Uncertainty in hemodynamic predictions in the pulmonary vasculature

Cardiovascular Dynamics Group

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INTRODUCTION

- Pulmonary hypertension (PH) is defined as a mean pulmonary arterial blood pressure ≥ 25 mmHg. Comorbid heart failure accounts for over 80% of incidents. PH has been recognized as the third most common cardiovascular condition behind coronary heart disease and systemic hypertension.
- Definitive diagnosis requires invasive right heart catheterization (RHC), typically performed 3-4 years after the disease onset. Despite advancements in drug therapy there is no cure.
- Disease progression is monitored via frequent noninvasive imaging and recurrent RHCs, increasing the risk of morbidity and infection.
- This study shows how non-invasive image acquisition combined with mathematical modeling, sensitivity analysis, and uncertainty quantification can be used to identify biomarkers modulated by disease.

MODEL

Conservation laws

- Conservation of mass

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

- Conservation of momentum

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

- Constitutive equation

$$p(r_0,A)=\beta\left(\sqrt{\frac{A}{A_0}}-1\right),\qquad \beta=\frac{4}{3}\frac{Eh}{r_0}$$

Boundary conditions:

- **Inflow:** Specified from measured flow data
- **Junction conditions**

$$q_p=q_{d_1}+q_{d_2},\quad p_p=p_{d_1}=p_{d_2}$$

- **Outflow** (Windkessel model)

$$\frac{dp}{dt}-R_1\frac{dq}{dt}=q\frac{R_1+R_2}{R_2C}-\frac{p}{R_2C}$$

$$R_1=r_1R_{1,nom},\qquad R_T=R_1+R_2=r_TR_{T,nom},\qquad C_T=cC_{T,nom}$$

Parameters estimated minimizing the least squares cost

$$\hat{\theta}=\arg\min_\theta\ J(\theta),\qquad \theta=\{r_1,r_T,c,\beta\}$$

$$J=\frac{1}{N}\sum_{i=1}^{n}\left(p(t_i,\theta)-p_{mpa}(t_i)\right)^2$$

Pulmonary arterial network geometry variation

Vessel lengths, radius, and network connectivity obtained by segmenting micro-CT images from 7 healthy and 5 hypertensive (hypoxia induced) mice.

