Simulation based planning of surgical interventions in pediatric cardiology

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Hemodynamics plays an essential role in the progression and treatment of cardiovascular disease. However, while medical imaging provides increasingly detailed anatomical information, clinicians often have limited access to hemodynamic data that may be crucial to patient risk assessment and treatment planning. Computational simulations can now provide detailed hemodynamic data to augment clinical knowledge in both adult and pediatric applications. There is a particular need for simulation tools in pediatric cardiology, due to the wide variation in anatomy and physiology in congenital heart disease patients, necessitating individualized treatment plans. Despite great strides in medical imaging, enabling extraction of flow information from magnetic resonance and ultrasound imaging, simulations offer predictive capabilities that imaging alone cannot provide. Patient specific simulations can be used for *in silico* testing of new surgical designs, treatment planning, device testing, and patient risk stratification. Furthermore, simulations can be performed at no direct risk to the patient. In this paper, we outline the current state of the art in methods for cardiovascular blood flow simulation and virtual surgery. We then step through pressing challenges in the field, including multiscale modeling, boundary condition selection, optimization, and uncertainty quantification. Finally, we summarize simulation results of two representative examples from pediatric cardiology: single ventricle physiology, and coronary aneurysms caused by Kawasaki disease. These examples illustrate the potential impact of computational modeling tools in the clinical setting.

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I. INTRODUCTION

Patient specific cardiovascular simulations have the potential to provide clinicians with predictive tools to augment clinical imaging and clinician experience to positively impact patient care. While image data can provide increasingly detailed pictures of anatomy and flow, imaging alone is not a predictive tool. Simulations have potential to fill this gap, providing quantitative predictive tools for virtual surgery, treatment planning, and risk stratification. Simulations can non-invasively provide temporally- and spatially-varying hemodynamics data, including wall shear stress (WSS), particle residence times (PRT), and pressure data often not directly attainable by imaging or clinical measurement. Perhaps more importantly, multiscale modeling methods now offer insight into circulatory physiology. Recent advances in computational technology and development of efficient algorithms have led to increasingly realistic and accurate simulations, which now capture physiologic levels of blood pressure, detailed anatomy, feedback mechanisms in the circulatory system, and vessel wall deformations.^{3–15}

Analysis and simulation of blood flow in the cardiovascular system necessitate a combination of image analysis and model construction, boundary condition and material property selection, accurate solution of the governing equations, physiology models, and high-performance computing. Patient specific cardiovascular simulations typically start with 3D reconstruction of the vascular anatomy and progress through stages of meshing, boundary condition and parameter assignment, and hemodynamic simulation. This produces a wealth of data from which we aim to

extract clinically relevant information to improve patient care. Examples of patient specific modeling include new surgical designs for congenital heart disease,^{7,8,16–19} risk assessment in coronary artery disease,^{20,21} thrombotic risk stratification in Kawasaki disease²² and cerebral and abdominal aneurysm treatment.^{23,24} Device simulations have included evaluation of wall shear stress patterns in stents,^{25,26} stent optimization,^{27,28} ventricular assist devices,²⁹ device migration,³⁰ and pacemaker lead placement.³¹ We are fast approaching a time when simulations, with proper validation, will be incorporated into day to day clinical practice. However, while great strides have been made, hurdles remain before ordering a patient-specific simulation becomes as integral to a patient's overall diagnostic plan as, for example, a chest x-ray.

In this paper, we first provide a brief historical perspective on the development of cardiac surgery and the partnerships between engineering and medicine that have facilitated clinical advances. We then outline key fundamentals in the development and methodology of patient specific modeling. Building on this, we attempt to provide insight into current challenges in the field, including image segmentation, multiscale modeling, optimization and uncertainty quantification. Finally, we review the application of these tools to two clinically relevant examples in pediatric cardiology.

Pediatric cardiology lends itself particularly well to patient specific modeling because of the complex interplay between local flow and pressure and circulatory physiology. In addition, the wide variation in anatomy necessitates the need for individualized treatment planning, and small patient numbers often impede large-scale clinical studies. In this paper, we discuss two applications of patient specific modeling to pediatric cardiology: single ventricle physiology and coronary artery aneurysms caused by Kawasaki disease. Both examples illustrate how strong interactions between engineers and clinicians, together with state-of-the-art modeling tools, can simultaneously advance the field of cardiovascular simulation while positively impacting patient care. This work builds on a long history of collaborations between engineers and clinicians that has advanced surgical technology, medical devices, and medical imaging.

II. HISTORICAL PERSPECTIVE

The first heart surgery was performed by Alfred Blalock at Johns Hopkins University in 1944 to treat “blue baby syndrome.” This surgery, now known as the Blalock Taussig (BT) Shunt, was developed by an unlikely trio of collaborators, including surgeon Alfred Blalock, cardiologist Helen Taussig, and lab technician Thomas.³² Taussig had overcome severe dyslexia as a child, and later became profoundly deaf, but went on to make crucial contributions in the treatment of children with congenital heart disease. Thomas, an African American with only a high school education, self-trained as a surgical technician, and rose above poverty and racism to advance the field of infant heart surgery. Both made key contributions that ultimately enabled Blalock's completion of the first series of successful surgeries to treat “blue” babies with Tetralogy of Fallot. Variants of this surgery, including the Norwood, Sano, hybrid, and modified BT procedures, are still performed today, primarily to treat patients with single ventricle heart defects.

