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A Stochastic Collocation Method for Uncertainty Quantification and Propagation in Cardiovascular Simulations

Simulations of blood flow in both healthy and diseased vascular models can be used to compute a range of hemodynamic parameters including velocities, time varying wall shear stress, pressure drops, and energy losses. The confidence in the data output from cardiovascular simulations depends directly on our level of certainty in simulation input parameters. In this work, we develop a general set of tools to evaluate the sensitivity of output parameters to input uncertainties in cardiovascular simulations. Uncertainties can arise from boundary conditions, geometrical parameters, or clinical data. These uncertainties result in a range of possible outputs which are quantified using probability density functions (PDFs). The objective is to systemically model the input uncertainties and quantify the confidence in the output of hemodynamic simulations. Input uncertainties are quantified and mapped to the stochastic space using the stochastic collocation technique. We develop an adaptive collocation algorithm for Gauss-Lobatto-Chebyshev grid points that significantly reduces computational cost. This analysis is performed on two idealized problems – an abdominal aortic aneurysm and a carotid artery bifurcation, and one patient specific problem – a Fontan procedure for congenital heart defects. In each case, relevant hemodynamic features are extracted and their uncertainty is quantified. Uncertainty quantification of the hemodynamic simulations is done using (a) stochastic space representations, (b) PDFs, and (c) the confidence intervals for a specified level of confidence in each problem. [DOI: 10.1115/1.4003259]

1 Introduction

Over the past decade, computational simulations have become an increasingly powerful tool to study the cardiovascular system. There has been a significant increase in the sophistication and clinical applicability of computational tools for patient-specific modeling of blood flow. This includes the capacity to build realistic and complex three-dimensional models directly from image data, to obtain velocities, pressure data, and mechanical properties of blood vessels from clinical and experimental data, and to perform simulations with greater physiologic reality. Simulations have played a key role in understanding hemodynamics of bypass grafting [1-3], cardiovascular treatment planning [4,5], atherosclerosis in the carotid artery [6], and abdominal aorta [7,8], the effects of exercise on aortic flow conditions [7], congenital cardiovascular disease [9–12], and coronary stents [13–15]. Yet, for simulations to be reliable and be put into widespread clinical use, it is essential to systematically quantify the level of confidence we can place on simulation outputs.

Usually, a single computational simulation is performed and results such as shear stresses and velocities are deterministically quantified. However, our hypothesis is that in a variety of situations, the outputs can be quantified only probabilistically due to the presence of noise in the input data. Simulations are only as accurate as the data that goes into them and a thorough study is needed to determine how variations in these input data affects the outputs. In addition, when evaluating new surgical designs, we need to ensure that the changes due to design parameters are more significant than noise caused by input uncertainties. In this paper, we will focus on hemodynamic simulations in the cardiovascular system, while emphasizing that the techniques presented are generic in nature.

Some common sources of uncertainties in cardiovascular simulations include the following:

- 1. *Boundary conditions:* Computational simulation of blood flow requires boundary condition data that typically consist of (a) inlet velocities, (b) resistances, (c) impedances, or (d) lumped parameter models at the outlets. Each of these is subject to variability in measured flow distribution to distal branches, changing flow rates, and physiologic conditions.
- 2. *Geometry:* Anatomical models (blood vessels, aneurysms, stenosis regions, etc.) are constructed directly from image data. Construction of the geometrical model is polluted with image noise, geometrical approximations (approximation to nearest circles, ellipses, etc.), variations in segmentation methods (for example, using thresholding or level set), and user variability.
- 3. *Flow-split:* In general, there is a lack of clinical data to determine flow distribution to multiple distal branches. In our third example, the Fontan surgery, we study the uncertainty in the flow-split between the left pulmonary artery (LPA) and right pulmonary artery (RPA).
- 4. *Material properties:* Uncertainty in the properties of bloodvessel walls are important when performing simulations with nonrigid walls.

Due to the above-mentioned reasons, computational simulations need to be performed over a set of fuzzy parameters to determine how robust simulation outputs are to variation in the input parameters. Noise in reconstruction of geometric models from MRI images is a well known problem. Moore et al. [16,17] carefully identified sources of such error and provided computational techniques to reduce them. However, uncertainties originat-

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ing from limited spatial resolution, image segmentation, and model construction cannot be completely eliminated [16].

Currently, there is no systematic way of determining the effect of uncertain inputs on simulation results. One option is to manually perturb different parameters using a design of experiment strategy. Recently, Steinman and co-workers [18,19] performed computational simulations to evaluate sensitivities in quantities such as wall shear stress and oscillatory shear index to variations in blood rheology, secondary flows, etc., in human subjects. These were some of the first studies showing the relationship between fluctuations in input parameters and output quantities for patientspecific cardiovascular simulations. However, if we need to compute sensitivities over a wide range of parameters, and if there are a large number of parameters, this method can become unwieldy due to the huge computational cost involved.

In identifying an appropriate stochastic method for uncertainty quantification, there are several options. Traditionally, and the most widely known, Monte Carlo techniques have been employed for performing probabilistic analysis. However, they are plagued with poor convergence rates, and it is impractical to employ them for computationally expensive three-dimensional problems involving complex geometries. In this work, we use the concept of stochastic spaces for representing random parameters [20]. This concept has been used successfully in many engineering approaches over the past 2 decades. In the same way that space and time are seen as dimensions, randomness is seen as an additional dimension. The generalized polynomial chaos expansion (GPCE) has been successfully used to tackle engineering problems involving uncertainties [21], including computational fluid dynamics [22]. However, one disadvantage of this technique is the coupled nature of resultant matrix equations that need to be solved in the random domain. This is a disadvantage for legacy codes because it requires the solver to be entirely rewritten.

