What Can We Learn From Integrative Modeling of the Heart ?

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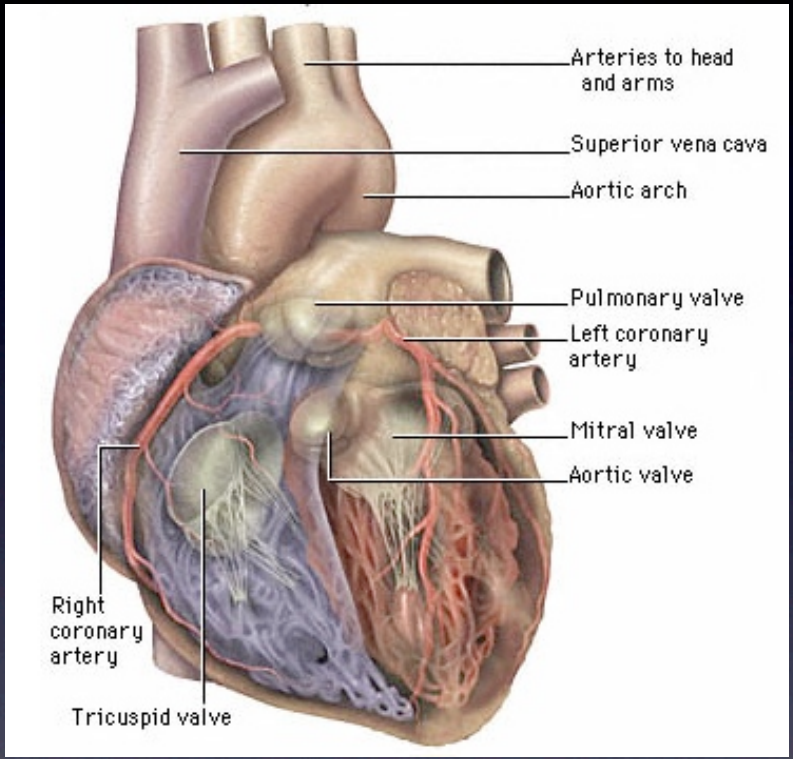
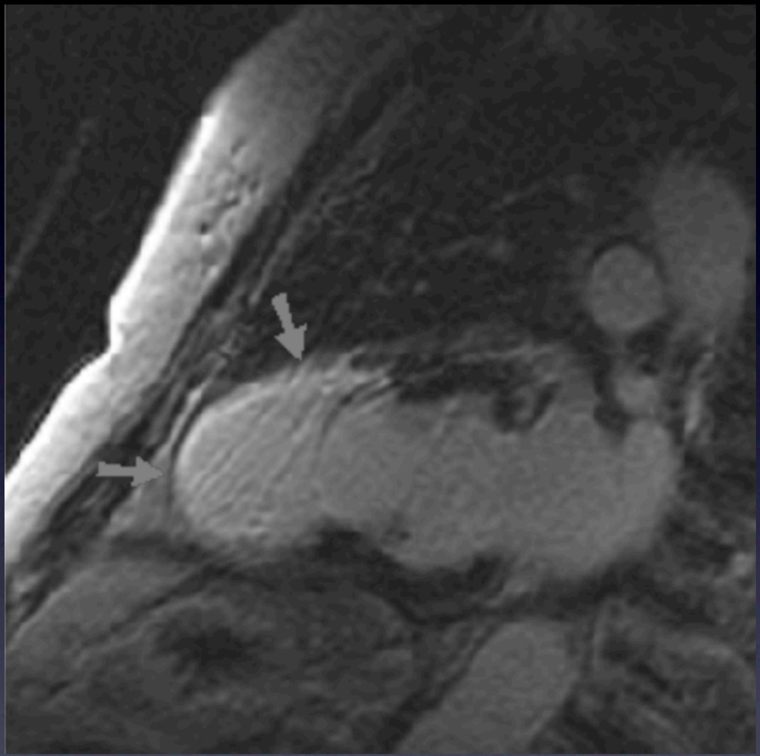
The Human Heart in Health and Disease

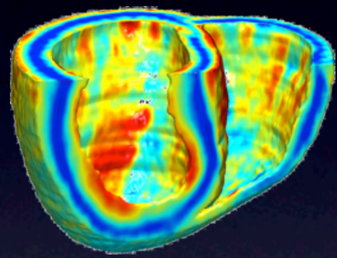
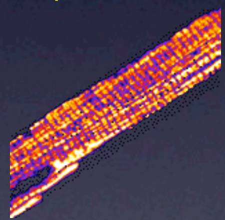
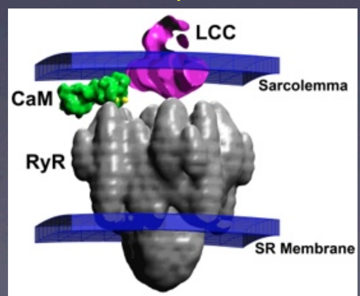


~ 3 billion beats per lifetime



Courtesy Dr. Joao Lima

Vertical Integration

Domain	Biological Hierarchy	Spatial Scale	Time Scale
Physiology	Heart (Macro-scale) 	~ 10^5 μm	~ 10^2 Sec
Cell Biology	Cells (Meso-scale) 	~ 10^2 μm	~ 10^{-3} Sec
Molecular Biology	Molecules (Nano-scale) 	~ 10^{-3} μm	~ 10^{-9} Sec

50 Years of Cardiac Modeling !

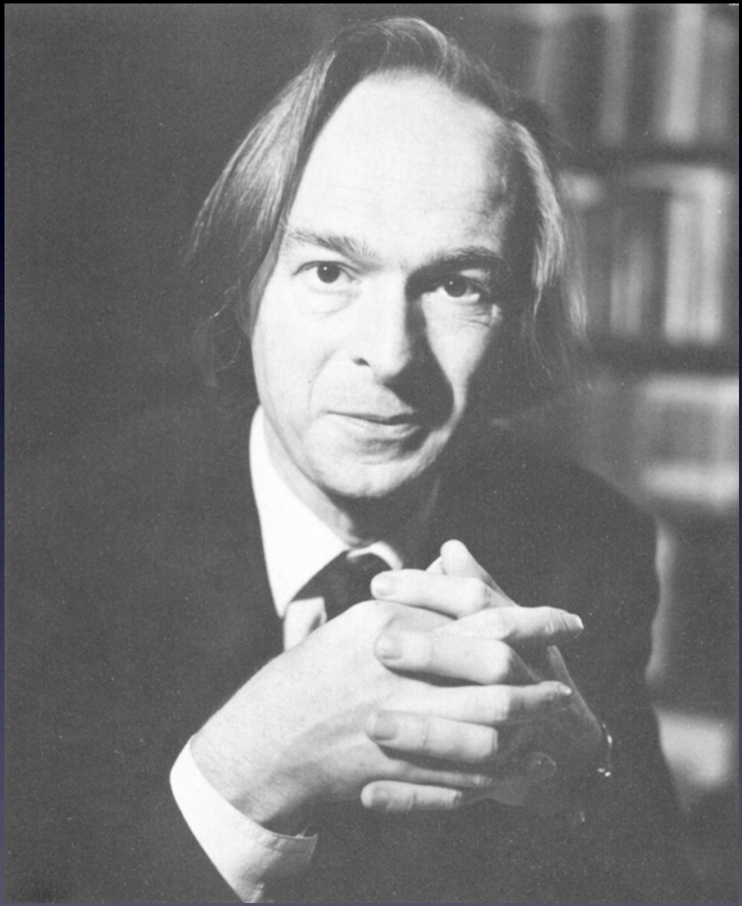
Cardiac Action and Pacemaker Potentials based on the Hodgkin–Huxley Equations

SINCE the equations describing the nerve action potential were formulated by Hodgkin and Huxley[1], the range of phenomena to which they have been shown to apply has been greatly extended. Huxley[2] has applied them to the influence of temperature on the propagated response and to the repetitive firing observed in low calcium concentrations. More recently, Fitzhugh[3] has shown that the long action potentials induced by tetraethylammonium ions in squid nerve may also be reproduced.

The computations described in this communication were carried out with the aim of reconstructing the long-lasting action potential and pacemaker potential of cardiac muscle. Although this work was done independently, the results agree with those of Fitzhugh in showing that action potentials of long duration may be accounted for by Hodgkin and Huxley's formulation of the membrane properties. The description of the potassium current, however, differs from that used by Fitzhugh and provides a better description of the conductance changes.

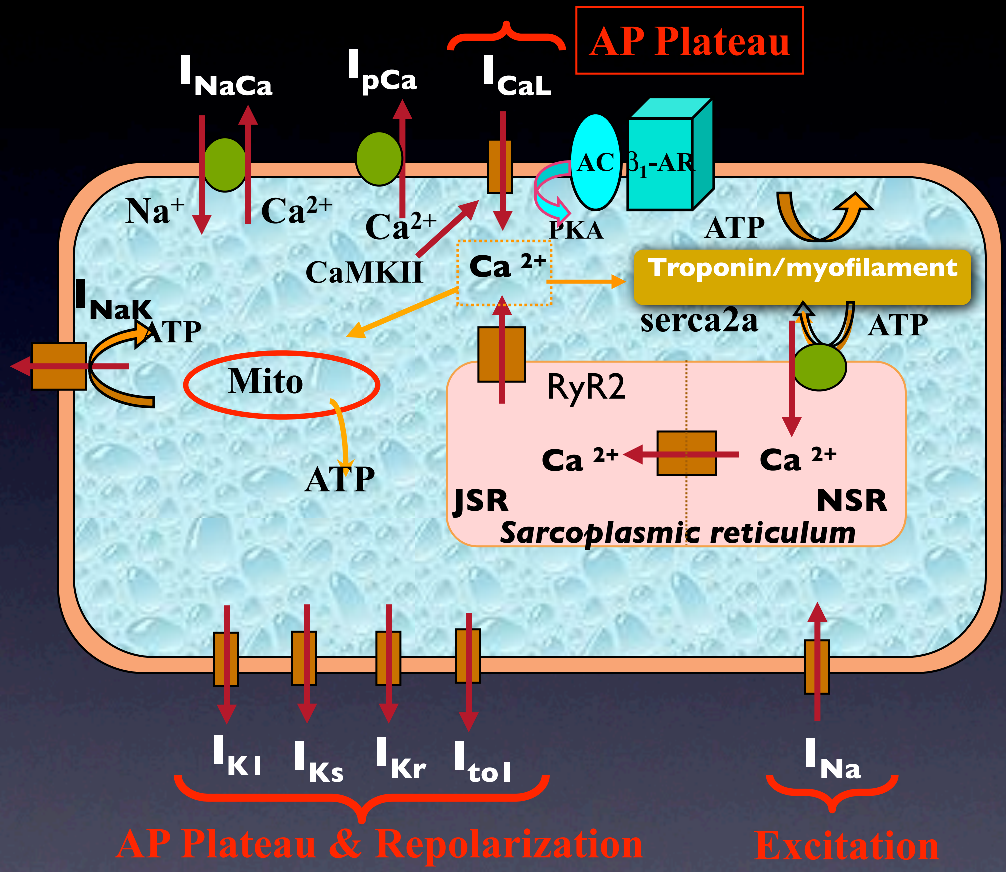
The equations I have used to describe the sodium current are very similar to Hodgkin and Huxley's,

D. Noble (1960). *Nature*, 188:495
November 5, 1960



Denis, *circa* 1984

Integrative Cell Models: State of the Art



- **Constraining data**
  - Functional_measurements (t)
  - ***low-throughput***
- **Model Components**
  - Ion channels & membrane transporters
  - Ca^{2+}-induced Ca^{2+}-release (CICR) and Ca^{2+} cycling
  - Ca^{2+}-driven force generation
  - Mitochondrial energetics
  - CaMKII, PKA signaling

Top

Down

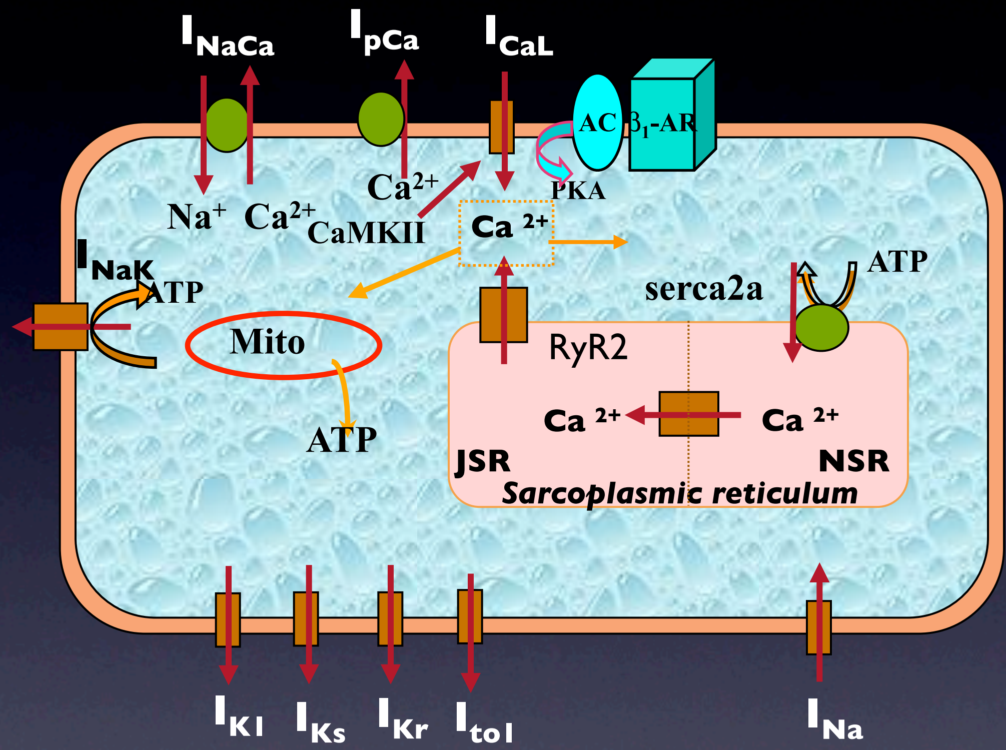
Integrative Modeling Case Study
Heart Failure

- Diverse origins, common phenotype
- Reduced contractility, mechanical pump failure
- Increased risk of Sudden Cardiac Death
- *The* primary U.S. hospital discharge diagnosis
  - Incidence ~ 400,000/year, prevalence ~ 4.5 million
  - 15% mortality at 1 Yr, 80% mortality at 6 Yr
  - Medical expenditures ~ $20 billion per year

