Predicting Cardiovascular Disease Progression with Personalized Simulations

Alison Marsden
Associate Professor
Departments of Bioengineering and Pediatrics, and by courtesy, of Mechanical Engineering
Institute for Computational and Mathematical Engineering
Stanford University

@MarsdenStanford

Stanford MEDICINE

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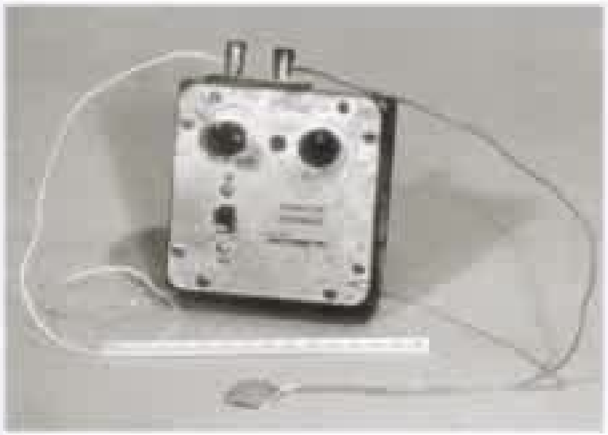
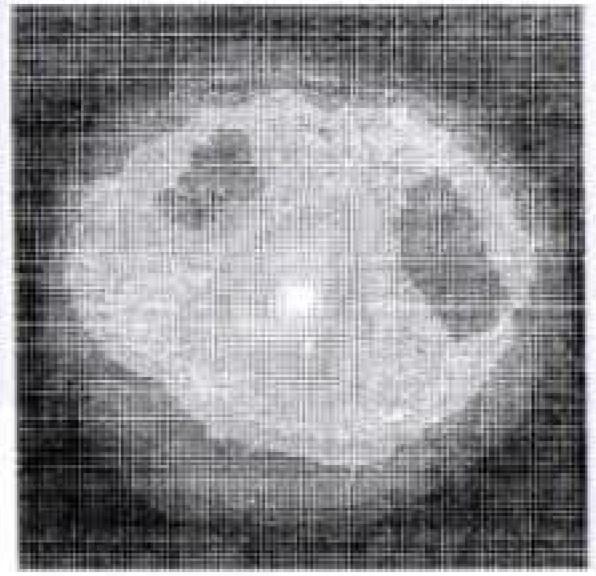
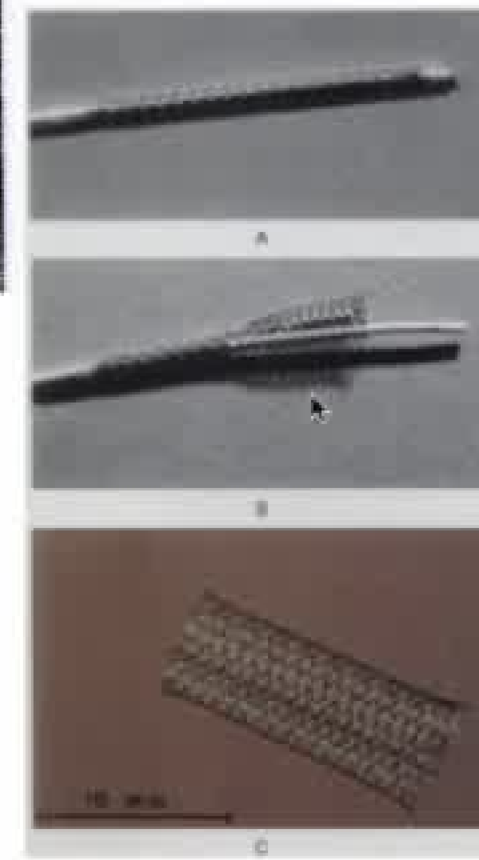
Lucile Packard Children's Hospital AT STANFORD

Engineer-Clinician Partnerships







Patient care advanced by Technology

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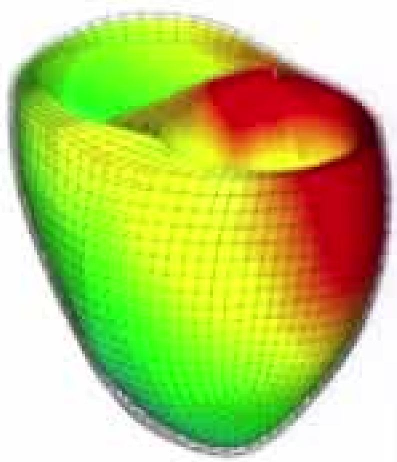
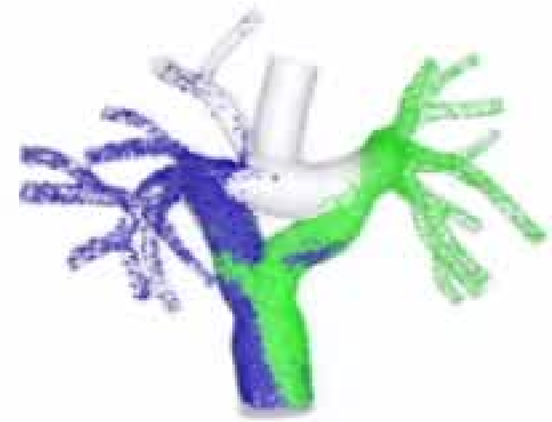
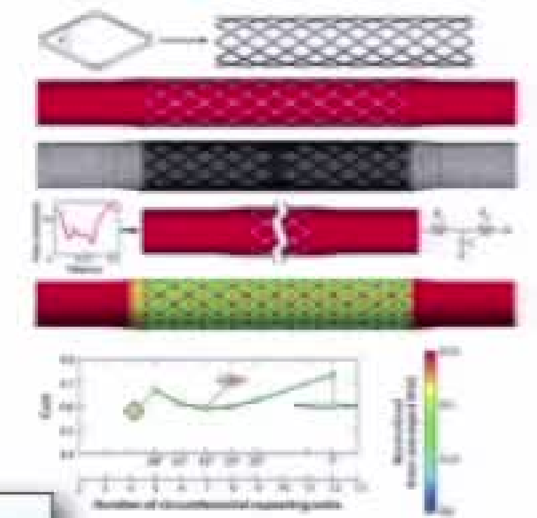
Technology driven by clinical needs

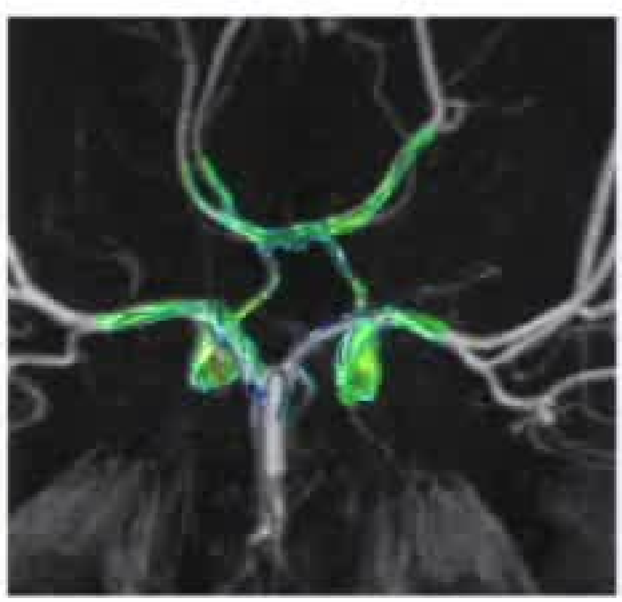
Engineer-Clinician Partnerships

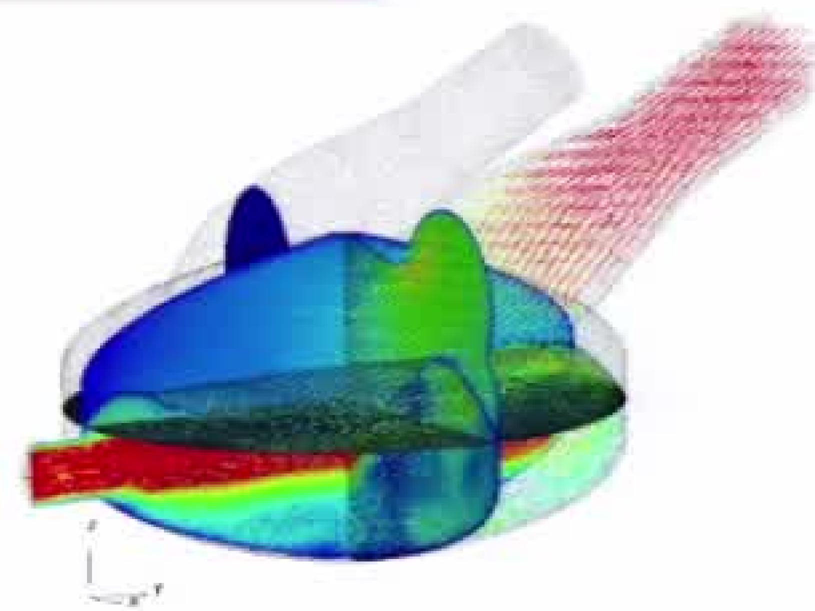




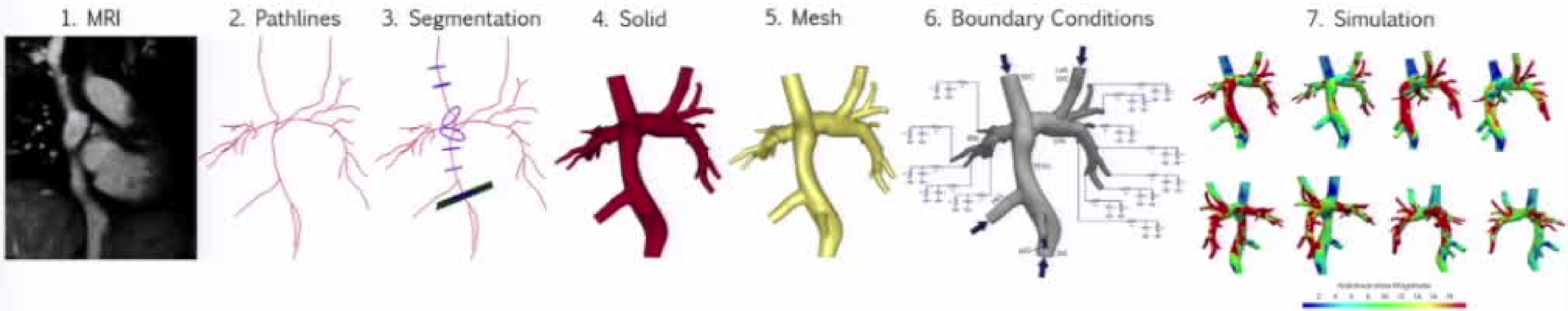


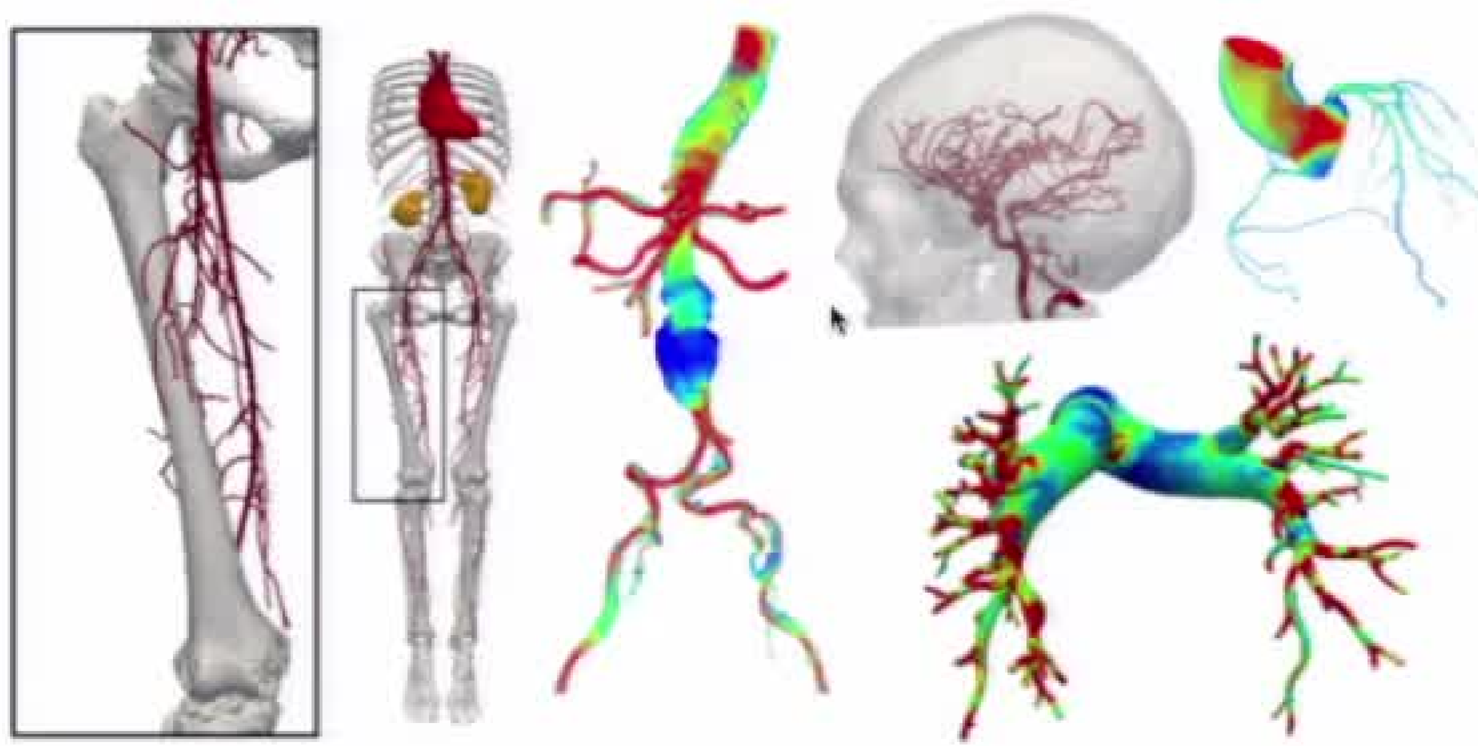
Simulation is a critical next step in the partnership



