Committee on Credible Practice of
Modeling & Simulation in Healthcare
https://simtk.org/home/cpms

Ten Simple Rules of Credible Practice of Modeling and Simulation: *Application to Bone Remodeling and Heart Valve Modeling*

Presented by Lealem Mulugeta and Andrew Drach
On Behalf of the Committee

ROSA Worldwide Webinar Series:
Impact of Modeling & Simulation in Drug Development
May 17, 2018

Objectives

- Introduction to The Committee on Credible Practice of Modeling & Simulation in Healthcare
- Overview of the current draft of the Ten Simple Rules of Credible Practice
- Example Applications
  - Bone Remodeling Model (L. Mulugeta)
  - Heart Valve Model (A. Drach)

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The Challenge

Am I applying credible practice?

Common practice guidelines <u>do not</u> exist to ensure that appropriate credibility processes are followed

Adapted from http://beaver1003.com

About the Committee

Credible Practice of M&S in Healthcare

To establish credible practice guidelines, consistent terminology and a model certification process, as well as to demonstrate workflows and identify new areas of research for reliable development and application of M&S in healthcare practice and research

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IMAG & Multiscale Modeling (MSM) Consortium

NIH FDA NASA USDA MITACS IARPA

Overview of Committee's Charges

- **Guidelines & Procedures**
  - Credible practice in computational medicine
  - Leveraging readily available techniques
  - Define novel translational workflows to enhance credibility practice
- **Demonstrate Workflows**
  - Conduct studies to develop novel credibility assessment procedures
  - Disseminating examples of credibility assessment
- **Consistent Terminology**
  - Unify the use of M&S vocabulary across all stakeholders
- **Promote Good Practice**
  - Bridge synergistic activities within the M&S communities
  - conduct outreach activities.
- **Target End Products**
  I. "Guidelines for Credible Practice of M&S in Healthcare"
  II. Proposed model certification process
  III. Identify new areas of research to advance I & II

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Ten Simple Rules (TSR) of Credible Practice

Primary deliverable: *"Guidelines for Credible Practice of Modeling and Simulation in Healthcare"*

Goal Oriented Activity: The CPMS Task Teams were charged to identify ten key elements or simple rules of credible practice in order to establish a foundation from which the *"Guidelines for Credible Practice of Modeling and Simulation in Healthcare"* can be developed.

Full details of this activity is available at:
http://wiki.simtk.org/cpms/Ten_Simple_Rules_of_Credible_Practice

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Two Main Approaches for TSR

1. Surveyed the Committee
   – Publication in progress
2. Surveyed the Global Community
   – A forum discussion thread has been initiated: https://simtk.org/forums/viewtopic.php?f=848&t=5616&sid=fdcab3f040d5c52b8667a0b0812d2e2b
   – The raw data is also available at: https://simtk.org/websvn/wsvn/cpms/dat/Survey/Complete%20Survey%20Results_Clean_04242015.xlsx
   – Publication in Progress

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Draft: The Ten Simple Rules of Credible Practice

Rule	Description
R1: Define context clearly	Develop and document the subject, purpose, and intended use(s) of the model or simulation.
R2: Use appropriate data	Employ relevant and traceable information in the development or operation of a model or simulation.
R3: Evaluate within context	Verification, validation, uncertainty quantification, and sensitivity analysis of the model or simulation are accomplished with respect to the reality of interest and intended use(s) of the model or simulation.
R4: List limitations explicitly	Restrictions, constraints, or qualifications for or on the use of the model or simulation are available for consideration by the users or customers of a model or simulation.
R5: Use version control	Implement a system to trace the time history of M&S activities including delineation of contributors' efforts.
R6: Document adequately	Maintain up-to-date informative records of all M&S activities, including simulation code, model mark-up, scope and intended use of M&S activities, as well as users' and developers' guides.
R7: Disseminate broadly	Publish all components of M&S activities, including simulation software, models, simulation scenarios and results.
R8: Get independent reviews	Have the M&S activity reviewed by nonpartisan third-party users and developers.
R9: Test competing implementations	Use contrasting M&S execution strategies to check the conclusions of the different execution strategies against each other.
R10: Conform to standards	Adopt and promote generally applicable and discipline specific operating procedures, guidelines, and regulations accepted as best practices.

Alignment between Committee survey and the Global Community survey

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APPLICATION OF THE TEN SIMPLE RULES TO COMPUTATIONAL MODEL OF BONE REMODELING

Presented by Lealem Mulugeta

Summary of

J. Pennline and L. Mulugeta (2014), "A Computational Model for Simulating Spaceflight Induced Bone Remodeling", *44th International Conference on Environmental Systems*, ICES2014-083.

PURPOSE OF THIS PRESENTATION

- Demonstrate:
  - The **deliberate** processes (NASA-STD-7009) we used to demonstrate the credibility of a computational model of bone remodeling intended for NASA's spaceflight bone physiology research efforts [1-4]
  - How the processes align/translate with *the Ten Simple Rules of Credible Practice of M&S in Healthcare*
- The purpose of this presentation is NOT to discuss modeling techniques or science
- For more information about M&S methodologies, please refer to the following publication, and additional references

J. Pennline and L. Mulugeta (2014), "A Computational Model for Simulating Spaceflight Induced Bone Remodeling", *44th International Conference on Environmental Systems*, ICES2014-083.

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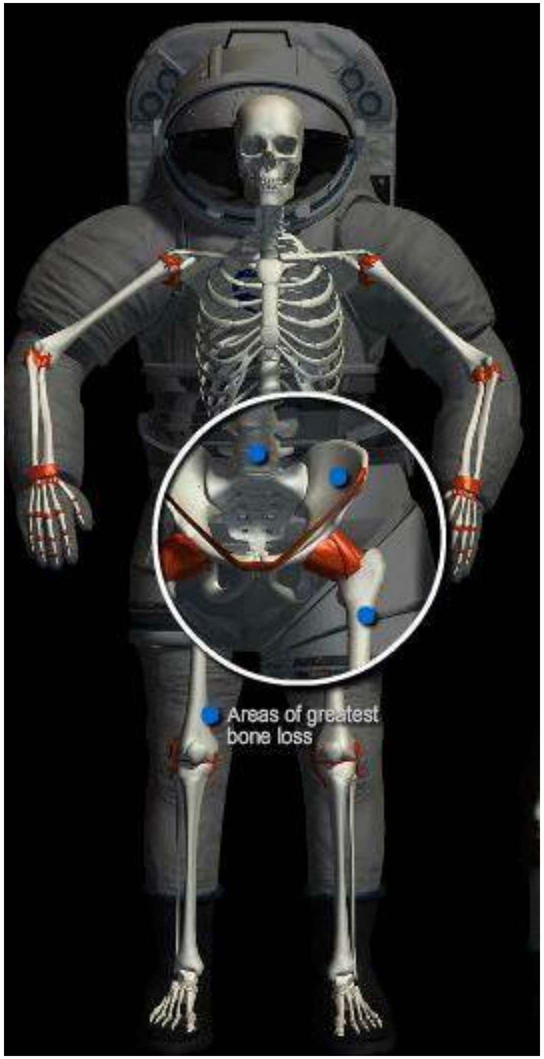
Problem Statement



- Astronauts experience bone demineralization at a rate of 1% to 2% a month in microgravity (“weightlessness”)
- These losses are most pronounced at load bearing lower extremities (e.g. proximal femur)
- Existing exercise countermeasures do not completely eliminate bone loss in long duration, 4 to 6 months, spaceflight
- Health risks to astronauts:
  - *Early onset osteoporosis*
  - *Fracture later in their lives*

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Objective

- Understand bone remodeling and demineralization mechanisms in microgravity in order to:
  - Appropriately quantify long term bone health risks (osteoporosis & bone fracture), and
  - Establish appropriate countermeasures

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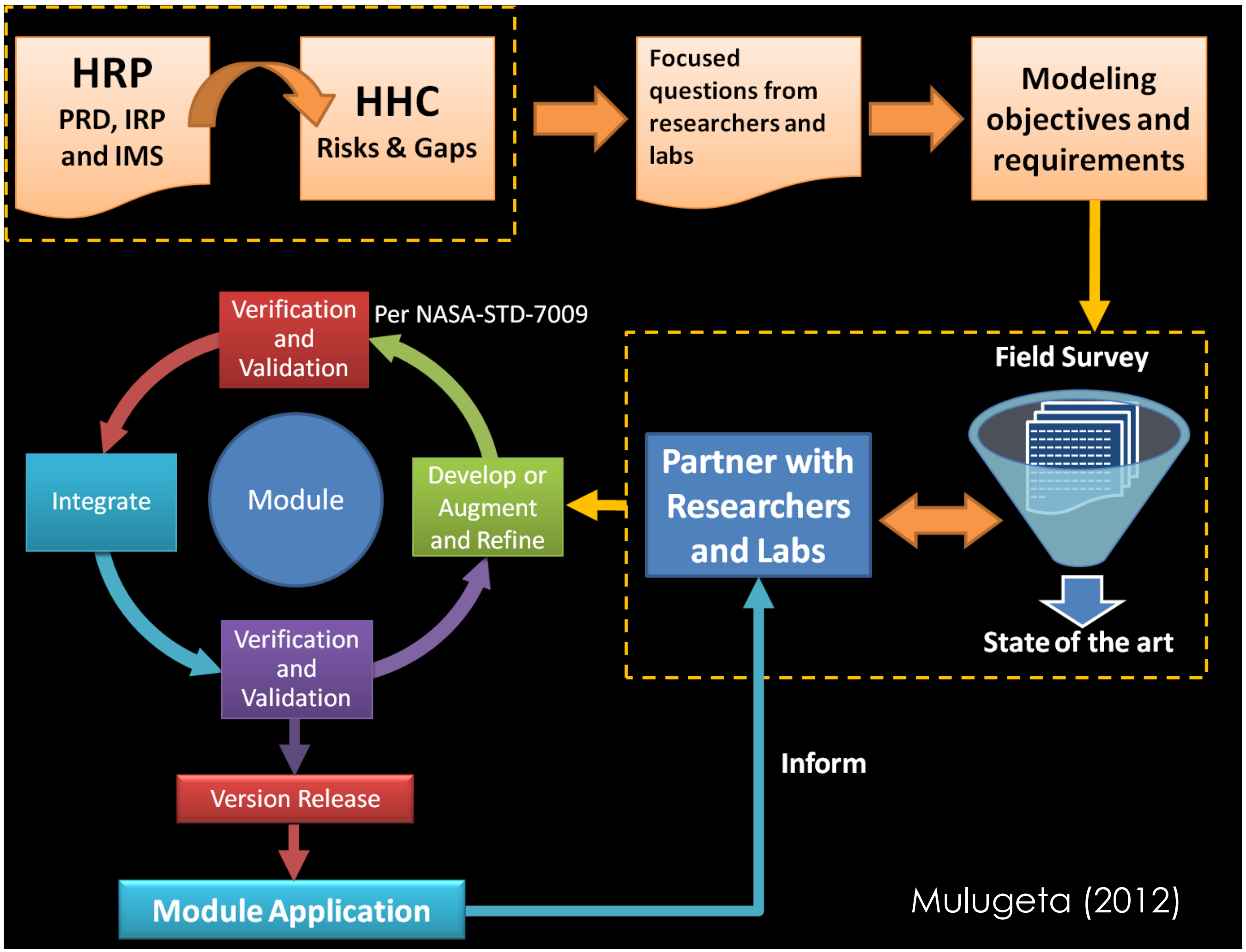
Proposed Tool: Computational M&S

NASA's Digital Astronaut Project (DAP) worked with NASA's bone specialists to apply computational modeling to elucidate changes in weight-bearing skeletal sites that are most susceptible to bone loss in microgravity, and thus at higher risk for fracture



Mulugeta (2012)

R1: Define context clearly (1/3)

The DAP computational model of bone remodeling was developed:

1) Primarily as <u>a research</u> tool, and <u>not as a clinical</u> tool
2) To augment bone research and exercise countermeasure development

It was intended to provide additional data to:

1) Gain insight on the mechanisms of bone demineralization due to exposure to microgravity,
2) Gain insight on the volumetric changes at the various bone sites in response to in-flight and post-flight exercise countermeasures, and
3) Be used with finite element methods to gain insight on how bone strength may change during and after flight

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R1: Define context clearly (2/3)

It was not developed to predict bone fracture

The initial model reported by Pennline and Mulugeta (2014a) focused on the femoral neck since this bone site:

1) Is a dynamic load bearing sight,
2) Is highly susceptible to microgravity induced demineralization, and
3) Presents potentially debilitating fracture risk

Future work will include other key load bearing bone sites: greater trochanter, lower lumbar vertebrae, proximal femur and calcaneus.

