Importance of initial aortic properties on the evolving regional anisotropy, stiffness and wall thickness of human abdominal aortic aneurysms

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Complementary advances in medical imaging, vascular biology and biomechanics promise to enable computational modelling of abdominal aortic aneurysms to play increasingly important roles in clinical decision processes. Using a finite-element-based growth and remodelling model of evolving aneurysm geometry and material properties, we show that regional variations in material anisotropy, stiffness and wall thickness should be expected to arise naturally and thus should be included in analyses of aneurysmal enlargement or wall stress. In addition, by initiating the model from best-fit material parameters estimated for non-aneurysmal aortas from different subjects, we show that the initial state of the aorta may influence strongly the subsequent rate of enlargement, wall thickness, mechanical behaviour and thus stress in the lesion. We submit, therefore, that clinically reliable modelling of the enlargement and overall rupture-potential of aneurysms may require both a better understanding of the mechanobiological processes that govern the evolution of these lesions and new methods of determining the patient-specific state of the pre-aneurysmal aorta (or correlation to currently unaffected portions thereof) through knowledge of demographics, comorbidities, lifestyle, genetics and future non-invasive or minimally invasive tests.

Keywords: growth and remodelling; material properties; stress analysis; finite elements; rupture

1. INTRODUCTION

It has long been recognized that mechanics plays fundamental roles in the development, enlargement and eventual rupture of abdominal aortic aneurysms (AAAs). For this reason, serious attempts to compute wall stresses in AAAs date back many decades [1,2]. Work by Fillinger et al. [3,4] marks a turning point in such computations, however, for they demonstrated that wall stress determined from patient-specific geometric models can better predict rupture potential than the longstanding clinical metric of maximum diameter. Part of the increasing success of mechanics-based approaches is due to continuing modelling sophistication [5–7], moving from early linearly elastic isotropic models of idealized geometries to current nonlinearly elastic models with patient-specific geometric models can better predict rupture potential than the longstanding clinical metric of maximum diameter. Part of the increasing success of mechanics-based approaches is due to continuing modelling sophistication [5–7], moving from early linearly elastic isotropic models of idealized geometries to current nonlinearly elastic models with patient-specific geometries, some of which account for both the wall mechanics and haemodynamics. Nevertheless, most computational models [3,4,8–12] retain the assumptions of material isotropy, homogeneity and uniform wall thickness, despite data to the contrary [13–16].

In this paper, we employ a finite-element-based growth and remodelling (G&R) model that is motivated by the hypothesis of local mechanical homeostasis to suggest that mechanobiological responses by intramural cells (e.g. smooth muscle cells, fibroblasts and macrophages) should be expected to lead naturally to an evolving regional material anisotropy, stiffness and wall thickness—a consequence not emphasized in prior G&R studies of AAAs [17–20]. That is, if intramural cells synthesize, organize and degrade extracellular matrix in an attempt to achieve, maintain and restore a local homeostatic mechanical environment [21], then complex evolving properties have the potential to arise to offset perturbations in geometry or haemodynamic loading [22].

To demonstrate potential G&R-induced material and structural heterogeneity in evolving AAAs, we developed a simplified axisymmetric membrane model whose stress and material properties can be assessed at any axial position during the development of an AAA from different subject-specific non-aneurysmal aortas. We emphasize, therefore, that the goal of this study is to glean general insights into effects of G&R on the enlargement of AAAs (such as evolving heterogeneity and dependency on the initial state of the aorta), not to create a fully patient-specific model. Notwithstanding multiple simplifications (e.g. axisymmetry and lack of fluid–solid interactions or intraluminal
thrombus), the model predicts salient aspects of the enlargement of non-aneurysmal aortas, having initial material properties based on subject-specific biaxial testing data, into AAAs having realistic diameters, thicknesses, material behaviours and rates of enlargement. We submit, therefore, that such G&R models represent another advance towards the ultimate goal of assessing patient-specific rupture risk.

2. METHODS

2.1. Growth and remodelling theory

Our theoretical framework and finite-element implementation follow Baek et al. [18] and Zeinali-Davarani et al. [23]. Briefly, linear momentum balance was enforced quasi-statically and in weak form, using a virtual work approach, while accounting for the continuous turnover of structurally significant constituents via a rule-of-mixtures relation for the overall stored energy function \( w_{\text{R}}(s) \), defined per unit reference area for a nonlinear membrane. In particular, \( w_{\text{R}}(s) = \sum w_{\text{R}}^i(s) \) for \( i = 1, 2, \ldots, 6 \) structurally significant families of constituents at any G&R time \( s \), where

\[
w_{\text{R}}^i(s) = M^i_r(0) Q^i(s) \mathcal{P}^i(C^{\text{u}}_{\text{n}(0)}(s)) + \int_0^s m^i_r(\tau) q^i(s, \tau) \mathcal{P}^i(C^{\text{u}}_{\text{n}(\tau)}(s)) d\tau,
\]

where \( M^i_r(0) \) are mass densities defined per unit reference area at time 0, \( Q^i(s) \in [0,1] \) represent the survival fraction of constituent \( i \) that was present at time 0 and remains at time \( s \), \( m^i_r(\tau) \) are stress-dependent mass density production rates defined per reference area at G&R time \( \tau \in [0, s] \), \( q^i(s, \tau) \in [0,1] \) represent the survival fraction of constituent \( i \) that was produced at time \( \tau \) and survives to time \( s \), and \( \mathcal{P}^i(C^{\text{u}}_{\text{n}(\tau)}(s)) \) are stored energy functions defined per unit mass of constituent \( i \) that was produced at time \( \tau \) and survives to time \( s \). The six general ‘families’ of constituents are isotropic elastin \((e)\), circumferentially oriented smooth muscle \((m)\) and four families of collagen \((c_k, k = 1,2,3,4)\), initially oriented circumferentially, axially and symmetric diagonally. G&R thus commences at \( s = 0 \), that is, the time immediately before the aneurysm begins to develop from a non-aneurysmal aorta at its homeostatic (or, maintenance) state.

