# My Research Experience
## (Duke in a nutshell)

Rami Guirguis, MS

January 26, 2004

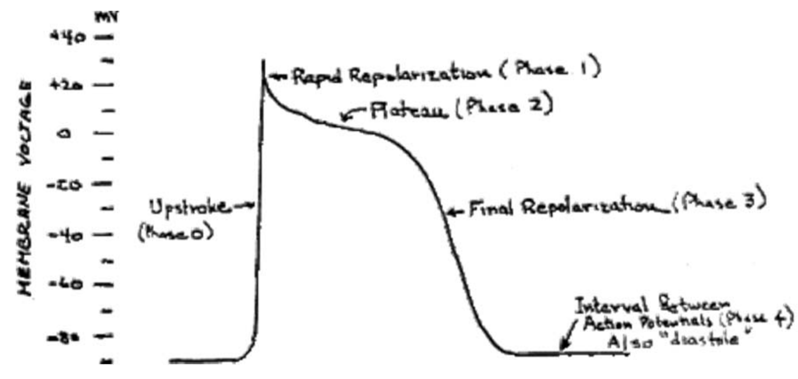
# Outline

- Introduction
- Governing Equations
- Numerical methods
- Parallelization
- Luo Rudy Dynamic (LRD)
- Cable experiments
- Membrane dynamics

# Introduction

- Computational Modeling
  - Collects much more data than experiments
  - Can be implemented without loss of life
  - Can test new methods with minimal human error

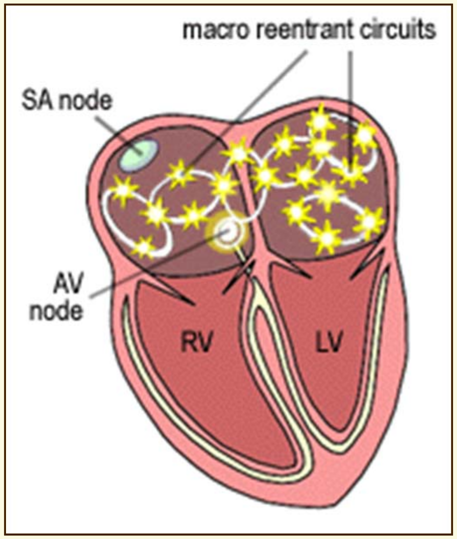
- Model Characteristics
  - Domain Structure
  - Homogeneity
  - Isotropy
  - Membrane dynamics
  - Numerical Methods
  - Stimulus Type

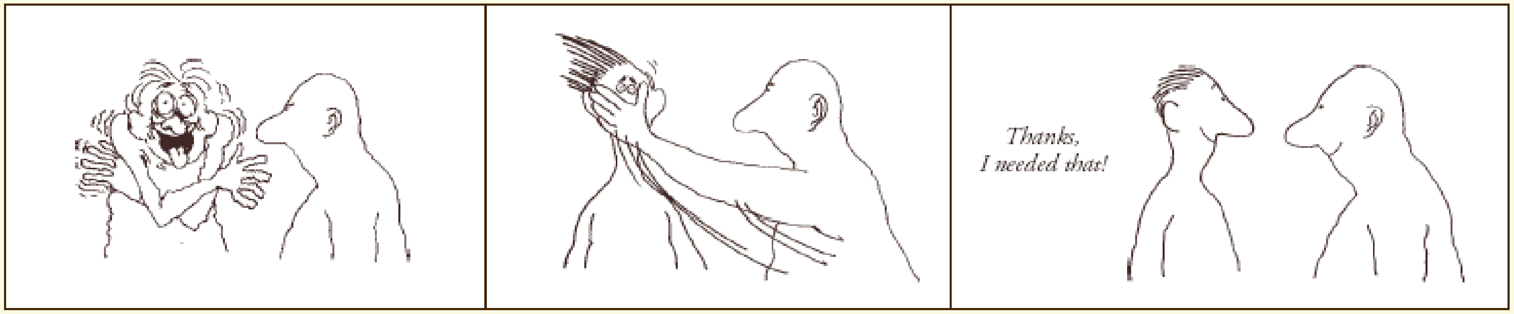



http://physioweb.med.uvm.edu/cardiacep/NewHandout/cardiac3.htm

# Introduction

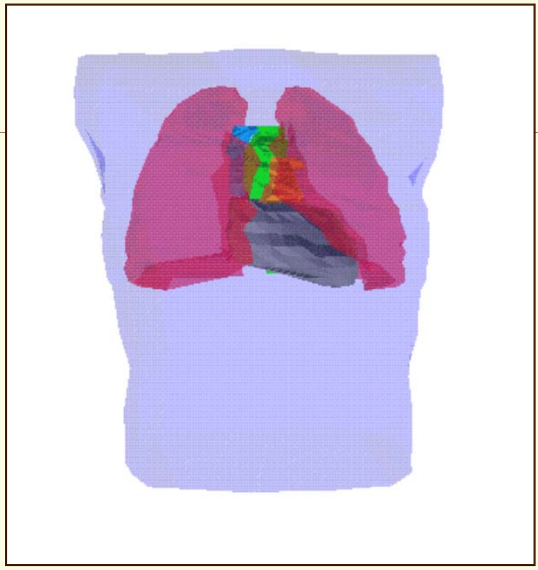
- Attempt to model different arrhythmias
  - Re-entry, Tachycardia, Fibrillation, etc
  - Condition - region reactivated by the same wavefront
  - Requires uni-directional block
- Defibrillation is one solution
  - large voltage applied across a tissue to simultaneously depolarize all tissue
  - 95% of tissue must meet defibrillation threshold (DFT) for successful cardioversion.



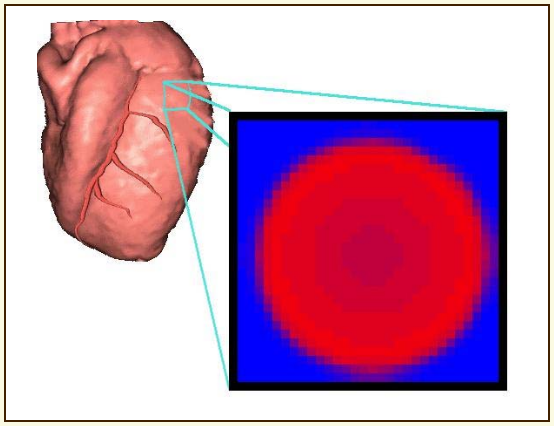



# Introduction

- Full scale model
  - Complex 3-D mesh of torso
  - different tissues and conductivities

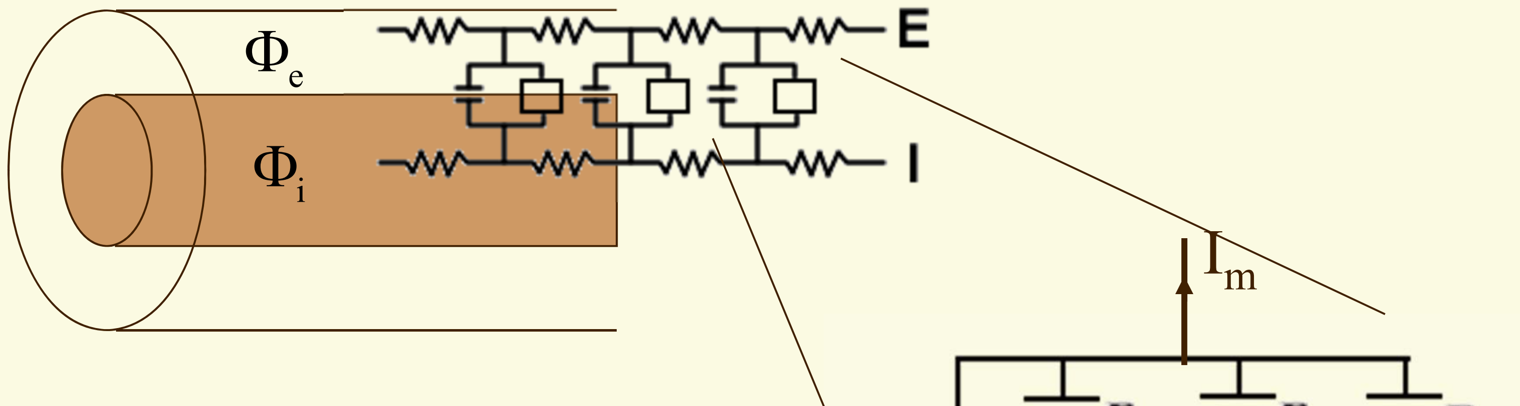


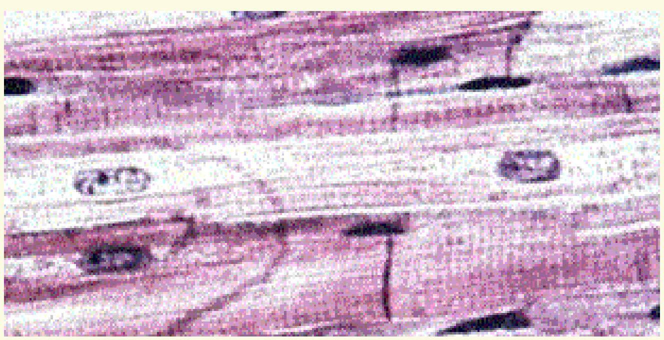
- Simplified model
  - Simple mesh of cells (2-D, Square)
  - Single tissue type (homogenous)
  - Isotropic
  - 4 connections for each cell



# Resistor Model of Cell

- Represented as a series of resistors joined in parallel by an RC circuit

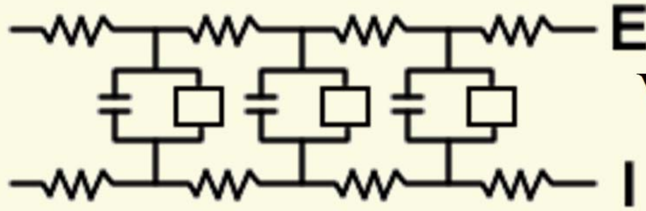


# Governing Equations

Bidomain

$$\nabla \cdot (\sigma_i \nabla \Phi_i) = \beta \left( C_m \frac{dV_m}{dt} + I_{ion} \right) \qquad \nabla \cdot (\sigma_e \nabla \Phi_e) = -\beta \left( C_m \frac{dV_m}{dt} + I_{ion} \right)$$

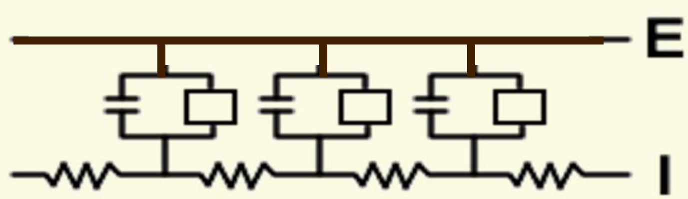



$$V_m = \Phi_i - \Phi_e$$

Monodomain

$$\nabla \cdot (\sigma_i \nabla V_m) = \beta \left( C_m \frac{dV_m}{dt} + I_{ion} \right)$$

*Assumes*: $\sigma_e = \infty \quad (R_e = 0) \qquad \therefore \; \Phi_e = 0$

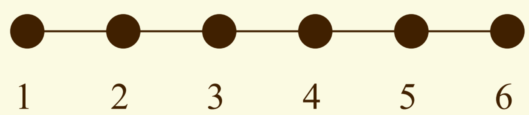



$$V_m = \Phi_i$$

# LHS - Current Diffusion

$$\nabla \cdot \left(\sigma \nabla V_m\right) \rightarrow M V_m$$

Numerical Approximation (Finite difference)




(1-D homogenous cable)

$$M \rightarrow \left(\sigma \frac{d}{dx}\frac{d}{dx}\right)$$

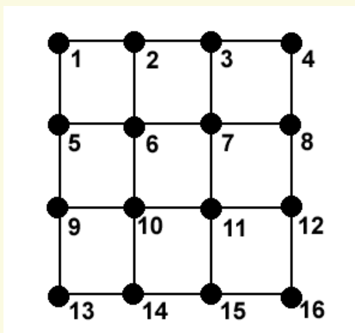
$$\frac{d^2 V_{m(i)}}{dx^2} = \frac{V_{m(i-1)} - 2V_{m(i)} + V_{m(i+1)}}{\Delta x^2}$$

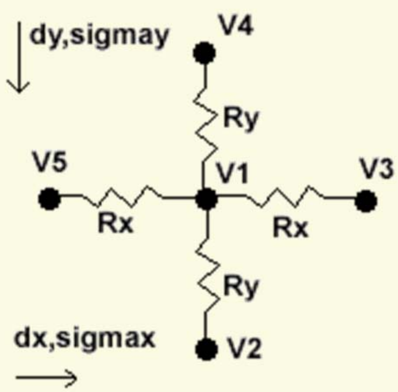
$$M = \frac{\sigma}{\Delta x^2}\begin{bmatrix} \text{O} & & & & & \\ 1 & -2 & 1 & & & \\ & 1 & -2 & 1 & & \\ & & 1 & -2 & 1 & \\ & & & 1 & -2 & 1 \\ & & & & & \text{O} \end{bmatrix}$$

Boundary Condition needed

# 2-D Diffusion Matrix

- Every row is representative of the relationship between that node with its neighbors




