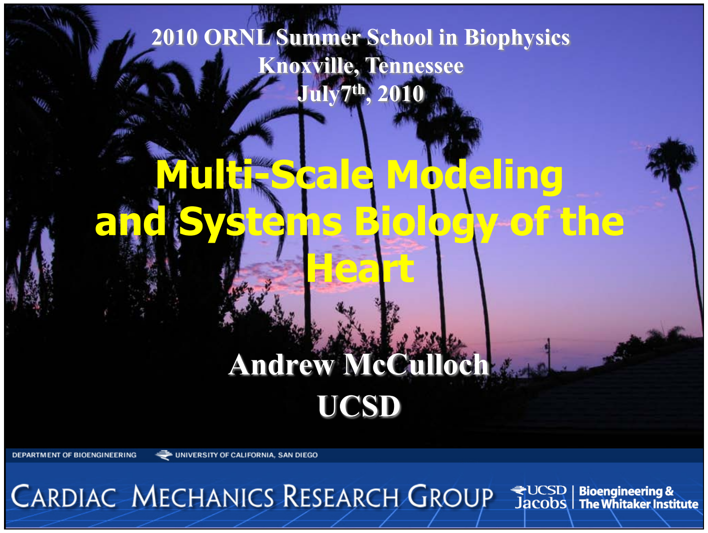


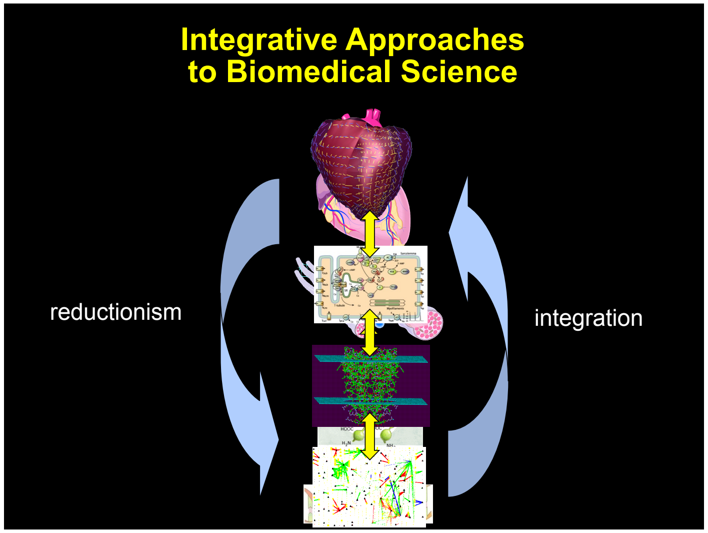
2010 ORNL Summer School in Biophysics
Knoxville, Tennessee
July 7th, 2010

Multi-Scale Modeling and Systems Biology of the Heart

Andrew McCulloch
UCSD

DEPARTMENT OF BIOENGINEERING UNIVERSITY OF CALIFORNIA, SAN DIEGO

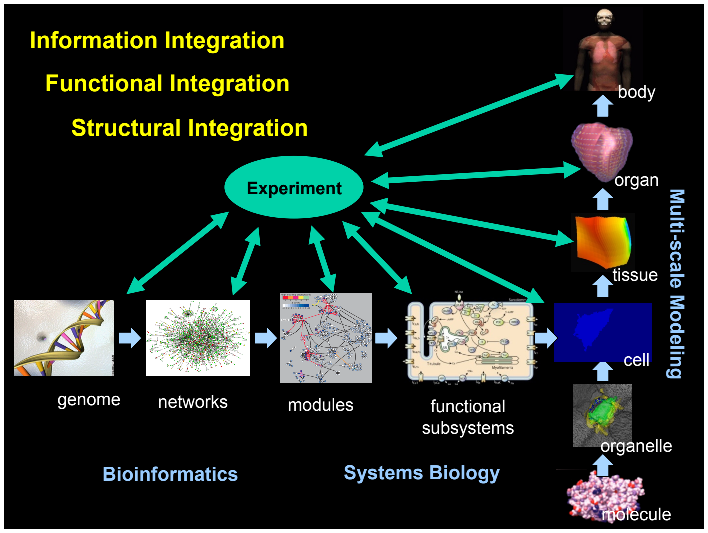
CARDIAC MECHANICS RESEARCH GROUP UCSD Jacobs | Bioengineering & The Whitaker Institute



Integrative Approaches to Biomedical Science

reductionism

integration



Information Integration

Functional Integration

Structural Integration

Experiment

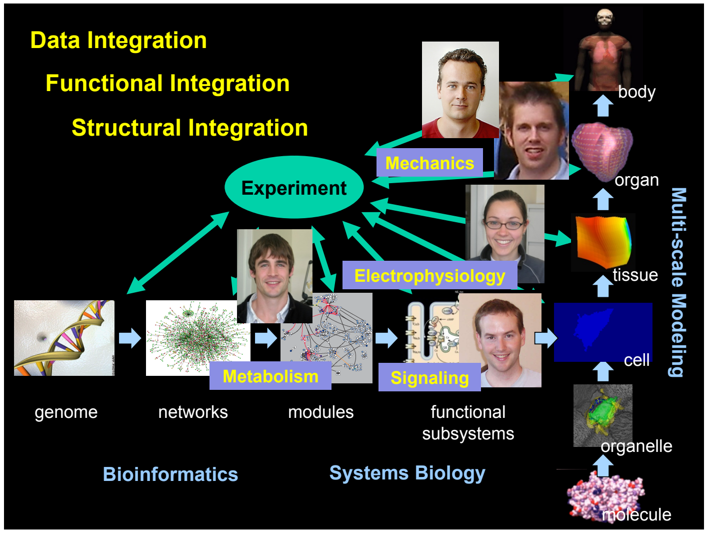
genome
networks
modules
functional subsystems

body
organ
tissue
cell
organelle
molecule

Multi-scale Modeling

Bioinformatics

Systems Biology



Data Integration

Functional Integration

Structural Integration

Experiment

Mechanics
Electrophysiology
Metabolism
Signaling

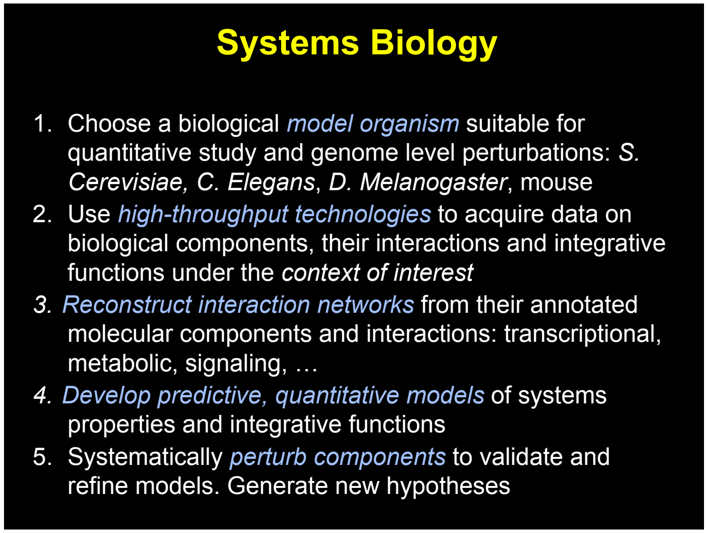
genome
networks
modules
functional subsystems

body
organ
tissue
cell
organelle
molecule

Multi-scale Modeling

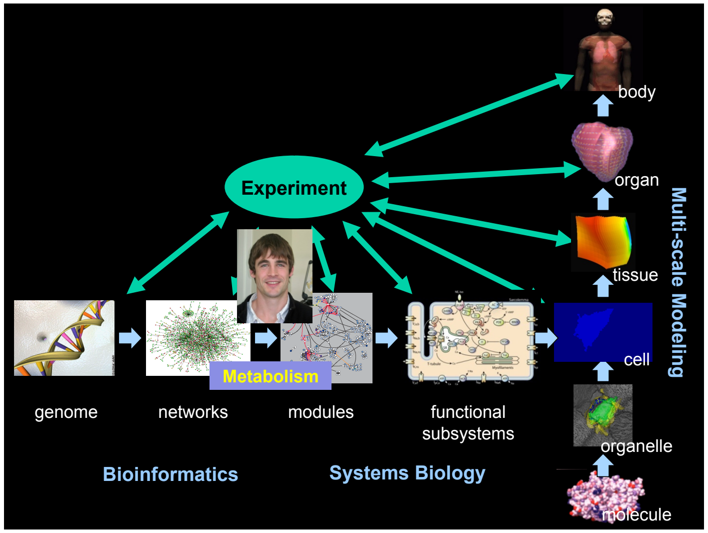
Bioinformatics

Systems Biology



Systems Biology

1. Choose a biological *model organism* suitable for quantitative study and genome level perturbations: *S. Cerevisiae, C. Elegans*, *D. Melanogaster*, mouse
2. Use *high-throughput technologies* to acquire data on biological components, their interactions and integrative functions under the *context of interest*
3. *Reconstruct interaction networks* from their annotated molecular components and interactions: transcriptional, metabolic, signaling, …
4. *Develop predictive, quantitative models* of systems properties and integrative functions
5. Systematically *perturb components* to validate and refine models. Generate new hypotheses



Experiment

Metabolism

genome

networks

modules

functional subsystems

Bioinformatics

Systems Biology

Multi-scale Modeling

body

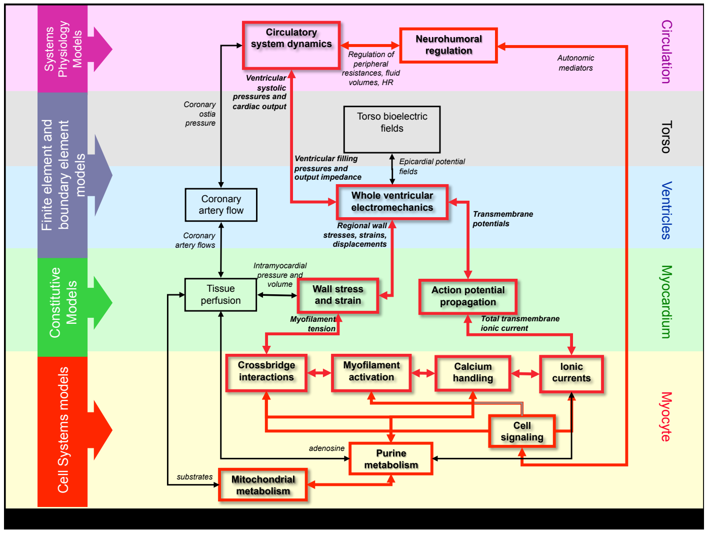
organ

tissue

cell

organelle

molecule



Systems Physiology Models

Finite element and boundary element models

Constitutive Models

Cell Systems models

Circulation

Torso

Ventricles

Myocardium

Myocyte

Circulatory system dynamics

Neurohumoral regulation

Regulation of peripheral resistances, fluid volumes, HR

Autonomic mediators

Ventricular systolic pressures and cardiac output

Coronary ostia pressure

Torso bioelectric fields

Ventricular filling pressures and output impedance

Epicardial potential fields

Coronary artery flow

Whole ventricular electromechanics

Transmembrane potentials

Coronary artery flows

Regional wall stresses, strains, displacements

Intramyocardial pressure and volume

Tissue perfusion

Wall stress and strain

Action potential propagation

Myofilament tension

Total transmembrane ionic current

Crossbridge interactions

Myofilament activation

Calcium handling

Ionic currents

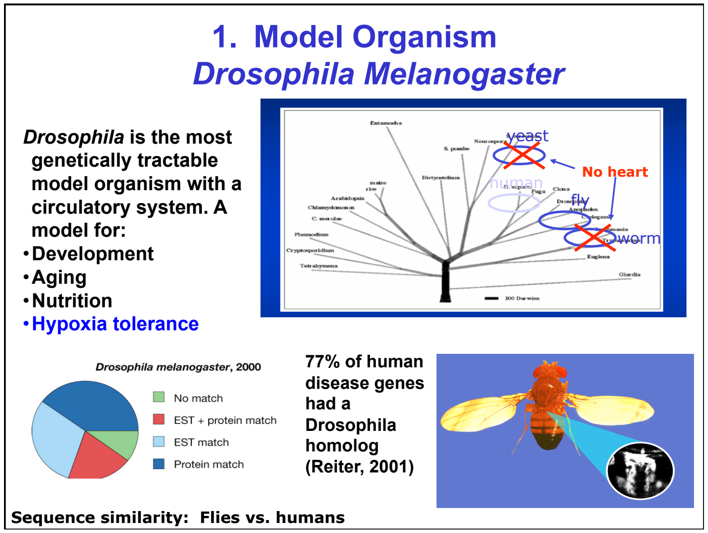
Cell signaling

adenosine

Purine metabolism

substrates

Mitochondrial metabolism



1. Model Organism
Drosophila Melanogaster

Drosophila **is the most genetically tractable model organism with a circulatory system. A model for:**

