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Characterizing Patients with Pulmonary Hypertension Using Dynamical Modeling

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Overview

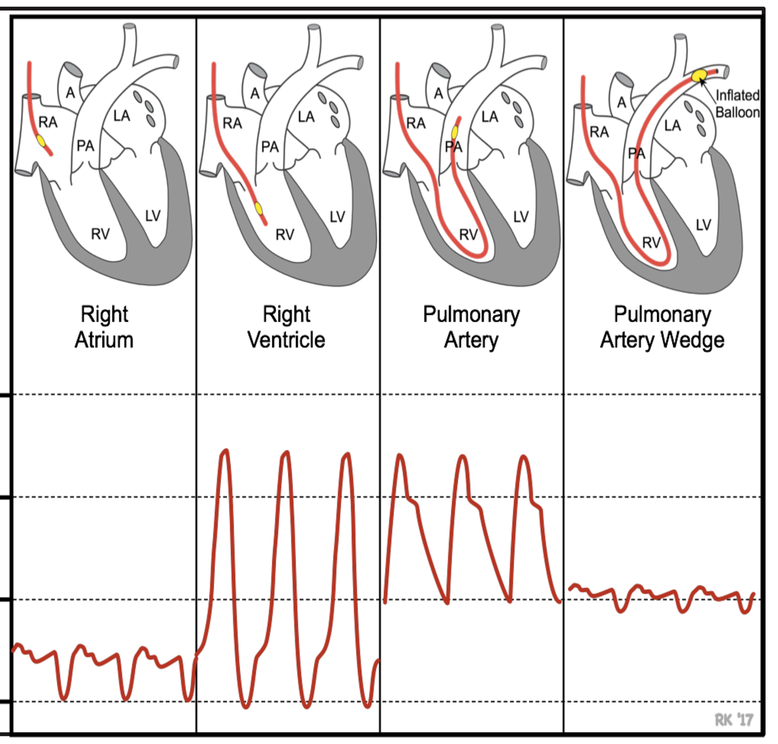
Pulmonary hypertension (PH) is a deadly and progressive disease characterized by pulmonary arterial pressure above 25 mmHg. This study uses a 0D system of differential equations to predict pressure, flow, and volume of the cardiovascular system. Influential, identifiable parameters are optimized to improve the model fit to the data. By adjusting resistance and compliance values, we simulate the effect of PH treatments on pressure. Results show time-varying data and parameters improve right heart predictions. PH patients "treated" using surgical intervention reach normotensive ranges. Overall, model outcomes are consistent with physiological understanding of the disease.

Data

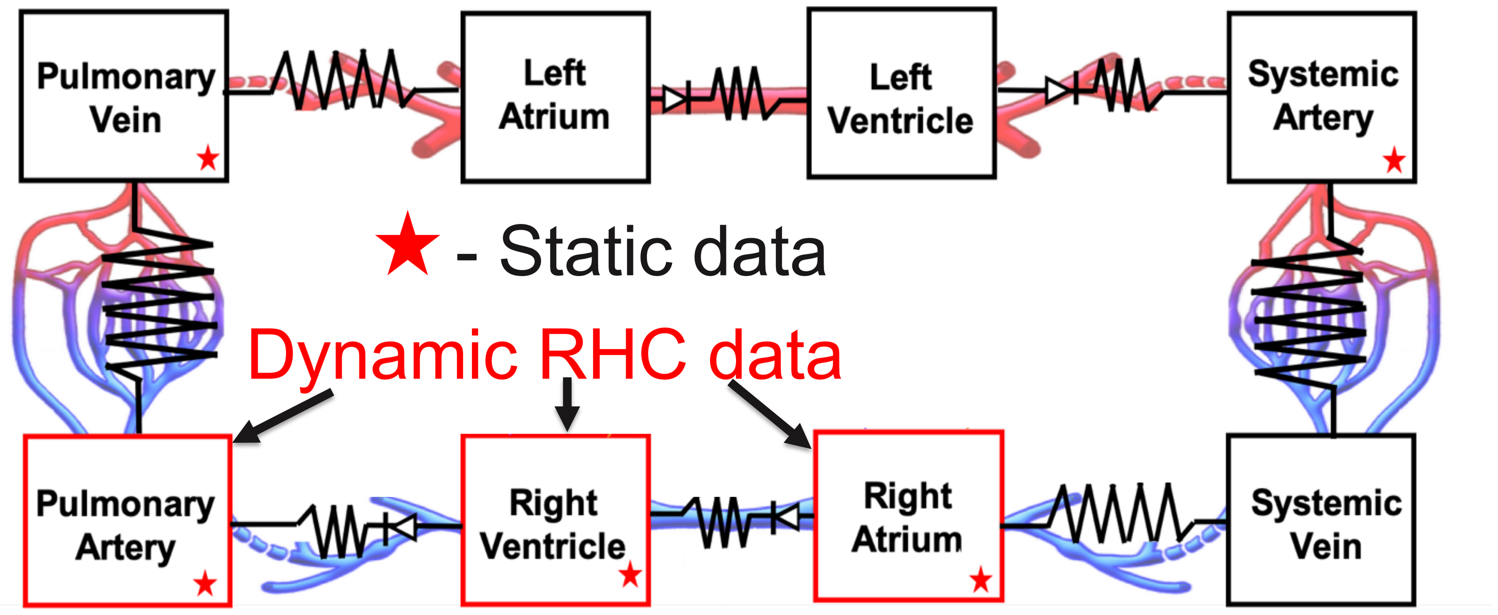
5 PH patients – RHC measurements:

- right atrium/ventricle pressure waveforms
- main pulmonary artery, and pulmonary artery wedge pressure waveforms
- Cardiac output

Systolic and diastolic systemic arterial pressure measured with a cuff



Cardiovascular System Model



Compartment model analogous to an electric circuit

- Pressure p (mmHg) – Voltage
- Flow q (mL/s) – Current
- Volume V (mL) – Charge
- Resistance R (mmHg·s / mL) – Resistance
- Compliance C (mL/mmHg) – Capacitance

25 parameters and 8 states

Conservation of volume

$$dV_{s,i}/dt = q_{in} - q_{out}$$

Ohm's law

$$q_i = \frac{p_{in} - p_{out}}{R_i}$$

$$q_{valve} = \begin{cases} q_i & \text{if } p_{in} > p_{out} \\ 0 & \text{otherwise} \end{cases}$$

Pressure-volume relation

$$V_i - V_{un,i} = C_i(p_{int} - p_{ext})$$

Pressure in the heart

$$p_h = E_h(t)(V_h - V_{un,h})$$

Time-varying elastance function $E_h(t)$

Parameter Subset Selection and Inference

Sensitivity and correlation analyses determine which parameters, θ_j, are sensitive and identifiable. Optimizing a subset of such parameters minimizes least squares cost for the model to better fit the data.

