Neuroinformatics 2016

March 3, 2016

Neuron, synapse and neuron models

Biological background

A. Schematic neuron

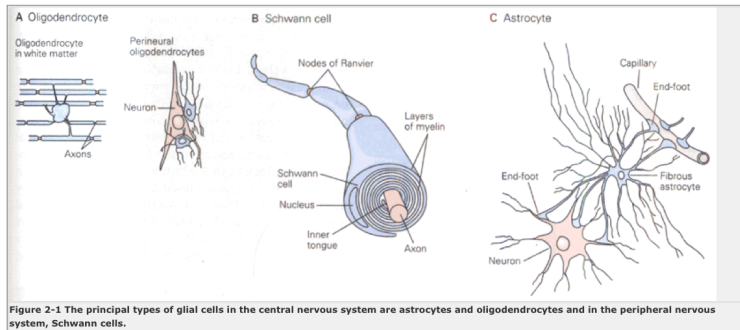Dendrites

Nucleus

Inhibitory axon terminal

Excitatory axon terminal

Soma

Axon hillock

Axon

Ranvier node

Myelin sheath

Synaptic cleft

Postsynaptic neurons

B. Pyramidal cell

Axon

C. Granule cell

D. Spiny cell

E. Purkinje cell

Glial cells
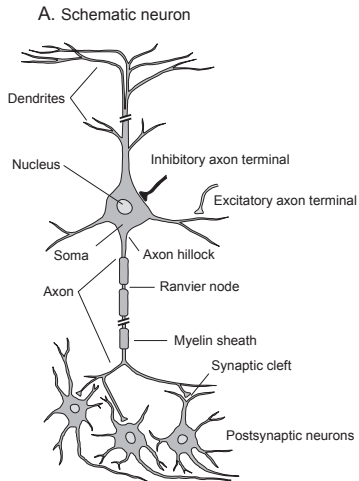
Figure 2-1 The principal types of glial cells in the central nervous system are astrocytes and oligodendrocytes and in the peripheral nervous system, Schwann cells.
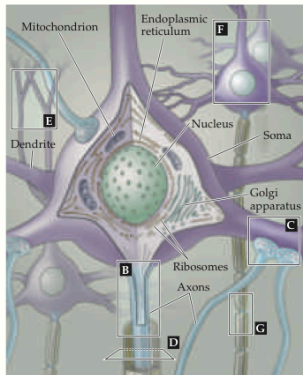
Four components of neurons
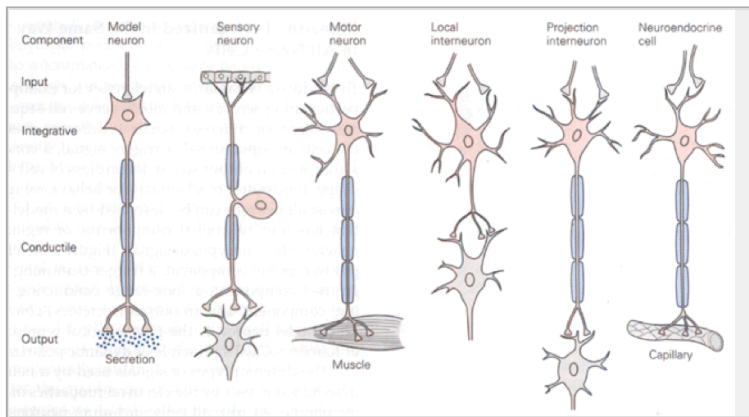
Microscopical features of neurons

(A)

Mitochondrion
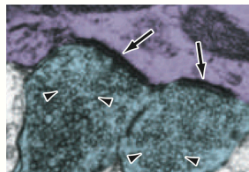Endoplasmic reticulum
F
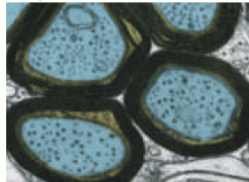E
Dendrite
Nucleus
Soma
Golgi apparatus
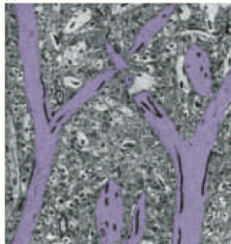C
B
Ribosomes
Axons
D
G

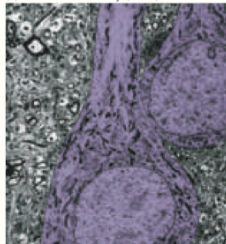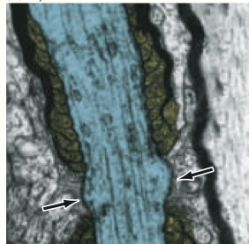(B) Axon
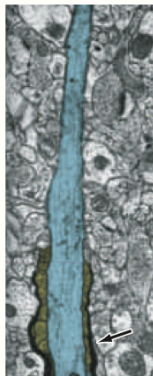
(C) Synaptic endings (terminal boutons)

(D) Myelinated axons

(E) Dendrites

(F) Neuronal cell body (soma)

(G) Myelinated axon and node of Ranvier

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
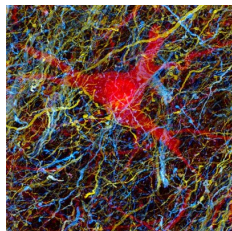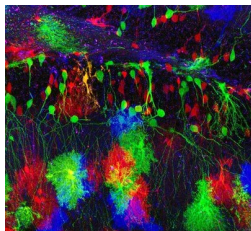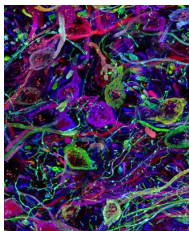
Neuron as input-output device
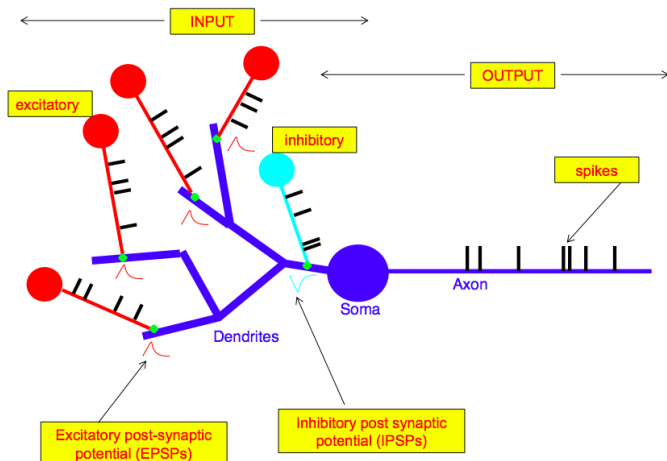
Neuron types