- **Development**
- **Aging**
- **Nutrition**
- **Hypoxia tolerance**

Entamoeba
S. pombe
Neurospora
yeast
No heart
Dictyostelium
human
maize
rice
Fugu
Ciona
Arabidopsis
Drosophila
fly
Chlamydomonas
Anopheles
C. merolae
C. elegans
Plasmodium
worm
Cryptosporidium
Euglena
Tetrahymena
Giardia
100 Darwins

***Drosophila melanogaster*, 2000**

🟩 No match

🟥 EST + protein match

🟦 EST match

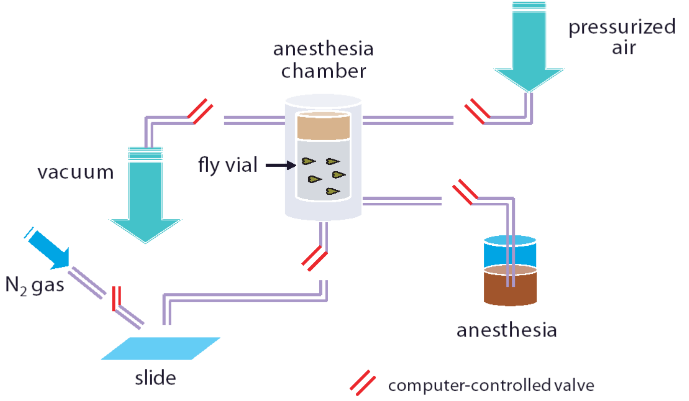
🟦 Protein match

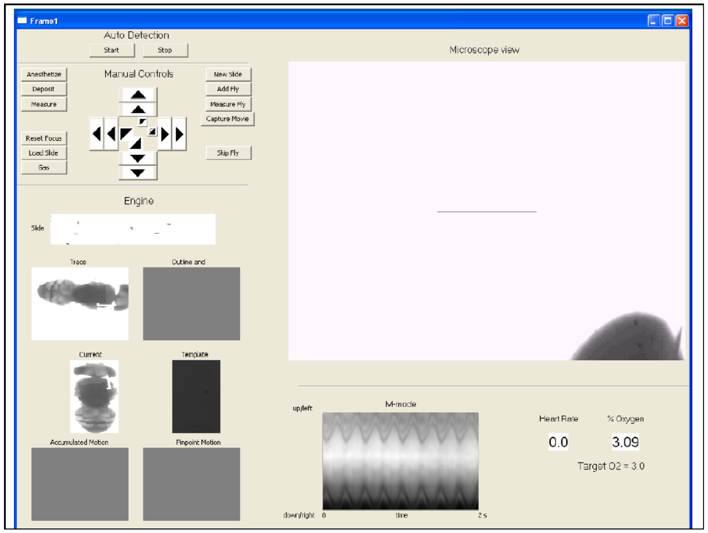
77% of human disease genes had a Drosophila homolog (Reiter, 2001)

Sequence similarity: Flies vs. humans

2. High Throughput Technologies
Automated Cardiac Phenotyping

Automated anesthesia and mounting


pressurized air
anesthesia chamber
vacuum
fly vial
N_2 gas
anesthesia
slide
computer-controlled valve


Frame1
Auto Detection
Start
Stop
Microscope view
Anesthetize
Deposit
Measure
Manual Controls
New Slide
Add Fly
Measure Fly
Capture Movie
Reset Focus
Load Slide
Gas
Skip Fly
Engine
Side
Trace
Outline and
Current
Template
Accumulated Motion
Pinpoint Motion
M-mode
up/left
down/right
0
time
2 s

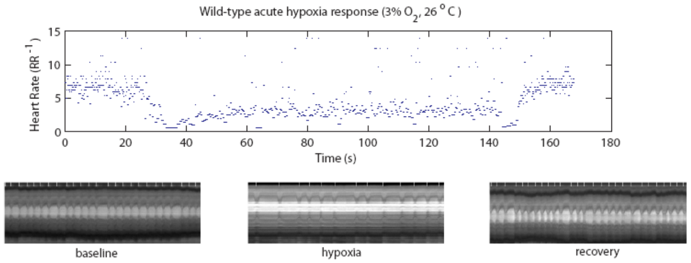
Heart Rate 0.0

% Oxygen 3.09

Target O2 = 3.0

Drosophila cardiac hypoxia

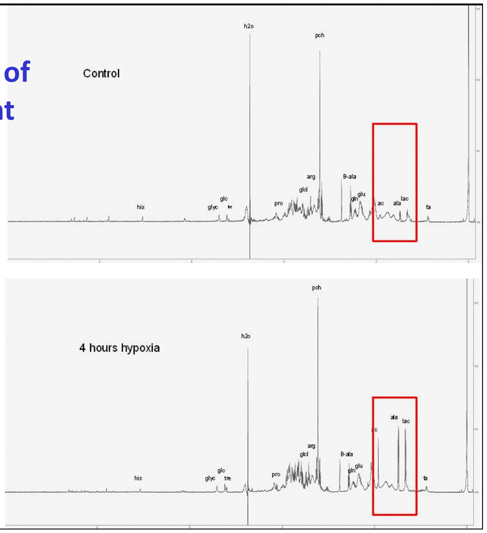
The fly heart organ responds quickly to oxygen levels, suggesting regulatory ***control***



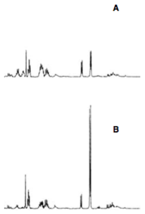
Feala JD, Omens JH, Paternostro G, McCulloch AD (2008) Discovering regulators of the drosophila cardiac hypoxia response using automated phenotyping technology.*Ann NY Acad Sci* 2008;1123:169-177

^{1}H NMR spectroscopy of hypoxic flight muscle

- 0.5% O_2
- 240 minutes



MAMMALIAN TISSUE:



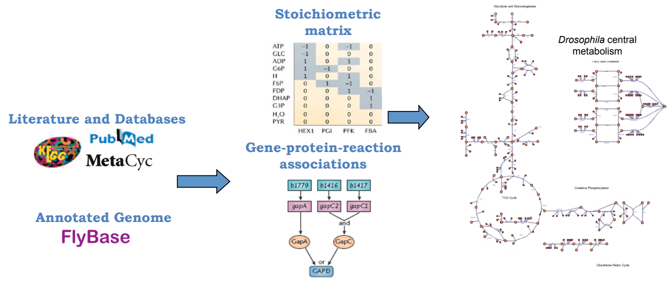
Troy H et. al. Metabolomics 2005; 1: 293-303

3. Reconstruct Interaction Networks

Genome-Scale Model of Drosophila Central Metabolism

- 142 genes, 115 reactions (74 associated with genes), 7 pathways
- Glycolysis, TCA cycle, oxidative phosphorylation, β –oxidation, amino acid degradation, glutathione redox cycle, superoxide production and scavenging
- Elementally- and charge-balanced

Metabolic network reconstruction



Literature and Databases

PubMed

MetaCyc

Annotated Genome

FlyBase

Stoichiometric matrix

	HEX1	PGI	PFK	FBA
ATP	−1	0	−1	0
GLC	−1	0	0	0
ADP	1	0	1	0
G6P	1	−1	0	0
H	1	0	1	0
F6P	0	1	−1	0
FDP	0	0	1	−1
DHAP	0	0	0	1
G3P	0	0	0	1
H_2O	0	0	0	0
PYR	0	0	0	0

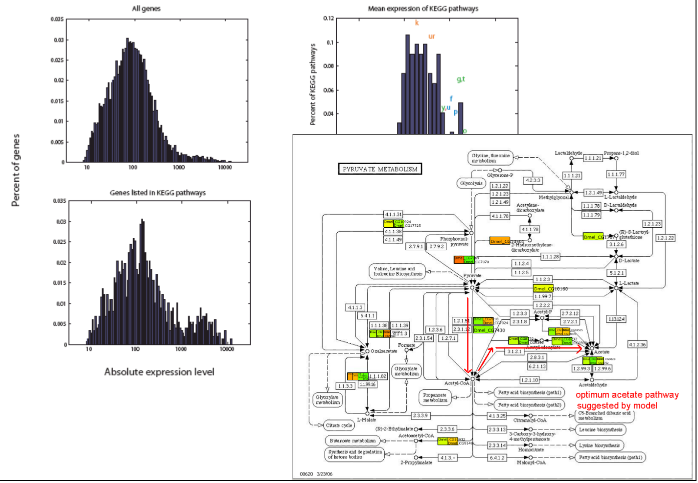
Gene-protein-reaction associations

KEGG
b1779
b1416
b1417
gapA
gapC2
gapC1
and
GapA
GapC
or
GAPD
Glycolysis and Gluconeogenesis
Fatty acid Oxidation
TCA Cycle
Oxidative Phosphorylation
Glutathione Redox Cycle

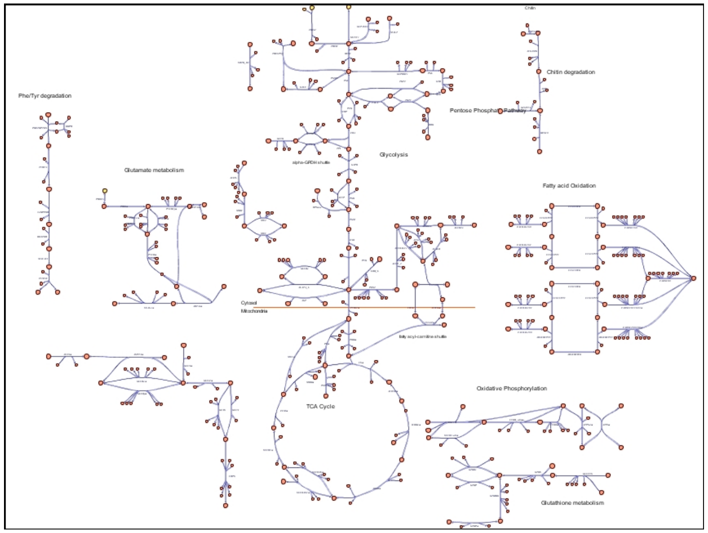
Drosophila central metabolism

Feala JD *et al* (2008) *Prog Biophys Molec Biol* 96(1-3):209-225

Gene Expression Profile (adult thorax)

