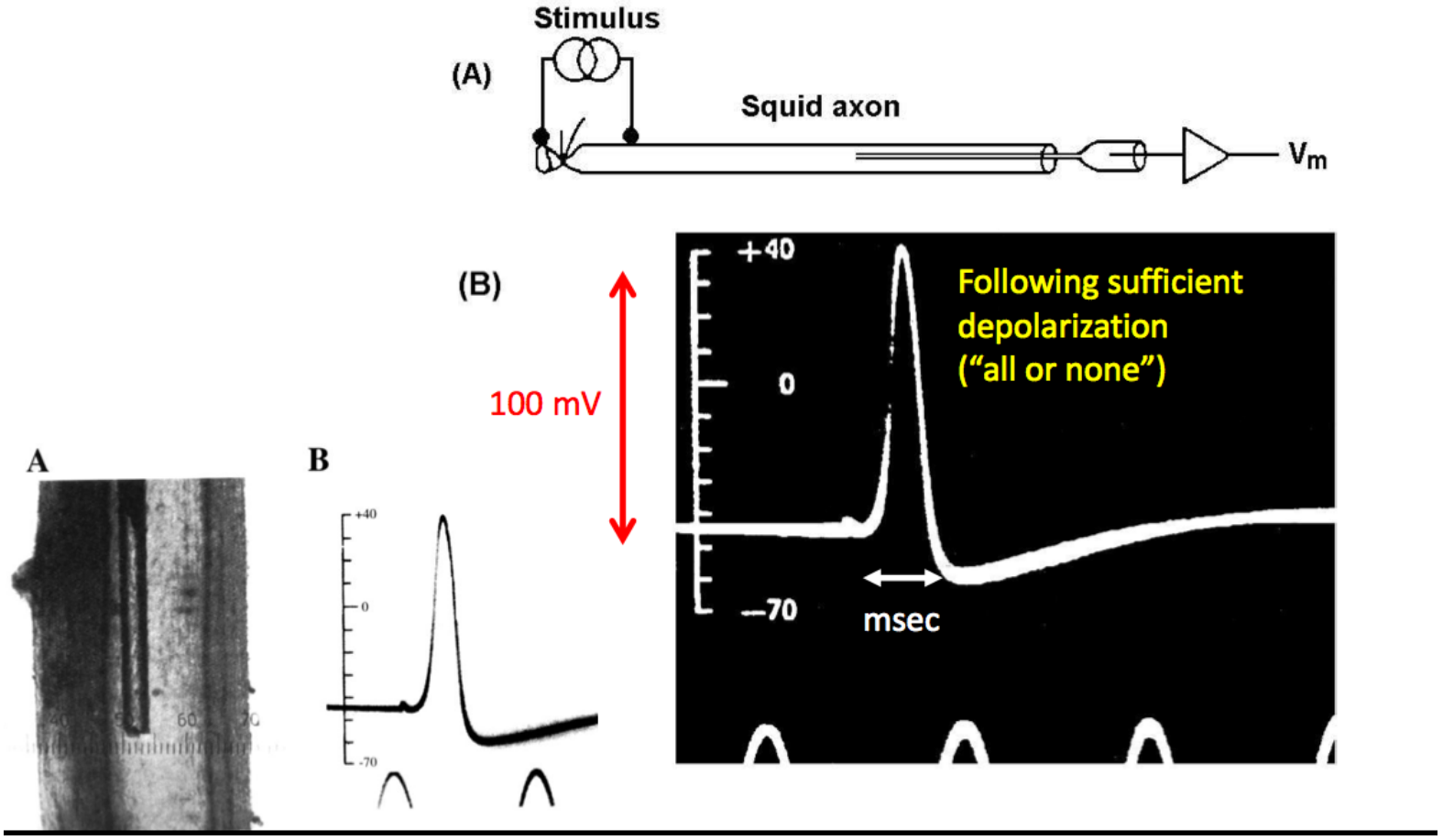
Neuroinformatics 2022, Prague

March 2, 2022

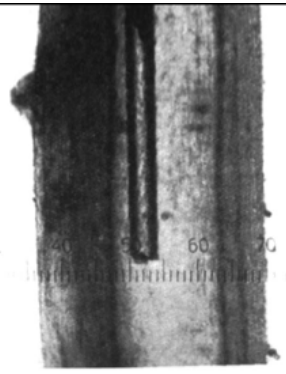
Hodkin and Huxley models

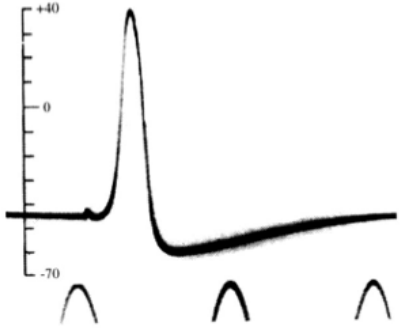
First direct (intracellular) recorded action-potential (spike) - 1939!!



Very nice theory

Sir Alan Lloyd Hodgkin





Sir Andrew Fielding Huxley

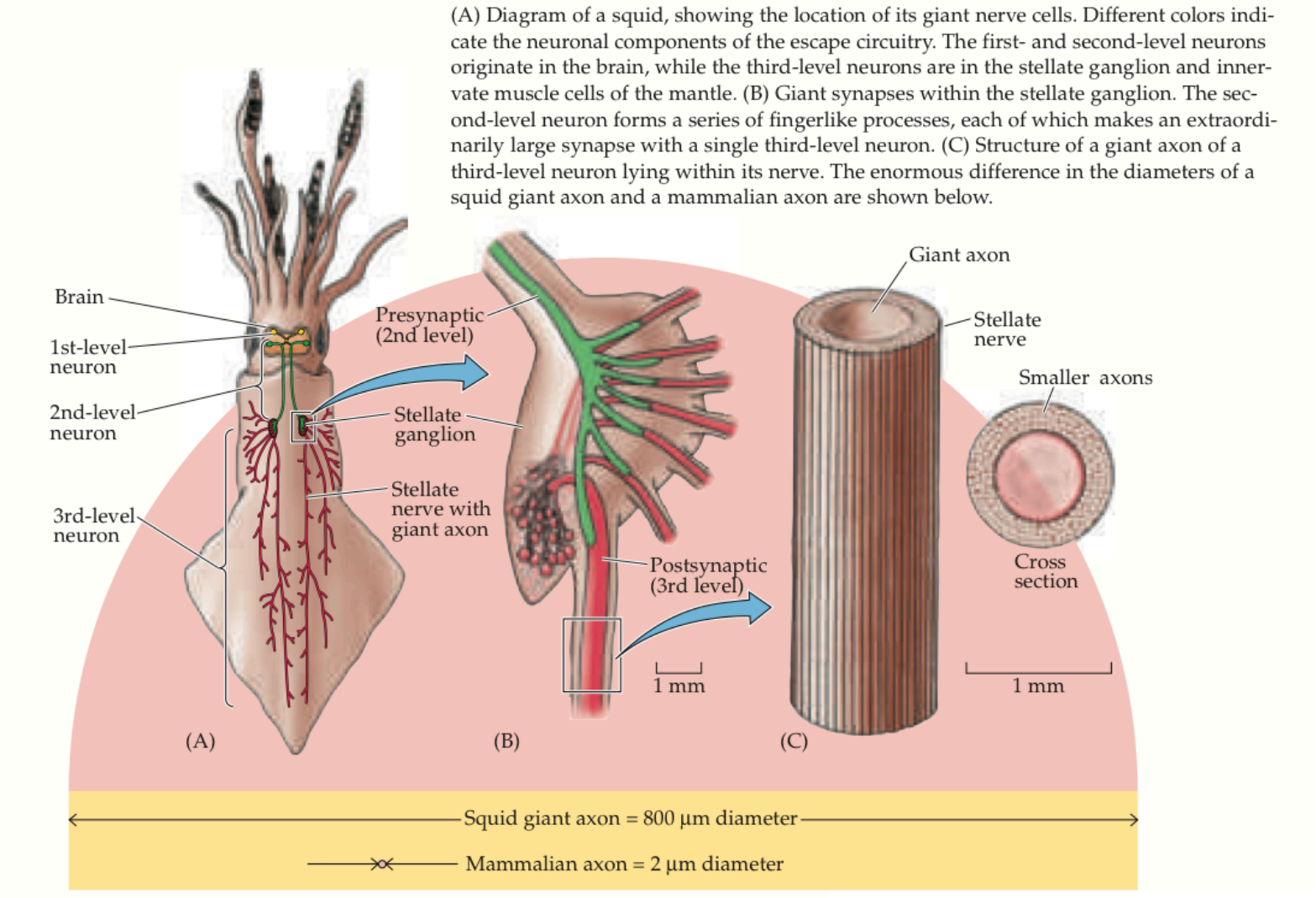
$$I = C_m \dot{V} + g_{Na}\, h\, m^3\, (V - V_{Na}) + g_K\, n^4\, (V - V_k) + G_L\, (V - V_L) \qquad (1)$$

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

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

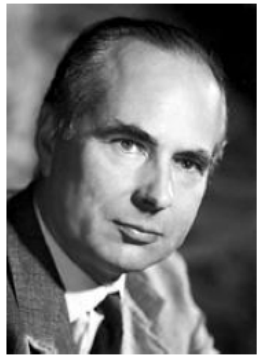
$$\frac{d}{dt} h = \alpha_h (V)\ (1 - h) - \beta_h (V)\ h \qquad (4)$$

