Dynamics of Neural Systems

Membrane Channels / Hodgkin-Huxley Equation

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Overview

- Active ion channels
- Hodgkin Huxley equation

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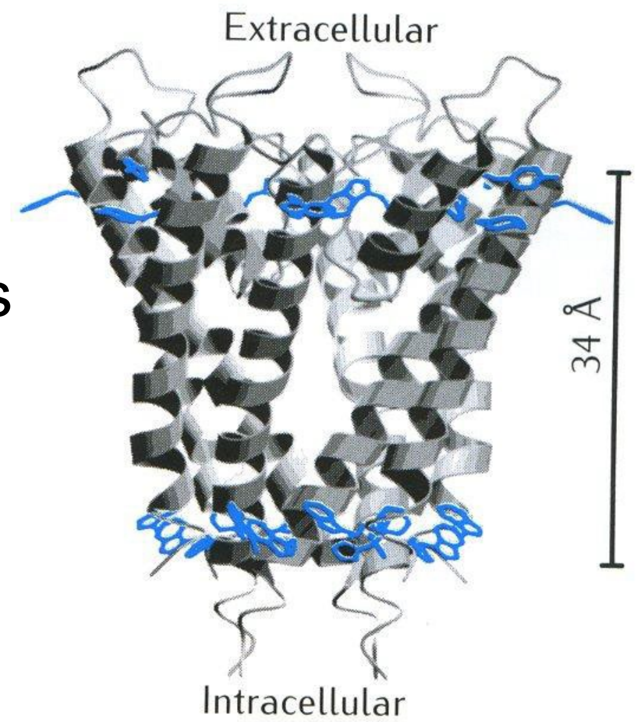
- Active ion channels
- Hodgkin Huxley equation

Active ion channels I

- More than 100 types of ion channels known.
- Typically, multiple types of channels in the same membrane (dependent on neuron type).
- 3D structure can be investigated by X-ray crystallography.

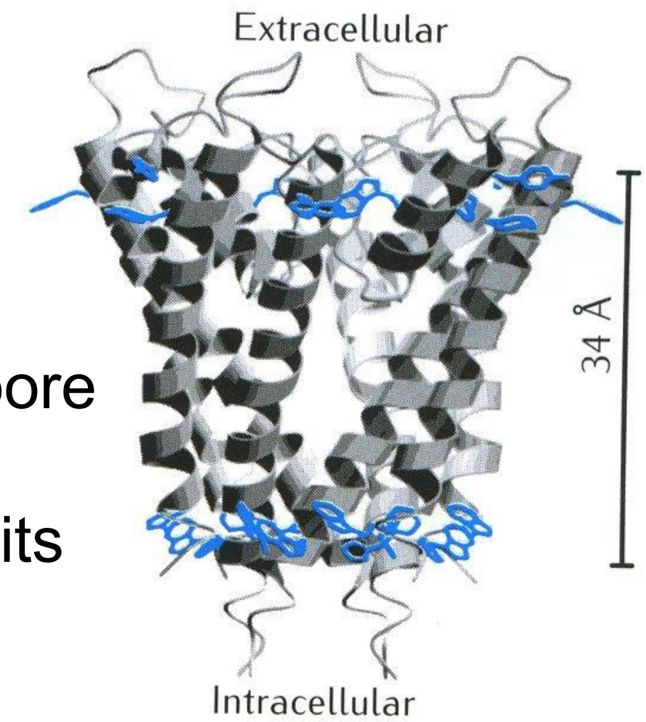
KcsA potassium channel



Active ion channels I

- One or multiple protein **subunits**:
  principal subunits: form membrane pore
  auxiliary subunits: modulate function of principal subunits
  multimers: channels with multiple principal units
  homomer: principal units all identical
  heteromer: different principal subunits

KcsA potassium channel

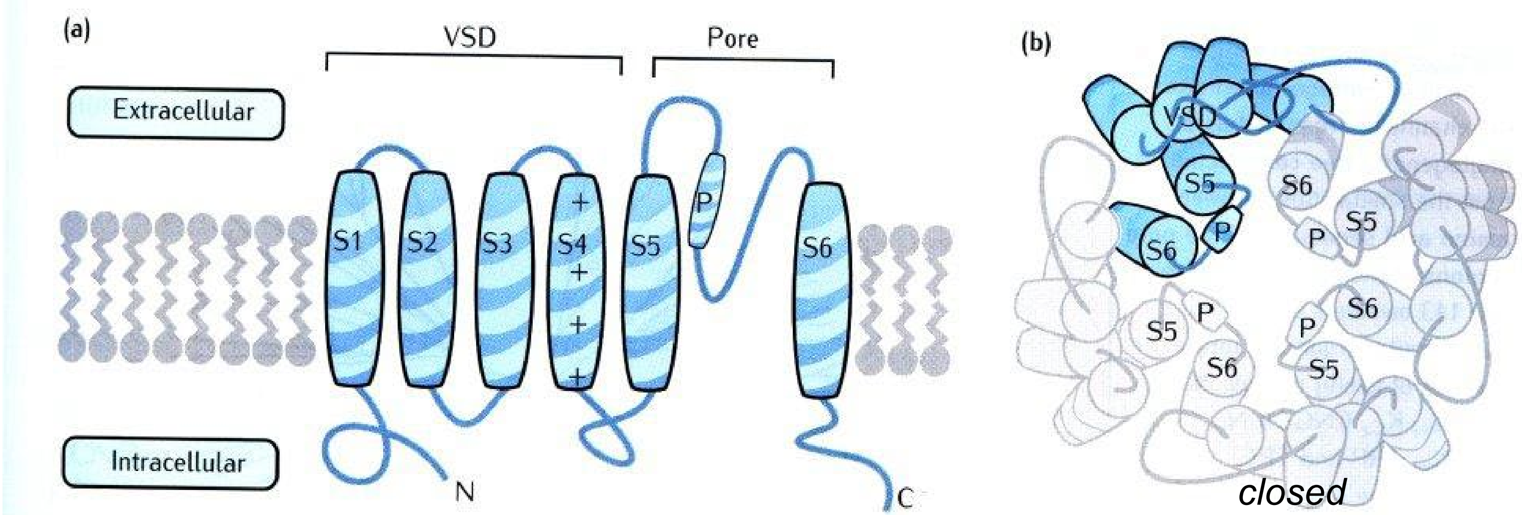


Active ion channels II

Example:

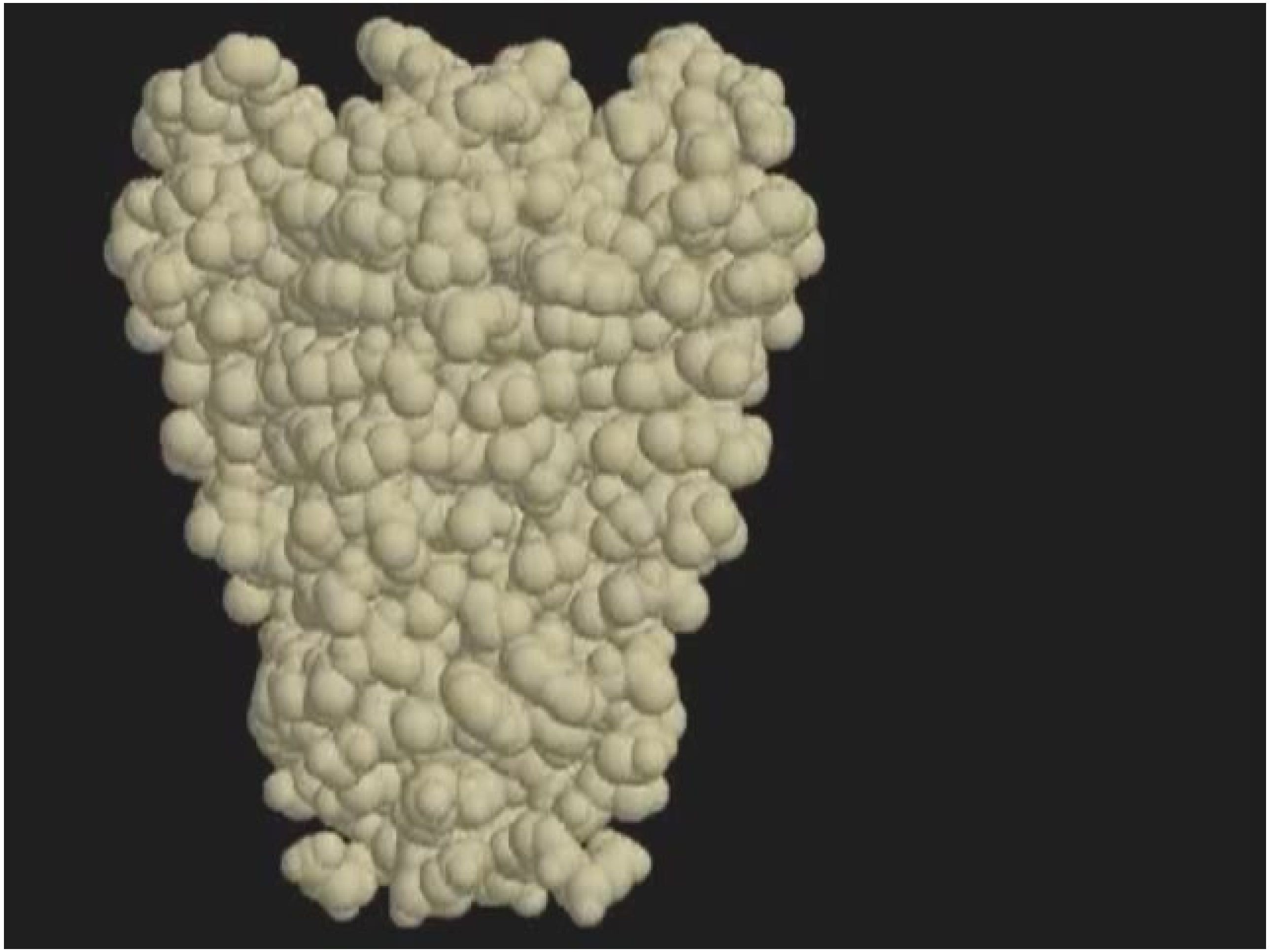
- Secondary structure: α-helices + connecting loops
- Membrane pore: segments S5-6 and P
- Voltage-sensitive region (VSD): segments S1-4
- S4 contains gating charges that experience force through membrane potential.

