Synapses, neurons and brains

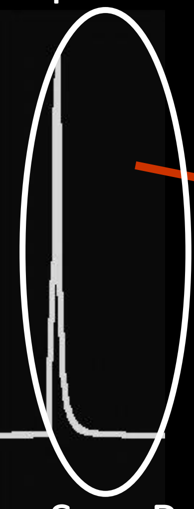
Idan Segev

Lesson #4

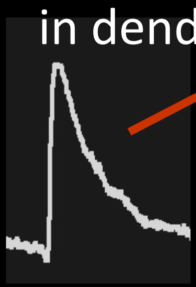
Electrifying brains – active electrical signals

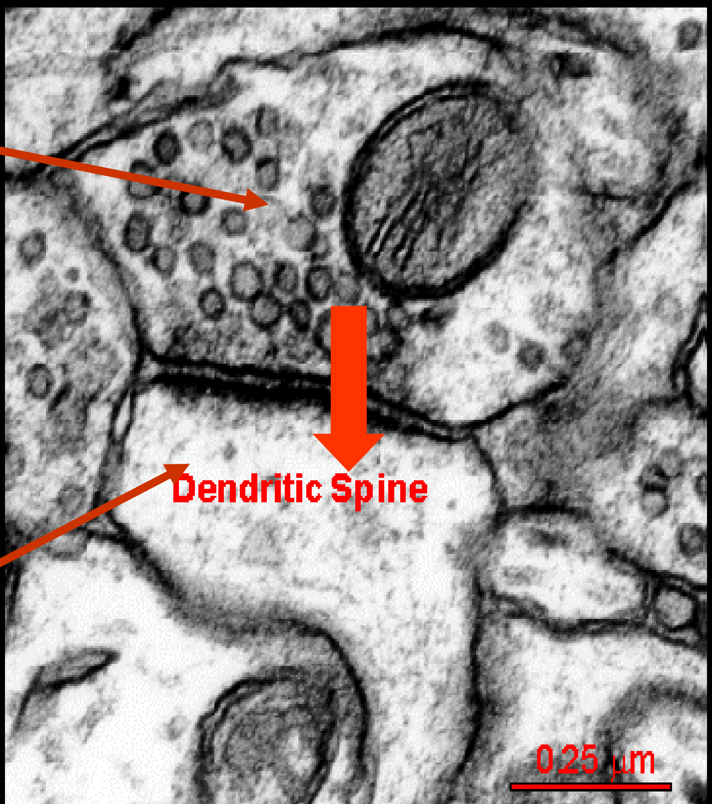
the spike

Spike in axon



Syn. Poten.
in dendrite





The excitable ("spiking") axon .1

The Hodgkin & Huxley experiments .2

Space clamp and voltage clamp .3

Membrane conductances/currents .4
underlying the spike

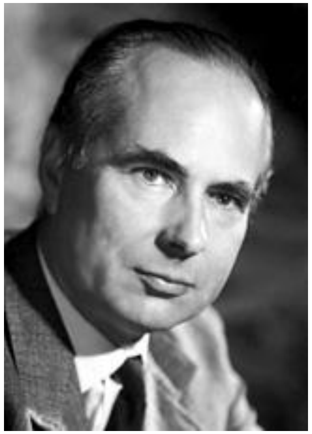
The H&H model for spike initiation .5

Spike propagation in axons .6

From synapses to spikes .7

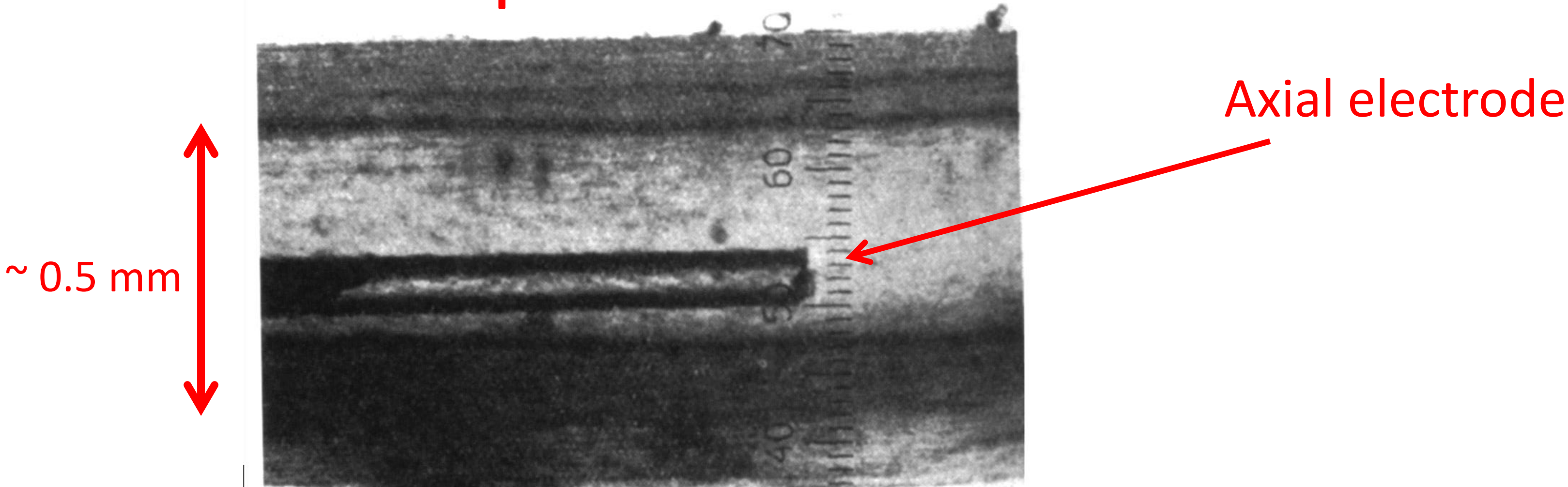
THE SPIKE - Hodgkin and Huxley (H&H) – NOBEL 1963)

Sir Alan Lloyd Hodgkin

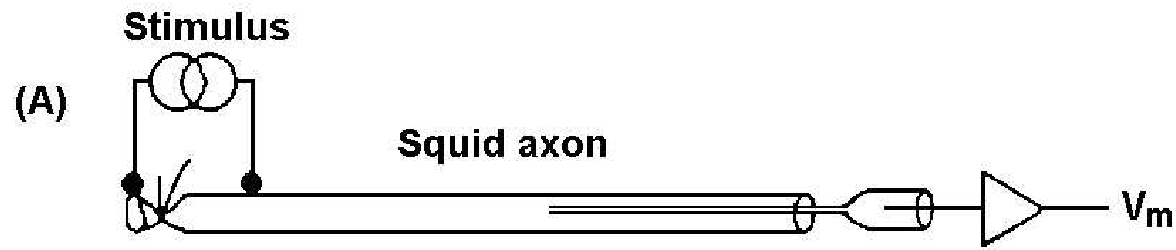


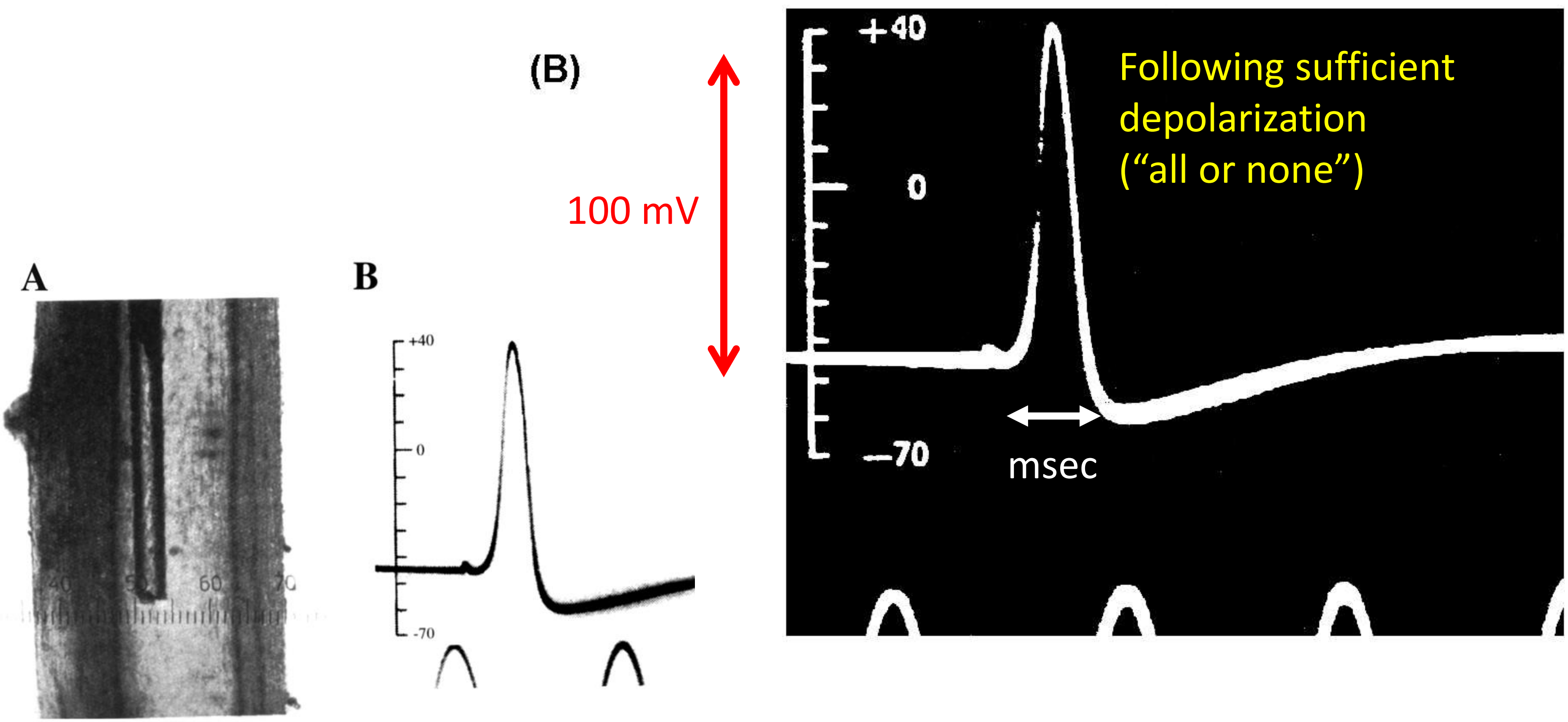
Sir Andrew Fielding Huxley

The Squid Giant Axon



First direct (intracellular) recorded action-potential (spike) in the squid giant axon *(Hodgkin and Huxley, 1939)*