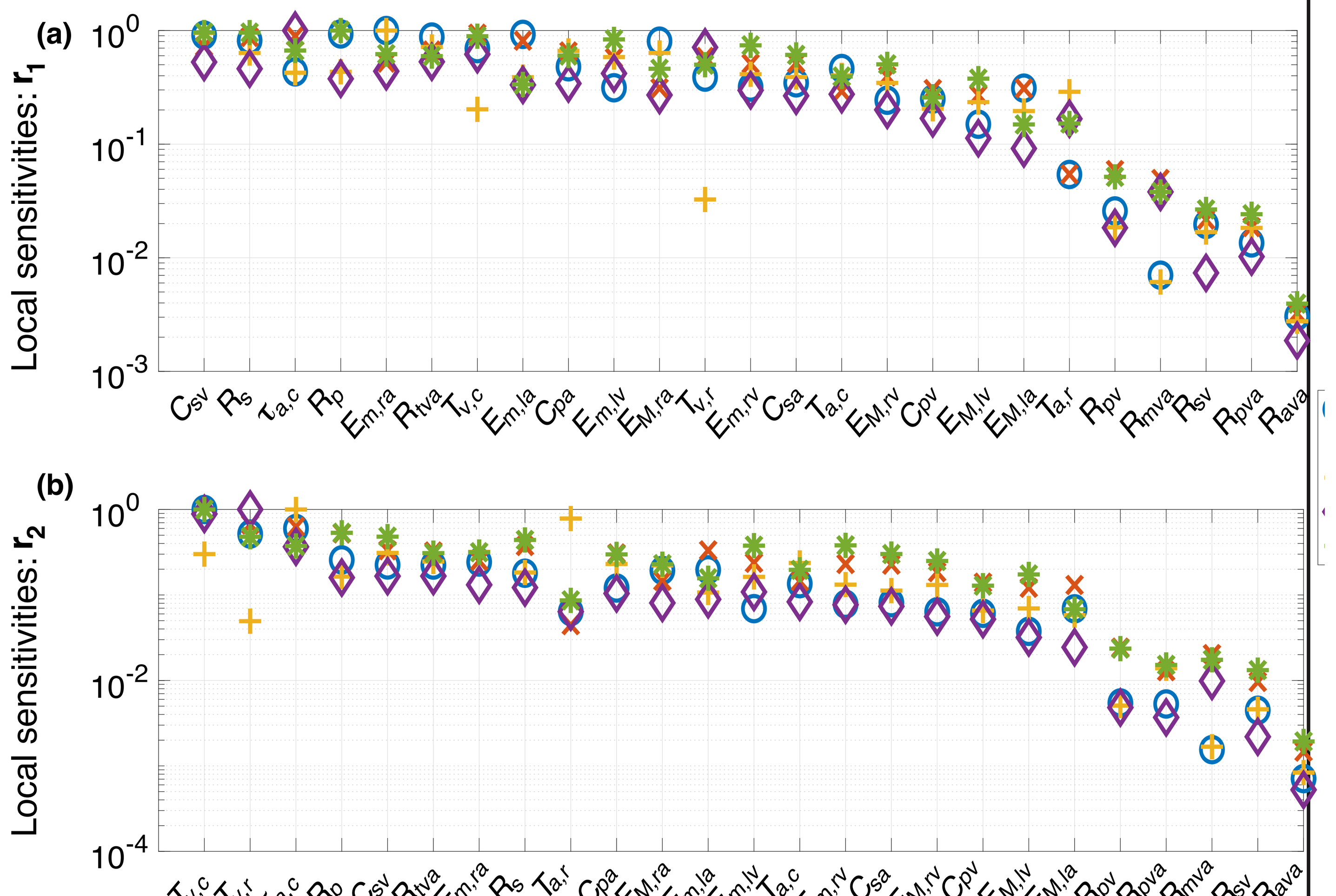
Sensitivity Analysis

The sensitivity matrix, S, and ranking parameters from most to least sensitive is the first step in determining a parameter subset. Sensitivity matrix, parameter sensitivity, and sensitivity ranking are respectively defined by

$$S = \begin{pmatrix} S_{11} & \cdots & S_{1n} \\ \vdots & \ddots & \vdots \\ S_{n1} & \cdots & S_{nn} \end{pmatrix} \quad for\ i,j = 1 \ldots n$$

