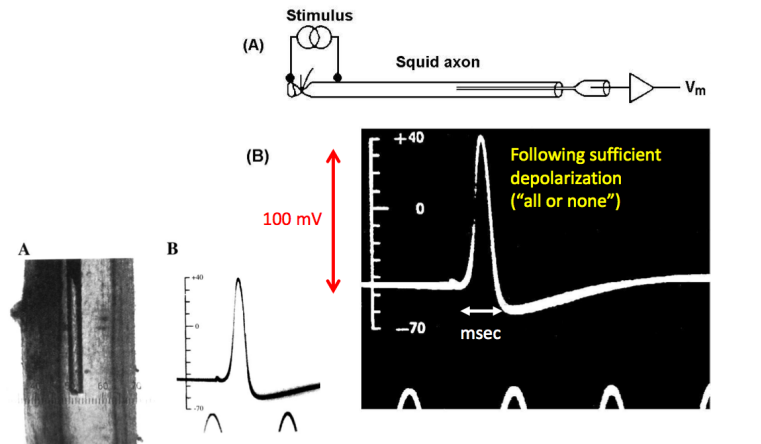


Neuroinformatics 2023, Prague

March 6, 2024

Hodkin and Huxley models

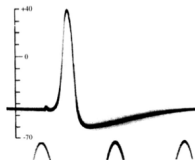
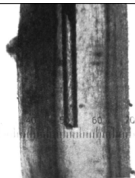
First direct (intracellular) recorded action-potential (spike) - 1939!!



Very nice theory



Sir Alan Lloyd
Hodgkin



Sir Andrew Fielding
Huxley

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

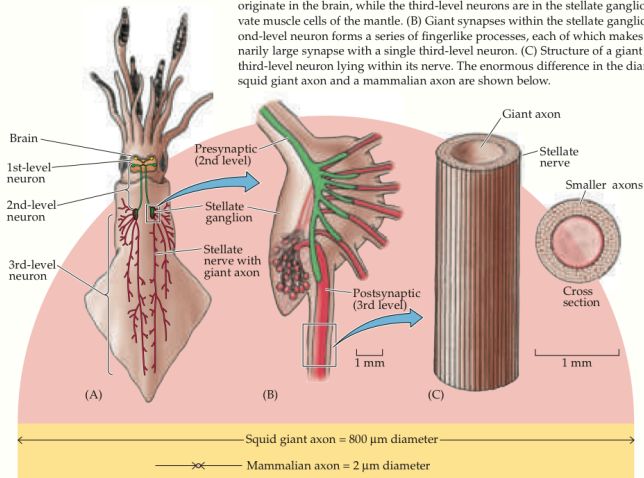
$$\frac{d}{dt} m = \alpha_m (V) (1 - m) - \beta_m (V) m \quad (2)$$

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

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

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 lying within its nerve. (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.



