How Multiscale Modeling can impact Biomedical and Clinical Research

VPH/Physiome perspective

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Talk plan

Scales:

1. Population
2. Whole body
3. Cell-tissue-organ
4. Pathways & networks
5. Atomic & molecular

Charge: Look at ..

Perception/acceptance
Future biomed applications
Future clinical applications
Directions for modeling
Standards, open source
Peer review

Case studies:

- ***Cardiac models***
- ***Cerebral aneurysm models***
- ***Musculo-skeletal models***
- ***Lens & whole eye models***

VPH/Physiome infrastructure

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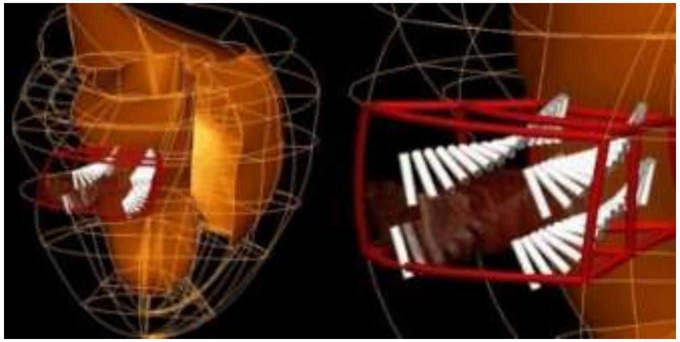
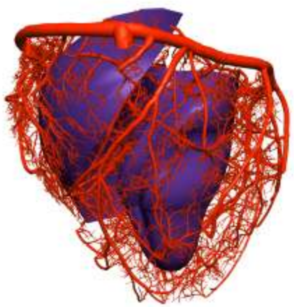
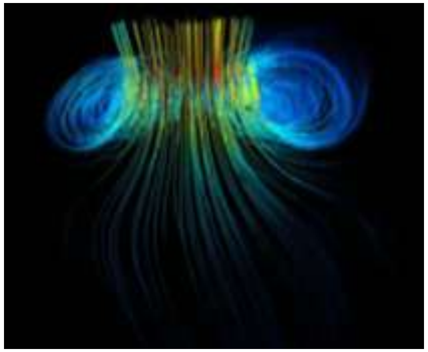
Cardiac models

1. **Myocardial mechanics**



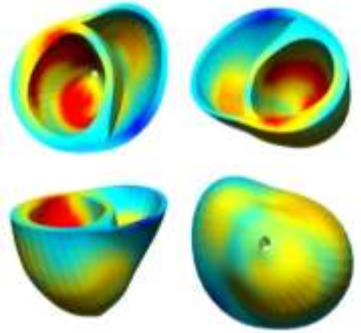
2. **Fluid mechanics**

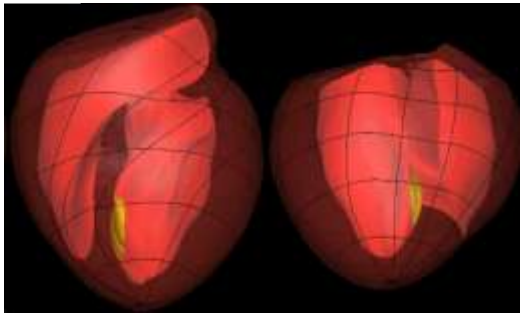




3. **Coronary flow**

4. **Myocardial activation**

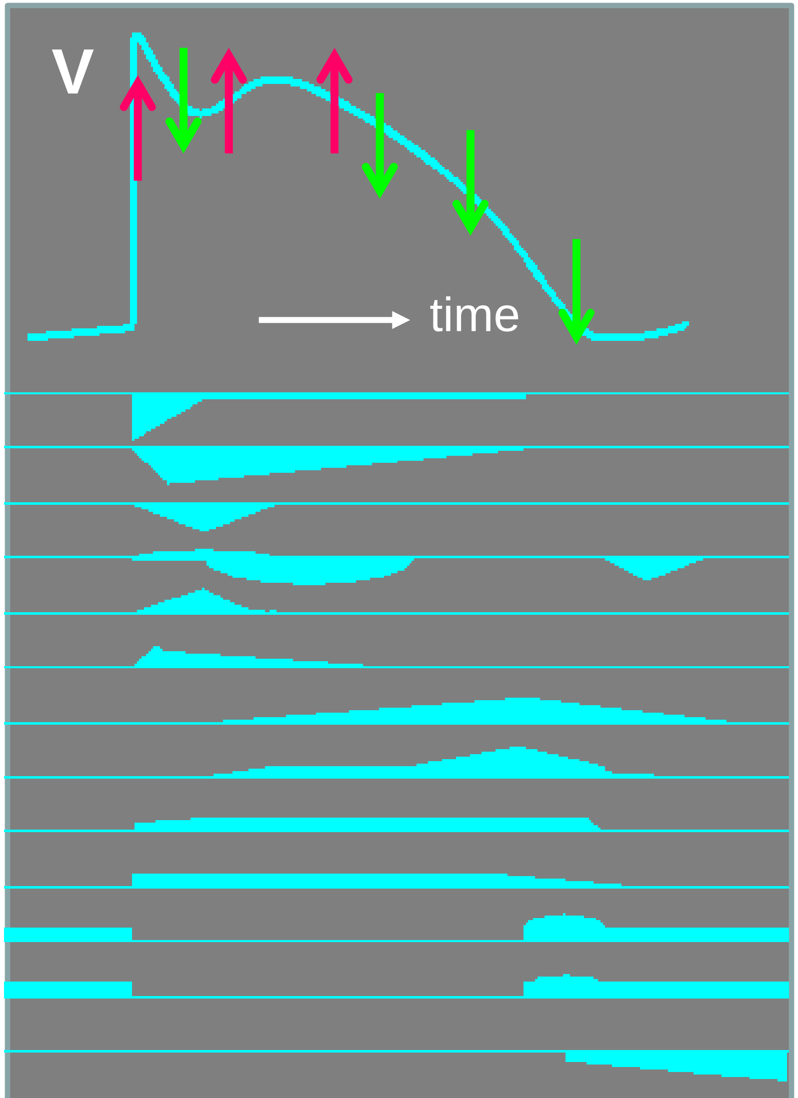




5. **Coupling .. Mechano-electro-fluid model**

Membrane ion channels

CellML



$$\frac{dV_m}{dt} = \frac{\Sigma I_m}{C_m}$$

Outward current

	Probable clones
Sodium current	SCN5A + subunits
L-type calcium current	CACH1C
T-type calcium current	
Na-Ca exchange	NCX
I_{TO1} (4-AP-sensitive)	Kv4.x
I_{TO2} (Ca-activated)	
I_{Ks}	KvLQT1 + minK
I_{Kr}	HERG + MiRP-1
I_{Kur} or I_{Kq}	Kv1.5
I_{Cl} or I_{Kp}	CFTR, TWIK
I_{K1} (inward rectifier)	Kir2.x
I_K ATP/ACh	Kir3.1/3.4, Kir6.x/SUR
I_f (pacemaker)	hCNG

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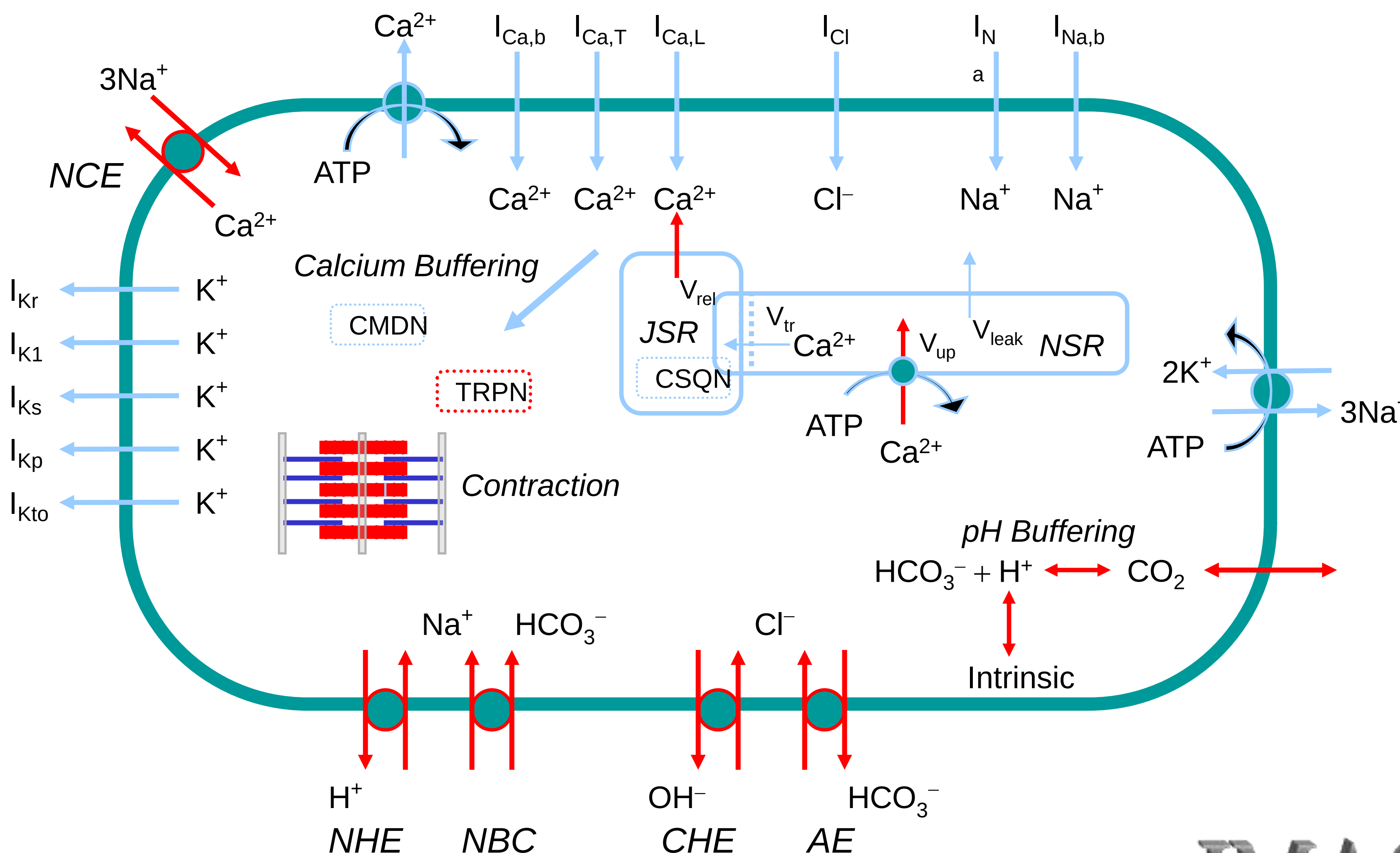
Cell processes



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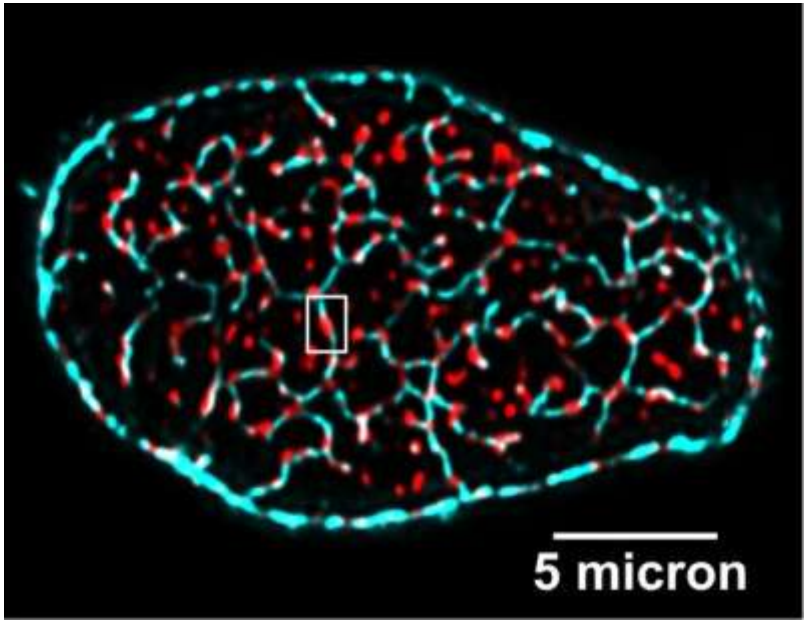
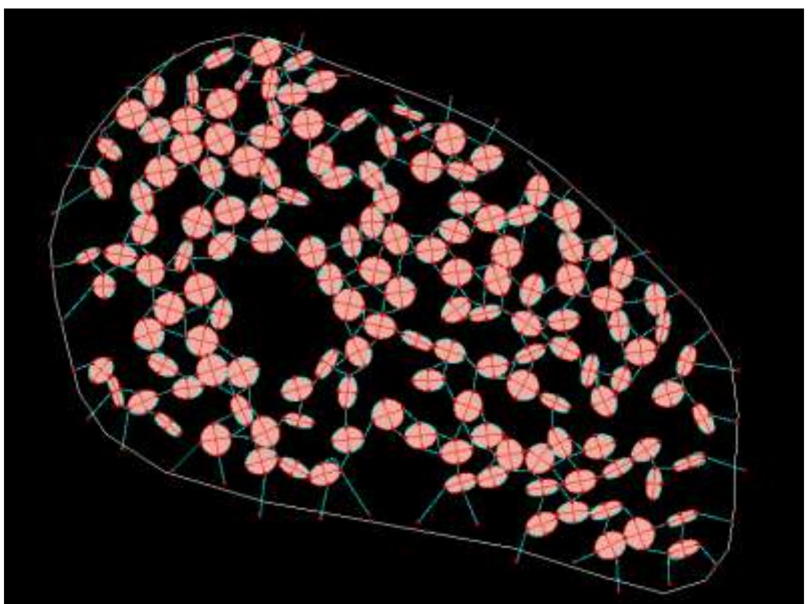
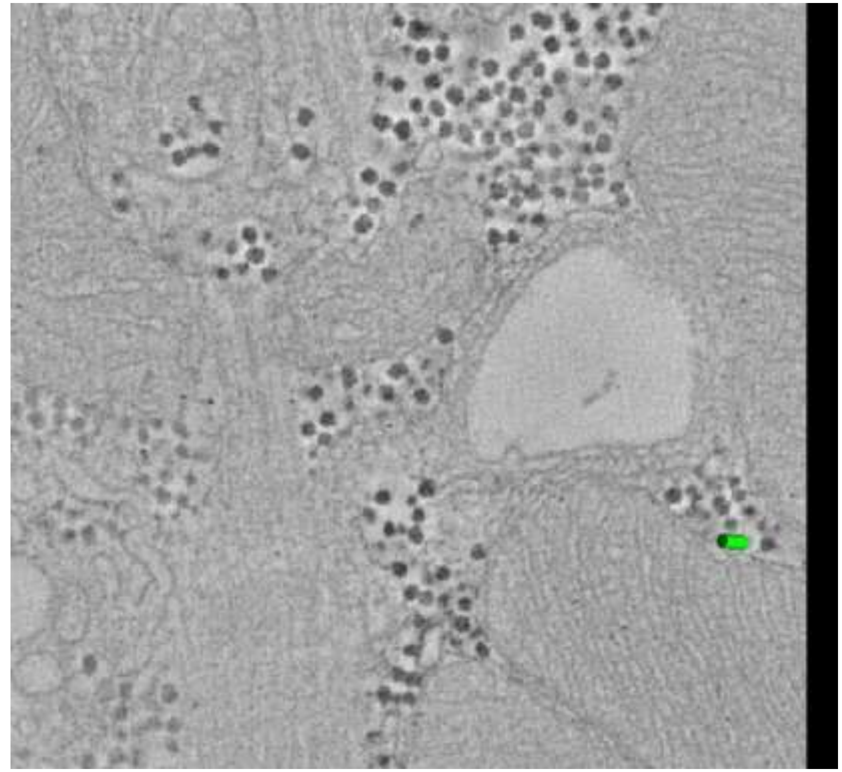
3D cardiac cell models







Vijay Rajagopal, Mark Ellisman, Peter Kohl

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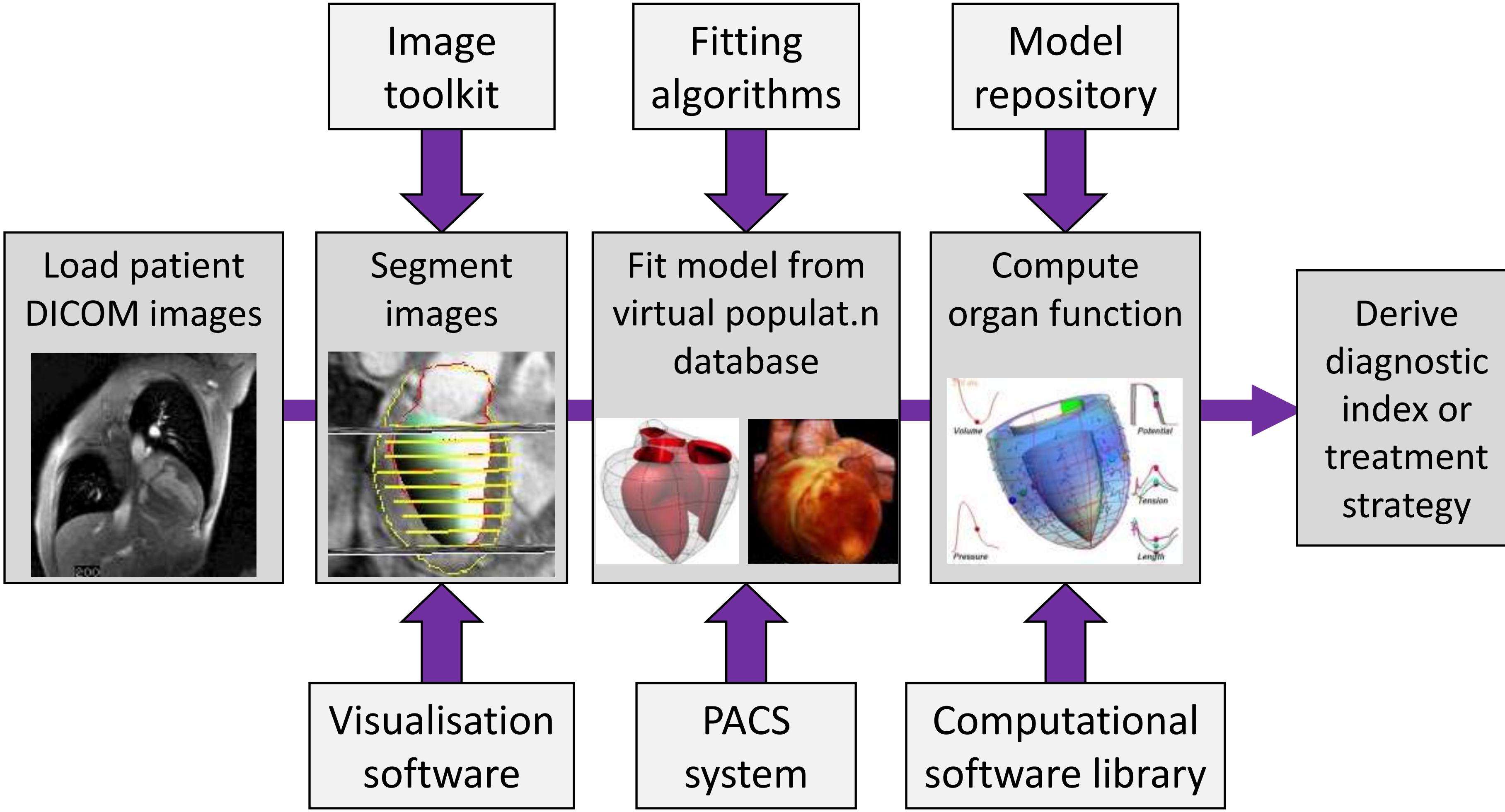
Clinical workflows



