Influence of image segmentation on pulse wave propagation models of the pulmonary circulation

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ABSTRACT

Computational fluid dynamics (CFD) models are emerging as mathematical tools to assist in the diagnostic assessment of cardiovascular disease. Recent advances in medical imaging and computational algorithms for analyzing said images have made subject-specific modeling of the cardiovascular system a feasible task. This is particularly important in the case of pulmonary hypertension, as the pulmonary circulation transports oxygen to the lungs via a rapidly bifurcating network of highly compliant blood vessels. However, medical image analysis is subject to uncertainty, which can lead to variation in fluid model predictions. This study addresses this issue by developing a computational algorithm to determine pulmonary hemodynamics (blood pressure and flow) in a large network of arterial vessels and subsequently quantify the uncertainty of these predictions to geometric variation associated with image segmentation. We introduce uncertainty in the blood vessel network by generating multiple segmentations of a pulmonary tree from a single image of an excised mouse lung using randomly selected pre-segmentation parameters. We use a custom MATLAB algorithm to extract vessel radii, length, and connectivity for each pulmonary network generated. We quantify the uncertainty in geometric features of the network using density estimation techniques to specify probability densities for vessel radius and length. We sample from these distributions, compute model parameters, and propagate uncertainties to pressure and flow predictions using a one-dimensional (1D) fluid dynamics model. Results show that variation in network connectivity is a larger contributor to hemodynamic uncertainty in comparison to changes in vessel radius and length.
NEW & NOTEWORTHY
This study investigates the effects of pre-segmentation parameters on fluid dynamic predictions by using cutting edge statistical and uncertainty quantification techniques. This includes novel analysis of the effects of vessel length and radius uncertainty and the uncertainty in network size and connectivity on 1D fluid dynamic predictions in the pulmonary circulation.

Keywords: Hemodynamics, fluid dynamics, uncertainty quantification, image segmentation, medical imaging

INTRODUCTION
Pulmonary hypertension (PH) is defined as a mean pulmonary arterial blood pressure ≥ 25 mmHg. Definitive diagnosis requires a series of medical tests including right heart catheterization (RHC, invasive) and non-invasive imaging of the heart and lungs via computed tomography (CT), magnetic resonance imaging (MRI), or echocardiogram (9, 48, 94). Most diagnostic protocols interpret each data source independently to make an ultimate decision about the disease type and severity (31, 72). Recent studies have proposed that assimilation of hemodynamic and imaging data using computational fluid dynamics (CFD) modeling can provide further insight into the structure and function of the pulmonary system (2, 65, 96), leading to a better understanding of the disease stages and its progression. However, modeling a large network of the pulmonary circulation remains an effort only one other group (13, 14) has considered to date, and is the focus of this work. Moreover, this study builds upon earlier results by investigating how changes in network geometry impact hemodynamic predictions from CFD models.

Medical imaging and image segmentation have emerged as a powerful noninvasive tool of disease diagnostics (6, 9, 16, 57, 59, 63, 91, 97, 112). Medical examinations lead to a wealth of imaging data which is used to analyze the structure and function of the cardiovascular system, both under physiological and pathological conditions (35, 48, 106). Recent advances in image segmentation algorithms have led to semi- and fully-automated approaches to reconstruct geometries of complex vascular regions including the pulmonary vasculature (7, 32, 63, 75). Although these algorithms have greatly improved the efficiency of medical image analysis, inherent inaccuracies are still present as human intervention is required to identify the anatomical regions of interest based on subjective definitions of acceptable image intensities. Most image segmentation software requires manual specification of the image intensity thresholds between background and foreground (pre-segmentation parameters), which can lead to premature network truncation. A previous study by van Horssen et. al (34) showed that the cumulative volume of the coronary arterial tree varied with image resolution and hence vessel segmentation. Moreover, the choice of segmentation algorithm (deterministic versus probabilistic
methods) (46, 49, 108) also introduce uncertainties. This was discussed by Rempfler et. al (70), who compared posterior probability estimates for retinal vascular network segmentations using different perturbation techniques. This study takes these observations one step further by quantifying how changes in segmentation parameters impact vessel radius and length. There is also uncertainty associated with the network connectivity due to the rapidly branching structure of the pulmonary vasculature (12, 13, 56, 76, 99), which is further analyzed in this work.

Hemodynamic simulations of the cardiovascular system can be conducted using one-dimensional (1D) blood flow models. This model framework allows for blood pressure and flow predictions in large networks of arteries and veins (61, 67). Abundant literature discusses the application of such models to the pulmonary circulation (11, 44, 51, 65, 67, 68). Recent studies have also quantified uncertainty in 1D cardiovascular models (4, 28, 34, 77, 84) to understand how uncertain inputs, e.g. hemodynamic and boundary condition parameters, propagate to model predictions. Few studies have quantified uncertainty related to vascular geometry (34, 81, 84). For example, Sankaran et. al (82) computed 3D CFD sensitivity to coronary stenosis by quantifying the uncertainty in stenosis diameters using information about the image resolution. Gounley et. al (28) studied the effects of aortic stenosis size on shear stress predictions by artificially narrowing the aorta by 65%. One 1D study (37) quantified the uncertainty in vessel radius using variation extracted across the literature, but to our knowledge no studies have propagated the uncertainty of network connectivity or vessel dimensions introduced by image segmentation to predictions of hemodynamics.

This study tests the robustness of the computational model under the influence of uncertain inputs (vessel radii, length and network connectivity) by quantifying how uncertainty in these quantities determined from image segmentation impact CFD predictions. We argue that this is an essential step in the model analysis, especially if computational tools are to be integrated into clinical protocols. Multiple segmentations of a microcomputed tomography (micro-CT) image of a mouse pulmonary arterial tree were carried out and constitute what we consider the “total variation” of the model predictions. We propagated this uncertainty to hemodynamic predictions using a 1D CFD model of the pulmonary arterial system. The segmentations are used to construct the domain for the model and we perform inverse uncertainty quantification (UQ) by constructing probability density functions for the vessel radius and length. We used the computed probability densities and Monte Carlo sampling to propagate uncertainties (i.e. forward UQ) through our pulmonary circulation model, which is termed the variation due to vessel parameter values, in a representative network from the networks created from multiple segmentations. We analyze the variation due to network size and connectivity and contrast predictions of systolic, diastolic, and mean pressure, and flow rates between the three defined variations in the present study.
METHODS

This section includes a description of the experimental protocols used for collecting imaging and hemodynamic data, followed by a description of the image segmentation process, the mathematical model, and UQ techniques (illustrated in Fig. 1). To quantify the total variation introduced by image segmentation, we randomly selected 25 pre-segmentation parameter sets within predetermined intervals to segment the same micro-CT image. Variability in model predictions due to the total variation is described along with the variability seen in a single representative network when changing either the vessel dimensions and model parameters or changing the size and connectivity of the network.

Figure 1: Workflow of paper

**Experimental data**

This study uses existing micro-CT and hemodynamic data from male C57BL6/J control mice age 10-12 weeks. A detailed description of experimental protocols can be found in Vanderpool et. al (103) and Tabima et. al (95), respectively. Both procedures were approved by the University of Wisconsin-Madison Institutional Animal Care and Use Committee. Here we summarize the experimental protocols used for acquiring the data (as shown at the start of the flowchart in Fig. 1).

**Imaging Data.** Micro-CT imaging of the pulmonary arterial tree was performed on an excised lung from a male control mouse. The arterial network was pressurized to 17.2 mmHg to ensure the in-vivo pressure at rest. The mouse was then anesthetized with an intraperitoneal injection of pentobarbital sodium (52 mg/kg of body weight) and euthanized via exsanguination. The MPA was cannulated using a PE-90 tubing with a fixed outer diameter of 0.127 cm and inner diameter 0.086 cm. Lungs were perfused with Rho kinase inhibitor to eliminate smooth muscle cell contraction and then with perfluorooctyl bromide to provide contrast for imaging. Lungs were rotated in the X-ray beam at 1° increments to obtain 360 planar images and averaged over seven frames to minimize noise and maximize vascular contrast. The Feldkamp cone-beam algorithm (22) was used to reconstruct 360 planar images, which are then converted to Dicom 3.0. The arterial network was pressurized to 17.2 mmHg in order to approximate the in-vivo diameters of vessels at peak systole.

**Hemodynamics data.** Pulsatile pressure and flow data were obtained from a male mouse as previously published in (95). The mouse was tracheotomized after being anesthetized with intraperitoneal injection of urethane solution (2mg/g body weight). The animal was connected to a rodent respirator and the chest
wall is removed to expose the right ventricle. A stabilized pressure contour in the MPA was recorded at 5 KHz on a hemodynamic work station (Cardiovascular Engineering, Norwood, MA, USA). Volumetric flow rate was calculated by spectral analysis of the digitized broadband Doppler audio signal obtained in the proximal MPA and MPA inner diameter. MPA inner diameter was measured by using the long-axis view from leading edge to leading edge in B-mode imaging during the end of systole and was subsequently averaged from three cardiac cycles. The flow profile was then calculated from the flow velocity and MPA inner radius. Pressure and flow waveforms were aligned and averaged using the electrocardiograph as a reference point.

**Pulmonary Vascular Network Reconstruction**

The image is segmented using the open source software ITK-SNAP (113) and transformed into a network described by centerlines using the Vascular Modeling ToolKit (VMTK) (6). The image segmentation requires two pre-segmentation parameters, chosen to preserve the foreground of the large arteries. The network of centerlines is then converted to a directed graph encoding the vessel length and radius and network connectivity. These data-assimilation steps are highlighted in Fig. 1.

*Image segmentation.* The micro-CT image is stored as a DICOM 3.0 file with voxel dimensions $497 \times 497 \times 497$. The gray-scale image (shown in Fig. 4a) is transformed to a binary map identifying vascular regions of interest (collectively the ‘foreground’) and the non-vascular regions (the ‘background’) using image segmentation and global thresholding. Global thresholding is a pre-segmentation technique which requires a priori selection of an upper and lower threshold to determine the image intensity bounds that should be considered in the foreground. The user can select threshold bounds in an *ad hoc* manner to ensure that regions of interest are captured. In addition, ITK-SNAP requires specification of a smoothing parameter to determine the boundary between the foreground and the background, shown in Fig. 2. Due to the experimental protocol and use of perfused contrast, the image segmented here does not contain high intensity voxels from other anatomical features (e.g. the heart, spine, or other tissues) within the region of interest. This eliminates the need to set an upper threshold and only requires specification of a lower threshold and smoothing pre-segmentation parameters.

To analyze uncertainty associated with network segmentation, we selected 25 sets of pre-segmentation parameters $(\theta_1, \theta_2)$ (given in Table 1) using the random number generator function *rand* in MATLAB (Mathworks, Nantick, MA). Intervals for possible sets of pre-segmentation parameters were predetermined to preserve foregrounds for the large vessels across segmentations. For the image analyzed here, we assumed a uniform distribution for the two parameters and used a lower threshold range of $20 \leq \theta_1 \leq 45$ and a smoothing parameter range $3 \leq \theta_2 \leq 8$. As shown in Fig. 3, the foreground for distal
vascular segments can significantly change when pre-segmentation parameters are varied, but maintains features of the large, proximal vessels.

