Computational Modeling of the Cardiovascular System

Electrophysiological Modeling of Membranes and Ion Channels

CVRTI

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Overview

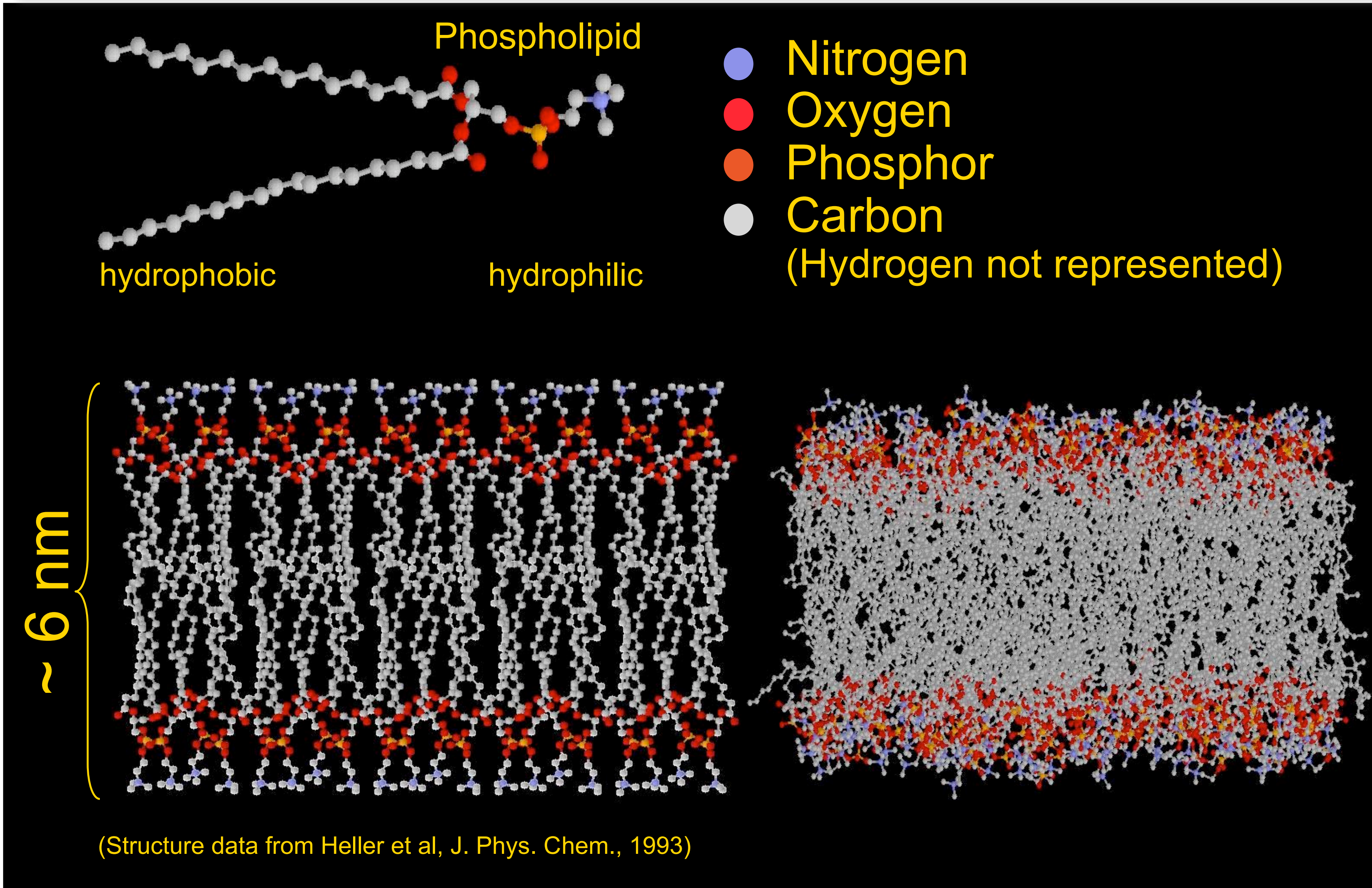
- Membranes
  - Resistor-Capacitor Model
  - Equations of Nernst and Goldman-Hodgkin-Katz
  - Squid Axon Model

Group work & pause

- Channel Modeling
  - Structure
  - Experimental Studies
  - Markov Modeling
- Numerical Methods

Group work

Molecular Structure of Phospholipid Bilayers

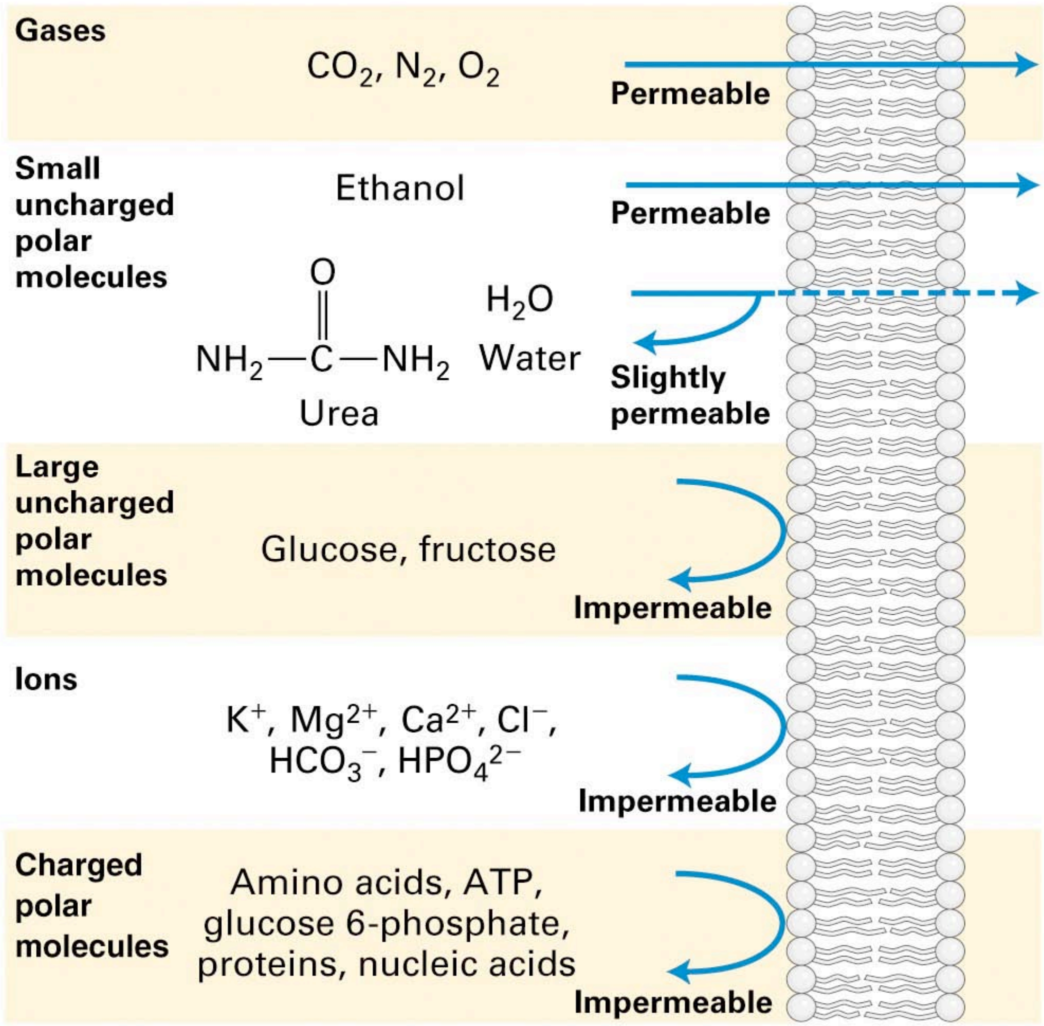


Phospholipid Bilayers

- Plasma membrane
- Membrane of organelle

Selective permeability

Transmembrane proteins responsible for transport:
- Ion Channels
- Pumps
- Exchangers



(Lodish et al., Molecular Cell Biology, Fig. 7-1, 2004)

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Modeling of Membrane: Resistor-Capacitor Circuit

$$C_m = \frac{Q}{V_m}$$

C_m : membrance capacity $[F]$

Q : electrical charge $[As]$

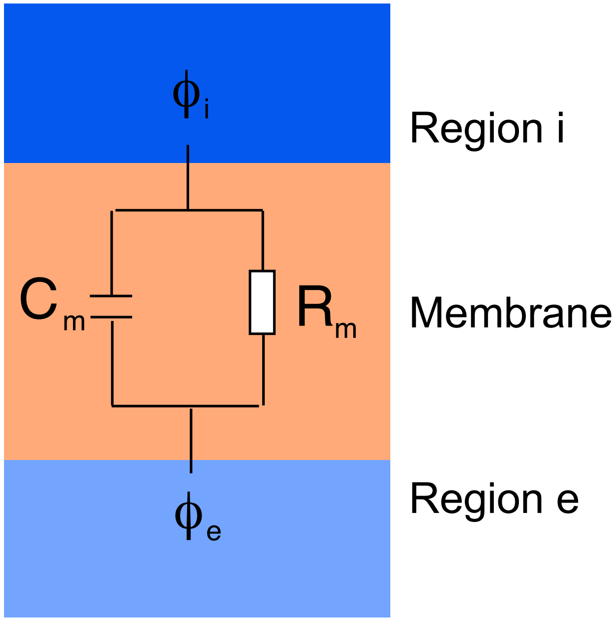
$V_m = \phi_i - \phi_e$: voltage over membrane $[V]$

$$\frac{d}{dt} V_m = \frac{d}{dt} \frac{Q}{C_m} = \frac{I_m}{C_m}$$

I_m : Current through membrane $[A]$

$$R_m = -\frac{V_m}{I_m}$$

R_m : Resistance of membrane $[\Omega]$



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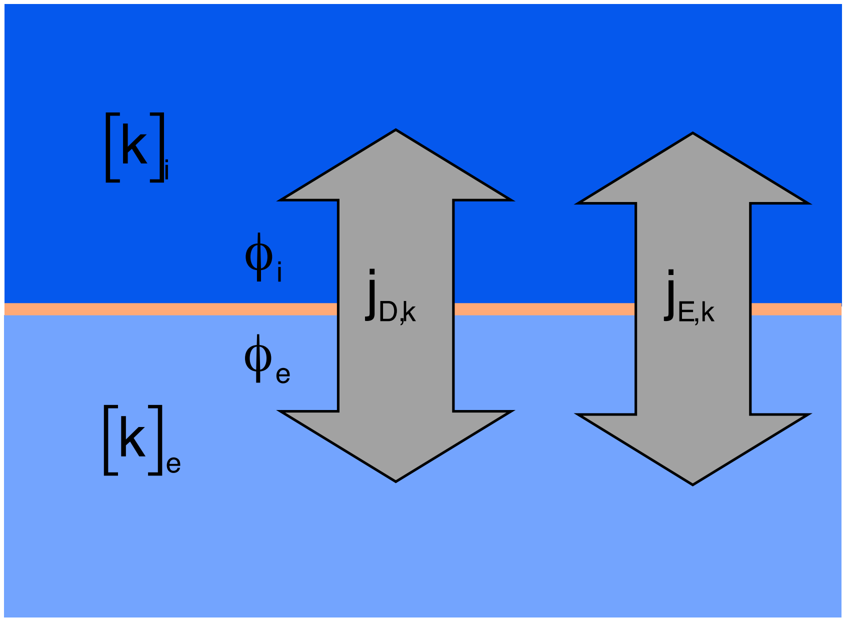
Modeling of Membrane: Nernst Equation



Region i

Membrane
- permeable for ion type k
- homogeneous, planar, infinite

Region e

$[k]_i$: Concentration of k in region i

$[k]_e$: Concentration of k in region e

ϕ_i : Potential in region i

ϕ_e : Potential in region e

$j_{D,k}$: Ionic current by diffusion

$j_{E,k}$: Ionic current by electrical forces

Modeling of Membrane: Nernst Potential

In Equilibrium

Malmivuo, Plonsey 3.2.3

$$j_{E,k} + j_{D,k} = 0$$

$$V_{m,k} = \phi_i - \phi_e = -\frac{R\,T}{z_k\,F} \ln \frac{[k]_i}{[k]_e}$$

k : Ion type

$V_{m,k}$: Nernst potential $[V]$

R : Gas constant [J/mol/K]

T : Absolute temperature $[K]$

z_k : Valence

F : Faraday's constant $[C/mol]$

$[k]_i$: intracellular concentration of ion type k $[M]$

$[k]_e$: extracellular concentration of ion type k $[M]$

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Modeling of Membrane: Nernst Equation - Example

Nernst equation explains measured transmembrane voltage of animal and plant cells

