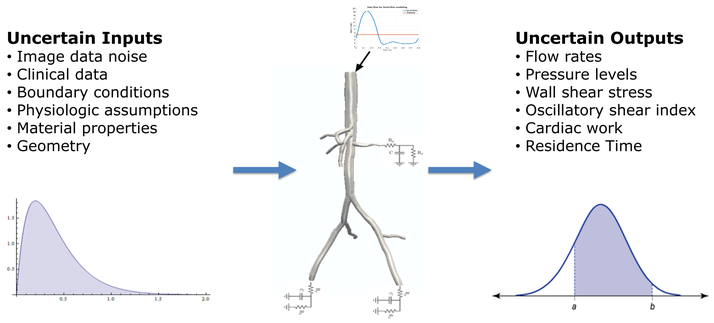
Enabling reliable cardiovascular simulations via uncertainty quantification

Alison Marsden[1], Jongmin Seo[1], Casey Fleeter[3], Daniele Schiavazzi[4], Andrew Kahn[5]

[1]Bioengineering, ICME, and Pediatrics, Stanford University, [3]ICME, Stanford University, [4]ACMS, University of Notre Dame, [5]Department of Medicine, UCSD

Introduction and Motivation

Patient-specific computational cardiovascular models are successfully employed in a wide range of clinical applications from disease diagnosis, surgical planning, and medical device design. Results, however, are often reported as deterministic, neglecting variations that could occur due to uncertain input parameters. Examples of uncertain input parameters include noisy and limited resolution medical image data, clinical measurement of patient data, or population variability in results published in the literature. Systematic quantification of uncertainties is a necessary step towards clinical adoption of computational tools.



We present a suite of efficient and automated tools for 1) propagation of uncertainty to assign confidence intervals to simulations and predictions in a three dimensional anatomic model 2) multi-fidelity methods to reduce the computational cost of the propagation.

Patient-specific cardiovascular flow simulations

Patient-specific cardiovascular modeling in the open source software SimVascular (www.simvascular.org) consists of several steps that start from medical image data and ends with solving the incompressible Navier-Stokes equations on a finite element mesh.

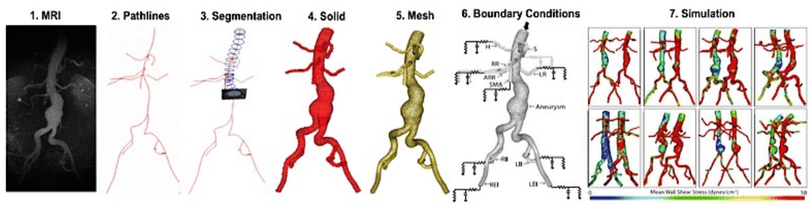


Image reproduced from Updegrove et. al. and Les et. al.

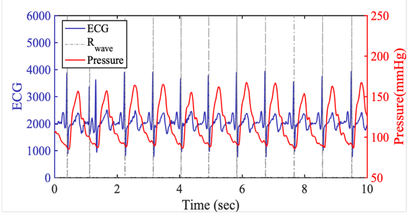
First, centerline paths are generated for all vessels of interest. Next, the vessel cross sections are segmented along these centerline paths. These segmentations are then lofted together to form a solid model, which is then typically meshed into tetrahedral finite elements. Boundary conditions are then applied before solving the incompressible Navier-Stokes. Once the simulations finish, they can be post-processed to compute hemodynamic quantities of interest. Typical quantities of interest from these simulations include pressure, flow, wall shear stress, and wall strain.

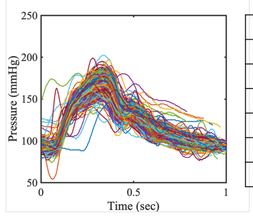
Simplifying assumptions lead to the formulation of lower-fidelity models as well. The Hughes and Lubliner 1D Navier-Stokes formulation with a linear constitutive equation is used in our 1D solver, while a 0D model can be formulated as a lumped parameter network using a circuit analogy.

Uncertainty quantification in coronary artery simulations with fluid-structure interaction

Uncertainty in an input parameter in cardiovascular simulation causes the variabilities of simulation outcomes. The relationships between input parameter and output quantities of interest are quantified after injecting uncertainty in the input parameter. The goal of this study is to understand how much the outputs of the numerical simulation are affected by the degree of uncertainties in uncertain input parameters.

