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Computational Simulation of the Adaptive Capacity of Vein Grafts in Response to Increased Pressure

Vein maladaptation, leading to poor long-term patency, is a serious clinical problem in patients receiving coronary artery bypass grafts (CABGs) or undergoing related clinical procedures that subject veins to elevated blood flow and pressure. We propose a computational model of venous adaptation to altered pressure based on a constrained mixture theory of growth and remodeling (G&R). We identify constitutive parameters that optimally match biaxial data from a mouse vena cava, then numerically subject the vein to altered pressure conditions and quantify the extent of adaptation for a biologically reasonable set of bounds for G&R parameters. We identify conditions under which a vein graft can adapt optimally and explore physiological constraints that lead to maladaptation. Finally, we test the hypothesis that a gradual, rather than a step, change in pressure will reduce maladaptation. Optimization is used to accelerate parameter identification and numerically evaluate hypotheses of vein remodeling. [DOI: 10.1115/1.4029021]

1 Introduction

CABG surgery is a clinical scenario in which a vein is subjected to a dramatic increase in blood flow and pressure and undergoes complex G&R evidenced by changes in its composition, size, and mechanical properties. CABG surgery is performed to revascularize diseased coronary arteries, using (in order of preference) arterial, venous, or synthetic grafts. Vein grafts, used in 70% of CABG procedures, have failure rates as high as 10–40% within 1 yr and more than 50% within 10 yr [1,2]. An increasing number of patients undergoing these procedures thus require repeat procedures, which carry higher morbidity and mortality rates [3,4]. The exceedingly high failure rates and the continuing clinical need for the use of veins as grafts in CABG procedures motivates further investigation into the biomechanical mechanisms of vein (mal)adaptation.

Arteries and veins serve very different functions; the former are high pressure, high flow conduits whereas, the latter are low pressure, low flow conduits with high capacitance. It is not surprising, therefore, that arteries and veins have very different structures and properties [5,6]. Indeed, there should be little expectation that a vein should behave like an artery when transplanted to an arterial environment. The mechanisms of long-term failure differ between arterial and vein grafts in CABG. Arterial graft failure results primarily from fibrointimal hyperplasia at the site of anastomosis [7]. Vein graft failure results primarily from thrombosis during the acute period (<1 month), wall thickening during the intermediate period (1–12 months), and atherosclerosis in the long-term (3–5 yr) [5]. There is substantial evidence relating hemodynamic loads to vein graft remodeling [8–11]. Understanding the kinetics of these (mal)adaptive processes could be facilitated by a computational model that relates macroscopic hemodynamic quantities and structural adaptations to underlying cellular mechanisms, thus providing a mechanobiological understanding of vein adaptation versus maladaptation or failure.

A constrained mixture theory of G&R that models cell-mediated responses of arteries to altered chemomechanical stimuli has provided insights into normal responses to injury, adaptation, and disease progression [12–15]. This theory incorporates cellular information phenomenologically within fundamental constitutive relations in a continuum context. Motivated by the robust performance of arterial G&R models, the current work extends this approach to vein grafts. Although previous arterial applications of the G&R framework have been restricted to moderate changes in blood pressure and flow, application to vein grafts necessitates extension to far larger changes in hemodynamic loads than previously investigated. Hence, in extending previous arterial models to vein grafts, one must identify and evaluate a new set of G&R model parameters, not just parameters for native wall properties. Since it is intractable to find these parameter sets by brute force, we propose a novel use of optimization to formulate a parameter identification problem in the context of G&R. This is in contrast to common uses of optimization in the context of empirical curve fitting to experimental data. The proposed optimization framework accelerates the problem sufficiently to render it computationally tractable.

As a first step in the development of a G&R model for vein grafts, this work focuses on the response of a vein to increased pressure and the associated intermediate period of wall thickening (1–12 months). This approach is motivated by prior studies that show medial thickening to associate best with increased intramural circumferential stress or strain [16]. There is also evidence that circumferential stress plays a primary role and wall shear stress plays a secondary role in determining overall vein graft dimensions [10], though shear stress likely controls neointimal formation [17]. Toward this end, we first identify constitutive parameters for a normal mouse vena cava based on published experimental data from pressure–diameter and axial force–length tests [18]. We then identify through optimization the set of G&R parameters that comes closest to achieving homeostatic conditions, given slight perturbations from normal hemodynamic loading, using difference from homeostatic values of stress as an objective function. Using these parameters, we numerically subject the vein to increasingly higher pressure loads and assess the

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Fig. 1 Schema of a G&R framework illustrating the configurations of a vessel (i.e., constrained mixture) and its constituents at instant $s=0$, without hemodynamic perturbations, and at G&R time s , with hemodynamic perturbation. The G&R framework enforces mechanical equilibrium at each instant while accounting for the evolving constituent mass fractions, natural configurations, and strain energy densities as the constituents turn over.

extent of its adaptation, within a biologically reasonable set of bounds for G&R parameters. We then explore possible physiological constraints that lead to maladaptation by identifying through optimization different sets of G&R parameters that numerically enabled adaptations under different pressure loads. Finally, we test the hypothesis that a gradual, rather than a step, change in pressure will lessen such maladaptations. We submit that the proposed computational model forms a basis for guiding mechanobiological experiments and can help provide new insights into the causes, effects, and mechanisms of vein graft G&R and thereby may be used to guide mechanobiological studies or the design of new clinical methods.

2 Methods

2.1 Computational Framework for G&R. The G&R formulation is based on a constrained mixture theory developed for arteries, details of which can be found in prior work [12,14,19–21]. A point-to-point comparison [22] between 2D and 3D models showed that the 2D models accurately predict adaptive changes in geometry and stiffness and thereby capture salient

aspects of G&R sufficient for clinical and fluid–structure interaction studies [19,23]. Hence, here, we briefly describe pertinent aspects for a thin-walled cylindrical tube. Responses to perturbations in pressure or flow rate from homeostatic values occur via changes in (a) lumen geometry, (b) wall thickness and microstructure, and (c) stiffness by the addition and removal of material in evolving configurations (Fig. 1). Optimal G&R responses often involve a combination of vasoconstriction/vasodilation and constituent turnover to achieve homeostatic values of intramural and wall shear stress.

The Cauchy stress response of a vessel, σ , can be approximated as a sum of contributions from passive elasticity and smooth muscle activation. Experiments suggest that strain energy functions (W), within the context of pseudo-elasticity, adequately describe the passive behavior of veins [24,25]. Hence, Cauchy stress, σ , is given by

$$\sigma = \frac{1}{\det \mathbf{F}} \mathbf{F} \frac{\partial W}{\partial \mathbf{F}^T} + \sigma_\theta^{\text{act}} \mathbf{e}_\theta \otimes \mathbf{e}_\theta \quad (1)$$

where $\mathbf{F}$ is the deformation gradient and $\sigma_\theta^{\text{act}}$ is the contribution from activation of circumferentially oriented smooth muscle.

