

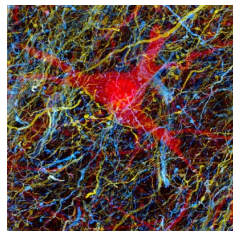
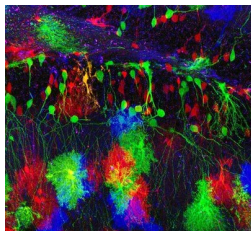
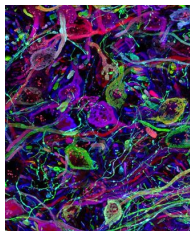
Neuroinformatics 2012

February 21, 2013

Basic neuron models-brainbows

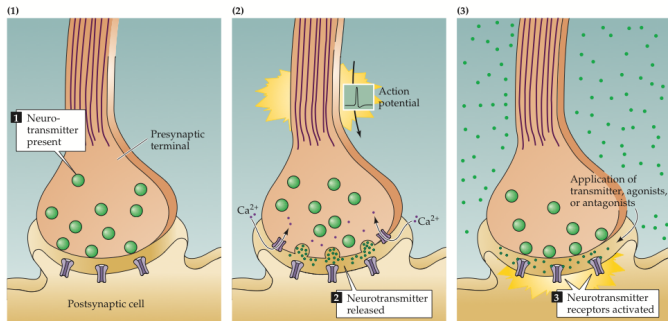
Brainbows

- ▶ Auditory portion of a mouse brainstem. A special gene (extracted from coral and jellyfish) was inserted into the mouse in order to map intricate connection. As the mouse thinks, fluorescent proteins spread out along neural pathways
- ▶ This view of the hippocampus shows the smaller glial cells (small ovals) in the proximity of neurons (larger with more filaments).
- ▶ A single neuron (red) in the brainstem
- ▶ http://www.wired.com/science/discoveries/multimedia/2007/10/gallery_fluorescentneurons



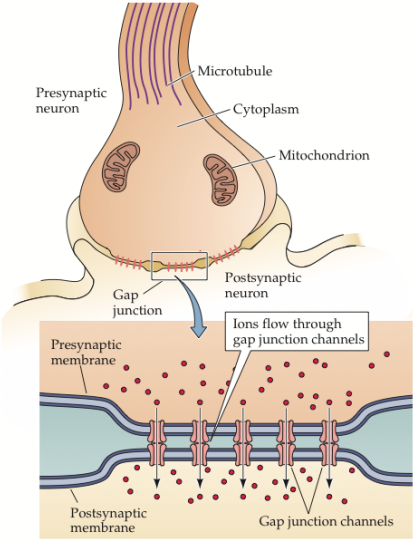
Neurotransmitter release

Demonstrating the identity of a neurotransmitter at a synapse requires showing (1) its presence, (2) its release, and (3) the postsynaptic presence of specific receptors.

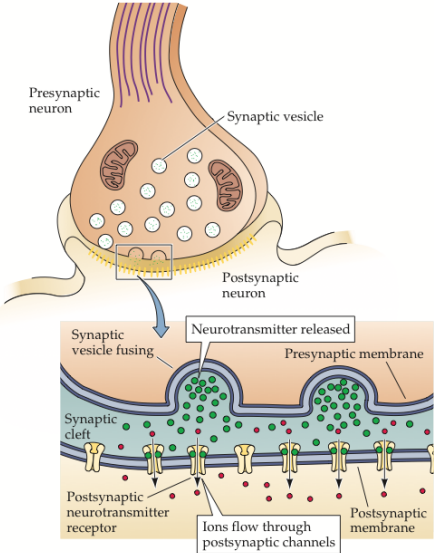


Electrical Synapse

(A) ELECTRONIC SYNAPSE

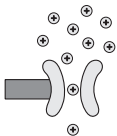


(B) CHEMICAL SYNAPSE

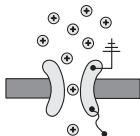


Ion channels

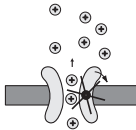
A. Leakage channel



B. Voltage-gated ion channel

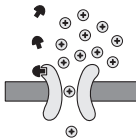


C. Ion pump

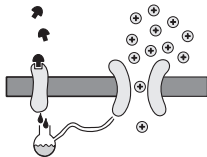


Neurotransmitter-gated ion channels

D. Ionotropic

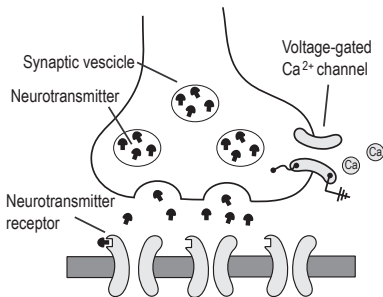


E. Metabotropic (second messenger)



Synapse

- ▶ excitatory neurotransmitters-DA (dopamine), Gu (glutamate), GABA (A-fast, B-slow)
- ▶ inhibitory-neurotransmitters GABA (Gamma-aminobutyric acid), http://cs.wikipedia.org/wiki/Kyselina_gamma-aminomseln
- ▶ synaptic cleft - 1μ , synaptic vesicles



