10th Anniversary IMAG MSM Meeting
NIH, Bethesda, MD
March 22nd, 2017

Multi-Scale Modeling of the Heart: Past, Present and Future

Andrew McCulloch

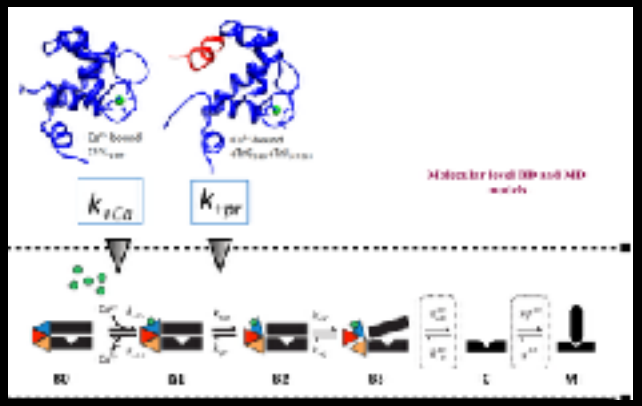
University of California San Diego

Disclosure

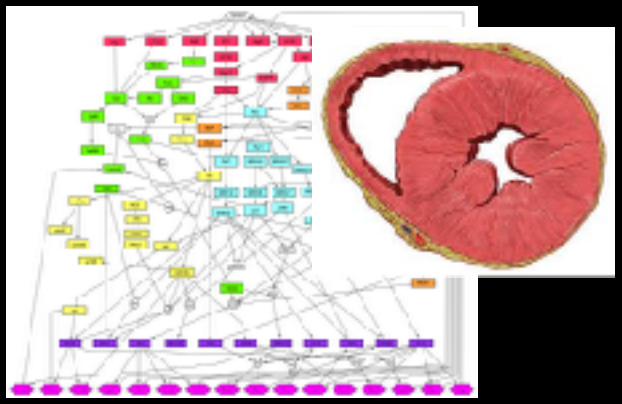
Dr. McCulloch is a co-founder of and has an equity interest in Insilicomed, Inc., and he serves on the Scientific Advisory Board. Some of his research grants have been identified for conflict of interest management based on the overall scope of the project and its potential benefit to Insilicomed, Inc., however the research reported here did not involve Insilicomed, Inc. The terms of this arrangement have been reviewed and approved by the University of California San Diego in accordance with its conflict of interest policies.

Evolution of Multi-Scale Models of the Heart

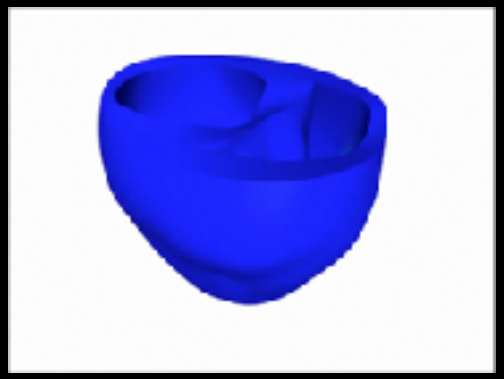
Extending models to *smaller* spatial scales and *shorter* temporal scales: Molecular to Markov Models



Extending models to *longer* time-scales: Ventricular growth & remodeling models

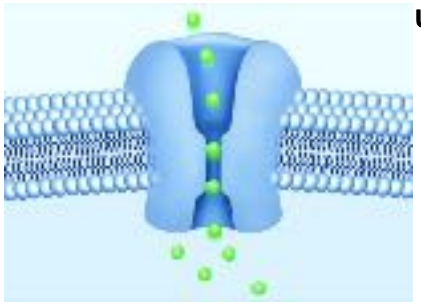


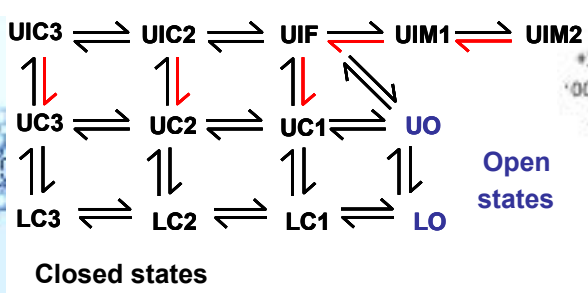
Extending models from the laboratory to the clinic: *Patient-specific models* of heart failure

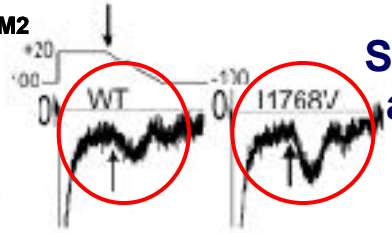


Subcellular

THEN



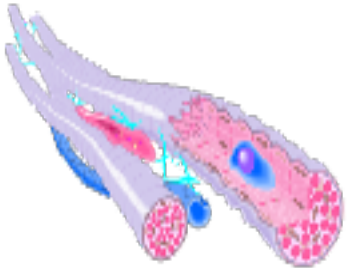


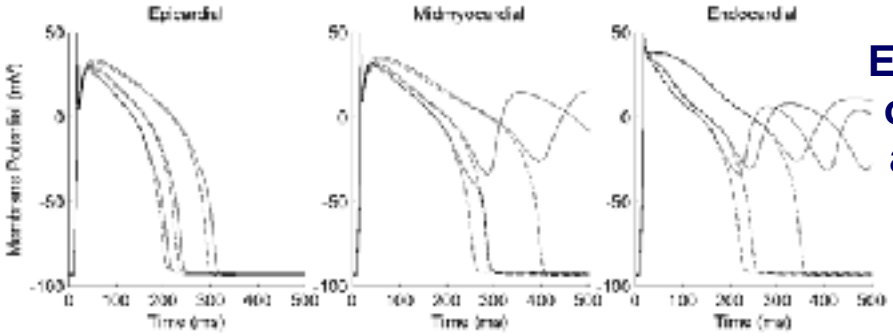


SCN5A-I1768V mutation augments the late Na^+ current

Clancy et al, Circ 2003

Cellular

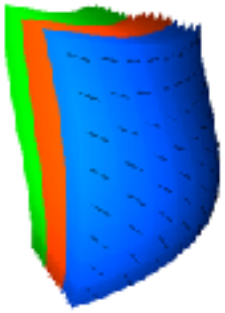


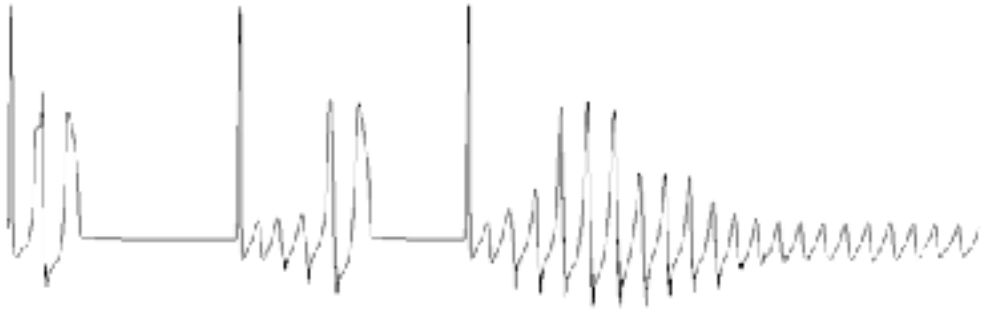


Early afterdepolarizations occur in midmyocardial and endocardial but not epicardial myocytes

Flaim et al., AJP 2006

Tissue

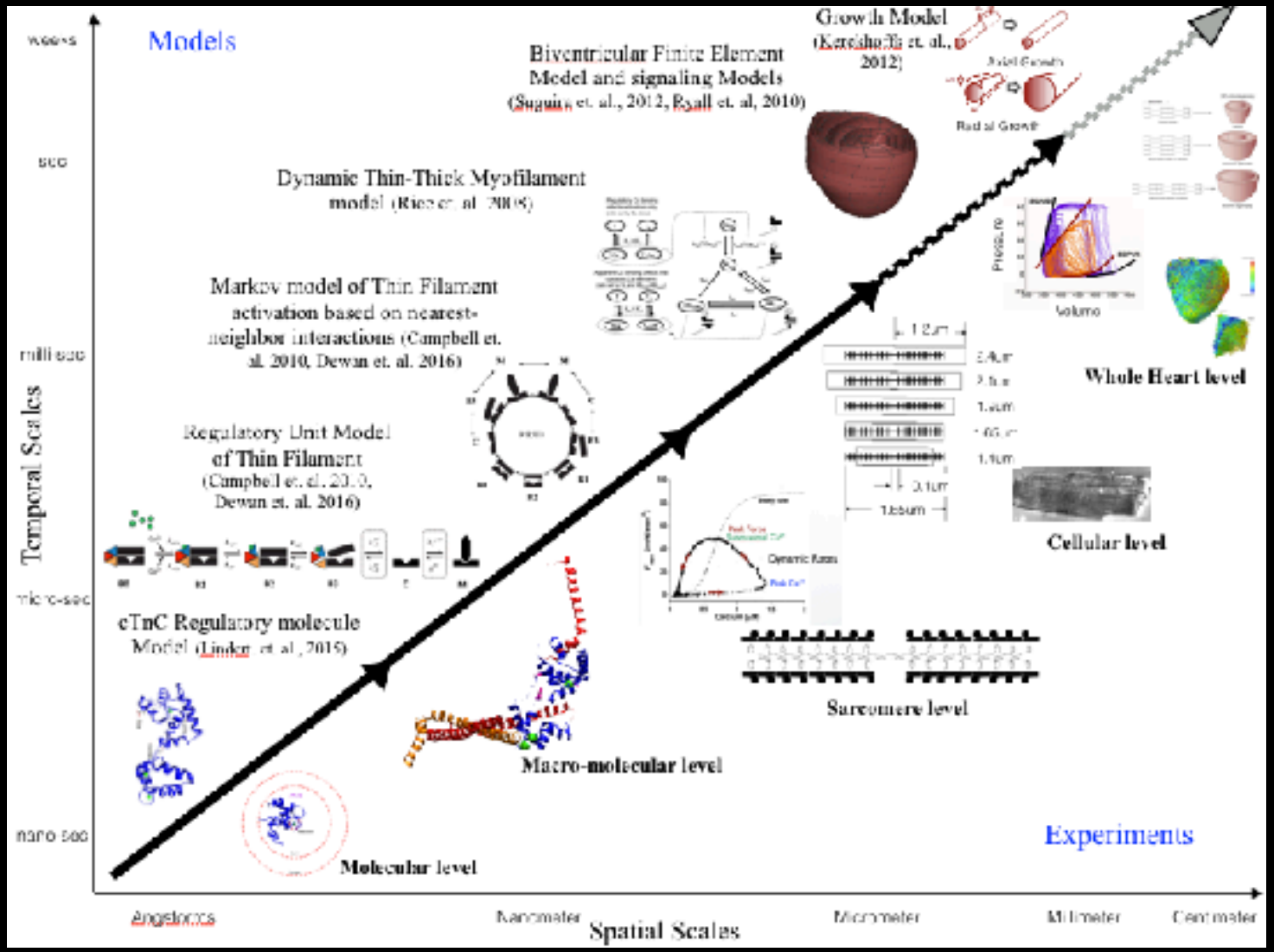




Endocardial afterdepolarizations trigger epicardial APs resulting in "R or T" extrasystoles