Hodkin and Huxley experiment NOBEL 1963



**Sir Alan Lloyd
Hodgkin**

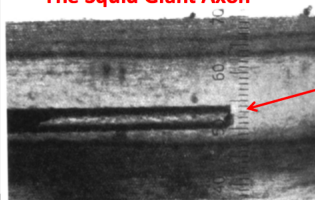


The Squid Giant Axon



**Sir Andrew Fielding
Huxley**

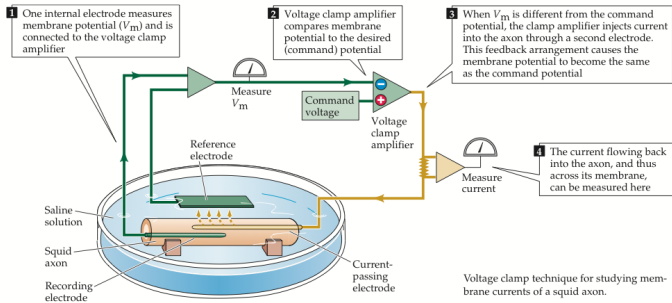
~ 0.5 mm



Axial electrode

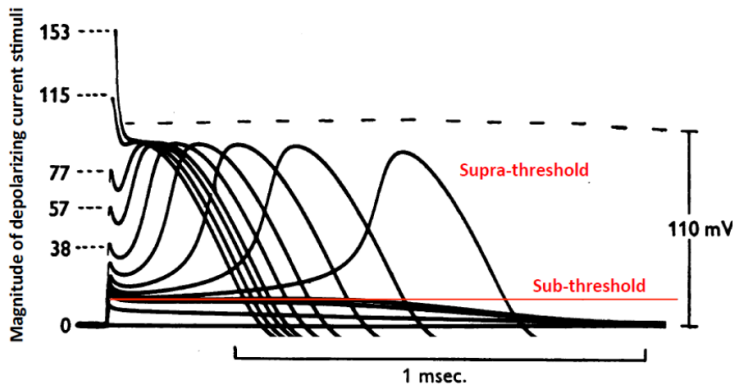
60

Voltage Clamp Method



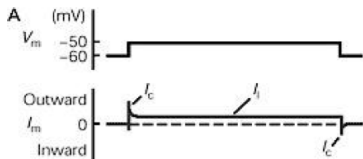
All or None

The “all or none” nature of the spike

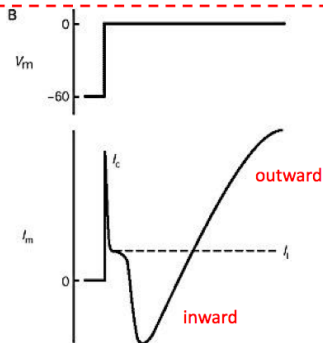


Hodgkin, Huxley and Katz, 1952

Membrane current in response to voltage clamp (VC)



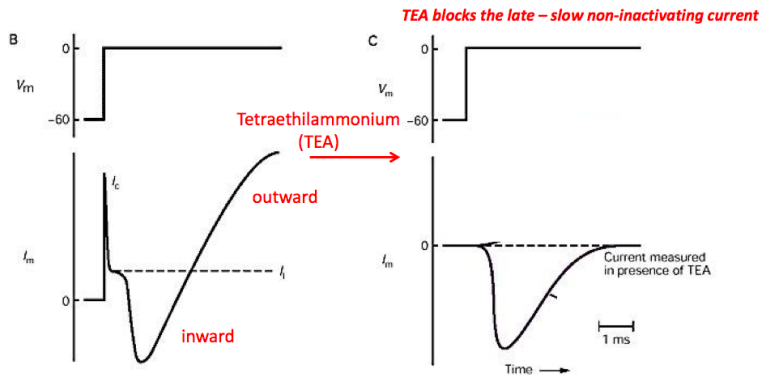
For **subthreshold** depolarizing voltage clamp, the recorded membrane current is the current that flows via the leak (passive) conductance + a small capacitive current (at start and end of the VC)



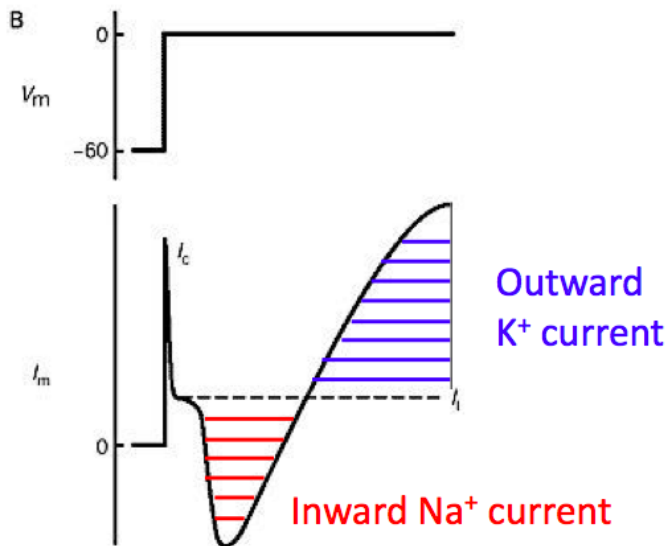
For **suprathreshold** depolarizing voltage clamp, the recorded membrane current (after the fast capacitive current) flows **first inwards** (into the axon) and later **outward** (from inside to the outside)