excitatory and inhibitory potentials

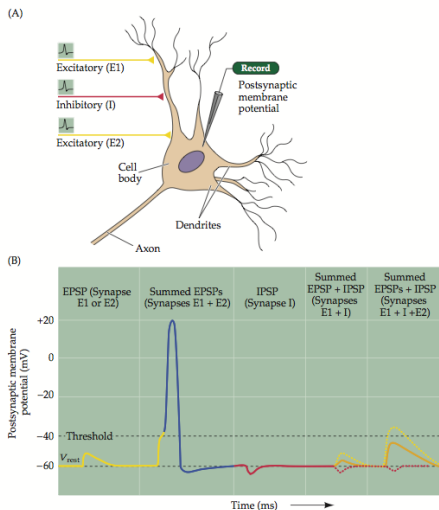
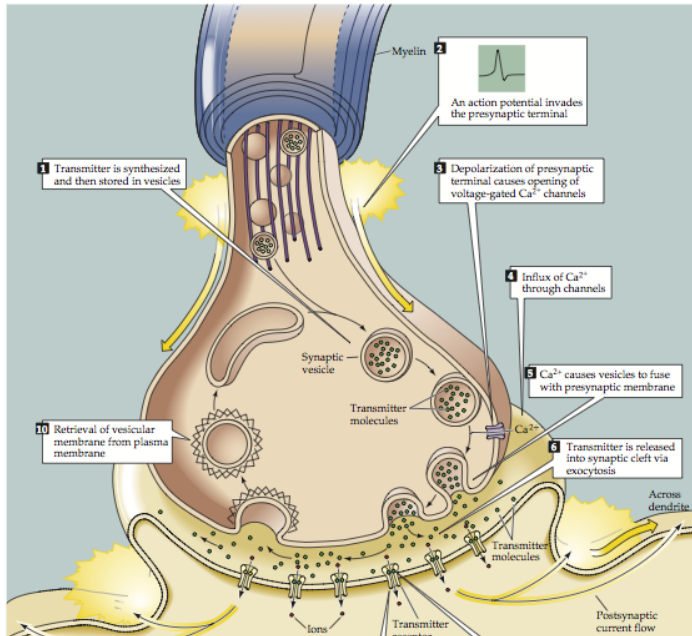


Figure 5.20 Summation of postsynaptic potentials. (A) A microelectrode records the postsynaptic potentials produced by the activity of two excitatory synapses (E1 and E2) and an inhibitory synapse (I). (B) Electrical responses to synaptic activation. Stimulating either excitatory synapse (E1 or E2) produces a subthreshold EPSP, whereas stimulating both synapses at the same time (E1 + E2) produces a suprathreshold EPSP that evokes a postsynaptic action potential (shown in blue). Activation of the inhibitory synapse alone (I) results in a hyperpolarizing IPSP. Summing this IPSP (dashed red line) with the EPSP (dashed yellow line) produced by one excitatory synapse (E1 + I) reduces the amplitude of the EPSP (orange line), while summing it with the suprathreshold EPSP produced by activating synapses E1 and E2 keeps the postsynaptic neuron below threshold, so that no action potential is evoked.

