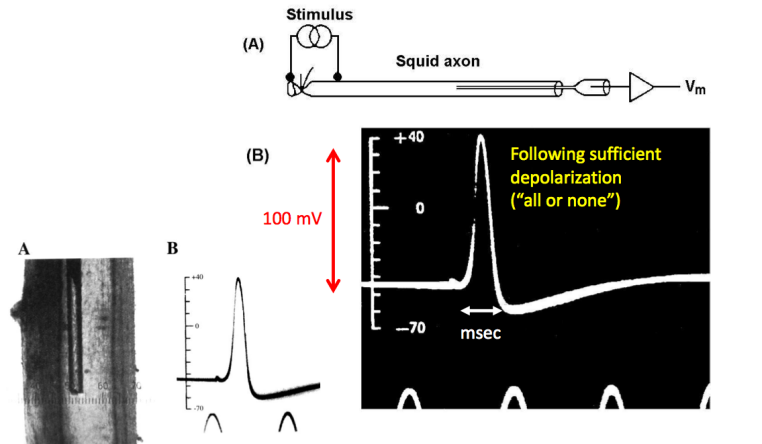# Neuroinformatics 2018, Prague
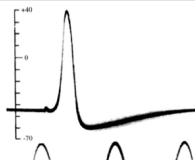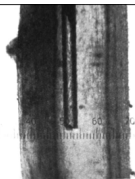
March 8, 2018

Hodkin and Huxley models

First direct (intracellular) recorded action-potential (spike) - 1939!!

Very nice theory

Sir Alan Lloyd Hodgkin

Sir Andrew Fielding Huxley

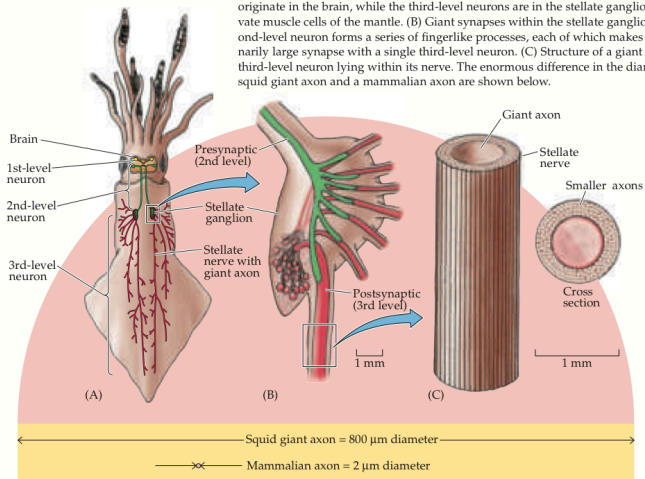$$I = C_m \, \dot{V} + g_{Na} \, h \, m^3 \, (V - V_{Na}) + g_K \, n^4 \, (V - V_k) + G_L \, (V - V_L) \qquad (1)$$

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

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

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

Giant Nerve Cells of Squid

(A) Diagram of a squid, showing the location of its giant nerve cells. Different colors indicate the neuronal components of the escape circuitry. The first- and second-level neurons originate in the brain, while the third-level neurons are in the stellate ganglion and innervate muscle cells of the mantle. (B) Giant synapses within the stellate ganglion. The second-level neuron forms a series of fingerlike processes, each of which makes an extraordinarily large synapse with a single third-level neuron. (C) Structure of a giant axon of a third-level neuron lying within its nerve. The enormous difference in the diameters of a squid giant axon and a mammalian axon are shown below.

Brain

1st-level neuron

2nd-level neuron

3rd-level neuron

Presynaptic (2nd level)

Stellate ganglion

Stellate nerve with giant axon

Postsynaptic (3rd level)

Giant axon

Stellate nerve

Smaller axons

Cross section

1 mm

1 mm

(A)

(B)

(C)

Squid giant axon = 800 µm diameter

Mammalian axon = 2 µm diameter

Hodkin and Huxley experiment NOBEL 1963

Sir Alan Lloyd Hodgkin

Sir Andrew Fielding Huxley

The Squid Giant Axon

~ 0.5 mm
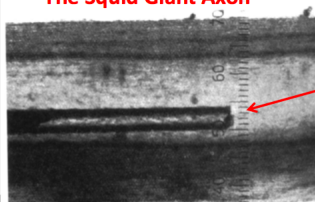
Axial electrode

Voltage Clamp Method

1 One internal electrode measures membrane potential (V_{m}) and is connected to the voltage clamp amplifier

2 Voltage clamp amplifier compares membrane potential to the desired (command) potential

3 When V_{m} is different from the command potential, the clamp amplifier injects current into the axon through a second electrode. This feedback arrangement causes the membrane potential to become the same as the command potential

4 The current flowing back into the axon, and thus across its membrane, can be measured here

Measure V_{m}

Command voltage

Voltage clamp amplifier

Reference electrode

Measure current

Saline solution

Squid axon

Recording electrode

Current-passing electrode

Voltage clamp technique for studying membrane currents of a squid axon.