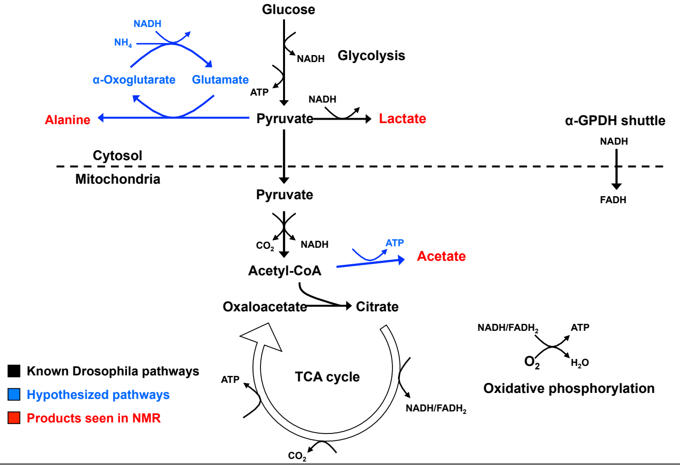


optimum acetate pathway suggested by model



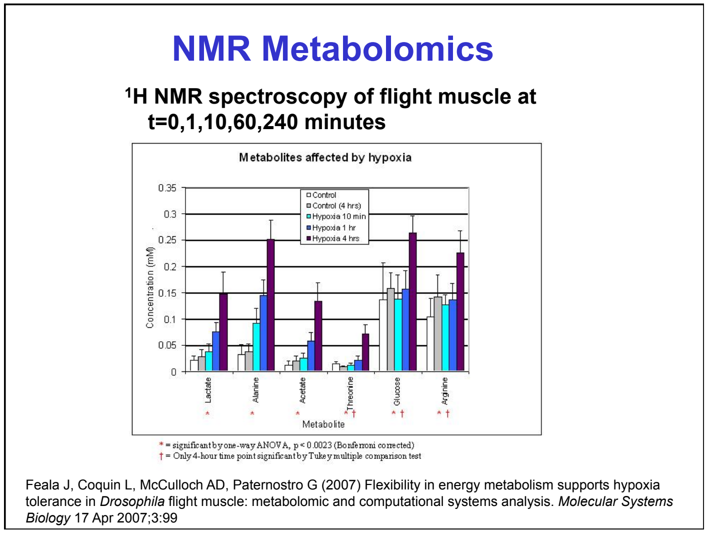
Chitin
Chitin degradation
Phe/Tyr degradation
Glutamate metabolism
Pentose Phosphate Pathway
Glycolysis
alpha-GPDH shuttle
Fatty acid Oxidation
Cytosol
Mitochondria
fatty acyl-carnitine shuttle
TCA Cycle
Oxidative Phosphorylation
Glutathione metabolism

Main Energetic Pathways in Model



Glucose
NADH
Glycolysis
ATP
NADH
NH_4
NADH
α-Oxoglutarate
Glutamate
Alanine
Pyruvate
Lactate
α-GPDH shuttle
NADH
Cytosol
Mitochondria
FADH
Pyruvate
CO_2
NADH
ATP
Acetate
Acetyl-CoA
Oxaloacetate
Citrate
NADH/$FADH_2$
ATP
O_2
H_2O
Oxidative phosphorylation
ATP
TCA cycle
NADH/$FADH_2$
CO_2

- ■ Known Drosophila pathways
- 🟦 Hypothesized pathways
- 🟥 Products seen in NMR



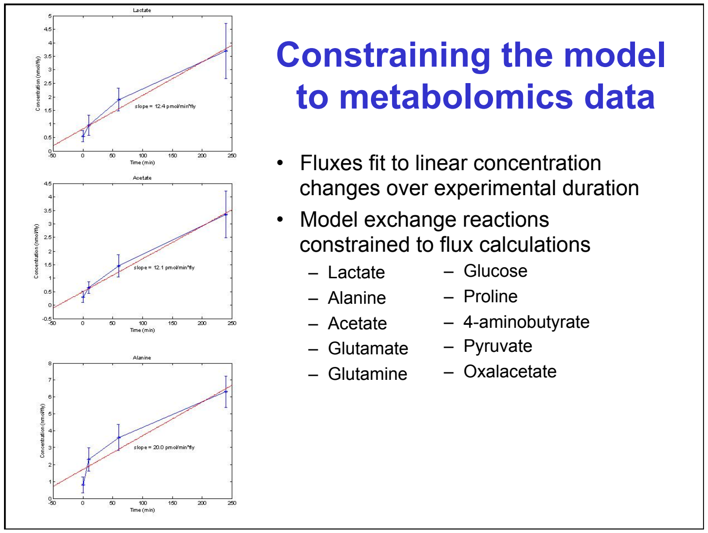
NMR Metabolomics

^{1}H NMR spectroscopy of flight muscle at t=0,1,10,60,240 minutes

* = significant by one-way ANOVA, $p < 0.0023$ (Bonferroni corrected)

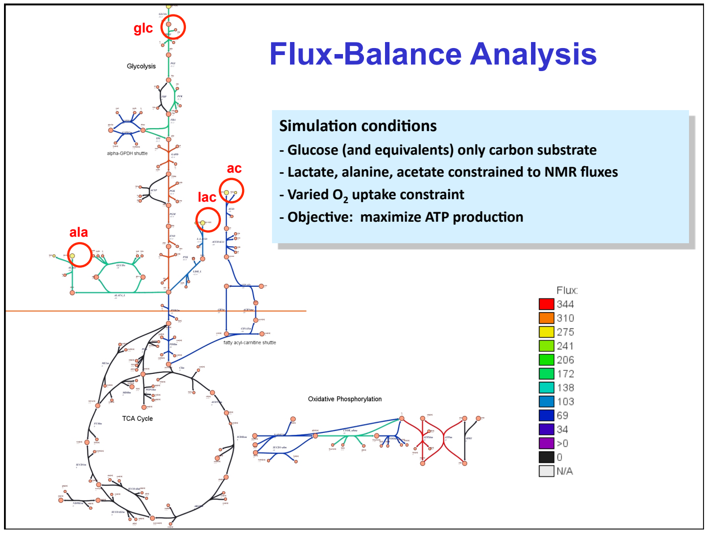
† = Only 4-hour time point significant by Tukey multiple comparison test

Feala J, Coquin L, McCulloch AD, Paternostro G (2007) Flexibility in energy metabolism supports hypoxia tolerance in *Drosophila* flight muscle: metabolomic and computational systems analysis. *Molecular Systems Biology* 17 Apr 2007;3:99



Constraining the model to metabolomics data

- Fluxes fit to linear concentration changes over experimental duration
- Model exchange reactions constrained to flux calculations
  - Lactate
  - Alanine
  - Acetate
  - Glutamate
  - Glutamine
  - Glucose
  - Proline
  - 4-aminobutyrate
  - Pyruvate
  - Oxalacetate

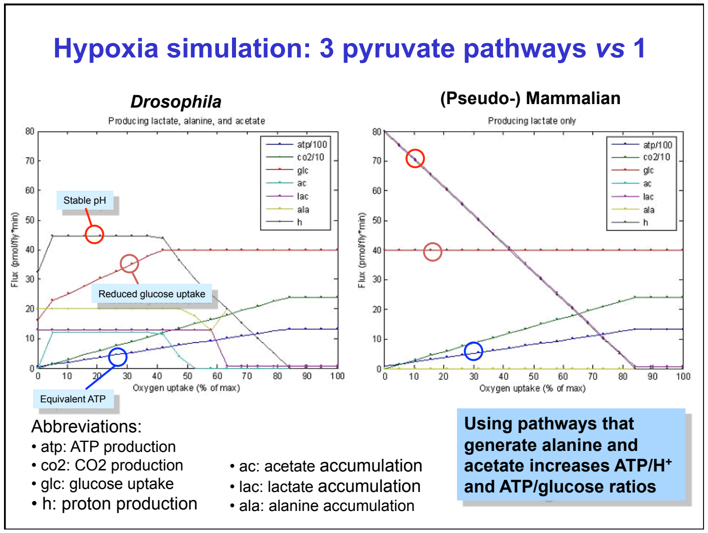


glc
Glycolysis
alpha-GPDH shuttle
ac
lac
ala
fatty acyl-carnitine shuttle
TCA Cycle
Oxidative Phosphorylation
Flux:
344
310
275
241
206
172
138
103
69
34
>0
0
N/A

Flux-Balance Analysis

Simulation conditions

- Glucose (and equivalents) only carbon substrate
- Lactate, alanine, acetate constrained to NMR fluxes
- Varied O_2 uptake constraint
- Objective: maximize ATP production



Hypoxia simulation: 3 pyruvate pathways *vs* 1

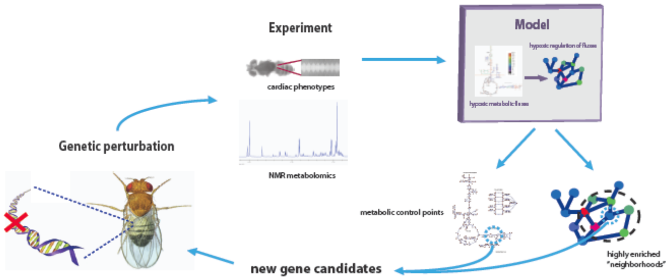
Abbreviations:

- atp: ATP production
- co2: CO2 production
- glc: glucose uptake
- h: proton production
- ac: acetate accumulation
- lac: lactate accumulation
- ala: alanine accumulation

Using pathways that generate alanine and acetate increases ATP/H$^+$ and ATP/glucose ratios

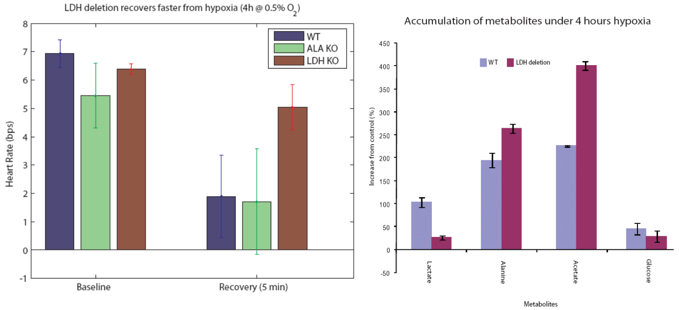
5. Analyze Perturbations

Perturbation analysis of hypoxic myocardium


Experiment
cardiac phenotypes
NMR metabolomics
Model
hypoxic regulation of fluxes
hypoxic metabolic fluxes
Genetic perturbation
metabolic control points
highly enriched "neighborhoods"
new gene candidates

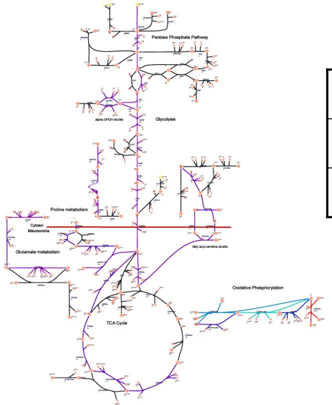
LDH Knockout

Heart Rate Recovery and Metabolite Accumulation



Feala J, Coquin L, McCulloch AD, Paternostro G (2007) Flexibility in energy metabolism supports hypoxia tolerance in *Drosophila* flight muscle: metabolomic and computational systems analysis. *Molecular Systems Biology* 17 Apr 2007;3:99

Flux Balance Analysis of LDH deletion


Pentose Phosphate Pathway
alpha-GPDH shuttle
Glycolysis
Proline metabolism
Cytosol
Mitochondria
Glutamate metabolism
fatty acyl-carnitine shuttle
Oxidative Phosphorylation
TCA Cycle

