

Neuroinformatics 2016

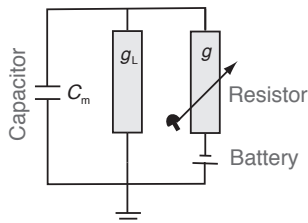
March 3, 2016

Neuron, synapse and neuron models - continued

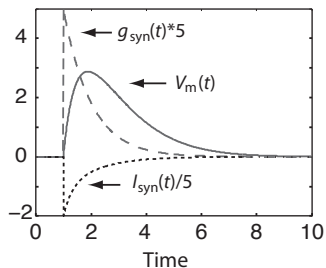
Conductance-based models

$$\begin{aligned}-I_C(t) &= C_m \frac{dV_m(t)}{dt} \\ I_C(t) &= g_L V_m(t) + I_{syn}(t), I_{ext} = 0 \\ I_{syn} &= g_{syn}(t)(V_m(t) - E_{syn}) \\ \tau_{syn} \frac{dg_{syn}(t)}{dt} &= -g_{syn}(t) + \delta(t - t_{pre} - t_{delay})\end{aligned}$$

A. Electric circuit of basic synapse



B. Time course of variables



MATLAB Program

```
1  %% Synaptic conductance model to simulate an EPSP
2  clear; clf; hold on;
3
4  %% Setting some constants and initial values
5  c_m=1; g_L=1; tau_syn=1; E_syn=10; delta_t=0.01;
6  g_syn(1)=0; I_syn(1)=0; v_m(1)=0; t(1)=0;
7
8  %% Numerical integration using Euler scheme
9  for step=2:10/delta_t
10     t(step)=t(step-1)+delta_t;
11     if abs(t(step)-1)<0.001; g_syn(step-1)=1; end
12     g_syn(step)= (1-delta_t/tau_syn) * g_syn(step-1);
13     I_syn(step)= g_syn(step) * (v_m(step-1)-E_syn);
14     v_m(step) = (1-delta_t/c_m*g_L) * v_m(step-1) ...
15                 - delta_t/c_m * I_syn(step);
16 end
17
18 %% Plotting results
19 plot(t,v_m); plot(t,g_syn*5,'r--'); plot(t,I_syn/5,'k:')
```

Hodkin and Huxley experiment NOBEL 1963



**Sir Alan Lloyd
Hodgkin**

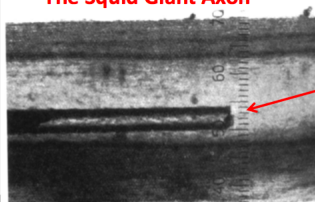


The Squid Giant Axon



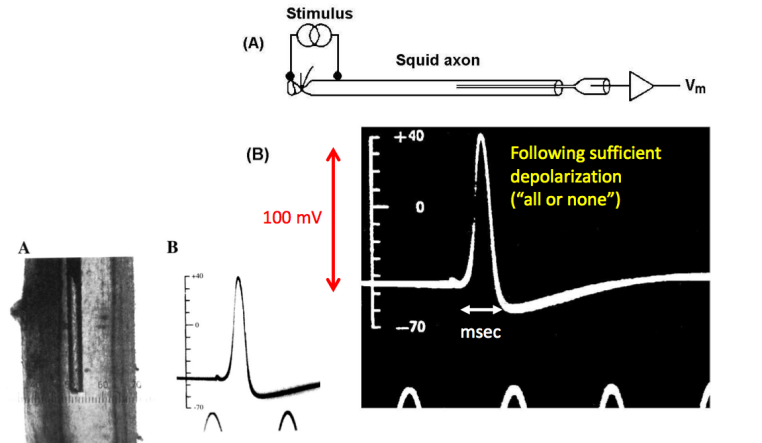
**Sir Andrew Fielding
Huxley**

~ 0.5 mm



Axial electrode

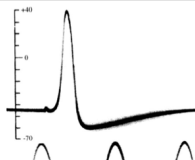
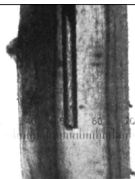
First direct (intracellular) recorded action-potential (spike) - 1939!!



