Computational Methods for Personalized Medicine in Cardiovascular Disease

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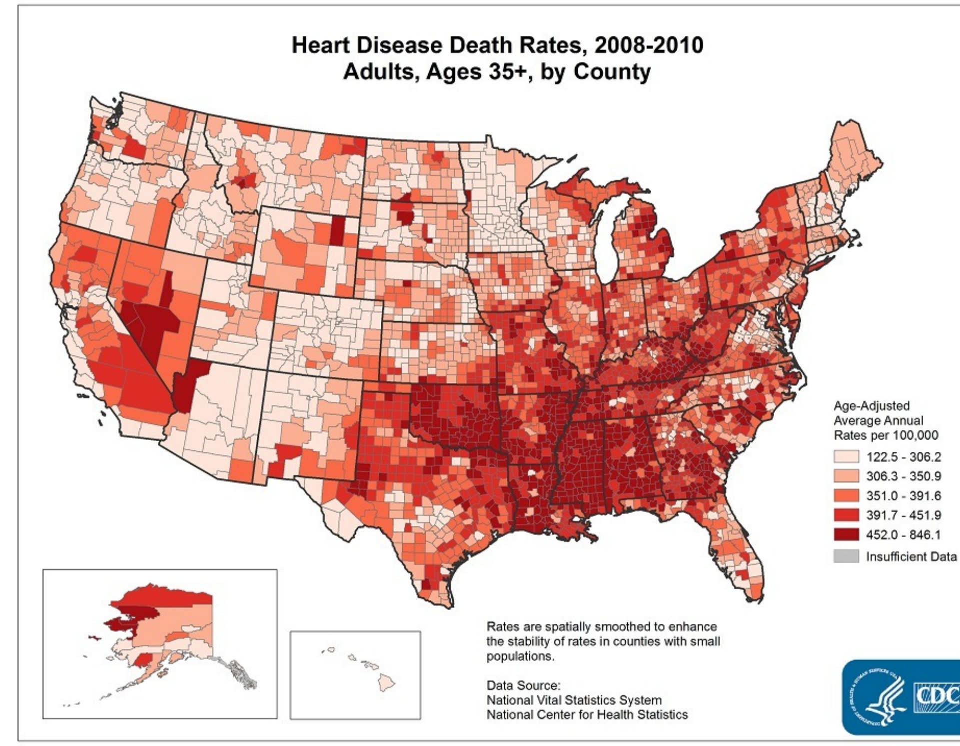
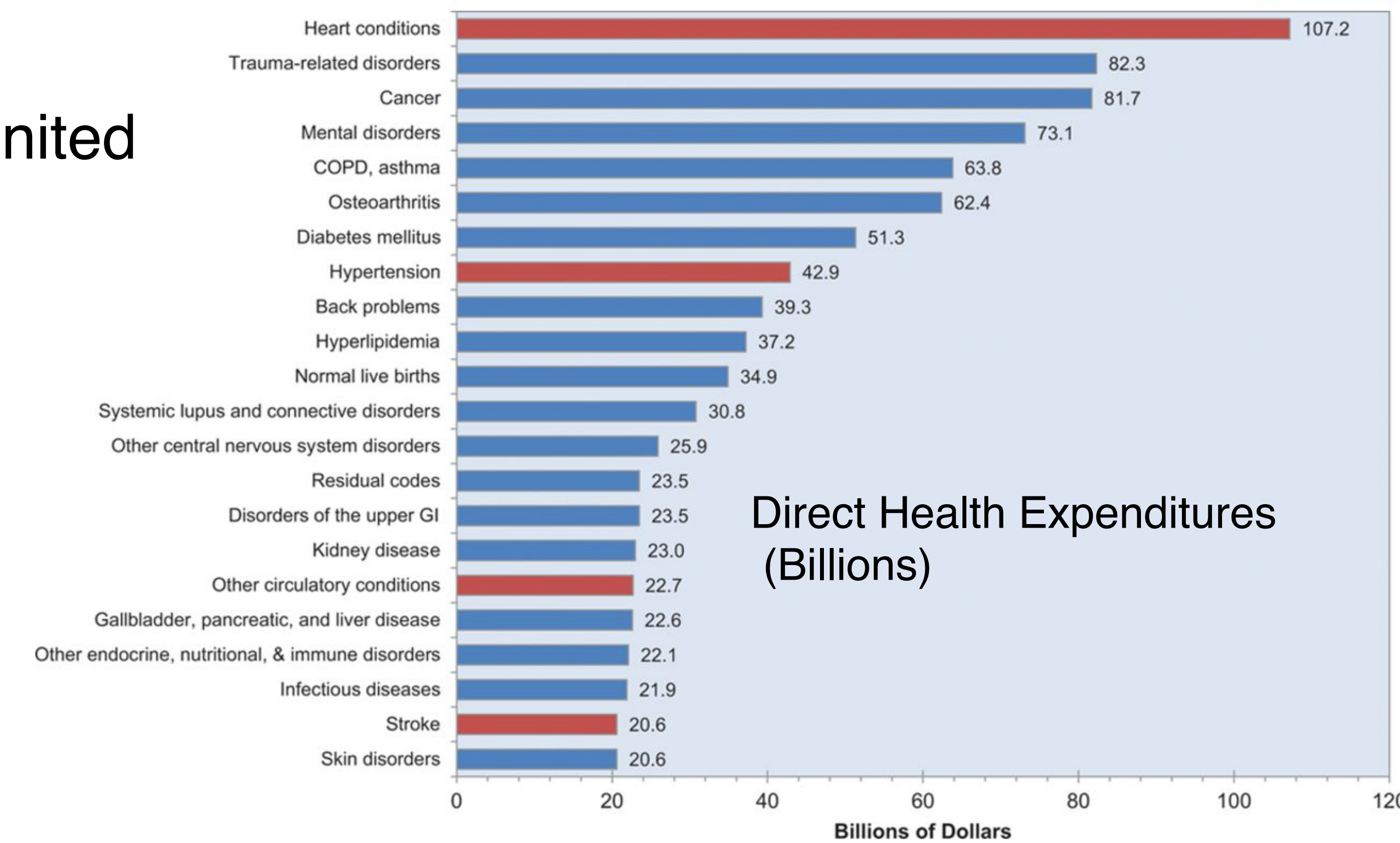
Cardiovascular Disease

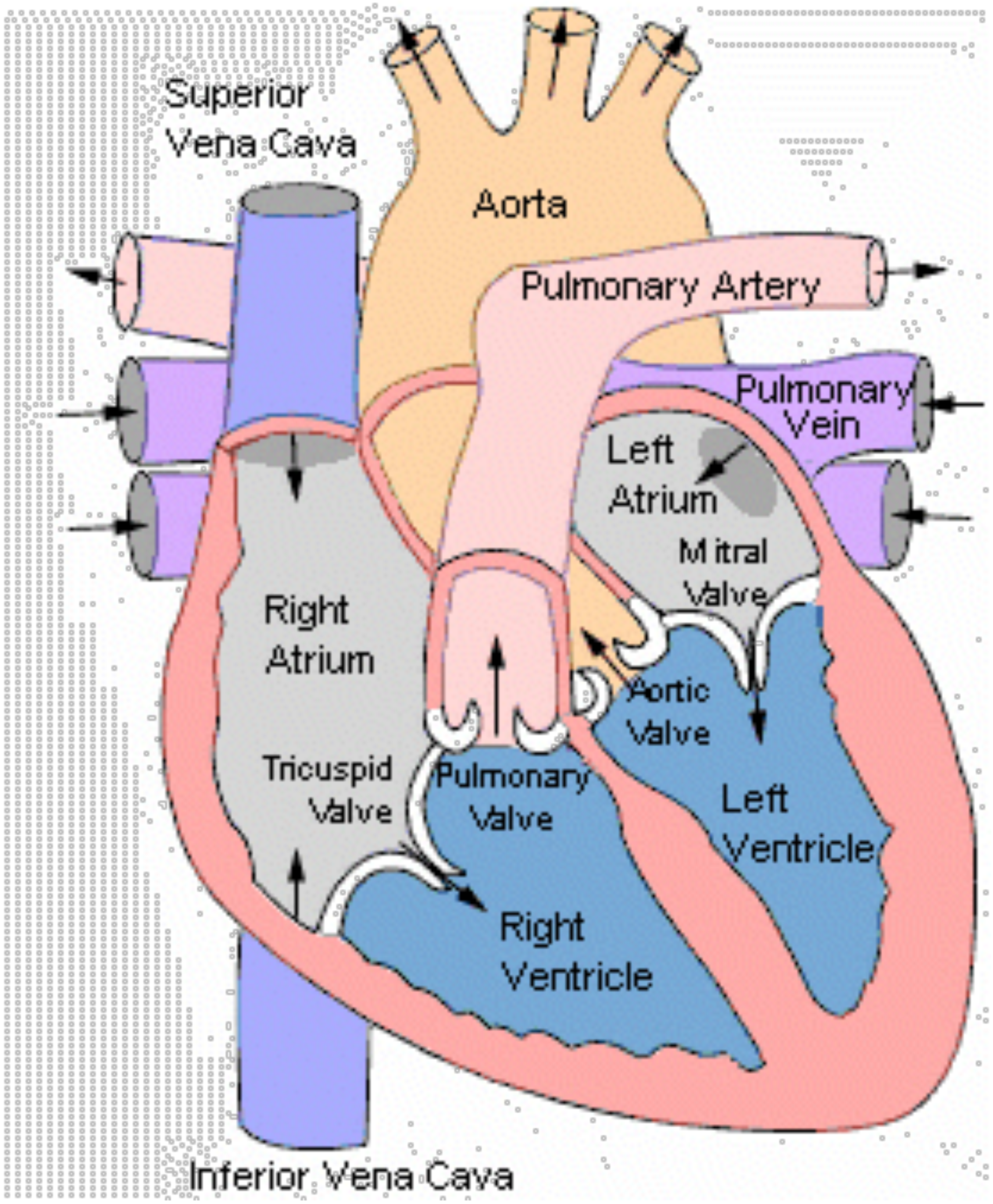
- CVD is the **leading cause of death for men and women globally** ~17 Million deaths worldwide
- ~ **600,000 Americans** die from heart disease each year ~ **1 in every 4 deaths**
- Cardiovascular disease costs the United States >**$500 billion** each year
- 1/100 children are born with a **congenital heart defect**



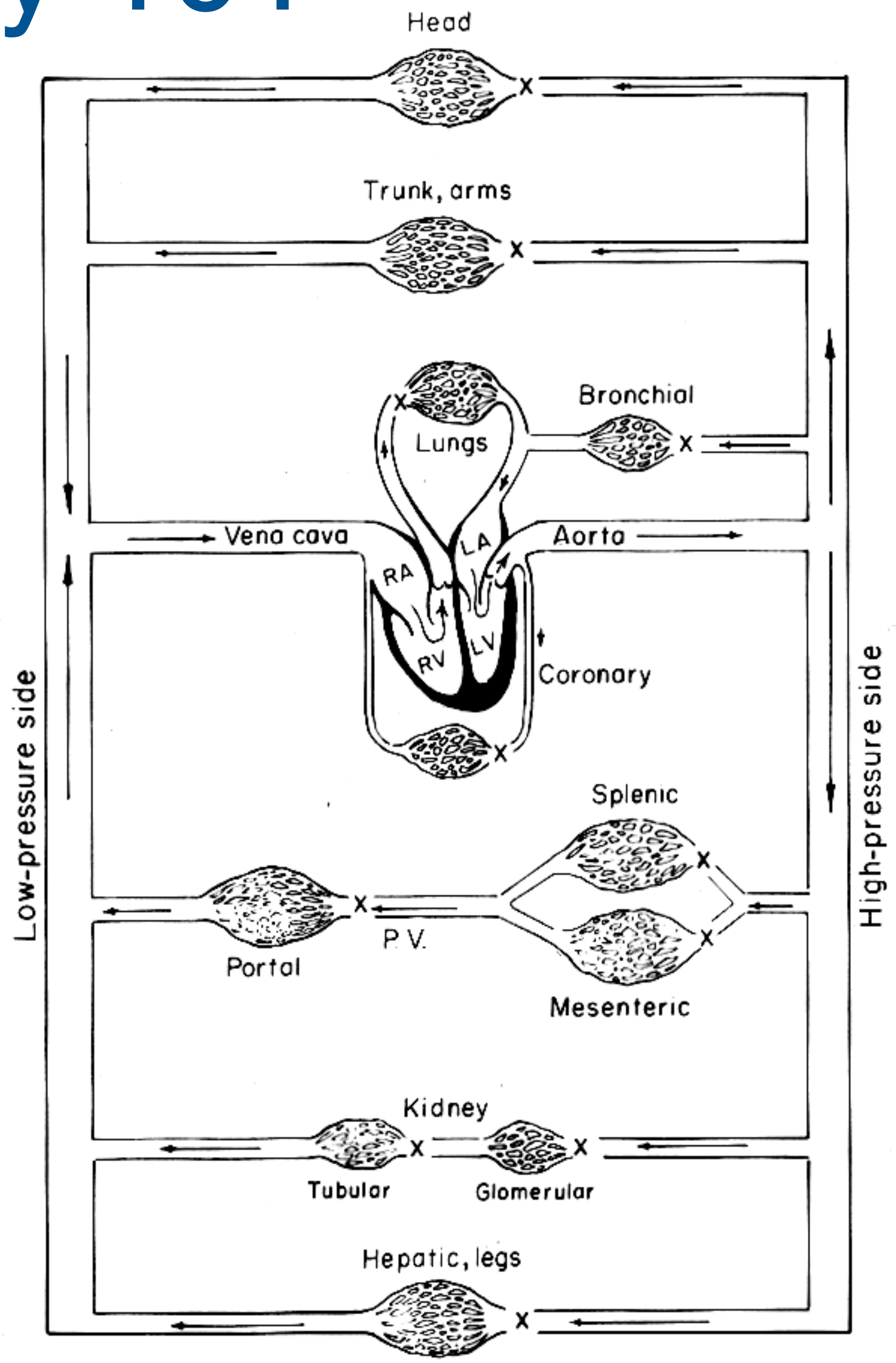


Centers for Disease Control and Prevention
AHA 2014 Statistics Report, Circulation

Anatomy 101

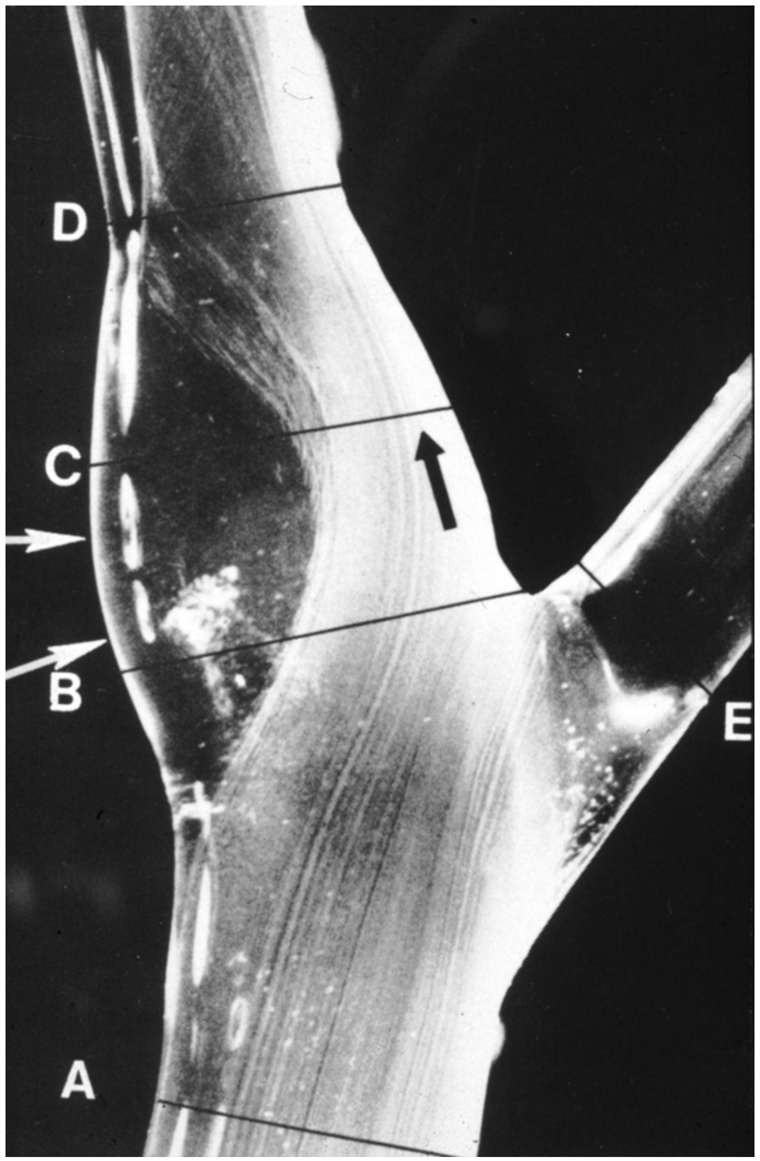


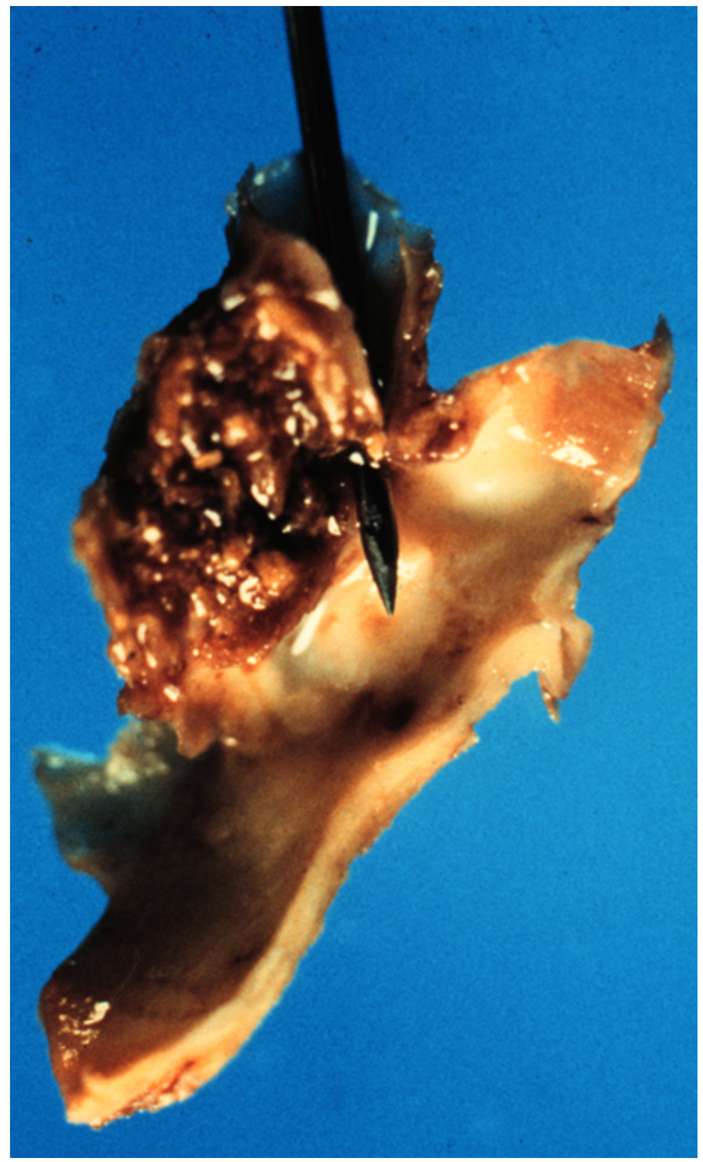
Superior Vena Cava
Aorta
Pulmonary Artery
Pulmonary Vein
Left Atrium
Mitral Valve
Right Atrium
Aortic Valve
Tricuspid Valve
Pulmonary Valve
Left Ventricle
Right Ventricle
Inferior Vena Cava

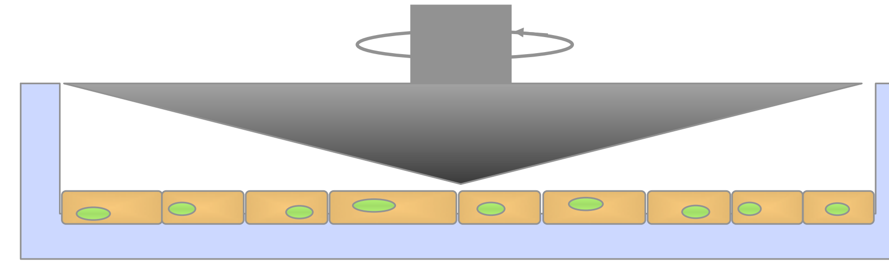


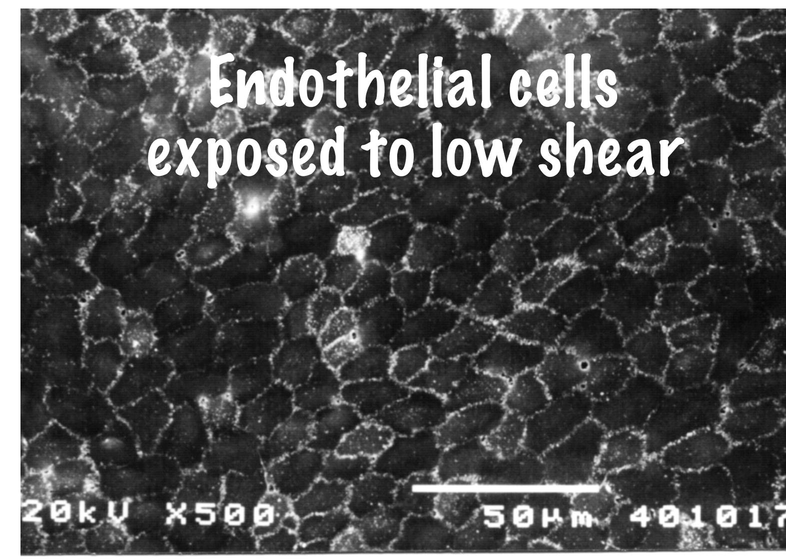
Head
Trunk, arms
Bronchial
Lungs
Vena cava
Aorta
RA
LA
RV
LV
Coronary
Splenic
Portal
P.V.
Mesenteric
Kidney
Tubular
Glomerular
Hepatic, legs
Low-pressure side
High-pressure side