Flaim et al., Heart Rhythm 2007

NOW: Smaller Spatial and Temporal Scales

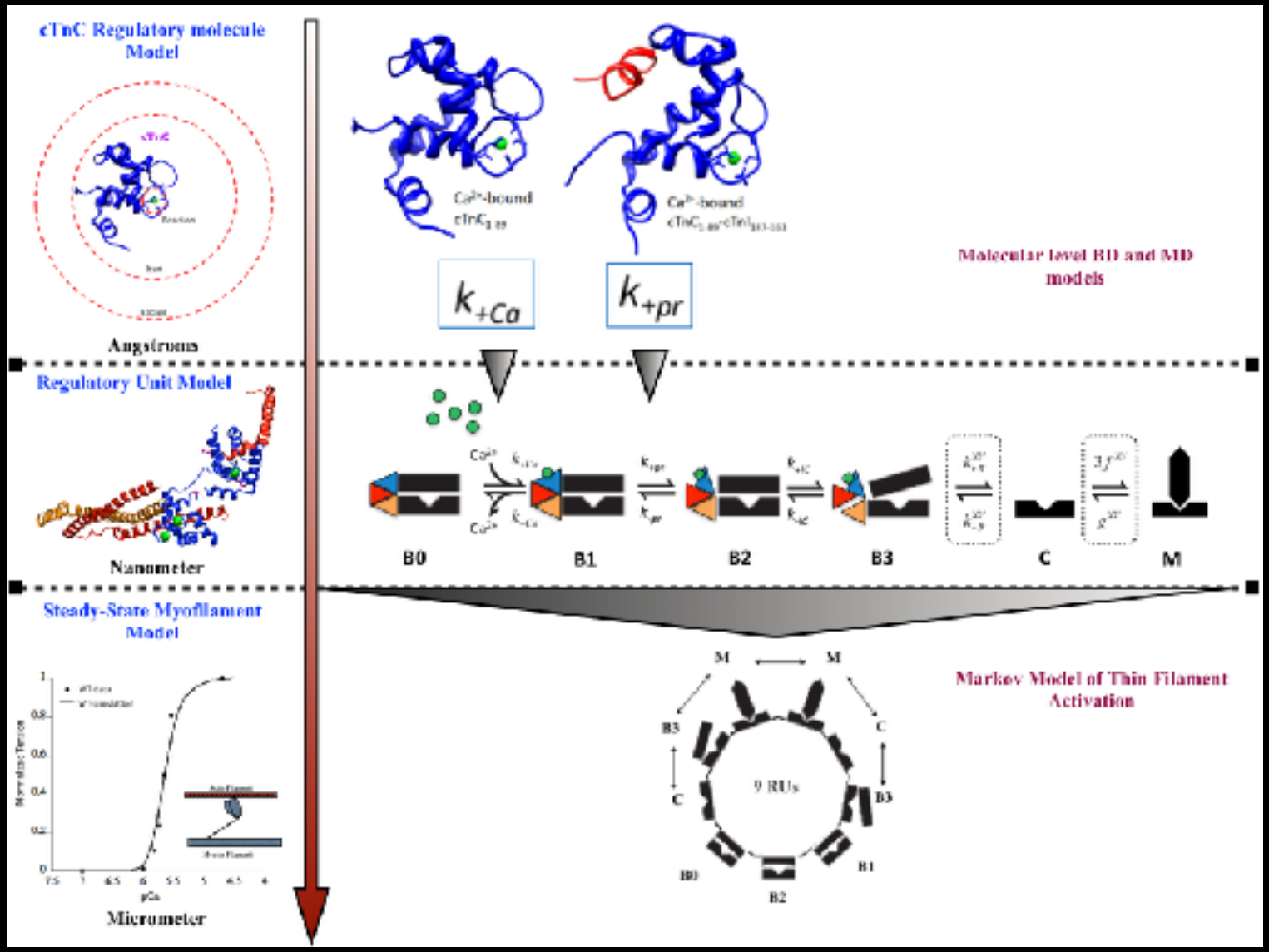


frontiers

Insights and Challenges of Multi-scale Modeling of Sarcomere Mechanics in cTn and Tm DCM mutants – Genotype to Cellular Phenotype

Sukriti Dewan[1*], Kimberly J. McCabe[1,2], Michael Regnier[2], Andrew D. McCulloch[1,3*]

NOW: Thin Filament Activation by Calcium



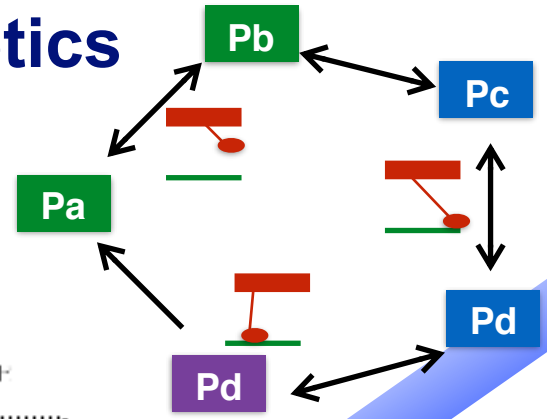
THE JOURNAL OF PHYSICAL CHEMISTRY B

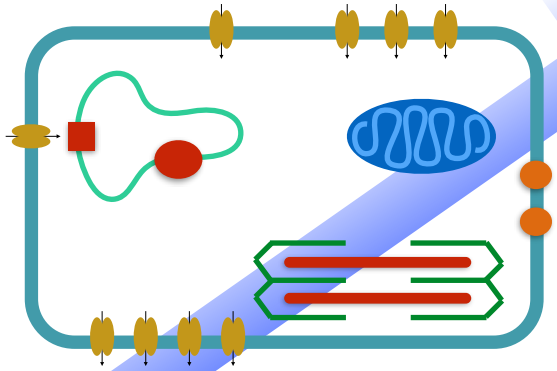
J Phys Chem B. 2016 Aug 25;120(33):8361-75. doi: 10.1021/acs.jpcb.6b01964. Epub 2016 May 6.

Molecular Effects of cTnC DCM Mutations on Calcium Sensitivity and Myofilament Activation-An Integrated Multiscale Modeling Study.

Power GR[1], McDaniel KJ[1], Regnier M[2,3], VanBuren AD[1], Lindert S[4].

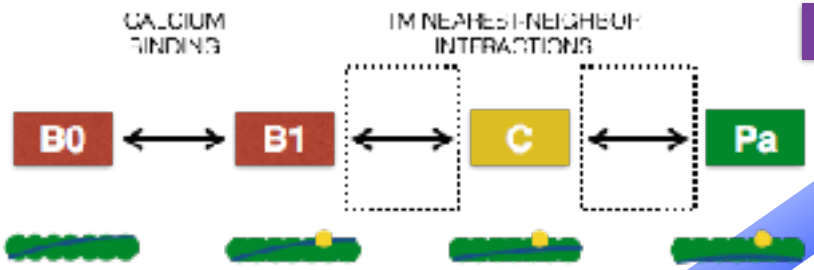
NEXT: Extending to Thick Filament and Whole Cell Mechanoenergetics





Whole Cell

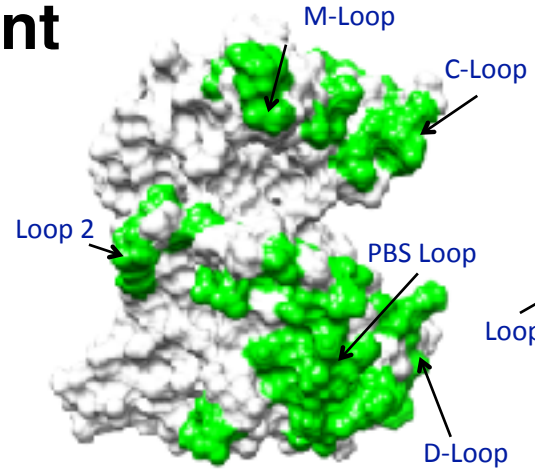
Thick Filament



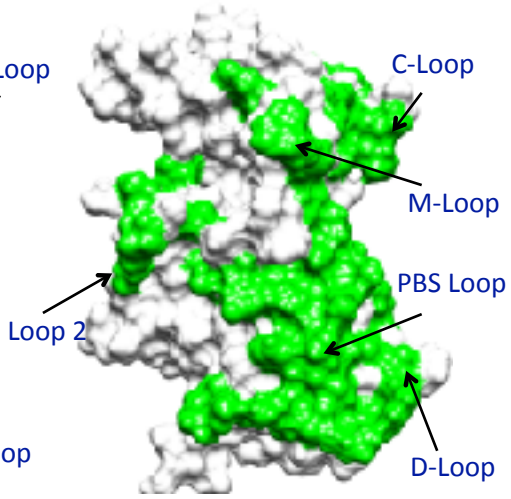
Thin Filament

dATP to Myosin Molecule

Myosin-ADP.Pi, 50ns



Myosin-dADP.Pi, 50ns



With Bassingthwaighte & Regnier (UW) and Beard (UM)

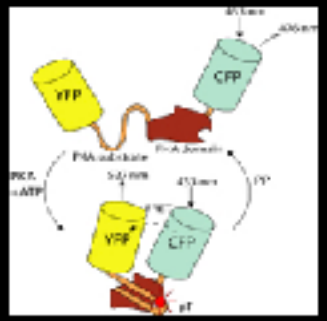
Cardiac Mechanics Research Group

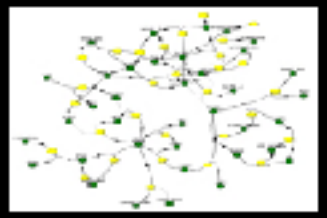
UCSD Jacobs | Bioengineering & The Whitaker Institute

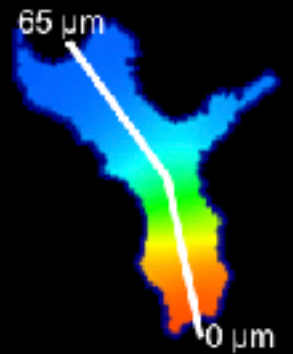
Multi-scale modeling of the mouse heart: From genotype to phenotype

PKA-mediated phosphorylation gradients

THEN







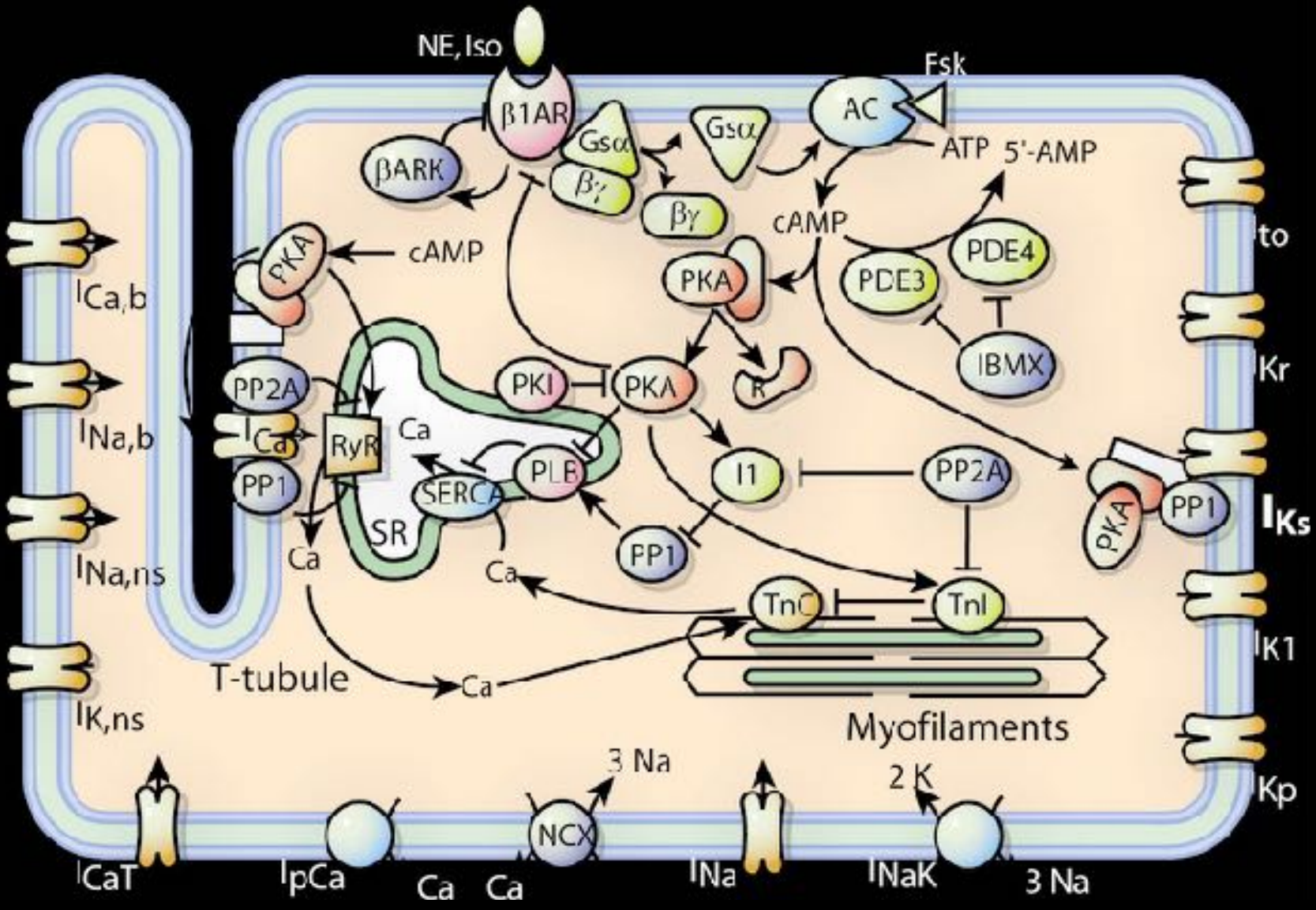
Saucerman et al., Proc Nat Acad Sci 2006

Andrew McCulloch (PI)
Tom Borg (Co-PI), University of South Carolina
Bob Price (Co-PI), University of South Carolina

