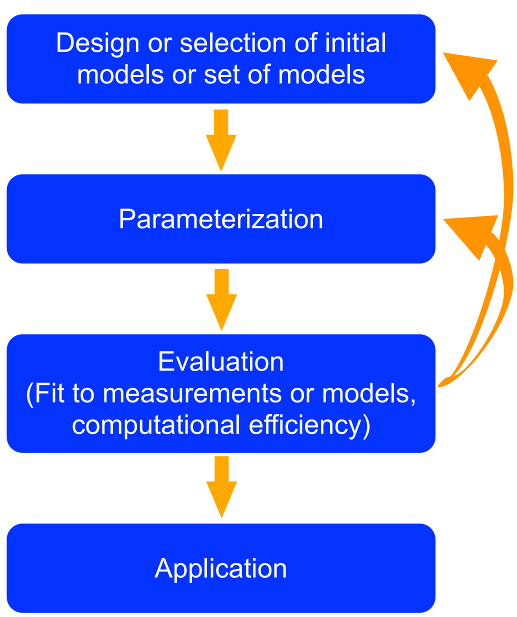
Whole Cell Simulation

Motivation and Approach



From Sachse Lectures

Types of Cellular Electrophysiology Models

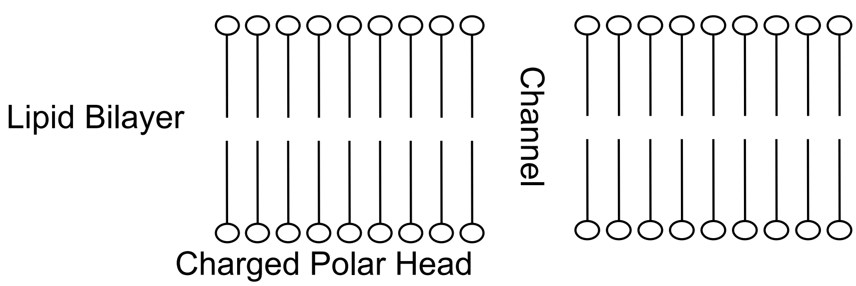
- Molecular Models
  - Structure and dynamics
  - Molecular interactions, drug binding, ion movement
- Markov Models
  - Current through a single channel and population of channels as well as gating currents
  - Based on states and transitions

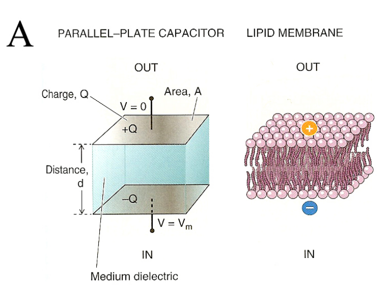
Lecture Week 6 (Frank Sachse)

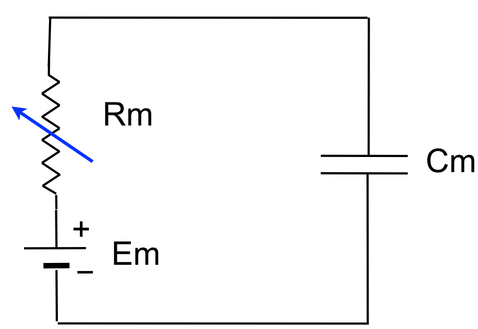
- Hodgkin-Huxley Models
  - Current through a population of channels and single channels as well as gating currents
  - Based on gating variables and rate coefficients
  -

This week!

Membrane Equivalent Circuit







Modeling Excitable Membranes

- Main concepts
  - Driving Force
    - V-Veq for each ion independently
  - Model Formalism (Hodgkin-Huxley)
    - continuous vs. discrete/stochastic
    - describes whole cell not single channels
  - Changes required for cardiac cells
    - additional currents, different coefficients
  - Numerical solutions
    - solve set of ODEs at discrete time steps
- Background
  - Week #7 lectures/slides (Frank Sachse)

