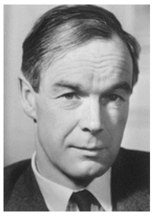
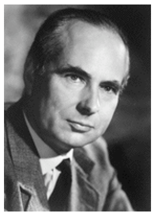
Systems Biology: Theoretical Biology

Levien van Zon, Theoretical Biology, UU

The Neuron Mystery



Alan Hodgkin

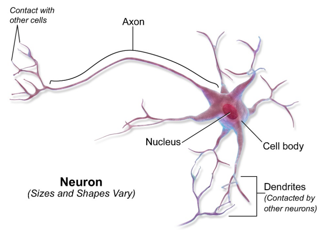


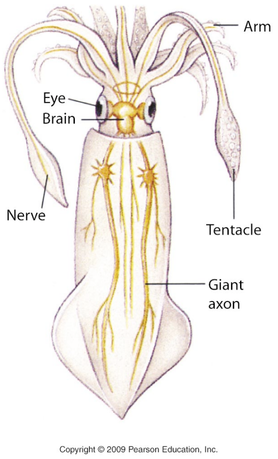
Andrew Huxley

Loligo forbesii

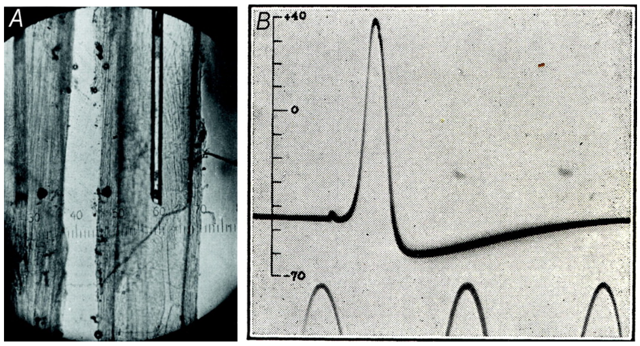
Introducing The Giant Squid Neuron

Loligo forbesii



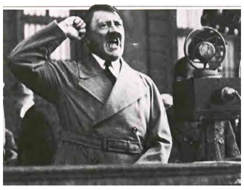


1939: First Recorded Action Potential (Inside an Axon)

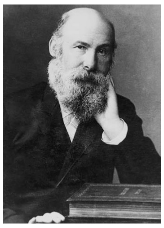


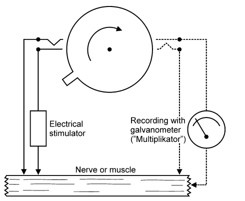
Hodgkin, A. L., & Huxley, A. F. (1939). Action potentials recorded from inside a nerve fibre. Nature, 144(3651), 710-711.

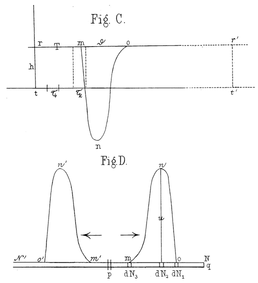
A Five-Year Interruption



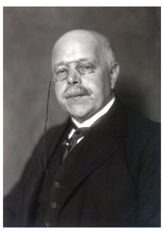
Back In Time: Julius Bernstein (1839-1917)





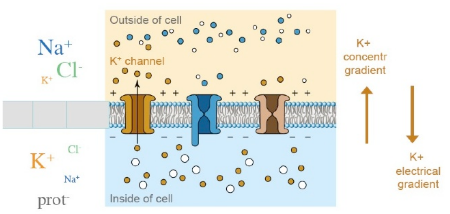


Bernstein's Membrane Theory (1902)



Walther Nernst
(1864-1941)