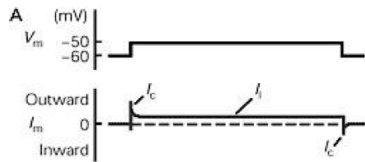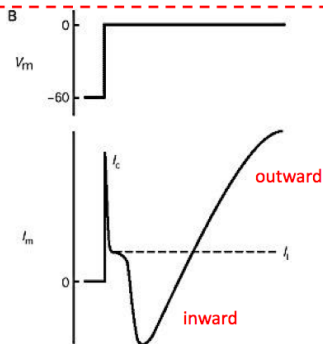# The "all or none" nature of the spike
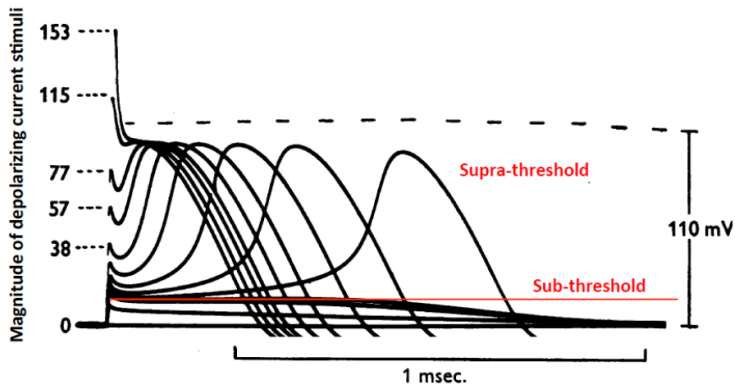
Hodgkin, Huxley and Katz, 1952

Membrane current in response to voltage clamp (VC)

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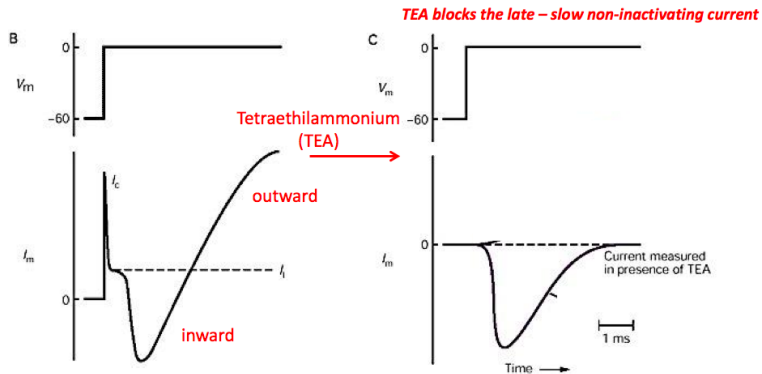
For **suprathreshold** depolarizing voltage clamp, the recorded membrane current (after the fast capacitaticve current) flows **first inwards** (into the axon) and later **outward** (from inside to the outside)

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


TEA blocks the late – slow non-inactivating current

Tetraethilammonium (TEA)

B — V_m, I_m, I_c, I_l, outward, inward

C — V_m, I_m, Current measured in presence of TEA, 1 ms, Time

Changing ion concentration at bath with giant axon showed that early current is carried by Na+ ions and late one by K+ ions
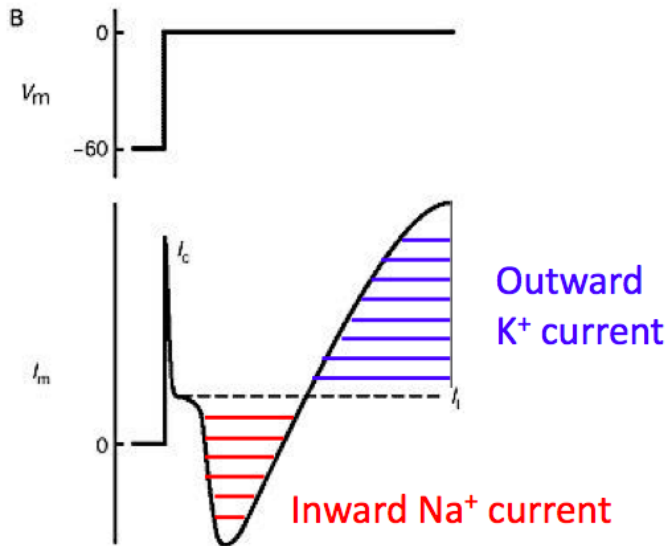
Ion currents (K+ and Na+) for various depolarizing voltage clamp (and extracting respective ion conductances)

$$I_K = g_K (V_m - E_K); \quad I_{Na} = g_{Na} (V_m - E_{Na})$$
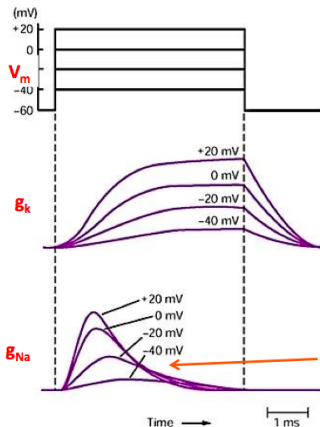
1. The slow (K) current (conductance) does not inactivate during VC