For potassium (monovalent cation) at temperatures of 37ºC:

$$V_{m,K} = -\frac{310K}{+1}\frac{R}{F}\ln\frac{[K]_i}{[K]_o} = -61mV\log\frac{[K]_i}{[K]_e}$$

For typical intra- and extracellular concentrations:

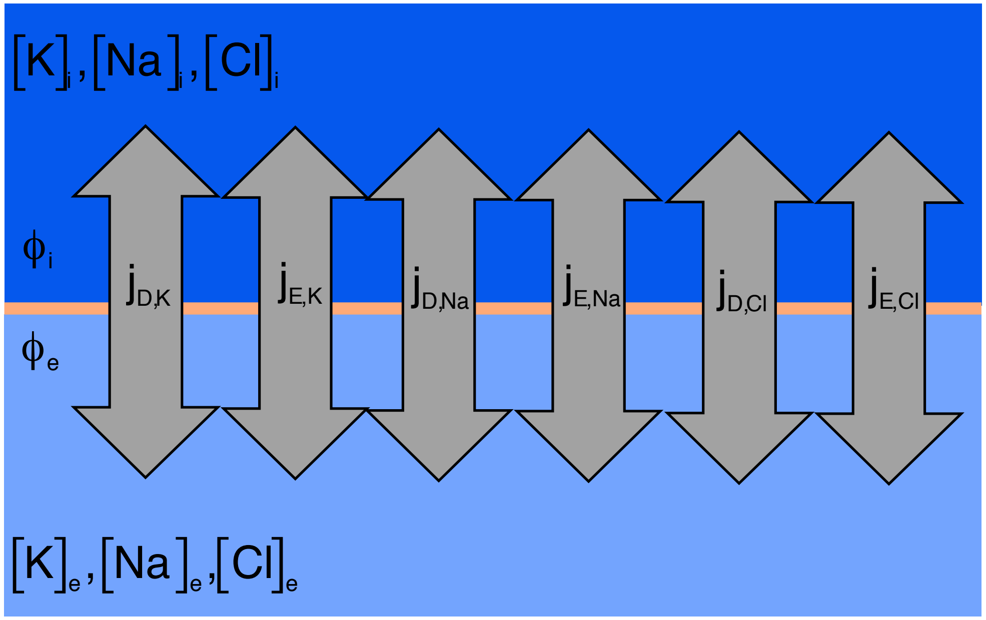
$[K]_i = 150$ mM

$[K]_e = 5.5$ mM

$$V_{m,K} = -88mV$$

Commonly, several types of ions are contributing to transmembrane voltage!

Modeling of Membrane: Goldman-Hodgkin-Katz Equation



Region i

Membrane
- permeable for Na, K, Cl ions
- homogeneous, planar, infinite

Region e

$[Na]_i, [K]_i, [Cl]_i$: Concentration in region i

ϕ_i : Potential in region i

$j_{D,Na}, j_{D,K}, j_{D,Cl}$: Ionic current by diffusion

$[Na]_e, [K]_e, [Cl]_e$: Concentration in region e

ϕ_e : Potential in region e

$j_{E,Na}, j_{E,K}, j_{E,Cl}$: Ionic current by electrical forces

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Modeling of Membrane: Goldman-Hodgkin-Katz Equation

$$V_m = \phi_i - \phi_e = -\frac{RT}{F} \ln \frac{P_K[K]_i + P_{Na}[Na]_i + P_{Cl}[Cl]_e}{P_K[K]_e + P_{Na}[Na]_e + P_{Cl}[Cl]_i}$$

V_m : Equilibrium voltage over membrane $[V]$

R : Gas constant $[J/mol/K]$

T : Absolute Temperature $[K]$

F : Faraday constant $[C/mol]$

$[K]_i,[Na]_i,[Cl]_i$: Intracellular concentrations $[M]$

$[K]_e,[Na]_e,[Cl]_e$: Extracellular concentrations $[M]$

P_K, P_{Na}, P_{Cl} : Permeabilites $[cm/s]$

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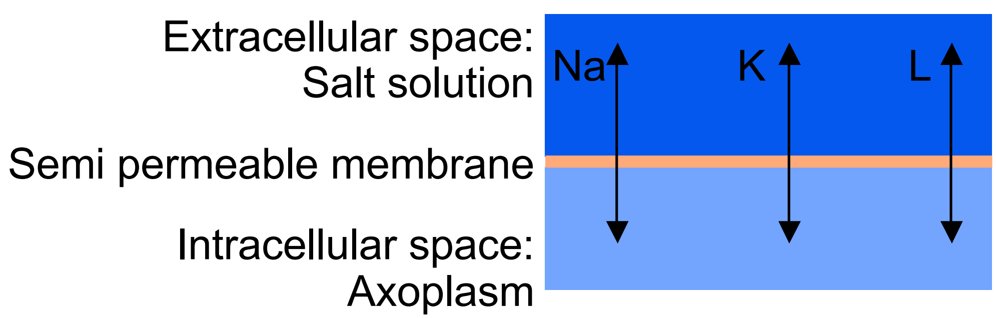
Hodgkin and Huxley: Measurements

Measurement and mathematical modeling of electrophysiological properties of cell membrane (published 1952, Nobel prize 1963)

“Giant” axon from squid with ~0.5 mm diameter

Techniques
- Space clamp
- Voltage clamp

Simplifications:



Na:	Sodium ions
K:	Potassium ions
L:	Other ions (primarily chlorine)

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Hodgkin-Huxley: Clamp Techniques

- **Space Clamp**
  Electrophysiological properties are independent of x

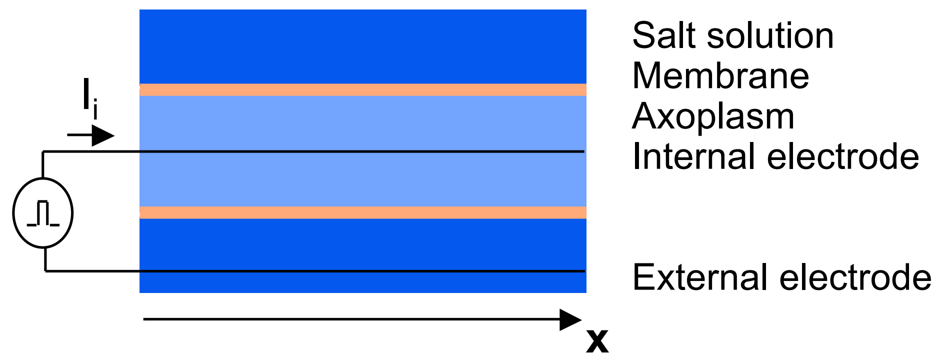
$$I_m = I_i + C_m \frac{d}{dt} V_m$$

I_i : Injected current $[A]$

I_m : Current through membrane $[A]$

C_m : Membrane capacitor $[F]$

V_m : Membrane voltage $[V]$



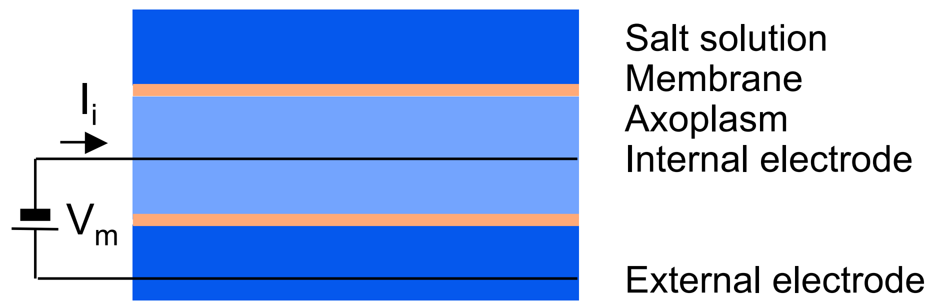
- **Voltage Clamp**
  Voltage V_m is kept constant by injection of current I_i