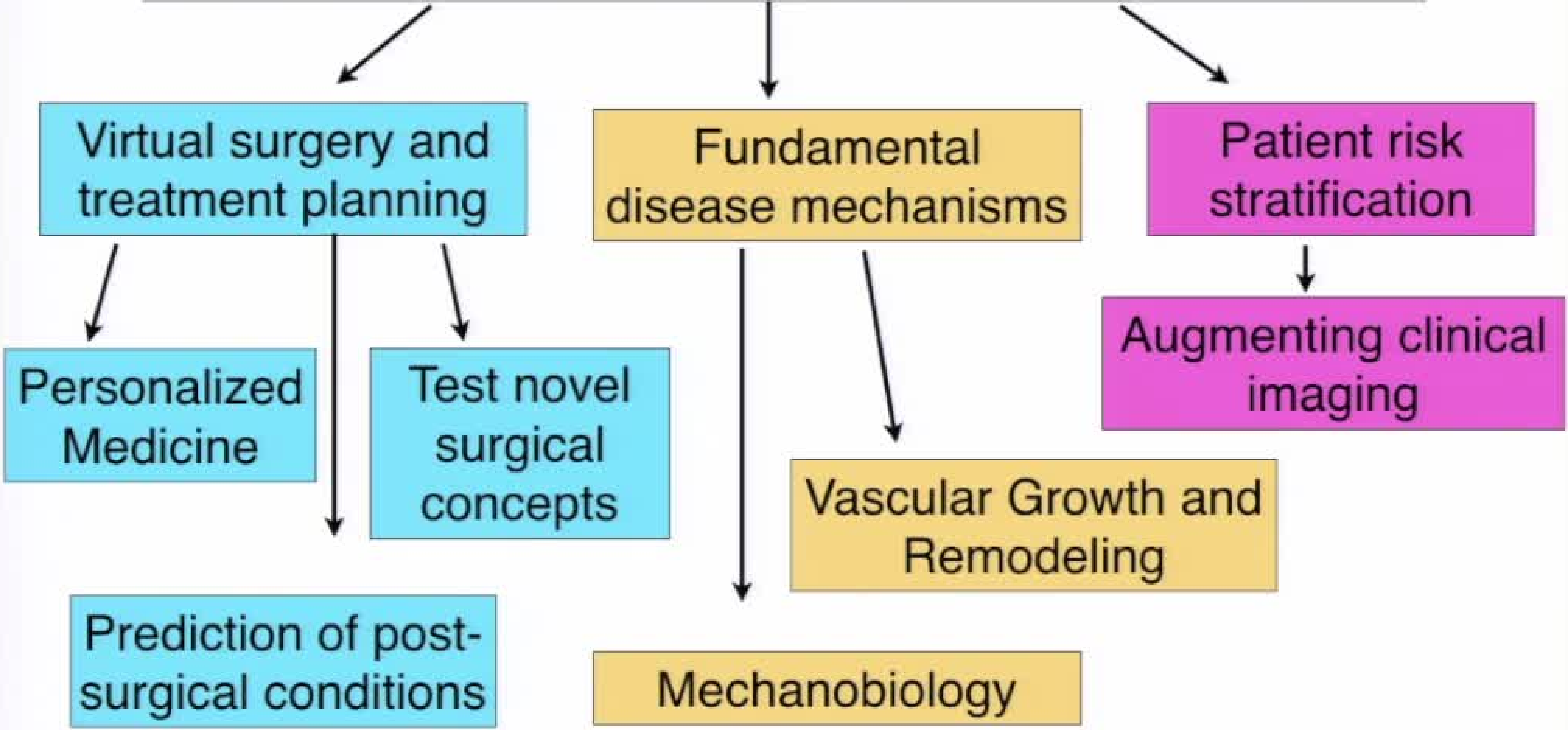


Predictive Patient-Specific Modeling

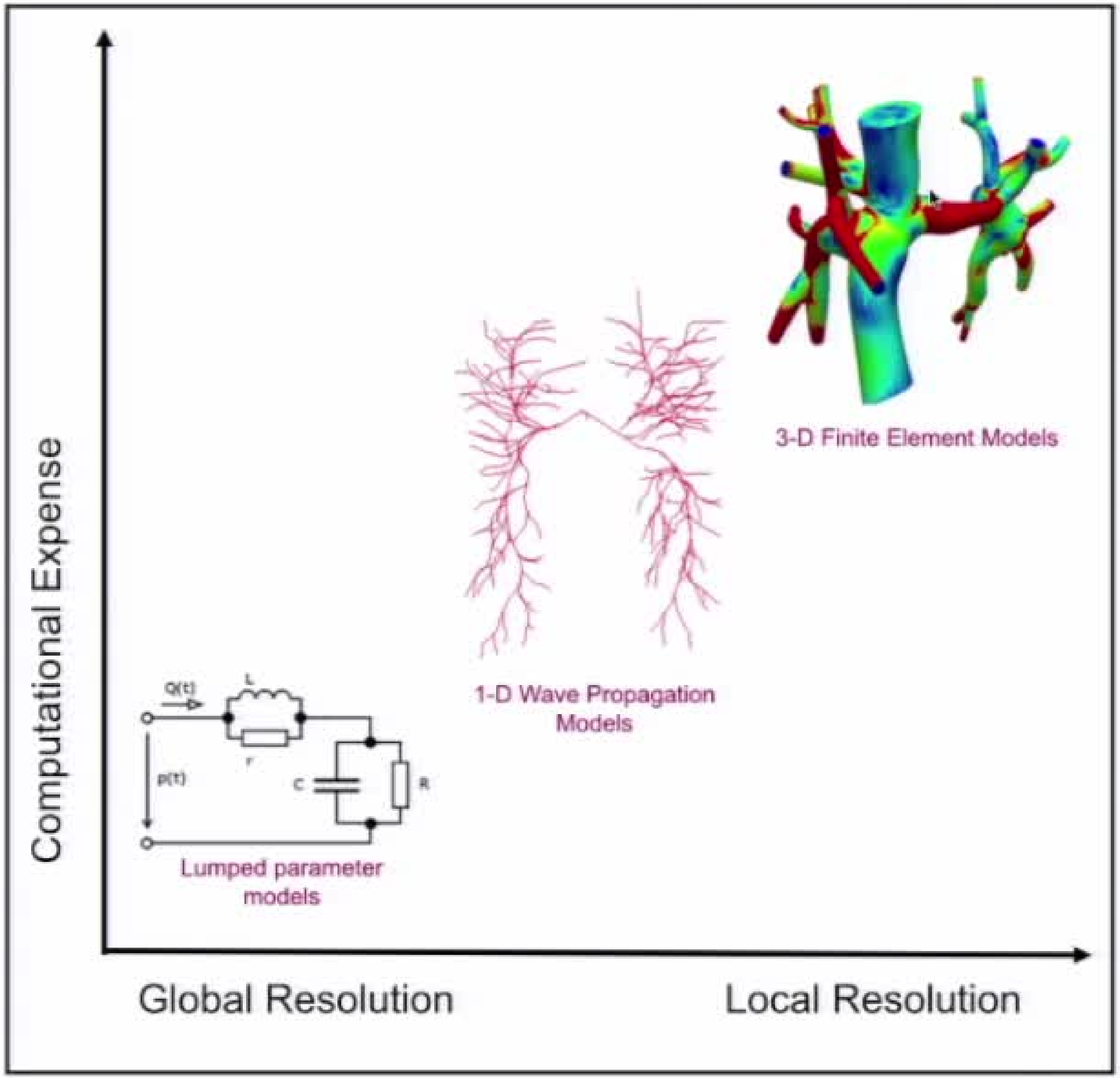




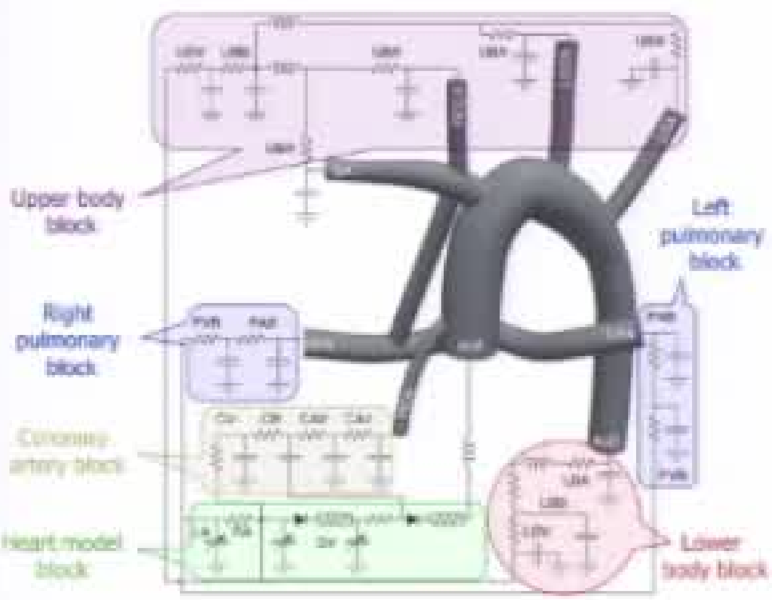
Motivation for Cardiovascular Modeling



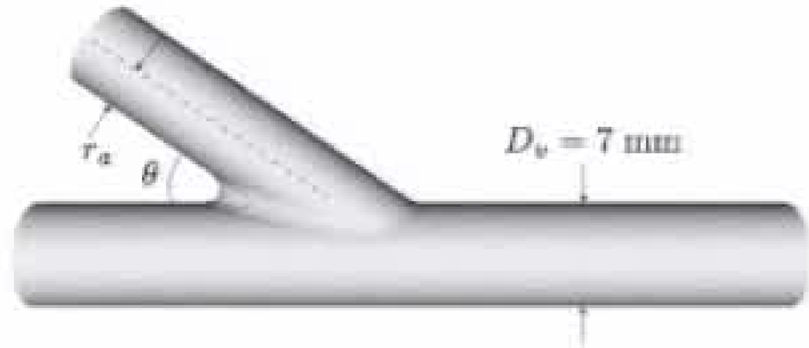
Cardiovascular Model Fidelity



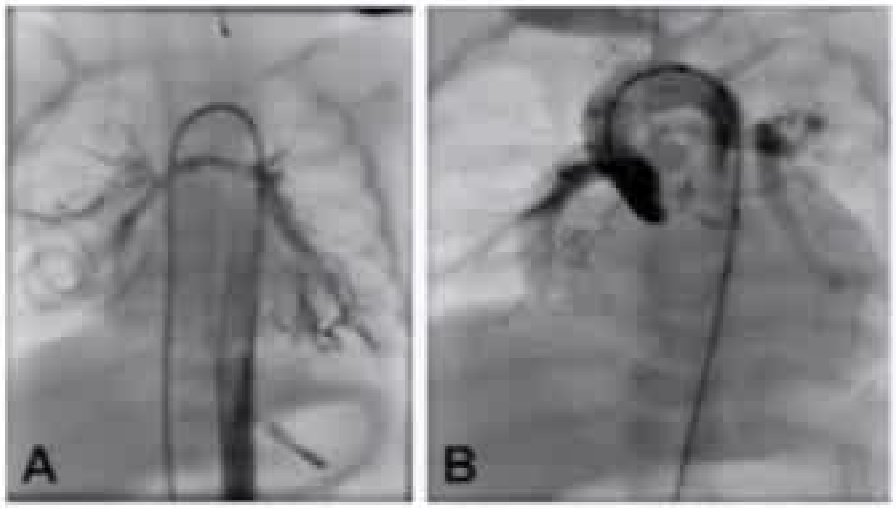
Cardiovascular Modeling: Challenges



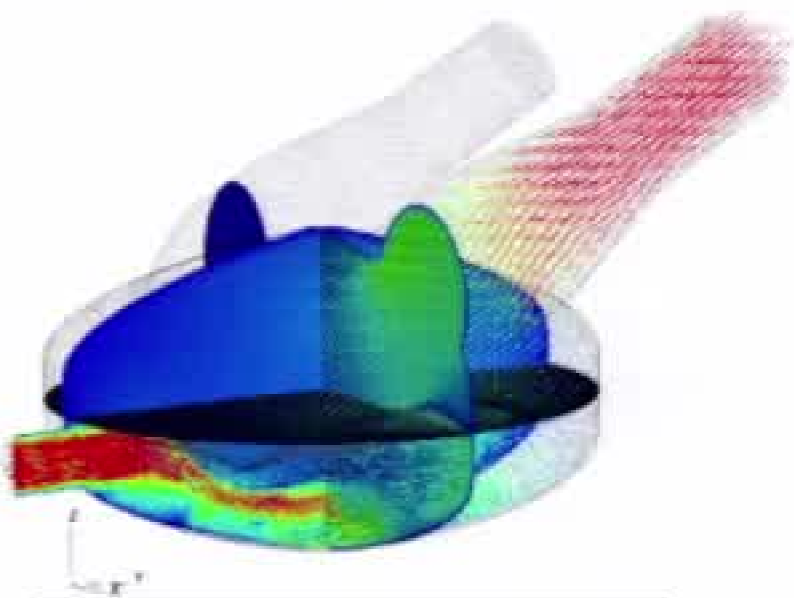
Assimilation of clinical data



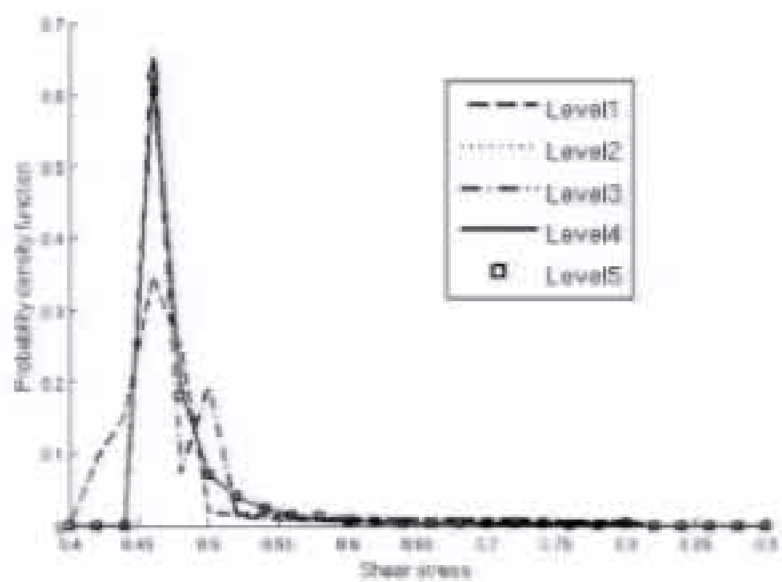
Shape Optimization



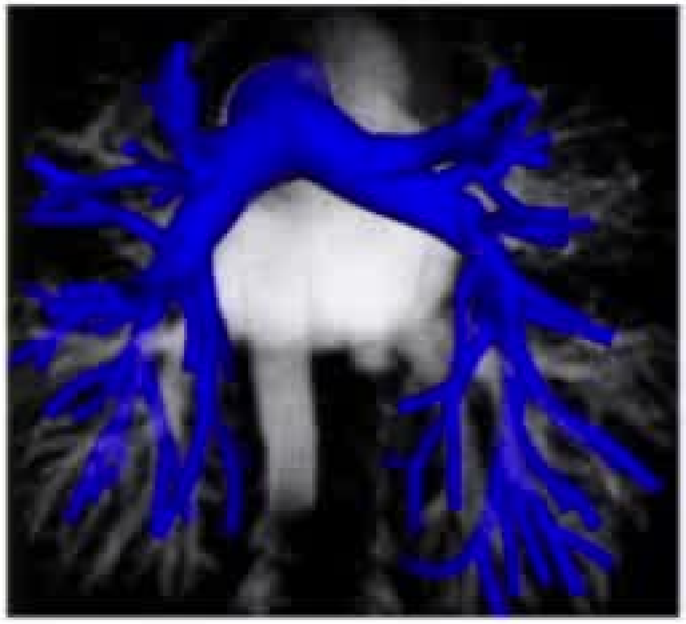
Interactive Virtual Surgery



Fluid Structure Interaction

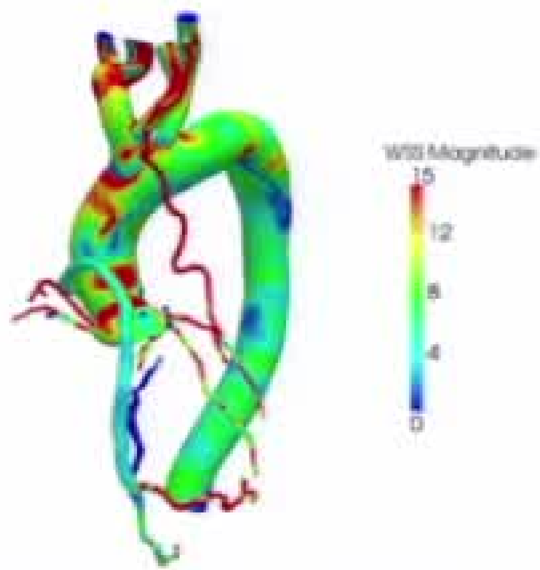


Uncertainty Quantification

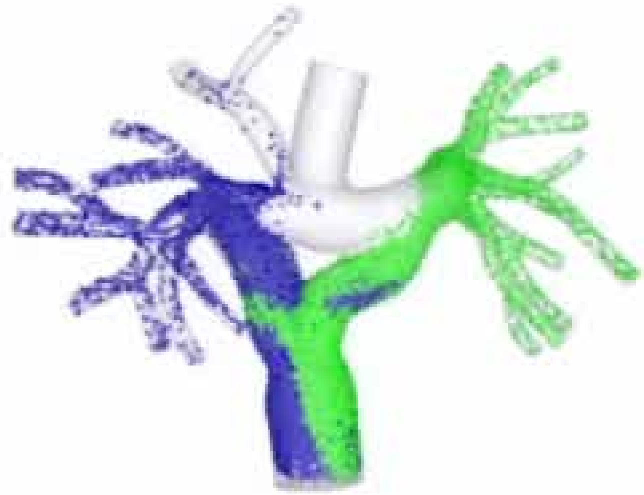


Machine Learning for Image Segmentation

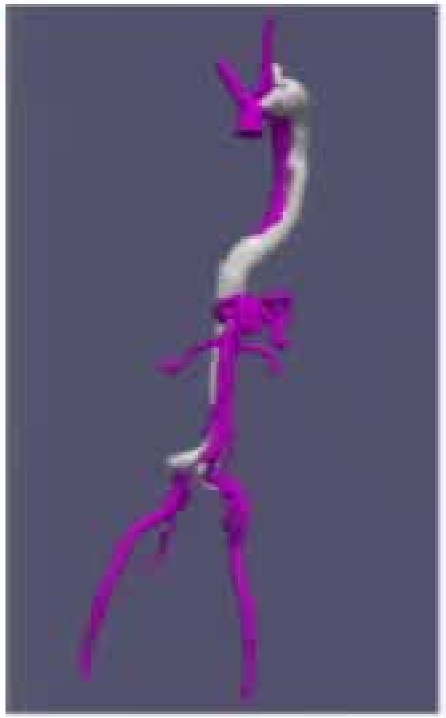
Clinical Applications



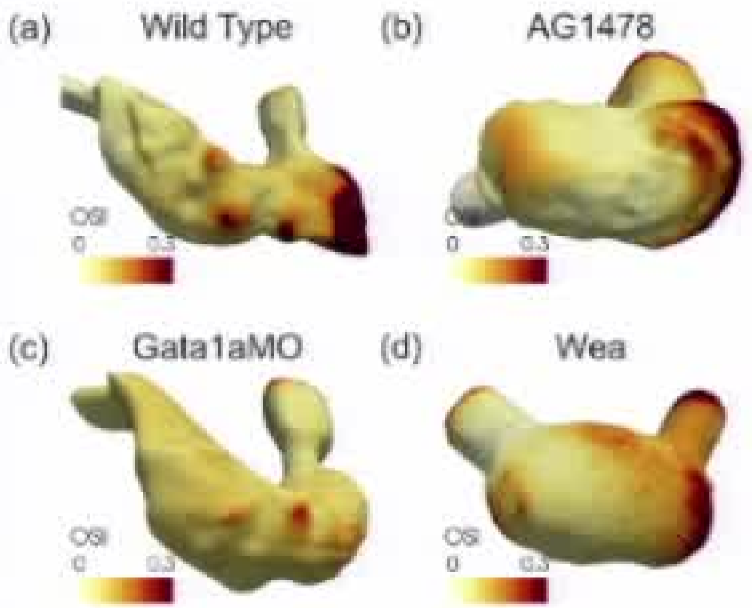
Coronary Artery Bypass Grafts



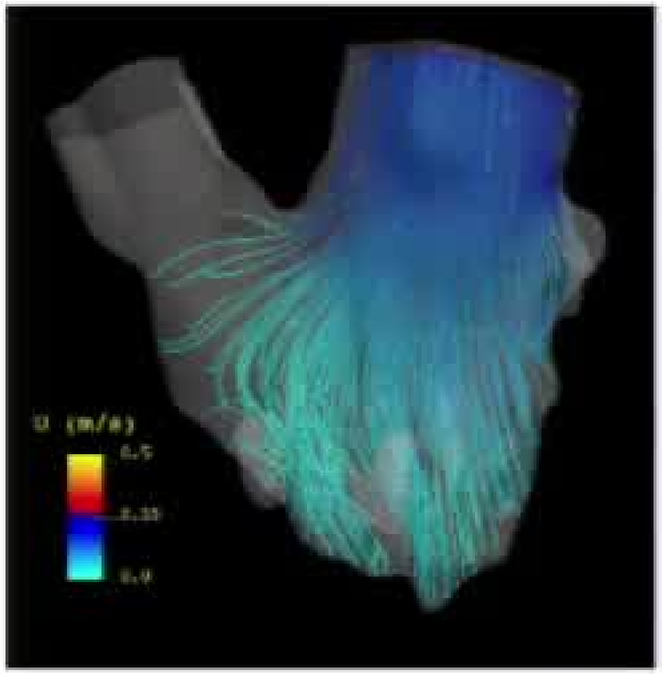
Single Ventricle Hearts



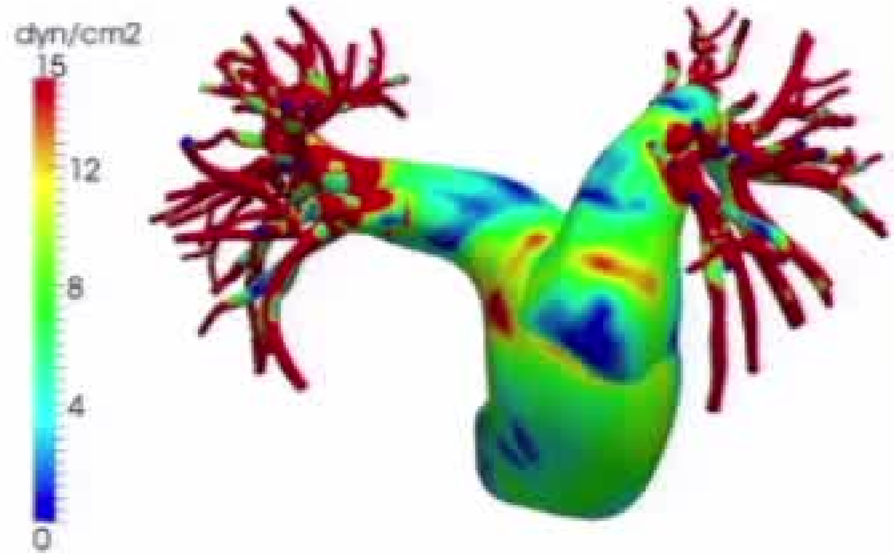
Aortic Dissection



Cardiac Development



Ventricular Hemodynamics



Pulmonary Hypertension

Abhay Ramachandra

Justin Tran

Owais Khan

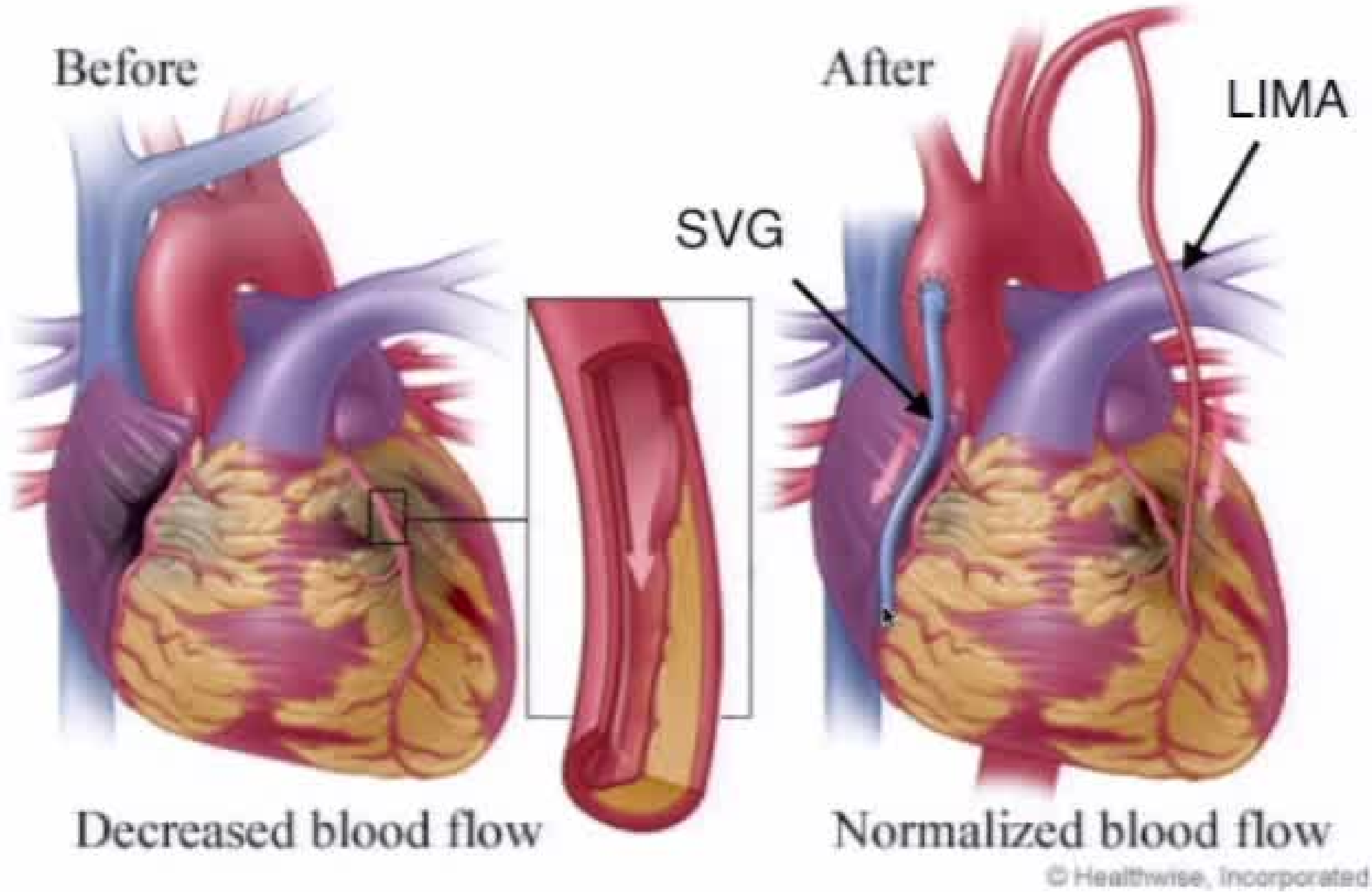
Clinical Examples

Coronary Artery Bypass Surgery

With Andrew Kahn, Jack Boyd, Daniele Schiavazzi

CABG Surgery

- CABG surgery performed in ~400,000 cases annually in US
- Graft options: arterial graft (LIMA), saphenous vein graft (SVG), artificial grafts
- Most patients require multiple grafts
  - SVGs are used in majority of patients (70%)
  - 50% graft failure within 10 years



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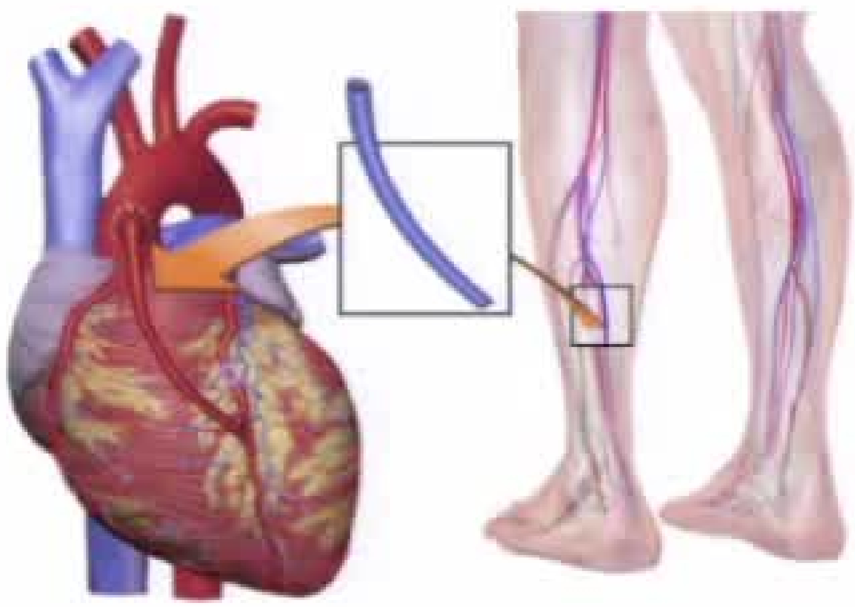
Vein Graft Failure: changing biomechanical loads

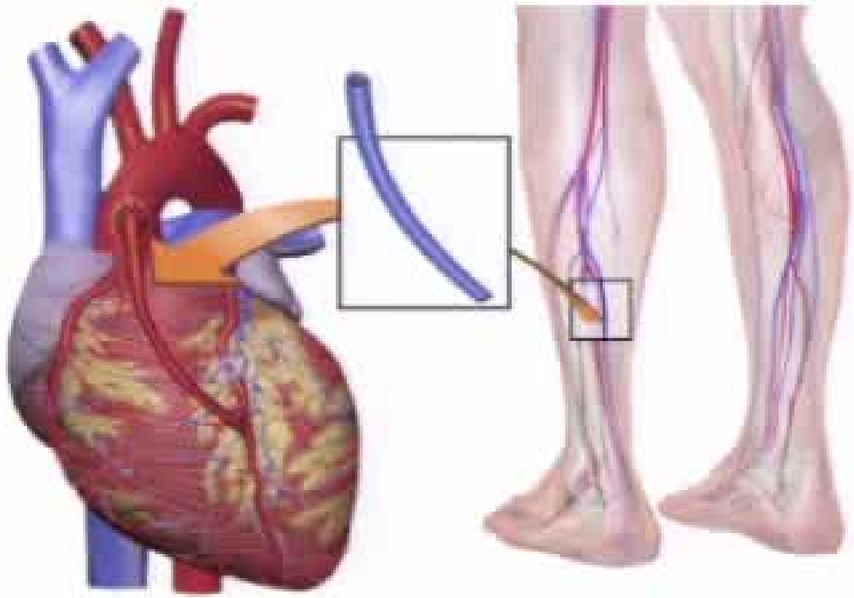


Surgical clamps removed

Pre-op
Native vein
low pressure, low flow

Post-op
20X increase in pressure
4X increase in flow

Vein Graft Failure: changing biomechanical loads



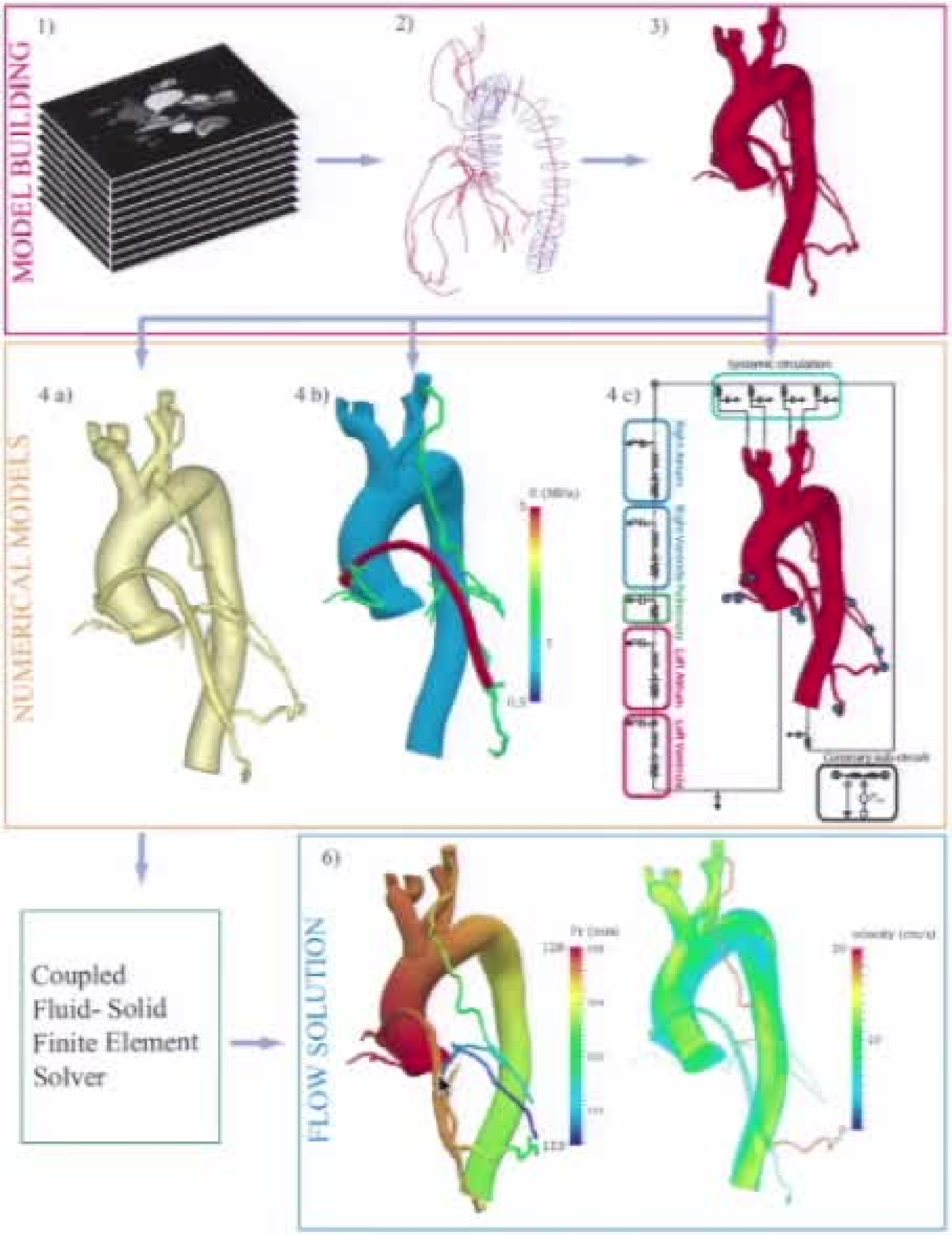
Surgical clamps removed

Pre-op
Native vein
low pressure, low flow

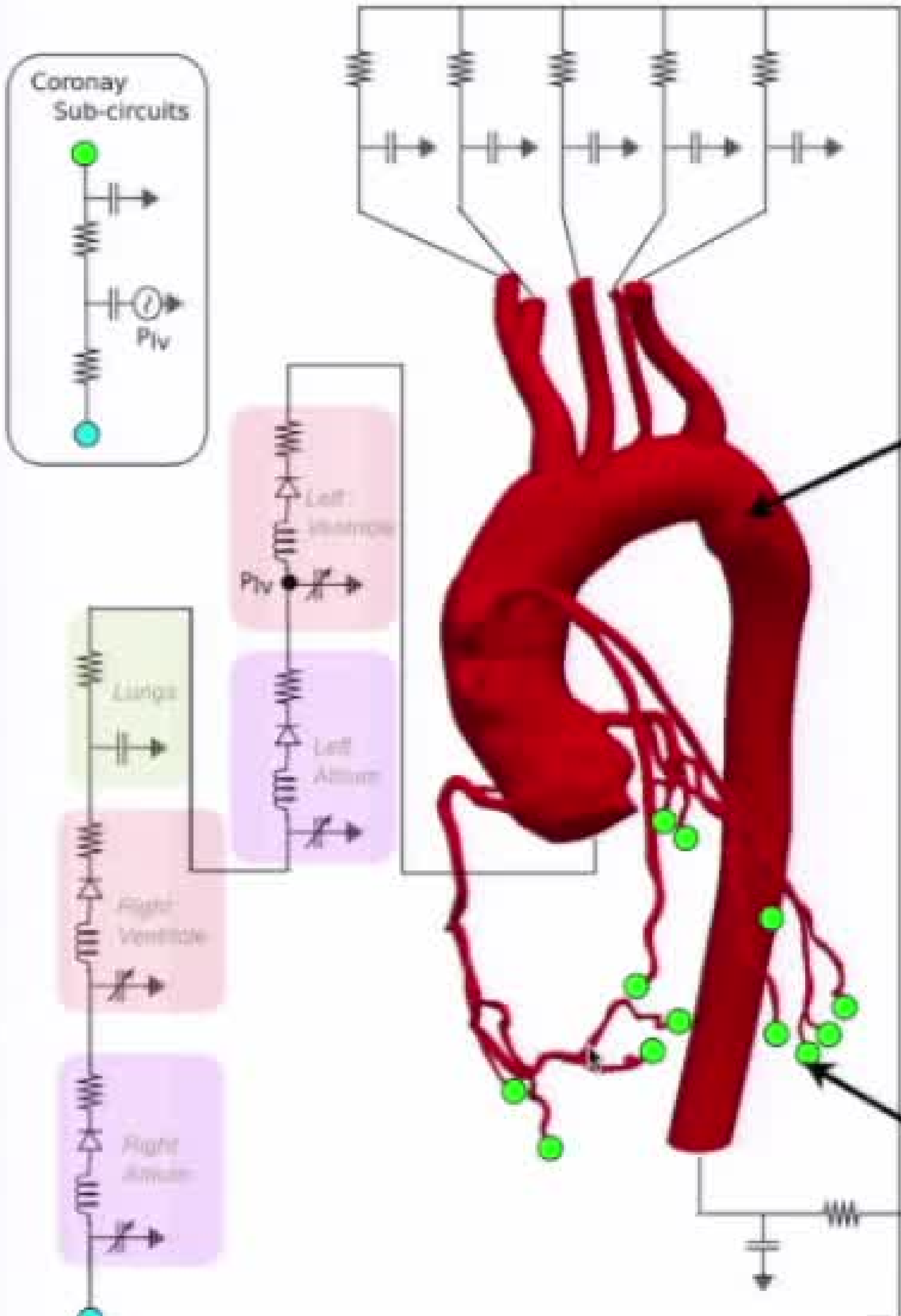
Post-op
20X increase in pressure
4X increase in flow

