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# Aneurysm strength can decrease under calcification



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#### ABSTRACT

Aneurysms are abnormal dilatations of vessels in the vascular system that are prone to rupture. Prediction of the aneurysm rupture is a challenging and unsolved problem. Various factors can lead to the aneurysm rupture and, in the present study, we examine the effect of calcification on the aneurysm strength by using micromechanical modeling. The calcified tissue is considered as a composite material in which hard calcium particles are embedded in a hyperelastic soft matrix. Three experimentally calibrated constitutive models incorporating a failure description are used for the matrix representation. Two constitutive models describe the aneurysmal arterial wall and the third one - the intraluminal thrombus. The stiffness and strength of the calcified tissue are simulated in uniaxial tension under the varying amount of calcification, i.e. the relative volume of the hard inclusion within the periodic unit cell. In addition, the triaxiality of the stress state, which can be a trigger for the cavitation instability, is tracked. Results of the micromechanical simulation show an increase of the stiffness and a possible decrease of the strength of the calcified tissue as compared to the non-calcified one. The obtained results suggest that calcification (i.e. the presence of hard particles) can significantly affect the stiffness and strength of soft tissue. The development of refined experimental techniques that will allow for the accurate quantitative assessment of calcification is desirable.

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# 1. Introduction

Aneurysms are abnormal dilatations of vessels in the vascular system. For example, abdominal aortic aneurysm (AAA) is found in  $\sim 2\%$  of men aged 65 years (Earnshaw, 2011; Svensjo et al., 2011). In many cases AAA gradually expands until rupture causing a mortality rate of 74–90% (Acosta et al., 2006). Medical doctors consider a surgery option for enlarging AAA when its maximum diameter reaches 5.5 cm and/or expansion rate is greater than 1 cm per year. These simplistic

geometrical criteria may underestimate the risk of rupture of small aneurysms as well as overestimate the risk of rupture of large aneurysms. Biomechanical approaches to modeling aneurysm growth are needed and have been developed (Watton et al., 2004; Baek et al., 2006; Kroon and Holzapfel, 2007; Chatziprodromou et al., 2007; Watton et al., 2009; Martufi and Gasser, 2012; Volokh and Vorp, 2008; Balakhovsky et al., 2014). Despite variety of biomechanical models we still do not understand the mechanisms of aneurysm rupture. Even a simple question of whether the

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strength of the aneurysmal arterial wall is lower than the strength of the healthy arterial wall does not have a simple answer. On the one hand, there is some experimental evidence (Humphrey, 2002; Holzapfel and Ogden, 2009; Pierce et al., 2015) of the similar strength ( $\sim$ 1.2 MPa) in healthy and aneurysmal arterial walls. Intuitively, it is possible to explain the strengths' closeness by the fact that the ultimate stress is controlled by collagen fibers which are present in both diseased and healthy tissues. On the other hand, some studies (Vorp, 2007; McGloughlin, 2011) suggest that the aneurysm strength is lower in ruptured as compared to unruptured tissues. The latter conclusion may be confronted by other data (Raghavan et al., 2011) suggesting that both ruptured and unruptured aneurysms have similar strength. Finally, we mention the most recent work (Robertson et al., 2015) reporting the test results that suggest that even the strength of unruptured aneurysms can vary. We note, however, that the latter finding refers to cerebral aneurysms and similar results for AAA are not known yet.

In summary, the strength of the aneurysmal wall can alter. What factors are responsible for the strength alterations? There is no clear answer to this question. Some authors suggest that calcification can affect mechanical properties of the arterial wall (Inzoli et al., 1993; Basalyga et al., 2004; Marra et al., 2006; Speelman et al., 2007; Li et al., 2008; Maier et al., 2010; Buijs et al., 2013). The most comprehensive study of calcified versus non-calcified tissue to date is presented in (O'Leary et al., 2015) in which actual human tissue was tested. There is an encouraging correlation between the experimental results presented in (O'Leary et al., 2015) and the analyses of the present work, which is discussed below. The suggestion that mechanical properties of the artery alter is reasonable because calcification means the embedment of hard particles into the soft matrix. Such particles change the stress-strain state of the tissue. Indeed, the inclusion of hard particles normally leads to the material stiffening (Lau et al., 2015). Whether the stiffening is accompanied by the increase of the material strength? This is the question we address in the present study.