Hodgkin Huxley Formalism

$$i_m = i_1 + i_2 + i_3 \ldots + I_c$$

$$i_m = i_K + i_{Na} + i_L + I_c$$

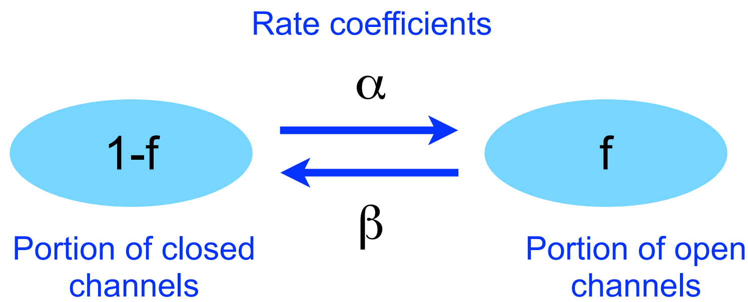
$$i_K(V,t) = (V_m - E_K)g_K(V,t)$$

$$i_{Na}(V,t) = (V_m - E_{Na})g_{Na}(V,t)$$

$$i_L = (V_m - E_L)g_L$$

$$I_C = -C\frac{dV}{dt}$$

Basic HH Concept



$$\frac{df}{dt} = \alpha_f(1-f) - \beta_f f$$

$$f = \text{Gating variable}$$

Potassium Current

$$i_K(V,t) = (V_m - E_K)g_K(V,t)$$

We can write an expression for the conductivity of this ion as

$$g_K = \bar{g}_K\, n^4(V,t)$$

And then assume a simple first order kinetic behavior of the gating variable *n*

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

Which has a solution for the case of constant *V* (voltage clamp) of the form

$$n(t) = n_\infty(v_o) - (n_\infty(v_o) - n_0)e^{-t/\tau_n(v_o)}$$

Potassium Current II

With the voltage dependent variables defined as follows:

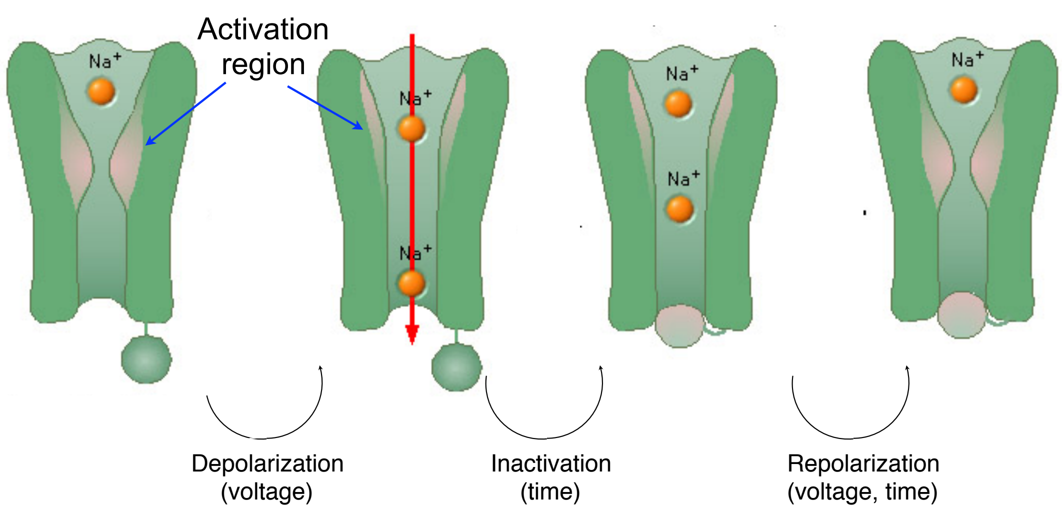
$$\alpha_n(V) = \frac{n_\infty}{\tau_n} \qquad \beta_n(V) = \frac{(1 - n_\infty)}{\tau_n}$$

and

$$n_0 = \frac{\alpha_{n0}}{\alpha_{n0} + \beta_{n0}}$$

the value of n with the membrane at rest

Sodium Channel Behavior



Sodium Current Activation I

$$i_{Na}(V,t) = (V_m - E_{Na})g_{Na}(V,t)$$

which we write as the product of two first order kinetic terms

$$g_{Na} = \bar{g}_{Na}\, m^3(V,t)\, h(V,t)$$

Taking the first of these, we can write

$$\frac{dm}{dt} = \alpha_m(V)(1-m) - \beta_m(V)m = \frac{1}{\tau_m}(m_\infty(V) - m)$$

Sodium Current Activation II

With constant voltage (voltage clamp)

$$m = m_\infty(v_o) - (m_\infty(v_o) - m_0)e^{-t/\tau_m(v_o)}$$

with the constants

$$\tau_m = \frac{1}{\alpha_m(V) + \beta_m(V)}$$

$$m_\infty = \frac{\alpha_m(V)}{\alpha_m(V) + \beta_m(V)}$$

Sodium Current (Inactivation)

$$g_{Na} = \bar{g}_{Na}\, m^3(V,t)\, h(V,t)$$

for which we write a similar ordinary differential equation

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

$$\frac{1}{\tau_h}(h_\infty(V) - h)$$

Sodium Current (Inactivation) II

If we hold $V=v_0$, a constant (voltage clamp) then

$$h = h_\infty(v_o) - (h_\infty(v_o) - h_0)e^{-t/\tau_h(v_o)}$$

with

$$h_\infty = \frac{\alpha_h(V)}{\alpha_h(V) + \beta_h(V)}$$

and

$$\tau_h = \frac{1}{\alpha_h(V) + \beta_h(V)}$$

Whole Cell Simulation
Bioengineering 6003 Cellular Electrophysiology & Biophysics