To segment the pulmonary vascular images, we used the active contour evolution, a semi-automated segmentation algorithm available in ITK-SNAP. This algorithm is initialized by placing seed points within the region of interest in the image, and iteratively updates a parametric contour representing the boundary of the segmented image (112, 113). We placed a seed point at the inlet of the MPA for each segmentation and allowed the active contour to evolve over 2000 iterations, which ensured that the largest arteries carrying the majority of the blood volume are included. In addition, vessels as small as 50 μm in radius were captured within the 2000 iterations of the evolution. The imaging protocol described in Vanderpool et al (103) had a spatial resolution between 30-40 μm, which provides a lower bound for the measurement uncertainty due to segmentation. The image segmentation can only include vessels with a diameter ≥ 1 voxel, guaranteeing the inclusion of vessels with a radius ≥ 20 μm. This implies that the imaging uncertainty, and hence the segmentation uncertainty, is bounded below by 20 μm for radius estimates, providing a quantitative constraint on the variability induced by the segmentation process. We note that because the arteries are excised and then inflated, vessel radii did not reach the lower bound dictated by the image resolution.

**Figure 2: ITK-SNAP interface**

*Network reconstruction.* Once the image was segmented, the 3D geometry was exported as a surface mesh and converted to a VTK polygonal file using Paraview (101) (Kitware, Clifton Park, NY). Centerlines were extracted from the surface meshes using native VMTK scripts. The centerline files contain spatial coordinates (x, y, z) and associated radii estimates (in units of voxels), corresponding to the maximally inscribed sphere that fits inside the 3D structure (5).

The centerlines from VMTK start at each terminal vessel and end at the inlet of the MPA; hence centerline data is duplicated in regions where two vessels merge. We developed a custom MATLAB algorithm to extract the network connectivity and identify all the vessels in the segmented tree. The algorithm identified all of the unique centerline coordinates obtained from VMTK by finding intersection points at each bifurcation. These intersections were labeled as network junctions, while all points between two junctions were labeled as vessels. The individual blood vessels were then identified and saved as separate data structures (see Algorithm 1 in Appendix A for the pseudocode of this process). A recursive algorithm was used to construct a connectivity matrix that identified the geometry of the tree, which was subsequently used in the 1D model (described in detail as Algorithm 2 in Appendix A). The workflow in
Fig. 4 illustrates how the micro-CT image was segmented to form the 3D structure and subsequently reduced and translated into a connected tree.

**Figure 3: Change in segmentation map when changing parameters**

**Figure 4: Workflow of going from image to constructed network**

Radius and length estimates for the vessels used in the 1D model were obtained after extracting all vessels in the network. A scaling factor is used to convert measurements in voxels to cm by relating voxels in the MPA to the known dimensions of the cannula clamp (0.086 cm diameter). This scaling factor was used to translate length and radii measurements in the entire network (103). The vessel length was calculated as the sum of the Euclidean distances between successive spatial points. To conduct fluid simulations with the 1D model, vessels with length less than the spatial resolution of the numerical solver ($2.5 \times 10^{-3}$ cm) were augmented to satisfy the Courant-Friedrichs-Lewy (CFL) condition (52). For each vessel, the radius is calculated as the mean over the center 80% of the individual radii estimates, which ensures that the larger ostium regions opening to each bifurcation did not skew the predicted radius values. The MPA radius was estimated using measurements in the region of the vessel that was most distal from the cannula but before the bifurcation to the left and right pulmonary artery (LPA and RPA, respectively). Figure 5d shows radius variation along a single vessel over all 25 segmentations.

Finally, since the 1D model only considers bifurcating vessels, we eliminated trifurcations by selecting branches that led to the largest downstream vasculature. The mean radius value and length were used in conjunction with the connectivity matrix to setup the geometry used by the 1D model. Network features including number of vessels, number of bifurcations (i.e. generations), and total vascular volume were calculated for each segmented network in order to compare the effects of different segmentation parameters.

**Figure 5: Representative vessels and example radius plots**

**Hemodynamics Modeling**

*Blood flow model.* Similar to previous studies (61, 66), we used a 1D CFD model to predict flow, pressure, and area as functions of time in each vessel. This model was further used for forward uncertainty propagation (described below and depicted in all three of the variation aspects of Fig. 1). Model equations are derived under the assumptions that the fluid is viscous, incompressible, and homogeneous, the flow is axisymmetric and laminar, and swirls are negligible. Vessel walls are
considered impermeable with no-slip conditions at the fluid-wall interface. Under these assumptions, the conservation of mass conservation and balance of momentum take the form

\[ \frac{\partial A}{\partial t} + \frac{\partial Q}{\partial x} = 0, \]  
\[ \frac{\partial Q}{\partial t} + \frac{\partial}{\partial x} \left( \frac{Q^2}{A} \right) + \frac{A}{\rho} \frac{\partial P}{\partial x} = -\frac{2\pi v r Q}{\delta A}, \]

where \( x \) (cm) and \( t \) (s) are the axial and temporal coordinates, respectively. \( A(x, t) \) (cm\(^2\)) denotes the cross-sectional area, \( Q(x, t) \) (cm\(^3\)/s) the volumetric flow rate, \( P(x, t) \) (mmHg) the transmural blood pressure, and \( r(x, t) \) (cm) the vessel radius. The blood density \( \rho = 1.057 \) (g/cm\(^3\)) and the kinematic viscosity \( \nu = 0.0462 \) (cm\(^2\)/s) are assumed constant (73, 110).

An equation of state (or tube law) relating pressure and area is required to close the system of equations. We assume that the vessel is an orthotropic and elastic cylindrical tube with thin walls having a thickness \( h \ll r_0 \), in which the deformation and loading is axisymmetric. Similar to previous studies (62, 66), a linear wall model

\[ P - P_0 = \frac{4}{3} \beta \left( 1 - \frac{A_0}{A} \right), \]

satisfies these assumptions, where \( \beta = Eh/r_0 \) is the arterial stiffness, \( E \) (mmHg) is the Young’s modulus in the circumferential direction, \( h \) (cm) the wall thickness, and \( A_0 = \pi r_0^2 \) (cm\(^2\)) is the reference area obtained at the reference pressure \( P_0 \) (mmHg).

**Inflow, outflow and junction conditions.** The system governed by Eqs. (1)-(3) is hyperbolic with characteristics pointing in opposite directions. As a result, boundary conditions need to be imposed at the inlet of the network, across vessel junctions, and at the distal end of the terminal vessels. We prescribed a flow waveform \( Q_{data}(t) \) over a cardiac cycle, obtained from measurements as described previously, at the inlet of the MPA. We impose conservation of flow and a negligible pressure drop across each junction to give

\[ Q_p(l, t) = Q_{d_1}(0, t) + Q_{d_2}(0, t), \quad P_p(l_p, t) = P_{d_1}(0, t) = P_{d_2}(0, t), \]

where the subscripts \( p, d_1, d_2 \) indicate the parent and daughters at a given vessel junction, respectively, and \( l_p \) denotes the length of the parent vessel.

Similar to previous studies (19, 65, 109), we used a three element Windkessel model as the outlet boundary condition. The Windkessel model relates pressure and flow at the outlet of each terminal vessel.
while accounting for effects of proximal and distal resistance and compliance via the parameters \( R_1, R_2, \) and \( C_T, \) respectively (62, 71). The zero-dimensional boundary conditions were coupled to the 1D fluids model as described in (61).

**Parameter values.** There are two main sets of parameters in this model: those attributed to the geometry (e.g. length, radius, and connectivity) and those attributed to the hemodynamics (viscosity, density, wall stiffness, and boundary conditions). In this study, we assumed that only viscosity, density, and wall stiffness are independent of the network geometry. We prescribed a constant arterial stiffness \( \beta = 37.5 \) mmHg throughout the network (47, 51, 66, 68), whereas parameters for the Windkessel boundary conditions \((R_1, R_2, C_T)\) were computed using the network structure and vessel dimensions. Since the Windkessel parameters are dependent on the network geometry, a new set of parameter values is obtained for each of the 25 networks obtained from the segmentation.

The total compliance of the vascular beds \( C_T \) is determined from the time constant \( \tau = R_T C_T, \) where \( R_T = R_1 + R_2 \) is the total vascular resistance. The parameter \( \tau \) is obtained by fitting an exponential function to pressure and flow data for the diastolic pressure (65),

\[
P_d(t) = P(t_d) e^{\left(\frac{t-t_d}{\tau}\right)},
\]

where \( t_d \) is the time in which flow is zero and the diastolic pressure \( P_d(t) \) decays throughout diastole (92). Assuming \( \tau \) to be constant throughout the network, we computed compliance as \( C_T^i = \tau / R_T^i \) for each vessel \( i. \)

The total vascular resistance \( R_T \) was computed as the mean pressure over the mean flow, i.e. \( R_T = \bar{P} / \bar{Q}. \) As shown in previous studies (15, 65), a priori resistance values for each terminal vessel can be calculated analytically using Poiseuille’s equation relating mean pressure and flow via the vessel dimensions, i.e.

\[
\bar{Q}_i = \frac{\bar{P}_i}{R_i} = \frac{\bar{P}_i \pi \left( r_i^4 \right)}{8 \mu \left( l_i \right)} = \frac{\bar{P}_i \pi}{8 \mu} \xi_i,
\]

where \( \bar{Q}_i \) (cm\(^3\)/s), \( \bar{P}_i \) (mmHg), and \( R_i \) (mmHg s / cm\(^3\)) are the mean flow, mean pressure and resistance in the vessel \( i \), respectively. Both junction conditions in Eq. (4) were used in conjunction with Eq. (6) to give the following mean flow distribution relationship between the daughter vessels at a junction

\[
\bar{Q}_{d_1} = \bar{Q}_p \frac{\xi_{d_1}}{\xi_{d_1} + \xi_{d_2}}, \quad \bar{Q}_{d_2} = \bar{Q}_p \frac{\xi_{d_2}}{\xi_{d_1} + \xi_{d_2}},
\]

where \( \xi_i \) represents the ratio \( r_i^4 / l_i. \) Finally, the proximal resistance \( R_1 \) and peripheral resistance \( R_2 \) were obtained by setting \( R_1 = 0.2 R_T \) and \( R_2 = 0.8 R_T \) (65).
Inverse Uncertainty Quantification

Inverse UQ was employed to estimate length and radius distributions over 25 segmented networks. Probability distribution functions (PDFs) were computed for radius and length values from a 32-vessel subset after data standardization (corresponding to the length and radius variation in Fig. 1). Two different estimation techniques, kernel density estimation (KDE) and Gaussian process (GP) density estimation, were used to construct the PDFs. Weighted least squares regression and Gaussian process regression are compared in their ability to quantify the relationship between the measured radius and length and coefficient of variation (CV) values. These regression techniques were used to remedy the issues of non-constant variance, i.e. heteroscedasticity, in the data.

Data standardization. We chose a subset of 32 pulmonary vessels of various caliber (see Fig. 5a) to study geometric variations across the 25 segmentations. The 32 vessels used in the density estimation procedure were visible in all 25 networks and contained radius and length measurements that encompassed the full range of measurements in a given network. A PDF representing the distribution of length and radius measurements was constructed by analyzing the dimensions of the 32-vessel subset. We first standardized the vessel measurements of length and radius as

\[ s_{i,j}^* = \frac{s_{i,j} - \bar{s}_i}{\sigma_{s_i}}, \]

where \( s_{i,j} = r, l \) are the measured quantities from the \( i \)th vessel and \( j \)th segmentation, and \( \bar{s}_i \) and \( \sigma_{s_i} \) are the mean and the standard deviations of these quantities across the 25 networks, respectively. The standardization above rescaled the quantities so that the expectation and variance for all measurements in a given vessel were 0 and 1, respectively.