Table 1 Parameter values used to simulate response of a vein to altered pressure

Muscle activation parameters [27]
$\lambda_m = 1.35$, $\lambda_0 = 0.5$
Vasoactive parameters [19]
$C_B = 0.68$, $C_S = 20C_B$
Initial mass fractions [55]
$\phi_0^e = 0.42$, $\phi_0^c = 0.10$, $\phi_0^m = 0.48$
Homeostatic values
$\sigma_\theta^h = 18$ kPa, $\tau_w^h = 0.6$ Pa [49]
$P_0 = 5$ mmHg = 0.67 kPa

By the rule of mixtures, the total stored energy is a weighted sum of the energy stored in all constituents (k), hence conceptually $W = \sum \phi^k \hat{W}^k$ where ϕ^k are constituent mass fractions. The venous wall is assumed to consist of the following structurally significant constituents: elastin (isotropic), collagen fibers (oriented in circumferential, axial, and diagonal directions), and smooth muscle cells (oriented in the circumferential direction). Because inertial effects are negligible when considering the wall mechanics, we employ stress equilibrium equations in the circumferential (θ) and axial (z) directions in a thin walled vessel, at G&R time s , namely,

$$\sigma_\theta(s) = \sigma_\theta^{\text{pas}}(s) + \sigma_\theta^{\text{act}}(\text{Ca}^{++})(s) = \frac{P(s)a(s)}{h(s)} \quad (2)$$

$$\sigma_{zz}(s) = \sigma_{zz}^{\text{pas}}(s) = \frac{f(s)}{\pi h(s)(2a(s) + h(s))} \quad (3)$$

where P is the transmural pressure, a is the luminal radius, h is the deformed wall thickness, f is the axial force, and Ca^{++} denotes intracellular calcium [19]. The superscripts “pas” and “act” indicate passive and active, respectively. The contribution of active smooth muscle, $\sigma_\theta^{\text{act}}$, is governed by

$$\sigma_\theta^{\text{act}}(s) = T_{\text{max}} \phi^m(s) \left(1 - \exp(-C(s)^2)\right) \lambda_\theta^{m(\text{act})}(s) \times \left(1 - \left(\frac{\lambda_M - \lambda_\theta^{m(\text{act})}(s)}{\lambda_M - \lambda_0}\right)^2\right) \quad (4)$$

where T_{max} (N m⁻²) is a scaling parameter, λ_M is the circumferential stretch at which the active stress is maximum, and λ_0 is the circumferential stretch at which the active stress goes to zero [26]. $C(s)$ is the net ratio of constrictors to dilators and $\lambda_\theta^{m(\text{act})}(s)$ evolves via a first order equation [15,19]. Similar to the earlier work on arterial adaptations [15,19], $C(s) = C_B - C_S \Delta\tau_w$, where C_B is the basal constrictor to dilator ratio and C_S is a scaling factor for shear stress induced changes in constrictor concentration. The active behavior is taken with respect to individual unloaded configurations for smooth muscle, not the entire mixture. The values of λ_M and λ_0 are chosen to be consistent with values in the literature for a rat vein, which are different from those of arteries (Table 1) [27].

The mass and stored energy of the constituents can evolve with time. Assuming G&R commences at $s=0$, Baek et al. [12] proposed the following evolution equations:

$$M^k(s) = M^k(0)Q^k(s) + \int_0^s m^k(\tau)q^k(s, \tau)d\tau \quad (5)$$

$$W^k(s) = \frac{M^k(0)}{\rho(s)}Q^k(s)\hat{W}^k(C_{n(0)}^k(s)) + \int_0^s \frac{m^k(\tau)}{\rho(s)}q^k(s, \tau)\hat{W}^k(C_{n(\tau)}^k(s))d\tau \quad (6)$$

where $M^k(s)$ and $\hat{W}^k(s)$ are mass per unit area and energy stored in constituent k per unit volume, respectively, and $\rho(s)$ is the current overall (constant) mass density. Note that the stored elastic energy for a constituent k depends on the right Cauchy-Green tensor ($\mathbf{C}_{n(\tau)}^k$) for that constituent defined with respect to its individual natural configuration $n(\tau)$ [19]. Equations (5) and (6) each have two terms: the first accounts for material that existed at or before the initial time $s=0$ and the second accounts for material produced at time $\tau \in [0, s]$ that survived until time s . $Q^k(s)$ and $q^k(s, \tau) \in [0, 1]$ are fractions of material produced at or before $s=0$ and fractions of material produced at $\tau \in [0, s]$, respectively, that have survived until time s . The survival of constituents grossly follows first order kinetics and can be modeled with survival functions of the form $q(s, \tau) = \exp(-\int_\tau^s K^k(\tilde{\tau})d\tilde{\tau})$. The rates of removal depend explicitly on changes in the tension within the fibers; here, we consider the specific form [19] $K^k(\tilde{\tau}) = K_h^k + K_h^k \Delta_\zeta^k(\tilde{\tau})^2$ where

$$\zeta^{k(\tau)}(s) = \frac{\partial \hat{W}^k}{\partial \lambda_n^k(\lambda_{n(\tau)}^k(s))} \quad (7)$$

is the level of tension on constituent k that was produced at time τ and $\Delta_\zeta^k(\tilde{\tau})$ is the difference in fiber tension from its homeostatic value.

Mechanical stress-mediated production rates m^k ($k=1, 2, 3$, and 4 for collagen fiber families, $k=m$ for the smooth muscle cell and $k=e$ for the elastin) are given by

$$m^{k=e} = 0, \quad m^k = m_0^k(1 + K_1^k \Delta\sigma - K_2^k \Delta\tau_w) \quad (8)$$

where m_0^k denotes original (basal) values and the normalized deviations from homeostatic stress values (indicated with superscript h) are defined for the intramural stress and wall shear stress, respectively, as

$$\Delta\sigma = \frac{\sigma - \sigma^h}{\sigma^h}, \quad \Delta\tau_w = \frac{\tau_w - \tau_w^h}{\tau_w^h} \quad (9)$$

with gain parameters K_1^k and K_2^k quantifying the rate of production of constituents in response to perturbations from their homeostatic states. Note that we assume no elastin turnover in the time-frame considered for G&R, since it is produced during the perinatal period, cross-linked, and stretched elastically during development and is biologically stable [28].

In this study, we consider changes in stress resulting from either a step increase (jump) or a linearly varying (gradual) increase in pressure from a venous toward an arterial value. Step and gradual changes in load, in the context of a numerical adaptation, are defined as:

- Step change: A step increase is achieved by a change in the load from homeostatic to the new value over one time step (Fig. 2(a)).
- Gradual change: A gradual increase in loading is characterized by a linear increase in load from homeostatic to the new value over a prescribed period (Fig. 2(b)). The vessel tends to recover from endothelial denudation in approximately 21 days and the initial 4 weeks is characterized by an increase in cellularity and matrix in the intima [3,5]. Motivated by these findings, the period for a gradual increase in load was fixed at 15 days.

The G&R formulation solves equations for stress equilibrium in the vessel wall (Eqs. (2) and (3)), accounting for evolving constituent mass densities, strain energy (Eqs. (5) and (6)), and constituent turnover (Eq. (8)). The problem is discretized using a

Fig. 2 Illustration of (a) a step increase in pressure and (b) a gradual increase in pressure, both illustrated for $\gamma = 2$

time step of ≈ 6 h and the Newton–Raphson method is used to numerically solve the resulting equations. The evolution and constituent turnover equations are biologically motivated. Values for radius and stress are found from the stress equilibrium equations, with mass computed from the constituent turnover equation. Simulations are run to a minimum of 365 days to evaluate possible intermediate steady state responses.

