A layer-specific 3D model for the simulation of balloon angioplasty using MR imaging and mechanical testing¹

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Abstract. A detailed understanding of the mechanical procedure of balloon angioplasty requires three-dimensional modeling and efficient numerical simulations. We have developed a 3D model for eight distinct arterial components associated with specific mechanical responses. The 3D geometrical model is based on in vitro MRI of a human stenotic post-mortem artery and is represented by NURBS surfaces. Mechanical tests of the corresponding vascular tissues provide a fundamental basis for the formulation of large strain constitutive laws, which model the typical anisotropic, highly nonlinear and inelastic mechanical characteristics under supra-physiological loadings. The 3D finite element realization considers the balloon-artery interaction and accounts for vessel-specific axial in situ prestretches. 3D stress states of the investigated artery during balloon expansion and stent deployment were analyzed. Furthermore, we studied the changes of the 3D stress state due to model simplifications, which are characterized by neglecting axial in situ prestretch, assuming plane strain states and isotropic material responses, as commonly utilized in previous works. Since these simplifications lead to maximum stress deviations of up to 600% – where even the stress character may interchange – the associated models are in general inappropriate. The proposed approach provides a tool that has the potential (i) to improve procedural protocols and the design of interventional instruments on a lesion-specific basis, and (ii) to determine post-angioplasty mechanical environments, which may be correlated with restenosis responses.

Keywords—Atherosclerosis, Balloon angioplasty, Stent, MRI, Mechanical model, Mechanical stresses, Finite element analysis.
1 Introduction

Balloon angioplasty and stenting are purely mechanical procedures, which aim to dilate stenotic or occluded arteries in order to restore blood flow. A more detailed understanding of the underlying mechanics of angioplasty and an optimization of the interventional protocols may lead to significant improvements of the outcome. Surprisingly, only a small number of physical and computational models concerned with balloon angioplasty have been published, although this interventional treatment is of great and steadily growing medical, economical and scientific interest. Based on experimental data of arterial tissues involved, appropriate geometrical and physical modeling, and efficient numerical realizations using the finite element method. In particular, the model must operate in both the physiological and the supra-physiological loading domain.

Interventionists are interested in methods that allow the determination of appropriate procedural parameters such as diameter ratio (balloon to artery), balloon length, inflation pressure etc., as well as optimal instruments such as stents with specific designs. Moreover, models that allow the prediction of the primary success of interventional treatments on a lesion-specific basis may improve patient selection, i.e. the selection of patients for which balloon angioplasty is the optimal therapeutical choice. Additionally, for biomedical engineers, appropriate models may help develop novel designs of interventional instruments such as balloons and stents and to study their performance on a computational basis. From a computational point of view these types of problems are of particular interest since they involve a number of challenging fields in computational mechanics, such as nonlinear continuum and contact mechanics and the numerical simulation of nonlinear material behavior at large strains.

To the authors’ knowledge for all existing computational models developed for the simulation of balloon angioplasty, the non-diseased arterial wall is modeled as a homogeneous and single-layer structure. This is clearly inconsistent with histological evidence, since even the native arteries are three-layer structures. Moreover, all of these studies assumed a homogeneous plaque, except the study by Lee et al., who assumed the plaque to consist of two different materials. A unique feature of the work is that the geometrical models of arterial cross-sections (post-mortem human iliacs) are based on intravascular ultrasound imaging, while all other works are based on hypothetical geometries. However, Lee and colleagues do not model the balloon, whereas the other studies incorporate balloon-artery interaction as a computational contact problem. Most of the studies use material properties of animal vascular tissues, which are more distensible in comparison with aged human tissues. Concerning the physical model, it turns out that only Oh et al. considered a failure criterion for the plaque (regarding the fracture at the plaque-artery junction site), which is, however, not based on experimental data. In particular, no model exists, which captures non-recoverable deformations caused by balloon dilatation as observed in experiments.

It is well established in the literature that non-diseased arterial walls behave cylindrically orthotropic (see, for example, the classical paper by Patel and Fry) and exhibit a nonlinear stress-strain response with a typical stiffening effect at higher pressures. For the mechanics of arterial walls see the excellent survey text by Humphrey. Surprisingly, concerning the
numerical simulation of balloon angioplasty, there is only the study by HOLZAPFEL et al.\textsuperscript{18} who model the non-diseased arterial wall as an orthotropic material at finite strains, whereas all others assume isotropic material responses. LEE and colleagues\textsuperscript{25} use even more simplified constitutive models representing linear elastic and isotropic behavior, which are clearly not valid for the considered large strain domain. Analogous to the arterial wall, the plaque is modeled as an isotropic material in all existing models, where, again LEE et al.\textsuperscript{25} use constitutive laws which are additionally linear elastic. To the authors’ knowledge it appears that none of the discussed models considered three-dimensional non-axisymmetrical geometries. Furthermore, there is only the paper by HOLZAPFEL et al.,\textsuperscript{18} which models axial \textit{in situ} prestretch, a well-known phenomenon in arterial wall mechanics.\textsuperscript{3,33} In summary: the existing models do not consider essential mechanical characteristics of arterial stenoses undergoing large deformations at therapeutic loadings, which are far beyond the physiological domain.

The present paper aims to describe a refined model, which considers three-dimensional morphological data coming from high-resolution magnetic resonance imaging and associated histological analyses of an individual human stenosis. Data from mechanical tests were used to establish constitutive laws, whereas eight different arterial tissues are considered. The constitutive laws represent anisotropic and nonlinear material responses at large strains. The model is suitable to describe non-recoverable deformations due to therapeutic loadings. In addition, the model incorporates balloon-artery interactions, simulates three-dimensional geometries and considers axial \textit{in situ} stretches.

We begin, in section ‘Methods’, by giving a brief description of the human stenotic artery investigated and present a technique for geometrical modeling, which employs NURBS surfaces (Non-Uniform Rational B-Splines) fitted to MR image-based morphological data. NURBS have become the \textit{de facto} standard for representing free-form models of objects processed by computers.\textsuperscript{37} An essential objective of this paper is to present the physical and numerical modeling of stenotic arteries. In particular, we study the numerical simulation of balloon dilatation of the human stenotic artery investigated and the influences of model simplifications on the stress results. As an additional application the numerical simulation of stent deployment is presented. The paper closes with a critical discussion of the obtained results and points out the limitations of the proposed model.