2. The K conductance rises slower than it decays at end of VC

3. The fast (early) Na conductance inactivates during VC

Direction reversed

Fitting an equation for the K current (K-conductance) during/following VC
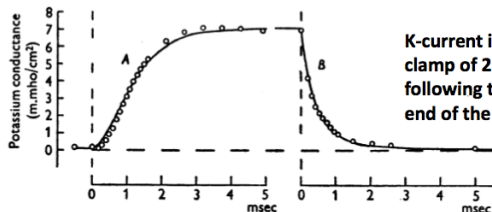
K-current in response to a step voltage clamp of 25 mV (upstroke) – **slow rise** following the VC and **faster decay** at the end of the VC

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

Graphical interpretation of H&H model for the K channel

Closed K channel (by 4 n gates)
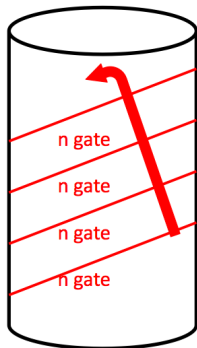
n gate

n gate

n gate

n gate

4 n gates open with depolarization

K^+
INSIDE

Open K channel (by 4 n gates)

K^+
INSIDE
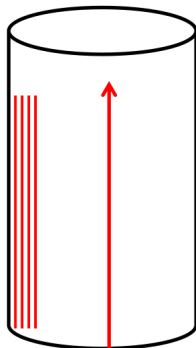
$$g_{\mathbf{K}} = \bar{g}_{\mathbf{K}} n^4,$$

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

where $\bar{g}_{\mathbf{K}}$ is a constant with the dimensions of conductance/cm², α_n and β_n are rate constants which vary with voltage but not with time and have dimensions of [time]⁻¹, n is a dimensionless variable which can vary between 0 and 1.

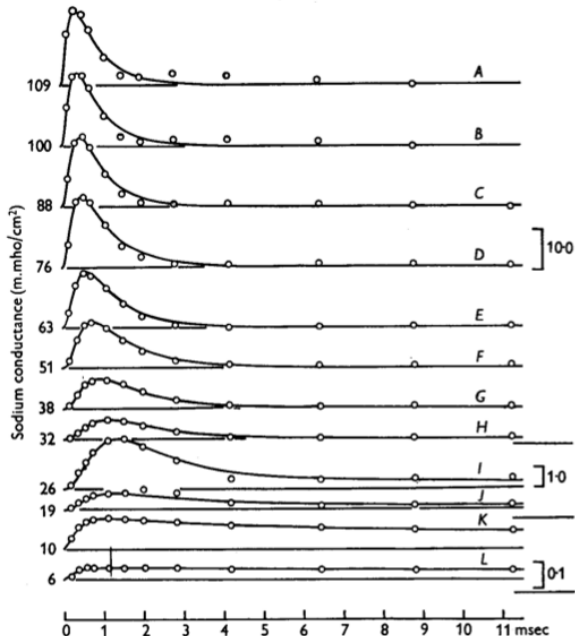Similar procedure is used to extract the activation (m) and inactivation (h) parameters for the Na current
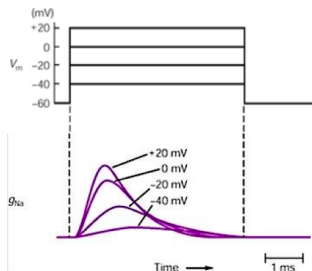
$$g_{\mathrm{Na}} = m^3 h \bar{g}_{\mathrm{Na}},$$

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

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

Fitting Na current for different VC depolarizing values
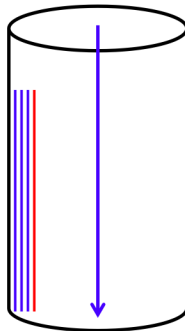
Graphical interpretation of H&H model for the Na channel

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

m gate

m gate

m gate

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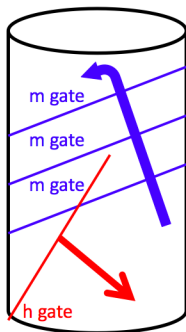
3 (fast) m (activated) gates open with depolarization