2.2 Material Characterization of Native Vein. A recent study showed that a four fiber family model for collagen plus a neo-Hookean model for elastin could reasonably describe the full passive experimental dataset and predict the inflation/extension response of porcine veins outside the data range employed for parameter identification [24]. Another study, using uniaxial tension tests on arteries and veins in a rat, speculated that similar constitutive models may be valid for arteries and veins [6]. Motivated by these two studies, the constitutive relations (though not the specific parameter values) used to model structural constituents within venous wall are similar to those used previously for arterial G&R [12,13,19]. The strain energy function for both collagen and smooth muscle is defined by the well known “Fung-type” exponential function

$$\hat{W}^k = c_1^k \left(e^{(c_2^k ((\lambda_{n(\tau)}^k)^2 - 1)^2)} - 1 \right) \quad (10)$$

where c_i^k are material constants, the superscript k represents the collagen fiber family or smooth muscle, and $\lambda_{n(\tau)}^k(s)$

$= G_h^k(\lambda(s)/\lambda(\tau))$, where G_h^k is the deposition prestretch for constituent k [12,19].

Vascular elastin is assumed to be isotropic and exhibit a neo-Hookean-type response [19,29], hence

$$\hat{W}^e = \frac{c^e}{2} (\lambda_\theta^2 + \lambda_z^2 + \lambda_r^2 - 3) \quad (11)$$

where c^e is a material constant. Segments of mouse inferior vena cava were previously tested under biaxial loads [18]. The circumferential (λ_θ) and axial stretches (λ_z) were measured and the radial stretch (λ_r) was computed using the incompressibility constraint. The stretch $\lambda^k(\tau)$ experienced by fibers is computed as

$$\lambda^k(\tau) = \sqrt{\lambda_z(\tau)^2 \cos^2 \alpha_0^k + \lambda_\theta(\tau)^2 \sin^2 \alpha_0^k} \quad (12)$$

where α_0^k is the angle between the fiber and the z -axis in a common reference configuration for the mixture; α_0^k is 0 deg for the axial component and 90 deg for circumferential components. The angle for the diagonal family of collagen (α_0^{diag}) was determined through parameter estimation.

Assuming that the tests were quasi-static and the response was passive, the constitutive equations and equilibrium equations together yield

$$P(s)a(s) = T_\theta(s) = \lambda_\theta \sum \frac{\partial W^k}{\partial \lambda_\theta} \quad (13)$$

and

$$\frac{f(s)}{\pi(2a(s) + h(s))} = T_z(s) = \lambda_z \sum \frac{\partial W^k}{\partial \lambda_z} \quad (14)$$

where $T_i = \sigma_i h$ are the principal intramural tensions in the θ and z directions.

Contributions of the circumferential collagen family and smooth muscle are physically indistinguishable; hence, the material constants representing both these constituent families were modeled together. The coefficients of the two diagonal collagen families were constrained to be the same to impose symmetry and avoid twisting of the vessel along the longitudinal axis due to pressurization. Hence, the proposed constitutive equation for the passive behavior has eight unknown parameters: $c_1^z, c_2^z, c_1^\theta, c_2^\theta, c_1^{\text{diag}}, c_2^{\text{diag}}, c^e$, and α_0^{diag} .

A normalized cost function

$$\mathcal{J} = \sqrt{\left(\frac{\sigma_z^{\text{exp}} - \sigma_z^{\text{mod}}}{\sigma_z^{\text{exp}}} \right)^2 + \left(\frac{\sigma_\theta^{\text{exp}} - \sigma_\theta^{\text{mod}}}{\sigma_\theta^{\text{exp}}} \right)^2} \quad (15)$$

was minimized to identify the set of material parameters that best-fit the experimental data (superscripts “exp” and “mod” indicate values calculated from experiment and model, respectively). A pattern search class of derivative-free optimization algorithms, described below, was used to find the optimum set of parameters for the constitutive equations (10) and (11).

2.3 Surrogate Management Framework (SMF). The SMF has been used successfully in a variety of complex problems, including unsteady fluid mechanics [30–32], helicopter rotor blade design [33,34], quantifying uncertainty in bypass graft models [35] and identifying arterial G&R parameters [36]. The SMF method was originally developed for computationally expensive simulations and can be applied to discontinuous functions and problems with nonlinear constraints [37]. It requires no information on function gradients and has the advantage that the function can be treated as a black box. Here, linear bound constraints

Fig. 3 Flowchart of the SMF used for identifying the optimal parameter set for vein G&R

enforce non-negativity of the strain energy function and impose biologically realistic bounds on the parameters of interest.

The SMF algorithm is summarized in Fig. 3. As in our previous work, our implementation generates initial sampling points using a Latin hypercube sampling scheme. The algorithm then proceeds using a combination of SEARCH and POLL steps. In the SEARCH step, a Kriging surrogate function is used to identify one or more points that are likely to improve the cost function and the true function is evaluated at these points. The Kriging model is then updated to incorporate new data in every iteration. When the SEARCH step fails to give an improved solution, the POLL step is performed whereby a positive spanning set is identified around the current best solution. If the POLL step also fails, the mesh in the parameter space is refined until it reaches a preset threshold. The design variables converge to a mesh local optimizer with proven convergence based on a pattern search theory. In this work, a mesh adaptive direct search (MADS) [37] is used for the POLL step. MADS offers superior convergence compared to earlier generalized pattern search methods because it generates a dense set of POLL directions. Further details on convergence theory and algorithm structure can be found elsewhere [33,37].

2.4 Parameter Selection and Bounds. Model parameters were first determined to match the native passive biaxial data, then determined to capture G&R. Some parameters needed to model the G&R can be measured directly (e.g., constituent mass

Table 2 Parameters for optimization and their prescribed bounds

Component	Parameter	Lower bound	Upper bound
Collagen gain ($\Delta\sigma_\theta$)	K_1^c	0.1	10 or 20
Collagen gain ($\Delta\tau_w$)	K_2^c	0.1	10 or 20
SMC gain ($\Delta\sigma_\theta$)	K_1^m	0.1	10 or 20
SMC gain ($\Delta\tau_w$)	K_2^m	0.1	10 or 20
Collagen half life	$\frac{1}{K_h^c}$ (days)	1	100
SMC half life	$\frac{1}{K_h^m}$ (days)	1	100
Collagen prestretch	G_h^c	1.01	2
SMC prestretch	G_h^m	1.1	1.8 or 2
Elastin prestretch— θ direction	$G_{h,\theta}^e$	1.5	2
Elastin prestretch— z direction	$G_{h,z}^e$	1.5	2

fractions) or inferred (e.g., homeostatic stresses and pressure) from data (Table 1). Following our earlier work on parameter sensitivity in arterial G&R [36], these parameters can be broadly classified into material parameters (p^c), gain parameters (p^k), half life parameters (p^{kq}), and prestretch parameters (p^G). Parameter bounds for p^k , p^{kq} , and p^G are chosen consistent with the literature or simply biologically reasonable when data are lacking [19,38,39] (Table 2). We explored the following combinations of gain parameters (K_1^k and K_2^k) and SMC prestretch (G_h^m) to understand the interplay between the location of the optimum and choice of parameter bounds. The four cases considered were