6 →

$$M'=\begin{bmatrix}
-2 & 1 & & & 1 & & & & & & & & & & & \\
1 & -3 & 1 & & & 1 & & & & & & & & & & \\
 & 1 & -3 & 1 & & & 1 & & & & & & & & & \\
 & & 1 & -2 & 0 & & & 1 & & & & & & & & \\
1 & & & 0 & -3 & 1 & & & 1 & & & & & & & \\
 & 1 & & & 1 & -4 & 1 & & & 1 & & & & & & \\
 & & 1 & & & 1 & -4 & 1 & & & 1 & & & & & \\
 & & & 1 & & & 1 & -3 & 0 & & & 1 & & & & \\
 & & & & 1 & & & 0 & -3 & 1 & & & 1 & & & \\
 & & & & & 1 & & & 1 & -4 & 1 & & & 1 & & \\
 & & & & & & 1 & & & 1 & -4 & 1 & & & 1 & \\
 & & & & & & & 1 & & & 1 & -3 & 0 & & & 1 \\
 & & & & & & & & 1 & & & 0 & -2 & 1 & & \\
 & & & & & & & & & 1 & & & 1 & -3 & 1 & \\
 & & & & & & & & & & 1 & & & 1 & -3 & 1 \\
 & & & & & & & & & & & 1 & & & 1 & -2
\end{bmatrix}$$

Banded structure of M evolves from uniform domain structure

# Computational Issues

- Simple EP models can get computationally expensive
  - domain size
  - domain structure/complexity
  - membrane model
  - time step required for dynamics

- Motivation: Attempt to speed up computation time while preserving quality of results.

$$\nabla \cdot \left( \sigma \nabla V_m \right) = \beta \left( C_m \frac{dV_m}{dt} + I_{ion} \right)$$

# Numerical Methods

- Explicit - Forward Euler

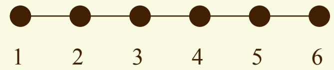
$$\nabla \cdot (\sigma \nabla V_m) = \beta\left( C_m \frac{dV_m}{dt} + I_{ion} \right) \longrightarrow MV_m{}^t = \beta\left( C_m \frac{V_m{}^{t+1} \text{-} V_m{}^t}{\Delta t} + I_{ion}{}^t \right)$$

Rearranging:

$$V_m{}^{t+1} = V_m{}^t + \frac{\Delta t}{C_m}\left( \frac{1}{\beta} MV_m{}^t - I_{ion}{}^t \right)$$

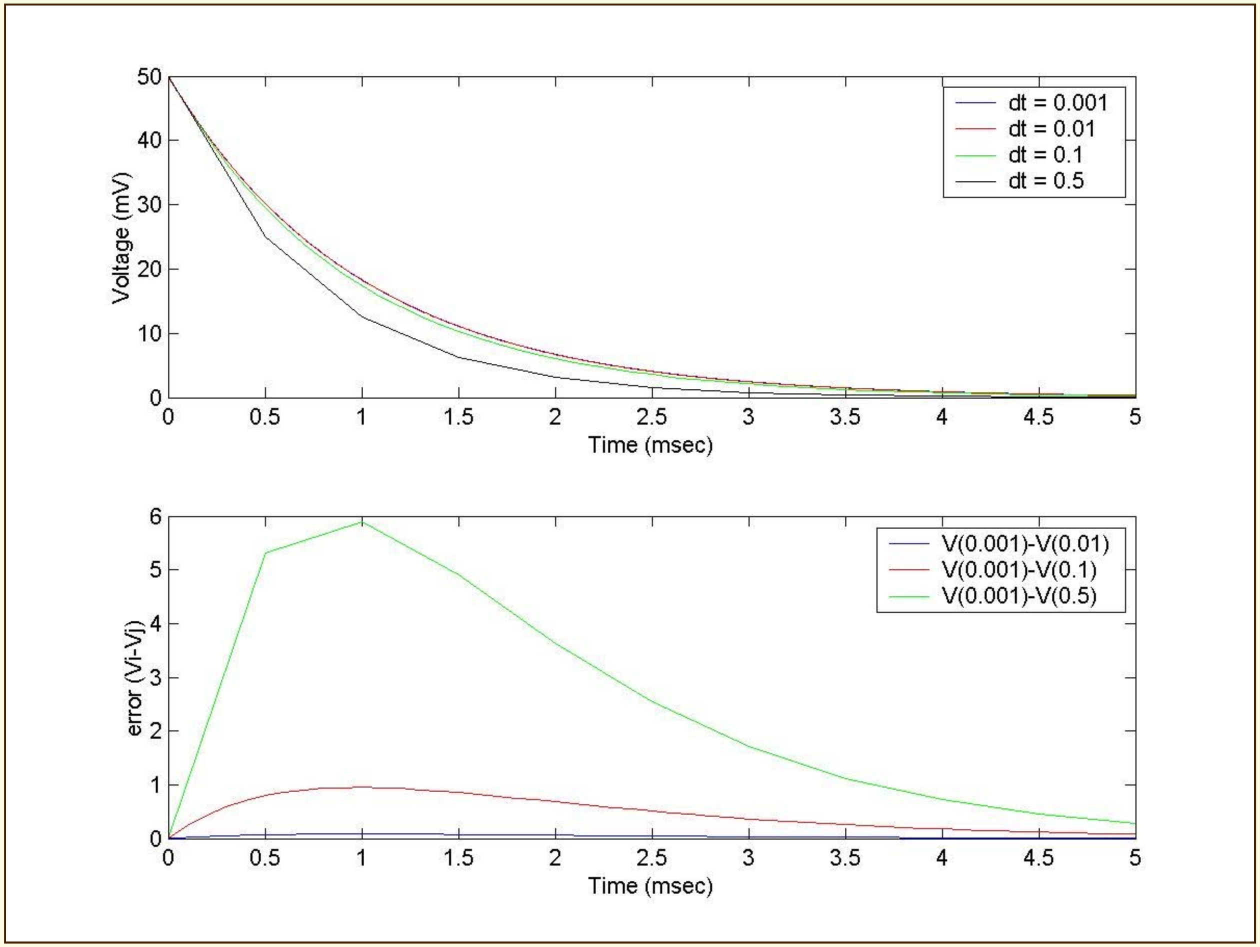
$$V_m{}^{t+1} = f\ (V_m{}^t, I_{ion}{}^t)$$

# Methods - FE




$$V_m^{t+1} = V_m^{t} + \frac{\Delta t}{C_m}\left(\frac{1}{\beta} M V_m^{t} - I_{ion}^{t}\right)$$

Issues: Choosing optimal dt is critical!



# Methods

- Semi-Implicit

$$MV_m = \beta\left(C_m \frac{dV_m}{dt} + I_{ion}\right) \longrightarrow MV_m^{t+1} = \beta\left(C_m \frac{V_m^{t+1} - V_m^{t}}{\Delta t} + I_{ion}^{t}\right)$$

Rearranging:

$$\left(M - \frac{\beta C_m}{\Delta t} I\right) V_m^{t+1} = -\frac{\beta C_m}{\Delta t} V_m^{t} + \beta I_{ion}^{t}$$

$$Ax = b$$

$$x = A^{-1} b$$

# Method - SI

$$\left(M - \frac{\beta C_m}{\Delta t} I\right) V_m^{t+1} = -\frac{\beta C_m}{\Delta t} V_m^{t} + \beta I_{ion}^{t}$$

Recall:

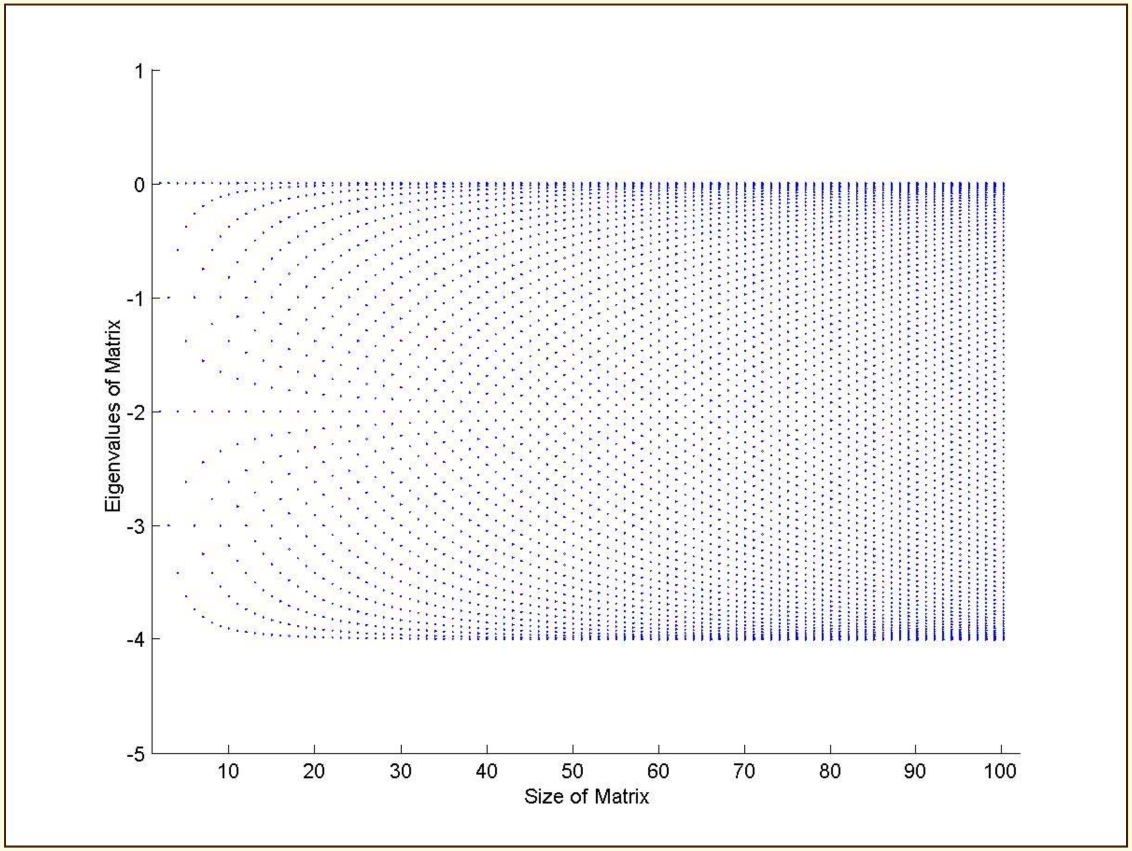
$$\det(A - \lambda I) = 0$$

$$\det(\text{Singular}) = 0$$

- Issues:
  - $A^{-1}$ requires that $\left(M - \frac{\beta C_m}{\Delta t} I\right)$ be non-singular
    - i.e. $\left(\frac{\beta C_m}{\Delta t}\right)$ cannot be an eigenvalue of $\left(M - \frac{\beta C_m}{\Delta t} I\right)$

# Results - Semi Implicit

- All eigenvalues range from [-4,0]

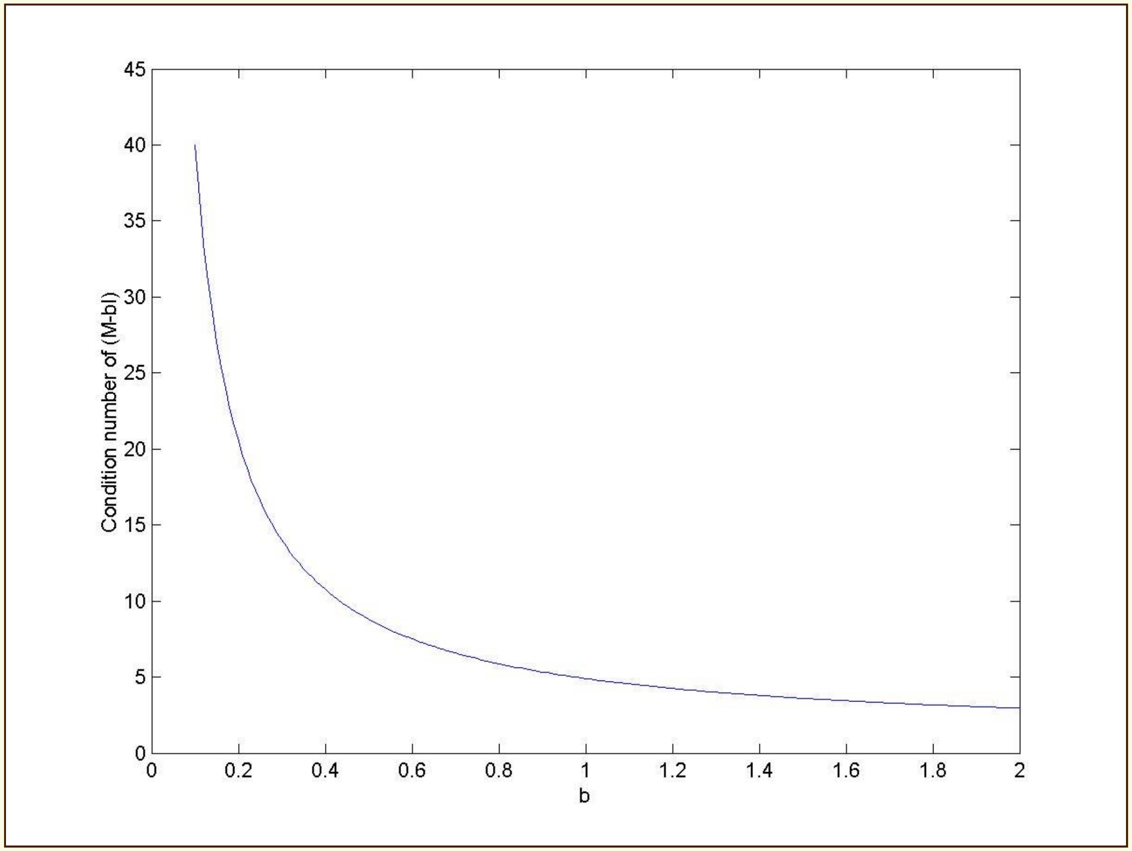



$$\left(\frac{\beta C_m}{\Delta t}\right) \neq 0$$

M is already singular

$$\therefore \left(\frac{\beta C_m}{\Delta t}\right) > 0$$

# Results - Semi Implicit $\left(M - \frac{\beta C_m}{\Delta t} I\right) V_m^{t+1} = -\frac{\beta C_m}{\Delta t} V_m^{t} + \beta I_{ion}^{t}$




