Parameter inference in a computational model of hemodynamics in pulmonary hypertension

Mitchel J. Colebank*, Amanda L. Colunga*, Macie King, Christopher Schell, Matt Shelden, Mariam Kharbat, Robert Sternquist, Mette S. Olufsen

Abstract Abstract here.

1 Introduction

Pulmonary hypertension (PH) is defined as a mean blood pressure greater than or equal to 25 mmHg in the main pulmonary artery (MPA) at rest (Kheyfets *et al.*, 2013). While PH is a relatively rare disease, it has no cure and progresses rapidly, leading to vascular remodeling (i.e., thickening and stiffening of the pulmonary arteries and veins), vascular-ventricular decoupling, and ultimate right ventricular failure if left untreated (Fayyaz *et al.*, 2018). Symptoms of PH do not appear until 1-2 years after disease onset (Hoeper *et al.*, 2017), hence patients diagnosed via right heart catheterization (RHC) have suffered severe vascular remodeling. For this reason, an understanding of how cardiovascular parameters (e.g., pulmonary vascular resistance (PVR)) change in PH can assist in early detection and better therapeutic interventions. To address this, we consider a mathematical, systems level model of the cardiovascular circuit, and subsequently estimate hemodynamic parameters using both static and dynamic PH patient data.

Under homeostatic conditions, the pulmonary circulation is network of compliant arteries, emerging from the right ventricle (RV), that distributes deoxygenated blood to the lungs, and subsequently through the pulmonary veins and left atrium. Blood is then ejected from the left ventricle (LV) and transported to the major organs of the body via the systemic arteries, finally returning to the right atrium via the systemic veins to complete the cardiovascular circuit. PH leads to changes in pulmonary circulation characteristics, most notably a decreased vessel compliance and increase right

ventricular afterload (Hoeper *et al.*, 2017; Fayyaz *et al.*, 2018).There are five main etiologies of PH, including pulmonary arterial hypertension (PAH) and chronic thromboembolic pulmonary hypertension (CTEPH), which all lead to the aforementioned changes in pulmonary vascular structure. [ADD MORE HERE]

Mathematical modeling is becoming increasingly useful as an addition tool in monitoring and understanding the progression of cardiovascular disease (Ellwein *et al.*, 2008; Kung *et al.*, 2014; Marquis *et al.*, 2018; Colebank *et al.*, 2019; Colunga *et al.*, 2020). For instance, Ellwein et al. (Ellwein *et al.*, 2008) developed a systemic circulation model including the upper and lower body circulation, heart, and cerebral circulation, and subsequently estimated parameters informed by noninvasively measured systemic pressure and cerebral flow velocity. The mathematical model was a lumped parameter (zero-dimensional, 0D), system level model derived from electrical circuit theory (Ohm's law); however, model predictions were in agreement with measured data. Additional studies have had success in predicting pulmonary hemodynamics using lumped parameter models. Kung et. al (Kung *et al.*, 2014) used the 0D framework to simulate exercise conditions in Fontan patients and predict pulmonary pressures with and without exercise, which is an important indicator of Fontan patient survival rate. However, only noninvasive cardiac output and heart rate data was available to calibrate the model, which limits the certainty of the parameter estimates. Moreover, parameter estimation in this model type can be difficult, as parameters may not be independent in their effects on model predictions. To quantify the influence of parameters and parameter interaction, sensitivity analyses can be employed (Ellwein *et al.*, 2008; Olufsen & Ottesen, 2013). Schiavazzi et al. (Schiavazzi *et al.*, 2017) used a lumped-parameter model to predict outcomes from single-ventricle palliation surgery, and subsequently estimated parameters in the model using pulmonary hemodynamic data from single-ventricle patients with Norwood physiology. The authors used local and global identifiability techniques apriori to determine which parameters could be uniquely identified from available data and showed that optimal model predictions were in line with static pressure and flow rate data. Previous work by our group (Colunga *et al.*, 2020) used similar methods for heart-transplant patients, showing that model predictions align with static RHC data from both single patient recordings and

longitudinal patient data. While the aforementioned studies have used noninvasive and static data, none of them attempted to match invasively measured, dynamic waveforms.

Previous one-dimensional fluid dynamics studies (Colebank *et al.*, 2019; Chambers *et al.*, 2020) were able to match model predictions of pulmonary pressure to time-series waveforms measured in-vivo, yet the use of time-series data in 0D models is largely underutilized. A study by Gerringer et. al (Gerringer *et al.*, 2018) used 3 and 4 element Windkessel models to predict MPA hemodynamics and compare them to measured MPA pressure in control and PH induced mice. While both models were able to match control and PH waveforms, a combination of local sensitivity analysis and Akaike information criteria (AIC) showed that the simpler, 3 element Windkessel model was preferred. However, by only modeling the MPA, information regarding heart and peripheral artery dynamics could not be accounted for. Marquis et. al (Marquis *et al.*, 2018) used a 5-compartment model of the cardiovascular system and calibrated their model using simultaneously recorded pressure-volume data from mice, showing that model predictions could align with time-series data. While this study did utilize time-varying data, human data, like that obtained from PH patients during RHC, is not measured simultaneously. For this reason, parameter estimation studies with human data typically only use static values (Kung *et al.*, 2014; Colunga *et al.*, 2020). In addition, to the authors' knowledge, no previous studies have investigated the benefits of using a combination of dynamic and static hemodynamic measurements in the 0D modeling framework.

To this extent, we propose the use of a lumped parameter model, including the systemic and pulmonary circulations and an elastance based model of the atria and ventricles, to estimate physiological parameters based on PH data. Model parameters are analyzed via local and global sensitivity analyses, the results of which are used to construct a subset of influential, identifiable parameters. To quantify the benefits of time-series data in parameter estimation, we consider several residual vectors in both the sensitivity analysis and parameter estimation techniques; these residuals consist of static data (mean pressures and cardiac output), dynamic data (RHC measurements), and a combination of the two. Results highlight how inclusion of dynamic data in the optimization objective function changes the parameter subsets, and that time-series

data can be matched to model predictions via optimization of timing parameters in the heart.

Table 1

2 Materials and Methods

2.1 Hemodynamic data

2.1.1 Ethics and approval

Patient specific data was obtained from two different medical clinics, adhering to their respective institutional review boards (IRB) guidelines. Deidentified right heart catherization (RHC) patient data was obtained from the Scottish Pulmonary Vascular Unit at Golden Jubilee National Hospital (IRB XXX). Deidentified RHC data was also obtained from the Center from Pulmonary Vascular Disease at Duke university (IRB reference ID 307905).

2.1.2 Catheterization data

NEED PROTOCOL FROM GEESH

This study utilizes RHC data from five patients with confirmed PH (two with Group I, pulmonary arterial hypertension (PAH) and three patients with group IV, chronic thromboembolic pulmonary hypertension (CTEPH)). Two CTEPH datasets from Duke University were used in combination with one CTEPH and two PAH datasets from Golder Jubilee Hostpial. Static patient data for both hospitals includes demographics (height, weight, gender, age; see Table 2), heart rate, and systolic, diastolic, and mean systemic blood pressure measured by cuff pressure. Patients underwent RHC during which a catheter was advanced from the right atrium (RA), to the right ventricle (RV), and finally to the main pulmonary artery (MPA), providing dynamic pressure waveforms for each. A catheter balloon was then inflated in a distal artery providing pulmonary arterial wedge pressure (PAWP) measurements, an estimate of left atrial pressure.

