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Using parameter estimation to analyzing outcome for heart transplant patients

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RTG – Parameter Estimation Workshop 2019

CARDIOVASCULAR DYNAMICS GROUP

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Parameter Estimation and UQ

- What question is the model addressing and what data are available

- Uncertainty in
  - Model assumptions
  - Model parameters

Heart Transplant and Pulmonary Hypertension (PH)

- Heart transplant patients are followed for up to a year with periodic right heart catheterizations (RHCs) to identify post-transplant complications and guide treatment
- The repeated right heart catheterization (RHC) measurements of ventricular and pulmonary arterial pressure are used to monitor post-transplant pulmonary hypertension, which if not resolved or increases in magnitude can lead to complications in post-transplant recovery

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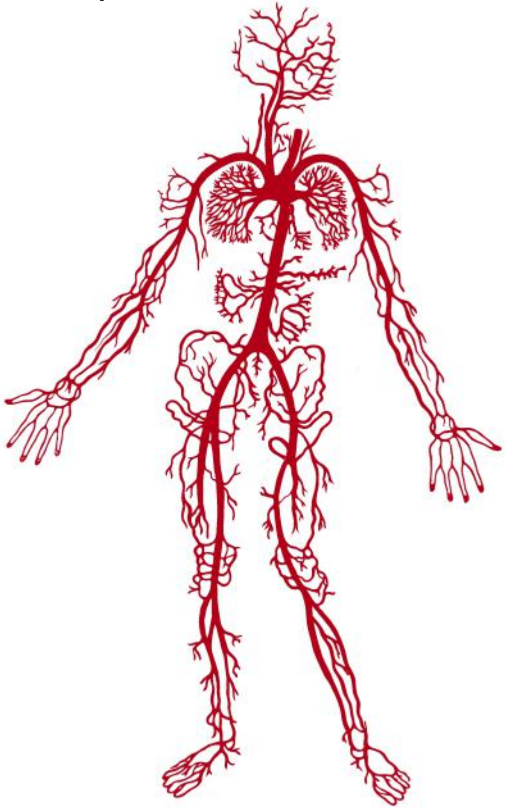
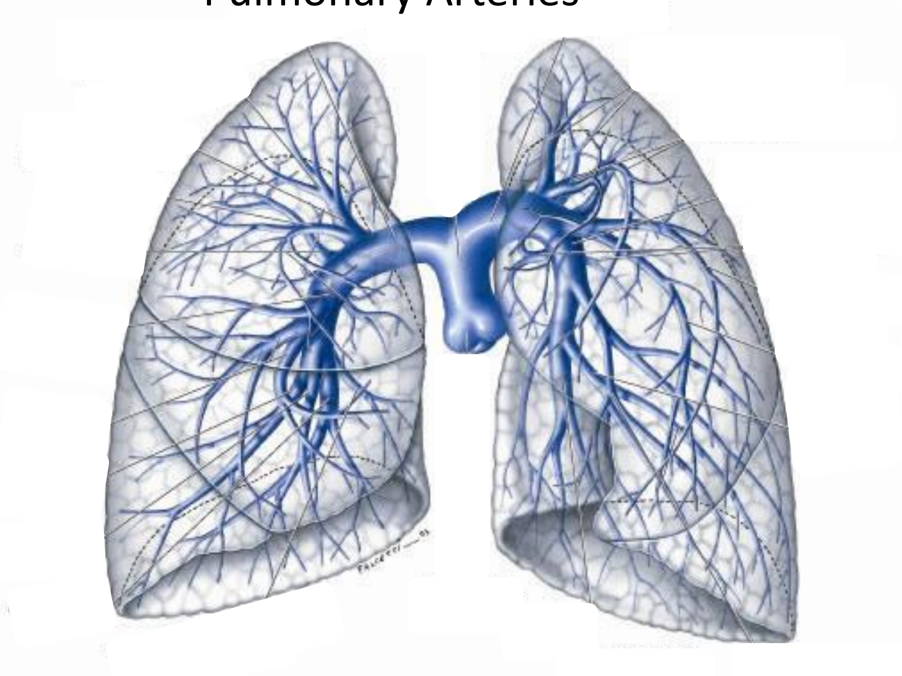
Pulmonary Hypertension

Systemic Arteries



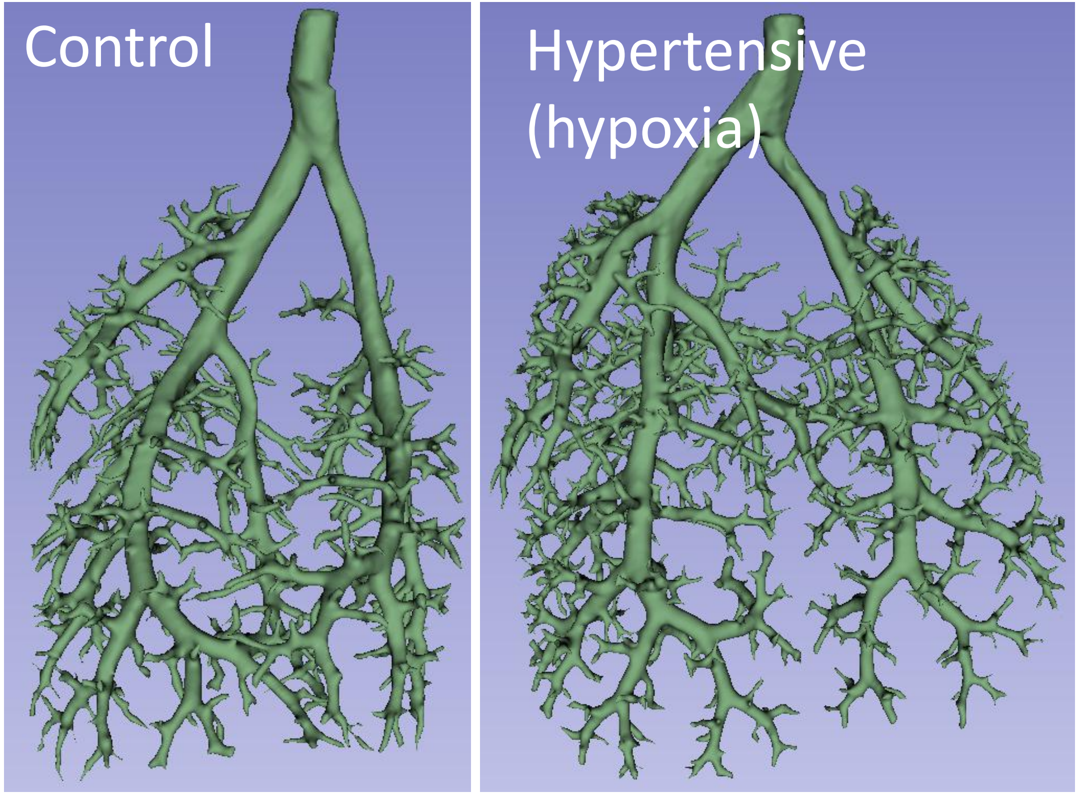
Pulmonary Arteries

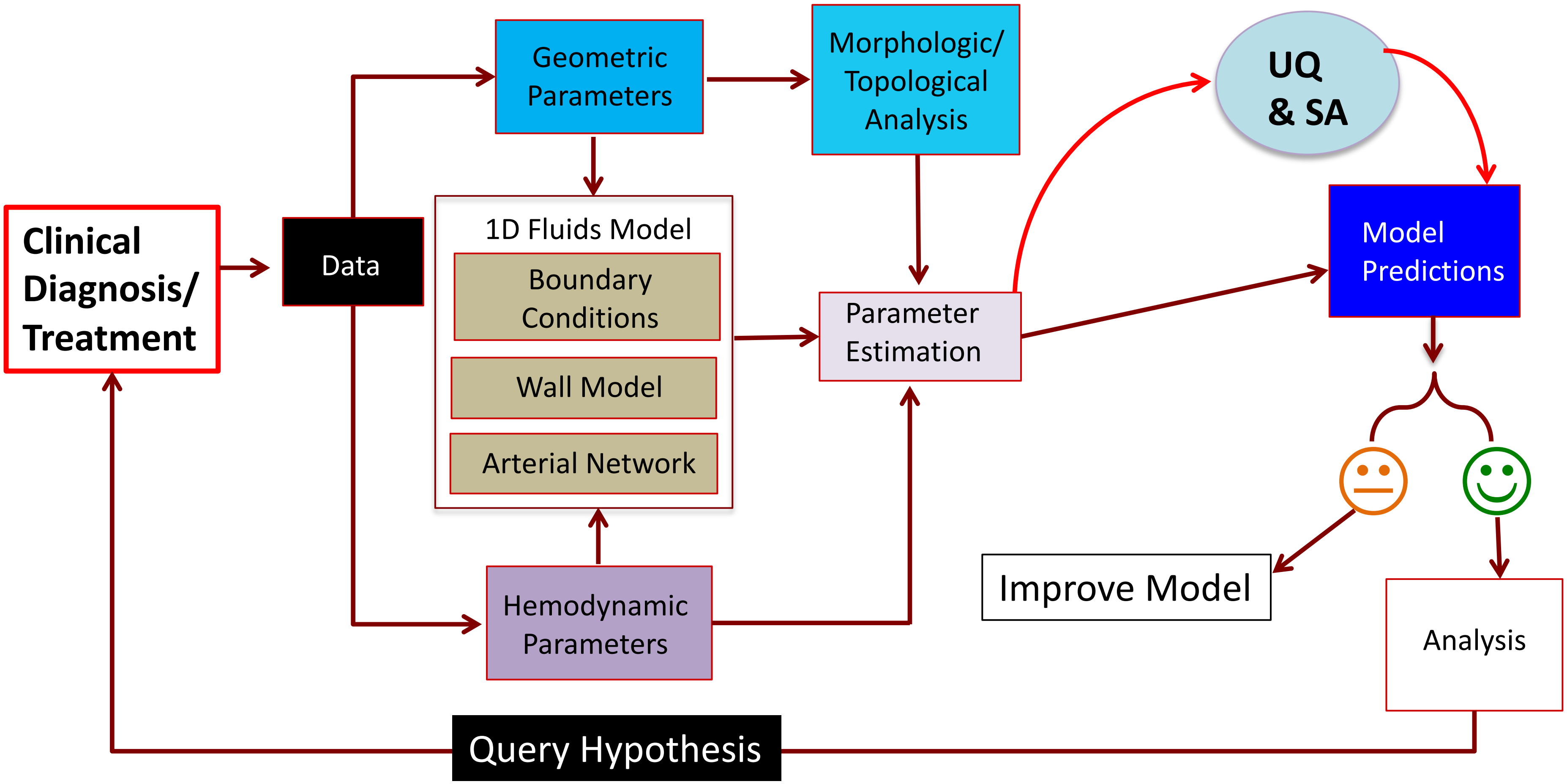


- Rapidly branching network
- Low pressure, low resistance, high compliance

Pulmonary Hypertension

- Pulmonary hypertension associated with vascular remodeling
- Tissue remodeling (wall thickness and stiffness)
- Morphological remodeling (changes in geometry and topology)
  - Larger vessels dilate
  - Smaller vessel constrict




Geometric Parameters
Morphologic/ Topological Analysis
UQ & SA
Clinical Diagnosis/ Treatment
Data
1D Fluids Model
Boundary Conditions
Wall Model
Arterial Network
Parameter Estimation
Model Predictions
Improve Model
Analysis
Hemodynamic Parameters
Query Hypothesis

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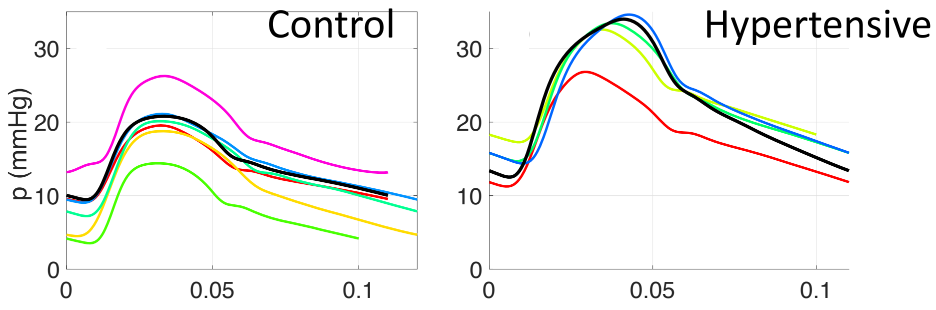
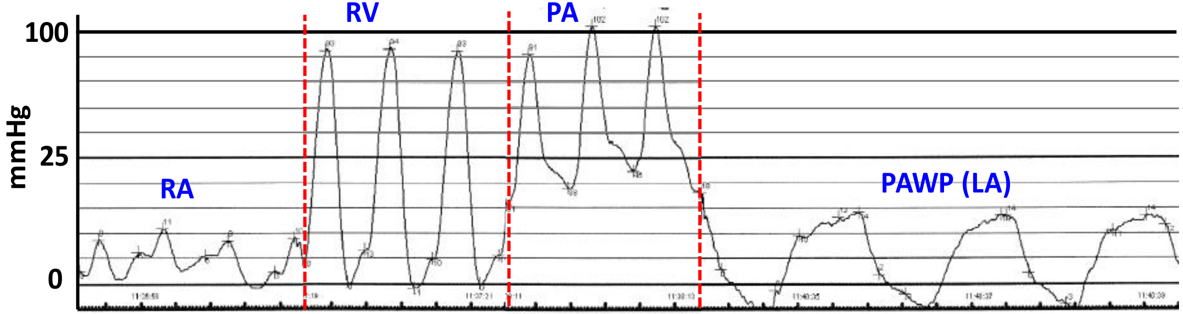
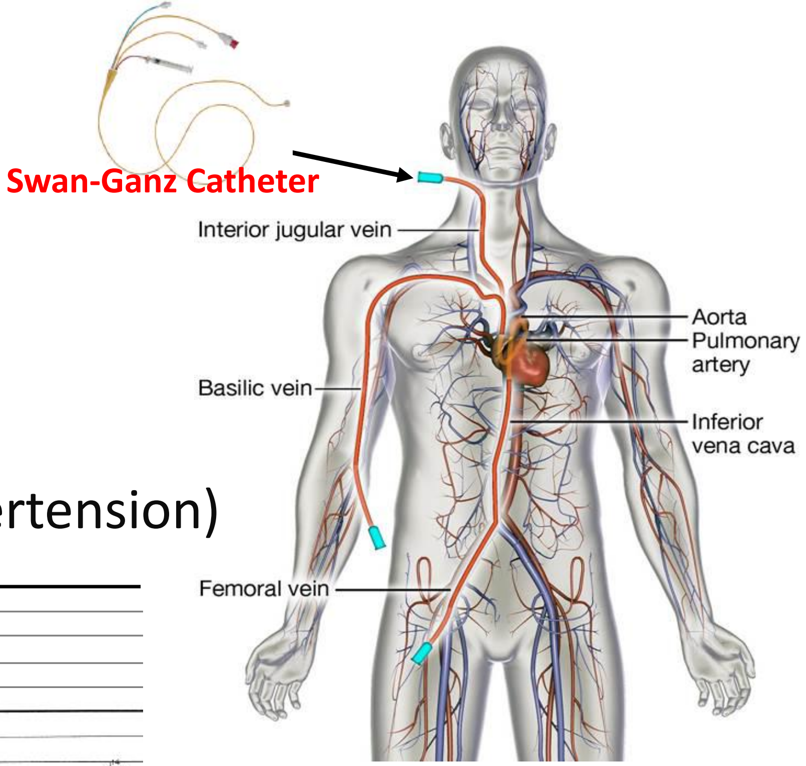
Blood Pressure Data (RHC)

Mouse with hypoxia induced PH



Patient with PAH (Pulmonary Arterial Hypertension)





