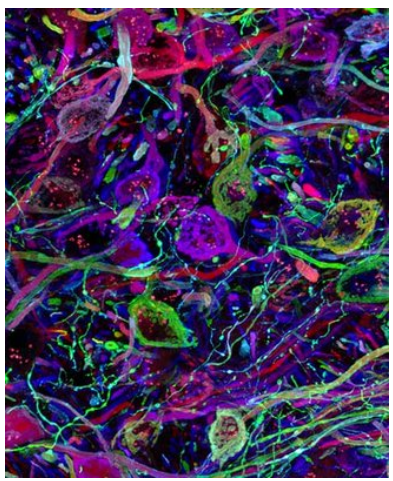
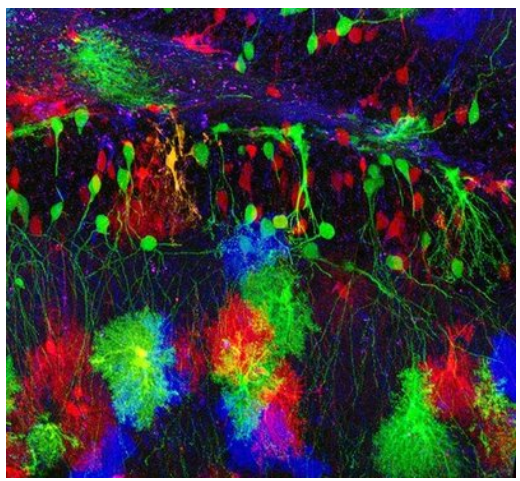
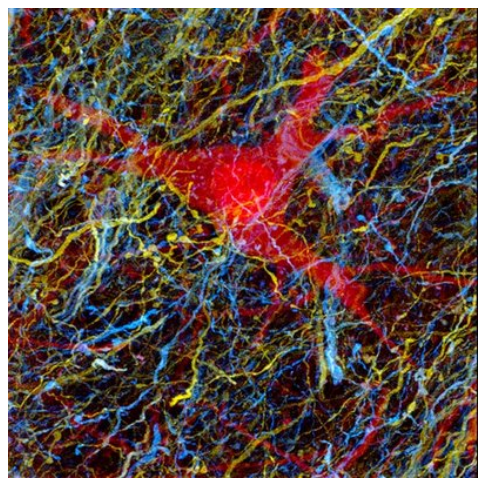
Neuroinformatics 2012

March 13, 2014

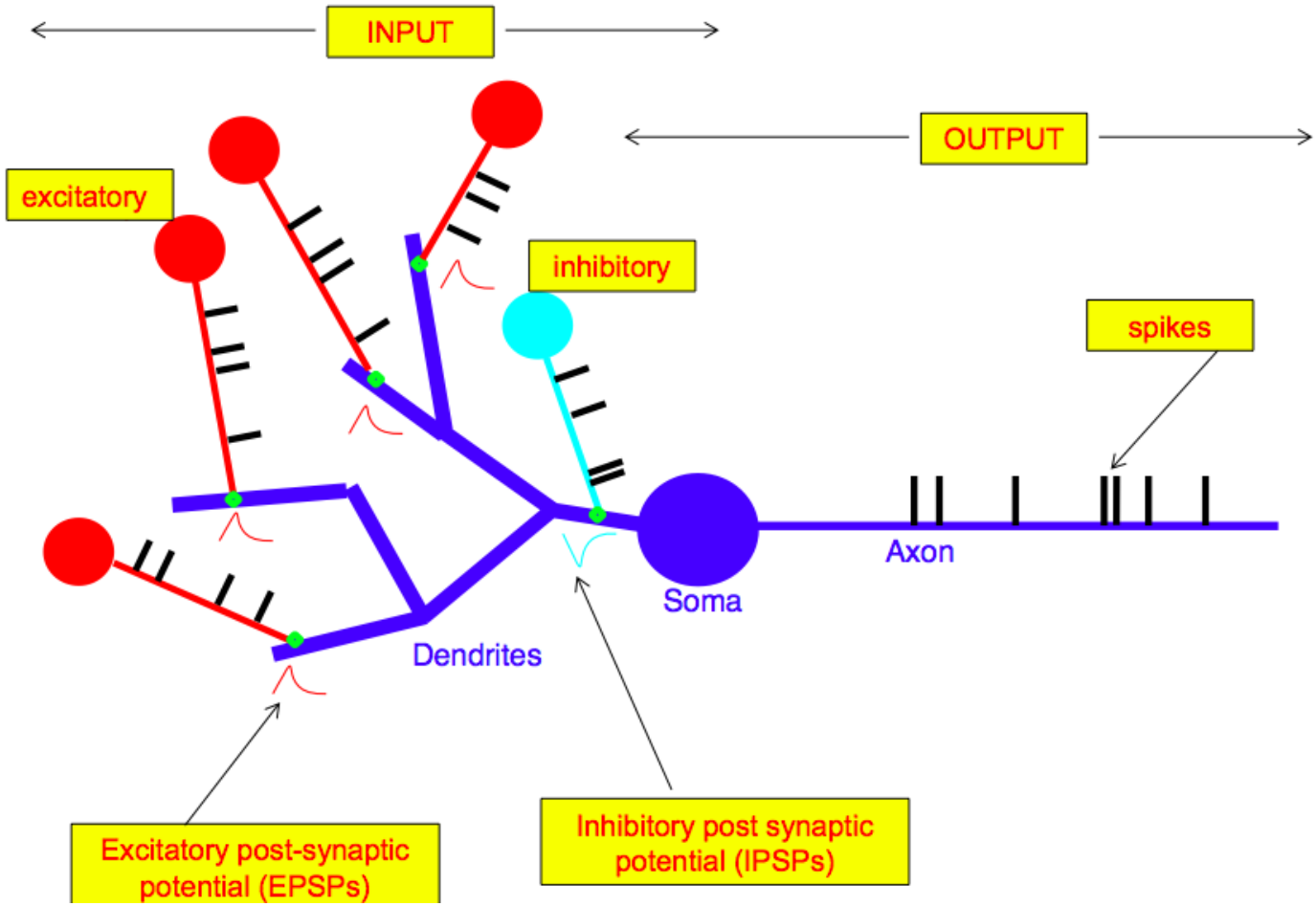
Basic neuron models-brainbows

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`

Neuron as input-output device



Neuron types

Classification by anatomical features ("the face" of dendrites and axons)

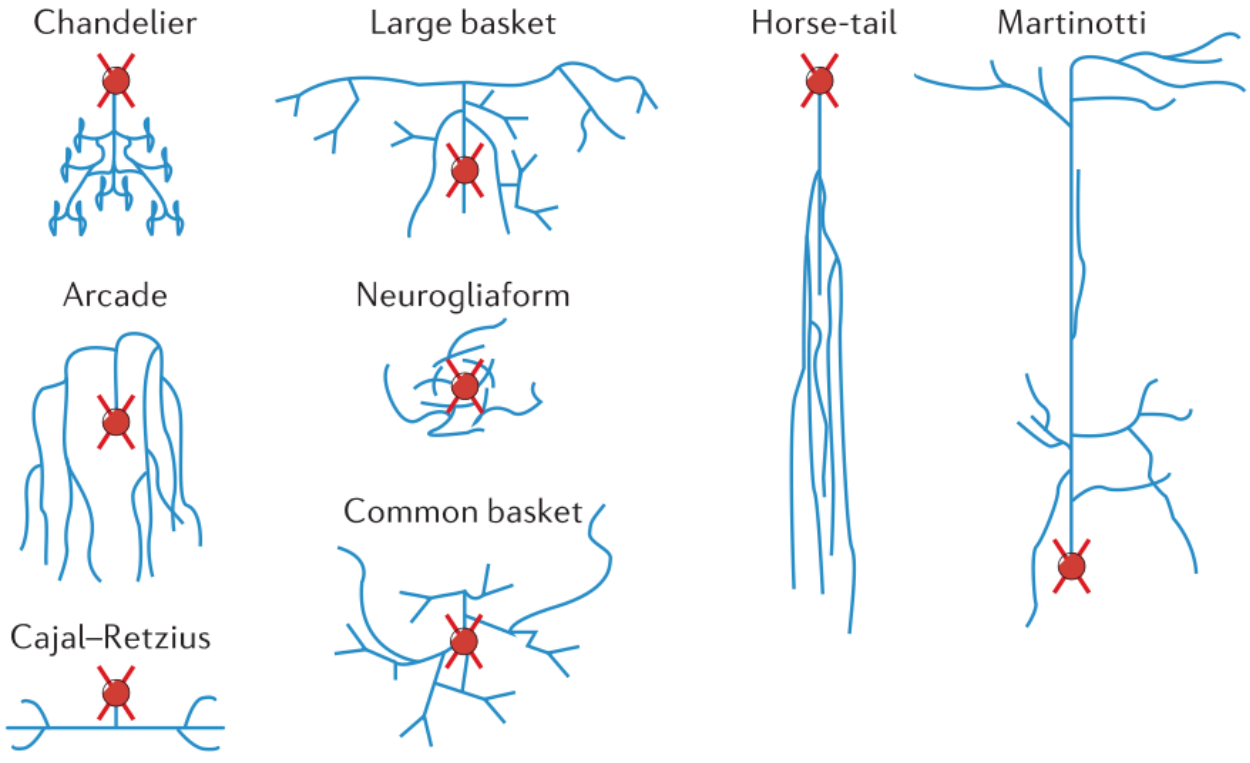
Classification – functional (e.g., Excitatory (principal) vs. Inhibitory (inter) neurons)

Classification using electrical/spiking activity pattern

Classification using chemical characteristics

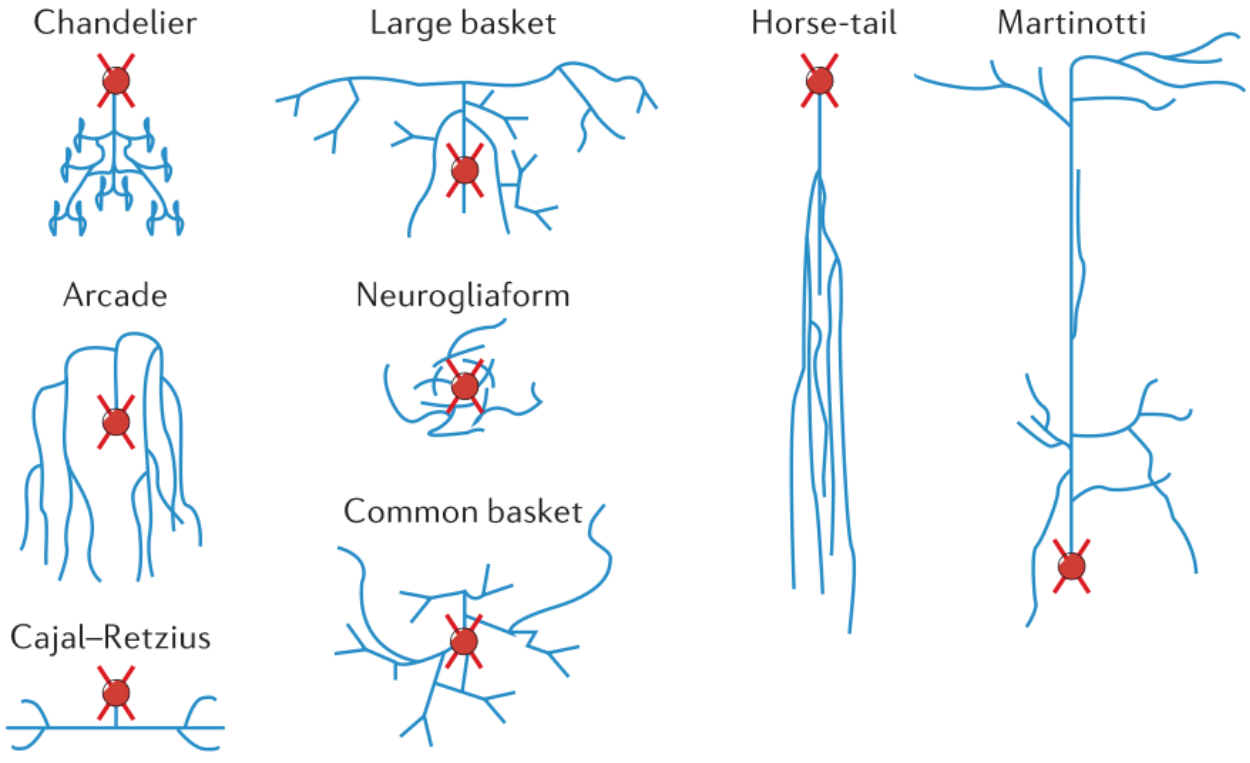
Classification using gene expression

Morphometric-based classification of (inhibitory) interneurons



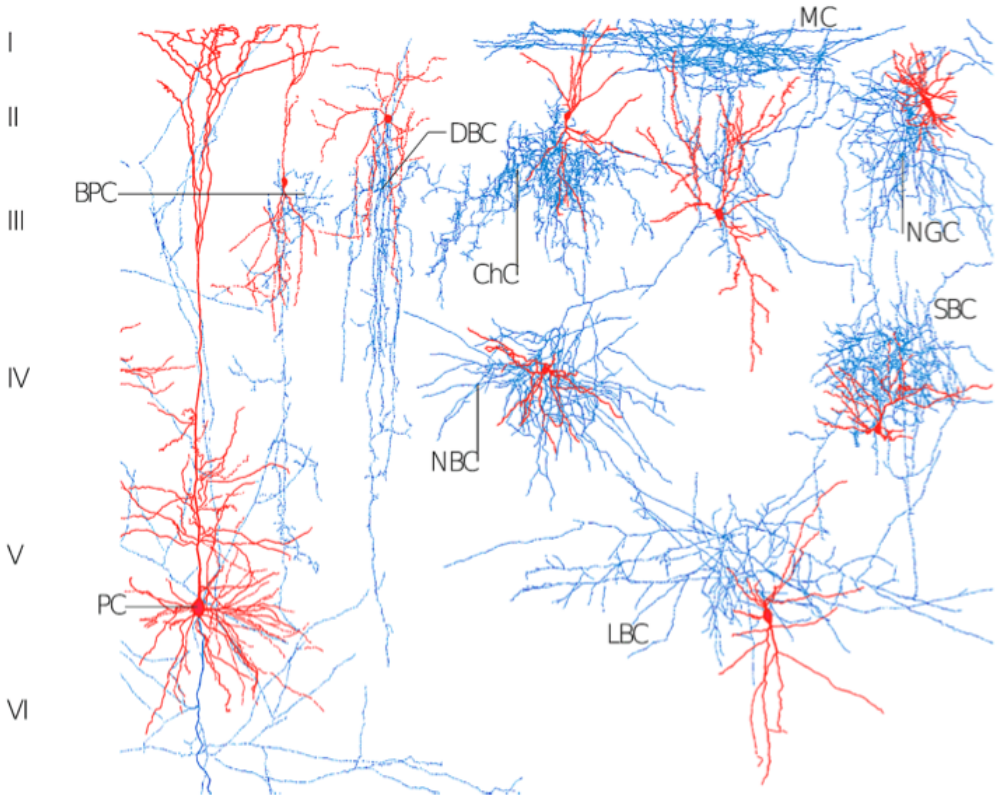
DeFelipe et al., Nature Review neuroscience, 2013