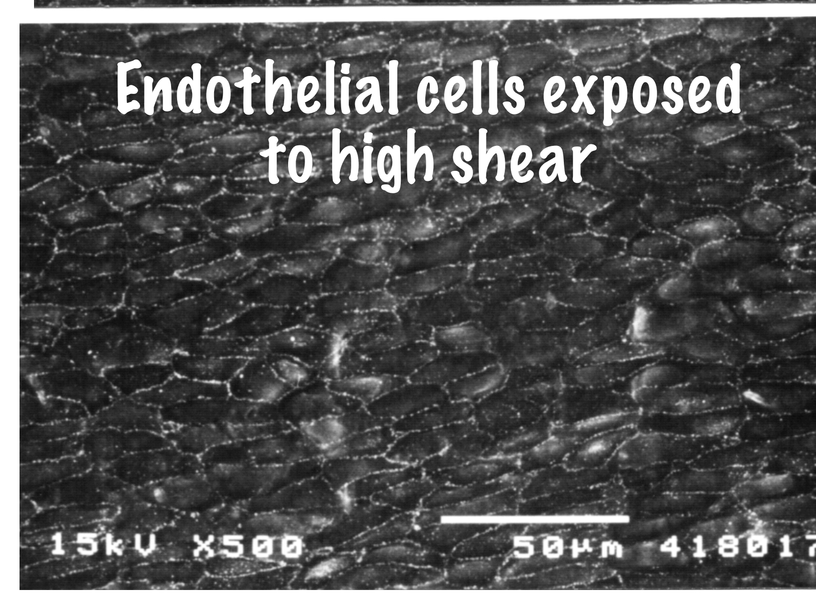
Mechanical Forces Alter Disease Progression





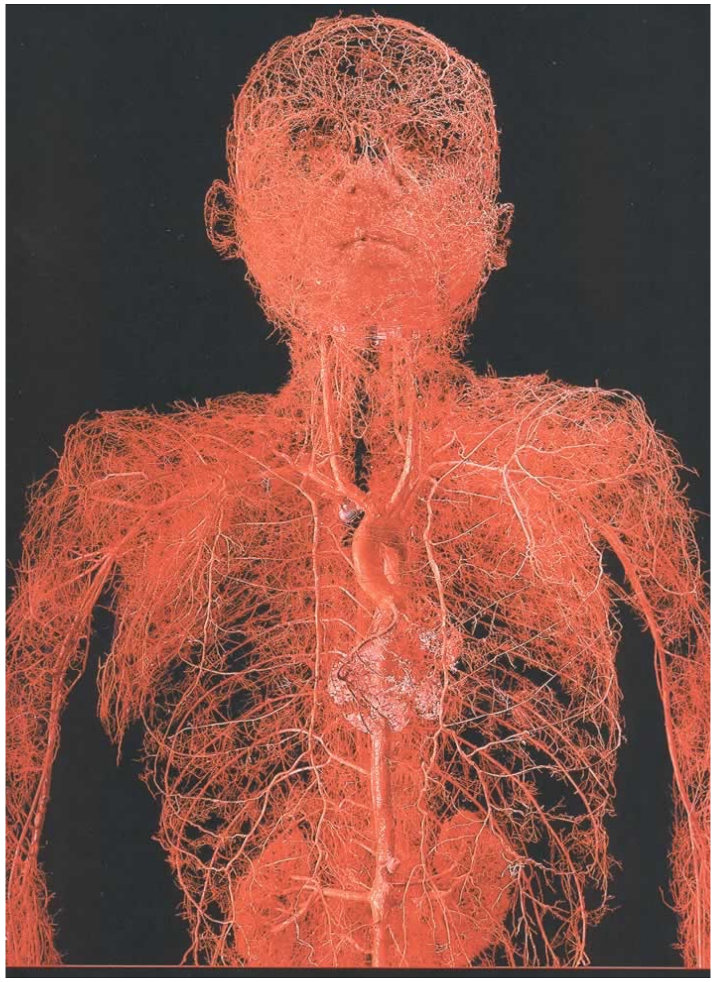


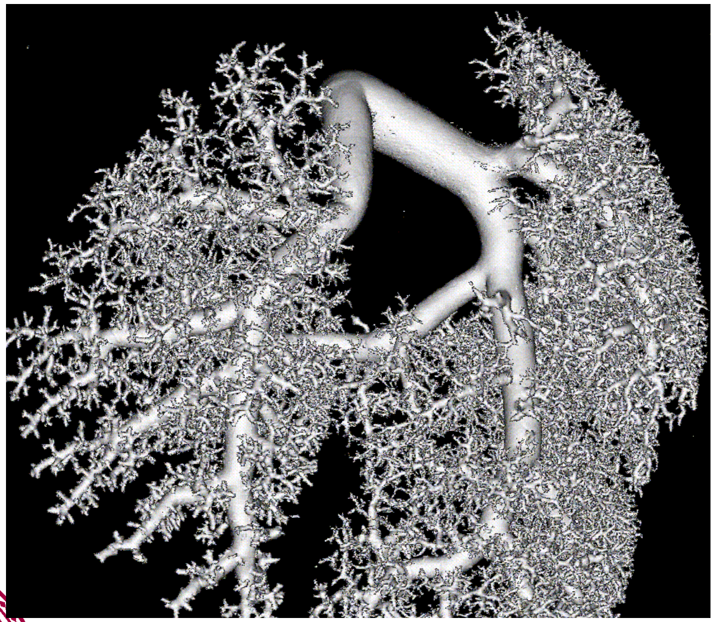




Glagov S., Zarins C.K., Giddens D.P., Ku D.N. (1988) Establishing the Hemodynamic Determinants of Human Plaque Configuration, Composition and Complication. Role of Blood Flow in Atherogenesis. Springer.

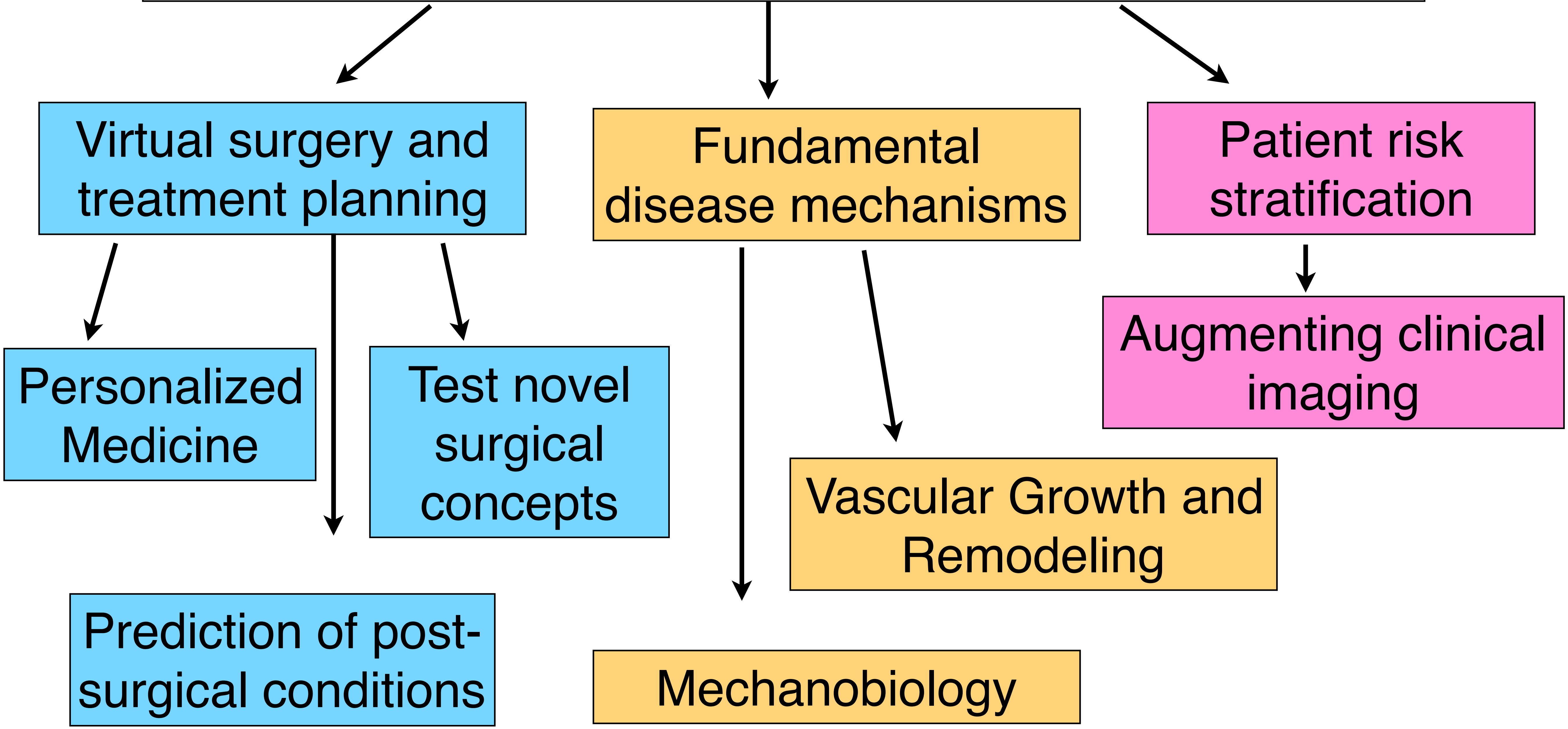
Cardiovascular System Complexity



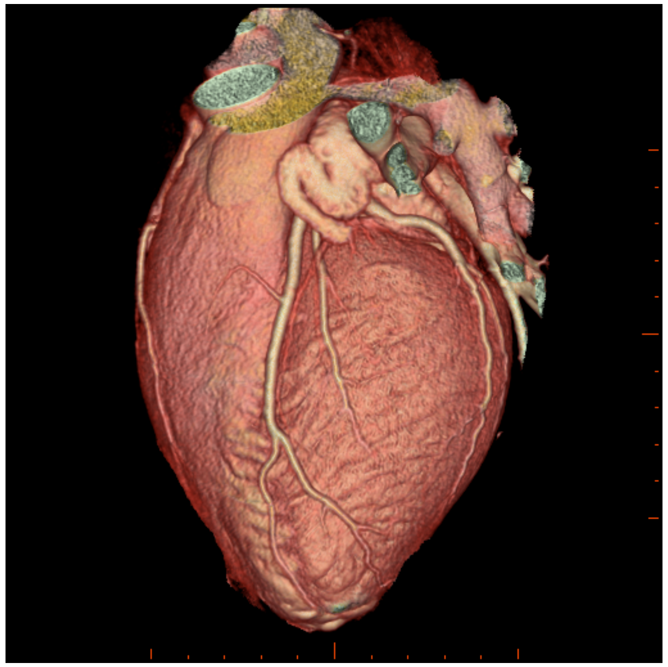


- Cardiovascular system is comprised of billions of blood vessels
    - Most are beyond the limits of our imaging resolution
- Transport and delivery system for oxygen, nutrients, hormones
- Adaptive and dynamic
    - Fluid and solid mechanics
    - Biological response - mechanobiology
    - Physiology
- Health and disease models