$$S_{i,j} = \frac{\partial y(t_i, \theta)}{\partial \theta_j}$$

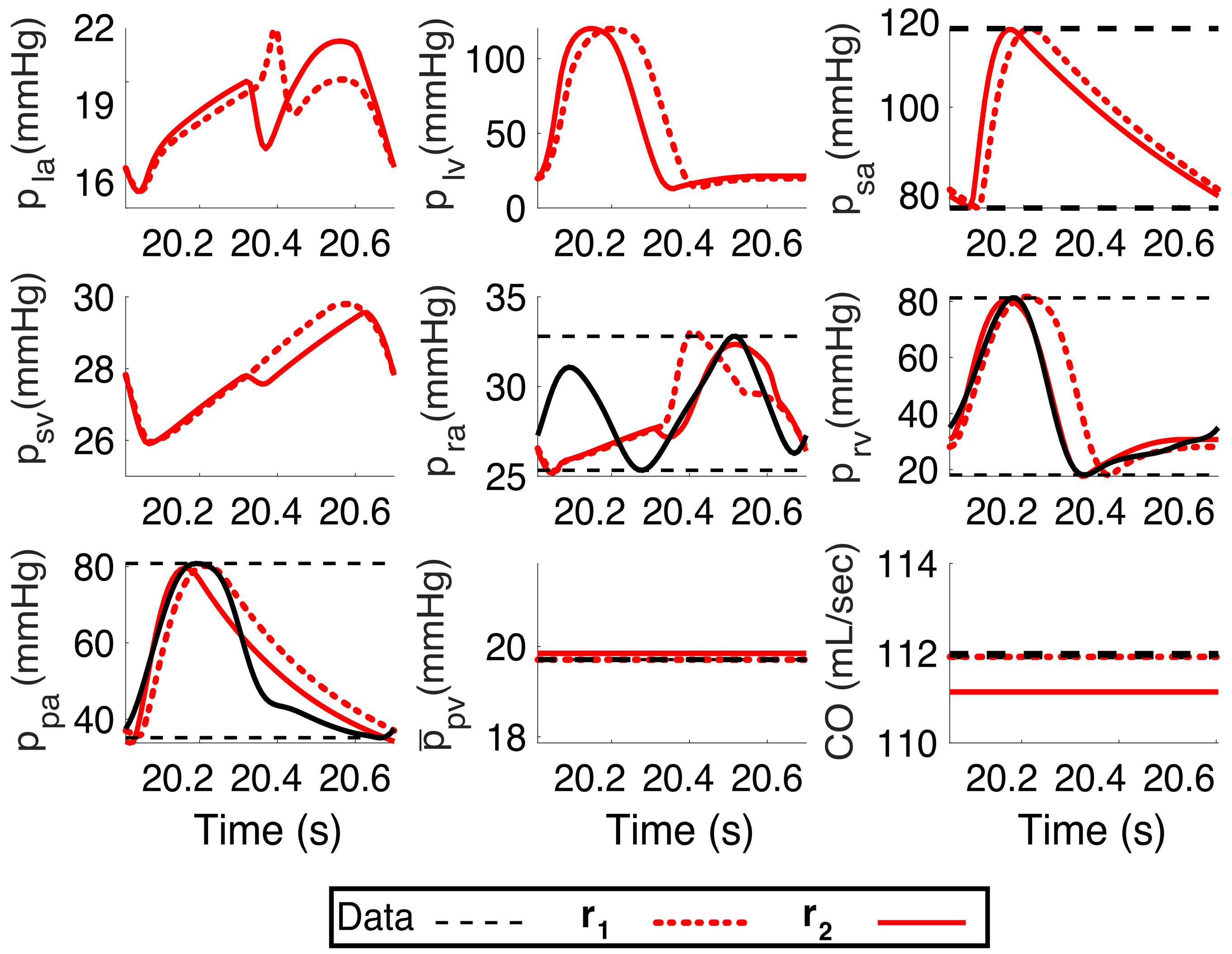
$$R_j = \left(\sum_{i=1}^{N} S_{i,j}^2 \right)^{\frac{1}{2}}$$



Subset selections

Identifiable parameters determined from the covariance matrix. Parameters with pairwise correlation below $\gamma < .95$ identifiable

$$\widetilde{c_{ij}} = \frac{C_{ij}}{\sqrt{C_{ii}C_{jj}}} < \gamma \qquad C = (S^T S)^{-1}$$



Optimization

Influential, identifiable parameter subsets are estimated using least squares optimization (using the Levenberg Marquardt method) minimizing the least squared cost, J_i.

$$J_i = r_i^t r_i, \qquad r_i = r_1, r_2$$

Residual Functions

Residual vectors capture the relative differences between measured data and model predictions.