Taken From: http://hcp.cteph.com/diagnosis/right-heart-catheterization

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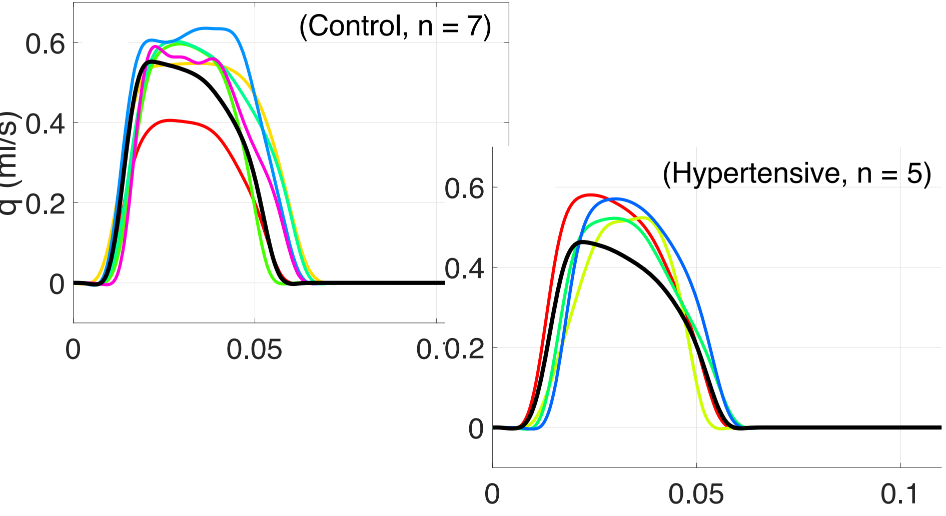
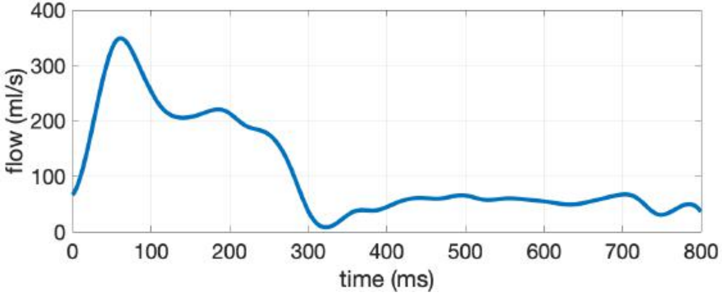
Blood Flow Data

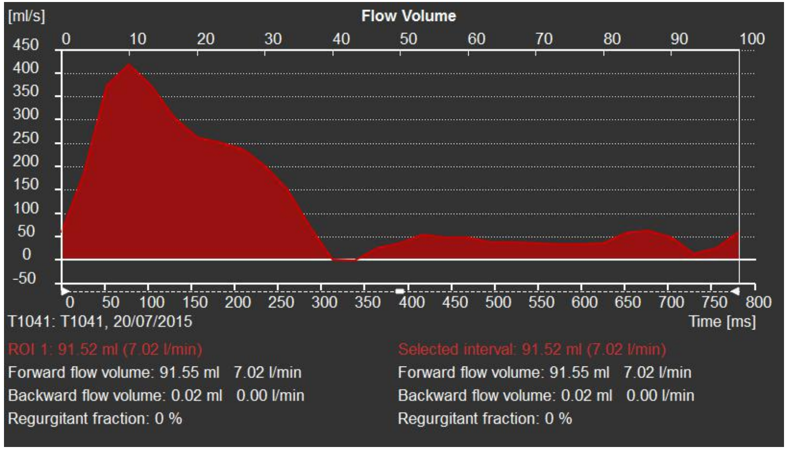
Non-invasive blood flow measurements from Magnetic Resonance Imaging (MRI)

Mouse with hypoxia induced PH



PAH Patient





Network Data

Non-invasive domain measurements from computed tomography (CT)

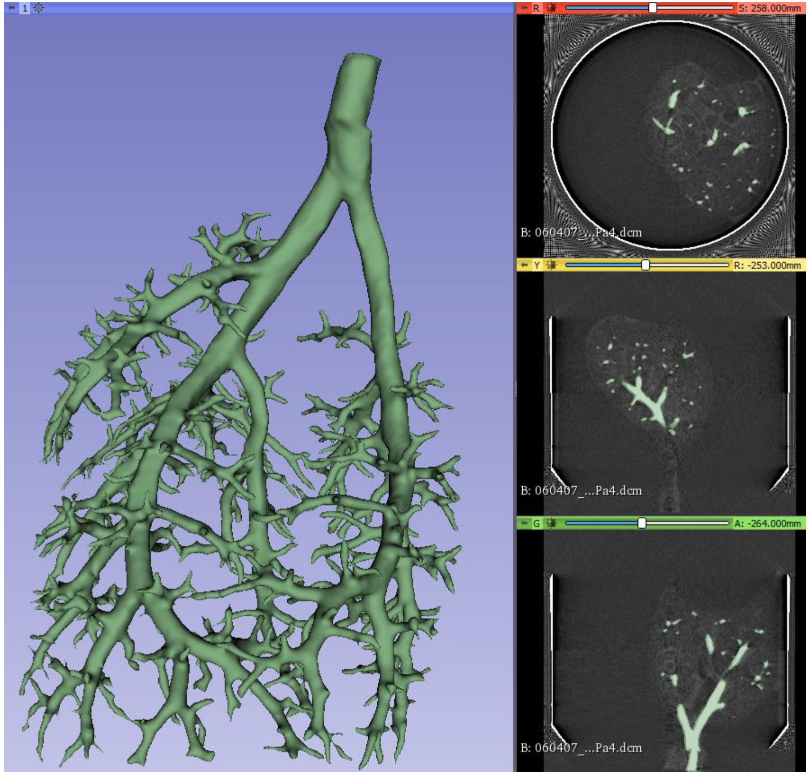
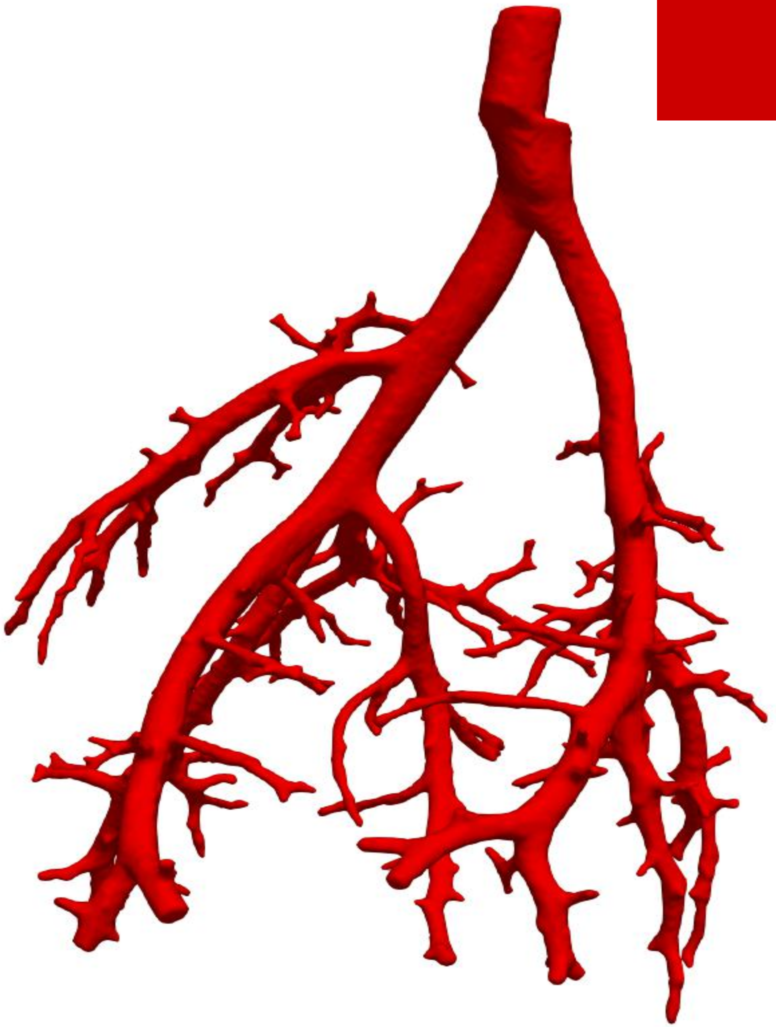


Image segmentation

→

Directed graph



Model Parameters

Image segmentation:

$$\theta_{im} = \{\text{Threshold}, \text{Smoothing}\}$$

Fluid dynamics:

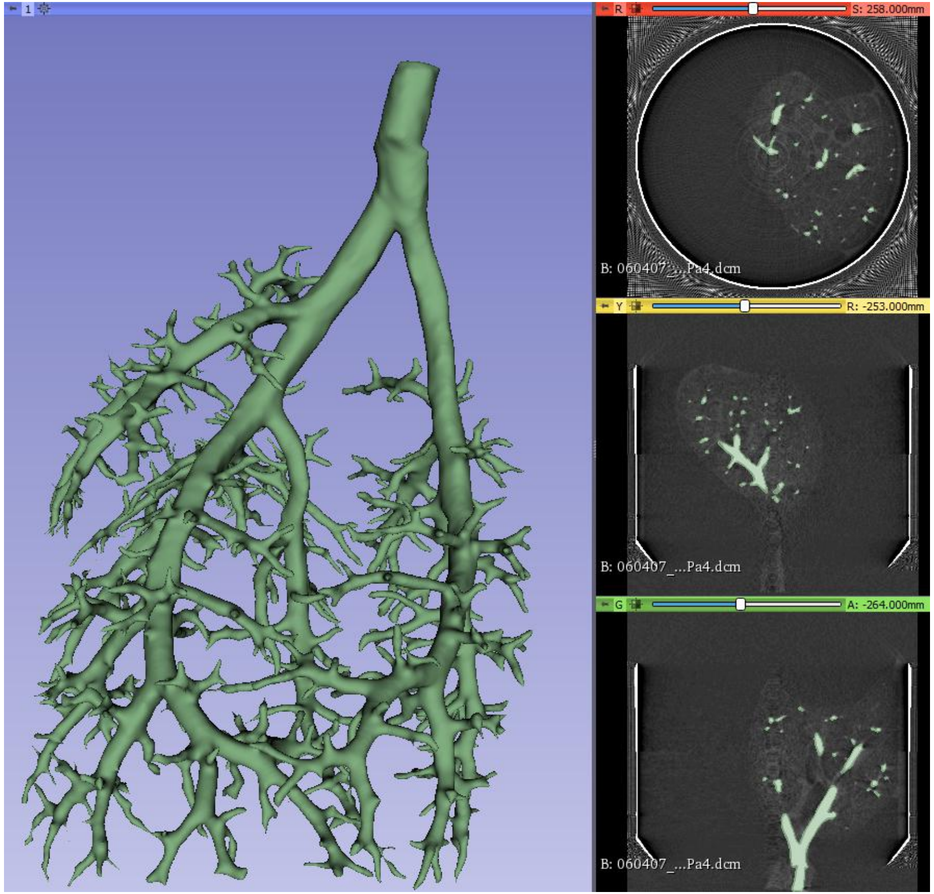
$$\theta_{fd} = \left\{\rho, \nu, \delta, \frac{Eh}{r_0}\right\}$$

Boundary conditions:

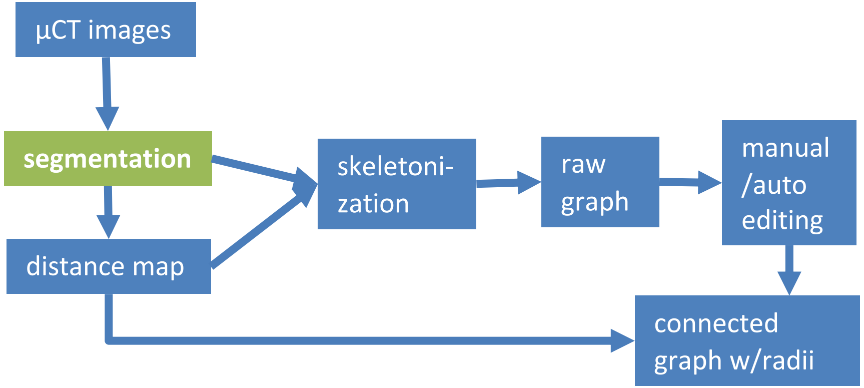
$$\theta = \{\alpha, \beta, q_{in}(t)\}$$

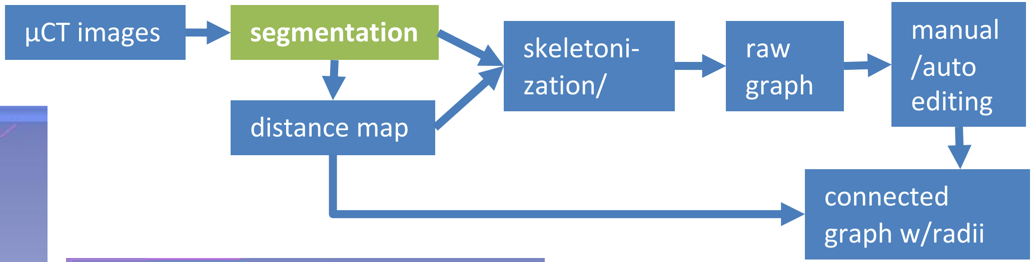
$$\theta = \{R_1, R_2, C, q_{in}(t)\}$$

Image Segmentation

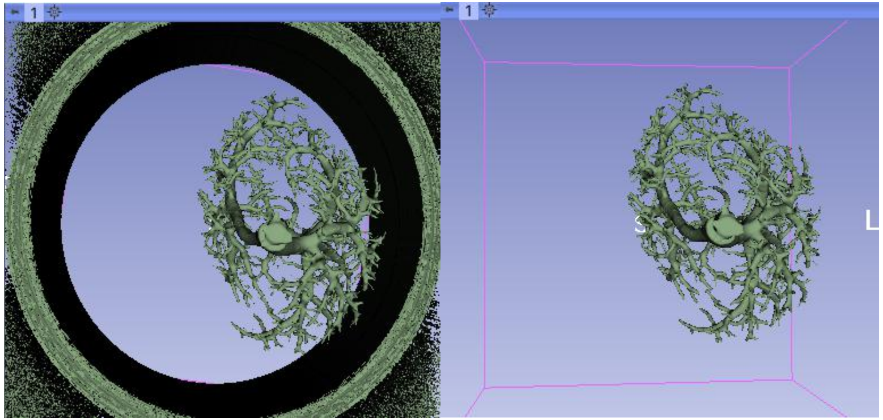


- Separate image foreground from background
- ***Thresholding***: Defines the intensity range for voxels included in the foreground