Morphometric-based classification of (inhibitory) interneurons



DeFelipe et al., Nature Review neuroscience, 2013

Microcircuit of the Neocortex

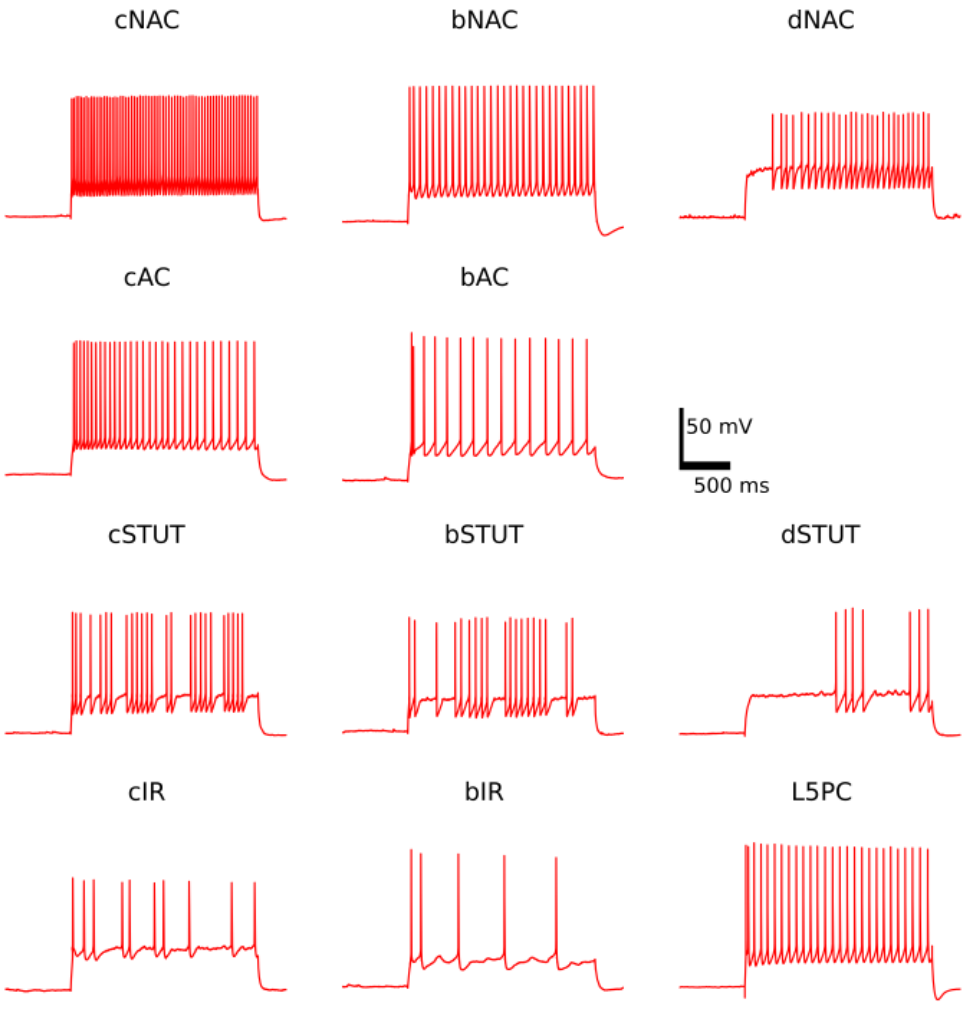


Principal neurons (excitatory) - axon projects to other brain regions

Interneurons (inhibitory) – local axonal projection

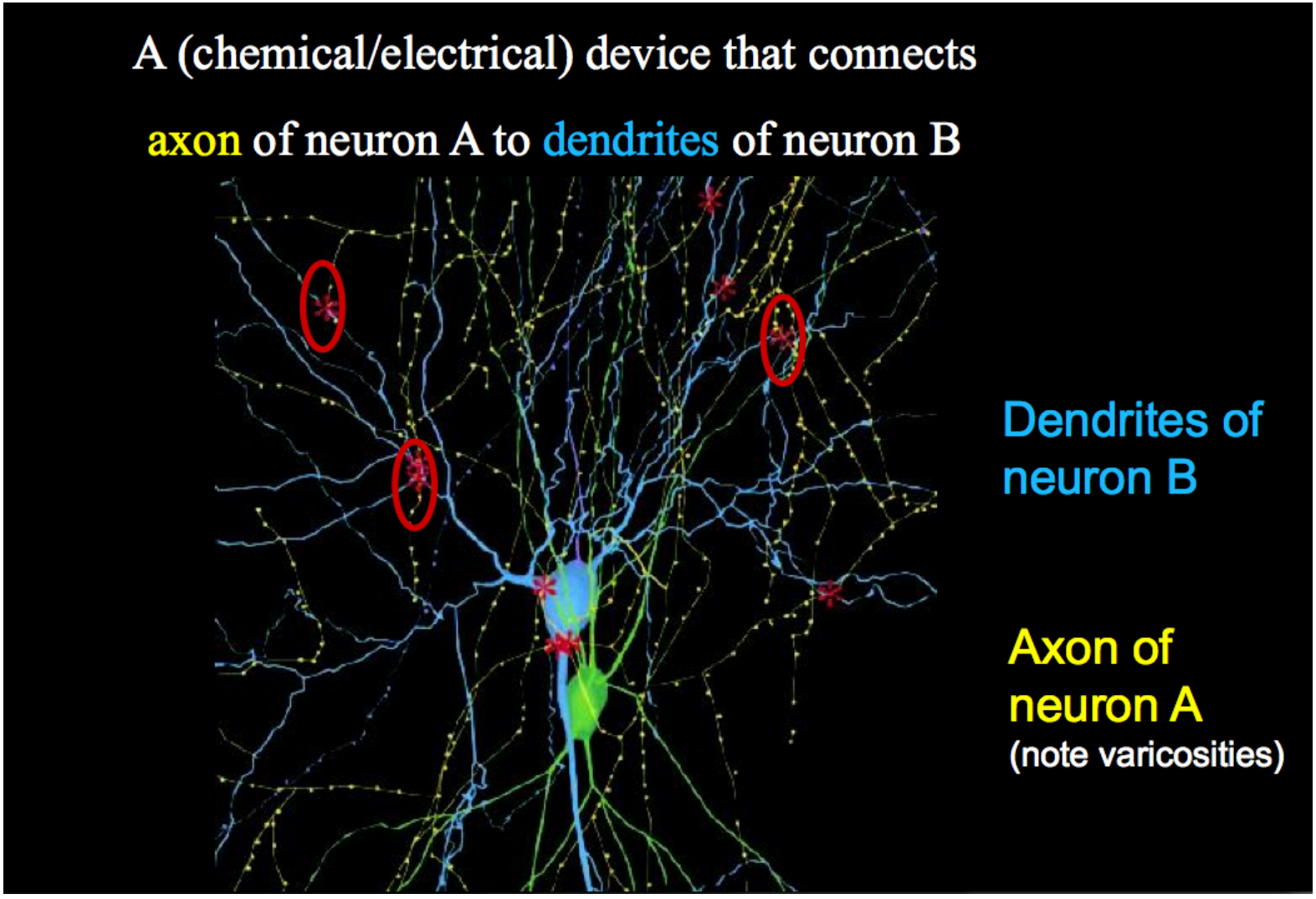
Z. J. Huang, G. Di Cristo & F. Ango
Nature Reviews Neuroscience 8, 673-686 (September 2007)

Electrically based neuron classification

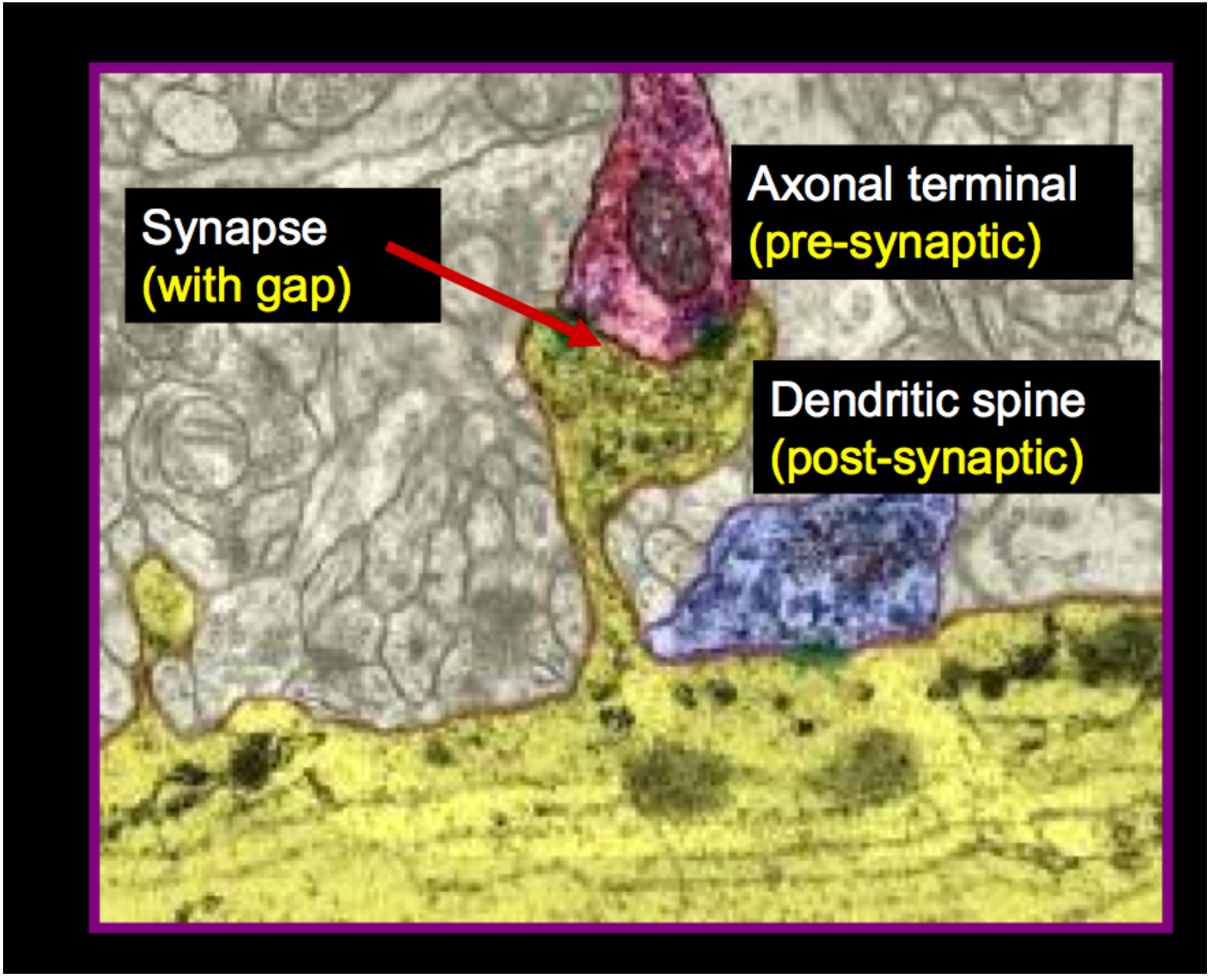


Courtesy of the Blue Brain data-base

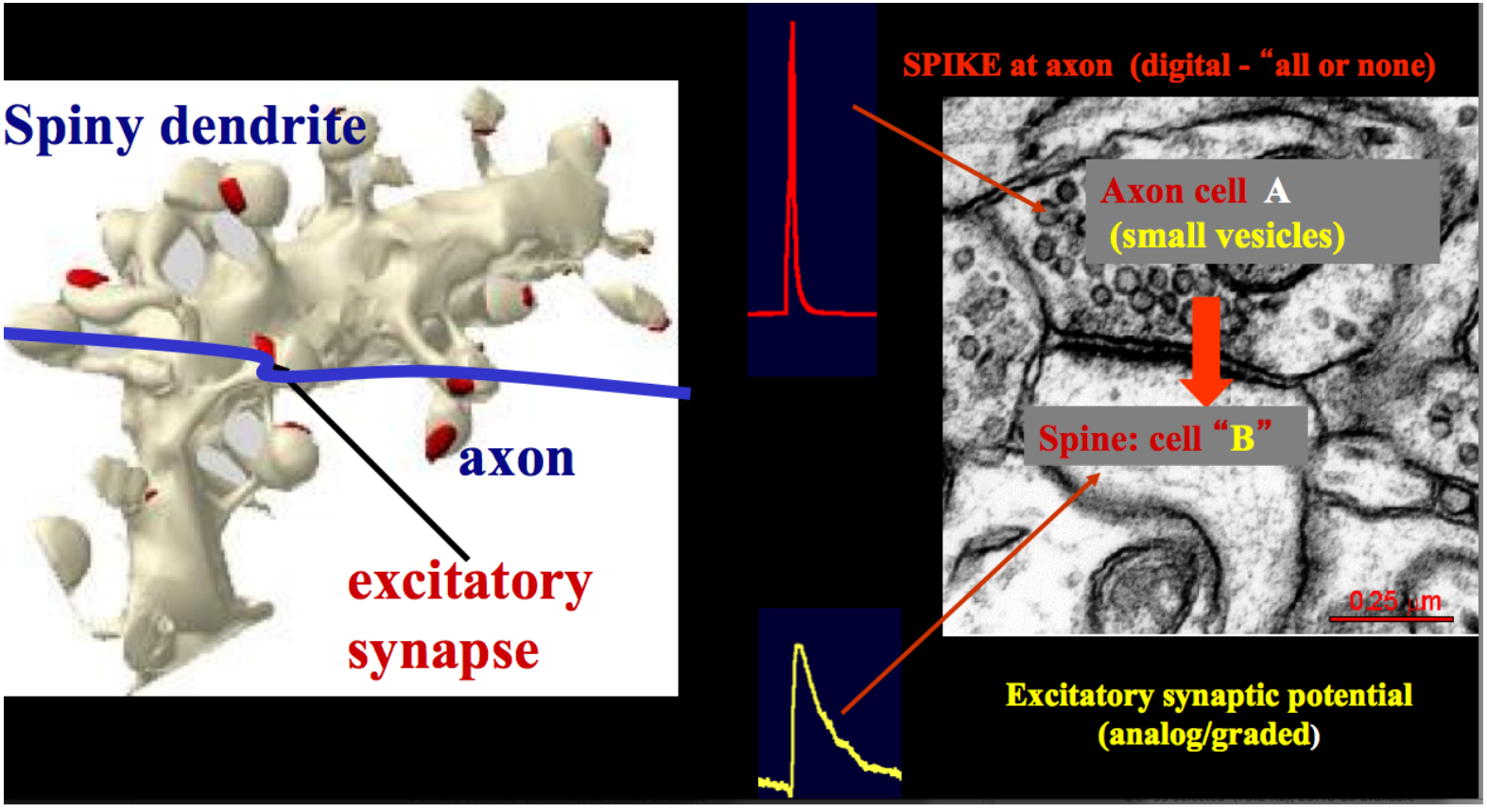
Synapse


A (chemical/electrical) device that connects
axon of neuron A to dendrites of neuron B
Dendrites of neuron B
Axon of neuron A
(note varicosities)

