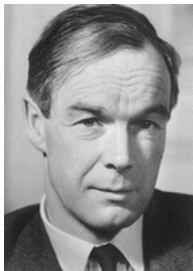


Systems Biology: Theoretical Biology

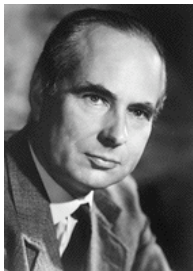


Levien van Zon, Theoretical Biology, UU

The Neuron Mystery



Alan Hodgkin



Andrew Huxley

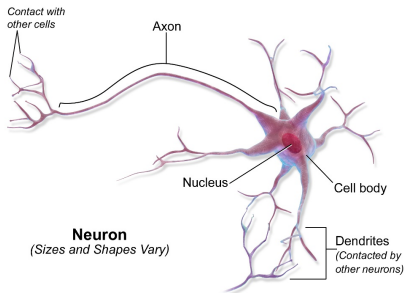
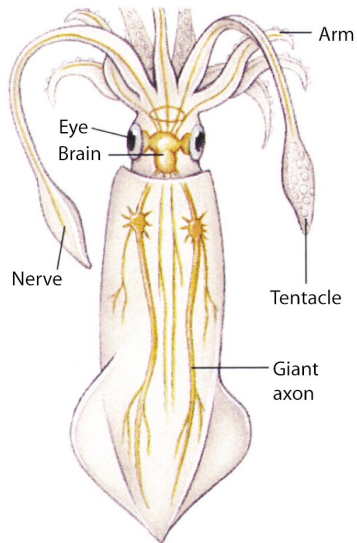


Loligo forbesii

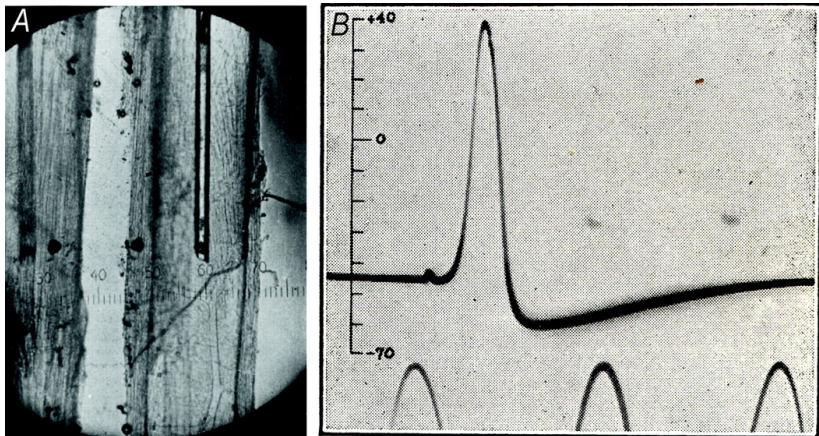
Introducing The Giant Squid Neuron



Loligo forbesii



1939: First Recorded Action Potential (Inside an Axon)

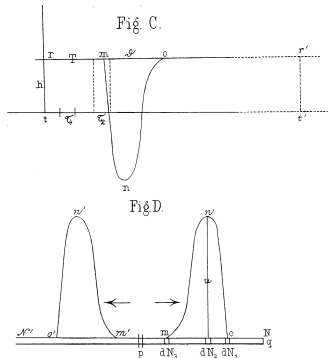
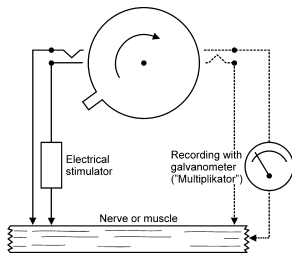
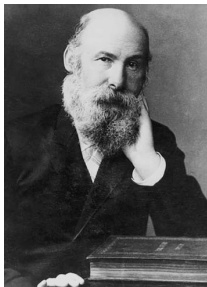


Hodgkin, A. L., & Huxley, A. F. (1939). Action potentials recorded from inside a nerve fibre. *Nature*, 144(3651), 710-711.