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

Chandelier   Large basket   Horse-tail   Martinotti

Arcade   Neurogliaform

Common basket

Cajal–Retzius
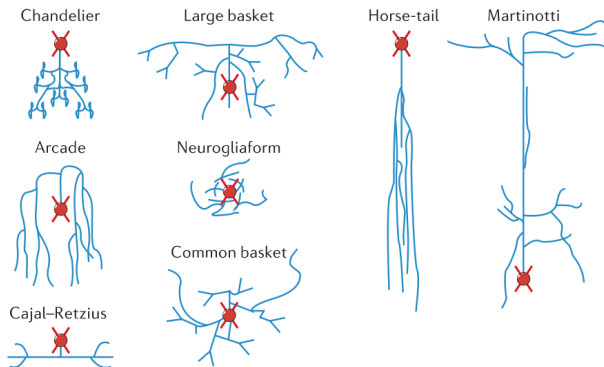
DeFelipe et al., Nature Review neuroscience, 2013

Microcircuit of the Neocortex
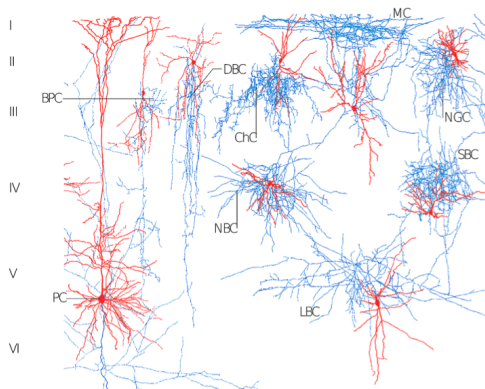
Principal neurons (excitatory) - axon projects to other brain regions

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
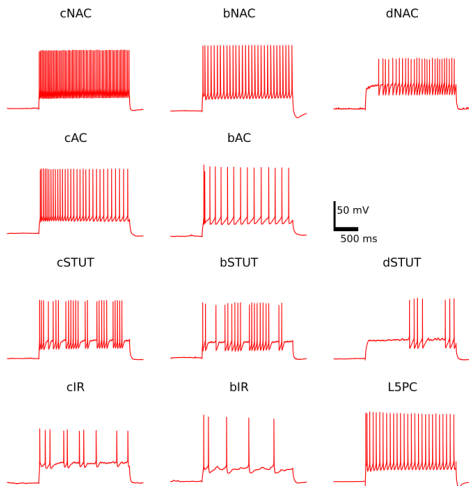
Courtesy of the Blue Brain data-base

Synapse

A (chemical/electrical) device that connects

axon of neuron A to dendrites of neuron B
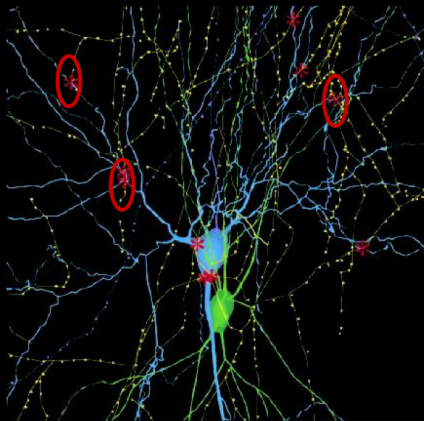
Dendrites of neuron B

Axon of neuron A
(note varicosities)