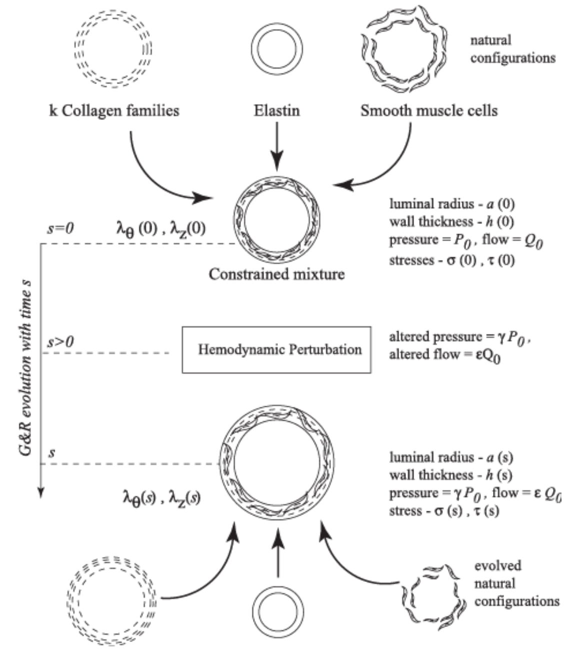
Motivation for Cardiovascular Modeling



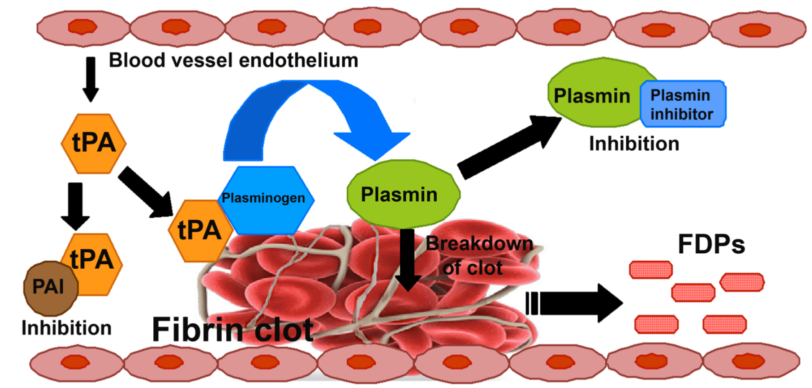
Cardiovascular Modeling: Physics



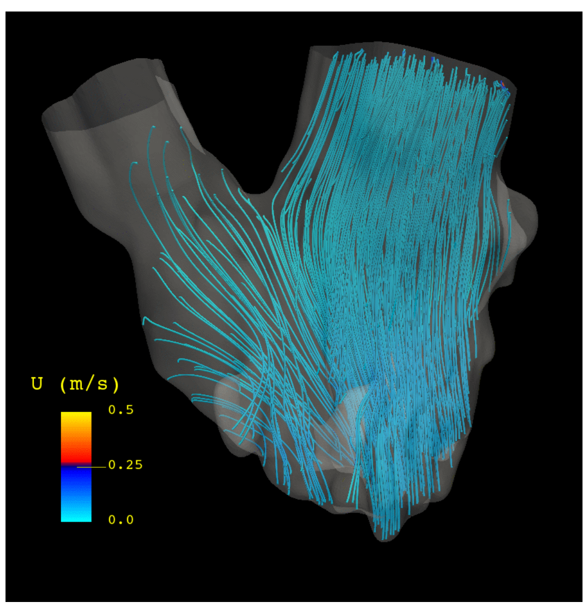
Multi-physics, Multi-scale



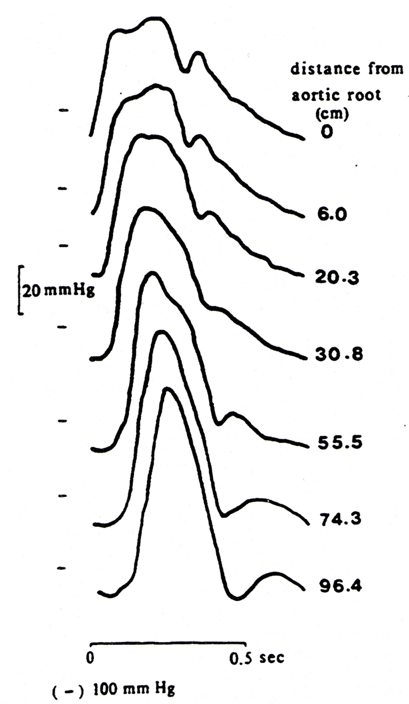
Vascular Mechanobiology



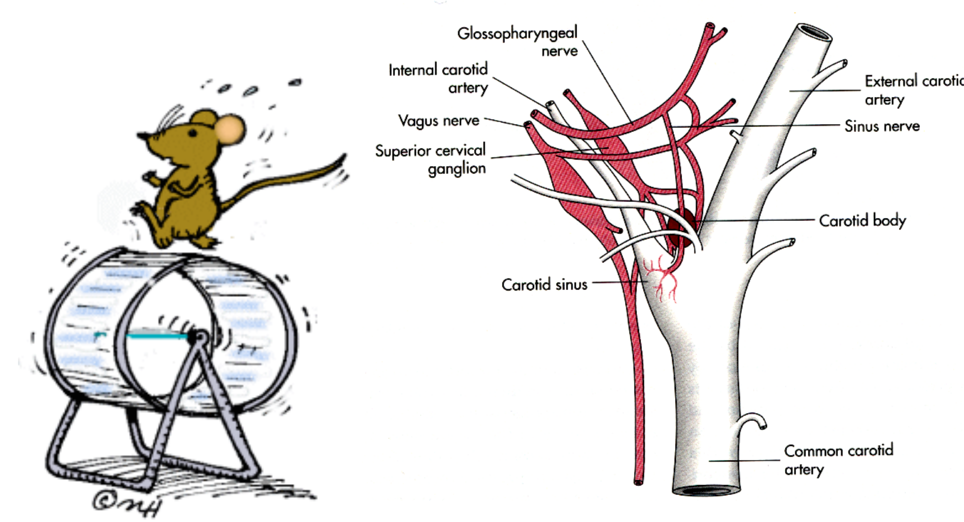
Thrombosis and Biochemistry



Fluid-structure interaction

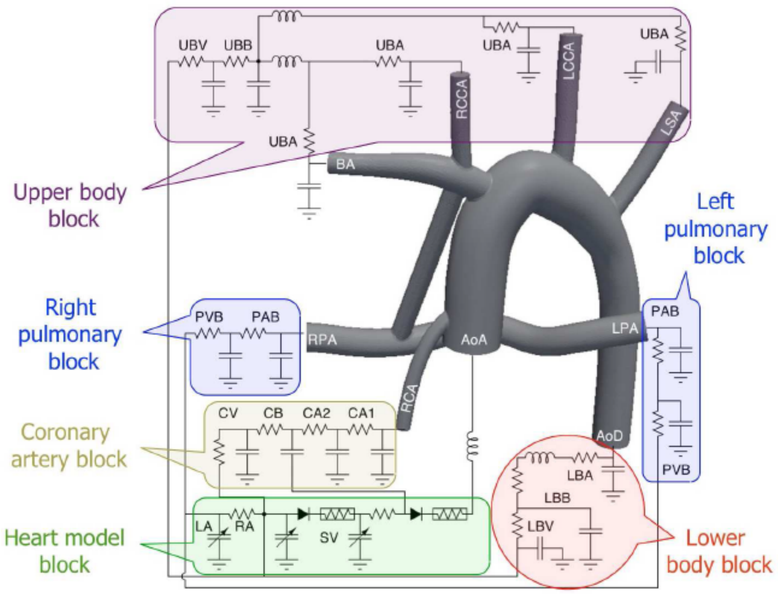


Wave Propagation

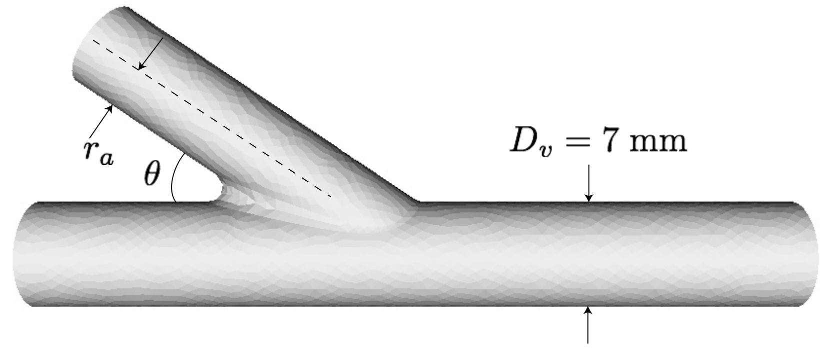


Autoregulation and Adaptation

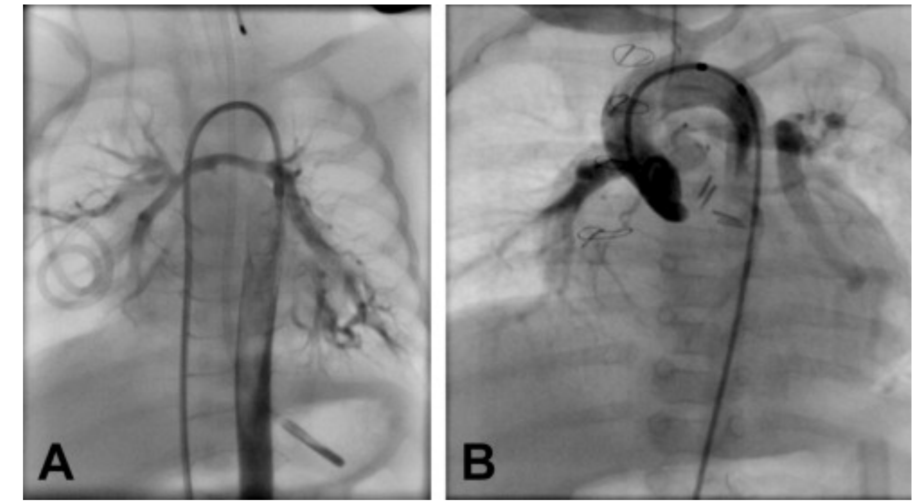
Cardiovascular Modeling: Tools



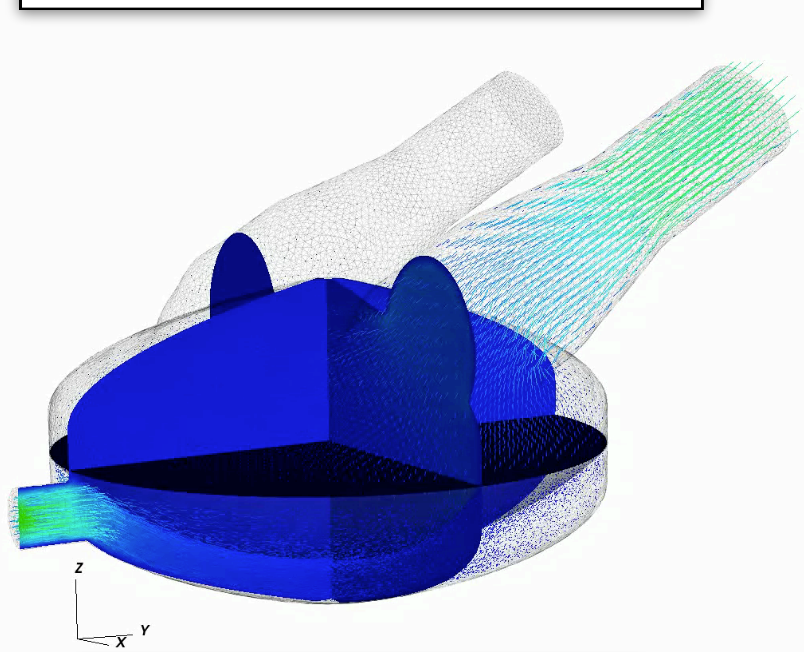
Physiology and clinical data



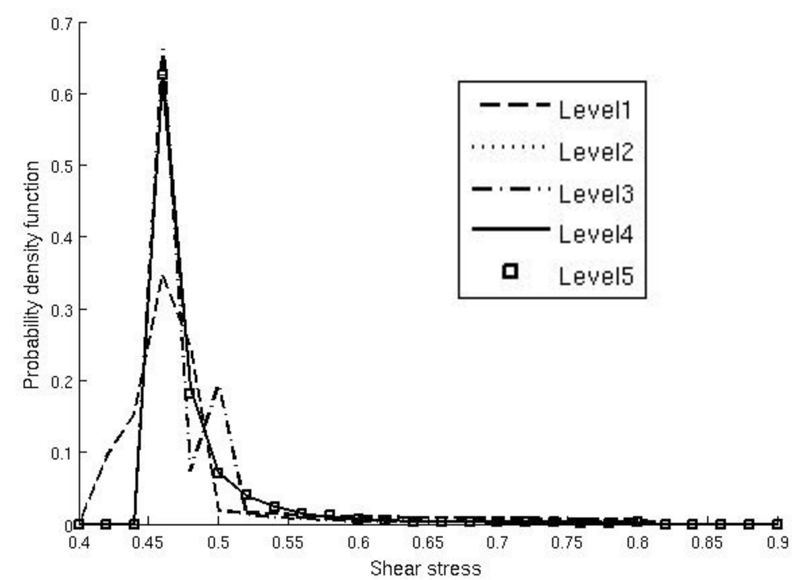
Shape Optimization



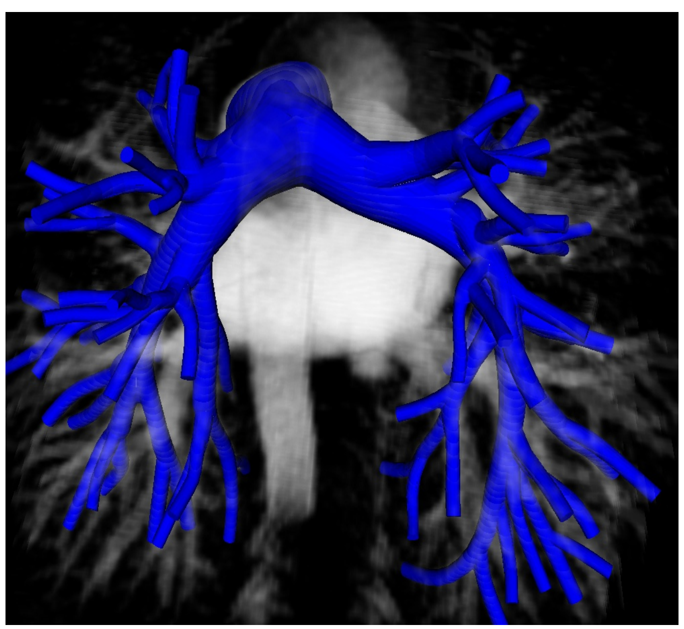
Predicting Clinical Outcomes



Medical Device Design



Uncertainty Quantification

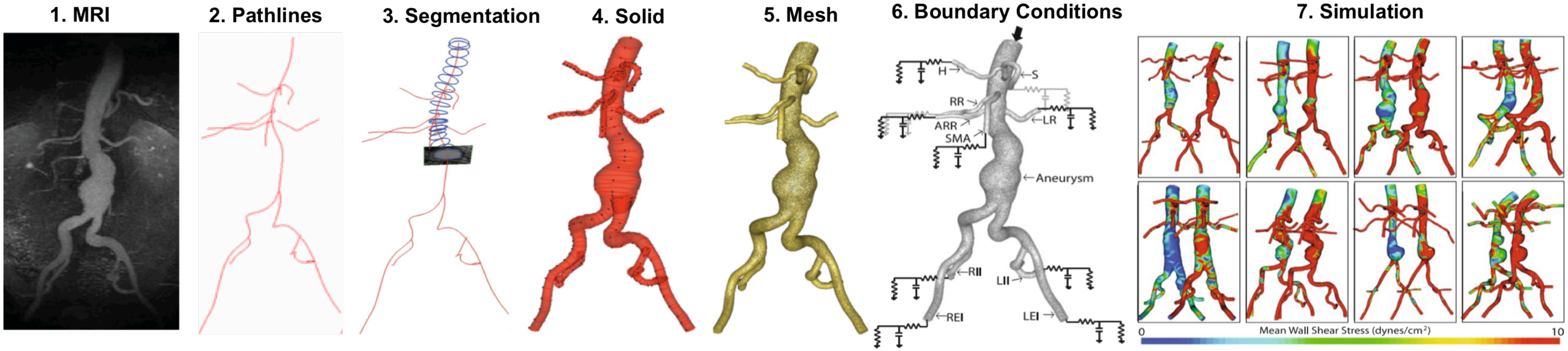


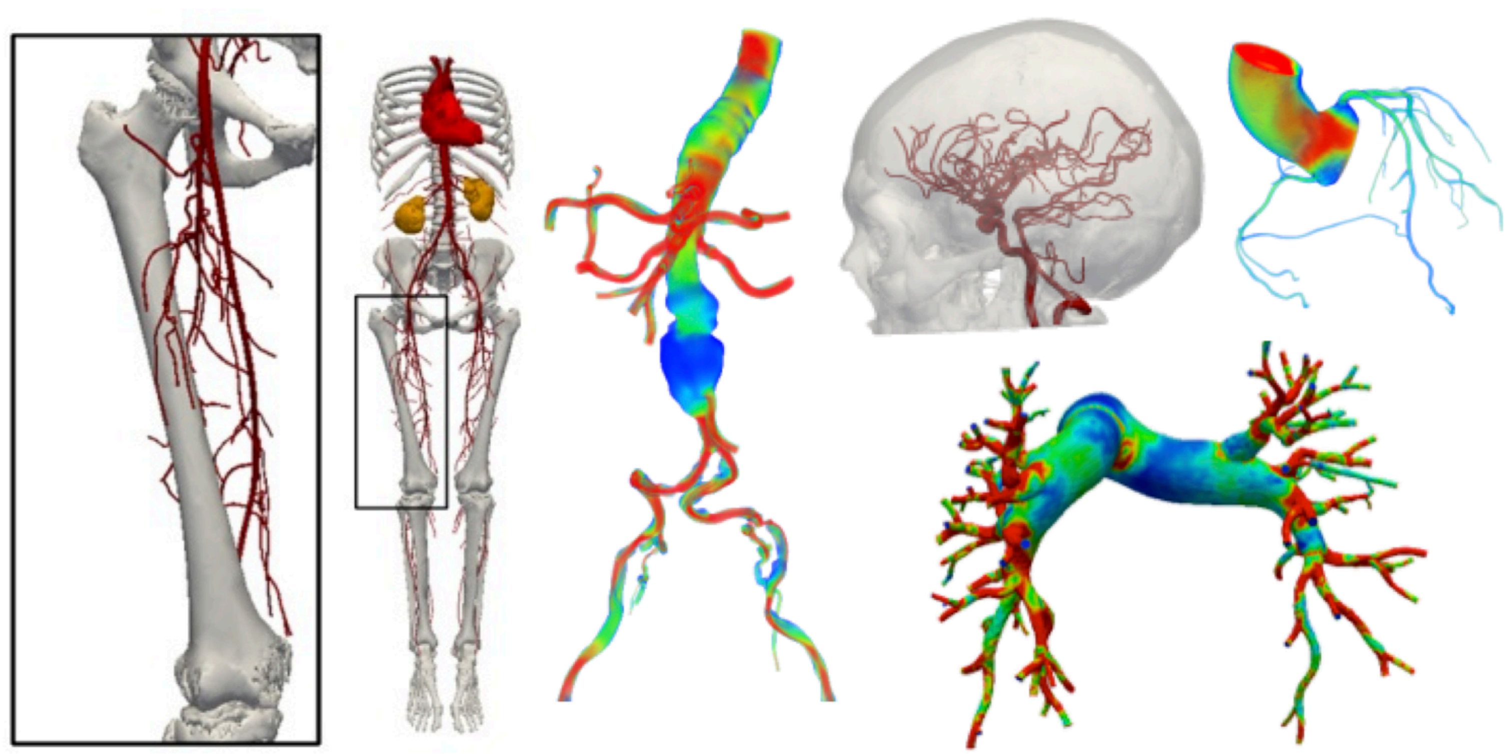
Machine Learning for Image Segmentation

Computational Methods

Making Patient-Specific Predictions

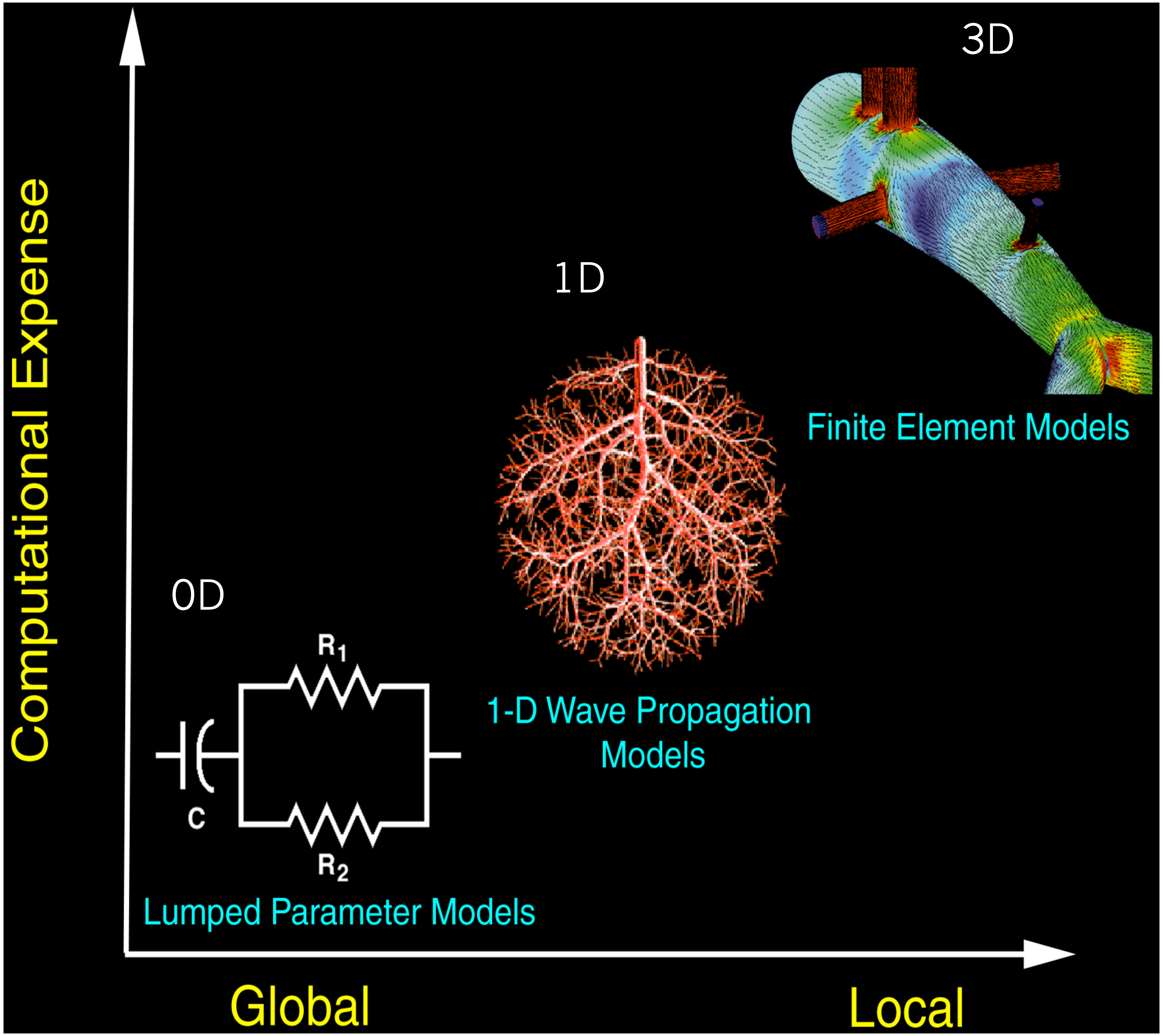
Patient-Specific Modeling





Updegrove, A., Wilson, N.M., Merkow, J., Lan, H., Marsden, A.L., Shadden, S. C., “SimVascular - An Open Source Pipeline for Cardiovascular Simulation,” *Annals of Biomedical Engineering*, Vol 45 (3), pp. 525-541, (2017).

Cardiovascular Model Fidelity



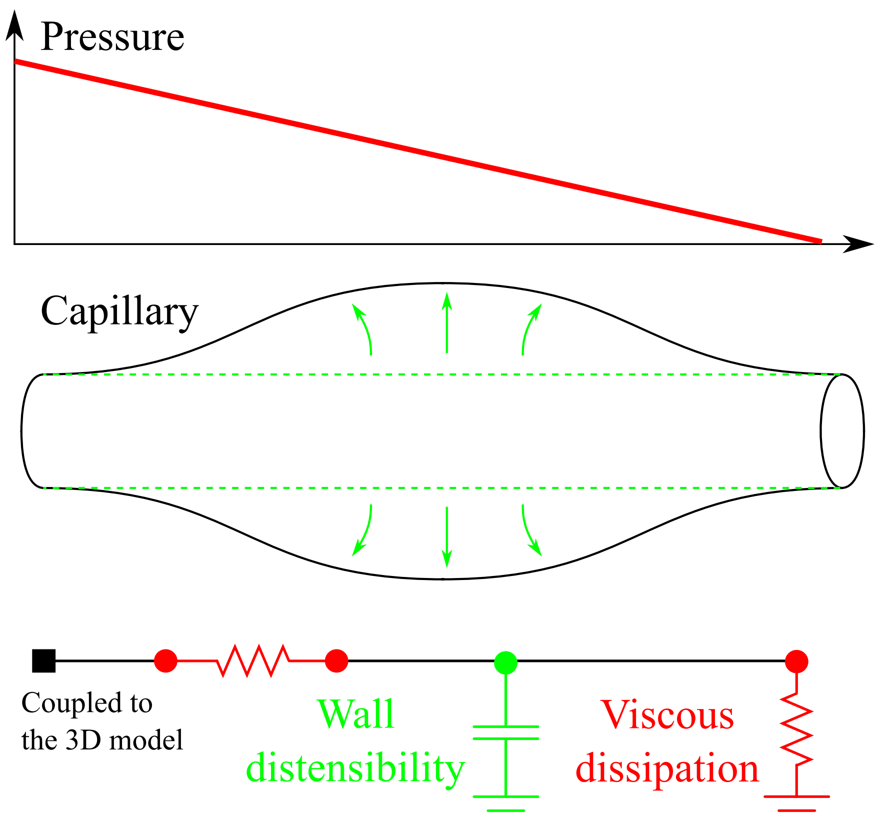
0D Lumped Parameter Circuits

Circuit Analogy:

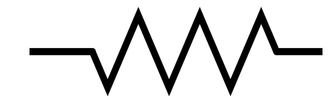
Flow ⟷ Current

Pressure Drop ⟷ Voltage

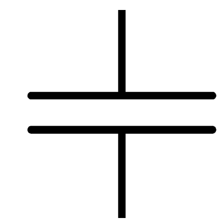
Ohm's Law V=IR



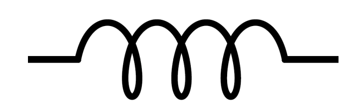
$$\Delta P = RQ$$



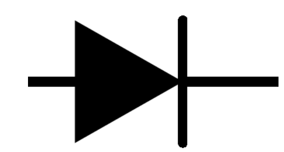
$$Q = C\frac{\mathrm{d}P}{\mathrm{d}t}$$



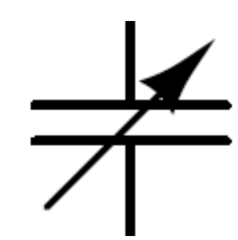
$$\Delta P = L\frac{\mathrm{d}Q}{\mathrm{d}t}$$



$$Q = \frac{|Q| + Q}{2}$$



$$P = A(t)E(V - V_0) + P_0\left(e^{K(V-V_0)} - 1\right)$$

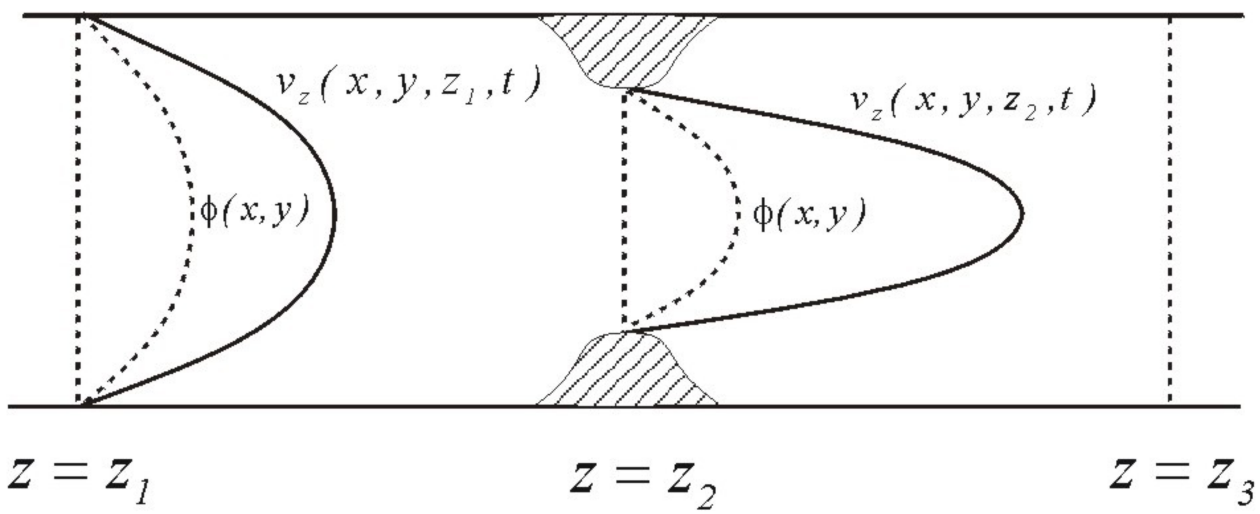


1D Wave Propagation Models

NS Eqs: Conservation of mass and momentum

$$\frac{\partial u_z}{\partial z} + \frac{1}{r}\frac{\partial}{\partial r}(r u_r) + \frac{1}{r}\frac{\partial}{\partial \theta}(u_\theta) = 0$$

$$\frac{\partial u_z}{\partial t} + u_z \frac{\partial u_z}{\partial z} + u_r \frac{\partial u_z}{\partial r} + \frac{u_\theta}{r}\frac{\partial u_z}{\partial \theta} + \frac{1}{\rho}\frac{\partial p}{\partial z} = \frac{\nu}{r}\frac{\partial}{\partial r}(r\frac{\partial u_z}{\partial r}) + \nu\frac{\partial^2 u_z}{\partial z^2} + \frac{\nu}{r^2}\frac{\partial^2 u_z}{\partial \theta^2}$$