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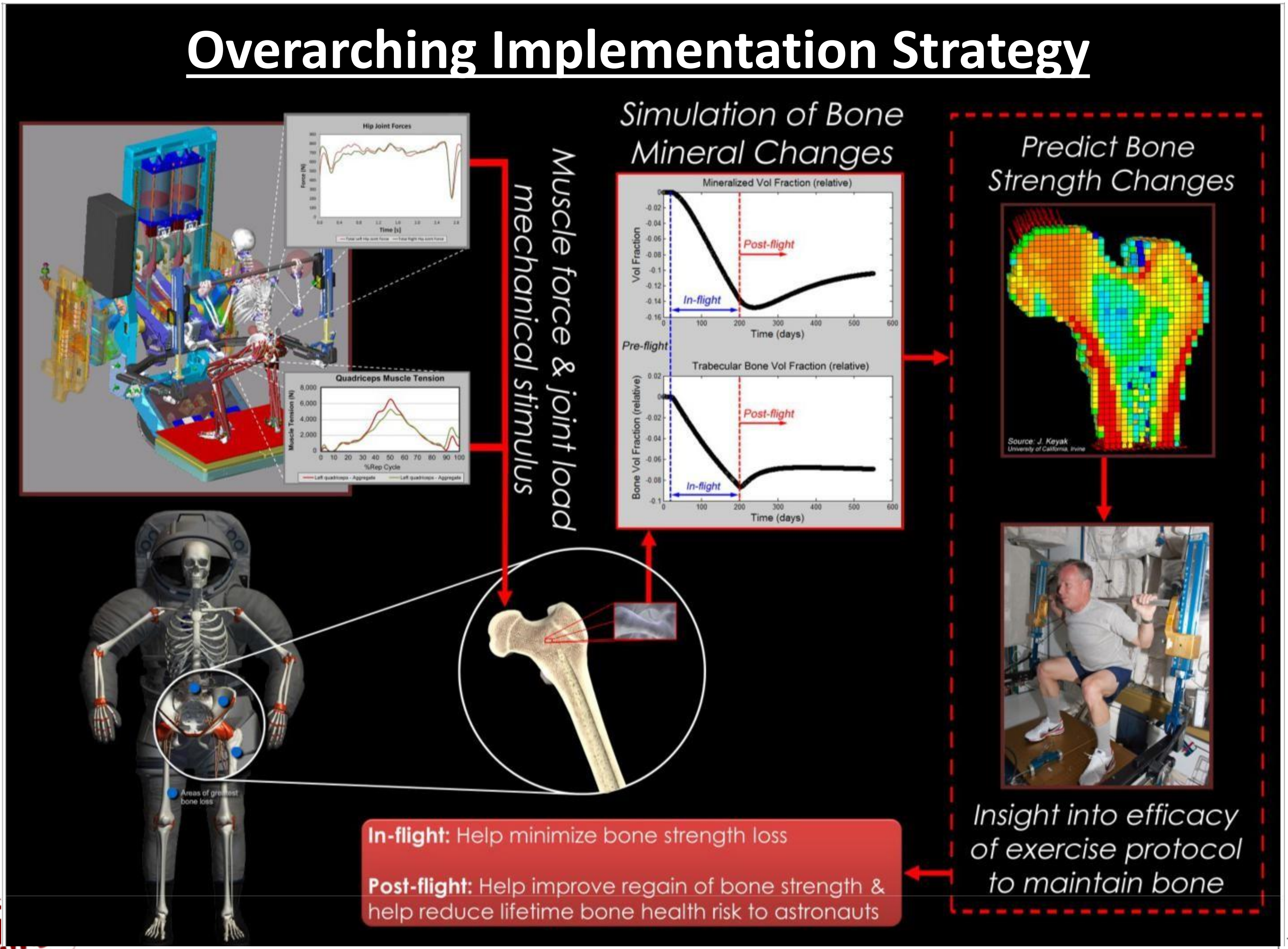
R1: Define context clearly (3/3)



Pennline and Mulugeta (2014a)

R2: Use appropriate data (1/2)

- Since bone parameter values are still under active research by the scientific community, we used average values from the scientific literature – see Pennline and Mulugeta (2014a) for details
- **Examples**
  - ***Resorption depth (depth of remodeling unit):*** *0.05 mm for trabecular hemi-osteon, and 0.0955 mm and 0.0271mm for cortical bone*
  - ***Activation frequency:*** *0.001/day*
  - ***TGF-beta 1:*** *200 µg/kg*

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R2: Use appropriate data (2/2)

- Since most of the bone mineral density(BMD) data available was DEXA aBMD, we created a regression equation that maps aBMD with QCT vBMD
- The regression was developed using total femur DEXA and QCT data from the flight study reported in Lang et al. (2004) – raw data was provided by NASA's Life Science Data Archives
- This regression "sub-model" helped expand the data set we were able to draw on to validate the computational mode, as well as run investigative simulations

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R3: Evaluate within context (1/3) – Criteria & Definitions

Validation?

- does not mean the absolute substantiation of the model's capability to predict bone adaptation
- refers to the degree which the model is able to reproduce the observed behavior under consideration (e.g. BMD or BVF changes) in comparison to an appropriate referent.

Validation Criteria:

1. Bone Volume Fraction (BVF) - Base Equation
2. Volumetric BMD (vBMD) – Quantitative Computed Tomography (QCT)
   i. Trabecular
   ii. Cortical
3. Areal BMD (aBMD) - Dual-Energy X-ray Absorptiometry (DEXA)

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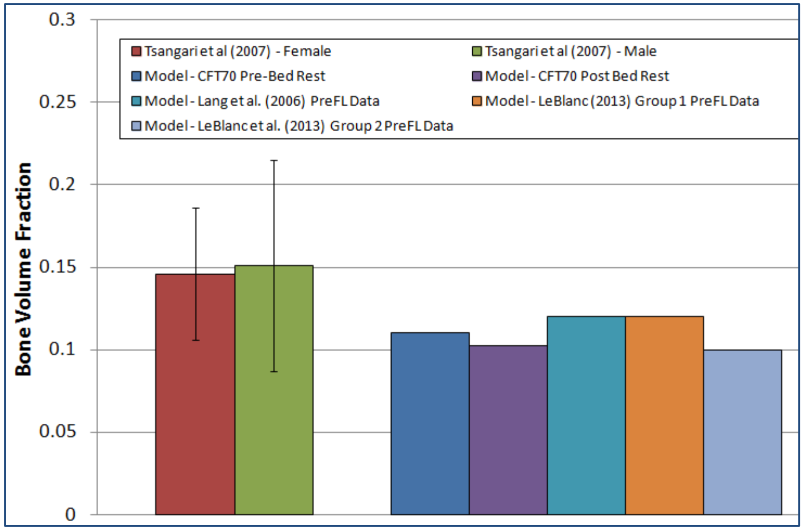
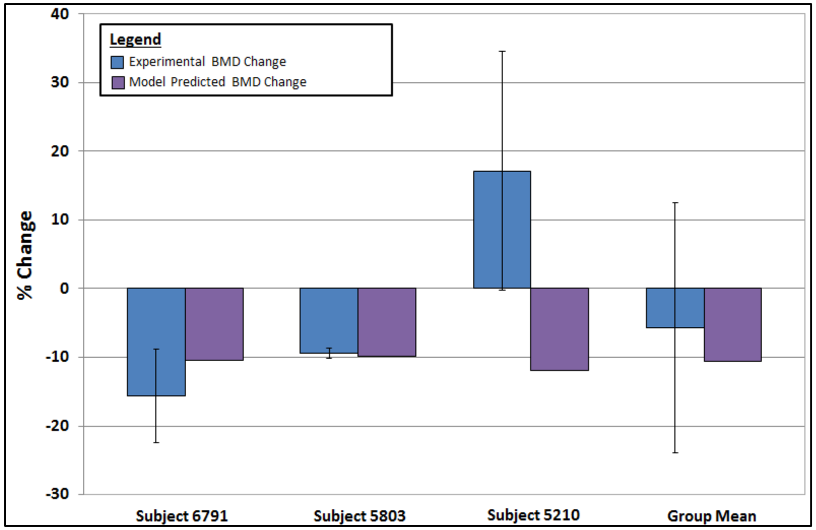
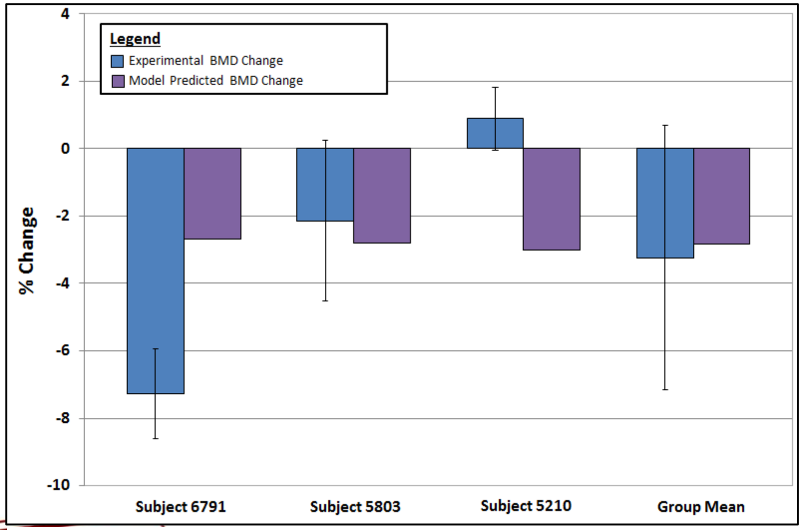
R3: Evaluate within context (2/3) – Prelim. Validation



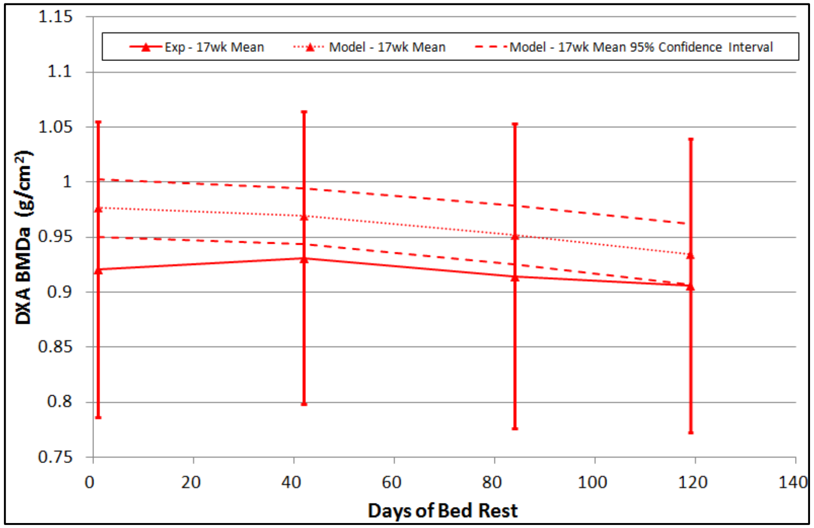
Group mean BVF prediction.



70-day bed rest trabecular bone loss (4 subj.)

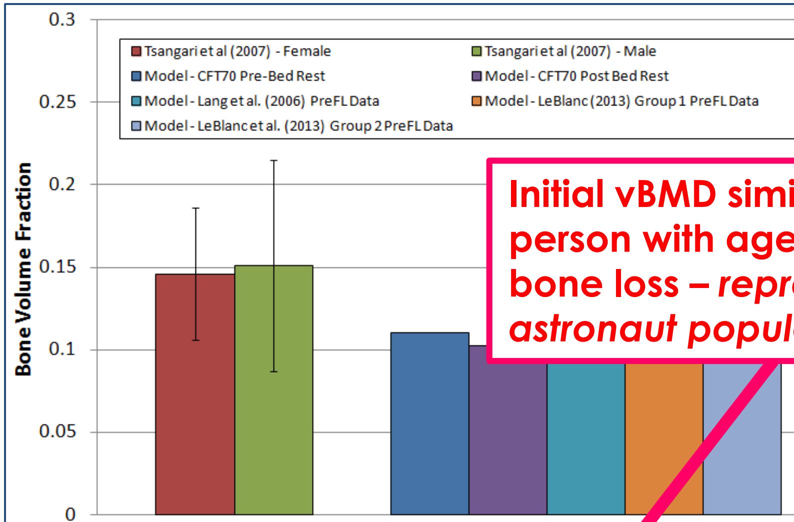


70-day bed rest cortical bone loss (4 subj.)



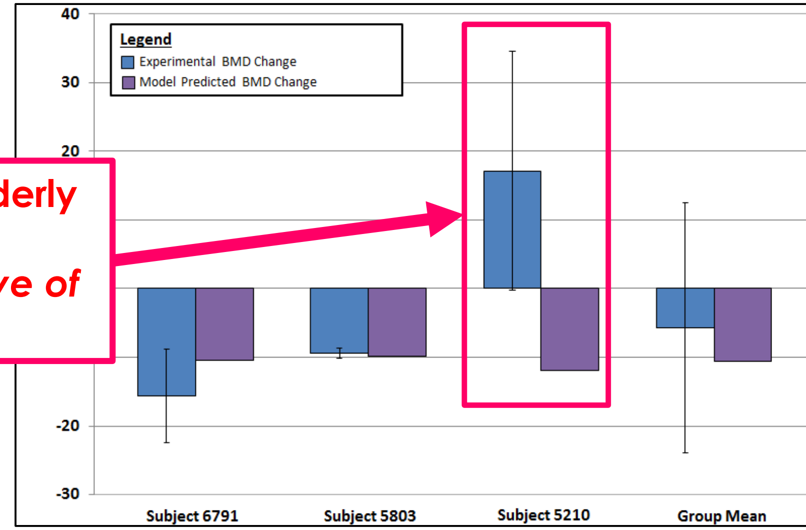
Time course mean aBMD change for 18 subjects during 17 weeks of bed rest [8].