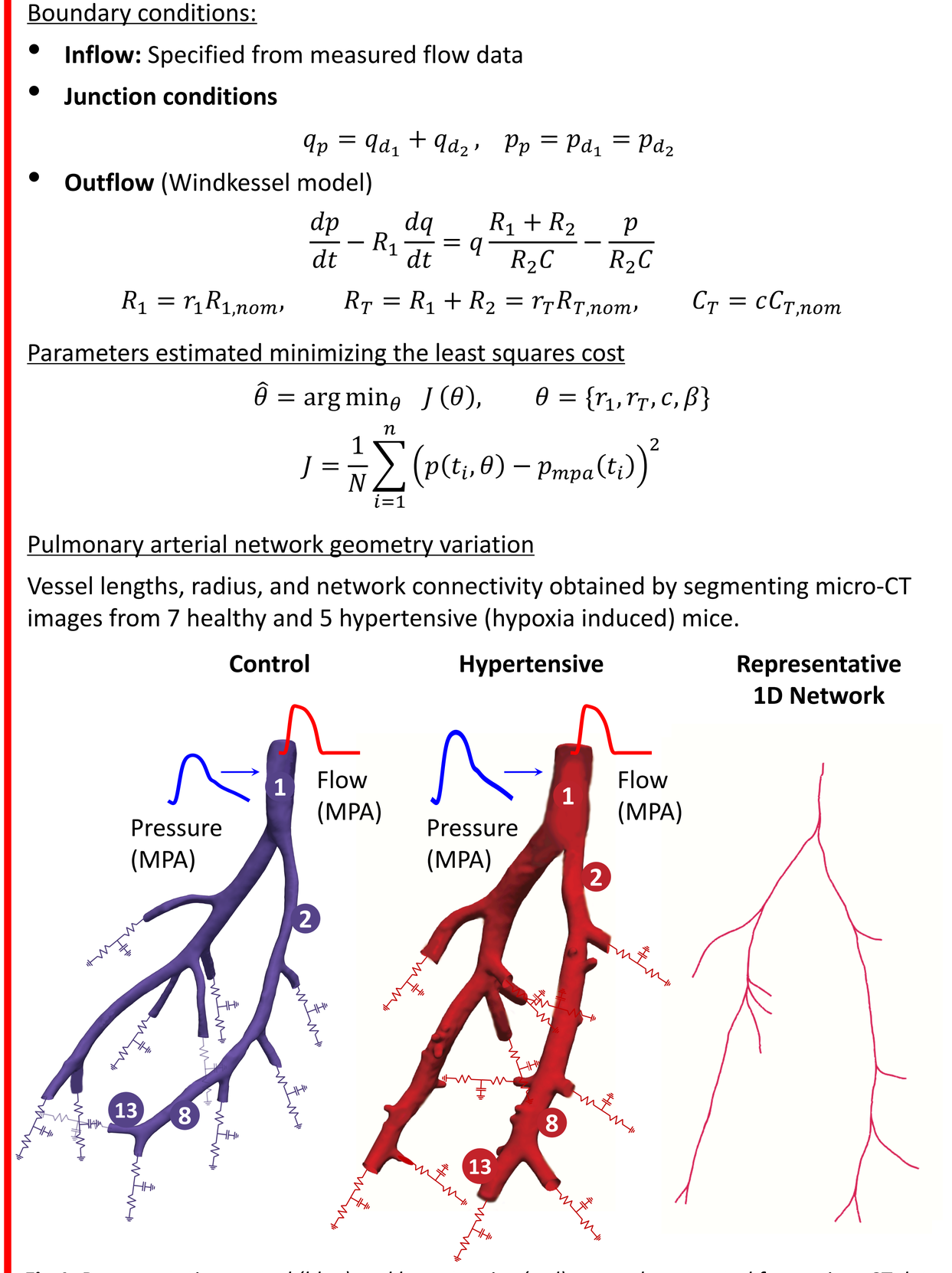

Fig 1. *Representative control (blue) and hypertensive (red) networks extracted from micro-CT data.*

SENSITIVITY ANALYSIS

- Local sensitivities

$$S(t,\theta_i)=\frac{\partial p_{mpa}(0,t,\theta)}{\partial\theta_i}\frac{\theta_i}{\bar{p}_{mpa}},\qquad \bar{S}(\theta_i)=\|S(t,\theta_i)\|_2$$

- Morris indices (global)

$$d^j(\theta_i)=\frac{f\left(\theta^j+e_i\Delta,t\right)-f\left(\theta^j,t\right)}{\Delta},\qquad \mathrm{j}=1,\dots,K,\qquad \Delta=\frac{L}{2(L-1)}$$

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

UNCERTAINTY QUANTIFICATION

- Confidence ($X=0$) and prediction ($X=1$) intervals (asymptotic)

$$y_I(t_i)=y\left(t_i,\hat{\theta}\right)\pm t_{n-p}^{\alpha/2}\hat{\sigma}(X+g_i(S^TS)^{-1}g_i)^{1/2}$$

where g_i^T is the i'th row of the sensitivity matrix S, $\hat{\theta}$ are the optimized parameters, and $\hat{\sigma}=J$ is the estimated variance.