Giant Nerve Cells of Squid



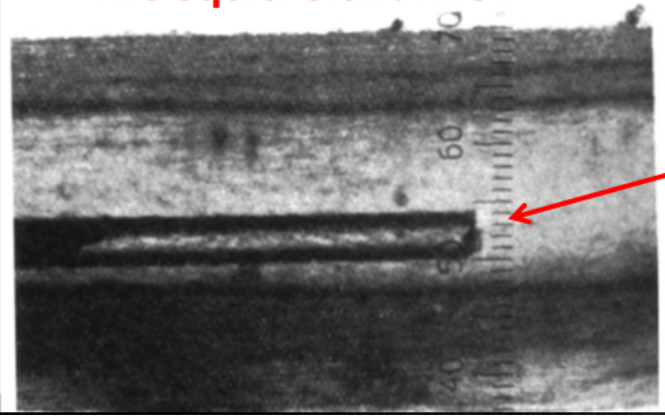
Hodkin and Huxley experiment NOBEL 1963

Sir Alan Lloyd Hodgkin

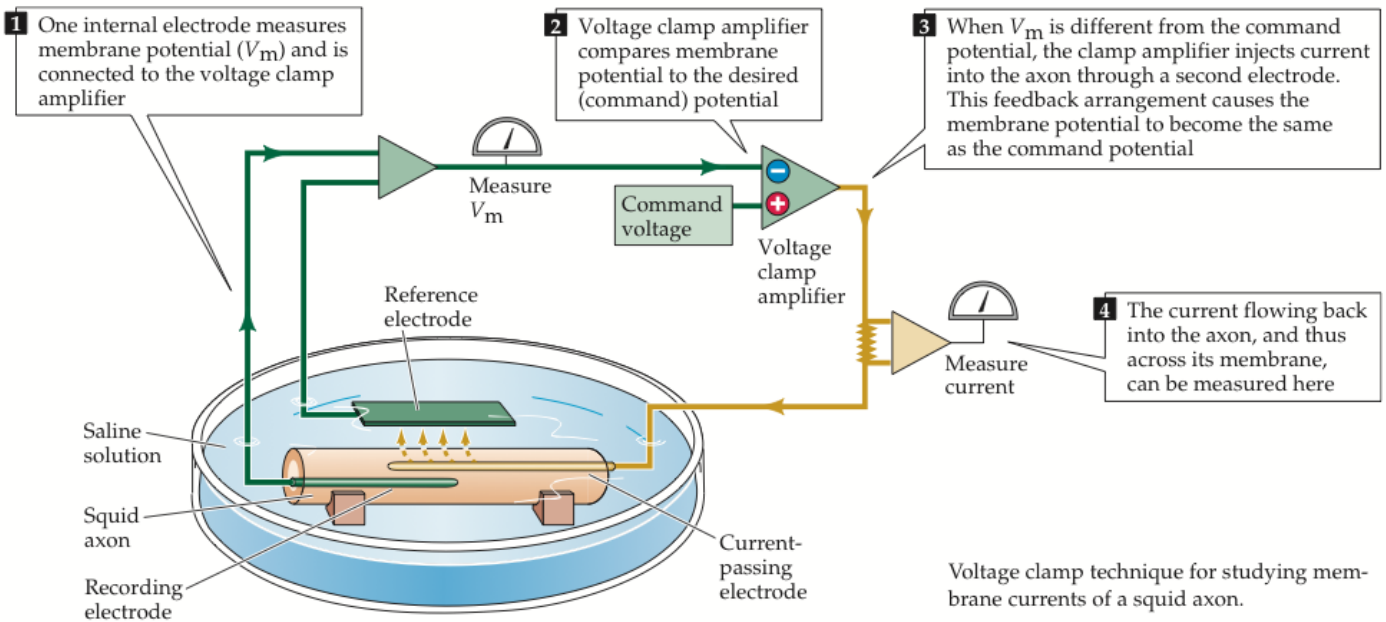


Sir Andrew Fielding Huxley

The Squid Giant Axon



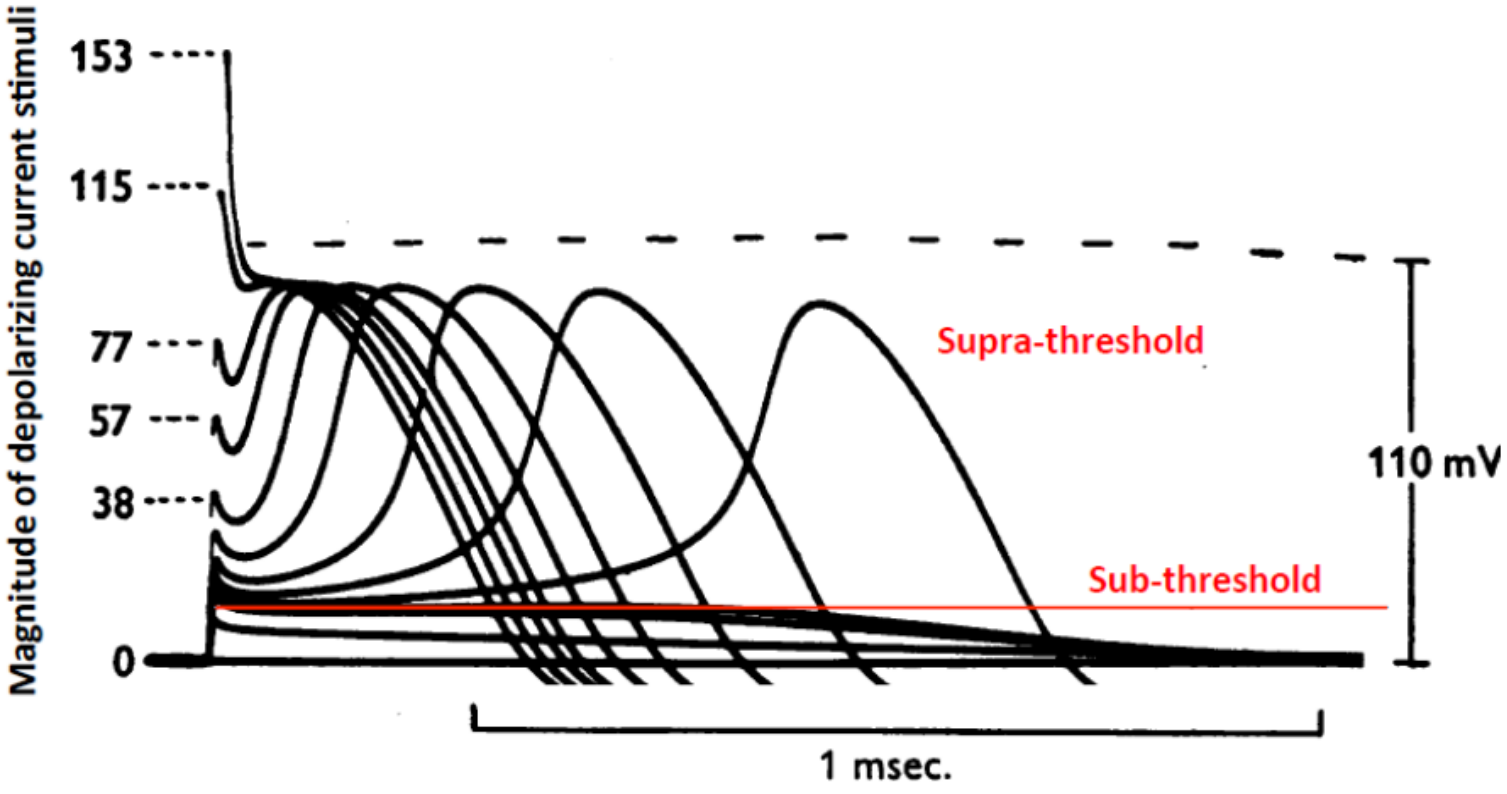
Voltage Clamp Method



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

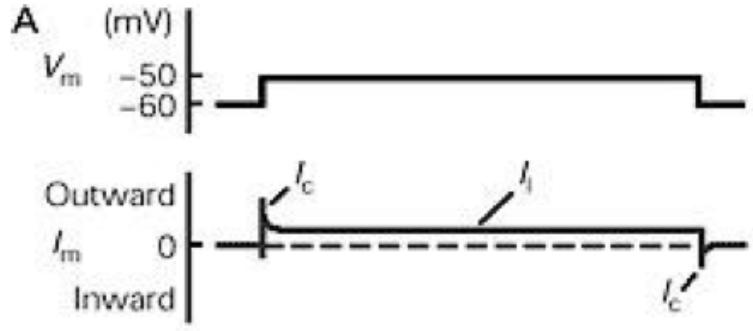
All or None

The “all or none” nature of the spike

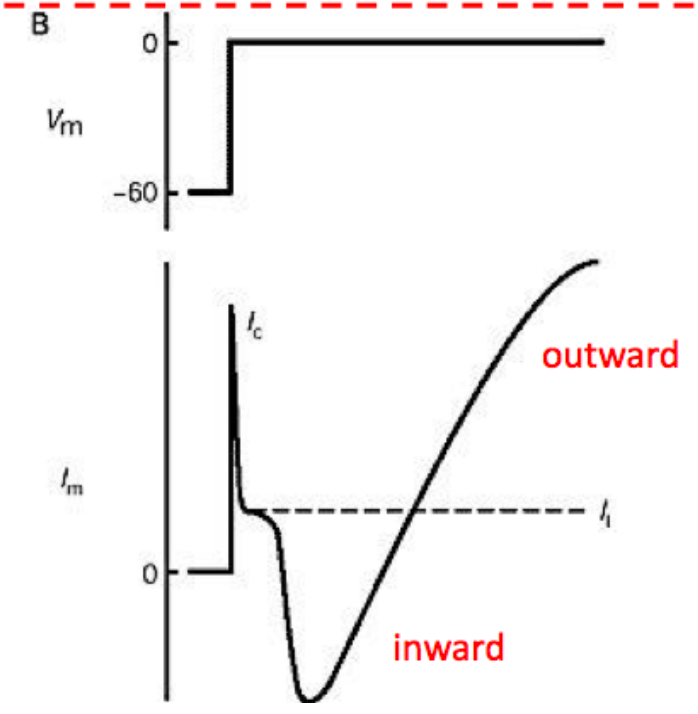


Hodgkin, Huxley and Katz, 1952

Membrane current in response to voltage clamp (VC)

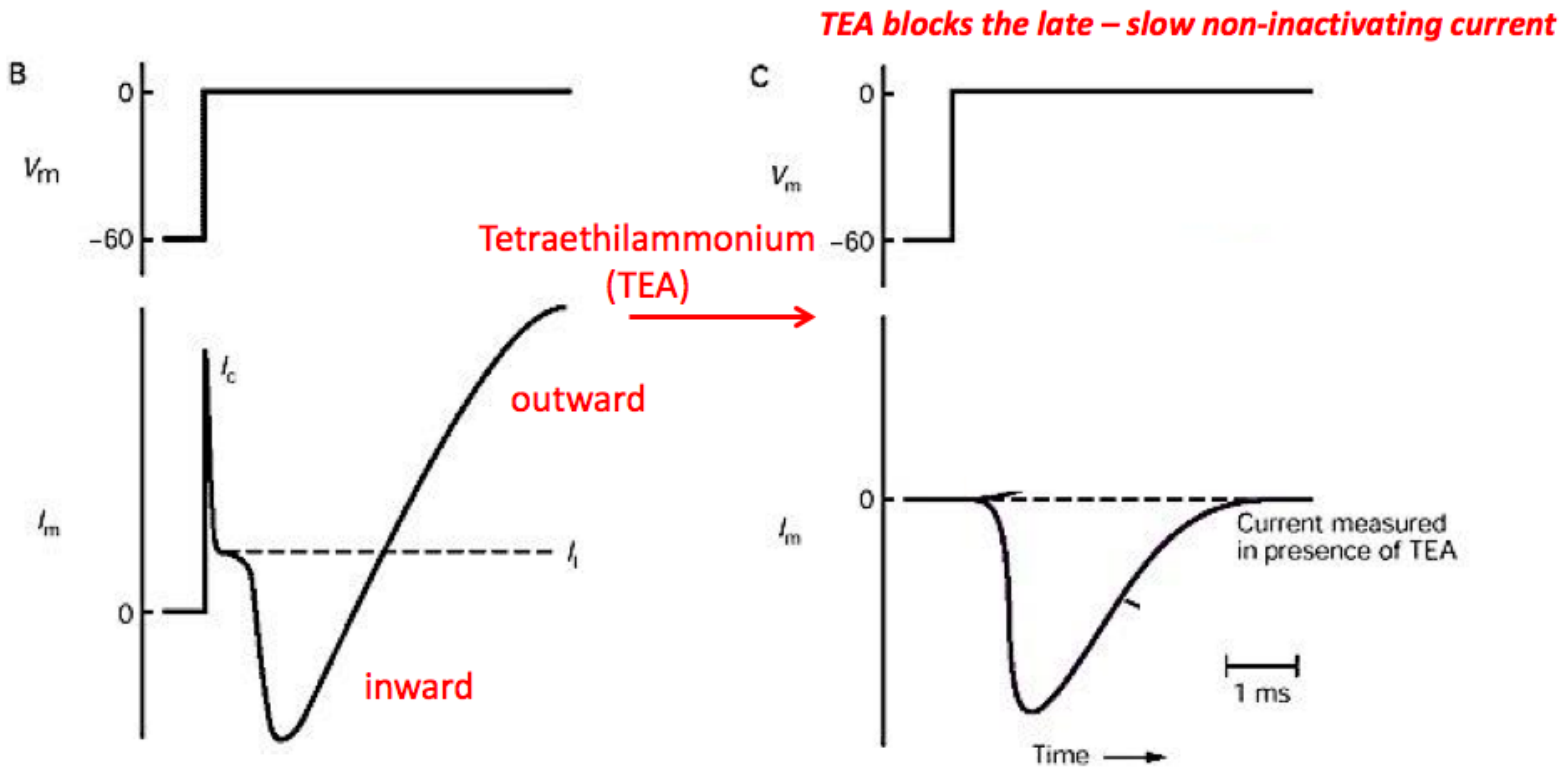


For subthershold depolarizing voltage clamp, the recorded membrane current is the current that flows via the leak (passive) conductance + a small capacitative current (at start and end of the VC)

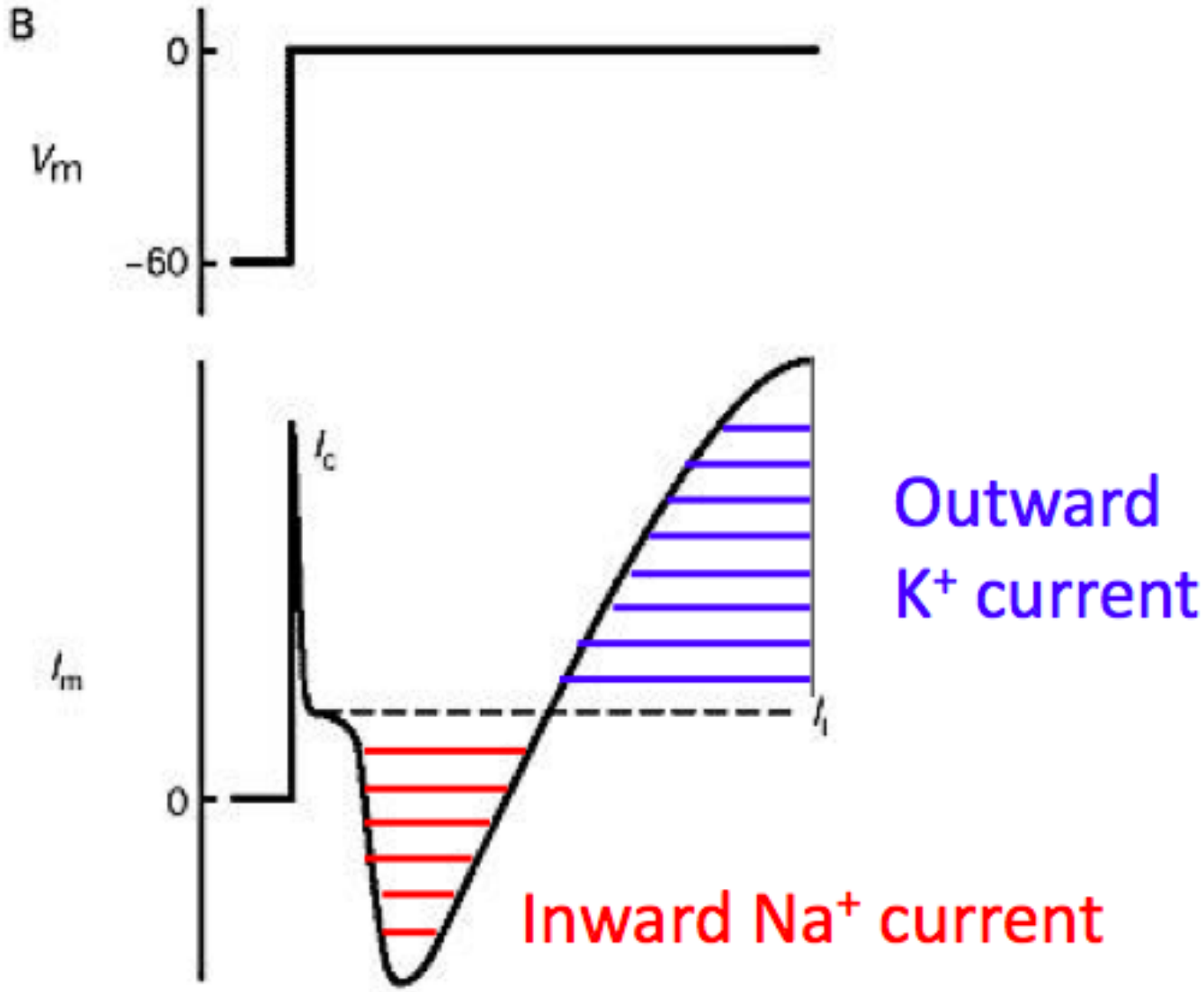


For suprathershold depolarizing voltage clamp, the recorded membrane current (after the fast capacitaticve current) flows first inwards (into the axon) and later outward (from inside to the outside)

