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Vascular Adaptation in the Presence of External Support - A Modeling Study

--Manuscript Draft--

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Abstract:	Vascular grafts have long been used to replace damaged or diseased vessels with considerable success, but a new approach is emerging where native vessels are merely supported, not replaced. Although external supports have been evaluated in diverse situations - ranging from aneurysmal disease to vein grafts or the Ross operation - optimal supports and procedures remain wanting. In this paper, we present a novel application of a growth and remodeling model well suited for parametrically exploring multiple designs of external supports while accounting for mechanobiological and immunobiological responses of the supported native vessel. These results suggest that a load bearing external support can reduce vessel thickening in response to pressure elevation. Results also suggest that the final adaptive state of the vessel depends on the structural stiffness of the support via a mechano-driven adaptation, although luminal encroachment may be a complication in the presence of chronic inflammation. Finally, the supported vessel can stiffen (structurally and materially) along circumferential and axial directions, which could have implications on overall hemodynamics and thus subsequent vascular remodeling. The proposed framework can provide valuable insights into vascular adaptation in the presence of external support, accelerate rational design, and aid translation of this emerging approach
Suggested Reviewers:	Jeffrey Holmes holmes@virginia.edu Jonathan Vande Geest jpv20@pitt.edu Nele Famaey nele.famaey@kuleuven.be
Response to Reviewers:	The response to reviewer comments are in the document 'Response to Reviewers'

24 Apr 2020

Dear Editor,

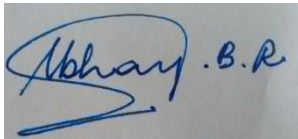
Re: Second revision of manuscript JMBBM_2019_1583R2 entitled "Vascular Adaptation in the Presence of External Support - A Modeling Study" for consideration of publication in Journal of Mechanical Behavior of Biomedical Materials.

We are pleased to submit a revised version of our manuscript JMBBM_2019_1583 entitled "Vascular Adaptation in the Presence of External Support - A Modeling Study" for consideration in Journal of Mechanical Behavior of Biomedical Materials. Our response to reviewers is addressed in line with their questions in 'Response to Reviewers' document. In addition, we have made modifications and additions to the text (text changes are highlighted in red font). The reviewer comment has improved the manuscript and we thank the reviewers for their time.

All authors were fully involved in the study and preparation of the manuscript and that the material within has not been submitted for publication elsewhere. All authors declare no conflict of interest.

We thank you for considering our manuscript for review.

Sincerely,

A handwritten signature in blue ink that reads "Abhay .B.R." with a stylized flourish underneath.

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JMBBM_2019_1583R1 - Vascular Adaptation in the Presence of External Support - A Modeling Study: Response to Reviewers

Editor and Reviewer comments:

Reviewer #1: The authors' response addressed adequately most of my concerns.

One issue that remains unclear is the physiological validity of Eq. (12). The authors' response justifies its validity based on the fact that in the absence of mechanical perturbations the term within bracket reduces to 1, and one recovers a balanced turnover (production is offset precisely by the removal). But other mathematical forms can recover such a balance as well. The question is if there is experimental evidence for linking the basal term with the stress, shear and inflammatory ones in the multiplicative form of Eq. (12)? Another question, what is the range of validity of the system (12)-(14)? Is it valid also under atrophy (which may be the case in the externally supported vessel)?

Thank you for this insightful question, which has multiple parts that are discussed separately.

Constitutive equations for nonlinear materials are not unique, hence one must seek relations that best describe the data under conditions of interest. Here, we emphasize that our phenomenological forms for mass production and removal were iteratively refined via a series of early papers on arteries for diverse situations, resulting in the general forms now used with good success in many different cases (including ageing, aneurysm, hypertensive remodeling, vein graft adaptation, and tissue engineering). Hence, they were the preferred candidate functions for this application also.

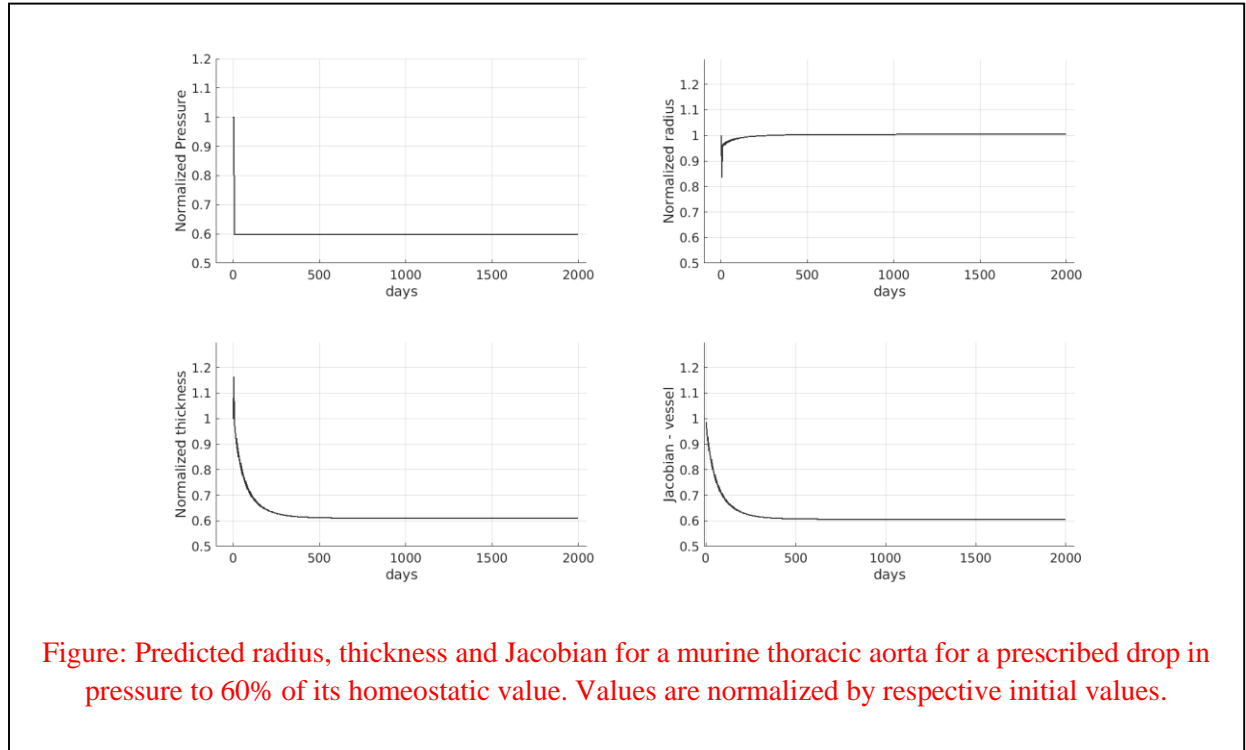
Note that many papers in vascular biology report fold-increases in cells or matrix. For us, this fold change is simply $m^\alpha(\tau)/m_B^\alpha$, at each G&R time, where the basal homeostatic value m_B^α is related to the original apparent mass density and basal removal rate to ensure homeostatic processes over long periods. Data suggest that the homeostatic fold-change of 1 (by definition) can be augmented when stress deviates from its homeostatic value. Hence, our relation is, in a sense, the simplest that one might imagine – additive stress-mediated effects, in this case with inflammatory effects added too. Remarkably, this simple form has proven sufficient in many cases and was assumed here.

Regarding range of validity of the functions, most mechanobiological response functions are sigmoidal (as seen in many in vitro studies, reviewed previously), yet in vivo conditions typically operate along the linear part of the sigmoid curve (since responses tend to be relatively rapid and effective). Hence, our linear stimulus functions provide a simple form that approximates the salient feature of a sigmoidal response. In some cases, however, the sigmoidal or similar nonlinear functions are needed to model more dramatic perturbations (cf. Valentin et al., ABME, 2011).