R3: Evaluate within context (2/3) – Prelim. Validation

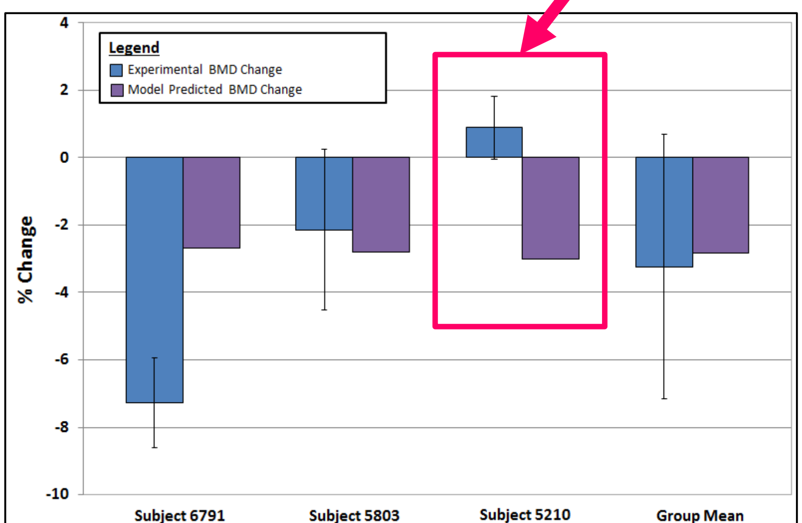


Group mean BVF prediction.

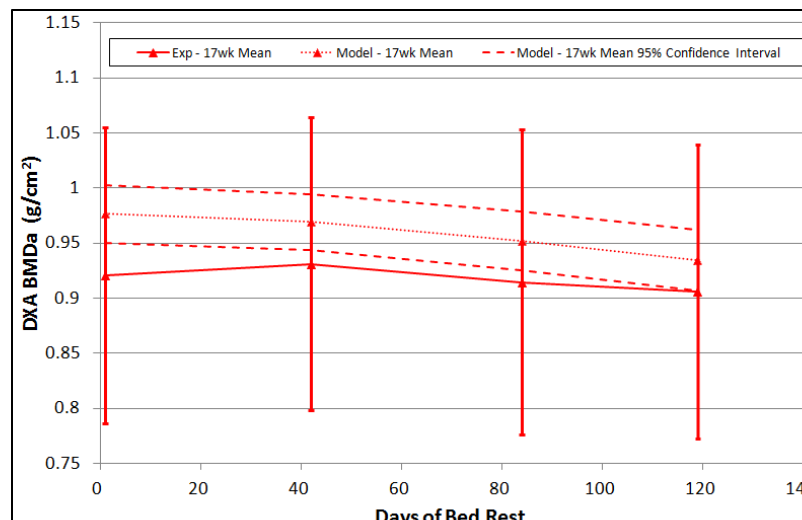
Initial vBMD similar to elderly person with age-related bone loss – *representative of astronaut population?*



70-day bed rest trabecular bone loss (4 subj.)



70-day bed rest cortical bone loss (4 subj.)



Time course mean aBMD change for 18 subjects during 17 weeks of bed rest [8].

R3: Evaluate within context (3/3)

- Validation results suggest that the model reported in Pennline and Mulugeta (2014):
  - Is most reliable for prediction of group mean BVF, vBMD and aBMD changes under bedrest conditions (spaceflight analog).
  - Has limited capability to predict subject specific trends in vBMD changes under bedrest conditions
- A good foundation was laid to establish a physiologically meaningful bone remodeling model to simulate site specific bone adaptation for spaceflight bone physiology research
- ***Future work:*** Rigorous verification, sensitivity and uncertainty analysis of the system of equations, parameters and variables

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R4: List limitations explicitly (1/2)

Limitations in the modeling approach:

1. Remodeling formulation is limited to porosity, thus restricting it to density changes within the trabecular region and to intracortical density changes
2. It does not cover periosteal apposition or endocortical change.
3. Geometry changes in the bone site are not modeled.
4. Preliminary validation analysis of the computational predictions for deconditioning has only been done for up to 4 months in duration.
5. The validation data used is from bed rest control subjects as an analog to gravitational unloading due to exposure to microgravity
6. Age and gender differences are not yet factored in when initializing model variables
7. Limited capability to make subject specific predictions
8. The computational model is best suited for the mature adult between 25 and 55 years of age, or typical age of an astronaut.
9. The model does not include the effects of sclerostin, calcitonin, osteopontin, or Interleukins, some of which may play a role bone loss in microgravity and with disuse in 1g.

R4: List limitations explicitly (2/2)

Limitations imposed by the state of knowledge in bone science:

1. There is a degree of uncertainty and variation in remodeling unit geometry and dimensions reported in the literature
2. It is difficult to guarantee that the remodeling unit values used in the model agree for the particular skeletal site of interest
3. There is uncertainty in the way ash fraction is modeled, and the full potential range of values estimated from experimental studies is not completely understood.
4. Activation frequency and activation density are inherently difficult to appropriately model due to the lack of human values at skeletal sites other than the iliac crest or rib
5. There are several potential algebraic schemes for mapping initial data values to model state variables. They depend on several possible definitions of ash fraction and how the steady state version of their respective equations are used

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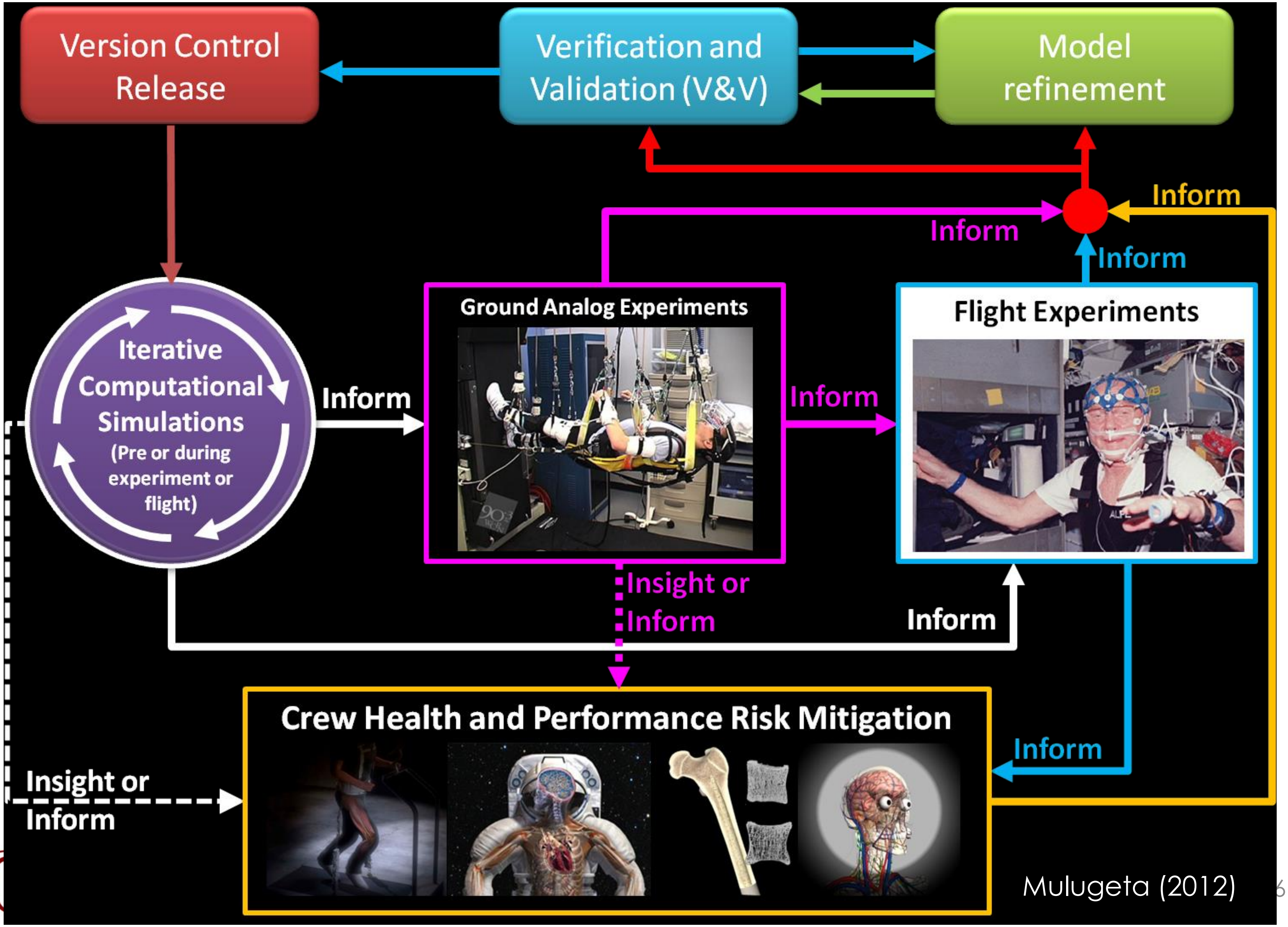
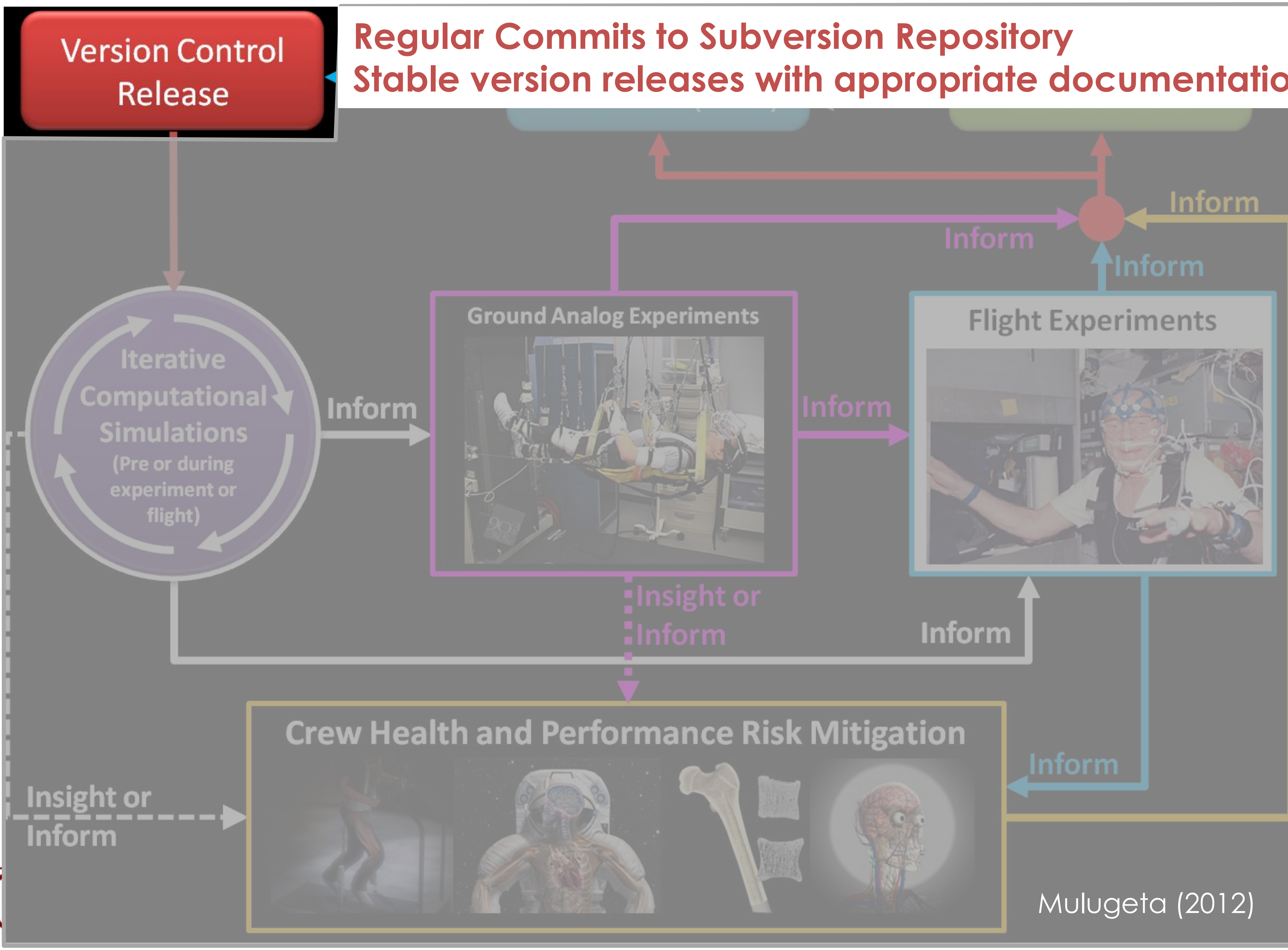
R5: Use version control – Applied to all DAP Projects



R5: Use version control – Applied to all DAP Projects

Regular Commits to Subversion Repository
Stable version releases with appropriate documentation



R6: Document adequately

- Code was documented sufficiently for modelers and scientists
- Graphical user interface was developed for intuitive use by end-users
- Every model delivery to stakeholders was accompanied with a report summarizing model features and credibility.
  - E.g. J. Pennline and L. Mulugeta, "The Digital Astronaut Project Computational Bone Remodeling Model (Beta Version) Bone Summit Summary Report", Bone Summit II Research and Clinical Advisory Panel Meeting, 1-5 Nov. 2013, Houston, TX, https://go.nasa.gov/2KvQi43.
- Presentations and briefings provided to stakeholder community at quarterly meetings, annual agency reports, and annual HRP Investigators' Workshop[7,8]
- Peer reviewed articles, conference presentations and technical memos were produced regularly (search Pennline and Mulugeta at https://ntrs.nasa.gov/)

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R7: Disseminate broadly

- The code was developed for use by NASA researchers, so it was not intended for release to the general public (at least not the beta model)

- However, peer reviewed articles and conference presentations are available for public consumption via the NASA Technical Report Server (search Pennline and Mulugeta at https://ntrs.nasa.gov/)

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R8: Get independent reviews

- In accordance to NASA-STD-7009, technical reviews were conducted to ensure critique from key stakeholders [4].

