CENTER FOR CARDIOLOGICAL INNOVATION



Welcome to the SUURPh Summer School!

Introduction to Computational Physiology: Multi-scale Cardiac Electromechanics

Andrew D. McCulloch, UC San Diego

UC San Diego

DEPARTMENT OF BIOENGINEERING · UNIVERSITY OF CALIFORNIA, SAN DIEGO

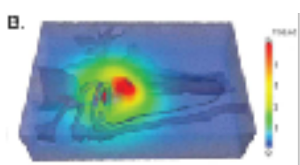
CARDIAC MECHANICS RESEARCH GROUP

Physiology of excitable tissues

- *Introduction to cardiac electrophysiology and biomechanics*
- *Fundamental processes in ventricular pumping function*
- *Mathematical and computational modeling are key tools for integrating across scales of biological organization from molecule to organ system*

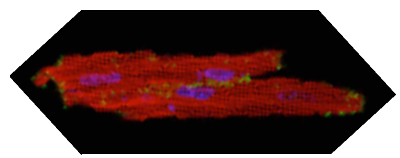
Channel

nm/μs



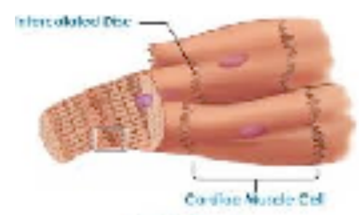
CRU

μm/ms



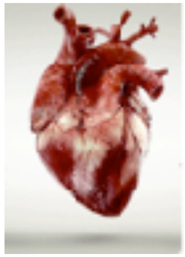
Cell

100's of μm/
10's sec



Tissue

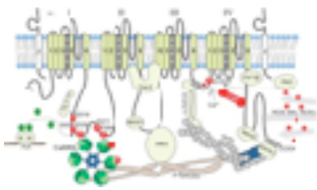
mm/weeks



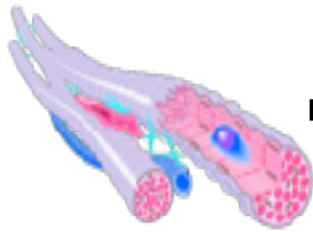
Organ

cm/months

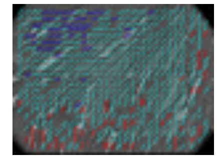
Electrophysiology



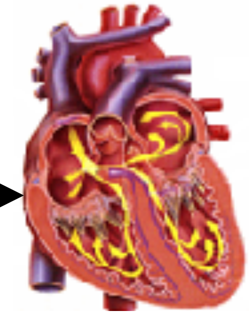
Ion channel



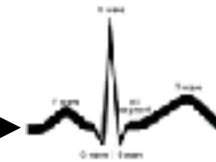
Whole myocyte



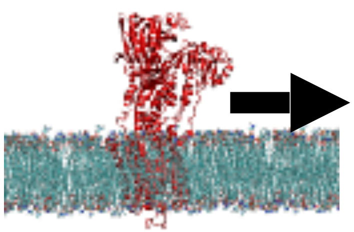
Myocardium



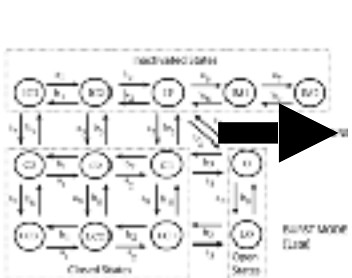
Whole heart



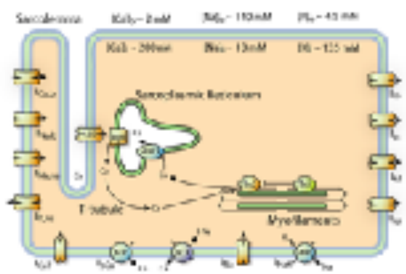
Electro-cardiogram



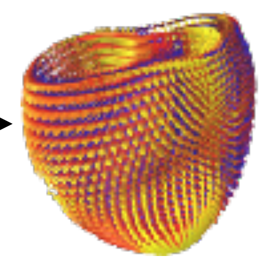
Atomistic molecular model



Markov model of channel gating



Whole cell ionic model



Bidomain continuum model

Torso bioelectric field model

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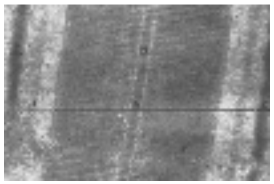
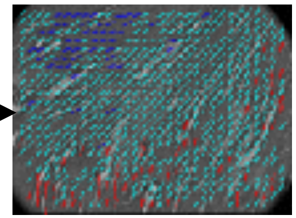
Biomechanics

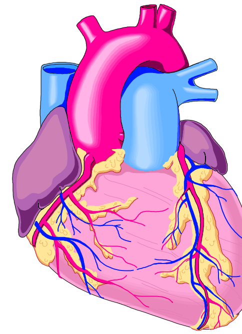
Cross-bridges



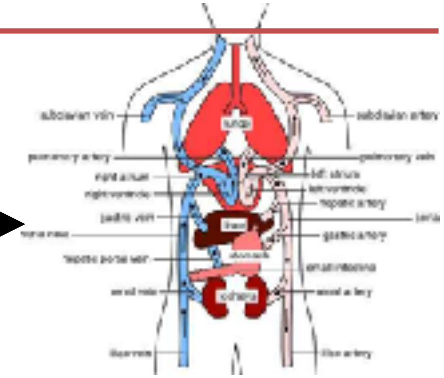
Myofilaments



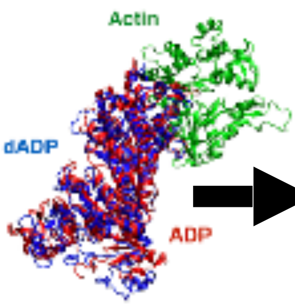
Myocardium



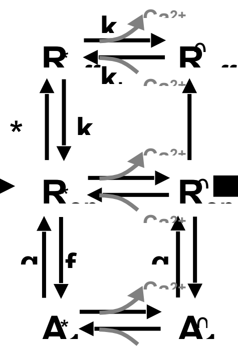
Ventricles



Circulation



Molecular model



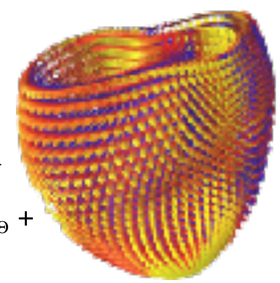
Myofilament Markov model

$$W = \frac{1}{2} C e^{Q}$$

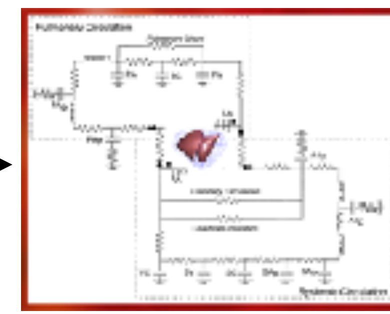
where

$$Q = b_1 E_{\Theta\Theta}^2 + b_2 E_{ZZ}^2 + b_3 E_{RR}^2 + 2b_4 E_{\Theta\Theta} E_{ZZ} + 2b_5 E_{ZZ} E_{RR} + 2b_6 E_{RR} E_{\Theta\Theta} + b_7 E_{\Theta Z}^2 + b_8 E_{ZR}^2 + b_9 E_{R\Theta}^2$$

Tissue constitutive model



Continuum model of wall stress



Circulatory systems model

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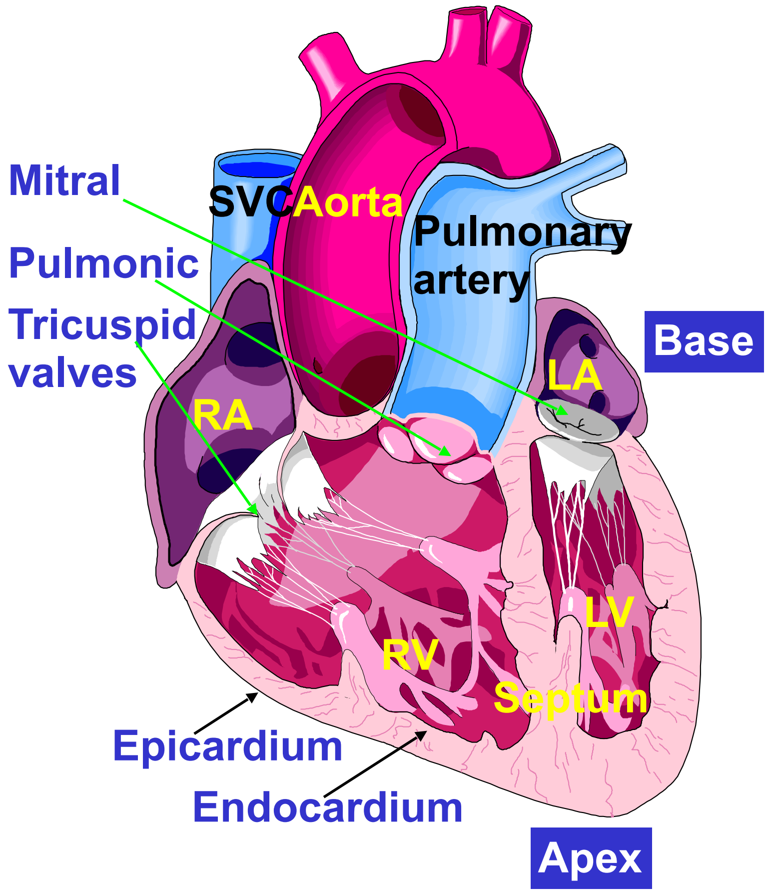
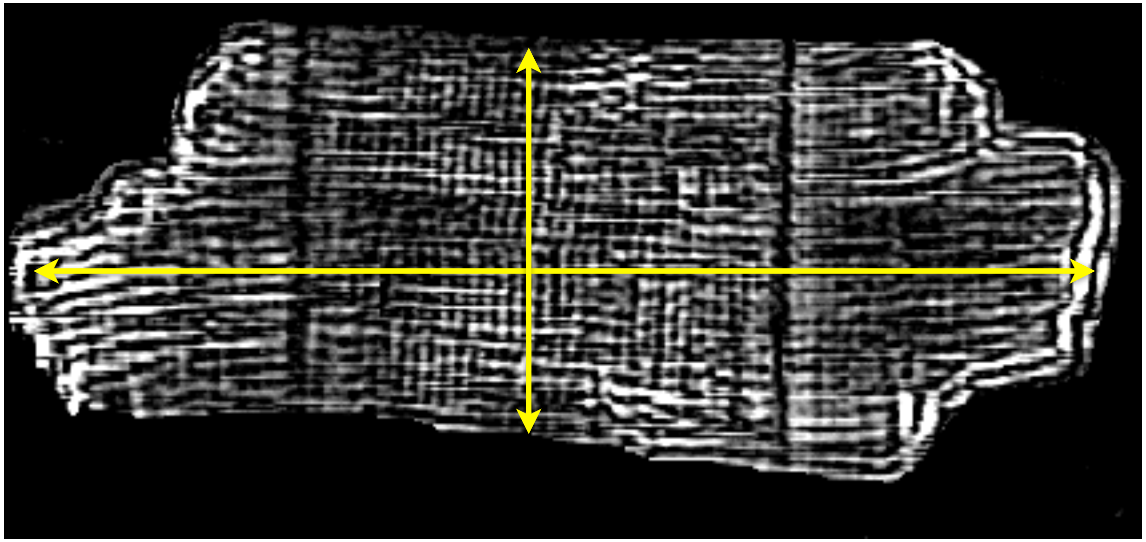
Cardiac anatomy