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

2 different currents flow via the membrane during the spike

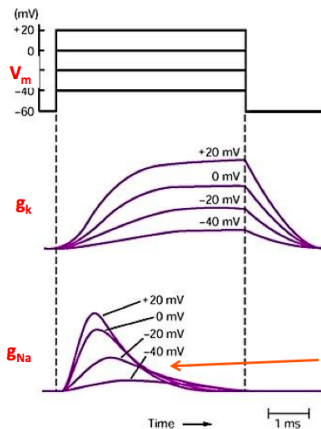


Changing ion concentration at bath with giant axon showed that early current is carried by Na^+ ions and late one by K^+ ions



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

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

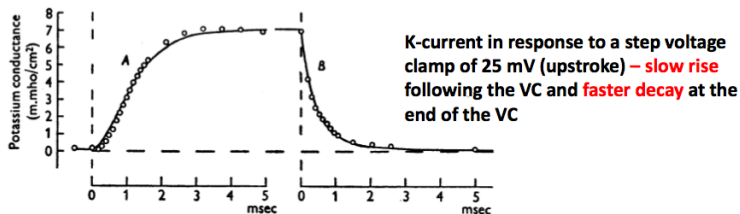


1. The slow (K) current (conductance) does not inactivate during VC

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

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

Fitting an equation for the K current (K-conductance) during/following 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 $\exp(-4t)$)

$$g_K = \bar{g}_K n^4$$

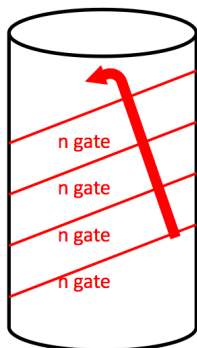
n represents the proportion of K-ion channels in the open state

"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

13 אפריל

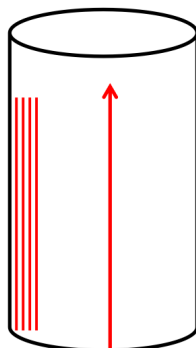
Graphical interpretation of H&H model for the K channel

Closed K channel (by 4 n gates)



K^+
INSIDE

Open K channel (by 4 n gates)



K^+
INSIDE

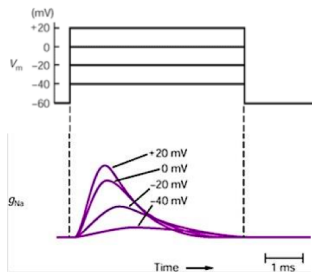
4 n gates open with
depolarization

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

$$g_{\mathbf{K}} = \bar{g}_{\mathbf{K}} n^4,$$
$$\frac{dn}{dt} = \alpha_n (1 - n) - \beta_n n,$$

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

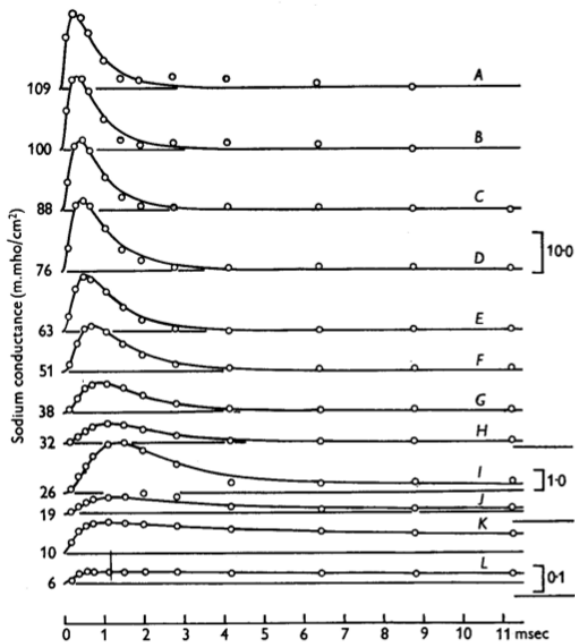


$$g_{Na} = m^3 h \bar{g}_{Na},$$

$$\frac{dm}{dt} = \alpha_m (1 - m) - \beta_m m,$$

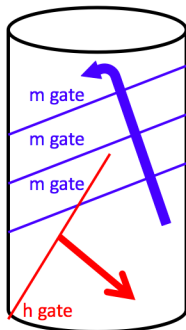
$$\frac{dh}{dt} = \alpha_h (1 - h) - \beta_h h,$$