Integrate over vessel cross section
Assume parabolic velocity profile

$$\frac{\partial A}{\partial t} + \frac{\partial Q}{\partial z} = 0$$

$$\frac{\partial Q}{\partial z} + \frac{\partial}{\partial z}\left(\frac{4}{3}\frac{Q^2}{A}\right) + \frac{A}{\rho}\frac{\partial P}{\partial z} = -8\pi\nu\frac{Q}{A} + \nu\frac{\partial^2 Q}{\partial z^2}$$

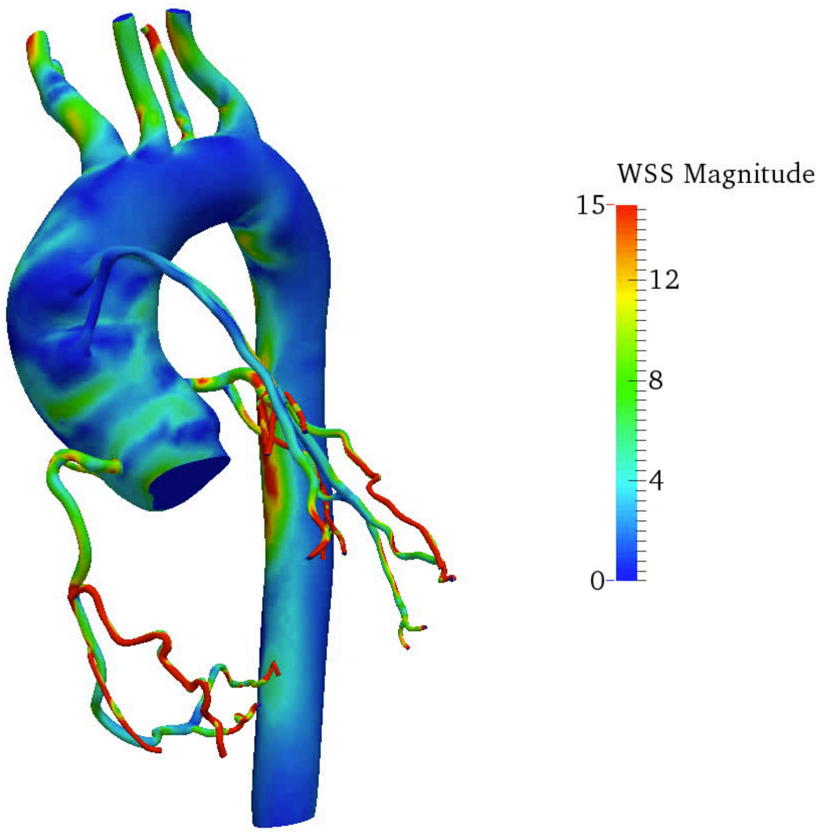
1D PDE for flow rate and area

Hughes and Lubliner, Mathematical Biosciences, 1973

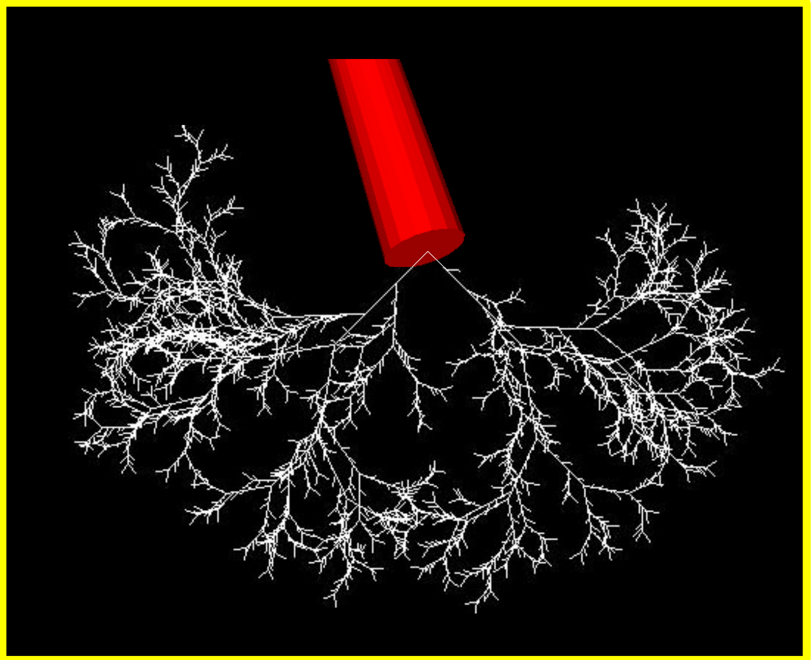
3D Computational Fluid Dynamics

$$\rho \vec{v}_{,t} + \rho \vec{v} \cdot \nabla \vec{v} = -\nabla p + \nabla \cdot \tau + \vec{f}$$
$$\nabla \cdot \vec{v} = 0$$

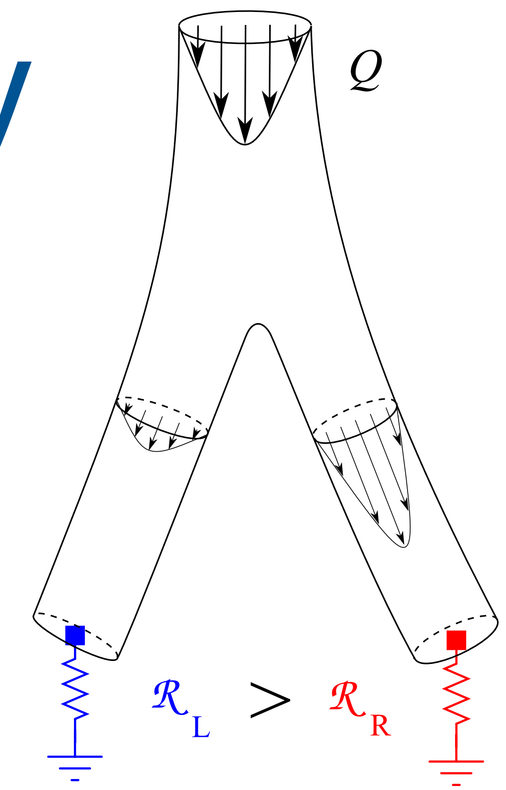
$$\begin{bmatrix} \boldsymbol{K} & \boldsymbol{G} \\ \boldsymbol{D} & \boldsymbol{L} \end{bmatrix} \begin{bmatrix} \boldsymbol{y}_{\mathrm{u}} \\ \boldsymbol{y}_{\mathrm{p}} \end{bmatrix} = - \begin{bmatrix} \boldsymbol{R}_{\mathrm{m}} \\ \boldsymbol{R}_{\mathrm{c}} \end{bmatrix}$$



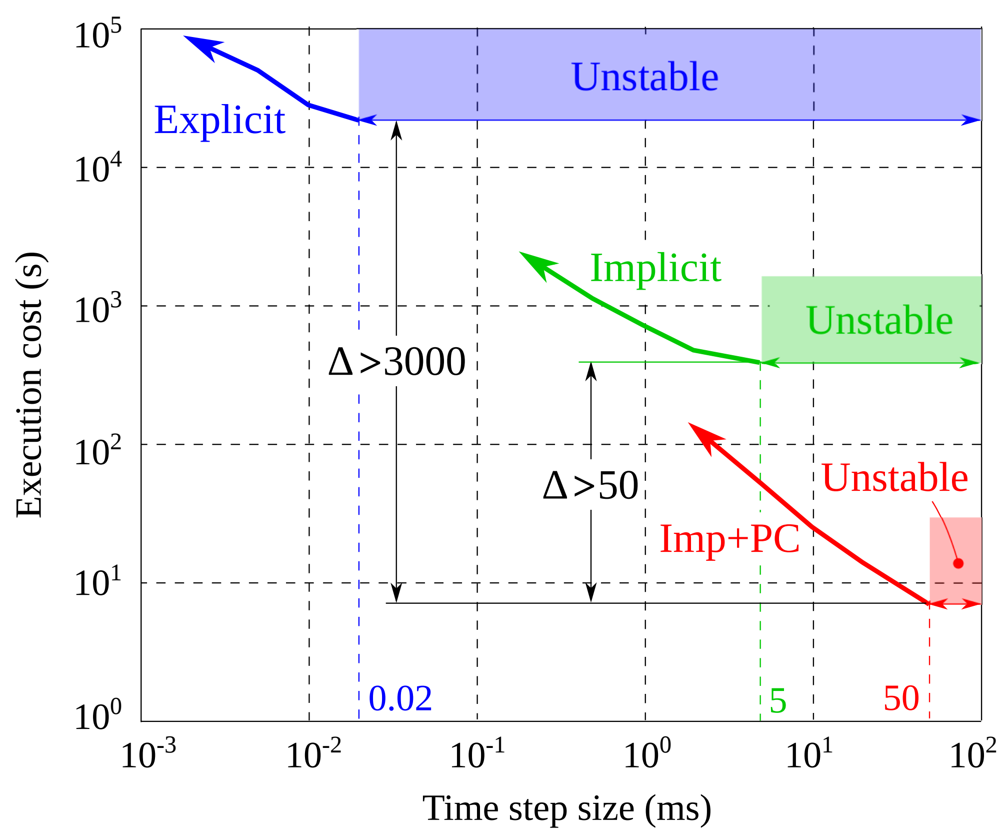
- Finite element method SUPG
- Generalized-alpha time discretization
- Linear tetrahedral elements
- Physiologic boundary conditions



Solver Methodology



- Implicit coupling to LPN BCs
- Backflow stabilization
- Fluid structure interaction with
  - Coupled momentum method
  - ALE for large deformations
- Variable wall material properties: thickness, elastic modulus
- Custom linear solver with resistance-based preconditioner



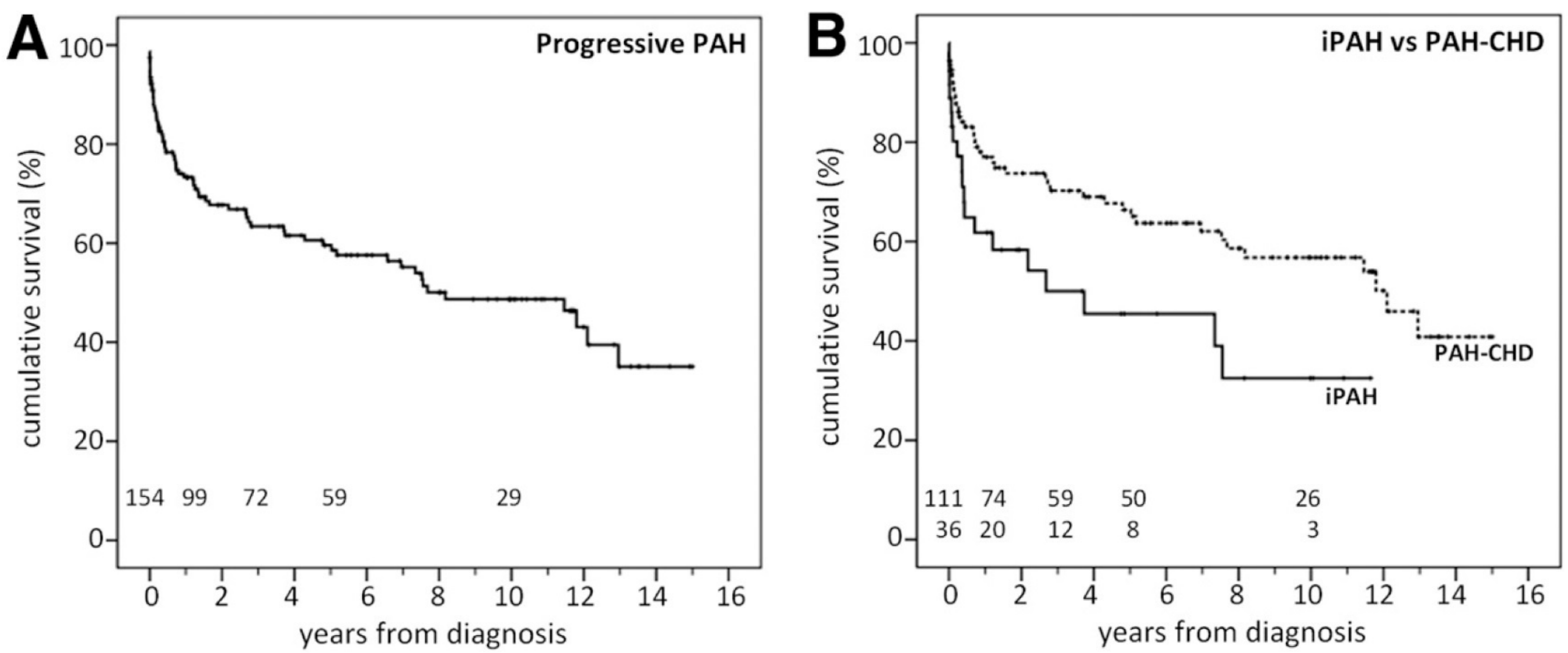
Esmaily-Moghadam, Bazilevs, Marsden, Comp. Mech. 2013
Marsden and Esmaily Moghadam, AMR, 2015
Figueroa and Taylor, CMAME 2006

Clinical Examples

Pulmonary Hypertension

Pulmonary Hypertension

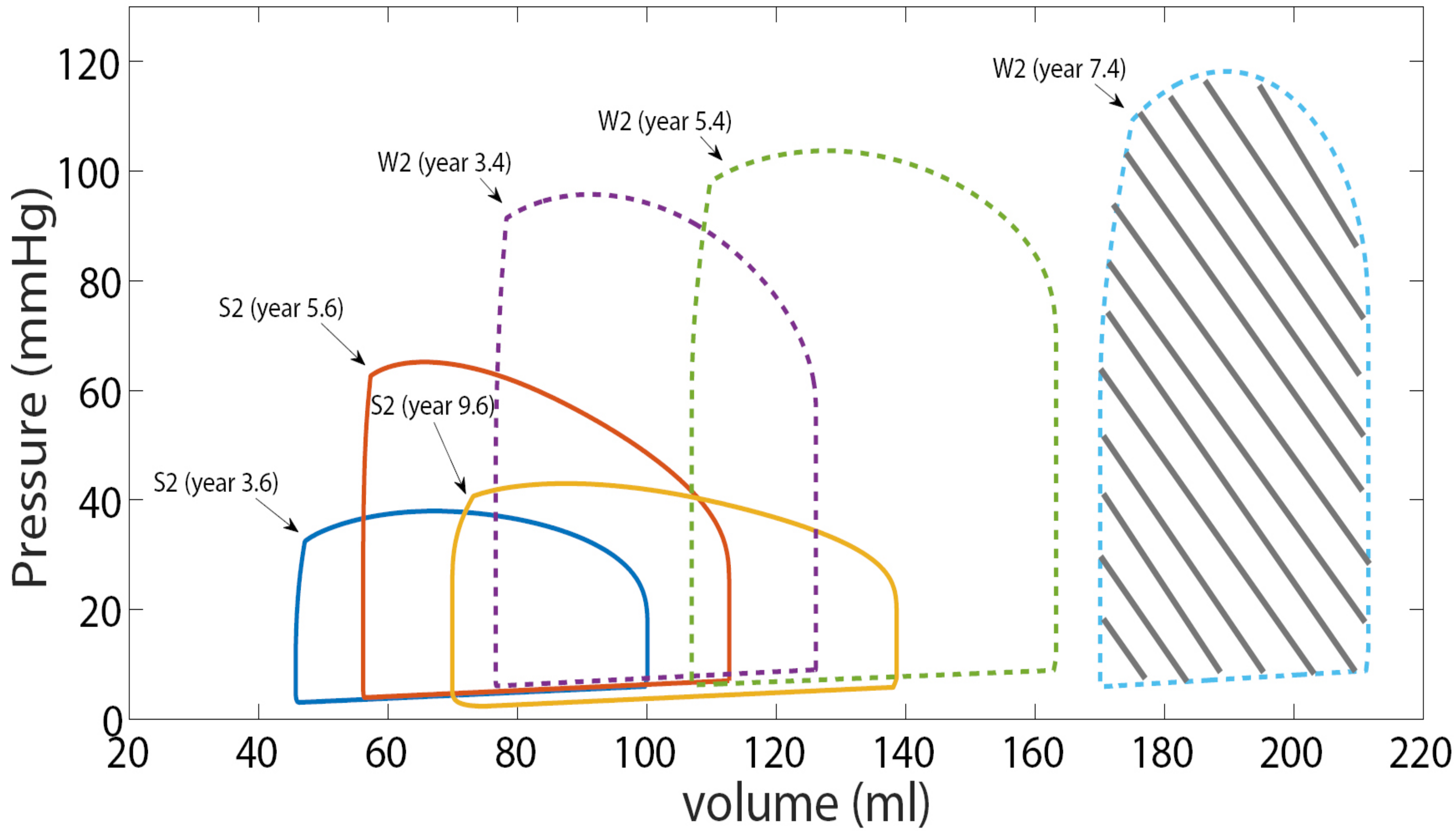
- Severely elevated pulmonary pressure >25mmHg and vascular resistance >3WU
- Progression is highly variable and poorly understood **(5-year survival rates: 60-70%).**
- Need predictive tools for clinical decision making
  - When to list patients for transplant?



Van Loon et al., Circulation, 2011

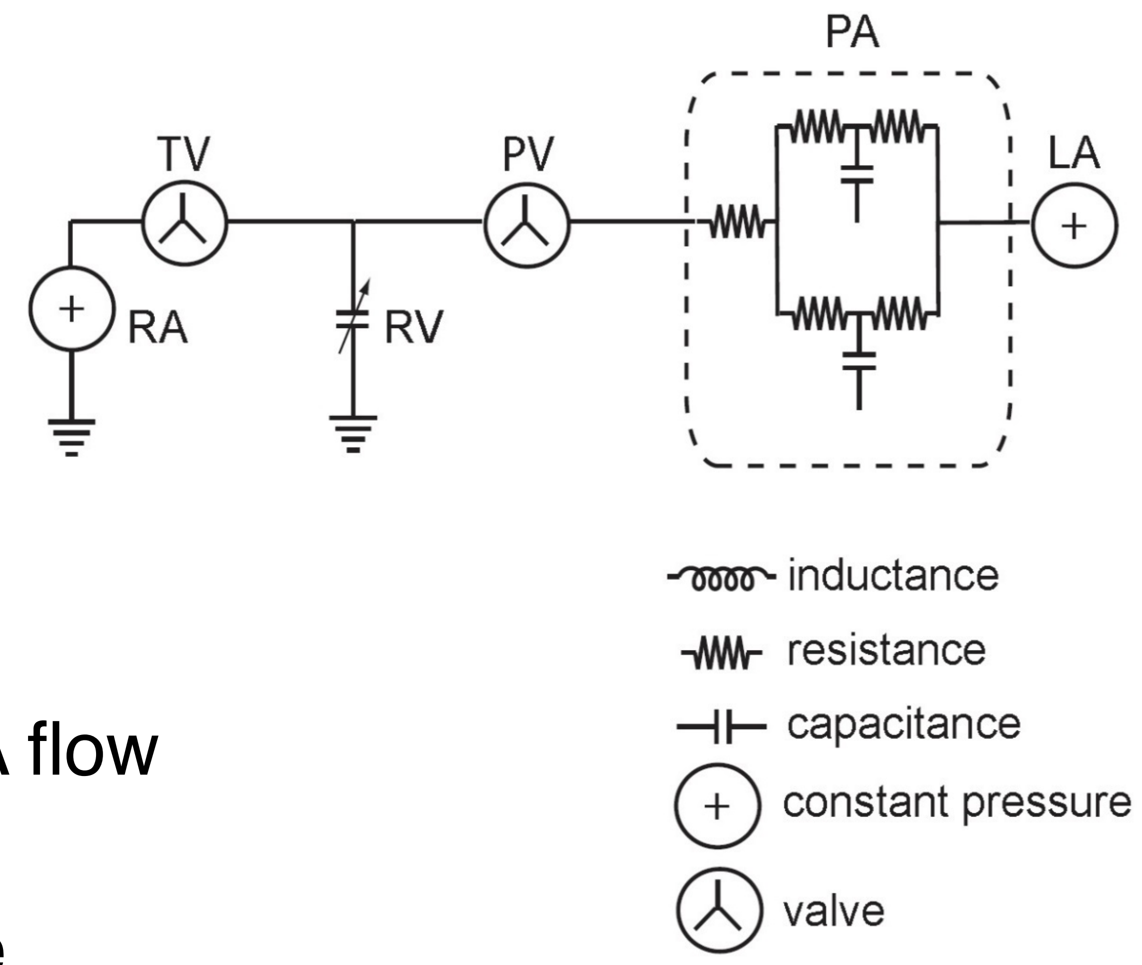
Right Ventricular Stroke Work

- Stroke work found from area enclosed in cardiac pressure-volume loop
  - Work done by the heart in each beat
- Challenging to measure routinely in clinic
- Use LPN heart model to compute RVSW from clinical data



