1 Introduction

Tissue engineering presents a promising alternative technology to overcome the disadvantages of currently used heart valve replacements [1]. So far, tissue-engineered heart valves have only been placed in the pulmonary position [2], where the construct is subjected to smaller stresses compared to the aortic position. Successful tissue engineering of functional aortic heart valves requires that the engineered valve has mechanical properties similar to the native valve. In order to engineer heart valves that are able to withstand the stresses in the aortic position, the mechanical properties of the construct have to be improved. Conditioning the cell-seeded scaffold with (gradually increasing levels of) flow and pressure in a pulse duplicator bioreactor is one of the possibilities to increase matrix synthesis within the tissue-engineered aortic valve [3,4]. To optimize these conditioning programs and the mechanical integrity of the construct, a mathematical model has to be formulated to relate tissue remodeling to the local mechanical state within the construct and to predict the effects of changes in its mechanical environment. The model should focus on mechanically induced collagen remodeling, as the load-bearing properties of the leaflet are mainly determined by the well organized collagen fiber network (Fig. 1). Remodeling of collagen fibers includes changes in fiber orientation, net collagen turnover, fiber thickness, collagen type, and cross-linking [6,7].

Numerical simulations contribute to the analysis and understanding of the local mechanical state of the valve. Nonlinear finite-element simulations of fiber-reinforced heart valves demonstrate significant changes in the distribution of the stress patterns due to the anisotropic mechanical properties [8,9]. Peskin and McQueen [10] derived the fiber structure of the aortic valve by considering mechanical equilibrium between the fiber forces and the pressure load acting on the surface. The computed fiber architecture resembled the branching braided structure of the collagen fibers that support the native aortic valve. However, the evolution of changes in the fiber architecture, which is of interest for tissue-engineering applications, was not studied. Cowin [11] and Cowin et al. [12] presented a theory to study the interrelation between the mechanical loading condition and remodeling of trabecular bone. Dallon, Sherratt, and co-workers [13–15] presented models to study collagen deposition and alignment during dermal wound healing. Nevertheless, their theories did not account for mechanical factors involved in tissue remodeling. Olsen et al. [16] presented a model to study stress-induced alignment of matrix fibers, and Barocas and Tranquillo [17,18] presented an anisotropic bi-phasic theory to account for traction-induced matrix reorganization within compacting tissue equivalents. In these studies, however, the effect of fiber alignment on the mechanical properties of the extracellular matrix was left out of consideration.

As the biological processes of matrix remodeling are complex and not yet fully understood, we concentrated on a relatively simple model for analyzing collagen fiber remodeling. The objective of this study was to predict the evolution of collagen fiber content and orientation in the aortic heart valve, considering both the causes and consequences of fiber alignment and changes in fiber content. In order to accomplish this, a theory capable of (1) describing the mechanical state within the tissue and (2) accounting for the effects of fiber remodeling on the tissue’s constitutive behavior was formulated. We used a discrete number of collagen fiber directions and hypothesized that the collagen fibers aligned with principal strain directions. This hypothesis compares with the theory presented by Cowin and co-workers for remodeling of trabecular bone [11,12], which states that the trabecular architecture reorients towards the strain/stress field according to Wolff’s law. In addition, we assumed that collagen content was linearly related to the square of the fiber stretch.

2 Materials and Methods

2.1 Constitutive Equations. The leaflet of the aortic heart valve was modeled as an incompressible fiber-reinforced material. A constitutive law for this transversely isotropic composite material was described by van Oijen et al. [19]. The fibers were modeled as a one-dimensional material exerting only stresses in the fiber direction ($\hat{e}_f$). The Cauchy stress ($\sigma$) is written as

$$\sigma = -pI + \hat{\tau}(\mathbf{B}) + \delta f (\psi f (\lambda^2) - \hat{e}_f \cdot \hat{\tau} \cdot \hat{e}_f ) \hat{e}_f \hat{e}_f,$$  

