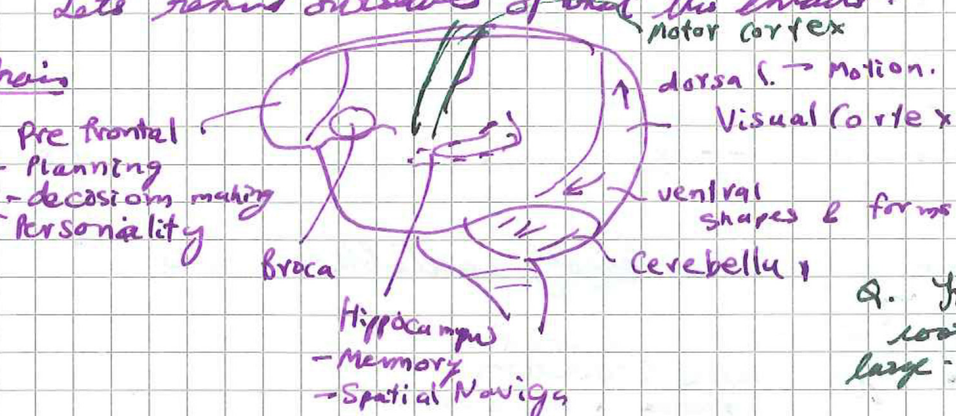
ICTP Trieste 2014 winter school - Introductory Lecture

- Welcome everyone & show of hands about their background.
- This is a school that mostly focuses on systems approaches to neuroscience
  ↳ i.e. emergent behaviors arising from the interactions of many components ~~of the~~ that make up the system. → sequence of lectures ~~make shaping~~ → more neuroscience
  ↳ ~~We~~ We'll do this at multiple scales, from the whole brain to neurons. Let's remind ourselves of what this entails.

Whole brain



Areas associated to a specific function - ~~coordinate to create overall behavior~~.

Q. How do these areas coordinate to produce large-scale behaviors?

Each area is divided up

Visual Cortex
- V1 - primary visual cortex - edges, orientations, patterns
- V2 - color, more complex patterns
- V3, V4 - Shape fragments...
- MT (dorsal) - motion
- IT (inferior temporal) - form vision (eg - face areas)

Q. How do these areas produce visual percepts?

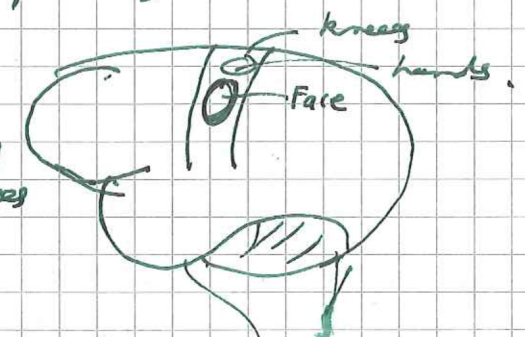
Q. How do ~~lower~~ sensory inputs & higher order influences ~~comp~~ affect vision in these areas to produce behaviorally relevant & flexible sensory percepts?

Each area has many subdivisions & laminae

- each neo-cortical area has 6 layers which are anatomically & functionally distinct

- Many segregated circuits with specific functions

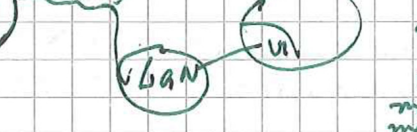
Q. How are these wired up by development processes & learning rules?



Each area or sub-area is made of circuits

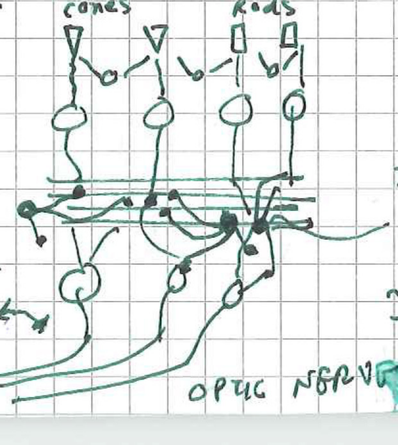
↳ Many types of neurons & network architectures
- ⓐ anatomy & connectivity
- ⓑ biophysics
- ⓒ function

eg: Retina



LIKE A VLSI circuit

EACH TYPE makes a mosaic on retina



~ 4 Photoreceptors
~ 2 Horizontal cells (INHIBITORY)
~ 10 BIPOLAR CELLS
INNER PLEXIFORM LAYER
~ 30 AMACRINE CELLS (INHIBITORY)
~ 20 ganglion cells types

~ 65 Types.