In order to assess the effect of the increasing volume of calcification on the strength of an aneurysm for a particular patient it is necessary to have the data on the specific tissue microstructure. Unfortunately, such detailed patient-specific data is still out of our routine reach, while the progress in the development of experimental techniques is promising - (Irkle et al., 2015). Thus, consideration of a tissue pattern is unavoidably qualitative and idealized yet. In the light of the latter notion we simulate uniaxial tension of an idealized calcified aneurysmal tissue up to failure, that is we micromechanically predict its strength. For the latter purpose we combine two methods: elasticity with energy limiters for the description of matrix deformation and failure (Volokh, 2011, 2013, 2014), and a finite strain high-fidelity generalized method of cells (HFGMC) for micromechanical modeling the matrix-particle composite (Aboudi et al., 2013; Aboudi and Volokh, 2015). We study the effect of the varying amount of calcification (10%, 40%, and 70%), i.e. the relative volume of the hard inclusion within the periodic elementary cell, on the tissue stiffness and strength. We consider three experimentally calibrated tissue models: two for the AAA wall and one for the AAA intraluminal

thrombus (ILT). In addition, we track the stress triaxiality, which is important for the cavitation onset.

We find, in correspondence with the previous studies, that the increase of the relative volume of calcium particles unconditionally leads to the stiffening of the tissue. At the same time the strength does not increase in the most considered cases; just the opposite, it can significantly decrease. Our quantitative results emphasize the importance of the experimental studies of calcification and the pressing need to improve the experimental techniques which "remain highly observer-dependent" (Buijs et al., 2013). Not only the amount of calcification but also the connectivity of the calcium particles might be of great value in analysis of the strength of the diseased tissue and possible considerations of the aneurysm rupture.

#### 2. Methods

#### 2.1. Constitutive modeling

In order to model deformation and failure of a soft tissue matrix we use a variant of the continuum description of bulk failure – *elasticity with energy limiters* (Volokh, 2011, 2013, 2014). The limiters enforce saturation – *the failure energy* – in the strain energy function, which indicates the maximum amount of energy that can be stored and dissipated by an infinitesimal material volume during rupture. The limiters bound stresses in the constitutive equations *automatically*.

The strain energy function can be written in the following general form

$$\psi = \psi^{f} - \mathbf{H}(\alpha)\psi^{e}(\mathbf{F}), \tag{1}$$

$$\psi^f = \psi^e(\mathbf{1}), \text{ and } \psi^e(\mathbf{F}) \to 0, \text{ when } \|\mathbf{F}\| \to \infty,$$
 (2)

where  $\psi^f$  and  $\psi^e(\mathbf{F})$  designate a constant bulk failure energy and an elastic energy respectively; H(z) is a unit step function, i.e. H(z) = 0 if z < 0 and H(z) = 1 otherwise; **1** is a second-order identity tensor;  $\mathbf{F} = \text{Grad } \mathbf{x}(\mathbf{X})$  is the deformation gradient where  $\mathbf{x}$  is the current placement of a material point which occupied position  $\mathbf{X}$  in a reference configuration; and  $\|\mathbf{F}\| = \mathbf{F} : \mathbf{F}$ , for example.

The switch parameter  $\alpha \in (-\infty, 0]$  is defined by the evolution equation

$$\dot{\alpha} = -H(\varepsilon - \psi^e / \psi^f), \quad \alpha(t=0) = 0, \tag{3}$$

where  $0 < \varepsilon < <1$  is a dimensionless tolerance constant.

The physical interpretation of (1)–(3) is straightforward: material response is hyperelastic as long as the stored energy is below its limit,  $\psi^f$ . When the latter limit is reached, then the stored energy remains constant for the rest of the deformation process, thereby making material healing impossible. Parameter  $\alpha$  is not an internal damage variable – it works as a switch: if  $\alpha = 0$ , then the process is hyperelastic and reversible, and if  $\alpha < 0$ , then the material is irreversibly damaged and the stored energy is dissipated.

Using the dissipation inequality it is possible to derive constitutive law in the following form (Volokh, 2014)

$$\mathbf{P} = -H(\alpha)\frac{\partial\psi^e}{\partial\mathbf{F}},\tag{4}$$

where **P** is the first Piola–Kirchhoff stress tensor.

The elastic energy can be defined as follows (Volokh, 2013), for example,

$$\psi^{e} = \frac{\Phi}{m} \Gamma\left(\frac{1}{m}, \frac{W^{m}}{\Phi^{m}}\right),\tag{5}$$

where  $\Gamma(s, x) = \int_{x}^{\infty} t^{s-1}e^{-t} dt$  is the upper incomplete gamma function;  $W(\mathbf{F})$  is the strain energy of intact, i.e. without failure, material and  $\Phi$  is the energy limiter, which can be calibrated by macroscopic experiments; *m* is a dimensionless material parameter, which controls sharpness of the transition to material instability on the stress–strain curve. Increasing or decreasing *m* it is possible to simulate more or less steep ruptures of the internal bonds accordingly.

For the human abdominal aortic aneurismal wall we further employ Yeoh constitutive relation for the intact material behavior (Volokh, 2015a)

$$W = c_1(I_1 - 3) + c_2(I_1 - 3)^2$$
,  $I_1 = \mathbf{F} : \mathbf{F}$ ,  $det\mathbf{F} = 1$ ,  $m = 1$ . (6)

This constitutive model has three material constants  $c_1, c_2, \Phi$  that are fitted to the results of uniaxial tension tests by using a least squares minimization procedure.