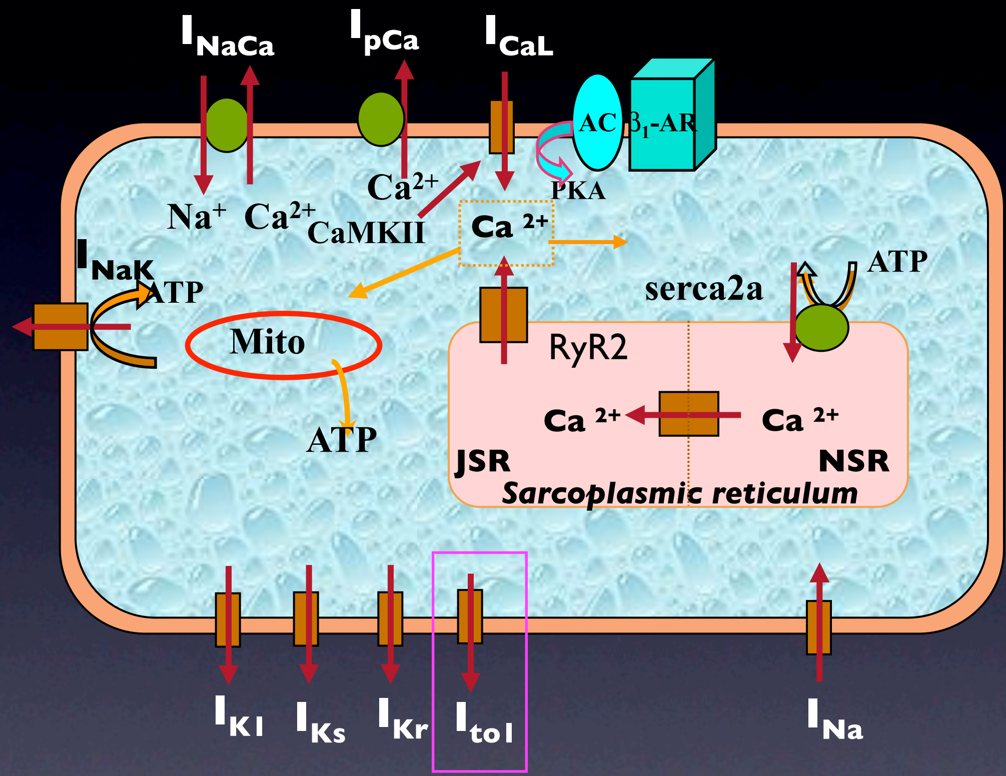
Using Models to Understand the Phenotypes of Heart Failure

- ***Molecular phenotype***
  - altered protein expression
  - disruption of protein co-localization
- ***Pathway phenotype***
  - increased B-adrenergic input, PKA hyper-phosphorylation
- ***Cellular phenotype***
  - Action potential prolongation, repolarization abnormalities
- ***Organ phenotype***
  - Reduced contractility
  - High risk of re-entrant arrhythmias

The *Molecular Phenotype* of Heart Failure

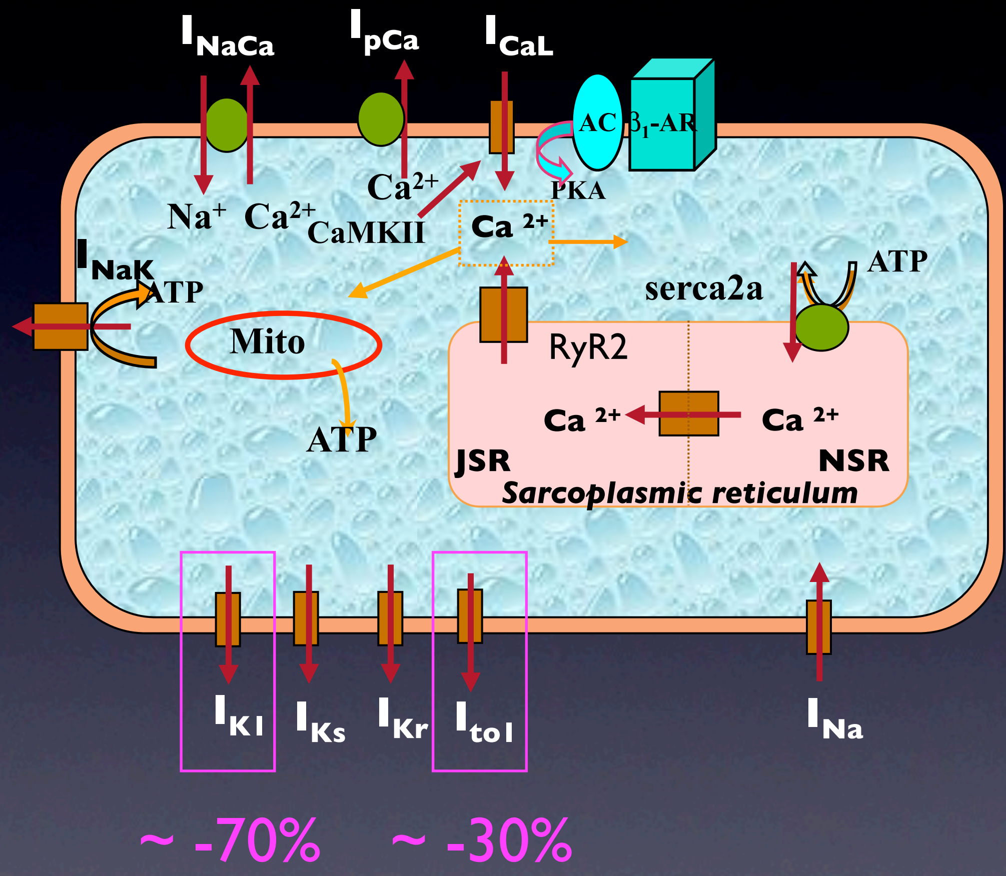


The *Molecular Phenotype* of Heart Failure

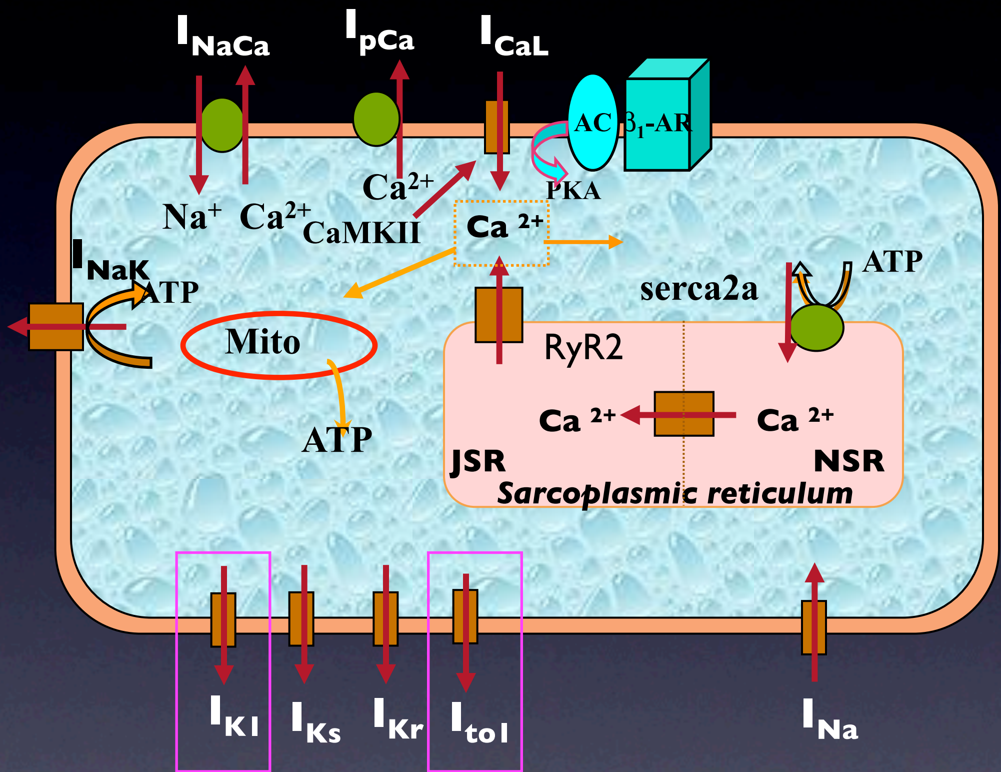


~ -30%

The *Molecular Phenotype* of Heart Failure



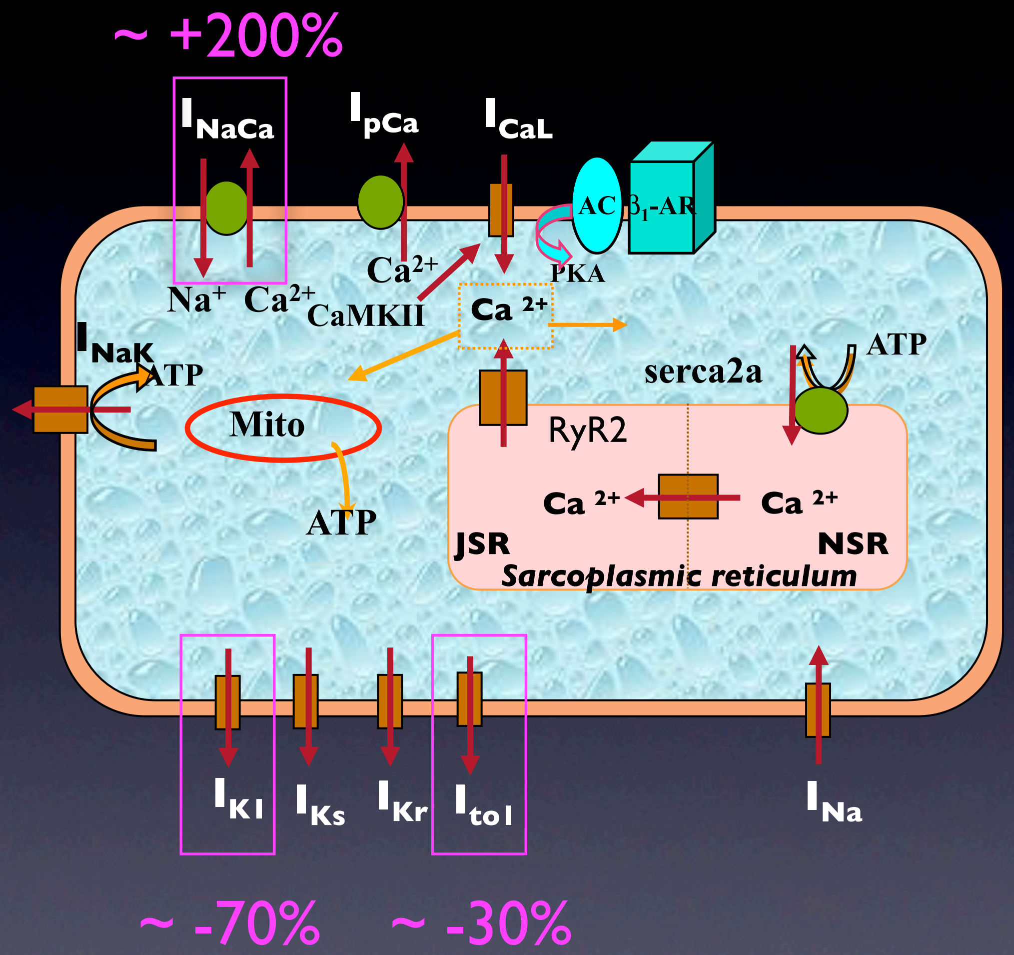
The *Molecular Phenotype* of Heart Failure



~ -70% ~ -30%

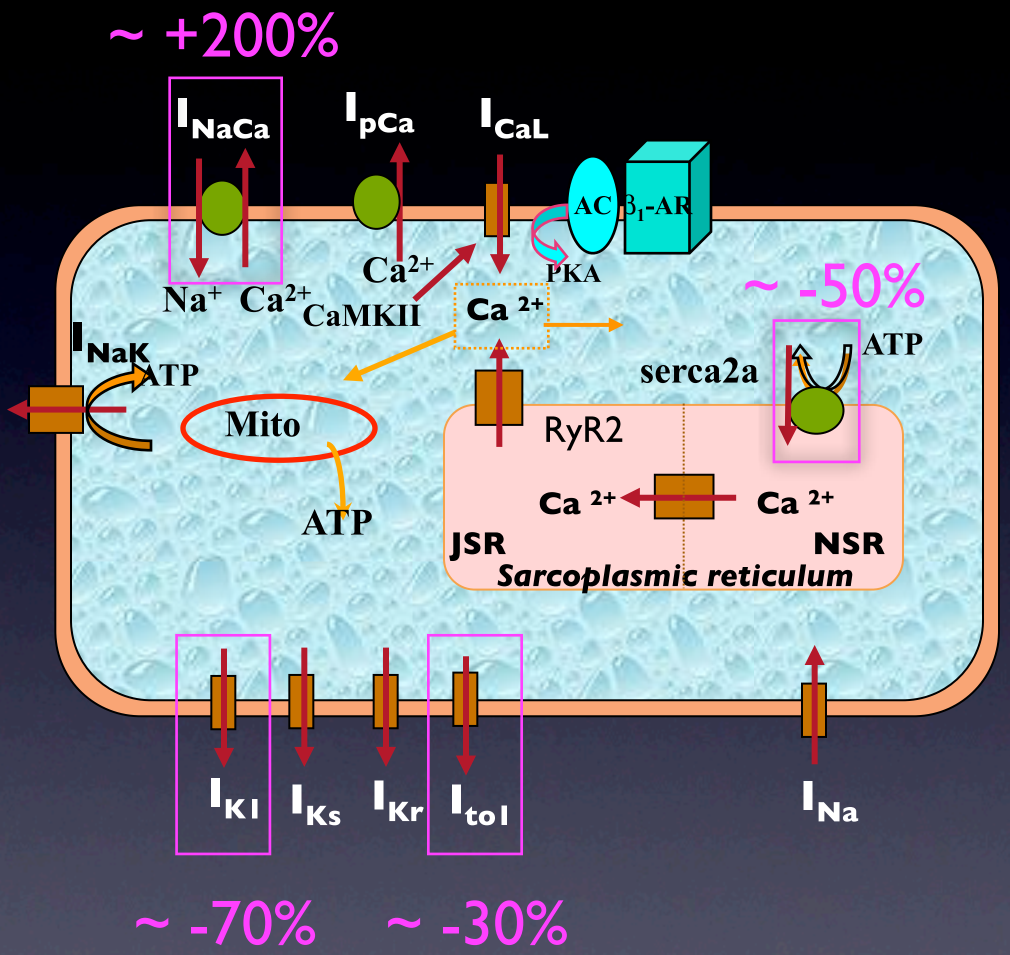
Hypothesis:Reduced Outward Current Prolongs APD