Very nice theory



Sir Alan Lloyd
Hodgkin



Sir Andrew Fielding
Huxley

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

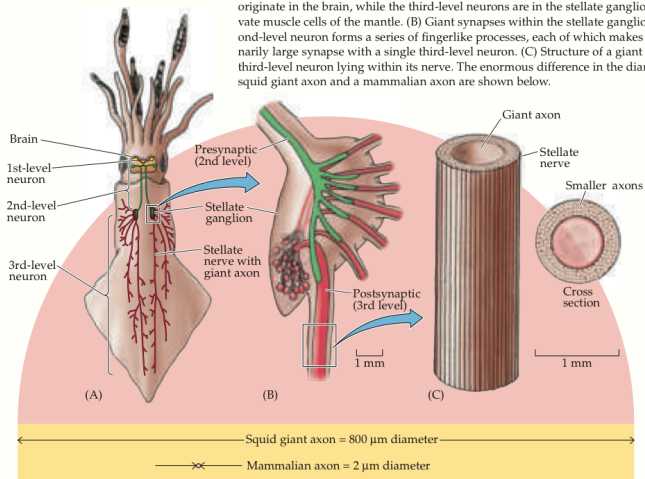
$$\frac{d}{dt} m = \alpha_m (V) (1 - m) - \beta_m (V) m \quad (2)$$

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

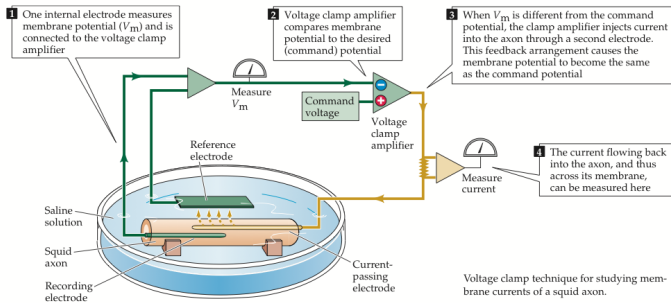
$$\frac{d}{dt} h = \alpha_h (V) (1 - h) - \beta_h (V) h \quad (4)$$

Giant Nerve Cells of Squid

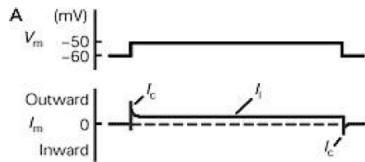
(A) Diagram of a squid, showing the location of its giant nerve cells. Different colors indicate the neuronal components of the escape circuitry. The first- and second-level neurons originate in the brain, while the third-level neurons are in the stellate ganglion and innervate muscle cells of the mantle. (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. (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.



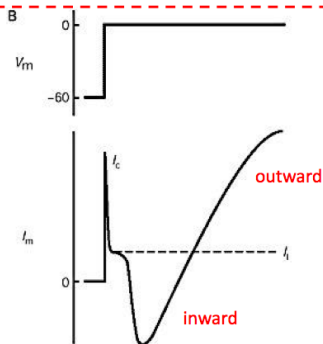
Voltage Clamp Method



Membrane current in response to voltage clamp (VC)



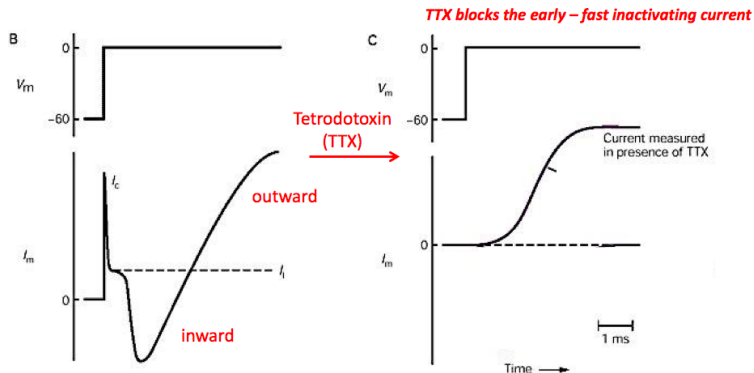
For **subthreshold** depolarizing voltage clamp, the recorded membrane current is the current that flows via the leak (passive) conductance + a small capacitive current (at start and end of the VC)