Kernel Density Estimation. To estimate the PDFs, we used KDE, a nonparametric technique often used in modeling physical systems and machine learning applications (89). Standard KDE constructs the PDF \( p \) using

\[ p(s) = \frac{1}{nH} \sum_{i=1}^{n} K\left( \frac{s - s_{i}^*}{H} \right), \]

where \( s_{i}^* \) denotes the \( i \)th standardized measurement of the vessel, \( n \) is the number of samples used for the density estimate, \( H \) is the bandwidth parameter, and \( K \) is the kernel function, which was fixed to be a Gaussian kernel in this study.

We considered two approaches for finding the optimal KDE bandwidth: Silverman’s rule-of-thumb (89) and maximum likelihood, leave-one-out cross validation (MLCV) (17, 30). Silverman’s rule-of-thumb calculates the bandwidth as
\[
H^S = \hat{\sigma} \left( \frac{4}{3n} \right)^{\frac{1}{5}},
\]

where \( \hat{\sigma} = \hat{\sigma}_{MAD} / (0.6745) \) is the estimate of the standard deviation using the median absolute deviation \( \hat{\sigma}_{MAD} \) under the assumption that the data is normally distributed (80). This method has been shown to minimize the integrated mean squared error of the density estimate (89). These estimates were calculated using the \texttt{ksdensity} function from MATLAB’s Statistics and Machine Learning Toolbox.

The MLCV technique changes the standard KDE procedure in Eq. (9) to

\[
p_i(s_i^*) = \frac{1}{(n-1)H_{MLCV}} \sum_{j=1}^{n} K \left( \frac{s_j^* - s_i^*}{H_{MLCV}} \right),
\]

where \( s_i^*, i = 1 \ldots n \) denotes the data point which is left out of the sample. To find the optimal bandwidth parameter \( H_{MLCV} \), we maximized the log-likelihood of Eq. (11) (see Appendix B for more details). Each sample that is left out affects the calculation of the standardized quantities, and hence required recalculation of the standardized measurements for each iteration of the leave-one-out cross validation.

\textit{Gaussian process density estimation}. To test the robustness of the estimated density, we compare the KDE methods with logistic GP density estimation (74) using the \textit{GP Stuff} toolkit in MATLAB (104). GPs are flexible nonparametric regression models that naturally incorporate smoothness via covariance functions. GP models define a distribution over noiseless latent functions (corresponding to the noisy observations), typically with mean zero and an assigned covariance function characterizing the smoothness of the function.

To construct the PDF \( p(S) \) for the covariates \( S = (l_{i,j}, r_{i,j}) \), we considered the logistic density transformation of some latent function \( f(S) \). This gives the estimate

\[
p(S) = \frac{\exp(f(S))}{\int_{\Omega} \exp(f(\alpha)) \, d\alpha},
\]

which is analytically intractable due to the normalization factor in the denominator. To combat this, the density was estimated using Laplace approximation methods (74). A GP prior was placed on \( f(S) \) with a nonstationary neural network kernel covariance function, whose hyperparameters \( \theta \) were found (see Appendix B) by maximizing the log-likelihood, \( L(p) \),

\[
\max_{\theta} L(p) = \max_{p(S) \geq 0} \left( \sum_{i=1}^{n} \log p(S_i) \right).
\]

\textit{Statistical models for computing the length and radius variance}. The PDFs constructed from the 32-vessel subset were representative of the overall variation in the length and radius throughout all the
networks analyzed. However, the magnitude of $\sigma_l$ and $\sigma_r$ varied from vessel to vessel and were modeled explicitly in order to perturb the geometry parameters in the forward uncertainty propagation. The CV, defined as the ratio of the standard deviation to the mean and calculated as $c_v^{si} = \sigma_z/\bar{z}_i$, was used as a metric for comparing the length and radius measurements to their variability.

Our next goal was to find a function $\phi(\bar{z}_i) = c_v^{si}$ that related the average measurements of radius and length across segmentations to their variation. We observed that the variance of the measurements in question exhibited heteroscedasticity since smaller vessel segments in the image were expected to be more sensitive to segmentation parameters. This violated the typical assumption of constant variance in ordinary linear regression, hence we used weighted least squares (WLS) regression (93) and GP regression with input-dependent noise (27).

Traditional deterministic WLS regression iteratively fits a regression model to the data, updates weights on each of the observations by setting them to equal the inverse of the variance, and then fits the regression model again using the newly updated weights. For simplicity, we set the weights as the inverse of the residual of each observation, i.e. $w_i = 1/\epsilon_i^2$, where $\epsilon_i$ is the residual from the unweighted regression model. This reduced the impact that highly variable observations had on the regression prediction. We considered exponential, logarithmic, square root, and linear WLS regression models in this study. For GP regression, we considered two GPs: one for the response, namely the CV $c_v$, and a second for the latent variance of $c_v$. The GPs used the Matérn covariance function (69) with a smoothness parameter $\nu = 5/2$ (more details on the covariance function used for the regression can be found in Appendix C).

Forward Uncertainty Quantification

Forward UQ propagates model and parameter uncertainties to simulated quantities of interest. One issue with the model employed here is that both the network size (number of vessels and connectivity) and the model parameters (length, radius, and boundary conditions) give rise to uncertainty. To analyze the posterior variation, we set up three simulations to determine (i) total variation associated with segmenting the network, (ii) variation to changes in model parameters, and (iii) variation to network size and connectivity. The first set of simulations (i) used the 25 segmented networks, whereas the last two (ii-iii) were conducted in a representative network.

Total Variation. To quantify the total variation of flow and pressure predictions in the MPA, LPA, and RPA, we evaluated the fluid dynamics model using each of the 25 networks. The variation observed is attributed to several sources of uncertainty, including the parameters of the model and the size and
connectivity of the network. Once the total variation was calculated, we quantified the relative contributions of the two.

*Parameter Variation.* Changes in model parameters impact computational predictions. As mentioned previously, we assumed that density, viscosity, and vessel stiffness are constant while parameters impacted by image segmentation, including vessel length, radius, and boundary conditions, vary. The outflow boundary conditions were calculated as functions of vessel length and radius; therefore, we analyzed the model predictions associated with variation in vessel length and radius only. We conducted the computations in a representative network and explicitly studied what part of the variation is contributed to these model parameters.

*Representative network.* We selected a representative network by first computing the pressure waveform in the MPA for each of the 25 networks. We calculate the least squares cost between the pressure waveform and the ensemble averaged waveform from all 25 networks. The representative network was chosen as the network with the smallest least squares cost.

*Variation in vessel radius and length.* The WLS and Gaussian process regression techniques were used to estimate \( \phi(\bar{s}_i) \), relating the average measurements of radius and length across segmentations to their variation. We computed inverse cumulative distribution functions (CDFs) for the length and radius PDFs. The inverse CDF \( F^{-1}_s(y) \) is a nondecreasing function defined on the interval \([0,1]\) that provides values from the original PDF. Realizations for forward uncertainty propagation were drawn using inverse transform sampling (29). Briefly, let \( u \) be a realization from a uniform distribution \( u \sim \mathcal{U}(0,1) \), and define the realization from the inverse CDF as \( F^{-1}_s(u) \). There exists a mapping from the realization to the inverse CDF for the radius and the length via \( \gamma_r = F^{-1}_r(u) \) and \( \gamma_l = F^{-1}_l(u) \), respectively, which allowed for effective sampling using the inverse transform method. The sampling drew from the inverse CDF to provide values that represented the standardized measurement \( l^* \) and \( r^* \) for length and radius, respectively.

We defined a mapping from the inverse CDF of the mean measurements \( \bar{s}_i \) in vessel \( i \) to the perturbed values \( \bar{s}_i \) in units of cm. We write \( F^{-1}_s(u) = (\bar{s}_i - \bar{s}_i)/\sigma_{s_i} \) and rewrite the standard deviation as

\[
\sigma_{s_i} \equiv c_s^{s_i} \cdot \bar{s}_i = \phi(\bar{s}_i) \cdot \bar{s}_i,
\]

which gives

\[
\hat{s}_i = (F^{-1}_s(u) \cdot \phi(\bar{s}_i) + 1) \cdot \bar{s}_i \tag{14}
\]

for each average measurement \( \bar{s}_i \) in vessel \( i \). The values \( \hat{s} \) were used as the dimensions for each vessel in the 1D model when doing the forward uncertainty propagation to study parameter variation. For this
study, we propagated uncertainties through the representative network by setting the average measurement \( \bar{s}_i \) equal to the measurements of radius and length \( x_i \) from the representative network.

In general, forward uncertainty propagation must be iterated numerous times in order to achieve convergence. In this study, we drew \( M = 10^4 \) realizations using Monte Carlo sampling to perturb the length and radius values in a given vascular geometry, which illustrated convergence in the overall results. The vessel radii and lengths obtained from the sampling were used in the 1D model and provided \( M \) predictions of pressure and flow. The general algorithm for the propagation is given as follows:

1. Draw a random sample \( u \sim U(0,1) \).
2. Map the sample to \( F_r^{-1}(u) \) and \( F_l^{-1}(u) \).
3. Perturb the nominal radius and length by using Eq. (14).
4. Run 1D fluids model with new radius and length values.
5. Repeat steps 1-4 \( M \) times.

**Connectivity and size variation.** To study what part of the total variation stems from network size and connectivity, we altered the total size of a network and measured the variability in model predictions. We considered the same representative network used before but fixed each vessel’s length and radius and instead altered the number of vessels in the tree. The smallest terminal vessels in the tree contained the least number of voxels and were the most susceptible to change in pre-segmentation parameters. We simulated this by systematically eliminating the terminal vessels of the representative network to quantify how network size and connectivity affected model predictions. We calculated the total volume of each set of terminal vessels in the network (i.e. \( V_{tot} = \pi (r_{d_1}^2 l_{d_1} + r_{d_2}^2 l_{d_2}) \) for terminal daughters \( d_1 \) and \( d_2 \)) and removed the terminal pair of vessels with the smallest volume, which corresponded to the terminal vessels most likely to change because of pre-segmentation parameters. The truncation began at the smallest set of terminal vessels in the network and continued until only the MPA, LPA, and RPA were remaining. While reducing the size of the network, we ensured, using Eq. (7), that the total resistance and total compliance of the network were preserved, and that the total mean flow throughout the network was also conserved. This is an important step in isolating the effects of boundary parameters from the geometric variations as these quantities dictate the calculated resistance and compliance at each terminal vessel.

**RESULTS**

We analyzed the total variation of flow and pressure predictions and identified the relative contributions from variation in model parameters and variation in network size and connectivity. For the total variation, we constructed 25 networks changing the pre-segmentation parameter sets using one micro-CT image. Each network was constructed as a set of vessels with bifurcation points. We computed the Euclidean
length and mean radius using information extracted from the centerlines of the 3D geometry and assigned them to each vessel as input parameters for the 1D model. The total variation in the model predictions, attributed to changes in vessel length and radius as well as network size and connectivity, was quantified by comparing model simulations in the MPA, LPA, and RPA using each of the 25 networks. We compared total variation over the 25 networks with variation in model parameters (radius and length) as well as variation in connectivity and network size.

*Network statistics.* We defined each bifurcation in the pulmonary tree as a new generation in the system. Figure 6 summarizes network characteristics, including the number of vessels as well as average and total cross-sectional area for each generation number. The average number of vessels in the tree was $437 \pm 76$ and the mean of generations across segmentations was approximately 17. Results show that the number of vessels and total cross-sectional area of the networks are relatively consistent across segmentations up until the 6th generation, after which the results deviate. Analysis over all networks show that one network (generated from the pre-segmentation parameters $(\theta_1, \theta_2) = (44, 7.6)$ and shown in Fig. (6d) stands out as having significantly fewer vessels and a lower total cross-sectional area. Most of the segmentations had a maximum number of vessels and cross-sectional area between generations 8 and 14. In contrast to total cross-sectional area, the average cross-sectional area rapidly decreased from generation 0 to generation 5, and then remained fairly constant afterward. Table 1 includes all segmentation parameter values used in the repeated segmentations as well as network level features.

