The Hodgkin & Huxley Theory on Action Potentials

Term Paper

Max Jakob
Albert-Ludwigs-Universität Freiburg

08.11.16

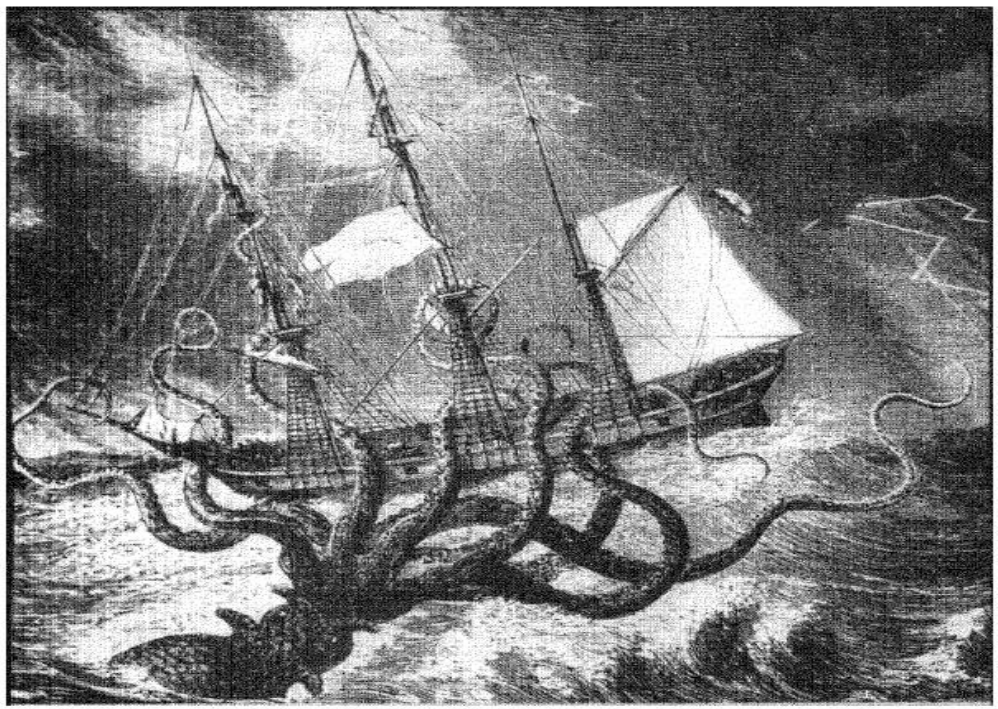


Table of contents

Table of contents

Physiology of a nerve cell

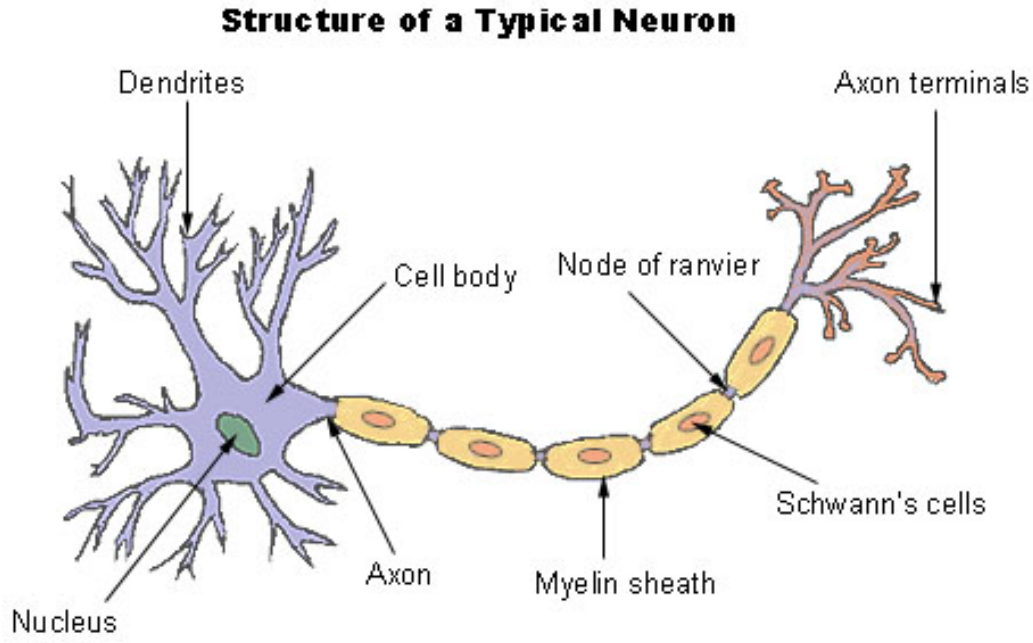


Figure: Quelle:

- Cells that can receive and transmit information
- Cell body: Soma
- Receives information via Dendrites
- Transmits information via the Axon.

Cell types

Cells can be divided in excitable and non-excitable cells:

Non-excitable cells:

- No ability to conduct information
- Example: Skin cells, wall of intestines

Excitable cells:

- Able to conduct electrical signals
- Example: Muscle or nerve cells

Cell types

Cells can be divided in excitable and non-excitable cells:

Non-excitable cells:

- No ability to conduct information
- Example: Skin cells, wall of intestines

Excitable cells:

- Able to conduct electrical signals
- Example: Muscle or nerve cells

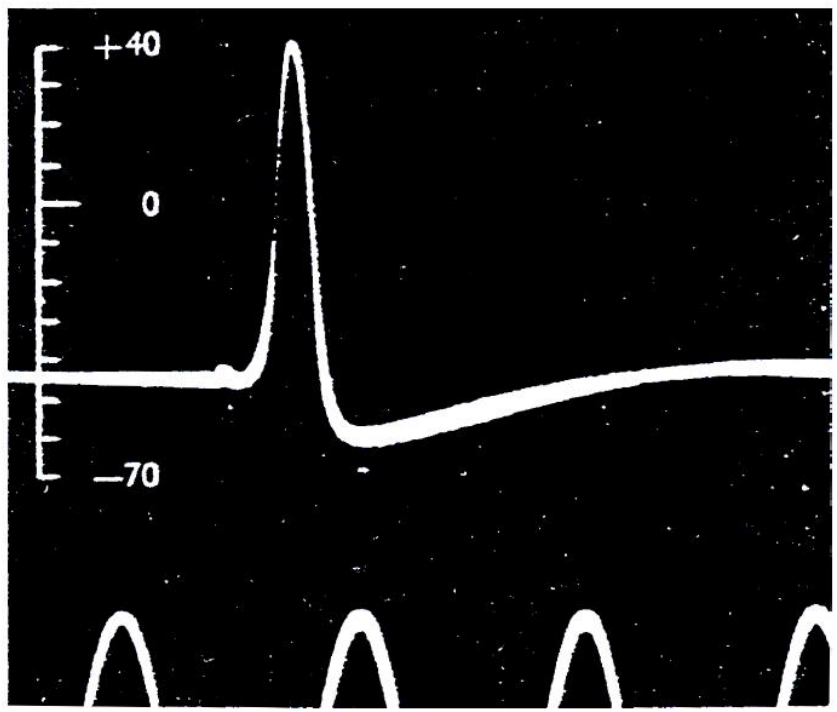


Figure: Action Potential: All or nothing principle [4].

Threshold behaviour of excitable cells

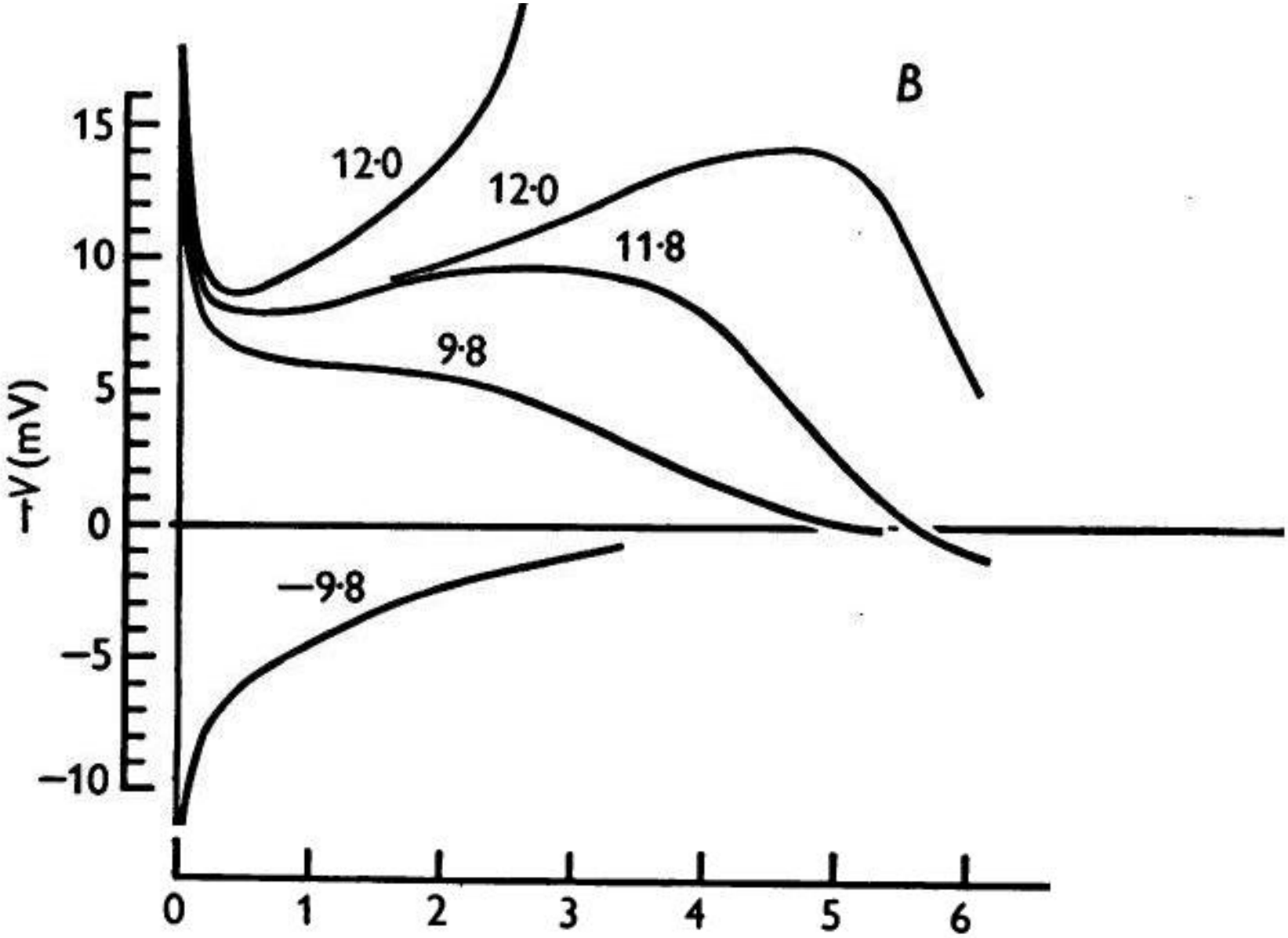
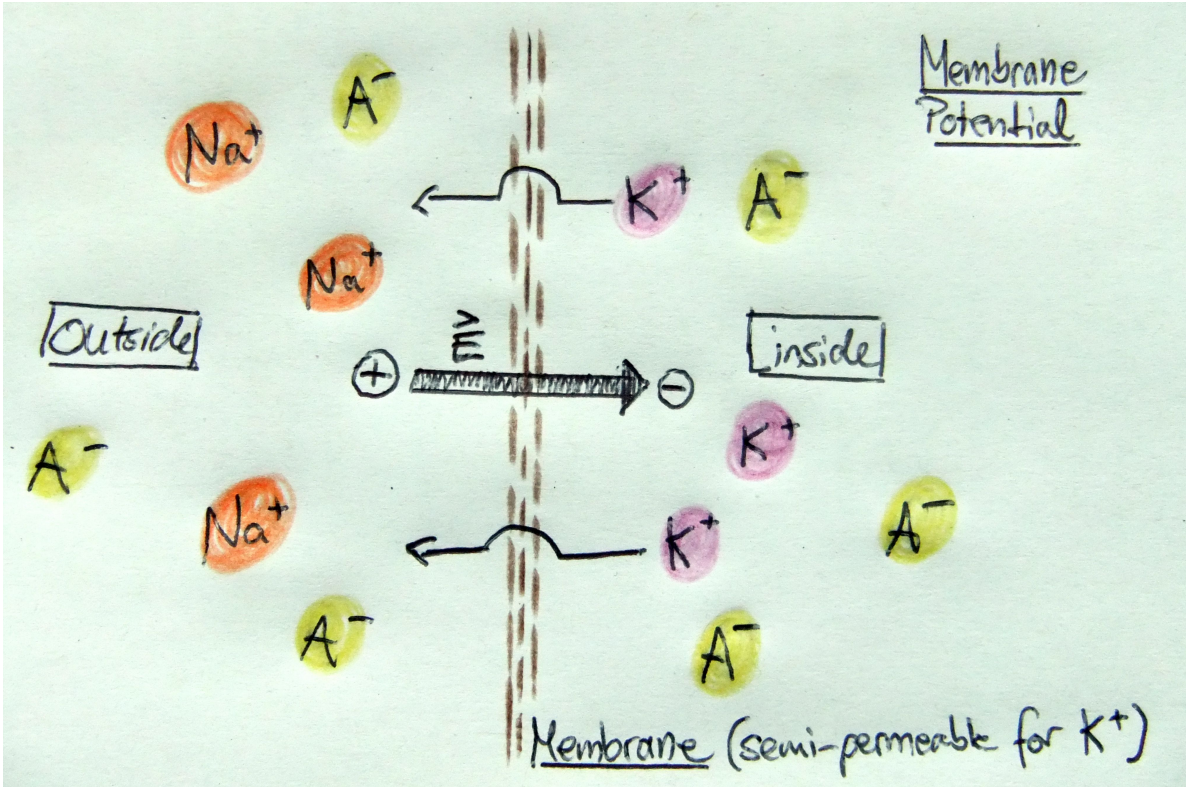


Figure: Experiment: V(t) for various stimulus intensities [1].

