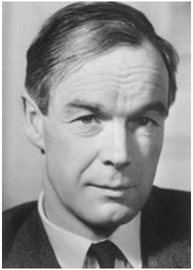
Systems Biology: Theoretical Biology

Levien van Zon, Theoretical Biology, UU

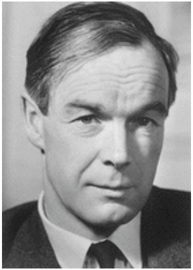
The Neuron Mystery

The Neuron Mystery



Alan Hodgkin

The Neuron Mystery



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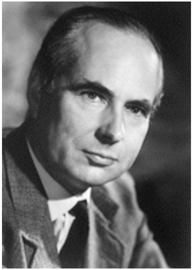
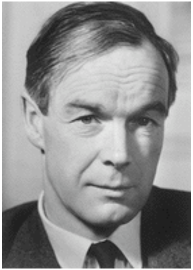


Andrew Huxley

The Neuron Mystery



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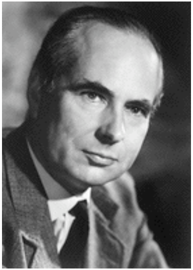
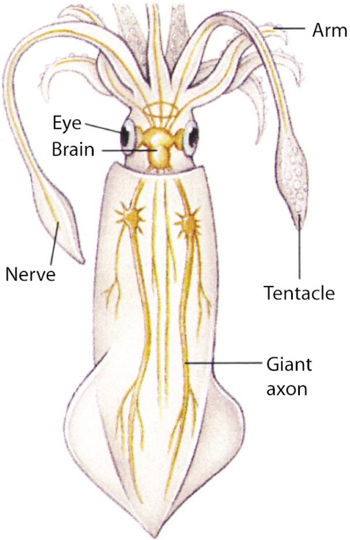


Andrew Huxley

Loligo forbesii

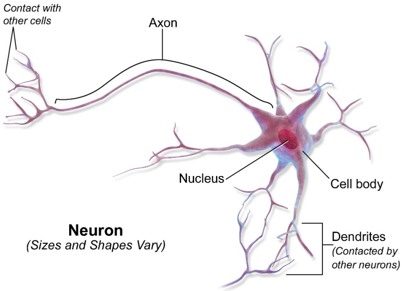
Introducing The Giant Squid Neuron

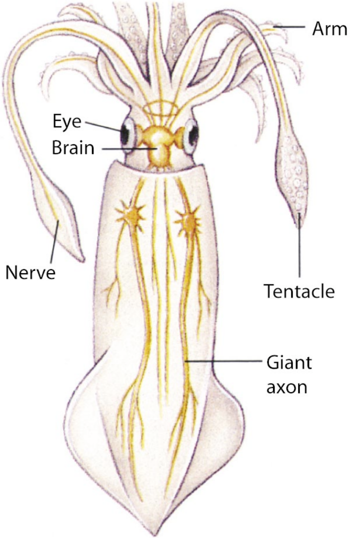
Loligo forbesii



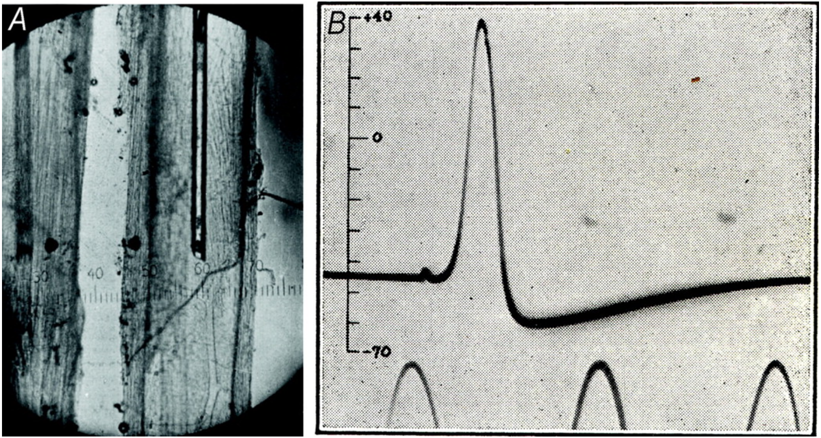
Introducing The Giant Squid Neuron

Loligo forbesii





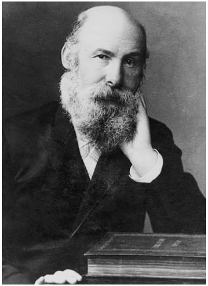
1939: First Recorded Action Potential (Inside an Axon)

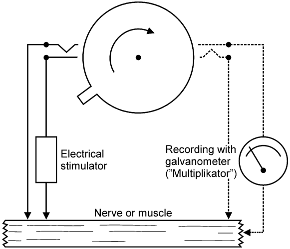


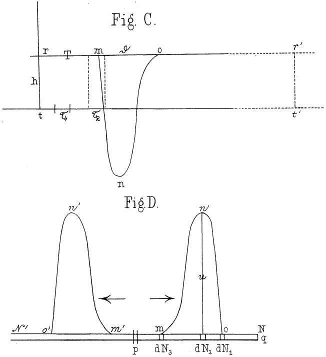
Hodgkin, A. L., & Huxley, A. F. (1939). Action potentials recorded from inside a nerve fibre. Nature, 144(3651), 710-711.

A Five-Year Interruption

Back In Time: Julius Bernstein (1839-1917)

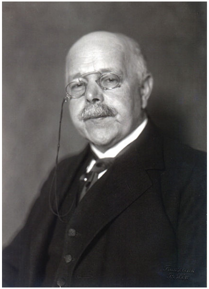




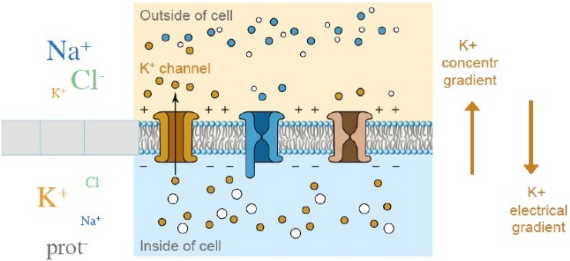


Bernstein's Membrane Theory (1902)

Electrochemical Equilibrium



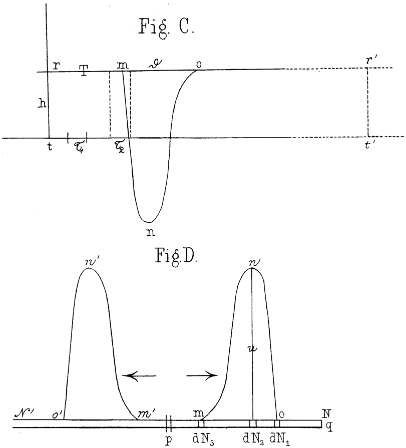
Walther Nernst
(1864-1941)

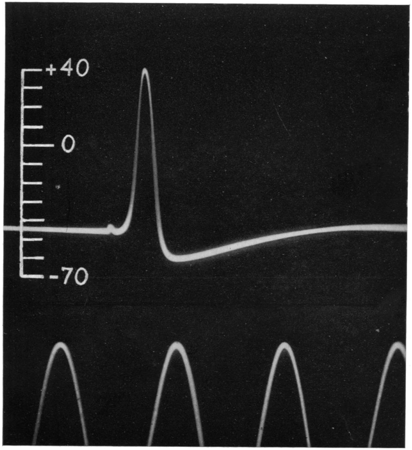


Nernst Equilibrium:

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

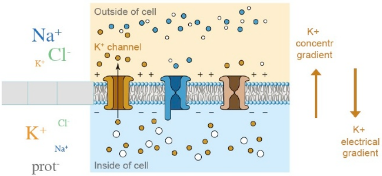
Bernstein's Membrane Theory Scrutinised





The Role Of Sodium?