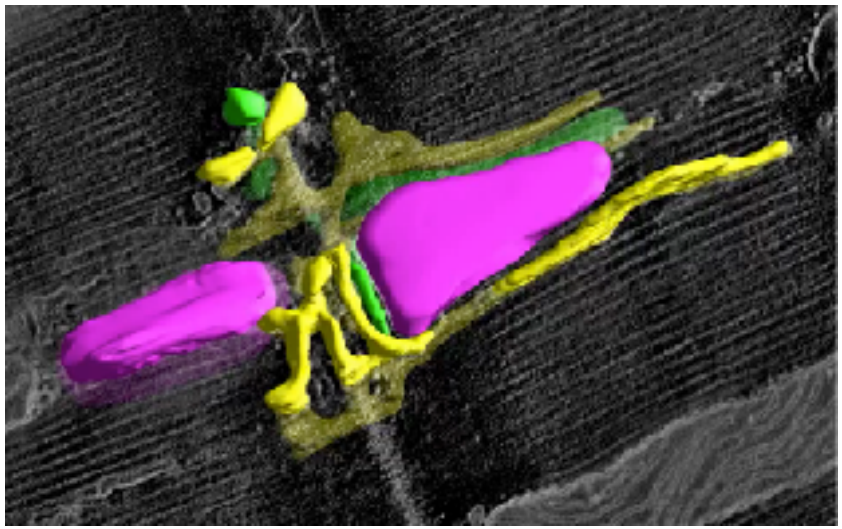
Award number: BES-0506252

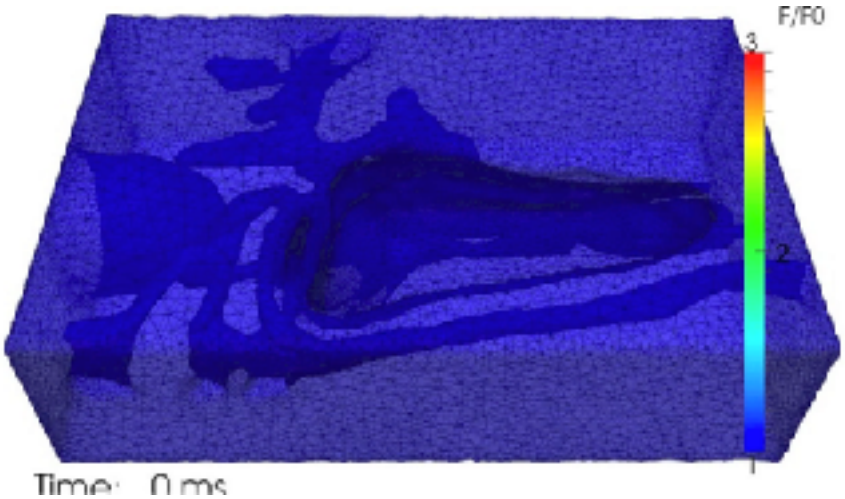
April 12, 2007, NSF

β-adrenegeric regulation of myocyte excitation-contraction coupling

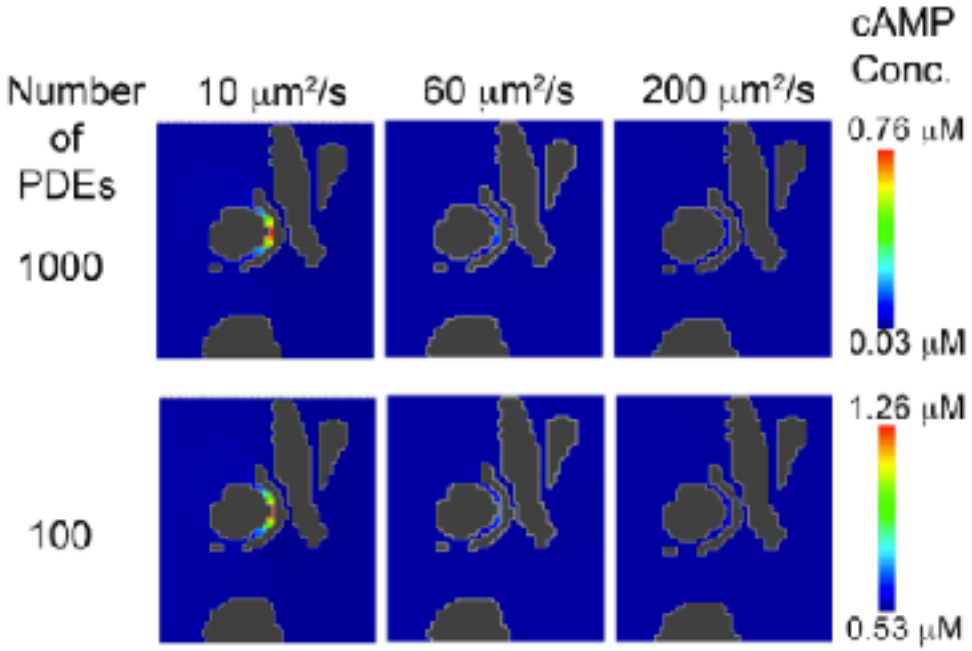


NOW: Extending to Smaller Spatial Scales





Hake J *et al* (2012) *J Physiol* **590**:4403-4422



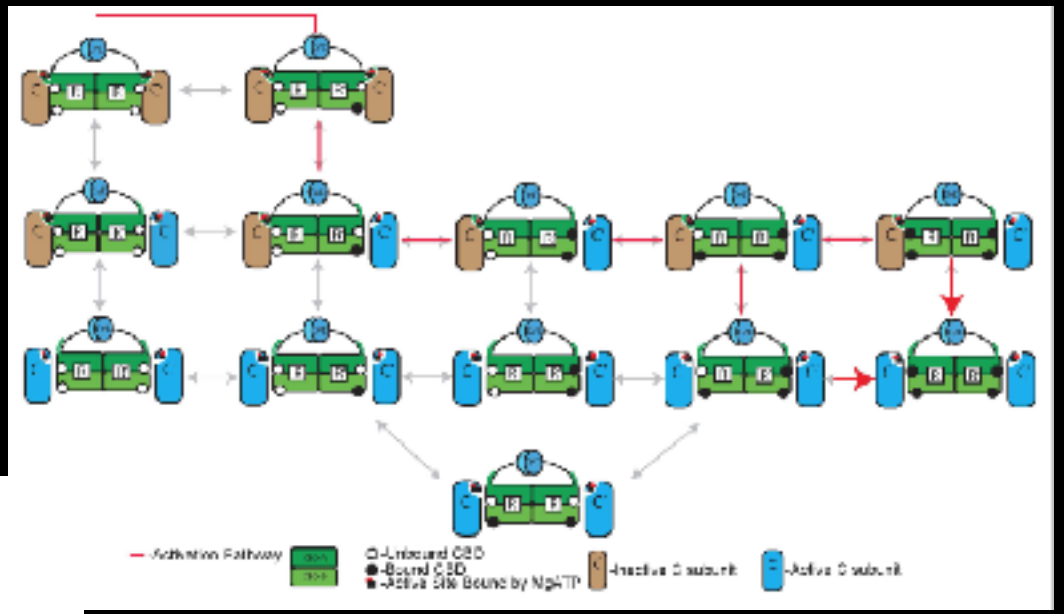
A Computational Modeling and Simulation Approach to Investigate Mechanisms of Subcellular cAMP Compartmentation

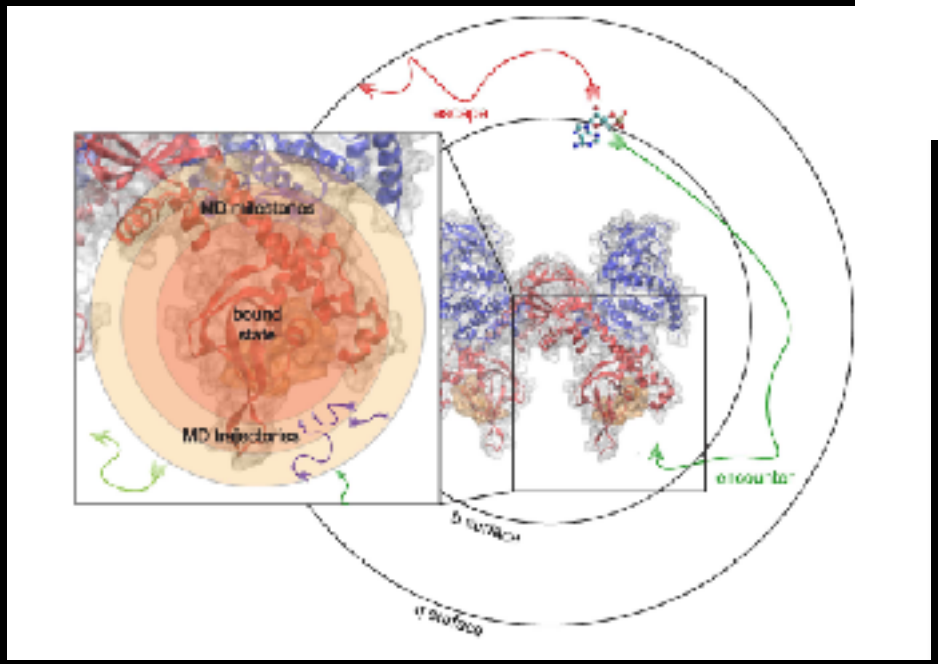
Pei-Chi Yang[1], Britton W. Boras[2], Mao-Tsuen Jeng[1], Steffen S. Docken[1,4], Timothy J. Lewis[3*], Andrew D. McCulloch[2*], Robert D. Harvey[1*], Colleen E. Clancy[1*]

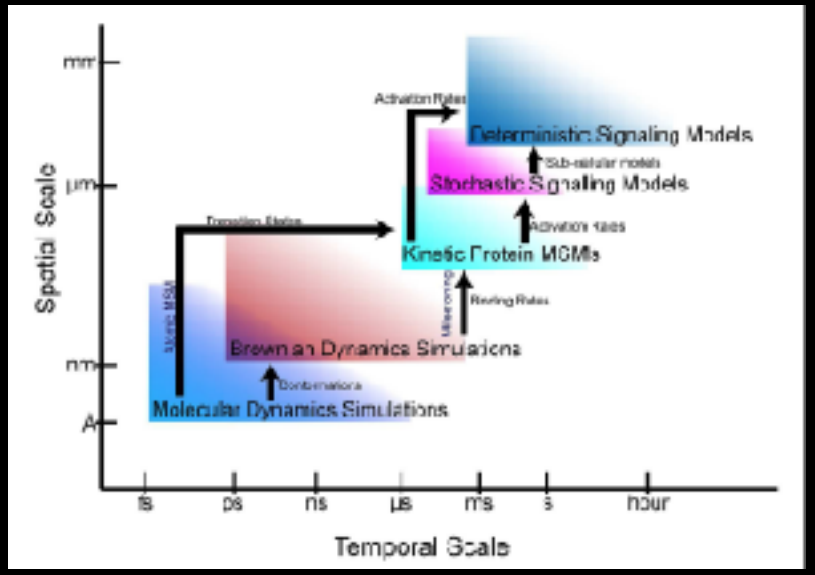
PLOS Computational Biology | DOI:10.1371/journal.pcbi.1005005 July 13, 2016

With Colleen Clancy (UCD) and Robert Harvey (Univ Nevada Reno)

NEXT:
From Thermodynamic to Kinetic Markov Models of PKA Activation and Regulation