Recently, a stochastic collocation scheme has been introduced in which simulations are performed at specific collocation points in the stochastic space [23,24]. This technique combines the exponential convergence rates of the GPCE scheme with the decoupled nature of Monte Carlo techniques. Using this technique, we can quantify the complete probabilistic variability of fields of interest as opposed to extracting only limited statistics.

In this paper, we use the concept of stochastic collocation to account for uncertainties. A stochastic space is defined for each problem depending on the uncertainty in the parameters. Further, collocation points are identified in this stochastic space and computational simulations of the Navier-Stokes equations are performed. From the results, interpolants are constructed in the stochastic space and are quantified using probability density functions (PDFs) and confidence intervals. The number of collocation points is chosen based on a factor called depth of interpolation that is explained in Sec. 2.1.1. Convergence of these methods is guaranteed as the depth of interpolation is increased. This can be tailored according to the expense of the function. It is to be noted that the choice of input uncertainties play a crucial role in evaluating the PDF as well as confidence intervals on the outputs. While Gaussian distributions are suitable to represent random noise in images, PDFs describing the variability in the blood flow velocities, or the flow-splits, are not readily available in the clinical literature. In these cases, accurate modeling of input PDFs can be made using data-driven techniques such as MaxEnt [25]. However, in this work, we restrict ourselves to studying analytical distributions with the goal of elucidating the capabilities of our technique. Whenever available, these analytical distributions are motivated from data in literature. For instance, the variability in the inlet velocities for the carotid artery bifurcation problem or the variability in the flow-splits is modeled using available information.

In an attempt to minimize the number of stochastic collocation points, we develop and test a new scheme that adaptively chooses points based on the known function values. We demonstrate that this scheme can reduce computational cost by as much as 50%.

This paper is organized as follows: we give a brief description of the mathematical formalism and uncertainty quantification in Sec. 2. We provide details of numerical implementation, including the adaptive algorithm, in Sec. 3. Numerical examples are detailed in Sec. 4 and we follow it up with discussions in Sec. 5.

2 Mathematical Background

In this section, we provide some basic characteristics of the stochastic collocation technique. We describe how the method is nonintrusive, can be used for large-dimensional parametric spaces by using the sparse grid collocation algorithm, and converges as the depth of interpolation is increased.

A probability space is a triple $(\Omega, \mathcal{F}, \mathcal{P})$, where Ω is a set of outcomes, \mathcal{F} is a σ -algebra of subsets of Ω , and \mathcal{P} is a probability measure on \mathcal{F} . A random variable X is a map from Ω to the real line R and is written $X: \Omega \mapsto \mathbb{R}$ [26]. A discrete random variable is a random variable that takes values in a discrete set of the real line. A continuous random variable is a random variable that admits a density function.

2.1 Stochastic Collocation Scheme. In the stochastic collocation technique, instead of dealing with PDFs directly, we use the concept of stochastic spaces in our numerical solutions. Stochastic space is the space of $\boldsymbol{\xi} = [\xi^1, \xi^2, \dots, \xi^N]$, where ξ^i represents either uniform or normally distributed random variables. Any construct on the stochastic space has a unique PDF associated with it. A finite dimensional random support space is described by its truncated descriptor (random vector) $\boldsymbol{\xi}$ so that

$$\boldsymbol{\xi} = [\xi^1, \xi^2, \dots, \xi^N]: \Omega \to \mathbb{R}^N \tag{1}$$

where the dimensionality N of the stochastic support space is problem dependent. We denote the approximations to a function g by $g(\mathbf{x}, \mathbf{t}, \mathbf{\xi}_i)$.

In the collocation scheme, the stochastic space is approximated using mutually orthogonal interpolating functions. To represent a function at any point in the stochastic space, the function $g(\mathbf{x}, \mathbf{t}, \boldsymbol{\xi})$ is written as $g(\mathbf{x}, \mathbf{t}, \boldsymbol{\xi}) = \sum_{i} g(\mathbf{x}, \mathbf{t}, \boldsymbol{\xi}_i) \mathcal{L}_i(\boldsymbol{\xi})$ where $\mathcal{L}_i(.)$ are the orthogonal interpolating polynomials. The stochastic space can then be queried at any point and PDFs can be constructed.

2.1.1 Construction of Interpolating Polynomials. We represent a stochastic field using its values at specific collocation points in the stochastic space with an interpolating polynomial. In general, for one-dimensional functions, Gauss points and Chebechev points have the least interpolation error [27]. A trivial means to extend the above-mentioned scheme for multidimensions is by constructing a simple tensor product space. However, this is subject to the curse of dimensionality as the number of points grows exponentially. As a result, we employ computationally efficient schemes of searching the stochastic space. The Smolyak algorithm is a method for choosing the collocation points. The Smolyak algorithm reduces the number of collocation points necessary for interpolation in multidimensional random space while simultaneously minimizing the resulting error. This has been explained in Ref. [28]. Further details of the algorithm are given in Refs. [27,29]. Algorithms for integration based on sparse grids are provided in Ref. [30]. Collocation points constructed using Smolyak's algorithm in two-dimensional stochastic space are shown in Fig. 1.

We use Lagrange interpolating polynomials with Chebyshev based Smolyak sparse grids in this paper. The number of collocation points is increased in discrete steps. This is to ensure that all points with an equal predicted error are evaluated simultaneously. The depth of interpolation [27] defines the number of simulations to be run and error indicators have been previously computed for each depth of interpolation. In practice, the depth of interpolation



Fig. 1 The figure shows (*a*) stochastic collocation points in a two-dimensional stochastic space using a level-4 depth of interpolation and (*b*) level-6 depth of interpolation. (*c*) shows the function $g(\cdot)$, which is a sum of two Gaussian distributions, $\mathcal{N}(2, 0.2^2)$ and $\mathcal{N}(1, 0.1^2)$. The PDF of *g* is shown in (*d*).

allows for flexibility in implementation because it can be adjusted according to the computational expense of the computations.