2 Methods

\textbf{Specimen.} An external iliac artery (male, 68 years) was excised from a corpse during autopsy within 24 hrs after death. For subsequent mechanical testing only fresh tissues were used. Axial \textit{in situ} prestretch, defined as \textit{in situ} length/\textit{ex situ} length denoted by $\lambda_{\text{ist}}$, was 1.04. A straight segment of the artery (20.0 mm) with an eccentric stenosis was scanned by means of high-resolution magnetic resonance imaging (cross-sections with an in-plane resolution of 0.3 mm and an axial resolution of 1.0 mm). Then the artery was cut through transversely into two halves. One half was used for corresponding histological analyses to allow material characterization, while the other half was dissected anatomically into its major components, which are
non-diseased intima I-nos*, collagenous cap I-fl (fibrotic part at the luminal border), fibrotic intima at the medial border I-fm, calcification I-c, lipid pool I-lp, non-diseased media M-nos, diseased fibrotic media M-f and adventitia A. From these components, stripes with axial and circumferential orientations were cut out and underwent cyclic uniaxial extension tests with continuous recording of tensile force, stripe width and gauge length at a constant crosshead speed of 1 mm/min. Two black colored straw chips were glued transversely in parallel onto the middle part of the strips to act as gauge markers for the axial deformation measurements. For most specimens preconditioning was achieved by executing five successive loading cycles. Typical specimen geometries can be estimated from Figure 1. The calcification and the lipid pool were excluded from the tests and considered as rigid body and incompressible (very soft) solid, respectively.

The histological information of the vessel half, which was analyzed histologically, was used to correlate the multiphasic hrMRI-data with the histological tissue type. These correlations were also applied to the second vessel half for which no histology was available. Similarly, the constitutive equations determined for the arterial components of the vessel half tested mechanically were used for the other half. A more detailed description of the procedure and the experimental results obtained can be found in HOLZAPFEL et al.21

The resulting data sets, which contain geometrical information, histological characterizations and mechanical behaviors serve as a fundamental basis for the generation of the physical and numerical models.

**MR Image Based Geometrical Modeling.** For each scanned cross-section, the borders of the arterial components were traced manually by a series of points. The traced cross-sections were combined along the arterial axis, which resulted in a set of 3D point clouds representing the boundary surfaces of the components. Finally, each of the boundary surfaces was represented as a NURBS spatial model,37 which was fitted to the associated point cloud. In our days, NURBS are a standard approach for the representation of complex geometric information processed by computers. For a complete source on the underlying concept the interested reader is referred to the books by HOSCHEK and LASSER,22 and PIEGEL and TILLER.37

The use of NURBS provides smooth surfaces, which are typically present in biological structures of the investigated type. They provide a suitable basis for mesh adaption procedures that allow mesh refinement with respect to the (original) reference geometry.

**Physical Modeling.** The investigated arterial components are assumed to be (nearly) incompressible fiber-reinforced composites, which exhibit strongly nonlinear anisotropic responses and which undergo large strains.17 They show a pronounced stiffening behavior in the large strain domain due to collagen fiber recruitment.17,24 Specific parallel arrangements of the collagen fibers in form of fiber families38 lead to anisotropic material responses. For the arterial tissues investigated we observed that most tissue types responded with abrupt failure when exposed to loads that are far beyond the physiological range, while the non-diseased media responded with non-recoverable deformations before tissue failure occurred (for the stress-strain

*The abbreviation ‘nos’ is frequently used in histopathology and stands for not otherwise specified. In the context of the present study it means ‘no appreciable disease’, or, more precisely ‘non-atherosclerotic’.
response of the non-diseased media, see Holzapfel et al.\textsuperscript{21}). The physiological range of tissue stresses is assumed to be in the order of $50 - 100\text{ kPa}$ at the mean arterial pressure of $100\text{ mmHg}$ and axial \textit{in situ} stretch. This is justified by experimental data published by Cox\textsuperscript{7} for circumferential wall stresses in dog iliac arteries, by Fang et al.\textsuperscript{12} for wall stresses of rabbit iliac arteries in both directions, and by unpublished data of human aged iliac arteries performed in the authors’ laboratory.\textsuperscript{42}

The non-recoverable deformations may come mainly from damage mechanisms and also from plastic-type phenomena. In order to trace a practicable approach and due to the lack of appropriate data about microstructural processes associated with non-recoverable deformations, we decided to apply the theory of plasticity. The non-recoverable deformations in the supra-physiologically loaded non-diseased media are modeled as follows:

(i) the assumed model fibers slip relative to each other, which leads to ‘plastic’ deformations and associated energy dissipation, and

(ii) hardening effects occur due to rearrangements of the histological structure.

Clearly, we do not postulate a molecular mechanism which is based on plastic behavior. However, we apply the theory of plasticity for the phenomenological description of the material response of arterial specimens tested subjected to supra-physiological loadings. For all fiber-reinforced soft tissues involved, we propose, as a general description of the energy stored per reference volume in the material (denoted by $\Psi$), the following additive formulation

\begin{equation}
\Psi(F_e, a_1, a_2, \xi) = \Psi_e(F_e, a_1, a_2) + \Psi_h(\xi),
\end{equation}

where the first term $\Psi_e$ is the strain-energy contribution associated with the elastic response of the material. The second term $\Psi_h$ is the energy associated with hardening effects governed by the (scalar) variable $\xi$. It is an internal variable and is referred to as the equivalent plastic strain in the constitutive theory of plasticity. Consequently, this term is zero if only elastic responses are considered. In eq. (1) the tensor variable $F_e$ refers to the elastic component of the multiplicatively decomposed deformation gradient $F$ (see, for example, Simo and Hughes\textsuperscript{44}). Further arguments in $\Psi$ refer to the preferred fiber orientations within an individual arterial tissue in form of the unit vectors $a_1$ and $a_2$ with respect to the reference configuration. The unit vectors are supposed to represent the average directions of two fiber families embedded in the ground substance and are given as the two angles $\delta_1$ and $\delta_2$, measured from the circumferential direction. The fiber orientations used for the proposed model are determined by means of histology and customized image processing tools.\textsuperscript{20,21} Hence, this approach leads to an anisotropic \textit{histomechanical} constitutive model.\textsuperscript{19} It turned out that the arterial components investigated exhibit a symmetric arrangement of the two fiber families,\textsuperscript{21} such that $\delta_1 = \delta_2$.