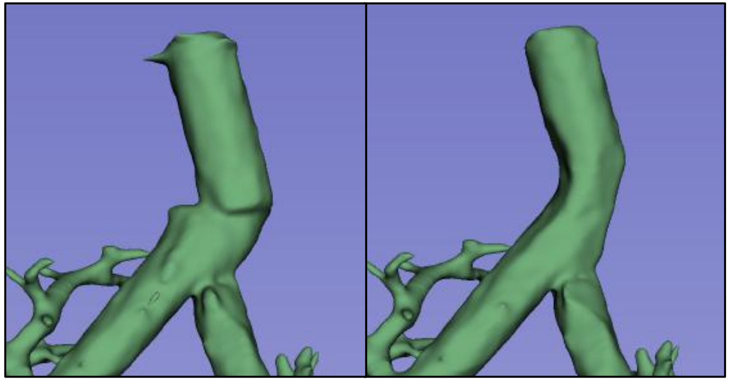


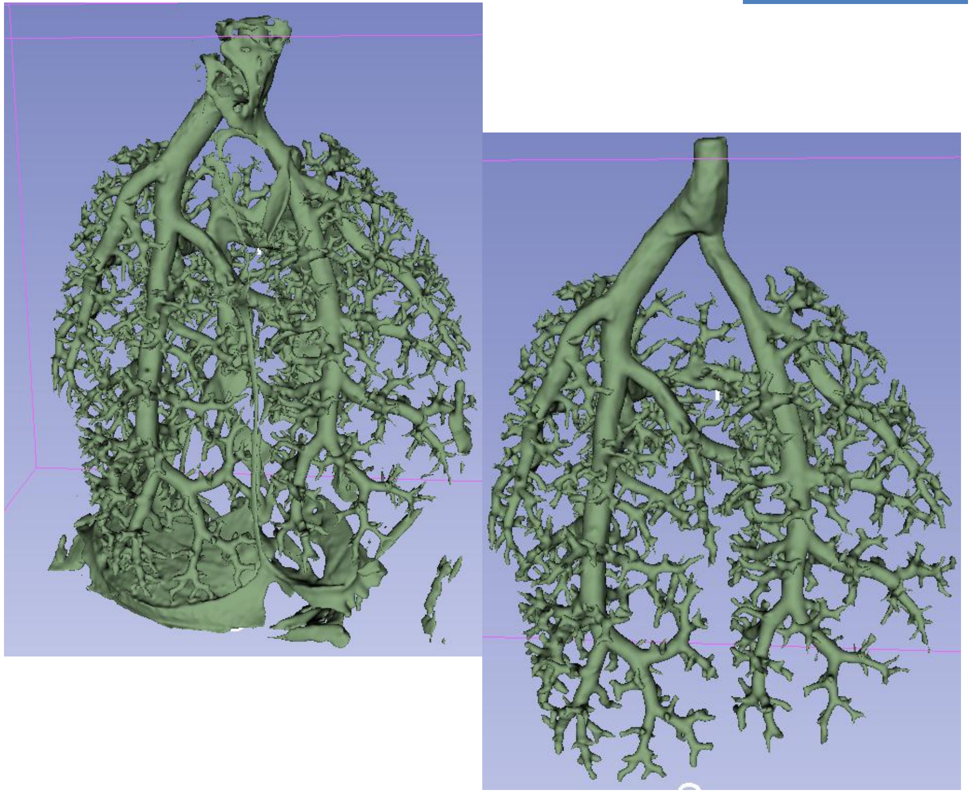


Keep selected island



Cut/paint/**smoothing**





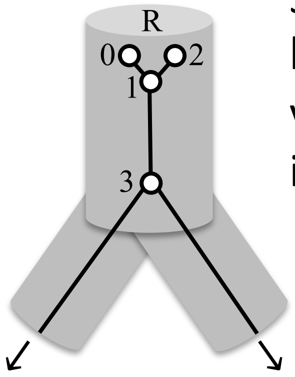
Directed graph

m2p4_072709_points.txt

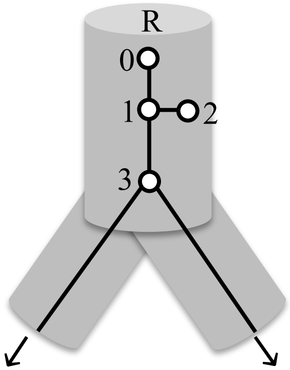
```
graph G {
0 [spatial_node="218 119 242"];
1 [spatial_node="217 118 243"];
2 [spatial_node="250 115 307"];
3 [spatial_node="248 119 312"];
4 [spatial_node="92 95 375"];
5 [spatial_node="91 111 365"];
6 [spatial_node="14 143 221"];
7 [spatial_node="19 155 222"];
8 [spatial_node="193 162 329"];
9 [spatial_node="191 163 329"];
10 [spatial_node="164 241 273"];
11 [spatial_node="155 218 258"];
12 [spatial_node="277 62 390"];
13 [spatial_node="283 58 374"];
14 [spatial_node="252 58 389"];
15 [spatial_node="252 56 390"];
16 [spatial_node="196 233 399"];
17 [spatial_node="196 235 398"];
18 [spatial_node="258 142 260"];
19 [spatial_node="270 146 252"];
20 [spatial_node="80 193 348"];
```

```
0--1  [spatial_edge="[]"];
2--3  [spatial_edge="[{250 116 308},{249 117 309},{248 118 310},{248 119 311}]"];
4--5  [spatial_edge="[{92 96 375},{93 97 375},{93 98 374},{94 99 374},{94 100
373},{95 101 373},{95 102 372},{95 103 372},{96 104 371},{96 105 370},{96 106
369},{96 107 368},{96 108 368},{95 109 367},{95 110 367},{94 111 366},{93 111
365},{92 111 365}]"];
6--7  [spatial_edge="[{14 144 221},{15 145 221},{15 146 221},{16 147 221},{16 148
221},{17 149 221},{17 150 220},{17 151 220},{17 152 220},{18 153 220},{19 154
221}]"];
8--9  [spatial_edge="[{192 162 329}]"];
10--11  [spatial_edge="[{165 240 274},{165 239 274},{166 238 274},{165 237 273},
{166 236 273},{165 235 272},{165 234 271},{165 233 271},{165 232 270},{165 231
269},{166 230 268},{165 229 269},{165 228 269},{164 227 268},{164 226 267},{163
225 266},{162 224 265},{162 223 264},{161 222 263},{160 221 262},{159 220 261},
{158 220 260},{157 220 260},{156 219 259}]"];
12--13  [spatial_edge="[{277 62 389},{278 61 388},{278 61 387},{279 61 386},{279
62 385},{279 62 384},{279 62 383},{280 62 382},{280 62 381},{280 62 380},{280 62
379},{281 61 378},{281 61 377},{282 60 376},{283 59 375}]"];
14--15  [spatial_edge="[{252 57 390}]"];
16--17  [spatial_edge="[{196 234 399}]"];
18--19  [spatial_edge="[{258 142 259},{259 142 258},{260 142 257},{261 142 256},
{262 143 255},{263 144 254},{264 145 253},{265 145 252},{266 146 252},{267 147
251},{268 146 251},{269 146 251}]"];
```

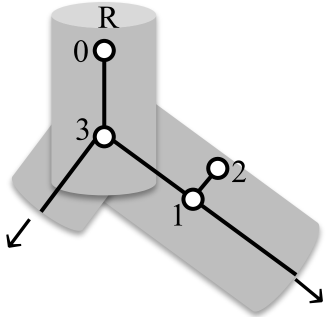
Generating directed graphs

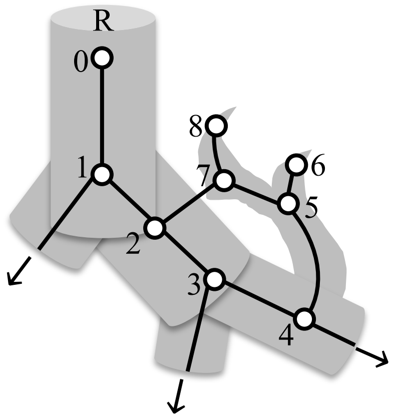


Small false branches at root vessel connected in a “v” shape



Small false branch connected nearly perpendicular to main branch





Occurs when a branch from a later generation bends upward and gets close to a previous generation. A branch falsely connects the close branch to the previous generation

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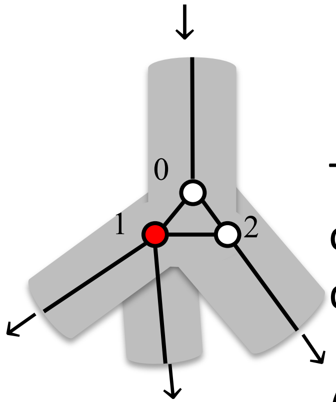
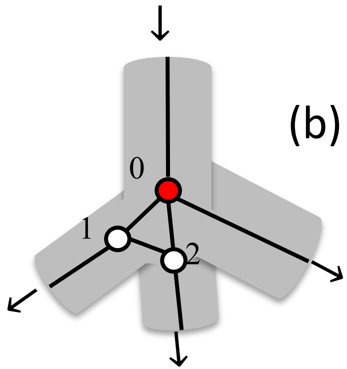
Generating directed graphs

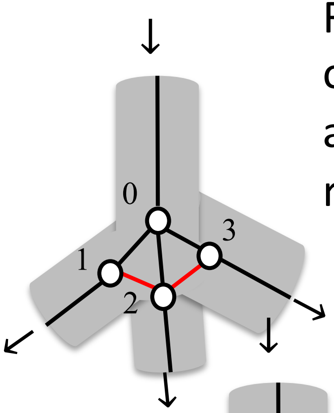


Three nodes in a cycle, one of which has degree 4.

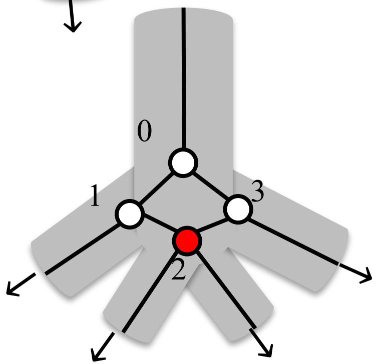
(a) Dijkstras algorithm removes edges: 1-2



(b) Dijkstras algorithm removes edges: 1-2

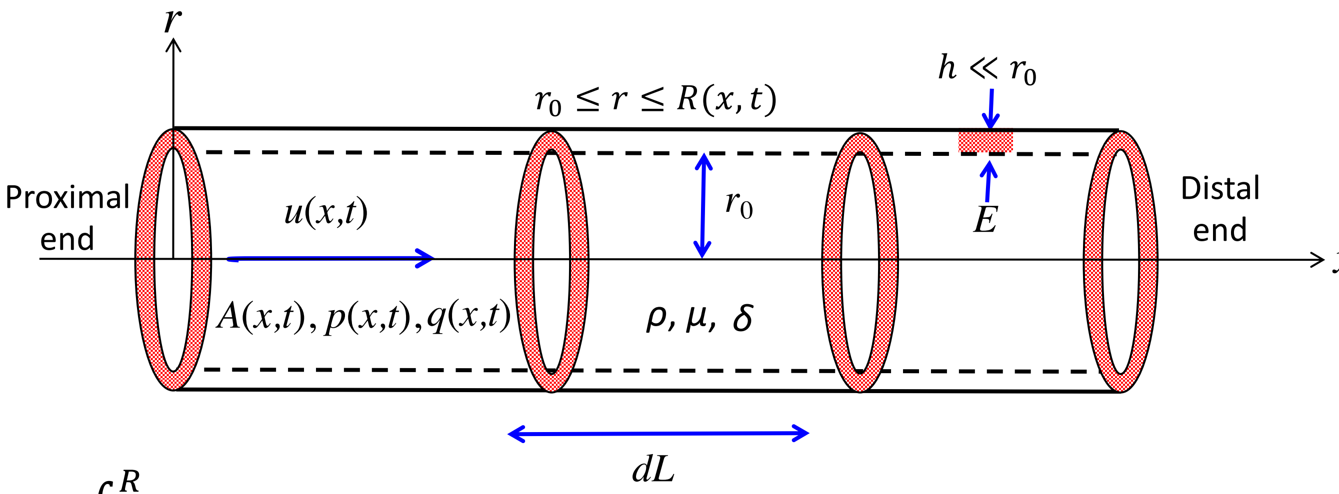


Four nodes forming two cycles of three nodes each which share a side. Dijkstras algorithm removes edges: 1-2 and 2-3



Four nodes in a cycle. Dijkstra's algorithm removes edges: 1-2 and 2-3. Manually add an edge from 0-2

1D Fluid Dynamics Model



Continuity equation

$$\frac{\partial q}{\partial x} + \frac{\partial A}{\partial t} = 0, \qquad q = 2\pi \int_0^R u_x \, r dr$$

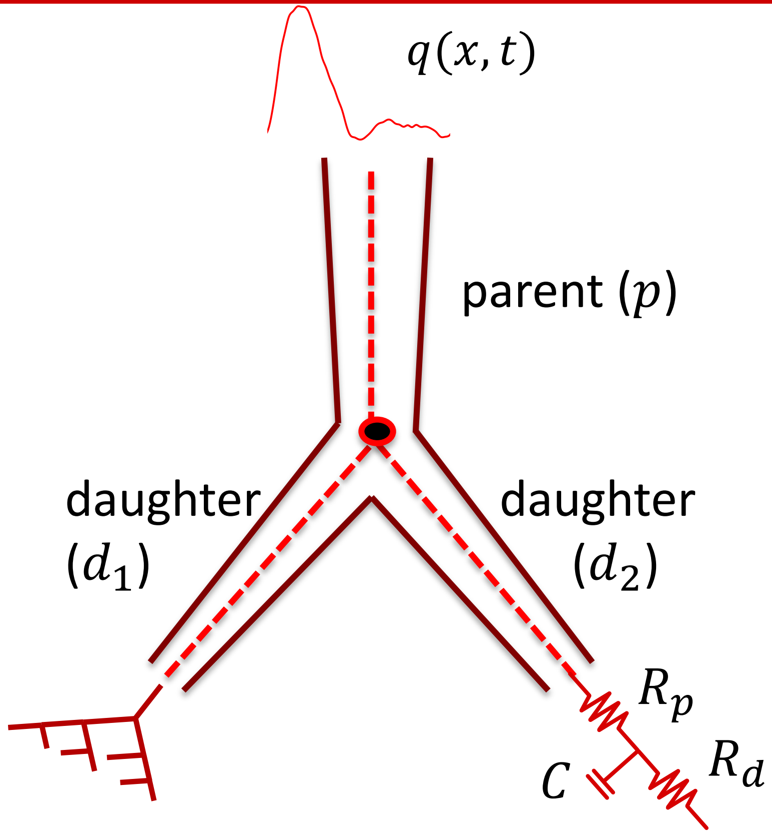
Axial momentum equation

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

Wall model/state equation

$$p(x,t) - p_0 = \frac{Eh}{r_0}\left(\sqrt{\frac{A}{A_0}} - 1\right), \qquad A_0 = \pi r_0^2$$

Boundary Conditions



Junction Conditions

$$q_p = q_{d_1} + q_{d_2}$$

$$p_{p(L,t)} = p_{d_1}(0,t) = p_{d_2}(0,t)$$

Outflow Boundary Condition

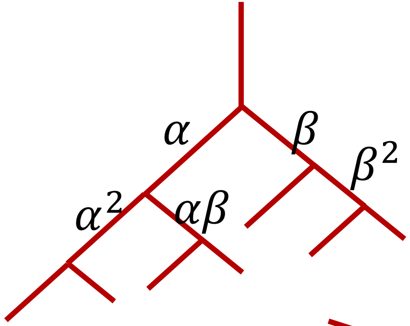
$$\frac{dp}{dt} - R_p\frac{dq}{dt} = q\left(\frac{R_p + R_d}{R_d C_T}\right) - \frac{p}{R_d C_T}$$

$$p = \int_0^T z(x, t-\tau) q(x,t)\, d\tau$$

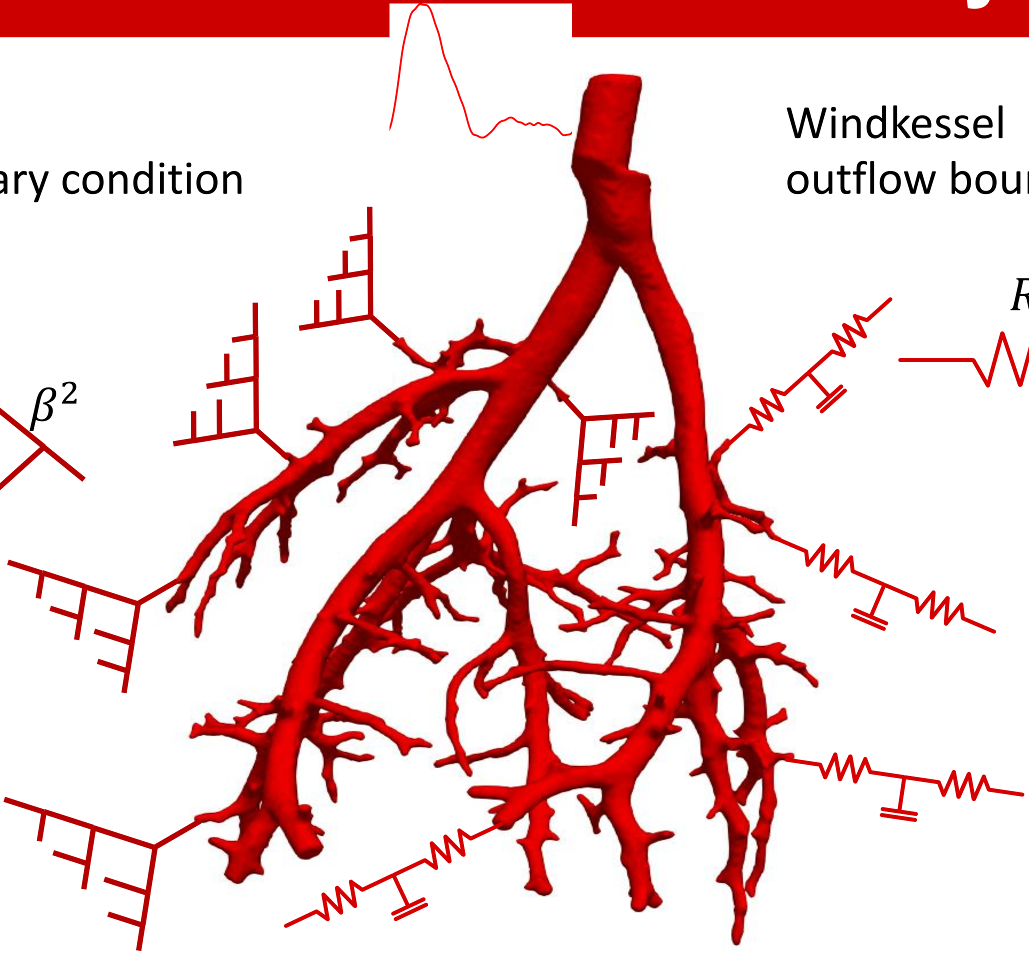
$$P(x,\omega) = Q(x,\omega) Z(x,\omega)$$

Boundary Conditions

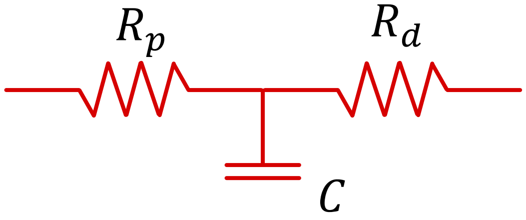
Structured tree
outflow boundary condition