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

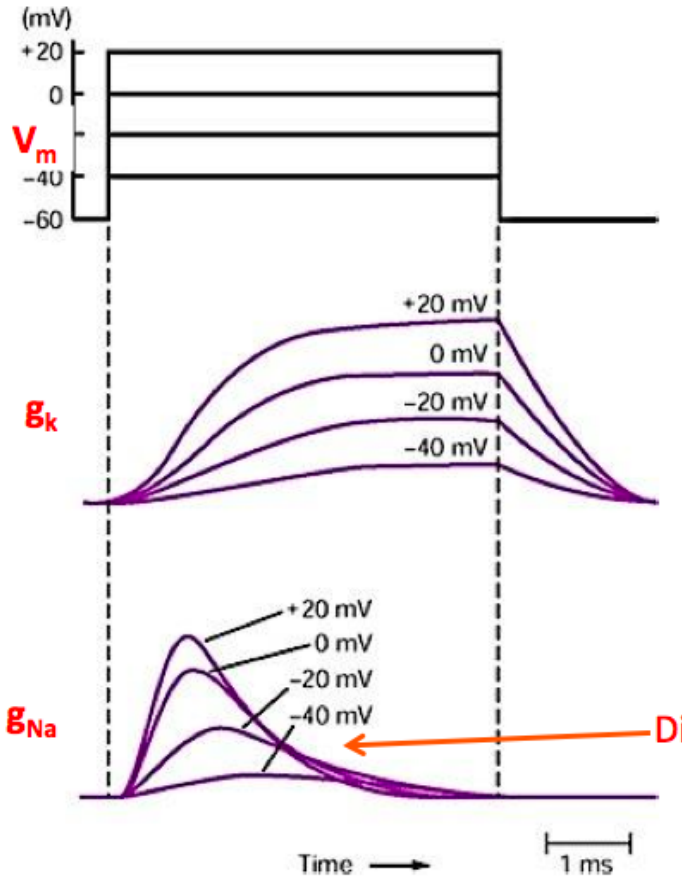


Changing ion concentration at bath with giant axon showed that early current is carried by Na+ ions and late one by K+ ions



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

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

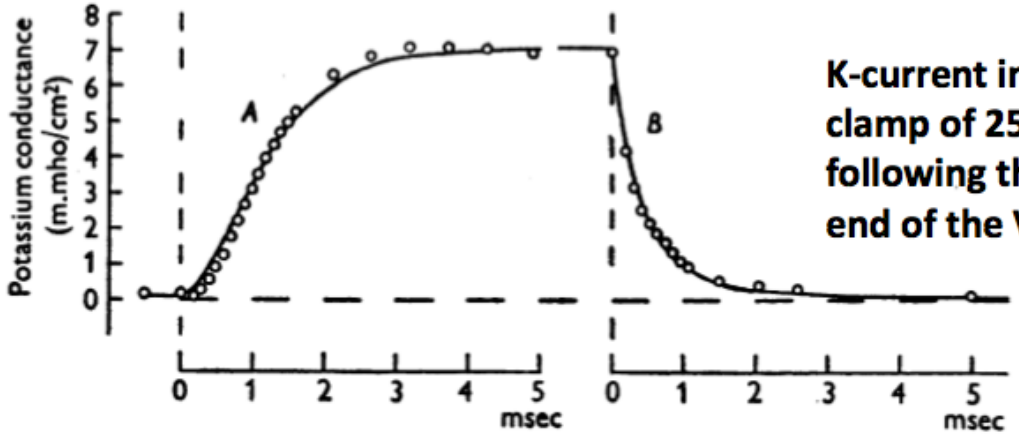


The slow (K) current (conductance) does not inactivate during VC .1

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

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

Fitting an equation for the K current (K-conductance) during/following VC



K-current in response to a step voltage clamp of 25 mV (upstroke) – slow rise following the VC and faster decay at the end of the VC

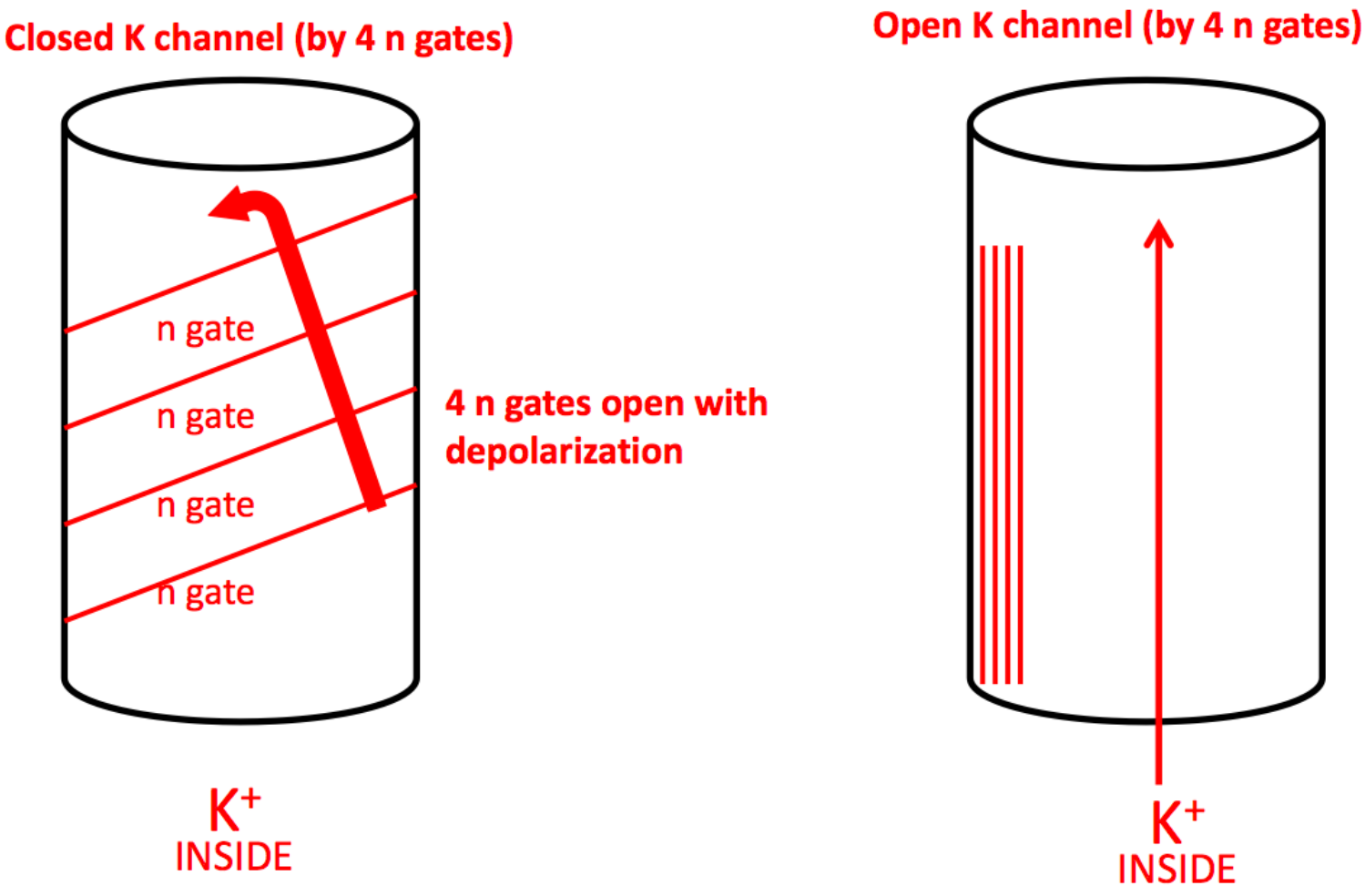
Mathematically – the rising phase of K-current can be described as a power of 4 (namely as $(1 - \exp(-t))^4$ and the decay as $\exp(-4t)$

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

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

"These equations may be given a physical basis if we assume that potassium ions can only cross the membrane when four similar particles occupy a certain region of the membrane..." Hodgkin AL, Huxley AF. 1952 J Physiol (Lond) 117:500–544

Graphical interpretation of H&H model for the K channel



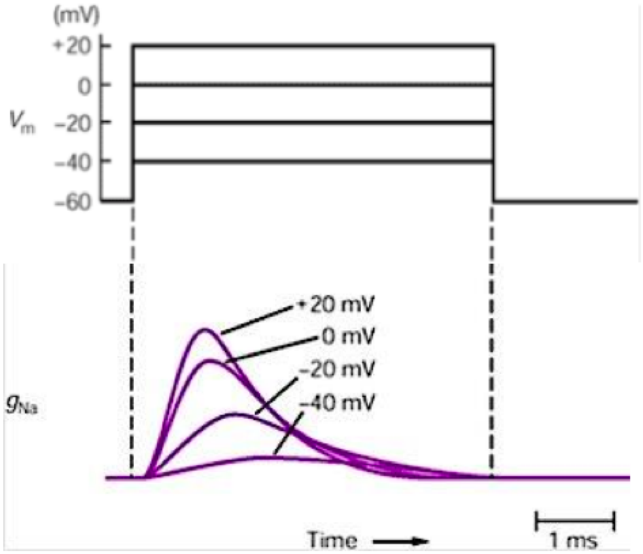
The activation function, n, and the rate functions α_n and β_n

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

$$\frac{dn}{dt} = \alpha_n (1 - n) - \beta_n n,$$

where $\bar{g}_K$ is a constant with the dimensions of conductance/cm^2, α_n and β_n are rate constants which vary with voltage but not with time and have dimensions of [time]$^{-1}$, n is a dimensionless variable which can vary between 0 and 1.

Similar procedure is used to extract the activation (m) and inactivation (h) parameters for the Na current