A Five-Year Interruption



Back In Time: Julius Bernstein (1839-1917)

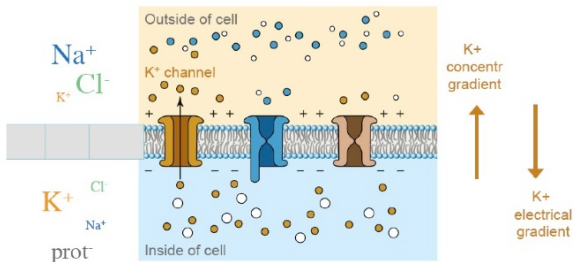


Bernstein's Membrane Theory (1902)

Electrochemical Equilibrium



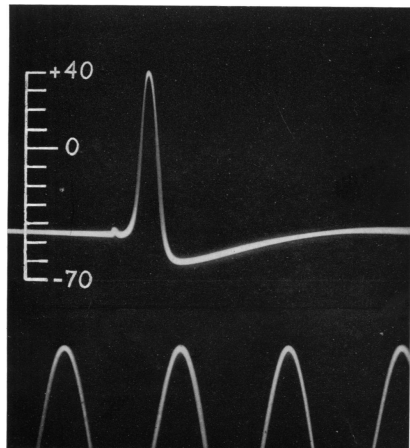
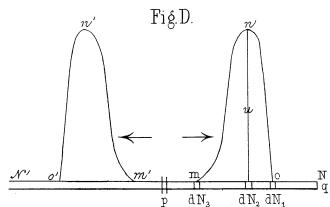
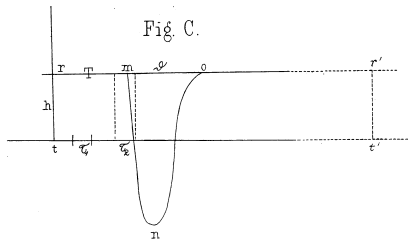
Walther Nernst
(1864-1941)



Nernst Equilibrium:

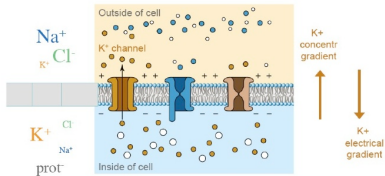
$$\overline{V_{K^+}} = \frac{RT}{z_K F} \ln \frac{[K^+]_o}{[K^+]_i} \approx -80 \text{ mV}$$

Bernstein's Membrane Theory Scrutinised



The Role Of Sodium?

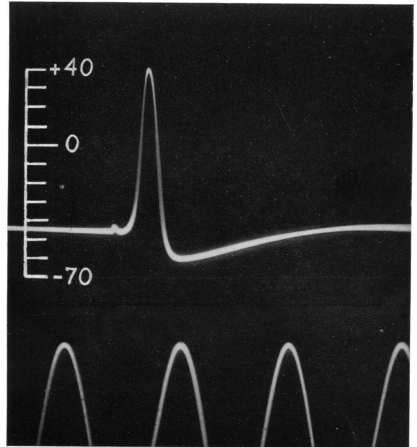
Electrochemical Equilibrium



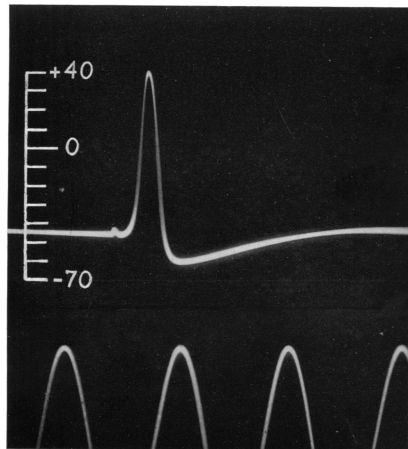
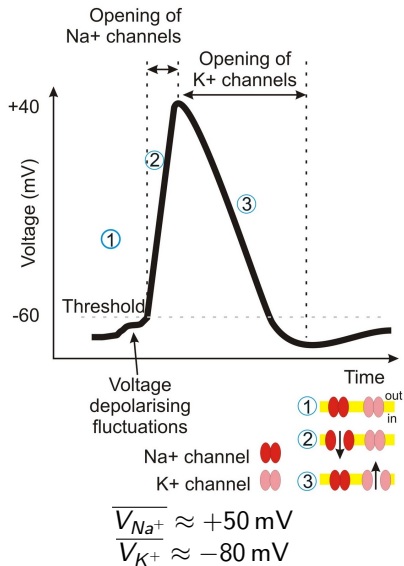
Nernst Equilibria:

$$\overline{V_{K^+}} \approx -80 \text{ mV}$$

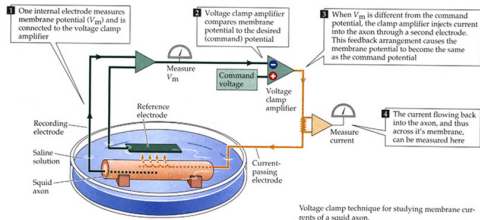
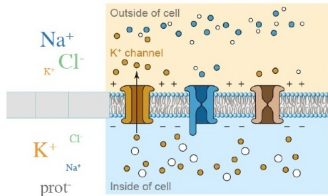
$$\overline{V_{Na^+}} \approx +50 \text{ mV}$$



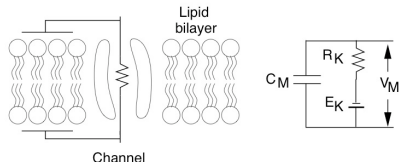
Hodgkin & Huxley's Theory



The Voltage Clamp



Membrane Currents and Voltages



Current I and charge Q :

$$I = \frac{dQ}{dt}$$

Ohm's Law, resistance R and conductance G :

$$V = I \times R$$

$$I = \frac{1}{R} \times V$$

$$I = G \times V$$

Capacitance C , storing charge:

$$Q(t) = V(t) \times C$$

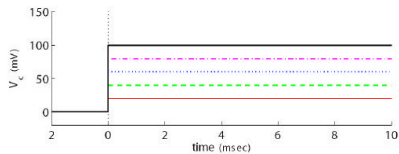
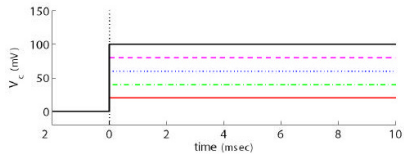
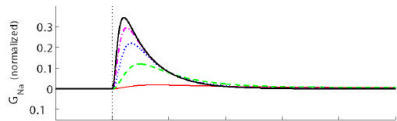
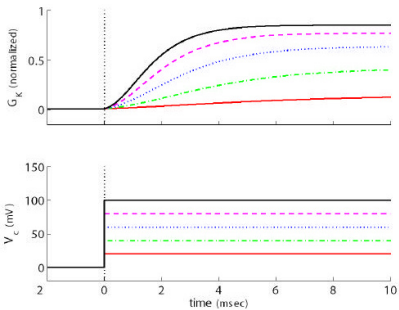
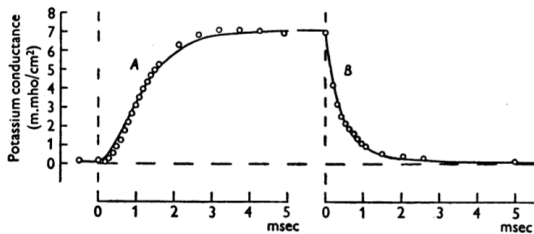
$$\frac{dQ}{dt} = \frac{dV}{dt} \times C$$

$$I = \frac{dV}{dt} \times C$$

$$\frac{dV}{dt} = \frac{1}{C} \times I$$

$$\frac{dV}{dt} = \frac{1}{C} \times G(V) \times V$$

Voltage Clamp Results



A Simple Model for Channels

$$\frac{dx}{dt} = \alpha(1 - x) - \beta x$$

Fraction of open channels: x

Fraction of closed channels: $(1 - x)$

Rate at which channels open: α

Rate at which channels close: β

Equilibrium \bar{x} :