Following this breakthrough surgery, a flurry of developments in cardiac surgery ensued during the 1940s and 1950s. Dr. C. Walton Lillehei was a pioneer in surgical innovation, performing the first open heart surgery to treat atrial septal defect in 1952.³³ A brash young surgeon, Lillehei went on to perform the first surgery to correct a ventricular septal defect using a cross-circulation technique in which the parent was connected to the child during surgery to provide circulatory support. In the late 1950s, a unique partnership formed between Lillehei and Earl Bakken, a local electrical engineer who went on to found the medical device company Medtronic, leading to the development of the first battery powered pacemaker in 1957. During the same period, in 1953 Dr. John Gibbon performed the first successful open heart procedure on a human utilizing a heart lung machine. Since that time, partnerships between engineers and clinicians have led to significant technological breakthroughs including the development and commercialization of the heart-lung bypass machine, cardiac magnetic resonance imaging, stents, total artificial hearts, and ventricular assist devices.

During the same time period, progress in the field of fluid mechanics led to increased physical understanding of blood flow phenomena. Early work in fluid mechanics of blood flow focused

on analytical solutions of the Navier-Stokes equations for pulsatile flow in rigid and elastic tubes. These solutions were derived by Womersley in the 1950s and are now widely used,³⁴ particularly as boundary conditions for large-scale flow simulations.

Starting in the 1960s, lumped parameter network (LPN) models of the circulatory system were developed by analogy to electrical circuits.^{35,36} Because these models are governed by ordinary differential equations (ODEs), they can be readily solved in near real time on a desktop computer. While LPNs alone do not provide spatial information, they can provide a surprisingly realistic representation of circulatory dynamics. Hughes and Lubliner introduced the one-dimensional equations of blood flow in the 1970s.³⁷ This approach offers an attractive means to obtain near real-time solutions of circulatory flow dynamics, while providing one degree of spatial information and capturing wave propagation phenomena. While both 0D and 1D systems can be solved independently, they are perhaps most useful as boundary conditions coupled to 3D simulations, enabling simulations to capture the dynamic interplay between local hemodynamics and circulatory physiology. Advantages of 0D boundary conditions include easier implementation (e.g., an ODE instead of a PDE solver) and no need for distal anatomic information which is often not available from imaging. Advantages of 1D boundary conditions include the ability to capture wave propagation and wave reflection phenomena, which is particularly attractive for simulations with deformable vessel walls.

The advent of patient specific modeling in the 1990s paved the way for increasingly detailed flow and pressure information to be solved in three dimensions on an individualized basis.^{6,38,39} Starting from patient image data (typically MRI or CT) a three-dimensional model is constructed to represent a portion of the anatomy, often including a diseased region of interest. Since only a portion of a patient's anatomy can be included in the 3D model, both due to computational expense and limits of image resolution, boundary conditions must be applied at inlets and outlets of the model to accurately represent the vascular network outside. In Secs. III and IV, we outline advances and remaining challenges in computational methodology, before presenting two clinically relevant examples of patient specific modeling.

III. MODELING PRELIMINARIES

Numerical simulation methodology for cardiovascular disease is becoming increasingly sophisticated.³⁻¹⁵ Models are typically constructed from MRI or CT data, including detailed anatomy with multiple vessel bifurcations and outlets (Fig. 1). Boundary conditions for simulations are often derived from 2D (and increasingly 4D) phase contrast MRI measurements of flow. Outflow boundary conditions are particularly challenging, and recent advances in multiscale lumped parameter modeling, 1D wave propagation equations, and numerical stability have increased physiological

FIG. 1. Steps in the process of patient specific modeling, from left to right for a patient with coronary aneurysms caused by Kawasaki disease: (1) volume rendered CT image data, (2) patient specific model with aorta and coronary arteries, (3) adapted mesh, (4) contours of wall shear stress from simulation results.

realism. Fluid structure interaction simulations provide wall deformations, stresses, and strains through solving a coupled fluid-solid problem.

Both finite element and finite volume methods, implemented in custom and commercial solvers, have been used to solve the Navier-Stokes equations in cardiovascular applications. Finite element methods (FEM), which are most widely used, are well suited to complex geometries with unstructured meshes. Most recent work has used stabilized (e.g., streamline-upwind/Petrov-Galerkin SUPG) methods with linear elements, but higher order elements have also been employed.⁴⁰ In the FEM approach, the weak form of the Navier-Stokes equations is solved. While commercial solvers can be used successfully, custom solvers offer more flexibility and control over numerical scheme and boundary condition implementation, which is essential for obtaining an accurate solution. Unstructured finite volume methods have been used in a few studies, offering the advantage of conservative numerical schemes with no artificial dissipation.