  ➡

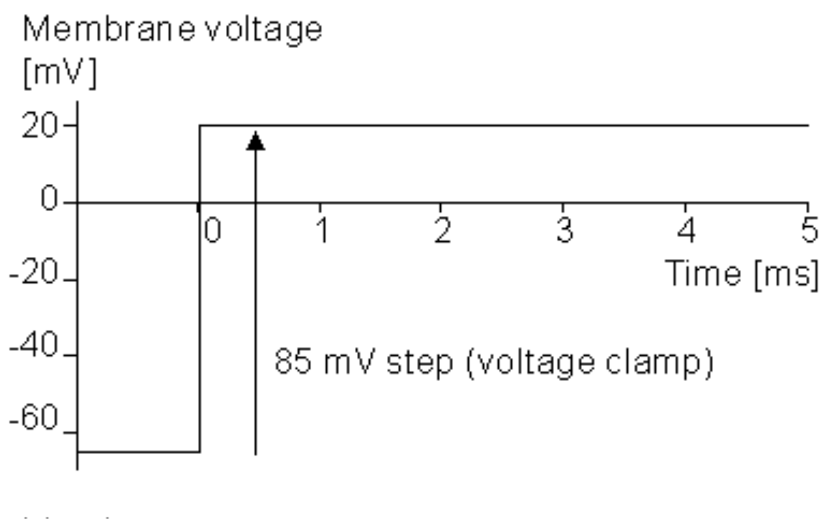
  neglect of capacitive currents

  ➡

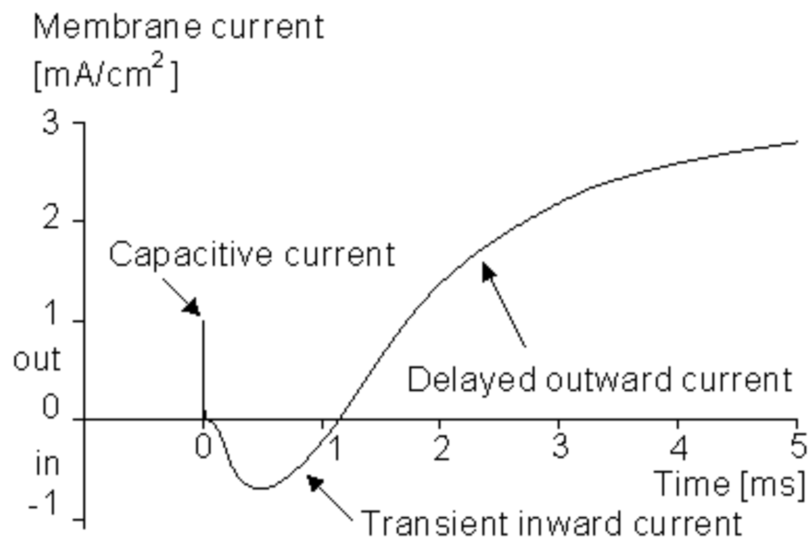
  $I_m = I_I$



Hodgkin-Huxley: Voltage clamping

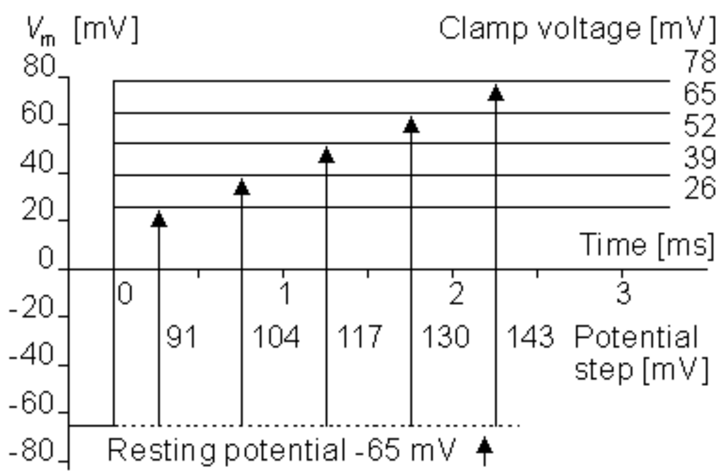


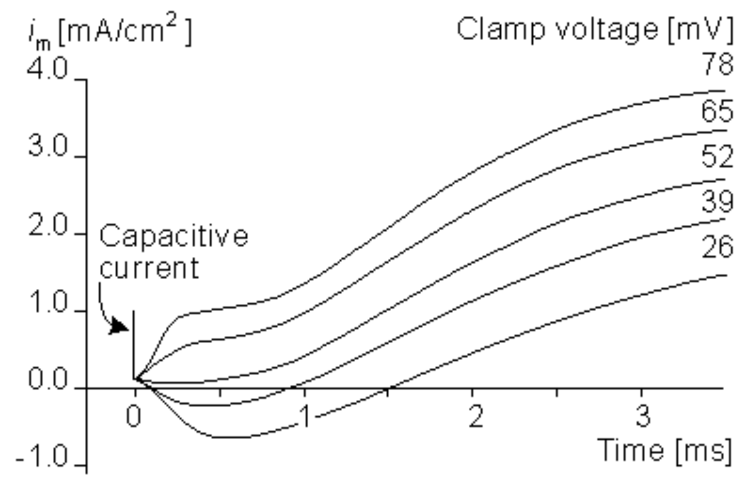
Clamped voltage



Measured current

Hodgkin-Huxley: Measurement Protocols

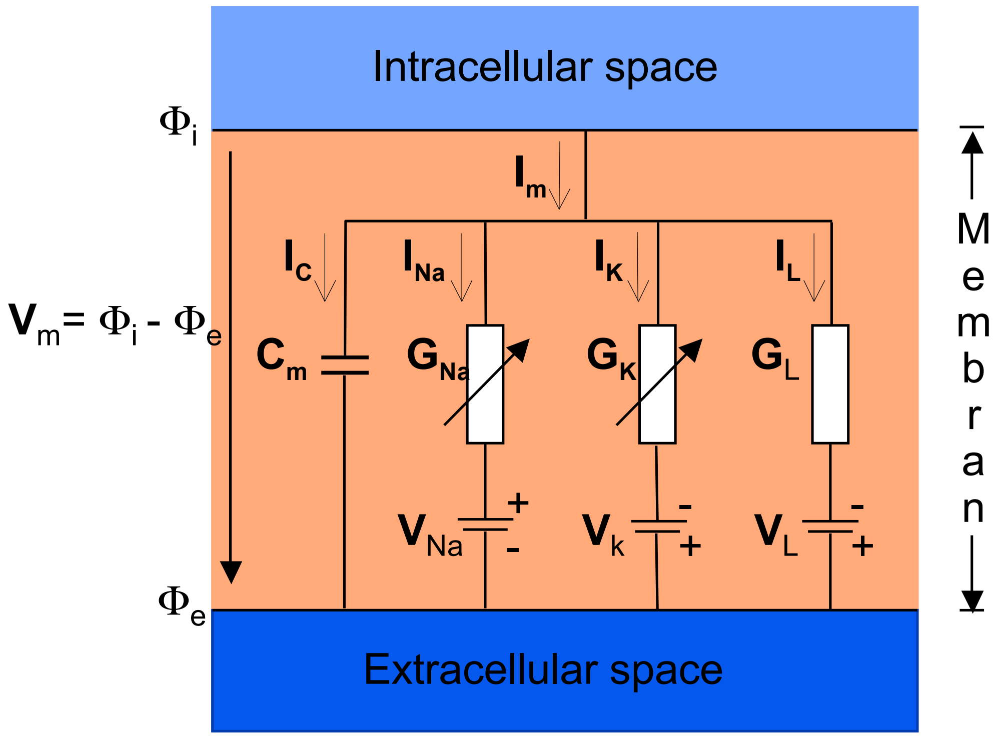




Protocols

Variation of clamped voltages
Extraction of parameters from measured curves, e.g. peak current
Substitution of ions in intra- and extracellular space
(Curve fitting for modeling)

Hodgkin-Huxley Model: Equivalent Circuit Diagram



$$I_m = C_m \frac{dV_m}{dt} + (V_m - V_{Na})G_{Na} + (V_m - V_K)G_K + (V_m - V_L)G_L$$

G_{Na}, G_K, G_L
Membrane conductivity of Na, K and other ions [S/cm^2]

I_{Na}, I_K, I_L
Currents of Na, K and other ions [mA/cm^2]

V_{Na}, V_K, V_L
Nernst voltages of Na, K and other ions [mV]

C_m , I_m , V_m
Membrane capacitor [F/cm^2], current [mA /cm^2] and voltage [mV]

Hodgkin-Huxley Model: Principles

Ohm's law:

$$G_{Na} = \frac{I_{Na}}{V_{Na}} \quad G_K = \frac{I_K}{V_K} \quad G_{Na} = \frac{I_L}{V_L}$$

Nernst voltages for correction!

$$G_{Na} = \frac{I_{Na}}{V_m - V_{Na}} \quad G_K = \frac{I_K}{V_m - V_K} \quad G_{Na} = \frac{I_L}{V_m - V_L}$$

Hodgkin-Huxley Model: Constants

Voltages are related to resting voltage V_r
Conductivity and capacitance are related to membrane area

Relative Na voltage	$V_r - V_{Na}$	-115	mV
Relative K voltage	$V_r - V_k$	12	mV
Relative voltage of other ions	$V_r - V_L$	-10.6	mV
Membrane capacitance	C_m	1	$\mu F/cm^2$
Maximal conductivity of Na	$G_{Na\ max}$	120	mS/cm^2
Maximal conductivity von K	$G_{K\ max}$	36	mS/cm^2
Conductivity for other ions	G_L	0.3	mS/cm^2

} All ion channels open (applies to $G_{Na\ max}$ and $G_{K\ max}$)

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Hodgkin-Huxley Model: ODEs Describe Conductivities

$$G_{Na} = G_{Na\,max} m^3 h \qquad \frac{dm}{dt} = \alpha_m (1-m) - \beta_m m$$

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

} Sodium current

$$G_K = G_{K\,max} n^4 \qquad \frac{dn}{dt} = \alpha_n (1-n) - \beta_n n$$

} Potassium current

$$G_L = const$$

} Current by other ions

$$\alpha_m = \frac{0.1(25-V')}{e^{0.1(25-V')}-1}\frac{1}{ms} \qquad \beta_m = \frac{4}{e^{V'/18}}\frac{1}{ms}$$

$$\alpha_h = \frac{0.07}{e^{V'/20}}\frac{1}{ms} \qquad \beta_h = \frac{1}{e^{0.1(30-V')}+1}\frac{1}{ms}$$

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

Voltage and time-dependent

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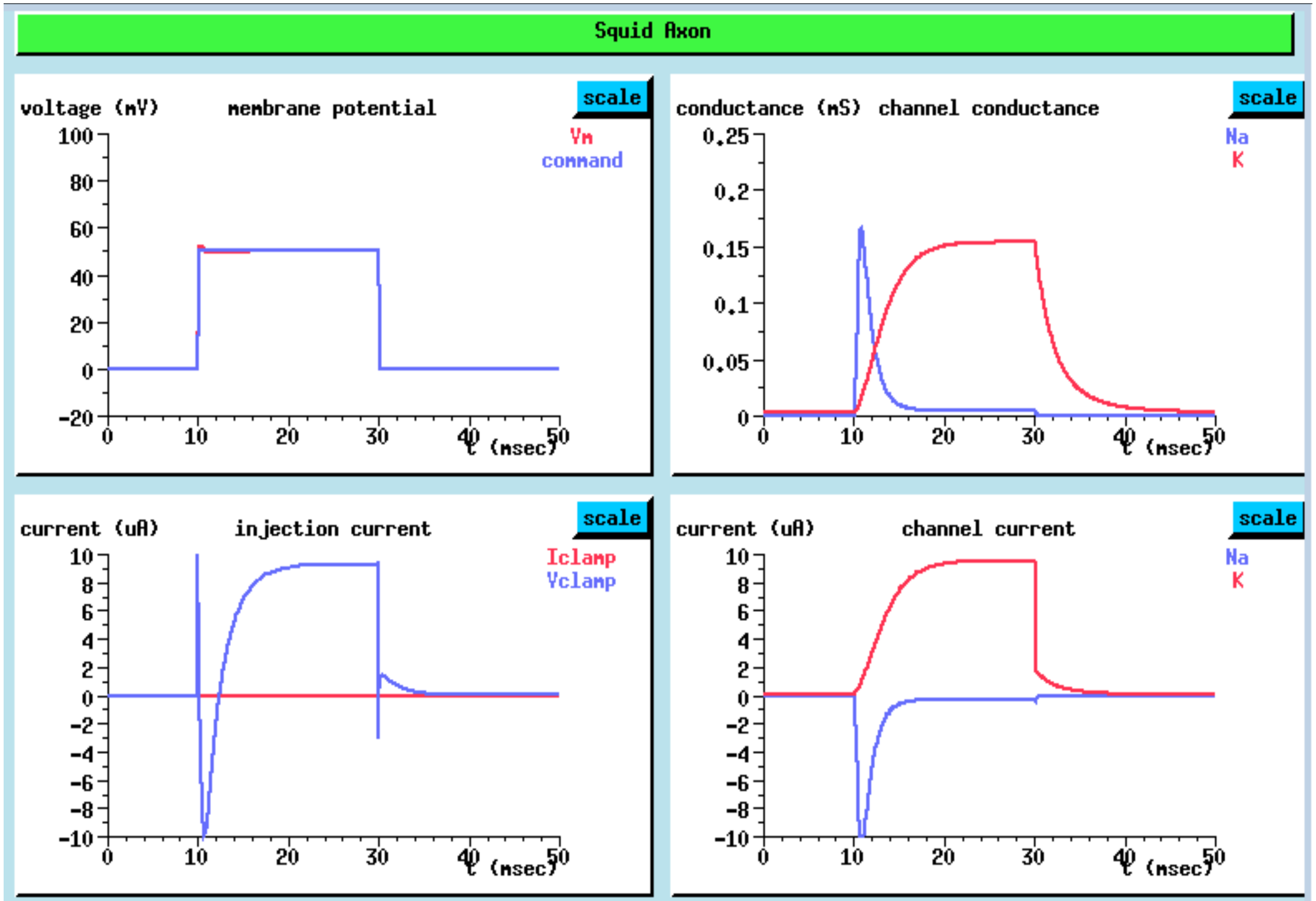
Hodgkin-Huxley Model: Simulation of Voltage Clamp Measurements