Parameters:
$\theta = \{\alpha, \beta\}$



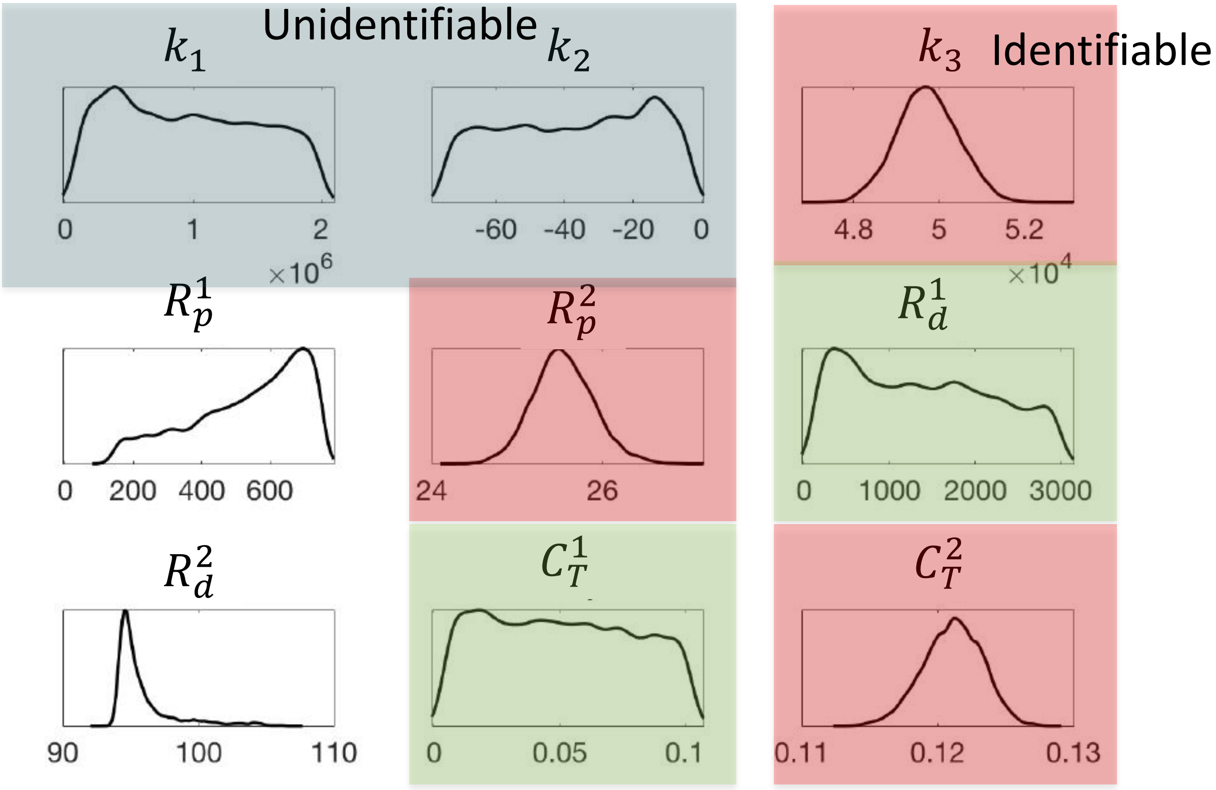
Windkessel
outflow boundary condition



Parameters:
$\theta = \{\mathrm{R}_p, R_d, C\}$

BCs parameter correlations

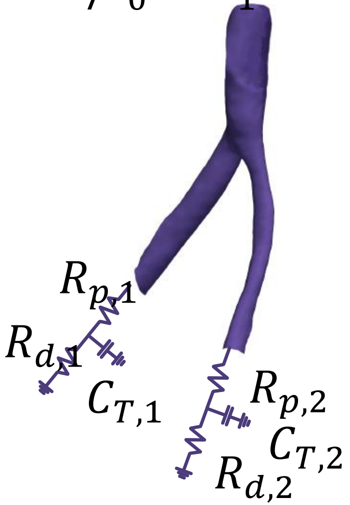
$$Eh/r_0 = \mathbf{k_1} e^{\mathbf{k_2} r_0} + \mathbf{k_3}$$

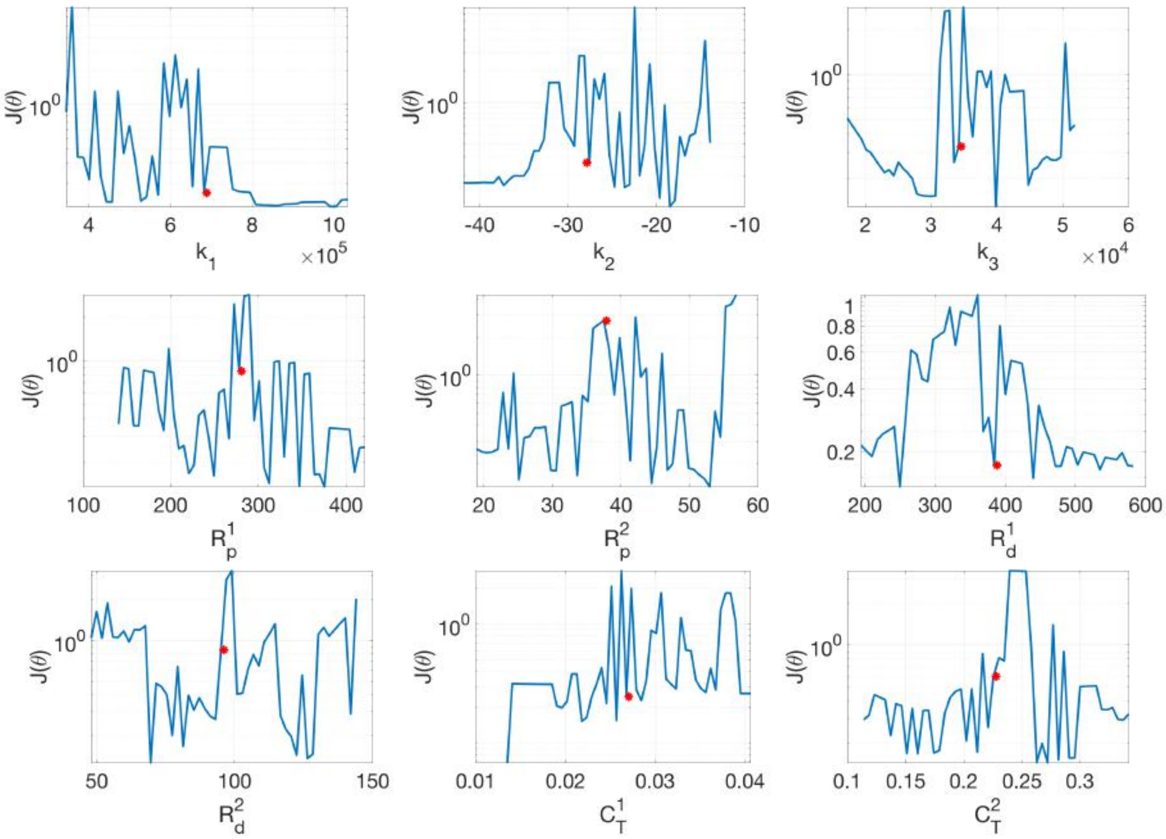


Distribution close to uniform

Profile Likelihoods

$$Eh/r_0 \approx k_1 e^{k_2 r_0} + k_3$$

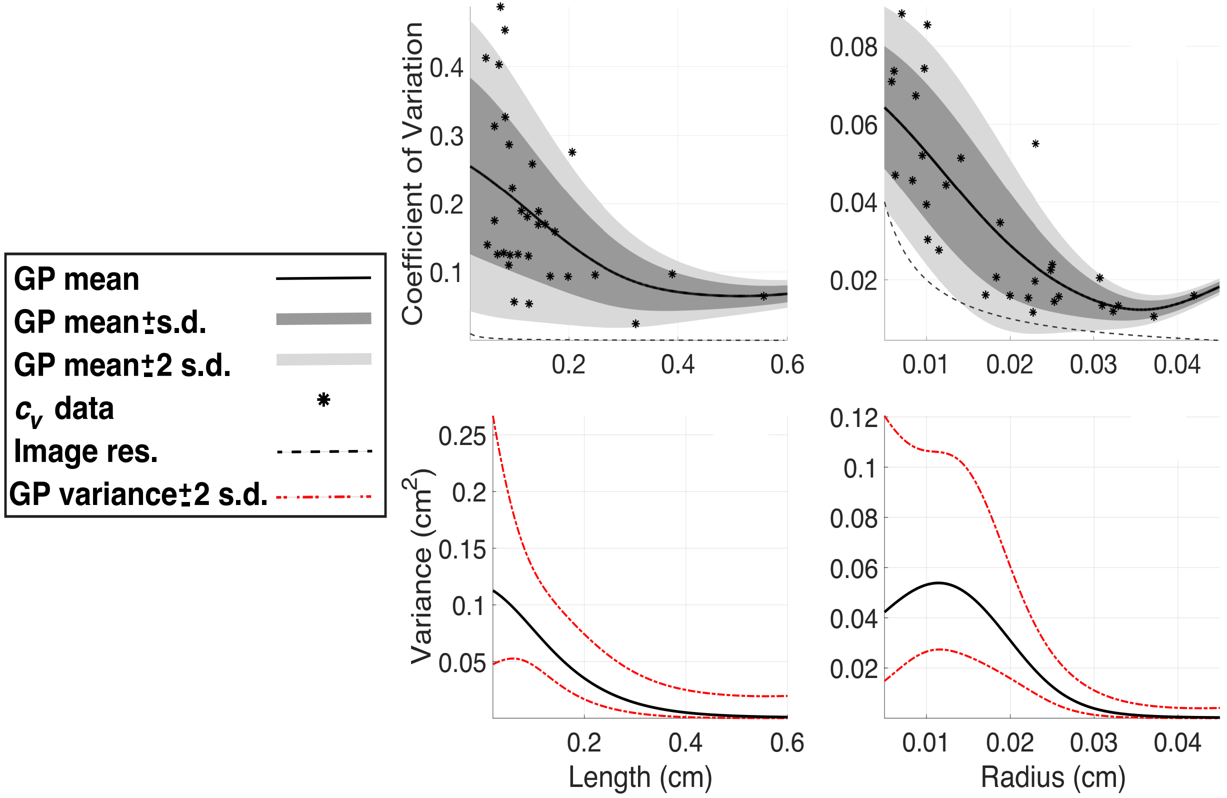




UQ: Segmentation

- **Total variation:** Sampled 25 networks from the same CT image varying segmentation threshold and smoothness. Computed MPA flow and pressure in each network
- **Parameter variation:** Extracted radius and length from 32 vessels of different caliber used Gaussian processes to get parameter distributions and MCMC to predict uncertainty of flow and pressure
- **Connectivity and size variation:** Cropped network, iteratively removing junction with smallest vessels. Recalculated BCs and computed flow and pressure

Uncertainty to segmentation (GP)



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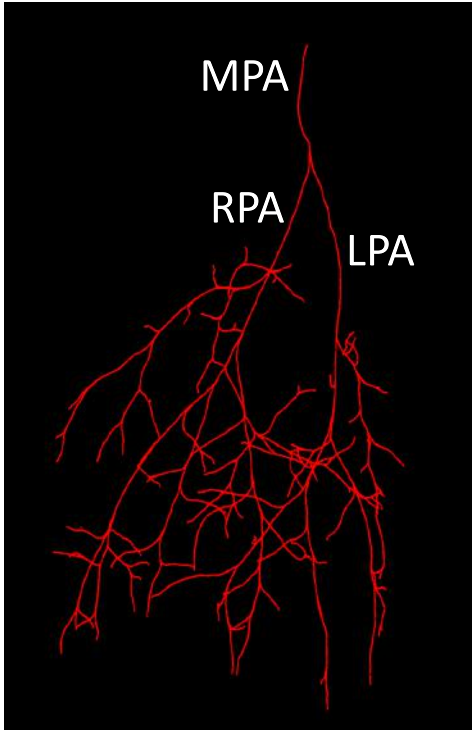
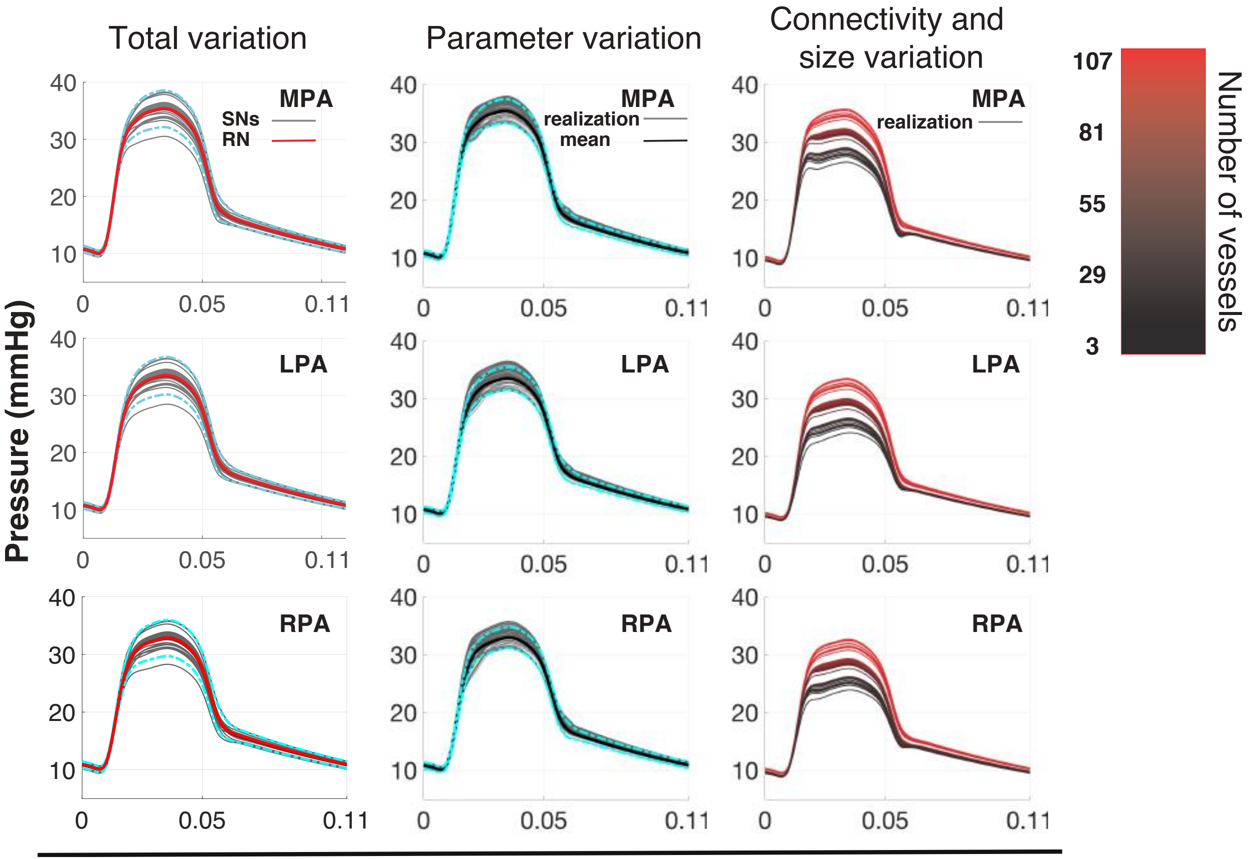
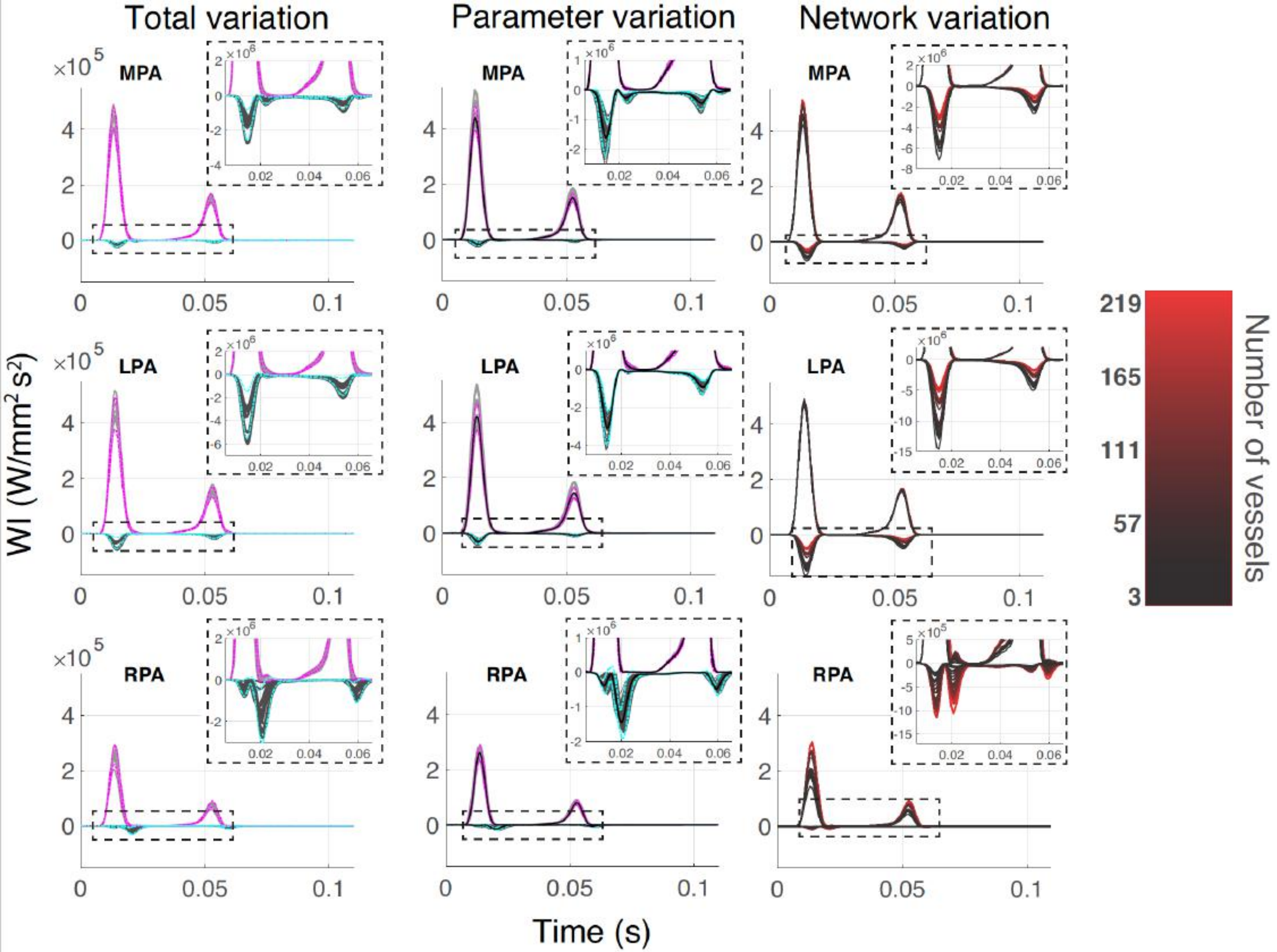
Uncertainty to segmentation