	WT	LDH KO
ATP/H$^+$	16.8	22.9
ATP/glucose	27.0	34.1

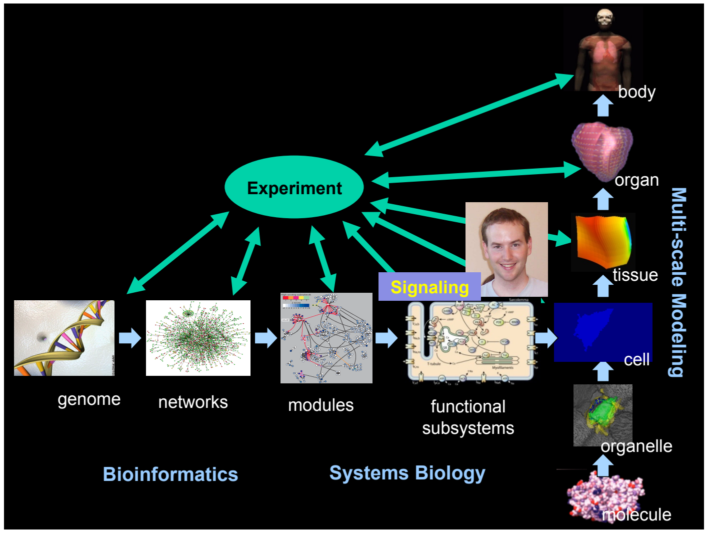
6. Generate New Hypotheses

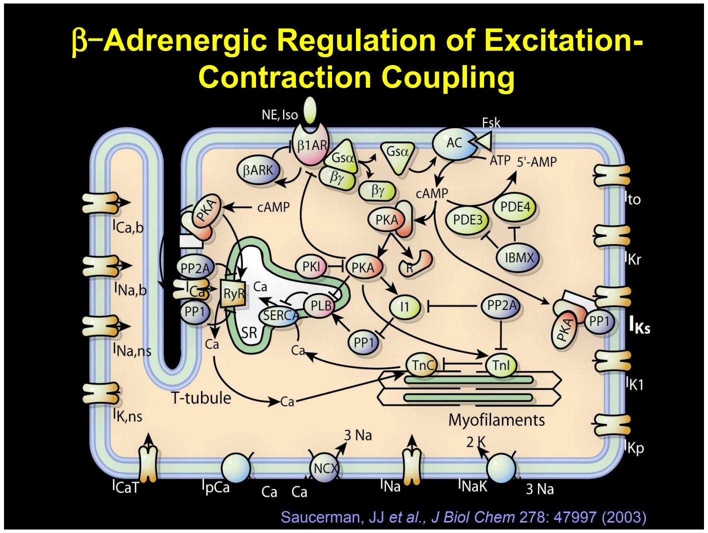
Pathway mechanisms of altered hypoxia tolerance

degraded ← Hypoxia tolerance → improved

Aging	Wild type	Adapted
↓ ATP/H$^+$ ↓ ATP/substrate ↑ pyruvate → acetate ↓ recovery of respiration		↑ ATP/H$^+$ ↑ ATP/substrate ↓ pyruvate carboxylase flux ↓ glycolysis ↑ complex I vs complex II ↑ respiratory efficiency

Coquin L, Feala JD, McCulloch AD, Paternostro G (2008) Metabolomic and flux-balance analysis of age-related decline of hypoxia tolerance in Drosophila muscle tissue. *Mol Syst Biol* 2008;4:233

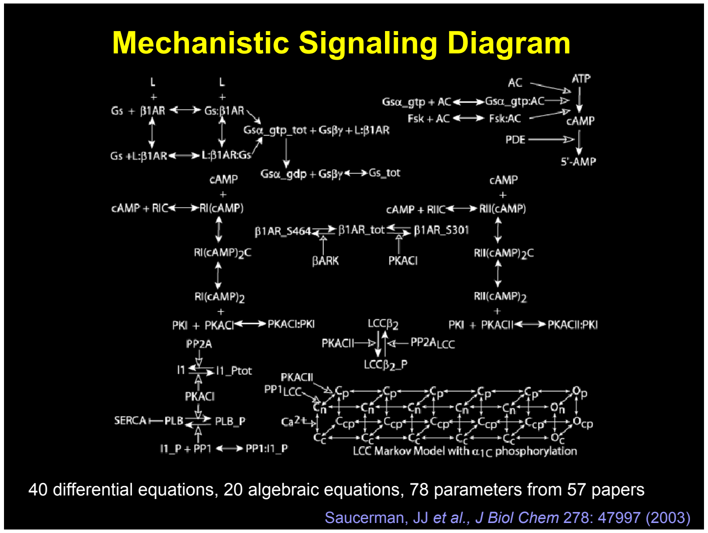

body
organ
tissue
cell
organelle
molecule
Multi-scale Modeling
Experiment
Signaling
genome
networks
modules
functional subsystems
Bioinformatics
Systems Biology



β−Adrenergic Regulation of Excitation-Contraction Coupling

NE, Iso
β1AR
Gsα
βγ
βARK
Gsα
βγ
AC
Fsk
ATP
5'-AMP
cAMP
PDE4
PDE3
IBMX
PKA
cAMP
PKA
PKI
PKA
R
PP2A
Ca
RyR
PP1
Ca
SERCA
PLB
SR
Ca
I1
PP2A
PP1
TnC
TnI
PKA
PP1
T-tubule
Ca
Myofilaments
3 Na
2 K
NCX
$I_{Ca,b}$
$I_{Na,b}$
$I_{Na,ns}$
$I_{K,ns}$
I_{CaT}
I_{pCa}
Ca
Ca
I_{Na}
I_{NaK}
3 Na
I_{to}
I_{Kr}
I_{Ks}
I_{K1}
I_{Kp}

Saucerman, JJ *et al.*, *J Biol Chem* 278: 47997 (2003)

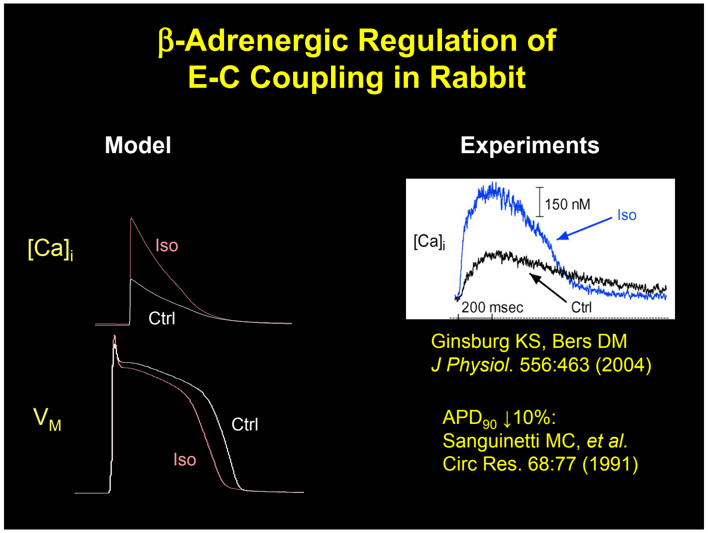


Mechanistic Signaling Diagram

L + Gs + β1AR ⟷ Gs:β1AR
L + Gs:β1AR
Gs +L:β1AR ⟷ L:β1AR:Gs
Gsα_gtp_tot + Gsβγ + L:β1AR
Gsα_gdp + Gsβγ ⟷ Gs_tot
AC
ATP
Gsα_gtp + AC ⟷ Gsα_gtp:AC
Fsk + AC ⟷ Fsk:AC
cAMP
PDE
5'-AMP
cAMP + RIC ⟷ RI(cAMP)
RI(cAMP)2C
RI(cAMP)2
PKI + PKACI ⟷ PKACI:PKI
β1AR_S464 ⇄ β1AR_tot ⇄ β1AR_S301
βARK
PKACI
cAMP + RIIC ⟷ RII(cAMP)
RII(cAMP)2C
RII(cAMP)2
PKI + PKACII ⟷ PKACII:PKI
LCCβ2
PKACII
PP2ALCC
LCCβ2_P
PP2A
I1 ⇄ I1_Ptot
PKACI
SERCA ⊣ PLB ⇄ PLB_P
I1_P + PP1 ⟷ PP1:I1_P
PKACII
PP1LCC
Ca2+
Cp
Cn
Ccp
Cc
Op
On
Ocp
Oc
LCC Markov Model with α1C phosphorylation

40 differential equations, 20 algebraic equations, 78 parameters from 57 papers

Saucerman, JJ *et al.*, *J Biol Chem* 278: 47997 (2003)



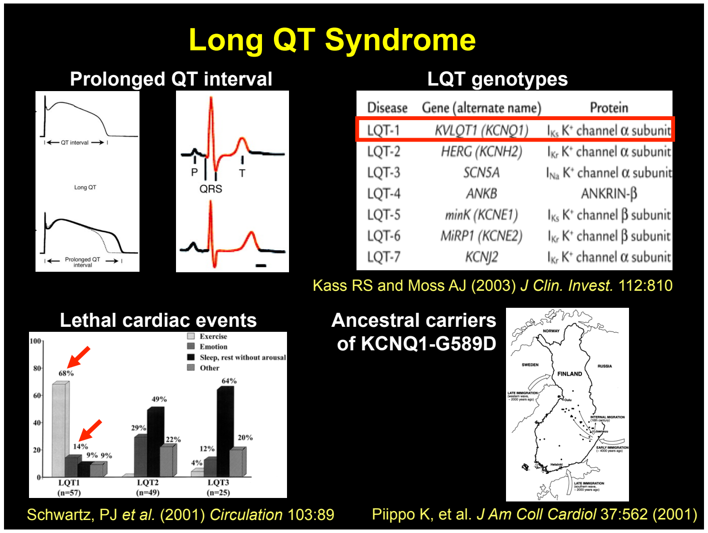
β-Adrenergic Regulation of E-C Coupling in Rabbit

Model

Experiments

Ginsburg KS, Bers DM
J Physiol. 556:463 (2004)

APD_{90} ↓10%:
Sanguinetti MC, *et al.*
Circ Res. 68:77 (1991)



Long QT Syndrome

Prolonged QT interval

QT interval
Long QT
Prolonged QT interval
P
QRS
T

LQT genotypes

Disease	Gene (alternate name)	Protein
LQT-1	*KVLQT1 (KCNQ1)*	I_{Ks} K^+ channel α subunit
LQT-2	*HERG (KCNH2)*	I_{Kr} K^+ channel α subunit
LQT-3	*SCN5A*	I_{Na} K^+ channel α subunit
LQT-4	*ANKB*	ANKRIN-β
LQT-5	*minK (KCNE1)*	I_{Ks} K^+ channel β subunit
LQT-6	*MiRP1 (KCNE2)*	I_{Kr} K^+ channel β subunit
LQT-7	*KCNJ2*	I_{Kr} K^+ channel α subunit

Kass RS and Moss AJ (2003) *J Clin. Invest.* 112:810

Lethal cardiac events

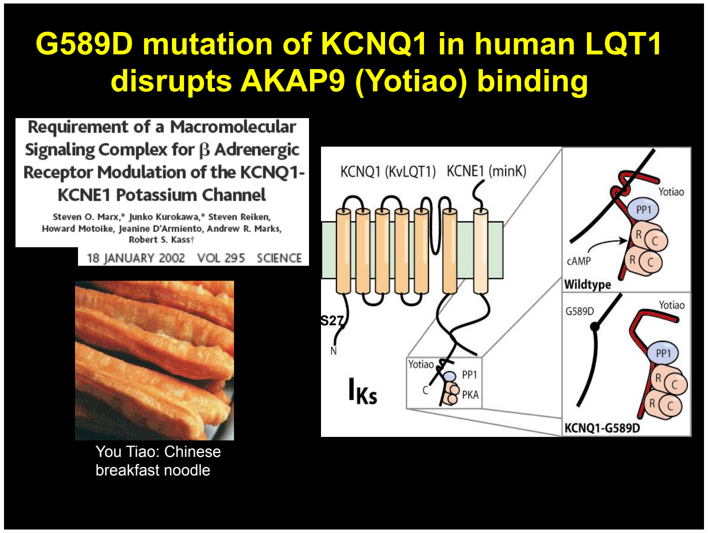
Exercise
Emotion
Sleep, rest without arousal
Other
100
80
60
40
20
0
68%
14%
9%
9%
29%
49%
22%
64%
12%
4%
20%
LQT1 (n=57)
LQT2 (n=49)
LQT3 (n=25)