Chemical Synapse
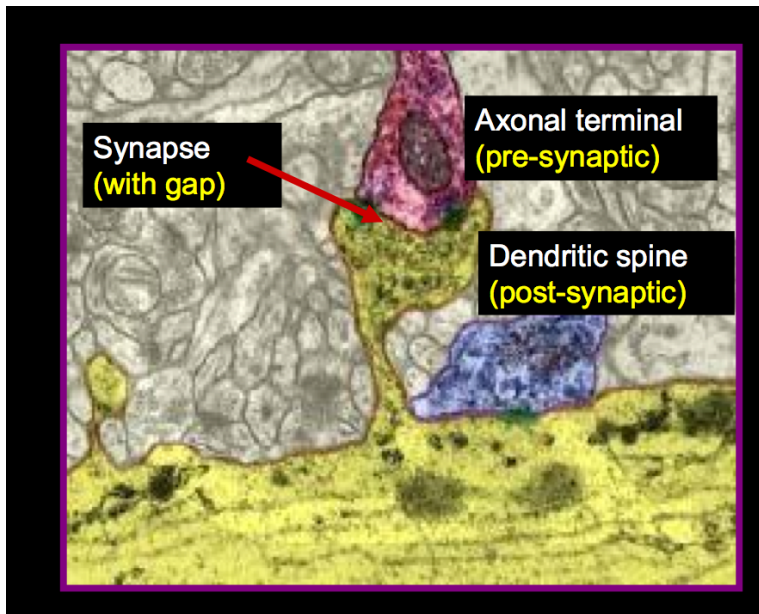
Digital Analog Device
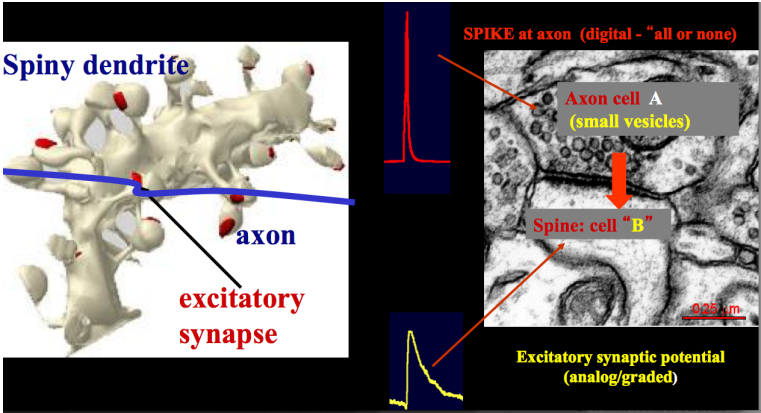
Electrical and Chemical Synapse
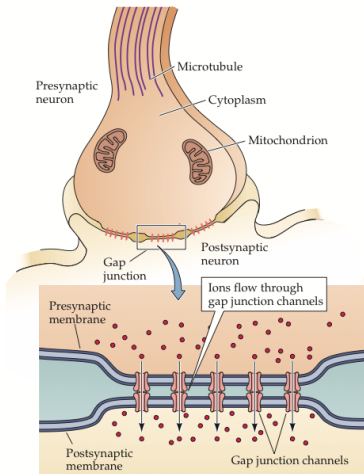
gap 3.5 nm, delay .2 ms, no gain   gap 40 nm, delay 2ms, gain
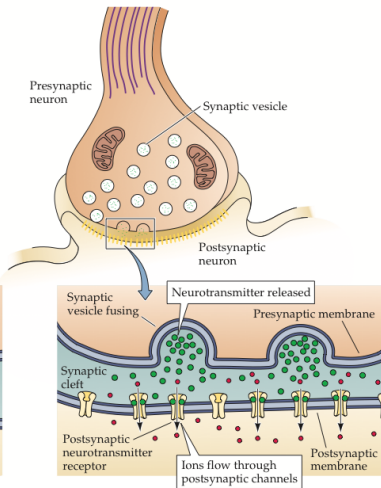
Ion channels

A. Leakage channel
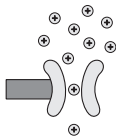
B. Voltage-gated ion channel
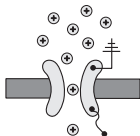
C. Ion pump
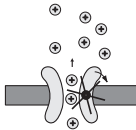
Neurotransmitter-gated ion channels

D. Ionotropic
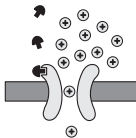
E. Metabotropic (second messenger)
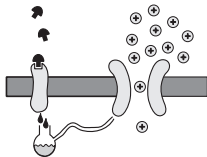
Synapse

- ▶ pre-synaptic neuron
- ▶ synaptic cleft - 1μ,
- ▶ synaptic vescicles
- ▶ release of vescicles controlled by voltage-gated Ca++ channels
- ▶ post-synaptic membrane with neurotransmitter receptors
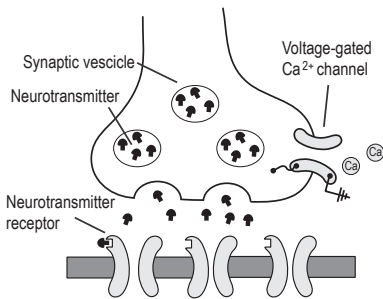
Excitatory vs inhibitory synapses

Excitatory

- increase potential of post-synaptic neuron
- found at dendrites
- neurotransimitters:
  - Glu (glutamate - most common),
  - ACh (acetylcholine - neuromuscular junction)
  - DA (dopamine - motor behavior, motivation, arousal)

Inhibitory

- decrease potential of post-synaptic neuron
- found at body of post-syn. neuron
- neurotransimitters:
  - GABA (Gamma-aminobutyric acid)

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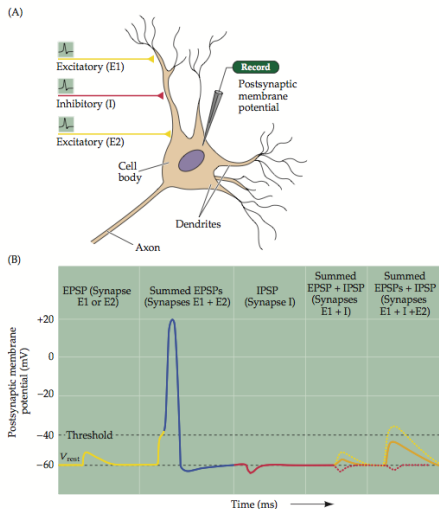
Figure 5.20 Summation of postsynaptic potentials. (A) A microelectrode records the postsynaptic potentials produced by the activity of two excitatory synapses (E1 and E2) and an inhibitory synapse (I). (B) Electrical responses to synaptic activation. Stimulating either excitatory synapse (E1 or E2) produces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