Summary of Fitted Rate Constants

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

$$\beta_m = 4e^{-v/18}$$

$$\alpha_h = 0.07e^{-v/20}$$

$$\beta_h = \frac{1}{e^{\frac{30-v}{10}}+1}$$

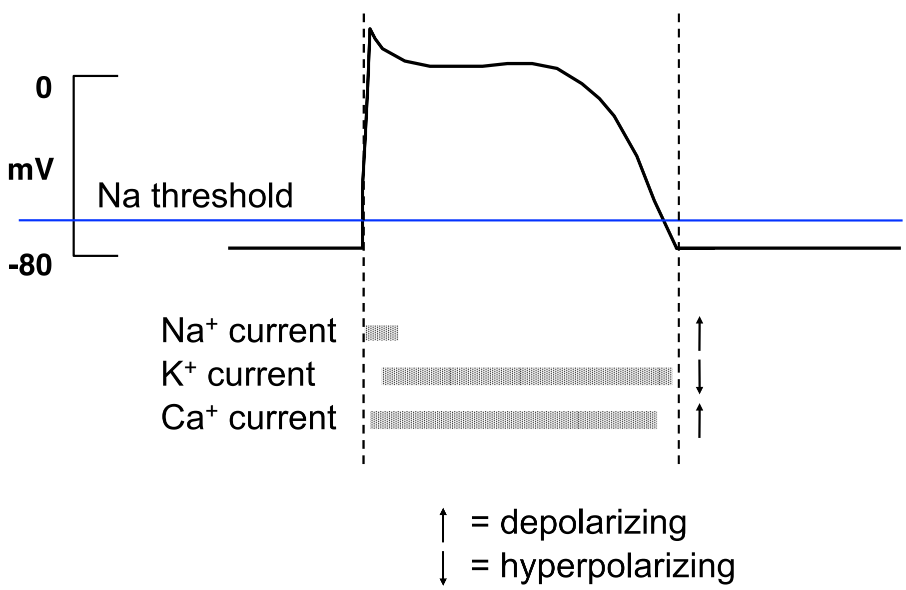
$$\alpha_n = 0.01 \frac{10-v}{e^{\frac{10-v}{10}}-1}$$

