane patch has been excised from a cultured rat myotube and is bathed on both sides by Na salt solutions. Approximately 300 nM of the neurotransmitter, acetylcholine, applied to the extracellular membrane face is causing channels to open occasionally. At the −140 mV applied membrane potential, one open channel passes −6.6 pA, corresponding to a prodigious flow of 4.1×10^7 ions per second through a single pore. $T = 23^\circ$C. [From Sánchez et al., 1986.]

6C. Sodium ions are involved in action potential generation.



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- Hodgkin and Huxley (1952): Action potential generation may be described quantitatively using
  - voltage-current-capacitance relationships, and
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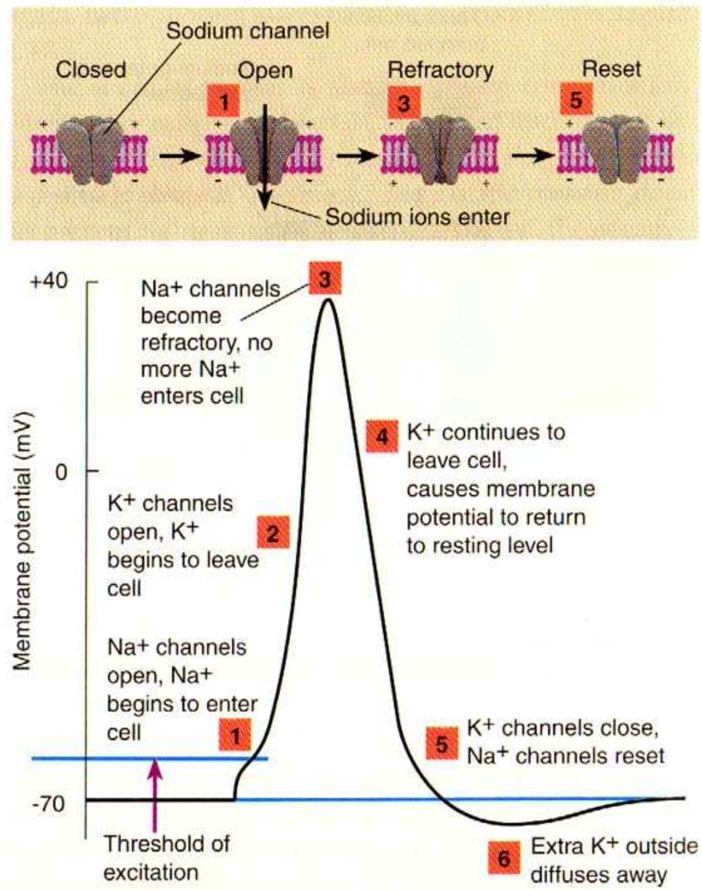
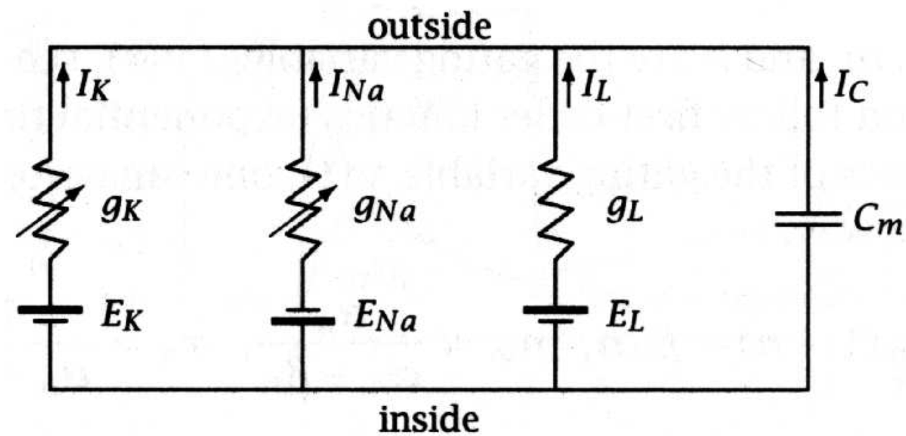
6D. Hodgkin-Huxley Model (1)



6D. Hodgkin-Huxley Model (2)

Hodgkin-Huxley model



6D. Hodgkin-Huxley Model (3)

Hodgkin-Huxley equations

$$C_m \frac{dV}{dt} = -g_L\left(V - V_L\right) - \overline{g}_{Na} m^3 h\left(V - V_{Na}\right) - \overline{g}_K n^4 \left(V - V_K\right)$$

$$\frac{dm}{dt} = \alpha_m\left(V\right)\left(1 - m\right) - \beta_m\left(V\right) m$$

$$\frac{dh}{dt} = \alpha_h\left(V\right)\left(1 - h\right) - \beta_h\left(V\right) h$$

$$\frac{dn}{dt} = \alpha_n\left(V\right)\left(1 - n\right) - \beta_n\left(V\right) n$$

Potassium Channel Kinetics

For each “gate,” consider transition from time t to time $t + dt$

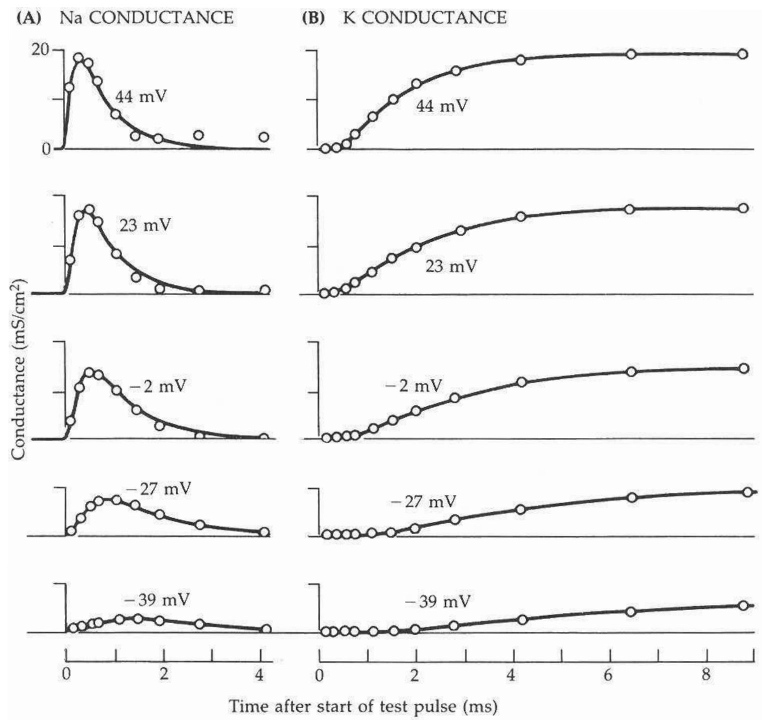
$P($open at time $t) = n(t)$
$P($transition open $\rightarrow$ closed$) = \beta dt$
$P($transition closed $\rightarrow$ open$) = \alpha dt$

These imply

$$dn = (1 - n(t))\alpha dt - n(t)\beta dt$$

And if 4 gates operate independently,
$P($all gates open at time $t) = n(t)^4$

6D. Hodgkin-Huxley conductance measurements



6E. Successes of Hodgkin-Huxley Model

150-year-old problem of “animal electricity” solved; correct predictions of

- conductances (shown above);
- form of action potential (obtained by laborious solution of equations; 8 hours per 5 milliseconds), including “undershoot”;
- change in action potentials with varying concentrations of sodium;
- number of sodium ions involved in inward flux;
- speed of action potential propagation;
- voltage curves for sodium and potassium separately.