**Table 1: Network Features**

**Figure 6: Number of vessels, network area, and segmentation parameters**

*Inverse UQ*

_Density estimates and variance functions._ Figure 7 shows the estimated length and radius densities using KDE with bandwidths calculated via Silverman’s rule and MLCV, as well as densities obtained using GPs. The densities were constructed for 32 representative vessels (see Fig. 5), giving a total of 800 data points (32 vessels and 25 segmentations). The SDs for each of the 32 vessels are used to standardize the data points (see Eq. (8)) before applying density estimation techniques. The maximum CV across all 32 vessels is 21% for the radius (mean $2.95 \times 10^{-2}$ cm, SD $6.20 \times 10^{-3}$ cm) and 49% for the length estimate (mean $7.54 \times 10^{-2}$ cm, SD $3.67 \times 10^{-2}$ cm).

The bandwidths used in the KDE are depicted by the black and red curves, computed using _Eqs. (10) and (11)_ respectively, in Fig. 7. The GP density and 95% credible intervals are also included. The bandwidth estimates for Silverman’s rule were $H_l^S = 2.038 \times 10^{-1}$ and $H_r^S = 1.573 \times 10^{-1}$ while the
estimated bandwidth using MLCV were $H_l^{MLCV} = 1.808$ and $H_r^{MLCV} = 6.887 \times 10^{-1}$ for the length and radius densities, respectively. In general, the KDE with the Silverman’s rule bandwidth shows clear overfitting, while the KDE using the MLCV bandwidths tended to over-smooth the density relative to the GP. These results suggest that the GP is the best density approximation, and it was therefore chosen for the forward uncertainty propagation presented below.

**Figure 7: Density estimates and inverse cumulative distribution functions**

Several deterministic variance functions $\phi(\tilde{s}_i)$ were used in the attempt to find the best relationship between $c_v$ and the measured length and radius values. The WLS regression approach assigned weights to each sample point $s_i$ as $w_i = 1/\epsilon_i^2$, as stated previously. We found that exponential, logarithmic, square root, and linear regression functions were unable to resolve the heteroscedastic nature of the data (plots not shown). To remedy this problem, we used the GP regression model with input dependent noise to construct an estimate of $\phi(\tilde{s}_i)$. The GP model identified the function $\phi(\tilde{s}_i)$ while also computing the variance of the CV for each measurement of radius and length, which resolved the issue of heteroscedasticity. Figures 8a and 8c show the GP regression for the length and radius, respectively, along with ± one and two SDs from the mean. The CV for individual vessel measurements across multiple segmentations increase as the measurements decrease in magnitude. Figures 8b and 8d show the GP estimate for the variance of the CV and ± 2 SDs. The variance for $c_v^l$ increases as the length value decreases, yet the variance of $c_v^r$ has a sharp decrease in radius measurements smaller than $1.2 \times 10^{-2}$ cm, due to the abundance of the measurements at that size. Additionally, both GP models shown stay above the minimum variability of $20\mu m$ that is a consequence of the imaging protocol (curve plotted in blue).

**Figure 8: Gaussian process plots**

**Forward UQ**

*Total variation.* Simulations with the 25 networks produced pressure and flow profiles at the inlet of the MPA, LPA, and RPA. The inlet MPA flow was used as an inflow boundary condition and as a result did not change in any of the simulations. The ensemble averaged network prediction was computed using the 25 MPA pressure waveforms and is shown along with ± two SDs in Fig. 9. The mean pressure value (i.e. the mean pressure over the cardiac cycle) in the MPA, LPA, and RPA is 20.36, 19.66, and 19.52 (SDs of 0.78, 0.79, and 0.78) mmHg, respectively. The mean for the systolic pressure was $35.35\pm1.63$, $33.46\pm1.67$, and $32.83\pm1.60$ mmHg for the MPA, LPA, and RPA, respectively. Additional quantities,
such as diastolic and pulse pressure and max flow, min flow, and total volume, are given in Table 2. The ensemble averaged pressure waveform calculated from the 25 networks was used to identify the representative network, which corresponded to the pre-segmentation parameter set \((\theta_1, \theta_2) = (33, 5.1)\).

**Figure 9: Total Variation**

**Table 2: Results from variation studies**

*Parameter variation.* We used the inverse sampling methodology defined in \(Eq. (14)\) to propagate \(10^4\) realizations of perturbed radius and length values for the representative network. Figure 10 shows the model predictions using the realizations of radius and length along with the mean and one and two SDs from the mean. The variation in the MPA, LPA, and RPA systolic and pulse pressure values that were much larger than the variation seen in the mean and diastolic pressure (see Table 2). The flow prediction in the LPA and RPA had larger variability with respect to the mean and max flow in comparison to the minimum flow.

**Figure 10: Length and radius variation**

*Connectivity and size variation.* The effects of connectivity on model prediction was studied in the representative network. Each vessel’s radius and length value were left at the measured value obtained from the original centerline extraction and network construction. To simulate the effects of missing branches outside of the imaging resolution, we reduced the full network iteratively, starting at the smallest branches and moving towards the proximal vasculature. Windkessel boundary conditions were adjusted for each simulation based on the reduced network. Figure 11 shows pressure and flow predictions in the first bifurcation of the pulmonary tree for different numbers of vessels in the system. The maximum systolic pressure in the MPA, LPA, and RPA had a SD of 2.07, 2.13 and 1.96 mmHg while the pulse pressure had a SD of 1.91, 1.97, and 1.77 mmHg for the respective vessels. The SD of the mean pressure in the MPA, LPA, and RPA was 0.84, 0.86, and 0.83 mmHg, respectively.

**Figure 11: Connectivity and network size variation**

**DISCUSSION**

Results confirmed that the pre-segmentation parameters alter morphometric quantities and hence the 1D CFD model predictions. We investigated three types of variation: the total variation arising from changes...
in pre-segmentation parameters, variation due to changes in vessel length and radius, and variation with respect to network connectivity and size. Results showed that pressure predictions in the MPA, LPA, and RPA show relatively larger variation when changing network size and connectivity in comparison to variation in model parameters.

**Segmentation and construction of network graphs.** Results from the 25 segmentations show that the number of vessels in a given segmentation can change drastically, while the number of generations remains relatively consistent. It is apparent that the extent of the network obtained from image segmentation is strongly linked to the range of image intensities considered in the foreground via choice of pre-segmentation parameter. The techniques employed here studied the uncertainty induced by segmenting an image using global thresholding, yet this is only one of the many techniques that can be used to differentiate foreground and background images for segmentation. For instance, Payer et. al (63) used vessel enhancement, subtree extraction, and Voronoi diagrams to assist in automatic voxel labeling of arteries and veins in the entire pulmonary tree, and ultimately achieved high accuracy in vessel segmentation. The use of multiple filters and machine learning can further assist in reducing the segmentation’s dependency on a single thresholding function. However, the images used in this study exclude any other tissues and thus makes the analysis based on global thresholding valid and novel.

The variability in the total number of vessels for a given set of pre-segmentation parameters is particularly notable as it highlights the variation attributed to segmentation and image resolution limits. This result may not characterize the imaging of the aortic branches, but would play a role in capturing more dispersive branching patterns that often occur in the pulmonary vasculature (studied here), coronary arteries (40, 102), or any organ with large vascular networks such as the eye or cerebral vasculature (10, 98). We employed a traditional labeling scheme for the bifurcations in the pulmonary tree, where each bifurcation is considered a new generation of blood vessels. In contrast, multiple authors (42, 50, 78) have used other ordering systems, e.g. Strahler (36) and Horsfield (33) schemes, to identify structural properties of the pulmonary system rather than using the vascular networks in model predictions. The bifurcation-based ordering scheme is ideal for computational fluid dynamics, since each vessel’s parent and daughters must be explicitly identified in order to construct the 1D network domain.

The protocol for the contour evolution in the segmentation can be altered to increase the number of vessels obtained in the segmentation process. The protocol used in this study, though, is more likely to be employed by researchers interested in applying computational fluid dynamics to cardiovascular networks obtained. The largest vascular tree used in this study contained 500 vessels, which is few compared to the thousands of blood vessels that comprise full pulmonary arterial system(32, 36, 78). The arterioles of the pulmonary tree are too small to detect in the imaging protocol, which limits the ability to
construct the entire pulmonary tree. The trends seen in Fig. 5 may continue if more vessels could be detected by the imaging protocol.

*Image-to-CFD simulation integration.* This work is the first study to integrate a large pulmonary network extracted from CT images with nonlinear fluid dynamics simulations. Some previous studies (20, 58, 96) have used large networks in 1D models, yet none have integrated expansive pulmonary trees from images into their computational framework. Moreover, only one other study (77) has analyzed how imaging and segmentation protocols might affect the vascular tree used in 1D fluid models of wave propagation. Many of the 1D models consider simple bifurcations, which is a limitation in the pulmonary vasculature, since trifurcations and quadfurcations are not uncommon in the pulmonary airways, arteries, and veins (55).

However, the network used in this study only contained at most two trifurcations in the system, limiting the effects of neglecting trifurcations in the model. Additionally, the 1D model takes in a graph representation of the network and does not take information about the branching angles, which should be investigated further.

*Quantification of inverse uncertainty.* The use of KDEs and GPs in estimating probability densities and CDFs is a commonly used technique (27, 43, 54, 74) that has received little to no attention in cardiovascular modeling. Numerous studies have investigated how to choose the bandwidth parameter to ensure that a variable’s predicted PDF is not over or under smoothed (23, 89), yet no studies have considered the use of a Gaussian process in density estimation of measurement data from medical imaging. It is often the case that UQ will be carried out by assuming a parametric parameter distribution *a priori*, which forces prior assumptions (i.e. uniform or normal distribution) on the unknown parameter distributions. By estimating the density directly from repeated measurements, we constructed a representative density describing the uncertainty of the measurements between segmentations.

Using standardized measurements further allowed us to generalize the uncertainty of the 32-vessels in the truncated tree to the entire vascular network. This increased the robustness of the density estimates by including more data, thus leading to a better representation of the distribution. As shown in Fig. 8, the three density estimates are similar in regard to the mode of the distribution (which is close to zero). However, the use of GP density estimation allowed for additional quantification of uncertainty (74) in both the density and CDF estimates. In addition, we constructed marginal density estimates for the PDFs of radius and length. This is a limitation, as this assumes independence among the two quantities, which encourages PDF estimation methods that account for dependencies between radius and length measurements.

Use of GPs in regression was necessary in the case of the data provided, WLS did not correct the effects of heteroscedasticity. As expected, the CV of the measurements increased as the measurements
decreased in size. Vessels that are smaller in diameter contain fewer voxels, and hence may have large fluctuations in radius or length measurements based on small changes in the pre-segmentation parameters. Similar conclusions have been made for predicting fractional flow reserve in coronary crowns (34), as the smaller regions of flow are susceptible to higher segmentation error. The ability to sample from the estimated densities and propagate uncertainty in a nonparametric manner via the CV is, to the authors’ knowledge, novel. Moreover, the gradual increase in CV indicates that the variation of the vessel measurements increased quicker than the measured values.