- Case 1: K_1^k & $K_2^k \leq 10$ and $G_h^m \leq 1.8$
- Case 2: K_1^k & $K_2^k \leq 20$ and $G_h^m \leq 1.8$
- Case 3: K_1^k & $K_2^k \leq 10$ and $G_h^m \leq 2.0$
- Case 4: K_1^k & $K_2^k \leq 20$ and $G_h^m \leq 2.0$

2.5 Increased Pressure. The cell-mediated G&R model, explained above, was then used to simulate the 1-yr evolution of a vein subjected to increased pressure. Biologically, a vessel tries to evolve toward target homeostatic values of stress during adaptation. To model this behavior, we minimized a normalized cost function

$$\mathcal{J}_{\text{adapt}} = \sqrt{\left(\frac{\tau_w^h - \tau_w}{\tau_w^h}\right)^2 + \left(\frac{\sigma_\theta^h - \sigma_\theta}{\sigma_\theta^h}\right)^2} \quad (16)$$

using the SMF optimization algorithm to determine the best adaptation to a given pressure perturbation ($\gamma = P/P_0$, where P_0 is the average pressure in the vessel's native environment). The (mal)adaptation of the vein to an increase in pressure was analyzed systematically using three numerical experiments which are elaborated in Sec. 3.

3 Results

The optimal set of material parameters for the normal wall, reported in Table 3, was obtained by minimizing the cost function $\mathcal{J}$. The best curve fit ($\mathcal{J} \approx 0.15$) for the passive biaxial experiment is shown in Fig. 4. The contribution from the circumferential family was relatively small and the contribution of the stiffer diagonal fiber family dominated at high stretch ratios. This trend is consistent with the prior results reported in the literature for veins [6,40]. These material parameters were held fixed in the three numerical experiments described below.

The goal of numerical experiment 1 was to identify an optimal set of parameters ($p_{\gamma_{\text{mod}}}$) that enabled a successful adaptation under a moderate increase in pressure ($\gamma_{\text{mod}} = 1.5$) and then, keeping these parameters fixed, to evaluate possible (mal)adaptations under increasingly higher pressure perturbations (γ_{high}). The vein

Table 3 Material coefficients estimated from the biaxial test, using the SMF algorithm

Coefficient	c_1^z (kPa)	c_2^z	c_1^θ (kPa)	c_2^θ	c_1^{diag} (kPa)	c_2^{diag}	c^e (kPa)	α_0^{diag}
Value	24.0220	0.1000	1.000	0.0503	0.0712	1.0350	1.0	36.60 deg

was subjected to successively higher γ until there was either a breakdown in adaptation (defined as an unbounded increase in radius and/or thickness over time) or achievement of the highest pressure ($\gamma = 20$). The results, in Table 4, were classified as optimal ($\Delta a < 10\%$ and $h \approx h_{\text{theoretical}}$), suboptimal ($\Delta a < 10\%$ but $h \not\approx h_{\text{theoretical}}$), stable maladaptive ($\Delta a > 10\%$ and $h \approx h_{\text{theoretical}}$), unstable maladaptive (unbounded growth in thickness and/or radius), or failure (did not reach the final time step). As it can be seen in the table (step cases in Table 4), responses to $p_{\gamma \text{mod}}$ were progressively maladaptive with increasing pressure load. Table 4 shows further the effects of the choice of parameter bounds on the extent of adaptation/maladaptation. Case 2, with a more constrained range of smooth muscle prestretch, helped the vein adapt over a greater range of pressure, albeit suboptimally when compared to case 4, with a less constrained range.

The purpose of numerical experiment 2 was to test the hypothesis that a gradual, compared with a step, change in pressure would extend the adaptive capacity of the vein. Simulations for numerical experiment 1 were thus repeated with a gradual increase in pressure, using the same optimal G&R parameters. Adaptations to

the gradual loading consistently had lower cost function values ($\mathcal{J}_{\text{adapt}}$) than the corresponding step change cases (Table 4) when the simulations converged (note: a convergence test evaluated the effect of time step size for all cases reported in Table 4). Due to unbounded growth in radius and/or thickness, one must exercise caution when interpreting cost functions as a measure of the extent of maladaptation for unstable maladaptive cases). For cases 1, 2, and 4, the gradual change enabled the vessel to adapt more favorably up to a higher pressure compared to a step change. Maladaptation also occurred at a higher pressure in case 2 compared to case 4 (Table 4). Since case 2 was most favorable, its parameter bounds were chosen for numerical experiment 3.

The purpose of numerical experiment 3 was to subject the vein to successively higher pressure perturbations and to identify through optimization the parameter values that allowed best adaptation ($\mathcal{J}_{\text{adapt}}$) individually for each level of perturbation. In contrast to experiments 1 and 2, optimization was rerun for each pressure increase from $\gamma = 1.5$ to $\gamma = 20$. Figure 5 shows the resulting evolution of luminal radius and wall thickness for the optimized parameters. The thickness evolution curves and the cost function values (Fig. 6) revealed increasingly larger deviations from an ideal adaptation with increasingly larger pressure perturbations. Overall, the vein graft response was suboptimal for increases as small as $3P_0$. That the optimal gain parameters were consistently high indicated the need for enhanced mass production to combat the increased wall stress resulting from the increased pressure. At every pressure, the circumferential gain parameter saturated at the upper bound and the half life of the constituents dropped as low as ≈ 1 day for some cases. The half lives affected the evolution of radius and thickness, but did not affect the final state of the vessel. The SMC prestretch values were also consistently high and near the upper bound while the collagen prestretch values were comparable to arteries. The adaptations were most

Fig. 4 Biaxial stress–stretch data (dashed lines) for a mouse vena cava and the associated best-fits achieved in the parameter estimation: (a) $\sigma_\theta - \lambda_\theta$, (b) $\sigma_z - \lambda_\theta$

Table 4 Summary of cost functions ($\mathcal{J}_{\text{adapt}}$) for numerical experiments 1 and 2. We know that for a cylinder, $\tau_w^h = 4(\mu Q_h / \pi a_h^3)$, and $\sigma_\theta^h = (P_h a_h / h_h)$. For a change to new values of flow ($Q = \varepsilon Q_h$) and pressure ($P = \gamma P_h$), we expect $a \rightarrow \varepsilon^3 a_h$ and $h \rightarrow \varepsilon^3 \gamma h_h$, if homeostatic stress values are restored. In our numerical experiments $\varepsilon = 1$, hence $h_{\text{theoretical}} \approx \gamma h_h$.