Electrochemical Equilibrium



Nernst Equilibria:
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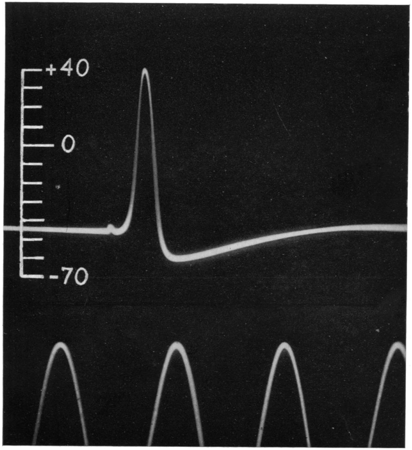

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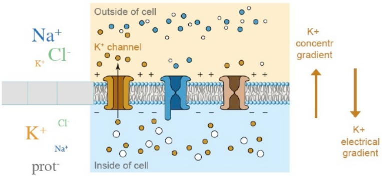
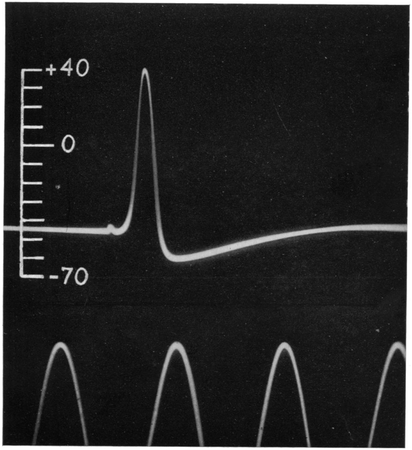
Electrochemical Equilibrium



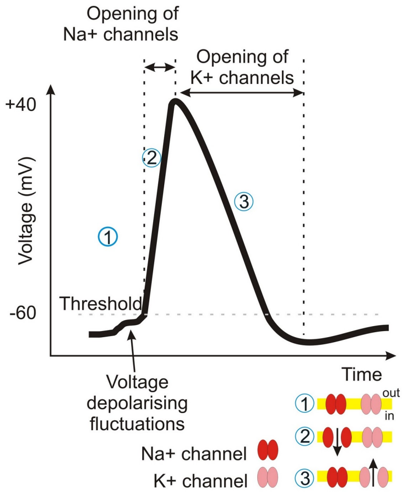
Nernst Equilibria:

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

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



Hodgkin & Huxley's Theory



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

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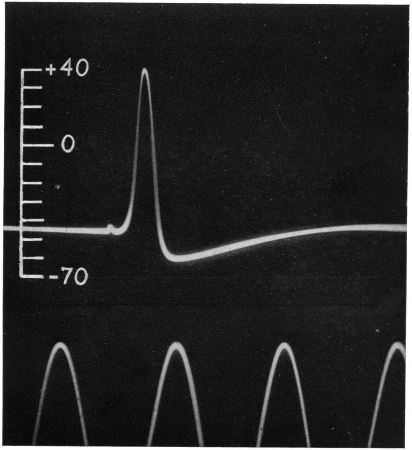
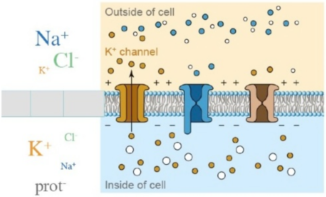
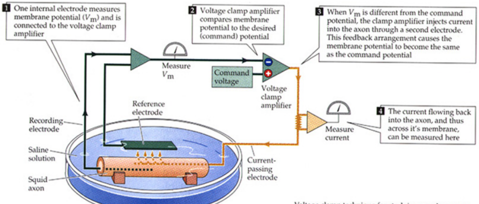


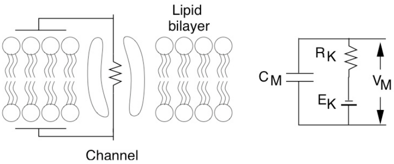
The Voltage Clamp



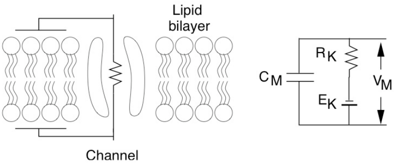


Voltage clamp technique for studying membrane currents of a squid axon.

Membrane Currents and Voltages



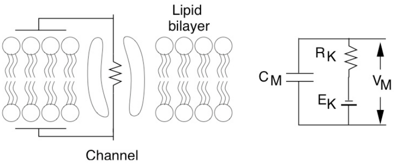
Membrane Currents and Voltages



Current I and charge Q:

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

Membrane Currents and Voltages



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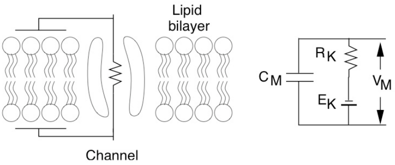
Ohm's Law, resistance R and conductance G:

$$V = \quad I \times R$$

Membrane Currents and Voltages



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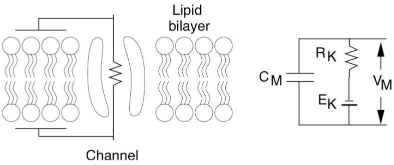
Membrane Currents and Voltages



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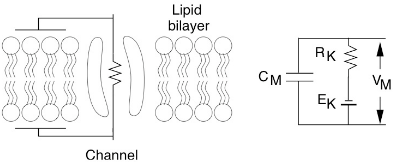

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$$Q(t) = V(t) \times C$$

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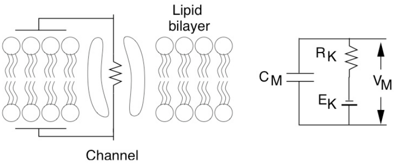
Membrane Currents and Voltages



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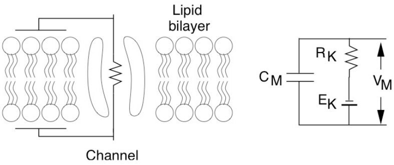

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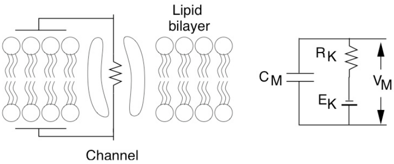

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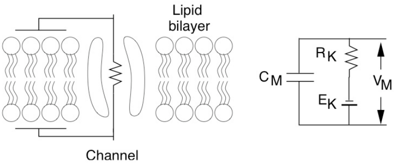
Membrane Currents and Voltages



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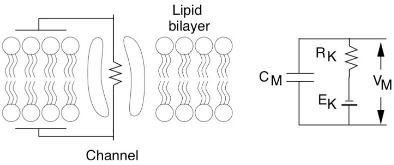
$$\frac{dV}{dt} = \frac{1}{C} \times G \times V$$

Membrane Currents and Voltages



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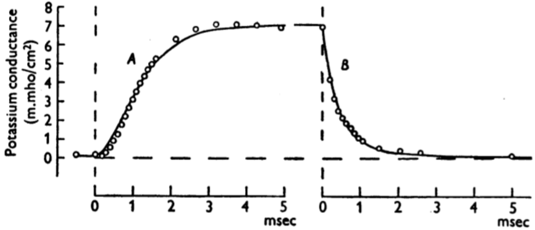
$$\frac{dV}{dt} = \frac{1}{C} \times G(V) \times V$$

Voltage Clamp Results



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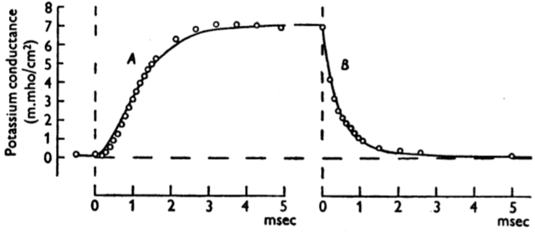

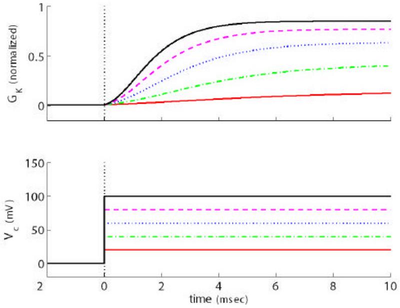

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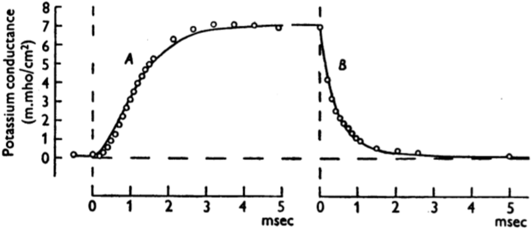