- DRAM: Credible intervals sampled from parameter distributions

$$\pi(\theta|y)=\frac{\pi(y|\theta)\pi_0(\theta)}{\pi(y)}$$

RESULTS

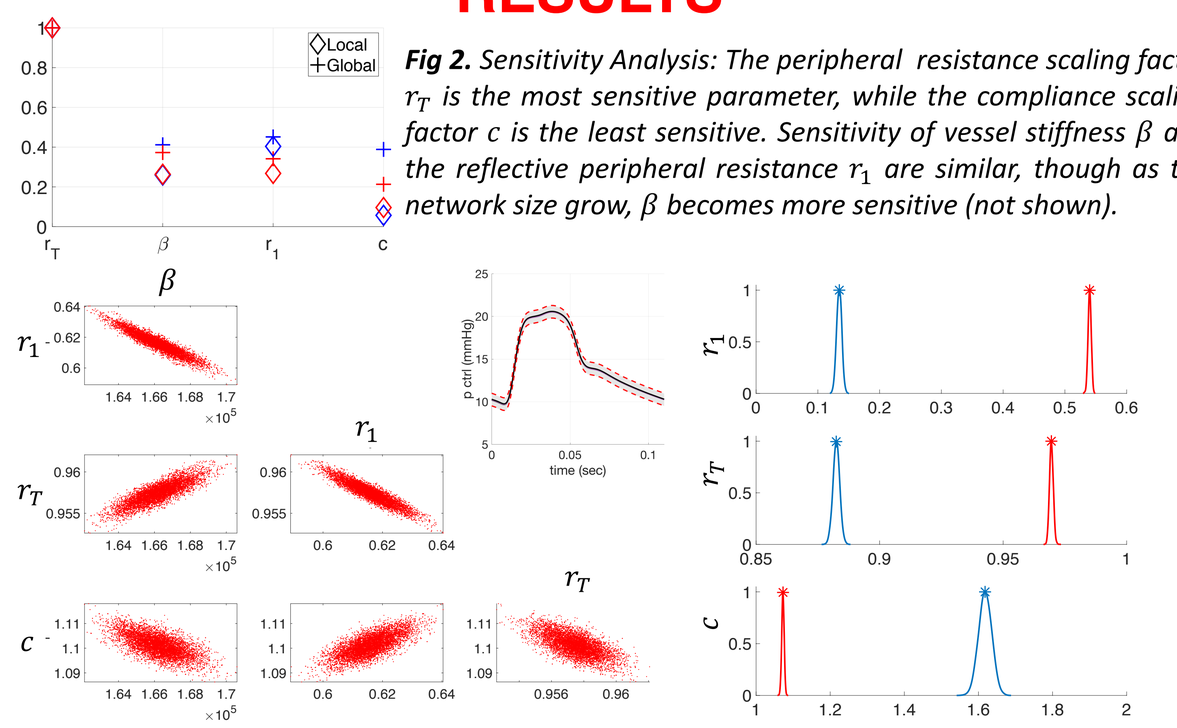

Fig 2. *Sensitivity Analysis: The peripheral resistance scaling factor r_T is the most sensitive parameter, while the compliance scaling factor c is the least sensitive. Sensitivity of vessel stiffness β and the reflective peripheral resistance r_1 are similar, though as the network size grow, β becomes more sensitive (not shown).*

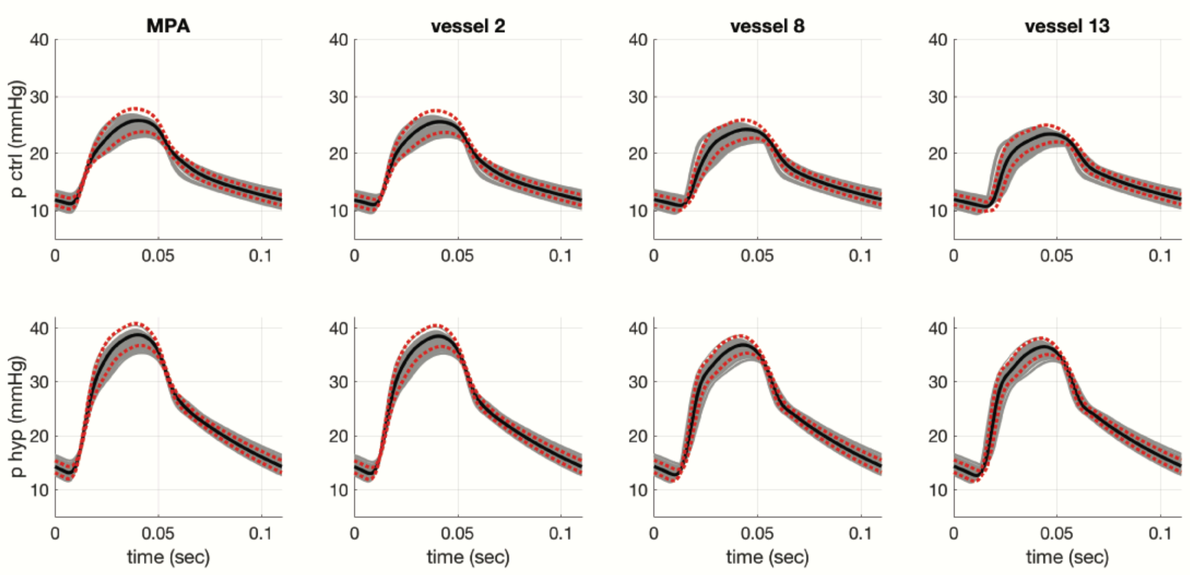

Fig 4. *Predictions of pressure obtained from 1000 simulations varying the geometry (length and diameter) accounting for population variation (analysis on 7 control and 5 hypertensive mice). As expected geometry variation is more significant than variation around internal parameters (compare MPA panel with prediction intervals displayed above).*

CONCLUSIONS

- The peripheral resistance scaling factor r_T is the most sensitive parameter.
- Parameters r_1 and β (and r_T) are correlated, fixing β gives an uncorrelated subset.
- Pressure predictions show that the variation with geometry is more influential than internal parameters $\theta=\{r_1,r_T,c,\beta\}$.
- Predictions of flow vary less (marked on Fig 1.) as it is specified at the inlet.

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