The flow simulations described in Sec. V of this paper are performed using a custom in-house finite element (FEM) Navier-Stokes solver using a Newtonian flow assumption. While blood is known to be a non-Newtonian shear thinning fluid at small scales, a Newtonian assumption generally holds in large vessels, and we refer the reader to other relevant discussions of non-Newtonian effects in blood flow.^{1,2} The weak form of the Navier-Stokes equations is solved using SUPG, discretized in space with linear finite elements, and in time using the generalized- α method.^{5,41} The solver is parallelized with the message passing interface (MPI), and includes capabilities for physiologic impedance and lumped parameter boundary conditions,^{3,42} fluid structure interaction,^{4,13} adaptive meshing,⁴³ and particle tracking.¹⁰ Recent numerical advancements also include (1) outflow stabilization to prevent divergence due to backflow,⁴⁴ (2) scalar advection and diffusion, (3) variable wall properties for deformable vessels,^{4,13,45} and (4) an implicit algorithm for coupling closed loop lumped parameter circuit models to capture global dynamics of the circulatory system.⁴⁶ Typical mesh sizes for patient specific simulations range upwards of $1\text{--}4 \times 10^6$ elements, with run times ranging from hours to days for a single simulation covering 5–10 cardiac cycles on a modest 10–20 core machine. Patient-specific models are constructed using a custom version of the SimVascular software package open sourced as part of the Simbios project at Stanford University.⁴⁷

IV. CURRENT CHALLENGES IN PATIENT SPECIFIC MODELING

A. Image segmentation

Patient specific simulations are typically performed on three-dimensional models of vascular anatomy derived from patient image data. Depending on the disease and anatomy, either CT or MRI data is commonly used. Image data may be segmented using 2D or 3D level set or thresholding methods, or by hand. Popular packages for image segmentation include open source packages Simvascular (simtk.org)⁴⁷ and ITK-SNAP, and commercial package Mimics (Materialise, Leuven, Belgium). The typical steps for model construction using 2D methods in SimVascular (as used in the present work) are (1) to create paths along vessels of interest, (2) to manually or automatically draw segmentations of the vessel lumen at discrete locations along the paths, (3) to loft (interpolate) the segmentations together to create a 3D solid model, and (4) to mesh the model for use with a CFD solver (Figure 1). Advantages of 2D methods include the ability to smoothly represent bifurcating vascular branching patterns, such as in the pulmonary and coronary arteries. Advantages of 3D methods include the ability to capture local complex geometry, particularly in aneurysms or complex surgical connections such as the Fontan. Likely, a combination of both methods will ultimately prove most advantageous in future work. While automated methods exist for both 2D and 3D segmentation, noise in the image data often leads to significant user intervention and the need for manual segmentation. Model construction performed entirely with manual segmentation can require several days time by an expert user. Improvements in automated segmentation methods, for example, by applying machine learning algorithms, would greatly improve efficiency, reduce user input, and enable high-throughput model construction for clinical applications. Additionally, future segmentation algorithms should account for uncertainty in the segmentation process arising from noise and imaging artifact.^{48–50}

B. Boundary conditions and multiscale modeling

The choice of boundary conditions is of paramount importance in cardiovascular simulations, as the local flow dynamics are influenced by conditions upstream and downstream of the 3D model. Typical choices include zero pressure or zero traction conditions applied at the outlet, resistance or impedance conditions, reduced order LPN models which can be open or closed loop, or one-dimensional wave propagation equations. Numerous studies have demonstrated drastic differences in flow solutions with incorrect boundary condition choices, even with simple geometries, and particularly in models with multiple outlets.^{3,51} The use of zero-pressure boundary conditions, for example, can lead to unrealistic flow distribution in models with multiple outlets, inaccurate wall deformation predictions in fluid-structure interaction (FSI) simulations, and the inability to capture physiologic levels of pressure. Zero pressure outlet conditions should not be used for fluid-structure interaction problems since the wall deformation depends directly on the pressure waveform in the vessel.

In an open loop configuration, one imposes an inlet flow or pressure waveform together with outlet models of the distal vasculature. Inflow boundary conditions typically impose a velocity profile on the inflow face of the model. Inflow waveforms are commonly derived from clinical measurements, including phase contrast MRI or invasive cardiac catheterization. While plug flow or parabolic profiles are common, the most accurate choice in large vessels is generally the analytic solution of Womersley for pulsatile flow in a rigid or elastic tube.^{34,52} Outlet models can consist of coupled resistance or impedance conditions, lumped parameter networks, or the 1D equations of blood flow. In lumped models, one makes an analogy to an electrical circuit and lumps the resistive, elastic, and inertial properties of blood flow through the vessels into electrical elements. One then solves the associated set of ODEs governing the electrical circuit. Simple circuit models such as resistors, Windkessel models (“RCR” circuits comprised of two resistors and a capacitor), or coronary models can be solved analytically and implemented using an implicit monolithic coupling approach.^{3,53,54} More complex LPN models must be solved numerically.

In a closed loop configuration (Figure 2), one typically uses a LPN to capture the interplay between the 3D domain and the dynamics of the circulation. The values of circuit elements are tuned

FIG. 2. Typical boundary condition specification for a patient specific model of the Fontan surgery. (a) Open loop boundary conditions with prescribed inflow and RCR Windkessel outflow conditions. (b) Multiscale closed loop boundary conditions using a lumped parameter network. Blocks representing different portions of the anatomy (heart, lungs, etc.) are shown.

