Published in final edited form as:

Comput Methods Appl Mech Eng. 2019 March 1; 345: 402–428. doi:10.1016/j.cma.2018.10.024.

Uncertainty quantification of simulated biomechanical stimuli in coronary artery bypass grafts

Justin S. Tran^a, Daniele E. Schiavazzi^b, Andrew M. Kahn^c, and Alison L. Marsden^d

^aDepartment of Mechanical Engineering, Stanford University, Stanford, CA, USA

^bACMS Department, University of Notre Dame, Notre Dame, IN, USA

^cDepartment of Medicine, University of California San Diego, La Jolla, CA, USA

^dDepartment of Pediatrics (Cardiology), Bioengineering and ICME, Stanford University, Stanford, CA, USA

Abstract

Coronary artery bypass graft surgery (CABG) is performed on more than 400,000 patients annually in the U.S. However, saphenous vein grafts (SVGs) implanted during CABG exhibit poor patency compared to arterial grafts, with failure rates up to 40% within 10 years after surgery. Differences in mechanical stimuli are known to play a role in driving maladaptation and have been correlated with endothelial damage and thrombus formation. As these quantities are difficult to measure in vivo, multi-scale coronary models offer a way to quantify them, while accounting for complex coronary physiology. However, prior studies have primarily focused on deterministic evaluations, without reporting variability in the model parameters due to uncertainty. This study aims to assess confidence in multi-scale predictions of wall shear stress and wall strain while accounting for uncertainty in peripheral hemodynamics and material properties. Boundary condition distributions are computed by assimilating uncertain clinical data, while spatial variations of vessel wall stiffness are obtained through approximation by a random field. We developed a stochastic submodeling approach to mitigate the computational burden of repeated multi-scale model evaluations to focus exclusively on the bypass grafts. This produces a two-level decomposition of quantities of interest into submodel contributions and full model/submodel discrepancies. We leverage these two levels in the context of forward uncertainty propagation using a previously proposed multi-resolution approach. The time- and space-averaged wall shear stress is well estimated with a coefficient of variation of <35%, but ignorance about the spatial distribution on the wall elastic modulus and thickness lead to large variations in an objective measure of wall strain, with coefficients of variation up to 100%. Sensitivity analysis reveals how the interactions between the flow and material parameters contribute to output variability.

Publisher's Disclaimer: This is a PDF file of an unedited manuscript that has been accepted for publication. As a service to our customers we are providing this early version of the manuscript. The manuscript will undergo copyediting, typesetting, and review of the resulting proof before it is published in its final citable form. Please note that during the production process errors may be discovered which could affect the content, and all legal disclaimers that apply to the journal pertain.

Keywords

Uncertainty quantification; coronary bypass graft; cardiovascular modeling; submodelling; sensitivity analysis; random field

1. Introduction

Atherosclerotic coronary artery disease continues to be a major cause of mortality worldwide. Severe forms of coronary artery disease are typically treated with bypass grafts surgery (CABG), which re-routes blood downstream of a stenotic lesion to oxygenate the myocardium. In the United States, CABG surgery is performed in over 400,000 patients each year [1], and continues to be the gold standard treatment for patients with diffuse and multi-vessel coronary artery disease. Arterial grafts are preferred for their superior patency rates, but are often limited in availability, thus venous grafts are often used since most patients require multiple bypass grafts. Unfortunately, venous grafts have poor patency rates with only about 60% remaining patent 10 years after surgery [2, 3], leading to high-risk and high-cost revascularization procedures. While it is known that hemodynamics and wall biomechanics play a key role in the onset and progression of vein graft failure [4, 5], these quantities are often difficult to measure *in vivo*.

Computational models are increasingly used for treatment planning and assessment of disease progression, and can now be non-invasively generated from routinely collected data [6]. For example, CFD models have been used to assess fractional flow reserve in patients with coronary artery stenoses [7] and also to investigate risk of thrombosis in coronary artery aneurysms in patients with Kawasaki disease [8, 9]. In this context, a recent patient-specific modeling study investigated differences in the hemodynamics and vessel wall biomechanics between arterial and venous grafts, in an effort to elucidate the mechanisms responsible for vein graft failure [10]. Across a cohort of patients, this study revealed statistically significant differences in wall shear stress, percentage of atheroprone area, and wall strain between arterial and venous grafts. Another recent contribution used a constrained mixture theory to show how rapid increases in flow and pressure lead to maladaptation of venous grafts, but gradual increases in flow and pressure over the course of a few days significantly improved the chances of a successful adaptation [11].

Cardiovascular models necessitate assimilation of clinical data, images and population studies from the literature to define the model geometry, boundary conditions and material properties. However, these data are not known precisely due to measurement errors and population variability. Despite these uncertainties, results fail to report confidence in model predictions. Uncertainty quantification (UQ) now offers a means to rigorously quantify confidence in the outputs from computer models. Therefore UQ constitutes a fundamental step towards increasing rigor of simulation methods and remains key to future clinical adoption in disease diagnosis and treatment. Recent studies have begun to examine the effects of uncertainty in cardiovascular simulation outputs [12]. These include studies of the impact of random field wall thickness on wall stress in abdominal aortic aneurysms [13], stochastic collocation to investigate uncertainties in a one-dimensional human arterial

network [14], shape optimization of idealized bypass grafts under uncertainty [15], uncertainties in wall model parameters for one-dimensional approximations of blood flow [16], variability in coronary fractional flow reserve under uncertainty in geometry and boundary conditions [17], uncertainty in the context of virtual palliation surgery for single ventricle congenital heart disease [18], and others [19, 20, 21].

Our study considers two main sources of uncertainty: the closed loop lumped parameter (LPN) boundary conditions at the inflows and outflows, and the material properties of the vascular walls. Boundary condition uncertainty is inferred through the solution of an inverse problem in uncertainty analysis, assimilated from clinical and literature data using the automated tuning framework outlined in [22]. Parameter sets whose outputs are consistent with uncertain clinical measurements are sampled through adaptive Markov chain Monte Carlo [23]. In addition, we model material property uncertainty using a random field approximation for the wall elastic modulus and thickness with mean and standard deviations from the literature [24, 25, 26], which we sample independently from the boundary conditions.

A challenge we address in this study is to reduce the large computational cost of propagating the input uncertainty through a full multi-scale coronary model, given our interest in computing biomechanical indicators only on a small region of interest, the arterial and venous bypass grafts. We address this issue through *stochastic submodeling*, i.e., by shifting as much of the computational cost as possible to the solution of a large number of less expensive graft submodels.

We also consider the effect of an uncertain spatial variation of material properties, specifically the elastic modulus and thickness for a linearly elastic vessel wall. Despite the widespread tendency to assume these quantities are spatially uniform, experiments have shown that material properties instead exhibit significant spatial variations in certain parts of the vasculature [27, 25]. Given the limited data and expected interpatient variability, we introduce a *random field* approximation for these quantities, previously adopted for cardiovascular modeling under uncertainty [27]. Specifically, we employ the Expansion Optimal Linear Estimation (EOLE) [28] method to generate Gaussian random fields of elastic modulus and thickness focusing on the coronary bypass grafts, under the assumption that a local change in material properties will not affect the full multi-scale model boundary conditions.

Finally, we perform uncertainty propagation through spectral stochastic expansion [29], i.e., by constructing stochastic surrogates for two quantities of interest: the space-time averages of wall shear stress and wall strain. This approach leverages prior methodological developments that improve efficiency of sampling methods to appropriately handle functions with sharp gradients or discontinuities.

The paper is outlined as follows. Section II describes the methods and workflow used in this study. We first describe the multi-scale model used to compute flow in coronary bypass grafts, then discuss the submodeling approach with the polynomial surrogate, then describe the random field methodology, and discuss key details about the propagation strategy.

Section III provides results from the analysis for three patient-specific models, accounting for discrepancies in the submodelling, probability distributions for output quantities of interest, and a sensitivity analysis. In Section IV we discuss the results, and concluding remarks are given in Section V.

2. Methods

2.1. Workflow overview

We first present an overview of the proposed framework, shown in Figure 1, with details in the subsequent sections to describe the different components. The first step is to assimilate all clinical and literature data into an automated tuning framework based on adaptive Markov chain Monte Carlo (MCMC) to sample from the posterior distributions of the inflow and outflow parameters of the patient-specific computational model. These samples are used to run simulations on the entire aorta-coronary-bypass graft geometry (henceforth referred to as the *full model*) for the purpose of uncertainty quantification. Because of the high computational cost of these models, we instead utilize a *submodelling* approach where the bulk of the simulations are run on a subregion of interest, which is comprised of only the bypass grafts in this study. To produce consistent boundary conditions on the graft submodel, a surrogate model is trained to quickly predict the boundary conditions on the submodel from a previously computed library of full model inputs. We used an expansion of Hermite polynomials for this surrogate, and used sparse regression to estimate their coefficients from a training set of $n_I = 125$ deformable full model simulations. Random field modeling is then employed to model the spatial variability of the material properties in the graft submodel. At this point, we perform $n_I + n_{II} = 1000$ submodel simulations at each of the arterial and venous grafts for each patient. The number of submodel evaluations was determined by examining the convergence profiles of the statistical moments of all quantities of interest on the grafts. We finally perform post-processing to compute the quantities of interest and use multi-resolution forward propagation to compute the output statistics.

2.2. Stochastic modeling of coronary flow

State-of-the-art modeling in coronary artery hemodynamics is obtained through a *geometrically multiscale approach* [30, 31, 32] where a three-dimensional flow model, including aorta and coronary arteries, receives boundary conditions from a lumped parameter network (LPN) representation of the peripheral circulation [33], (Figure 2). The solution of a multiscale model depends on several parameters governing different aspects of the underlying physics. In this study, we focus on two specific types of parameters, those in the boundary LPN governing blood flow and pressure in the coronaries, and those in the three-dimensional anatomy characterizing the spatial distribution of vessel wall material properties. Instead of assuming these parameters as completely determined, we treat them here as stochastic quantities, subject to uncertainty, and aim to determine the variability this uncertainty produces on model predictions of relevant clinical indicators. The next sections describe in detail the two components of a stochastic multi-scale approach to study coronary hemodynamics.

2.2.1. Stochastic three-dimensional flow model—The patient-specific three-dimensional anatomic model is generated through CT image segmentation followed by lofting and boolean union of multiple vessels. The resulting model is meshed into tetrahedral elements and fed to an unsteady incompressible Navier-Stokes solver using stabilized finite elements in space and generalized- α time integration [34, 6]. Vessel wall deformability is included through the coupled- momentum method (CMM), which assumes a linear elastic constitutive model characterized by membrane and shear stiffness [35]. Model creation, meshing and flow solution are performed within the SimVascular open source software platform [36, 37, 38, 39].