Secondary and tertiary structure of voltage-gated potassium channel



Active ion channels III

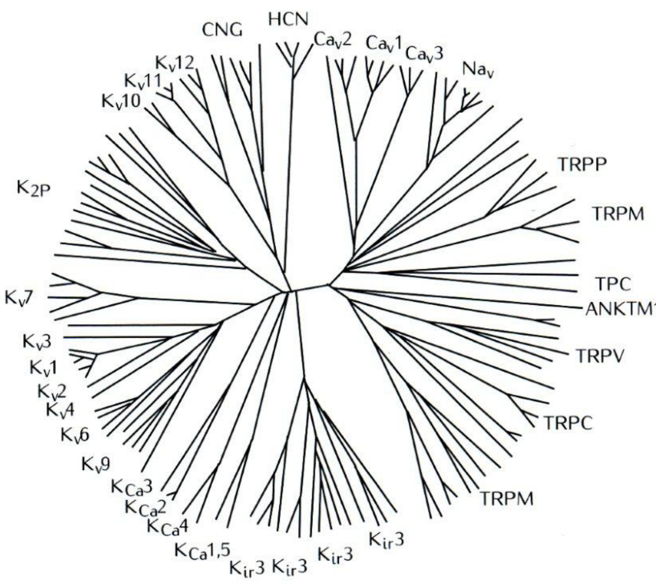
Function principle (other type of potassium channel)



Active ion channels IV

- Since 1980 sequencing of related genes; **knock-out** studies showing selective deficits; **transfection** with DNA or RNA to ‘build channels in’.
- Generation of family trees based on related DNA sequences; provides basis for systematic nomenclature.

Family tree of mammalian voltage-gateded channels



Active ion channels IV

- Today often related membrane currents are classified according to systematic names of channel.
- Activation by voltage, Ca^{2+}, or intracellular ligands and second messengers.

Table 5.1 Families of channel genes and their corresponding proteins

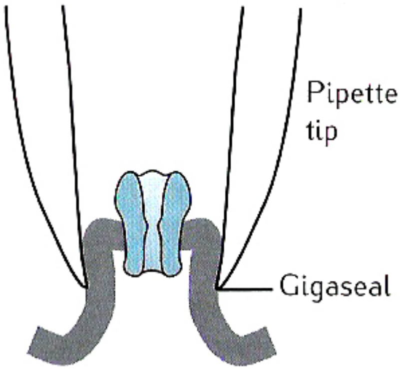
Human gene prefix	IUPHAR protein prefix	Ion selectivity	Activators
SCN	Na_v	Na^+	V↑
CACN	Ca_v	Ca^{2+}	V↑
KCN	K_v	K^+	V↑
KCNA	K_v1	K^+	V↑
KCNB	K_v2	K^+	V↑
KCNC	K_v3	K^+	V↑
KCND	K_v4	K^+	V↑
KCNQ	K_v7	K^+	V↑
KCNMA	$K_{Ca}1$	K^+	Ca^{2+}, V↑
KCNN	$K_{Ca}2$	K^+	Ca^{2+} ↑
KCNJ	K_{ir}	K^+	G-proteins, V↑
KCNK	K_{2P}	K^+	Leak, various modulators
HCN	HCN	K^+, Na^+	V↓
CNG	CNG	Ca^{2+}, K^+, Na^+	cAMP, cGMP
TRP	TRP	Ca^{2+}, Na^+	Heat, second messengers
CLCN	–	Cl^-	V↓, pH
CLCA	–	Cl^-	Ca^{2+}

Data from IUPHAR *Compendium of Voltage-Gated Ion Channels* (Catterall *et al.*, 2005a, b; Gutman *et al.*, 2005; Wei *et al.*, 2005; Kubo *et al.*, 2005; Goldstein *et al.*, 2005; Hofmann *et al.*, 2005; Clapham *et al.*, 2005; Jentsch *et al.*, 2005).

Experimental technique I

- **Patch clamping** as fundamental technique to investigate individual channels; recordings with low noise.
- Invented by Neher & Sakmann (1976); Nobel prize 1991.
- Thin glass pipette pressed against side of cell; high resistance seal ('gigaseal') around very small patch of the membrane.

Patch clamp technique



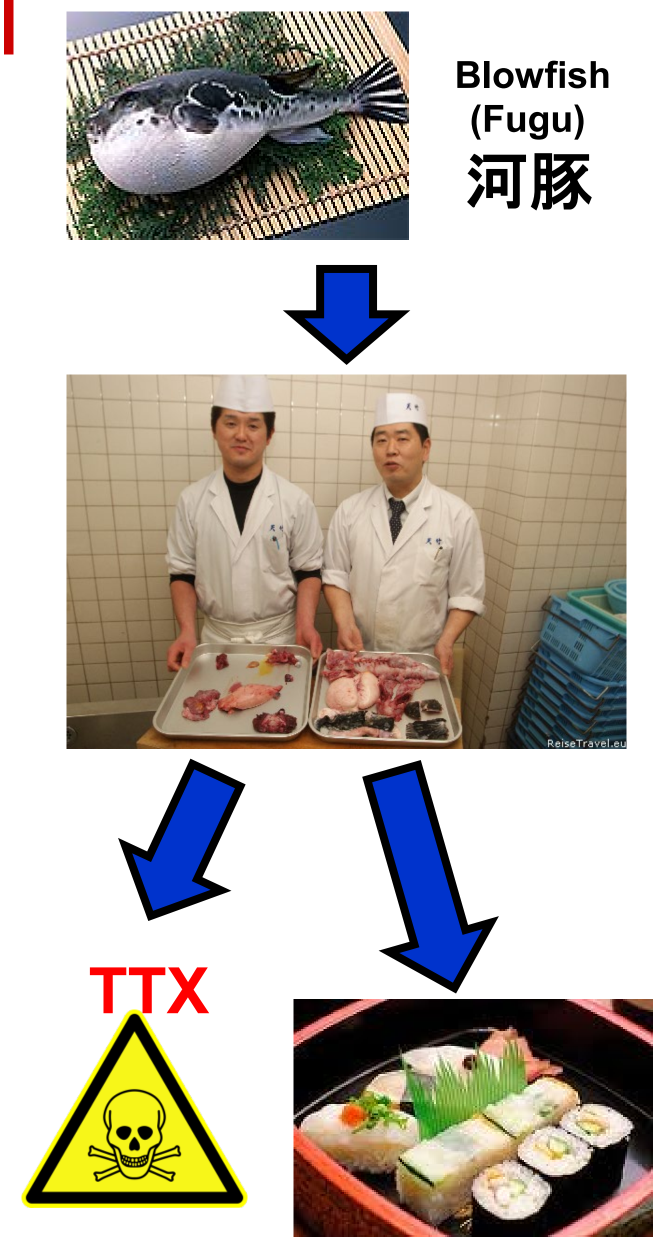
E. Neher

B. Sakmann

Experimental technique II

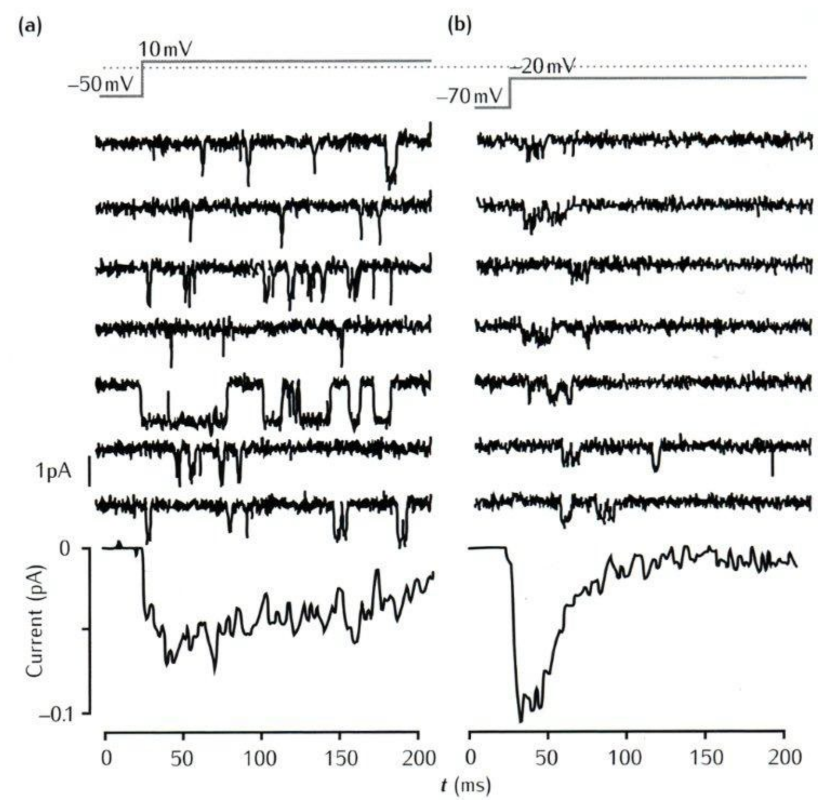
- Individual channels types can be **blocked** pharmacologically (e.g. Na^+ channels by the poison tetrodotoxin (TTX)).
- Alternatively, ions in the extracellular medium can be replaced by others that cannot passage the membrane.

Tetrodotoxin (TTX)



Channel activation

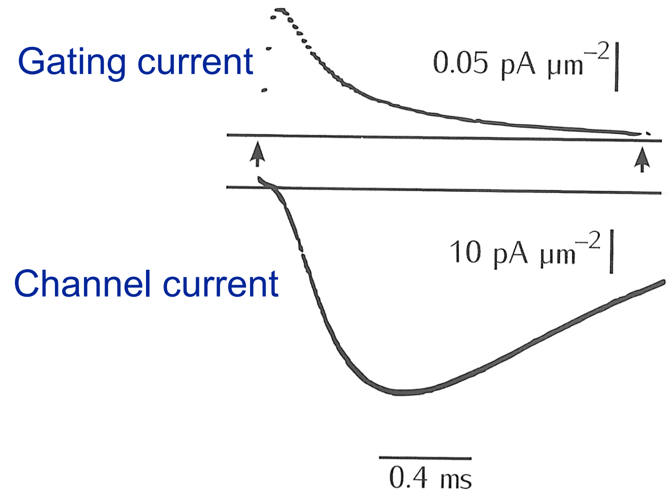
- 'Binary' activation; channel current jumps between zero and a few pA.
- Opening and closing times random.
- Averaging over many trials: systematic behavior of average current (~ P(channel open)).
- Channels with long-lasting (a) and transient (b) currents.