Cardiac output (*CO*) was measured during RHC by thermodilution. All pressure readings were obtained over 7-8 heart beats.

2.1.3 Data extraction and preparation

Time-series data was manually digitized using GraphClick version 3.0.3 for Mac OS. Beat-to-beat hemodynamic profiles for each patient were obtained by aligning each pressure profile to ECG signals obtained during RHC. The time-series profiles were then separated using the ECG R-R intervals and stored as separate data files. For this study, a single representative RA, RV, and MPA signal was obtained from each patient (shown in Figure 1). Since RHC data is not simultaneously measured, the representative waveforms were selected during expiration and were assigned a cardiac cycle length that was averaged across RA, RV, and MPA data for each patient. To ensure signals are aligned during the cardiac cycle, we shifted RA and MPA signals in time so that RA contraction occurs before the start of RV systole and that peak RV pressure occurs immediately before peak MPA pressure. Magnitudes of the pressure signals are shifted slightly to ensure that pressures in the RA, RV, and MPA allow for physiological valve dynamics.

Lastly, we construct a control patient using pressure and volume values from literature (Krohn Therkelsen *et al.*, 2006; Boron & Boulpaep, 2017). Pressure values used for the control model are displayed in table 3. Control parameters and model predictions are compared to those obtained using PH data.

Table 2

Figure 1

2.2 Mathematical model

This study uses a systems level, ODE compartment model (Marquis *et al.*, 2018; Colunga *et al.*, 2020), predicting dynamic pressure, flow, and volume in the systemic and pulmonary cardiovascular circuits. The model consists of 8 compartments: four

heart chambers comprising the left and right atria and ventricles, the systemic arteries and veins, and the pulmonary arteries and veins.

Model equations relate pressure, flow, and volume following an electrical circuit analogy, where pressure p (mmHg), flow q (ml/s), and volume V (ml) are analogous to voltage, current, and charge, respectively. To ensure proper flow between compartments, valve dynamics are modeled using diodes, i.e. valves are either open or closed depending on the pressure gradient between compartments. We include four heart values, two semilunar (tricuspid and mitral) and two atrioventricular (pulmonary and aortic).

The compartments of the model (i.e. the systemic and pulmonary arteries and veins) mimic the system of equations in circuit theory, giving

$$\frac{dV_i}{dt} = q_{i-1} - q_i \tag{1}$$

$$q_i = \frac{p_i - p_{i+1}}{R_i} \tag{2}$$

$$V_i = V_{un} + C_i(p_i - p_{i+1}) \tag{3}$$

where V_i, q_i, and p_i are the volume, flow, and pressure in compartment i, V_{un} is the unstressed volume (the volume of blood not transported during the cardiac cycle), R_i (mmHg s / ml) is the resistance across the compartments, and C_i (ml / mmHg) is the compartment compliance.

The chambers of the heart are modeled as a time-varying, elastic chamber (Ellwein *et al.*, 2008; Marquis *et al.*, 2018). The pressure in each chamber is calculated as the product of elastance $E_i(t)$ (mmHg / ml) (inverse of compliance) and volume

$$p_i(t) = E_i(t)\big(V_i - V_{i,un}\big), \tag{4}$$

where $i = a, v$ denotes atrial or ventricular pressure, respectively. The elastance function $E_i(t)$ modeling both atrial and ventricular contraction (Liang *et al.*, 2009) is a

piecewise continuous function, accounting for systolic and diastolic dyamics. Starting from ventricular contraction, the ventricular elastance function is defined as

$$E_v(t) = \begin{cases} \frac{(E_{v,M} - E_{v,m})}{2}\left(1 - \cos\left(\frac{\pi t}{T_{v,c}}\right)\right) + E_{v,m}\,, & 0 \le t \le T_{v,c} \\ \frac{(E_{v,M} - E_{v,m})}{2}\left(1 + \cos\left(\frac{\pi\left(t - T_{v,c}\right)}{(T_{v,r} - T_{v,c})}\right)\right) + E_{v,m}\,, & T_{v,c} \le t \le T_{v,r} \\ E_{v,m}\,, & T_{v,r} \le t \le T \end{cases} \quad (5)$$

where $E_{v,m}$ and $E_{v,M}$ are the minimal and maximal ventricular elastances, $T_{v,c}$, $T_{v,r}$ (s) are the durations of ventricular contraction and relaxation, respectively, and T (s) is the cardiac cycle length.

The atrial elastance function is described in a similar fashion,

$$E_a(t) = \begin{cases} \frac{E_{a,M} - E_{a,m}}{2}\left(1 - \cos\left(\frac{\pi\left(t - T_{a,r}\right)}{(T - T_{a,c} + T_{a,r})}\right)\right) + E_{a,m}\,, & 0 \le t \le T_{a,r} \\ E_{a,m}\,, & T_{a,r} \le t \le \tau_{a,c} \\ \frac{E_{a,M} - E_{a,m}}{2}\left(1 - \cos\left(\frac{\pi\left(t - \tau_{a,c}\right)}{(T_{a,c} - \tau_{a,c})}\right)\right) + E_{a,m}\,, & \tau_{a,c} \le t \le T_{a,c} \\ \frac{E_{a,M} - E_{a,m}}{2}\left(1 + \cos\left(\frac{\pi\left(t - T_{a,c}\right)}{(T - T_{a,c} + T_{a,r})}\right)\right) + E_{a,m}\,, & T_{a,c} \le t \le T \end{cases} \quad (6)$$

Here, $E_{a,m}$ and $E_{a,M}$ are the minimum and maximum elastances of the atria, and $T_{a,r}$, $\tau_{a,c}$ and $T_{a,c}$(s) are timing parameters corresponding to the start of atrial relaxation (e.g., $E(t) = E_{a,m}$), the start of atrial contraction, and the point of maximum atrial contraction, respectively. The elastance model is parameterized such that $0 \le T_{a,r} \le \tau_{a,c} \le T_{a,c} \le T$. $E(t)$ is solved at the beginning of ventricular isovolumic contraction, hence ventricular elastance increases at $t = 0$. In contrast, atrial elastance decreases back towards $E_{a,m}$ during isovolumic contraction and then increases prior to ventricular contraction, consistent with cardiac physiology (Boron & Boulpaep, 2017). An example plot of the elastance relationships can be found in Figure 2.

In regard to heart timing parameters, RHC only records dynamic right heart data. For this reason, timing parameters for the left ventricle and left atrium are set at a fixed value relative to the right heart timing parameters.