Consider a subset $D \subset \mathbb{R}^3$ occupied by blood and characterized by a sufficiently smooth boundary D . The boundary is partitioned into D_h, D_g, D_s , where Neumann, Dirichlet, and wall boundary conditions are respectively applied. To prevent rigid body motion, a mechanically fixed boundary condition (i.e. zero relative displacement and zero velocity) is applied on the perimeters of all inlet and outlet vessels (denoted as Γ_s). There is no external force applied on D_s , so the vessel wall expansion is constrained only by the hemodynamic forces from the blood and the elastic properties of the wall. We also consider a mesh on D , consisting of an assembly of n_{el} linear tetrahedral elements $D_e, e = 1, \dots, n_{el}$. The combined weak form of the stabilized incompressible Navier-Stokes equations and CMM-FSI coupling can be written as

$$\begin{aligned}
 & \int_D \left[\vec{w} \cdot \left(\rho \frac{\partial \vec{v}}{\partial t} + \rho \vec{v} \cdot \nabla \vec{v} - \vec{f} \right) + \nabla \vec{w} : (-p \underline{I} + \underline{\tau}) - \nabla q \cdot \vec{v} \right] d\vec{x} - \int_{\partial D_h} \vec{w} \cdot \vec{h} ds + \\
 & \int_{\partial D_h} q v_n ds + \int_{\partial D_g} q v_n ds + \sum_{e=1}^{n_{el}} \int_{D_e} \nabla q \cdot \frac{\tau_M}{\rho} \vec{\mathcal{Z}}(\vec{v}, p) d\vec{x} + \sum_{e=1}^{n_{el}} \int_{D_e} \left[(\vec{v} \cdot \nabla) \vec{w} \cdot \tau_M \vec{\mathcal{Z}}(\vec{v}, p) + \nabla \cdot \vec{w} \tau_C \nabla \cdot \vec{v} \right] d\vec{x} \\
 & + \sum_{e=1}^{n_{el}} \int_{D_e} \left[\vec{w} \cdot (\rho \widehat{\vec{v}} \cdot \nabla \vec{v}) + (\vec{\mathcal{Z}}(\vec{v}, p) \cdot \nabla \vec{w}) (\bar{\tau} \vec{\mathcal{Z}}(\vec{v}, p) \cdot \vec{v}) \right] d\vec{x} \\
 & + \zeta \int_{\partial D_s} \left[\vec{w} \cdot \rho_s \frac{\partial \vec{v}}{\partial t} + \nabla \vec{w} : \underline{\sigma}^s(\vec{u}) \right] ds - \zeta \int_{\Gamma_s} \vec{w} \cdot \vec{h}_s dl + \\
 & \int_{\partial D_s} q v_n ds = 0,
 \end{aligned} \tag{1}$$

where $\vec{v}$ is velocity, p is pressure, ρ is the blood density, $\underline{\tau} = \mu(\nabla \vec{v} + (\nabla \vec{v})^T)$ is the viscous stress tensor, ζ and $\underline{\sigma}^s$ are the prescribed vessel walls thickness and stress tensor, respectively. Tensors of order one (vectors) and order two (matrices) are also denoted by $\vec{\cdot}$ and $\underline{\cdot}$, respectively. Hemodynamic quantities of interest are obtained by post-processing, as discussed in Section 2.3.

Stochasticity is injected in (1) in the form of an uncertain Young's modulus (implicitly defined in the derivation of $\underline{\sigma}^S$ and thickness ζ). To be more precise, consider a complete probability space $(\Omega, \mathcal{F}, P)$ where Ω is the sample space, $\mathcal{F}$ is a Borel σ -algebra of events, and P is a probability measure defined over events in $\mathcal{F}$. This means that the thickness $\zeta = \zeta(\mathbf{x}, \mathbf{y}_T)$ is a function of the spatial coordinates $\mathbf{x} \in D$ and the random variables $\mathbf{y}_T: \Omega \rightarrow \Sigma_{\mathbf{y}_T}$ and similarly, the Young's modulus $E = E(\mathbf{x}, \mathbf{y}_Y)$. The material property parameters $\mathbf{y}_M = (\mathbf{y}_T, \mathbf{y}_Y)$ are statistically characterized by the density $\rho_M(\mathbf{y}_M) = \rho_T(\mathbf{y}_T) \rho_Y(\mathbf{y}_Y)$, i.e. thickness and elastic modulus are assumed independent.

2.2.2. Stochastic peripheral circulation network—The selected LPN layout extends previous work [40] and models viscous resistance, vessel compliance, and blood inertia through an electrical circuit analogy. It consists of multiple compartments including the pulmonary arteries, an RC model of the systemic circulation, coronary arteries and the four heart chambers. Ventricular contractility is mimicked through an elastance formulation [41], while atrial contraction is simulated through an activation function. Note that a key feature of LPN models for coronary circulation is their ability to capture the diastolic nature of the coronary flow, i.e., the delay in time between maximum coronary flow and systemic pressure [42, 43]. Coronary flow at systole is impeded by high intramyocardial pressure due to ventricular systolic contraction, approximated, in this study, by ventricular pressure, directly inserted into the coronary outlet circuits. All parameters of this peripheral circulation model (resistance, capacitance, inductance and heart model) are referred to as *boundary condition* parameters and denoted by $\mathbf{y}_B$.

To increase patient specificity, we have developed an automated tuning framework [22] where model parameters are assimilated from a combination of clinical and literature data. LPN parameters $\mathbf{y}_B: \Omega \rightarrow \Sigma_{\mathbf{y}_B}$ are treated as random variables, whose probability distribution must be inferred from uncertain clinical targets $d_i, i = 1, \dots, m$ with known variance $\sigma_i^2, i = 1, \dots, m$. To do so, their posterior distribution is first constructed using Bayes' Rule $\rho_B(\mathbf{y}_B | \mathbf{d}) \propto \rho(\mathbf{d} | \mathbf{y}_B) \rho_B(\mathbf{y}_B)$ from a uniform prior $\rho(\mathbf{y}_B)$ and Gaussian likelihood

$$\rho(\mathbf{d} | \mathbf{y}_B) = \frac{1}{\sqrt{(2\pi)^m \prod_{i=1}^m \omega_i \sigma_i^2}} \exp\left(-\frac{1}{2} \sum_{i=1}^m \frac{[d_i - G_i(\mathbf{y}_B)]^2}{\omega_i \sigma_i^2}\right), \quad (2)$$

where $G_i(\mathbf{y}_B)$ are the model predictions for target d_i and ω_i are user-defined weights allowing target prioritization. Second, we sample from the distribution $\rho_B(\mathbf{y}_B | \mathbf{d})$ using adaptive Markov chain Monte Carlo (MCMC) [23]. Finally, a maximum a posteriori estimate of $\mathbf{y}_B$ is determined through Nelder-Mead optimization [44], selecting the initial guess at the the maximum of the posterior sampled through MCMC.

We note that the variances for the uncertain clinical targets $d_i, i = 1, \dots, m$ only reflect uncertainties due to measurement precision in this work. Additional variation in these measurements occurs due to natural physiologic variation and our framework could be

extended to include these in future work, though it would require additional data collection. Because the anatomical geometry was constructed from a snapshot of a patient's possible range of physiologic states, we chose to use measurements consistent with this in the present study. The automated tuning framework accounts for these uncertainties in the data and samples LPN parameters consistent with the data.

2.2.3. Parameter descriptions and uncertainties—Table 1 shows the uniform prior ranges and resulting posterior means and standard deviations from the automated tuning framework for all of the LPN parameters to quantify how much uncertainty is introduced. We also briefly describe the meaning and role of each of the LPN parameters. E_{rv} , E_{lv} are scaling factors for the elastance functions of the right and left ventricles, which define the volume-pressure relationships as the ventricles contract [41]. E_{lvp} is a scaling factor for the derivative of the left ventricle elastance, which is used in specifying the coronary intramyocardial pressure. C_{ao} is the lumped capacitance of the aortic outlets. Kxp_{ra} and Kxp_{la} are scaling factors for the right and left atrium pressures, which uses an activation function formulation to describe its pressure-volume relationship. R_{am} is a scaling factor for the distal coronary resistances. C_{amp} , C_{ap} , C_{amr} , and C_{ar} are scaling factors for the left and right coronary capacitances. R_{rcr} is a scaling factor for the distal aortic resistance. $dPdt_r$ is a down scaling factor for the right coronary intramyocardial pressure.

Table 2 outlines the variability in the material properties for the aorta, coronary, and bypass grafts, which were obtained from the literature [25, 24]. The coronary thickness values and standard deviations were assigned based on morphometric measurements [26], and these thickness values were varied in the model by multiplying the thickness by an uncertain fraction that was derived from [26].

2.3. Patient selection and quantities of interest

Three patients with at least one arterial and one venous graft were considered in this study, selected to represent a wide range of graft configurations (Figure 3). In all three patients, the left internal mammary artery (LIMA) was used for the arterial graft, and the saphenous vein from the leg was used for the venous graft (SVG). Patient 1 has an arterial graft feeding the left circumflex and a venous graft feeding the left anterior descending artery, both of which feed vessels cut off from the occluded native coronaries. Patient 2 has an arterial graft feeding the left anterior descending artery and a venous graft feeding the left circumflex. Patient 3 has an arterial graft feeding the left anterior descending artery, one venous graft that feeds the obtuse marginal (SVG_1), and another venous graft feeding the right coronary artery (SVG_2). Table 3 summarizes the geometry characteristics of all grafts considered in this study, including average cross sectional area, length, average curvature, and average circularity.

We focus on two measures of stress resulting from hemodynamics and wall mechanics, respectively. The instantaneous wall shear stress $\vec{\tau}(\mathbf{x}, t, \mathbf{y})$ evaluated at a single spatial location measures the mean viscous force that the blood exerts on the vessel wall, where $\mathbf{y} = (\mathbf{y}_B, \mathbf{y}_M)$. Our interest focuses, in this study, on time and space-time averages of the magnitude of $\vec{\tau}(\mathbf{x}, t, \mathbf{y})$, i.e.

$$\vec{\tau}_t(\mathbf{x}, \mathbf{y}) = \frac{1}{T_C} \left| \int_0^{T_C} \vec{\tau}(\mathbf{x}, t, \mathbf{y}) dt \right|, \text{ and } \vec{\tau}_{st}(\mathbf{y}) = \frac{1}{A_g} \int_{A_g} \vec{\tau}_t(\mathbf{x}, \mathbf{y}) d\mathbf{s}, \quad (3)$$

where T_C is the duration of the cardiac cycle in seconds and A_g is the lumen surface of the bypass graft or walls of a specific coronary branch. Additionally, we normalize $\vec{\tau}_{st}(\mathbf{y})$ by $\vec{\tau}_{st}^A$, i.e., the space-time average in the aorta computed at the maximum a posteriori estimate of the boundary conditions parameters. This facilitates the comparison of $\vec{\tau}_{st}(\mathbf{y})$ across patients, consistent with the approach suggested in [10]. Expectation with respect to the random inputs $\mathbf{y}$ is denoted as usual with $\mathbb{E}[\vec{\tau}_{st}(\mathbf{y})]$, i.e., $\int_{\Sigma_y} \vec{\tau}_{st}(\mathbf{y}) \rho(\mathbf{y}) d\mathbf{y}$.

Our second quantity of interest is an objective measure of vessel wall strain, i.e., the first Green strain invariant $I^1(\mathbf{x}, t, \mathbf{y})$. This quantity is computed using relative displacements with respect to the diastolic configuration [45], i.e.

$$I^1(\mathbf{x}, t, \mathbf{y}) = \text{tr} \left[\frac{1}{2} (\underline{\mathbf{F}} \underline{\mathbf{F}}^T - \underline{\mathbf{I}}) \right], \text{ where } \underline{\mathbf{F}} = \nabla (\vec{u} - \vec{u}_0), \quad (4)$$

where $\underline{\mathbf{F}}$ is the displacement gradient tensor, $\underline{\mathbf{I}}$ is the identity matrix, $\text{tr}[\cdot]$ is the trace operator and $\vec{u}_0(\mathbf{x}, \mathbf{y})$ denotes the diastolic displacements at a single material point. Time, space-time averages and expectations are computed similarly to the wall shear stress, introducing $I_t^1(\mathbf{x}, \mathbf{y})$, $I_{st}^1(\mathbf{y})$ and $\mathbb{E}[I_{st}^1(\mathbf{y})]$.