to match physiologic and clinical values. While by-hand iterative tuning has generally been standard practice, automated tuning using Kalman filtering or optimization approaches are gaining favor. Automated tuning should ultimately account for uncertainties and associated confidence levels in clinical data as part of a fully automated process. The closed loop configuration poses numerical challenges since the ODE network must be solved numerically, and coupled to the 3D domain. Iterative coupling can be performed using explicit methods, as implemented in prior work using commercial solvers, with the drawback that it can be time step restricted. Recent advances in coupling algorithms have produced implicit methods that are both modular and efficient, allowing for solution of more complex models and networks in reasonable time. Using this treatment, inlets and outlets can be treated either as Neumann or Dirichlet boundaries and the overall computational cost is nearly the same as the 3D simulation alone.⁴⁶

A major difference from the open loop configuration is that closed loop models generate their own inflow boundary conditions, avoiding the need to impose a waveform directly. In this situation, it is common to tune the model parameters, including the heart model, to match other available clinical data such as cardiac output or ejection fraction measured in echocardiography. This is particularly advantageous when inflow waveforms are not available directly from clinical data, or when one is attempting to predict hemodynamic changes following surgery or device implantation.

Another important issue is that of numerical instabilities due to back flow. Flow reversal occurs physiologically, for example during diastole in the descending aorta. This issue also arises when enforcing a Neumann condition on an inflow face of a model, such as when the inflow is connected to a LPN model (e.g., the ascending aorta). While this is an often un-discussed problem in the field of cardiovascular simulation, backflow can lead to simulation divergence if boundaries are not properly treated. Methods to avoid divergence include adding outlet extensions to dissipate flow structures before they exit the domain, enforcing a known velocity profile using a Lagrange multiplier constraint, or enforcing that the velocity vectors be normal to the outflow face, which is a common option in commercial solvers. Alternately, stable solutions can be achieved using outlet stabilization, in which a small traction force is added only on nodes where there is reversed flow, which has been shown to stabilize the flow while still allowing for flow reversal, with minimal impact on the flow physics and no additional computational cost.^{44,55}

C. Validation

Cardiovascular simulations are typically verified against analytic solutions and validated against *in vitro* experiments to ensure accurate solution of the governing equations in a realistic patient specific geometry. Prior *in vitro* experiments using rigid and compliant phantoms have shown excellent agreement^{56,57} using the same flow solver that we employ here. Recent studies have also employed sophisticated mock circuits to represent not only the local hemodynamics, but the entire circulatory physiology in a closed loop in the laboratory setting. This approach has been successful in the context of single ventricle physiology to examine all three stages of surgical repair and to assess the impact of respiration on hemodynamics.⁵⁸ While both validation and verification with *in vitro* models are important, validation against *in vivo* clinical data is ultimately needed to demonstrate the predictive capability of simulations in the clinical setting. Demonstrating that numerical models are clinically useful requires validation to show that results are accurate, as well as correlation with clinical outcomes data to show that results are clinically meaningful. In this vein, preliminary validation of Fontan surgery simulations has demonstrated good agreement between flow distribution predictions and lung perfusion data as shown in Figure 4(b). In addition, coronary artery simulation predictions of fractional flow reserve (FFR_{CT}) have shown promising correlation with clinical measurements obtained via cardiac catheterization.⁵⁹

D. Optimization

Coupling shape optimization to cardiovascular blood flow simulations has potential to improve current surgical designs and to enable customized treatment planning for individual patients. While optimization has become a routine part of the design process in many industries (automotive,

aeronautics) the full potential of optimization to accelerate and refine the design process has not yet been realized for surgical planning and the medical device industry. When choosing an appropriate optimization method, the primary choice is between gradient-based and derivative-free methods. Factors contributing to this choice include the availability of cost function gradients, computational cost of the function evaluations, the level of noise and discontinuities in the function, complexity of implementation, the number of design parameters, convergence properties, efficiency, and scalability.

The coupling of optimization algorithms to complex fluid mechanics simulations (such as blood flow problems) is particularly challenging because each cost function evaluation requires an unsteady, 3D solution of the Navier-Stokes equations on multiple processors. These evaluations are computationally expensive, and usually provide no gradient information. In traditional gradient-based optimization, gradients are generally obtained using adjoint solutions or brute-force finite difference methods. While impressive strides have been made using adjoints for efficiently obtaining gradient information in aerodynamics problems,^{65,66} application in a fully time-dependent setting using unstructured solvers, fluid structure interaction, complex geometries and constraints remains intractable. The cost of finite difference methods also quickly becomes intractable as the number of design parameters grows. As such, much of the prior surgery and device optimization has been mostly limited to gradient-based methods in small scale two-dimensional and/or steady flow problems^{60–63} or limited testing via trial and error.⁶⁴

To achieve the goal of efficiently optimizing patient specific vascular models, several crucial challenges must be addressed. First, simulation results must be physiologically accurate and methods thoroughly validated. Second, appropriate measures of performance (cost functions) for cardiovascular designs must be defined based on physiologic information. Third, the choice of optimization method must be appropriate for computationally expensive, unsteady, 3D fluid mechanics problems. And fourth, new tools must be developed for seamless parameterization of patient-specific geometries with a reasonable number of variables. Perhaps the most challenging aspect of cardiovascular optimization is the choice of cost function. This choice is highly disease or device specific, and ideally should relate directly to clinical outcomes and biological response.