For the modeling of the elastic contribution $\Psi_e$ of the strain energy, we use a \textit{unique} decoupled representation, which consists of \textit{volumetric} and \textit{isochoric} parts,\textsuperscript{19} of the form

\begin{equation}
\Psi_e(F_e, a_1, a_2) = U(J) + \Psi_{gs}(\bar{J}_1) + \sum_{\alpha=1}^{2} \Psi_f(\bar{J}_4^\alpha),
\end{equation}
where $U$, $\Psi_{gs}$ and $\Psi_{f}^0$ are given (objective) scalar-valued functions. This decoupled formulation is standard for the finite element simulation of (nearly) incompressible materials.\textsuperscript{19}

With the particularization $U = \kappa ((J - 1)^2 / 2$ we describe the volumetric and isotropic elastic response, where $J = \det \mathbf{F}_e > 0$ is the volume ratio and $\kappa > 0$ serves as a user-specified and mathematically motivated penalty parameter. An increase of $\kappa$ reduces the violation of the incompressibility constraint $J = 1$. An appropriate value for $\kappa$ is determined through numerical experiments. The isochoric and isotropic elastic response is represented by the neo-Hookean model $\Psi_{gs} = \mu (I_1 - 3) / 2$, where $\mu$ denotes a (stress-like) material parameter and $I_1 = \text{tr} \mathbf{C}_e$ is the first invariant of the modified (elastic) right Cauchy-Green tensor\textsuperscript{16} $\mathbf{C}_e = J^{-2 / 3} \mathbf{F}_e^T \mathbf{F}_e$. Finally, the isochoric and anisotropic elastic response is characterized by $\Psi_{f}^0 = (k_1 / k_2) \left[ \exp \left( k_2 (I_1^0 - 1)^2 \right) - 1 \right]$, with the material parameters $k_1$, $k_2$, and the pseudo-invariant $I_1^0 = \mathbf{C}_e : \mathbf{a}_n \otimes \mathbf{a}_n$. If $I_1^0 < 1$, we define $\Psi_{f}^0$ to be zero, which means that the collagen fibers cannot resist compressive loads.

The inelastic response of the non-diseased media M-nos is modeled by constitutive equations including the linear hardening parameter $h$ and the initial yield stress $\tau_0$. In our proposed approach two (independent) yield criterion functions and evolution equations for multisurface plastic flow are used to characterize the model fiber slips. The association of the strain-energy contribution $\Psi_h$ due to hardening effects, and the hardening variable $\xi$ with the used elastoplastic constitutive model is not trivial. In brief, the variable $\xi$ is phenomenologically related with the associated stress by a linear or a nonlinear function (concept of linear or exponential hardening). For the case of linear hardening as used for the present analysis the associated stresses are simply determined by the product $h \xi$ (see, for example, SIMO and HUGHES\textsuperscript{44}).

For more details on the underlying non-associative rate-independent elastoplastic constitutive model, the associated continuum basis and the algorithmic formulation of the inelastic mechanical behavior the reader is referred to GASSER and HOLZAPFEL.\textsuperscript{13}

The ratios of the penalty parameters $\kappa$ to the shear moduli for the arterial components were chosen to be different from tissue to tissue but are roughly equivalent to three orders of magnitude. Particular physical models of the arterial components were obtained by fitting the general constitutive formulations to the corresponding experimental data using the Levenberg-Marquardt algorithm. The squared Pearson correlation coefficients $r^2$ for experimental versus model stresses in circumferential and axial directions were better than 0.95. Standard deviations for the fiber angles for the intimai and medial components were about $\pm 10.0^\circ$, and for the adventitia $\pm 15.0^\circ$. Best fit constitutive parameters, fiber direction angles used for the subsequent numerical simulation, and root mean squared errors (RMSE) of the model fits are summarized in Table 1. Moreover, the material parameters for the inelastic response not only of M-nos but also of I-nos are specified in Table 1. In tensile tests, which were performed by the authors, I-nos exhibited abrupt failure without previous material softening. However, our proposed material model does not incorporate fracture. For the eccentric stenosis considered we believe that balloon dilatation will lead to small localized cracks (fissures) in the non-diseased intima I-nos due to overstretch of the non-diseased arterial wall. These cracks will occur at positions where the ultimate tensile stress of the I-nos is exceeded. Hence, the best possible approximation for the structural response is to simulate the material by elastic behavior up to the ultimate tensile
**Table 1**: Material parameters characterizing the elastic response $\mu$, $k_1$, $k_2$ and the inelastic response $\tau_0$ and $h$, and fiber angles $\delta_1 = \delta_2$ of different arterial tissues adopted from Holzapfel et al.$^{21}$. The considered arterial tissues are: non-diseased intima I-nos, collagenous cap I-fl, fibrotic intima I-fm at the medial border, non-diseased media M-nos, diseased fibrotic media M-f and adventitia A. The table also contains the root mean squared error (RMSE) of the model fits. The original data are published in Holzapfel et al.$^{21}$. The calcification I-c and the lipid pool I-lp are modeled as a rigid body and an incompressible solid ($\mu = 0.1 \text{kPa}$), respectively.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Intima</th>
<th>Media</th>
<th>Adventitia</th>
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<tbody>
<tr>
<td></td>
<td>I-nos</td>
<td>I-fl</td>
<td>I-fm</td>
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<tr>
<td>$\mu$ (kPa)</td>
<td>31.0</td>
<td>78.9</td>
<td>30.8</td>
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<tr>
<td>$k_1$ (kPa)</td>
<td>51.0</td>
<td>23.7</td>
<td>45.0</td>
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<tr>
<td>$k_2$ (°)</td>
<td>1.1</td>
<td>26.3</td>
<td>9.8</td>
</tr>
<tr>
<td>$\tau_0$ (kPa)</td>
<td>450.0</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>$h$ (kPa)</td>
<td>1.0</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>$\delta_1 = \delta_2$ (°)</td>
<td>5.0</td>
<td>0.0</td>
<td>0.0</td>
</tr>
<tr>
<td>RMSE (kPa)</td>
<td>20.9</td>
<td>22.4</td>
<td>25.5</td>
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</table>

Strength and by fully plastic behavior beyond this point. Except for local effects due to cracks, the overall behavior of the I-nos and the adjoint tissues at supra-physiological loadings are represented sufficiently with this approach.