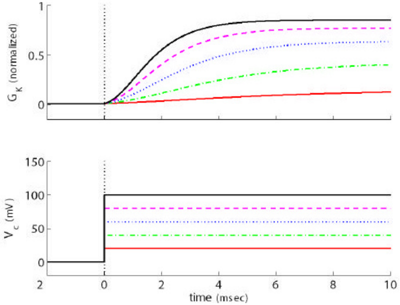

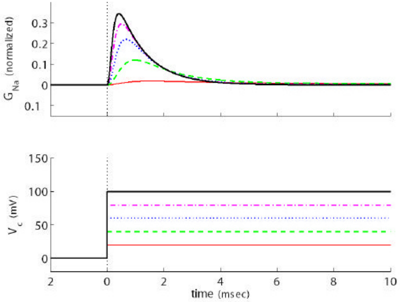

A Simple Model for Channels

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

Fraction of open channels: x

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

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

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Rate at which channels open: α

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Equilibrium $\overline{x}$:

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

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

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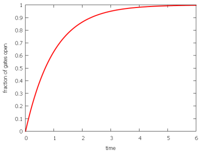
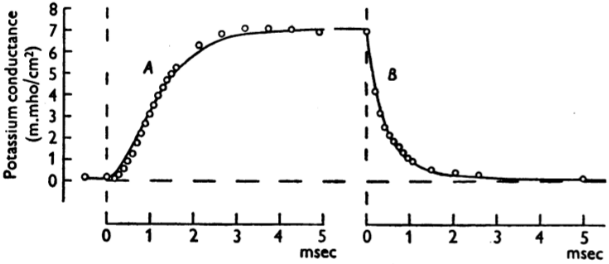


Voltage Clamp Results vs. Channel Model



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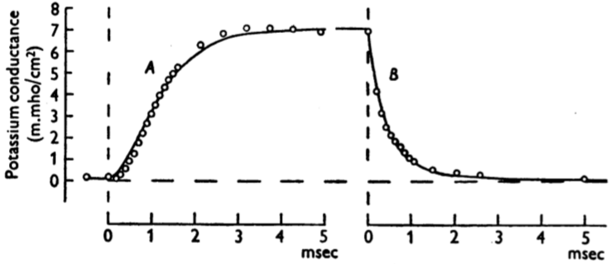
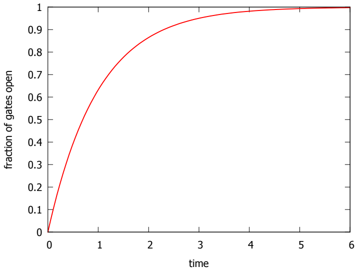
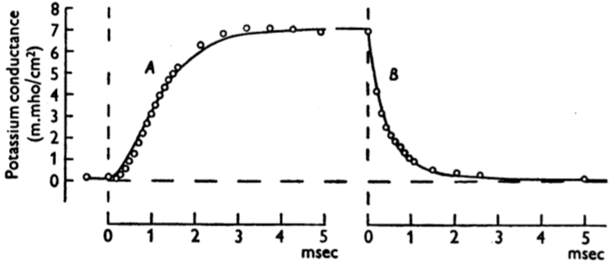
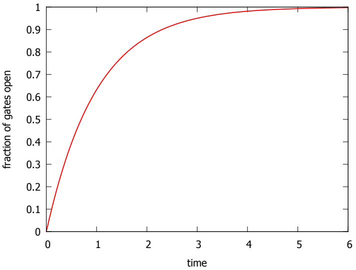
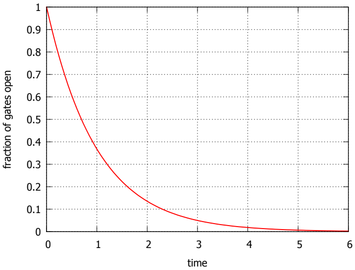




Voltage Clamp Results vs. Channel Model







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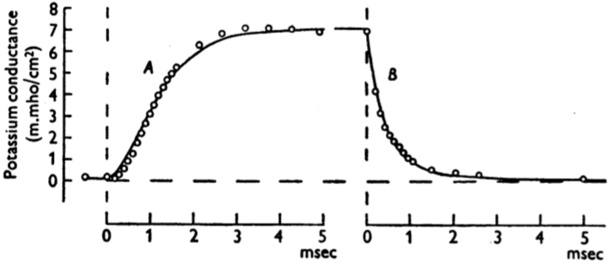
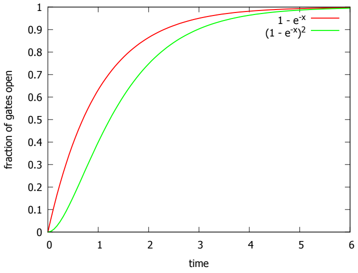
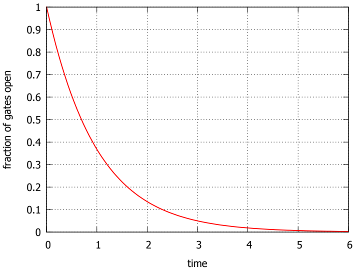
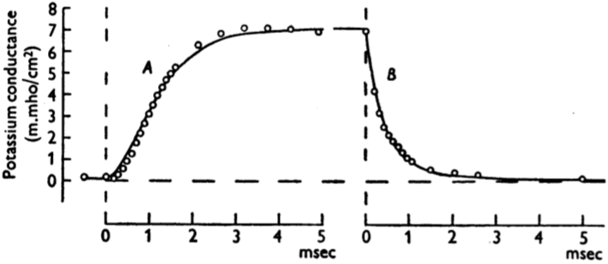
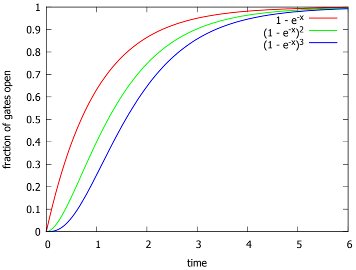