where $p$ is the hydrostatic pressure, $I$ the unity tensor, $\hat{\tau}$ the (isotropic) matrix stress, $\phi$ the fiber volume fraction, $\psi f$ the fiber stress, and $\lambda$ the fiber stretch. $\phi$ is defined as the ratio of the volume occupied by the fiber and the volume of the total material. The Finger strain or left Cauchy-Green deformation tensor ($\mathbf{B}$) is defined as $\mathbf{B} = \mathbf{F} \mathbf{F}^T$, with $\mathbf{F}$ the deformation gradient tensor. It was assumed that the matrix stress was elastic and that $\hat{\tau}$ represented the contribution of all matrix components (e.g., elastin and proteoglycans), except the collagen fibers, to the total constitutive

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behavior. The extra stress is defined as $\tau = \hat{\tau} + \phi(\psi_f - \hat{\epsilon}_f \cdot \hat{\epsilon}_f) \hat{\epsilon}_f$. Then, it can be seen that in the fiber direction, the fiber stress and the matrix stress contribute to the extra stress with fractions $\phi$ and $1 - \phi$, respectively (rules of mixtures). Hence, $\epsilon_f \cdot \tau \hat{\epsilon}_f = (1 - \phi) \epsilon_f \cdot \hat{\tau} \hat{\epsilon}_f + \phi \psi_f$. On the other hand, the extra stress in any direction $a$ perpendicular to $\epsilon_f$ is defined by the matrix stress, $a \cdot \tau a = a \cdot \hat{\tau} a$. Note that Eq. (1) represents an elastic material, whereas most biological tissues, including the aortic valve [20], exhibit viscoelastic or multiphasic behavior. Equation (1) is not restricted to one fiber direction and can be extended to account for multiple fiber directions. If there is no interaction between the fibers, the total stress of the composite with $N$ fiber directions is written as

$$\sigma = -p I + \hat{\tau} + \sum_{j=1}^{N} \phi(\psi_f - \hat{\epsilon}_f \cdot \hat{\epsilon}_f) \hat{\tau} \hat{\epsilon}_f.$$  

The stress in the fiber $(\psi_f)$ is a function of the square of the fiber stretch ($\lambda^2$). Assuming that the matrix and the fiber undergo the same deformation (i.e., affine deformation), the fiber direction in the deformed configuration ($\hat{\epsilon}_f$) is determined from the fiber direction in the undeformed configuration ($\epsilon_f$):

$$\lambda \hat{\epsilon}_f = F \cdot \epsilon_f$$

with

$$\lambda = \|F \cdot \epsilon_f\|.$$  

We attempted to model the mechanical properties of the leaflet with a discrete number of fiber directions. We assumed that the fibers oriented towards a positive principal strain direction (discussed in a subsequent section). The maximum number of positive principal strains equals two for an incompressible material, and therefore two fiber directions were used. The matrix material was assumed to behave as an incompressible neo-Hookean material:

$$\hat{\tau} = G (B - I)$$

with $G$ the shear modulus of the material. To express the nonlinear behavior of the collagen fibers present in the valve, an exponential constitutive equation was used:

$$\phi_f = k_1 \lambda^2 \left[ e^{k_2 (\lambda^2 - 1)} - 1 \right]$$

with $k_1$ and $k_2$ as material parameters. For the fibers the following assumptions were made:

1. The fibers can only take tensile stresses; hence $\phi_f = 0$ when $\lambda < 1$.
2. Since the tensile loads are primarily carried by the collagen fibers, only one family of fibers was considered. The thickness and stiffness of the fibers were assumed constant, resulting in constant mechanical properties. At this stage the effect of cross-linking between the fibers was left out of consideration.

(3) Since collagen fiber crimp is difficult to quantify and is highly variable, Eq. (6) was used to describe the effective stress-strain relationship (as suggested in the study of Billiar and Sacks [21]).