Equation (2.1) reveals that three classes of constitutive relations must be prescribed for each family of constituents: \( m^i_r(\tau), Q^i(s) \) and \( q^i(s, \tau) \) and \( \mathcal{P}^i(s) \). Material frame indifference requires \( \mathcal{P}^i(s) \) to depend on the deformation gradient \( F^{\text{u}}_{\text{n}(\tau)}(s) \) through the right Cauchy–Green tensor \( C^{\text{u}}_{\text{n}(\tau)}(s) = (F^{\text{u}}_{\text{n}(\tau)}(s))^T F^{\text{u}}_{\text{n}(\tau)}(s) \). Thus, the overall stored energy function depends on deformations experienced individually by each constituent to its specific natural configuration \( k^i_r(\tau) \), at time \( \tau \) when it was produced and incorporated within the extant matrix. \( F^{\text{u}}_{\text{n}(\tau)}(s) \) depends on both the deposition stretch \( G^i(\tau) \) at time \( \tau \) when the constituent was formed and the subsequent deformation from the configuration at \( \tau \) to that at time \( s \) [18]. Note, therefore, that collagen and smooth muscle fibres were assumed to be at a homeostatic state in the \textit{in vivo} configuration at \( s = 0 \) owing to their continuous turnover; that is, their deposition stretches equalled their preferred pre-stretches \((A_b^i, A_w^i)\). In contrast, owing to its predominately perinatal production and long half-life [24,25], pre-stretches for elastin \((A_{b,1}^i, A_{w,2}^i)\) accounted for both the deposition stretch and subsequent developmental changes up to \( s = 0 \).

Because we focused on the possible development of regional variations in properties along an aneurysm and possible effects of the initial state of the aorta on subsequent enlargement, not modelling a specific lesion, we restricted our attention to an idealized axisymmetric geometry [17–19]. We also employed a membrane model, noting that such models have been shown to capture salient changes in geometry and structural stiffness by arteries during G&R [26]. Moreover, we only considered effects of intramural stress, induced by a uniform distending pressure, on the cell-mediated turnover of collagen and smooth muscle, not possible effects owing to fluid–solid interactions or intraluminal thrombus.

2.2. Production, degradation and failure of elastin

Because load-bearing vascular elastin is produced primarily during the perinatal period, \( m^e_r(\tau) = 0 \). Although elastin normally degrades slowly during maturity, it can become increasingly fragmented mechanically or degraded biochemically with ageing and hypertension [27,28], and it diminishes further in aneurysmal development [2]. Hence, we let

\[
Q^e_{\text{init}}(Z, s) = 1 - (1 - \exp(-ks))f_w(Z),
\]

where

\[
f_w(Z) = d \left\{ \exp \left[ -c_1 \left( \frac{Z - Z_0}{r_h} \right)^{c_2} \right] \right\}.
\]

\(Q^e_{\text{init}}(Z, s)\) is a spatially non-uniform survival function describing the early loss of elastin that initiates the development of an AAA, \( Z \) is the axial position in the reference configuration, \( Z_0 \) is the fixed axial length from the end of the aorta to its midpoint, \( r_h \) is the initial (homeostatic) aortic radius \textit{in vivo}, and \( d, k, c_1 \) and \( c_2 \) are model parameters. We let \( Z_0 = 15 \text{ cm}, r_h = 1 \text{ cm}, d = 0.99, k = 1/40 \text{ d}^{-1}, c_1 = 0.7, \) and \( c_2 = 6.0 \). Note that \( Z_0 \) was selected to extend the computational domain well beyond the AAA to minimize complexities owing to fixed axial boundary conditions at the ends.

Similar to Zeinali-Davarani et al. [23], we also allowed the elastin to undergo further mechanical damage (failure)—a key consideration since elastin, unlike collagen and smooth muscle, does not turn over during the enlargement of an AAA wherein the diameter can increase from 2 cm to greater than 6 cm (i.e. more than a threefold increase in circumferential stretch). Estimating the failure stretch for pure elastin is difficult, particularly for humans, owing to limitations in obtaining tissue and the processing requirements to isolate the elastin. One study using porcine aortas estimated the ultimate uniaxial stretch to be 2.2 in the descending thoracic aorta [29]. We generalized this uniaxial value \( \lambda_{\text{thr}}^e \) for our two-dimensional model via the first invariant of the right