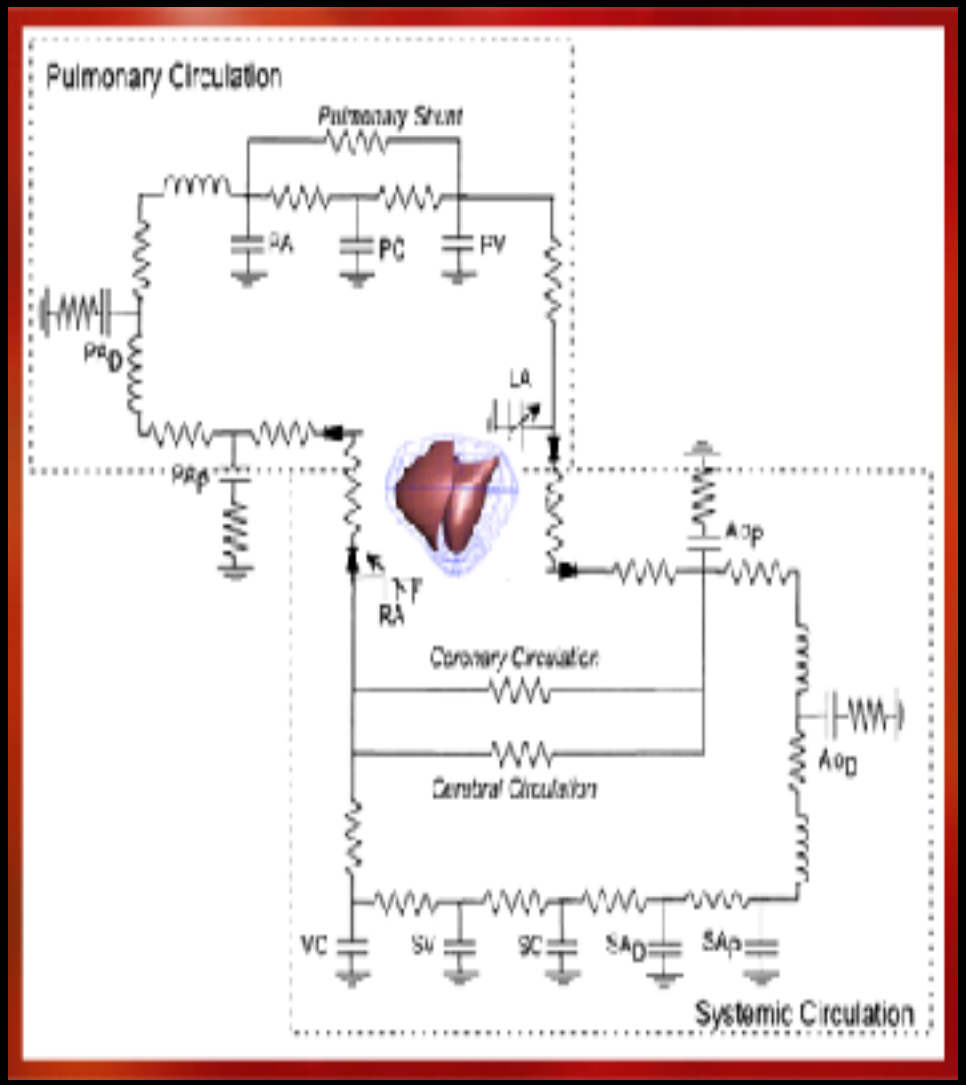


Bridging scales through multiscale modeling: a case study on protein kinase A

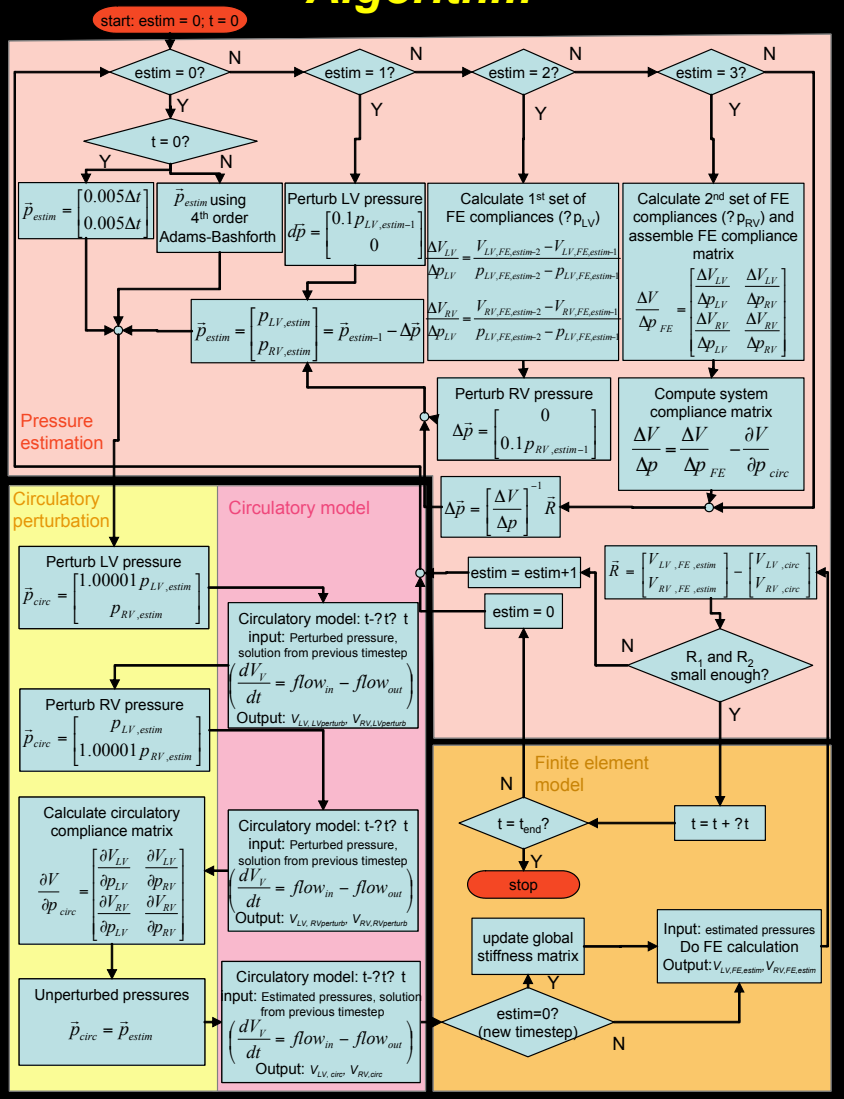
Britton W. Bowles[1,2], Sophia P. Hirakis[2], Lase W. Votapka[1], Robert D. Malmstrom[3], Romme C. Amaro[1,4*] and Andrew D. McCulloch[1,2,4*]

Then

Ventricular-Vascular Coupling Model



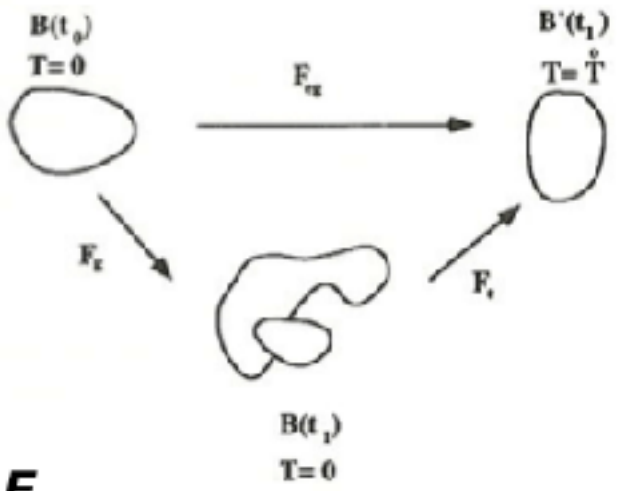
Algorithm



Kerckhoffs et al., Ann Biomed Eng 2007

Way Before Then

Decomposing the Growth Deformation



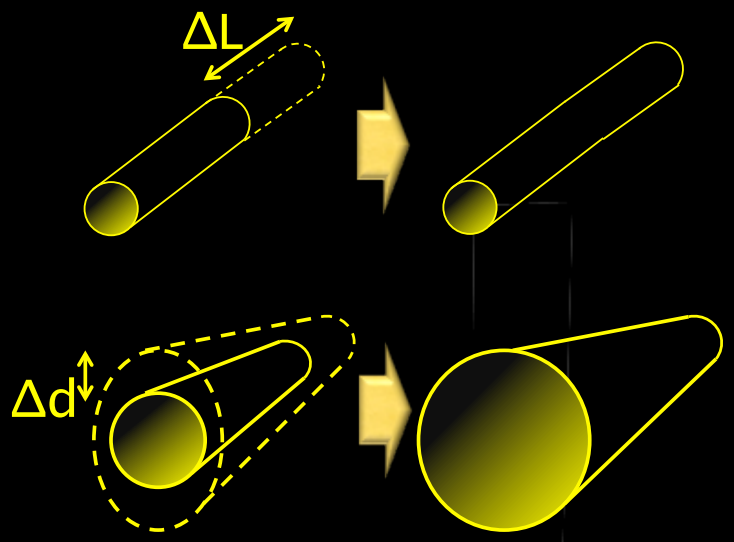
$$\boldsymbol{F}_{eg} = \boldsymbol{F}_{e} \bullet \boldsymbol{F}_{g}$$

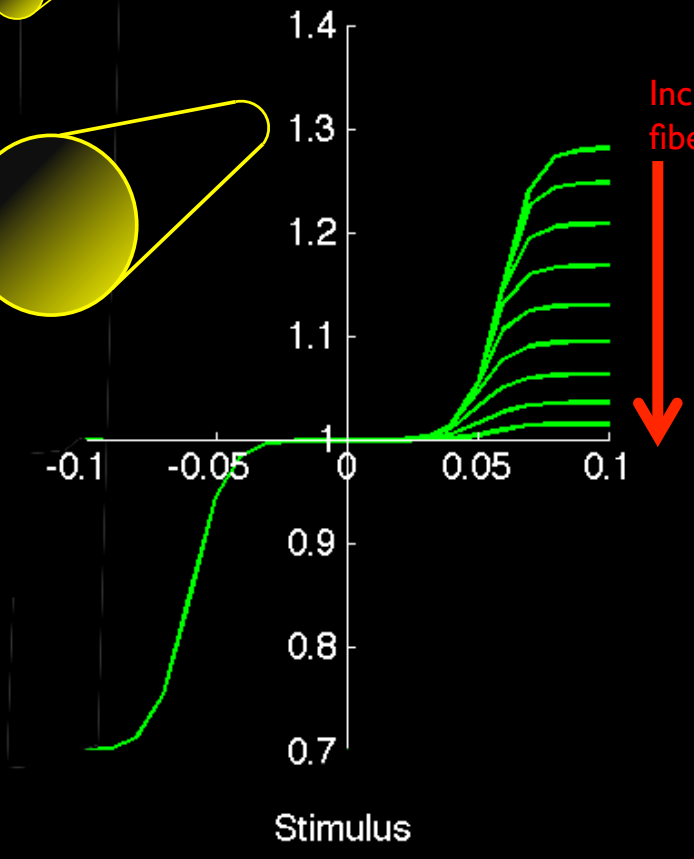
$\boldsymbol{F}_{e}$ is the elastic part of the growth deformation required to maintain compatibility. Therefore, the residual stress is

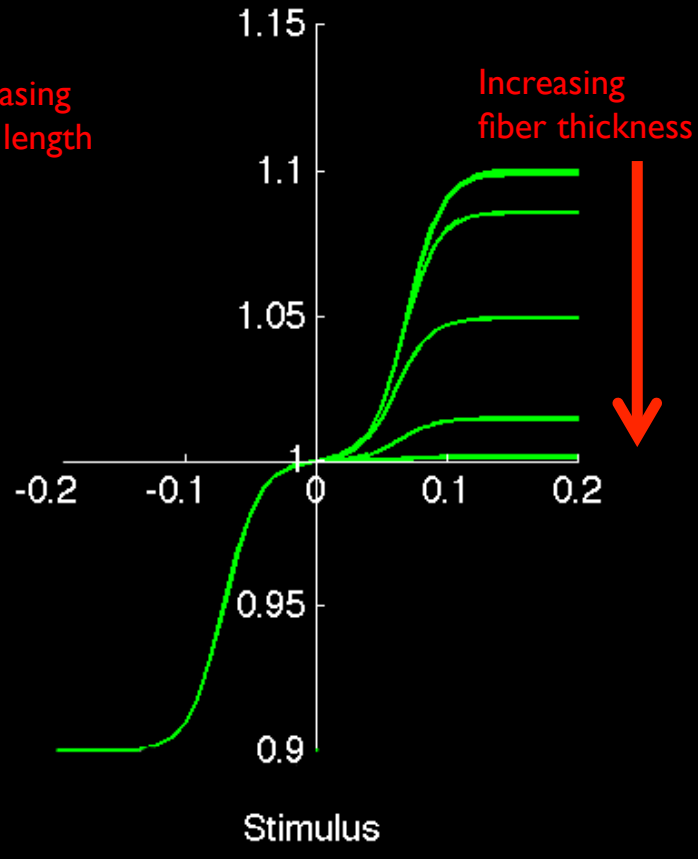
$$\overset{o}{\boldsymbol{T}} = \hat{\boldsymbol{T}}\left(\boldsymbol{F}_{e}^{T} \bullet \boldsymbol{F}_{e}\right)$$

Rodriguez EK, Hoger A, McCulloch AD (1994) Stress-dependent finite growth in soft elastic tissues. *J Biomech* 27:455-467

Chronic Remodeling: Anisotropic Myocyte Growth Model







Kerckhoffs et al. *Europace* 2012.