Fitting Na current for different VC depolarizing values



Graphical interpretation of H&H model for the Na channel

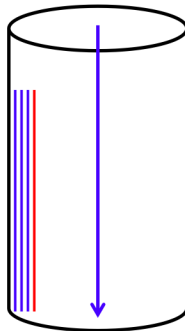
Na channel (by 3 activated m gates and 1 inactivated h gate)



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

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

Open Na channel
Na outside



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

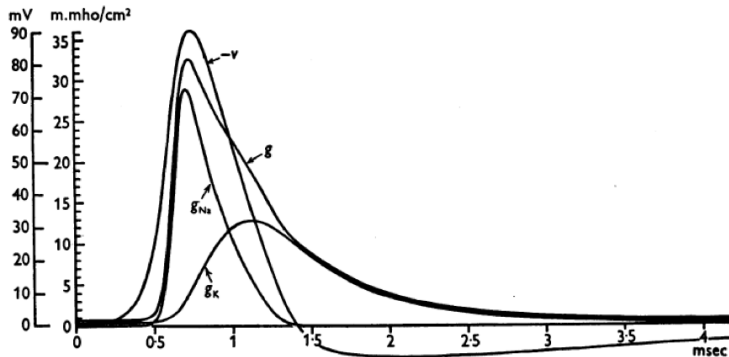


Fig. 17. Numerical solution of eqn. (31) showing components of membrane conductance (g) during propagated action potential ($-V$). Details of the analysis are as in Fig. 15.

Hodgkin–Huxley model

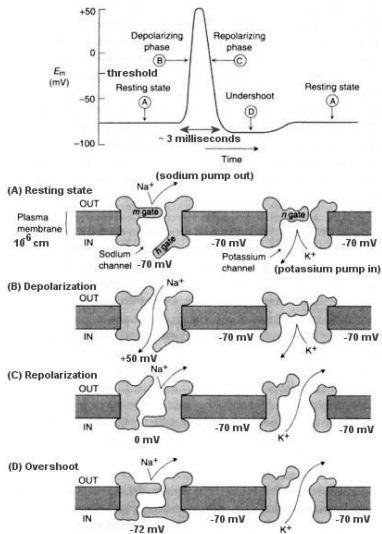
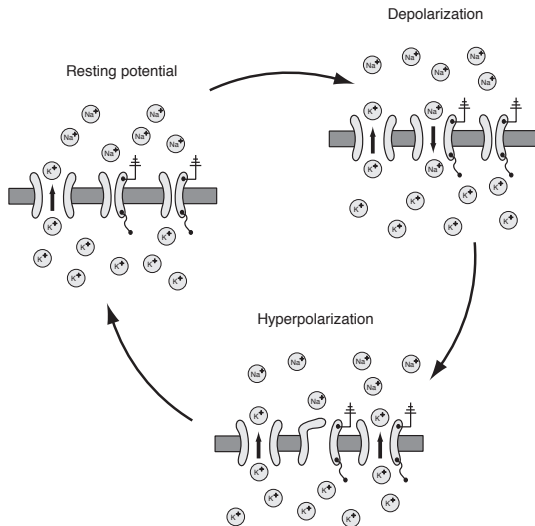


Figure: Typical form of an action potential; redrawn from an oscilloscope picture from Hodgkin and Huxley (1939).