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
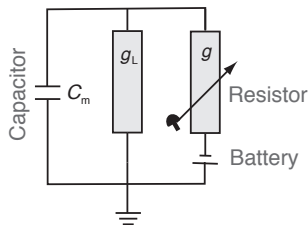
B. Time course of variables
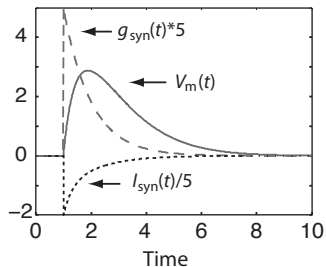
MATLAB Program

```
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

Sir Andrew Fielding Huxley

The Squid Giant Axon
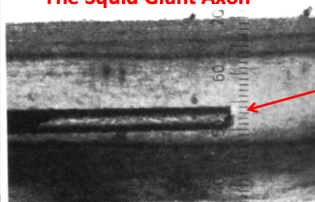
~ 0.5 mm

Axial electrode

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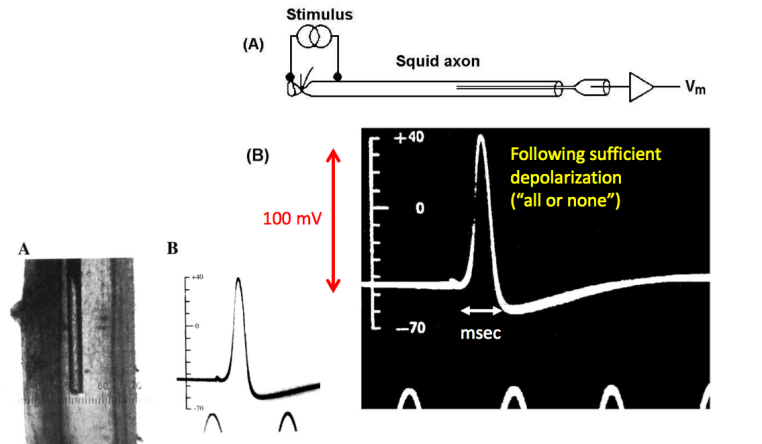
Very nice theory

Sir Alan Lloyd Hodgkin
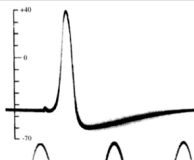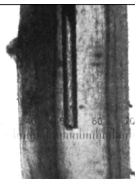
Sir Andrew Fielding Huxley

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

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

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

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

Giant Nerve Cells of Squid

(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.

Brain

1st-level neuron

2nd-level neuron

3rd-level neuron

(A)

Presynaptic (2nd level)

Stellate ganglion

Stellate nerve with giant axon

Postsynaptic (3rd level)

1 mm

(B)

Giant axon

Stellate nerve

Smaller axons

Cross section

1 mm

(C)

Squid giant axon = 800 μm diameter

Mammalian axon = 2 μm diameter

Voltage Clamp Method

1. One internal electrode measures membrane potential (V_m) and is connected to the voltage clamp amplifier

2. Voltage clamp amplifier compares membrane potential to the desired (command) potential

3. When V_m is different from the command potential, the clamp amplifier injects current into the axon through a second electrode. This feedback arrangement causes the membrane potential to become the same as the command potential

4. The current flowing back into the axon, and thus across its membrane, can be measured here

Measure V_m

Command voltage

Voltage clamp amplifier

Reference electrode

Measure current

Saline solution

Squid axon

Recording electrode

Current-passing electrode

Voltage clamp technique for studying membrane currents of a squid axon.
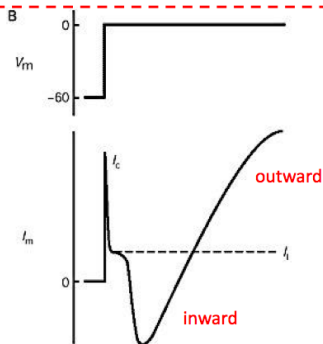
Membrane current in response to voltage clamp (VC)
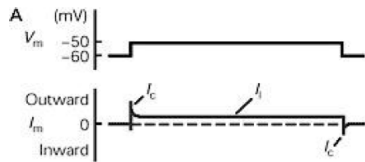