The *Molecular Phenotype* of Heart Failure



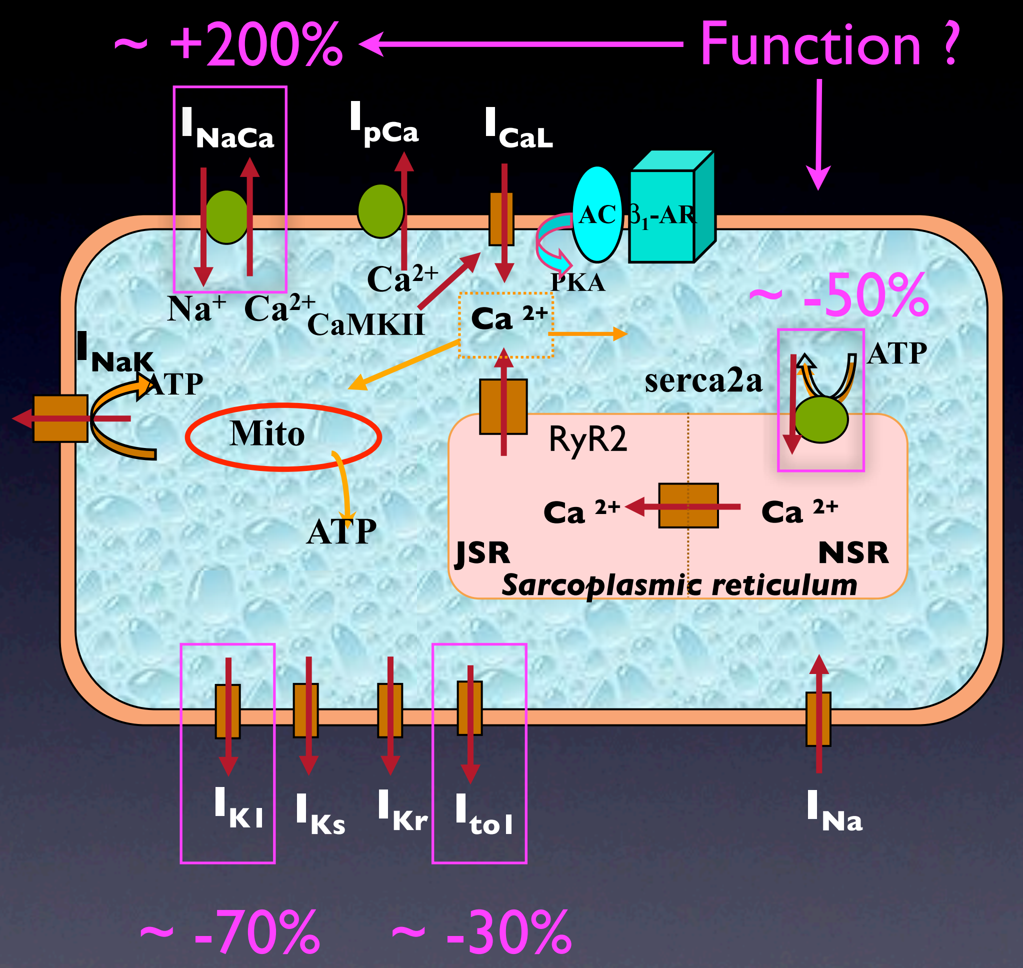
Hypothesis:Reduced Outward Current Prolongs APD

The *Molecular Phenotype* of Heart Failure



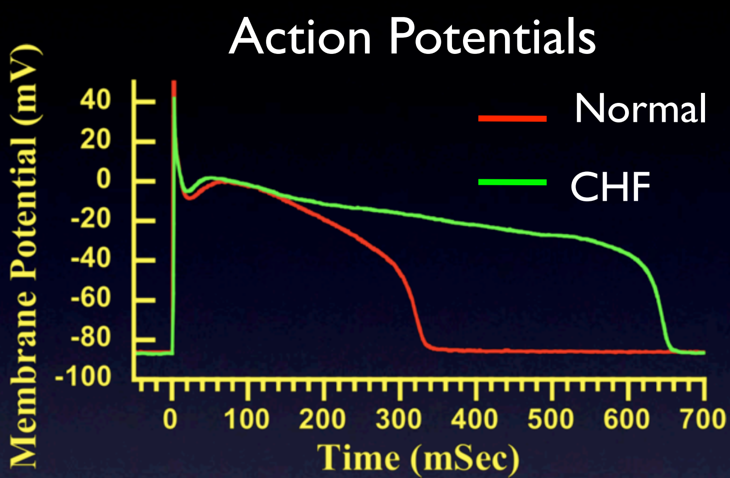
Hypothesis:Reduced Outward Current Prolongs APD

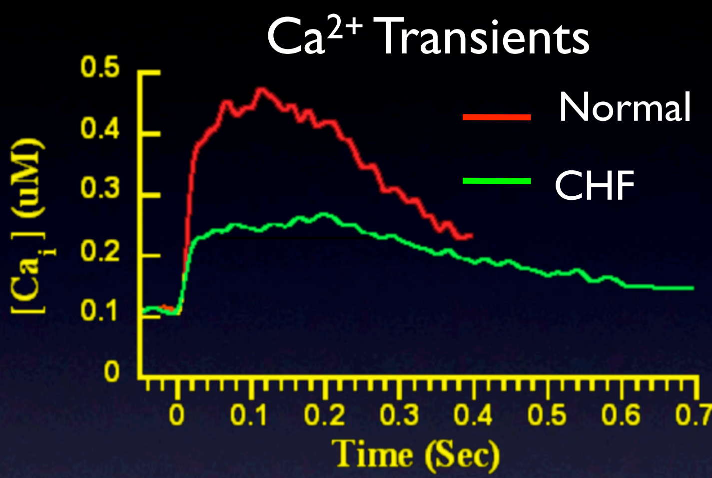
The *Molecular Phenotype* of Heart Failure



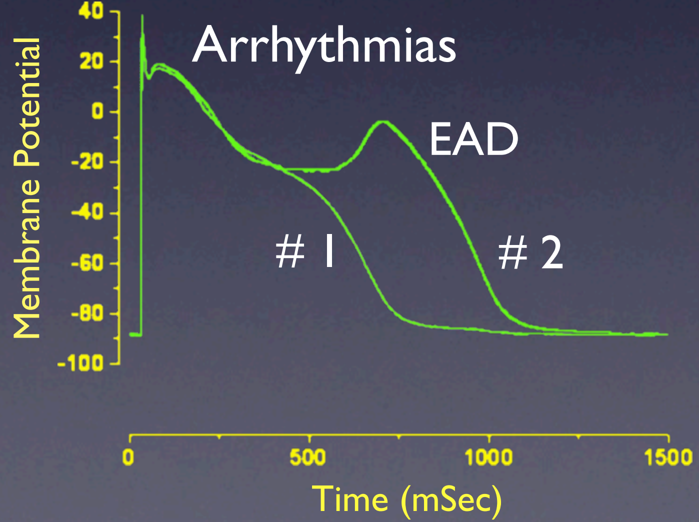
Hypothesis:Reduced Outward Current Prolongs APD

The *Cellular Phenotype* of Heart Failure





O'Rourke, et al. Circ. Res. 84: 562, 1999
Winslow et al. Circ. Res. 84: 571, 1999



- APD prolongation
- reduced Ca^{2+} transient magnitude
- Increased APD increases risk of EADs

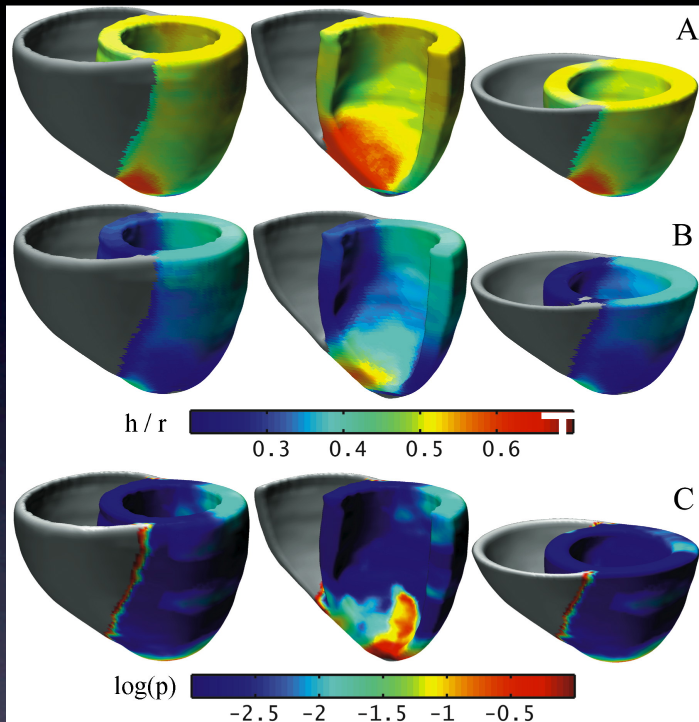
The Anatomic Phenotype of Heart Failure

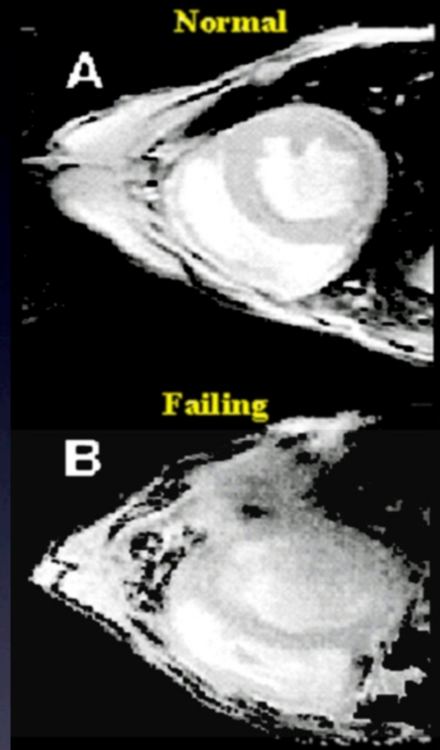
Helm et al (2006) Circ. Res. 98(1): 125

RWT Normal

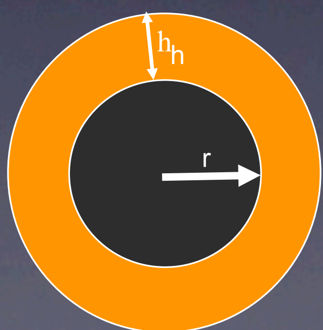
RWT Failing

log(p)





MR heart image pre- and post-tachycardia pacing (McVeigh et al)



Relative Wall Thickness (RWT) = h/r

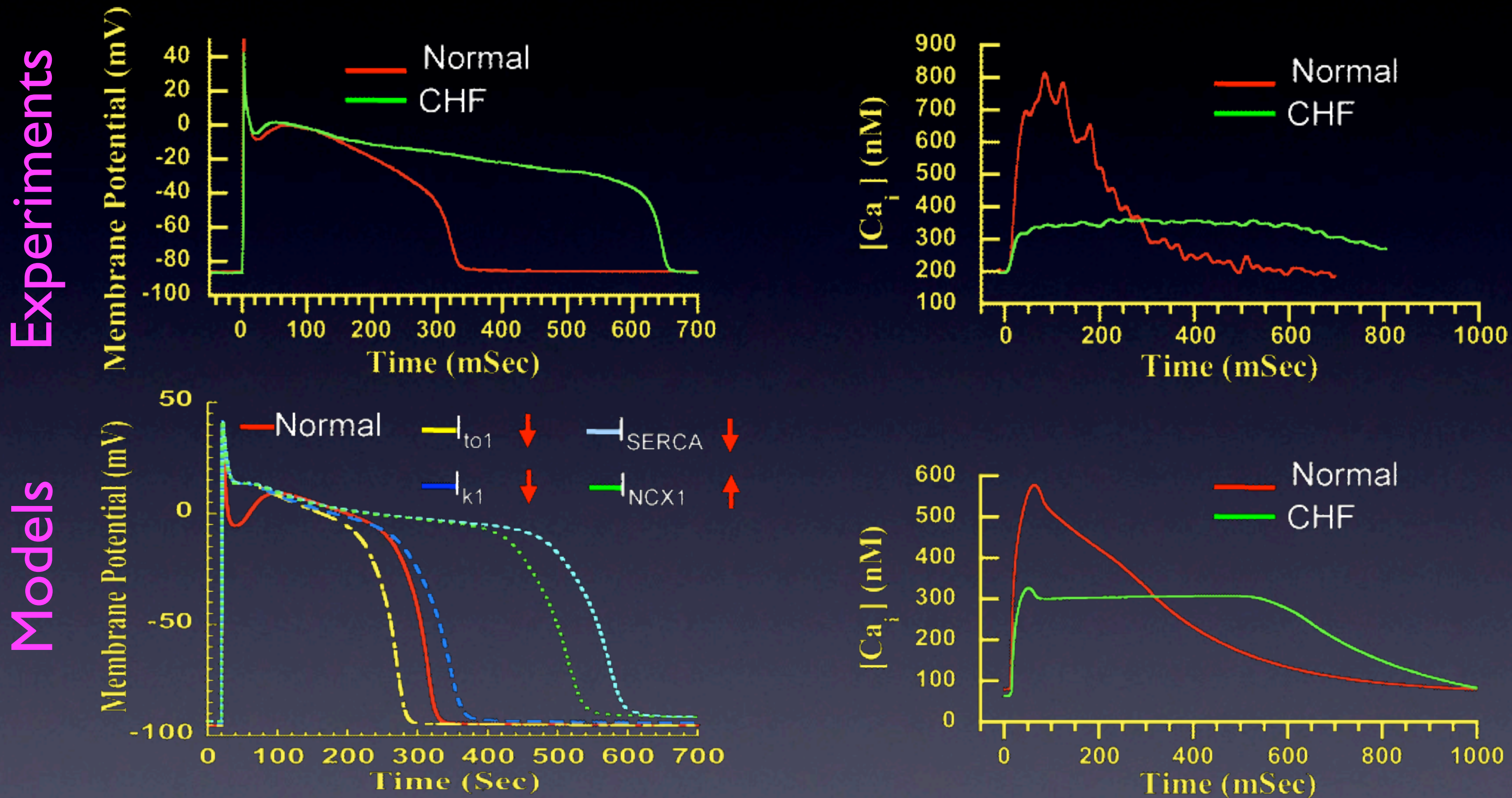
Modeling Approaches

- *"Nano-scale" model of Ca^{2+} signaling in the dyad*
  - Fokker-Planck equation
- *"Meso-scale" models of integrative cell function*
  - Stochastic ordinary differential equations
  - Deterministic ordinary differential equations
- *"Macro-scale" models of ventricular conduction*
  - reaction-diffusion partial differential equations
- *There are approaches for moving across these scales*