Prior studies have shown that these two quantities differ substantially for arterial vs. venous grafts, and that these differences are consistent over multiple patients [10]. This study complements and extends previous work by quantifying how boundary conditions and material model uncertainty affect this result.

2.4. Stochastic Submodeling

Repeated evaluations of a multi-scale model in the context of non-intrusive uncertainty propagation can easily exceed a reasonable computational budget. However, in this case all quantities of interest derive from either the arterial or venous bypass grafts, which comprise only a small fraction of the total degrees of freedom. This suggests that it would be desirable to solve only for the graft hemodynamics (i.e. *submodel*) to greatly reduce the overall computational effort (Figure 4). The submodel boundary conditions must be consistent with the primary variables (velocity and pressure) of the full model. In other words, given a realization of the random inputs $\mathbf{y}$, both the full model and submodel must produce the same solution within the graft. To enforce consistency, we first developed an automatic procedure to extract velocities and pressures at the inlets and outlets of the graft submodel from a training set of 125 full model simulations. We then used sparse regression to train a

polynomial surrogate to re-parameterize the submodel boundary conditions in terms of the full model random inputs $\mathbf{y}$. This polynomial surrogate can then be interrogated for new cases to predict submodel boundary conditions at any other point in the parameter space of the full model inputs without having to run full model simulations. Specifically, we used this surrogate to predict submodel boundary conditions for 875 additional full model parameter sets, avoiding 2625 costly full model simulations across the three patients.

2.4.1. Mapping full model solutions onto submodel boundary conditions—

Submodels for each patient and each graft were generated in SimVascular by re-using the full model segmentation groups. Thus, graft tetrahedral meshes containing approximately 250,000 finite elements (for comparison, a full model discretization contains approximately 2 million elements) were generated, minimizing discrepancies in mesh density between the two models at the grafts. Additionally, a boundary layer mesh was applied to both models, to guarantee mesh independence in the computation of wall-shear stress.

Submodel analysis was performed using Dirichlet velocity boundary conditions at the inlets and Neumann pressure boundary conditions at the outlets. Note that a rigorous way to perform submodel analysis would be through the application of all main variables (velocity and pressure) at both the inlets and outlets. This, however, is not possible due to the nature of the underlying equations. We thus choose to apply Dirichlet velocity boundary conditions at the graft submodel inlet and Neumann pressure boundary conditions at the outlet to ensure spatial velocity profile information is preserved at the inlet and the pressure is computed accurately throughout. The graft submodel also experiences rigid body motion since the inlet and outlet are not fixed in the full model simulation. To account for this motion, the initial displacement is applied to the perimeter nodes of the graft submodel, and their wall velocities are also subsequently applied throughout the simulation.

Velocities at the graft inlet, pressures at the graft outlet, and initial displacements on the perimeter nodes of the inlet and outlet faces were systematically obtained from full model slices through a Python VTK script, followed by shape function interpolation to transfer velocities and pressures across models. Nearest neighbor interpolation was finally used for boundary nodes in the submodel that were found external to the full model mesh.

We assessed the consistency between full model and submodel solutions by comparing differences in inlet pressure, outlet flow, $\vec{\tau}_{st}(\mathbf{y})$, and $I_{st}^1(\mathbf{y})$ on Patient 1, as summarized in Figure 5. The accuracy in the submodel results was found to be affected by the frequency of velocity and pressure extraction during time integration of the full model. The timestep size was set such that 1000 timesteps would complete a full heart cycle (for both the full model and submodel), which resulted in timestep sizes of 1.30 ms for Patient 1, 1.11 ms for Patient 2, and 0.61 ms for Patient 3. At submodel timesteps where full model results were not extracted, linear interpolation was used between the two closest full model saves to determine appropriate values of velocity and pressure. Saving full model results at every timestep would thus result in no interpolation error in time and more accurate submodels, however this resulted in impractical memory requirements. We therefore decided to save the full model results every five timesteps to provide a reasonable trade-off between memory

and submodel accuracy. This produced 200 timepoints of data over the entire cycle, with a time resolution of 6.5 ms for Patient 1, 5.55 ms for Patient 2, and 3.05 ms for Patient 3.

2.4.2. Parameterization of submodel boundary conditions through sparse regression—In this section, we discuss how we parameterized stochastic surrogates of the submodel boundary conditions as functions of $\mathbf{y}$, to associate a reduced-order model to any specific realization of the random inputs. To do so, we employed a sparse polynomial chaos surrogate using Hermite polynomials, following prior work [46]. Boundary pressure and velocities are expressed as

$$u_i(\mathbf{x}, t) = \sum_{j=1}^{n_b} \alpha_{j,i}(\mathbf{x}, t) \phi_j(\mathbf{y}), \quad (5)$$

where $u_i(\mathbf{x}, t)$ is a nodal velocity or pressure at a specific timepoint, $\phi_j(\mathbf{y})$ are multi-variate Hermite polynomials and $\alpha_{j,i}(\mathbf{x}, t)$ are expansion coefficients. We trained this polynomial surrogate using 125 full model simulations, and used Relevance Vector Machines (RVM, a sparsity promoting Bayesian regression framework) [47, 48], to compute the coefficients by solving a regression problem in 17 dimensions (corresponding to the 17 full model LPN parameters $\mathbf{y}_B$). This number of full model simulations was selected based on the submodel's ability to produce results consistent with the full model. We trained the coefficients $\alpha_{j,i}(\mathbf{x}, t)$ using the first 100 full model simulations, and used the remaining 25 full model simulations to compare with the submodel predictions of the $\vec{\tau}_{st}(\mathbf{y})$ and $I_{st}^1(\mathbf{y})$. We found that stochastic surrogate-based submodel produced $\vec{\tau}_{st}(\mathbf{y})$ with a maximum discrepancy error of 5.7% and $I_{st}^1(\mathbf{y})$ with a maximum discrepancy error of 4.8% from the full model simulations. The coefficients were then updated with the additional 25 full model simulations of the testing to improve their accuracy. The parameters for these 125 simulations were chosen such that they provided strong coverage over the entire parameter space by maximizing a normalized distance metric between all the parameter sets in the selection.

The accuracy of an RVM regressor was compared with that of an ordinary least squares (OLS) regressor (see, e.g., [49]) using a training and testing set of 100 and 25 simulations, respectively and found that RVM produced more accurate results in the pressure and velocity 70% of the time. Figure 6 compares the estimated waveforms using RVM and OLS with comparison to the extracted full model waveforms. The bias observed in the OLS pressure waveform in Figure 6a and the oscillations in the OLS velocity waveform in Figure 6b can be attributed to the tendency for OLS regressors to overfit the training data. That is, the OLS regressor computes coefficients such that the results match very well for the training data, but it exhibits poor generalization on other datasets. Due to the sparsity in the coefficients generated by the RVM regressor, it is far less likely to overfit and thus generally produces more accurate results for conditions outside of the training set.

We emphasize that all nodal quantities have separate, independent surrogate models. This may affect their consistency and create oscillations, particularly in time. To mitigate this effect, we used a Savitzky-Golay filter [50], which performs convolution of the oscillatory velocity/pressure profiles with a polynomial obtained by fitting the neighboring m data points using least squares. For equally spaced data points, the filtered quantity u_j is obtained as

$$u_j = \sum_{i = -(m-1)/2}^{(m-1)/2} C_i u_{j+i}, \frac{m-1}{2} \leq j \leq n - \frac{m-1}{2} \quad (6)$$

where j is a discrete time, C_i are the filter weights and n is the total number of time points. Additionally, the small inconsistencies remaining between full model and submodels hemodynamics due to the oscillations mentioned above are further mitigated in the uncertainty propagation task, as discussed in Section 2.6.

2.5. Random field modeling of material properties

Deformable wall simulations require specification of material properties on all vessel wall surface meshes. A typical approach, is to assign spatially uniform Young's moduli and thickness to specific vessels/branches such as the aorta and coronary arteries [10]. Although this accounts for large differences in material properties between vessels, it neglects the local spatial variation of these properties, in contrast to experimental findings conducted on the human aorta [27, 25]. Despite this, exact distributions of material properties remain largely unknown due to challenges of measuring material properties with medical imaging, differences between patients, and local remodeling. Even less is known about the spatial variation of material properties in coronary bypass grafts, where published results are limited to average values and standard deviations over the entire graft [24]. In this context, random fields provide a natural tool for modeling spatial variations in material properties while at the same time capturing the ensemble statistics reported in the literature. A random field is a collection of random variables F_z indexed by the elements of a topological space Z , i.e., $\{F_z : z \in Z\}$. In this study, we neglect the variation in the material properties over the graft circumference, and parameterize the random field only over the distance z along the vessel centerline. The resulting one-dimensional random field is both physiologically realistic given the small graft cross section, but also efficiently reduces the number of independent parameters needed to describe the field, and hence the dimensionality of our uncertainty quantification task.

Random fields can be discretized in a finite number of random variables through many approaches proposed in the literature, e.g., spectral representation [51], a weak solution of a stochastic partial differential equation [52], or using the well-known Karhunen-Loève expansion [53]. The Expansion Optimal Linear Estimation (EOLE) approach is followed throughout this study [28]. In this approach, the graft centerline is discretized uniformly at the s spatial locations $\{\mathbf{x}_1, \mathbf{x}_2, \dots, \mathbf{x}_s\}$. These are further partitioned in a set of control points $\{\tilde{\mathbf{x}}_i, i = 1, \dots, s_c$ and the remaining $\{\bar{\mathbf{x}}_i, i = 1, \dots, s - s_c$. The thickness and Young modulus random fields are assumed Gaussian (since only the first two statistical moments are

available from the literature), and expressed through a linear combination of random variables at the control points and modal shape functions (see Figure 7a). Additionally, the Gaussian distribution is closed with respect to linear transformations and this facilitates the decomposition in independent random variable determined through the EOLE approach. The modes are determined from an eigenvalue decomposition of the control point covariance $\tilde{\mathbf{C}}$, i.e.

$$v(\mathbf{x}) = \mu + \sum_{i=1}^N \frac{\xi_i}{\sqrt{\theta_i}} \psi_i^T \Sigma_{v(\mathbf{x})v(\mathbf{x})}. \quad (7)$$

In equation (7), $v(\mathbf{x})$ is the resulting random field, θ_i and ψ_i are the eigenvalues and eigenvectors of $\tilde{\mathbf{C}}$, respectively, $\Sigma_{v(\mathbf{x})v(\mathbf{x})}$ is the cross covariance between $\{\tilde{\mathbf{x}}_i\}$ and $\{\tilde{\mathbf{x}}_i\}$, and the ξ_i are independent Gaussian random variables. The mean function μ is assumed to be constant, consistently with other approaches in the literature [54, 24]. The number of modes N included in the expansion (7) was chosen to be 10, as further increases in the number of modes would not increase the accuracy in the random field (see Figures 7b and 7c). This allowed modeling of relatively fine scale spatial variations in material properties, and kept our forward propagation problem to a reasonable cost.

The covariance matrix is determined from a squared exponential correlation function which has been previously used in the literature [27], i.e.

$$\rho(\mathbf{x}, \mathbf{x}') = \sigma^2 \exp\left[-\frac{(\mathbf{x} - \mathbf{x}')^2}{a^2}\right], \quad (8)$$

where σ^2 is the process variance [54, 24] and a is the selected correlation length.

As little is known about the spatial correlation in the material properties for bypass coronary grafts, we have used a plausible correlation length from the literature [27] for all patients, and have also investigated how a change in this quantity affects the statistics of hemodynamic and mechanical indicators. A reference correlation length equal to 3.7 cm was considered for the three patients included in this study. Additionally, Patient 1 and 2 are analyzed for correlations lengths of 7.2 and 0.95 cm, respectively.