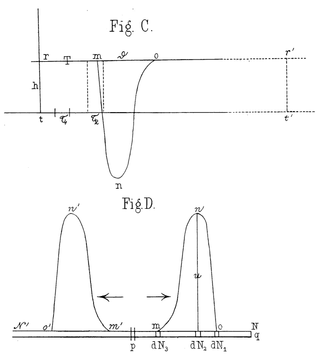
Electrochemical Equilibrium

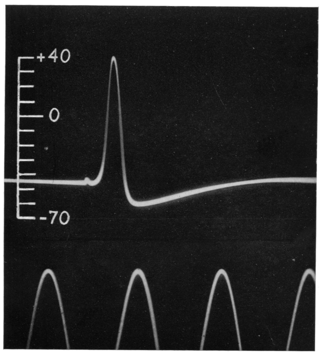


Nernst Equilibrium:

$$\overline{V_{K^+}} = \frac{RT}{z_K F} \ln \frac{[K^+]_o}{[K^+]_i} \approx -80\,\text{mV}$$

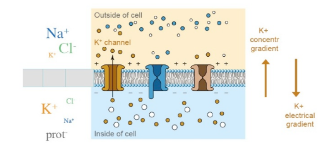
Bernstein's Membrane Theory Scrutinised



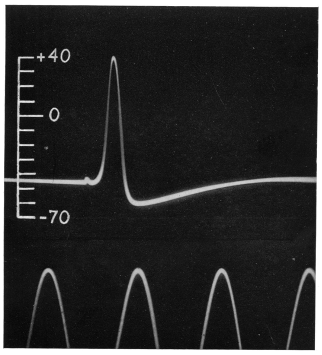


The Role Of Sodium?

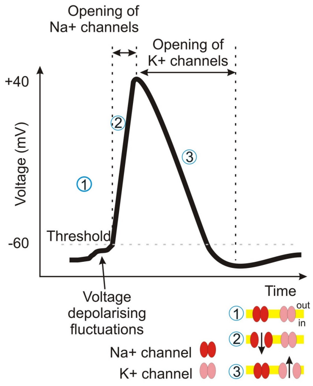
Electrochemical Equilibrium



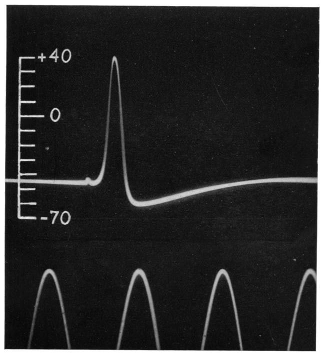
Nernst Equilibria:
$\overline{V_{K^+}} \approx -80\,\mathrm{mV}$
$\overline{V_{Na^+}} \approx +50\,\mathrm{mV}$



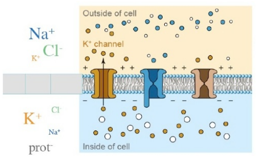
Hodgkin & Huxley's Theory

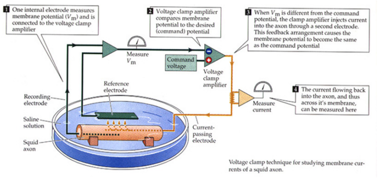


$\overline{V_{Na^+}} \approx +50\,\mathrm{mV}$
$\overline{V_{K^+}} \approx -80\,\mathrm{mV}$

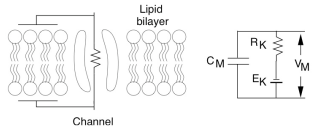


The Voltage Clamp





Membrane Currents and Voltages



Current I and charge Q:

$$I = \frac{\mathrm{d}Q}{\mathrm{d}t}$$

Ohm's Law, resistance R and conductance G:

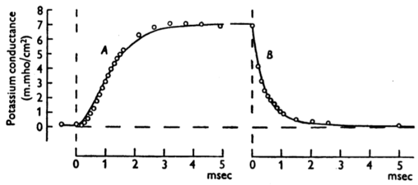
$$\begin{aligned} V &= I \times R \\ I &= \tfrac{1}{R} \times V \\ I &= G \times V \end{aligned}$$