Channel activation

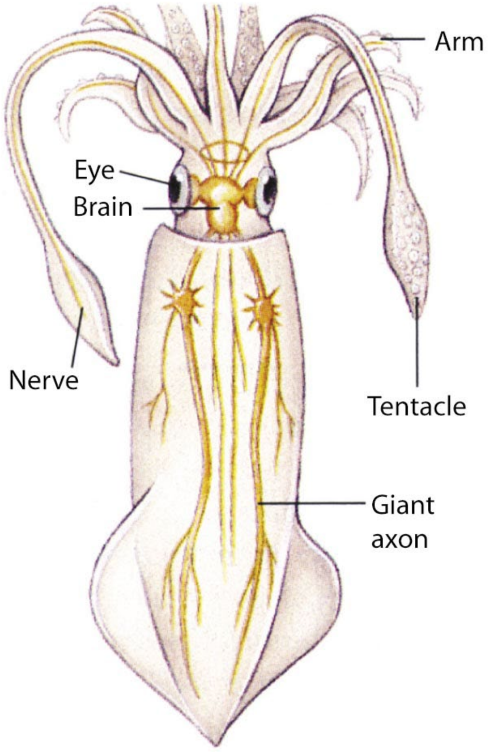
- Movement of the gating charges results in a (very small) gating current.

Gating current



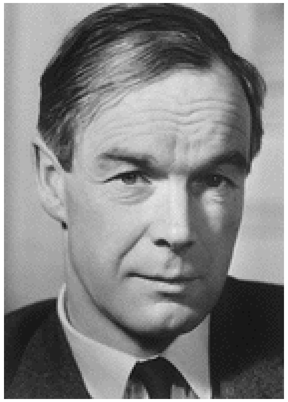
Overview

- Active ion channels
- Hodgkin Huxley equation

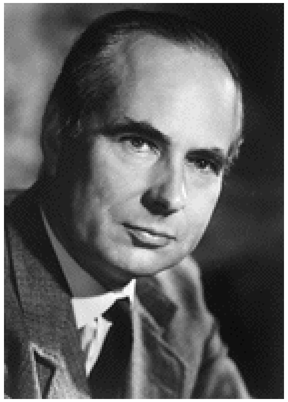


Theory for action potentials

- Central mechanism for the active propagation of signals in the CNS (last lectures: focusing on passive membrane properties).
- First quantitative theory developed by Hodgkin and Huxley (1952), partially together with Katz.
- Nobel prize 1963, shared with Eccles for his work on synaptic transmission.



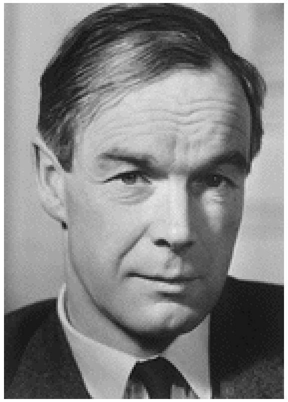
A.L. Hodgkin



A.F. Huxley

Theory for action potentials

- Intracellular recordings of the squid giant axon.
- Quantitative mathematical model: **Hodgkin Huxley (HH) equation**.
- Basic methodology still relevant today.



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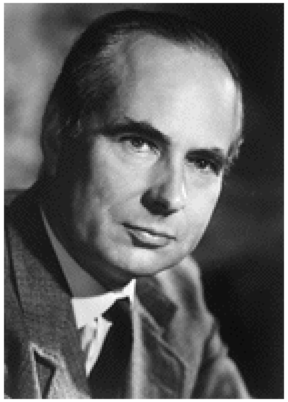

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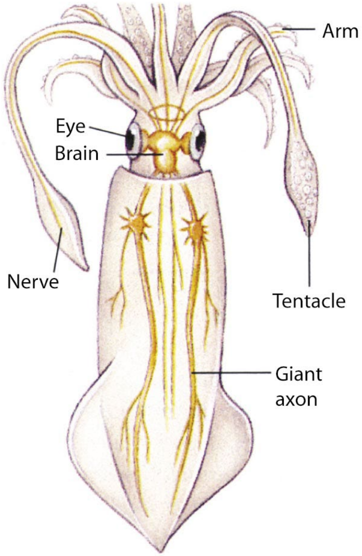
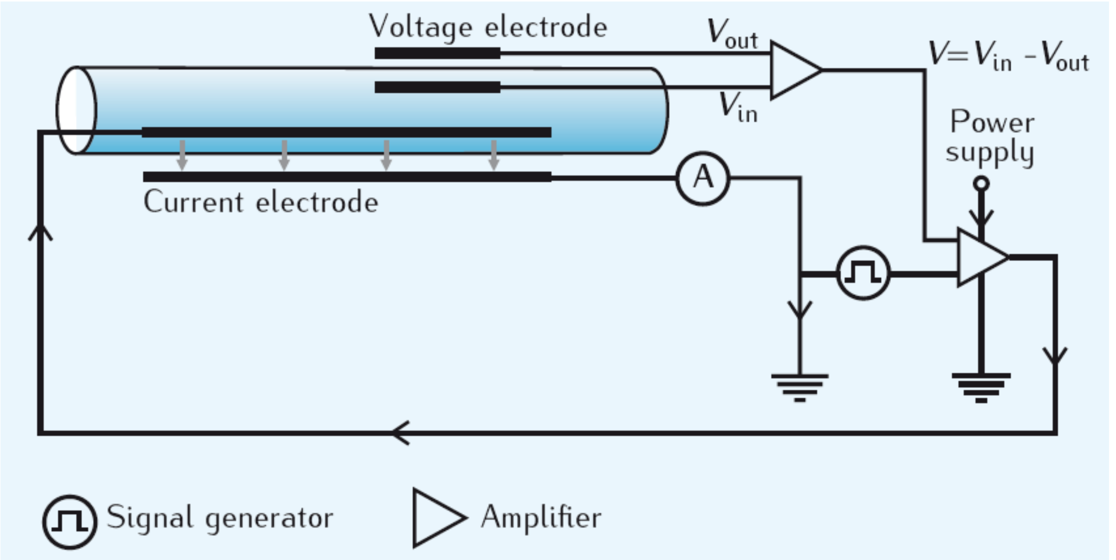


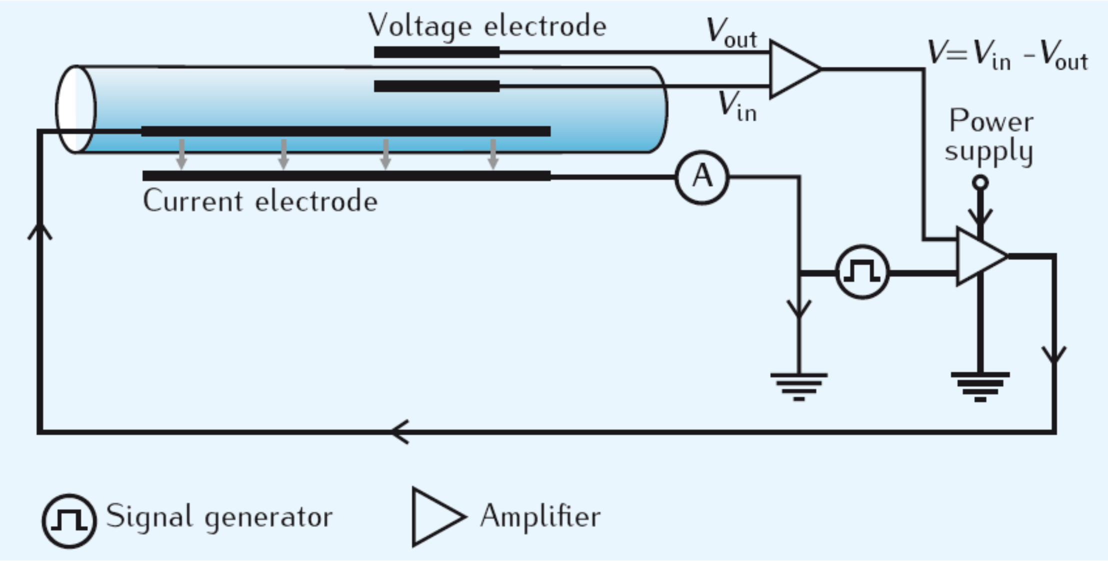
Voltage clamp technique

- Allows to study nonlinear dependence of current on membrane potential; developed by Cole and Marmont (1949).
- Membrane voltage clamped to a constant value.
- Implies $\mathrm{d}V / \mathrm{d}t = 0 \Rightarrow$ Membrane capacitor can be ignored; ion flow measured directly.
- Control loop that injects current that makes the membrane voltage V equal to external reference voltage V_{ref}.



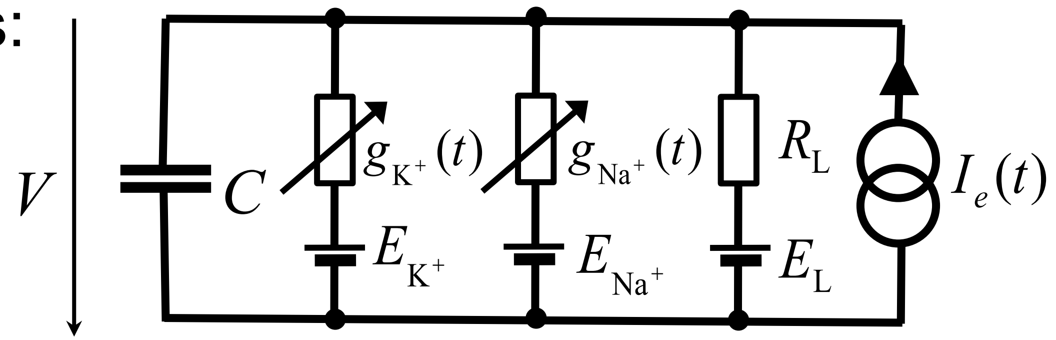
Voltage clamp technique

- Hodgkin and Huxley used very long electrodes along the axon to ensure equal potential along whole axon ('space clamp').



