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A Computational Model of Biochemomechanical Effects of Intraluminal Thrombus on the Enlargement of Abdominal Aortic Aneurysms

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Abstract

Abdominal aortic aneurysms (AAAs) typically develop an intraluminal thrombus (ILT), yet most computational models of AAAs have focused on either the mechanics of the wall or the hemodynamics within the lesion, both in the absence of ILT. In the few cases wherein ILT has been modeled directly, as, for example, in static models that focus on the state of stress in the aortic wall and the associated rupture risk, thrombus has been modeled as an inert, homogeneous, load-bearing material. Given the biochemomechanical complexity of an ILT, there is a pressing need to consider its diverse effects on the evolving aneurysmal wall. Herein, we present the first growth and remodeling model that addresses together the biomechanics, mechanobiology, and biochemistry of thrombus-laden AAAs. Whereas it has been shown that aneurysmal enlargement in the absence of ILT depends primarily on the stiffness and turnover of fibrillar collagen, we show that the presence of a thrombus within lesions having otherwise the same initial wall composition and properties can lead to either arrest or rupture depending on the biochemical effects (e.g., release of proteases) and biomechanical properties (e.g., stiffness of fibrin) of the ILT. These computational results suggest that ILT should be accounted for when predicting the potential enlargement or rupture risk of AAAs and highlight specific needs for further experimental and computational research.

Keywords

growth and remodeling; wall stress; proteolytic activity; elastin degradation; collagen remodeling

1. Introduction

Abdominal aortic aneurysms (AAAs) are focal dilatations of the infrarenal abdominal aorta that result primarily from an altered deposition and degradation of extracellular matrix.

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These lesions tend to enlarge over decades, but can rupture abruptly whenever wall stress exceeds wall strength. Although the pathogenesis is still not well understood, accumulating clinical, histopathological, mechanical, and cell biological data has enabled significant progress over the past 20 years in the biomechanical modeling of AAAs¹⁶. Nevertheless, an ability to predict whether a specific lesion will arrest, continue to enlarge either slowly or rapidly, or ultimately rupture remains wanting. Clinical interventions thus continue to be based on symptoms (e.g., pain) or simple metrics derived from imaging (e.g., the maximum dimension or expansion rate of the lesion) despite the observation that many small lesions rupture whereas some large lesions may remain asymptomatic³⁷. One possible reason for this variability in clinical outcomes is intraluminal thrombus (ILT). A large population-based study showed that all AAAs larger than 6 cm contain ILT, as do a majority of smaller lesions⁴. An ILT can have a complex natural history, composition, and microstructure; it can vary in thickness from a few millimeters to several centimeters and often be eccentric in shape. Whereas specific biochemical and biomechanical roles of ILT in the progression and potential rupture of AAAs remain controversial, computational models can help generate and test competing hypotheses and focus future experimentation. Such work is fundamental to understanding better how the evolving heterogeneous biochemomechanical properties of ILT can affect the natural history of the aneurysmal wall.

ILT within AAAs is a complex, fibrin-rich structure that shows few signs of healing by endothelial cell coverage or replacement of the fibrin network with collagen (cf. Franck et al.¹¹). Hemodynamics is likely a key factor in the development of ILT; complex vascular geometries lead to disturbed flows that can result in a shear-history induced platelet activation and endothelial dysfunction sufficient to develop thrombus⁷. Computational models that couple biochemical factors in blood clotting¹ with analyses of the complex hemodynamics²⁴ have promise to move us towards an integrated biochemomechanical understanding of mechanisms of ILT formation and progression⁵. We submit herein that similar models are needed to understand the effects of an evolving ILT on the wall of the AAA. Towards that end, note that the portion of ILT closest to the flowing blood (i.e., the luminal layer) is characterized by an aggregation of activated platelets as well as the entrapment of erythrocytes (RBCs) and leukocytes within an evolving fibrin mesh that appears to remodel continuously²⁵. Leukocytes within the luminal layer can produce matrix metalloproteinases (MMPs), serine proteases, urokinase plasmin activator (uPA), and other biologically active molecules. It is intuitive that this proteolytically active luminal layer can significantly affect the biochemical state of the underlying aortic wall, potentially leading to additional degradation and weakening⁴³. Because most cells and proteins within the ILT (e.g., platelets, neutrophils, macrophages, fibrinogen, and plasminogen) originate from the flowing blood, their concentrations are highest in the luminal layer (~2 mm), with a sharp decrease in the deeper layers of the ILT^{1,14}. In contrast, the degradation of fibrin tends to outpace its deposition in the deeper layers of thick thrombi, often referred to as medial (middle) and abluminal (next to the aneurysmal wall). These deeper layers are also mostly devoid of cells^{1,14}.

Thrombus was ignored in AAA modeling until 1993, when it was Inzoli et al.¹⁹ suggested that an ILT might mechanically shield the aortic wall from hemodynamic loads and thereby decrease the peak wall stress and associated rupture risk. This suggestion led to a number of

studies – some that rejected this concept³⁰, but many that supported it^{8,39}. It was recently suggested that the geometry of the ILT relative to the aneurysmal wall may further affect the peak value of wall stress and its location within the lesion²⁸. The hypothesis that the effects of ILT on AAAs are more than just mechanical is more recent, but there is vast and increasing evidence that ILT is biologically active^{4,23}. For example, an ILT recruits and entraps inflammatory cells that have proteolytic activity¹⁰, and it can decrease oxygen diffusion from the bloodstream to the underlying thrombus and aneurysmal wall³⁸. Clearly, proteolysis and hypoxia could contribute to the chronic inflammation characteristic of AAAs. There is, therefore, a pressing need for greater understanding. In particular, there is a need for increased insight into how biochemical and biomechanical properties of an ILT can influence the growth (G – that is, changes in mass) and remodeling (R – that is, changes in microstructure) of the aneurysmal wall.

The goal of this research was to develop a mathematically tractable, first generation G&R model of enlargement and possible rupture of thrombus-laden AAAs, including a framework for quantifying and predicting interrelationships between the biochemistry and biomechanics. Motivated by diverse experimental results from the literature⁴³, we developed a new model of thrombus progression and combined it with a previously proposed model⁴² of the evolving mechanical behavior of the aneurysmal abdominal aorta. Illustrative simulations that integrate biochemical and biomechanical effects of thrombus on the aortic wall reveal potentially important mechanisms by which some lesions may arrest while others may rupture. We submit that computational biochemomechanical G&R modeling has the promise to improve our understanding of the evolution of AAAs, to encourage the design of future experiments, and to move us closer to predicting patient-specific AAA enlargement and rupture risk.

2. Methods

Our primary goal was to develop a theoretical framework for modeling biochemomechanical interactions between the ILT and aneurysmal wall; that is, to develop and test constitutive assumptions. Hence, we employed an idealized geometry. Specifically, we assumed that AAAs initiate from aged non-aneurysmal aortas and focused on idealized axisymmetric, cylindrical geometries; effectively, this focused attention on the central region of a fusiform lesion. We also assumed that the luminal radius remained constant, meaning that additional ILT was deposited in every time step in which the aneurysm enlarged. These assumptions yielded a mathematically tractable initial-boundary value problem that allowed us to focus on the constitutive behaviors independent of complex changes in geometry. Moreover, it allowed a straightforward extension of an existing three-dimensional G&R model of an initially healthy aortic wall²⁰ to include a novel model of the biochemical and biomechanical effects of an ILT on the progression of an evolving aneurysm.