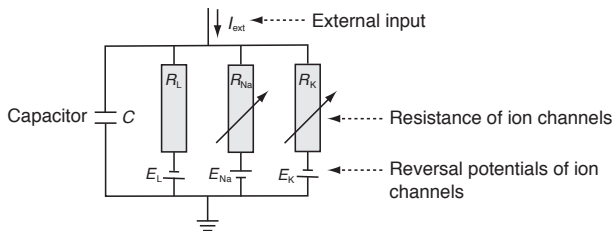
The minimal mechanisms



HH stucture

- ▶ $I_{ion} = g_{ion}(V - E_{ion})$
- ▶ 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

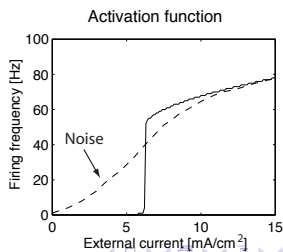
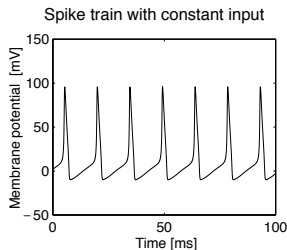
$$C \frac{dV}{dt} = -g_K n^4 (V - E_K) - g_{Na} m^3 h (V - E_{Na}) - g_L (V - E_L) + I_{ext}(t)$$

$$\tau_n(V) \frac{dn}{dt} = -[n - n_0(V)]$$

$$\tau_m(V) \frac{dm}{dt} = -[m - m_0(V)]$$

$$\tau_h(V) \frac{dh}{dt} = -[h - h_0(V)]$$

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



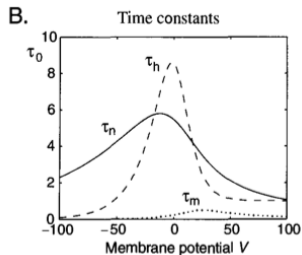
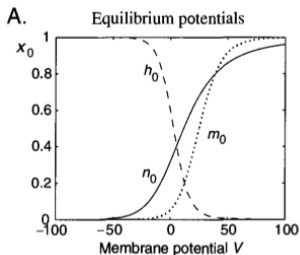
Ion channels resistance

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

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

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

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



Matlab implementation

```
%% 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=400
    % 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_x=1./(Alpha+Beta);
    x_0=Alpha.*tau_x;
    % leaky integration with Euler method
    x=(1-dt./tau_x).*x+dt./tau_x.*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
end
```