2.2 Solving Hemodynamic Equations With Uncertainty. Blood flow in the cardiovascular system is governed by the Navier–Stokes equations. The velocities u and pressures p are expanded using finite elements in space and the finite difference technique in time. We define the residual as [31] $\mathcal{R}=(\rho(u_{,t}+(u\cdot\nabla)u)+\nabla p-\mu\nabla^2u-f)$, where μ denotes the viscosity, ρ denotes density, and f represents all body forces.

In the stochastic dimension, Lagrange interpolates are used to represent *u* and *p*. Hence, we have $u(x,t,\xi) = \sum_{i=1}^{M} u_i(x,t,\xi_i) \mathcal{L}_i(\xi)$ and $p(x,t,\xi) = \sum_{i=1}^{M} p_i(x,t,\xi_i) \mathcal{L}_i(\xi)$. These interpolating polynomials have the property, $\mathcal{L}_i(\xi_i) = 1$ if and only if i = j and 0 otherwise. By imposing the residuals, \mathcal{R} to be 0 at $\xi = \xi_i$, we get a set of decoupled equations at the stochastic collocation points. As a result, we need only solve *M* deterministic equations when performing uncertainty analysis. Note that the boundary conditions imposed on the problem will also be decoupled. This is significant because the method is nonintrusive and solvers need not be rewritten in order to implement the method.

3 Numerical Implementation

3.1 Modeling and Solution of Deterministic Hemodynamic Equations. A customized version of the SIMVASCULAR software package is used for cardiovascular geometry modeling as well as solving the Navier–Stokes equations [32,33]. Models can be constructed for idealized as well as patient-specific models using this software. Idealized models are parametrized using a set of geometrical variables. Scripts are written that can be interfaced with the software to generate idealized models from their analytic description.

Patient specific models are constructed directly from image data. Based on the image data, three basic steps are performed to construct the model [12,32]: (i) centerline paths are created along all blood vessels, (ii) segments are drawn along these paths that are perpendicular to the vessel using a 2D level set method, and (iii) the segments are lofted to generate the 3D model. Once the model is generated, it is meshed using tetrahedral elements to be used with the finite element solver.

The stabilized finite element technique using the generalized- α method [34,35] is employed with linear basis elements and fourth

order Runge-Kutta time stepping. Walls are assumed to be rigid, and Newtonian constitutive behavior is assumed, with a viscosity of blood set to 0.04 g/cm s and density set to 1.06 g/cm³. The number of elements and time steps are chosen based on the problem. Both steady-state and pulsatile inflow boundary conditions are imposed at the inflow face. We assume a parabolic flow profile for simplicity but the methods presented here do not restrict the use of other flow profiles, such as the Womerseley solution. Outflow boundary conditions are imposed using the coupled multidomain method [36] using resistance, impedance, or RCR models. These lump the vasculature downstream of the outlets and manifest as additional terms in the finite element weak form. In each example, we choose the finite element grid size so that the velocity and pressure fields do not change significantly with further refinement. The maximum, minimum, and mean of these fields, as well as the contour plots, are checked and tested to be invariant with grid refinement. Uncertain parameters that are studied in this paper include (a) uncertainty in geometry, (b) uncertainty in boundary conditions, and (c) uncertainty in flow-split.

3.2 Uncertainty Quantification in NS Equations Using Stochastic Collocation. The main advantage of the stochastic collocation technique is its nonintrusive nature; i.e., it can be seamlessly integrated over the existing simulation software with no modifications to the solver. Hence, the interpolation in the stochastic space is built independently on top of the hemodynamic solver. The stochastic code was implemented in MATLAB using the following steps:

- 1. The collocation points are generated based on the stochastic dimensions as well as the depth of interpolation. The sparse grid toolkit *spinterp* [29] is employed for this purpose. Each collocation point represents a different value of the uncertain parameters in physical space.
- 2. If moments are to be computed, the weights corresponding to each collocation point are computed by integrating the Lagrange functions over the stochastic space
- 3. At each collocation point, a 3D Navier–Stokes simulation is performed and the relevant outputs are stored. When all simulations have been performed, statistics, PDFs, as well as confidence intervals are estimated.
- 4. The depth of interpolation is increased until sufficient convergence of the PDF has been reached.

To couple the collocation tools with the model generation and flow solver, the geometries in this paper (except the Fontan problem) are generated using automated scripts. The interface to the fluid-solver is also automated using scripts. All scripts are directly interfaced with SIMVASCULAR and call internal SIMVASCULAR functions for meshing, boundary conditions, postprocessing, etc., automatically. The PDF and confidence intervals are computed by taking a very large number of input variables (of the order of 100,000) and using *spinterp* to obtain the interpolated values. From this, the histogram and hence PDF and confidence intervals can be computed.

3.3 Adaptive Collocation. The stochastic collocation method chooses points that minimize the overall error. However, this does not take into account any information about the function itself. Dimension independent adaptivity has been proposed in previous work, wherein a dimension is refined based on its error indicator. Yet, the refinement of each dimension itself is uniform, and hence adaptivity over a specific region in the stochastic space is not done. Dimensional adaptivity refines each dimension conventionally but operates on the more important dimensions first [28]. Hence, it does not account for steep function variations and reduces to a conventional adaptivity has been attempted for locally linear basis functions [37]. However, such interpolates with discontinuous gradients are not appropriate for our application. We have therefore developed a method to adaptively choose col-

location points for Lagrange interpolating polynomials. The goal is to reduce computational cost because of the large expense of performing multiple cardiovascular simulations.