$$\beta_n = 0.125e^{-v/80}$$

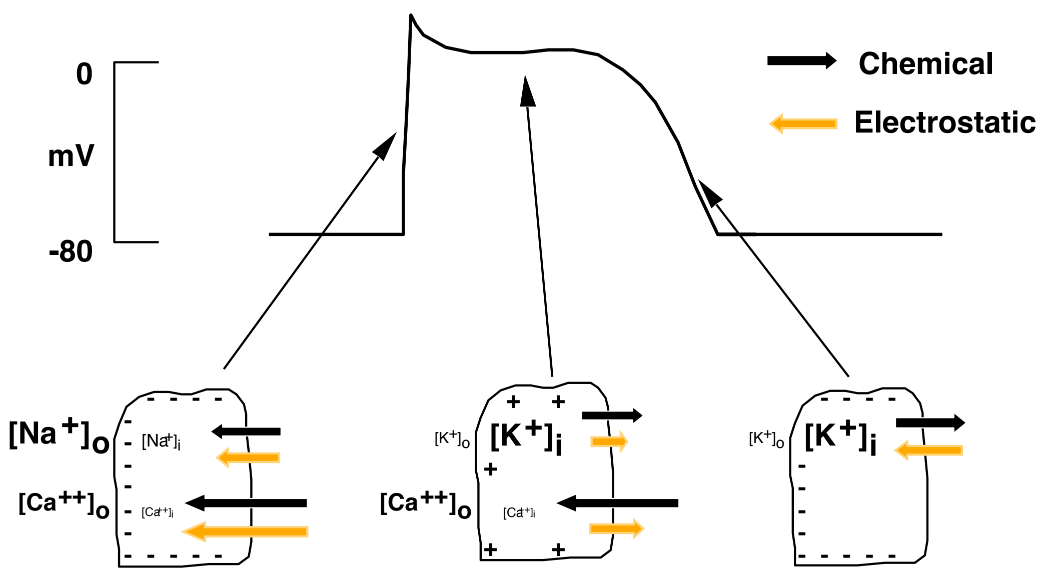
$$v = V - V_{eq}$$

$$\bar{g}_{Na} = 120;\ \bar{g}_K = 36;\ g_L = 0.3$$

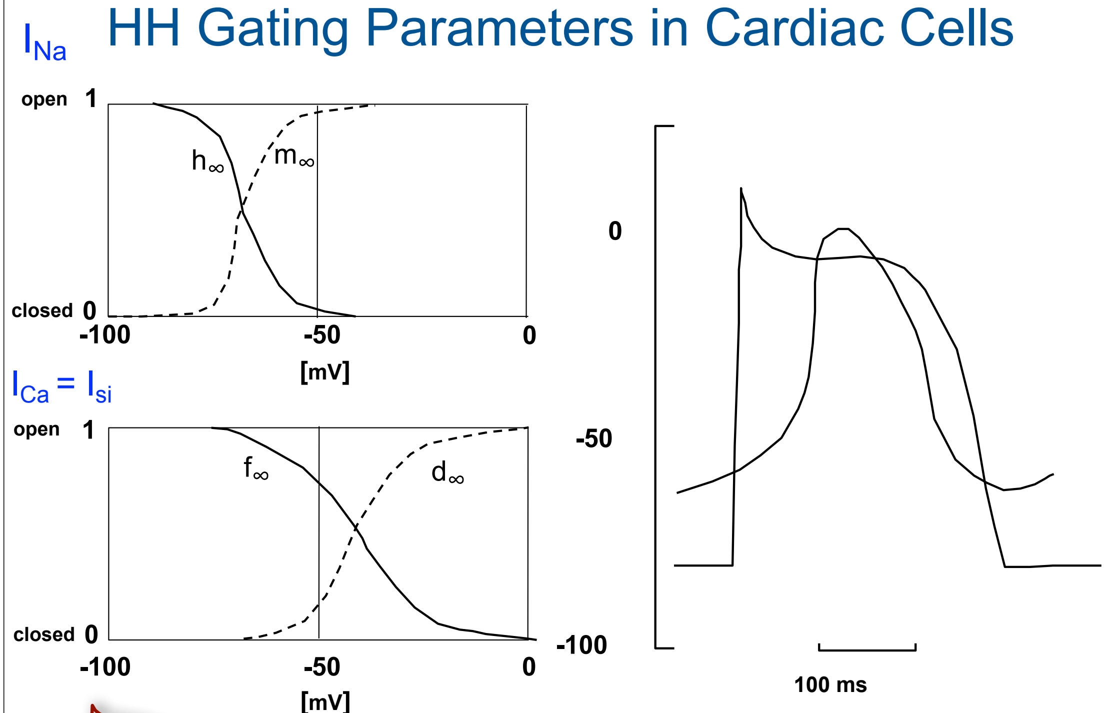
Cardiac Action Potential



Cardiac Cell Currents



HH Gating Parameters in Cardiac Cells



Elements of Cell Simulation

- Currents
  - Sodium
  - Potassium (20+ types)
  - Calcium (L type and T type)
  - Leak/background currents
- Pumps
  - Sodium/potassium
  - Calcium
  - Proton
- Exchangers
  - Calcium/Sodium
- Buffers
  - Sarcoplasmic Reticulum (SR)
  - Mitochondria

Challenges of Cardiac Cell Modeling

- Range of ionic channels
  - Across cells and within single cells
- Range of cell types
  - Discrete (e.g., SA nodal, AV nodal, ventricular)
  - Heterogeneity within the heart (e.g., endocardial, epicardial, and midmyocardial)
- Range of species
- Results:
  - Models are more qualitative than quantitative
  - Each requires balance of detail and tweaking to match experiments

Cardiac Membrane Models (a sampling)

- Nobel(1962) Purkinje cells (first cardiac cell model)
- McAllister, Noble, & Tsein (1975) Purkinje muscle
- Beeler-Reuter (1977) mammalian ventricle (first of its kind)
- Ebihara & Johnson (1981) B&R + updated sodium channel
- Luo-Rudy Phase I (1991) guinea pig ventricular muscle
- Luo-Rudy Phase II (1994) guinea pig ventricular muscle
- Demir, Clark Murphey, & GIles (1994) rabbit SA Node
- Priebe & Beukelmann (1998) human ventricle
- Courtemanche & Ramirez (1998) human atrium
- Nobel, Varghese, Kohl, & Noble (1998) guinea pig ventricle
- Winslow, Rice, et al. (1999) canine ventricle + EC coupling
- Sachse, Seemann, Chaisaowong & Wieß (2003) human ventricle
- Ten Tussher, Noble, Noble, Panfilov (2003) human ventricle