- In addition to obtaining feedback from the key stakeholders, NASA's Research and Clinical Advisory Panel (external subject matter experts) were provided a summary report [9]

- The Research and Clinical Advisory Panel used this report to provide feedback to the NASA Bone Discipline Lead regarding the potential utility and weakness of the DAP Bone Remodeling Model with respect to its context of use

R9: Test competing implementations

- The foundational model was formed by comparing, contrasting, combine and modify previously developed set of biochemical, cellular dynamics, and mechanical stimulus equations in the literature [10,11]

- This is an ongoing process

R10: Conform to standards

- The model and simulations were developed and applied in accordance to NASA's Standard for Models and Simulations (NASA-STD-7009) [2]

- All human subject data were used in accordance to HIPAA

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REFERENCES

1. J. Pennline and L. Mulugeta (2014), "A Computational Model for Simulating Spaceflight Induced Bone Remodeling", *44th International Conference on Environmental Systems*, ICES2014-083.
2. Standard for Models and Simulations (2016), NASA-STD-7009, https://go.nasa.gov/2GrwDji.
3. L. Mulugeta, "The Digital Astronaut Project: Applying computational modeling and simulation to inform space life science research", *USRA DSLS Brown Bag Lunch Seminar*, 19 April 2012, https://bit.ly/2rN96F8.
4. E.S. Nelson, L. Mulugeta, M. Walton and J.G. Myers, "How to Develop and Interpret Credibility Assessments of Numerical Models for Human Research: NASA-STD-7009 Demystified", *Human Research Program Investigators' Workshop*, 12-13 Feb. 2014, Galveston, TX, https://go.nasa.gov/2lsGEP8.
5. Lang T, LeBlanc A, Evans H, Lu Y, Genant H, Yu A: Cortical and trabecular bone mineral loss from the spine and hip in long-duration spaceflight. J Bone Min Res 2004, 19:1006–1012.
6. LeBlanc AD, Driscol TB, Shackelford LC, Evans HJ, Rianon NJ, Smith SM, Feeback DL, Lai D: Alendronate as an effective countermeasure to disuse induced bone loss. Journal of musculoskeletal & neuronal interactions 2002, 2:335–43.
7. J.A. Pennline, L. Mulugeta, B.E. Lewandowski, W.K. Thompson, and J.D. Sibonga, "The Digital Astronaut Project Bone Remodeling Model", *Human Research Program Investigators' Workshop*, 12-13 Feb. 2014, Galveston, TX, https://go.nasa.gov/2KuCYwL.
8. NASA, Human Research Program, 2013 Fiscal Year Annual Report, 2014, https://go.nasa.gov/2L5YKYM.
9. J. Pennline and L. Mulugeta, "The Digital Astronaut Project Computational Bone Remodeling Model (Beta Version) Bone Summit Summary Report", Bone Summit II Research and Clinical Advisory Panel Meeting, 1-5 Nov. 2013, Houston, TX, https://go.nasa.gov/2KvQi43.
10. Pennline JA (2009), *Simulating Bone Loss in Microgravity Using Mathematical Formulations of Bone Remodeling,* ", *NASA Glenn Research Center,* Cleveland, OH: Technical Memorandum, NASA/TM-2009-215824, https://go.nasa.gov/2lpXi67.
11. J. Pennline and L. Mulugeta (2014b), "Evaluating Daily Load Stimulus Formulae in Relating Bone Response to Exercise", *NASA Glenn Research Center,* Cleveland, OH: Technical Memorandum, NASA/TM-2014-218306, https://go.nasa.gov/2k5fdQZ.

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Forum discussions: https://simtk.org/forums/viewforum.php?f=848

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For more information, questions and suggestions, please contact us at:

CPMS Info
cpmsinhealthcare@gmail.com

Credible Image-Based Modeling and Simulation of Mitral Valve

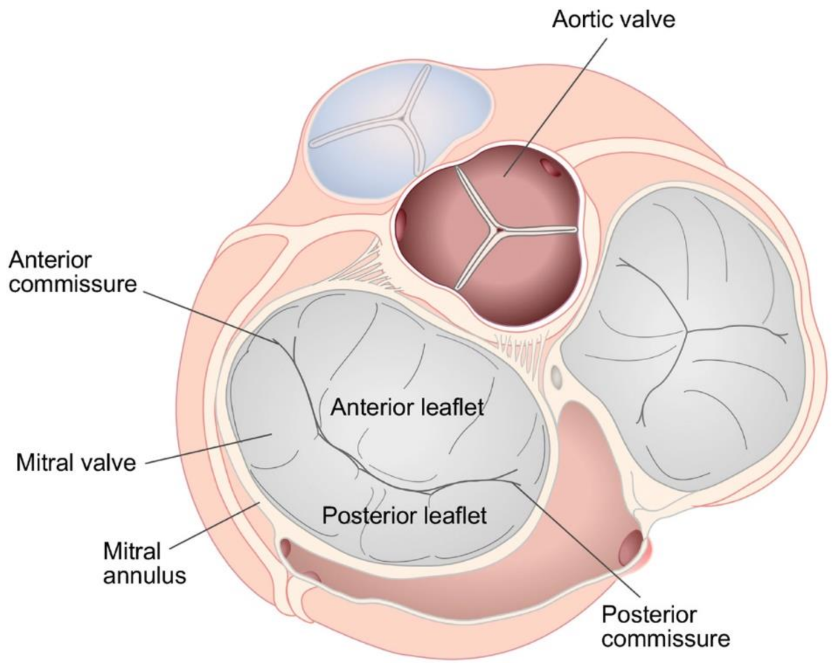
Andrew Drach [1], Amir H. Khalighi [1], Bruno V. Rego [1], Michael S. Sacks [1], Joseph H. Gorman III [2], Robert C. Gorman [2]

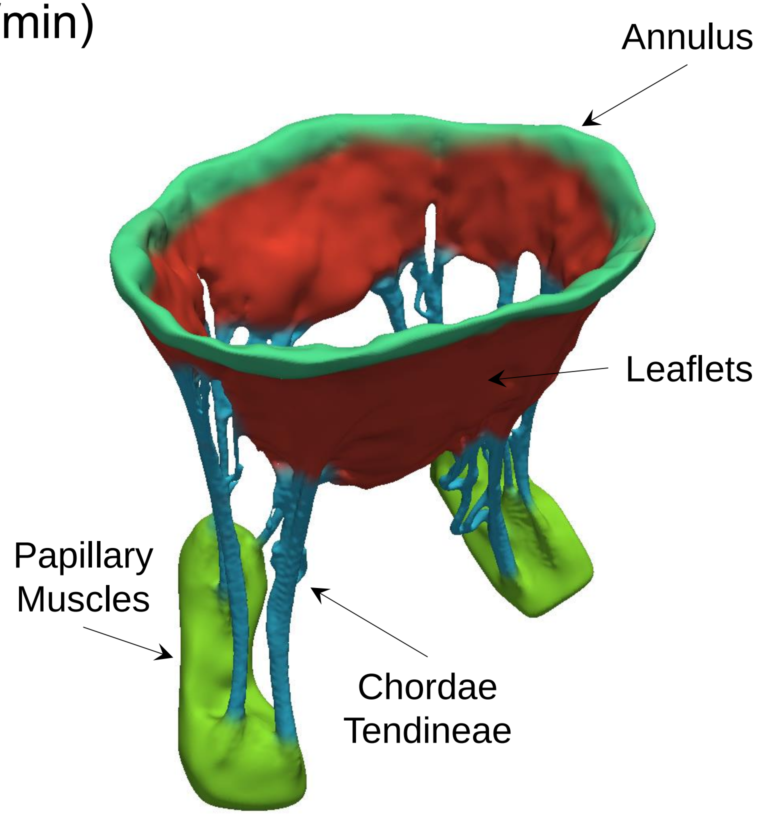
[1] Willerson Center for Cardiovascular Modeling & Simulation
Institute for Computational Engineering and Science
The University of Texas at Austin

[2] Gorman Cardiovascular Research Group
Perelman School of Medicine
University of Pennsylvania

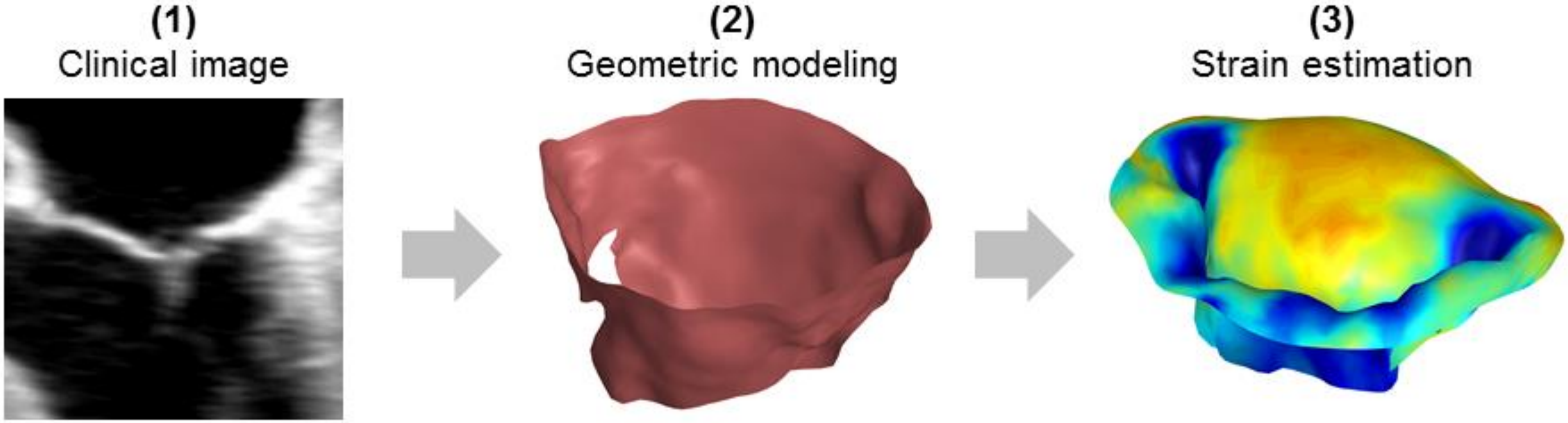
Mitral Valve (MV)

- 2 cusps (unique)
- 4~6 cm^2 orifice area (largest)
- Bearing >100 mmHg transvalvular pressure (healthy)
- “Beating” >100,000 a day (~80 beats/min)





R1: Define context clearly

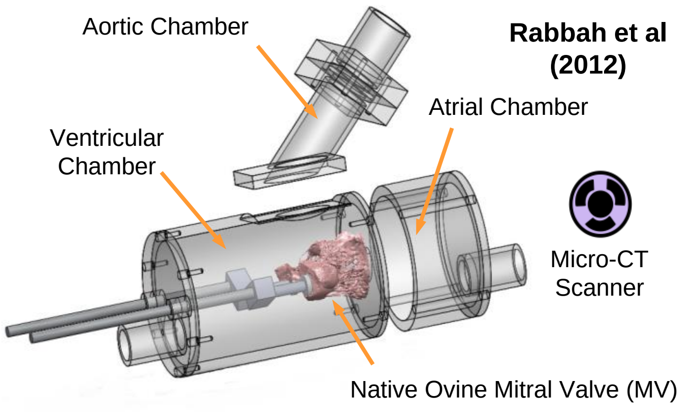


- Objectives
  - Provides local strain estimates across entire valve
  - Extendible to *in silico* perturbation studies
  - Non-invasive image-based method
- Physics-based morphing approach, calibrated using acquired imaging data
- Rely only on geometric data extractable *in vivo*

R2: Use appropriate data

Materials

- Five ovine MVs
- Dimensionally Compatible with the Georgia Tech Left Heart Simulator (GTLHS)



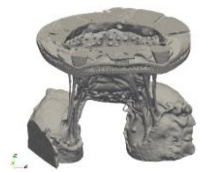
Methods

- In-vitro simulation of 9 states in GTLHS with tristate annulus holder
- Each MV was instrumented with ~100 fiducial markers
- Micro-CT imaging of MV geometry in each sate
- Collagen-fiber architecture imaging using SALS

