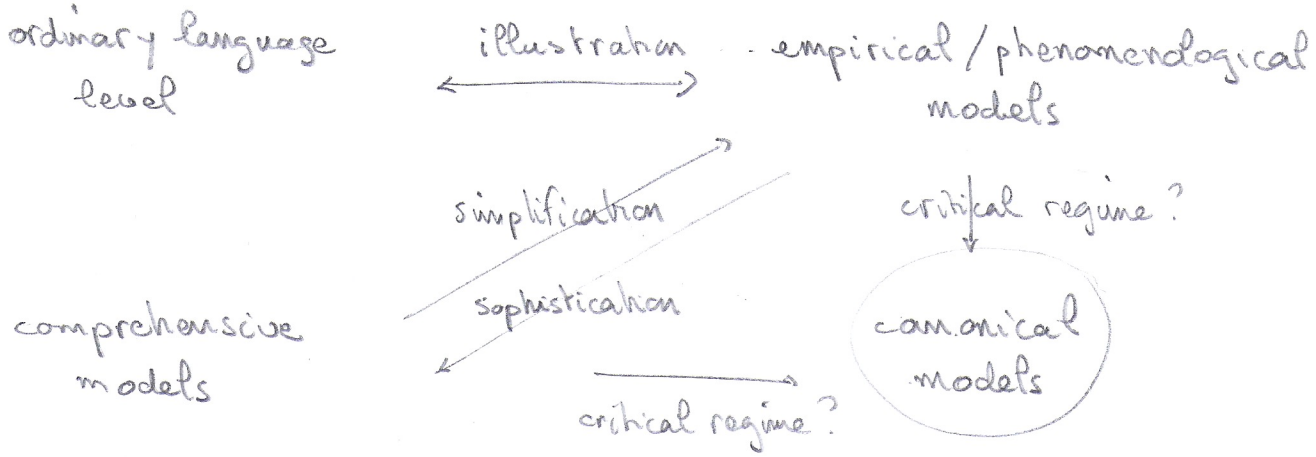
Neural networks:

A few facts:
* human brain ≃ 10^{11} neurons organized in a network via ≃ 10^{15} synapses (chemical and electrical)
* brain is structured in different areas (e.g. cortex v.s. cerebellum) with varying cell type composition and connectivity patterns (e.g. visual pathways: retina → LGN → V1, V2 v.s. auditory pathways hair cells → many brain stem nuclei → MGN → A1, A2)
* neurons = "electrically excitable" cells that receives, processes, and transmit information via electrical and chemical agents
* neuron cell types determined on the basis of
  - → morphology (size, polarization, dendrite/axon shape...)
  - → physiology (electrical response properties)
  - → molecular (genetic expression profile)
  - → connectomics (number and nature of synapses)

Various level of modeling



Single cell modeling

Comprehensive ⟷ Empirical

In-silico models

discrete-event simulation in spatially structured environment

Biophysical models

* multicompartment models: Rall's model, ball-and-stick model..
* single compartment model: Hodgkin-Huxley (1952)

↓

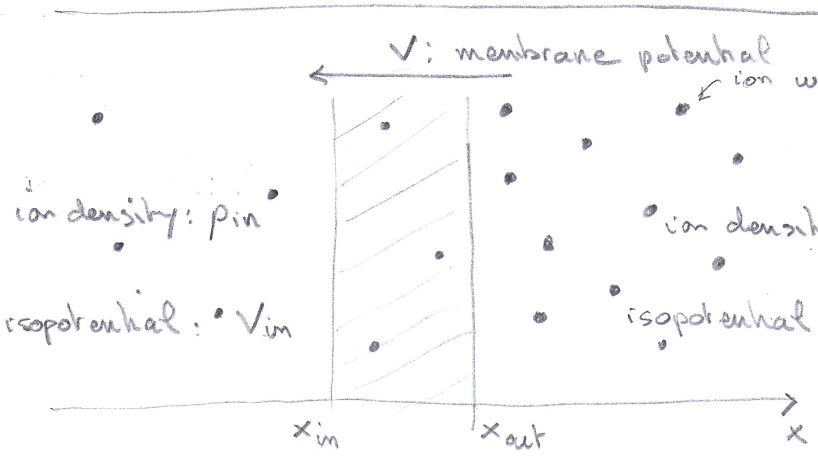
Nobel prize in 1963

Mathematical caricature

* deterministic models; excitable dynamical systems, rate-model networks..
* stochastic models: intensity-based model, integrate-and-fire model..