The first model – Fig. 1 – was calibrated in (Volokh and Vorp, 2008) as follows;

$$c_1 = 0.103 \text{ MPa}, \quad c_2 = 0.18 \text{ MPa}, \quad \Phi = 0.402 \text{ MPa}.$$
 (7)

The second model based on the tests reported in (Raghavan and Vorp, 2000) – Fig. 2 – was calibrated in (Volokh, 2015a) as follows;

$$c_1 = 0.52 \text{ MPa}, \quad c_2 = 3.82 \text{ MPa}, \quad \Phi = 0.255 \text{ MPa}.$$
 (8)

We note that the models are different. The first model exhibits softer response with smaller critical stress and greater critical stretch as compared to the second one. We will further use both models to study the effect of calcification.

The reader should note that the descending part of the stress-stretch curve is due to the energy limiter in (5). The limit point on the curve designates the onset of material failure. Traditional hyperelastic models of intact materials do



Fig. 1 – Cauchy stress [MPa] versus stretch (ratio of the final and initial lengths of the tissue sample) for theory (solid line) and experiment (♦) in uniaxial tension for AAA material (Volokh and Vorp, 2008).



Fig. 2 – Cauchy stress [MPa] versus stretch (ratio of the final and initial lengths of the tissue sample) for theory (solid line) and experiment (♦) in uniaxial tension for AAA material (Volokh, 2015a).



Fig. 3 – Cauchy stress [MPa] versus stretch (ratio of the final and initial lengths of the tissue sample) in uniaxial tension for ILT material (Volokh, 2015b).

not show any limit points on the stress-stretch curve and they are unable to describe failure.

In addition to the models of the aneurysmal wall we also use a constitutive model of the intraluminal thrombus for human AAA. ILT is present in about 70% of the developing abdominal aneurysms and might influence the stress distribution in the artery (Wang et al., 2001; Humphrey and Holzapfel, 2012; Tong and Holzapfel, 2015)

For ILT abluminal layer we use (Volokh, 2015b)

$$W = c_3(I_2 - 3) + c_4(I_2 - 3)^2,$$
  

$$2I_2 = \mathbf{F} : \mathbf{F} - (\mathbf{F}\mathbf{F}^T) : (\mathbf{F}\mathbf{F}^T), \quad \det \mathbf{F} = 1, \quad m = 10.$$
(9)

This model has three material constants  $c_3$ ,  $c_4$ ,  $\phi$  that were calibrated in (Volokh, 2015b) based on the experimental data from (Wang et al., 2001)

$$c_3 = 0.0337 \text{ MPa}, \quad c_4 = 0.0347 \text{ MPa}, \quad \Phi = 0.184 \text{ MPa}.$$
 (10)

The stress-stretch curve for the uniaxial tension described by the ILT model is presented in Fig. 3.

Again, the limit point of the stress-stretch curve corresponds to the onset of material instability and failure.

In simulations we assume that the calcium particles do not fail and the traditional Kirchhoff–Saint-Venant constitutive model can be used for them

$$\psi = \frac{\lambda}{2} (\mathrm{tr}\mathbf{E})^2 + \mu \mathbf{E} : \mathbf{E}, \tag{11}$$

where  $\mathbf{E} = (\mathbf{F}^T \mathbf{F} - \mathbf{1})/2$  is the Green strain tensor;  $\mathbf{1}$  is the second-order identity tensor; and Lame parameters can be defined via engineering constants as follows

$$\mu = \frac{E}{2(1+\nu)}, \quad \lambda = \frac{E\nu}{(1+\nu)(1-2\nu)}.$$
(12)

In simulations the elasticity modulus and the Poisson ratio take the following values

$$E = 10 \text{ GPa}, \quad \nu = 0.25.$$
 (13)

We note that in the case of small strains Eq. (11) coincides with the generalized Hooke law. However, the use of the Green strain suppresses the effect of the rigid body motion and, thus, it is preferable in calculations. We also note that the specific magnitude of the elasticity modulus of calcium particles is of no importance because the elasticity modulus of the soft matrix is lower by orders of magnitude and, therefore, the calcium particles can be considered as essentially rigid inclusions.

# 2.2. High-fidelity generalized method of cells micromechanics analysis

The details of the HFGMC micromechanics analysis for doubly-periodic composites at finite strains have been presented in (Aboudi and Volokh, 2015). Its generalization to the triply-periodic case which is needed for the modeling of particulate composites can be performed in the same manner. Presently, it is not necessary to derive the details of these analyses but they are briefly described in the following. Both micromechanical analyses are based on the homogenization technique in which a repeating unit cell of the periodic composite is identified.