Basic structure of the model

- Single compartment model with three types of ions:
  - Potassium (K^+)
  - Sodium (Na^+)
  - Leak current (mainly Cl^-)



- Differential equation:

$$\boxed{C\frac{\mathrm{d}V}{\mathrm{d}t}+g_{K^+}(V)\big(V(t)-E_{K^+}\big)+g_{Na^+}(V)\big(V(t)-E_{Na^+}\big)+g_L\big(V(t)-E_L\big)=I_e(t)}$$

- For voltage clamp capacitor can be neglected.
- Measurement of g_i for different values of V by fitting of the individual ion currents by the relationship:

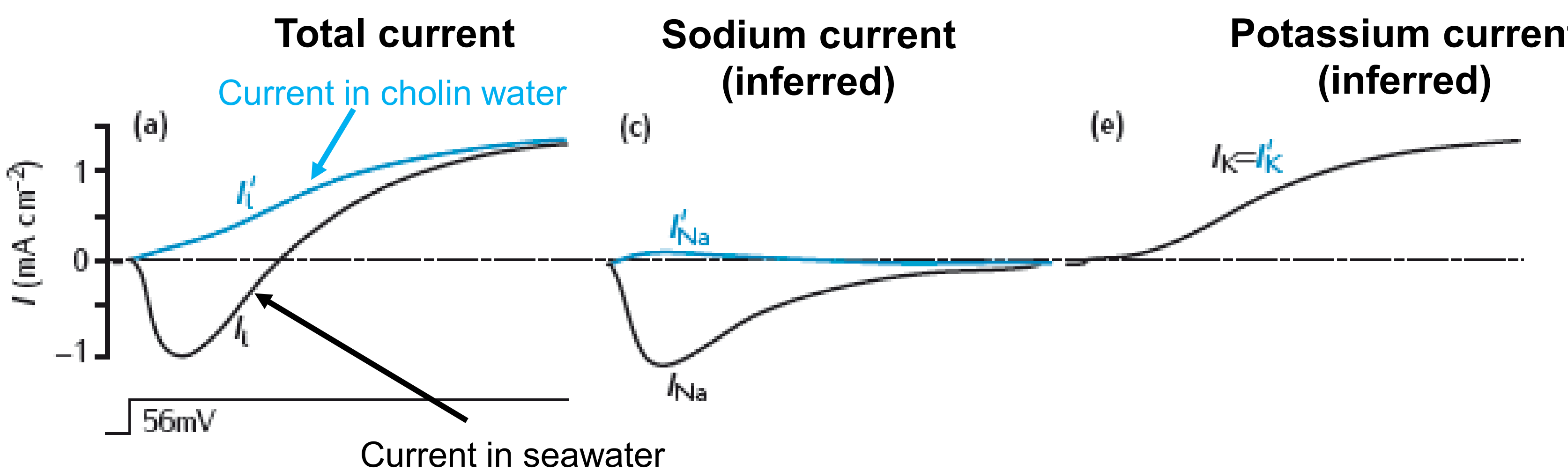
$$\boxed{g_i(V)\big(V(t)-E_i\big)=I_i}$$

Ion substitution method

- Total current is sum of ion flows:

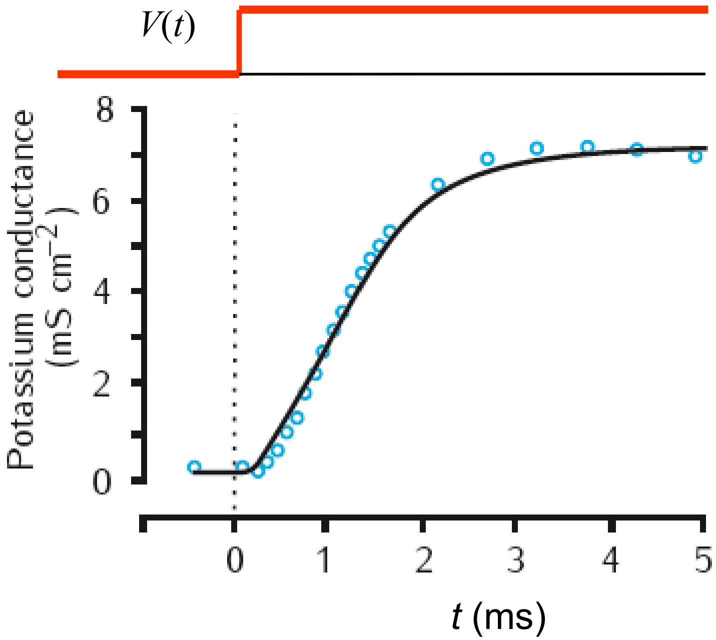
$$\boxed{I_{\mathrm{e}}(V) = I_{\mathrm{K}^+}(V) + I_{\mathrm{Na}^+}(V) + I_{\mathrm{L}}(V)}$$

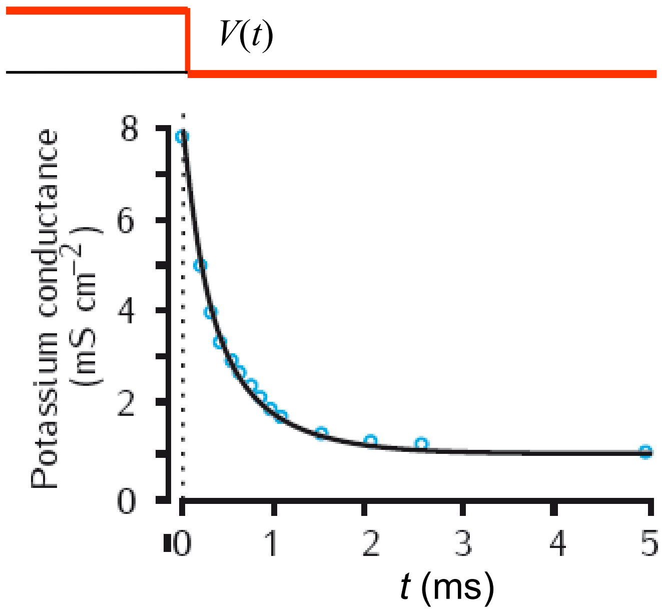
- Isolation of sodium current by replacing sodium in sea water by choline (does not permeate membrane).
- Leak current estimated by clamping voltage to reversal potential of K^+; remaining current is caused by Cl^- and other ions.



Potassium current I

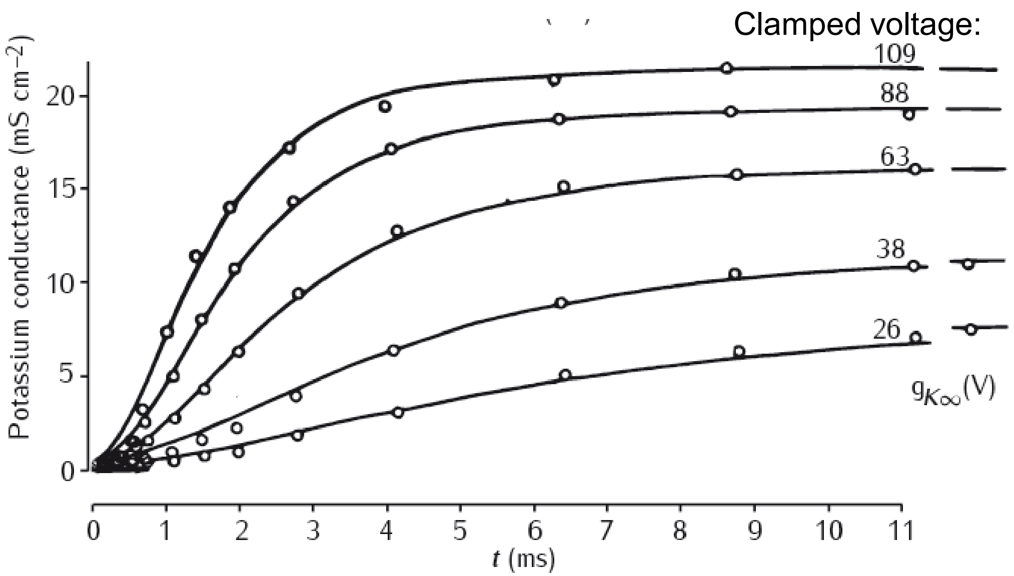
- Potassium conductance raises to constant level that is determined by V.
- Depolarization increases g_{K^+} (**activation**).
- After voltage goes back decay of conductance with faster time constant (**de-activation**).





Potassium current II

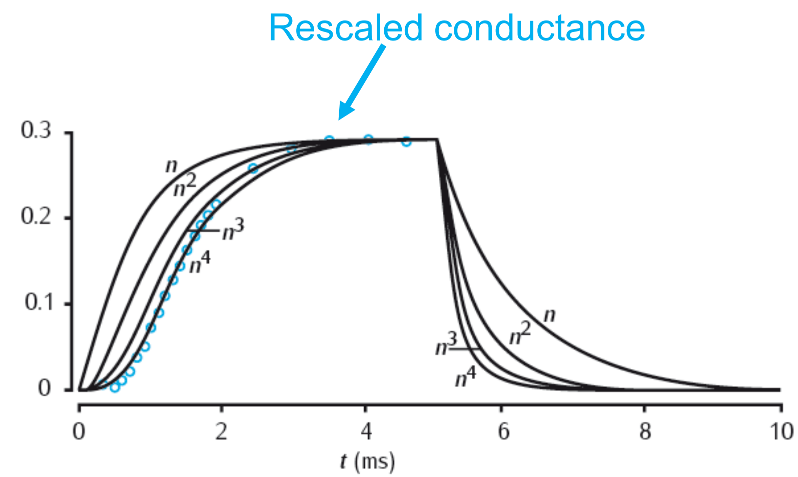
- Maximum potassium conductance $\bar{g}_{K^+}$ increases with clamped voltage V.
- Speed of increase increases (effective time constant decreases) with clamped voltage V.
- Model: $\boxed{g_{K^+} = \bar{g}_{K^+} n^4}$
- Interpretation by HH:
  Four 'gating particles' must be in open state;
  n: probability that one
  is in open state
- Modern theory: multiple independent conformation changes, each with probability n necessary to open the channel pore.