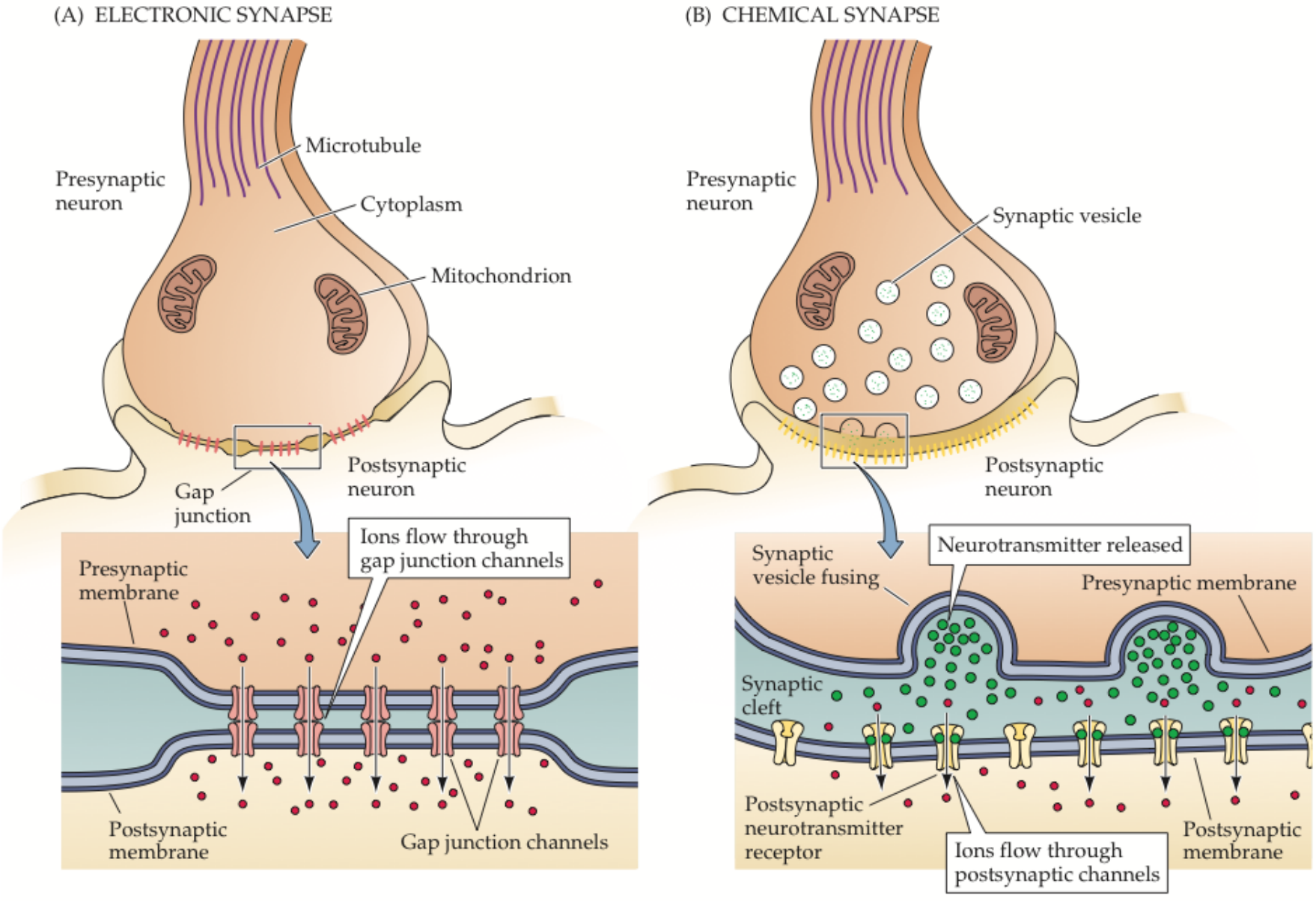
Chemical Synapse



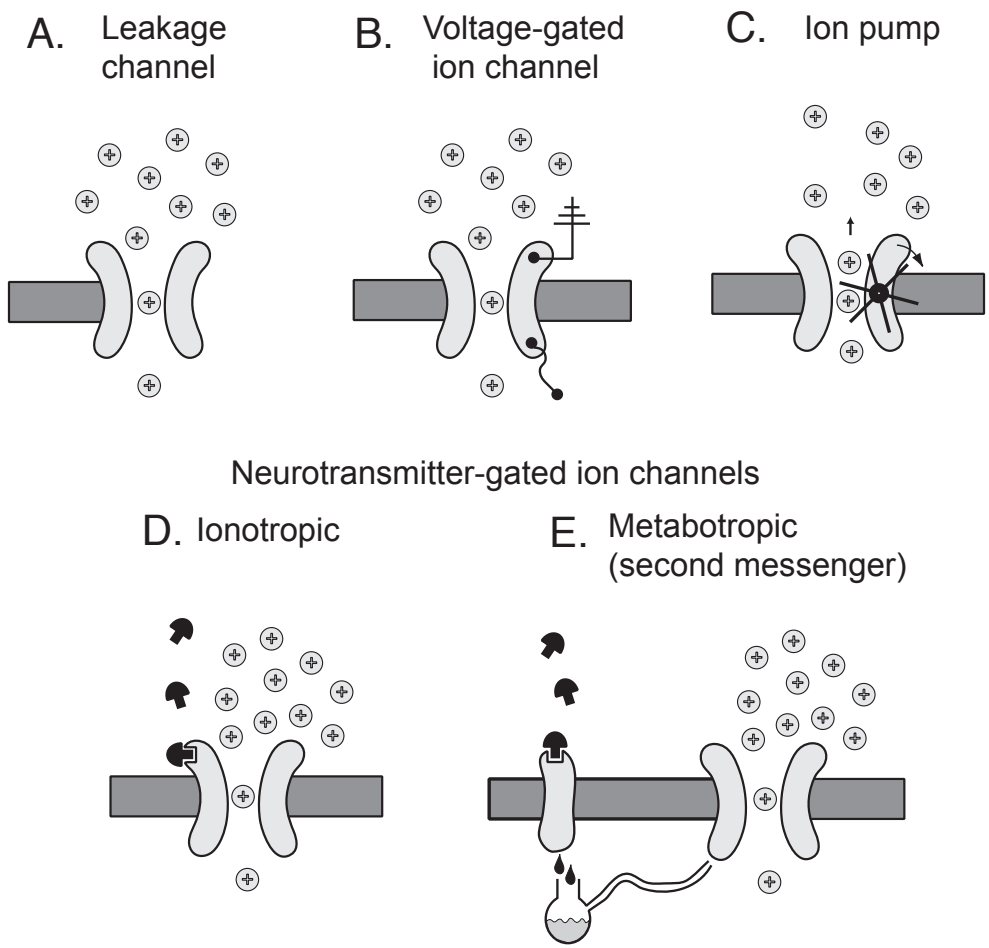
Digital Analog Device



Electrical and Chemical Synapse

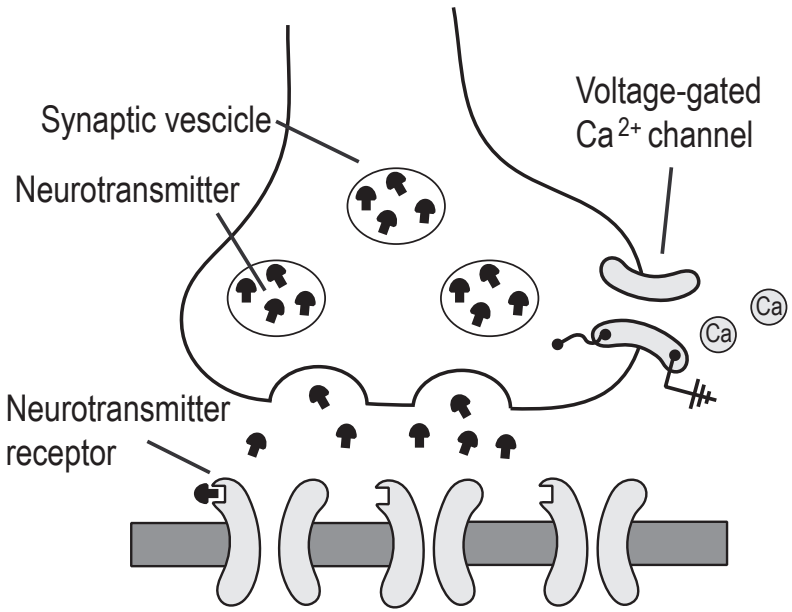


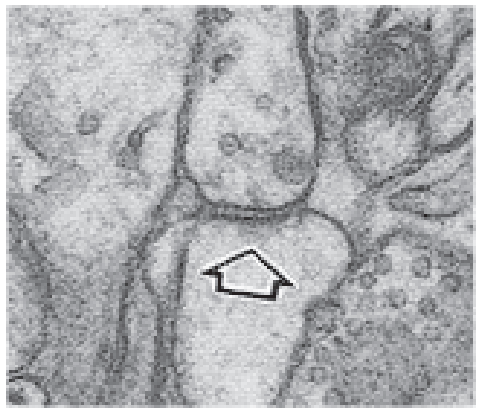
Ion channels



Synapse

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





excitatory and inhibitory potentials

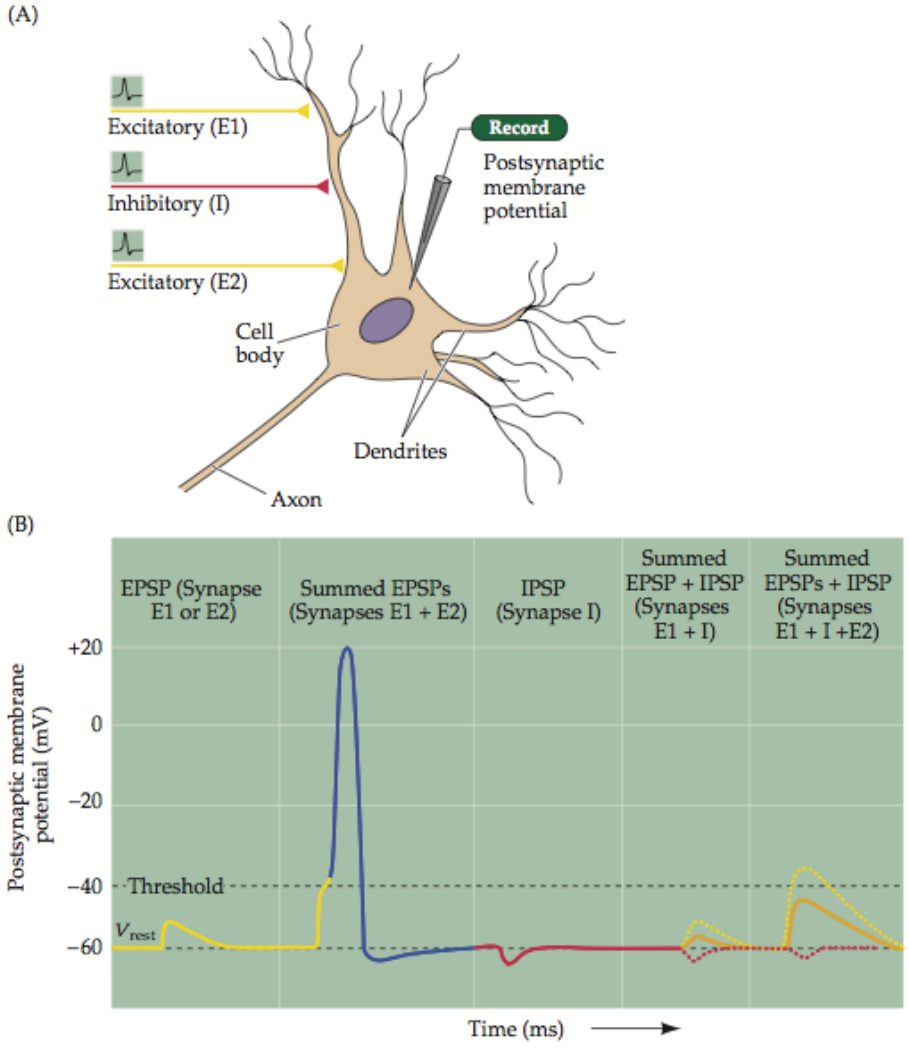
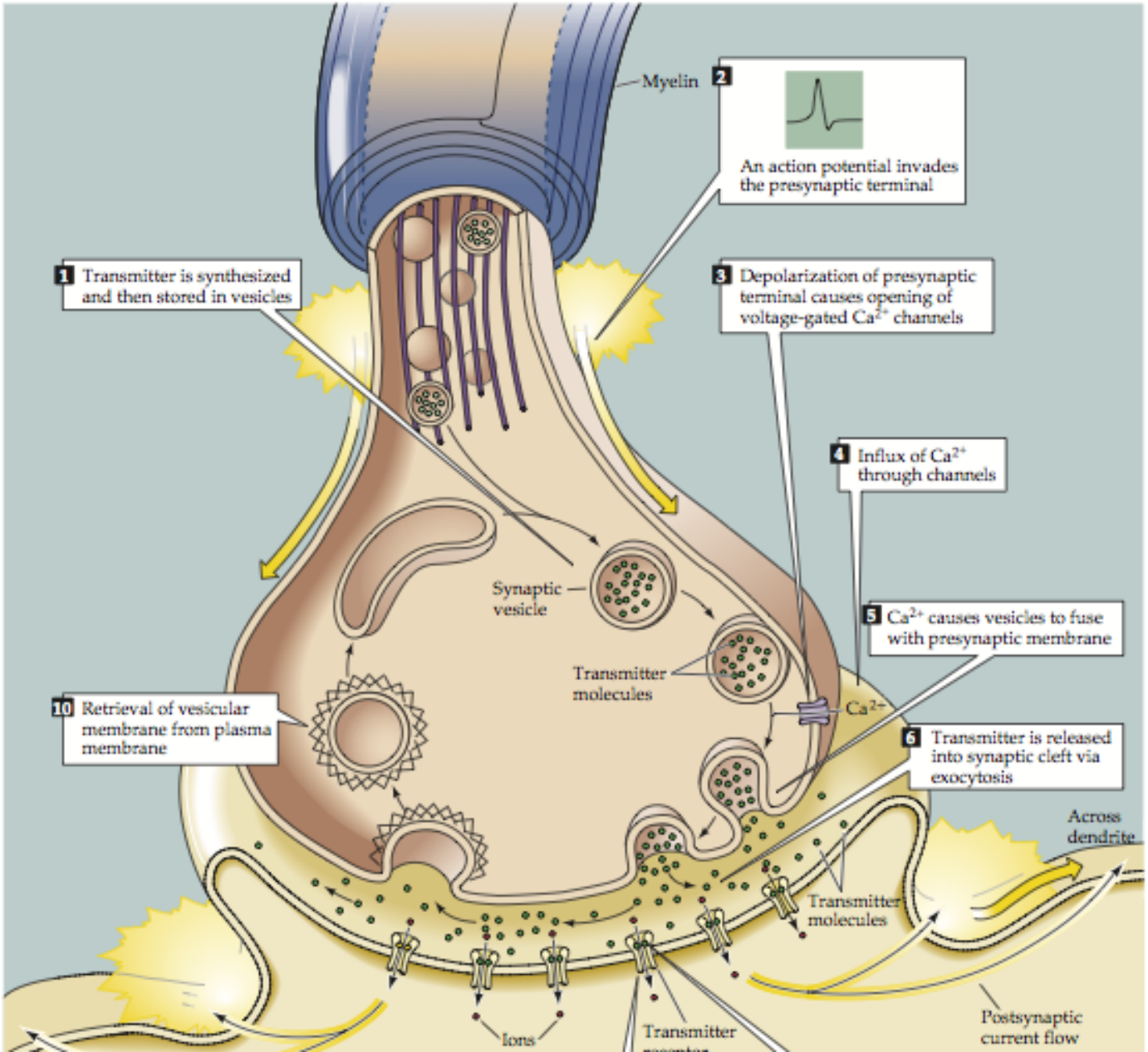


Figure 5.20 Summation of postsynaptic potentials. (A) A microelectrode records the postsynaptic potentials produced by the activity of two excitatory synapses (E1 and E2) and an inhibitory synapse (I). (B) Electrical responses to synaptic activation. Stimulating either excitatory synapse (E1 or E2) produces 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.