Total variation of model simulations. The total network size obtained from the segmentation procedure had various effects on the model output. As shown in Table 2, the change in network topology based on changes in pre-segmentation parameters induced approximately 6 times larger variation in systolic pressure than in diastolic pressure. Moreover, we observe that the total variation for the systolic and pulse pressure is larger in magnitude in comparison to the mean and diastolic pressure. Regarding clinical applications, all four of these pressure metrics are typically used in diagnostic tools of diseases such as systemic hypertension (87) and pulmonary hypertension (24, 31, 39, 72). Though systolic pressure and pulse pressure have a small SD (approximately 5% relative to the mean systolic and pulse pressure, shown in Table 2), studies investigating coronary related mortality found that these systolic and pulse pressure quantities were important for risk assessment in patients with congenital heart disease (45). This further indicates that proper quantification of these measures and their possible uncertainty is a necessity if used in cardiovascular disease diagnostics and risk assessment.

The effects of pre-segmentation parameters must be accounted for if researchers seek to use computational models of the cardiovascular system as a means for non-invasive assessment, especially when pressure quantities are indicative of disease progression. Recent advances in parameter estimation techniques have made subject-specific modeling a reality (8, 15, 21, 25, 41, 53, 79, 105). However, our results show that combined effects of network morphometry and vessel dimensions can induce variability in pressure predictions, thus limiting parameter inference in the presence of segmentation uncertainty. Previous studies have addressed uncertainty in vascular geometry in 3D CFD computations (4, 28, 81, 84), yet few have addressed geometric uncertainty in the 1D modeling scenario (15, 54, 90).

Parameter variation on model prediction. The effects of changing vessel length and radius on model simulations were smaller in magnitude compared to the effects of changing connectivity and network size. Specifically, the variation in radius and length is only greater than the latter variation when diastolic pressure is the quantity of interest. Radius and length variation only accounted for approximately 30% of the total variation in the pulse pressure, making it less significant in this study. However, should the computational model become a prominent noninvasive diagnostic tool in diseases such as pulmonary
hypertension, the uncertainty in the radius and length estimates should be kept in mind as the corresponding variation in pressure prediction could lead to a false classification of a patient as healthy versus diseased. Larger networks encompassing the entirety of the pulmonary tree will likely increase the level of uncertainty in the problem, as larger networks will correspond to more uncertain parameters. This will further increase the uncertainty bounds of the pressure predictions in the proximal pulmonary arteries, and could cause an issue when trying to estimate hemodynamic parameters (18, 81). This study does not consider the effects of other uncertain inputs such as the inflow profile, viscosity, or arterial stiffness, which have been investigated elsewhere (15, 62, 81, 85, 86, 100, 111).

Variation to network size and connectivity. The largest effect on the model prediction is attributed to the change in downstream vasculature, as seen in Fig. 11. The general trend seen is that pressure predictions increase in magnitude as more vessels are added to the system. The reason for this is twofold. First, increasing blood vessels in the model increases the number of bifurcations in the system. While it is not discussed at length here, reflected pressure waves can start to become prevalent as successive bifurcations are added to the system and can lead to increased pressure (26, 38, 77, 88). The second reason for the increase in pressure magnitude is due to the increased number of Windkessel models. This increases resistance at the terminal end of the network and likely contributes to increased pressure at the MPA.

The level of vascular tree truncation can cause a large change in nominal predictions, which can ultimately affect the ability to carry out parameter estimation. It is often the case that hemodynamic data is only made available in select locations of the vascular system (15, 62, 64, 65), which makes parameter estimation an ill-posed problem as parameter inference describing stiffness, compliance, and vascular resistance of the full network is dependent on only select data measurements. Moreover, the size of the network contributes to posterior parameter estimates, and parameters obtained can only describe the dynamics of the model using that specific geometry. The size of the network used in simulations should therefore be accounted for in every subject-specific model, should parameter inference be of interest in clinical diagnosis. A limitation to our methods used here is that we only considered successive truncation of a full tree, but did not investigate the inclusion or exclusion of small side branches, called supernumerary vessel, that are found throughout the pulmonary tree (13).

Future directions. This study has used 3 element Windkessel models as boundary conditions for the 1D model for simplicity. Windkessel models are often used in cardiovascular parameter estimation (3, 15, 53, 62, 79), but lack physiological relevance in regards to downstream resistance. In contrast, structured tree boundary conditions (60, 61, 67, 68) can provide a more physiological means for approximating downstream resistance. By using a tree-like structure at the limit of the image resolution, it may be possible to characterize the full topology of the pulmonary arterial tree. In addition, future subject specific
models of the pulmonary circulation need to be able to account for trifurcations and angles in the vascular tree in order to account for more physical traits of the networks.

CONCLUSIONS

We have presented an in-depth study of the uncertainty that arises from subject-specific medical image geometries in 1D CFD models. Moreover, this work identifies the uncertainties pertaining to medical segmentation by explicitly measuring the variation in radius and length measurements of a subset of vascular segments. The propagation of geometric uncertainties through CFD models has been done previously (28, 81, 83), but, to our knowledge, this is the first time these techniques have been used in the 1D CFD framework of the pulmonary circulation. Moreover, the novelty of this work has been in constructing densities of radius and length from data obtained using state-of-the-art techniques from nonparametric, as opposed to assuming a distribution \textit{a priori}. Finally, this study is the first to address the effects of uncertainty in the dimensions and network topology of a 1D model of blood flow in an expansive pulmonary vascular network. We have shown that the connectivity of blood vessel networks can largely influence the nominal predictions of pressure using a 1D CFD model while changes in vessel dimensions are less influential.

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AUTHOR CONTRIBUTIONS

M.J.C., M.S.O, and L.E.F conception and design of research; M.J.C. and N.C. performed experiments; M.J.C., L.M.P, and D.H. analyzed data; M.J.C., M.U.Q., M.S.O., and L.E.F. interpreted results of experiments; M.J.C. prepared figures; M.J.C., M.S.O., and L.E.F. drafted manuscript; M.J.C., L.M.P, M.U.Q., D.H., N.C., M.S.O., and L.E.F. edited manuscript.
APPENDIX A

Unique points of the entire data file were stored into a matrix using MATLAB’s `unique` function. Every full pathway was tracked until it reached a point shared by another full pathway, which was then identified as an intersection node. We then labeled the vessels of the arterial tree as the arcs that align between any two nodes. We used the fact that any $n$ number of nodes in a network are guaranteed to have exactly $(n - 1)$ arcs between the nodes themselves. This limits the ability to double count any section of the tree and allows us to allocate space for the storage of individual vessels.

Algorithm 1: Find shared and unique points

1. Define $C$, $R$, $U$, $L$, and $N$, where $C$ is the matrix of centerline points $(x, y, z)$, $R$ is the vector of radii values, $U$ is the matrix of full pathways, and $N$ is the size of the centerline file.
2. for $k = 1, ..., N-1$ do
3. | Calculate distance from $C(k)$ to $C(k+1)$
4. | Calculate $R(k) + R(k+1)$
5. | if distance $C(k)$ to $C(k+1) > R(k) + R(k+1)$
6. | Append the full pathway ending at $C(k)$ into the matrix $U$
7. end if
8. end for
9. for $k = 1$ to number of pathways in $U$
10. | if $U(k)$ intersects $U(\sim k)$ then
11. | | Calculate the number of points $\gamma_i$ from start of $U(k)$ to intersection
12. | end if
13. | End of unique points in full pathway $\tilde{\gamma} = \min_{\gamma_i}$
14. | New Vessel $v = U(k$ to $\tilde{\gamma})$
15. end for
Algorithm 2: Find network and connectivity

1: Call Function
2: | Inputs: Current network vector $N_{old}$, the vector of unidentified vessels $U$, the current generation increment $g_i$, the current vessel number $v_j$, and the current parent end node of interest $n^p$.
3: | for $i = 1$ to the size of $U$ do
4: | | if the start of the vessel in $U_i$ matches $n^p$
5: | | | Save $U_i$ as a daughter branch of vessel $v_j$ in $\tilde{U}_i$
6: | | end if
7: | end for
8: | if $\tilde{U}_i = \emptyset$
9: | | Construct the new network vector $N_{new} = N_{old} \cup U_i$
10: | | Construct the new vector of unidentified vessels $U^* = U / \tilde{U}_i$
11: | for $k = 1$ to the size of $\tilde{U}_i$
12: | | Set $g_{i+1} = g_i + 1$ and $v_{j+1} = v_j + 1$
13: | | Set $n^{p+1}$ to the end node in $\tilde{U}_i^k$
14: | | call Algorithm 2 with $N_{new}, U^*, g_{i+1}, v_{j+1}$, and $n^{p+1}$.
15: | end for
16: end function
APPENDIX B

For the density estimation procedure, the maximum likelihood objective function for the leave-one-out cross validation (MLCV) is

$$\begin{align*}
H_{MLCV} &= \max_{H>0} \left( \frac{1}{n} \sum_{i=1}^{n} \log \left( \sum_{j=1}^{n} K\left( \frac{X_j - X_i}{H} \right) \right) - \log((n - 1)H) \right) \tag{B1}
\end{align*}$$

which provides the MLCV bandwidth parameter $H_{MLCV}$. For the Gaussian process, several covariance functions are available (e.g. squared exponential, Matérn, neural network, etc.) which control the degree of smoothness and non-stationarity of the functions. These covariance functions depend on unknown hyperparameters, which define typical length scales (corresponding to the bandwidth in KDE) over which function variations are expected, function amplitudes, and observational noise levels (69). The nonstationary neural network covariance kernel used for the covariance function in Eq. (12) is defined as

$$\begin{align*}
\kappa(x_i,x_j) &= \frac{2}{\pi} \arcsin \left( \frac{2\bar{X}_i^T \Sigma \bar{X}_j}{(1 + 2\bar{X}_i^T \Sigma \bar{X}_i)(1 + 2\bar{X}_j^T \Sigma \bar{X}_j)} \right) \tag{B2}
\end{align*}$$

where $\bar{X} = (1, X_1, ..., X_d)^T$ is an input vector of covariates with an inserted 1 in the first entry. The covariance for the weight parameters $\Sigma = \text{diag}(\sigma_0^2, \sigma_1^2, ..., \sigma_n^2)$ is a diagonal weight prior, where $\sigma_0^2$ is a variance for the bias parameter controlling the functions offset from the origin and the variances for the weight parameters are $\sigma_1^2, \sigma_2^2, ..., \sigma_n^2$. Small values of these variances generate smooth functions, whereas large values increase the flexibility of the GP. The diagonal elements of the matrix $\Sigma$ were the covariance hyperparameters $\Theta$, which were found via maximization of the marginal likelihood.
APPENDIX C

The GPs for the heteroscedastic regression used the Matérn covariance function (69) with a smoothness parameter \( \nu = 5/2 \). The covariance function was given as

\[
k_\nu(x_i, x_j) = \alpha^2 \frac{2^{1-\nu}}{\Gamma(\nu)} (r\sqrt{2\nu})^\nu K_\nu(r\sqrt{2\nu}), \quad r = \left( \sum_{k=1}^{d} \frac{(x_{i,k} - x_{j,k})^2}{\ell_k^2} \right)^{1/2}
\]  

(C1)

where the parameter \( \nu \) governs the smoothness of the process (e.g. \( k_\nu \) in Eq. (C1)) is \( \nu - 1 \) times differentiable) and \( K_\nu \) is a modified Bessel function (1). The hyperparameters \( \alpha^2 \) and \( \ell_k \) denote the amplitude and parameter length scale, respectively, which are estimated using maximum likelihood.
TABLES:

Table 1: Summary of pre-segmentation parameters and network features

| Pre-segmentation parameters ($\theta_1$, $\theta_2$) | Number of vessels | Number of generations | Number of terminal vessels | Total volume |
|--------------------------------------------------|-------------------|-----------------------|-----------------------------|--------------|
| (22, 5.0)                                        | 276               | 15                    | 149                         | 21.0871      |
| (25, 6.0)                                        | 422               | 17                    | 226                         | 21.3407      |
| (26, 4.7)                                        | 415               | 17                    | 219                         | 22.3524      |
| (26, 4.8)                                        | 425               | 18                    | 227                         | 22.8591      |
| (26, 5.1)                                        | 441               | 17                    | 234                         | 22.7031      |
| (27, 5.8)                                        | 450               | 17                    | 240                         | 22.9599      |
| (28, 6.0)                                        | 333               | 15                    | 178                         | 20.6542      |
| (30, 4.6)                                        | 428               | 16                    | 230                         | 21.7283      |
| (30, 5.7)                                        | 461               | 17                    | 245                         | 23.0039      |
| (30, 6.5)                                        | 476               | 18                    | 252                         | 23.1922      |
| (30, 8.0)                                        | 409               | 16                    | 220                         | 21.7642      |
| (31, 5.6)                                        | 462               | 18                    | 246                         | 23.3346      |
| (31, 6.1)                                        | 310               | 15                    | 164                         | 18.2311      |
| (32, 4.1)                                        | 419               | 16                    | 220                         | 22.2851      |
| (33, 4.2)                                        | 446               | 18                    | 239                         | 23.0664      |
| (33, 5.1)                                        | 505               | 18                    | 269                         | 24.6089      |
| (34, 3.3)                                        | 495               | 18                    | 265                         | 24.1804      |
| (34, 3.4)                                        | 474               | 17                    | 257                         | 24.2923      |
| (35, 3.6)                                        | 459               | 17                    | 242                         | 23.2488      |
| (35, 4.8)                                        | 470               | 17                    | 250                         | 23.0868      |
| (35, 6.8)                                        | 404               | 17                    | 214                         | 22.7536      |
| (36, 4.0)                                        | 419               | 17                    | 226                         | 22.0391      |
| (36, 4.1)                                        | 376               | 16                    | 197                         | 22.5833      |
| (37, 3.9)                                        | 409               | 17                    | 221                         | 21.6596      |
| (44, 7.6)                                        | 185               | 12                    | 98                          | 20.4368      |
Table 2: Results for simulations studying total variation, variation due to length and radius parameters, and variation due to network size and connectivity.

| Pressure (mmHg) | Total variation | Mean pressure (SD) | Systolic pressure (SD) | Diastolic pressure (SD) | Pulse pressure (SD) |
|-----------------|-----------------|--------------------|------------------------|------------------------|---------------------|
| MPA             |                 | 20.36 (0.78)       | 35.35 (1.63)           | 10.02 (0.27)           | 25.33 (1.39)        |
| LPA             |                 | 19.66 (0.79)       | 33.46 (1.67)           | 10.00 (0.27)           | 23.45 (1.43)        |
| RPA             |                 | 19.52 (0.78)       | 32.83 (1.60)           | 10.10 (0.28)           | 22.74 (1.34)        |

| Length and radius variation | Mean pressure (SD) | Systolic pressure (SD) | Diastolic Pressure (SD) | Pulse Pressure (SD) |
|-----------------------------|--------------------|------------------------|-------------------------|---------------------|
| MPA                         | 20.38 (0.54)       | 35.37 (1.03)           | 10.04 (0.23)            | 25.33 (0.82)        |
| LPA                         | 19.68 (0.53)       | 33.46 (0.99)           | 10.02 (0.23)            | 23.43 (0.78)        |
| RPA                         | 19.56 (0.50)       | 33.46 (0.90)           | 10.11 (0.24)            | 22.80 (0.69)        |

| Connectivity variation | Mean pressure (SD) | Systolic pressure (SD) | Diastolic Pressure (SD) | Pulse Pressure (SD) |
|------------------------|--------------------|------------------------|-------------------------|---------------------|
| MPA                    | 18.29 (0.84)       | 31.70 (2.07)           | 9.08 (0.18)             | 22.63 (1.91)        |
| LPA                    | 17.44 (0.86)       | 29.34 (2.13)           | 9.08 (0.17)             | 20.27 (1.97)        |
| RPA                    | 17.31 (0.83)       | 28.71 (1.96)           | 9.15 (0.20)             | 19.56 (1.77)        |

| Flow (cm³/s) | Total variation | Mean flow (SD) | Max Flow (SD) | Min flow (SD) | Volume (SD) (cm³) |
|--------------|-----------------|----------------|---------------|---------------|-------------------|
| LPA          |                 | 0.142 (0.004)  | 0.447 (0.013) | -0.000 (0.000) | 0.016 (0.000)     |
| RPA          |                 | 0.027 (0.004)  | 0.113 (0.009) | -0.015 (0.004) | 0.003 (0.000)     |

| Length and radius variation | Mean flow (SD) | Max flow (SD) | Min flow (SD) | Volume (SD) |
|-----------------------------|----------------|---------------|---------------|-------------|
| LPA                         | 0.140 (0.001)  | 0.439 (0.006) | 0.000 (0.015) | 0.015 (0.000) |
| RPA                         | 0.029 (0.001)  | 0.119 (0.007) | -0.014 (0.002) | 0.003 (0.000) |

| Connectivity variation | Mean flow (SD) | Max flow (SD) | Min flow (SD) | Volume (SD) |
|------------------------|----------------|---------------|---------------|-------------|
| LPA                    | 0.141 (0.001)  | 0.447 (0.009) | -0.001 (0.001) | 0.016 (0.000) |
| RPA                    | 0.027 (0.001)  | 0.009 (0.010) | -0.014 (0.004) | 0.003 (0.000) |
REFERENCES

1. Abramowitz M, Stegun IA. Handbook of Mathematical Functions with Formulas, Graphs, and Mathematical Tables. Washington, DC: U.S. Department of Commerce, NIST, 1972.

2. Acosta S, Puelz C, Rivière B, Penny DJ, Brady KM, Rusin CG. Cardiovascular mechanics in the early stages of pulmonary hypertension: a computational study. Biomech Model Mechanobiol 16: 2093–2112, 2017.

3. Alastruey J, Parker KH, Pei O J, Sherwin SJ. Lumped Parameter Outflow Models for 1 - D Blood Flow Simulations : Effect on Pulse Waves and Parameter Estimation. Commun Comput Phys 4: 317–336, 2008.

4. Alastruey J, Siggers JH, Peiffer V, Doorly DJ, Sherwin SJ. Reducing the data: Analysis of the role of vascular geometry on blood flow patterns in curved vessels. Phys Fluids 24, 2012.

5. Antiga L, Ene-Iordache B, Remuzzi A. Computational geometry for patient-specific reconstruction and meshing of blood vessels from MR and CT angiography. IEEE Trans Med Imaging 22: 674–684, 2003.

6. Antiga L, Piccinelli M, Botti L, Ene-Iordache B, Remuzzi A, Steinman DA. An image-based modeling framework for patient-specific computational hemodynamics. Med Biol Eng Comput 46: 1097–1112, 2008.

7. Armato III SG, Sensakovic WF. Radiology and Surgery Original Investigations Automated Lung Segmentation for Thoracic CT : Impact on Computer -Aided Diagnosis. Comput. Radiol. Surg. (2004). doi: 10.1016/j.xacra.2004.06.005.

8. Arnold A, Battista C, Bia D, German YZ, Armentano RL, Tran H, Olufsen MS. Uncertainty Quantification in a Patient-Specific One-Dimensional Arterial Network Model: EnKF-Based Inflow Estimator. J Verif Valid Uncertain Quantif 2: 011002, 2017.

9. Ascha M, Renapurkar R, Tonelli A. A review of imaging modalities in pulmonary hypertension. Ann Thorac Med 12: 61, 2017.

10. Asl ME, Koohbanani NA, Frangi AF, Gooya A. Tracking and diameter estimation of retinal vessels using Gaussian process and Radon transform. J Med Imaging 4: 1, 2017.

11. Bordones AD, Leroux M, Kheyfets VO, Wu YA, Chen CY, Finol EA. Computational
Fluid Dynamics Modeling of the Human Pulmonary Arteries with Experimental Validation. *Ann Biomed Eng* 46: 1309–1324, 2018.

12. **Burrowes KS**. An anatomically-based mathematical model of the human pulmonary circulation. 1994, 2005.

13. **Burrowes KS, Hunter PJ, Tawhai MH, Kelly S**. Anatomically based finite element models of the human pulmonary arterial and venous trees including supernumerary vessels. *J Appl Physiol* 99: 731–738, 2005.

14. **Clark a R, Burrowes KS, Tawhai MH**. Contribution of serial and parallel microperfusion to spatial variability in pulmonary inter- and intra-acinar blood flow. *J Appl Physiol* 108: 1116–26, 2010.

15. **Colebank M, Qureshi MU, Olufsen MS**. Sensitivity analysis and uncertainty quantification of 1D models of the pulmonary circulation. 

16. **Davidoiu V, Hadjilucas L, Teh I, Smith NP, Schneider JE, Lee J**. Evaluation of noise removal algorithms for imaging and reconstruction of vascular networks using micro-CT. *Biomed Phys Eng Express* 2: 045015, 2016.

17. **Duin RPW**. On the Choice of Smoothing Parameters for Parzen Estimators of Probability Density Functions. *IEEE Trans Comput* : 1175–1179, 1975.

18. **Dumas L, El Bouti T, Lucor D**. A Robust and Subject-Specific Hemodynamic Model of the Lower Limb Based on Noninvasive Arterial Measurements. *J Biomech Eng* 139: 011002, 2016.

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

20. **Epstein S, Willemet M, Chowienczyk PJ, Alastruey J**. Reducing the number of parameters in 1D arterial blood flow modeling: less is more for patient-specific simulations. *Am J Physiol Circ Physiol* 309: H222–H234, 2015.

21. **Epstein S, Willemet M, Chowienczyk PJ, Alastruey J**. Reducing the number of parameters in 1D arterial blood flow modeling: less is more for patient-specific simulations. *Am J Physioalogy-Heart Circ Physiol* 309: H222–H234, 2015.

22. **Feldkamp, L. A., Davis LC, Kress JW**. Practical cone-beam algorithm. *J Opt Soc Am A* 1: 612–619, 1984.
23. Fortmann-Roe S, Starfield R, Getz WM. Contingent kernel density estimation. *PLoS One* 7, 2012.

24. Galiè N, Humbert M, Vachiery J-L, Gibbs S, Lang I, Torbicki A, Simonneau G, Peacock A, Vonk Noordegraaf A, Beghetti M, Ghofrani A, Gomez Sanchez MA, Hansmann G, Klepetko W, Lancellotti P, Matucci M, McDonagh T, Pierard LA, Trindade PT, Zompatori M, Hoeper M. 2015 ESC/ERS Guidelines for the diagnosis and treatment of pulmonary hypertension. *Eur Heart J* 37: 67–119, 2016.

25. Gamilov T, Ivanov Y, Kopylov P, Simakov S, Vassilevski Y. Patient Specific Haemodynamic Modeling after Occlusion Treatment in Leg. *Math Model Nat Phenom* 9: 85–97, 2014.

26. Gandhi S a., Singal a., Gadela N, Kelner H, Carlson C, Pritzker M, Thenappan T. Comparison of Pulmonary Artery (PA) Wave Reflections in Pulmonary Arterial Hypertension (PAH) and Pulmonary Hypertension Due to Heart Failure With Preserved Ejection Fraction (PH-HFpEF). *J Hear Lung Transplant* 34: S118–S119, 2015.

27. Goldberg P, Williams C, Bishop C. Regression with input-dependent noise: A gaussian process treatment [Online]. *Adv Neural Inf Process Syst* 10: 493–499, 1997. http://eprints.aston.ac.uk/1219/.