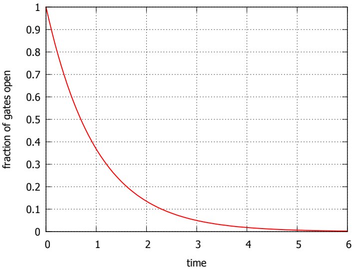




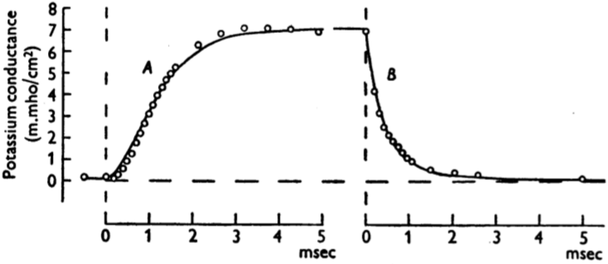
Voltage Clamp Results vs. Channel Model

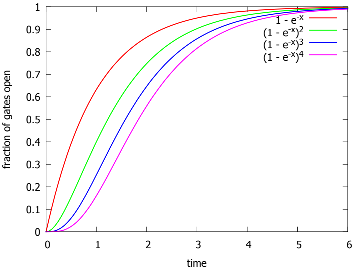


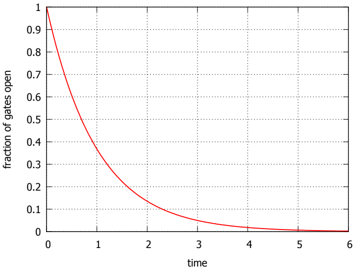




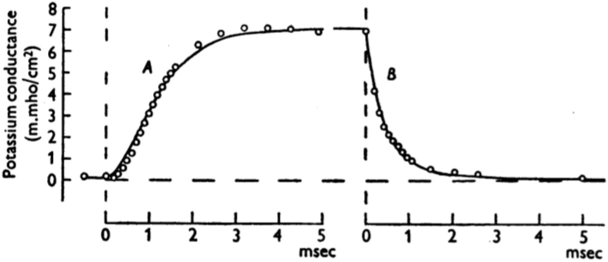
Voltage Clamp Results vs. Channel Model

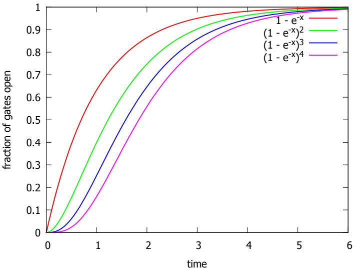


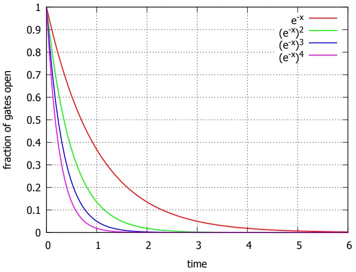




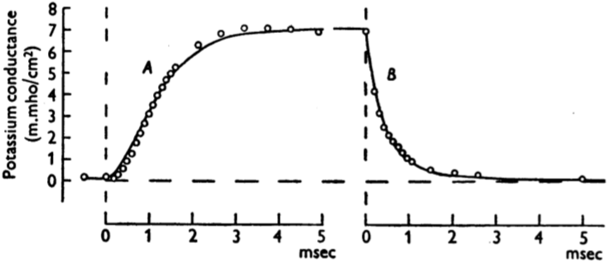
Voltage Clamp Results vs. Channel Model

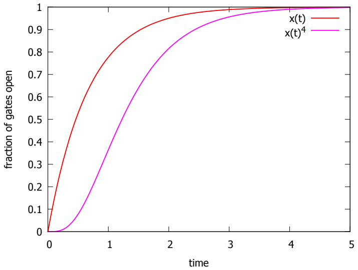


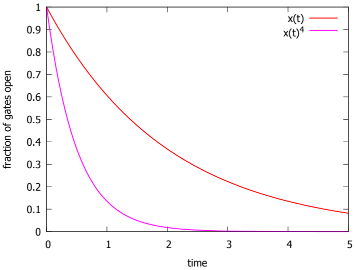




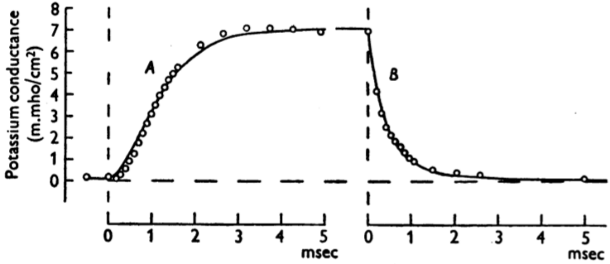
Voltage Clamp Results vs. Channel Model

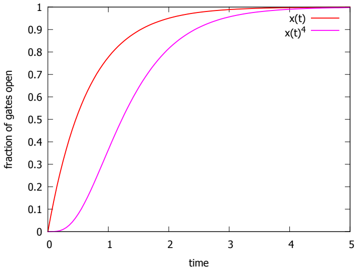






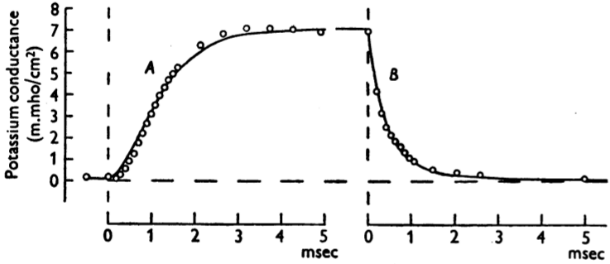
Voltage Clamp Results vs. Channel Model

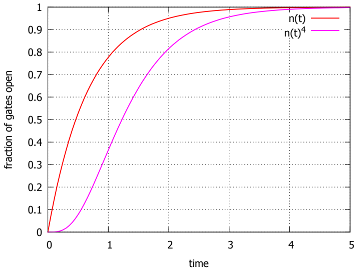




$$G = x \times G_{max}$$

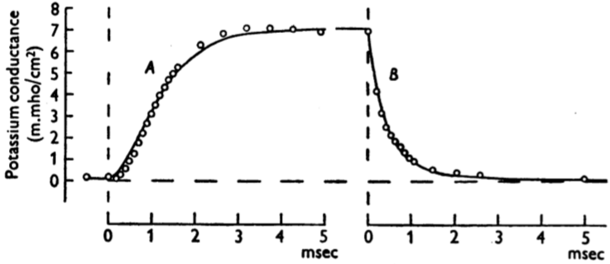
Voltage Clamp Results vs. Channel Model

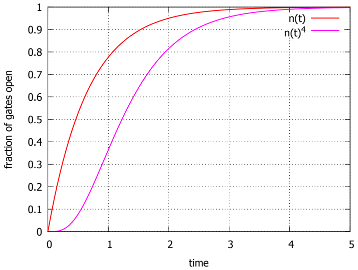




$$G = n \times G_{max}$$

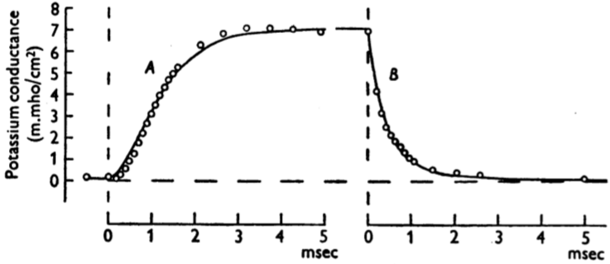
Voltage Clamp Results vs. Channel Model

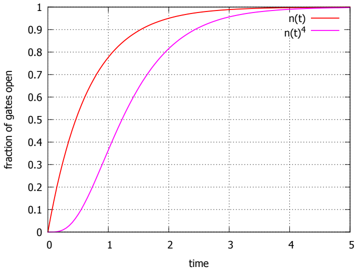




$$G = n^4 \times G_{max}$$

Voltage Clamp Results vs. Channel Model

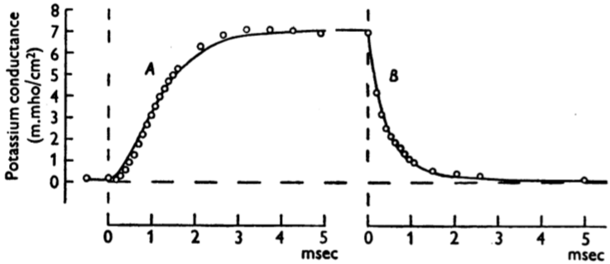


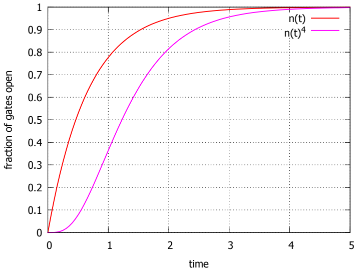


$$G = n^4 \times G_{max}$$

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

Voltage Clamp Results vs. Channel Model



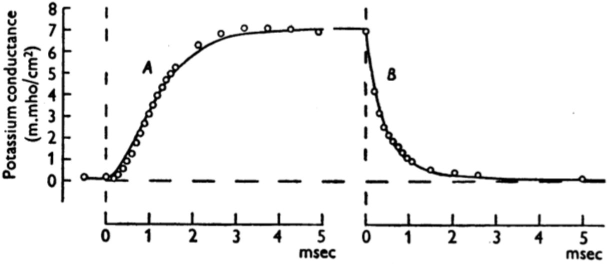


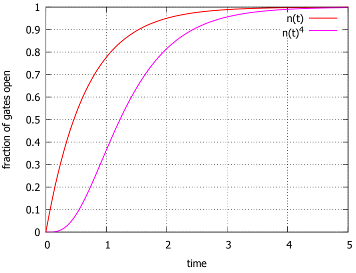
$$G = n^4 \times G_{max}$$

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

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

Voltage Clamp Results vs. Channel Model





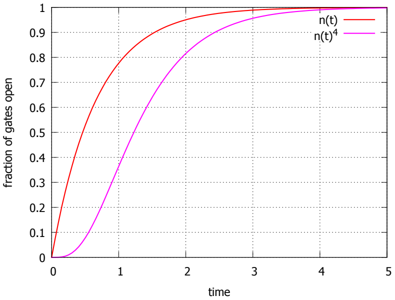
$$G(V) = n(V)^4 \times G_{max}$$

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

A Simple Model for Potassium Gates

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

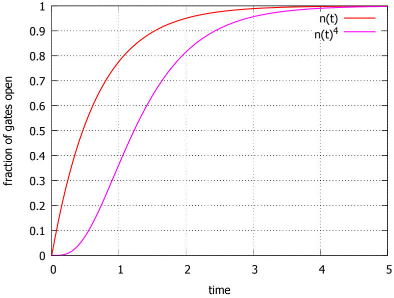
Fraction of open K^+ gates: n



A Simple Model for Potassium Gates