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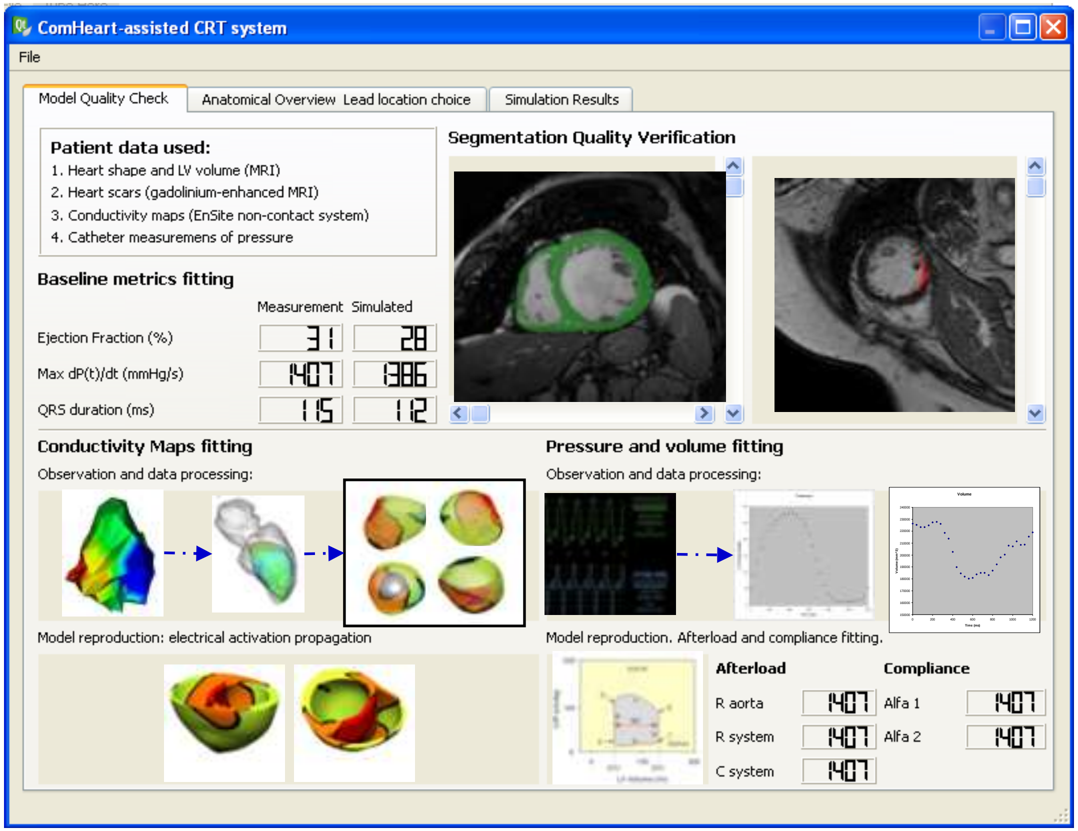
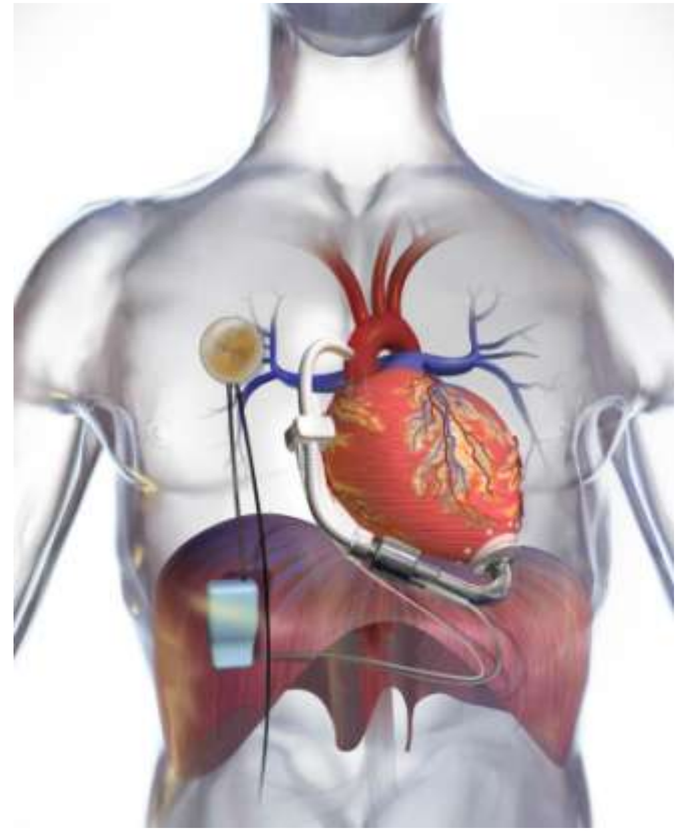
Clinical applications

euHeart: Philips Technologie GmbH



Berlin Heart



Personalised models, Multi-scale, Population databases

Aim for clinical trials within next few years

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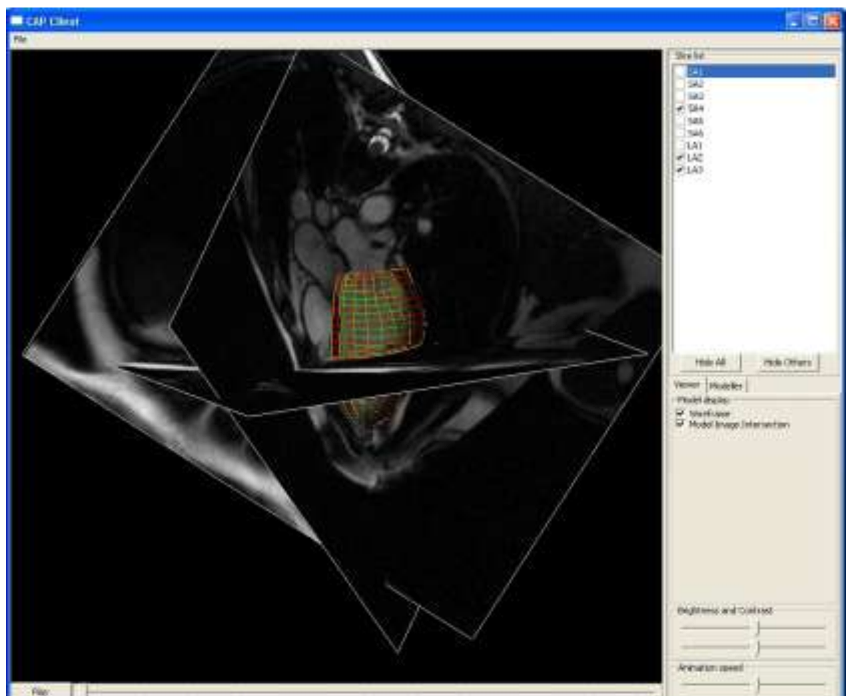
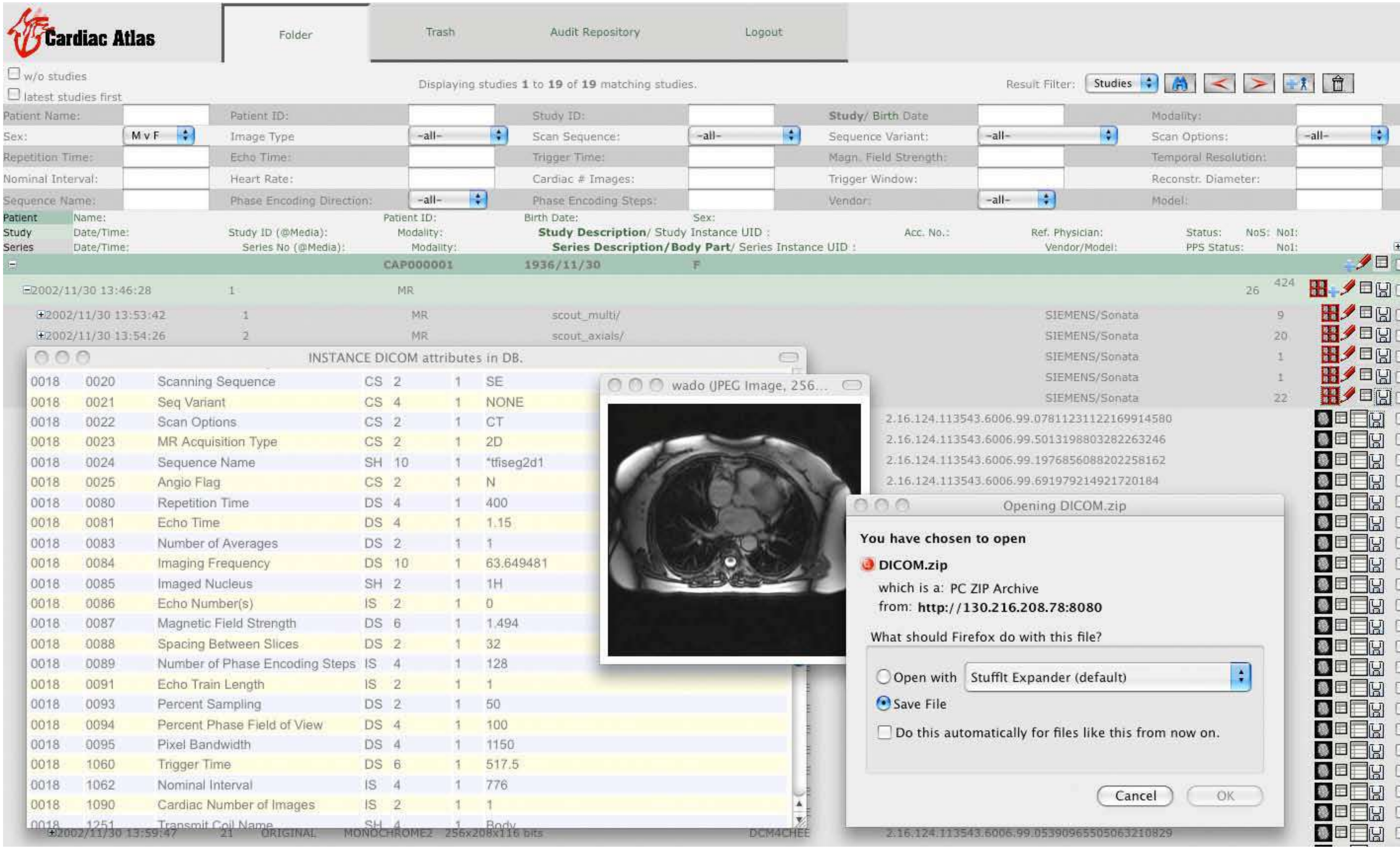
Cardiac Atlas Project (NIH funded)

- www.cardiacatlas.org
- Structural and functional atlas of the heart
- Cardiac MRI examinations
- Fit model to each case and then derive subject specific functional analyses and associated clinical variables



CAP database



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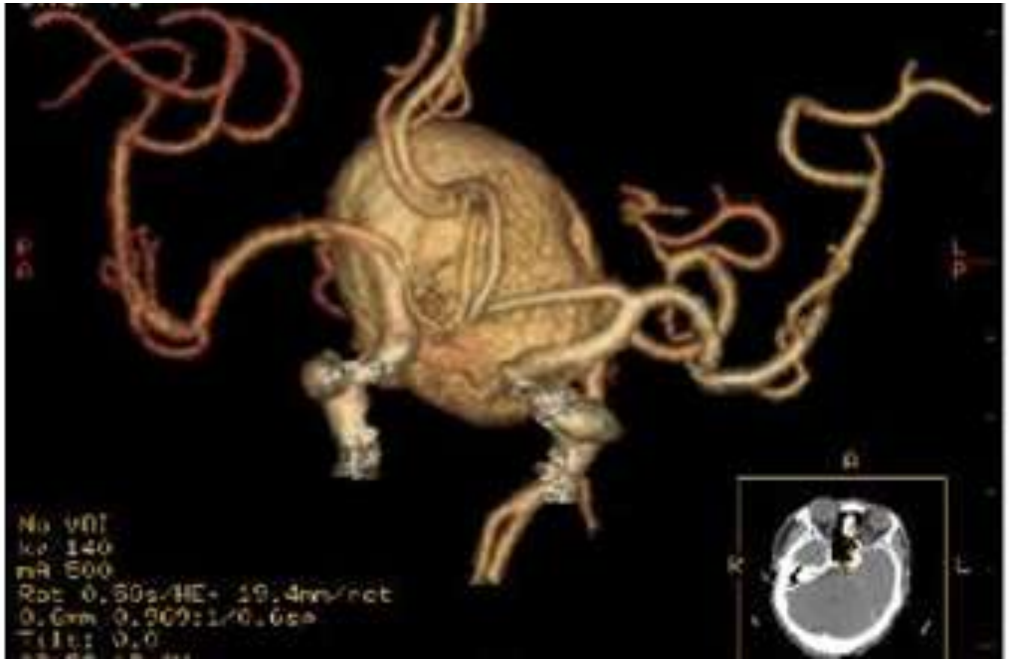
Cerebral aneurysm models

An intracranial aneurysm with CTA scanning
(55 yr old male patient)



How should this aneurysm be treated?

- Clipping?
- Endovascular treatment?
- Others (e.g. ligature)?

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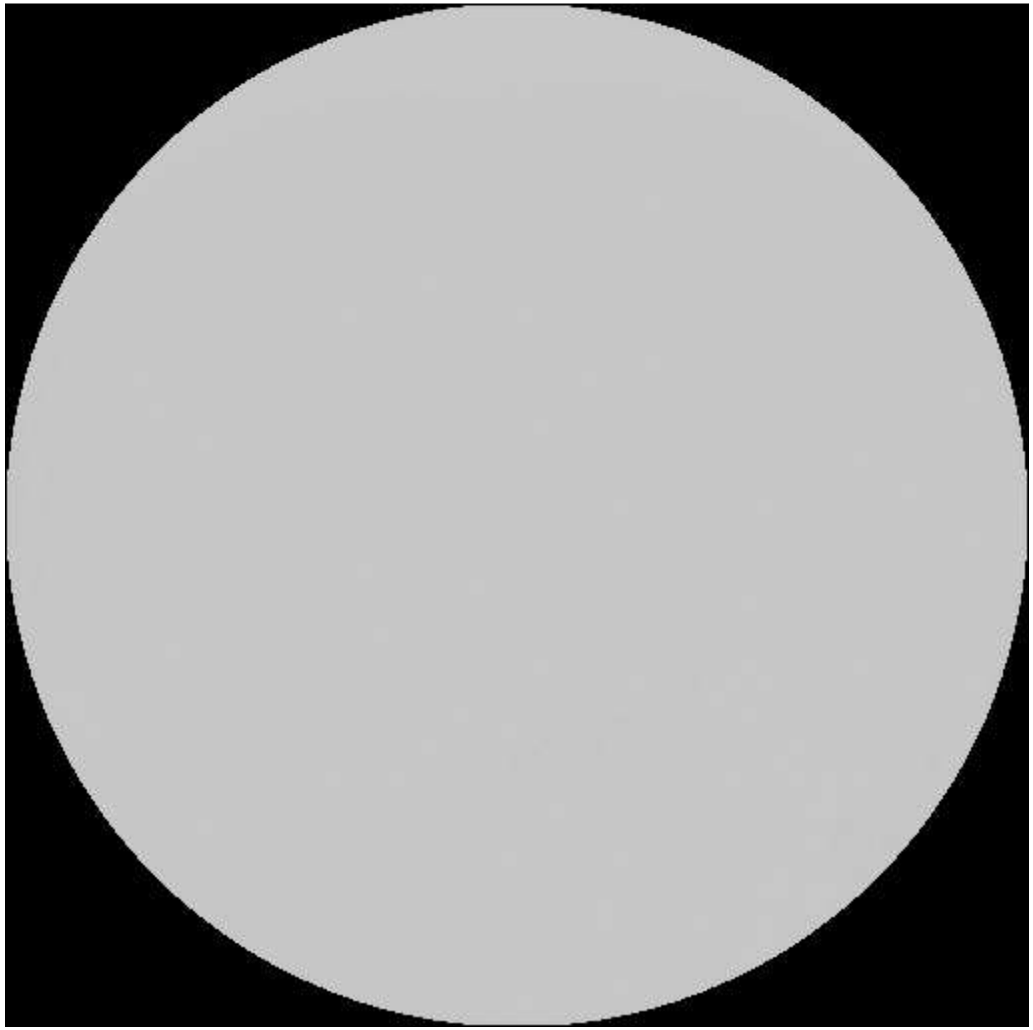
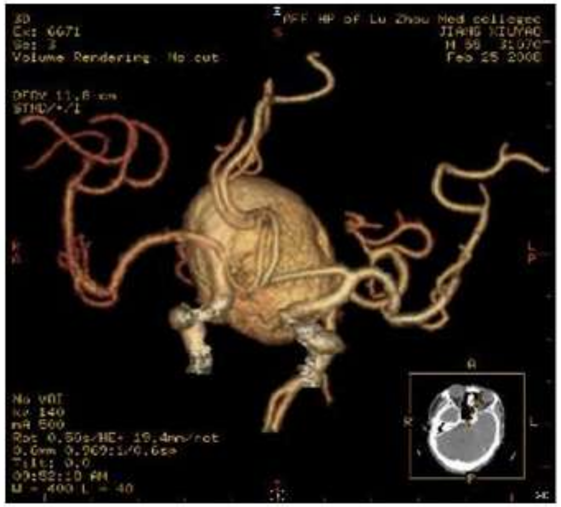
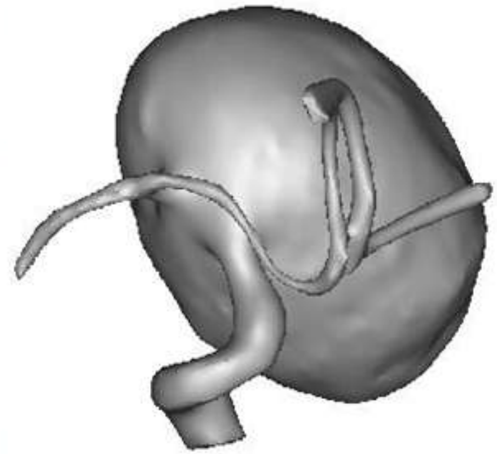
Blood perfusion with Digital Subtraction Angiography (DSA)

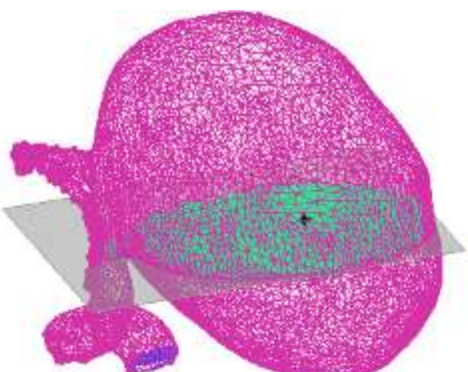


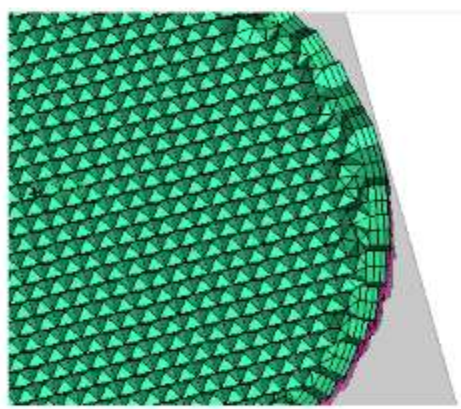
Aneurysm model construction

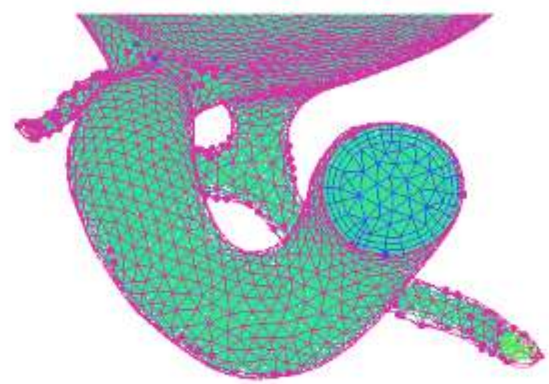




Volume image → surface model







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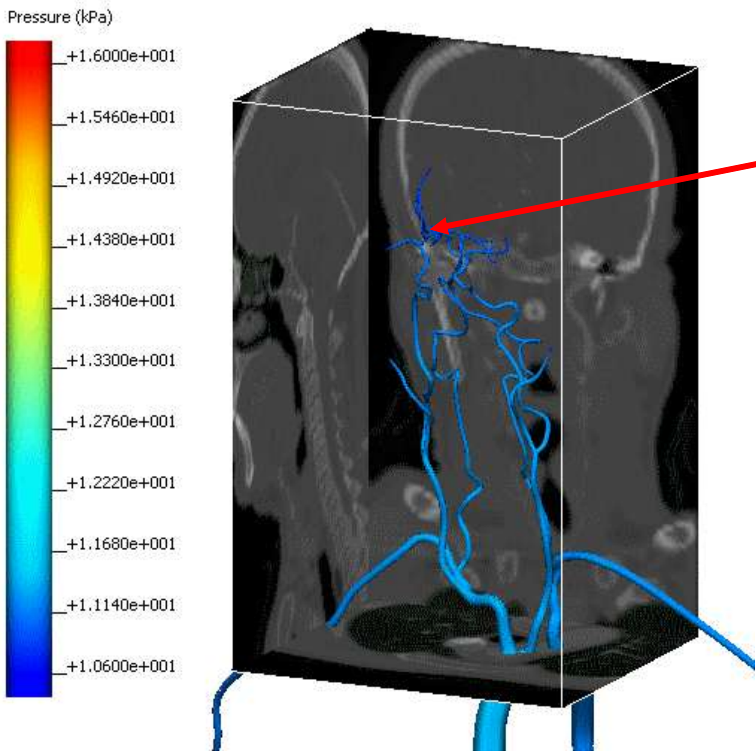
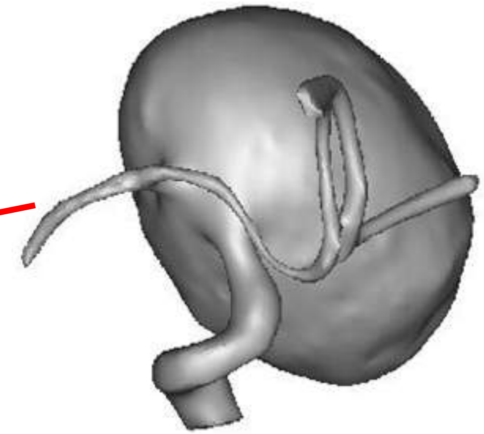
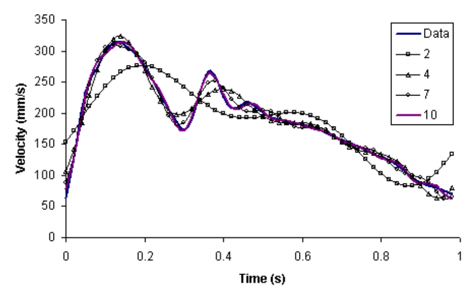
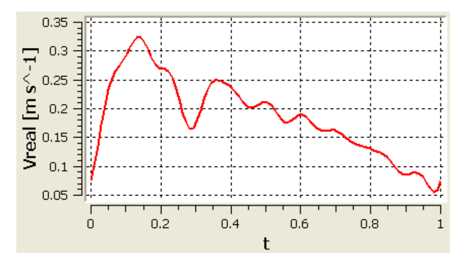
Define boundary conditions