Vein undergoes a complex remodeling process in response to sudden change in mechanical load

CABG Simulation Pipeline



Solution Domains



$$\rho \vec{v}_{,t} + \rho \vec{v} \cdot \nabla \vec{v} = -\nabla p + \nabla \cdot \tau + \vec{f}$$

$$\nabla \cdot \vec{v} = 0$$

Navier-Stokes in 3D domain

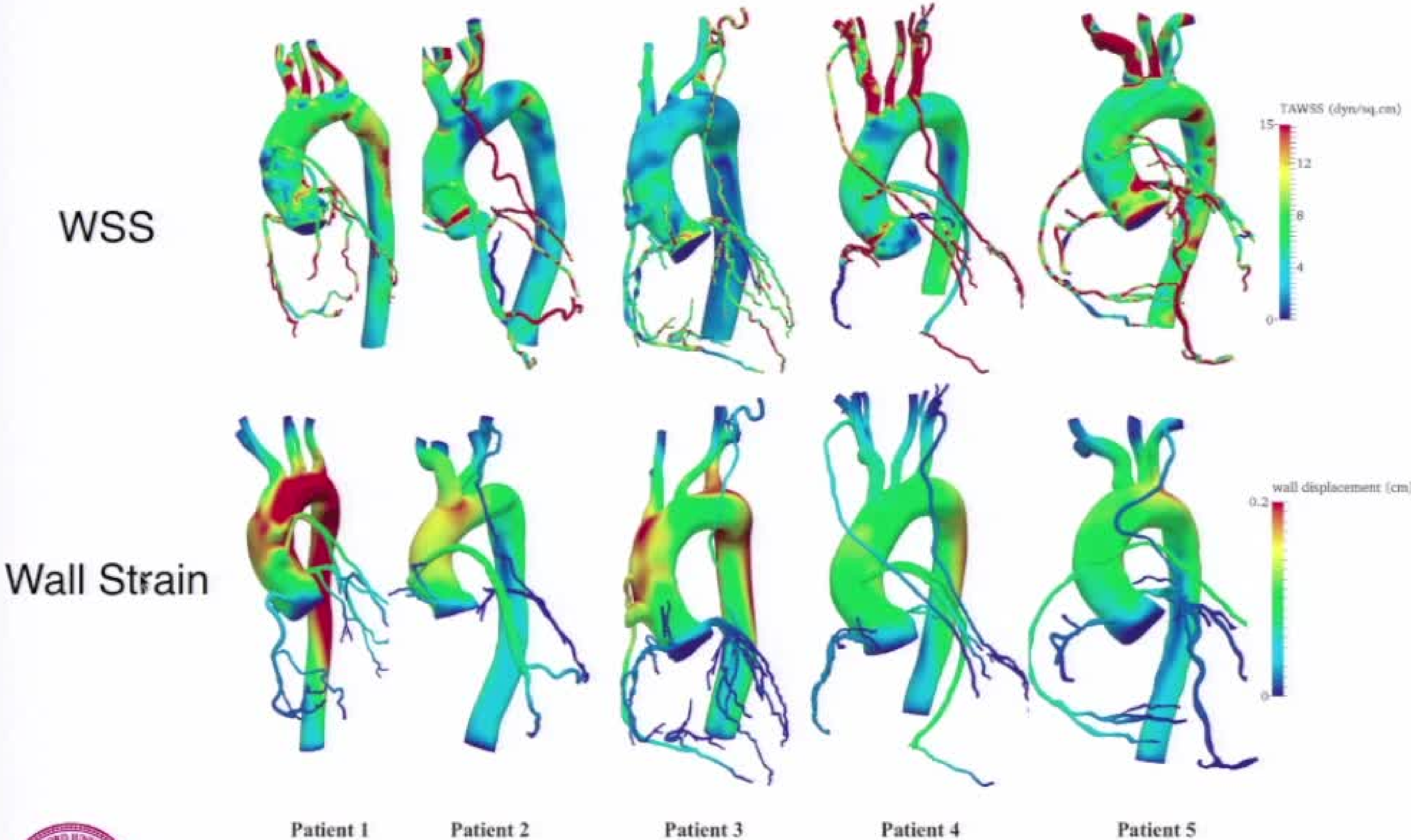
numerically coupled system of equations

$$p_2 \frac{d^2 P}{dt^2} + p_1 \frac{dP}{dt} + p_0 P = q_2 \frac{d^2 Q}{dt^2} + q_1 \frac{dQ}{dt} + q_0 Q + b_1 \frac{dP_{im}}{dt}$$

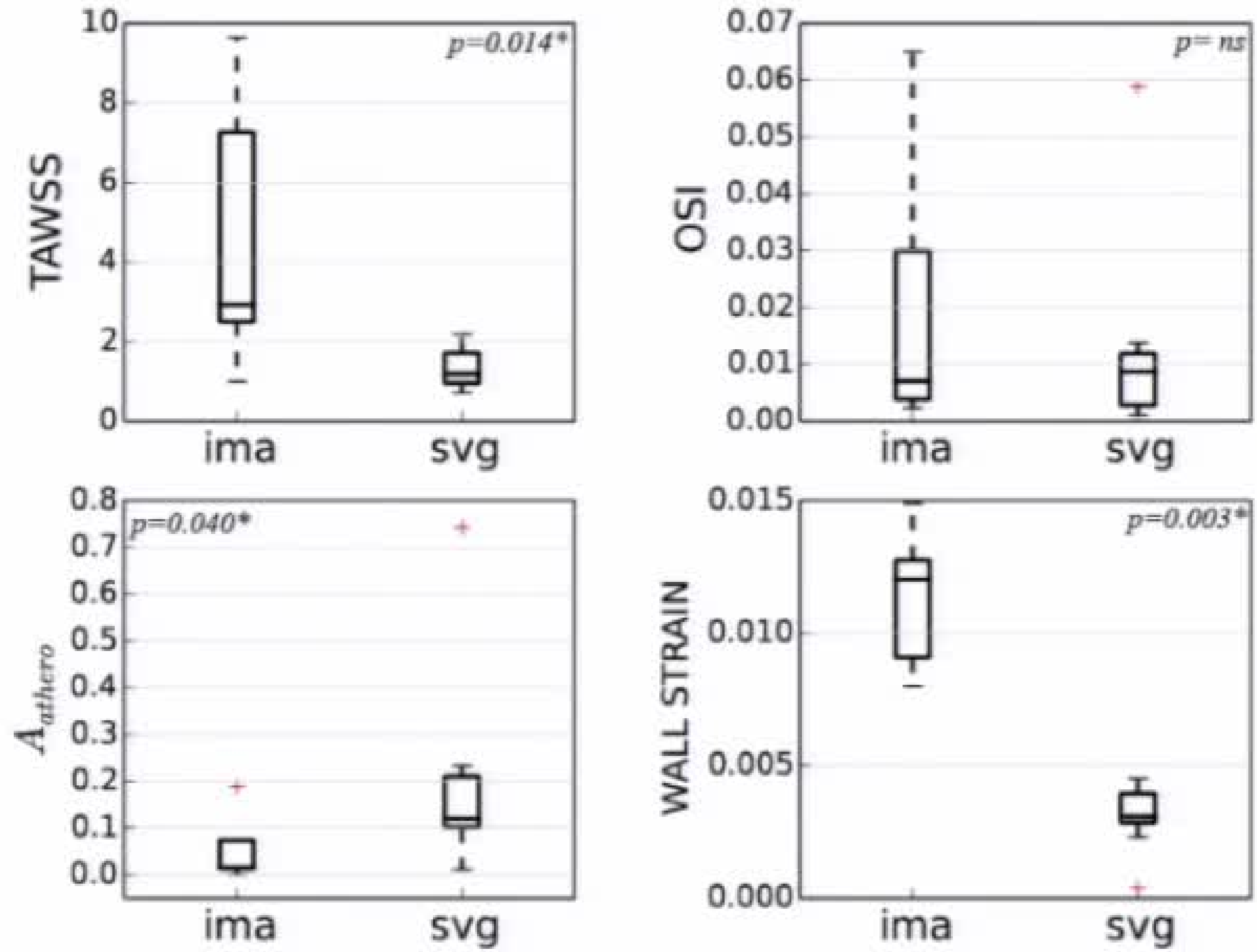
ODEs for LPN coupled to outlets

Sankaran, S., Esmaily Moghadam, M., Kahn, A.M., Guccione, J., Tseng, E., and Marsden, A.L., "Patient-specific multiscale modeling of blood flow for coronary artery bypass graft surgery," Annals of Biomedical Engineering 40(10), (2012).

Simulation Results



Mechanical Stimuli: Arterial vs. Vein Grafts

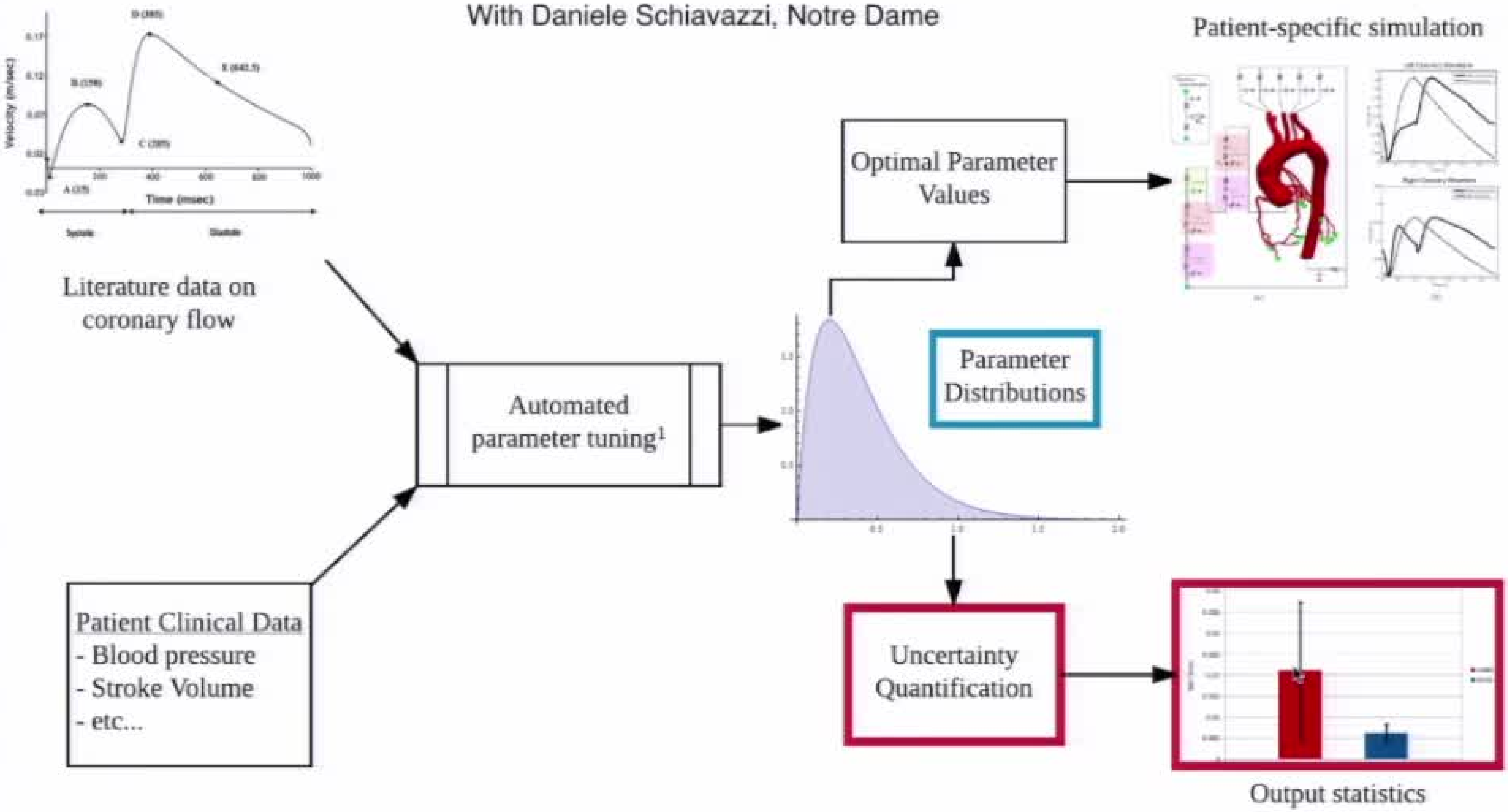


Statistically significant differences in WSS, area of low WSS, wall strain

Ramachandra, A. B., Kahn, A. M., Marsden, A.L., "Patient specific simulations reveal significant differences in mechanical stimuli in venous and arterial coronary grafts," *Journal of Cardiovascular Translational Research*, Vol. 9 (4), pp 279–290, (2016).

Parameter Estimation and UQ

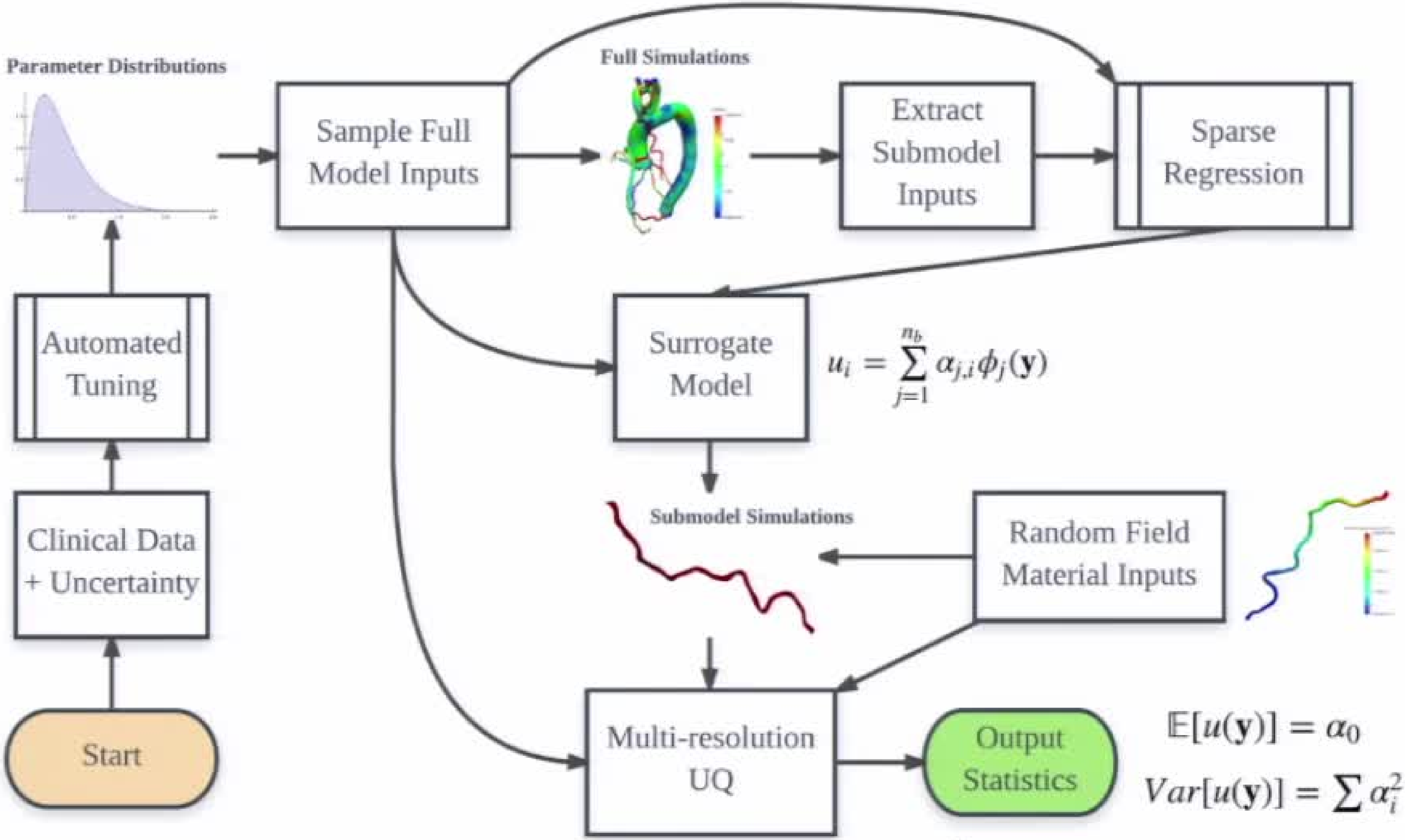
With Daniele Schiavazzi, Notre Dame



Schiavazzi, D. E., Doostan, A., Iaccarino, G., Marsden, A. L., "A Generalized Multi-resolution Expansion for Uncertainty Propagation with Application to Cardiovascular Modeling," *Computer Methods in Applied Mechanics and Engineering*, Vol. 314 (1), pp. 196-221, (2017).

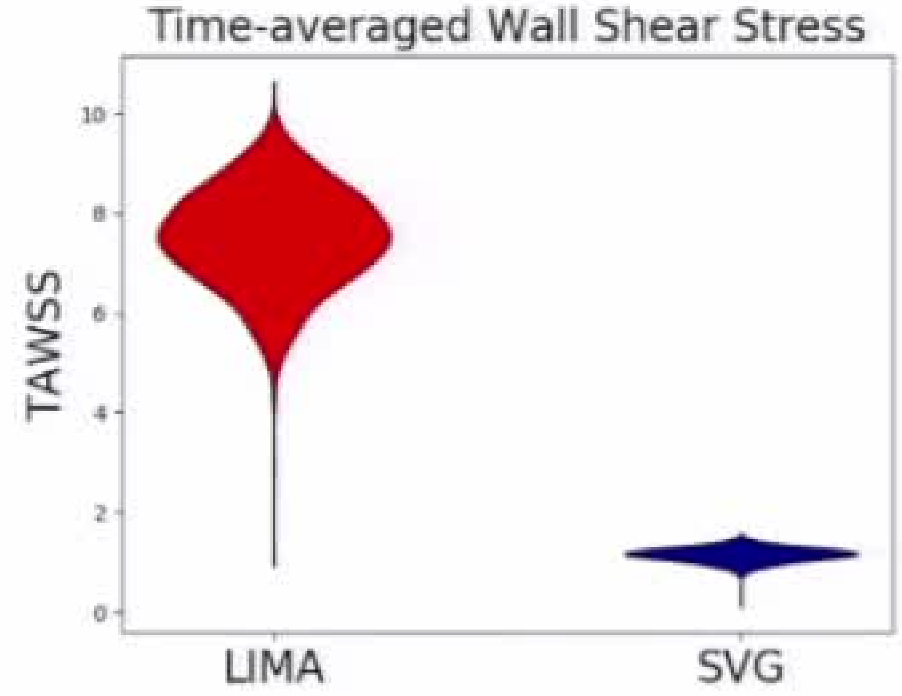
Schiavazzi, D. E., Hsia, T. Y., Marsden, A. L. "On a sparse pressure-flow rate condensation of rigid circulation models," *Journal of Biomechanics*, Vol. 49 (11), pp. 2174-2186, (2016).

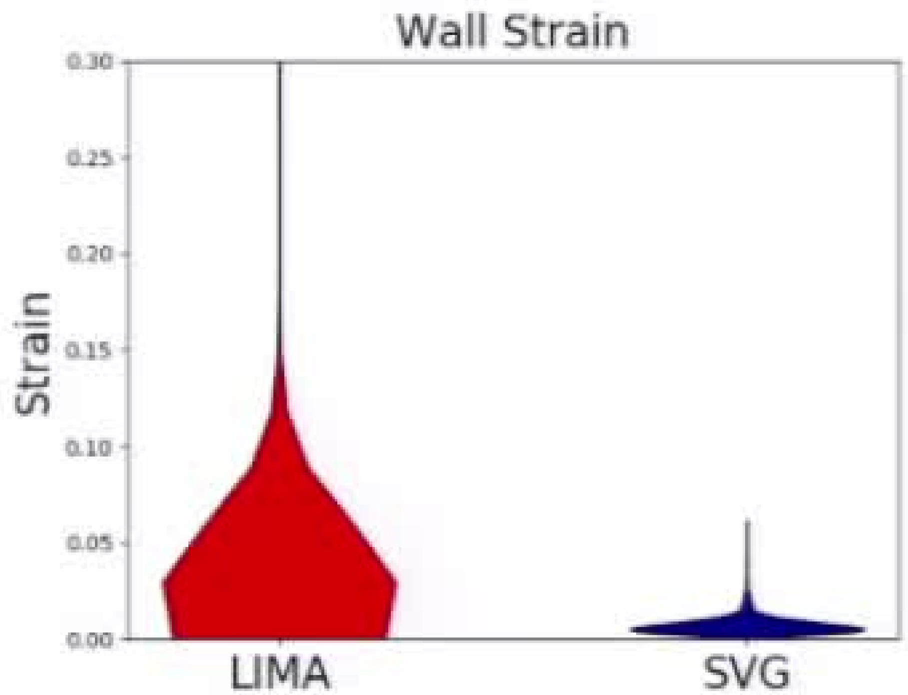
Uncertainty Propagation

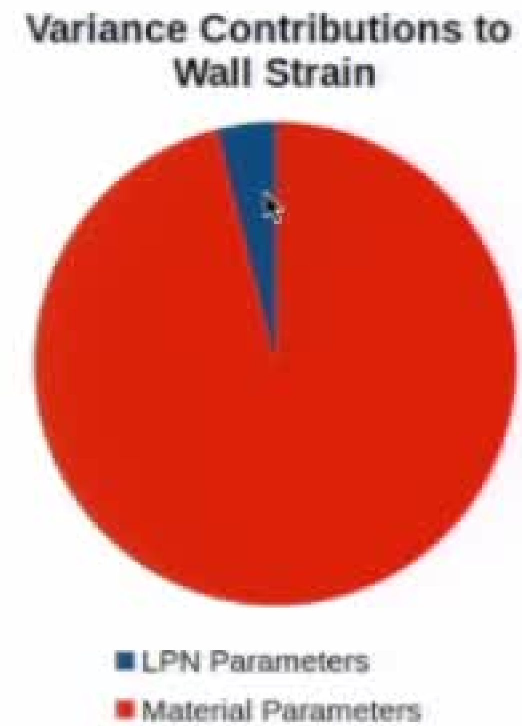


Tran, J. S., Schiavazzi, D. E., Kahn, A. M., and Marsden, A.L., "Uncertainty quantification of simulated biomechanical stimuli in coronary bypass grafts," in review.

Statistics on model predictions



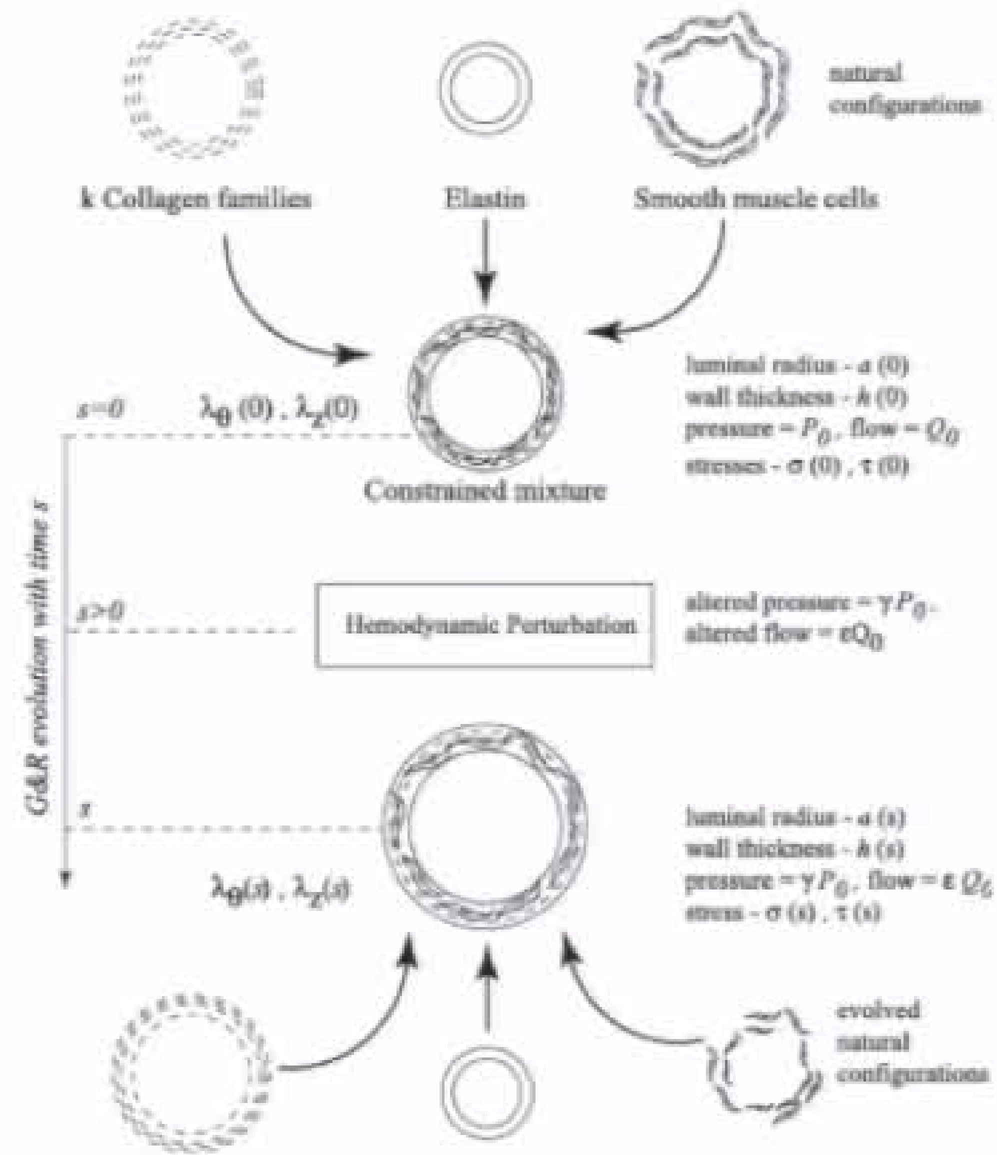




Tran, J. S., Schiavazzi, D. E., Kahn, A. M., and Marsden, A.L., "Uncertainty quantification of simulated biomechanical stimuli in coronary bypass grafts," in review.