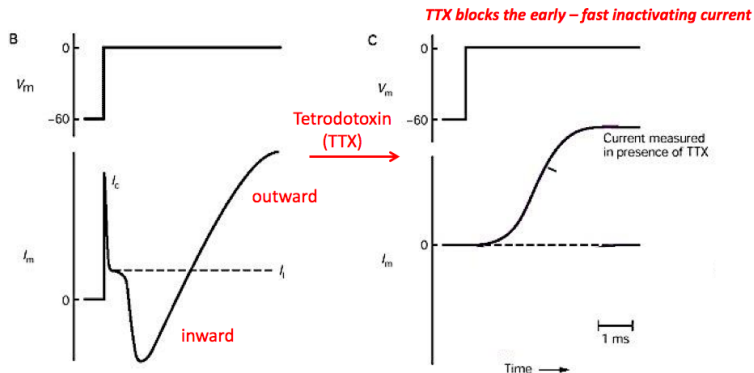For subthreshold depolarizing voltage clamp, the recorded membrane current is the current that flows via the leak (passive) conductance + a small capacitative current (at start and end of the VC)

For suprathreshold 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)

אפריל 13

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

TTX blocks the early – fast inactivating current

B

V_m

0

-60

I_c

outward

I_m

0

inward

I_i

Tetrodotoxin (TTX)

C

V_m

0

-60

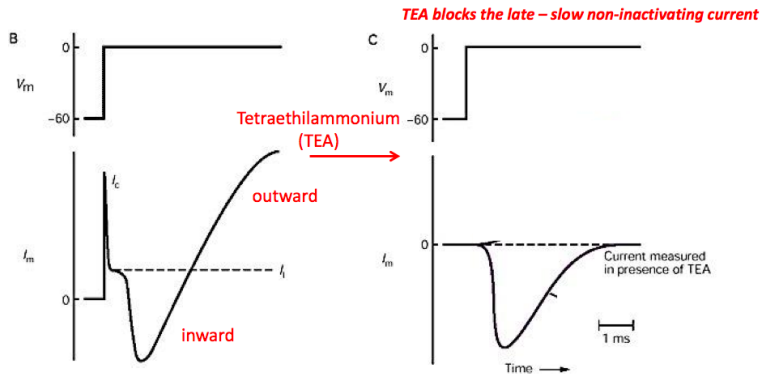Current measured in presence of TTX

I_m

0

1 ms

Time

אפריל 13

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

TEA blocks the late – slow non-inactivating current

Tetraethilammonium (TEA)

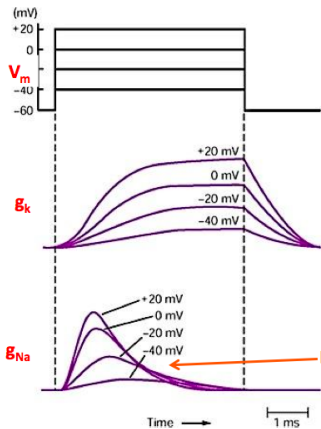outward

inward

Current measured in presence of TEA

1 ms

Changing ion concentration at bath with giant axon showed that early current is carried by Na+ ions and late one by K+ ions
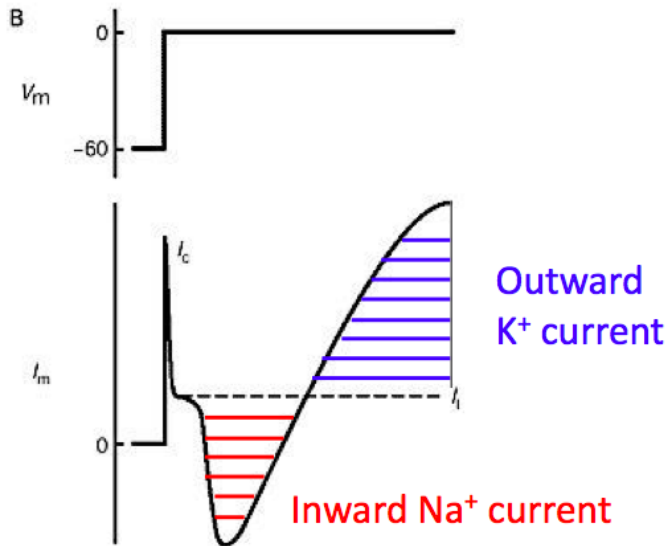
Ion currents (K+ and Na+) for various depolarizing voltage clamp (and extracting respective ion conductances)

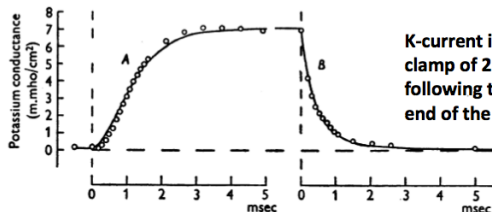$$I_K = g_K (V_m - E_K); \quad I_{Na} = g_{Na} (V_m - E_{Na})$$

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

Direction reversed

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 $\exp(-4t)$
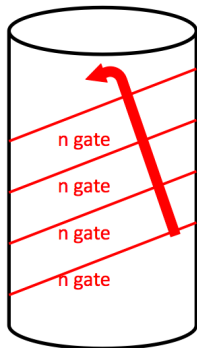
$$g_K = \bar{g}_K n^4$$

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
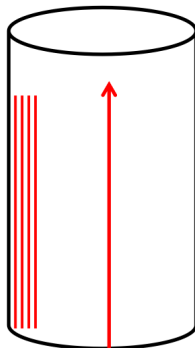
Graphical interpretation of H&H model for the K channel

Closed K channel (by 4 n gates)

Open K channel (by 4 n gates)

n gate

n gate

n gate

n gate

4 n gates open with depolarization

K⁺ INSIDE

K⁺ INSIDE

$$g_{\mathbf{K}} = \bar{g}_{\mathbf{K}} n^4,$$

$$\frac{\mathrm{d}n}{\mathrm{d}t} = \alpha_n \left(1 - n\right) - \beta_n n,$$

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.

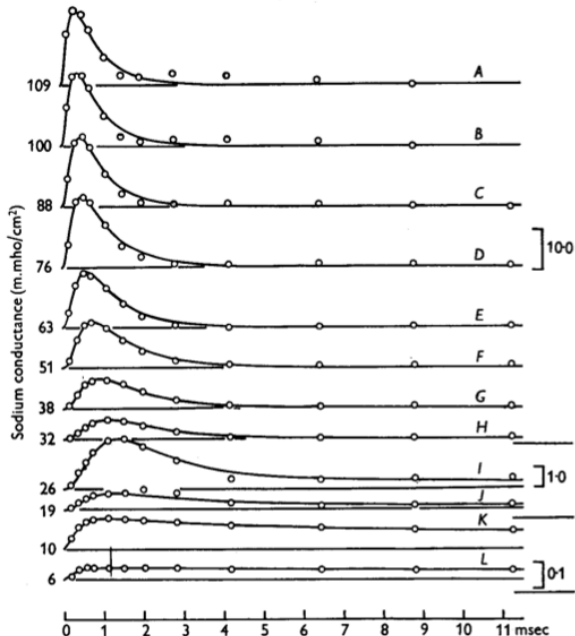Similar procedure is used to extract the activation (m) and inactivation (h) parameters for the Na current
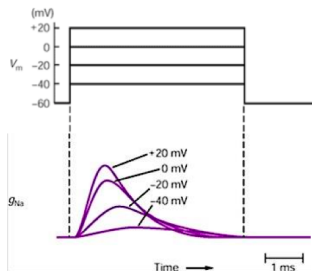