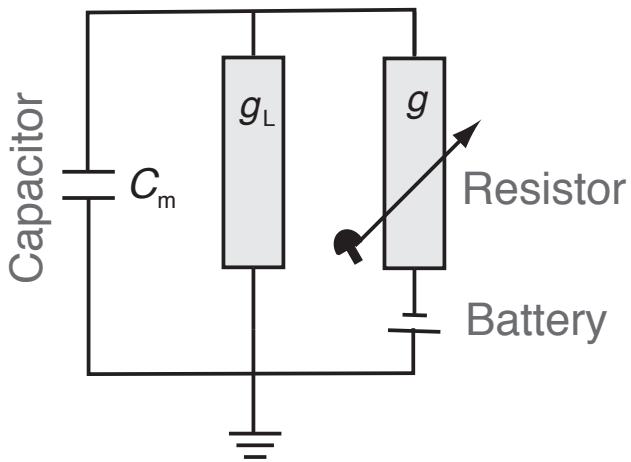
Ca signalling



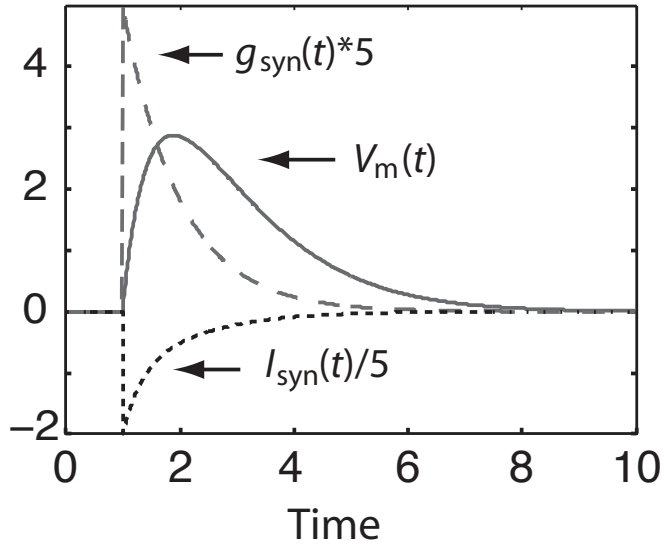
Conductance-based models

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

A. Electric circuit of basic synapse



B. Time course of variables

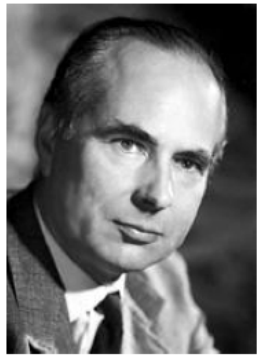


MATLAB Program

```
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:')
```

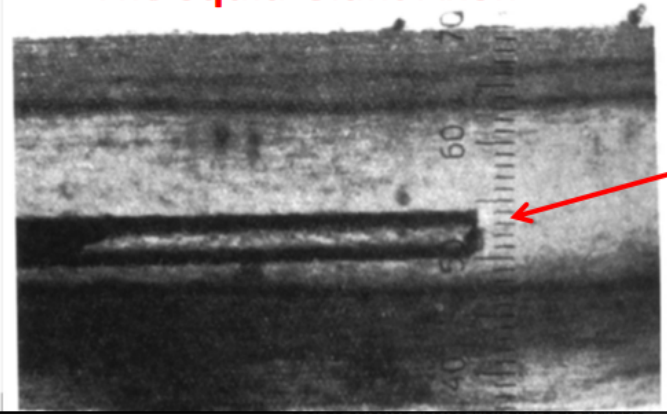
Hodkin and Huxley experiment NOBEL 1963

Sir Alan Lloyd Hodgkin



Sir Andrew Fielding Huxley

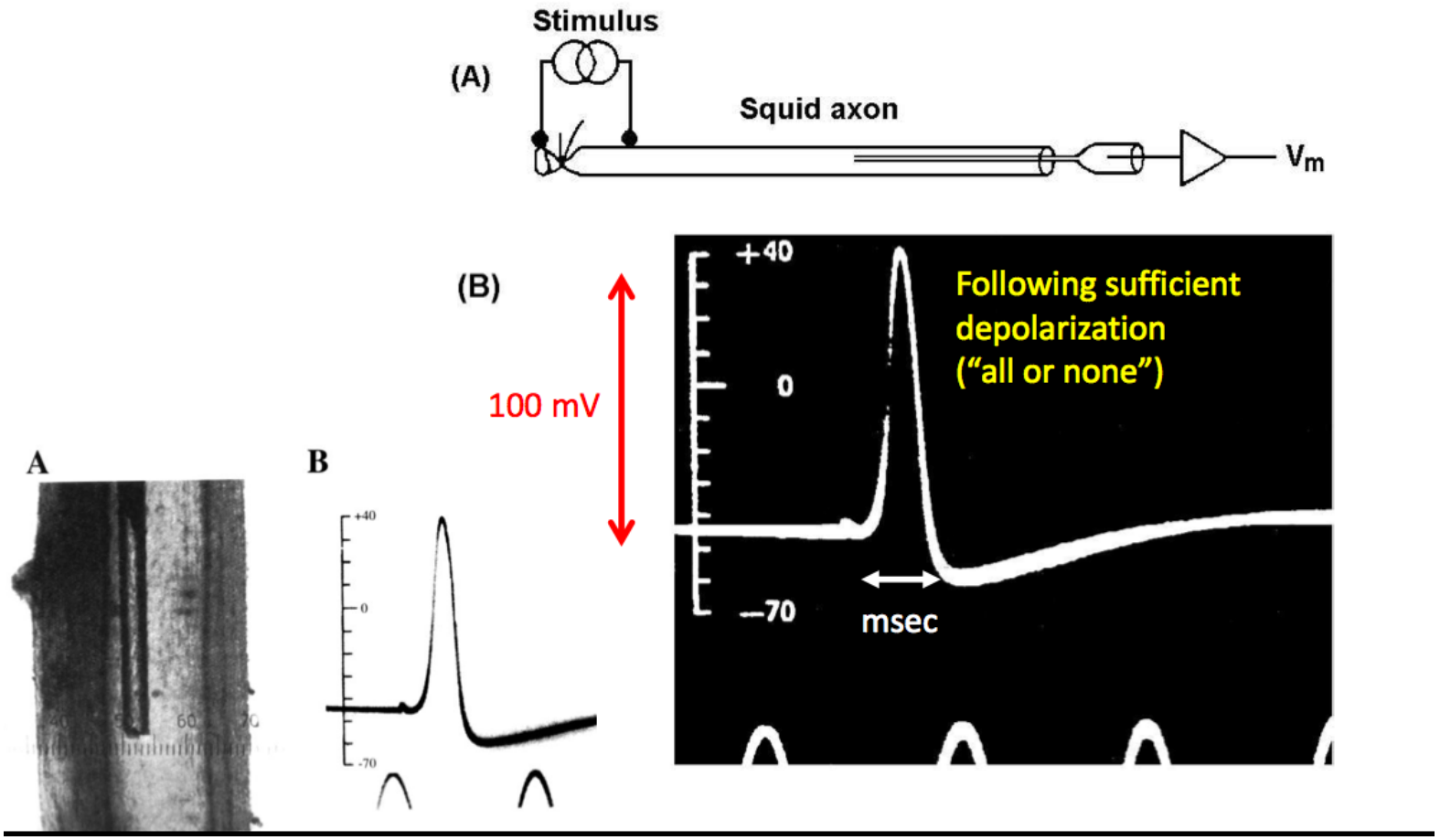
The Squid Giant Axon



~ 0.5 mm

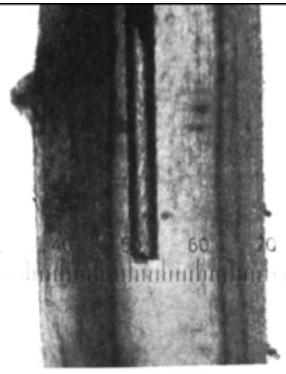
Axial electrode

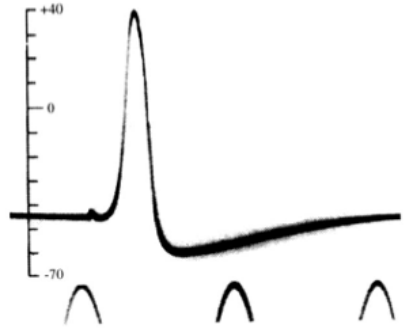
First direct (intracellular) recorded action-potential (spike) - 1939!!

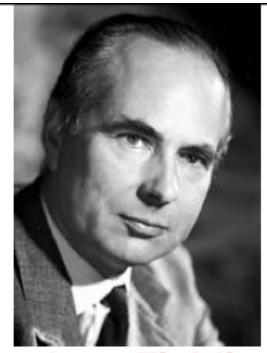


Very nice theory

Sir Alan Lloyd Hodgkin







Sir Andrew Fielding Huxley

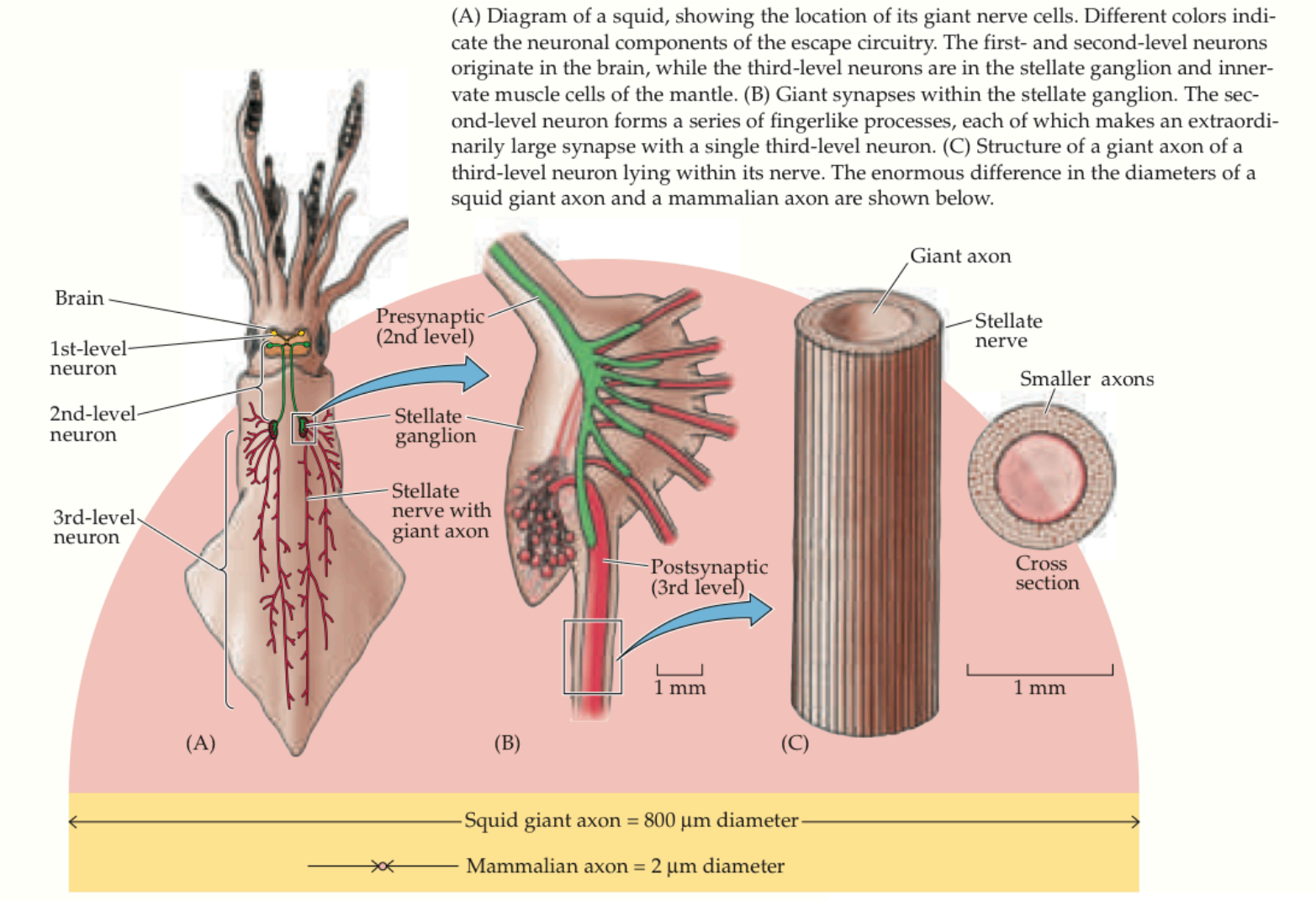
$$I = C_m \dot{V} + g_{Na}\, h\, m^3\, (V - V_{Na}) + g_K\, n^4\, (V - V_k) + G_L\, (V - V_L) \qquad (1)$$

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

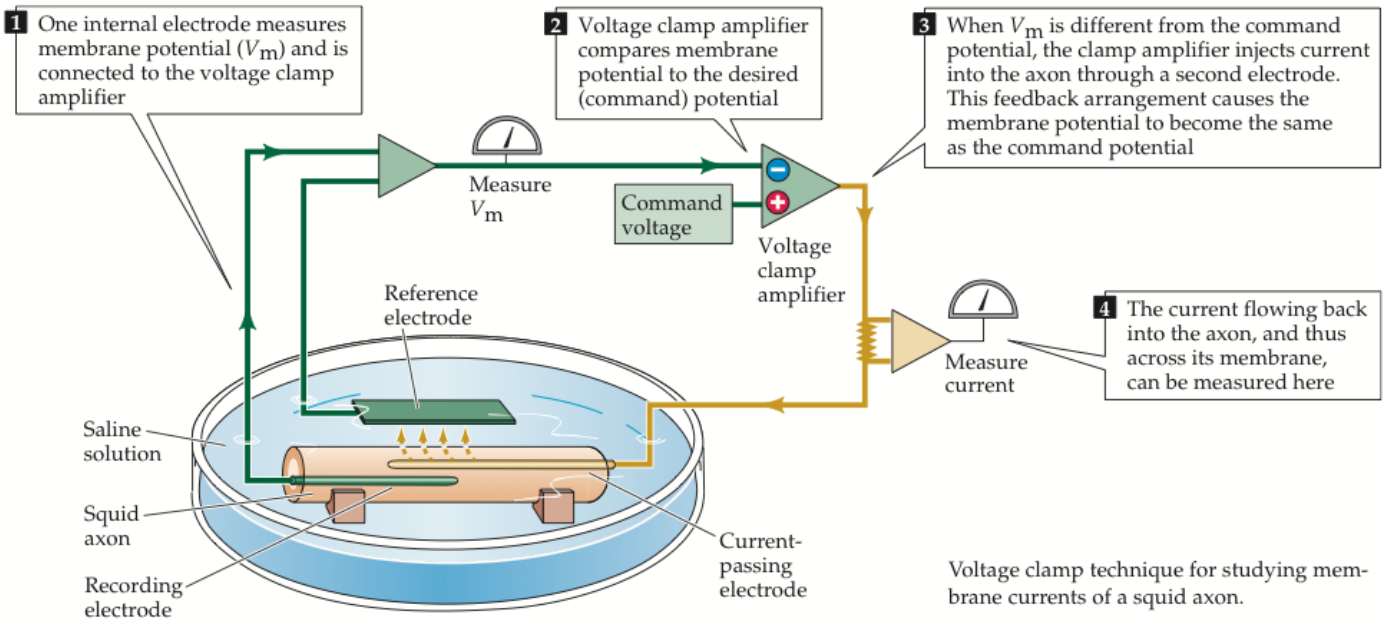
$$\frac{d}{dt} n = \alpha_n\, (V)\, (1 - n) - \beta_n\, (V)\, n \qquad (3)$$