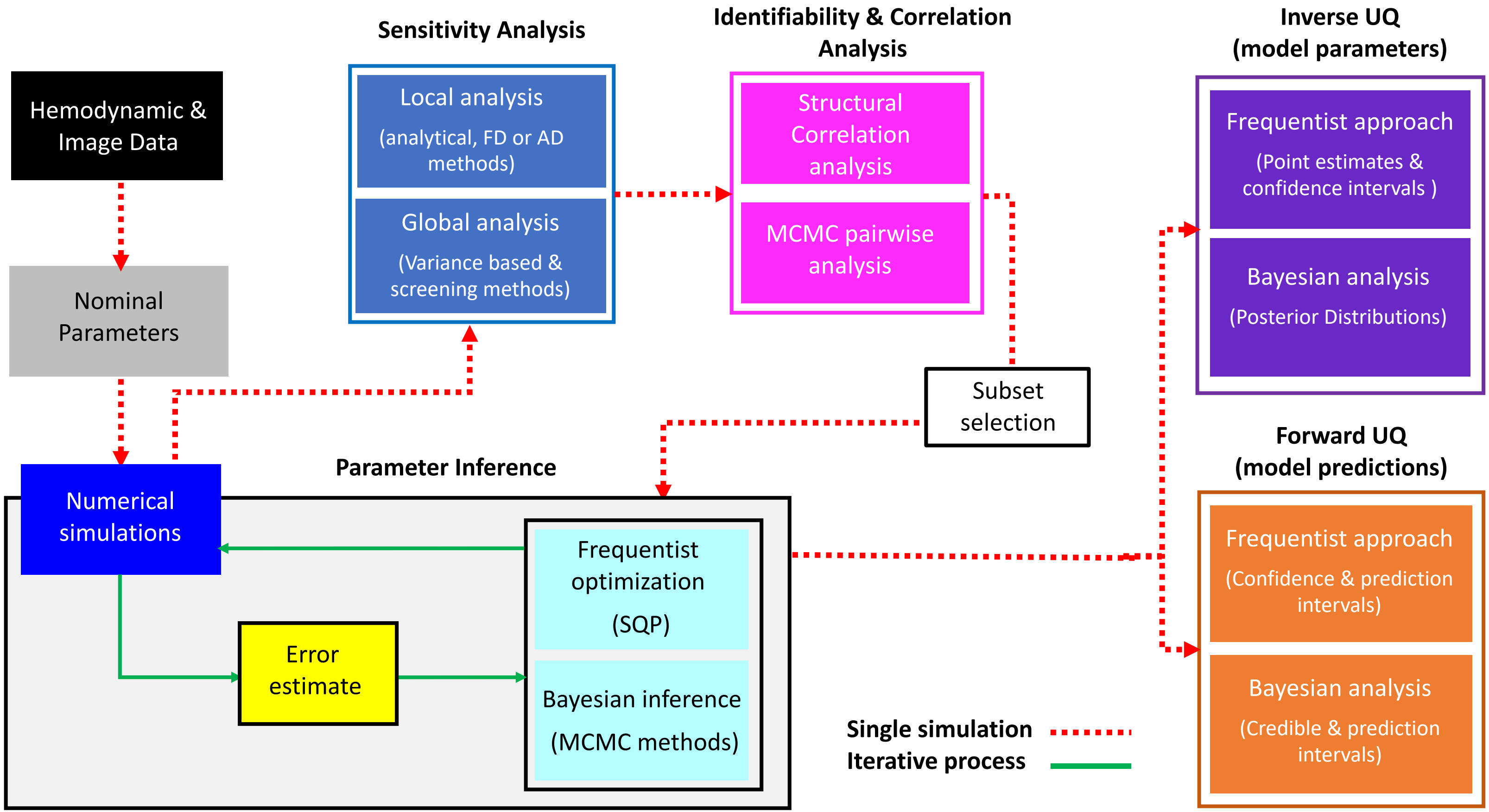






Total variation
Parameter variation
Network variation
MPA
LPA
RPA
WI (W/mm^2 s^2)
Time (s)
Number of vessels
219
165
111
57
3

UQ: Hemodynamic parameters

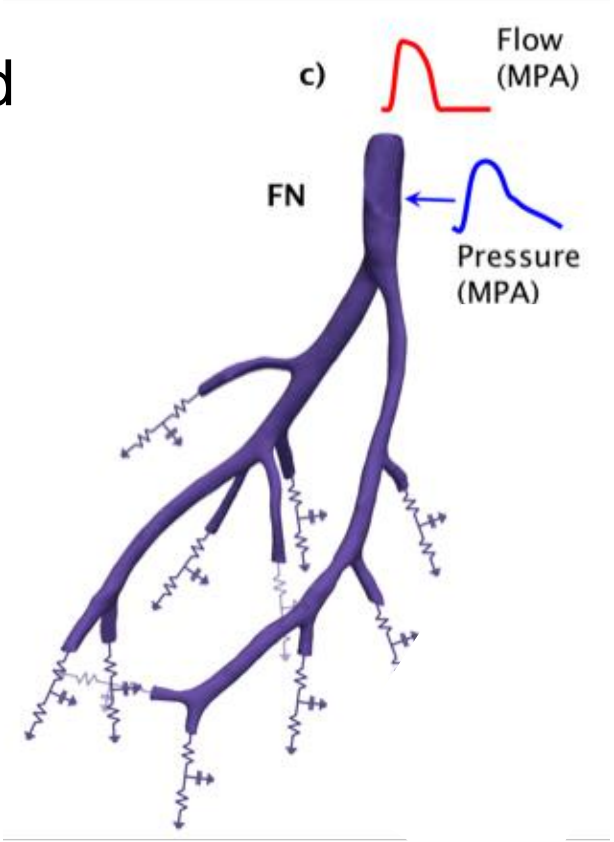


UQ: Windkessel BCs

- Windkessel parameters are correlated
- Introduce scaling factors (r_p, r_d, c)
- $R_{pi} = r_p R_{pi},\ R_{di} = r_d R_{di},\ C = cC_i$

- Reduced parameter set:

$$\theta = \left\{ r_p, r_d, c, \frac{Eh}{r_0} \right\}$$

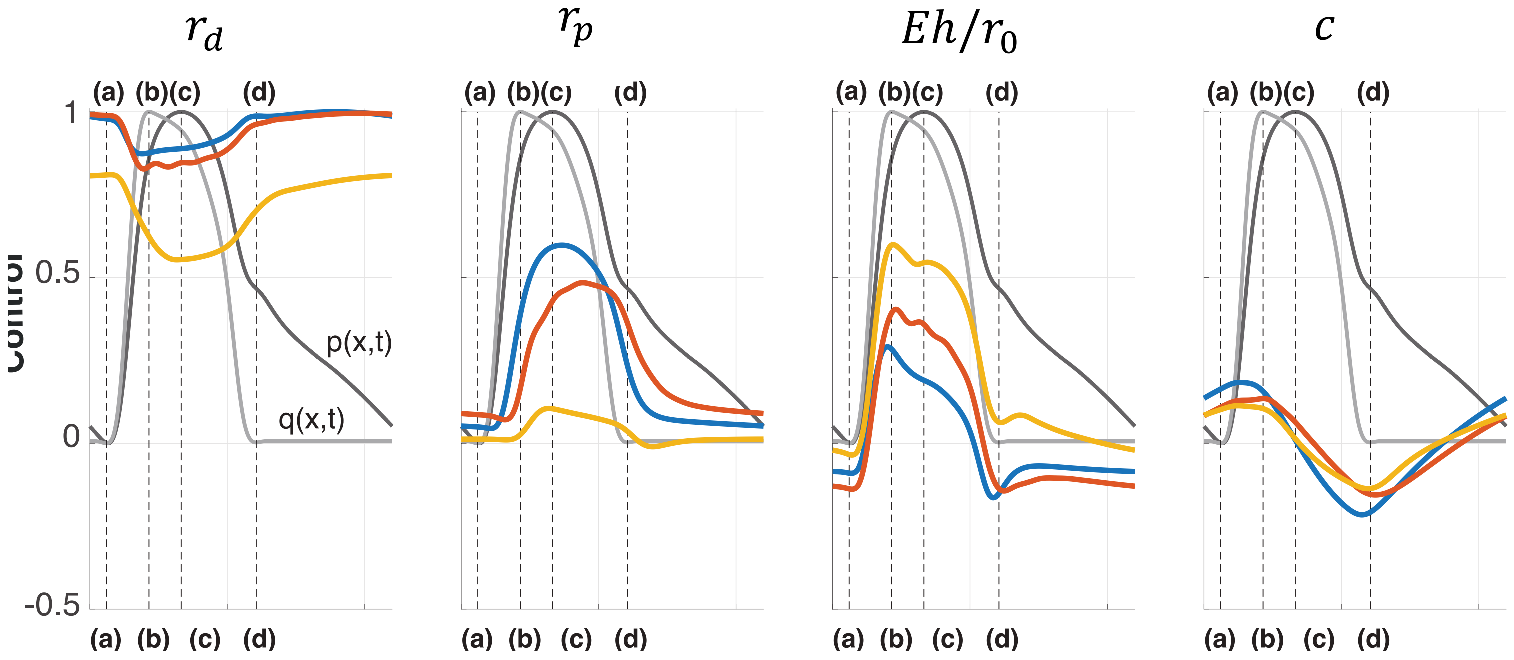


Uncertainty to BCs

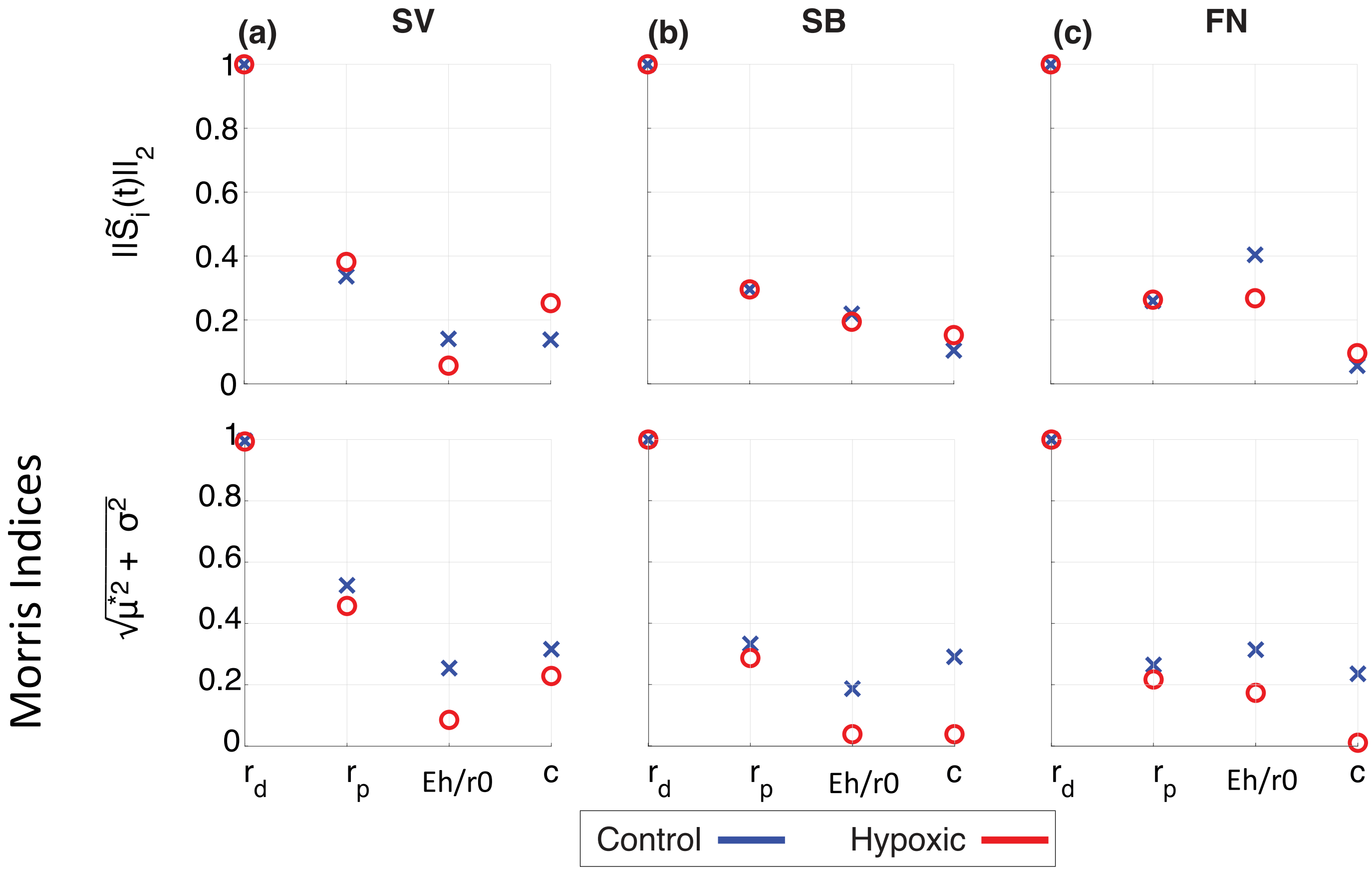
Single vessel

Single junction

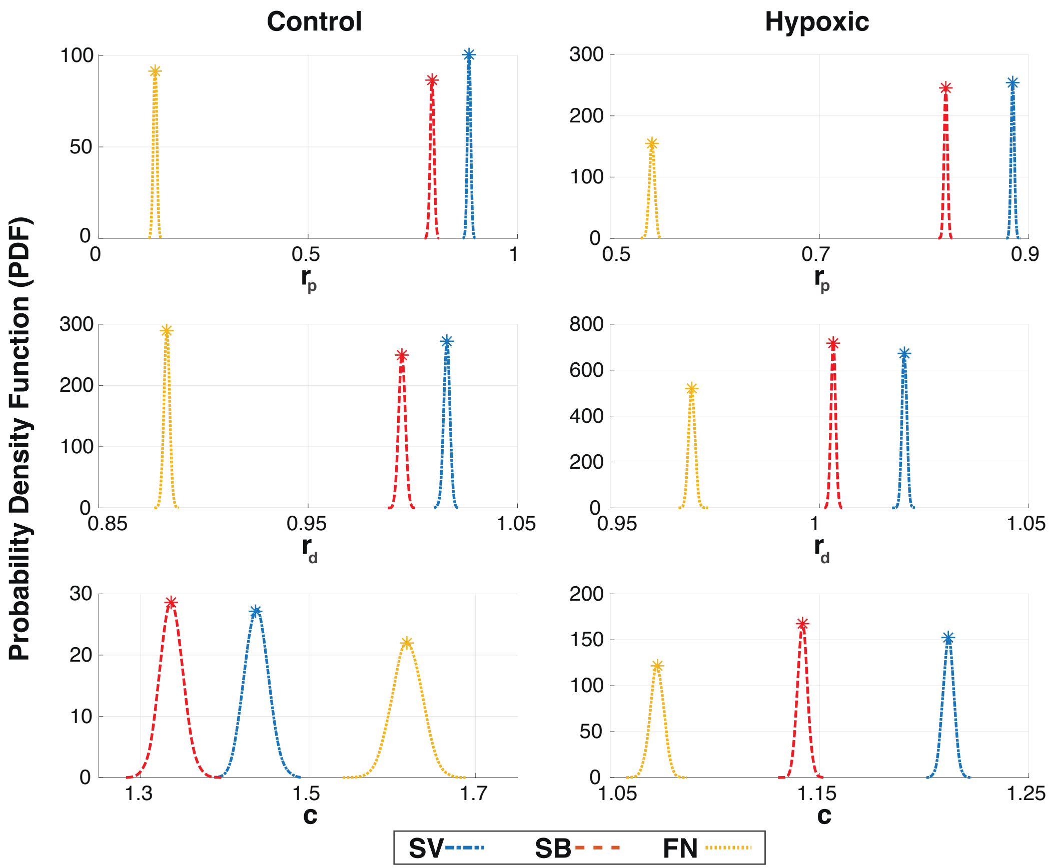
Large network

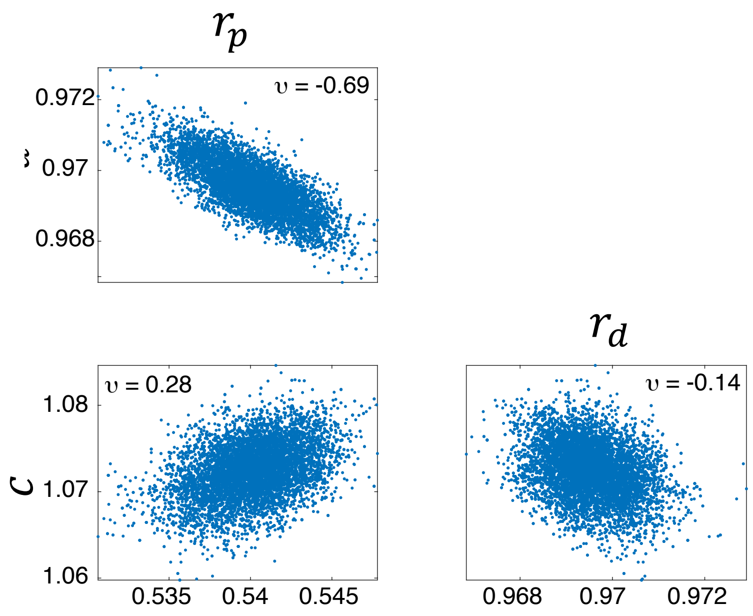


Global Sensitivity Analysis



Uncertainty to BCs

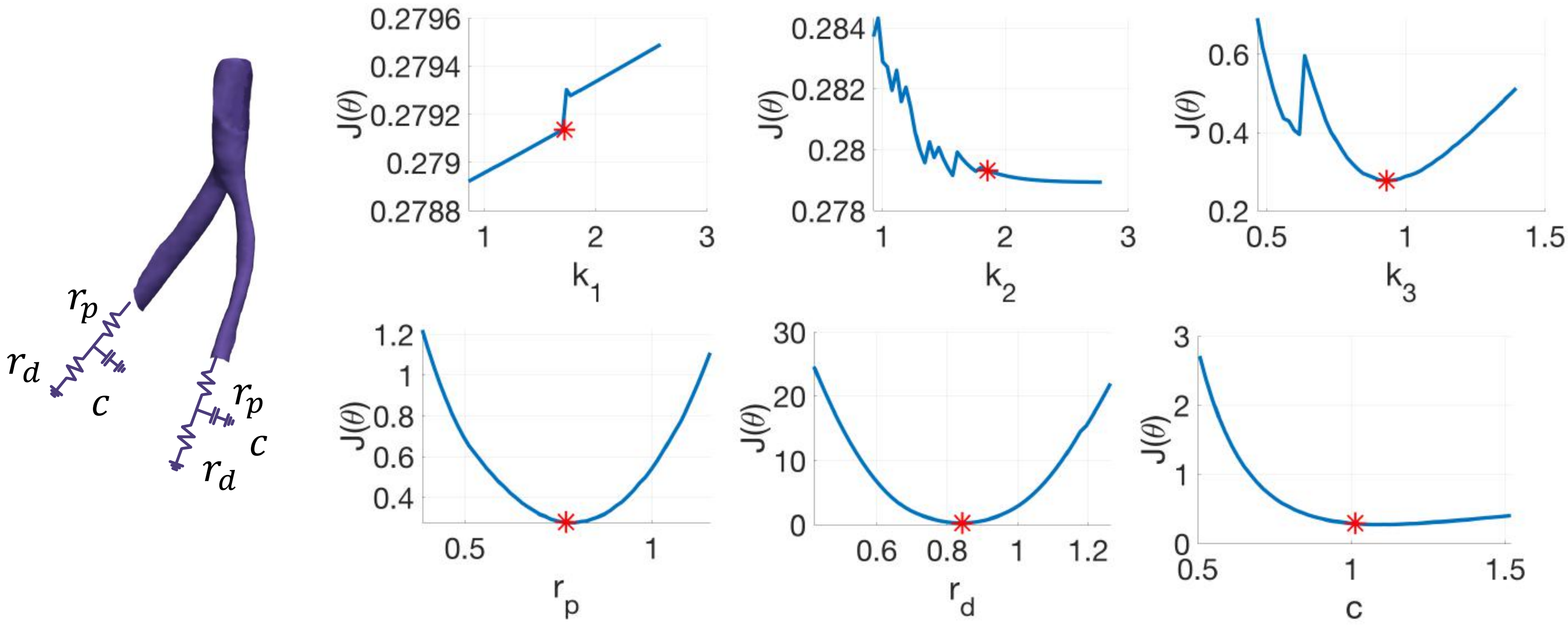


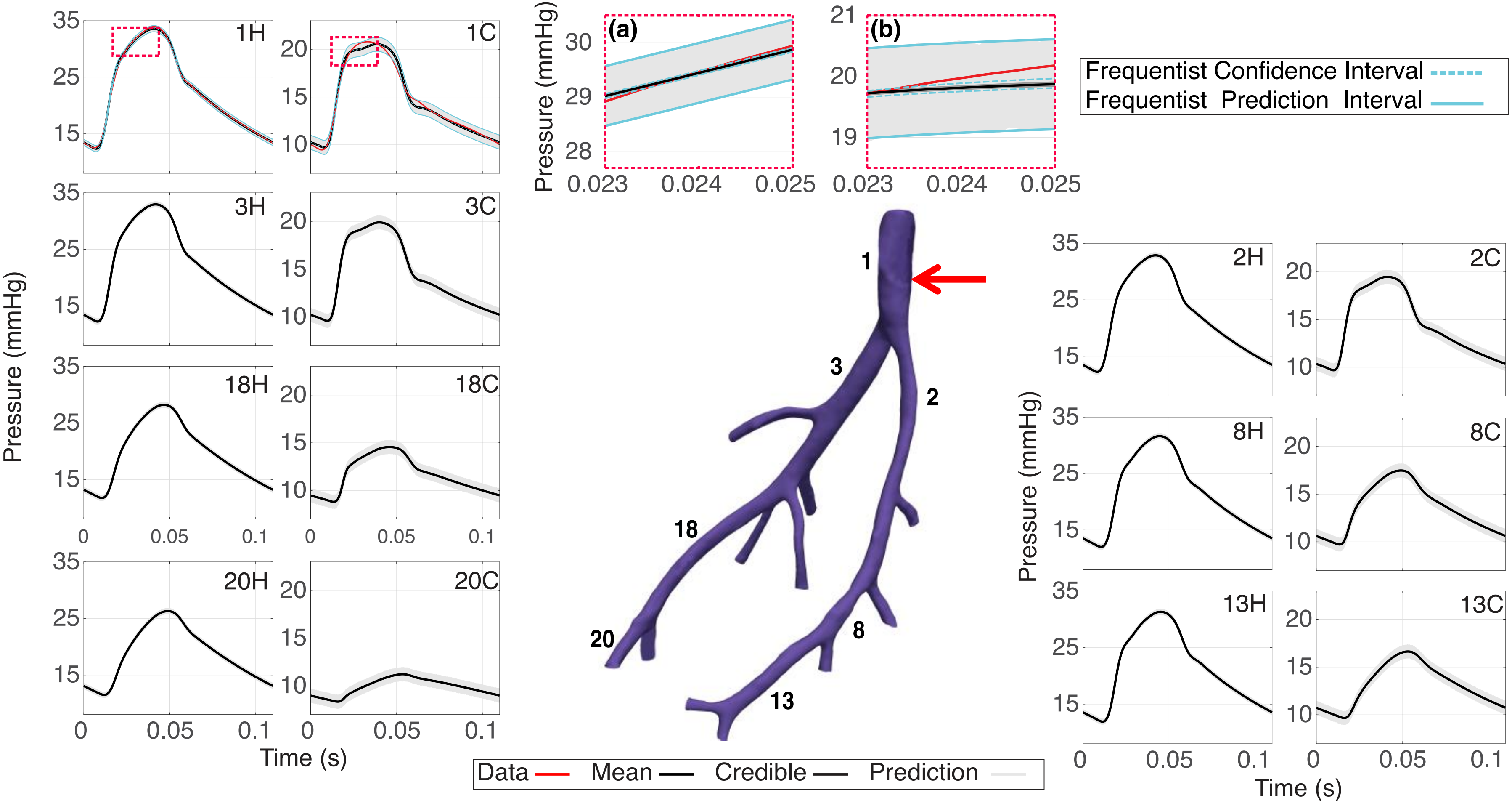


DRAM: Delayed Rejection Adaptive Metropolis

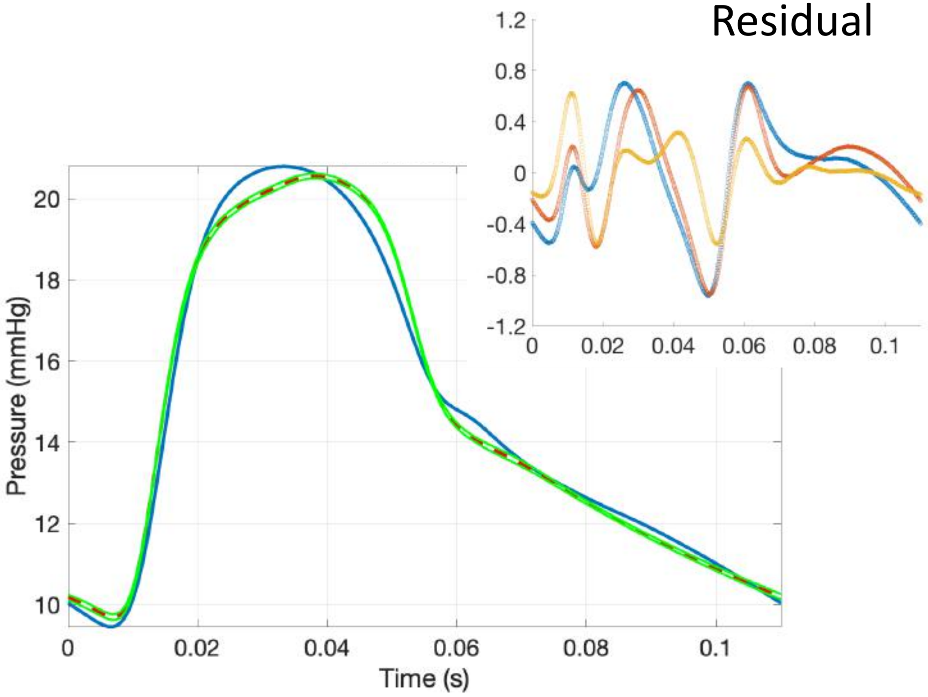
Profile Likelihoods

$$Eh/r_0 \approx k_1 e^{k_2 r_0} + k_3$$




1H
1C
3H
3C
18H
18C
20H
20C
2H
2C
8H
8C
13H
13C
(a)
(b)
Pressure (mmHg)
Time (s)
Frequentist Confidence Interval
Frequentist Prediction Interval
Data
Mean
Credible
Prediction
1
2
3
8
13
18
20

Uncertainty to BCs

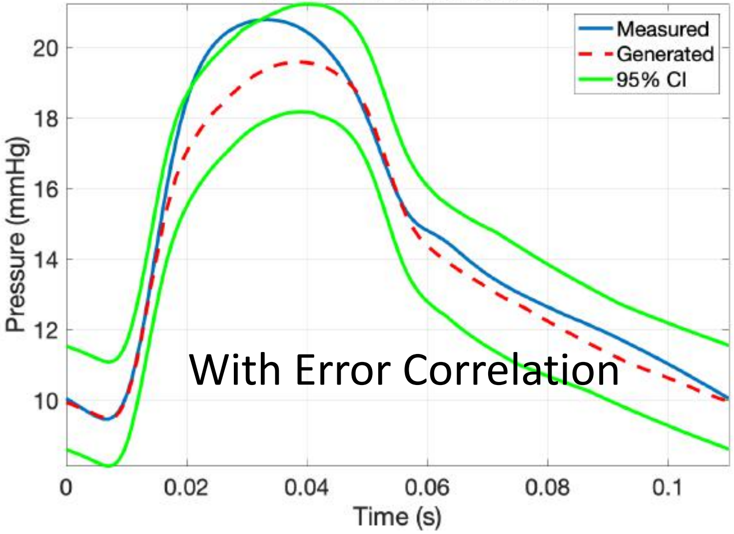


No Error Correlation
(assuming r is i.i.d.)