28. Gounley J, Vardhan M, Randles A. A Computational Framework to Assess the Influence of Changes in Vascular Geometry on Blood Flow. *Proc. Platf. Adv. Sci. Comput. Conf.* (2017). doi: 10.1145/3093172.3093227.

29. Grzelak LA, Witteveen JAS, Suárez-Taboada M, Oosterlee CW. The stochastic collocation Monte Carlo sampler: highly efficient sampling from ‘expensive’ distributions. *Quant. Financ.* (2015). doi: 10.1080/14697688.2018.1459807.

30. Guidoum AC. Kernel Estimator and Bandwidth Selection for Density and its Derivatives. 1–22, 2015.

31. Haeck MLA, Vliegen HW. Diagnosis and treatment of pulmonary hypertension. 

32. Helmberger M, Pienn M, Urschler M, Kullnig P, Stollberger R, Kovacs G, Olschewski A, Olschewski H, Bálint Z. Quantification of tortuosity and fractal dimension of the lung vessels in pulmonary hypertension patients. *PLoS One* 9, 2014.

33. Horsfield K. SOME MATHEMATICAL PROPERTIES OF BRANCHING TREES WITH APPLICATION TO THE RESPIRATORY SYSTEM Midhurst Medical Research
Institute, The branching trees formed by rivers were first studied mathematically by Gravelius (1914), and subsequently by Herren (194...)

34. van Horssen P, van Lier MG, van den Wijngaard JP, VanBavel E, Hoefer IE, Spaan JA, Siebes M. Influence of segmented vessel size due to limited imaging resolution on coronary hyperemic flow prediction from arterial crown volume. *Am J Physiol Circ Physiol* 310: ajpheart.00728.2015, 2016.

35. Howard LS, Grapsa J, Dawson D, Bellamy M, Chambers JB, Masani ND, Nihoyannopoulos P, Gibbs JSR. Echocardiographic assessment of pulmonary hypertension: Standard operating procedure. *Eur Respir Rev* 21: 239–248, 2012.

36. Huang W, Yen RT, McLaurine M, Bledsoe G. Morphometry of the human pulmonary vasculature. *J Appl Physiol* 81: 2123–2133, 1996.

37. Huberts W, Donders WP, Delhaas T, van de Vosse FN. Applicability of the polynomial chaos expansion method for personalization of a cardiovascular pulse wave propagation model. *Int j numer method biomed eng* 30: 1679–1704, 2014.

38. Hughes AD, Parker KH. Forward and backward waves in the arterial system: Impedance or wave intensity analysis? *Med Biol Eng Comput* 47: 207–210, 2009.

39. Hunter KS, Lammers SR, Shandas R. Pulmonary vascular stiffness: measurement, modeling, and implications in normal and hypertensive pulmonary circulations. *Compr Physiol* 1: 1413–1435, 2011.

40. Huo Y, Kassab GS. Intraspecific scaling laws of vascular trees. *J R Soc Interface* 9: 190–200, 2012.

41. Itu L, Sharma P, Suciu C, Moldoveanu F, Comaniciu D. Personalized blood flow computations: A hierarchical parameter estimation framework for tuning boundary conditions. *Int. j. numer. method. biomed. eng.* (2017). doi: 10.1002/cnm.2803.

42. Jiang ZL, Kassab GS, Fung YC. Diameter-defined Strahler system and connectivity matrix of the pulmonary arterial tree. *J Appl Physiol* 76: 882–892, 1994.

43. Jones MC, Henderson DA. Maximum likelihood kernel density estimation. .

44. Kheyfets VO, Rios L, Smith T, Schroeder T, Mueller J, Murali S, Lasorda D, Zikos A, Spotti J, Reilly JJ, Finol EA. Patient-specific computational modeling of blood flow in the pulmonary arterial circulation. *Comput Methods Programs Biomed* 120: 88–101, 2015.
45. **Kind T, Faes TJC, Vonk-Noordegraaf A, Westerhof N.** Proportional Relations Between Systolic, Diastolic and Mean Pulmonary Artery Pressure are Explained by Vascular Properties. *Cardiovasc Eng Technol* 2: 15–23, 2011.

46. **Kline TL, Zamir M, Ritman EL.** Accuracy of microvascular measurements obtained from micro-CT images. *Ann Biomed Eng* 38: 2851–2864, 2010.

47. **Krenz GS, Dawson CA.** Flow and pressure distributions in vascular networks consisting of distensible vessels. *Am J Physiol Circ Physiol* 284: H2192–H2203, 2003.

48. **Lang IM, Plank C, Sadushi-Kolici R, Jakowitsch J, Klepetko W, Maurer G.** Imaging in pulmonary hypertension. *JACC Cardiovasc Imaging* 3: 1287–1295, 2010.

49. **Lê M, Unkelbach J, Ayache N, Delingette H.** Sampling image segmentations for uncertainty quantification. *Med Image Anal* 34: 42–51, 2016.

50. **Leach MO, Morgan B, Tofts PS, Buckley DL, Huang W, Horsfield MA, Chenevert TL, Collins DJ, Jackson A, Lomas D, Whitcher B, Clarke L, Plummer R, Judson I, Jones R, Alonzi R, Brunner T, Koh DM, Murphy P, Waterton JC, Parker G, Graves MJ, Scheenen TWJ, Redpath TW, Orton M, Karczmar G, Huisman H, Barentsz J, Padhani A.** Imaging vascular function for early stage clinical trials using dynamic contrast-enhanced magnetic resonance imaging. *Eur Radiol* 22: 1451–1464, 2012.

51. **Lee P, Carlson BE, Chesler NC, Olufsen MS, Qureshi MU, Smith NP, Sochi T, Beard DA.** Heterogeneous mechanics of the mouse pulmonary arterial network. *Biomech Model Mechanobiol* 15: 1245–1261, 2016.

52. **Lewandowski CM.** The CFL condition. 2015.

53. **Marsden AL.** Optimization in Cardiovascular Modeling. *Annu Rev Fluid Mech* 46: 519–546, 2014.

54. **Melis A, Clayton RH, Marzo A.** Bayesian sensitivity analysis of a 1D vascular model with Gaussian process emulators. *Int J Numer Method Biomed Eng* 33: 1–11, 2017.

55. **Miyawaki S, Tawhai MH, Hoffman EA, Wenzel SE, Lin CL.** Automatic construction of subject-specific human airway geometry including trifurcations based on a CT-segmented airway skeleton and surface. *Biomech Model Mechanobiol* 16: 583–596, 2017.

56. **Molthen RC, Karau KL, Dawson CA.** Quantitative models of the rat pulmonary arterial tree morphometry applied to hypoxia-induced arterial remodeling. *J Appl Physiol* 97: 2372–2384; discussion 2354, 2004.
57. Moore JA, Steinman DA, Holdsworth DW, Ethier CR. Accuracy of computational hemodynamics in complex arterial geometries reconstructed from magnetic resonance imaging. *Ann Biomed Eng* 27: 32–41, 1999.

58. Mynard JP, Smolich JJ. One-Dimensional Haemodynamic Modeling and Wave Dynamics in the Entire Adult Circulation. *Ann Biomed Eng* 43: 1443–1460, 2015.

59. Nakanishi R, Sankaran S, Grady L, Malpeso J, Yousfi R, Osawa K, Ceponiene I, Nazarat N, Rahmani S, Kissel K, Jayawardena E, Dailing C, Zarins C, Koo B-K, Min JK, Taylor CA, Budoff MJ. Automated estimation of image quality for coronary computed tomographic angiography using machine learning. *Eur. Radiol.* (2018). doi: 10.1007/s00330-018-5348-8.

60. Olufsen MS, Hill NA, Vaughan GDA, Sainsbury C, Johnson M. Rarefaction and blood pressure in systemic and pulmonary arteries. *J Fluid Mech* 705: 280–305, 2012.

61. Olufsen MS, Peskin CS, Kim WY, Pedersen EM, Nadim A, Larsen J. Numerical simulation and experimental validation of blood flow in arteries with structured-tree outflow conditions. *Ann Biomed Eng* 28: 1281–1299, 2000.

62. Paun LM, Qureshi MU, Colebank M, Hill NA, Olufsen MS, Haider MA, Husmeier D. MCMC methods for inference in a mathematical model of pulmonary circulation. *Stat Neerl* : 1–33, 2018.

63. Payer C, Pienn M, Bálint Z, Shekhovtsov A, Talakic E, Nagy E, Olschewski A, Olschewski H, Urschler M. Automated integer programming based separation of arteries and veins from thoracic CT images. *Med Image Anal* 34: 109–122, 2016.

64. Quarteroni A, Veneziani A, Vergara C. Geometric multiscale modeling of the cardiovascular system, between theory and practice. *Comput Methods Appl Mech Eng* 302: 193–252, 2016.

65. Qureshi MU, Colebank M, Paun M, Ellwein L, Chesler N, Haider MA, Hill NA, Husmeier D, Olufsen MS. Hemodynamic assessment of pulmonary hypertension in mice: a model based analysis of the disease mechanism. *Biomech. Model. Mechanobiol.* (2017). doi: 10.1007/s10237-018-1078-8.

66. Qureshi MU, Colebank M, Paun M, Ellwein LM, Chesler N, Haider MA, Hill NA, Husmeier D, Olufsen MS. A computational study of pulmonary hemodynamics in healthy and hypoxic mice [Online]. http://arxiv.org/abs/1712.01699.
67. **Qureshi MU, Hill NA.** A computational study of pressure wave reflections in the pulmonary arteries. *J Math Biol* 71: 1525–1549, 2015.

68. **Qureshi MU, Vaughan GDA, Sainsbury C, Johnson M, Peskin CS, Olufsen MS, Hill NA.** Numerical simulation of blood flow and pressure drop in the pulmonary arterial and venous circulation. *Biomech Model Mechanobiol* 13: 1137–1154, 2014.

69. **Rasmussen CE, Williams CKI.** Gaussian processes for machine learning.

70. **Rempfler M, Andres B, Menze BH.** Graphs in Biomedical Image Analysis, Computational Anatomy and Imaging Genetics. 10551: 42–52, 2017.

71. **Reymond P, Merenda F, Perren F, Ru D.** Validation of a One-Dimensional Model of the Systemic Arterial Tree. *Am J Physiol Circ Physiol* 297: 208–222, 2009.

72. **Rich JD, Rich S.** Clinical diagnosis of pulmonary hypertension. *Circulation* 130: 1820–1830, 2014.

73. **Riches AC, Sharp JG, Thomas DB, Smith S V.** Blood volume determination in the mouse. *J Physiol* 228: 279–284, 1973.

74. **Riihimäki J, Vehtari A.** Laplace approximation for logistic gaussian process density estimation and regression. *Bayesian Anal* 9: 425–448, 2014.

75. **Van Rikxoort EM, Van Ginneken B.** Automated segmentation of pulmonary structures in thoracic computed tomography scans: A review. *Phys Med Biol* 58, 2013.

76. **Ritman EL.** Micro-Computed Tomography of the Lungs and Pulmonary-Vascular System. *Proc Am Thorac Soc* 2: 477–480, 2005.

77. **Rivolo S, Hadjilucas L, Sinclair M, van Horssen P, van den Wijngaard J, Wesolowski R, Chiribiri A, Siebes M, Smith NP, Lee J.** Impact of coronary bifurcation morphology on wave propagation. *Am J Physiol Circ Physiol* 311: H855–H870, 2016.

78. **Rol N, Timmer EM, Faes TJC, Noordegraaf AV, Grünberg K, Bogaard HJ, Westerhof N.** Vascular narrowing in pulmonary arterial hypertension is heterogeneous: rethinking resistance. *Physiol Rep* 5: 1–9, 2017.