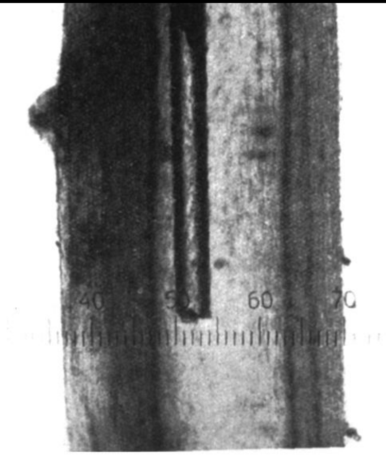


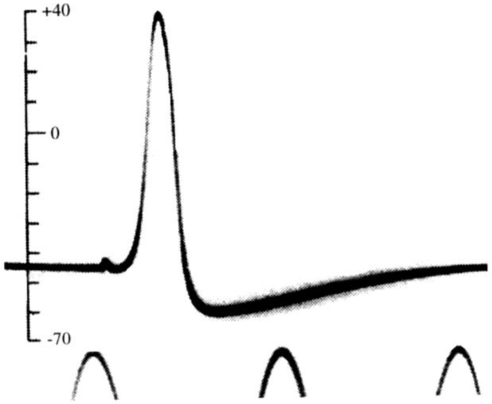


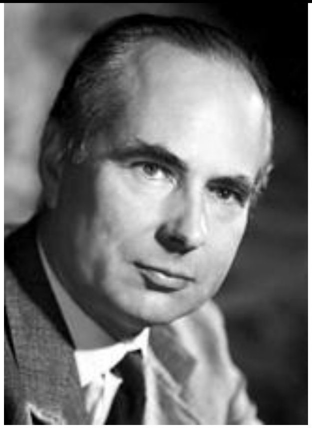
The H&H equations for spike initiation

The triumph of theory

Sir Alan Lloyd Hodgkin







Sir Andrew Fielding Huxley

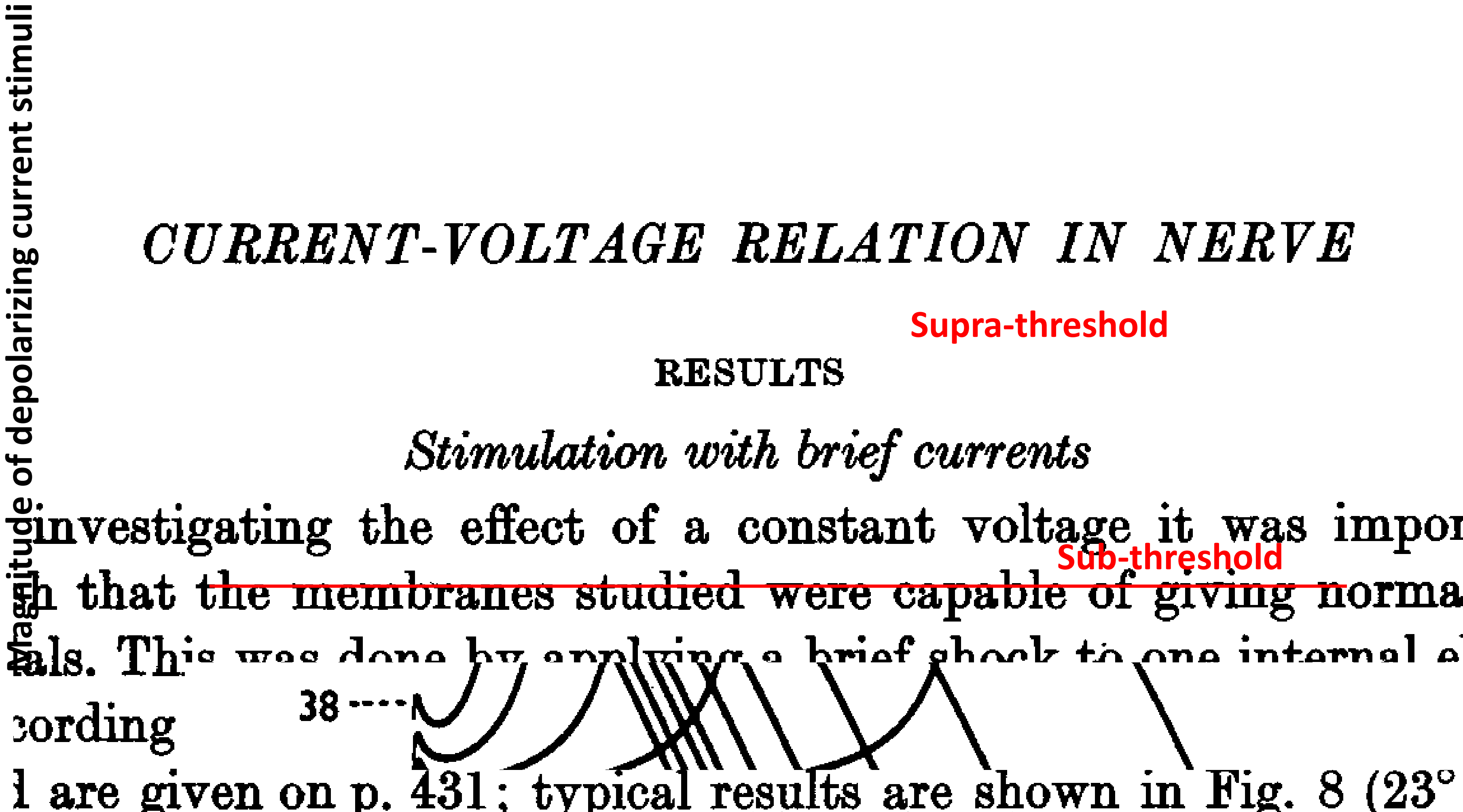
$$I = C_m \dot{V} + g_{Na}\, h\, m^3 (V - V_{Na}) + g_K\, n^4 (V - V_k) + G_L (V - V_L) \qquad (1)$$

$$\frac{d}{dt} m = \alpha_m (V)\, (1 - m) - \beta_m (V)\, m \qquad (2)$$

$$\frac{d}{dt} n = \alpha_n (V)\, (1 - n) - \beta_n (V)\, n \qquad (3)$$

$$\frac{d}{dt} h = \alpha_h (V)\, (1 - h) - \beta_h (V)\, h \qquad (4)$$

The “all or none” nature of the spike

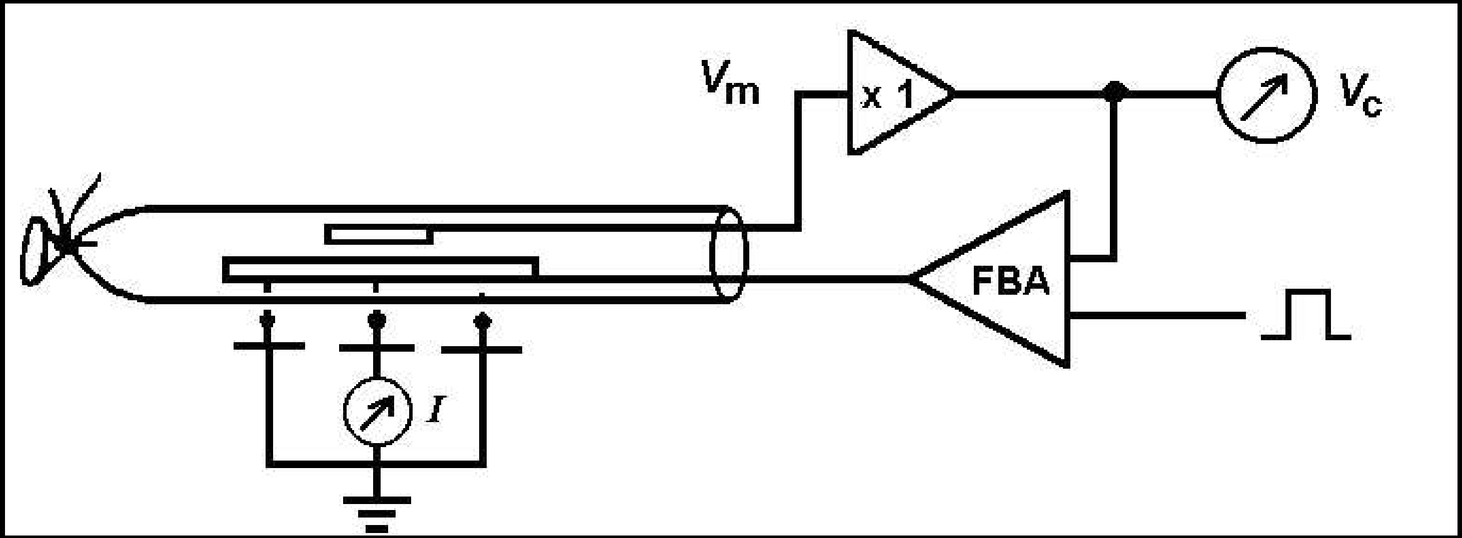


Hodgkin, Huxley and Katz, 1952

What are the membrane currents underlying the spike?

