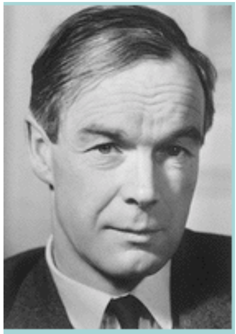
Simulation of Action Potentials

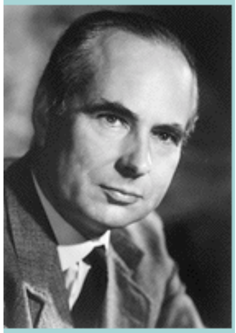
The Hodgkin-Huxley Formalism

Hodgkin-Huxley Formalism

- Qualitative concepts
- Quantitative formulation and simulation (see next lecture)
- Sir Alan Hodgkin
  - 1914-1988
- Sir Andrew Huxley
  - 1917-2012
  - brother of Aldous Huxley
- Nobel Prize: 1963



Hodgkin

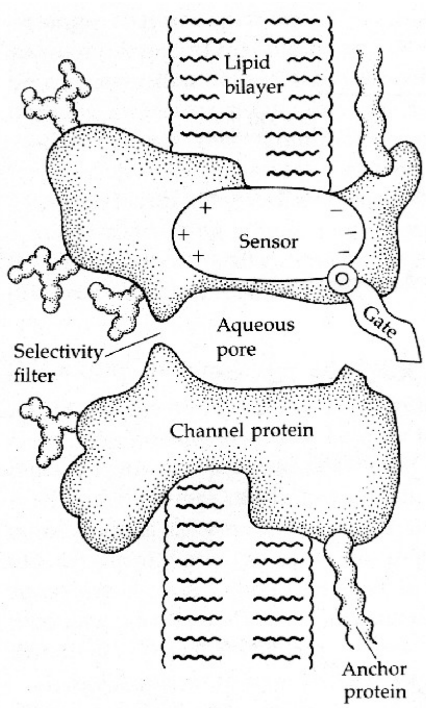


Huxley

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