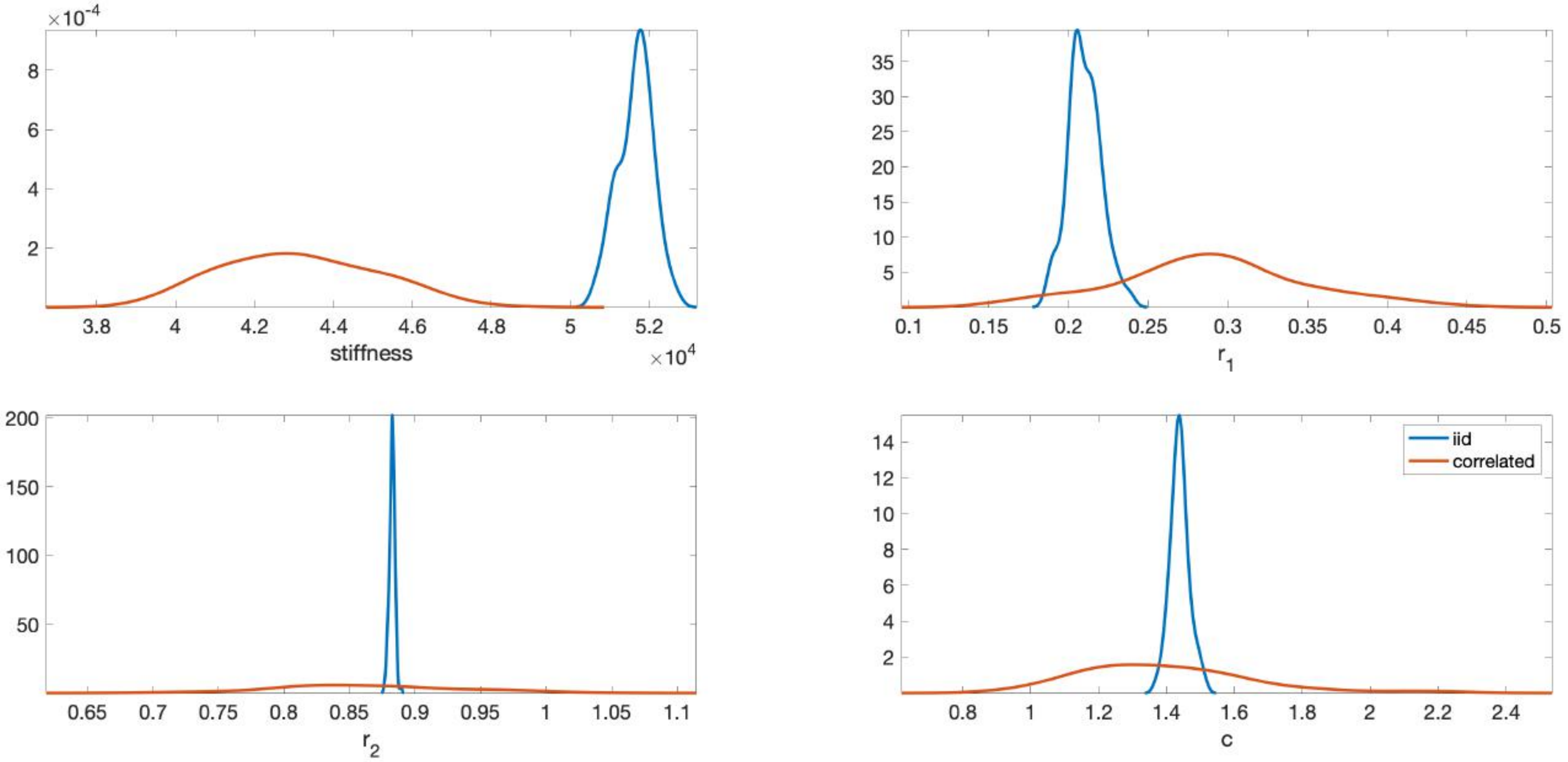
Least squares cost:

$$J = r^T r$$

$$r = \frac{1}{\sqrt{N}} \left\{ \frac{x_m(t_1) - x_d(t_1)}{x_d(t_1)}, \frac{x_m(t_2) - x_d(t_2)}{x_d(t_2)}, \ldots \right\}$$



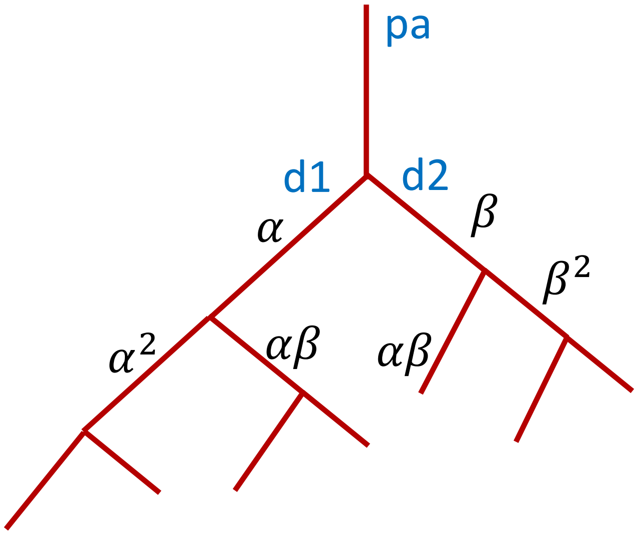
With Error Correlation



w/ Err Correlation

wo/ Err Correlation

Structured-tree BCs

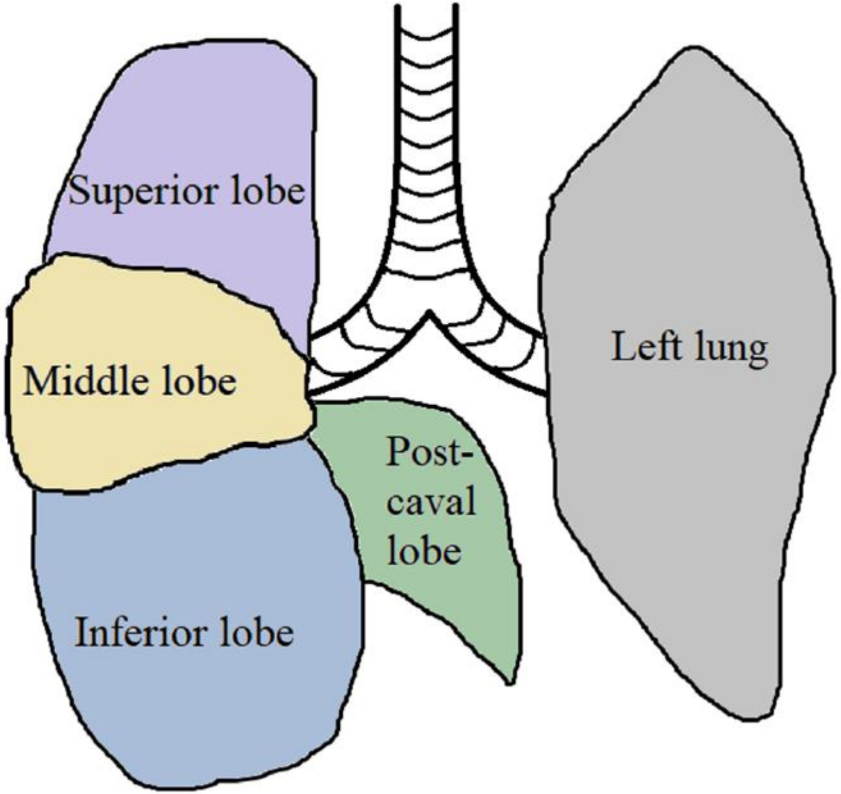


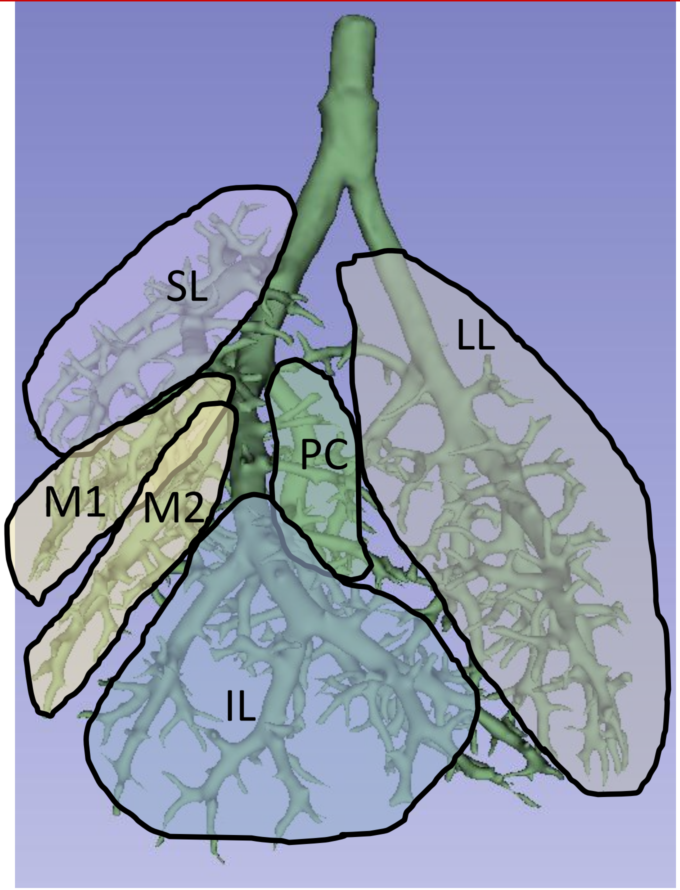
Radius relation	$(r_{pa})^{\xi} = (r_{d_1})^{\xi} + (r_{d_2})^{\xi}$
Area ratio	$\eta = \frac{(r_{d_1})^2+(r_{d_2})^2}{(r_{pa})^2}$
Asymmetry ratio	$\gamma = (r_{d_2}/r_{d_1})^2$
Parameters relation	$\eta = \frac{1+\gamma}{(1+\gamma^{\xi/2})^{2/\xi}}$
Length to radius ratio	$l_{rr} = L/r$

$$\alpha = \left(1+\gamma^{\xi/2}\right)^{-1/\xi} \qquad \beta = \alpha\sqrt{\gamma}$$

Olufsen et al., 2000, Annals Biomed Eng

Zones within the Lung





Results

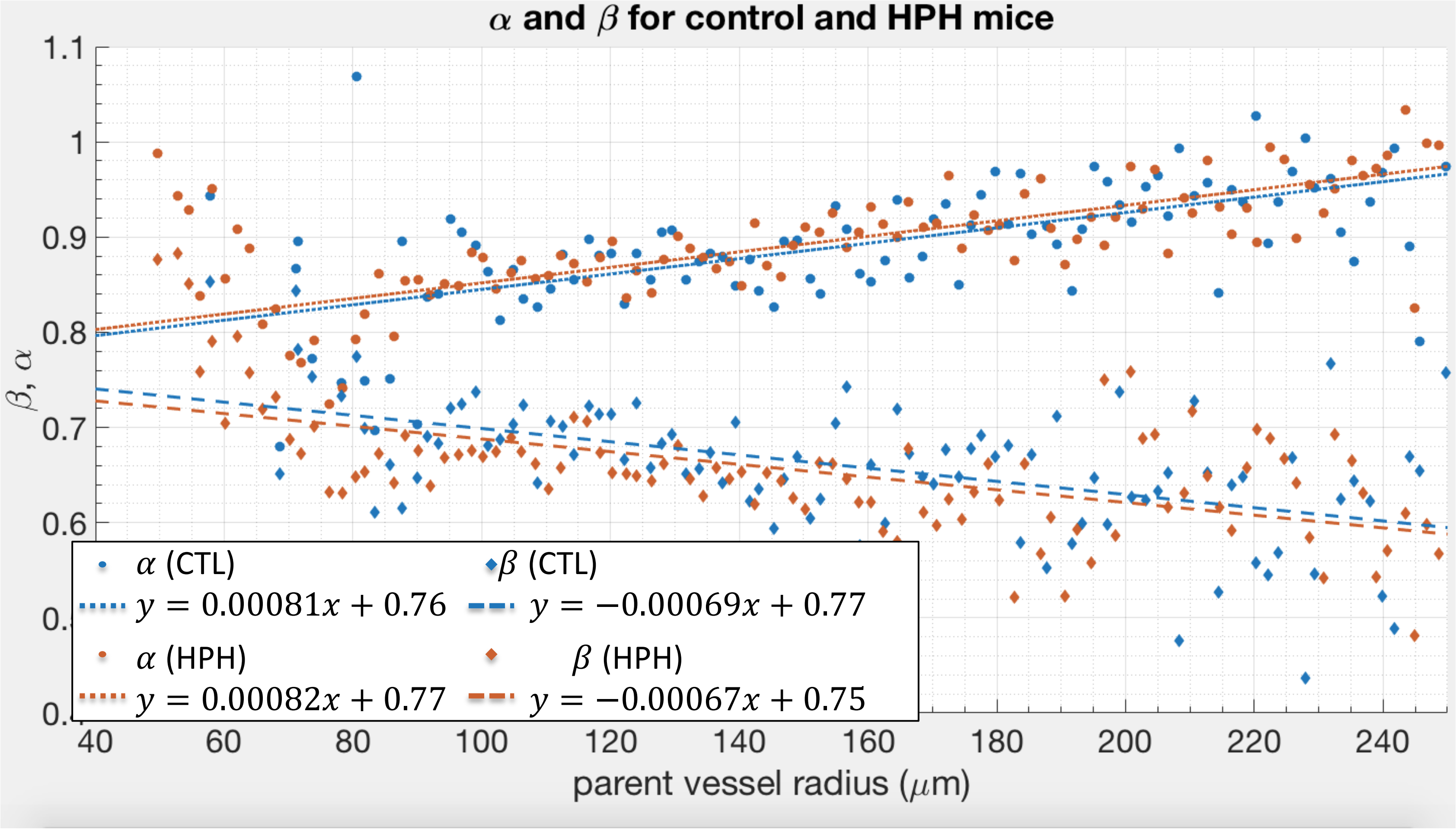
Whole tree

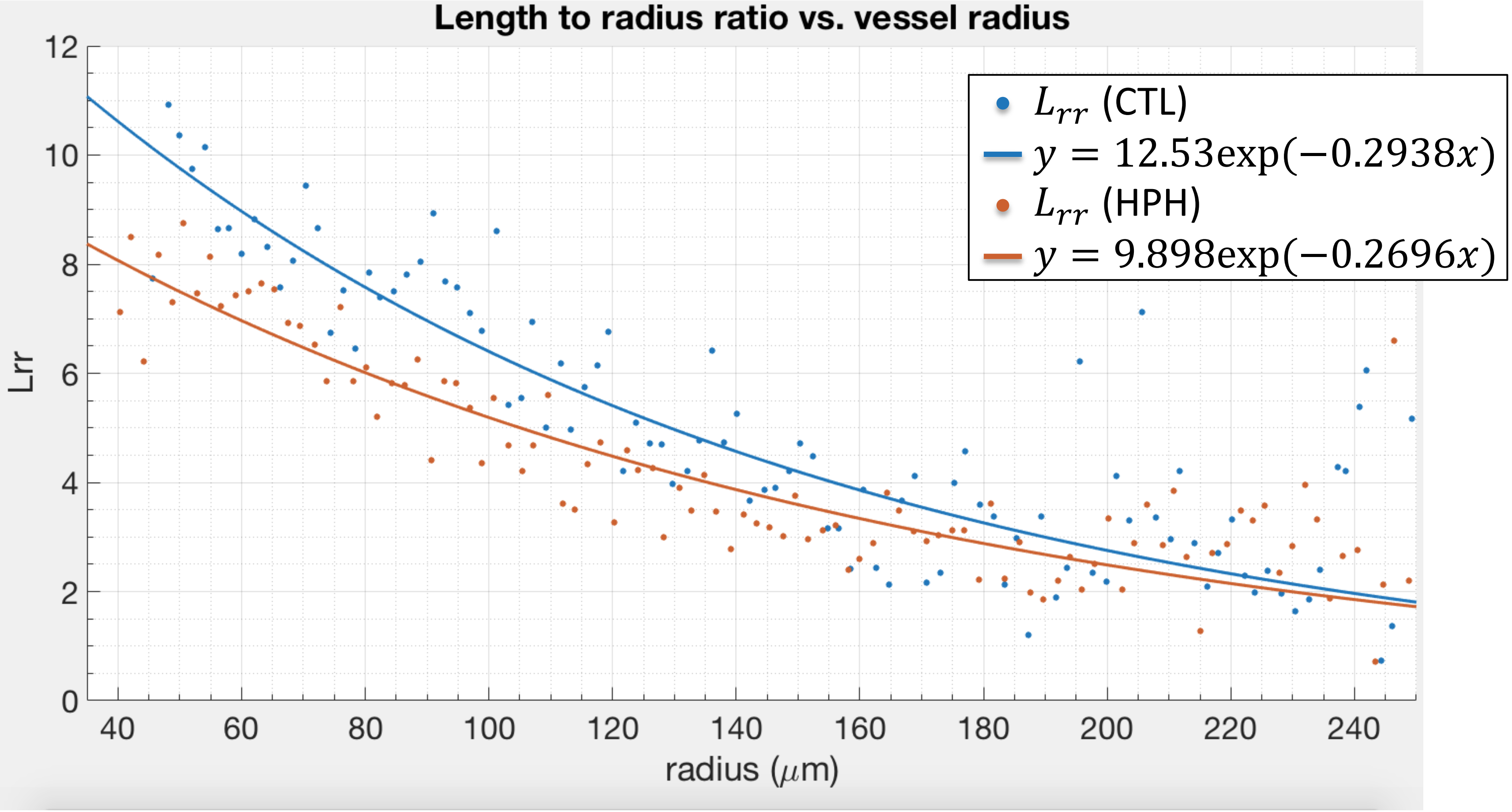
	α	β
Control	0.87±0.13	0.69±0.12
Hypertensive	0.86±0.15	0.69±0.13

All lobes
(excluding principal pathway)