### 2.2 Balance Equations

In order to determine the local deformations and the mechanical loading condition of the tissue, the balance equations had to be solved. On the domain of interest, conservation of momentum and mass in every material point should hold. Neglecting inertia and assuming that no body forces are present, conservation of momentum reads:

$$\nabla \cdot \sigma = 0.$$  

In the anisotropic biphasic theory of Barocas and Tranquillo [17,18] Eq. (7) was extended to account for contractile cell traction forces, which are especially important in compacting gels. In this study, the effects of these internally generated forces were neglected. The volume of an incompressible material remains constant and the mass balance reduces to:

$$J = 1$$

where $J = \det(F)$ represents the volume change between the initial and the current configurations. The set of equations has to be supplemented with appropriate boundary conditions.

A finite-element (FE) formulation [22] was derived to find an approximate solution of the unknown displacement and pressure field from Eqs. (7) and (8). The weak form of the balance equations was obtained by transforming Eqs. (7) and (8) using a weighted residual formulation followed by partial integration. The resulting equations were nonlinear with respect to the unknown displacement and pressure field. The Newton-Raphson iteration process was used to find an approximate solution and required linearization of the equations with respect to a known reference configuration. An updated Lagrange formulation was employed such that the last known (converged) configuration was taken as the reference configuration. After linearization, the (Bubnov) Galerkin method was used for spatial discretization of the weighting functions and the error in the displacement and pressure field. Numerical integration was performed with Gauss integration. Because a mixed formulation was used to account for incompressibility, the set of interpolation functions for the displacement and the pressure field had to satisfy the Babuska-Brezzi or inf-sup condition. In this work, the displacements were interpolated with quadratic functions and consequently the pressure was interpolated linearly ($Q_2/Q_1$ element). A Taylor-Hood element with continuous pressure interpolation was chosen. The numerical framework was implemented in the software package sepran [23].

### 2.3 Collagen Fiber Remodeling

#### 2.3.1 Fiber Content

It is known that fiber content increases with strain [24–26]. In this study, it was assumed that the (steady-state value of the) fiber volume fraction $(\phi_m)$ was related linearly to $\lambda^2$. The fiber content was limited by a lower value $\phi_{\text{min}}$ (at a fiber stretch $\lambda_u$) and an upper value $\phi_{\text{max}}$ (at a fiber stretch $\lambda_u$):

$$\phi_{\text{min}} \leq \phi < \phi_{\text{max}}$$

if $\lambda < \lambda_u$.

$$\phi = \phi_{\text{min}}$$

if $\lambda > \lambda_u$.

(9)

(10)

(11)

Since an instantaneous response of the fiber volume fraction $\phi$ to a change in the fiber stretch is not plausible, the evolution of $\phi$ was modeled by a first-order rate equation:

$$\frac{d\phi_f}{dt} = \mu (\phi_{\text{eq}}(\lambda^2) - \phi_f), \quad j = 1, 2$$

(12)
Fig. 2. Schematic representation of fiber reorientation. The fiber (\(\mathbf{\hat{e}}_f\)) is rotated over an angle \(\Delta \theta\) towards the principal strain direction (\(\mathbf{\hat{e}}^{\ast}_p\)), resulting in the new fiber direction (\(\mathbf{\hat{e}}'_f\)). \(\alpha_j\) denotes the angle between \(\mathbf{\hat{e}}_f\) and \(\mathbf{\hat{e}}'_f\).

In Eq. (12), \(d\phi_j/dt\) is the rate of net fiber turnover for fiber direction \(j\) and \(\mu\) denotes the rate constant. Although the rate of matrix protein synthesis increases with the magnitude of stretch [25], \(\mu\) was assumed to be constant for simplicity.