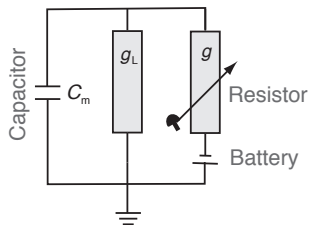
Ca signalling



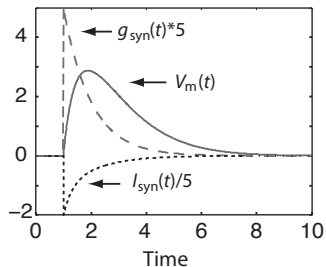
Conductance-based models

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

A. Electric circuit of basic synapse



B. Time course of variables

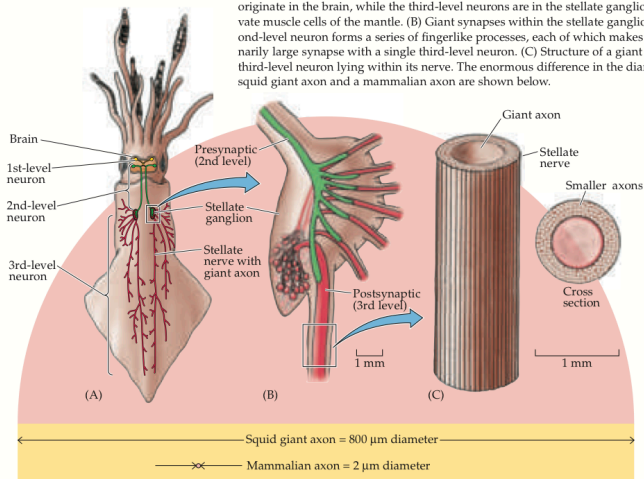


MATLAB Program

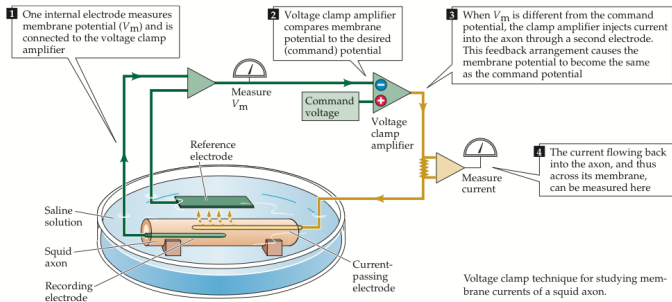
```
1  %% Synaptic conductance model to simulate an EPSP
2  clear; clf; hold on;
3
4  %% Setting some constants and initial values
5  c_m=1; g_L=1; tau_syn=1; E_syn=10; delta_t=0.01;
6  g_syn(1)=0; I_syn(1)=0; v_m(1)=0; t(1)=0;
7
8  %% Numerical integration using Euler scheme
9  for step=2:10/delta_t
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:')
```

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



Hodgkin–Huxley model

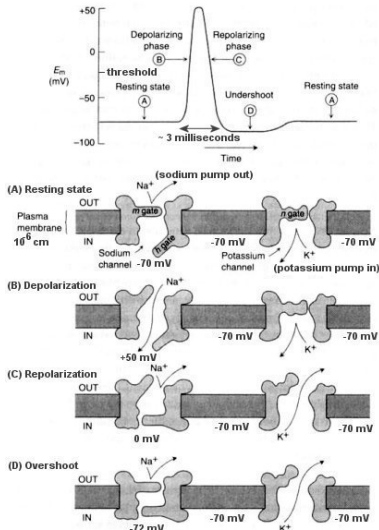
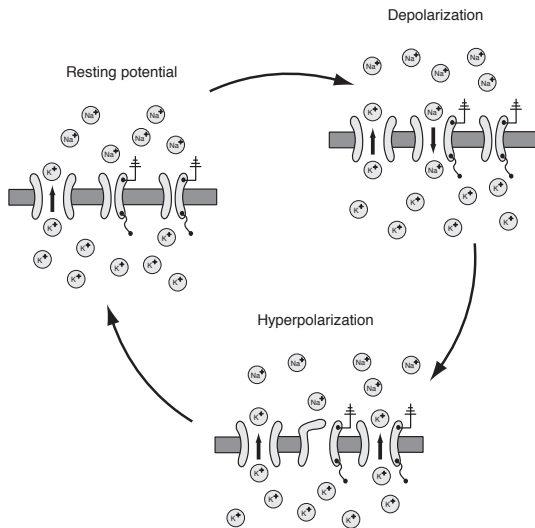


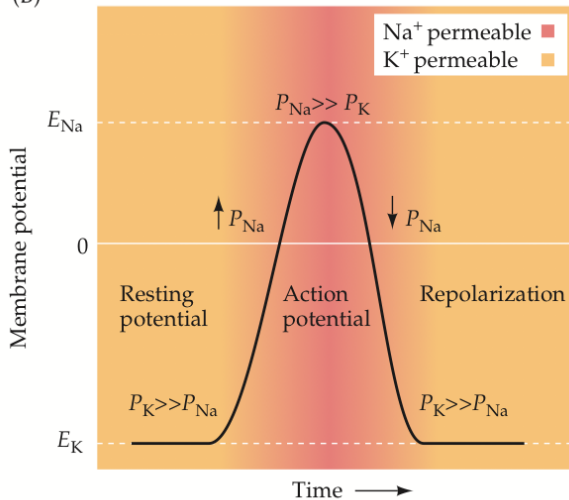
Figure: Typical form of an action potential; redrawn from an oscilloscope picture from Hodgkin and Huxley (1939).