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Cauchy–Green tensor,

\[ F_c = (\lambda_{n,1}^c)^2 + (\lambda_{n,2}^c)^2 + (\lambda_{n,3}^c)^2, \]

for all G&R times \( s \) and axial positions \( Z \), where for the available uniaxial data,

\[ F_{c, \text{ult}} = (\lambda_{n,1}^c)^2 + 2(\lambda_{n,1}^c)^{-1} = 5.75, \]

where \( \lambda_{n,1}^c \) and \( \lambda_{n,2}^c \) represent stretches from the natural configuration of elastin in circumferential and axial directions, respectively. We then modeled stretch-induced damage of elastin in terms of a complementary survival function

\[ Q^{\text{dimg}}(I_c^c) = 1 - \exp[k_{dimg}^{e}(I_c^c - F_{c, \text{ult}})], \]

for \( I_c \leq F_{c, \text{ult}} \) and \( Q^{\text{dimg}}(I_c^c) = 0 \) or \( I_c > F_{c, \text{ult}} \), where \( k_{dimg}^{e} \) was defined by prescribing a 99 per cent survival at a uniaxial elastin stretch of 2.0 from its natural configuration. In summary, the overall survival function for elastin combined losses owing to initial and subsequent stretch-induced damage, namely

\[ Q'(Z, s) = Q'^{\text{init}}(Z, s)Q^{\text{dimg}}(I_c^c(Z, s)). \]

### 2.3. Production of collagen and smooth muscle

Collagen and smooth muscle undergo continuous turnover in maturity, which requires modelling both production and removal. Of particular importance here, smooth muscle cells and fibroblasts increase their production of collagen in response to increasing stress or stretch [21,30]. Hence, we let stress-mediated production of all four collagen families be given by [18]

\[ m^k_{R}(s) = \frac{M^k_{R}(s)}{M^k_{R}(0)} m^k_{R, \text{basal}} \left[ k^k_{\sigma} \left( \sigma^k(s) - \sigma^k_{c} \right) \right] + 1, \]

where \( m^k_{R, \text{basal}} \) is the basal rate of production of the \( k \)-th family of collagen, determined by

\[ m^k_{R, \text{basal}} = \frac{M^k_{R}(0)}{a^k_{m}}, \]

with \( M^k_{R}(s) \) the mass density of collagen defined per unit reference area at time \( s \), \( k^k_{\sigma} \) a gain-type parameter for stress-dependent collagen production, \( \sigma^k(s) \) a convenient scalar metric of the Cauchy stress experienced by the \( k \)-th collagen fibre family at time \( s \), and \( a^k_{m} \) a homeostatic (target) value for collagen fibre stress calculated from prescribed and best-fit properties of an initial non-aneurysmal aorta.

By definition, \( a^k_{m} \) is the mean age of the collagen fibres such that

\[ a^k_{m} = \int_0^{\Delta t^k_{\text{max}}} q^k(\tau) \, d\tau, \]

where \( \Delta t^k_{\text{max}} \) is a prescribed maximum age for an individual collagen fibre (300 days herein), and \( q^k(\tau) \) is the survival function describing the basal loss of collagen, namely

\[ q^k(\tau) = \exp(-k^k_{q} \tau), \]

where \( k^k_{q} \) is the homeostatic rate parameter of collagen degradation. This relation served to couple basal collagen production and removal rates to ensure tissue maintenance prior to the initiation of an AAA.

We assumed the production rate of the circumferentially oriented smooth muscle to be similar, that is,

\[ m^m_{R}(s) = \frac{M^m_{R}(s)}{M^m_{R}(0)} m^m_{R, \text{basal}} \left[ \alpha^m(s) - \sigma^m_{c} \right] \]

\[ + 1, \]

\[ m^m_{R, \text{basal}} = \frac{M^m_{R}(0)}{a^m_{m}}, \]

and \( a^m_{m} \) introduced as a novel weighting function given by

\[ w^k_{c} = \int_0^{\Delta t^k_{\text{H}}} \int_0^{\Delta t^k_{\text{U}}} q^k_{\text{H}}(\tau) \, d\tau, \]

\[ w^k_{U} = \int_0^{\Delta t^k_{\text{H}}} \int_0^{\Delta t^k_{\text{U}}} q^k_{\text{U}}(\tau) \, d\tau, \]

where \( \Delta t^k_{\text{H}} \) and \( \Delta t^k_{\text{U}} \) are the half-lives of fibres when held at the homeostatic tension or completely unloaded, respectively. Consistent with
first-order kinetics, \( \tilde{c}_{1/2} = \ln(2)/k_{c} \). Thus, only one extra parameter was needed to prescribe an underloaded tension-dependent collagen degradation [32], which result from an increased proteolytic efficiency of matrix metalloproteinases (MMPs) in degrading unloaded fibres. We let \( \tilde{t}_{1/2} = 1 \) day based on parametric studies that yielded near-normal wall properties in the non-aneurysmal end regions following formation of a centrally located AAA that otherwise decreased the radius and increased wall thickness peripherally (likely in response to changes in axial loading in the presence of fixed boundaries while disallowing aortic buckling). Of course, the basal collagen survival function (equation (2.11), where \( \tilde{r} = s - \tau \)) is recovered when fibres remain at their homeostatic tension.

Data suggest that smooth muscle can lose its contractile capacity in ageing and be further compromised or lost in aneurysmal development [33]. Hence, for simplicity, let us let its survival function at each axial position \( Z \) decrease proportional to the loss of elastin according to

\[
Q^m(s, \tau) = \exp[-k_{b}^m(s - \tau)]Q'(s),
\]

where \( k_{b}^m \) is the homeostatic rate parameter related to the half-life according to \( \tilde{t}_{1/2} = \ln(2)/k_{b}^m \) and \( Q'(s) \) describes the additional loss of smooth muscle integrity related to the loss of elastin (see equation (2.7)). For completeness, note that \( Q'(s) = q'(s,0) \) and \( Q^m(s,0) = q^m(s,0) \) in equations (2.16) and (2.20), respectively.