2.3.2 Fiber Reorientation. We hypothesized that collagen fibers aligned with the (positive) principal strain directions, as calculated from \(B\). However, the driving force for collagen fiber alignment is not restricted to mechanical stimuli. Several reports on magnetic alignment of collagen fibers [27,28], which were left out of consideration in the present study. Collagen fiber reorientation was modeled by a first-order rate equation:

\[
\frac{d\theta_j}{dt} = \kappa [1 - |\mathbf{\hat{e}}'_j \cdot \mathbf{\hat{e}}'^{\ast}_p|], \quad j = 1, 2
\]

\[
= \kappa [1 - |\cos(\alpha_j)|], \quad j = 1, 2
\]  
(13)

In Eq. (13) \(d\phi_j/dt\) is the rate of reorientation for fiber direction \(j\). \(\kappa\) denotes its maximum value, and \(\mathbf{\hat{e}}'^{\ast}_p\) is a positive principal strain direction. The angle between the principal strain direction and the fiber direction \(j\) is denoted by \(\alpha_j\). The absolute value of the dot product between \(\mathbf{\hat{e}}'_j\) and \(\mathbf{\hat{e}}'^{\ast}_p\) is taken, because the signs of \(\mathbf{\hat{e}}'_j\) and \(\mathbf{\hat{e}}'^{\ast}_p\) are not of interest. The rate of orientation reaches a maximum when the fiber direction and the principal strain direction are perpendicular, whereas the rate equals zero when both are aligned. Although the rate of remodeling can be influenced by biochemical stimuli [29], the magnitude of the strain or the type of mechanical stimulus [24] \(\kappa\) was assumed to be constant. In fact, \(\kappa\) might even account for the presence of a delaying in the remodeling process. Figure 2 shows a schematic representation of Eq. (13). The fiber vector \(\mathbf{\hat{e}}'_j\) is rotated by an angle \(\Delta \theta_j\) towards the principal strain direction \(\mathbf{\hat{e}}'^{\ast}_p\), yielding the new fiber direction \(\mathbf{\hat{e}}'_j\).

2.3.3 Implementation of Fiber Remodeling. The fiber content and direction were updated after each time step, because the new values affect the constitutive behavior of the construct. An Euler explicit or forward Euler scheme was performed for the temporal discretization of the remodeling rules [Eqs. (12) and (13)]. A constant and sufficiently small time step \(\Delta t\) [with \(100\Delta t \approx \min(\kappa^{-1}, \mu^{-1})\)] was chosen to yield a stable integration process and to determine the new fiber content and the angle of rotation \(\Delta \theta_j\). The explicit dependency on direction \(j\) is omitted in the following discussion.

A rotation tensor \(\mathbf{R}\), based on \(\Delta \theta\) and the normalized rotation axis \(\mathbf{\hat{e}}_f\), was used to rotate \(\mathbf{\hat{e}}'_j\) towards \(\mathbf{\hat{e}}'_p\):

\[
\mathbf{\hat{e}}'_j = \mathbf{R}(\Delta \theta, \mathbf{\hat{e}}_f) \cdot \mathbf{\hat{e}}'_j
\]

The rotation axis was calculated from

\[
\mathbf{\hat{e}}_r = \frac{\mathbf{\hat{e}}'_j \times \mathbf{\hat{e}}'_p}{\|\mathbf{\hat{e}}'_j \times \mathbf{\hat{e}}'_p\|}
\]  
(15)

Because the rotation axis is undefined for two parallel vectors, \(\mathbf{R}\) was set to \(\mathbf{I}\) when \(\mathbf{\hat{e}}'_j\) and \(\mathbf{\hat{e}}'_p\) align (i.e., \(\alpha \rightarrow 0^\circ\)). Note that \(\Delta \theta\) had to be sufficiently small, because small changes in \(\alpha\) can result in relatively large changes of the fiber stress. When the angle between the fiber and the principal strain direction was obtuse, the rotation was performed with \(-\Delta \theta\).

