One-dimensional modeling of fractional flow reserve in coronary artery disease: Uncertainty quantification and Bayesian optimization

Minglang Yin\textsuperscript{a,b}, Alireza Yazdani\textsuperscript{c}, George Em Karniadakis\textsuperscript{c,}\textsuperscript{*}

\textsuperscript{a} Center for Biomedical Engineering, Brown University, Providence, RI, 02912, USA
\textsuperscript{b} School of Engineering, Brown University, Providence, RI, 02912, USA
\textsuperscript{c} Division of Applied Mathematics, Brown University, Providence, RI, 02912, USA

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Highlights

- The nonlinear 1D FFR values are within 2% error of the 3D results for mean pressure and flow rates.
- The global sensitivity analysis signifies the high impact of the segmentation error in the stenosis lumen radius.
- Among the lumped network parameters, the aortic resistance accounts for most of the uncertainty in FFR.
- Multifidelity surrogate models along with Bayesian optimization is shown to be efficient in addressing parameter inference problems.

Abstract

Non-invasive estimation of fractional flow reserve (FFR) values, the key index in the diagnosis of obstructive coronary artery disease, is a promising alternative to traditional way of performing invasive coronary angiography. With the advances in computational fluid dynamics (CFD), one can estimate FFR based on the solution obtained in a reconstructed coronary geometry from coronary computed tomography (CT) angiography. However, the computational cost to perform three-dimensional (3D) simulations has limited the use of CFD in most clinical settings. This could become more restrictive if one aims to quantify the uncertainty associated with FFR calculations due to the uncertainty in anatomic and physiologic properties as a significant number of 3D simulations is required to sample a relatively large parametric space. We have developed a predictive probabilistic model of FFR, which quantifies the uncertainty of the predicted values with significantly lower computational costs. Based on global sensitivity analysis, we first identify the important physiologic and anatomic parameters that impact the predictions of FFR. Our approach is to employ one-dimensional blood flow simulations of coronary trees that offer fast FFR predictions with uncertainty quantification in computing blood pressure and flow distributions within the coronaries. This is complemented with a multifidelity algorithm that is used to infer their optimal values using available patient-specific clinical measurements.

Keywords: 1D/3D modeling; Bayesian optimization; Computational fluid dynamics; ANOVA sensitivity analysis; Gaussian process regression; Multifidelity modeling

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E-mail addresses: minglang_yin@brown.edu (M. Yin), alireza_yazdani@brown.edu (A. Yazdani), george_karniadakis@brown.edu (G.E. Karniadakis).
1. Introduction

Patients with coronary artery disease (CAD) suffer from plaque built up from fat or cholesterol on the arterial wall that leads to progressive narrowing of one or several coronary arteries. Blood flow through these narrowed vessels experiences sudden pressure drop, which could impede the oxygen transport from upstream oxygenated blood to downstream cardiac tissue. Upon plaque rupture, a large portion of myocardial tissue may become dysfunctional due to ischemic heart attack that could be triggered under certain circumstances such as exercise or other causes of hyperemia. Clinically, fractional flow reserve (FFR) in coronary artery disease patients has been shown to be the gold standard to assess the hemodynamic significance of a stenotic lesion [1]. FFR is defined as the maximal blood flow to the myocardium in a stenotic coronary artery, divided by the normal maximal flow in the same artery and it is estimated as the ratio of the mean distal coronary-artery pressure to the aortic pressure during maximal vasodilatation [1,2]. The traditional technique to acquire FFR in-vivo is invasive, where a catheter with a pressure sensor is inserted into the femoral artery or the radial artery, and is directed by angiography toward the site of the stenosis. The mean distal pressure around the stenosis and aortic pressure are measured and recorded separately and they are averaged during several cardiac cycles by a pullback procedure [3]. Considering the critical FFR value of 0.8 as a threshold for ischemia [2], cardiologists can decide on possible treatment, such as implanting drug-eluting stents or coronary bypass graft surgery.

The computed tomography (CT) and imaging reconstruction technology enable several non-invasive ways to visualize stenosed arteries, where based on simple evaluation an experienced cardiologist might be able to diagnose the severity of the stenosis. However, accurate predictions of FFR are noticeably difficult due to the nonlinear nature of the equations governing blood flow and the irregularity of artery shape with the relation between lumen diameter and FFR being elusive and complex. Clinical data show [4] that only 32% of patients exhibit ischemia among the patients with 70% stenosis. This weak correlation between ischemia and lumen diameter may encourage unnecessary FFR measurements using catheters given its invasive and expensive nature. Here, the severity of stenosis is defined as the ratio of reduction in lumen radius to the proximal lumen radius, for instance, a 70% stenosis yields a radius contracted to 30% of its original.

Non-invasive estimations of FFR with high accuracy, sensitivity, and specificity are fast growing. Thanks to the advancement of computational fluid dynamics (CFD) and CT image reconstruction, non-invasive FFR estimations with good accuracy have been developed [5,6]. The patient-specific 3D coronary artery geometry is reconstructed from CT images for which CFD simulations are performed given the patient-specific boundary conditions. This methodology has been proved to have high diagnostic accuracy for the significance of CAD compared with invasive FFR measurements [7,8]. Numerical solution of blood flow inside blood vessels is widely used to understand vascular hemodynamics: Taylor et al. [9] developed a numerical framework to construct smoothed vascular geometry and perform finite element analysis to calculate the flow field and visualize the key features from the data. Blood flow modeling also provides a non-invasive approach to assess blood flow in cerebral aneurysm [10] and intracranial vascular network [11]. Sen Gupta et al. [12] investigated the blood pressure and velocity in a patient-specific coronary artery tree with Kawasaki disease. Taylor et al. [13] and Marsden [14] provide several detailed reviews of CFD applications in biomechanics including the comparison of invasive FFR and patient-specific modeling.

In patient-specific coronary flow modeling, however, the accuracy of FFR computation does not solely depend on a specific numerical scheme, and other factors such as the reconstructed geometry, boundary condition values and patient-specific physiologic parameters such as blood viscosity and arterial wall compliance also affect the predictive capability of the numerical models. Any uncertainty in the aforementioned properties may cause variation in FFR values, which deems uncertainty quantification (UQ) necessary to assess the sensitivity of the computed FFR. Sankaran et al. [15,16] have quantified the uncertainties by varying a set of parameters such as lumped parameter network boundary conditions and the lumen diameter. Their studies showed that uncertainty in the minimum lumen diameter of the stenosis has the highest impact on the computed FFR followed by coronary lumped parameter network parameters, blood viscosity, and the lesion length. These studies were, however, limited by the computational power, and the coupling between each uncertain parameter was not fully understood from the results. In addition, few methods have been proposed for inferring the various parameters involved in coronary simulations such as the work by Tran et al. [17] that used a Bayesian method with adaptive Markov chain Monte Carlo sampling in the parameter design space and by Sharma et al. [18], who used a PID control system to calibrate the cardiac output and systemic resistance. Fossan et al. [19] show the validation of the accuracy of 1D model along with the
sensitivity analysis using their reduced-order model. Their results, based on the FFR analysis of 13 patients, indicate that the most influential parameter on FFR uncertainty is the segmentation error for patients that exhibit low FFR.