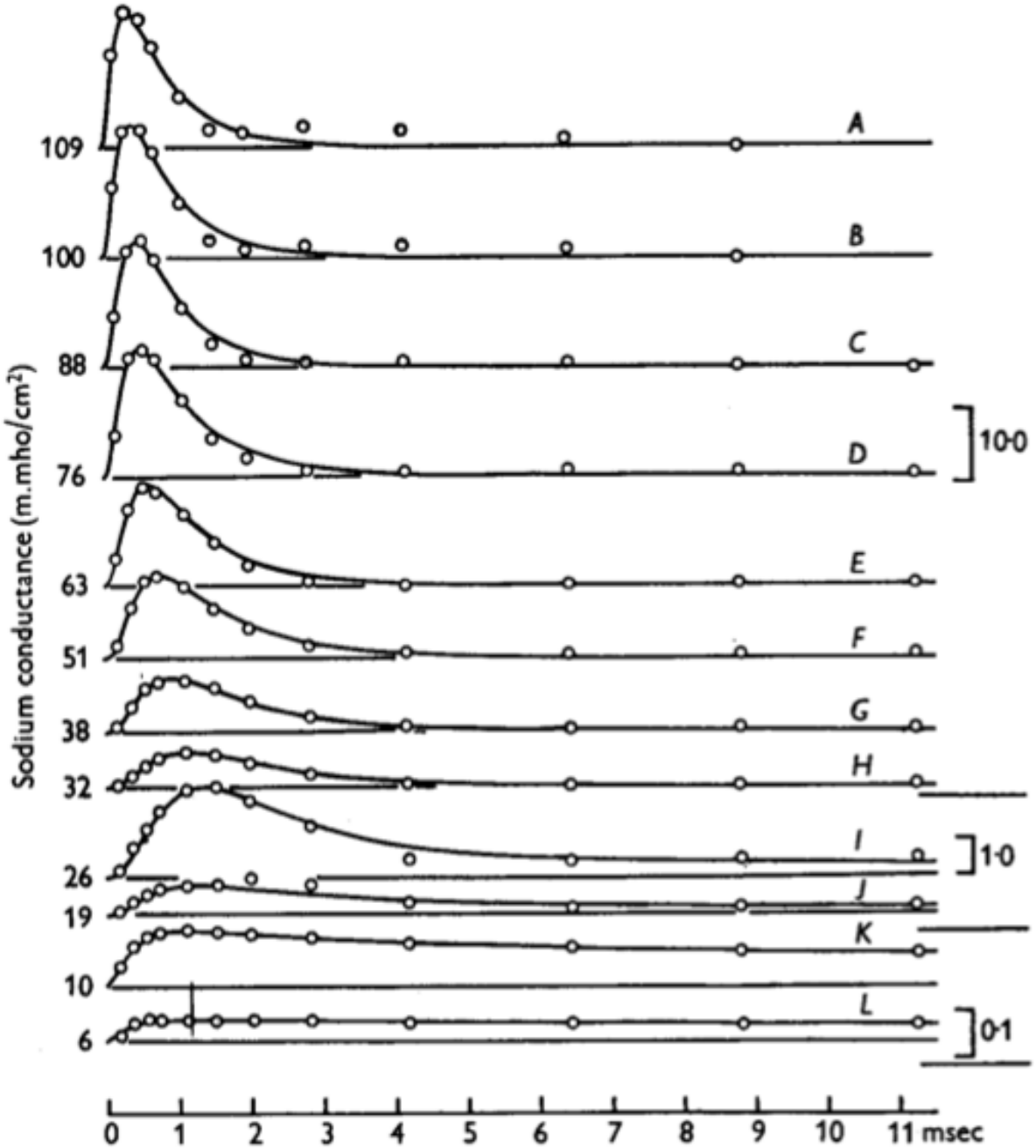


$$g_{\mathrm{Na}} = m^3 h \bar{g}_{\mathrm{Na}},$$

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

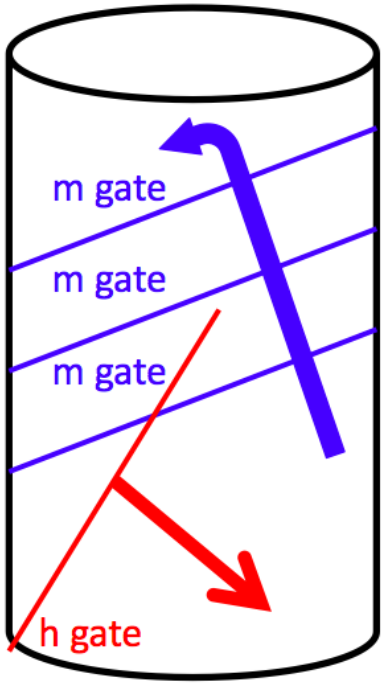
$$\frac{\mathrm{d}h}{\mathrm{d}t} = \alpha_h (1-h) - \beta_h h,$$

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)

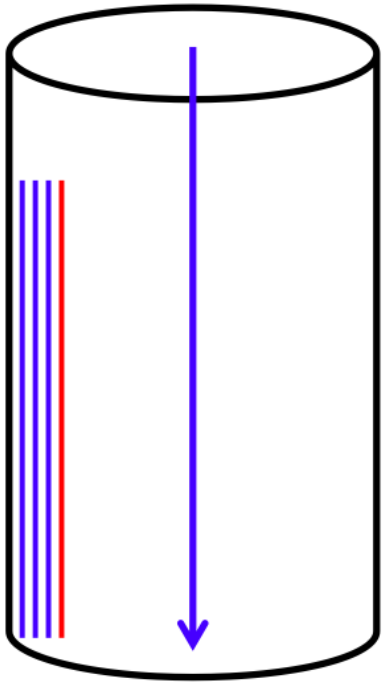


3 (fast) m (activated) gates open with depolarization

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

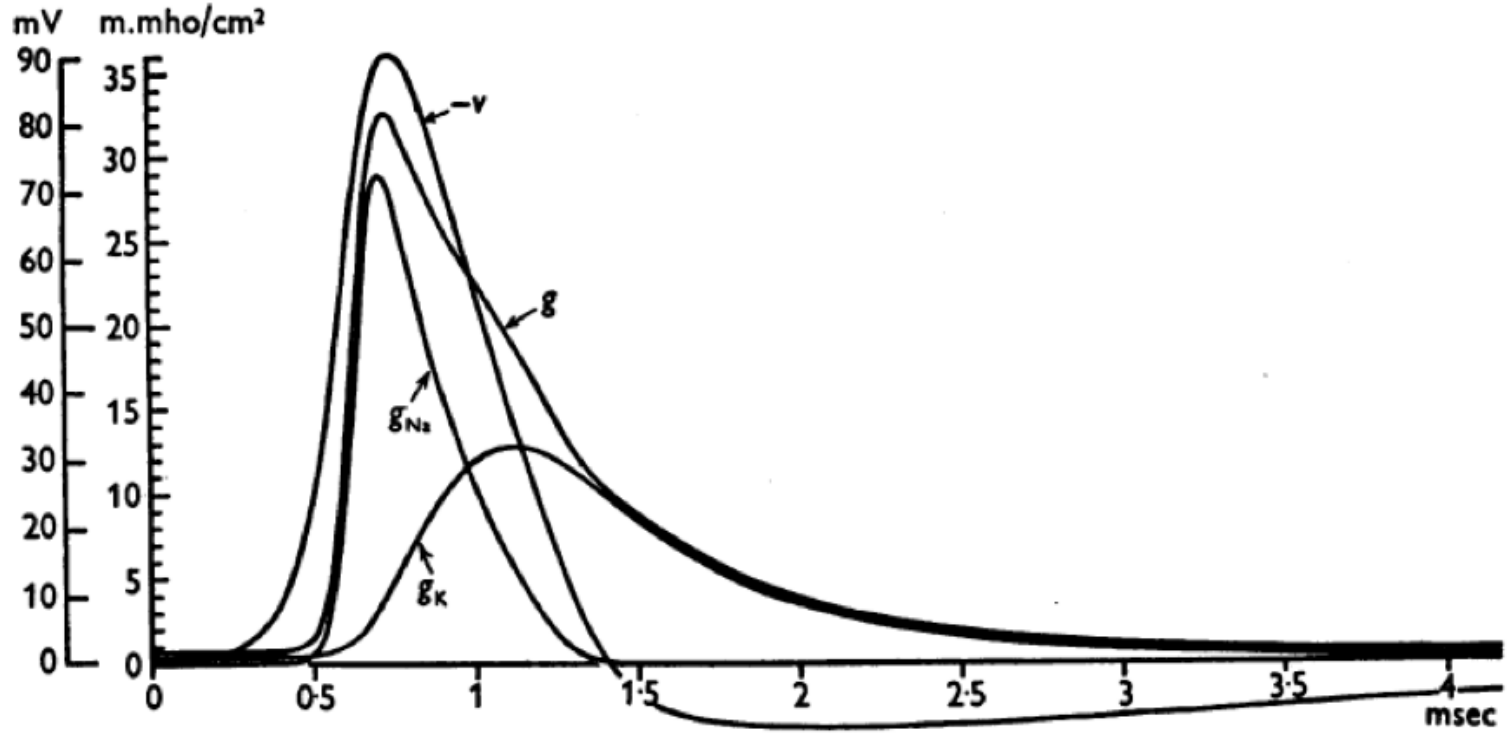


Fig. 17. Numerical solution of eqn. (31) showing components of membrane conductance (g) during propagated action potential ($-V$). Details of the analysis are as in Fig. 15.

Hodgkin–Huxley model

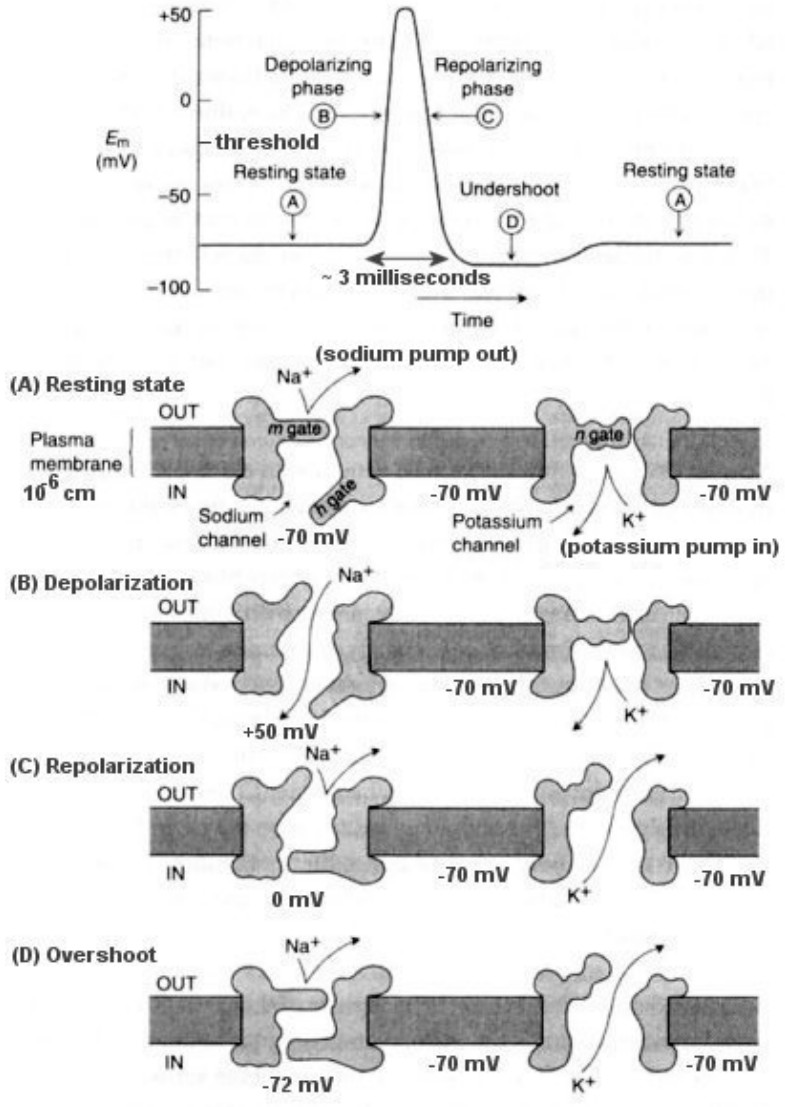
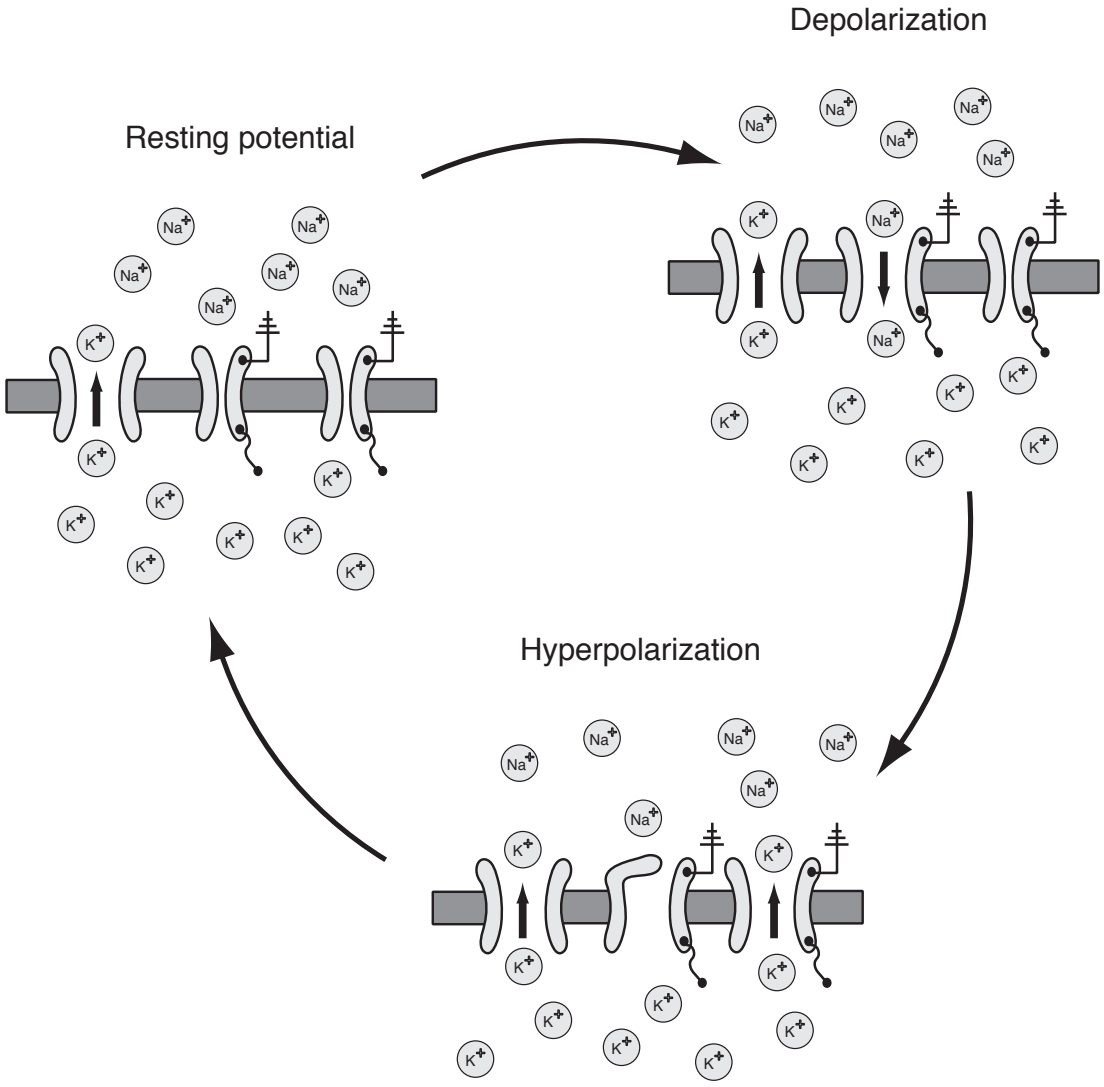


Figure: Typical form of an action potential; redrawn from an oscilloscope picture from Hodgkin and Huxley (1939).