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

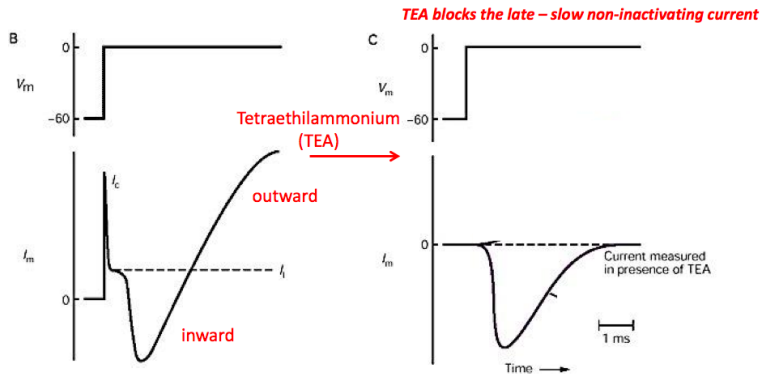


2

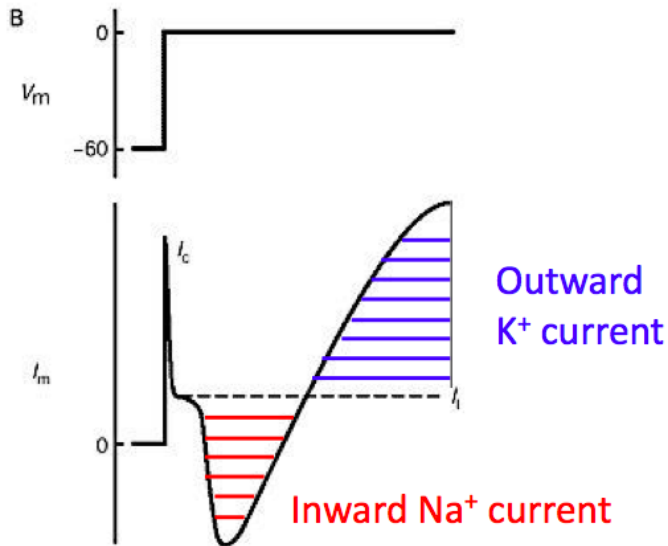
אפריל 13

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

2 different currents flow via the membrane during the spike

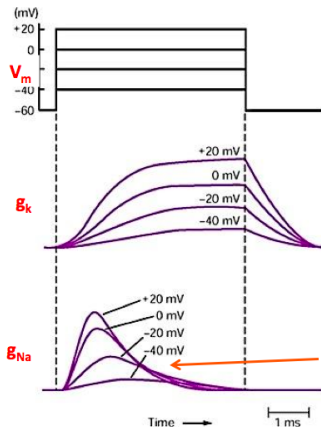


Changing ion concentration at bath with giant axon showed that early current is carried by Na^+ ions and late one by K^+ ions



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

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

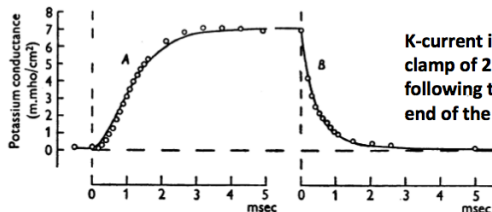


1. The slow (K) current (conductance) does not inactivate during VC

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



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 $\exp(-4t)$)

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

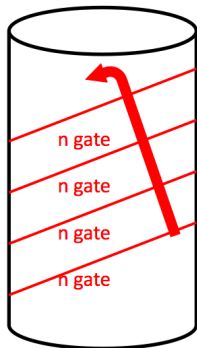
n represents the proportion of K-ion channels in the open state