Tuning to clinical data

- Right heart catheterization (RHC):
  - RV and PA pressures
- Magnetic resonance imaging (MRI):
  - RV volumes (EDV and ESV) and PA flow
- Lumped parameter network (LPN): use electric circuits to model hemodynamics
- Tune LPN to match clinical data with optimization



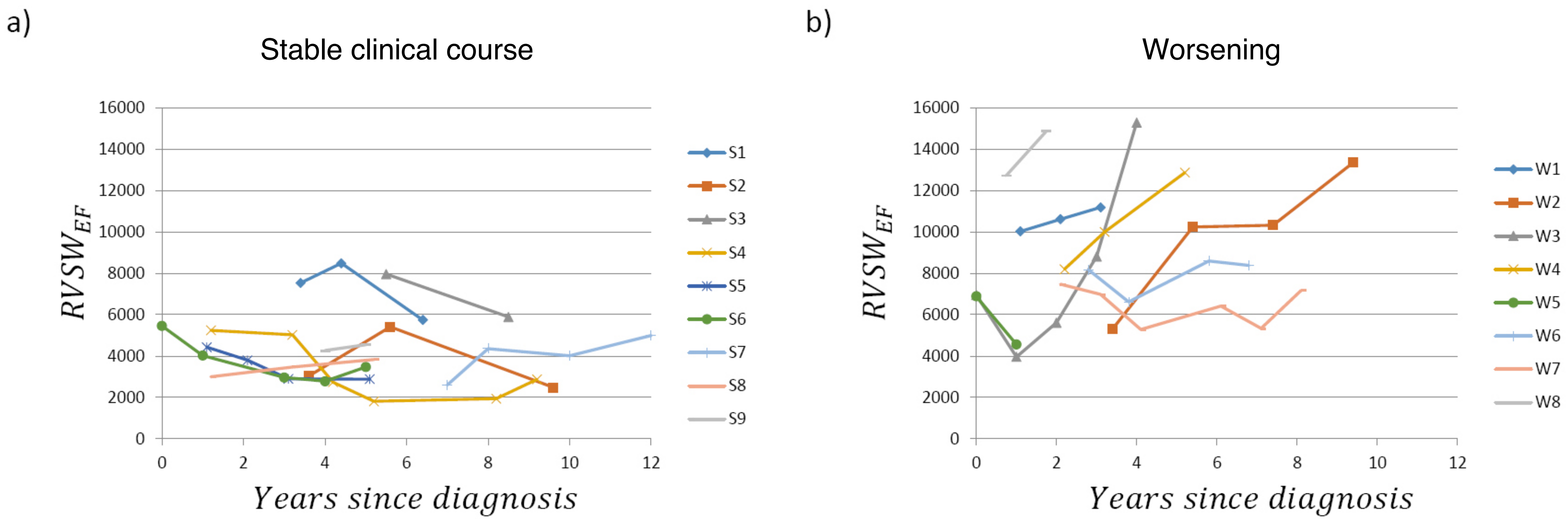
Study Design: Inclusion Criteria

	Stable n=9	Worsening* n=8
Male	n=4	n=4
IPAH	n=5	n=7
Follow-up:	4.2 (1.2-8)	3.7 (1.1-6)

- Inclusion criteria
  - Age < 18
  - IPAH or PAH-CHD
  - multiple paired RHC/MRI (n≥2)
  - 17 patients with 61 data points

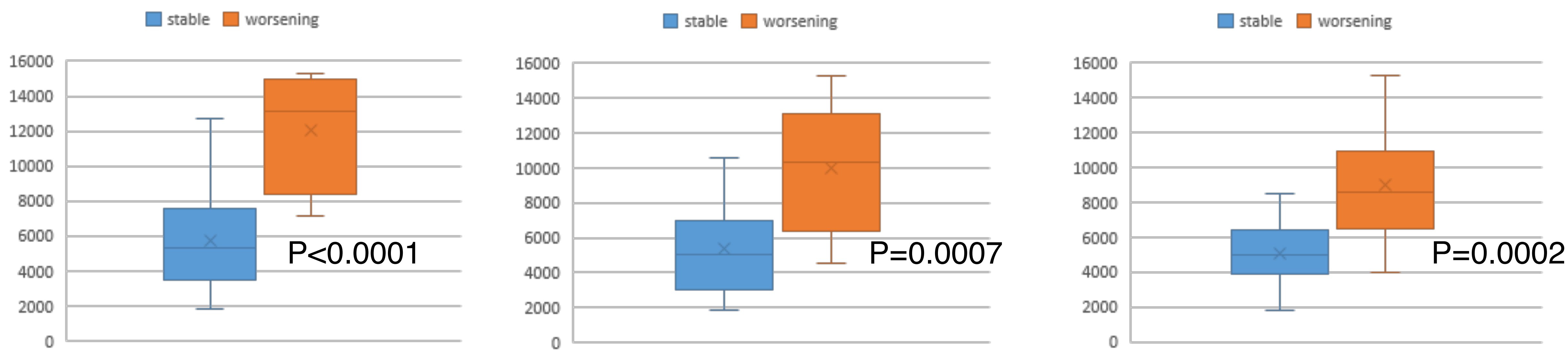
Clinical worsening: death, listed or considered for transplantation, poor hemodynamic responses to maximal therapy

Stroke work and disease progression



Patients with clinical worsening have increased RVSW.

RV Stroke Work predicts Clinical Worsening in PH



1 year 2 years 5 years

RVSW outperformed other standard clinical metrics used to predict the need for heart transplant

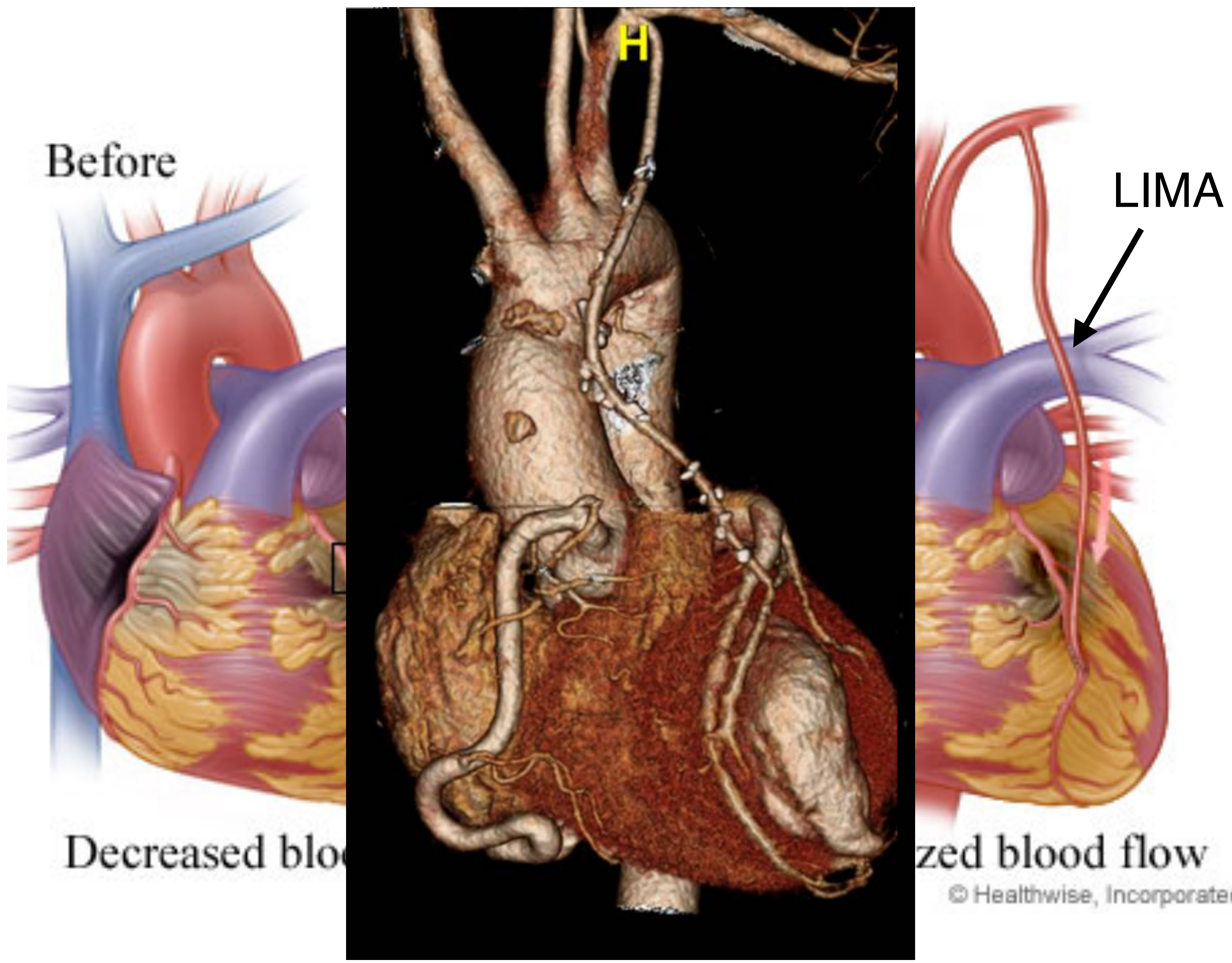
Yang, W., Marsden, A.L., Ogawa, M.T., Sakarovitch,C., Phillips, K. K., Rabinovitch, M., Feinstein, J.A., “Right Ventricular Stroke Work Correlates with Outcomes in Pediatric Pulmonary Arterial Hypertension,” submitted for review.

Clinical Examples

Coronary Artery Bypass Surgery

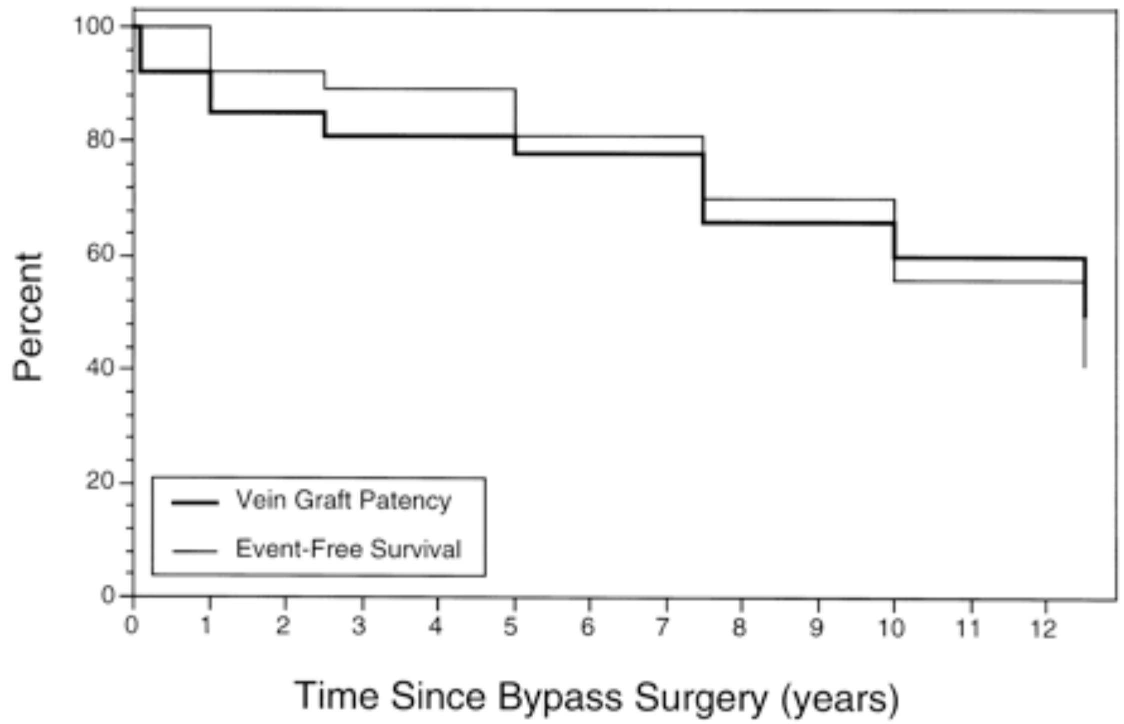
CABG Surgery

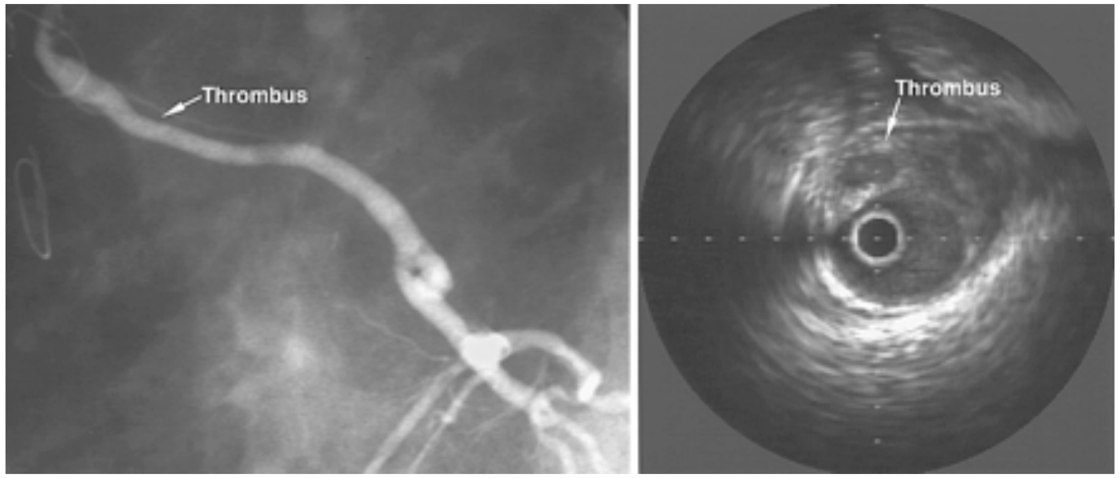
- CABG surgery performed in ~400,000 cases annually in US
- Graft options: arterial graft (LIMA), saphenous vein graft (SVG), artificial grafts
- Most patients require multiple grafts
  - SVGs are used in majority of patients (70%)



CABG: Vein Graft Failure

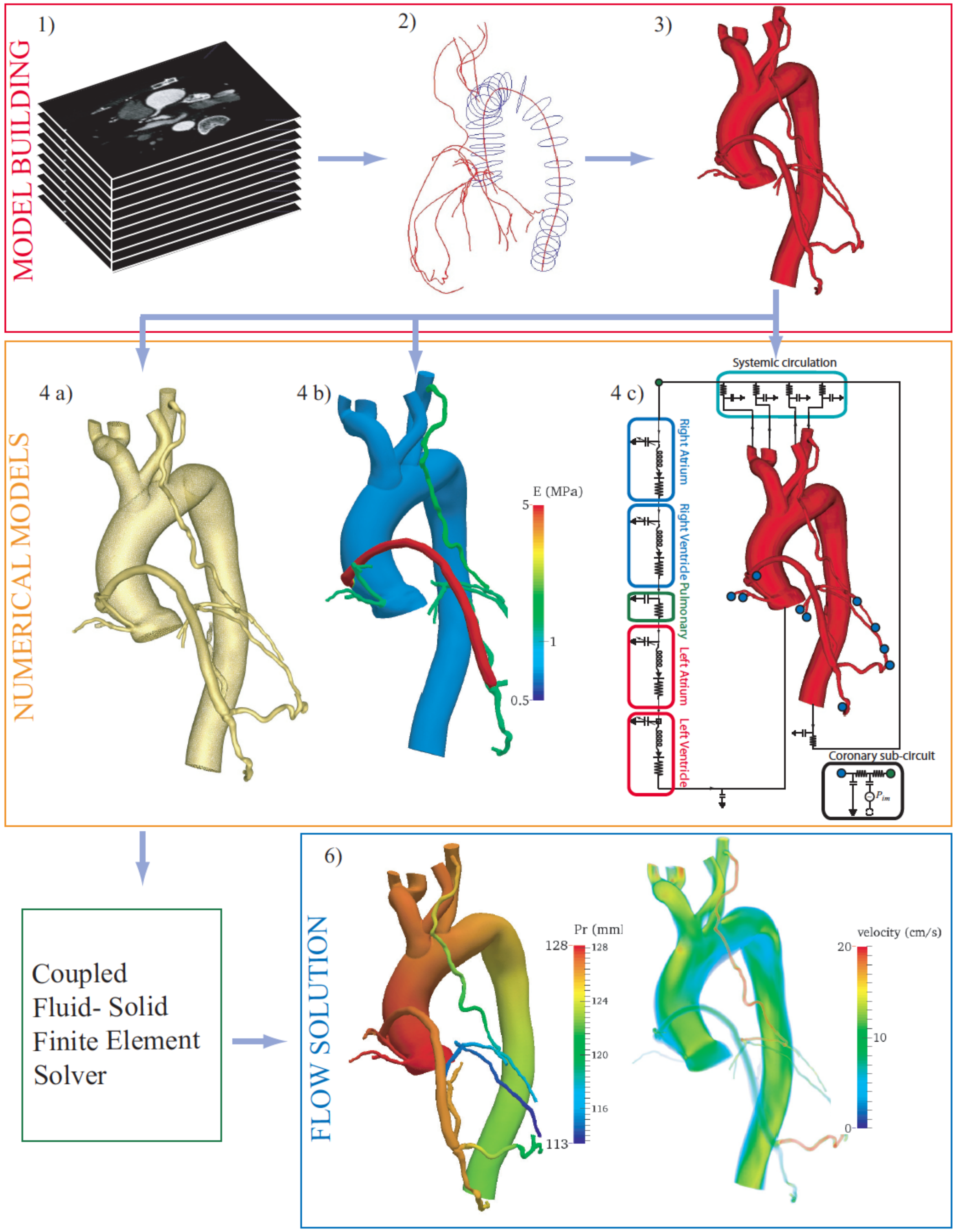
- Vein graft failure is a significant clinical problem
  - 5-10% of SVGs fail within 1 month
  - 40-50% fail within 10 years
- Clamps removed: vein subjected to 20X increase in pressure, 4X increase in flow
  - How does vessel adapt to changing mechanical loads?
- *What hemodynamic and biomechanical conditions lead to vein graft failure?*



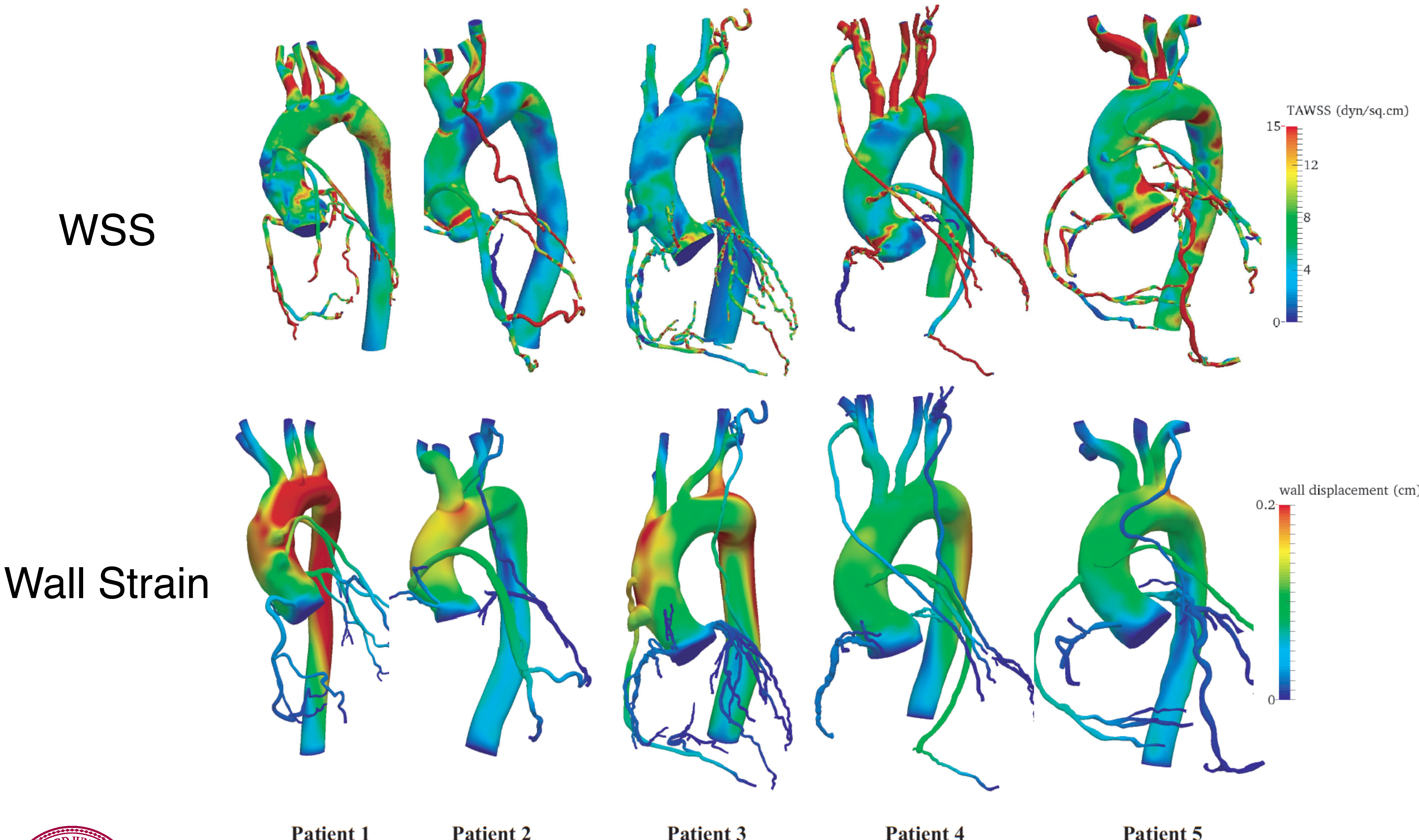


Aortocoronary Saphenous Vein Graft Disease: Pathogenesis, Predisposition, and Prevention, Joseph G. Motwani, MD; Eric J. Topol, MD, Circulation 1998