Schwartz, PJ *et al.* (2001) *Circulation* 103:89

Ancestral carriers of KCNQ1-G589D

NORWAY
SWEDEN
FINLAND
RUSSIA

Piippo K, et al. *J Am Coll Cardiol* 37:562 (2001)



G589D mutation of KCNQ1 in human LQT1 disrupts AKAP9 (Yotiao) binding

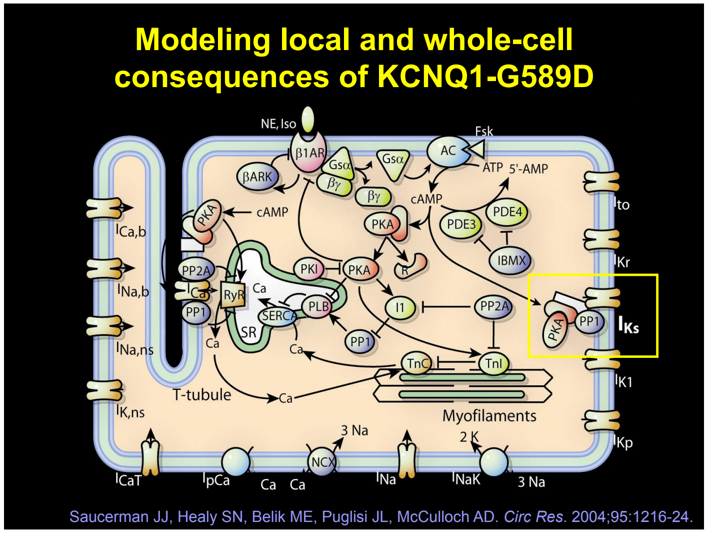
Requirement of a Macromolecular Signaling Complex for β Adrenergic Receptor Modulation of the KCNQ1-KCNE1 Potassium Channel

Steven O. Marx,* Junko Kurokawa,* Steven Reiken, Howard Motoike, Jeanine D'Armiento, Andrew R. Marks, Robert S. Kass†

18 JANUARY 2002 VOL 295 SCIENCE

You Tiao: Chinese breakfast noodle

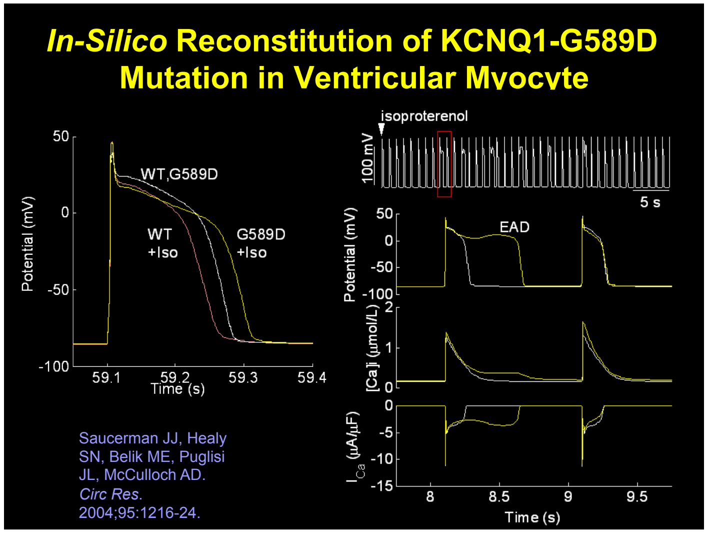
KCNQ1 (KvLQT1)
KCNE1 (minK)
S27
N
C
Yotiao
PP1
PKA
I_{Ks}
Yotiao
PP1
R
C
cAMP
Wildtype
G589D
KCNQ1-G589D



Modeling local and whole-cell consequences of KCNQ1-G589D

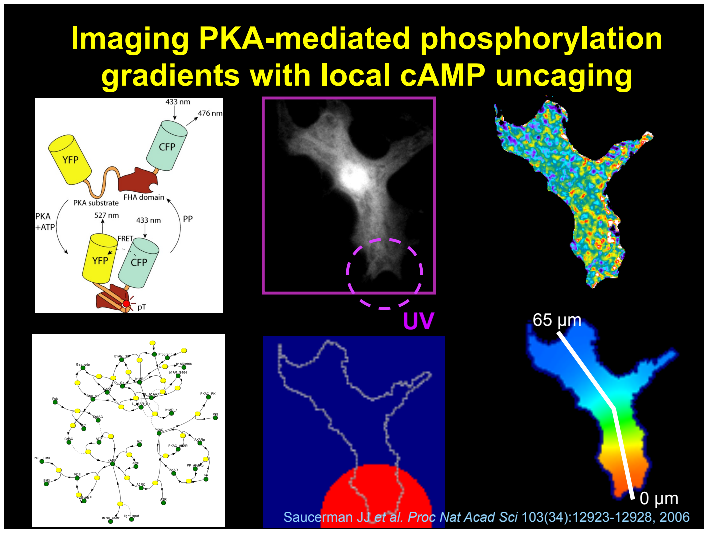
NE, Iso
β1AR
Gsα
βγ
Fsk
AC
ATP
5'-AMP
βARK
cAMP
PKA
PDE3
PDE4
IBMX
PP2A
PKI
PLB
SERCA
SR
RyR
Ca
I1
PP1
TnC
TnI
T-tubule
Myofilaments
$I_{Ca,b}$
$I_{Na,b}$
$I_{Na,ns}$
$I_{K,ns}$
I_{to}
I_{Kr}
I_{Ks}
I_{K1}
I_{Kp}
I_{CaT}
I_{pCa}
NCX
3 Na
I_{Na}
I_{NaK}
2 K

Saucerman JJ, Healy SN, Belik ME, Puglisi JL, McCulloch AD. *Circ Res.* 2004;95:1216-24.



In-Silico Reconstitution of KCNQ1-G589D Mutation in Ventricular Myocyte

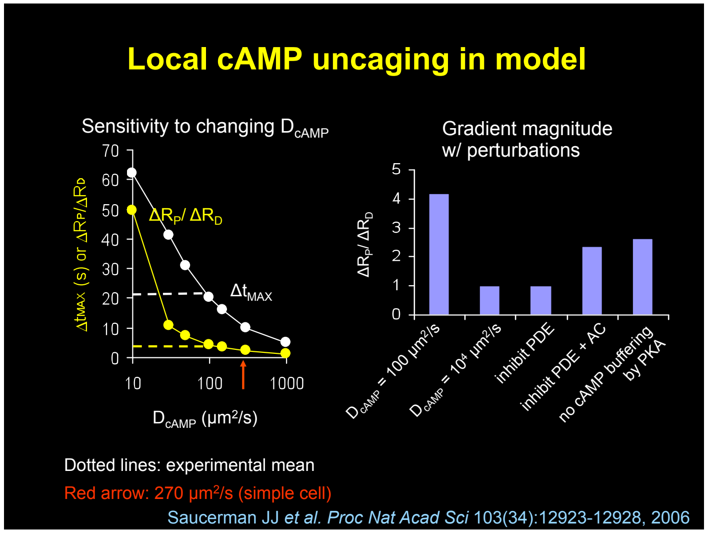
Saucerman JJ, Healy SN, Belik ME, Puglisi JL, McCulloch AD. *Circ Res.* 2004;95:1216-24.



Imaging PKA-mediated phosphorylation gradients with local cAMP uncaging

433 nm
476 nm
YFP
CFP
PKA substrate
FHA domain
PKA
+ATP
527 nm
433 nm
PP
FRET
YFP
CFP
pT
UV
65 µm
0 µm

Saucerman JJ *et al. Proc Nat Acad Sci* 103(34):12923-12928, 2006



Local cAMP uncaging in model

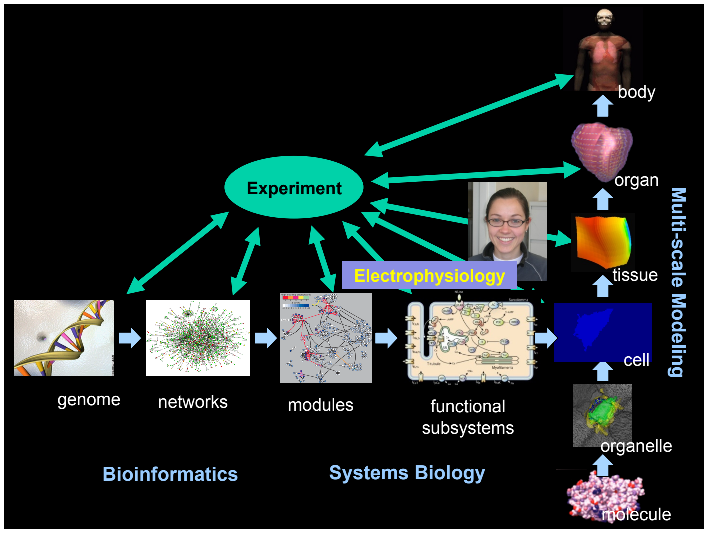
Sensitivity to changing D_{cAMP}

Gradient magnitude w/ perturbations

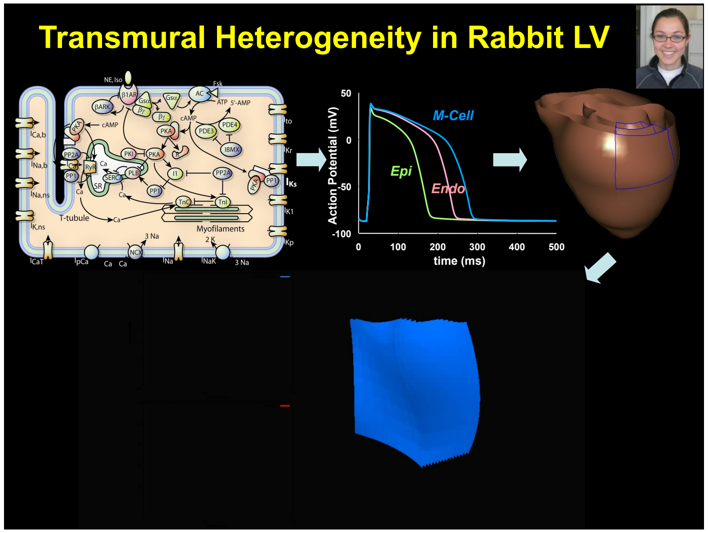
Dotted lines: experimental mean

Red arrow: 270 µm²/s (simple cell)

Saucerman JJ *et al. Proc Nat Acad Sci* 103(34):12923-12928, 2006



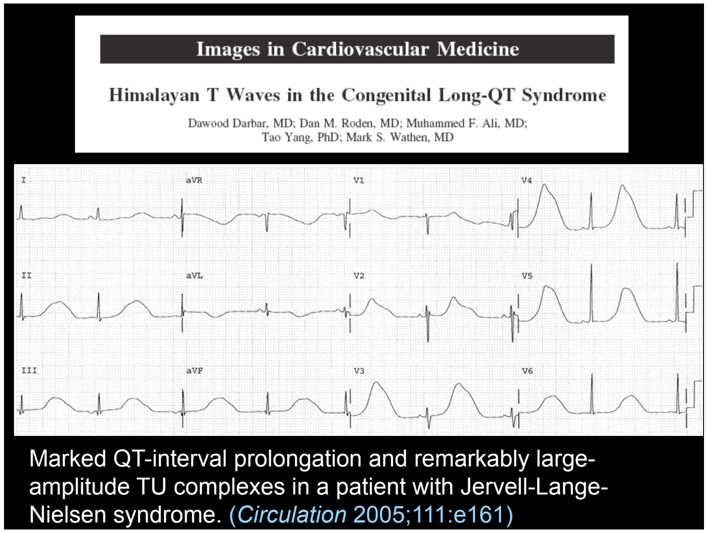
Experiment
Electrophysiology
body
organ
tissue
cell
organelle
molecule
genome
networks
modules
functional subsystems
Bioinformatics
Systems Biology
Multi-scale Modeling



Transmural Heterogeneity in Rabbit LV

T-tubule
Myofilaments
SR
PKA
cAMP
AC
Action Potential (mV)
50
0
-50
-100
0
100
200
300
400
500
time (ms)
M-Cell
Epi
Endo

Saucerman JJ, Healy SN, Belik ME, Puglisi JL, McCulloch AD. *Circ Res*. 2004;95:1216-24.