Nobel (1962): Purkinje

Noble, D. *The Initiation of the Heartbeat*, 1975

Goal: show that oscillation possible in a membrane model

$$i_m = i_{Na} + i_{Na,b} + i_{K1} + i_{K2} + i_{An}$$

and a background current with constant conductivity

$$i_{Na,b} = g_{Na,b}(V_m - E_{Na})$$

as well an anion current with constant conductivity

$$i_{An} = g_{An}(V_m - E_{An})$$

Nobel (1962): Sodium Currents

There are two different inward (Na^+) currents,

1) Voltage dependent that switches on and then off very quickly (with increasing V_m)

$$i_{Na} = g_{Na}(V_m - E_{Na})$$

$$g_{Na} = g_{\bar{N}a}\, m^3 h$$

2) Time dependent, acts like a classic HH K^+ current but with long time constant, i.e., 100 times longer than in nerve. “Delayed rectifier” because it is slow and primarily outward.

$$i_{K2} = g_{K2}(V_m - E_k)$$

$$g_{K2} = g_{\bar{K}2}\, n^4$$

Nobel (1962): Potassium Currents

There are two different outward (K^+) currents,

1) Voltage dependent that switches on and then off very quickly (with increasing V_m)

$$i_{K1} = g_{K1}(V_m - E_K)$$

$$g_{K1} = 1.2\, e^{-\frac{V_m}{50}} + 0.015\, e^{\frac{V_m+90}{60}}$$

2) Time dependent, acts like a classic HH K^+ current but with long time constant, i.e., 100 times longer than in nerve. “Delayed rectifier” because it is slow and primarily outward.

$$i_{K2} = g_{K2}(V_m - E_k)$$

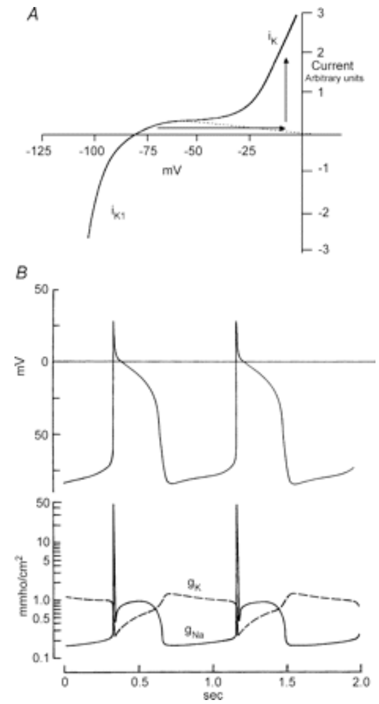
$$g_{K2} = g_{\bar{K}2}\, n^4$$

Nobel (1962): Results

"So my research day started at 1:30 a.m.; a quick coffee, and then two hours at the *Mercury* computer. Then on to the slaughterhouse at 5 a.m. to pick up the sheep hearts with which the day's experiments would be done. Those experiments sometimes lasted until the time came to return to programming *Mercury*. I think that experience completely wrecked my circadian rhythms, but let's return to that kind of rhythm later in this chapter."

Denis Noble. The Music of Life: Biology beyond the Genome. (Oxford University Press, USA, 2006). Page 61.

- Modeled pacemaker activity without explicit oscillator
- Physiologically incorrect:
  - Developed before voltage clamp of cardiac cells
  - Prolonged AP produced by Na current rather than Ca current, which was missing!



McAllister, Noble, and Tsien (1975)

- Extension of Noble's 1962
- Included Ca^{2+}, 9 gating parameters
- Inward currents
  - I_{Na}: typical HH current
  - I_{SI}: similar to I_{Na} but with slower kinetics
  - $IN_{a,b}$: background sodium current
- Outward currents
  - I_{K1}: background current
  - I_{K2}: pacemaker current, activation variable
  - I_{X1}: plateau current, activation variable
  - I_{X2}: plateau current, activation variable
  - I_{Cl}: time and voltage dependent Cl current

Beeler-Reuter (1977)

$$i_m = i_{Na} + i_{Na,b} + i_{K1} + i_{X1} + i_S$$

$$i_{Na} = g_{\bar{N}a}\, m^3 hj(V_m - E_{Na})$$

Modified Na current (h,j inactivation)

$$i_{Na,b} = g_{Na,b}(V_m - E_{Na})$$

Background Na current (time dependent

$$i_{K1} = f(t, V_M)$$

Outward K current, contributes to plateau

$$i_{X1} = x1\ f(t, V_M)$$

Mostly K outward current, slow to activate, contributes to repolarization

Beeler-Reuter (1977)

$$i_S = g_s\, df(V_m - E_s)$$

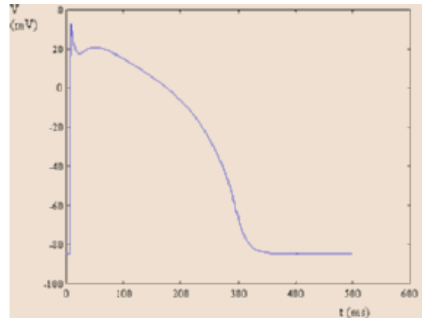
Inward, slow, largely Ca current, d activation, f inactivation.