$$g_{\mathbf{Na}} = m^3 h \bar{g}_{\mathbf{Na}},$$

$$\frac{\mathrm{d}m}{\mathrm{d}t} = \alpha_m \left(1-m\right) - \beta_m m,$$
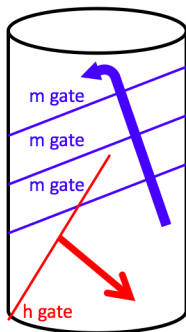
$$\frac{\mathrm{d}h}{\mathrm{d}t} = \alpha_h \left(1-h\right) - \beta_h h,$$

Fitting Na current for different VC depolarizing values
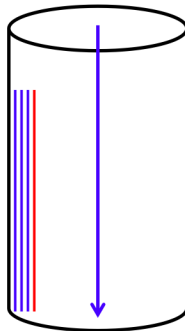
Graphical interpretation of H&H model for the Na channel

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

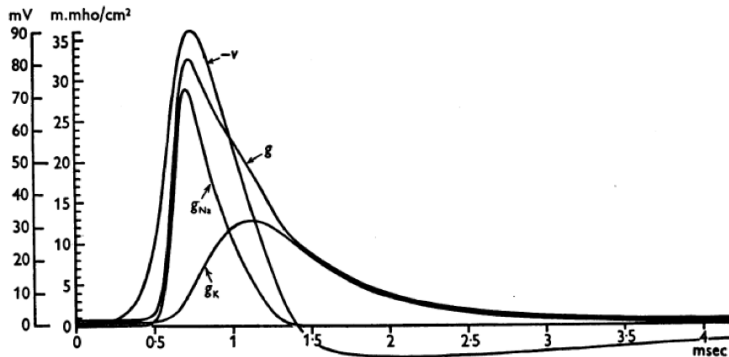Fig. 17. Numerical solution of eqn. (31) showing components of membrane conductance (g) during propagated action potential ($-V$). Details of the analysis are as in Fig. 15.

Hodgkin–Huxley model
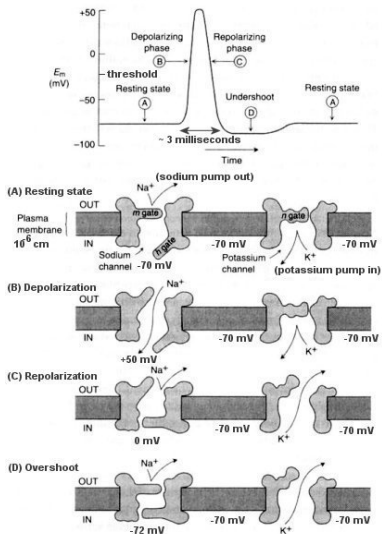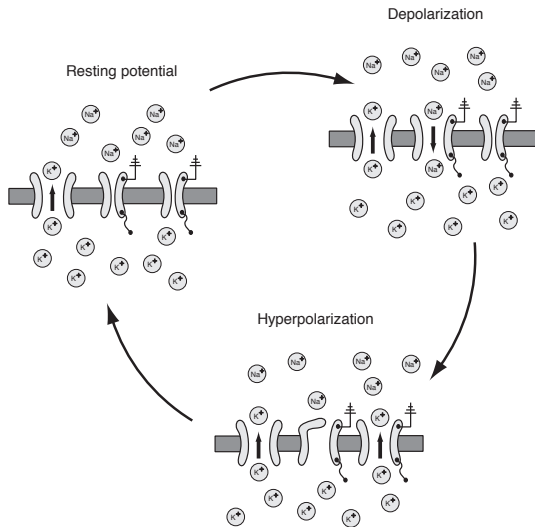

Figure: Typical form of an action potential; redrawn from an oscilloscope picture from Hodgkin and Huxley (1939).

The minimal mechanisms
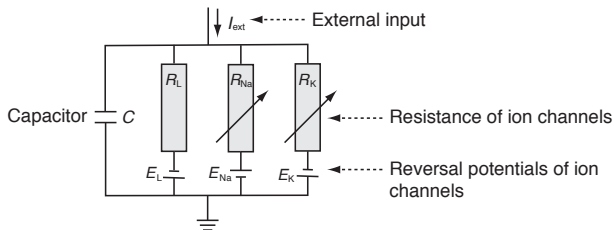

Resting potential

Depolarization

Hyperpolarization

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

$$C\frac{\mathrm{d}V}{\mathrm{d}t} = -g_{\mathrm{K}}n^4(V - E_{\mathrm{K}}) - g_{\mathrm{Na}}m^3h(V - E_{\mathrm{Na}}) - g_{\mathrm{L}}(V - E_{\mathrm{L}}) + I_{ext}(t)$$

$$\tau_{\mathrm{n}}(V)\frac{\mathrm{d}n}{\mathrm{d}t} = -[n - n_0(V)]$$

$$\tau_{\mathrm{m}}(V)\frac{\mathrm{d}m}{\mathrm{d}t} = -[m - m_0(V)]$$

$$\tau_{\mathrm{h}}(V)\frac{\mathrm{d}h}{\mathrm{d}t} = -[h - h_0(V)]$$

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

Spike train with constant input
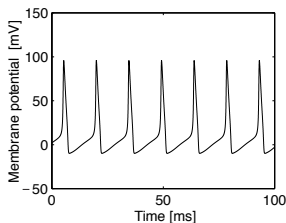
Activation function

Ion channels resistance

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

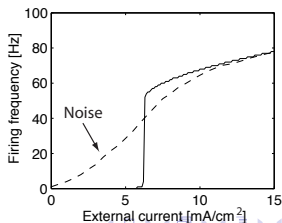$$\alpha_n = \frac{10 - V}{100(e^{\frac{10-V}{10}} - 1)}, \beta_n = 0.125e^{-\frac{V}{80}}$$

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

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

A. Equilibrium potentials — x_0 vs Membrane potential V (h_0, m_0, n_0)

B. Time constants — τ_0 vs Membrane potential V (τ_h, τ_n, τ_m)
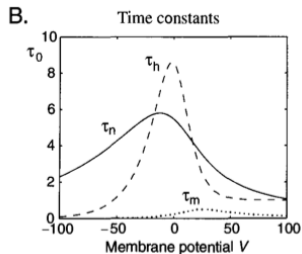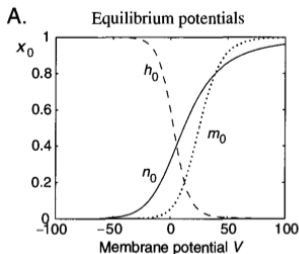
Matlab implementation