	Case 1	Case 1	Case 2	Case 2	Case 3	Case 3	Case 4	Case 4
γ	Step	Gradual	Step	Gradual	Step	Gradual	Step	Gradual
1.5	0.0773	0.0773	0.0429	0.0429	0.0534	0.0534	0.0245	0.0307
2	0.64985	0.1478	0.8578	0.0840	0.1119	0.1119	0.0842	0.0533
4	1.7620	0.3852	1.7245	0.2293	0.4762	0.4761	0.3272	0.2137
6	1.9432	0.5757	1.8661	0.3522	1.1261	1.1061	0.5227	0.3928
8	2.0489	0.7376	1.9406	0.4607	3.8781	3.0243	0.7157	0.5880
10	X	0.8794	1.9946	0.5591	X	11.0726	0.9413	0.8056
12	X	3.7106	2.0394	0.6498	X	X	1.1977	1.0446
14	X	X	2.0780	0.7345	X	X	X	1.2996
16	X	X	X	0.8152	X	X	X	1.5651
18	X	X	1.3622	1.0082	X	X	X	1.8367
20	X	X	3.5626	1.7392	X	X	X	2.1107

Legend

Optimal	$\Delta a (= (a_{\text{end}} - a_0)/a_0) < 10\%$ and $h \approx h_{\text{theoretical}}$
Suboptimal	$\Delta a < 10\%$ but $h \not\approx h_{\text{theoretical}}$
Stable maladaptive	$\Delta a > 10\%$ and $h \approx h_{\text{theoretical}}$
Unstable maladaptive	Unbounded growth in thickness and/or radius
Failure—X	Did not reach the final time step

Fig. 5 Summary of (a) radius and (b) thickness evolution with time for numerical experiment 3 for case 2: K_1^k & $K_2^k \leq 20$ and $G_m^h \leq 1.8$. The radius curves are within a 10% deviation. The arrows indicate the thickness for an ideal adaptation. Thickness curves exhibit a larger deviation from an ideal adaptation for a larger pressure.

Fig. 6 Comparison of cost functions ($\mathcal{J}_{\text{adapt}}$) for a step change in load with $p_{\gamma_{\text{mod}}}$, a gradual change in load $p_{\gamma_{\text{mod}}}$, and the optimized values from numerical experiment 3. All values reported are for case 2: K_1^k & $K_2^k \leq 20$ and $G_m^h \leq 1.8$. Adaptation for a gradual change in load with $p_{\gamma_{\text{mod}}}$ is comparable to the best possible adaptation a vein can achieve.

sensitive to the collagen prestretch (G_c^h) followed by the SMC prestretch (G_m^h) and the gain parameters. Elastin prestretch was found to have negligible effect on the adaptation.

For a given pressure, the response to a gradual increase in load with $p_{\gamma_{\text{mod}}}$ was comparable to the optimized adaptation (Fig. 6), making a compelling case for further probing of the potential clinical benefits of a gradual change in pressure through experiments and animal models.

4 Discussion

It is well known that blood vessels change their caliber in response to changes in flow and increase their wall thickness in response to increased pressure [19,41]. In some cases, these changes restore wall shear stress and wall stress close to original values, which is said to be adaptive. In cases where homeostasis is achieved, the vessel reaches a new equilibrium state in which production balances removal. In other cases, however, such changes may be maladaptive. Our results suggest that a vein can adapt to modest changes in blood pressure, but its adaptive capacity appears limited (Fig. 5). Because of its elasticity, the vein distends upon pressurization, which decreases wall shear stress (recall $\tau_w = 4\mu Q/\pi a^3$, with a as the inner radius) and increases mean circumferential stress ($\sigma_\theta = Pa/h$ with h as the wall thickness). Both changes in stress should thus initiate a mechanobiologically driven G&R process, provided that the endothelial and smooth muscle cells/fibroblasts remain functional. Due to an early adjustment in vascular tone, the radius was quickly restored to its homeostatic value. A simple force balance indicates, in an ideal adaptation, that the increase in thickness should be proportional to the increase in pressure. The venous adaptation (Figs. 5 and 6) was found to be suboptimal for pressure perturbations as small as $\gamma = 3$, well below the $\gamma > 20$ expected in a typical vein graft procedure. Since the parameter bounds for optimization were biologically motivated and the target values for adaptation were for a venous system, these results suggest that the venous wall has a limited capacity to respond adequately to a dramatic increase in pressure. In other words, clinical observations of maladaptation should not be surprising.

While knowledge of the homeostatic state can suggest the final state of an adaptation [42], cell-mediated G&R models can shed light on mechanisms of these adaptations. Some previous attempts at modeling vein graft adaptations have prescribed changes in geometry as functions of time and stress [17,43]. In contrast, the current model makes changes in geometry, structure, and composition of the vessel a consequence of the cell mediated G&R that tries to restore homeostatic stresses; that is, the results of the present model are “emergent.” The model captured salient features of pressure-induced adaptation in a vein graft, including an increase in constituent mass production. Recent histological results show an ≈ 3 fold increase in collagen content in the walls of veins subjected to a pressure and flow overload [40]. A 15-fold increase in SMC proliferation has also been reported for arteries in hypertensive rats [39]. The pressure perturbations in the current work are higher than the hypertensive case in arteries and the aforementioned observations qualitatively support the optimization algorithm’s prediction of an enhanced mass production. The passive properties imply that the vein is initially stiff in the axial direction but compliant in the circumferential direction. The high mass production predicted in the circumferential direction in numerical experiment 3 can be interpreted as a mechanism by which the vein negotiates an increase in circumferential stress due to an increased pressure.

If one interprets the gain parameter as a measure of mass production and prestretch as a measure of stiffness of material being deposited, the numerical experiments suggest that the vein may prefer to deposit larger quantities of normal material than small quantities of stiffer material along the circumferential direction. This scenario may be consistent with cells trying to maintain local

material stiffness while increasing structural stiffness to offset the increase in loading, which could be mechanically favorable [44].

Experimental data reported on (mal)adaptations of vein grafts do not yet provide sufficient details to make quantitative longitudinal validations with the current model. The few available studies concentrate on short term responses [16,17,40,45]. Nonetheless, parallels can be drawn between the current results and observed trends in arterial G&R in hypertension (which is a modest pressure perturbation relative to that considered here). Nissen et al. [38] showed that the half life of collagen in a rat aorta reduced from 60 to 70 days under normotension to 17 days in hypertension ($\approx 1.5P_0$). The pressure perturbations herein are an order of magnitude higher than the systemic hypertension that leads to an exuberant turnover of matrix. The value of ≈ 1 day for collagen half life, as predicted by the optimization for a few cases, thus seems reasonable, if biologically possible.

One aim of any G&R framework is to guide the design and interpretation of experiments and clinical studies. The differences in response to step and gradual changes in pressure demonstrate the ability of numerical models to compare and contrast potential clinical treatment strategies. Current practice in CABG surgery involves removing the vascular clamp at each end of a graft following implantation. This situation is analogous to a step change in pressure. A biodegradable coating on the graft could be envisioned that would expose the vein to a gradual increase in pressure [46,47], mimicking numerical experiment 2. Observations from this experiment could have potential implications in the design of synthetic sheaths and alternate clinical procedures. Of course, many other issues would need to be addressed, not the least of which would be changes in the G&R due to a foreign body response.

The current work also demonstrates utility of a modular optimization tool to accelerate parameter estimation and numerically test competing hypotheses in vascular G&R. The proposed methods are nonintrusive and scalable. Each level of the algorithm is parallelizable and can be run as a multiprocessor job. By formulating the parameter identification problem as an optimization problem with an objective function measuring differences from homeostatic targets, parameter sets were efficiently identified without the need for expensive brute force trial and error approaches.