Inflow: pulsatile velocity





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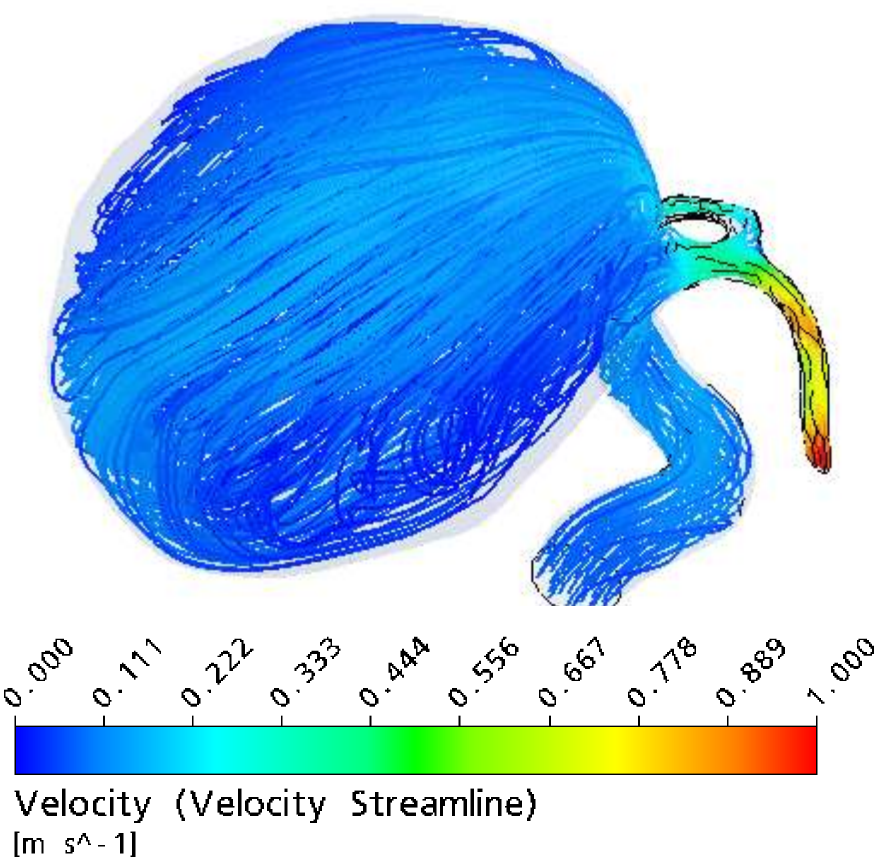
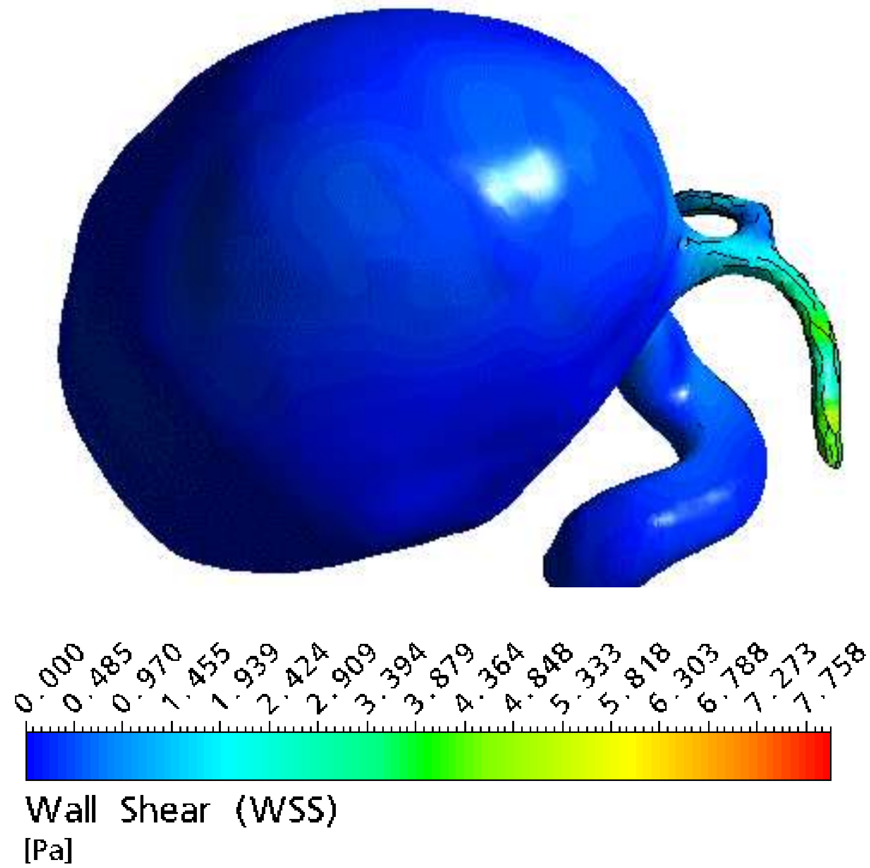
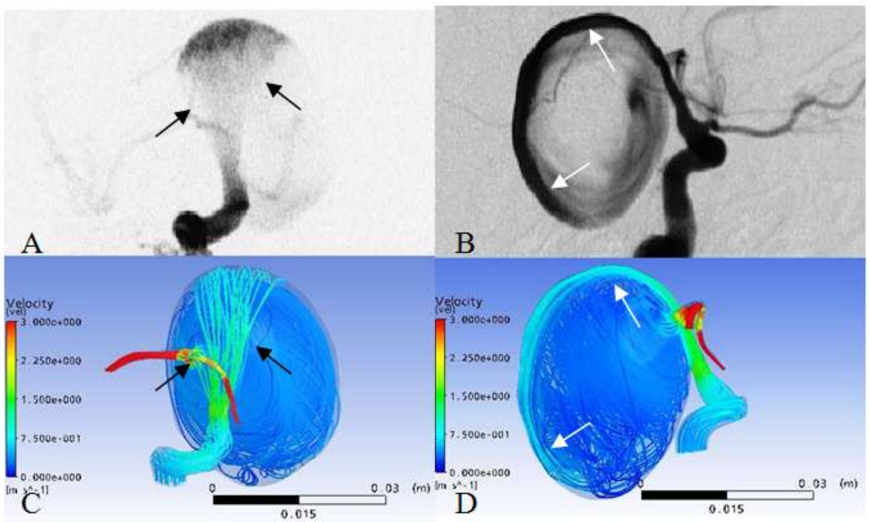
Particle streamlines

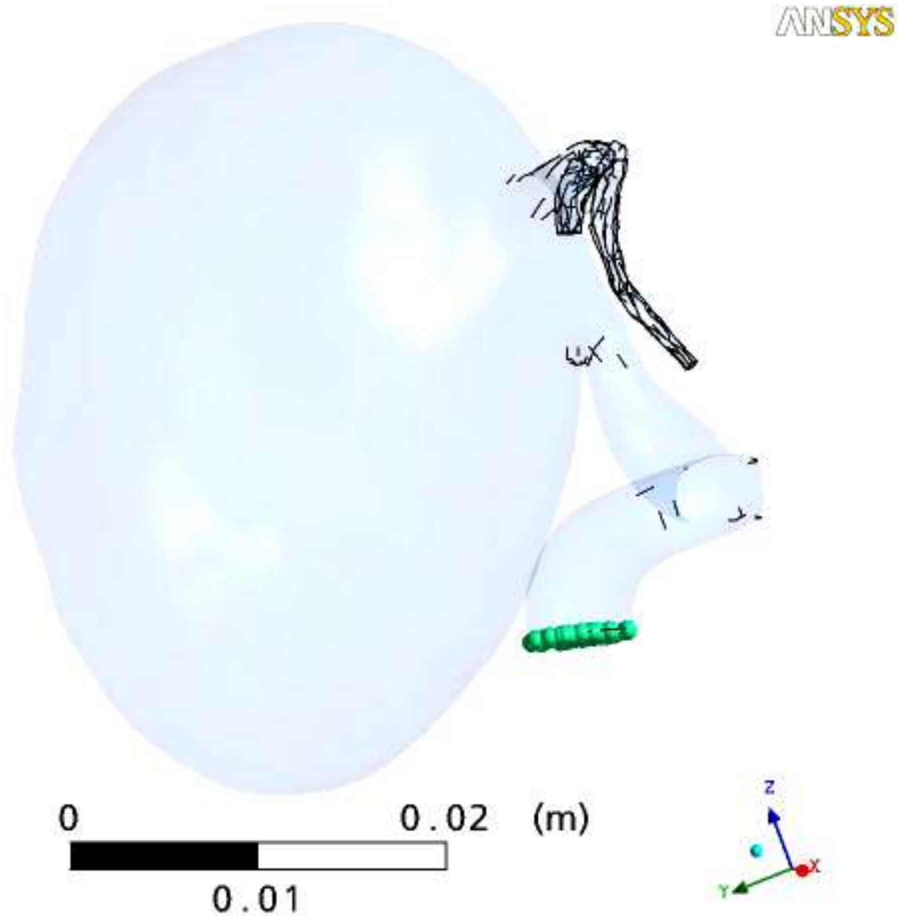


Wall shear stress



Validation: flow patterns





Particle tracking:

Particle size: 20μm

Density: 2300kg/m^3

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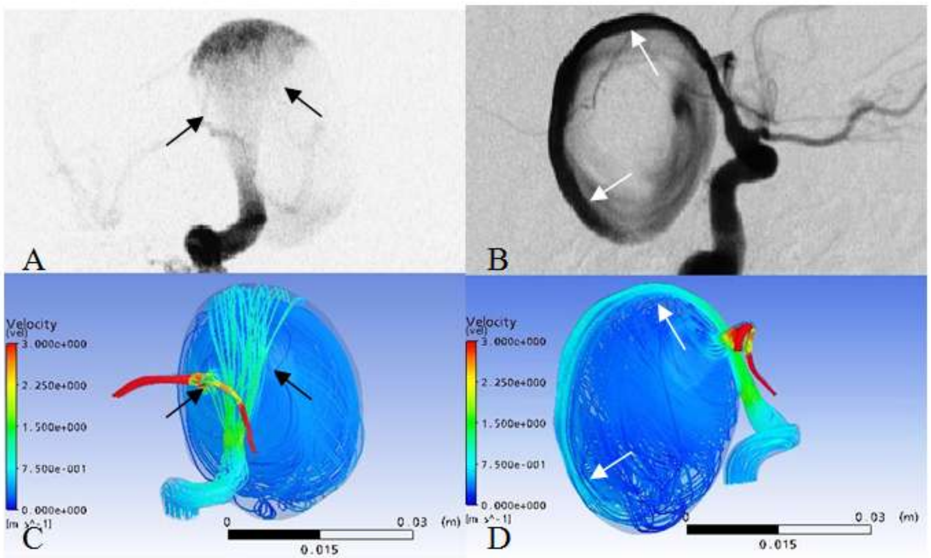
Wall mechanics



Shear Stress

↓

Compensatory Vascular Tone

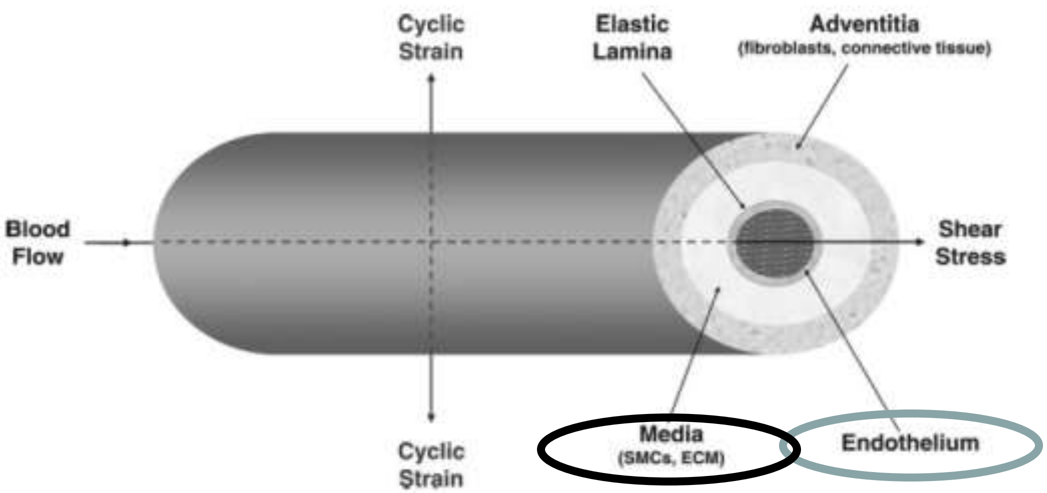
↓

Growth and Remodelling

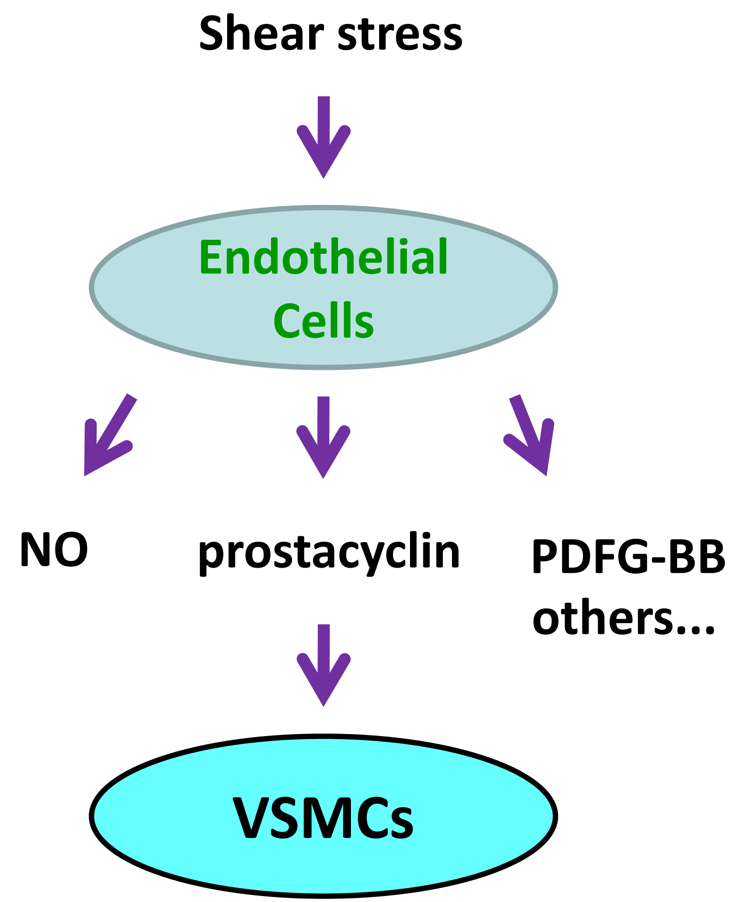
↓

Aneurysm

Tissue to cellular



Cummins et al. (2007) *Am J Physiol Heart Circ Physiol:292*, Fig 1.



Approach

- **Multiple pathways with significant crosstalk**
- **Multiple cell types**
- **Multiple networks on multiple time scales**
- **Emergent properties important**

  Biophysically-based systems biology approach necessary

- **Library of biochemical module models**
- **Reparameterised and reused**

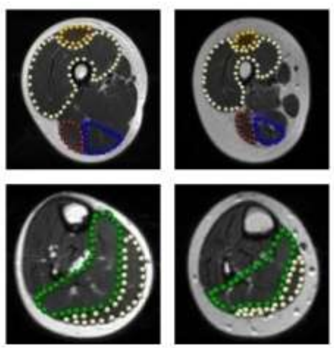
Musculo-skeletal models

Subject-specific modelling of gait dynamics in orthopaedic research

Joint degradation with age ▷

Subject-specific loading → Bone remodelling → Osteo-arthritis

Cerebral palsy ▷



Morphological Alterations → Pathological gait → Bone deformities

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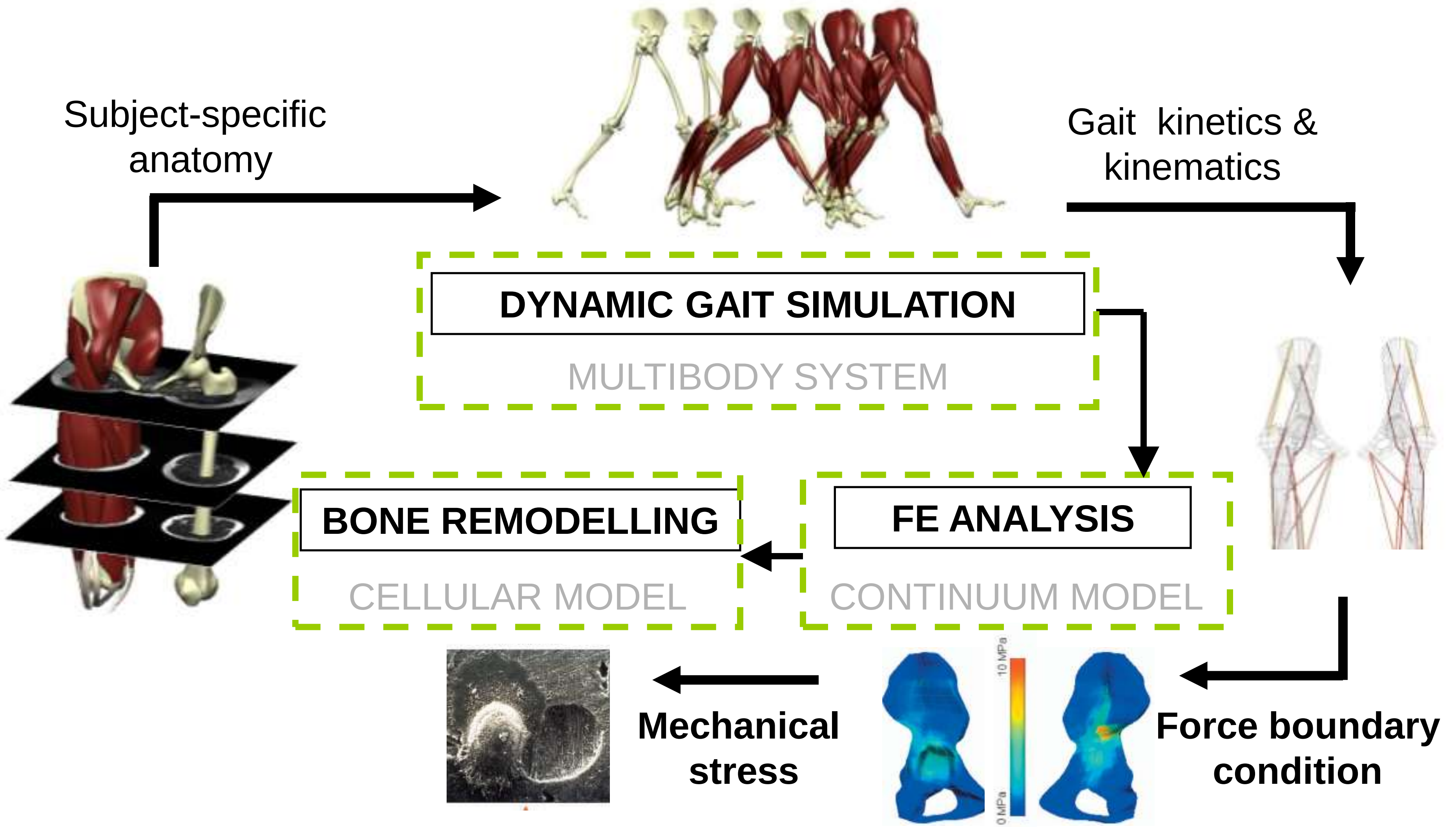
Workflow



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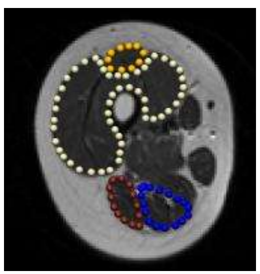
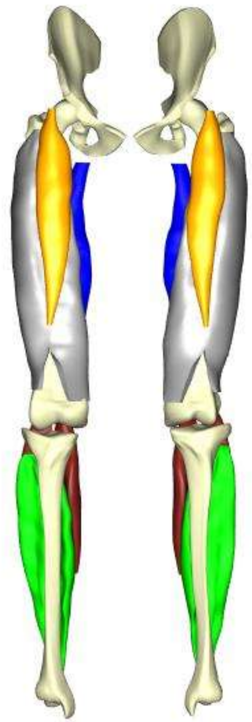
Gait Analysis

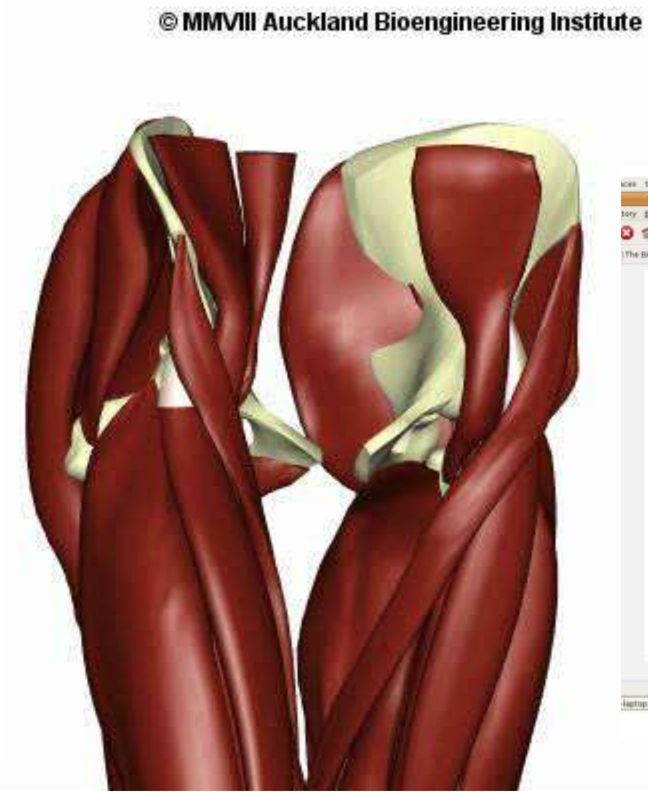
from measurement

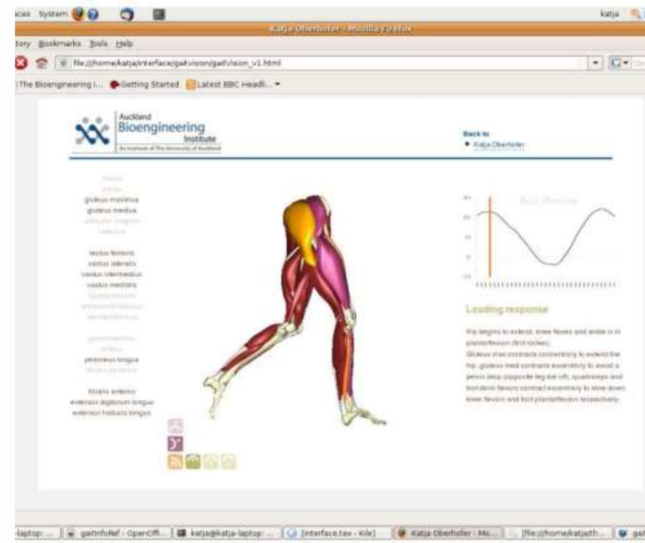
to simulation

ABI Gait research









Muscle architecture in CP[1]

Muscle deformation during walking[2]