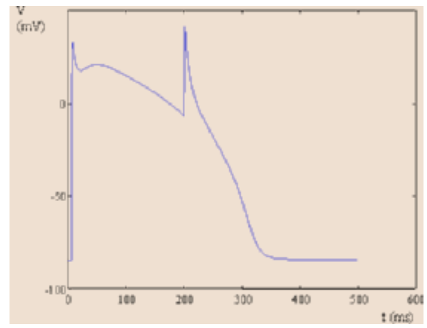
$$\frac{\partial [Ca^{2+}]_i}{\partial t} = -10^{-7}\ i_s + 0.07(10^{-7} - [Ca^{2+}]_i)$$

Ca concentration changes with i_s current!

Beeler-Reuter (1977)

- Online version: thevirtualheart.org/java/BR.html
- Simulated rate dependence of AP duration
- Included refractory period
- Supported premature stimulus (see example)
- Implicit Ca current, similar to Na, activation and inactivation variables



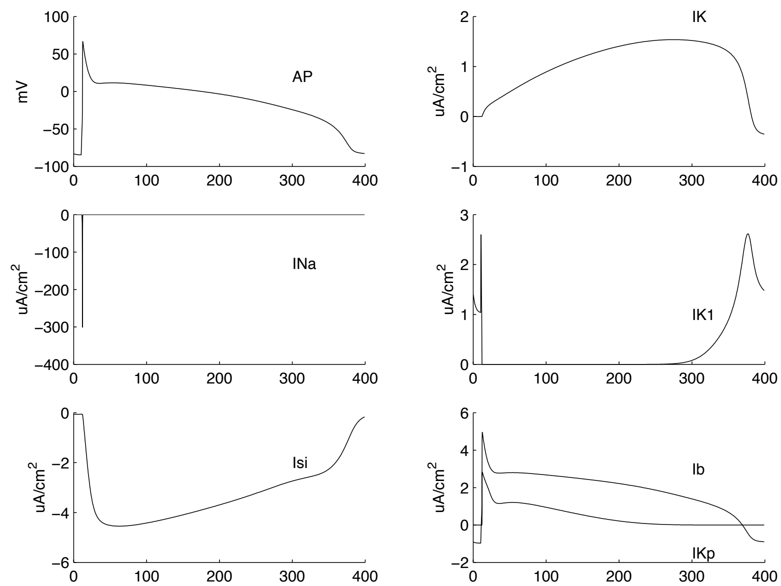


Luo-Rudy I (1991)

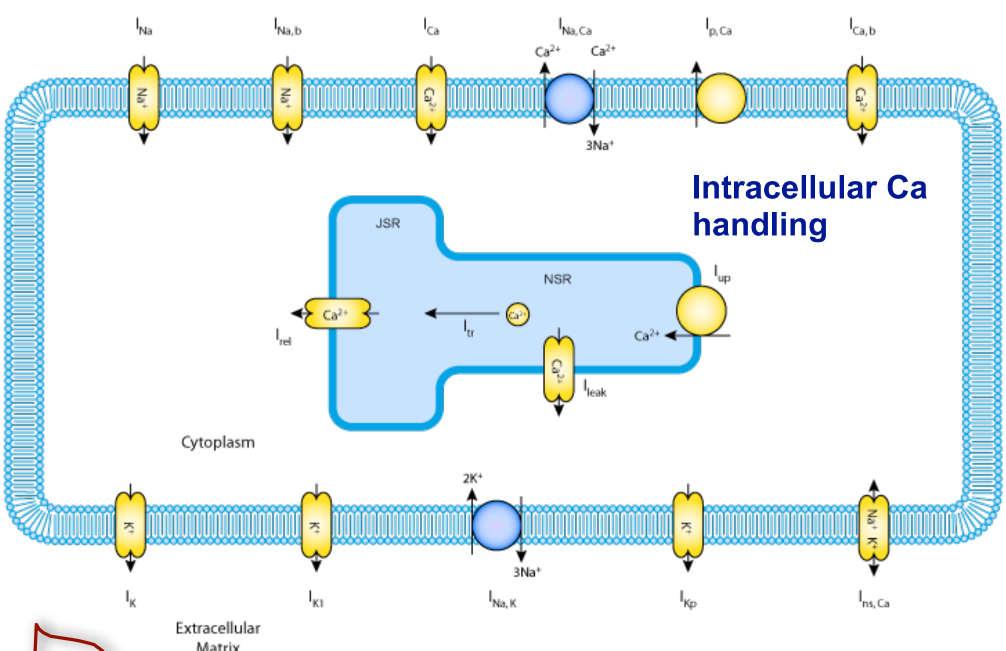
$$i_m = i_{Na} + i_{si} + i_K + i_{K1} + i_{Kp} + i_b$$