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

Open Na channel

Na outside

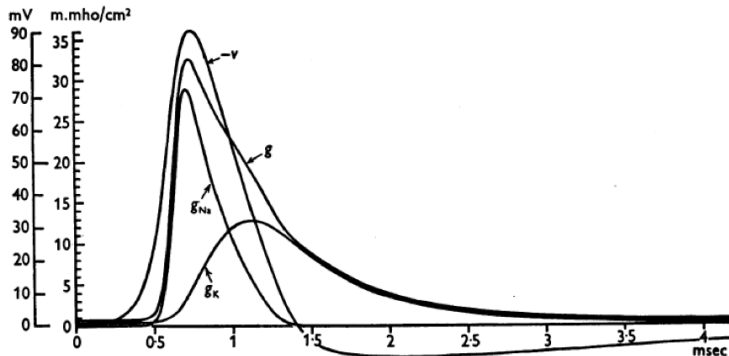# Overlay of the action potential (voltage) and underlying Na and K conductances

Fig. 17. Numerical solution of eqn. (31) showing components of membrane conductance (g) during propagated action potential ($-V$). Details of the analysis are as in Fig. 15.
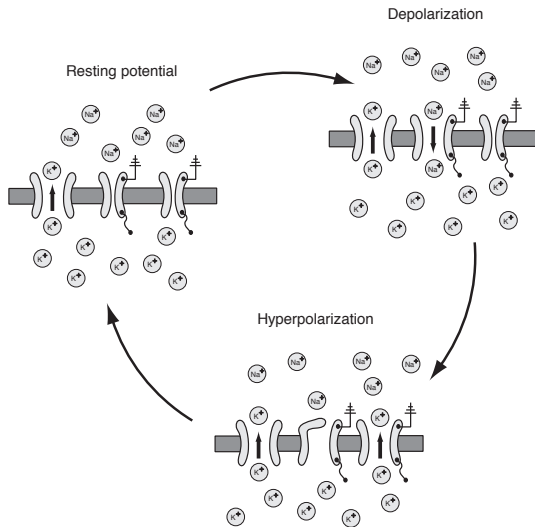
Hodgkin–Huxley model
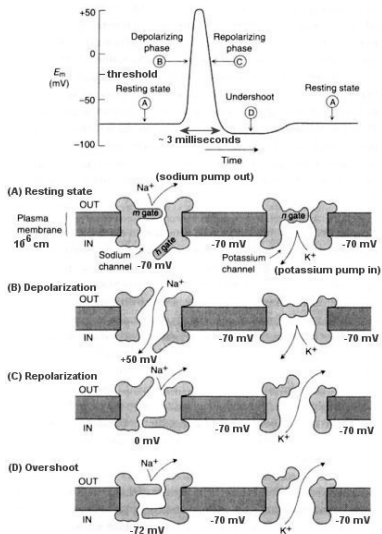
Figure: Typical form of an action potential; redrawn from an oscilloscope picture from Hodgkin and Huxley (1939).
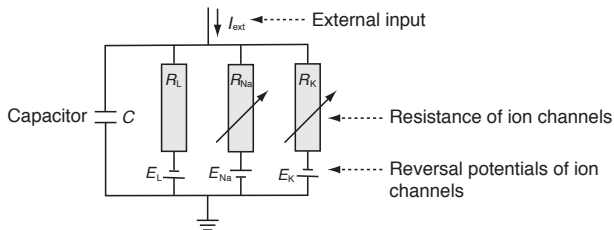
The minimal mechanisms

HH stucture

- $I_{ion} = \hat{g_{ion}}(V - E_{ion})$
- voltage and time dependent variables $n(V,t)$, $m(V,t)$, $h(V,t)$

$$\hat{g_K}(V,t) = g_K n^4$$
$$\hat{g_{Na}}(V,t) = g_{Na} m^3 h$$

Hodgkin–Huxley equations and simulation

$$C\frac{\mathrm{d}V}{\mathrm{d}t} = -g_{\mathrm{K}}n^4(V - E_{\mathrm{K}}) - g_{\mathrm{Na}}m^3h(V - E_{\mathrm{Na}}) - g_{\mathrm{L}}(V - E_{\mathrm{L}}) + I_{ext}(t)$$

$$\tau_{\mathrm{n}}(V)\frac{\mathrm{d}n}{\mathrm{d}t} = -[n - n_0(V)]$$

$$\tau_{\mathrm{m}}(V)\frac{\mathrm{d}m}{\mathrm{d}t} = -[m - m_0(V)]$$

$$\tau_{\mathrm{h}}(V)\frac{\mathrm{d}h}{\mathrm{d}t} = -[h - h_0(V)]$$

$$\frac{dx}{dt} = -\frac{1}{\tau_x(V)}[x - x_0(V)] \rightarrow x(t + \Delta t) = (1 - \frac{\Delta t}{\tau_x})x(t) + \frac{\Delta t}{\tau_x}x_0$$