**Numerical Modeling.**

*Variational principle and finite element method.* The material model stated above has been implemented in the finite element program ABAQUS V5.8,$^{15}$ using the UEL programming interface. To capture the incompressibility constraint, the three-field variational principle, originally proposed by Simo et al.$^{46}$ was utilized. It incorporates displacement, pressure and the Jacobian as independent field variables and is known as the mixed Jacobian-pressure formulation. Based on this particular approach the incompressibility constraint is enforced by means of an augmented Lagrangian method,$^{45}$ which provides superior numerical performance compared with standard penalty methods.$^{16}$

*Discretization.* Based on the geometrical model, a mesh generator creates finite element meshes with a user-defined degree of refinement. For convenience, throughout the entire discretized structure, the numbers of finite elements in the radial, circumferential and axial directions are constant. This allows easy access to the node numbers, as required for the prescription of boundary conditions and contact surfaces. We used 8-node isoparametric brick elements. It uses linear interpolation functions for the displacement field and constant (discontinuous) interpolation functions for the independent (dilatation and pressure) variables over a given element domain without having to satisfy continuity across the element boundaries. This type of formulation is known as the mean dilatation technique, leading to the quite robust $Q1/P0$-element, which goes back to Nagtegaal et al.$^{32}$ The volumetric variables are eliminated on the ele-
A layer-specific 3D model for the simulation of balloon angioplasty

Figure 1: Exploded view of the 3D discretization of a human stenotic artery distinguished by two major regions: the non-diseased wall (consists of I-nos, M-nos and the associated part of A), and the eccentric plaque region (consists of I-fl, I-lp, I-c, I-fm, M-f and the associated part of A).

ment level. This well-known technique circumvents numerical difficulties that arise from the overstiffening of the system associated with the analysis of isochoric constitutive responses of arterial walls.

Figure 1 shows the mesh obtained in an exploded view, where the specific discretizations of the individual arterial tissues can be seen. In the radial direction the intima, media and adventitia consist of four elements each. The whole arterial model is generated with 3828 isoparametric 8-node brick elements. Each finite element is associated with one out of eight distinguished material responses (see Table 1). Thus, there is an abrupt change of material properties across element boundaries, which separate different arterial components. Because of the lack of according experimental data, no interpolation for a smooth transition of material properties was applied. Hence, stress analysis seems to be more reliable within an arterial component than at its boundaries.

As seen from Figure 1, two major regions can be distinguished: the non-diseased wall, which consists of the non-diseased intima I-nos, the non-diseased media M-nos, the associated part of the adventitia A, and the eccentric plaque region, which consists of the collagenous cap I-fl, the lipid pool I-lp, the calcification I-c, the fibrotic intima at the medial border I-fm, the diseased fibrotic media M-f and the associated part of the adventitia A. Note that in contrast to young laboratory animals, the non-diseased intima I-nos exhibits considerable thickness (and mechanical strength). This is caused by intimal hyperplasia, which is defined as proliferation of intimal cells and increase of extracellular matrix without any lipid deposits. Arteries with diffuse intimal hyperplasia are non-diseased by definition. For human arteries, thickness ratios of intima/media from about 0.1 to 1.0 or more are documented (see the review article by STARY...
et al.\textsuperscript{47}). Non-published measurements performed in the authors’ laboratory showed an average thickness ratio of intima/media/adventitia of $13/56/31$ for aged non-diseased iliac arteries.\textsuperscript{42}

The (fully inflated) balloon is modeled as a rigid cylinder-shaped structure of hexahedral finite elements with a diameter of $10.0$ (mm) and a length chosen to be equal to the stretched vessel segment. The assumption of a rigid cylinder is justified by the fact that fully inflated angioplasty balloons behave as non-compliant cigar-shaped structures. Additionally, a Palmaz-Schatz stent with a length of $13.5$ (mm) (non-expanded) was modeled by means of 190 three-node beam elements, based on a hybrid formulation. The Young’s modulus, the Poisson’s ratio and the yield stress were assumed to be $2.1 \times 10^8$ kPa, $0.3$ and $2.0 \times 10^9$ kPa, respectively.

\textit{Boundary conditions.} Regarding boundary conditions, the artery is fixed axially at one end, while the other end is exposed to displacements according to the axial \textit{in situ} prestretch. Additional boundary conditions are prescribed in order to avoid rigid-body motions of the artery and the angioplasty balloon. During the experimental preparations a significant axial retraction of the adventitia was documented after dissection from the remaining arterial tissues (for a general discussion see Schulze-Bauer et al.\textsuperscript{42}). Therefore, we included the observed adventitial axial prestretch in the numerical model, which was measured as $\lambda = 1.2$. Each of the discretized arterial components is tied to its adjacent components, i.e. we just prescribe displacement continuities across the boundaries of neighboring components. This is motivated by the fact that the ‘adherence materials’ that interconnect the arterial components have small thicknesses compared with the dimensions of the components (for the case of healthy arteries these materials are called internal and external elastic membranes). Hence, even if these materials are highly deformable, only minor movements of the components against each other are possible. Moreover, for diseased tissues these materials are rather stiff due to the high content of collagen fibers. Cracking of these layers, which may occur during angioplasty procedures, is not implemented in the proposed numerical model.

\textit{Loading process.} We consider three consecutive states of loading: (i) intraluminal pressure of $13.3$ kPa ($100$ mmHg, which is the regular mean arterial pressure) before balloon angioplasty, (ii) full expansion of the angioplasty balloon ($d = 10.0$ mm diameter) in addition to the applied intraluminal pressure, and (iii) intraluminal pressure of $13.3$ kPa after balloon angioplasty. Note that, during the whole angioplasty process a surface (pressure) load of $13.3$ kPa is applied to the inner boundary surface of the artery. Both the balloon inflation and the stent expansion are modeled as displacement-driven processes. At the beginning of the unloading process the prescribed displacements are then replaced by equivalent reaction forces at each node, which are driven to zero.