Fig. 4 – (a) A doubly-periodic array of fiber-reinforced composite defined with respect to global initial coordinates in the plane  $X_2 - X_3$ ; (b) the repeating unit cell is defined with respect to local initial coordinates in the plane  $Y_2 - Y_3$ ; (c) a characteristic subcell  $(\beta\gamma)$  in which a local initial system of coordinates  $(\overline{Y}_2^{(\beta)}, \overline{Y}_3^{(\gamma)})$  is introduced the origin of which is located at the center; (d) A triply-periodic array of particulate composite defined with respect to global initial coordinates in  $X_1, X_2, X_3$ ; (e) the repeating unit cell is defined with respect to local initial coordinates  $Y_1, Y_2, Y_3$ ; (f) a characteristic subcell  $(\alpha\beta\gamma)$  in which a local initial system of coordinates  $(\overline{Y}_1^{(\alpha)}, \overline{Y}_2^{(\beta)}, \overline{Y}_3^{(\gamma)})$  is introduced the origin of which is located at the center.

In Fig. 4(a), a fiber-reinforced composite thus forming a doubly periodic array, defined with respect to the initial global coordinates of the  $X_2 - X_3$  plane, is shown. Its repeating unit cell, defined with respect to the initial material coordinates  $Y_2 - Y_3$ , is shown in Fig. 4(b). The repeating unit cell is divided into  $N_\beta$  and  $N_\gamma$  subcells in the  $Y_2$  and  $Y_3$  directions, respectively. Each subcell is labeled by the indices  $(\beta\gamma)$  with  $\beta = 1, ..., N_\beta$  and  $\gamma = 1, ..., N_\gamma$  and may contain a distinct homogeneous material. The initial dimensions of subcell  $(\beta\gamma)$  in the  $Y_2$  and  $Y_3$  directions are denoted by  $h_\beta$  and  $l_\gamma$ , respectively, see Fig. 4(c). A local initial coordinate system  $(\overline{Y}_2^{(\beta)}, \overline{Y}_3^{(\gamma)})$  is introduced in each subcell whose origin is located at its center.

In the framework of the doubly periodic HFGMC, the increments of the displacement vector  $\Delta \mathbf{u}^{(\beta\gamma)}$  in subcell ( $\beta\gamma$ ) are expanded into second-order polynomials as follows

$$\Delta \mathbf{u}^{(\beta\gamma)} = \Delta \overline{\mathbf{F}} \mathbf{X} + \Delta \mathbf{W}^{(\beta\gamma)}_{(00)} + \overline{Y}_{2}^{(\nu)} \Delta \mathbf{W}^{(\beta\gamma)}_{(10)} + \overline{Y}_{3}^{(\gamma)} \Delta \mathbf{W}^{(\beta\gamma)}_{(01)} + \frac{1}{2} \left( 3\overline{Y}_{2}^{(\beta)2} - \frac{h_{\beta}^{2}}{4} \right) \Delta \mathbf{W}^{(\beta\gamma)}_{(20)} + \frac{1}{2} \left( 3\overline{Y}_{3}^{(\gamma)2} - \frac{l_{\gamma}^{2}}{4} \right) \Delta \mathbf{W}^{(\beta\gamma)}_{(02)}.$$
(14)

(0)

where  $\Delta \overline{\mathbf{F}}$  denotes the increment of the global (macroscopic) deformation gradient. The term  $\Delta \overline{\mathbf{F}} \mathbf{X}$  stands for the increment of the externally applied loading on the composite. The unknown coefficient  $\Delta \mathbf{W}_{(mn)}^{(\beta\gamma)}$  are determined, as shown in (Aboudi and Volokh, 2015), from the satisfaction of the equilibrium equations, interfacial and periodic conditions.

Next, consider a particulate periodic composite, described with respect to the initial global coordinates  $(X_1, X_2, X_3)$ , see Fig. 4(d). Fig. 4(e) shows a repeating unit cell, defined with respect to initial local coordinates  $(Y_1, Y_2, Y_3)$ , of the periodic composite. Presently, the parallelepiped repeating unit cell of the composite is divided into  $N_\alpha, N_\beta$  and  $N_\gamma$  subcells in the  $Y_1, Y_2$  and  $Y_3$  directions, respectively. Each subcell is labeled by the indices  $(\alpha\beta\gamma)$  with  $\alpha = 1, ..., N_\alpha, \beta = 1, ..., N_\beta$  and  $\gamma = 1, ..., N_\gamma$ . The dimensions of subcell  $(\alpha\beta\gamma)$  in the  $Y_1, Y_2$  and  $Y_3$  directions are denoted by  $d_\alpha, h_\beta$  and  $l_\gamma$ , respectively. A local coordinate system  $(\overline{Y}_1^{(\alpha)}, \overline{Y}_2^{(\beta)}, \overline{Y}_3^{(\gamma)})$  is introduced in each subcell whose origin is located at its center, see Fig. 4(f).