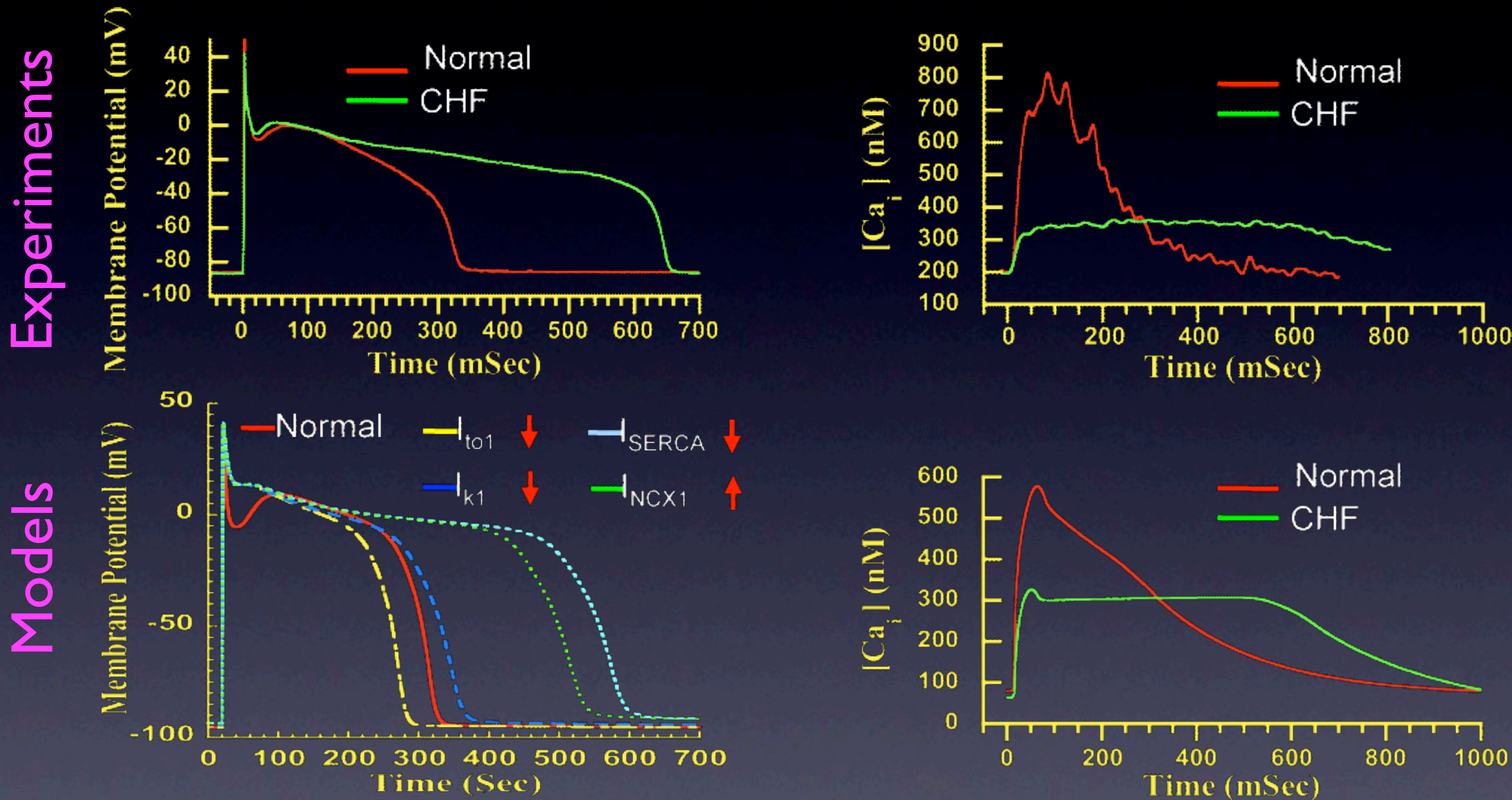
Dis-regulation of Protein Expression and Cell Function

- ***Molecular phenotype***
  - altered protein expression
  - disruption of protein co-localization
- ***Pathway phenotype***
  - increased B-adrenergic input, PKA hyper-phosphorylation
- ***Cellular phenotype***
  - Action potential prolongation, repolarization abnormalities
- ***Organ phenotype***
  - Reduced contractility
  - High risk of re-entrant arrhythmias

Relate Molecular to Cellular Phenotype Using “Meso-Scale” ODE Model



Relate Molecular to Cellular Phenotype Using "Meso-Scale" ODE Model



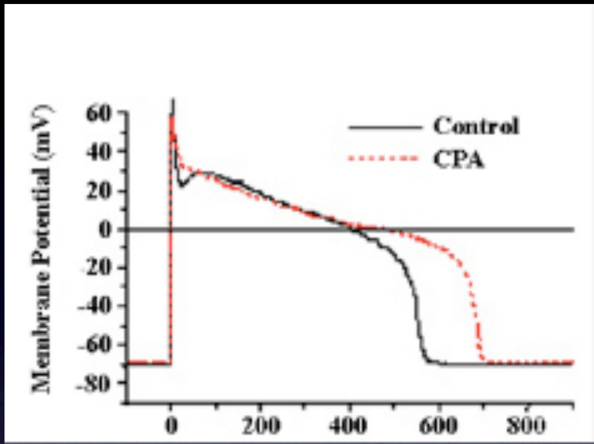
Non-Intuitive Result: Altered Ca^{2+} Handling Key to APD Prolongation

Experimental Validation of Model Predictions

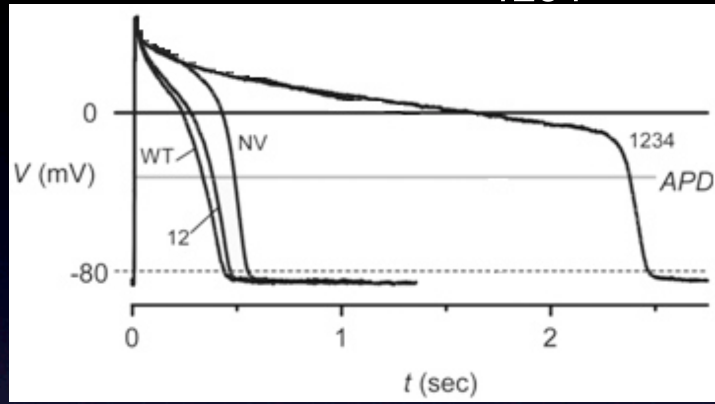
Serca Reduction

Mutant CaM_{1234}

Experiment

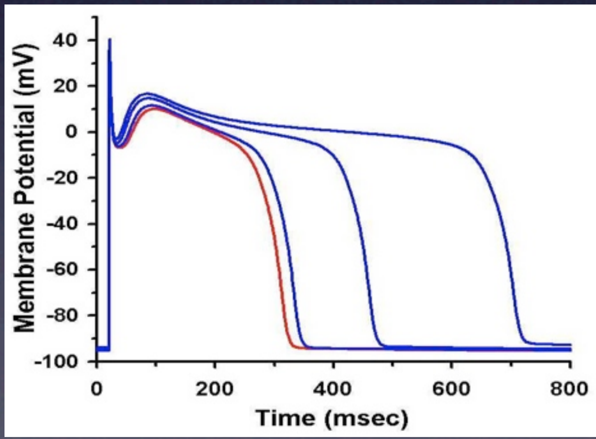


Winslow et al *Phil. Trans. Roy. Soc. Lond. A* 359: 1187

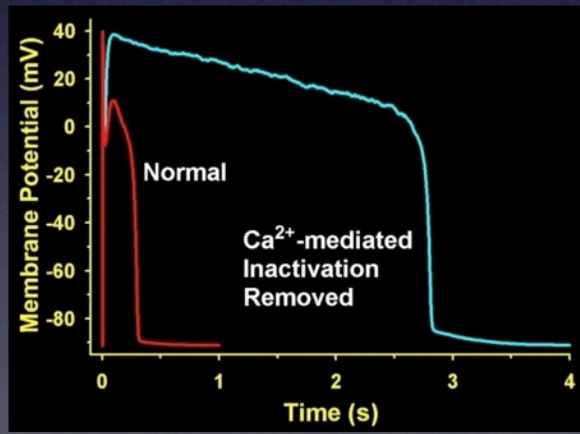


Alseikhan et al *PNAS* 99(26): 17185

Model



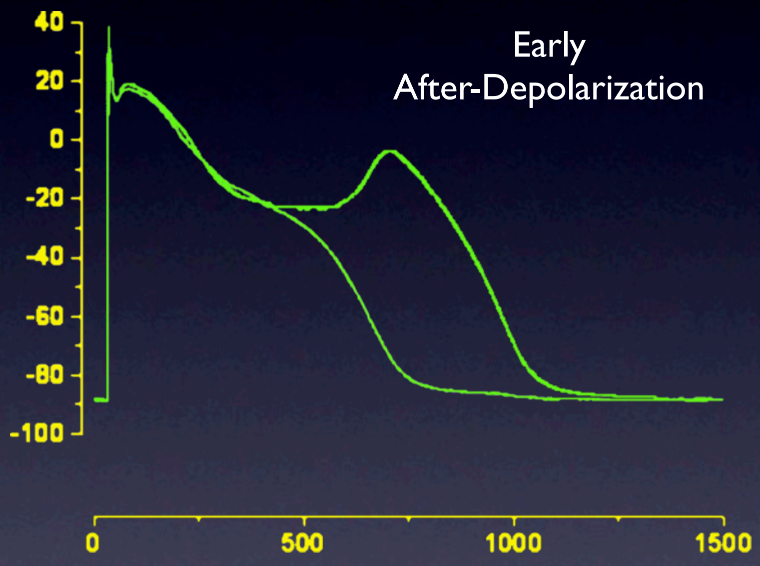
Winslow et al *Phil. Trans. Roy. Soc. Lond. A* 359: 1187



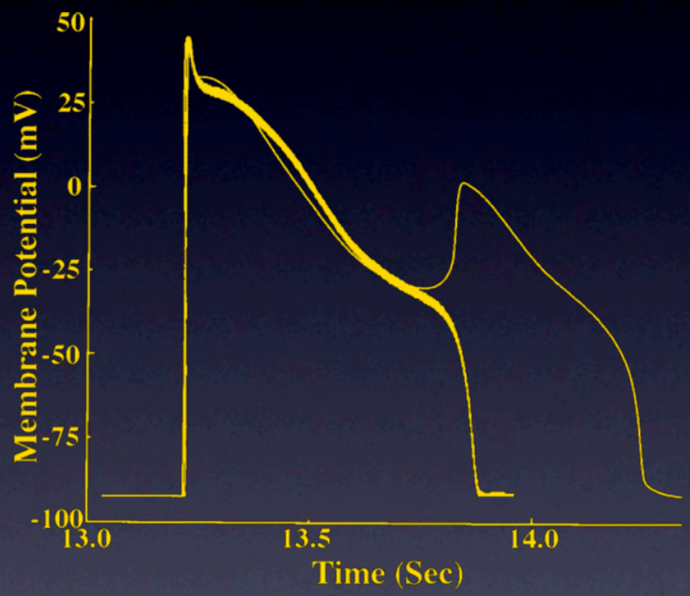
Greenstein & Winslow et al *Biophys. J. 83(6): 2918*

Functional Consequences of APD Prolongation in HF

Experiment



Model



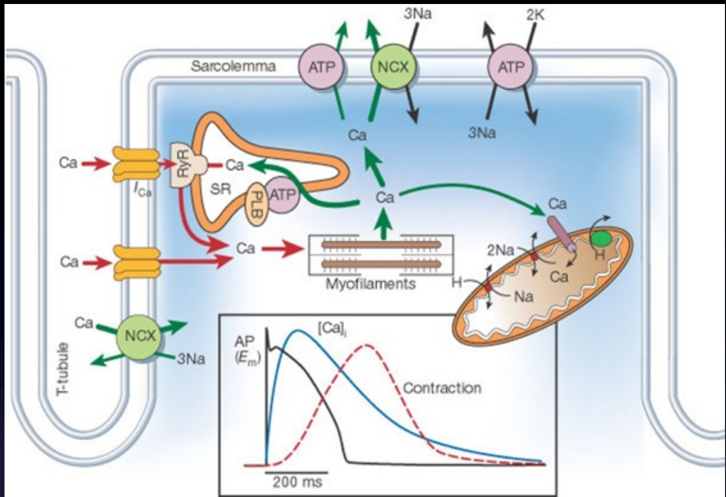
APD Prolongation => EADs

Models Have Explained the Mechanism

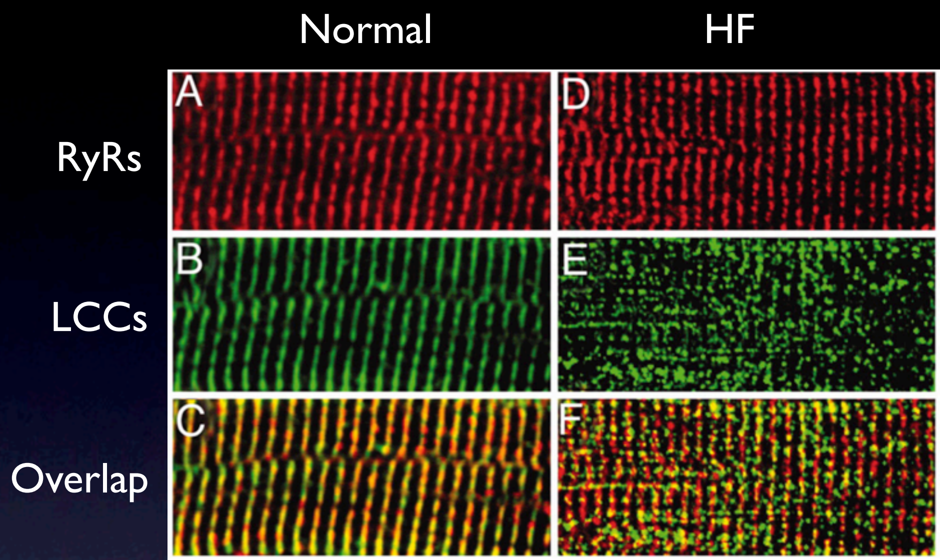
Protein Localization and Mechanical Function

- ***Molecular phenotype***
  - altered protein expression
  - disruption of protein co-localization
- ***Pathway phenotype***
  - increased B-adrenergic input, PKA hyper-phosphorylation
- ***Cellular phenotype***
  - Action potential prolongation, repolarization abnormalities
- ***Organ phenotype***
  - Reduced contractility
  - High risk of re-entrant arrhythmias