2.1. G&R model of the aortic wall

Growth and remodeling of the aortic wall was described using a continuum-based constrained mixture model of adaptation¹⁷. Specifically, the wall was assumed to behave initially as a constrained mixture of isotropic elastin, four predominant families of oriented

collagen fibers, and circumferential smooth muscle. Structurally significant elastin was assumed to be produced only during perinatal development, not maturity. Note that the aging of elastin is described not only by its mechanical properties, but also with its initial mass and prestretch. The initial state in these simulations corresponds to a 40-year-old patient, see Table 1. Hence, only the collagen and smooth muscle were allowed to turnover as the lesion enlarged. Original constituents k (elastin, four families of collagen fibers and smooth muscle cells) were incorporated within the wall at a prestretch $\mathbf{G}^k(0)$ at G&R time $\tau = 0$, while new materials were incorporated within extant matrix at each time step $\tau \in (0, s]$ via a deposition stretch $\mathbf{G}^k(\tau)$; see Figure 1 for the associated kinematics. Herein we assumed that $\mathbf{G}^k(\tau)$ was constant for all τ , though it may vary in disease.

The turnover of collagen and smooth muscle was defined by rates of production $\dot{m}^k$ and degradation. The latter was described using survival functions $q^k(s - \tau)$ that accounted for the percentage of constituent k produced at past time τ that remained at current time s . The mass of each constituent k thus evolved according to its individual production and removal rates, namely^{13,17}

$$M^k(s) = M^k(0) Q^k(s) + \int_0^s \dot{m}^k(\tau) q^k(s - \tau) d\tau, \quad (1)$$

where $M^k(s)$ and $M^k(0)$ are total (point-wise) masses of constituent k at current time s and initial time 0, respectively. The survival function q^k was modeled consistent with a first order decay, that is,

$$q^k(s - \tau) = \exp\left(-\int_{\tau}^s K^k(\tilde{\tau}) d\tilde{\tau}\right), \quad (2)$$

where K^k is a rate-type parameter for mass removal. Note that $Q^k(s)$ represents a special case, at $\tau = 0$, such that $Q^k(s) = q^k(s-0)$.

We assumed that G&R of the aortic wall is driven, in large part, by deviations in wall stress from a homeostatic target $\|\mathbf{t}_h^k\|$, which represents the norm of the homeostatic Cauchy stress tensor. The mechanobiologically driven rate of mass production $\dot{m}^k(\tau)$ of each constituent k was thus defined as a function of the basal production rate m_B^k and changes in Cauchy stress $\mathbf{t}^k$ relative to the homeostatic value:

$$\dot{m}^k(\tau) = m_B^k \left(1 + K_{\sigma}^k \frac{\|\mathbf{t}^k(\tau)\| - \|\mathbf{t}_h^k\|}{\|\mathbf{t}_h^k\|} \right). \quad (3)$$

K_{σ}^k is rate parameter governing constituent level stress-driven mass production.

The Cauchy stress $\mathbf{t}$ within the aortic wall (mixture) was calculated under the assumption of a constrained mixture by first determining the overall stored energy function $W = \sum_k W^k$, where

$$\mathbf{t} = \frac{2}{\det(\mathbf{F})} \mathbf{F} \frac{\partial W}{\partial \mathbf{C}} \mathbf{F}^T + t^{\text{active}} \mathbf{e}_\theta \otimes \mathbf{e}_\theta, \quad (4)$$

with $\mathbf{F}$ the overall deformation gradient (which can be related to constituent-specific deformation gradients via the kinematics shown in Figure 1), $\mathbf{C} = \mathbf{F}^T \mathbf{F}$ is the right Cauchy-Green tensor, and t^{active} is the active stress contribution from smooth muscle contractility (in the circumferential direction). Moreover, we let the constituent-specific stored energy functions W^k be given by (see section 4 in Baek et al.³),

$$W^k(s) = \frac{M^k(0)}{\sum_k M^k(s)} \hat{W}^k(\mathbf{C}_{n(0)}^k(s)) Q^k(s) + \int_0^s \frac{\dot{m}^k(\tau)}{\sum_k M^k(s)} \hat{W}^k(\mathbf{C}_{n(\tau)}^k(s)) q^k(s - \tau) d\tau, \quad (5)$$

with $\mathbf{C}_{n(\tau)}^k(s)$ the right Cauchy-Green tensor for constituent k , calculated by

$\mathbf{C}_{n(\tau)}^k(s) = (\mathbf{F}_{n(\tau)}^k(s))^T \mathbf{F}_{n(\tau)}^k(s)$, where $\mathbf{F}_{n(\tau)}^k(s)$ is the deformation gradient from the natural configuration to the current configuration at time s for constituent k produced at time τ (see Figure 1).

Collagen and smooth muscle were modeled as fiber-like structures without significant compressive stiffness, as in most prior G&R models. The stored energy function per unit mass for the smooth muscle-dominated behavior was defined as in Humphrey and Rajagopal¹⁷

$$\hat{W}^{SMC} = \frac{c_2^{SMC}}{4c_3^{SMC}} \left[\exp \left(c_3^{SMC} (I_4 - 1)^2 \right) - 1 \right], \quad (6)$$

with c_2 and c_3 material parameters and I_4 the fourth invariant of right Green-Cauchy tensor $(I_4 = \mathbf{m}^k(\tau) \mathbf{C}_{n(\tau)}^k(\mathbf{m}^k(\tau))^T)$, with $\mathbf{m}^k(\tau)$ being orientation of the constituent k). Collagen may reorient out of the cylindrical plane in aneurysms²⁹, but we did not include radially reoriented fibers because experimental data are lacking. In this case, elastin would bear all of the compressive radial stress. Because elastin is significantly lost as an AAA evolves, unrealistic radial stresses would result as the elastin content approached zero. Noting that glycosaminoglycans / proteoglycans typically associate with collagen fibers and can contribute to the overall compressive stiffness of the extracellular matrix, we added a neo-Hookean component to the stored energy function that described the (proteoglycan-augmented) collagen-dominated behavior, such that

$$\hat{W}^c = c_1^c \left(\text{tr}(\mathbf{C}_{n(\tau)}) - 3 \right) + \frac{c_2^c}{4c_3^c} \left[\exp \left(c_3^c (I_4 - 1)^2 \right) - 1 \right], \quad (7)$$

with corresponding material parameters c_1^c, c_2^c, c_3^c . Values were chosen to fit the original exponential stored energy function while simultaneously ensuring an equivalent homeostatic stress at the deposition stretch $G_h^c = 1.08$.

2.2. G&R model of thrombus

The present model for the formation and maturation of ILT was motivated by our prior review of the literature⁴³ and expectation that the aortic wall in closest proximity to the luminal layer of ILT (i.e., underneath thin thrombus) could experience augmented G&R and potential weakening secondary due to thrombus-derived proteases^{10,14}. Note that the thickness of the luminal layer is limited by the depth (~ 2 mm)³⁶ to which blood components can penetrate the evolving fibrin mesh. The medial and abluminal layers in thicker ILTs are largely acellular and consist of a variably degraded fibrin mesh. Apoptosis and degradation of fibrin can create fluid-filled voids that form transmural canaliculi of increasing cross-sectional area from the lumen to the wall¹. Such canaliculi could allow transport of blood borne cells and proteins deeper within the ILT, but this possibility has not been confirmed experimentally and was not considered herein. Rather, from the above considerations, we assumed that fibrin, fibrin degradation products (FDPs), RBCs, and voids were the most significant space-occupying constituents of a layered ILT. Although we neglected contributions of inflammatory cells and proteases to overall clot volume, the leukocytes and associated proteolysis (which are critical to the biological activity of the thrombus) were nevertheless included within the luminal layer.