The whole retina produces ~20 types of parallel channels that convert light into electrical signals sent down the optic nerve.

~~Q. How do the parallel channels achieve their~~

Q. What are the parallel channels encoding?

Q. How do the retinal circuits & cell types collectively produce these channels?

Q. Why these channels & not others? & why are they organized the way they are

{ Normative theories (eg. information maximization) ↳ PHYSICS-STYLE

(Can take these approaches at different levels of organization)

Neurons : ~~compute~~ The basic computational units of the brain

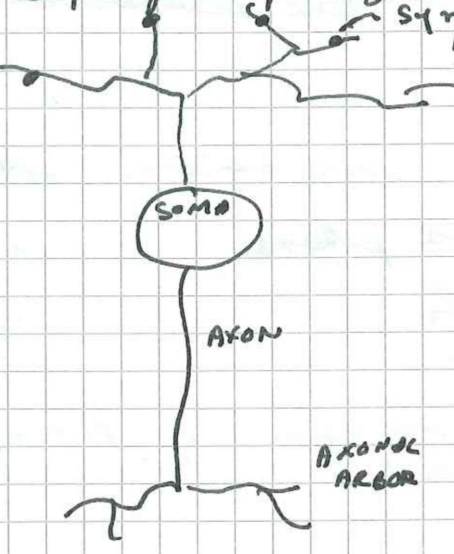
↳ Neuron doctrine → Ramon y Cajal vs. Golgi

↳ ~~Neurons are cells~~

↳ Neurons are cells with electrically excitable membranes

[Brains also have many kinds of glia in support function]

Morphological Specializations

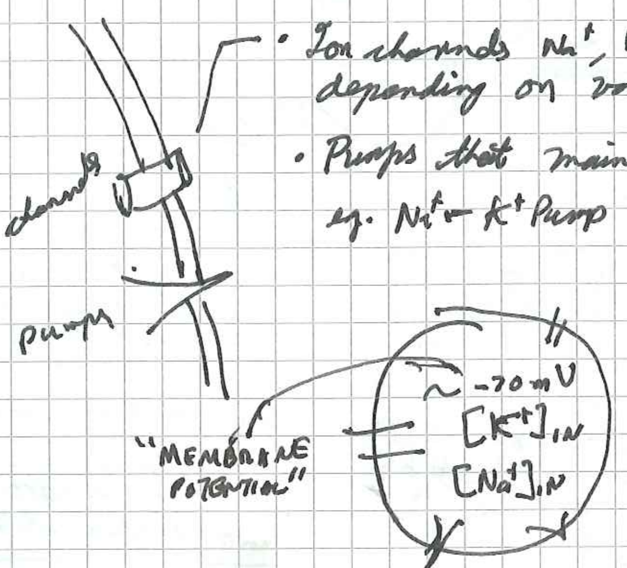


Synapses (chemical receptors)
↳ where neurons connect & communicate via neurotransmitters

DENDRITES in dendritic arbor.

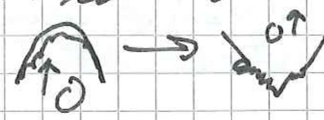
- Dendrites: ~2 synapses/μm
- Axons: ~180 synapses/mm.
- SOMA : 10-100μm diam.
- ~100×10⁹ neurons in human brain
- ~10¹⁴-10¹⁵ synapses.
- ≤1mm³ of volume has ~4 km of wire
- ~12 W of power. (cheap)
- ~2% of body weight, but 20% of metabolic load. (expensive)

Physiological specializations



- Ion channels Na^+, K^+, Ca^{2+}, Cl^- - ~~allow~~ open & close depending on voltage & concentration gradient
- Pumps that maintain concentration gradient

eg. Na^+-K^+ Pump



$[K^+]_{OUT}$

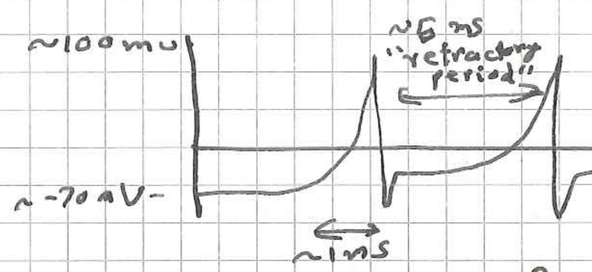
$[Na^+]_{OUT}$

$[Na^+]_{OUT} > [Na^+]_{IN}$

$[K^+]_{OUT} < [K^+]_{IN}$

HYPERPOLARIZATION → Move -ve memb pot.