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

Fraction of open K^+ gates: n

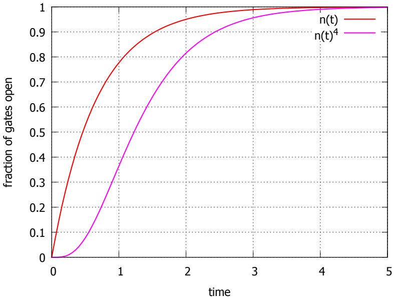


A Simple Model for Potassium Gates

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

Fraction of open K^+ gates: n

Equilibrium $\overline{n}$:
$\overline{n} = \frac{\alpha}{\alpha+\beta}$

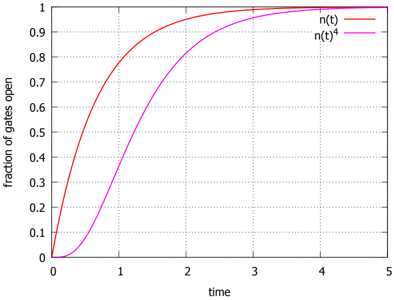


A Simple Model for Potassium Gates

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

Fraction of open K^+ gates: n

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



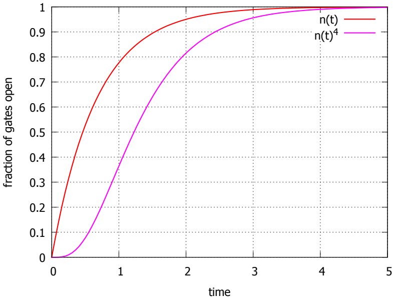
A Simple Model for Potassium Gates

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

Fraction of open K^+ gates: n

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

Time constant τ:
$\tau_n = \frac{1}{\alpha+\beta}$



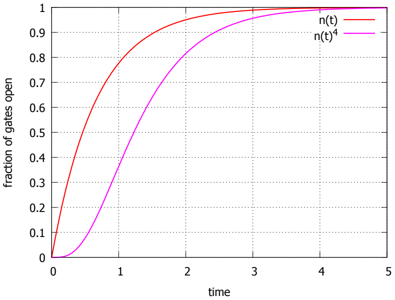
A Simple Model for Potassium Gates

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

Fraction of open K^+ gates: n

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

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



A Simple Model for Potassium Gates

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

Fraction of open K^+ gates: n

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$\overline{n} = \frac{\alpha}{\alpha+\beta}$

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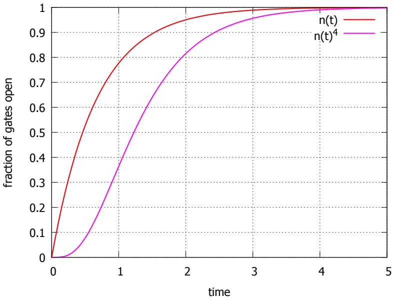


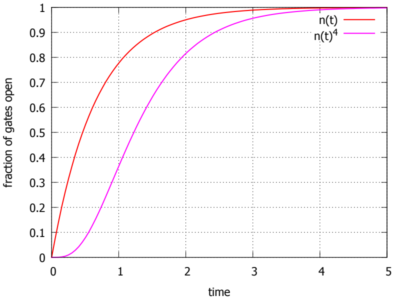
A Simple Model for Potassium Gates

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

Fraction of open K^+ gates: n

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

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



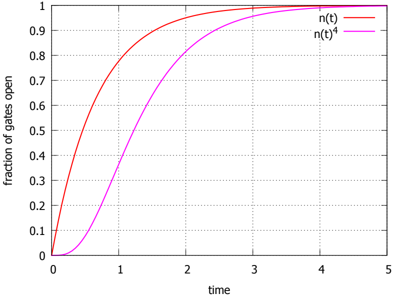
A Simple Model for Potassium Gates

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

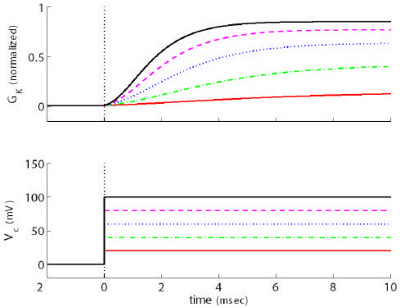
Fraction of open K^+ gates: n

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

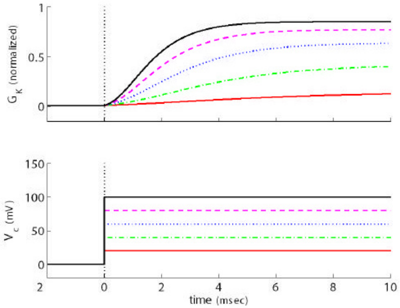
Time constant τ(V):
$\tau_n = \frac{1}{\alpha+\beta}$