$$\alpha(1 - x) - \beta x = 0$$

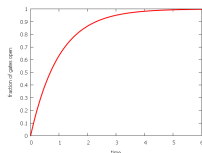
$$\alpha - \alpha x - \beta x = 0$$

$$-(\alpha + \beta)x = -\alpha$$

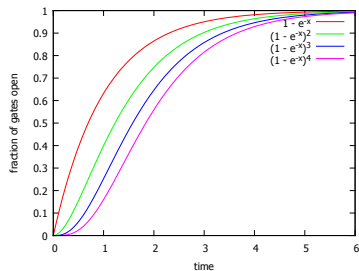
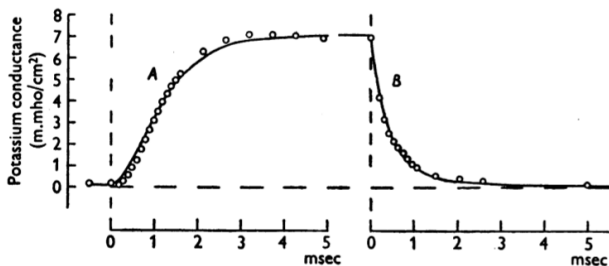
$$\bar{x} = \frac{\alpha}{\alpha + \beta}$$

Solution $x(t)$:

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



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

$$\frac{dn}{dt} = \alpha(V)(1 - n) - \beta(V)n$$
$$\frac{dn}{dt} = \frac{1}{\tau_n}(\bar{n} - n)$$

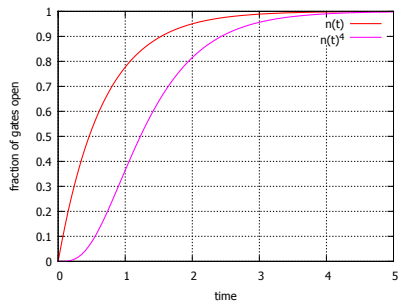
Fraction of open K^+ gates: n

Equilibrium $\bar{n}(V)$ or n_∞ :

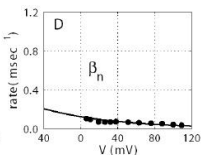
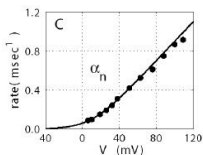
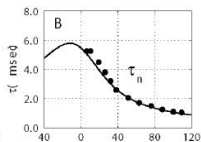
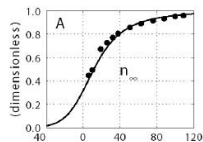
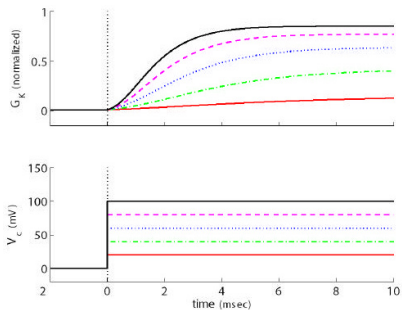
$$\bar{n}(V) = \frac{\alpha(V)}{\alpha(V) + \beta(V)}$$

Time constant $\tau(V)$:

$$\tau_n(V) = \frac{1}{\alpha(V) + \beta(V)}$$



Finding \bar{n} , τ , α and β



$$\alpha_n(V) = \frac{\bar{n}(V)}{\tau_n(V)}$$

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

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

$$\beta_n(V) = 0.125e^{-\frac{V}{80}}$$

A “Simple” Model for Potassium Gates

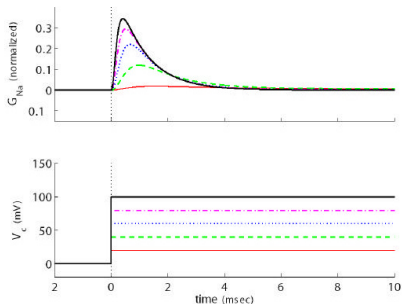
$$\frac{dn}{dt} = \alpha_n(1 - n) - \beta_n n$$

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:

$$\alpha_m = 0.1 \frac{25 - V}{e^{\frac{25 - V}{10}} - 1}$$

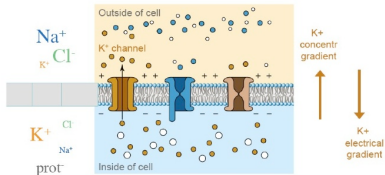
$$\beta_m = 4e^{(-\frac{V}{18})}$$

$$\alpha_h = 0.07e^{(-\frac{V}{20})}$$

$$\beta_h = \frac{1}{e^{(\frac{30 - V}{10})} + 1}$$

What Were We Modelling Again?