The minimal mechanisms



Concentration of Na , K

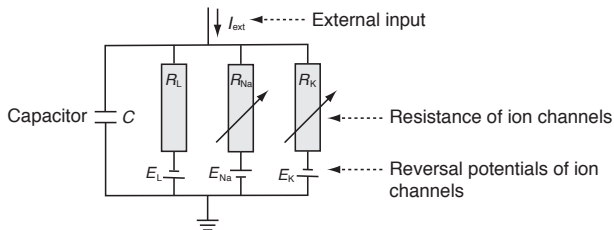
(B)



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

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

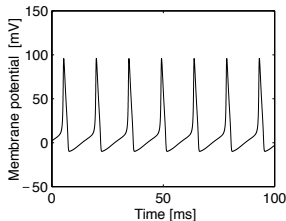
$$\tau_n(V) \frac{dn}{dt} = -[n - n_0(V)]$$

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

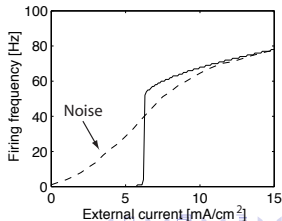
$$\tau_h(V) \frac{dh}{dt} = -[h - h_0(V)]$$

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

Spike train with constant input



Activation function



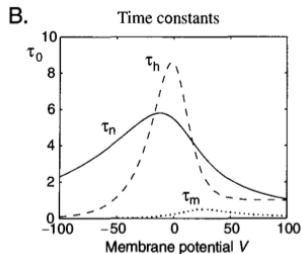
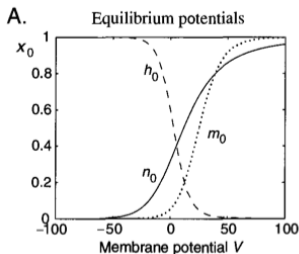
Ion channels resistance

