Mathematical Modeling of Cardiac Arrhythmias

May 27, 2009

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Quantitative Biology Final Project

Cardiac Arrhythmia: the Dry Definition

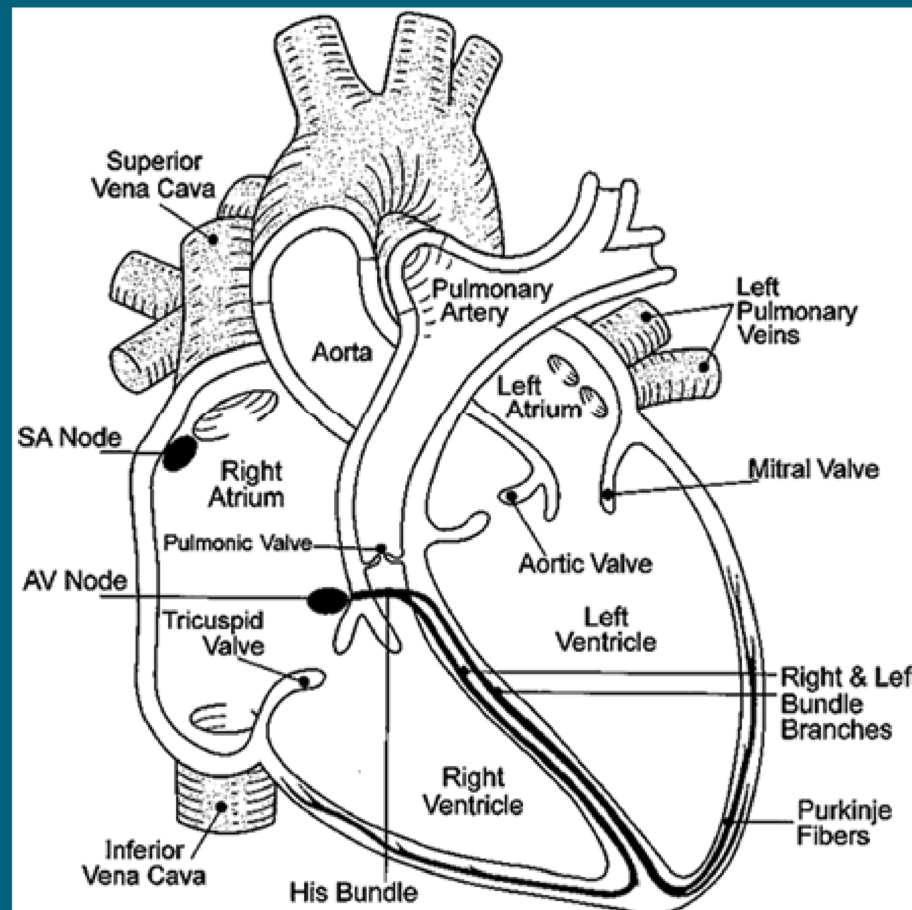
- Any disorder of your heart rate or heart rhythm, such as beating too fast (tachycardia), too slow (bradycardia), or irregularly.

  \- NIH Medical Encyclopedia

- Can lead to:
  - Angina
  - Heart Attack
  - Heart Failure
  - Stroke

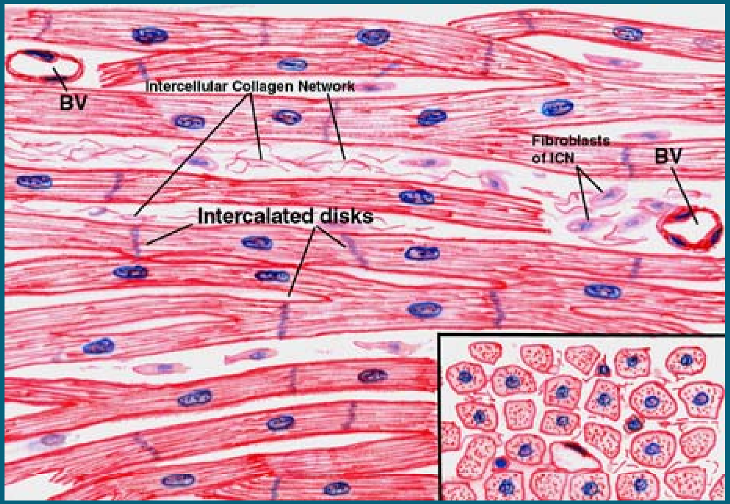
Review of Physiology: Anatomy

- Anatomy:
  - 4 Chambers
    - Ventricles
    - Atria
  - SA Node
  - AV Node
  - Bundle of His
  - Purkinje Fibers



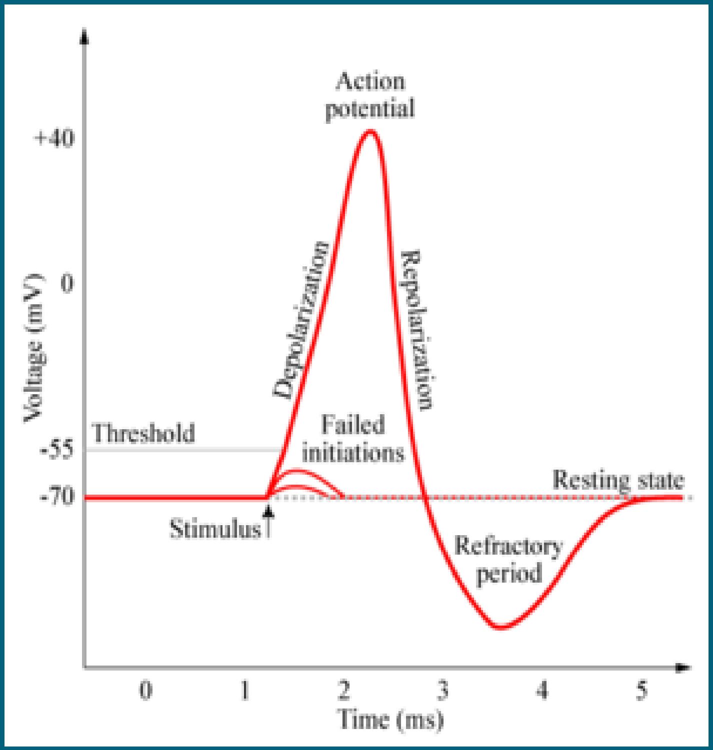
Review of Physiology: Myocardium Composition

- Myocardial Cells have properties of:
  - Muscle Cells
    - Contract when stimulated
  - Nerve Cells
    - Propagate Action Potential



Review of Physiology: Nanoscale Structure

- At the nano level
  - Cascade of ion channels
  - K and Na ion concentration change
  - Nernst potential gives V_m, membrane potential



Review of Physiology: Nanoscale Structure

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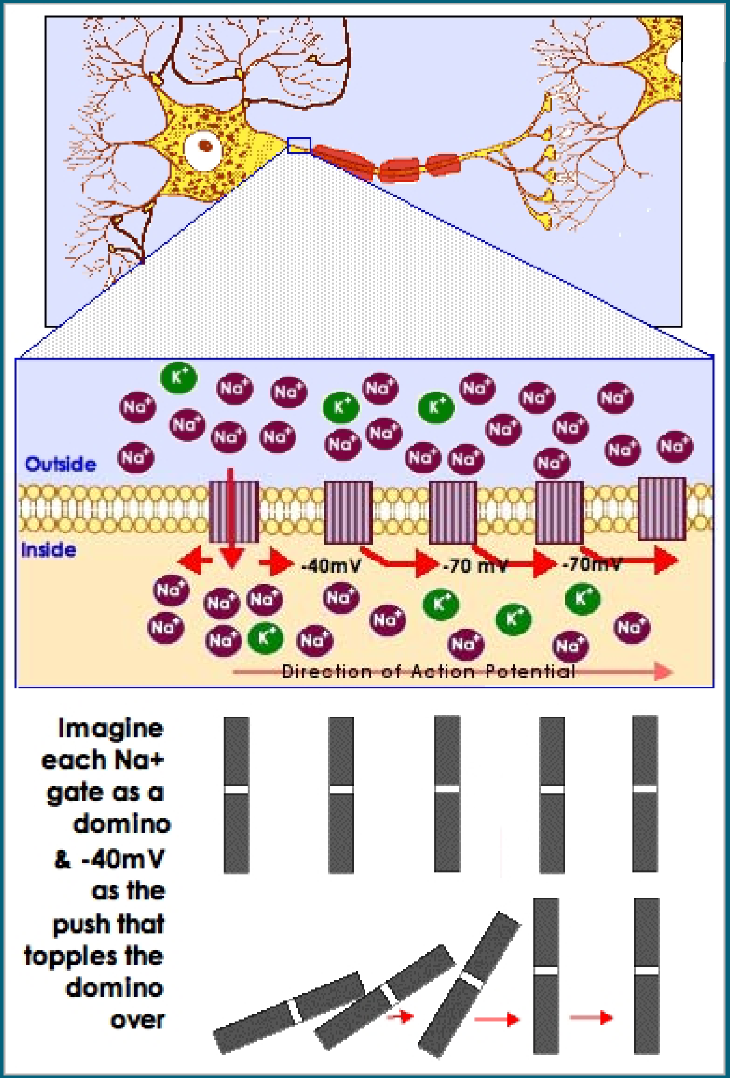


Understanding Arrhythmias

- Understand the underlying mechanism of how Action Potential results in Arrhythmias

1. Examine a mathematical model
2. Understand what happens in a healthy model
3. Change conditions to identify diseased heart

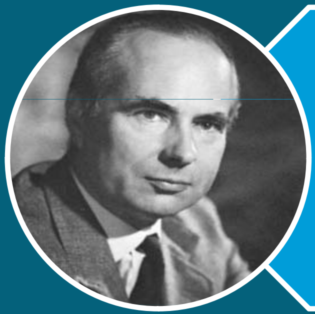
Outline of the Presentation

- Modeling an Action Potential
  - Hodgkin-Huxley Model
  - Cable Theory
- Simulations in MATLAB
  - Linear, Ring, and 2D Mesh Models
  - ECG (Extracellular Potential)
  - Defibrillator
- Discussion and Conclusion

Review of Dr. Clancy's Lectures: Hodgkin and Huxley

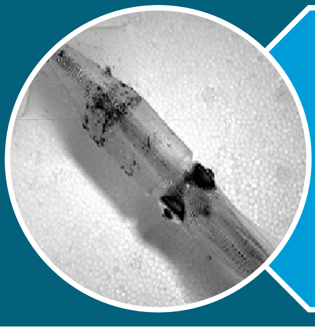
Sir Alan Hodgkin

- Physiologist and Biophysicist
- 1914 - 1998



Sir Andrew Huxley

- Nobel Laureate, 1963
- 1917 -

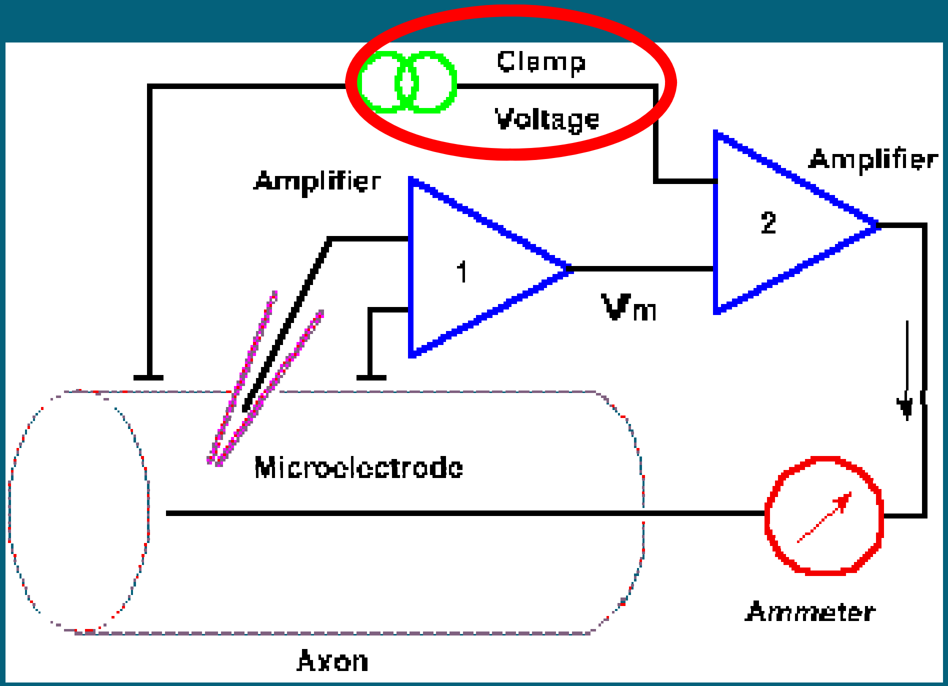


Loligo forbesi, the Squid

- 1 mm diameter axon
- Axon used in experiment

Review of Dr. Clancy's Lectures: Voltage Clamp

1. User sets clamp potential, V_{clamp}
2. Voltage electrode records V_m
3. Current amp injects + or - current if V_m is different from V_{clamp}
4. Injected current compensates fast enough such that V_m stays at V_{clamp}