Table of contents

Nernst equilibrium potential



Equilibrium between osmosis and electric field creates potential difference:

$$V_{\text{Nernst}} = \frac{kT}{zq} \ln\left(\frac{[S]_e}{[S]_i}\right)$$

Components of the membrane

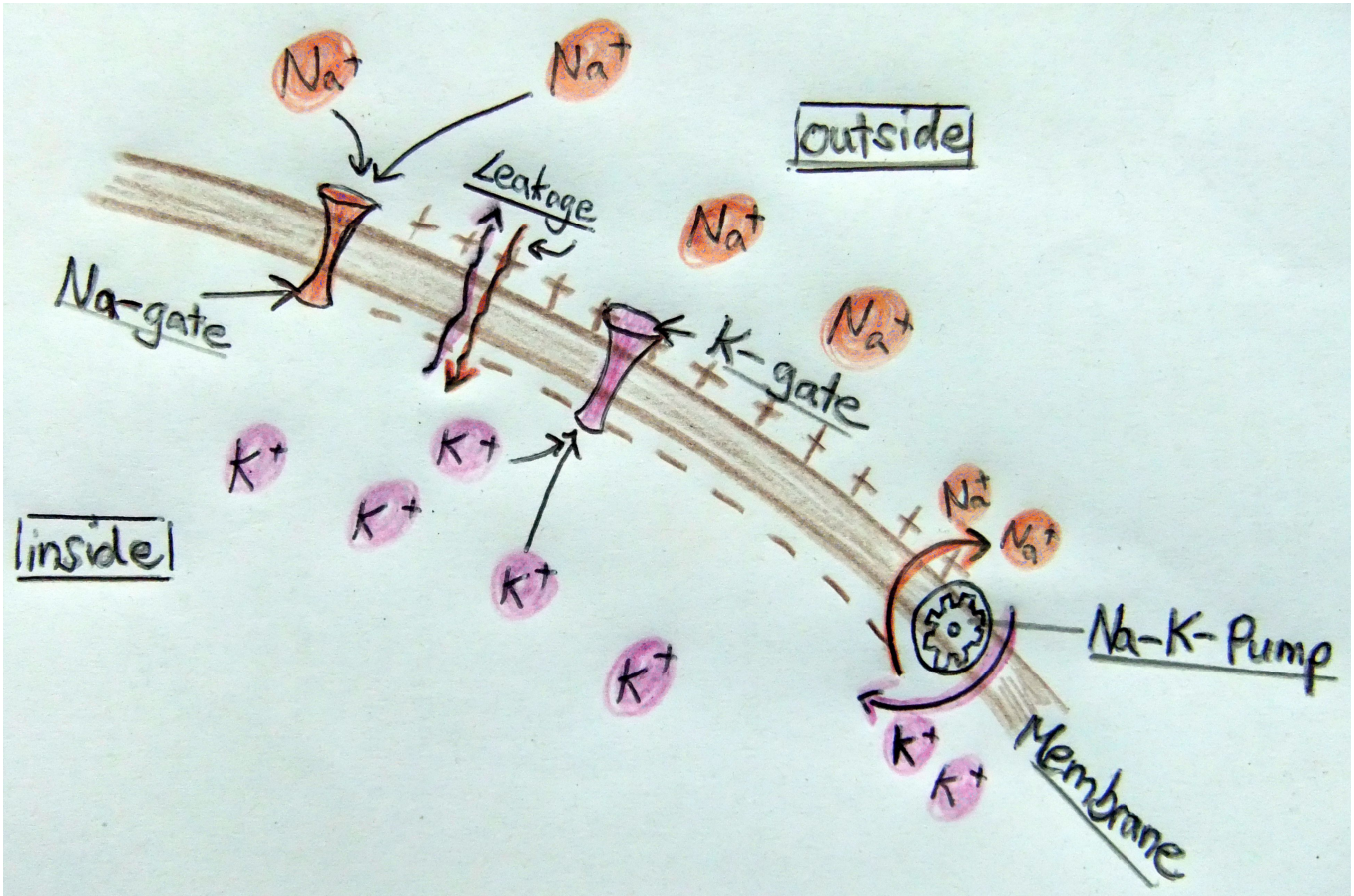


Figure: Visualisation of membrane components: Ionic gates, Sodium-Potassium-Pump, leakage.

Electric circuit

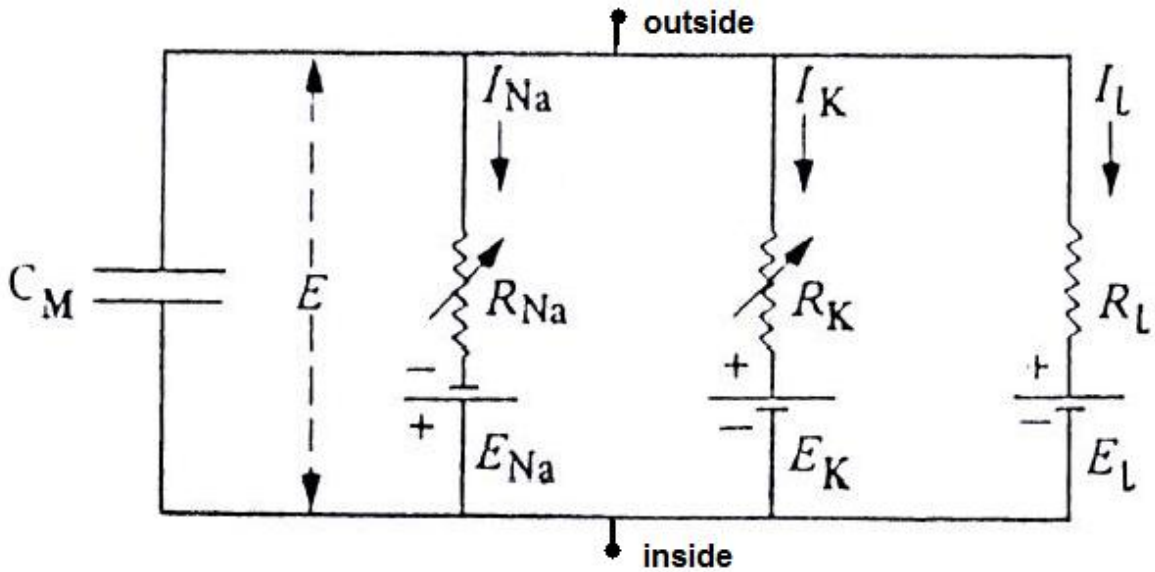


Figure: Electric circuit for cell membrane [1].

$$C_m \frac{\mathrm{d}V}{\mathrm{d}t} + I_{\mathrm{Ion}}(V,t) = I_{\mathrm{app}}$$

$$I_{\mathrm{Ion}}(V,t) = I_{\mathrm{Na}} + I_{\mathrm{K}} + I_{\mathrm{l}}$$

Linear relation between I_{Ion} and V?

Suggested linear relation ($I \propto V$):
The Hodgkin & Huxley equation

$$C_m \frac{\mathrm{d}V}{\mathrm{d}t} = -g_{\mathrm{Na}}(V - V_{\mathrm{Na}}) - g_{\mathrm{K}}(V - V_{\mathrm{K}}) - g_{\mathrm{l}}(V - V_{\mathrm{l}}) + I_{\mathrm{app}}$$

Rewritten:

$$C_m \frac{\mathrm{d}V}{\mathrm{d}t} = -g_{\mathrm{eff}}(V - V_{\mathrm{eff}}) + I_{\mathrm{app}}$$

with

$$g_{\mathrm{eff}} = g_{\mathrm{Na}} + g_{\mathrm{K}} + g_{\mathrm{l}}, \qquad V_{\mathrm{eff}} = \frac{g_{\mathrm{Na}} V_{\mathrm{Na}} + g_{\mathrm{K}} V_{\mathrm{K}} + g_{\mathrm{l}} V_{\mathrm{l}}}{g_{\mathrm{eff}}}$$

Constants for orientation:

$$R_{\mathrm{m}} = 1/g_{\mathrm{eff}} \approx 10^3 \Omega \mathrm{cm}^2, \qquad \tau_{\mathrm{m}} = C_{\mathrm{m}} R_{\mathrm{m}} \approx 1\mathrm{ms}$$

Linear relation between I_{Ion} and V?

For a constant applied current the voltage should also be time independent:

$$\frac{\mathrm{d}V}{\mathrm{d}t} = 0 \quad \rightarrow \quad V = V_{\mathrm{eff}} + R_{\mathrm{m}} I_{\mathrm{app}}$$

Experiment shows: True for small currents but not for large ones!

Ohm's law does not hold here!

Solution: Voltage dependent conductances $g_{\mathrm{K,Na}}(V, t)$

Accomplishment of Hodgkin & Huxley: Measurement of I_{Ion} for determination of $g(V, t)$!

$\rightarrow$ 1963 Nobel Prize in medicine and physiology

Table of contents

The Hodgkin & Huxley Model 1952

Unique in history of biophysics:

- First successful model of propagation of electrical signals in nerves

The Hodgkin & Huxley Model 1952

Unique in history of biophysics:

- First successful model of propagation of electrical signals in nerves
- No knowledge about molecular composition of membrane!

The Hodgkin & Huxley Model 1952

Unique in history of biophysics:

- First successful model of propagation of electrical signals in nerves
- No knowledge about molecular composition of membrane!
- Brilliant conduction of both: Experiment and theory

The Hodgkin & Huxley Model 1952

Unique in history of biophysics:

- First successful model of propagation of electrical signals in nerves
- No knowledge about molecular composition of membrane!
- Brilliant conduction of both: Experiment and theory
- Surprising: Very unphysiological experiments yield good description of events in living organisms.

The Hodgkin & Huxley Model 1952

Unique in history of biophysics:

- First successful model of propagation of electrical signals in nerves
- No knowledge about molecular composition of membrane!
- Brilliant conduction of both: Experiment and theory
- Surprising: Very unphysiological experiments yield good description of events in living organisms.