The choice of the error indicator plays an important role in the adaptive algorithm. Finite element simulations have used Hessian information for applications with linear finite elements [31,38] to create adaptive meshing schemes. The rationale is that if a Taylor expansion is used for the functions, the second order term is the least order that cannot be captured. Further, finite elements use local interpolants, which makes the choice of Hessians inappropriate in the context of global interpolation. Since the theory behind collocation relies on convergence of the function value with increasing depth of interpolation (which is global), we use error indicators based on the function itself (rather than its gradients or hessians). For a collocation point c_k , we denote its neighbors as $\mathcal{N}(c_k)$.

The essence of the algorithm is to split collocation points into a frozen set and an active set. An existing collocation point will be refined if there is at least one active point in a local neighborhood surrounding that point. We present the adaptive algorithm formally below.

Compute the function values for depth of interpolation d=0 and d=1. Denote this set as C_d . Set $\mathcal{F}=\emptyset$ (\mathcal{F} represents the set of frozen collocation points). Perform the following until the termination criterion is met:

- 1. Evaluate neighbors of a collocation point, and check if the function value needs to be evaluated: Set d=d+1 and evaluate the function (using Lagrange interpolation) at $C_{adapt,d+1} \equiv (C_{d+1}-C_d)$, the set of collocation points that are in C_{d+1} but not in C_d . If a collocation point $c \in C_{adapt,d+1}$ has at least one neighbor, *h* that is not in the frozen set, i.e., $\exists h \in \mathcal{N}(c) \notin \mathcal{F}$, perform a simulation at *c*. Otherwise, add *c* to \mathcal{F} .
- 2. Compute hierarchical error indicator: Compute the hierarchical error indicator, $\mathcal{E}(c_t) = f(c_t) \mathcal{I}f(c_t)$, the difference between the function value and the interpolated value, at each collocation point where the function was evaluated in step 1.
- 3. Update the set of frozen points: For each point c evaluated in step 1, add the collocation point to the set \mathcal{F} if $\mathcal{E}(c) < \epsilon$, where ϵ is the chosen tolerance value.
- 4. *Check termination criterion:* If all of the collocation points are frozen, terminate. Else, go to step 1.

Using this method, when we increment the depth of interpolation, we perform simulations only at those points, which are not a subset of frozen patches that are computed according to our error estimate. This algorithm preserves the interpolation error up to ϵ . Further, setting ϵ =0 makes this algorithm equivalent to the conventional sparse grid algorithm. The value of ϵ can be chosen according to the smoothness of the function and the expense of computing function values. This is similar to the adaptive parameter used in Ref. [27]. Figure 2 shows a flowchart of the procedure for performing uncertainty analysis with adaptivity.

4 Numerical Examples

In this section, we apply these stochastic methods to three cardiovascular model problems: an idealized abdominal aortic aneurysm, an idealized carotid artery bifurcation, and a patient-specific Fontan surgery problem.

4.1 Abdominal Aortic Aneurysm. In this example, we evaluate uncertainties in an idealized model of an abdominal aortic aneurysm (AAA). Current research in AAA hemodynamics revolves around three questions: (a) What is the cause of aneurysm? (b) What determines their rate of expansion? (c) When do they rupture? The exact pathogenesis of AAA is unknown and is hypothesized to be a combination of factors such as genetic disorders, mycotic infection, high blood pressure, smoking, atherosclerosis, and aging [39]. The rate of expansion of the aneurysm is a



Fig. 2 A schematic of the stochastic collocation technique procedure for performing uncertainty analysis in cardiovascular simulations

valuable indicator to determine the risk of rupture and decide if surgical intervention is necessary [39]. This, however, depends on factors such as the formation of endoluminal thrombus (anomalous response of the endothelium to low and oscillatory shear stress [40,41]) and the mechanical properties of the arterial wall. This has motivated researchers to perform hemodynamic and FSI simulations and study shear stresses and recirculation near walls of the AAA.

Idealized models have been widely used to study flow patterns and hemodynamic stresses in the AAA [42-44]. Flow separation in the aneurysm and shear stresses on AAA walls help to determine formation of regions of stasis as well as growth dynamics of the AAA [43]. Parametric in vitro studies of the effect of increase in AAA radius on the flow patterns and wall stresses have been studied to identify the critical size for rupture of the aneurysm [43]. Realistic patient-specific studies have been performed to assess the risk of aneurysm rupture using solid mechanics [45] as well as fluid-structure interaction simulations [46]. It has been reported that surgical interventions should not be based on radius alone but on other factors such as wall shear stress [47]. Here, we perform the task of computing the effect of uncertainty in AAA radius using the sparse grid collocation technique. The goal is to illustrate the stochastic collocation method by evaluating the effect of uncertainty in the aneurysm size on output parameters. While we use an idealized model here, we emphasize that the technique we present is generally applicable to the patient-specific case as well.