Potassium current III

- Hodgkin and Huxley postulated a **kinetic equation** for the ‘particle open probability’ n:

$$\boxed{\frac{\mathrm{d}n}{\mathrm{d}t} = \alpha_n(1-n) - \beta_n n \quad \Leftrightarrow \quad \frac{\mathrm{d}n}{\mathrm{d}t} = \frac{n_\infty - n}{\tau_n}}$$



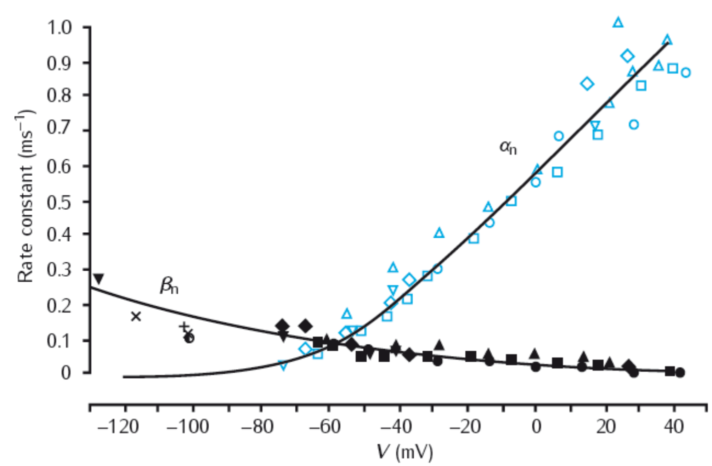
- By fitting data by the solution of this DEQ and the exponent of n^k the parameters α_n and β_n were fitted for different values of the voltage V.

- Fitted voltage relationships:

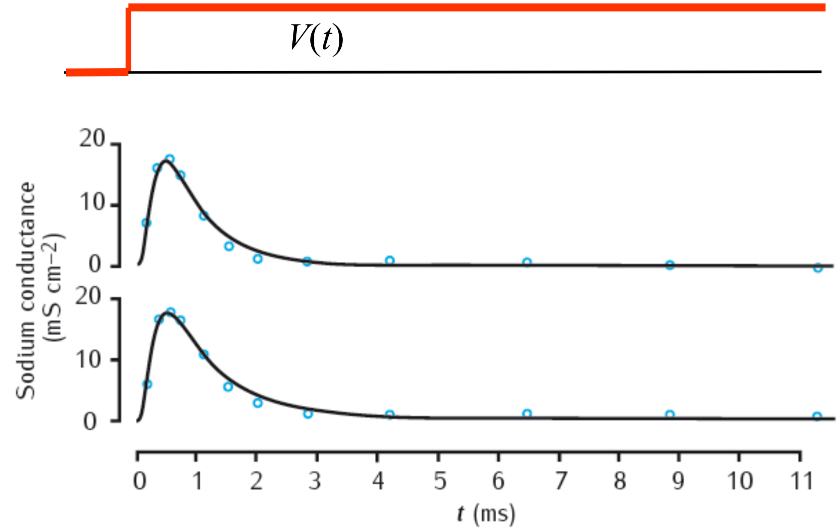
$$\alpha_n = 0.01\frac{V+55}{1-\exp(-(V+55)/10)}$$

$$\beta_n = 0.125\exp(-(V+65)/80)$$

(V [mV] relative to resting potential)



Sodium current I



- Sodium conductance increa-ses and decays back to rest (transient!). $\Rightarrow$ Active **inactivation**.
- Special **inactivation gating variable** h following the kinetic equation:

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

- In addition, normal 'opening particle' with activation variable:

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

Sodium current II, leak current

- Dynamic variation of sodium conductance successfully modeled by: $\boxed{g_{\mathrm{Na}^+} = \bar{g}_{\mathrm{Na}^+} m^3 h}$
- Voltage dependence of rate coefficients fitted to be:

$$\alpha_{\mathrm{m}} = 0.1 \frac{V+40}{1-\exp\left(-(V+40)/10\right)}, \quad \alpha_{\mathrm{h}} = 0.07 \exp\left(-(V+65)/20\right)$$

$$\beta_{\mathrm{m}} = 4 \exp\left(-(V+65)/18\right), \quad \beta_{\mathrm{h}} = \frac{1}{\exp\left(-(V+35)/10\right)+1}.$$

(V [mV] relative to resting potential)

- Some additional current that is not carried by sodium or potassium; potentially from a mixture of other ions: 'leak current'; modeled by linear circuit:

$$\boxed{I_{\mathrm{L}} = \bar{g}_{\mathrm{L}} \left(V - E_{\mathrm{L}}\right)}$$

Complete HH model

- Putting the last equations together we obtain the full **Hodgkin-Huxley model**:

$$C\frac{\mathrm{d}V}{\mathrm{d}t} + \bar{g}_{\mathrm{K}^+} n^4 \left(V - E_{\mathrm{K}^+}\right) + \bar{g}_{\mathrm{Na}^+} m^3 h \left(V - E_{\mathrm{Na}^+}\right) + \bar{g}_{\mathrm{L}} \left(V - E_{\mathrm{L}}\right) = I_{\mathrm{e}}(t)$$

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

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

$$\alpha_{\mathrm{n}} = 0.01 \frac{V + 55}{1 - \exp(-(V + 55)/10)}$$

$$\beta_{\mathrm{n}} = 0.125 \exp(-(V + 65)/80)$$

($V\,[\mathrm{mV}]$ relative to resting potential in these last equations)

$$\alpha_{\mathrm{m}} = 0.1 \frac{V + 40}{1 - \exp(-(V + 40)/10)}, \qquad \alpha_{\mathrm{h}} = 0.07 \exp(-(V + 65)/20)$$

$$\beta_{\mathrm{m}} = 4 \exp(-(V + 65)/18), \qquad \beta_{\mathrm{h}} = \frac{1}{\exp(-(V + 35)/10) + 1}.$$

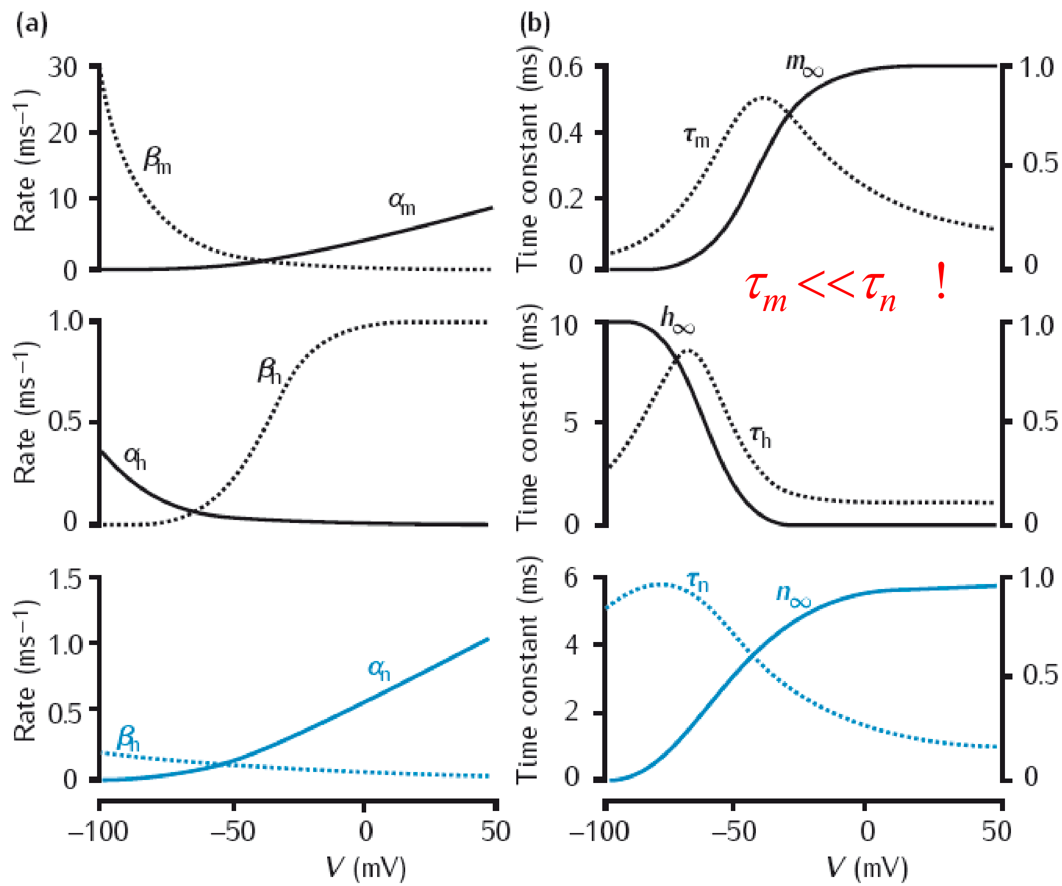
Overview of voltage dependence

- Overview of the voltage dependence of rate coefficients, saturation levels and time constants for HH model:

Na⁺ activation:

Na⁺ inactivation:

K⁺ activation:



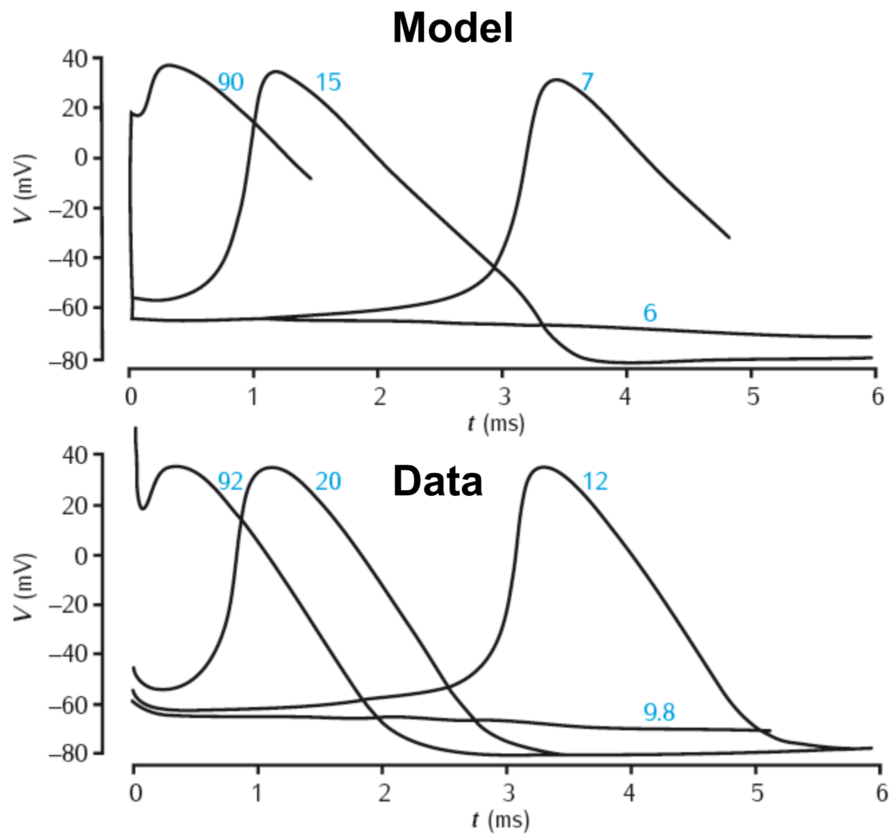
$$\frac{dx}{dt} = \alpha_x(1-x) - \beta_x x$$

$$\Leftrightarrow \quad \tau_x \frac{dx}{dt} = x_\infty - x$$

$$\tau_x = \frac{1}{\alpha_x+\beta_x} \qquad x_\infty = \frac{\alpha_x}{\alpha_x+\beta_x}$$

Simulation of an action potential

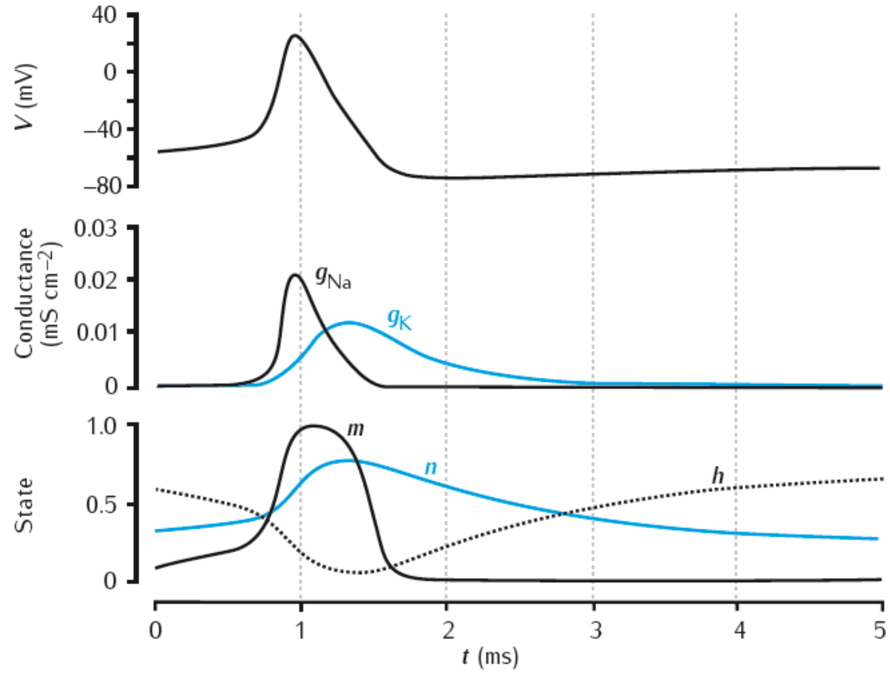
- Hodgkin and Huxley simulated on hand-operated calculator (3 weeks per simulation !).
- Simulation of space clamp (potential not changing over space).
- High similarity to experimental data.



Dynamics during action potential I

- Model allows to understand processes during AP.

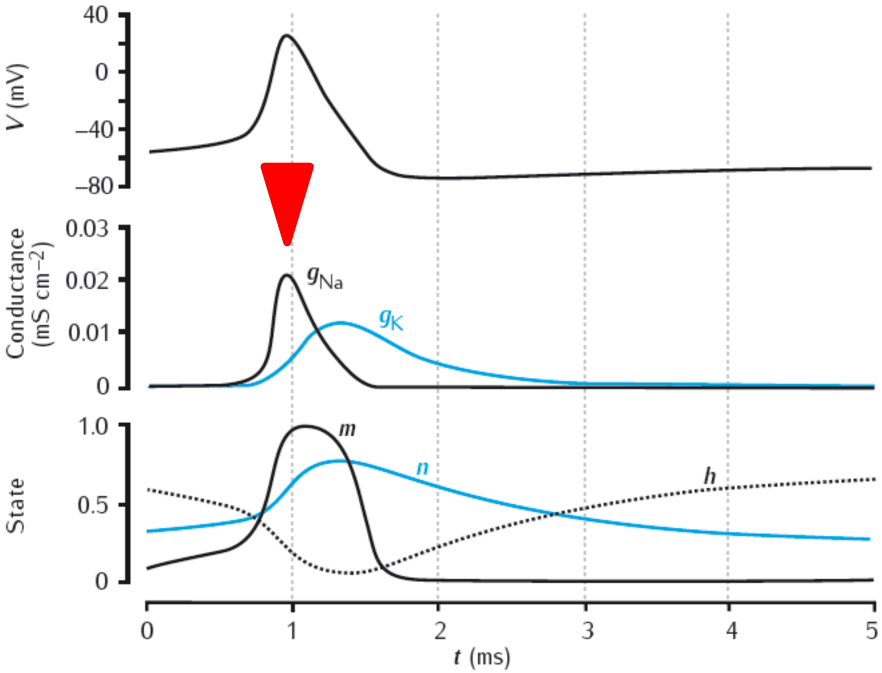
Action potential



Dynamics during action potential I

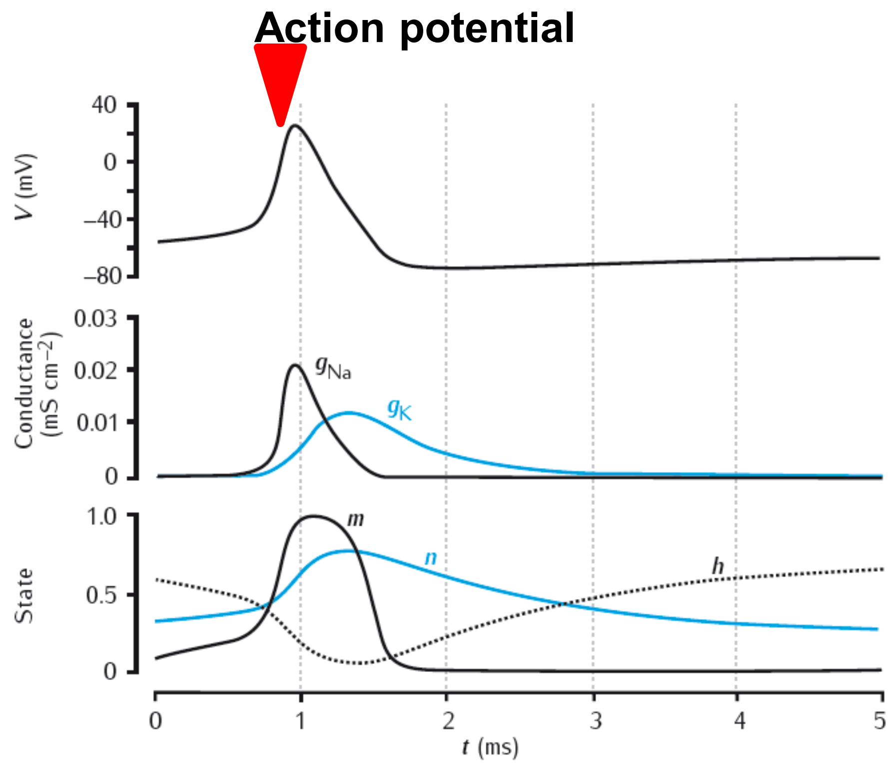
- Model allows to understand processes during AP.
- After depolarization first sodium current is activated.

Action potential



Dynamics during action potential I

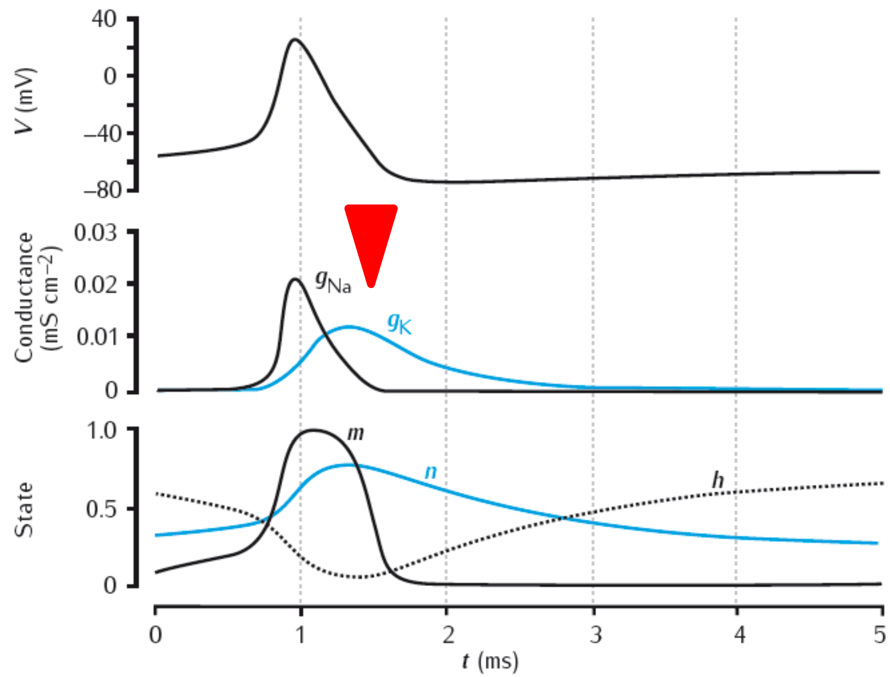
- Model allows to understand processes during AP.
- After depolarization first sodium current is activated.
- This increases depolarization because $E_{\mathrm{Na}^+} > 0$ (positive feedback!!); $\Rightarrow$ Positive flank of V.



