



An efficient framework for optimization and parameter sensitivity analysis in arterial growth and remodeling computations



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ABSTRACT

Computational models for vascular growth and remodeling (G&R) are used to predict the long-term response of vessels to changes in pressure, flow, and other mechanical loading conditions. Accurate predictions of these responses are essential for understanding numerous disease processes. Such models require reliable inputs of numerous parameters, including material properties and growth rates, which are often experimentally derived, and inherently uncertain. While earlier methods have used a brute force approach, systematic uncertainty quantification in G&R models promises to provide much better information. In this work, we introduce an efficient framework for uncertainty quantification and optimal parameter selection, and illustrate it via several examples. First, an adaptive sparse grid stochastic collocation scheme is implemented in an established G&R solver to quantify parameter sensitivities, and near-linear scaling with the number of parameters is demonstrated. This non-intrusive and parallelizable algorithm is compared with standard sampling algorithms such as Monte-Carlo. Second, we determine optimal arterial wall material properties by applying robust optimization. We couple the G&R simulator with an adaptive sparse grid collocation approach and a derivative-free optimization algorithm. We show that an artery can achieve optimal homeostatic conditions over a range of alterations in pressure and flow; robustness of the solution is enforced by including uncertainty in loading conditions in the objective function. We then show that homeostatic intramural and wall shear stress is maintained for a wide range of material properties, though the time it takes to achieve this state varies. We also show that the intramural stress is robust and lies within 5% of its mean value for realistic variability of the material parameters. We observe that prestretch of elastin and collagen are most critical to maintaining homeostasis, while values of the material properties are most critical in determining response time. Finally, we outline several challenges to the G&R community for future work. We suggest that these tools provide the first systematic and efficient framework to quantify uncertainties and optimally identify G&R model parameters.

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1. Introduction

Arterial development, maintenance, disease progression, and responses to injury all result from the balanced or imbalanced turnover of cells and extracellular matrix under mechanical loading. Computational models of growth and remodeling (G&R) have been developed to study long-term responses of vessels to sustained alterations in hemodynamic and mechanical loads [1–4]. Since experiments to elucidate G&R responses can involve long periods, simulations can augment experimental knowledge and help to identify and test hypotheses of growth or remodeling responses. Additionally, computer simulations can provide

detailed information on wall thickness, mass fractions of constituents, stress–strain behaviors, and lumen size, which are not always easily obtained *in vivo*.

Two main classes of G&R models are [5–10]: (a) models that evolve stress-free configurations of each constituent and assemble them into a composite body through an elastic deformation, or (b) models that evolve a mixture of constituents, in which new components are added at a prestretched state. We adopt the second approach, the constrained mixture model, which requires three constitutive equations for individual constituents: stored energy functions, production functions, and survival functions. Valentin and Humphrey [11] showed that stress-mediated production and constituent-specific deposition stretches are essential for simulating realistic arterial adaptations, but the requisite constitutive equations require many parameters to capture accurate behaviors

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[3,12]. Therefore, there is a pressing need for rigorous methods to quantify uncertainties and to systematically choose optimal parameters.

Input uncertainties to G&R simulations may propagate non-linearly to the outputs, resulting in significant output uncertainties for some quantities of interest. Prior sensitivity studies of Valentin and Humphrey [13] used uniform sampling methods in which one or two parameters were varied at a time while keeping the others fixed. This approach quickly becomes intractable for the large number of parameters required to describe arterial G&R. Our aim is to quantify and compare these output uncertainties for multiple parameters and to evaluate the robustness of the simulation output for different scenarios. In certain cases, the range of possible inputs is large enough that we use optimization to identify a set of input parameters leading to a known output response. Through a combination of these two tools, we aim to improve the reliability of G&R simulations.

The stochastic collocation method has been used for uncertainty quantification in fluid mechanics, solid mechanics, heat transfer, and similar applications [14–16]. Sparse grid collocation approaches have been particularly successful for computationally expensive problems, offering an alternative to more expensive Monte-Carlo methods. Adaptive collocation methods further extend traditional methods, while maintaining scalability and convergence. Such methods have been developed recently for uncertainty quantification in simulations of abdominal aortic aneurysms, the Fontan surgery, and bypass graft surgery [15]. With this method, we can place error bars and confidence intervals on simulation outputs given a range of input values.

In cases for which model parameters are unknown, optimization offers a systematic method for identifying values that lead to expected behaviors. The surrogate management framework (SMF) is a robust derivative-free algorithm developed for simulation-based-optimization [17]. This method has been used in cardiovascular examples such as optimal branching of arteries [18], the Fontan surgery [19], and bypass graft surgeries [20,14,21]. In this paper, we use the SMF with Kriging surrogate functions to accelerate the search process.