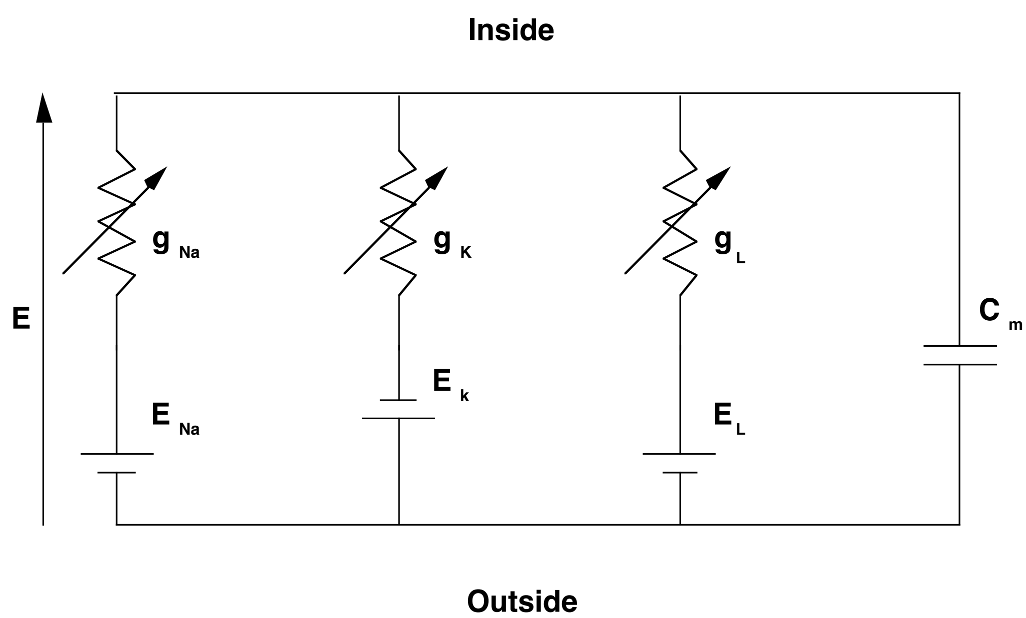
Membrane Channel Model



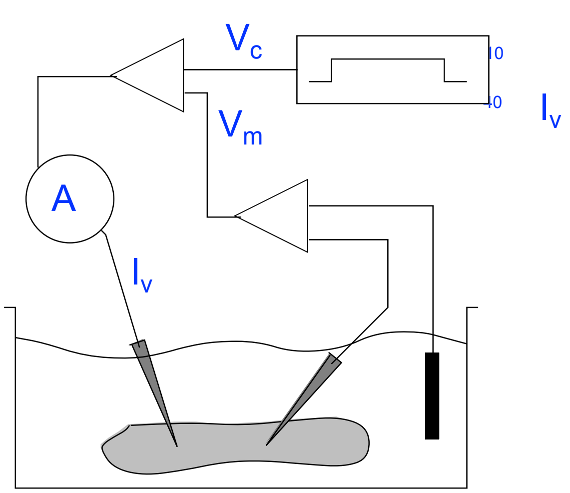
3 WORKING HYPOTHESIS FOR A CHANNEL

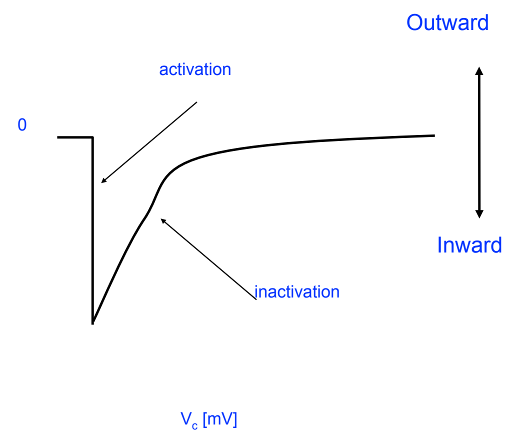
The channel is drawn as a transmembrane macromolecule with a hole through the center. The external surface of the molecule is glycosylated. The functional regions, selectivity filter, gate, and sensor are deduced from voltage-clamp experiments but have not yet been charted by structural studies. We have yet to learn how they actually look.