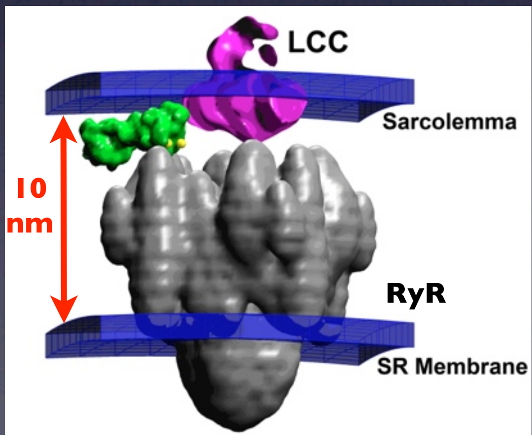
The Architecture of Ca^{2+} Signaling



Bers (2002) Nature 415(6868): 198



Song et al (2006). PNAS 103(11): 4305



Structure of the LCC (4Å), calmodulin (1Å) and RyR (14Å)

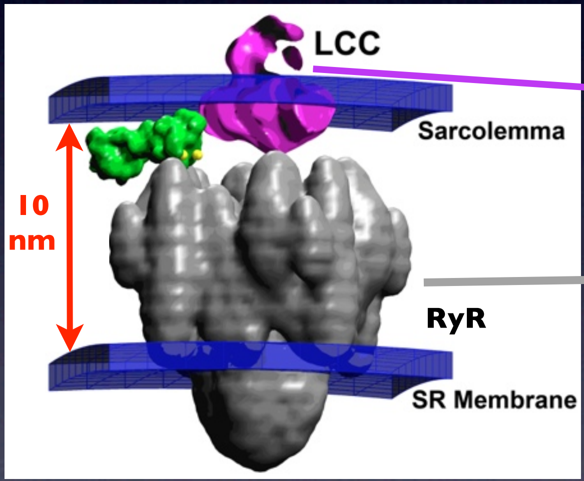
Number of Ca^{2+} ions mediating LCC-RyR signaling may be very small

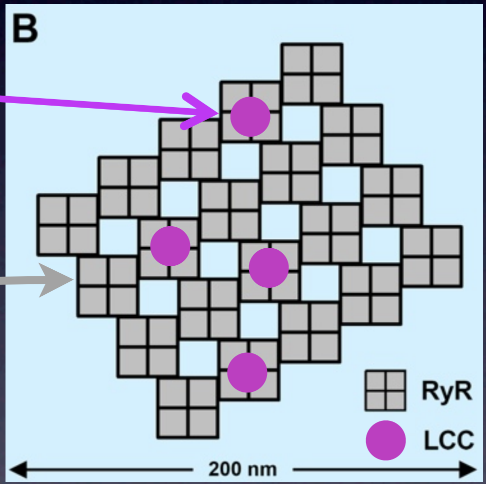
LCC & RyR co-localization may be disrupted

Functional consequences ?

"Nano-scale" Model of Ca^{2+} Signaling in the Dyad

Model dyad LCC:RyR 4:20 ~5,000 dyads/cell





"Nano-scale" Model of Ca^{2+} Signaling in the Dyad

Brownian Motion in a Potential Field

$$\frac{\partial P(\boldsymbol{r}_1,\ldots,\boldsymbol{r}_N,t)}{\partial t} = D\sum_{i=1}^{N}\frac{\partial}{\partial \boldsymbol{r}_i}\cdot\left[\frac{1}{k_B T}\frac{\partial V(\boldsymbol{r}_1,\ldots,\boldsymbol{r}_N)}{\partial \boldsymbol{r}_i}P(\boldsymbol{r}_1,\ldots,\boldsymbol{r}_N,t)+\frac{\partial P(\boldsymbol{r}_1,\ldots,\boldsymbol{r}_N,t)}{\partial \boldsymbol{r}_i}\right]$$ FP Eq.

$$\frac{\partial}{\partial \boldsymbol{r}_i} = \left[\begin{array}{ccc}\frac{\partial}{\partial r_{i,1}} & \frac{\partial}{\partial r_{i,2}} & \frac{\partial}{\partial r_{i,3}}\end{array}\right]$$

$$\underbrace{V(\boldsymbol{r}_1,\ldots,\boldsymbol{r}_N)}_{\text{Potential Energy}} = \sum_{i=1}^{N}[\underbrace{2q\varphi(\boldsymbol{r}_i)}_{\text{Surface Charge}} + \underbrace{u(\boldsymbol{r}_i)}_{\text{Hard Core}}] + \underbrace{U(\boldsymbol{r}_1,\ldots,\boldsymbol{r}_N)}_{\text{Ion Interaction}}$$

Signaling Mediated by Ten's of Ca^{2+} Ions

LCC Open | **RyR Open**

Single LCC
0 mV
Open at t=0

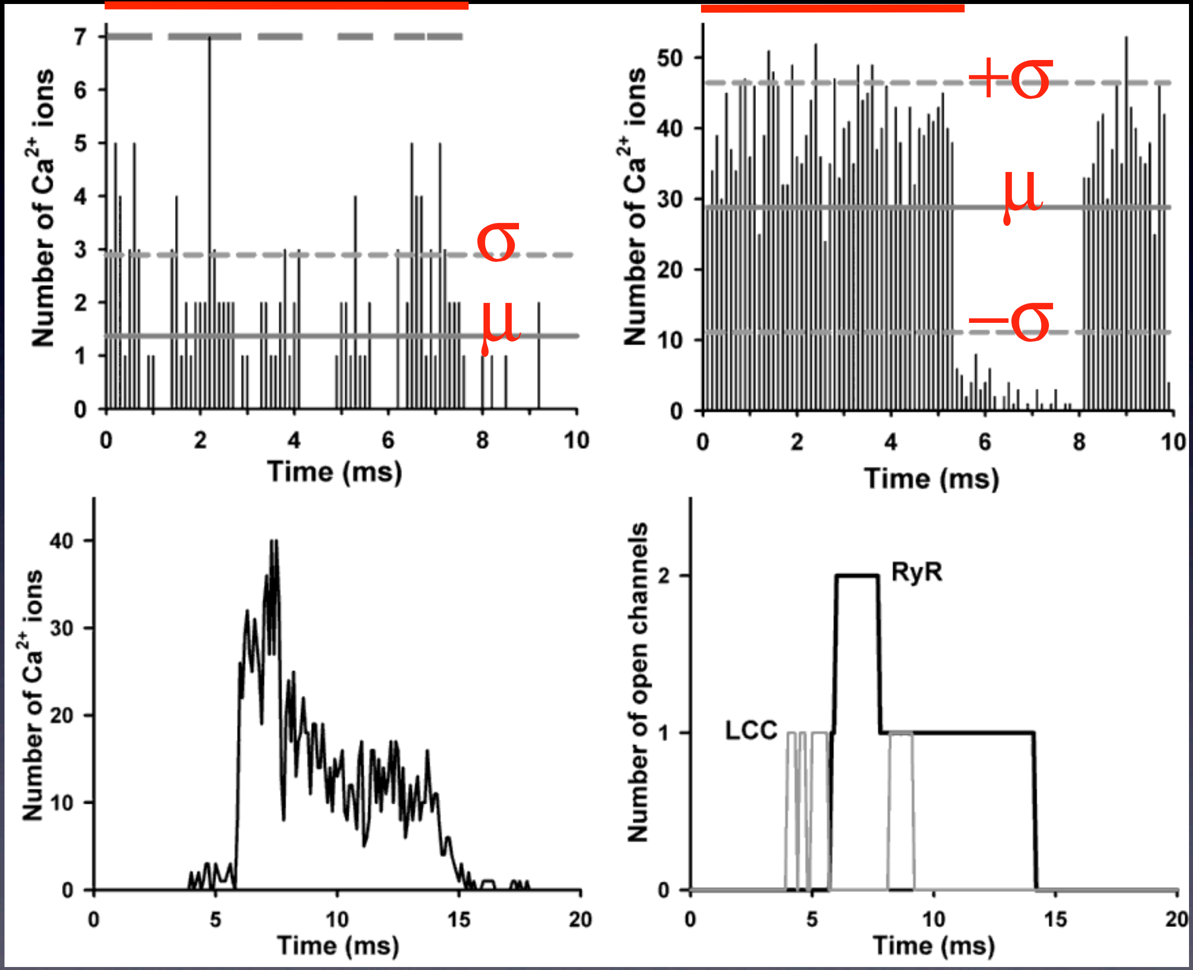
1.4 ± 1.4
Ca^{2+} ions

Single RyR
0 mV
Open at t=0

28.8 ± 17.7
Ca^{2+} ions

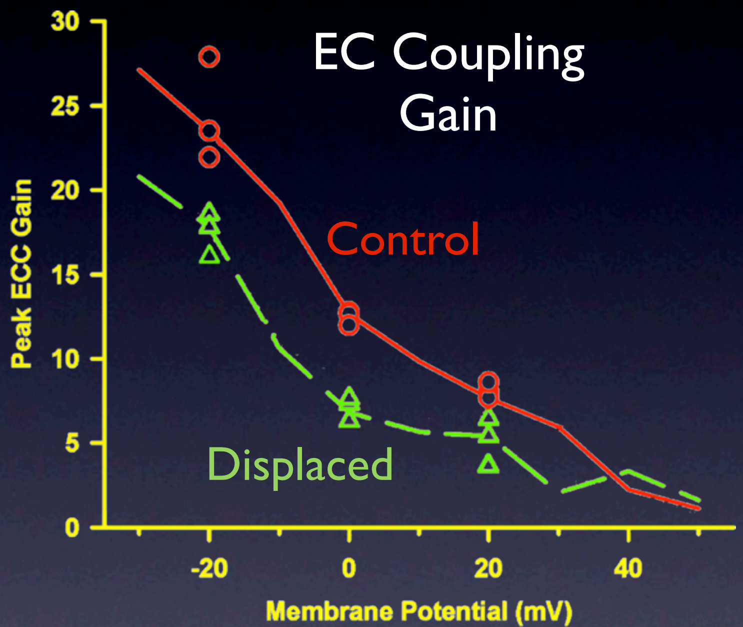
Single CaRU
4 LCC, 20 RyR2
0 mV

~ 10 Ca^{2+} ions
In late phase



Tanskanen et al Biophys. J. 92: 3379

Disruption of LCC-RyR Co-Location



ECC gain *very sensitive* function of relative channel placement

Reduced gain => less Ca^{2+} release

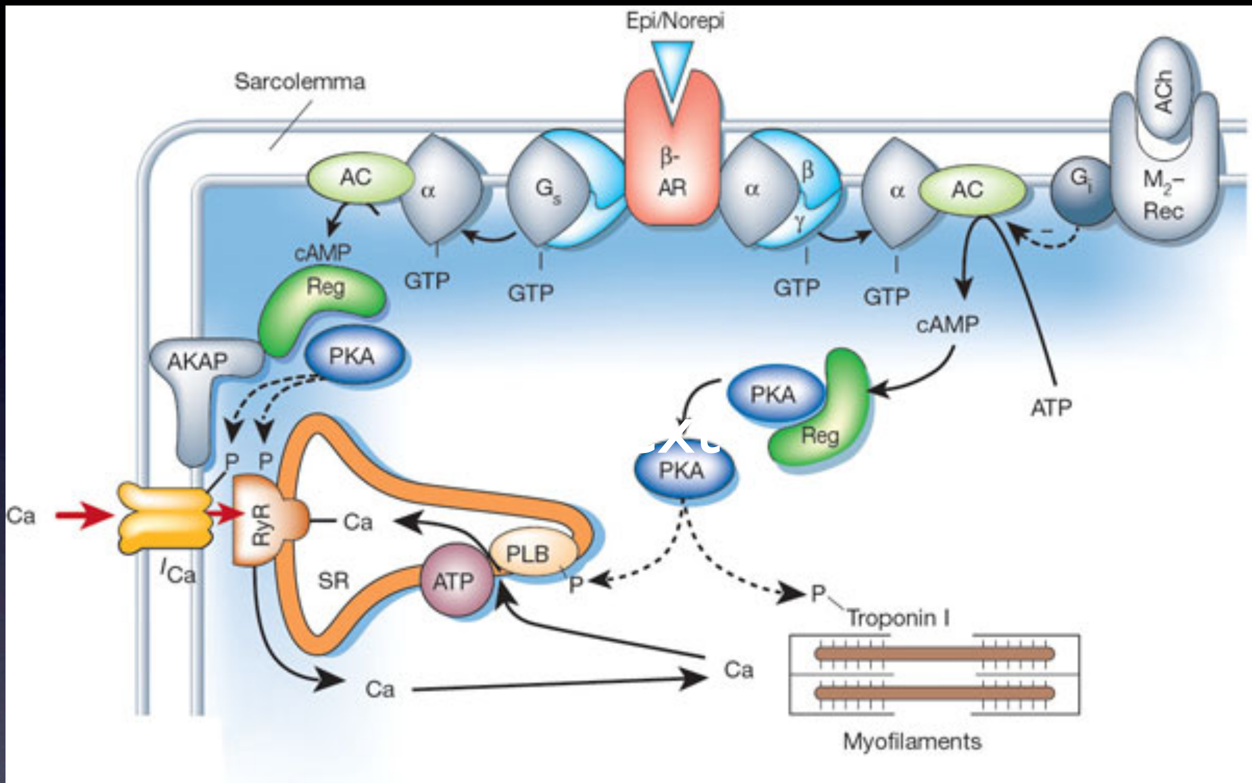
Disruption in heart failure could impair muscle contraction

$$\text{EC Coupling Gain} = \frac{\text{Total } Ca^{2+} \text{ Release Flux}}{\text{Total } Ca^{2+} \text{ Trigger Flux}}$$