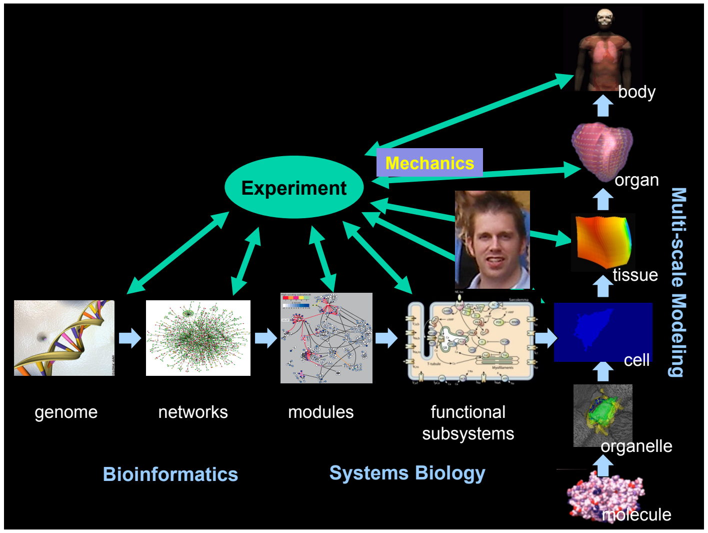
Images in Cardiovascular Medicine

Himalayan T Waves in the Congenital Long-QT Syndrome

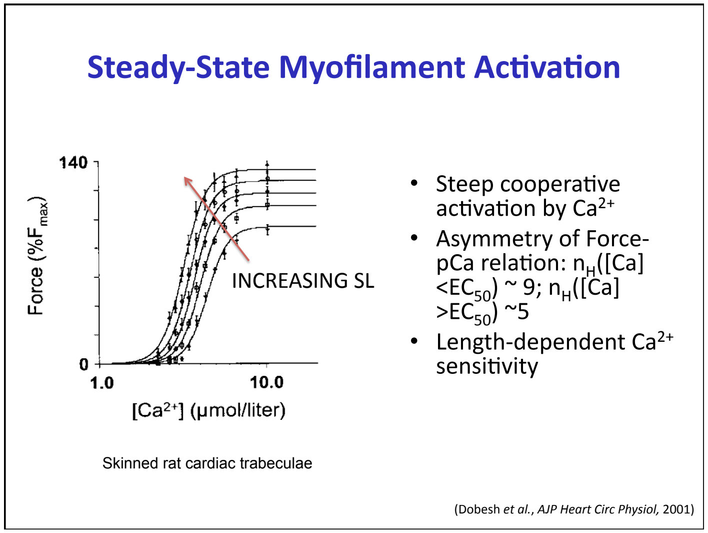
Dawood Darbar, MD; Dan M. Roden, MD; Muhammed F. Ali, MD;
Tao Yang, PhD; Mark S. Wathen, MD

I
aVR
V1
V4
II
aVL
V2
V5
III
aVF
V3
V6

Marked QT-interval prolongation and remarkably large-amplitude TU complexes in a patient with Jervell-Lange-Nielsen syndrome. (*Circulation* 2005;111:e161)



Experiment
Mechanics
body
organ
tissue
cell
organelle
molecule
Multi-scale Modeling
genome
networks
modules
functional subsystems
Bioinformatics
Systems Biology

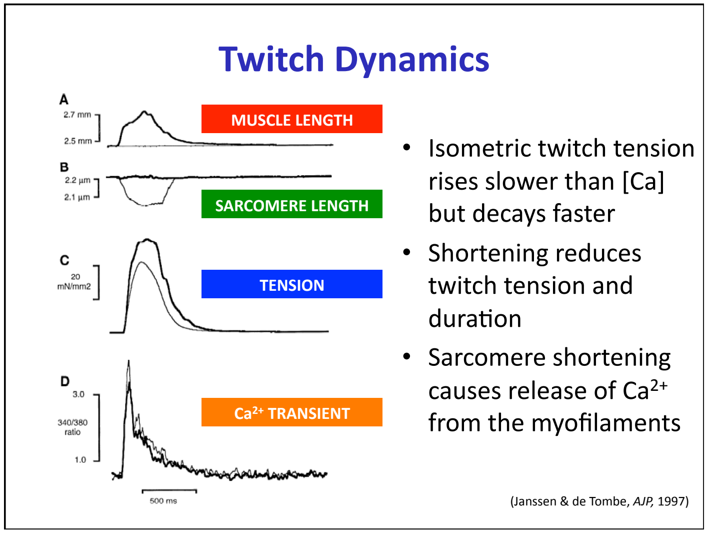


Steady-State Myofilament Activation

Skinned rat cardiac trabeculae

- Steep cooperative activation by Ca^{2+}
- Asymmetry of Force-pCa relation: n_H([Ca] <EC_{50}) ~ 9; n_H([Ca] >EC_{50}) ~5
- Length-dependent Ca^{2+} sensitivity

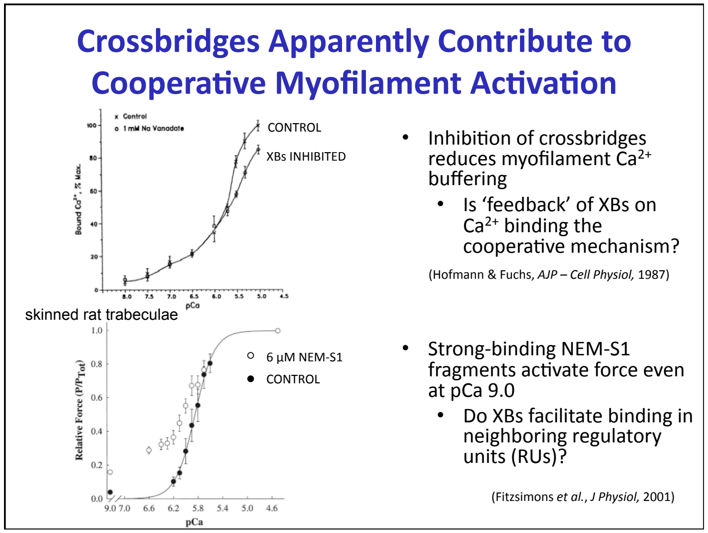
(Dobesh *et al.*, *AJP Heart Circ Physiol*, 2001)



Twitch Dynamics

- Isometric twitch tension rises slower than [Ca] but decays faster
- Shortening reduces twitch tension and duration
- Sarcomere shortening causes release of Ca^{2+} from the myofilaments

(Janssen & de Tombe, *AJP*, 1997)



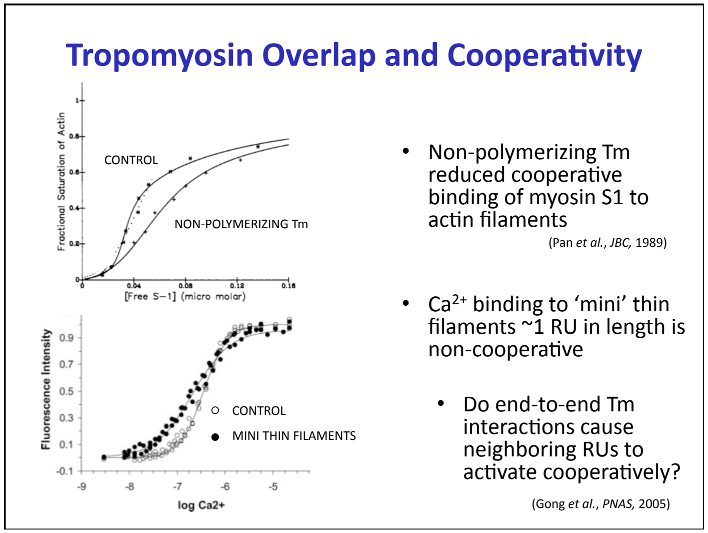
Crossbridges Apparently Contribute to Cooperative Myofilament Activation

- Inhibition of crossbridges reduces myofilament Ca^{2+} buffering
    - Is ‘feedback’ of XBs on Ca^{2+} binding the cooperative mechanism?

(Hofmann & Fuchs, *AJP – Cell Physiol*, 1987)

- Strong-binding NEM-S1 fragments activate force even at pCa 9.0
    - Do XBs facilitate binding in neighboring regulatory units (RUs)?

(Fitzsimons *et al.*, *J Physiol*, 2001)



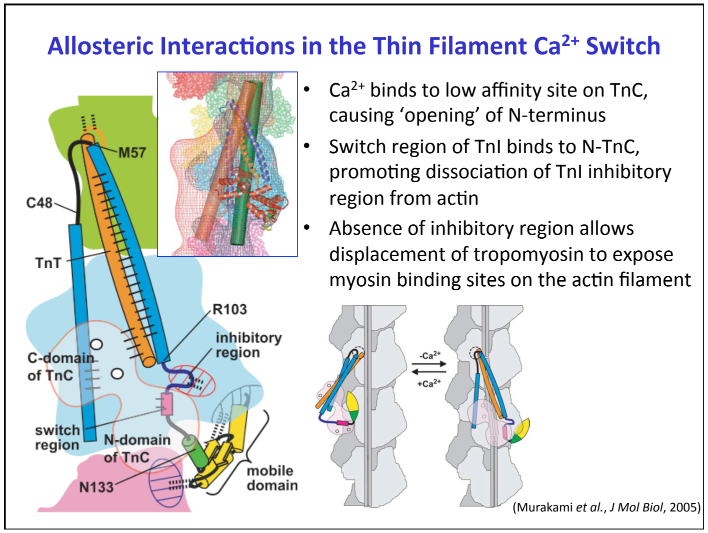
Tropomyosin Overlap and Cooperativity

- Non-polymerizing Tm reduced cooperative binding of myosin S1 to actin filaments

(Pan *et al.*, *JBC*, 1989)

- Ca^{2+} binding to ‘mini’ thin filaments ~1 RU in length is non-cooperative
    - Do end-to-end Tm interactions cause neighboring RUs to activate cooperatively?