DEPOLARIZATION → Move +ve memb pot.

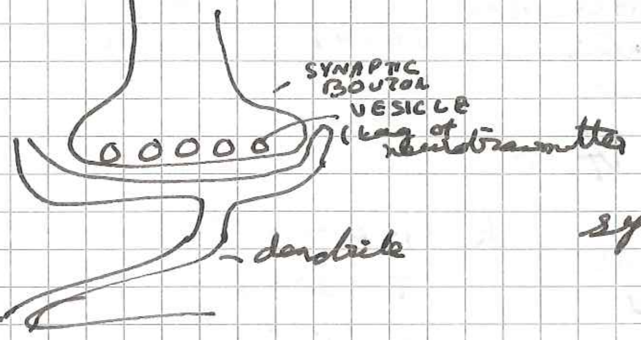


ACTION POTENTIALS (spikes) occur when voltage increases sufficiently to trigger +ve feedback (Na^+ rushes in)

↳ K^+ rushes out when potential is sufficiently +ve

- Pumps later restore the ~~contration~~ concentrations of ions.

↳ Action potentials at a synapse open Ca^{2+} ion channels which lead to neurotransmitter release.



} neurotransmitter binds to receptors on the post-synaptic site to send message. (excitatory or inhibitory)

↓

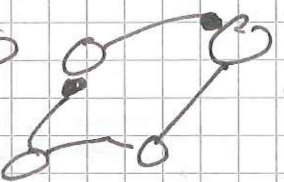
synapses can be - created / destroyed
- strengthened / weakened

perhaps the basis of all learning and memory

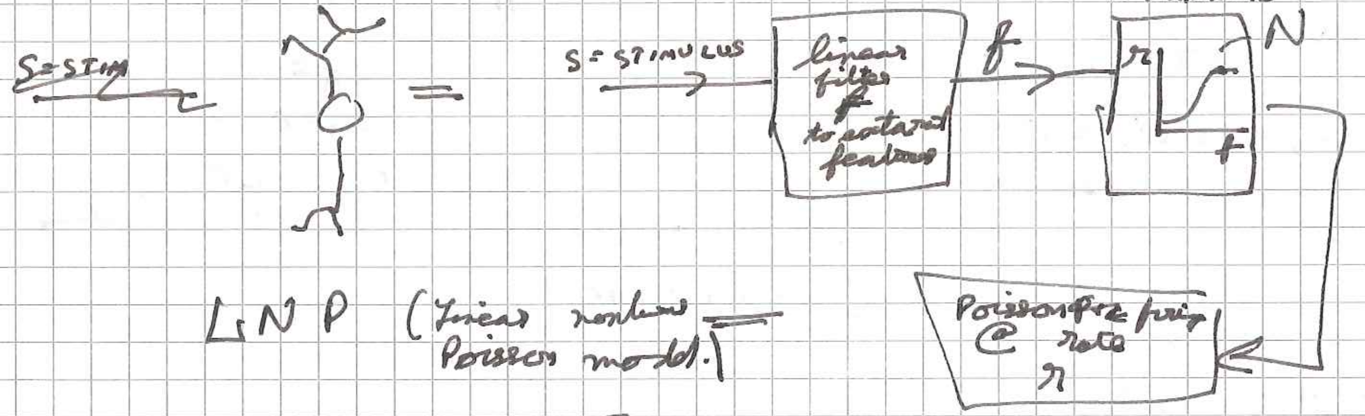
- Neural firing is stochastic (since ion channel open/closing is stochastic, brownian noise, external noise)...)

~~Most~~ Often, for systems analysis we ~~tr~~ model all of this as

↳ often modeled as memoryless = Poisson

①  etc. } i.e abstract network of active elements ~~with exc~~ which excite or inhibit each other (spikes/s)

② S=STIM



LNP (linear nonlinear Poisson model.)