Based on the assumption that the stress-free state of the (reoriented) fiber remains the undeformed configuration (\(F = I\)), we chose to update the fiber directions in this configuration. As a result, the stress-free state before and after remodeling remained the same. The old fiber directions in the undeformed configuration (\(\mathbf{\hat{e}}_{f0}\)) were updated using a tensor \(\mathbf{U}\) to obtain the new fiber directions in the undeformed configuration (\(\mathbf{\hat{e}}'_{f0}\)):

\[
\mathbf{\hat{e}}'_{f0} = \mathbf{U} \cdot \mathbf{\hat{e}}_{f0}
\]  
(16)

In order to obtain the expression for \(\mathbf{U}\), \(\mathbf{\hat{e}}'_{f0}\) is first obtained by back transformation of the new fiber directions in the deformed configuration (\(\mathbf{\hat{e}}'_{f}\)):

\[
\mathbf{\hat{e}}'_{f0} = \mathbf{F}^{-1} \cdot (\lambda_{\text{new}} \mathbf{\hat{e}}'_{f})
\]  
(17)

In Eq. (17), \(\lambda_{\text{new}}\) denotes the fiber stretch in the updated configuration. Then, substitution of Eq. (14) in Eq. (17), yields

\[
\mathbf{\hat{e}}'_{f0} = \lambda_{\text{new}} \mathbf{F}^{-1} \cdot \mathbf{R} \cdot \mathbf{\hat{e}}_{f}
\]  
(18)

Next, the old fiber directions in the deformed configuration (\(\mathbf{\hat{e}}_{f}\)) have to be expressed in terms of \(\mathbf{\hat{e}}_{f0}\):

\[
\mathbf{\hat{e}}_{f} = \frac{1}{\lambda_{\text{old}}} \mathbf{F} \cdot \mathbf{\hat{e}}_{f0}
\]  
(19)

In Eq. (19), \(\lambda_{\text{old}}\) denotes the fiber stretch in the old configuration. Finally, substituting Eq. (19) in Eq. (18) and comparing the result with Eq. (16) yield the expression for \(\mathbf{U}\):

\[
\mathbf{U} = \left(\frac{\lambda_{\text{new}}}{\lambda_{\text{old}}}\right) \left(\mathbf{F}^{-1} \cdot \mathbf{R} \cdot \mathbf{F}\right)
\]  
(20)

This process is schematically represented in Fig. 3.

2.4 Problem Definition

2.4.1 Structure and Geometry. Collagen fiber remodeling was assumed to be mainly triggered during the diastolic phase. On the one hand, the diastolic phase relatively takes the longest period of time of the cardiac cycle; on the other hand, the aortic valve is maximally loaded during this phase. In this study, most attention was therefore paid to the closed configuration of the leaflets. Assuming the time constant of a periodic pressure load is small compared to the time constant of collagen fiber remodeling, the transvalvular pressure was applied quasistatically. In this case, the magnitude of the applied pressure load has to be interpreted as a representative value of the periodically varying pressure level. For simplicity, only the solid mechanics of the valve were considered and any interaction with fluid (other than the pressure) was not modeled. Contact between the three separate leaflets of the
The aortic valve was left out of consideration. The three layers of the leaflet, the fibrosa, spongiosa, and ventricularis, have different compositions [30] and different mechanical properties [31]. Only the fibrosa was modeled in this stage as this is considered to be the main load-bearing structure of the leaflet [32]. Both a stented and a stentless valve geometry were used. The aortic root was modeled to apply realistic boundary and loading conditions.

2.4.2 Parameters. The shear modulus of the leaflet’s matrix material was chosen as $G_{\text{leaflet}}=0.5$ MPa. The value of $k_2$, indicating the degree of nonlinearity of the fiber stress, was set to 6.0, comparable to the estimated parameter in the study of Billiar and Sacks [21]. The value of $k_1$ was set to 2.0 MPa to ensure that the fibers were much stiffer than the matrix for all tensile strains. At compressive fiber strains, the fiber content was set equal to zero because these fibers are nonfunctional. Hence, $\phi_{\text{max}}=0.0$ and $\lambda_f=1.0$. The value of $\phi_{\text{max}}$ (at $\lambda_f=1.25$) was assumed to be 0.3. As the time scale of the remodeling rules was arbitrary, time was scaled with $\kappa_0=1.0$ s^{-1}. The values of $\kappa_1/\kappa_0$ and $\mu/\kappa_0$ were arbitrarily set to 1.0 and 5.0, respectively. The aortic root was modeled as an incompressible neo-Hookean material with $G_{\text{root}}=4.0$ MPa.