"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

13 אפריל

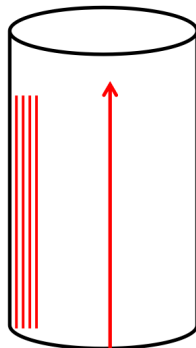
Graphical interpretation of H&H model for the K channel

Closed K channel (by 4 n gates)



K^+
INSIDE

Open K channel (by 4 n gates)



K^+
INSIDE

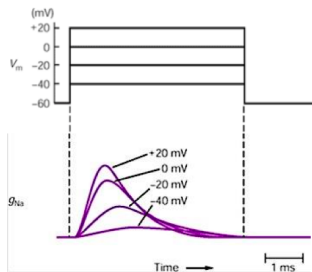
4 n gates open with
depolarization

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

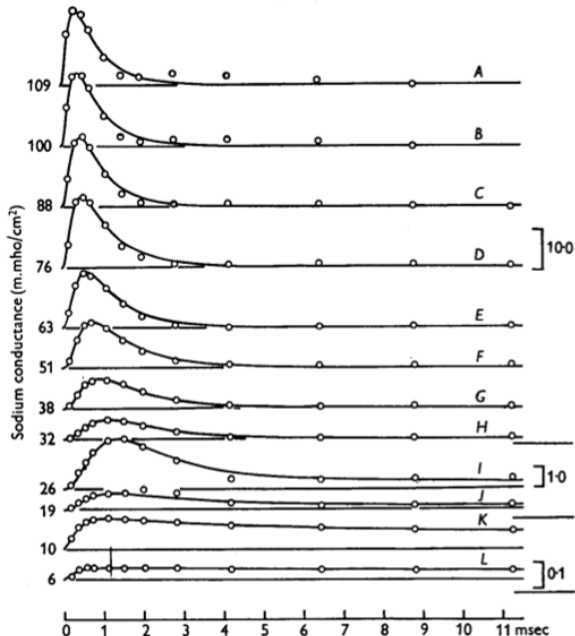


$$g_{Na} = m^3 h \bar{g}_{Na},$$

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

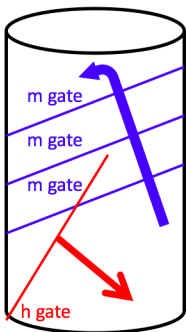
$$\frac{dh}{dt} = \alpha_h (1 - h) - \beta_h h,$$

Fitting Na current for different VC depolarizing values



Graphical interpretation of H&H model for the Na channel

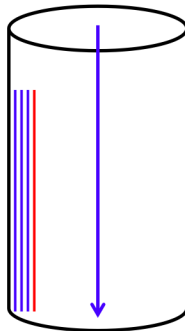
Na channel (by 3 activated m gates and 1 inactivated h gate)



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

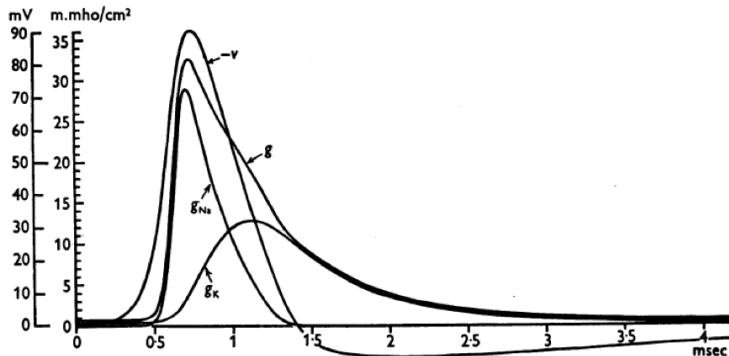


Fig. 17. Numerical solution of eqn. (31) showing components of membrane conductance (g) during propagated action potential ($-V$). Details of the analysis are as in Fig. 15.