As noted above, we assumed a constant overall luminal diameter as the AAA evolved; that is, once a thrombus initiated, it continuously filled the available space within the aneurysm to maintain a constant luminal diameter as seen on many medical images of large AAAs. Thus, pre-existing thrombus was effectively pushed deeper into the model ILT as the AAA dilated and new thrombus formed luminally. A new layer of thrombus layer deposited on any previous ILT, at each time step to maintain a constant luminal diameter, is hereinafter labeled as layer i . Naturally, this suggests that deposited thrombus transitions from initially luminal to medial and eventually abluminal. Thus, medial and abluminal layers were not prescribed a priori, they emerged as a result of AAA progression. In this way, our mathematical model of an ILT within an AAA could describe evolving biomechanical and biochemical behaviors of the thrombus and its constituents (e.g., fibrin, FDPs, RBCs, and voids) as a function of time and position.

2.2.1. Fibrin—Fibrin accumulates when activated thrombin cleaves fibrinogen into fibrin, which then polymerizes to form an interconnected cross-linked mesh. Formation of fibrin has been modeled in several ways^{2,45}, typically based on *in vitro* studies that do not necessarily represent *in vivo* behavior. Such models necessarily describe clots that develop in minutes and dissolve in hours, highly atypical for ILT in aneurysms. Clearly, there is a need for more understanding of the *in vivo* mechanisms and mechanics.

Similar to G&R models for arterial adaptations and disease progression, we assumed that there is always a sufficient supply of fibrinogen at the luminal surface of an ILT such that the rate of production of fibrin ($\dot{m}_i^f$) in layer i does not depend on the concentration of hemodynamically supplied fibrinogen. Rather, the production of new fibrin decreased with increasing fibrin density ϕ_i^f or increased with an increased number of platelets M_i^{plt} ,

$$\dot{m}_i^f(\tau) = K_{plt,\phi}^f M_i^{plt}(\tau) (1 - \phi_i^f(\tau)), \quad (8)$$

where $K_{plt,\phi}^f$ is a simple correlation parameter. In contrast, degradation of fibrin depends on the concentration of plasmin, which is derived from the conversion of plasminogen in the blood. Interestingly, fibrinolysis appears to be inversely proportional to the density of the fibrin mesh and mechanical stretch³¹. Thus, we considered a rate-type parameter for the removal of fibrin as

$$K_q^f(\tau) = k_q^f + w_q^f \frac{M_i^{pls}(\tau) (1 - \phi_i^f(\tau))}{\lambda_i(\tau)}, \quad (9)$$

where k_q^f is a homeostatic value independent of plasmin, stretch, and mesh density. M_i^{pls} is the mass of plasmin, λ_i is the fibrin stretch, and w_q^f is a weighting function. Hence, similar to constituents in the wall, the mass of fibrin was computed as:

$$M_i^f(s) = M_i^f(0) Q_i^f(s) + \int_0^s \dot{m}_i^f(\tau) q_i^f(s - \tau) d\tau, \quad (10)$$

where $M_i^f(0)$ is the initial mass of fibrin in a newly deposited luminal layer, and

$$Q_i^f(s) = q_i^f(s - 0) = \exp\left(-\int_0^s K_q^f(\tilde{\tau}) d\tilde{\tau}\right).$$

2.2.2. Cells/Platelets—The majority of blood-derived cells within an ILT reside in the luminal layer^{1,14}. It has been proposed that the proximity of the luminal layer to flowing blood allows these cells to be replenished; as new layers are deposited, however, cells can generally not penetrate into or survive within the deeper medial and abluminal layers. Hence, we assumed a first order decay process for cells previously in a luminal layer that became buried during new deposition of ILT as the lesion enlarged (with a half-life of 7-11 days for platelets and 120 days for erythrocytes).

The boundary of the luminal layer was defined by either: (a) a critical fibrin mesh density $\phi_{crit}^{f,RBC}$ that was reached when RBCs were excluded or (b) a critical radius r_{crit} that was attained beyond which cells could not be replenished. This critical radius was defined as a function of a critical mass of fibrin M_{crit}^f , such that

$$\int_{r_i}^{r_{crit}} M_i^f(r) dr = M_{crit}^f. \quad (11)$$

Therefore, the quantity of platelets (or other blood-borne cells) in the luminal layer depended on the quantity in the luminal blood, M_i^{plt} , which could potentially vary in time (e.g., in a flow field having evolving vortical structures⁵). In the deeper layers, these

platelets were presumed to degrade according to a first-order process, with the rate-type parameter inversely related to the half-life $\tau_{1/2}^{plt}$:

$$K_q^{plt} = \frac{\ln 2}{\tau_{1/2}^{plt}}. \quad (12)$$

In this way, consistent with histological findings³³, new fibrin was predominately deposited in the luminal layer where the mass of platelets was necessarily highest.

In summary, the mass of platelets was calculated as

$$M_i^{plt}(\tau) = \begin{cases} M_l^{plt}(\tau) & r_i(\tau) < r_{crit}(\tau) \quad \text{and} \quad \phi_j^f < \phi_{crit}^{f,plt}, \quad \forall j \geq i \\ M_l^{plt}(\tau_{crit}^{i,1}) \cdot e^{-K_q^{plt}(\tau - \tau_{crit}^{i,1})}, & r_i(\tau) \geq r_{crit}(\tau) \\ M_l^{plt}(\tau_{crit}^{i,2}) \cdot e^{-K_q^{plt}(\tau - \tau_{crit}^{i,2})} & \phi_j^f(\tau) \geq \phi_{crit}^{f,plt}, \quad \forall j \geq i \end{cases}, \quad (13)$$

where $\tau_{crit}^{i,1}$ is the time at which a critical mass of fibrin (and r_{crit}) was achieved, thus transitioning the initial luminal layer to medial with a low platelet count. Similarly, the time $\tau_{crit}^{i,2}$ represents when the limit of the luminal layer was achieved by reaching the critical mass fraction of fibrin.

The distribution of RBCs within the ILT was defined similarly, with the exception of using a mass fraction instead of the mass. Note that $\phi_i^{RBC}(\tau) = 1 - \phi_i^f(\tau)$ in the luminal layer because the sum of the mass fractions over all constituents must equal one,

$\phi_i^f + \phi_i^{RBC} + \phi_i^v + \phi_i^{FDP} = 1$, and voids and fibrin degradation products are generally absent in the luminal layer. Thus,

$$\phi_i^{RBC}(\tau) = \begin{cases} 1 - \phi_i^f(\tau) & r_i(\tau) < r_{crit}(\tau) \quad \text{and} \quad \phi_j^f < \phi_{crit}^{f,RBC} \\ \min\left(\left(1 - \phi_i^f(\tau_{crit}^{i,1})\right) \cdot e^{-K_q^{RBC}(\tau - \tau_{crit}^{i,1})}, 1 - \phi_i^f(\tau)\right) & r_i(\tau) \geq r_{crit}(\tau) \\ \min\left(\left(1 - \phi_i^f(\tau_{crit}^{i,2})\right) \cdot e^{-K_q^{RBC}(\tau - \tau_{crit}^{i,2})}, 1 - \phi_i^f(\tau)\right) & \phi_j^f(\tau) \geq \phi_{crit}^{f,RBC} \end{cases} \quad (14)$$

Like the platelets, the leukocytes were assumed to not contribute significantly to the volume of the ILT; hence, they were excluded from the mass fraction summation. Their presence was important nonetheless for the production of proteases such as plasmin, MMPs, and macrophage or neutrophil elastases. Thus, the quantity of leukocytes (primarily neutrophils) M_i^N was modeled similar to the mass of platelets, with defined concentrations in the luminal layer and a first-order decay within the deeper layers.