Altered Signaling and Cellular Arrhythmias

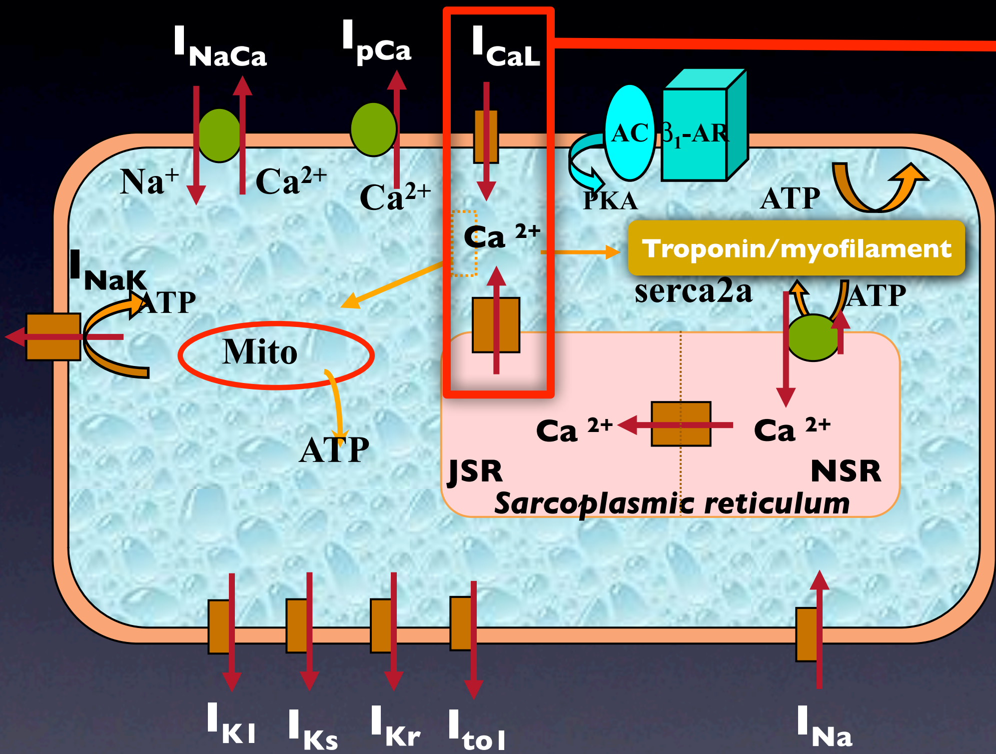
- ***Molecular phenotype***
  - altered protein expression
  - disruption of protein co-localization
- ***Pathway phenotype***
  - increased B-adrenergic input, PKA hyper-phosphorylation
- ***Cellular phenotype***
  - Action potential prolongation, repolarization abnormalities
- ***Organ phenotype***
  - Reduced contractility
  - High risk of re-entrant arrhythmias

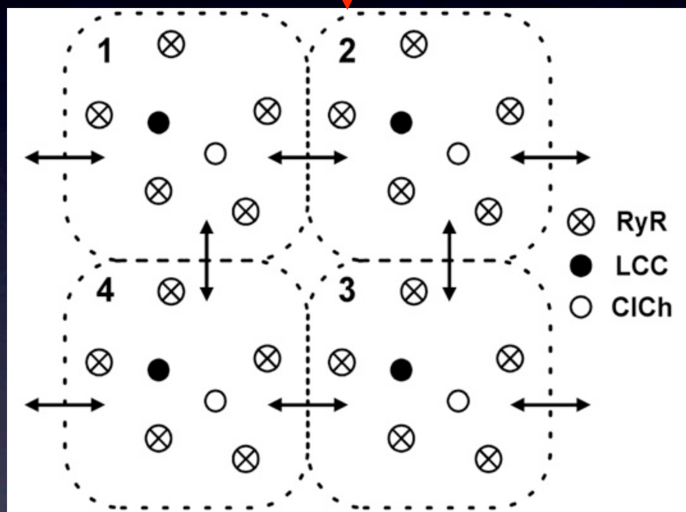
Hyper-Phosphorylation of LCCs in HF



Phosphorylated LCCs have 10x longer mean open times

"Meso-scale" Stochastic ODE Model

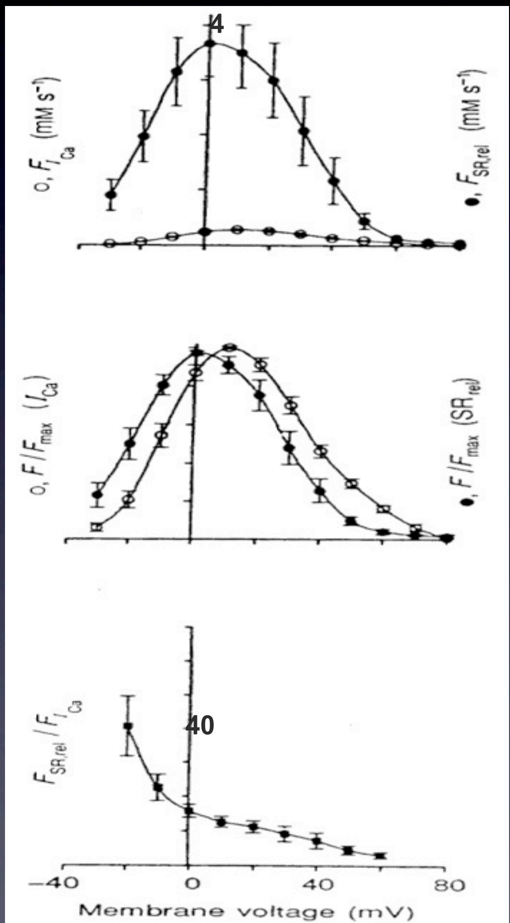


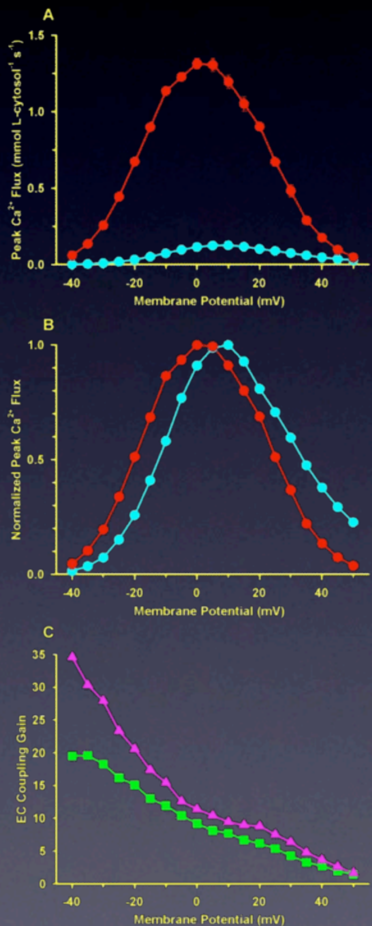


Course approximation to dyad

Stochastic Model Reproduces Important Properties of Ca^{2+} Release

Experiment **Model**

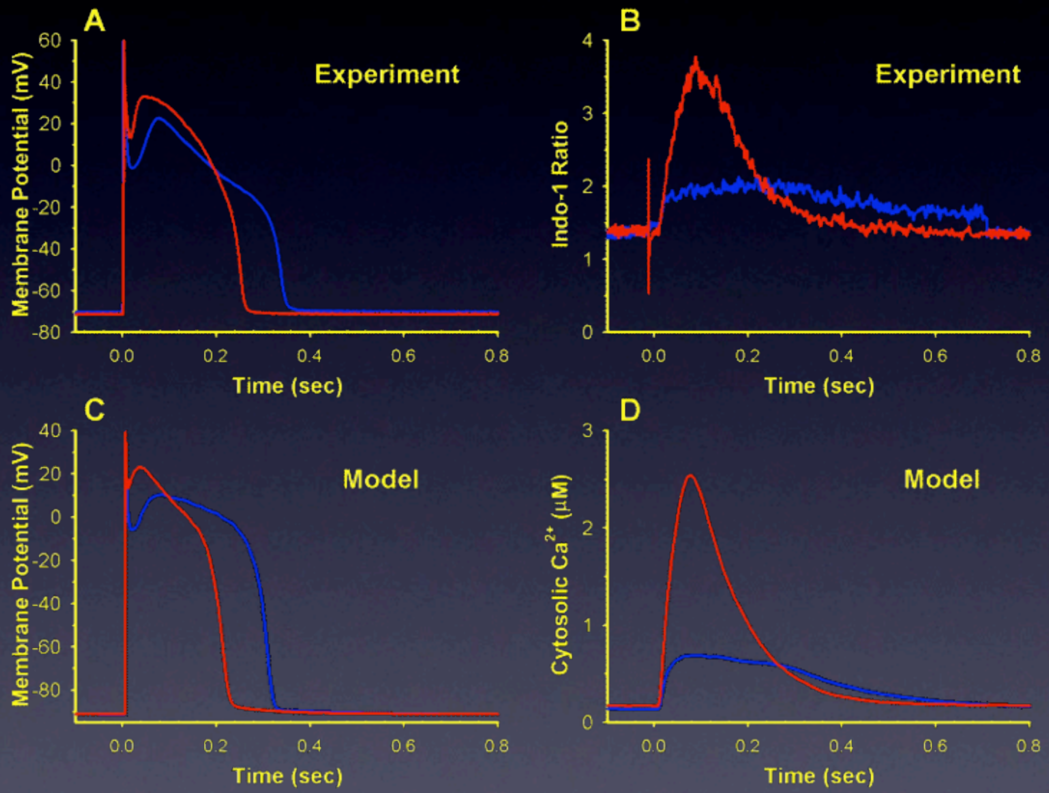




~ 10 Sec for 1 simulation-Sec on 64 dual-core Intel 2.8 GHz MHz nodes

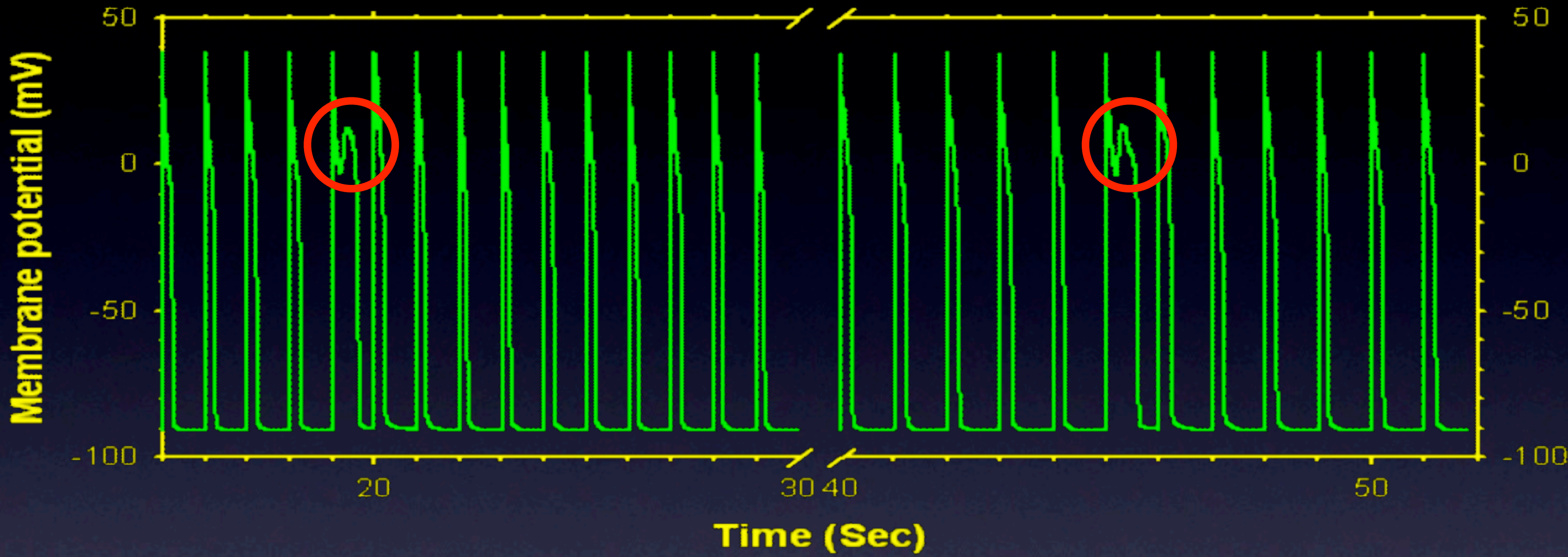
Greenstein & Winslow, Biophys. J. 83: 2918-2945

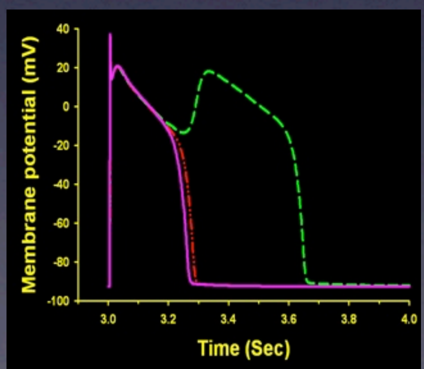
Use Stochastic Cell Model to Study Chronic PKA Activation in HF



- **β-AR activation of PKA**
  - Chronic activation in HF
  - phosphorylates PLN, up-regulates serca2α pump
  - phosphorylates and down-regulates membrane K^+ current
  - phosphorylates LCCs, switch from Mode 1 to Mode 2 gating
  - mean channel open time in Mode 2 is 10x larger than in Mode 1

Functional Consequence of Increased Open Time:
Random Early After-Depolarizations



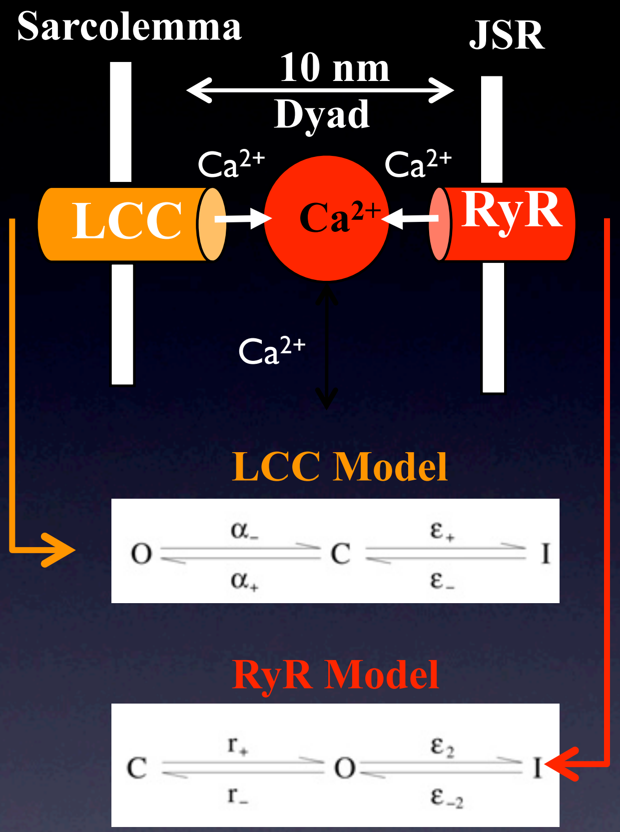


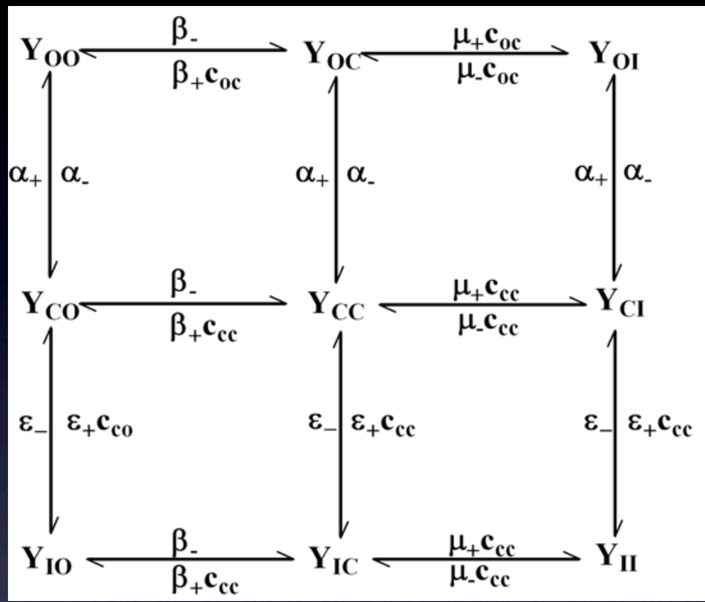
- EADs produced by PKA phosphorylation of Ca^{2+} channels
- MECHANISM - Clustered openings of Ca^{2+} channels with long open time
- EADs inherently stochastic, discovered using stochastic ODE model
- EADs correlated with Sudden Cardiac Death