$\rightarrow$ Experiments on the squid's giant axon

Measuring techniques

Two difficulties to overcome in measuring of g(V,t):

- Voltage needed to be spatially uniform

Measuring techniques

Two difficulties to overcome in measuring of g(V,t):

- Voltage needed to be spatially uniform
- Voltage had to be held constant in time

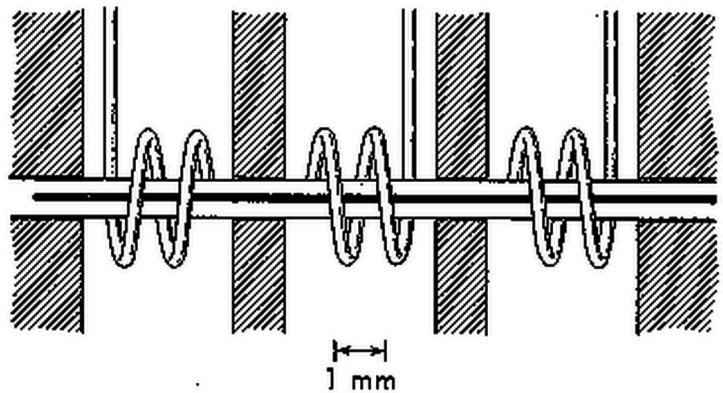
Measuring techniques

Two difficulties to overcome in measuring of g(V,t):

- Voltage needed to be spatially uniform
- Voltage had to be held constant in time

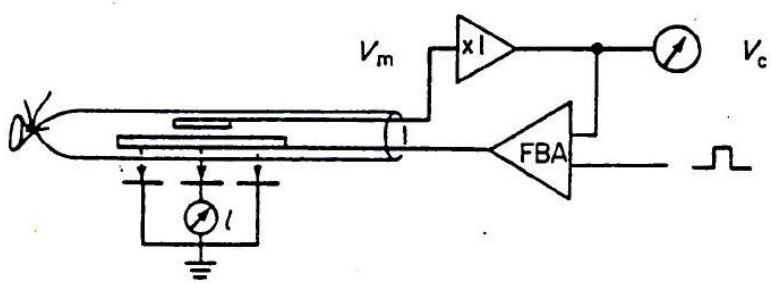
Solutions by Marmont & Cole: Space Clamp and Voltage Clamp

Space Clamp technique [3] $\rightarrow$



Voltage Clamp technique [4] $\rightarrow$

$$\dot{V} = 0 \longrightarrow \; g(t) = \frac{I_{\mathrm{app}}(t)}{V - V_{\mathrm{eq}}}$$



Sodium and Potassium conductances

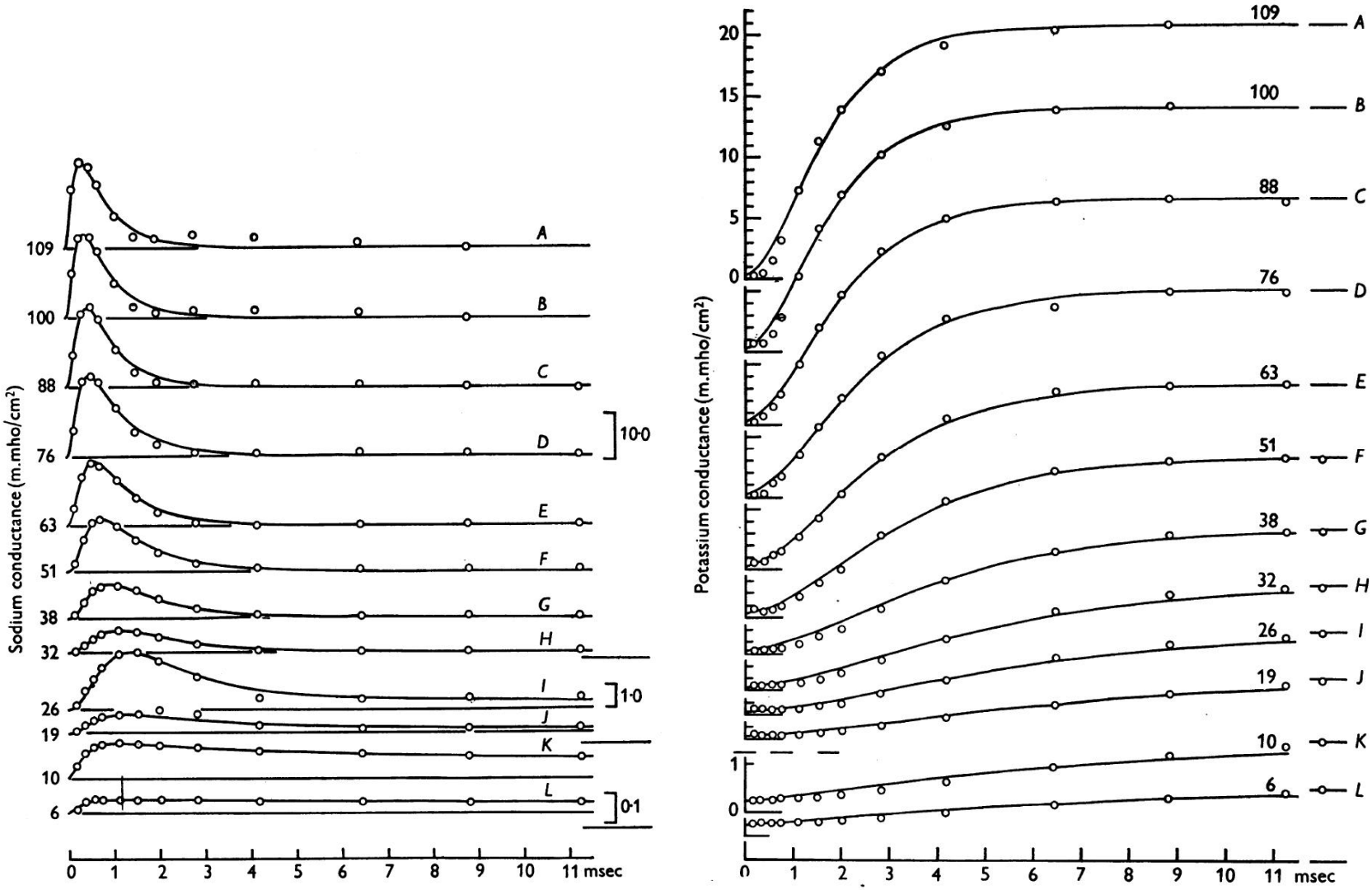


Figure: Sodium(l) and Potassium(r) conductances over time for various depolarisations

Modelling

By looking at the curves Hodgkin & Huxley suggested:

Potassium

$$\frac{\mathrm{d}n}{\mathrm{d}t} = \alpha_n(1-n) - \beta_n n$$

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

Sodium

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

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

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

Where:

- V dependent variables: $\alpha(V)$ and $\beta(V)$
- Gating variables between 0 and 1: n,m,h
- Constants: $\bar{g}_{\mathrm{Na,K}}$

Boundary conditions:

Example potassium:

- Resting value: $n(t = 0) = n_0$
- Stationary value: $n(t \to \infty) = n_\infty$
- Time constant: τ_n

$\to$ with n_0, n_∞ and τ_n functions of α and β.

$\to$ simple DEQ:

$$\tau_n \dot{n} = n_\infty - n$$

$\to$ solution:

$$\boxed{n(t) = n_\infty - (n_\infty - n_0)e^{-t/\tau_n}}$$

The same can be done for Sodium particles: Just replace n by m,h

Studies of the solution

Potassium: $g_{\mathrm{K}} \propto n^4$

- During depolarisation $V = (0 \to V_{\mathrm{dep}})$:

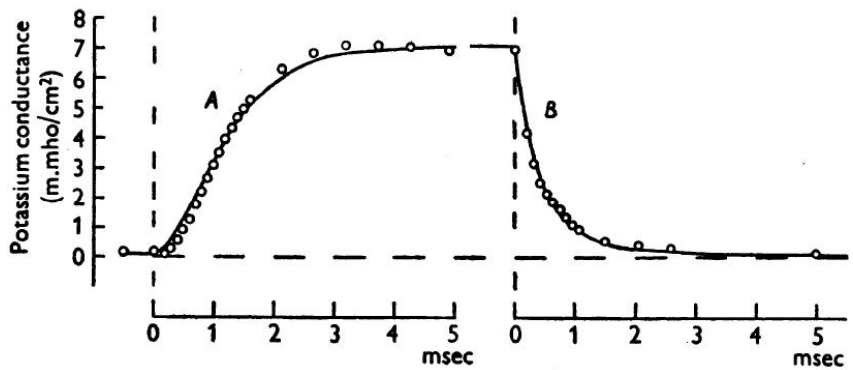
$$n_0 = 0 \qquad n_\infty = n_{\mathrm{dep}}$$

$$\longrightarrow \; g_{\mathrm{K}} \propto (1 - e^{-t/\tau_n})^4 \quad \text{sigmodial increase!}$$

- During repolarisation:

$$n_0 = n_{\mathrm{dep}} \qquad n_\infty = 0$$

$$\longrightarrow \; g_{\mathrm{K}} \propto (e^{-t/\tau_n})^4 \quad \text{Simple exponential!}$$



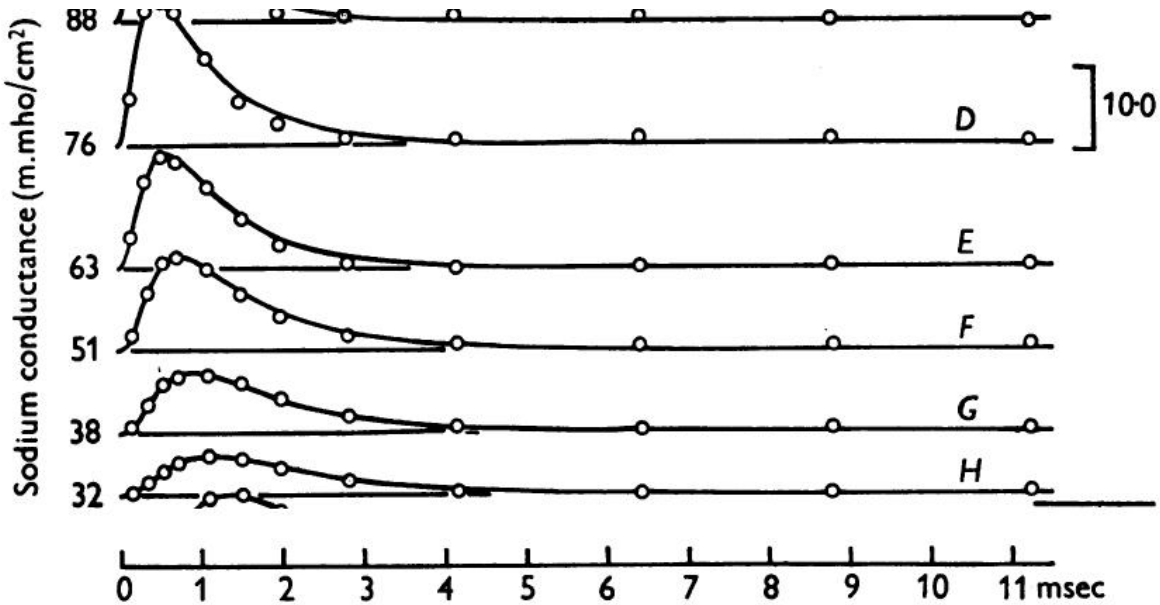
Studies of the solution

Sodium: $g_{\mathrm{Na}} \propto m^3 h$

- During depolarisation $V = (0 \rightarrow V_{\mathrm{dep}})$:

$$m_0 = 0 \qquad m_\infty = m_{\mathrm{dep}}$$
$$h_0 = h_{\mathrm{rest}} \qquad h_\infty = 0$$
$$\longrightarrow \; g_{\mathrm{Na}} \propto (1 - e^{-t/\tau_m})^3 (e^{-t/\tau_h})^1$$

- Sigmodial increase for small t
- Exponential decrease for large t



Interpretation of the model

Hodgkin & Huxley give meaning to their model:

Potassium $g_{\mathrm{K}} \propto n^4$

- n $\hat{=}$ probability of particle to be in position (i.e. inside)
- (1-n) $\hat{=}$ not in position (i.e. outside)
- $\alpha_n(V)\hat{=}$ Transfer rate from outside to inside
- $\beta_n(V)\hat{=}$ Transfer rate from inside to outside
- $g_{\mathrm{K}} \propto$ probability that four particles are in position

Interpretation of the model

Hodgkin & Huxley give meaning to their model:

Potassium $g_{\mathrm{K}} \propto n^4$

- n $\hat{=}$ probability of particle to be in position (i.e. inside)
- (1-n) $\hat{=}$ not in position (i.e. outside)
- $\alpha_n(V)\hat{=}$ Transfer rate from outside to inside
- $\beta_n(V)\hat{=}$ Transfer rate from inside to outside
- $g_{\mathrm{K}} \propto$ probability that four particles are in position

Sodium $g_{\mathrm{Na}} \propto m^3 h$

- m $\hat{=}$ probability of particle to be in position
- h $\hat{=}$ probability of **another** particle **not** to be in position
- Activating (m) and inactivating (h) particles
- $\alpha_{m,h}(V)$, $\beta_{m,h}(V)\hat{=}$ Transfer rates
- $g_{\mathrm{Na}} \propto$ probability of three particles in position and **another** particle **not** in position

Interpretation of the model

"[...] we [...] must emphasize that the interpretation given is unlikely to provide a correct picture of the membrane." [1, p.506]

Interpretation of the model

"[...] we [...] must emphasize that the interpretation given is unlikely to provide a correct picture of the membrane." [1, p.506]

But: They hit the nail on the head.