In summary, the system of ODE's contains eight states and 25 parameters, and can be written as

$$\frac{d\boldsymbol{x}}{dt} = g(t, \boldsymbol{x}; \boldsymbol{\theta})$$

$$\boldsymbol{x} = \{V_{la}, V_{lv}, V_{sa}, V_{sv}, V_{ra}, V_{rv}, V_{pa}, V_{pv}\}$$

$$\begin{gathered}\boldsymbol{\theta} = \{R_s, R_p, R_{ava}, R_{mva}, R_{pva}, R_{tva}, R_{pv}, R_{sv},\\ C_{sa}, C_{sv}, C_{pa}, C_{pv},\\ T_{a,r}, \tau_{a,c}, T_{a,c}, T_{v,c}, T_{v,r}\\ E_{la,M}, E_{la,m}, E_{ra,M}, E_{ra,m}, E_{lv,M}, E_{lv,m}, E_{rv,M}, E_{rv,m}\}\end{gathered}$$

$$\boldsymbol{y} = \{p_{la}, p_{lv}, p_{sa}, p_{sv}, p_{ra}, p_{rv}, p_{pa}, p_{pv}, CO\}$$

where $\boldsymbol{x}$ are the state variables, $g(t, x; \boldsymbol{\theta})$ is the evolution of the states (see equations (1)-(3)), $\boldsymbol{\theta}$ are the parameters of the system, and $\boldsymbol{y}$ are the model outputs of interest.

Figure 2

2.3 Parameter values and initial conditions

As noted, the systems level model contains 25 parameters and eight states. The combination of sparse data and numerous parameters makes it imperative that nominal parameter values and initial conditions are physiologically defined and patient specific. To do this, we use a combination of patient specific data (where available) and literature-based values. A summary of nominal pressure and volume values can be found in Table XXX in the Appendix.

2.3.1 Volumes

Total blood volume for each patient was calculated using body surface area, ($BSA = \sqrt{W \cdot H/3600}$, height ($H$), weight, ($W$)) and gender (Williams *et al.*, 2019)

$$V_{tot} = \begin{cases} (3.47 \cdot BSA - 1.954) \cdot 1000, & if \text{ Female} \\ (3.29 \cdot BSA - 1.229) \cdot 1000, & if \text{ Male.} \end{cases} \quad \_(7)$$

Initial volumes (i.e., initial values for the states) for each compartment were calculated as a proportion of the stressed volume using previously published data (Beneken & DeWit, 1966). The total volumes for the arteries and veins were assumed to be 13% and 65% of V_{tot} in the systemic circulation, and 3% and 11% for the pulmonary circulation. The stressed volumes were then set to be 27% and 7.5% of the total volume in the systemic arteries and veins, while stressed volumes for the pulmonary arteries and veins were 60% and 11%, respectively, of their total volumes. For the heart chambers, we assumed the atrial and ventricular volumes were 1.5% and 2.5% of the total blood volume, and that the unstressed volume was 5 and 10 ml for the respective chambers. An ejection fraction of 60% is assumed in the ventricles while the atrial ejection fraction is assumed to be 47% (Lin *et al.*, 2008).

2.3.2 Pressures

Nominal pressure values in the pulmonary circuit were deduced from RHC data. In particular, systolic and diastolic pressure data in the RA and RV were assigned as the nominal values for $p_{ra}(t)$ and $p_{rv}(t)$, while MPA data was used for $p_{pa}(t)$ (see Table 2). (Mariam and Rob are editing this?)

Systolic, diastolic, and mean pressures for the systemic and pulmonary arteries are calculated from RHC data. Systolic and diastolic values from the right atrium and ventricle are recorded as well, as is the mean PAWP value, which we use as the mean pulmonary venous pressure. Nominal systolic, diastolic, and mean pressure values for compartments without data (i.e., left atrium, left ventricle, and systemic veins) are calculated by scaling pressures in their adjacent compartments where data is known, ensuring that flow travels in the correct direction.

2.3.3 Resistance

Utilizing Ohm's law, the nominal vascular resistance is calculated as

$$R_i = \frac{p_i - p_{i-1}}{CO}, \tag{8}$$

where the resistance in compartment i depends on the pressure in the current and previous compartment and the cardiac output. The heart valves' resistances are calculated in a similar fashion; the aortic and pulmonary valve resistances are calculated as

$$R_{ava} = \frac{p_{lv,M} - p_{sa,M}}{CO} \quad \text{and} \quad R_{pva} = \frac{p_{rv,M} - p_{pa,M}}{CO} \tag{9}$$

whereas the mitral valve is calculated as

$$R_{mva} = \frac{p_{la,M} - p_{lv,m}}{CO} \tag{10}$$

to ensure the left atrium drains into the left ventricle during diastole. In the case of PH, RA pressure is elevated (Alenezi *et al.*, 2020) and equation (10) hence overestimates valve resistance. To circumvent this, we set $R_{tva} = 0.055$ for all five PH patients.

2.3.4 Compliance

Compliance is formally defined as the relative change in volume for a given change in pressure (Wang *et al.*, 2013), and quantifies the ability of the vasculature to distend under load. In this study, our nominal compliance estimates for the arteries and veins are

$$C_i = \frac{V_i}{p_{i,M}} \quad \text{and} \quad C_i = \frac{V_i}{\bar{p}_i}. \tag{11}$$

2.3.5 Heart parameters

Parameters for the heart include elastance and timing parameters. Noting that compliance is the inverse of elastance and that the compliance in the heart is minimal during end systole (i.e. maximum pressure and minimal volume) (Marquis *et al.*, 2018), we calculate the maximum and minimum elastances as

$$E_{i,M} = \frac{p_{i,M}}{V_{i,m}}\ , \qquad E_{i,m} = \frac{p_{i,m}}{V_{i,M}} \tag{10}$$

where $i = la, ra, lv, rv$.

Nominal timing parameters for the RA and RV elastance functions are calculated using the time-series data. Specifically, maximum and minimum RV elastance occur at peak systole and the beginning of diastole, corresponding to $T_{v,c}$ and $T_{v,r}$, respectively. For the atrium, the end of atrial systole, the start of atrial contraction, and peak atrial contraction are used to calculate the timing parameters $\tau_{a,r}, T_{a,c}$ and $T_{a,r}$, respectively..

2.4 Model analysis

Systems level models like the one used here contain numerous parameters but suffer from limited available data. For this reason, a model analysis including sensitivity analyses and parameter ranking are needed to reduce the parameter dimensionality. However, these analyses depend on the quantity of interests from the model. Below we summarize the quantities of interest used (the residual vectors) and our analysis techniques.