The set of equations 12-14 is generally valid, including atrophy wherein removal outpaces production. Note, therefore, that the stress-mediated terms can reduce the overall production rate below homeostatic. To illustrate this, the figure below shows an adaptation of a (unilayered) vessel at a pressure = 60% of its homeostatic value. The associated loss of wall thickness, and Jacobian, are indicative of atrophy of the vessel (which is a natural consequence of the general model). Note that this is mechanically equivalent to a vessel unloading from its homeostatic (transmural) pressure due to the presence of an external support. We believe, however, that there is need for additional data (e.g. sizing of external support, mechanism of atrophy) and systematic parameter

estimation to simulate atrophy with a bilayered theory since the media and adventitia could respond very differently. Hence, we did not simulate atrophy with the bilayered model.

Some of these details are now included in the Methods and Discussion sections of the manuscript.



Reviewer #2: The authors have addressed all comments in a clear manner. In my opinion, the manuscript is ready for publication.

Thank you

Reviewer #3: please have the authors take care of the question marks on their prior response (copied below):

The removal term represents the fraction of the mass deposited at time τ that survives at time s , hence it must depend on two time variables - the instant when the material was deposited and the current G&R time s (also see equation 13). Mass production (by deposition), however, is dependent on basal production rate, the mechanical stimuli (wall stress and wall shear stress) and inflammatory stimulus - all functions of instantaneous G&R time s , which is also one of the limits of integration. Integration on the deposition time τ over the past history in Eq. (4) yields the current value of stress at time s (see also Eq. (8) for mass density). The details of the functional forms are explained in detail in some of our earlier publications (e.g. Baek et al., JBME, 2006, Baek et al., ABME, 2007, Valentin et al., RSIF, 2009).

The τ should have been the greek symbol τ , one of the time variables in equation (4) and (8). We apologize for this error, which seems to have occurred when word document was uploaded to journal interface.

Vascular Adaptation in the Presence of External Support - A Modeling Study

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Abstract

Vascular grafts have long been used to replace damaged or diseased vessels with considerable success, but a new approach is emerging where native vessels are merely supported, not replaced. Although external supports have been evaluated in diverse situations - ranging from aneurysmal disease to vein grafts or the Ross operation - optimal supports and procedures remain wanting. In this paper, we present a novel application of a growth and remodeling model well suited for parametrically exploring multiple designs of external supports while accounting for mechanobiological and immunobiological responses of the supported native vessel. These results suggest that a load bearing external support can reduce vessel thickening in response to pressure elevation. Results also suggest that the final adaptive state of the vessel depends on the structural stiffness of the support via a mechano-driven adaptation, although luminal encroachment may be a complication in the presence of chronic inflammation. Finally, the supported vessel can stiffen (structurally and materially) along circumferential and axial directions, which could have implications on overall hemodynamics and thus subsequent vascular remodeling. The proposed framework can provide valuable insights into vascular adaptation in the presence of external support, accelerate rational design, and aid translation of this emerging approach.

Keywords: external support, graft, computational modeling, inflammation, growth and remodeling

1. Introduction

Many medical devices have been designed to augment vascular function in disease and injury. External support is a promising medical technology that has found applications in multiple clinical scenarios, including aortic dilatation [1], Marfan syndrome [2, 3], the Ross procedure [4, 5], vein graft disease [6–8], and tissue engineering [9]. The objective of external support in each of these applications is

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different - for example, it can maintain valve function and prevent over distension and rupture in Marfan syndrome, provide structural reinforcement against elevated pressure and flow in a vein graft, and reduce the potential of collapse in a tissue engineered trachea. A common underlying theme across these applications is the complex interaction between a foreign body and a soft tissue in the presence of a potentially altered mechanical environment. Multiple animal studies and human trials have reported results superior to standard care/sham controls [2, 4, 5, 8, 10] while other human studies have been disappointing [11]. We still lack a fundamental understanding of the effect of both the foreign body response and the altered mechanical loading on acute and chronic remodeling of the vessel. There is, therefore, a pressing need for a systematic approach to the design of these supports. To that end we propose a computational bilayered model that can simulate mechano-adaptation of a vessel in the presence of an external support that promotes inflammation. Motivated by our prior work [12] and availability of experimental data [13], we use a C57BL6/J murine descending thoracic aorta as our model system.

2. Methods

2.1. Bilayered Growth and Remodeling Theory

Mechano-adaptation in the presence of an external support is modeled using a bilayered constrained mixture theory of soft tissue growth (change in mass) and remodeling (change in structure), denoted herein as G&R [12, 14]. Global equilibrium equations for the bilayered construct, at each G&R time s , expressed in terms of layer-specific mean stresses, are given by [12, 14],

$$\sigma_{V\theta\theta}h_V + \sigma_{S\theta\theta}h_S = Pa, \quad (1)$$

$$\sigma_{Vzz}\pi h_V(2a + h_V) + \sigma_{Szz}\pi h_S(2a + 2h_V + h_S) = f_z, \quad (2)$$

along the circumferential (θ) and axial (z) directions, respectively; P is transmural pressure, f_z axial force, a luminal radius, and h_V and h_S the thickness of the vessel (V) and external support (S), respectively. Each layer is modeled as an independent constrained mixture of multiple structurally significant constituents [15] with its own local variables. Layer-specific Cauchy stress, at any G&R time s , is

$$\boldsymbol{\sigma}_\Gamma(s) = \sum_{\alpha=1}^{N_\Gamma} \boldsymbol{\sigma}_\Gamma^\alpha(s) - p_\Gamma(s)\mathbf{I}, \quad (3)$$

wherein both layers ($\Gamma = V, S$) are assumed to be incompressible under transient loading, enforced through a respective layer-specific Lagrange multiplier p_Γ , while the mixture as a whole can change mass/volume with G&R; $\boldsymbol{\sigma}$ is the Cauchy stress, with $\alpha = 1, \dots, N_\Gamma$ denoting structurally significant constituents within each layer.

The mechanical contribution of constituent α to the layer-specific Cauchy stress at the mixture level is then given by [12],

$$\boldsymbol{\sigma}_\Gamma^\alpha(s) = \frac{1}{\rho} \int_{-\infty}^s m_\Gamma^\alpha(\tau) q_\Gamma^\alpha(s, \tau) \widehat{\boldsymbol{\sigma}}_\Gamma^\alpha(s, \tau) d\tau \quad (4)$$

where $\tau \in [0, s]$ is the G&R time at which a constituent is deposited following a perturbation at G&R time 0, with the initial homeostatic state established between some distant past time $-\infty$ and 0; $m_\Gamma^\alpha(\tau) \geq 0$ governs layer-specific constituent mass production per unit current volume per time and $q_\Gamma^\alpha(s, \tau) \in [0, 1]$ governs constituent removal (see equations (12) and (13) for particularization details) and ρ is the total mass density [16]; the symbol $\hat{\cdot}$ is used to distinguish variables defined at constituent level (e.g. $\hat{\boldsymbol{\sigma}}$) from variables defined at mixture level (e.g. $\boldsymbol{\sigma}$). $\hat{\boldsymbol{\sigma}}_\Gamma^\alpha(s, \tau)$ is Cauchy stress at the constituent level,

$$\hat{\boldsymbol{\sigma}}_\Gamma^\alpha(s, \tau) = \frac{1}{J_{\Gamma n(\tau)}^\alpha(s)} \mathbf{F}_{\Gamma n(\tau)}^\alpha(s) \hat{\mathbf{S}}_\Gamma^\alpha(\mathbf{C}_{\Gamma n(\tau)}^\alpha(s)) \mathbf{F}_{\Gamma n(\tau)}^{\alpha T}(s), \quad (5)$$

where $\mathbf{C}_{\Gamma n(\tau)}^\alpha(s) = \mathbf{F}_{\Gamma n(\tau)}^{\alpha T}(s) \mathbf{F}_{\Gamma n(\tau)}^\alpha(s)$ and $\mathbf{F}_{\Gamma n(\tau)}^\alpha(s) = \mathbf{F}_\Gamma(s) \mathbf{F}_\Gamma^{-1}(\tau) \mathbf{G}_\Gamma^\alpha(\tau)$ [17]. Here, \mathbf{F}_Γ maps differential position vectors from a reference configuration to the in vivo loaded mixture configurations at G&R time τ when new material is deposited or the current G&R time s . \mathbf{G}_Γ^α is the deposition stretch at which constituent α is incorporated within the mixture, and $J_{\Gamma n(\tau)}^\alpha(s) = \det(\mathbf{F}_{\Gamma n(\tau)}^\alpha(s)) = J_\Gamma(s)/J_\Gamma(\tau)$ [18]. Moreover, $\hat{\mathbf{S}}_\Gamma$ represents the constituent and layer-specific second Piola-Kirchhoff stress determined with respect to potentially evolving natural configuration $n(\tau)$ from a stored energy function \widehat{W}^α as [12, 14],

$$\hat{\mathbf{S}}_\Gamma^\alpha(\mathbf{C}_{\Gamma n(\tau)}^\alpha(s)) = 2 \frac{\partial \widehat{W}^\alpha(\mathbf{C}_{\Gamma n(\tau)}^\alpha(s))}{\partial \mathbf{C}_{\Gamma n(\tau)}^\alpha(s)}. \quad (6)$$