The proposed model for venous G&R has several assumptions and simplifications, many of which are due to the lack of experimental and/or clinical data. The structure and properties of a vein vary with age, location in the body, and species [48]. Although the prescribed single layer model is based on a healthy murine inferior vena cava, a three-layer G&R model would obviously provide more detail on the (mal)adaptations, perhaps elucidating salient aspects of vein graft G&R such as clinically observed medial versus neointimal thickening. Lack of a clear distinction between intima and media in a mouse vein, and challenges of dissecting layers without damaging the wall, impose practical constraints on obtaining biaxial data for the different layers [45]. There is also recent histological evidence challenging the assumption of elastin isotropy in veins [40]. In the light of more experimental evidence, anisotropic models for elastin can be easily incorporated into the current framework, including the use of anisotropic elastin prestretch.

There is uncertainty associated with the target homeostatic circumferential and wall shear stress in the current study. Data on potential differences in homeostatic wall shear stress across species are lacking, hence the current target values of stress were chosen to reasonably represent existing experiments on veins independent of species [24,27,49]. Experiments looking at venous and arterial markers suggest that the venous identity is lost but an arterial identity is not fully gained during a vein graft adaptation [50]. There is a need for more experimental data to answer questions on arterialization of a vein graft. The homeostatic stress values in arteries are larger than veins [19]; hence, the current study will serve as an upper bound for optimal adaptation. A

similar study, where the target homeostatic values are for an artery, should serve as a lower bound. The question of target homeostatic stress is one of the many instances where computational models become useful in testing hypotheses in vein graft remodeling, thus pointing out the gaps in knowledge and setting directions for future experiments.

It is still not clear if the manifestations of G&R in a vein graft are an adaptation or an injury response [2]. Endothelial cell functionality is likely compromised after bypass graft surgery, hence the vein could lose its ability to sense and restore wall shear stress [2,8]. The current work disregards possible effects of compromised endothelial function; subsequent studies will need to take this effect into account once additional data are available. An endothelial injury response function similar to the one used by Baek et al. [15] could be incorporated into the current model to capture such an injury response, noting that normal veins are more sensitive to vasoconstrictors and less sensitive to vasodilators than arteries [5]. Nitric oxide and prostacyclin, which are potent vasodilators and inhibitors of platelet adhesion and aggregation, are released in greater amounts in arterial than venous coronary bypass vessels [51]. Since the mechanobiology of vasodilation/vasocontraction is not completely understood, it poses challenges when modeling the response of veins to altered flow and needs to be considered in future work. With the absence of endothelial injury and a venous value for homeostatic stress, the current representation is a best-case scenario for a vein graft adaptation.

Although the framework is general enough to accommodate perturbations to pressure and flow, we only examined the effect of altered pressure. Although all blood vessels appear to respond to changes in both intramural and wall shear stresses, a comparison of the responses of large elastic arteries, muscular arteries, and arterioles in hypertension suggests that the most robust response is to thicken the wall to restore σ_θ toward normal while τ_w may decrease, be maintained, or increase. Herein, we similarly assumed that thickening in response to increased pressure may be the best indicator of possible adaptivity. There is a need to consider possible smooth muscle damage in response to the dramatic increase in pressure experienced by a vein graft, however, which could adversely affect the overall response. Again, therefore, there is need for more data.

Another common clinical example of vein remodeling is in arteriovenous fistula (AVF). However, the hemodynamic conditions in AVFs differ from those of CABG vein grafts in several important ways. While CABG grafts experience relatively uniform pressure conditions and largely laminar flow, flow in AVFs is highly complex, perhaps turbulent, with large pressure drops from systemic to venous levels. The failure in venous segments of the AVF is associated with intimal hyperplasia and associated thickening of the intima [52] (in contrast to thickening of the media in vein grafts). Hence, one needs to look at the combined effects of nonuniform alterations in pressure and flow to understand the failure of veins in AVF. With appropriate modifications, the models and the methods presented in this paper could be used to study venous G&R in AVFs, which is of significant importance in a relatively large and high-risk population. We note that optimization would also be useful in this context to identify appropriate parameter changes.

Though other hemodynamic parameters, such as oscillatory shear, can be important in areas of branching and anastomosis, we neglected them here for several reasons. First, there is a lack of quantitative in vivo experimental data on venous endothelial responses to oscillatory shear. Second, this work focused on salient features of G&R in the central region of a long straight vessel using a 2D model, where oscillatory shear is likely to be less important. Indeed, patient specific modeling of CABG grafts has shown very low values of oscillatory shear in grafts. Third, we focused on G&R during the first year during which atherosclerosis tends not to be the major concern; oscillatory shear is most important in atherogenesis in arteries [53].

Despite several simplifications and assumptions (elastostatics, axisymmetry, no fluid–solid interactions, and a single layer vessel), the present G&R framework produced results consistent with general observations in the literature. Perhaps most importantly, however, the current work illustrates that a G&R framework can provide a platform to quickly test multiple hypotheses and gain insights into consequences of changes in hemodynamics. There is, however, a pressing need for more data and focused experiments to motivate better constitutive relations and make quantitative comparisons and validations. Future efforts should be directed toward modeling the response of a vein to simultaneous increases in flow and pressure and extending the formulation to a 3D vein accounting for injury responses. The modeling community should begin to move toward an all encompassing model coupling G&R to patient specific fluid–structure simulations and furthering the feasibility of personalized treatments employing vein grafts.

5 Conclusion

A typical goal of a computational model is to capture experimental observations, as, for example, the time course of changes in geometry, composition, and mechanical properties of an implanted vein graft. In the case of these grafts, it is known that such changes often reflect a maladaptive rather than an adaptive response to the higher pressures and flows experienced in the arterial system. The goal of our work was very different, however. We sought to identify upper and lower bounds on the adaptive capacity of a vein as a means to understand better why vein grafts often maladapt. Toward this end, we first assumed that veins can adapt well to modest changes in hemodynamics and identified associated “homeostatic” G&R parameters that enabled such adaptations. These parameters were then used to assess responses to increases in pressure that would be experienced by a vein graft. Next, we identified different sets of G&R parameters that numerically enabled adaptations to increasingly higher pressures, from venous to arterial levels; there was no constraint on this parameter identification regarding whether or not an actual vein could achieve such adaptations in vivo. Interestingly, neither the homeostatic nor the numerically optimized values of G&R parameters enabled venous adaptations to pressures actually experienced in the arterial circulation ($P > 20P_{\text{venous}}$). Hence, our numerical results are consistent with the preponderance of the experimental and clinical observations that veins maladapt. Given this finding, and motivated by some prior empirical (e.g., Ref. [46]) and computational (e.g., Refs. [36,54]) studies, we then explored possible advantages of increasing the pressure gradually rather than abruptly, as occurs during surgical procedures when the arterial clamps are released. The simulations suggested that gradual increases in pressure, and thus vascular wall stress, may allow a more favorable adaptation. Indeed, noting that we did not include potential cellular damage due to the abrupt increase in pressure, these results are thus likely conservative. We submit, therefore, that first, computational G&R models can play an important role in understanding mechanobiological mechanisms of vascular (mal)adaptation and, second, a gradual loading of vein grafts may provide a means to improve mural adaptations and hence outcomes.

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References

- [1] Sankaran, S., Esmaily Moghadam, M., Kahn, A. M., Guccione, J., Tseng, E., and Marsden, A. L., 2012, “Patient-Specific Multiscale Modeling of Blood Flow for Coronary Artery Bypass Graft Surgery,” *Ann. Biomed. Eng.*, **40**(10), pp. 2228–2242.