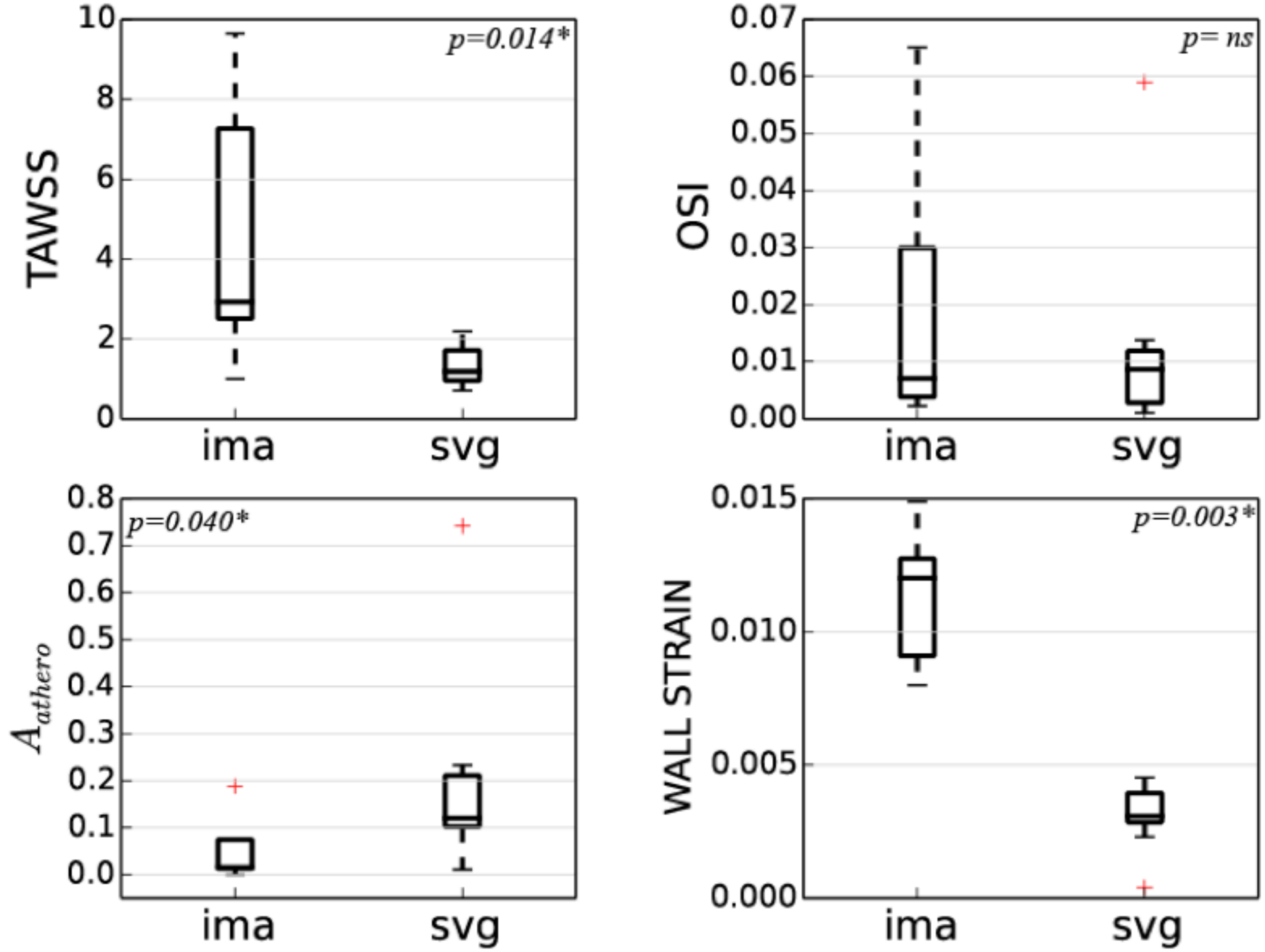
CABG Simulation Pipeline



Simulation Results



Mechanical Stimuli: Arterial vs. Vein Grafts

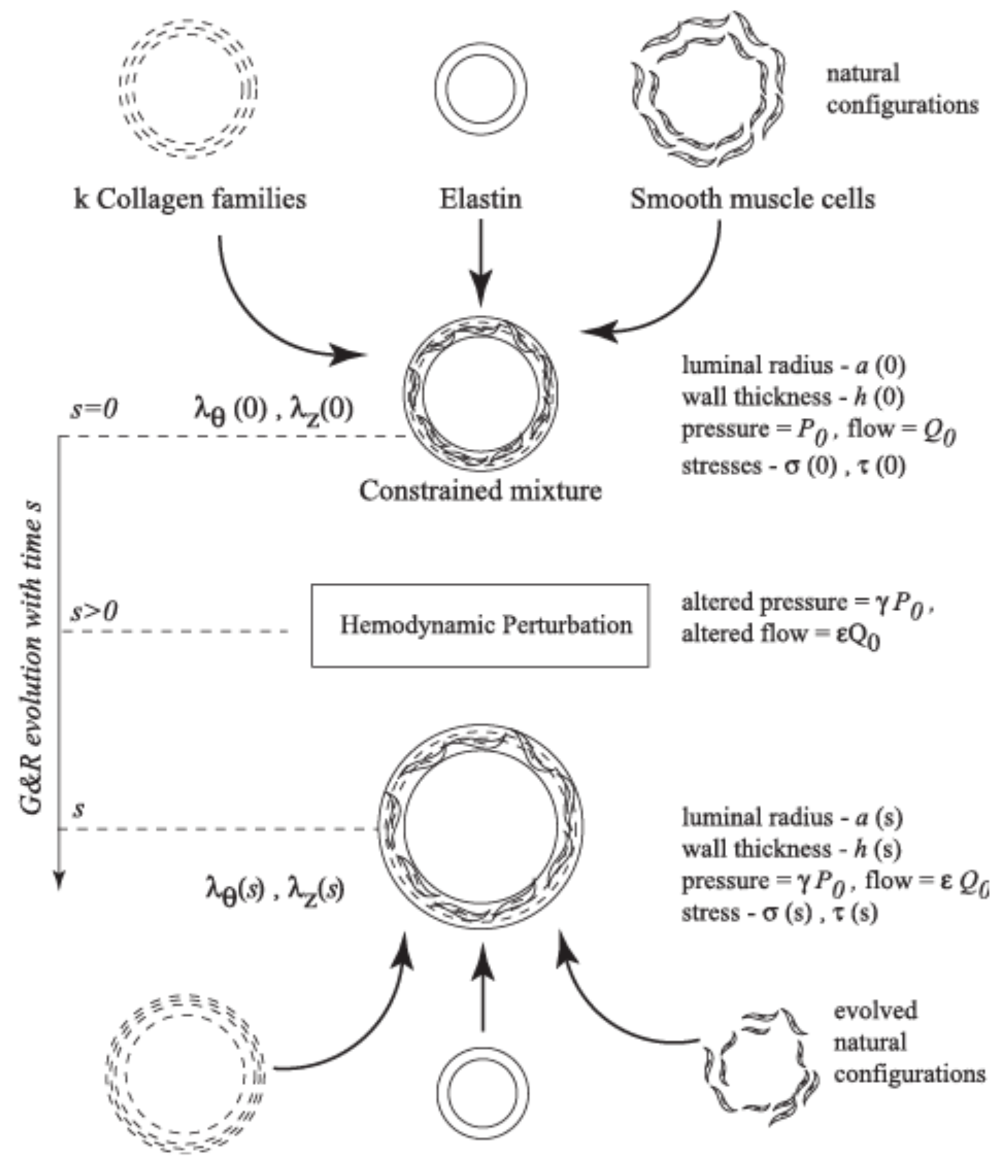


Statistically significant differences in WSS, area of low WSS, wall strain

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).

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

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

Removal

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

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

Evolution

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

Stored Energy

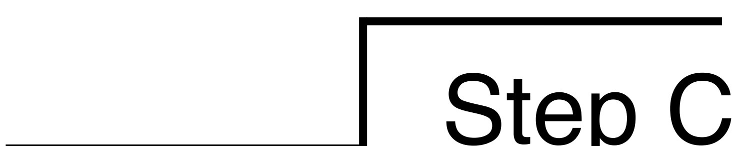
$$W^k(s) = \frac{M^k(0)}{\rho(s)} Q^k(s)\widehat{W^k}(\mathbf{C}_{n(0)}^k(s)) + \int_0^s \frac{m^k(\tau)}{\rho(s)} q^k(s,\tau)\widehat{W^k}(\mathbf{C}_{n(\tau)}^k(s))d\tau,$$

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

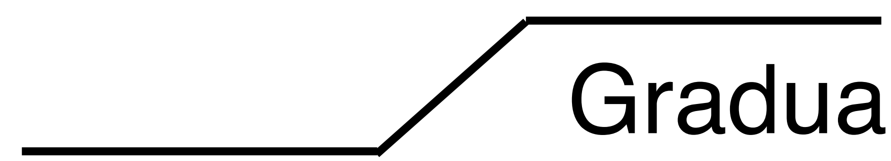
Could gradual loading ameliorate vein maladaptation?

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

Measure deviation from homeostasis



Step Change



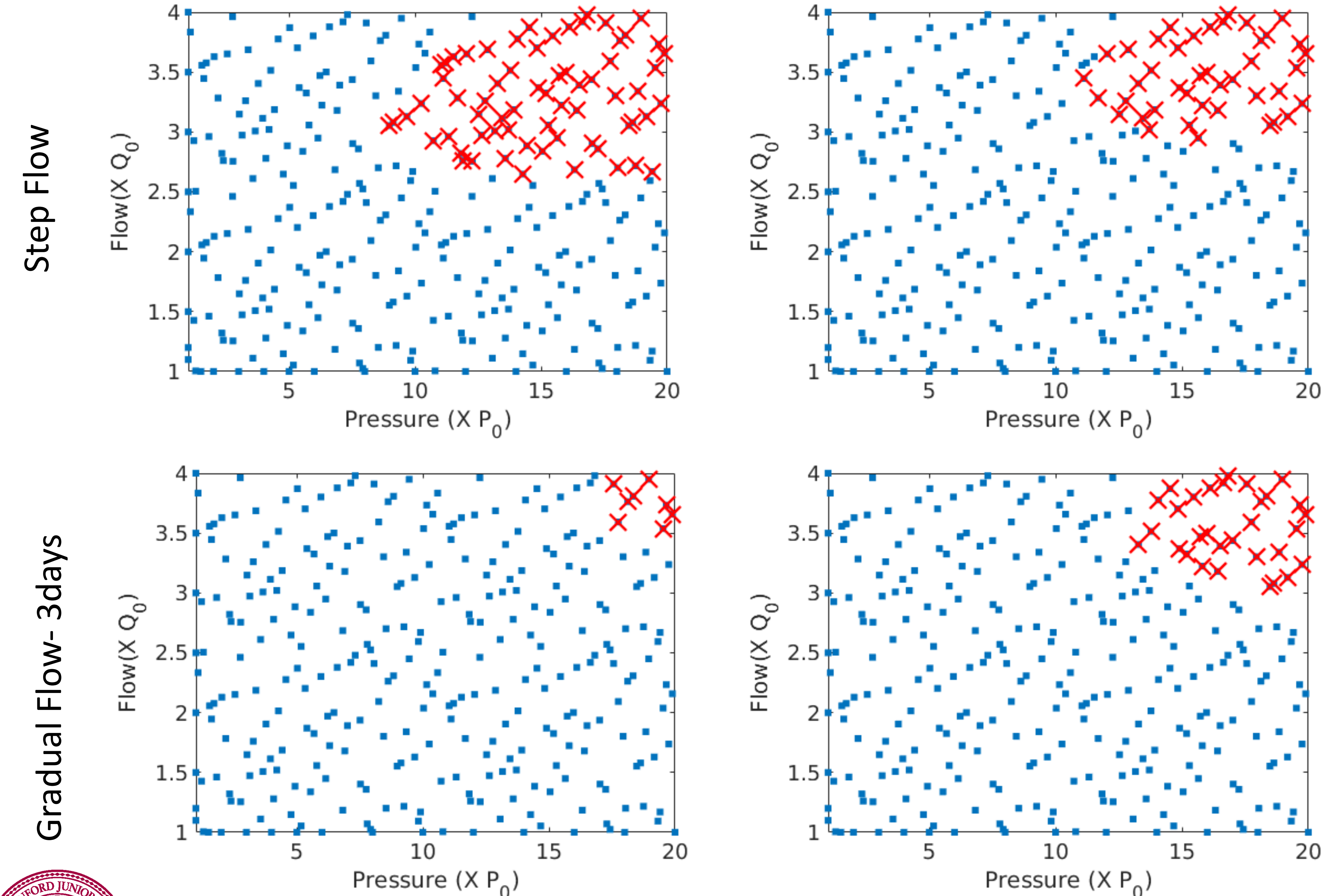
Gradual Change

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.