### 2.5. Stored energy functions and membrane stress

Because G&R commences from the initially non-aneurysmal aorta, the model must capture the initial material properties of the wall, which necessarily represent an aged wall [34]. We assumed that elastin endows the wall with an isotropic behaviour, whereas both smooth muscle and collagen endow the wall with anisotropic, fibre-like behaviours. Hence, we let the stored energy functions per unit mass for these constituents be [18,19,33]

\[
\Psi^c(C_{n}(\tau))(s) = \frac{c^c}{2} \left( C_{n[1]} + C_{n[2]} + \frac{1}{C_{n[1]}C_{n[2]} - C_{n[12]}^2} \right) - 3,
\]

\[
\Psi^m(C_{m}(\tau))(s) = \frac{c^m}{4c_2^m} \left( \exp[c^m_2/(\lambda_{m}(\tau)(s)^2 - 1)^2] - 1 \right),
\]

and

\[
\Psi^s(C_{s}(\tau))(s) = \frac{c^s}{4c_2^s} \left( \exp[c^s_2/(\lambda_{s}(\tau)(s)^2 - 1)^2] - 1 \right)
\]

where \( C_{n[1]}, C_{n[2]} \) and \( C_{n[12]} \) are components of \( C_{n}(\tau)(s) \), \( \lambda_{m}(\tau)(s) \) is the stretch of the circumferentially oriented smooth muscle from its natural to its current configurations, \( \lambda_{s}(\tau)(s) \) is the stretch of the circumferentially oriented collagen from its natural to its current configurations, \( M_{m}(\tau)(s) \) and \( M_{s}(\tau)(s) \) are unit vector describing the orientation of the \( k \)th collagen fibre family, and \( c^c, c^m_2, c^s_2, c_1^c, c_1^m, c_1^s \) are intrinsic material parameters. Finally, note the assumption that constituents that turnover continuously do so within unchanging configurations over long periods prior to \( s = 0 \), thus allowing single individual natural configurations to be employed for the initial properties.

We modelled the active contribution by smooth muscle via the potential function [23,36]

\[
\rho\Psi^m_{act}(\tau, s) = S \left\{ \lambda_{act}(\tau, s) + \frac{1}{3} \left( \lambda_{M} - \lambda_{act}(\tau, s) \right)^2 \right\},
\]

where \( \rho \) is wall density, \( S \) the maximum contractile stress, \( \lambda_{act}(\tau, s) \) the active circumferential stretch defined by \( \lambda_{act}(\tau, s) = \lambda_1(\tau)/\lambda_1(s) \), and \( \lambda_M \) and \( \lambda_0 \) represent stretches at maximum and zero-active force generation, respectively. We assumed that the reference configuration for active muscle evolves with overall adaptation (i.e. \( \lambda_{act}(\tau, s) = 1 \) for each time \( s \)) and let \( \rho = 1050 \text{ kg m}^{-3} \), \( S = 54 \text{ kPa} \), \( \lambda_M = 1.4 \) and \( \lambda_0 = 0.8 \). The active smooth muscle tension in the circumferential direction was thus calculated as

\[
T_{act}(s) = \frac{M_R(s)\rho}{\lambda_1(s)\lambda_2(s)} \frac{\partial\Psi^m_{act}(\tau, s)}{\partial\lambda_1(\tau)} \big|_{\lambda_{act}(\tau, s)=1}.
\]

Finally, given the overall stored energy function \( \Psi(s) \) in equation (2.1), the membrane stress (tension) in the wall was calculated at each position and time by [23]

\[
T(s) = \frac{2}{\det F_{2D}(s)} F_{2D}(s) \frac{\partial\Psi(s)}{\partial C_{2D}(s)} F_{2D}(s)^T + T_{act}(s) \mathbf{e}_2 \otimes \mathbf{e}_2,
\]

where \( F_{2D}(s) \) and \( C_{2D}(s) \) are the two-dimensional deformation gradient and right Cauchy–Green tensors describing the motion from the reference homeostatic configuration to the \textit{in vivo} configuration at G&R time \( s \). Caucy stress was then calculated in post-processing by dividing the membrane stress by the current wall thickness \( h(s) \), where

\[
h(s) = \frac{M_R(s)}{\lambda_1(s)\lambda_2(s)}
\]

and \( M_R(s) \) is the total wall mass density defined per unit reference area.

### 2.6. Model initiation and application

To investigate the possible dependency of AAA G&R on the initial material properties of the non-aneurysmal aorta from which it arises, we used data from four middle-aged aortas (47 year-old male, 50 year-old female, 66 year-old male and 69 year-old male) that were tested biaxially by Vande Geest et al. [37] using five tension-controlled protocols with circumferential-to-axial ratios of 0.5:1, 0.75:1, 1:1, 1:0.75, and 1:0.5. Subject-specific material parameters for the constituent stored energy functions (equation (2.21)–(2.23)) and pre-stretches were determined via nonlinear regression with a weighted penalty method, while assuming that each constituent in the initial aorta was at its preferred homeostatic state.
Because neither wall thickness nor mass fractions ($\phi$) were provided with the biaxial testing data for the initial aortas, we used the following approach for consistency for each simulation. First, preliminary simulations revealed that elastin and collagen contributed much more to the initial whole-wall stress than passive muscle, hence $\phi^m$ was fixed at 0.15 to reduce the number of variables. Second, these simulations also revealed that the average homeostatic stress of elastin $\sigma^e_{h, \text{avg}}$ for a given $\phi^e$ was less sensitive to changes in wall thickness than the homeostatic stress of collagen $\sigma^c_{h}$ for a given $\phi^c$; hence, the value of $\phi^e$ was prescribed such that $\sigma^e_{h, \text{avg}} = 100 \pm 5$ kPa. Finally, using the constraint $\phi^c + \phi^e + \phi^k = 1$, the predicted value of the wall thickness for the weighted penalty within the nonlinear regression was adjusted to provide a best-fit wall thickness that yielded $\sigma^e_{h} = 100 \pm 5$ kPa. The initial collagen fraction was subdivided among the four collagen fibre families in the ratio 1:4:4:1 for circumferential, first diagonal, second diagonal and axial directions. While smooth muscle was modelled with identical parameters in tension or compression, we assumed that a proteoglycan-supported collagen fibre in compression had similar values of $c_2$ but only 7.5 per cent of the value of $c_1$ compared with its values in tension (see equation (2.23)). Whereas the best-fit material parameters, pre-stretches, collagen compression ratio for $c_1$ and homeostatic stresses were assumed constant throughout G&R, future experimental studies will be needed to evaluate these assumptions.