Hodgkin–Huxley model

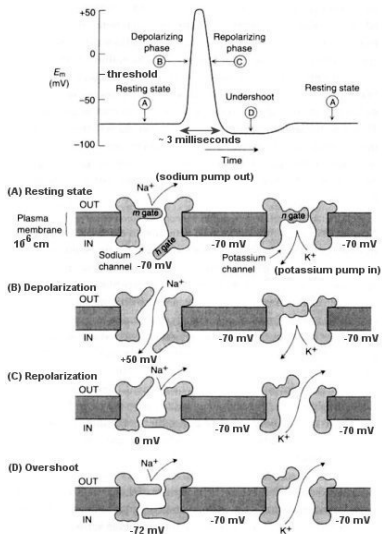
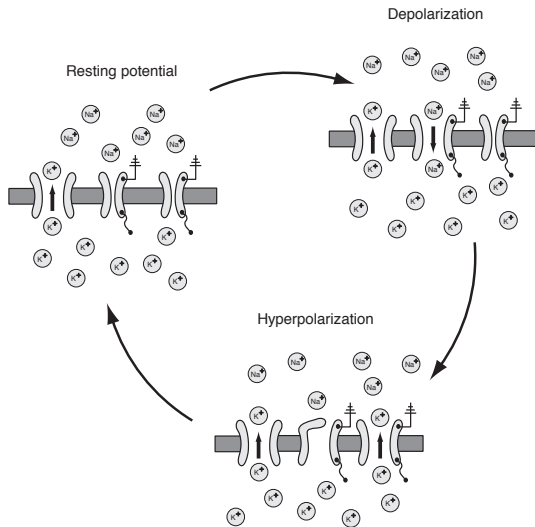


Figure: Typical form of an action potential; redrawn from an oscilloscope picture from Hodgkin and Huxley (1939).

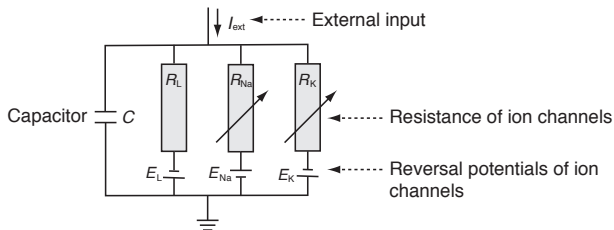
The minimal mechanisms



HH stucture

- ▶ $I_{ion} = \hat{g}_{ion}(V - E_{ion})$
- ▶ 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

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

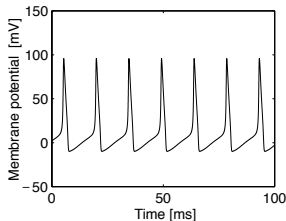
$$\tau_n(V) \frac{dn}{dt} = -[n - n_0(V)]$$

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

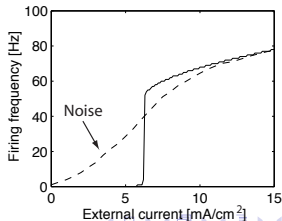
$$\tau_h(V) \frac{dh}{dt} = -[h - h_0(V)]$$

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

Spike train with constant input



Activation function



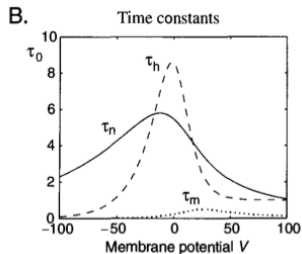
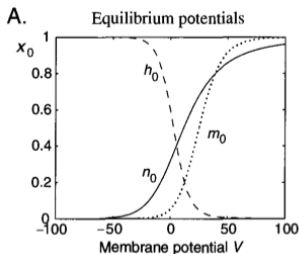
Ion channels resistance