Given the above challenges, our recent work has focused on a class of derivative-free pattern search optimization methods called the Surrogate Management Framework (SMF). The main idea behind the SMF method is to increase efficiency by using a surrogate function to “stand in” for an expensive function evaluation, while at the same time retaining the convergence properties of pattern search methods. In contrast to genetic algorithms, pattern search methods are among the only derivative-free methods with established convergence theory.^{72–74} Advantages of SMF are its non-intrusive nature, ease of implementation, efficiency, and parallel structure. The SMF method was successfully applied to the constrained optimization of an airfoil trailing-edge for noise suppression in turbulent flow in prior work.^{67–71}

Using SMF, a general optimization problem may be formulated with linear bound constraints as follows:

$$\begin{aligned} &\text{minimize} && J(\mathbf{x}) \\ &\text{subject to} && \mathbf{x} \in \Omega, \end{aligned} \tag{1}$$

where $J : \mathbb{R}^n \rightarrow \mathbb{R}$ is the cost function, and $\mathbf{x}$ is the vector of design parameters. The parameter space is defined by $\Omega = \{\mathbf{x} \in \mathbb{R}^n | \mathbf{l} \leq \mathbf{x} \leq \mathbf{u}\}$, where $\mathbf{l} \in \mathbb{R}^n$ is a vector of lower bounds on $\mathbf{x}$ and $\mathbf{u} \in \mathbb{R}^n$ is a vector of upper bounds on $\mathbf{x}$. In a cardiovascular design problem, the function $J(\mathbf{x})$ depends on the solution of the Navier-Stokes equations, and the cost function value is computed in a post processing step from the simulation results. All steps of the process, from model construction, flow solution, to post processing, must be linked and executed via automated scripts.

The SMF algorithm consists of a SEARCH step, employing a surrogate model for improved efficiency, together with a POLL step to guarantee convergence to a local minimum. In our work, the surrogate model was an interpolation using Kriging, a method based on Gaussian processes

originally developed for geostatistics applications. In SMF, all points are restricted to lie on a mesh in the parameter space. The exploratory SEARCH step uses the surrogate to select points that are likely to improve the cost function, but is not strictly required for convergence. Convergence is guaranteed by the POLL step, in which points neighboring the current best point on the mesh are evaluated in a positive spanning set of directions to check if the current best point is a mesh local optimizer. A positive spanning set of a matrix is simply the set of positive linear combinations of its column vectors. A set of $n + 1$ POLL points are required to generate a positive basis, where n is the number of optimization parameters.

SMF has been applied in the cardiovascular setting to optimize idealized geometries, including an end-to-side anastomosis, and vessel bifurcation.⁷⁵ The SMF method has also been applied in constrained shape optimization of a novel Y-graft conduit design for surgical palliation in single ventricle congenital heart patients.^{76,77,100} This graft concept was designed, simulated, and optimized using patient-specific modeling tools. Cost function choices have aimed to reduce energy loss (to reduce cardiac workload), or improve hepatic flow distribution to the lungs (to reduce pulmonary arteriovenous malformations). Additional constraints have been added to limit areas of low wall shear stress, assumed to be linked to thrombotic risk. In bypass graft optimization, optimization has aimed to reduce areas of low wall shear stress, reduce wall shear stress gradients, and reduce oscillatory shear index, because of demonstrated biological links to atherosclerosis localization and thrombosis.⁷⁹

Because each SEARCH and POLL step requires multiple function evaluations, the SMF algorithm can be easily parallelized with linear scalability. This will result in a multi-layered parallel structure, in which multiple cost function evaluations are performed simultaneously, and each of these, in turn, requires a finite element simulation on multiple processors. For example, if n is the number of design parameters, $n + 1$ multi-processor finite element jobs can be submitted in parallel to complete a single POLL step of the SMF method.

The SMF method was also expanded to include uncertainties using stochastic collocation by Sankaran *et al.*⁷⁸ Using this method, Sankaran and Marsden⁷⁹ demonstrated a shift in optimal bypass graft anastomosis angles and radius when incorporating uncertainties to perform robust optimization. Robust optimization has also been applied for parameter identification in vascular growth and remodeling (G&R) studies, demonstrating efficiency with up to 12 parameters and several thousand G&R simulations.⁸⁰

E. Uncertainty quantification

An important pitfall of current cardiovascular simulation approaches is that they often fail to quantify the numerous sources of uncertainties involved in the modeling process. Because of this, simulations typically produce deterministic quantities that users are expected to accept as “truth.” This in-turn leads to competing claims of accuracy, with little means for validation, and justified skepticism on the part of the medical community. As simulation data are increasingly incorporated into clinical trials and the FDA approval process, there is a pressing need to establish methods for assessing the impact of uncertainty on simulation outputs. The creation of new tools for uncertainty quantification (UQ), will ultimately enable increased clinical utility of cardiovascular simulations.

As cardiovascular simulations typically require multiple hours of run time on a large parallel cluster, manually perturbing different parameters using a design of experiments strategy quickly becomes computationally intractable for problems with a large number of uncertain parameters. Thus, specialized computational tools are required to efficiently quantify uncertainties.

We have demonstrated efficient application of UQ to idealized and patient-specific models using a small number of stochastic parameters.^{79,81} We used the method of stochastic collocation with Smolyak sparse grids to handle uncertainties, and quantify outputs using probability density functions (PDFs) and confidence intervals^{82–85} (see Fig. 3(a)). This method offers substantially better convergence than traditional Monte Carlo methods,^{79–81} is non-intrusive to implement, and highly parallelizable.