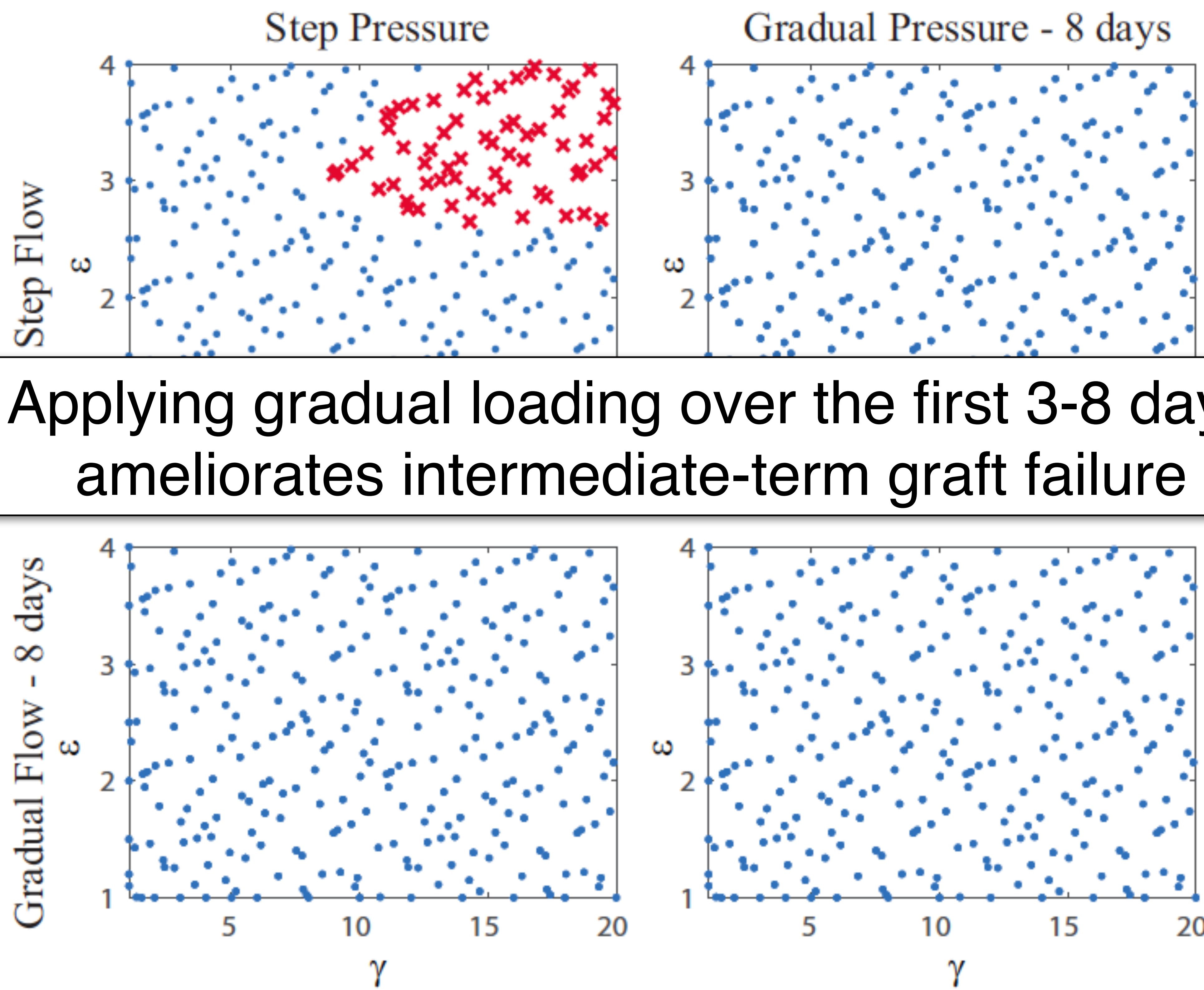
Step vs. Gradual Loading

Step Pressure | Gradual Pressure – 3days



X = Model predicts failure
500 days post CABG

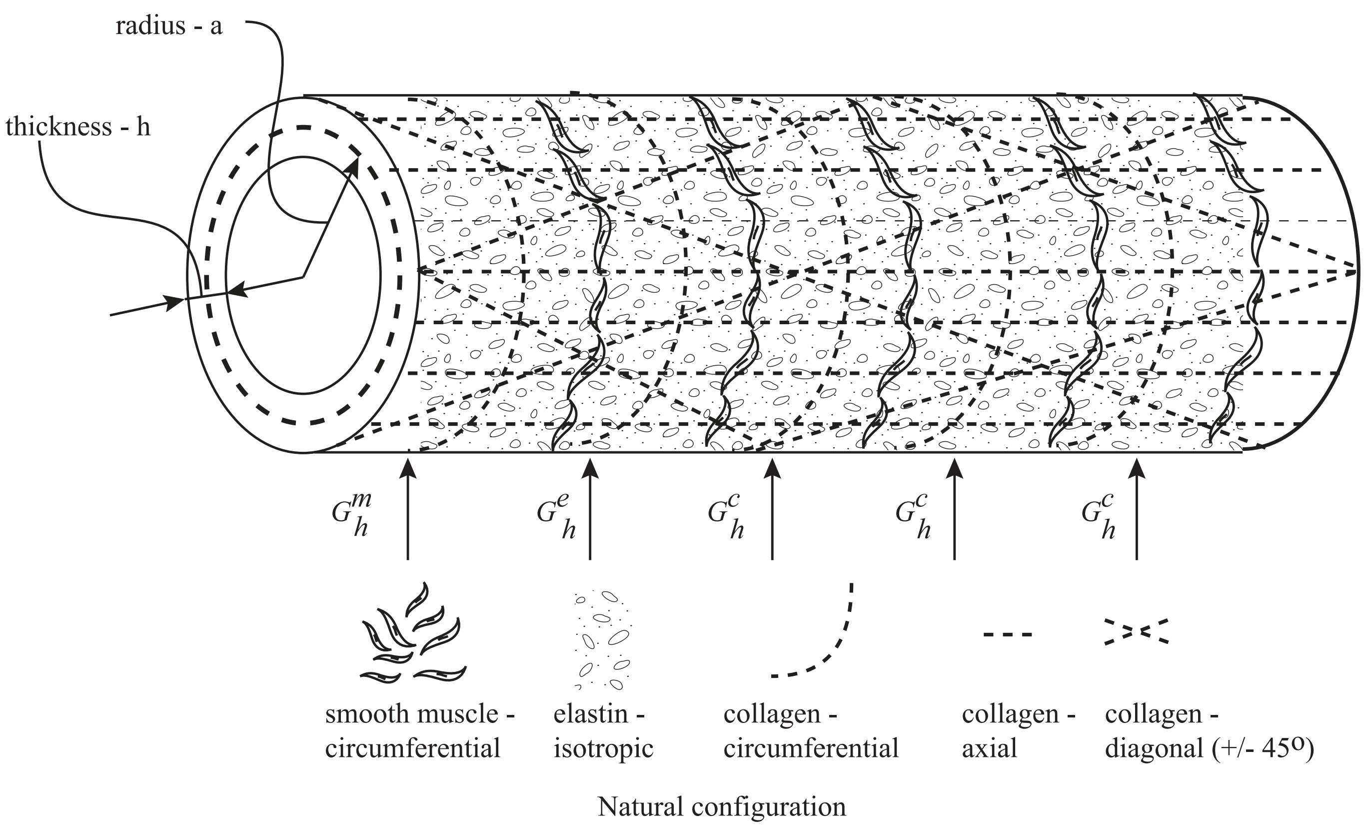
Step vs. Gradual Loading

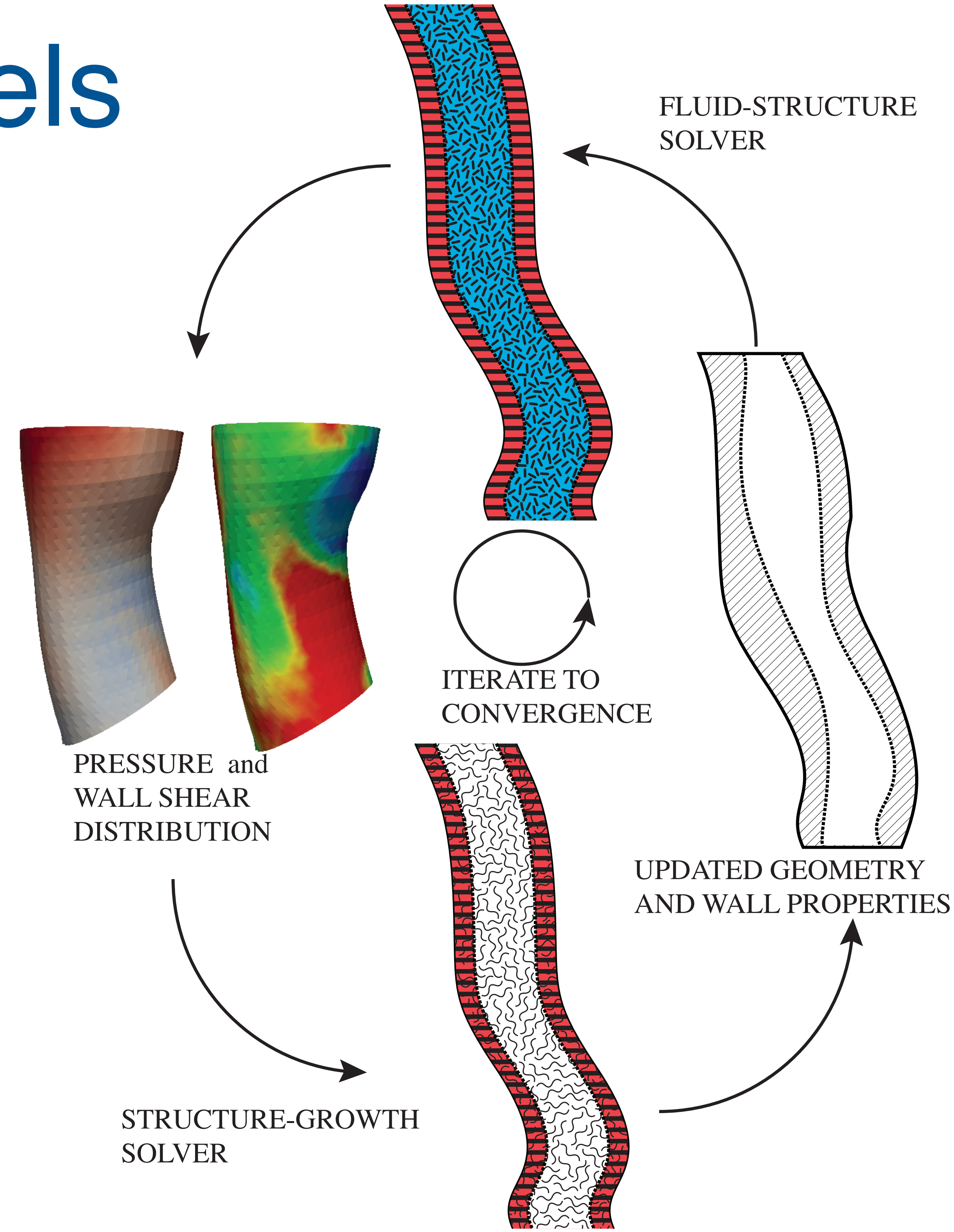


Applying gradual loading over the first 3-8 days ameliorates intermediate-term graft failure

X = Model predicts failure
500 days post CABG

Towards Fluid-Solid-Growth Models

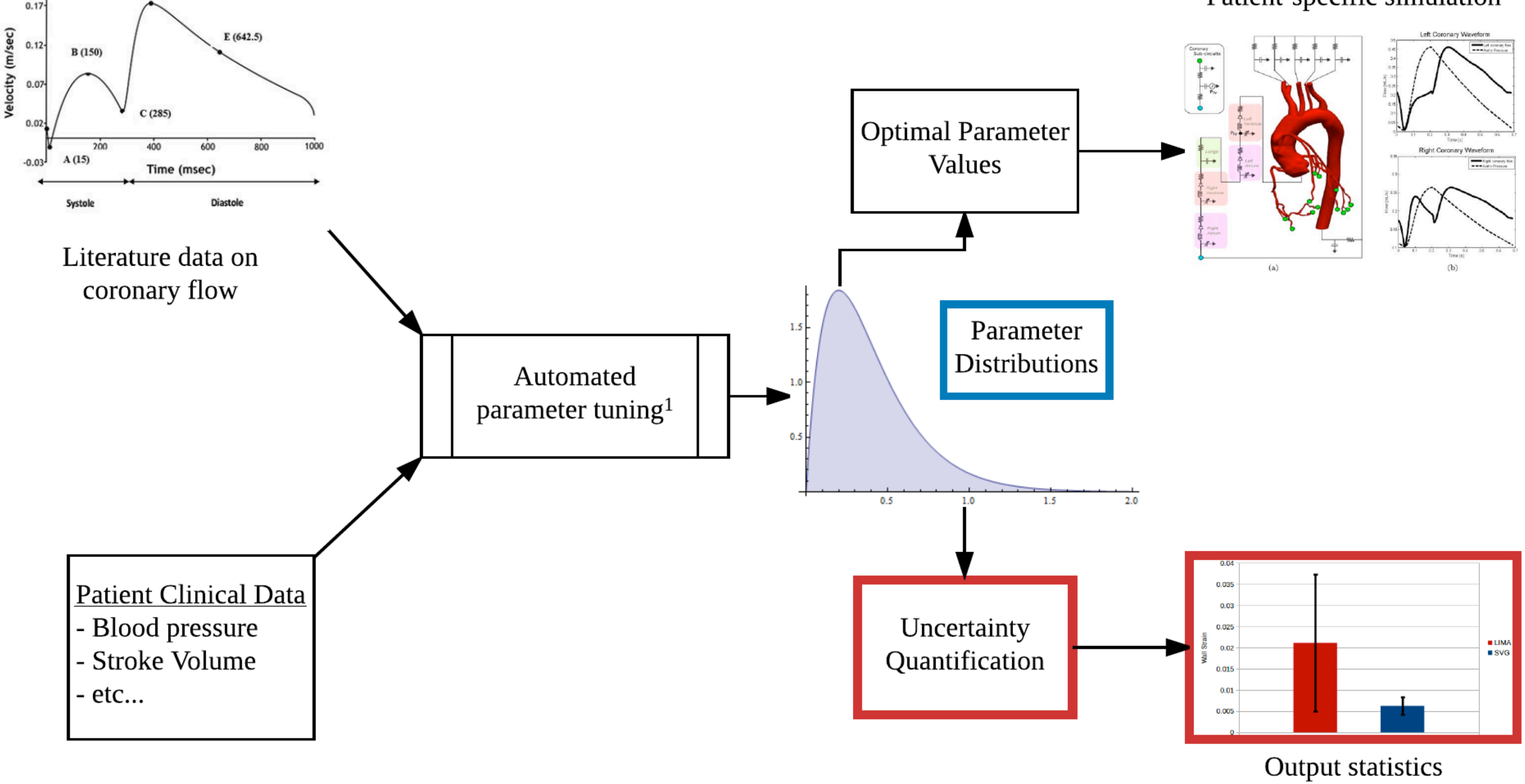




with Chris Breuer and Jay Humphrey

Parameter Estimation and UQ

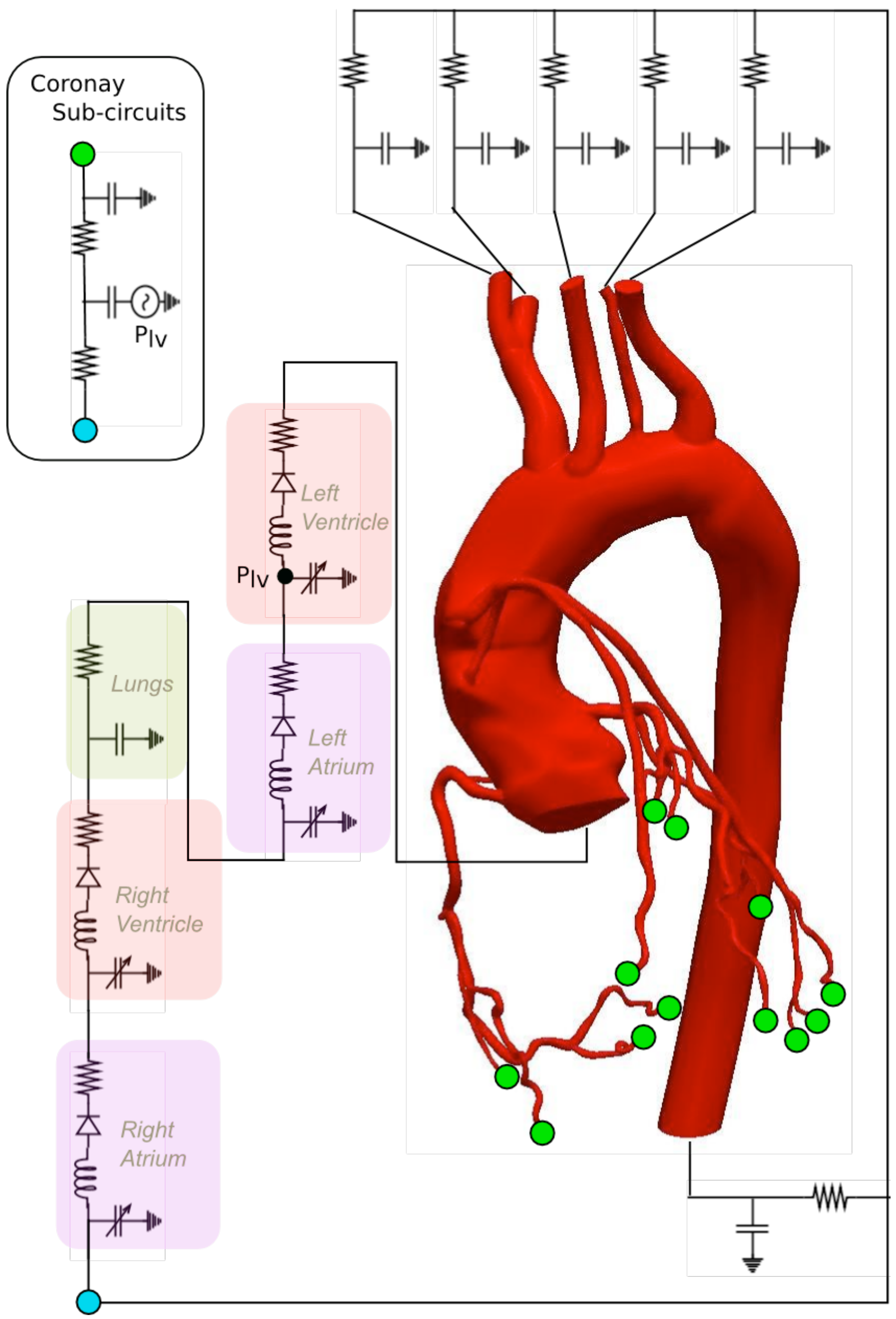
With Daniele Schiavazzi, Notre Dame

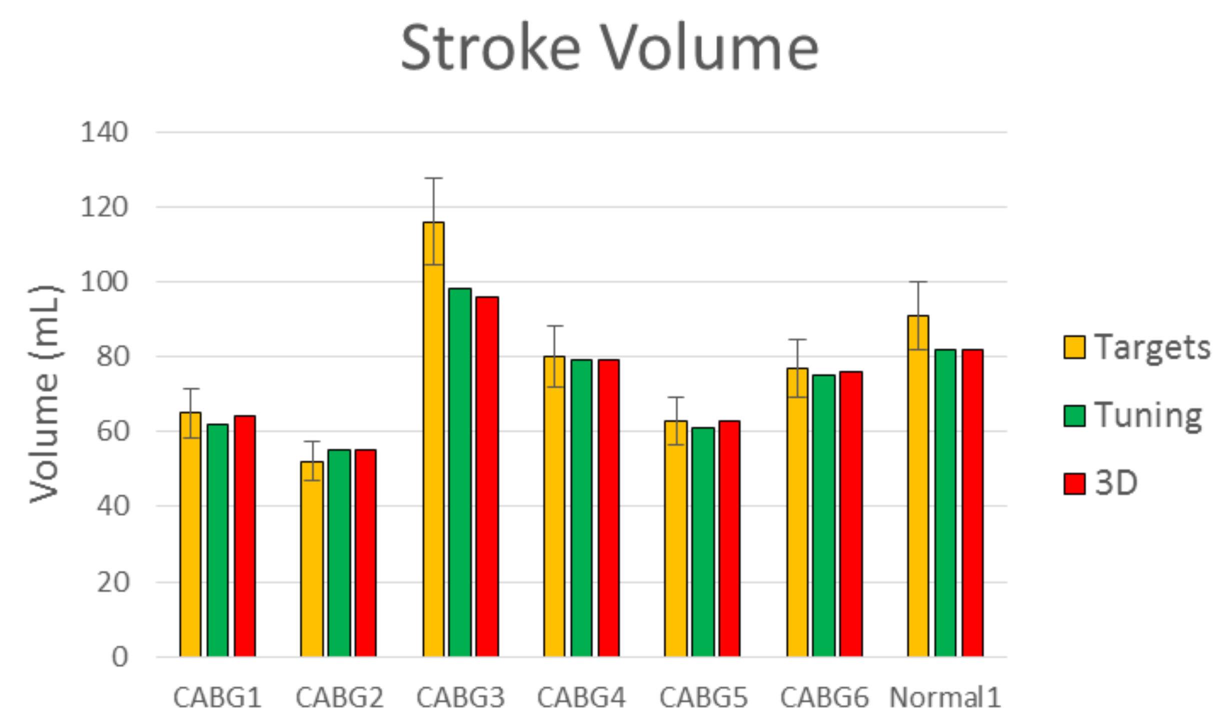


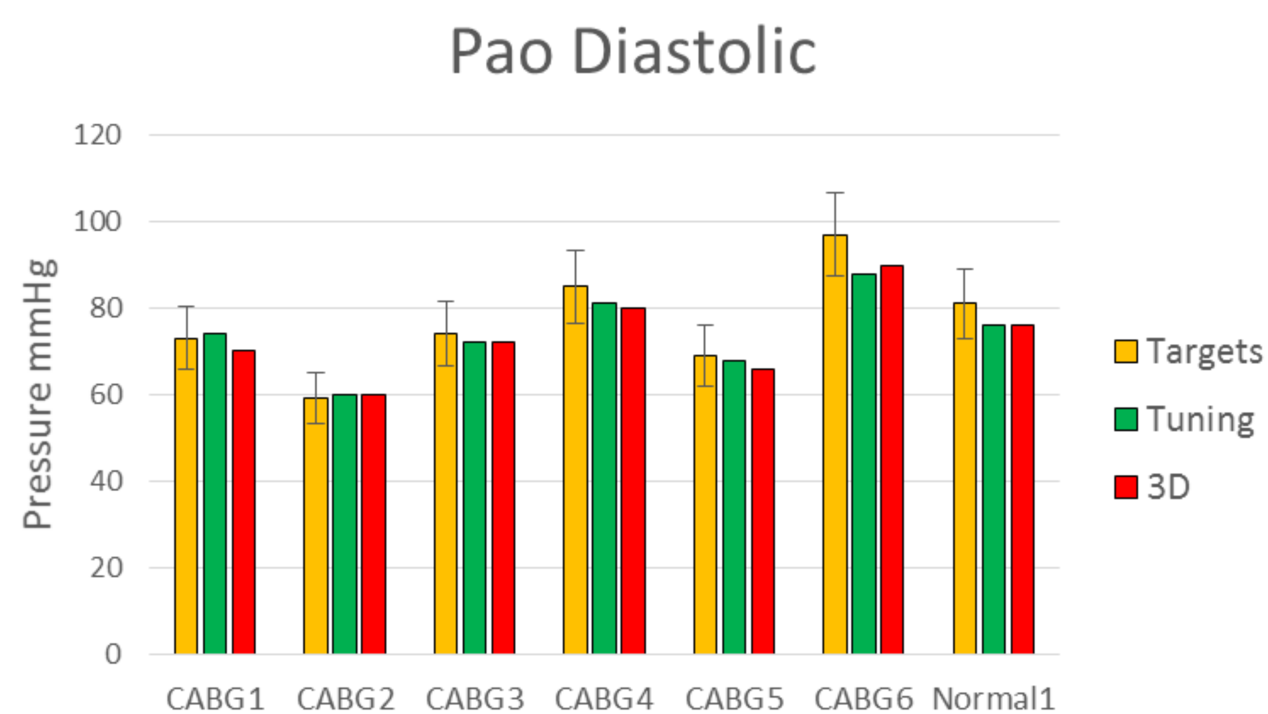
Schiavazzi, D. E., Doostan, A., Iaccarino, G., Marsden, A. L., “A Generalized Multi-resolution Expansion for Uncertainty Propagation with Application to Cardiovascular Modeling,” *Computer Methods in Applied Mechanics and Engineering*, Vol. 314 (1), pp. 196-221, (2017).

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).