- [2] Humphrey, J. D., 2002, *Cardiovascular Solid Mechanics: Cells, Tissues, and Organs*, Springer, NY.
- [3] Lüscher, T. F., Turina, M., and Braunwald, E., 1994, *Coronary Artery Graft Disease: Mechanisms and Prevention*, Springer-Verlag, Berlin, Germany.
- [4] Kanterman, R. Y., Vesely, T. M., Pilgram, T. K., Guy, B. W., Windus, D. W., and Picus, D., 1995, “Dialysis Access Grafts: Anatomic Location of Venous Stenosis and Results of Angioplasty,” *Radiology*, **195**(1), pp. 135–139.
- [5] Cox, J. L., Chiasson, D. A., and Gotlieb, A. I., 1991, “Stranger in a Strange Land: The Pathogenesis of Saphenous Vein Graft Stenosis With Emphasis on Structural and Functional Differences Between Veins and Arteries,” *Prog. Cardiovasc. Dis.*, **34**(1), pp. 45–68.
- [6] Sokolis, D. P., 2008, “Passive Mechanical Properties and Constitutive Modeling of Blood Vessels in Relation to Microstructure,” *Med. Biol. Eng. Comput.*, **46**(12), pp. 1187–1199.
- [7] Shelton, M. E., Forman, M. E., Virmani, R., Bajaj, A., Stoney, W. S., and Atkinson, J. B., 1988, “A Comparison of Morphologic and Angiographic Findings in Long-Term Internal Mammary Artery and Saphenous Vein Bypass Grafts,” *J. Am. Coll. Cardiol.*, **11**(2), pp. 297–307.
- [8] Liu, S. Q., and Fung, Y. C., 1998, “Changes in the Organization of the Smooth Muscle Cells in Rat Vein Grafts,” *Ann. Biomed. Eng.*, **26**(1), pp. 86–95.
- [9] Liu, S. Q., 1998, “Influence of Tensile Strain on Smooth Muscle Cell Orientation in Rat Blood Vessels,” *ASME J. Biomech. Eng.*, **120**(3), pp. 313–320.
- [10] Galt, S. W., Zwolak, R. W., Wagner, R. J., and Gilbertson, J. J., 1993, “Differential Response of Arteries and Vein Grafts to Blood Flow Reduction,” *J. Vasc. Surg.*, **17**(3), pp. 563–570.
- [11] Fillinger, M., Cronenwett, J. L., Besso, S., Walsh, D. B., and Zwolak, R. M., 1994, “Vein Adaptation to the Hemodynamic Environment of Intrainguinal Grafts,” *J. Vasc. Surg.*, **19**(6), pp. 970–979.
- [12] Baek, S., Rajagopal, K. R., and Humphrey, J. D., 2006, “A Theoretical Model of Enlarging Intracranial Fusiform Aneurysms,” *ASME J. Biomech. Eng.*, **128**(1), pp. 142–149.
- [13] Eberth, J. F., Cardamone, L., and Humphrey, J. D., 1995, “Evolving Biaxial Mechanical Properties of Mouse Carotid Arteries in Hypertension,” *J. Biomech.*, **21**, pp. 460–471.
- [14] Humphrey, J. D., Baek, S., and Niklason, L. E., 2007, “Biochemomechanics of Cerebral Vasospasm and Its Resolution: I. A New Hypothesis and Theoretical Framework,” *Ann. Biomed. Eng.*, **35**(9), pp. 1485–1497.
- [15] Baek, S., Valentin, A., and Humphrey, J. D., 2007, “Biochemomechanics of Cerebral Vasospasm and Its Resolution: II. Constitutive Relations and Model Simulations,” *Ann. Biomed. Eng.*, **35**(9), pp. 1498–1509.
- [16] Dobrin, P., Littooy, F. N., and Endean, E. D., 1989, “Mechanical Factors Predisposing to Intimal Hyperplasia and Medial Thickening in Autogenous Vein Grafts,” *Surgery*, **105**, pp. 393–400.
- [17] Tran-Son-Tay, R., Hwang, M., Garbey, M., Jiang, Z., Ozaki, C. K., and Berceci, S., 2008, “An Experiment-Based Model of Vein Graft Remodeling Induced by Shear Stress,” *Ann. Biomed. Eng.*, **36**(7), pp. 1083–1091.
- [18] Lee, Y. U., Naito, Y., Kurobe, H., Breuer, C. K., and Humphrey, J. D., 2013, “Biaxial Mechanical Properties of the Inferior Vena Cava in C57BL/6 and CB-17 SCID/bg Mice,” *J. Biomech.*, **46**(13), pp. 2277–2282.
- [19] Valentin, A., Cardamone, L., Baek, S., and Humphrey, J. D., 2009, “Complementary Vasoactivity and Matrix Remodelling in Arterial Adaptations to Altered Flow and Pressure,” *J. R. Soc. Interface*, **6**(32), pp. 293–306.
- [20] Humphrey, J. D., and Rajagopal, K. R., 2002, “A Constrained Mixture Model for Growth and Remodeling of Soft Tissues,” *Math. Models Methods Appl. Sci.*, **12**(3), pp. 407–430.
- [21] Gleason, R. L., and Humphrey, J. D., 2004, “A Mixture Model of Arterial Growth and Remodeling in Hypertension: Altered Muscle Tone and Tissue Turnover,” *J. Vasc. Res.*, **41**(4), pp. 352–363.
- [22] Karšaj, I., and Humphrey, J. D., 2012, “A Multilayered Wall Model of Arterial Growth and Remodeling,” *Mech. Mater.*, **44**, pp. 110–119.
- [23] Humphrey, J. D., and Taylor, C. A., 2008, “Intracranial and Abdominal Aortic Aneurysms: Similarities, Differences, and Need for a New Class of Computational Models,” *Ann. Rev. Biomed. Eng.*, **10**, pp. 221–246.
- [24] Sokolis, D. P., 2013, “Experimental Investigation and Constitutive Modeling of the 3D Histomechanical Properties of Vein Tissue,” *Biomech. Modell. Mechanobiol.*, **12**(3), pp. 431–451.
- [25] Fung, Y. C., 1993, *Biomechanics: Mechanical Properties of Living Tissues*, Springer-Verlag, NY.
- [26] Rachev, A., and Hayashi, K., 1999, “Theoretical Study of the Effects of Vascular Smooth Muscle Contraction on Strain and Stress Distributions in Arteries,” *Ann. Biomed. Eng.*, **27**(4), pp. 459–468.
- [27] Zhang, R., Gashev, A. A., Zawieja, D. C., and Davis, M. J., 2007, “Length–Tension Relationships of Small Arteries, Veins, and Lymphatics From the Rat Mesenteric Microcirculation,” *Am. J. Physiol. Heart Circ. Physiol.*, **292**, pp. H1943–H1952.
- [28] Langille, B. L., 1996, “Arterial Remodeling: Relation to Hemodynamics,” *Can. J. Physiol. Pharmacol.*, **74**(7), pp. 834–841.
- [29] Holzapfel, G. A., Gasser, T. C., and Ogden, R. W., 2000, “A New Constitutive Framework for Arterial Wall Mechanics and a Comparative Study of Material Models,” *J. Elast. Phys. Sci. Solids*, **61**, pp. 1–48.
- [30] Marsden, A. L., Wang, M., Dennis, J. E., and Moin, P., 2007, “Trailing-Edge Noise Reduction Using Derivative-Free Optimization and Large-Eddy Simulation,” *J. Fluid Mech.*, **572**, pp. 13–36.
- [31] Marsden, A. L., Wang, M., Dennis, J. E., Jr., and Moin, P., 2004, “Suppression of Vortex-Shedding Noise via Derivative-Free Shape Optimization,” *Phys. Fluids*, **16**(10), pp. L83–L86.