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

Giant Nerve Cells of Squid



Voltage Clamp Method



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

Hodgkin–Huxley model

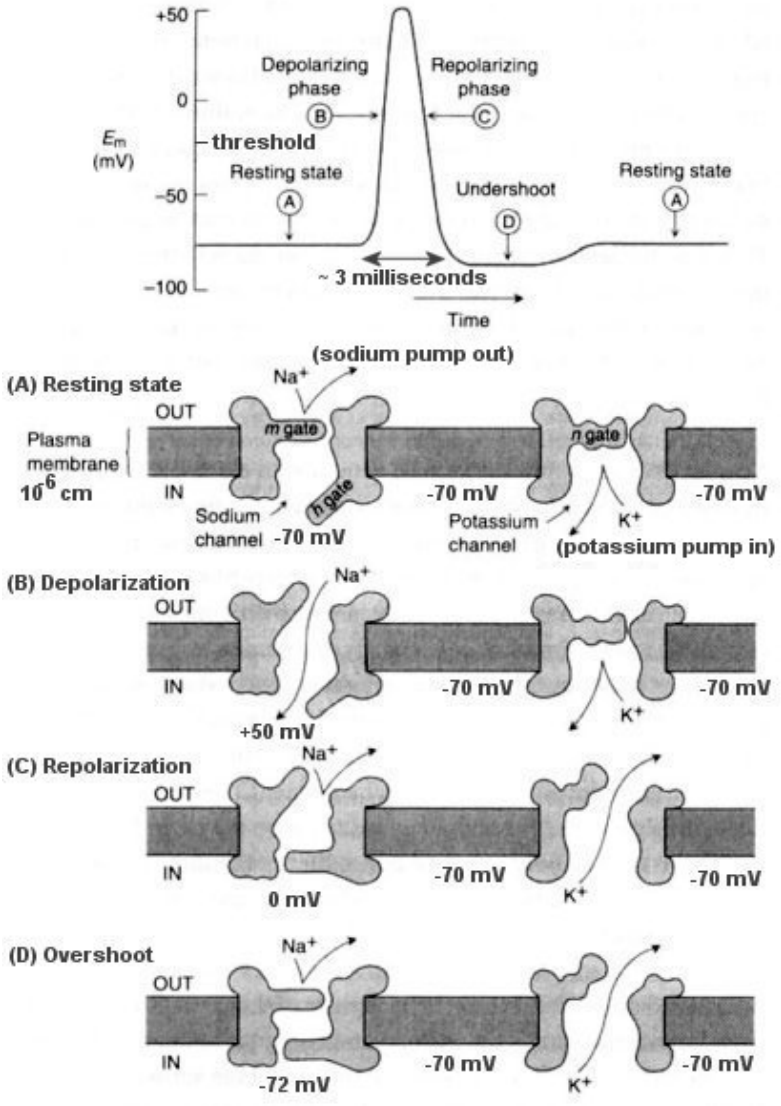
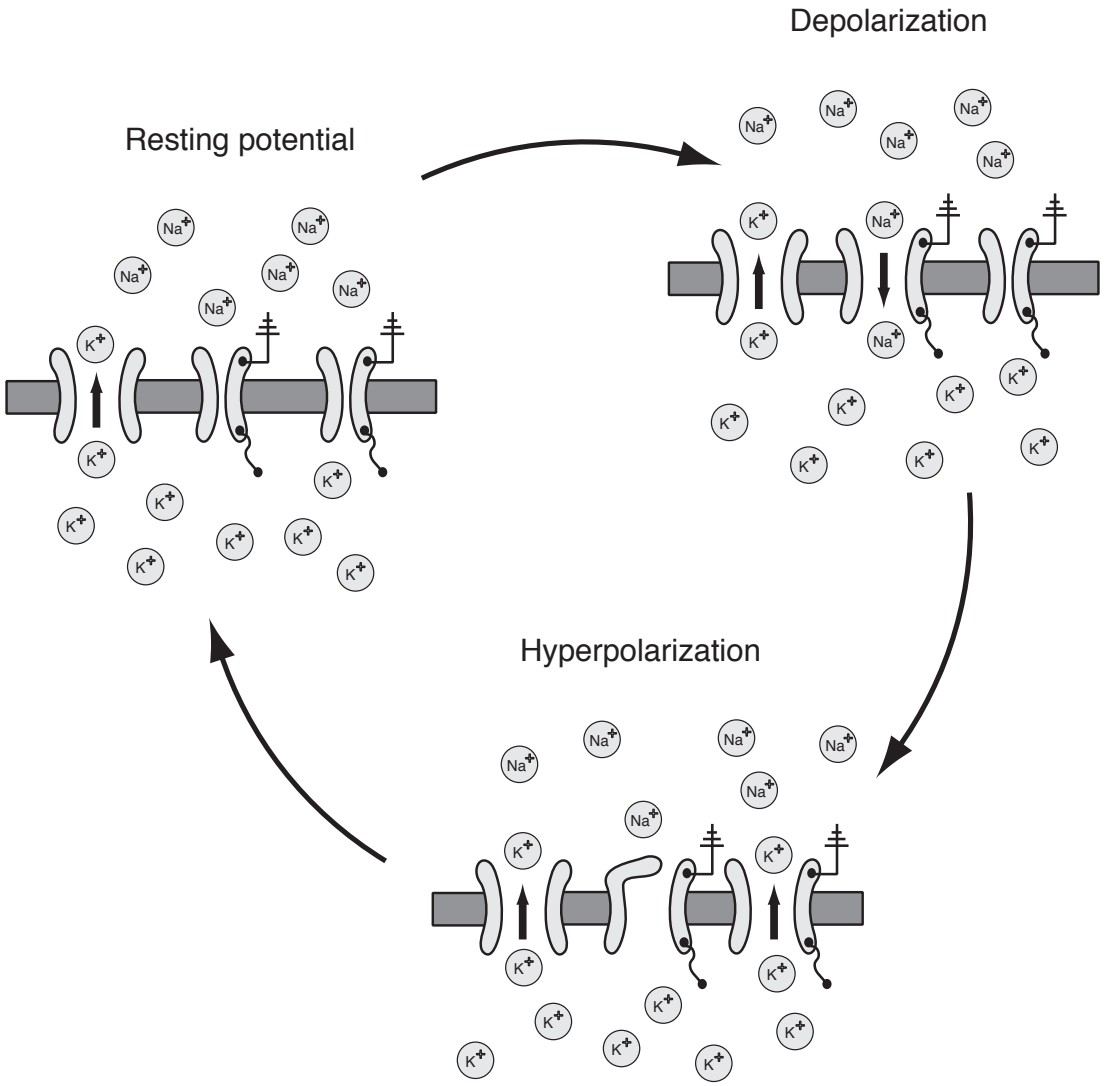
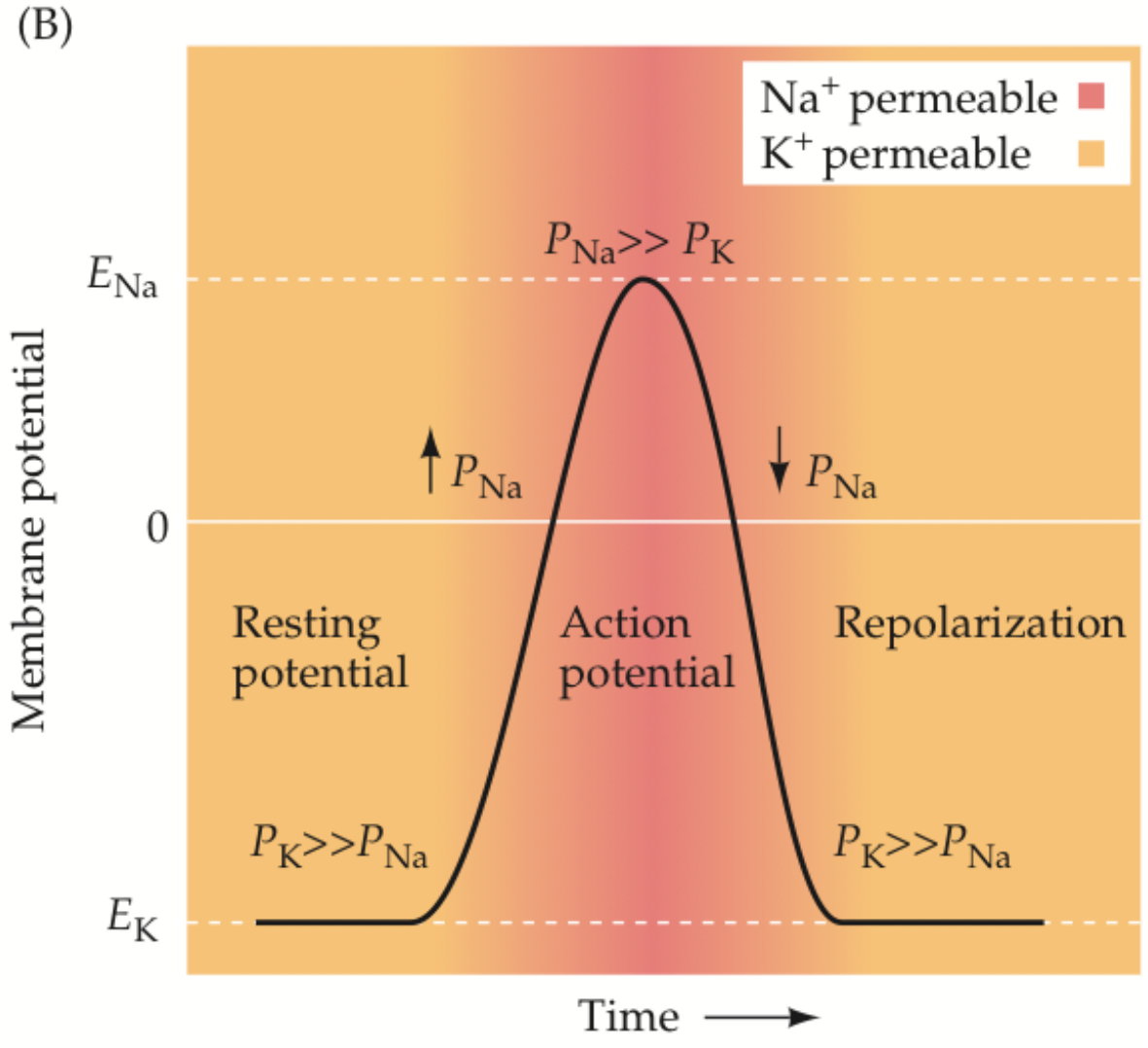


Figure : Typical form of an action potential; redrawn from an oscilloscope picture from Hodgkin and Huxley (1939).

The minimal mechanisms



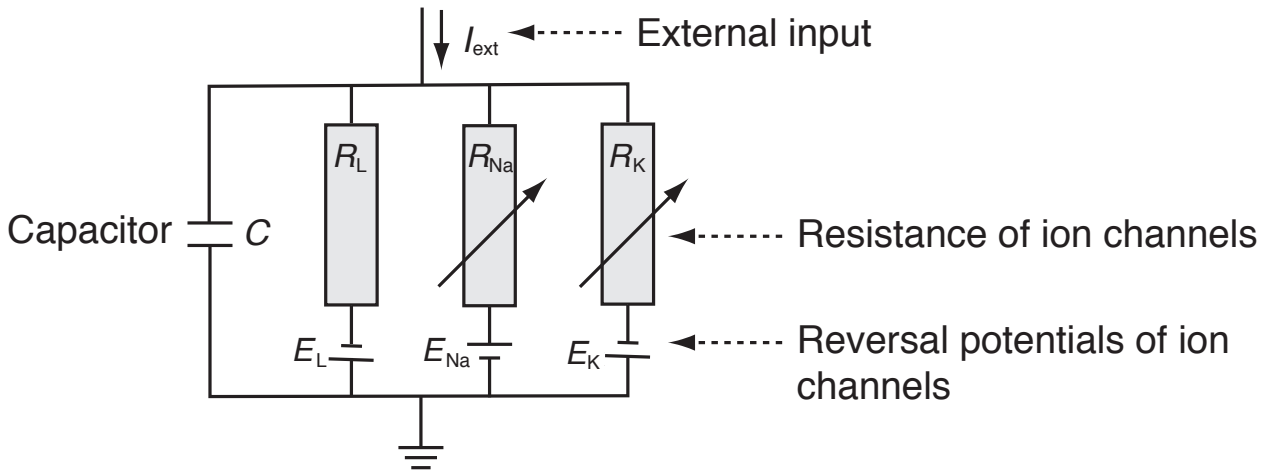
Concentration of Na , K



HH stucture

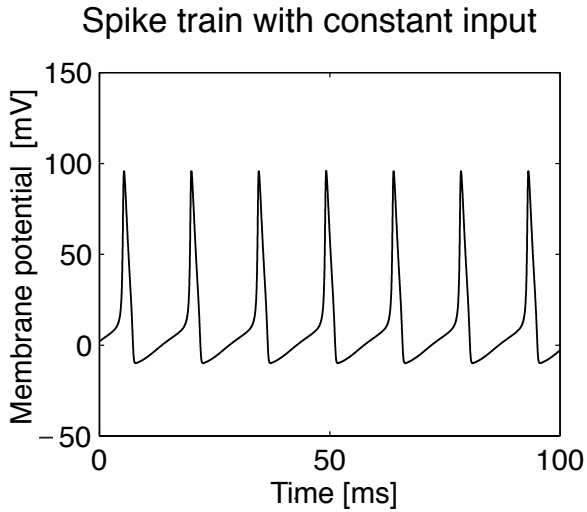
- $I_{ion} = \hat{g_{ion}}(V - E_{ion})$
- voltage and time dependent variables $n(V,t)$,$m(V,t)$,$h(V,t)$

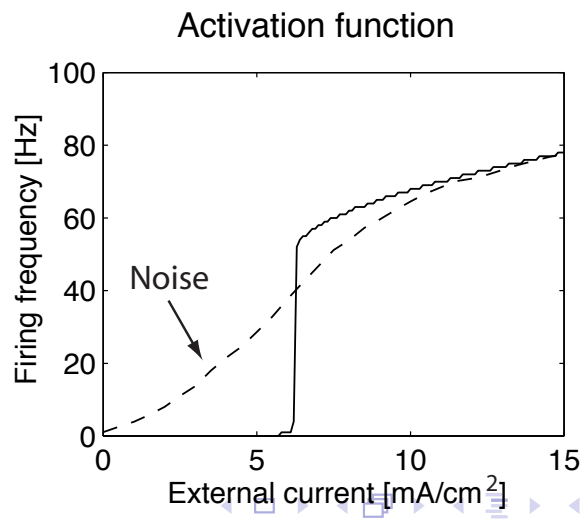
$$\hat{g_K}(V,t) = g_K n^4$$
$$\hat{g_{Na}}(V,t) = g_{Na} m^3 h$$



Hodgkin–Huxley equations and simulation

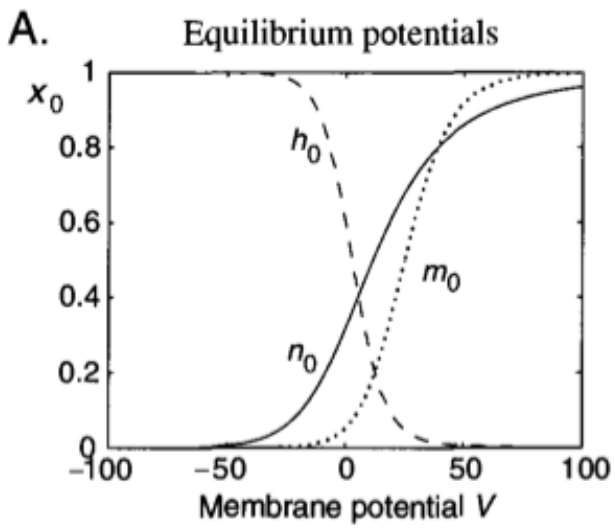
$$
\begin{aligned}
C\frac{\mathrm{d}V}{\mathrm{d}t} &= -g_{\mathrm{K}}n^4(V-E_{\mathrm{K}}) - g_{\mathrm{Na}}m^3h(V-E_{\mathrm{Na}}) - g_{\mathrm{L}}(V-E_{\mathrm{L}}) + I_{ext}(t) \\
\tau_{\mathrm{n}}(V)\frac{\mathrm{d}n}{\mathrm{d}t} &= -[n-n_0(V)] \\
\tau_{\mathrm{m}}(V)\frac{\mathrm{d}m}{\mathrm{d}t} &= -[m-m_0(V)] \\
\tau_{\mathrm{h}}(V)\frac{\mathrm{d}h}{\mathrm{d}t} &= -[h-h_0(V)] \\
\frac{dx}{dt} &= -\frac{1}{\tau_x(V)}[x-x_0(V)] \rightarrow x(t+\Delta t) = (1-\frac{\Delta t}{\tau_x})x(t) + \frac{\Delta t}{\tau_x}x_0
\end{aligned}
$$

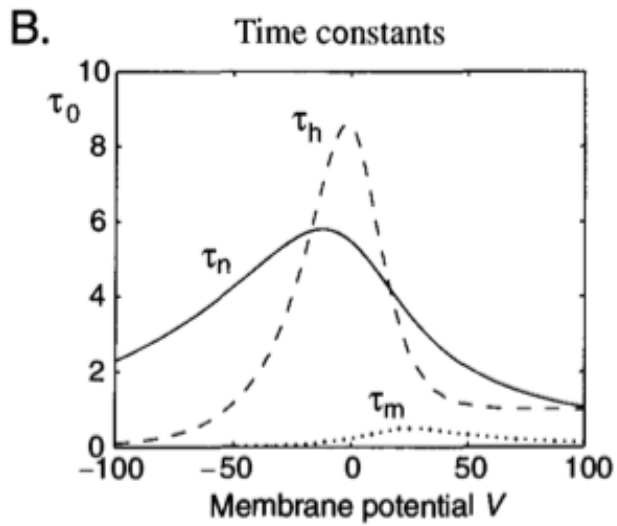




Ion channels resistance

$$
\begin{aligned}
x(0) &= \frac{\alpha}{\alpha+\beta}, t_x = \alpha\beta, x \in= \{n, m, h\} \\
\alpha_n &= \frac{10 - V}{100(e^{\frac{10-V}{10}} - 1)}, \beta_n = 0.125e^{-\frac{V}{80}} \\
\alpha_m &= \frac{25 - V}{10(e^{\frac{25-V}{10}} - 1)}, \beta_m = 4e^{-\frac{V}{18}} \\
\alpha_h &= 0.07e^{\frac{V}{20}}, \beta_h = \frac{1}{e^{\frac{30-V}{10}} + 1}
\end{aligned}
$$