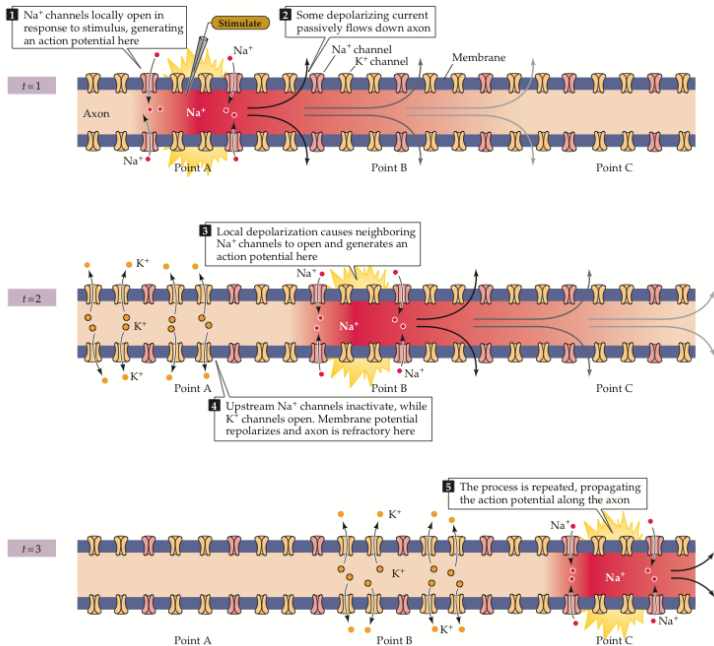

Refractory period

- ▶ 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

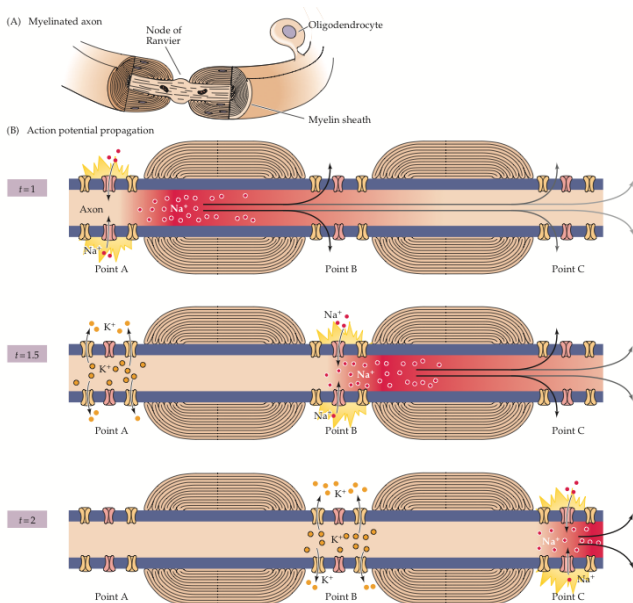
Propagation of action potentials

- ▶ 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

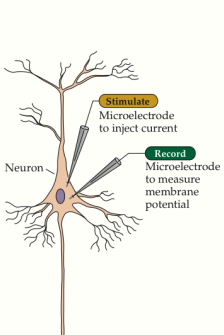


LOSSY transfer

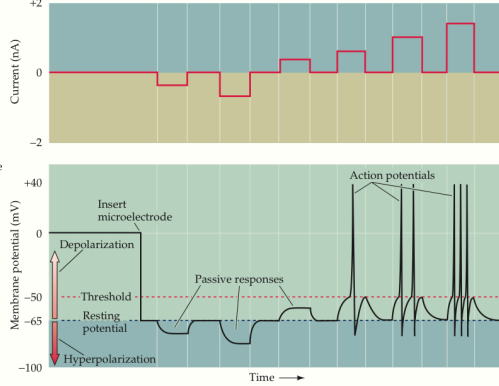


Stimulation of neuron

(A)



(B)



HH - simplification: Hugh Wilson model for neocortical neurons

- ▶ $h = 1 - n$
- ▶ $\tau_m \approx m_0(V)$
- ▶ $h = 1$ 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

$$C \frac{dV}{dt} = -g_K R (V - E_K) - g_{Na}(V)(V - E_{Na}) + I_{ext}(t)$$

$$\tau_R \frac{dR}{dt} = -[R - R_0(V)]$$

Wilson model

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

$$C \frac{dV}{dt} = -g_{Na}(V - E_{Na}) - g_K R(V - E_K) - g_T(V - E_T) - g_H H(V - E_H)$$

$$\tau_R \frac{dR}{dt} = -[R - R_0(V)]$$

$$\tau_T \frac{dT}{dt} = -[T - T_0(V)]$$

$$\tau_H \frac{dH}{dt} = -[H - 3T(V)]$$

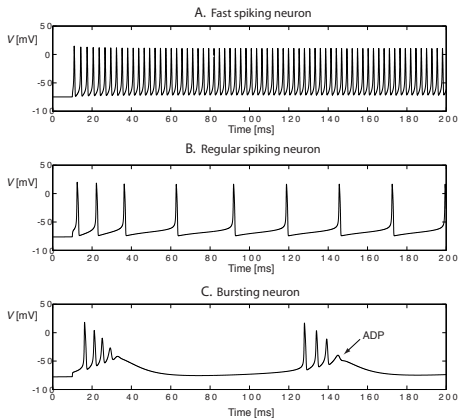
$$g_{Na}(V) = 17.8 + 0.476V + 33.8V^2$$

$$R_0(V) = 1.24 + 3.7V + 3.2V^2$$

$$T_0(V) = 4.205 + 11.6V + 8V^2$$

Wilson model:results

- ▶ RS: regular spiking neuron
- ▶ FS: fast spiking neuron
- ▶ CS: continuously spiking neuron
- ▶ IB: bursting neuron



Matlab implementation

```
%% 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

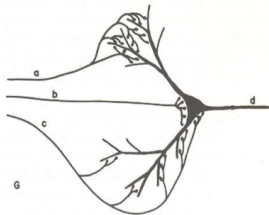
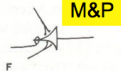
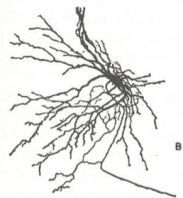
%% Plotting results
plot(x_plot,100*y_plot); xlabel('Time'); ylabel('Membrane potential');
```