The voltage clamp (+ space clamp)

The technique that made the whole difference

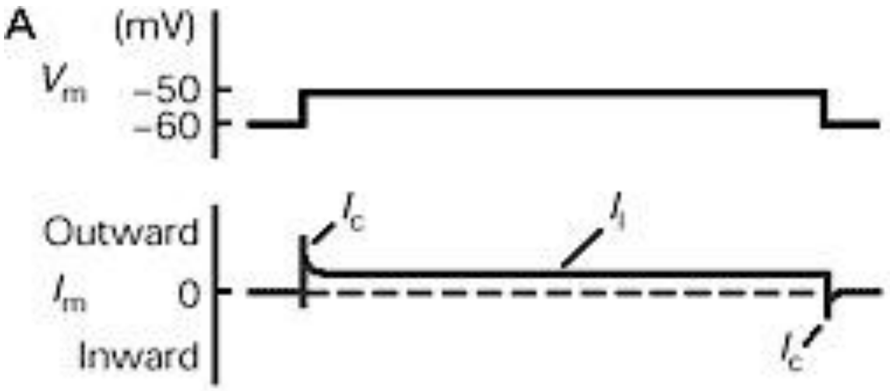


Space clamp - making the (long) axon effectively isopotential via the insertion of an axial conductive wire.

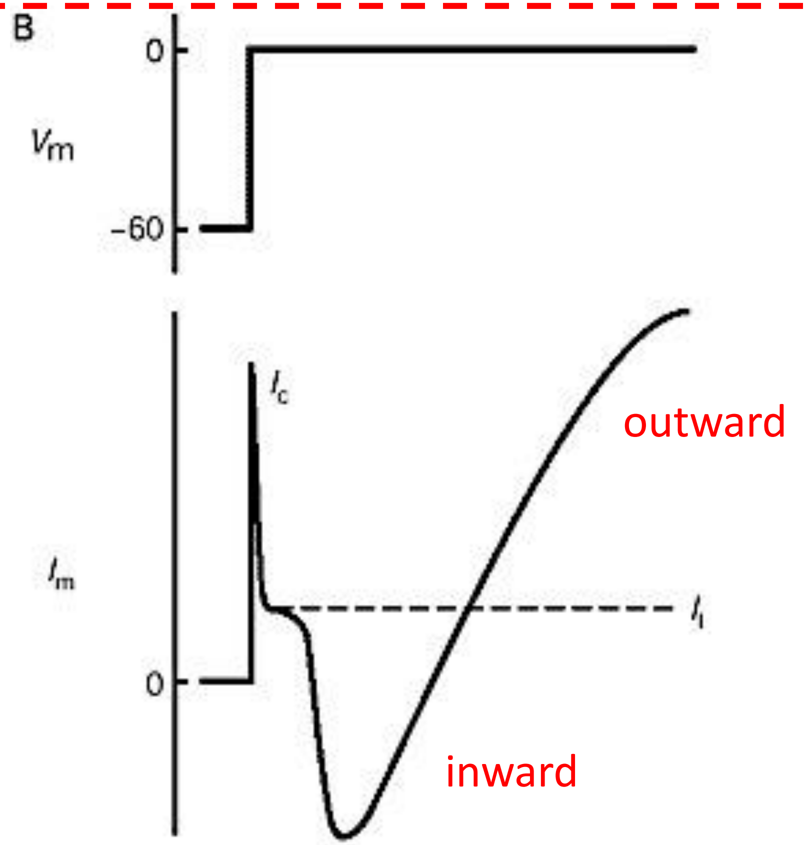
Voltage clamp – enables the experimenter to dictate the desired voltage difference between the inside and the outside of the membrane.
The electronic feedback system injects current to exactly counterbalance the (excitable – voltage-dependent) membrane current.

Developed by Kenneth Cole and George Marmont

Membrane current in response to voltage clamp (VC)



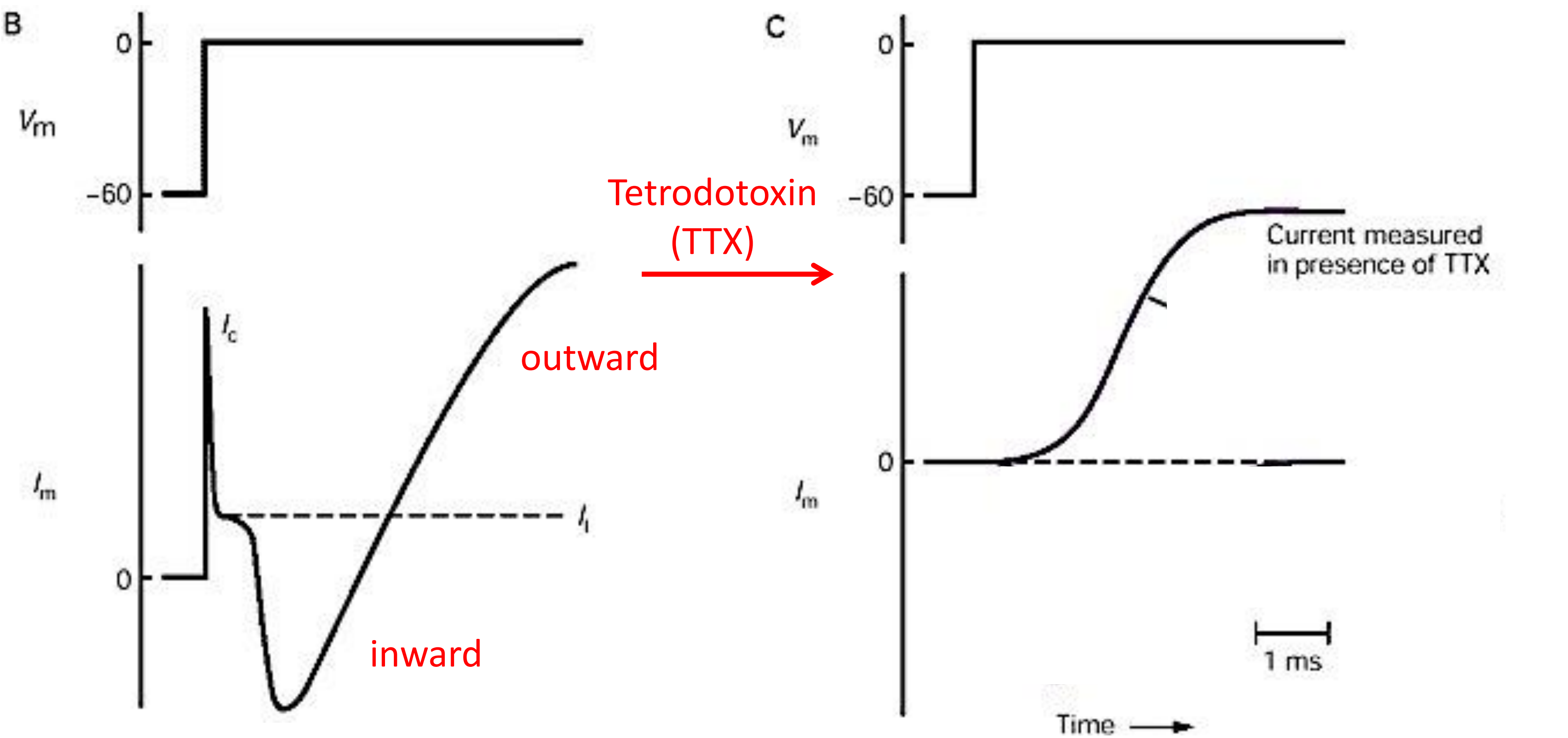
For subthershold depolarizing voltage clamp, the recorded membrane current is the current that flows via the leak (passive) conductance + a small capacitative current (at start and end of the VC)



For suprathershold depolarizing voltage clamp, the recorded membrane current (after the fast capacitaticve current) flows first inwards (into the axon) and later outward (from inside to the outside)