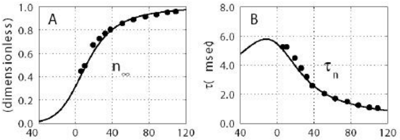


Finding $\overline{n}$, τ, α and β

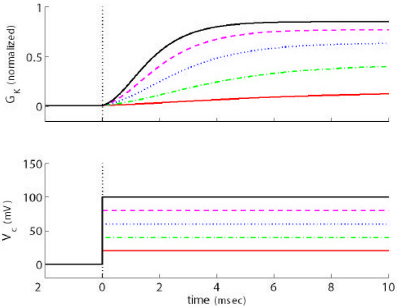


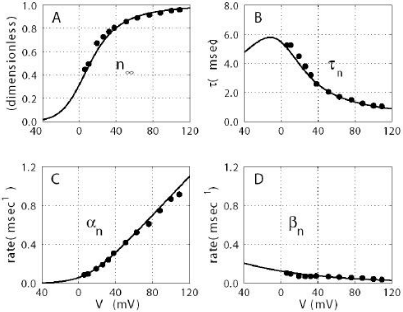
Finding $\overline{n}$, τ, α and β



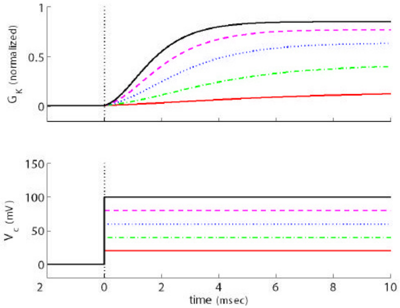


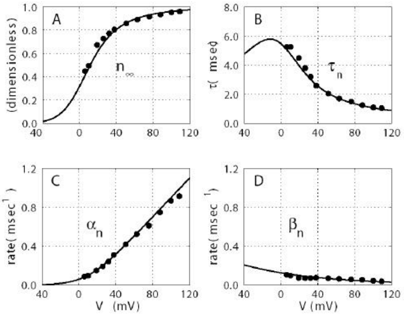
Finding $\overline{n}$, τ, α and β



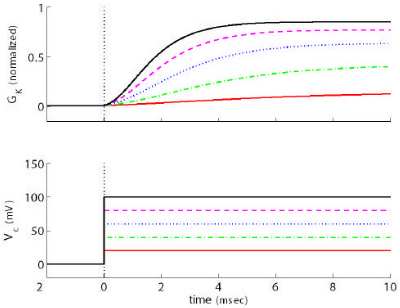


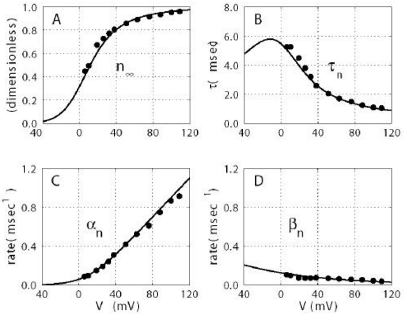
Finding $\bar{n}$, τ, α and β





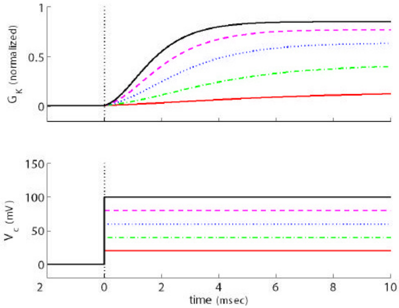
Finding $\overline{n}$, τ, α and β

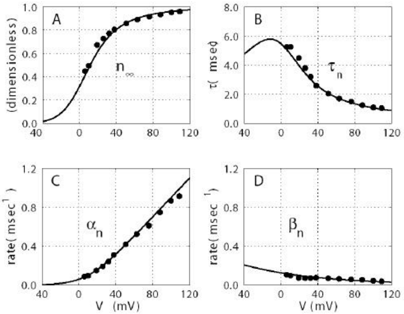




$$\alpha_n(V) = \frac{\overline{n}(V)}{\tau_n(V)}$$

Finding $\overline{n}$, τ, α and β

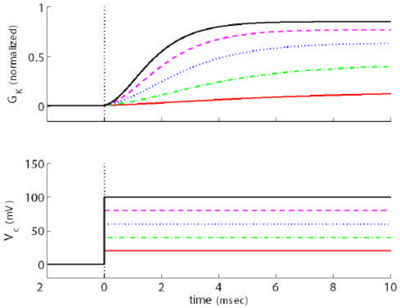


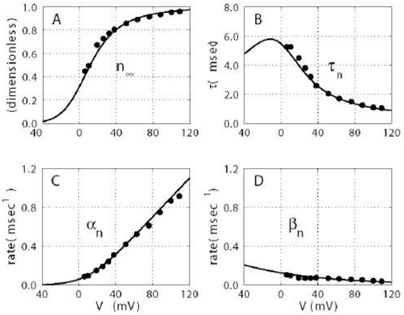


$$\alpha_n(V) = \frac{\overline{n}(V)}{\tau_n(V)}$$

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

Finding $\overline{n}$, τ, α and β





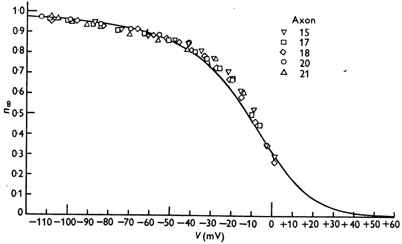
$$\alpha_n(V) = \frac{\overline{n}(V)}{\tau_n(V)}$$

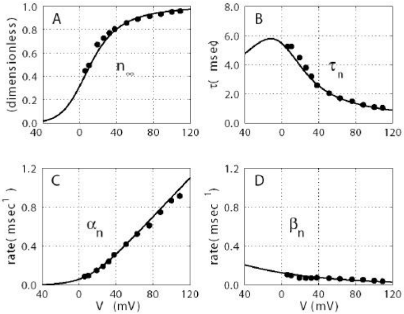
$$\beta_n(V) = \frac{1 - \overline{n}(V)}{\tau_n(V)}$$

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

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

Finding $\overline{n}$, τ, α and β





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

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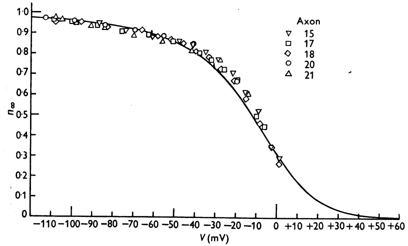
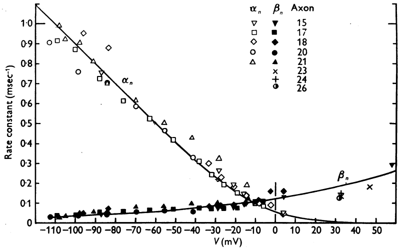
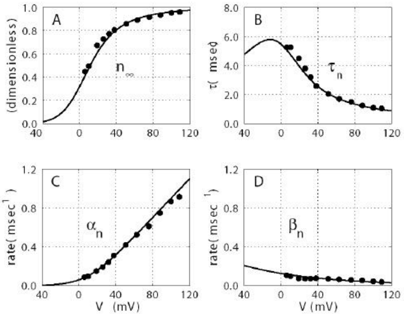
Finding $\bar{n}$, τ, α and β







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

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

A "Simple" Model for Potassium Gates

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

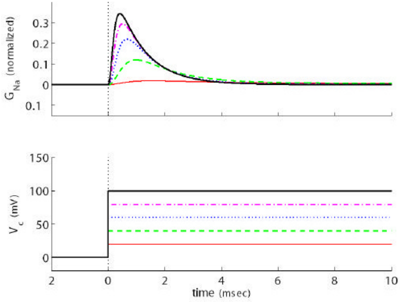
Fraction of open K^+ gates: n

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

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

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

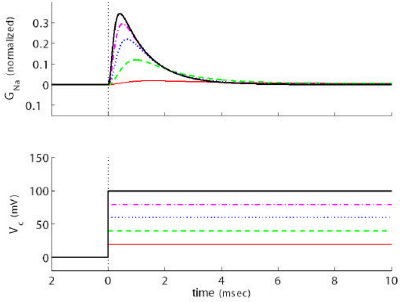
A Simple Model for Sodium Gates



$$\frac{\mathrm{d}m}{\mathrm{d}t} = \alpha_m(1-m) - \beta_m m$$

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

A Simple Model for Sodium Gates

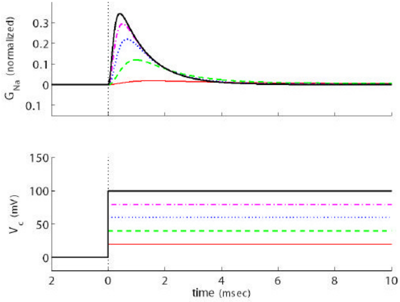


$$\frac{\mathrm{d}m}{\mathrm{d}t} = \alpha_m(1-m) - \beta_m m$$

$$\frac{\mathrm{d}h}{\mathrm{d}t} = \alpha_h(1-h) - \beta_h h$$

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

A Simple Model for Sodium Gates



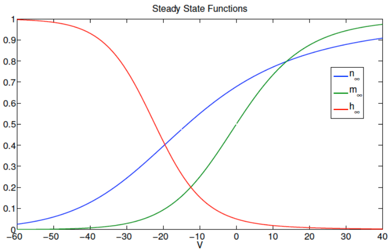
$$\frac{dm}{dt} = \alpha_m(1-m) - \beta_m m$$
$$\frac{dh}{dt} = \alpha_h(1-h) - \beta_h h$$

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 Sodium Gates



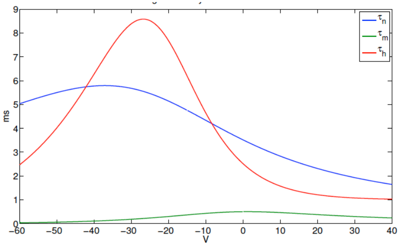
$$\frac{\mathrm{d}m}{\mathrm{d}t} = \alpha_m(1 - m) - \beta_m m$$
$$\frac{\mathrm{d}h}{\mathrm{d}t} = \alpha_h(1 - h) - \beta_h h$$

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 Sodium Gates



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

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

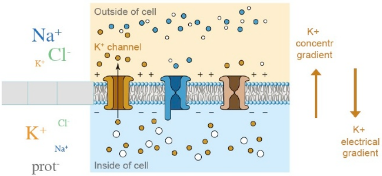
$$\frac{\mathrm{d}m}{\mathrm{d}t} = \alpha_m(1 - m) - \beta_m m$$
$$\frac{\mathrm{d}h}{\mathrm{d}t} = \alpha_h(1 - h) - \beta_h h$$

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

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

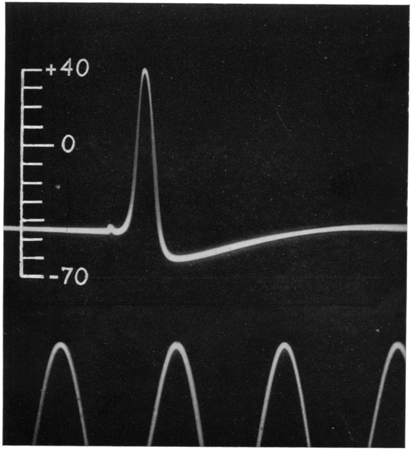
What Were We Modelling Again?

