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Uncertainty Quantification in Cardiovascular Models

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ncsu

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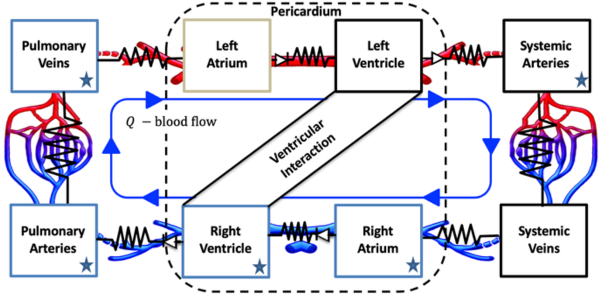
Sources of uncertainty

- **0D-compartmental models**
  - electrical circuit analogues (RC or RCL circuits)

$$\frac{dx}{dt} = f(x,t;\theta), \qquad x(0) = x_0$$

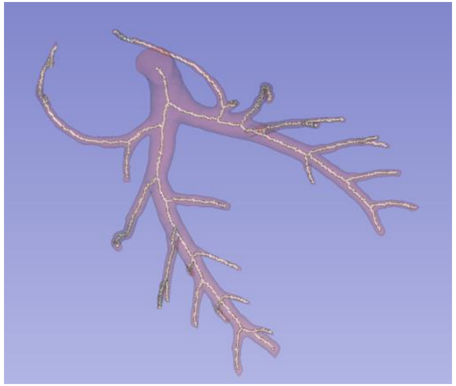


- **1D-fluid dynamics models**
  - Conservation of flow and balance of momentum (NS equations)

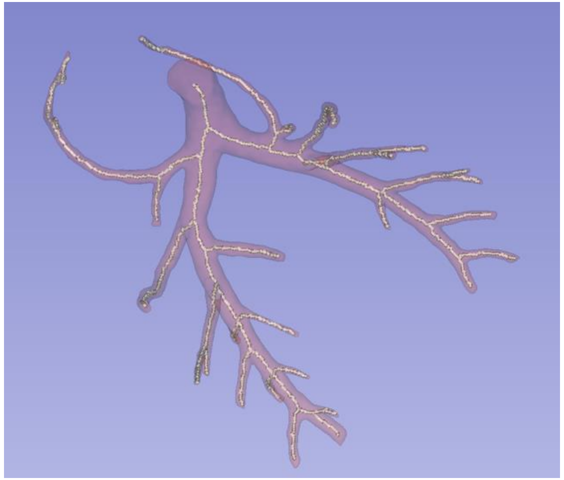
$$\frac{\partial A}{\partial t} + \frac{\partial q}{\partial x} = 0, \qquad \frac{\partial q}{\partial t} + \frac{\partial}{\partial x}\left(\frac{q^2}{A}\right) + \frac{A}{\rho}\frac{\partial p}{\partial x} = -\frac{2\pi\nu R}{\delta}\frac{q}{A}$$

- **3D-CFD or FSI models**
  - Incompressible NS equations

$$\nabla \cdot u = 0, \;\; \rho u_t + \rho v \cdot \nabla v + \nabla p - \nabla \cdot \tau + f = 0$$



Sources of uncertainty



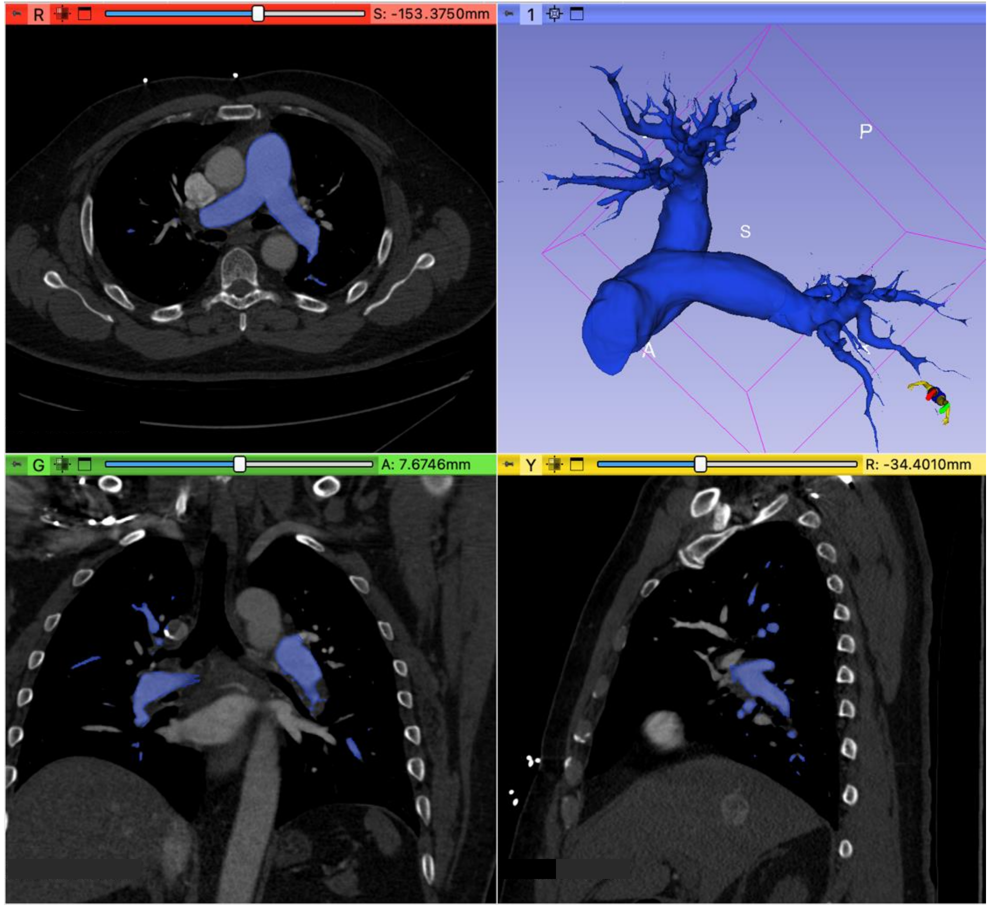
- **3D rendering (1D/3D)**
  - Smoothing, painting, thresholding
- **Geometry – model domain (1D/3D)**
  - 1D: vessel lengths, vessel radii, connectivity
  - 3D: meshing, smoothing
- **Inflow/Outflow (1D/3D -** boundary conditions**)**
- **Vessel wall parameters (tissue mechanics -** Youngs modulus, compliance**)**
- **Fluid dynamics parameters (viscosity, density, gravity, resistance)**
- **Patient characteristics (0D)** (Height, Weight, BSA, …)

3D rendering

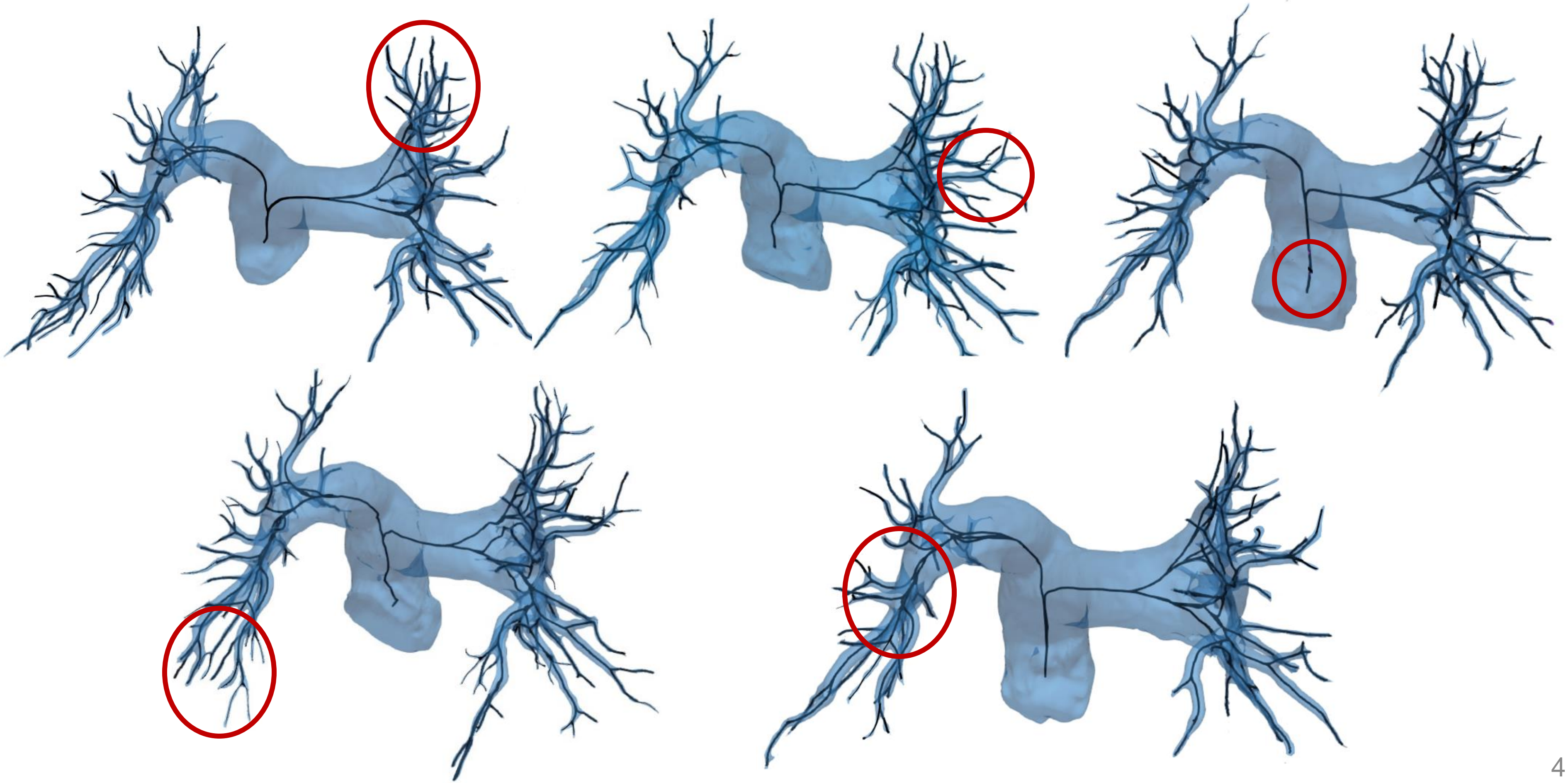
3DSlicer

Separates image foreground from the background to extract arteries from CT scans

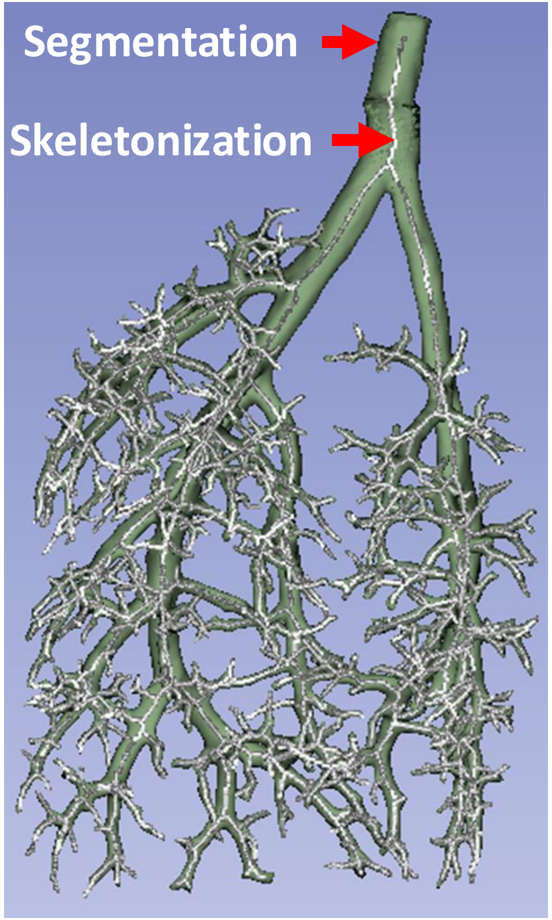
- Threshold
- Smooth
- Erase
- Scissors
- Paint



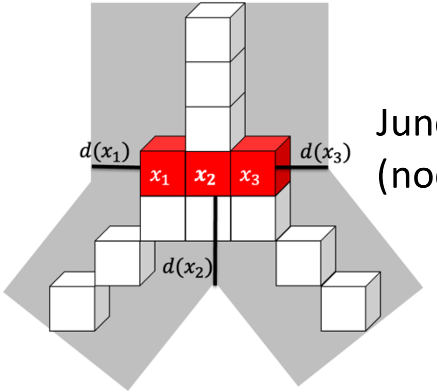
3D rendering



Geometry – skeletonization (SgExt)



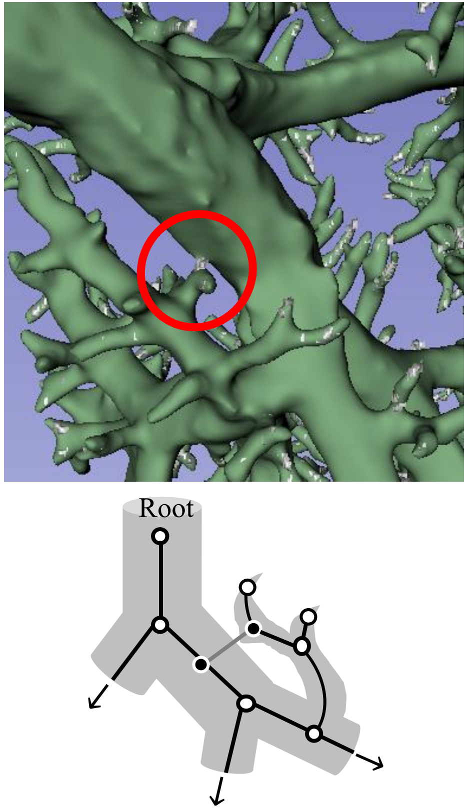
Pablo Hernandez: https://phcerdan.github.io/projects/2017-01-01-SGEXT/

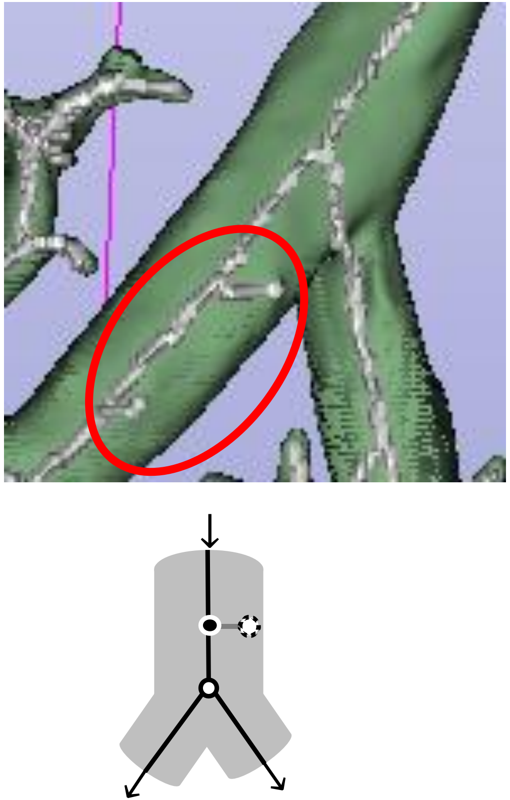


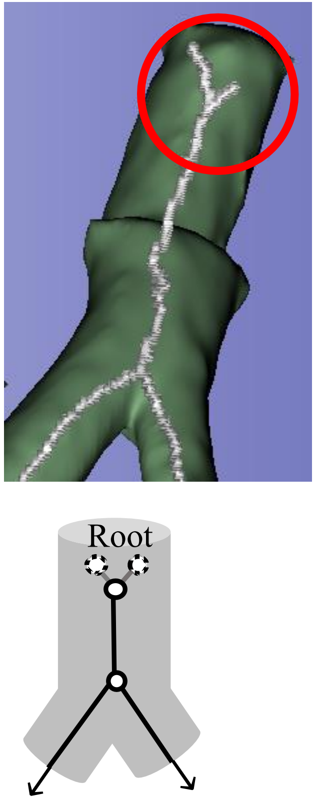
Chambers et al. (2020) **Structural and hemodynamic properties of murine pulmonary arterial networks under hypoxia-induced pulmonary hypertension.** 10.1177/0954411920944110