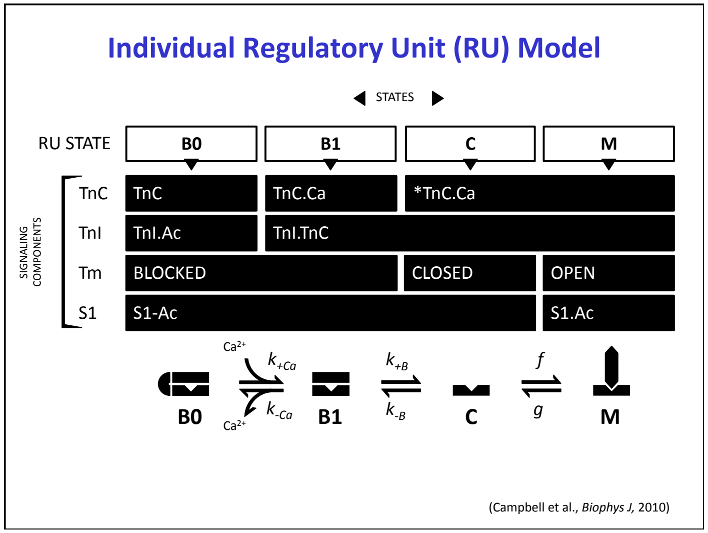
(Gong *et al.*, *PNAS*, 2005)



Allosteric Interactions in the Thin Filament Ca^{2+} Switch

- Ca^{2+} binds to low affinity site on TnC, causing ‘opening’ of N-terminus
- Switch region of TnI binds to N-TnC, promoting dissociation of TnI inhibitory region from actin
- Absence of inhibitory region allows displacement of tropomyosin to expose myosin binding sites on the actin filament

(Murakami *et al.*, *J Mol Biol*, 2005)



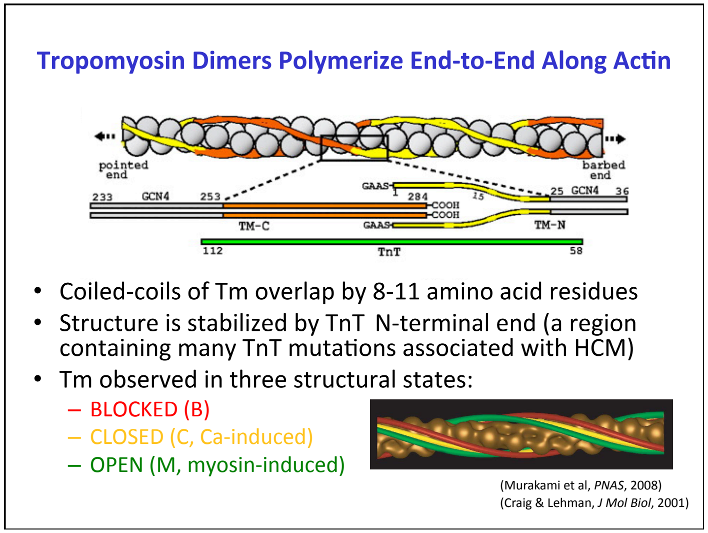
Individual Regulatory Unit (RU) Model

STATES
SIGNALING COMPONENTS

RU STATE	B0	B1	C	M
TnC	TnC	TnC.Ca	*TnC.Ca	
TnI	TnI.Ac	TnI.TnC		
Tm	BLOCKED		CLOSED	OPEN
S1	S1-Ac			S1.Ac

$$B0 \underset{k_{-Ca}\; Ca^{2+}}{\overset{Ca^{2+}\; k_{+Ca}}{\rightleftharpoons}} B1 \underset{k_{-B}}{\overset{k_{+B}}{\rightleftharpoons}} C \underset{g}{\overset{f}{\rightleftharpoons}} M$$

(Campbell et al., *Biophys J*, 2010)

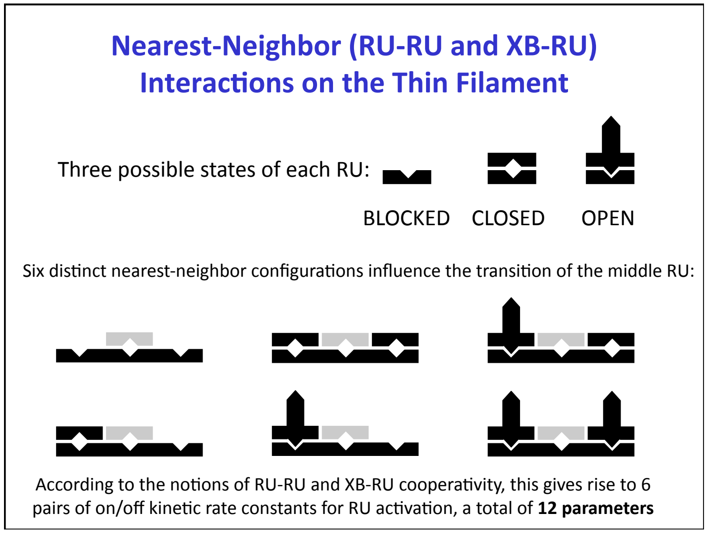


Tropomyosin Dimers Polymerize End-to-End Along Actin

pointed end
barbed end
233
GCN4
253
GAAS
1
284
15
COOH
COOH
25
GCN4
36
TM-C
GAAS
TM-N
112
TnT
58

- Coiled-coils of Tm overlap by 8-11 amino acid residues
- Structure is stabilized by TnT N-terminal end (a region containing many TnT mutations associated with HCM)
- Tm observed in three structural states:
  - BLOCKED (B)
  - CLOSED (C, Ca-induced)
  - OPEN (M, myosin-induced)

(Murakami et al, *PNAS*, 2008)
(Craig & Lehman, *J Mol Biol*, 2001)



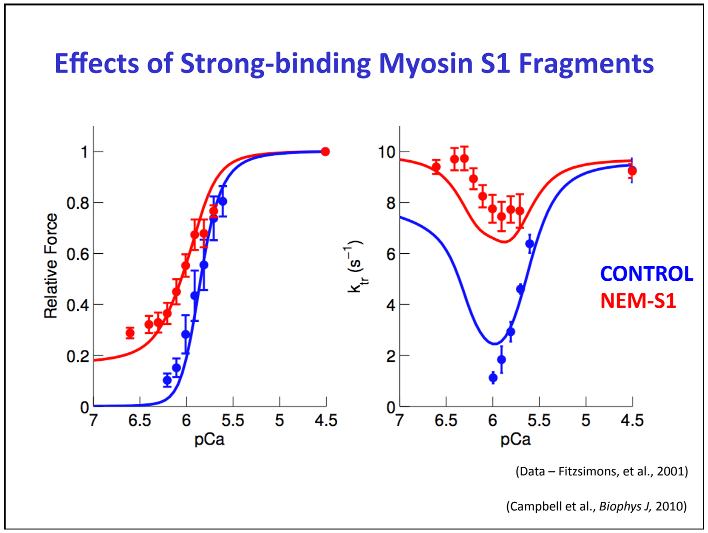
Nearest-Neighbor (RU-RU and XB-RU) Interactions on the Thin Filament

Three possible states of each RU:

BLOCKED
CLOSED
OPEN

Six distinct nearest-neighbor configurations influence the transition of the middle RU:

According to the notions of RU-RU and XB-RU cooperativity, this gives rise to 6 pairs of on/off kinetic rate constants for RU activation, a total of **12 parameters**

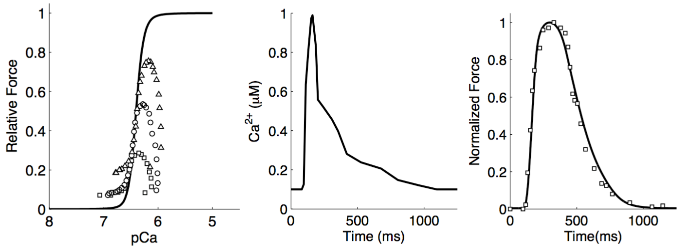


Effects of Strong-binding Myosin S1 Fragments

(Data – Fitzsimons, et al., 2001)

(Campbell et al., *Biophys J*, 2010)

Sarcomere Isometric Twitch Dynamics



PHARMACOLOGICALLY-SLOWED CONTRACTIONS

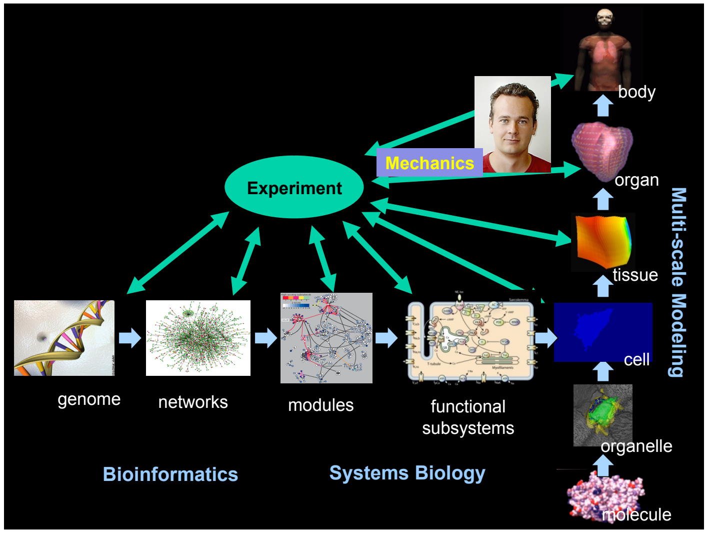
CONSTANT SARCOMERE LENGTH TWITCH

MODEL SIMULTANEOUSLY REPRODUCES STEADY-STATE AND DYNAMIC FORCE-Ca^{2+} RELATIONS

(Data - Dobrunz et al., 1995)

(Data – Janssen & de Tombe, 1997)

(Campbell et al., *Biophys J*, 2010)



body

organ

tissue

cell

organelle

molecule

Mechanics

Experiment

genome

networks

modules

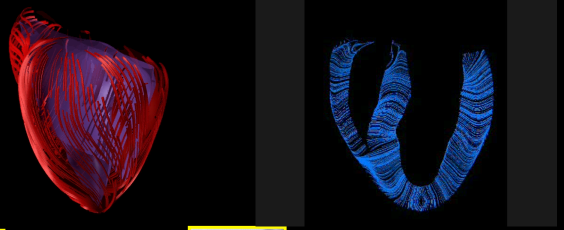
functional subsystems

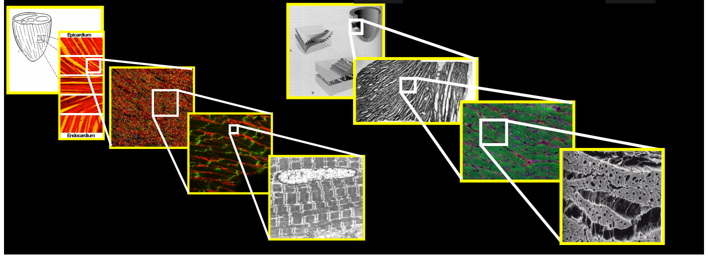
Multi-scale Modeling

Bioinformatics

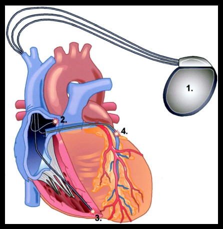
Systems Biology

Organ Scale: Ventricular Models



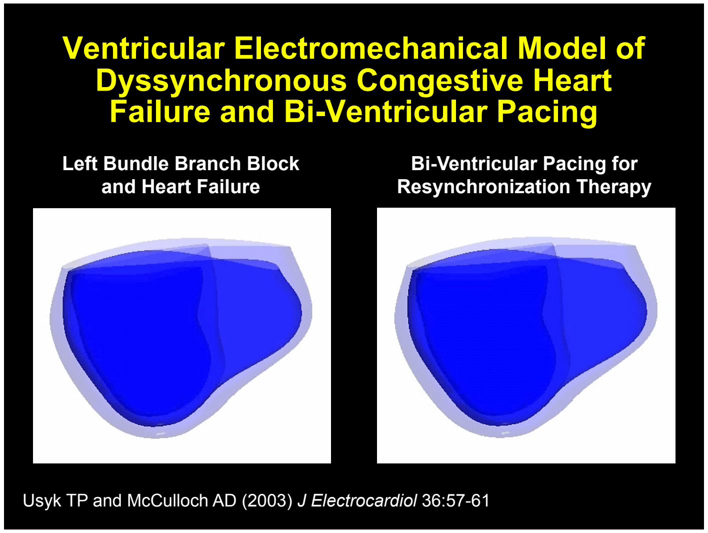


Cardiac Resynchronization Therapy for Congestive Heart Failure



- Heart failure: 250,000 deaths/year in US alone
- Pump dysfunction frequently associated with electrical dysynchrony
- Cardiac resynchronization therapy (CRT)
  - improves timing between LV and RV contraction
  - improves quality of life*
  - reduces mortality*
- ~30% of patients do not respond to CRT, especially those with myocardial infarcts