Mass fractions satisfy the constraints,

$$\sum_{\alpha=1}^{N_\Gamma} \phi_\Gamma^\alpha = \sum_{\alpha=1}^{N_\Gamma} \frac{\rho_\Gamma^\alpha}{\rho_\Gamma} = 1, \quad (7)$$

and, consistent with equation (4), current mass density ($\rho_\Gamma^\alpha(s) = \rho_{\Gamma R}^\alpha(s)/J_\Gamma(s)$) evolves according to

$$\rho_\Gamma^\alpha(s) = \int_{-\infty}^s \frac{J_\Gamma(\tau)}{J_\Gamma(s)} m_\Gamma^\alpha(\tau) q_\Gamma^\alpha(s, \tau) d\tau. \quad (8)$$

2.2. Particularization for a native vessel with external support

The bilayered construct consists of a native vessel (V) as the inner layer and external support (S) as the outer layer (Figure 1). Based on prior work [16, 19], we assume that the vessel is a mixture of structurally significant constituents: elastic fiber-dominated (e), collagen fiber-dominated (c), and smooth muscle cells (m). For illustrative purposes, we assume the external support is made of a single synthetic constituent (e.g. polymer, $\alpha = p$), though the theory is general enough to accommodate multiple constituents, including co-polymer blends. The media and adventitia of the native vascular wall [12] have been homogenized through the thickness and are considered as a unilayered structure here (inner layer, $\Gamma = V$), not due to a limitation of the theory but rather a paucity of data on differential medial and adventitial

remodeling in mice in the presence of an external polymeric support.

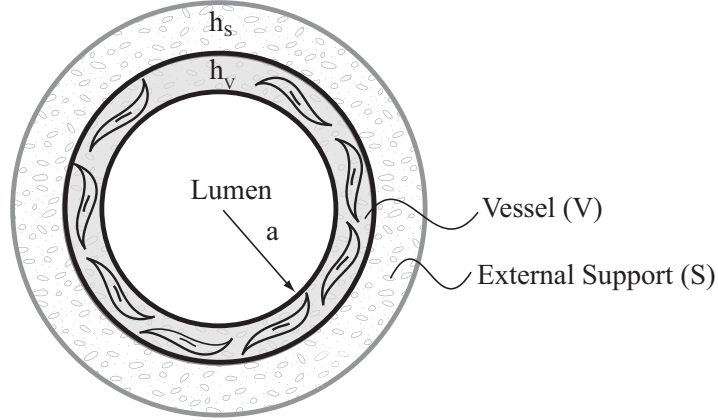


Figure 1: Bilayered construct with a homogenized native vessel (V) as the inner layer and a polymeric external support (S) as the outer layer. Total wall thickness $h = h_V + h_S$. It is assumed that the external support runs the length of the vessel segment of interest without affecting the in vivo axial stretch of the native vessel, which is the stretch at which the axial force does not change when the vessel is pressurized cyclically near the in vivo value.

In the inner layer, the stored energy for the elastin-dominated isotropic behavior is assumed to be of a neoHookean form,

$$\widehat{W}^e(\mathbf{C}_\Gamma^e(s)) = \frac{c^e}{2}(\text{tr}(\mathbf{C}_\Gamma^e) - 3), \quad (9)$$

where $\text{tr}(\mathbf{C}_\Gamma^e)$ is the layer-specific first invariant of the right Cauchy-Green tensor for elastin and c^e is the elastin-dominated material parameter. Smooth muscle and collagen-dominated anisotropic behaviors are assumed to be described by a ‘Fung-type’ exponential form,

$$\widehat{W}^\alpha(\lambda_{n(\tau)}^\alpha(s)) = \frac{c_1^\alpha}{4c_2^\alpha}(e^{c_2^\alpha(\lambda_{n(\tau)}^\alpha - 1)^2} - 1), \quad \alpha = c, m, \quad (10)$$

where $\lambda_{n(\tau)}^\alpha(s)$ is the current constituent-specific stretch [16, 17], with c_1^α and c_2^α the corresponding constituent-specific material parameters.

For illustration, the external support is modeled using a neoHookean form,

$$\widehat{W}^p(\mathbf{C}_\Gamma^p(s)) = \frac{c^p}{2}(\text{tr}(\mathbf{C}_\Gamma^p) - 3). \quad (11)$$

where c^p is the shear modulus of the synthetic material [20], for simplicity held constant over time.

For the vessel, $\Gamma \equiv V$, in equations (4) and (8), we assume a mass production function of the form [12, 16]

$$m_V^\alpha(\tau) = k_V^\alpha(\tau)\rho_V^\alpha(\tau)(1 + K_{V\sigma}^\alpha\Delta\sigma(\tau) - K_{V\tau}^\alpha\Delta\tau_w(\tau) + K_{V\varphi}^\alpha\Delta\varphi(\tau)), \quad (12)$$

which is modulated by three factors: changes in pressure-induced wall stress from homeostatic values ($\Delta\sigma$), flow-induced wall shear stress from homeostatic values

$(\Delta\tau_w)$, and a foreign body response induced inflammatory burden $(\Delta\rho_\varphi)$, assuming that the basal inflammatory state is negligible; $k_V^\alpha(\tau)\rho_V^\alpha$ represents a basal production rate of constituent α in vivo, written in terms of a basal rate parameter for removal and the mass density **which automatically satisfies the condition of perfectly matched production and removal at the homeostatic state** [18]. Note that in the absence of mechanical and inflammatory perturbations, or, more generally, for any state under mechanobiological equilibrium [14], the term within bracket reduces to 1, and one recovers **the homeostatic values. Note, further, that dividing the mass production by its basal value yields the fold-change, as frequently reported in vascular biology studies.** Constituent removal, in equations (4) and (8), is assumed to follow first-order kinetics given by the decay function

$$q_V^\alpha(s, \tau) = \exp\left(-\int_\tau^s k_V^\alpha(t) dt\right), \quad (13)$$

where k_V^α is a rate parameter for removal (assumed constant herein for illustrative purposes) while $K_{V\sigma}^\alpha, K_{V\tau}^\alpha$ and $K_{V\varphi}^\alpha$ in equation (12) are non-dimensional gain parameters that modulate the response to deviations in wall stress (σ), shear stress (τ_w), and inflammation (ρ_φ) from homeostatic values, respectively. The deviations from homeostatic stress values are defined as,

$$\Delta\sigma = \frac{\sigma_{V\theta\theta} + \sigma_{Vzz}}{\sigma_{V\theta\theta o} + \sigma_{Vzz o}} - 1 \quad \text{and} \quad \Delta\tau_w = \frac{\tau_w}{\tau_{wo}} - 1 \quad (14)$$

where subscript o denotes an original homeostatic value. The total mass density ($\rho = \Sigma\rho_V^\alpha$) of the vessel remains constant for all G&R times s . Despite evidence of cellular infiltration and proliferation in some external supports [8, 10], data are not sufficient to quantify inflammatory pathways or to build a mechanistic model of inflammation-mediated neotissue deposition in or encapsulation of an external support. One could use inflammatory cell density relative to its maximum possible density to quantify inflammatory responses [12] - where a homeostatic condition with no external support (i.e., no inflammation) corresponds to $\Delta\rho_\varphi = 0$ and maximum inflammation corresponds to $\Delta\rho_\varphi = 1$. Since no such measurements were available for an external support application, we phenomenologically explore different inflammatory responses within the vessel ($\Delta\rho_\varphi$) which can be broadly classified into an acute response (modeled using a gamma function, Figure 2a, [21]), a chronic response (modeled using a sigmoid function, Figure 2b, [22]), or an acute followed by a persistent chronic response (modeled using a linear combination of the gamma and sigmoid functions, Figure 2c). Material properties of the constituents are assumed to be unchanged in the presence of inflammation due, in part, to lack of data (unlike in [12, 23]). Since synthetic material is not produced in vivo, $m_S^p = 0$, with superscript p denoting polymer. The referential mass density of the synthetic material is held constant for nondegradable support simulations. For degradable support, referential density is reduced according to a sigmoidal function [21].