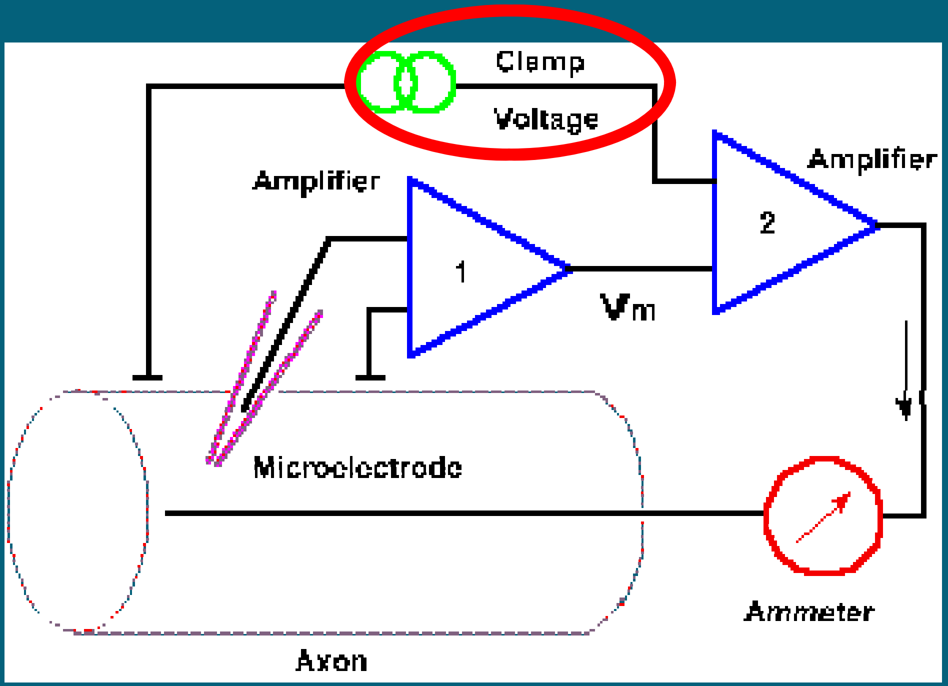


Review of Dr. Clancy's Lectures: Voltage Clamp

5. Measure V_m and current I.

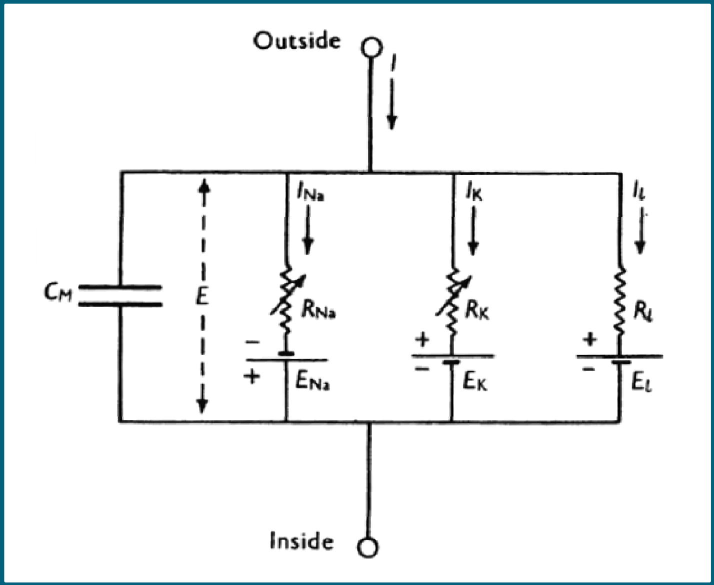
Advantages:

Can measure E_K, I_K, E_{Na}, or I_{Na}



Review of Dr. Clancy's Lectures: Membrane Circuit Assumptions

- Membrane Circuit
  - Circuit representation of the membrane
  - K component
  - Na Component
  - Loading Component



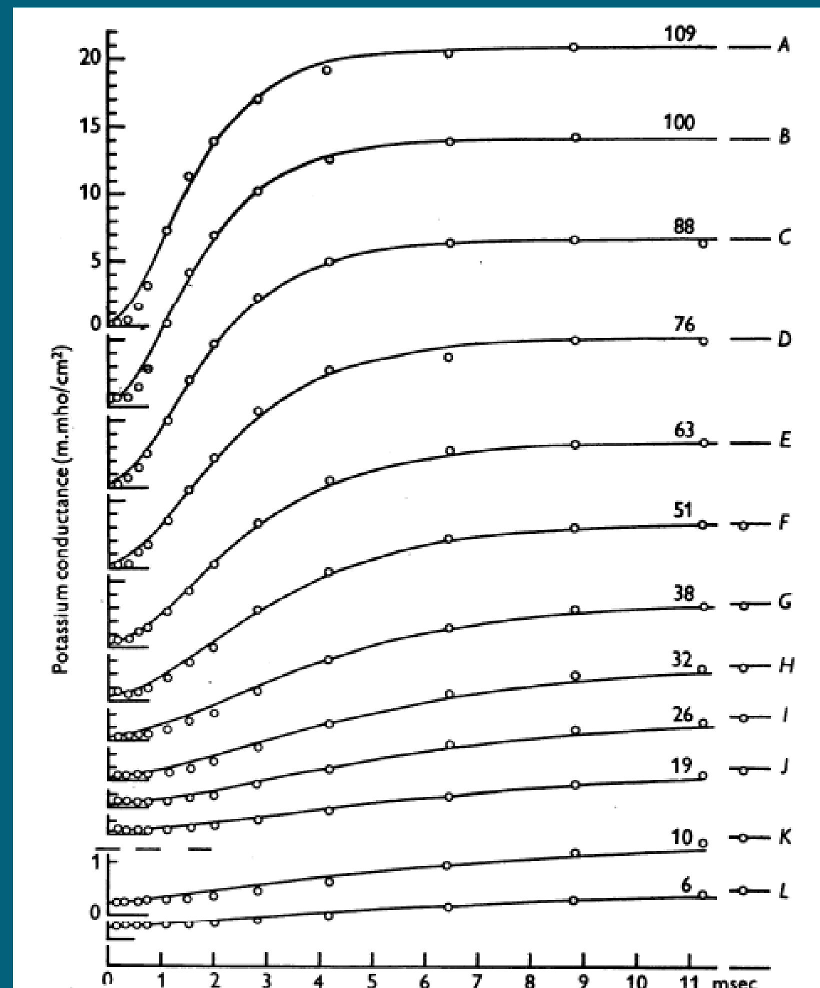
A Quick Summary of HH

- For the K channel
  - Developed response to clamped Voltage
  - Conductance g_K vs t plotted for different V_c

Fixed

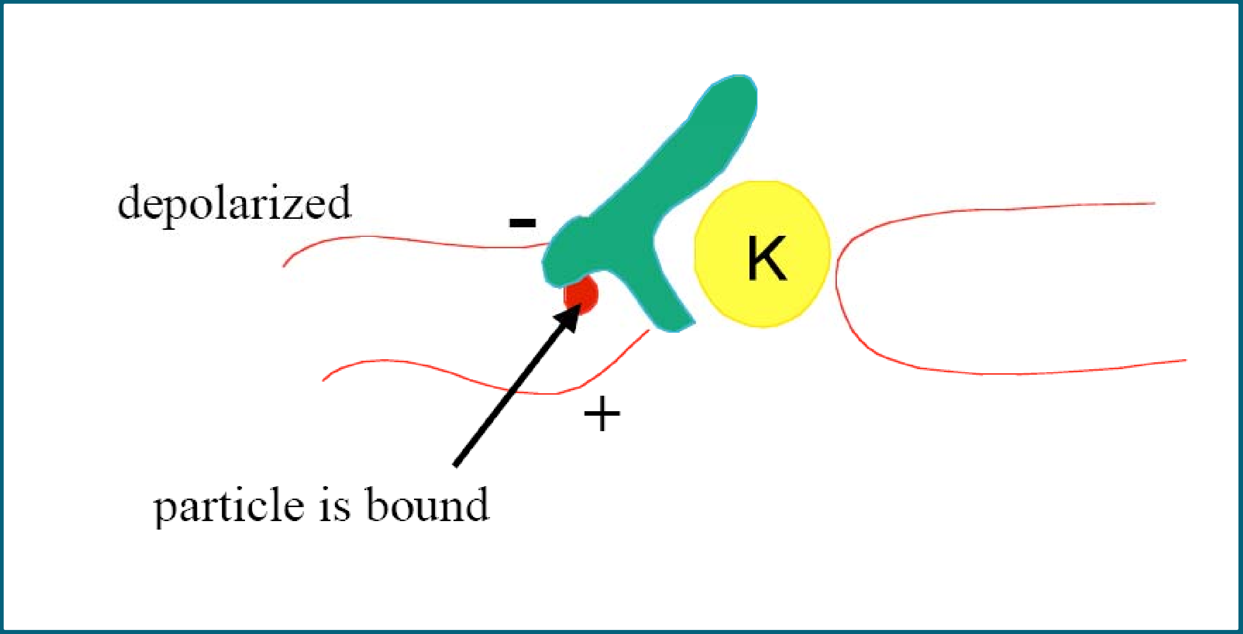
$$g_K = I_K / (V_c - E_K)$$

Measured



A Quick Summary of HH

- Hypothesized Voltage Gate for Potassium



- Defined n : (1-n) as ratio between bound to unbound particle, where n is a fraction.