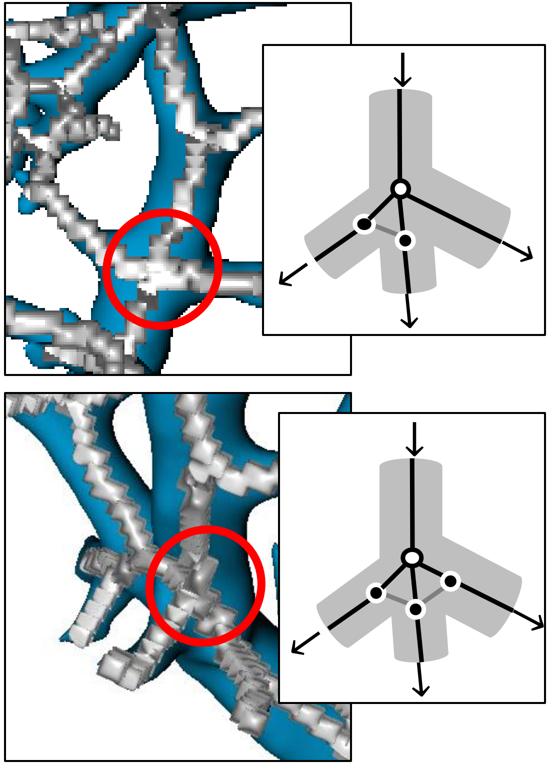
Geometry - skeletonization errors

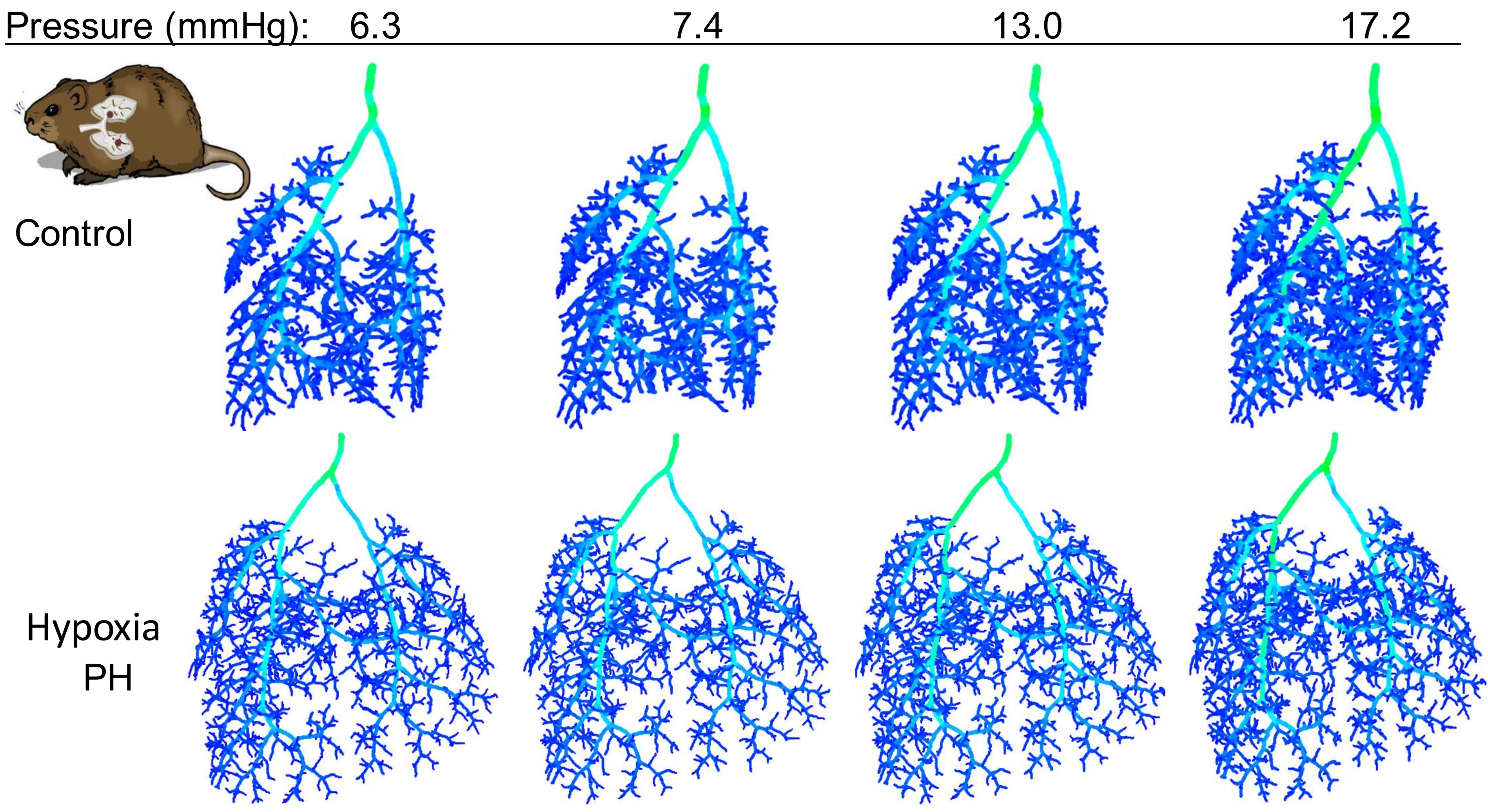
Pablo Hernandez: https://phcerdan.github.io/projects/2017-01-01-SGEXT/





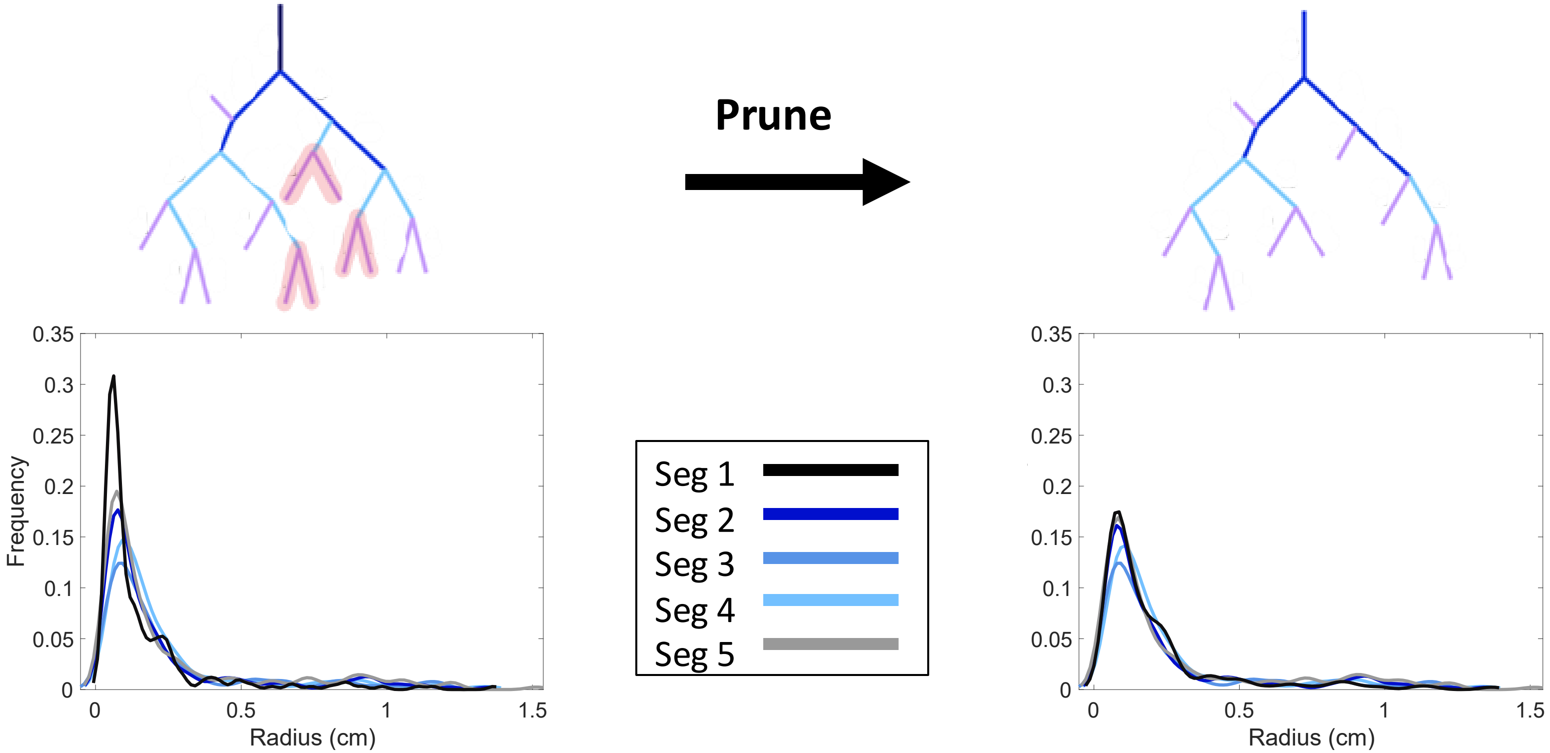




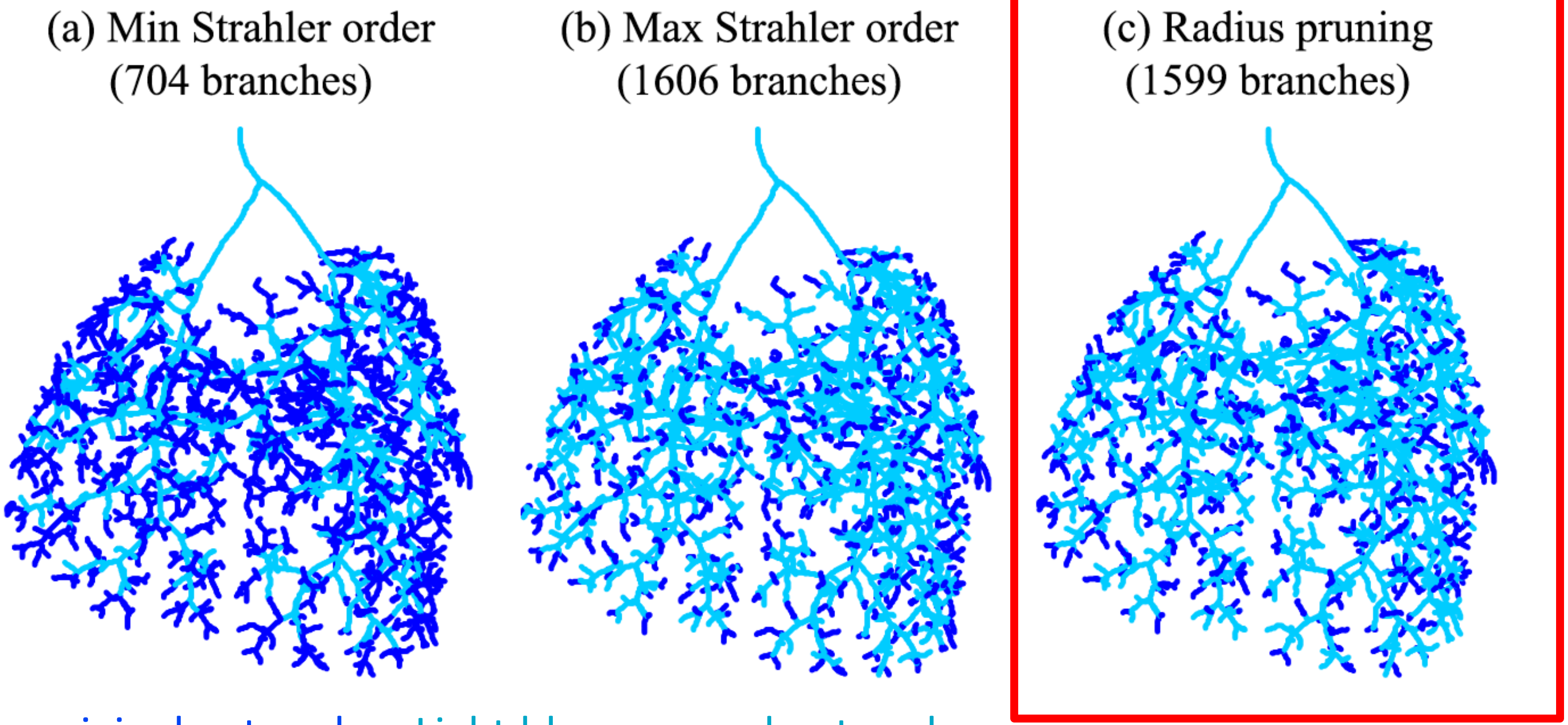

Pressure (mmHg): 6.3
7.4
13.0
17.2
Control
Hypoxia PH

Geometry - network complexity

- Multiple segmentations generate different number of vessels
- Iteratively remove smallest terminal vessels until networks are standardized



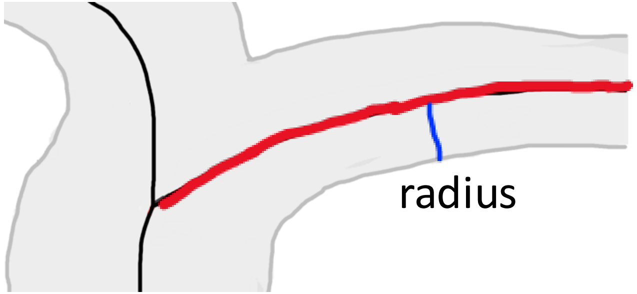
Geometry – comparative networks



Dark blue original network, Light blue cropped network

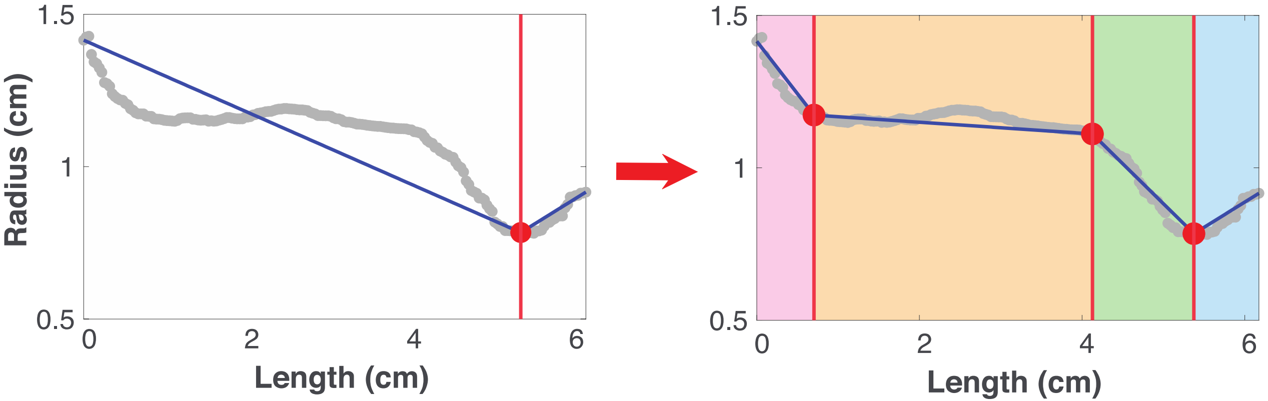
Miller et al. (2023) **A topological data analysis study on murine pulmonary arterial trees with pulmonary hypertension.**
10.1016/j.mbs.2023.109056

Geometry - vessel radii



- To determine what part of the vessel has a well-defined radius, we utilize statistical changepoints
- Changepoints are placed where there are abrupt changes in the mean, variance, and slope of radii
- Piecewise linear functions are fit between changepoints by the linear regression model

$$\boldsymbol{r}(l) = \beta_0 - \beta_1 l$$

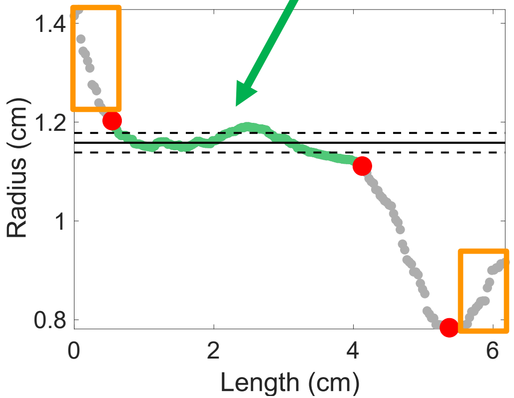


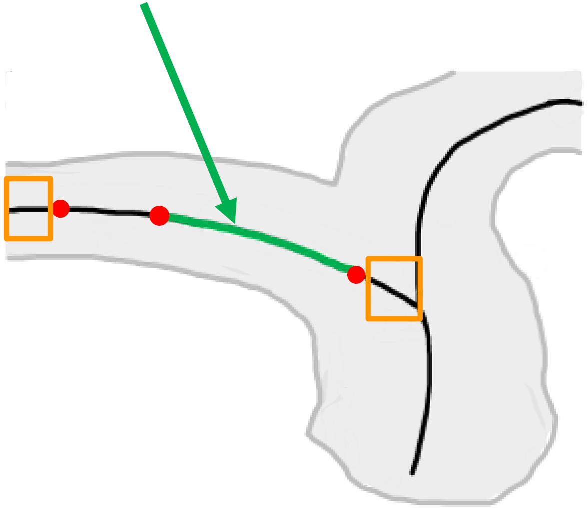
Bartolo et al. (2024) **Computational framework for the generation of one-dimensional vascular models accounting for uncertainty in networks extracted from medical images.** 10.1113/JP286193

Geometry - vessel radii

Find the segment within each vessel where the radius could be reliably estimated

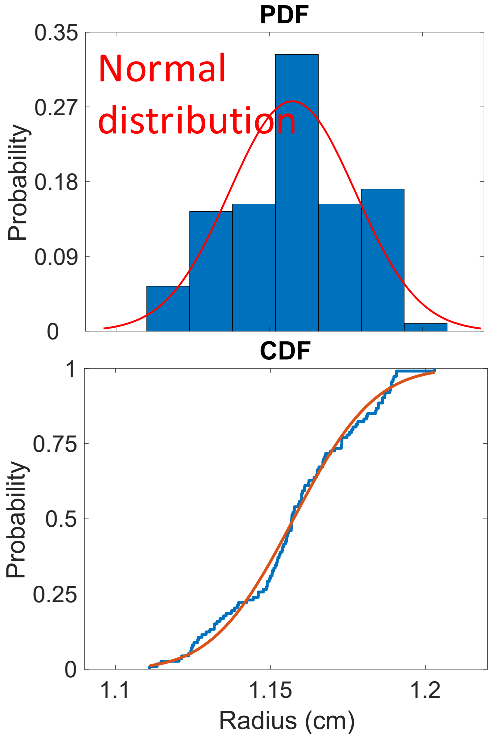
- Section with smallest slope is a stable representation of a vessel
- Average over this section and extend radius to whole vessel
- Calculate standard deviation to quantify uncertainty