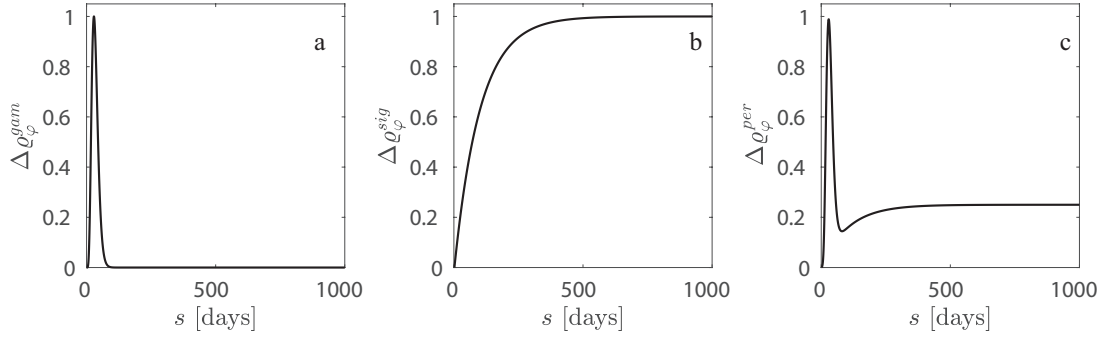


Figure 2: Phenomenologically modeled inflammatory responses include a) an acute response, b) a chronic response, and c) an acute response followed by a persistent residual inflammation.

Parameter	Symbol	Value
Arterial mass density	ρ	1050 kg/m^3
Original inner vessel radius	r_{io}^V	0.6468 mm
Original outer vessel radius	r_{oo}^V	0.6870 mm
Elastin material parameter	c^e	89.71 kPa
Collagen material parameters	c_1^c, c_2^c	234.9 kPa, 4.080
Smooth muscle material parameters	c_1^m, c_2^m	261.4kPa, 0.24
Collagen diagonal fiber orientation	α	29.91°
Elastin prestretch parameters	G_θ^e, G_z^e, G_r^e	1.90, 1.62, $1/(G_\theta^e G_z^e)$
Prestretch parameters	G^m, G^c	1.20, 1.25
Collagen gains	$K_\sigma^c, K_\tau^c, K_\phi^c$	2.0, 2.5, 1
Smooth muscle gains	$K_\sigma^m, K_\tau^m, K_\phi^m$	$0.8K_\sigma^c, 0.8K_\tau^c, 0.8K_\phi^c$
Mass fractions	$\phi^e, \phi^m, \phi_z^c, 2\phi_d^c$	0.252 0.263 0.034 0.451
Mass removal rates	k^m, k^c	1/80, 1/80 day^{-1}

Table 1: Values of model parameters used in the G&R simulations - parameters were fit to experimental data from [13] and details of the fit can be found in the appendix of [12], albeit for a bilayered vessel (media and adventitia). Here we adapt it to model a unilayered vessel. Note that contributions from collagen and smooth muscle in the circumferential direction are physically indistinguishable, hence material parameters in the circumferential direction were melded.

2.3. Simulation Setup

An integro-differential system of equations that constitutes equilibrium equations (2) and (3), complemented with constitutive equations for constituent stresses (4) and mass densities (8) within a constrained mixture of constituents (3) and (7), and the layer-specific Jacobian (that relates mass densities to the cylindrical geometry through layer-specific stretches) were solved numerically. Formulations were implemented in a MATLAB (R2017a) numerical environment. At the initial time ($s = 0$), the native vessel is at its basal loaded state ($P_o \approx 97$ mmHg, consistent with parameters in Table 1) and external support is oversized with no vessel contact. At every time step we check if the outer radius of the vessel \geq inner radius of external support. Once contact is detected we solve a bilayered equilibrium equation with external support as the outer layer. External support is load bearing only when pressure is increased above a certain threshold (set to $\approx 5\%$ above basal) to

avoid a self-compensatory regime of adaptation [24]. To simulate preemptive treatment, we setup the simulation for the basal conditions and then subject the vessel to pressure elevation. We choose a representative 1.5 fold increase in pressure for our simulations, as the insult is severe enough to show qualitatively the utility of the framework. The thickness of the external support is 25% of the initial loaded thickness of the vessel, unless mentioned otherwise. The material and G&R parameters for the vessel have been adapted (homogenized through the thickness) from our previous work on the murine thoracic aorta (Table 1), which included validations against multiple data sets [12].

3. Results

3.1. Effect of Support Stiffness - Nondegradable Support, No Inflammation

Prior applications have used materials ranging from natural tissue to synthetic polymers [2, 4, 8, 10, 25] as external supports. We simulate mechano-adaptation of a native vessel to simulated pressure elevation in the presence of an external support with modulus c^p equal to 1, 10, 100 and 1000 times the modulus of elastin (c^e), to reflect the wide range of potential materials (Figure 3). The acute pressure-distended radius of the vessel drops with increasing stiffness of the external support as it constrains overdilation of the vessel (Figure 3b). Interestingly, long term radius returns to normal values in all cases. An inverse relation is observed between final wall thickness and support modulus (Figure 3c) as the load-bearing external support offloads the underlying vessel (Figure 3f and h). The vessel is yet able to recover its homeostatic stress state along both axial and circumferential directions independent of the stiffness of the external support (Figure 3e and g). Adaptation of the vascular wall in the presence of a thin-stiff support ($c^p = 40c^e, h_S = 0.25h_V$) is similar to that for a thick-compliant support ($c^p = 10c^e, h_S = h_V$), suggesting the final configuration of the vessel in a mechano-driven adaptation is governed by the structural stiffness of the external support (Figure 4) rather than material stiffness (Figure 3) or thickness (Figure A1).

3.2. Degradation of the External Support - No Inflammation

Biodegradable external supports have proved promising, and in some cases superior to nondegradable ones [8]. To simulate adaptation of a vessel in response to a pressure elevation in the presence of a biodegradable external support, we considered three representative degradation profiles: slow ($\approx 25\%$ degradation in 2000 days), medium ($\approx 100\%$ degradation in 2000 days), and fast (100% degradation in ≈ 100 days). We choose a support modulus 10x greater than that of elastin and a 1.5 fold increase in pressure to illustrate the results; the remaining parameters are the same as in previous simulations.

The degradation profile of the external support dictates the kinetics of adaptation (Figure 5) but not the final resolved stress state of the vessel, which remains the same in all cases because of the overall homeostatic tendency in the absence of inflammation [12, 23]. For example, the change in thickness is more gradual in a moderate degradation case (Figure 5 b) and could be physiologically more favorable