Regarding parameter inference, a few studies have addressed the calibration of the hemodynamic parameters in the vascular system such as systemic vascular resistance and left ventricular elasticity based on a surrogate model [20] or a zero-dimensional reduced-order model [21]. Spilker et al. [22] used a zero-dimensional circuit analogue model with quasi-Newton method to tune the boundary conditions for 3D hemodynamic simulations. This model was successfully applied to carotid artery, iliac arterial bifurcation and patient-specific abdominal aorta. Using a multifidelity Bayesian optimization algorithm, Perdikaris et al. considered a generic arterial bifurcation and inferred the Windkessel parameters for the terminal outlet conditions [23]. We will employ this method in the current study and extend it to patient-specific coronary flow modeling.

From a practical standpoint, solving the 3D Navier–Stokes equations taxes heavily computational resources, hence limiting its applicability in the clinical setting. Thus, seeking a robust reduced-order model for fast diagnosis, such as 1D blood flow modeling, has received more attention recently [24]. By formulating the Navier–Stokes equations in cylindrical coordinates and assuming dominance of axial velocity component, the Navier–Stokes equations reduce to a 1D nonlinear partial-differential equation system [25–27]. Blanco et al. [28] carried out 1D and 3D simulations over a moderately large sample of patients, where the computed FFR showed a very good agreement between 1D and 3D. The terminal resistance boundary conditions for coronary vessels were estimated based on the total coronary resistance that is distributed according to the Murray’s law. We investigate the robustness of 1D modeling with parameter uncertainty based on the probabilistic collocation method (PCM) [29], which quantifies the impact of each parameter independently on the computed FFR. Furthermore, we will employ a multifidelity optimization technique using available clinical measurements to infer the highly influential parameters (e.g. systemic resistance and capacitance) in the coronary flow modeling. Our objective in this work is to (a) verify the accuracy of 1D versus 3D simulations; (b) investigate the global sensitivity of the anatomic and physiologic parameters on the computed FFR; and (c) apply a multifidelity Bayesian optimization method to infer the optimal set of parameters.

The remainder of the paper is organized as follows. In Section 2, we present the 3D and 1D governing equations of blood flow, the stenosis model, boundary conditions, the UQ method, and Gaussian process regression models. In Section 3, we present the pressure and flow rate comparison of 3D versus 1D models in a healthy and stenotic coronary artery tree, followed by UQ analysis using the 1D model, and parameter inference. In Section 4, we conclude with the strength and limitations of our proposed method.

2. Methods

3D flow model

Blood flow in large arterioles and arteries of cardiovascular system can be treated as an incompressible, Newtonian flow with Reynolds number (Re) varying in the range of 100–1000. Considering a 3D coronary artery domain $\Omega$ with its boundary $\Gamma$, we seek the velocity $u$ and the pressure $p$, which satisfy the following Navier–Stokes and continuity equations

$$\rho(u_t + (u \cdot \nabla) u) = \nabla \cdot \sigma + f, \quad (x, t) \in \Omega \times (0, T),$$  \hspace{1cm} (1)

$$\nabla \cdot u = 0,$$ \hspace{1cm} (2)

where the fluid stress tensor $\sigma$, initial and boundary conditions are given as

$$\sigma = -pI + \mu(\nabla u + \nabla u^T),$$ \hspace{1cm} (3)

$$u(x, 0) = u_0(x), \quad x \in \Omega,$$ \hspace{1cm} (4)

$$u = g, \quad (x, t) \in \Gamma_g \times (0, T),$$ \hspace{1cm} (5)

$$u = 0, \quad x \in \Gamma_w,$$ \hspace{1cm} (6)

where $x$ is the position vector, $\mu$ is the blood viscosity, and the density $\rho$ is assumed to be constant in $\Omega$. $\Gamma_g$ denotes the boundary of $\Omega$ where a Womersley velocity profile is imposed at the inlet and Windkessel boundary conditions.
are imposed at each outlet. We assume no-slip condition on the arterial wall \( \Gamma_w \). The 3D Navier–Stokes equations are solved using the spectral/hp element method that leads to high-order spatial discretization [30].

**1D flow model**

The 3D governing equations can be reduced to a 1D system of equations assuming that velocity is predominantly along the vessel axis, i.e. \( \mathbf{u}(x, t) \equiv \{U(x, t), 0, 0\} \). The governing equations of the 1D system can be written in the following form

\[
\frac{\partial A}{\partial t} + \frac{\partial A U}{\partial x} = 0
\]

(7)

\[
\frac{\partial U}{\partial t} + \frac{1}{2} \frac{\partial U^2}{\partial x} + \frac{1}{\rho} \frac{\partial p}{\partial x} = -\frac{1}{\rho} (K_r \frac{U}{A} - S),
\]

(8)

where \( x \) is the axial coordinate along the vessel, \( A(x, t) \) and \( p(x, t) \) are the cross-sectional area and intraluminal pressure, respectively. Furthermore, \( K_r \) is the friction loss coefficient representing the viscous resistance of flow per unit length of the vessel, and \( S \) accounts for any tapering effect (contraction or expansion losses) along the vessel, which are written as

\[
K_r = \frac{2\alpha \mu \pi}{\alpha - 1}; \quad S = -\frac{\partial p}{\partial A} \frac{\partial A}{\partial x},
\]

(9)

where \( \alpha = 4/3 \) assuming a laminar blood flow with parabolic velocity profile through the vessels. To close the above system of 1D equations, Laplace’s law for the pressure-area relationship is written as the third equation

\[
p = p_{ext} + C_w \beta (\sqrt{A} - \sqrt{A_o}),
\]

(10)

where \( p_{ext} \) is a uniform external pressure, \( C_w \) is a constant coefficient and \( \beta \) characterizes the arterial wall compliance, which is defined as

\[
\beta = \frac{\sqrt{\pi} h E}{(1 - \nu^2) A_o},
\]

(11)

where \( \nu \) is the Poisson ratio taken as 0.5 for most incompressible biological tissues, \( h \) and \( A_o \) are the vessel wall thickness and undeformed cross sectional area, respectively, and \( E \) is the Young’s modulus of the arterial wall [25,31]. Normally, the variation of coronary artery lumen diameter due to the arterial wall compliance is about 5 to 10% during a cardiac cycle, which could also influence the pressure pulse waves throughout the coronaries [32]. Although wall elasticity and motion can be taken into account in a coupled fluid–structure interaction (FSI) framework, 3D FSI modeling could drastically increase the computational cost. Thus, we consider rigid walls for 1D–3D validation tests and throughout the rest of the paper, which can be achieved in the 1D model by simply setting a higher wall compliance coefficient \( C_w = 10 \). More numerical simulations for the validity of this assumption are provided in the Appendix.

**Stenosis model**

In the presence of a stenosis in vessels with CAD, there is typically a sudden contraction in the vessel which could trigger vortices and secondary flows downstream of the stenosis. Specifically, the radial velocity components are no longer negligible, leading to underestimation of the pressure drop through the stenosis based on the 1D equations. Therefore, to accurately estimate the pressure loss through a stenosis, an additional loss term using empirical correlations derived by Young et al. [33] has to be introduced to the momentum equation (2). This term is written as

\[
\Delta p = \frac{\mu K_v}{2\pi a_p^3} q + \frac{\rho K_t}{2A_p^2} (\frac{A_p}{A_S} - 1)^2 |q| q + \frac{\rho K_u L_s}{A_p} \frac{\partial q}{\partial t},
\]

(12)

where \( q \) is the flow rate, \( a_p \) and \( A_p \) are the proximal radius and cross sectional area of the vessel lumen, respectively, \( A_s \) is the minimum cross-sectional area at the throat of the stenosis, \( L_s \) is the length of the stenosis, and \( K_u, K_v \) and \( K_t \) are the constants defined as

\[
K_v = 16 \frac{L_s}{a_p} (\frac{A_p}{A_s})^2, \quad K_t = 1.52, \quad K_u = 1.2.
\]

(13)
Boundary conditions

A circuit analogue lumped parameter network is constructed to model coronary flow and pressure at each outlet. This approach consists of additive combinations of equivalent electrical elements, such as resistors R, capacitors C and inductors L that aim to capture the effective resistance, compliance and inertial effects of the neglected arterial networks, respectively [32,34]. The total coronary flow is known to be \( \approx 4\% \) of the cardiac output [32], while the flow percentages to the right and left coronaries are typically 40\% and 60\% of the total coronary flow, respectively [35]. The resting total coronary flow is distributed among the coronary vascular network following Murray’s law [36], which gives an empirical relationship between the vessel diameter \( d \) and the flow rate. More details on the lumped parameter network parameters for coronary outlets are given in Appendix. Furthermore, a patient-specific Womersley flow waveform is prescribed at the aortic inlet, whereas a three-element “Windkessel” (i.e. RCR) boundary conditions are applied to the other main outlets such as the aorta.