2.4.1 Residual vectors

To understand how increased quantities of data improve parameter inference, we consider data vectors with combinations of static and dynamic RHC data. Since the data used in model calibration dictates the quantities of interest from the model, we consider 4 residual vectors; a static residual $\boldsymbol{r}_s$

$$\boldsymbol{r}_s = \frac{1}{\sqrt{N_s}} \frac{\boldsymbol{y} - \boldsymbol{y^d}}{\boldsymbol{y^d}} \tag{11}$$

$$\boldsymbol{y} = \left[p_{ra,M}, p_{ra,m}, p_{rv,M}, p_{rv,m}, p_{pa,M}, p_{pa,m}, p_{sa,M}, p_{sa,m}, p_{pv,m}, CO\right]$$

where $\boldsymbol{y}$ is the model output, $\boldsymbol{x^d}$ represents the corresponding data values, and N_s is the number of points in the residual, as well as three dynamic data residual vectors

$$\boldsymbol{r}_{ra} = \frac{1}{\sqrt{N_{ra}}} \frac{\boldsymbol{p}_{ra}(t) - \boldsymbol{p}_{ra}^{d}(t)}{\boldsymbol{p}_{ra}^{d}(t)} \tag{12}$$

$$\boldsymbol{r}_{rv} = \frac{1}{\sqrt{N_{rv}}} \frac{\boldsymbol{p}_{rv}(t) - \boldsymbol{p}_{rv}^{d}(t)}{\boldsymbol{p}_{rv}^{d}(t)} \tag{13}$$

$$\boldsymbol{r}_{pa} = \frac{1}{\sqrt{N_{pa}}} \frac{\boldsymbol{p}_{pa}(t) - \boldsymbol{p}_{pa}^{d}(t)}{\boldsymbol{p}_{pa}^{d}(t)} \tag{14}$$

where again $\boldsymbol{p}_i(t)$, $\boldsymbol{p}_i^d(t)$, and N_i are the model output, data, and number of residual points, respectively, for the RA, RV, and pulmonary arteries. Utilizing the above residual vectors, we consider two combinations of data as our quantity of interest

1) $\boldsymbol{r} = \boldsymbol{r}_s$

2) $\boldsymbol{r} = [\boldsymbol{r}_s, \boldsymbol{r}_{ra}, \boldsymbol{r}_{rv}, \boldsymbol{r}_{pa}]$

Previous authors have considered elastance functions for both atria and ventricles (Ellwein *et al.*, 2008; Liang *et al.*, 2009), yet the entire dynamic response of the atria may not be captured via an elstance model (Pironet *et al.*, 2013). To account for this model limitation, we include atrial data before and after peak contraction at $t = T_{a,c}$, as well as the first and last time point, in the vector r_{ra}.

Each time-series contribution is weighted by the number of points in the signal, N_i. While all patients in this study have right atrial, right ventricular, and pulmonary artery time-series data, analyzing the above data combinations will illustrate how informative certain sources of data are in model calibration and prediction.

2.4.2 Sensitivity analyses

Sensitivity analyses quantify parameters' influence on specified quantities of interest. In this study, we utilize local, derivative based sensitivity analysis as well as global sensitivity analysis (GSA) via Sobol' indices. The former methods are valid at the nominal parameter values and quantify the gradient of a quantity of interest with respect to the parameter. The latter methods are variance based analyses, providing a measure

of model sensitivity throughout physiological parameter space. In both cases, we consider the residual vectors from Sec. 2.4.1 as our quantities of interest.

Local sensitivity analysis

Let $f(t, \boldsymbol{x}; \boldsymbol{\theta})$ denote the quantity of interest, which depends on time t, the states $\boldsymbol{x}$, and the parameters $\boldsymbol{\theta}$. In this study, we consider the log-scaled sensitivity of f with respect to θ_i

$$\frac{\partial f(t, \boldsymbol{x}; \boldsymbol{\theta})}{\partial \log(\theta_i)} = \frac{\partial f(t, \boldsymbol{x}; \boldsymbol{\theta})}{\partial \theta_i} \theta_i, \quad i = 1,2, \cdots, \mathcal{M} \tag{15}$$

where $\mathcal{M}$ is the number of parameters in our system. Log-scaling the sensitivities puts parameters of different magnitude on a similar scale (Marquis *et al.*, 2018; Colebank *et al.*, 2019; Colunga *et al.*, 2020), as is the case here. We approximate these sensitivity equations via the forward finite difference

$$\frac{\partial f(t, \boldsymbol{x}; \boldsymbol{\theta})}{\partial \theta_i} \approx \frac{f(t, \boldsymbol{x}; \boldsymbol{\theta} + \boldsymbol{e}_i \Delta\theta_i) - f(t, \boldsymbol{x}; \boldsymbol{\theta})}{\Delta \boldsymbol{\theta}_i} \tag{16}$$

where $\Delta\theta_i$ is the step size and e_i is the unit vector in the i^{th} direction. Typically, one computes the sensitivity of the model states (Donders *et al.*, 2015; Eck *et al.*, 2016), but we instead compute the sensitivity of the residual vectors (defined in Sec. 2.4.1), as we are interested in understanding which parameters best inform the objective function used for parameter inference. The sensitivity of the residual with respect to θ_i is then the column vector

$$\frac{\partial f(t, \boldsymbol{x}; \boldsymbol{\theta})}{\partial \theta_i} = \boldsymbol{\chi}_i(t), \tag{17}$$

which composes the linearized Fisher information matrix $\mathbf{F} = \boldsymbol{\chi}_i^T \boldsymbol{\chi}_i$ (Cintrón-Arias *et al.*, 2009). Lastly, we use the 2-norm of the sensitivity results, i.e. $\left|\left|\boldsymbol{\chi}_i\right|\right|_2, i = 1,2I, \mathcal{M}$, to rank the parameters from most to least influential i.e. $\left|\left|\chi_i\right|\right|_2, j = 1,2\ldots, \mathcal{M}$.

Global sensitivity

In contrast to local sensitivity, GSA quantifies the global influence of parameters by sampling throughout the plausible parameter space. While GSA methods are more computationally expensive than local methods, they can expose undiscovered relationships between parameters by varying multiple parameters at a time (Eck *et al.*, 2016).

In this study, we use variance-based, Sobol' indices (Sobol, 2001; Saltelli *et al.*, 2010) to quantify parameters' influence on the variance of the residual vetors. We begin by constructing physiological parameter regimes, enforcing a parameter space of $\pm 30\%$ from the nominal parameter estimates; these regimes were analyzed to ensure that model outputs were physiological (see appendix).

Consider the quantity of interest $f(t, \boldsymbol{x}; \boldsymbol{\theta})$ as before, with parameters $\boldsymbol{\theta} = [\theta_1, \cdots, \theta_{\mathcal{M}}]$ (note that we drop the dependence of f on $\boldsymbol{x}$ and t for clarity hereon). Each parameter i lies within the physiologically admissible parameter space Γ_i, i.e. the entire parameter domain is $\bigcup_i^{\mathcal{M}} \Gamma_i = \Omega^{\mathcal{M}} \subset \mathbf{R}^{\mathcal{M}}$ The expectation and variance of f are defined as

$$E\big(f(\boldsymbol{\theta})\big) = \int_{\Omega^{\mathcal{M}}} f(\boldsymbol{\theta})\, d\boldsymbol{\theta}\,, \tag{18}$$

$$V\big(f(\boldsymbol{\theta})\big) = \int_{\Omega^{\mathcal{M}}} \Big(f(\boldsymbol{\theta}) - E\big(f(\boldsymbol{\theta})\big)\Big)^2\, d\boldsymbol{\theta} = E(f(\boldsymbol{\theta})^2) - E\big(f(\boldsymbol{\theta})\big)^2. \tag{19}$$

We are interested in computing the conditional expectation and variance of our quantity interest when a single parameter θ_i is known; hence, we can define the operators

$$E_{\theta \sim i}\big(f(\boldsymbol{\theta}|\theta_i)\big) = \int_{\Omega^{\mathcal{M}-1}} f(\boldsymbol{\theta}|\theta_i) d\theta\,, \qquad \Omega^{\mathcal{M}-1} = \Omega^{\mathcal{M}} \backslash \Gamma_i \tag{20}$$

which does not include θ_i , and the partial variance

$$V_{\theta_i} = V\big(E_{\theta \sim i}(f|\theta_i)\big)\,. \tag{21}$$

Equation (21) measures the variance of the expected value of f, conditioned on the fixed, known parameter θ_i ; i.e., it measures the variance of the mean not attributed to θ_i .