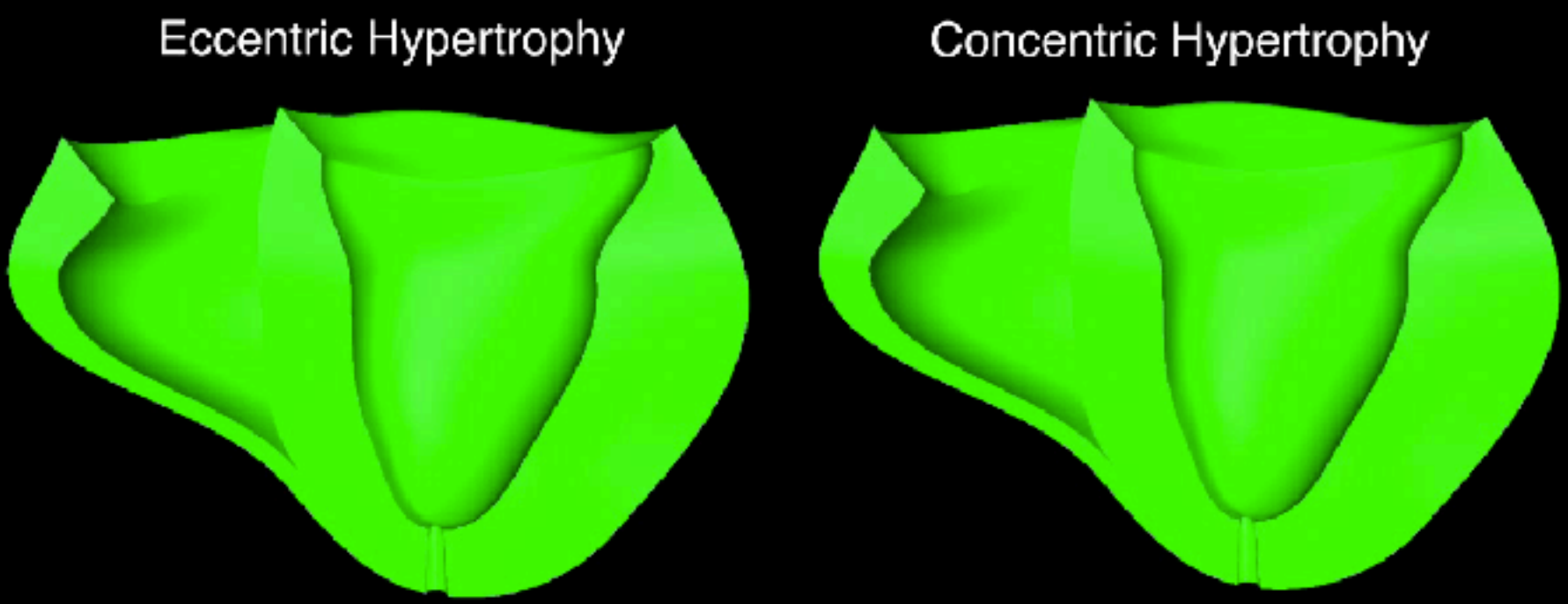
Lengthening growth ratio [1/day]

Thickening growth ratio [1/day]

Ventricular Hypertrophy and Residual Stress

Mitral Valve Regurgitation

Aortic Stenosis



Residual fiber stress [kPa]

-2.0 2.0

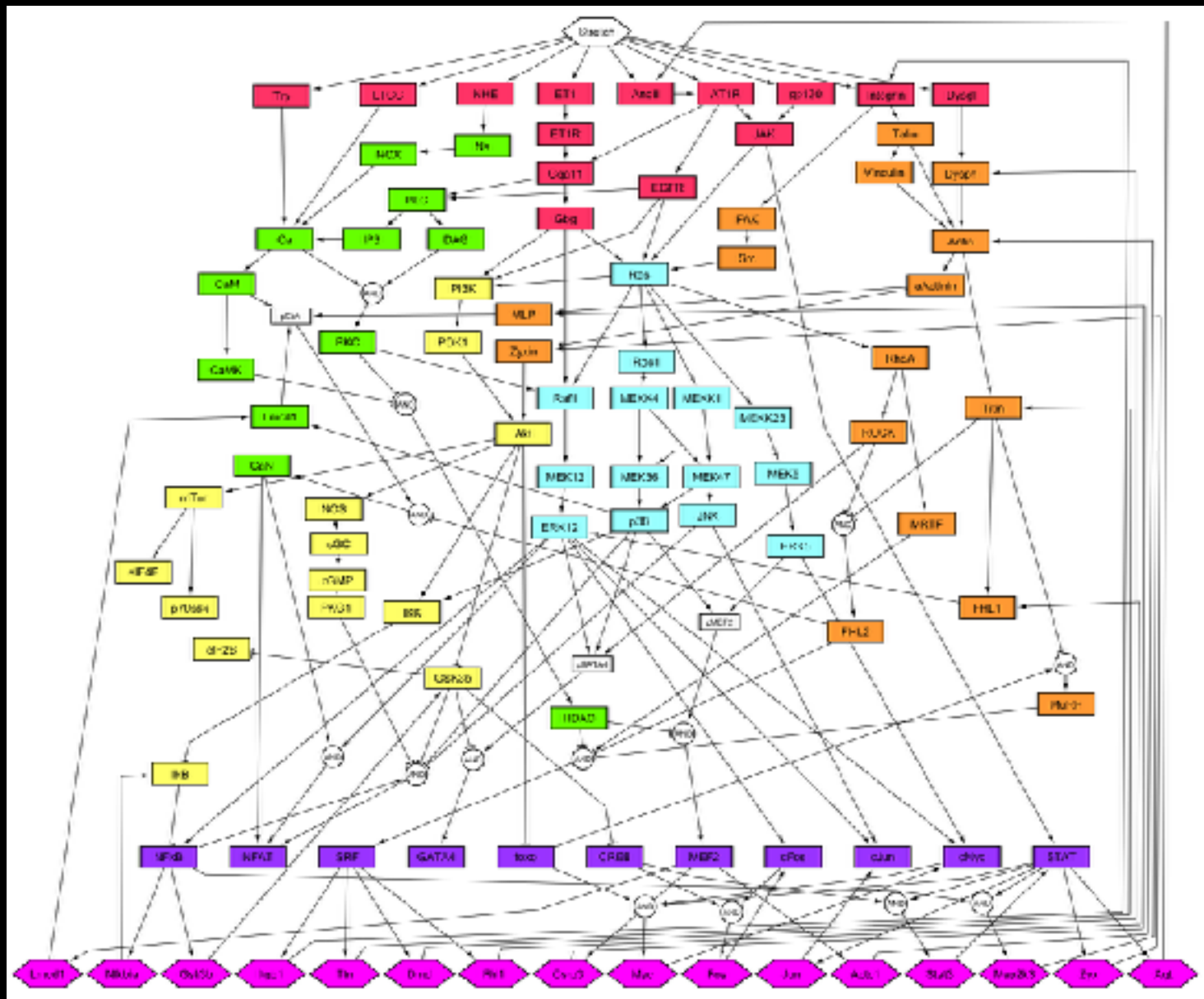
Kerckhoffs et al. *Mech Res Comm* 2012.

Cardiac Mechanics Research Group

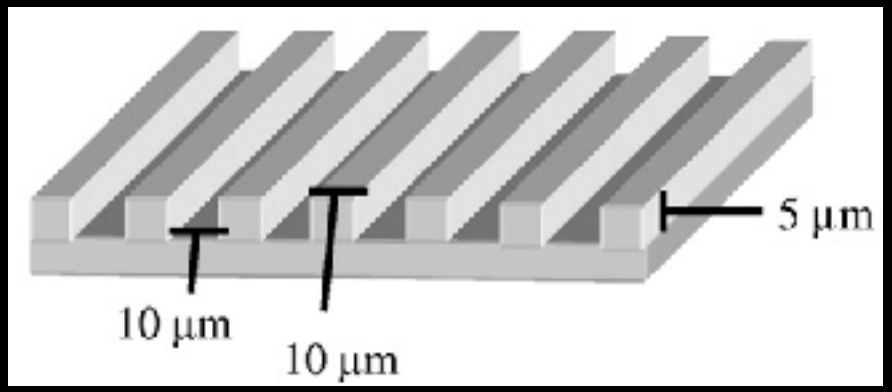
NOW: Myocyte Mechanosignaling Network Model

- Calcium
- MAPK
- Cytoskeleton
- PI3K-Akt
- Receptors
- Transcription
- Genes

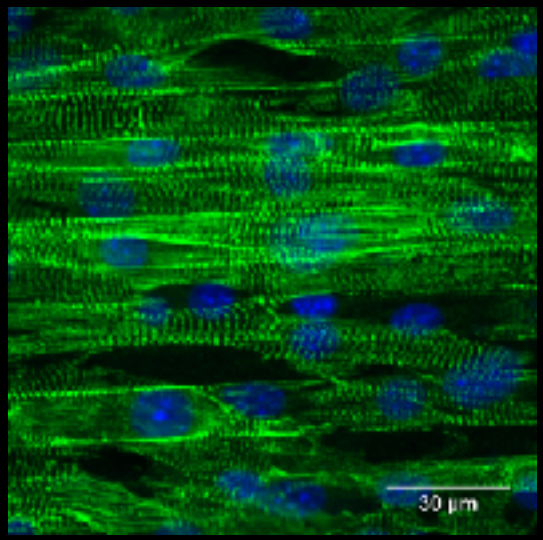
9 receptors
65 signaling molecules
11 transcription factors
645 target genes
116 signaling reactions
645 transcriptional reactions
16 translation reactions
115 references (45 heart or myocyte studies)