i_{si}	Slow inward current, Ca
i_K	Time dependent K current
i_{K1}	Time independent K current
i_{Kp}	Plateau K current
i_b	Background K current

Luo-Rudy I (1991)



Luo-Rudy II (1994)



Multiscale Simulation

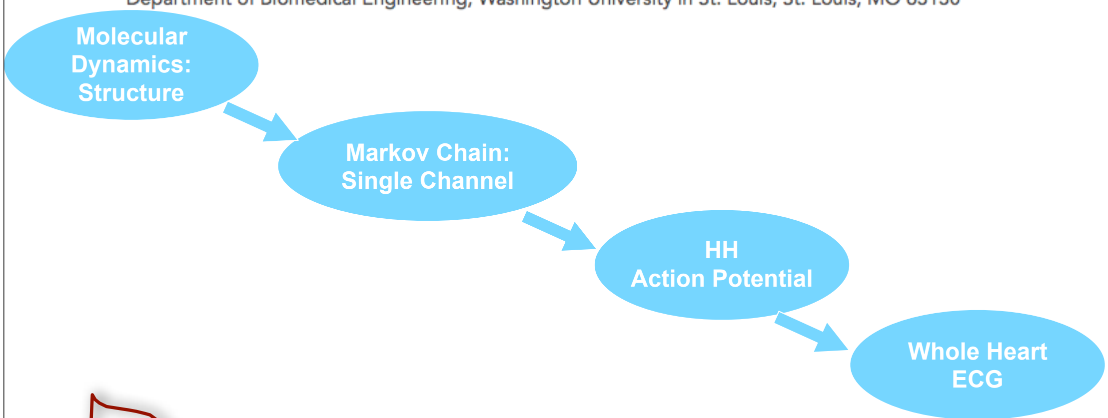
Perspectives on: Molecular dynamics and computational methods

Multi-scale electrophysiology modeling: from atom to organ

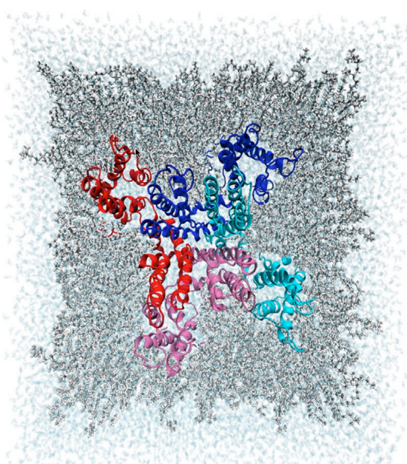
Jonathan R. Silva[1] and Yoram Rudy[2]

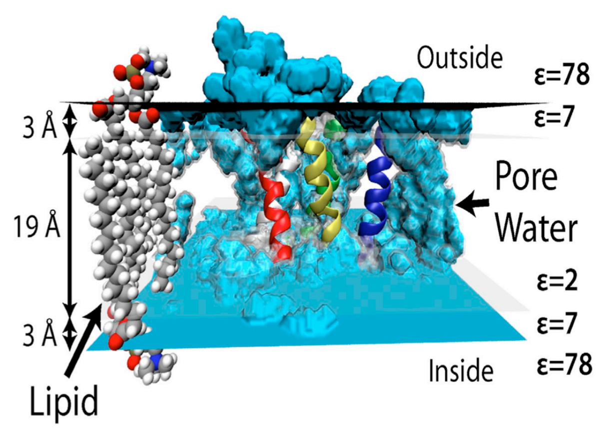
J Gen Physiol. 135(6): 575-581

[1]Department of Pediatrics, University of Chicago, Chicago, IL 60637
[2]Department of Biomedical Engineering, Washington University in St. Louis, St. Louis, MO 63130