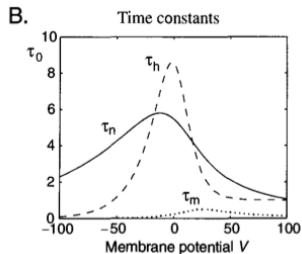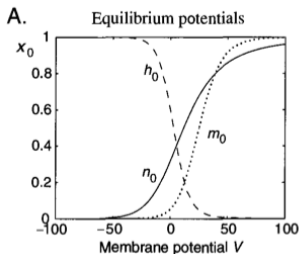Spike train with constant input
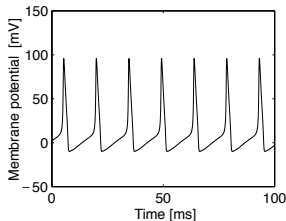
Activation function
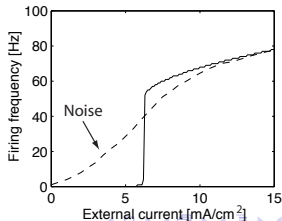
Ion channels resistance

$$x(0) = \frac{\alpha}{\alpha + \beta}, t_x = \alpha\beta, x \in = \{n, m, h\}$$

$$\alpha_n = \frac{10 - V}{100(e^{\frac{10-V}{10}} - 1)}, \beta_n = 0.125e^{-\frac{V}{80}}$$

$$\alpha_m = \frac{25 - V}{10(e^{\frac{25-V}{10}} - 1)}, \beta_m = 4e^{-\frac{V}{18}}$$

$$\alpha_h = 0.07e^{\frac{V}{20}}, \beta_h = \frac{1}{e^{\frac{30-V}{10}} + 1}$$

A. Equilibrium potentials

x_0

h_0

m_0

n_0

Membrane potential V

B. Time constants

τ_0

τ_h

τ_n

τ_m

Membrane potential V

Matlab implementation

```matlab
%% Integration of Hodgkin--Huxley equations with Euler method
  clear; figure;%clf;
%% Setting parameters
  % Maximal conductances (in units of mS/cm^2); 1=K, 2=Na, 3=R
  g(1)=36; g(2)=120; g(3)=0.3;
  % Battery voltage ( in mV); 1=n, 2=m, 3=h
  E(1)=-12; E(2)=115; E(3)=10.613;
  % Initialization of some variables
  I_ext=0; V=-10; x=zeros(1,3); x(3)=1; t_rec=0;
  % Time step for integration
    dt=0.01;
%% Integration with Euler method
  for t=-30:dt:500
    if t==10; I_ext=6; end  % turns external current on at t=10
    if t==400; I_ext=0; end    % turns external current off at t=40
    % alpha functions used by Hodgkin-and Huxley
    Alpha(1)=(10-V)/(100*(exp((10-V)/10)-1));
    Alpha(2)=(25-V)/(10*(exp((25-V)/10)-1));
    Alpha(3)=0.07*exp(-V/20);
    % beta functions used by Hodgkin-and Huxley
    Beta(1)=0.125*exp(-V/80);
    Beta(2)=4*exp(-V/18);
    Beta(3)=1/(exp((30-V)/10)+1);
    % tau_x and x_0 (x=1,2,3) are defined with alpha and beta
    tau=1./(Alpha+Beta);
    x_0=Alpha.*tau;
    % leaky integration with Euler method
    x=(1-dt./tau).*x+dt./tau.*x_0;        % x is m,n,h
    % calculate actual conductances g with given n, m, h
    gnmh(1)=g(1)*x(1)^4;
    gnmh(2)=g(2)*x(2)^3*x(3);
    gnmh(3)=g(3);
    % Ohm's law
    I=gnmh.*(V-E);
    % update voltage of membrane
    V=V+dt*(I_ext-sum(I));
    % record some variables for plotting after equilibration
    if t>=0;
        t_rec=t_rec+1;
        x_plot(t_rec)=t;
        y_plot(t_rec)=V;
    end
```
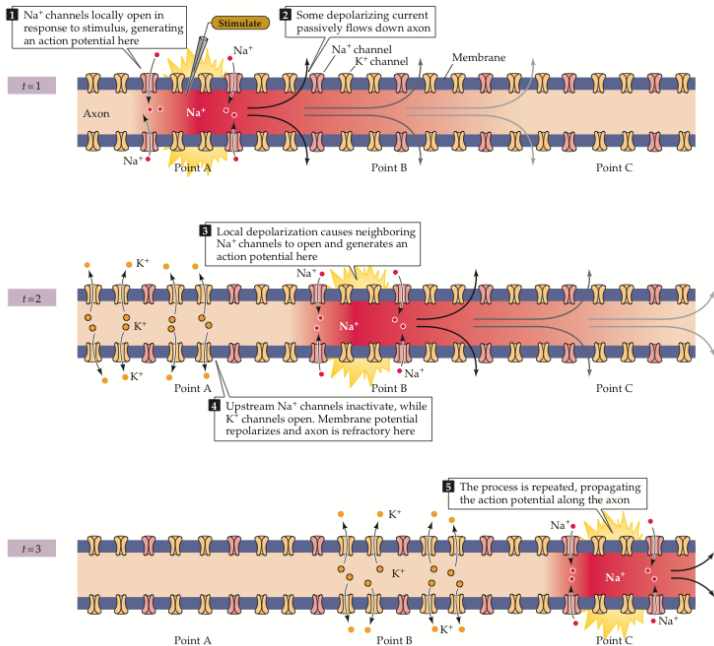
Refractory period