Uncertainty quantification

We employ a fast high-order algorithm, PCM, developed by Xiu et al. [29] to quantify the uncertainty in the computed FFR associated with random input parameters. The parameter space is sampled at collocation points generated by a sparse grid (Smolyak) [37] algorithm using a Gauss–Legendre quadrature rule in a proper physiological range.

The mean and standard deviation of the quantity of interest (QoI), i.e. the FFR, are then estimated by the following equations

\[
\bar{f}(x, t) = \sum_{i=1}^{N} f(x, t, \xi_i) \omega_i
\]

(14)

the standard deviation:

\[
\sigma(x, t) = \sqrt{\sum_{i=1}^{N} \left( \bar{f} - f(x, t, \xi_i) \right)^2 \omega_i}
\]

(15)

where \( \xi \) is the vector of the collocation points, \( \omega \) is the vector of integration weights and \( N \) is the number of samples.

Furthermore, we use a global sensitivity analysis based on variance decomposition [38] to quantify the impact of each parameter. The variance of the output is decomposed into zero-mean contributions of increasing dimensionality from which the so-called Sobol indices are computed, representing the impact attributed to the set of inputs. Accordingly, first-order indices quantify the impact of a single parameter, while the second-order indices represent the combined effect of two parameters. The Sobol indices were computed through a Monte Carlo framework, and the total unconditional variance can be decomposed to the summation of variance at all order:

\[
V(y) = \sum_i V_i + \sum_i \sum_{j>i} V_{ij} + \cdots + V_{12\ldots k},
\]

(16)

where

\[
V_i = V(E(y|x_i)),
\]

(17)

\[
V_{ij} = V(E(Y|x_i, x_j)) - V_i - V_j,
\]

(18)

\( V_i \) is the variance of the system when \( x_i \) is fixed. The Sobol indices can be defined as the variance at different order normalized by total variance:

\[
S_i = \frac{V_i}{V(y)},
\]

(19)

\[
S_{ij} = \frac{V_{ij}}{V(y)}.
\]

(20)

\( S_i \) and \( S_{ij} \) are the first and second Sobol indices. Since there is little or no knowledge of the parameter distributions such as the clinical measurement of cardiac output or CT-induced lumen diameter error, the sampling distribution for each parameter is assumed to be uniform.
Gaussian process regression and multifidelity framework

In this work, we adopt a multifidelity framework for parameter inference [39], which is based on Gaussian process regression and an auto-regressive model [40]. In GP regression, we model \( n \) scattered observations \( y_i, i = 1, \ldots, n \) in the form of \( y = f(x) + \epsilon \), where we set a zero-mean GP prior distribution on \( f(x) \) as

\[
    f(x) \sim \mathcal{GP}(0, K(x, x'; \theta)), \quad x \in \mathbb{R}^d,
\]

(21)

where \( \epsilon \) is the possible noise in the data assumed to be Gaussian \( \epsilon \sim \mathcal{N}(0, \sigma^2_{\epsilon}) \), \( d \) is the dimension of the input parameter space, and \( \mathbb{I} \) is the identity matrix. The GP prior is characterized by its expectation \( \mathbb{E}[f(x)] = 0 \) and its covariance \( K \), where \( \theta \) is the set of the hyper-parameters originated from the covariance kernel function (e.g., the squared exponential functions or Matérn family kernels). Particularly, all results shown in this work are produced using the squared exponential kernels. The optimal hyper-parameter set \( \hat{\theta} \) as well as the variance of the noise \( \hat{\sigma}^2_{\epsilon} \) can be estimated by minimizing the negative log-marginal likelihood function. More details on GPs can be found in the book by Rasmussen and Williams [41]. Once the parameters are estimated, inference on \( m \) unobserved points \( x^* \) is possible through the conditional posterior distribution \( f(x^*)|y, \hat{\theta} \sim \mathcal{N}(\mu(x^*), s^2(x^*, x^*)) \) where the posterior mean is defined by

\[
    \mu(x^*) = \mathbf{r}^T(\mathbf{R} + \hat{\sigma}_x^2\mathbb{I})^{-1}\mathbf{y},
\]

(22)

and the variance is

\[
    s^2(x^*, x^*) = [\mathbf{r}^* - \mathbf{r}^T(\mathbf{R} + \hat{\sigma}_x^2\mathbb{I})^{-1}\mathbf{r}]_i.
\]

(23)

where \( \mathbf{R} = K(x, x'; \hat{\theta}) \) stands for the \( n \times n \) covariance matrix of \( f(x) \) given \( n \) training data points, \( \mathbf{r} = K(x, x^*; \hat{\theta}) \) is the \( n \times m \) covariance matrix between the prediction and training points, and \( \mathbf{r}^* = K(x^*, x^*; \hat{\theta}) \) denotes the covariance matrix of prediction points.

The GP regression model could potentially be extended to a hierarchical probabilistic model, which can harness the information from several sources of various fidelities. This framework, originally proposed by Kennedy and O’Hagen [40], is also known as multifidelity (MF) surrogate modeling. Assuming that there are different sources of information at various fidelity as \( f_i(x_i) \) sorted by increasing order of fidelity, the information at each level \( f_i(x_i) \) can be seen as a GP model with \( x_i \notin D_i \subset R^d, \quad t = 1, \ldots, s, \quad s \geq 2 \). Hence, \( f_s \) is considered as the most accurate source of information (with significant cost to produce), while \( f_1 \) is the least accurate one (with relatively lower cost to produce). The MF framework can be written in an auto-regressive scheme as

\[
    f_t(x) = \rho_{t-1} f_{t-1}(x) + \delta_t(x), \quad t = 2, \ldots, s,
\]

(24)

where \( \delta_t(x) \) is taken as a Gaussian random field independent of \( \{f_{t-1}, \ldots, f_1\} \) with a zero-mean prior as \( \delta_t(x) \sim \mathcal{N}(0, \sigma^2_{\delta_t}) \), and \( \rho_{t-1} \) is a scalar factor that quantifies the correlation between \( f_t \) and \( f_{t-1} \) for which independent GP priors are assigned.

In particular, we construct the MF model with two fidelity levels hence, the MF predictive mean reads

\[
    \mu_2(x^*) = \rho_1 \mu_1(x^*) + r^T_2 (R_2 + \sigma^2_{\delta_2})^{-1}(f_2(x^*_2) - \rho_1 \mu_1(x^*_2)),
\]

(25)

and the variance is

\[
    s^2_2(x^*, x^*) = \rho^2 s^2_1(x^*, x^*) + r^T_2 - r_2^T (R_2 + \sigma^2_{\delta_2})^{-1} r_2^T,
\]

(26)

where \( R_2 = K_2(x, x'; \hat{\theta}_2) \), \( r_2 = K_2(x, x^*; \hat{\theta}_2) \), and \( r^* = K_2(x^*, x^*; \hat{\theta}_2) \) are the covariance matrices.