Growth and Remodeling

- Adapted Humphrey arterial G&R model to veins
- Predict response to changes in hemodynamics (pressure, shear stress)
    - radius, thickness, wall composition
- Test hypotheses of vein graft failure



What is the biomechanical response to altered hemodynamics and wall mechanics in a vein graft?

A. Valentín and J. D. Humphrey, Phil. Trans. R. Soc. A 2009

Vascular G&R Model

Equilibrium Equations

$$P(s)a(s) = T_\theta(s) = \lambda_\theta \sum \frac{\partial W^k}{\partial \lambda_\theta}$$ Circumferential

$$\frac{f(s)}{\pi(2a(s)+h(s))} = T_z(s) = \lambda_z \sum \frac{\partial W^k}{\partial \lambda_z}$$ Axial

Constitutive Equations

$$W^{elastin} = \frac{c^e}{2}(\lambda_\theta^2 + \lambda_z^2 + \lambda_r^2 - 3)$$ Elastin

$$W^k = \frac{c_1^k}{4c_2^k}(e^{(c_2^k(\lambda)^2-1)^2} - 1)$$ SMC + Collagen

Mass Addition and Removal

$$m^k = m_0^k(1 + K_1^k \Delta\sigma - K_2^k \Delta\tau_w)$$ Addition

$$q^k(s,\tau) = e^{-\int_\tau^s K^k(\tilde{\tau})d\tilde{\tau}}$$

$$K^k(\tilde{\tau}) = K_h^k + K_h^k \Delta\zeta(\tilde{\tau})^2$$ Removal

Evolution

$$M^k(s) = M^k(0)Q^k(s) + \int_0^s m^k(\tau)q^k(s,\tau)d\tau$$ Mass

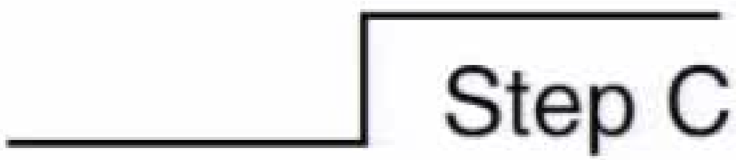
$$W^k(s) = \frac{M^k(0)}{\rho(s)}Q^k(s)\widehat{W^k}(\mathbf{C}_{n(0)}^k(s)) + \int_0^s \frac{m^k(\tau)}{\rho(s)}q^k(s,\tau)\widehat{W^k}(\mathbf{C}_{n(\tau)}^k(s))d\tau,$$ Stored Energy

A. Valentín and J. D. Humphrey, Phil. Trans. R. Soc. A 2009

Could gradual loading ameliorate vein maladaptation?

$$\mathcal{J}_{adapt} = \sqrt{\left(\frac{\tau_w^h - \tau_w}{\tau_w}\right)^2 + \left(\frac{\sigma_\theta^h - \sigma_\theta}{\sigma_\theta}\right)^2}$$

Measure deviation from homeostasis



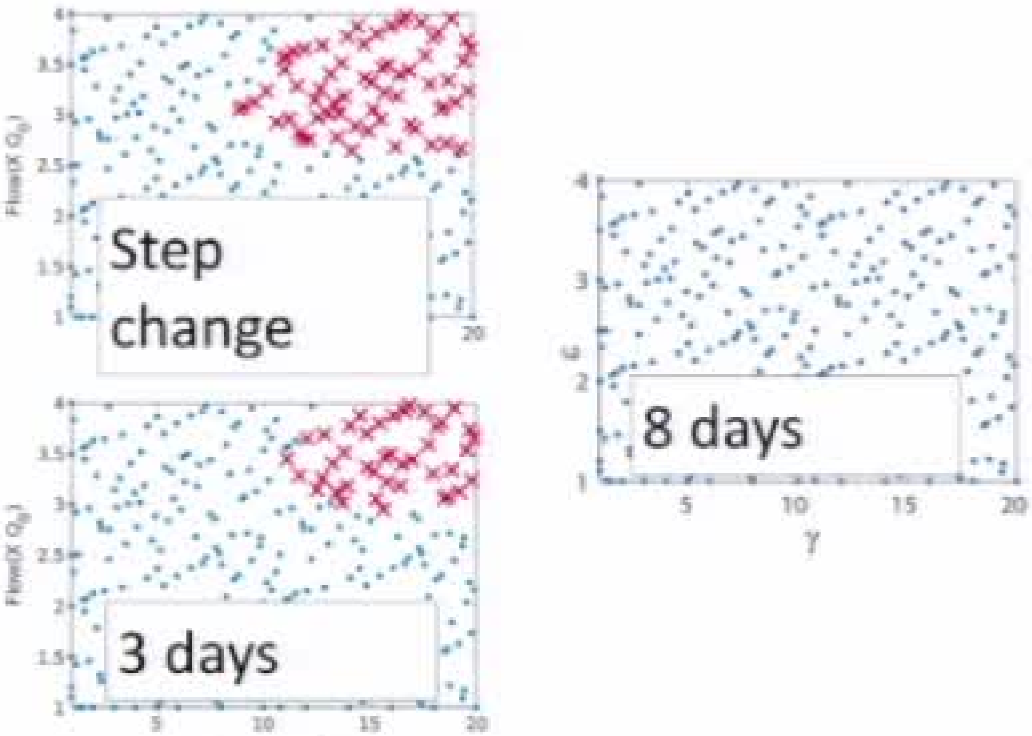
Step Change

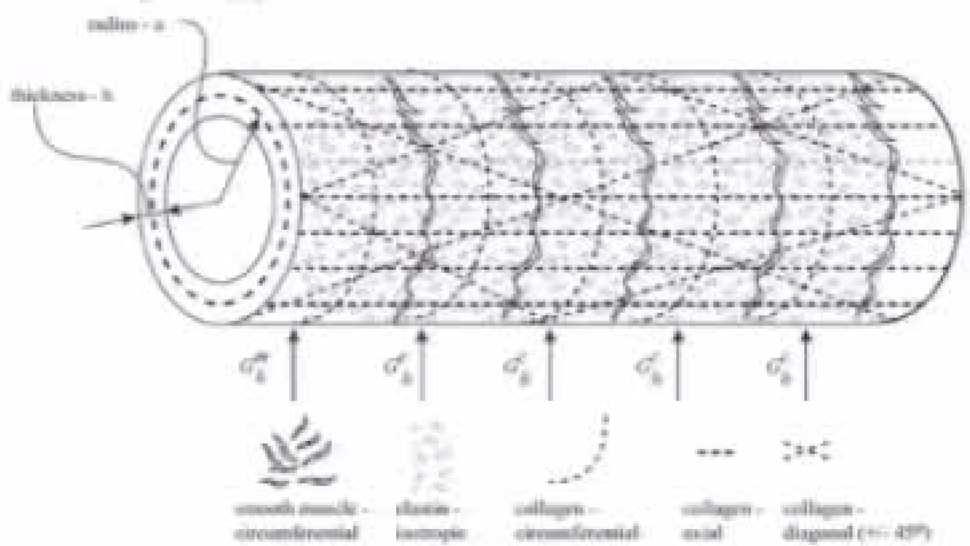
Gradual Change

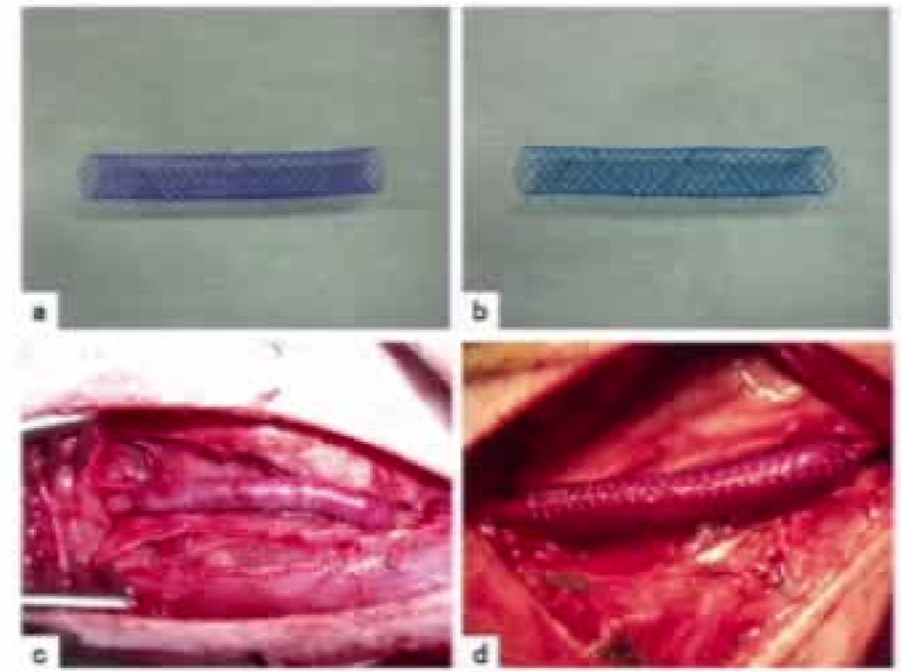
Ramachandra, A. B., Sankaran, S., Humphrey, J.D., Marsden, A.L., "Computational simulation of the adaptive capacity of vein grafts in response to increased pressure," Journal of Biomechanical Egnineering, Vol. 137, pp. 031009-1, (2015).

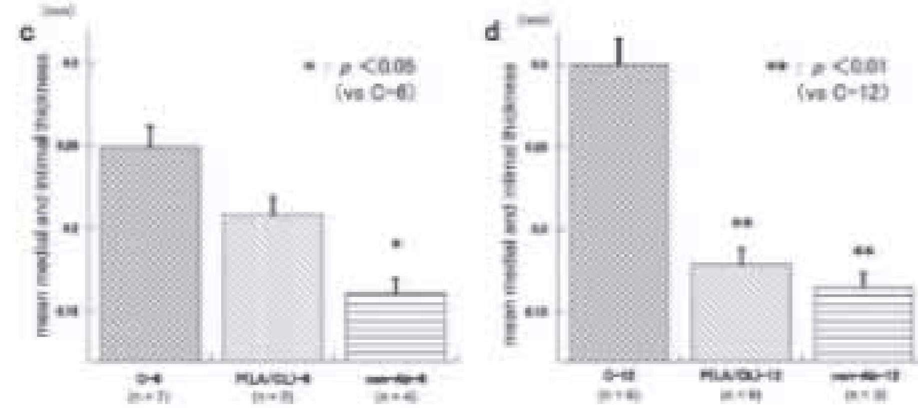
Ramachandra, A. B., Humphrey, J. D., Marsden, A. L., "Gradual loading ameliorates maladaptation in computational simulations of vein graft growth and remodeling," *Journal of the Royal Society Interface*, Vol. 14 (130), May 2017.

Evidence of benefit of gradual loading









A novel biodegradable external mesh stent improved long-term patency of vein grafts by inhibiting intimal–medial hyperplasia in an experimental canine model

Weiguang Yang

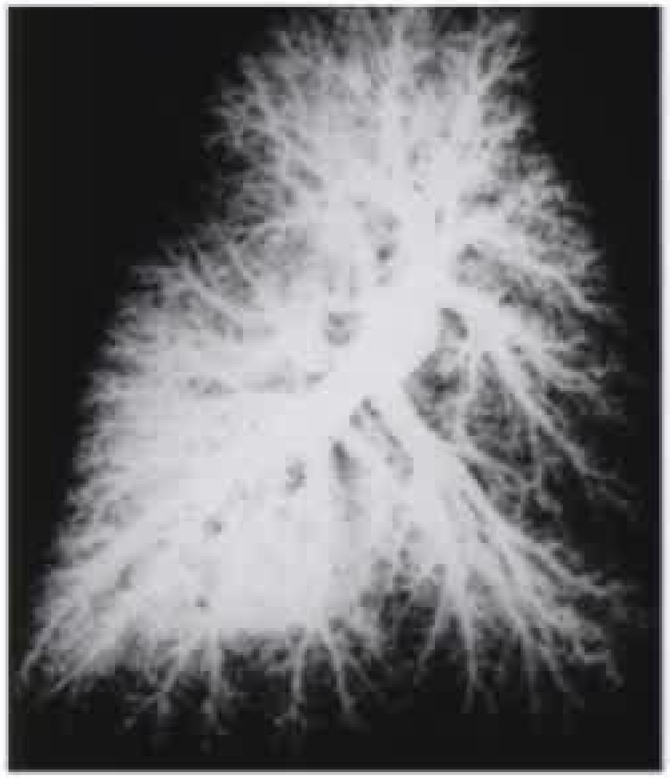
Melody Dong

Clinical Examples

Hemodynamics in Pulmonary Hypertension

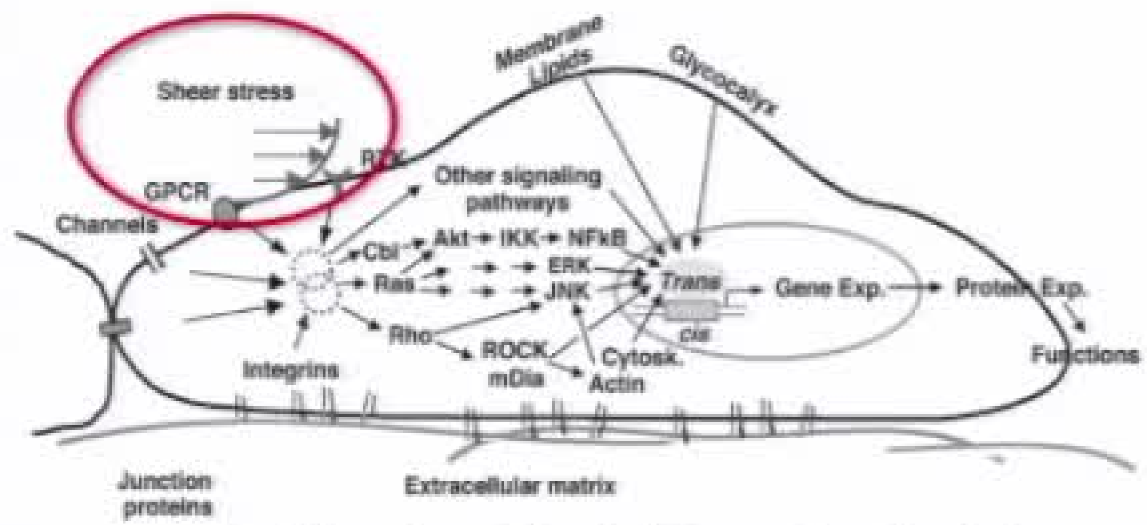
With Jeff Feinstein and Marlene Rabinovitch

Altered Hemodynamics contributes to PAH Progression



Normal

IPAH for 6 months
J.D. Rich & S. Rich, *Circ*, 2014.

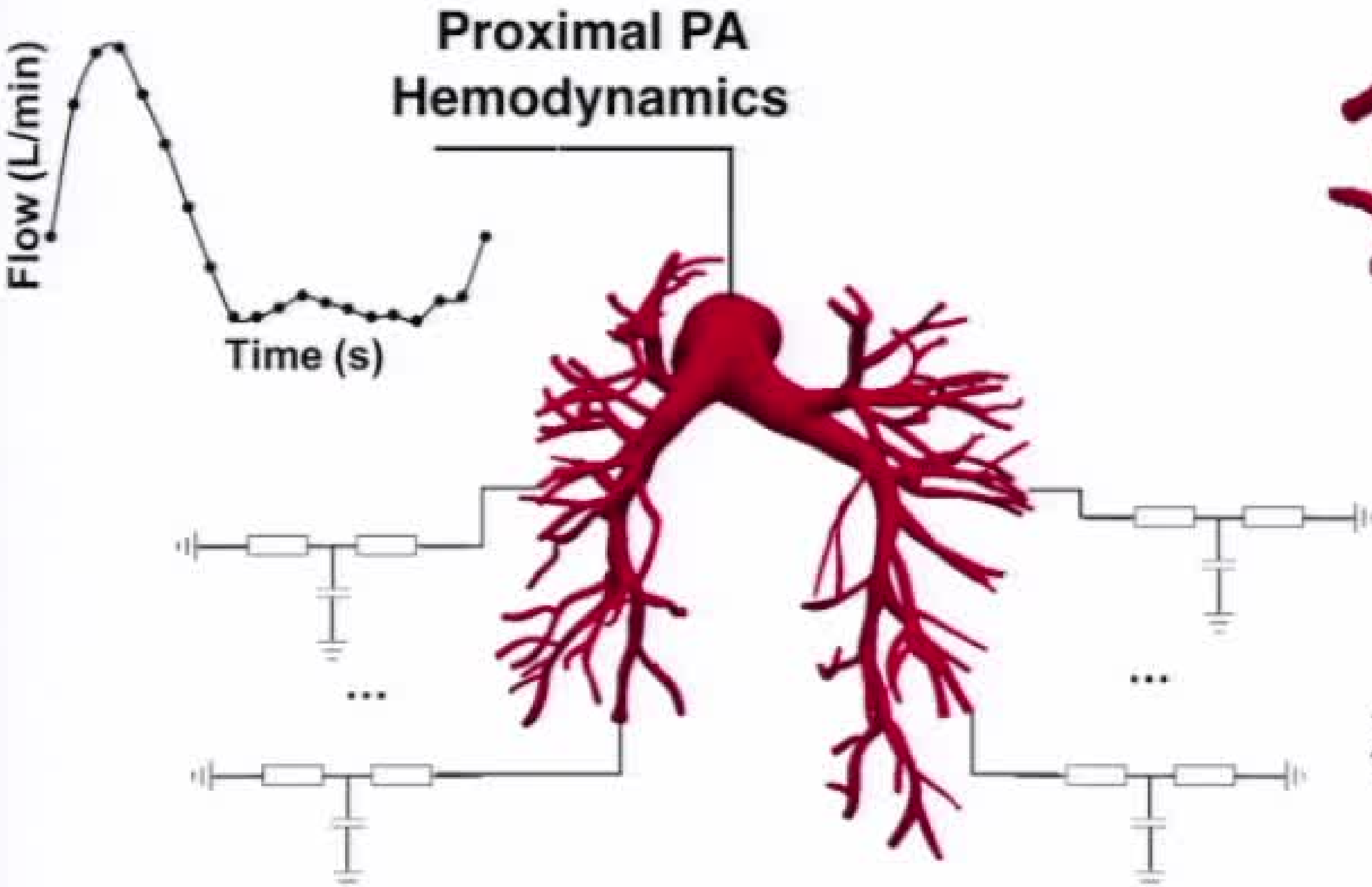


S. Chien, *Am J Physiol Heart Circ Physiol*, 2007

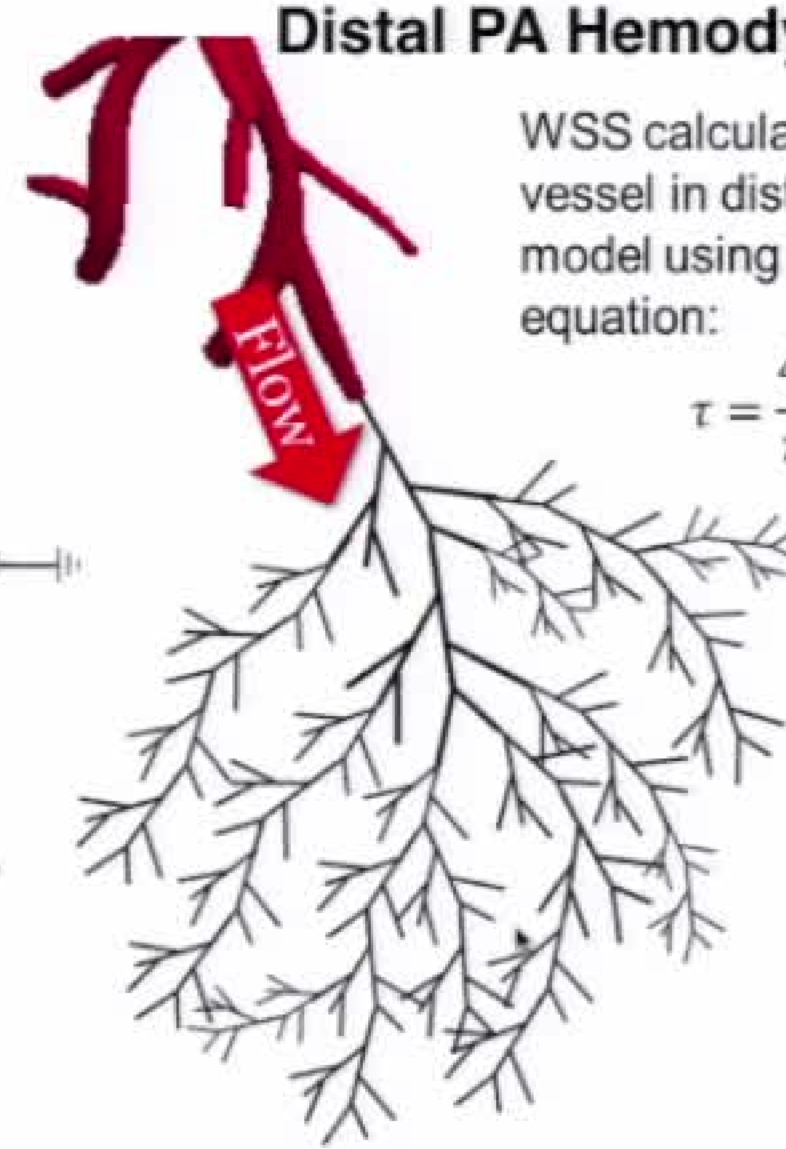
Elevated pulmonary artery (PA) pressure (>25 mmHg) and abnormal shear contribute to pulmonary vascular remodeling

5 year survival rate for children of 60-70%

Methods: Simulating hemodynamics in entire PA tree



Distal PA Hemodynamics



WSS calculated at each vessel in distal PA model using Poiseuille's equation:

$$\tau = \frac{4\mu Q}{\pi r^3}$$

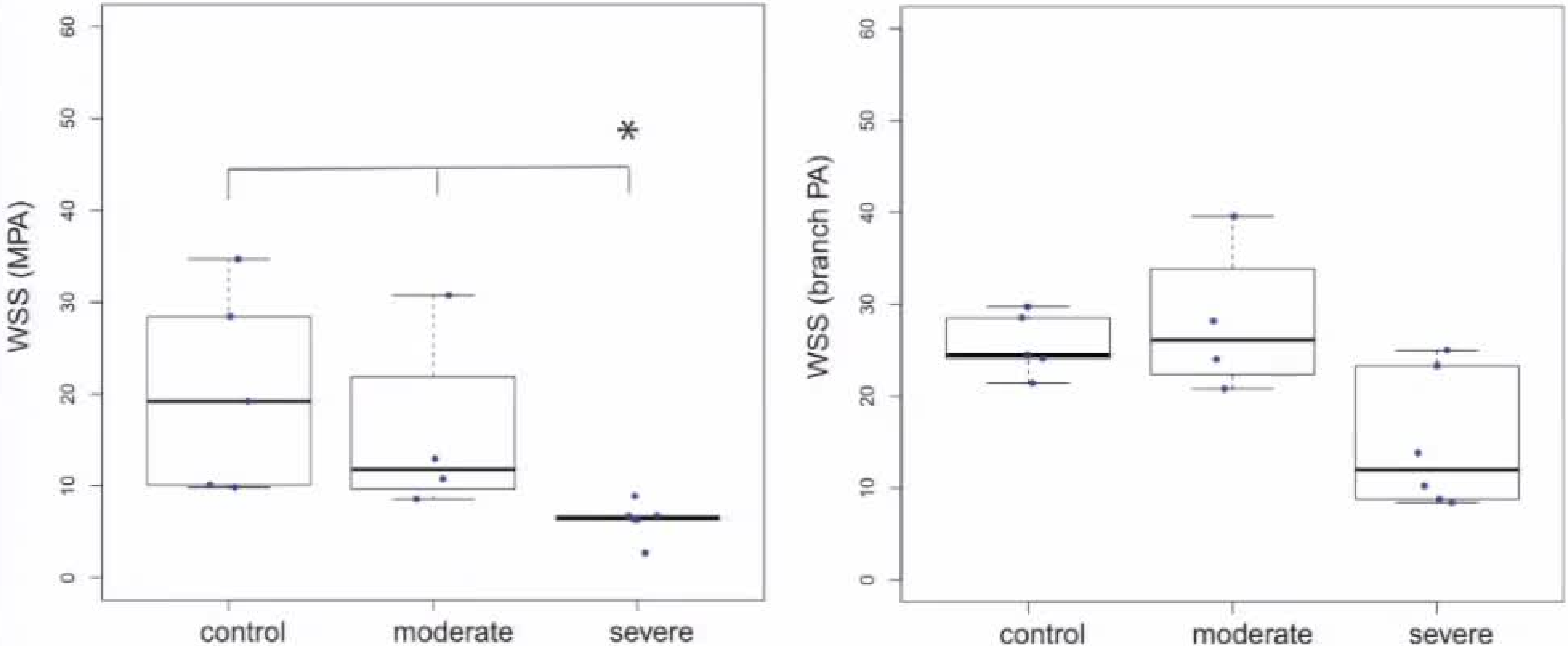
PA Morphometry tree

[1]Huang W., et al., "Morphometry of the human pulmonary vasculature," *J Appl Physiol*, 81(5):2123-33, 1996.