From this we can define the first order sensitivity measure S_i as

$$S_i = \frac{V_{\theta_i}}{V(f)} \ . \tag{22}$$

Similarly, we quantify the first order and higher order effects via the total effect index

$$S_{T_i} = \frac{E_{\theta \sim i}\left(V_{\theta_i}(f|\theta_{\sim i})\right)}{V(f)} \ . \tag{23}$$

Sobol' originally introduced a Monte Carlo sampling approach to numerically estimate S_i and S_{T_i}, requiring N^2 evaluations per parameter (Sobol, 2001). Instead use the method by Saltelli et al. (Saltelli *et al.*, 2010), requiring only $N(\mathcal{M} + 2)$ evaluations (see appendix).

2.4.3 Parameter subsets

Given the numerous parameters and limited data, the model parameters are not identifiable, i.e. a unique parameter set that provides the best fit to the data is not available. Moreover, knowledge of electrical circuit theory tells us that resistors and capacitors in parallel cannot be estimated uniquely unless data is available adjacent to the circuit component. For this reason, it is important to construct a subset of influential, identifiable parameters.

A subset of the most influential parameters can be identified using a combination of the aforementioned sensitivity analyses and physiological intuition. The latter is important so that biomarkers used in-clinic are estimated as patient-specific (Pope *et al.*, 2008; Colunga *et al.*, 2020). We take several steps to ensure our subset is both identifiable and influential with respect to the residual vectors. We use both local and global sensitivity results to determine which parameters are non-influential or correlated.

Local sensitivity-based subset selection

Results from the local analysis provide information about which parameters (at their nominal values) are the most influential on a given quantity of interest (the residuals outlined in Sec. 2.4.1). As mentioned earlier, asymptotic analyses (Cintrón-Arias *et al.*, 2009) show that these sensitivities construct a linear approximation of the Fisher information matrix, $\boldsymbol{F} = \boldsymbol{\chi}^T\boldsymbol{\chi}$. The correlation matrix of the parameters $\boldsymbol{c}$ is calculated as

$$c_{ij} = \frac{C_{ij}}{\sqrt{C_{ii}C_{jj}}}, \quad \boldsymbol{C} = \boldsymbol{F}^{-1} \tag{24}$$

where $-1 \leq c_{ij} \leq 1$ for $i, j = I \ldots, \mathcal{M}$. As noted previously [22,26,11], the correlation matrix provides information about pairwise relationships between parameters; the higher the correlation (e.g., $|c_{ij}| \to 1$) the more difficult it is to estimate parameters i and j simultaneously. For this reason, a parameter cutoff, $|\boldsymbol{c}| < 0.95$, is used to fix parameters so that others can be estimated.

Global sensitivity-based subset selection

The first order effects S_i from the GSA describe a single parameter's influence on the variance of the quantity of interest. Since the Sobol' indices are defined in terms of variance, several properties hold ture. First, by definition, $\Sigma_i S_i \leq 1$, hence the difference $1 - \Sigma_i S_i$ describes the variance attributed to higher order effects. Second, the difference between the total and first-order effects, $S_{T_i} - S_i$, quantifies the proportion of higher order (interaction) effects attributed to the parameter, with $S_i = S_{T_i}$ suggesting only first-order effects. Lastly, note that by definition

$$\begin{aligned} S_{T_i} = 0 \;\Rightarrow\; 1 &= \frac{V\left(E_{\theta_i}(f|\theta_{\sim i})\right)}{V(f)} \\ \Rightarrow V_{\theta_{\sim i}}\left(E_{\theta_i}(f|\theta_{\sim i})\right) &= V(f). \end{aligned} \tag{25}$$

Hence, $S_{T_i} \approx 0$ means that parameter i does not affect the variance of the quantity of interest and can be fixed prior to parameter inference [10,31].

2.4.4 Parameter inference

After determining an influential, identifiable subset of parameters for each residual vector, model predictions are fit to data via parameter inference. In this study, we use a Levenberg-Marquardt scheme for the nonlinear least-squares optimization [16]. In general, the observed data $\boldsymbol{y}$ (static or time-series) is assumed to be of the form

$$\boldsymbol{y} = f(t, \boldsymbol{x}; \boldsymbol{\theta}) + \boldsymbol{\epsilon} \tag{24}$$

where $f(t, \boldsymbol{x}; \boldsymbol{\theta})$ is the (possibly dynamic) output from the model, and $\boldsymbol{\epsilon}$ is the measurement error, assumed to be independent and identically distributed white Gaussian noise, i.e. $\boldsymbol{\epsilon} \sim \mathcal{N}(0, \sigma_\epsilon^2)$, with mean $E(\boldsymbol{\epsilon}) = 0$ and variance $V(\boldsymbol{\epsilon}) = \sigma_\epsilon^2$.

Using this framework, we are interested in minimizing the sum of squared errors,

$$J = \boldsymbol{r}^T \boldsymbol{r} \tag{25}$$

where $\boldsymbol{r}$ is the residual vector, encompassing differences between the measured data y and the model predictions $f(t, \boldsymbol{x}, \boldsymbol{\theta})$.

Previous authors have considered a similar approach to the above when fitting 0D cardiovascular models to data [25,7,26,11]. However, previous studies have not investigated the improvements in parameter inference when including dynamic waveforms. As mentioned in Sec. 2.4, we consider several different residual vectors in both the sensitivity analyses and parameter estimation framework. Similar to the work of [22], each residual is computed by using the last 30 cycles of the model predictions compared to the data. In addition, each residual is appropriately weighted by the number of time points, ensuring that each source of data contributes equally in the cost function J.

2.4.5 Model selection

While the methods used in Sec. 2.4.2 can deduce identifiable subsets, choosing the "best" subset requires further analysis. Since fixing certain parameters effectively changes the model used in parameter inference, model selection criteria can be applied

to choose the best subset for each residual. In particular, we consider two types of information criteria: corrected Akaike information criteria (AICc) and Bayesian information criteria (BIC):

$$AICc = 2\log(J) + 2\mathcal{M}' + 2\frac{\mathcal{M}'(\mathcal{M}'+1)}{N-\mathcal{M}'-1}\,, \tag{26}$$

$$BIC = 2\log(J) + \mathcal{M}'\log(N). \tag{27}$$

Here, $\mathcal{M}' \leq \mathcal{M}$ is the number of parameters in the subset, N is the number of data points in the residual, and J is the least-squares cost as defined in equation (23). These metrics have been used in previous cardiovascular modeling studies [27,14], and accounts for a model's goodness-of-fit while penalizing for redundant or unnecessary model complexity. These criteria are used to select the most informative subset for each residual based on a single patient's data, after which the best subsets are used for parameter estimation in the remaining four patients.