Where:

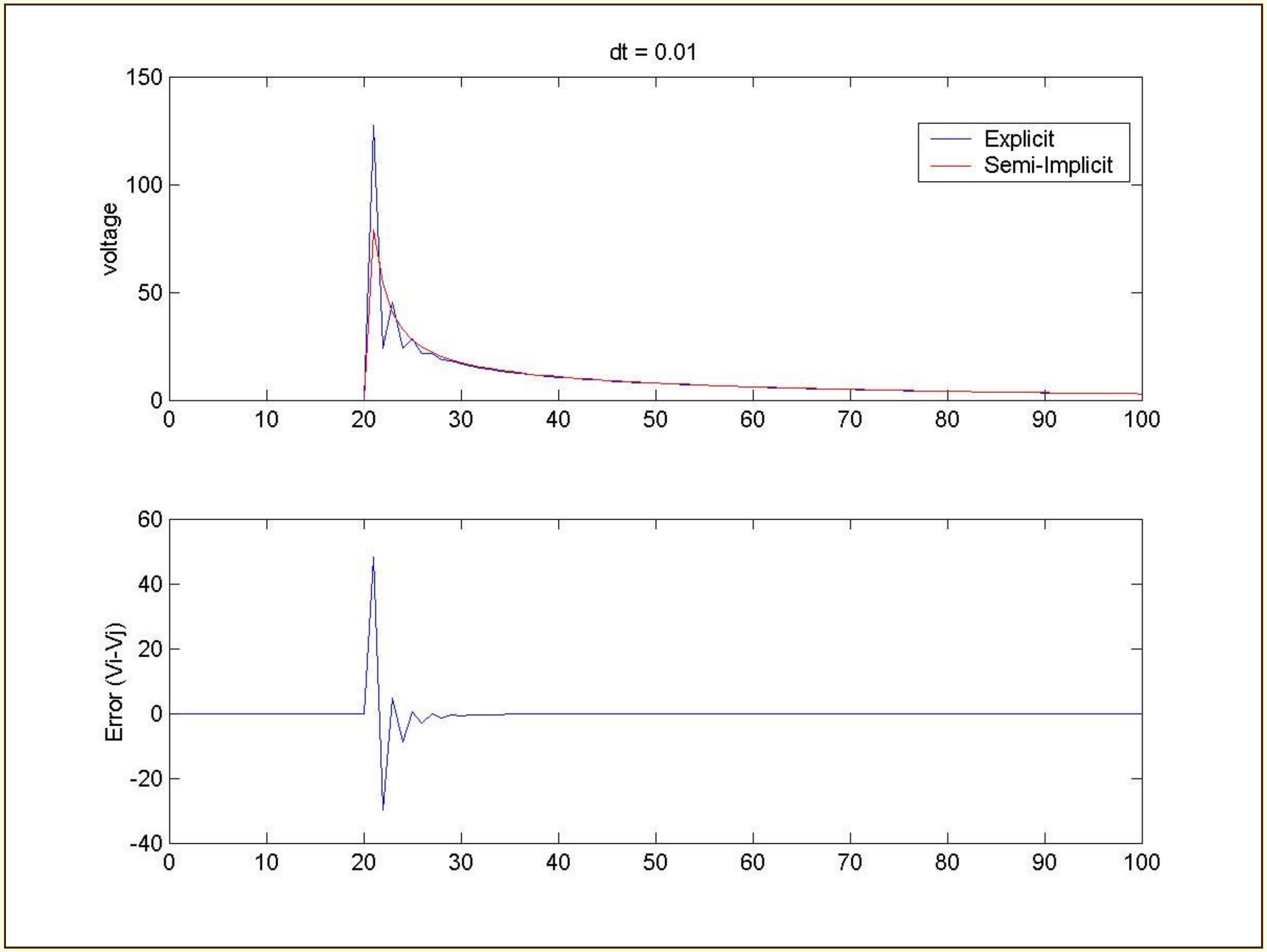
$$b = \left(\frac{\beta C_m}{\Delta t}\right)$$

K(M) = 3.6e16

(Size = 10)

# Results - Both

Semi Implicit is more stable at larger values of dt



# Methods

## Implicit

$$MV_m = \beta\left(C_m \frac{dV_m}{dt} + I_{ion}\right) \longrightarrow MV_m^{t+1} = \beta\left(C_m \frac{V_m^{t+1} - V_m^{t}}{\Delta t} + I_{ion}^{t+1}\right)$$

Rearranging:

$$MV_m^{t+1} - \beta\left(C_m \frac{V_m^{t+1} - V_m^{t}}{\Delta t} + I_{ion}^{t+1}\right) = 0$$

Recall: $I_{ion}^{t+1} = f\,(V_m^{t+1})$

Use non-linear solver

Very Expensive!

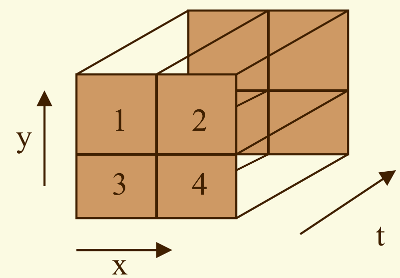
# Summary

- Forward Euler
  - less operations per iteration
  - needs small dt (more total iterations needed)
  - less stable

- Semi-implicit
  - more operations per iteration
  - can use larger dt (less total iterations needed)
  - more stable

# Parallel distribution for 2-D domain

- Essentially a 3-D problem (x,y,time)
  – Can only divide up in space, since voltages at t+1 are dependent on values at t



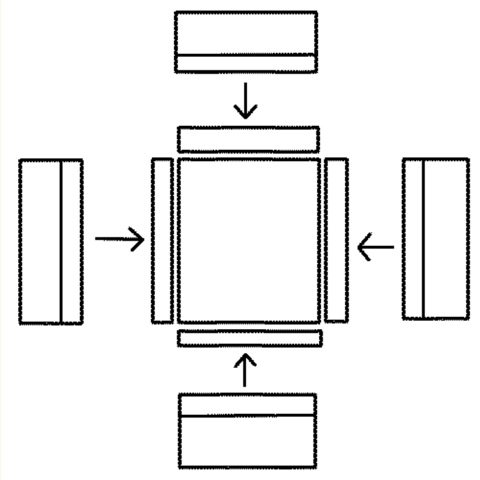

- Implement Domain Decomposition Method
  – Processors will exchange information with other processors that share common boundaries

# After Iion is determined...

- Recall the equation for Forward Euler:

$$V_m^{t+1} = V_m^{t} + \frac{\Delta t}{C_m}\left(\frac{1}{\beta} M V_m^{t} - I_{ion}^{t}\right)$$

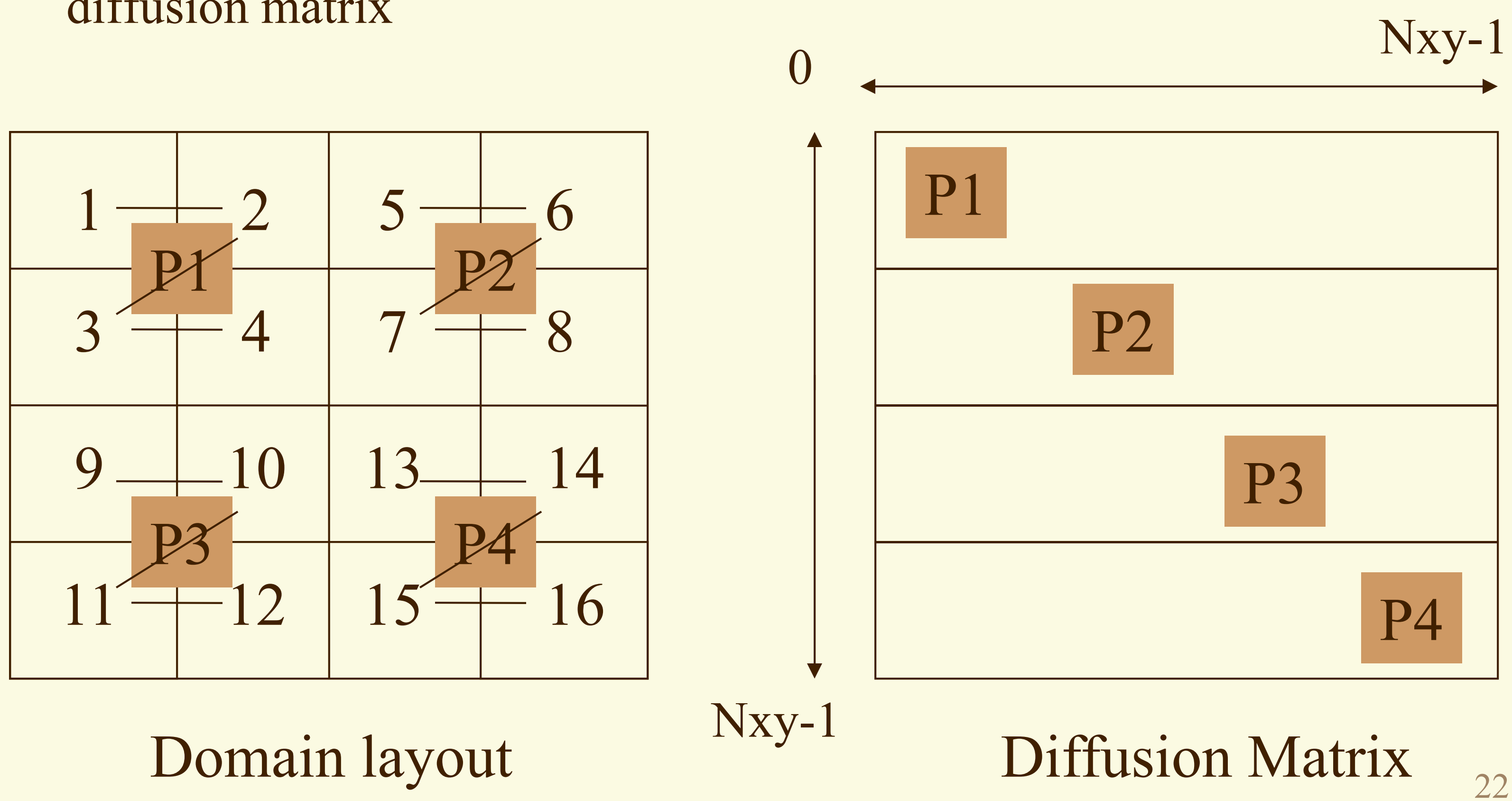
- Data must be exchanged prior to current diffusion to consider current passing over processor boundaries.



- Only a fraction of the M matrix will be required for each sub domain
  - How can we take advantage of this structure?

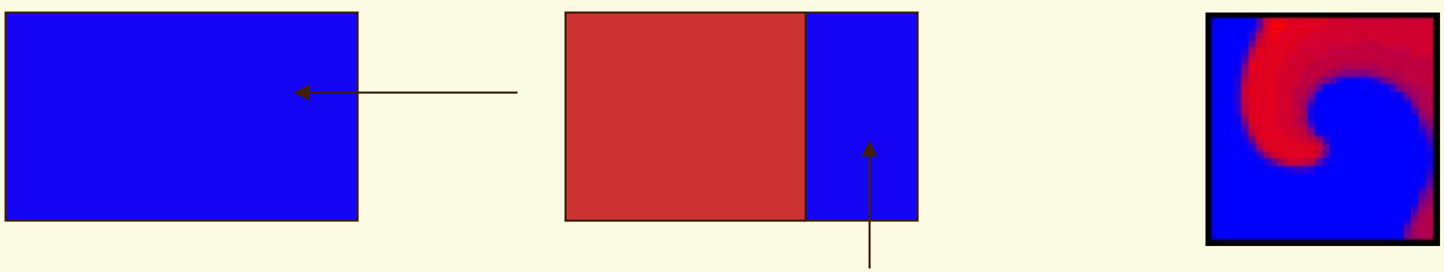
# Morton ordering (z ordering)

- This technique was used to help group nearby nodes together in the diffusion matrix