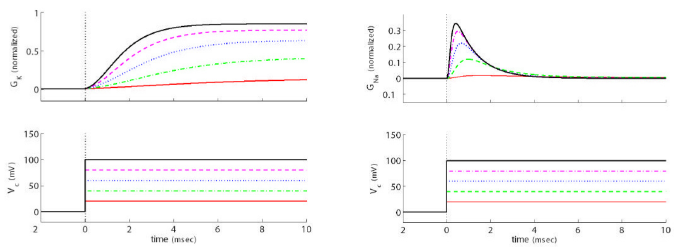
Capacitance C, storing charge:

$$\begin{aligned} Q(t) &= V(t) \times C \\ \frac{\mathrm{d}Q}{\mathrm{d}t} &= \tfrac{\mathrm{d}V}{\mathrm{d}t} \times C \\ I &= \tfrac{\mathrm{d}V}{\mathrm{d}t} \times C \\ \frac{\mathrm{d}V}{\mathrm{d}t} &= \tfrac{1}{C} \times I \end{aligned}$$

$$\frac{\mathrm{d}V}{\mathrm{d}t} = \frac{1}{C} \times G(V) \times V$$

Voltage Clamp Results





A Simple Model for Channels

$$\frac{\mathrm{d}x}{\mathrm{d}t} = \alpha(1-x) - \beta x$$

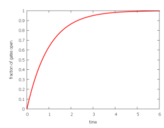
Fraction of open channels: x
Fraction of closed channels: $(1-x)$
Rate at which channels open: α
Rate at which channels close: β

Equilibrium $\overline{x}$:

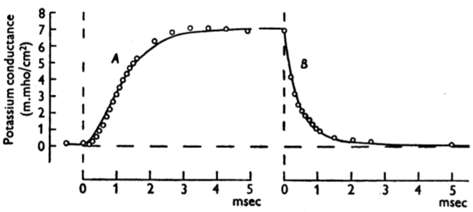
$$\begin{aligned} \alpha(1-x) - \beta x &= 0 \\ \alpha - \alpha x - \beta x &= 0 \\ -(\alpha+\beta)x &= -\alpha \\ \overline{x} &= \frac{\alpha}{\alpha+\beta} \end{aligned}$$

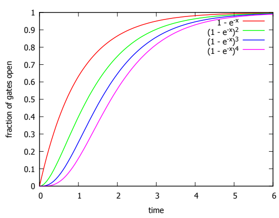
Solution $x(t)$:

$$x(t) = \overline{x} - (\overline{x} - x_0)\mathrm{e}^{-(\alpha+\beta)t}$$



Voltage Clamp Results vs. Channel Model





$$G(V) = n(V)^4 \times G_{max}$$

$$G = n \times n \times n \times n \times G_{max}$$

4 gates need to open,
before 1 channel is open!

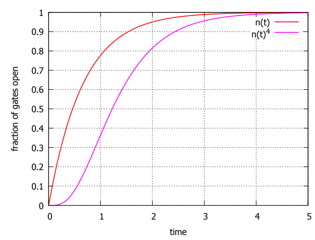
A Simple Model for Potassium Gates

$$\frac{\mathrm{d}n}{\mathrm{d}t} = \alpha(V)(1-n) - \beta(V)n$$
$$\frac{\mathrm{d}n}{\mathrm{d}t} = \frac{1}{\tau_n}(\overline{n} - n)$$

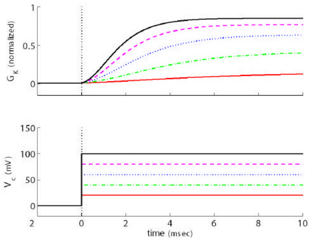
Fraction of open K^+ gates: n

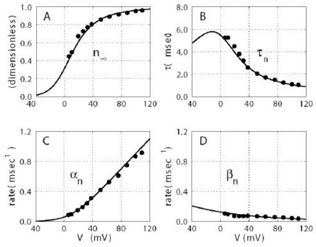
Equilibrium $\overline{n}(V)$ or n_∞:
$\overline{n}(V) = \frac{\alpha(V)}{\alpha(V)+\beta(V)}$

Time constant $\tau(V)$:
$\tau_n(V) = \frac{1}{\alpha(V)+\beta(V)}$



Finding $\overline{n}$, τ, α and β





$$\alpha_n(V) = \frac{\overline{n}(V)}{\tau_n(V)}$$
$$\beta_n(V) = \frac{1-\overline{n}(V)}{\tau_n(V)}$$

$$\alpha_n(V) = \frac{0.01(10-V)}{e^{(1-0.1V)}-1}$$
$$\beta_n(V) = 0.125e^{-\frac{V}{80}}$$