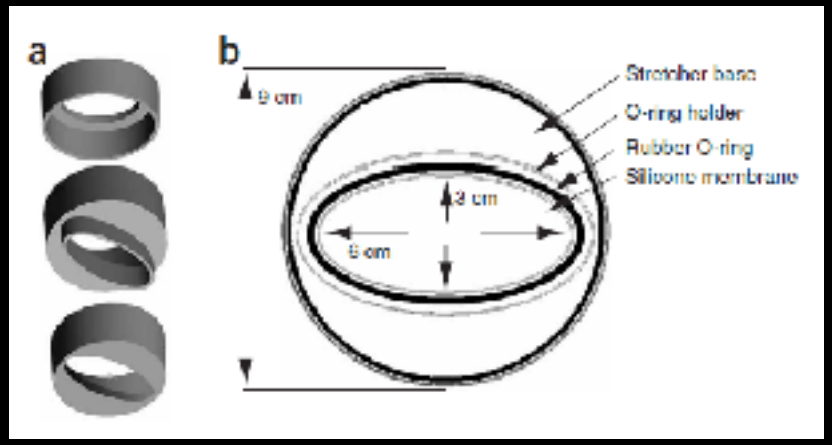


Anisotropic Biaxial Stretch of Aligned Neonatal Mouse Ventricular Myocytes

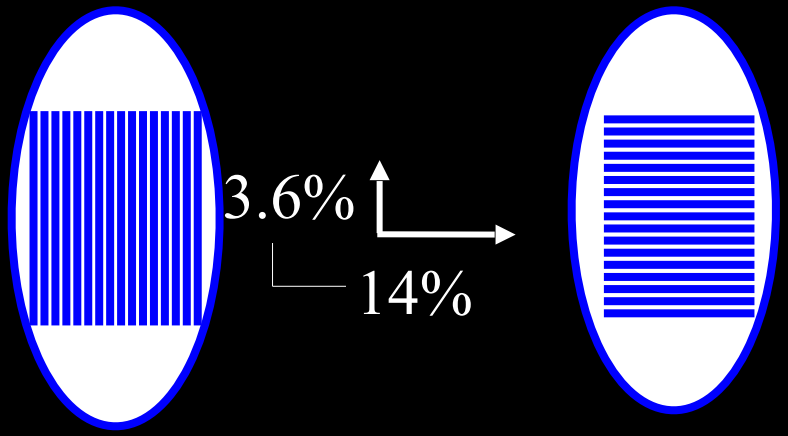


Boateng 2009





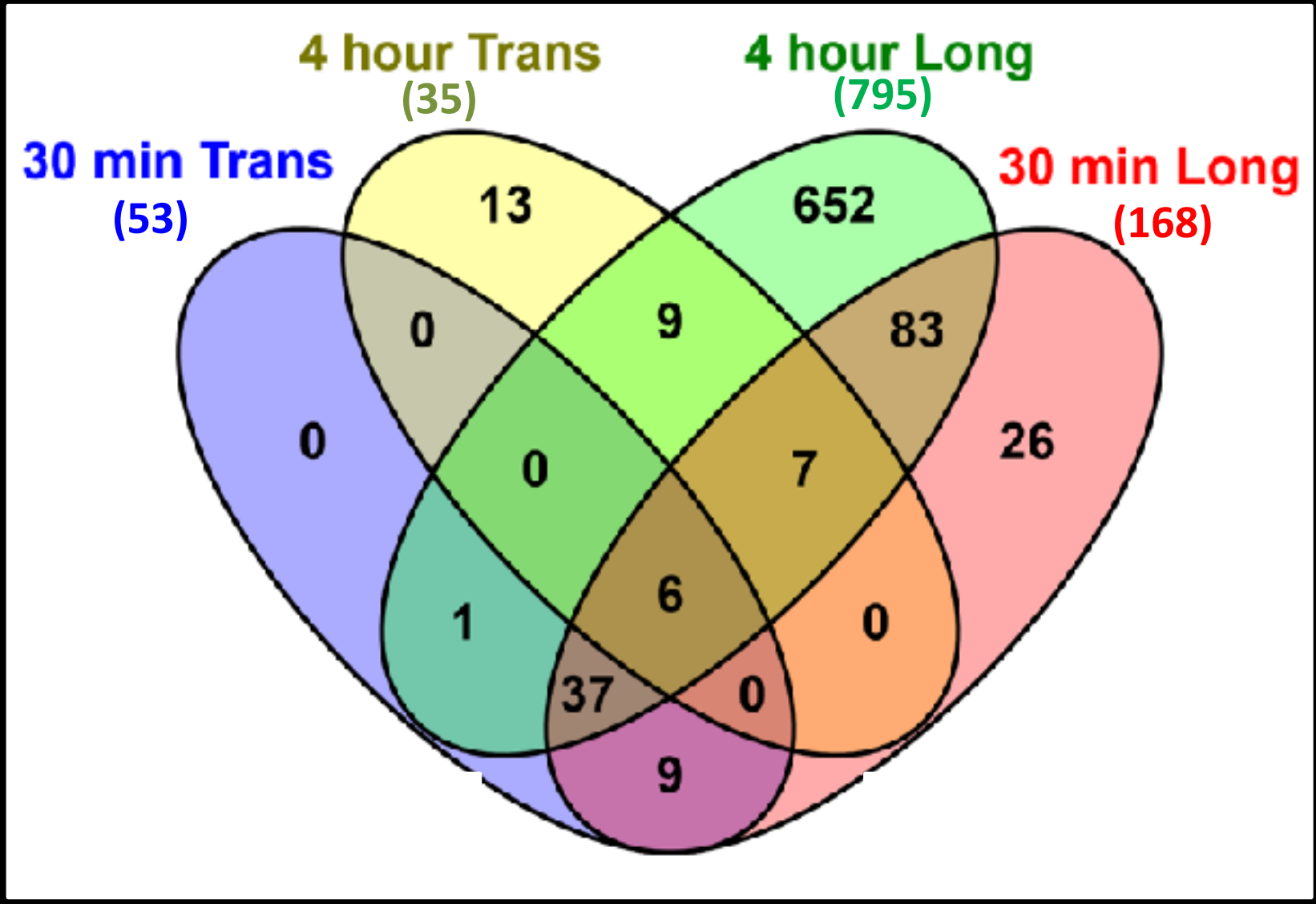
Camelliti 2006



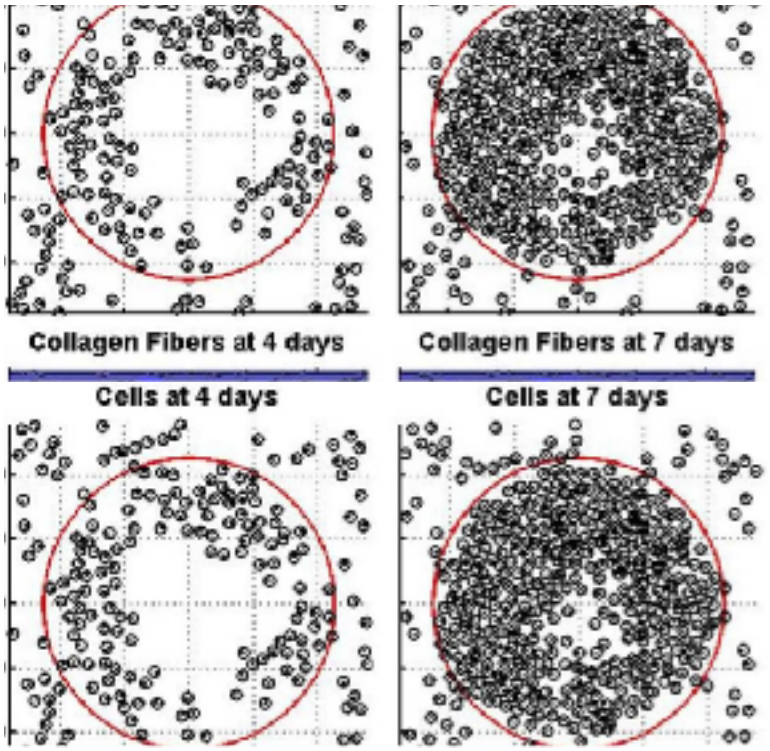
Transverse Stretch

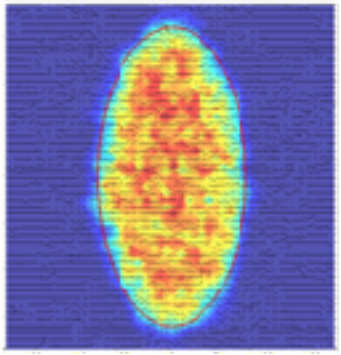
Longitudinal Stretch

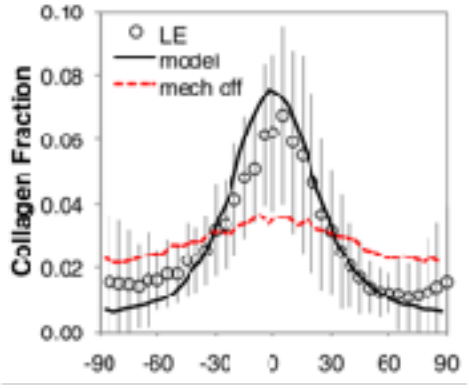
Differentially Expressed Genes (FDR<0.05)

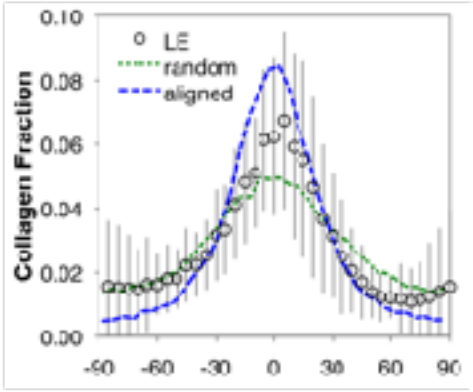


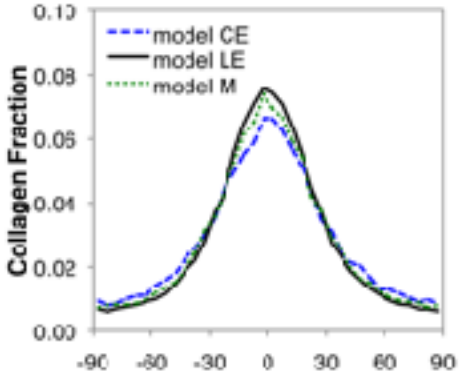
Agent-Based Model of Scar Remodeling





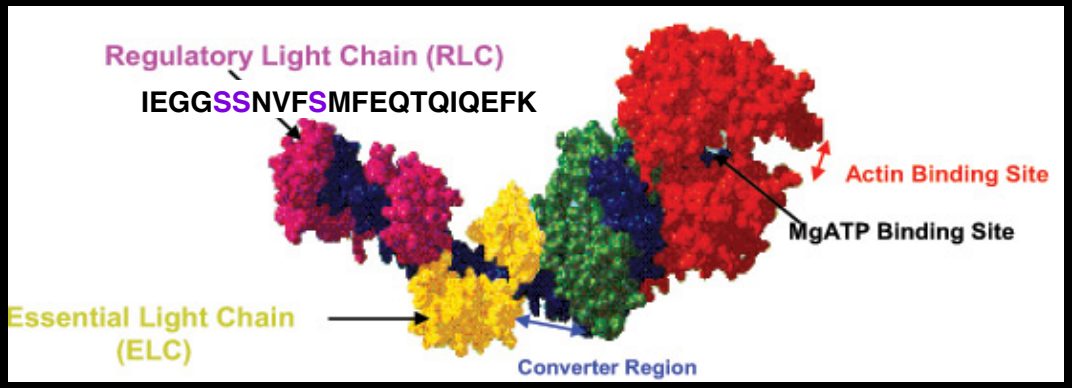


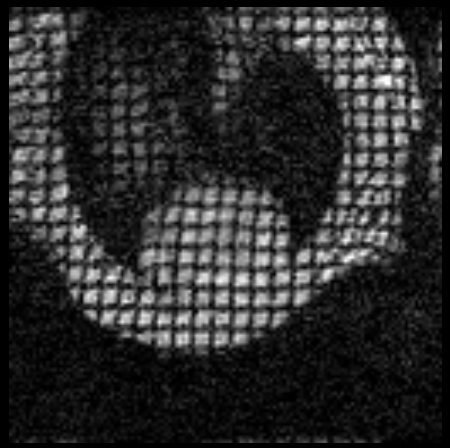


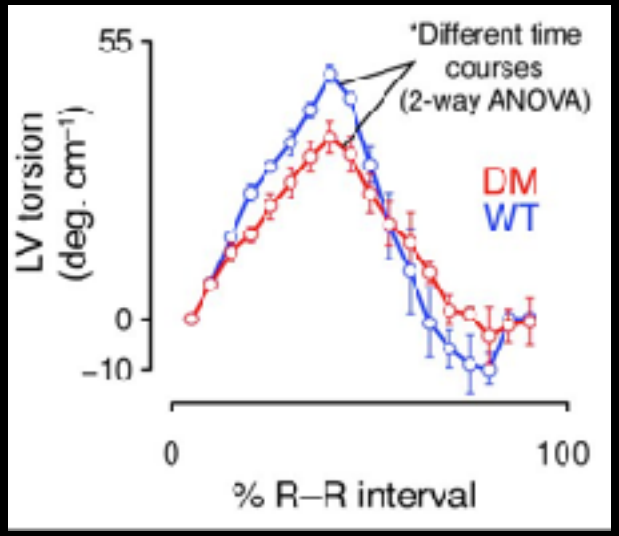


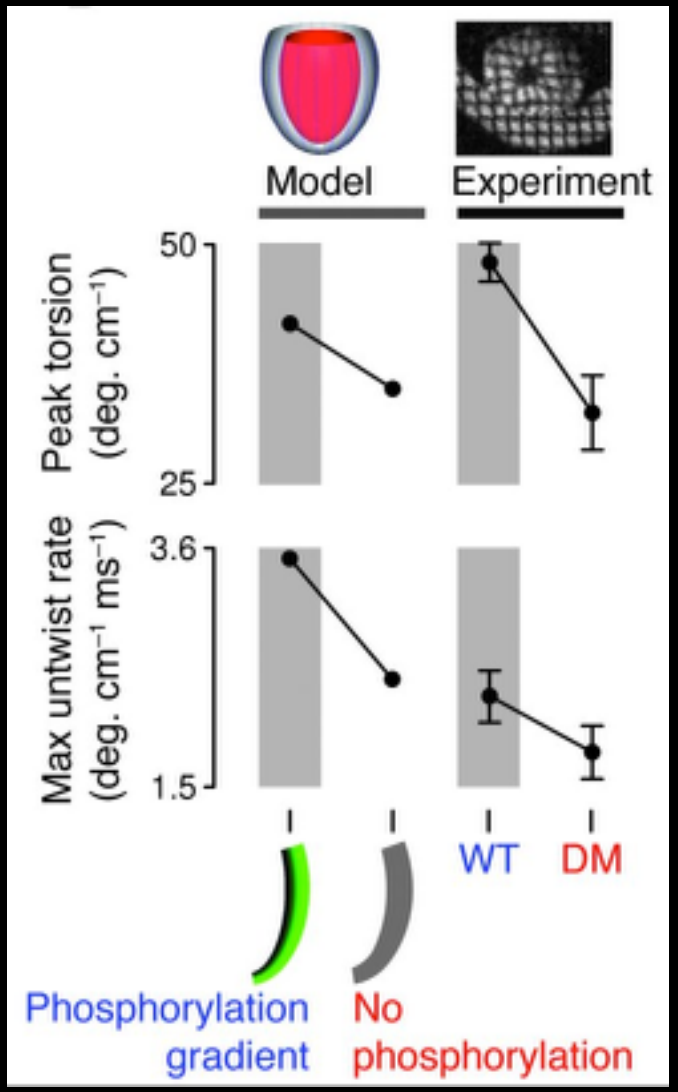
Rouillard et al. *J Physiol* 2012, Rouillard et al. *J Mol Cell Cardiol* 2012

THEN: Peak Torsion and Maximum Untwisting Rate Decrease When MLC2V is Dephosphorylated in the Mouse