Electrochemical Equilibrium

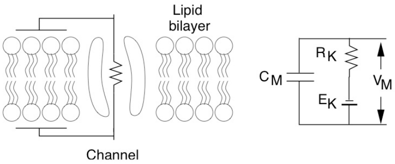


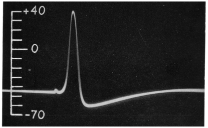
Nernst Equilibria:

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



Membrane Currents and Voltages Revisited

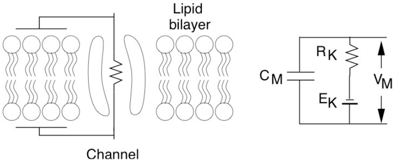


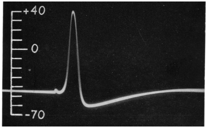


Describing the voltage:

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

Membrane Currents and Voltages Revisited





Describing the voltage:

$$
\begin{aligned}
\frac{\mathrm{d}V}{\mathrm{d}t} &= \frac{1}{C} \times G \times V \\
&= \frac{1}{C} \times (I_{K^+} + I_{Na^+} + I_R)
\end{aligned}
$$

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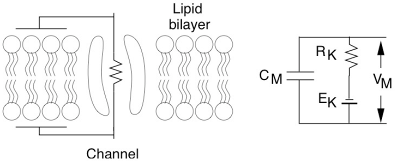

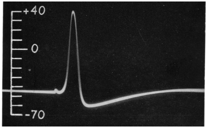

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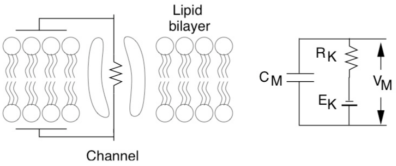
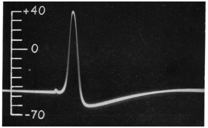
\end{aligned}
$$

Membrane Currents and Voltages Revisited





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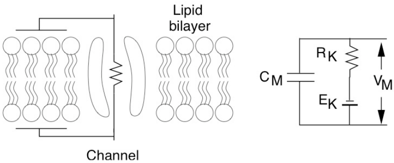

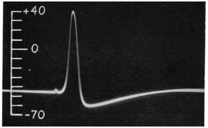

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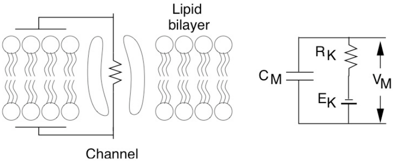
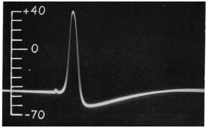
Membrane Currents and Voltages Revisited





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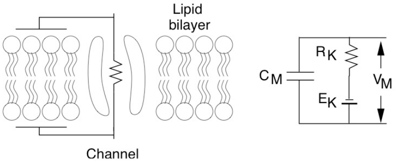
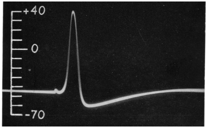
Membrane Currents and Voltages Revisited





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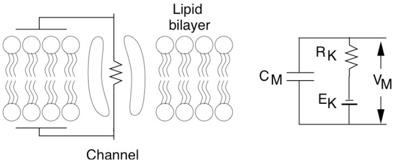
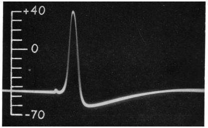
Membrane Currents and Voltages Revisited





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with

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

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

$$G_K = n^4 G_{K\,max}$$

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

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

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

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

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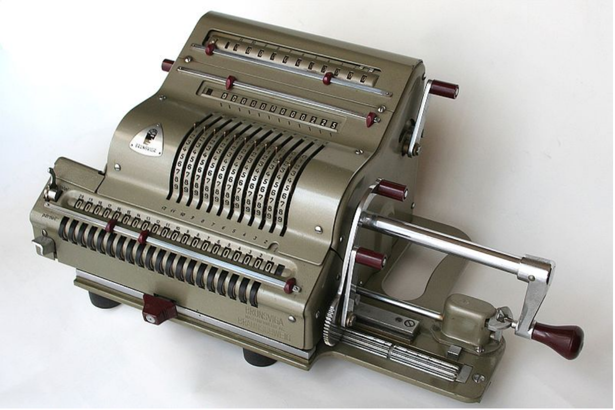
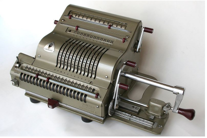
But, how to test all this?

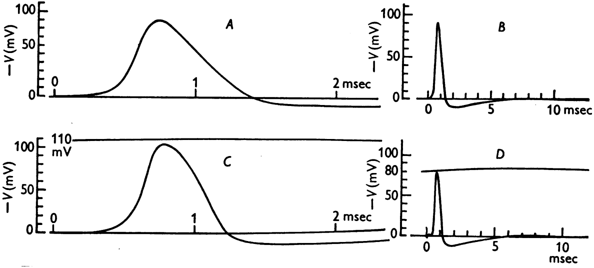
Please Wait, Calculating...



Brunsviga 20 — “Brains of Steel”

Please Wait, Calculating...



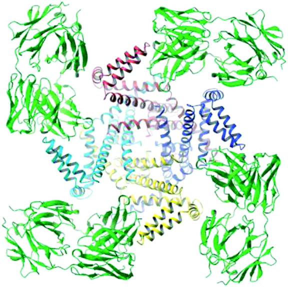


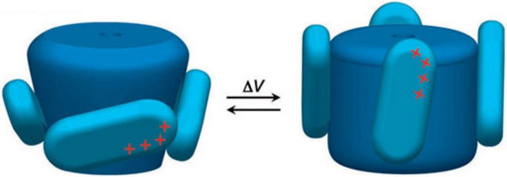
1963: Nobel Prize!

NERVE-CELL ENIGMA SOLVED

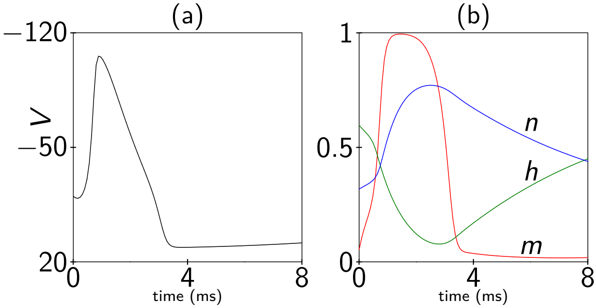
The British scientists, A. L. Hodgkin and A. F. Huxley, experimenting with the nerve fibers of squids and lobsters.

2003: Prediction Confirmed!





2014: Running it in GRIND



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

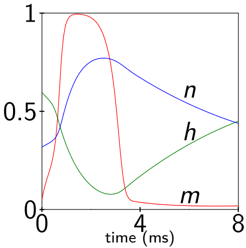
Note that in the original model, rest potential is 0 mV and AP is -90 mV

Simplifying the model

Quasi Steady State assumption

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

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



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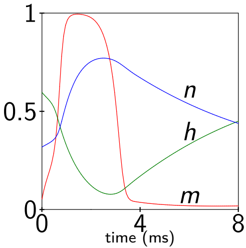
Conservation assumption

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

$$n = 0.91 - h$$



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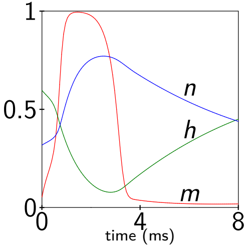
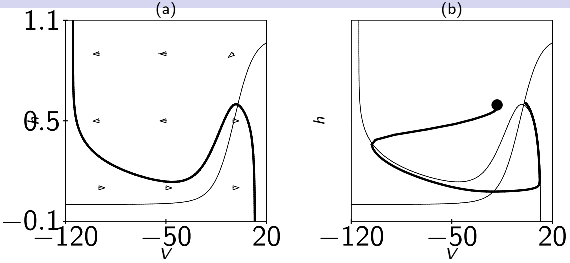


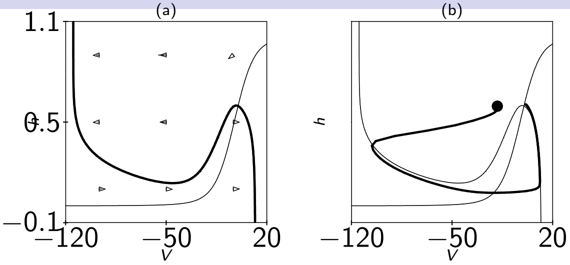
This reduces the model to 2 variables: V and h!