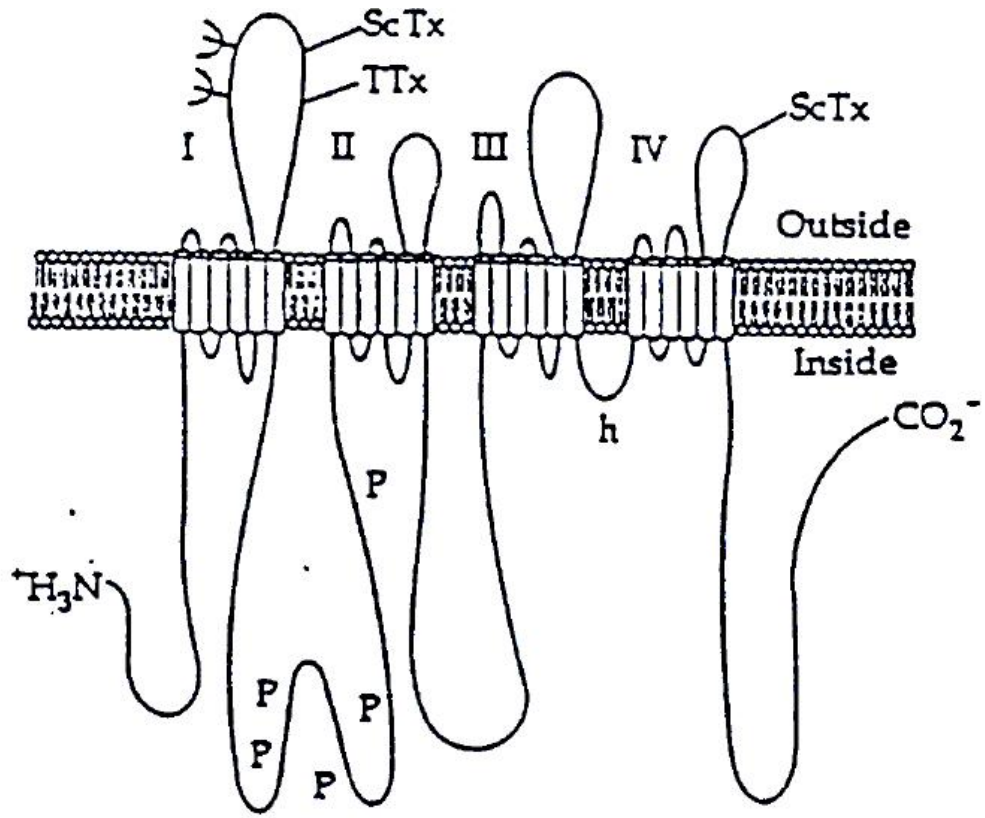
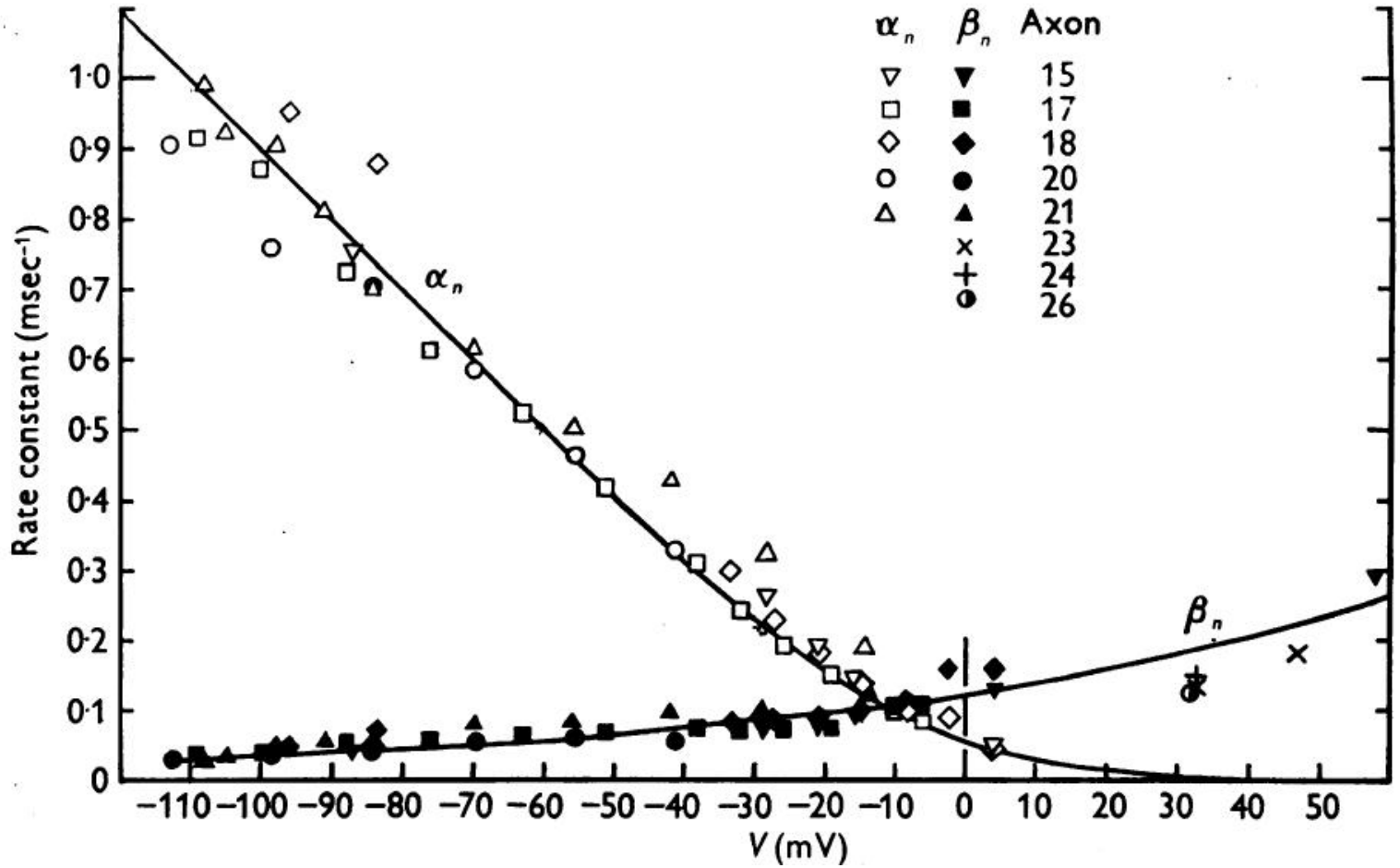


Figure: Proteinstructure of the sodium ion channel.

Fitting procedure

Fitting of the experimental data points for fixed depolarisations gives (here for potassium):

- τ_n and n_∞ that gave the best fit for each Voltage step
- Thereafter: V-dependent transfer rates: $\alpha_n(V)$, $\beta_n(V)$



Rate constants

Equations gained by fitting of data points:

$$\alpha_n = \frac{0.01(V+10)}{e^{(V+10)/10}-1} \qquad \beta_n = 0.125e^{V/80}$$

$$\alpha_m = \frac{0.1(V+25)}{e^{(V+25)/10}-1} \qquad \beta_m = 4e^{V/18}$$

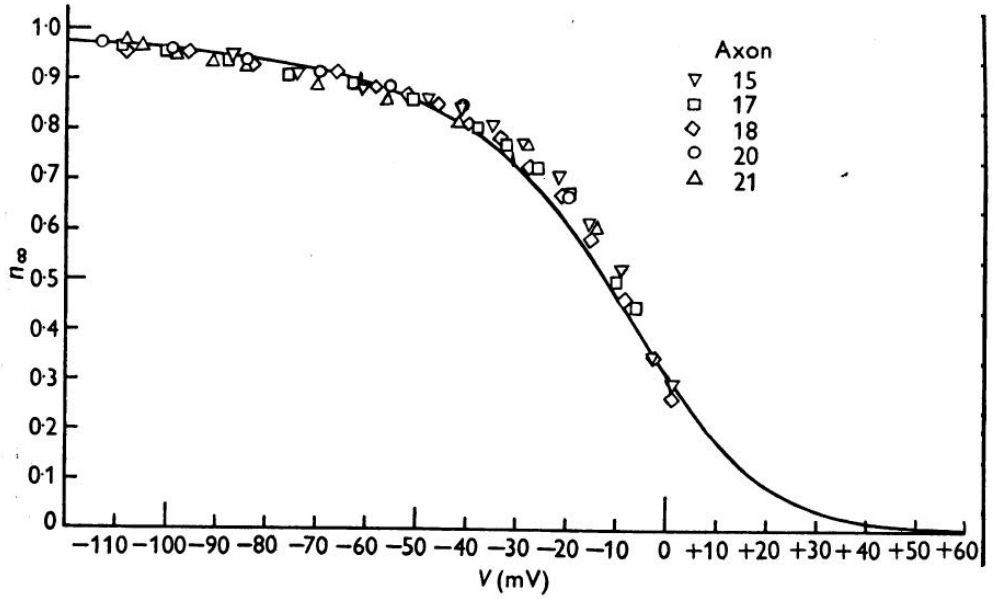
$$\alpha_h = 0.07e^{V/20} \qquad \beta_h = \frac{1}{e^{(V+30)/10}+1}$$

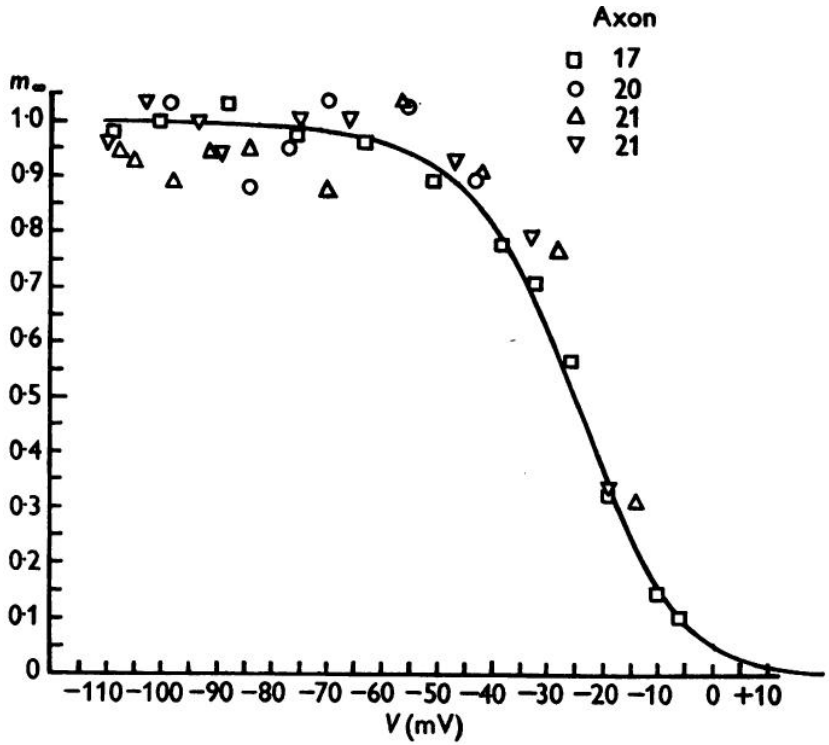
Partially computed by hand!!