Dynamics during action potential I

- Model allows to understand processes during AP.
- After depolarization first sodium current is activated.
- This increases depolarization because $E_{\mathrm{Na}^+} > 0$ (positive feedback!!); $\Rightarrow$ Positive flank of V.
- With delay potassium current increases; since this re-polarizes the membrane decreases (**delayed rectifier current**).

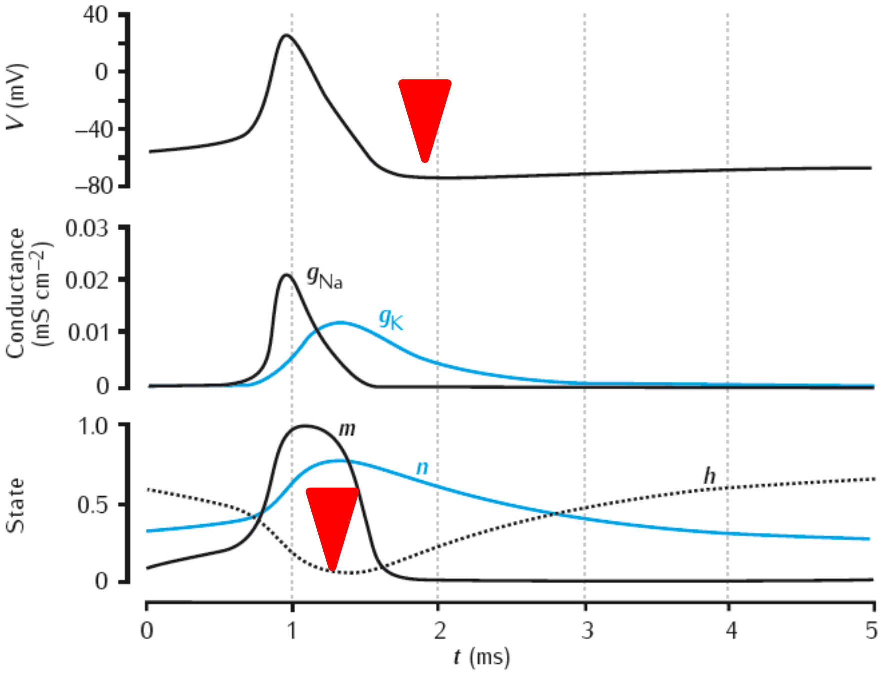
Action potential



Dynamics during action potential II

- Rapid inactivation of the sodium current by variable h; causes slight hyperpolarization.

Action potential

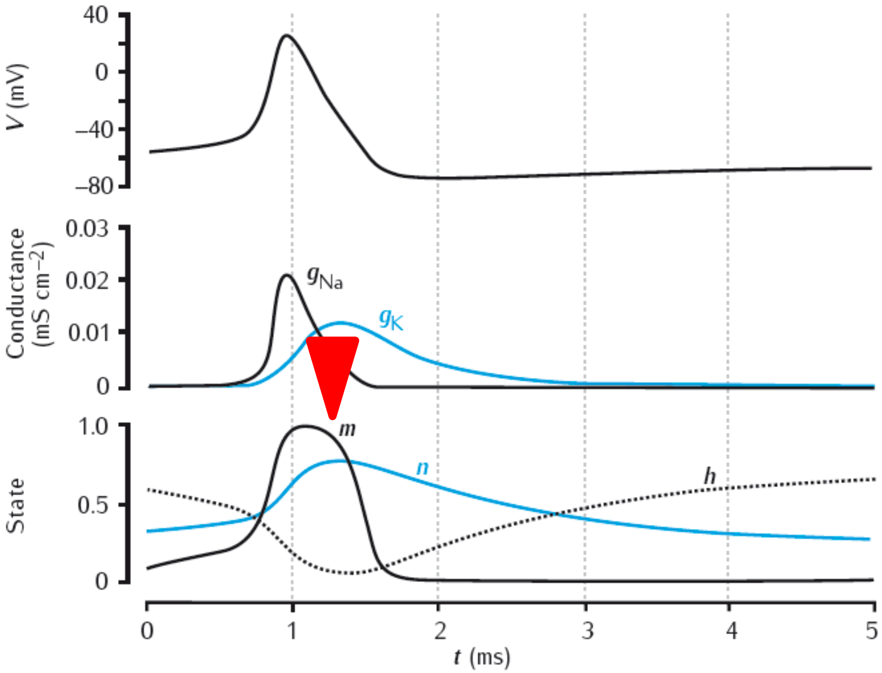


g_{K^+}

Dynamics during action potential II

- Rapid inactivation of the sodium current by variable h; causes slight hyperpolarization.
- As consequence m decays.

Action potential

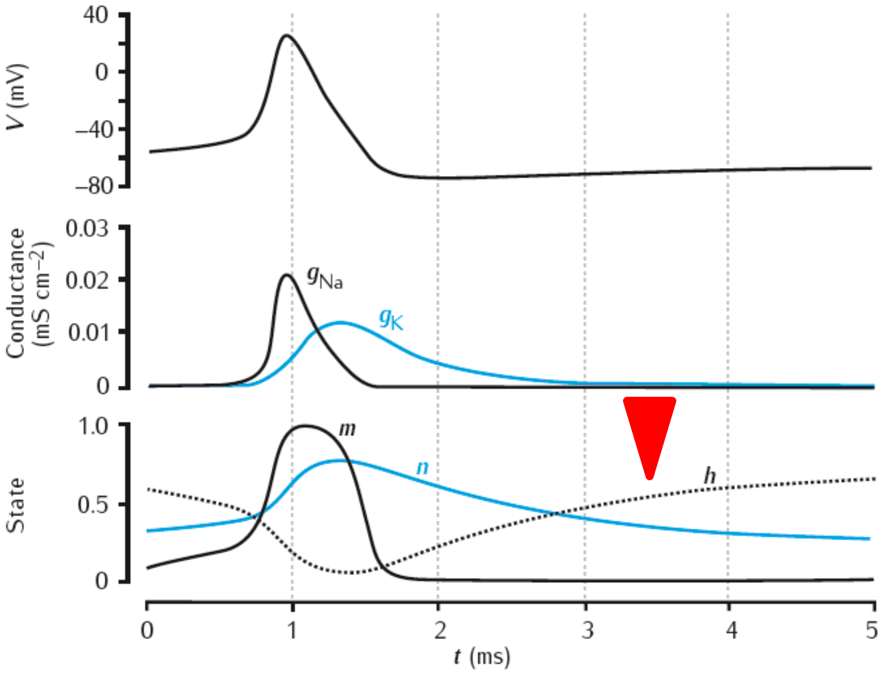


g_{K^+}

Dynamics during action potential II

- Rapid inactivation of the sodium current by variable h; causes slight hyperpolarization.
- As consequence m decays.
- **Deinactivation:** Inactivation is released, since h increases again.