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

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

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

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



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)=x;
        y_plot(t_rec)=V;
    end
end
```

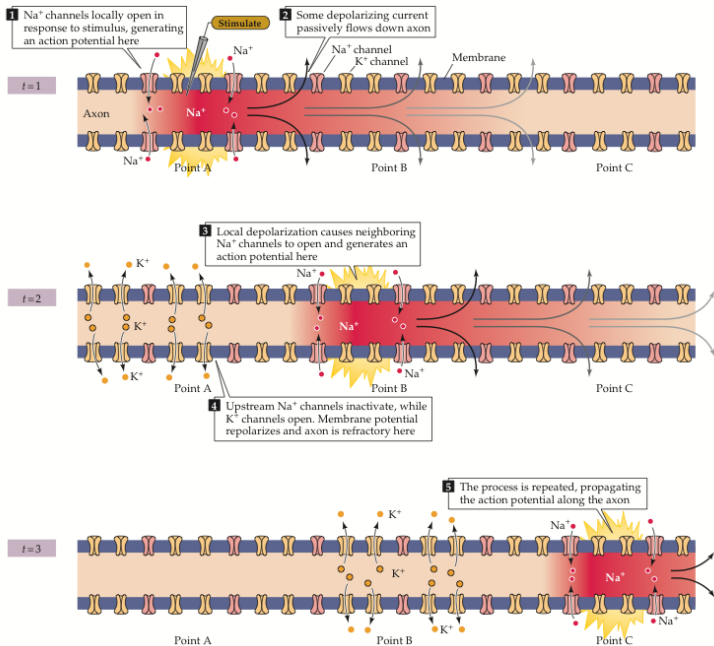
Refractory period

- ▶ 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

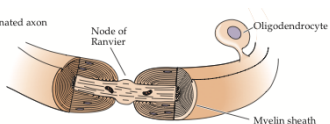
- ▶ action potentials=spikes travel about 10 m/s.
- ▶ non-loss signal transfer - SLOW
- ▶ myelin = FAST lossy signal transfer in axon
- ▶ Ranvier nodes = AP regeneration
- ▶ myelination happens after second year of age
- ▶ Alzheimer disease - Demyelination!

NON-LOSS transfer

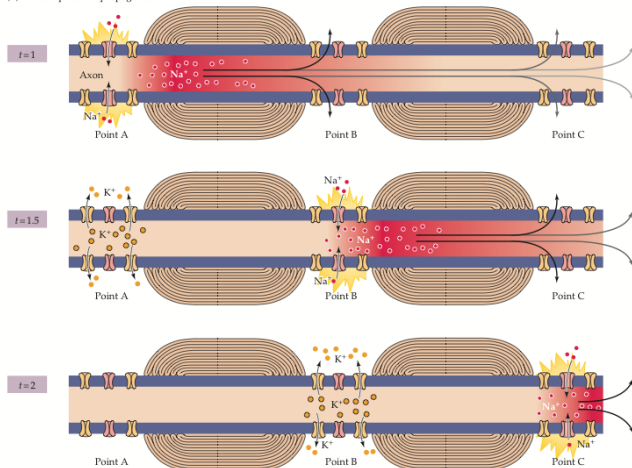


LOSSY transfer

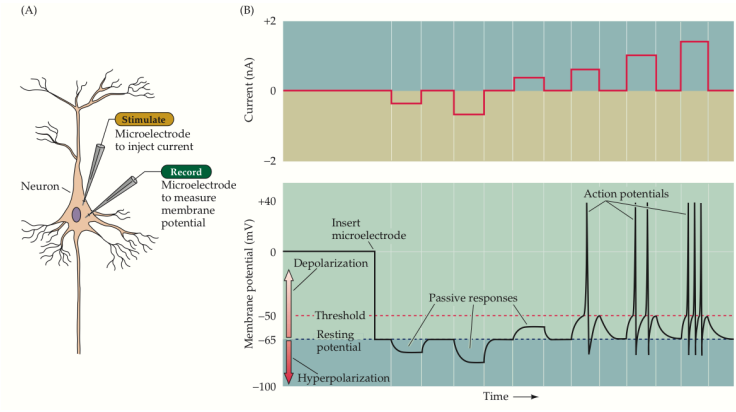
(A) Myelinated axon



(B) Action potential propagation



Stimulation of neuron



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

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

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

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

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

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

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

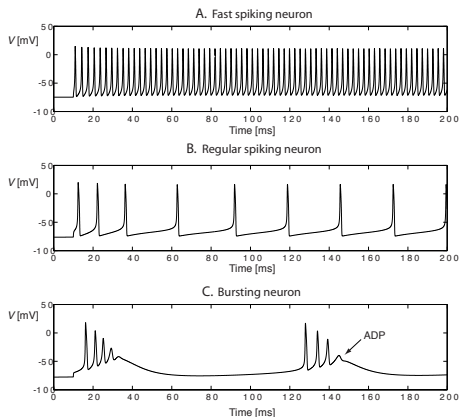
$$g_{Na}(V) = 17.8 + 0.476V + 33.8V^2$$

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

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

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

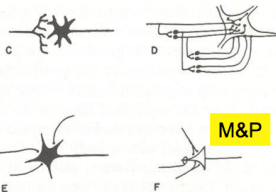
%% Plotting results
plot(x_plot,100*y_plot); xlabel('Time'); ylabel('Membrane potential');
```