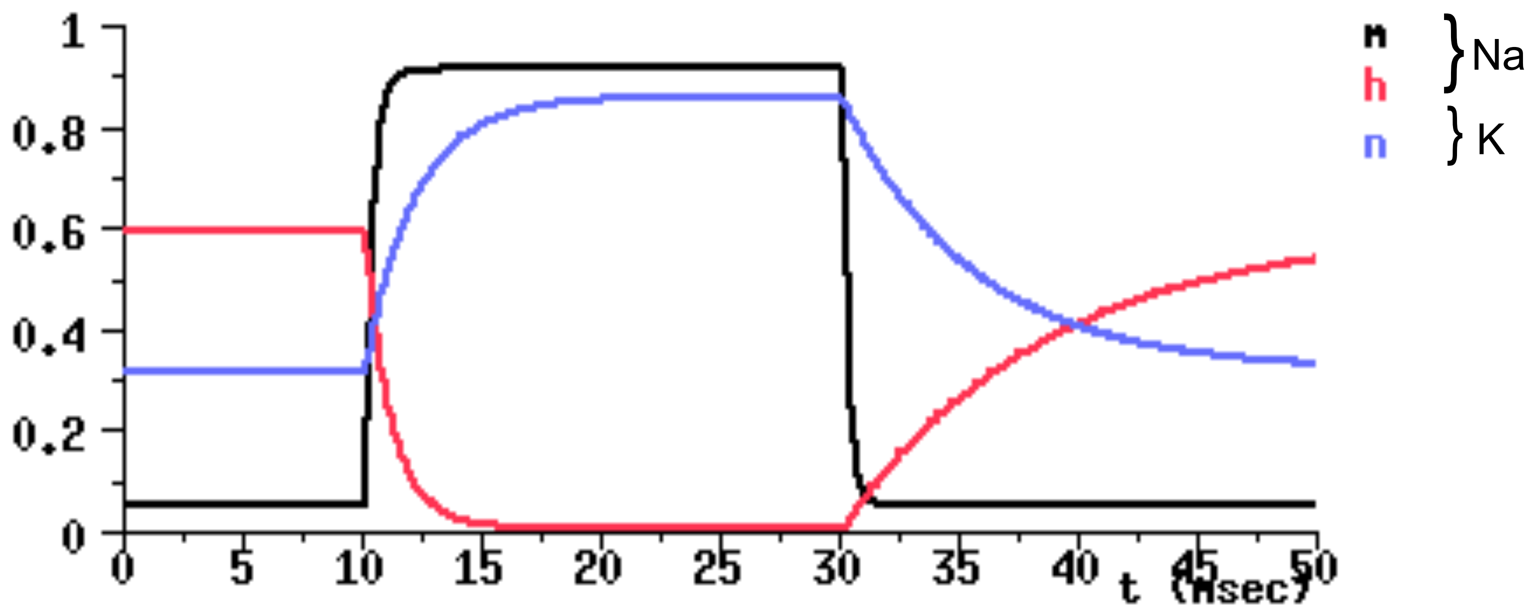


http://www.bbb.caltech.edu/GENESIS

Hodgkin-Huxley Model: Simulation of Voltage Clamp Measurements

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

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



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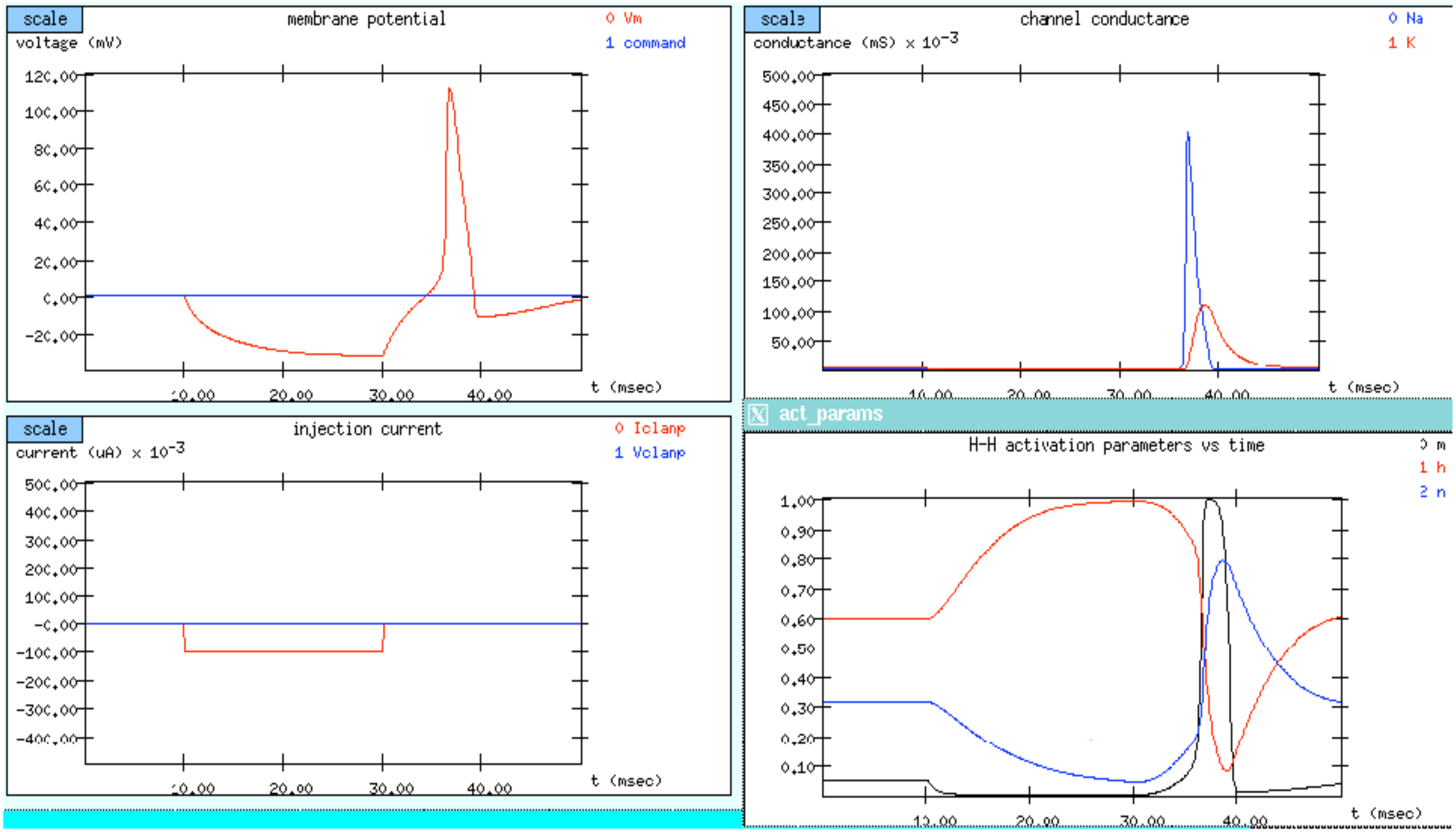
Hodgkin-Huxley Model: Activation by Hyperpolarization



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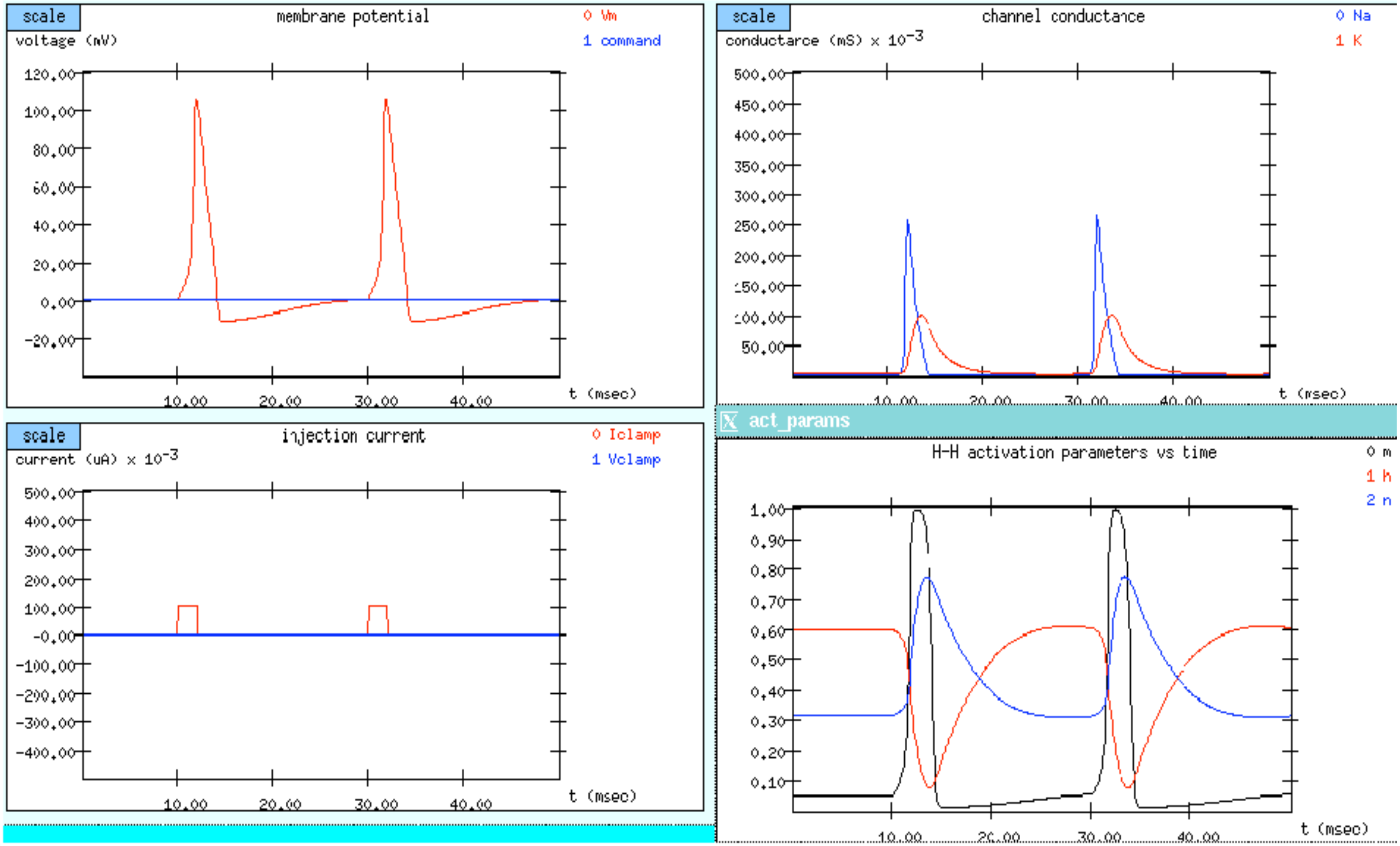
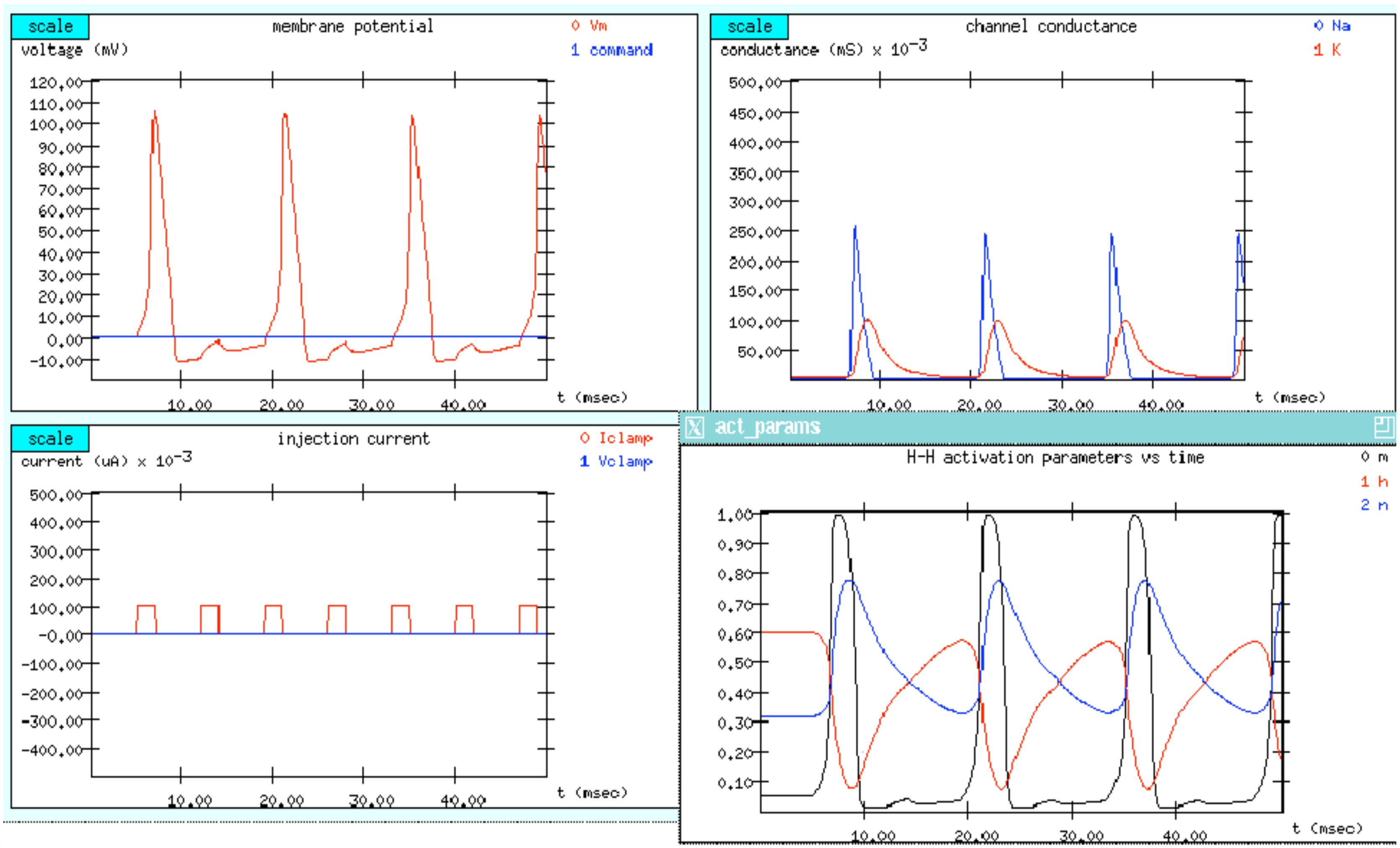
Hodgkin-Huxley Model: Stimulus After Refractory Period



Hodgkin-Huxley: Stimulus During Refractory Period



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Group Work

Sodium channels allow fast upstroke of action potentials of neurons and myocytes.

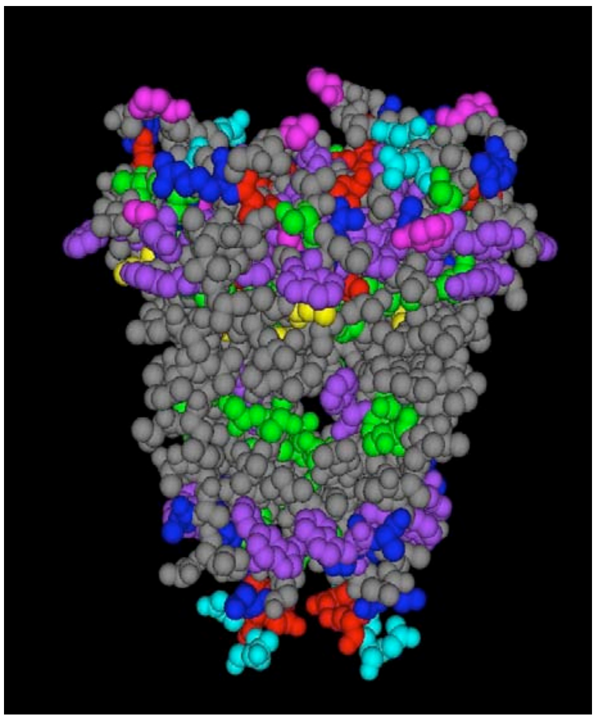
Speculate why fast voltage-dependent inactivation of these channels might be important.