Goal of this lecture: derive Hodgkin-Huxley model and qualitatively describe spike generation via excitable dynamical systems.

Ionic distributions and Nernst potentials



conservation equation: $\partial_t \rho + \partial_x \left[J_{drift} + J_{diff} \right] = 0$

(ρ: ionic density)

* drift current: $J_{drift} = \mu F \rho$ with $F = ze\,E = -ze\,\partial_x V$

(μ: mobility, F: force, E: electric field, $\partial_x V$: voltage gradient)

* diffusion current: $J_{diff} = -D \partial_x \rho$ ← Fick's law with $D = \mu k_B T$

(D: diffusivity, k_B: Boltzmann constant)

* approximation: equilibrium condition at constant E within the cell membrane yields:

$$J_{drift} + J_{diff} = 0 \Rightarrow \quad 0 = ze\,E\,\rho - k_B T \partial_x \rho$$

$$\Rightarrow \quad \ln \frac{\rho_{out}}{\rho_{in}} = \frac{ze\,E}{k_B T} (x_{out} - x_{in}) = \frac{ze}{k_B T} \underbrace{\left(V_{in} - V_{out} \right)}_{V_{ion}}$$

Nernst potential: $V_{ion} = \frac{RT}{zF} \ln \left(\frac{[ion]_{out}}{[ion]_{in}} \right)$

(R: universal gas constant, F: Faraday constant, $[ion]$: concentrations)

No net flux when $V = V_{ion}$, otherwise inward or outward fluxes depending on sign of z

Ionic currents and resting potentials

* for each ionic species, when $V \neq V_{ion}$ ionic currents are given by: $I_{ion} = g_{ion}(V - V_{ion})$
  ionic conductance ↑ ↑ Nernst reversal potential

* conservation of charge through a membrane modeled as a capacitance C: $I = C\partial_t V + \sum_i I_{ion}$

$$\Rightarrow C\partial_t V = I - \sum g_{ion}(V - V_{ion})$$

* resting potential: $\partial_t V = 0 \Rightarrow V_{rest} = \dfrac{\sum_{ion} g_{ion} V_{ion}}{\sum_{ion} g_{ion}}$

Nonlinear conductances

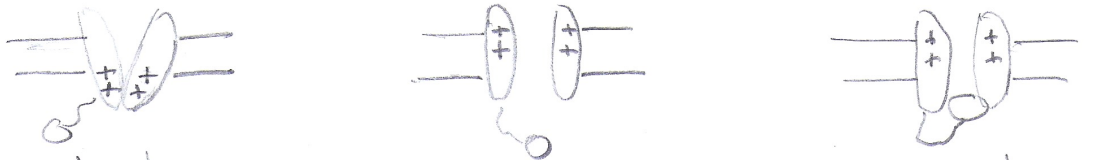
* conductances measure ionic permeabilities of membranes, which are established by ionic channels.

* ionic channels are transmembrane molecular complexes which may exist in different conformations allowing ionic fluxes (open state) or not (closed state).

$$g_{ion} = \bar{g}_{ion}\, p_{ion}$$

$\bar{g}_{ion}$: maximum conductance; p_{ion}: probability of finding an ion channel in open state

* Voltage dependent channel



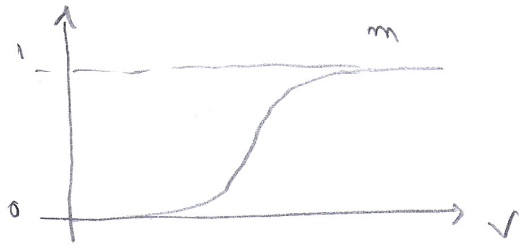
* Probability of open channels modeled via gating variables

$p = m^a h^b$ ← inactivation gates, a, b: number of independent gates.
↑ activation gates

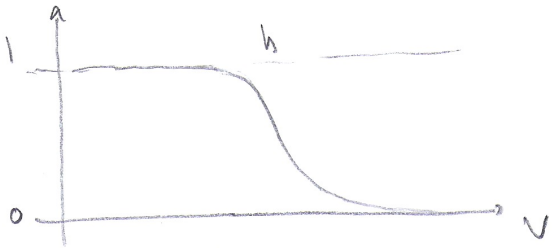
* Gating variables follows 1st order ODE:

$$\partial_t x = \frac{x_\infty(V) - x}{\tau(V)}$$

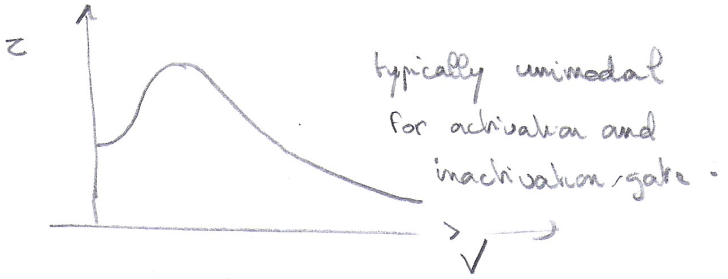
where the steady-state level x_∞ and the time constant τ depends on the membrane potential



activation gate



inactivation gate



typically unimodal for activation and inactivation gate.

Hodgkin - Huxley model

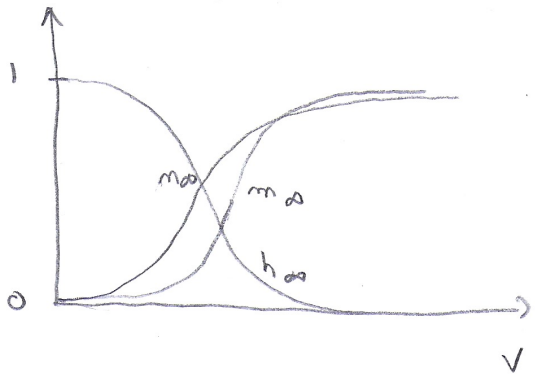
* Specifying the H-H model essentially consists in proposing functional forms for the steady-state level x_∞ and the time constant τ associated to the main class of ion channels associated with spike generation.

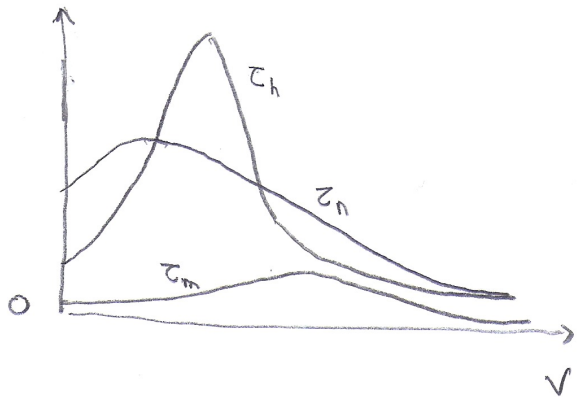
* Hodgkin and Huxley determined that 3 major currents are involved in spike generation in the giant squid axon: sodium ion current I_{Na}, potassium ion current I_K, and passive leak current:

$$C\partial_t V = I - g_L(V-V_L) - \bar{g}_{Na}\, m^3 h\,(V-V_{Na}) - \bar{g}_K\, n^4\,(V-V_K)$$

Key observations: $V_K < V_L < V_{Na}$, $g_L \ll \bar{g}_K < \bar{g}_{Na}$

Steady-state level and time constant fitted by low-dimensional rational expression of exponential functions.





Spiking in Hodgkin-Huxley model

↳ see figures on the webpage.

* A "sufficiently large" current injection elicits a transient depolarization called action potential or spike
* For "sufficiently large" sustained current injection, action potentials a regularly generated : bursting regime.
* The above behavior represents simple, canonical spike generation. Atypical spikes, which are observed experimentally, can also be generated for model with different gating dynamics

Reduction of Hodgkin Huxley to simpler model

* 4-dimensional dynamics ⟶ 2-dimensional dynamics

Empirically : * dichotomy between slow and fast variable.

↳ $\tau_m \ll \tau_h, \tau_n$ ⇒ quasi-static approximation $m = m_\infty(V)$

* numerical simulation ; $h = 0.89 - 1.1n$

Reduced model : $\cdot C\partial_t V = I - \bar{g}_{Na} m_\infty(V)(0.89-1.1n)(V-V_{Na}) - \bar{g}_K n^4(V)(V-V_K) - g_L(V-V_L)$

electrophysiologically equivalent $\cdot \partial_t n = \dfrac{n_\infty(V)-n}{\tau_n(V)}$