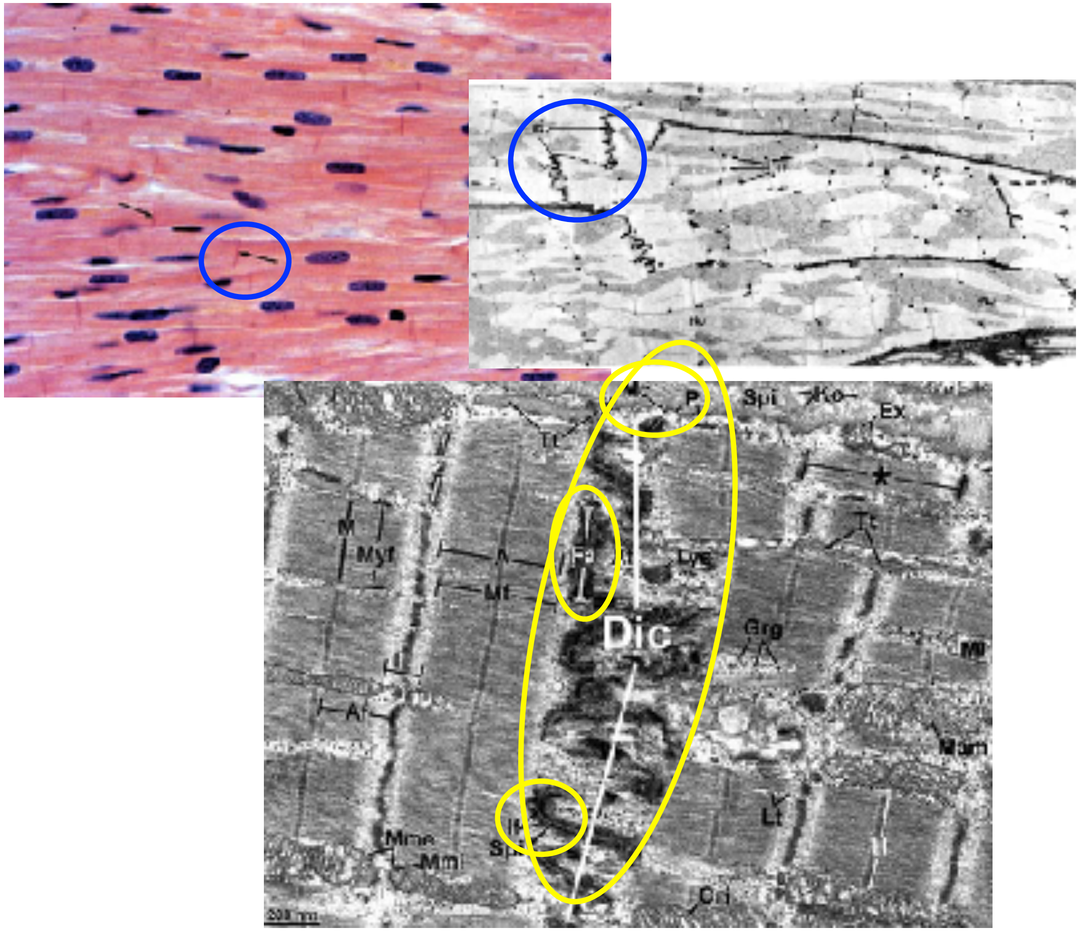


Cardiac myocyte



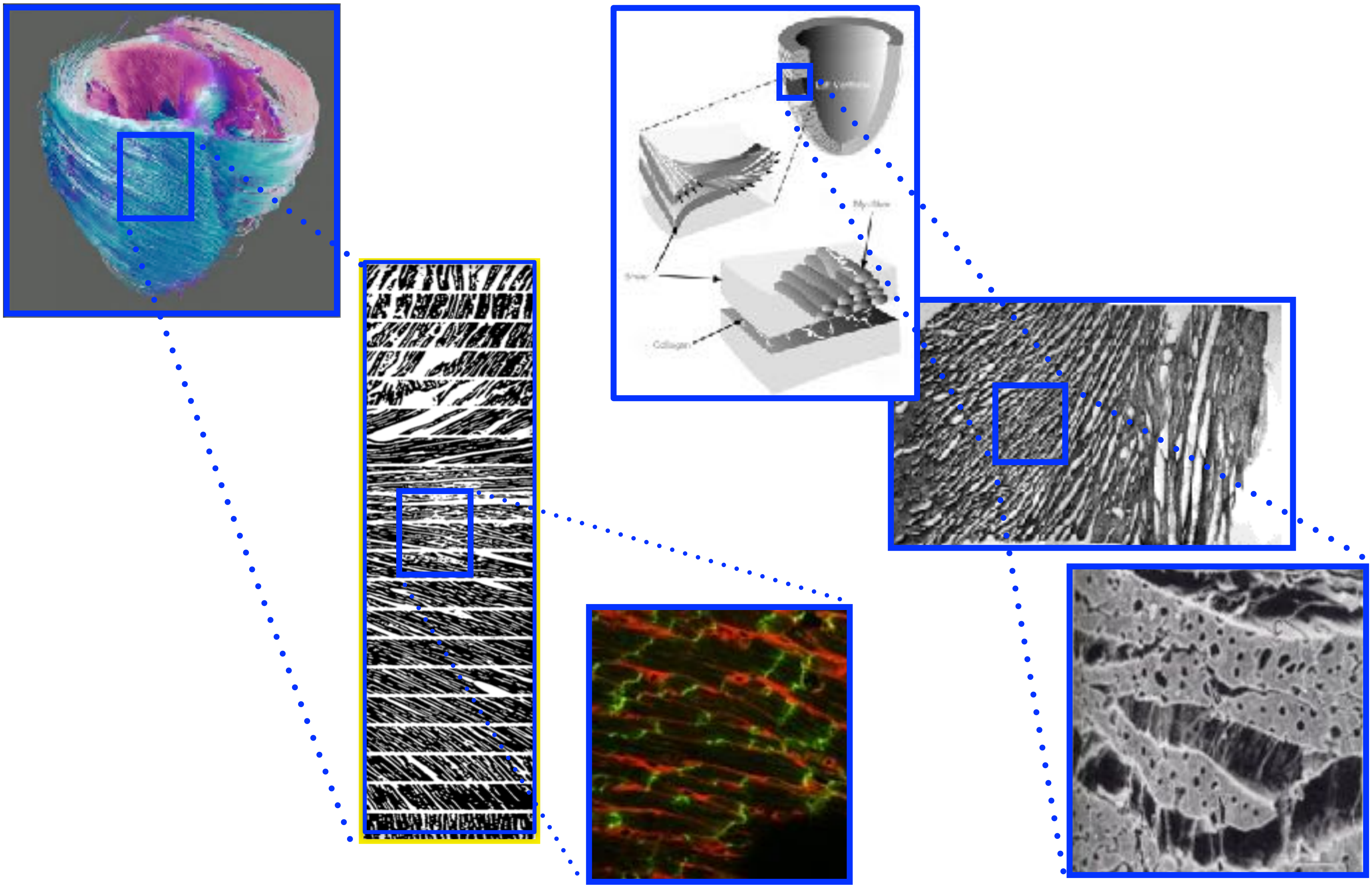
- Rod-shaped
- Striated
- 80-100 μm long
- 15-25 μm diameter

Cardiac myocyte connections

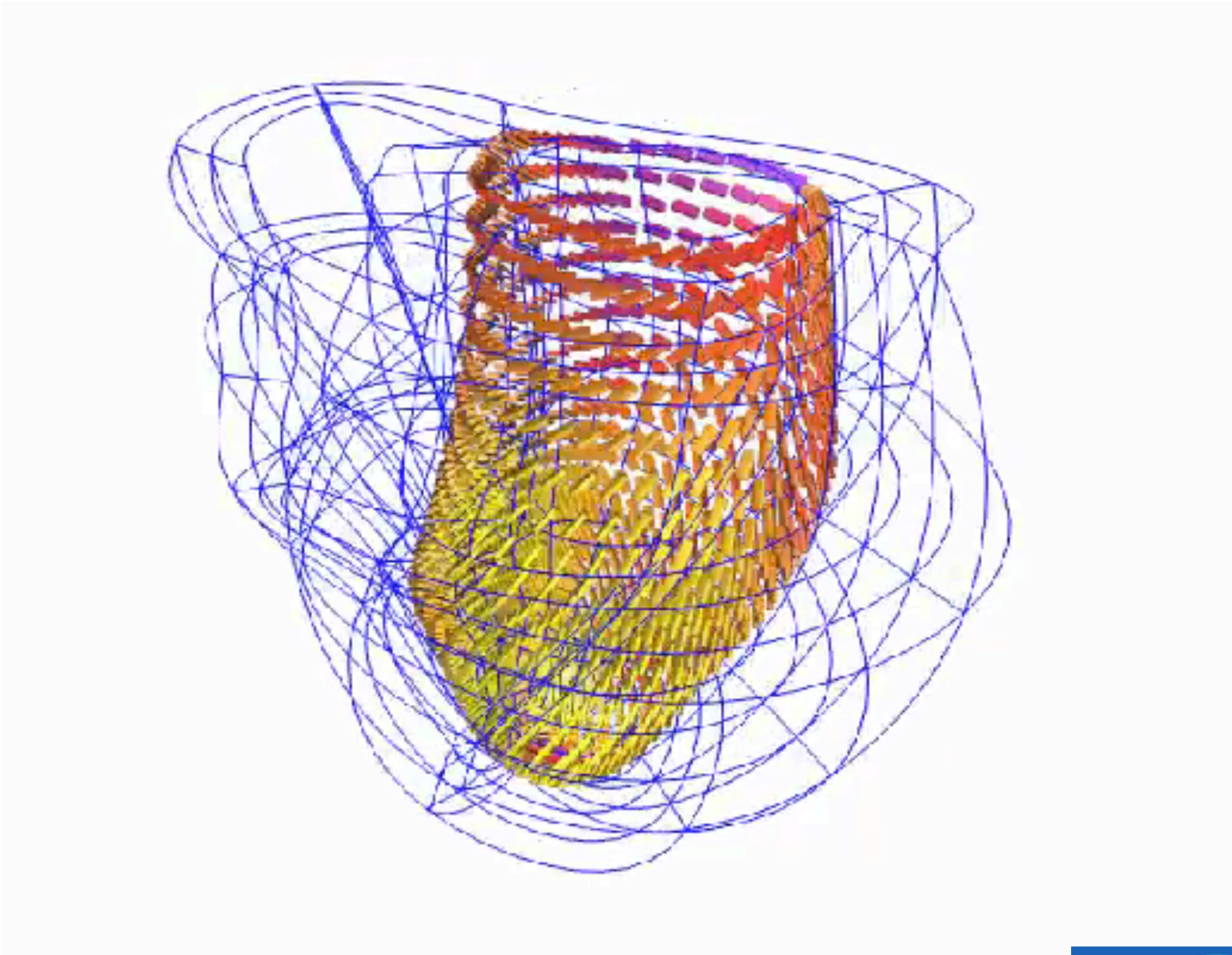


- Myocytes connect to an average of 11 other cells
- Intercalated discs
  - gap junctions
    - connexons
      - connexins
  - adherens junctions (fascia adherens)
    - anchoring sites for sarcomeres (actin)
  - desmosomes (macula adherens)
    - connect cytoskeleton (intermediate filaments) between cells.

Laminar myofiber tissue architecture



Laminar myofiber tissue architecture



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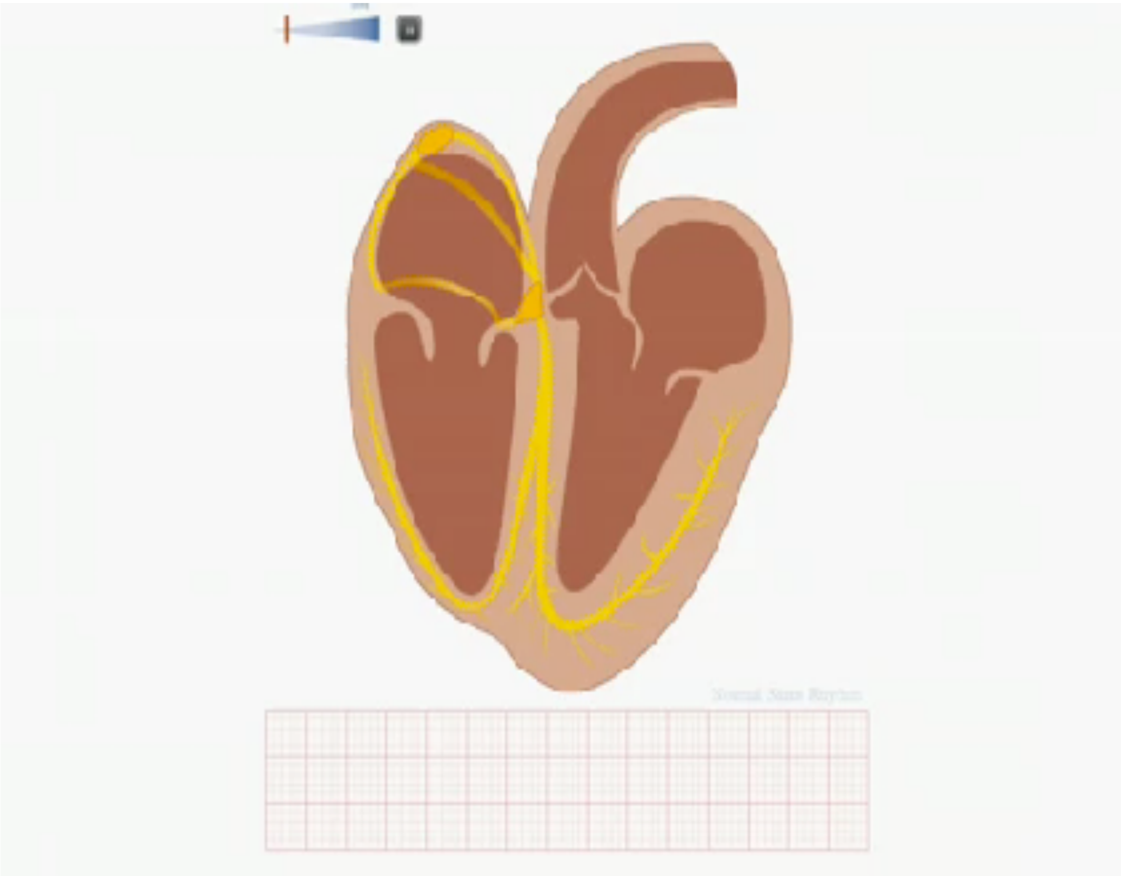
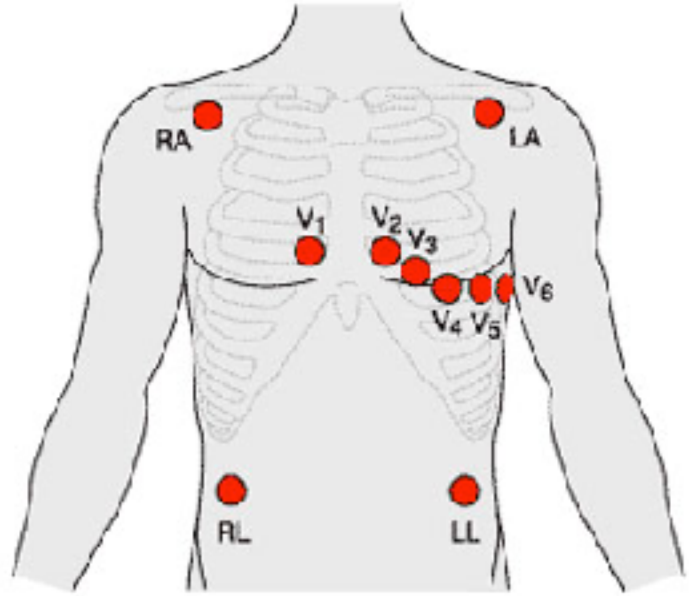
Cardiac electrical activity





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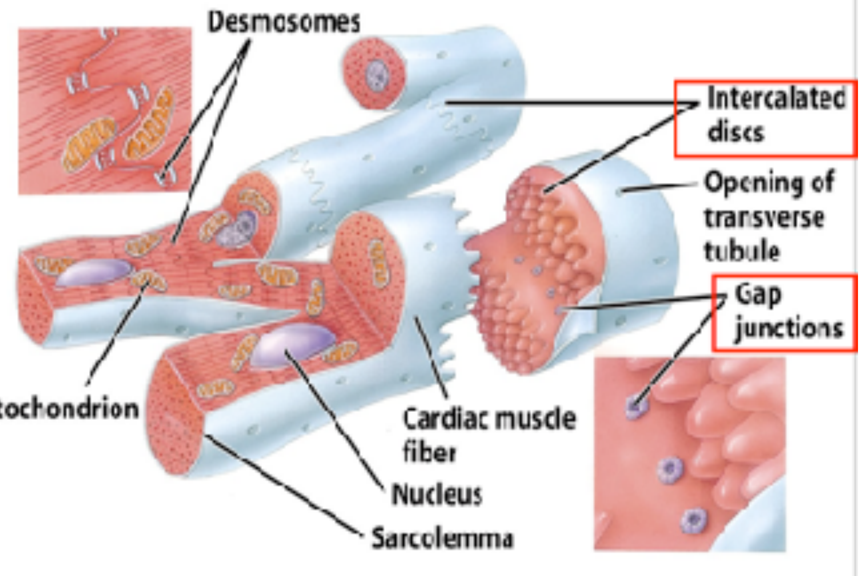
The heart is an electrical syncytium