- waiting for inactivation of sodium channels about 1 ms
- absolute refractory period limiting firing rate to 1000Hz
- hyperpolarizing activity further limits the neuron's rate
- relative refractory period
- brainstem neurons 600Hz, cortical neurons 3Hz
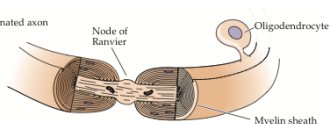
Propagation of action potentials

- action potentials=spikes travel about 10 m/s.
- non-loss signal transfer - SLOW
- myelin = FAST lossy signal transfer in axon
- Ranvier nodes = AP regeneration
- myelination happens after second year of age
- Alzheimer deased - DESmyelination!

NON-LOSS transfer

LOSSY transfer

(A) Myelinated axon — Node of Ranvier — Oligodendrocyte — Myelin sheath

(B) Action potential propagation
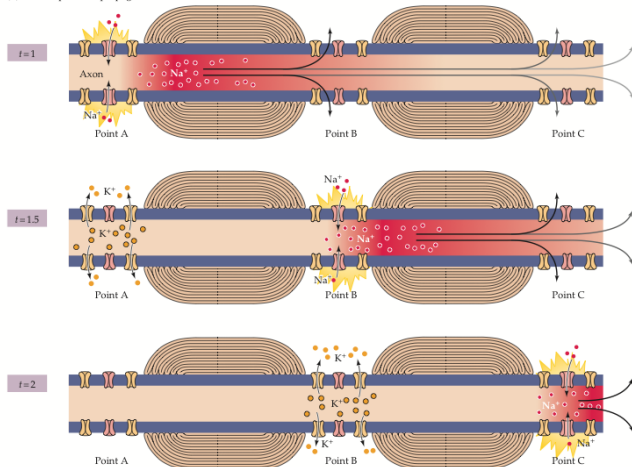
$t = 1$ — Axon — Na$^+$ — Point A — Point B — Point C

$t = 1.5$ — K$^+$ — Na$^+$ — Point A — Point B — Point C

$t = 2$ — K$^+$ — Na$^+$ — Point A — Point B — Point C

Stimulation of neuron
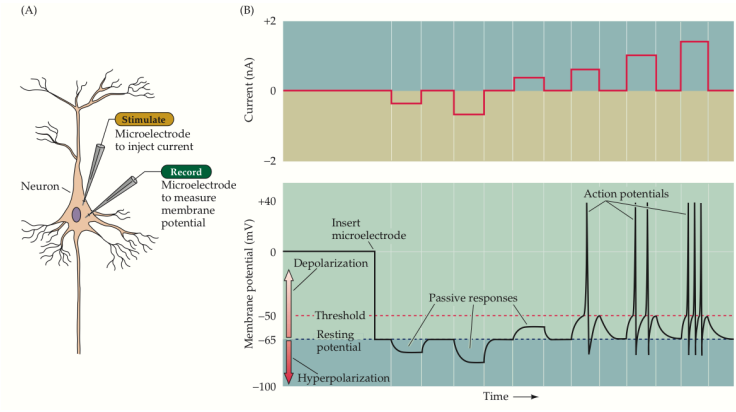
- $h = 1 - n$
- $\tau_m \approx m_0(V)$
- $h = 1$ no inactivation of the fast Na^+ channel combining leakage and Na channel, only for cortical neurons
- R describes recovery of membrane potential
- 2 differential equations

$$
\begin{aligned}
C\frac{dV}{dt} &= -g_K R(V - E_K) - g_{Na}(V)(V - ENa) + I_{ext}(t) \\
\tau_R \frac{dR}{dt} &= -[R - R_0(V)]
\end{aligned}
$$

Wilson model

- more realistic mammalian neocortical neurons
- two more channels types $\rightarrow$ more diverse firing
- cation C_a^{2+} described by gating variable T
- slow hyperpolarizing current Ca^{2+}-mediated K^+ described by gating variable H

$$
\begin{aligned}
C\frac{dV}{dt} &= -g_{Na}(V - E_{Na}) - g_K R(V - E_K) - g_T(V - E_T) - g_H H(V - E_H) \\
\tau_R \frac{dR}{dt} &= -[R - R_0(V)] \\
\tau_T \frac{dT}{dt} &= -[T - T_0(V)] \\
\tau_H \frac{dH}{dt} &= -[H - 3T(V)] \\
g_{Na}(V) &= 17.8 + 0.476V + 33.8V^2 \\
R_0(V) &= 1.24 + 3.7V + 3.2V^2 \\
T_0(V) &= 4.205 + 11.6V + 8V^2
\end{aligned}
$$