Avoids junction region

Find probability density function of extracted region



Hemodynamic data

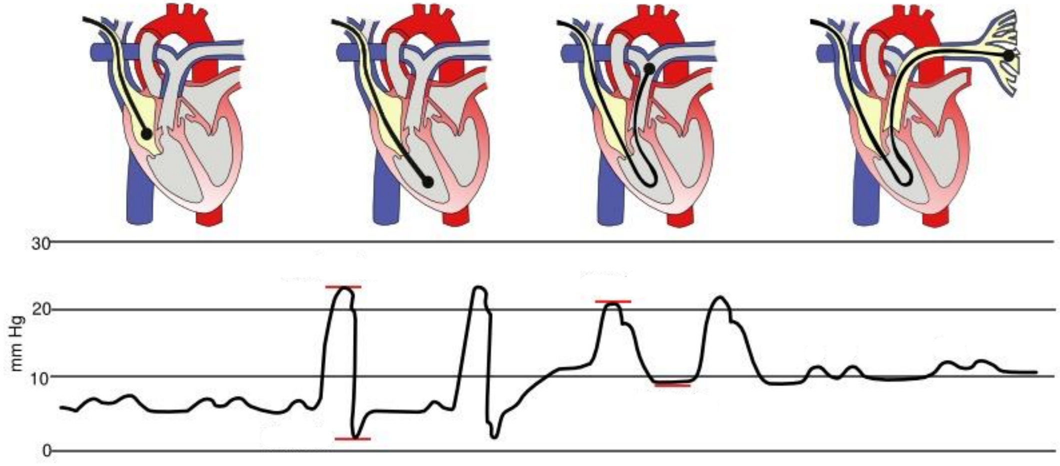
- 4D Magnetic Resonance Images (4D-MRI) registered on MRA
  - Flow (mL/s) [time varying]
- Right heart catheterization (BP, mmHg) [time varying]
- Blood pressure (cuff – systolic and diastolic BP, mmHg)
- Electronic health records (CO, height, weight, gender)

$P_{rv,syst}$	30.5	$P_{sa,syst}$	

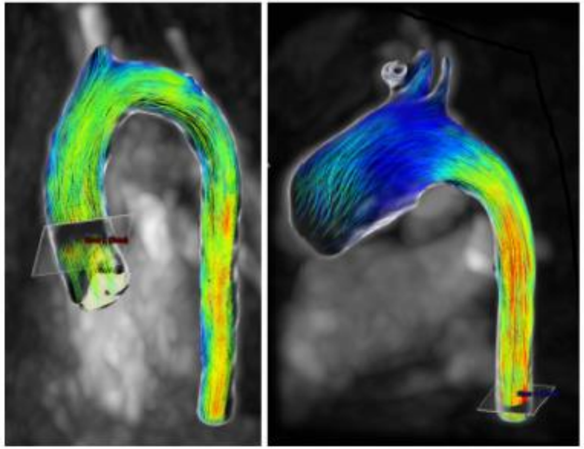
Patient 266			
$P_{rv,syst}$	37	$P_{sa,syst}$	154
			81
			90
			75
			169
			M

Patient 233			
$P_{rv,syst}$	40	$P_{sa,syst}$	149
$P_{rv,diast}$	4	$P_{sa,diast}$	83
$P_{pa,syst}$	34	*Heart Rate*	83
$P_{pa,diast}$	14	*Weight*	96
P_{wedge}	11	*Height*	172
Cardiac Output	6	*Sex*	F

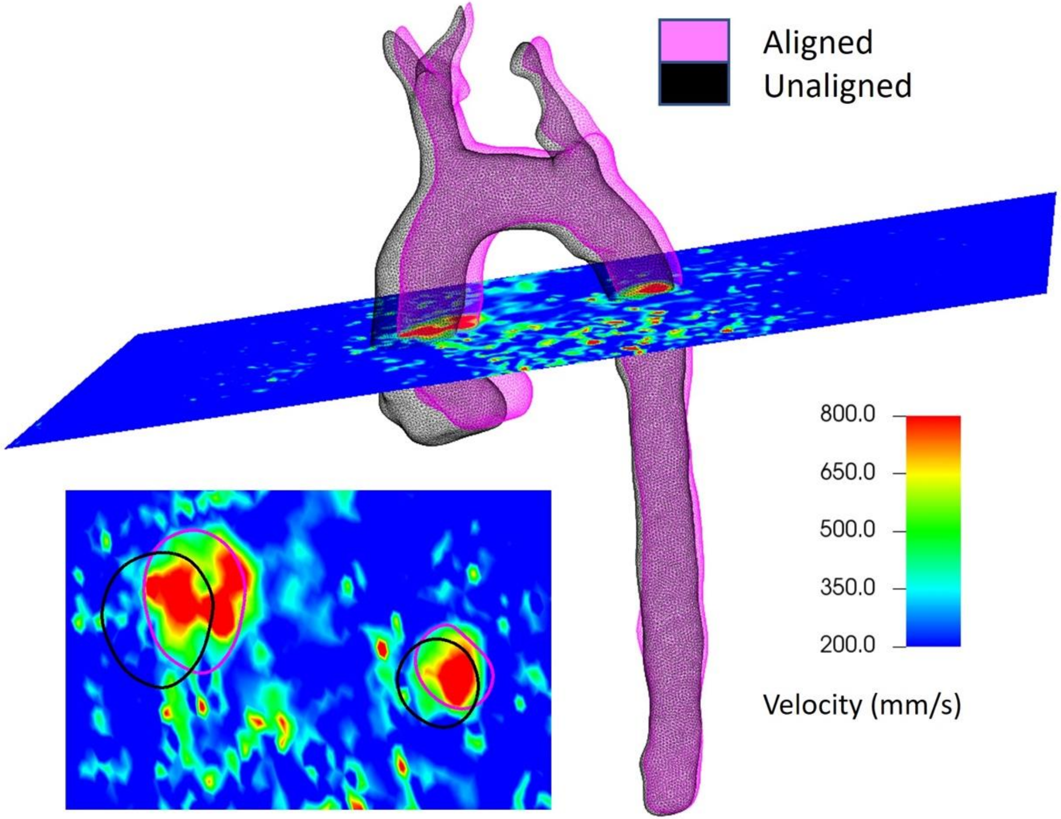
Right heart catheterization

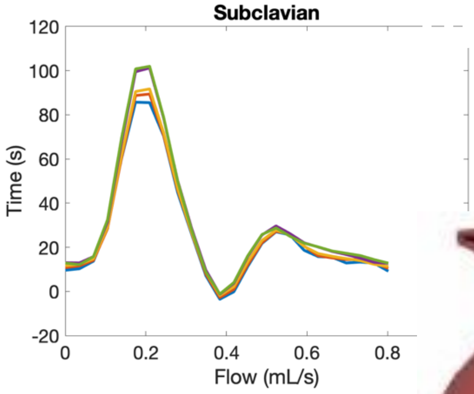


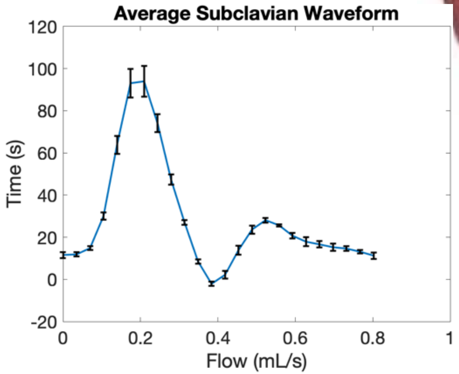
4D-MRI

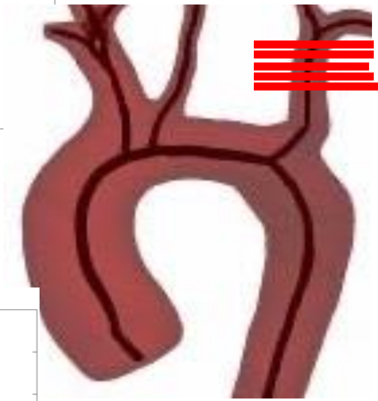


Hemodynamic data - 4D-MRI









Lior et al. (2024) **Deformable Registration of MRA and 4D Flow Images to Facilitate Accurate Estimation of Flow ….** arXiv:2312.03116

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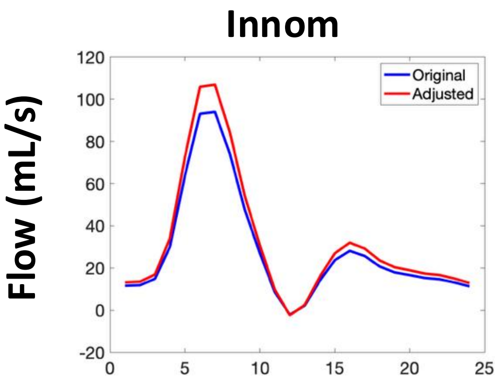
Hemodynamic data - flow conservation

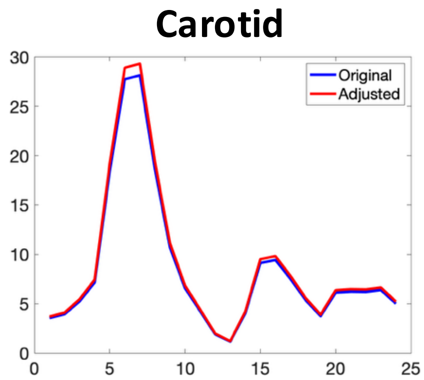
Flow conserved as a linear system

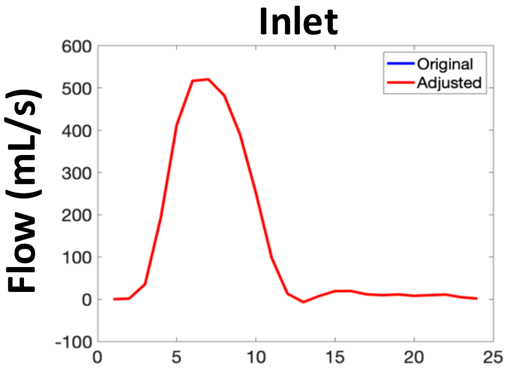
$$q_{inlet} = \sum_{i=1}^{4}(1+\alpha_i)q_i$$

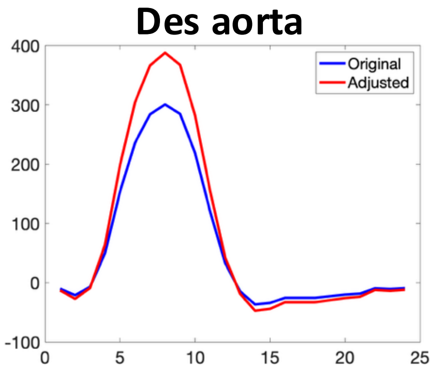
$$f = \lambda\left(\left(\sum_{i=1}^{4}(1+\alpha_i)q_i\right) - q_{inlet}\right) + \frac{1}{2}\left(\sum_{1}^{4}\alpha_i^2\right)$$

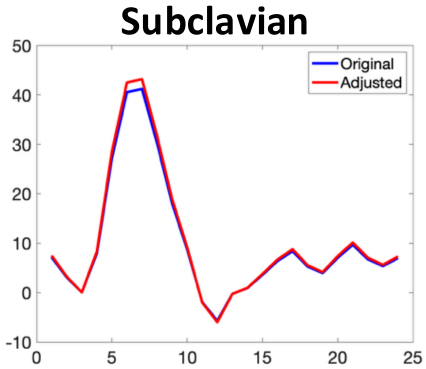
Minimizing f

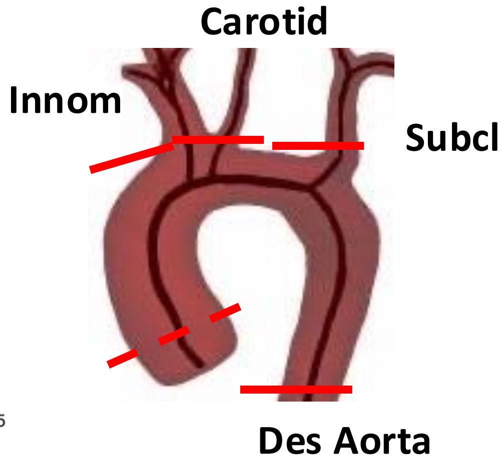






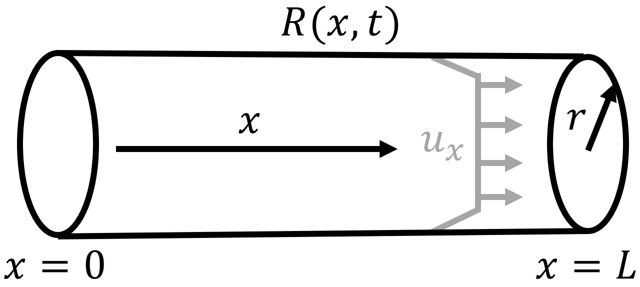






Taylor-LaPole et al. (2023) **A computational study of aortic reconstruction in single ventricle patients.** 10.1007/s10237-022-01650-w.

1D fluid dynamics model

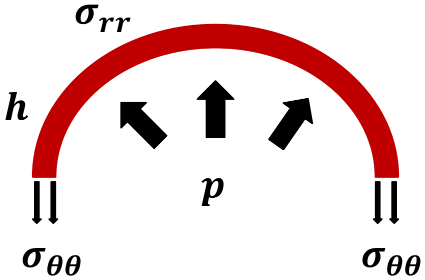


Mass Conservation

$$\frac{\partial A}{\partial t} + \frac{\partial q}{\partial x} = 0$$

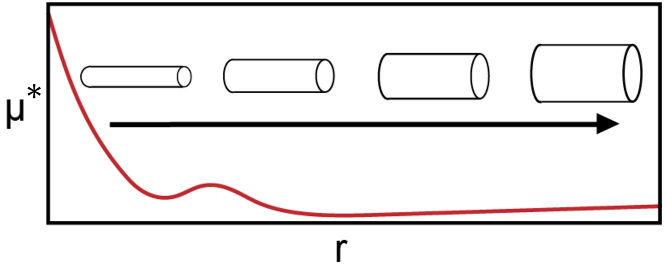
Momentum Balance

$$\frac{\partial q}{\partial t} + \frac{\partial}{\partial x}\left(\frac{q^2}{A}\right) + \frac{A}{\rho}\frac{\partial p}{\partial x} = -\frac{2\pi\nu R}{\delta}\frac{q}{A}$$



Linear Elastic Constitutive Law

$$p(x,t) = \frac{4}{3}\frac{Eh}{r_0}\left(\sqrt{\frac{A}{A_0}} - 1\right), \qquad \frac{Eh}{r_0} = k_1 e_2^{-k_2 r_0} + k_3$$



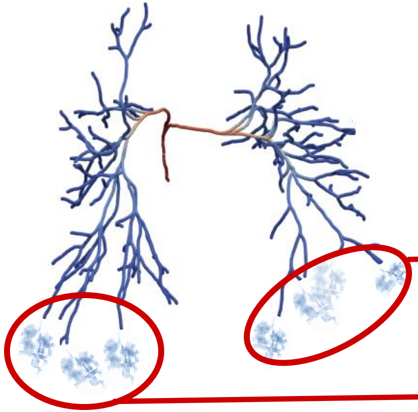
Radius Dependent Viscosity

$$\mu^*(r_0) = \frac{1}{3.2}\left(1 + (\mu_{0.45} - 1)\left(\frac{2r_0}{2r_0 - 1.1}\right)^2\right)\left(\frac{2r_0}{2r_0 - 1.1}\right)^2$$

Outflow boundary - small vessels

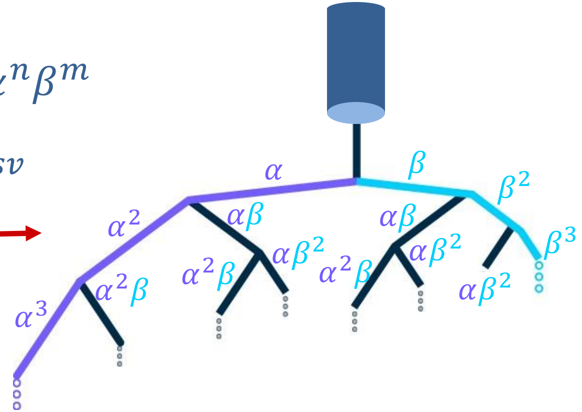
Viscous effects are dominant, ignore the nonlinear inertial term and make all variables periodic, consistent with a pumping heart

	Linearized Equation	Fourier Space
Mass Conservation:	$C\dfrac{\partial p}{\partial t}+\dfrac{\partial q}{\partial x}=0,\ \mathrm{C}=\dfrac{dA}{dp}\approx\dfrac{3A_0r_0}{2Eh}$	$i\omega CP+\dfrac{\partial Q}{\partial x}=0$
Momentum Balance:	$\dfrac{\partial u_x}{\partial t}+\dfrac{1}{\rho}\dfrac{\partial p}{\partial x}=\dfrac{\nu}{r}\dfrac{\partial}{\partial r}\left(r\dfrac{\partial u_x}{\partial r}\right)$	$i\omega Q=\dfrac{-A_0}{\rho}\dfrac{\partial P}{\partial x}(1-F_J)$



$$r_{0,sv}=r_{term}\,\alpha^n\beta^m$$

$$l=\ell_{rr}\,r_{0,sv}$$



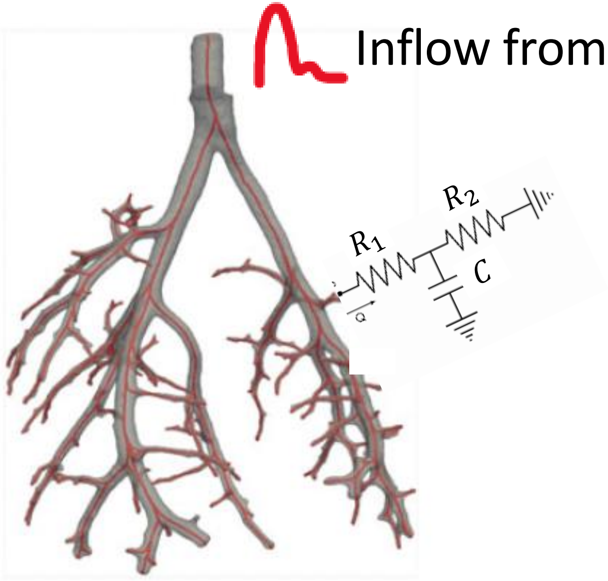
Ex 1: pulmonary arterial network

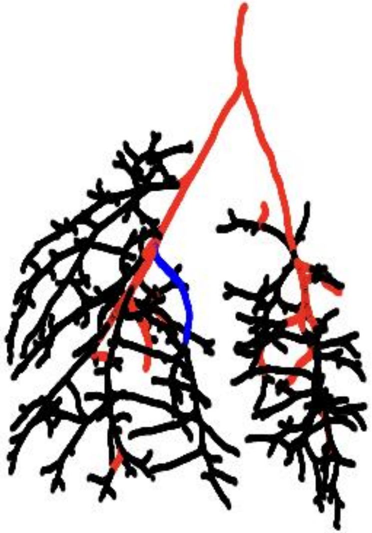
Outflow BCs: Windkessel model

$$\frac{dp}{dt} = R_1 \frac{dq}{dt} + q\left(\frac{R_1 + R_2}{R_2 C}\right) - \frac{p}{R_2 C},$$

$$R_T = R_1 + R_2 = \frac{\bar{p}}{\bar{q}}$$

Inflow from data





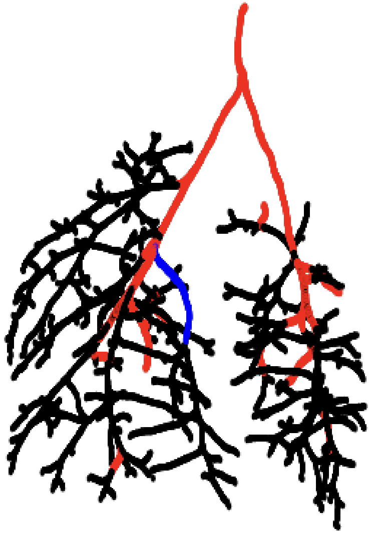
Total variation:
Run simulations in 25 rendered networks adjusting BCs

Parameter variation:
Sample radii and length from GP generated distributions. BC parameters fixed.