Physiology versus Neurons Models

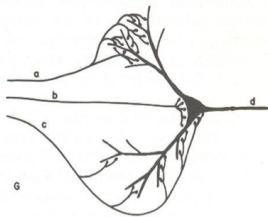
Rall (1964)

Histological Vs. Schematic Neurons

Histological Neurons

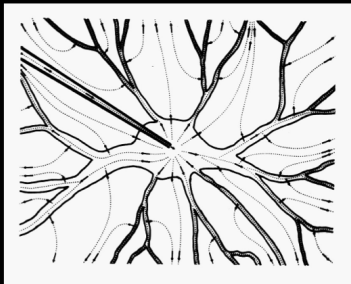


Schematic Neurons



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

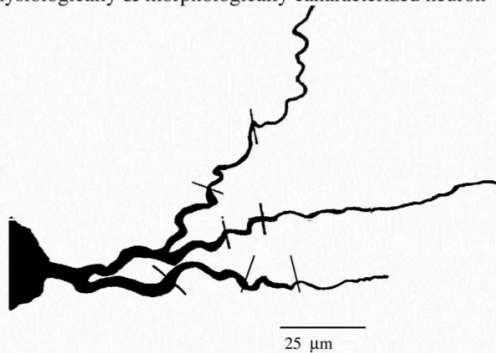
Understanding (mathematically) the impact of (remote) dendritic synapses (the input) on the soma/axon (output) region