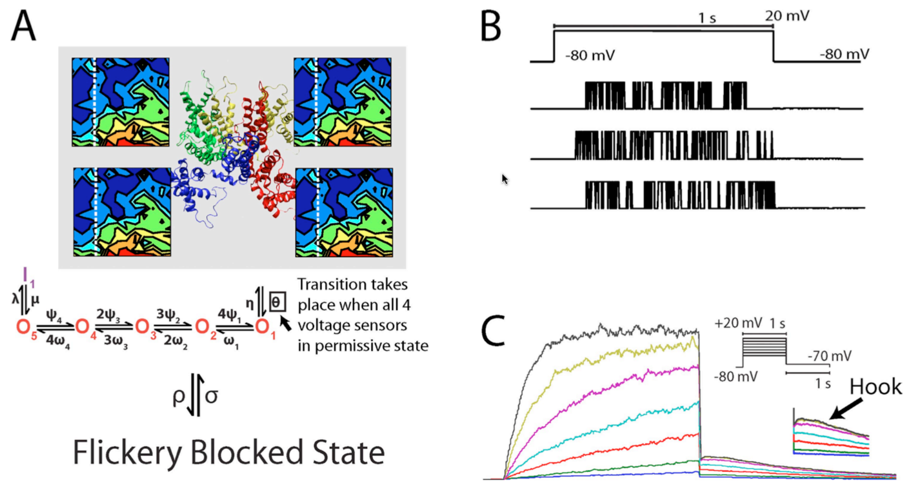
Multiscale: Molecular Dynamics





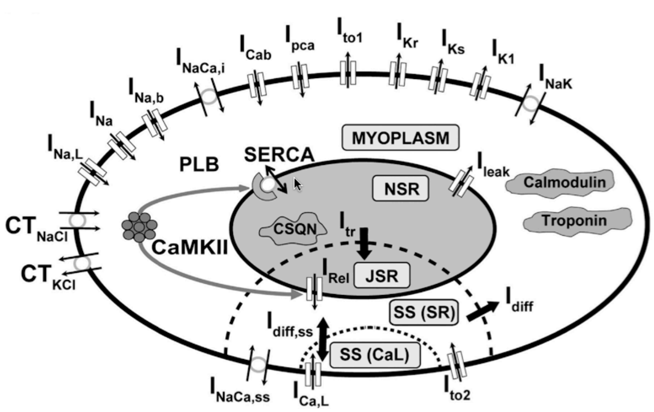
- Purpose
  - Channel shape, conformal changes, interaction with environment
- Challenges
  - Parameter choices, computational, validation

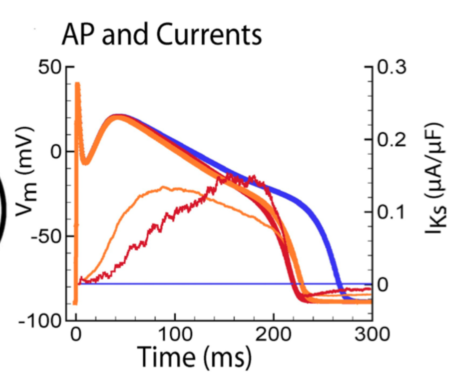
Multiscale: Markov Models



- Purpose
  - Capture conformal states, voltage and time dependence, single channel behavior (normal and after mutations)
- Challenges
  - Parameter choices, computational, validation

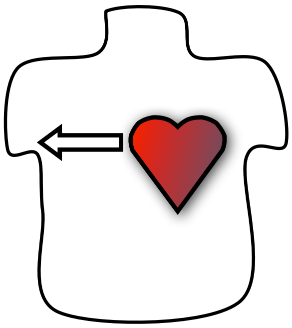
Multiscale: Action Potentials

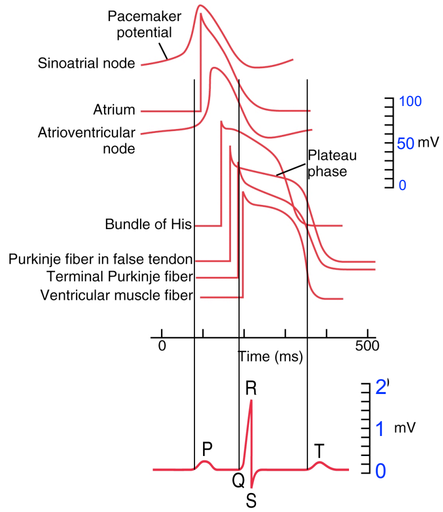


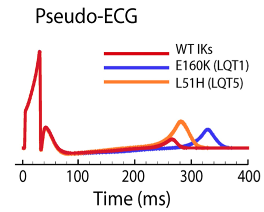


- Purpose
  - Whole cell behavior, EP and ECC, ionic currents, effect of environment, multiple beat behavior
- Challenges
  - Parameter choices, computational, geometry, diffusion

Multiscale: ECG







- Purpose
  - Whole heart behavior, link to clinic, integration
- Challenges
  - Parameter choices, geometry, computational