Medical education www.gaitworld.com

[1]*Oberhofer et al., Clinical Biomechanics, **2009**, online first*

[2] *Oberhofer et al., The Visual Computer, **2009**, 25(9), 843-851*

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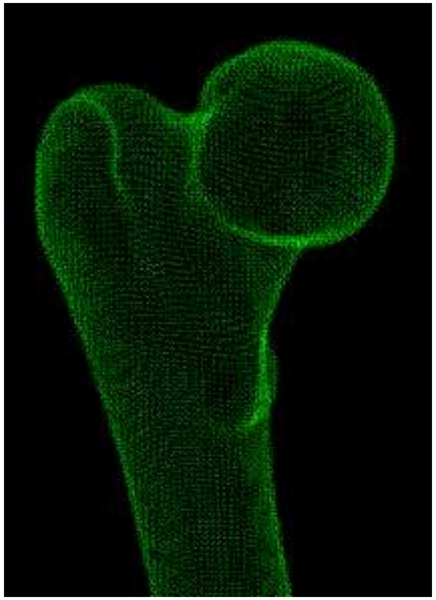
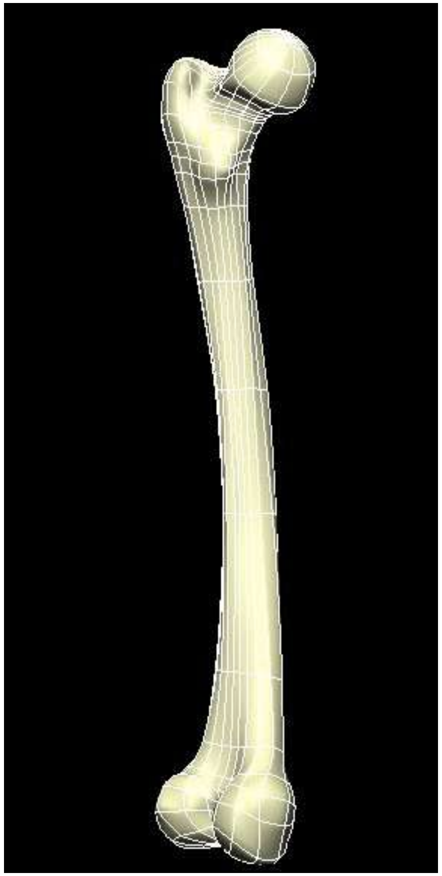
Principal component analysis

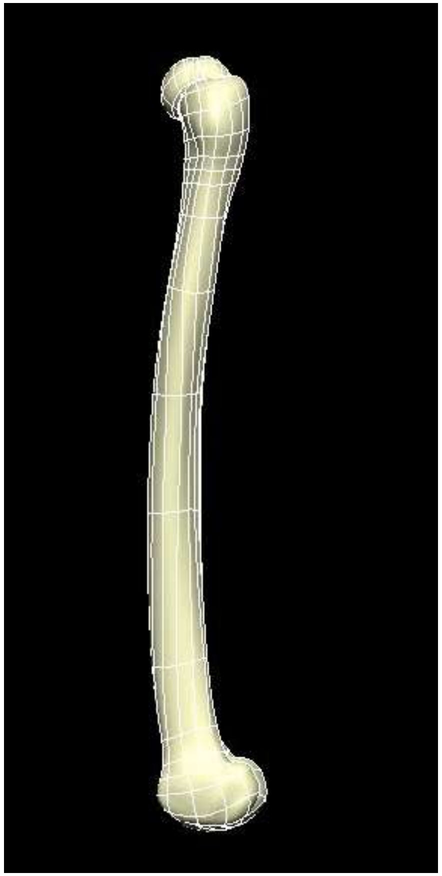
17 left femurs



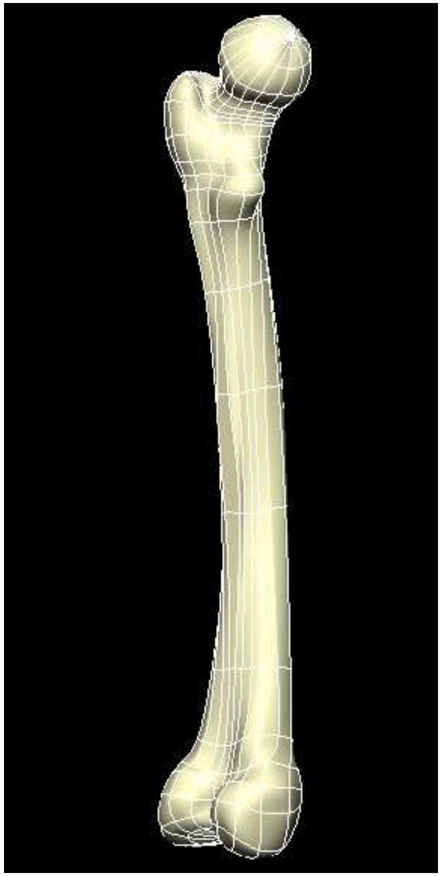
PC1 - 97%



PC2 - 0.94%



PC3 - 0.82%



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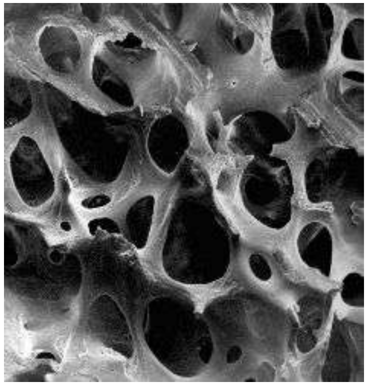
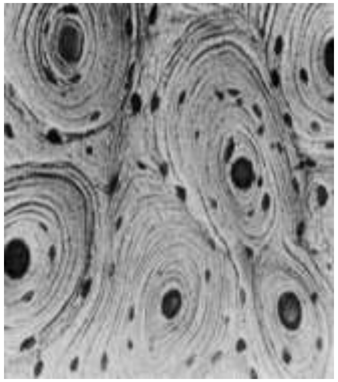
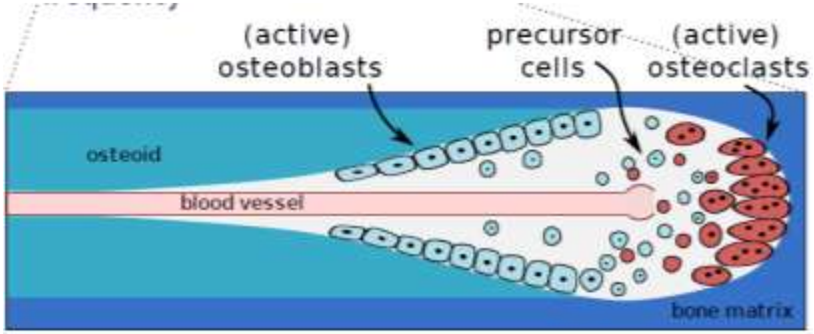
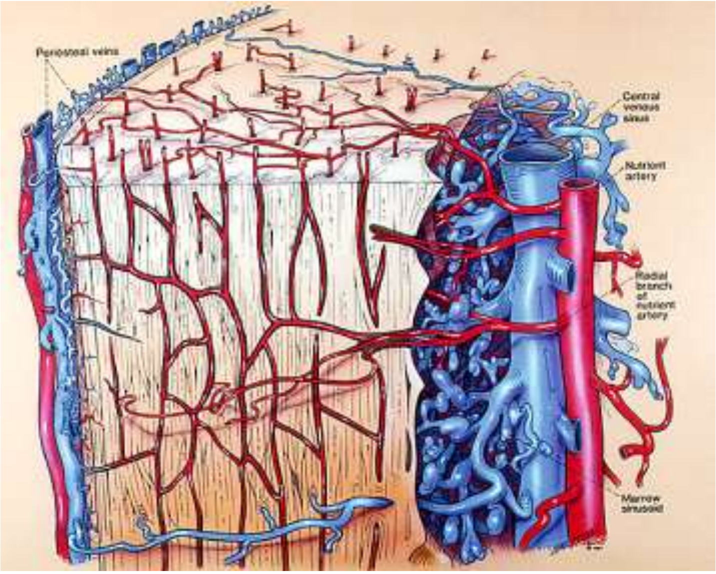
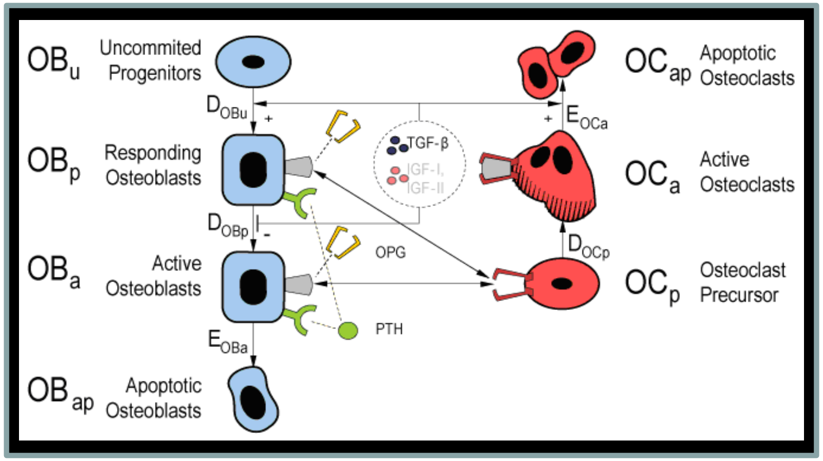
Multiscale modeling of bone











David Smith, UWA

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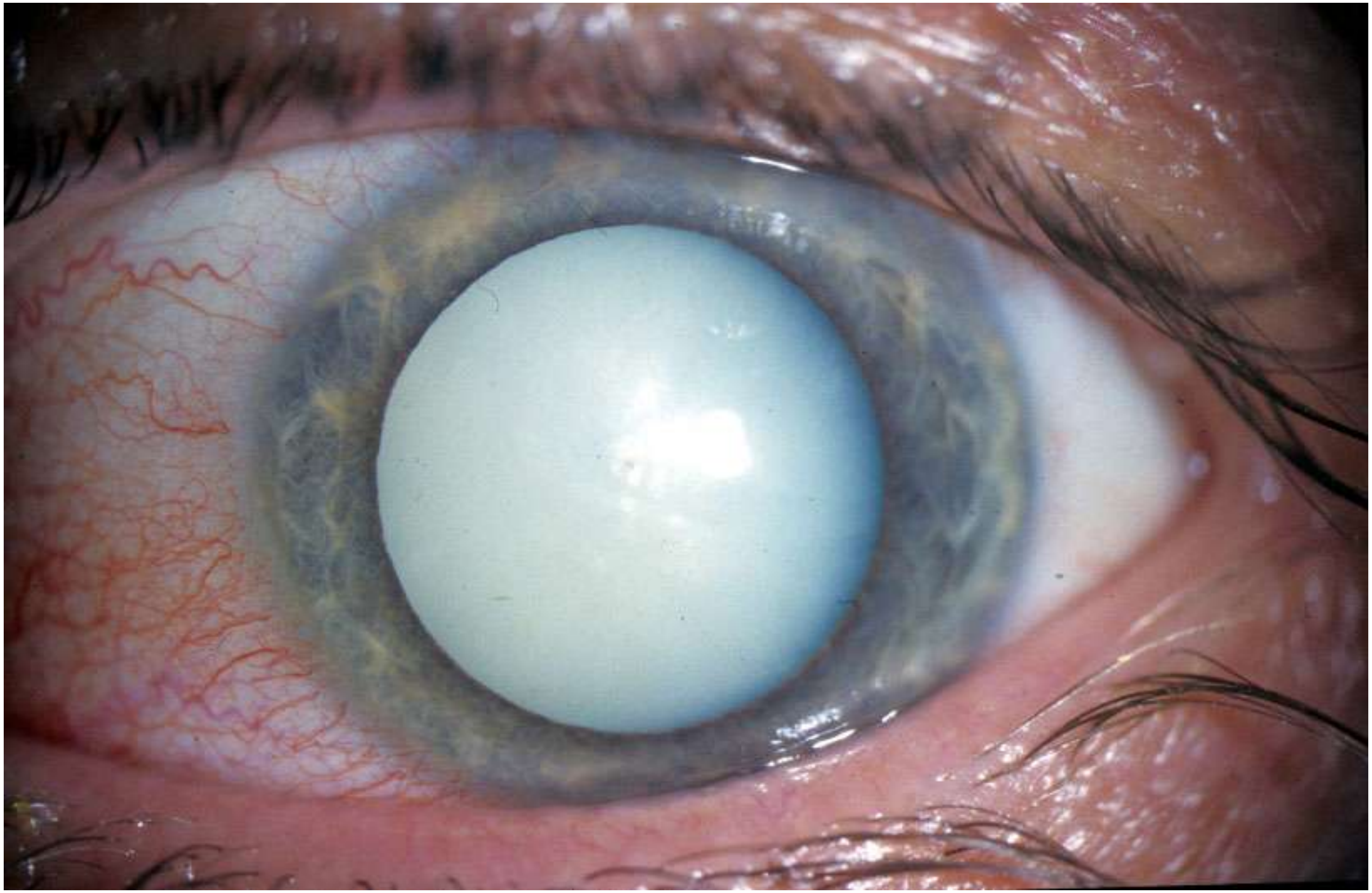
Lens & eye models

Medical therapies for cataracts



Paul Donaldson, Marc Jacobs and Ehsan Vaghefi

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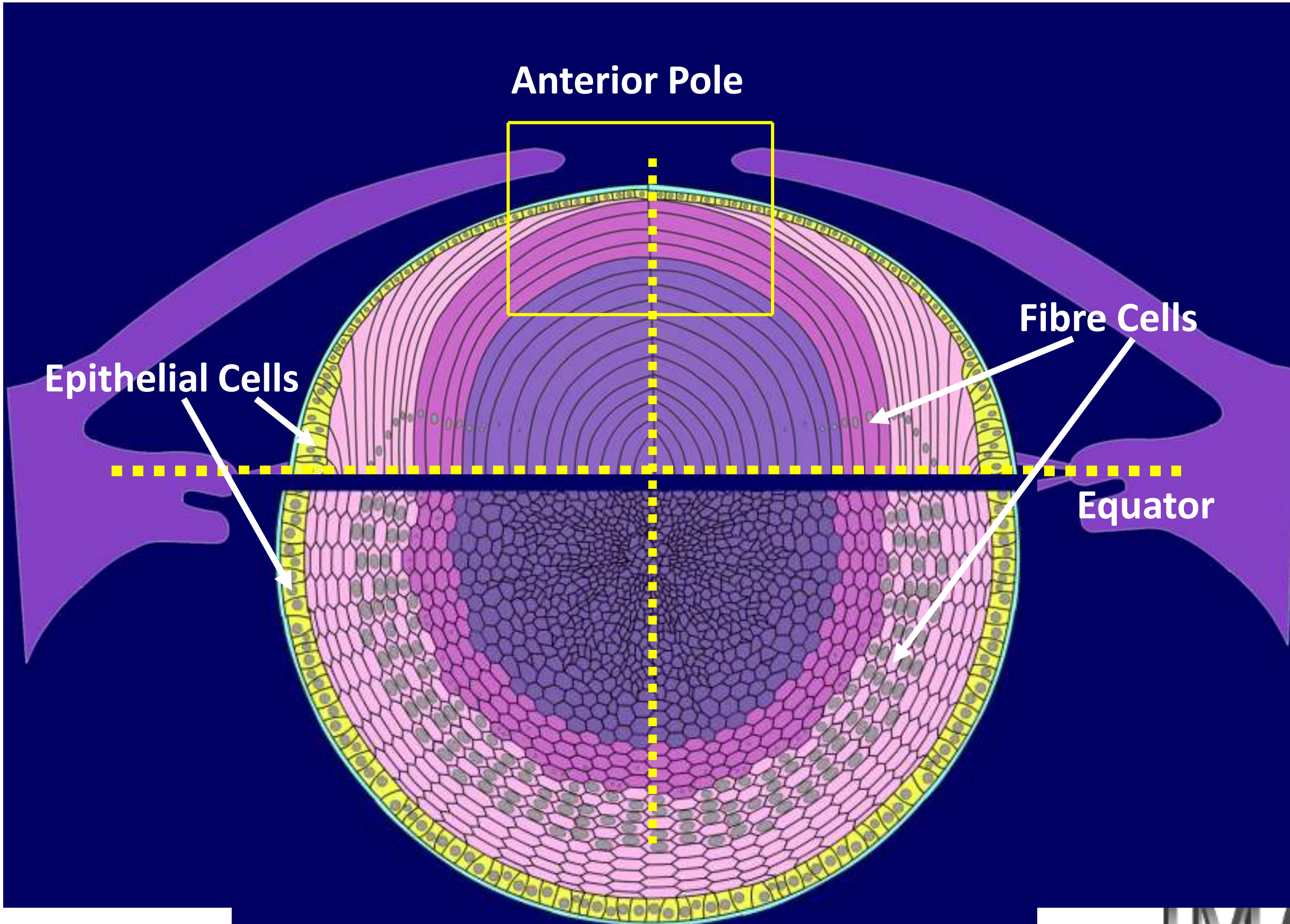
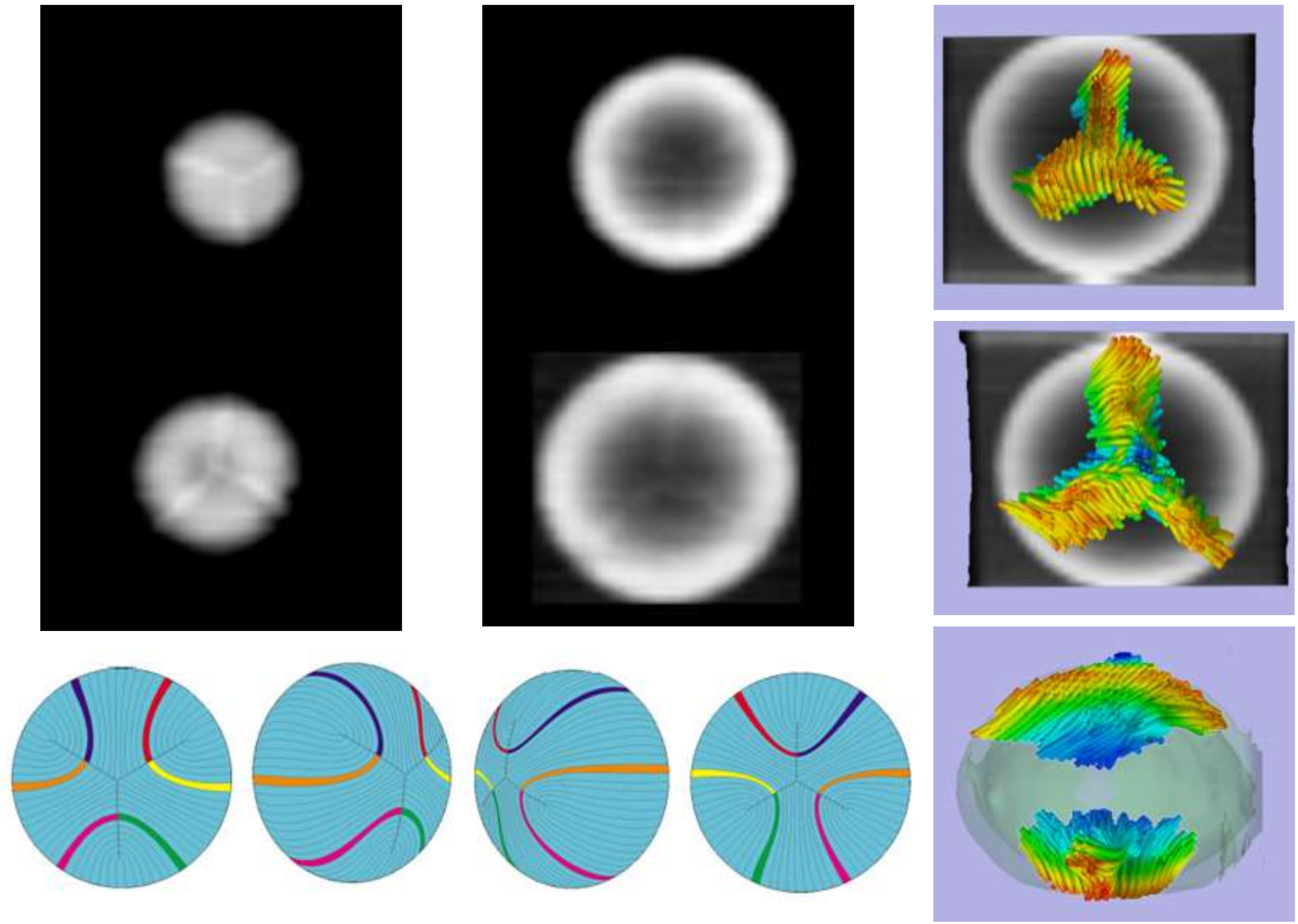
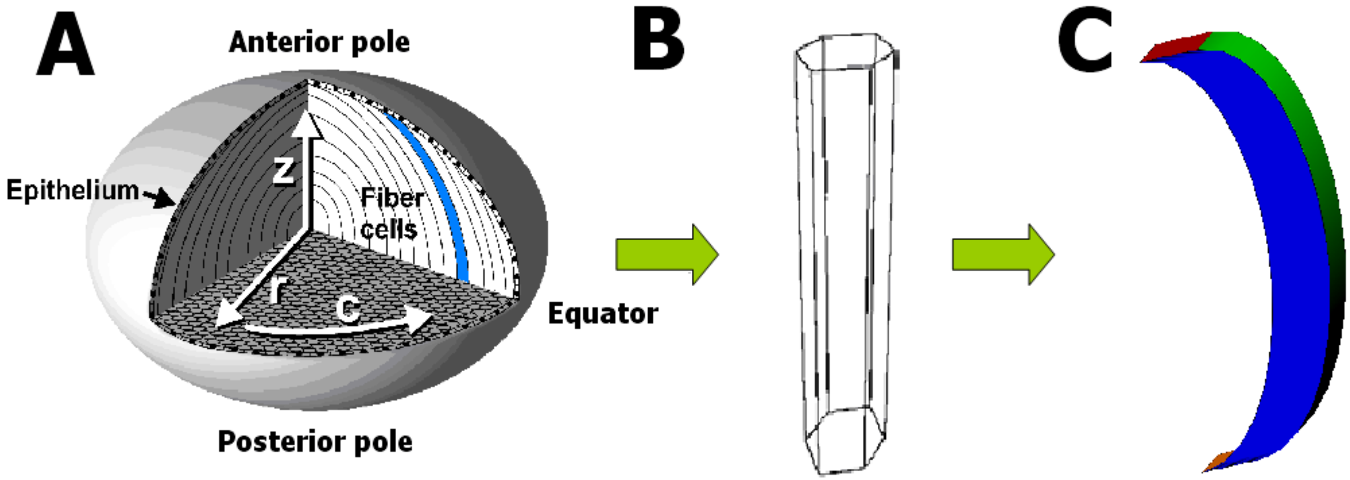
Lens structure