AAA development was simulated from each of the four subject-specific non-aneurysmal aortas using identical G&R and initial elastin degradation parameters (table 1). Separately, the stability of the homeostatic condition (i.e. tissue maintenance) was confirmed to 10 000 days using data from the 47 year-old male by Vande Geest et al. [37] are listed in table 2, along with the prescribed or calculated mass fractions and homeostatic stresses determined by the novel-fitting method to help reduce the inherently underdetermined nature of this system. Goodness of fit revealed $R^2 \geq 0.95$ for all cases. An example fitting for both circumferential and axial data for the 47 year-old male is shown in figure 1; associated material behaviour under simulated equibiaxial stress testing is shown in figure 2 for all four non-aneurysmal aortas. Whereas the oldest (69 years old) aorta was the stiffest in both circumferential and axial directions, the other aortas did not follow a clear chronological pattern for this small dataset. The 47 and 66 year-old male aortas had more compliant biaxial behaviours, whereas the 50 year-old female aorta had a stiff circumferential behaviour but more compliant axial behaviour.

3. RESULTS

3.1. Non-aneurysmal aortic properties

Best-fit values of constitutive parameters for the four selected non-aneurysmal aortas tested by Vande Geest et al. [37] are listed in table 2, along with the prescribed or calculated mass fractions and homeostatic stresses determined by the novel-fitting method to help reduce the inherently underdetermined nature of this system. Goodness of fit revealed $R^2 \geq 0.95$ for all cases. An example fitting for both circumferential and axial data for the 47 year-old male is shown in figure 1; associated material behaviour under simulated equibiaxial stress testing is shown in figure 2 for all four non-aneurysmal aortas. Whereas the oldest (69 years old) aorta was the stiffest in both circumferential and axial directions, the other aortas did not follow a clear chronological pattern for this small dataset. The 47 and 66 year-old male aortas had more compliant biaxial behaviours, whereas the 50 year-old female aorta had a stiff circumferential behaviour but more compliant axial behaviour.

3.2. Dependency on initial aortic state

Clear differences in the rate of enlargement (i.e. change in maximum radius over time) and evolving material properties arose for the four different initial aortas despite nearly identical final geometries, similar initial wall thicknesses and common mass production gain parameters and homeostatic half-lives (figures 3–5). Wall thickness at the final diameter varied axially along each of the four simulated AAAs, most dramatically in the shoulder region where elastin initially became mechanically damaged but also in the body of...

Table 1. Key growth and remodelling parameters for collagen, smooth muscle and elastin.

<table>
<thead>
<tr>
<th>Constituent</th>
<th>G&amp;R parameter</th>
<th>Symbol</th>
<th>Value</th>
<th>Units</th>
</tr>
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<tbody>
<tr>
<td>Collagen</td>
<td>Production gain</td>
<td>$k^p$</td>
<td>0.04</td>
<td>—</td>
</tr>
<tr>
<td></td>
<td>Half-life (homeostatic)</td>
<td>$k^{c, \text{fit}}$</td>
<td>50</td>
<td>days</td>
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<tr>
<td></td>
<td>Half-life (unloaded)</td>
<td>$k^{c, \text{U}}$</td>
<td>1</td>
<td>day</td>
</tr>
<tr>
<td></td>
<td>Maximum age of fibre</td>
<td>$A^c_{\text{max}}$</td>
<td>300</td>
<td>days</td>
</tr>
<tr>
<td>Smooth muscle</td>
<td>Production gain</td>
<td>$k^m$</td>
<td>0.02</td>
<td>—</td>
</tr>
<tr>
<td></td>
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<td>$k^{m, \text{fit}}$</td>
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<tr>
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<td>Maximum age of fibre</td>
<td>$A^m_{\text{max}}$</td>
<td>300</td>
<td>days</td>
</tr>
<tr>
<td>Elastin</td>
<td>Ultimate stretch</td>
<td>$A^{e, \text{fit}}$</td>
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<td></td>
<td>Initiation rate constant</td>
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<td></td>
<td>Initiation magnitude (max)</td>
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<tr>
<td></td>
<td>Initiation shape factor 1</td>
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<td>—</td>
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<tr>
<td></td>
<td>Initiation shape factor 2</td>
<td>$c_2$</td>
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</table>
the AAA where heterogeneities occurred in stress and expansion rates. Differences in simulated equibiaxial stress testing are also shown in figure 6 for the apex of each 6.5 cm diameter AAA. For comparison to the best-available experimental data, the ranges of stretches induced by approximately 80 kPa of equibiaxial stress in the AAAs tested by Vande Geest et al. [13] are represented by thin horizontal solid lines, with the diamond indicating the median value. Recall that the non-aneurysmal and AAA tissues used for initial conditions and comparisons, respectively, were unrelated and tested independently.