79. **Romarowski RM, Lefieux A, Morganti S, Veneziani A, Auricchio F.** Patient-specific CFD modelling in the thoracic aorta with PC-MRI-based boundary conditions: A least-square three-element Windkessel approach. *Int j numer method biomed eng : e3134*, 2018.

80. **Rousseeuw PJ, Croux C.** Alternatives to the Median Absolute Deviation. *J Am Stat Assoc* 88: 1273–1283, 1993.
81. **Sankaran S, Grady L, Taylor CA.** Impact of geometric uncertainty on hemodynamic simulations using machine learning. *Comput Methods Appl Mech Eng* 297: 167–190, 2015.

82. **Sankaran S, Grady L, Taylor CA.** Fast Computation of Hemodynamic Sensitivity to Lumen Segmentation Uncertainty. *IEEE Trans Med Imaging* 34: 2562–2571, 2015.

83. **Sankaran S, Jin H, Choi G, Taylor CA.** Uncertainty quantification in coronary blood flow simulations: Impact of geometry, boundary conditions and blood viscosity. 49: 2540–2547, 2016.

84. **Sankaran S, Kim HJ, Choi G, Taylor CA.** Uncertainty quantification in coronary blood flow simulations: Impact of geometry, boundary conditions and blood viscosity. *J Biomech* 49: 2540–2547, 2016.

85. **Sankaran S, Marsden AL.** A Stochastic Collocation Method for Uncertainty Quantification and Propagation in Cardiovascular Simulations. *J Biomech Eng* 133: 031001, 2011.

86. **Schiavazzi, D. E., Arbia G, Baker C, Hlavacek AM, Hsia TY, Marsden AL, Vignon-Clementel IE, Investigators TM of CHA.** Uncertainty quantification in virtual surgery hemodynamics predictions for single ventricle palliation. : 1–25, 2016.

87. **Schillaci G, Pirro M, Mannarino E.** Assessing cardiovascular risk should we discard diastolic blood pressure? *Circulation* 119: 210–212, 2009.

88. **Sherwin SJ, Franke V, Peiró J, Parker K.** One-dimensional modelling of a vascular network in space-time variables. *J Eng Math* 47: 217–250, 2003.

89. **Silverman BW.** *Density Estimation for Statistics and Data Analysis*. Boca Raton, FL: Chapman & Hall/CRC Press, 1998.

90. **Spilker RL, Feinstein JA, Parker DW, Reddy VM, Taylor CA.** Morphometry-based impedance boundary conditions for patient-specific modeling of blood flow in pulmonary arteries. *Ann Biomed Eng* 35: 546–559, 2007.

91. **Steinman DA, Taylor CA.** Flow imaging and computing: Large artery hemodynamics. *Ann Biomed Eng* 33: 1704–1709, 2005.

92. **Stergiopulos N, Meister JJ, Westerhof N.** Evaluation of methods for estimation of total arterial compliance. *Am J Physiol* 268: H1540-8, 1995.

93. **Su L, Zhao Y, Yan T, Li F.** Local Polynomial Estimation of Heteroscedasticity in a
Multivariate Linear Regression Model and Its Applications in Economics. *PLoS One* 7, 2012.

94. **Swift AJ, Wild JM, Nagle SK, François CJ, Fain S, Johnson K, Capener D, Beek EJR Van, Kiely DG.** Quantitative MR imaging of pulmonary hypertension: A practical approach to the current state of the art. *J Thorac Imaging* 29: 68–79, 2014.

95. **Tabima DM.** Persistent vascular collagen accumulation alters hemodynamic recovery from chronic hypoxia. *J Biomech* 45: 799–804, 2013.

96. **Tawhai MH, Clark AR, Burrowes KS.** Computational Models of the Pulmonary Circulation: Insights and the Move towards Clinically Directed Studies. *Pulm Circ* 1: 224–238, 2011.

97. **Taylor CA, Steinman DA.** Image-based modeling of blood flow and vessel wall dynamics: Applications, methods and future directions: Sixth international bio-fluid mechanics symposium and workshop, March 28-30, 2008 Pasadena, California. *Ann Biomed Eng* 38: 1188–1203, 2010.

98. **Toro EF.** Brain venous haemodynamics, neurological diseases and mathematical modelling. A review. *Appl Math Comput* 272: 542–579, 2016.

99. **Townsley MI.** Structure and composition of pulmonary arteries, capillaries, and veins. *Compr Physiol* 2: 675–709, 2012.

100. **Tran JS, Schiavazzi DE, Ramachandra AB, Kahn AM, Marsden AL.** Automated tuning for parameter identification and uncertainty quantification in multi-scale coronary simulations. *Comput Fluids* 142, 2017.

101. **Utkarsh A.** *The Paraview Guide: A Parallel Visualization Application*. USA: Kitware, Inc., 2015.

102. **VanBavel E, Spaan JAE.** Branching patterns in the porcine coronary arterial tree: Estimation of flow heterogeneity. *Circ Res* 71: 1200–1212, 1992.

103. **Vanderpool RR, Kim AR, Molthen RC, Chesler NC.** Effects of acute Rho kinase inhibition on chronic hypoxia-induced changes in proximal and distal pulmonary arterial structure and function Effects of acute Rho kinase inhibition on chronic hypoxia-induced changes in proximal and distal pulmonary arterial. 1609: 188–198, 2014.

104. **Vanhatalo J, Riihimäki J, Hartikainen J, Jylänki P, Tolvainen V, Vehtari A.** GPstuff: Bayesian Modeling with Gaussian Processes [Online]. *J Mach Learn Res* 14: 1175–1179,
105. Veneziani A, Vergara C. Inverse problems in Cardiovascular Mathematics: toward patient-specific data assimilation and optimization. *Int j numer method biomed eng* 29: 723–725, 2013.

106. Vennin S, Mayer A, Li Y, Fok H, Clapp B, Alastruey J, Chowienczyk P. Non-invasive calculation of the aortic blood pressure waveform from the flow velocity waveform: a proof of concept. *Am. J. Physiol. Circ. Physiol.* (2015). doi: 10.1152/ajpheart.00152.2015.

107. van de Vosse FN, Stergiopulos N. Pulse Wave Propagation in the Arterial Tree. *Annu Rev Fluid Mech* 43: 467–499, 2011.

108. Weckenmann A, Krämer P. Assessment of measurement uncertainty caused in the preparation of measurements using computed tomography. *19th IMEKO World Congr 2009* 3: 1787–1791, 2009.

109. Westerhof N, Lankhaar JW, Westerhof BE. The arterial windkessel. *Med Biol Eng Comput* 47: 131–141, 2009.

110. Windberger U, Bartholovitsch A, Plasenzetti R, Korak KJ, Heinze G. Whole blood viscosity, plasma viscosity and erythrocyte aggregation in nine mammalian species: Reference values and comparison of data. *Exp Physiol* 88: 431–440, 2003.

111. Xiu D, Sherwin SJ. Parametric uncertainty analysis of pulse wave propagation in a model of a human arterial network. *J Comput Phys* 226: 1385–1407, 2007.

112. Yushkevich PA, Gao Y, Gerig G. ITK-SNAP: An interactive tool for semi-automatic segmentation of multi-modality biomedical images. *Proc Annu Int Conf IEEE Eng Med Biol Soc EMBS 2016–Octob* 3342–3345, 2016.

113. Yushkevich PA, Piven J, Hazlett HC, Smith RG, Ho S, Gee JC, Gerig G. User-guided 3D active contour segmentation of anatomical structures: Significantly improved efficiency and reliability. *Neuroimage* 31: 1116–1128, 2006.
Figure 1: Flowchart of methods using in this paper. Hemodynamic and imaging data are integrating in inverse and forward uncertainty quantification methods. Results from these methods are then analyzed.
Figure 2: Screenshot from ITK-SNAP graphical user interface (GUI). The voxel intensities are mapped to a histogram where users can adjust parameters to provide different foreground and background levels. Adjusting the thresholding and smoothness parameters changes the threshold function (red curve). The threshold function maps all intensities to a probability map, where a value of 1 indicates foreground and a value of 0 indicates the background.
Fig. 3: Qualitative differences in changing the lower threshold ($\theta_1$) and smoothing parameter ($\theta_2$) for the same slice of a micro-CT image. Top: Changes in lower thresholding parameter show that increasing its value decreases the number of voxels included (from a to b), while decreasing the lower threshold increases the number of voxels included (a to c). Bottom: Increasing the smoothing parameter from 3 to 5 shows an increase in the number of voxels included at the boundary of the vessels seen in white while decreasing the smoothness parameter to 1.5 shows an increase in the number of background voxels, which gives a black edging to the vessels.
Figure 4: Example network in four stages. (a) The vascular tissue as seen from the micro-CT image; (b) the segmented image; (c) centerlines constructed from the segmented image; (d) vessels labeled after passing the centerlines through Algorithm 1 and 2. The multiple colors in (d) illustrate the different vessels in the tree.
Figure 5: (a) Truncated network with 32 vessels, with a focus on one of the mouse’s arteries (in red); (b) truncated network with maximally inscribed sphere cross sections; (c) magnified view of a left pulmonary artery; (d) radius plots for multiple segmentations in the vessel shown in (b) and (c). Note that the radius estimates have similar behavior leaving the ostium region across segmentations but show variation in radius estimates over the length of the vessel.
Figure 6: Morphometric features from 25 segmentations, given by different colored plot lines. The number of vessels (a) is consistent between segmentations until the 5th generation. The average volume (b) decreases rapidly after the 1st generation of vessels while the total volume (c) is more volatile from segmentation to segmentation. The segmentation parameters used are plotted against each other in (d).
Figure 7: Density Estimates ((a) and (b)) and inverse cumulative distribution functions ( (c) and (d) ) for the standardized radius and length values measured in the proximal vasculature. The bandwidth parameters used for the length and radius KDEs were determined using Scott’s rule (black curve) and Maximum Likelihood Cross-Validation (MLCV, red curve). The Gaussian process (GP) mean and 95% credible interval are included as well (black curve and grey bands, respectively).
Figure 8: Gaussian Process (GP) regression using nonconstant variance between length (top) and radius (bottom) for coefficient of variation ($c_v$). The GP mean and standard deviations are computed from the $c_v$ data obtained from the 32-vessel truncated network (red asterisks) and plotted against the analytical bound of the image resolution (blue, dash-dot curve). The mean of the GPs and ± one and two SDs from the mean are shown in black, dark grey, and light grey, respectively ((a) and (c)). The variance of the GPs ((b) and (d)) are predicted using an additional GP and provide a mean (black) and variance (red dash-dot) for the variance estimate.
Figure 9: Simulated pressure and flow waveforms at the proximal location of the first bifurcation ((a) and (d), MPA, (b) and (e) LPA, and (c) and (f) RPA) in the network for all 25 segmentations. The representative network is shown in cyan, while black curves denote the mean values at each time point and red dotted curves represented two standard deviations from the mean. The flow in the MPA is used as the inflow, hence its variability is minimal.
Figure 10: Predicted pressure and flow profiles in the MPA ((a) and (d)), LPA ((b) and (e)), and RPA ((c) and (f)) for 10,000 realization of radius and length. The simulations are plotted along with the mean value and one SD from the mean.
Figure 11: Pressure predictions in the first pulmonary bifurcation with different numbers of modeled vessels. The largest network includes 109 vessels while the smallest network consisted of only the main, left, and right pulmonary arteries (MPA, LPA, and RPA, respectively). In general, the larger networks yielded larger pressure predictions (in brightest red) while smaller networks produced the smallest pressure predictions (black) using nominal estimates.