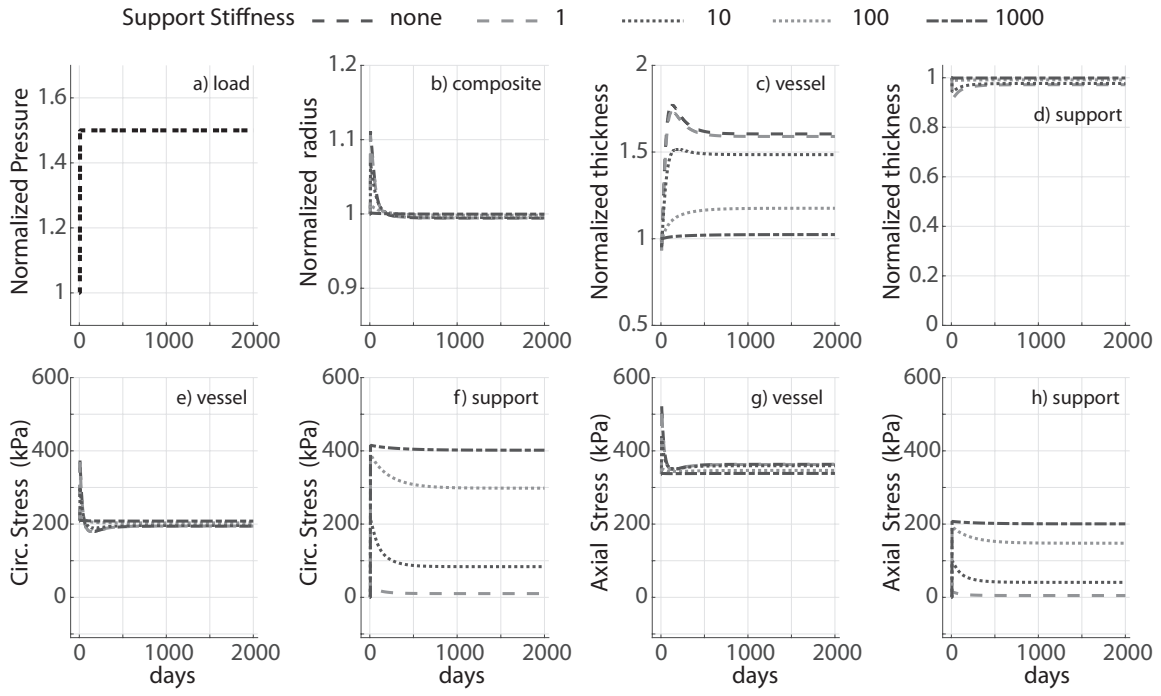


Figure 3: Evolution of the prescribed luminal pressure (a) and predicted responses: luminal radius (b), wall thickness (c and d), circumferential and axial stress in the native vessel (e and g) and nondegradable external support (f and h) for a 1.5 fold increase in pressure. Results compare supports with four different values of stiffness (fold change of 1, 10, 100 and 1000 with respect to c^e). Adaptation without an external support ('none') is shown for reference. Pressure, radius, and thickness are normalized by respective initial values.

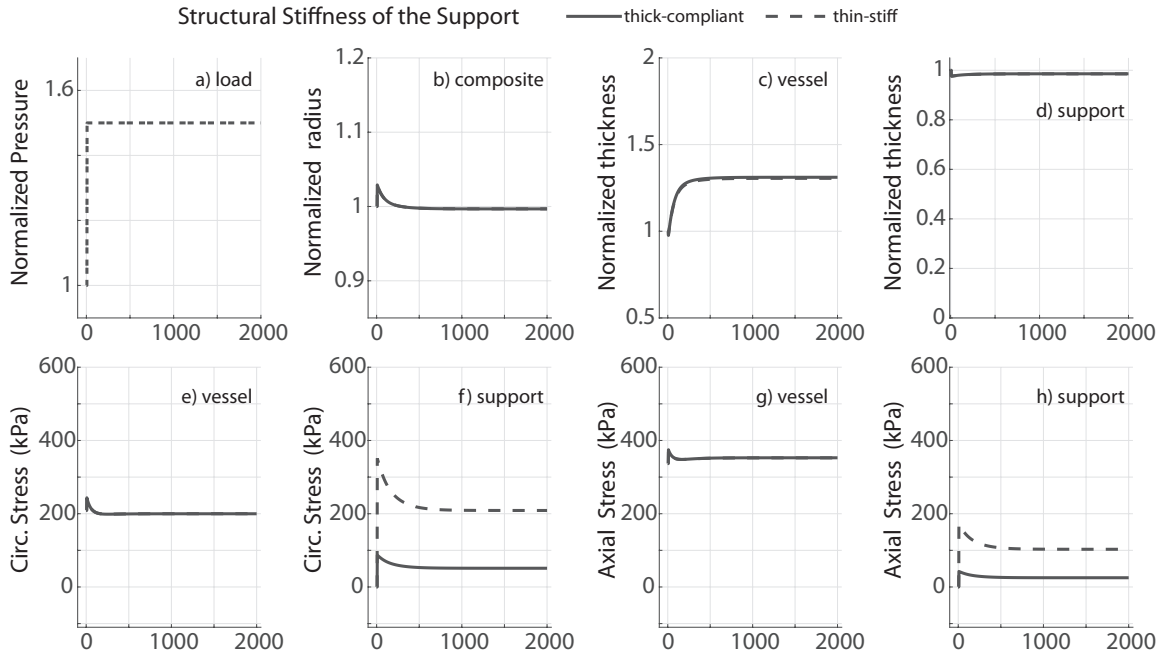


Figure 4: Prescribed pressure (a) and predicted evolving responses: luminal radius (b), thickness (c and d), circumferential and axial stress in the vessel (e and g) and nondegradable external support (f and h) for a 1.5 fold change in pressure. Results compare adaptation of the vessel in the presence of a thin-stiff support ($c^p = 40c^e$, $h_S = 0.25h_V$) or a thick-compliant support ($c^p = 10c^e$, $h_S = h_V$). Pressure, radius and thickness are normalized by respective initial values.

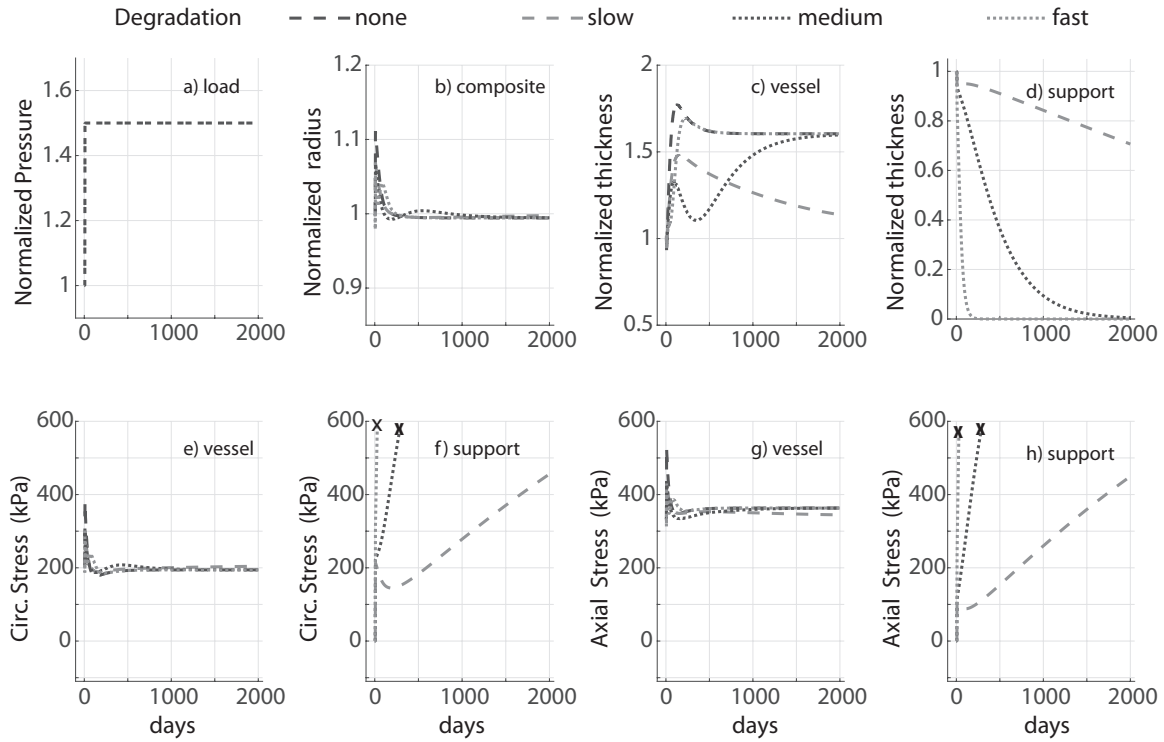


Figure 5: Prescribed pressure (a) and predicted evolving responses: luminal radius (b), thickness (c and d), and circumferential and axial stress in the vessel (e and g) for a 1.5 fold increase in pressure. Degradable materials lose load-bearing ability well before full degradation, so the stress curves for external support are truncated at $\approx 60\%$ degradation (denoted by \times). Results compare external supports with three different degradation profiles (slow, moderate, and fast). The modulus of the support $c^p = 10c^e$. Adaptation without an external support (‘none’) is shown for reference. Pressure, radius and thickness are normalized by respective initial values.

as it allows the vessel sufficient time to produce matrix. Not surprisingly, the final vessel thickness depends on the degradation profile of the support if it is not fully degraded. For a full degradation at $s = 2000$ days, in the absence of inflammation, the vessel mechano-adapts to the same thickness as in a no external support case (Figure 5 c, ‘medium’ and ‘fast’). In all simulations, the homeostatic state is recovered in both the axial and circumferential directions (Figure 5 e and f). In a physiological setting, external support is accompanied by neotissue formation which we have not modeled here [3, 8]. Hence these simulations highlight only some contributors to the response.