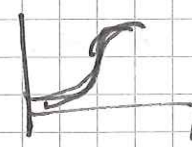
$$\Rightarrow \quad r = N\Big[\underset{\substack{\uparrow \\ \text{FILTER}}}{F(t)} * S(t)\Big]$$

STIMULUS

CONVOLUTION

eg. sigmoid

$$\frac{A \quad e^{\alpha X}}{B + C e^{\alpha X}}$$



~~Pr(spike)=~~

$Pr(\text{spike}) = (r\Delta t)$

$$Pr(n \text{ spikes}) = \frac{(r\Delta t)^n}{n!} e^{-r\Delta t}$$

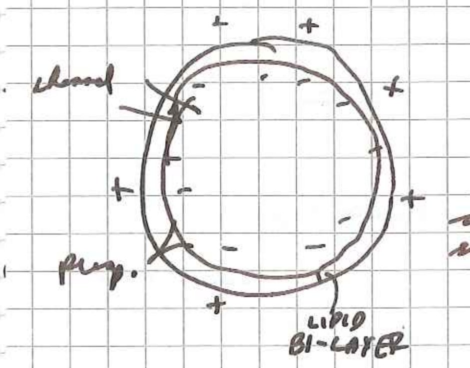
$\boxed{\text{These are effective models}}$

BUT we could model the biophysical details - MICROSCOPIC model

} great ~~triump~~ classical triumph of biophysics - Hodgkin & Huxley

↳ I'll explain this

Electrical Properties of Neurons



- Cell wall acts like a capacitor
- + 2 types of highly selective ion channels gated by
  - VOLTAGE
  - CONCENTRATION of intra-cellular messengers (e.g. Ca^{2+})
  - EXTRACELLULAR neurotransmitters

  (open & close stochastically)
- Pumps maintain concentration gradients

ESTIMATE of magnitude

$kT \approx q V_T$

$V_T \approx \frac{kT}{q}$

~~$\approx$~~ $= 30\ mV$

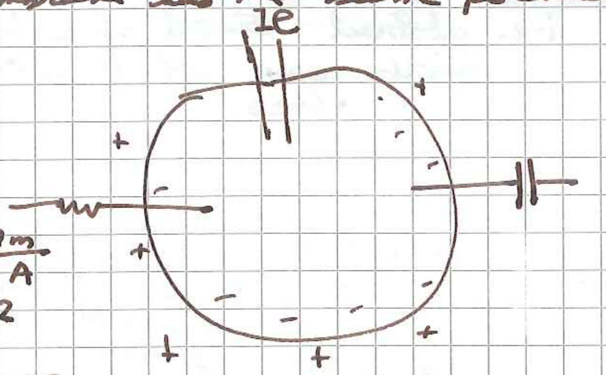
$k \sim 1.4 \times 10^{-23}\ J/K$

$T \sim 300°K$

$q \sim 1.6 \times 10^{-19}\ C$

indeed action membrane potentials are $\sim 2\times3\ V_T$

Consider "Electronically compact" (or single compartment) neuron — i.e. cell membrane has the same potential everywhere.



$\Delta V = I_e R_m$

R_m = membrane resistance $= \frac{r_m}{A}$

$r_m = 1\ M\Omega\ mm^2$ ← specific resistance

$A \sim 0.01 - 0.1\ mm^2$

$C_m \sim 0.1 - 1\ nF$

$Q = C_m V$ (membrane capacitance)

$C_m = c_m A$

$c_m = 10\ nF/mm^2$ (specific capacitance)

ESTIMATES

- # of ions / action potential

$\Rightarrow Q \approx (1\times10^{-9}\ F) \times (70\times10^{-3}\ V) \sim 7\times10^{-11}\ C$

$\Rightarrow n_{ions} \sim \frac{Q}{1.6\times10^{-19}\ C/ion} \sim 10^9$ ions $<<$ # ions in cell (10^5 times less)

$\Rightarrow$ can do perturbation theory

- timescales. 1nA delivers this charge ~~in how long~~?