Membrane Analog Circuit



Voltage Clamp Concepts

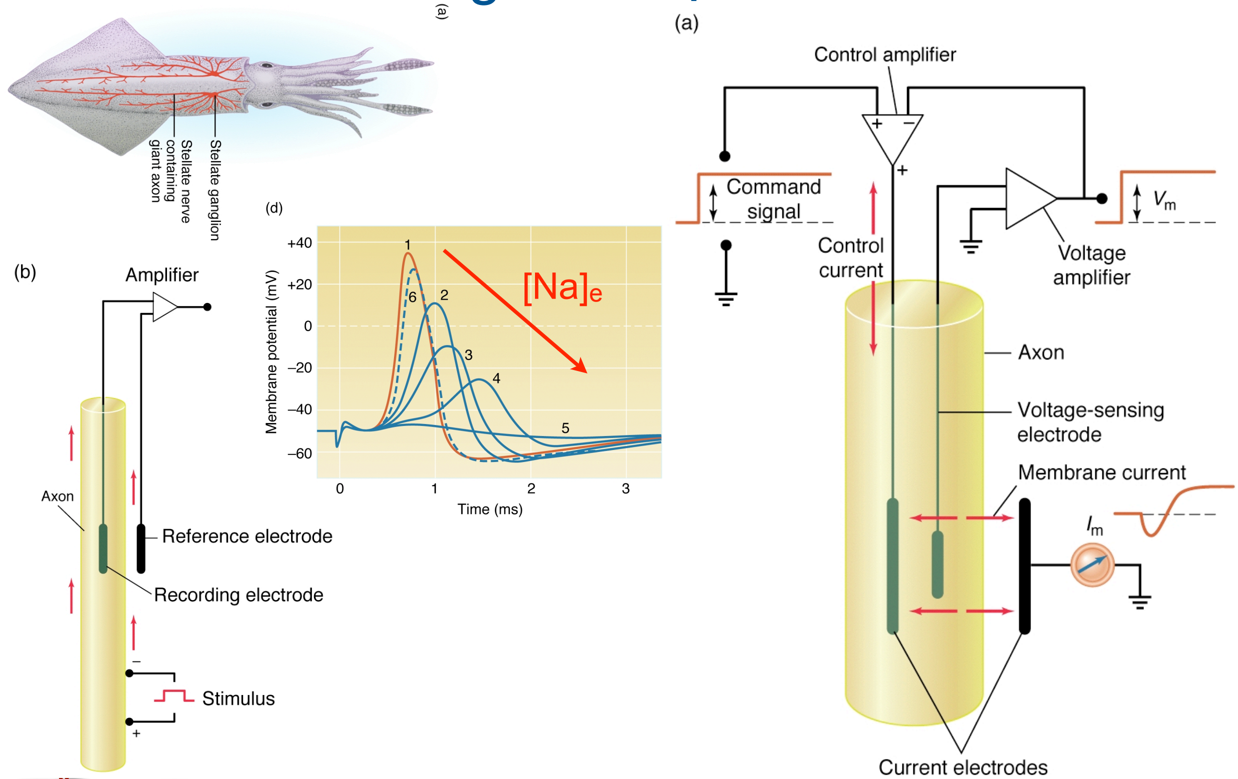




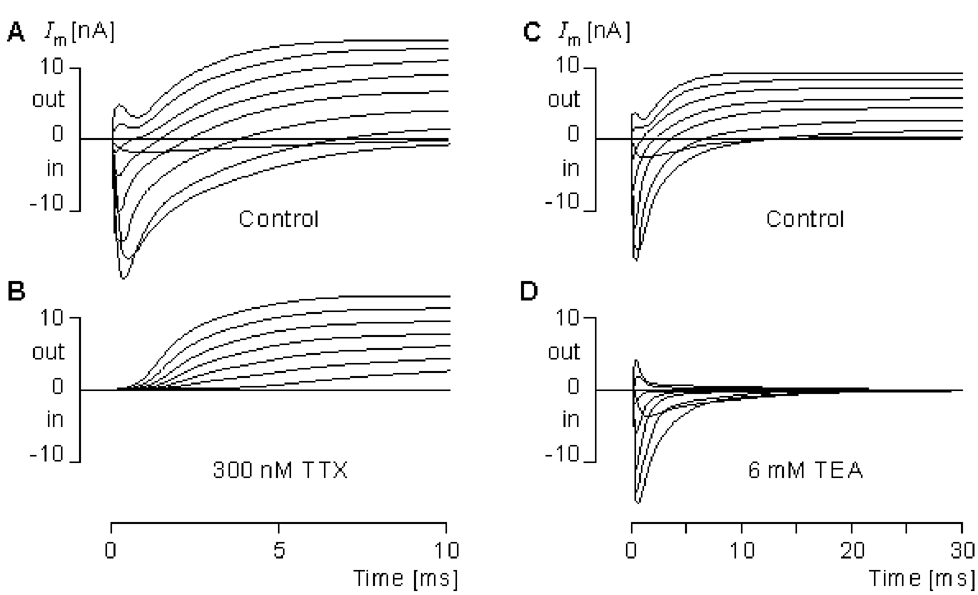
For each ion type:

$i_v = g\,(V_m - V_{eq})$

Voltage Clamp in HH



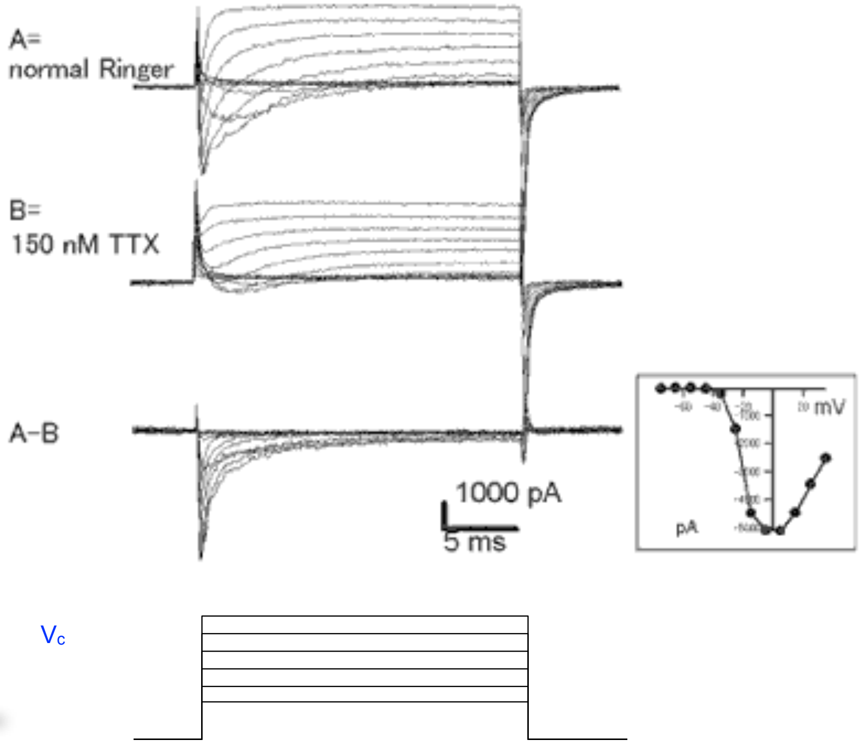
Hodgkin & Huxley Voltage Clamp Data



TTX = Na channel blocker

TEA = K channel blocker

Hodgkin & Huxley IV Curve



Hodgkin Huxley Formalism

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

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

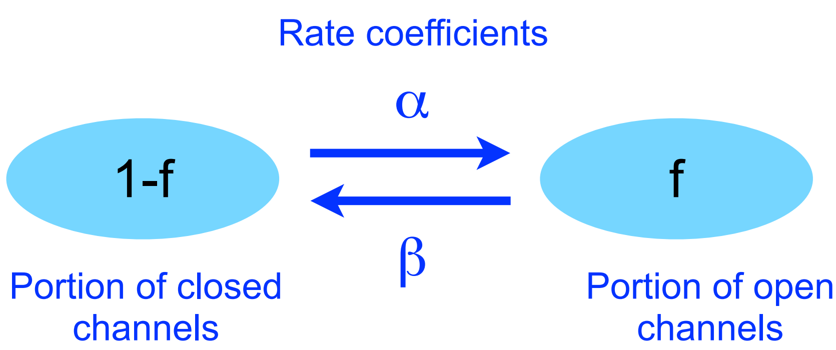
$$i_K(V,t) = (V_m - E_K)g_K(V,t)$$

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