To illustrate this method, Figure 3(b) shows an idealized model of an abdominal aortic aneurysm (AAA), for which we aimed to quantify the mean WSS in the aneurysm. We assumed a 20%

FIG. 3. (a) The process of UQ with stochastic collocation. (b) Application of UQ to CV simulation example. The diameter is assumed to have 20% uncertainty. Simulations are run at collocation points to evaluate WSS. Confidence intervals and probability density functions are computed.

uncertainty in the diameter, such as would arise with noisy image data, with a Gaussian distribution. Collocation was used to carefully select a set of simulations to run with different input conditions (in this case model diameters). Statistics were generated on the set of simulation outputs (in this case aneurysm WSS), and the depth of interpolation was increased until convergence was reached. The required number of simulations was 145 for a non-adapted level 5 sparse grid. Convergence was measured using (a) convergence of the PDFs and (b) convergence of the stochastic space

representations. We computed confidence intervals for specified levels (99%, 95%, etc.). Figure 3(b) shows the probability density function convergence for WSS with increasing depth of interpolation. We developed an adaptive method that further reduced the number of required simulations by as much as 50%.⁸¹ In addition, UQ was applied in a patient-specific model of the Fontan surgery.⁸¹ This demonstrated the utility of UQ for ranking the relative sensitivity of output parameters such as pressure drop and energy loss.

F. Fluid structure interaction

Deformation of the vessel walls can be included via FSI simulations, in which the solid and fluid domain problems are solved simultaneously using either iterative or strong coupling. Strongly coupled formulations such as the arbitrary Lagrangian-Eulerian (ALE) method are particularly attractive for large deformation problems with mesh motion, including membrane buckling, valves, and ventricular mechanics.^{13,86} However, the computational cost of ALE can be prohibitively expensive for some applications. ALE has been recently applied to model a pediatric ventricular assist device with complex membrane buckling and two fluid domains²⁹ as well as wall deformation in Fontan surgery simulations.⁸⁷ Immersed boundary methods, originally motivated by the need for methods to handle cardiac fluid mechanics, are also widely used for ventricular fluid mechanics, medical device simulations, and complex geometries.⁸⁸ Other approaches to reduce computational cost include the coupled momentum method of Figueroa and Taylor,⁴ which relies on a small deformation approximation based on Womersley theory to impose forces on the fluid domain without requiring mesh motion. This method is highly efficient and has been recently extended to model variable wall properties and external tissue support.⁴⁵

V. APPLICATIONS TO CLINICAL PROBLEMS

In this section, we provide two recent examples of patient specific modeling with direct applications to clinical problems in pediatric cardiology.

A. Single ventricle physiology

Heart defects are among the most prevalent form of birth defects, occurring in roughly 1% of births. Among the most serious of these are single ventricle defects, such as hypoplastic left heart syndrome, in which the heart has only one functional pumping chamber. These patients typically undergo three open heart surgeries, culminating with the Fontan surgery, in which the veins returning blood to the heart from the upper and lower body (inferior and superior vena cava, IVC, SVC) are directly connected to the pulmonary arteries.⁸⁹ Fontan patients subsequently experience high morbidity rates including exercise intolerance, protein losing enteropathy, arteriovenous malformations, thrombosis, and heart failure.⁹⁰⁻⁹²

Many simulation studies have established links between the geometry of the Fontan junction and hemodynamic performance.^{64,91,93-96} Recent Fontan simulations have improved the state of the art by including multiscale modeling with a closed loop network, respiration, exercise, fluid structure interaction, detailed pulmonary anatomy, cardiac catheterization data, and particle tracking.^{3,10,13,94,97,98} This simulation framework has been used to design and test novel surgical concepts prior to clinical implementation.

Using simulation-based design, Marsden *et al.* proposed a novel Fontan Y-graft that aims to address the clinical problem of uneven hepatic flow distribution, which refers to an unknown liver factor contained in blood coming from lower body through the IVC.¹⁶ A lack of hepatic flow to one lung has been shown to result in pulmonary arteriovenous malformations, contributing to poor outcomes in many Fontan patients.⁹⁹ Therefore, a goal of the Y-graft is to distribute the IVC flow as evenly as possible to the left and right pulmonary arteries without increasing energy dissipation. Simulations used an open loop configuration in which Inflow conditions were obtained from phase contrast MRI and outflow conditions were tuned to match pressures measured during cardiac catheterization. Preliminary simulations and optimization showed substantial improvement

FIG. 4. (a) Post-operative image data for three patients who received a Y-graft and their corresponding patient specific models. (b) Comparison between early post-operative simulation-derived hepatic flow distribution and clinical lung perfusion scan results for three Fontan Y-graft patients. Pulmonary flow split (PFS) is provided for each patient. Hepatic flow distribution is measured by distribution of flow from the inferior vena cava (IVC) going to the right pulmonary artery (blue) or left pulmonary artery (red).

in hepatic distribution (e.g., from 70/30% to 50/50%) as well as gains in energy efficiency,^{16,76,100} and suggest that customized Y-graft designs should be designed for each patient. Successful Y-graft surgeries were then performed on six patients in a pilot study at Stanford University starting in June 2010 (Fig. 4(a)). Excellent comparison between simulated hepatic flow distribution and lung perfusion scans was demonstrated (Fig. 4(b)). A similar bifurcated graft concept was also introduced by Yoganathan and co-workers, and a related clinical study at Emory University showed successful implementation of a modified Y-graft design in 20 patients.¹⁰¹