2.5 Simulations

- Static residual
- Shifting of data
- Time-varying
- Control – use textbook values
- Therapies – which parameters do we need to change to reduce PH
    - Table with parameter values
    - Change parameters that might not be estimated in PH

3 Results

Local sensitivity analysis was ran for all 8 residuals, revealing the parameters that were the most influential. In addition, results from the Sobol' indices were used to reinforce fixing of noninfluential parameters prior to subset selection. Both sensitivity methods were used to construct several subsets of influential, identifiable parameters, which were compared and analyzed by running multiple optimizations for a single patient, using all 8 different residuals. After analyzing all possible subsets, the best subset for

each residual was used to find optimal values for each patient data set. Waveforms were shifted appropriately so that the model could best fit the data. These details are described in depth below.

Figure 3

Figure 4

3.1 NOMINAL PREDICTIONS

DISCUSS WE DID IT

3.2 Sensitivity results

The relative influence of parameters depends on both the residual considered and the nominal parameters used, which is dictated by the patient data. A summary of the average ranking of the 25 parameters across all 8 residuals is provided in the appendix. Figures 3 and 4 shows the local sensitivity results, normalized by the most influential parameter for each patient, when using residual 1 (static values only) and residual 8 (all static and time-series data) as the quantity of interest. Sensitivity results for residuals 2-7 can be found in the appendix. When only using static values, the most influential parameters tend to be those attributed to compliance, resistance, and elastance. In contrast, inclusion of all three time-series data in the residual causes $T_{c,rv}, T_{r,rv}$ and $\tau_{c,ra}$ to become the most influential parameters in the subset. This is expected, as these parameters influence the timing of systole and diastole in the ventricles and atria. Note that while most patients showed consistent parameter ranking, the residual vectors for patient 3 were less sensitive to changes in $T_{c,rv}$ and $T_{r,rv}$. Overall, the parameter set

$$\boldsymbol{\theta}^{NI} = \left[R_{ava}, R_{mva}, R_{pva}, R_{pv}, R_{sv}\right] \tag{28}$$

was consistently noninfluential for all residuals, suggesting that these parameters be neglected as candidates during subset selection.

For the GSA, 10^3 samples were generated for each parameter using a Sobol sequence, ensuring adequate coverage for each parameter space. First order and total effect sensitivities are shown in Figure 5, where the quantity of interest was the cost using residual 1 (static values only) and residual 8 (all static and dynamic data). The total indices S_{T_i} are approximately zero for $\boldsymbol{\theta}^{NI}$, consistent with the local sensitivity results. For this reason, we can say with confidence that $\boldsymbol{\theta}^{NI}$ should not be regarded in any of the possible subsets used for parameter inference. When using residual 1, the most influential parameters are the systemic resistance, pulmonary resistance, systemic vein compliance, and tricuspid valve resistance. In contrast, residual 8 shows that the timing parameters in right ventricle are most influential, with the pulmonary resistance R_p and the compliance in the systemic veins C_{sv} being the next most influential parameters. First and total order effects for the other 6 residual vectors can be found in the appendix.

Figure 5

3.3 PARAMETER SUBSETS

In order to determine the optimal subset for parameter estimation, each local sensitivity result was analyzed via construction of the correlation matrix defined in equation (21). Prior to this, noninfluential parameters, as dictated by the averaged local sensitivity results and the GSA outcomes, were left out of all subsets considered. Parameter pairs that exhibited a correlation greater than $\gamma = 0.95$ were used to reduce the subsets, with the most influential parameters being withheld. This procedure leads to several subsets for each residual vector; hence we ran the optimization for one data set (patient 2) over all the possible subsets to ensure the most informative one was used for the other four patients. The resulting subsets for each residual can be found in Table 4, along with the recorded cost value J and the AICc and BIC scores.

Table 4

3.4 PARAMETER INFERENCE AND MODEL SELECTION

Upon selection of the best subset for each residual, patient data underwent optimization. In order to achieve the most consistent match between the model and time-series data, we considered both forward and backward shifts in the data. Figure 6 shows changes in the cost for different data shifts for patient 2, where the optimal shift was chosen as the minimum in the curve. A subsequent procedure was carried out for the other four patients. This optimal shift was then used to achieve the best model fit in optimization, with estimated parameters being deemed optimal for each patient. The optimal parameter values for each patient using residuals 1 and 8 are presented as box-whisker plots in Figure 7.

Figure 6

Post-optimization predictions of pressure and CO for each patient are found in Figure 8. We also display predictions from a control patient, who's parameter values come from literature. PH predictions are shown after optimizing to both residual 1 (static data) and residual 8 (all data). The static residual enforces that the maximum and minimum pressure values are obtained, while optimization using residual 8 tries to account for the time-series course of the RHC data. The qualitative fits to right atrial dynamics improve in nearly all patients, with the exception of patient 3 (panel d), when including atrial timeseries data. In contrast, it appears that pulmonary artery predictions do not improve when addition time-series data while right ventricle predictions do improve. CO predictions in all but patient 1 do not match the data as well when including time-series data in the residual.

Pressure-volume loops for the four heart chambers are shown in Figure 9 for the control and 5 PH patients. Results from optimizing to residual 1 and residual 8 are shown. In general, the ventricular pressure-volume loops shown little change when

including dynamic time-series data in the residual. However, the difference in residual does affect the atrial loops, due to the estimation of the atrial timing parameters.

3.5 CONTROL VS HYPERTENSION

ALL 5 PATIENTS (AND CONTROL) AND RESIDUAL 1 & 8 SHOW PREDICTIONS (9 PANEL AND PV LOOPS)

Important physiological biomarkers

What can a physiologist use predictions for?

Can we convert any parameters to physiological quantitites?

Afterload, preload, power, work, EF, PVR, compliance, contractility

3.6 Therapies?

4 Discussion

This study examines the effects of including combinations of static and timeseries data when performing parameter estimation in a 0D cardiovascular model. Using a combination of sensitivity analyses, subset selection, and information criteria, we deduced the smallest parameter sets fit the aforementioned combinations of patient data. By shifting time-series data, model predictions are fine-tuned to fit time-dependent hemodynamic waveforms and reveals which model components can or cannot fit physiological data.

4.1 Sensitivity results AND PARAMETER SUBSETS

Sensitivity analysis is as a crucial step in model analysis and can illustrate which parameters are influential on a given quantity of interest. The model in this study has a total of 25 parameters, yet the lack of detailed data renders inference of all these parameters infeasible. Both local and GSA results revealed that there was a noninfluential set of parameters θ^{NI} that could be fixed. Within this set were the mitral and aortic valves, which are noninfluential on quantities of interest in the pulmonary circuit, consistent with our previous study [7]. However, we would expect these parameters to become more influential if we were interested in quantities derived from

left heart dynamics, which would be important when studying group 2 PH attributed to left-heart failure.