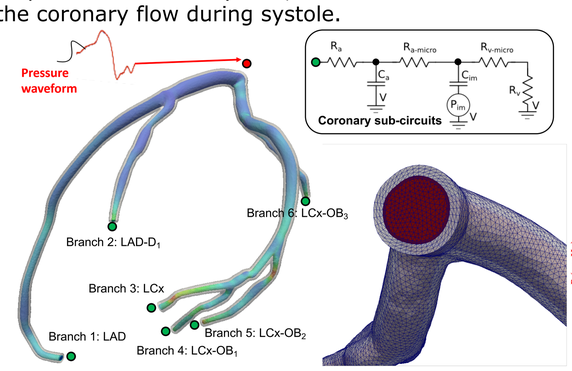
Uncertainty in the clinical measurements is quantified using cardiac catheterization measurements from six patients, performed at the UCSD Medical Center. The intracoronary pressure waveform P_{in} was measured from a catheter over more than 100 heart cycles while acquiring an EGC signal. The duration of a heart cycle was measured through ECG, and the pressure waveforms were registered to lie within the same heart cycle. Ensemble statistics were determined (mean and standard deviation), with coefficient of variation in the 5-7% range. Additionally, uncertainty was injected into the time-derivative of the intramyocardial pressure, P_{im}, with a standard deviation equal to 10% of its peak value.



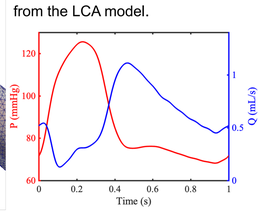


mmHg	$\mu(P)$	$\sigma(P)$	σ/μ
Patient 1	122.1	7.8	6.4%
Patient 2	81.8	4.4	5.3%
Patient 3	83.3	6.2	7.4%
Patient 4	75.8	4.4	5.8%
Patient 5	97.7	6.0	6.1%
Patient 6	92.1	6.8	7.4%

A 3D multi-scale left coronary artery (LCA) model shown below is constructed from a CT imaging study using the open-source package Simvascular. The 3D LCA model has lumen and deformable vessel wall. The interaction between fluid and structure is simulated through an Arbitrary Lagrangian-Eulerian framework in the Simvascular svFSI solver. The inlet pressure waveform P_{in} was extracted from a complete aorto-coronary model investigated in previous studies and used to validate the submodel. The lumped-parameter boundary conditions at the coronary outlets were designed to reproduce the physiologic response in a coronary flow, in which the cardiac muscle contraction impedes the coronary flow during systole.

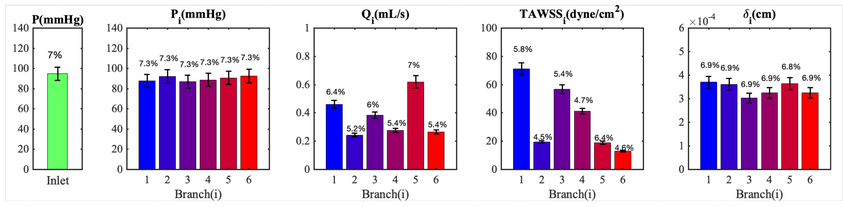


Left: LCA model
Top: Lumped-parameter network boundary condition
Bottom: Lumen (red) and wall (gray)
Right: Pressure and flow waveform from the LCA model.

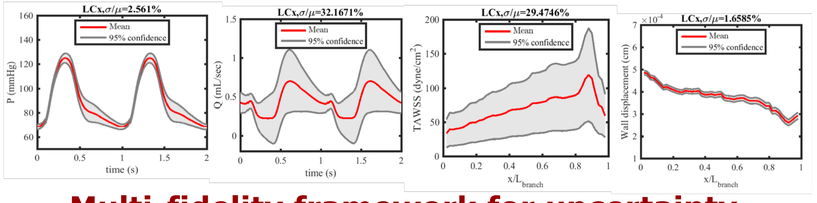


Inlet pressure P_{in} and intramyocardial pressure P_{im} uncertainty were modeled as a Gaussian stochastic process in time with an exponential autocovariance function. P_{in} is then approximated through a finite collection of independent N(0,1) random variables and eigenfunctions of the autocovariance function following a Karhunen-Loeve expansion. The standard deviation σ is set to 7 percent of the cycle-averaged inlet pressure at the inlet. Samples are obtained by projecting a four-dimensional Sobol sequence through a multivariate Gaussian CDF.