Wilson model:results

- ▶ RS: regular spiking neuron
- ▶ FS: fast spiking neuron
- ▶ CS: continously spiking neuron
- ▶ IB: bursting neuron
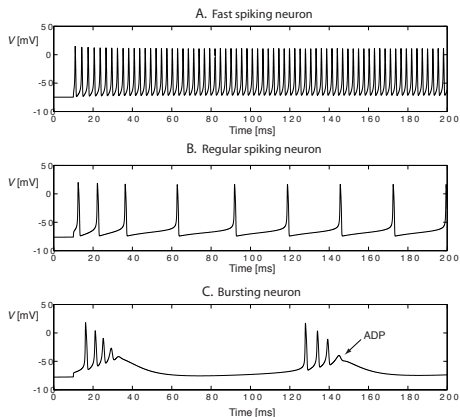
Matlab implementation

```matlab
%%  Integration of Wilson model with the Euler method
 clear; clf;
%% Parameters of the model: 1=K,R  2=Ca,T  3=KCa,H  4=Na
 g(1)=26; g(2)=2.25; g(3)=9.5; g(4)=1;
 E(1)=-.95; E(2)=1.20; E(3)=E(1); E(4)=.50;

%% Initial values
 dt=.01; I_ext=0; V=-1; x=zeros(1,4);
 tau(1)=dt./4.2; tau(2)=dt./14; tau(3)=dt./45; tau(4)=1;

%% Integration
 t_rec=0;

 for t=-100:dt:200
   switch t;
       case 0; I_ext=1;
   end

   x0(1)=1.24  +   3.7*V + 3.2*V^2;
   x0(2)=4.205 + 11.6*V + 8  *V^2;
   x0(3)=3*x(2);
   x0(4)=17.8  + 47.6*V +33.8*V^2;

   x=x-tau.*(x-x0); %rem x(4)=x0(4) because tau(4)=1
   I=g.*x.*(V-E);
   V=V+dt*(I_ext-sum(I));

   if t>=0;
       t_rec=t_rec+1;
       x_plot(t_rec)=t;
       y_plot(t_rec)=V;
   end
 end % time loop

%% Plotting reults
 plot(x_plot,100*y_plot); xlabel('Time'); ylabel('Membrane potential');
```

Rall (1964)
Histological Vs. Schmetic Neurons
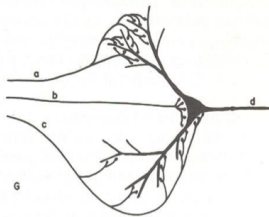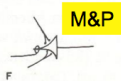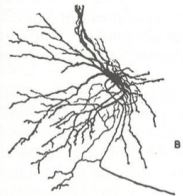
Physiology versus Neurons Models

Understand experimental synaptic potentials recorded at the soma

1. **Most of the input current flows into the dendrites** (not directly to soma)

2. **Dendrites are non-isopotential electrical devices**

   (i) voltage attenuates from synapse to soma;

   (ii) it takes time (delay) for the PSP to reach the soma;

   (iii) somatic EPSP/IPSP shape is expected to change with synaptic location

Rall Cable Theory for Dendrites

Understanding (mathematically) the impact of
(remote) dendritic synapses (the input)
on the soma/axon (output) region

Wilfrid Rall

Cylindric model

A. Physiologically & morphologically caharacterized neuron

25 μm
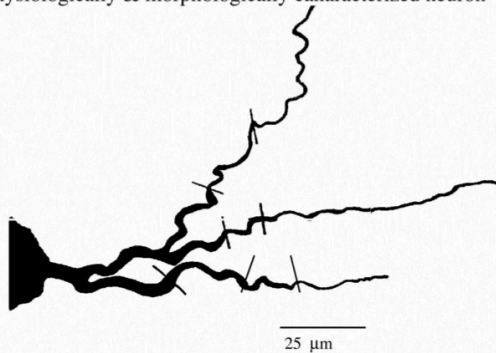
B. Cable model
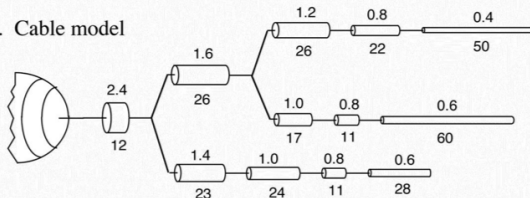
Voltage attenuation