2.2.3. Plasmin, EDPs, and neovascularization—Plasminogen is converted to plasmin by different enzymes, most importantly tissue plasminogen activator (tPA) and urokinase plasminogen activator (uPA). The tPA is found on endothelial cells, while the uPA comes mainly from the blood stream via mesenchymal and inflammatory cells. For our simplified model, we considered two primary sources of active plasmin: the leukocyte-rich luminal layer of the ILT and the aortic wall itself. The latter may be due to an influx of inflammatory

cells into the aneurysmal wall from multiple sources, including an increased *vasa vasorum*²⁶. Regardless of the source, we assumed an increased production of plasmin within an evolving wall consistent with immunohistological reports⁹. While we sought to capture phenomenologically the overall increase in activated plasmin (while excluding the kinetics associated with changing concentrations of plasminogen, tPA, uPA, and the inhibitors PAI-1 and alpha-2 antiplasmin), future studies should seek to quantify and incorporate these complexities spatially and temporally. For now, however, we assumed that the mass of activated plasmin M_i^{pls} that degrades fibrin was

$$M_i^{pls}(\tau) = K_N^{pls} M_i^N(\tau) + \underbrace{M_{wall}^{pls}(\tau) - \sum_{j=1}^i K_f^{pls} M_j^f(\tau)}_{\geq 0}, \quad (15)$$

where K_N^{pls} is a correlation factor between plasmin and neutrophils in the thrombus, K_f^{pls} is the amount of plasmin consumed per unit of fibrin, and $M_{wall}^{pls}(\tau)$ is the mass of plasmin in the wall calculated by

$$M_{wall}^{pls}(\tau) = K_{EDP}^{pls} M_{tot}^{EDP}(\tau) + K_{VV}^{pls} A_{tot}^{VV}(\tau). \quad (16)$$

We suggest that plasmin generated within the wall depends largely on the total mass of elastin degradation products M_{tot}^{EDP} , which are chemoattractants for inflammatory cells and stimulate neovascularization of the wall (i.e., increase the amount/area of *vasa vasorum* A_{tot}^{VV} that allows increased migration of inflammatory cells into the remodeling wall²⁷). Correlations between plasmin and EDPs/*vasa vasorum* were accounted for by K_{EDP}^{pls} and K_{VV}^{pls} , respectively.

The production rate of EDPs, $\dot{m}_i^{EDP}$, was prescribed by the amount of elastin degraded over the previous time step, that is,

$$\dot{m}_i^{EDP}(\tau) = -\frac{dM_i^e}{d\tau} = \frac{M_i^e(\tau - \Delta\tau) - M_i^e(\tau)}{\Delta\tau}, \quad (17)$$

while the EDPs degraded with rate-type parameter K_q^{EDP} :

$$q_i^{EDP}(s - \tau) = \exp\left(-\int_{\tau}^s K_q^{EDP} d\tilde{\tau}\right). \quad (18)$$

Thus the total mass of EDPs in each layer i was

$$M_i^{EDP}(s) = \int_0^s \dot{m}_i^{EDP}(\tau) q_i^{EDP}(s - \tau) d\tau, \quad (19)$$

and the total mass of EDPs, M_{tot}^{EDP} for the aortic wall was

$$M_{tot}^{EDP}(s) = \sum_i M_i^{EDP}(s). \quad (20)$$

Development of *vasa vasorum* has been thought to be connected with increased hypoxia due to thick ILTs³⁸. Yet, Mäyränpää et al.²⁶ reported that the expression of genes associated with intramural neovascularization is the same or only slightly increased in thrombus-covered versus thrombus-free walls in AAAs. Interestingly, EDPs also appear to affect neovascularization²⁷. For example, both intraluminal infusion of the rat aorta with elastase (to create AAAs) and direct delivery of EDPs to the wall cause comparable neovascularization²⁷. We modeled the development of *vasa vasorum* as a function of the mass of EDPs, but neglected the influence of hypoxia. Thus,

$$A_{tot}^{VV}(s) = A_0^{VV} + \int_0^s K_{EDP}^{VV} M_{tot}^{EDP} d\tau, \quad (21)$$

where A_0^{VV} denotes a homeostatic area of *vasa vasorum* in healthy aorta and K_{EDP}^{VV} is a correlation factor that relates *vasa vasorum* growth per unit of EDPs per unit time.

2.2.4. Voids and fibrin degradation products—The fibrin mesh in the luminal layer is characterized by thick primary fibers and fine interconnecting secondary fibers. Since thinner fibers cleave more quickly than thicker ones⁴¹, these secondary interconnections are lost in the medial layer, thus leaving small interconnected channels (“voids” or “canaliculi”) throughout much of the ILT¹. We assumed that degraded fibrin partly turns into fibrin degradation products (FDPs) and is partly removed by macrophages, which leaves voids. Overall, the mean void area increased from the luminal toward the abluminal layer.

2.3. Biochemomechanical interaction of ILT and the wall

To model biochemomechanical interactions between the aortic wall and ILT, two models must be interconnected. Stress in the ILT was modeled similar to that in the wall. The stored energy of fibrin-rich ILT was assumed to be³³,

$$\hat{W}^f = \mu (I_1 - 3) + \frac{k_1}{k_2} \left[\exp \left(k_2 (1 - \rho) (I_1 - 3)^2 + \rho (I_4 - 1)^2 \right) - 1 \right], \quad (22)$$

where μ and k_1 have units of stress, k_2 is dimensionless, $I_1 = \text{tr}(\mathbf{C}_{n(\tau)}^f)$, and $I_4 = \mathbf{m}(\tau) \cdot \mathbf{C}_{n(\tau)}^f \cdot \mathbf{m}^T(\tau)$. Similar to that for intramural matrix, $\mathbf{C}_{n(\tau)}^f$ is the right Cauchy-Green tensor, $\mathbf{m}$ represents the orientation of the fibers, and $\rho \in [0, 1]$ is a measure of mechanical anisotropy. Since anisotropy of the luminal layer may increase with aging³³, ρ was modeled as a function of the time that the layer was in contact with the flowing blood and associated wall shear stress, that is

$$\rho(\tau, \tau_w) = f(\tau) g(\tau_w) = K_{max}^{aniso} \left(1 - \exp \left(-K_t^{aniso} (\tau - \tau_{i,0}) \right) \right) \exp \left(K_{\tau_w}^{aniso} \left(\frac{\tau_w}{\tau_{w,h}} - 1 \right) \right), \quad (23)$$

where K_{max}^{aniso} , K_t^{aniso} and $K_{\tau_w}^{aniso}$ are correlation factors and $\tau_{i,0}$ is the time at which the current luminal layer was formed. In cases of isotropic ILT, $\rho = 0$, and Eq. (22) reduces to:

$$\hat{W}^f = \mu (I_1 - 3) + \frac{k_1}{k_2} \left[\exp \left(k_2 (I_1 - 3)^2 \right) - 1 \right]. \quad (24)$$

Similar to elastin, a neo-Hookean strain energy function was used to model the mechanics of the fibrin degradation products:

$$\hat{W}^{FDP} = \mu^{FDP} \text{tr} \left(\mathbf{C}_{n(\tau)}^{FDP} - \mathbf{1} \right). \quad (25)$$

Erythrocytes (RBCs) and voids only affected the compressive properties.