Molecular Structure of Ion Channels

Transmembrane proteins: connexons, **ion channels**, pumps and exchangers

Example: Molecular structure of potassium channel Kcsa of bacterium streptomyces lividans, color-coded amino acids
Structure data from Molecular Modeling Database, NIH, USA

~ 6 nm



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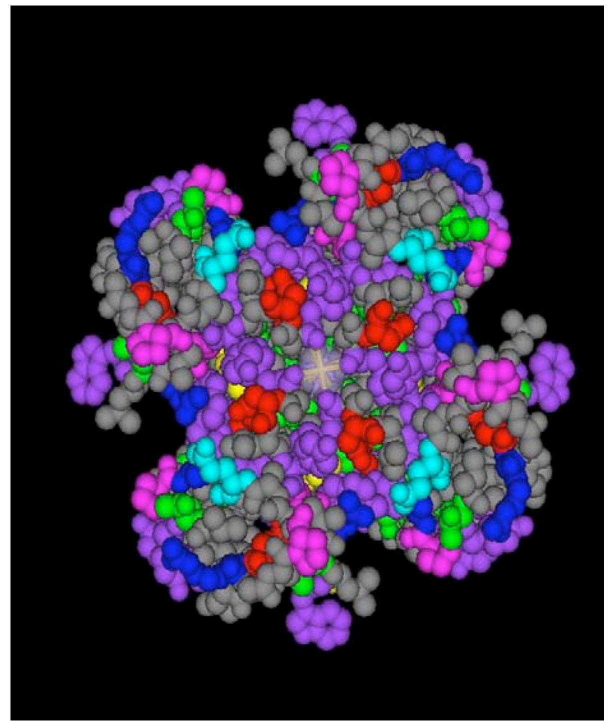

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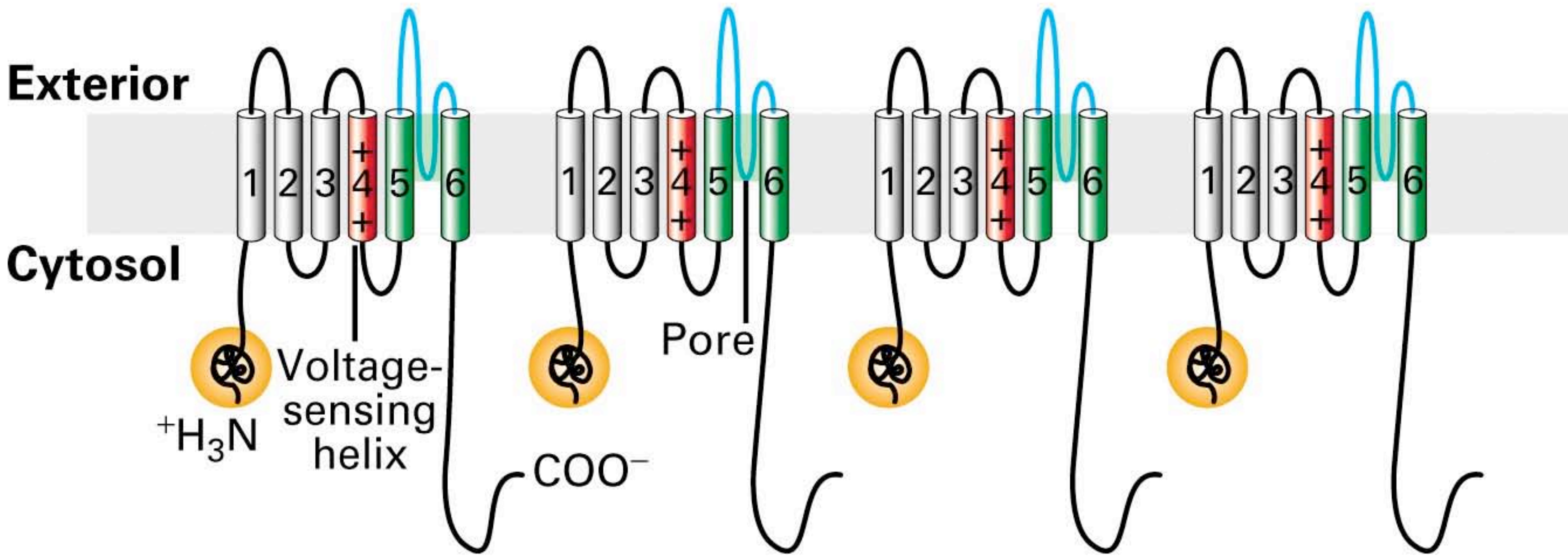
Schematic Depiction of Voltage-Gated K^+ Channel (Tetramer)



(Lodish et al., Molecular Cell Biology, Fig. 7-36a, 2004)

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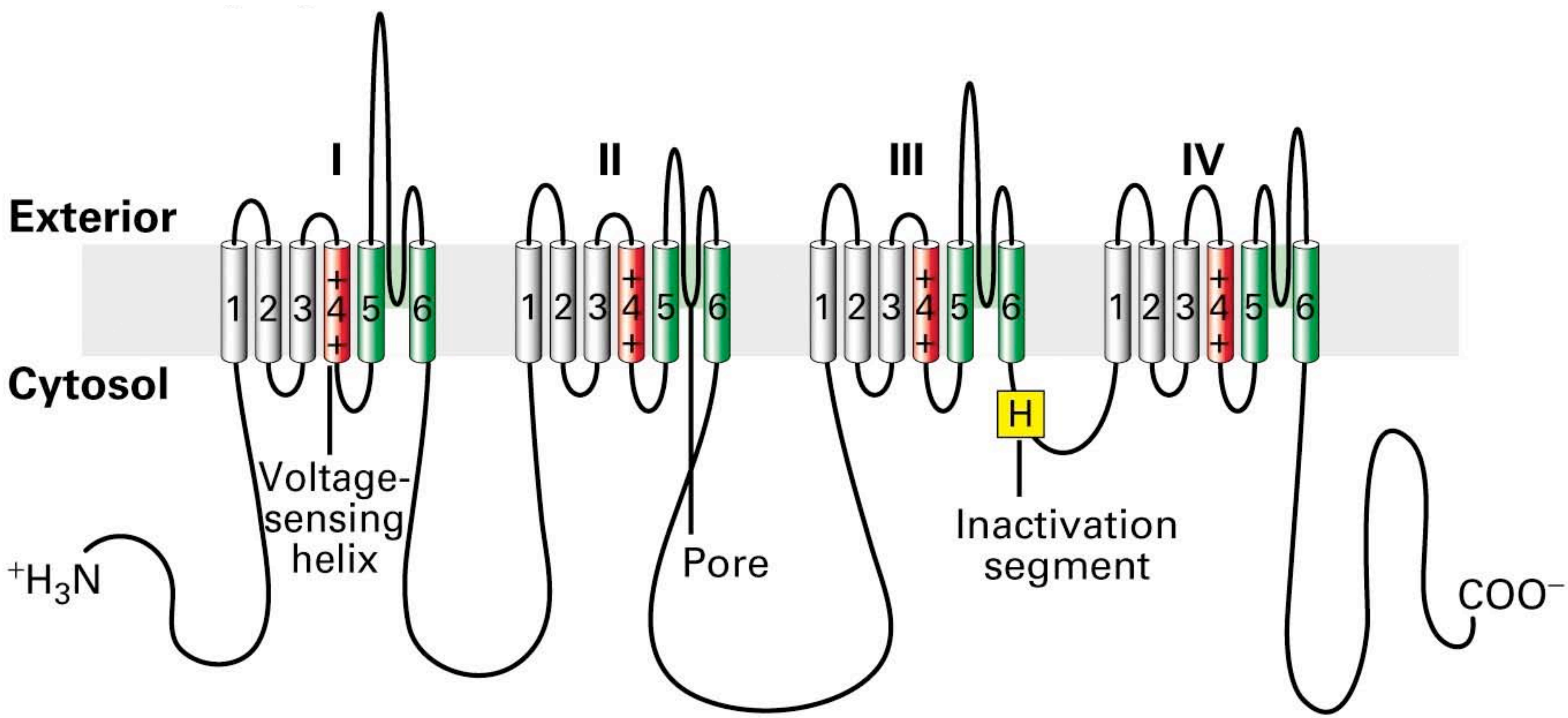
Schematic Depiction of Voltage-Gated Na^{+}/Ca^{2+} Channel (Monomer)



(Lodish et al., Molecular Cell Biology, Fig. 7-36b, 2004)

Experimental Studies: Patch Clamp Techniques

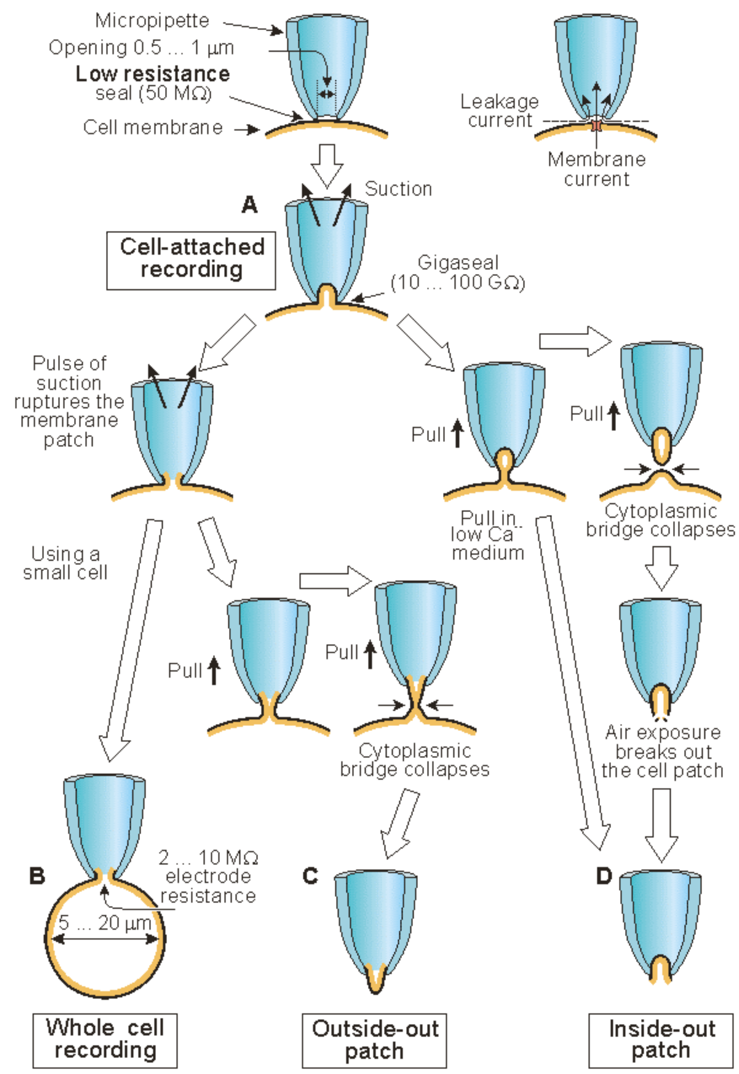
Measurement technique developed by Neher, Sakmann et al.
(published 1976, Nobel prize 1991)

Micropipettes
- heat polished fluid filled glass pipette
- diameter of opening: 0.5-1 µm

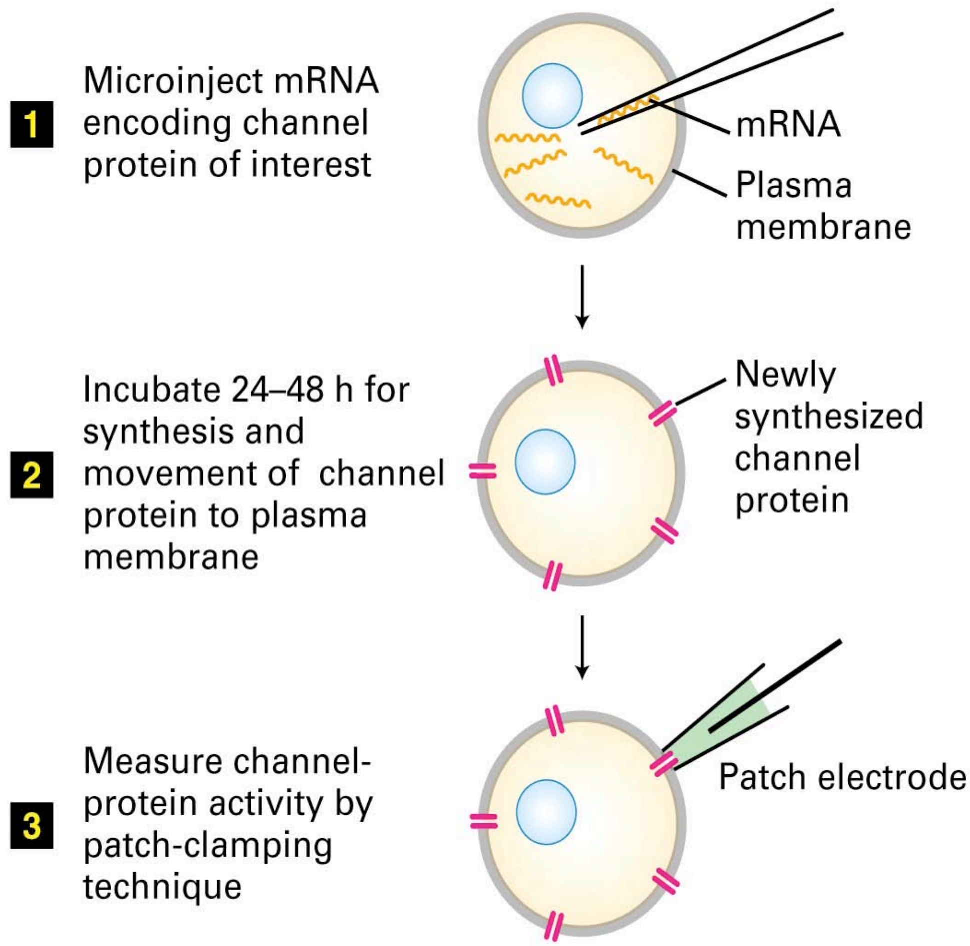
Major configurations
- Cell attached recording
- Whole cell recording
- Outside-out patch
- Inside-out patch

Measurement of single ion channels possible!