Due to the unbounded support of the Gaussian distribution, some of the random field realizations were found to be associated with negative or extremely small thickness and, similarly, large variations in the elastic modulus. These negative and extremely small values of thickness and Young's modulus caused either divergence or non-sensical values in our numerical solution. We therefore rejected any random field realization producing an elastic modulus or thickness less than two standard deviations from the mean. We also considered a two-way rejection of material property realizations, i.e. rejecting thickness or Young's modulus values that were either two standard deviations above or below the mean. Errors in the mean and standard deviation of the random field with no rejection, one-way rejection,

and two-way rejection are summarized in Figures 7b and 7c. Performing one-way rejection for only small and negative values shifts the random field mean up by $\sim 2.8\%$ from the true mean, while performing no rejection or two-way rejection results in negligible errors. Both one-way rejection and two-way rejection caused the random field standard deviation to be underestimated relative to the true standard deviation, with one-way rejection producing $\sim 8.2\%$ error and two-way rejection producing $\sim 17.5\%$ error. Our chosen method of one-way rejection thus only incurs minimal errors in the modeled mean and standard deviation of the random field, while also ensuring stable and reliable numerical solutions. The number of control points appears to have no effect on the accuracy of the random field approximations.

This rejection process directly affects the Gaussianity of the independent random variables ξ_j and new distributions need to be determined for these variables which produce admissible thickness and elastic modulus. Thus, these distribution were determined through rejection sampling and re-fitted using kernel density estimation. An alternative way to prevent negative or small values of the Gaussian random field estimation of the material properties would be to use a non-Gaussian random field, such as a log-normal field. Monotonic transformations can be used to generate non-Gaussian random fields, however it is a delicate matter to work with such variables in the context of uncertainty propagation due to the convergence in L_2 of the associated generalized polynomial chaos expansion, as discussed in reference [55]. But through the rejection of inadmissible material properties, we are *de facto* using other distributions, a justified compromise that uses the data available from the literature.

2.6. Forward uncertainty propagation

Here, we focus on the statistical characterization of a generic multi-scale model result $u(\mathbf{x}, t, \mathbf{y})$ due to the variability of the random inputs $\mathbf{y}$, at a fixed spatial location and time.

In a previous study from our group [22], boundary conditions random inputs $\mathbf{y}_B$ in multi-scale coronary models were first assimilated from uncertain clinical data, followed by propagation to $u(\mathbf{y})$ using Monte Carlo sampling, i.e., using the estimators

$$\mu_u = \frac{1}{n_{MC}} \sum_{i=1}^{n_{MC}} u_i, \sigma_u = \sqrt{\mathbb{V}[u]} = \sqrt{\frac{1}{n_{MC}-1} \sum_{i=1}^{n_{MC}} (u_i - \mu_u)^2}, \quad (9)$$

where n_{MC} is the total number of Monte Carlo samples and u_i the quantity of interest evaluated at the i -th realization of the random inputs $\mathbf{y}_B$.

In this study, we instead adopt a multi-resolution approach to forward uncertainty propagation [29], motivated by the large number of samples typically required by Monte Carlo and hence its large expected computational cost. This extends the generalized polynomial chaos expansion (gPCE) [56, 55], and determines a truncated representations of $u(\mathbf{y})$ in terms of generalized Alpert multi-wavelets [29]

$$u(\mathbf{y}) \approx \sum_{i=0}^{P-1} \alpha_i \psi_i(\mathbf{y}), \quad (10)$$

where the multi-wavelets $\psi_i(\mathbf{y})$ are orthogonal with respect to the underlying distribution of the random inputs $\mathbf{y}$ such that,

$$\langle \psi_i, \psi_j \rangle = \int \psi_i(\mathbf{y}) \psi_j(\mathbf{y}) \rho(\mathbf{y}) d\mathbf{y} = \delta_{ij}. \quad (11)$$

An orthonormal multi-resolution expansion naturally encodes refinement metrics for multi-element partitions of the random inputs, and is particularly effective if the stochastic response is characterized by sharp gradients or discontinuities. The coefficients α_i , $i=0, \dots, P-1$ are computed through stochastic regression from an ensemble of model evaluations at randomly sampled input realizations, and directly used to determine the statistical moments

$$\mathbb{E}[u(\mathbf{y})] = \alpha_0, \text{ and } \mathbb{V}[u(\mathbf{y})] = \sum_{i=1}^{P-1} \alpha_i^2. \quad (12)$$

In this study, we assume that the parameters in $\mathbf{y}$ are statistically independent for computational convenience. To assess the validity of this assumption, we have plotted the correlation coefficients for all inputs in Figure 9. We first observe that all the parameter correlations for the random field parameters (i.e. parameters 14 through 37) have 0 correlation, as expected. The first 13 LPN parameters exhibit correlation as a result of their MCMC sampling, with select cases exhibiting significant coefficients. The maximum magnitude correlations for each of the three patients was found to be 0.6011, 0.7213, and 0.6658, with the average correlation in each patient being 0.0852, 0.1113, and 0.1304. We computed the total sensitivity indices for the five parameters with the highest correlations to assess their effect on the variance of the result. Averaged across all patients and quantities of interest, parameters 2, 3, 6, 8, and 11 (see Table 1) had total sensitivities of 0.0223, 0.0388, 0.0303, 0.0279, and 0.0044 showing that the results would be minimally impacted had these correlations been considered.

The same coefficients can be used for sensitivity analysis [57]. Consider a *Sobol'* or ANOVA variance decomposition [58] of the response quantity of interest $u(\mathbf{y})$

$$\mathbb{V}[u(\mathbf{y})] = \int u(\mathbf{y})^2 \rho(\mathbf{y}) d\mathbf{y} - \bar{u}^2 = \sum_{j=1}^d \sigma_j^2 + \sum_{j=1}^{d-1} \sum_{k=j+1}^d \sigma_{j,k}^2 + \dots + \sigma_{1,\dots,d}^2, \quad (13)$$

into contributions accounting for an increasing number of interacting inputs. The so-called Sobol' direct sensitivity indices can be computed from this decomposition by dividing each contribution by the total variance $\mathbb{V}[u(\mathbf{y})]$, i.e.

$$S_{j_1, \dots, j_l} = \frac{\sigma_{j_1, \dots, j_l}^2}{\sigma^2}, \quad \text{where,} \quad \sum_{j=1}^d S_j + \sum_{j=1}^{d-1} \sum_{k=j+1}^d S_{j,k} + \dots + S_{1, \dots, d} = 1. \quad (14)$$

It is important to remark how, due the orthogonality of the generalized Alpert multi-wavelets used in this study, the expansion (10) determines a Sobol' decomposition with the additional property that contributions of increasing polynomial orders, multi-wavelet and multi-scaling functions can also be identified. This means that the coefficients $\alpha_{\hat{p}}$ can also be used directly to identify the contributions of single and combined inputs to the total variance $\mathbb{V}[u(\mathbf{y})]$.

To mitigate the computational cost of forward propagation and to accommodate possible small inconsistencies between full model and graft submodel, we combine their evaluations through a *telescopic expansion* of the form

$$u_F = u_S + (u_F - u_S), \quad (15)$$

where u_F represents an output quantity generated by the full model, u_S represents the submodel output, and $u_F - u_S$ represents their discrepancy. We note that the submodel approximates well the response of the parent multi-scale model within the graft, but small discrepancies may be generated due to interpolation and mapping of boundary conditions. We therefore consider the graft submodel as a low fidelity representation and expect the difference $u_F - u_S$ to be sufficiently smooth and therefore well approximated by a multi-resolution representation determined by regression from a sufficiently small number of model evaluations. Statistical moments for the multi-scale results can then be computed by

$$\mathbb{E}[u_F] = \underbrace{\mathbb{E}[u_S]}_{\text{variability due to } \mathbf{y}_B \text{ and } \mathbf{y}_M} + \underbrace{\mathbb{E}[u_F - u_S]}_{\text{variability due to } \mathbf{y}_B} \quad (16)$$

$$\mathbb{V}[u_F] = \mathbb{V}[u_S] + \mathbb{V}[u_F - u_S] + 2C(u_S, u_F - u_S). \quad (17)$$

The response u_S is computed using the submodel, and $[u_F - u_S]$ results from both models evaluated at the same realization $\mathbf{y}_B$ of the boundary condition parameters, while $C(u_S, u_F - u_S)$ is determined from the sample covariance of the stochastic surrogates constructed, separately, for u_S and $u_F - u_S$. The terms in this telescopic expansion are used to correct the statistical moments generated from the submodel so they more accurately reflect the full model output statistics.

Specifically, submodel result statistics (i.e., $\mathbb{E}[u_S]$) are obtained from the $n_I + n_{II}$ submodel evaluations. Statistics on the difference between the multi-scale and sub-models (i.e., $\mathbb{E}[u_F - u_S]$) are instead computed by additional sub-model evaluations at $\mathbf{y}_{B,I}^{(i)}$, $i = 1, \dots, n_I$ but using

the mean spatial thickness and elastic modulus, consistent with the multi-scale model solutions evaluated at the same realizations. Thus, the difference term in the telescopic expansion (15) relates only to the error in the submodel flow approximation, due to extraction of boundary conditions and regression, while material property variability is only accounted for in the expectation $\mathbb{E}[u_S]$. In other words, we assume that the material properties in the multi-scale model do not affect the assimilation of LPN boundary parameters and we use a random field description of thickness and elastic modulus only in the region of interest, i.e., the grafts. For an elastic homogeneous straight cylindrical vessel free to expand in the axial direction, the compliance (inverse stiffness) can be approximately computed according to the following expression:

$$\frac{\delta_r}{p} = \frac{r^2}{bE},$$

where r is the cylinder radius, p the internal pressure, b its thickness and E the elastic modulus. Therefore, an average compliance ratio between aorta and arterial coronary graft, assuming their elastic modulus to be very similar, can be approximated using

$$\frac{C_A}{C_C} = \frac{r_A^2}{b_A E_A} \cdot \frac{b_G E_G}{r_G^2} \approx \frac{r_A^2 b_G}{r_G^2 b_A} = \frac{1.7^2 \cdot 0.01}{0.1^2 \cdot 0.17} \approx 17,$$

and therefore the ideal aortic compliance is approximately one order of magnitude greater than in the venous graft. We thus assume the flow boundary conditions on the graft to be independent of the stiffness of its elastic walls.

3. Results

3.1. Submodel cost analysis

Table 4 shows the average computational cost in CPU hours per full and submodel simulations in all patients. We performed 125 full simulations to train the sparse surrogate, then 1000 of each submodel simulation to achieve convergence in the first and second statistical moments. This is compared with the projected cost of running 1000 full simulations to reach similar convergence, resulting in a computational savings of 2270402 CPU hours.

3.2. Calculation of full model statistics

We now present the computed full model statistics for the time-averaged wall shear stress and wall strain. The submodel statistics $\mathbb{E}[u_S]$ and $\mathbb{V}[u_S]$ are computed using multi-resolution stochastic regression from $n_I + n_{II}$ samples, while $\mathbb{E}[u_F - u_S]$, $\mathbb{V}[u_F - u_S]$, and $\mathbb{C}[u_S, u_F - u_S]$ are computed using n_I samples, with both multi-scale and sub-model evaluated at the same parameter realizations. The assembled multi-scale model statistics ($\mathbb{E}[u_F]$ and $\mathbb{V}[u_F]$) are reported in Table 5 for $\vec{\tau}_{st}$ where full model statistics are closely approximated by sub-modeling. The sub-model approximation is worse in Patient 3 than in the other two patients, especially with respect to the variance. One possible reason is related

to the higher heart rate for this patient, 99 bpm, compared to 46 bpm and 54 bpm for Patients 1 and 2, respectively, which leads to increased velocities of the deformable vessel wall (0.518 cm/s for Patient 1, 0.721 cm/s for Patient 2, and 1.512 cm/s for Patient 3). As discussed in Section 2.4.1, the perimeter node velocities at the inlet and outlet faces were estimated with a nearest neighbor approximation, as opposed to the more accurate barycentric interpolation used for the interior velocities. The lower order approximation of the wall velocities negatively affected the submodel accuracy of Patient 3, where the wall velocities were higher. Table 6 illustrates how wall strain values are very well estimated from the submodel, which is likely because the wall displacements do not depend as much on the sub-model inflow and outflow conditions.