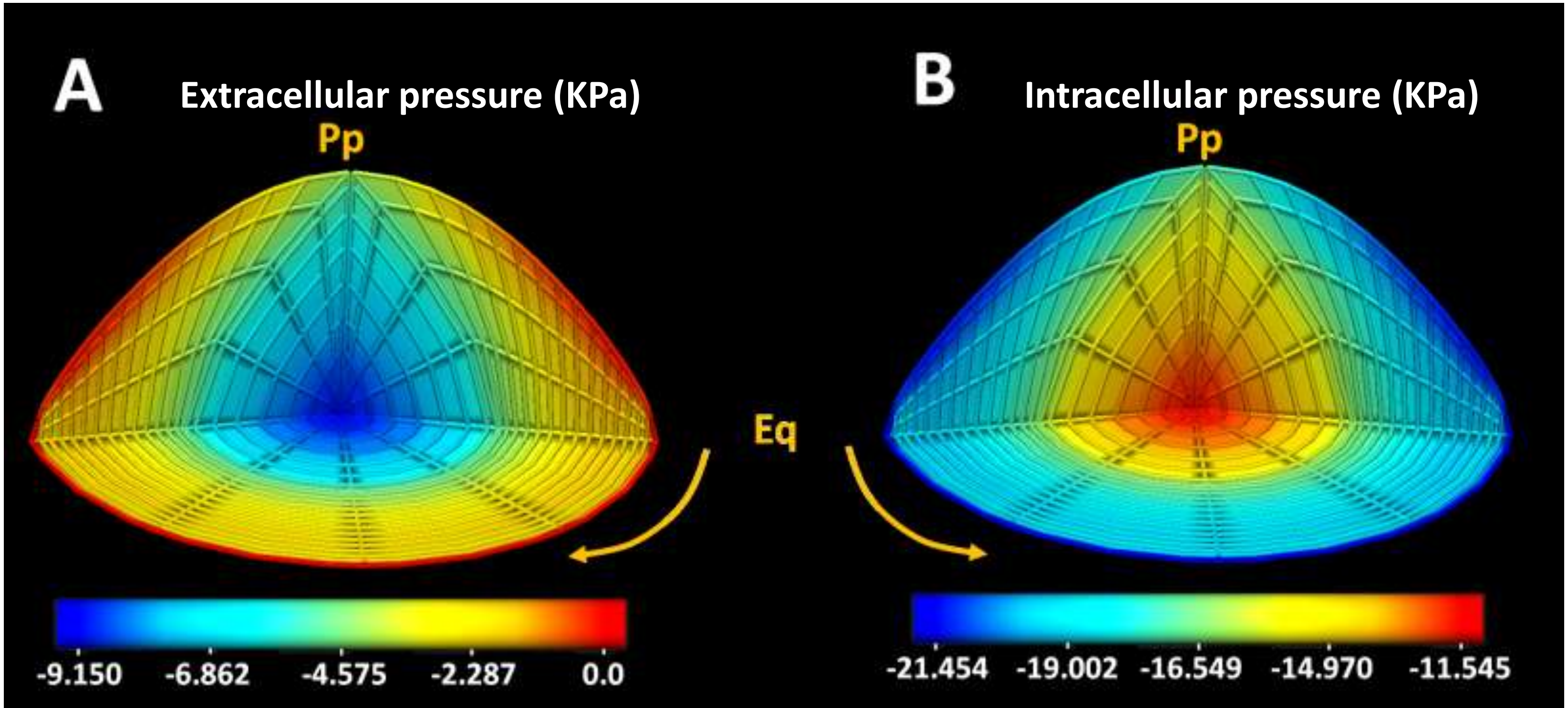


3D structure of lens sutures using diffusion tensor imaging

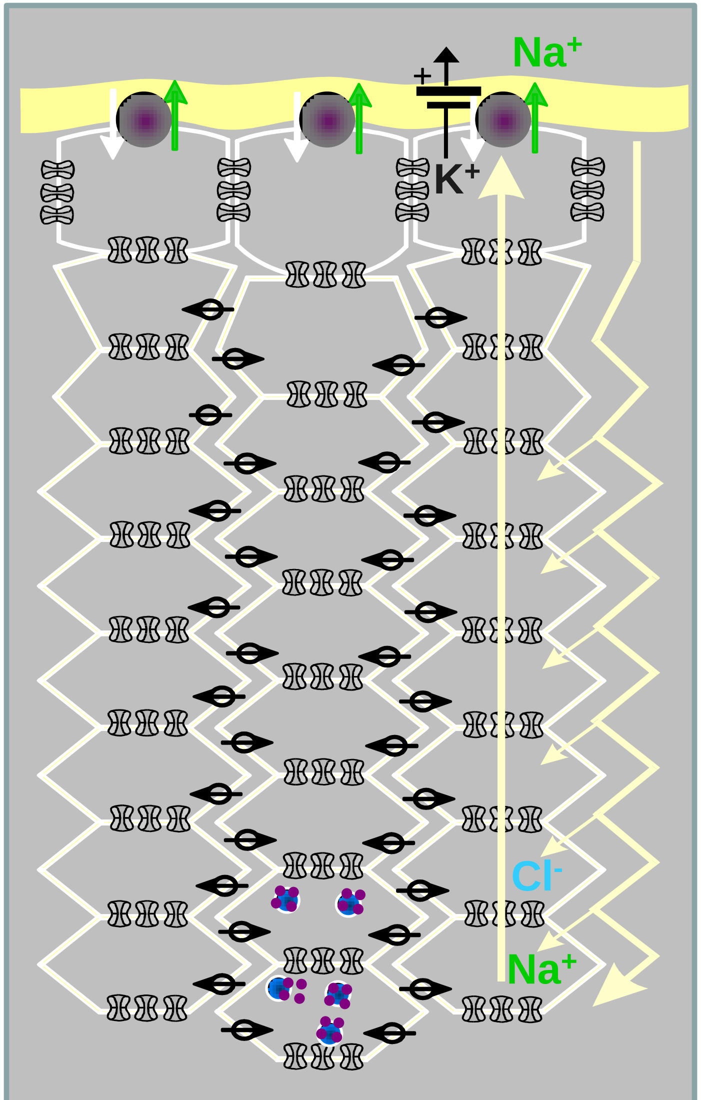


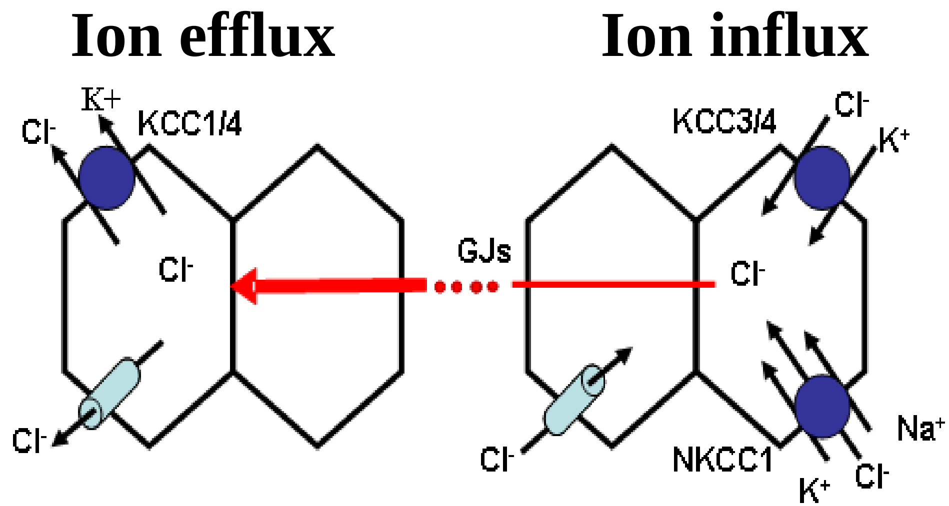
Modeling mechanics of lens shape changes



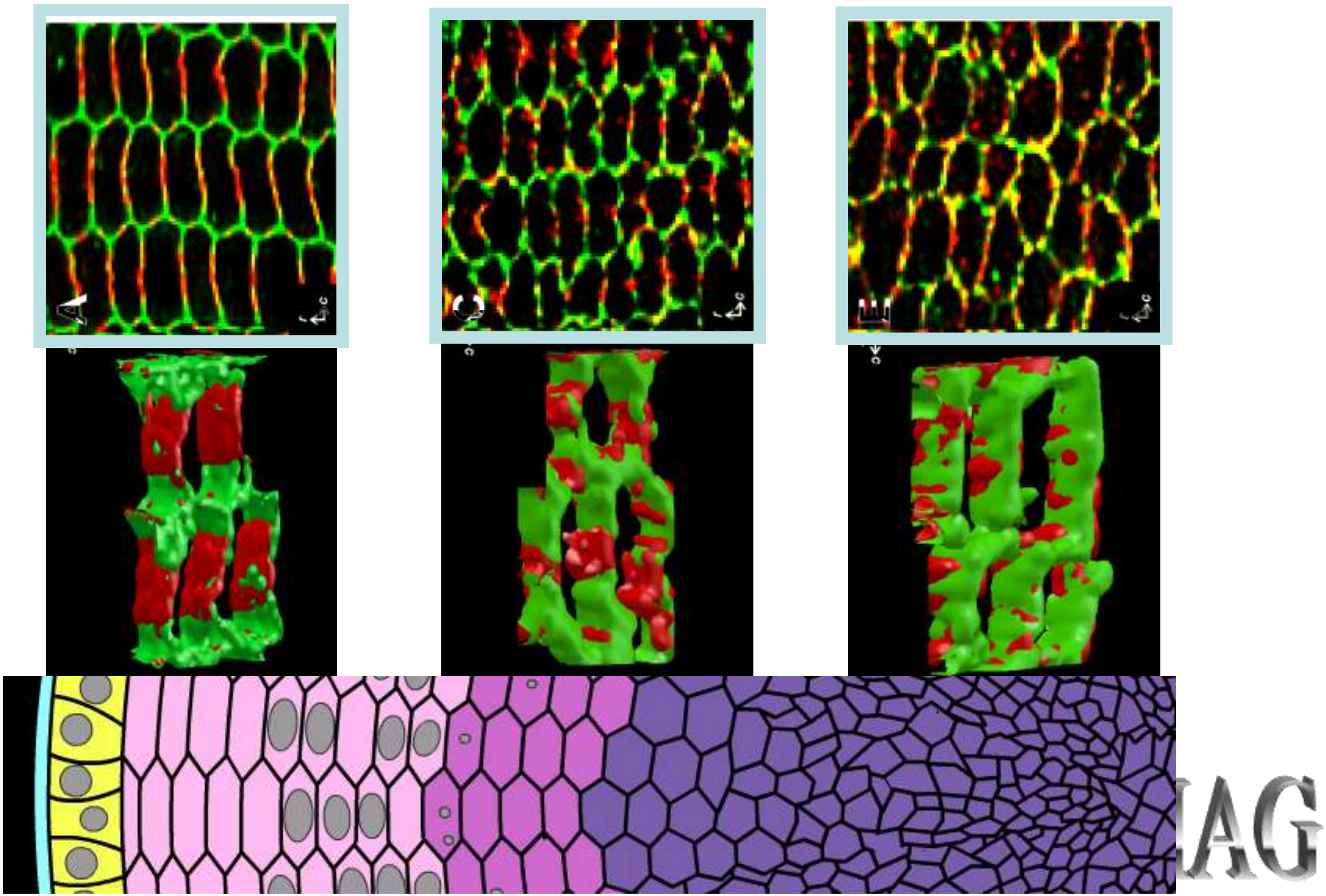


Lens function: the internal circulation system





Differentiation dependent changes in the subcellular distribution of gap junctions



Osmotic stress changes the subcellular distribution of $P2X_4$

Isotonic condition

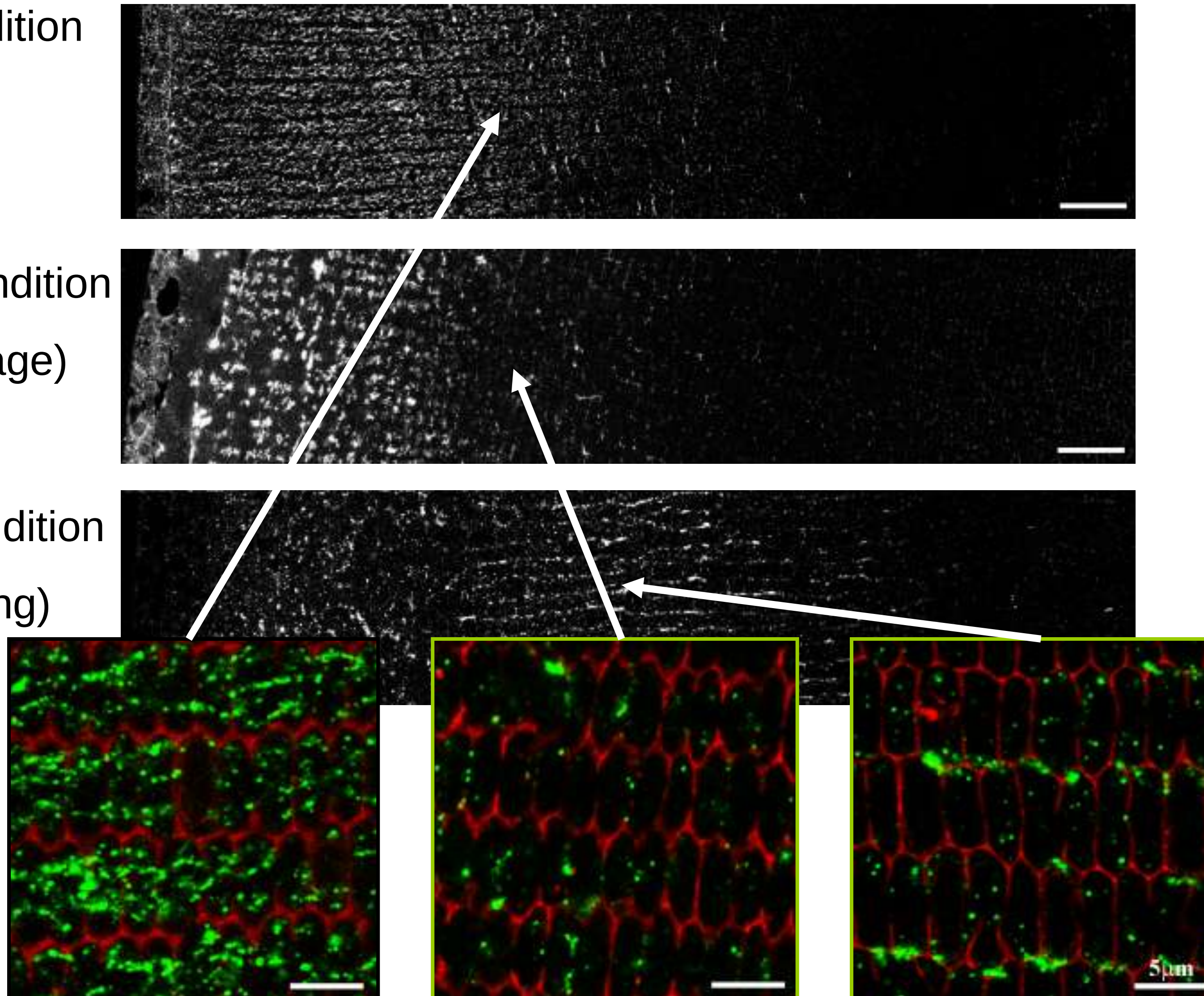
(Normal)

Hypertonic condition

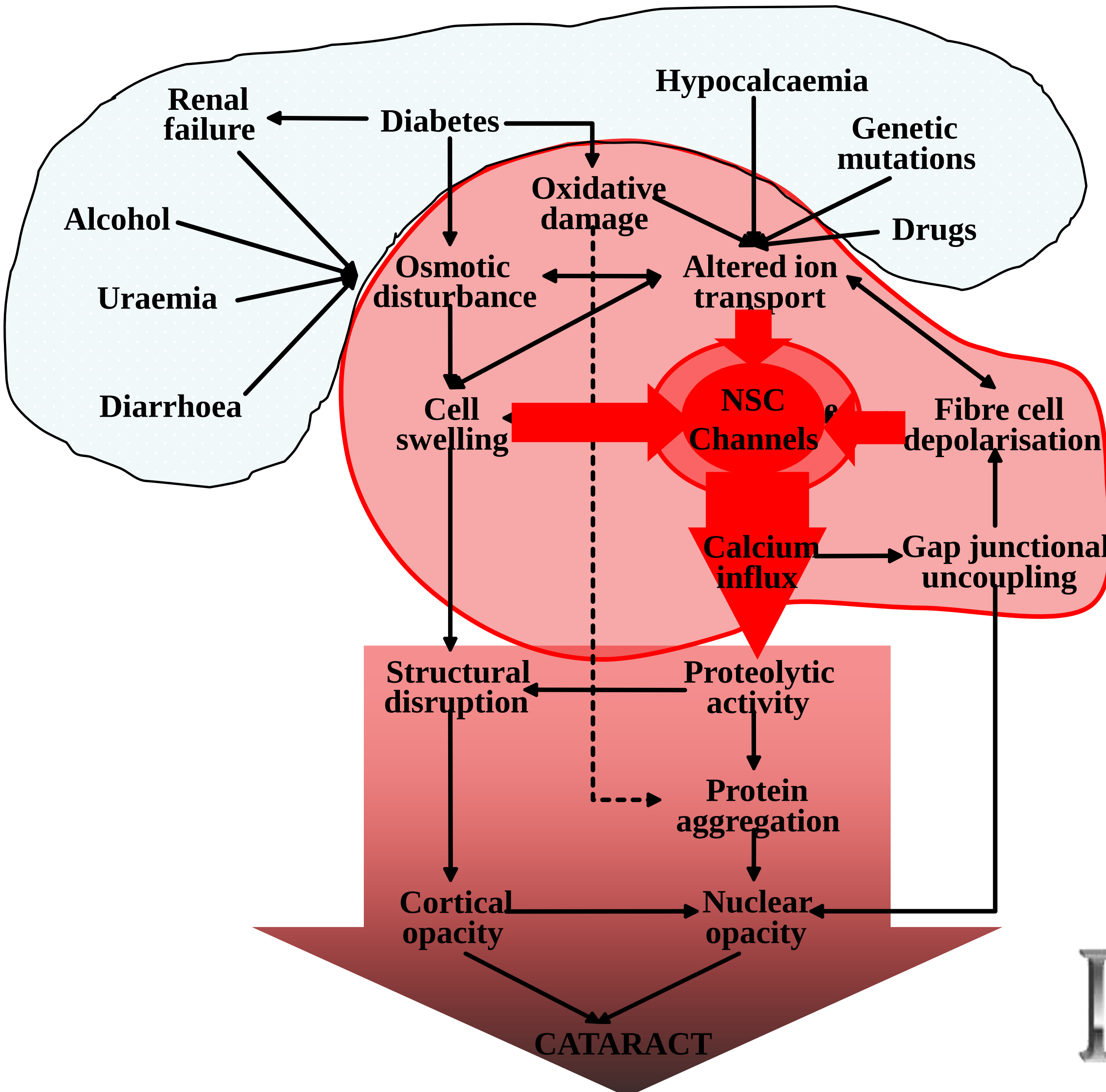
(Cell shrinkage)

Hypotonic condition

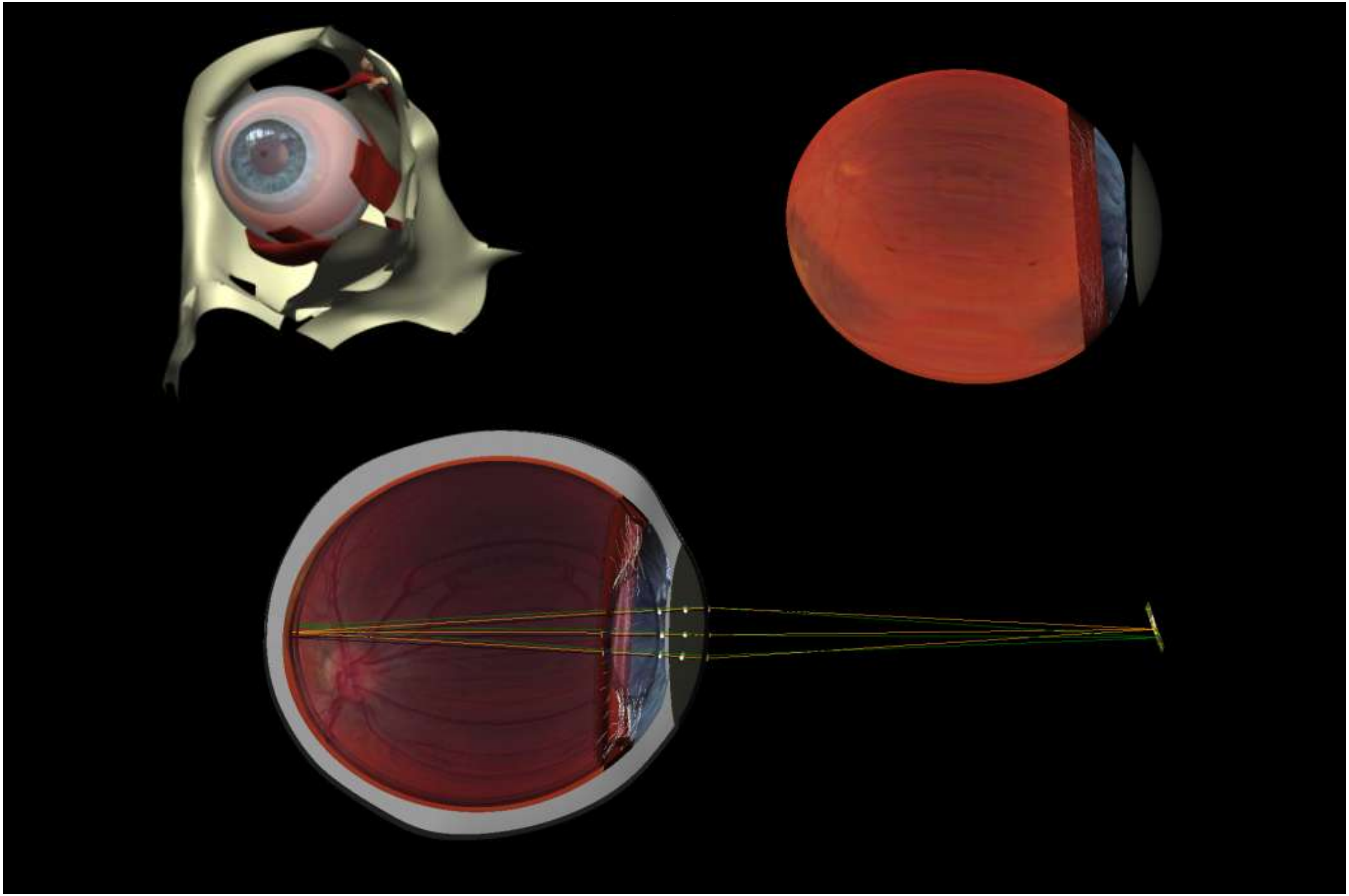
(Cell swelling)



Calcium influx and initiation of cataract



An integrated eye model



VPH/Physiome infrastructure

Modeling multiple cell processes

Individual models

- **Pandit et al. (2001): Cardiac electrophysiology**
  - ion channels, pumps, sarcoplasmic reticulum
- **Hinch et al. (2004): Calcium regulation**
  – LCC channels, dyadic space and RyR complexes
- **Niederer et al. (2006): Myofilament mechanics**
  - calcium binding to troponin, tropomyosin kinetics and cross-bridge dynamics.