Testing the equations

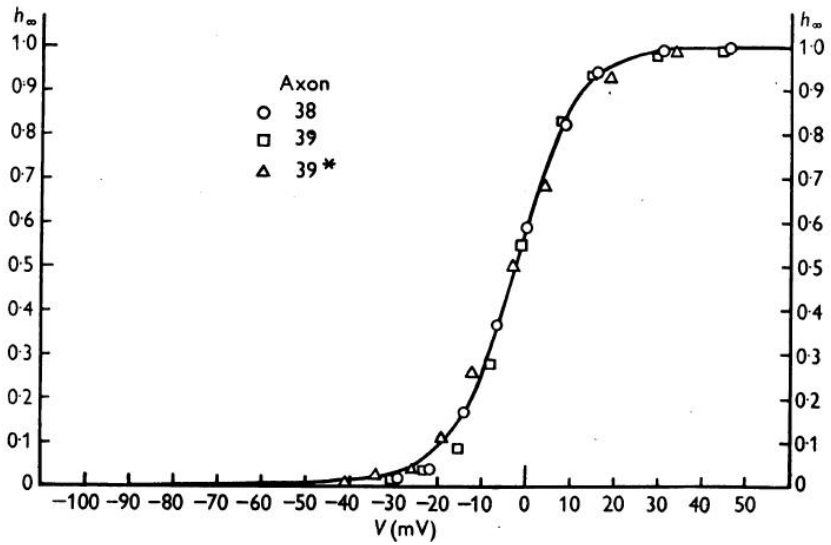
Values for $n_\infty, m_\infty, h_\infty$:
Experimental vs. calculated

(a) $n_\infty(V)$ $\rightarrow$





(b) $m_\infty(V)$



(c) $h_\infty(V)$

Time constants

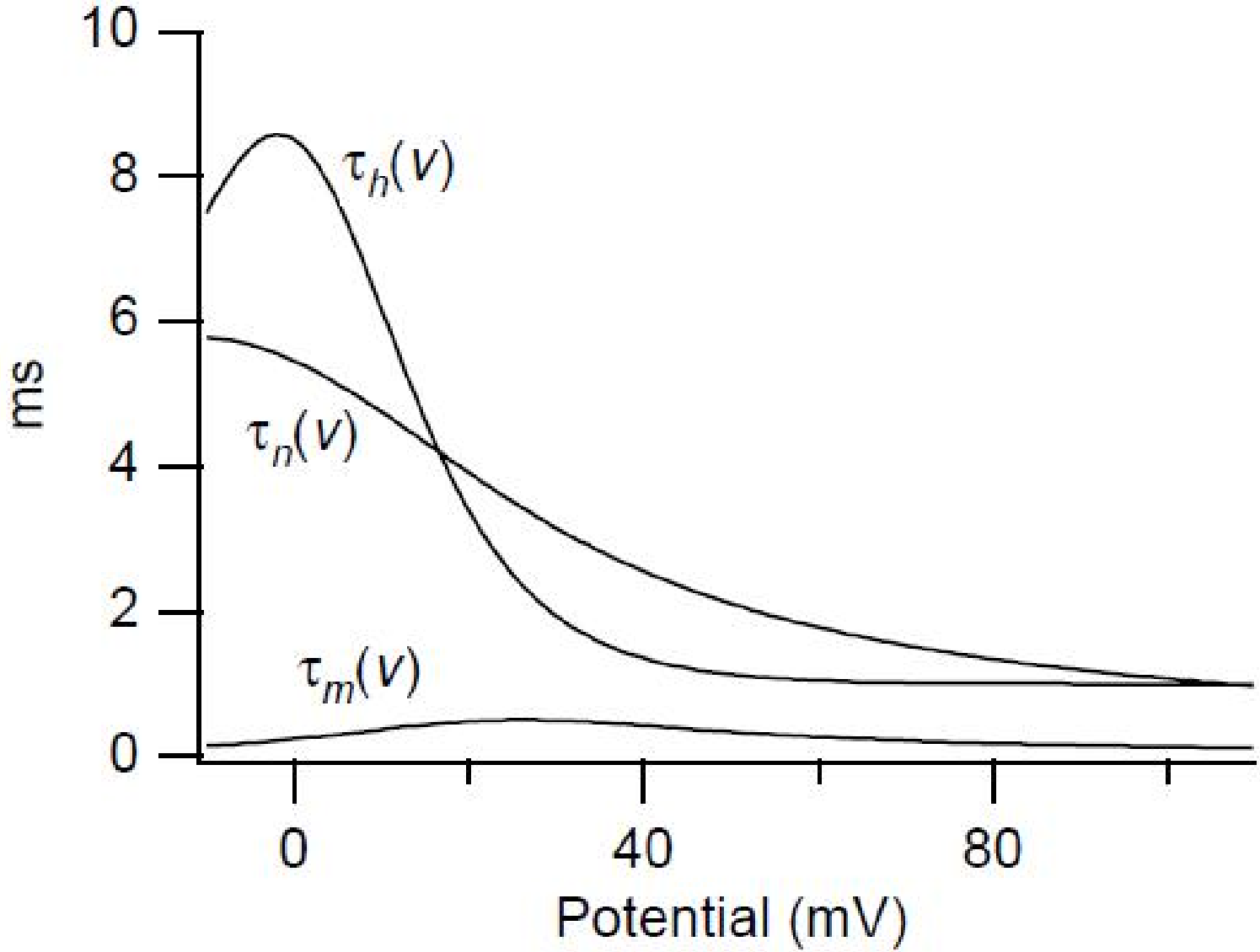


Figure: Time constants [2].

Membrane Action Potential

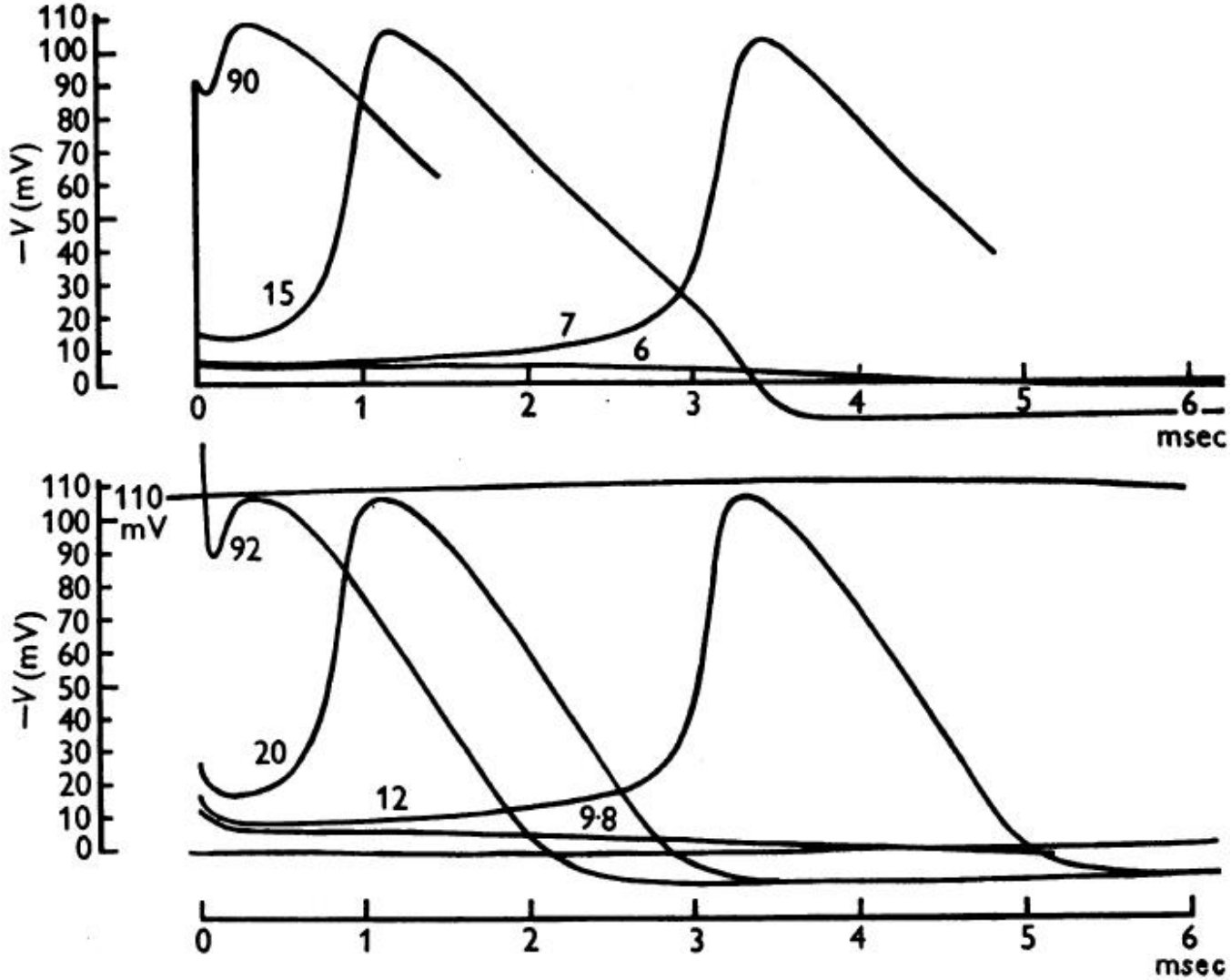
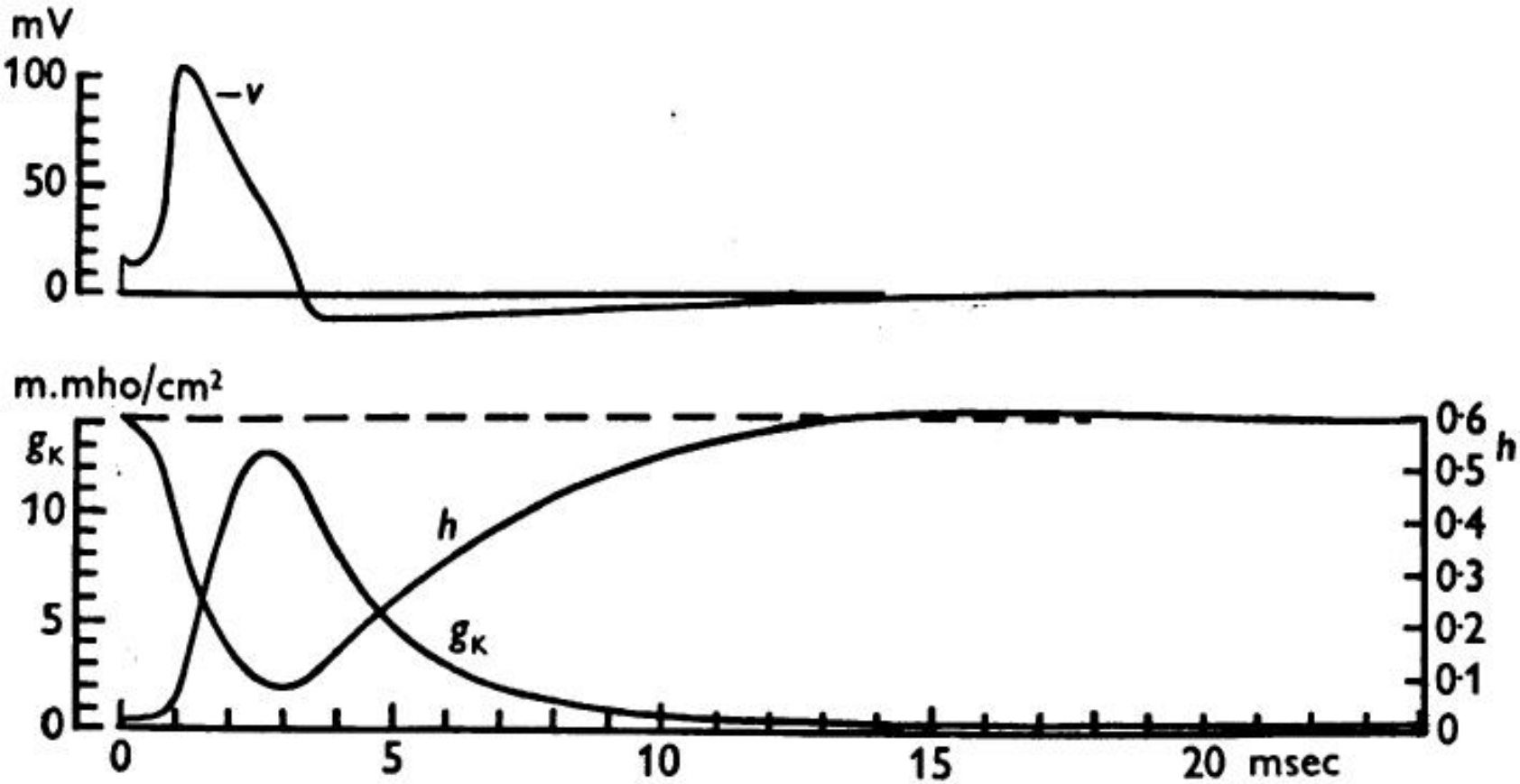