Study Cohort Clinical Data

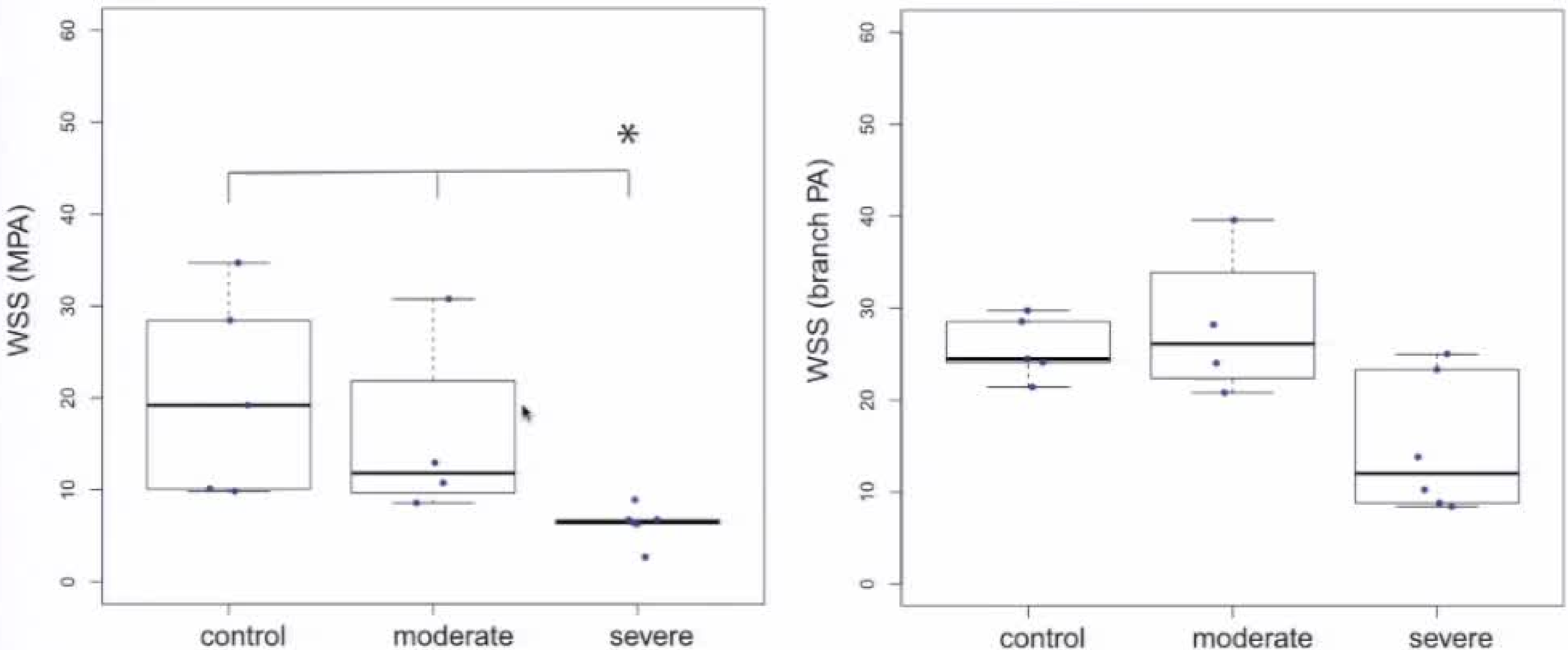
Group	Patient	Age (year)	EDV (ml)	EF	PVRI ($WU \times m^2$)
Control	C1	7.0	69	46%	NA
	C2	15.0	99	52%	NA
	C3	9.0	102	57%	NA
	C4	15.2	85	56%	NA
	C5	17.0	45	62%	NA
Moderate	M1	14.0	101	68%	8.6
	M2	10.6	101	55%	6.4
	M3	5.3	132	48%	10
	M4	4.3	93	60%	8.4
Severe	S1	10.6	125	49%	19
	S2	10.3	123	39%	13
	S3	17.0	140	22%	24
	S4	16.9	115	32%	37.5
	S5	17.6	117	51%	12
	S6	9.1	118	27%	17.9

Proximal vessels: WSS



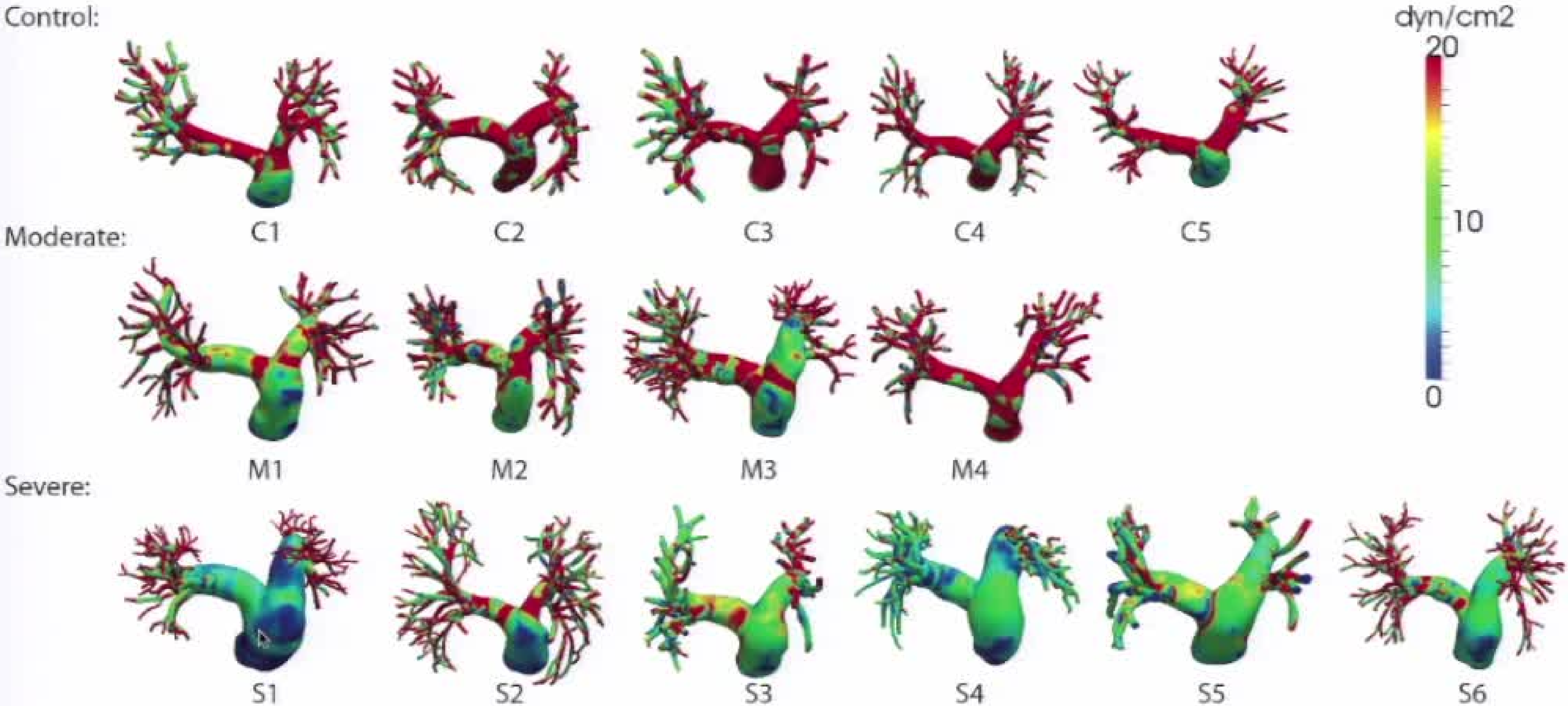
MPA WSS is significantly decreased in moderate and severe patients

Proximal vessels: WSS

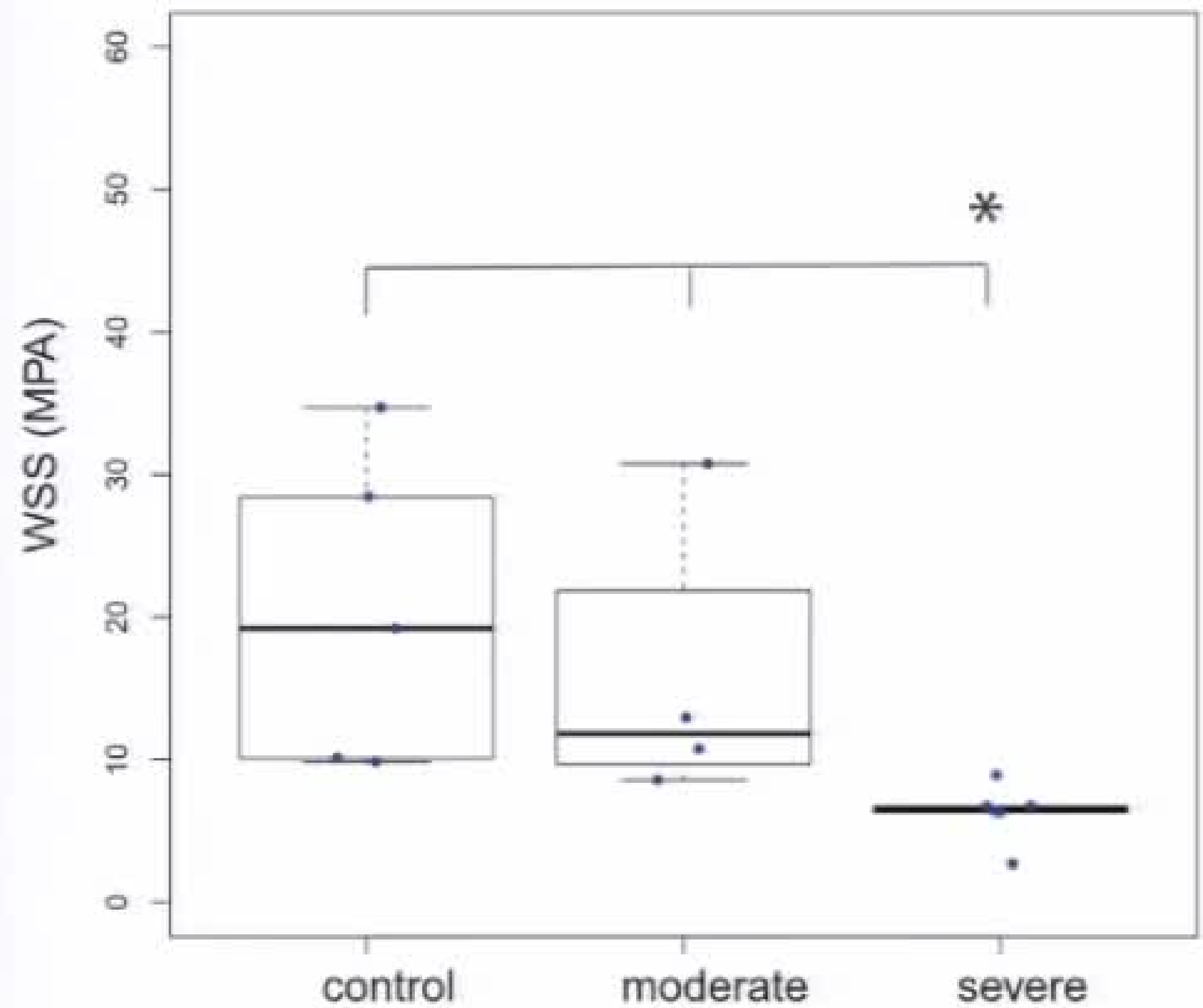


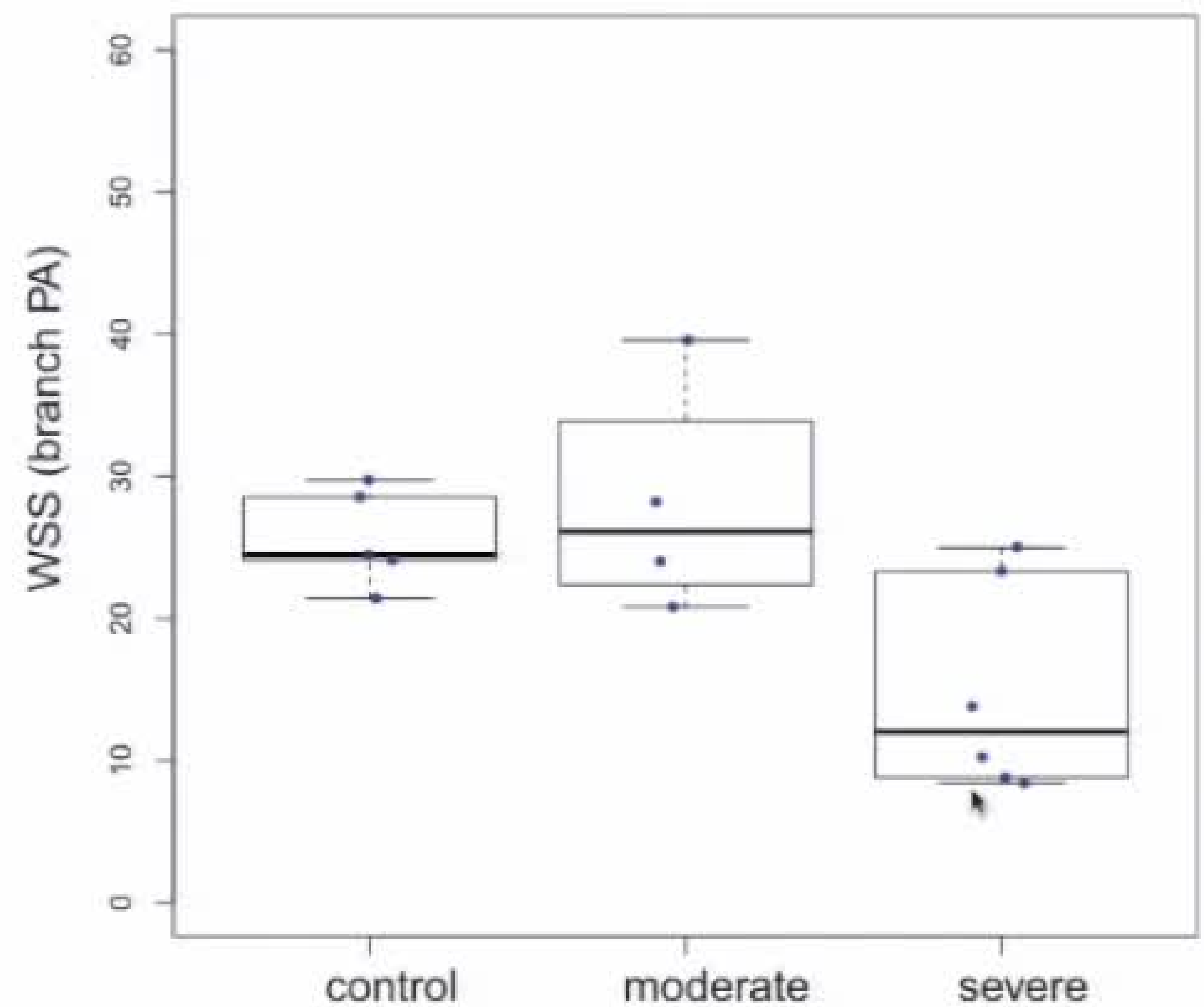
MPA WSS is significantly decreased in moderate and severe patients

PH Cohort with Varying Disease Severity



Proximal vessels: WSS

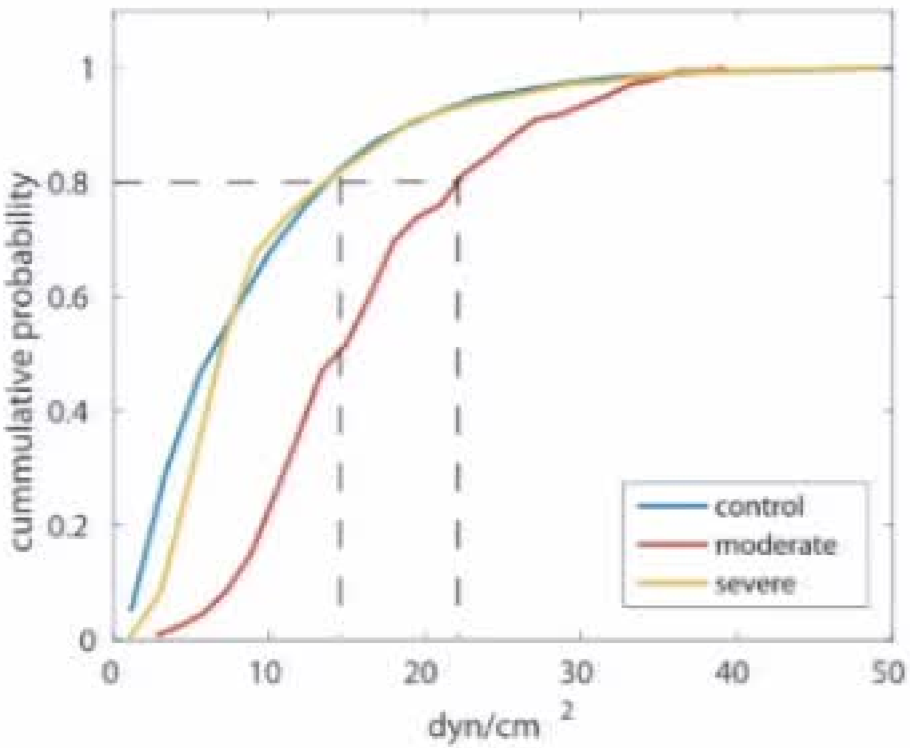




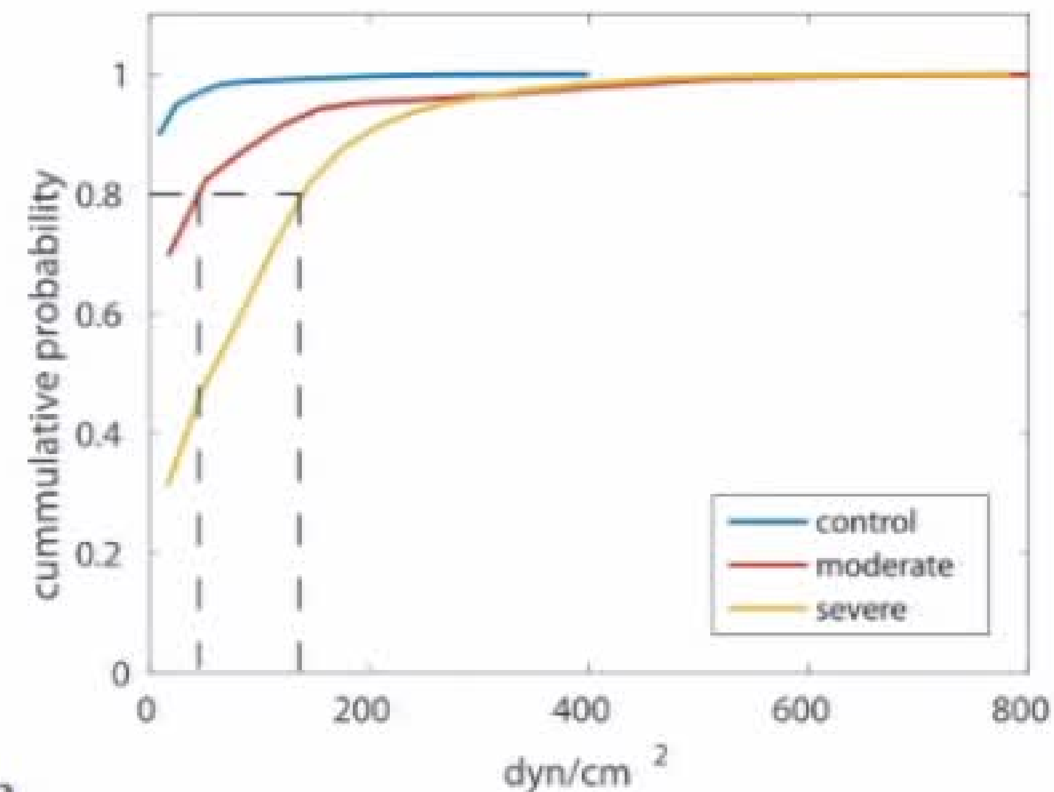
MPA WSS is significantly decreased in moderate and severe patients

Distal vessels: WSS

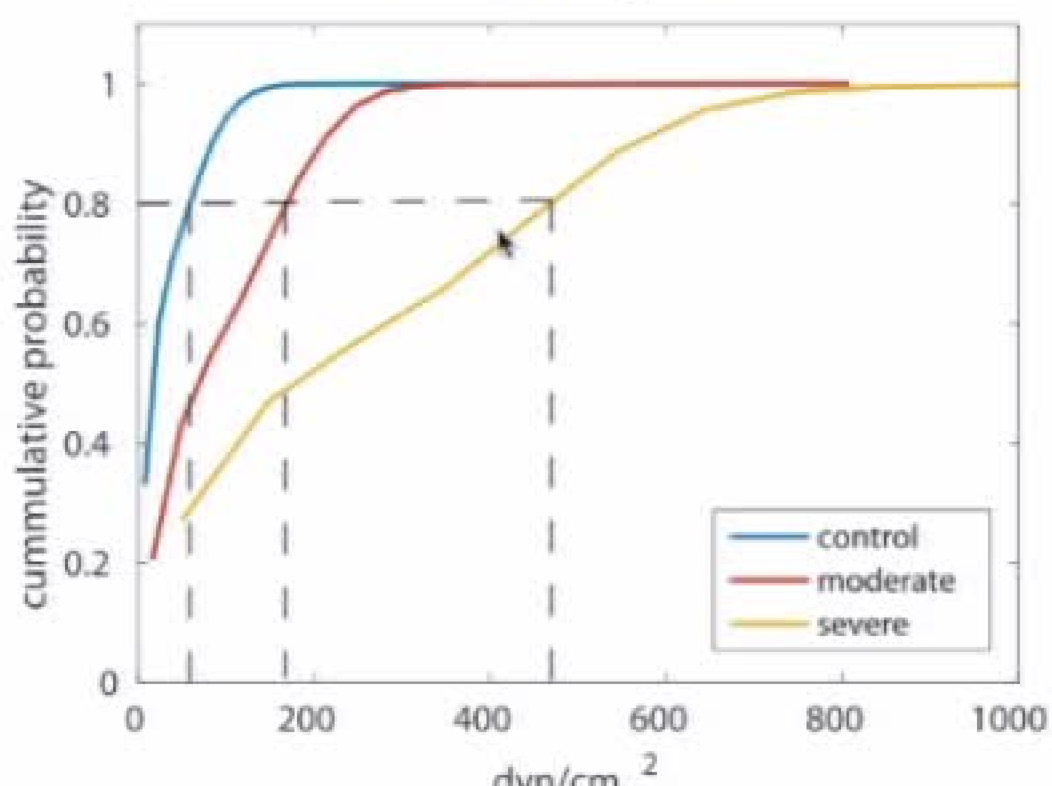
$D > 500\mu m$



$100\mu m < D < 500\mu m$



$D < 100\mu m$



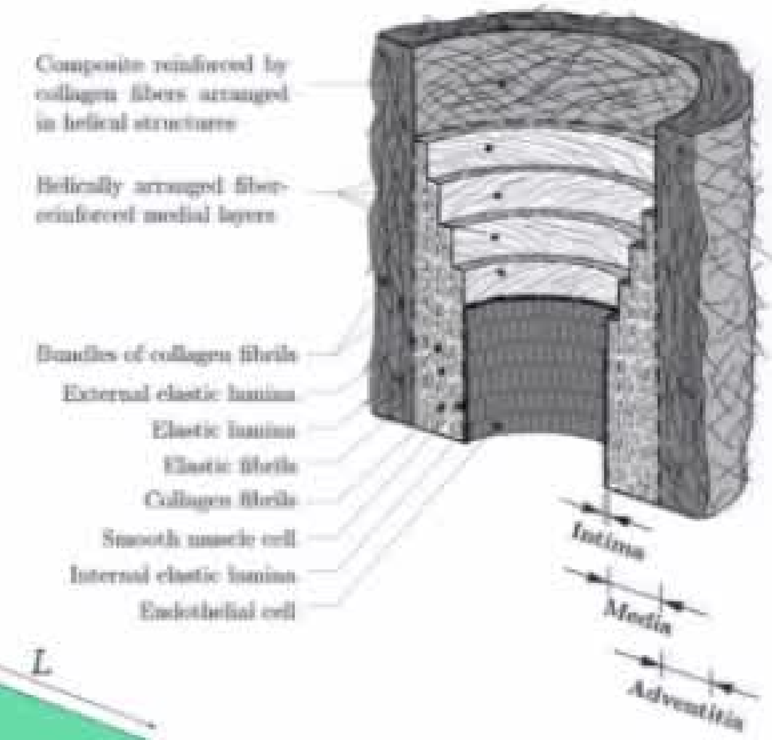
Ju Liu

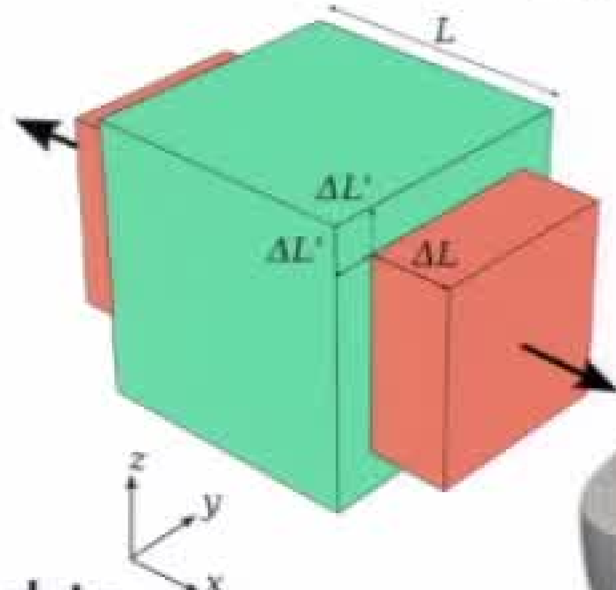
Towards Fluid Solid Growth

An integrated framework for solid-fluid mechanics

Challenges of incompressible solids

- Biological tissues are incompressible with Poisson ratio = 0.5
- Most solid mechanics codes inadequately deal with incompressible materials
  - Limitations in element type or model complexity
  - "Fudge" material properties
  - Linear tetrahedral elements lead to well-known "locking" phenomenon