IMAG

Pandit et al. Model of cardiac action potential

Pandit SV, Clark RB, Giles WR, et al. A mathematical model of action potential heterogeneity in adult rat left ventricular myocytes. *Biophys J* 81(6):3029-51, 2001.

www.cellml.org/models/pandit_clark_giles_demir_2001_version11

A Mathematical Model of Action Potential Heterogeneity in Adult Rat Left Ventricular Myocytes

Download Model (151Kb)	Solve model in: (help) PCEnv JSim COR PCEnv Session (What's this?)
Curation Status:	

Model Documentation

Model Status

This CellML version of the model represents the epicardial cell. A number of inconsistencies in units and errors in equations from version 07 were fixed in this version. In addition to the formulation given by the paper and the author's later Corrections document, the IStim current has been adjusted to produce 1 Hz stimulations for 10 seconds.

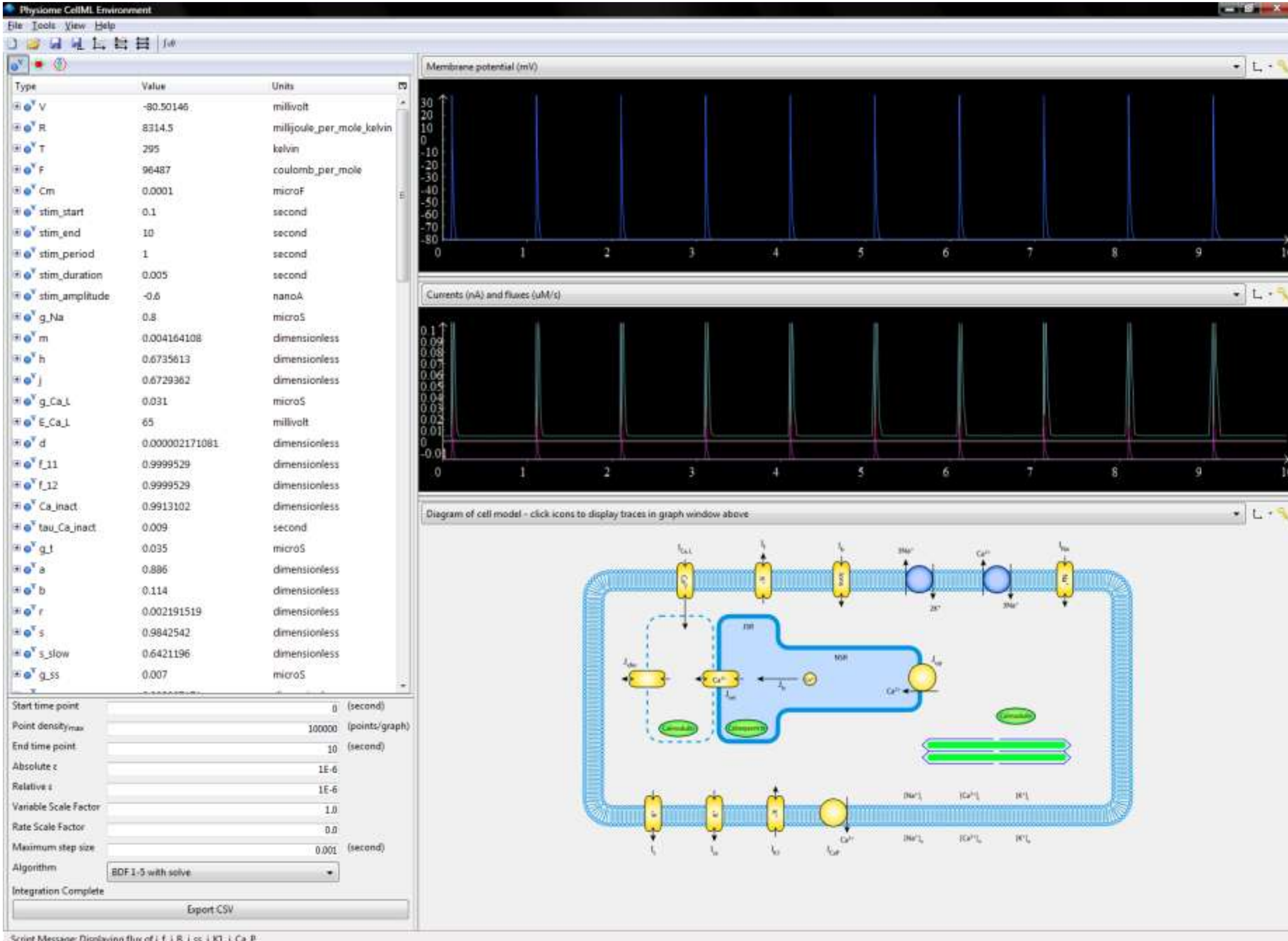
Model Structure

Over the past decade electrophysiological studies have revealed transmural heterogeneity, or differences in the action potential waveforms recorded in cells isolated from the epicardial and the endocardial tissues in the left ventricles of mammalian hearts.

The adult rat has been widely used as an experimental model to investigate the electrical heterogeneity in the left ventricle under normal conditions and pathophysiological states. From this biophysical, experimental data, derived from patch clamp experiments, Sandeep V. Pandit, Robert B. Clark, Wayne R. Giles and Semahat S. Demir have developed a mathematical model of action potential heterogeneity in adult rat left ventricular myocytes (see the figure below). The mathematical models for the epicardial and endocardial cells of the rat left ventricle are based on the classical formulation of Hodgkin and Huxley (please see the CellML version of The Hodgkin-Huxley Squid Axon Model, 1952 for more details), and are therefore similar to previous computational work carried out by this research group (see Demir *et al.* Sinoatrial Node Model 1994 and Demir *et al.* Sinoatrial Node Model 1999). The endocardial cell model is based on the epicardial formulation with only slight modifications in certain parameters and equations.

The complete original paper reference is cited below:

A Mathematical Model of Action Potential Heterogeneity in Adult Rat Left Ventricular Myocytes, , Sandeep V. Pandit, Robert B. Clark, Wayne R. Giles and Semahat S. Demir, 2001, *Biophysical Journal* , 81, 3029-3051. (Full text and PDF versions of the article are available for Journal Members on the Biophysical Journal website.) PubMed ID: 11720973


Physiome CellML Environment
File Tools View Help
Type Value Units
V -80.50146 millivolt
R 8314.5 millijoule_per_mole_kelvin
T 295 kelvin
F 96487 coulomb_per_mole
Cm 0.0001 microF
stim_start 0.1 second
stim_end 10 second
stim_period 1 second
stim_duration 0.005 second
stim_amplitude -0.6 nanoA
g_Na 0.8 microS
m 0.004164108 dimensionless
h 0.6735613 dimensionless
j 0.6729362 dimensionless
g_Ca_L 0.031 microS
E_Ca_L 65 millivolt
d 0.000002171081 dimensionless
f_11 0.9999529 dimensionless
f_12 0.9999529 dimensionless
Ca_inact 0.9913102 dimensionless
tau_Ca_inact 0.009 second
g_t 0.035 microS
a 0.886 dimensionless
b 0.114 dimensionless
r 0.002191519 dimensionless
s 0.9842542 dimensionless
s_slow 0.6421196 dimensionless
g_ss 0.007 microS
Start time point 0 (second)
Point density max 100000 (points/graph)
End time point 10 (second)
Absolute ε 1E-6
Relative ε 1E-6
Variable Scale Factor 1.0
Rate Scale Factor 0.0
Maximum step size 0.001 (second)
Algorithm BDF 1-5 with solve
Integration Complete
Export CSV
Membrane potential (mV)
Currents (nA) and fluxes (uM/s)
Diagram of cell model - click icons to display traces in graph window above
Script Message: Displaying flux of i_f, i_B, i_ss, i_K1, i_Ca_P

Hinch et al. Model of Ca-induced Ca release

Hinch R, Greenstein JR, Tanskanen AJ, et al. A simplified local control model of Ca-induced Ca release in cardiac ventricular myocytes. *Biophys J* 87:3723-3736, 2004.

www.cellml.org/models/hinch_greenstein_tanskanen_xu_winslow_2004_version02

A Simplified Local Control Model of Calcium-Induced Calcium Release in Cardiac Ventricular Myocytes

Download Model (113Kb)	Solve model in: (help) PCEnv ★★☆ JSim ☆☆☆ COR ★★☆ PCEnv Session (What's this?)
Curation Status: ★★☆	

Model Documentation

Model Status

This model is known to run in PCEnv and COR to reproduce the output shown in the publication. A PCEnv session file is also associated with this model.

Model Structure

This CellML model was based on the December 2004 paper:

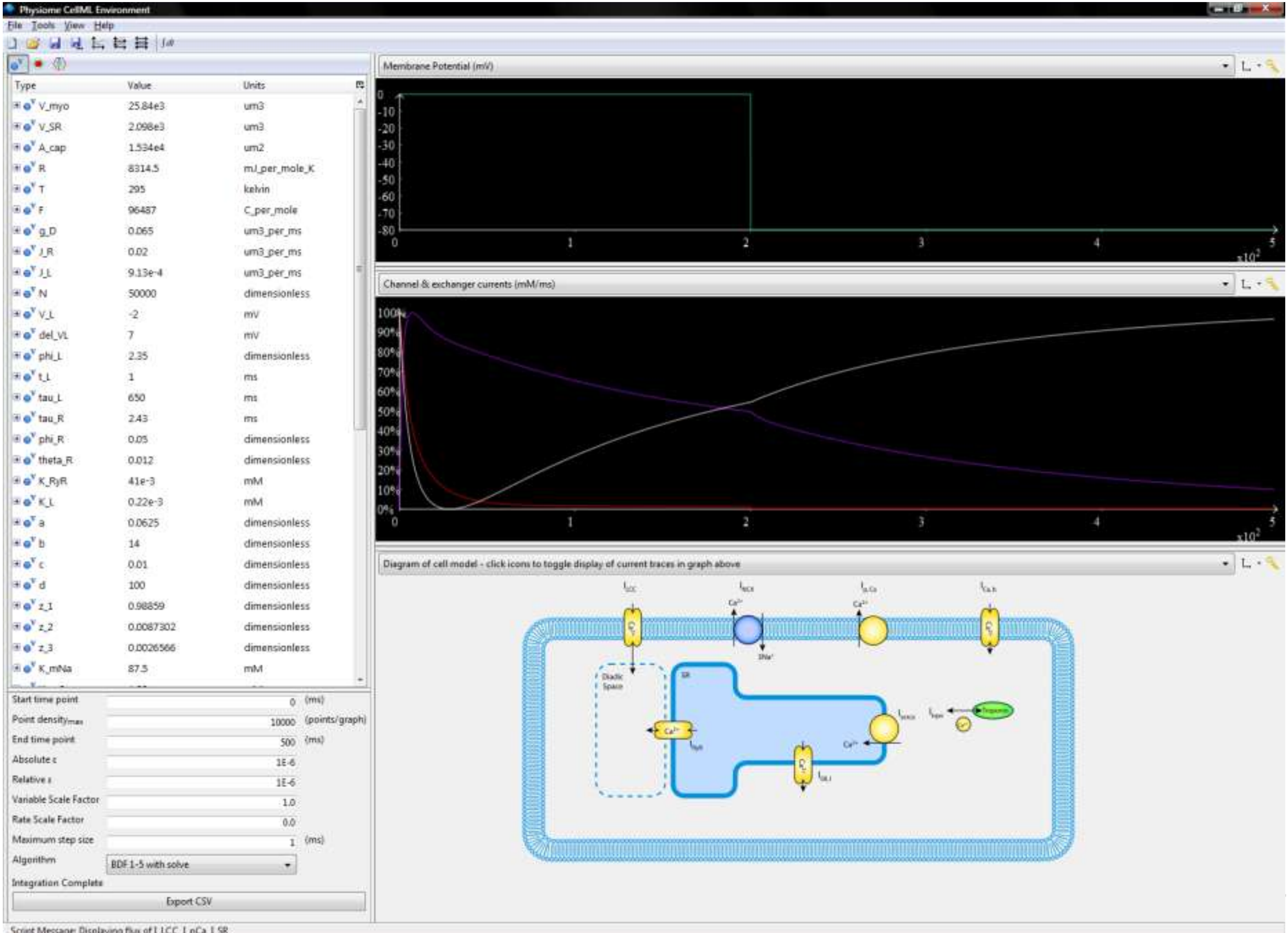
"A Quantitative Analysis of Cardiac Myocyte Relaxation: A Simulation Study" by Hinch, Greenstein, Tanskanen, Xu and Winslow.

The following is the abstract of this paper:

Calcium (Ca2+)-induced Ca2+ release (CICR) in cardiac myocytes exhibits high gain and is graded. These properties result from local control of Ca2+ release. Existing local control models of Ca2+ release in which interactions between L-Type Ca2+ channels (LCCs) and ryanodine-sensitive Ca2+ release channels (RyRs) are simulated stochastically are able to reconstruct these properties, but only at high computational cost. Here we present a general analytical approach for deriving simplified models of local control of CICR, consisting of low-dimensional systems of coupled ordinary differential equations, from these more complex local control models in which LCC-RyR interactions are simulated stochastically. The resulting model, referred to as the coupled LCC-RyR gating model, successfully reproduces a range of experimental data, including L-Type Ca2+ current in response to voltage-clamp stimuli, inactivation of LCC current with and without Ca2+ release from the sarcoplasmic reticulum, voltage-dependence of excitation-contraction coupling gain, graded release, and the force-frequency relationship. The model does so with low computational cost.

The complete original publication reference is cited below:

A Simplified Local Control Model of Calcium-Induced Calcium Release in Cardiac Ventricular Myocytes, R. Hinch, J.R. Greenstein, A.J. Tanskanen, L. Xu, R.L. Winslow, 2004 *Biophysical Journal*, Volume 87 pp.3723-3736, PubMed ID: 15465866



Physiome CellML Environment
File Tools View Help
Type Value Units
V_myo 25.84e3 um3
V_SR 2.098e3 um3
A_cap 1.534e4 um2
R 8314.5 mJ_per_mole_K
T 295 kelvin
F 96487 C_per_mole
g_D 0.065 um3_per_ms
J_R 0.02 um3_per_ms
J_L 9.13e-4 um3_per_ms
N 50000 dimensionless
V_L -2 mV
del_VL 7 mV
phi_L 2.35 dimensionless
t_L 1 ms
tau_L 650 ms
tau_R 2.43 ms
phi_R 0.05 dimensionless
theta_R 0.012 dimensionless
K_RyR 41e-3 mM
K_L 0.22e-3 mM
a 0.0625 dimensionless
b 14 dimensionless
c 0.01 dimensionless
d 100 dimensionless
z_1 0.98859 dimensionless
z_2 0.0087302 dimensionless
z_3 0.0026566 dimensionless
K_mNa 87.5 mM
Start time point 0 (ms)
Point density max 10000 (points/graph)
End time point 500 (ms)
Absolute ε 1E-6
Relative ε 1E-6
Variable Scale Factor 1.0
Rate Scale Factor 0.0
Maximum step size 1 (ms)
Algorithm BDF 1-5 with solve
Integration Complete
Export CSV
Membrane Potential (mV)
0
-10
-20
-30
-40
-50
-60
-70
-80
0 1 2 3 4 5
x10²
Channel & exchanger currents (mM/ms)
100%
90%
80%
70%
60%
50%
40%
30%
20%
10%
0%
0 1 2 3 4 5
x10²
Diagram of cell model - click icons to toggle display of current traces in graph above
Diadic Space
SR
Troponin
Script Message: Displaying flux of I_LCC, I_pCa, I_SR

Niederer et al. Model of myofilament mechanics

Niederer SA, Hunter PJ, Smith NP. A quantitative analysis of cardiac myocyte relaxation: a simulation study. *Biophys J* 90(5):1697-722, 2006.

www.cellml.org/models/niederer_hunter_smith_2006_version02

overview | edit | view math | model metadata | curation | view cellml | data | procedural code

A quantitative analysis of cardiac myocyte relaxation: a simulation study

Download Model (52Kb)	Solve model in: (help) PCEnv JSim COR PCEnv Session (What's this?)
Curation Status:	

Model Documentation

Model Status

This model is known to run in PCEnv and COR to reproduce the output shown in the publication. A PCEnv session file is also associated with this model.

Model Structure

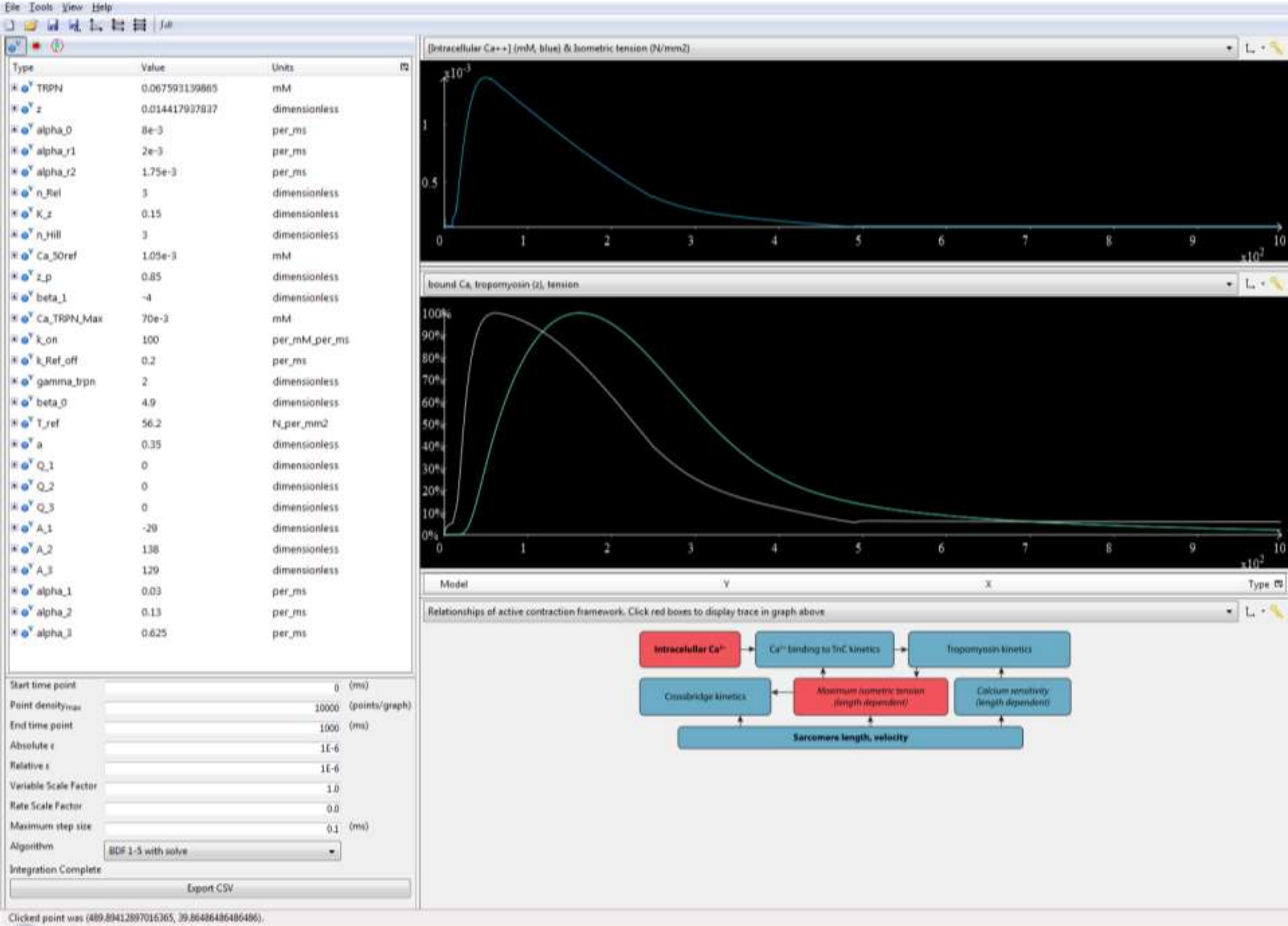
This CellML model was based on the March 2007 paper:

"A Quantitative Analysis of Cardiac Myocyte Relaxation: A Simulation Study" by S.A. Niederer, P.J. Hunter and N.P. Smith.

The following is the abstract of this paper: The determinants of relaxation in cardiac muscle are poorly understood, yet compromised relaxation accompanies various pathologies and impaired pump function. In this study, we develop a model of active contraction to elucidate the relative importance of the [Ca++]i transient magnitude, the unbinding of Ca++ from troponin C (TnC), and the lengthdependence of tension and Ca++ sensitivity on relaxation. Using the framework proposed by one of our researchers, we extensively reviewed experimental literature, to quantitatively characterize the binding of Ca++ to TnC, the kinetics of tropomyosin, the availability of binding sites, and the kinetics of crossbridge binding after perturbations in sarcomere length. Model parameters were determined from multiple experimental results and modalities (skinned and intact preparations) and model results were validated against data from length step, caged Ca++, isometric twitches, and the half-time to relaxation with increasing sarcomere length experiments. A factorial analysis found that the [Ca++]i transient and the unbinding of Ca++ from TnC were the primary determinants of relaxation, with a fivefold greater effect than that of length-dependent maximum tension and twice the effect of tension-dependent binding of Ca++ to TnC and length-dependent Ca++ sensitivity. The affects of the [Ca++]i transient and the unbinding rate of Ca++ from TnC were tightly coupled with the effect of increasing either factor, depending on the reference [Ca++]i transient and unbinding rate.