Bayesian optimization

The motivation for utilizing a surrogate model i.e., a multifidelity GP model, is to construct response surfaces and identify global optimal points with optimal computationally efficiency. However, there is no guarantee for the surrogate model to achieve a response surface with low variance and high accuracy just by using the initial selected sampling points. Thus, an automatic sampling strategy, namely Bayesian optimization, to optimize the surrogate model is adapted herein. Bayesian optimization utilizes prior knowledge on the objective function to establish an “acquisition function” [42]. Based on certain criteria for the acquisition function (e.g., maximum value), new best sample points are generated as an automatic trade-off between exploration and exploitation i.e., exploring regions with high variance versus exploiting regions where the mean Gaussian process posterior has a minimum. Consider
Presented here, blood is considered to be Newtonian with density and dynamic viscosity of 1 g/cm\(^2\) s and 4 cP, respectively. We use the spectral/hp element method \[30\] for 3D simulations and the discontinuous Galerkin method for 1D modeling \[25\]. For the simulations to extract the centerlines of the arteries based on which we perform 1D simulations. We use the open source software, VMTK \[45\], of the 1D model and the subsequent sensitivity analysis and parameter inference. The geometry consists of an aortic outlet and nine coronary outlets, three of which are on the right side. We use the Bayesian optimization method, we seek for the new sample point \(x^* = \arg\max(E[I_t(x)])\), \(x \in \mathbb{R}^d\) that will be added to the design set \(D_t\), and is used to retrain the MF surrogate for the next iteration. This procedure, also known as “active learning”, is iterative and will be stopped once a certain criterion (e.g., a certain value for expected improvement or minimum value for the objective function) is met.

### 3. Results

We adopt a coronary artery tree from an open source medical imaging repository OSMSC \[44\] for the validation of the 1D model and the subsequent sensitivity analysis and parameter inference. The geometry consists of an aortic outlet and nine coronary outlets, three of which are on the right side. We use the open source software, VMTK \[45\], to extract the centerlines of the arteries based on which we perform 1D simulations. We use the spectral/hp element method \[30\] for 3D simulations and the discontinuous Galerkin method for 1D modeling \[25\]. For the simulations presented here, blood is considered to be Newtonian with density and dynamic viscosity of 1.06 g/cm\(^3\) and 4 cP, respectively. We use 65,549 tetrahedral elements and 4th order Legendre polynomials for 3D simulations, which gives 262,196 degrees of freedom, whereas 41 elements with 4th order Legendre polynomials are used to discretize the 1D arterial network. 3D simulations required about 900 core-hours per cardiac cycle on Intel Xeon E5-2670 cores, whereas 1D simulations took only about 41 s/cardiac cycle on a single-core Intel i7 processor.

#### Part 1: 1D versus 3D modeling

We perform simulations of a healthy and stenotic coronary network at rest and under hyperemia, respectively. To compare the results from 1D simulations with the 3D model, we impose the same boundary conditions for both simulations, whereas we use a sufficiently high value for \(C\) to make the vessel walls rigid in 1D simulations. A patient-specific flow waveform is prescribed at the aortic inlet with an average cardiac output of 5.4 L/min (Fig. 1c), while a RCR boundary condition is connected at the aortic outlet (Fig. 1a) and lumped parameter networks are considered at each coronary outlet (Fig. 1d). The boundary condition parameter values are estimated based on the Murray’s law at each outlet and are listed in Table 5 of Appendix.

We compare the pressure and flow rate profiles at three representative outlets in Fig. 1(e) including the main aortic, the left anterior descending (LAD) and the right marginal artery (RMA) outlets. We observe very good agreement between 1D and 3D results with systolic and diastolic pressures around 120 mmHg and 64 mmHg, respectively. Though the instantaneous pressure difference can be as large as 12.7 mmHg, the overall maximum error for the mean pressure and flow rate is less than 2% among all the outlets. The ventricular pressure modeled by the intra-myocardial pressure in the lumped parameter network causes out-of-phase flow waveforms in RMA that is characterized in both 1D and 3D simulations indicating that the main characteristics of pressure waves are well described in the 1D model.

Next, we consider a coronary artery network under hyperemia with a 30% stenosis, which is manually introduced to the LAD branch. The hyperemic condition is assumed to be induced by intravenous administration of 140 μg/kg/min adenosine diphosphate, which will cause around four-fold increase of blood flows into the coronary arteries. Thus, the total coronary artery resistance at maximal hyperemia is expected to drop down to approximately one-quarter of that at the rest condition \[5\].

We present the pressure and flow rate profiles at the aortic and LAD outlets for 1D and 3D simulations under hyperemia in Fig. 2. We observe good agreement between the two models with a minor discrepancy in the LAD pressure at systole and before the diastole. Under hyperemia, the aortic pressure does not drop much, while the blood flow into the coronary branches is increased four times. Furthermore, the FFR value from 1D simulation is estimated to be 0.84, whereas it is 0.83 from 3D modeling. These results suggest that the 1D coronary flow modeling is robust and accurate with less than 2% error in the mean pressure and flow values.

#### Part 2: Parameter sensitivity analysis

We consider the same stenotic coronary artery network used for the validation with uncertain physiologic and anatomic parameters. In our first analysis, we exclude the uncertainties due to the boundary conditions and consider
five parameters to investigate including the cardiac output $Q$, vessel wall compliance scaling factor $C_w$, blood viscosity $\mu$, CT-induced lumen radius error $\epsilon_R$ and stenosis length error $\epsilon_L$. To quantify the uncertainty and confidence in FFR values, we sample this set of parameters within their corresponding range listed in Table 1. We set the normal cardiac output from 4.4 L/s to 6.4 L/s. The lower and upper limits of viscosity are chosen as the mean value for human blood at 20% (2.5 cP) and 60% hematocrit (6.5 cP) at 37 °C [46]. The lesion length error is assumed to be uniformly distributed between $-1$ and 1 mm. In addition, the CT-induced radius error in the segmentation process is defined as the error in minimum lumen radius, which is defined as $r_s \pm \epsilon_R$, where $r_s$ is the minimum lumen radius in the stenosis. This error typically depends on the image resolution at the sub-voxel level and is considered to be $\epsilon_R = 0.2$ mm [15] in our analysis. The wall compliance factor $C_w$ is selected from 0.5 to 5. The total coronary resistance index (TCRI), which represents the decreasing factor of coronary artery resistance at maximum hyperemia, is chosen from a range of 0.19 to 0.29 [47].
Fig. 3. UQ analysis of uncertain physiologic and anatomic parameters. (a) Mean and standard deviation of FFR from PCM analysis plotted against the degree of stenosis. This result is based on global sensitivity analysis. The horizontal dashed line denotes the FFR = 0.8, which is the threshold to characterize functionally severe stenosis. The blue dashed lines correspond to the highest and lowest FFR values. (b) Fraction of samples with FFR = 0.8 ± 0.01 from 20% to 60% stenosis. (c–e) Comparison of first and second-order Sobol indices are plotted for each uncertain parameter including the cardiac output, wall compliance, blood viscosity and segmentation errors in the lumen radius and lesion length at three different stenosis severity. First-order indices are characterized by the size of the circles and second-order indices are represented by the connecting lines, where the line thickness shows their magnitude. The figure shows that at mild stenosis, viscosity has bigger impact, whereas with the increased degree of stenosis, the uncertainty in the lumen radius $\epsilon_R$ dominates. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

Table 1
The list of physiologic and anatomic parameters of interest and their range of values for UQ analysis.