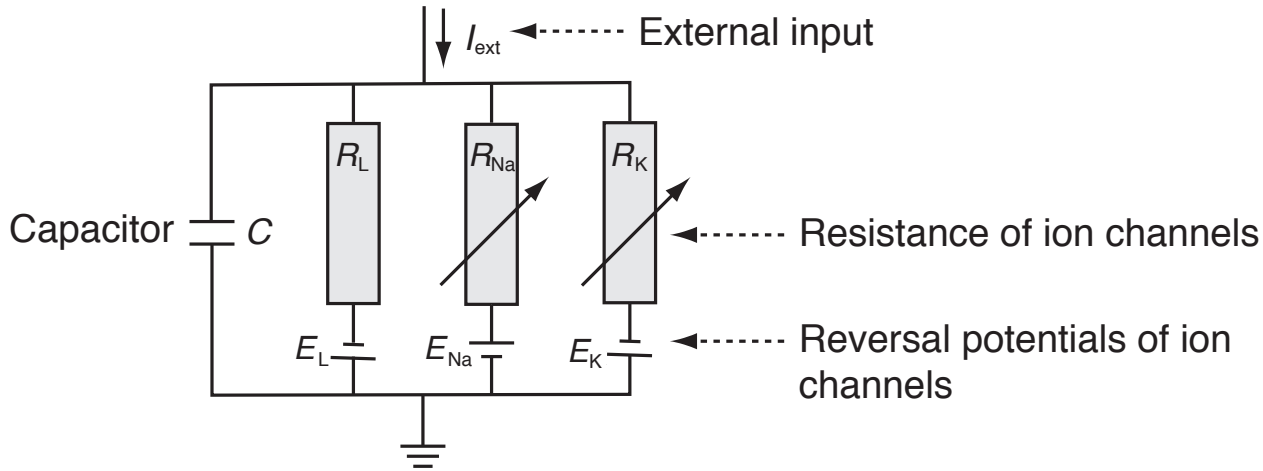
The minimal mechanisms



HH stucture

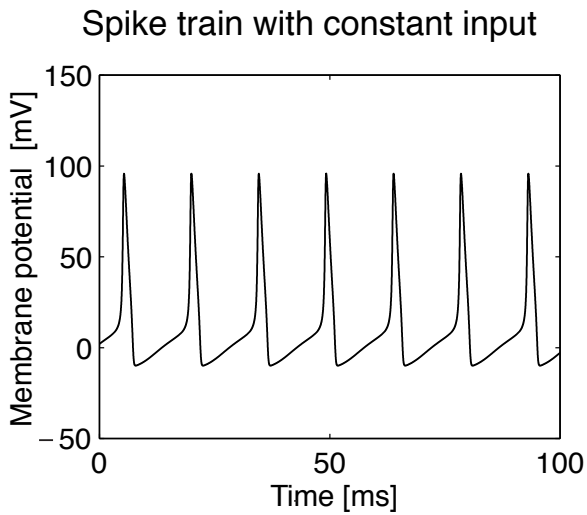
- $I_{ion} = \hat{g_{ion}}(V - E_{ion})$
- voltage and time dependent variables $n(V,t)$,$m(V,t)$,$h(V,t)$

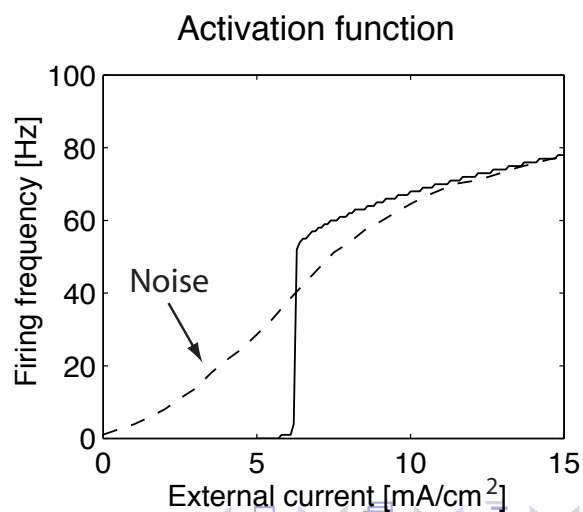
$$\hat{g_K}(V,t) = g_K n^4$$
$$\hat{g_{Na}}(V,t) = g_{Na} m^3 h$$



Hodgkin–Huxley equations and simulation

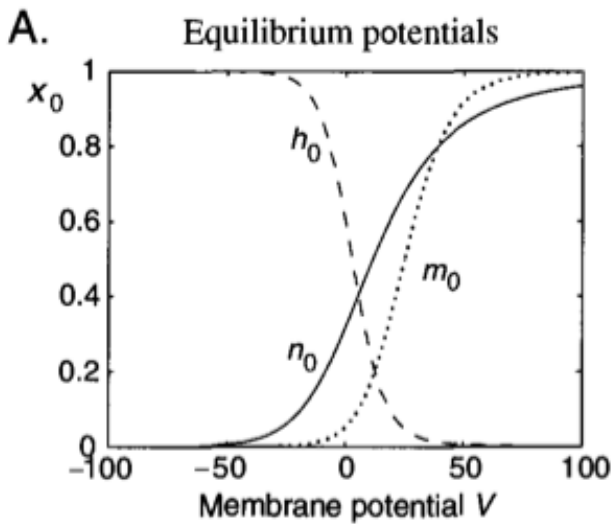
$$
\begin{aligned}
C\frac{\mathrm{d}V}{\mathrm{d}t} &= -g_{\mathrm{K}}n^4(V-E_{\mathrm{K}}) - g_{\mathrm{Na}}m^3h(V-E_{\mathrm{Na}}) - g_{\mathrm{L}}(V-E_{\mathrm{L}}) + I_{ext}(t) \\
\tau_{\mathrm{n}}(V)\frac{\mathrm{d}n}{\mathrm{d}t} &= -[n-n_0(V)] \\
\tau_{\mathrm{m}}(V)\frac{\mathrm{d}m}{\mathrm{d}t}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