Early work on single ventricle modeling focused on energy loss as the primary metric of performance for comparing surgical geometries. Initial simulation studies demonstrated improved energy efficiency in Fontan surgical geometries with an offset between the IVC and SVC, leading to widespread adoption of the offset concept in the surgical community.^{93,102} Numerous studies of Yoganathan and colleagues have also suggested that high energy loss is likely linked to poor clinical outcomes and high ventricular work loads, and that energy reduction is of primary importance in surgical design.^{103–105}

Multiscale modeling, first applied to single ventricle physiology by Migliavacca and co-workers, now extends simulation tools to predict not only local hemodynamics such as energy loss but also global quantities of clinical interest. Multiscale simulations can predict, among other quantities, ventricular work load, pressure volume loops, systemic and pulmonary pressure levels, and oxygen delivery. In contrast to prior work, recent multi scale studies comparing different surgical geometries found little difference in physiologic quantities of interest, even among designs with large differences in energy loss. This has led some groups to question the use of energy loss reduction as the primary objective of surgical design, instead examining this and other quantities in the context of the global physiology of the patient.

FIG. 5. Modeling process for virtual surgery, beginning with model construction from imaging data followed by virtual surgery comparing the Glenn and Hemi-Fontan surgery options, as well as the influence of LPA stenosis.

To illustrate these differences, we note two studies, both comparing surgical approaches for the second stage surgery for single ventricle repair, the Glenn and Hemi-Fontan. The first, a study of Pekkan *et al.*, concluded that the Glenn surgery had higher hemodynamic efficiency compared to the hemi-Fontan approach, suggesting that this should be used as a metric for selection of surgical approach.¹⁰⁶ The second study, of Kung *et al.*⁵⁶ compared the Glenn and Hemi-Fontan methods using closed loop multi scale modeling, as illustrated in Figure 5, with model parameters iteratively tuned to match patient specific clinical data. It was shown that while the Glenn surgery resulted in an energy loss about 50% of that of the Hemi-Fontan, the energy loss incurred in the surgical connection was a small fraction of the total pulmonary and systemic power loss. The value of multi scale modeling was in illustrating that despite the large difference in energy loss and local hemodynamics (Fig. 6), the difference in other quantities such as flow and pressure in the major vessels (IVC, LPA, etc.) was insignificant. The use of a LPN model also allows for prediction of additional clinically

FIG. 6. Simulation results from Glenn and Hemi-Fontan models with varying degrees of left pulmonary stenosis. Large differences in local hemodynamics are observed. However, these do not translate into significant differences in global circulatory parameters.

relevant quantities including oxygen delivery, atrial and ventricular pressures, and ventricular power, and minimal changes were also observed in these quantities. Furthermore, even when imposing a stenosis in the left pulmonary artery, resulting in increase energy loss, changes in other quantities remained minimal. Thus, while the numerical results of the two studies were in agreement, the two studies reached different conclusions as a result of their different modeling approaches.

B. Kawasaki disease

Kawasaki disease (KD) is the leading cause of acquired heart disease in children,¹⁰⁷ with over 4000 cases diagnosed annually in the USA. If it is not promptly diagnosed and treated, it can result in irreversible damage to the heart and coronary arteries.¹⁰⁸ KD is an acute, self-limited vasculitis of childhood that results in coronary artery aneurysms or ectasia in 25% of untreated children (Fig. 1) and may lead to ischemic heart disease, myocardial infarction (MI), congestive heart failure, and sudden death. The risk of KD in children is 2–10 times higher than rheumatic fever and the incidence in Japan is particularly high, where approximately one in 150 children will suffer from KD during the first 10 years of life. Aneurysms caused by KD differ from other common aneurysms (abdominal, cerebral) in that they typically develop thrombosis (clot) as opposed to a sudden vessel wall rupture.

There are no established guidelines to aid physicians in the choice and timing of treatment for KD patients, which may include anticoagulation, coronary artery interventions such as stenting, and coronary artery bypass surgery.^{109–111} While standard imaging can define the morphology of the aneurysm, this does not yield sufficient information about wall shear stress and the altered dynamics of blood flow. Hence, in clinical practice, treatment decisions are typically based upon the aneurysm geometry alone, despite the belief that flow characteristics are critical determinants of thrombotic risk. As a result, clinicians are left with a difficult choice to either subject an otherwise normal, healthy young adult to the risks associated with surgery or intervention, or to wait and watch, knowing the risks of a devastating event. Simulations can be used to bridge the gap between anatomic information and hemodynamic conditions contributing to thrombotic risk in KD patients.

In the first study applying CFD to KD, Sengupta *et al.* simulated hemodynamics in aneurysms of a 10-year-old KD patient.²² Coronary outflow boundary conditions were coupled to a lumped parameter heart model to reproduce realistic flow and pressure conditions in the coronary arteries. Boundary condition parameters were tuned to match clinical and echocardiography data. Inflow conditions were obtained from MRI for two patients, or generated by the heart model to match cardiac output measured by echocardiography. This study produced the first quantitative values of wall shear stress (WSS), oscillatory shear index (OSI), wall shear stress gradients (WSSG), and particle residence times (PRT) in coronary aneurysms caused by KD. A virtual control model was created by replacing aneurysmal regions with normal coronary geometry, allowing for direct comparison of pathological to normal hemodynamics. Order of magnitude changes in hemodynamic parameters related to thrombus formation were observed. Prior animal models and *in vitro* experiments show that markers of thrombosis and inflammation are increased in the range of hemodynamic values found in simulations.