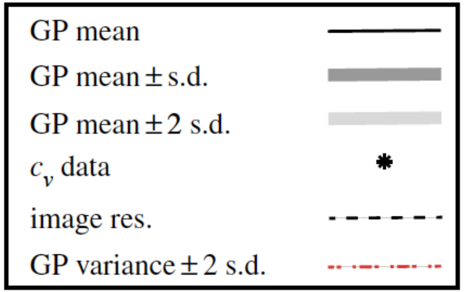
Network variation:
Change network connectivity and size adjusting BCs.

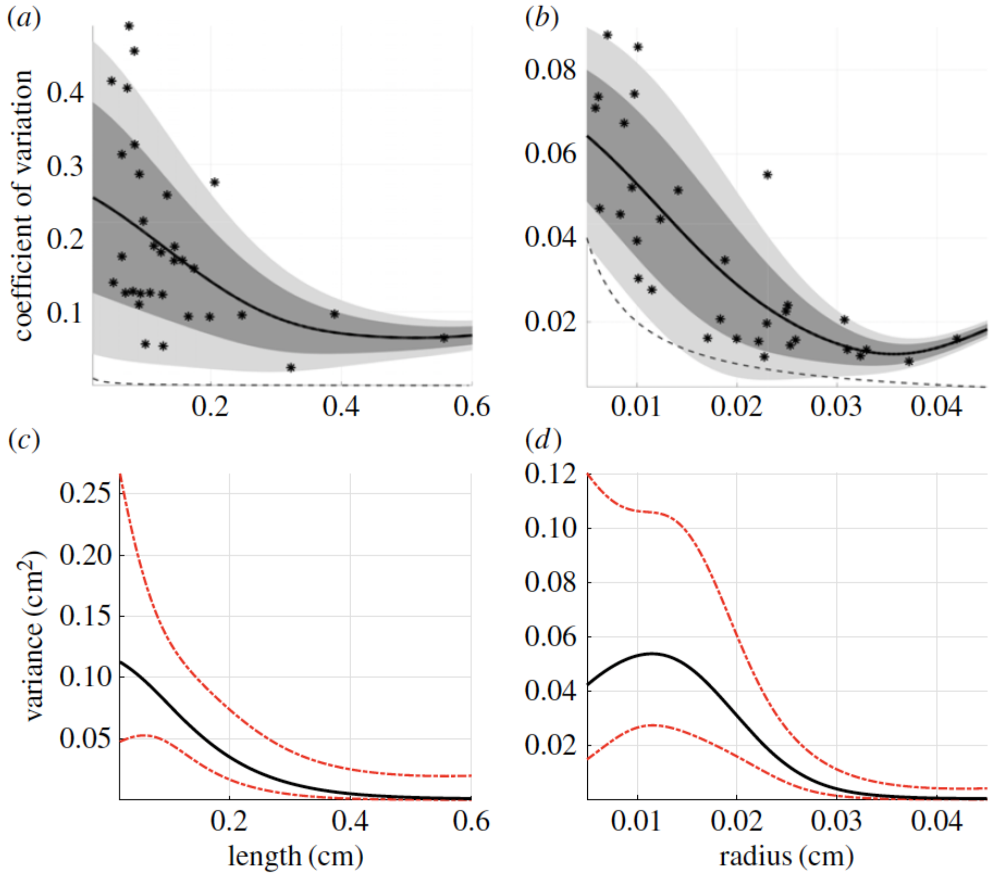
Colebank et al. (2019) **Influence of image segmentation on one-dimensional fluid dynamics predictions** …. 10.1098/rsif.2019.0284

NC STATE UNIVERSITY Ex 1: vessel radii variance across 3D renderings

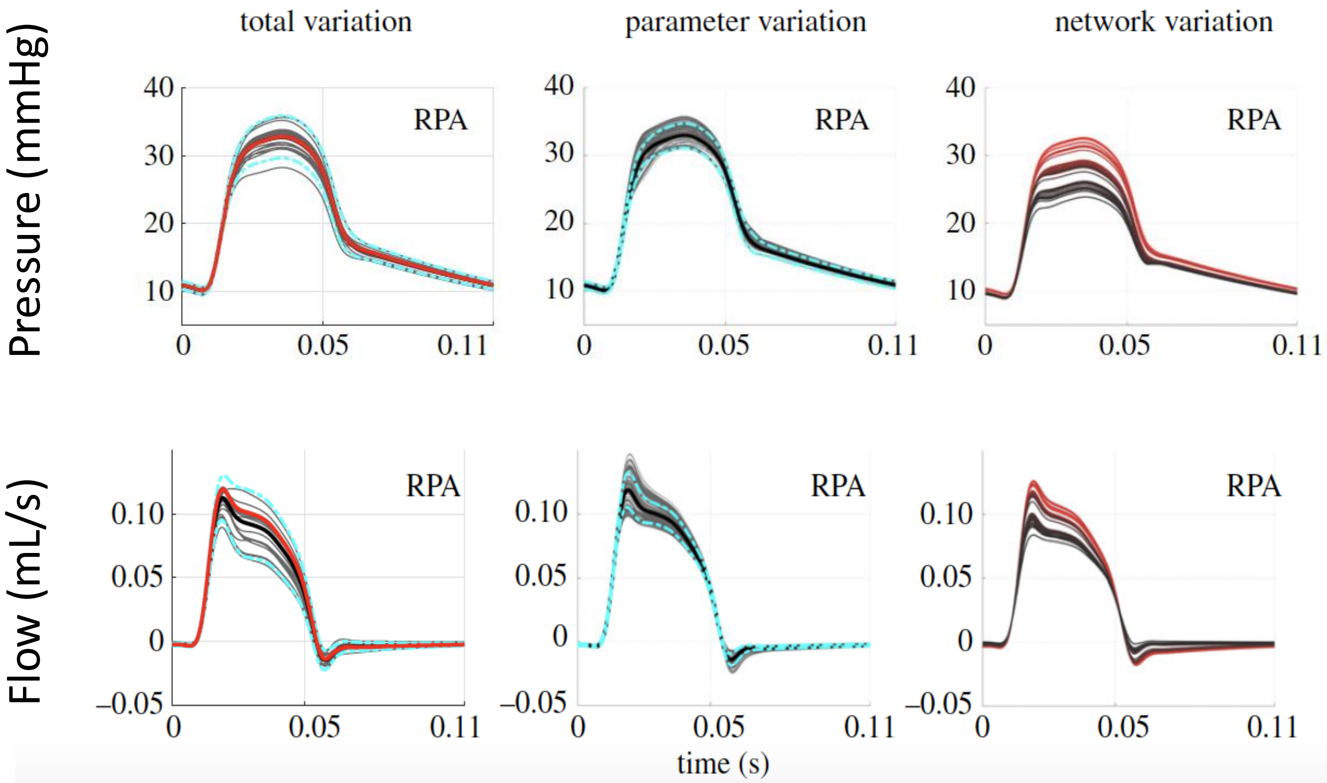


- Extracted radii from 32 unique vessels w/ varying caliber in 25 renderings of the same image
- Generated PDF/CDF
- Sampled from GP





Ex 1: Fluid dynamics predictions

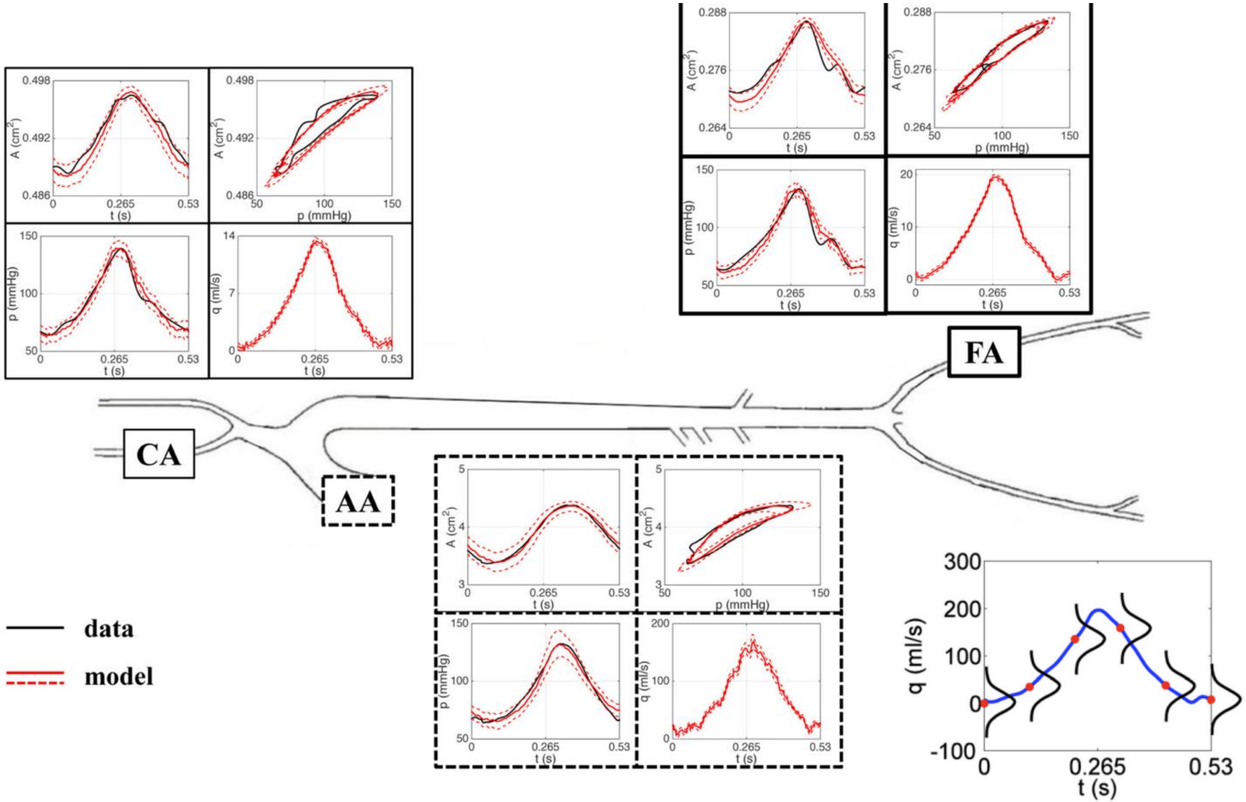


Total variation:
Run simulations in 25 rendered networks adjusting BCs.

Parameter variation:
Sample radii and length from GP posteriors. Network topology and BC parameters fixed.

Network variation:
Change network connectivity and size adjusting BCs.

Ex 2: Inflow estimation

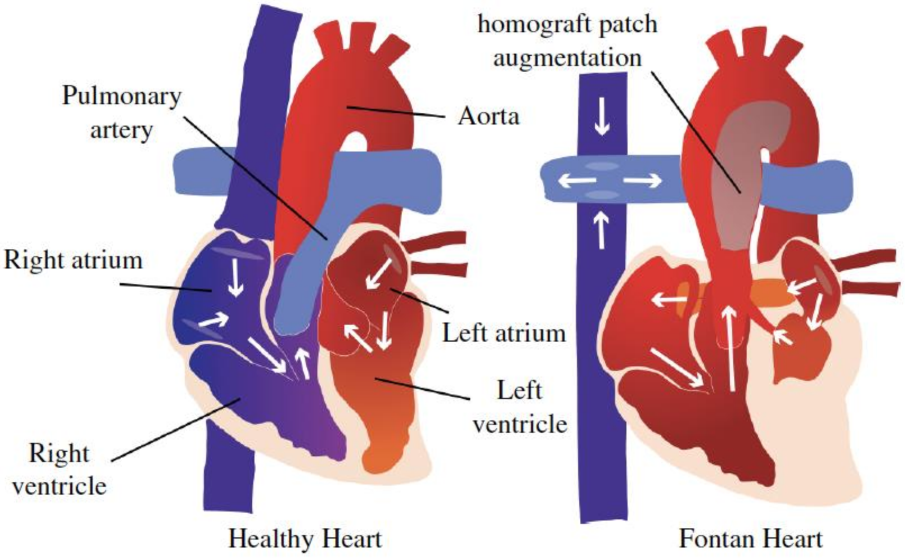


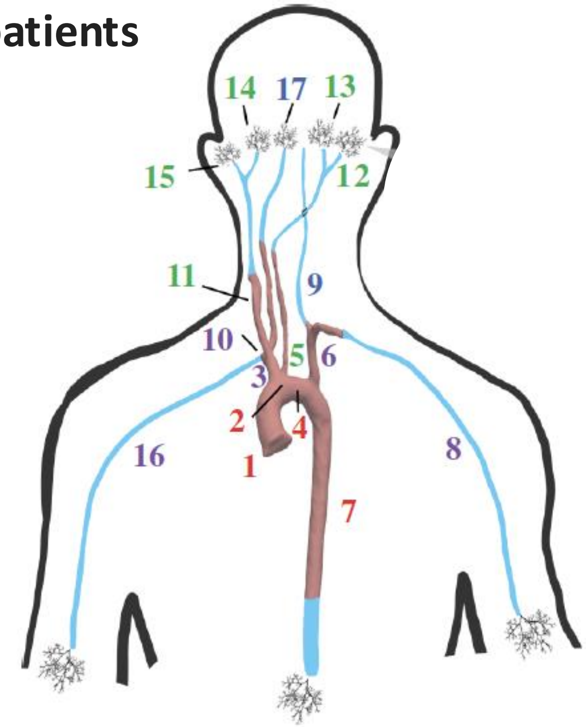
Gaussian prior at discretized points along the inflow w/ fixed standard deviations

Arnold et al. (2017) **Uncertainty quantification in a patient-specific one-dimensional arterial network model: EnKF-based Inflow estimator.** 10.1115/1.4035918

Ex 3: Fontan circulation

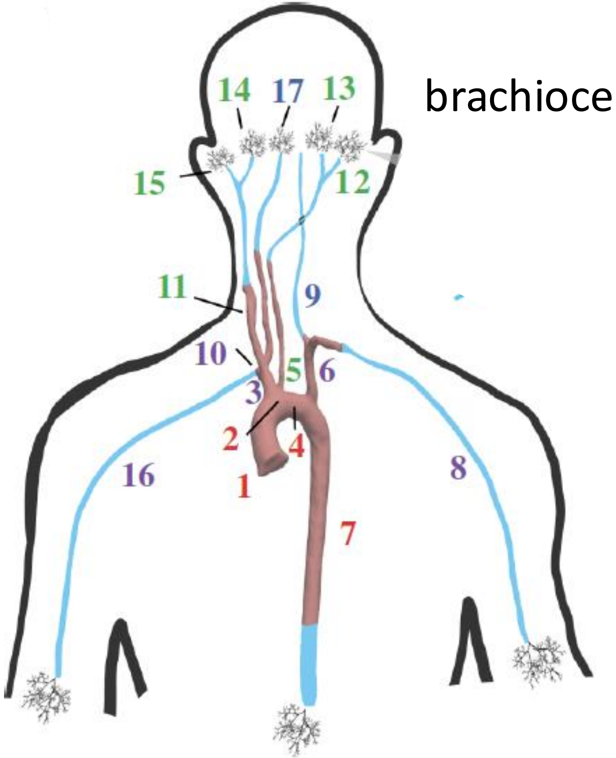
Understand effects of aortic remodeling in hyperplastic left heart syndrome (HLHS) and double outlet right ventricle (DORV) patients