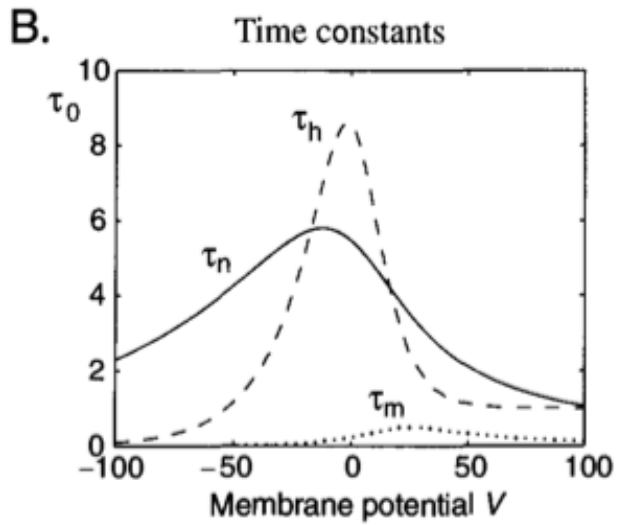




Ion channels resistance

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





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
```

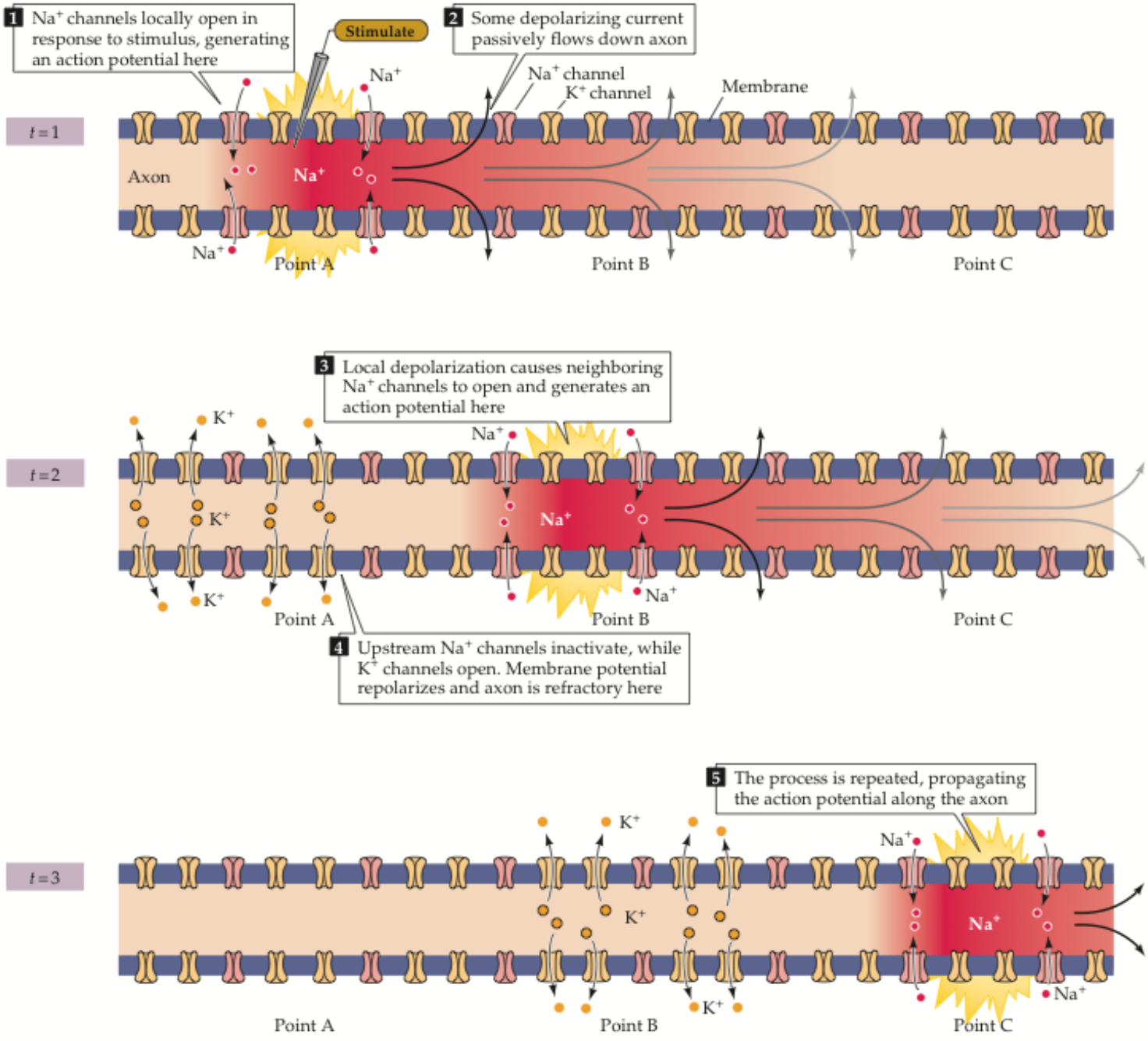
Refractory period

- 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

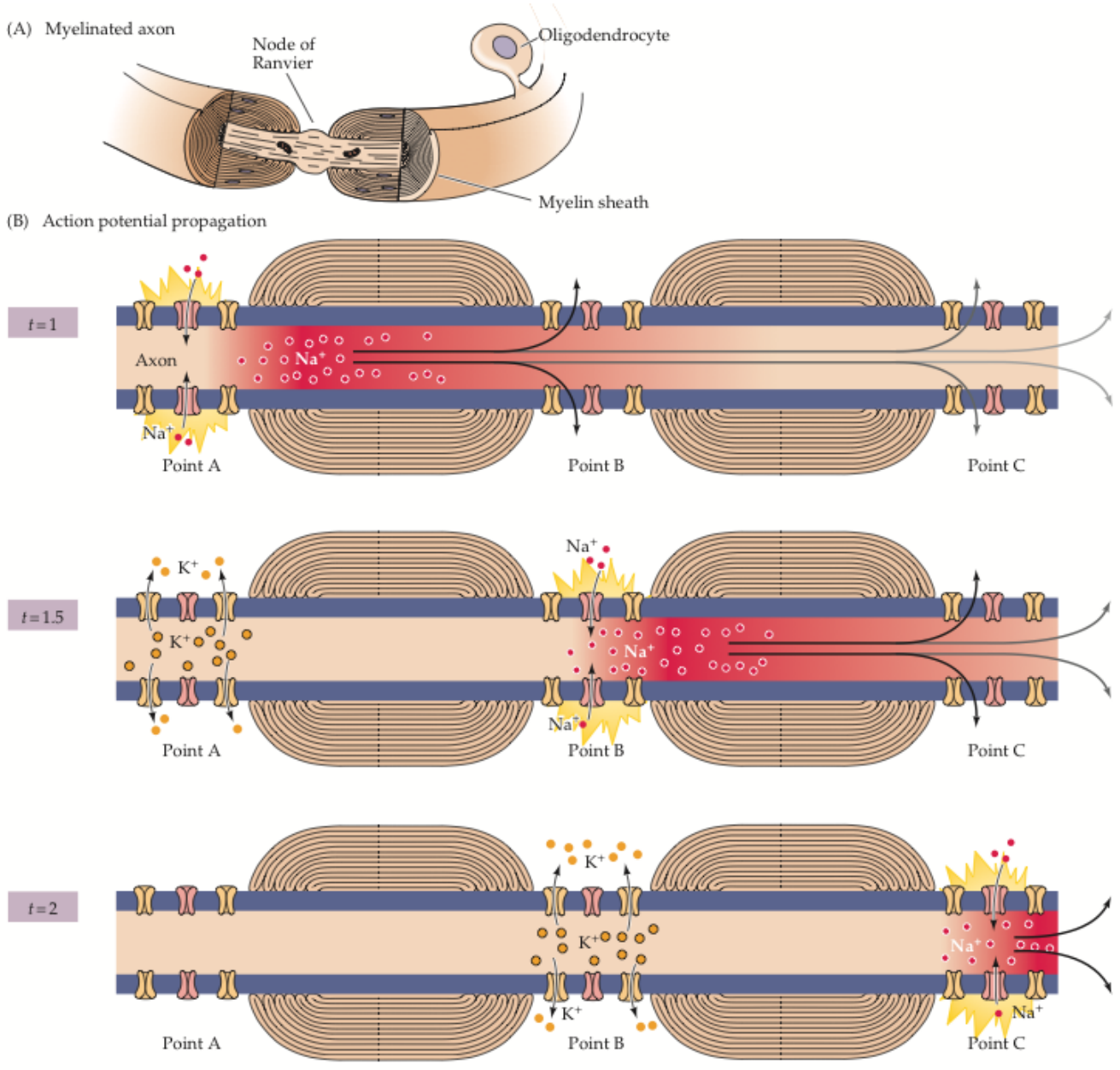
Propagation of action potentials

- 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!

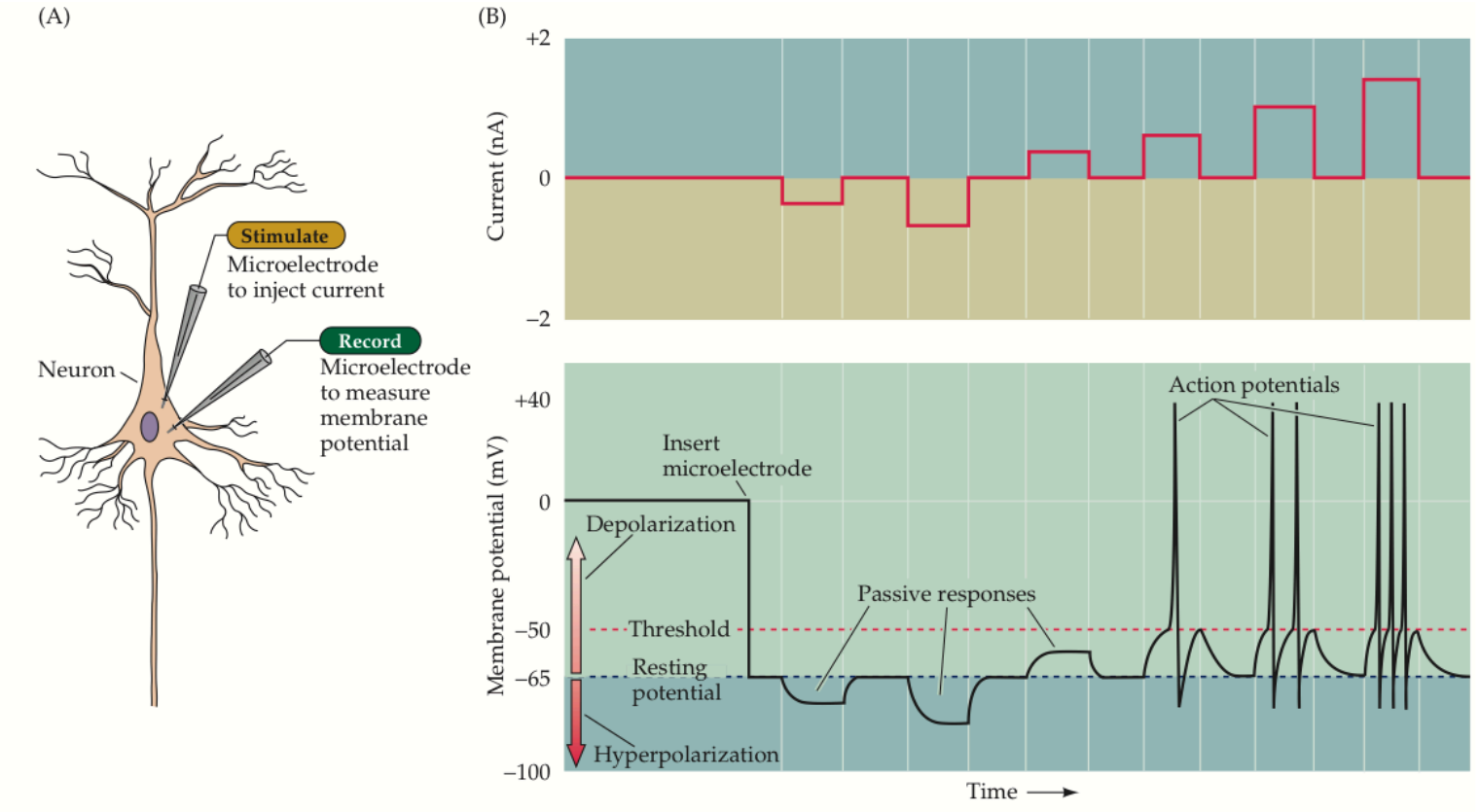
NON-LOSS transfer



LOSSY transfer



Stimulation of neuron



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

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

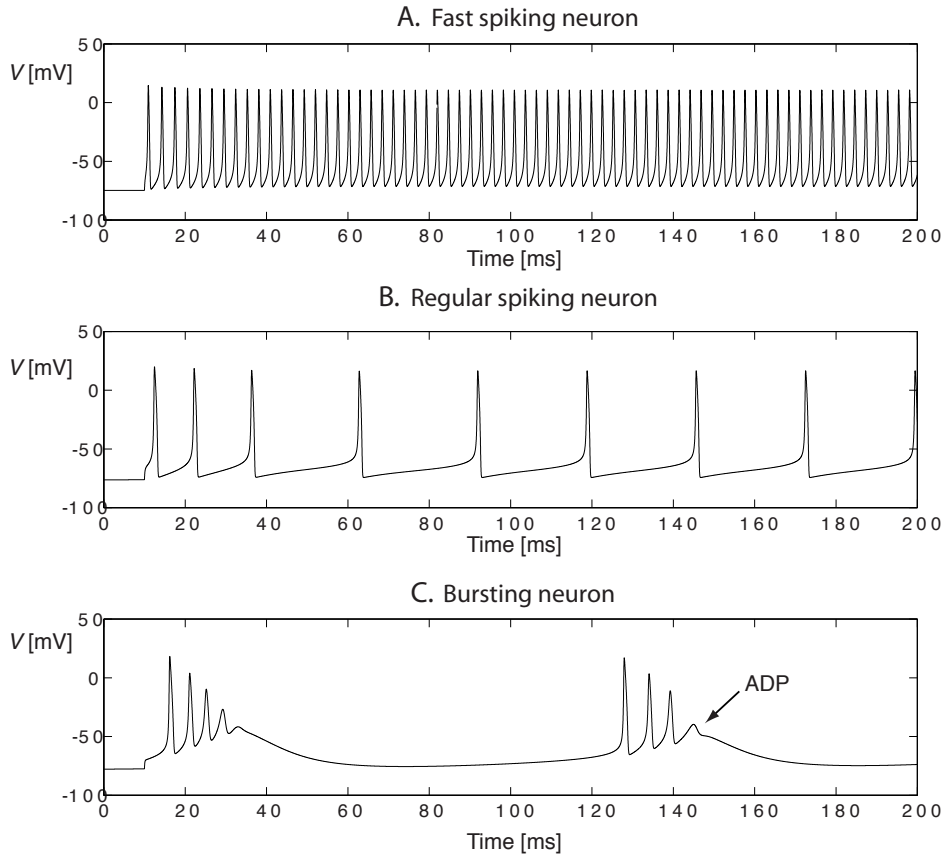
Wilson model

- 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

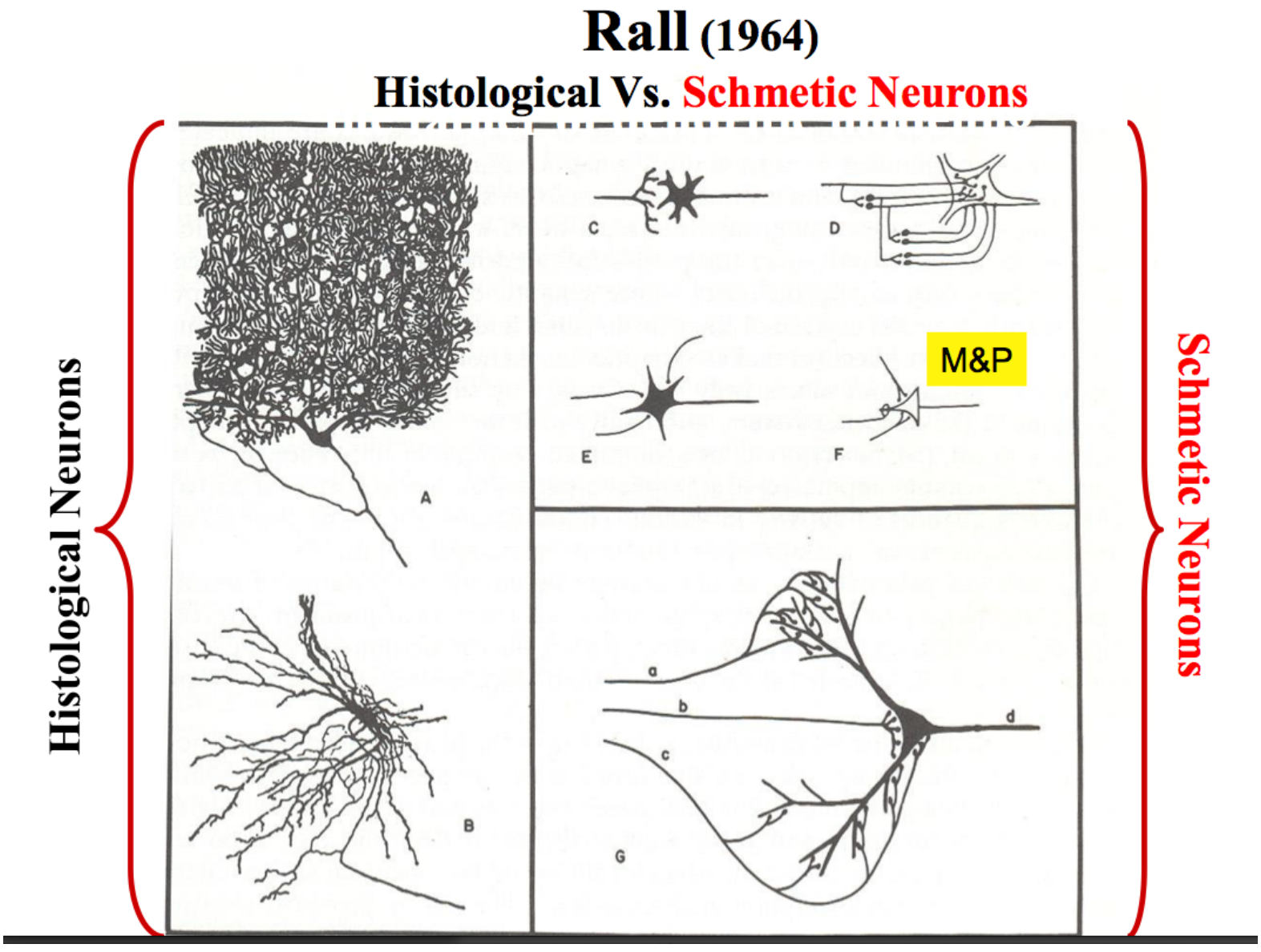
- RS: regular spiking neuron
- FS: fast spiking neuron
- CS: continously spiking neuron
- IB: bursting neuron



Matlab implementation

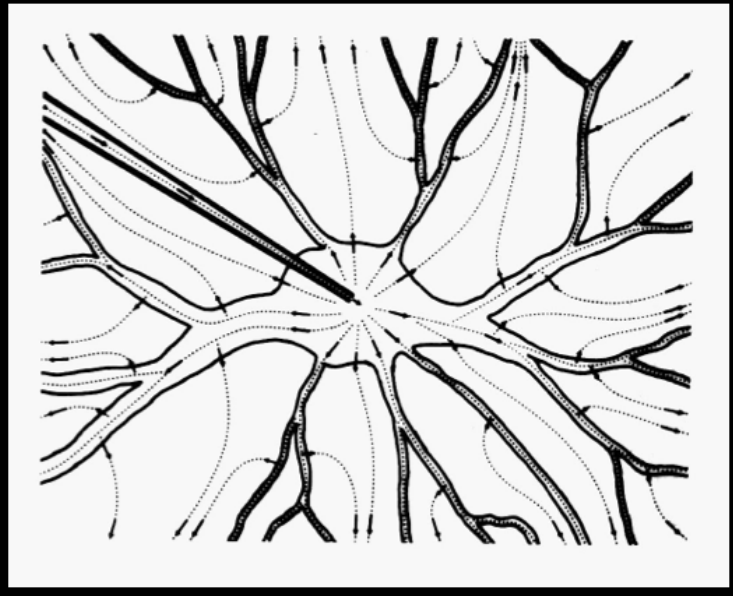
```
%%  Integration of Wilson model with the Euler method
 clear; clf;
%% Parameters of the model: 1=K,R  2=Ca,T  3=KCa,H  4=Na
 g(1)=26; g(2)=2.25; g(3)=9.5; g(4)=1;
 E(1)=-.95; E(2)=1.20; E(3)=E(1); E(4)=.50;