Biochemical effects of the proteolytically active luminal layer were incorporated via additional terms in the degradation functions for collagen and elastin. In general, the survival function of all structurally important constituents was modeled by a first order decay, similar to Eq. (2):

$$q_i^k(s - \tau) = \exp \left(- \int_{\tau}^s K_q^k(\tilde{\tau}) d\tilde{\tau} \right). \quad (26)$$

The K_q^k in Eq. (26) need not be constant as were K^k in Eq.(2). For example, whereas K^e for elastin in a normal aging aorta depends primarily on its natural half-life ($\tau_{1/2}^e$) of ~40 years,

namely $K^e = k_q^e = \frac{\ln(2)}{\tau_{1/2}^e}$, the increased degradation of elastin in an aneurysm due to inflammation was modeled as

$$K_q^e(t) = k_q^e + w_{q,elas}^e M^{elas}(r, t), \quad (27)$$

where, k_q^e is the constant degradation rate associated its normal half-life and the second term represents further degradation due to an increased concentration of inflammatory cell released elastases, M^{elas} , with weighting factor $w_{q,elas}^e$.

For collagen, we let²⁰

$$K_q^c(t) = \frac{\frac{\partial W^c}{\partial \mathbf{F}_{n(\tau)}^c}}{\frac{\partial W^c}{\partial \mathbf{F}_{n(0)}^c}} k_q^c + w_{q,MMP}^c M^{MMP}(r, \tau), \quad (28)$$

where K_q^c depends on the ratio of the current $\left(\frac{\partial W^c}{\partial \mathbf{F}_{n(\tau)}^c} \right)$ to the homeostatic $\left(\frac{\partial W^c}{\partial \mathbf{F}_{n(0)}^c} \right)$ value of fiber tension, and k_q^c is the homeostatic half-life; the additional terms account for the presence of MMPs (i.e., collagenases) that were activated by ILT-related plasmin as well as other mechanisms.

Similar to plasmin and oxygen, the distribution of MMPs may depend on two cell sources: those from the luminal layer in the ILT and those coming from the *vasa vasorum* within the aortic wall. Each of these sources may evolve as the lesion expands. This situation implies diffusion with two sources and a line sink. As a first approximation, considering only a quasi-static solution, we solved

$$\frac{\partial M^{elas}}{\partial t} = \nabla \cdot [D \nabla M^{elas}] \quad (29)$$

using available experimental data on the radial distribution of proteases^{10,14}, where D is the diffusion coefficient. The luminal boundary condition was defined as the elastase/MMPs available from the luminal layer, $K_N^{elas} M_{tot}^N$ (or $K_N^{MMP} M_{tot}^N$ for MMPs), where $K_N^{elas/MMP}$ describes how much elastase/MMP was produced per unit of leukocytes per time step. The location of the source of the proteases was prescribed at radius r_L by:

$$r_L(s) = \frac{1}{M_{tot}^N(s)} \sum_i M_i^N(s) r_i(s), \quad (30)$$

similar to a center of gravity calculation for each layer i . The concentration of elastase/MMPs at the outer radius depended on the area of *vasa vasorum* and quantity of inflammatory cells: $K_{WBC}^{elas} M_{tot}^{WBC}(s) + K_{VV}^{elas} A_{tot}^{VV}(s)$. Thus, the overall distribution of proteases was:

$$M^k(r, s) = \frac{K_N^k M_{tot}^N(s) - K_{WBC}^k M_{tot}^{WBC}(s) - K_{VV}^k A_{tot}^{VV}(s)}{\ln(r_L(s)/r_0)} \ln\left(\frac{r(s)}{r_0}\right) + K_N^k M_{tot}^N(s), \quad (31)$$

where k can indicate elastases or collagenases (indeed any MMP).

With the above survival functions, the mass of collagen can be calculated by Eq. (1); because there is no production of elastin, its evolving mass can be calculated by the reduced expression:

$$M^e(s) = M^e(0) Q^e(s). \quad (32)$$

The half-life of SMCs was also prescribed by a first order decay rate²⁰, but its degradation was additionally linked to the degradation of elastin to model anoikis (a type of apoptosis caused by loss of attachment to the surrounding matrix). We assumed that an AAA initiates when there is a local loss of elastin, which in turn results in a local loss of smooth muscle via anoikis. The elastin degradation function was prescribed similar to that used by Valentín et al.³⁵, namely

$$q_i^{SMC}(s - \tau) = \exp\left(-\int_{\tau}^s K_q^{SMC}(\tilde{\tau}) d\tilde{\tau}\right) Q^e(s). \quad (33)$$

Yet, smooth muscle cells can also become more synthetic, so maximal active stress T_m decreased as³⁵

$$T_m(s) = T_m(0) \cdot (\beta_m + (1 - \beta_m) Q_e(s)), \quad (34)$$

where β_m is a scaling parameter that controlled the degree of proportionality between elastin content and vasoactivity.

To summarize, Figure 2 outlines interactions among the primary contributors that affect the G&R of a thrombus-laden AAA. The left side of the schema highlights the most important reactions in the thrombus: fibrin is produced by thrombin and degraded by plasmin. The right side refers to processes within the aortic wall: MMPs degrade structurally significant constituents, thus releasing elastin degradation products and increasing neovascularization. Arrows connecting the two boxes delineate the impact of thrombus on the wall and the influence of intramural cells on the maturation of thrombus. Of particular note, plasmin produced in the ILT by leukocytes can diffuse into the wall and help activate proMMPs. Conversely, inflammatory cells within the wall can impact the conversion of plasminogen to plasmin by degrading the fibrin to which it was bound. Clearly, there are complex biochemical interactions between the ILT and wall of the AAA.

3. Equilibrium equations and geometry

While this new G&R framework can, and eventually should, be implemented in simulations based on patient-specific geometries and with fluid-solid-growth coupling^{32,44}, it is first important to verify and test a new constitutive model in a geometrically simple case. Hence, similar to many prior G&R studies of AAAs^{16,18,40,42}, we focused on a simple axisymmetric geometry for illustrative purposes and to gain initial insights. Given differences in time scales between the cardiac cycle and the evolution of a lesion, we considered a quasi-static motion of the lesion whereby

$$\text{div}(\mathbf{t}) = \mathbf{0}, \quad (35)$$

which, for an axisymmetric cylindrical geometry, reduces to

$$P = \int_{r_l}^{r_i} (t_{\theta\theta} - t_{rr}) \frac{dr}{r} + \int_{r_i}^{r_m} (t_{\theta\theta} - t_{rr}) \frac{dr}{r} + \int_{r_m}^{r_a} (t_{\theta\theta} - t_{rr}) \frac{dr}{r} + \int_{r_a}^{r_o} (t_{\theta\theta} - t_{rr}) \frac{dr}{r}, \quad (36)$$

where P is the luminal pressure distending the vessel and r_l , r_i , r_m , r_a , r_o are radii at the following interfaces: lumen/ILT, ILT/intima, intima/media, media/adventitia, adventitia/outer surface. Similarly, the overall axial force L was computed as:

$$L = \pi \left(\int_{r_l}^{r_i} (2t_{zz} - t_{\theta\theta} - t_{rr}) \frac{dr}{r} + \int_{r_i}^{r_m} (2t_{zz} - t_{\theta\theta} - t_{rr}) \frac{dr}{r} + \int_{r_m}^{r_a} (2t_{zz} - t_{\theta\theta} - t_{rr}) \frac{dr}{r} + \int_{r_a}^{r_o} (2t_{zz} - t_{\theta\theta} - t_{rr}) \frac{dr}{r} \right). \quad (37)$$

4. Results

4.1. Parameter values

Similar to previous implementations of constrained mixture models for arterial G&R^{20,34,35}, we classified constitutive relations and parameters by level of consensus and function (Table

1). We classified as “observed” any parameters that were measured easily (such as arterial geometry, volumetric flowrates, or thrombus stiffness³³). In contrast, “bounded” parameters were less well-known and either defined via a parametric study³⁴ or estimated from indirect experimental observations, as, for example, on the extent of the *vasa vasorum*³⁸ or the critical mass of a luminal layer of thickness 2 mm³⁶. “Empirical” parameters have not been quantified directly, but were chosen to model findings reported in the literature (e.g., spatial distribution of MMPs and elastases¹⁰).