Local analyses are only valid at the nominal parameter values used; hence model sensitivity may change depending on how nominal parameter values are set. This can be seen in Figures 3 and 4, which show that model predictions for patient 3 are less sensitive to ventricular timing parameters than the other four patients. Similar results were obtained in [22], illustrating that changes in nominal parameter values influence the ranking of parameters via local sensitivity. These discrepancies can be circumvented by using GSA, which revealed that the ventricular timing parameters are in-fact the most influential, suggesting that the nominal estimates for patient 3 are the reasoning for the change in parameter ranking in the local analysis.

Physiologically, the global sensitivity analysis reveals that parameters in the right ventricular, pulmonary arteries, and systemic veins are most influential when considering dynamic pressure output from the model. PH slowly degrades the right ventricle via increased afterload and leads to an elongated ventricular systole [9], which can be captured by changing $T_{c,rv}$ and $T_{r,rv}$. Increased pulmonary vascular resistance and decreased pulmonary artery compliance are also expected [33,17] which are controlled by R_p and C_{pa}. In addition, the right atrium has been known to undergo changes during PH [1], with right atrial reservoir and active contraction functions being strong predictors of mortality in PH. Atrial filling is dictated by systemic vein dynamics and the ability of the tricuspid vale to function properly, which support C_{sv} and R_{tva} being influential, and atrial contraction in the model is largely dictated by minimum elastance $E_{m,ra}$. However, the GSA results suggest both pulmonary valve resistance (R_{pva}) and pulmonary vein compliance (C_{pv}) are noninfluential, conflicting with hypotheses regarding group 2 PH. This may be corrected when implementing a more physiological valve model, see, e.g., [23].

4.2 Parameter INFERENCE

Several authors have used a 0D systems level models to predict hemodynamic function in the pulmonary circulation [18,7,32]. However, to the authors' knowledge no study has addressed the potential improvements in model calibration when using different

RHC data sources in parameter estimation. We tested several different residuals consisting of some, all, or none of the dynamic RHC pressure recordings, and conducted sensitivity analyses and optimizations using these residual vectors. The parameter subset selection routine was enforced using a combination of correlation analysis and information criteria (AICc and BIC). While utilizing subset selection [25,24] and information criteria [14] for parameter reduction has been used, the combination of the two in deriving the most influential subset is underutilized. The best subsets identified for each residual tended to share parameters, suggesting that additional data does not alter the most informative parameters in the system. While modeling will not replace RHC anytime soon, this consistency strengthens the idea of using this model type in PH assessment.

As shown in Figure 8, model predictions are able to match the systolic, diastolic, and mean data values when including only these data values in the residual vector as shown previously [7,11]. However, our model is one of the first to verify that static right atrial values can be matched using a systems level model under PH conditions.

The inclusion of time-series data in the residual vector allows for the estimation of ventricular and atrial timing parameters. However, time-series data had to be shifted to ensure adequate alignment between the model and the data [22]. The model begins during ventricular isovolumic contraction, hence ventricular and main pulmonary artery waveforms needed to align with the upstroke in model predictions of ventricular pressure. Atrial dynamics are nonlinear, and consist of three distinct phases [1], where the atria function as a reservoir, conduit, and contractile chamber. The model used here is able to capture the contractile phase of the atria, which motivated our approach using only the contractile phase of the data during parameter estimation with residuals 4, 7, and 8. Previous modelling approaches that couple 0D with higher fidelity (one or three dimensional) models are able to predict all three phases [20,23], and will be considered in future projects. However, acknowledging the limitations of the model is crucial before performing parameter estimation and ensures that parameters are correctly calibrated to the data.

4.3 CONTROL

4.4 PH PREDICTIONS

4.5 Limitations

5 Conclusions

Appendix

Global sensitivity algorithm

Algorithm 1: Sobol' Indices

1) Generate two ($\mathcal{N} \times \mathcal{M}$) sample matrices A and B, with pseudorandom entries θ_i^j and $\hat{\theta}_i^j$ drawn from respective densities

$$A = \begin{bmatrix} \theta_1^1 & \cdots & \theta_{\mathcal{M}}^1 \\ \vdots & \ddots & \vdots \\ \theta_1^{\mathcal{N}} & \cdots & \theta_{\mathcal{M}}^{\mathcal{N}} \end{bmatrix} \quad B = \begin{bmatrix} \hat{\theta}_1^1 & \cdots & \hat{\theta}_{\mathcal{M}}^1 \\ \vdots & \ddots & \vdots \\ \hat{\theta}_1^{\mathcal{N}} & \cdots & \hat{\theta}_{\mathcal{M}}^{\mathcal{N}} \end{bmatrix}$$

2) Generate $\mathcal{M}$ matrices A_B^i which is equal to the matrix A except the i^{th} column is the i^{th} column from B. Similarly, create B_A^i.

3) To estimate the total variance, generate a matrix appending B to A

$$C = \left[\frac{A}{B}\right]$$

4) Evaluate the model at each row of the matrices A and B, with outputs $f(A)_j$ and $f(B)_j$ for $j = 1, \cdots, \mathcal{N}$. This requires $2\mathcal{N}$ model evaluations

5) Evaluate the model at each row of the matrices A_B^i and B_A^i, with outputs $f\left(A_B^i\right)_j$ and $f\left(B_A^i\right)_j$ for $j = 1, \cdots, \mathcal{M}$. This requires $2\mathcal{N}\mathcal{M}$ model evaluations

6) Estimate the first order Sobol indices approximated by

$$S_i \approx \frac{\frac{1}{\mathcal{N}} \sum_{j=1}^{\mathcal{N}} \left[f(A)_j f\left(B_A^i\right)_j - f(A)_j f(B)_j \right]}{\frac{1}{2\mathcal{N}} \sum_{j=1}^{2\mathcal{N}} f(C)_j f(C)_j - E^2[f(C)]}$$

Estimate the total Sobol indices approximated by

7)
$$S_{Ti} \approx \frac{\frac{1}{2\mathcal{N}} \sum_{j=1}^{\mathcal{N}} \left[f(A)_j - f\left(A_B^i\right)_j \right]^2}{\frac{1}{2\mathcal{N}} \sum_{j=1}^{2\mathcal{N}} f(C)_j f(C)_j \; - E^2[f(C)]}$$

To computed first and total order Sobol indices, we use the Saltelli algorithm. Let ...

References

Alenezi F, Rajagopal S & Kutty S (2020). Assessing right atrial function in pulmonary hypertension: Window to the soul of the right heart? *Am J Physiol - Hear Circ Physiol* **318,** H154–H155.

Beneken JEW & DeWit B (1966). A physical approach to hemodynamic aspects of the human cardiovascular system. In *Physical Bases of Circulatory Transport: Regulation and Exchange.*, ed. Guyton A & Reeve E, pp. 1–45. Saunders, Philadelphia.