In the framework of the triply periodic HFGMC, the increments of the displacement vector  $\Delta \mathbf{u}^{(\alpha\beta\gamma)}$  in the subcell  $(\alpha\beta\gamma)$ are expanded into second-order polynomials as follows

$$\begin{split} \Delta \mathbf{u}^{(a\beta\gamma)} &= \Delta \overline{\mathbf{F}} \mathbf{X} + \Delta \mathbf{W}^{(a\beta\gamma)}_{(000)} + \overline{Y}^{(a)}_{1} \Delta \mathbf{W}^{(a\beta\gamma)}_{(100)} + \overline{Y}^{(\beta)}_{2} \Delta \mathbf{W}^{(a\beta\gamma)}_{(010)} \\ &+ \overline{Y}^{(\gamma)}_{3} \Delta \mathbf{W}^{(a\beta\gamma)}_{(001)} \\ &+ \frac{1}{2} \left( 3 \overline{Y}^{(\alpha)2}_{1} - \frac{d^{2}_{\alpha}}{4} \right) \Delta \mathbf{W}^{(a\beta\gamma)}_{(200)} + \frac{1}{2} \left( 3 \overline{Y}^{(\beta)2}_{2} - \frac{h^{2}_{\beta}}{4} \right) \Delta \mathbf{W}^{(a\beta\gamma)}_{(020)} \\ &+ \frac{1}{2} \left( 3 \overline{Y}^{(\gamma)2}_{3} - \frac{l^{2}_{\gamma}}{4} \right) \Delta \mathbf{W}^{(a\beta\gamma)}_{(002)} \end{split}$$
(15)

where  $\Delta \overline{FX}$  consists of the externally applied loading, and the coefficients  $\Delta \mathbf{W}_{(lmn)}^{(\alpha\beta\gamma)}$  are determined by implementing the equilibrium equations together with the interfacial conditions. In addition, periodic conditions must be imposed to ensure that the tractions and displacements are equal at the opposite sides of the repeating unit cell.

Both micromechanical analyses ultimately establish at the current loading increment the 4th-order instantaneous concentration tensor  $\mathbf{A}^{(\alpha\beta\gamma)}$  which relates the increment of the local deformation gradient (in the subcell)  $\Delta \mathbf{F}^{(\alpha\beta\gamma)}$  to the current externally applied far-field global deformation

gradient increment  $\Delta \overline{\mathbf{F}}$ , namely

$$\Delta \mathbf{F}^{(\alpha\beta\gamma)} = \mathbf{A}^{(\alpha\beta\gamma)} : \Delta \overline{\mathbf{F}}.$$
(16)

For the three hyperelastic strain energy functions discussed above, it is possible to establish the first Piola–Kirchhoff stress tensor  $\mathbf{P}^{(\alpha\beta\gamma)}$  and the corresponding fourth-order tangent tensor  $\mathbf{R}^{(\alpha\beta\gamma)}$  in the form

$$\Delta \mathbf{P}^{(\alpha\beta\gamma)} = \mathbf{R}^{(\alpha\beta\gamma)} : \Delta \overline{\mathbf{F}}.$$
(17)

The increment of the average stress in the composite is given by

$$\Delta \overline{\mathbf{P}} = \frac{1}{DHL} \sum_{\alpha=1}^{N_{\alpha}} \sum_{\beta=1}^{N_{\beta}} \sum_{\gamma=1}^{N_{\gamma}} d_{\alpha} h_{\beta} l_{\gamma} \Delta \mathbf{P}^{(\alpha\beta\gamma)}$$
(18)

Substituting the incremental constitutive Eq. (17) for  $\Delta \mathbf{P}^{(\alpha\beta\gamma)}$ and employing Eq. (16) establishes in the macroscopic (global) incremental constitutive equation of the composite

$$\Delta \overline{\mathbf{P}} = \mathbf{R}^* : \Delta \overline{\mathbf{F}},\tag{19}$$

where  $\mathbf{R}^*$  is the effective instantaneous 4th order first tangent tensor of the composite which is given by

$$\mathbf{R}^{*} = \frac{1}{DHL} \sum_{\alpha=1}^{N_{\alpha}} \sum_{\beta=1}^{N_{\beta}} \sum_{\gamma=1}^{N_{\gamma}} d_{\alpha} h_{\beta} l_{\gamma} \mathbf{R}^{(\alpha\beta\gamma)} : \mathbf{A}^{(\alpha\beta\gamma)}.$$
(20)

In conclusion, the HFGMC micromechanical method for both doubly-periodic and triply-periodic composites can establish the macroscopic constitutive equations which govern the behavior of composites that are composed of hyperelastic materials characterized by softening effects which lead to loss of static stability. This loss of static stability in a subcell which is filled by a hyperelastic material affects the composite response and indicates the occurrence of the initiation of failure in the composite.