```matlab
%% 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
```
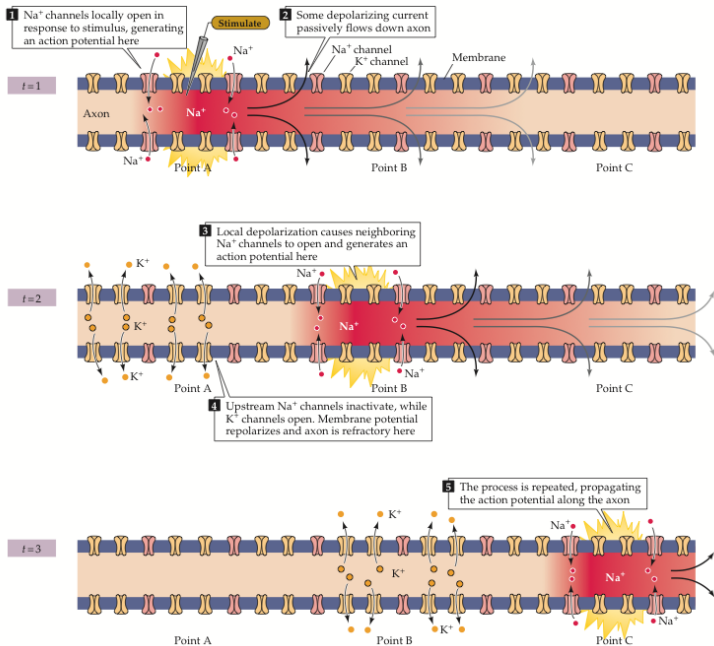
Refractory period

- 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
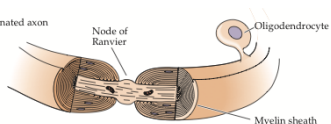- brainstem neurons $600 Hz$, cortical neurons $3 Hz$

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
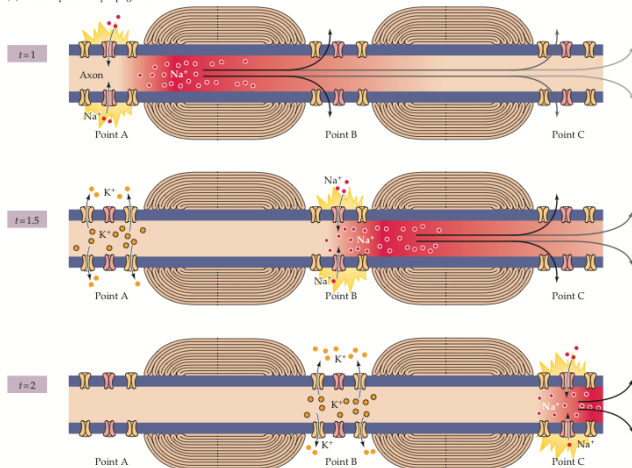- Alzheimer disase - DEmyelination!

NON-LOSS transfer

t = 1

1 Na⁺ channels locally open in response to stimulus, generating an action potential here

Stimulate

2 Some depolarizing current passively flows down axon

Na⁺

Na⁺ channel
K⁺ channel

Membrane

Axon

Na⁺

Na⁺

Point A

Point B

Point C

t = 2

3 Local depolarization causes neighboring Na⁺ channels to open and generates an action potential here

K⁺

Na⁺

K⁺

Na⁺

Na⁺

K⁺

Point A

Point B

Point C

4 Upstream Na⁺ channels inactivate, while K⁺ channels open. Membrane potential repolarizes and axon is refractory here

t = 3

5 The process is repeated, propagating the action potential along the axon

K⁺

Na⁺

K⁺

Na⁺

K⁺

Na⁺

Point A

Point B

Point C

LOSSY transfer
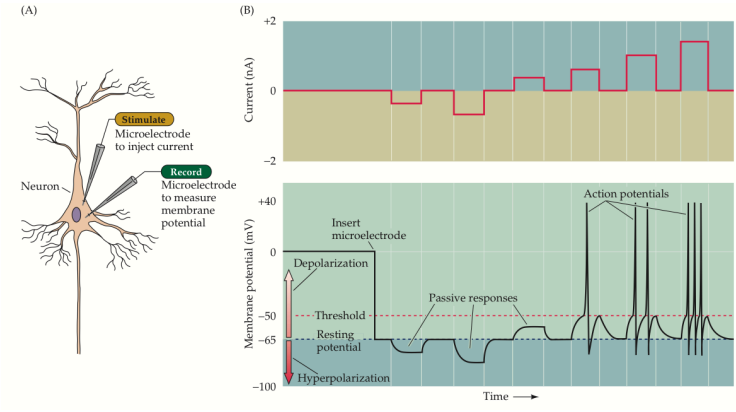

(A) Myelinated axon — Node of Ranvier, Oligodendrocyte, Myelin sheath

(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 $\rightarrow$ 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
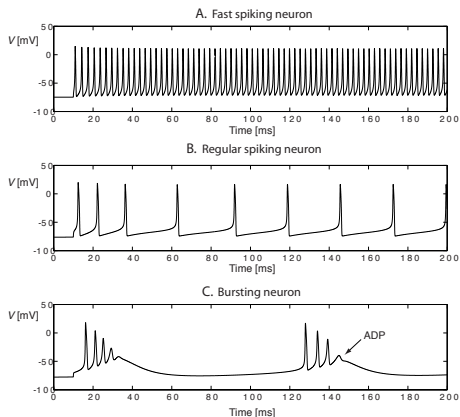
Matlab implementation