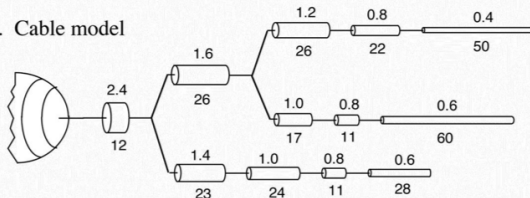
Wilfrid Rall

Cylindric model

A. Physiologically & morphologically characterized neuron

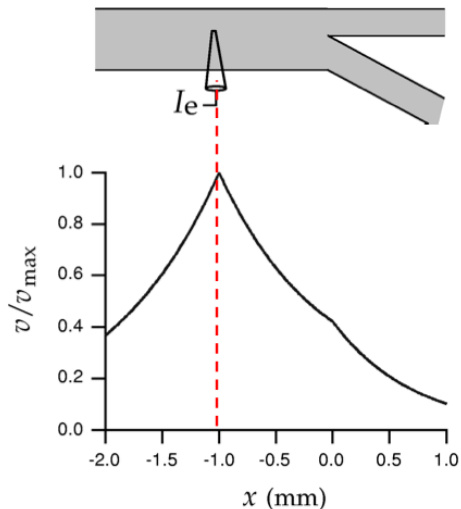


B. Cable model

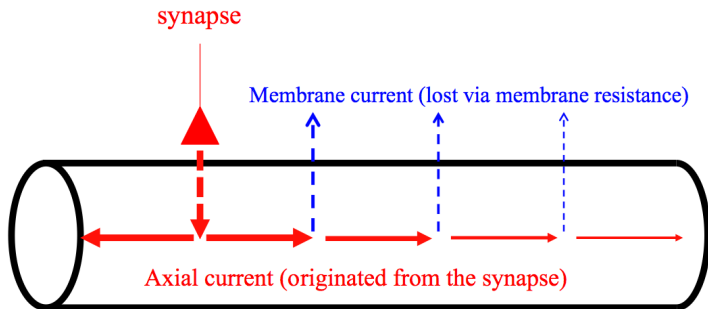


Voltage attenuation

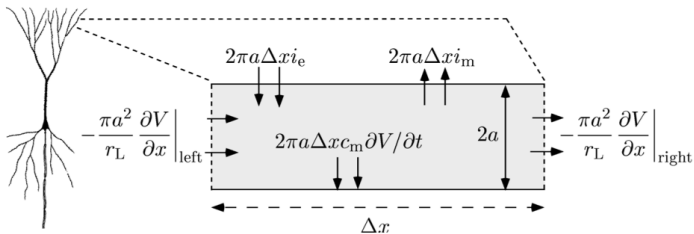
Synaptic potentials attenuate from the synapse origin towards other regions of the dendrites



Axial and membrane current



Passive cable equations



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

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

$$X = x/\lambda$$

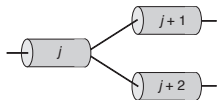
$$T = t/\tau_m$$

Compartmental models

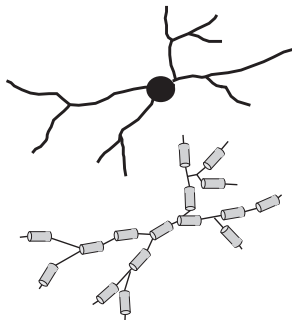
A. Chain of compartments



B. Branching compartments



C. Compartmental reconstruction



Cable theory

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

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

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

$$\tau_m = R_m C_m$$

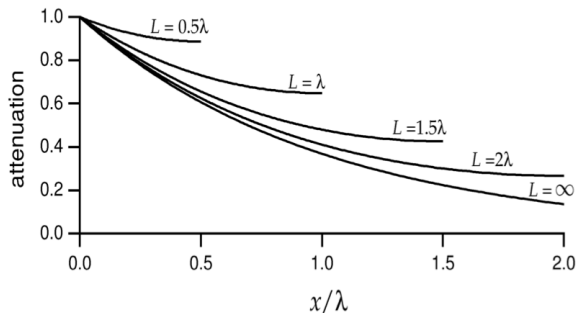
$$V_m = V_0 e^{-\frac{x}{\lambda}}$$

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

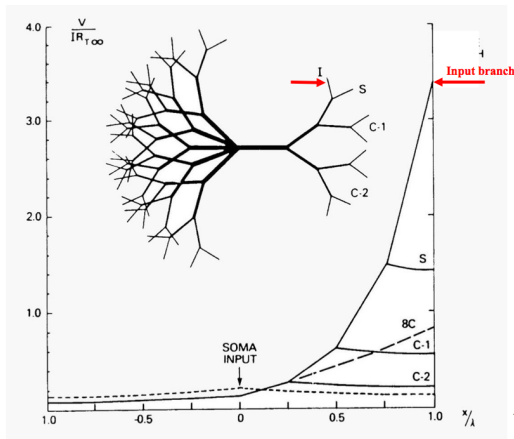
Steady state condition

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

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



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
- Graph[0]:** x: -0.5 : 5.5 y: -92 : 52. Plot of somav(.5) showing a membrane potential spike from -65 mV to approximately 10 mV, peaking at t=0.5 ms.
- 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 inv (s) 0.05; Real Time (s) 0.07
- NEURON Demonstrati...:** Pyramidat: HH soma, passive dendrites; Patch: HH; Stylized; Pyramidat; 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
- PointProcessManager:** SelectPointProcess; Show; IClamp[0] at: soma(0.5); A diagram of a neuron with a vertical dendrite and a basal soma.

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.