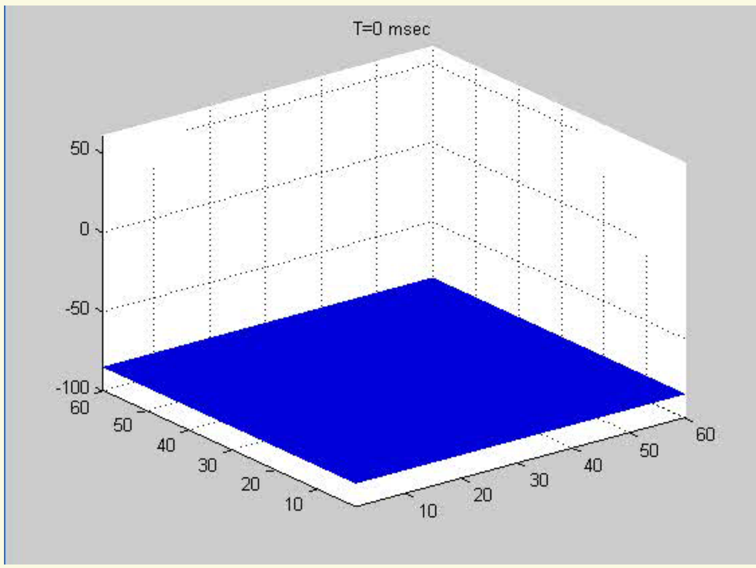
# Once program is complete…

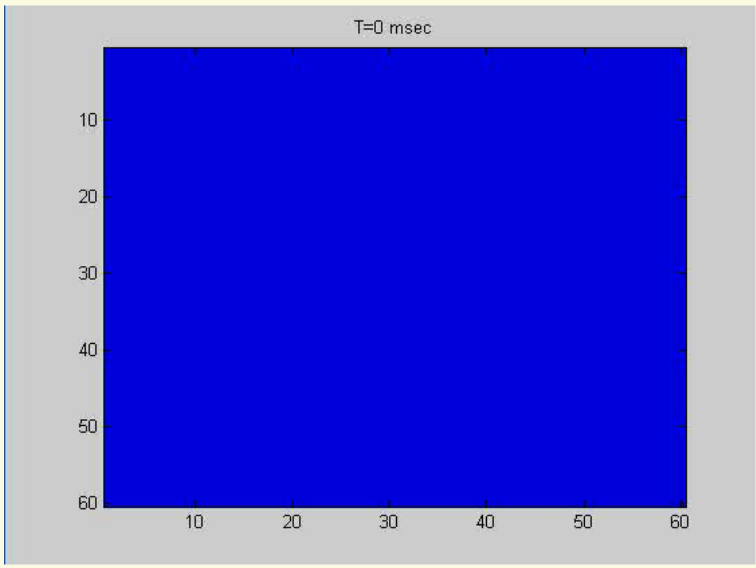
- A stimulus can be applied and studied
- Re-entry is difficult to achieve within small domain
- There is one sure-fire method to always achieve re-entry



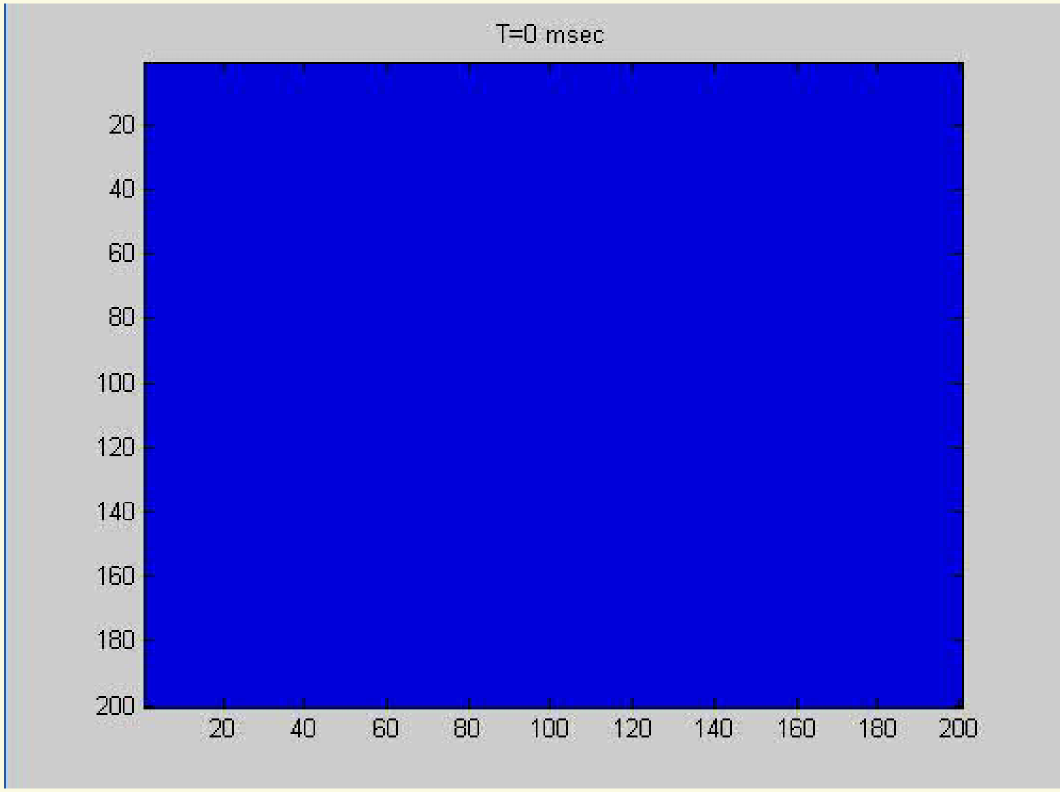
# Visualization

- A Matlab script was used to manipulate data
  - Data must be rearranged from z-ordered vector format into a rectangular matrix



# More Movies




Double Spirals

# Performance Results

- Speed up: (20 nodes x 20 nodes x 3000 time steps)

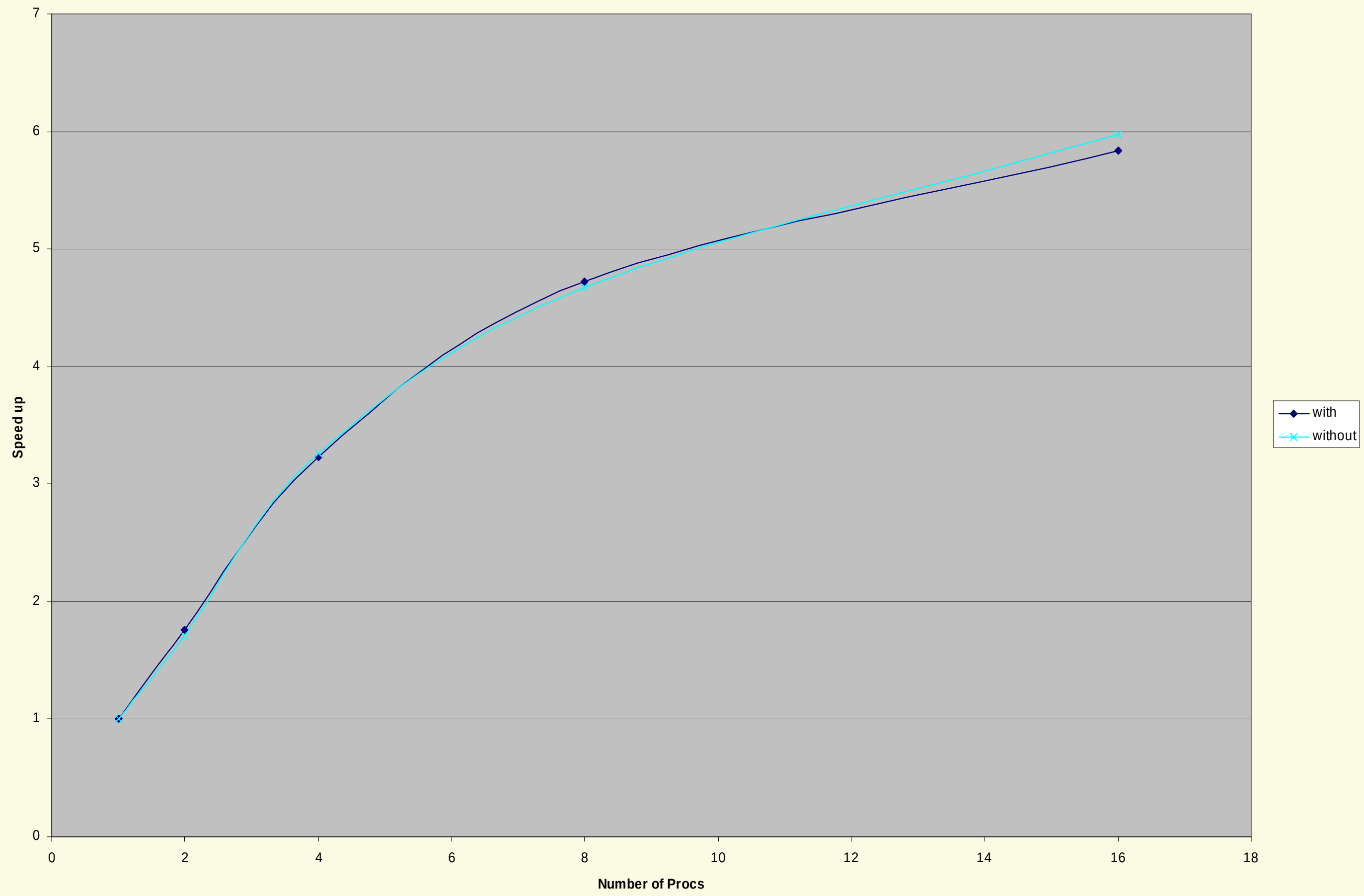
| **With File I/O** # of Procs | Time | Speed up |
|---|---|---|
| 1 | 16.59 | 1 |
| 2 | 9.41 | 1.76 |
| 4 | 5.13 | 3.23 |
| 8 | 3.58 | 4.72 |
| 16 | 2.84 | 5.84 |

| **w/o File I/O** # of Procs | Time | Speed up |
|---|---|---|
| 1 | 15.63 | 1 |
| 2 | 9.09 | 1.71 |
| 4 | 4.79 | 3.26 |
| 8 | 3.34 | 4.67 |
| 16 | 2.61 | 5.98 |

(full matrix)

File I/O is the writing of voltage data to file.
This was turned of for benchmarking purposes

# Performance Results



# Luo Rudy Equations

- **Fast Sodium current**

$$I_{Na} = 23(m^3)(h)(j)(V - E_{Na})$$

- **For V ≥ -40 mV**

$$\beta_h = \frac{1}{0.13(1+e^{\frac{V+10.66}{-11.1}})} \qquad \alpha_h = \alpha_j = 0.0$$

$$\beta_j = \frac{(0.3)e^{-2.535(V)(10^{-7})}}{1+e^{-0.1(V+32)}}$$

- **For V < -40 mV**

$$\alpha_h = (0.135)e^{\frac{80+V}{-6.8}} \qquad \beta_j = (0.1212)\frac{e^{(-0.01052V)}}{1+e^{-0.1378(V+40.14)}}$$

$$\beta_h = (3.56)e^{(0.079V)} + 3.1(10^5)e^{(0.35V)}$$

- **For all range of V**

$$\beta_m = (0.08)e^{\frac{-V}{11}} \qquad \alpha_m = (0.32)\frac{(V+47.13)}{1-e^{-0.1(V+47.13)}}$$

- **Slow inward current**

$$E_{si} = 7.7 - (13.0287)\ln([Ca]_i)$$

$$I_{si} = (0.09)(d)(f)(V-E_{si})$$

$$\alpha_d = (0.095)\frac{e^{-0.01(V-5)}}{1+e^{-0.072(V-5)}}$$

$$\beta_d = (0.07)\frac{e^{-0.017(V+44)}}{1+e^{0.05(V+44)}}$$

$$\alpha_f = (0.012)\frac{e^{-0.008(V+28)}}{1+e^{0.15(V+28)}}$$

$$\beta_f = (0.0065)\frac{e^{-0.02(V+30)}}{1+e^{-0.2(V+30)}}$$

- **Calcium Uptake**

$$\frac{d([Ca]_i)}{dt} = -(I_{si})(10^{-4}) + 0.07(10^{-4} - [Ca]_i)$$

# Luo Rudy Equations

- **Outward currents**
- **Time-dependent potassium current**

$$I_K = \overline{G}_K (X)(X_i)(V-E_K) \qquad \alpha_X = (0.0005)\frac{e^{0.083(V+50)}}{1+e^{0.057(V+50)}}$$

$$\overline{G}_K = 0.282\sqrt{\frac{[K]_o}{5.4}} \qquad \beta_X = (0.0013)\frac{e^{-0.06(V+20)}}{1+e^{-0.04(V+20)}}$$

- **For V > -100mV**

$$X_i = 2.837\frac{(e^{0.04(V+77)}-1)}{(V+77)e^{0.04(V+35)}}$$

- **For V ≤ -100 mV**

$$X_i = 1$$

- **Total time-independent potassium current**

$$I_{K1(T)} = I_{K1} + I_{Kp} + I_b$$

- **Time-independent potassium current**

$$I_{K1} = (\overline{G}_{K1})(K1_\infty)(V-E_{Kp}) \qquad \overline{G}_{K1} = (0.6047)\sqrt{\frac{[K]_o}{5.4}}$$

$$\alpha_{K1} = \frac{1.02}{1+e^{0.2385(V-E_{K1}-59.215)}}$$

$$\beta_{K1} = \frac{(0.49124)e^{0.08032(V-E_{K1}+5.476)} + e^{0.06175(V-E_{K1}-594.31)}}{1+e^{-0.5143(V-E_{K1}+4.753)}}$$