Figure: Membrane potential for various depolarisations. Top: Theory, Bottom: Experiment. [1]

Refractory Period

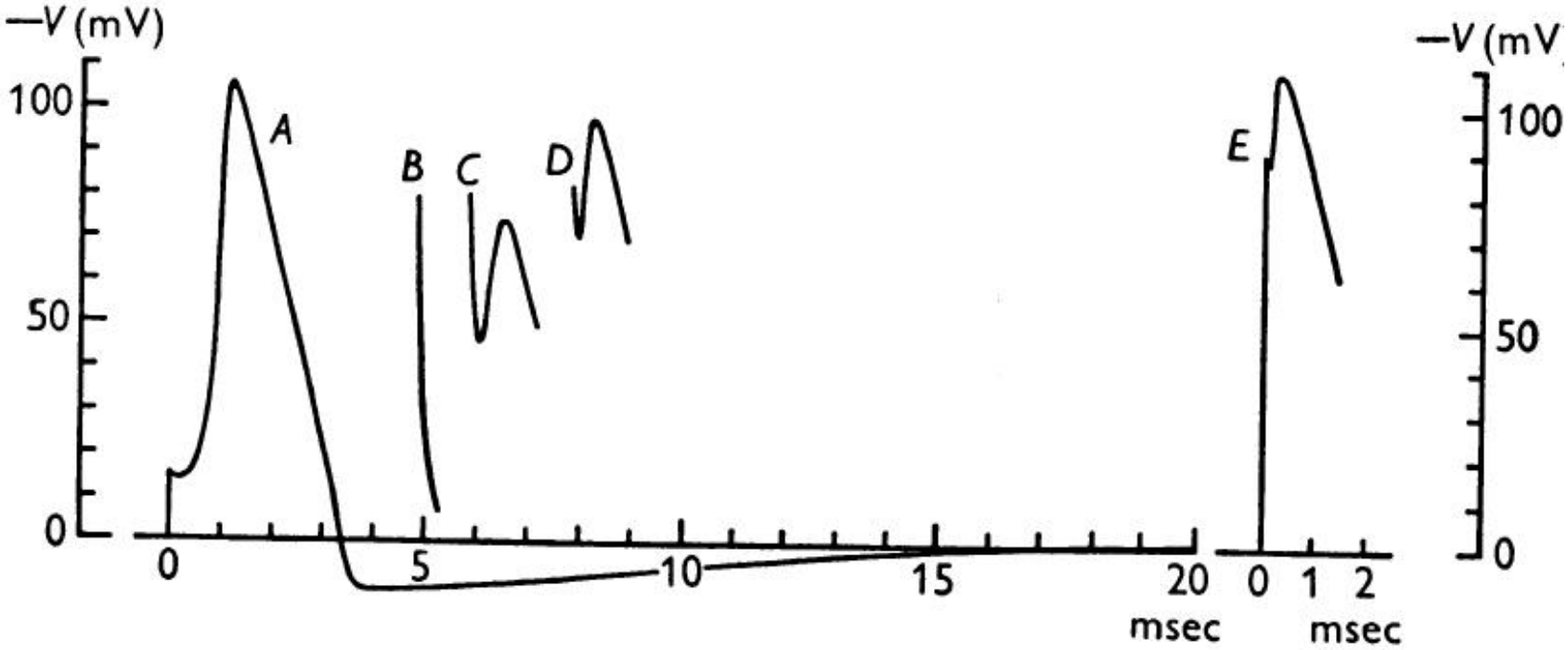
Membrane is not able to respond to another stimulus within the Refractory Period for two reasons:

- Sodium inactivation particle
- Delay in rise of potassium conductance



Absolute vs. relative Refractory Period

Application of 90mV shocks at various stages of Refractory Period



Propagation of the Action Potential

- So far: Space-Clamp $\rightarrow$ V(x,t) = V(t)
- Therefore: Current along Axon $I = 0$
- How do propagated Action Potentials look like?

Adjustment of H&H-Equation by

$$I = \frac{a}{2R}\frac{\partial^2 V}{\partial x^2}$$

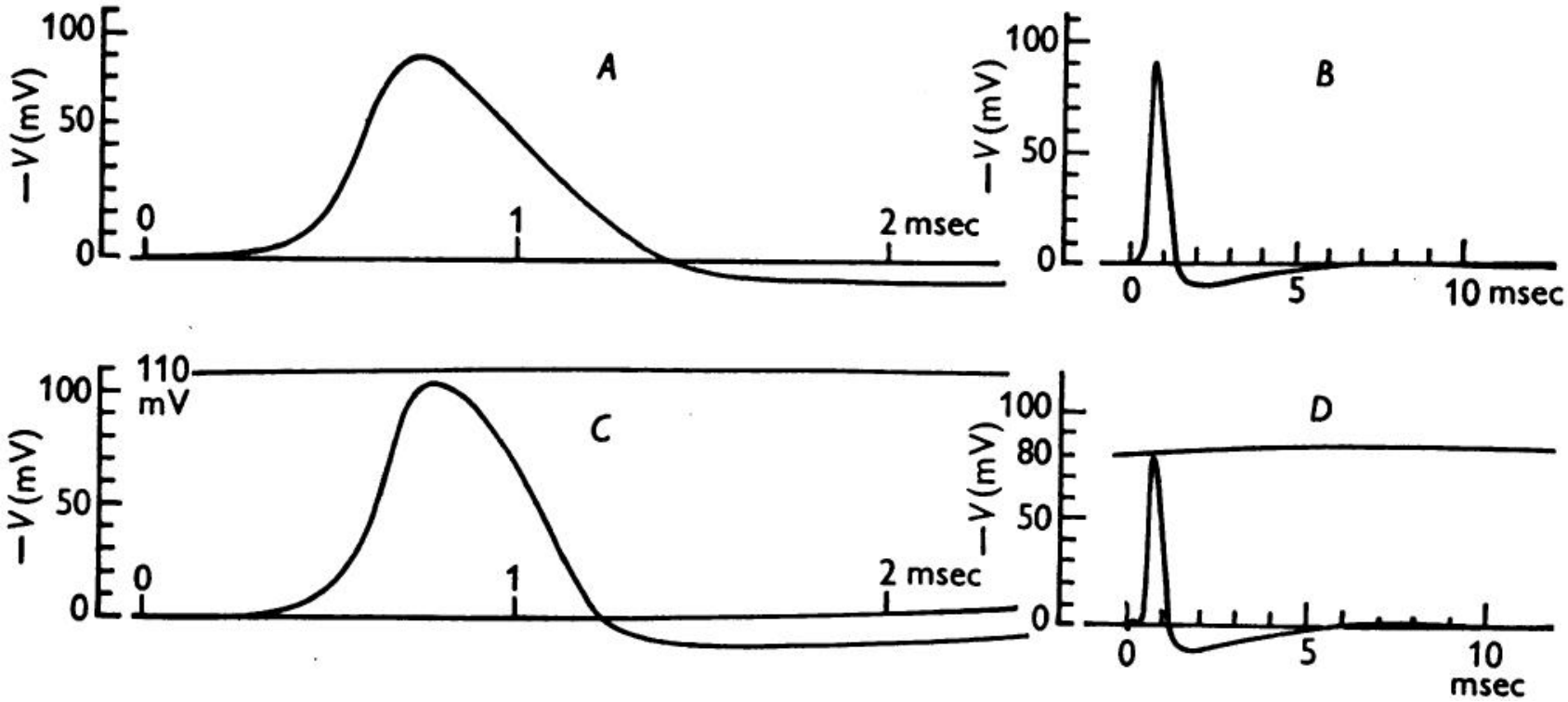
and assuming that wave travels linearly in time with velocity c

$$V(x,t) = V(x - ct) \quad \longrightarrow \quad \frac{\partial^2 V}{\partial x^2} = \frac{1}{c^2}\frac{\partial^2 V}{\partial t^2}$$

This leads to the H&H-equation:

$$\frac{a}{2Rc^2}\frac{\mathrm{d}^2 V}{\mathrm{d}t^2} = C_m\frac{\mathrm{d}V}{\mathrm{d}t} + \bar{g}_{\mathrm{K}} n^4 (V - V_{\mathrm{K}}) + \bar{g}_{\mathrm{Na}} m^3 h (V - V_{\mathrm{Na}}) + \bar{g}_{\mathrm{l}} (V - V_{\mathrm{l}})$$

Propagated Action Potential



Graphs C and D: Experimental data
Conduction velocities:

$$c_{\text{theo}} = 18,8\text{m/s}$$
$$c_{\text{exp}} = 21,2\text{m/s}$$

Table of contents

Summary

About nerve cells:

- Ionic concentrations build up equilibrium potential across membrane

Summary

About nerve cells:

- Ionic concentrations build up equilibrium potential across membrane
- Action potential after stimulus: All or nothing principle

Summary

About nerve cells:

- Ionic concentrations build up equilibrium potential across membrane
- Action potential after stimulus: All or nothing principle

How come?? $\rightarrow$ Answer given by Hodgkin & Huxley in 1952.

Summary

About nerve cells:

- Ionic concentrations build up equilibrium potential across membrane
- Action potential after stimulus: All or nothing principle

How come?? $\rightarrow$ Answer given by Hodgkin & Huxley in 1952.

Divide & conquer method

- Conduction of experiments on tiny sub-elements of the nervous system

Summary

About nerve cells:

- Ionic concentrations build up equilibrium potential across membrane
- Action potential after stimulus: All or nothing principle

How come?? $\rightarrow$ Answer given by Hodgkin & Huxley in 1952.

Divide & conquer method

- Conduction of experiments on tiny sub-elements of the nervous system
- Measuring techniques: Space and Voltage Clamp (not physiological!)

Summary

About nerve cells:

- Ionic concentrations build up equilibrium potential across membrane
- Action potential after stimulus: All or nothing principle

How come?? $\rightarrow$ Answer given by Hodgkin & Huxley in 1952.

Divide & conquer method

- Conduction of experiments on tiny sub-elements of the nervous system
- Measuring techniques: Space and Voltage Clamp (not physiological!)
- Forming a model which predicts successfully nerve behaviour in living organisms

Summary

About nerve cells:

- Ionic concentrations build up equilibrium potential across membrane
- Action potential after stimulus: All or nothing principle

How come?? $\rightarrow$ Answer given by Hodgkin & Huxley in 1952.

Divide & conquer method

- Conduction of experiments on tiny sub-elements of the nervous system
- Measuring techniques: Space and Voltage Clamp (not physiological!)
- Forming a model which predicts successfully nerve behaviour in living organisms
- Awarded with 1963 Nobel Prize in medicine and physiology

Bibliography

[1] A. F. Huxley A. L. Hodgkin. A quantitative description of membrane current and its application to conduction and excitation in nerve. *The Journal of physiology*, 4(117):500–544, 8 1952.

[2] J. Sneyd J. Keener. *Mathmatical Physiology*, volume 8. Springer, 1998.

[3] Neurolab. Tools that simplify the problem: The space clamp and the voltage clamp. http://fohs.bgu.ac.il/nia/nia2003/neurolab/appendix/simplequ.htm, 2003.

[4] J. Rinzel. Electrical excitability of cells, theory and experiment: Review of the hodgkin-huxley foundation and an update. *Bull. Math. Biol.*, 52:5–23, 1990.