Nullclines and Phase space



thin line: h nullcline
heavy line: V nullcline

Nullclines and Phase space



thin line: h nullcline
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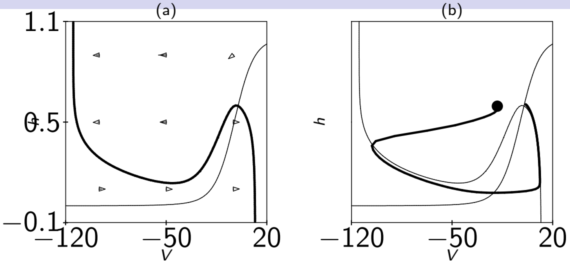
- Stable equilibrium

Nullclines and Phase space



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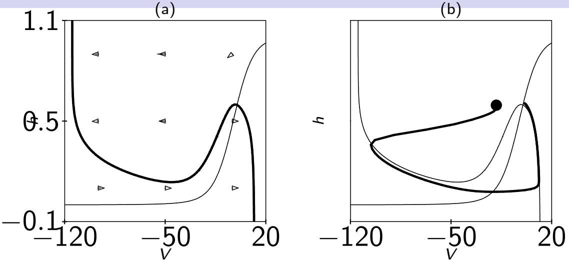
Nullclines and Phase space



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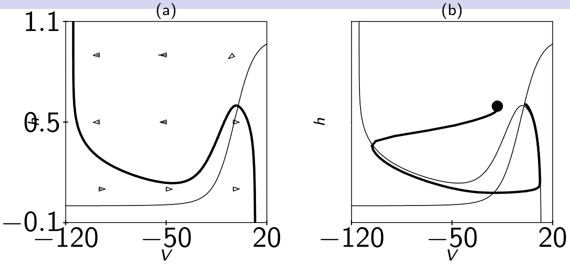

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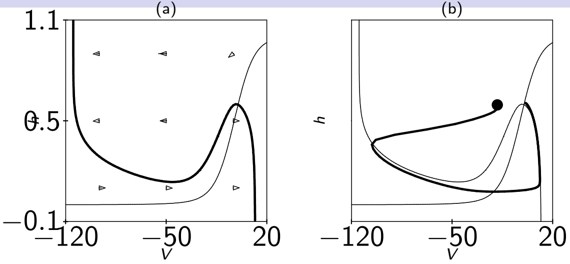

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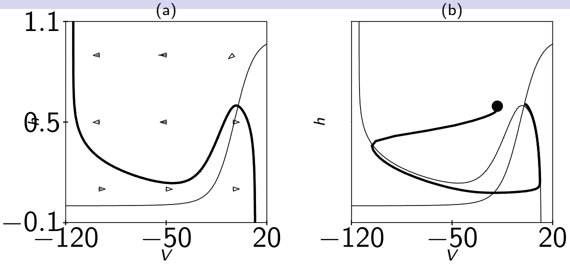
- Recovery of the *h*-gates also takes time, causing refractory period

Nullclines and Phase space



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- Stable equilibrium
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- 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

$$G_K = (0.91 - h)^4 G_{K\,max}$$
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Can't we do this simpler?

Yes We Can: The FitzHugh-Nagumo Model

$$\begin{cases} \frac{\mathrm{d}V}{\mathrm{d}t} = -V(V-a)(V-1) - W \\ \frac{\mathrm{d}W}{\mathrm{d}t} = \epsilon(V - bW) \end{cases}$$

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- Not mechanistic, but a phenomenological model

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- V is voltage, W causes inactivation, refractoriness

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- The $\frac{\mathrm{d}V}{\mathrm{d}t} = 0$ nullcline is a cubic function: $W = -V(V-a)(V-1)$

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$$\begin{cases} \frac{\mathrm{d}V}{\mathrm{d}t} = -V(V-a)(V-1) - W \\ \frac{\mathrm{d}W}{\mathrm{d}t} = \epsilon(V - bW) \end{cases}$$

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- The $\frac{\mathrm{d}W}{\mathrm{d}t} = 0$ nullcline is a straight line: $W = \frac{1}{b}V$
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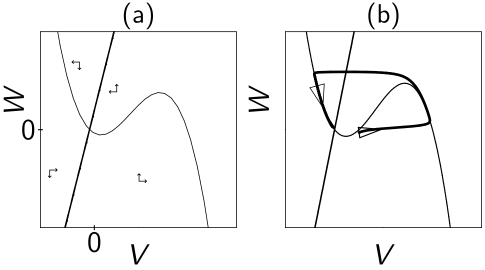
- The V-nullcline intersects the V-axis at: $V = 0$, $V = a$ and $V = 1$

FitzHugh-Nagumo: What Does It Look Like?



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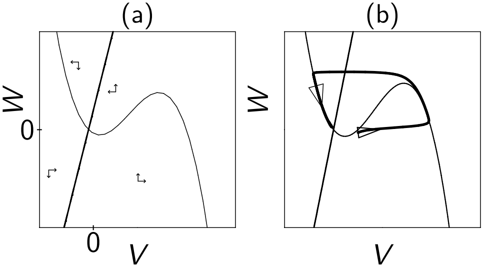

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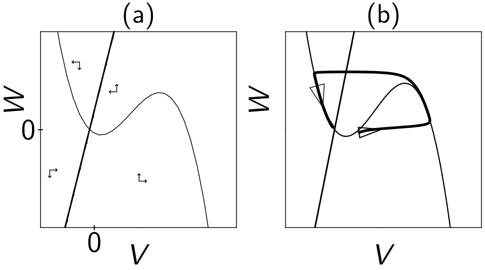

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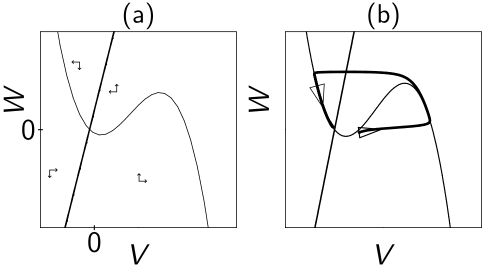

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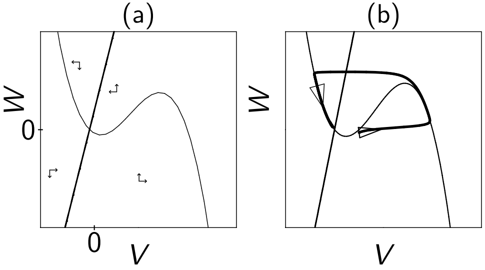

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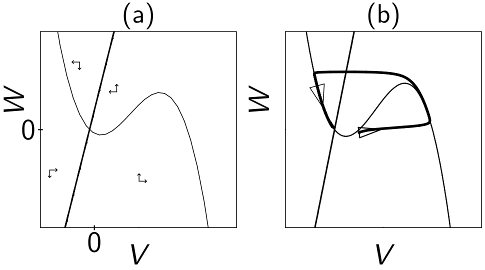

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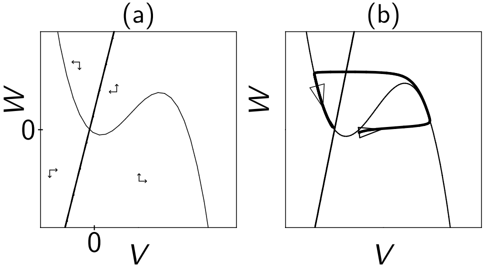

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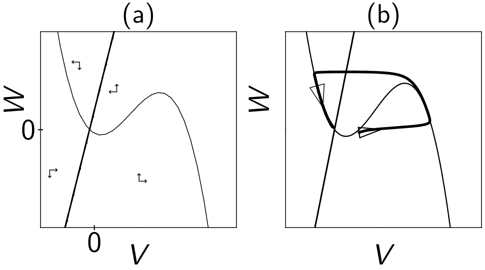

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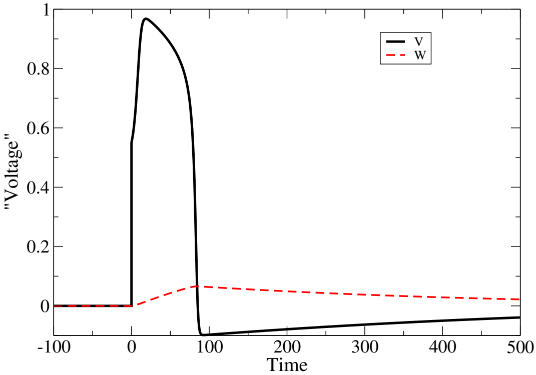
- The voltage V changes much faster than the variable W

FitzHugh-Nagumo: Behavior in time



Behavior of V resembles an action potential.

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

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Hodgkin-Huxley model

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- The model *predicted* voltage sensitive, time dependent transmembrane protein channels, long before they were found!

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- Slow W-variable represses fast V-variable, and ensures refractoriness