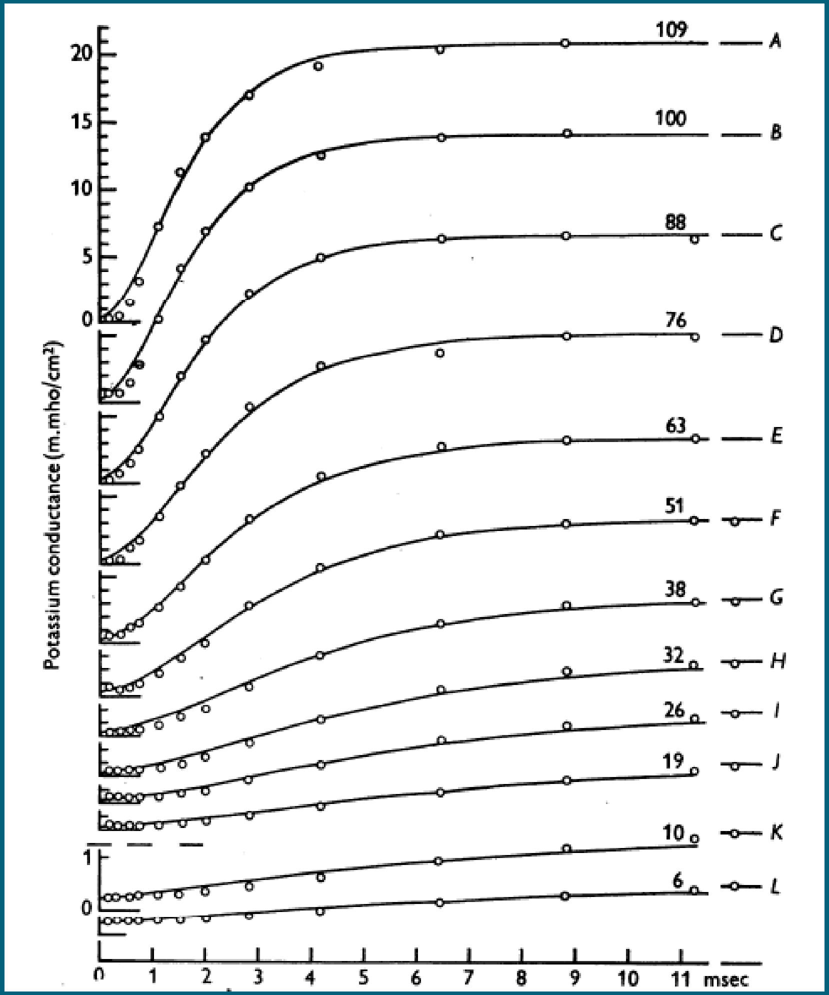
A Quick Summary of HH

- From Plot:

Found Eqn.

$$g_K = \bar{g}_K n^4$$

HH found n^4
fitted data well.



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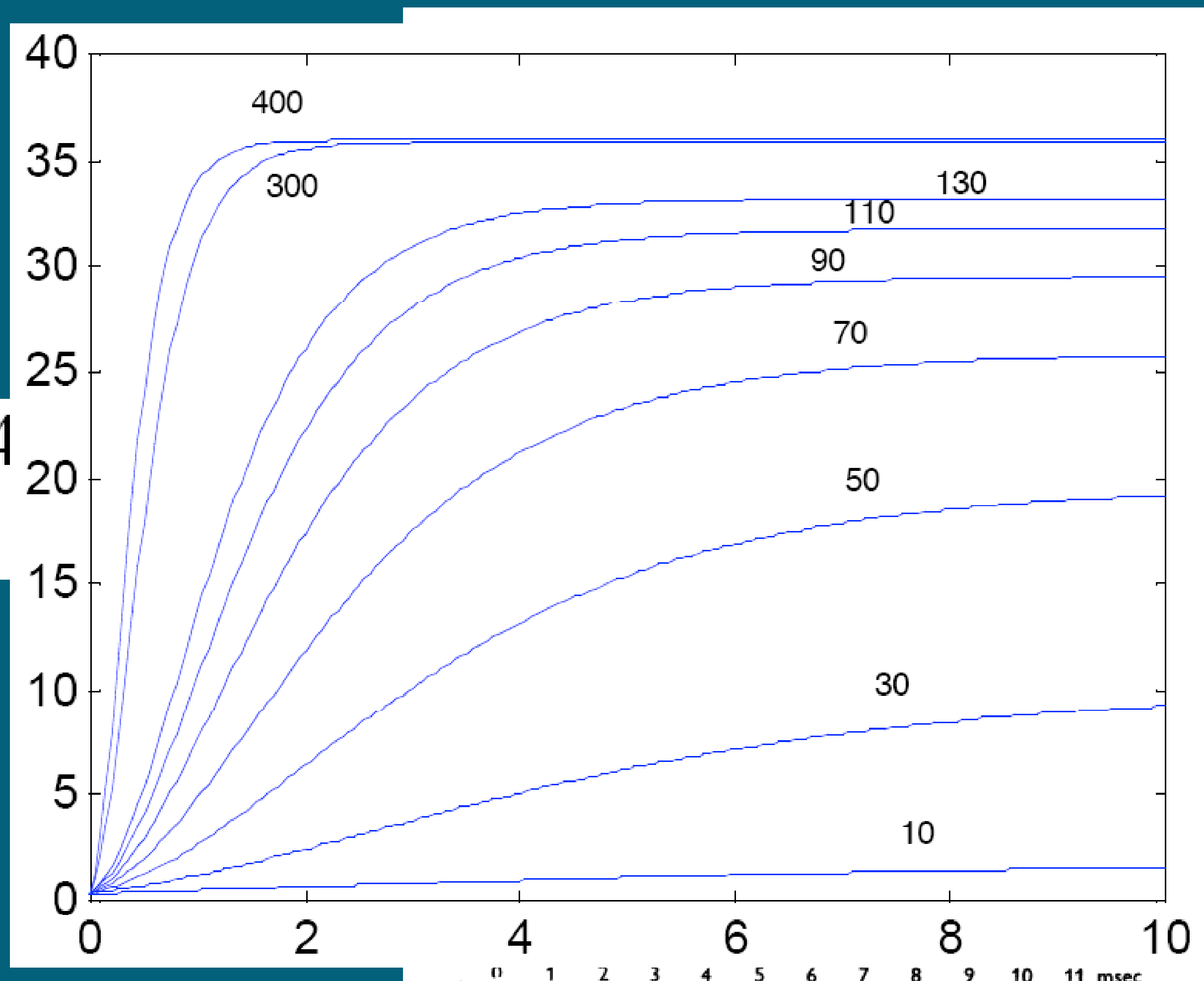
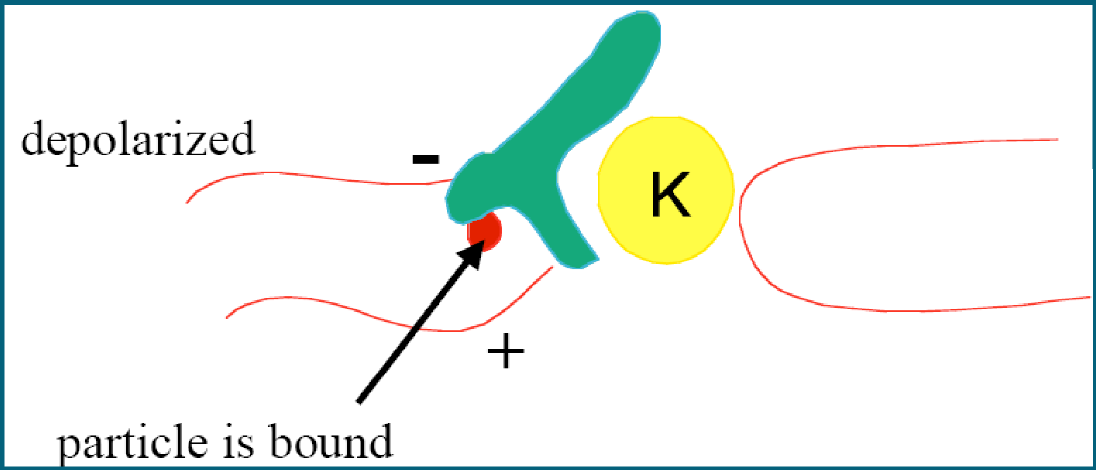


A Quick Summary of HH

Q. Why do we have an n^4?

A. n^4 means 4 particles needed to open gate
Thus, P(open gate) = $n \times n \times n \times n = n^4$



A Quick Summary of HH

Q. How do we get n in:

$$g_K = \bar{g}_K n^4$$

A. Define n, a function of time as:

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

Its derivative takes form:

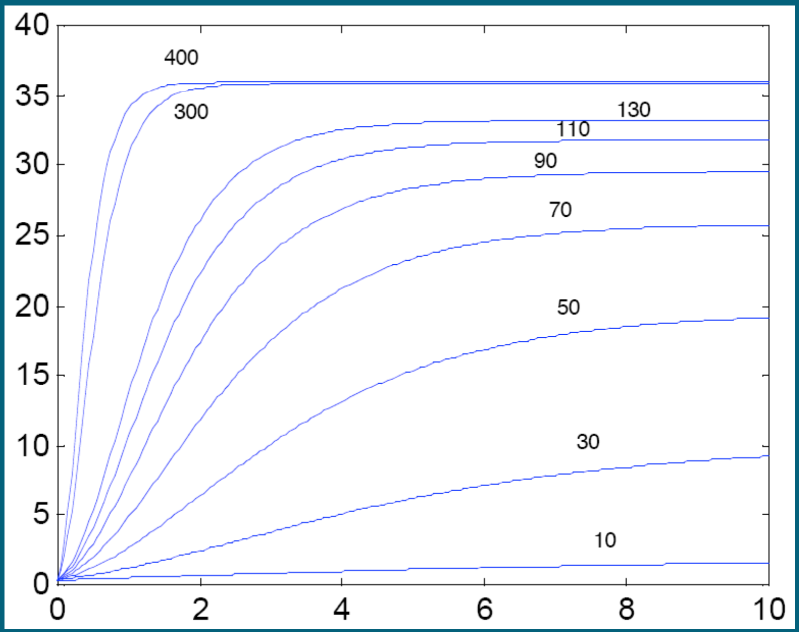
$$\frac{dn}{dt} = \alpha_n(1-n) - \beta_n n$$

A Quick Summary of HH

Q. How do we get n in:

$$g_K = \bar{g}_K n^4$$

A. Find time constant τ and n_∞ from plot



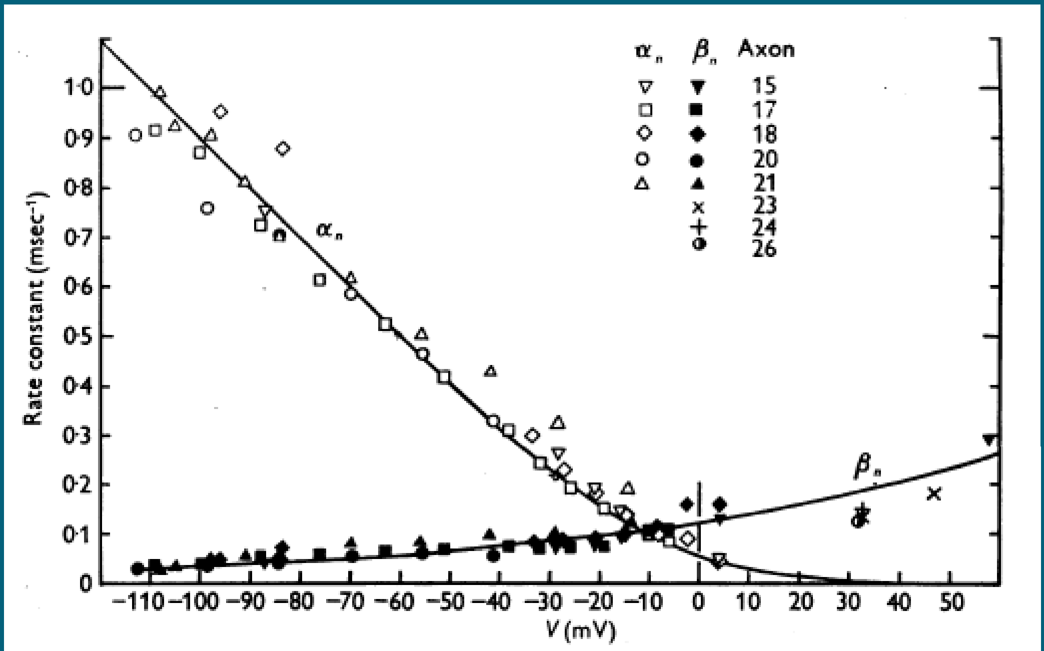
$$\tau_n = \frac{1}{\alpha_n(V_{Clamp}) + \beta_n(V_{Clamp})}$$

$$n_\infty = \frac{\alpha_n(V_{Clamp})}{\alpha_n(V_{Clamp}) + \beta_n(V_{Clamp})}$$