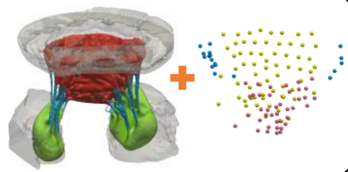
Normal / Healthy	Dilated	Surgically Modified
healthy annulus healthy PM positions	dilated flat annulus displaced PMs	dilated flat annulus displaced PMs

Major Data Processing Steps

End-diastolic (unloaded) state images

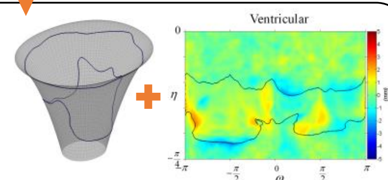


Filtering/Segmentation
Morphological labeling

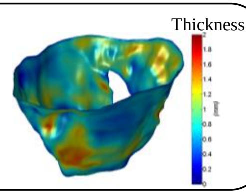


Trimming

Geometric modeling of leaflets:
Superquadric fitting + spectral analysis

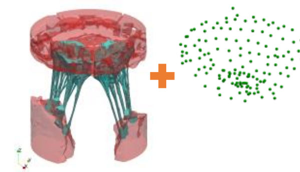


Reconstructed median surface with superimposed thickness field



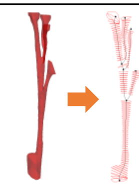
End-systolic (pressurized) state images

Filtering/Segmentation
Morphological labeling

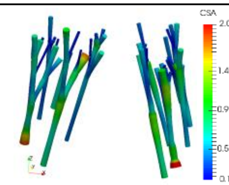


Trimming

Extraction of centerlines & pointwise CSA
(curve-skeleton representation)



Reconstructed Chordae Tendineae
with superimposed CSA



python · FEniCS project · OPEN CASCADE · VTK · jupyter · ParaView
SciPy · matplotlib · NumPy · Fiji · ImageJ · MeshLab

simpleware ScanIP · ZBrush

R5: Use version control [GIT]

Bitbucket

Author	Commit	Message	Date
Andrew Drach	b0cd2bb	refactoring, minor fixes, add new features + Add [Leaflets] histogram fro...	2017-03-07
Andrew Drach	5e438c3	refactoring, minor fixes	2017-02-25
Andrew Drach	11400be	minor updates, refactoring	2017-02-20
Andrew Drach	eac5d2b	new features, bug fixes + [Abaqus]: added MVCT prestrain; 2D leaflet ou...	2017-01-25
Andrew Drach	ce4eba3	+ [Abaqus]: added Abaqus pre- and post-processing module + [BCS]: a...	2016-12-15
Andrew Drach	bf0da9d	+ [Chordae]: added a module to perform projection, flaring, and export ...	2016-10-08
Andrew Drach	c5f0826	+ Added a new module [BCS] for processing of boundary conditions data	2016-10-08
Andrew Drach	6660236	+ [Leaflets]: added thickness processing functionality + [CFA]: added affi...	2016-10-08
Andrew Drach	3c6ee58	- added the pipeline for processing of CFA data - minor update to the O...	2016-09-20
Andrew Drach	cf4bda6	updated the code for Chordae processing, added the meshing module	2016-09-20
Andrew Drach	191cbcd	- Added a script to design new marker locations - Minor update to the ...	2016-08-23
Andrew Drach	3d70a85	- Finished the morphing scripts [OpenClosed-02 and Open-Closed-03] -...	2016-08-18
Andrew Drach	f813266	- Added export of boundary curves to MAT file in [Leaflets-02-map_mar...	2016-08-15
Andrew Drach	f5a3918	finished working on [Leaflets-02-map_markers]	2016-08-12
Andrew Drach	26dc516 M	Merged in parameterize-env (pull request #1) added parameterization o...	2016-08-11
Andrew Drach	7fcb814	added parameterization of environmental variables in env.paths	2016-08-11
Andrew Drach	0e7cc51	Strippped down version	2016-08-10
Andrew Drach	91509ab	Initial commit	2016-08-10

Unfortunately, no version control for the documentation (user guides)

R6: Document adequately

Name	Last Modified	File size
env	10 months ago	
old	a year ago	
post-processing	8 months ago	
utils	a year ago	
Abaqus-01-input.ipynb	8 months ago	58.4 kB
Abaqus-02-post-chordae.ipynb	a year ago	7.78 kB
Abaqus-02-post-leaflets-Copy1.ipynb	a year ago	24.2 kB
Abaqus-02-post-leaflets.ipynb	a year ago	26.2 kB
Abaqus-03-post-leaflets-CAS.ipynb	8 months ago	13.7 kB
Abaqus-03-post-leaflets-histogram.ipynb	8 months ago	1.29 MB
Abaqus-03-post-leaflets-stats.ipynb	8 months ago	8.67 kB
Abaqus-04-marker-errors.ipynb	10 months ago	2.24 MB
Abaqus-04-post-leaflets-averaging.ipynb	8 months ago	15.9 kB
BCS-01-extract-data.ipynb	a year ago	11.7 kB
BCS-01-in-vivo-annulus.ipynb	a year ago	50.9 kB
BCS-02-annulus-disps.ipynb	a year ago	11.3 kB
BCS-03-origin-disps.ipynb	a year ago	6.57 kB
BCS-04-compare-annuli.ipynb	2 years ago	180 kB
CalcTriMeasures.ipynb	2 years ago	11 kB
CFA-01-readSALS.ipynb	a year ago	1.98 MB

R6: Document adequately

Import modules

```
#!/usr/bin/env python

###############################################################################
"""This script processes CSV file with boundary representation of the leaflets
   and generates finite element mesh with mapped markers"""
__author__     = "Andrew Drach"
__copyright__  = "(c) 2017 Andrew Drach"
__credits__    = "Andrew Drach"
__license__    = "<license>"
__version__    = "1.0.1"
__maintainer__ = "Andrew Drach"
__email__      = "andrew.drach@utexas.edu"
__status__     = "Development"
###############################################################################

import os, sys, itertools, math, copy
import logging
from time import clock
from functools import wraps
import numpy as np
import scipy.io as sio
import scipy.interpolate as sint

import triangle
import triangle.plot as triplot
import matplotlib.pyplot as plt
from mpl_toolkits.axes_grid1 import make_axes_locatable
%matplotlib inline

from env.paths import *
from utils.bSpline_utils import *
from utils.VTK_utils import *
from utils.SQfunctions import *
from utils.leaflets_utils import *
from utils.marker_utils import *

import vtk
```

```
# Define the function which performs 2D ball pivoting to build the curve connectivity from scatter data
# INPUT ARGUMENTS:
#     lim_a -- angle constraint
#     lim_d -- radius constraint
#     scl_y -- y scaling
# OUTPUT: sorted indices of a connected curve
def BallPivoting2D(data1,lim_a=120,lim_d=0.025,scl_y=5,duptol1=1e-9):

    vnorm = lambda x  : np.sum(x**2)**0.5
    vcos  = lambda x,y: np.sum(x*y)/vnorm(x)/vnorm(y)
    acosd = lambda x  : math.degrees( math.acos(x) )

    data        = np.copy(data1)
    data[:,1] *= scl_y

    len1       = len(data)
    pnt1       = data[0]
    dir1       = np.array([1.0,0.0])
    mask1      = np.ones(len1,dtype=bool)
    mask1[0] = False
    sort1      = [0]
```

Import modules

Initialize variables and setup logging

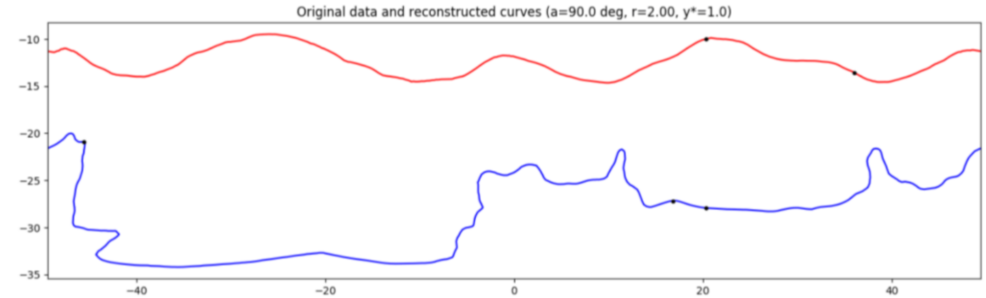
```
INFO     ----------  START OF Leaflets-02-map_markers  ----------
```

Read CSV and MAT files

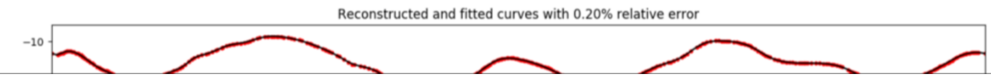
```
INFO     Opening [c:\Andrew\Academia\___MV\UT09\leaflets\input\UT09_atr_boundaries.csv]
INFO     The point cloud consists of 2800 vertices
INFO     X range: -1.000  1.002
INFO     Y range: -0.266 -0.074
INFO     Total of 1708 duplicates removed
INFO     Total of 142 edge points removed
INFO     Opening [c:\Andrew\Academia\___MV\UT09\leaflets\input\UT09_sq_fit_params.mat]
```

Reconstruct, visualize, and export the boundaries in AC coordinate system

```
INFO     Ball pivoting parameters: angle = 90.0 degrees, radius = 2.00, y scaling = 1.0
INFO     Reconstructing curve 1
INFO     [BallPivoting2D]: The pivoting step (10.730) is larger than the limit (2.0)
INFO     [BallPivoting2D]: Total number of points in the curve: 422
INFO     Reconstructing curve 2
INFO     [BallPivoting2D]: The pivoting step (15.300) is larger than the limit (2.0)
INFO     [BallPivoting2D]: Total number of points in the curve: 523
```




```
INFO     [Fit2Dcurve]: 0.2% with 58 coefficients. Status: 0
INFO     [Fit2Dcurve]: 0.2% with 85 coefficients. Status: 0
```