Cellular to Whole-Heart Arrhythmias

- ***Molecule***
  - dis-regulation of protein expression
  - disruption of protein co-localization
- ***Pathway***
  - PKA pathway & hyper-phosphorylation
- ***Cell***
  - Action potential prolongation, cellular arrhythmias
- ***Organ***
  - Reduced contractility
  - Re-entrant arrhythmias

Step from the Stochastic ODE Model to ODE Model Using the Rapid Equilibrium Approximation



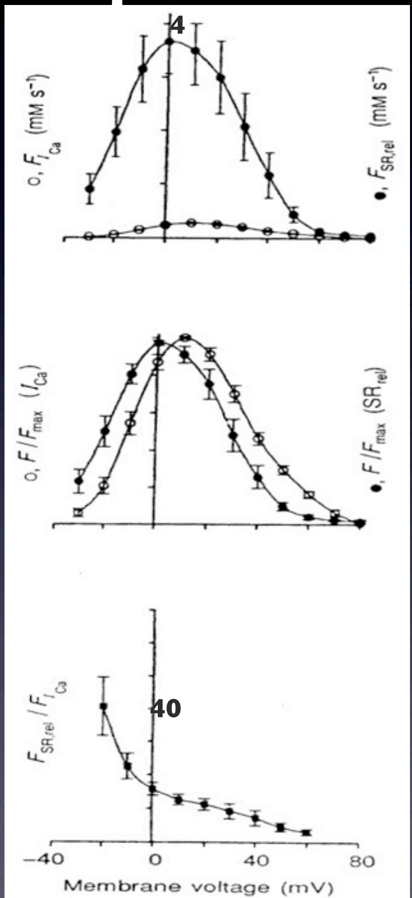


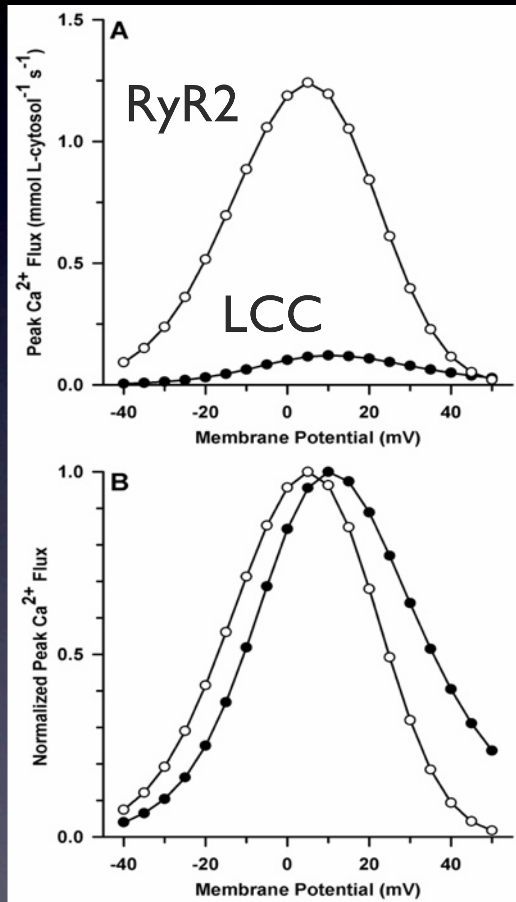
Hinch et al Biophys. J. 87: 3723

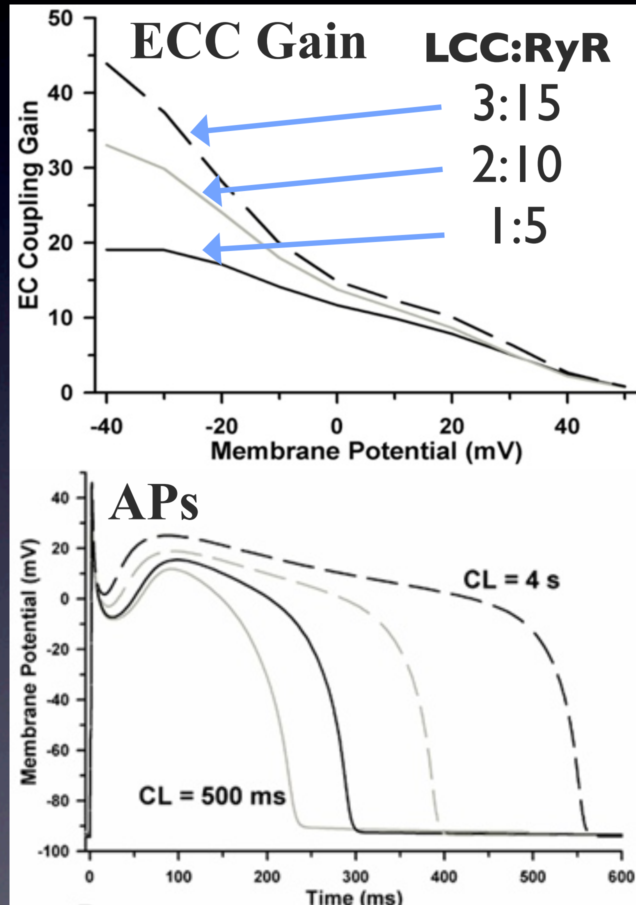
- **Dyad Ca^{2+} changes fast (~ 1 µSec) wrt channel kinetics (~ 100's µSecs)**
- **Dyad Ca^{2+} is in rapid equilibrium, algebraic function of other slow state variables**
- **Complex model reduced to low-dimensional system of coupled ODEs**
- ***~ 10 mSec for 1 simulation-Sec on one dual-core Intel Xeon 2.8 GHz node***

Resulting ODE Model Reconstructs Broad Range of Data, Can be Used in Whole Heart Simulations

Experiment **Model**

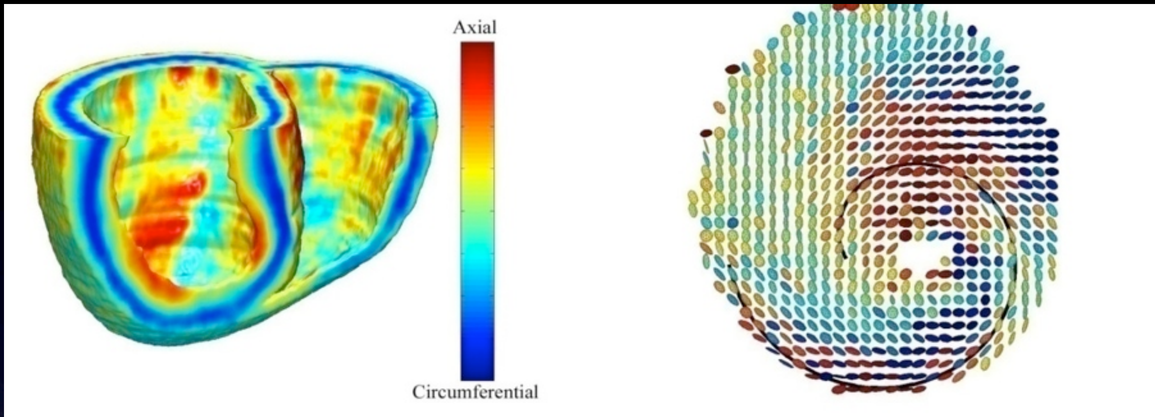


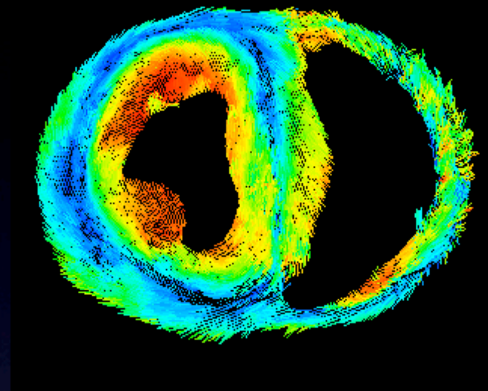




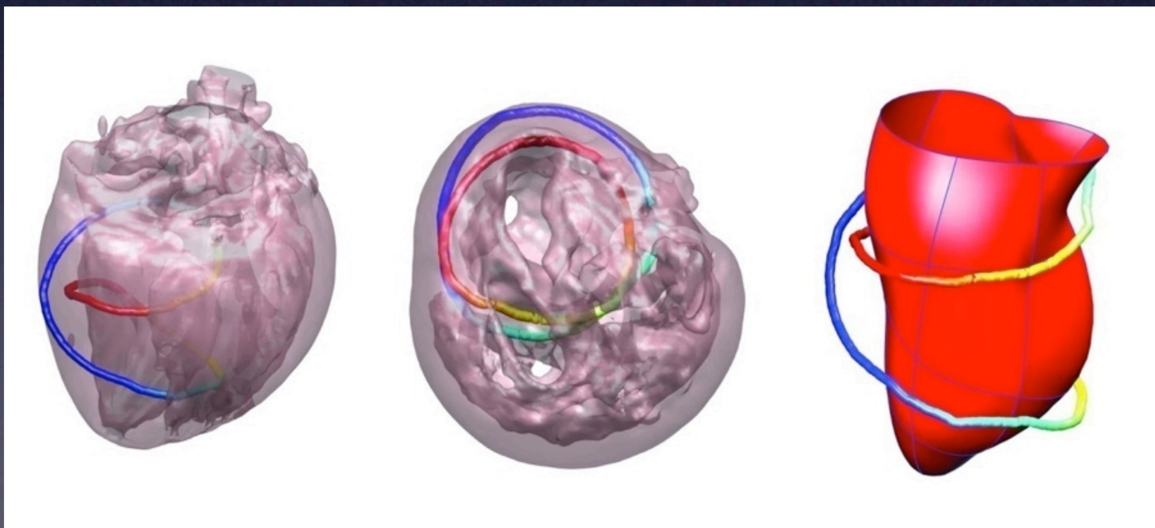
Diffusion Tensor MR Imaging

Whole-Heart Geometry, Fiber & Sheet Structure





Helm, PA (2005). Magn. Reson. Med. 54(4): 850



Helm, PA (2005). *Circ. Res.* 98(1): 125

- Fixed Heart (canine)
- 3D-FSE
- Imaging time ~ 60 Hrs
- 1.5T Clinical Magnet
- 350 μm in-plane, 800 μm out-of-plane resolution
- > 10^6 myocardial points

"Macro-scale" Model of Whole-Heart

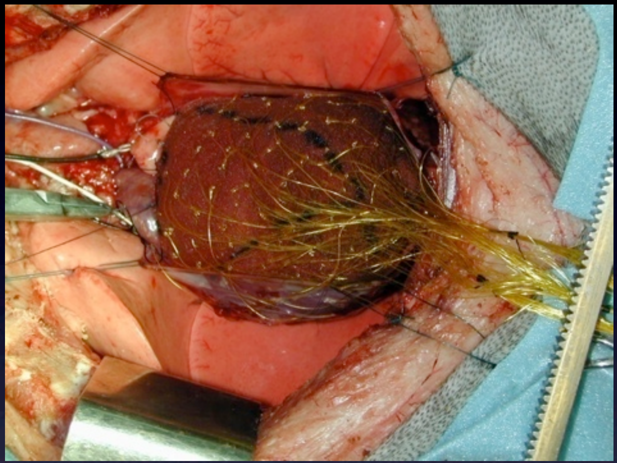
$$\frac{\partial v(\underline{x},t)}{dt} = \frac{1}{C_m}\left[-I_{ion}\left(v(\underline{x},t)\right) - I_{app}(\underline{x},t) + \frac{1}{\beta}\frac{\kappa}{1+\kappa}\nabla \bullet \left(M_i(\underline{x})\nabla v(\underline{x},t)\right)\right] \quad \forall \quad \underline{x} \quad \in \quad H$$

Reaction Term ***Applied Current*** ***Diffusion term***

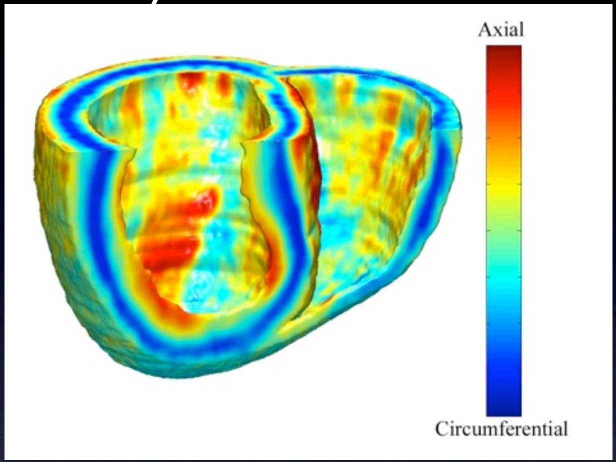
- **Model describes electrical conduction in the cardiac ventricles**
- **Constraining data**
  - ***H*** **and diffusion term defined by heart fiber structure**
  - ***Reaction term*** **$I_{ion}(\underline{x},t)$ defined by the whole cell model state variables**
- **Model structure**
  - **Mesh myocardium at 100 um resolution, ~10^6 mesh elements**
  - **Numerically integrate resulting system of coupled ODEs (~ N x 10^6 ODEs)**
  - ***1 Simulation-Sec in ~ 3.5 hrs on 64 nodes***
  - **~ 8*N GB/simulation-sec of data, where N is # state variables**