An idealized AAA model is constructed using an automated script that takes the radius as an input parameter. The values of the parameters are chosen based on typical sizes for humans [48] with the diameter of the parent vessel, $d_p = 2.0$ cm, bifurcation angle

 θ =36 deg, and iliac artery diameter, d_i =1.4 cm. Steady state velocity boundary conditions are assumed at the inlet to the abdominal aorta with flow rate $Q=30 \text{ cm}^3/\text{s}$. The outlets are modeled using resistance boundary conditions to represent the downstream vasculature and are appropriate for steady-state flows with fully developed velocities at the outlet. The pressure and flow rate are related as p = QR, where R is the resistance and Q is the flow rate. Resistance boundary conditions with R=443.4 dynes s/cm⁵ are employed at the outlet iliac arteries. The uncertainty in radius is expressed as a normal random variable, $r(\xi) \sim \mathcal{N}(r_{\mu}, r_{\sigma}^2)$ with mean $r_{\mu}=1.8$ and standard deviation $r_{\sigma}=0.2$. The radius is given as $r(\xi) = r_{\mu} + r_{\sigma}\xi$. A tetrahedral mesh with roughly 80,000 elements, which ensured spatial convergence, was generated for each AAA model. A time step of 0.005 s was used and the simulation was run for 400 timesteps to ensure convergence to steady-state conditions.

A one-dimensional stochastic space is represented using Chebyshev nodes and Lagrange polynomial interpolates. The Navier– Stokes equations are solved at each collocation point. The mean spatial wall shear stress (MWSS) across the aneurysmal region is chosen as the output variable. A plot of the MWSS in the stochastic space and its convergence using Lagrange polynomials is shown in Fig. 3. Locally linear interpolating functions did a poor job of refining the function near ξ =0. The shape of the shear stress plot is due to a combination of increasing cross-sectional area of the aneurysm and reduction in traction due to recirculation of blood. Increased area reduces the velocity across the aneurysm for a constant volumetric inflow rate but once recirculation sets in, forward flow is confined to the central portion or the core of the artery. The one-dimensional plot shown in Fig. 3 has regions of



Fig. 3 (a) Stochastic space representation of mean shear stress over the abdominal aneurysm. Different depths of interpolation using conventional sparse grids are shown in the figure. (b) shows the onset of recirculation depicted using the vertical blood velocities.



Fig. 4 The figure shows wall shear stress plots at different radii corresponding to the extremes and mean of the stochastic space

steep function variation (corresponding to initial variation with increasing radius) and regions where it is almost constant (once recirculation sets in). Shear stress plots are shown in Fig. 4 for three different radius values. Figure 5 shows contours of v_z illustrating recirculation for different radii of the abdominal aneurysm. The recirculation region develops between ξ =0.02 and ξ =0.14 but does not vary significantly from ξ =0.14 to ξ =0.5. This explains the initial steep variation in the shear stresses but moderate variation beyond ξ =0.1.

To further reduce the number of required flow simulations, we used the adaptive algorithm with $\epsilon = 5 \times 10^{-3}$. This resulted in a significant reduction in the number of collocation points because points were not added in the flat region of the function. For a level 7 Smolyak sparse grid, 129 points were required, but 41 points sufficed for the adaptive algorithm. For levels 5 and 6, 29 and 35 points were required using the adaptive algorithm as opposed to 33 and 65 points, respectively, as shown in Fig. 6. The adaptive algorithm resulted in savings of almost 50%.



Fig. 5 Contours of v_z for the recirculating regions (with positive component of v_z) (from left) ξ =0.02, ξ =0.09, ξ =0.14, and ξ =0.5

Further, we compute the PDF of shear stresses, which is shown in Fig. 7. This figure shows the probability of average shear stresses across the aneurysm. The PDF does not change significantly beyond level 6 and hence, a depth of interpolation 6 is found to be sufficient for this problem. From the PDF, we extracted confidence intervals as well as confidence levels. A confidence interval, CI, is given by $CI=[\tau_L, \tau_U]$, where $Pr(\tau_L < \tau$ $< \tau_U)=1-\alpha$ and $(1-\alpha) \times 100\%$ is the confidence level. The confidence bounds are given in Table 1. This table indicates that for the given uncertainty in the radius, we can be 99.9% certain that the MWSS is between 0.46 and 0.81 g/(cm-s^2).

4.2 Carotid Artery Bifurcation. The carotid artery is a major vessel that provides oxygenated blood to the neck and head. Pioneering work of Zarins and co-workers [49] demonstrated a link between atherogenesis and hemodynamic variations to the bifurcation geometry (obtained from human cadaver data) using in vivo steady-state flow experiments on the carotid bifurcation. Intimal thickening (formation of atherosclerotic plaque) was found to be inversely proportional to the shear stresses and the measured shear stresses were significantly lower at the locations of plaque formation. Subsequently, strong correlations were found between the inverse of maximum shear stress, inverse of mean shear stress, and oscillatory shear stress with the intima thickness under pulsatile flow conditions [50]. The carotid sinus, which occurs at the bifurcation of the common carotid artery into the interior and exterior carotid arteries, has been the focus of many computational studies [6,34,48]. The study of hemodynamics and wall shear stresses near the carotid sinus is an area of significant interest. Milner et al. [6] performed a detailed computational study of hemodynamics in the carotid bifurcation. In this example, we examine hemodynamics in an idealized carotid artery due to uncertainties in geometry as well as boundary conditions. Thomas et al. reported [51] that the sinus geometry, as well as flow rate, can vary significantly in humans if measured over a time period of a couple of weeks. Geometrical uncertainty can be associated with changing positions of the patient and limitations of the measurement instrument [51]. Marshall et al. [52] used magnetic resonance imaging (MRI) with cine phase contrast to measure blood velocities in the carotid bifurcation. This example illustrates the use of the stochastic collocation method with more than one uncertain parameter.