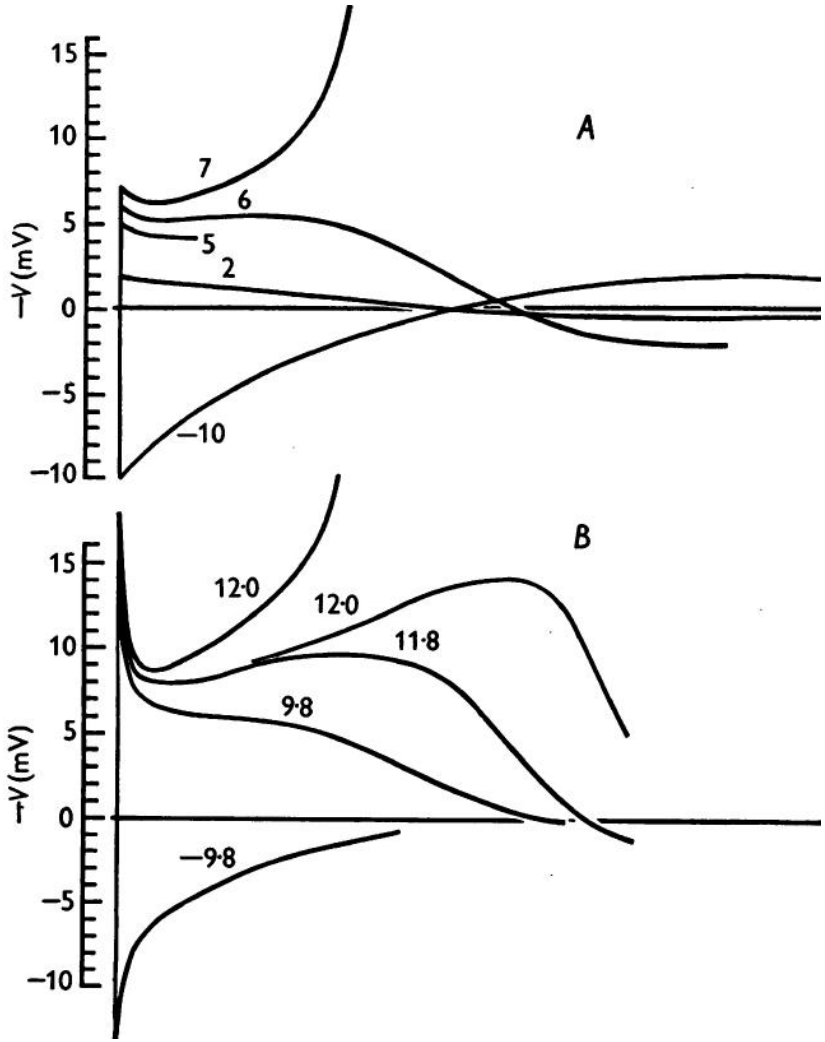
BACKUP

Excitation

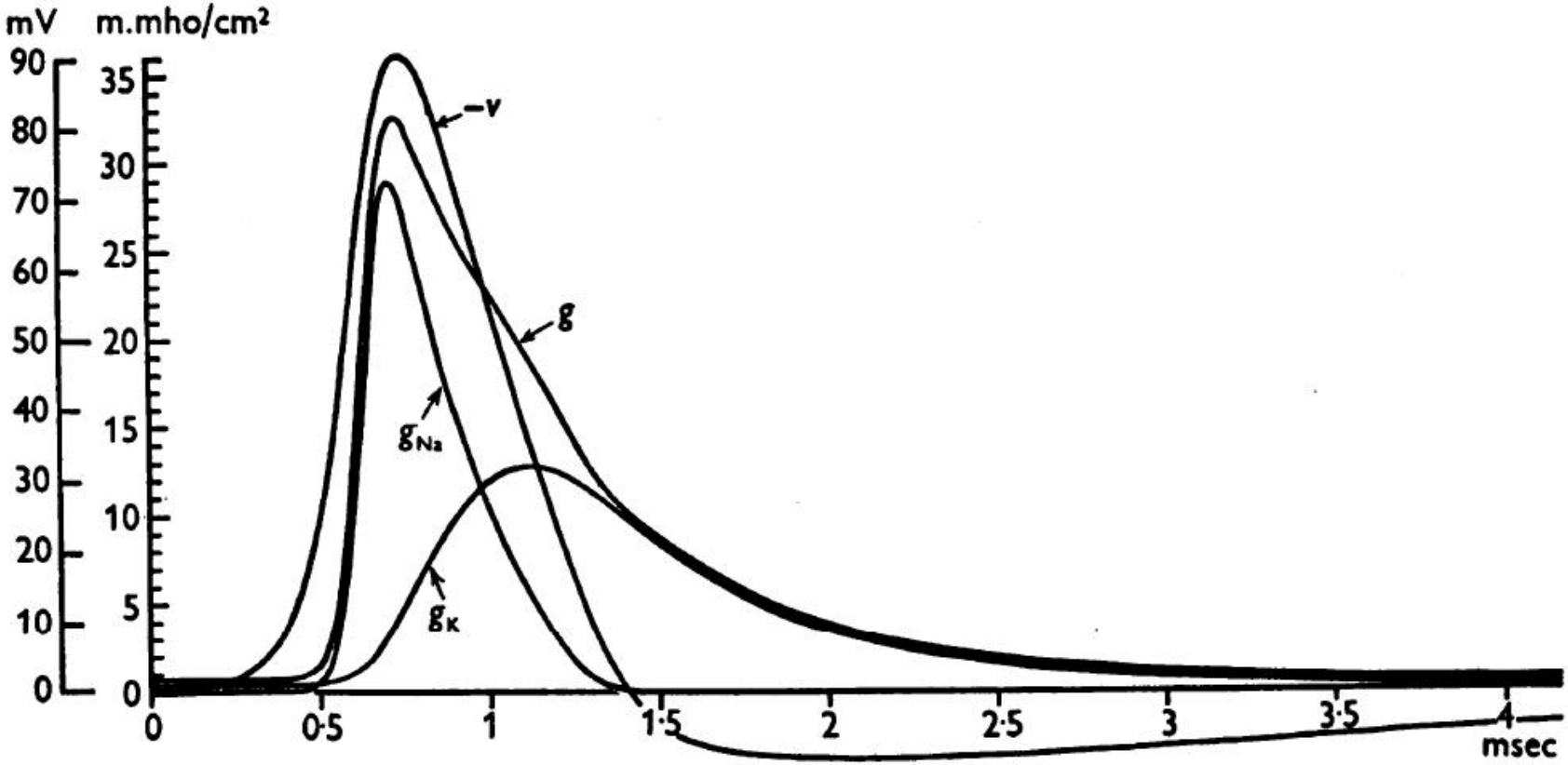
Threshold

Note:

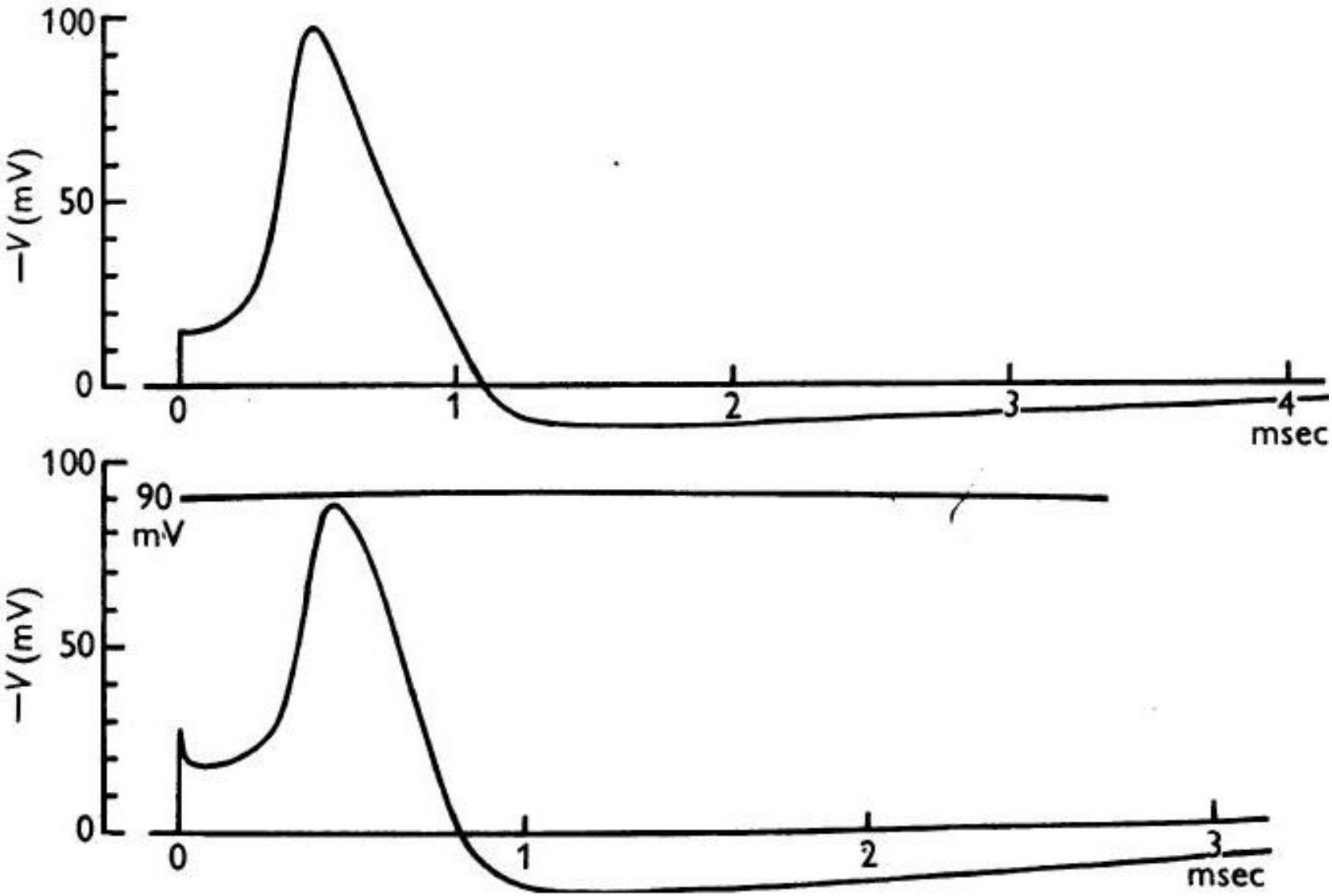
- Threshold ($T = 6°C$):
  Theory $\approx 6\mathrm{mV}$,
  Experiment $\approx 8\mathrm{mV}$
- Difference reasonable since threshold depends on leak conductance
- Refractory period never the less!
- Interesting:
  Accommodation takes place