4.2. Predictions

The simulated development of an AAA was initiated by prescribing a uniform 5% loss of elastin in an initially healthy, but aged aorta (defined by the original material parameters). This insult led to acute changes in stress, and stress-mediated G&R, and an early dilatation. Assuming a space-filling deposition of thrombus, and its associated biochemical effects (e.g., further degradation of the aortic wall via increased quantity of MMPs), allowed the potential effects of thrombus to be modeled for the first time.

Geometric changes—The progression of a representative AAA for the aforementioned model parameters (cf. Table 1) is shown in Figure 3. For the first 2.5 years (i.e., until the inner radius dilated by 2 mm, the maximum thickness of a luminal layer), the lesion continued to expand significantly as the proteolytically active luminal layer remained in contact with the aortic wall. In particular, the intimal-medial thickness decreased due to the loss of elastin (proteolytically) and smooth muscle (via anoikis). As the lesion enlarged, intermediate and abluminal layers of ILT formed and acted as a barrier to the diffusion of biomolecules from the luminal layer, effectively diminishing the direct biochemical influence of the ILT. Thus the adventitia thickened, and the concavity of the growth curve switched from positive to negative (i.e., the lesion slowed its growth, perhaps moving towards stabilization). In this idealized geometry, the thrombus had a minimal biochemical effect on progression of the lesion as soon as sufficiently thick intermediate layers of ILT formed; in actual fusiform AAAs, however, the lesion geometry is often complex and the thrombus is often eccentric, hence unique locations of thin thrombus (e.g., the shoulder of the lesion) could exist throughout development wherein clot-related enzymatic activity could remain important to the overall G&R of the wall.

Elastases/collagenases distribution—Figure 4(a) highlights the evolution of proteolytic activity (e.g., from MMPs) in the wall due to the evolving thickness of the ILT. The MMPs within the neighboring wall initially increased as the thickness of the luminal layer of the ILT increased, but fell sharply as the less proteolytically active intermediate layer formed. After 25 years, the final MMP concentration was reduced ~3 fold relative to the peak value, but was yet higher than the initial value due to an increased *vasa vasorum* (and thus intramural inflammation) secondary to the production of EDPs (see Eq. (21), Figure 4 (b)).

Composition of the aortic wall and ILT—The evolution of elastase in the wall was analogous to that of the general MMPs, leading to an initially rapid degradation of elastin that diminished as the thrombus thickened (Figure 5). Likewise, the collagen decreased

rapidly as the luminal layer formed, yet thickening of the thrombus and increased stress-mediated deposition yielded a net increase in collagen over time. Smooth muscle increased briefly as stress increased, but then declined as elastin was lost and anoikis occurred.

Distributions of constituents within the ILT at the end of simulation are shown in Figure 6. Fresh thrombus at the luminal interface (i.e., near a radius of 9.925 mm) was characterized by low amounts of fibrin and large numbers of RBCs (recall that the volume fraction of platelets was neglected). In the deeper, more mature parts of the luminal layer, fibrin was increased and RBCs diminished. The border between the luminal and intermediate layer was evident by the steep decrease in RBCs as they could not penetrate farther into the thrombus. Similarly, platelets were unable to reach deeper parts of the ILT, wherein new fibrin production was impaired. As a result, the mass fraction of this fibrin decreased as its degradation exceeded production. The distinction between intermediate and abluminal layers was less evident; both were devoid of platelets and characterized by increasing fibrin degradation products (FDPs) and voids as the fibrin degraded. It is possible that development of an abluminal layer may be influenced by (a) a large deposition of initial thrombus with deeper regions that were not luminal long enough for the fibrin mesh to mature fully, (b) degradation of the clot from activated plasmin generated at the ILT/wall interface, and/or (c) structural disruption of the thrombus that allows fresh blood into deeper layers – none of which were considered in this initial model. Nevertheless, our results correspond qualitatively to the reported distribution of constituents in four phases of an aging, layered ILT³³: phase I (fresh thrombus, new luminal layer) was characterized by 90% RBCs and 10% thin fibrin bundles; phase II (older luminal layer) had less than 10% RBCs, some condensed proteins (FDPs), and increasing thin and thick fibrin fibers; phases III and IV (i.e., older thrombus) had few RBCs and condensed proteins dominated as fibrin degraded.

Stress distribution—To examine the mechanical influence of the ILT, radial stress and pressure (calculated as $1/3\text{tr}(\mathbf{t})$) were plotted versus depth through the thrombus and wall (Figures 7 (a) and (b)). A prior clinical study¹² reported that the ratio of pressure (at end systole) within the thrombus to that within the flowing blood was 0.90 ± 0.09 , 0.86 ± 0.10 , and 0.81 ± 0.09 at depths of 1, 2, and 3 cm, respectively. Figure 7 reveals that our predicted reductions in pressure at depths of 1 and 1.5 cm (maximum thrombus depth in this simulation) were comparable, 0.94 and 0.93, respectively.

To evaluate the mechanical predictions of the model further, numerical equibiaxial tension tests of the aneurysmal wall underlying fresh and old thrombus were compared with experimental finding³³ (Figures 7 (c)). It was found that the model and data shared two major features. First, the wall under fresh thrombus was more compliant when compared with that under older thrombus. Second, anisotropy of the wall increased with maturation of thrombus. Note, therefore, that a numerical biaxial test of the initially non-aneurysmal aorta revealed an almost isotropic behavior due to the homeostatic definition: four families of collagen fibers oriented axially, circumferentially, and helically at $\pm 45^\circ$, intact, isotropic elastin, and circumferentially oriented smooth muscle that was highly compliant. Wall stiffening thus occurred due to the progressive loss of elastin and stiffening of collagen over time while anisotropy increased due to an active re-orientation of collagen fibers towards the

circumferential direction. Although the experimental values represented average findings, not those obtained by following changes in one aneurysm over time as in our model, the overall agreement was nonetheless encouraging.

Comparison of numerical and experimental equibiaxial tension tests of fresh, luminal, medial, and abluminal thrombi (Figure 7(d)) also shows good agreement. The luminal layer is the stiffest and possesses the highest amount of the primary load-bearing material (fibrin); the mass fraction of fibrin (Figure 6), and thus stiffness, decreases in other layers.