A follow up study evaluated KD hemodynamics using multiple patient-specific models. Models were constructed from CTA data for 5 KD patients (A-E) with aneurysms and one KD patient with normal coronary arteries (F) (Fig. 7(a)). Simulations were run using multiscale modeling in a custom finite element solver, and hemodynamic parameters linked to thrombus formation were computed for all vessels and compared to clinical outcomes. Aneurysmal arteries ($N = 11$) had significantly lower WSS than normal arteries ($N = 3$) (4.9 for aneurysmal vs. 20.9 for normal, $P < 0.01$). Aneurysmal arteries also required significantly more cardiac cycles for particles to exit the domain (6.1 for aneurysmal vs. 1.1 for normal, $P < 0.01$). Regions of stagnant flow persisted throughout the cardiac cycle in aneurysmal regions, which were not observed in normal arteries.

Aneurysms with thrombosis ($N = 6$) required almost twice as many cardiac cycles (mean 7.8 vs. 4.0) for particles to exit the aneurysm domain in simulation, and had 108% lower mean WSS

FIG. 7. (a) Patient specific models constructed from CT image data for KD patients with aneurysms (A-E) and without aneurysms (F). Patient D had a fully occluded RCA that was not modeled. (b) Comparison of hemodynamic parameters between aneurysmal arteries with ($n = 6$) and without ($n = 5$) thrombus. Vessels were considered to have thrombosis if there was any evidence of thrombus (occlusive or non-occlusive) observed in by CT. (None of these differences were statistically significant.)

(1.5 compared to 3.2 dynes/cm²) at maximum diameter compared to aneurysms without thrombosis ($N = 5$). Aneurysm diameter was found to be a poor predictor of thrombosis in this group, and had the smallest percentage difference (15%) between the two groups of all the parameters examined. Mean data (Fig. 7(b)) suggest that hemodynamic factors are a better predictor of thrombotic risk than diameter.

This study included one particularly striking example of a simulation prediction correlating with a clinical outcome. The RCA of subject B had the lowest levels of WSS and highest PRT compared to all other arteries. After simulations were performed, subject B developed thrombosis in two of the three major coronary arteries, despite being treated with warfarin, and required urgent CABG. Regions of thrombosis correlated remarkably well to regions of near-zero WSS in simulations, as shown in Fig. 8. However, a larger cohort of patients is needed before a threshold level of shear that is correlated to thrombotic risk can be defined.

The above data suggest that hemodynamic parameters, particularly WSS, are useful in identifying aneurysms at increased risk of thrombosis. Results also indicate that fusiform aneurysms

FIG. 8. Pre- and post thrombosis CT imaging in patient B (left) and simulation results showing correlation between WSS predictions in simulation and locations of thrombosis.

may have a greater propensity toward thrombus formation than previously thought. These findings are contrary to current AHA guidelines that rely solely on aneurysm diameter as a predictor of thrombotic risk. Future studies should incorporate data from a larger cohort of KD patients to better correlate clinical outcomes with simulation predictions. These data could be used to develop a risk stratification index that could be used to better select at-risk patients for anticoagulation therapy.

VI. DISCUSSION AND FUTURE CHALLENGES

Patient specific modeling has arisen as a powerful tool to augment clinical imaging data and physician expertise with quantitative predictions of patient risk, disease progression, and surgical outcomes. Recent advances in simulation methodologies have increased clinical utility and physiologic realism by incorporating multi scale modeling, realistic material properties, fluid structure interaction, exercise physiology, and realistic boundary conditions that capture coronary physiology and wave reflection.

In this paper, we outlined key numerical challenges that contributed to increased model accuracy and sophistication. These included methods to handle back flow stabilization, uncertainty quantification, optimization, and coupling algorithms for multi scale modeling. Key modeling challenges to be addressed in the near future include efficient uncertainty quantification with multiple parameters, parameter identification, and automated boundary condition tuning, and automated image segmentation methods.

In the historical context, simulations should be viewed as the next technology in a long history of partnerships between engineers and clinicians that have resulted in technological advancements for improved patient care. We provided two examples from pediatric cardiology in which simulations are currently being used to develop new surgical methods and to improve patient selection for medical

therapies. It is of paramount importance that future simulation tool development is done in close collaboration with clinicians, and validated against *in vivo* clinical data whenever possible.

Many clinical decisions are currently made based on anatomy alone even though it is clear that the fluid mechanics of blood flow plays a key role in the initiation and progression of cardiovascular disease. A systematic and physics-based approach will likely lead to drastic improvements in understanding, and to the discovery of new and improved surgical designs. Engineering design tools will bring a paradigm shift to the medical community by offering the first quantitative and systematic methods for optimizing surgeries at no risk to the patient. Simulations will ultimately be used to design individual treatments for patients suffering from many types of heart disease, both congenital and acquired. These tools have potential to improve quality of life for patients, delay the need for a heart transplant, increase exercise tolerance for children with heart defects, and in some cases reduce mortality.

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