%% 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

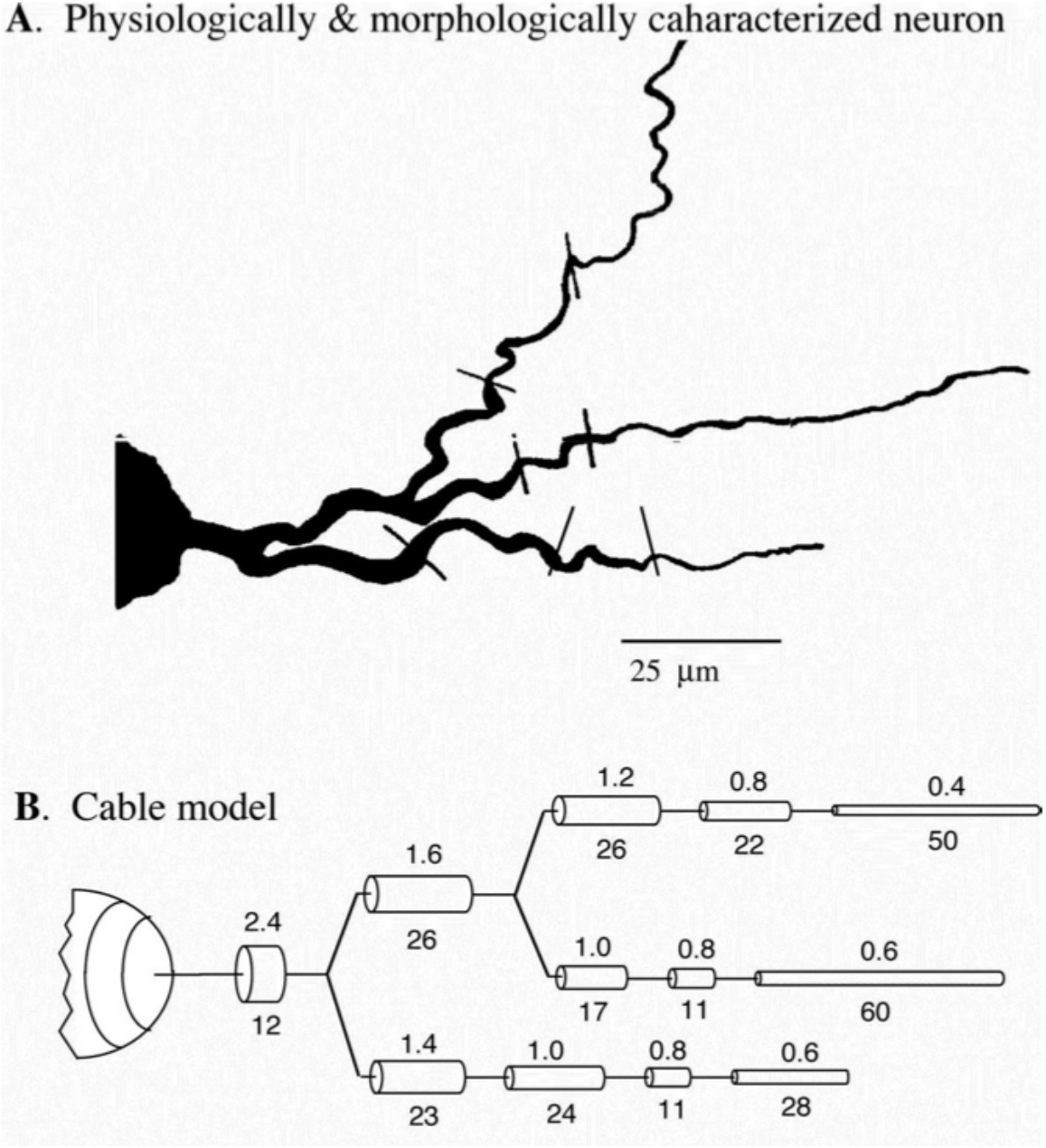
Dendrit Cable Theory

Rall Cable Theory for Dendrites

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

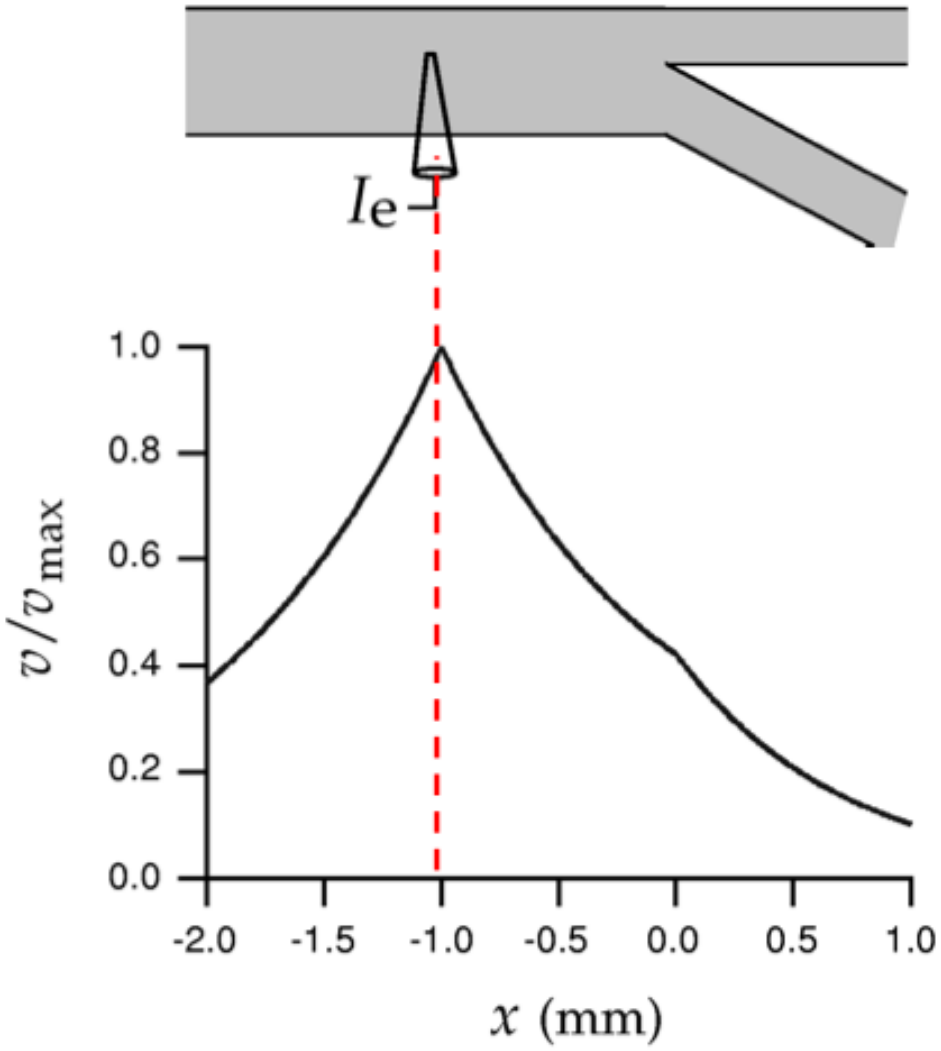
Wilfrid Rall

Cylindric model

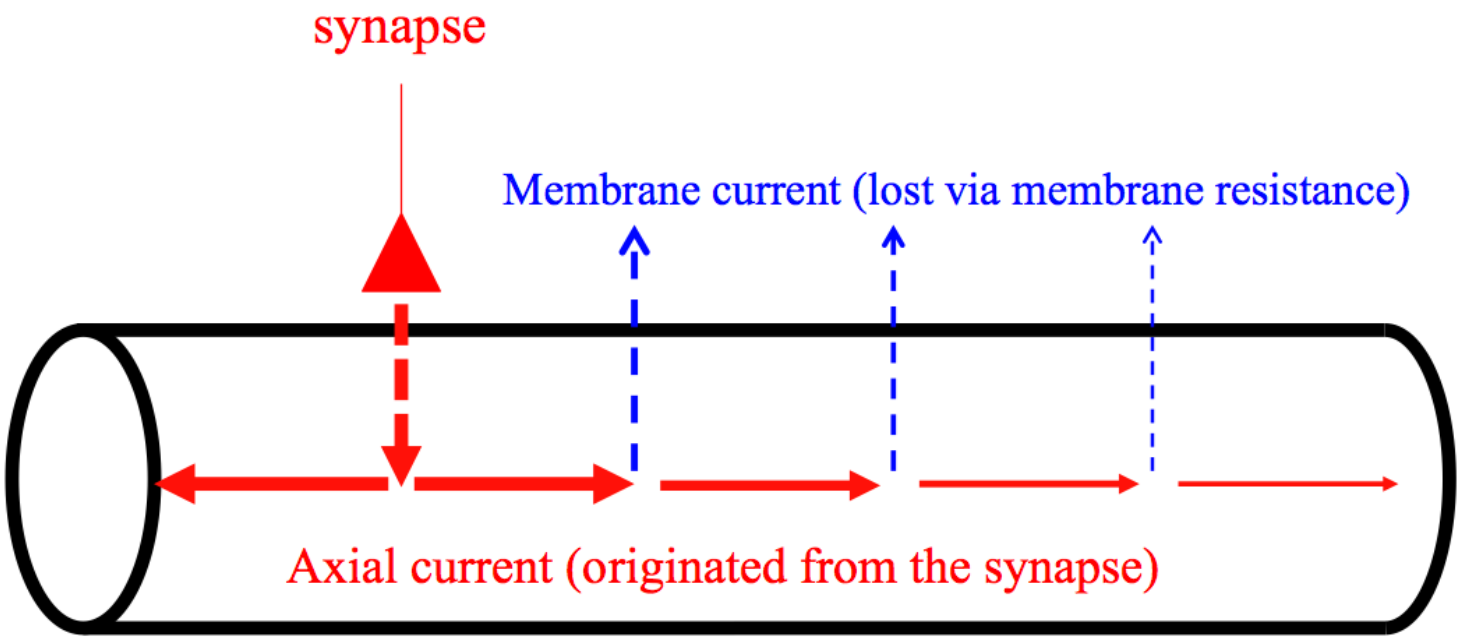


Voltage attenuation

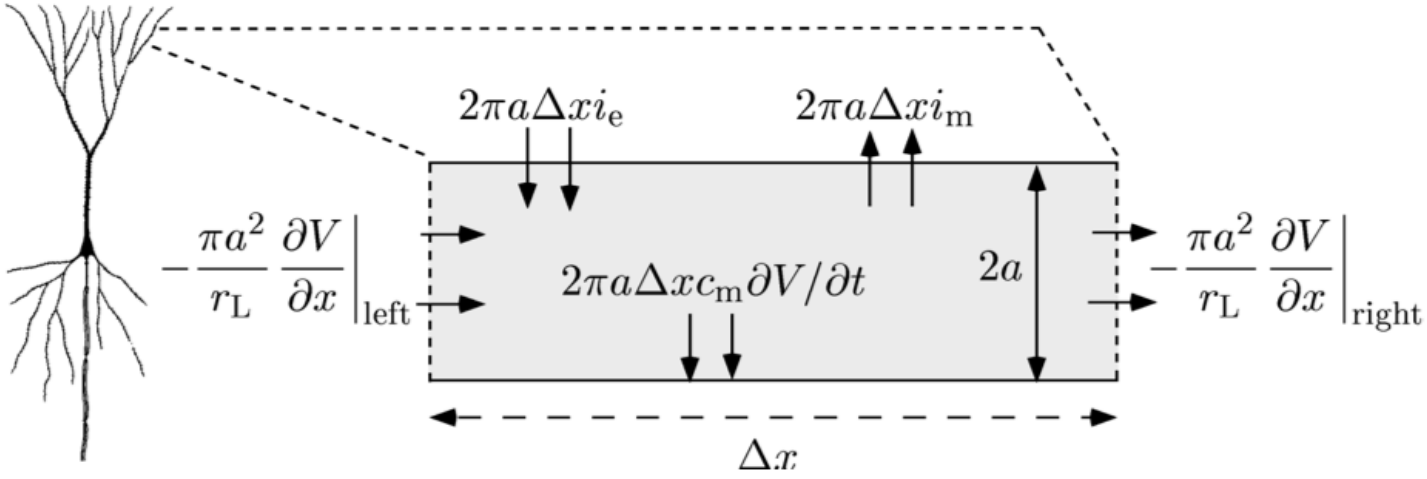
Synaptic potentials attenuate from the synapse origin towards other regions of the dendrites