Possible clinical outcomes—In our prior G&R simulations of AAAs without thrombus, we have explored parametrically the effects of key aspects of collagen turnover on AAA progression, including rates of production and values for the half-life, deposition stretch, and stiffness⁴². Similarly, we considered three cases for collagen stiffness in AAAs herein: loss of stiffness, constant stiffness, or increased stiffness. For simplicity, we modeled changes in stiffness relative to the homeostatic value and the ratio of the current to the initial stretch:

$c_3^c(s) = c_3^c(0) \frac{\lambda^c(s)}{\lambda^c(0)}$ for stiffening, the inverse of this ratio for softening, and $\lambda^c(s) = \lambda^c(0)$ for maintenance in the healthy aorta (i.e., constant stiffness in maintenance). Our model confirmed the prior results that a sufficiently high production can stabilize AAA enlargement in the absence of thrombus (results not shown). To consider the effect of increased ILT stiffness on lesion expansion, four cases were modeled with different fibrin properties (Figure 8). Stiffer ILT was modeled using the upper limit of model parameters for the isotropic luminal layer determined in Tong et al.³³ ($\mu = 0.0099$ MPa, $k_1 = 0.016$ MPa, $k_2 = 0.9$); compliant ILT was modeled with the lower limit ($\mu = 0.0065$ MPa, $k_1 = 0.0086$ MPa, $k_2 = 0.3$). Each case was modeled with and without stiffening of collagen in the aortic wall.

Results indicated that stiffening either the fibrin in the thrombus or the collagen in the aneurysmal wall reduced the diameter at which the AAA slowed its growth, with possible stabilization. That is, stiffening of collagen alone may not be necessary for ultimately arresting enlargement in thrombus-laden AAAs (at least for the range of parameters tested). Further simulations using more realistic geometries may prove useful to better explore the mechanical contribution of fibrin.

Discussion

Prior computational models of the growth and remodeling of abdominal aortic aneurysms have failed to include the potential effects that intraluminal thrombus can have on the natural history of the lesion^{16,18}. While both classic stress analyses³⁹ and the present model suggest that stiffer thrombi may favorably reduce wall stress, our data-driven G&R model further predicted a potentially negative biochemical impact that the luminal layer of a thrombus may exert on the structural integrity of the underlying wall, consistent with histology²³. Our model similarly suggested that increased neovascularization of the aneurysmal wall (i.e., evolving *vasa vasorum*), resulting in part from decreased oxygen transport from the lumen through a thick thrombus, may negatively impact the wall via increased inflammatory infiltrates^{26,27,38}. These findings were possible because, in contrast to prior models of thrombus that assume an inert homogeneous layer, our G&R model

allowed the first simulation of the natural evolution of multi-layered ILT having distinct mechanical and biological properties. We submit that each of these potential effects of ILT on AAAs should be included henceforth. Because the present model is fundamentally a collection of point-wise constitutive relations, it can be incorporated easily, in principle, within geometrically realistic and patient-specific models that account for fluid-solid-growth mechanics (cf. references^{16,18,32,44})

Notwithstanding advantages of this first generation model, it was necessarily limited by the assumed cylindrical geometry, which did not admit local dilatations of the aneurysmal wall and thus axial or circumferential variations in thrombus properties (e.g., shoulder regions of an aneurysm with continued thin thrombus). Similarly, the assumption of a space-filling thrombus did not allow a hemodynamically-driven progression of the ILT, which likely occurs *in vivo*. To continue to gain increased insight, subsequent finite element based G&R models should probably consider, in order of increasing complexity, axisymmetric, non-axisymmetric, and finally patient-specific geometries¹⁸. Fortunately, computational models of lesions having complex geometries have already been achieved^{32,44}, though not with an evolving thrombus. The final goal, of course, is a comprehensive fluid-solid-growth model that integrates the diverse biochemomechanical factors that govern the hemodynamics, endothelial (dys)function (e.g., shear stress induced paracrine signaling), thrombus formation and progression (e.g., platelet activation and turnover of fibrin), inflammation, intramural cellular proliferation and apoptosis (e.g., phenotypic switching and anoikis of smooth muscle cells), and chemomechanical-dependent turnover of extracellular matrix. We submit, however, that our focus herein on a geometrically simple model was prudent for exploring and verifying the new constitutive frameworks and assumptions for the roles of ILT on the evolution of the aneurysmal wall.

Prior G&R studies showed that the stiffness of collagen plays a dominant role in predicting clinical endpoints (e.g., arrest, progressive expansion, or rupture) in AAAs that do not harbor an ILT⁴². Our model confirmed these prior results, but suggested further that factors in addition to collagen may also be important in thrombus-laden lesions. In particular, simulations herein with identical properties of the aneurysmal wall were capable of differential clinical outcomes depending on properties of the ILT. These results follow directly from the ability of the thrombus to not only bear load, but also to affect the turnover of extracellular matrix in the underlying wall via proteolysis. Of course, there is a need for novel experiments to better determine the many related G&R parameters in Table 1, ultimately in a patient-specific manner. For example, although experimental determination of concentrations of MMPs and elastases in different layers of the ILT and AAA wall has revealed insight into the biological activity of heterogeneous thrombi, there is a need for data on continuous distributions from the lumen to the outer wall of the aneurysm. Experimentally motivated studies of the mechanical influence of ILT on the wall have similarly been provocative, yet this issue remains controversial. Even though most of the studies support a “cushioning” effect on the wall, some suggest that whether the thrombus will decrease or increase the peak wall stress depends on its porosity and attachment to the wall. Apart from data on the existence of a “liquid interphase” in some large ILTs with a completely disrupted abluminal layer⁹, which may suggest that attachment weakens with

age, there are no data on this issue. Likewise, there is still a need for further data on regional variations in the composition, structure, and mechanics of the aneurysmal wall (e.g., better information on the reorientation of collagen fibers and, crucially, changes in the stiffness of collagen due to altered prestretches or cross-linking). Such data promise to improve our current models.

In conclusion, while there is a clear need for future experiments to quantify better the heterogeneous biochemomechanical properties of thrombus-laden AAAs and the appropriate growth and remodeling parameters that represent them, the present computational model provides a useful initial framework for exploring the evolution of these complex and potentially fatal lesions. We suggest that the greatest likelihood for improving patient-specific diagnostics and therapeutics for AAAs will be achieved through continued integrative research and modeling that considers both the biomechanical and biochemical influences that govern AAA development, including the unique contributions of proteolytically active, multilayered intraluminal thrombus.

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Figure 1.

Schema of configurations (dark circles / ellipses) and deformations ($\mathbf{F}$ or $\mathbf{G}$, see text for details) relevant to aortic growth and remodeling (G&R) for times $\tau \in [0, s]$. Note that time $\tau = 0$ denotes the beginning of the simulation when the aged aorta suffers an instantaneous but minimal loss of elastin; time τ is a generic instant at which new constituents are produced and incorporated within the ILT or aneurysmal wall; time $\tau = s$ is the current computational time at which quantities are interpreted. Note, too, that the natural configurations are stress-free and unique for each constituent. Modified based on Figure 1 in Karšaj et al.²¹.

Figure 2.

Schematic representation of effectors of the biochemomechanics of an evolving AAA. A solid black arrow indicates “increases the amount or activity,” a dashed black line indicates “degrades,” and a solid line indicates “modulates the effect.” (WBC: white blood cell, RBC: red blood cell, EDP: elastin degradation products, FDP: fibrin degradation products). Equations modeling each of the behaviors are explained in listed section numbers (2.1. to 2.2.4.). Modified based on Fig 8. in Wilson et al.⁴³.

Figure 3.

Simulated evolution of the central region of an idealized axisymmetric AAA harboring a space-filling thrombus. The dot-dashed line at 9.925 mm denotes the constant luminal radius, which enforces a space-filling thrombus. The lower-most gray line denotes the extent of the luminal layer of ILT, typically about 2 mm thick. The solid black line denotes the interface between the abluminal layer of the ILT and the intima, the dashed gray (barely visible) line denotes that between the intima and media, the dashed black line denotes that between the media and adventitia, and the upper-most gray line denotes the outer radius of the aneurysmal wall.