3.3. Comparison of output distributions on graft quantities of interest

Figure 10 shows the output distributions for $\vec{\tau}_{st}(\mathbf{y})$ and $I_{st}^1(\mathbf{y})$ obtained by following the workflow discussed in Section 2.1. First, Figure 10a examines the distributions of $\vec{\tau}_{st}(\mathbf{y})$ for patients 1, 2 and 3. Significant differences of this indicator were observed in [10] between arterial and venous grafts, with higher values found, as expected, in arterial grafts. This difference is confirmed in our study with the exception of Patient 3, for whom the arterial and venous grafts had similar cross sectional area, unlike the other two patients. The differences in wall shear for Patient 3 resulted from differences in flow rates in the grafts. Venous graft 2 ($SV G_2$) of Patient 3 feeds the entire right coronary artery tree, requiring a higher flow rate, while the arterial graft and other venous graft each feed a portion of the left coronary arteries (Figure 3c). Higher flow rates lead to higher velocity gradients at the wall, and thus higher shear. Figure 16 confirms that $SV G_2$ had roughly 5× the flow as the arterial graft in Patient 3, leading to much higher wall shear stress values.

Figure 10b shows the output distributions for the wall strain. The computed I_{st}^1 was significantly different between arterial and venous grafts across patients in [10], but this is not true when considering uncertainties in the data. Even though the two grafts have relatively different means, they exhibit significant variation (Table 6). Similarly, the output distributions show significant qualitative overlap, and so it is difficult to attribute any significant difference. One possible reason for the large discrepancy between the intra- and inter-patient results may relate to the different treatment of the material properties in the two studies. Wall strain is computed directly from the displacement gradient of the vessel walls, and therefore is significantly affected by the Young's modulus and thickness. In [10], the same material properties were assumed for the arterial and venous grafts for all patients, which led to a limited variance for the computed I_{st}^1 across patients. In the current study, we instead consider uncertain material properties, so I_{st}^1 exhibits a significantly larger variability.

3.4. Sensitivity analysis

Figures 11 and 12 show the total sensitivity indices for $\vec{\tau}_{st}$ and I_{st}^1 , respectively. We used these to examine the contributions of single parameter effects and two parameter interactions to the computed variance. The full model LPN parameters are tagged as either Systemic (i.e.

heart model, downstream aortic RCR) or Coronary (i.e. downstream coronary outlet BCs). Random field material property parameters are tagged as either Modulus (i.e. Elastic modulus) or Thickness (i.e. vessel wall thickness). Bar heights represent total sensitivity contributions from all single and two parameter effects from each groups.

The sensitivity analysis for $\vec{\tau}_{st}$ in Figure 11 generally show LPN parameters (i.e. affecting flow) in the systemic and coronary groups have a higher relative contribution to the variance, with the exception of $SV G_2$ in Patient 3. Total inflow into the grafts has a significant impact on the wall shear since it strongly affects the velocity magnitudes at the walls. Both the arterial and venous graft for Patient 1 receive the largest contribution to the variance from the coronary parameters. Patient 1 was unique in that the left main coronary artery had completely occluded, so that the bypass grafts had to provide the flow to the left anterior descending and the left circumflex and thus had the highest total inflow. The downstream coronary resistance thus significantly contributed to the variance of $\vec{\tau}_{st}$. For Patient 2, the arterial graft shows a larger contribution from the coronary parameters while the venous graft shows larger contribution from the systemic parameters. One possible reason could be the difference in graft geometry. The arterial graft outlet directly empties into a coronary outlet, so the coronary outlet resistance will significantly impact the flow through the graft. In contrast, the outlet of the venous graft is farther away from the coronary outlets, and its inlet is close to the aortic inlet justifying a larger systemic contribution. Finally, results for Patient 3 appear different from the other two patients. Since Patient 3 had relatively high wall velocities due to the high heart rate, the motion of the wall (and hence the modulus and thickness parameters) strongly influenced the wall velocity gradients. The arterial graft of Patient 3 also exhibits relatively large contribution from the systemic group likely due to the proximity of the graft inlet to an aortic outlet. This illustrates that different patients can have different sensitivities, and highlights the importance of performing uncertainty analysis across multiple patients. The prevailing observation is that all the parameter groups make a significant contribution to the variance of $\vec{\tau}_{st}$, and their interactions must be accounted for in an uncertainty analysis.

Figure 12 shows the sensitivity analysis for I_{st}^1 . Across all three patients, we observe that the wall material properties (i.e. modulus and thickness groups) contribute most to the uncertainty. We also observe that the relative contributions of elastic modulus and thickness are roughly the same in all grafts. The systemic and coronary groups also make significant contributions to the variance of I_{st}^1 , as these parameters determine the magnitude of the pressure oscillations, which are the driving forces for wall deformation. Although the material property parameters contribute most to the uncertainty in I_{st}^1 , their interactions with other parameters must also be accounted for.

3.5. Spatial distributions of uncertainty

We next examine spatial distributions for the statistics of pressure, $|\vec{\tau}_t(\mathbf{x}, \mathbf{y})|$ and $I_t^1(\mathbf{x}, \mathbf{y})$, and possible correlations with the geometric features of the graft, as shown in Figure 13 for the $SV G_2$ in Patient 3. The distribution of the mean time-averaged pressure in Figure 13a shows

a gradual decrease along the length of the graft. This graft experiences a pressure drop of about 1.3 mmHg, which is expected given its patent status. The standard deviation is instead nearly constant in space, as a change in the outlet resistance produces a uniform shift in pressure throughout the vessel.

Figure 13b shows the spatial distribution of $|\vec{\tau}_t(\mathbf{x}, \mathbf{y})|$, which, unlike the pressure, exhibits significant oscillations down the length of the graft. These oscillations are attributed to geometrical changes, producing local perturbations in the streamwise and wall velocities (Figure 14). A significant negative correlation is observed between the cross sectional area and wall shear stress, as expected. The spatial distribution of $E[|\vec{\tau}_t(\mathbf{x}, \mathbf{y})|]$ and $V[|\vec{\tau}_t(\mathbf{x}, \mathbf{y})|]$ are qualitatively similar, indicating that the variance produced by a change in flow is magnified by the local graft geometry. Indeed, Figure 16 shows a positive correlation between total inflow and $|\vec{\tau}_{st}|$ for all patients.

The spatial distribution of I_{st}^1 , has a coefficient of variation that appears to be significantly larger than for the pressure or $|\vec{\tau}_{st}|$ (Figure 13c). This shows that the uncertainty in the material properties induces variations in wall strain all throughout the graft. Also, the nearly uniform distribution of coefficient of variation of $I_t^1(\mathbf{x}, \mathbf{y})$ suggests that the wall strain distribution is driven by the graft geometry, as observed for the wall shear stress. In other words, since the pressure drop is minimal over the length of the graft and the strain component along the centerline can be neglected, circumferential strains should be proportional to the diameter as suggested by the Mariotte formula for an ideal straight cylindrical vessel, i.e. $\epsilon_C = \sigma_C/E = pd/(2\zeta E)$, where ϵ_C and σ_C are the circumferential strain and stress components, respectively, E is the elastic modulus of the wall, p the pressure, d the vessel diameter and ζ the vessel thickness. Hence, both the largest mean strain and its standard deviation should occur at the location of maximal cross sectional area. We observe a general positive correlation between the cross-sectional area and I_{st}^1 down the length of the graft (Figure 15) as expected. To examine the effect of the random field on the spatial distribution of mean and standard deviation of I_{st}^1 , we contrasted the above results with the mean and standard deviation of I_{st}^1 from our training set of 125 full model simulations for $SV G_2$ of Patient 3, where the material properties were kept spatially constant. The mean and standard deviation exhibit the same positive correlation with the cross-sectional area as expected, but the magnitudes of the standard deviation are lower due to the constant material properties (Figure 15c). It is also worth noting that despite the random field variations of material properties, the spatial distribution looks similar to the constant material property case. In the limit of increasing number of realizations of the random field, their ensemble statistics resemble that of the mean field. Since the mean field is exactly the spatially constant material properties, it makes sense for the two cases to exhibit similar spatial distributions of I_{st}^1 .

3.6. Random field material parameter effects on wall strain

Variations in vessel wall stiffness for coronary artery grafts models have been described, in this study, through random field theory. These variations have been found to significantly impact the spatial distribution of wall strain (Figure 17). To analyze the impact of the random field correlation length on our quantities of interest, we repeated the analysis for Patients 1 and 2 with correlation lengths of 7.2 cm (longer, Patient 1) and 0.95 cm (shorter, Patient 2) and compared them to the baseline value of 3.7 cm (Table 7). We observe negligible differences when using a longer correlation length, and lower variance when using a shorter correlation length. Shorter correlation lengths produce modes with higher spatial frequency, increasing the likelihood that the combined effects of the modes will trend towards the mean, leading to lower variance in the wall strain. This shows that proper selection of correlation length is important to consider for future studies using random field variations of material properties. In this study, we used a plausible correlation length from the literature, but more measurements on the variations of material properties in bypass grafts need to be done to accurately assign this parameter.

3.7. Effect of total flow and geometry on computed wall shear

The spatial distribution of wall shear stress appears to be significantly affected by the graft cross sectional geometry at a specific location along its centerline. In this regard, we evaluated how much the cross section distribution and tortuosity along the graft centerline affects the computed wall shear stress and the resulting degree of departure from ideal Poiseuille flow conditions. A strong correlation is observed between total inflow and $|\vec{\tau}_t(\mathbf{x}, \mathbf{y})|$ in both the grafts in Patient 1 and $SV G_2$ in Patient 3, characterized by a larger total inflow (Figure 16). In these cases, the ratio between the centerline flow velocity and the wall velocity was high, indicating that the flow was the most significant factor in affecting the wall shear. The average ratio of centerline velocity to wall velocity for the arterial graft in Patient 1, the venous graft in Patient 1, and $SV G_2$ in Patient 3 were, respectively, 38.85, 18.17, and 9.29. Conversely, the total inflow is limited for the remaining grafts, where the deformation of the vessel walls plays a significant role in affecting the wall shear stress and causes dispersion in the inflow vs. $|\vec{\tau}_{st}|$ relationship. The average ratio of centerline velocity to wall velocity was much lower in these cases. For the arterial graft in Patient 2, the venous graft in Patient 2, and the arterial graft in Patient 3, this ratio was computed to be 5.28, 4.39, and 3.46. As observed above, the large discrepancies in total inflow can be justified by considering the fraction of the coronary flow carried by the various grafts, which differs significantly in the three patients. Additionally, an ideal Poiseuille linear relation is superimposed in Figure 16, where $|\vec{\tau}_{st}| = 32\mu V / (T\pi D^3)$, μ is the dynamic viscosity of blood, V is the total inflow in mL, T is the heart cycle period in seconds, and D is the mean vessel diameter. Deviations from the Poiseuille approximation show the extent to which the velocity profile deviates from parabolic, with $|\vec{\tau}_t(\mathbf{x}, \mathbf{y})|$ values in the arterial grafts having as much as a 400% difference due to their rapidly oscillating cross-sectional area (Figure 14).