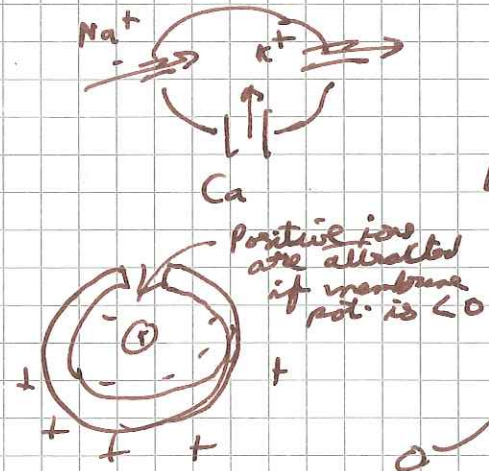
$\Delta t = \frac{\Delta Q}{I} = \frac{10^{-10}\ C}{10^{-9}\ A} \approx 0.1\ s \approx 100\ ms$

This is the typical "integration time" to produce an action potential

BASIC EQUATION: $Q = C_m V$ $\Rightarrow$ $\boxed{I = \frac{dQ}{dt} = C_m \frac{dV}{dt}}$

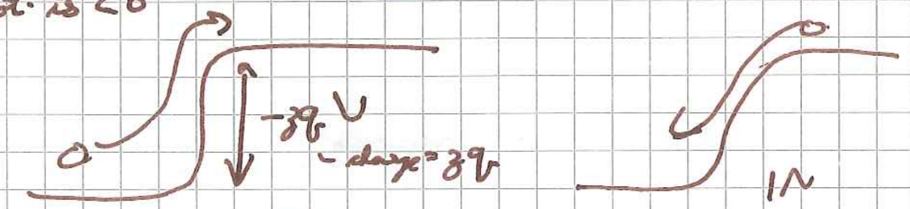
↳ lets work out I in terms of biophysical parameters

Properties of equilibrium



~~Voltage~~ Concentration gradients drive ionic flows that are opposed by voltage gated ion channels.

EQUILIBRIUM (REVERSAL) potential = membrane potential at which current flows due to concentration & voltage cancel.



FLOW OUT REQUIRES ENERGY FOR +ve ions

$Pr[E > V] = e^{zqV/kT} = e^{z\frac{V}{V_T}}$

EQUILIBRIUM: flow in = flow out

[OUTSIDE] = [INSIDE] e^{zE/V_T} E = BALANCE POINT

$\Rightarrow E = \frac{V_T}{z}\left(\frac{[OUTSIDE]}{[INSIDE]}\right)$ — Nernst equation

reversal pot.

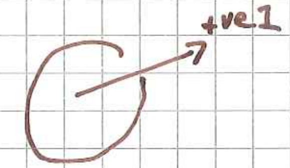
K^+ : $E_K \sim -70 - -90\ mV$

Na^+ : $E_{Na} \sim 50\ mV$

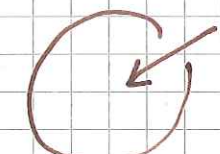
Ca^{2+} : $E_{Ca} \sim 150\ mV$

Cl^- : $E_{Cl} \sim -60 - 65\ mV$

$V > E$



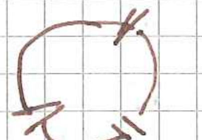
$V < E$



→ Na^+ & Ca^{2+} → tend to depolarize neurons (cause firing)

K^+ ↳ tends to hyperpolarize (suppress firing)

Membrane current



· Many channels: $i_m = \sum_{i=1}^{k} g_i \,(V - E_i)$ ~~conductance~~ = NONLINEAR FUNCTION ~~of~~ ~~V in~~ general

~~Leak current~~

· In general g_i is a nonlinear function of V.

For some currents (eg. from ion pumps) g_i = const

$g_L (V - E_L) \cdot I_{Leak}$ ⟸ = leak current.

Voltage dependence of Conductances

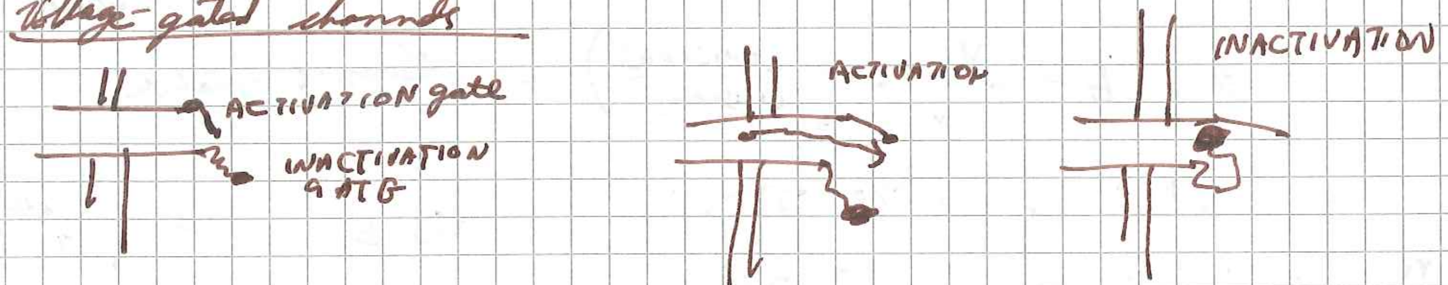
Large #s of channels

$\Rightarrow$ MEMBRANE CONDUCTANCE = (SINGLE CHANNEL CONDUCTANCE) × (CHANNEL DENSITY) × (PROBABILITY OF BEING OPEN)

$$g_i = \bar{g}_c \quad P_i$$

Consider K^+ & Na^+ following Hodgkin & Huxley.