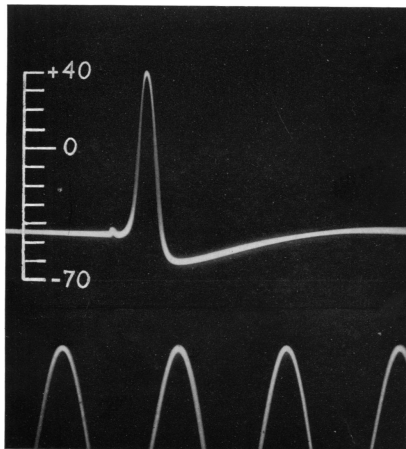
Electrochemical Equilibrium



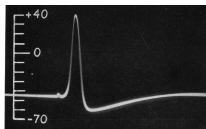
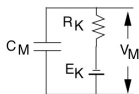
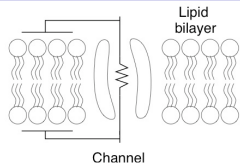
Nernst Equilibria:

$$\overline{V_{K^+}} \approx -80 \text{ mV}$$

$$\overline{V_{Na^+}} \approx +50 \text{ mV}$$



Membrane Currents and Voltages Revisited



Describing the voltage:

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

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

The Full Model

$$\left\{ \begin{array}{l} \frac{dV}{dt} = \frac{1}{C}(G_K(\overline{V}_K - V) + G_{Na}(\overline{V}_{Na} - V) + G_R(\overline{V}_R - V)) \\ \frac{dm}{dt} = \alpha_m(1 - m) - \beta_m m \\ \frac{dh}{dt} = \alpha_h(1 - h) - \beta_h h \\ \frac{dn}{dt} = \alpha_n(1 - n) - \beta_n n \end{array} \right.$$

with

$$G_K = n^4 G_{Kmax}$$
$$G_{Na} = m^3 h G_{Na max}$$

But, how to test all this?

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

$$\beta_n = 0.125e^{-\frac{V}{80}}$$

$$\alpha_m = 0.1 \frac{25 - V}{e^{\frac{25-V}{10}} - 1}$$

$$\beta_m = 4e^{(-\frac{V}{18})}$$

$$\alpha_h = 0.07e^{(-\frac{V}{20})}$$

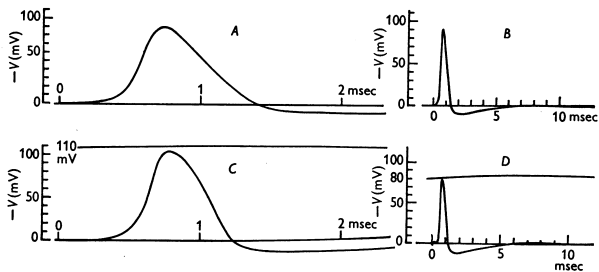
$$\beta_h = \frac{1}{e^{(\frac{30-V}{10})} + 1}$$

Please Wait, Calculating...



Brunsviga 20 — “Brains of Steel”

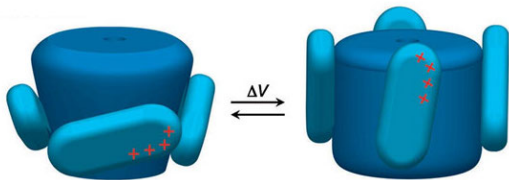
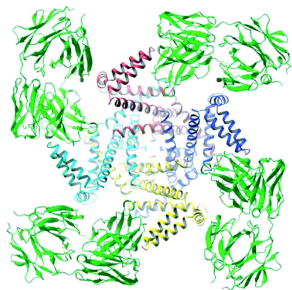
Please Wait, Calculating...