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=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
```

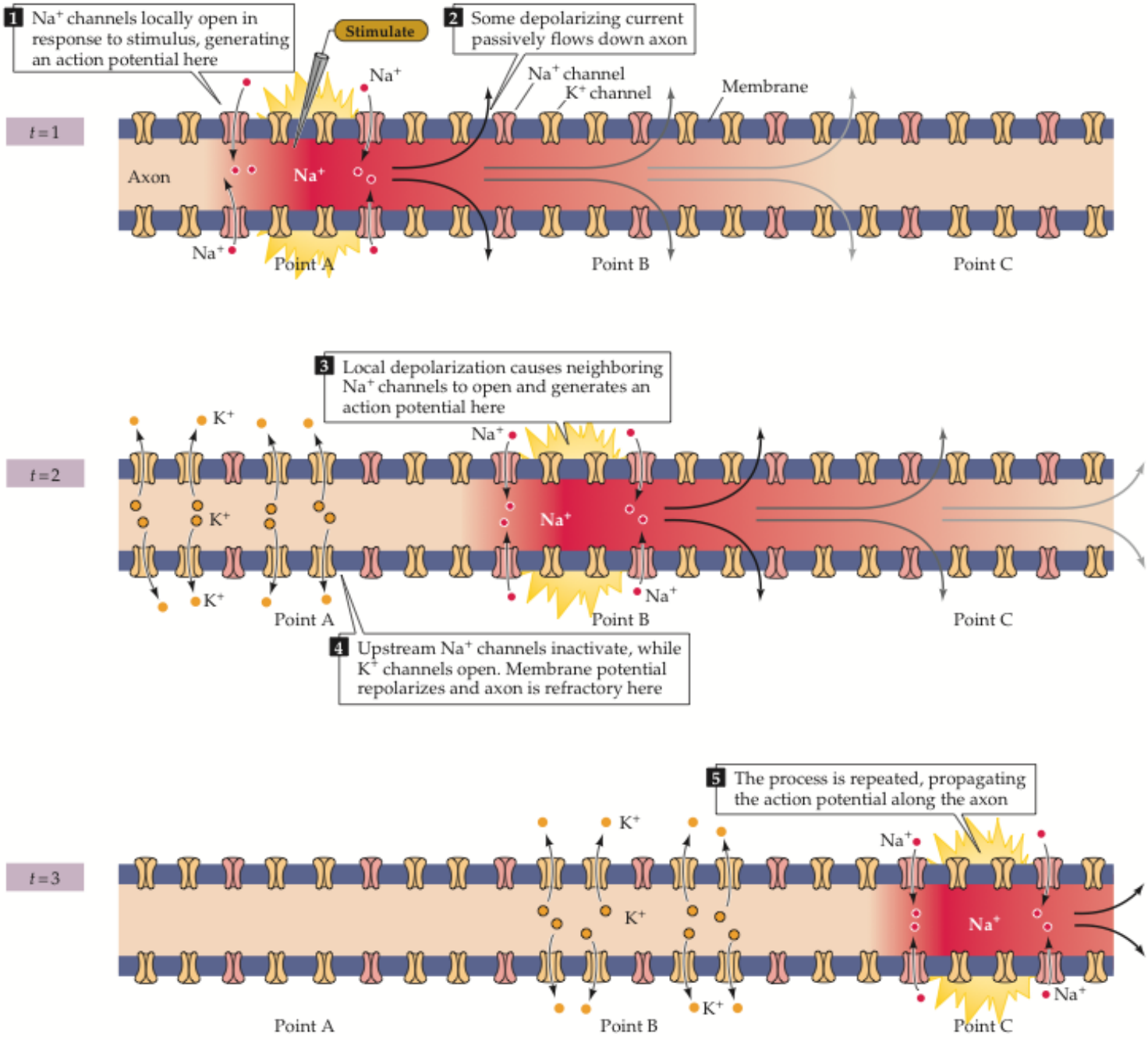
Refractory period

- 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

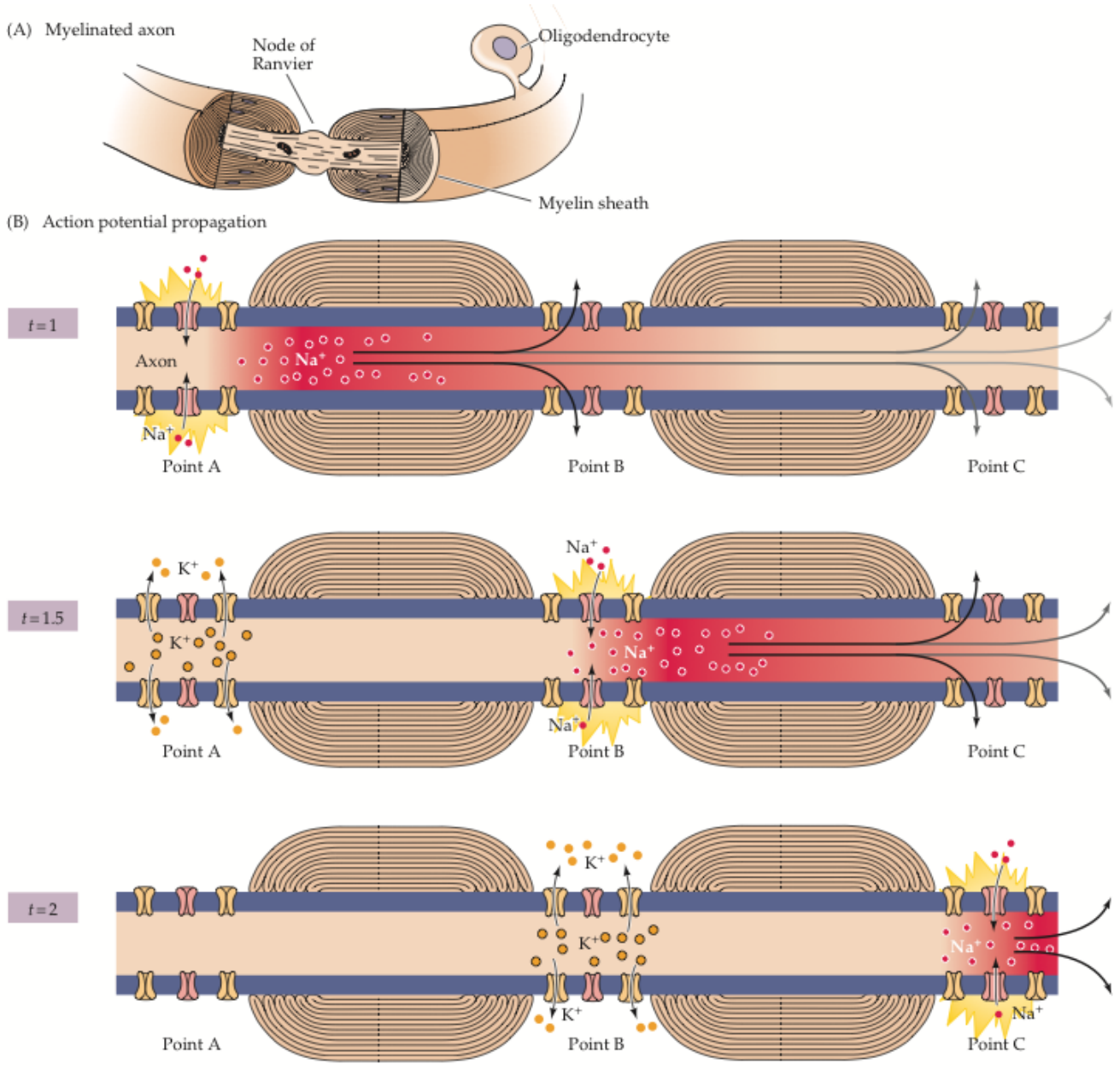
Propagation of action potentials

- 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!

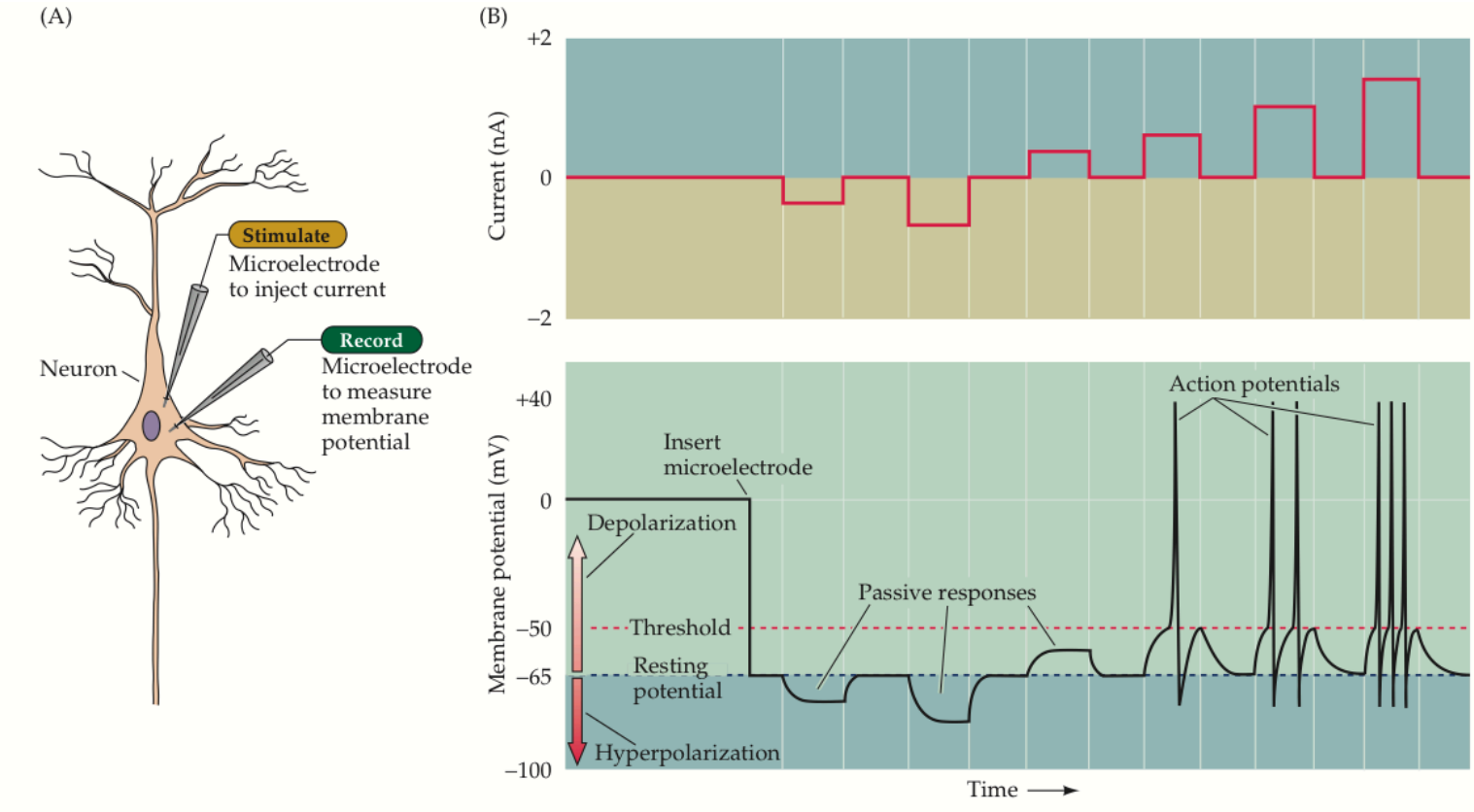
NON-LOSS transfer



LOSSY transfer



Stimulation of neuron



Signal transmission

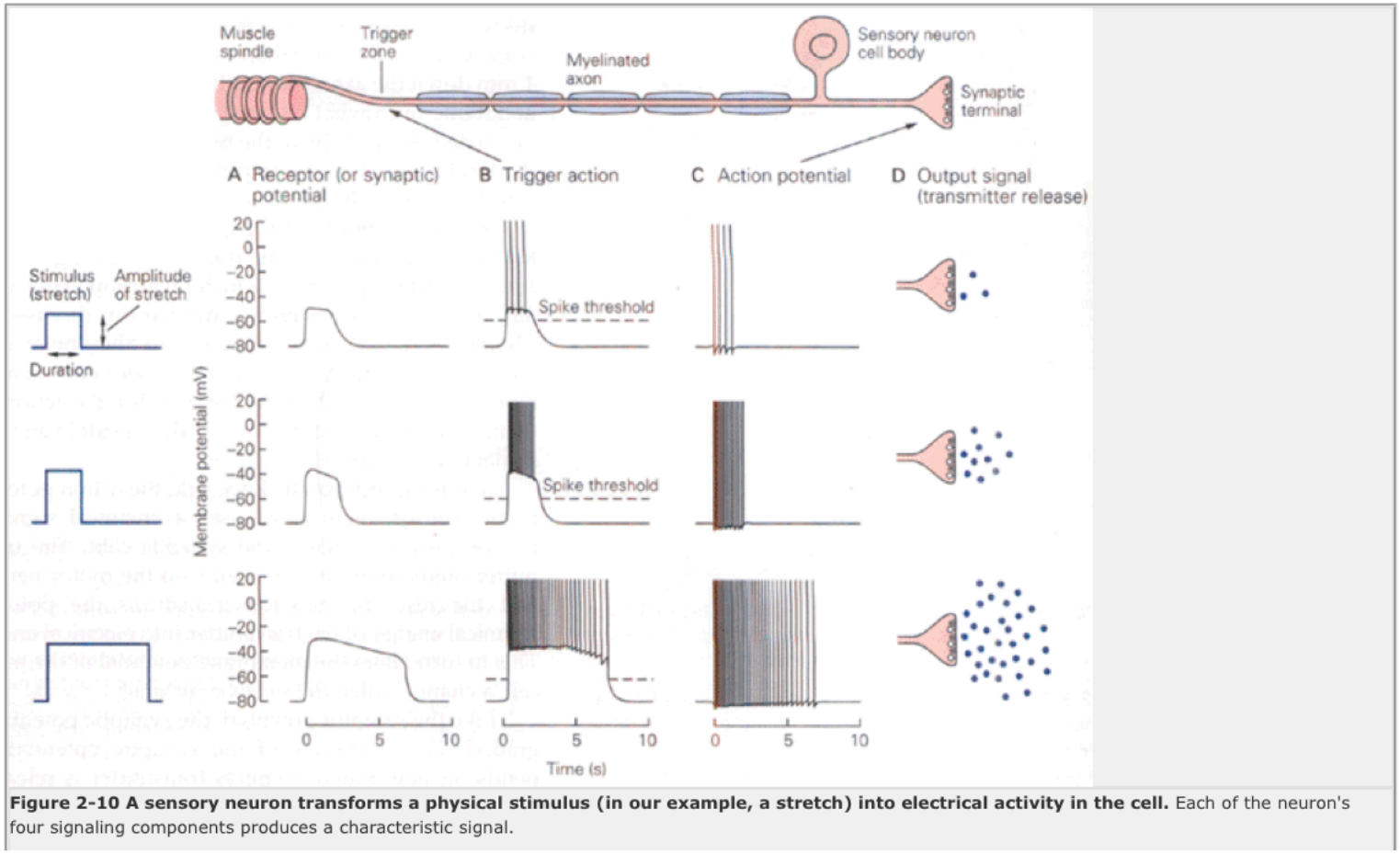


Figure 2-10 A sensory neuron transforms a physical stimulus (in our example, a stretch) into electrical activity in the cell. Each of the neuron's four signaling components produces a characteristic signal.

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

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

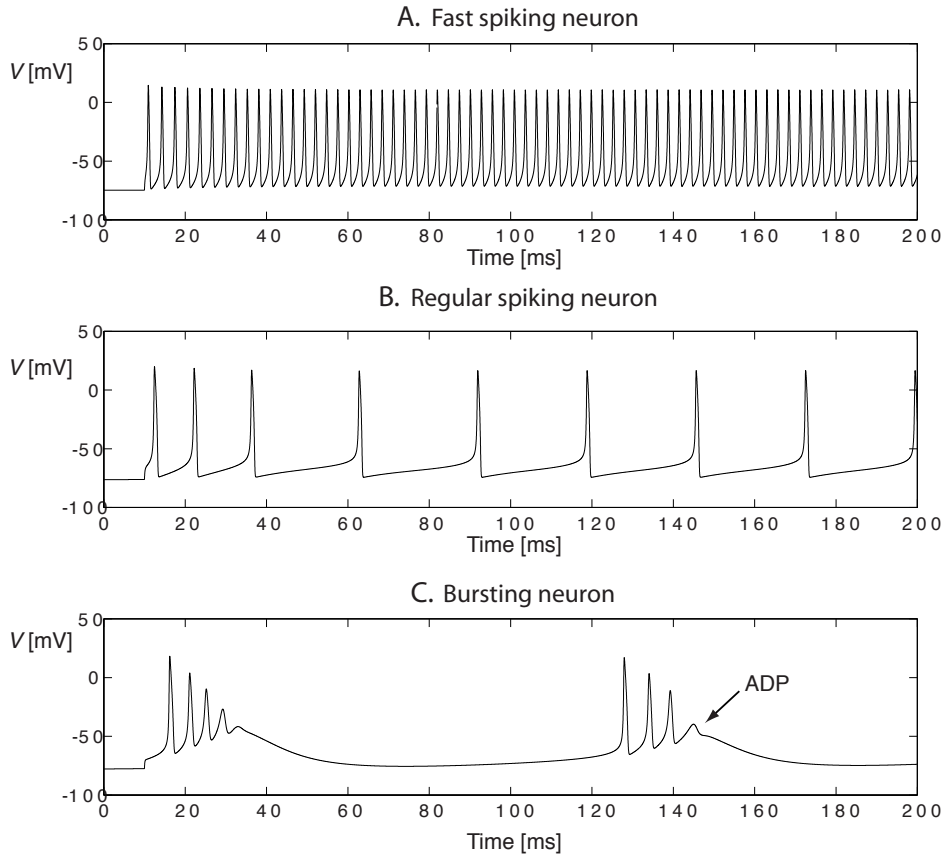
Wilson model

- 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

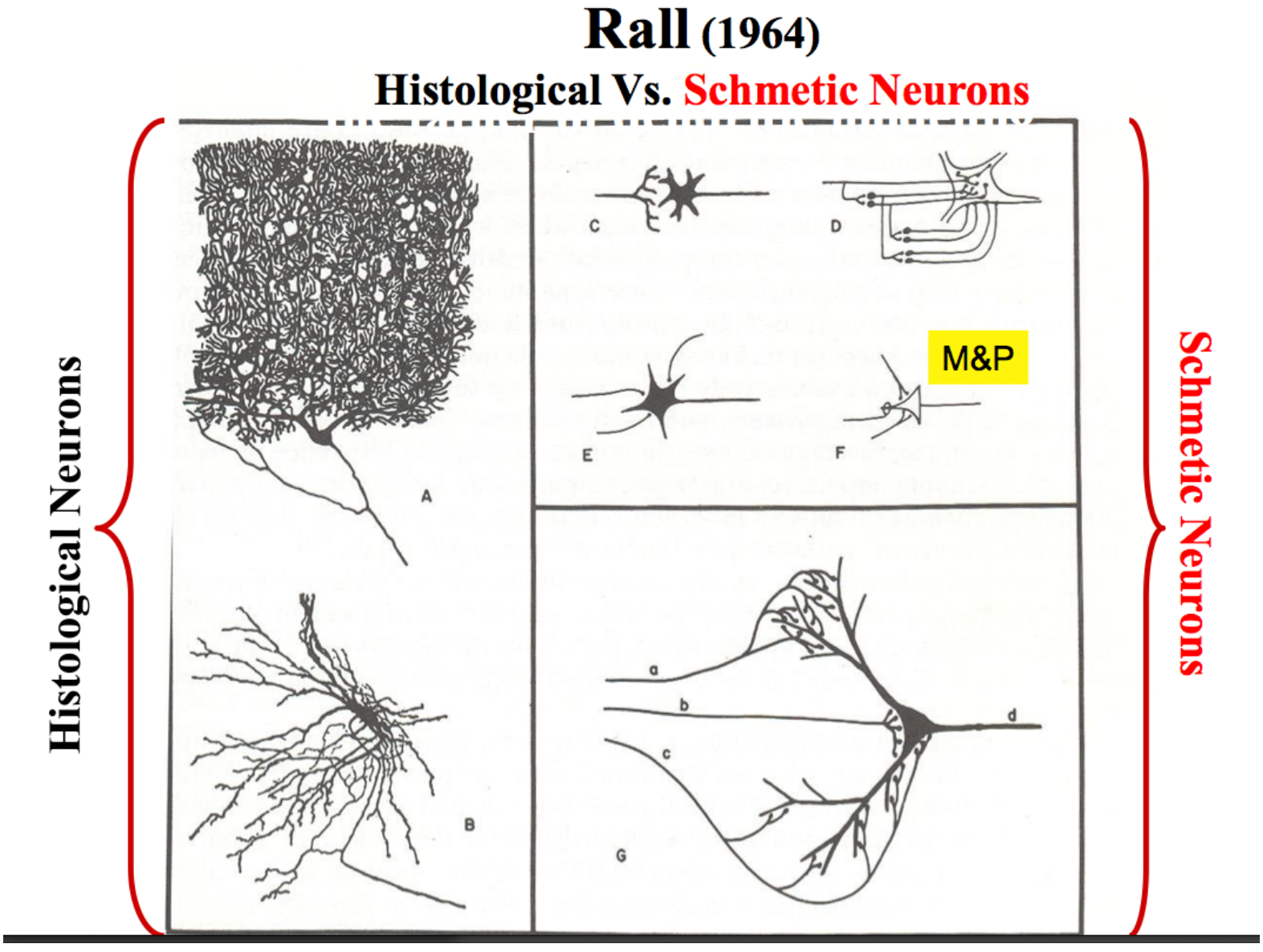
- RS: regular spiking neuron
- FS: fast spiking neuron
- CS: continously spiking neuron
- IB: bursting neuron



Matlab implementation

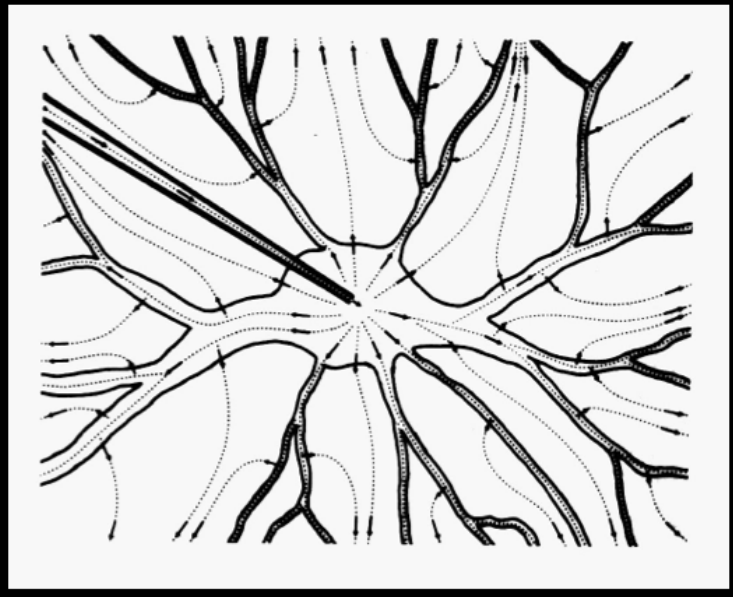
```
%%  Integration of Wilson model with the Euler method
 clear; clf;
%% Parameters of the model: 1=K,R  2=Ca,T  3=KCa,H  4=Na
 g(1)=26; g(2)=2.25; g(3)=9.5; g(4)=1;
 E(1)=-.95; E(2)=1.20; E(3)=E(1); E(4)=.50;