Axial and membrane current



Passive cable equations



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

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

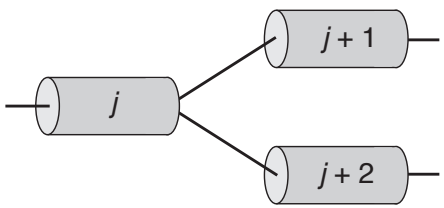
$X = x/\lambda$

$T = t/\tau_m$

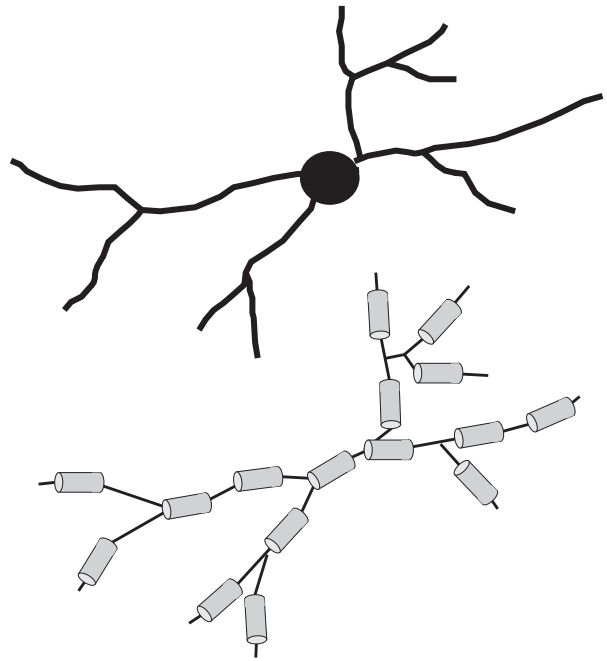
Compartmental models

A. Chain of compartments

B. Branching compartments



C. Compartmental reconstruction



Cable theory

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

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

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

$$\tau_m = R_m C_m$$

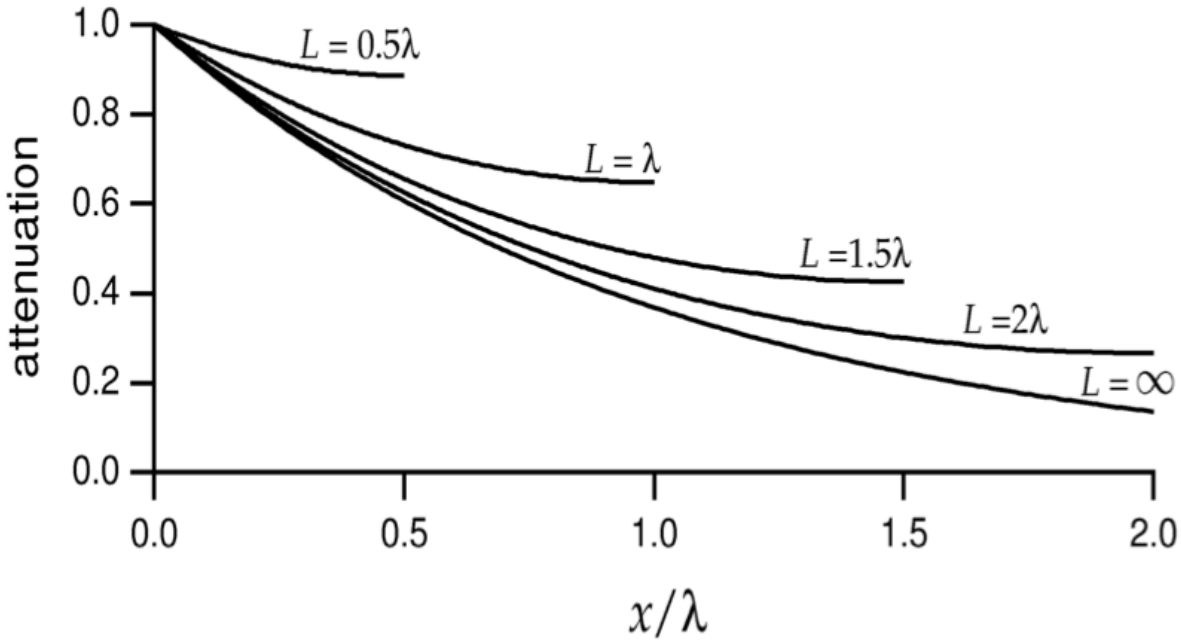
$$V_m = V_0 e - \frac{x}{\lambda}$$

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

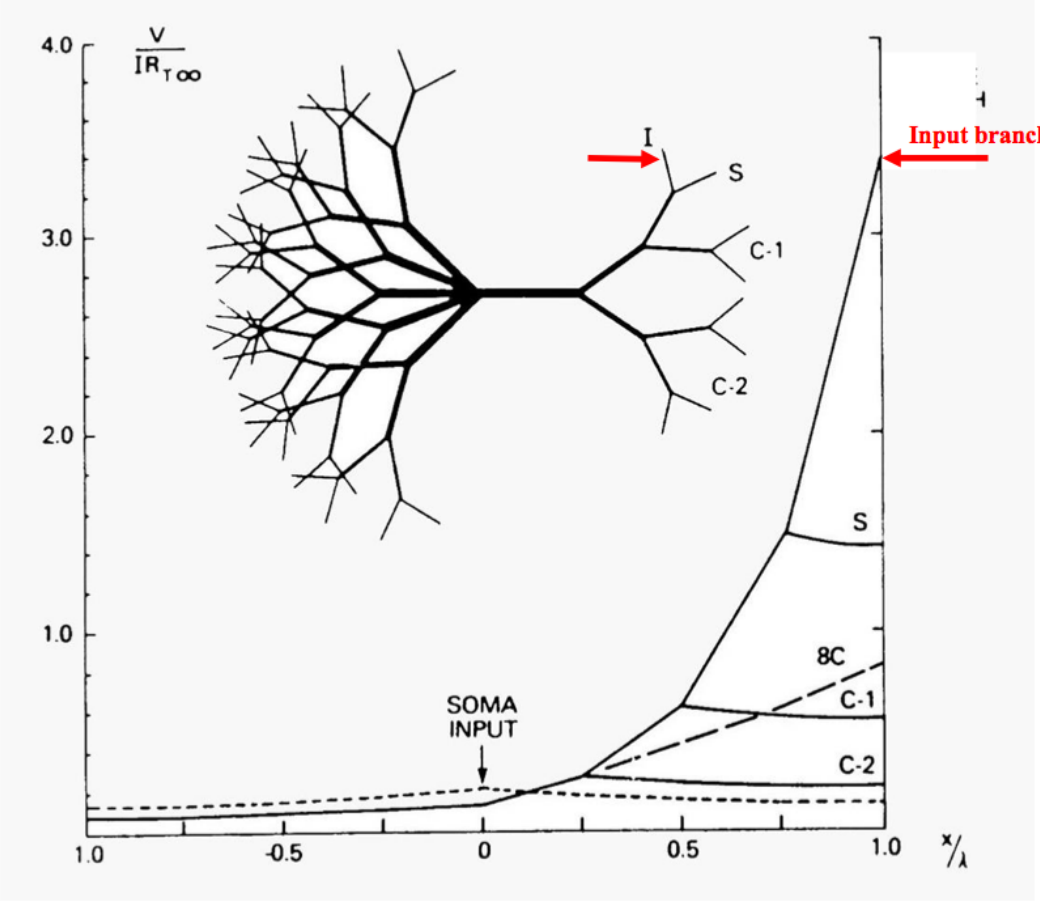
Steady state condition

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

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

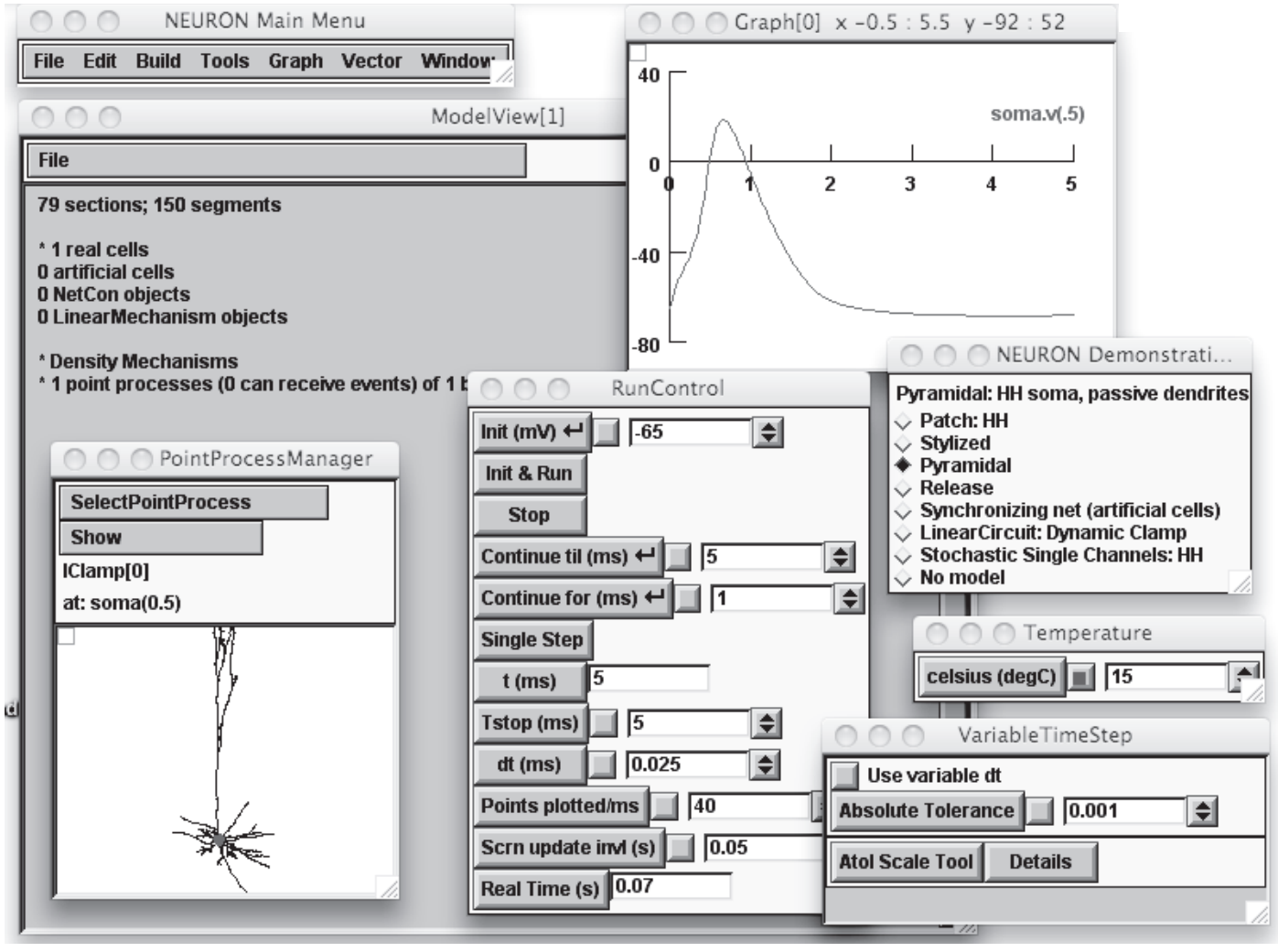


Simulating voltage attenuation



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
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
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
PointProcessManager
SelectPointProcess
Show
IClamp[0]
at: soma(0.5)
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.

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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.