R1: Define context clearly

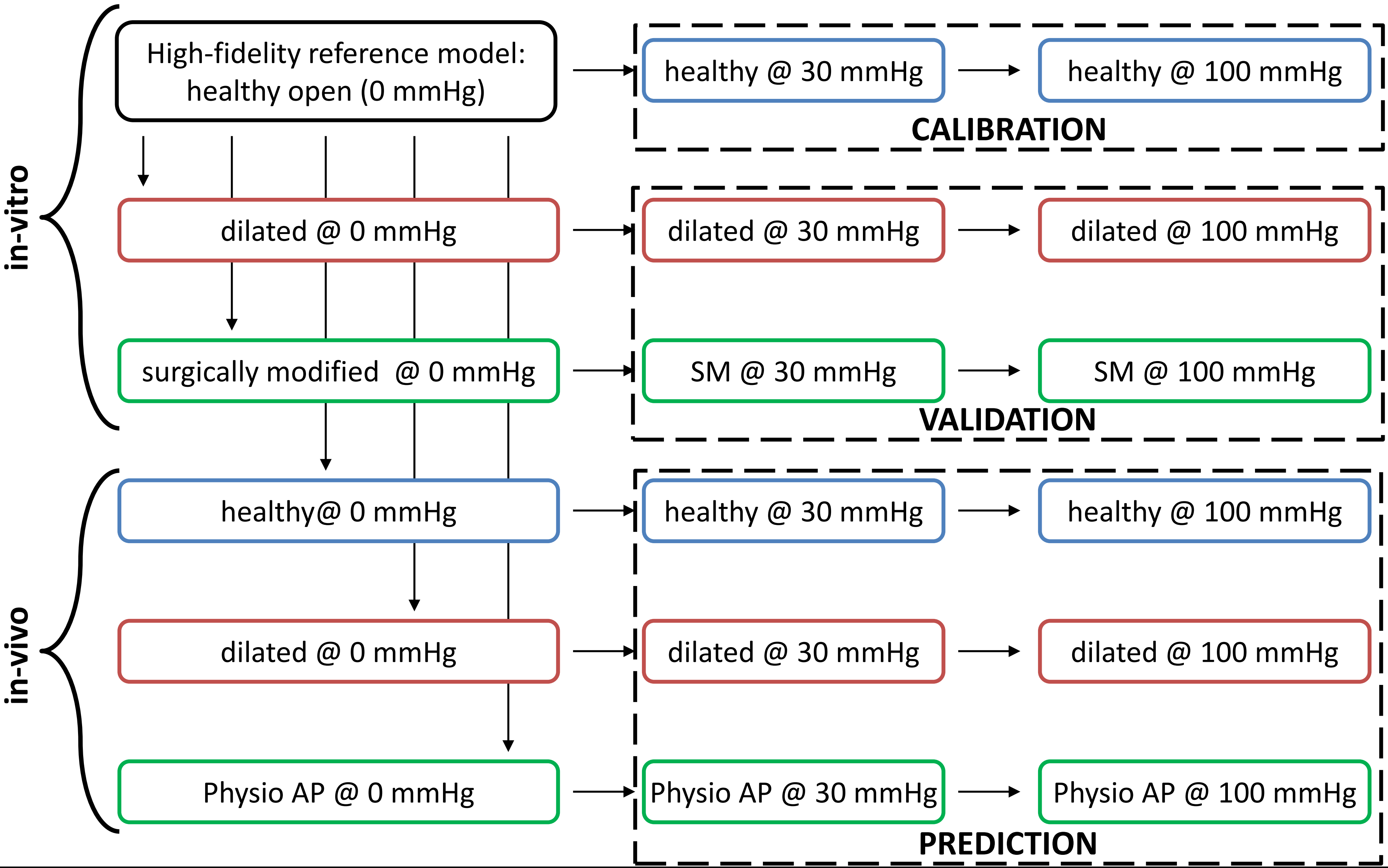
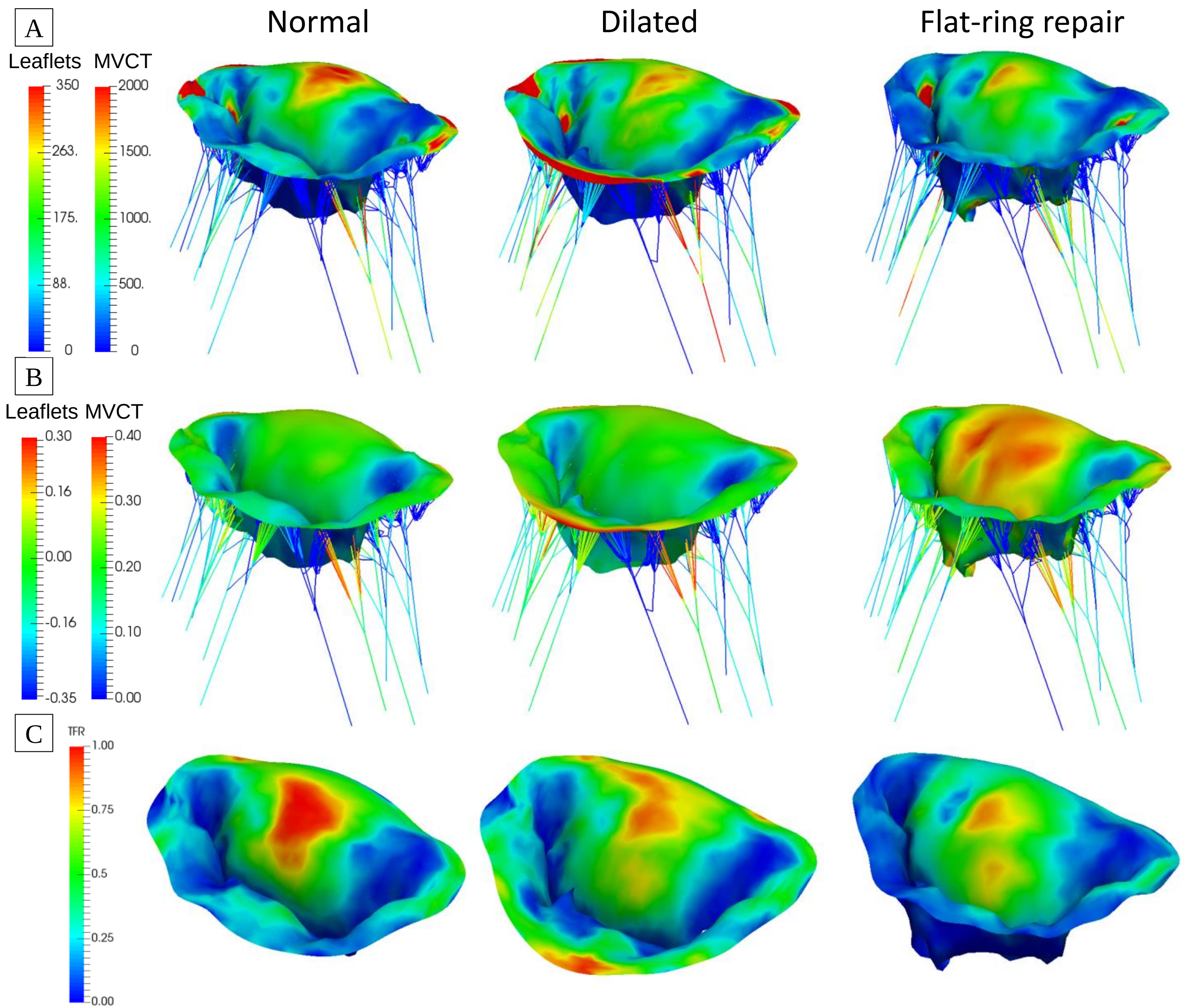


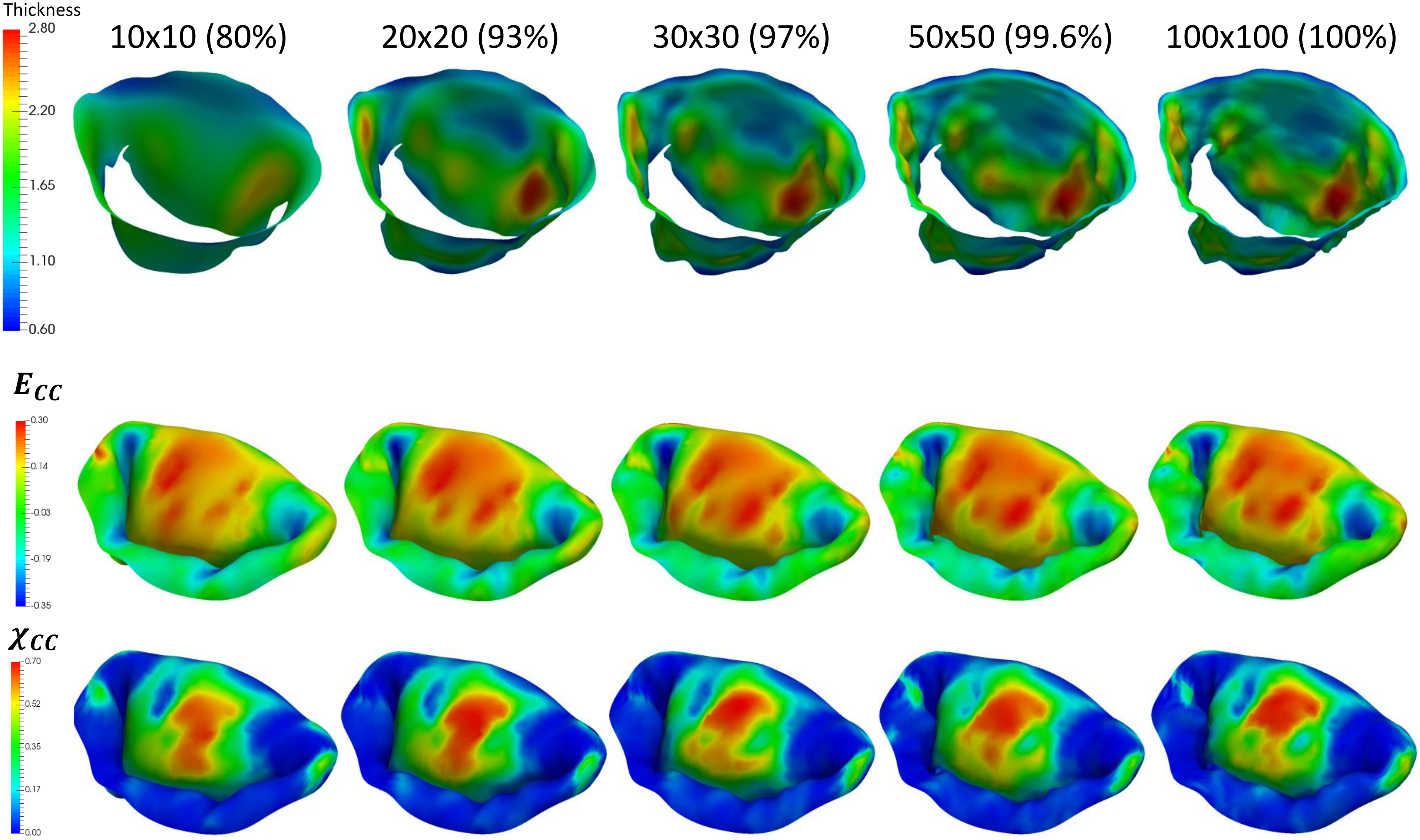
Illustration of Simulation Results



R9: Test competing implementations
R10: Conform to standards

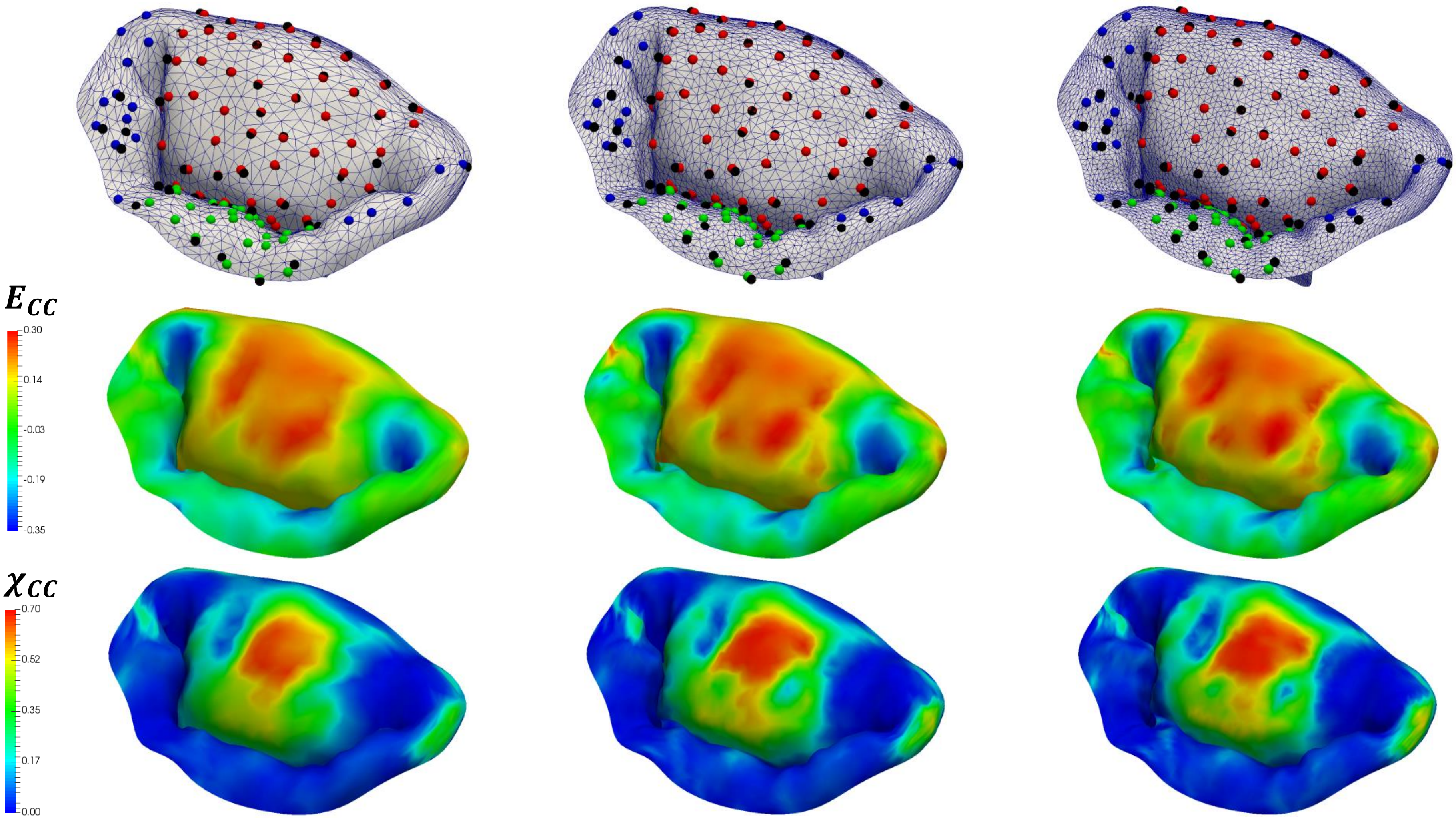
Unfortunately, no comparison to the external / independent models, approaches or standards