Commonly, signals have small signal-to-noise ratios

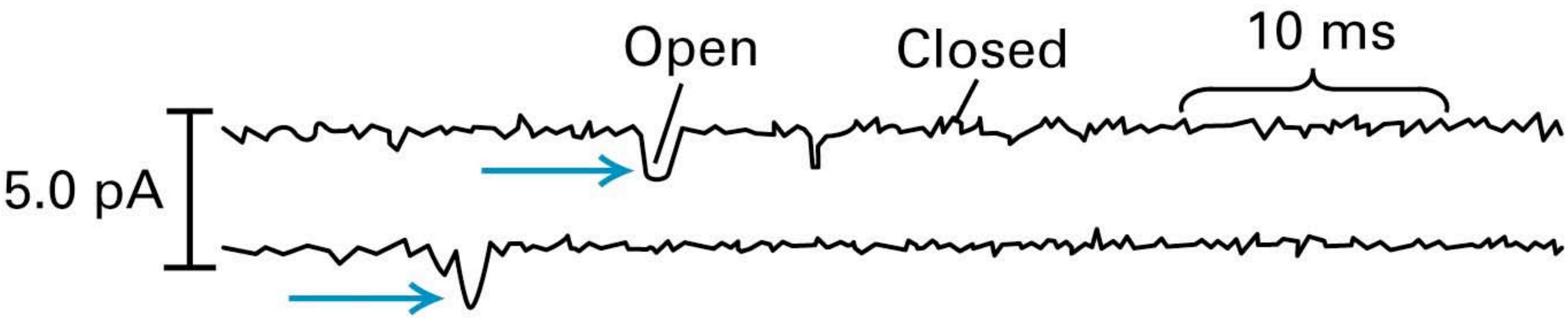


Channel Characterization in Oocyte Expression Array



(Lodish et al., Molecular Cell Biology, Fig. 7-19, 2004)

Currents Through Single Ion Channel



Current traces of patch with single sodium channel

Average current per channel: 1.6 pA ~ 9900 ions/ms

Inside-out patch

(Lodish et al., Molecular Cell Biology, Fig. 7-18, 2004)

Currents Through Ion Channels

Current traces of patch with 2 potassium channels at different voltages

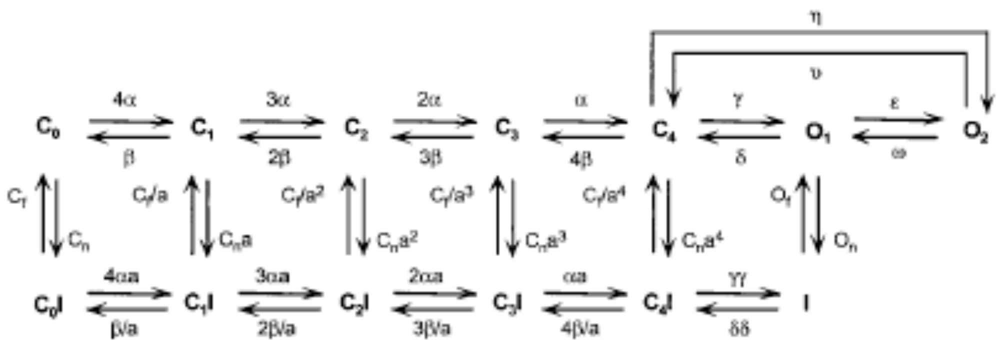
Transmembrane voltages determine

- open probability
- open time
- current amplitude

(Lodish et al., Molecular Cell Biology, Fig. 7-34, 2004)

Markov Modeling of Ion Channels and Mutations

Markov models allow
- reconstruction of single channel behavior
- to be based upon thermodynamic principals
- assignment of physical meaning to rate constants



Example: State diagram of cardiac sodium channel model
O: Open, I: Inactivated, C: Closed

(Irvine et al. Biophys J. 1999)

- Markov models consist of sets of 1st order ODEs
- Commonly, one channel description of a "traditional" Hodgkin-Huxley type cell model is substituted by an appropriate Markov model
- Recently, the inclusion of Markov models in newly developed cell models increased

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2-State Markov Model

$$\frac{dO}{dt} = \alpha\, C - \beta\, O$$

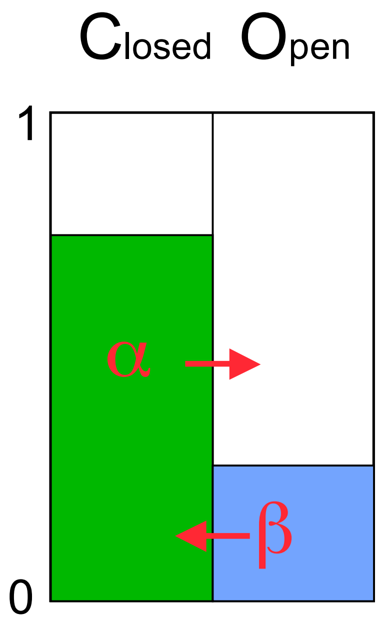
$$\frac{dC}{dt} = \beta\, O - \alpha\, C$$

O : Probability of channel is in open state

C : Probability of channel is in closed state

α, β : Rate coefficients.

Function of e.g. V_m and ion concentration



Exemplary Rate Coefficient Functions

$\alpha = \alpha_0$	Constant
$\alpha = \alpha_0 V_m + a$	Linear
$\alpha = \alpha_0 e^{V_m / a}$	Exponential
$\alpha = \dfrac{\alpha_0}{e^{-(V_m - V_a)/a} + 1}$	Sigmoid
$\alpha = \alpha_0 \dfrac{V_m - V_a}{e^{-(V_m - V_a)/a} - 1}$	Linear for extreme case

α_0, V_a, a : Parameters

V_m : Membrane voltage

Calculation of Membrane Currents: Variants

$$I_{chan} = N\,G\,O\,(V_m - E_{ion})$$

Nernst approach

$$I_{chan} = N\,O\,I_{ion}$$

$$I_{ion} = P\,z^2 \frac{F^2 V_m}{RT} \frac{[ion]_i - [ion]_o e^{-z F V_m / RT}}{1 - e^{-z F V_m / RT}}$$

Goldman – Hodgkin – Katz current equations

G : Conductivity of single channel

O : Open probability of channels

N : Number of channels

V_m : Membrane voltage

P : Membrane permeability for ion

$[ion]_i$, $[ion]_o$: Concentration of ion in intra- and extracellular space

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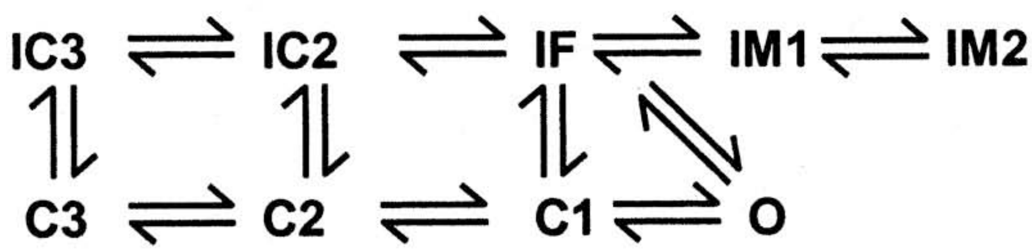
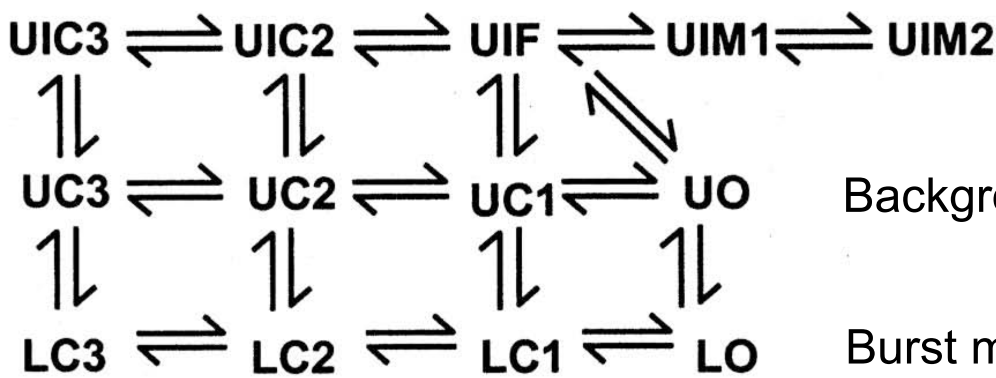
Markov Models for WT and 1795insD Cardiac Na Channels

Wild-type Na channel



1795insD Na channel



Background mode (normal)

Burst mode (pathological)

(Clancy and Rudy. Circulation 2002;105:1208-1213)