- **Plateau potassium current**

$$I_{Kp} = 0.0183(Kp)(V-E_{Kp}) \qquad E_{Kp} = E_{K1}$$

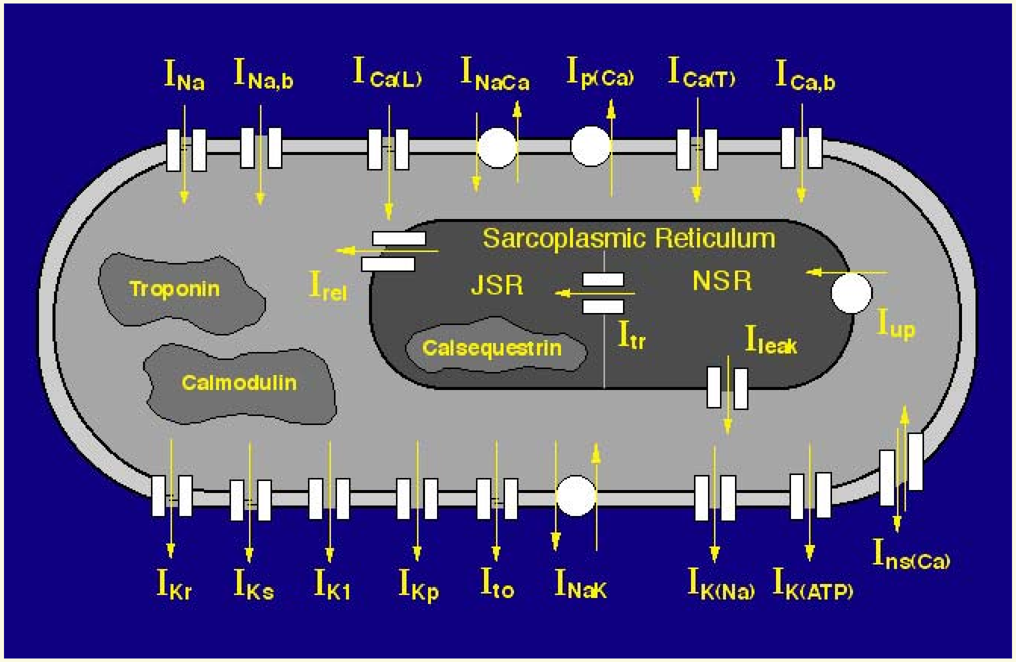
$$Kp = \frac{1}{1+e^{\frac{7.488-V}{5.98}}}$$

- **Background current**

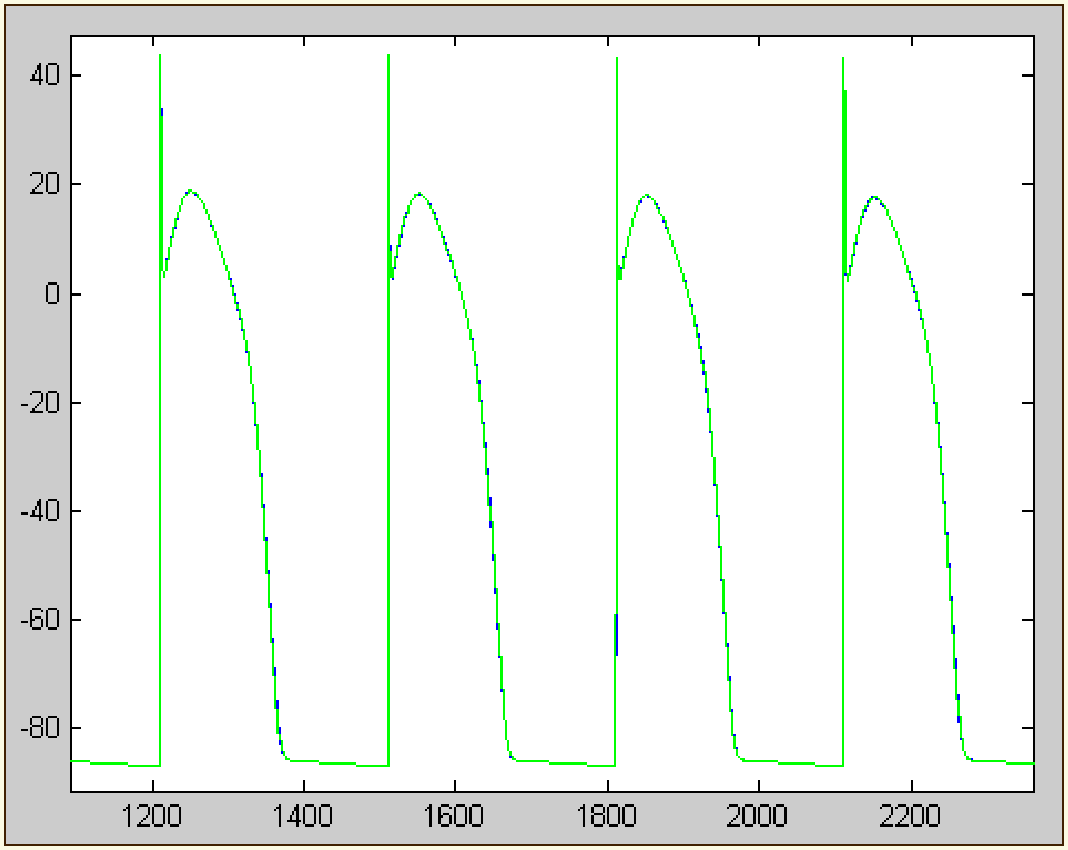
$$I_b = 0.03921(V+59.87)$$

# Luo Rudy Dynamic (LRD)

- More complex than Luo Rudy I (LRI)
- More currents and concentrations
- Event dependent internal currents
  - CICR
- $Ca^{2+}$ overload
  - csqn > csqnth
- Cleft concentrations
- Physiological currents
  - Ito, Ikna, Insns, Insk

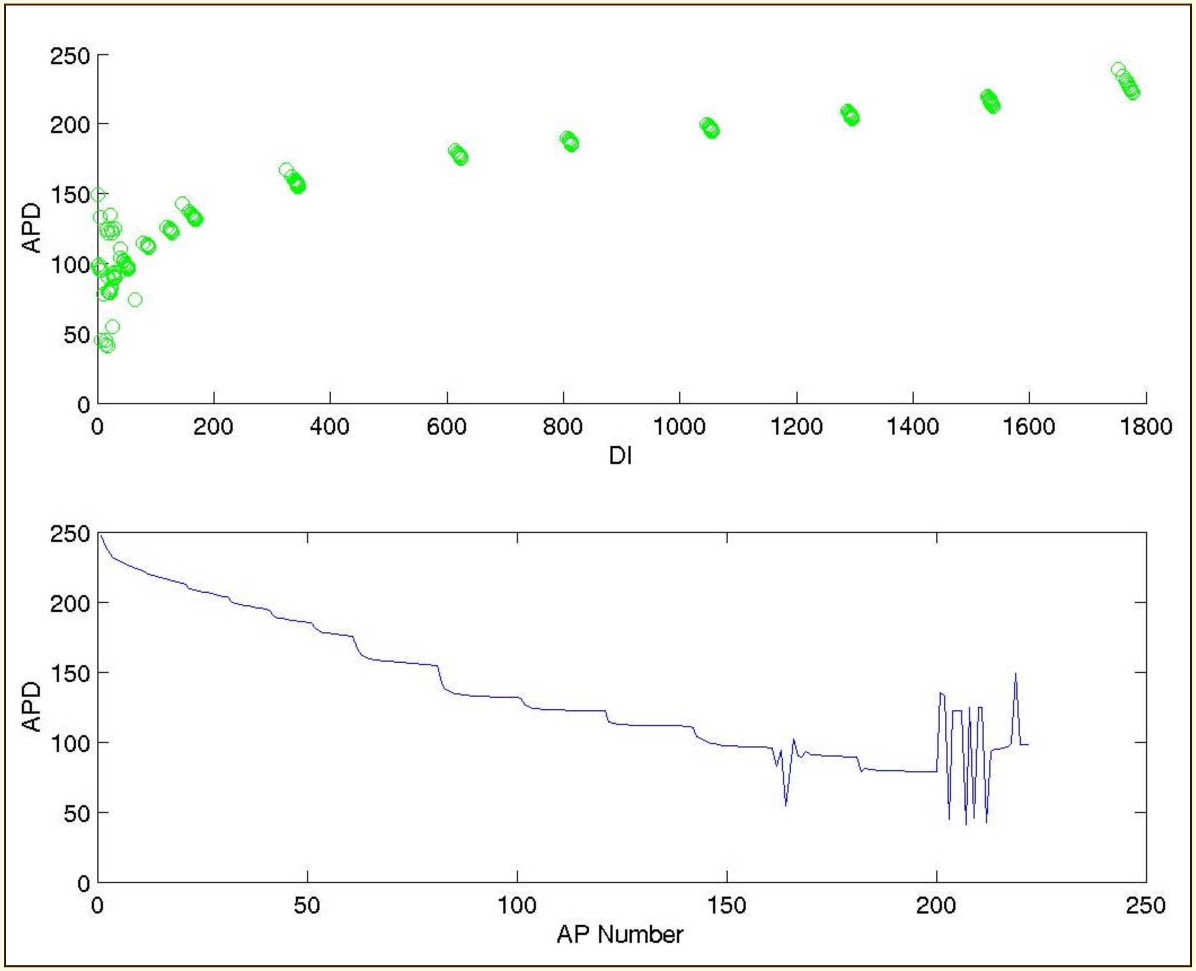


# LRD – Action potential



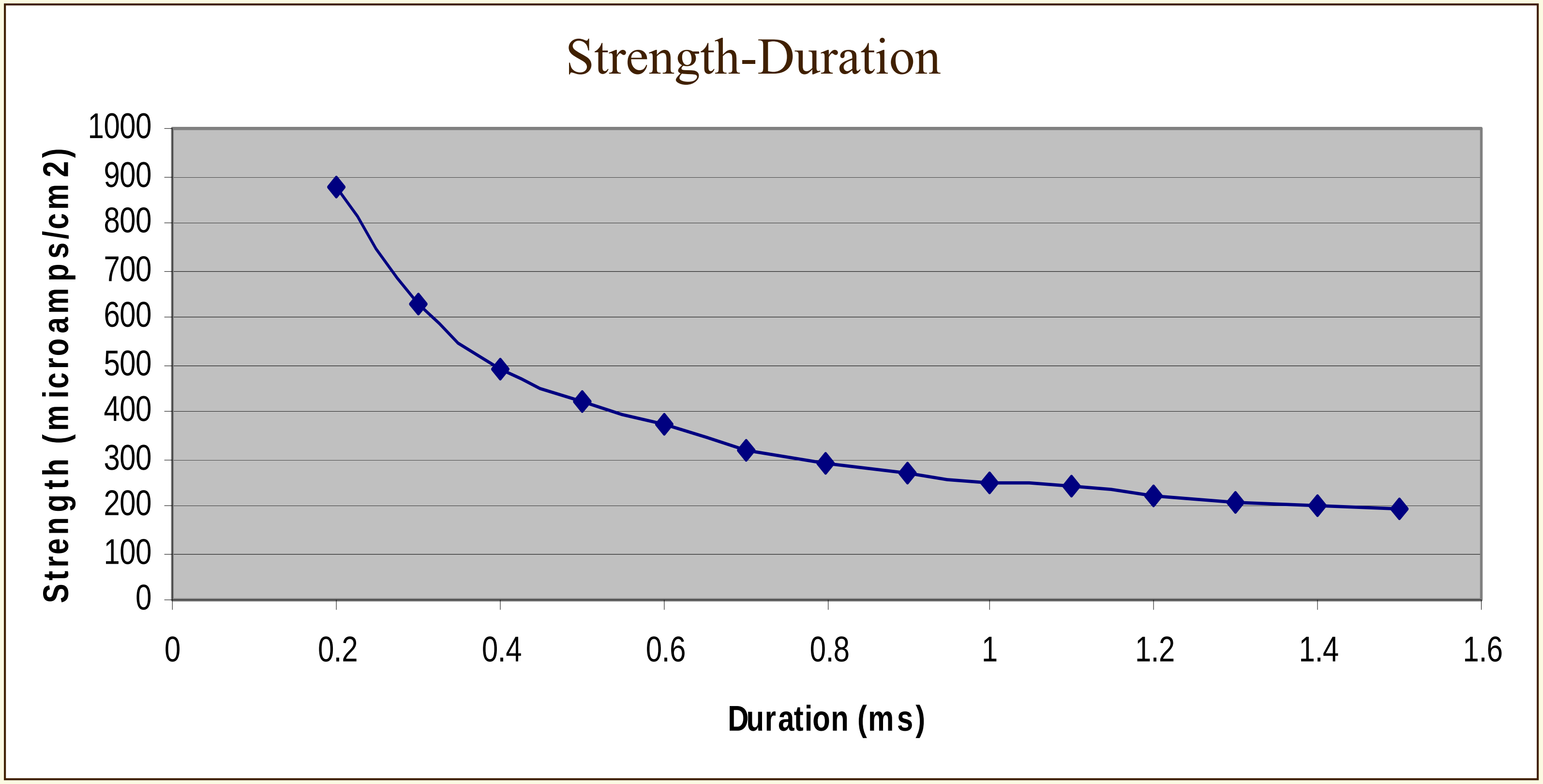

$$\text{Error} = \frac{\sqrt{\sum (x_1 - x_2)^2}}{\text{length}\,[x_1]} = 0.0230 \text{ mV}$$

# LRD – Pacing Downsweep

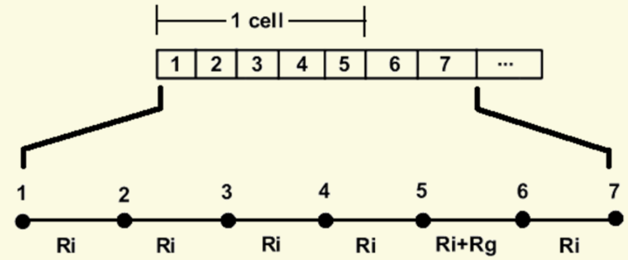



| # of Stim | BCL |
|---|---|
| 10 | 2000 |
| 10 | 1750 |
| 10 | 1500 |
| 10 | 1250 |
| 10 | 1000 |
| 10 | 800 |
| 20 | 500 |
| 20 | 300 |
| 20 | 250 |
| 20 | 200 |
| 20 | 150 |
| 20 | 100 |
| 20 | 70 |
| 20 | 50 |