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Range</th>
</tr>
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<tbody>
<tr>
<td>Cardiac output (Q) [L/s]</td>
<td>[4.4, 6.4]</td>
</tr>
<tr>
<td>Blood viscosity ($\mu$) [cP]</td>
<td>[2.5, 6.5]</td>
</tr>
<tr>
<td>Lesion length error ($\epsilon_L$) [mm]</td>
<td>[−1, 1]</td>
</tr>
<tr>
<td>CT-induced radius error ($\epsilon_R$) [mm]</td>
<td>[−0.2, 0.2]</td>
</tr>
<tr>
<td>Wall compliance scaling factor $C_w$</td>
<td>[0.5, 5]</td>
</tr>
<tr>
<td>Total coronary resistance index (TCRI)</td>
<td>[0.19, 0.29]</td>
</tr>
</tbody>
</table>

Each sample requires a forward simulation of coronary flow, which is performed using the 1D model due to its much lower computational cost. We use PCM to calculate the mean and variance of FFR associated with the set of uncertain parameters. Further, the uncertainty may be amplified or contained at different stenosis severity levels (measured in terms of % radius reduction of the vessel lumen). To investigate this, 13 sets of UQ analysis are performed with increasing stenosis severity, where each set contains 389 samples.

In Fig. 3 the calculated mean and variance of FFR and extreme scenario are plotted versus the severity of stenosis in the LAD. As shown in the figure, the mean of FFR monotonically decreases as the stenosis severity increases, especially at around 30% stenosis the average FFR falls below the clinical threshold value of 0.8. Importantly, the variance of FFR increases with the stenosis severity, meaning that there is more uncertainty in FFR as the vessel further narrows. The highest and lowest values of FFR from our sensitivity analysis are 0.91 and 0.76, respectively, at 20% stenosis, which reduced to 0.71 and 0.14 at 60% stenosis. Even with stenosis around 53%, there is still a chance that the FFR value is close to the threshold. From Fig. 3(b) we see the percentage of the samples with FFR value of 0.8 ± 0.01 among all degrees of stenosis, where a wide distribution is observed from 20% to 50%.
Table 2
The list of boundary condition parameters of interest and their uncertainty range.

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aortic resistance ($R_{\text{aor}}$) [10^{-8} Pa s m^{-3}]</td>
<td>[1. 2]</td>
</tr>
<tr>
<td>Aortic capacitance ($C_{\text{aor}}$) [10^{-8} m^{3} Pa^{-1}]</td>
<td>[1. 4]</td>
</tr>
<tr>
<td>Right coronary total capacitance ($C_{\text{right}}$) [10^{-8} m^{3} Pa^{-1}]</td>
<td>[0.01, 0.04]</td>
</tr>
<tr>
<td>Left coronary total capacitance ($C_{\text{left}}$) [10^{-8} m^{3} Pa^{-1}]</td>
<td>[0.01, 0.04]</td>
</tr>
</tbody>
</table>

Fig. 4. UQ analysis of the boundary condition parameters for 30% stenosis in the LAD. (a) Results from PCM that show the sensitivity of FFR to each parameter. □ represent the mean FFR values, and the error bars denote the standard deviation in the FFR. (b) Global sensitivity analysis for the aortic and the coronary boundary conditions, namely the resistance and capacitance of aorta, and the capacitance of left and right coronary arteries.

The majority of samples happen to have $30 \pm 10\%$ stenosis, which corresponds to the mean FFR value of 0.8 in Fig. 3(a).

To quantify the impact of each parameter on the uncertainty in FFR values, analysis of variance decomposition is employed to compute the first and second-order Sobol indices [38], where first-order indices show the impact of each parameter on the FFR variance while the second-order indices indicate the combined impact of two parameters together. Fig. 3(c–e) show the global first and second-order Sobol indices at 20, 40 and 60% degrees of stenosis. For mild stenosis at 20%, blood viscosity contributes most to the uncertainty of FFR, whereas CT-induced lumen radius error comes second, followed by the cardiac output and TCRI. For moderate and severe lesions (> 40%), the impact of CT error becomes dominant, where we observe that the order of Sobol index for $\epsilon_R$ is orders higher than that for the rest of parameters. The results of Fig. 3(c–e) also suggest that the coupling of various parameters may contribute to the uncertainty in the FFR (characterized by the thickness of the connecting lines). For example, for all degrees of stenosis, the combined impact of wall compliance and blood viscosity remains the most significant. However, the second-order indices are not as significant compared to the first-order indices that contribute to around 95% of the total variance.

The above uncertain quantities are affected by image segmentation errors and physiologic uncertainties. In the second UQ analysis, we investigate the model parameters i.e., the boundary condition parameters at the aortic and coronary outlets. We consider four parameters to infer including the resistance and capacitance of aorta, and the total capacitance of left and right coronary arteries for the geometry of Fig. 2(b) with 30% stenosis in the LAD. Fig. 4(a) shows results from PCM for the sensitivity of FFR to each individual parameter as well as the total uncertainty, where the parameters are sampled within the ranges shown in Table 2. The aortic resistance causes the highest uncertainty in FFR, while the uncertainty due to the rest of the parameters is negligible. The four-parameter PCM result indicates a mean FFR value at 0.78 with variance of 0.03 that is lower than the mean value for a single variable analysis, which suggests a combined effect between parameters on the FFR. Thus, we plot in Fig. 4(b), the global sensitivity analysis using variance decomposition. We observe that the aortic resistance accounts for most
of the variance in the computed FFR, whereas its coupling with the other parameters has negligible impact on the uncertainty of FFR.

**Part 3: Multifidelity parameter inference**

We aim to demonstrate the effectiveness and efficiency of a multifidelity framework for parameter inference in coronary blood flow modeling. The sensitivity analysis suggests that the boundary condition parameters, specifically the systemic resistance and capacitance could have significant impact on FFR predictions, which makes patient-specific parameter inference highly crucial in coronary flow modeling. Thus, we use the clinical measurement of the aortic pressure, which is the most available information for each patient, to infer the aortic resistance and capacitance with both single-fidelity and multifidelity models. Next, we extend the multifidelity Bayesian optimization and apply it to a higher dimensional parameter inference problem. Here, we use the same healthy coronary artery geometry as in the validation part, while this framework can be used to infer the parameters for any healthy or diseased coronary network.

**Systemic boundary conditions inference**

We start with a two-parameter single-fidelity inference that enables clear visualization of the response surface for the objective function as a function of the parameters. The optimization problem is set up to infer the aortic resistance $R_{aorta}$ and capacitance $C_{aorta}$ such that the estimated systolic and diastolic pressures in the aorta match the patient-specific measurements, which are 110 mmHg for the systolic and 70 mmHg for the diastolic pressure in the healthy coronary artery plotted in Fig. 1. Considering that the coronary blood flow is approximately 4% of the cardiac output, the total coronary resistance can be estimated once the aortic resistance is inferred by $R_{tot,cor} \approx 24 \times R_{aorta}$. The terminal resistances for each coronary outlet was then estimated based on the Murray’s law. Given that the typical values for aortic resistance and capacitance lie in a reasonable range, we choose a generic range of values $[1, 2]$ (10$^8$ Pa m/s) for the aortic resistance and $[0.7, 4]$ (10$^{-8}$ m$^3$/Pa) for the aortic capacitance. Subsequently, the corresponding objective function is formulated using the relative error of the pressures

$$g(x) = \frac{(p_s^* - p_s(x))^2}{(p_s^*)^2} + \frac{(p_d^* - p_d(x))^2}{(p_d^*)^2},$$

(28)

where $x$ stands for the design parameters $x = \{R_{aorta}; C_{aorta}\}$, $p_{s,d}(x)$ are the systolic and diastolic pressures evaluated at the sampling points and $p_{s,d}^*$ are the clinical measurements. We seek the optimal values of $x$ such that $x^* = \arg\min_{x \in D} [g(x)]$, where $D$ is the design set of sampling points.