Boron WF & Boulpaep EL (2017). *Medical physiology*. Philadelphia, PA : Elsevier, [2017]. Available at: http://catalog.lib.ncsu.edu/catalog/NCSU3738615.

Chambers MJ, Colebank MJ, Qureshi MU, Clipp R & Olufsen MS (2020). Structural and hemodynamic properties of murine pulmonary arterial networks under hypoxia-induced pulmonary hypertension. *Proc Inst Mech Eng Part H J Eng Med*095441192094411.

Cintrón-Arias A, Banks HT, Capaldi A & Lloyd AL (2009). A sensitivity matrix based methodology for inverse problem formulation. *J Inverse Ill-Posed Probl* **17,** 545–564.

Colebank MJ, Umar Qureshi M & Olufsen MS (2019). Sensitivity analysis and uncertainty quantification of 1-D models of pulmonary hemodynamics in mice under control and hypertensive conditions. *Int j numer method biomed eng*1–29.

Colunga AL, Kim KG, Woodall NP, Dardas TF, Gennari JH, Olufsen MS & Carlson BE (2020). Deep phenotyping of cardiac function in heart transplant patients using cardiovascular system models. *J Physiol* **0,** 1–20.

Donders WP, Huberts W, van de Vosse FN & Delhaas T (2015). Personalization of models with many model parameters: an efficient sensitivity analysis approach. *Int j numer method biomed eng*1–18.

Eck V, Donders W, Sturdy J, Feinberg J, Delhaas T, Hellevik L & Huberts W (2016). A guide to uncertainty quantification and sensitivity analysis for cardiovascular applications. *Int j numer method biomed eng* **26,** 807–827.

Ellwein LM, Tran HT, Zapata C, Novak V & Olufsen MS (2008). Sensitivity analysis and model assessment: Mathematical models for arterial blood flow and blood pressure. *Cardiovasc Eng* **8,** 94–108.

Fayyaz AU, Edwards WD, Maleszewski JJ, Konik EA, DuBrock HM, Borlaug BA, Frantz RP, Jenkins SM & Redfield MM (2018). Global pulmonary vascular remodeling in pulmonary hypertension associated with heart failure and preserved or reduced ejection fraction. *Circulation* **137,** 1796–1810.

Gerringer JW, Wagner JC, Vélez-Rendón D & Valdez-Jasso D (2018). Lumped-parameter models of the pulmonary vasculature during the progression of pulmonary arterial hypertension. *Physiol Rep* **6,** 1–12.

Hoeper MM, Ghofrani H-A, Grünig E, Klose H, Olschewski H & Rosenkranz S (2017). Pulmonary Hypertension. *Dtsch Arztebl Int* **114,** 73–84.

Kheyfets VO, O'Dell W, Smith T, Reilly JJ & Finol EA (2013). Considerations for Numerical Modeling of the Pulmonary Circulation—A Review With a Focus on Pulmonary Hypertension. *J Biomech Eng* **135,** 061011.

Krohn Therkelsen S, Aaris Groenning B, Hastrup Svendsen J & Boje Jensen G (2006). Atrial and Ventricular Volume and Function Evaluated by Magnetic Resonance Imaging in Patients With Persistent Atrial Fibrillation Before and After Cardioversion. *Am J Cardiol* **97,** 1213–1219.

Kung E, Pennati G, Migliavacca F, Hsia TY, Figliola R, Marsden A, Giardini A & Investigators M (2014). A simulation protocol for exercise physiology in fontan patients using a closed loop lumped-Parameter Model. *J Biomech Eng* **136,** 1–14.

Liang F, Takagi S, Himeno R & Liu H (2009). Multi-scale modeling of the human cardiovascular system with applications to aortic valvular and arterial stenoses. *Med Biol Eng Comput* **47,** 743–755.

Lin FY, Devereux RB, Roman MJ, Meng J, Jow VM, Jacobs A, Weinsaft JW, Shaw LJ, Berman DS, Callister TQ & Min JK (2008). Cardiac Chamber Volumes, Function, and Mass as Determined by 64-Multidetector Row Computed Tomography. Mean Values Among Healthy Adults Free of Hypertension and Obesity. *JACC Cardiovasc Imaging* **1,** 782–786.

Marquis AD, Arnold A, Dean-bernhoft C, Carlson BE & Olufsen MS (2018). Practical identifiability and uncertainty quantification of a pulsatile cardiovascular model. *Math Biosci* **304,** 9–24.

Olufsen MS & Ottesen JT (2013). A practical approach to parameter estimation applied to model predicting heart rate regulation. *J Math Biol* **67,** 39–68.

Pironet A, Dauby PC, Paeme S, Kosta S, Chase JG & Desaive T (2013). Simulation of Left Atrial Function Using a Multi-Scale Model of the Cardiovascular System. *PLoS One*; DOI: 10.1371/journal.pone.0065146.

Pope S, Ellwein LM, Zapata C, Novak V, Kelley C & Olufsen MS (2008). Estimation and identification of parameters in a lumped cerebrovascular model. *Math Biosci Eng* **6,** 93–115.

Saltelli A, Annoni P, Azzini I, Campolongo F, Ratto M & Tarantola S (2010). Variance based sensitivity analysis of model output. Design and estimator for the total sensitivity index. *Comput Phys Commun* **181,** 259–270.

Schiavazzi DE, Baretta A, Pennati G, Hsia TY & Marsden AL (2017). Patient-specific parameter estimation in single-ventricle lumped circulation models under uncertainty. *Int j numer method biomed eng* **33,** 1–34.

Sobol IM (2001). Global sensitivity indices for nonlinear mathematical models and their Monte Carlo estimates. *Math Comput Simul* **55,** 271–280.

Wang Z, Lakes RS, Golob M, Eickhoff JC & Chesler NC (2013). Changes in large pulmonary arterial viscoelasticity in chronic pulmonary hypertension. *PLoS One*; DOI: 10.1371/journal.pone.0078569.

Williams ND, Brady R, Gilmore S, Gremaud P, Tran HT, Ottesen JT, Mehlsen J & Olufsen

MS (2019). Cardiovascular dynamics during head-up tilt assessed via pulsatile and non-pulsatile models. *J Math Biol* **79,** 987–1014.

Tables

Symbol	
$\boldsymbol{\mathcal{N}}$	Sample size
$\boldsymbol{\mathcal{M}}$	Number of parameters
$\boldsymbol{\Gamma_i}$	Prescribed parameter space for the i^{th} parameter
$\boldsymbol{\Omega^{\mathcal{M}}}$	$\mathcal{M}$ dimensional parameter space for the model
$\boldsymbol{\theta}$	Parameter set
$\boldsymbol{f}$	Quantity of interest
$\boldsymbol{V_{\theta_i}}(\cdot), \boldsymbol{E_{\theta_i}}(\cdot)$	Variance or expected value of the argument f taken over θ_i
$\boldsymbol{V_{\theta_{\sim i}}}(\cdot), \boldsymbol{E_{\theta_{\sim i}}}(\cdot)$	Variance or expected value of the argument f taken over all parameters except θ_i

Table 1 Mathematical symbols and abbreviations

BEGIN FIGURES