	α	β
Control	0.87±0.13	0.69±0.12
Hypertensive	0.86±0.15	0.69±0.13

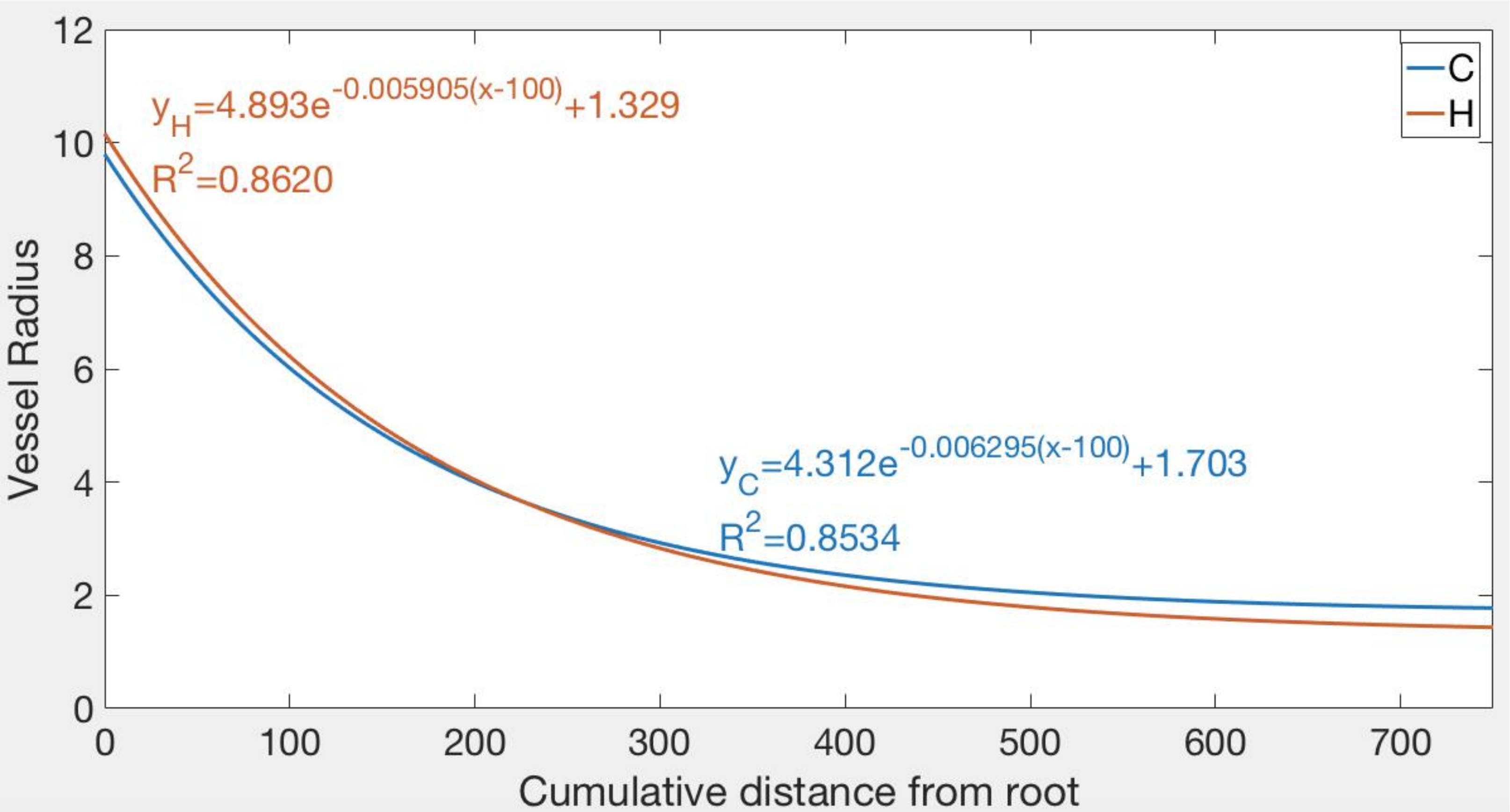
- Data supports literature values (for humans) $\alpha = 0.9$ and $\beta = 0.6$
- Excluding principal pathway does not change fractal dimensions
- α and β do not differ between control and hypertensive networks


α and β for control and HPH mice
1.1
1
0.9
0.8
0.7
0.6
β, α
40
60
80
100
120
140
160
180
200
220
240
parent vessel radius (μm)
α (CTL)
$y = 0.00081x + 0.76$
β (CTL)
$y = -0.00069x + 0.77$
α (HPH)
$y = 0.00082x + 0.77$
β (HPH)
$y = -0.00067x + 0.75$



Length to radius ratio vs. vessel radius
Lrr
radius (μm)
0
2
4
6
8
10
12
40
60
80
100
120
140
160
180
200
220
240
L_{rr} (CTL)
$y = 12.53\exp(-0.2938x)$
L_{rr} (HPH)
$y = 9.898\exp(-0.2696x)$

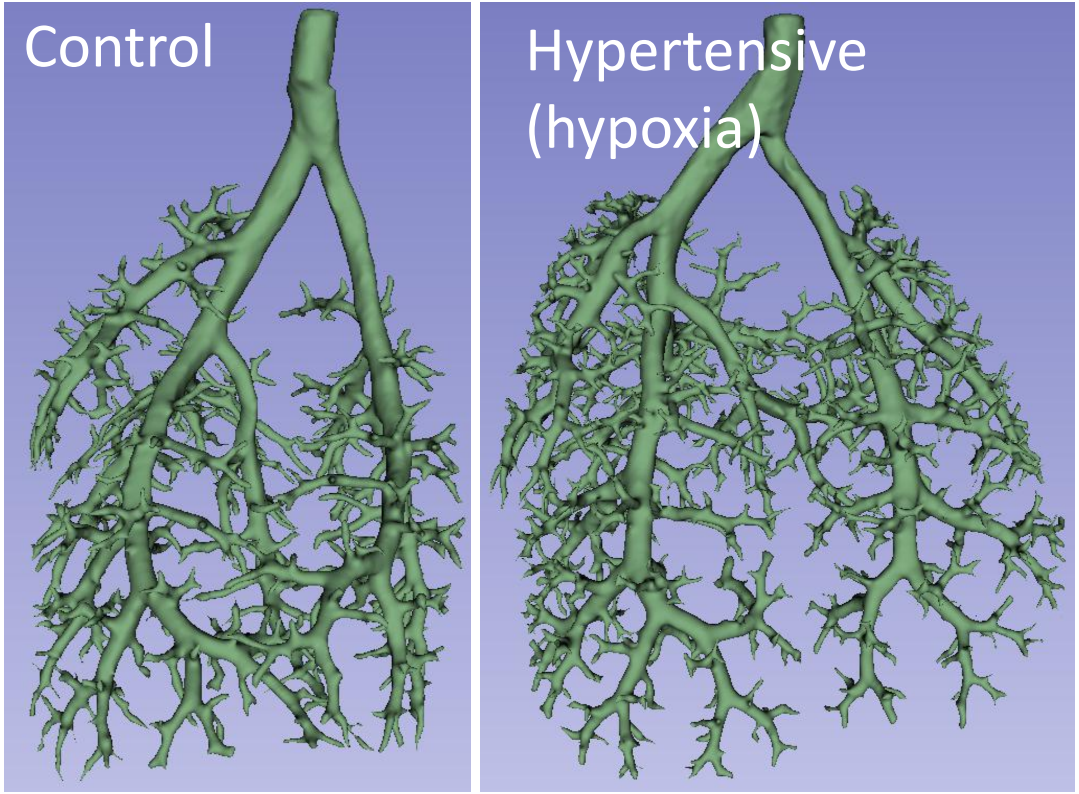
Vessel radii



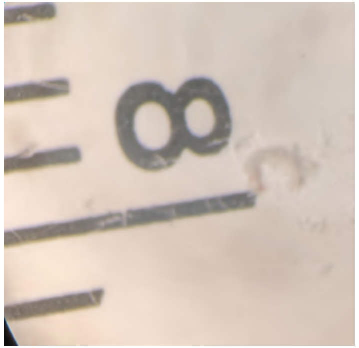
In hypertension, larger vessels dilate and smaller vessels constrict

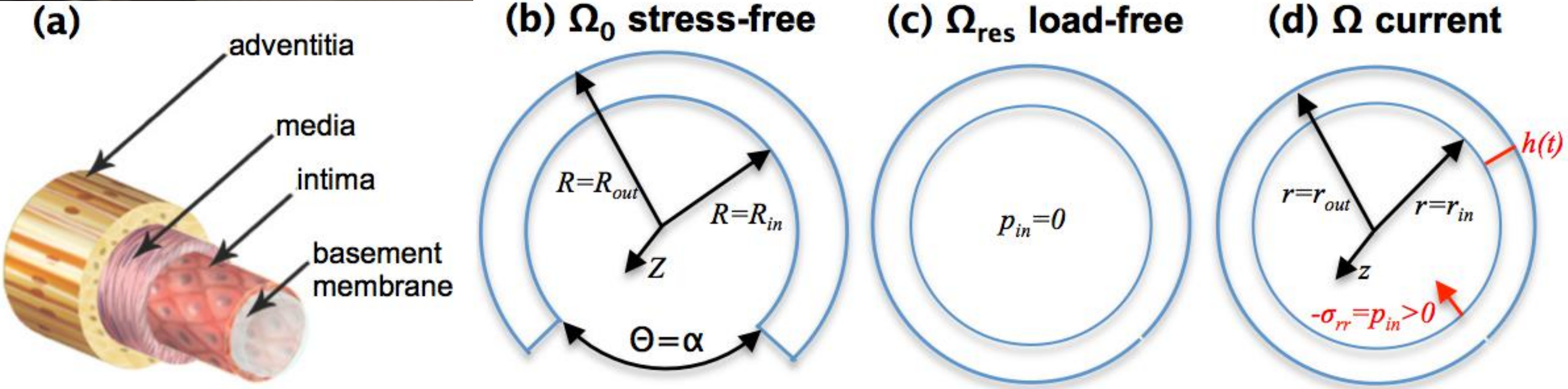
Hypothesis

- Data supports previously computed α and β values for humans
- α and β do not differ (overall) in control and hypertensive networks
- Hypertension causes angiogenesis
- In hypertensive networks, larger vessels dilate and smaller vessels constrict

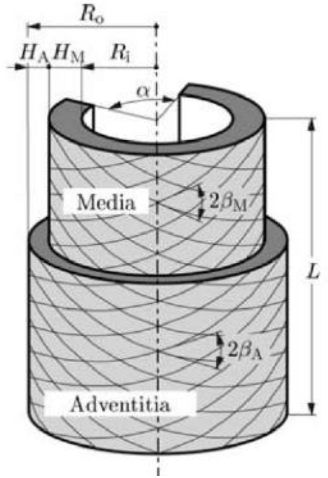


Vascular Remodeling





State of Deformation – Elastic Tube



Strain-free reference (undeformed) configuration

$$\Omega_0 = \{(R, \Theta, Z) : R_{in} \le R \le R_{out}, 0 \le \Theta \le 2\pi - \alpha, 0 \le Z \le L\}.$$

Current (deformed) configuration

$$\Omega = \{(r, \theta, z) : r_{in} \le r \le r_{out}, 0 \le \theta \le 2\pi, 0 \le z \le l\}$$

Assumed deformation

Twist angle (const)

$$r(R) = \sqrt{\frac{R^2 - R_{in}^2}{k\lambda_z} + r_i^2}\,, \quad \theta = k\Theta + Z\frac{\Phi}{L}\,, \quad z = \lambda_z Z, \qquad \text{where } k = \frac{2\pi}{2\pi - \alpha},$$

Axial stretch (const)

Opening angle

Pressure-Area Relation – 2 Layers

Media

$$\sigma^M = c_M dev(J^{-2/3}\mathbf{b}) + 2\frac{\partial \Psi^M_{aniso}}{I^M_1} dev(\vec{a}^M_1 \otimes \vec{a}^M_1) + 2\frac{\partial \Psi^M_{aniso}}{I^M_2} dev(\vec{a}^M_2 \otimes \vec{a}^M_2)$$

$$\Psi^M_{aniso} = \frac{k^M_1}{2k^M_2}\left[e^{k^M_2 (I^M_1 - 1)^2} + e^{k^M_2 (I^M_2 - 1)^2} - 2\right]$$

Adventitia

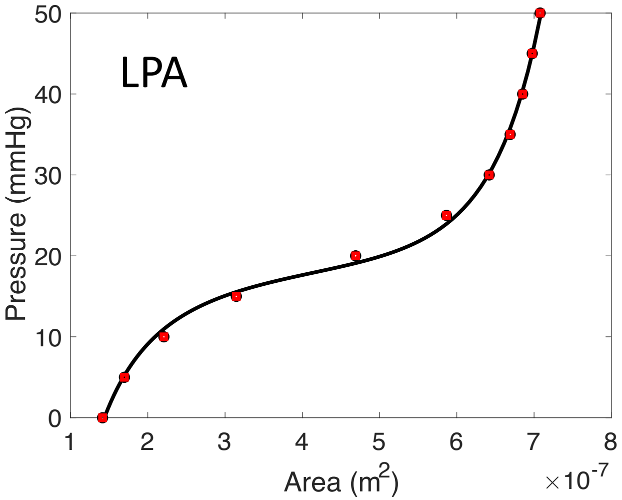
$$\sigma^A = c_A dev(J^{-2/3}\mathbf{b}) + 2\frac{\partial \Psi^A_{aniso}}{I^A_1} dev(\vec{a}^A_1 \otimes \vec{a}^A_1) + 2\frac{\partial \Psi^A_{aniso}}{I^A_2} dev(\vec{a}^A_2 \otimes \vec{a}^A_2)$$

$$\Psi^A_{aniso} = \frac{k^A_1}{2k^A_2}\left[e^{k^A_2 (I^A_1 - 1)^2} + e^{k^A_2 (I^A_2 - 1)^2} - 2\right]$$

Pressure-area relation

$$\underline{p_{in}} = \int_{\underline{r_{in}}}^{r_{MA}} \mathcal{F}_M(\underline{r_{in}}, r; \vec{\theta}, \vec{\theta}_M)dr + \int_{r_{MA}}^{r_{out}} \mathcal{F}_A(\underline{r_{in}}, r; \vec{\theta}, \vec{\theta}_A)dr$$

Media-adventitia interface (current configuration)



Stress equilibrium equation

$$\frac{d\sigma_{rr}}{dr} + \frac{\sigma_{rr} - \sigma_{\theta\theta}}{r} = 0$$

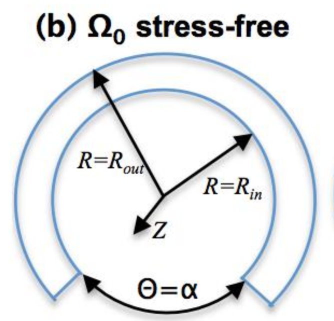
Relation to the pressure

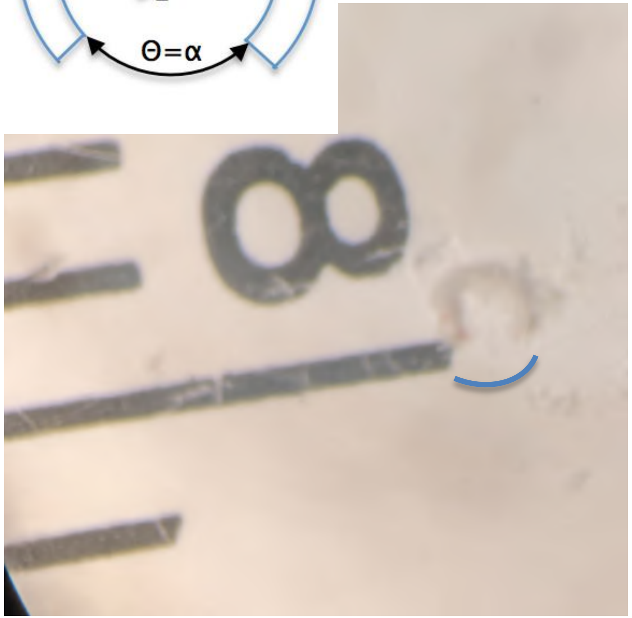
$$p_{in} = -\sigma_{rr}|_{r=r_{in}} \quad \Rightarrow \quad p_{in} = \int_{r_{in}}^{r_{out}} \frac{\bar{\sigma}_{rr} - \bar{\sigma}_{\theta\theta}}{r} dr.$$

$$p = \int_{r_{in}}^{r_{MA}} \mathcal{F}_M(r_{in}, r; \vec{\gamma}, \vec{\gamma}_M) dr + \int_{r_{MA}}^{r_{out}} \mathcal{F}_A(r_{in}, r; \vec{\gamma}, \vec{\gamma}_A) dr,$$

General	$\Phi = 0°$ $\alpha = 94.2°$ [1]	$H = 0.1 R_{diastolic}$ $\lambda_z = 1.4$ [2]	$H_{MA} = \frac{2H}{3}$ $R_{in} = 0.347$ mm
Media	$\beta_M = 29°$ [3] $c_M = 38.152$ kPa	$k_{2M} = 1.091$ $k_{1M} = 0.506$ kPa	
Adventitia	$\beta_A = 62°$ [3] $c_A = 7.771$ kPa	$k_{2A} = 1.043$ $k_{1A} = 1.091 \cdot 10^{-3}$ kPa	

Opening Angle





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Acknowledgements

- Mathematicians: Umar Qureshi , Mitchel Colebank, Mansoor Haider, Megan Chambers (NCSU),
- Laura Ellwein (VCU), Nick Hill (Glasgow)
- Statisticians: Dirk Husmeier, Mihaela Paun (Glasgow)
- Experimentalists: Martin Johnson (Glasgow), Naomi Chesler (Madison)

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