A "Simple" Model for Potassium Gates

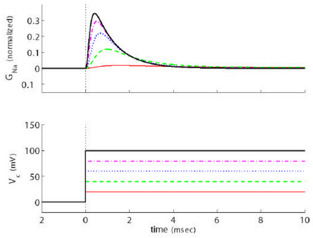
$$\frac{dn}{dt} = \alpha_n(1-n) - \beta_n n$$

Fraction of open K^+ gates: n

Rate "constants" α and β are not constant, but depend on voltage:

$$\alpha_n(V) = \frac{0.01(10-V)}{e^{(1-0.1V)}-1}$$
$$\beta_n(V) = 0.125e^{-\frac{V}{80}}$$

A Simple Model for Sodium Gates



$$\frac{dm}{dt} = \alpha_m(1-m) - \beta_m m$$
$$\frac{dh}{dt} = \alpha_h(1-h) - \beta_h h$$

Two types of Na^+ gates:

1. m-gates open rapidly in response to voltage
2. h-gates close slowly in response to voltage

m and h are the fractions of m-gates and h-gates that are open.

A "Simple" Model for Na^+ Gates

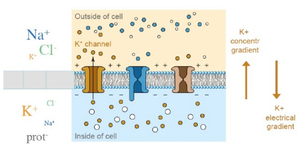
$$\frac{dm}{dt} = \alpha_m(1-m) - \beta_m m$$
$$\frac{dh}{dt} = \alpha_h(1-h) - \beta_h h$$

Rate "constants" α and β are not constant, but depend on voltage:

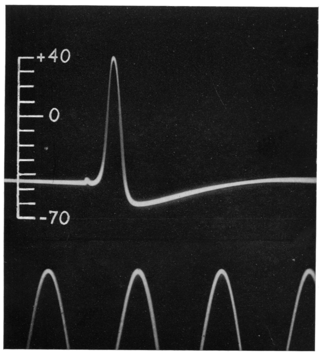
$$\alpha_m = 0.1\frac{25-V}{e^{\frac{25-V}{10}}-1}$$
$$\beta_m = 4e^{(-\frac{V}{18})}$$
$$\alpha_h = 0.07e^{(-\frac{V}{20})}$$
$$\beta_h = \frac{1}{e^{(\frac{30-V}{10})}+1}$$

What Were We Modelling Again?

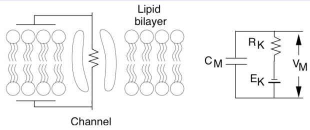
Electrochemical Equilibrium

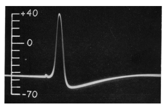


Nernst Equilibria:
$\overline{V_{K^+}} \approx -80\,\text{mV}$
$\overline{V_{Na^+}} \approx +50\,\text{mV}$



Membrane Currents and Voltages Revisited





Describing the voltage:

$$\frac{dV}{dt} = \frac{1}{C} \times G \times V$$
$$= \frac{1}{C} \times (I_{K^+} + I_{Na^+} + I_R)$$
$$= \frac{1}{C} \times (G_{K^+} \times (\overline{V_{K^+}} - V) + G_{Na^+} \times (\overline{V_{Na^+}} - V) + G_R \times (\overline{V_R} - V))$$

$$\frac{dV}{dt} = \frac{1}{C} \times (G_{K^+} \times (\overline{V_{K^+}} - V) + G_{Na^+} \times (\overline{V_{Na^+}} - V) + G_R \times (\overline{V_R} - V))$$

The Full Model

$$\begin{cases} \frac{dV}{dt} = \frac{1}{C}(G_K(\overline{V_K} - V) + G_{Na}(\overline{V_{Na}} - V) + G_R(\overline{V_R} - V)) \\ \frac{dm}{dt} = \alpha_m(1-m) - \beta_m m \\ \frac{dh}{dt} = \alpha_h(1-h) - \beta_h h \\ \frac{dn}{dt} = \alpha_n(1-n) - \beta_n n \end{cases}$$