Voltage-gated channels



Persistent Conductances (eg K^+)

k identical indep. activating gates. ~~subunits the~~

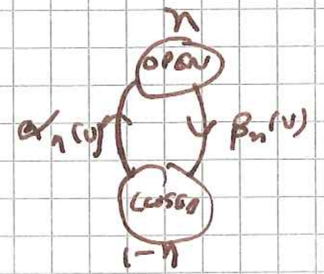
$\Rightarrow$ ~~P_n(open) = $P_k = n^k$~~

$n = P_n$ (open subunit) $\quad (1-n) = P_n$ (closed subunit)

$\Rightarrow P_n(\text{open}) = P_K = n^k$

k chosen to fit data $\longrightarrow K^+$, $k = 4$

Each subunit



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

$$\Rightarrow \boxed{\tau_n(V)\frac{dn}{dt} = n_\infty(V) - n}$$

$$n_\alpha(V) = \frac{\alpha_n(V)}{\alpha_n(V) + \beta_n(V)}$$

$$\tau_n(V) = \frac{1}{\alpha_n(V) + \beta_n(V)} = \text{timescale}$$

Hodgkin Huxley did a fit to find: $\beta_n = 0.125\, e^{-0.0125(V+65)}$

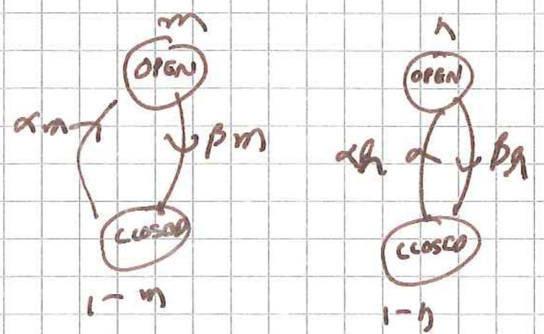
$$\alpha_n = \frac{0.01\,(V+55)}{1 - e^{-0.1(V+55)}}$$

Transient Conductances (eg Na^+

$P_{Na} = m^k h$

m = Prob. of activation

h = Prob. of de-inactivation



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

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

$\beta_m = 4e^{-0.0556(V+65)}$ $\qquad \alpha_m = \dfrac{0.1\,(V+40)}{1 - e^{-0.1(V+40)}}$

$\beta_h = \dfrac{1}{1 + e^{-0.1(V+35)}}$ $\qquad \alpha_h = 0.07 e^{-0.05(V+65)}$

Hodgkin-Huxley Model

· Leak, K^+, Na^+

$$c_m \frac{dV}{dt} = -i_m + \frac{I_e}{A} \quad \leftarrow \text{external current.}$$

$$\cdot\; i_m = \bar{g}_L (V - E_L) + \bar{g}_K\, n^4 (V - E_K) + \bar{g}_{Na}\, m^3 h\,(V - E_{Na})$$

· MAX COND:

$\bar{g}_L = 0.003\ mS/mm^2$

$\bar{g}_K = 0.36\ mS/mm^2$

$\bar{g}_{Na} = 1.2\ mS/mm^2$

Reversal pots

$E_L = -54.4\ mV$

$E_K = -77\ mV$

$E_{Na} = 50\ mV$

HOMEWORK

Put these equations together to build a spiking neuron on your computer

↓

some people view the task of neuro as building the brain this way.

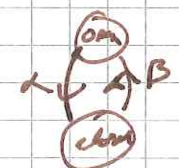
Conductance dynamics

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

$\frac{dm}{dt}$

$\frac{dh}{dt}$

as above



Voltage gating

$\beta_n = 0.125\ e^{\dots}$

$\alpha_n =$

$\beta_m =$

$\alpha_m =$

$\beta_h =$

$\alpha_h =$

As above