Table 2. Best-fit material parameters ($c$) and homeostatic pre-stretches ($h$), prescribed mass fractions ($f$), and calculated values of Cauchy stress ($t$) and wall thickness ($h$) for four subject-specific non-aneurysmal initial aortas. Note the dimensions of J kg$^{-2}$ for parameters in a stored energy function defined per unit mass. (*Elastin, *smooth muscle, *collagen, *circumferential, *axial, *homeostatic, *pass passive).

<table>
<thead>
<tr>
<th>aorta</th>
<th>age/sex (yr)</th>
<th>$c^e$ (J kg$^{-1}$)</th>
<th>$c^m$ (J kg$^{-1}$)</th>
<th>$c^l$ (J kg$^{-1}$)</th>
<th>$c^2$</th>
<th>$\lambda_{h,1}^e$</th>
<th>$\lambda_{h,2}^e$</th>
<th>$\lambda_h^m$</th>
<th>$\lambda_h^l$</th>
</tr>
</thead>
<tbody>
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<td>1</td>
<td>47 / M</td>
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<td></td>
<td></td>
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<td>1747</td>
<td>10.6</td>
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Figure 1. Best-fit constitutive modelling (closed circles) for a biaxially tested non-aneurysmal aorta from a 47 year-old male. Data (open circles) are from Vande Geest et al. [37] for five tension-controlled protocols: (a) 0.5:1, (b) 0.75:1, (c) 1:1, (d) 1:0.75, (e) 1:0.5. (a) Circumferential. (b) Axial.

Figure 2. Simulated equibiaxial stress-testing protocols for the four initial non-aneurysmal aortas endowed with best-fit constitutive parameters for a 47 year-old male (solid line), 50 year-old female (dashed line), 66 year-old male (dashed-dotted line) and 69 year-old male (dotted line). (a) Circumferential. (b) Axial.
3.3. Material heterogeneity and anisotropy

Equibiaxial stretch tests of the simulated AAAs from the least stiff (66 year-old) and stiffest (69 year-old) initial aortas at four different axial positions (apex, body, shoulder and non-aneurysmal portion) are shown in figure 7. Results from the body of the AAA and the non-aneurysmal portion were similar to those for the apical and shoulder regions, respectively, and thus are omitted for clarity. The simulated initial non-aneurysmal equibiaxial behaviours are included for comparison.

Figure 3. Variations in (i) radius, (ii) expansion rate and (iii) wall thickness of simulated AAAs resulting from initial non-aneurysmal parameters for a 47 year-old male (solid line), 50 year-old female (dashed line), 66 year-old male (dashed-dotted line) and 69 year-old male (dotted line). (a) Apical values for each AAA over time. (b) Values over axial position for each AAA when the maximum diameter is approximately 6.5 cm.

Figure 4. Variations in whole-wall (i) circumferential stress, (ii) axial stress and (iii) total mass area density of simulated AAAs resulting from initial non-aneurysmal parameters for a 47 year-old male (solid line), 50 year-old female (dashed line), 66 year-old male (dashed-dotted line) and 69 year-old male (dotted line). (a) Apical values for each AAA over time. (b) Values over axial position for each AAA when the maximum diameter is approximately 6.5 cm.
4. DISCUSSION

Using patient-specific geometric models of AAAs, Fillinger et al. [3,4] demonstrated a potential clinical advantage of assessing rupture risk based on computed wall stresses rather than simply the maximum diameter of the lesion. Maier et al. [12] recently confirmed this finding, suggesting further that both wall stress and a proposed ‘rupture potential index’ [38] can serve as reliable criteria for assessing rupture risk. Nevertheless, despite tremendous advances in computational modelling of AAAs—including methods for accurately capturing patient-specific geometries [3,39], considering potential localized concentrations of calcium [10], inferring unloaded configurations from in vivo states using inverse methods or accounting for pre-stresses that exist in vivo [9,11], including material anisotropy [5,6], and accounting simultaneously for the wall mechanics and haemodynamics [6,8,40]—nearly all prior stress analyses have assumed material homogeneity and constant wall thickness. Yet, regional heterogeneities can directly affect predicted stresses and significantly influence the underlying mechanobiological responses of cells [21] and thereby differentially alter the production of extracellular matrix constituents, the production and the activation of MMPs and the effectiveness of MMPs in degrading stressed proteins [41]. Indeed, similar heterogeneities should be expected in thoracic aortic aneurysms as well [42]. Thus, the clinical reliability of computational modelling will continue to improve as the models more faithfully represent not just the mechanics, but also the underlying mechanobiology.

In this paper, we showed that a cell-mediated G&R model can simulate the evolution of an initially non-aneurysmal aorta endowed with realistic subject-specific material properties into an idealized axisymmetric AAA having a maximum diameter, rate of enlargement and biaxial material behaviour comparable to the best-available human data. Although more complex, non-axisymmetric lesions could have been generated, we focused on idealized lesions to gain intuition into the G&R approach itself. Other complexities such as patient-specific geometry, non-uniform shear stresses that arise from fluid–solid interactions and evolving intraluminal thrombus can and should be considered in the future.