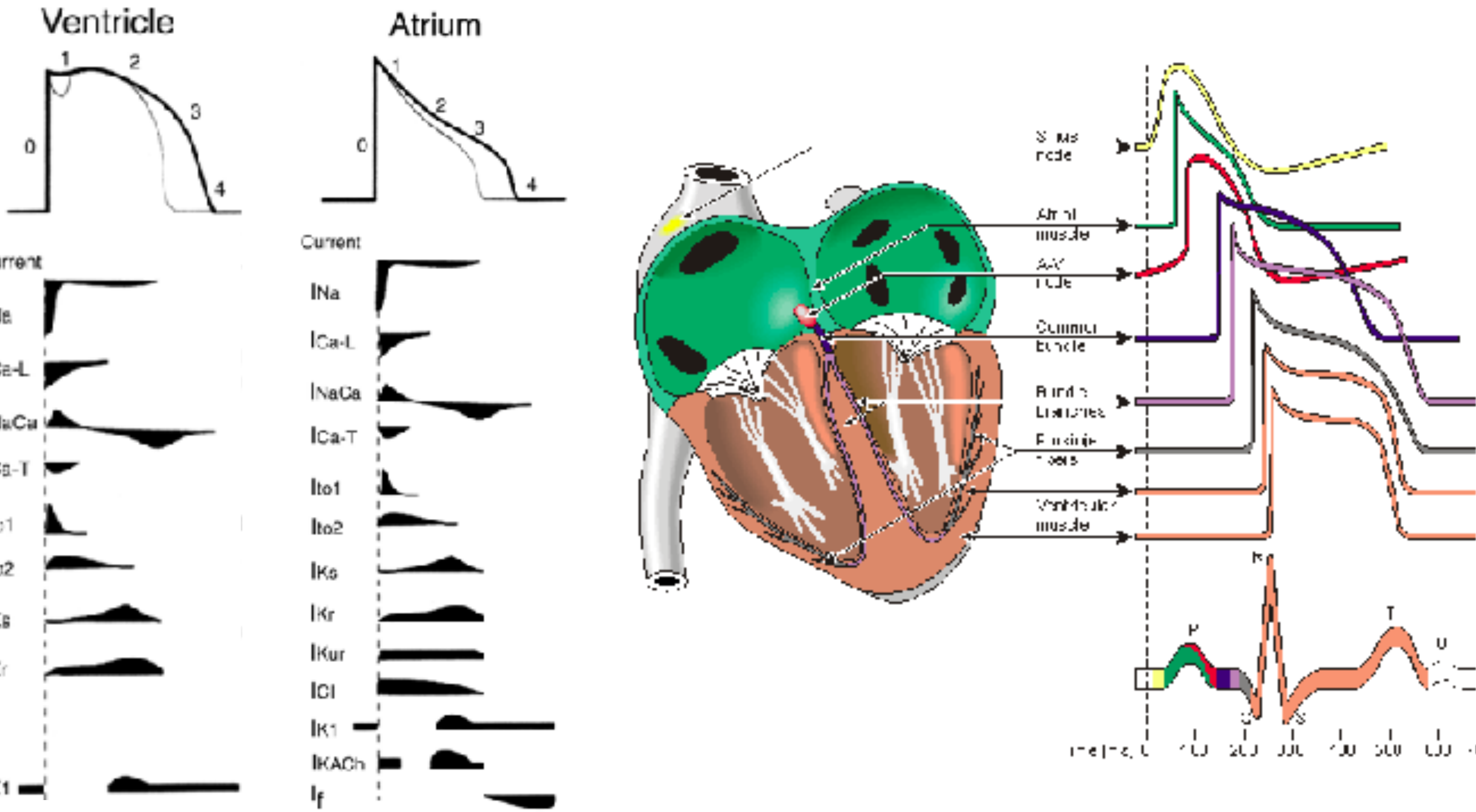
[The Cardiac Action Potential]



Cardiac muscle fibers

Figure 20-9a Principles of Anatomy and Physiology, 11/e
© 2006 John Wiley & Sons

Differential expression of currents shapes the action potential in a cell-specific manner



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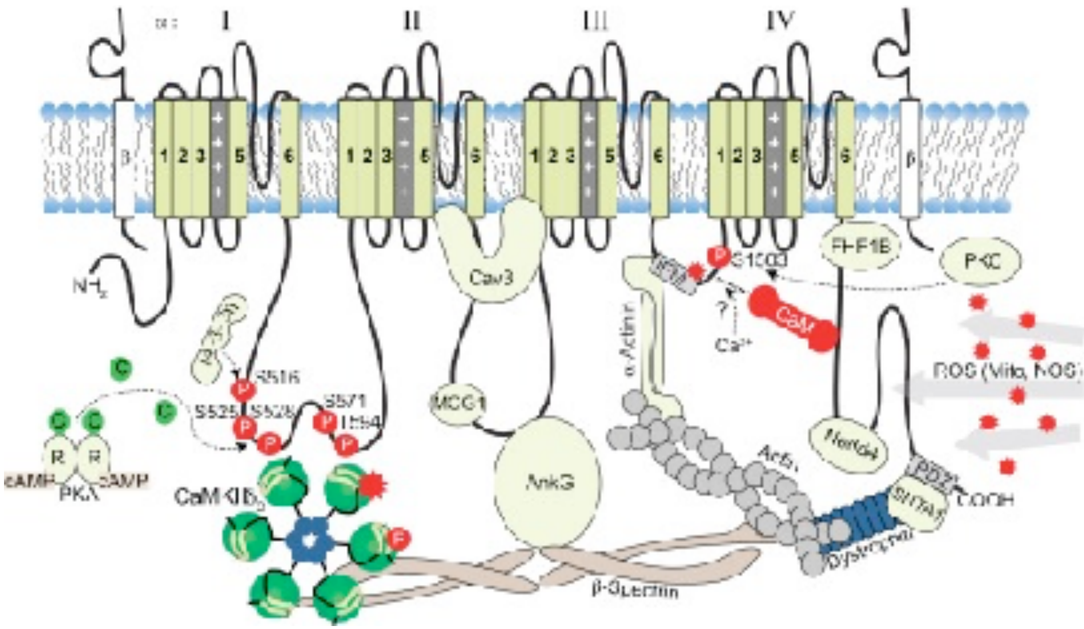
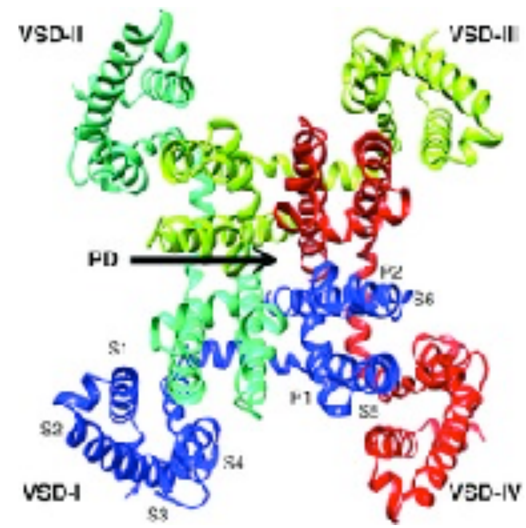
Voltage-gated on channels underlie excitability





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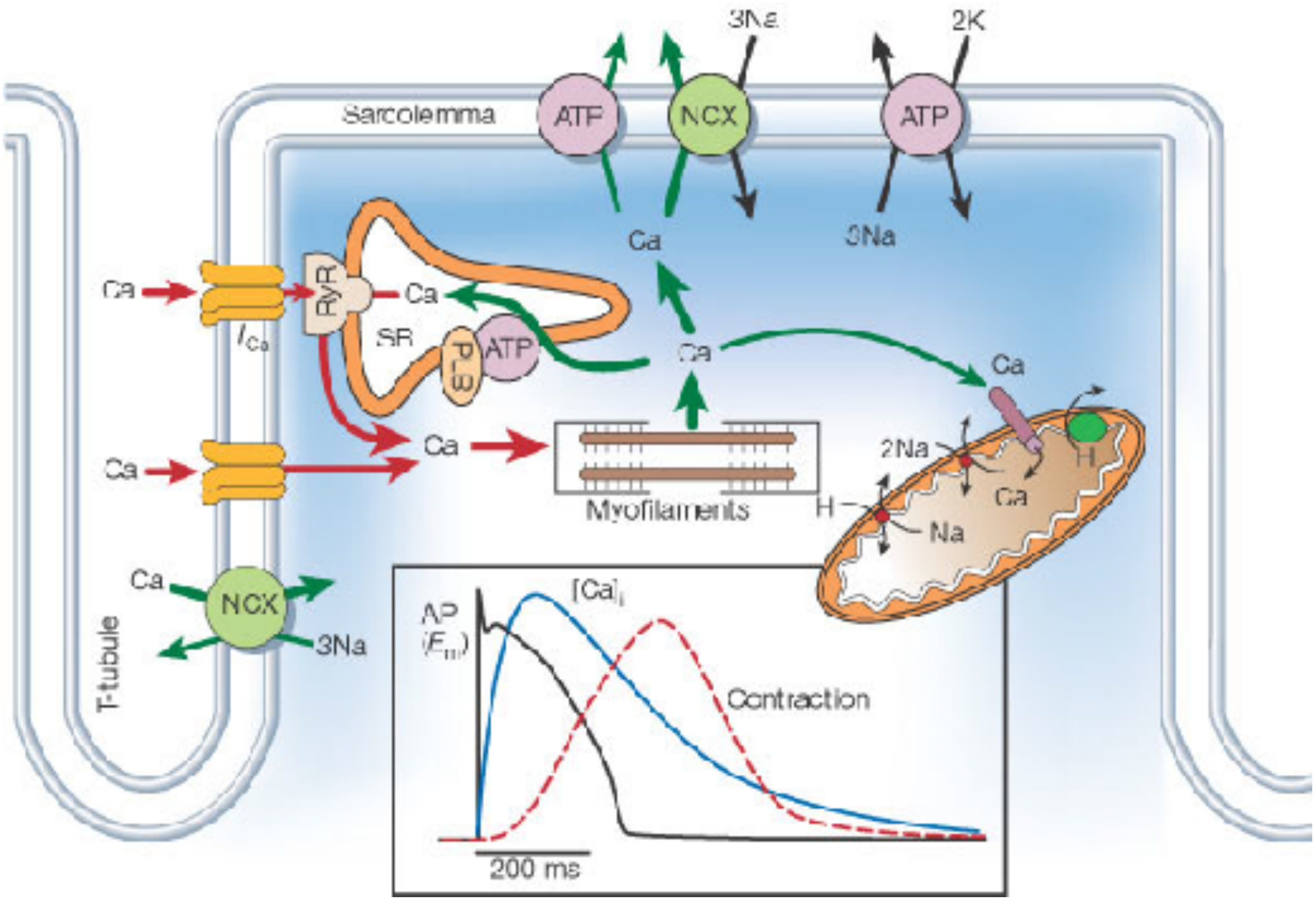
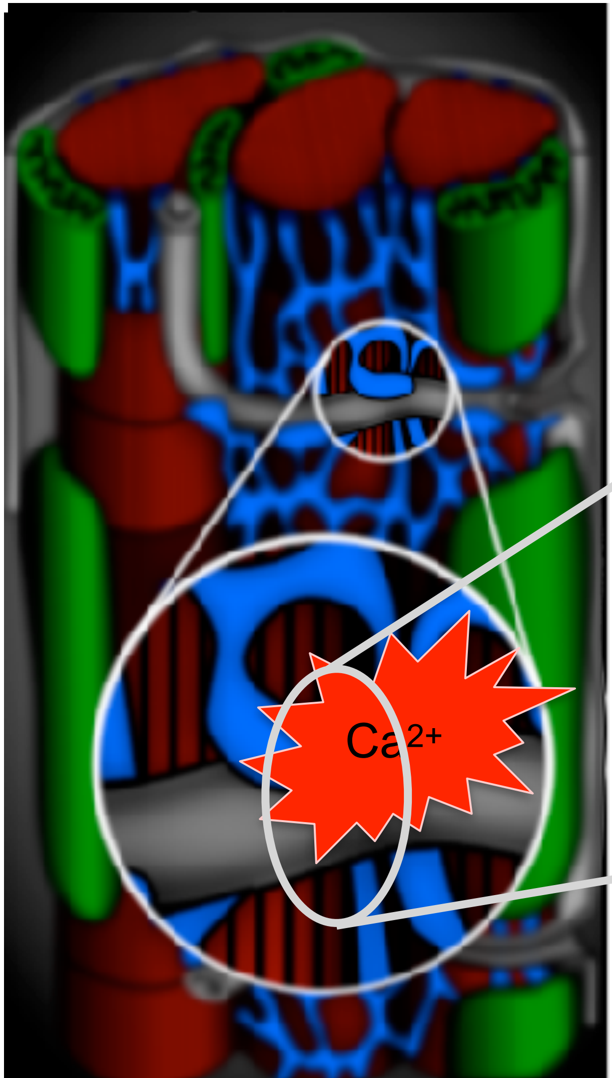
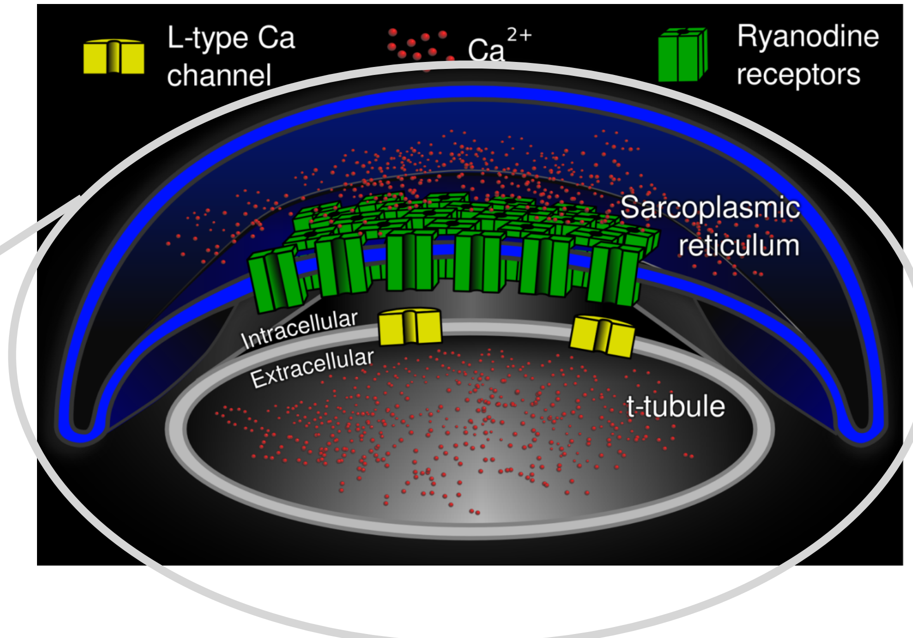
Myocyte excitation-contraction coupling