The radius of the carotid artery sinus and the inflow velocity waveform are assumed to be uncertain. Impedance boundary conditions are imposed at the outlets [36]. In this method, the flow rate at any time depends on the pressure history over one time period and utilizes Womersley's linear wave theory. The split angle is 50 deg, the diameter of the CCA is 6.2 mm, the ICA is 3.5 mm, and that of the OCA is 4.4 mm. Outflow and the inflow velocity profiles were taken from literature values [52]. The outflow selocity was used to specify the flow-split to the two outflows. This information was used together with a typical pressure waveform to compute impedance values. The finite element mesh contained 100,000 tetrahedral elements and a time step of 0.003067 was chosen. The time period of a cardiac cycle is 0.923 s. Three cardiac cycles (900 time steps) were simulated to ensure convergence of the results.



Fig. 6 The stochastic collocation points for a depth of interpolation 6 using (left) conventional sparse grid and (right) adaptive sparse grid



Fig. 7 The figure shows convergence of the PDF of shear stresses (cgs units) as the level of interpolation is increased. The relatively long tail in the PDF is a manifestation of the plateau in Fig. 3.

The mean aneurysm radius is 4.0 mm and is uniformly distributed between 3.7 mm and 4.3 mm. The blood flow velocity depends on the state of the individual. Activities such as walking, sitting, standing, sleeping, and running have different flow rates associated with them. Uncertainty can occur due to physiological factors, as well as the absence of prior knowledge about how the subject spends his time. Based on the individual, the PDF of activities, and hence the blood flow rate, will change. For example, a construction worker might spend equal amount of time walking, standing, and sleeping, whereas a software engineer might spend most of his time sitting. While our framework can use data, if available, about the habits of a particular subject, we restrict ourselves to perform two representative studies here: (a) a uniform PDF of inlet velocities for subjects with a labor-intensive workhabit in which all velocities in the range are assumed to be equiprobable, $v = \mathcal{U}(0.8\overline{v}, 1.2\overline{v})$ and (b) a Gaussian distribution of inlet velocities for subjects with a sedentary lifestyle in which a mean value is assumed to be the most probable, with some variation $v = \mathcal{N}(\overline{v}, 0.2\overline{v}^2)$. v represents inflow velocity and \overline{v} , the mean velocity, is chosen from literature [52]. The analytical PDFs in (a) and (b) were chosen in the spirit of elucidating our technique and its applicability rather than being representative of the actual variations in the blood flow rate for human subjects. The input PDFs are chosen so that both have the same mean and range. For more complex input data, maximum entropy techniques can be used to compute the input distribution [25].

A two-dimensional Smolyak sparse grid using Gauss–Lobatto– Chebyshev points is constructed. Inflow velocities and carotid radius are assigned to each grid point and the Navier–Stokes equations are solved. The mean shear stress over the carotid sinus is extracted every 10 timesteps during the last simulated cardiac cycle. Figure 8 illustrates the variation of the shear stress over the stochastic space. Plots of the variation of the blood flow velocity due to uncertainties in the geometry and boundary conditions for

 Table 1
 The confidence intervals on shear stresses for the

 AAA problem corresponding to different confidence levels

CL	90	95	99	99.9
CI $(g/cm s^2)$	[0.46,0.57]	[0.46,0.62]	[0.46,0.765]	[0.46,0.81]

the carotid artery are shown in Fig. 9. We also performed a sensitivity analysis by computing the gradients of the interpolating Lagrange polynomials, as shown in Fig. 10. The shear stress shows positive sensitivity with respect to velocity and predominantly negative sensitivity to the radius owing to regions of recirculation. However, they are of a similar order of magnitude meaning that they are equally important stochastic dimensions.

The output PDFs corresponding to both the inlet PDFs are shown in Fig. 11. The shape of the output PDF is quite different for the two cases since the Gaussian case represents more information (mean and standard deviation) than a uniform distribution (no information). Table 2 shows the confidence intervals corresponding to the PDFs shown in Fig. 11. As expected, the Gaussian PDF has tighter confidence intervals, which means that the more information we have about the inputs, the higher the confidence on the outputs. For the uniform distribution, there is an almost linear variation in the confidence intervals.

Further, the adaptive algorithm was performed with ϵ =0.1. The choice of ϵ depends on the maximum value of the output stochastic variable that is computed. We choose ϵ to be less than 1% of the maximum value. A comparison of the reduction in grid points is shown in Fig. 12. For a level 4 sparse grid, 65 points are required for Smolyak sparse grid, while only 46 points are required for the adaptive sparse grid. Similarly, for a level 5 sparse grid, 145 points are necessary for a conventional sparse grid, while 73 points were required for the adaptive sparse grid. There is roughly a 50% reduction in the number of collocation points using the adaptive strategy.

4.3 Uncertainty in Patient-Specific Model of the Fontan Surgery. The Fontan surgery is performed to treat children with single ventricle heart defects. These defects are uniformly fatal if left untreated, as they leave a patient with only one functioning ventricle. Palliation usually requires three surgeries starting immediately after birth, and culminating in a Fontan procedure. The IVC and SVC are connected to the pulmonary arteries, resulting in a total cavo-pulmonary connection (TCPC) [53]. The Fontan surgery has been widely studied using computations, and quantities such as energy loss and wall shear stress have been extracted [54,55]. We have previously performed detailed simulations of Fontan hemodynamics at rest and exercise conditions and have extracted multiple parameters including wall shear stress, energy



Fig. 8 Comparison of stochastic space representation of the wall shear stress in cgs units using (left) depth of interpolation 3 and (right) depth of interpolation 4



Fig. 9 Plots of the magnitude of blood velocity in the carotid artery at four points in the stochastic space (from left) $\xi_1, \xi_2 = (0.5, 0), (0.5, 1), (0,0.5),$ and (0,1), where the first coordinate represents the stochastic velocity dimension and the second represents the stochastic radius dimension. The results were computed at t=0.923 s.

efficiency, pressure levels, and flow distribution [9,10,12]. We have also evaluated alternate surgical designs, such as a Y-graft design that improved hemodynamic performance in a single patient-specific model.