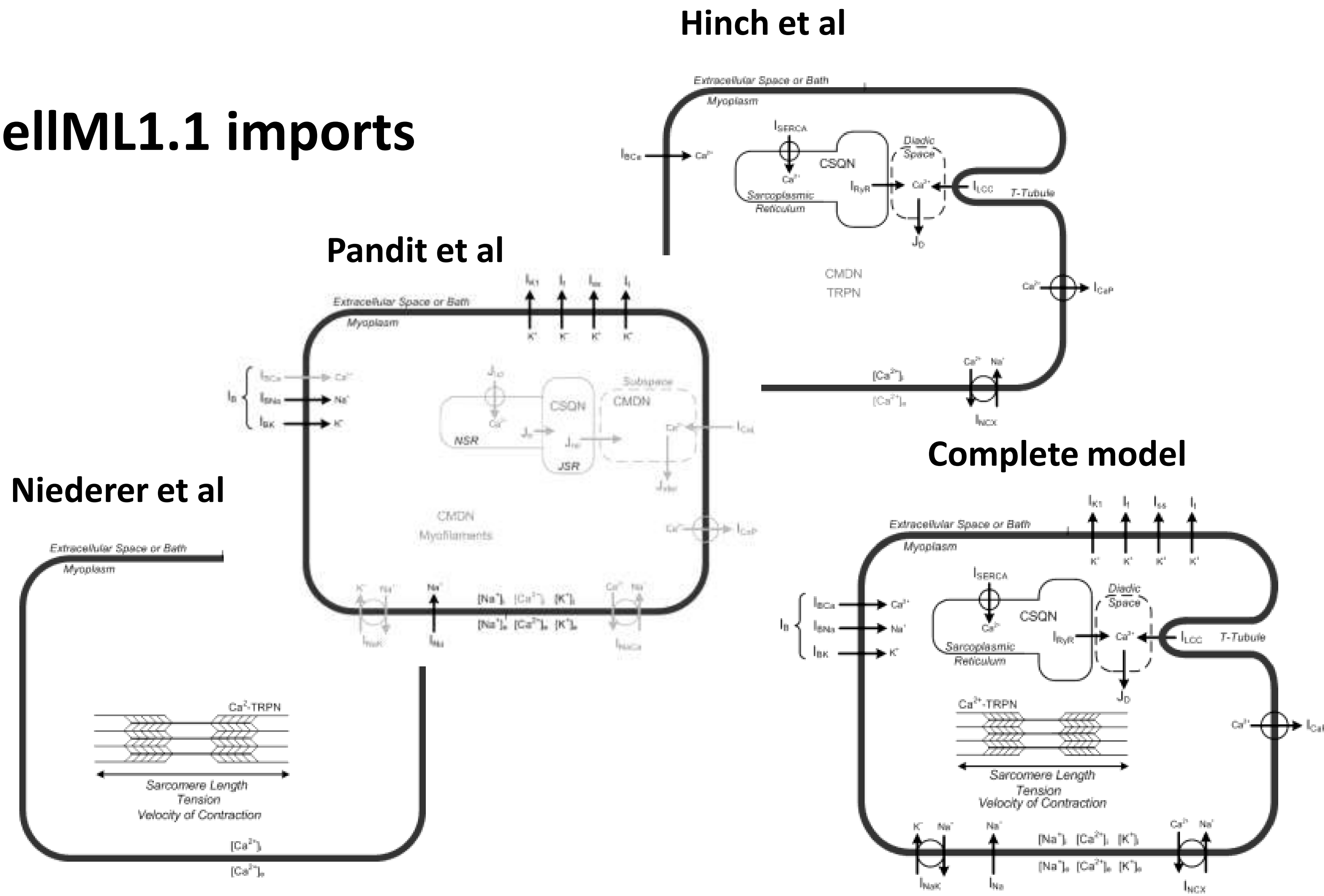
The complete original publication reference is cited below:

A Quantitative Analysis of Cardiac Myocyte Relaxation: A Simulation Study, Steven Niederer, Peter Hunter, Nicholas Smith, 2006 *Biophysical Journal* , 90 1697-1722 PubMed ID: 16339881


File Tools View Help
Type Value Units
TRPN 0.067593139865 mM
z 0.014417937837 dimensionless
alpha_0 8e-3 per_ms
alpha_r1 2e-3 per_ms
alpha_r2 1.75e-3 per_ms
n_Rel 3 dimensionless
K_z 0.15 dimensionless
n_Hill 3 dimensionless
Ca_50ref 1.05e-3 mM
z_p 0.85 dimensionless
beta_1 -4 dimensionless
Ca_TRPN_Max 70e-3 mM
k_on 100 per_mM_per_ms
k_Ref_off 0.2 per_ms
gamma_trpn 2 dimensionless
beta_0 4.9 dimensionless
T_ref 56.2 N_per_mm2
a 0.35 dimensionless
Q_1 0 dimensionless
Q_2 0 dimensionless
Q_3 0 dimensionless
A_1 -29 dimensionless
A_2 138 dimensionless
A_3 129 dimensionless
alpha_1 0.03 per_ms
alpha_2 0.13 per_ms
alpha_3 0.625 per_ms
Start time point 0 (ms)
Point density max 10000 (points/graph)
End time point 1000 (ms)
Absolute ε 1E-6
Relative ε 1E-6
Variable Scale Factor 1.0
Rate Scale Factor 0.0
Maximum step size 0.1 (ms)
Algorithm BDF 1-5 with solve
Integration Complete
Export CSV
[Intracellular Ca++] (mM, blue) & Isometric tension (N/mm2)
x10^-3
1
0.5
0 1 2 3 4 5 6 7 8 9 10
x10^2
bound Ca, tropomyosin (z), tension
100% 90% 80% 70% 60% 50% 40% 30% 20% 10% 0%
0 1 2 3 4 5 6 7 8 9 10
x10^2
Model Y X Type
Relationships of active contraction framework. Click red boxes to display trace in graph above
Intracellular Ca2+
Ca2+ binding to TnC kinetics
Tropomyosin kinetics
Crossbridge kinetics
Maximum isometric tension (length dependent)
Calcium sensitivity (length dependent)
Sarcomere length, velocity
Clicked point was (489.89412897016365, 39.86486486486486).

Integrated model of excitation-contraction coupling

CellML1.1 imports



Terkildsen,J.R., Niederer,S., Crampin,E.J., Hunter, P.J. and Smith, N.P. *Experimental Physiology* 93, pp919-929, 2008.

IMAG

Terkildsen et al. Integrated model of e-c coupling

Terkildsen JR, Niederer S, Crampin EJ, Hunter PJ, Smith NP. Using Physiome standards to couple cellular functions for cardiac excitation-contraction. *Experimental Physiology* 93, 919-929, 2008.

www.cellml.org/models/terkildsen_niederer_crampin_hunter_smith_2008_version02

overview | edit | view math | model metadata | curation | view cellml | data | procedural code

Using Physiome standards to couple cellular functions for rat cardiac excitation-contraction

Download Model (220Kb)	Solve model in: (help)
Curation Status:	PCEnv JSim COR PCEnv Session (What's this?)

Model Documentation

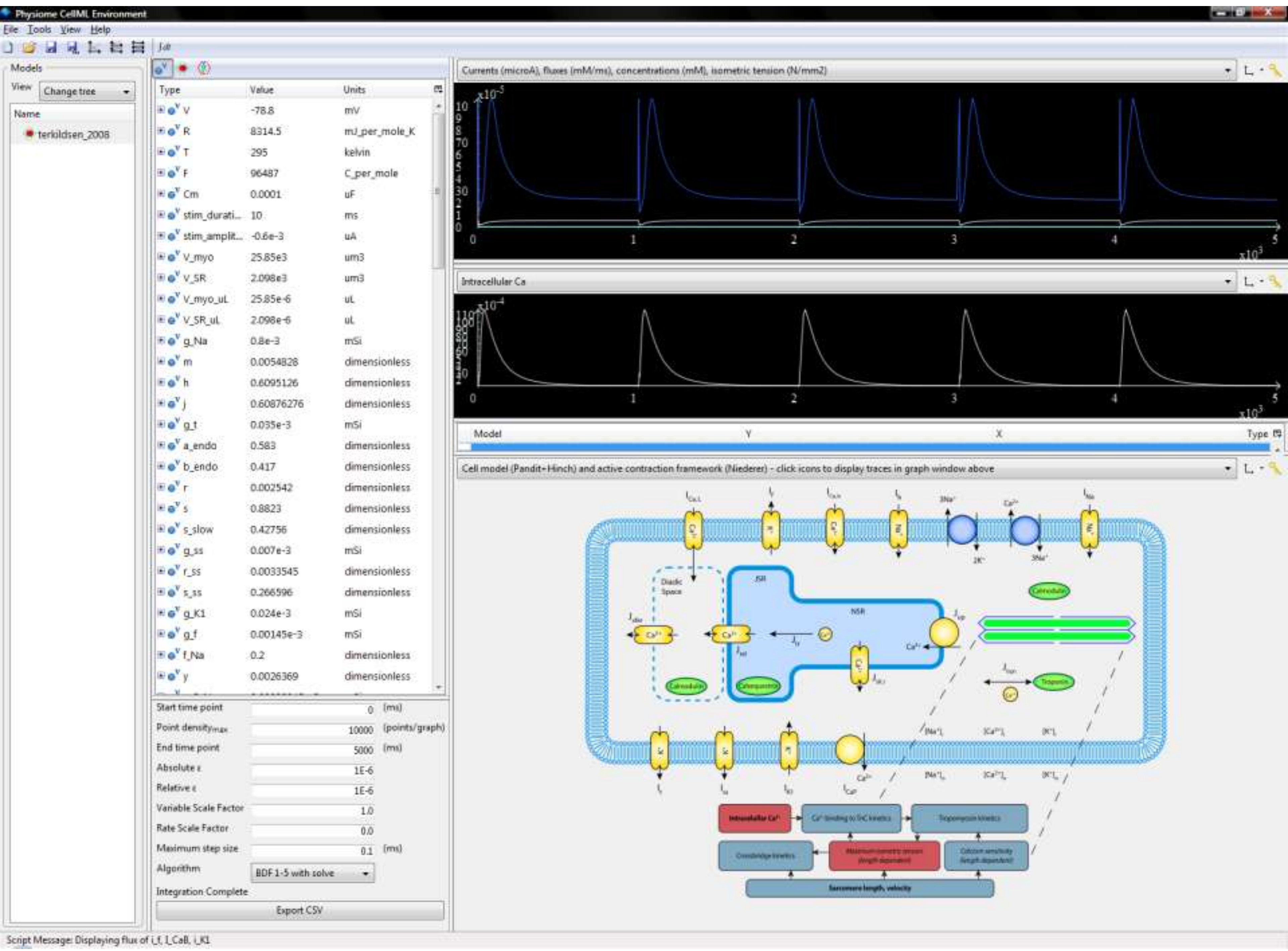
Model Status

Since this is the exact same model encoding which was used to create the results presented in the paper, this CellML model is known to accurately represent the published article.

Model Structure

ABSTRACT: Scientific endeavour is reliant upon the extension and reuse of previous knowledge. The formalization of this process for computational modelling is facilitated by the use of accepted standards with which to describe and simulate models, ensuring consistency between the models and thus reducing the development and propagation of errors. CellML 1.1, an XML-based programming language, has been designed as a modelling standard which, by virtue of its import and grouping functions, facilitates model combination and reuse. Using CellML 1.1, we demonstrate the process of formalized model reuse by combining three separate models of rat cardiomyocyte function (an electrophysiology model, a model of cellular calcium dynamics and a mechanics model) which together make up the Pandit-Hinch-Niederer et al. cell model. Not only is this integrative model of rat electromechanics a useful tool for cardiac modelling but it is also an ideal framework with which to demonstrate both the power of model reuse and the challenges associated with this process. We highlight and classify a number of these issues associated with combining models and provide some suggested solutions.

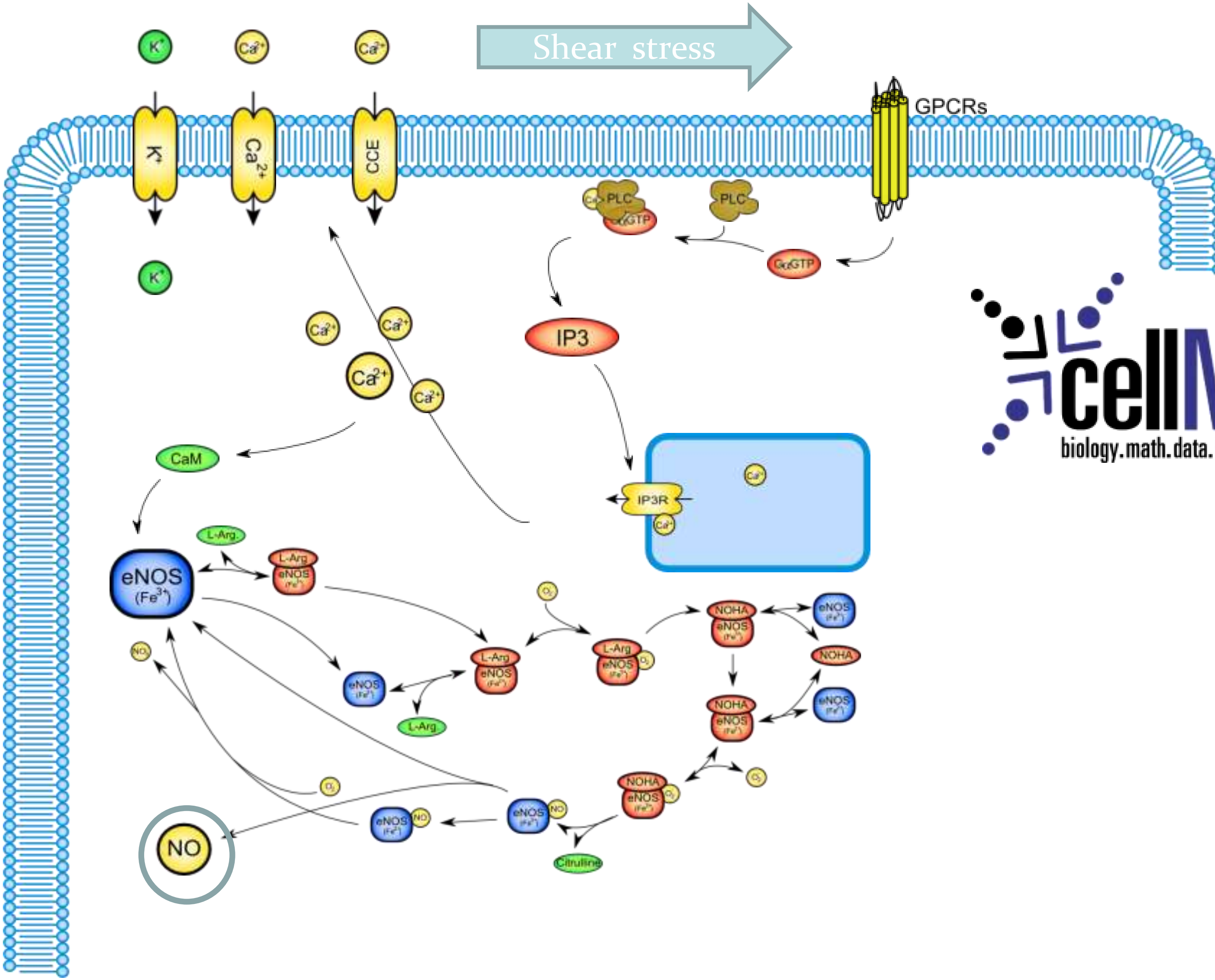
Using Physiome standards to couple cellular functions for rat cardiac excitation-contraction, Jonna R. Terkildsen, Steven Niederer, Edmund J. Crampin, Peter Hunter and Nicolas P. Smith, 2008, *Experimental Physiology* , 93, 919-929. (Full text and PDF versions of the article are available to journal subscribers on the *Experimental Physiology* website.)
PubMed ID: 18344258


Physiome CellML Environment
File Tools View Help
Models
View Change tree
Name
terkildsen_2008
Type Value Units
V -78.8 mV
R 8314.5 mJ_per_mole_K
T 295 kelvin
F 96487 C_per_mole
Cm 0.0001 uF
stim_durati... 10 ms
stim_amplit... -0.6e-3 uA
V_myo 25.85e3 um3
V_SR 2.098e3 um3
V_myo_uL 25.85e-6 uL
V_SR_uL 2.098e-6 uL
g_Na 0.8e-3 mSi
m 0.0054828 dimensionless
h 0.6095126 dimensionless
j 0.60876276 dimensionless
g_t 0.035e-3 mSi
a_endo 0.583 dimensionless
b_endo 0.417 dimensionless
r 0.002542 dimensionless
s 0.8823 dimensionless
s_slow 0.42756 dimensionless
g_ss 0.007e-3 mSi
r_ss 0.0033545 dimensionless
s_ss 0.266596 dimensionless
g_K1 0.024e-3 mSi
g_f 0.00145e-3 mSi
f_Na 0.2 dimensionless
y 0.0026369 dimensionless
Start time point 0 (ms)
Point density max 10000 (points/graph)
End time point 5000 (ms)
Absolute ε 1E-6
Relative ε 1E-6
Variable Scale Factor 1.0
Rate Scale Factor 0.0
Maximum step size 0.1 (ms)
Algorithm BDF 1-5 with solve
Integration Complete
Export CSV
Currents (microA), fluxes (mM/ms), concentrations (mM), isometric tension (N/mm2)
Intracellular Ca
Model Y X Type
Cell model (Pandit-Hinch) and active contraction framework (Niederer) - click icons to display traces in graph window above
Diadic Space
JSR
NSR
Calmodulin
Calsequestrin
Troponin
Intracellular Ca2+
Sarcomere length, velocity
Script Message: Displaying flux of i_f, I_CaB, i_K1

Example of module reuse

NO production in Endothelial Cells

- Stretch activated channels → Ca^{2+} → NO (< 1 min)
- Additional signalling pathways (1 min – 1 hr)
  - GPCRs → IP3 → Ca^{2+} → NO
  - Glycocalyx → NO?
  - PI3K → Akt → NO
  - Stretch activated channels → PKC → MAPK → NO
  - PI3K → MAPK → NO
  - Integrins (tensegritous) → MAPK →NO
- Gene regulation effects (1- 6 hours)



cellML
biology.math.data.knowledge.

Key requirements for modeling infrastructure

1. **Minimum information standards**
2. **Markup languages for models and data**
3. **ML standard for the simulation experiment**
4. **Models and data repositories**
5. **Meta data standards for annotating the models**
6. **Tools for authoring models, running simulations, visualising models and data**
7. **Mechanisms for handling the reference description of a model**

IMAG

1. Minimum information standards

1. MIRIAM for models

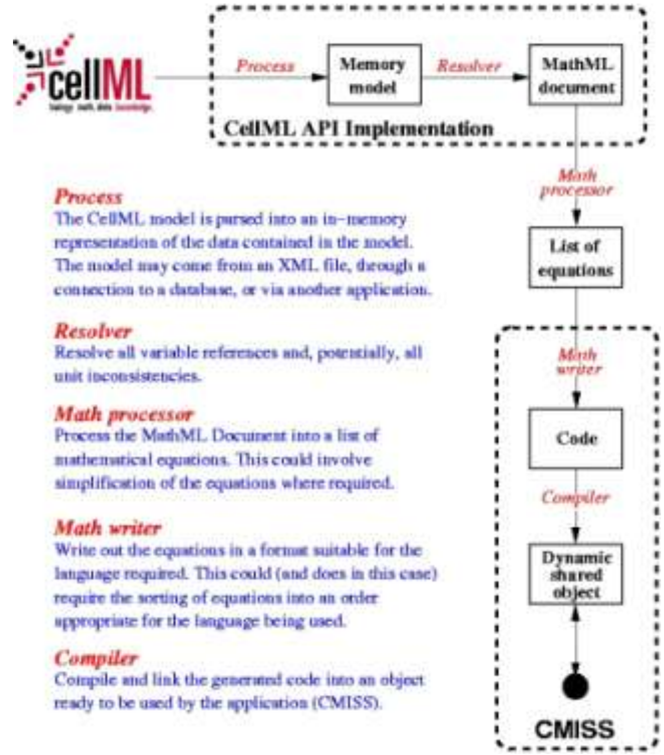
www.ebi.ac.uk/miriam/main/mdb?section=standard

2. MIASE for simulations

www.ebi.ac.uk/compneur-srv/miase/

IMAG

2. Markup languages for models and data



Models:	**CellML**	www.cellml.org
	SBML	www.sbml.org
	FieldML	www.fieldml.org
Data:	**DICOM, BioSignalML, ...**	

www.cellml.org

CellML

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Home | About CellML | Getting Started | Tools | Models | Specifications | Community

You are here: Home

The CellML project

The CellML language is an open standard based on the XML markup language. CellML is being developed by the Auckland Bioengineering Institute at the University of Auckland and affiliated research groups.

The purpose of CellML is to store and exchange computer-based mathematical models. CellML allows scientists to share models even if they are using different modelling tools. It also enables them to reuse components from one model in another, thus accelerating model development. Read more...

About CellML

Find out about the CellML language; what it can be used for, its history, and future directions.

Getting Started

New to CellML? This section collates information about CellML and tutorials that will help get you up and running with CellML.

Tools

The CellML community is committed to providing freely available tools for creating, editing, and using CellML models.

Model repository

The model repository is a resource where modelers can collaborate with each other to build and share models with the rest of the world.

Specifications

Read the CellML specifications - core language and a variety of metadata specifications are available.

Community

CellML is built around open source science and software. The cellml.org website is a community hub for all things CellML.

CellML at IUPS2009

Members of the CellML project will run a tutorial at IUPS2009 to provide hands-on experience of CellML and other Physiome Project software.

- Resources for tutorial attendees

Photo: flowzim

Featured articles

- Modelling Tools: PCEnv, COR & OpenCell
- CellML Workshop 2009 report
- CellML scope
- CellML publications listing
- OpenCell basic model building tutorial
- Frequently Asked Questions

More...

News

- CellML tutorial at IUPS2009
- IUPS2009 CellML workshop announcement
- CellML Tools page updated
- Notification: Representation of e-notation in CellML Repository models will be changing
- Request for details of CellML-related publications
- Friendfeed for CellML SBGN SBO BioPAX MIASE Workshop
- PCEnv 0.6 and CellML API 1.6 Released
- Request for model translations into CellML

More...

Funding agencies

Thanks to our funding partners: VPH NoE, Maurice Wilkins Centre for Molecular Biodiscovery, aneurIST, IUPS Physiome Project, Wellcome Trust.