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

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

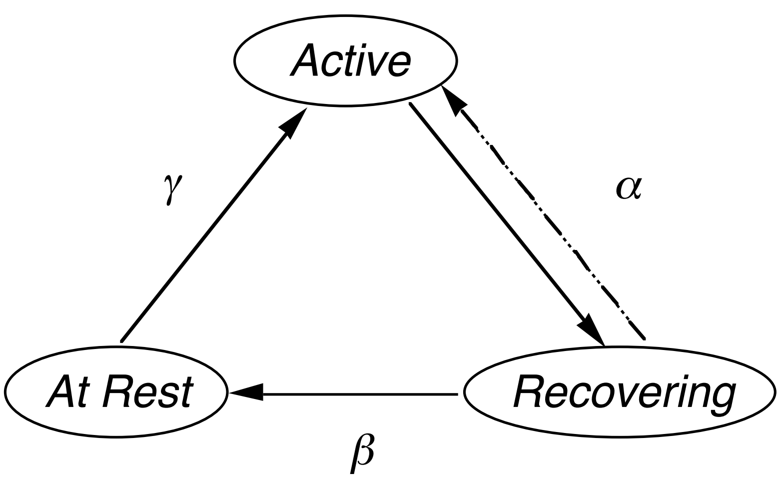
Basic HH Concept



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

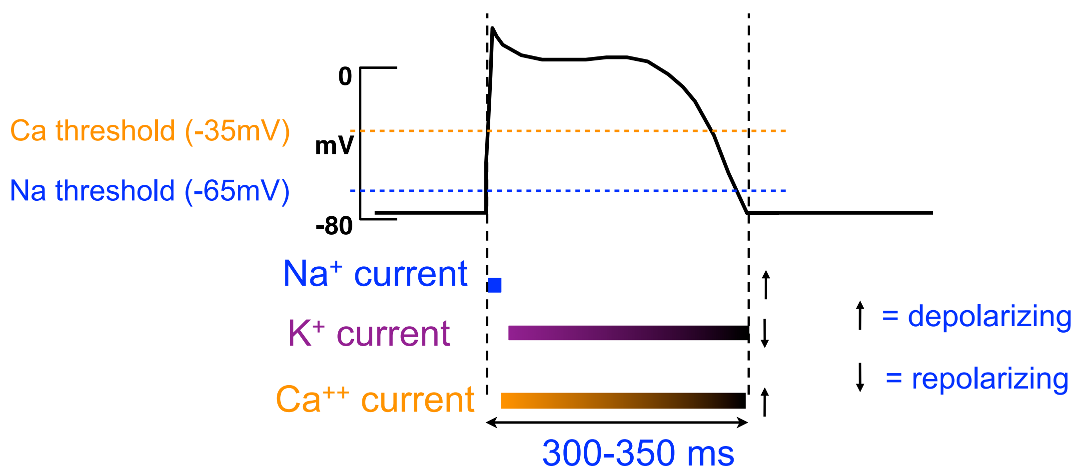
$$f = \text{Gating variable}$$

Single Channel Model

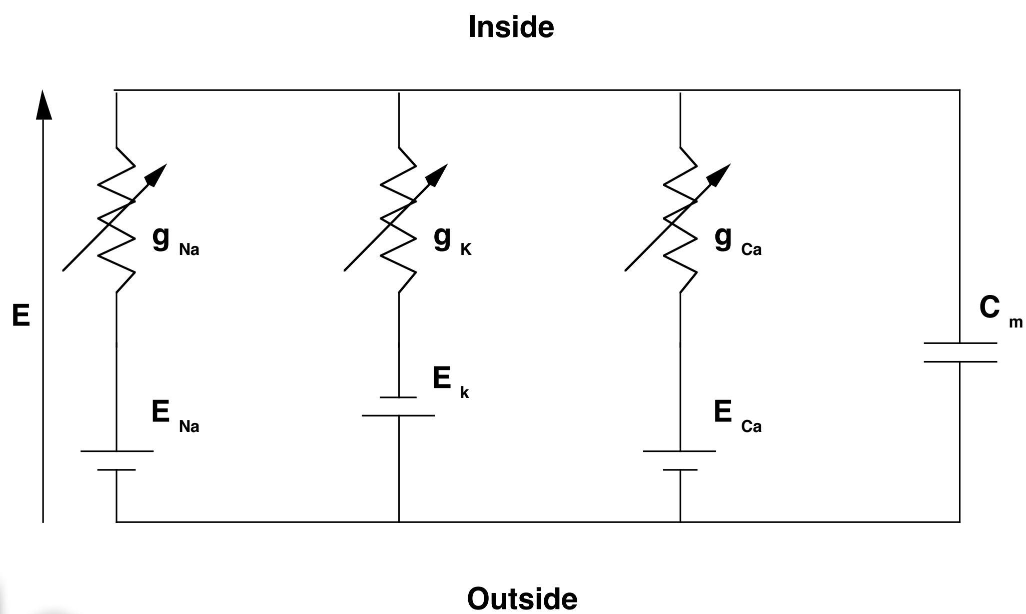


α, β, γ: state transition probabilities,
(functions of v and t)