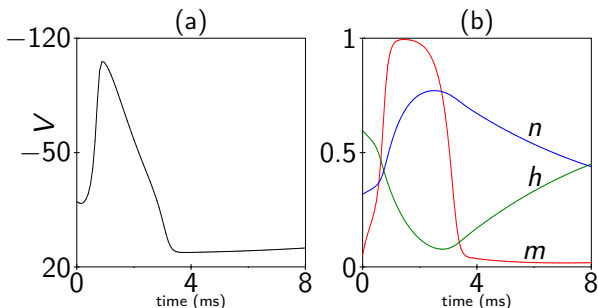
1963: Nobel Prize!



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

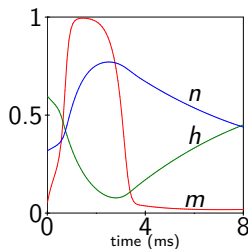
The m gate is much faster,
so replace m by its steady-state \bar{m} :

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

Conservation assumption

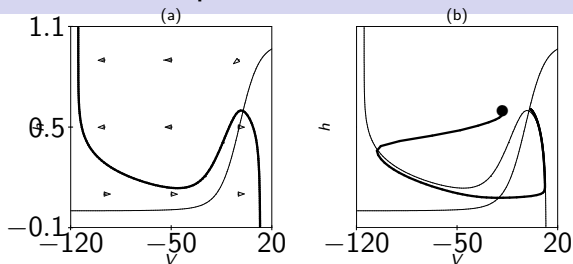
n and h are almost complementary: $n + h \simeq 0.91$
Use this to remove n :

$$n = 0.91 - h$$



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

$$G_K = (0.91 - h)^4 G_{Kmax}$$

$$G_{Na} = \overline{m}^3 h G_{Na max}$$

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

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

$$\beta_n = 0.125e^{-\frac{V}{80}}$$

$$\alpha_m = 0.1 \frac{25 - V}{e^{\frac{25-V}{10}} - 1}$$

$$\beta_m = 4e^{(-\frac{V}{18})}$$

$$\alpha_h = 0.07e^{(-\frac{V}{20})}$$

$$\beta_h = \frac{1}{e^{(\frac{30-V}{10})} + 1}$$

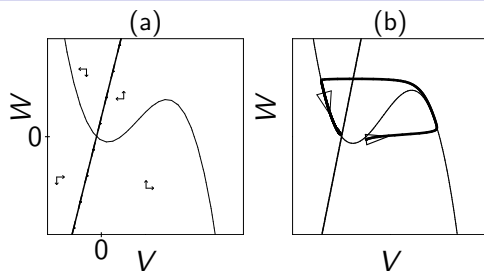
Can't we do this simpler?

Yes We Can: The FitzHugh-Nagumo Model

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

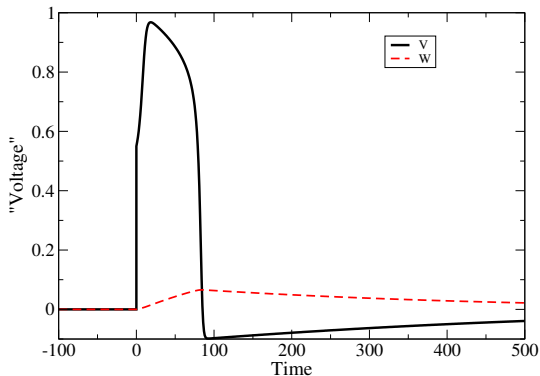
- Not mechanistic, but a phenomenological model
- V is voltage, W causes inactivation, refractoriness
- ϵ is small, so W is a slow variable that follows V
- The $\frac{dW}{dt} = 0$ nullcline is a straight line: $W = \frac{1}{b}V$
- The $\frac{dV}{dt} = 0$ nullcline is a cubic function:
 $W = -V(V - a)(V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

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 (K^+ , *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!

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