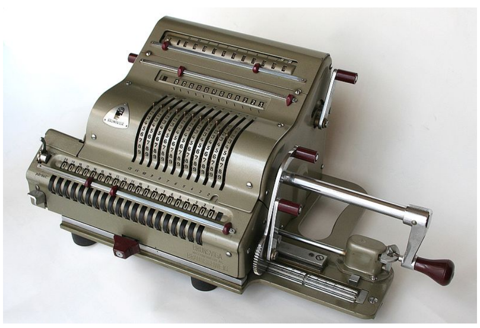
with

$$G_K = n^4 G_{K\,max}$$
$$G_{Na} = m^3 h G_{Na\,max}$$

$$\alpha_n = \frac{0.01(10-V)}{e^{(1-0.1V)}-1}$$
$$\beta_n = 0.125e^{-\frac{V}{80}}$$
$$\alpha_m = 0.1\frac{25-V}{e^{\frac{25-V}{10}}-1}$$
$$\beta_m = 4e^{(-\frac{V}{18})}$$
$$\alpha_h = 0.07e^{(-\frac{V}{20})}$$
$$\beta_h = \frac{1}{e^{(\frac{30-V}{10})}+1}$$

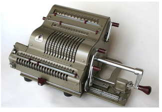
But, how to test all this?

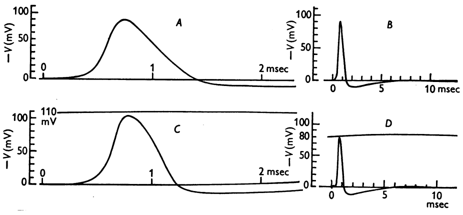
Please Wait, Calculating...



Brunsviga 20 — "Brains of Steel"

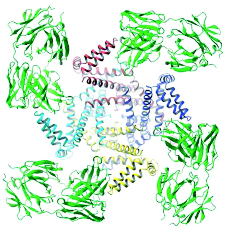
Please Wait, Calculating...

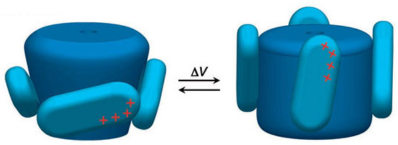




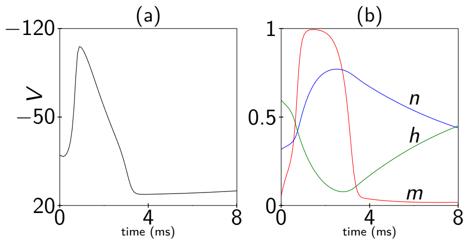
1963: Nobel Prize!

2003: Prediction Confirmed!





2014: Running it in GRIND



a Action potential: voltage dynamics
b Gate dynamics: m and h for Na^+, n for K^+

Note that in the original model, rest potential is 0 mV and AP is -90 mV

Simplifying the model

Quasi Steady State assumption

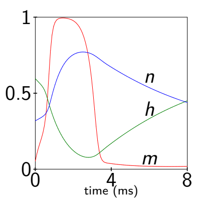
The m gate is much faster,
so replace m by its steady-state $\overline{m}$:

$$m = \overline{m} = \frac{\alpha_m}{\alpha_m + \beta_m}$$

Conservation assumption

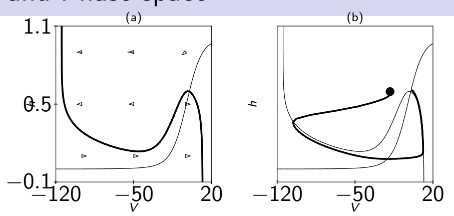
n and h are almost complementary: $n + h \simeq 0.91$
Use this to remove n:

$$n = 0.91 - h$$



This reduces the model to 2 variables: V and h!