The goals of this paper are twofold: (a) to perform a systematic and rigorous parameter sensitivity study of G&R simulations of normal arterial adaptations to modest changes in blood pressure and flow, and (b) to use a formal optimization procedure to identify a set of optimal parameter values that yield expected G&R responses. First, we test robustness by evaluating the sensitivity of outputs of G&R simulations resulting from uncertainty in material parameters. Rigorous parametric studies such as this can guide future work by identifying critical regions for further experimental studies. Second, we use optimization to select material property values in cases when experimental data are wanting. Optimal material properties insure that homeostatic conditions can be restored over a range of loading conditions. We compute sensitivity contours and confidence intervals to test the credibility of predicted outcomes. The non-intrusive nature of the optimization and uncertainty quantification algorithms makes integration of these tools with the G&R framework particularly attractive. Though we illustrate the proposed tools for a basilar artery, the framework is sufficiently general to be extended to other vascular applications. Whenever available, experimental data should be added as constraints or into the cost function of our framework.

2. Computational framework for growth and remodeling

The arterial wall is assumed to consist initially of elastin (oriented in axial and circumferential directions), four collagen fiber families (at angles of 0°, 90°, 45° and 135° relative to axial), and

circumferentially oriented smooth muscle cells (SMC). We assume that the elastin does not turn over during short periods of adaptation, since it is produced during the perinatal period, cross-linked, and stretched elastically during development; the collagen and smooth muscle are allowed to turnover continuously in evolving configurations, however.

Arterial growth and remodeling, leading to adaptation herein, is simulated using previously validated models [12,13]. Briefly, we assume that G&R is a quasi-static process whereby intramural and wall shear stresses can be computed via

$$\sigma_{\theta,\theta} = \frac{Pa}{h}, \quad \sigma_{zz} = \frac{f}{\pi h(2a+h)}, \quad \tau_w = \frac{4\mu Q}{\pi a^3}, \quad (1)$$

where P and Q are mean blood pressure and volumetric flow rate, f is the applied axial load, and a and h are inner radius and wall thickness. These equilibrium/steady state solutions for laminar flow of a constant viscosity fluid (μ) within a thin-walled cylindrical vessel provide the requisite values of stress for the G&R model. In particular, constitutively:

$$\sigma_{\theta,\theta} = \frac{1}{\lambda_z} \frac{\partial W}{\partial \lambda_\theta} + \sigma_{\theta\theta}^{\text{act}} \quad \text{and} \quad \sigma_{zz} = \frac{1}{\lambda_\theta} \frac{\partial W}{\partial \lambda_z}, \quad (2)$$

where $(\lambda_\theta, \lambda_z)$ are mean circumferential and axial wall stretches, $\sigma_{\theta\theta}^{\text{act}}$ is the active muscle contribution, and W is the stored energy function, which for a constrained mixture is given by $W = \Sigma W^k$ where

$$W^k(s) = \frac{M_0^k(0)}{\rho(s)} Q^k(s) \widehat{W}^k(\lambda_{n(0)}^k) + \int_0^s \frac{m^k(\tau)}{\rho(s)} q^k(\tau, s) \widehat{W}^k(\lambda_{n(\tau)}^k) d\tau,$$

where M_0^k is the initial mass density for constituent k ($=e$ for elastin, c for any of four families of collagen fibers, or m for the smooth muscle), $Q^k(s) \in [0, 1]$ is the fraction of constituent k that remains at G&R time s that was produced at time 0, $m^k(\tau)$ is a mass density production, $q^k(\tau, s) \in [0, 1]$ is the fraction of constituent k that remains at G&R time s that was produced at time $\tau \in [0, s]$, $\widehat{W}^k(\lambda_{n(\tau)}^k)$ is the energy stored in constituent k , which depends on the constituent stretch relative to its natural configuration $n(\tau)$. Finally, $\rho(s)$ is the mass density of the entire wall, which is assumed to remain constant.

Fundamental to this G&R framework is specification of the three classes of constituent-specific constitutive relations: \widehat{W}^k , m^k and q^k . Consistent with prior implementations [12,13], we let

$$\widehat{W}^e(\lambda_{n(\tau)}^e) = c^e \left(\lambda_\theta^{e2} + \lambda_z^{e2} + \frac{1}{\lambda_\theta^{e2} \lambda_z^{e2}} - 3 \right), \quad (3)$$

for elastin and

$$\widehat{W}^j(\lambda_{n(\tau)}^j) = c_1^j \exp\left(c_2^j (\lambda^j)^2 - 1\right),$$

for collagen ($j = c$) or smooth muscle ($j = m$). It should be noted that these constituent-specific stretches differ due to their deposition at different homeostatic values G_h^k , namely

$$\lambda_{n(\tau)}^k(s) = G_h^k \frac{\lambda(s)}{\lambda(\tau)}, \quad (4)$$

where $\lambda(\tau)$ is the stretch experienced by the artery in the direction of interest relative for $\tau \in [0, s]$.

Finally, note that we assume a stress-dependent production, namely

$$m^c = m_0^c (1 + K_1^c \Delta\sigma - K_2^c \Delta\tau_w), \quad (5)$$

$$m^m = m_0^m (1 + K_1^m \Delta\sigma - K_2^m \Delta\tau_w), \quad (6)$$

where m_0^k are basal values, K_1^k and K_2^k are gain type parameters and

$$\Delta\sigma = \frac{\sigma - \sigma_h}{\sigma_h}, \quad \Delta\tau_w = \frac{\tau_w - \tau_w^h}{\tau_w^h}, \quad (7)$$

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