Automated Parameter Tuning

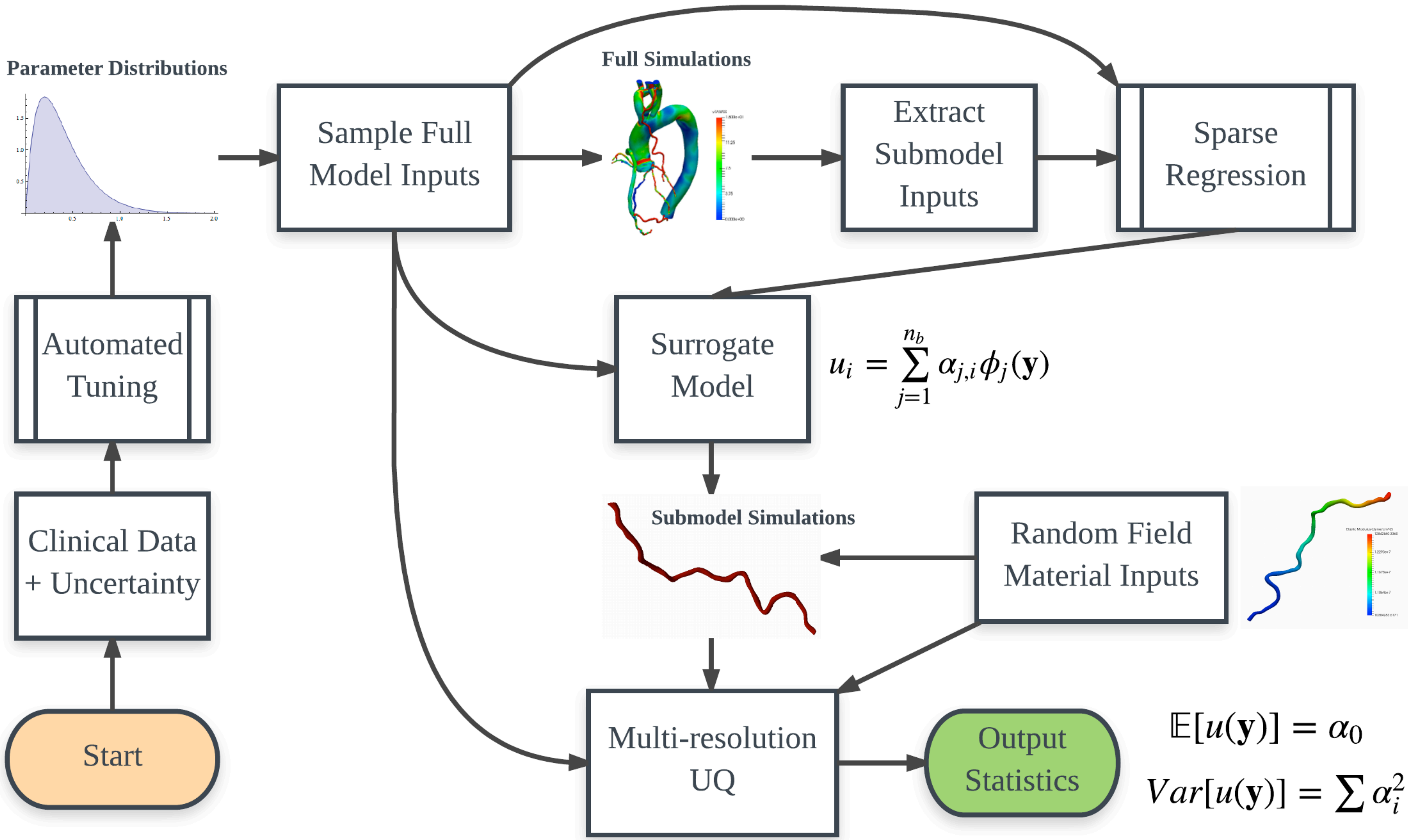




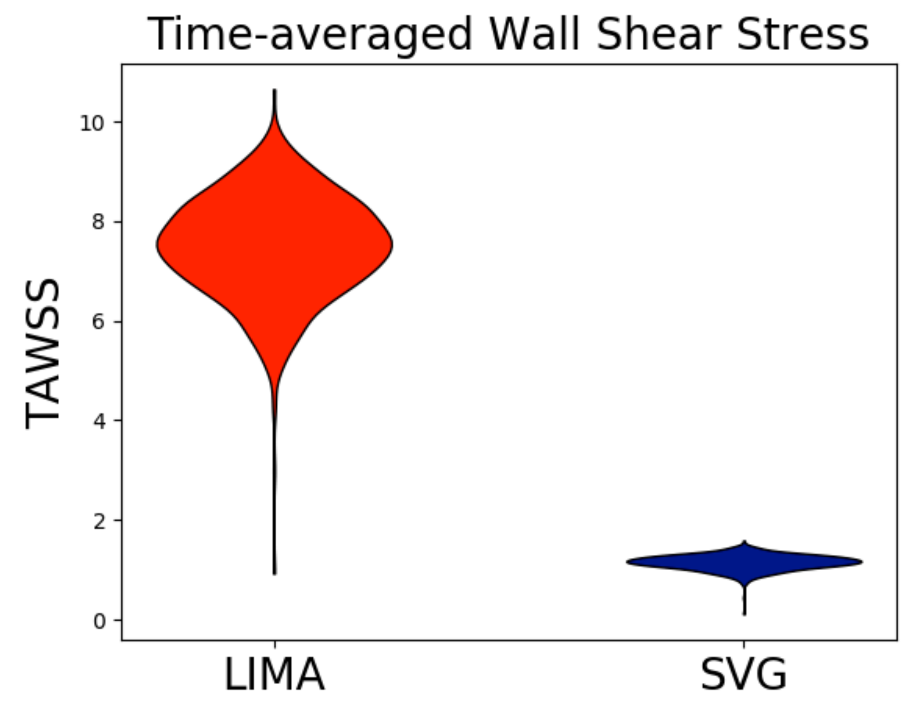


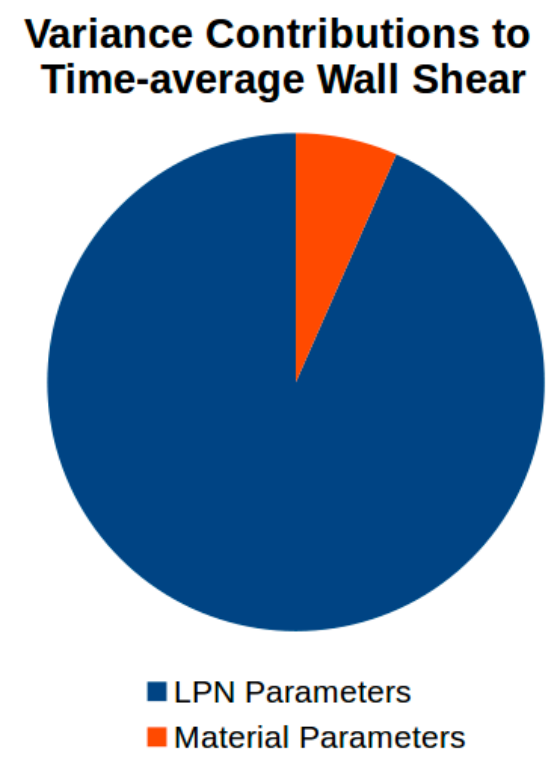
Tran, J. S., Schiavazzi, D. E., Ramachandra, A. B., Kahn, A. M., Marsden, A. L., "Automated Tuning for Parameter Identification in Multiscale Coronary Simulations," Vol. 142(5), pp. 128–138, *Computers and Fluids*, (2017)

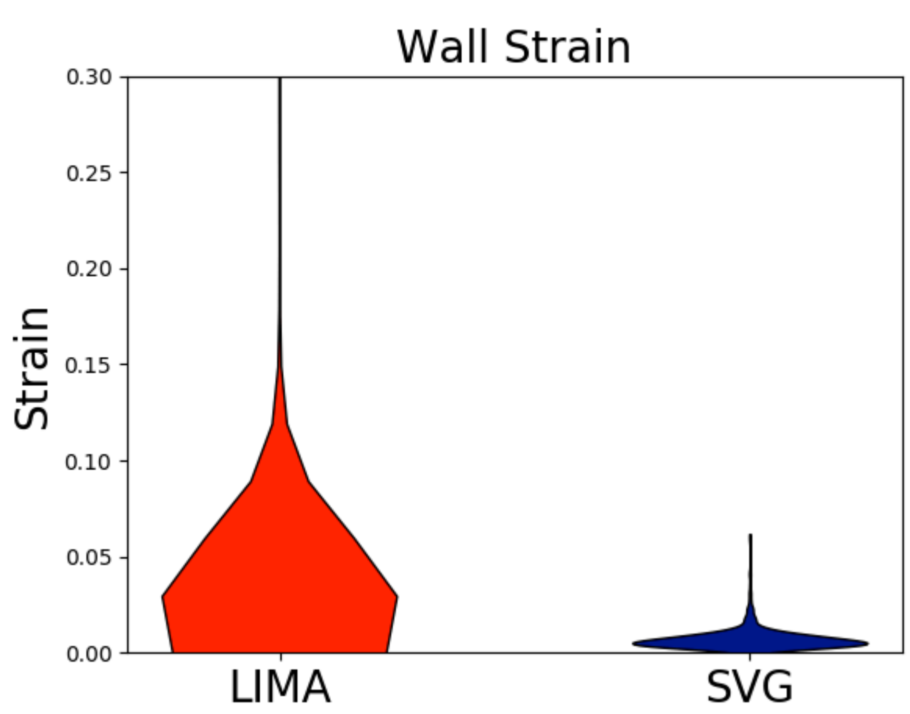
Uncertainty Propagation

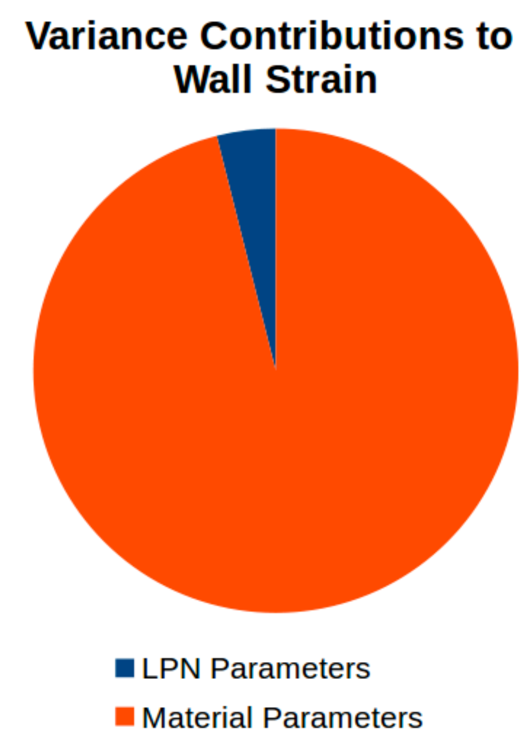


Statistics on model predictions









Open Source

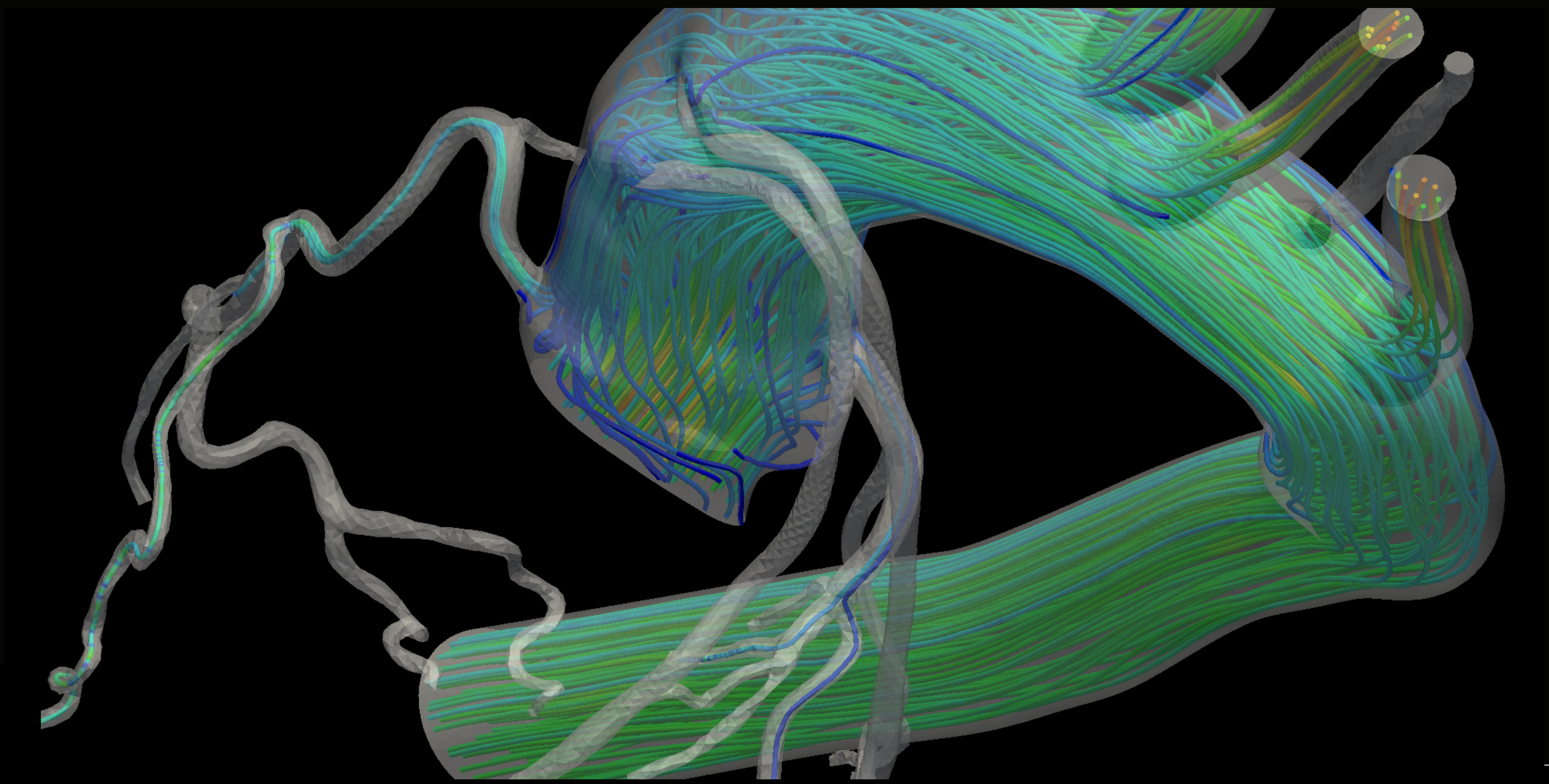
Providing tools to the research community

SimVascular

Alison Marsden
Stanford University

Shawn Shadden
UC Berkeley

Nathan Wilson
OSMSC



MAJOR FUNDING PROVIDED BY
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www.simvascular.org

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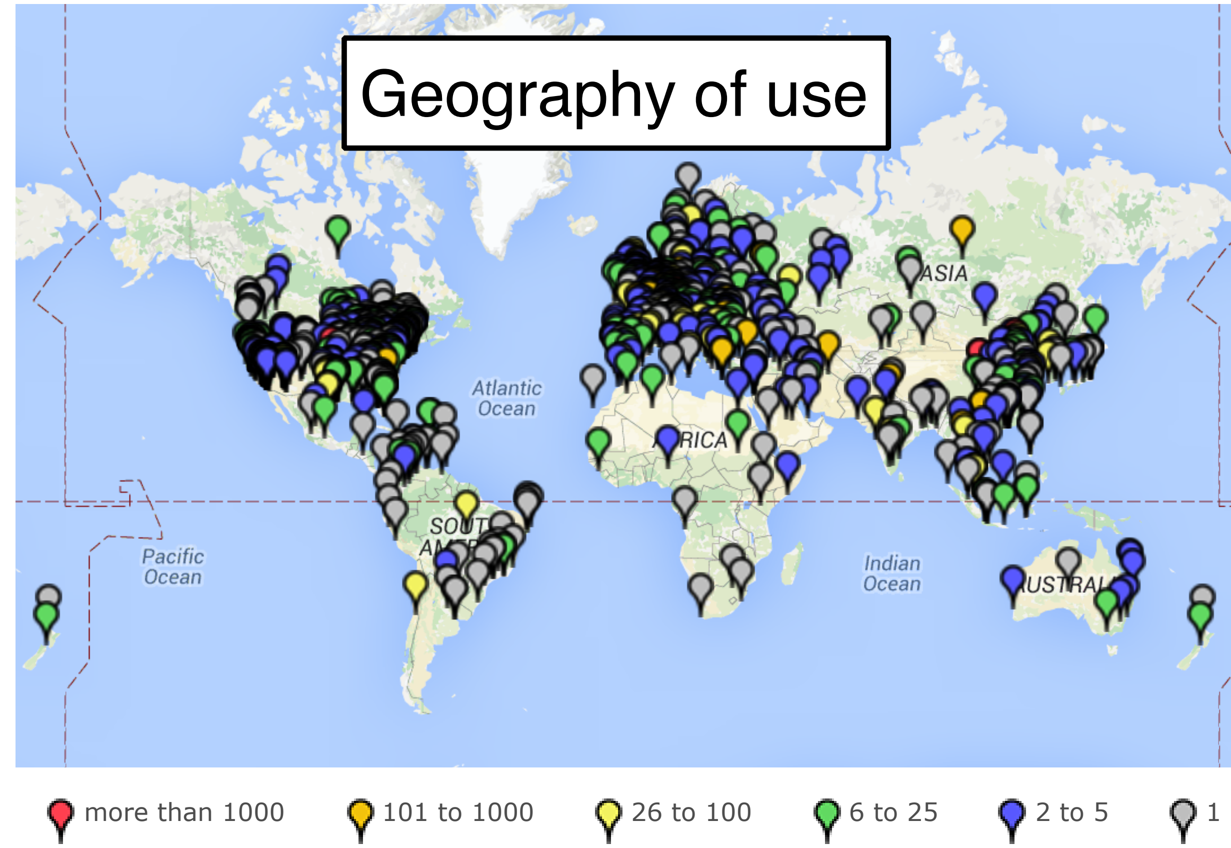
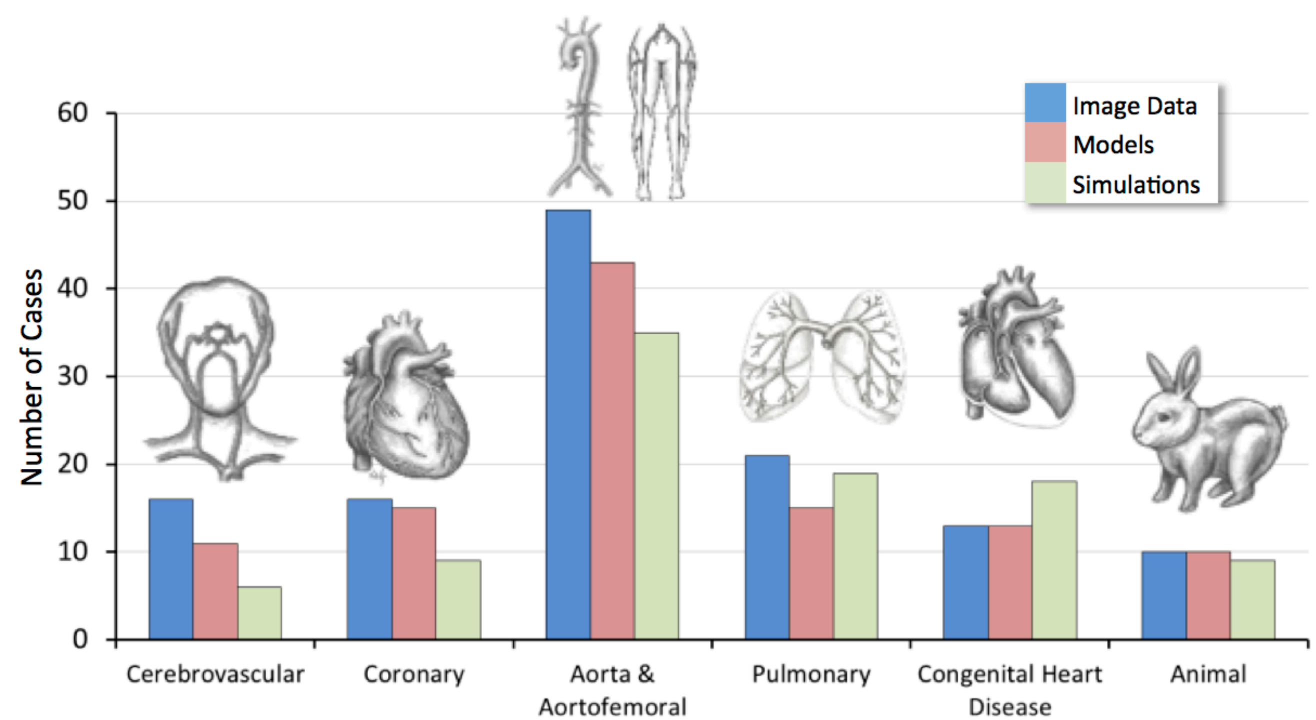
Project Stats

- 1,959 unique users
- 4,866 unique downloads
- Google Scholar search for "SimVascular" produces ~140 publications/abstracts
- Used in coursework for project-based learning
- Vascular Model Repository provides 120 compatible data sets
- Source on GitHub
- Cross-platform support



vascularmodel.com



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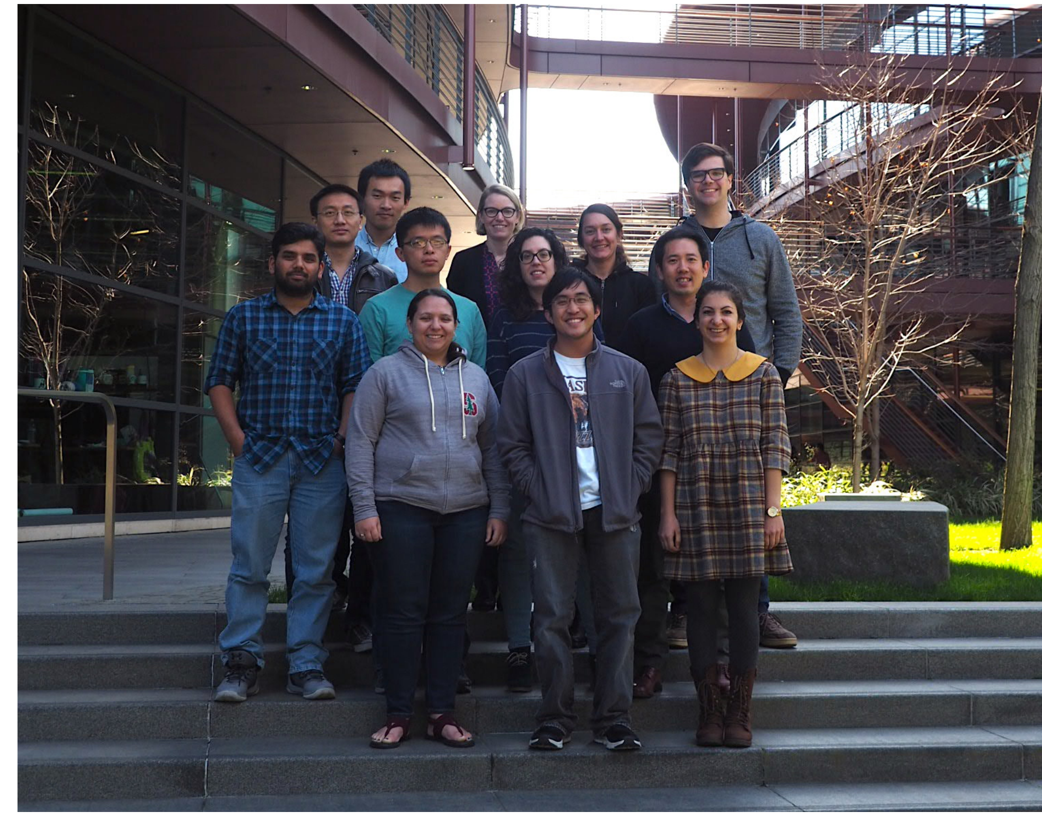

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