4. Discussion

This study analyzed the major contributions to uncertainty in simulation predictions in coronary hemodynamics stemming from boundary conditions and material properties. Material property uncertainty causes large variations in the computed wall strain, and therefore ignorance in elastic modulus and thickness may reduce the efficacy of the numerical prediction of wall strain as a reliable indicator of graft patency in comparison to other metrics like the wall shear stress. This places prior deterministic results in context, which showed large differences in wall strain among patients, highlighting the importance of including uncertainty to draw meaningful conclusions from simulation outputs.

The results from sensitivity analysis may also guide additional data collection to improve numerical predictions. In particular, patient-specific measurements of the flow distribution to different branches of the coronary vasculature could improve estimation of outlet resistances in the coronary arteries, and thereby improve estimation of graft flow. Also, patient-specific measurements of the elastic modulus and wall thickness, if available, could also improve the estimation of the wall strain. While patient-specific measurements of coronary flow and vessel wall material properties may not be widely available with current technology, certain quantities may offer possibilities for increased clinical data. For example, echocardiography can provide limited flow measurements in the left anterior descending coronary artery or and CT perfusion is increasingly used to measure cardiac perfusion to estimate coronary flow split [59]. Reducing the degree to which computational models rely on literature data, by replacing values with patient-specific measurements, could increase confidence in computational predictions. Note that the proposed approach is already general enough to include such additional information as it becomes available from advances in coronary flow measurement technology and multi-modality imaging.

A submodelling method was used in this study to determine boundary conditions on coronary bypass grafts, which are characterized by a single inlet and a single outlet. The method, however, makes no assumptions about the geometry of the submodel and could be extended to more complex anatomies and alternative surgical configurations such as Y-graft and sequential grafts. For cases where the submodel input is, for example, selected as a slice located on a bifurcation, the amplified variability in flow and pressure will be reflected by a larger variance in the boundary conditions extracted from the full model. We note that any discrepancy resulting from interpolating a complex flow field at a bifurcation is compensated by the $(\mathbb{E}_{yB}[u_F] - \mathbb{E}_{yB}[u_s])$ term in the expectation of the quantities of interest.

The current study has several limitations. First, we only considered uncertainty due to material properties and boundary conditions. Other interesting epistemic (i.e., model-form) uncertainties relate, for example, to the choice of the stabilization scheme in the finite element solver or a non-Newtonian blood rheology. Additionally, one could also examine the effect of the *layout* in the LPN boundary model, and whether alternative layouts could further reduce the variance in model outputs. Future studies should be devoted to tackling these issues using Bayesian model averaging. Another limitation comes from the specific deformable wall model adopted. Here we have used the Coupled Momentum Method [35]

which accounts for the essential effects of deformability in cardiovascular simulations like wave reflection with only a modest increase in computational cost. This model is however limited to deformations of approximately 10% of the vessel radius. More rigorous approaches, for example arbitrary Lagrangian Eulerian (ALE) FSI [60] could be used to model larger wall displacements and deformations with more realistic tissue material models.

To model the Young's modulus and thickness as random fields, a correlation length had to be assumed as part of the isotropic squared exponential covariance function due to lack of measurements on material properties of coronary bypass grafts. A reference correlation length was selected based on previous studies [27, 13] applying random field modelling in cardiovascular simulations, and additional correlation lengths were also explored due to lack of data. Experimental measurements can be used to estimate a proper correlation length. One such experiment is described in [13], where measurements of wall thickness at different spatial locations on abdominal aortic aneurysms to estimate a correlation length. The motivation for exploring a random field description of the material properties stems from studies showing large spatial variation of vascular material properties in experimental measurements [27,13,25], however in the absence of such data for coronary bypass grafts, a random field model was adopted.

While we also assumed the Young's modulus and thickness fields to be completely independent, they likely have some correlation due to their interdependency in vascular growth and remodeling. This was neglected in the current study, which may have led to increased variability in the wall strain. These results suggest the difference in wall strain for venous and arterial grafts is difficult to detect even in patient-specific simulations without additional measurements to reduce variance.

We are also limited in the number of patients considered in this study, which were selected to represent a range of physiological data and graft configurations. However, our uncertainty analysis may have been compounded by factors such as graft take-off and touch-down locations and size of downstream coronary region.

An additional limitation in this study comes from modeling only a single physiologic state of the patients in the tuning of the full model boundary conditions. We only considered the imaging data and clinical targets (blood pressure, stroke volume, etc) measured when the patient was in a rest condition, and the associated information about measurement uncertainty. This is only a snapshot of the many physiologic states the patient can undergo, which can result in significant variations throughout the course of a day and dramatic variations during exercise. Our framework could be extended to examine physiologic variability but additional data collection would likely be required.

Finally, all models presented in this study were obtained through semi-automatic lumen segmentation, an operator-dependent operation. As we have shown, geometry plays a significant role on the computed values of wall shear and strain. Future studies should explore the effects of geometrical uncertainty due to the variability in vessel segmentation.

5. Conclusion

With the rising clinical adoption of cardiovascular simulations, it is increasingly important that simulation predictions be accompanied by quantitative uncertainty analysis. We have demonstrated the use of a framework that propagates uncertainties from clinical measurements and literature data to simulation results through the combination of Bayesian parameter estimation and multi-resolution forward propagation within the context of coronary bypass grafts. Instead of assuming distributions on the model parameters, their uncertainty is informed by the precision of the available data, and propagated efficiently to model outputs. A novel submodelling approach was also developed to reduce the computational cost of the forward propagation. Inclusion of uncertainties in the boundary condition parameters and the vessel wall material properties resulted in significant variability for clinically relevant indicators such as the wall shear stress and wall strain. In particular, lack of sufficient data on the material properties for the vessel walls generates significant variability in the wall strain that were not captured by previous deterministic approaches, emphasizing how additional clinical measurements of the wall material properties would help reduce this variance. In contrast, the uncertainties included in the proposed stochastic framework did not change the deterministic conclusion that wall shear stress is statistically different between arterial and venous bypass grafts, exhibiting coefficients of variation $<35\%$. This is possibly due to the strong correlation between total inflow and wall shear stresses in the graft and a limited variability of graft flow. Uncertainty quantification is crucial for rigorous assessment of model predictions in personalized treatment planning, particularly in the context of clinical adoption.

6. Acknowledgements

This work was supported by NIH RO1-RHL123689A and NIH RO1-EB018302, a Burroughs Wellcome Fund Career award at the Scientific Interface, NSF CDSE CBET 1508794, and NSF CAREER OCI-1150184. Simulations were run using resources from the Extreme Science and Engineering Discovery Environment (XSEDE) and the Stanford Research Computing Center (SRCC). We also acknowledge support from the open source SimVascular project at www.simvascular.org. We also would like to thank the rigorous feedback from the two reviewers, whose insights were crucial in the development of this paper. We wish to confirm that there are no known conflicts of interest associated with this publication and there has been no significant financial support for this work that could have influenced its outcome.

References

- [1]. Braunwald E, Antman EM, Beasley JW, Califf RM, Cheitlin MD, Hochman JS, Jones RH, Kereiakes D, Kupersmith J, Levin TN, et al., Acc/aha 2002 guideline update for the management of patients with unstable angina and non-st-segment elevation myocardial infarction summary article, *Journal of the American College of Cardiology* 40 (7) (2002) 1366–1374. [PubMed: 12383588]
- [2]. Motwani JG, Topol EJ, Aortocoronary saphenous vein graft disease, *Circulation* 97 (9) (1998) 916–931. [PubMed: 9521341]
- [3]. Goldman S, Zadina K, Moritz T, Ovitt T, Sethi G, Copeland JG, Thottapurathu L, Krasnicka B, Ellis N, Anderson RJ, et al., Long-term patency of saphenous vein and left internal mammary artery grafts after coronary artery bypass surgery: results from a department of veterans affairs cooperative study, *Journal of the American College of Cardiology* 44 (11) (2004) 2149–2156. [PubMed: 15582312]
- [4]. Malek A, Alper S, Izumo S, Hemodynamic shear stress and its role in atherosclerosis, *Jama* 282 (21) (1999) 2035–2042. [PubMed: 10591386]

- [5]. Samady H, Eshtehardi P, McDaniel M, Suo J, Dhawan S, Maynard C, Timmins L, Quyyumi A, Giddens D, Coronary artery wall shear stress is associated with progression and transformation of atherosclerotic plaque and arterial remodeling in patients with coronary artery disease, *Circulation* 124 (7) (2011) 779–788. [PubMed: 21788584]
- [6]. Taylor C, Hughes T, Zarins C, Finite element modeling of blood flow in arteries, *Computer methods in applied mechanics and engineering* 158 (1) (1998) 155–196.
- [7]. Taylor C, Fonte T, Min J, Computational fluid dynamics applied to cardiac computed tomography for noninvasive quantification of fractional flow reserve: scientific basis, *Journal of the American College of Cardiology* 61 (22) (2013) 2233–2241. [PubMed: 23562923]
- [8]. Sengupta D, Kahn A, Kung E, Moghadam M, Shirinsky O, Lyskina G, Burns J, Marsden A, Thrombotic risk stratification using computational modeling in patients with coronary artery aneurysms following Kawasaki disease, *Biomechanics and Modeling in Mechanobiology* 13 (6) (2014) 1261–1276. [PubMed: 24722951]
- [9]. Gutierrez NG, Kahn A, Burns JC, Marsden AL, Computational blood flow simulations in kawasaki disease patients: Insight into coronary artery aneurysm hemodynamics, *Global Cardiology Science and Practice* 2017 (3).
- [10]. Ramachandra AB, Kahn AM, Marsden AL, Patient-specific simulations reveal significant differences in mechanical stimuli in venous and arterial coronary grafts, *Journal of cardiovascular translational research* 9 (4) (2016) 279–290. [PubMed: 27447176]
- [11]. Ramachandra AB, Humphrey JD, Marsden AL, Gradual loading ameliorates maladaptation in computational simulations of vein graft growth and remodelling, *Journal of The Royal Society Interface* 14 (130) (2017) 20160995.
- [12]. Sankaran S, Marsden AL, A stochastic collocation method for uncertainty quantification and propagation in cardiovascular simulations, *Journal of biomechanical engineering* 133 (3) (2011) 031001. [PubMed: 21303177]
- [13]. Biehler J, Wall W, The impact of personalized probabilistic wall thickness models on peak wall stress in abdominal aortic aneurysms, *International Journal for Numerical Methods in Biomedical Engineering*.
- [14]. Chen P, Quarteroni A, Rozza G, Simulation-based uncertainty quantification of human arterial network hemodynamics, *International journal for numerical methods in biomedical engineering* 29 (6) (2013) 698–721. [PubMed: 23653286]
- [15]. Sankaran S, Marsden AL, The impact of uncertainty on shape optimization of idealized bypass graft models in unsteady flow, *Physics of fluids* 22 (12) (2010) 121902.
- [16]. Eck V, Sturdy J, Hellevik L, Effects of arterial wall models and measurement uncertainties on cardiovascular model predictions, *Journal of biomechanics* 50 (2017) 188–194. [PubMed: 27890534]
- [17]. Sankaran S, Kim HJ, Choi G, Taylor CA, Uncertainty quantification in coronary blood flow simulations: impact of geometry, boundary conditions and blood viscosity, *Journal of biomechanics* 49 (12) (2016) 2540–2547. [PubMed: 26803339]
- [18]. Schiavazzi D, Arbia G, Baker C, Hlavacek AM, Hsia T-Y, Marsden A, Vignon-Clementel I, et al., Uncertainty quantification in virtual surgery hemodynamics predictions for single ventricle palliation, *International journal for numerical methods in biomedical engineering* 32 (3).
- [19]. Marquis AD, Arnold A, Dean-Bernhoft C, Carlson BE, Olufsen MS, Practical identifiability and uncertainty quantification of a pulsatile cardiovascular model, *Mathematical biosciences* 304 (2018) 9–24. [PubMed: 30017910]
- [20]. Brault A, Dumas L, Lucor D, Uncertainty quantification of inflow boundary condition and proximal arterial stiffness-coupled effect on pulse wave propagation in a vascular network, *International journal for numerical methods in biomedical engineering* 33 (10).
- [21]. Boccadifuoco A, Mariotti A, Celi S, Martini N, Salvetti M, Impact of uncertainties in outflow boundary conditions on the predictions of hemodynamic simulations of ascending thoracic aortic aneurysms, *Computers & Fluids* 165 (2018) 96–115.
- [22]. Tran JS, Schiavazzi DE, Ramachandra AB, Kahn AM, Marsden AL, Automated tuning for parameter identification and uncertainty quantification in multi-scale coronary simulations, *Computers & Fluids* 142 (2017) 128–138. [PubMed: 28163340]