$\boldsymbol{r_1} = \boldsymbol{r_s}$ [static values only]

$\boldsymbol{r_2} = [\boldsymbol{r_s}, \boldsymbol{r_{ra}}, \boldsymbol{r_{rv}}, \boldsymbol{r_{pa}}]$ [static and dynamic values]

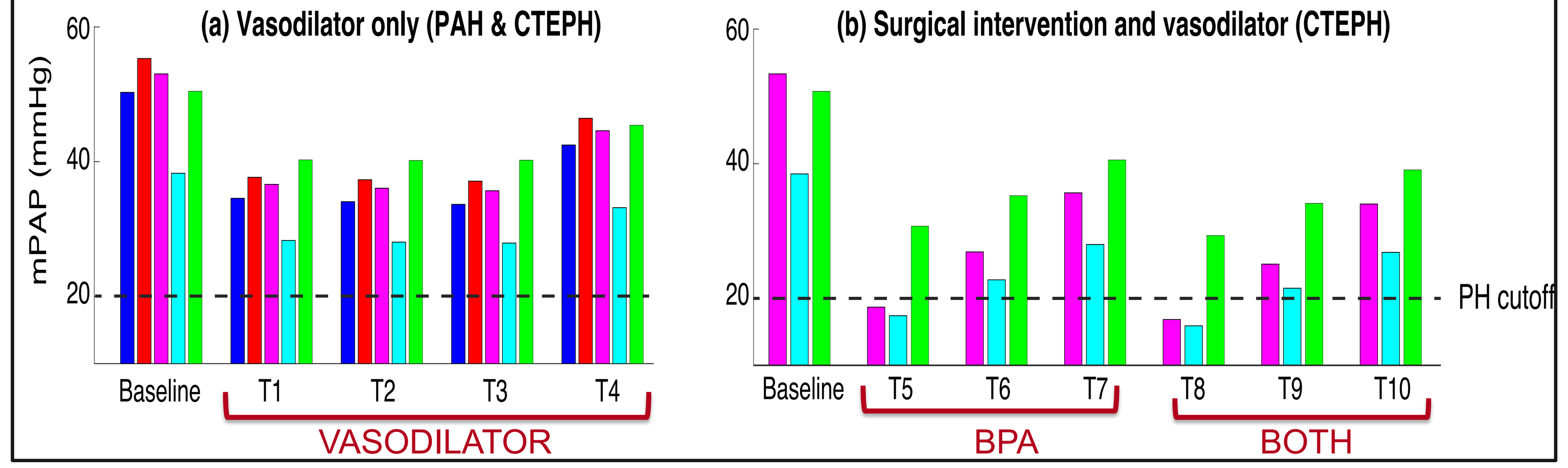
$$\boldsymbol{r_s} = \frac{1}{\sqrt{N_s}} \frac{y - y^d}{y^d}$$

Treatment

Simulate 2 types of PH treatments to improve hemodynamic predictions.

- treating by reducing resistance with and without an increase in compliance
- predictions are computed and compared to normotensive predictions.

Treatment	Parameter			
	R_p	R_s	C_{sa}	C_{pa}
Vasodilator	⇩	⇩	⇧	⇧
BPA	⇩			⇧
BPA with vasodilator	⇩	⇩	⇧	⇧



Results

- Subset selection analyses
  - Right side heart parameters most influential for r_1
  - T_{crv}, T_{rrv} and τ_{cra} are the most influential for r_2
  - $[R_{ava}, R_{mva}, R_{pva}, R_{pv}, R_{sv}]$ are consistently noninfluential
- Model predictions
  - Increase in R_p/R_s and a decrease in C_{pa}/C_{sa} in PH relative to normotension
  - r_1 improves CO and static max/min prediction
  - r_2 improves RA, RV (drastically) and PA (marginally) fit to waveforms
- Treatment
  - Changes in resistance are more influential on mPAP than compliance
  - Normotensive PA pressure ranges (below 20 mmHg) were achieved for T5 and T8: "cured" after treatment

Discussion

Results show that in among the different data types, the same set of parameters, excluding the timing parameters, were still most influential as we moved from static data to time varying data. The one set of consistently non-influential parameters is agreeing with previous studies. The compliance and elastance ratios increased and decreased respectively, but this hasn't been explored with larger sets of data, which could possibly differentiate between PH severities. Overall, model outcomes are consistent with physiological understanding of the disease. Future work will consist of developing a model selection program to better differentiate PH severities.

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