The reliability of the finite strain doubly-periodic HFGMC macroscopic response has been verified in (Aboudi and Volokh, 2015) by considering a hollow cylinder subjected to externally applied radial stretch and zero axial deformation. In the absence of softening effects, exact analytical solutions can be developed for several types of hyperelastic materials with substantially different stiffening and softening behavior. In the presence of softening however, finite-difference solutions have been established. Both solutions have been employed for comparisons with the predicted HFGMC response and excellent agreements observed. For the triply-periodic HFGMC the same approach for verifications can be followed, see (Aboudi and Arnold, 2000) where the less accurate HFGMC predecessor micromechanical model was verified.

## 3. Results

In this section we present results of micromechanical simulations of the calcified tissues in uniaxial tension. Our software is an in-house one and it is based on the detailed description of the micromechanical analysis given by Aboudi, Arnold and Bednarcyk (Aboudi et al., 2013). For the simulation we use the approaches discussed above which include a failure description of soft hyperelastic matrix and a micromechanical account of the hard inclusions. Three types of composites are examined. The first one is described by the constitutive Eqs. (6) and (7) for the aneurysmal tissue and it is called from now the Aneurysm model - 1 (A-1). The second one is described by the constitutive Eqs. (6) and (8) for the aneurysmal tissue and it is referred to as the Aneurysm model - 2 (A-2). The third one is described by the constitutive Eqs. (9) and (10) for the intraluminal thrombus and it is called the ILT model. The soft matrix is enhanced with hard inclusions which are assumed to be distributed periodically and placed in the center of unit cells as shown in Fig. 4. Doubly-periodic (2D) and triply-periodic (3D) micromechanical modeling are performed for every composite. In the 2D case the hard inclusion is cylindrical and in the 3D case the hard inclusion is cubic. We note that the shape of real calcium particles can vary and, consequently, we are interested in different shapes of inclusions for our idealized studies. Constitutive Eqs. (11)-(13) describe the mechanical behavior of the hard inclusions.

We emphasize that the constitutive description of the soft matrix includes failure - the limit points in Figs. 1-3. When the limit point is passed locally during loading then static equilibrium is lost and failure initiates, localizes, and propagates through the material. In the present study (and using the approaches described above) we only track the initiation of failure which is the material strength in uniaxial tension. Thus, we simulate the whole quasi-static loading path including the failure onset, namely, the strength. Twenty four simulation cases are presented in Figs. 5-8. The results for 2D models with the cylindrical inclusions and 3D models with cubic inclusions appear on the left and right sides of the figures accordingly. The stress-stretch curves are generated up to the starred failure points for the varying amount of calcification. We used the whole scale variation of the calcification including 10%, 40%, and 70%. We should remind the reader that the amount of calcification is equal to the relative volume of the hard inclusion in the unit material cell. The graphs present uniaxial Cauchy stress versus stretch (the ratio of a fiber length after and before deformation). Figs. 5–7 present stress–stretch curves for two aneurysmal matrix models and thrombus matrix model with hard inclusions of calcium particles. (In the 2D case the direction is transverse to the direction of the cylinder, namely, in the  $X_2$  direction.)

Observation of the results for the first calcified aneurysmal model - Fig. 5 - suggests that the increase of the amount of calcified particles unconditionally leads to the increase of the material stiffness in all simulated cases. This result perfectly corresponds with our knowledge of the mechanical behavior of composite materials as a whole. Indeed, hard particles always stiffen the matrix material. More subtle is the observation of the influence of calcification on the strength of the composite. The uniaxial strength of the matrix material is about 1.1 MPa - Fig. 1. The uniaxial strength of the composite - stars in Fig. 5 - is from 20% to 40% lower as compared to the pure matrix strength. It is interesting to note that in the case of cubic inclusions the strength monotonically decreases with the increase of calcification. In the case of cylindrical inclusions the strength decrease is not monotonic and 40% calcified tissue has higher relative strength that 10% and 70% calcified ones.

Observation of the results for the second calcified aneurysmal model – Fig. 6 – suggests that the increase of the amount of calcified particles again leads to the increase of the material stiffness in all simulated cases, as expected. The uniaxial strength of the matrix material is about 1.3 MPa – Fig. 1. The uniaxial strength of the composite – stars in Fig. 6 – alters in different ways for different amounts of calcification and different inclusion types. For example, the strength decreases to 1.2 MPa only for the cylindrical inclusions with 40% and 70% of calcification, while the decrease is more drastic (0.8 MPa) for the 10% calcification. The strength decreases to 1.0 MPa for cubic inclusions with 10% and 70% of calcification, while the strength slightly increases to 1.4 MPa for the 40% calcification.



Fig. 5 – Cauchy stress [MPa] versus stretch in uniaxial tension for the 1st aneurysmal material model with varying calcification.



Fig. 6 – Cauchy stress [MPa] versus stretch in uniaxial tension for the 2nd aneurysmal material model with varying calcification.