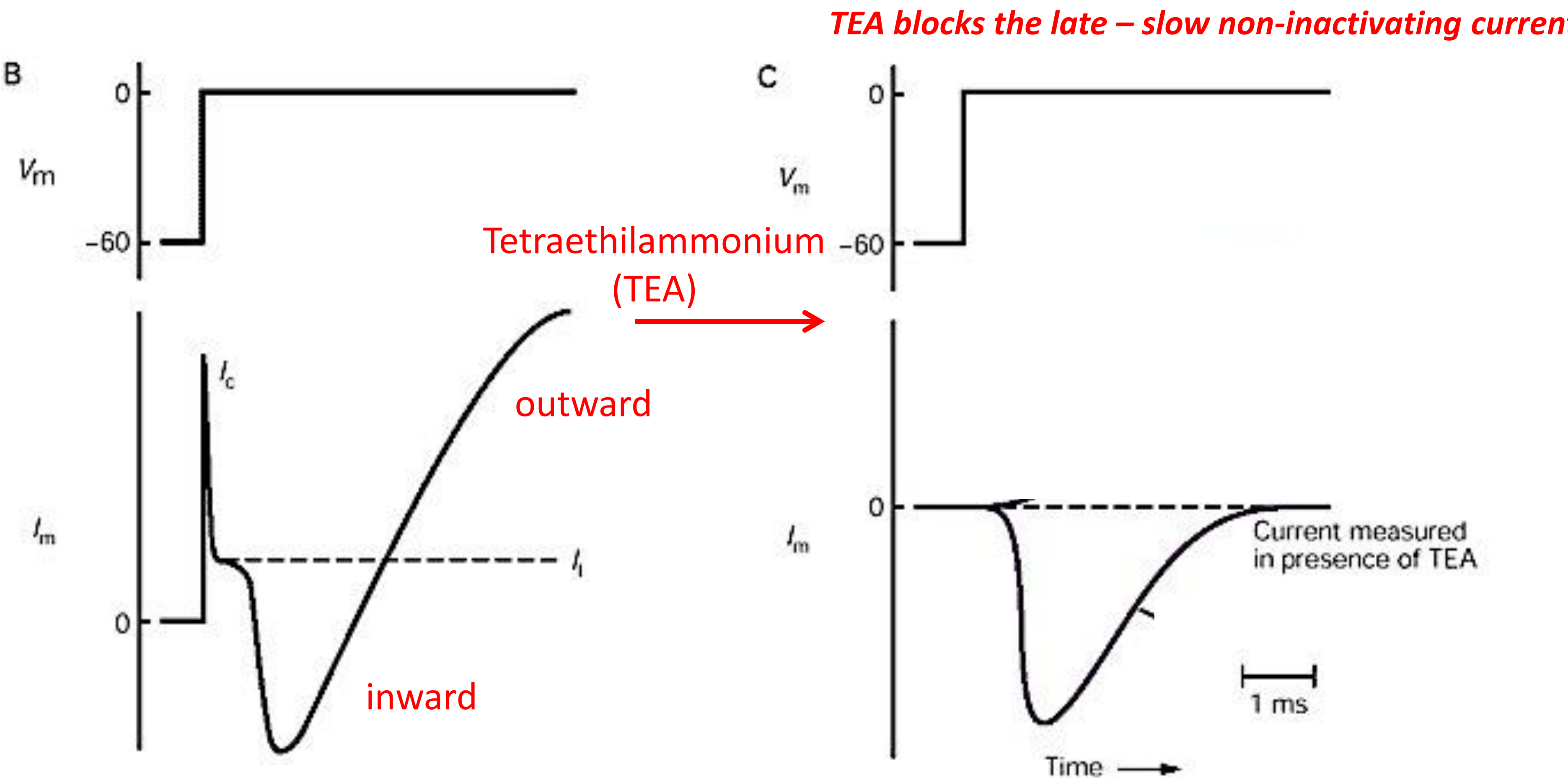
Separating voltage-dependent active (excitable) currents
Using pharmacological agents
2 different currents flow via the membrane during the spike

TTX blocks the early – fast inactivating current

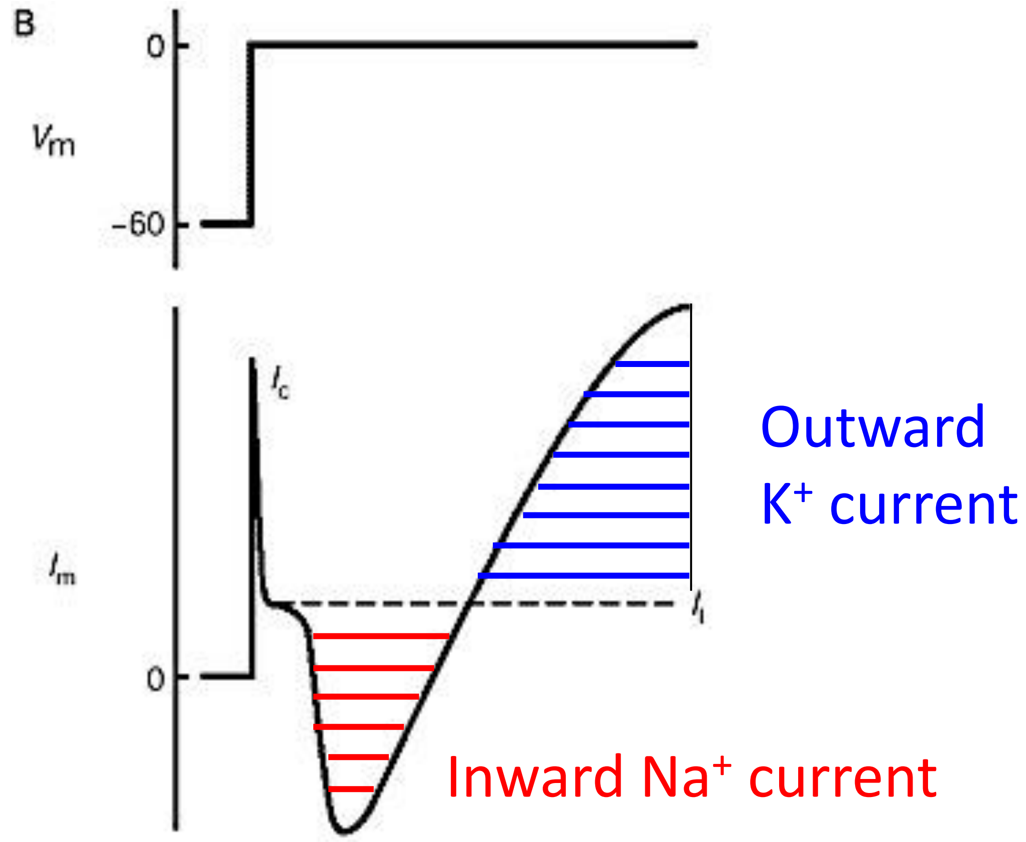


Separating voltage-dependent active (excitable) currents Using pharmacological agents

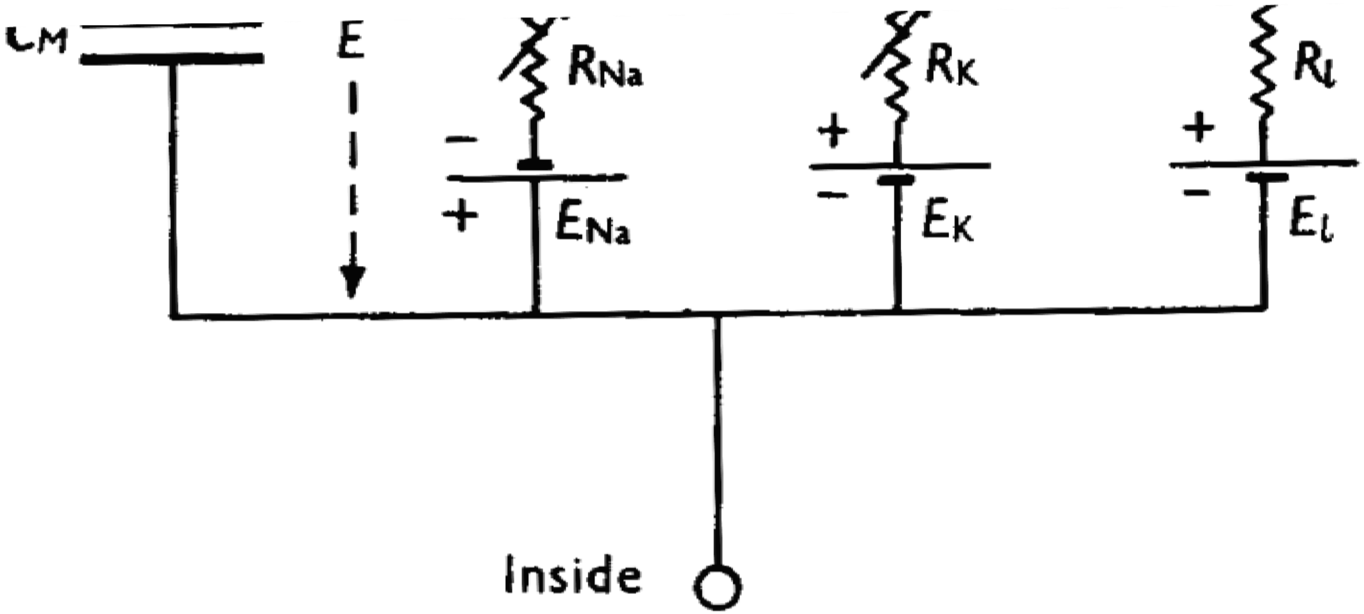
2 different currents flow via the membrane during the spike



Changing ion concentration at bath with giant axon showed that early current is carried by Na^+ ions and late one by K^+ ions