%% 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');
```

Physiology versus Neurons Models



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

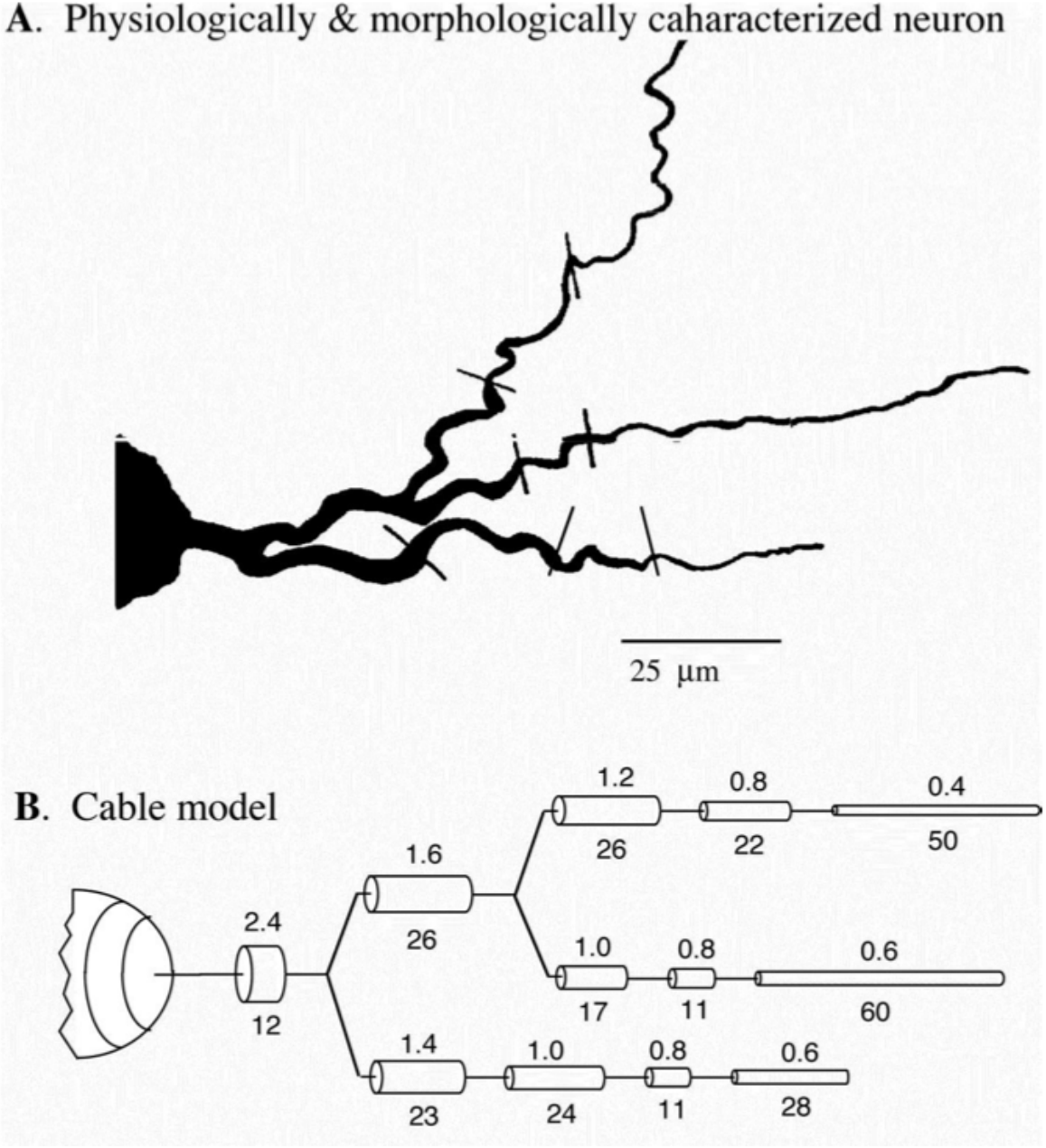
Dendrit Cable Theory

Rall Cable Theory for Dendrites

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

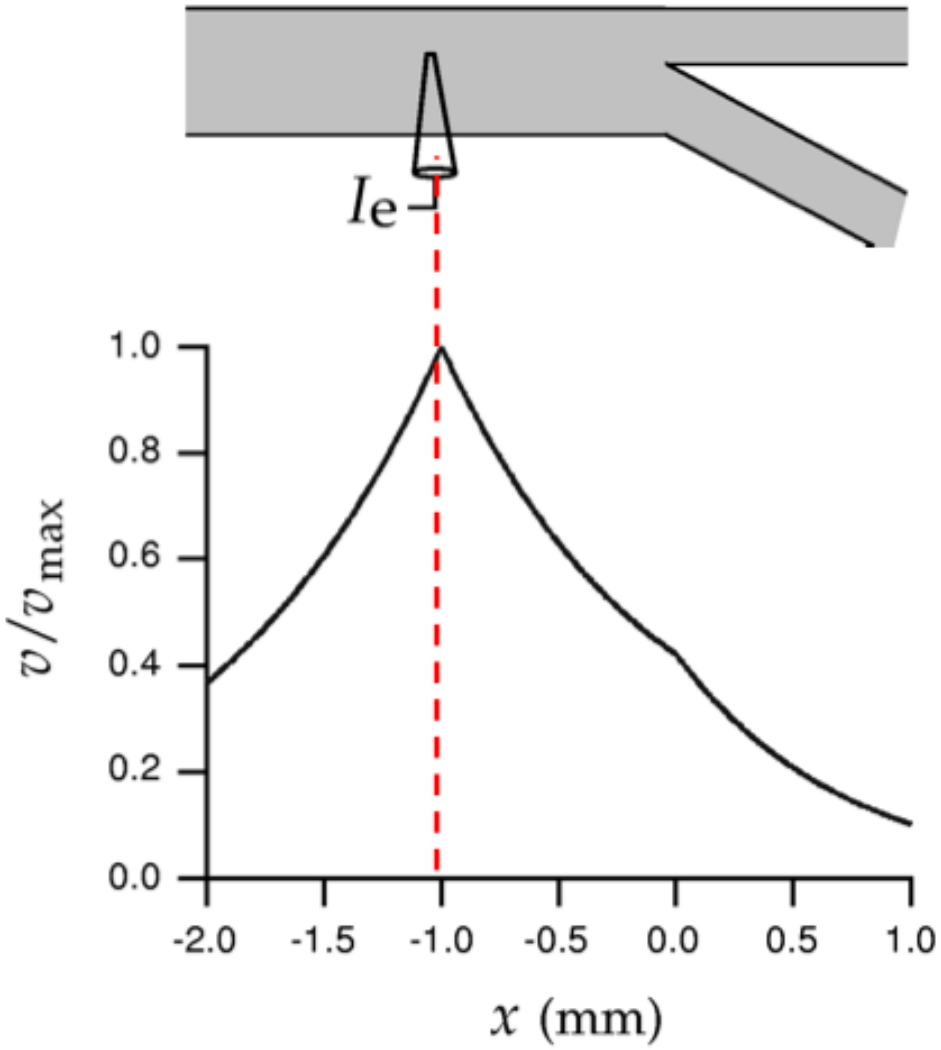
Wilfrid Rall

Cylindric model

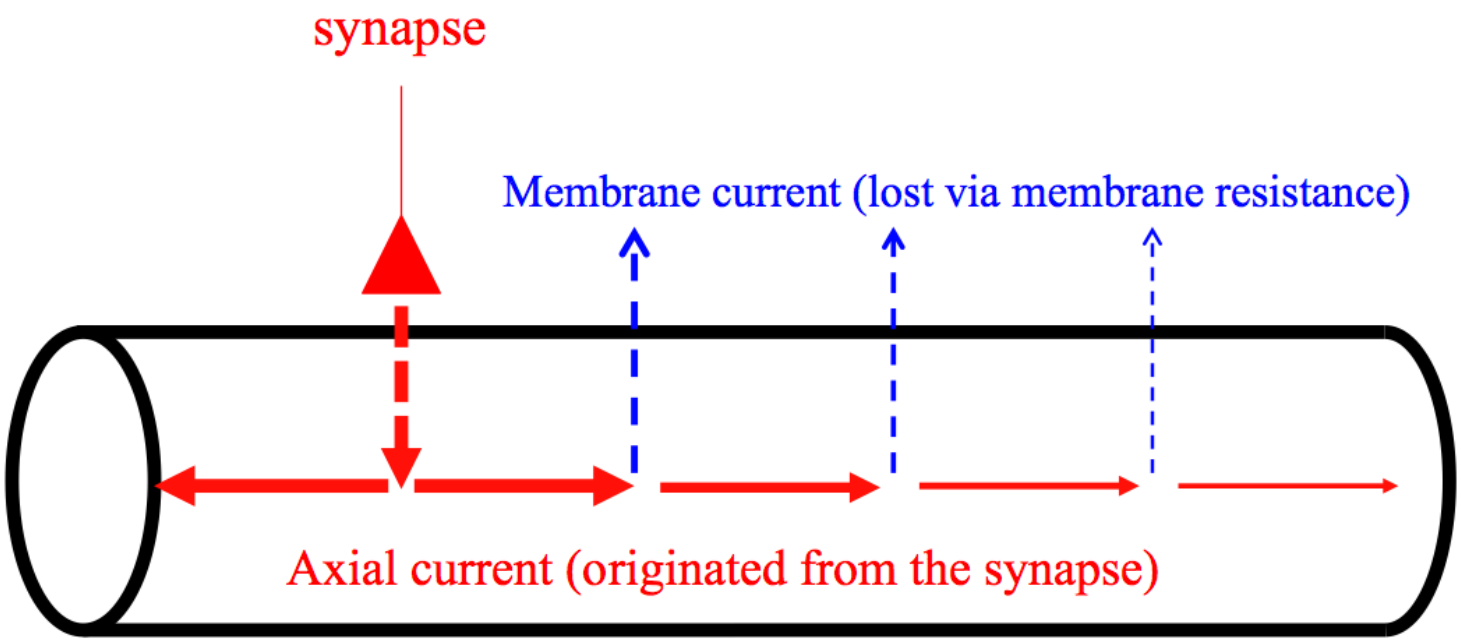


Voltage attenuation

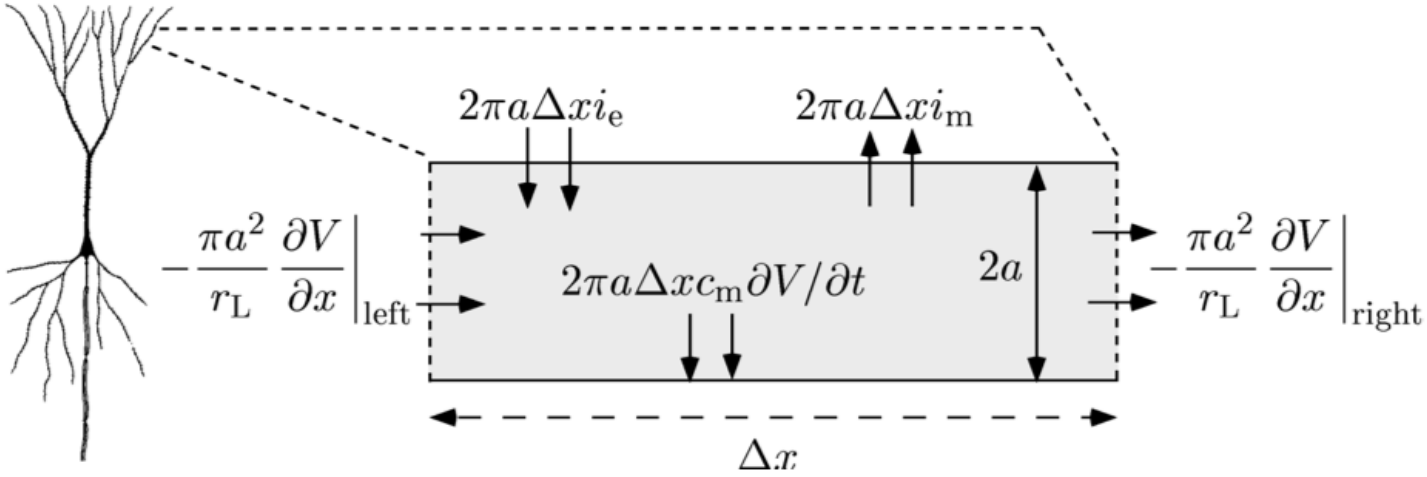
Synaptic potentials attenuate from the synapse origin towards other regions of the dendrites



Axial and membrane current



Passive cable equations



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

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

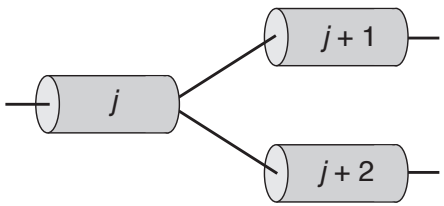
$X = x/\lambda$

$T = t/\tau_m$

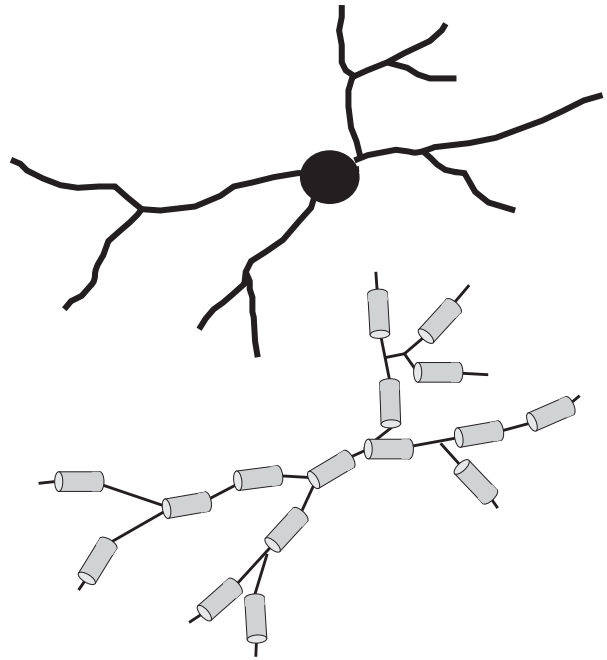
Compartmental models

A. Chain of compartments

B. Branching compartments



C. Compartmental reconstruction



Cable theory