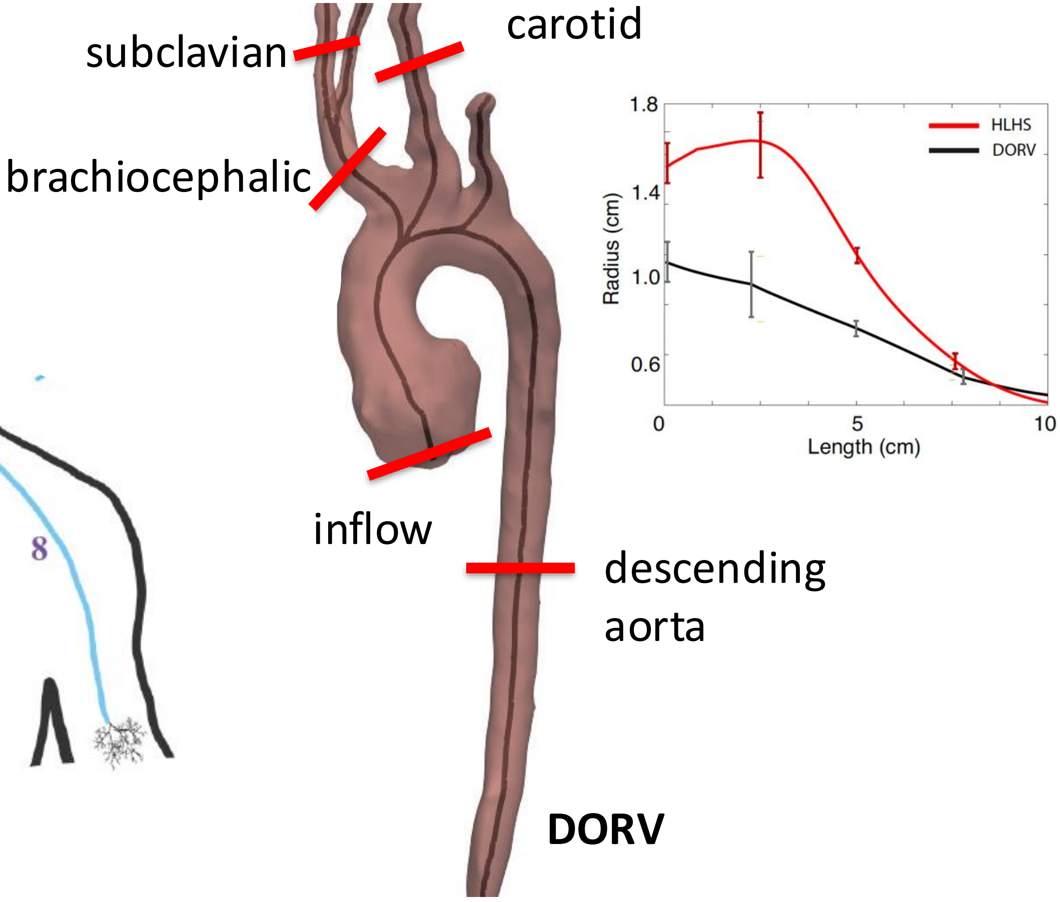


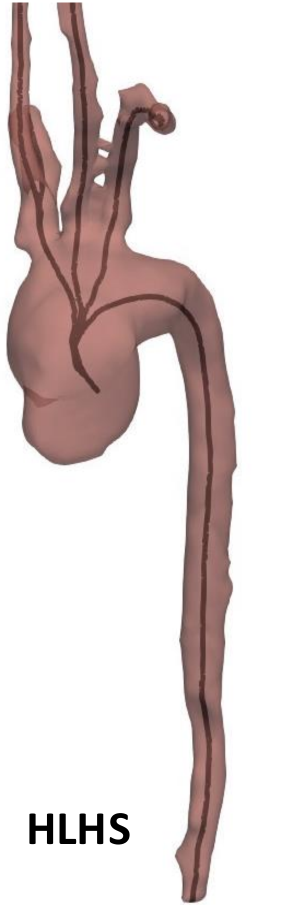


1. Taylor-LaPole et al. (2023) A computational study of aortic reconstruction in single ventricle patients. 10.1007/s10237-022-01650-w.
2. Taylor-LaPole et al. (2025) Parameter selection and optimization of a computational network model of blood flow …. 10.1098/rsif.2024.0663

Ex 3: HLHS vs DORV

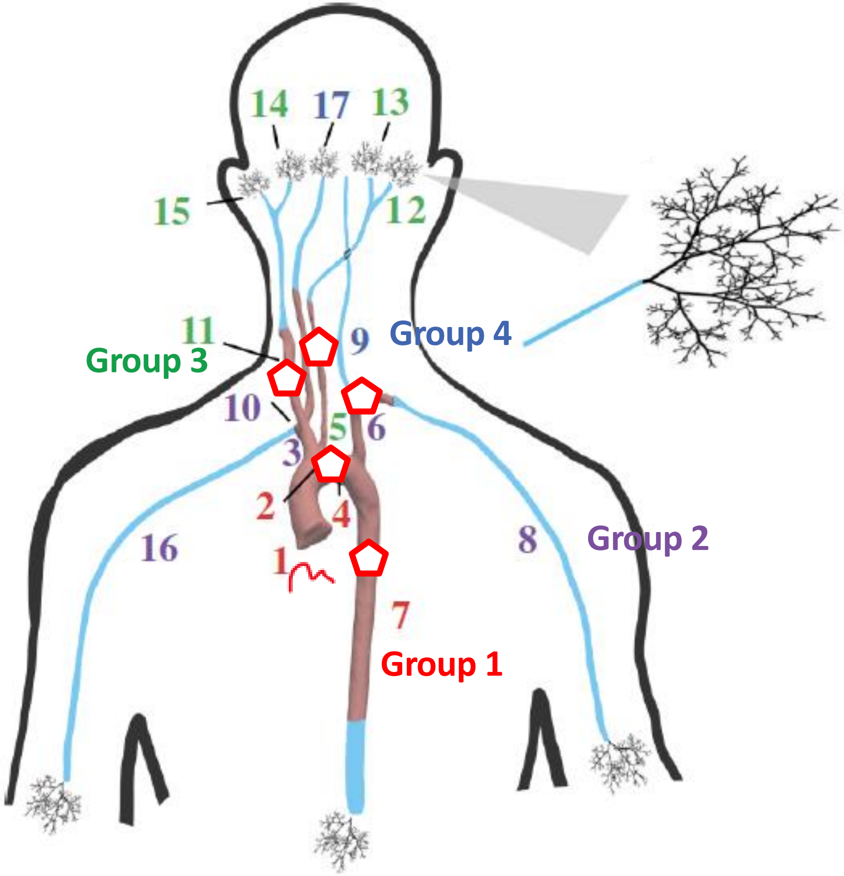






Taylor-LaPole et al. (2025) Parameter selection and optimization of a computational network model of blood flow …. 10.1098/rsif.2024.0663

Ex 3: Material & BC parameters



$$p(x,t) = \frac{4}{3}\frac{Eh}{r_0}\left(\sqrt{\frac{A}{A_0}} - 1\right), \qquad \frac{Eh}{r_0} = k_1 e_2^{-k_2 r_0} + k_3$$

For each large vessels (17 vessels – 4 groups)

$k_{1L},\ k_{2L},\ k_{3L}$

For each structured tree (9 outlets – 4 groups)

$k_{1S},\ k_{2S},\ k_{3S},\ \ \alpha,\ \beta,\ l_{rr},\ r_{min}$

4 Groups of small vessels (3 x 4 = 12)

4 Groups of small vessels (7 x 4 = 28)

Total: 12 + 28 = 40 parameters

Taylor LaPole et al. (2025) **Parameter selection and optimization of a computational network model of blood flow in single-ventricle patients.** 10.1098/rsif.2024.0663

Ex 3: Sensitivity analysis

Local sensitivity analysis

$$\tilde{S}_i(t) = \frac{dr(t;\theta)}{d(\log(\theta_i))} = \frac{dr(t;\theta)}{d\theta_i}\theta_i$$

$$i = 1,2,\ldots,P$$

Global sensitivity analysis (Morris Screening)

Elementary Effects:

$$d_i^j = \frac{r(\boldsymbol{\theta}^j + \boldsymbol{e}_i\Delta, t) - r(\boldsymbol{\theta}^j)}{\Delta}$$

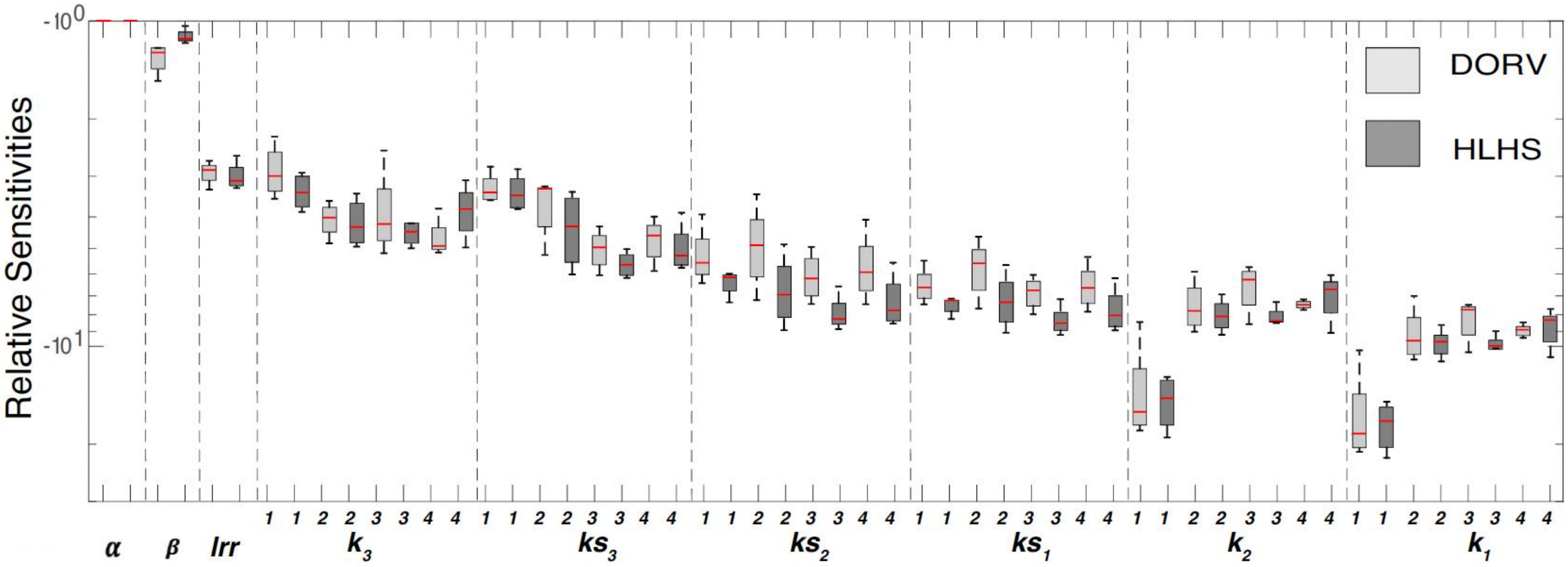
Individual effect:

$$\mu^* = \sum_{j=1}^{K} \left|d_i^j\right|$$

Individual effect:

$$\sigma_i^2 = \frac{1}{K-1}\sum_{j=1}^{K}\left(d_i^j - \mu_i\right)^2$$

Ex 3: Sensitivity analysis



Ex 3: Subset selection

Covariance matrix: $$C = s^2\left[\tilde{S}_s(t,\theta)^T\tilde{S}_s(t,\theta)\right]^{-1}$$

Correlation matrix:

$$c_{ij} = \frac{C_{ij}}{\sqrt{C_{ii}C_{jj}}}$$

SVD-QR factorization:

$$[U,S,V] = svd(S)$$

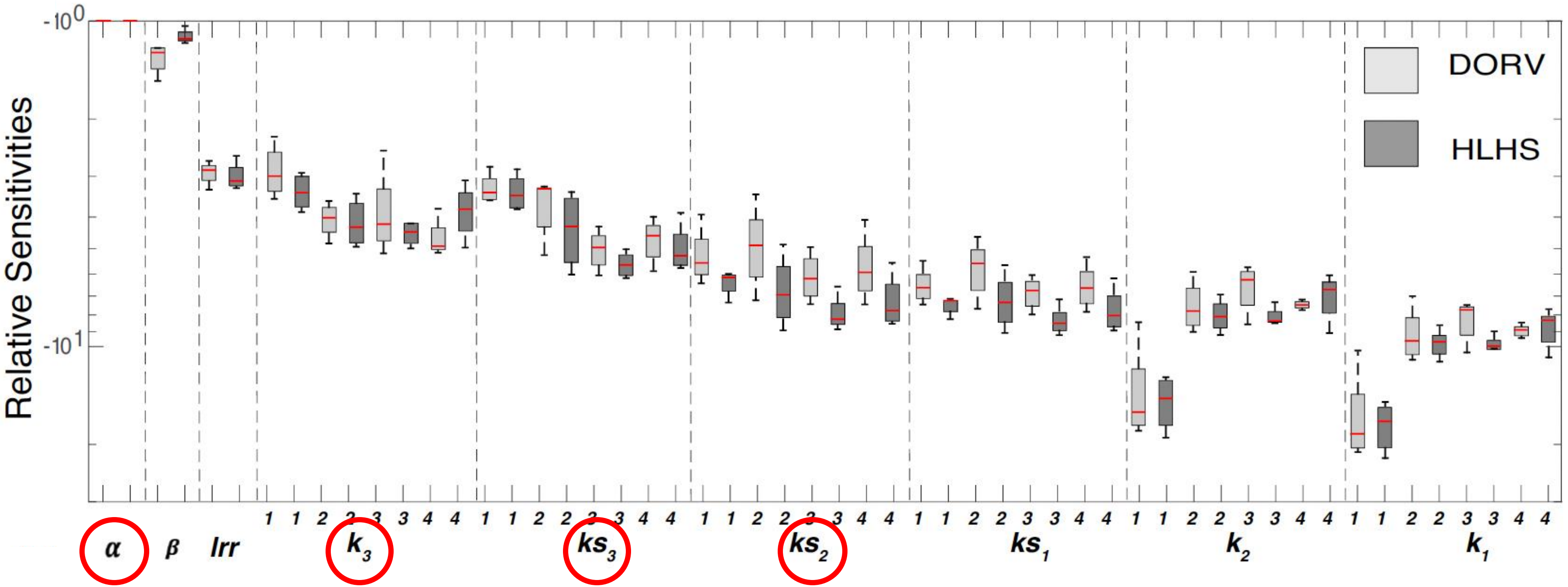
$$SV = diag(S)$$

$$SV_n = \frac{diag(S)}{SV(1)} > threshold$$

$$[Q,R,IMAP] = QR(V(:,n))$$

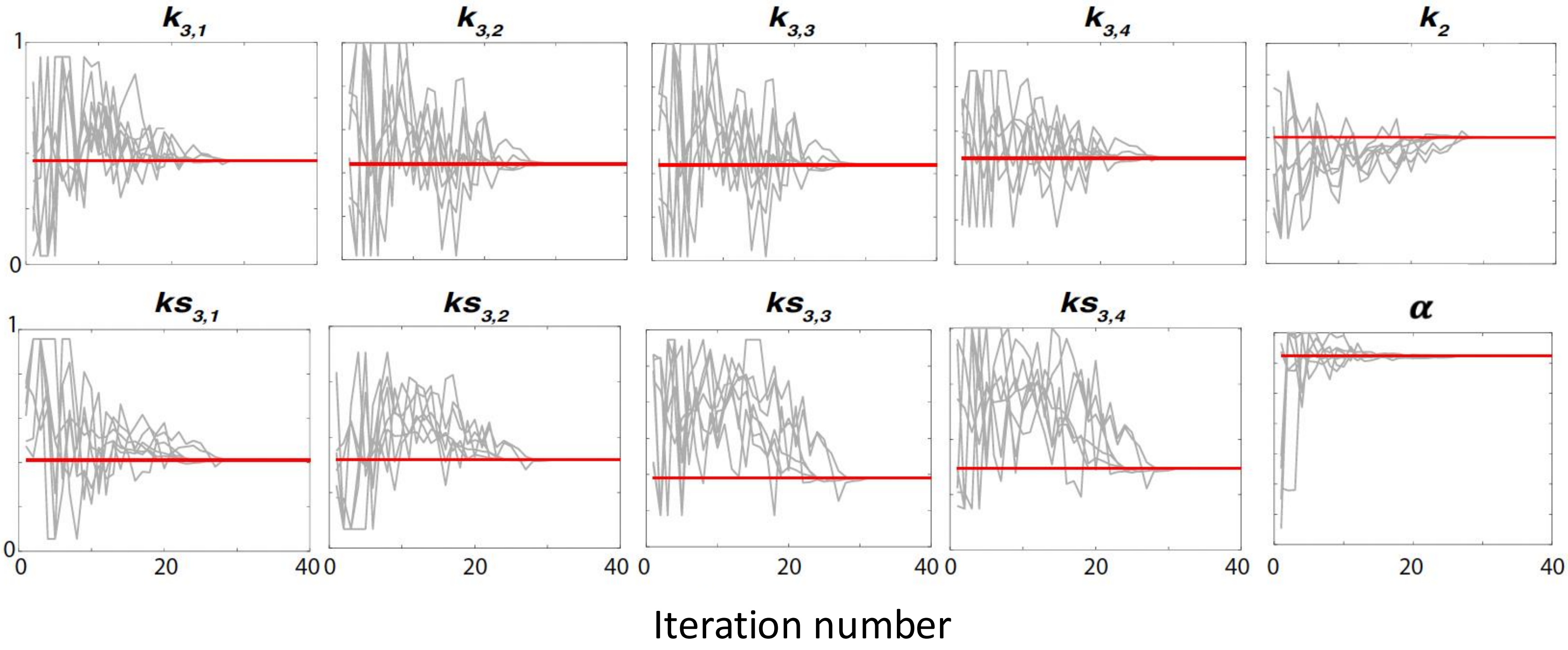
Active subspaces -

Ex 3: Sensitivity analysis

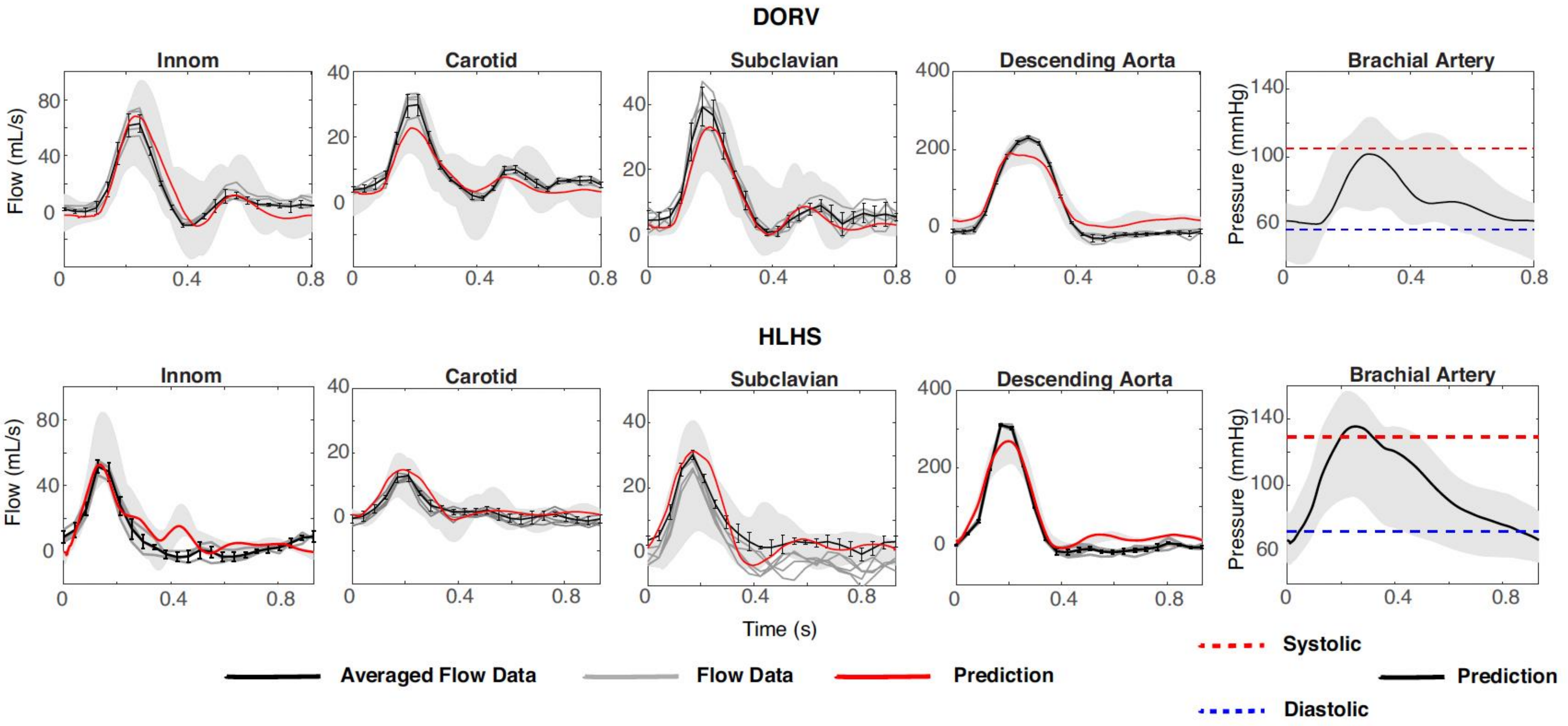


Parameter subset: $\tilde{\theta} = \{\alpha, k_{3i}, k_{s3,i}, k_{s2,i}\}$

Ex 3: multi-start parameter inference



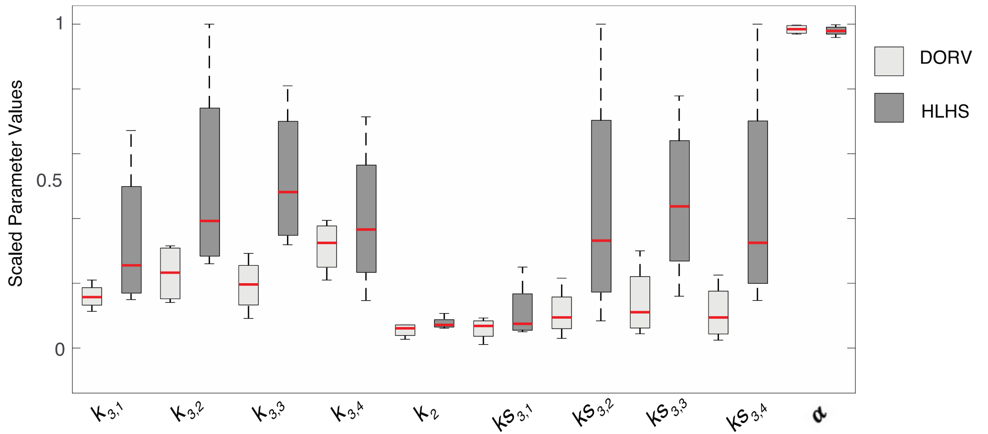
Ex 3: Hemodynamic predictions



Ex 3: DORV vs HLHS

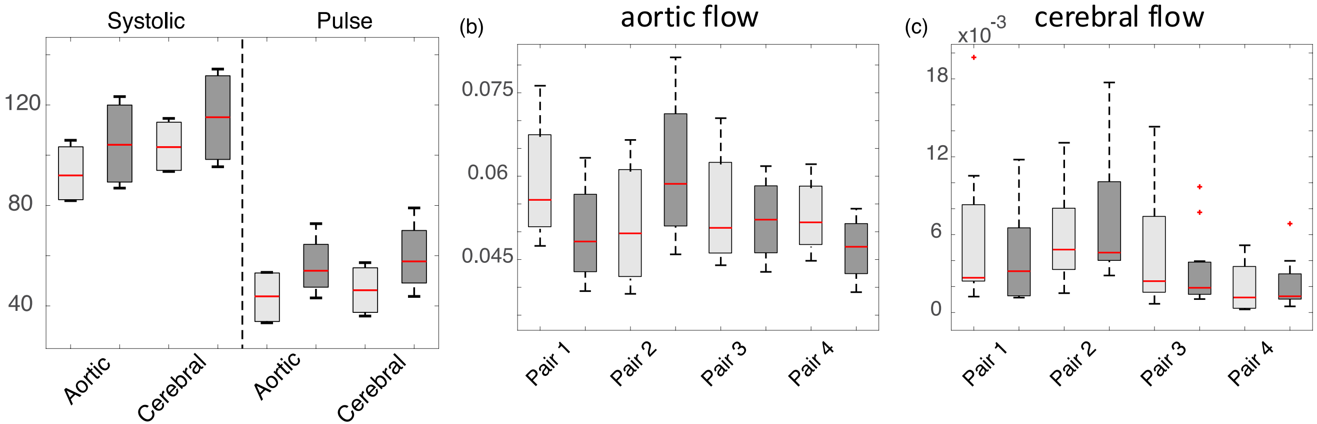
Parameter inference

- HLHS patients have higher large vessel vascular stiffness than DORV
- HLHS patients inferred parameters have greater variance compared to DORV

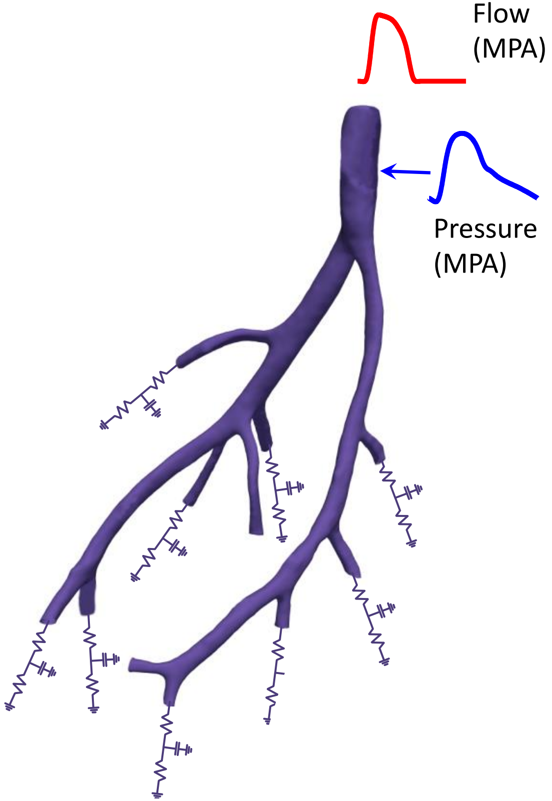


Predictions

- HLHS has higher systolic and pulse pressures
- HLHS patients have smaller variance and lower pulse flow in cerebral vessels



Ex 4: Sensitivity analysis & parameter inference



Boundary Condition (Windkessel model)

$$\frac{dp}{dt} = R_1 \frac{dq}{dt} - \frac{p}{R_2 C} + \frac{q(R_1 + R_2)}{R_2 C}$$

$$R_1 = 0.2 R_T, \qquad R_2 = 0.8 R_T, \qquad R_T = R_1 + R_2$$

Scaling factors

$$\hat{R}_{1,i} = r_1 \, R_{1,i}$$
$$\hat{R}_{2,i} = r_2 \, R_{2,i}$$
$$\hat{C}_i = c \, C_i$$

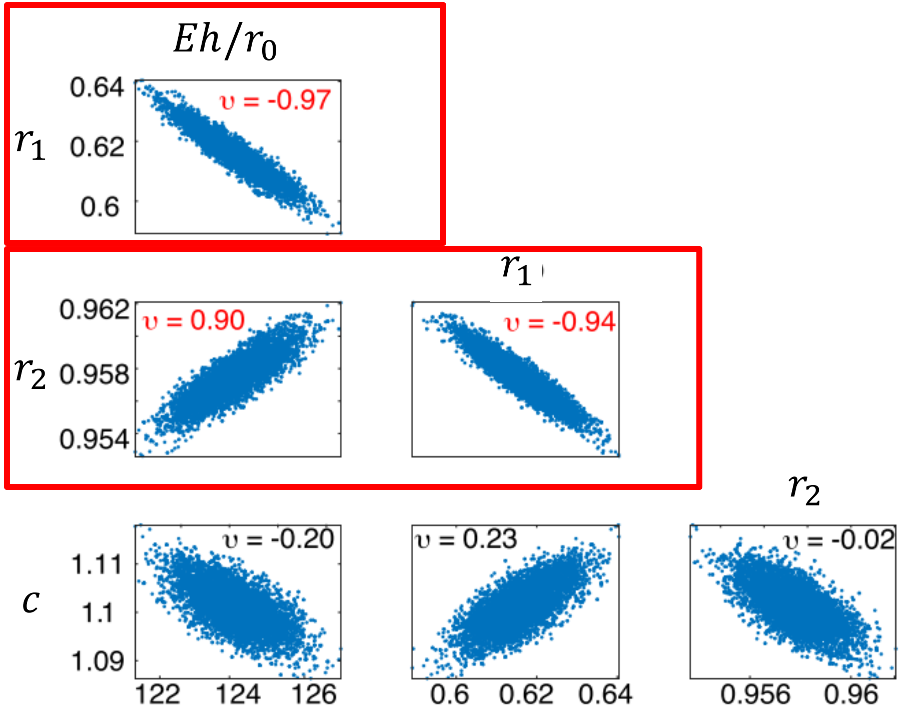
Constitutive equation

$$p(x,t) = \frac{Eh}{r_0}\left(\sqrt{\frac{A}{A_0}} - 1\right), \qquad \frac{Eh}{r_0} = k_1 e_2^{-k_2 r_0} + k_3$$

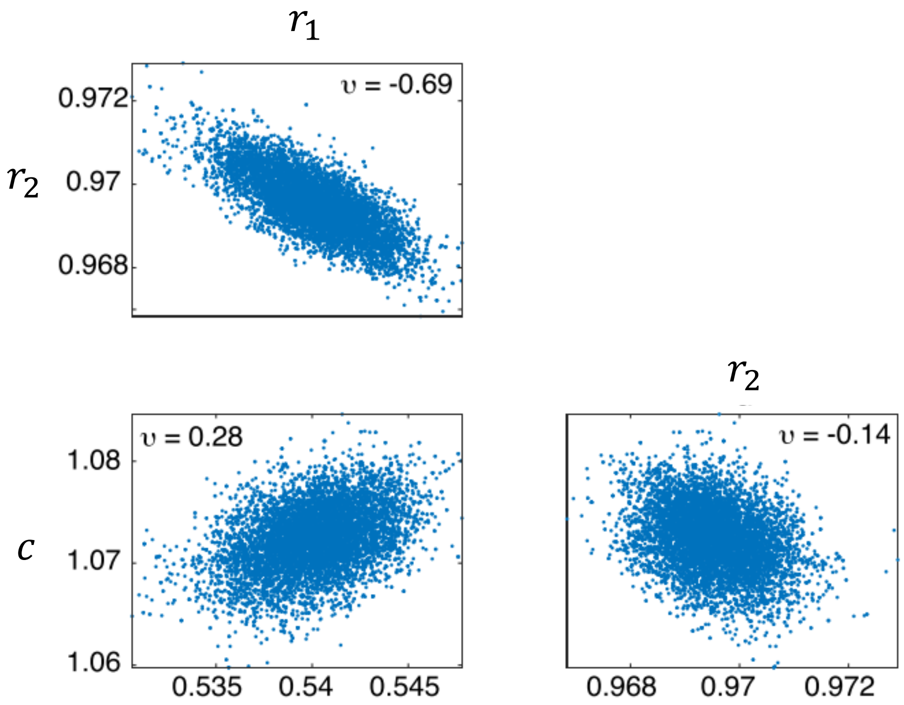
Colebank et al. (2022) **Sensitivity analysis and uncertainty quantification of 1D models of pulmonary hemodynamics ...** 10.1002/cnm.3242

Ex4: Pairwise posterior distributions

Original parameter set



Identifiable parameter set



Ex4: Uncertainty quantification

Frequentist parameter and model confidence intervals (asymptotic)

$$\theta_i^{CI} = \left[\hat{\theta}_i \pm t_{N-P}^{1-\alpha/2}\ \hat{s}\sqrt{(S^\top S)^{-1}}\right]$$

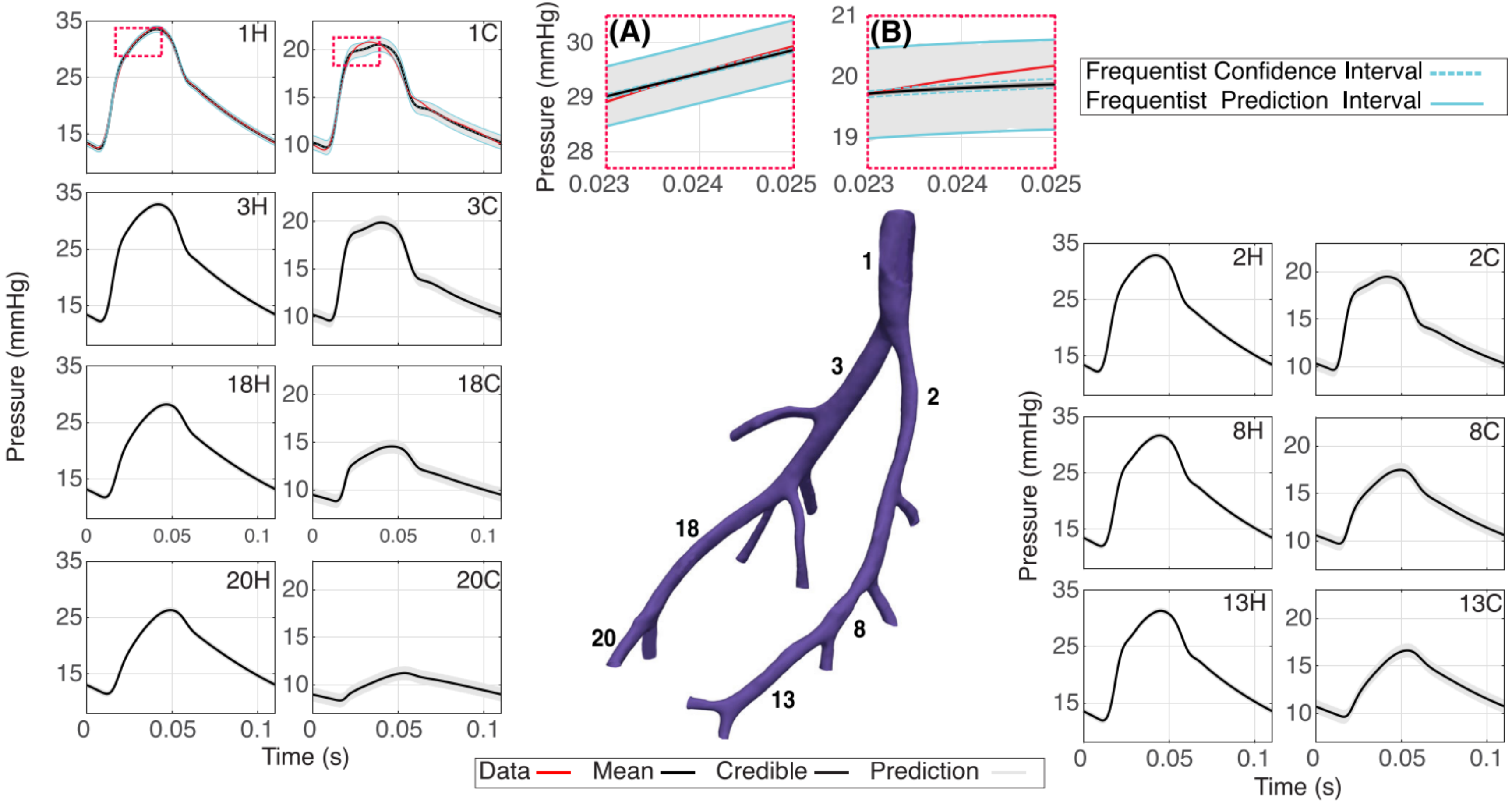
$$f(t_i;\theta)^{CI} = \left[f(t_i;\hat{\theta}) \pm t_{N-P}^{1-\alpha/2}\ \hat{s}\sqrt{S_i^\top (S^\top S)^{-1} S_i}\right]$$

Bayesian parameter posteriors

$$\pi(\theta|y) = \frac{\pi(y|\theta)\pi_0(\theta)}{\pi(y)}$$ “posterior ∝ likelihood × prior”

Bayesian credible intervals → sampling from posterior

Ex4: Uncertainty quantification



Ex4: Uncertainty quantification

Model Discrepancy

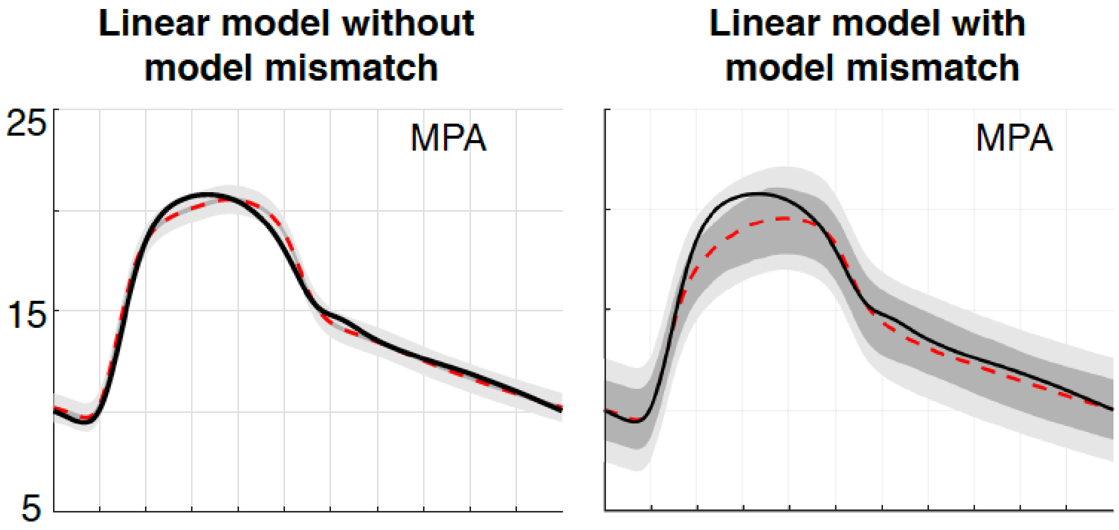
$$y(t_i) = f(t_i;\boldsymbol{\theta}) + \boldsymbol{\delta}(t_i) + \epsilon_i$$

$$\epsilon_i \sim N(0,\sigma^2)$$

$$\boldsymbol{\delta} \sim GP\big(m(t), k(x,x')\big)$$

The model is **always** wrong!