Calcium release unit





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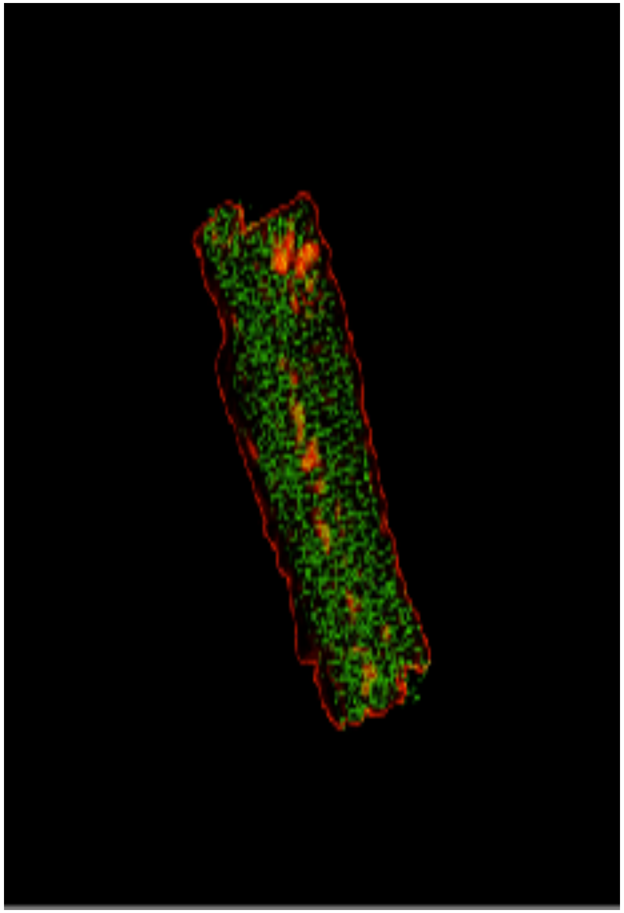
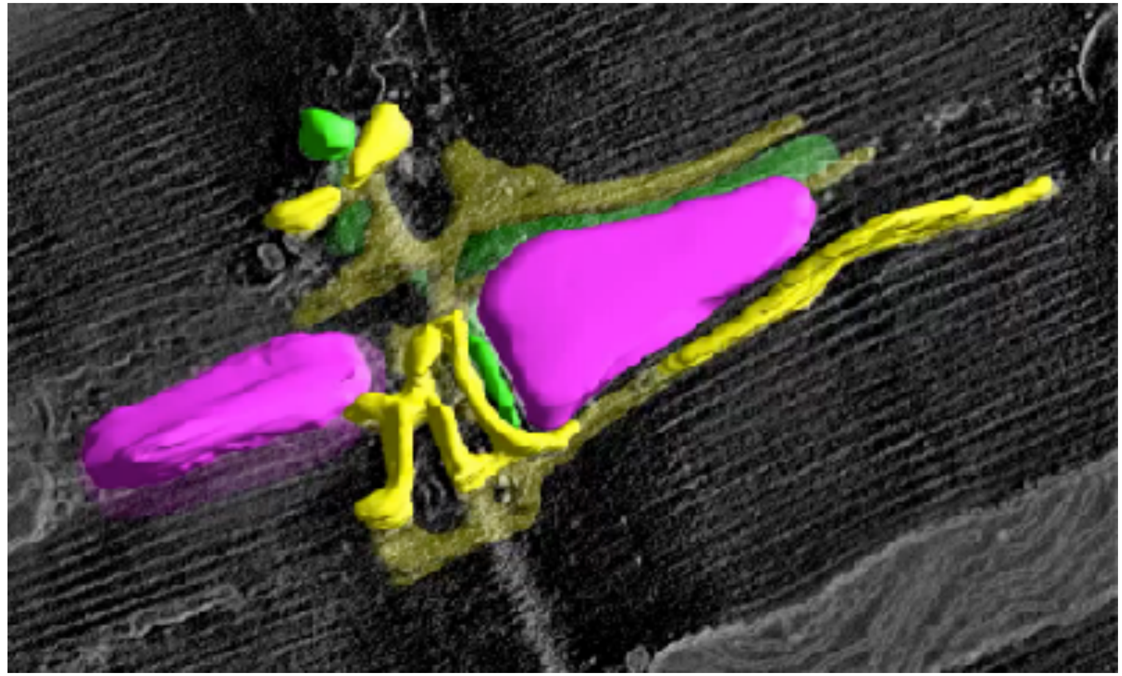
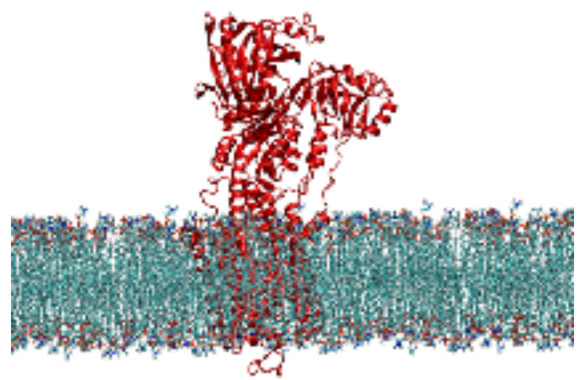
Structures involved in cardiac calcium signaling







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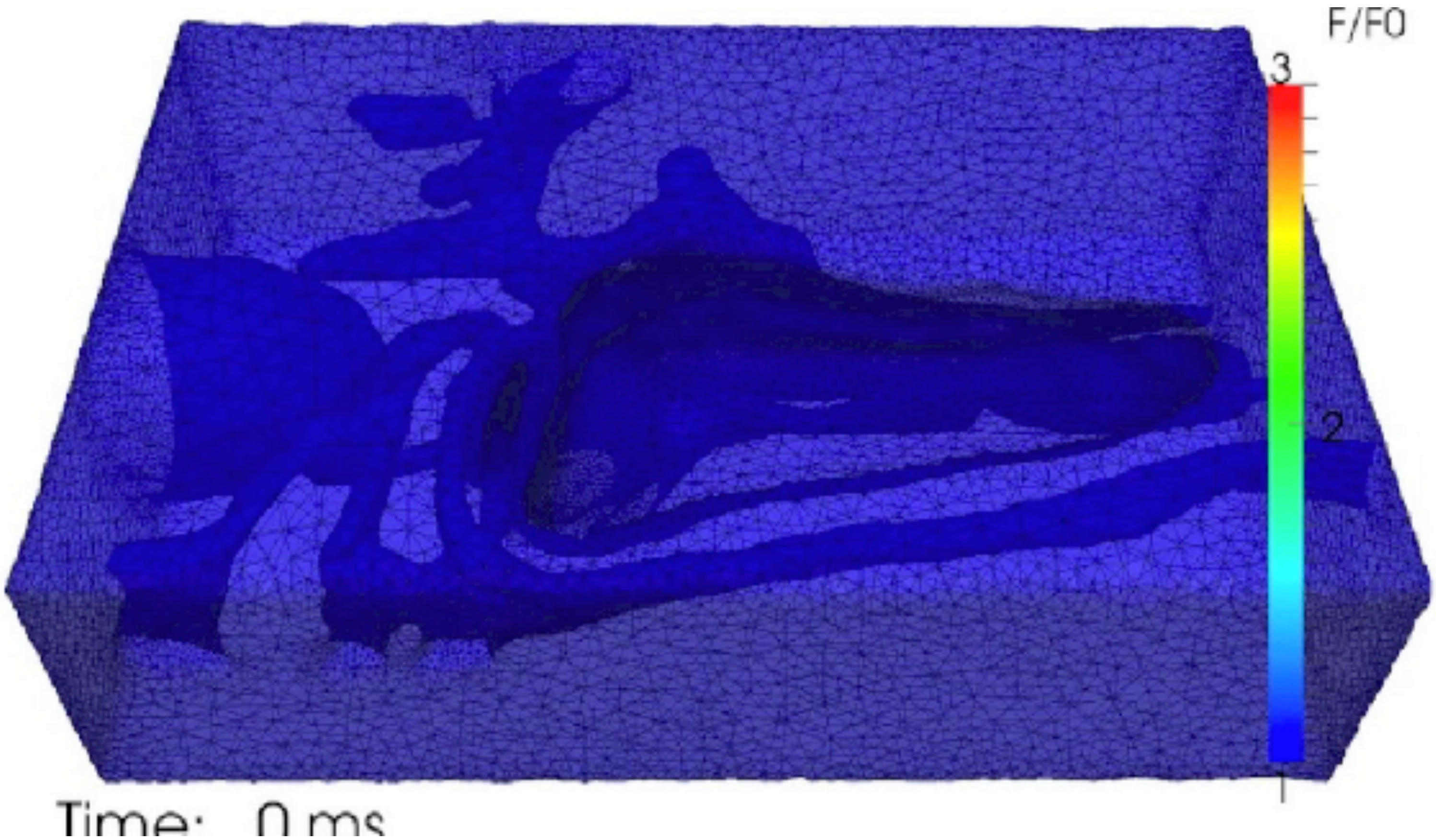
Simulation of a calcium spark



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

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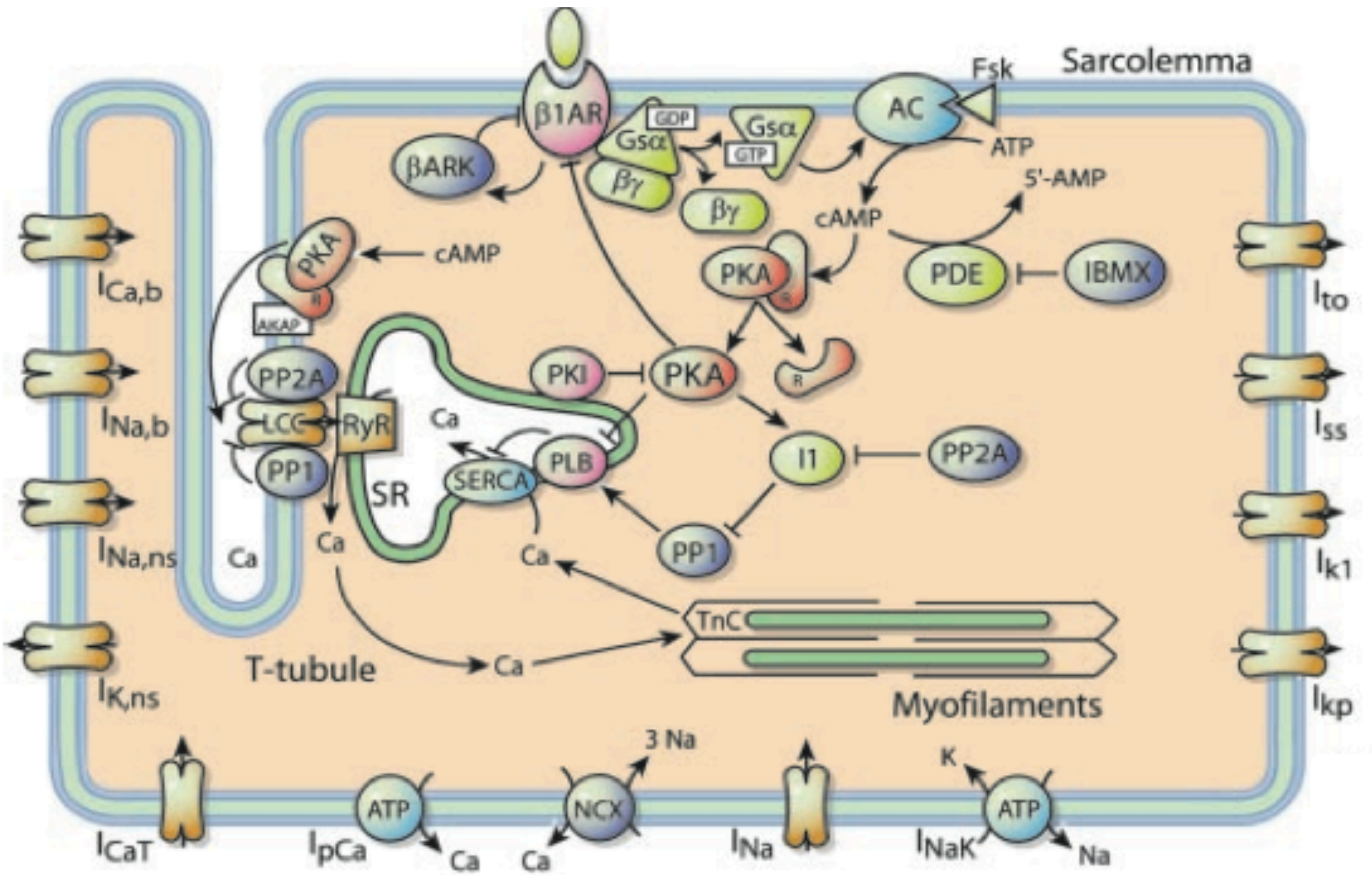
Regulation of excitation-contraction coupling



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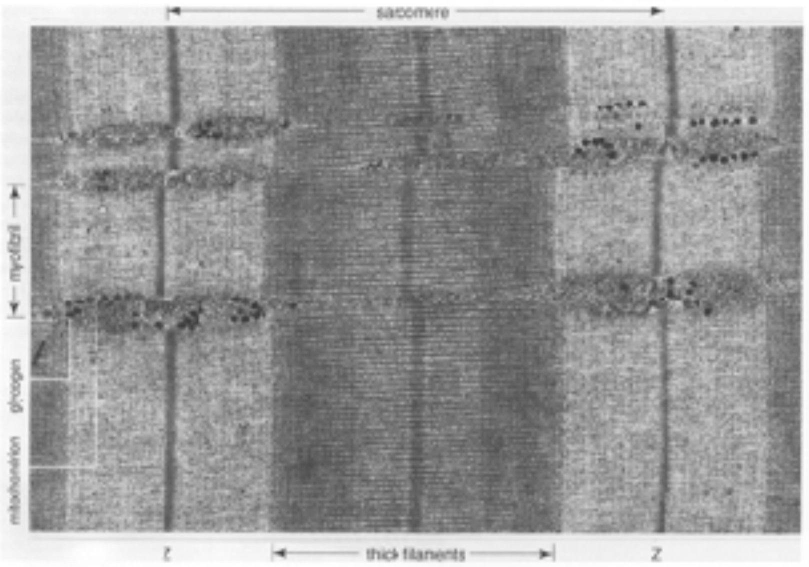
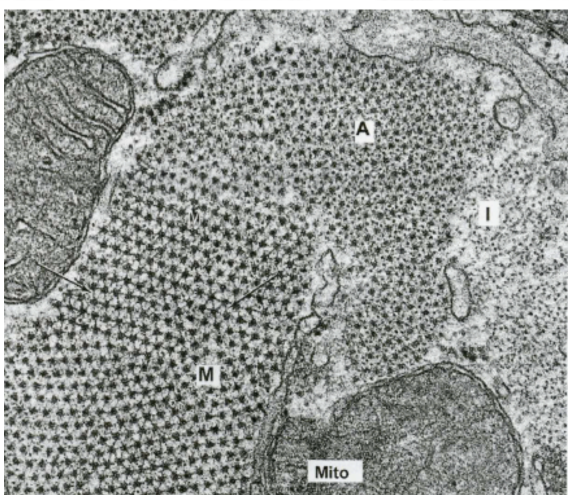
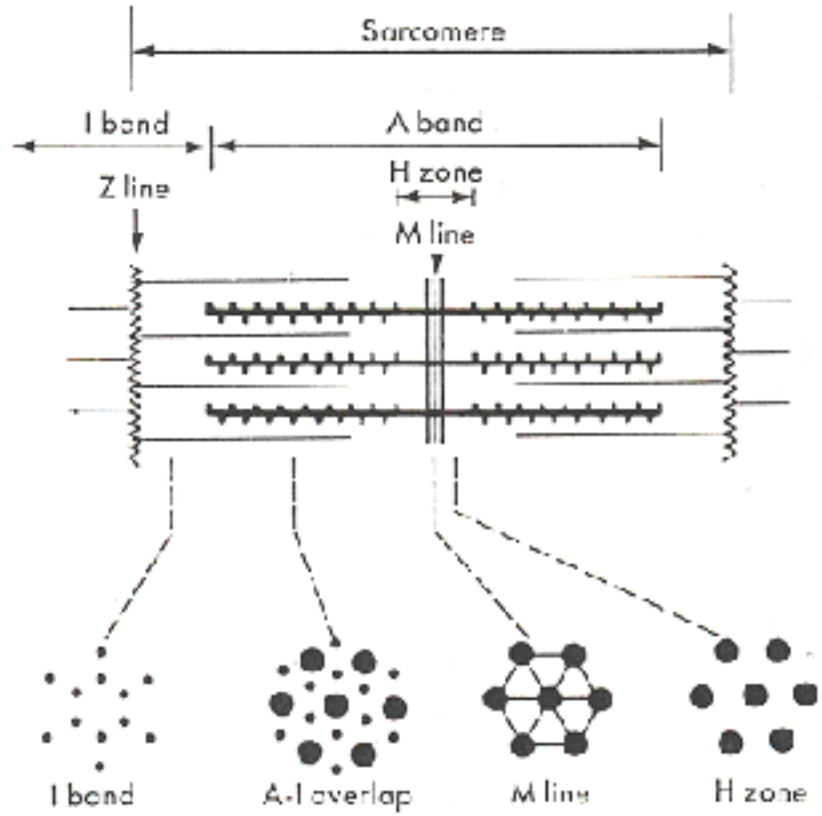
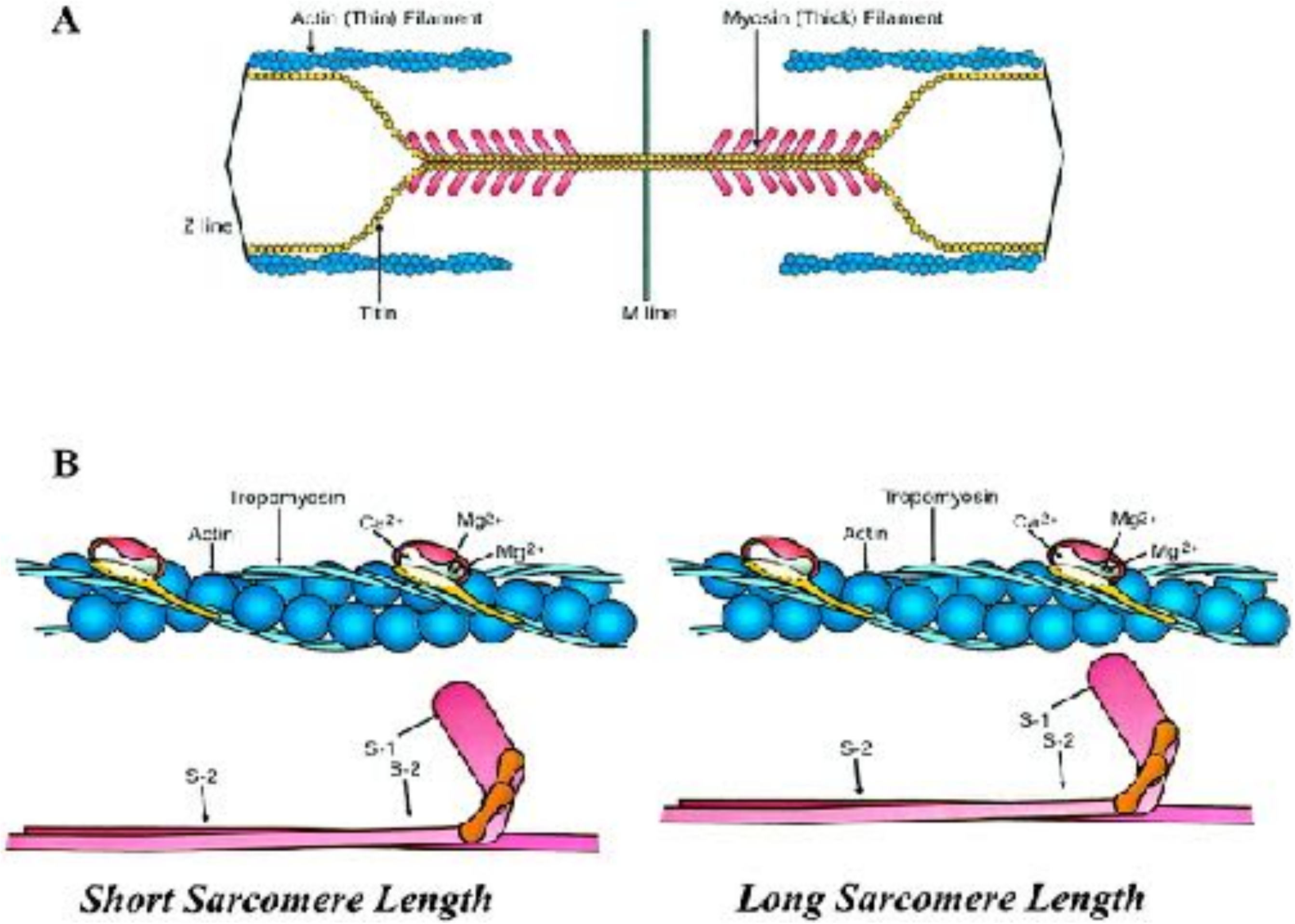
The Sarcomere and myofilaments