A Quick Summary of HH

Q. How do we get n in: $$g_K = \bar{g}_K n^4$$

A. Make a plot of rate constants α and β for each V_C



A Quick Summary of HH

$$g_K = \bar{g}_K n^4$$

Q. How do we get n in:

A. Curve fit for α and β to obtain:

$$\alpha_n = 0.01 \frac{10 - V_m}{\exp\left(\frac{10 - V_m}{10}\right) - 1}$$

$$\beta_n = 0.125 \exp\left(\frac{-V_m}{80.0}\right)$$

A Quick Summary of HH

Q. How do we get n in:

$$g_K = \bar{g}_K n^4$$

A. Substitute back α and β to obtain:

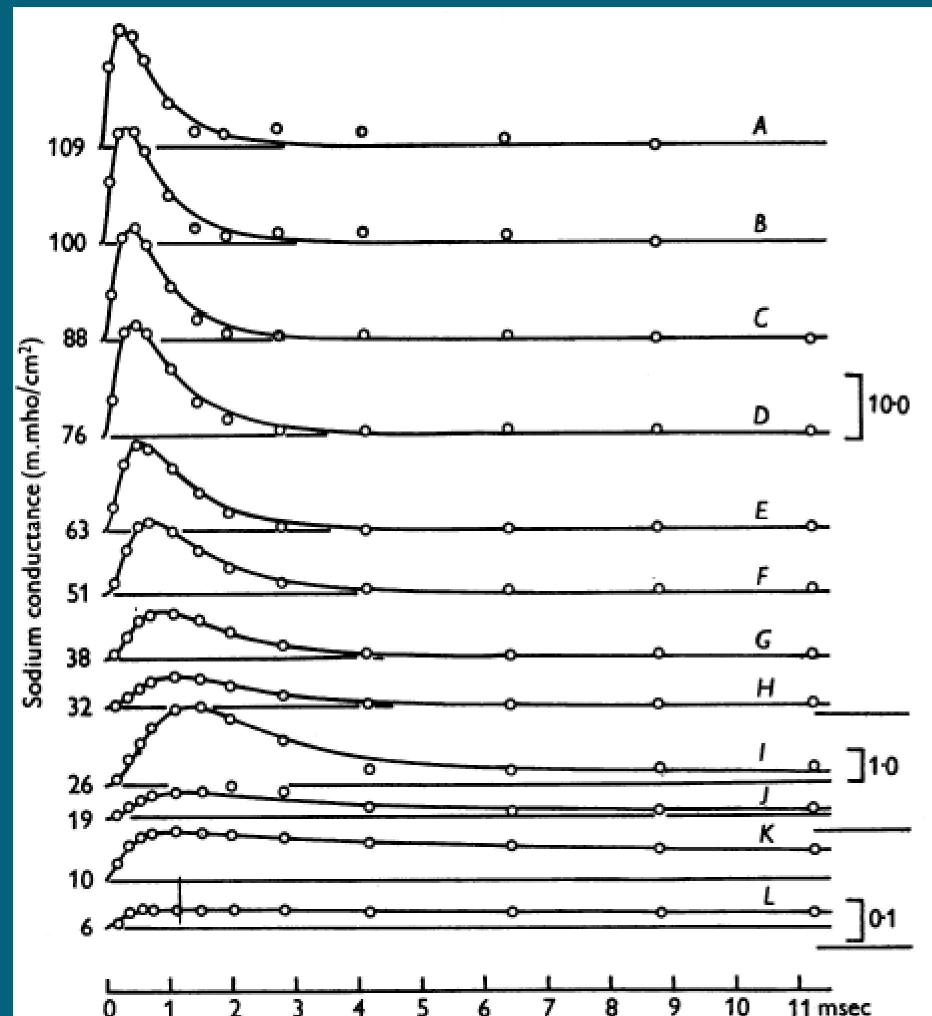
$$\frac{dn}{dt} = \alpha_n (1-n) - \beta_n n$$

Integrate this to finally obtain n.

A Quick Summary of HH

- For the Na channel
  - Found g_{Na}
  - Hypothesized Na gate satisfied the equation:

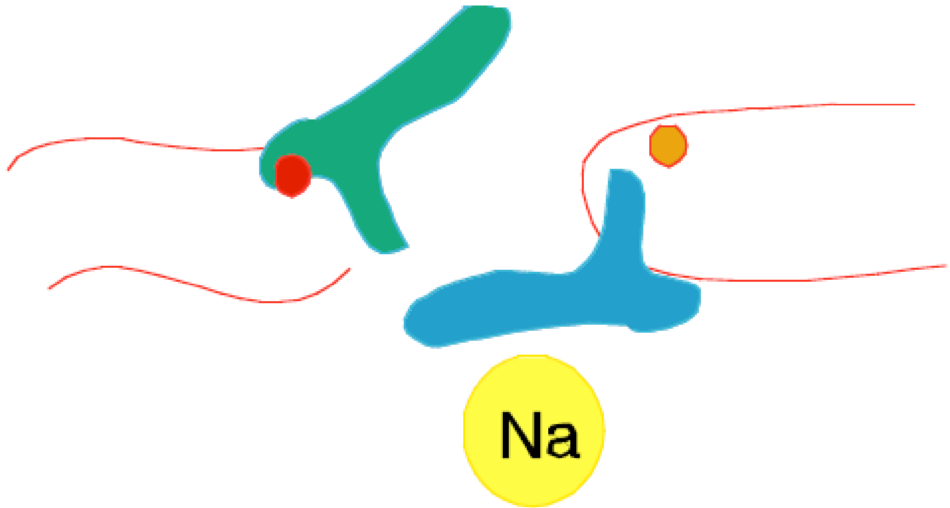
$$g_{Na} = \bar{g}_{Na} m^3 h$$



A Quick Summary of HH

Q. Why do we have an *m* and *h* this time?

late
depolar



Particles both on
outside

- Defined m : (1-m) and h : (1-h) as ratios for each of bound to unbound particles

A Quick Summary of HH

$$g_{Na} = \bar{g}_{Na} m^3 h$$

Q. How to get m, h in:

A. Find α_m, β_m and α_h, β_h just like last time:

$$\frac{dm}{dt} = \alpha_m (1 - m) - \beta_m m$$

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

A Quick Summary of HH

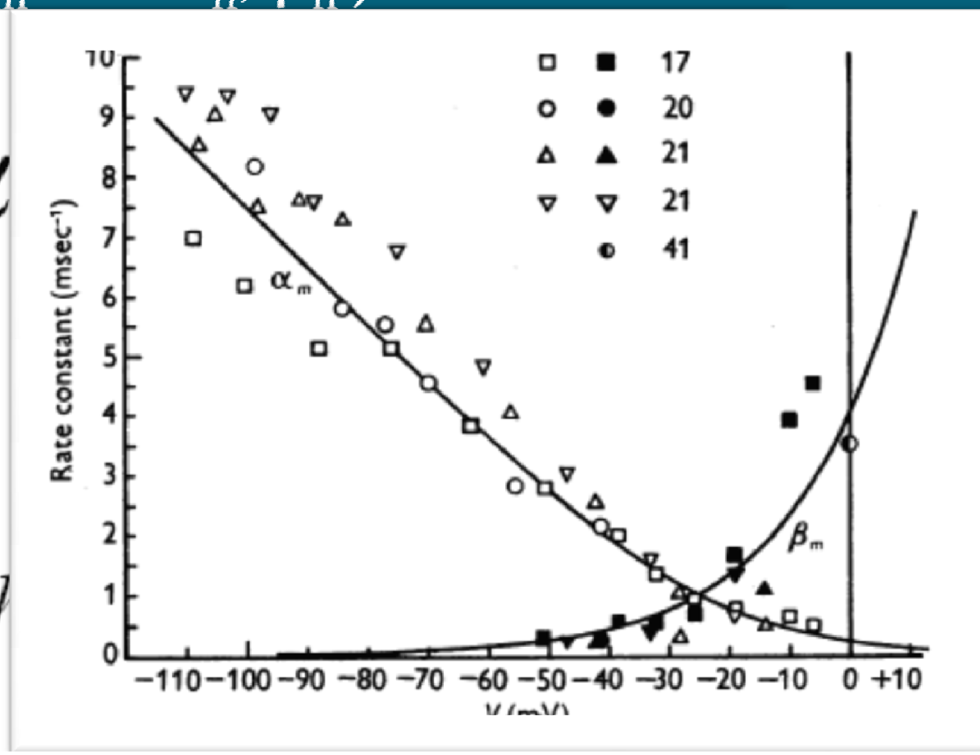
Q. How to get m, h in:

$$g_{Na} = \bar{g}_{Na} m^3 h$$

A. Find α_m, β_m and α_h, β_h just like last time:

$$\frac{dm}{dt} = \alpha$$

$$\frac{dh}{dt} = \alpha_h$$



A Quick Summary of HH

$$g_{Na} = \bar{g}_{Na} m^3 h$$

Q. How to get m, h in:

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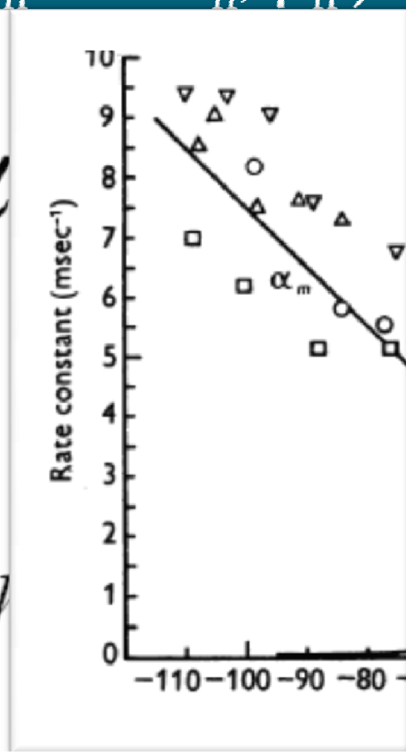
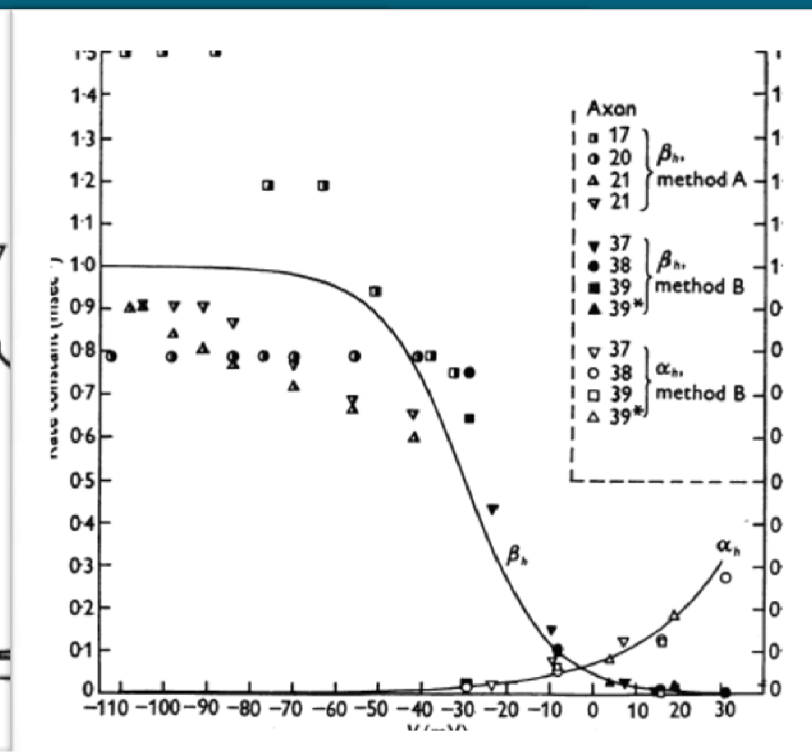