Nullclines and Phase space



thin line: h nullcline
heavy line: V nullcline

- Stable equilibrium
- V nullcline determines activation threshold
- Action potential is an excursion through phase space
- The Na^+ inactivation gate is slow, closing the h-gates takes time
- Recovery of the h-gates also takes time, causing refractory period
- The voltage V changes much faster than the h-gates

Simplified, But Still Pretty Complicated!

$$\begin{cases} \frac{dV}{dt} = \frac{1}{C}(G_K(\overline{V_K} - V) + G_{Na}(\overline{V_{Na}} - V) + G_R(\overline{V_R} - V)) \\ \frac{dh}{dt} = \alpha_h(1-h) - \beta_h h \end{cases}$$

with

$$G_K = (0.91 - h)^4 G_{K\,max}$$
$$G_{Na} = \overline{m}^3 h G_{Na\,max}$$
$$\overline{m} = \frac{\alpha_m}{\alpha_m + \beta_m}$$

$$\alpha_n = \frac{0.01(10-V)}{e^{(1-0.1V)} - 1}$$
$$\beta_n = 0.125e^{-\frac{V}{80}}$$
$$\alpha_m = 0.1\frac{25-V}{e^{\frac{25-V}{10}} - 1}$$
$$\beta_m = 4e^{(-\frac{V}{18})}$$
$$\alpha_h = 0.07e^{(-\frac{V}{20})}$$
$$\beta_h = \frac{1}{e^{(\frac{30-V}{10})} + 1}$$

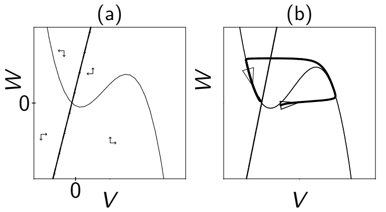
Can't we do this simpler?

Yes We Can: The FitzHugh-Nagumo Model

$$\begin{cases} \frac{dV}{dt} = -V(V-a)(V-1) - W \\ \frac{dW}{dt} = \epsilon(V - bW) \end{cases}$$

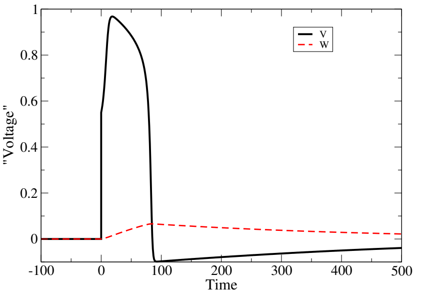
- Not mechanistic, but a phenomenological model
- V is voltage, W causes inactivation, refractoriness
- ϵ is small, so W is a slow variable that follows V
- The $\frac{dW}{dt} = 0$ nullcline is a straight line: $W = \frac{1}{b}V$
- The $\frac{dV}{dt} = 0$ nullcline is a cubic function:
  $W = -V(V-a)(V-1)$
- The V-nullcline intersects the V-axis at:
  $V = 0$, $V = a$ and $V = 1$

FitzHugh-Nagumo: What Does It Look Like?



- Similar to the simplified HH model (but V and W axis mirrored)
- Stable equilibrium
- $V = a$ is the activation threshold
- Action potential is an excursion through phase space
- The inactivation "gate" W is slow, inactivation takes time (right)
- Recovery of W also takes time (left), causing refractory period
- The voltage V changes much faster than the variable W

FitzHugh-Nagumo: Behavior in time



Behavior of V resembles an action potential.

http://www.scholarpedia.org/article/FitzHugh-Nagumo_model

Summary

Hodgkin-Huxley model

- **Key insight**: different currents through separate channels.
- **Approach**: measure and model them separately, then combine.
- Ugly equations are just to fit data precisely.
- Key is opening and closing of gates that control open state of channels.
- Different currents and gates control different phases of the action potential:
  - depolarization (Na^+, m-gate)
  - repolarization (Ka^+, n-gate)
  - refractoriness (Na^+, h-gate)
- Model can be simplified from 4 to 2 equations
- The model *predicted* voltage sensitive, time dependent transmembrane protein channels, long before they were found!

Summary

Fitzhugh-Nagumo model

- Reaching a simpler 2 variable model with similar behaviour, by considering which ingredients are necessary.
- Below the threshold a no real excitation occurs.
- Beyond the threshold a excitation must occur.
- After excitation refractoriness must occur.
- Slow W-variable represses fast V-variable, and ensures refractoriness