```matlab
%%  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');
```

Rall (1964)
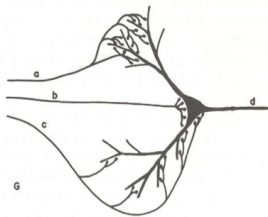Histological Vs. Schmetic Neurons
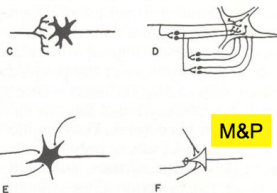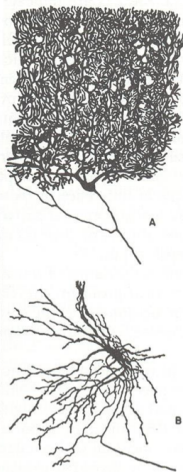
Physiology versus Neurons Models

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

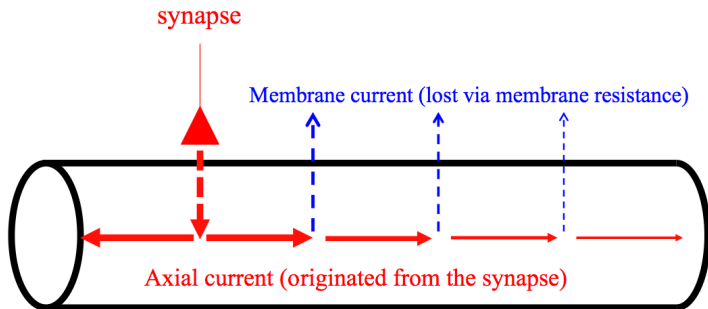A. Physiologically & morphologically caharacterized neuron
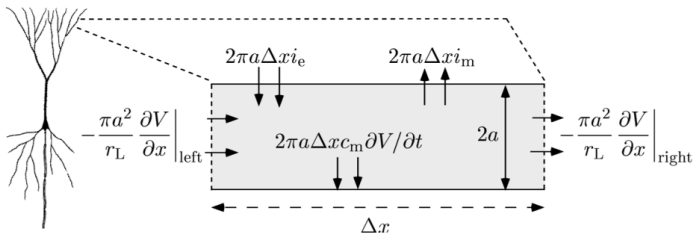
25 µm
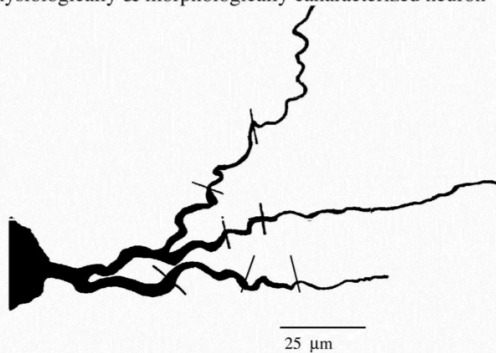
B. Cable model
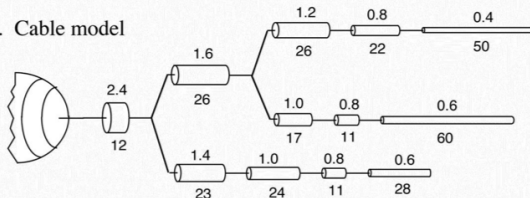
Voltage attenuation

Synaptic potentials attenuate from the synapse origin towards other regions of the dendrites
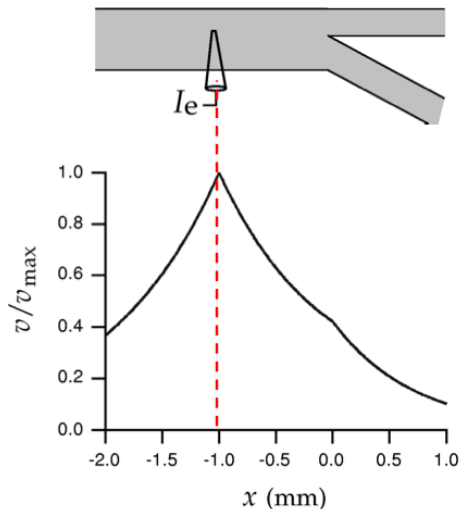
Axial and membrane current

synapse

Membrane current (lost via membrane resistance)

Axial current (originated from the synapse)

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
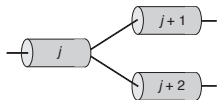
C. Compartmental reconstruction
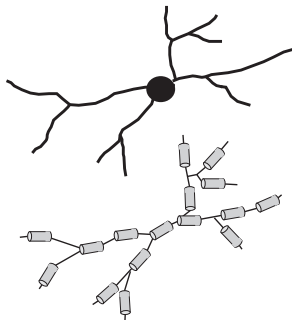
Cable theory

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

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

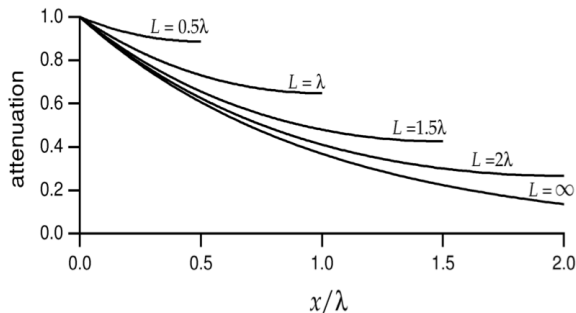$$\lambda = \sqrt{\frac{dR_m}{2R_i}}$$

$$\tau_m = R_m C_m$$

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

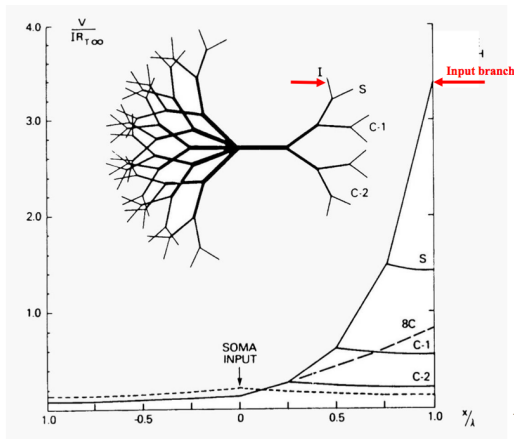$$\frac{\partial V_m(x,t)}{\partial x^2} \leftarrow \frac{V_{j+1} - 2V_j(t) + V_{j-1}(t)}{(x_{j-1} - x_j)^2}$$

Steady state condition

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

$L = 0.5\lambda$

$L = \lambda$

$L = 1.5\lambda$

$L = 2\lambda$

$L = \infty$

attenuation

x/λ

Simulating voltage attenuation

Rall and Rinzel, 1973

Simulators

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.