The HH Model of AP

- Putting it all together:

$$\frac{dv_m}{dt} = -\frac{1}{C_m}(I_{Na} + I_K + I_L) \qquad I_{Na} = \bar{g}_{Na} m^3 h (v_m - e_{Na})$$

$$\frac{dm}{dt} = \alpha_m (1 - m) - \beta_m m \qquad I_K = \bar{g}_K n^4 (v_m - e_K)$$

$$\frac{dh}{dt} = \alpha_h (1 - h) - \beta_h h \qquad I_L = \bar{g}_L (v_m - e_L)$$

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

The HH Model of AP

- Putting it all together:

$$\frac{dv_m}{dt} = \ldots$$

$$\frac{dm}{dt} = \ldots$$

$$\frac{dh}{dt} = \ldots$$

$$\frac{dn}{dt} = \ldots$$

$$\alpha_m = 0.1\frac{25 - V_m}{\exp\left(\frac{25 - V_m}{10}\right) - 1}$$

$$\beta_m = 4.0\exp\left(\frac{-V_m}{18.0}\right)$$

$$\alpha_h = 0.07\exp\left(\frac{-V_m}{20.0}\right)$$

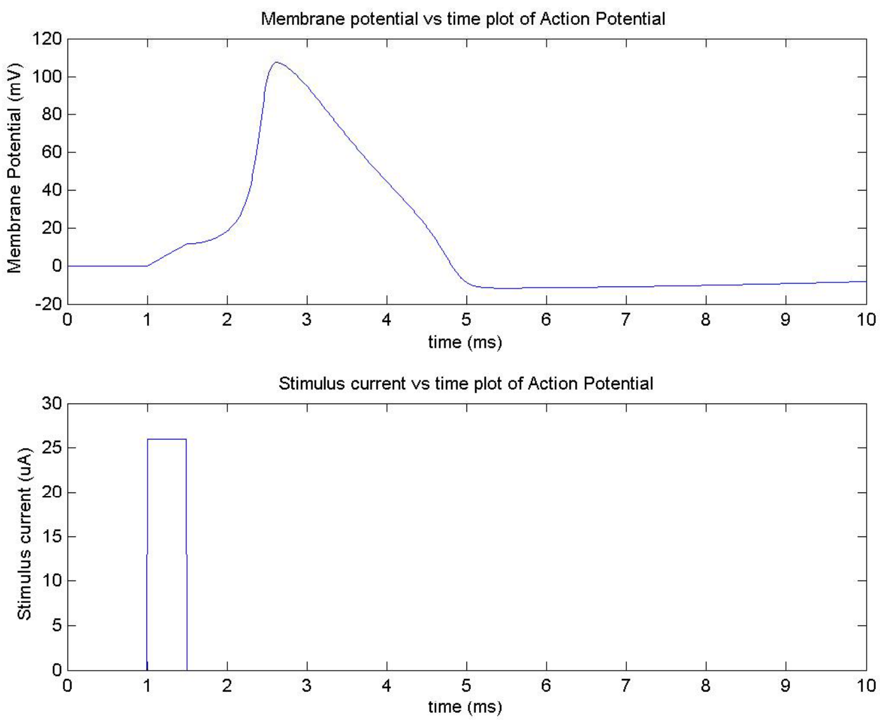
$$\beta_h = \frac{1}{\exp\left(\frac{30 - V_m}{10}\right) + 1}$$

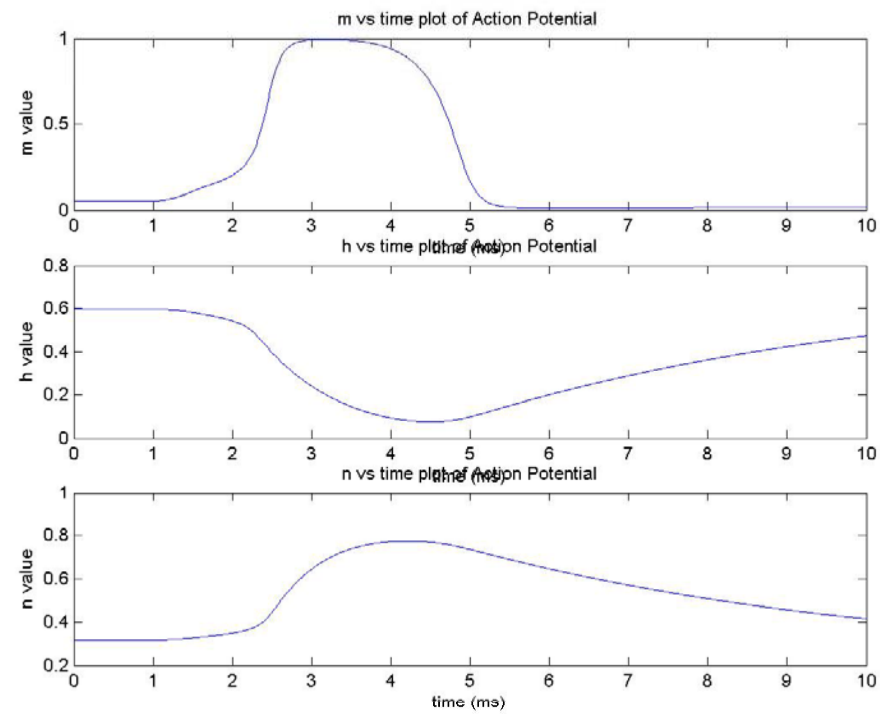
$$\alpha_n = 0.01\frac{10 - V_m}{\exp\left(\frac{10 - V_m}{10}\right) - 1}$$

$$\beta_n = 0.125\exp\left(\frac{-V_m}{80.0}\right)$$

The HH Model of AP

- Implementation in Matlab over 10 ms.





How do we propagate the AP?

Idea 1: Traveling Wave Solutions

Eg. Fitzhugh-Nagumo Equation

$$\frac{dV_m}{dt} = F_v = V_m\left(\frac{V_m}{V_t} - 1\right)\left(1 - \frac{V_m}{V_p}\right) - W$$
$$\frac{dW}{dt} = F_g = C(v_m + A - BW)$$

V = membrane potential

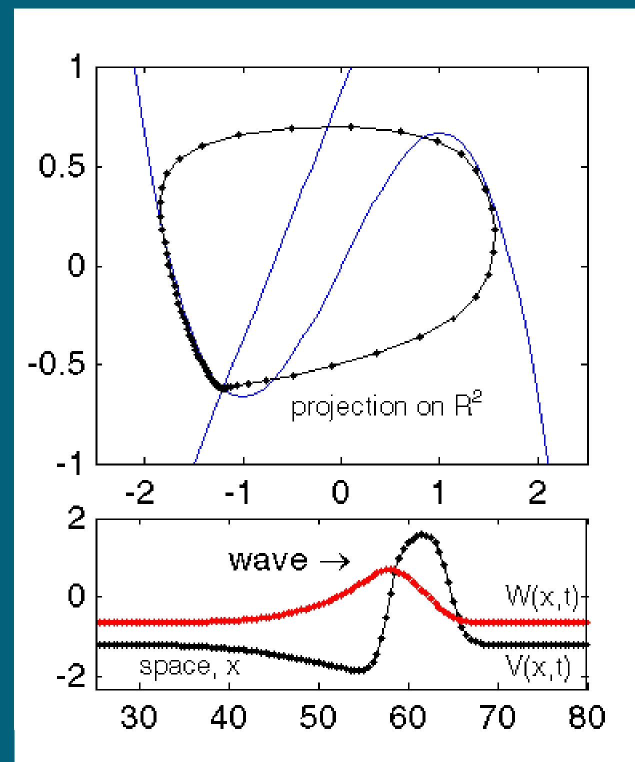
W = recovery variable

How do we propagate the AP?

Idea 1: Traveling Wave Solutions

$$\frac{dV_m}{dt} = F_v = V_m\left(\frac{V_m}{V_t} - 1\right)\left(1 - \frac{V_m}{V_p}\right) - W$$

$$\frac{dW}{dt} = F_g = C(v_m + A - BW)$$

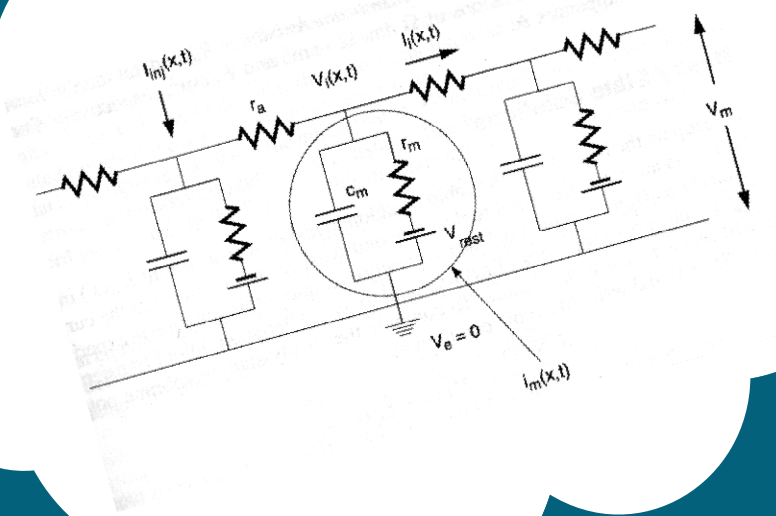


But... Incompatible with HH

We'd be happy to discuss this another day (please don't ask)

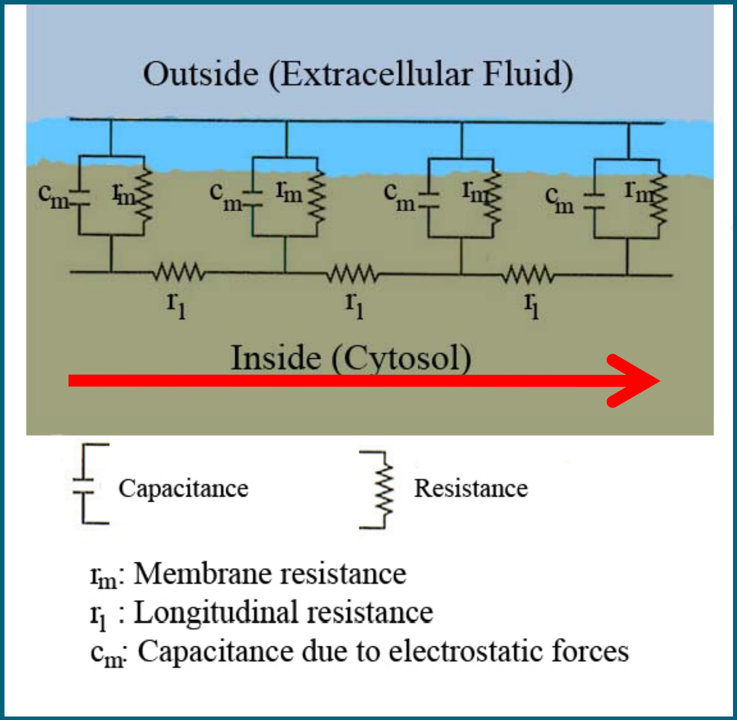
How do we propagate the AP?