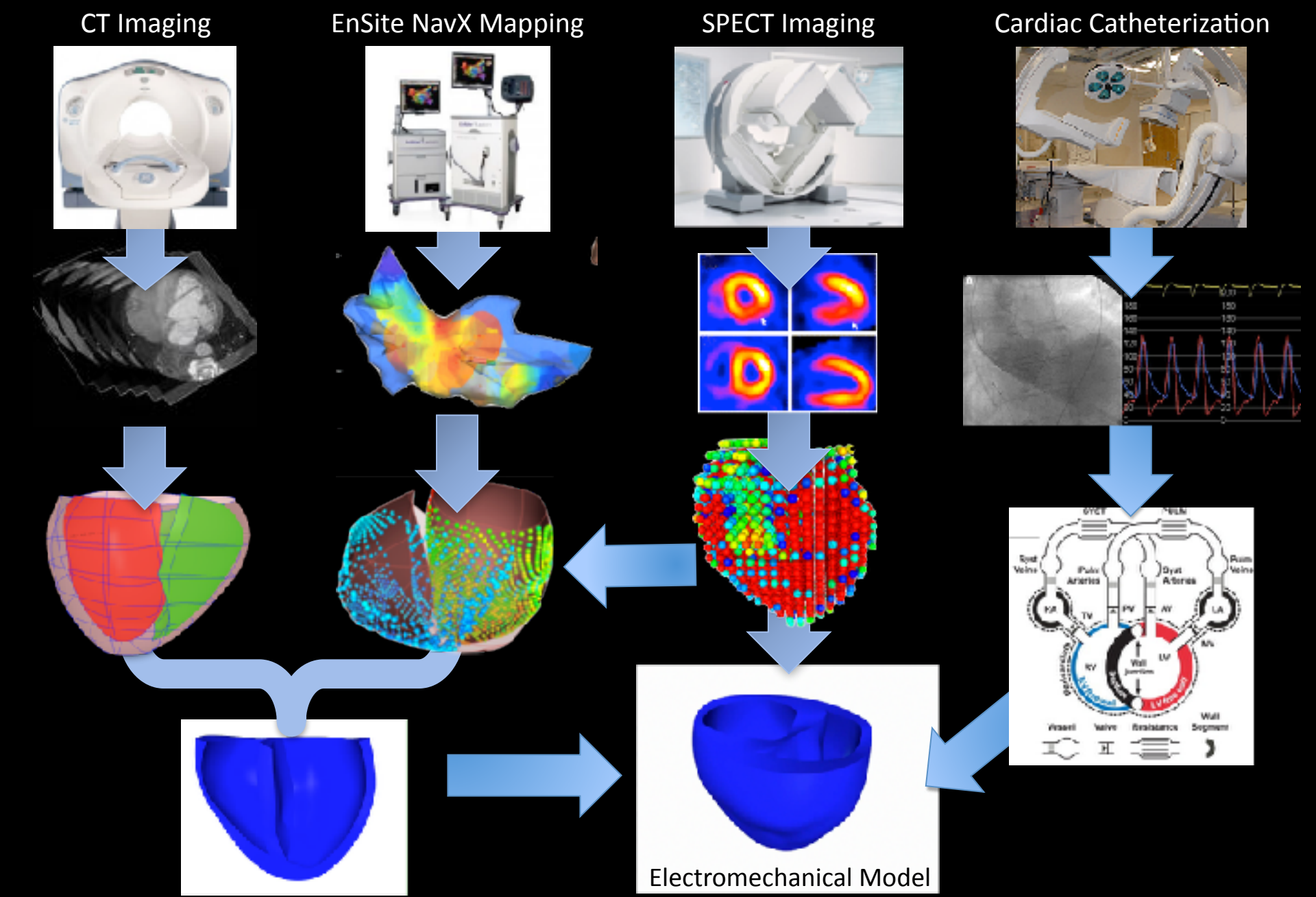




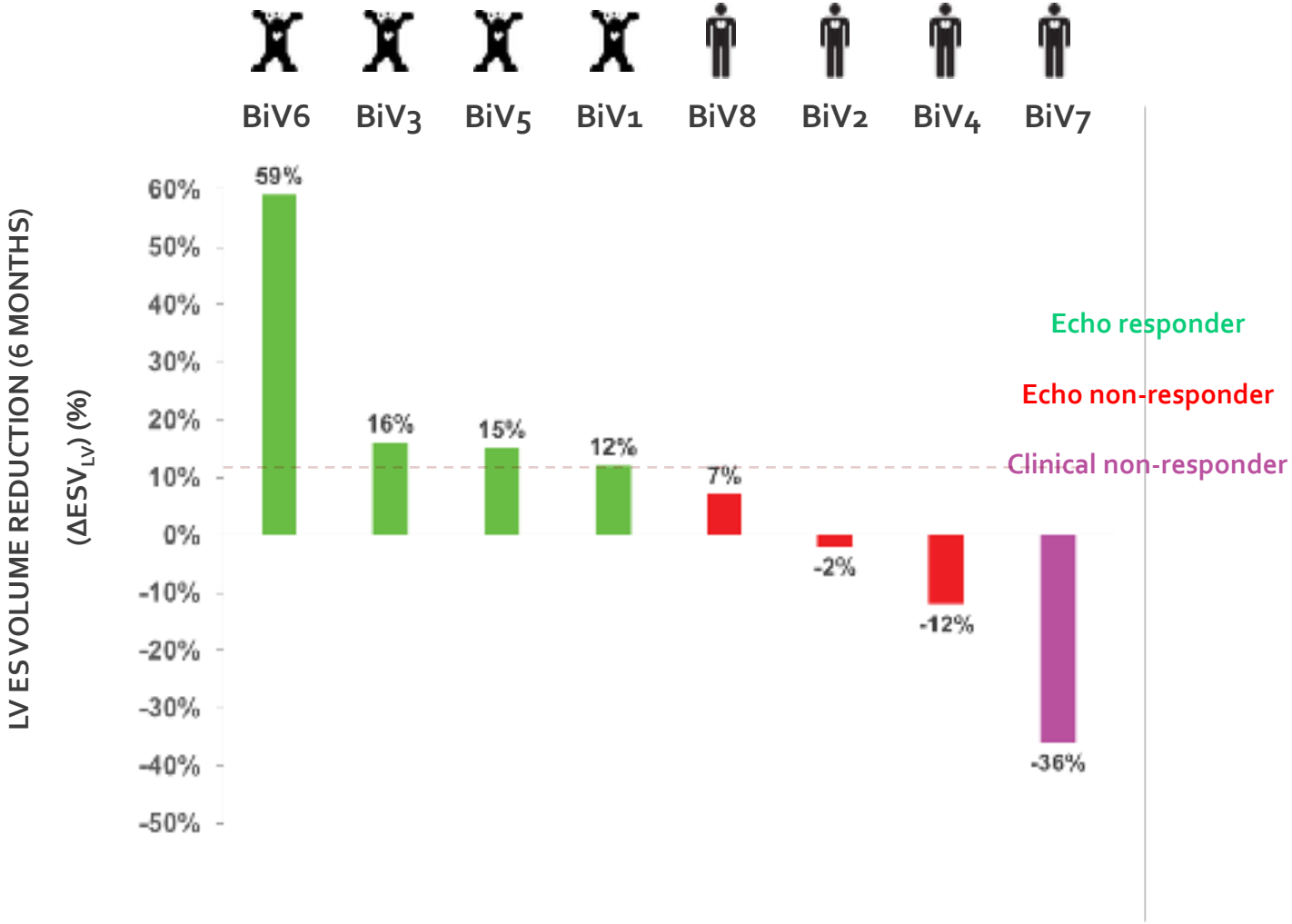


Sheikh *et al* (2012) *J Clin Invest*.

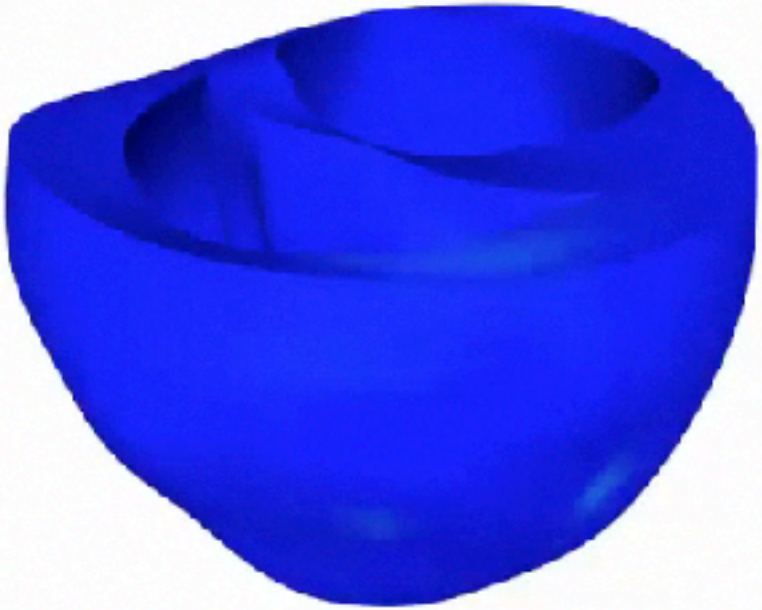
NOW: Patient-Specific Modeling of Dyssynchronous Heart Failure



Echocardiographic Responses to CRT



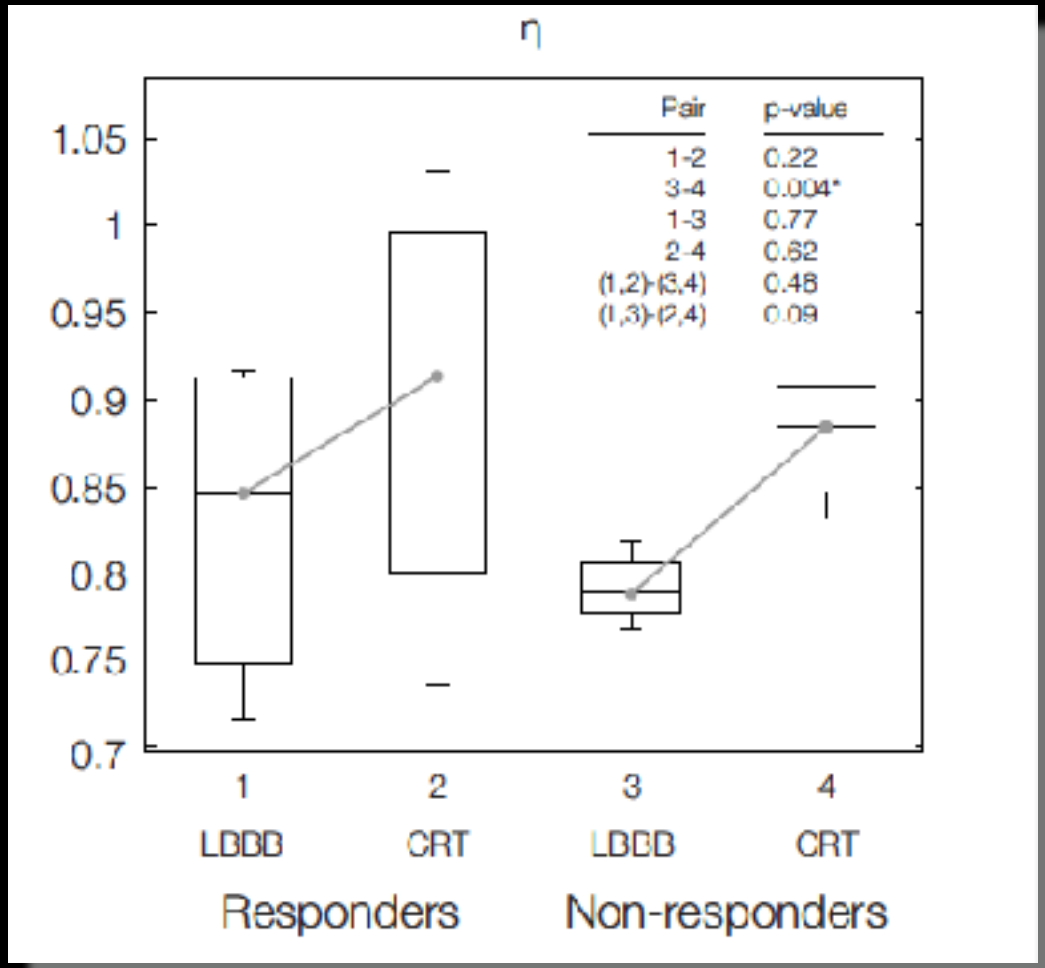
NOW: Add Ectopic Stimulation to Simulate CRT