Branch flow rate, pressure, time-averaged wall shear stress (TAWSS), wall deformation in six model branches were identified as the relevant quantities of interest (QoI). The selected 7% coefficient of variation in the inlet pressure P_{in} generated variability in all selected QoIs, with resulting standard deviations in a range between 5% to 7% of the corresponding mean, suggesting the variability in the output quantities of interest to be comparable to the inlet pressure variability, as shown in figure below.



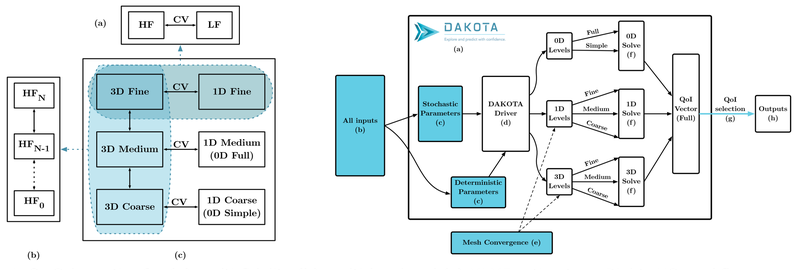
For an uncertain intramyocardial pressure P_{im}, the mean and the 95% confidence interval of Pi, Qi, wall deformation and the spatial distributions of TAWSS and in the circumflex branch of left coronary artery (LCx) were computed. Flow rate and TAWSS have significant variances, up to about 30% of their mean value, whereas pressure and wall displacements show coefficients of variation less than 3%.



Multi-fidelity framework for uncertainty quantification in cardiovascular simulations

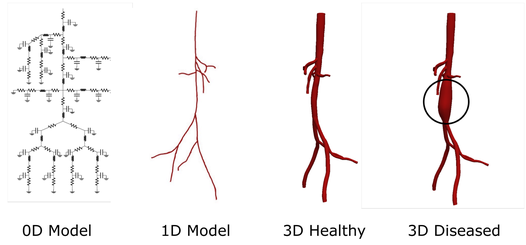
For cardiovascular UQ, Monte Carlo estimators have many desirable properties. They are unbiased, offer flexibility with respect to heterogeneous input sources, and their associated variance depends only on the true variance and number of model evaluations, not on the problem dimensionality. However, only a small fraction of these evaluations can typically be afforded when working with expensive deterministic solvers. By instead utilizing multi-level and multi-fidelity estimators, we can substantially reduce the variance associated with Monte Carlo estimators for the same computational cost.

Our workflow integrates multiple cardiovascular solvers with Sandia National Laboratories' Dakota toolkit for uncertainty analysis in a manner designed to automatically manage the solutions of multiple models to compute multi-level multi-fidelity (MLMF) estimators for a variety of quantities of interest.



Left: Schematics for (a) multi-fidelity (b) multi-level and (c) MLMF estimators. Right: UQ workflow

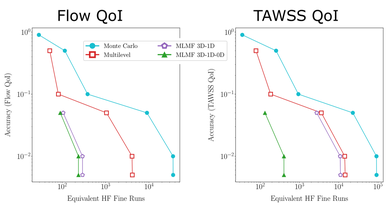
Both aorto-femoral and coronary model geometries were used to verify the performance of the MLMF estimators. Over 100 different quantities of interest (QoIs), ranging from global outlet flows and pressures to local time-averaged wall shear stress quantities, were examined to robustly demonstrate the power of the MLMF estimators. A range of uncertain parameters, including boundary conditions and vessel material properties, were explored in this study. Generally, these uncertain distributions can be heterogeneously assimilated from patient data or assumed from literature data. 3D, 1D, and 0D models were chosen following an extensive mesh convergence study. Both healthy and diseased models were included. Comparison of computational cost confirmed our expectation that multiple orders of magnitude cost savings are achieved by the low-fidelity models.



Healthy Model Representative Costs

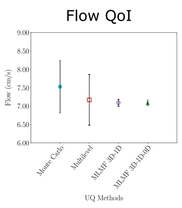
	Aorto-Femoral Healthy	
Fidelity & Level	Cost	Effective Cost
3D Fine Mesh	870.80 h	1
3D Medium Mesh	228.44 h	2.62×10^{-1}
3D Coarse Mesh	98.02 h	1.13×10^{-1}
1D Fine Mesh	11.60 m	2.22×10^{-4}
1D Medium Mesh	2.95 m	5.65×10^{-5}
1D Coarse Mesh	1.90 m	3.64×10^{-5}
0D Full Model	0.49 s	3.64×10^{-6}
0D Simple Model	0.03 s	6.60×10^{-7}