3.3. Effect of Inflammation and Support Degradation

Adaptation for a 1.5-fold increase in pressure in the presence of inflammation for a degradable external support with $c^p = 10c^e$ and a slow degradation profile for the support ($\approx 25\%$ degradation in 2000 days) is shown in Figure 6. The adaptation differs drastically across different inflammatory burdens. In particular, in both the chronic (sigmoid) and persistent case, luminal radius drops below the original value (Figure 6 b). In this case both an increase in transmural pressure and inflammation can lead to luminal encroachment. The axial and circumferential stresses are nevertheless restored to their homeostatic values in all of the simulated cases

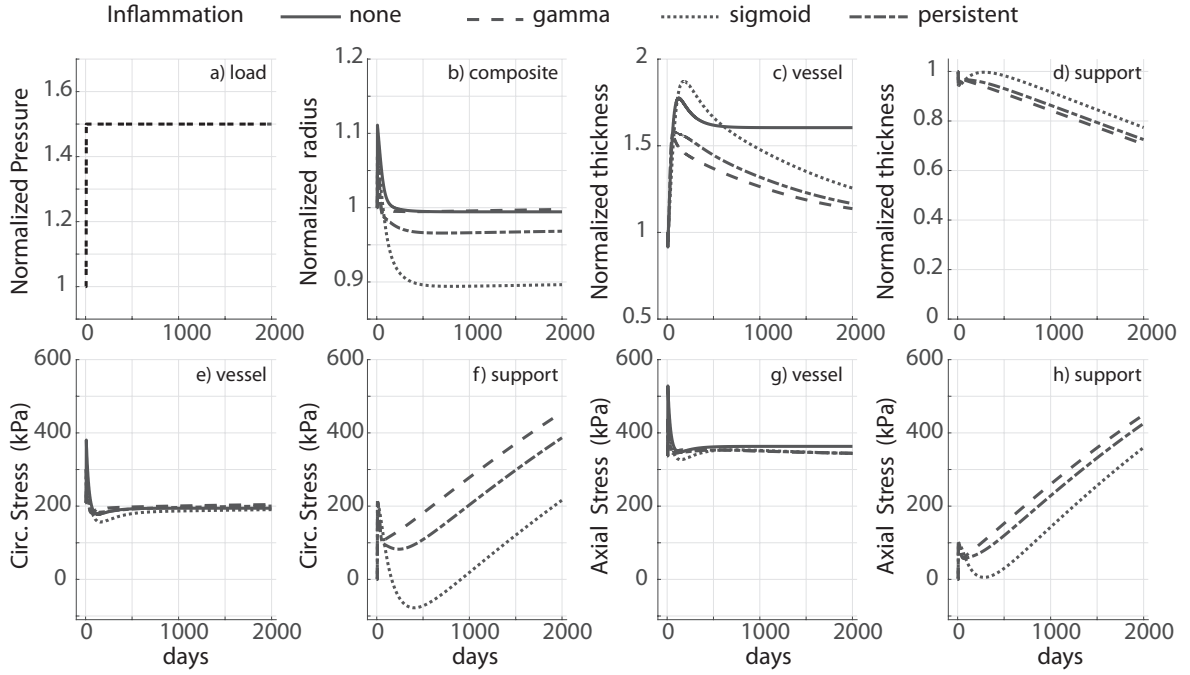


Figure 6: Prescribed pressure (a) and predicted evolving responses: luminal radius (b), thickness (c and d), circumferential and axial stress in the vessel (e and g) and degradable external support (f and h) with a slow degradation profile, for a 1.5-fold change in pressure. Results compare responses to different inflammatory stimuli (gamma, sigmoid and persistent). The modulus of the external support $c^p = 10c^e$. Adaptation without an external support ('none') is shown for reference, noting further the absence of inflammation in the absence of the foreign body. Pressure, radius and thickness are normalized by respective initial values.

(Figure 6e and g, also see Figure A2) though thickness is not resolved to its mechano-adaptive value yet at $s = 2000$ days, consistent with the response in Figure 5 for a slow degradation profile. Thickness evolution for fast and moderate degradation is reported in Figure A3. Predicted structural and material behaviors during numerically simulated biaxial tests for the bilayered construct in the presence and absence of inflammation are summarized in Figure 7; the corresponding prediction for a native vessel without external support, in a mechano-driven G&R adaptation, is provided for reference (Figure 7 a-d). Notice that the composite vessel-support exhibits stiffened pressure-diameter, axial force-stretch, and stress-stretch behaviors compared to the native vessel, consistent with an overall stiffening behavior (Figure 7 e-p). Noting the differences in evolving structural and material behaviors between the degradable (Figure 7 i-l) and non-degradable (Figure 7 e-h) supports, the final adaptive state is more extensible (Figure 7 j and l) and distensible (Figure 7 i and k) in the degradable case. Moreover, the structural response is more compliant with degradation of the support (Figure 7 i and j) tending towards a hypertensive mechano-driven native vessel adaptation. Improved adaptations with a degradable support are abated, however, in the presence of inflammation (Figure 7 m-p). Additional stiffening in the chronic inflammation case can be attributed to additional mass in the construct due to inflammation.