Action potential

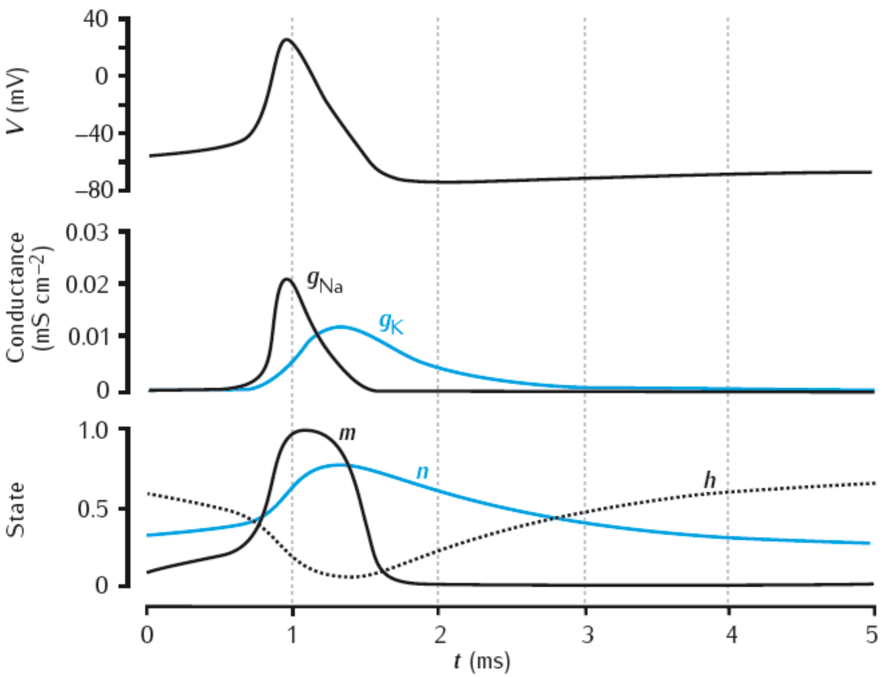


g_{K^+}

Dynamics during action potential II

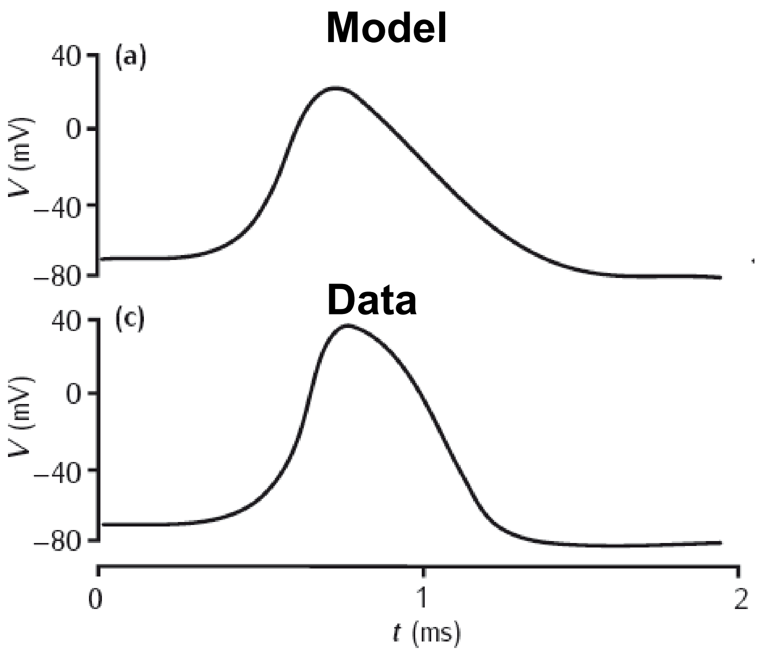
- Rapid inactivation of the sodium current by variable h; causes slight hyperpolarization.
- As consequence m decays.
- **Deinactivation:** Inactivation is released, since h increases again.
- Also **refractary period** can be explained:
  - As long as h is decreased it is more difficult to re-activate sodium current.
  - Increased potassium conductance g_{K^+} produces outwards current; new depolarization would have to counteract this current.

Action potential



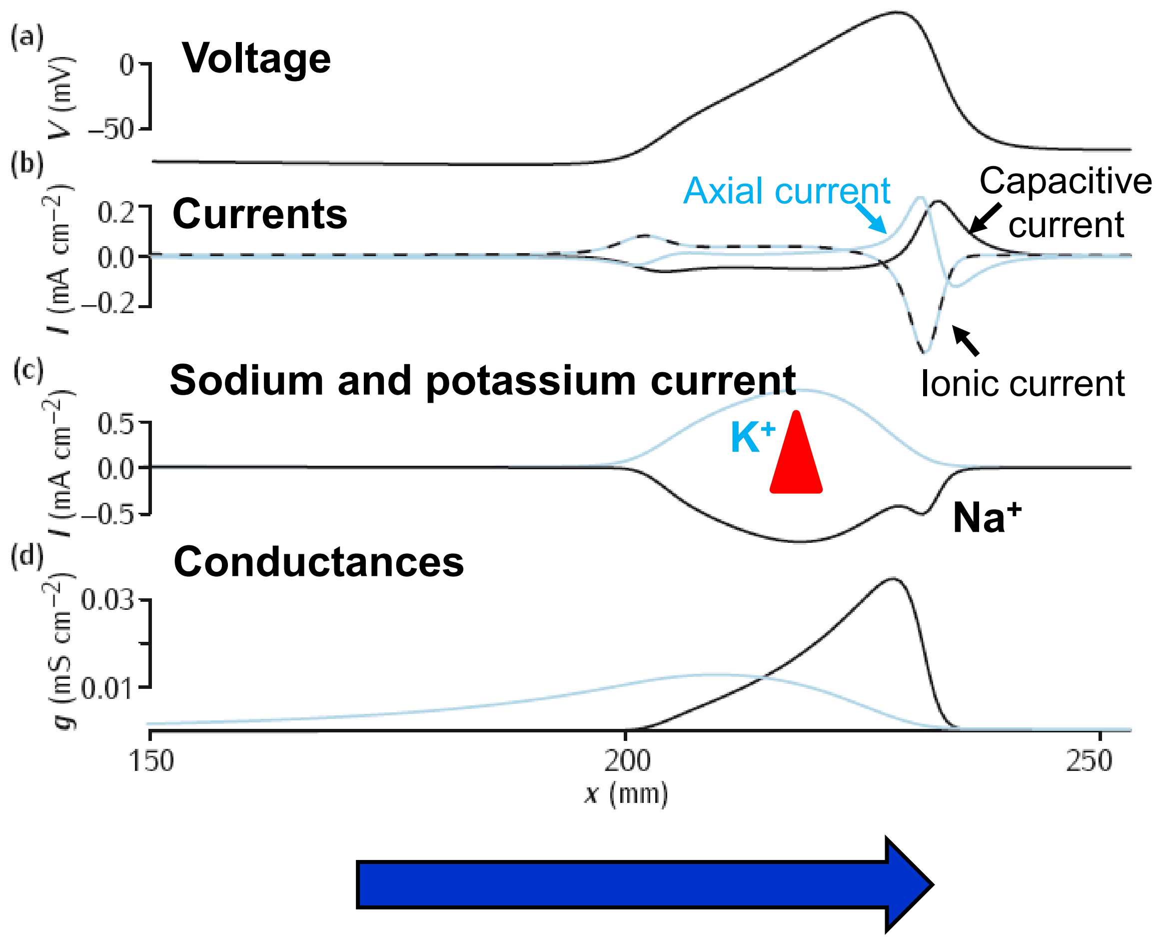
Propagating action potential I

- Multi-compartment model, integrating the nonlinear elements of the HH equation in the individual compartments.
- Very good fit of data.

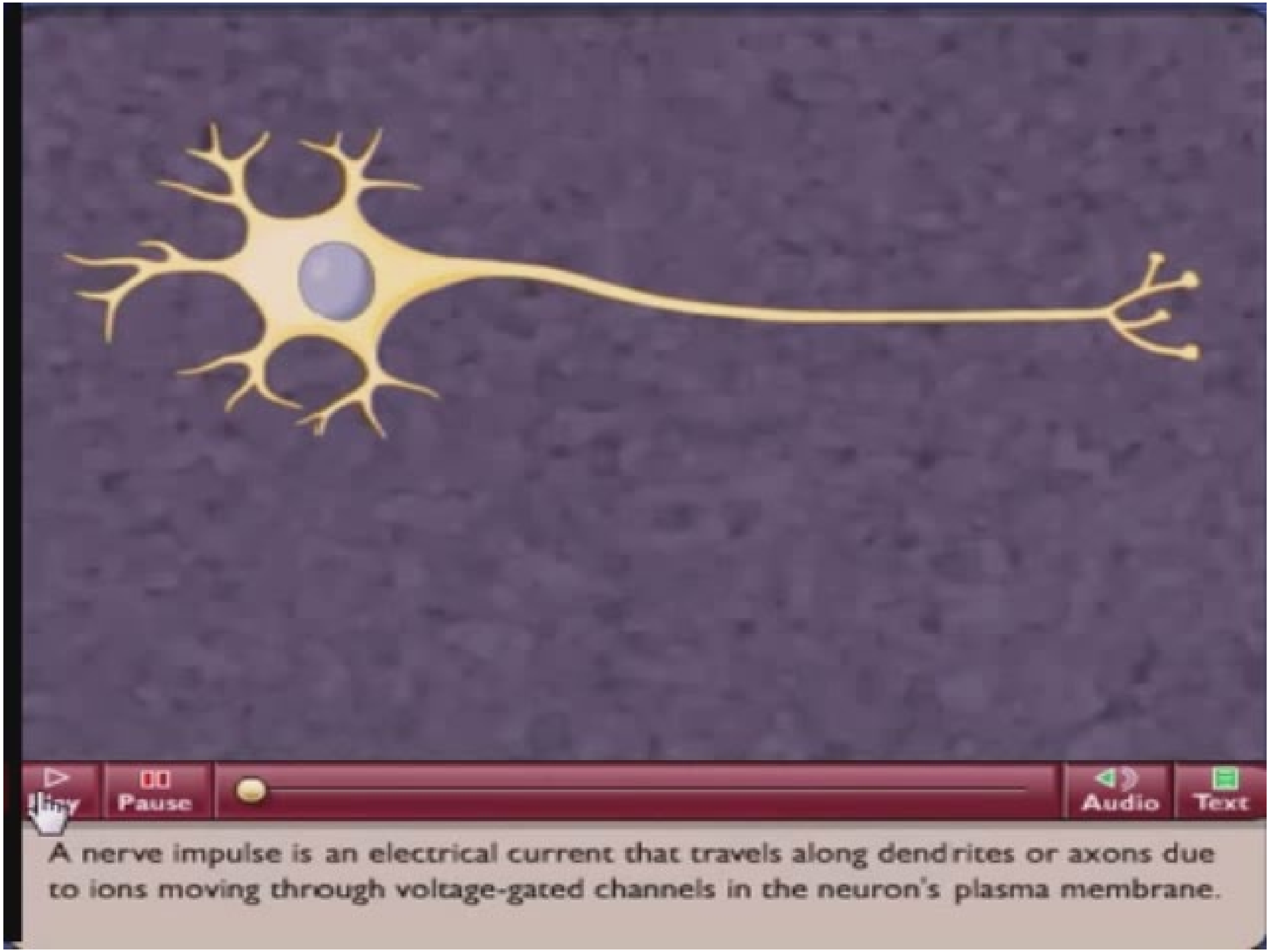


Propagating action potential II

- Propagating flank of depolarization caused by sodium inflow.
- Slower potassium outfow repolarises membrane.



Propagating action potential III



Things to remember

- How do active membrane channels work? $\rightarrow$ 2)
- Patch clamp; binary characteristics $\rightarrow$ 2)
- Gating charge and current $\rightarrow$ 2)
- Hodgkin Huxley model and how it was derived $\rightarrow$ 2)
- Activation vs. inactivation dynamics $\rightarrow$ 2)
- Principles of formation of an action potential at the membrane according to Hodgkin and Huxley $\rightarrow$ 1,2)

(Numbers relate to literature on next page.)

Literature (for this lecture)

1) Dayan P. & Abbott, L.F. (2001 / 2005) *Theoretical Neuroscience: Computational and Mathematical Modeling of Neural Systems.* MIT Press, Cambridge MA, USA. Chapter 5.

2) Sterratt, D., Graham, B, Gillies, A., Willshaw, D. (2011) *Principles of Computational Modelling in Neuroscience.* Cambridge University Press, UK. Chapters 3, and 5.