MLMF estimators outperform the other estimators for all categories of QoIs. The accuracy of each quantity of interest can be computed from a fixed number of simulations or the ideal number of simulations needed to obtain a fixed accuracy can be computed. Accuracy is defined as $6\sqrt{V[Q]}/E[Q]$ for each quantity of interest Q (six times the coefficient of variation). The formula for extrapolation to an accuracy ε is given by $N_l^{HF} = \frac{2}{\varepsilon^2}\left(\sum_{k=0}^{L_{HF}}\left(\frac{\sqrt{V_k^{HF}}C_k^{HF}}{1-\rho_k^2}\right)^{\frac{1}{2}}\Lambda_k(r_k)\right)\sqrt{(1-\rho_l^2)\frac{V_l^{HF}}{C_l^{HF}}}$ for each level l. The number of LF evaluations needed at each level is increased by a factor which depends on the cost ratio between fidelities (w_l) and the correlations (ρ_l).

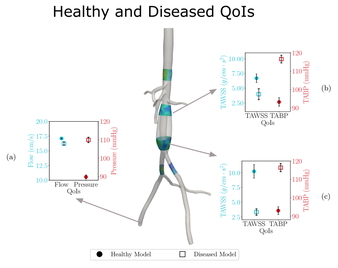


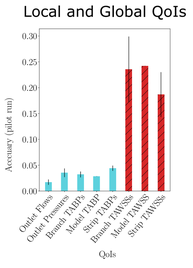
Extrapolation to Acc = 0.01

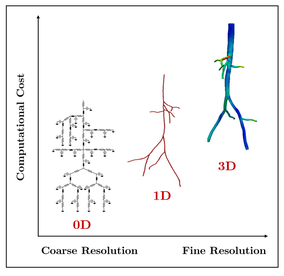
	QoI and Method	Healthy Model Effective Cost
Flow	MC	9 010.0
	ML	1 319.1
	MLMF (3D-1D)	74.8
	MLMF (3D-1D-0)	58.6
TAWSS	MC	22 869.0
	ML	4 327.8
	MLMF (3D-1D)	3 243.1
	MLMF (3D-1D-0D)	96.9



MLMF estimators for healthy models are general more accurate than for diseased models. Similarly, MLMF estimators for global QoIs are more accurate than for local QoIs. Both are explained by the complex dynamics seen in diseased models or for local QoIs, which rely more heavily on the more finely resolved (but more expensive) 3D models.







Multi-Level Multi-Fidelity (MLMF) uncertainty quantification approaches make UQ accessible for cardiovascular applications:

1. Easily attainable low fidelity models and mesh resolution levels for our cardiovascular models lends itself to a MLMF framework.
2. The automated SimVascular-Dakota framework minimizes work for the user.
3. MLMF estimators allow for well-resolved accuracy of QoIs on a limited computational budget.
4. MLMF estimators vary in accuracy depending upon properties of the QoIs, such as local or global and healthy or diseased models.

The promising results of the initial study will lead to future work utilizing the MLMF methods on a variety of patient models models.

References and Acknowledgments

Funding from NIH-NIBIB R01 EB018302, RO1 RHL123689A.

Computational resources from XSEDE and Stanford Research Computing Center's Sherlock cluster.

Updegrove A, Wilson NM, Merkow J, et. al.. SimVascular - An open source pipeline for cardiovascular simulation. *Ann Biomed Eng*. 2016; doi:10.1007/s10439-016-1762-8.

Tran, Justin S., et al. "Automated tuning for parameter identification and uncertainty quantification in multi-scale coronary simulations." Computers & fluids 142 (2017): 128-138.

Les A, Shadden S, Figueroa C, et. al.. Quantification of Hemodynamics in Abdominal Aortic Aneurysms During Rest and Exercise Using Magnetic Resonance Imaging and Computational Fluid Dynamics. *Ann Biomed Eng*. 2010; doi: 10.1007/s10439-010-9949-x

Geraci G, Eldred M, Iaccarino G. A multifidelity multilevel Monte Carlo method for uncertainty propagation in aerospace applications. *19th AIAA Non-Deterministic Approaches Conference.* 2017.

T.J.R. Hughes and J. Lubliner. On the One-Dimensional Theory of Blood Flow in the Larger Vessels. *Mathematical Biosciences*. 18(1-2) (1973), 161-170.

B. Adams, et al. Dakota, a multilevel parallel object-oriented framework for design optimization, parameter estimation, uncertainty quantification, and sensitivity analysis: Version 6.6 users manual. Sandia Technical Report SAND2014-4633, Updated May 2017.