- [23]. Vrugt J, Ter Braak C, Diks C, Robinson B, Hyman J, Higdón D, Accelerating Markov chain Monte Carlo simulation by differential evolution with self-adaptive randomized subspace sampling, *International Journal of Nonlinear Sciences and Numerical Simulation* 10 (3) (2009) 273–290.
- [24]. Han D-W, Park YH, Kim JK, Jung TG, Lee K-Y, Hyon S-H, Park J-C, Long-term preservation of human saphenous vein by green tea polyphenol under physiological conditions, *Tissue engineering* 11 (7–8) (2005) 1054–1064. [PubMed: 16144441]
- [25]. Roccabianca S, Figueroa C, Tellides G, Humphrey J, Quantification of regional differences in aortic stiffness in the aging human, *Journal of the mechanical behavior of biomedical materials* 29 (2014) 618–634. [PubMed: 23499251]
- [26]. Podesser B, Neumann F, Neumann M, Schreiner W, Wollenek G, Mallinger R, Outer radius-wall thickness ratio, a postmortem quantitative histology in human coronary arteries, *Cells Tissues Organs* 163 (2) (1998) 63–68.
- [27]. Biehler J, Gee MW, Wall WA, Towards efficient uncertainty quantification in complex and large-scale biomechanical problems based on a bayesian multi-fidelity scheme, *Biomechanics and modeling in mechanobiology* 14 (3) (2015) 489–513. [PubMed: 25245816]
- [28]. Li C-C, Der Kiureghian A, Optimal discretization of random fields, *Journal of engineering mechanics* 119 (6) (1993) 1136–1154.
- [29]. Schiavazzi D, Doostan A, Iaccarino G, Marsden A, A generalized multi-resolution expansion for uncertainty propagation with application to cardiovascular modeling, *Computer Methods in Applied Mechanics and Engineering* 314 (2017) 196–221. [PubMed: 28845061]
- [30]. Formaggia L, Nobile F, Quarteroni A, Veneziani A, Multiscale modelling of the circulatory system: a preliminary analysis, *Computing and visualization in science* 2 (2–3) (1999) 75–83.
- [31]. Quarteroni A, Veneziani A, Vergara C, Geometric multiscale modeling of the cardiovascular system, between theory and practice, *Computer Methods in Applied Mechanics and Engineering* 302 (2016) 193–252.
- [32]. Kim H, Vignon-Clementel I, Coogan J, Figueroa C, Jansen K, Taylor C, Patient-specific modeling of blood flow and pressure in human coronary arteries, *Annals of Biomedical Engineering* 38 (10) (2010) 3195–3209. [PubMed: 20559732]
- [33]. Moghadam M, Vignon-Clementel I, Figliola R, Marsden A, M. O. C. H. A. (mocha) Investigators, et al., A modular numerical method for implicit 0D/3D coupling in cardiovascular finite element simulations, *Journal of Computational Physics* 244 (2013) 63–79.
- [34]. Jansen K, Whiting C, Hulbert G, A generalized- α method for integrating the filtered navier-stokes equations with a stabilized finite element method, *Computer Methods in Applied Mechanics and Engineering* 190 (3) (2000) 305–319.
- [35]. Figueroa CA, Vignon-Clementel IE, Jansen KE, Hughes TJ, Taylor CA, A coupled momentum method for modeling blood flow in three-dimensional deformable arteries, *Computer methods in applied mechanics and engineering* 195 (41) (2006) 5685–5706.
- [36]. Updegrove A, Wilson NM, Merkow J, Lan H, Marsden AL, Shadden SC, Simvascular-an open source pipeline for cardiovascular simulation, *Ann. Biomed. Eng.*
- [37]. Moghadam M, Bazilevs Y, Hsia T, Vignon-Clementel I, Marsden A, et al., A comparison of outlet boundary treatments for prevention of backflow divergence with relevance to blood flow simulations, *Computational Mechanics* 48 (3) (2011) 277–291.
- [38]. Moghadam M, Bazilevs Y, Marsden A, A new preconditioning technique for implicitly coupled multidomain simulations with applications to hemodynamics, *Computational Mechanics* 52 (5) (2013) 1141–1152.
- [39]. Esmaily-Moghadam M, Bazilevs Y, Marsden AL, A bi-partitioned iterative algorithm for solving linear systems arising from incompressible flow problems, *Computer Methods in Applied Mechanics and Engineering* 286 (2015) 40–62.
- [40]. Sankaran S, Moghadam M, Kahn A, Tseng E, Guccione J, Marsden A, Patient-specific multiscale modeling of blood flow for coronary artery bypass graft surgery, *Annals of Biomedical Engineering* 40 (10) (2012) 2228–2242. [PubMed: 22539149]

- [41]. Senzaki H, Chen C, Kass D, Single-beat estimation of end-systolic pressure-volume relation in humans a new method with the potential for noninvasive application, *Circulation* 94 (10) (1996) 2497–2506. [PubMed: 8921794]
- [42]. Nichols W, O'Rourke M, Vlachopoulos C, McDonald's blood flow in arteries: theoretical, experimental and clinical principles, CRC Press, 2011.
- [43]. Wilson R, Laughlin D, Ackell P, Chilian W, Holida M, Hartley C, Armstrong M, Marcus M, White C, Transluminal, subselective measurement of coronary artery blood flow velocity and vasodilator reserve in man., *Circulation* 72 (1) (1985) 82–92. [PubMed: 3159506]
- [44]. Dennis J, Woods D, Optimization on microcomputers: The Nelder-Mead simplex algorithm, *New Computing Environments: Microcomputers in Large-Scale Computing* (1987) 116–122.
- [45]. Di Achille P, Humphrey JD, Toward large-scale computational fluid-solid-growth models of intracranial aneurysms, *The Yale journal of biology and medicine* 85 (2) (2012) 217. [PubMed: 22737050]
- [46]. Schiavazzi D, Hsia T, Marsden A, On a sparse pressure-flow rate condensation of rigid circulation models, *Journal of biomechanics* 49 (11) (2016) 2174–2186. [PubMed: 26671219]
- [47]. Tipping ME, Sparse bayesian learning and the relevance vector machine, *Journal of machine learning research* 1 (Jun) (2001) 211–244.
- [48]. Tipping ME, Faul AC, et al., Fast marginal likelihood maximisation for sparse bayesian models, in: *AISTATS*, 2003.
- [49]. Banks H, Hu S, Thompson W, *Modeling and Inverse Problems in the Presence of Uncertainty*, CRC Press, 2014.
- [50]. Gorry PA, General least-squares smoothing and differentiation by the convolution (savitzky-golay) method, *Analytical Chemistry* 62 (6) (1990) 570–573.
- [51]. Shinozuka M, Jan C-M, Digital simulation of random processes and its applications, *Journal of sound and vibration* 25 (1) (1972) 111–128.
- [52]. Lindgren F, Lindstrom J, Rue H, An explicit link between Gaussian fields and Gaussian Markov random fields: The SPDE approach, *Mathematical Statistics, Centre for Mathematical Sciences, Faculty of Engineering, Lund University*, 2010.
- [53]. Spanos PD, Ghanem R, Stochastic finite element expansion for random media, *Journal of engineering mechanics* 115 (5) (1989) 1035–1053.
- [54]. Coogan JS, Humphrey JD, Figueroa CA, Computational simulations of hemodynamic changes within thoracic, coronary, and cerebral arteries following early wall remodeling in response to distal aortic coarctation, *Biomechanics and modeling in mechanobiology* (2013) 1–15. [PubMed: 23483348]
- [55]. Ernst O, Mugler A, Starkloff H, Ullmann E, On the convergence of generalized polynomial chaos expansions, *ESAIM: Mathematical Modelling and Numerical Analysis* 46 (2) (2012) 317–339.
- [56]. Xiu D, Karniadakis G, The wiener-askey polynomial chaos for stochastic differential equations, *SIAM Journal on Scientific Computing* 24 (2) (2002) 619–644.
- [57]. Sudret B, Global sensitivity analysis using polynomial chaos expansions, *Reliability Engineering & System Safety* 93 (7) (2008) 964–979.
- [58]. Sobol IM, Global sensitivity indices for nonlinear mathematical models and their monte carlo estimates, *Mathematics and computers in simulation* 55 (1) (2001) 271–280.
- [59]. Wintermark M, Flanders AE, Velthuis B, Meuli R, Van Leeuwen M, Goldsher D, Pineda C, Serena J, Van Der Schaaf I, Waaijer A, et al., Perfusion-ct assessment of infarct core and penumbra: receiver operating characteristic curve analysis in 130 patients suspected of acute hemispheric stroke, *Stroke* 37 (4) (2006) 979–985. [PubMed: 16514093]
- [60]. Takizawa K, Bazilevs Y, Tezduyar T, Space-time and ALE-VMS techniques for patient-specific cardiovascular fluid-structure interaction modeling, *Archives of Computational Methods in Engineering* 19 (2) (2012) 171–225.

Figure 1:
Summary of workflow in computing uncertainties in coronary bypass simulations.

Figure 2:

(a) Schematic view of a multiscale patient-specific model of the coronary circulation and (b) typical left (top) and right (bottom) coronary artery flow waveforms. A scaled down aortic pressure waveform is shown to highlight the out of phase nature of coronary flow.

Figure 3: Anatomical models and clinical targets for the three patients considered in this study, with their graft submodels highlighted. Arterial grafts, which use the left internal mammary artery (LIMA), are highlighted in red and venous grafts, which use the saphenous vein (SVG), are highlighted in blue. $P_{ao,min}$ is the diastolic aortic pressure, $P_{ao,max}$ is the systolic aortic pressure, HR is heart rate, SV is stroke volume, EF is ejection fraction, and P_{ra} is the right atrial pressure.

Figure 4:

Extracting solution from full model simulations and interpolating onto submodel. Full model solution is sliced at submodel inlet and outlet, then barycentric interpolation used to determine solution on the submodel mesh nodes (red) from the sliced full model nodes (black) of the encompassing full model element.