The range of best-fit material properties, prescribed mass fractions and simulated equibiaxial material behaviour exhibited by the four middle-aged non-aneurysmal aortas (table 2 and figure 2) highlight the diversity of potential initial states for AAA formation. Presently, it is unclear whether certain initial states are more susceptible to aneurysm formation since the early stages of development are clinically silent and therefore undiagnosed. Thus, all middle-aged aortas must be considered potential candidates at this time—an assumption supported by the observation that the final AAA material behaviour of each simulation is well within the range of the independent, actual equibiaxial data of Vande Geest et al. [13] (figure 6).

Fitting of the initial aortic biaxial data was satisfactory numerically \((R^2 \geq 0.95\) for all cases), yet values in table 2 represent but single best-fit solutions each to this underdetermined system, thus highlighting the need for further experimentation to bound more narrowly the expected parameter values and, if possible,
to correlate values with non-invasive patient-specific metrics. Future mechanical testing of aortic samples that include both analyses of constituent mass fractions and wall thickness would alleviate the need for the assumptions required to prescribe the initial mass fractions and would improve determination of the initial homeostatic stresses. Nevertheless, these fits were adequate for the goal of investigating, for the first time, whether differing initial aortic states can affect the evolution of regionally heterogeneous anisotropy, stiffness and wall thickness in AAAs as well as the rate at which the lesion enlarges.

Regarding the G&R parameters chosen for this study, the collagen mass production gain parameter was selected after parametric studies (range: 0.02–0.06) revealed that a value of 0.04 allowed reasonable expansion rates, thicknesses and wall stresses for all four cases up to a diameter of 6.5 cm. Increasing the value of this parameter further could even arrest the expansion completely [18], but this was not studied in detail. Rather, to focus on potential differences in AAA development owing to different initial aortic states, we assumed a fixed production gain parameter to provide a more equitable comparison. Any insight in defining the potentially evolving collagen gain parameter in a patient-specific fashion would be extremely beneficial and could alter differences in AAA development from the initial aortic state. Since the normal half-life of aortic collagen is estimated to be 60–70 days, but can decrease greatly during disease progression [43], we chose 50 days to represent an average half-life for homeostatically stressed collagen throughout AAA development. Changes in smooth muscle G&R parameters over similar ranges displayed only minimal differences in AAA enlargement and properties (not shown).

Note that the simulated biaxial behaviours of the four initial aortas demonstrated slight irregularity or abrupt transitions between the elastin-dominated neo-Hookean behaviour at low strains and the smooth muscle and collagen-dominated exponential behaviour at higher strains (figure 2). These findings may have resulted from the assumption of mechanical uniformity of each constituent in the initial homeostatic state and contributions from the compression of the proteoglycan-supported matrix. In reality, a range of fibre stretches are present within each constituent family owing to the continual nature of remodelling, thus smoothing the whole-wall stress–stretch behaviour. It is unlikely that this numerical consequence affected subsequent predictions.

To estimate the sensitivity of the results to the initial mass fractions selected by the novel-fitting method, a small parametric study was conducted using the 47 year-old male data. Because the initial mass fractions
must sum to unity, increasing one mass fraction requires a decrease in at least one other constituent. Simulations revealed that small changes (±0.05 from the selected initial mass fraction of elastin in exchange for smooth muscle, with constant collagen, had minimal effect on the development and properties of the resulting AAA. On the other hand, similar changes in elastin content in exchange for collagen produced an approximately 10 per cent change in wall thickness (and thus whole-wall stresses) at the midpoint of the aneurysm at the cut-off diameter of 6.5 cm (not shown). Interestingly, the expansion rate and individual fibre properties (i.e. maximum fibre stretch, maximum deviation in normalized fibre tension and deviation in normalized fibre-family stress) remained nearly the same. Thus, for a given initial aortic state, moderate alterations in mass fraction appear to predominately affect thickness and thus whole-wall stress within the body of the AAA, as opposed to the character of the expansion itself, provided the changes affect the mass fraction of collagen. This finding is consistent with the observation that nearly all functional elastin and smooth muscle are lost from the aorta during AAA formation. Thus, the amount of initial (and remaining) collagen is likely of primary importance to estimating wall stress accurately.

Comparison of the AAAs formed using identical G&R parameters for the four initially non-aneurysmal aortas revealed similar results for the 47 and 66 year-old males, including initial and final equibiaxial material behaviours (figures 2–6). Yet, despite similar ages, results from the 47 and 50 year-olds, as well as from the 66 and 69 year-olds, clearly differed. These findings suggested that similarities (or differences) in simulated AAA properties are linked to the mechanical properties of the initial non-aneurysmal aortas and that the dependency on the initial aorta is not strictly owing to chronological age but rather to an ‘effective’ aortic age that likely depends on patient-specific factors such as genetics, co-morbidities, diet and exercise. While in vitro biomechanical testing appears to reveal this effective age, clinical utility will require non-invasive methods of correlating initial material properties and G&R parameters with patient-specific metrics.

When considered individually, the initially stiffest aorta (69 year-old male) demonstrated the slowest rate of enlargement as well as the lowest maximum circumferential collagen fibre stretch, lowest maximum deviation in normalized tension and lowest deviation in normalized fibre-family stress. Whether these characteristics would correlate with a lower rupture potential cannot be determined from this initial study, though we note evidence suggesting that diabetics, who frequently have stiff aortas, may have a lower risk of AAA rupture [44]. Likewise, the least stiff initial aortas (47 and 66 year-olds) demonstrated the most rapid expansion and highest stresses. While the AAA from the 69 year-old developed a greater wall thickness for a given aneurysmal size, the AAAs arising from less stiff initial conditions acquired mass (and thickness) more rapidly owing to increased stress-mediated production secondary to the rapid expansion. This rapid expansion likely resulted from both the lower values of collagen material parameters (table 2) and the increased percentage of wall mass that was lost owing to the initiation of the AAA (that is, a higher initial elastin content to lose).