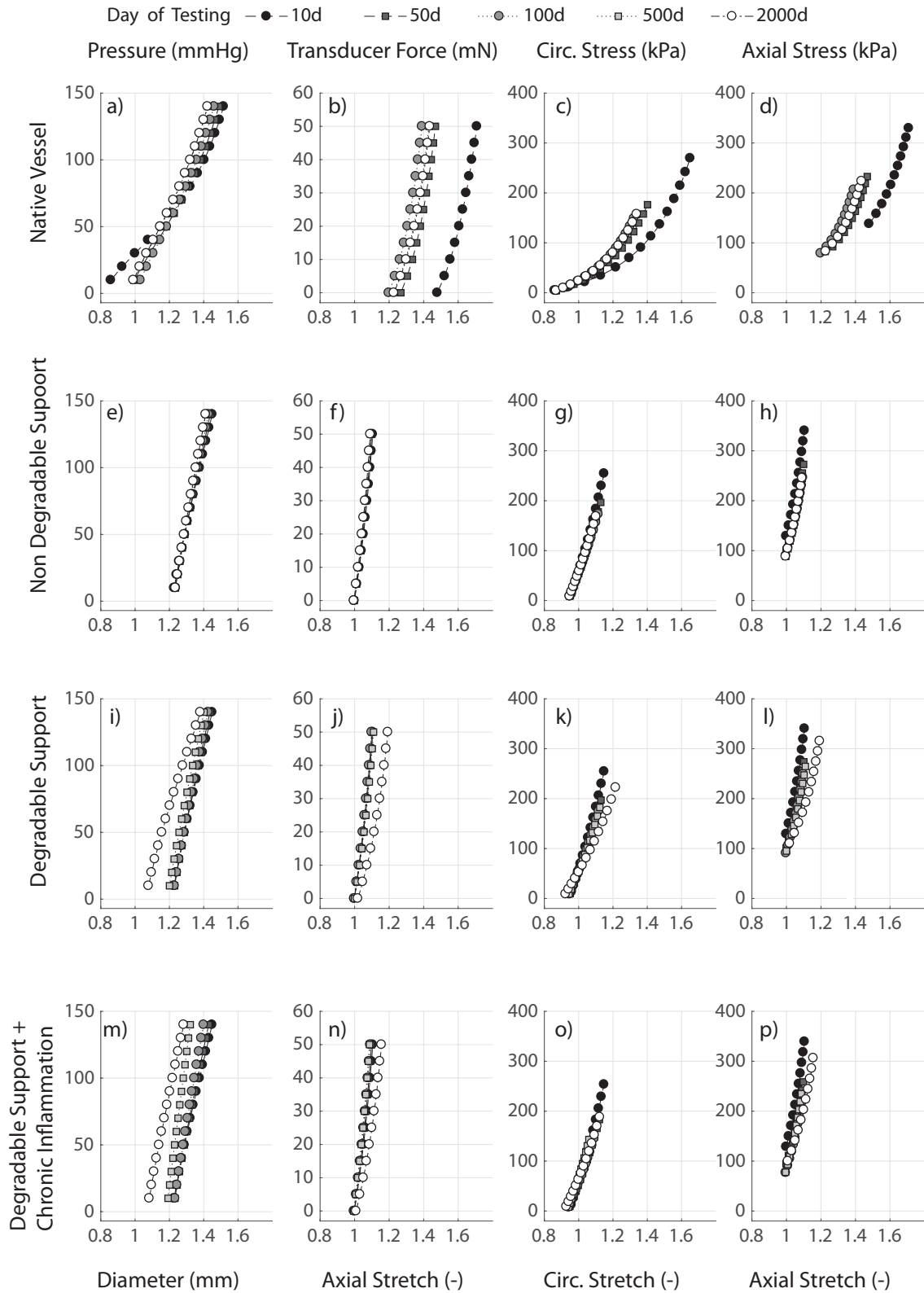


Figure 7: Simulated pressure-outer diameter, axial force-stretch, and circumferential and axial stress-stretch behavior for a native vessel with no external support (a-d), with a non-degradable external support (e-h), degradable support (i-l), and degradable support with a persistent (sigmoid-type) inflammatory burden (m-p), all at 10, 50, 100, 500 and 2000 days. Simulations are reported for an external support with $c^p = 10c^e$, $h_S = 0.25h_V$ and, where applicable, a slow degradation profile.

4. Discussion

Despite significant advances in both the development of new synthetic biomaterials and tissue engineering, transplant of autologous vessels remains the mainstay of vascular grafting procedures. The short- and long-term performance of these grafts is far from ideal [26–28], however, and the community continues to explore new avenues for augmenting graft adaptation. Of these, though still under evaluation, external support has emerged as a promising strategy [29]. While the need for better designed external supports has been widely accepted, a rational approach has yet to emerge ([30] being a notable exception). The present computational model of G&R in the presence of an external support may be a step in that direction.

This model yielded several insights into vessel adaptation in the presence of an external support. For example, the model shows how a load-bearing external support can offload the vessel, thus ameliorating the compensatory increase in thickness to reach a homeostatic state in the presence of a sustained increase in pressure (Figure 3). Further, the adaptation can be similar for thin-stiff and thick-compliant external supports, suggesting that the final state in a mechano-mediated adaptation depends on structural stiffness of the support, provided that peri-support biological responses are similar (Figure 4). That the circumferential stress state in a ‘thin-stiff’ case (Figure 4 f) reached a value that was close to the homeostatic state suggests the stress state in the presence of an external support could be an important parameter in the design of porous scaffolds, as it might aid or abate tissue ingrowth.

Simulations suggest possible luminal encroachment in the presence of slow degradation and a long-term inflammatory burden, which could require additional intervention or pharmacological treatment (Figure 6). Recalling previously observed adaptations in systemic hypertension with inflammation, where one observes exuberant thickening of the wall and a failure to restore homeostatic wall stress [13, 23], the current predictions suggest possible adaptations in the presence of external support that restore both circumferential and axial stress to homeostatic values even in the presence of chronic inflammation, a surprising result. Note, therefore, that the mass production function (equation 12) has contributions from wall stress, wall shear stress, and inflammation; these three stimuli need to balance to restore basal production. As the circumferential and axial stress are eventually restored to homeostatic values, our simulations suggest that the contribution from the shear stimulus counteracts the contribution from chronic inflammation. Although increased wall shear stresses should upregulate nitric oxide, which is anti-inflammatory, this requires a functional endothelium. Clearly, experimental studies are needed to study this model-generated hypotheses. The simulations nevertheless highlight the fact that there is a cost associated with inflammation [31, 32], in this case luminal encroachment. Other aspects of the model and its predictions demand experimental study. We assumed that the material properties of the matrix produced and deposited within the mixture are constant through the simulation though it is likely that the “inflammatory matrix” is stiffer. We also assumed that the preferred homeostatic stress state remains the same in the presence of external support or inflammation, yet it is possible that inflammation changes both the homeostatic set-points as well as other G&R parameters [23]. Again, more data will be needed to evaluate these and other aspects of the model.

Finally, our simulations draw attention to an often overlooked, but important, biaxial coupling between axial and circumferential loading in vivo [33]. The external support shifts the operating material and structural behavior of the construct leftwards at higher stretches for both the axial and the circumferential directions (Figure 7). Many vascular pathologies, including elastin deficiency and damage, hypertension, and ageing, exhibit a drop in the in vivo axial stretch and a leftward shift in the structural and material behavior [33]. Whether a leftward shift in these stress-stretch behaviors due to external support triggers a maladaptive response requires further investigation. Modeling the complex interplay amongst mechano-mediated adaptation, scaffold degradation profiles, and inflammatory burden and its influence on the long-term geometry, stress state, and composition of the vessel is nonetheless a novel application of the model and could motivate further hypothesis testing.

In treating Marfan syndrome or performing a Ross procedure, external support can be preemptive, preventing root dilatation and rupture and preserving valve function [29]. Several studies of external support have demonstrated short-term and long-term benefits of these procedures in both animal models and humans [2, 3, 34–36]. Among other advantages, external support can prevent dilatation and ameliorate thickening of the wall, thus preventing stretch-induced activation of monocytes and inflammation [25] and dysfunctional mechanosensing due to thickening. Prevention of overdistension and reduced thickening are captured qualitatively in our simulations (Figure 3). In contrast, however, there are also reports of the vessel thickening in the presence of external support due to neotissue formation and incorporation within the external support with effects on the adventitial tissue. We did not attempt to model such effects, but this would be possible given our prior simulations of in vivo neovessel development from degradable polymeric scaffolds [21, 37]. As a model should, the present simulations also identified important gaps in knowledge, including a lack of data on and understanding of inflammatory profiles in the presence and absence of biodegradable supports and different levels of pressure elevation **and how inflammation fundamentally affects mass turnover, that is, production and removal.**

The constitutive equations for mass production and removal (equation 12 and 13) are phenomenological and based on iterative refinement and success of our earlier work on vascular adaptations under diverse situations, including ageing, aneurysm, hypertension, vein graft modeling, and tissue engineering [12, 19, 22, 37, 38]. Basal mass production augmented with an additive stress- or inflammation-mediated term is perhaps the simplest way to capture the physiological effects of these stimuli. This simple form has proven sufficient in many cases and was adopted here. In particular, these stimulus functions for mass production provide a simple linear form (equation 14) that approximates a more general sigmoidal in vivo response, and is suitable for moderate perturbations. Sigmoidal or similar nonlinear functions would be needed to model more dramatic perturbations [22]. While these mass constitutive equations are generally valid and can also model atrophy (as observed in some instances of external support [36]), there is need for additional data (e.g. effect of external support sizing, mechanism of atrophy) and systematic parameter estimation to simulate atrophy with a bilayered theory.

We modeled the vessel as a single homogenous layer rather than modeling sep-

arate medial and adventitial remodeling. Residual stresses (captured here using prestretches in the homeostatic state) tend to homogenize the transmural distribution of wall stress; hence, estimates of mean wall stress are comparable in uni- and bi-layered models [39] thus allowing our mass production equations to be based on mean stress. Bilayered models of the vessel wall can better capture mechanobiological responses but there is not yet sufficient data on layer-specific stress states and responses, especially in the presence of an external support, to extend this model. Also, different materials and fabrication processes can induce nonlinearity and anisotropy in the external supports, none of which are considered in this first generation hyperelastic model. These could be potential extensions for the next generation model.