Ignoring this may bias estimates and reduce predictive uncertainty



Paun et al. (2020) **Assessing model mismatch and model selection in a Bayesian uncertainty quantification analysis** …. 10.1098/rsif.2020.0886

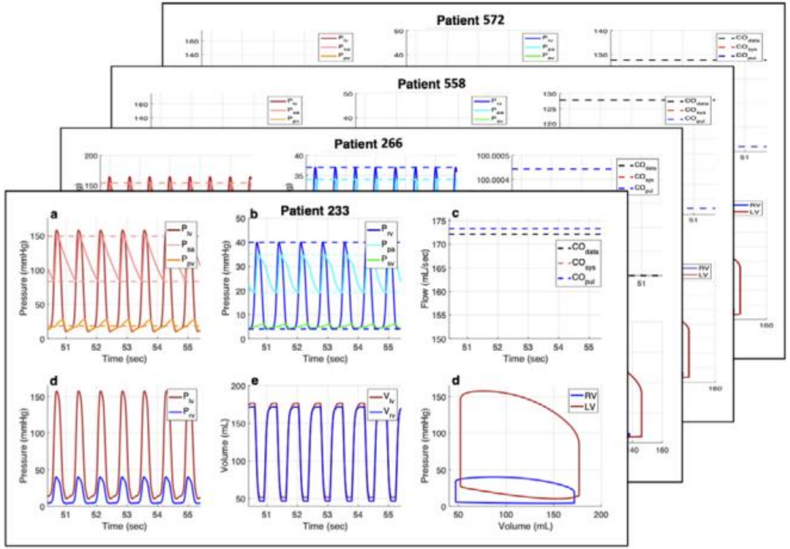
Ex5:
0D model

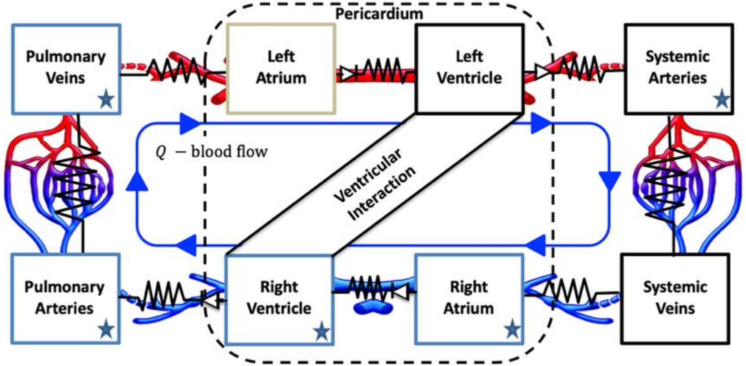
Patient 572			
$P_{rv,syst}$	31	$P_{sa,syst}$	116
			66
			100
			82
			180
			M

Patient 558			
$P_{rv,syst}$	30.5	$P_{sa,syst}$	114
			49
			90
			101
			170
			F

Patient 266			
$P_{rv,syst}$	37	$P_{sa,syst}$	154
			81
			90
			75
			169
			M

Patient 233			
$P_{rv,syst}$	40	$P_{sa,syst}$	149
$P_{rv,diast}$	4	$P_{sa,diast}$	83
$P_{pa,syst}$	34	*Heart Rate*	83
$P_{pa,diast}$	14	*Weight*	96
P_{wedge}	11	*Height*	172
Cardiac Output	6	*Sex*	F



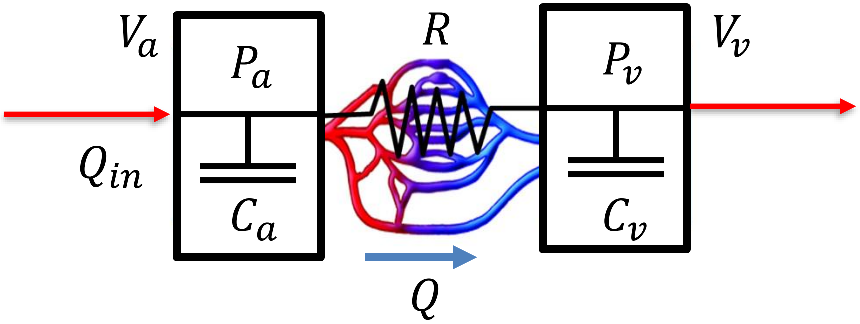


★ static BP data

☐ RHC dynamic BP data

Colunga et al. (2023) **Parameter inference in a computational model of haemodynamics in pulmonary hypertension.** 10.1098/rsif.2022.0735

Ex 5: Model equations



Conservation of volume

$$\frac{dV_a}{dt} = Q_{in} - Q$$

Ohm's law

$$Q = \frac{P_a - P_v}{R}$$

$$Q_{valve} = \begin{cases} \dfrac{P_{before} - P_{after}}{R} & \text{open} \\ 0 & \text{closed} \end{cases}$$

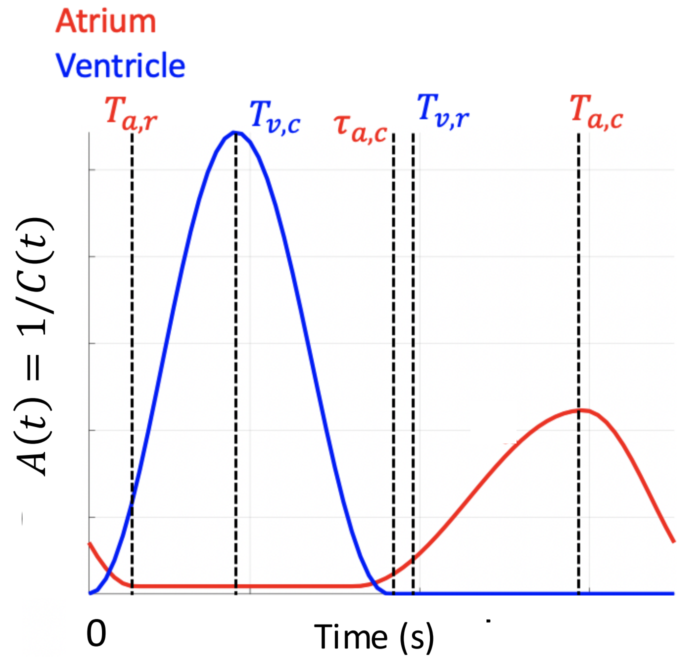
Pressure-Volume relation

$$P_i - P_{i,un} = E_i(V_i - V_{i,un})$$

Electrical circuit analogy

Current =	Flow (Q, mL/s)
Voltage =	Pressure (P, mmHg)
Charge =	Volume (V, mL/s)
Capacitance =	Compliance (C, mmHg/mL)
Elastance =	1/Compliance (E, mL/mmHg)
Resistance =	Resistance (R, mmHg s/mL)

Ex 5: Heart contraction



Ventricular contraction

Ventricular relaxation

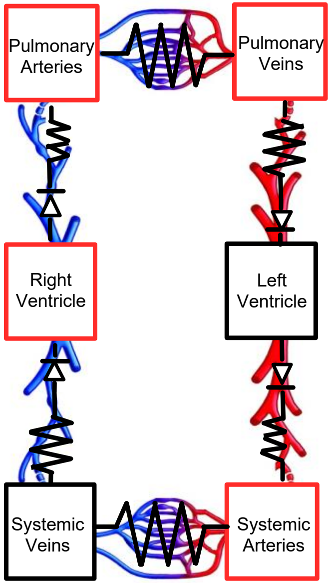
Active contraction

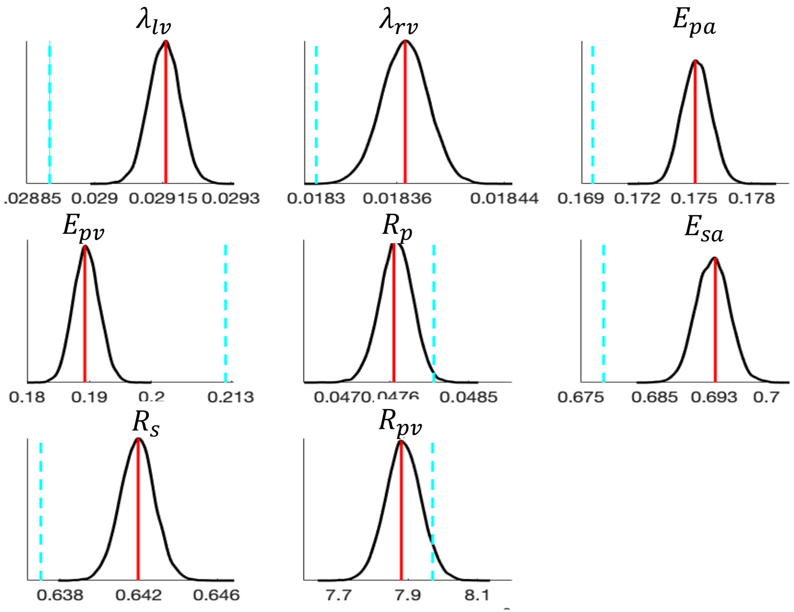
$$P_h - P_{h,un} = A(t) \; E_{lv}[(V_h - V_{h,un})] + (1 - A(t))P_0 \, [e^{\lambda(V_{lv} - V_{0,lv})} - 1]$$

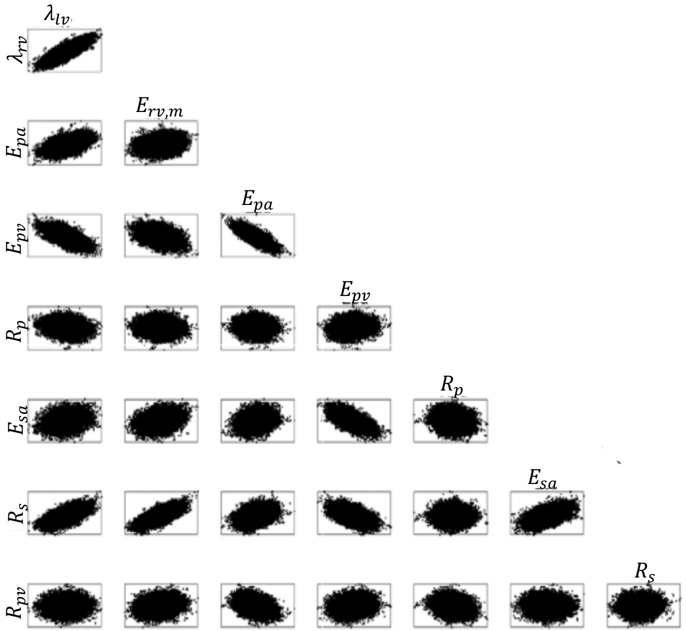
Passive relaxation (λ diastolic relaxation, unit: mL^{-1})

Ex 5: Parameter inference

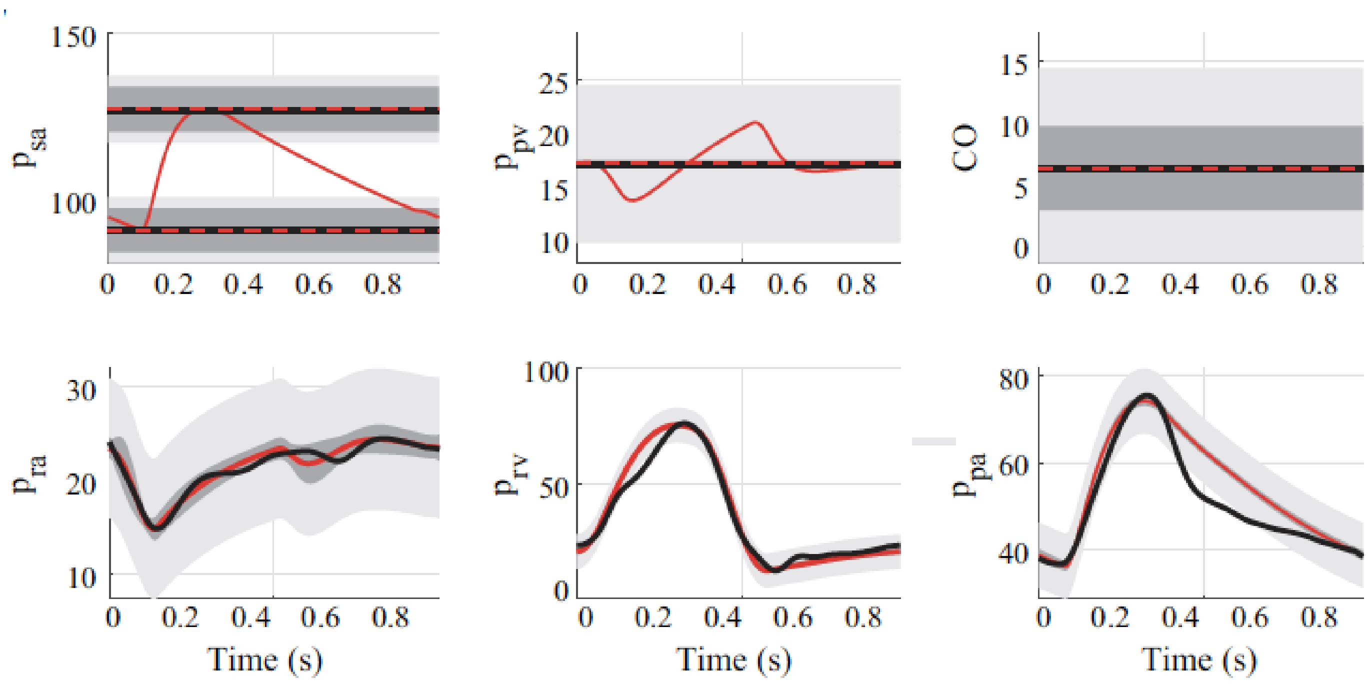
Identifiable subset $\hat{\theta} = \{ \lambda_{lv}, , \lambda_{rv}, E_{pa}, E_{pv}, R_p, E_{sa}, R_{pv}, R_s \}$







Ex 5: Uncertainty bounds



Optimal value **Confidence interval** **Prediction interval** **Data**

Colunga et al. (2023) **Parameter inference in a computational model of haemodynamics in pulmonary hypertension.** 10.1098/rsif.2022.0735

Ex 5: Model predictions – heart transplant

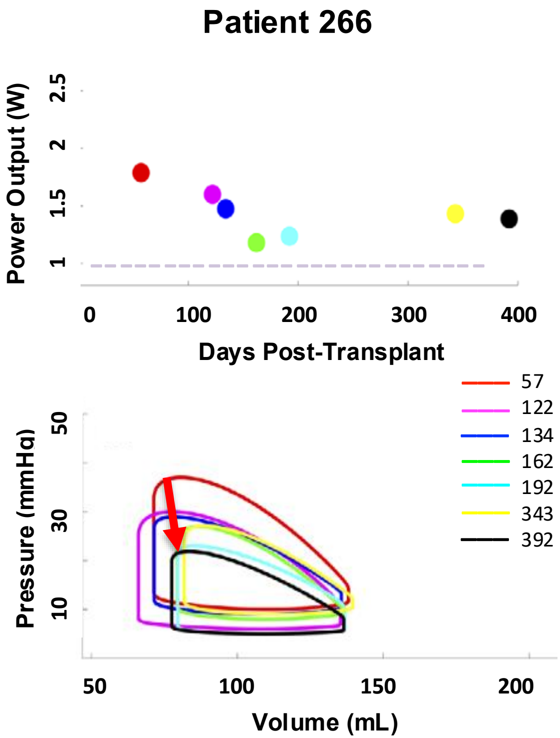
Day 57
Power: 1.8 W
mPAP > 20 mmHg

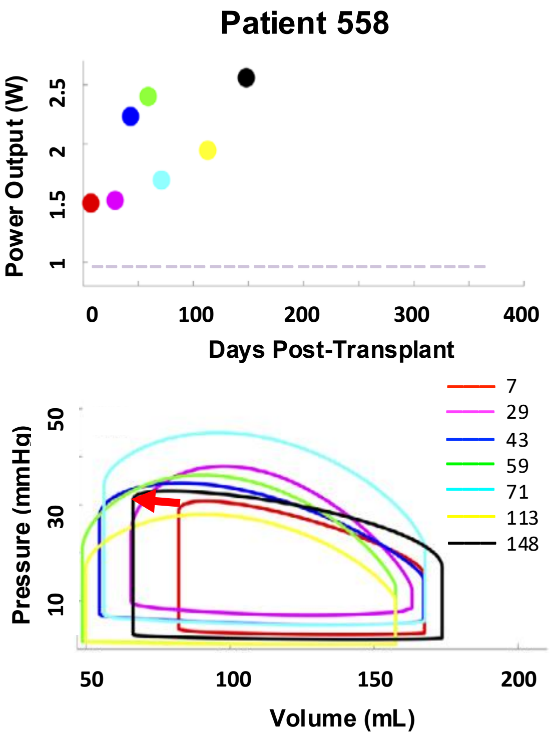
Day 392
Power: 1.4 W
mPAP < 20 mmHg

Compliance ⬆ ~100%
Resistance ⬇ ~17%

successful recovery

Clinical validation
Patient exhibited normal cardiovascular function 43-month post-transplant