- [32] Yang, W., Feinstein, J. A., and Marsden, A. L., 2010, "Constrained Optimization of an Idealized Y-Shaped Baffle for the Fontan Surgery at Rest and Exercise," *Comput. Methods Appl. Mech. Eng.*, **199**(33–36), pp. 2135–2149.
- [33] Booker, A. J., Dennis, J. E., Jr., Frank, P. D., Serafini, D. B., Torczon, V., and Trosset, M. W., 1999, "A Rigorous Framework for Optimization of Expensive Functions by Surrogates," *Struct. Optim.*, **17**(1), pp. 1–13.
- [34] Marsden, A. L., Wang, M., Dennis, J. E., Jr., and Moin, P., 2004, "Optimal Aeroacoustic Shape Design Using the Surrogate Management Framework," *Optim. Eng.*, **5**(2), pp. 235–262.
- [35] Sankaran, S., and Marsden, A. L., 2010, "The Impact of Uncertainty on Shape Optimization of Idealized Bypass Graft Models in Unsteady Flow," *Phys. Fluids*, **22**(12), p. 121902.
- [36] Sankaran, S., Humphrey, J. D., and Marsden, A. L., 2013, "An Efficient Framework for optimization and Parameter Sensitivity Analysis in Arterial Growth and Remodeling Computations," *Comput. Methods Appl. Mech. Eng.*, **256**, pp. 200–210.
- [37] Audet, C., and Dennis, J. E., Jr., 2006, "Mesh Adaptive Direct Search Algorithms for Constrained Optimization," *SIAM J. Optim.*, **17**(1), pp. 188–217.
- [38] Nissen, R., Cardinale, G. J., and Udenfriend, S., 1978, "Increased Turnover of Arterial Collagen in Hypertensive Rats," *Proc. Natl. Acad. Sci. U.S.A.*, **75**(1), pp. 451–453.
- [39] Xu, C., Lee, S., Singh, T. M., Sho, E., Li, X., Sho, M., Masuda, H., and Zarins, C. K., 2001, "Molecular Mechanisms of Aortic Wall Remodeling in Response to Hypertension," *J. Vasc. Surg.*, **33**(3), pp. 570–578.
- [40] Sassani, S. G., Theofani, A., Sokrates, T., and Sokolis, D. P., 2013, "Time-Course of Venous Wall Biomechanical Adaptation in Pressure and Flow-Overload: Assessment by a Microstructure-Based Material Model," *J. Biomech.*, **46**(14), pp. 2451–2462.
- [41] Dajnowiec, D., and Langille, B., 2007, "Arterial Adaptations to Chronic Changes in Haemodynamic Function: Coupling Vasomotor Tone to Structural Remodelling," *Clin. Sci.*, **113**, pp. 15–23.
- [42] Humphrey, J. D., 2008, "Mechanisms of Arterial Remodeling in Hypertension Coupled Roles of Wall Shear and Intramural Stress," *Hypertension*, **52**, pp. 195–200.
- [43] Hwang, M., Berceci, S. A., Garbey, M., Kim, N. H., and Tran-Son-Tay, R., 2012, "The Dynamics of Vein Graft Remodeling Induced by Hemodynamic Forces: A Mathematical Model," *Biomech. Modell. Mechanobiol.*, **11**(3–4), pp. 411–423.
- [44] Wagenseil, J. E., and Mecham, R. P., 2009, "Vascular Extracellular Matrix and Arterial Mechanics," *Physiol. Rev.*, **89**, pp. 957–989.
- [45] Kritharis, E. P., Kakisis, J. D., Giagini, A. T., Manos, T., Stergiopoulos, N., Tsangaris, S., and Sokolis, D. P., 2010, "Biomechanical, Morphological and Zero-Stress State Characterization of Jugular Vein Remodeling in Arteriovenous Fistulas for Hemodialysis," *Biorheology*, **47**, pp. 297–319.
- [46] El-Kurdi, M. S., Hong, Y. I., Stankus, J. J., Soletti, L., Wagner, W. R., and Vorp, D. A., 2008, "Transient Elastic Support for Vein Grafts Using a Constricting Microfibrillar Polymer Wrap," *Biomaterials*, **29**(22), pp. 3213–3220.
- [47] Liu, S. Q., Moore, M. M., and Yap, C., 2000, "Prevention of Mechanical Stretch-Induced Endothelial and Smooth Muscle Cell Injury in Experimental Vein Grafts," *ASME J. Biomech. Eng.*, **122**(1), pp. 31–38.
- [48] Rhodin, J. A. G., 2011, "Architecture of the Vessel Wall," *Compr. Physiol.*, pp. 1–31.
- [49] Kamiya, A., Bukhari, R., and Togawa, T., 1984, "Adaptive Regulation of Wall Shear Stress Optimizing Vascular Tree Function," *Bull. Math. Biol.*, **46**(1), pp. 127–137.
- [50] Kudo, F. A., Muto, A., Maloney, S., Pimiento, J. M., Bergaya, S., Fitzgerald, T. N., Westvik, T. S., Frattini, J., Breuer, C., Cha, C., Nishibe, T., Tellides, G., Sessa, W. C., and Dardik, A., 2007, "Venous Identity Is Lost but Arterial Identity Is Not Gained During Vein Graft Adaptation," *Arteriosclerosis*, **27**, pp. 1562–1571.
- [51] Lüscher, T. F., 1991, "Vascular Biology of Coronary Bypass Grafts," *Curr. Opin. Cardiol.*, **6**, pp. 868–876.
- [52] Manos, T. A., Sokolis, D. P., Giagini, A. T., Davos, C. H., Kakisis, J. D., Kritharis, E. P., Stergiopoulos, N., Karayannacos, P. E., and Tsangaris, S., 2010, "Local Hemodynamics and Intimal Hyperplasia at the Venous Side of a Porcine Arteriovenous Shunt," *IEEE Trans. Inf. Tech. Biomed.*, **14**(3), pp. 681–690.
- [53] Ku, D. N., Giddens, D. P., Zarins, C. K., and Glagov, S., 1985, "Pulsatile Flow and Atherosclerosis in the Human Carotid Bifurcation. Positive Correlation Between Plaque Location and Low Oscillating Shear Stress," *Arterioscler., Thromb., Vasc. Biol.*, **5**, pp. 293–302.
- [54] Karšaj, I., Sorić, J., and Humphrey, J. D., 2010, "A 3-D Framework for Arterial Growth and Remodeling in Response to Altered Hemodynamics," *Int. J. Eng. Sci.*, **48**(11), pp. 1357–1372.
- [55] Švejcár, J., Přerovský, I., Linhart, J., and Kruml, J., 1962, "Content of Collagen, Elastin, and Water in Walls of the Internal Saphenous Vein in Man," *Circ. Res.*, **2**, pp. 296–300.