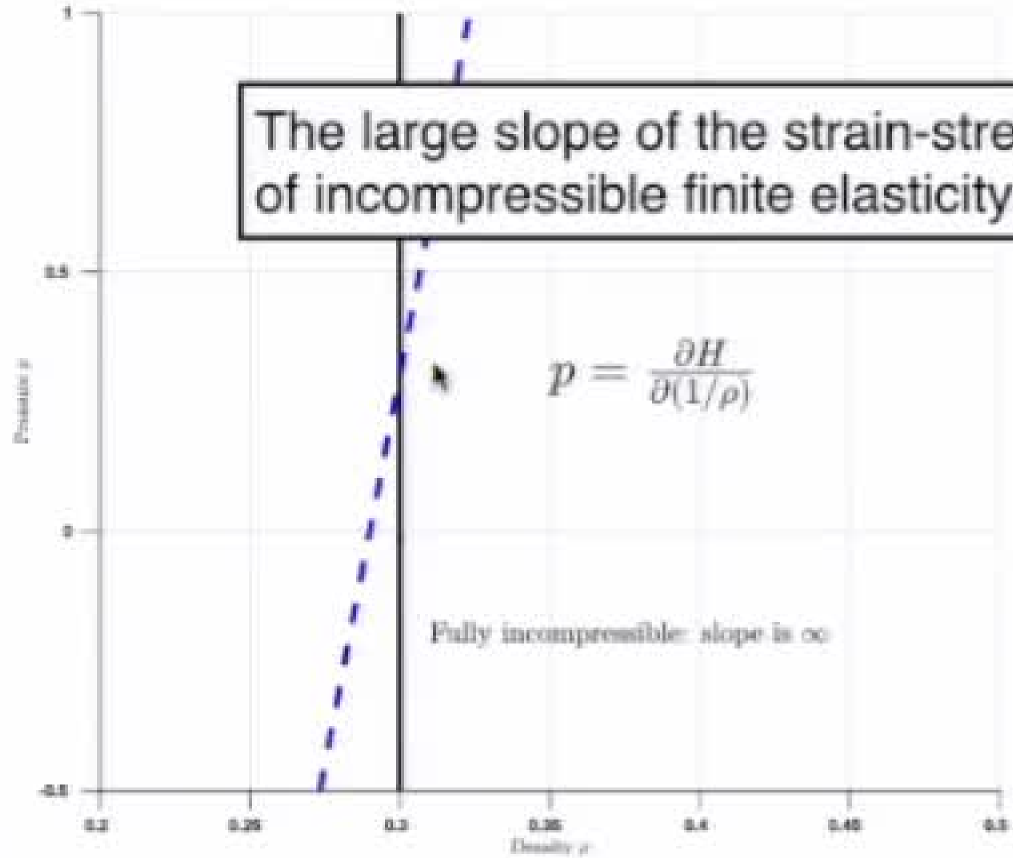
Helmholtz vs. Gibbs

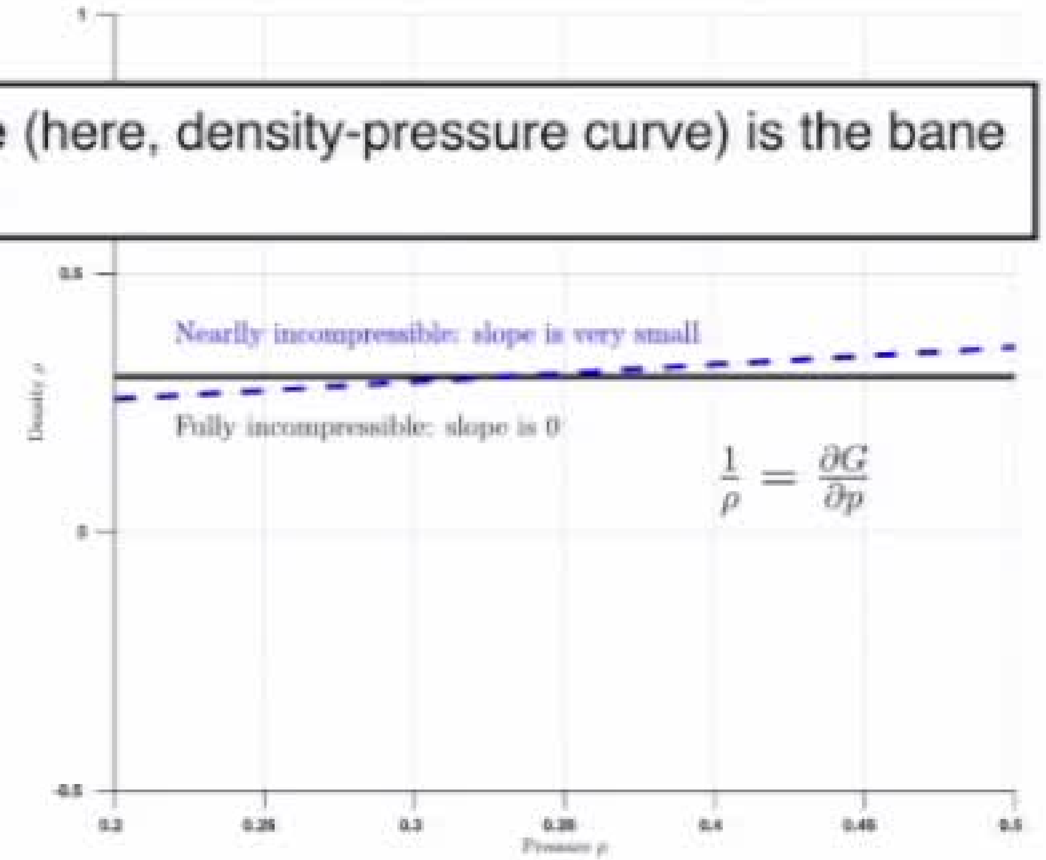
H. Helmholtz (1821-1894)

A.M. Legendre (1752-1833) →

J.W. Gibbs (1839-1903)

The large slope of the strain-stress curve (here, density-pressure curve) is the bane of incompressible finite elasticity solvers





A unified framework for fluids and solids

- Compressible and incompressible Navier Stokes
- Compressible and incompressible hyper-elastodynamics
- Inelastic materials (anisotropic visco-hyper-elastodynamics, elastoplasticity, etc.)

$$\begin{cases} 0 = \dfrac{d\mathbf{u}}{dt} - \mathbf{v}, \text{ or a mesh motion equation for ALE-CFD,} \\ 0 = \dfrac{d\rho}{dt} + \rho \nabla \cdot \mathbf{v} \\ 0 = \rho \dfrac{d\mathbf{v}}{dt} - \nabla \cdot \sigma^{dev} + \nabla p - \rho \mathbf{b} \end{cases}$$

Elasticity:

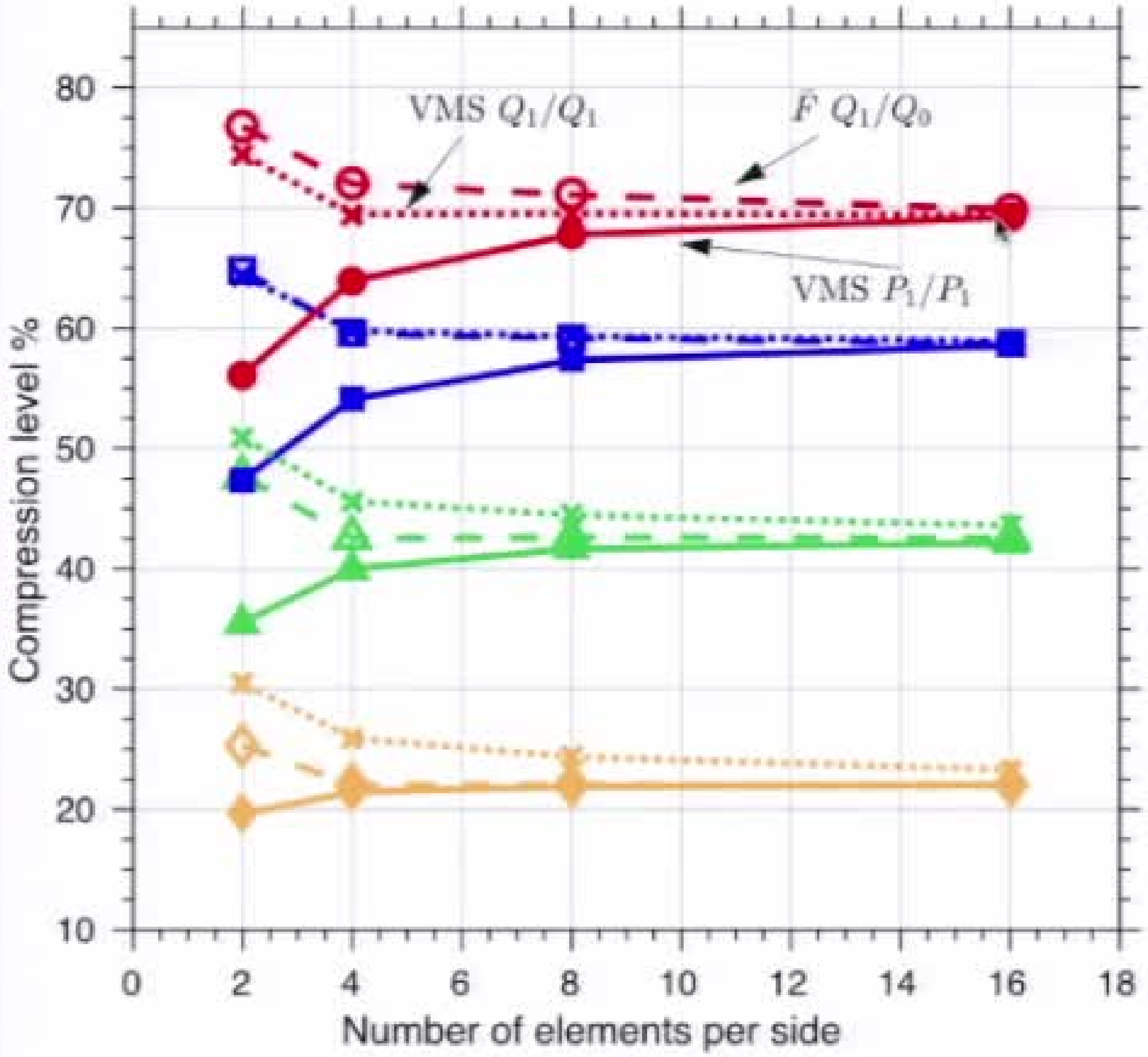
$$\sigma^{dev} = J^{-1} \tilde{\mathbf{F}} \left(\mathbb{P} : \tilde{\mathbf{S}} \right) \tilde{\mathbf{F}}^T, \quad \tilde{\mathbf{S}} = 2 \frac{\partial \tilde{G}}{\partial \tilde{C}}, \quad \rho^{-1} = \frac{d\hat{G}}{dp}, \quad \beta_\theta = - \frac{d^2 \hat{G}}{dp^2} \Big/ \frac{d\hat{G}}{dp}.$$

Viscous fluids:

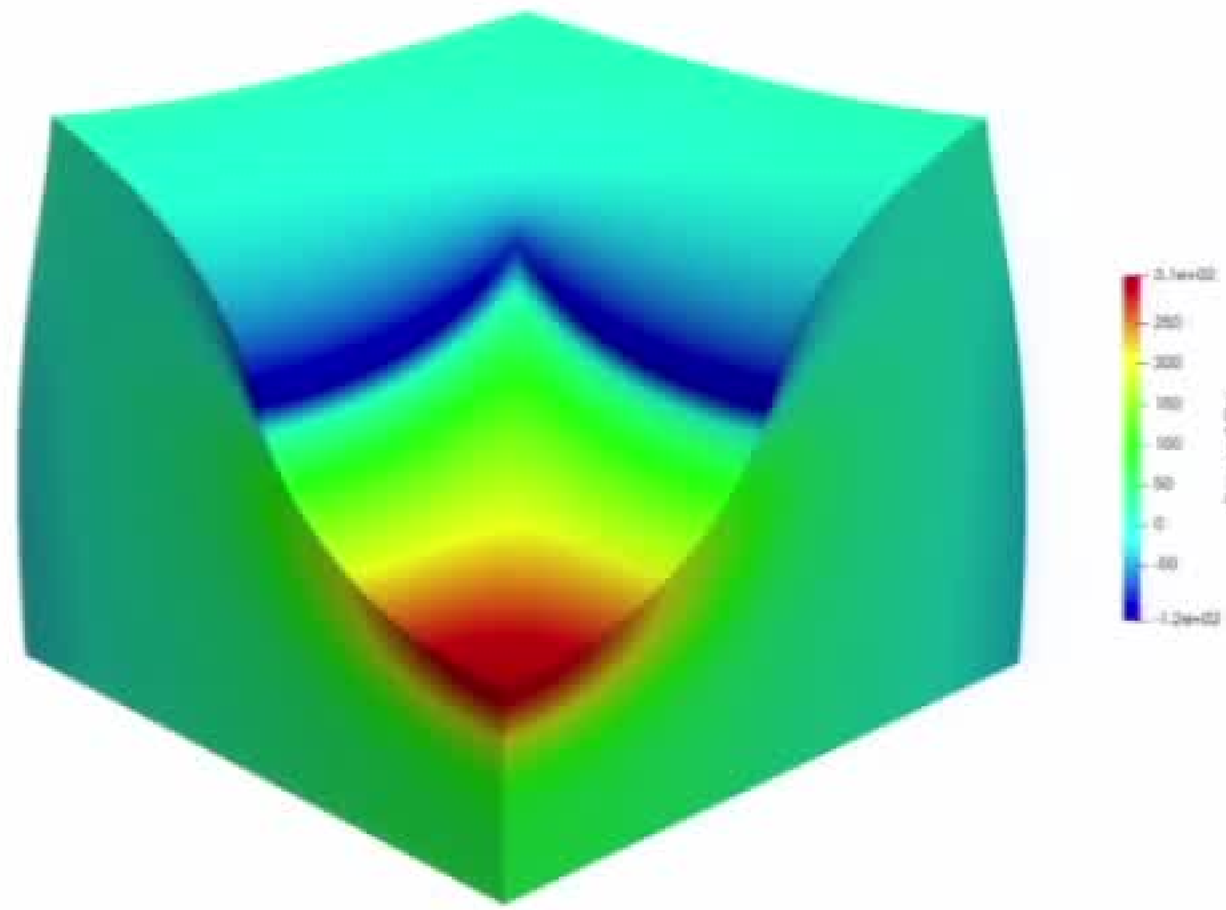
$$\sigma^{dev} = \bar{\mu} \left(\nabla \mathbf{v} + \nabla \mathbf{v}^T \right) + \bar{\lambda} \nabla \cdot \mathbf{v} \mathbf{I}.$$

J. Liu and A.L. Marsden. A unified continuum and variational multiscale formulation for fluids, solids, and fluid-structure Interaction. CMAME 2018.

Verification: Cube compression



Dashed line: F-bar projection; Solid line: VMS



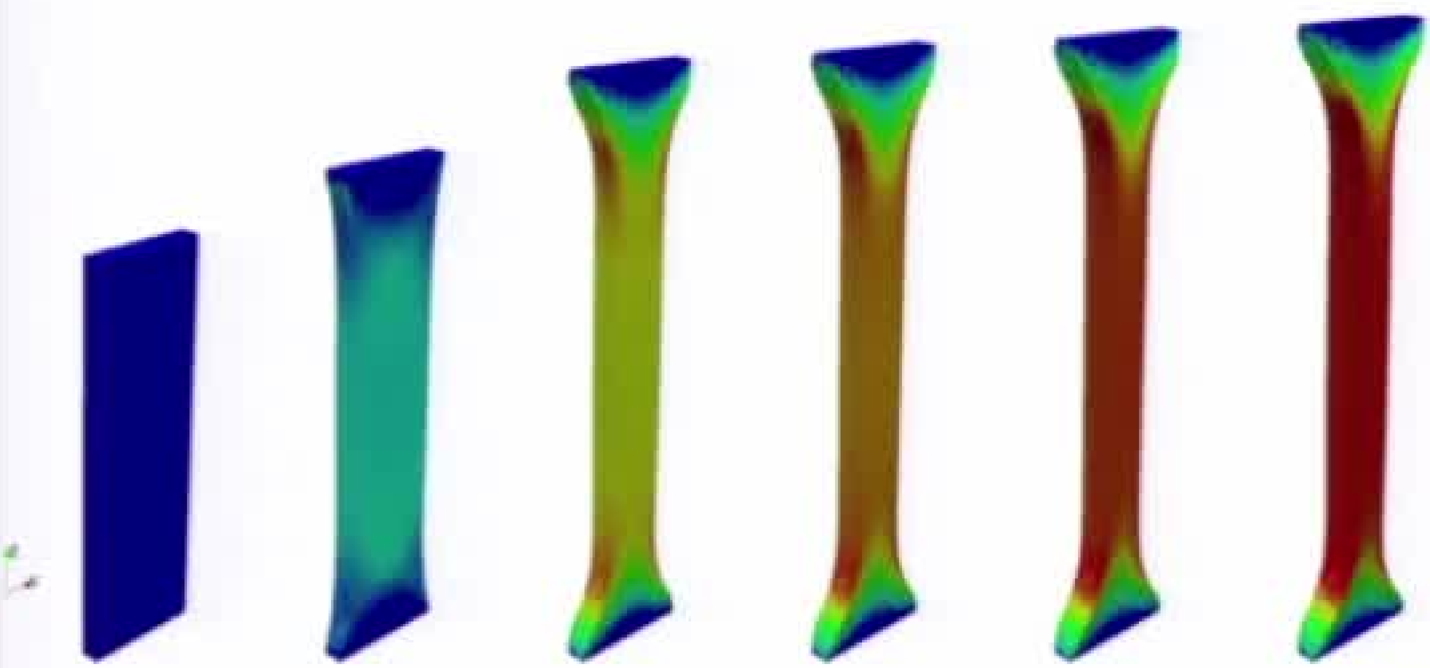
Pressure field simulated with 340 Million Tets.

J. Liu and A.L. Marsden. A unified continuum and variational multiscale formulation for fluids, solids, and fluid-structure Interaction. CMAME 2018.

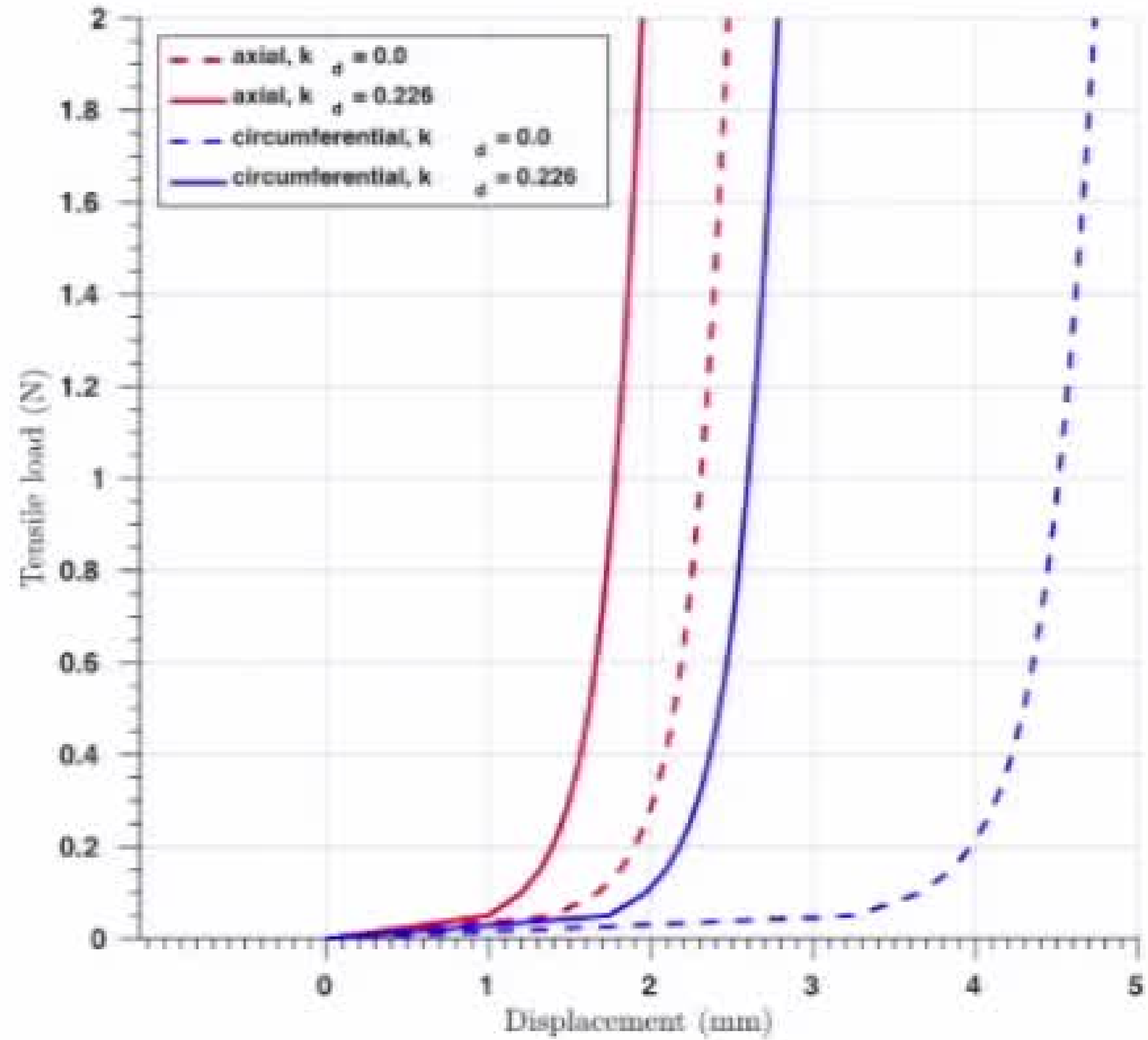
Verification: Anisotropic hyperelastic material

$$G(\tilde{\mathbf{C}},\mathbf{H}_i)=G_g(\tilde{\mathbf{C}})+\sum_{i=1,2}G_{fibre}(\tilde{\mathbf{C}},\mathbf{H}_i),$$

$$G_g(\tilde{\mathbf{C}})=\frac{c}{2}\left(tr(\tilde{\mathbf{C}})-3\right),\ \ G_{fibre}(\tilde{\mathbf{C}},\mathbf{H}_i)=\frac{k_1}{2k_2}\left(\exp\left(k_2\tilde{E}_i^2\right)-1\right).$$



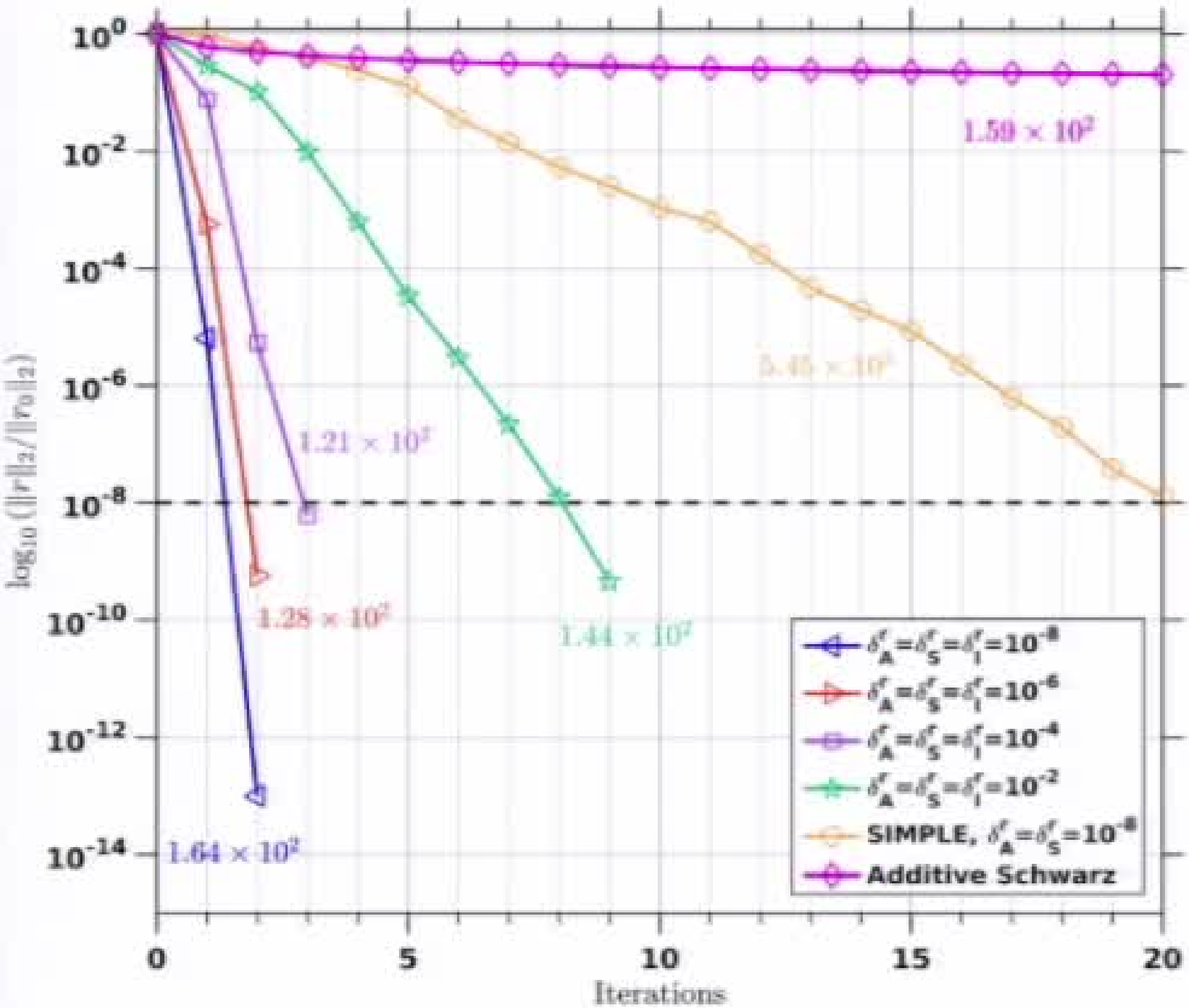
0.0 N   0.01 N   0.1 N   0.2 N   0.5 N   2.0 N