The electrical circuit for the squid axon (excitable) membrane



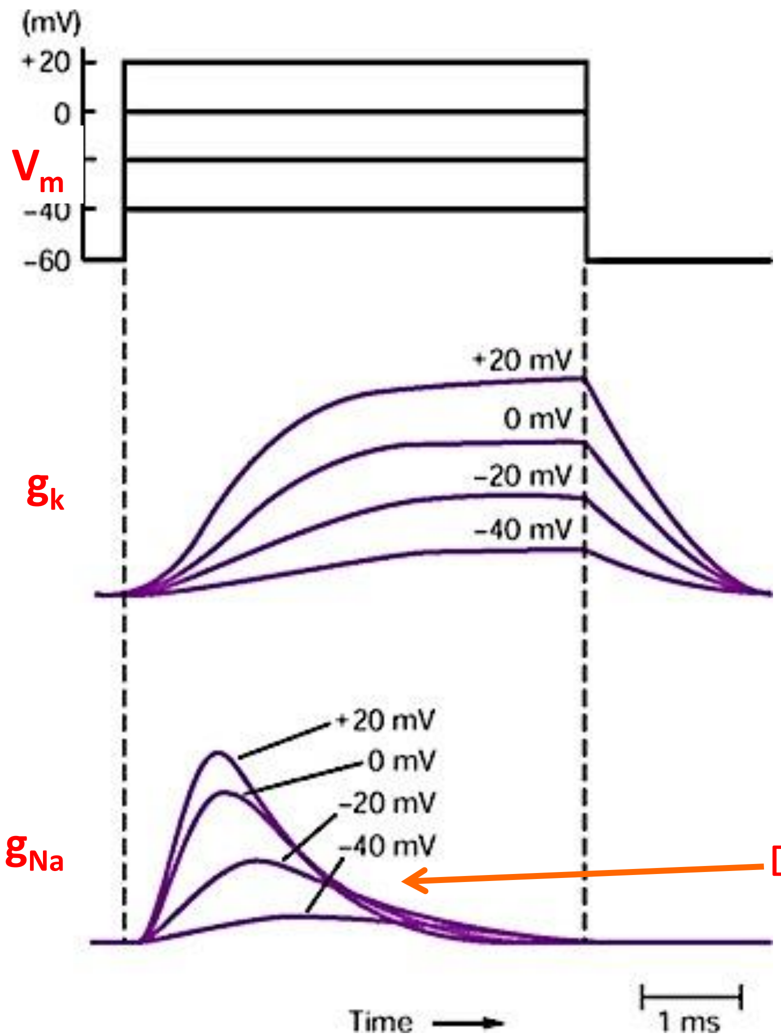
lectrical circuit representing membrane. $R_{Na} = 1/g_{Na}$; $R_K = 1/g_K$; $R_l = 1/\bar{g}_l$. R_{Na} an
vary with time and membrane potential; the other components are constant.

The nature of the permeability changes

esent the thickness and composition of the excitable membrane ar
n. Our experiments are therefore unlikely to give any certain informa
ut the nature of the molecular events underlying changes in perme
The object of this section is to show that certain types of theory ar

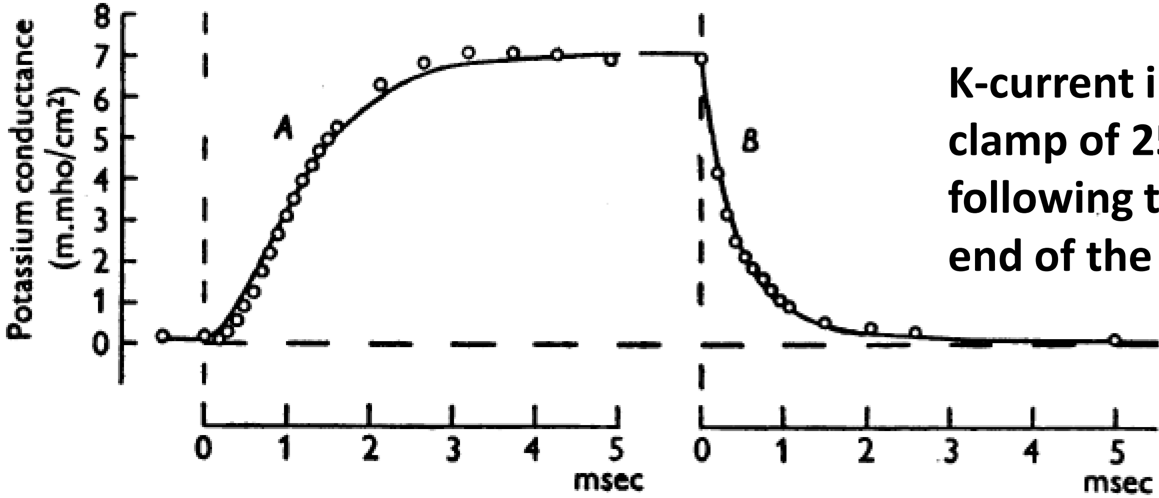
Ion currents (K^+ and Na^+) for various depolarizing voltage clamp
(and extracting respective ion conductances)

$$I_K = g_K\,(V_m - E_K); \qquad I_{Na} = g_{Na}\,(V_m - E_{Na})$$



1. The slow (K) current (conductance) does not inactivate during VC
2. The K conductance rises slower than it decays at end of VC
3. The fast (early) Na conductance inactivates during VC

Fitting an equation for the K current (K-conductance) during/following VC



K-current in response to a step voltage clamp of 25 mV (upstroke) – slow rise following the VC and faster decay at the end of the VC

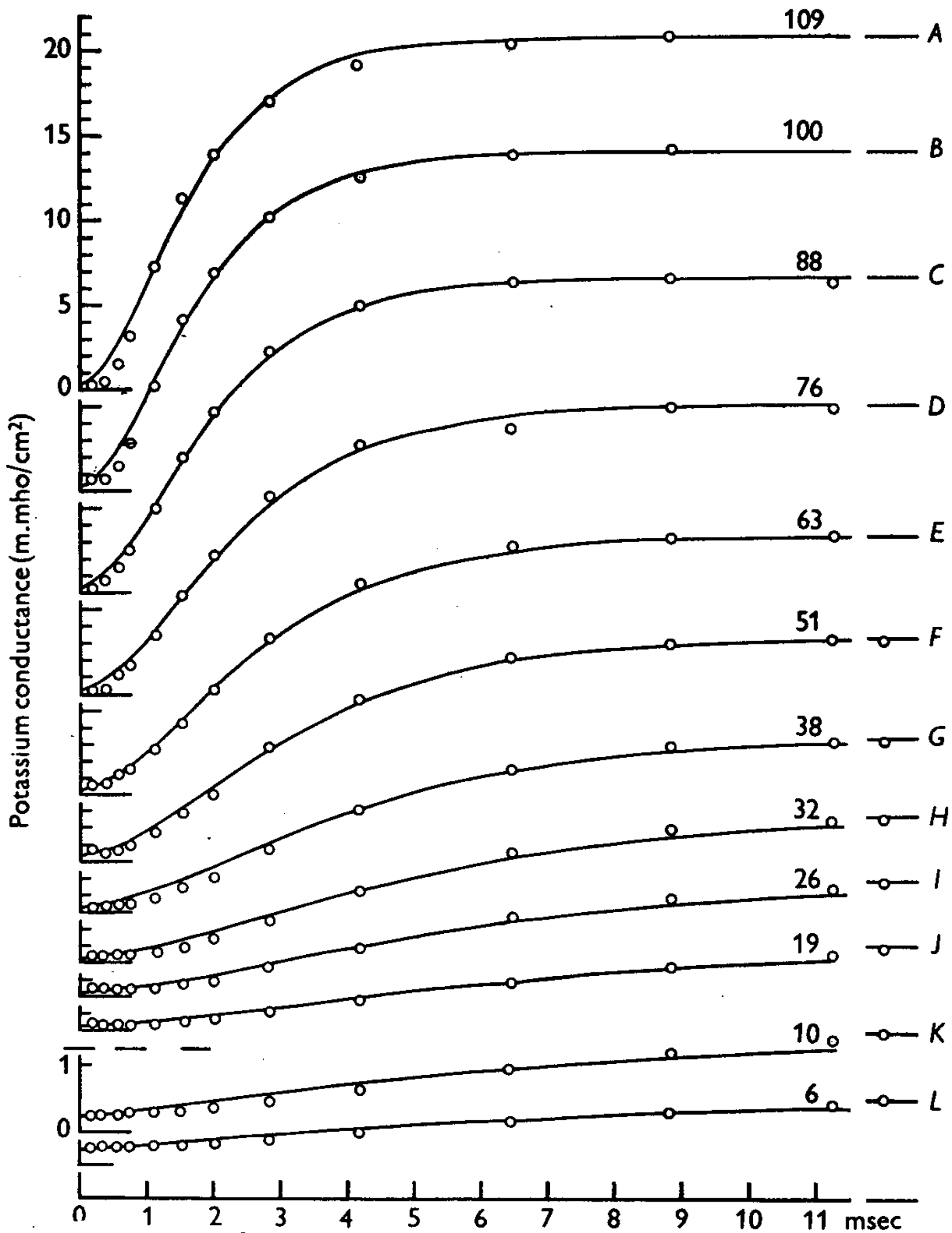
Mathematically – the rising phase of K-current can be described as a power of 4 (namely as $(1 – \exp(-t))^4$ and the decay as $\exp(-4t)$)