- Idea 2: Cable Theory!



Introduction to Cable Theory

- We want to see how an action potential travels forward through a fiber.
- Line up Resistor-Capacitor in parallel
- Potential propagates from left to right



Combining Cable with HH

Q. Can we run an action potential through a cable fiber?

A. Yes!

$$C_m \frac{\partial v_m}{\partial t} = \frac{a}{2R_i} \frac{\partial^2 v_m}{\partial x^2} - \frac{v_m}{R_m}$$

We can program this in MATLAB and solve for a system of differential equations.

Discretization in space and in time

Discretization in space

$$0 = \frac{1}{r_i}\frac{\partial^2 v_m}{\partial x^2} - \frac{v_m}{r_m}$$

$$\frac{\partial^2 v_m}{\partial x^2} = \frac{\Phi(x+\Delta x) - 2\Phi(x) + \Phi(x-\Delta x)}{\Delta x^2}$$

Discretization in space and in time

Discretization in space

$$\begin{vmatrix} BC & BC & 0 & 0 & 0 & BC \\ 1 & -2 & 1 & 0 & 0 & 0 \\ 0 & 1 & -2 & 0 & 0 & 0 \\ 0 & 0 & 1 & -2 & 1 & 0 \\ 0 & 0 & 0 & 1 & -2 & 1 \\ BC & 0 & 0 & 0 & BC & BC \end{vmatrix} \begin{vmatrix} \Phi(1) \\ \Phi(2) \\ \Phi(3) \\ \Phi(4) \\ \Phi(5) \\ \Phi(6) \end{vmatrix} = \frac{\Delta x^2 r_i}{r_m} \begin{vmatrix} \Phi(1) \\ \Phi(2) \\ \Phi(3) \\ \Phi(4) \\ \Phi(5) \\ \Phi(6) \end{vmatrix}$$

Markov-based Equation

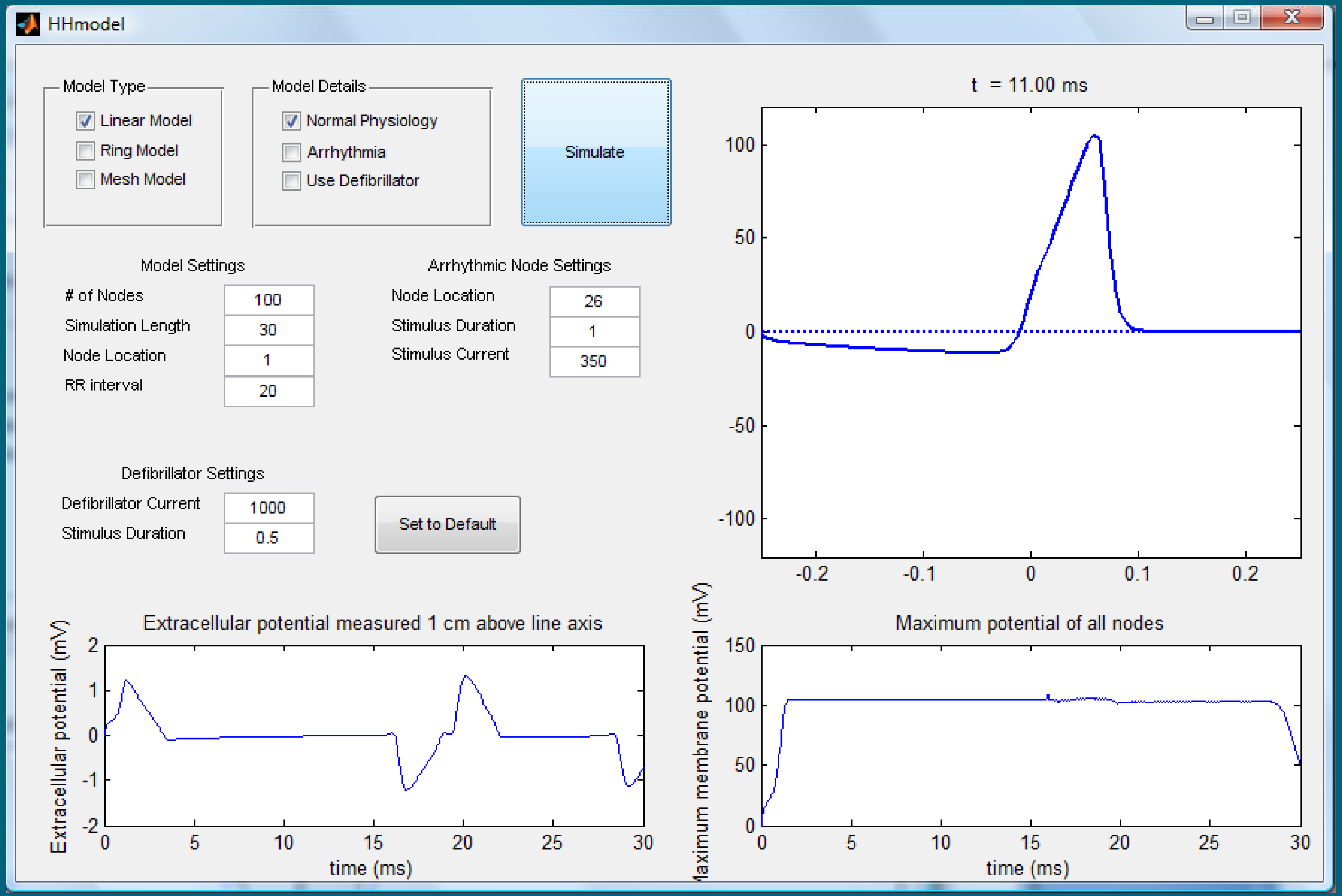
Discretization in time

$$C_m \frac{\partial v_m}{\partial t} = \frac{a}{2R_i} \frac{\partial^2 v_m}{\partial x^2} - \frac{v_m}{R_m}$$

$$C_m \frac{v_m^{t+1} - v_m^t}{dt} = \frac{a}{2R_i} \frac{\partial^2 v_m^t}{\partial x^2} - \frac{v_m^t}{R_m}$$

$$v_m^{t+1} = v_m^t + \frac{dt}{C_m}\left(diag\left(\frac{a}{2R_i}\right)Av_m^t - \frac{v_m^t}{R_m}\right)$$

Simulations: Linear and Ring



ElectroCardioGram (ECG)

- We can measure the extracellular potential
  - Need the position of the probe and the nodes
  - Principle of superposition

$$M(x) = \pi a^2 \sigma_i \frac{\partial^2 v_m}{\partial x^2}$$

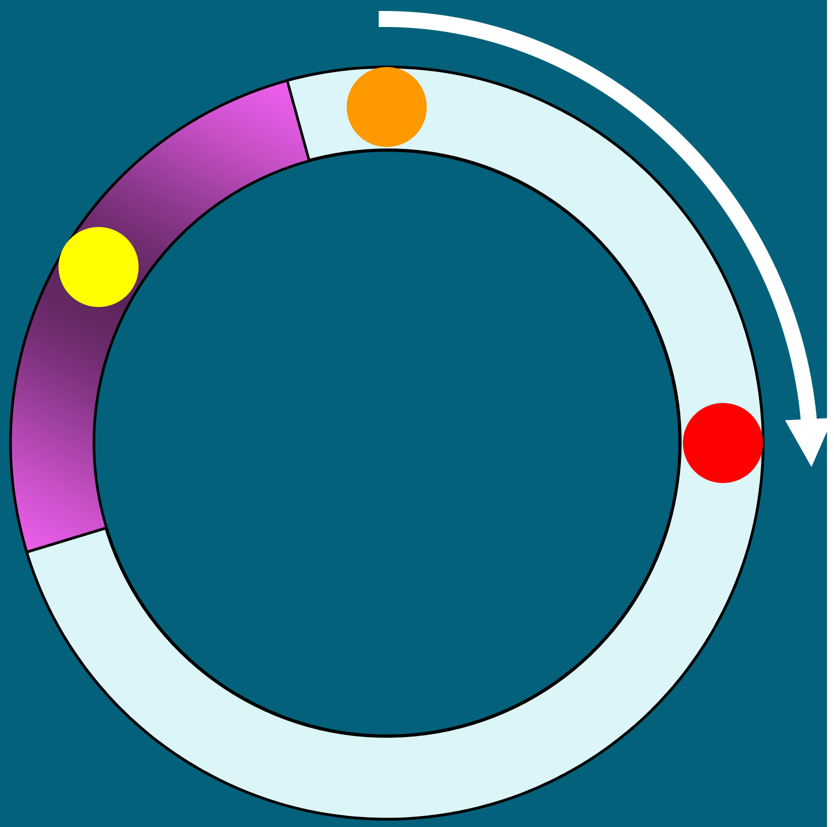
$$\Phi = \frac{1}{4\sigma_e}\left(\frac{M_1}{r_1} + \frac{M_2}{r_2} + \frac{M_3}{r_3} + \cdots\right)$$

Mechanism of an Arrhythmia

- Reentry
  - Normally the impulse spreads through the heart quickly enough that each cell will only respond once
  - If conduction velocity is abnormally slow in some areas, part of the impulse will arrive late and will be treated as a new impulse, which can then spread backward.