Cardiac Action Potential



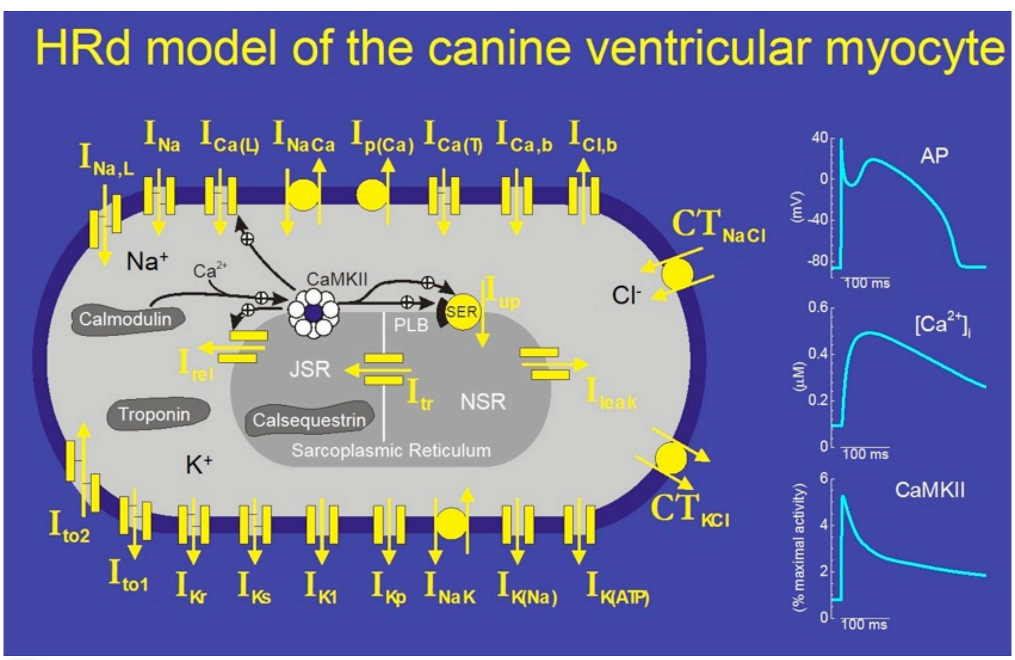
Membrane Analog Circuit: Heart Cell



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 Tusscher, Noble, Noble, Panfilov (2003) human ventricle