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

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

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

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



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
```

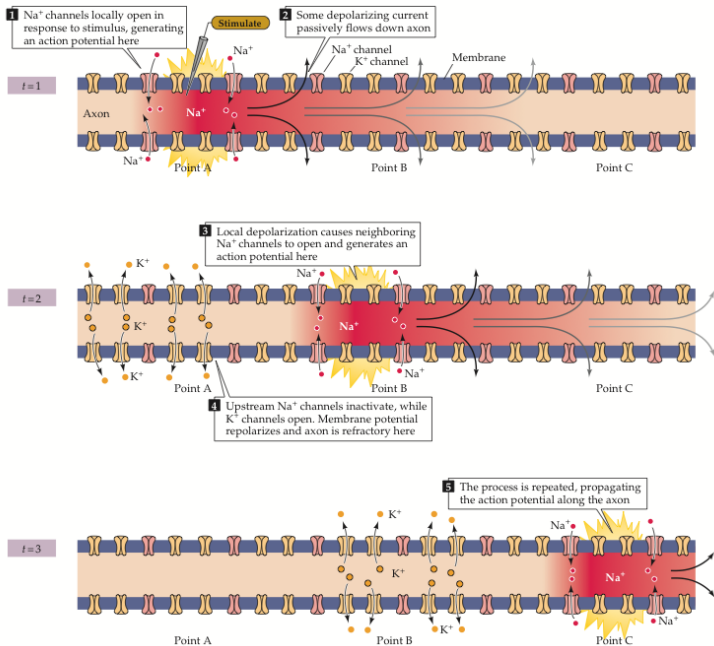
Refractory period

- ▶ 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

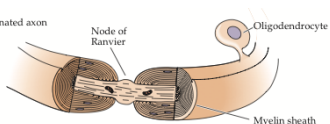
- ▶ action potentials=spikes travel about 10 m/s.
- ▶ non-loss signal transfer - SLOW
- ▶ myelin = FAST lossy signal transfer in axon
- ▶ Ranvier nodes = AP regeneration
- ▶ myelination happens after second year of age
- ▶ Alzheimer deased - DESmyelination!

NON-LOSS transfer

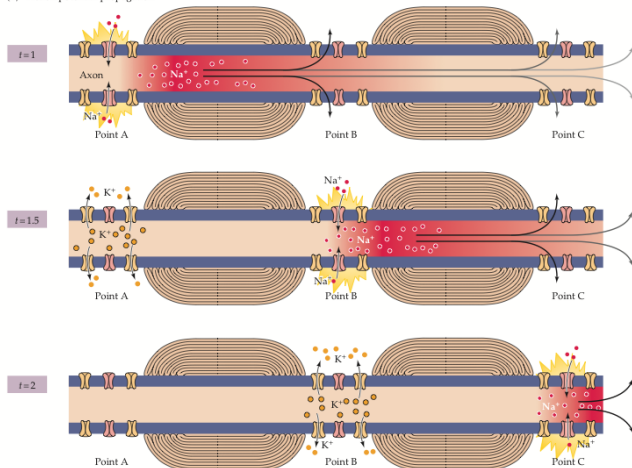


LOSSY transfer

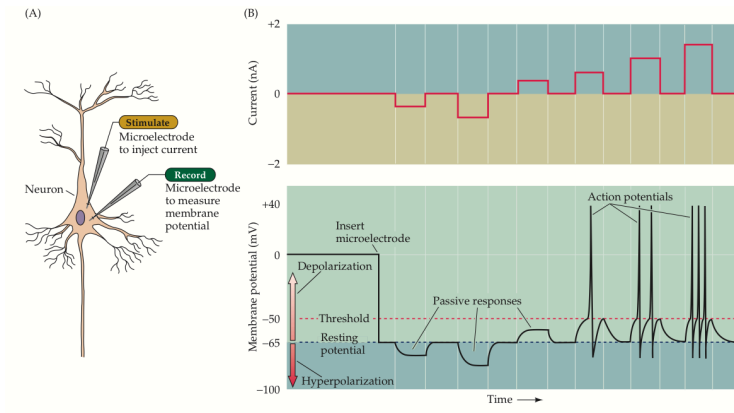
(A) Myelinated axon



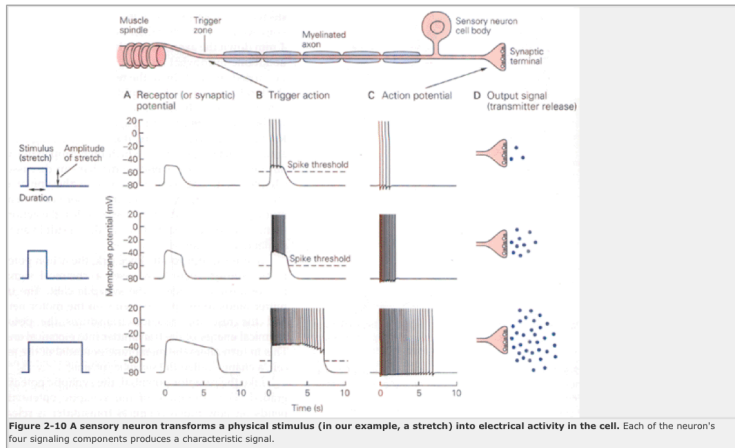
(B) Action potential propagation



Stimulation of neuron



Signal transmission



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

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

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

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

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

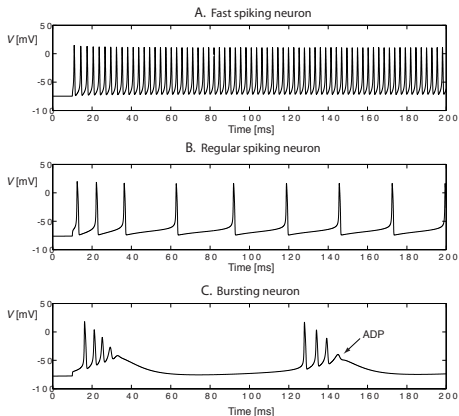
$$g_{Na}(V) = 17.8 + 0.476V + 33.8V^2$$

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

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

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

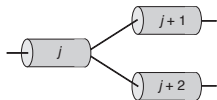
%% Plotting results
plot(x_plot,100*y_plot); xlabel('Time'); ylabel('Membrane potential');
```

Compartmental models

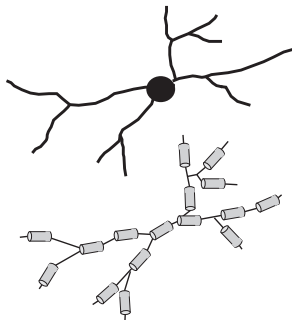
A. Chain of compartments



B. Branching compartments



C. Compartmental reconstruction



Cable theory

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

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

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

$$\tau_m = R_m C_m$$

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

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

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]:** Plot of somav(.5) vs time. The y-axis ranges from -80 to 40 mV, and the x-axis ranges from 0 to 5 ms. The plot shows a subthreshold depolarization peaking at approximately 20 mV around 0.5 ms.
- PointProcessManager:** SelectPointProcess; Show; IClamp[0] at: soma(0.5)
- 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

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
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- Christof Koch (1999), **Biophysics of computation; information processing in single neurons**, Oxford University Press
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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.