$$g_{K} = \bar{g}_{K} n^{4}$$

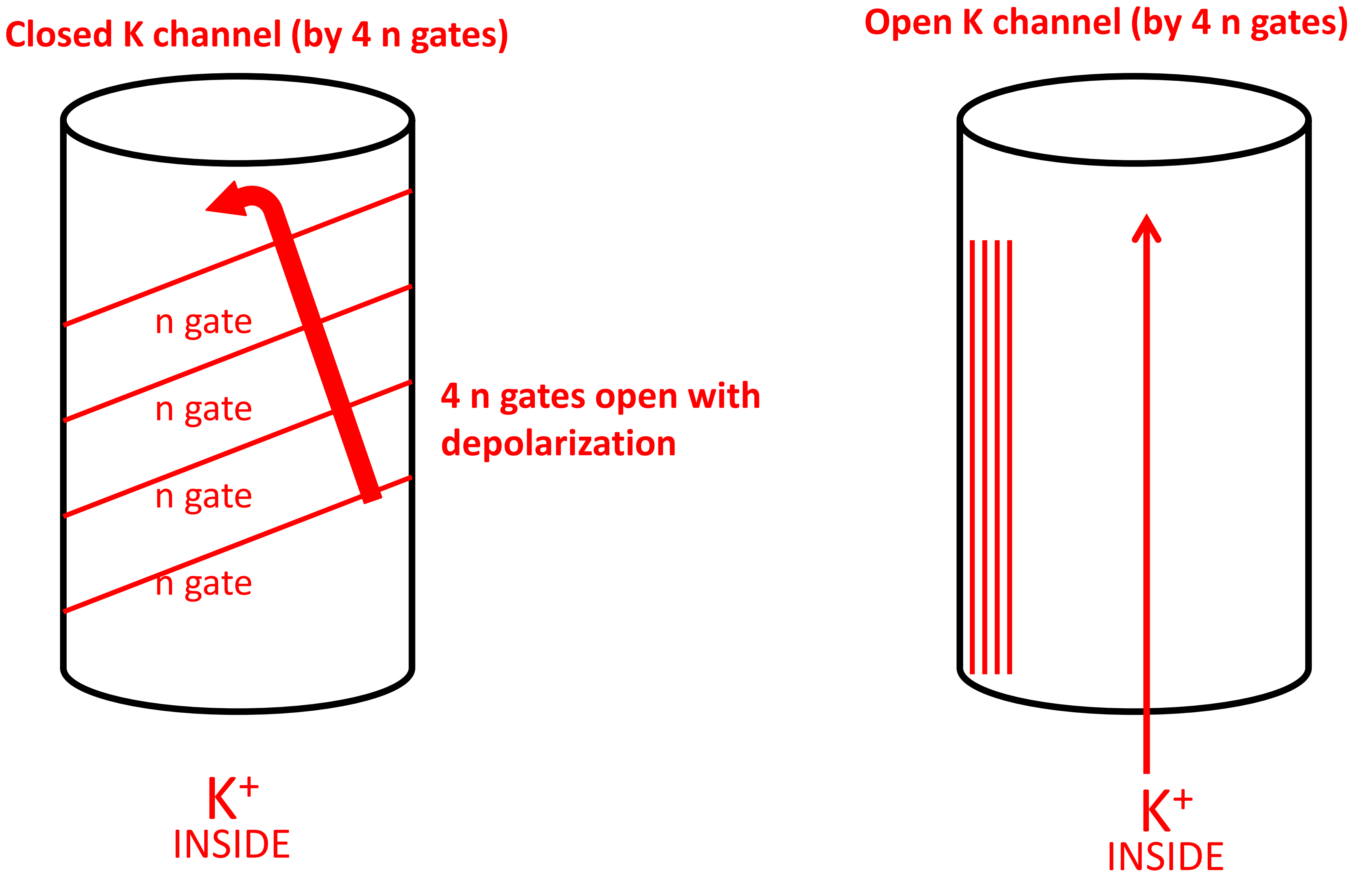
n represents the proportion of K-ion channels in the open state

"These equations may be given a physical basis if we assume that potassium ions can only cross the membrane when four similar particles occupy a certain region of the membrane..." Hodgkin AL, Huxley AF. 1952 J Physiol (Lond) 117:500–544

Fitting K current for different VC depolarizing values



Graphical interpretation of H&H model for the K channel



The activation function, *n*, and the rate functions α_n and β_n

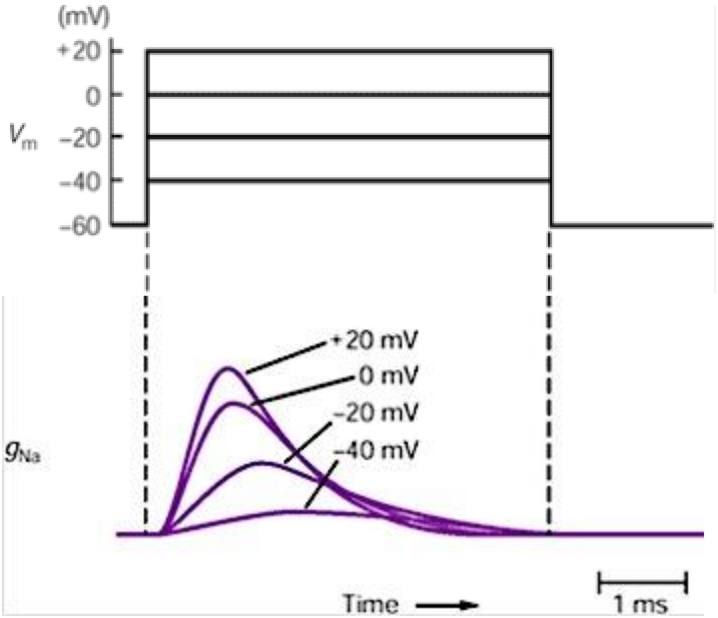
fer in the opposite directio

l increase and β_n should dec

quations will be discussed i

region of the membrane. n represents the proportion of the particles in a certain position (for example at the inside of the membrane) and $1-n$ represents the proportion that are somewhere else (for example at the outside of the membrane). α_n determines the rate of transfer from outside to inside, while

Similar procedure is used to extract the activation (m) and inactivation (h) parameters for the Na current

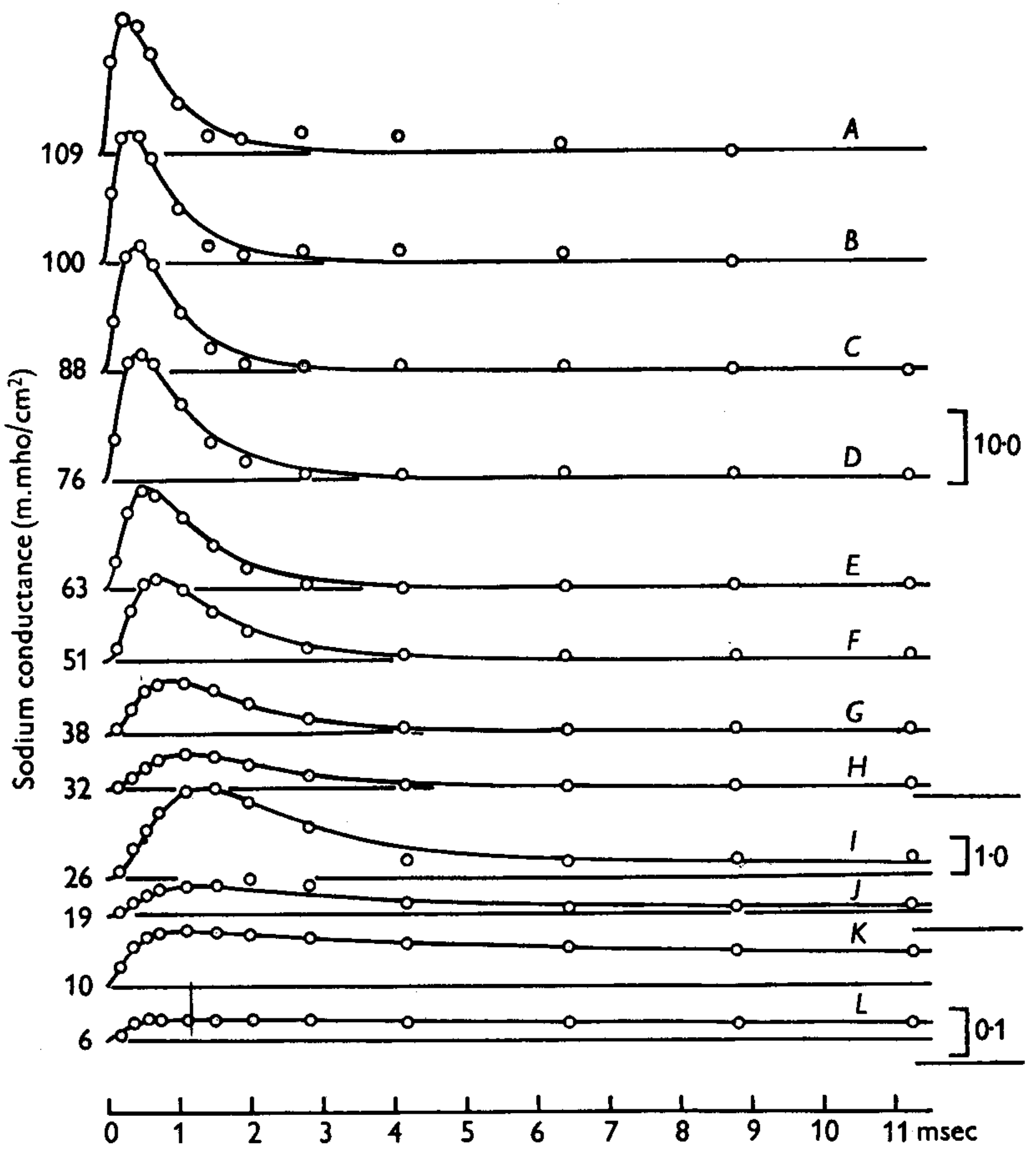


$$g_{\mathrm{Na}} = m^3 h \bar{g}_{\mathrm{Na}},$$

$$\frac{\mathrm{d}m}{\mathrm{d}t} = \alpha_m (1-m) - \beta_m m,$$

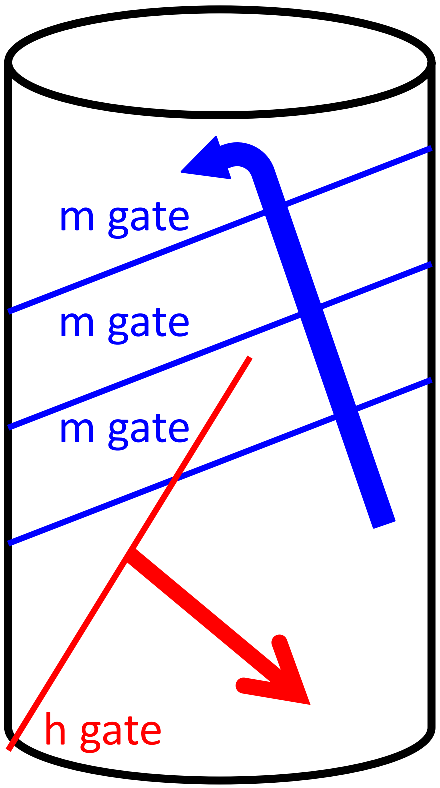
$$\frac{\mathrm{d}h}{\mathrm{d}t} = \alpha_h (1-h) - \beta_h h,$$