# Cable Experiments – LR I



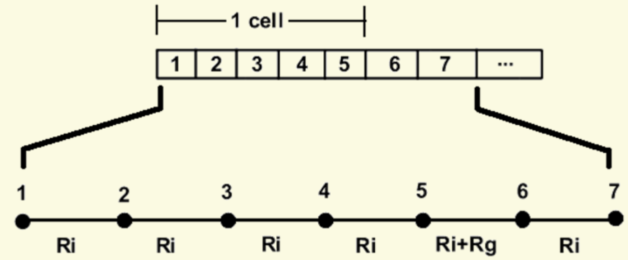
# Gap Junction Resistance




| Rg | Pavg | CVavg | CVcell | CVgap |
|---|---|---|---|---|
| 0 | 0.15 | 135 | 266.66 | 266.66 |
| 0.0015 | 0.3 | 95 | 200 | 80 |
| 0.003 | 0.45 | 76.25 | 235.29 | 72.72 |
| 0.01 | 1.15 | 47.15 | 400 | 44.44 |
| 0.05 | 5.15 | 21.05 | 1333.33 | 26.66 |
| 0.1 | 10.15 | 14.05 | 1600 | 18.77 |
| 0.5 | 50.15 | 3.68 | 10000 | 8.84 |
| 0.6 | 60.15 | 2.9412 | 20000 | 7.27 |
| 0.7 | 70.15 | 1.957 | 26666.67 | 7.27 |

Rg = $\Omega cm^2$
Pavg = $k\Omega cm$
CV = cm/sec

# GNa



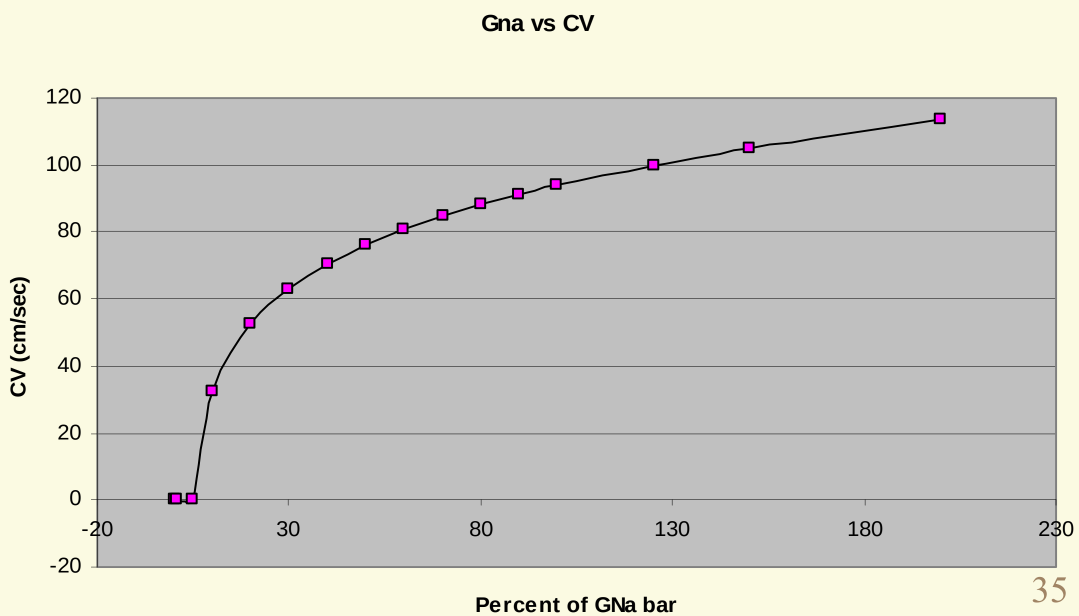

| GNA % | GNA | CV |
|---|---|---|
| 0 | 0 | 0 |
| 1 | 0.32 | 0 |
| 5 | 1.6 | 0 |
| 10 | 3.2 | 32.4 |
| 20 | 6.4 | 52.4 |
| 30 | 9.6 | 62.89 |
| 40 | 12.8 | 70.5 |
| 50 | 16 | 76.22 |
| 60 | 19.2 | 80.99 |
| 70 | 22.4 | 84.8 |
| 80 | 25.6 | 88.6 |
| 90 | 28.8 | 91.47 |
| 100 | 32 | 94.33 |
| 125 | 40 | 100.04 |
| 150 | 48 | 104.81 |
| 200 | 64 | 113.39 |

$$I_{Na} = \bar{G}_{Na}(m^3hj)(V_m - E_{Na})$$

Rg = 1.5 $\Omega cm^2$

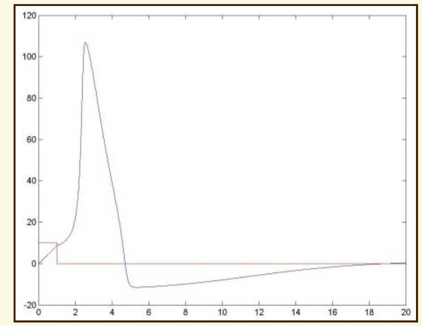
GNa = $mS/cm^2$

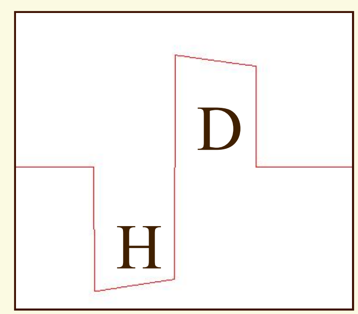
CV = cm/sec



# Fitzhugh-Nagumo (FN) vs Hodgkin-Huxley (HH)

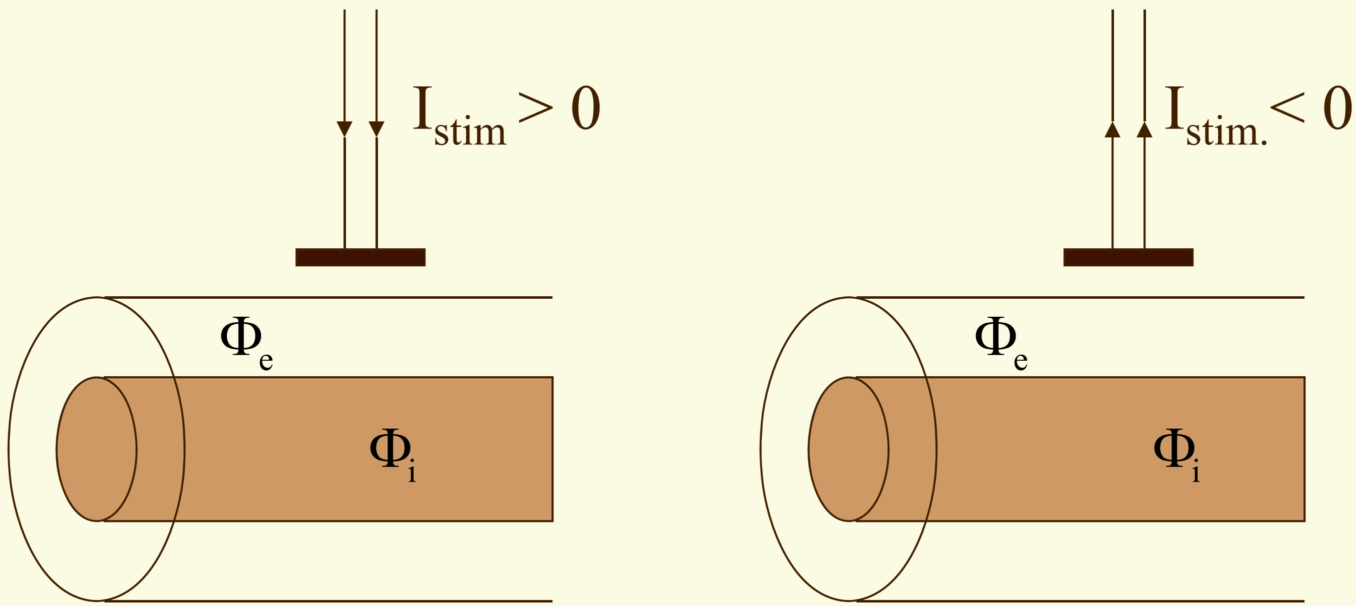
- HH (4-D) accurately represents physiology
  - Fast Variables (V, m)
  - Slow Variables (n, h)
- FN (2-D) is a reduced version of HH considers only the fast changing variables (x, y)
  - simplicity makes it a good tool to understand fundamentals of “excitableness”
- FN loses some realistic behavior
  - Bi-phasic stimulus
    - Decreases threshold (HH)
    - Increases threshold (FN)





# Stimulation (extracellular)

$$V_m = \Phi_i - \Phi_e$$



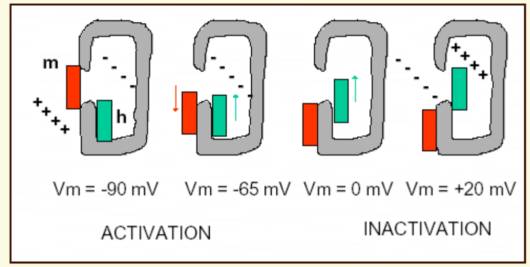

$\Phi_e \uparrow \quad \therefore \quad V_m \downarrow$

Hyperpolarizing

$\Phi_e \downarrow \quad \therefore \quad V_m \uparrow$

Depolarizing

# Gate performance for HH

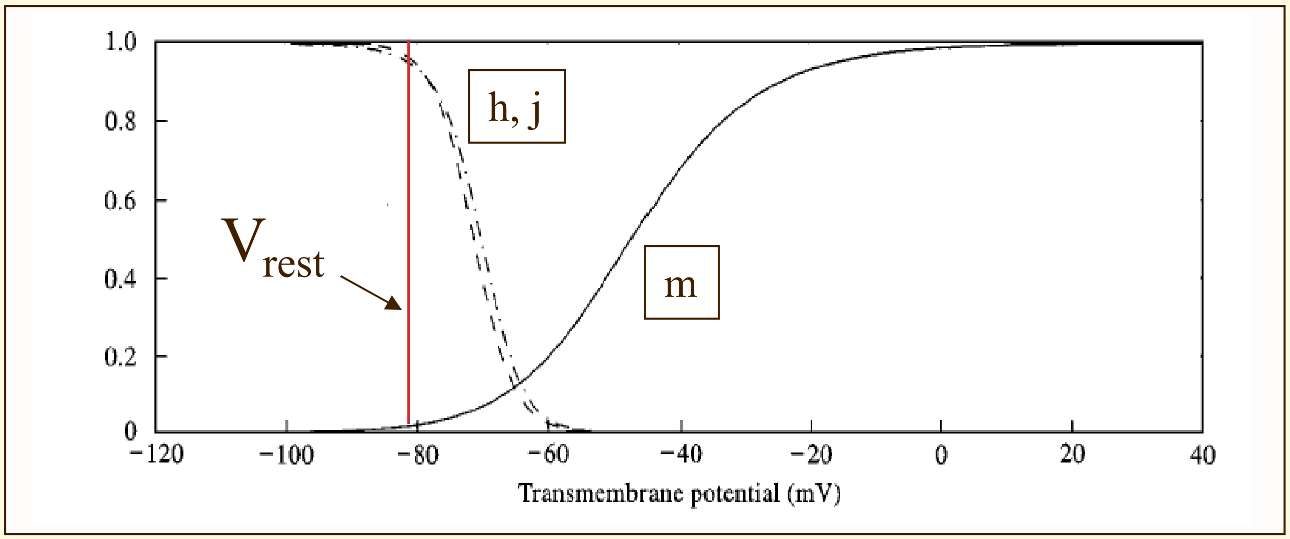



- Activation occurs when $I_{Na}$ is large enough to overcome outward currents

$$I_{Na} = \bar{G}_{Na}(m^3hj)(V_m - E_{Na})$$

$\tau_m$ is "small" $\rightarrow$ $m \approx m_\infty$ (fast)

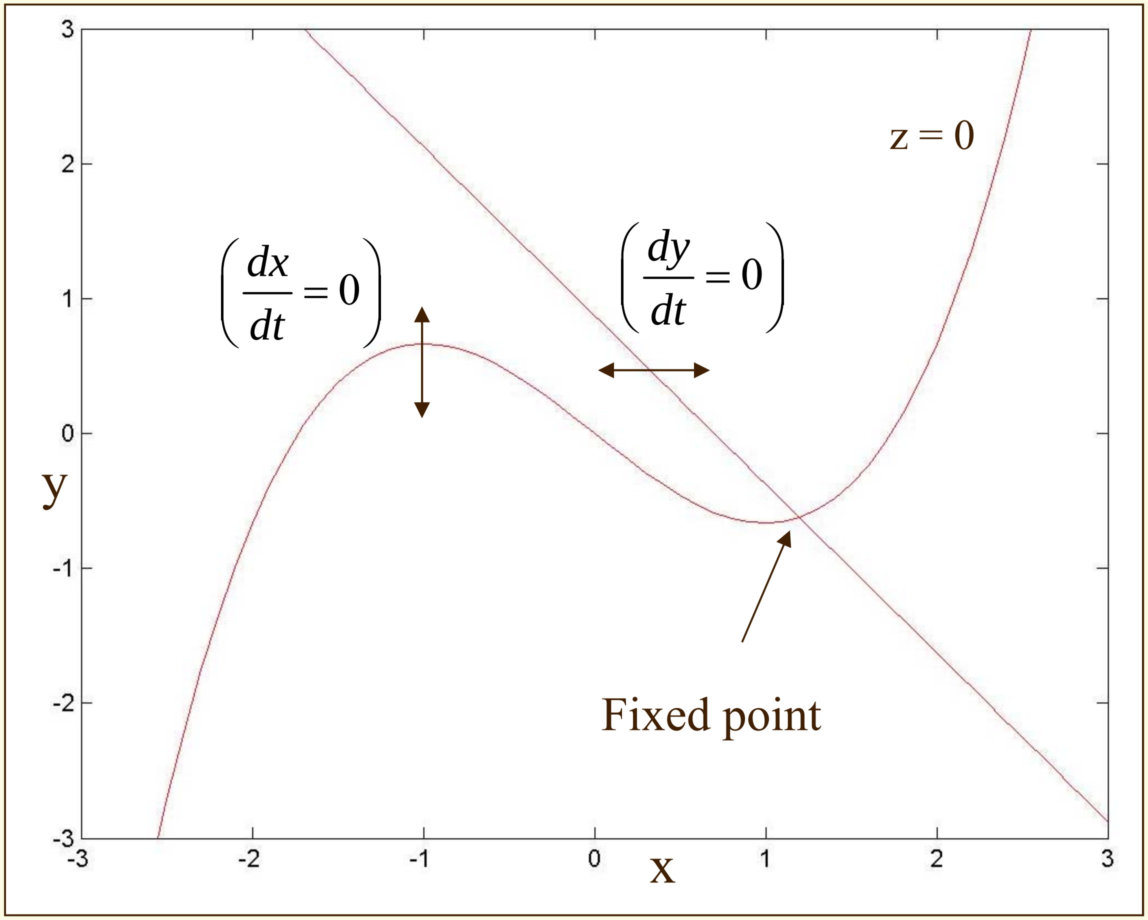
$\tau_h, \tau_j$ is "large" $\rightarrow$ $h \neq h_\infty, j \neq j_\infty$ (slow)




- Due to slow variables, a hyperpolarizing pre-pulse reduces the activation threshold which would require a smaller depolarizing pulse!