Sensitivity Studies: Resolution of Features



Sensitivity Studies: FE Discretization

N100 | N150 | N200



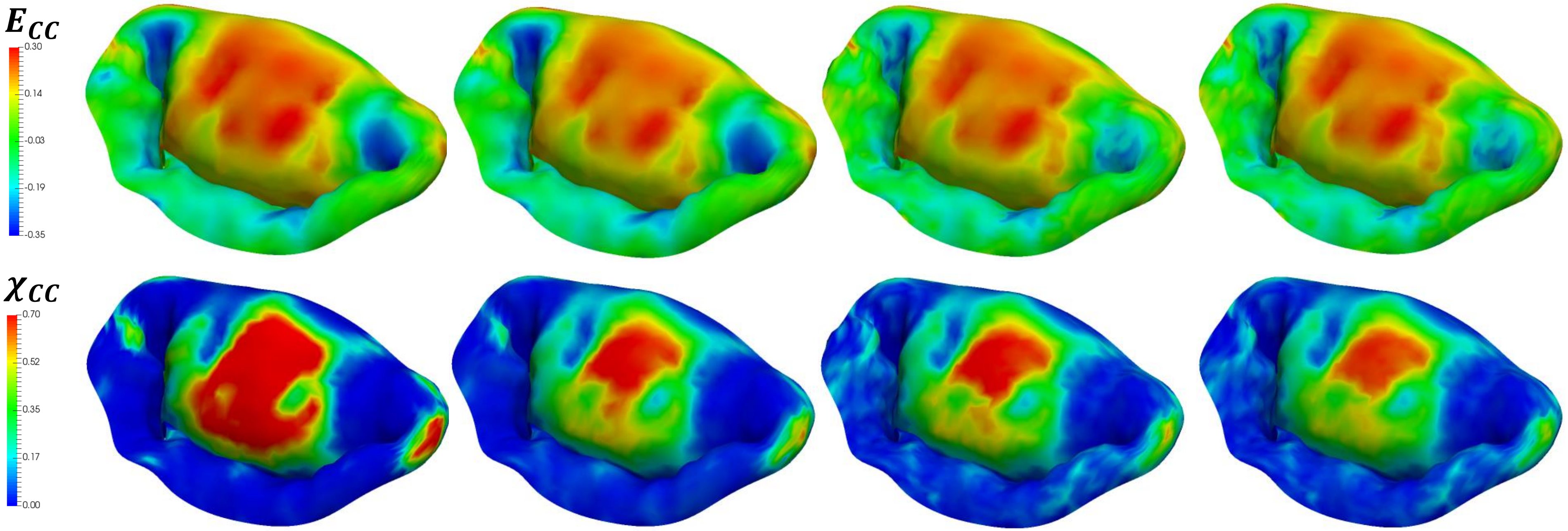
2,610 tri
elm.size ~0.94 mm

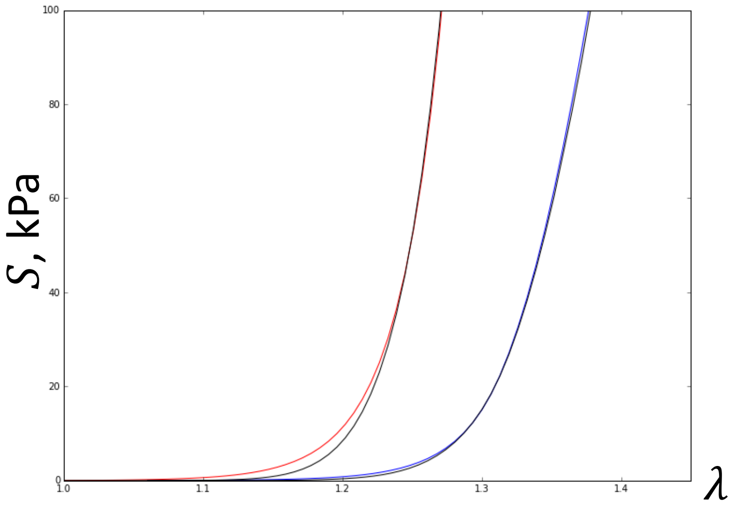
5,770 tri
elm.size ~0.63 mm

10,338 tri
elm.size ~0.47 mm

Sensitivity Studies: Material Model

Isotropic | PD = CC, σ=30° | PD = mapped, σ=30° | Fully mapped PD, σ



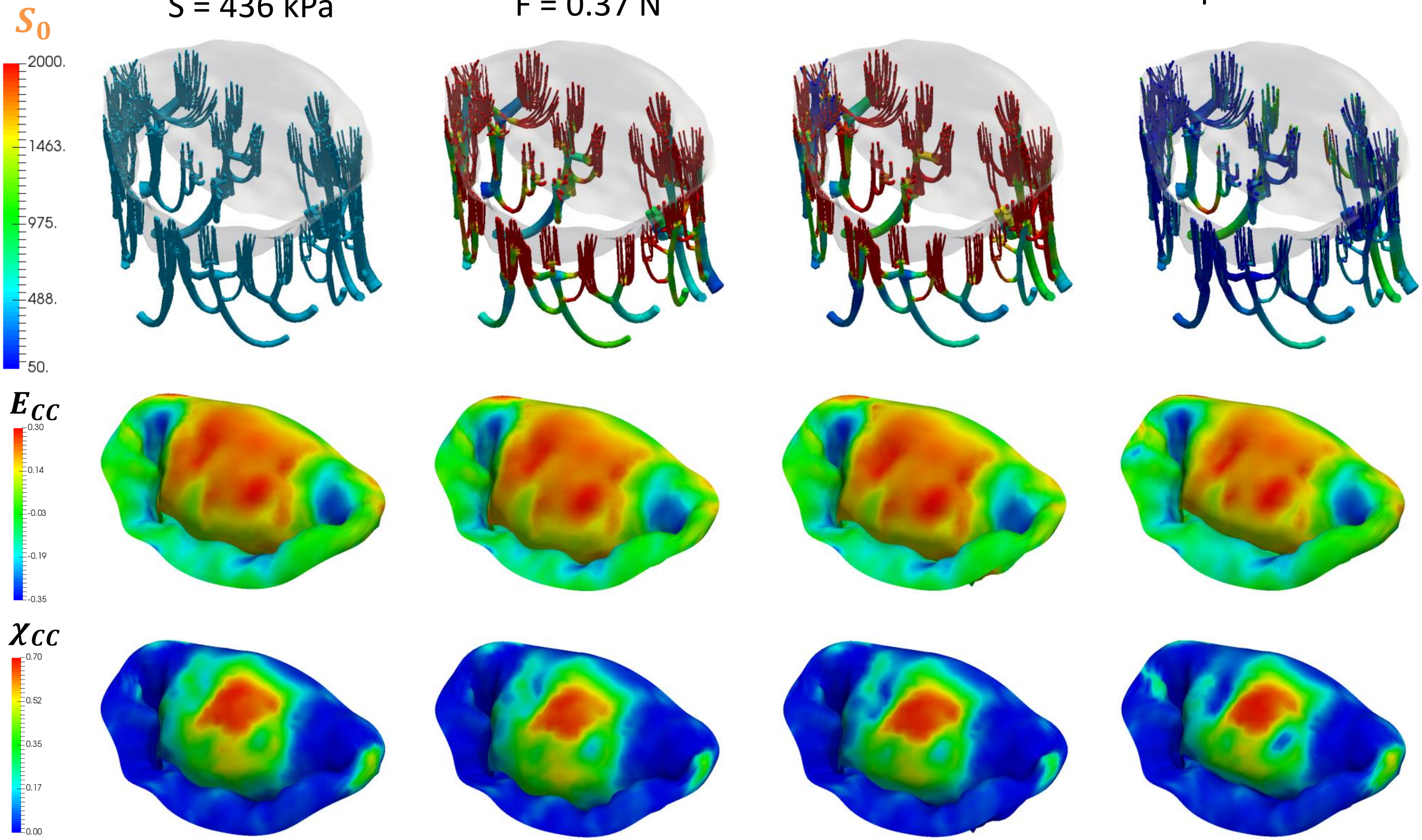


Simplified Structural Model (SSM)
by Fan&Sacks 2014

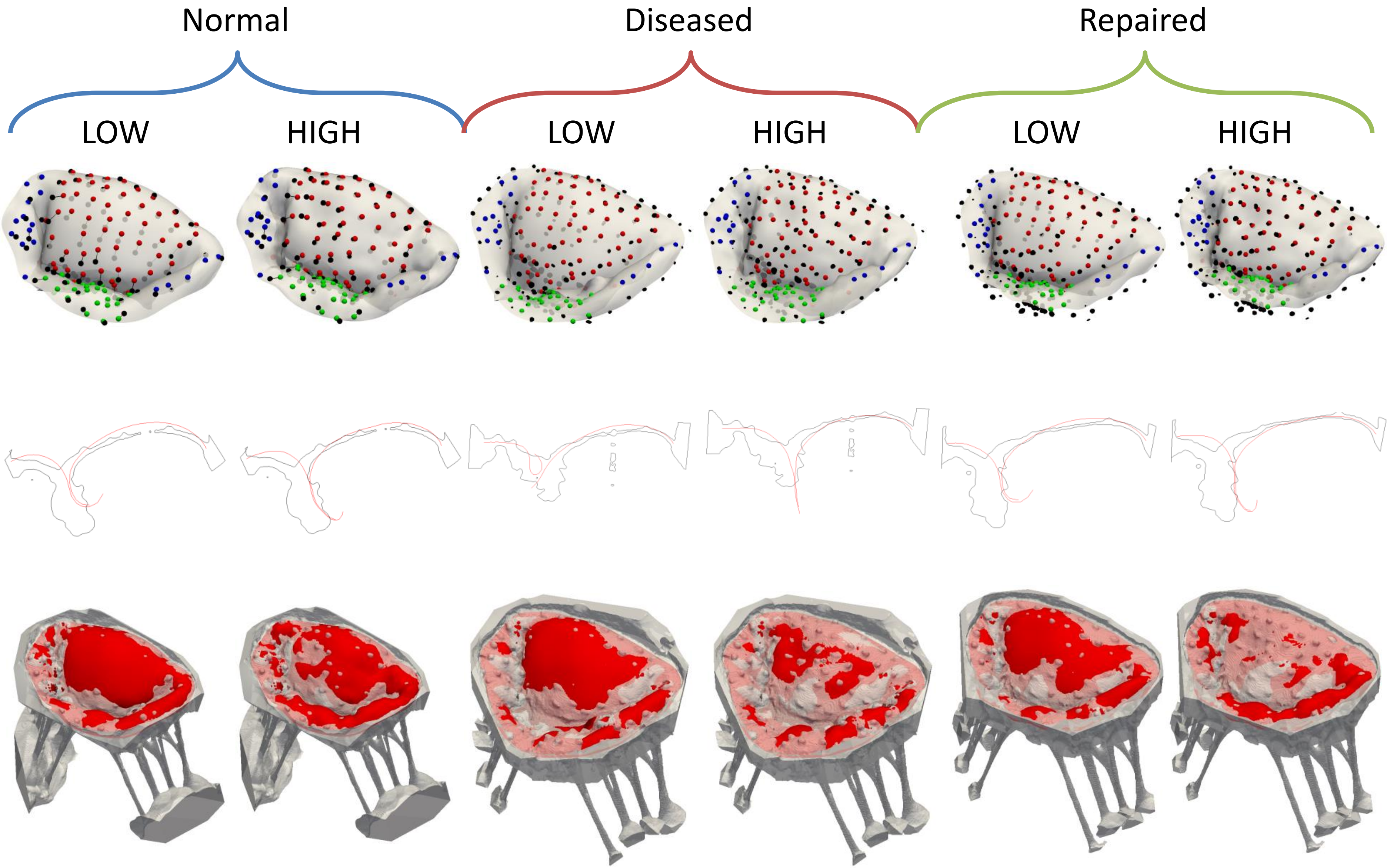
$\mu_m = 10.11$ kPa
$c_0 = 0.0485$ kPa
$c_1 = 24.26$
$\sigma = 22.94°$
$E_{ub} = 0.55$