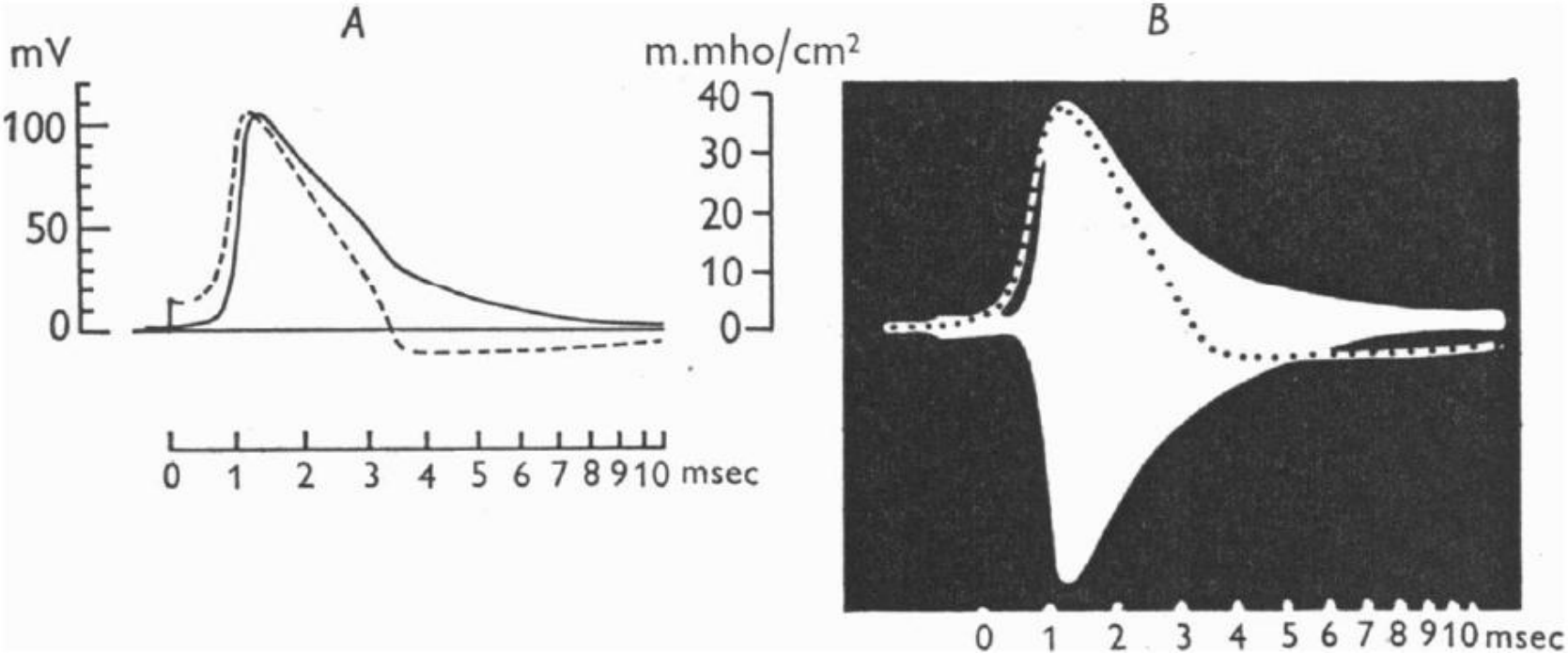
Propagated Action Potential



Membrane Action Potential at high Temperature



Propagated Action Potential

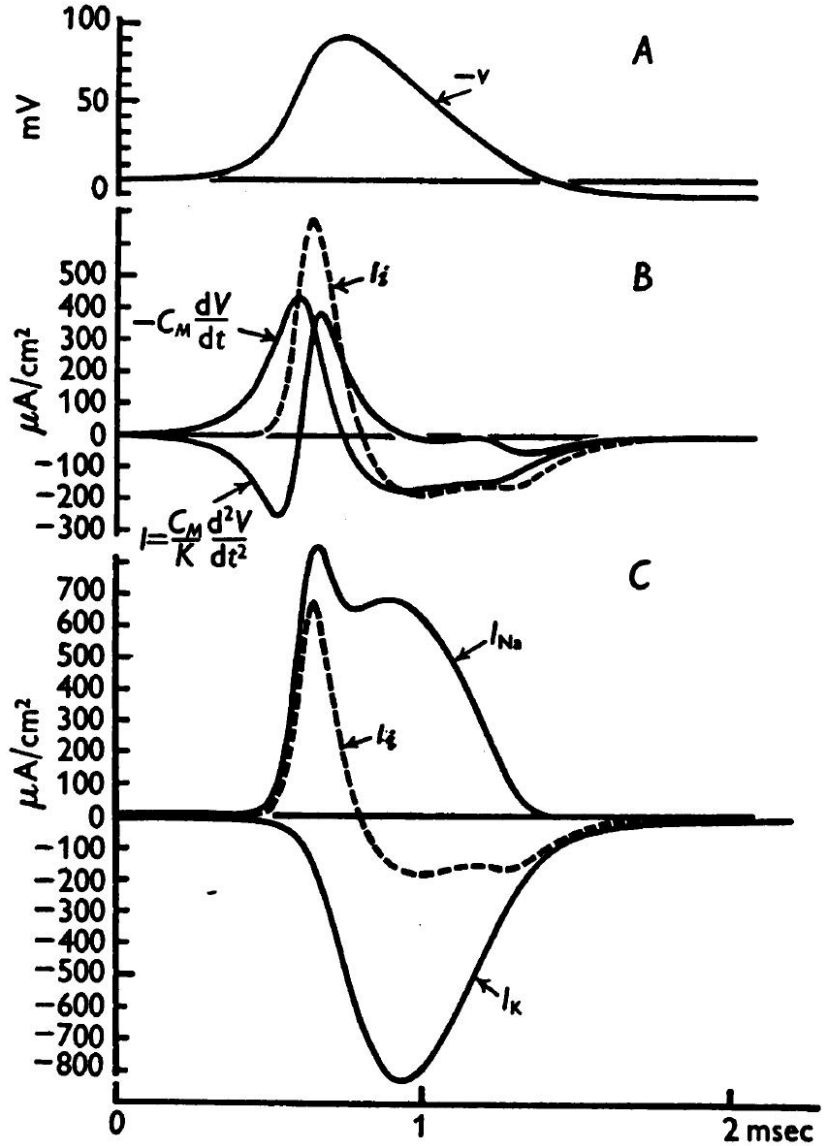


Ionic movements

Ionic Current is composed of:

$$I_{\text{Ion}} = -C_m \frac{\mathrm{d}V}{\mathrm{d}t} + \frac{a}{2Rc^2} \frac{\mathrm{d}^2 V}{\mathrm{d}t^2}$$

The net flux can be obtained by integration over the whole impulse.



Ionic fluxes

Ionic movements during an propagated Action Potential [Quelle].
All units in [$\mu\mu\mathrm{mole}/\mathrm{cm}^2$].

Ion	Na^+ Influx	Na^+ Outflux	Na^+ Net entry	K^+ Influx	K^+ Outflux	K^+ Net entry
Theo.	5,42	1,09	4,33	1,72	5,98	-4,26
Exp.	10,3	6,6	3,7	0,39	4,7	-4,3

Experiments conducted by Keynes [Quelle]!!

Voltage-Clamp technique

I_{app} is adjusted that $V = \text{constant} \rightarrow \dot{V} = 0$

$$\longrightarrow \; g(t)(V - V_{\text{eq}}) = I_{\text{app}}(t)$$

$$\longrightarrow \; g(t) = \frac{I_{\text{app}}(t)}{V - V_{\text{eq}}}$$

Conductance only varies with time!

Boundary conditions:

- Resting value: $n(t = 0) = n_0$ and $n(t \to \infty) = n_\infty$
- Stationary value: $n(t \to \infty) = n_\infty$
- Time constant: τ_n

with

$$n_0 = \frac{\alpha_{\mathrm{n},0}}{\alpha_{\mathrm{n},0} + \beta_{\mathrm{n},0}}, \quad n_\infty = \frac{\alpha_{\mathrm{n}}}{\alpha_{\mathrm{n}} + \beta_{\mathrm{n}}}, \quad \tau_n = \frac{1}{\alpha_{\mathrm{n}} + \beta_{\mathrm{n}}}$$

gives simple DGL:

$$\tau_n \dot{n} = n_\infty - n$$

With solution:

$$\boxed{n(t) = n_\infty - (n_\infty - n_0)e^{-t/\tau_n}}$$

The same can be done for Sodium particles: Just replace n by m,h

Fitting procedure

Fitting of the experimental data points for fixed depolarisations gives:

- τ_w and w_∞ that gave the best fit for each Voltage step (for $w = n, m, h$)
- Thereafter: V-dependent rate constants: $\alpha_w(V)$, $\beta_w(V)$

$$\alpha_n = \frac{0.01(V+10)}{e^{(V+10)/10} - 1} \qquad \beta_n = 0.125e^{V/80}$$

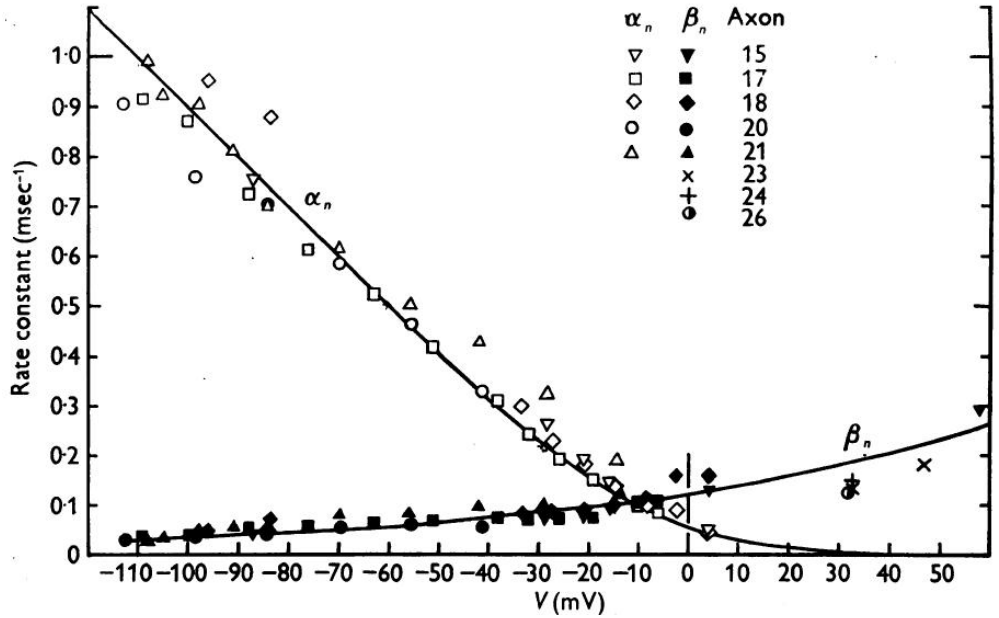
$$\alpha_m = \frac{0.1(V+25)}{e^{(V+25)/10} - 1} \qquad \beta_n = 4e^{V/18}$$

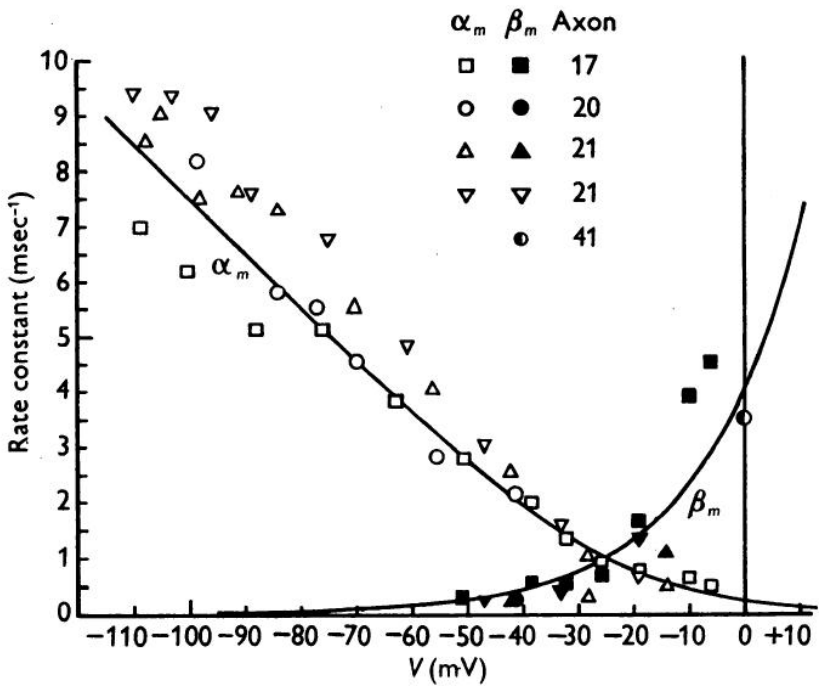
$$\alpha_h = 0.07e^{V/20} \qquad \beta_n = \frac{1}{e^{(V+30)/10} + 1}$$

Computed by hand!!

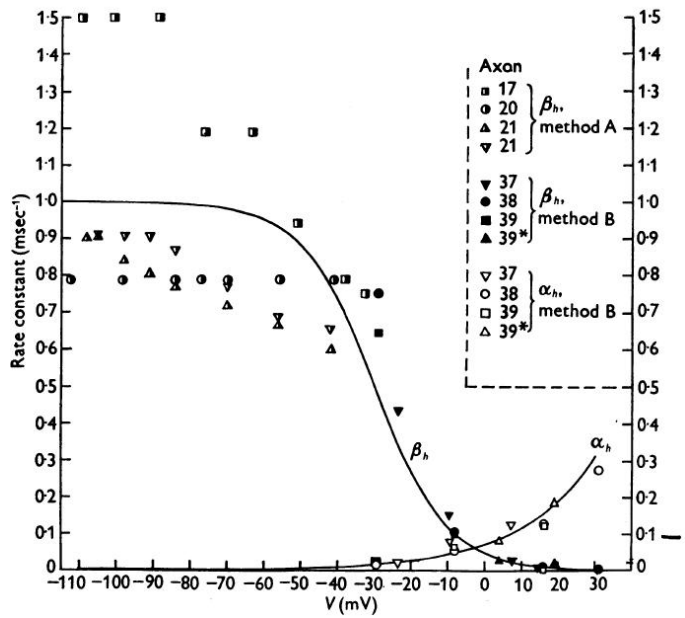
Rate Constants

(a)
K^+ activating particle (n) $\rightarrow$





(b) Na^+ activating particle (m)



(c) Na^+ inactivating particle (h)