Day 7
Power: 1.5 W
mPAP > 20 mmHg

Day 148
Power: 2.6 W
mPAP > 20 mmHg

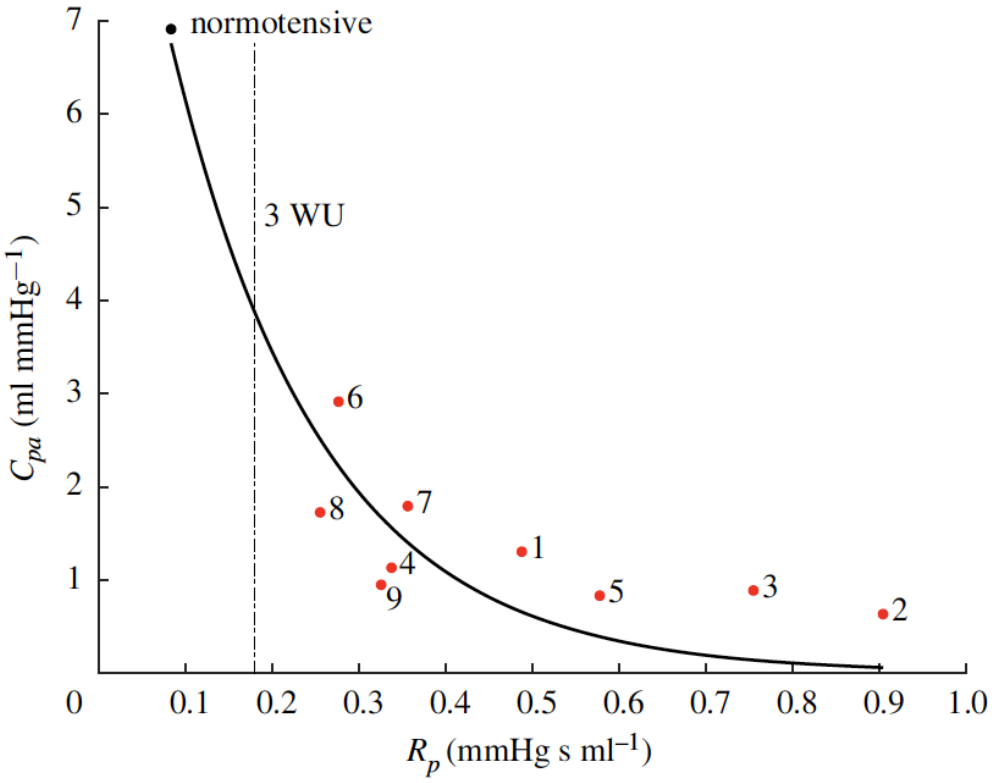
Compliance ⬆ ~38%
Resistance ⬆ ~80%

unsuccessful recovery

Clinical validation
Patient exhibited biventricular failure 48-month (post-transplant

Colunga et al. (2020). **Deep phenotyping of cardiac function in heart transplant patients ….** 10.1113/JP279393

Ex 5: Model predictions – disease severity



Colunga et al. (2023) **Parameter inference in a computational model of haemodynamics in pulmonary hypertension.** 10.1098/rsif.2022.0735

Ex 6: Ventricular ventricular interaction (VVI)

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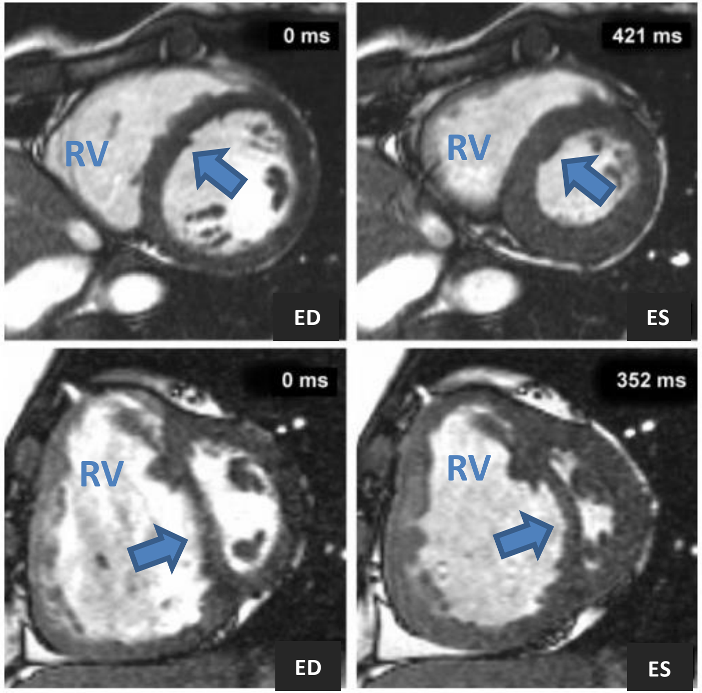
End Diastole (Relaxation) | End Systole (Contraction)

Control

Pulmonary Hypertension



Septal Pressure

$$P_{spt} = P_{lv} - P_{rv}$$

$$P_{spt} = \begin{cases} < 0\,, & P_{lv} < P_{rv} \\ > 0\,, & P_{lv} > P_{rv} \\ = 0\,, & P_{lv} = P_{rv} \end{cases}$$

Septal Volume

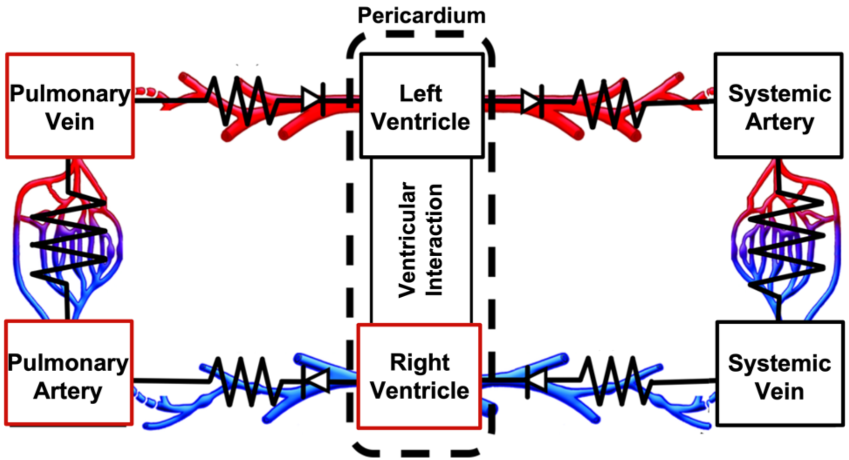
- volume attributed to septal position
- Right bowed septum
  $V > 0$
- Centered septum
  $V = 0$
- Left bowed septum (PH)
  $V < 0$

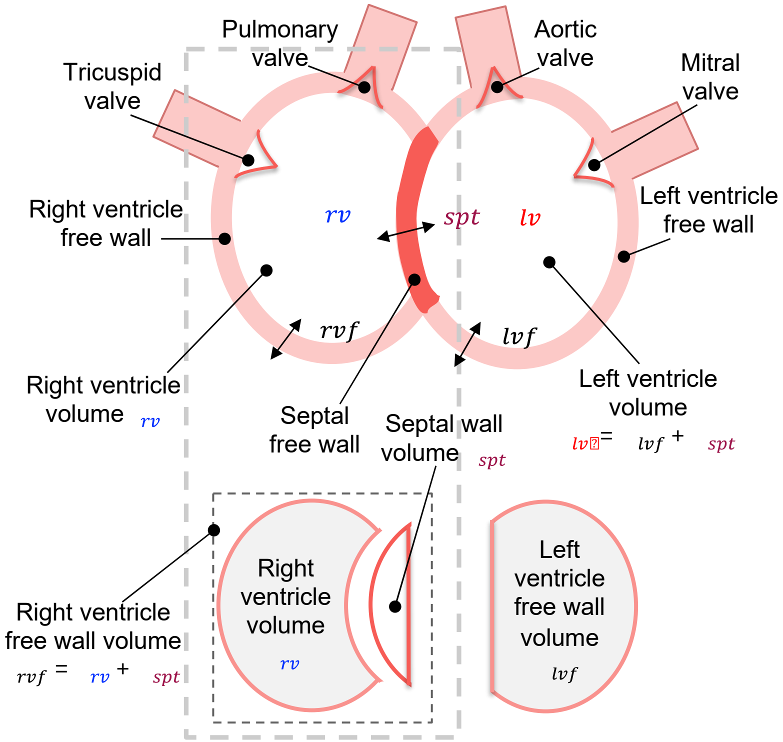
Goals:

1. Devise a model that can predict the effects of septal deviation
2. **Test if septal wall deviation impact left and right ventricular volume and pressure**

Colunga et al. (2024). **The importance of incorporating ventricular–ventricular interaction (VVI) …** 10.1016/j.mbs.2024.109242

Ex 6: Ventricular ventricular interaction (VVI)





Pressure and volume relations

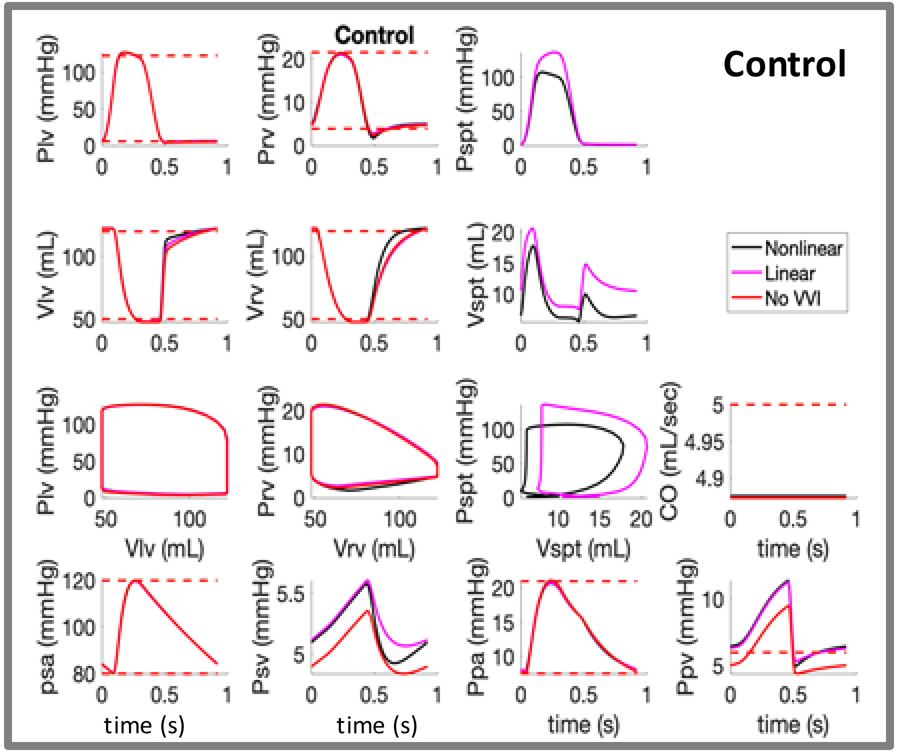
$$V_{lvf} = V_{lv} - V_{spt}$$
$$V_{rvf} = V_{rv} + V_{spt}$$

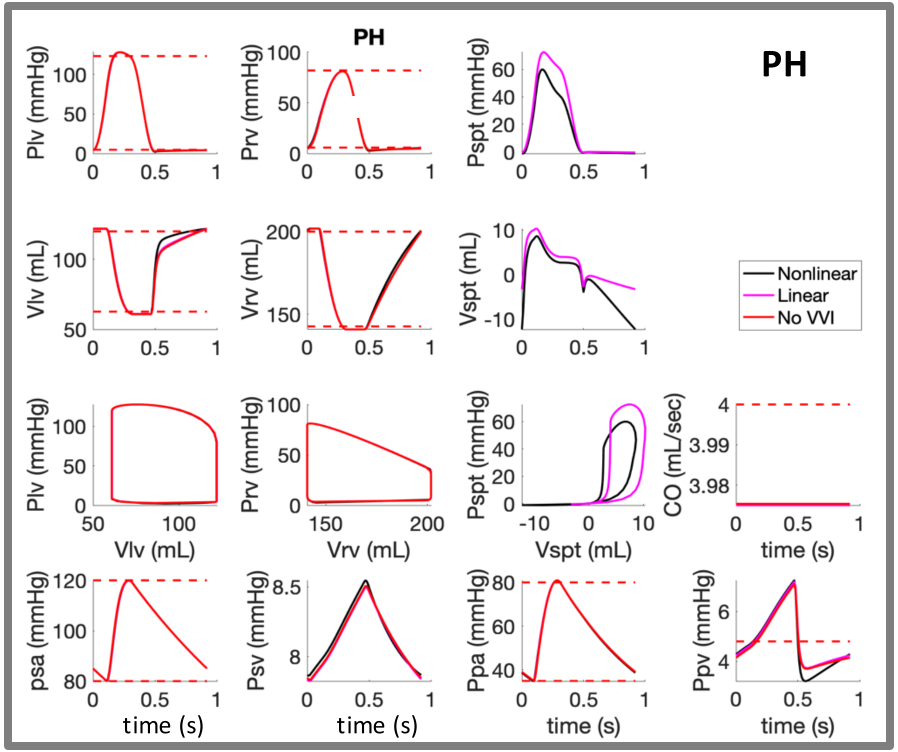
$$P_{lv} = P_{lvf}$$
$$P_{rv} = P_{rvf}$$
$$P_{spt} = P_{lv} - P_{rv}$$

Pressure-volume relation

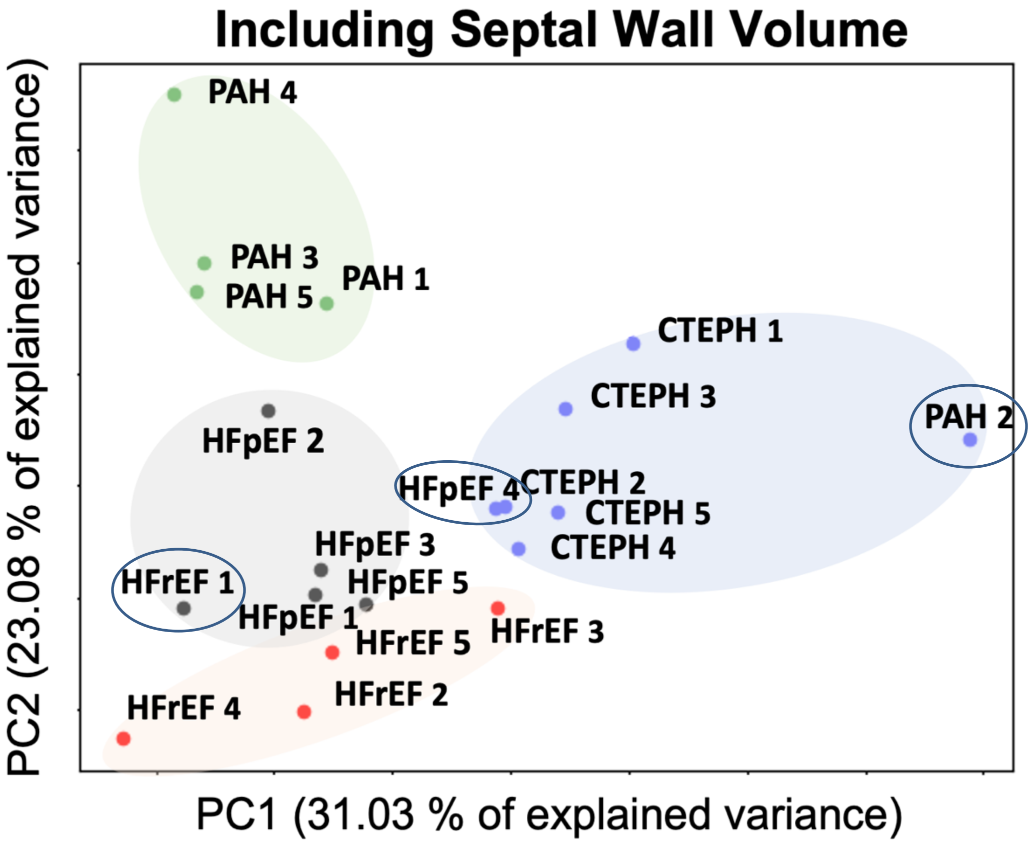
$$P(V) = e_v(t)P_{es}(V) + (1 - e_v(t))P_{ed}(V)$$

Ex 6: Ventricular ventricular interaction (VVI)





Ex 6: Clustering



Observations

- Including septal volumes improve clusters: 80% PAH, 100% CTEPH, 80% HFrEF, 80% HFpEF
- PAH 2, HFpEF 4, HFrEF 1: consistently clustered incorrectly
- $E_{rv,es}$ strongly correlated with PC2 when septal volume is excluded
- $E_{rv,es}$ becomes negligible when septal volume included

Summary

- Uncertainty exist at multiple levels (domain, fluid dynamics, inflow & outflow) each have similar level of uncertainty
- Important to understand data
- Local and global methods to determine sensitivities and uncertainty
- Essential to find a set of identifiable parameters (challenge – parameter fixing)
- Inferred parameters can help generate biomarkers making it easer to distinguish disease severity and phenotype used to improve targeted treatments
- Classification and clustering on model parameters can be done using less data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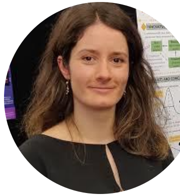
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Directed Research for Undergrads in Math and Stats

RTG: Uncertainty Quantification for Life Sciences

Thank you!

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