Fitting Na current for different VC depolarizing values



Graphical interpretation of H&H model for the Na channel

Na channel (by 3 activated m gates and 1 inactivated h gate)

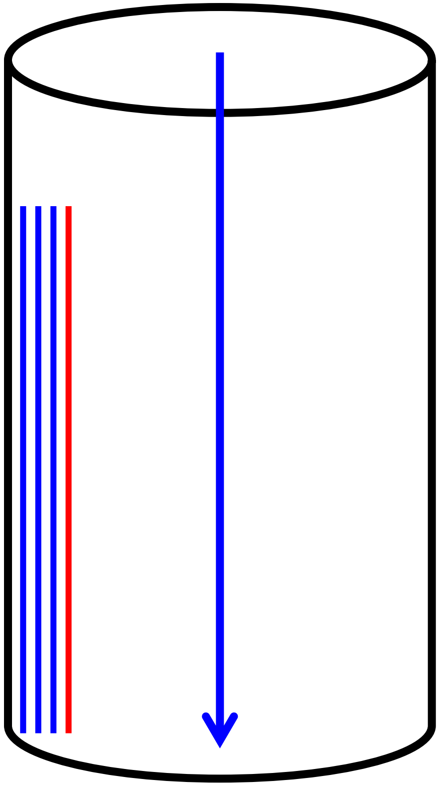


3 (fast) m (activated) gates open with depolarization

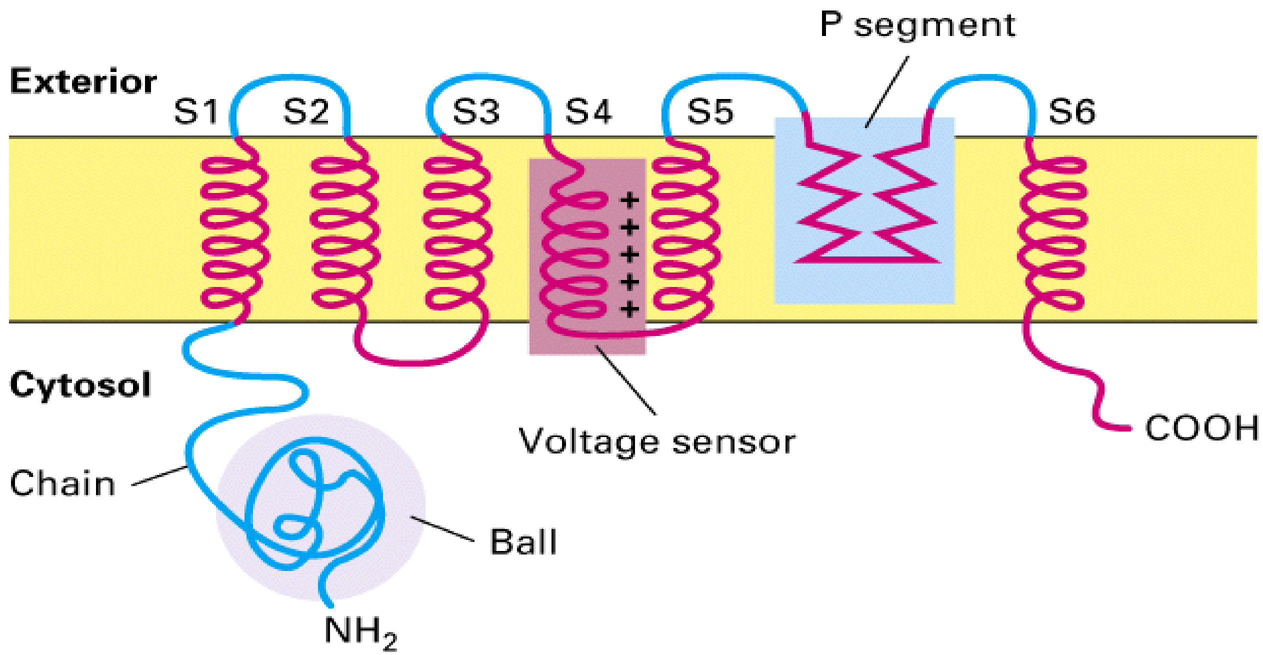
1 (slow) h (inactivated) gate closes with depolarization

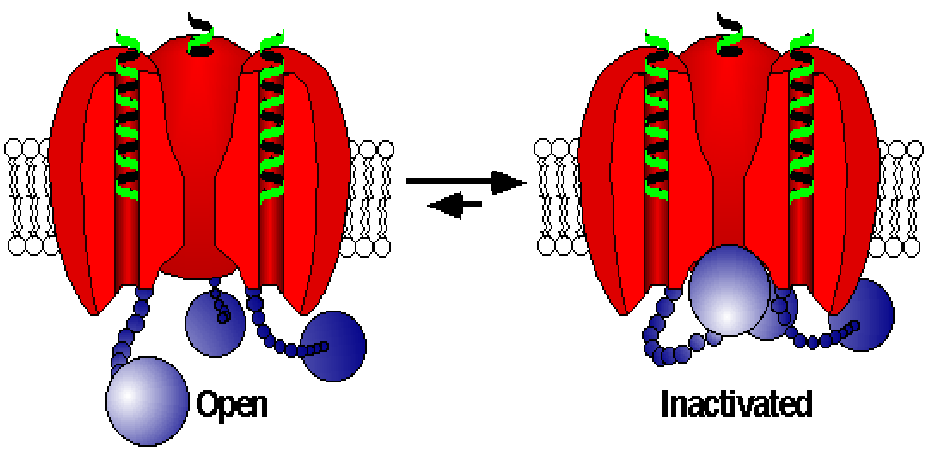
Open Na channel

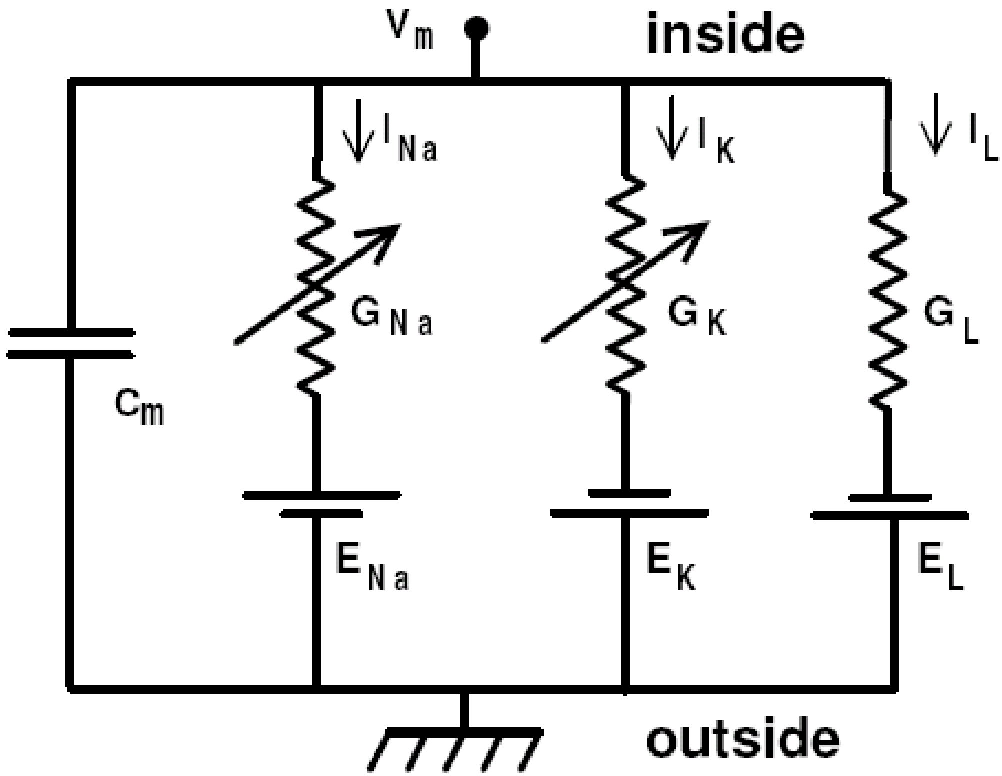
Na outside



Voltage-dependent Ion channels underlying the AP (later than H&H)







$$I = C_m \dot{V} + g_{Na}\, h\, m^3\ (V - V_{Na}) + g_K\, n^4\ (V - V_k) + G_L\ (V - V_L) \qquad (1)$$

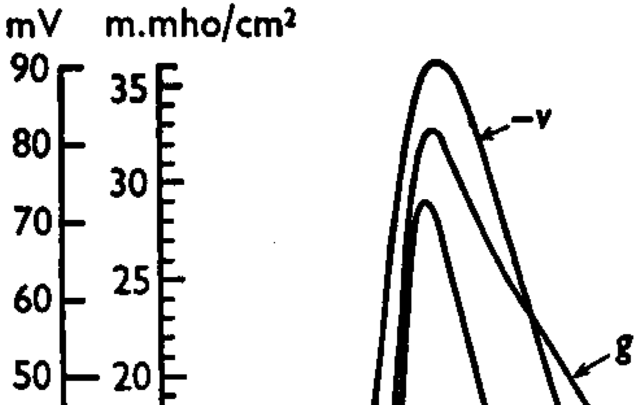
$$\frac{d}{dt} m = \alpha_m (V)\ (1 - m) - \beta_m (V)\ m \qquad (2)$$

$$\frac{d}{dt} n = \alpha_n (V)\ (1 - n) - \beta_n (V)\ n \qquad (3)$$

$$\frac{d}{dt} h = \alpha_h (V)\ (1 - h) - \beta_h (V)\ h \qquad (4)$$

Overlay of the action potential (voltage) and underlying Na and K conductances

conductance peak in Fig. 16 *A* and the half-amplitude of the bridge output in Fig. 16 *B* is due simply to the choice of scale. Nevertheless, our calculated action potentials agree well with Cole & Curtis's results in this respect. These authors found that the average membrane resistance at the peak of the impedance change was 25 Ω.cm^2, corresponding to a conductance of 40 m.mho/cm^2. The peak conductances in our calculated action potentials ranged from 31 to 53 m.mho/cm^2 according to the conditions, as shown in Table 4.