\textit{Contact problem.} For the modeling of the contact problem, which occurs between the boundary of the arterial wall and the angioplasty balloon, we use the \textit{master-slave approach} (slave nodes are constrained not to penetrate the master surface). The contact constraint is applied by means of the penalty method. For that purpose we used the contact algorithm which is implemented in ABAQUS. More details on the penalty method may be found, for example, in Wriggers.\textsuperscript{53} Additionally, the \textit{dual} contact problem (interchange master and slave surface) is solved in order to avoid problems with the contact algorithm associated with normal vector computations on the edges of the contact surfaces. Finally, frictionless contact is assumed between
Table 2: Shear modulus $\mu$ for the neo-Hookean model characterizing the isotropic response of different arterial tissues. The considered arterial tissues are: non-diseased intima I-nos, collagenous cap I-fl, fibrotic intima I-fm at the medial border, non-diseased media M-nos, diseased fibrotic media M-f and adventitia A. The table also contains the root mean squared error (RMSE) of the model fits. The calcification I-c and the lipid pool I-lp are modeled as a rigid body and an incompressible solid ($\mu = 0.1 \text{ kPa}$), respectively.

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<tr>
<td>$\mu$ (kPa)</td>
<td>150.0</td>
<td>165.0</td>
<td>221.0</td>
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<tr>
<td>RMSE (kPa)</td>
<td>107.3</td>
<td>207.6</td>
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the arterial boundary and the boundary of the angioplasty balloon. The interaction between the boundary of the arterial wall and the stent is modeled in analogy with the balloon-artery contact.

**Numerical simulations.** The numerical simulations aim to study (i) the three-dimensional stress states in the arterial components induced by balloon angioplasty and stent deployment, and (ii) the influences of three fundamental model features, i.e. axial *in situ* prestretch, three-dimensional model geometry and material anisotropy, on the resulting stress distributions.

The simulation, which incorporates the full complexity of the proposed model, is termed *reference simulation*. It serves as a basis for the subsequent discussion of the mechanics of angioplasty and for the comparisons with simplified models. In particular we define three simplified models which are characterized by (i) neglecting axial *in situ* prestretch, (ii) assuming plane strain states, or (iii) isotropic material responses. For comparison purposes, an axisymmetric model was not considered, because, apparently, this is an inappropriate model for the eccentric stenosis investigated.

To simulate the plane strain state we expose all finite elements to an axial prestretch of $\lambda = 1.04$. The nodes are restricted to deform only within a plane, orthogonal to the arterial axis. For the simplified simulation of isotropic material response a neo-Hookean model, with the shear modulus $\mu$, is fitted to the same experimental data. Best-fit data are summarized in Table 2. Note that the associated root mean squared errors (RMSE) of the model fits are about an order of magnitude higher than the corresponding errors for the anisotropic models (Table 1).

## 3 Results

**Numerical simulation of balloon angioplasty.** Figure 2 illustrates exploded views of the human stenotic artery at full expansion of the angioplasty balloon ($d = 10.0\text{ mm}$ diameter) showing circumferential and axial Cauchy stresses in kPa. Note that for the purpose of visualization a smoothing algorithm was developed. Mean values of Gauss point stresses were computed for each element in circumferential and axial directions. The stress value of a particular node is recovered by averaging the mean values of all involved elements. Then the internal stresses are obtained by a linear interpolation in the same manner as for the displacements.
Figure 2: Exploded views of the human stenotic artery at full expansion of the angioplasty balloon ($d = 10.0$ mm) showing circumferential and axial Cauchy stresses.

Generally, the global stress distribution is significantly higher (about $2 \sim 3\times$) in the circumferential than in the axial direction, as expected for the radial balloon expansion. In the non-diseased wall elastic tissue limits are exceeded, which causes non-recoverable deformations. They occur in the entire media M-nos and in parts of the intima I-nos, indicated in Figure 2 by hatched regions. In the clinical context the phenomenon of non-recoverable deformations, occurring predominantly in the media, is termed ‘controlled vessel injury’. This is known to be an essential mechanism for the luminal gain of the angioplasty procedure.\textsuperscript{5} For the non-diseased intima I-nos this may be interpreted as the occurrence of intimal fissures (compare with section ‘Methods’). Interestingly, although the adventitia is modeled as a homogeneous material and has a rather regular geometry, it exhibits a complex three-dimensional stress distribution, which strongly motivates the use of a 3D model. The high-stress region of the adventitia at $z = 0$ mm is an effect of the rigid calcification opposite to it and may also be caused by the prescribed boundary conditions.

The (eccentric) plaque region shows a sandwich-like stress pattern in the circumferential di-
rection. Here the (liquid-like) lipid pool and the calcification are low-stress regions. They are embraced by two stiff structures, i.e. the collagenous cap I-fl at the inner side, and the fibrotic part of the intima I-fm and the diseased media M-f at the outer side. These components undergo high stresses, which may lead to tissue failure. In particular, circumferential stress concentrations (> 700 kPa) are seen at the center of the collagenous cap (indicated by the thick arrow in Figure 2), which is a typical location for plaque rupture, as documented in pathological studies. 39 According to our experimental data the ultimate tensile stress of the collagenous cap was not reached in the simulation performed. Rupture of the collagenous cap is associated with the risk of subsequent thrombus formation in real-life procedures. In addition, tissue failure may also occur in the diseased media M-f, which may initiate layer dissection (indicated by a thin arrow in Figure 2). This observation has not been recognized in previous mechanical studies. Such an effect cannot be observed by means of standard clinical imaging modalities. Nevertheless, in real-life interventions, it may cause, for example, intramural hemorrhage, which subsequently may lead to dissecting aneurysm formation. For this specific morphology no stress concentrations are seen at the plaque shoulders, which are the lateral transition zones between the atherosclerotic plaque and the non-diseased intima. However, tissue failure at this location is a frequent clinical finding 29, 50 and may lead to dissection (delamination) of the plaque from the underlying arterial wall.