We use GP regression with one-level source of information, which may also be regarded as a single-fidelity model (SF), to construct the response surface. To sample the design parameter space for the single-fidelity model, a Latin Hypercube sampling algorithm is used, where the systolic and diastolic pressures in the aorta for each sample point are computed using the 1D nonlinear model. A detailed representation of the response surface is plotted in Fig. 5, where the global minimum on the surface is considered to give the optimal values for $x$. In Fig. 5(a)-(d), we show the resulting response surface constructed by the single-fidelity model with 10, 20, 40 and 80 training points, respectively, whereas Table 3 summarizes the values of optimal resistance and capacitance for these single-fidelity models along with the minimum objective function values (i.e., the relative error). Based on these results, we observe a monotonic decrease in the relative errors with the increasing number of sample points.

The rationale of using the 1D nonlinear model to train the Gaussian process is its relatively high-fidelity pressure and flow estimation to compute the FFR with high accuracy and importantly, much lower computational cost than the full 3D models. In addition, the 1D linear model described in the Appendix can be used as a low-fidelity model,

### Table 3

<table>
<thead>
<tr>
<th>Model</th>
<th>Resistance ($R_{aorta}$)</th>
<th>Compliance ($C_{aorta}$)</th>
<th>Minimum objective function value ($g$)</th>
</tr>
</thead>
<tbody>
<tr>
<td>SF10</td>
<td>1.88</td>
<td>4.00</td>
<td>0.0476</td>
</tr>
<tr>
<td>SF20</td>
<td>1.75</td>
<td>2.69</td>
<td>0.0013</td>
</tr>
<tr>
<td>SF40</td>
<td>1.67</td>
<td>2.39</td>
<td>9.44e−05</td>
</tr>
<tr>
<td>SF80</td>
<td>1.53</td>
<td>1.99</td>
<td>2.88e−05</td>
</tr>
</tbody>
</table>
Fig. 5. Systemic boundary condition parameters inference using the single-fidelity model. The response surface is constructed as a function of aortic resistance and capacitance at the aortic outlet. (a)–(d) The number of sample points are 10, 20, 40 to 80, respectively. * denotes the optimal solution and the parameters inferred by the single-fidelity model, whereas • represents the sample points from the 1D nonlinear model.

where the nonlinear model is further simplified to further reduce the computational cost. Hence, a multifidelity framework facilitates estimation of the optimal point with lower cost as the number of high-fidelity sample points can be reduced significantly when information from a lower-fidelity source is included to construct the response surface. To this end, we use data from two fidelity models to construct the surrogates for the objective function of Eq. (28): the 1D nonlinear model is used as the high-fidelity source of information, while the 1D linear model is used as the low-fidelity predictor. The 1D linear model is derived based on the small perturbation assumption, and naturally, the prediction from the linear model could have a noticeable deviation from that of the nonlinear model. Nevertheless, the data from the linear model is still quite informative since the two fidelity models are correlated. The computational set up remains the same as in the single-fidelity model.

To examine the effectiveness of the multifidelity model, we train two models with different number of (HF+LF) sample points, namely (10+60) and (20+120) points. Fig. 6(a) and (b) show the constructed response surfaces from these multifidelity models, where we observe that the (10+60) model prediction in Fig. 6(a) has significantly improved after including (10+60) more samples shown in Fig. 5(b). Quantitative results are given in Table 4, where we observe that the objective function value has reached its lowest value as for the SF model with 80 samples in Table 3. This is significant as we achieve the same level of accuracy with 60 fewer HF samples, while we save more computational resources given the lower cost of low-fidelity simulations. We relax the wall compliance factor $C_w$ to 0.1 so that the time step size can be increased by an order of magnitude. Generally, this makes the low-fidelity model more than 10 times faster than the high-fidelity model.

One important advantage of using Gaussian process regression is its ability to quantify the posterior variance in its predictions. With a smart use of the mean and variance of the objective function predicted by the trained MF surrogate, we can write an acquisition function in the form of the expected improvement (EI) (Eq. (27)) to be used in the process of Bayesian optimization also known as “active learning”. Active learning is a sequential
Multifidelity models are trained by (a) 10 high-fidelity and 60 low-fidelity sample points, (b) 20 high-fidelity and 120 low-fidelity sample points, (c) 6 high-fidelity and 30 low-fidelity points with two more active-learning points, and (d) 10 high-fidelity and 60 low-fidelity points with one more active-learning point. * denotes for the minimum of the objective function predicted by the multifidelity framework; • denotes high-fidelity sample points (1D nonlinear model) and ○ denotes low-fidelity sample points (1D linear model) and + is the active-learning point.

Table 4
Optimal terminal resistance and compliance and the corresponding objective function values using the multifidelity (first two rows), the multifidelity with active learning (AL) (rows 3 and 4), and single low-fidelity based on the linear 1D model (last three rows). The unit for resistance is $10^8 \text{Pa s/m}^3$ and for the capacitance is $10^{-8} \text{m}^3/\text{Pa}$.

<table>
<thead>
<tr>
<th>Model</th>
<th>Resistance ($R_{aorta}$)</th>
<th>Capacitance ($C_{aorta}$)</th>
<th>Minimum objective function value ($g$)</th>
</tr>
</thead>
<tbody>
<tr>
<td>HF + LF: 10 + 60</td>
<td>2.00</td>
<td>3.06</td>
<td>$1.80 \times 10^{-3}$</td>
</tr>
<tr>
<td>HF + LF: 20 + 120</td>
<td>1.52</td>
<td>1.96</td>
<td>$3.64 \times 10^{-5}$</td>
</tr>
<tr>
<td>HF( + AL) + LF: 6( + 2) + 30</td>
<td>1.51</td>
<td>1.95</td>
<td>$7.67 \times 10^{-4}$</td>
</tr>
<tr>
<td>HF( + AL) + LF: 10( + 1) + 60</td>
<td>1.52</td>
<td>1.97</td>
<td>$2.97 \times 10^{-5}$</td>
</tr>
<tr>
<td>LF: 30</td>
<td>2.00</td>
<td>2.50</td>
<td>$1.46 \times 10^{-2}$</td>
</tr>
<tr>
<td>LF: 60</td>
<td>1.63</td>
<td>1.93</td>
<td>$4.78 \times 10^{-3}$</td>
</tr>
<tr>
<td>LF: 120</td>
<td>1.59</td>
<td>1.81</td>
<td>$4.97 \times 10^{-3}$</td>
</tr>
</tbody>
</table>

design process, which identifies the most informative sample points through maximizing the EI and, thus, saving computational resources by reducing the number of sample points. The newly selected point will be added to the design set $D$ (usually at the high-fidelity inference level) with which the multifidelity model is retrained. This process is repeated until a termination criterion is met. Here, we choose this criterion as either the objective function value is below $10^{-3}$ or the active learning algorithm generates the same sample point as is provided in the previous iteration. Clearly, if we were using the 3D model as HF and the linear 1D model as LF the computational savings would have been truly substantial.