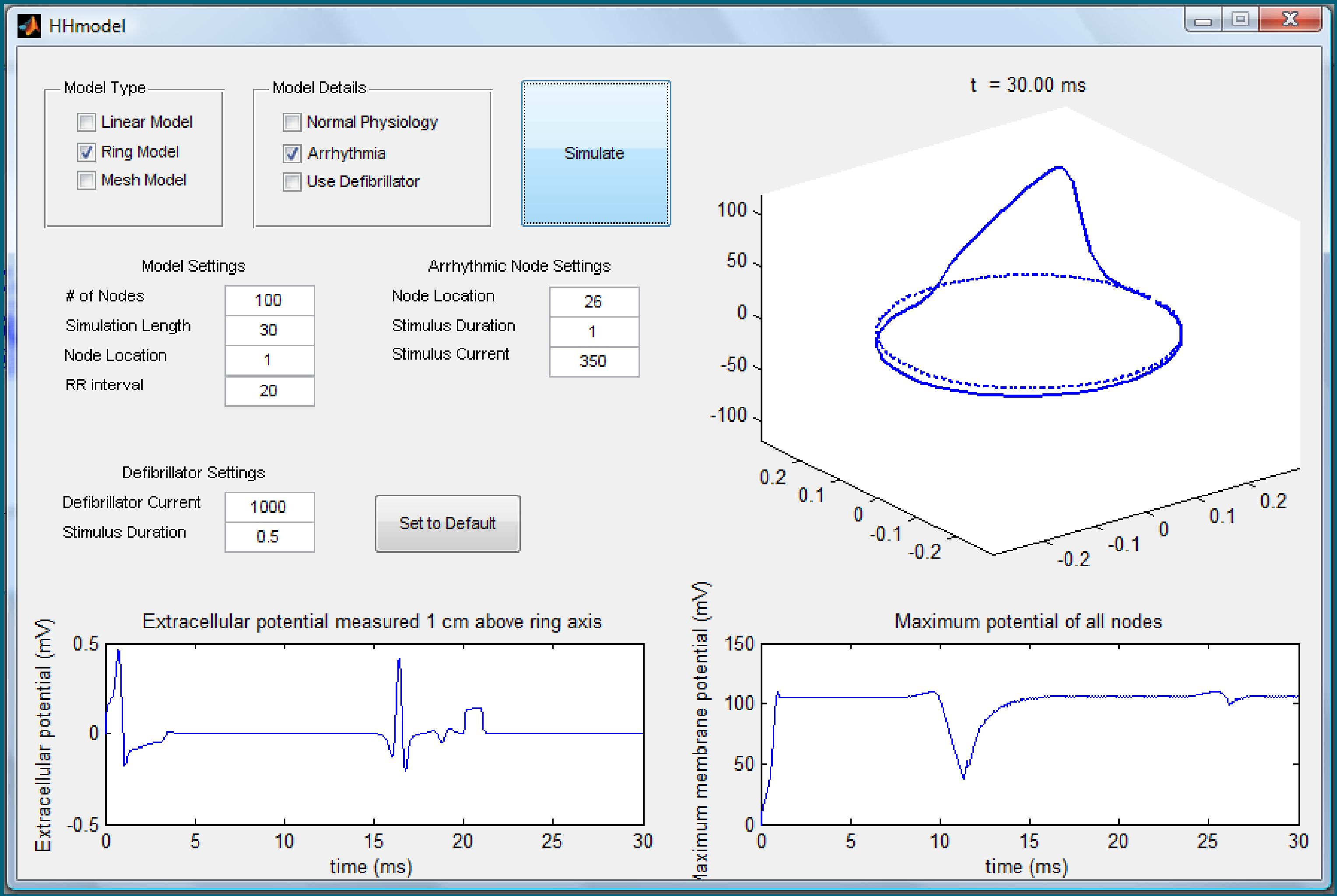
Diseased Ring Model

- Unidirectional Block and Reentry
  - Increased resistance values of select nodes (slows down)
  - Adjusted elements in Matrix A
    - All nonzero values in A were kept nonzero



$$\frac{dv_k}{dt} = v_{k-1} - v_k + v_{k+1}$$

Simulations: Ring Arrhythmia



Summary of Arrhythmia Model

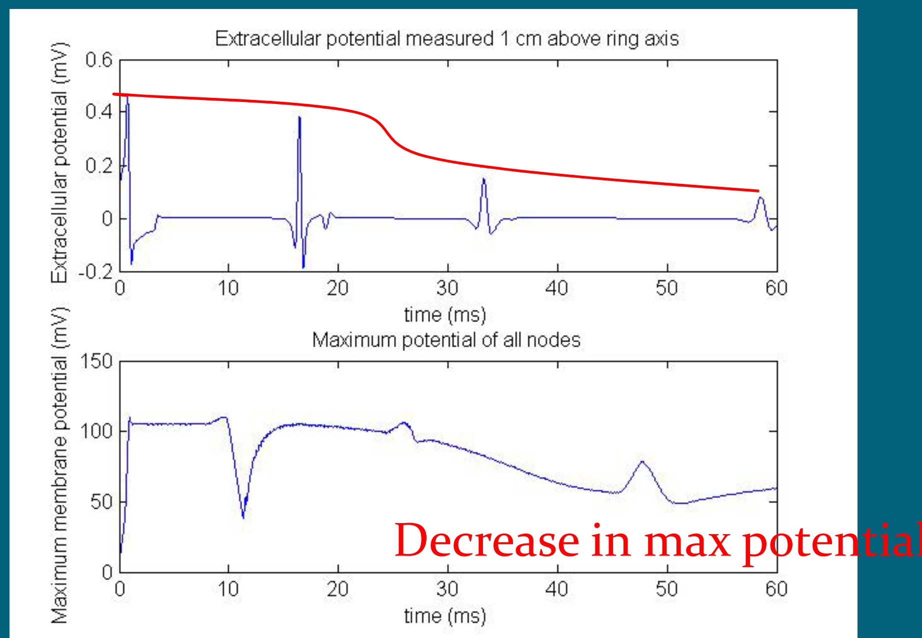
- Model Strengths:
  - Able to demonstrate a simplistic mathematical model of how an arrhythmia works.

- Model Weaknesses:
  - Single stimulus from select nodes prone to reentry
    - Unlikely in reality due to geometry of ring w/ respect to heart
    - Relative Geometry/location of unidirectional block IMPORTANT
  - Oversimplification of complex physiology

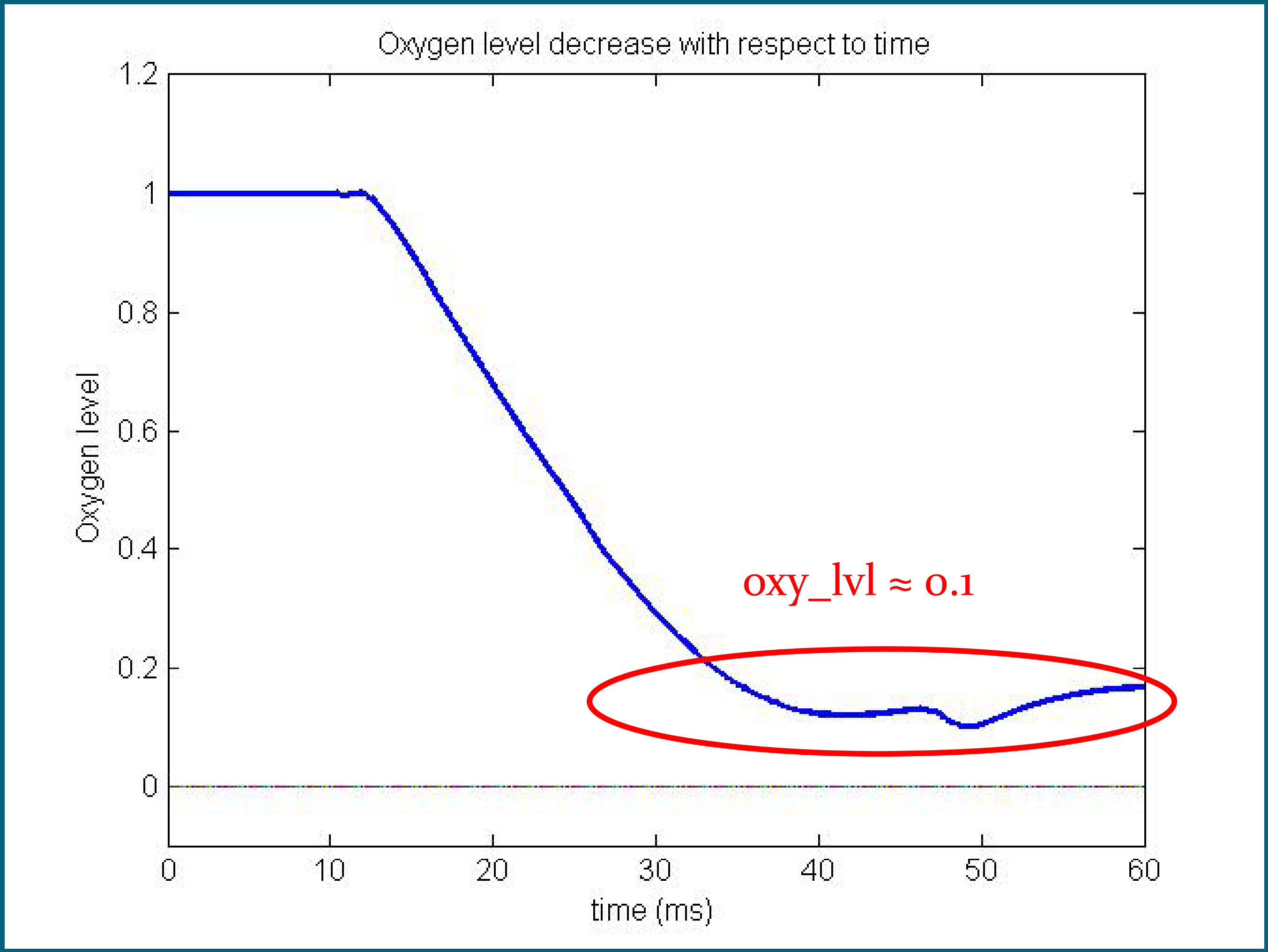
Programming a Defibrillator

- With ECG signal, can we program a defibrillator to shock our model out of arrhythmia?
- At first, this did not work
  - Needed additional parameter