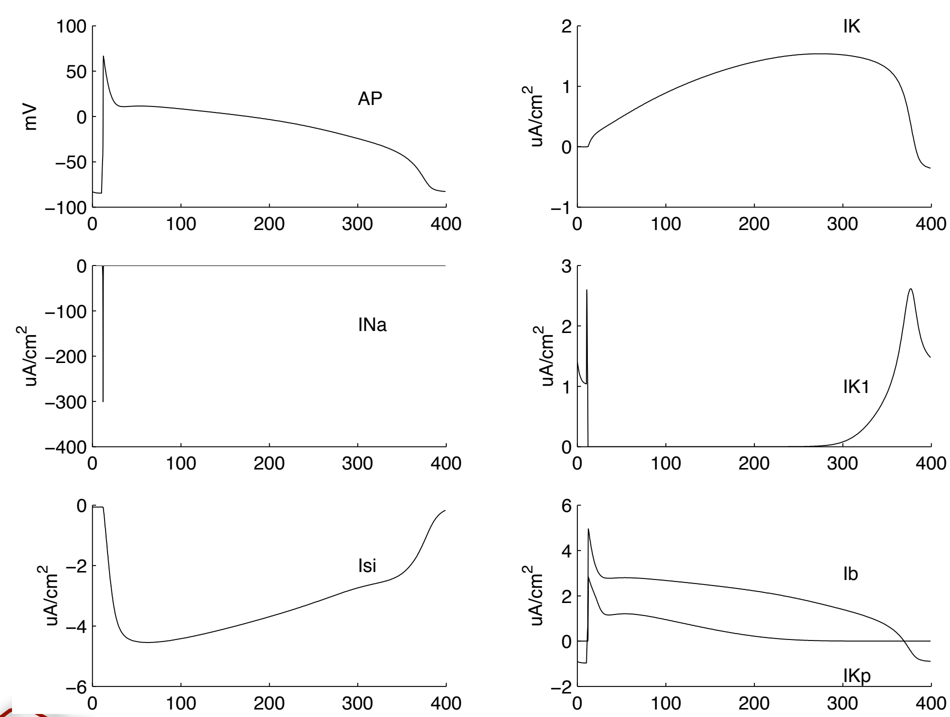
Lou-Rudy Membrane Models



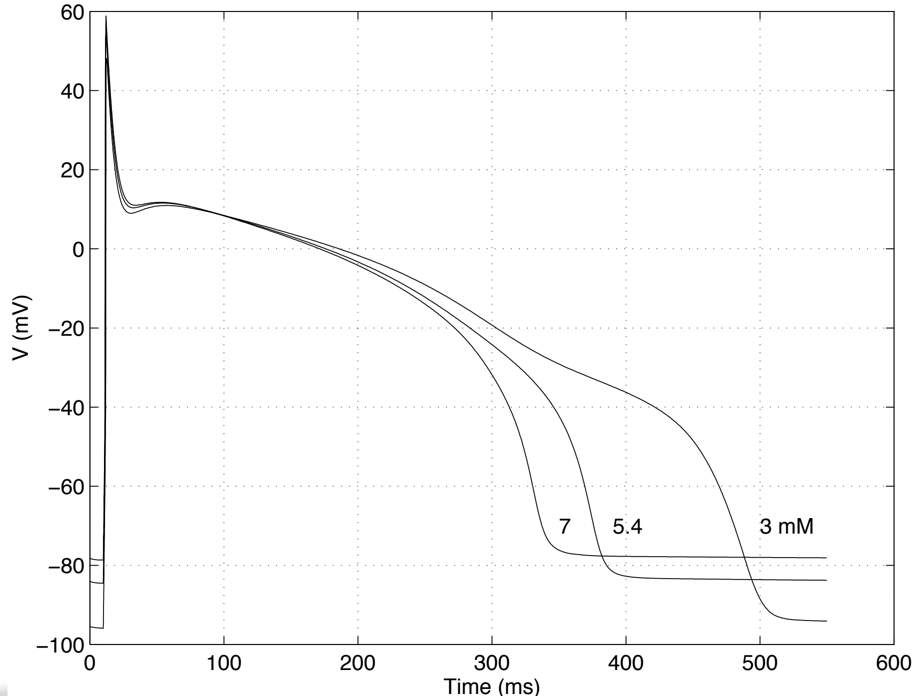
Homework Assignment

- Simulate cardiac action potentials
- Vary model parameters
- Display and analyze voltages, currents, and conductivities
- Make up (and answer) your own question

Sample Output



Varying Parameters



Cell Simulation: General I

- Organize simulations
  - Develop a strategy to answer the question
  - Vary as few parameters at a time as possible
  - Use reasonable (physiological) ranges of values
  - Examine the relevant parameters (often good to start by looking at all and identify relevant ones)
- Develop second order results where appropriate
  - e.g., plot of stimulus duration vs. stimulus
  - e.g., APD vs concentration
- Use results of analysis to motivate more simulations
  - Use to uncover mechanisms

Cell Simulation: General II

- Organization of report
  - Mimic the flow of the questions and answer all parts
- Plots and graphs
  - Include axes with labels
  - Include legends
  - Include concise captions
  - Export figures rather than screen capture
  - Embed all figures into the running text
- Text
  - Use past tense to report all methods and results
  - Adopt formal scientific prose style
  - Strive for concise, clear, accurate descriptions
- Use tables to show sets of results