For two MF models constructed with (6+30) and (10+60) initial samples, we perform Bayesian optimization by maximizing the expected improvement for the HF inference level and obtain additional sample points to add to the
design set. As shown in Fig. 6(c) and (d), the response surface constructed exhibits a highly similar topology to that from (80) single-fidelity model. Very few points are added to the HF design set, where the termination criterion is met for both MF models. The value of the objective function from the two models has lowered to $7.67 \times 10^{-4}$ and $2.97 \times 10^{-3}$, where they correspond to the optimal points obtained by the (20+120) MF or (80) SF models. Hence, we have achieved an accurate prediction by the MF model along with active learning using informative sampling which leads to further reduction in the computational cost. Furthermore, we list the predictions with only 30, 60 and 120 low-fidelity samples, where we observe less optimal values than those of the multifidelity model.

**Parameter inference in higher dimensions**

To further illustrate the applicability of multifidelity inference with active learning, we employ it for a higher dimensional inverse problem, where in addition to aortic resistance and capacitance, the total left and right coronary capacitances ($C_{tot,cor,R}, C_{tot,cor,L}$) are inferred. Given that the systolic and diastolic pressures in the aorta are not sufficient to infer the two additional parameters, we assume that the pressures in one of the left and right coronary branches have also been measured. We choose the systolic and diastolic pressures in the left anterior descending (LAD) and right marginal artery (RMA) branches of the healthy subject to be known and equal to [109.98, 67.72] and [109.12, 67.07] mmHg, respectively. We note that acquiring the pressure information in these two coronary arteries may require invasive measurements. Assuming the availability of such data, our goal here is to show the applicability of the multifidelity framework to infer parameters in higher-dimensional design space.

The workflow for this case is similar to previous MF example, however we use 50 HF along with 250 LF sample points randomly distributed using the Latin Hypercube method within the ranges $R_{aorta} \in [1, 4] \times 10^8$ Pa s/m$^3$, $C_{aorta} \in [1, 4]$, $C_{tot,cor,R}, C_{tot,cor,L} \in [0.01, 0.04] \times 10^{-8}$ m$^3$/Pa. The objective function in Eq. (28) is rewritten with the pressures of LAD and RMA included in the relative error as well. The active learning process ends after two new sample points are added to the HF design set as a threshold value of $10^{-3}$ is set for the objective function. Fig. 7(a) shows the response surface plotted against the aortic resistance and capacitance, where we have fixed the total left and right coronary capacitance at their optimal values. Further, we plot the pressure profiles calculated for the MF inferred parameters and their corresponding reference values in Fig. 7(b)–(d), where we observe very good agreement between these two (less than 2% deviation) due to very good estimates of the boundary condition parameters shown in Fig. 7(e).

4. Discussion

We have performed 3D and 1D simulations of pulsatile flow of the coronary arterial network under rest for healthy arteries and under hyperemia for stenotic arteries. In particular, we have focused on diseased LAD coronary with a 30% stenosis. At rest, we observed very good agreement between 3D and 1D predictions for pressure and flow rate under a high stiffness of the vessel wall; the maximum error is below 2 and 3% for mean pressure and flow rate, respectively. In order to study the cardiovascular hemodynamics under hyperemia for stenotic arteries, we decreased the total coronary resistance by a factor of four, which leads to approximately four-fold increase in the coronary blood flow rate. In this case, the computed FFR discrepancy between the 3D and 1D models is less than 1.5%. We note that the computed value of FFR depends strongly on the stenotic model, which is based on an in-vitro hydraulic empirical correlation. In this model, we assumed an axisymmetric stenosis shape, whereas in reality the stenosis may be asymmetric. Moreover, the 1D model is valid based on several other assumptions e.g., axially dominant flow with no secondary flows. Specifically, at the aorta inlet where the local Reynolds number may increase up to 1000, there exist strong secondary flows. This issue has been discussed in a similar study for the brain arterial network (Circle of Willis) [48]. Other uncertainties may be introduced due to the algorithm to extract the centerline, the extraction of equivalent lumen diameter or vessel surface roughness, and the bifurcation angles in the arterial networks.

In order to systematically investigate the effect of the various parameters on the value of FFR, we simulated FFR under hyperemia in the same stenotic geometry, whereas we treated five physiological parameters and four modeling parameters as uncertain. We employed the PCM and obtained a wide range of possible FFR values under the corresponding parameter uncertainty. For the five physiological parameters, the mean of FFR decreases with an increase in stenosis severity, where the variance of FFR also increased. Our global sensitivity analysis quantifies the importance of having an accurate description of the stenosis lumen radius from CT for an accurate FFR value for very severe stenosis whereas for mild stenoses the blood viscosity and the error in the lumen radius together account...
Fig. 7. Four-parameter inference using the multifidelity framework with active learning. (a) Response surface of the objective function with fixed $C_{tot,cor}$ and $C_{tot,R}$ at their optimal values $3.6 \times 10^{-10}$ and $2.5 \times 10^{-10}$ m$^3$/Pa, respectively. The MF model is trained based on 50 HF and 250 LF sample points. In the active learning process, two more sample points are added to the design set. (b)–(d) Pressure profile comparison with parameters inferred from MF model and their corresponding reference values. (e) Table of reference parameter values and MF model predictions.

for most of the uncertainty. We did not take into account uncertainties due the aortic or coronary capacitances as they do not have a significant effect on FFR. We note, however, that both the aortic and coronary resistances greatly affect the local pressure distribution along the stenosis. We also performed analysis of variance decomposition to assess the global uncertainty from model parameters on FFR values. We performed the UQ analysis on the same coronary geometry with a 30% stenosis since the mean FFR with a stenosis at this severity is approximately equal to 0.8. As expected, the aortic resistance accounts for most of the uncertainty, whereas the aortic and coronary capacitances only have minor impacts on the FFR.

In addition to the UQ analysis, we developed a probabilistic optimization method for parameter inference in coronary flow modeling. Our objective was to infer the terminal resistances and capacitances at an outlet of a vessel such that the systolic and diastolic pressures in that vessel (e.g., the aorta) agree with clinically measured values. Here, we used Gaussian process regression with single-fidelity and multifidelity surrogate models, along with the Bayesian optimization algorithm to infer the model parameters. In the first numerical example, given the cardiac output as known, we inferred the aortic resistance and capacitance with the knowledge of aortic systolic and diastolic pressures using either a SF or MF model. We observed that the MF model can render the same level of prediction accuracy as the SF model, but with much lower cost with the help of low-fidelity data. The efficiency of MF inference can be further improved by actively adding informative data using a Bayesian optimization method. A more involved inference problem with one resistance and three capacitances is then investigated, where the parameter inference results showed good agreement with the reference values. This general framework can be extended to address high-dimensional inference problems with more parameters to be optimized, however, the major obstacle would be the scarcity of patient-specific clinical measurements that the algorithm needs to construct the objective functions.

There are a few limitations in our proposed method such as the assumption of uniform distribution for parameters as there is no prior information available. In addition, by conditioning on available observations, a joint posterior distribution can be estimated using a Bayesian framework, which provides the full distribution of parameters rather than the point estimates from the PCM. Furthermore, as a vessel narrows down, the uncertainty in lumen radius may also decrease to a narrower range such that the assumption of a constant segmentation error may not be valid. We expect that the decrease in $\epsilon_R$ results in less uncertainty in the FFR as well as the first order indices. A more
detailed uncertainty quantification would require a larger dataset of patient-specific CAD geometries that contain various stenoses at different locations in the coronary arteries.