Physiology versus Neurons Models

Rall (1964)

Histological Vs. Schematic Neurons

Histological Neurons



Schematic 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

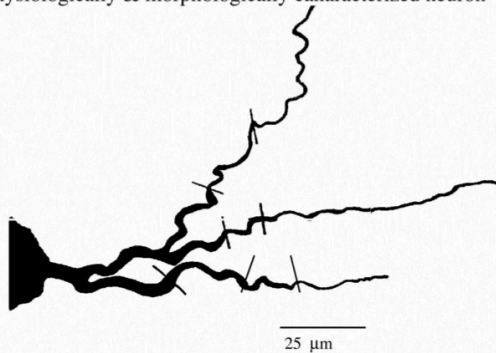
Understanding (mathematically) the impact of (remote) dendritic synapses (the input) on the soma/axon (output) region



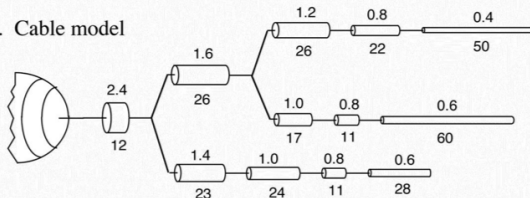
Wilfrid Rall

Cylindric model

A. Physiologically & morphologically characterized neuron

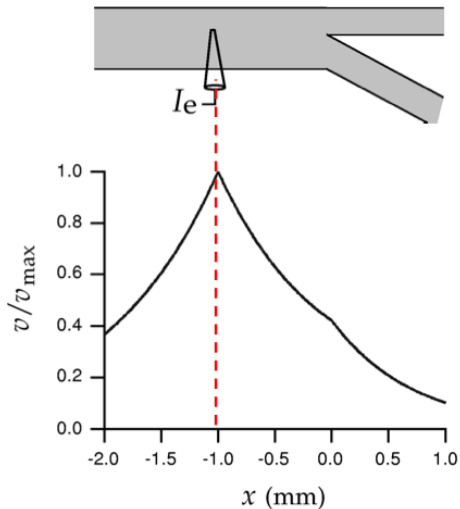


B. Cable model

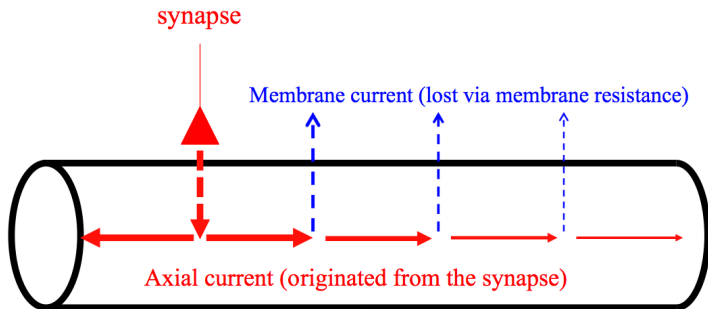


Voltage attenuation

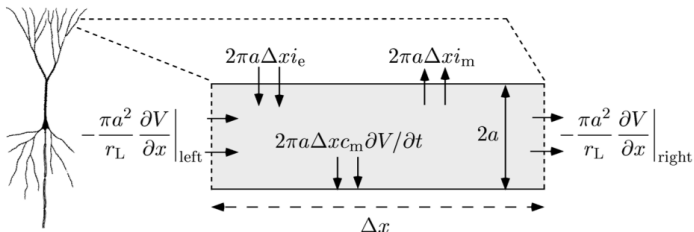
Synaptic potentials attenuate from the synapse origin towards other regions of the dendrites



Axial and membrane current



Passive cable equations



$$\frac{r_m}{r_i} \frac{\partial^2 V(x,t)}{\partial x^2} - r_m c_m \frac{\partial V(x,t)}{\partial t} - V(x,t) = 0$$