Phase portrait analysis of 2-D reduced model

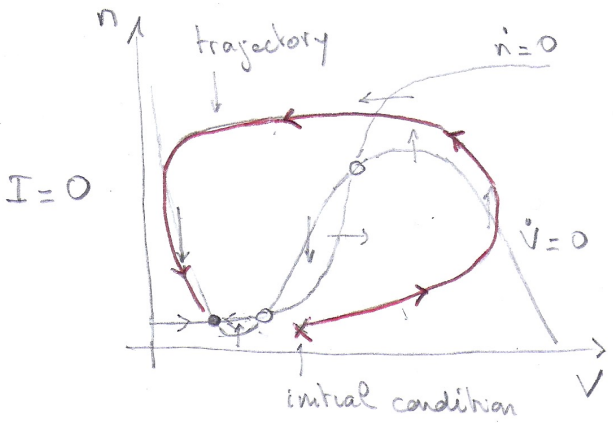
* Distinct possible reduced models depending on desired modeled behavior. A classical one is given by the persistent sodium plus potassium model:
  - ↳ sodium fast dynamics without inactivation ← fast positive feedback
  - ↳ potassium slow dynamics ← slow negative feedback

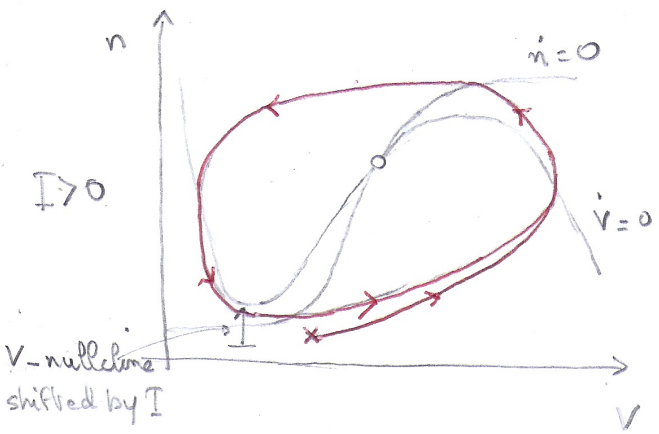
$$\begin{cases} C\partial_t V = I - g_L(V-V_L) - g_{Na}\, m_\infty(V)\,(V-V_{Na}) - g_K\, n\,(V-E_K) \\ \dot{n} = (n_\infty(V)-n)/\tau_V \end{cases}$$

(n: "activation variable"; $n_\infty(V)$: "recovery variable")

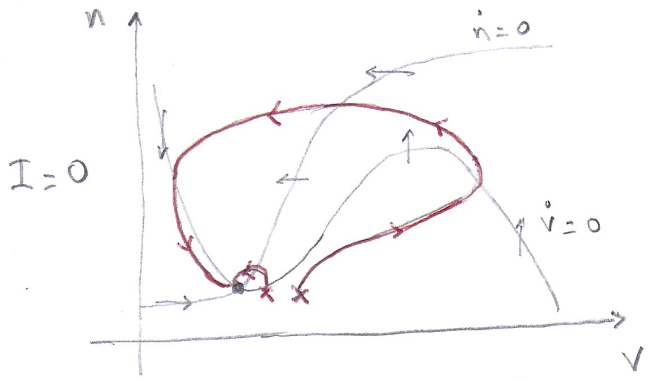
* 2-D vector flows and nullclines (curves $\dot{n}=0$, $\dot{V}=0$)

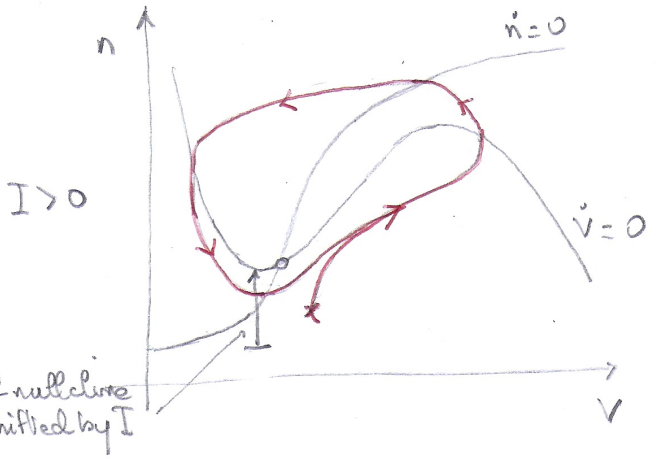
high threshold





low threshold





Resting, excitability, periodic spiking in 2D

Key elements:

* membrane voltage: key variable = electrical state
* activation variable, e.g., "m" (fast positive feedback)
* recovery variable, e.g., "h", "n" (slow negative feedback)

Phase portrait after quasistatic approximation $m = m_\infty(V)$