Figure 4.

Left - Evolution of the net concentration of matrix metalloproteinases (MMPs) in the aortic wall normalized to the value at G&R time $s = 0$. Right - Growth of *vasa vasorum* by cross-sectional area (dashed line) plus the mass of elastin degradation products (EDPs, solid line), each normalized by their initial, homeostatic value.

Figure 5.

Evolution of total masses of the primary structural constituents of the wall, normalized per unit axial length. The solid line represents elastin, the dashed line smooth muscle cells (SMC), and the dotted line collagen, all in the case of stiffening due to increased collagen accumulation.

Figure 6.

Radial distribution of mass fractions of structurally important constituents at the time $s = 25$ years. The solid black line represents fibrin, the dashed black line red blood cells (RBC), the gray solid line voids (canaliculi), and the gray dashed line fibrin degradation products (FDP). Note that luminal layer is easily distinguished, unlike the medial and abluminal layers (see Wilson et al.⁴³ for details on identifying different layers within ILT).

Figure 7.

Panel (a) Simulated transmural distribution of radial stress through the intraluminal thrombus (ILT) and aneurysmal wall for one (long-term) instant during the evolution of the lesion and clot. Note that the luminal and outer adventitial layers satisfy the prescribed traction boundary conditions. Panel (b) Simulated pressure throughout the intraluminal thrombus at the same instant. Panel (c) Comparison of emergent equibiaxial tension results for the simulated aneurysmal aortic wall with experimental data, both under younger ILT (black lines) or older thrombus (gray lines). Panel (d) Similar to panel (c) except for equibiaxial tension tests on different layers of intraluminal thrombus. All experimental data are from Tong et al.³³. Abbreviations: exp – experimental, sim – our model simulation, circ – stresses in circumferential direction.

Figure 8.

Simulated dilatation of AAAs having different mechanical properties of ILT. The black lines denote lesions with stiffer collagen and the gray lines baseline collagen properties. Moreover, the solid lines show results for stiffer ILT relative to the dashed lines which show results for more compliant ILT.

Table 1

Parameter values used for G&R of aortic wall and ILT. Note: ‘h’ denotes homeostatic.

Class	Role	Parameter value	Eq. #	Refs.
Observed	Physical constants	$\rho = 1050 \text{ kg m}^{-3}$, $\mu = 0.0037 \text{ Pa}\cdot\text{s}$, $r_i = 9.925 \text{ mm}$	See Karšaj et al. ²⁰	15
	Initial loading	$P_h = 104 \text{ mmHg}$, $\tau_h^w = 0.5 \text{ Pa}$, $t_h = 100 \text{ kPa}$		15
	Composition by layer	$\phi_{\text{int}} = 0.16$, $\phi_{\text{med}} = 0.52$, $\phi_{\text{adv}} = 0.32$ $\phi_{\text{int}}^c = 1$, $\phi_{\text{med}}^e = 0.55$, $\phi_{\text{med}}^c = 0.25$, $\phi_{\text{med}}^{\text{SMC}} = 0.20$, $\phi_{\text{adv}}^e = 0.25$, $\phi_{\text{adv}}^c = 0.75$		6,20
	Homeostatic kinetics	$\tau_{1/2}^c = \tau_{1/2}^{\text{SMC}} = 70 \text{ days}$, $\tau_{1/2}^e = 40 \text{ years}$, $\tau_{1/2}^{\text{RBC}} = 15 \text{ days}$, $\tau_{1/2}^{\text{PLT}} = 5 \text{ days}$, $\tau_{1/2}^{\text{WBC}} = 20 \text{ days}$, $\tau_{1/2}^e = 40 \text{ years}$, $\tau_{1/2}^{\text{EDP}} = 40 \text{ years}$, $\tau_{1/2}^f = 4 \text{ years}$	e.g., (12)	13,15,22
	Passive elasticity	$c_1^c = 0.025 \text{ MPa}$, $c_2^c = 498.2 \text{ kPa}$, $c_3^c = 23.52$ $c_2^{\text{SMC}} = 25.9 \text{ kPa}$, $c_3^{\text{SMC}} = 3.5$, $c_e = 134.96 \text{ kPa}$, $\mu = 0.0082 \text{ MPa}$, $k_1 = 0.0123 \text{ MPa}$, $k_2 = 0.6$	(6) (7) (24)	6,33
Bounded	Prestretches	$G_{\theta\theta}^e = G_{zz}^e = 1.2$, $G_h^{\text{SMC}} = 1.2$, $G_h^c = 1.08$, $G^f = 1.08$	See Fig 1	35
	SMC activation	$T_m(0) = 300 \text{ kPa}$, $\beta_m = 0.75$, $\lambda_m = 2$, $\lambda_0 = 0.4$	(34)	35
	Production	$K_{\sigma}^c = 3$, $K_{\sigma}^{\text{SMC}} = 3$	(3)	34
	Luminal layer definition	$M_{\text{crit}} = 0.9 \cdot 10^{-4} \text{ kg mm}^{-1}$, $\phi_{\text{crit}}^{\text{RBC}} = 0.9$, $\phi_{\text{crit}}^{\text{PLT}} = 0.9$, $\phi_{\text{crit}}^{\text{N}} = 0.9$	(13) (14)	33
	Vasa vasorum	$A_0^{\text{VV}} = 5.10^{-4} \text{ mm}^2$	(21)	1
	Masses of cells	$M_l^{\text{plt}} = 0.15 \text{ g mm}^{-1}$, $M_l^{\text{N}} = 0.2 \text{ g mm}^{-1}$	(13)	36
Empirical	Correlation factors	$K_{\text{EDP}, \text{VV}}^{\text{WBC}} = 150 \text{ mm}^2_{\text{VV}} (\text{kg}_{\text{EDP}} \cdot \text{day})^{-1}$, $K_N^{\text{pls}} = 0.01 \text{ g}_{\text{pls}} (\text{g}_N \cdot \text{day})^{-1}$, $K_{\text{plt}}^f = 0.25 \text{ g}_f (\text{g}_{\text{plt}} \cdot \text{day})^{-1}$, $K_N^{\text{MMP}} = 5.5 \text{ g}_{\text{MMP}} \text{ g}_N^{-1}$, $K_{\text{WBC}}^{\text{MMP}} = 0.01 \text{ g}_{\text{MMP}} \text{ g}_{\text{WBC}}^{-1}$ $K_{\text{VV}}^{\text{MMP}} = 0.00015 \text{ g}_{\text{MMP}} \text{ mm}_{\text{VV}}^{-2}$, $K_N^{\text{elas}} = 0.12 \text{ g}_{\text{elas}} \text{ g}_N^{-1}$, $K_{\text{WBC}}^{\text{elas}} = 0.002 \text{ g}_{\text{elas}} \text{ g}_{\text{WBC}}^{-1}$, $K_{\text{VV}}^{\text{elas}} = 0.00035 \text{ g}_{\text{elas}} \text{ mm}_{\text{VV}}^{-2}$	(16) (15) (31)	

Class	Role	Parameter value	Eq. #	Refs.
	Weighting factors	$w_q^f = 125 (g_{pls} \cdot \text{day})^{-1}$, $w_{q,elas}^e = 500 (g_{elas} \cdot \text{day})^{-1}$, $w_{q,MMP}^c = 750 (g_{MMP} \cdot \text{day})^{-1}$	(9) (27) (28)	

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