Figure 3 illustrates three consecutive deformed configurations of the half vessel based on the finite element simulation. The left hand sides of the plots show the non-diseased components of the arterial wall (intima I-nos, media M-nos and the associated part of adventitia A), while the right hand sides indicate the cross-section of the plaque with the components I-fl, I-lp, I-c, I-fm, M-f and the associated part of adventitia A. The deformed geometry in Figure 3(a) is associated with the intraluminal pressure of 13.3 kPa before balloon angioplasty. Figure 3(b) shows the deformed geometry during full expansion, where the inner boundary resembles the shape of the angioplasty balloon, while Figure 3(c) indicates the deformed geometry at intraluminal pressure of 13.3 kPa after balloon angioplasty. The luminal gain due to balloon angioplasty can be appreciated by comparing the geometry before balloon angioplasty (Figure 3(a)) with that after balloon angioplasty (Figure 3(c)). Moreover, ‘elastic recoil’ is evident by comparing the geometry during full expansion (Figure 3(b)) with that after balloon angioplasty (Figure 3(c)).

The proposed numerical model offers the opportunity to quantify the angioplasty-induced changes of the mechanical environment on a component-specific basis. One quantity, which characterizes the changes in the mechanical environment is the local stress difference, i.e. post-angioplasty stress minus pre-angioplasty stress. Figure 4 shows the circumferential stress differences at $z = 6.0$ mm for the previous simulation, whereas the stress differences are plotted onto the post-angioplasty configuration at 13.3 kPa. Additionally, the luminal shape before angioplasty at 13.3 kPa is indicated by a dashed curve in order to demonstrate the luminal gain.

There are significant local and component-specific changes of the mechanical environment indicated by a complex pattern of stress differences. It appears that the average stress level is elevated, which is an expected result because the luminal gain leads to higher stresses in the arterial wall. In particular, there is a marked stress difference in the fibrotic intima at the medial border I-fm, while the ‘innermost ring’ consisting of calcification I-c, the fibrous cap I-fl and
the non-diseased intima I-nos seem to show lower stresses after balloon angioplasty. This result may be explained by the inelastic deformations that have occurred in the non-diseased intima I-nos, which are associated with a significant stress relief in I-nos and the appending structures (I-fl and I-c). The fibrotic intima at the medial border I-fm, however, shows increased stresses after balloon angioplasty. This may be caused by the association with the outer arterial layers which in contrast to the ‘innermost ring’ (I-nos, I-fl, I-c) do not show stress relief.

In real-life interventions the stress differences that depend crucially on the interventional protocol used, may initiate component-specific biological responses, which ultimately may lead to a renarrowing of the dilated artery. This pathological process is called restenosis and is the major shortcoming of angioplasty (occurrence up to 40% within 6 months\textsuperscript{10,27}). Arterial tissues may be regarded as regulatory systems that control their physical and chemical environments. In other words these tissues compare actual values of these quantities with set point values and react on deviations with a specific biological response such as growth, remodeling, atrophy etc. in order to restore the set point values. In our case the stress differences may be seen as deviations of the actual stress state from the (tissue-specific) referential stress state. The subsequent biological reaction may lead to restenosis and thus, cause therapeutic failure. The proposed model allows to investigate the driving forces of this process, i.e. the stress differences, on a component-specific basis.
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Figure 4: Differences in circumferential stresses (post-angioplasty stresses minus pre-angioplasty stresses at 13.3 kPa) for a cross-section ($z = 6.0$ mm) after a full expansion of the angioplasty balloon with a diameter of $d = 10.0$ mm. Stresses are plotted onto the post-angioplasty configuration at 13.3 kPa. The luminal shape before angioplasty at 13.3 kPa is indicated by a dashed curve.

For the mechanics of arterial remodeling the reader is referred to the more recent works.\textsuperscript{40,48,49}

**Comparison of the proposed model with simplified models.** The special merits of the proposed model will be demonstrated by comparing the numerical results with those of simplified models (compare with section ‘Methods’). In particular, we study the influences of three fundamental model features (axial \textit{in situ} prestretch, three-dimensional geometry and material anisotropy) on the resulting stress distributions.

Figure 5(a) shows distributions of circumferential and axial Cauchy stresses (in kPa) in a representative cross-section at $z = 6.0$ mm for the loading state of a fully expanded angioplasty balloon with $d = 10.0$ mm in diameter. The numerical stress results are based on the proposed model (reference simulation) and are plotted onto the load-free configuration, where the arterial wall components are best visible. The structural composition, which is formed by the different tissues, is marked by the associated boundary curves. Figure 5(b)-(d) shows circumferential and axial stress difference plots, i.e. reference model stresses minus simplified model stresses, and study the influence of the three fundamental model features. As for Figure 5(a) the geometry of the plots refers to the load-free configuration. The following descriptions aim to identify the global influences of the simplifications on the arterial stress distribution.

Neglecting axial \textit{in situ} prestretch. The most significant stress changes appear in the non-diseased wall (see Figure 5(b)). The circumferential stresses are lower in the adventitia but higher in the media and the intima. For an explanation of this finding we have to consider that the fiber angle of the adventitia is much higher than those of the other involved tissues (see
Table 1). Therefore, the increase in stress due to axial \textit{in situ} prestretch is most pronounced in the adventitia. Neglecting the prestretch leads to a stress reduction in the adventitia and consequently to a (relative) overload in the media and intima. In contrast to the circumferential stresses, the axial stresses are generally lower in all layers, as expected. The plaque region is far less affected by the axial prestretch because the plaque behaves relatively stiff in axial direction.  

\textit{Plane strain states.} Apparently, a global shifting of circumferential stresses from the plaque region to the non-diseased wall is observed (see Figure 5(c)). The stress increase is most pronounced in the adventitia. This may be explained by the fact that for the plane strain assumption axial contractions of the adventitia due to radial balloon expansion are precluded. This constraint leads to a higher structural stiffness of the adventitia and consequently to higher stresses. As a result, the compression of the inner layers, in particular of the intima, is higher with respect to the reference simulation. Therefore, also the tendency to expand in axial direction is higher, which leads to an axial stress reduction.