Sensitivity Studies: Chordae Prestrain

avg S S = 436 kPa	avg F F = 0.37 N	F = Reaction	Fully mapped pre-strain

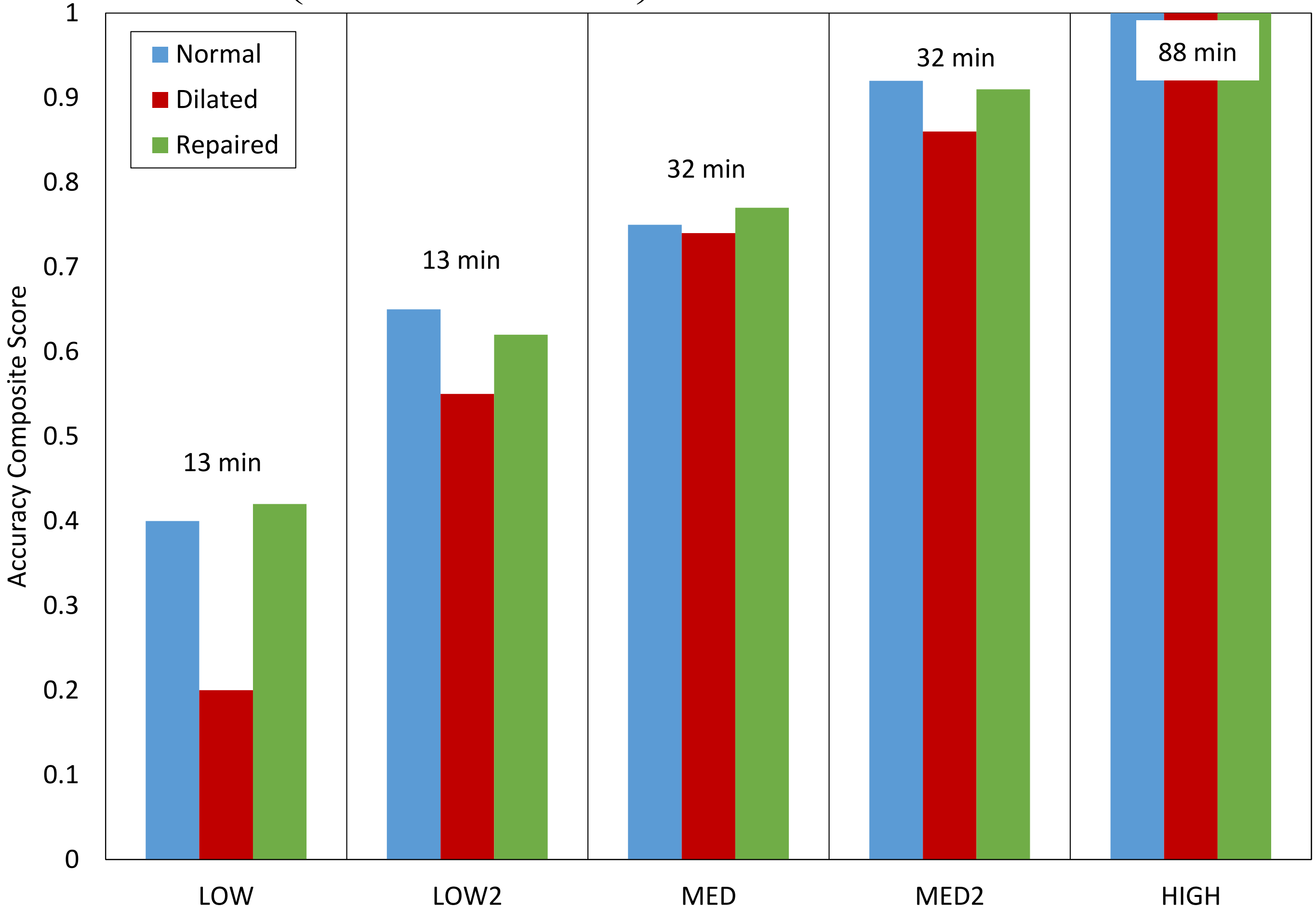


Simulation Results



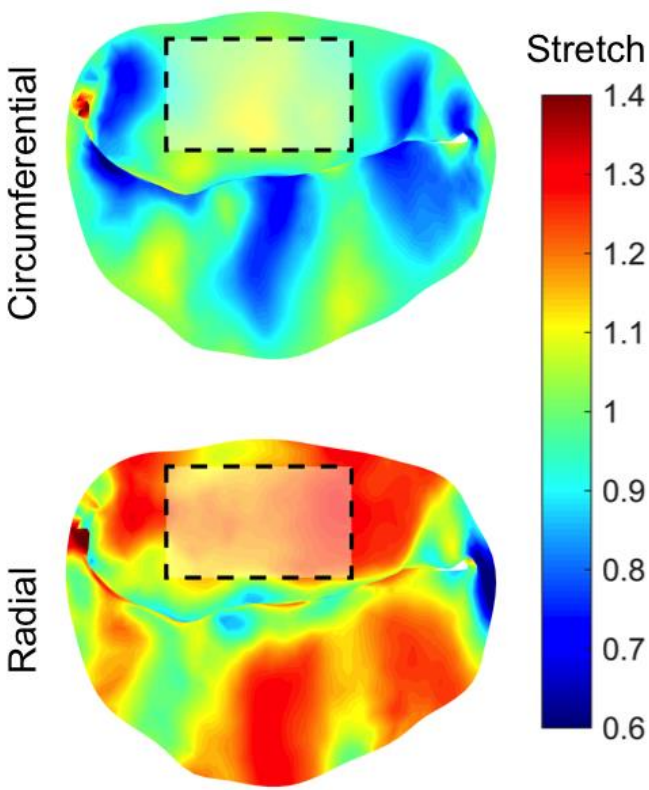
R3: Evaluate within context (in-vitro)

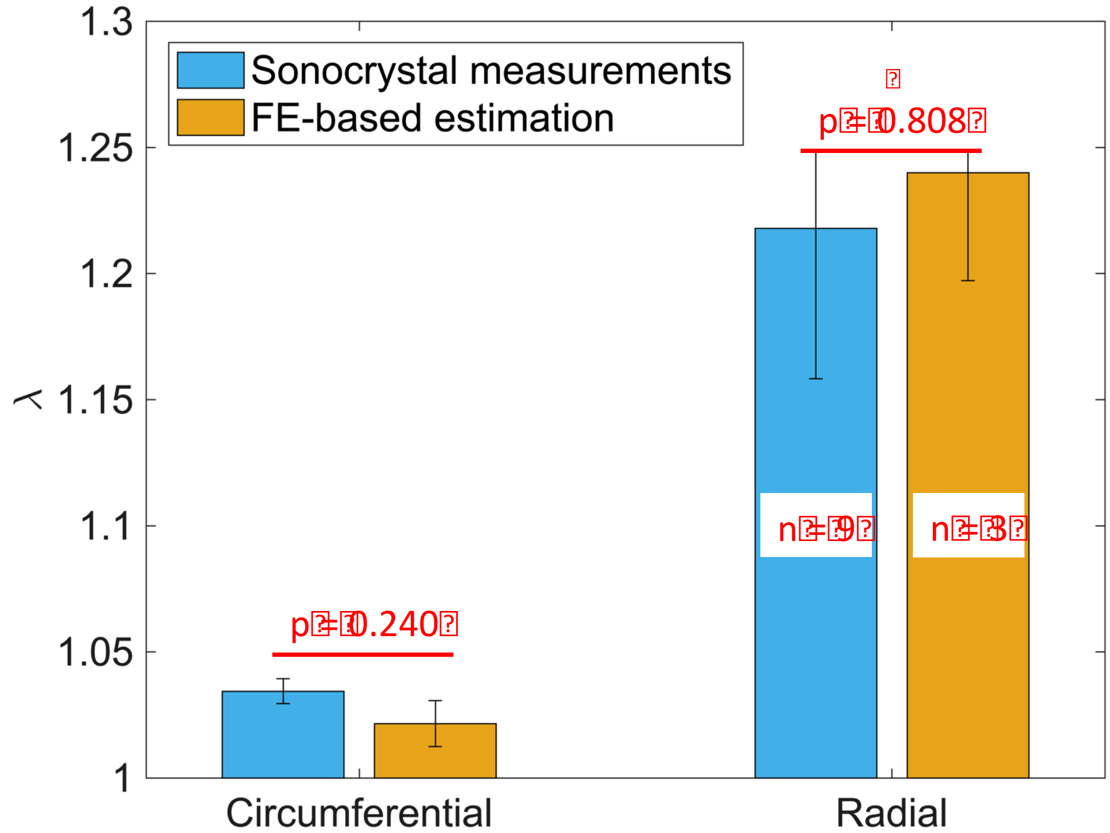
$$CAS = \sum_{k} \left(1 - \frac{\sqrt{\sum_{i}^{N} \left(q_{i,k} - \bar{q}_{i,k} \right)^2}}{\sigma_{i,k}} \right) / \dim(k) \qquad k = \left\{ S_{CC}, S_{RR}, E_{CC}, E_{RR}, \chi_{CC}, \chi_{RR}, \right\}$$



R3: Evaluate within context (in-vivo)

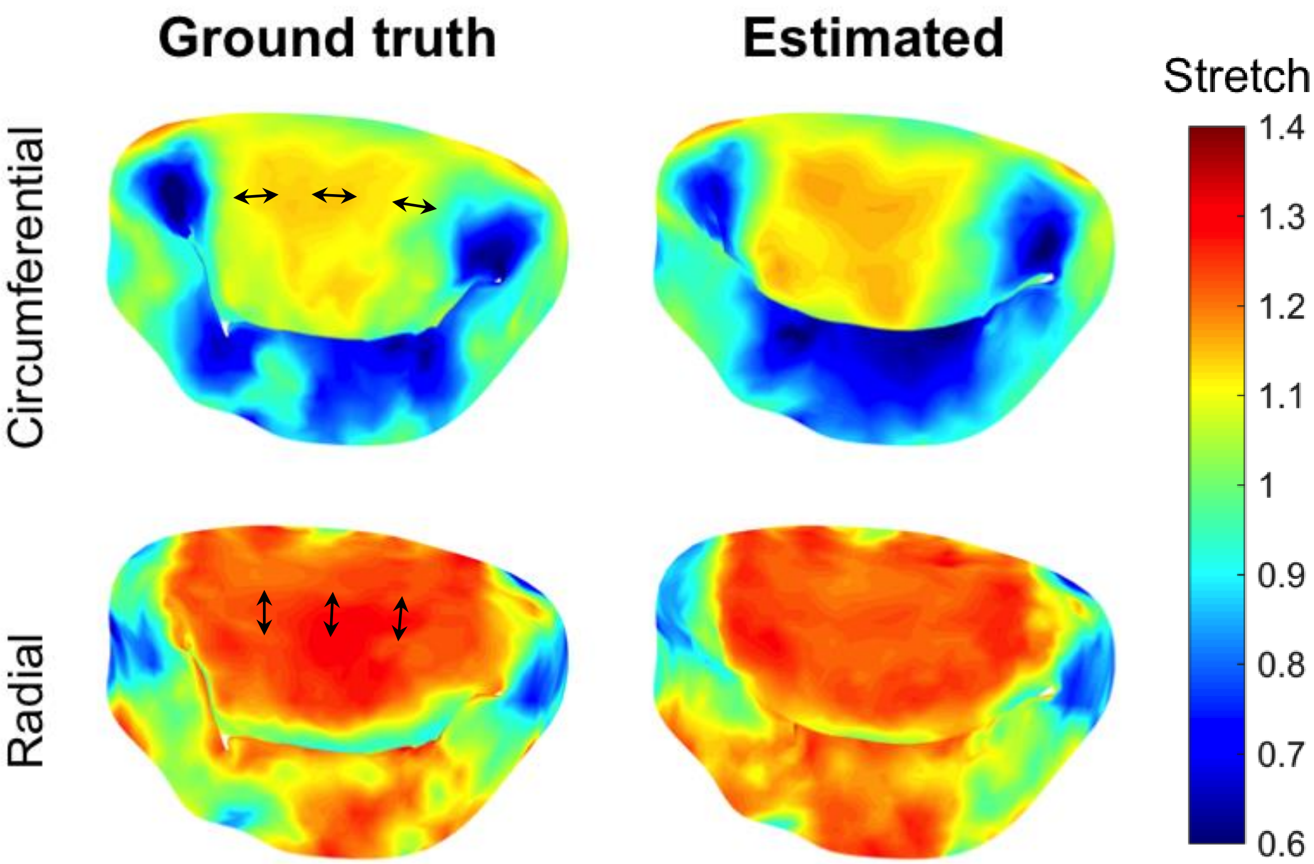
Accuracy of the Method





R4: List limitations explicitly

Accuracy of strain estimates



We have chosen to use a uniform thickness and uniform downward chord-mimicking force

R7: Disseminate broadly

R8: Get independent reviews

PEER-REVIEWED PUBLICATIONS

1. Khalighi AH, Rego BV, Drach A, Gorman RC, Gorman JH, Sacks MS. "Development of a Functionally Equivalent Model of the Mitral Valve Chordae Tendineae Through Topology Optimization" [Under Review] Annals of biomedical engineering. 2018
2. Rego BV, Khalighi AH, Drach A, Lai EK, Pouch AM, Gorman RC, Gorman JH, Sacks MS. "A non-invasive method for the determination of in vivo mitral valve leaflet strains" [Under Review]] International journal for numerical methods in biomedical engineering. 2018
3. Ayoub S. Tsai KC, Khalighi AH, Sacks MS. "The Three-Dimensional Microenvironment of the Mitral Valve: Insights into the Effects of Physiological Loads" [In press]. Cellular and Molecular Bioengineering
4. Sacks MS, Khalighi AH, Rego BV, Ayoub S, Drach A. "On the need for multi-scale geometric modelling of the mitral heart valve". Healthcare technology letters. 2017 Oct 25;4(5):150

…………

9. Drach A, Khalighi AH, ter Huurne FM, Lee CH, Bloodworth C, Pierce EL, Jensen MO, Yoganathan AP, Sacks MS. "Population-averaged geometric model of mitral valve from patient-specific imaging data". Journal of medical devices. 2015 Sep 1;9(3):030952.

PRESENTATIONS AT INTERNATIONAL CONFERENCES

2018: 9 presentations 2017: 16 presentations 2016: 6 presentations 2015: 7 presentations

Unfortunately, no external / independent users due to some limitations on dissemination

Acknowledgments

People:

- Charles H. Bloodworth IV (GeorgiaTech)
- Eric L. Pierce (GeorgiaTech)

Funding

- NHLBI NIH Grant R01HL119297

Summary

Rule	Status of Implementation
R1: Define context clearly	**GOOD**
R2: Use appropriate data	**GOOD**
R3: Evaluate within context	**GOOD**
R4: List limitations explicitly	**AVERAGE** (not comprehensive enough to be used immediately in the clinical applications)
R5: Use version control	**GOOD**
R6: Document adequately	**AVERAGE** (lack of tutorials, user guide)
R7: Disseminate broadly	**GOOD**
R8: Get independent reviews	**AVERAGE** (lack of review by independent users)
R9: Test competing implementations	**AVERAGE** (lack of comparison against independent models/approaches)
R10: Conform to standards	**BAD**