There are a number of uncertain parameters that should be evaluated to perform a comprehensive assessment of Fontan simulation output sensitivity. In this example, we choose to focus on the LPA/RPA flow-split as an illustration of the potential of the stochastic collocation method. The flow-split between the LPA and the RPA is an important factor that determines the hemodynamics. In healthy subjects, the flow-split can change with exercise conditions, age [56], and other physiologic factors. It has been reported that the pulmonary artery geometry can influence how the flow-split changes with increasing levels of exercise. In small patients, using PC-MRI to measure flow in the LPA and RPA can be challenging and subject to variability. Due to a combination of these factors, we assume the flow-split between RPA and LPA to vary from 70-30% to 40-60%, based on previous studies examining changes in flow-split. Here, we present a computational technique to efficiently compute the relationship between flow-split and both the energy efficiency and pressure drop



Fig. 10 The figure shows sensitivities of the wall shear stress to input uncertainties which is positive with velocity (left) $\partial \tau / \partial \xi_1$ and negative with radius (right) $\partial \tau / \partial \xi_1$. Contours illustrate similar order of magnitude of the sensitivity of wall shear stress to input parameters.



Fig. 11 A comparison of PDF of mean shear stress across the aneurysm using (left) a uniform PDF for velocity and (right) a Gaussian PDF for velocity

from the IVC to the LPA. We show that the stochastic collocation technique can be performed in a realistic time-frame with patient-specific models of the TCPC.

A patient-specific Fontan model geometry was generated directly from MRI image data [12]. Flow rates are chosen to simulate resting flow conditions of the patient. Pulsatile inflow rates were acquired from patient-specific PC-MRI data and a respiratory model was superimposed. A parabolic velocity profile is imposed at the inferior vena cava (IVC) and superior vena cava (SVC) inlets.

A three element Windkessel model (RCR) [57] was used to enforce downstream boundary conditions. This is a lumped parameter model, and is implemented in the Finite element solver using a coupled multidomain method. Initial RCR parameters were chosen to produce a 55%–45% flow-split between the left and right pulmonary arteries. The flow-split is assumed to be a Gaussian distribution with mean 55% and standard deviation of 5%. To produce a 3σ flow-split variation on either side of the mean, a Gaussian stochastic space with the flow-split varying between 40–60% and 70–30% was chosen. The desired flow-splits were achieved by adjusting the RCR parameters as explained below.

The lumped parameter RCR equations at the outlets in the model are given by

 $p_{\rm in} + R_2 C \frac{\partial p_{\rm in}}{\partial t} = p_{\rm out} + (R_1 + R_2) Q_{\rm in} + R_1 R_2 \frac{\partial Q_{\rm in}}{\partial t}$

(2)

 Table 2
 Confidence intervals on the shear stresses for the carotid artery bifurcation problem for different confidence levels

CL	90	95	99	99.9
CI (uniform, g/cm s ²)	[4.4,19.6]	[4.1,20.2]	[3.8,21.0]	[3.6,21.5]
CI (Gaussian, g/cm s ²)	[7.9,13.6]	[7.4,14.3]	[6.9,15.0]	[6.8,17.5]

where p_{in} and p_{out} represent the inlet and outlet pressures in the domain downstream of the outlets, Q_{in} is the flow leaving the outlet, R_1 and R_2 are resistances, and C is the capacitance of the



Fig. 12 The figure shows (left) an adaptive Chebyshev–Gauss–Lobatto grid and (right) a conventional sparse grid for the Carotid artery bifurcation problem. The adaptive method reduces the number of required simulations by roughly 50%.



Fig. 13 The figure shows mean flow velocities for the Fontan patient with uncertainty in flow-split. The plots show mean velocities at (top left) t=0.0, (top right) t=0.81, (bottom left) t=1.62, and (bottom right) t=2.43 s. The period of the respiratory cycle is 2.86 s

Windkessel model.

The flow through the outlet is modified as $\hat{Q} = kQ$ where $k = \mathcal{N}(1, 0.05^2)$ is chosen from the flow-split to be simulated. To maintain the same pressures, one choice is to modify the resistances as follows:

$$p_{\rm in} + \hat{R}_2 C \frac{\partial p_{\rm in}}{\partial t} = p_{\rm out} + k(\hat{R}_1 + \hat{R}_2)Q_{\rm in} + k\hat{R}_1 \hat{R}_2 \frac{\partial Q_{\rm in}}{\partial t}$$
(3)

Comparing Eqs. (2) and (3), we have $k\hat{R}_1\hat{R}_2 = R_1R_2 \equiv C_0$ and $k(\hat{R}_1 + \hat{R}_2) = (R_1 + R_2) \equiv C_1$. Solving, we obtain

$$\hat{R}_{2} = \frac{C_{1} \pm \sqrt{C_{1}^{2} - 4kC_{0}}}{2k}$$

$$\hat{R}_{1} = \frac{C_{1} \mp \sqrt{C_{1}^{2} - 4kC_{0}}}{2k}$$
(4)

Thus, the uncertainty in flow-split is transformed into uncertainties in the boundary resistances, \hat{R}_1 and \hat{R}_2 . Stochastic collo-



Fig. 14 The figure shows standard deviation of flow velocities for the Fontan patient with uncertainty in flow-split. The plots show standard deviations at (top left) t=0.0, (top right) t=0.81, (bottom left) t=1.62, and (bottom right) t=2.43 s.

cation points based on the Chebyshev grid are chosen in the [0,1]interval and transformed to [-2.57,2.57] (corresponding to [0.01,0.99] in the Chebyshev grid) using inverse Gaussian CDF. This is mapped to the flow-split from which k values are computed. The resistance values are computed from k using the equations described above. The Navier–Stokes solver was used for computing the velocity and pressure fields. A grid containing over 1,000,000 elements was employed using adaptive meshing with a time step size of 0.002 s and a total run time of two respiratory cycles. The size was chosen so that the finite element results do not change with further increase in grid resolution. The results were gathered over the final respiratory cycle. A single simulation took about 3 h to complete using 96 AMD processors in parallel.