**Figure 5:** Comparisons of the reference simulation with three simplified models. The plots show circumferential and axial stresses at a representative cross-section ($z = 6.0$ mm) for the loading state of a fully expanded angioplasty balloon with $d = 10.0$ mm, whereas stresses are plotted onto the load-free configuration: (a) reference simulation, (b)-(d) stress difference plots (reference model stresses minus simplified model stresses) for the three model simplifications, i.e. (b) neglecting axial \textit{in situ} prestretch, (c) assuming plane strains and (d) isotropic material response.
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Table 3: Maximum deviations of stresses (in %) regarding the whole stenosis at full balloon expansion \((d = 10\) mm) in eight arterial tissues for three model simplifications. Changes of compressive to tensile stresses (or \textit{vice versa}), are indicated by bold-face numbers (\(\sigma_0\) and \(\sigma_z\) stand for circumferential and axial stresses, respectively). The considered arterial tissues are: non-diseased intima I-nos, collagenous cap I-fl, fibrotic intima at the medial border I-fm, calcification I-c, lipid pool I-lp, non-diseased media M-nos, diseased fibrotic media M-f and adventitia A.

<table>
<thead>
<tr>
<th>Model simplifications</th>
<th>Intima</th>
<th>Media</th>
<th>Adventitia</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>I-nos</td>
<td>I-fl</td>
<td>I-fm</td>
</tr>
<tr>
<td>Without axial prestretch</td>
<td>(\sigma_0)</td>
<td>209</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td>(\sigma_z)</td>
<td>\textbf{409}</td>
<td>81</td>
</tr>
<tr>
<td>Plane strain</td>
<td>(\sigma_0)</td>
<td>211</td>
<td>25</td>
</tr>
<tr>
<td></td>
<td>(\sigma_z)</td>
<td>154</td>
<td>153</td>
</tr>
<tr>
<td>Isotropy</td>
<td>(\sigma_0)</td>
<td>308</td>
<td>42</td>
</tr>
<tr>
<td></td>
<td>(\sigma_z)</td>
<td>208</td>
<td>2</td>
</tr>
</tbody>
</table>

\textit{Material isotropy.} The reference simulation and the simulation which is based on the isotropic model (for the material parameters see Table 2), lead to similar stresses in the plaque region, since the plaque components, namely the calcification I-c and lipid pool I-lp, are modeled as isotropic materials. This finding is illustrated in Figure 5(d). The non-diseased wall does not show a general trend, it exhibits rather heterogeneous component-specific changes. Significantly lower stresses are obtained in the media M-nos in circumferential direction and in the adventitia A in axial direction, whereas stresses are significantly higher in the intima I-nos and media M-nos in axial direction. There are no straightforward explanations for these results since they are caused by a complex interaction of several factors. These factors are, for example, a generally higher compliance at large strains, different regional involvements regarding non-recoverable deformations, and the fact that the adventitia A is better represented by an isotropic model than the media M-nos and the intima I-nos.

In order to quantify the stress differences, deviations (in %) in the considered arterial tissues with respect to the reference simulation were determined for the three investigated model simplifications. The stress deviation was calculated according to \(100\left|\frac{r - s}{r}\right|\), where \(s\) denotes a stress value from a particular simplified model and \(r\) the corresponding value from the reference simulation. Table 3 summarizes the maximum stress deviations regarding the whole stenosis, for the loading state associated with the fully expanded angioplasty balloon (10 mm in diameter). Changes of the stress character, i.e. a change of compressive to tensile stress (or \textit{vice versa}), are indicated by bold-face numbers. The table demonstrates that some tissues, such as the adventitia A, the non-diseased intima I-nos and the diseased media M-f, appear to be more sensitive to model simplifications than others such as the lipid pool I-lp and the calcification I-c. Remarkably, the maximum computed stress deviation is about 600\% with an associated change of the stress character (axial stresses in the diseased media M-f for the isotropic model simplification). By analogy with the loading state of the fully expanded balloon, also for the loading states before and after balloon angioplasty at an intraluminal pressure of 13.3 kPa the...
Figure 6: Circumferential (a) and axial stress distributions (b) in kPa for a human stenotic artery at an intraluminal pressure of 13.3 kPa after stent deployment. At the stent edges, indicated by dashed lines, local stress concentrations occur.

maximum stress deviations were determined (not shown in Table 3). In general, the maximum stress deviations appeared to be smaller, however they still reached values up to 400%.

Stent deployment. Another application of the proposed model, which is of particular medical interest, is the simulation of stent deployment in a stenotic artery. Figure 6 shows the Cauchy stress distributions in the artery after stent deployment at an intraluminal pressure of 13.3 kPa. Note that the stent itself is not illustrated, and in order to visualize the inner (non-diseased) arterial wall, the plaque region has been cut away. The location of the stent is indicated by dashed lines. During the inflation procedure the stent retracts axially from the initial length of 13.5 (mm) to a final length of 10.8 (mm). As for the simple balloon dilatation, strains are higher in the non-diseased wall than in the plaque region since the thickness of the non-diseased wall is smaller.

Local stress concentrations in the non-diseased intima I-nos are seen at the stent edges. Interestingly, while the circumferential stresses at these sites are tensile as expected (see Figure 6(a)), the axial stresses are compressive (see Figure 6(b)). Even more remarkable is the fact that the adventitia exhibits high axial tensile stresses at the corresponding locations (not shown). This illustrates the complex three-dimensional and layer-specific stress-strain states caused by stent-artery interactions. Obviously, the three-dimensional stress-strain states strongly depend on the lesion-morphology and the utilized stent type.

In clinical practice, the stent would embed itself in the soft intimal and medial tissues. The present simulation, however, was not aimed to model this particular aspect. Clearly, simulation of the embedding process would require a much finer discretization than the present one.
Stent-induced loadings lead to stresses exceeding the elastic limit in the non-diseased intima and media, and consequently to non-recoverable deformations in these tissues. The associated regions exhibit a complex three-dimensional geometry. These patterns of mechanical injury may be interpreted as the individual initial conditions for subsequent biological responses such as restenosis.