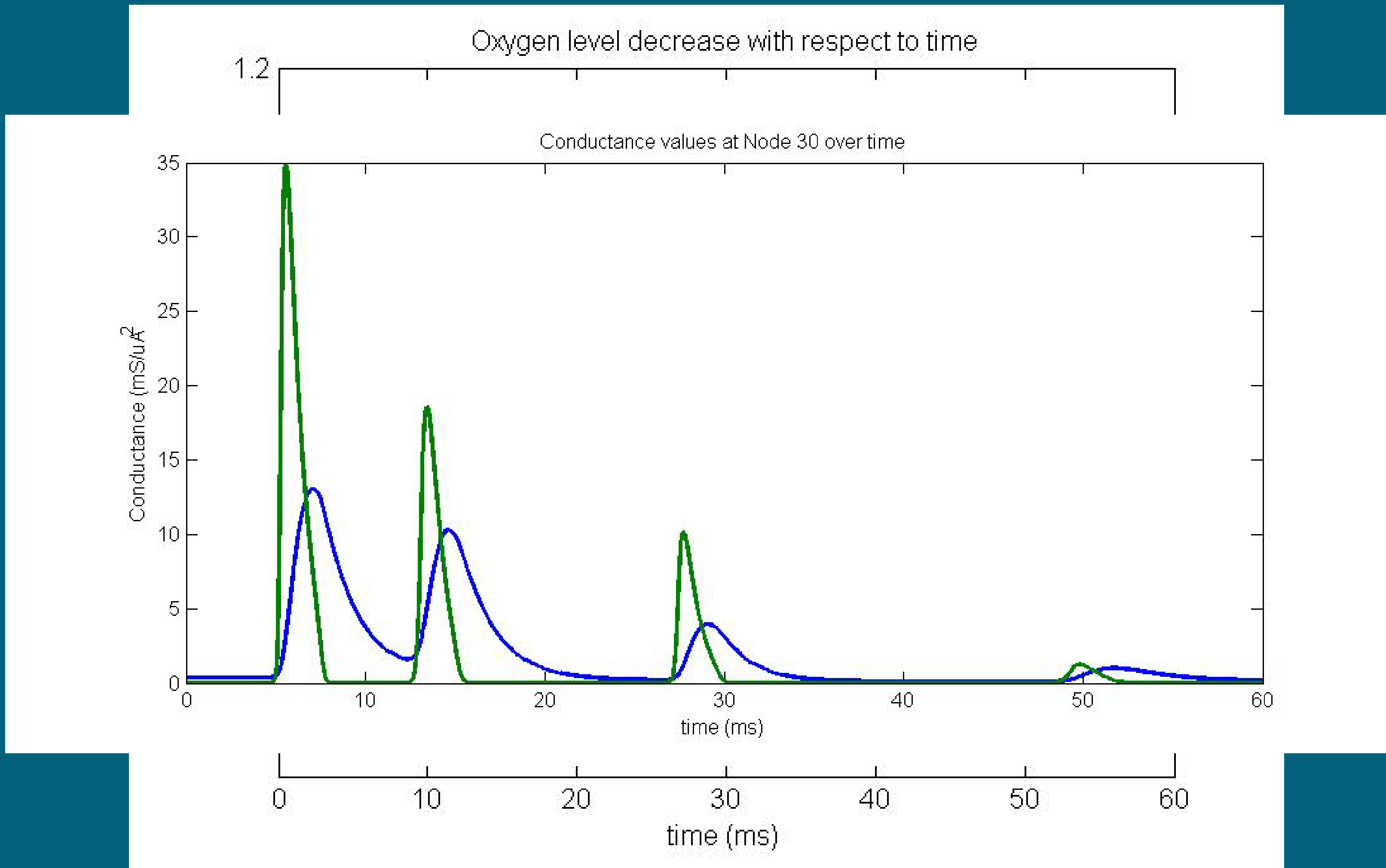
Oxygen-based propagation



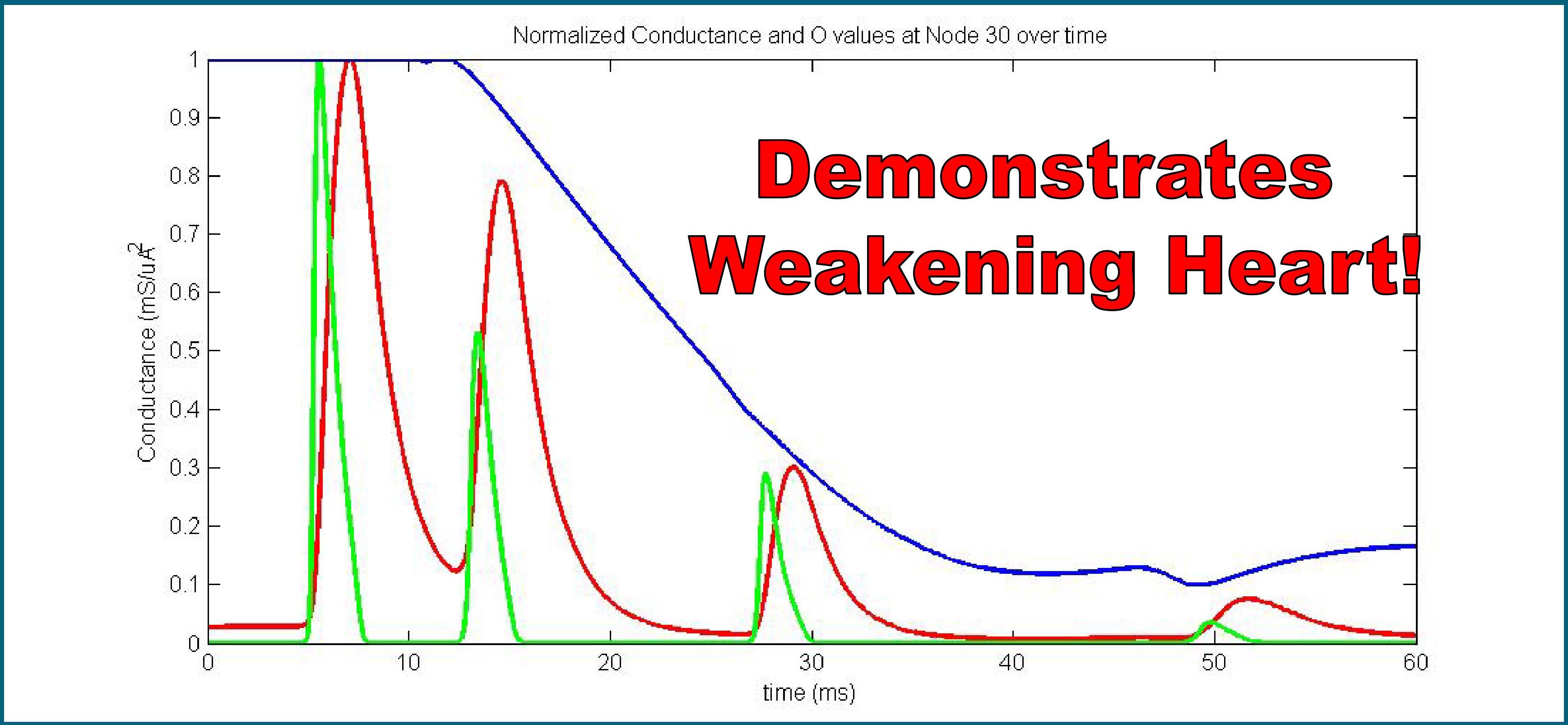
Oxygen-based propagation



Oxygen-based propagation

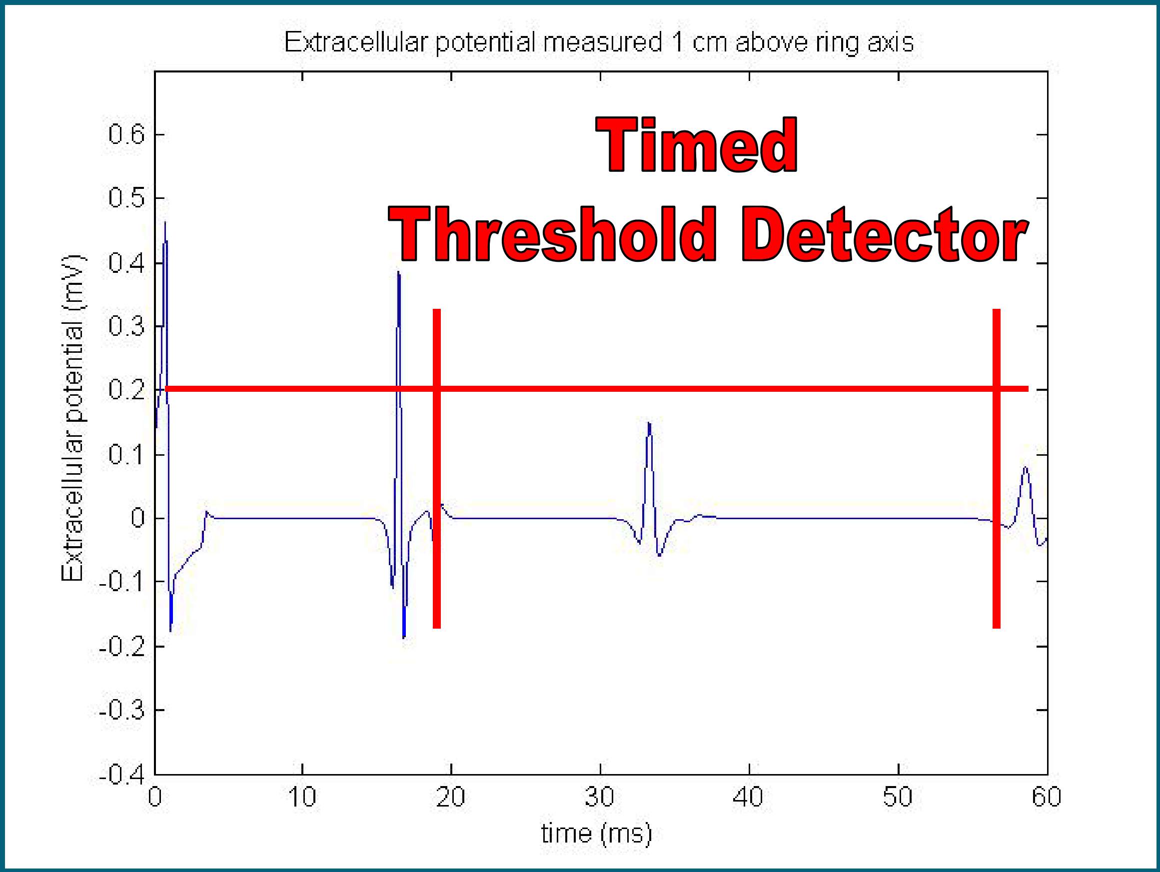


Model of Ventricular Fibrillation

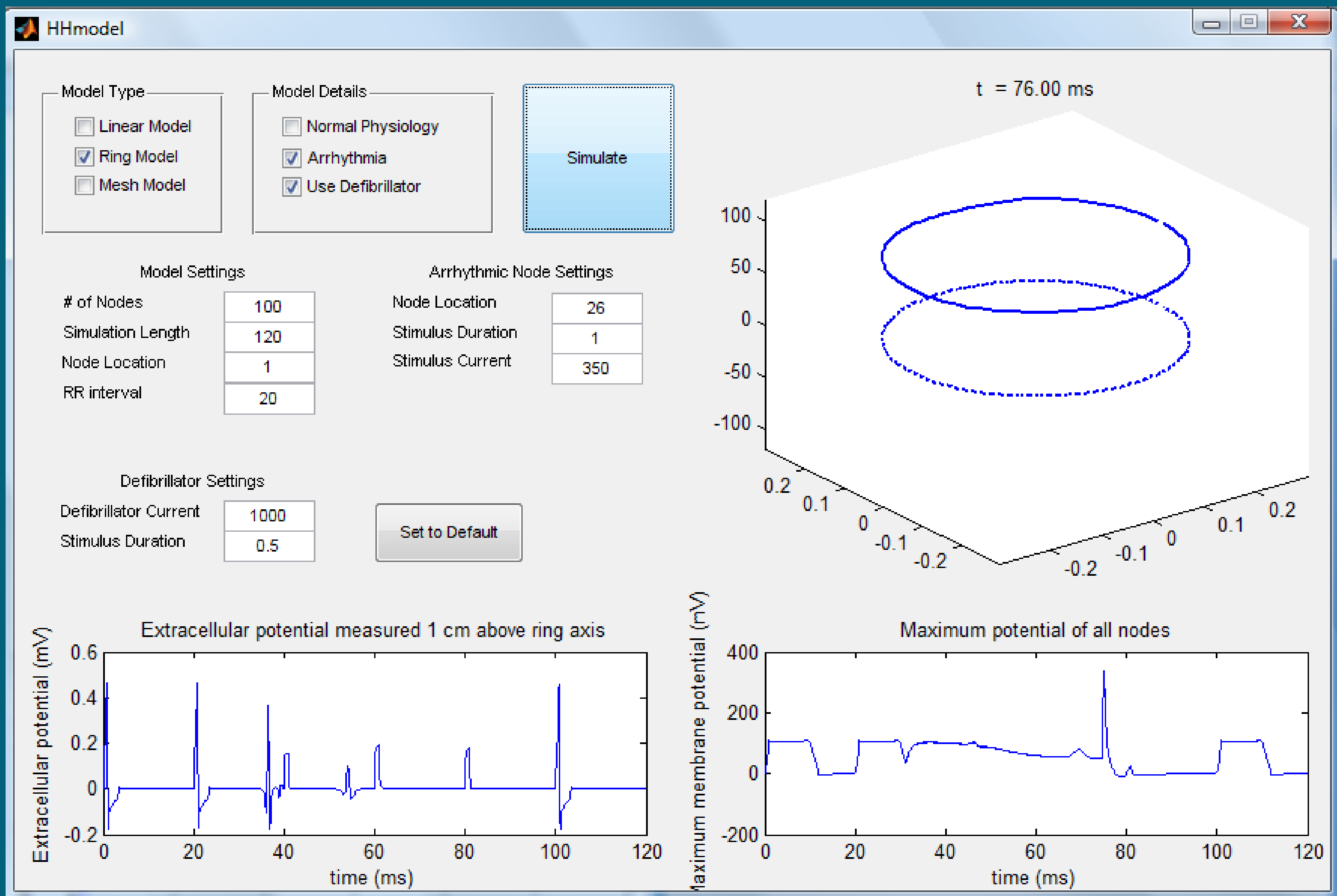


Defibrillator Algorithm

- Reality: Correlation of ECG with known VF ECG
- Our model:



Simulation with Defibrillator



Conclusion

- Successful created AP propagating HH Model
- Ring Model demonstrates concept of reentry and cardiac arrhythmia
- Using Electromagnetic Equations, we successfully simulated ECG
- Can use ECG-triggered defibrillator with dying heart model