Acknowledgments

We would like to thank Dr. Dongkun Zhang for discussions regarding the uncertainty quantification, and Dr. Shinong Fu and Dr. Jinzhu Yang from SinoVison, Inc. for supporting this research. This work was partially supported by SinoVision Inc., China, and by NIH, USA grant numbers U01HL116323 and U01HL142518. Computations were performed using the resources of Center for Computation and Visualization (CCV) at Brown University and NSF-XSEDE through the award No. TG-DMS140007.

Appendix

A.1. Lumped parameter network boundary conditions

We use the standard Windkessel-type boundary conditions for the aortic outlet and lumped coronary boundary conditions for coronary outlets to compensate for the pressure drop in the micro-vascular bed (see Fig. 8). Specifically, the boundary conditions are derived as

\[ q_{in} = \frac{P(A^*) - P_{c1}}{R_1}, \]  

\[ q_{in} = C_1 \frac{d P_c}{dt} + \frac{P_{out} - P(A^*)}{R_2}, \]

The lumped parameter network can be written as:

\[ q_{in} = \frac{P(A^*) - P_{c1}}{R_1}, \]  

\[ q_{in} = C_1 \frac{d P_{c1}}{dt} + q_{c2}, \]  

\[ P_{c1} = q_{c2} R_2 + P_{c2}, \]  

\[ q_{c2} = q_{out} + C_2 \frac{d P_{im}}{dt}, \]  

\[ P_{c2} = q_{out} R_3 + P_{out}, \]

where \( R_1, R_2, R_3 \) represent the resistances of truncated coronary arteries including the micro-circulation, micro-vascular and venous resistance, respectively, \( C_1 \) is the coronary capacitance, \( C_2 \) is the intra-myocardial capacitance, and \( P_{im} \) is the intra-myocardial pressure.

Furthermore, Murray’s law states that the resistance of vascular arteries at rest is proportional to its morphological size i.e., the radius of vessel. This principle can be expressed by \( R_i = R_{cor} \frac{\Sigma r_i^4}{\Sigma A_i} \), where \( R_{cor} \) is the total coronary resistance, \( R_i \) is the resistance of a single branch and \( r \) is the radius of the coronary vessel. An empirical value of \( \alpha = 2.6 \) for the coronary arteries [36]. Similarly for the capacitances at each coronary outlet we can write \( C_i = C_{cor} \frac{A_i}{\Sigma A_i} \). \( C_{cor} \) is the left or right coronary artery capacitance, \( A_i \) and \( C_i \) are the cross-sectional area and capacitance of a coronary branch. In Table 5 we see the values of resistances and capacitances at each coronary outlet as well as the aortic outlet.

Cardiac output and intra-myocardial pressure

We impose the cardiac output flow rate and intra-myocardial pressure profiles shown in Fig. 9. One possible way to estimate the patient-specific cardiac output is to use the lumped heart model described by Kim et al. [49], whereas a system of ODEs is used to estimate the intra-myocardial pressure [12]. In this work, we did not include these models since our main focus is to quantify the uncertainty and infer the existing parameters. Nevertheless,
Fig. 8. Terminal boundary conditions imposed at arterial outlets shown as (a) Windkessel and (b) lumped parameter network boundary conditions.

Fig. 9. Flow waveform imposed at the aortic inlet and the intra-myocardial pressure used in the coronary lumped network boundary condition.

<table>
<thead>
<tr>
<th>Outlet</th>
<th>$R_1$</th>
<th>$R_2$</th>
<th>$R_3$</th>
<th>$C_1$</th>
<th>$C_2$</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>8.27</td>
<td>13.44</td>
<td>4.14</td>
<td>8.68</td>
<td>70.25</td>
</tr>
<tr>
<td>2</td>
<td>9.69</td>
<td>15.75</td>
<td>4.85</td>
<td>7.69</td>
<td>62.19</td>
</tr>
<tr>
<td>3</td>
<td>5.99</td>
<td>9.74</td>
<td>3.00</td>
<td>11.13</td>
<td>90.07</td>
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<td>4</td>
<td>2.50</td>
<td>4.06</td>
<td>1.25</td>
<td>4.23</td>
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</tr>
<tr>
<td>5</td>
<td>2.74</td>
<td>4.46</td>
<td>1.37</td>
<td>3.93</td>
<td>31.77</td>
</tr>
<tr>
<td>6</td>
<td>13.61</td>
<td>22.12</td>
<td>6.81</td>
<td>6.74</td>
<td>54.51</td>
</tr>
<tr>
<td>7</td>
<td>10.18</td>
<td>16.54</td>
<td>5.09</td>
<td>8.42</td>
<td>68.15</td>
</tr>
<tr>
<td>8</td>
<td>21.19</td>
<td>34.44</td>
<td>10.59</td>
<td>4.79</td>
<td>38.76</td>
</tr>
<tr>
<td>9</td>
<td>6.80</td>
<td>11.04</td>
<td>3.40</td>
<td>11.49</td>
<td>93.01</td>
</tr>
</tbody>
</table>

Table 5
Values of lumped parameter network at rest. The unit for the resistance is $10^9$ Pa/m$^3$, whereas for the capacitance is $10^{-12}$ m$^3$/Pa.

the proposed multifidelity framework can be employed to infer the parameters of the heart model provided that patient-specific data such as the stroke volume and ejection fraction are measured as well [17].

1D linear model

The derivation of 1D linear blood flow model is based on the 1D nonlinear model. If we linearize the flow variables in the 1D nonlinear model as $(A, p, Q) = (A_o + \hat{A}, \hat{p}, \hat{Q})$, where $(A_o, 0, 0)$ is considered to be the reference state, then the nonlinear system of equations will be written as

$$\frac{A_o}{\rho c_o^2} \frac{\partial \hat{p}}{\partial t} + \frac{\partial \hat{Q}}{\partial x} = 0,$$

$$\frac{\rho}{A_o} \frac{\partial \hat{Q}}{\partial t} + \frac{\partial \hat{p}}{\partial x} = -K_r \frac{\hat{Q}}{A_o^2} + S,$$
\[ \hat{p} = \hat{a} \rho c_o^2 / A_o, \]  

where \( \hat{a} \), \( \hat{p} \), \( \hat{q} \) are the perturbations with respect to the reference state. The above equations are the 1D linear model for flow in a compliant vessel.

To mimic 1D blood flow in a rigid vessel, a proper coefficient \( C_w \) needs to be chosen to limit the mean variation in the cross-sectional area. Numerically, the overestimation of \( C_w \) could induce numerical instability due to the very stiff system. We performed a set of numerical experiments by varying \( C_w \) from 0.1 to 100, and plotted the results of mean area variation of a vessel, which is defined by \( (\bar{A} - A_o) / A_o \) where \( A_o \) is the reference area. Fig. 10 shows that the mean area variation decreases with the increase of the coefficient of \( C_w \), where at \( C_w = 10 \), the mean area changes are about 0.1%. Hence we take \( C_w = 10 \) in our numerical simulations.

References


[5] C.A. Taylor, T.A. Fonte, J.K. Min, Computational fluid dynamics applied to cardiac computed tomography for noninvasive quantification of fractional flow reserve: scientific basis, J. Am. Coll. Cardiol. 61 (22) (2013) 2233–2241.