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

$$X = x/\lambda$$

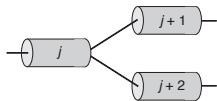
$$T = t/\tau_m$$

Compartmental models

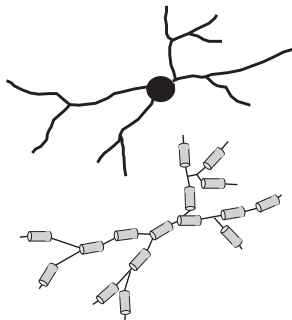
A. Chain of compartments



B. Branching compartments



C. Compartmental reconstruction



Cable theory

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

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

$$\lambda = \sqrt{\frac{dR_m}{2R_i}}$$

$$\tau_m = R_m C_m$$

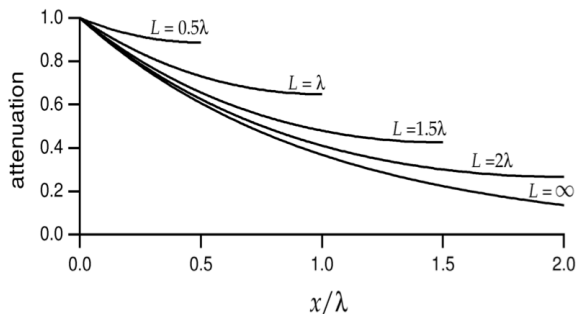
$$V_m = V_0 e^{-\frac{x}{\lambda}}$$

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

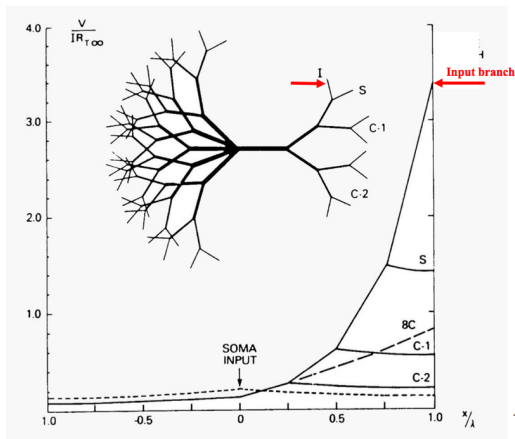
Steady state condition

(“Sealed-end” boundary) $dV/dX = 0$; $x=L$

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



Simulating voltage attenuation



Simulators

The screenshot displays the NEURON software interface with several windows open:

- NEURON Main Menu:** File Edit Build Tools Graph Vector Window
- ModelView[1]:** File menu; 79 sections; 150 segments; * 1 real cells; 0 artificial cells; 0 NetCon objects; 0 LinearMechanism objects; * Density Mechanisms; * 1 point processes (0 can receive events) of 1
- PointProcessManager:** SelectPointProcess; Show; IClamp[0] at: soma(0.5)
- Graph[0]:** Plot of `soma.v(.5)` showing a membrane potential spike from -65 mV to approximately 10 mV over time.
- RunControl:** Init (mV) ← -65; Init & Run; Stop; Continue til (ms) ← 5; Continue for (ms) ← 1; Single Step; t (ms) 5; Tstop (ms) 5; dt (ms) 0.025; Points plotted/ms 40; Scrn update intv (s) 0.05; Real Time (s) 0.07
- NEURON Demonstrati...:** Pyramid: HH soma, passive dendrites; Patch: HH; Stylized; Pyramidal; Release; Synchronizing net (artificial cells); LinearCircuit: Dynamic Clamp; Stochastic Single Channels: HH; No model
- Temperature:** celsius (degC) 15
- VariableTimeStep:** Use variable dt; Absolute Tolerance 0.001; Atol Scale Tool; Details

Further Readings

- Mark F. Bear, Barry W. Connors, and Michael A. Paradiso (2006), **Neuroscience: exploring the brain**, Lippincott Williams & Wilkins , 3rd edition.
- Eric R. Kandel, James H. Schwartz, and Thomas M. Jessell (2000), **Principles of neural science**, McGraw-Hill, 4th edition
- Gordon M. Shepherd (1994), **Neurobiology**, Oxford University Press, 3rd edition.
- Christof Koch (1999), **Biophysics of computation; information processing in single neurons**, Oxford University Press
- Christof Koch and Idan Segev (eds.) (1998), **Methods in neural modelling**, MIT Press, 2nd edition.
- 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.