Synaptic potentials attenuate from the synapse origin towards other regions of the dendrites
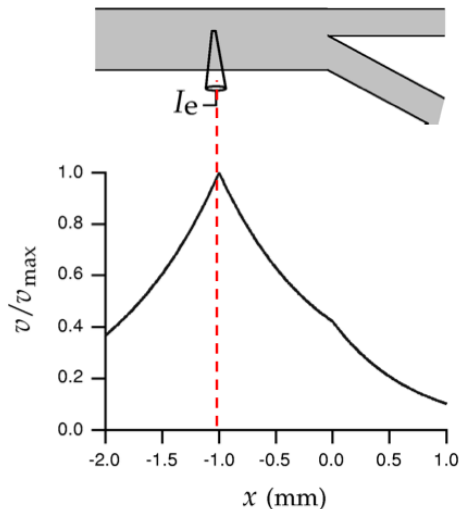
Axial and membrane current

synapse

Membrane current (lost via membrane resistance)

Axial current (originated from the synapse)
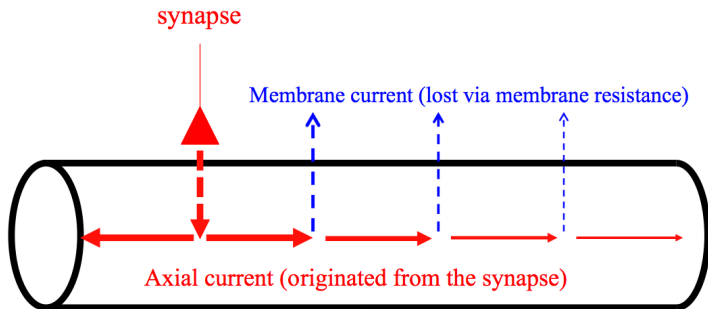
Passive cable equations
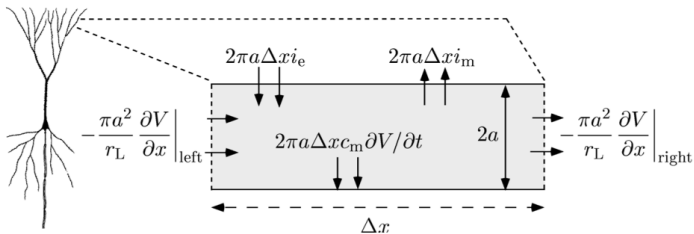
$$\frac{r_m}{r_i} \div \frac{^2V(x,t)}{x^2} \qquad r_m c_m \frac{V(x,t)}{t} \qquad V(x,t) = 0$$

$$\frac{^2V}{X^2} = \frac{V}{T} + V(X,T)$$

$$X = x/\lambda$$
$$T = t/\tau_m$$

Compartmental models

A. Chain of compartments

B. Branching compartments
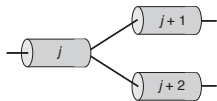
C. Compartmental reconstruction
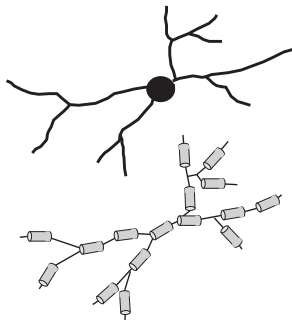
Cable theory

- discretization - compartments like branching $j, j+1, j+1$

$$\lambda^2 \frac{\partial V_m(x,t)}{\partial x^2} - \tau_m \frac{\partial V_m(x,t)}{\partial t} - V_m(x,t) + V_0 = R_m I_{inj}(x,t)$$

$$\lambda = \sqrt{\frac{d R_m}{2 R_i}}$$

$$\tau_m = R_m C_m$$

$$V_m = V_0 e - \frac{x}{\lambda}$$

$$\frac{\partial V_m(x,t)}{\partial x^2} \leftarrow \frac{V_{j+1} - 2V_j(t) + V_{j-1}(t)}{(x_{j-1} - x_j)^2}$$

Steady state condition

("Sealed-end" boundary) dV/dX = 0; x=L

$$\frac{^2V}{X^2} = \frac{V}{T} + V(X,T)$$
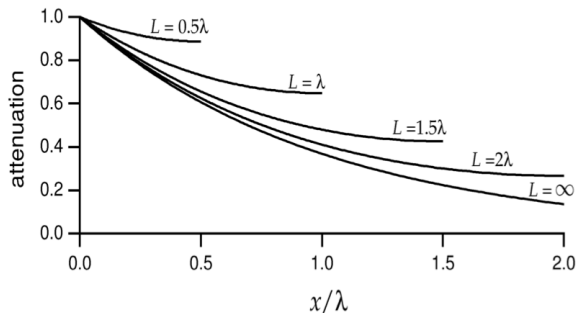
Simulating voltage attenuation

Rall and Rinzel, 1973

Simulators

Further Readings

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C. T. Tuckwell (1988), **Introduction to theoretical neurobiology**, Cambridge University Press.

Hugh R. Wilson (1999) **Spikes, decisions and actions: dynamical foundations of neuroscience**, Oxford University Press. See also his paper in J. Theor. Biol. 200: 375–88, 1999.