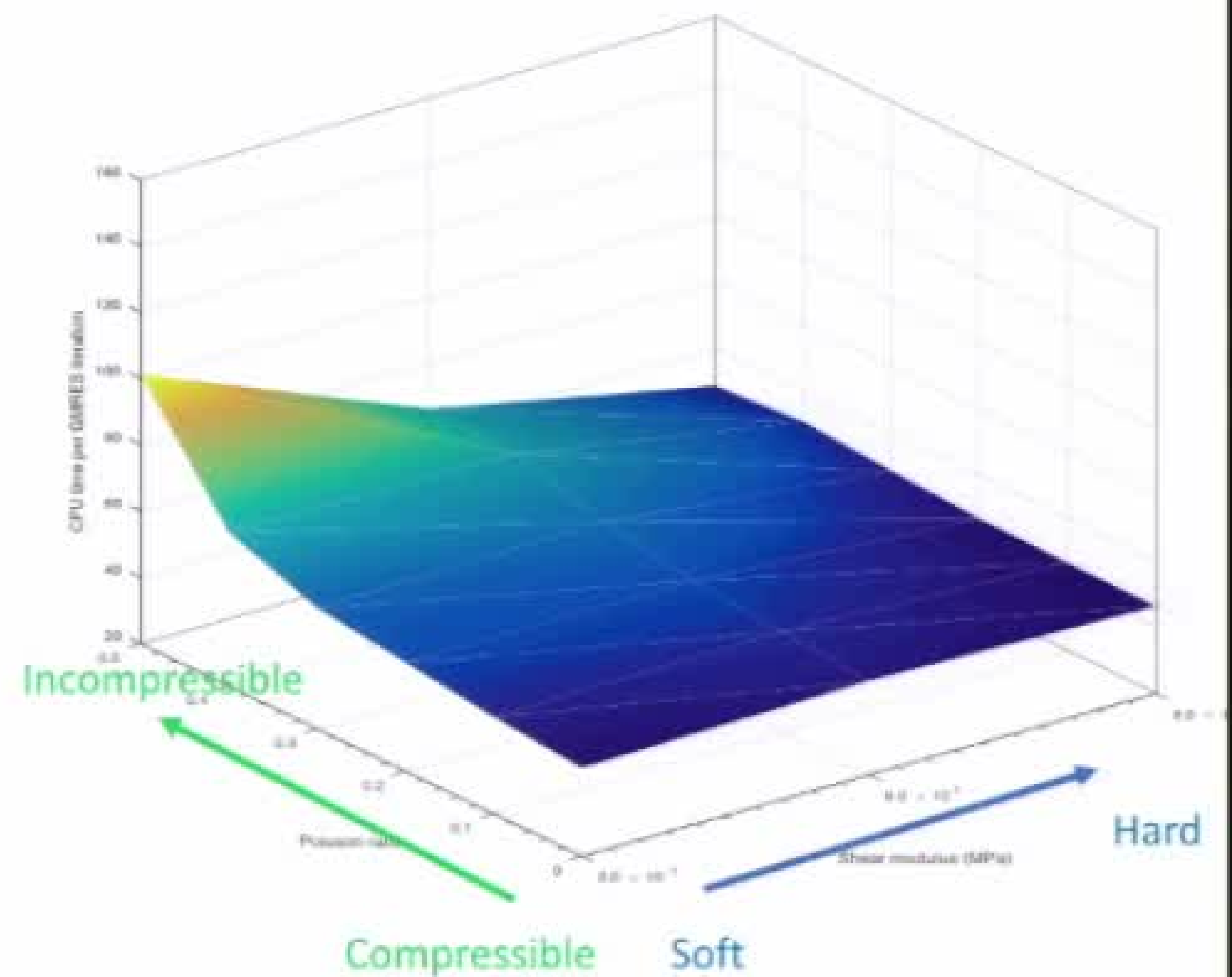
T. Gasser, et al. Hyperelastic modeling of arterial layers with distributed collagen fibre orientations. Journal of the Royal Society Interface, 2005.

J. Liu and A.L. Marsden. A robust and efficient iterative method for finite elastodynamics with nested block preconditioning. JCP, submitted.

Linear Solver Technology: Nested Block Preconditioner



Convergence history



Robustness w.r.t. material properties

J. Liu and A.L. Marsden. A robust and efficient iterative method for finite elastodynamics with nested block preconditioning. JCP, submitted.

Unified Framework for FSI

Solid domain | Fluid domain

Solve $\left\{ \begin{array}{c} \beta_\theta \dot{p} + \nabla \cdot v = 0 \\ \rho \dot{v} - \nabla \cdot \sigma^{dev} + \nabla p - \rho b = 0 \end{array} \right\}$ using VMS and Gen-α

$\sigma^{dev} = \sigma^{elastic}$

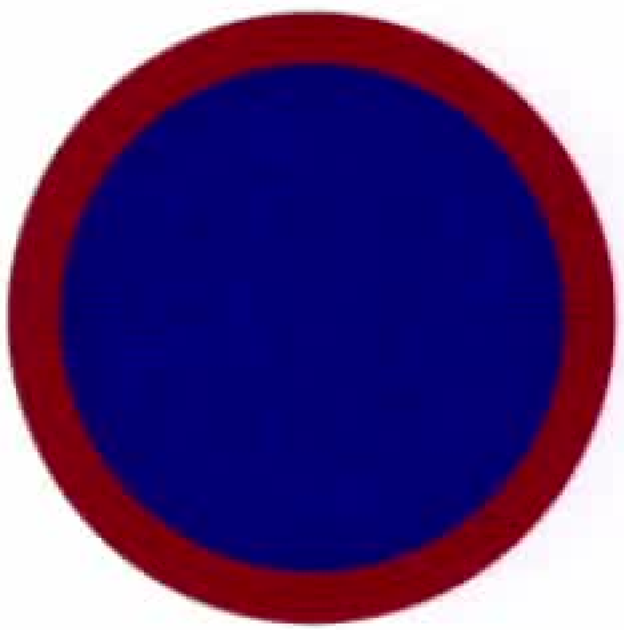
$\sigma^{dev} = \sigma^{viscous}$

Segregated algorithm

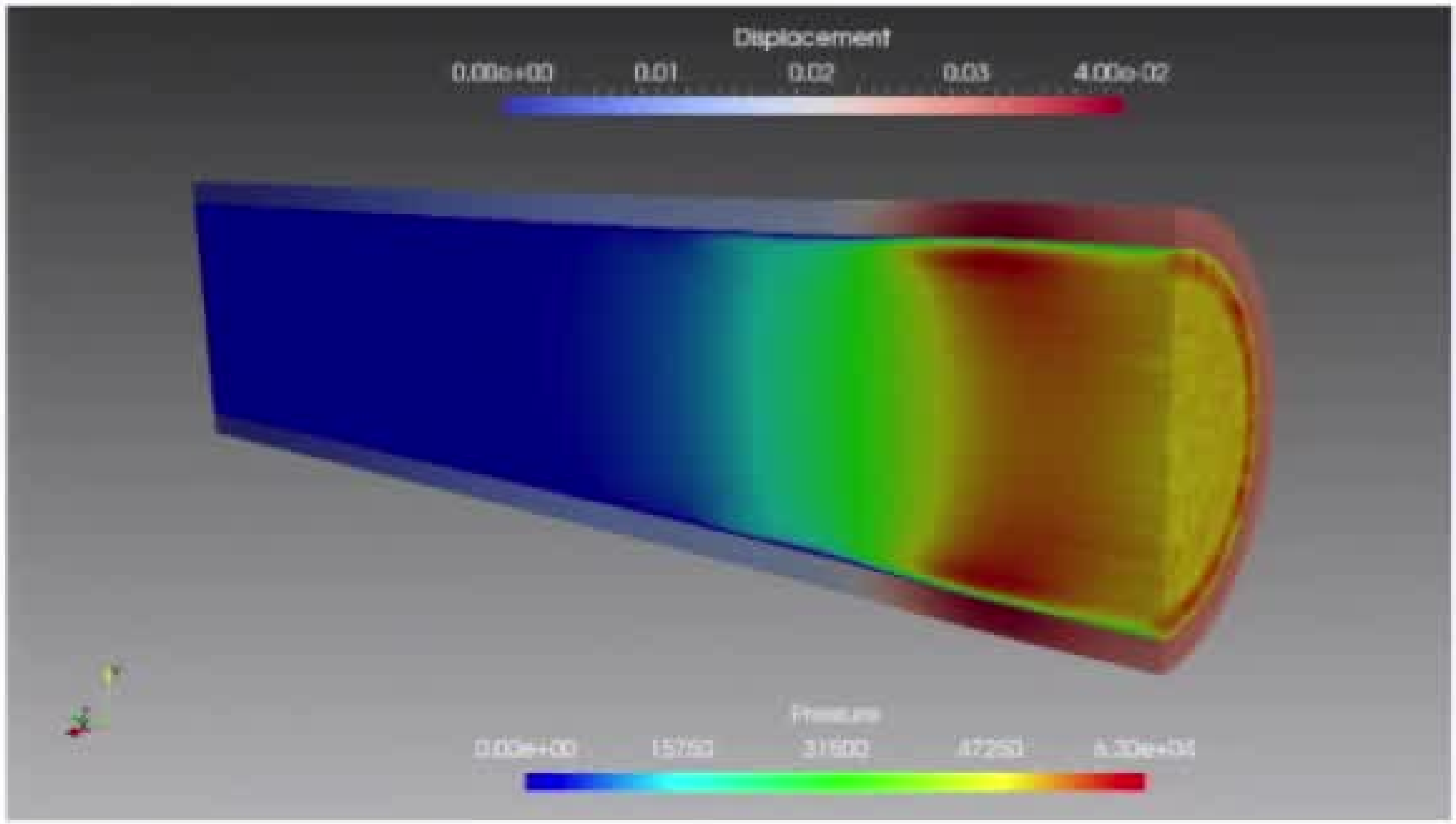
Calculate solid displacement

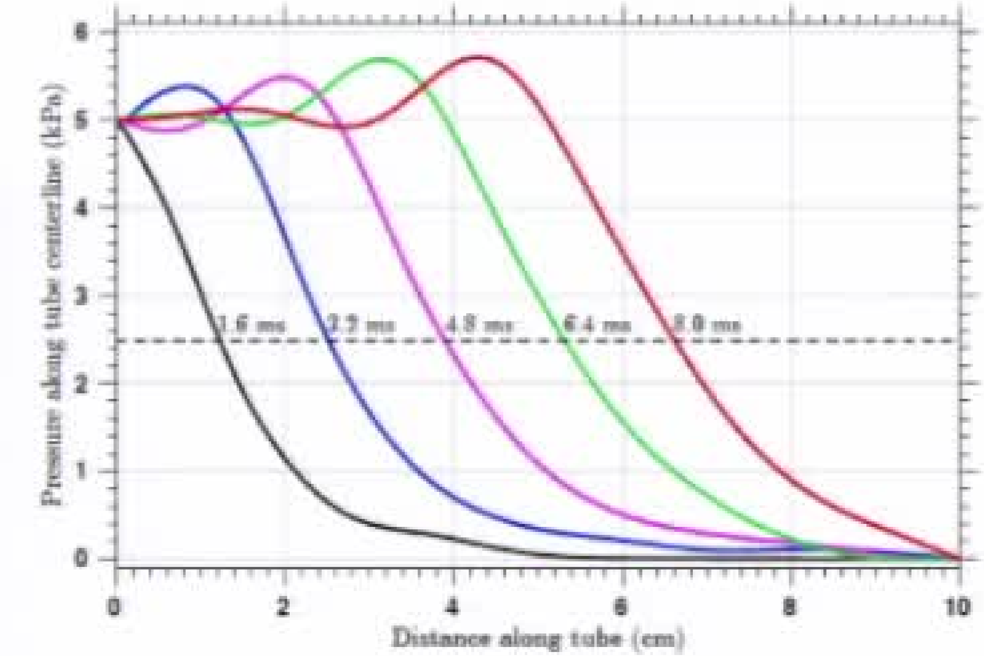
Solve a Laplace equation, or a system of linear elasticity for mesh motion

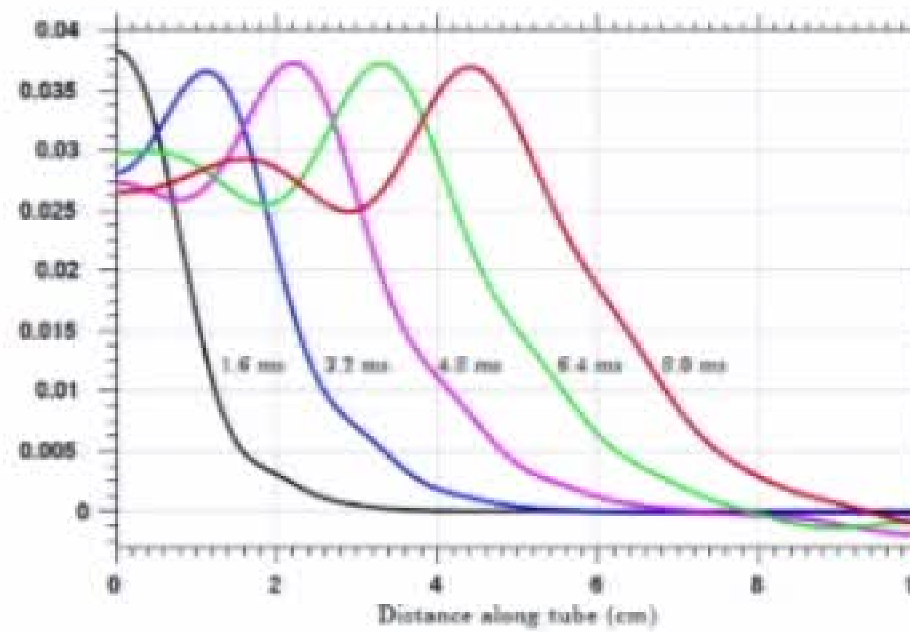
Calculate fluid mesh



Wave Propagation in an Elastic Tube





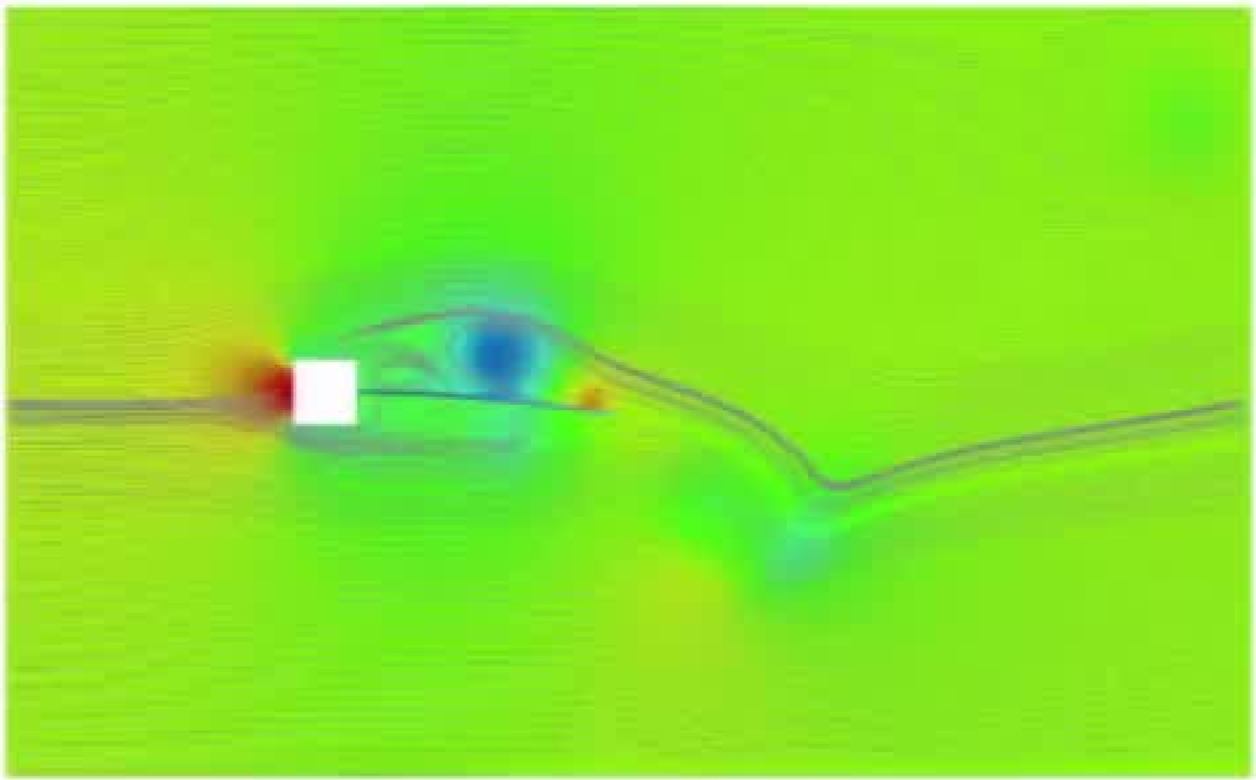


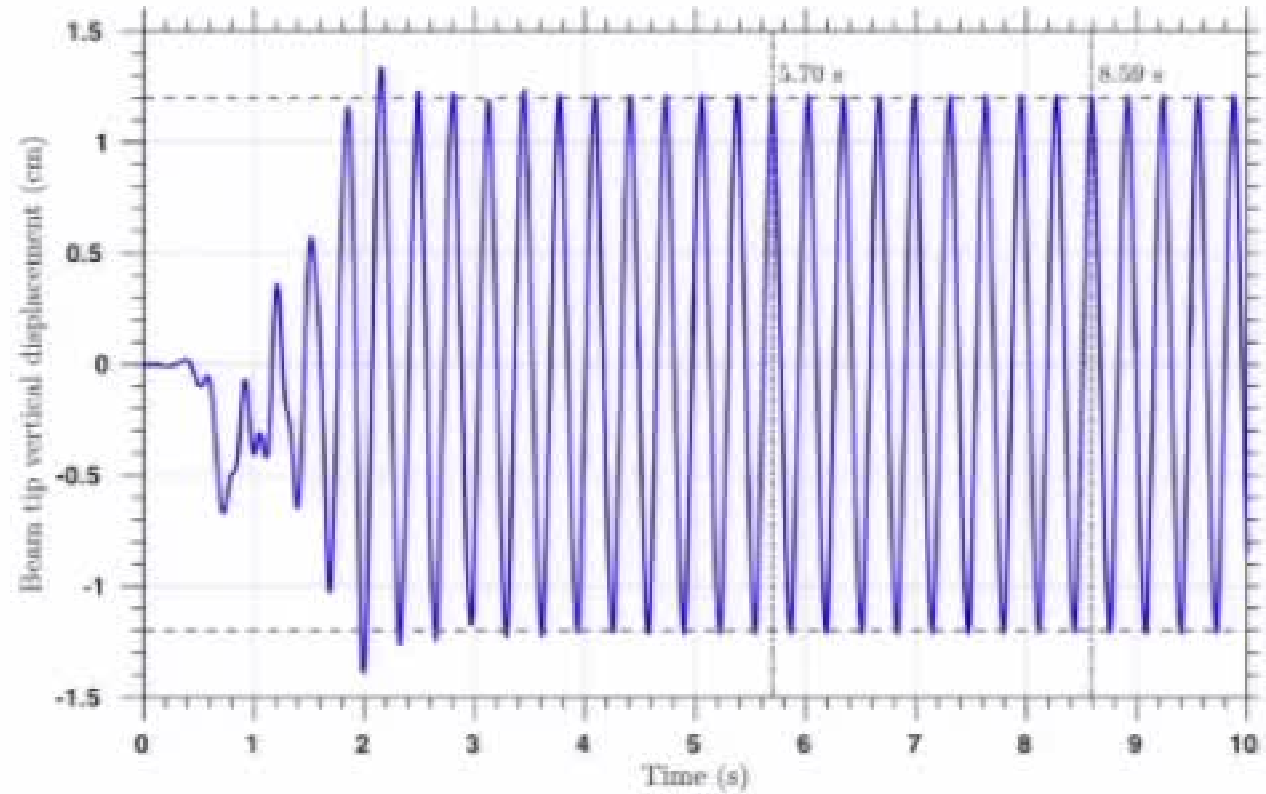
Numerical prediction of the wave frequency: 298.9 Hz
GW numerical prediction of the wave frequency: 318 Hz
Analytic value (3 different formulas): 269 Hz, 308 Hz, 336 Hz.

Liu, J., Marsden, A.L., "A unified continuum and variational multiscale formulation for fluids, solids, and fluid-structure interaction," CMAME 2018.

C.J. Greenshields and H.G. Weller, IJNME, 2005.

FSI Benchmark: Flow over an elastic beam

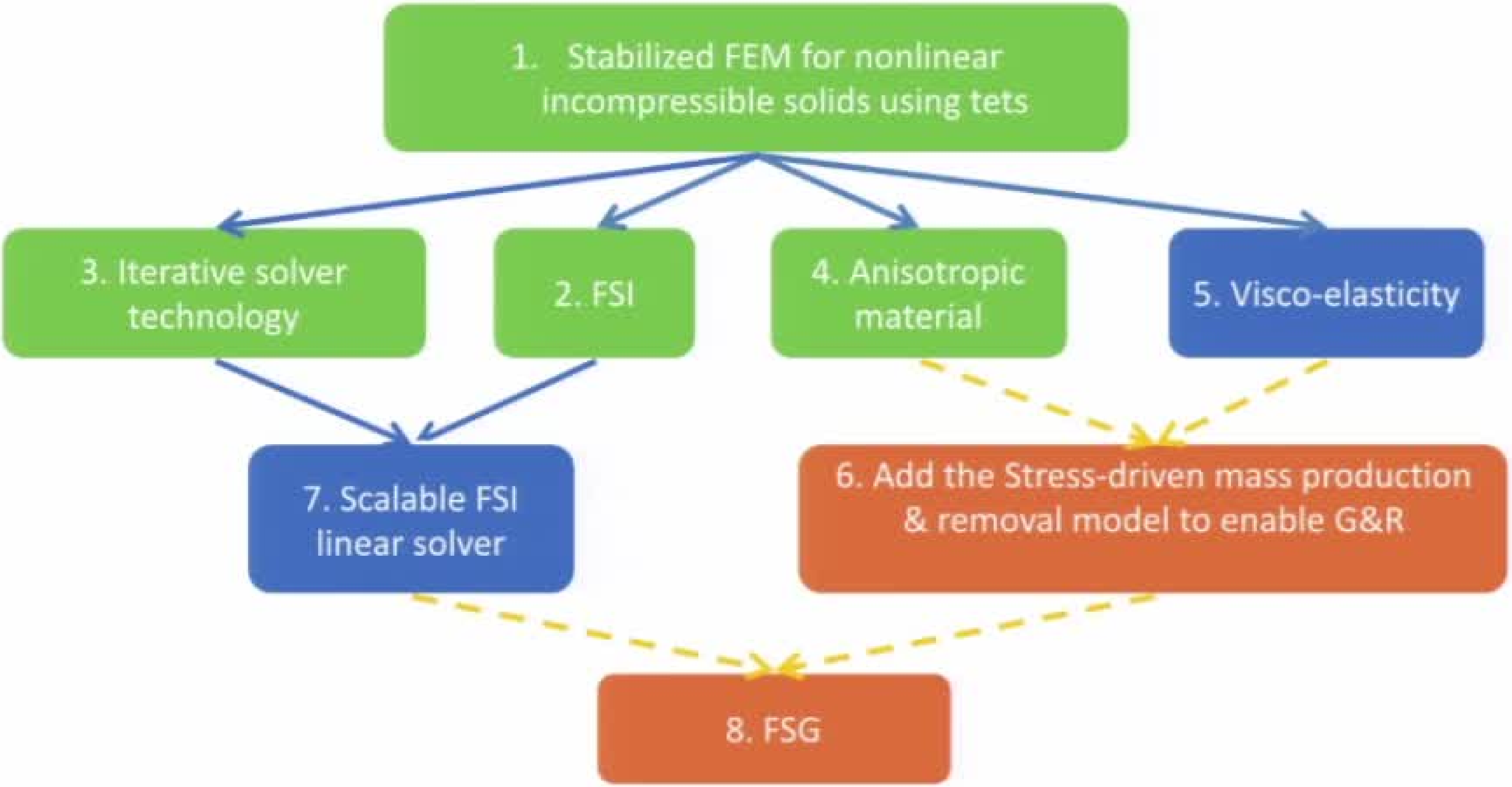




Author	Oscillation period (s)	Tip displacement (cm)
W.A. Wall	0.31 - 0.36	1.12 - 1.32
W.G. Dettmer and D. Perić	0.32 - 0.34	1.1 - 1.4
Y. Bazilevs, et al.	0.33	1.0 - 1.5
C. Wood, et al.	0.32 - 0.36	1.10 - 1.20
Current work	0.32	1.20

C.J. Greenshields and H.G. Weller. A unified formulation for continuum mechanics applied to fluid-structure interaction in flexible tubes. IJNME 2005
J. Liu and A.L. Marsden. A unified continuum and variational multiscale formulation for fluids, solids, and fluid-structure interaction. CMAME 2018.