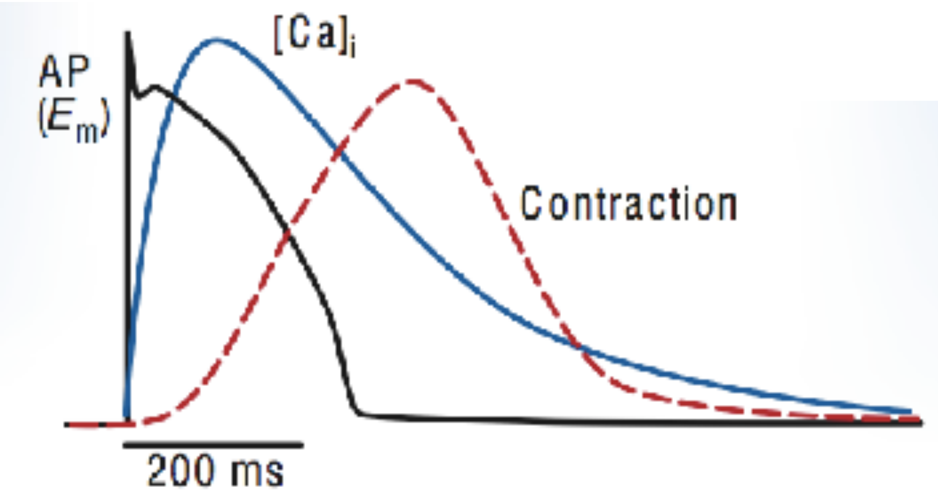


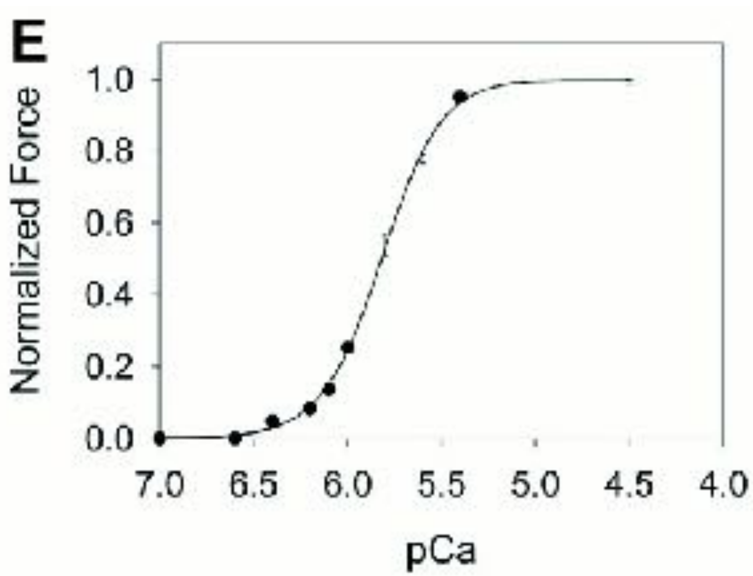


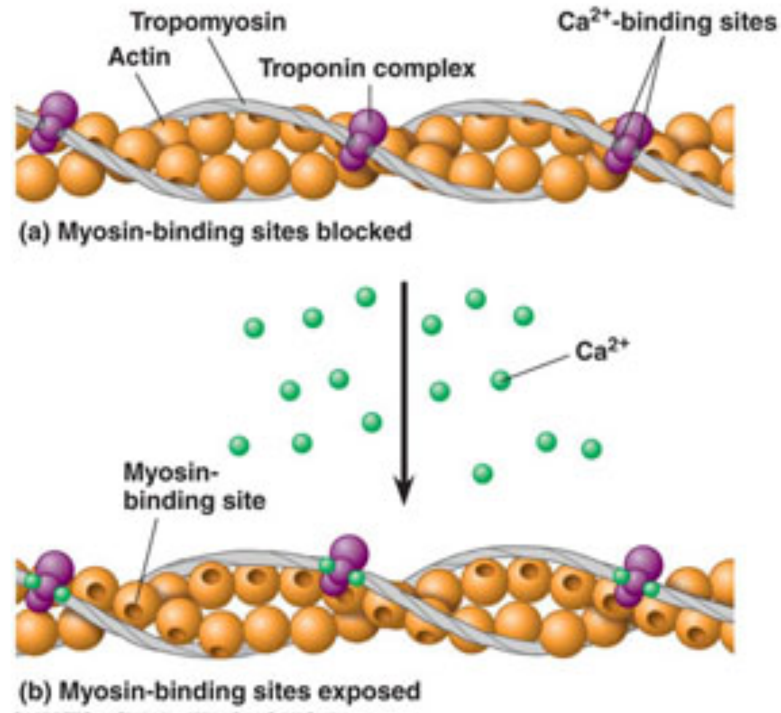
Myofilament proteins



Myofilament activation and crossbridge cycling







[Crossbridge Cycle]

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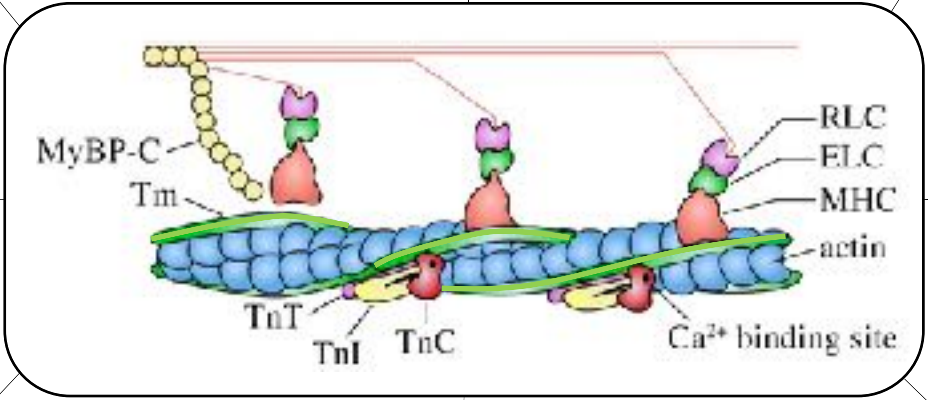
Myofilament Models

Mean Field Theory

A.F. Huxley-Like

Deterministic ODEs & PDEs

Nearest Neighbor Interactions



Crossbridge Cycling Mean Field

Continuous Flexible Chain (CFC)

Stochastic Models Brownian-Langevin SODEs

Molecular Dynamics, Monte Carlo Markov Chain

- Smith & Geeves (I & II) , Biophys. J., 2003
- Geeves et al., Biophys. J., 2011
- Mijailovich et al., & Geeves, Eur. Biophys. J., 2012

- K. S. Campbell et. al., Biophys. J., 2003
- S. G. Campbell et. al., Biophys. J., 2010
- Aboelkassem et. al., Biophys. J., 2015

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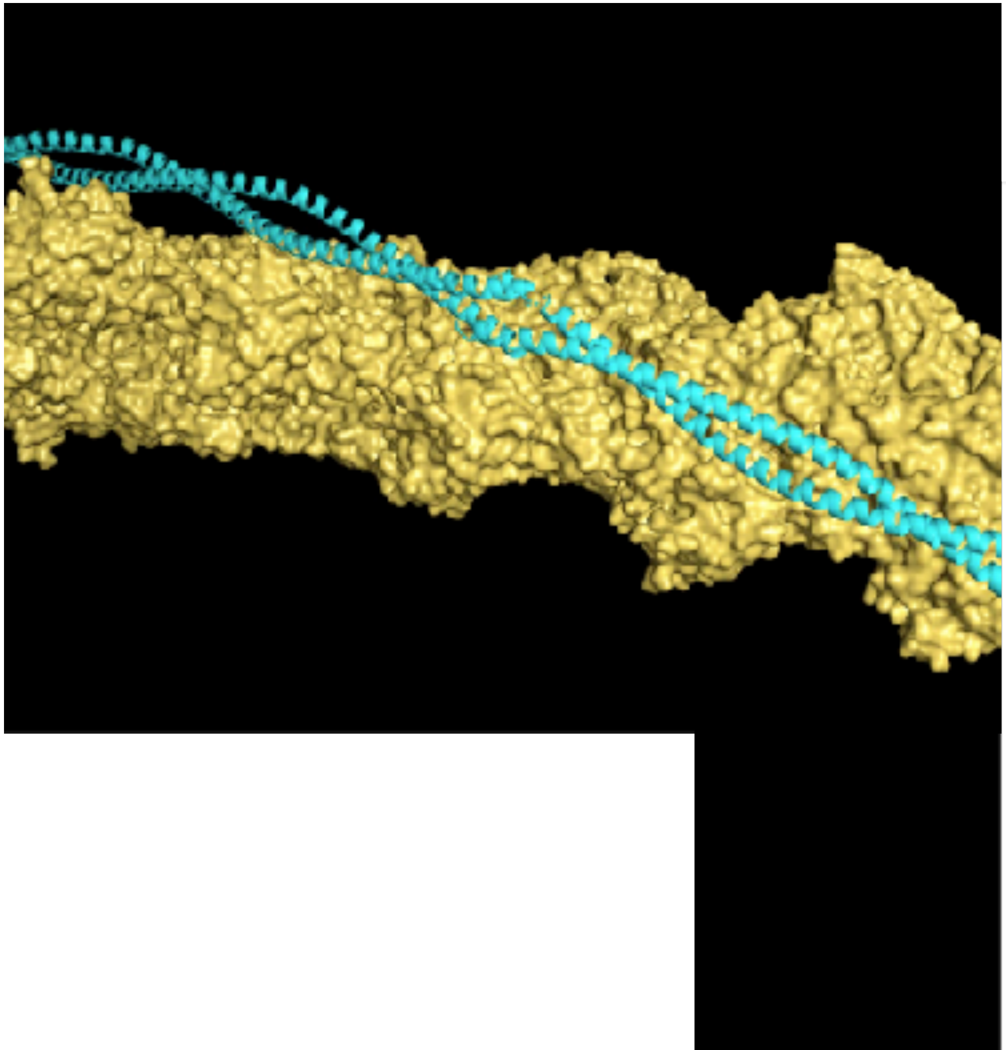
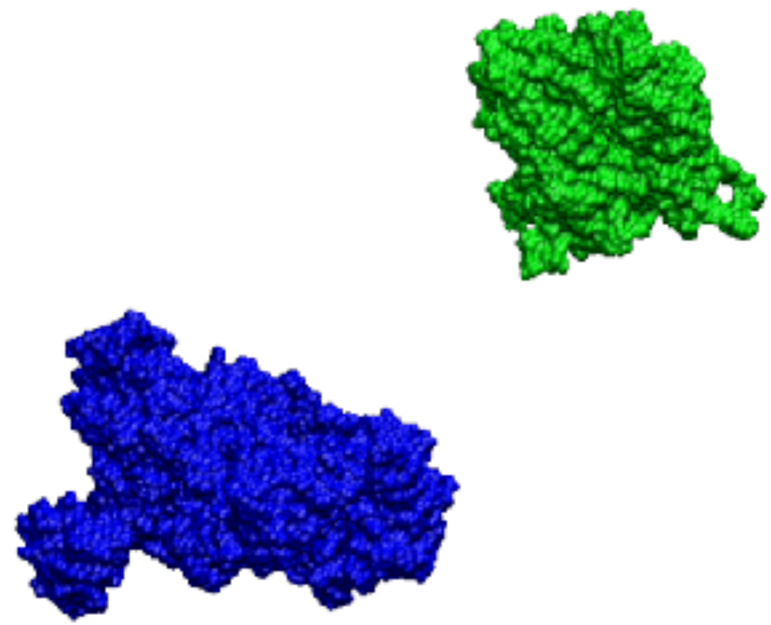
Brownian Dynamics Models of Tropomyosin, Actin and Myosin