4 Discussion

The fully three-dimensional model proposed consists of eight different arterial components and captures nonlinear anisotropic behavior at finite strains for supra-physiological loadings occurring during balloon angioplasty and stent deployment. Moreover, it considers the axial \textit{in situ} prestretch of an artery within the body and allows to simulate non-recoverable (inelastic) deformations, which occur at loadings above the physiological domain. The angioplasty balloon is included in the finite element analysis leading to a three-dimensional contact problem of the balloon-artery interaction. As a result this model allows a detailed study of the mechanical processes which occur during dilational procedures and has the potential to provide essential insights into their mechanisms. Additionally, the proposed model is based on an experimental data set and incorporates morphological and mechanical information about an individual stenosis. This is an inevitable prerequisite in order to obtain realistic results. To the authors’ knowledge there is no such model available in the literature which combines the specified model features.

The validity of a model depends crucially on the considered material characteristics. Simplified models, which do not consider either axial \textit{in situ} prestretch, three-dimensional geometries or material anisotropy, may lead to significant deviations of the stress states compared with the reference model (see Table 3 and Figure 5). This demonstrates the general significance of these features as essential requirements for an appropriate simulation.

In particular, for the investigated stenosis the greatest deviations due to simplifications have been identified in the non-diseased intima I-nos and the diseased fibrotic media M-f, where even changes of the stress character occur (interchange of tensile and compressive stresses, see Table 3). Medium deviations occur in the adventitia A and the non-diseased media M-nos, while the plaque, which involves the collagenous cap I-fl, the fibrotic part at the medial border I-fm, the calcification I-c and the lipid pool I-lp, appears to be relatively invariant. An obvious reason for this fact is that the plaque region undergoes relatively small strains due to its high structural stiffness. This suggests that for severely calcified stenoses, the use of simplified models may provide satisfactory numerical results for the plaque region. For the remaining arterial components, however, these models fail to represent the major structural mechanical behavior.

These statements may be inappropriate for generalization, since they are based on the computation of only one investigated stenosis. However, the aim of this paper is to introduce and describe the experimental and chiefly the numerical methodologies of a model, which yields the most sophisticated simulations of interventional procedures to date. It was not intended to study a larger number of stenotic arteries and to draw general conclusions on a statistical basis. For this
type of studies the proposed model will provide a suitable computational basis in the future. Based on a large number of investigated stenoses the approach may provide a ‘virtual work-bench’ for the design and evaluation of interventional instruments, such as stents. Moreover, the proposed model approach bears the potential for the determination of lesion-type specific procedures, i.e. the definition of optimal procedural protocols for certain plaque geometries and compositions with respect to certain target quantities such as the maximum luminal gain, intimal injury, medial overstretch etc. Another potential application evolves from the fact that for the first time it is possible to investigate the change in the mechanical environment caused by an interventional procedure on a layer-specific basis. This may allow a better understanding of the corresponding biological response, and hence could be a potential contributor for restenosis research. Morphological data for such investigations may come from high-resolution magnetic resonance imaging of the arterial wall and plaque, which holds great promise for characterizing atherosclerotic plaques and is, therefore, of huge interest for the medical community. MRI has shown to discriminate between various tissue types involved in atherosclerosis in vitro\cite{30,41,43,52}. Moreover, the challenging task of in vivo wall imaging yielded promising results for carotid arteries\cite{26,51,54}, for the aorta\cite{9}, and even for coronary arteries\cite{8}. Thus, it can be expected that in the near future MR wall and plaque imaging will become clinical reality so that morphological input for models as the proposed one are available. Clearly, the combination of mechanical analysis and morphological data has an enormous potential to significantly improve current diagnostics and interventional procedures.

However, in order to obtain results for these specific applications, which are reliable for all types of lesions, additional refinements have to be incorporated. Processes such as ruptures, cracking, fissuring, dissections, delaminations have been identified as major effects of successful balloon dilatation (see, for example, in vitro studies\cite{4,6,55} and in vivo studies\cite{28,50}). A significant limitation of the proposed model is that it does not incorporate these fracture mechanisms. This will be addressed in subsequent research.

In addition, residual stresses, which may occur in diseased arterial tissues, are not considered in the model (except for the adventitia, compare with section ‘Methods’). Actually, this is not included in any of the existing models concerned with the numerical simulation of balloon angioplasty. To overcome this major shortcoming appropriate experimental methods are required. Existing methods for the quantification of residual strains are mainly based on experiments with rings of arteries (see, for example, the monograph by Fung\cite{11}). If such a ring is cut radially it sprays open into a sector. The opening angle of this sector characterizes the circumferential (nonuniform) residual stress state of the artery. Apparently, this method, which was developed for healthy arteries, is not applicable for a multi-component arterial stenosis, since most of the involved arterial components are not ring-shaped structures but exhibit rather irregular shapes. Moreover, in such a structure individual residual axial strains may be as important as residual circumferential strains. Therefore, it is necessary to develop experimental methods that capture both axial and circumferential strains for single arterial components. Since the exact residual stress state of a multi-component arterial stenosis is not known yet, basically it is impossible to estimate the potential consequences of its influence. It is not justified to refer to existing knowledge about residual strains in (healthy) arterial walls because these concepts were not verified
for diseased arteries. The proposed model is certainly able to incorporate residual stresses when they are available.

Concerning the numerical solution, we have not performed systematic studies of convergence and error analysis, which would require a rigorous automatic mesh refinement. Additional limitations concern the assumptions of frictionless contact between balloon and vessel wall and the boundary constraints at \( z = 0 \). Basically, the effects of these assumptions can be easily tested by altering the conditions of the model and resolving.

Finally, it is unclear inasmuch the material properties of post-mortem tissue samples differ from their \textit{in vivo} properties, and whether stripe tests (with stripes in axial and circumferential directions) and associated histological information provide appropriate data for the determination of physical models of the arterial components that represent their \textit{in situ} behavior.

The ultimate validation of the proposed model requires an appropriate benchmark test. Therefore, an \textit{in vitro} angioplasty should be performed, which would provide post-angioplasty morphology that could be compared with the morphology computed by the numerical model, and thus allows to study the predictive capability of the model.

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\textbf{References}


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