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

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

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

$$\tau_m = R_m C_m$$

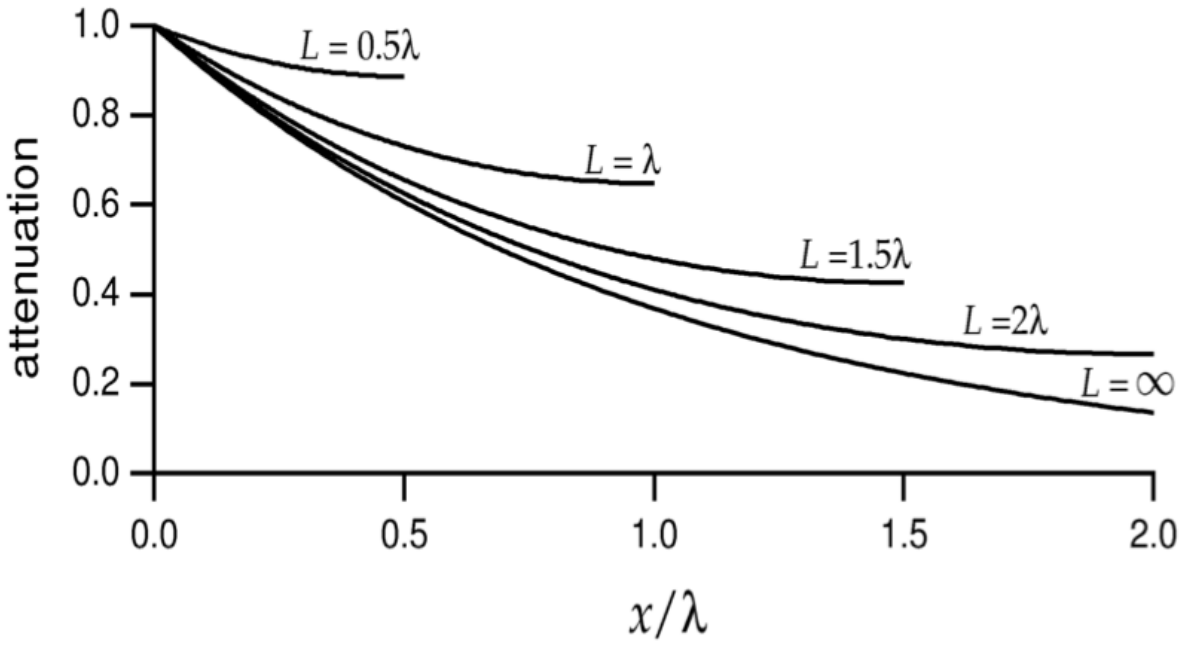
$$V_m = V_0 e - \frac{x}{\lambda}$$

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

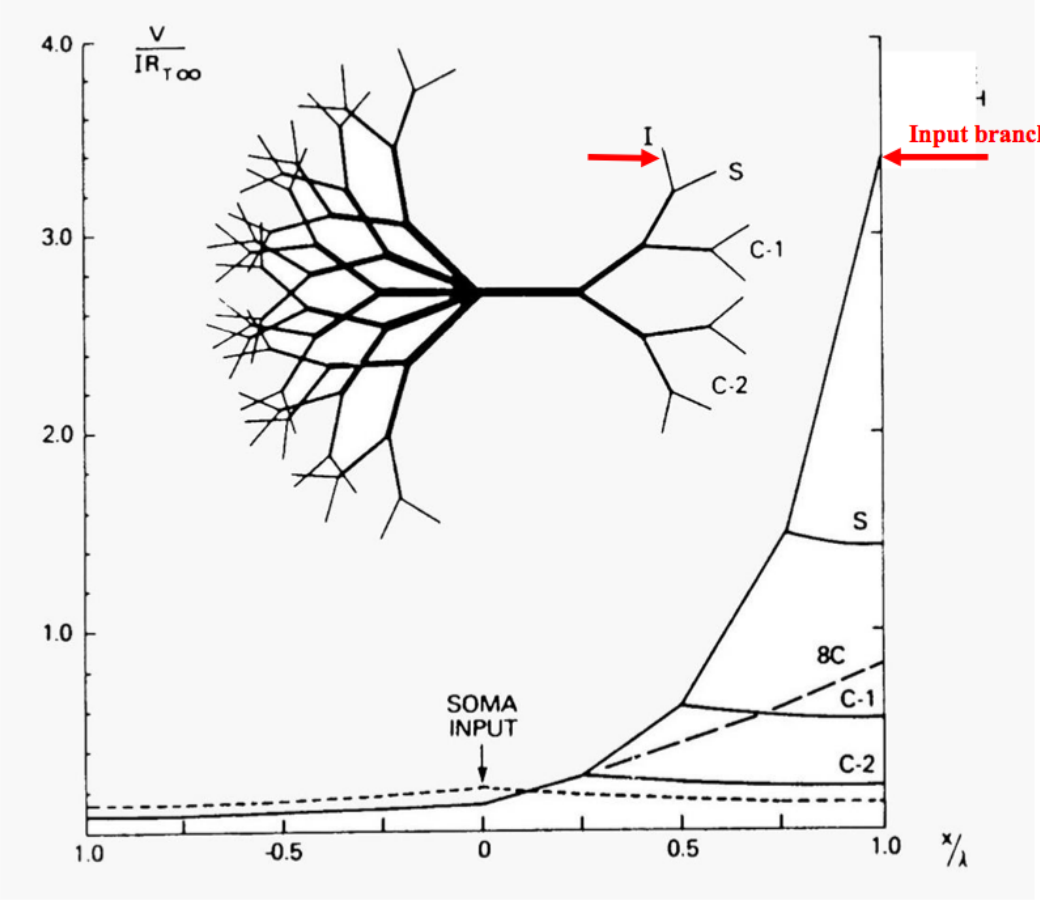
Steady state condition

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

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

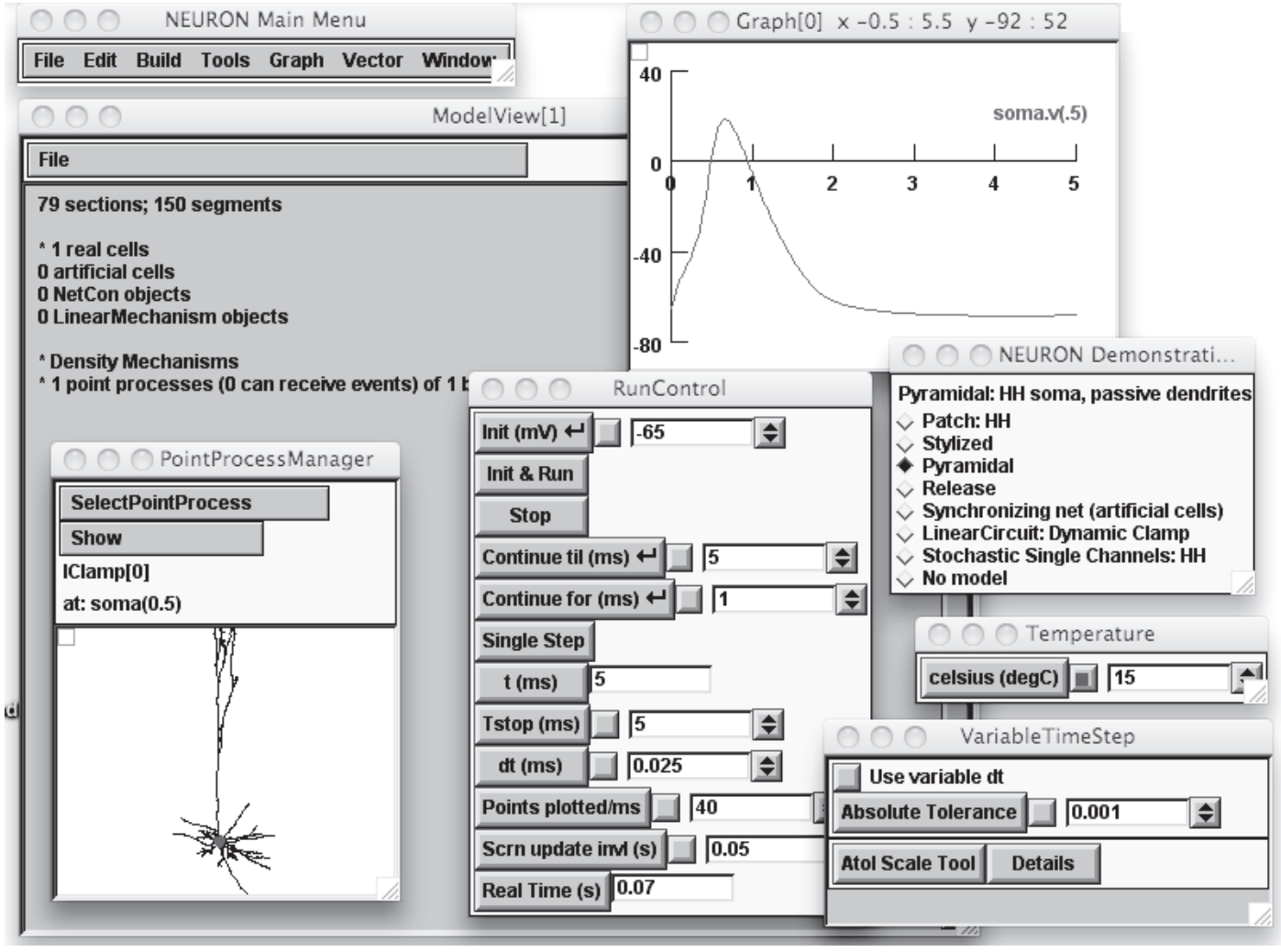


Simulating voltage attenuation



Rall and Rinzel, 1973

Simulators


NEURON Main Menu
File Edit Build Tools Graph Vector Window
ModelView[1]
File
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 b
Graph[0] x -0.5 : 5.5 y -92 : 52
40
0
-40
-80
soma.v(.5)
0 1 2 3 4 5
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 invl (s)
0.05
Real Time (s)
0.07
NEURON Demonstrati...
Pyramidal: 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

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