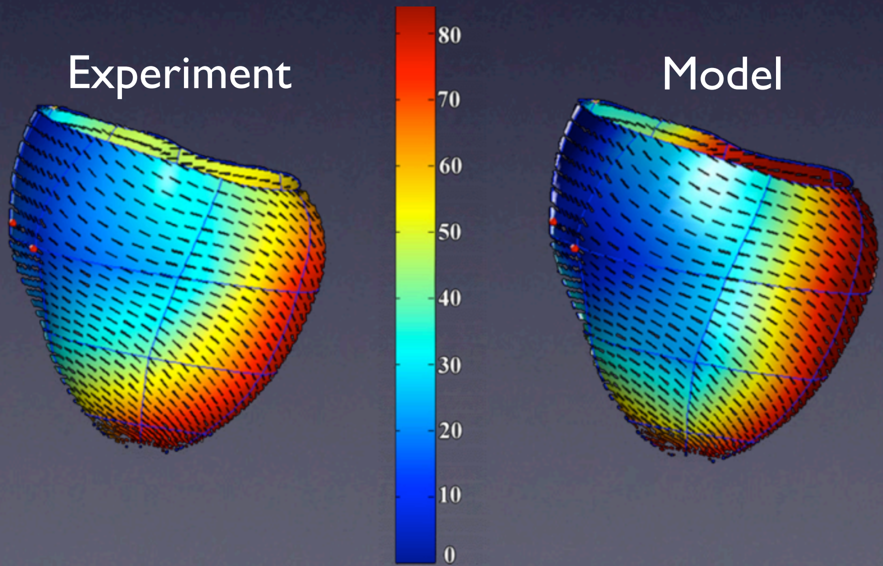
Model Validation

Whole Heart Electrical Mapping



Imaging-Based Measurement of Heart Geometry, Fiber and Sheet Structure



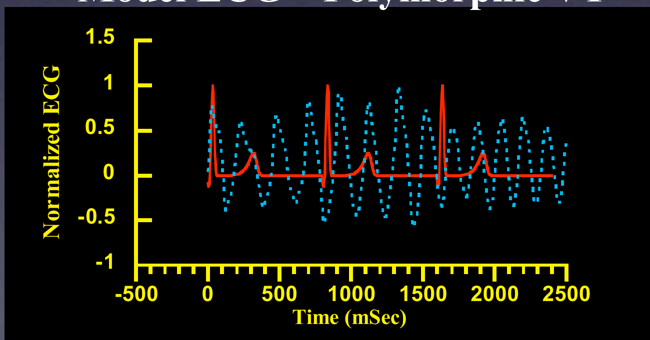


Use "Macro-Scale" Model to Study Mechanisms of Arrhythmia in HF

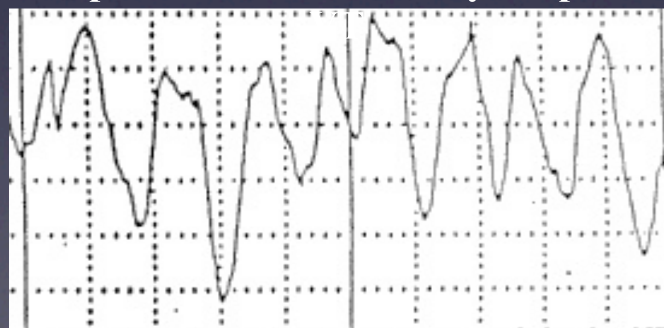
Simulation: Normal Heart Conduction 2 Stimulus Pulses

Simulation: Failing Heart, Single Stimulus Evokes EAD

Model ECG – Polymorphic VT



Experimental ECG – Polymorphic



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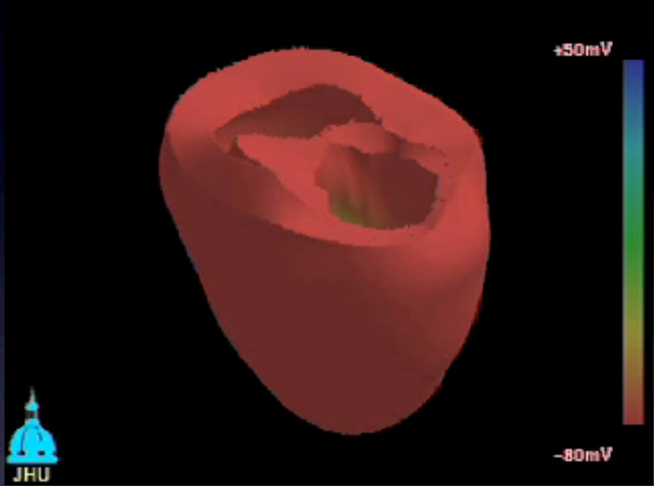
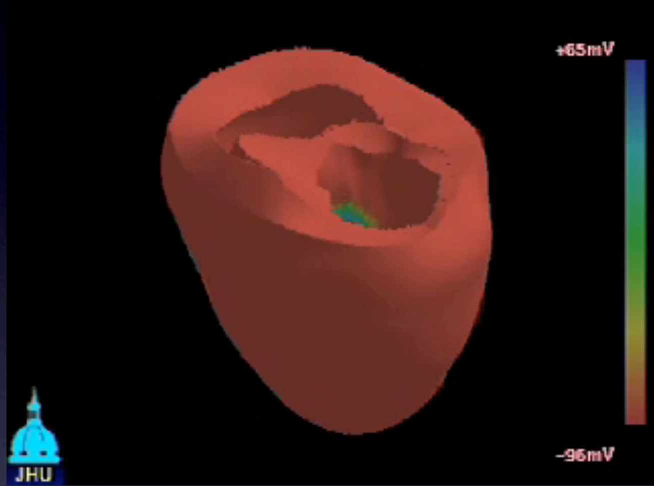
Simulation: Normal Heart Conduction
2 Stimulus Pulses



Simulation: Failing Heart, Single Stimulus
Evokes EAD



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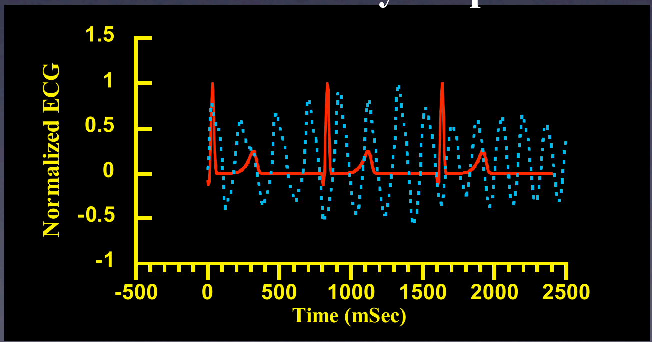

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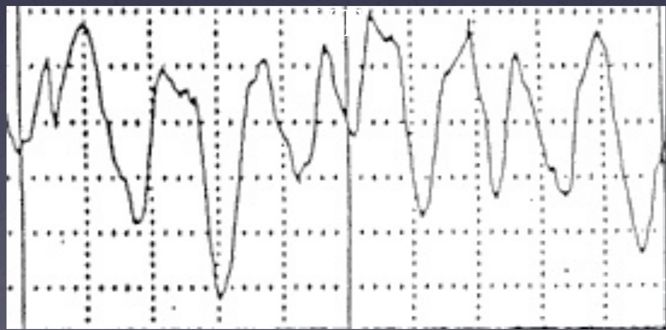

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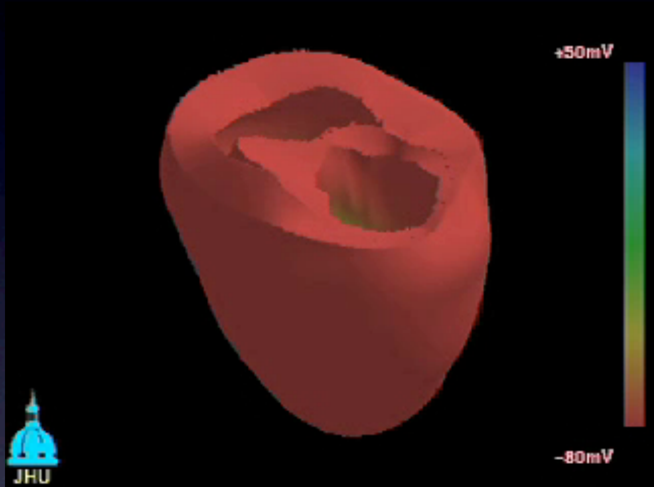

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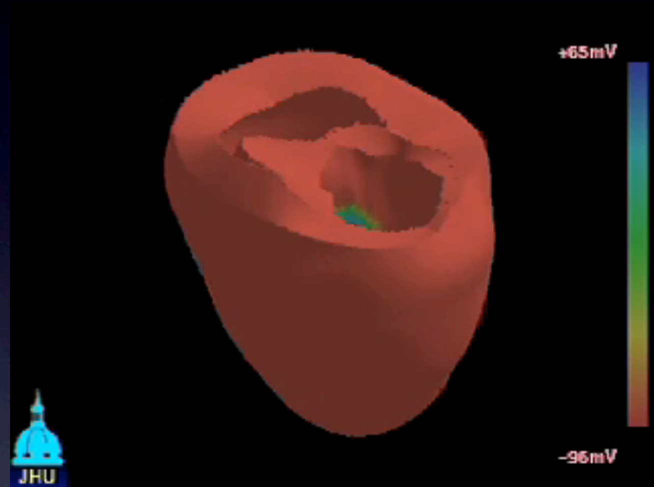

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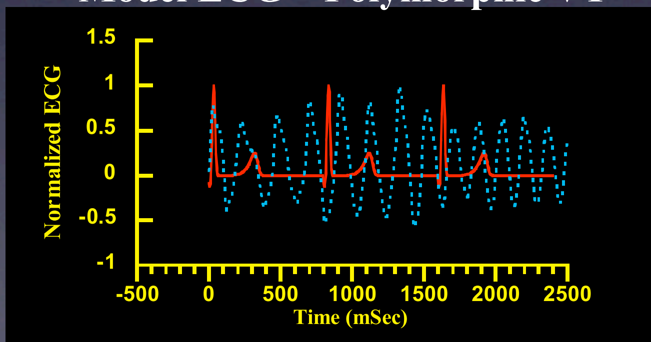
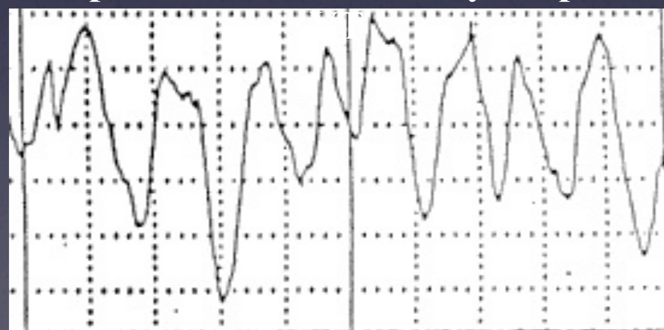
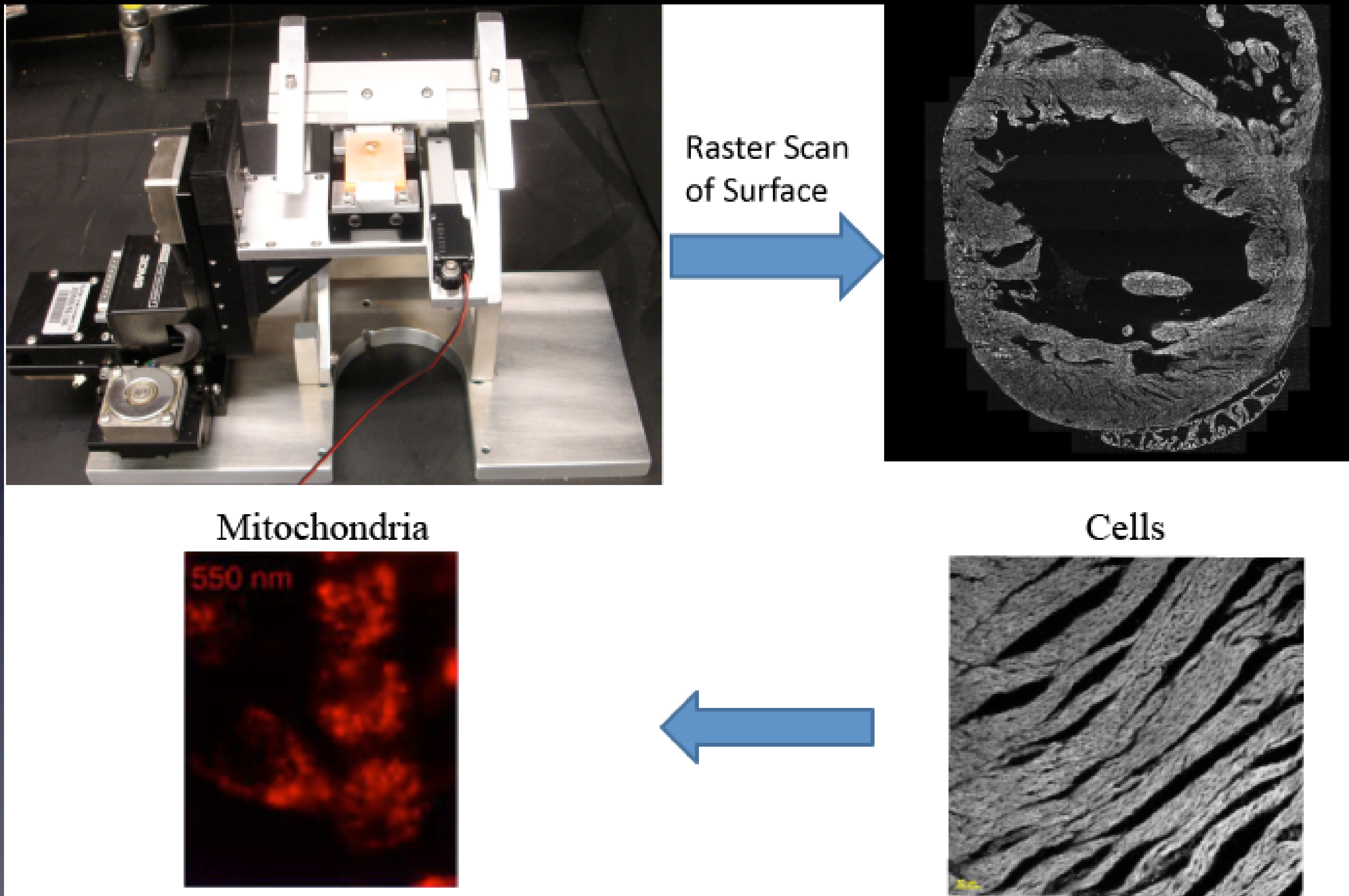


Experimental ECG – Polymorphic



Next Step: Super-High Resolution (~ 500 nm) Anatomic Reconstruction of Whole Hearts for Modeling



Challenges

- *Local signaling between proteins in micro-domains is a common biological design motif*
  - *protein structure, charge, position, hard calculations*
- *Regulation of cellular electrical function by gene and protein-signaling networks*
  - *few biological studies, need quantitative data, expands the complexity of models*
- *"Macro-scale" models and arrhythmia generation*
  - *Difficult to constrain and validate models, computational complexity*

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Antti Tanskanen
An-Chi Wei

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Patrick Helm
Alex Holmes
David Scollan

Experiments

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McVeigh Lab
O'Rourke Lab
Tomaselli Lab
Yue Lab

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