While each of the four trials suggested direct correlations between whole-wall stresses (figure 4) and individual measures of fibre load (figure 5), it is possible that two different aneurysms could develop while having similar whole-wall stresses at a common maximum diameter but unique individual fibre loads—suggesting that whole-wall stress measurements alone may not fully describe the vulnerability of the AAA. We confirmed this scenario in additional simulations by assigning mass fractions (elastin/collagen/smooth muscle) for the 47 and 50 year-olds of 27/10/63 per cent and 25/20/55 per cent, respectively (not shown). The ability of G&R to track individual fibre and fibre-family properties temporally and spatially is an advantage over more traditional stress analyses. In fact, with a maximum predicted collagen fibre stretch of 1.20 and normalized tension increase of over 50-fold, concern arose in this study for the potential of damage to or failure of individual collagen fibres prior to turnover. This possibility highlights the importance of considering wall strength, not just wall stress, in future predictive models of AAA rupture [45]. Conveniently, this G&R approach allows a straightforward way to include and test constitutive models of damage for individual constituents.

Overall, our results suggest that despite a nearly identical geometry (as seen in figure 3), critical characteristics such as expansion rate, wall thickness, wall stress and maximum fibre stretch can still vary widely depending on the unique initial aortic state. Thus, stress analyses based on patient-specific geometry alone, with homogeneous population-averaged material properties and wall thickness, may fail to predict a truly patient-specific rupture risk.

Comparison of the equibiaxial stress behaviour at the apex of each simulated 6.5 cm AAA with the equibiaxial data of Vande Geest et al. [13] also revealed a clear dependency on the initial non-aneurysmal aortic properties (figure 6). Although the measured range of the experimental stretches for equibiaxial stresses of 80 kPa is broad for both the circumferential and axial directions (approx. 1.01–1.11 and 1.01–1.19, respectively), our calculated behaviours for the four simulated AAAs distributed closely around the experimental median. These results affirm the ability of G&R to simulate the development of AAAs with reasonable material behaviour (even when considering idealized geometries) and suggest further that the initial patient-specific aortic state may be important in accounting for the wide range of experimentally observed material behaviours.

Simulated equibiaxial stretch plots for the least stiff (66 year-old) and stiffest (69 year-old) AAAs at four distinct axial locations (non-aneurysmal, shoulder, body and apex) revealed that spatial heterogeneity, including anisotropy, developed naturally along the AAA during G&R (figure 7). The results at the body and non-aneurysmal portion were similar to those at the apex and shoulder, respectively, and thus were omitted for clarity. The simulated equibiaxial stretch behaviours of the initial aortas were included for reference and emphasize the potential differences in evolving properties.
The 66 year-old aorta exhibited slight initial anisotropy with greater axial stiffness, which upon formation of the AAA broadened at the shoulder but inverted at the apex to become circumferentially stiffer. For the 69 year-old aorta, the remarkable initial isotropy gave way to development of slight anisotropy at the shoulder and moderate anisotropy at the apex. Comparison with the initial non-aneurysmal behaviour demonstrated that a general stiffening occurred at all wall locations, even in the portion of the model that remained non-aneurysmal—a finding likely owing to changes in axial stress induced in this region secondary to the central formation of the lesion, the fixed boundary conditions and possibly the effects of tension-dependent degradation of underloaded collagen (equation (2.17)). Although the current model does not allow out-of-plane deformations of the centreline of the aorta, such changes in axial loading could influence aortic tortuosity or buckling, commonly seen with AAAs. Overall, we note a greater change in material behaviour for the 66 year-old aorta, which possessed more initial elastin to lose during AAA formation. Thus, the degree of heterogeneity in the material behaviour, including anisotropy, also depended on the initial mechanical state of the aorta. 

We recognize, of course, that additional complexities must be addressed in future studies, but note that such complexities may only serve to increase further the predicted evolution of regional and temporal variations in AAA properties owing to complex luminal geometries, disturbed blood flows and shear stresses [20,46], heterogeneous recruitment and activation of inflammatory mediators and heterogeneous compositions and distributions of intraluminal thrombus [2,7].

5. CONCLUSIONS
Whereas others have previously measured heterogeneous material properties in actual AAAs [14–16], our results suggest that regionally heterogeneous material behaviours and wall thickness should be expected to arise naturally owing to G&R, as governed by cell-mediated mechanobiological responses to non-uniform distributions of stress generated by an initial localized dilation of a previously non-aneurysmal wall. Despite equivalent geometries, the extent of these heterogeneities, as well as the associated wall stresses and expansion rates, depended on the subject-specific mechanical state of the initial aorta. Thus, assigning population-averaged, homogeneous material properties and wall thickness to a computational model may fail to capture the very patient-specificity that is desired and necessary to assess rupture potential based on estimations of wall stress (and strength), despite using patient-specific geometries. This possibility is especially relevant considering the wide range of material behaviours observed via the best-available biaxial data on AAAs [13]. Clinically reliable modelling of aneurysmal progression and rupture risk may therefore require new and improved methods of assessing patient-specific variations in both the G&R process and the initial state of the pre-aneurysmal aorta (or correlation to the currently unaffected portions thereof) via knowledge of patient demographics, co-morbidities, lifestyle, genetics and future non-invasive or minimally invasive tests.

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