Fig. 7 - Cauchy stress [MPa] versus stretch in uniaxial tension for the ILT material model with varying calcification.

The results presented in Figs. 5 and 6 were obtained for an idealized calcified aneurysm tissue and they cannot be directly compared to the available experimental data. Nevertheless, some qualitative comparisons with the experimental data from (O'Leary et al., 2015) can be drawn. Indeed, O'Leary et al. (2015) report that "a statistically significant difference was found between the fibrous and partially calcified group for failure stress, i.e.  $1.20\pm0.33$  MPa versus  $0.87\pm0.32$  MPa..." Some correlation between these numbers and failure strength for 10% calcification in Figs. 5 and 6 is evident yet it should not be overstated because of the difference in the considered calcification distribution in (O'Leary et al., 2015) and the present study.

Observation of the results for intraluminal thrombus model – Fig. 7 – eventually shows that the increase of the amount of calcified particles leads to the increase of the material stiffness in all simulated cases. The uniaxial strength of the ILT material is about 0.55 MPa – Fig. 3. The uniaxial strength of the composite – stars in Fig. 7 – is lower as compared to the pure matrix strength. In the case of cubic inclusions the strength monotonically decreases with the increase of calcification. In the case of cylindrical inclusions the strength decrease is not monotonic and 40% calcified tissue has higher relative strength that 10% and 70% calcified ones. There is some qualitative resemblance between the strengths of the calcified ILT tissue and the first calcified aneurysmal tissue presented in Figs. 5 and 7.



Fig. 8 - Cauchy stress [MPa] versus stretch in uniaxial tension for the porous materials.

The simulations presented above have been done for hard particles embedded in a soft matrix. It is of interest also to generate the uniaxial stress–stretch curves for porous materials in which the hard particles are removed leaving empty voids. The simulation results for cylindrical (2D) and cubic (3D) voids with 10% porosity are presented in Fig. 8 for all material models. It is interesting that a drastic decrease of the material strength is observed for all models with cylindrical voids. For cubic voids, only the second aneurysmal model exhibited a significant strength decrease while two other models kept the strength level unaltered.

The simulations of porous materials described above were performed under the assumption of a significant amount of large (10% volume fraction) pre-existing voids. Such big voids do not necessarily exist in real tissues. However, the microscopic voids on the micron scale can exist. Indeed, the formation of thrombus and the development of the aneurysmal arterial wall are accompanied by significant morphological alterations that can leave microscopic voids inside tissues. Such voids can dramatically increase in diameter cavitation phenomenon - and, then, coalesce forming macroscopic crack. The cavitation occurs under hydrostatic tension and it can cause a significant decrease of tissue strength (Volokh, 2015a, 2015b). We emphasize that cavitation requires the state of hydrostatic tension and the inclusion of hard particles in soft tissue can produce such a state. It is commonly accepted in the literature to measure the state of hydrostatic Cauchy stress by using the triaxiality ratio

$$\kappa = \frac{\operatorname{tr} \boldsymbol{\sigma}}{3\sqrt{(3/2)\boldsymbol{\sigma}':\boldsymbol{\sigma}'}},\tag{21}$$

where the prime designates the deviatoric parts of the stress tensor.

To track the triaxiality ratio we generated the maps of  $\kappa$  for the three models of soft tissue defined above and enhanced with 10% cylindrical calcium particles. The maps presented in Figs. 9–11 correspond to the loads close to the critical failure loads – near the starred strength points in Figs. 5–7.

Triaxiality map: aneurysm model-1



Fig. 9 – Triaxiality ratio distribution for 10% calcification for aneurysm model-1 at the failure load.

The material points with high triaxiality ratio are circled in Figs. 9-11. This points appear at the vertical poles of the inclusion. The latter is reasonable, of course, because tension is applied in the vertical direction and deformations at the points near the poles are the most restrained ones. Indeed, the underlying hard inclusion does not allow the soft material at the poles to freely extend in the vertical direction and, thus, the inclusion creates the state of hydrostatic tension. Our finding corresponds well to the experimental results obtained for filled rubbers in which cavitation was observed near rigid inclusions (Gent, 2004, 2012). We also mention that we showed the triaxiality ratios for the 10% calcification where the points with hydrostatic tension are pronounced. However, we also generated maps for 40% and 70% calcification. The latter maps are not shown because no significant hydrostatic tension was observed. Thus, the smaller amounts

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Triaxiality map: aneurysm model - 2



Fig. 10 – Triaxiality ratio distribution for 10% calcification for aneurysm model-2 at the failure load.



Fig. 11 – Triaxiality ratio distribution for 10% calcification for ILT model at the failure load.

of calcification are more dangerous than the larger ones as a potential trigger of cavitation.