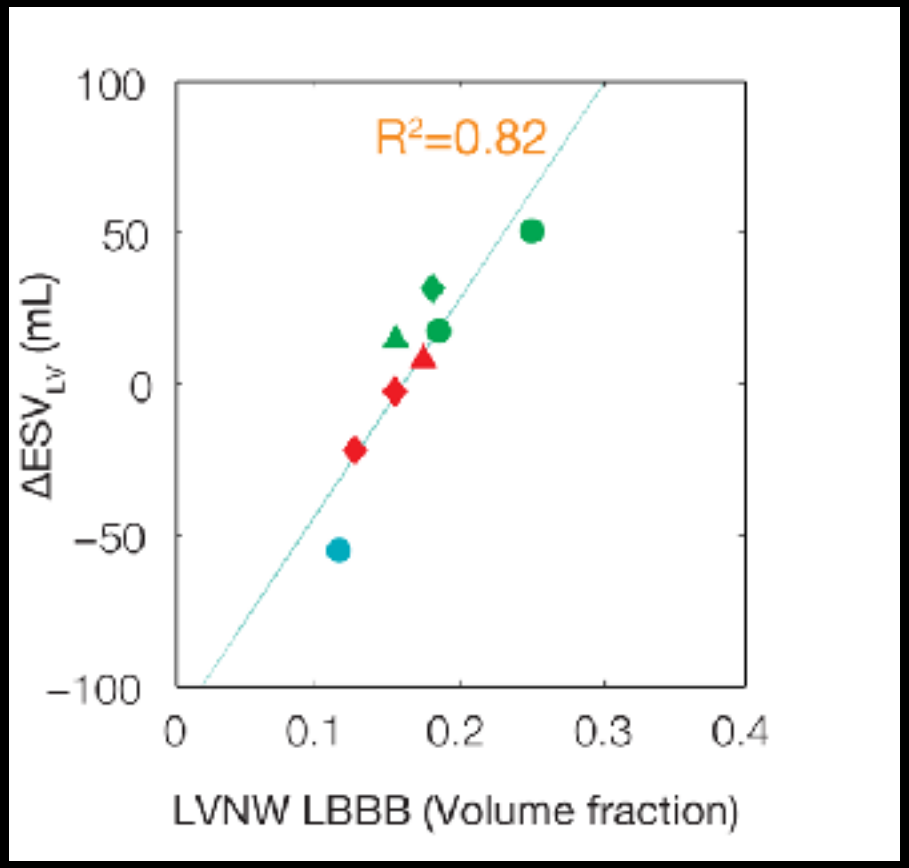
LBBB

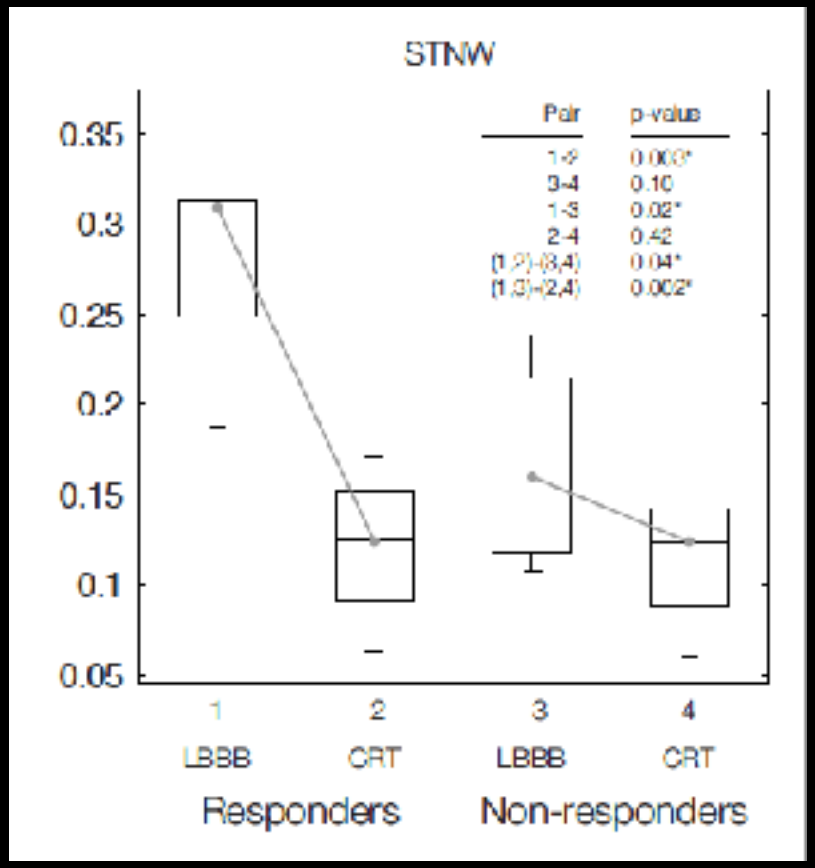
CRT

Does CRT Improve Ventricular Mechanical Efficiency?



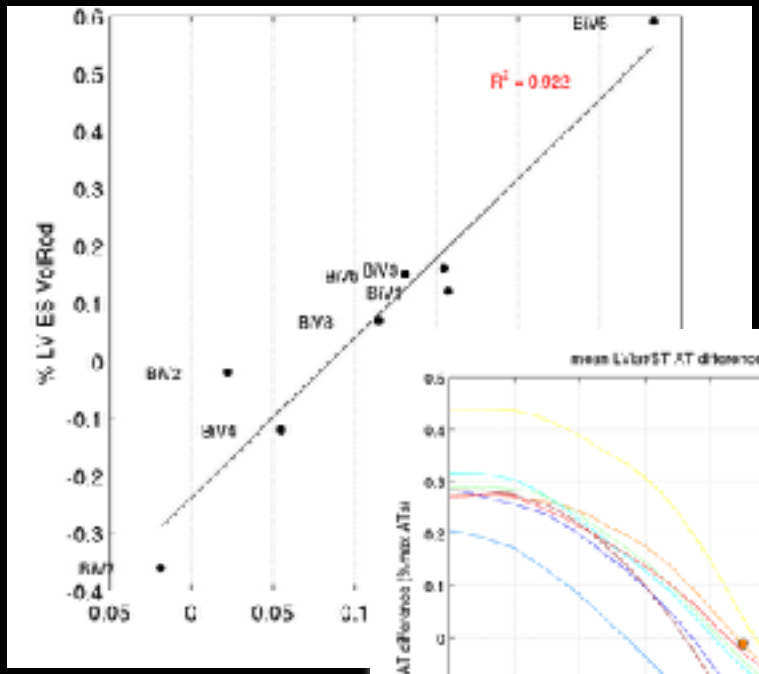
Computed Reduction in Septal Myocardium Performing "Negative" Work May Predict CRT Response

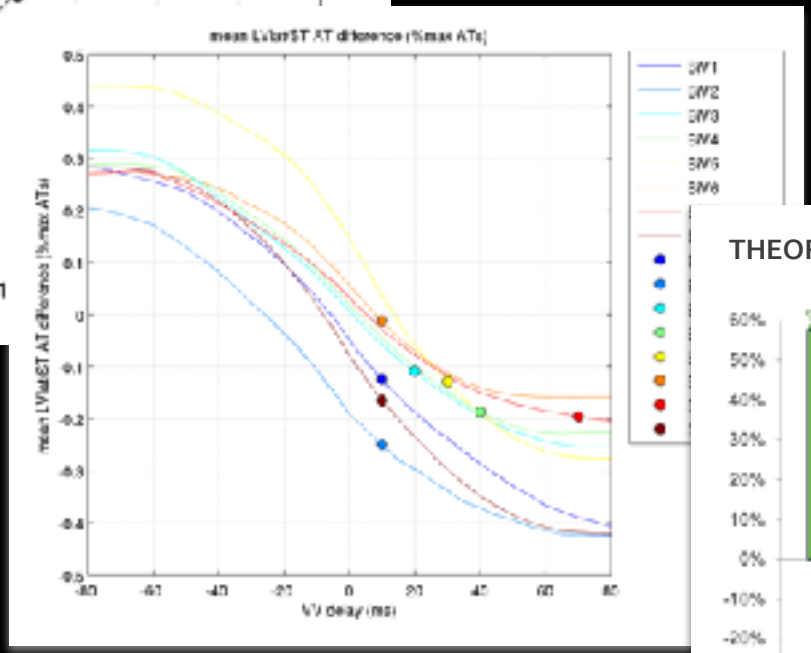


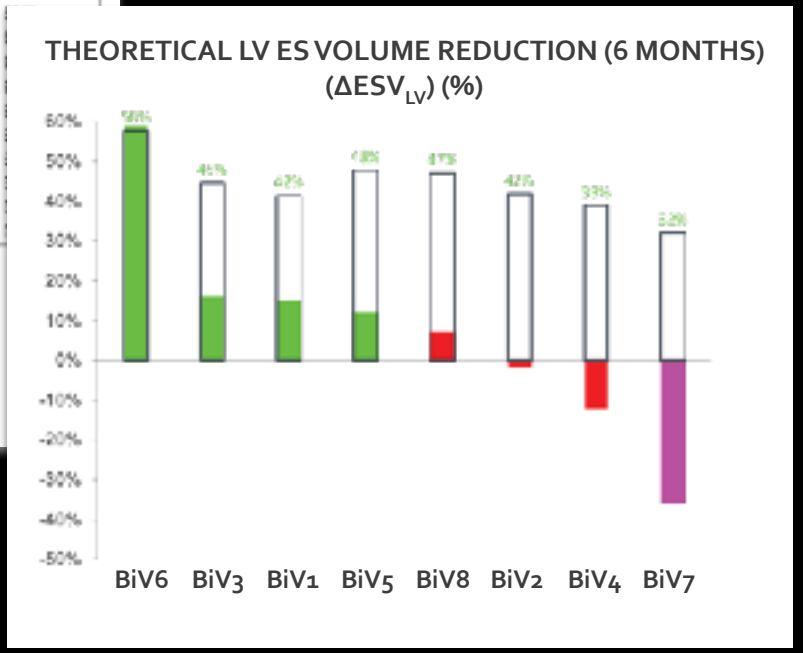


Legend: Responder Echo non-responder Clinical non-responder ● Non-ischemic ▲ Infarct ◆ Infarct + mitral regurgitation

Effect of V-V Pacing Delay on Electrical Dyssynchrony

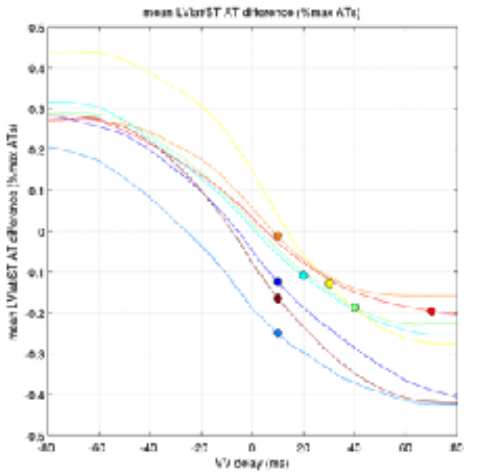




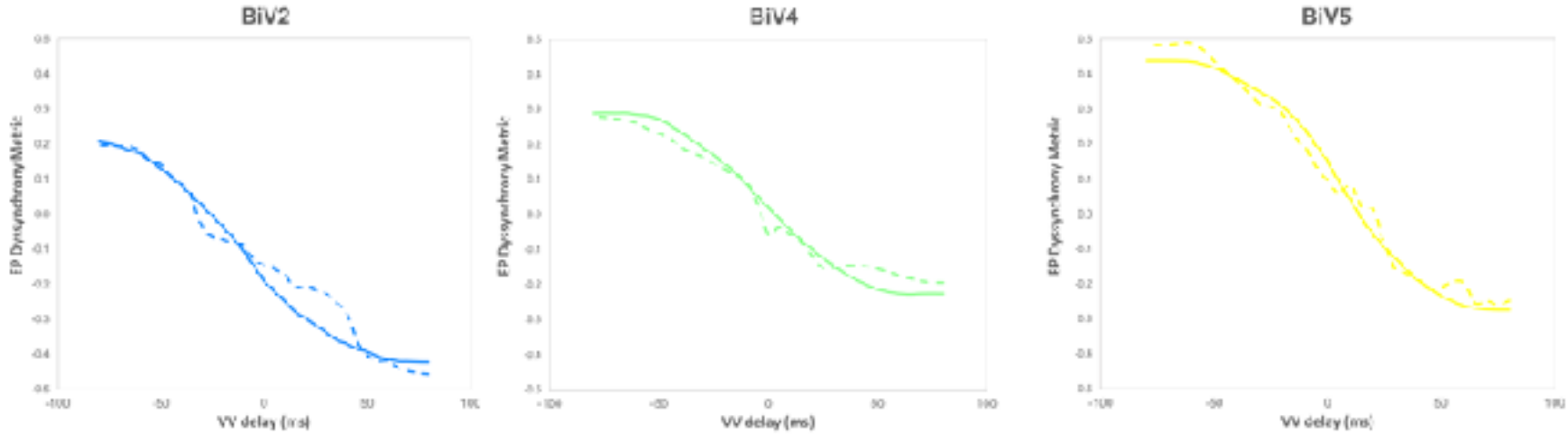


Next:
Machine Learning Hidden Features In Clinical Data From Models

TRAIN LEARNING ALGORITHM



PREDICTED DYSSYNCHRONY METRIC



RMSE: 4%


Stuart Campbell


Chris Villongco


Roy Kerckhoffs


Adarsh Krishnamurthy


Kyle Buchholz


Sukriti Dewan


Philip Tan


Britton Boras


Kim McCabe


Sophia Hirakis


Robert Malmstrom


Steffen Lindert


Jeff Saucerman


Jeff Omens


Alex Zambon


Farah Sheikh


Ju Chen


Dave Krummen


Tom Borg

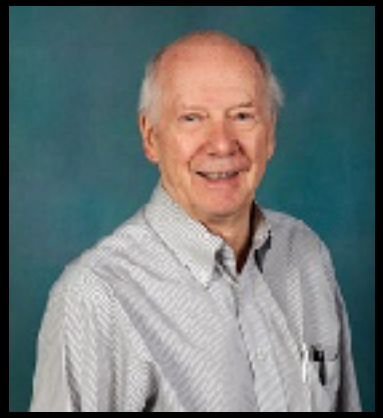

Don Bers


Rommie Amaro


Andy McCammon


Susan Taylor


Mark Ellisman



Jim Bassingthwaighte

Mike Regnier

Dan Beard

Jeff Holmes

Colleen Clancy

Jeff Omens

CARDIAC MECHANICS RESEARCH GROUP

National Centers for Systems Biology
NIH National Heart, Lung, and Blood Institute
National Institute of Biomedical Imaging and Bioengineering
National Institutes of Health National Institute of General Medical Sciences BASIC DISCOVERIES FOR BETTER HEALTH
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