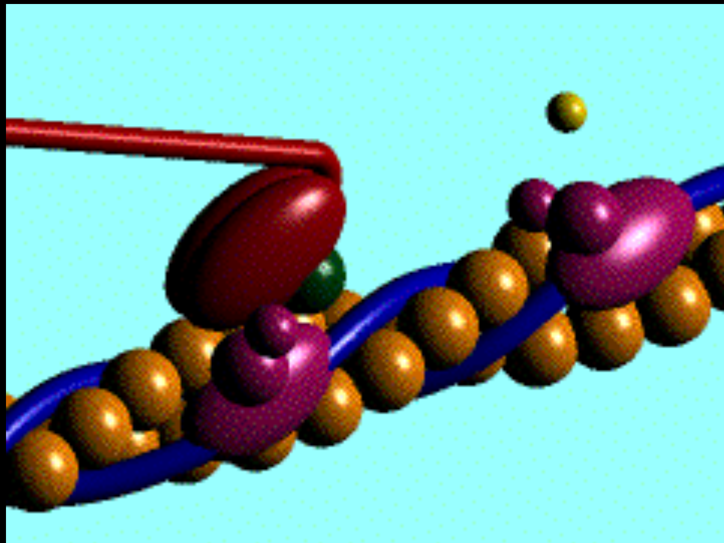


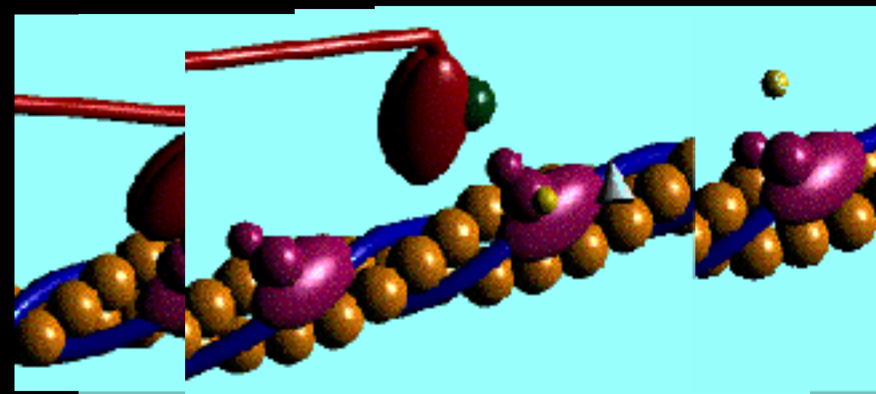
Actin

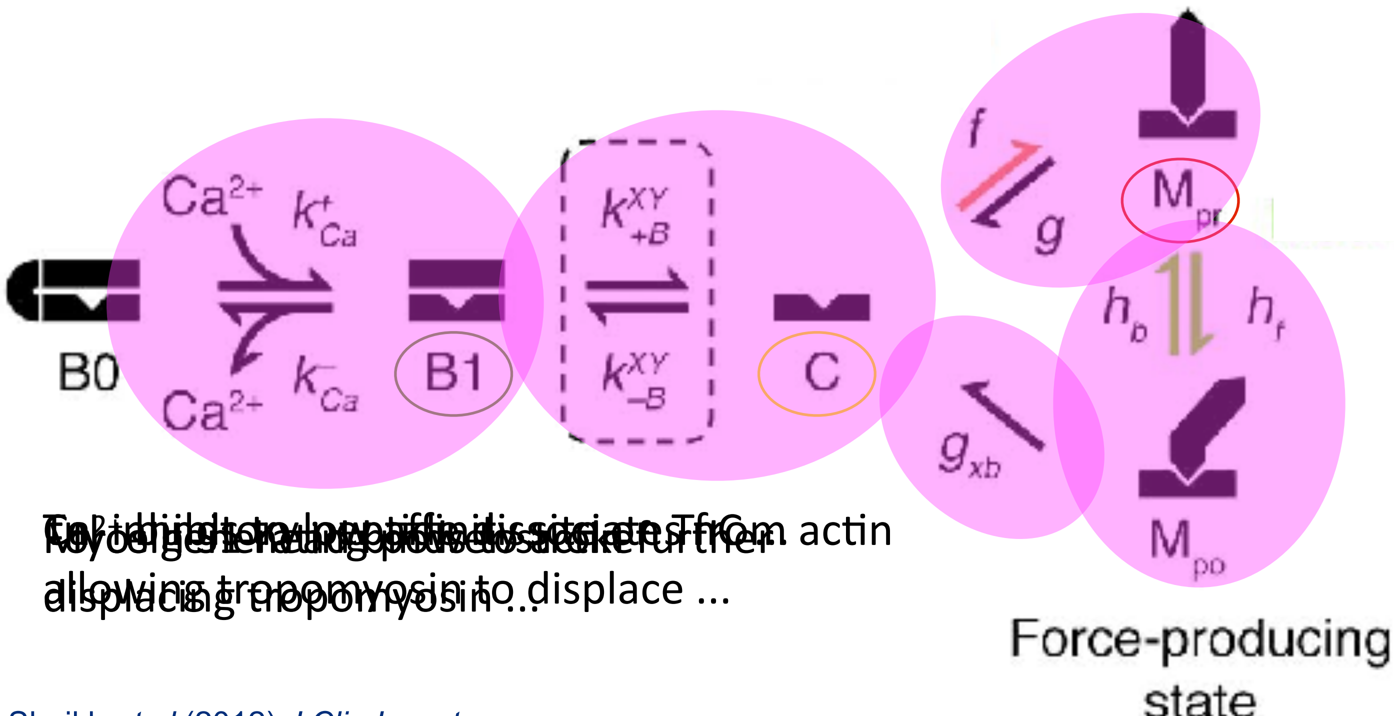


ADP-myosin

Markov Model of Myofilament Interactions





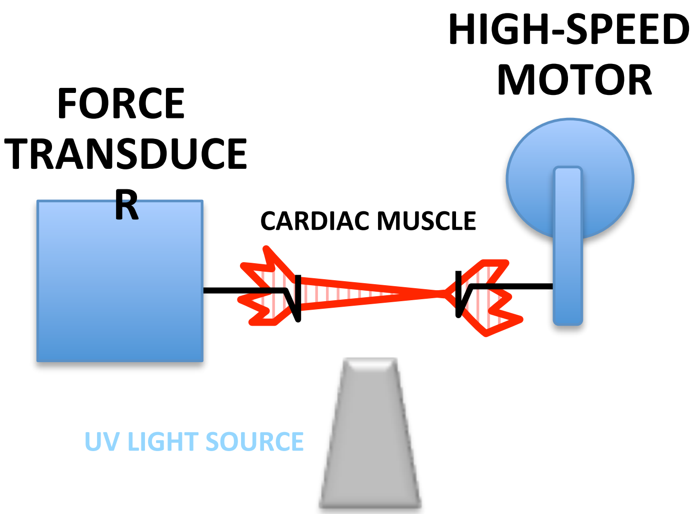


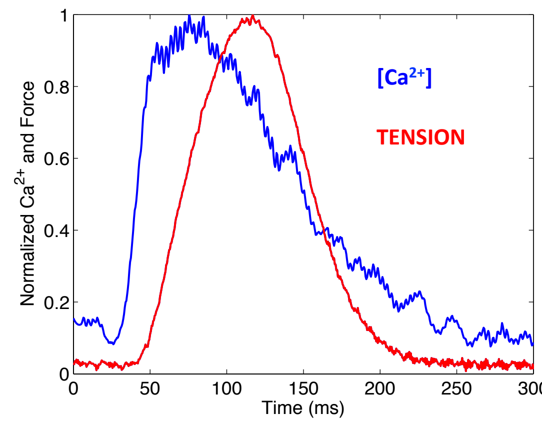
allowing tropomyosin to displace ...

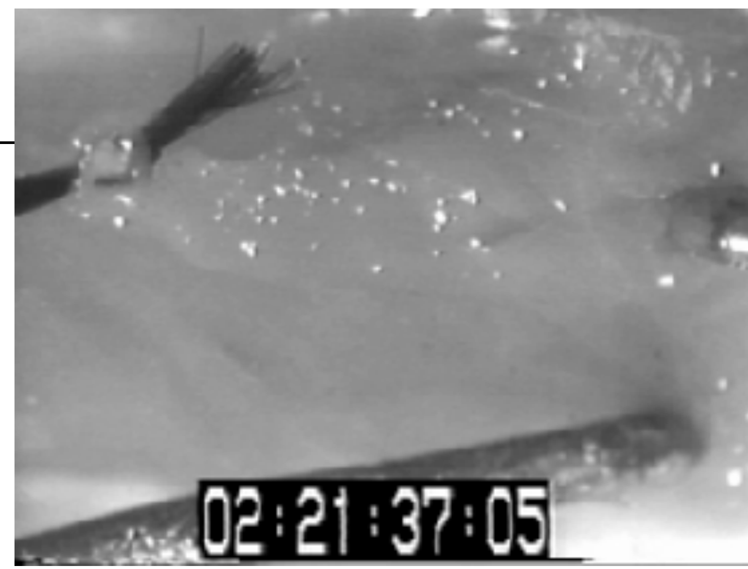
displacing tropomyosin ...

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

Measuring twitch force and calcium







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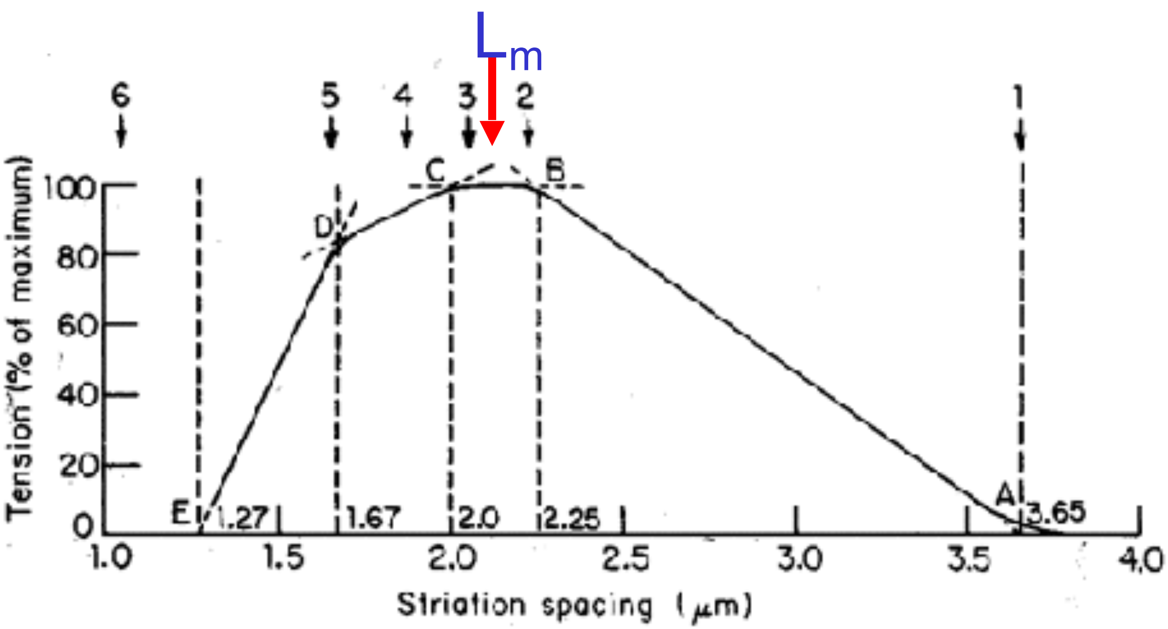
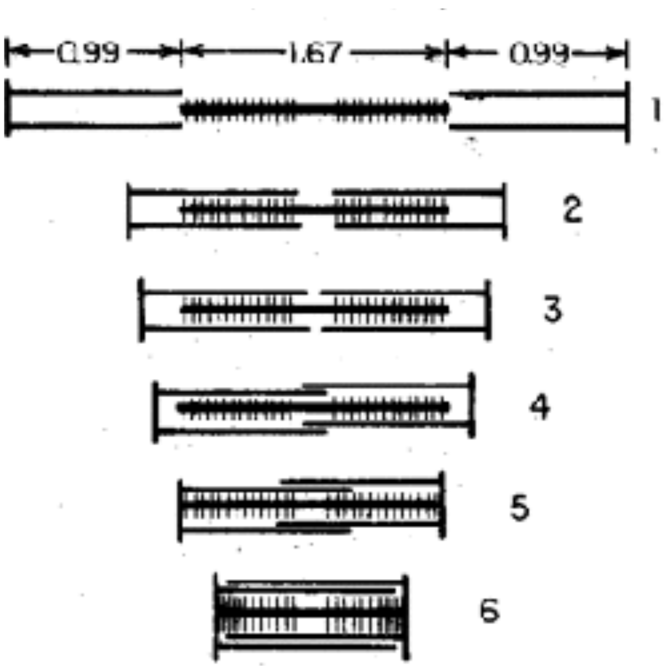
Isometric tension: Sliding filament theory



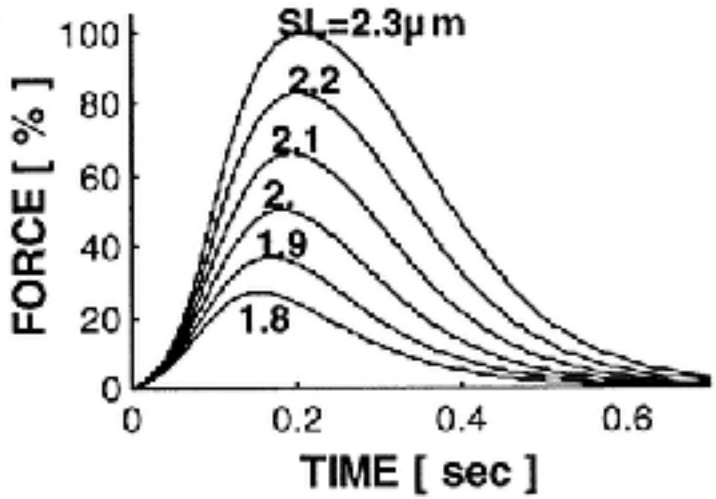
Sliding filament theory

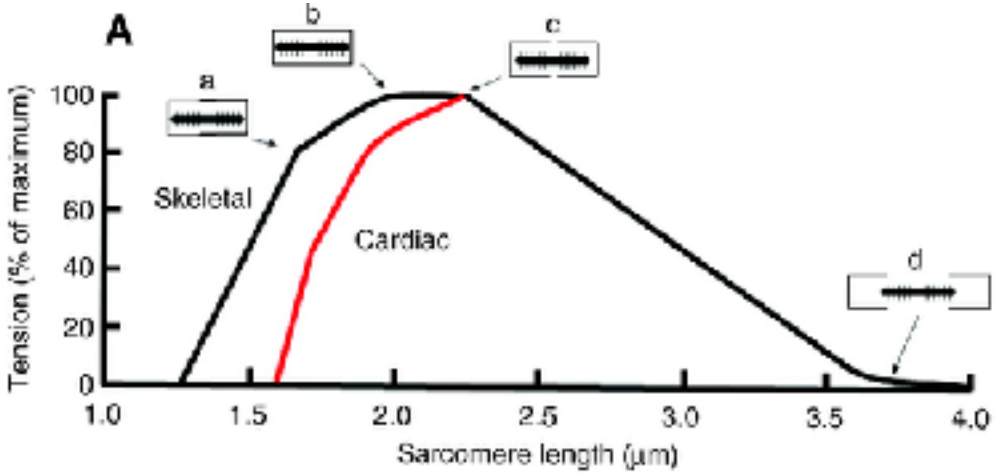


Developed tension versus length for a single isometric fiber of frog *skeletal* muscle

Isometric peak length-tension relation

Peak developed isometric twitch tension (total-passive)