## 4. Discussion

This theoretical study appears to be the first report on the influence of calcification on the strength (and stiffness) of the aneurysmal arterial wall including intraluminal thrombus. Novel modeling techniques have been developed in this study. First, hyperelasticity with energy limiters was used to describe deformation and *failure* of soft matrix material and three experimentally calibrated constitutive laws for the aneurysmal arterial wall and thrombus were applied. Second, the finite strain high-fidelity generalized method of cells (HFGMC) was used for the micromechanical modeling of the soft matrix–calcium particle composite. Combining these

techniques it became possible to perform full-scale micromechanical simulations of uniaxial tension in calcified tissues. These simulations allowed for generating stress–stretch curves including the point of the onset of mechanical failure – the strength. The stress–stretch curves were generated for 18 different cases of the aneurysmal composite materials containing cylindrical or cubic inclusions at various amounts of calcification: 10%, 40%, and 70%. In addition, the maps of the stress triaxiality ratio distribution were generated which indicated the locations of the possible occurrence of cavitation that might trigger the initiation of cracks.

Based on the simulation results we found that any amount of calcification leads to the aneurysm stiffening. This finding is in a good qualitative agreement with the similar findings for composite materials in general and calcified human cartilage tissue in particular (Lau et al., 2015). While the stiffening effect of the embedded hard particles is well documented in the literature on composite materials, the study of the strength (not stiffness) alterations is quite unusual. Such an asymmetry in results on stiffness and strength is not surprising, of course. The problem is that the constitutive description of the traditional material models does not include failure and, consequently, no strength predictions can be made. That is not the case of our study, however. We did include a material failure description in the constitutive model for soft matrix and, thus, we were able to study the strength of the composite.

Our simulations of the strength of the calcified tissue showed various outcomes. The strength may not alter or it may even increase as compared to the regular non-calcified tissue. The variability of the outcome of numerical simulations can be explained by the variability of the models and there is no one clear behavioral pattern that can be explained by one clear reason. Everything is case-dependent. However, in the majority of the considered cases the decrease of the strength with calcification was observed. Quantitatively, the strength decrease could vary from 10% to 40% and more. The reader might find it contrary to intuition that the strength can decrease while the stiffness always increases with calcification. This interesting finding emphasizes the difference between the concepts of stiffness and strength which is not always appreciated. The strength of a composite is significantly affected by the locally inhomogeneous state of deformation. Small hard particles rather than big ones can be stress concentrators amplifying the likelihood of the local material failure. Also the hard particles restrain deformation in their vicinity creating the state of hydrostatic tension which, in its turn, may trigger cavitation with the subsequent fracturing.

The obtained results have limitations, two of which we should mention. Firstly, it was assumed in our studies that the calcium particles were uniformly distributed within the tissue. That was an idealization, of course. Distribution of calcium is highly aneurysm-specific. Moreover, the calcium particles can be interconnected which may significantly affect the mechanical response of the composite tissue. The latter problem was considered in the recent study of the cartilage calcification presented in (Lau et al., 2015). Unfortunately, the lack of the experimental data and the difficulty of the calcium counting (Buijs et al., 2013) prevented us from the

more patient-specific simulations. There is no doubt, nevertheless, that the modeling approach considered in our work can be readily adapted to any patient-specific simulation based on the available experimental data. Secondly, we completely ignored possible compliance and failure properties of the matrix-particle interface. Such interface can be of importance as it can affect both overall stiffness and strength of the composite (Aboudi and Volokh, 2015). Strictly speaking, it is necessary to develop and calibrate a cohesive surface model for the matrix-particle interface. Unfortunately, no experimental data on the matrix-particle debonding in calcified aneurysms is available to do the calibration. When the test data is available then a cohesive surface model can be calibrated and the high-fidelity generalized method of cells (HFGMC) can be properly modified to incorporate the interface failure description (e.g. Aboudi and Volokh, 2015). Despite the mentioned limitations, we believe that the results presented in our study are valuable and give a qualitative assessment of the effect of calcification on the aneurysm strength.

**Remark 1.** The present study focused on the calcification effect in aneurysms. However, we should mention works (Maldonado et al., 2012; Cunnane et al., 2014) devoted to the studies of the calcification effect on the mechanical properties of atherosclerotic plaques. In these works a strength reduction in the plaques with the increasing volume of calcification was reported. Results of our numerical simulations echo the results for the atherosclerotic plaques.

**Remark 2.** Tissue stiffness inevitably increases with calcification under condition of the complete bonding between the particles and soft matrix. If the bonding is incomplete then the stiffness can obviously decrease. The latter situation cannot be excluded in the process of gradual calcification.

# 5. Conclusion

Results of the present study show an increase of the stiffness and a possible decrease of the strength of the calcified aneurysmal tissue as compared to the non-calcified one. The observation that calcification (i.e. the presence of hard particles) can significantly affect the stiffness and strength suggests the necessity to develop refined experimental techniques for the accurate quantitative and qualitative assessment of the calcification effect.

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