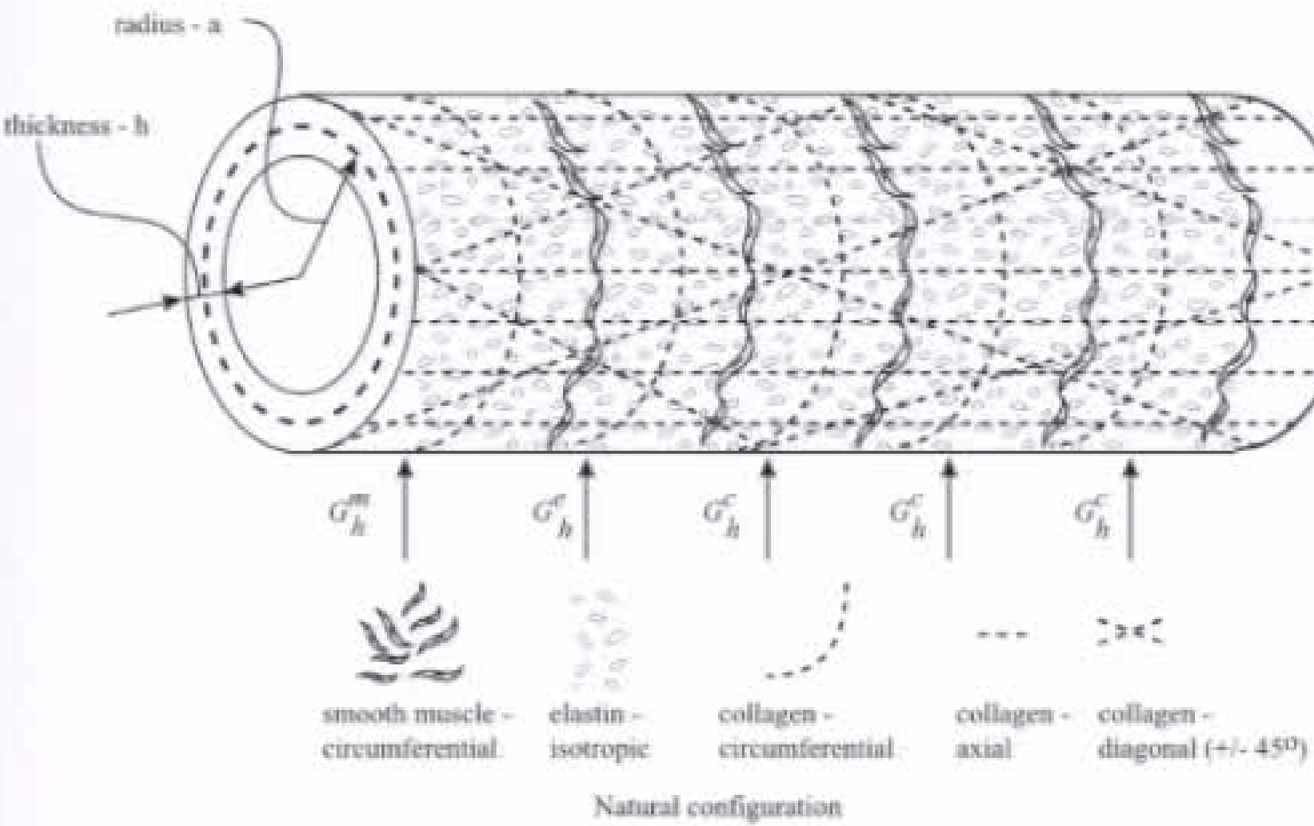
Roadmap to patient-specific FSG

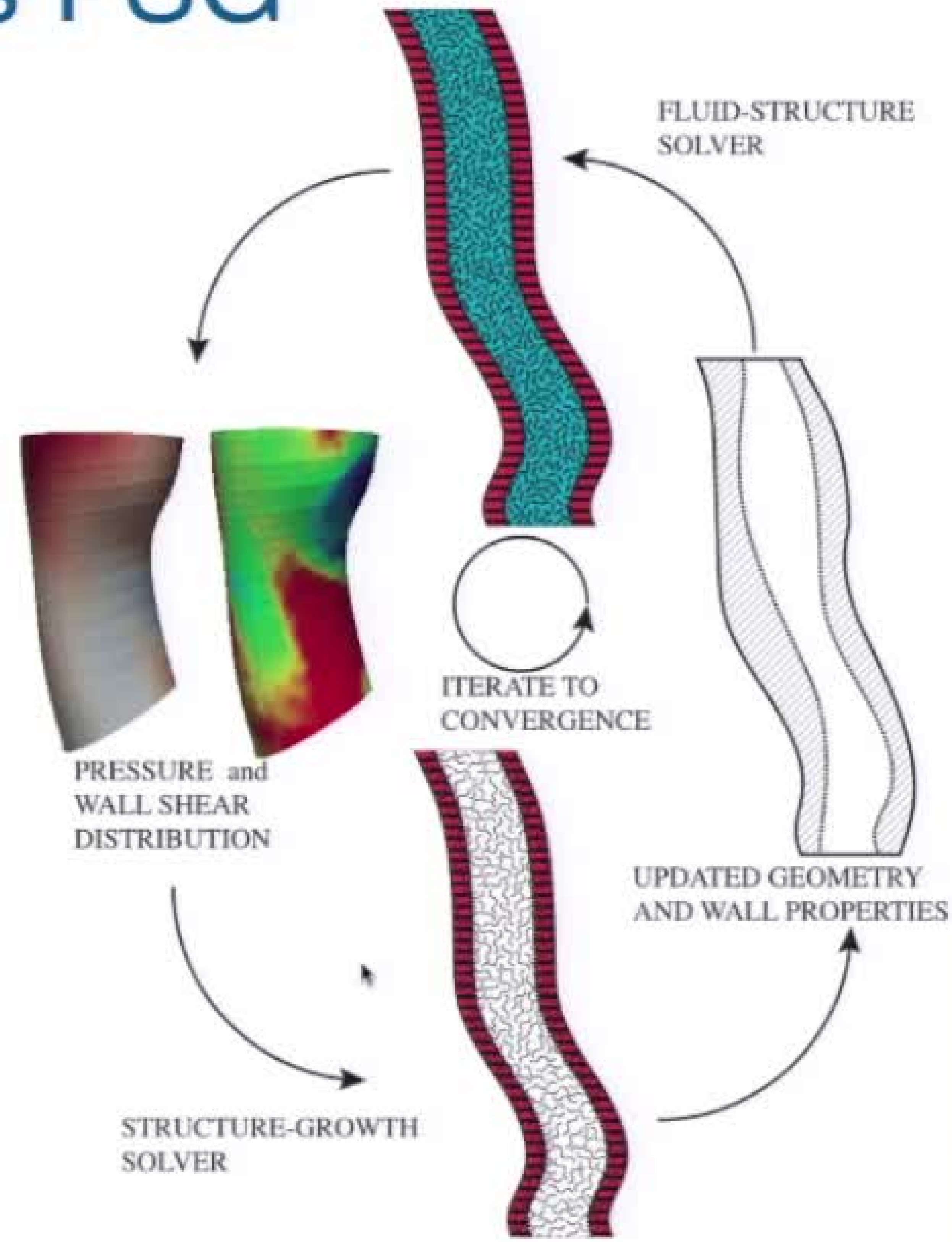


J. Liu and A.L. Marsden. A unified continuum and variational multiscale formulation for fluids, solids, and fluid-structure Interaction. CMAME 2018.

J. Liu and A.L. Marsden. A robust and efficient iterative method for finite elastodynamics with nested block preconditioning. JCP, submitted.

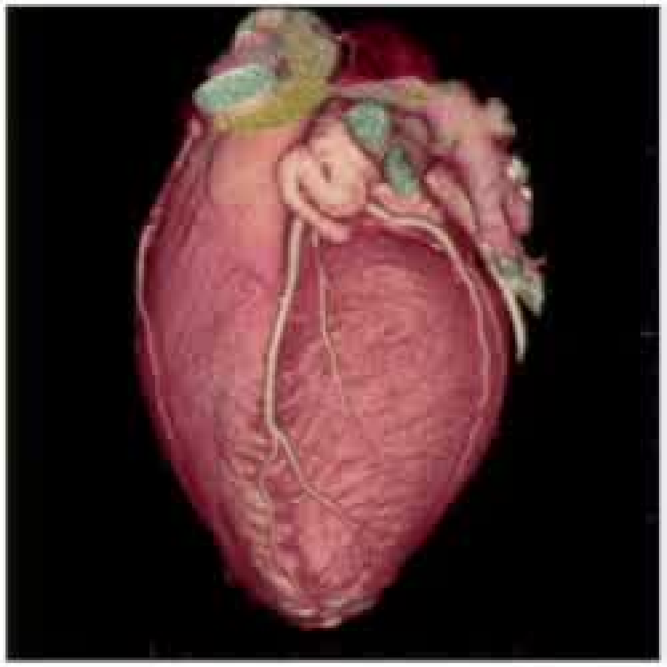
Towards FSG



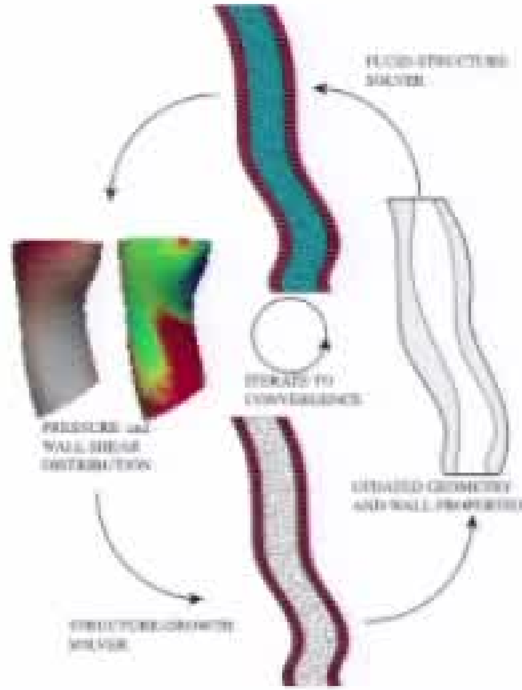


with Chris Breuer and Jay Humphrey

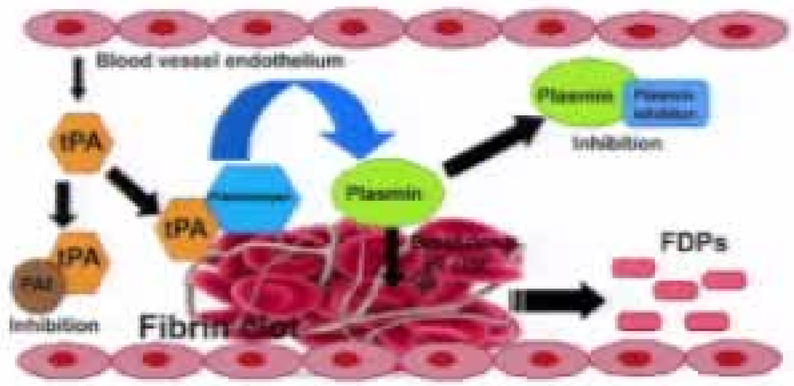
Cardiovascular Modeling: Challenges



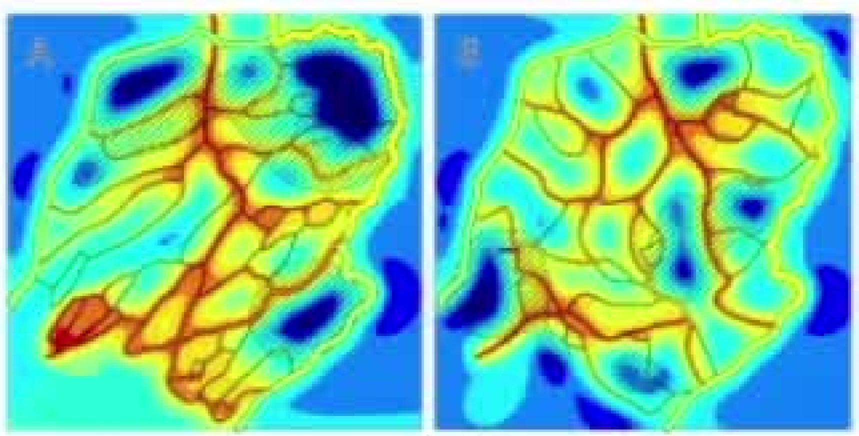
Whole heart modeling



Vascular Mechanobiology

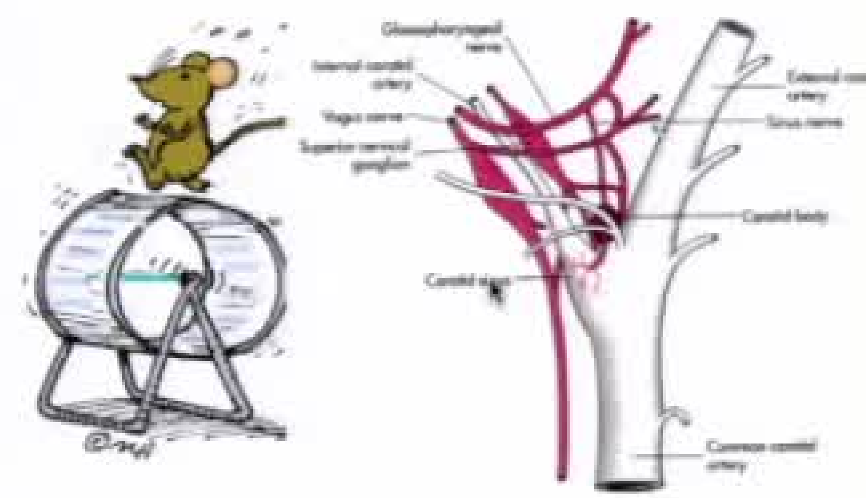


Thrombosis and Biochemistry



Microvasculature

Endothelial Gene Expression



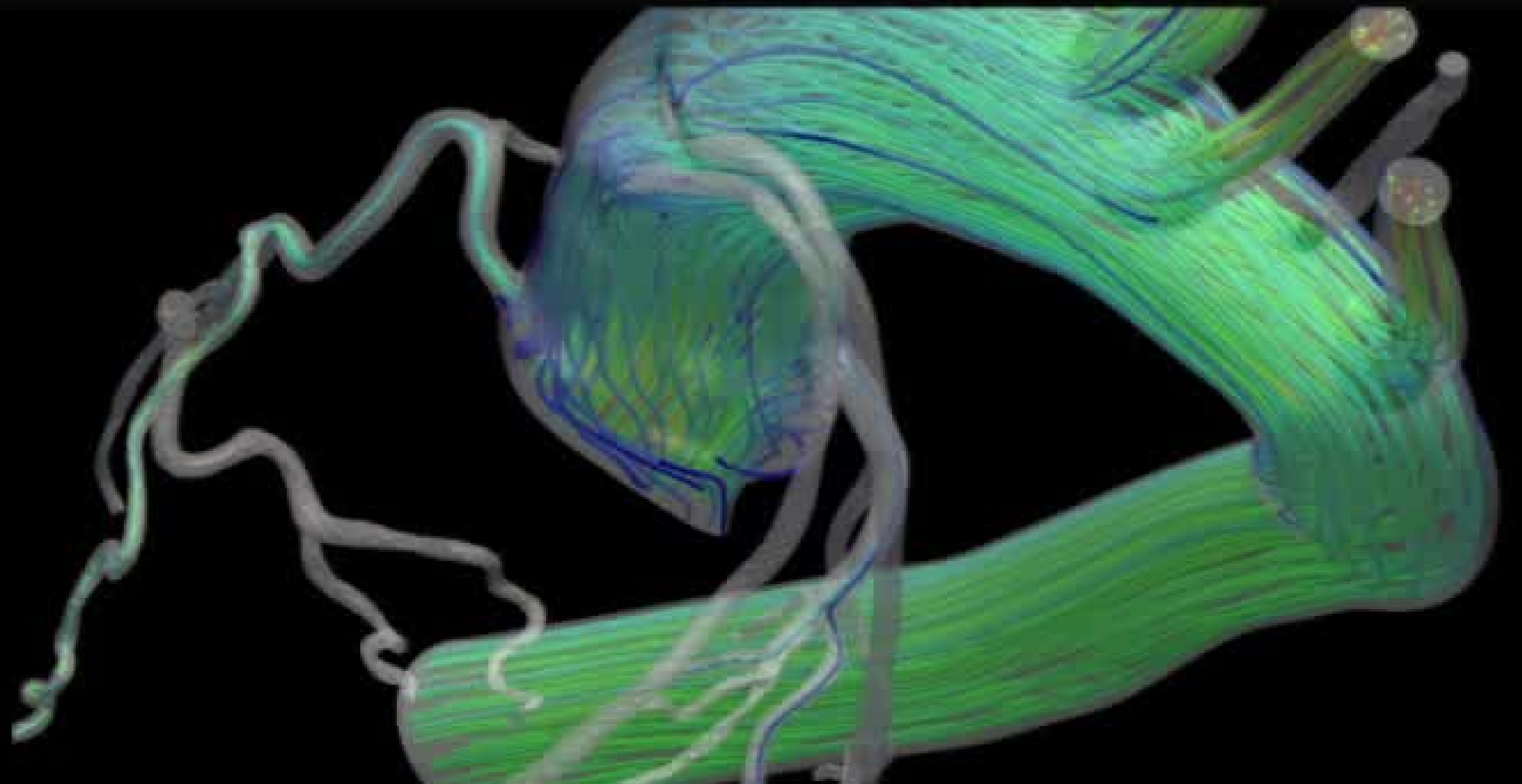
Autoregulation and Adaptation

SimVascular

Alison Marsden
Stanford University

Shawn Shadden
UC Berkeley

Nathan Wilson
OSMSC



MAJOR FUNDING PROVIDED BY

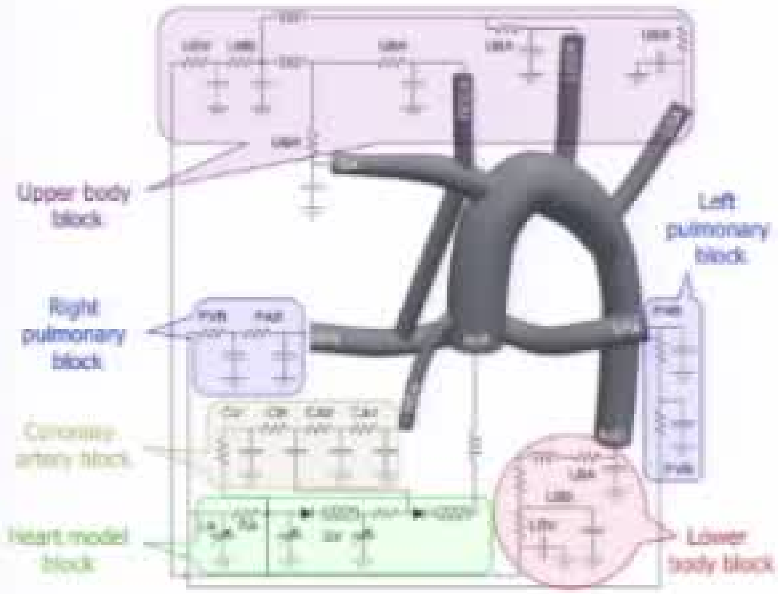
NSF

THE NATIONAL SCIENCE FOUNDATION

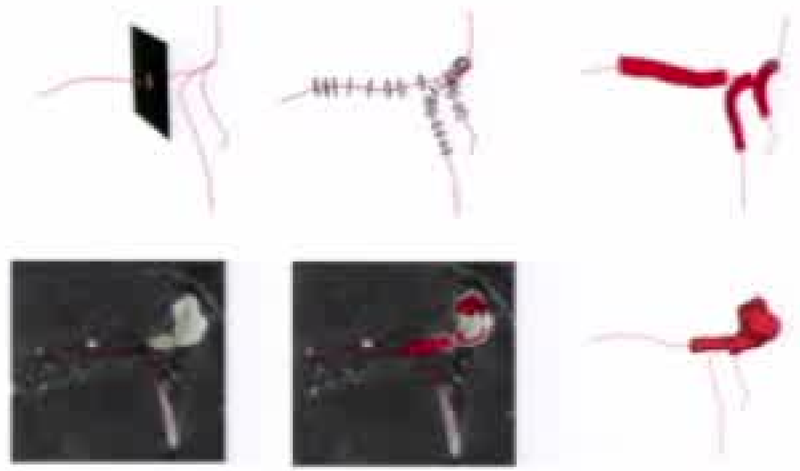
www.simvascular.org

@SimVascular

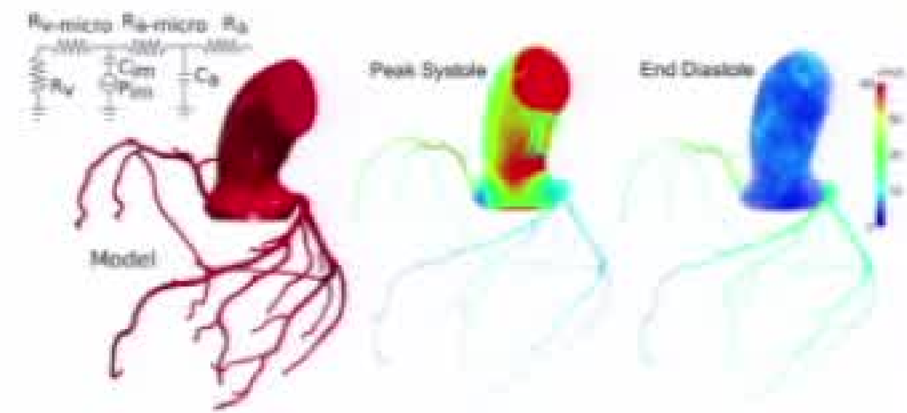
SimVascular Capabilities



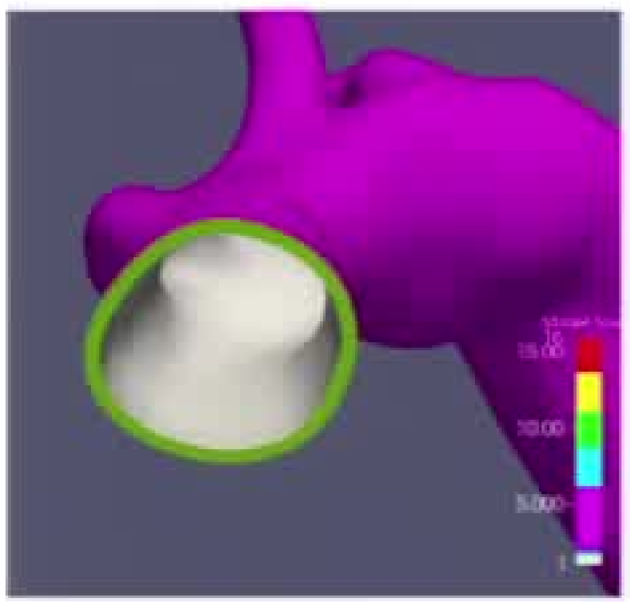
Coupled LPN Modeling



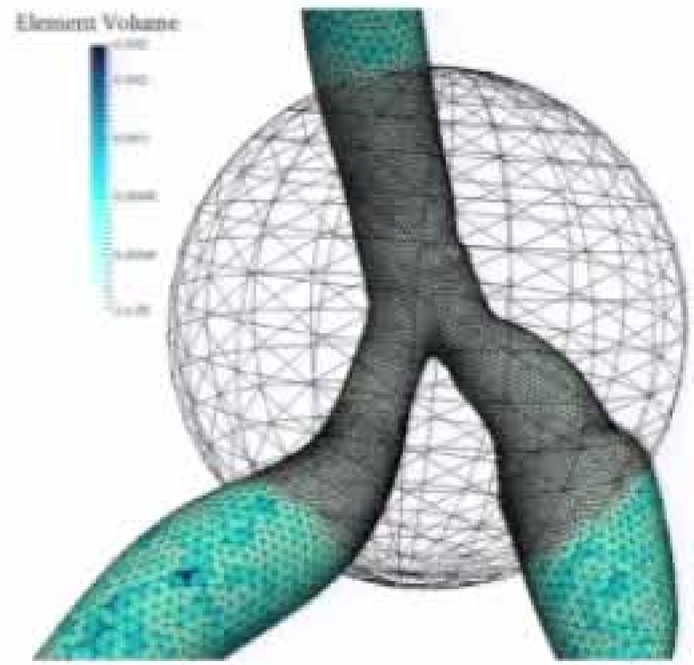
Combined 3D / 2D segmentation



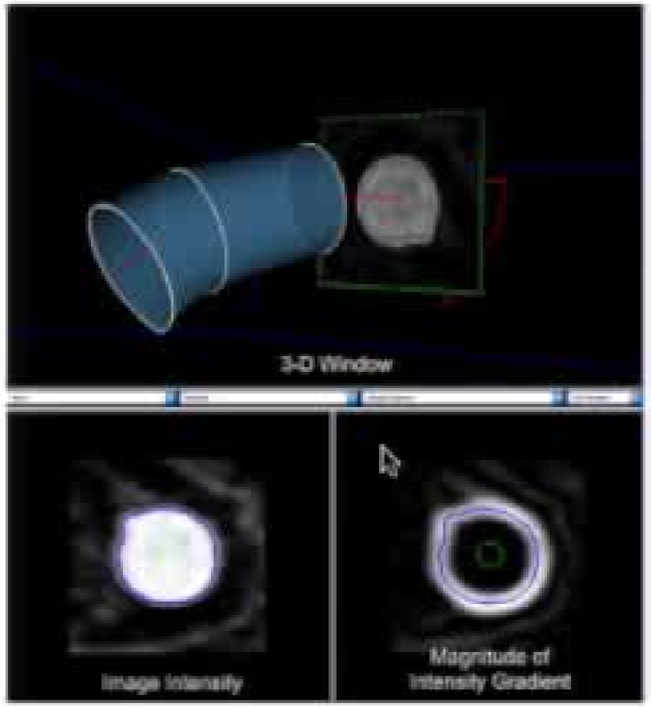
Coronary Physiology



FSI: CMM and ALE methods



Local / Adaptive Mesh Refinement



New GUI with Python

SimVascular

Project Stats

- 2,683 unique users
- 6,692 unique downloads
- Google Scholar search for "SimVascular" produces ~200 publications/abstracts since 2013
- Used in coursework for project-based learning via GATEWAY
- Vascular Model Repository provides 120 compatible data sets

Geography of use