(a)

(b)

Inlet Pressure	0.44%
Outlet Flow	1.22%
$\bar{\tau}_{st}(\mathbf{y})$	2.56%
$I_{st}^1(\mathbf{y})$	1.45%

(c)

Figure 5:

Comparison of full model and extracted submodel solutions for (a) inlet pressure in a characteristic case, (b) outlet flow in a characteristic case. Inlet pressure and outlet flow were selected for comparison since we do not directly specify these in our boundary conditions, showing strong agreement of our submodelling. Table (c) summarizes the percent differences in inlet pressure, outlet flow, $\bar{\tau}_{st}(\mathbf{y})$, and $I_{st}^1(\mathbf{y})$ between the full model and extracted submodel that result from interpolation errors for 125 parameter realizations in Patient 1.

Figure 6: Estimation of full model (a) pressure and (b) velocity waveforms using Relevance Vector Machine (RVM) regression and Ordinary Least Squares (OLS). Estimated waveforms using RVM match extracted waveforms much better than OLS.

Figure 7:

Properties and error estimates for EOLE representation of a Gaussian random field with a squared exponential correlation function. (a) Shape functions for the first seven modes. (b) Relative error in the mean as a function of the number of modes and the number of control points for a venous graft Young's modulus with a uniform mean of 5.0 MPa and a standard deviation of 1.3 MPa. (c) Relative error in the standard deviation as a function of modes and control points for a venous graft Young's modulus with a uniform mean of 5.0 MPa and a standard deviation of 1.3 MPa.

Figure 8:
Random field realizations for (a) stiffness and (b) thickness distributions generated with EOLE.

Figure 9:

Parameter correlations for all three patients. Parameters 1 through 17 comprise the full model boundary condition parameters, while the rest are independent random field parameters.

Figure 10: Violin plots showing output distributions of (a) TAWSS and (b) wall strain for the three patients.

Figure 11:

Sobol' sensitivity analysis for $\vec{\tau}_{st}$. LPN parameters are tagged as either Systemic (i.e. heart model, downstream aortic outlet BCs) or Coronary (i.e. downstream coronary outlet BCs). Random field material property parameters are tagged as either Modulus (i.e. Elastic modulus) or Thickness (i.e. vessel wall thickness). Bar heights represent relative contribution to the variance of $\vec{\tau}_{st}$ from the four groups.

Figure 12:

Sobol' sensitivity analysis for I_{st}^1 . LPN parameters are tagged as either Systemic (i.e. heart model, downstream aortic RCR) or Coronary (i.e. downstream coronary outlet BCs). Random field material property parameters are tagged as either Modulus (i.e. Elastic modulus) or Thickness (i.e. vessel wall thickness). Bar heights represent relative contribution to the variance of I_{st}^1 from the four groups.

Figure 13: Spatial distributions of means and coefficients of variation for (a) pressure, (b) TAWSS, and (c) wall strain in the $SV G_2$ graft of Patient 3.

Figure 14:
Plots of TAWSS and cross sectional area as a function of centerline distance in the (a) arterial and (b) venous grafts in each of the patients considered.

Figure 15: Plots of wall strain and cross sectional area as a function of centerline distance in the (a) arterial, (b) venous grafts in each of the patients considered, and (c) in the 125 training data cases for $SV G_2$ of Patient 3.

Figure 16:

Correlation plots showing correlation between area-averaged TAWSS and total inflow in the (a) arterial grafts and (b) venous grafts in each of the patients considered. A Poiseuille approximation for the wall shear stress is plotted in red.

Figure 17:
Different wall strain distributions for different random field realizations of material properties in the arterial graft of Patient 1.

Table 1:

Uniform prior ranges and posterior means, standard deviations, and coefficients of variation, c_v , for all LPN parameters. Elastances E are in $mmHg/mL$. Elastance time derivative scaling E_{tvp} is in $mmHg/mL.s$. Capacitances C are in $mL/mmHg$. Atrial pressure scalings Kxp are in $mmHg$. Resistances R are in $mHgs/mL$. Right coronary intramyocardial scaling $dPdt_r$ is dimensionless.

Number	Name	Prior			Patient 1			Patient 2			Patient 3		
		Min.	Max.		Mean	Std.	c_v	Mean	Std.	c_v	Mean	Std.	c_v
1	E_{rv}	0.10	1.50		1.26	0.19	0.15	0.93	0.29	0.31	0.47	0.08	0.17
2	E_{lv}	0.50	1.50		1.39	0.09	0.06	1.39	0.09	0.06	1.39	0.09	0.06
3	E_{tvp}	0.01	8.50		3.82	0.67	0.18	3.85	0.71	0.18	6.57	0.85	0.13
4	C_{ao}	0.01	2.50		0.47	0.17	0.36	0.54	0.14	0.26	0.65	0.17	0.26
5	Kxp_m	0.01	10.00		8.31	1.46	0.18	4.29	2.75	0.64	3.91	2.72	0.70
6	Kxp_{la}	0.01	10.00		9.00	0.77	0.09	7.58	1.20	0.16	7.61	1.53	0.20
7	R_{am}	0.01	5.00		1.01	0.16	0.16	1.15	0.15	0.13	1.00	0.20	0.20
8	C_{aml}	1.00	5.00		3.28	0.95	0.29	2.27	0.91	0.40	1.95	0.97	0.50
9	C_{al}	0.01	0.50		0.28	0.14	0.50	0.14	0.10	0.71	0.12	0.09	0.75
10	C_{amr}	1.00	5.00		2.32	1.11	0.48	1.86	0.86	0.46	2.89	1.16	0.40
11	C_{tr}	0.01	0.50		0.39	0.08	0.21	0.36	0.11	0.31	0.25	0.10	0.40
12	R_{cr}	0.10	5.00		0.97	0.06	0.06	0.91	0.06	0.07	0.80	0.08	0.10
13	$dPdt_r$	0.50	1.00		0.68	0.13	0.19	0.69	0.14	0.20	0.70	0.14	0.20

Table 2:

Mean, standard deviations, and coefficients of variation, C_v , for the Young's modulus (E) and thickness (ζ) for different vessels in the multi-scale model. Young's modulus is reported in dyne/cm^2 , thicknesses are reported as either a percentage of the mean vessel radius (for Aorta, LIMA, and SVG) or a fraction of the estimated thickness from the morphometric model (for Coronary).

Name	Mean	Std.	c_v
Aortic E Aortic ζ	7000000.0 10.0	1352458.14 4.0	0.19 0.40
Coronary E Coronary ζ	11500000.0 1.0	1700000.0 0.23	0.15 0.23
LIMA E LIMA ζ	14000000.0 10.0	1352458.14 4.0	0.10 0.40
SVG E SVG ζ	50000000.0 10.0	13066666.67 4.0	0.26 0.40

Table 3:

Summary of geometry characteristics in all considered bypass grafts. Avg. area is the average cross sectional area in cm^2 . Length is the length of the graft in cm . Average curvature measures the degree to which the centerline changes direction, computed from the derivative of the normal vectors along the centerline (i.e. Curvature = $|d\hat{n}/ds|$) and averaging over the graft. Average circularity measures deviation of the cross sections from a perfect circle as an index for shape eccentricity (i.e. Circularity = $4\pi(Area)/(Perimeter^2)$) and is averaged over the graft.

		Avg. Area	Length	Avg. Curvature	Avg. Circularity
Patient 1	LIMA	0.0397 cm^2	14.37 cm	10.173 cm^{-1}	0.9834
	SV G	0.1645 cm^2	12.03 cm	5.263 cm^{-1}	0.9900
Patient 2	LIMA	0.0400 cm^2	18.97 cm	14.988 cm^{-1}	0.9679
	SV G	0.0843 cm^2	8.54 cm	8.570 cm^{-1}	0.9765
Patient 3	LIMA	0.0316 cm^2	14.85 cm	12.426 cm^{-1}	0.9761
	SV G ₁	0.0464 cm^2	9.97 cm	10.332 cm^{-1}	0.9655
	SV G ₂	0.0532 cm^2	6.75 cm	8.930 cm^{-1}	0.9740

Table 4:

Computational cost in CPU hours for full model and submodel simulations, with estimated cost savings when compared to performing the same analysis with just full model simulations.

	Full cost	<i>LIMA</i> cost	<i>SV G₁</i> cost	<i>SV G₂</i> cost	N_{full}	N_{sub}	Total cost	Proj. full cost	Saving
Patient 1	876.67	48.98	77.38	-	125	1000	235944	876670	73.09%
Patient 2	1211.47	44.24	48.38	-	125	1000	244054	1211470	79.85%
Patient 3	929.60	46.04	62.93	42.17	125	1000	267340	929600	71.24%

Table 5:

Table of computed statistics and telescopic expansion terms for TAWSS. Values are normalized by aortic TAWSS. Highlighted columns are adjusted full model statistics.

		$\mathbb{E}[o_S]$	$\mathbb{E}[o_F - o_S]$	$\mathbb{E}[o_F]$	$\mathbb{V}[o_S]$	$\mathbb{V}[o_F - o_S]$	$\mathbf{C}[o_S, o_F - o_S]$	$\mathbb{V}[o_F]$
Patient 1	<i>LIMA</i>	7.399	0.049	7.448	2.225	0.094	0.037	2.393
	<i>SV G</i>	1.155	0.038	1.193	0.304	0.005	6.95e-4	0.309
Patient 2	<i>LIMA</i>	0.873	0.044	0.917	0.308	0.008	-7.93e-5	0.316
	<i>SV G</i>	0.386	0.013	0.399	0.100	0.001	-3.06e-4	0.101
Patient 3	<i>LIMA</i>	1.258	0.222	1.480	0.155	0.057	-8.68e-4	0.210
	<i>SV G₁</i>	1.223	0.222	1.445	0.081	0.048	3.20e-4	0.130
	<i>SV G₂</i>	2.864	0.268	3.132	0.177	0.115	0.004	0.301

Table 6:

Table of computed statistics and telescopic expansion terms for wall strain. Highlighted columns are adjusted full model statistics.

		$\mathbb{E}[o_S]$	$\mathbb{E}[o_F - o_S]$	$\mathbb{E}[o_F]$	$\mathbb{V}[o_S]$	$\mathbb{V}[o_F - o_S]$	$\mathbb{C}[o_S, o_F - o_S]$	$\mathbb{V}[o_F]$
Patient 1	LIMA SV G	0.0196 0.0068	3.44e-5 -1.54e-4	0.0196 0.0066	0.0229 0.0084	5.44e-7 1.52e-7	1.67e-8 -8.13e-9	0.0229 0.0084
Patient 2	LIMA SV G	0.0164 0.0077	-1.12e-5 -1.77e-4	0.0164 0.0075	0.0187 0.0063	1.23e-6 2.30e-7	-9.17e-7 -2.24e-7	0.0187 0.0063
Patient 3	LIMA SV G ₁ SV G ₂	0.0145 0.0040 0.0037	2.48e-4 4.03e-5 -9.27e-6	0.0147 0.0040 0.0037	0.0076 0.0025 0.0021	9.61e-6 8.72e-7 7.465e-7	2.90e-8 -5.384e-8 1.28e-8	0.0076 0.0025 0.0021

Table 7:

Comparison of I_{st}^1 mean and variance in cases with longer (Patient 1) and shorter (Patient 2) correlation lengths.

		$\mathbb{E}_{3.7}(I_{st}^1)$	$\mathbb{E}_{7.2/0.95}(I_{st}^1)$	$\mathbb{V}_{3.7}(I_{st}^1)$	$\mathbb{V}_{7.2/0.95}(I_{st}^1)$
Patient 1 (7.2 cm, longer)	<i>LIMA</i> <i>SV G</i>	0.0196 0.0066	0.0175 0.0065	0.0229 0.0084	0.0222 0.0087
Patient 2 (0.95 cm, shorter)	<i>LIMA</i> <i>SV G</i>	0.0164 0.0075	0.0168 0.0075	0.0187 0.0063	0.0119 0.0044