Nevertheless, we have shown how a relatively simple bilayered (vessel+support) growth and remodeling model can parametrically explore different effects of scaffold design and biological response – both mechanobiological and immunobiological. In combination with prior advances [21, 37], the present simulations suggest a way forward in the pursuit of improved external supports for diverse applications. Whereas we used material properties for a normal murine thoracic aorta for illustrative purposes, similar simulations can be specialized for diseased arteries (e.g. Marfan syndrome, [40]) as well as pulmonary arteries [4, 41] or veins placed within the systemic circulation or simply supported within their native circulations [38, 42]. Indeed, given that the research goal is different across applications, one will likely need to optimize each design according to different criteria, as, for example, radius, distensibility, structural strength, neotissue formation or reduced inflammatory response. A single, common computational framework, coupled with optimization algorithms [43], should accelerate the design process and aid translation for a truly ‘optimal’ longterm outcome.

5. Appendix

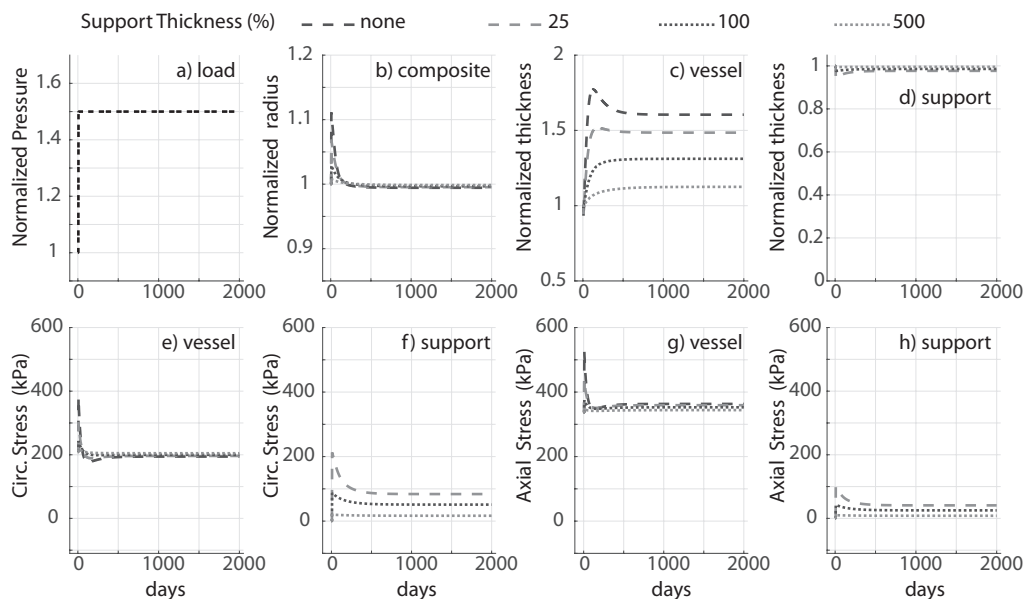


Figure A1: Prescribed pressure (a) and predicted evolving responses: luminal radius (b), thickness (c and d), circumferential and axial stress in the vessel (e and g) and degradable external support (f and h) for a 1.5-fold increase in pressure. Results for different initial values of the thickness (percent of vessel thickness) of the external polymeric support. Adaptation without an external support ('none') is shown for reference. Compare to Figure 3 (change in material stiffness) and Figure 4 (change in structural stiffness).

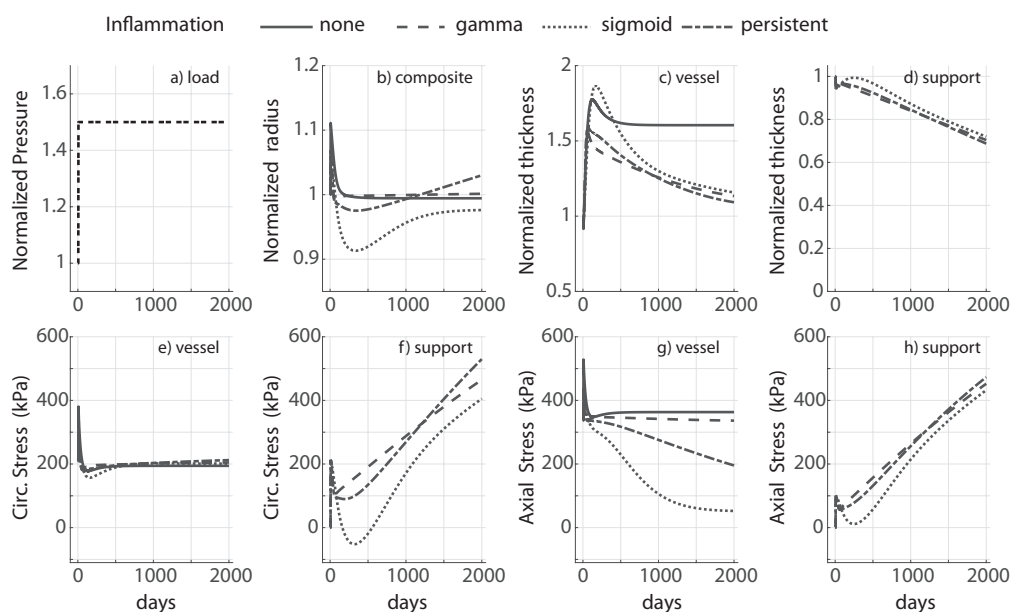


Figure A2: Prescribed pressure (a) and predicted evolving responses: luminal radius (b), thickness (c and d), circumferential and axial stress in native vessel (e and g) and degradable external support (f and h) with slow degradation profile, for a 1.5-fold increase in pressure. Results compare response to different inflammatory stimulus (gamma, sigmoid and persistent). In contrast to Figure 6, $K_{\varphi}^m/K_{\varphi}^c = 1$ in this case and notice the radius does not asymptote and axial homeostatic stress state is not restored for the sigmoid and persistent inflammation case. Modulus of external support $c^p = 10c^e$. Adaptation without an external support ('none') is shown for reference.

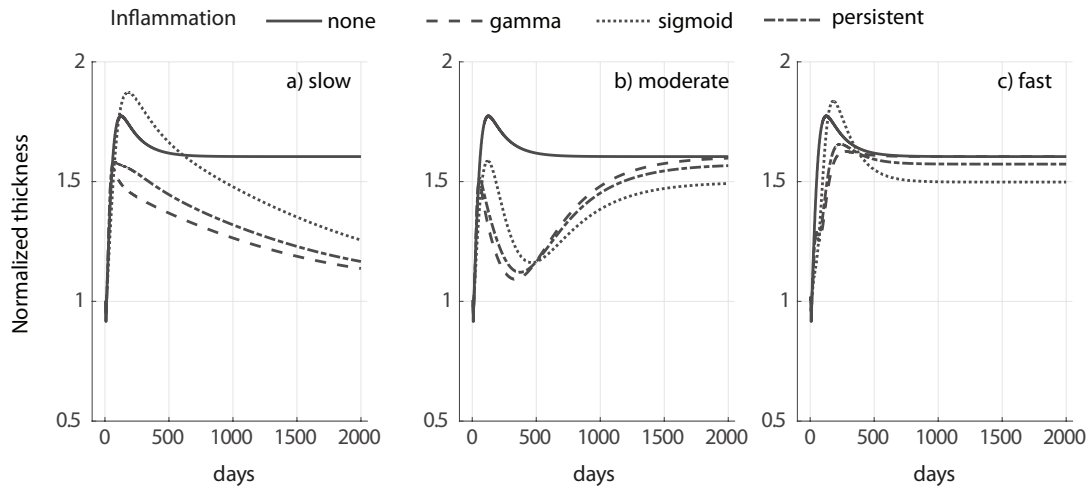


Figure A3: Evolution of native vessel thickness for a 1.5-fold increase in pressure and different inflammatory stimulus (gamma, sigmoid and persistent) for slow (a), moderate (b) and fast (c) degradation of an external polymeric support having a modulus $c^p = 10c^e$. Adaptation without an external support ('none') is shown for reference. Notice the different kinetics for the different degradation profiles. The circumferential and axial homeostatic stress states were restored in all the cases reported (similar to results in Figure 6).

6. Acknowledgements

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7. Competing Interests

All authors report no competing interests.

8. References

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Declaration of interests

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests:

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