# Nullclines

$$\frac{dx}{dt} = c\left(y + x - \frac{x^3}{3} + z\right) \qquad \frac{dy}{dt} = -\frac{(x - a + by)}{c}$$




<u>nullclines</u>

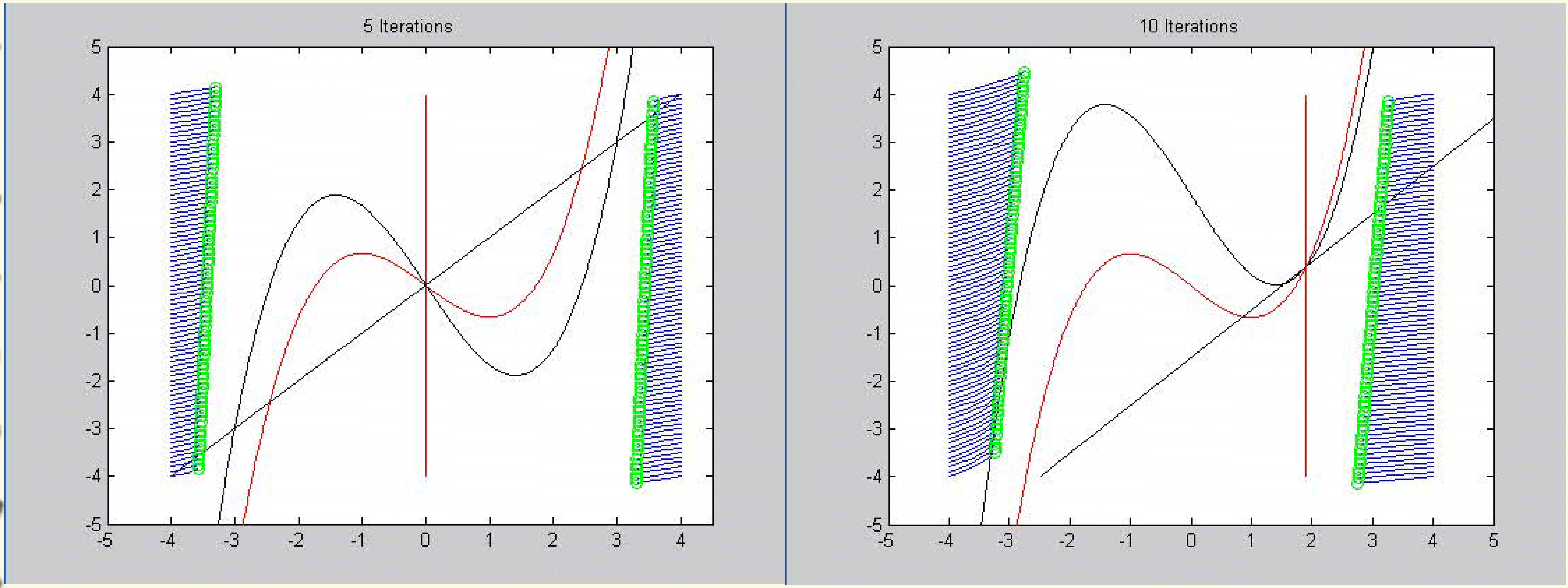
$$y = \frac{x^3}{3} - x - z \quad \left(\frac{dx}{dt} = 0\right)$$

$$y = \frac{a - x}{b} \quad \left(\frac{dy}{dt} = 0\right)$$

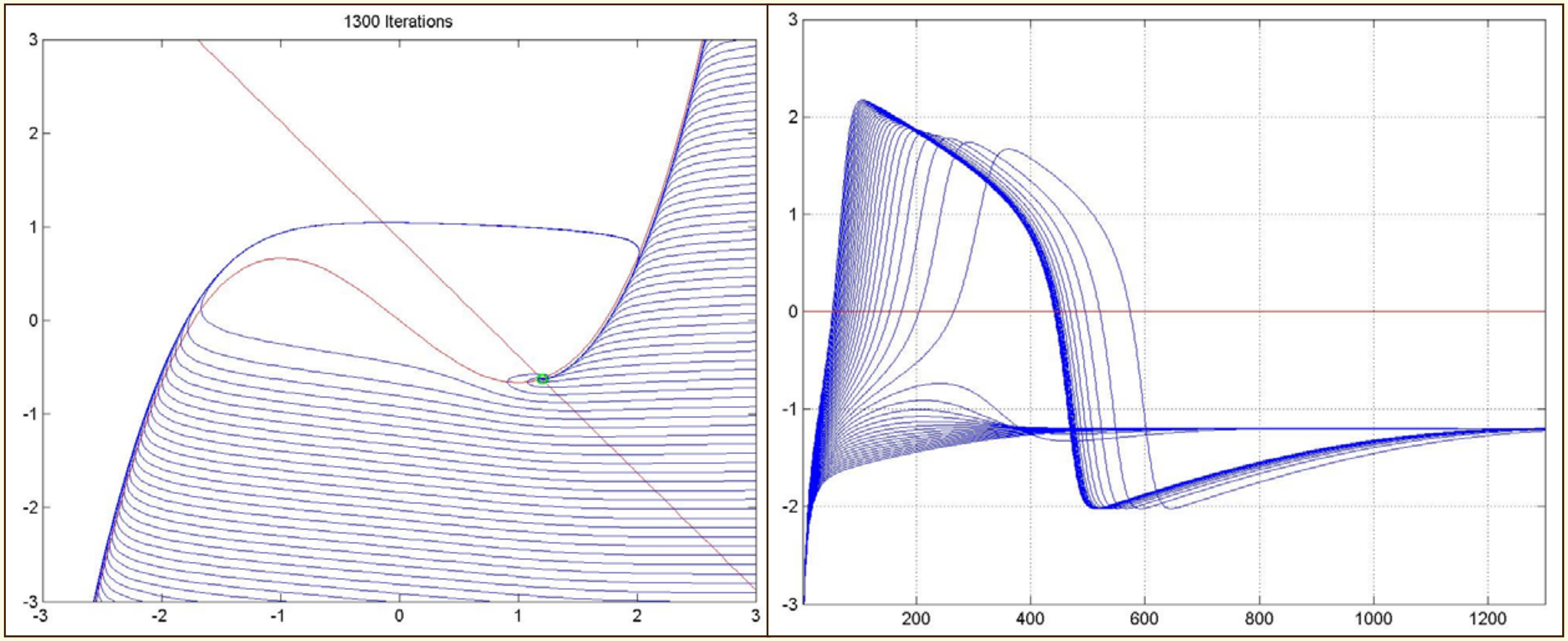
a = 0.7
b = 0.8
c = 3

# Cubic nullclines

- Produce oscillatory dynamics
- Shifting linear nullcline changes orbit
  - can cause limit cycle to collapse to single point



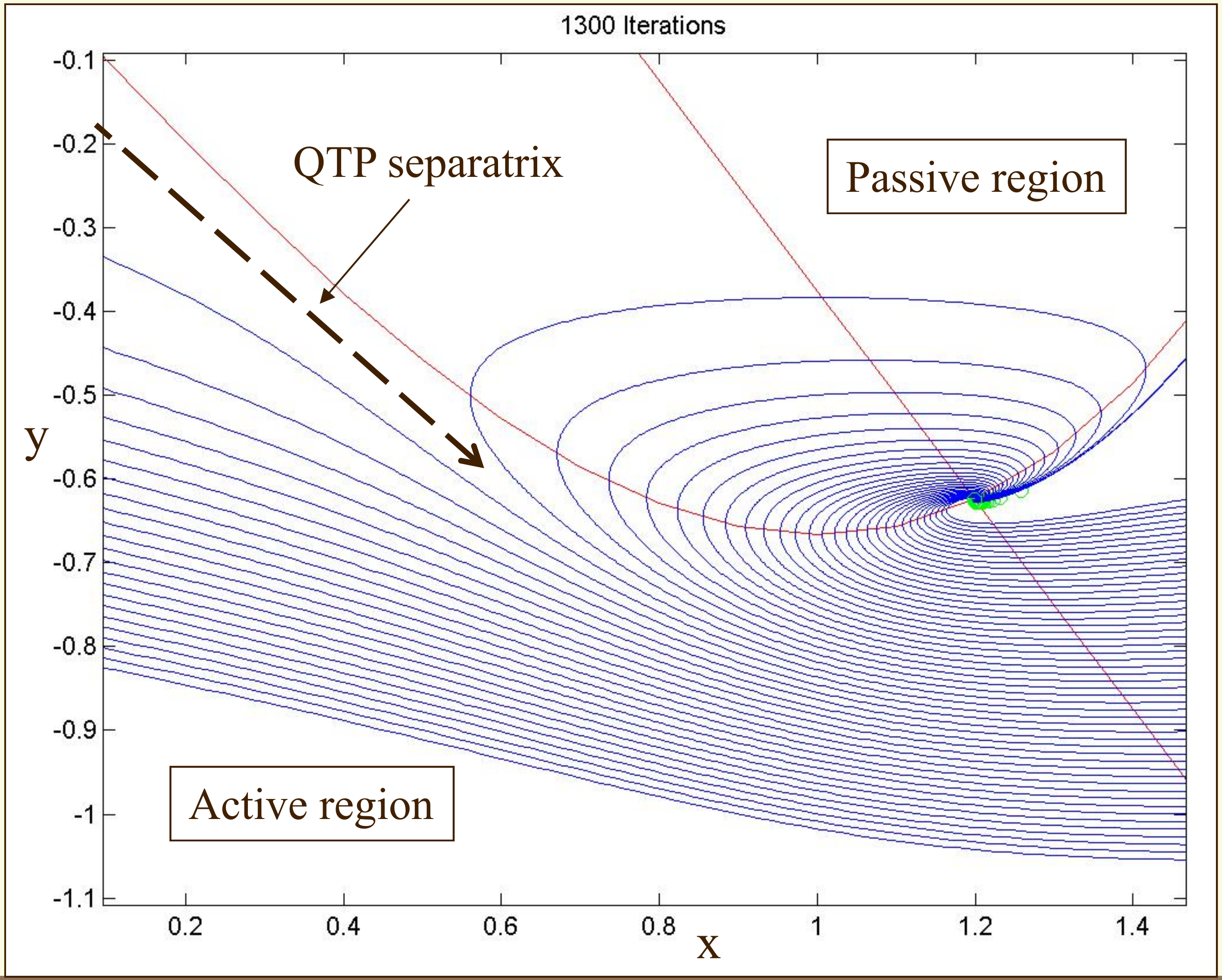
# Phase Space x = 4  (z = 0)