Model verification

MEMBRANE CURRENT IN NERVE 525

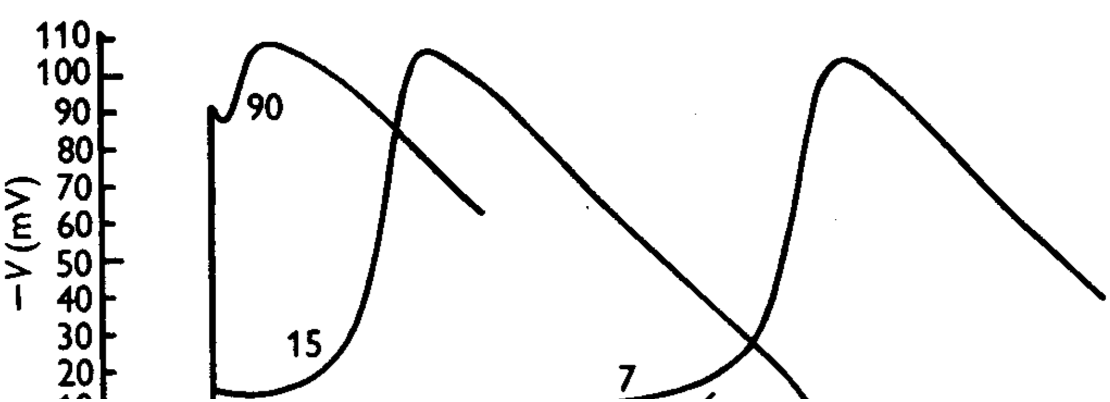
Model

RESULTS

Membrane action potentials

Form of action potential at 6° C. Three calculated membrane action potentials, with different strengths of stimulus, are shown in the upper part of Fig. 12. Only one, in which the initial displacement of membrane potential was 15 mV, is complete; in the other two the calculation was not carried beyond the middle of the falling phase because of the labour involved and because the solution

Experiment



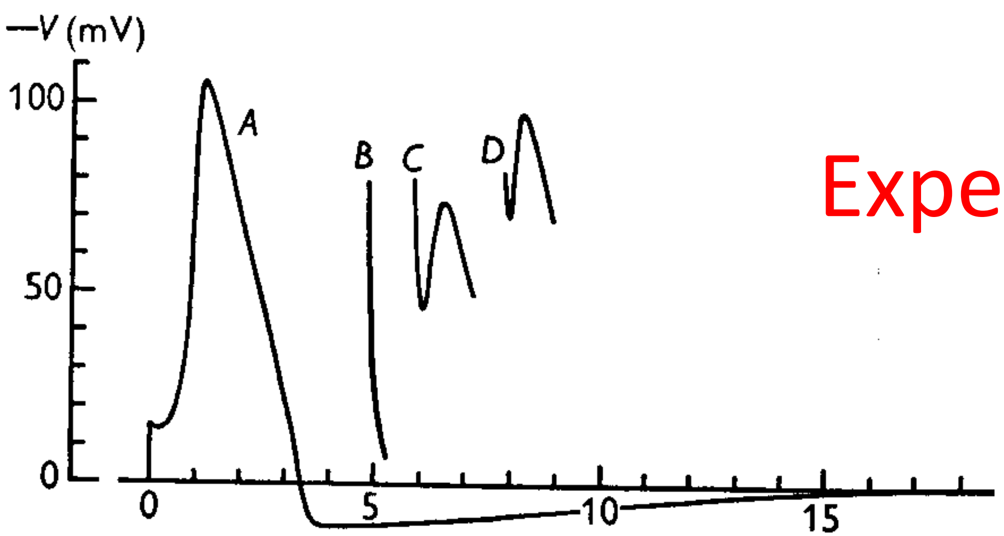
The refractory period

ettle down after a heavily damped oscillation of smal
een in the figure.

Responses to stimuli during positive phase. We ca

Model

he membrane when it was suddenly depolarized by
uring the positive phase of the membrane action pot
hown by the upper curves in Fig. 20. After th



Experiment

H&H explanation for the refractory period

Refractory period

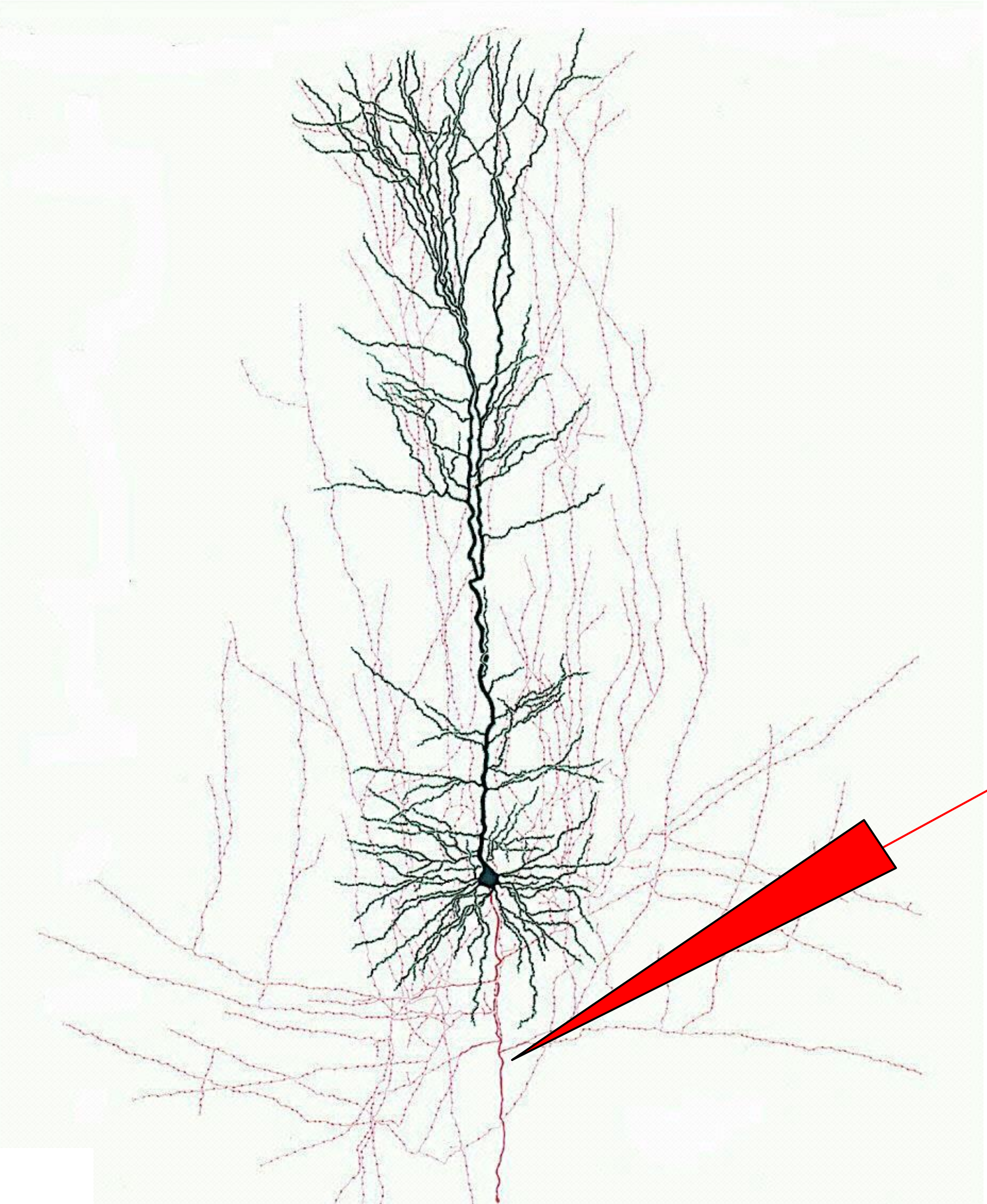
impulse. This has been done for the four complete action potentials th
calculated, and the results are given in Table 5. It will be seen that the
at 18·5° C are in good agreement with the values found experimenta
Keynes (1951) and Keynes & Lewis (1951), which were obtained at
parable temperatures.

Ionic fluxes. The flux in either direction of an ion can be obtained fro

Slow recovery from Na inactivation (h) and slow kinetics of K conductance, both make the following spike impossible (absolute refractory) or hard (relative refractory) to be initiated.

The universal nature of the spike

(from squid to cortical axons - carrying the brain code; effecting plasticity)



Response of Cortical Pyramidal Cell to Current Injection

Courtesy of D. McCormick (Yale Univ.)