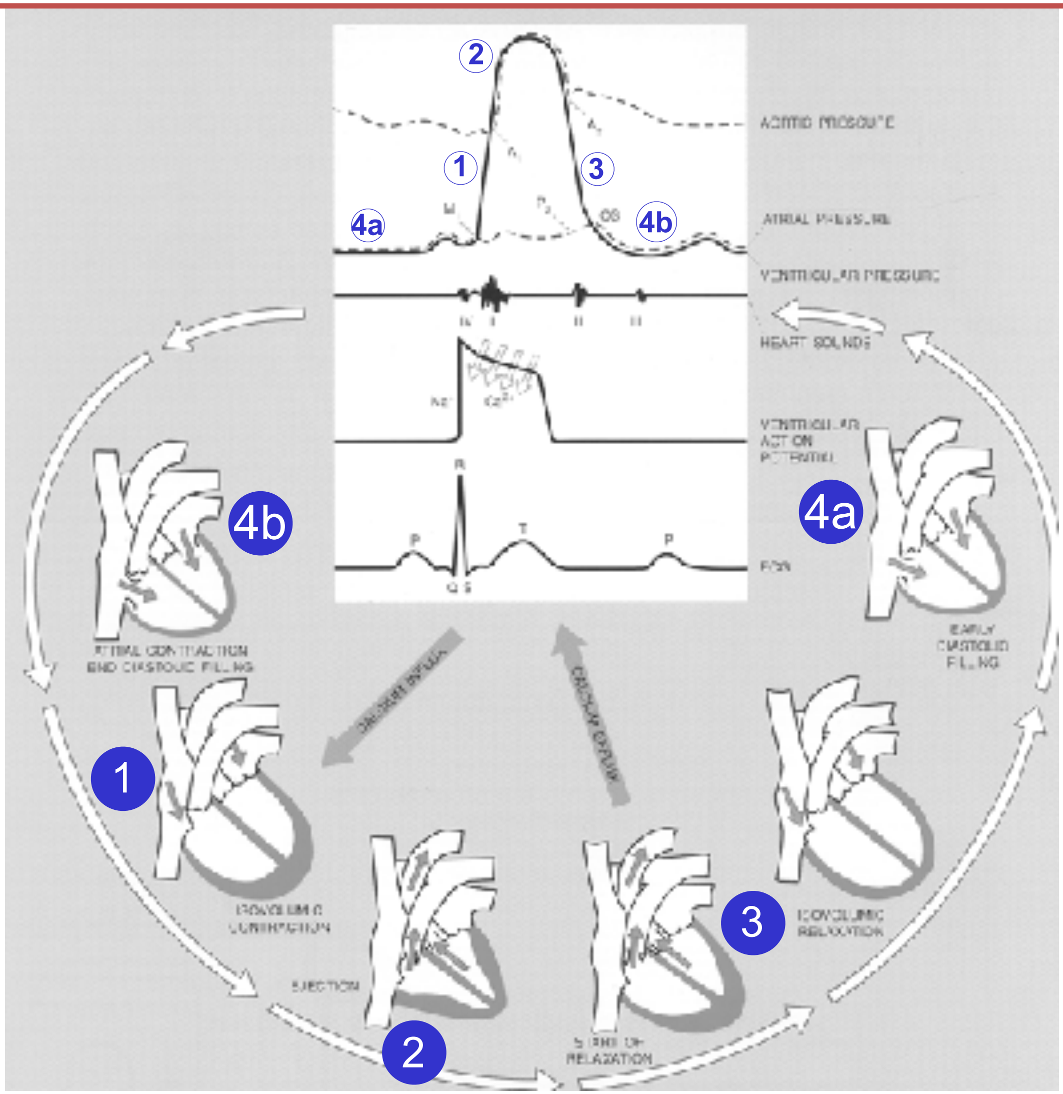


The cardiac cycle

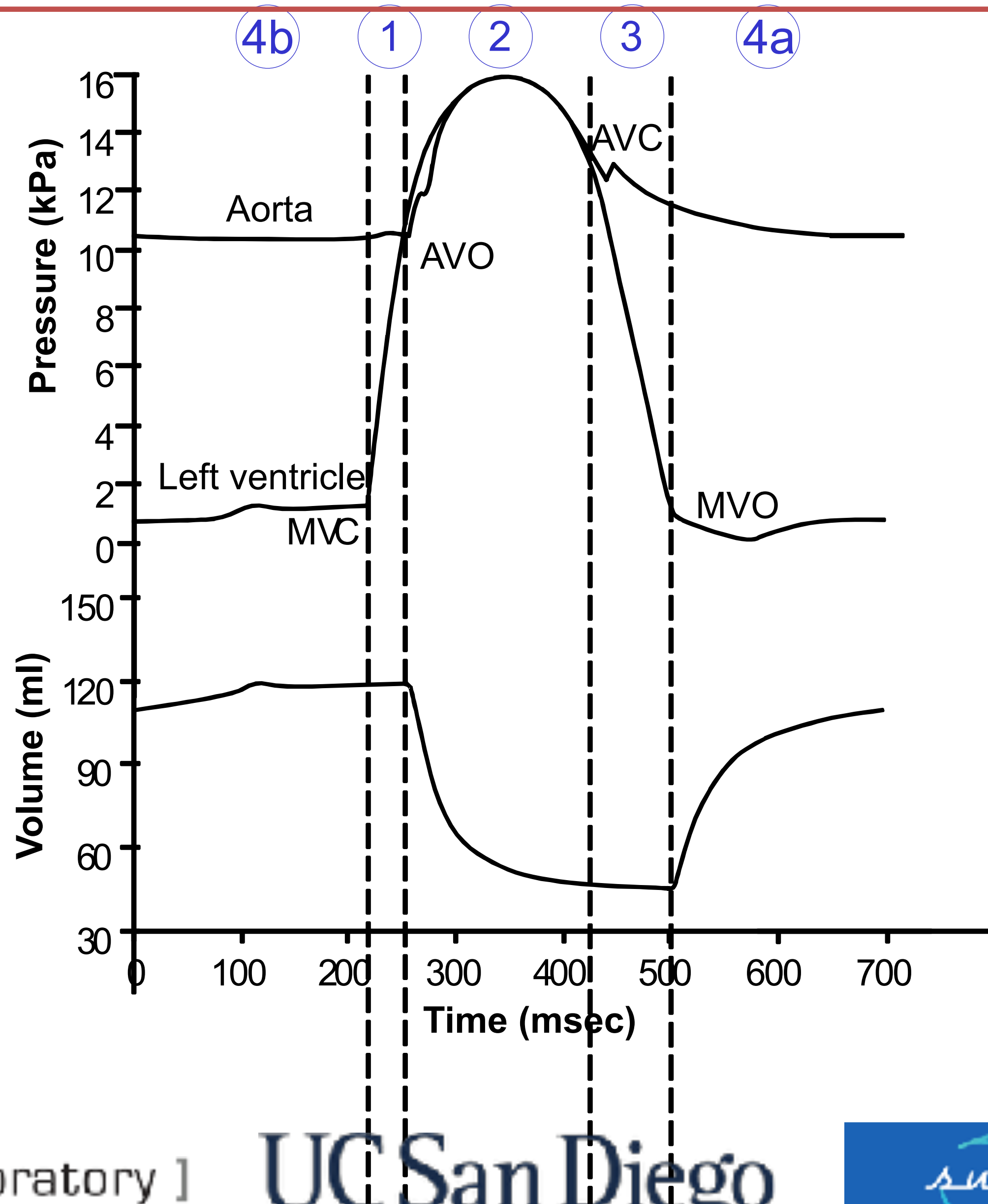
Systole:
1. Isovolumic contraction
2. Ejection

Diastole:

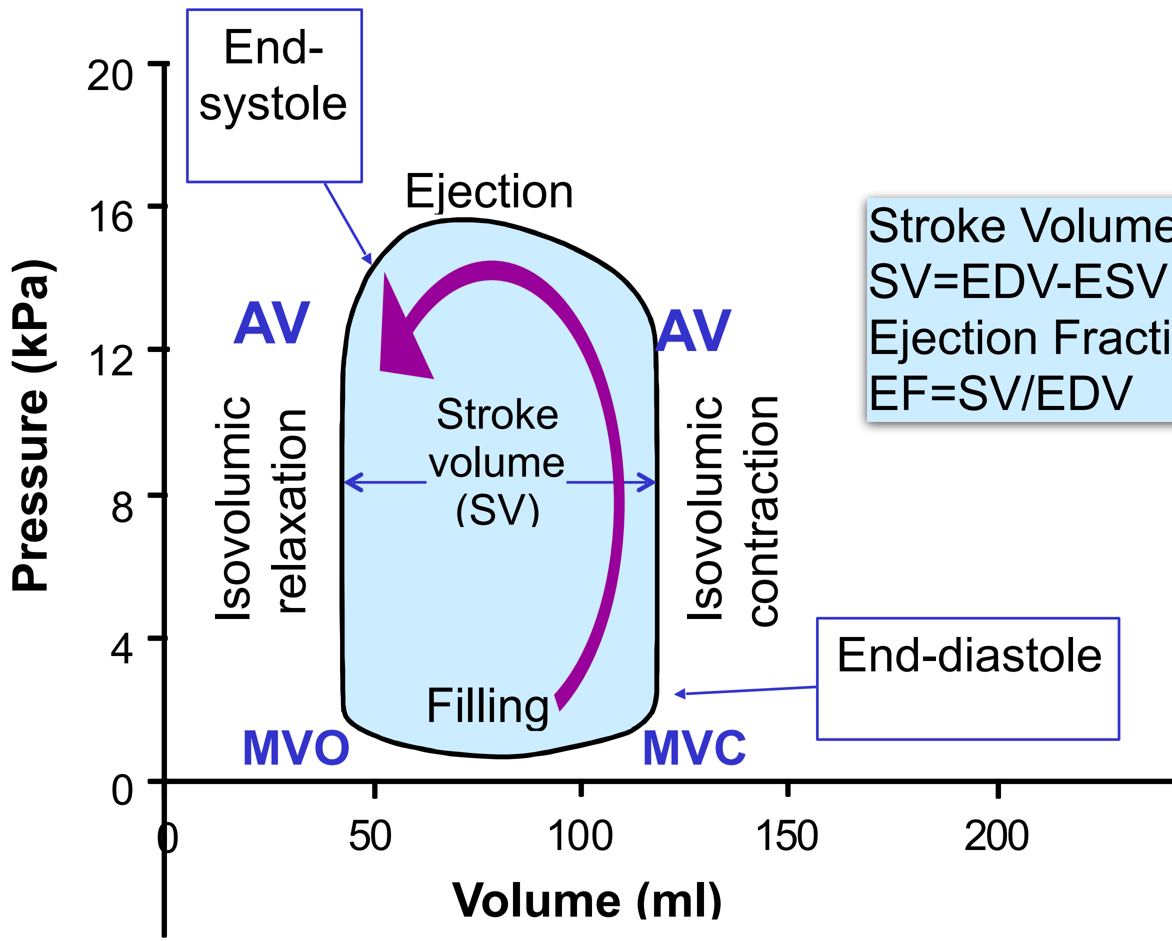
3. Isovolumic relaxation
4. Filling
   a) Early, rapid
   b) Late, diastasis