3. ML standard for simulation experiments

SED-ML: www.ebi.ac.uk/compneur-srv/sed-ml/

SED-OM is object model defined in UML

Top-level SED-OM classes:

- Model
- Simulation
- Task
- DataGenerator
- Output

SED-ML is XML serialization of SED-OM

Ontology is KiSAO : www.ebi.ac.uk/compneur-srv/kisao/

IMAG

4. Models and data repositories

CellML [**www.cellml.org/models**]

SBML [**www.biomodels.org**]

JSIM [**nsr.bioeng.washington.edu/jsim/models**]

IMAG

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Photo: flowzim

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- OpenCell basic model building tutorial
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More...

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- CellML tutorial at IUPS2009
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- Friendfeed for CellML SBGN SBO BioPAX MIASE Workshop
- PCEnv 0.6 and CellML API 1.6 Released
- Request for model translations into CellML

More...

Funding agencies

Thanks to our funding partners: VPH NoE, Maurice Wilkins Centre for Molecular Biodiscovery, aneurIST, IUPS Physiome Project, Wellcome Trust.

www.cellml.org/models

CellML Model Repository

Main Model Listing

The list of processed model exposures (formats: 100 per page | full list), which are models that have documentation pages generated from the metadata they contain. Alternatively, you may start browsing via the categories that are listed below:

Please note: Comments about the functional status or curation status of the models within this repository are the the opinions of the CellML Model Repository curators. We do our best to accurately represent these models, but please contact us if you have a query or issue with comments made on this site.

Browse by category

- Calcium Dynamics
- Cardiovascular Circulation
- Cell Cycle
- Cell Migration
- Circadian Rhythms
- Electrophysiology
- Endocrine
- Excitation-Contraction Coupling
- Gene Regulation
- Mechanical Constitutive Laws
- Metabolism
- Myofilament Mechanics
- pH Regulation
- Signal Transduction
- Synthetic Biology

Searching

Searching of models can be done anywhere on the site using the search box on the upper right hand corner.

Electrophysiology

Electrophysiology

Adrian, Chandler, Hodgkin, 1970
Voltage clamp experiments in striated muscle fibres

Albrecht, Colegrove, Friel, 2002
Differential Regulation of ER Ca2+ Uptake and Release Rates Accounts for Multiple Modes of Ca2+-induced Ca2+ Release

Albrecht, Colegrove, Hongpaisan, Pivovarova, Andrews, Friel, 2001
Multiple Modes of Calcium-induced Calcium Release in Sympathetic Neurons I: Attenuation of Endoplasmic Reticulum Ca2+ Accumulation at Low [Ca2+]i during Weak Depolarisation

Beeler, Reuter, 1977
Reconstruction of the action potential of ventricular myocardial fibres

Bernus, Wilders, Zemlin, Verschelde, Panfilov, 2002
A computationally efficient electrophysiological model of human ventricular cells

Bertram, Previte, Sherman, Kinard, Satin, 2000
The Phantom Burster Model for Pancreatic Beta Cells

Bertram, Satin, Zhang, Smolen, Sherman, 2004
Calcium and Glycolysis Mediate Multiple Bursting Modes in Pancreatic Islets (a)

Bertram, Sherman, 2004
A Calcium-based Phantom Bursting Model for Pancreatic Islets

Bertram, Smolen, Sherman, Mears, Atwater, Martin, Soria, 1995
A role for calcium release-activated current (CRAC) in cholinergic modulation of electrical activity in pancreatic beta-cells

Bondarenko, Szigeti, Bett, Kim, Rasmusson, 2004
A Computer Model for the Action Potential of Mouse Ventricular Myocytes (a)

Boyett, Zhang, Garny, Holden, 2001
Control of the pacemaker activity of the sinoatrial node by intracellular Ca2+. Experiments and modelling

Butera, Rinzel, Smith, 1999
Models of Respiratory Rhythm Generation in the Pre-Botzinger Complex. I. Bursting Pacemaker Neurons

Chang, Fujita, 1999
A kinetic model of the thiazide-sensitive Na-Cl cotransporter (a)

Chang, Fujita, 1999
A kinetic model of the thiazide-sensitive Na-Cl cotransporter (b)

Chang, Fujita, 1999
A numerical model of the renal distal tubule

Chang, Fujita, 2001
A numerical model of acid-base transport in rat distal tubule (renal_anion_exchanger_model)

Modulatory effect of calmodulin-dependent kinase II (CaMKII) on sarcoplasmic reticulum Ca2+ handling and interval-force relations: a modelling study.

General Information

PMR1 Curation

Curation Status:	★★☆
OpenCell:	☆☆☆
JSim:	☆☆☆
COR:	★★☆

Access model via:

Download

Solve using OpenCell

Solve using OpenCell Session File

Source:

Derived from workspace Iribe, Kohl, Noble, 2006 at changeset 1b57f226158b.

Documentation

Model Status

This model was created by Penny Noble of Oxford University. An unsupported predefined operator diff error in component intracellular_calcium_concentration was fixed to allow the model to run in PCEnv (19/04/07, James Lawson.) A stimulus protocol was then added to allow simulation of trains of action potentials (JL, 15/06/07.) This file is known to run COR and PCEnv. A PCEnv session file is also associated with this model.

Model Structure

This model was based on the paper:

Modulatory effect of calmodulin-dependent kinase II (CaMKII) on sarcoplasmic reticulum Ca2+ handling and interval-force relations: a modelling study.

by Iribe G, Kohl P, Noble D

Philos Transact A Math Phys Eng Sci. 2006 May 15;364(1842):1107-33

ABSTRACT:

We hypothesize that slow inactivation of Ca2+/calmodulin-dependent kinase II (CaMKII) and its modulatory effect on sarcoplasmic reticulum (SR) Ca2+ handling are important for various interval-force (I-F) relations, in particular for the beat interval dependency in transient alternans during the decay of post-extrasystolic potentiation. We have developed a mathematical model of a single cardiomyocyte to integrate various I-F relations, including alternans, by incorporating a conceptual CaMKII kinetics model into the SR Ca2+ handling model. Our model integrates I-F relations, such as the beat interval-dependent twitch force duration, restitution and potentiation, positive staircase phenomenon and alternans. We found that CaMKII affects more or less all I-F relations, and it is a key factor for integration of the various I-F relations in

Navigation

Documentation

Mathematics

Model Metadata

Procedural Code

Exposure Subpages

Modulatory effect of calmodulin-dependent kinase II (CaMKII) on sarcoplasmic reticulum Ca2+ handling and interval-force relations: a modelling study.

Mathematics

Component: transient_outward_current_r_gate

$$\frac{\mathrm{d}r}{\mathrm{d}\mathrm{time}} = 333\left(1 / \left(1 + e^{-(V+4)/5}\right) - r\right)$$

Component: L_type_Ca_channel

$$\mathrm{i\_Ca\_L\_Ca} = 4 d f \mathrm{P\_Ca\_L\_Ca}(V - 50)F / RT\left(1 - e^{-2(V-50)F/RT}\right)\left(\mathrm{Ca\_i}e^{100F/RT} - \mathrm{Ca\_o}e^{-2(V-50)F/RT}\right)$$

$$\mathrm{i\_Ca\_L\_K} = 0.002 d f \mathrm{P\_Ca\_L\_Ca}(V - 50)F / RT\left(1 - e^{-(V-50)F/RT}\right)\left(\mathrm{K\_i}e^{50F/RT} - \mathrm{K\_o}e^{-(V-50)F/RT}\right)$$

$$\mathrm{i\_Ca\_L\_Na} = 0.01 d f \mathrm{P\_Ca\_L\_Ca}(V - 50)F / RT\left(1 - e^{-(V-50)F/RT}\right)\left(\mathrm{Na\_i}e^{50F/RT} - \mathrm{Na\_o}e^{-(V-50)F/RT}\right)$$

$$\mathrm{i\_Ca\_L} = \mathrm{i\_Ca\_L\_Ca} + \mathrm{i\_Ca\_L\_K} + \mathrm{i\_Ca\_L\_Na}$$

Component: L_type_Ca_channel_d_gate

$$\mathrm{E0\_d} = V + 24 - 5$$

$$\mathrm{alpha\_d} = \begin{cases} \mathrm{speed\_d} \times 120 & \text{if } |\mathrm{E0\_d}| < 0.00001 \\ \mathrm{speed\_d} \times 30\mathrm{E0\_d} / \left(1 - e^{-\mathrm{E0\_d}/4}\right) & \text{if} \end{cases}$$

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General Information

PMR1 Curation

Curation Status: ★★☆
OpenCell: ☆☆☆
JSim: ☆☆☆
COR: ★★☆

Access model via:

Download
Solve using OpenCell
Solve using OpenCell Session File

Source:

Derived from workspace Iribe, Kohl, Noble, 2006 at changeset 1b57f226158b.

Documentation

Model Status

This model was created by Penny Noble of Oxford University. An unsupported predefined operator diff error in component intracellular_calcium_concentration was fixed to allow the model to run in PCEnv (19/04/07, James Lawson.) A stimulus protocol was then added to allow simulation of trains of action potentials (JL, 15/06/07.) This file is known to run COR and PCEnv. A PCEnv session file is also associated with this model.

Model Structure

This model was based on the paper:

Modulatory effect of calmodulin-dependent kinase II (CaMKII) on sarcoplasmic reticulum Ca2+ handling and interval-force relations: a modelling study.

by Iribe G, Kohl P, Noble D

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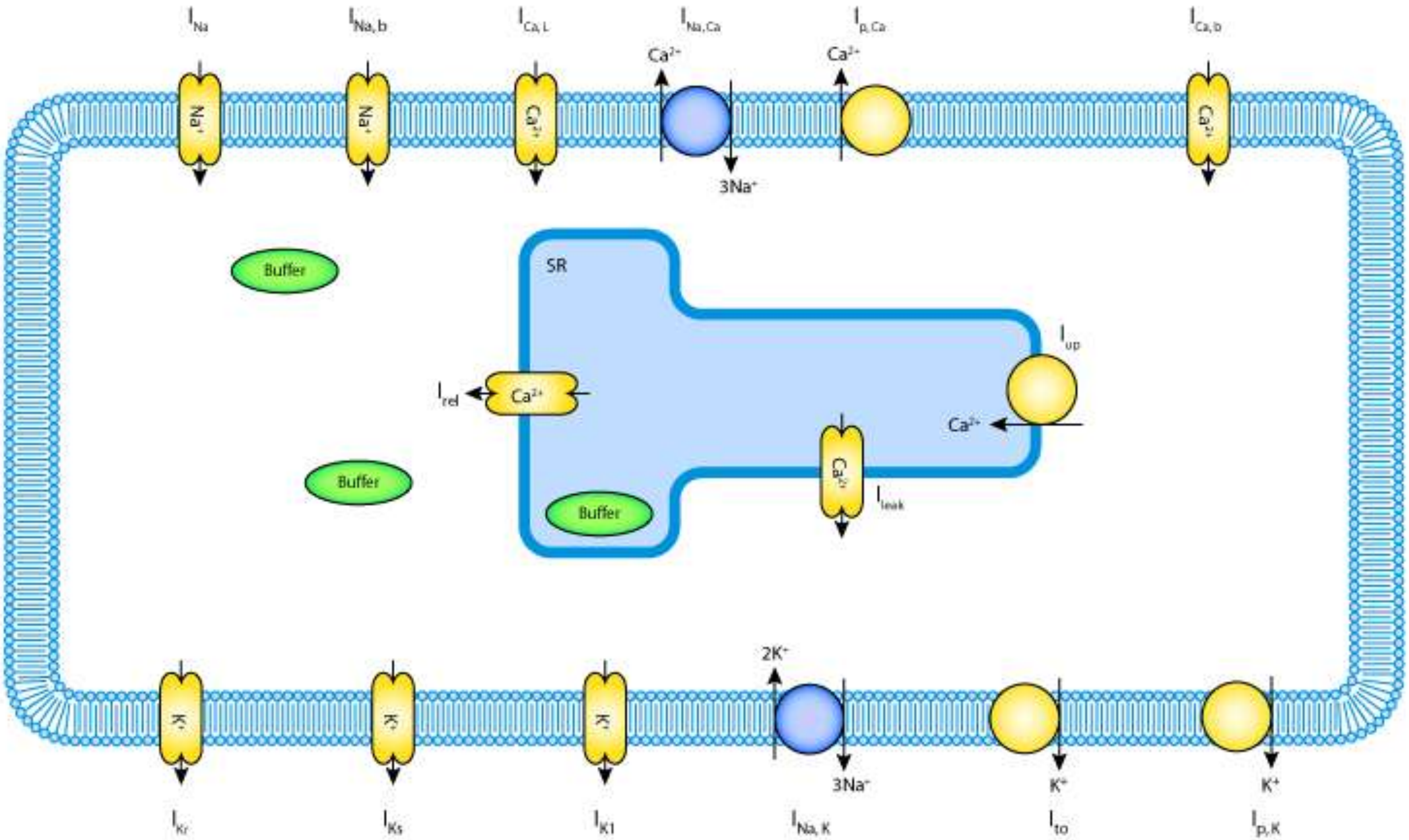
SVG diagrams



A schematic diagram describing the ion movement across the cell surface membrane and the sarcoplasmic reticulum, which are described by the Ten Tusscher *et al.* 2004 mathematical model of the human ventricular myocyte.

5. Meta data standards for annotating models

Graphing metadata:
www.cellml.org/specifications/metadata/graphs

Other work:
SemSim from Dan Cook, U Washington, Seattle
Saint from Allyson Lister, Newcastle University

Ontologies: GO, BioPax, FMA, etc
– adhere to OBO Foundry, EBI, NCBO

IMAG

6. Tools for authoring models, running simulations, visualising models and data

OpenCell	www.cellml.org/tools/opencell
OpenCMISS	www.cmiss.org/openCMISS
CMGUI	www.cmiss.org/cmgui
GIMIAS	www.gimias.org

Continuity, MAF5, OpenSIM, etc

IMAG

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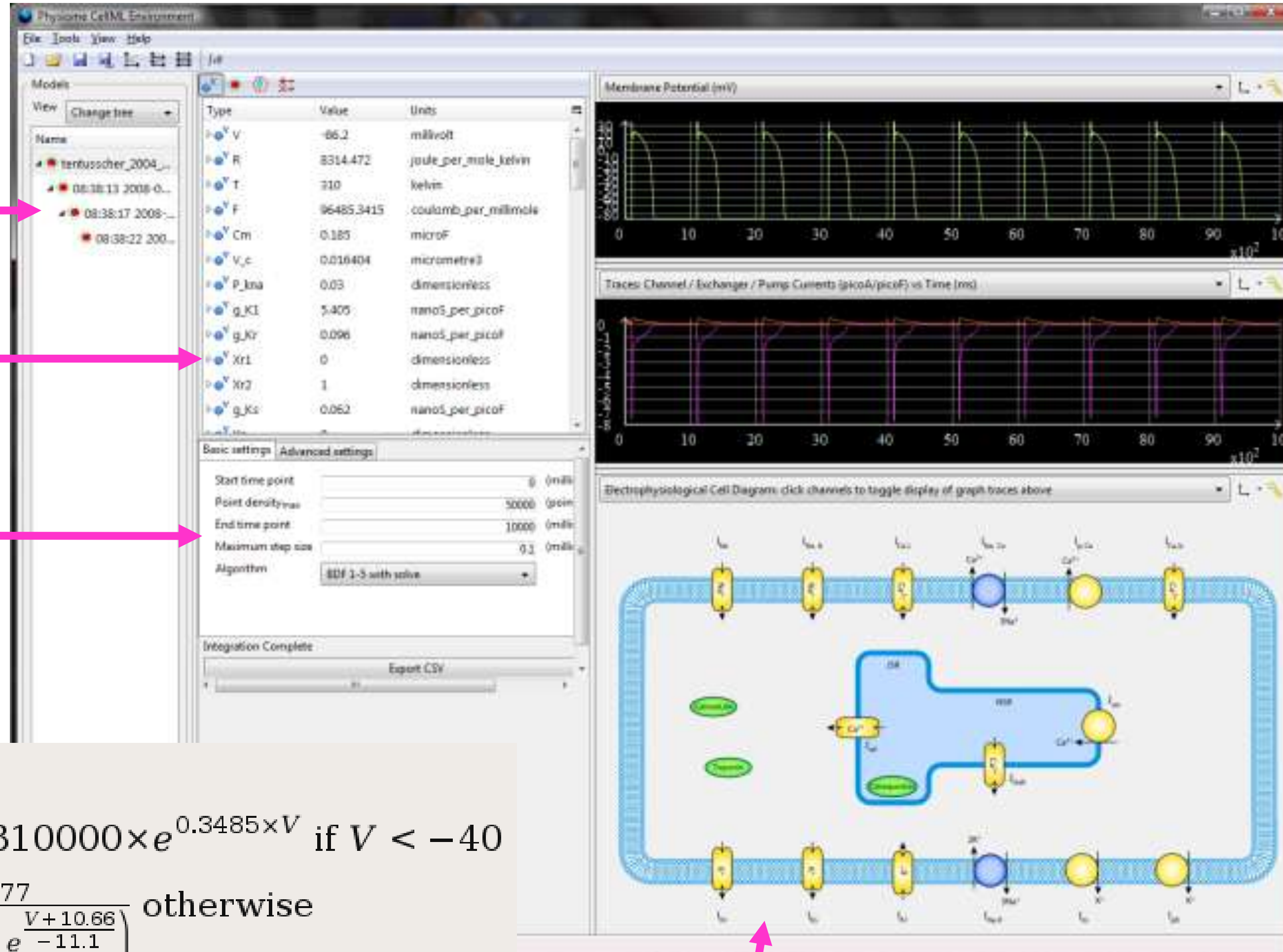
OpenCell simulation tool for CellML models

Multiple models or history of parameter changes

Parameter values & units

Parameters for control of numerical integration

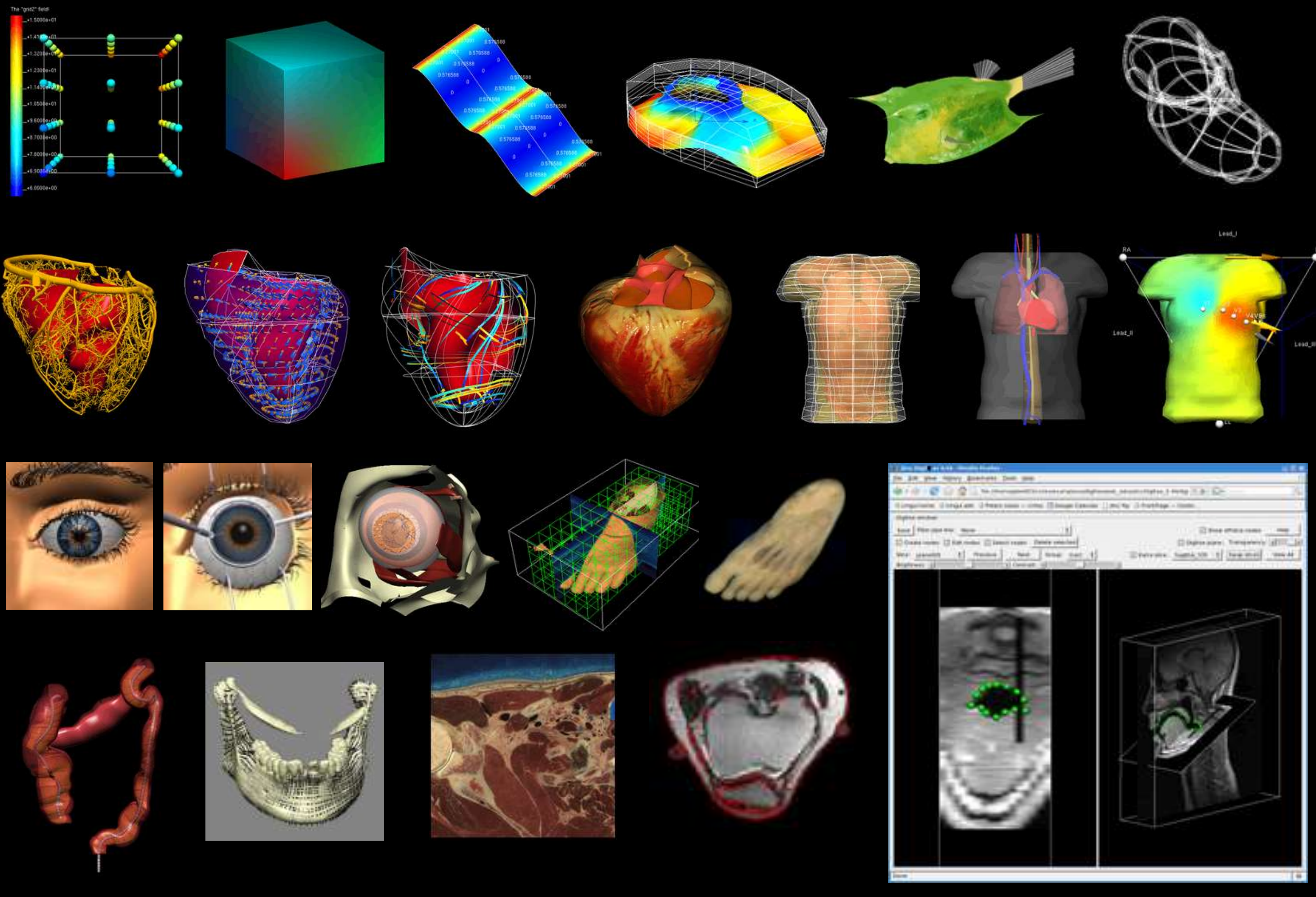
Equation for a component:



$$\text{beta\_h} = \begin{cases} 2.7\times e^{0.079\times V} + 310000\times e^{0.3485\times V} & \text{if } V < -40 \\ \dfrac{0.77}{0.13\times\left(1+e^{\frac{V+10.66}{-11.1}}\right)} & \text{otherwise} \end{cases}$$

Graphical user interface for displaying model topology and controlling visibility of displayed results

FieldML & Cmgui (www.cmiss.org/cmgui)



Key points

- Models now being built into some clinical workflows
- Good connection between imaging & modeling
- Connecting to systems biology is still not there
- Parameter variability in population hardly addressed
- Modeling standards in fairly good shape
- Alarming absence of data standards
- Model repositories OK but not yet data repositories
- Open source software for all scales is now available but need much more attention to multiscale/modules and automated model reduction
- Badly need demonstrated reproducibility of models/data i.e. Need model reference descriptions
- Need reference problems & competitions

IMAG