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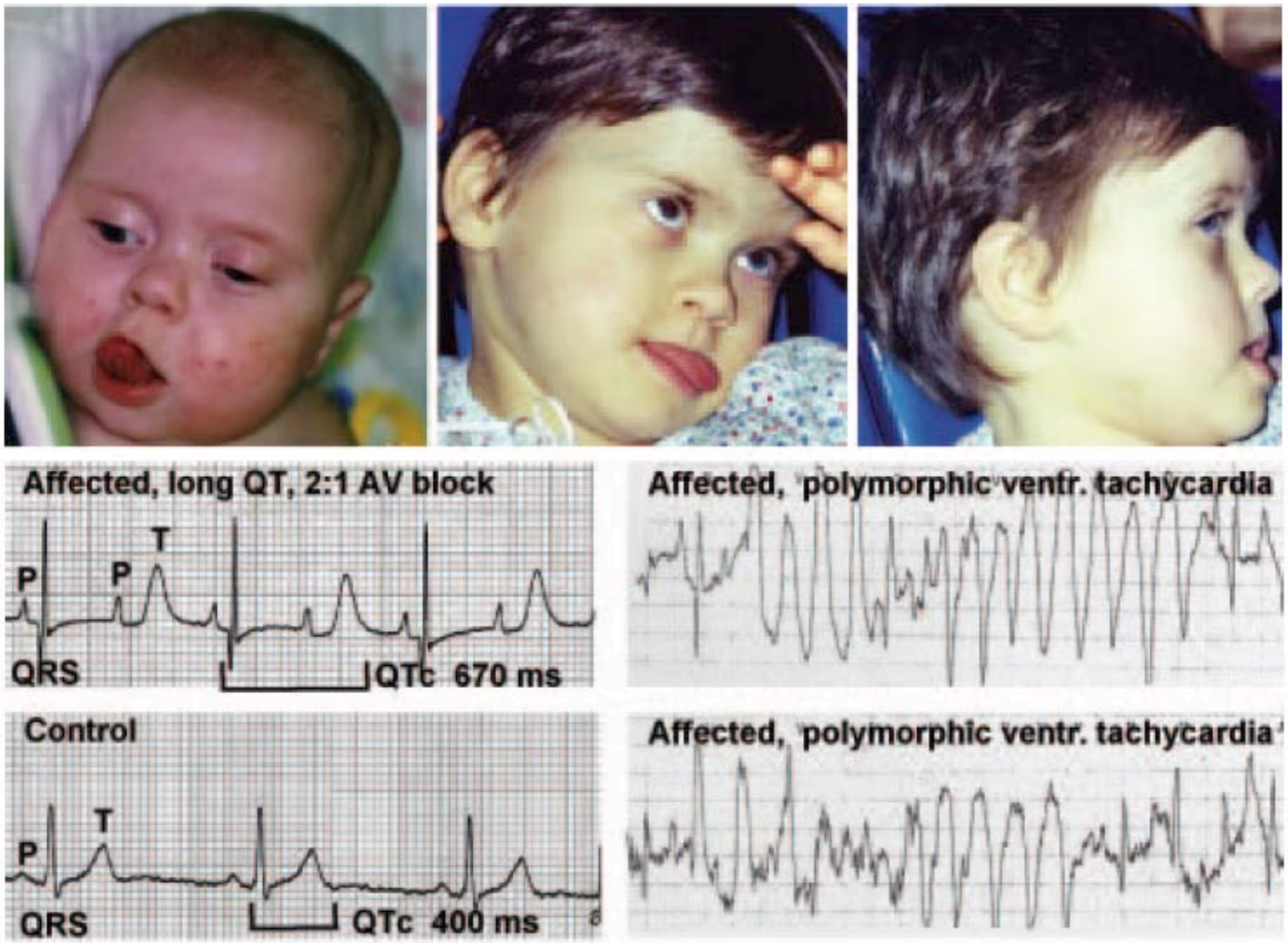
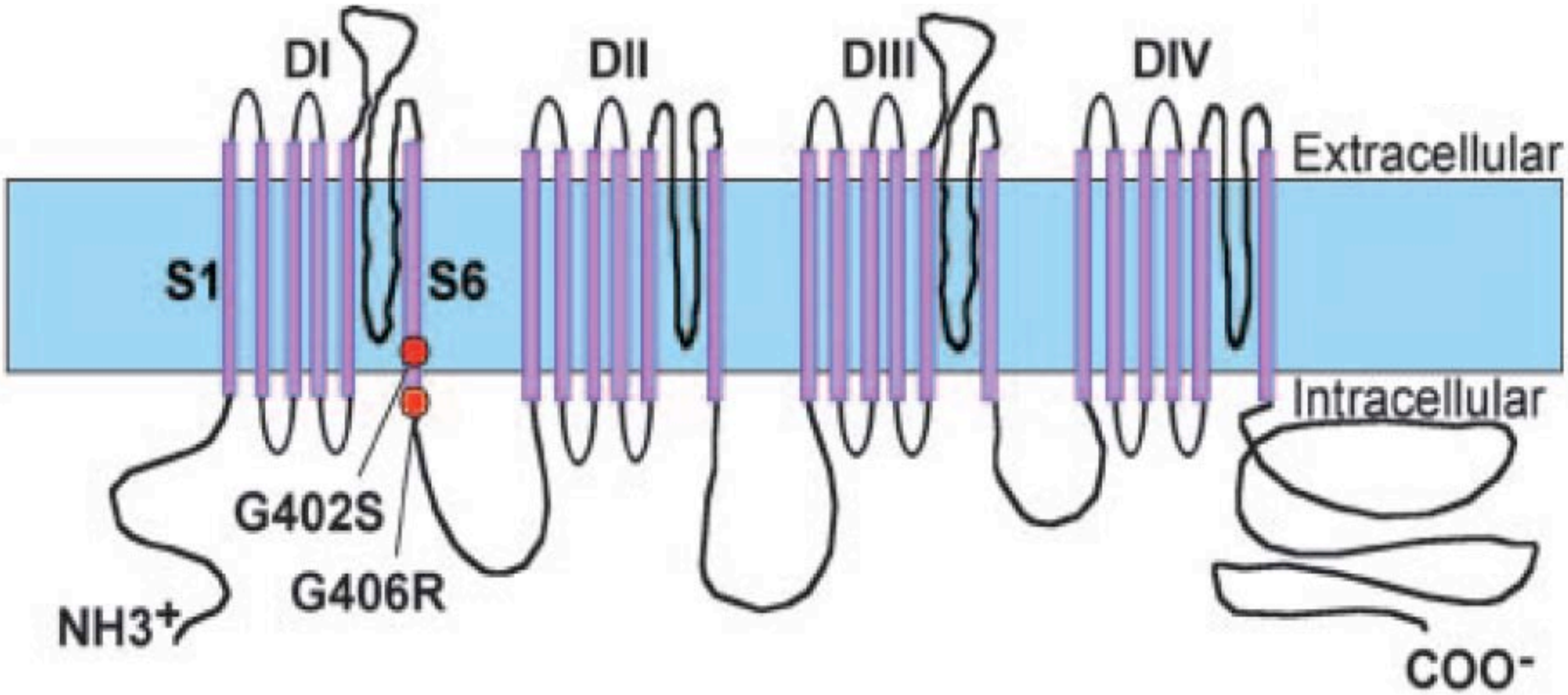
Genetic Disease: Timothy Syndrome



(Splawski et al, Proc Natl Acad Sci USA, 2005)

Topology of Ion Channel Protein $Ca_V1.2$



"De novo" mutations:

G402S	Glycine →	Serine
G406R	Glycine →	Arginine

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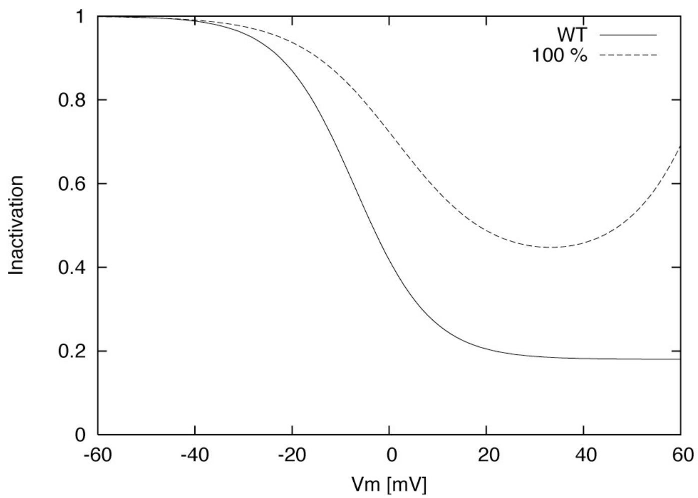
Modeling of Timothy Syndrome



Channel Modeling

Differences of
steady state inactivation
between wild type (WT)
and mutated channels

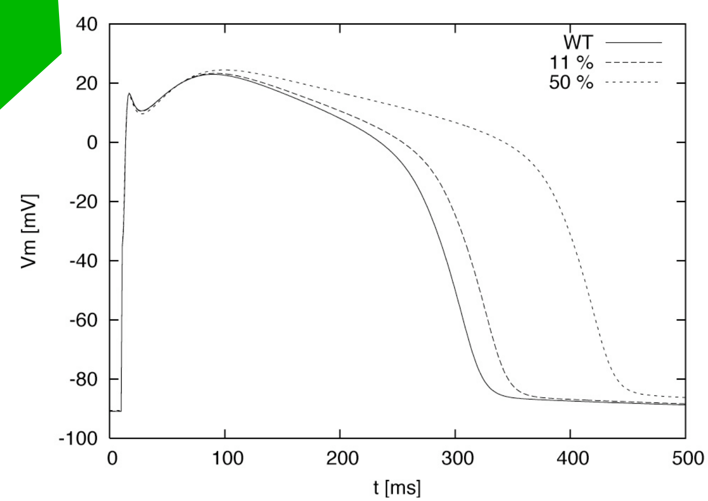
Numerical optimization

Integration in Myocyte Model

Prediction of course of transmembrane voltage in myocyte

Changes dependent on % of channels with mutation

Significant increase of action potential duration (and intracellular calcium concentrations)



Genetic Disease: Mutation of KCNQ1

Slow Inward Rectifying Potassium Current I_{Ks} { KCNQ1, KCNE1 }

KCNQ1

Mutations

- **S140G**
  Serine → Glycine
  found in family with hereditary atrial fibrillation
  (Chen et al., Science, 2003)

- **V141M**
  Valine → Methionine
  found in new born child with atrial fibrillation and short QT syndrome "de novo"
  (Kong et al., Cardiovasc Res, 2005)

* Location of Mutation S4: Voltage sensing subunit

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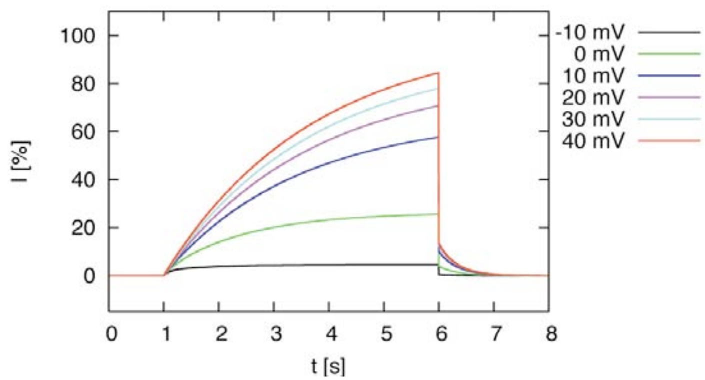
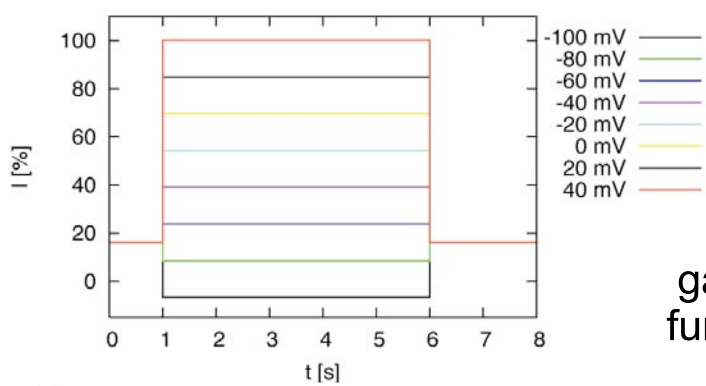
Modeled Channel Data

WT KCNQ1 + KCNE1

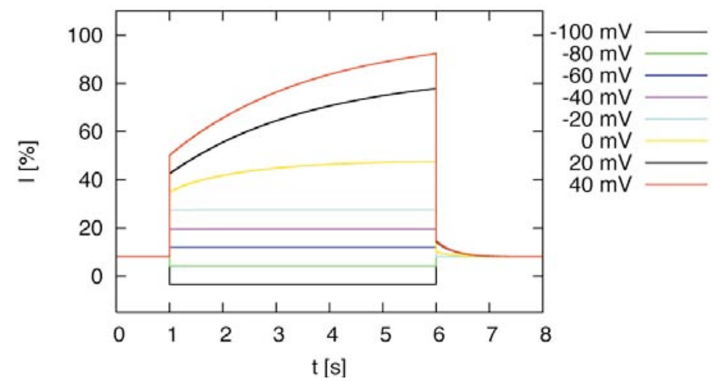


KCNQ1 (S140G or V141M) + KCNE1



gain of function!

50 % WT / 50 % mutation



(Kong et al., Cardiovasc Res, 2005)

Ordinary Differential Equations (ODEs)

ODEs of n-th order can be reduced to set of 1st order ODEs

2nd order ODE

$$\frac{\partial^2 u}{\partial x^2} + q(x)\frac{\partial u}{\partial x} = r(x)$$

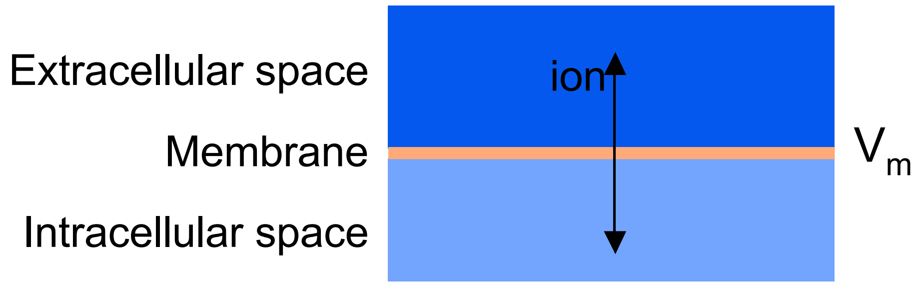
Rewrite

System of 1st order ODEs

$$\frac{\partial u}{\partial x} = z(x)$$

$$\frac{\partial z}{\partial x} = r(x) - q(x)z(x)$$

1st Order ODE for Describing Transmembrane Voltage



$$I_m = I_i + C_m \frac{d}{dt} V_m$$

I_i : Injected current [A]

I_m : Current through membrane [A]

C_m : Membrane capacitor [F]

V_m : Membrane voltage [V]

Numerical Solution of ODEs

Procedure

Discretization: $\frac{\partial u}{\partial x}$ ➡ $\frac{\Delta u}{\Delta x}$

Choose appropriate step length Δx: Distance between x_n and x_{n+1}
Determining factor for numerical error

Numerical Methods

- **Euler Method**
- **Runge-Kutta Method 2. Order**
- **Runge-Kutta Method 4. Order**
- Richardson-Extrapolation, Bulirsch-Stoer Method
- Predictor-Corrector Methods
- …