Ventricular pressure and volume

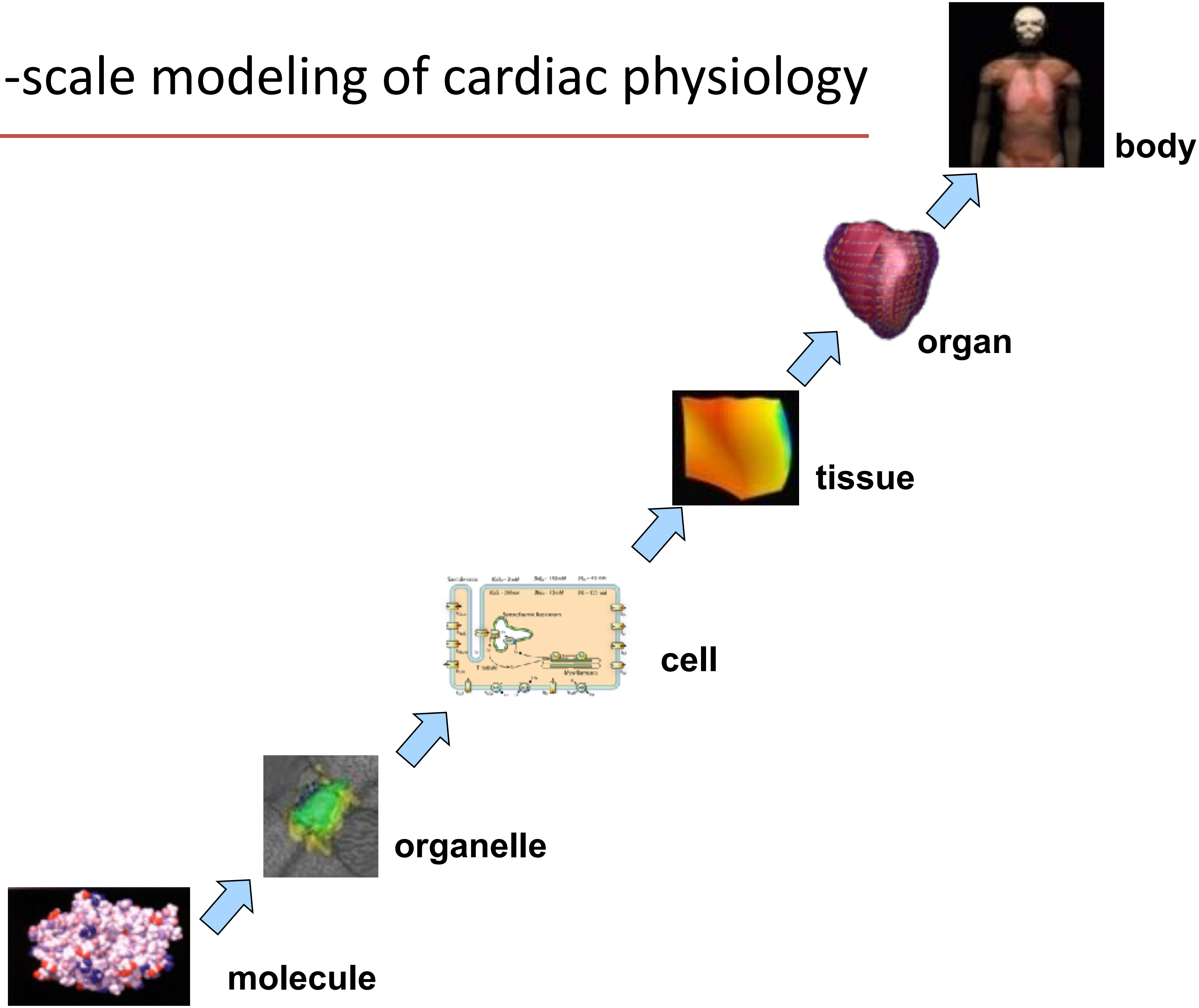


The pressure-volume diagram

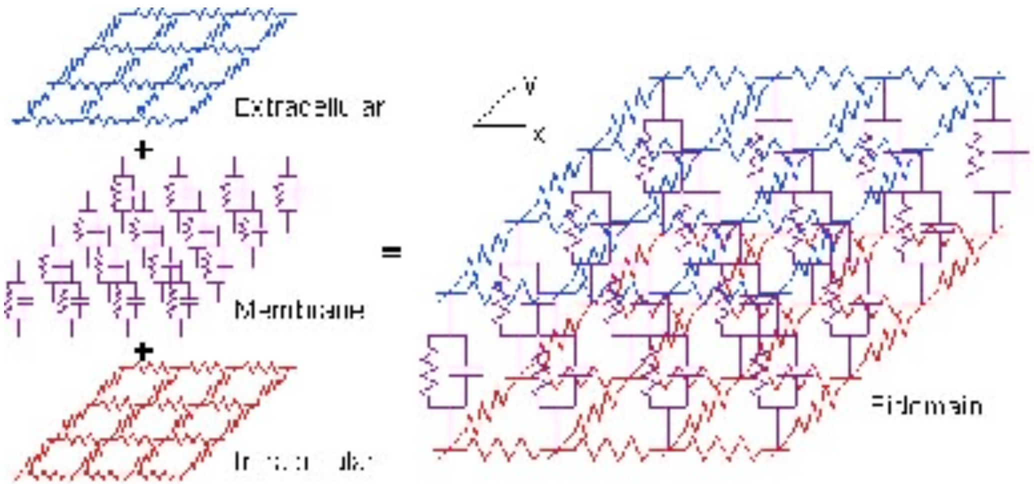


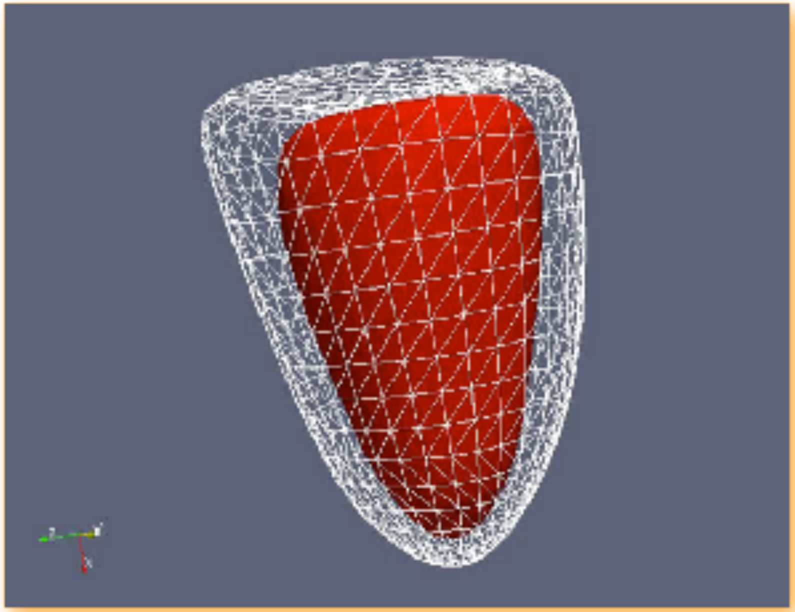
Stroke Volume:
SV=EDV-ESV
Ejection Fraction:
EF=SV/EDV

Multi-scale modeling of cardiac physiology



Discretization for continuum tissue models (heart), or collections of stochastic elements (brain)





$$\nabla \cdot (\boldsymbol{\Sigma}_i \nabla v) + \nabla \cdot (\boldsymbol{\Sigma}_i \nabla v_e) = \chi \left(C_m \frac{\partial v}{\partial t} + I_{\text{ion}} \right)$$

$$\nabla \cdot (\boldsymbol{\Sigma}_i \nabla v) + \nabla \cdot ((\boldsymbol{\Sigma}_i + \boldsymbol{\Sigma}_e) \nabla v_e) = 0$$

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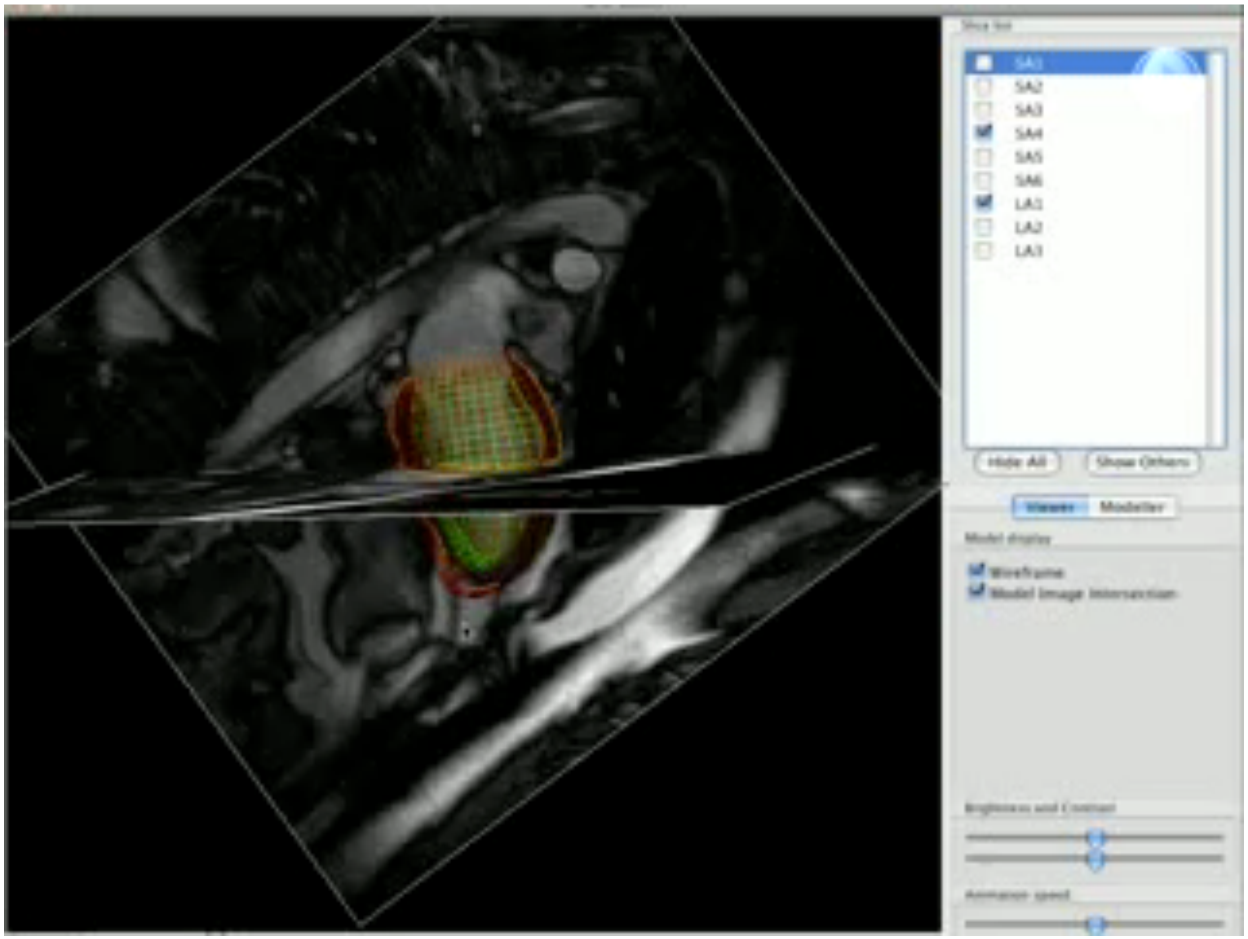
Image-based reconstruction allows geometry-specific simulation



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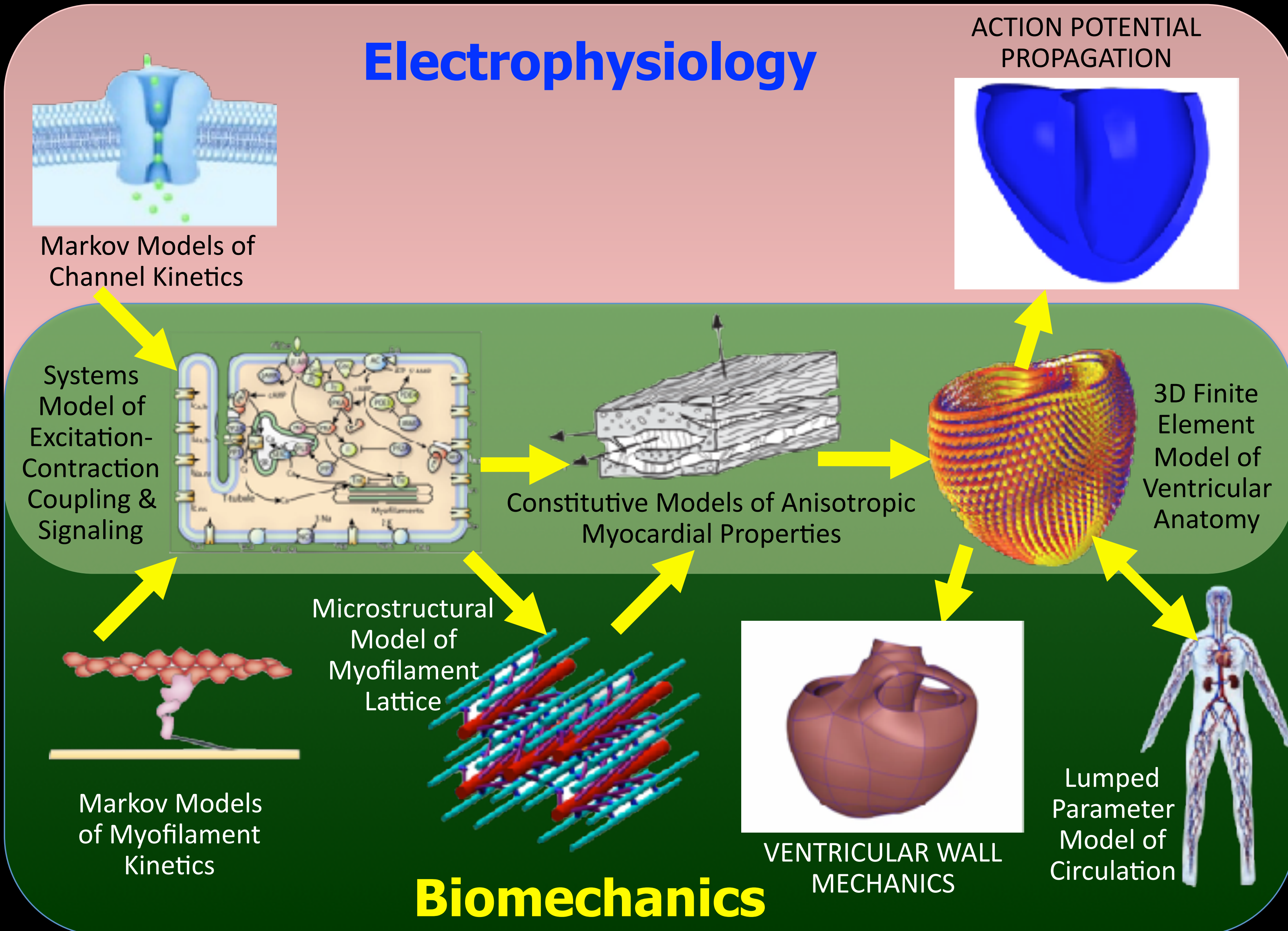
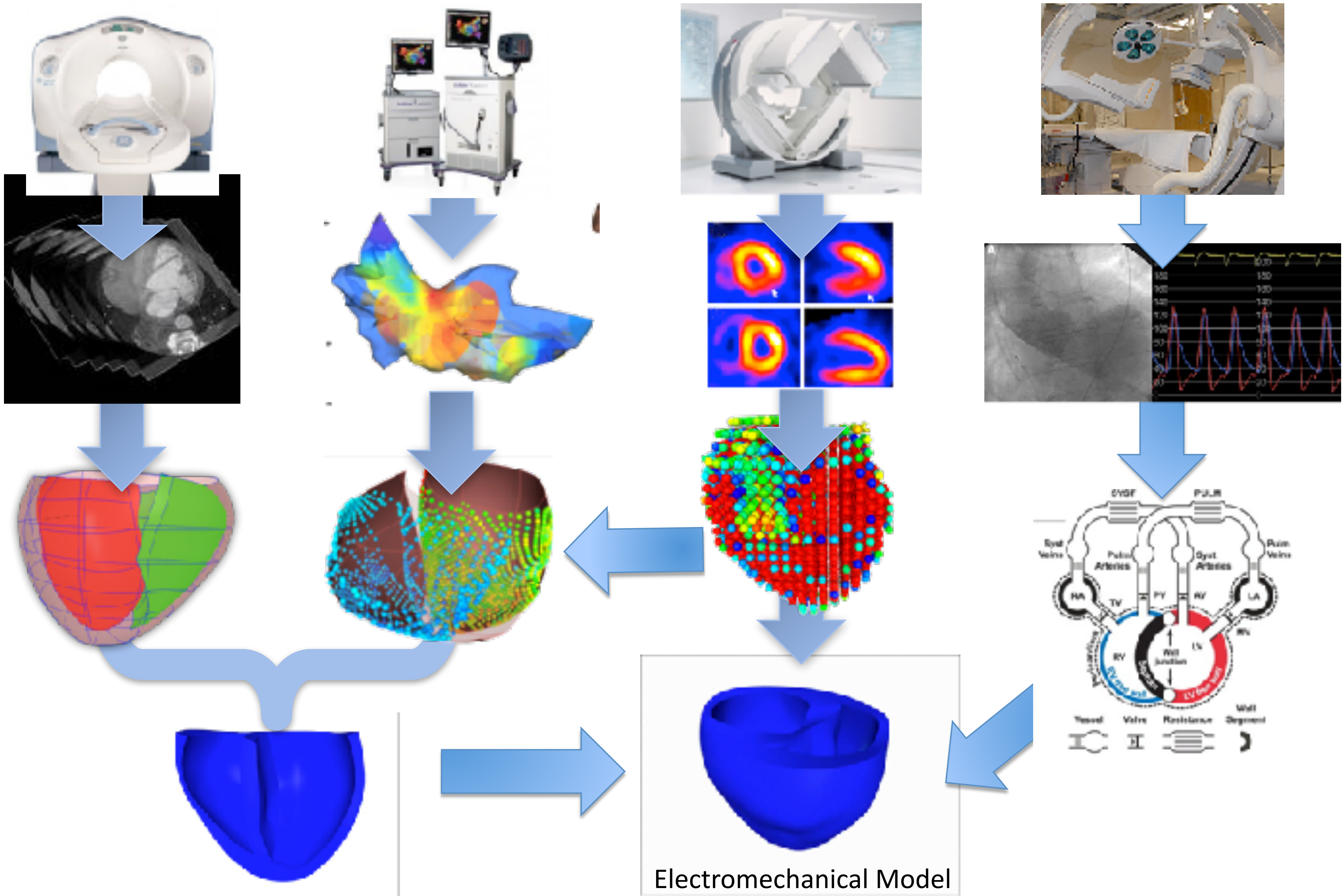

Electrophysiology
ACTION POTENTIAL PROPAGATION
Markov Models of Channel Kinetics
Systems Model of Excitation-Contraction Coupling & Signaling
Constitutive Models of Anisotropic Myocardial Properties
3D Finite Element Model of Ventricular Anatomy
Microstructural Model of Myofilament Lattice
Markov Models of Myofilament Kinetics
VENTRICULAR WALL MECHANICS
Lumped Parameter Model of Circulation
Biomechanics

Patient-specific electromechanical modeling of dyssynchronous heart failure



Today

L2: Physical chemistry and electrochemistry
Dr. Jonas van den Brink

- *Mass action*
- *Gibbs energy*
- *Enzyme kinetics and cooperativity*
- *Reaction rates and equilibria*
- *Code-based exercise*