*Cleland, 2005



Ventricular Electromechanical Model of Dyssynchronous Congestive Heart Failure and Bi-Ventricular Pacing

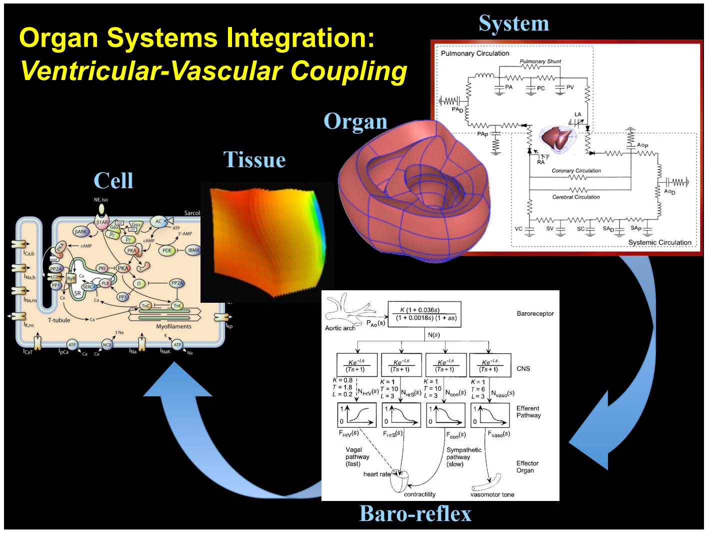
Left Bundle Branch Block and Heart Failure
Bi-Ventricular Pacing for Resynchronization Therapy

Usyk TP and McCulloch AD (2003) *J Electrocardiol* 36:57-61

3-D Model of CRT Predicts Observed Hemodynamic Improvements

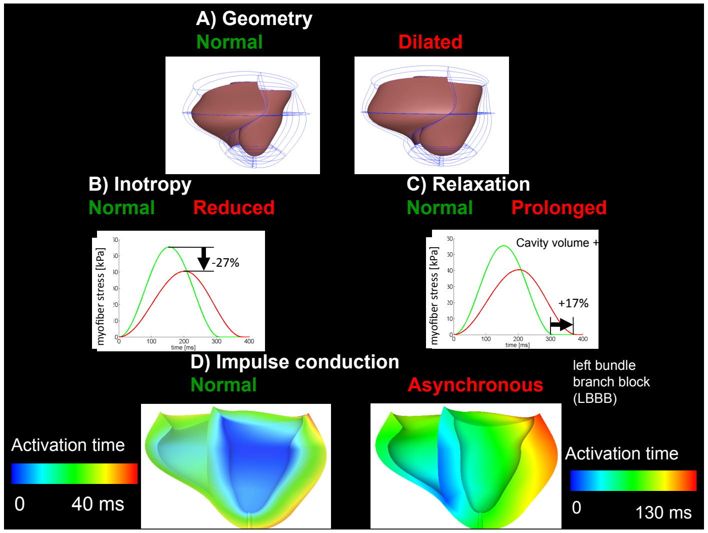
	LBBB		Bi-V pacing		Improvement, %	
	Model	Expt	Model	Expt	Model	Expt
dP/dt_{max} mm Hg/s	1230	1048±242	1680	1392 ± 413	36.6	32.8
dP/dt_{min} mm Hg/s	-1080	-960±162	-1220	-1152 ± 250	12.0	20.0
EF %	21.2	23.0±12.7	25.6	27.5 ±16.2	4.4	4.5

Usyk TP and McCulloch AD (2003) *J Electrocardiol* 36:57-61

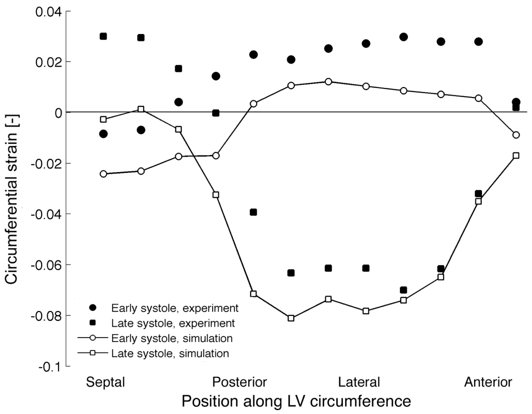


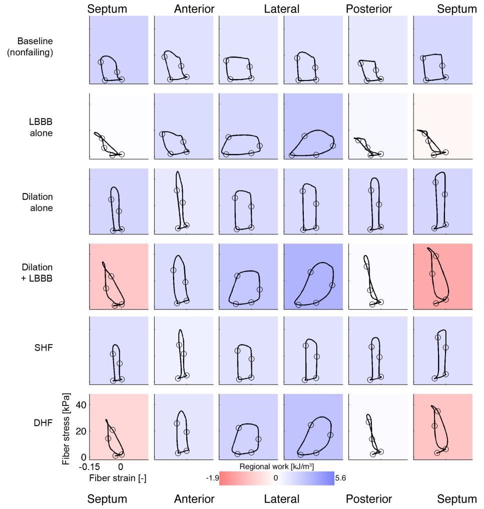
Organ Systems Integration: *Ventricular-Vascular Coupling*

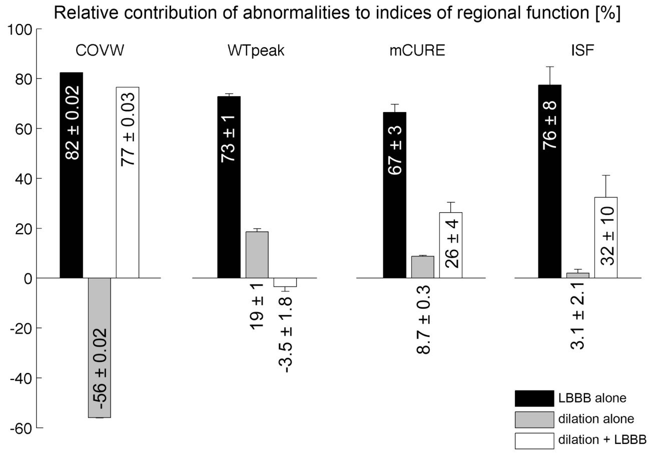
System
Organ
Tissue
Cell
Baro-reflex
Pulmonary Circulation
Pulmonary Shunt
PA
PC
PV
LA
RA
Coronary Circulation
Cerebral Circulation
Systemic Circulation
VC
SV
SC
Baroreceptor
Aortic arch
CNS
Efferent Pathway
Effector Organ
Vagal pathway (fast)
Sympathetic pathway (slow)
heart rate
contractility
vasomotor tone
T-tubule
Myofilaments



Regional Strains

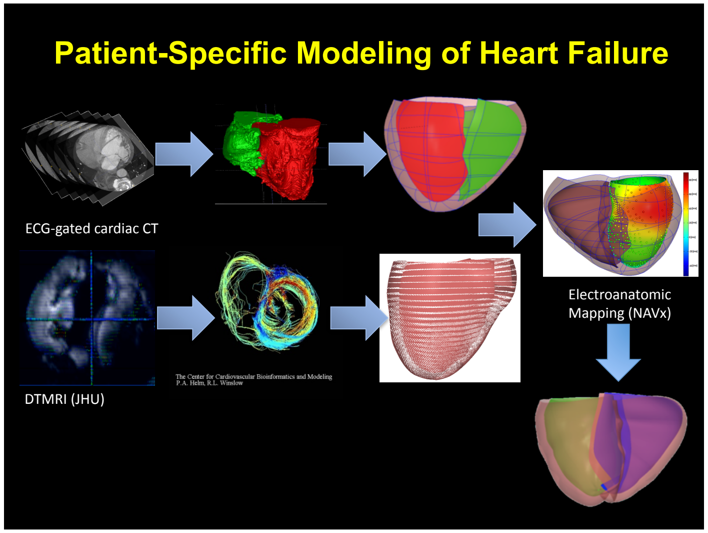





Relative contribution of abnormalities to indices of regional function [%]

Conclusions

- Dilation and LBBB combined synergistically decreased regional cardiac function.
- CURE and ISF were sensitive to this combination, but not WTpeak.
- CURE and ISF also reflected better than WTpeak the relative non-uniform distribution of regional work.
- These findings might explain why ISF and CURE are better predictors of reverse remodeling in cardiac resynchronization therapy.



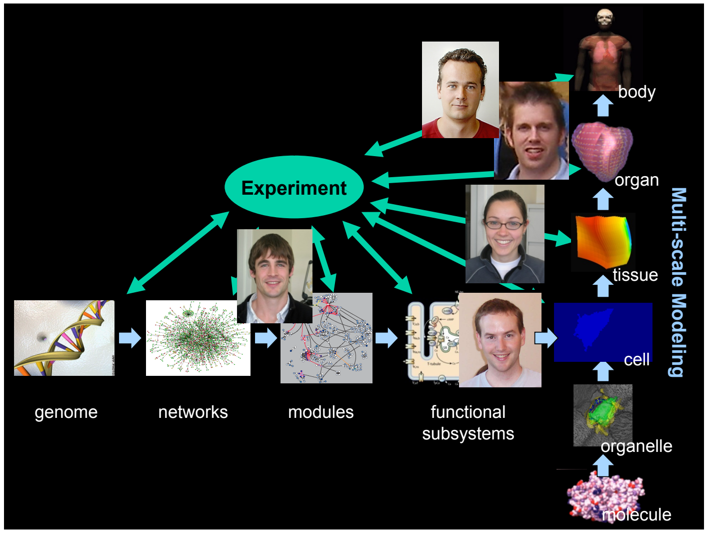
Patient-Specific Modeling of Heart Failure

ECG-gated cardiac CT

DTMRI (JHU)

The Center for Cardiovascular Bioinformatics and Modeling
P.A. Helm, R.L. Winslow

Electroanatomic Mapping (NAVx)



Experiment

genome

networks

modules

functional subsystems

body

organ

tissue

cell

organelle

molecule

Multi-scale Modeling

DEPARTMENT OF BIOENGINEERING UNIVERSITY OF CALIFORNIA, SAN DIEGO

CARDIAC MECHANICS RESEARCH GROUP

CMRG:

Jeff Saucerman
Anushka Michailova
Jeff Omens
Sarah Flaim
Stuart Campbell
Roy Kerckhoffs
Fred Lionetti
Jazmin Aguado Sierra
Elliot Howard
Mansi Sheth
Chris Villongco

Collaborators:

Laurence Coquin, Sanford-Burnham Institute
Larry Mulligan, Medtronic
Sanjiv Narayan, UCSD
Roger Tsien, UCSD
Antine Stenbit, UCSD
Jin Zhang, Johns Hopkins
Don Bers, UC Davis
Jose Puglisi, UC Davis
Bernhard Palsson, UCSD
Wayne Giles, University of Calgary
Giovanni Paternostro, Sanford-Burnham
Ken Campbell, University of Kentucky
Jim Bassingthwaighte, University of Washington

NBCR
HHMI HOWARD HUGHES MEDICAL INSTITUTE
NIBIB National Institute of Biomedical Imaging and Bioengineering
NCRR
NSF