Figure 13 shows the mean flow velocities computed using level-4 sparse grid interpolation. We show the results with level-4 since the results from level-5 were almost the same. Figure 14 shows the standard deviation of velocities computed using the sparse grid collocation technique. Since the uncertainties are defined on boundary resistances, the standard deviation propagates from the boundary to the center. During the period of retrograde flow in the IVC, the standard deviation of velocities propagates back to the IVC as depicted at t=2.43 in Fig. 14. However, it is 0



Fig. 15 The figure shows (left) PDF of hemodynamic efficiency and (right) PDF of pressure difference between the IVC and the LPA using level-4 sparse grid collocation

Table 3 Confidence intervals on the pressure difference between IVC and the LPA in mm Hg

CL	90	95	99	99.9
CI $\Delta p \pmod{\text{Hg}}$	[1.68,2.48]	[1.67,2.56]	[1.57,2.81]	[1.48,2.93]

in the SVC at all times.

Figure 15 shows PDFs of energy efficiency and pressure drop between the IVC and the LPA (Δp). We observe that the efficiency is not very sensitive to the flow-split. One reason for this observation might be that the efficiency is computed by summing the flow energies at all outlets, so rebalancing the flow has little effect. These variations are very small compared with the differences in efficiency between competing designs for the TCPC evaluated in our previous work [12].

In contrast, Δp computed at t=0.81 shows a large sensitivity to the flow-split, and confidence intervals on Δp are summarized in Table 3. The computed CIs are more than 1 mm Hg and are large enough that they could lead to a different clinical decision from one end of the range to the other. We therefore conclude that uncertainty in flow-split have a non-negligible effect on the Δp between the IVC and the LPA. Uncertainty in the overall (IVC +SVC) LPA/RPA flow-split will also influence predictions of IVC flow distribution to the LPA and RPA. This will influence the concentration of the hepatic factor that has been shown in clinical studies to impact normal lung development [58]. The distribution of the IVC flow is known to differ significantly from the overall flow distribution [59].

This work demonstrates that the required accuracy of the input data for Fontan simulations depends on what output quantity is being computed. However, this study was conducted assuming the IVC and SVC inflow velocities are known deterministically, and the reconstructed geometry is exact. A more extensive study could be performed to rank multiple output parameters according to sensitivity with respect to multiple input uncertainties.

5 Discussion

We have presented a generally applicable computational technique for incorporating uncertainties in hemodynamic simulations. Using the sparse grid collocation technique, we choose collocation points and interpolates in the stochastic space and perform a carefully chosen set of cardiovascular simulations. Further, we developed a new adaptive technique using Lagrange polynomials to reduce the number of required simulations, cutting down the overall computational cost by as much as 50%. We showed the applicability of the technique to three problems with different sources of uncertainties in (a) geometry, (b) inlet velocity, and (c) flow-split. Convergence was shown with increasing depths of interpolation in the stochastic space. Confidence bounds as well as PDFs were constructed for variables of interest. Shear stresses were studied across the aneurysm in an idealized AAA model and across the sinus in an idealized carotid bifurcation model. In the AAA problem, the 99% CI has almost a 30% variation around the mean value of WSS. In the carotid artery bifurcation problem, the sensitivity of shear stresses due to velocities was significantly higher than that due to uncertainties in the geometry. In both of these problems, uncertainty quantification plays an important role and outputs were very sensitive to input uncertainties. Uncertainties need to be accounted for if the actual input variability is close to what was used in this work. For the patient-specific Fontan problem, the energy efficiency was quite robust to variability in flow-split. However, the pressure difference between IVC and LPA showed significant variability. Additional patients should be evaluated so that a comprehensive ranking of multiple parameter sensitivities can be made.

This work demonstrates a promising approach that offers a systematic and efficient method to quantify uncertainties in cardiovascular simulations. This method has the potential to replace current "trial and error" sensitivity analyses by using a unified framework with sound mathematical convergence theory.

6 Limitations and Future Work

The technique presented in this work shows significant promise to be extended to robust design problems, i.e., problems in which the design cost is stable to small fluctuations in the problem parameters. We plan to couple these methods with a framework we have developed for cardiovascular optimization [60,61]. In addition to characterizing PDFs, we will use the technique to evaluate sensitivities and robustness of problem parameters. These will hopefully result in a better trust of simulation results that will eventually lead to adoption of these tools in the clinical setting. In the future, the adaptive stochastic collocation method could be applied to a wide range of cardiovascular simulations and other complex flow problems.

One limitation in this paper is that we use simple PDF models for input uncertainties. In the future, we plan to build realistic models for input uncertainties using data-driven techniques such as maximum entropy [25]. We have only examined two uncertain inputs. We plan to evaluate more sources, which will significantly increase computational cost. Another limitation is when there are flow transitions or bifurcation regions in the stochastic space, which cannot be captured using Lagrange interpolates. Wavelet interpolates may be a better choice to resolve such local regions of sharp variations [62] and is an area of ongoing research. In our simulations, we assume that the walls are rigid, and we plan to perform FSI simulations with uncertainties in material properties.

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