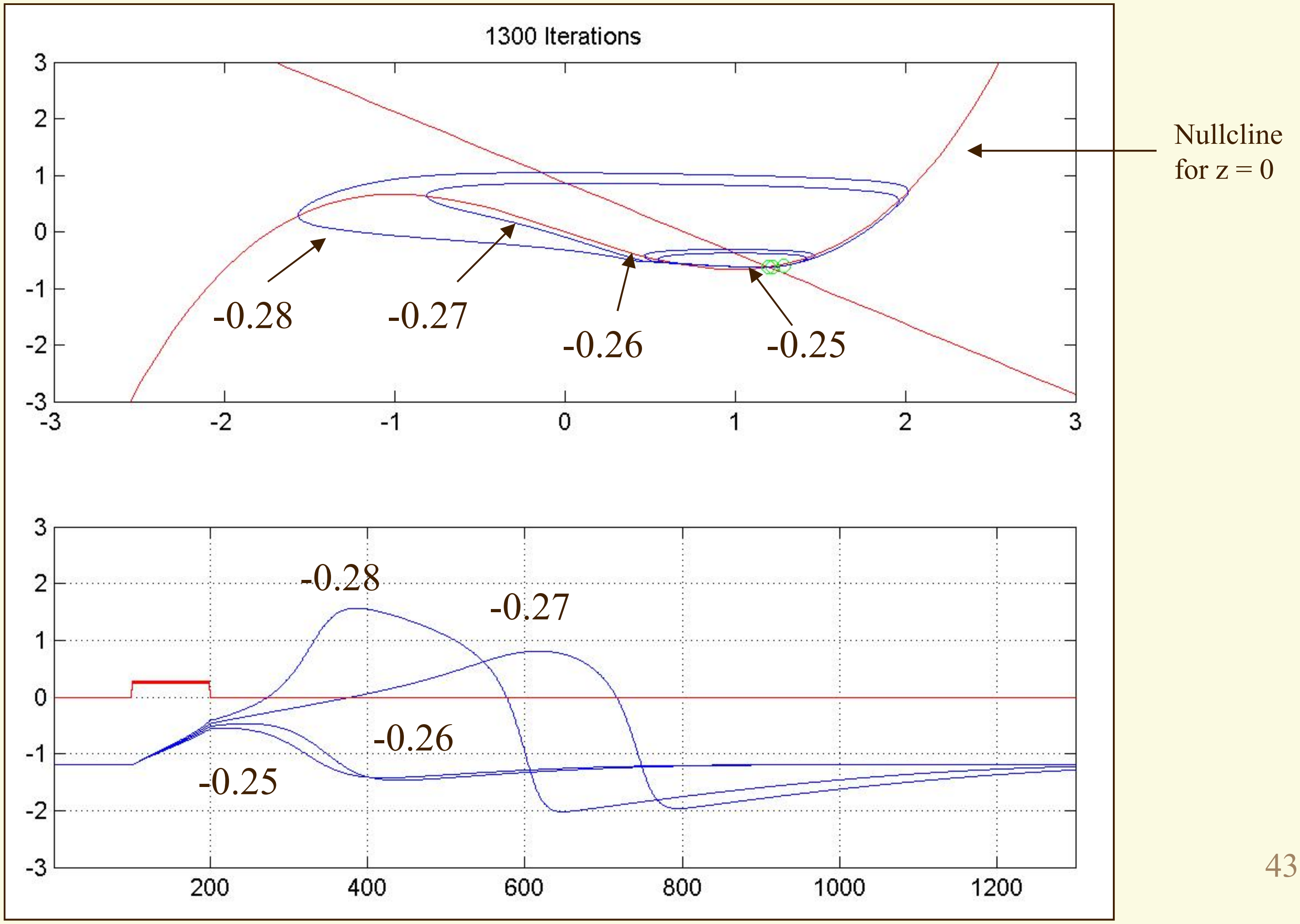

x vs y

x vs iteration number

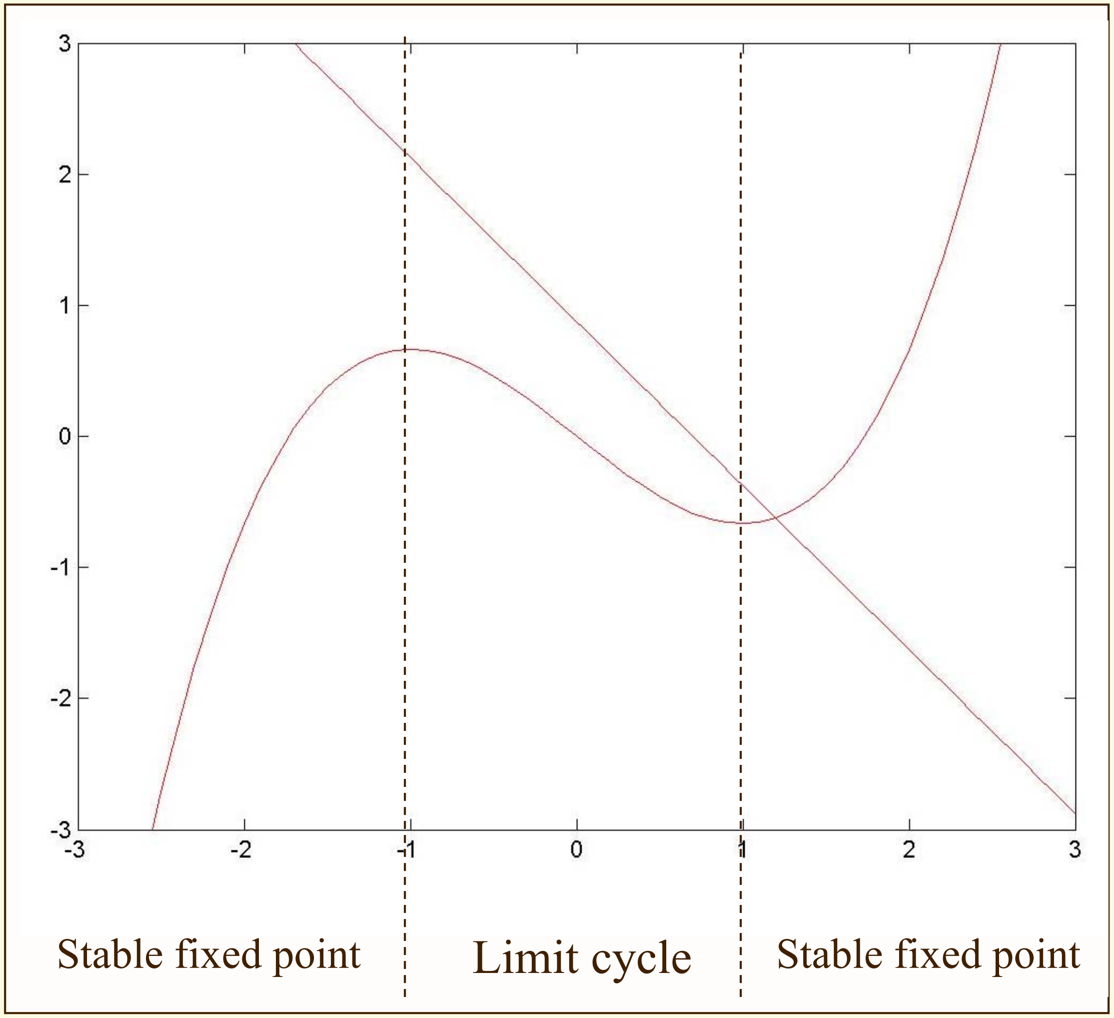
# Phase Space x = 4  (z = 0)



# Variations in stimulation strength (z)



# Intersection behavior

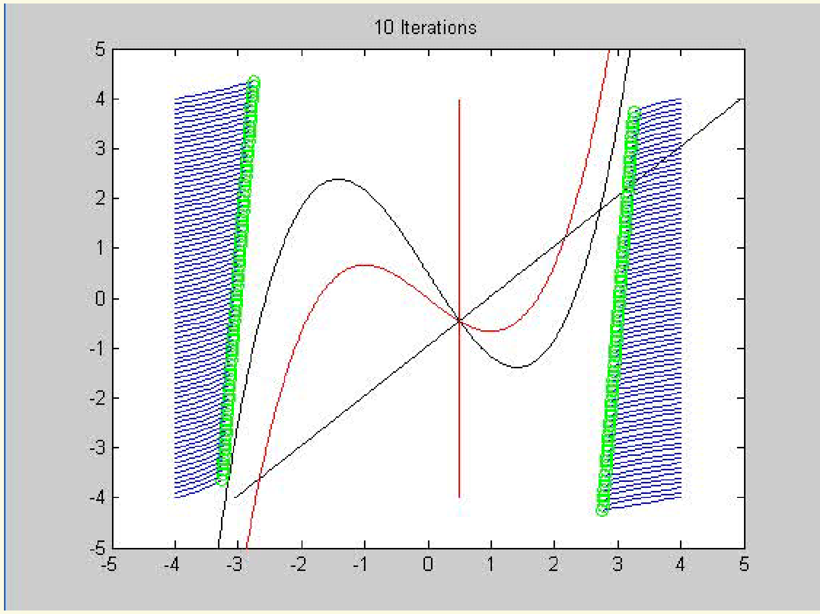


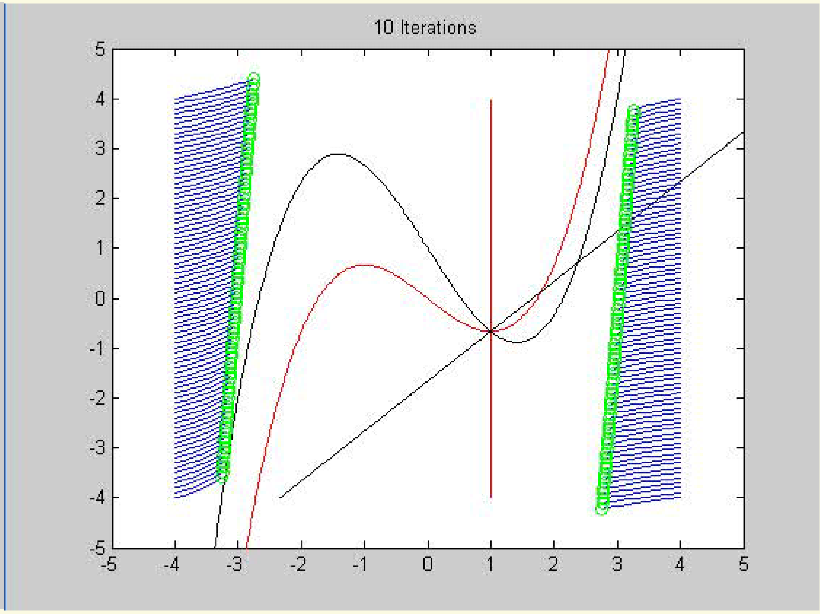

<u>nullclines</u>

$$y = \frac{x^3}{3} - x - z \quad \left(\frac{dx}{dt} = 0\right)$$

$$y = \frac{a - x}{b} \quad \left(\frac{dy}{dt} = 0\right)$$

# More Movies



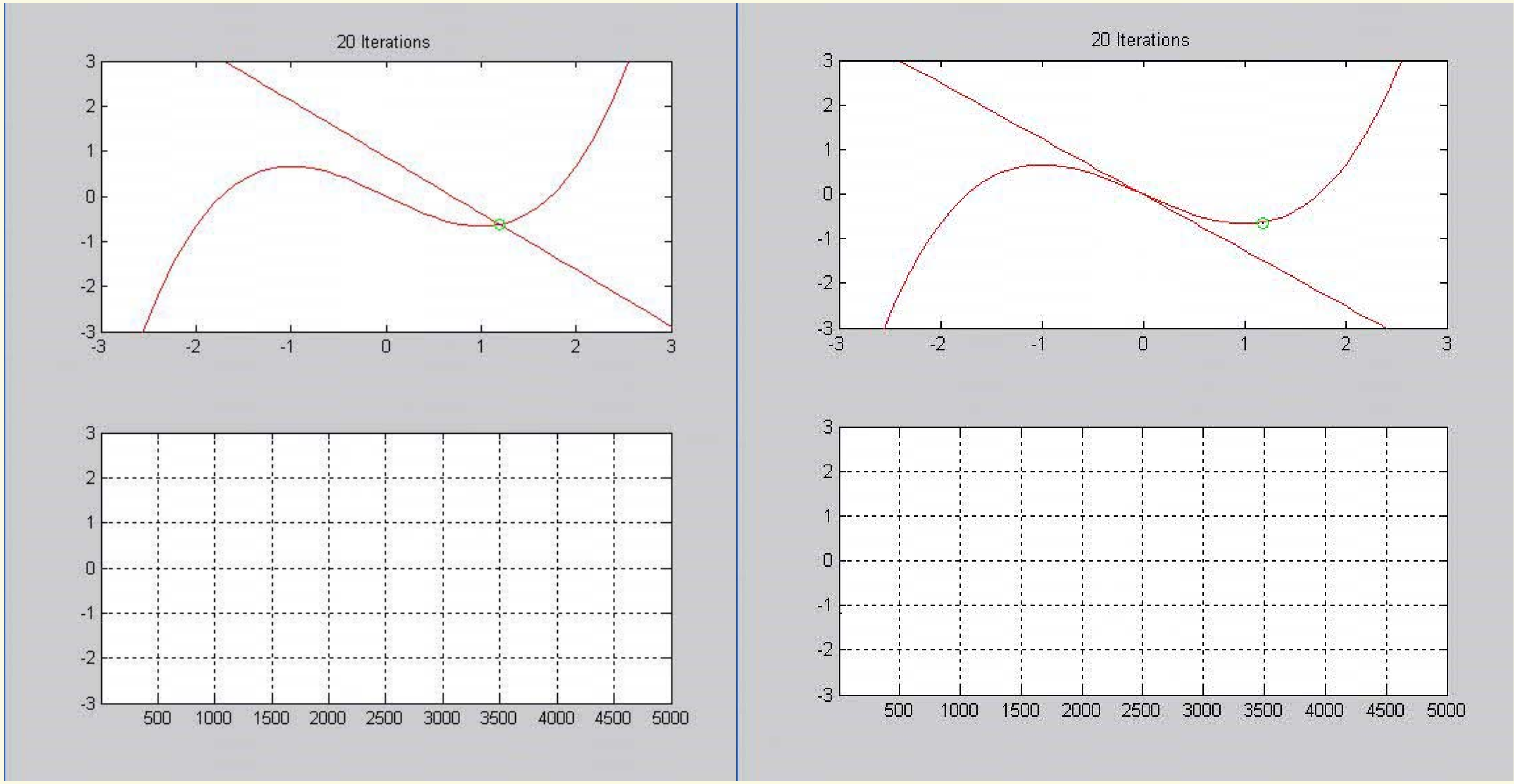




Limit Cycle

Limit Cycle

# Movies

$$\frac{dx}{dt} = c\left(y + x - \frac{x^3}{3} + z\right) \qquad \frac{dy}{dt} = -\frac{(x - a + by)}{c}$$




Long stim (z) a = 0, no stim

# Conclusions

- HH is a better representation of the physiology
- FN is a reduced version of HH
  - only considers fast changing variables
- FN is a good simple tool to understand why systems can be excitable.
  - People have trouble visualizing systems in 4 dimensions.
  - Contains important characteristics of action potential

# Thank you!