Euler Method

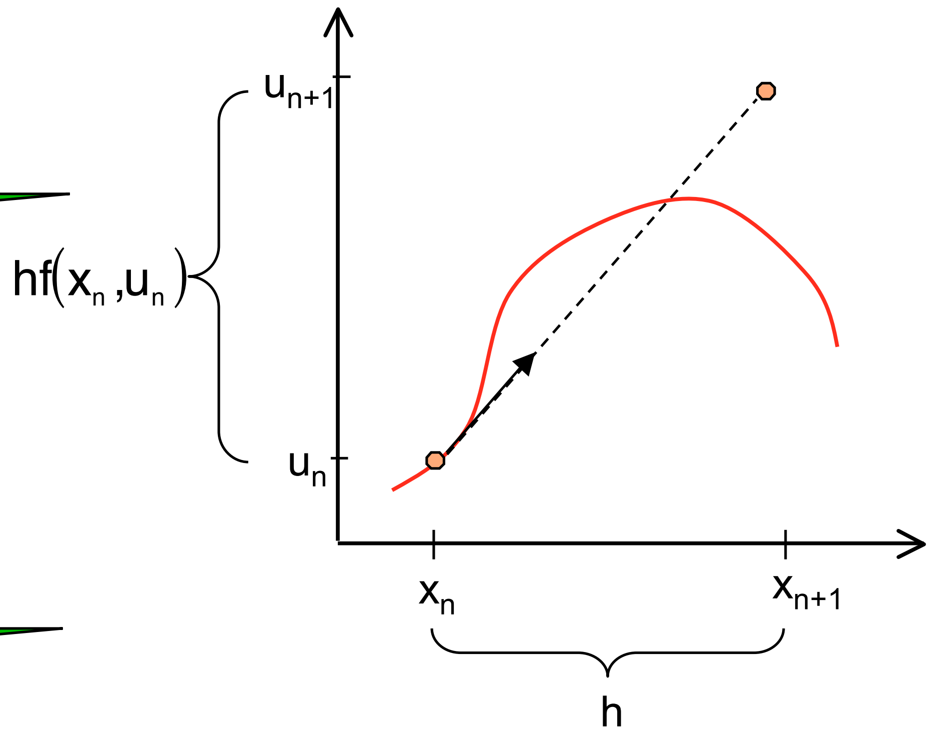
$$\frac{\partial u}{\partial x} = f(x,u)$$

Finite Difference Approximation

$$\frac{u_{n+1} - u_n}{x_{n+1} - x_n} = f(x_n, u_n)$$

Rewriting

$$u_{n+1} = u_n + h\,f(x_n, u_n)$$



CVRTI

Euler Method: Example

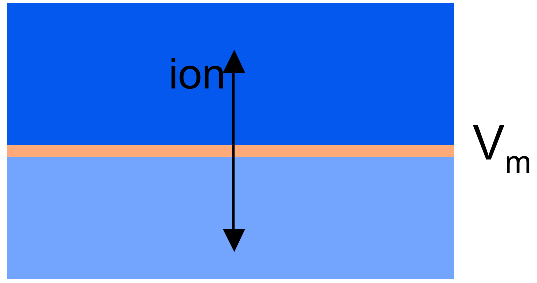
$$\frac{dV_m}{dt} = I_{stim}(t) - \frac{1}{C_m} I_{ion}(t, V_m)$$

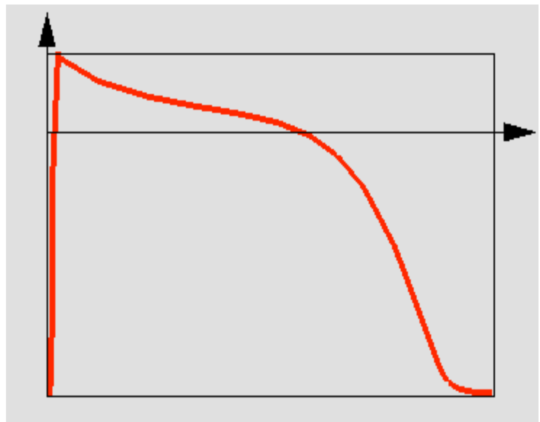
Finite Difference Approximation

$$\frac{V_{n+1} - V_n}{t_{n+1} - t_n} = I_{stim}(t_n) - \frac{1}{C_m} I_{ion}(t_n, V_n)$$

Rewrite

$$V_{n+1} = V_n + \Delta t \left(I_{stim}(t_n) - \frac{1}{C_m} I_{ion}(t_n, V_n) \right)$$





Runge-Kutta Method 2nd Order

$$\frac{\partial u}{\partial x} = f(x,u)$$

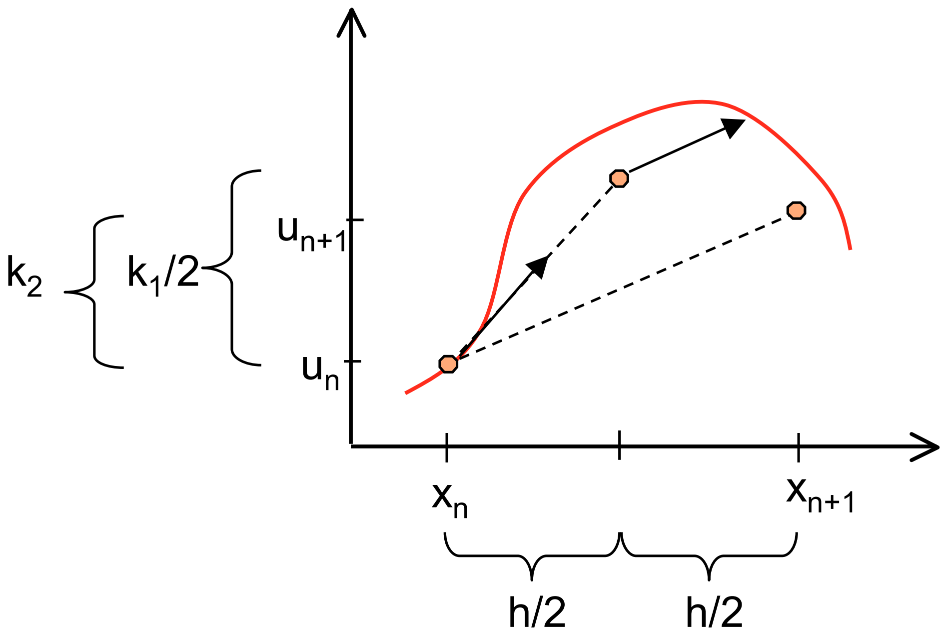
Discretization

$$k_1 = hf(x, u_n)$$

$$k_2 = hf\left(x_n + \frac{1}{2}h, u_n + \frac{1}{2}k_1\right)$$

Step

$$u_{n+1} = u_n + k_2$$



CVRTI

Runge-Kutta Method 2nd Order: Example

$$\frac{dV_m}{dt} = I_{stim}(t) - \frac{1}{C_m} I_{ion}(t, V_m)$$

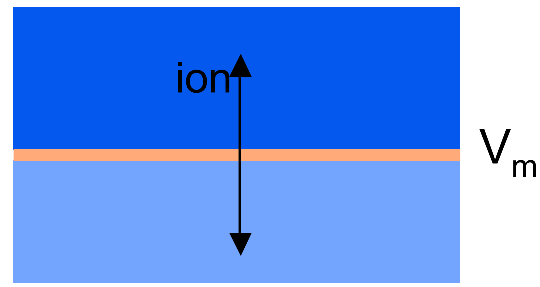
Discretization

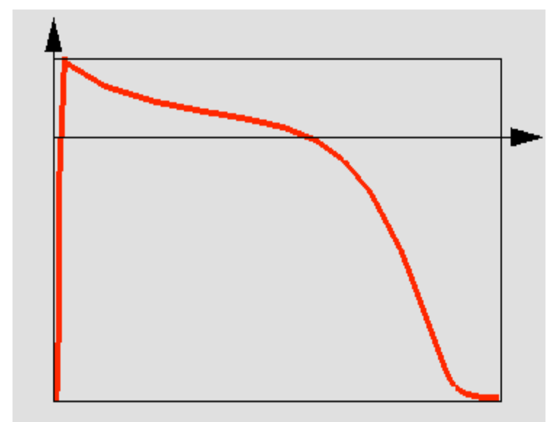
$$k_1 = \Delta t\left(I_{stim}(t_n) - \frac{1}{C_m} I_{ion}(t_n, V_n) \right)$$

$$k_2 = \Delta t\left(I_{stim}(t_n + \frac{h}{2}) - \frac{1}{C_m} I_{ion}(t_n + \frac{h}{2}, V_n + \frac{k_1}{2}) \right)$$

Step

$$V_{n+1} = V_n + k_2$$





CVRTI

Runge-Kutta Method 4th Order

$$\frac{\partial u}{\partial x} = f(x,u)$$

Discretization

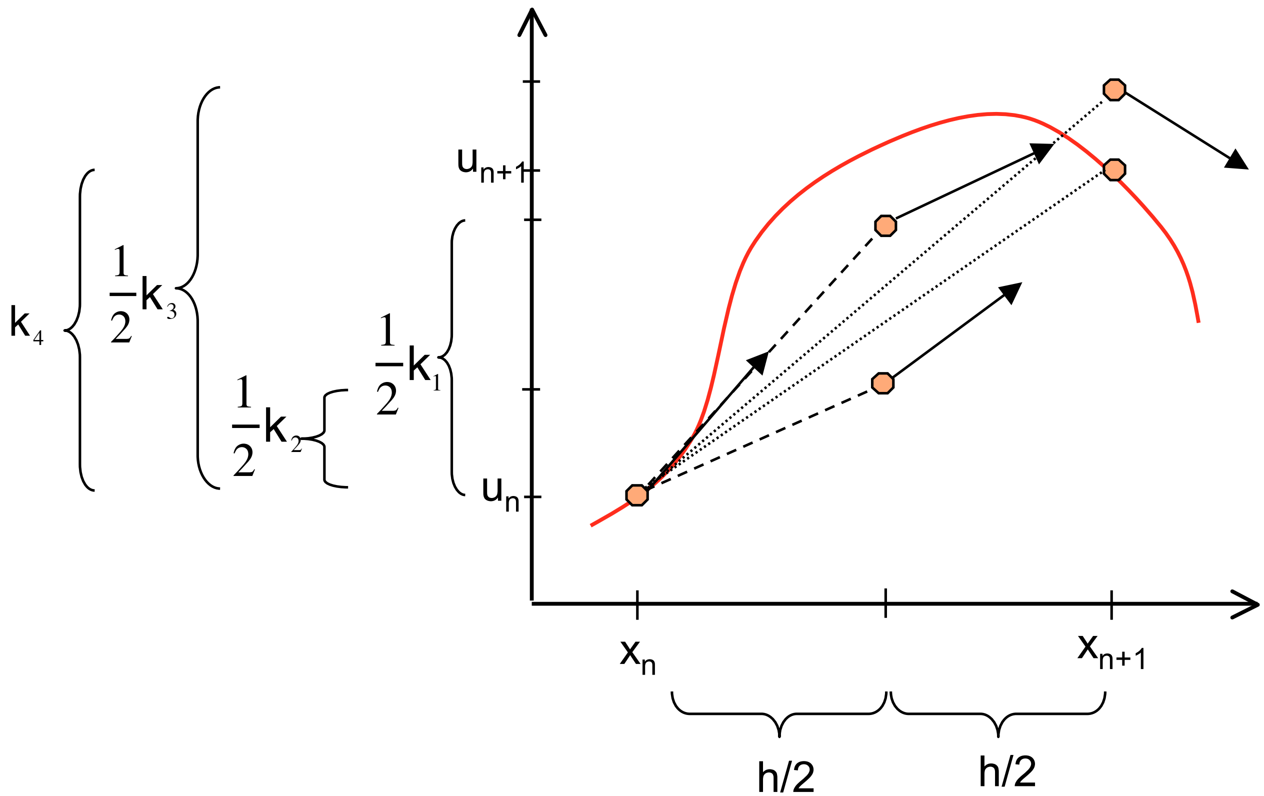
$$k_1 = h\,f(x,u_n) \qquad k_2 = h\,f\left(x_n + \frac{1}{2}h, u_n + \frac{1}{2}k_1\right)$$

$$k_3 = h\,f\left(x_n + \frac{1}{2}h, u_n + \frac{1}{2}k_2\right) \qquad k_4 = h\,f(x_n + h, u_n + k_3)$$

Step

$$u_{n+1} = u_n + \frac{k_1}{6} + \frac{k_2}{3} + \frac{k_3}{3} + \frac{k_4}{6}$$

Runge-Kutta Method 4th Order: Example



Group Work

Solve manually applying some steps of the Euler method:

$$\frac{dO}{dt} = \alpha\,(1-O) - \beta\,O$$

with $\alpha = 10,\ \beta = 1$ and $O(0) = 0.5$

Choose an appropriate time step *h*!