2.4.3 Initial Fiber Configuration. The initial fiber configuration was defined by taking fiber directions parallel to the x and y axes. Hence, $(\gamma_1, \gamma_2)=(0, \pi/2)$ with $\gamma_j$ denoting the angle between the initial fiber direction $j$ and the positive x axis. These fiber vectors were then projected tangent to the three-dimensional (3D) surface of the leaflet to form the initial fiber directions. The initial fiber volume fractions were set equal to zero.

2.4.4 Boundary Conditions. All nodal displacements on the fixed edge, the inlet, and the outlet wall were suppressed. At symmetry surfaces, nodal displacements in the normal direction were suppressed. To model the diastolic pressure difference over the aortic heart valve, a uniform pressure of 10 kPa ($p_{\text{max}}$) was applied on the aortic surface of the leaflet. To accomplish opening of the valve, in the absence of fluid-solid interaction, a uniform systolic pressure difference of 18 kPa was applied on the inner wall of the aortic root. This pressure caused the root to expand and as a consequence the valve opened. The opened valve configuration was only considered for the stentless valve geometry. The period of time to apply the pressure load was small compared to the time needed for the remodeling process. The pressure was held at a constant level after it had been applied, whereas the remodeling process continued.

2.4.5 Analyses. To analyze the effects of the remodeling process on the constitutive behavior of the leaflet, the displacement of the tip (nodule of Arantius) was monitored. The effect of different fiber properties and diastolic pressure levels on the final fiber configuration was investigated. The value of $k_1$ was varied from 2.0 MPa to 1.0 and 0.5 MPa, whereas the maximum pressure level $p_{\text{max}}$ was varied from 10 kPa to 5.0 and 1.0 kPa. To study the effect of the initial fiber directions, $(\gamma_1, \gamma_2)=(0, \pi/2)$ was changed to $(\gamma_1, \gamma_2)=(\pi/6, -\pi/3)$. The magnitudes of the scaled rate constants $\kappa_1/\kappa_0$ and $\mu/\kappa_0$ were arbitrarily varied from 1.0 and 5.0, respectively, to 5.0 and 1.0. The results of the stented and the stentless valve geometry (in the closed and opened configuration) were compared. These analyses are summarized in Table 1. Because the computed amount and distribution of fibers on the aortic and ventricular side differed, the mean value of the volume fractions on both sides was calculated.

3 Results

3.1 Tip Displacements. The tip displacement as a function of the (scaled) period of time is shown in Fig. 5. In the first part of these curves, the tip displacement increased due to pressure application. Thereafter, the tip displacements decreased as a result of...
the remodeling process. Because the fibers aligned with the principal strain directions and the fiber content increased, the strains within the construct and the tip displacements decreased. Clearly, the maximal tip displacement was larger at higher pressures and lower fiber stiffnesses [Figs. 5(a) and 5(b)]. The maximum value of the tip displacement was larger for $(γ_1, γ_2) = (0, π/2)$ than it was for $(γ_1, γ_2) = (π/6, −π/3)$ [Fig. 5(c)]. In the latter case, the initial fiber directions were more aligned with the principal strain directions. As a result, the material initially had a higher effective stiffness. The steady-state values of the tip displacements were nearly equal for both initial fiber directions considered (relative difference <2%). In Fig. 5(d), the highest value of the tip displacement was obviously found for $κ/κ_0 = 1.0$ and $μ/κ_0 = 1.0$, whereas the lowest value was obtained with $κ/κ_0 = 5.0$ and $μ/κ_0 = 5.0$. The maximum tip displacement for $κ/κ_0 = 5.0$ and $μ/κ_0 = 1.0$ was larger than for $κ/κ_0 = 1.0$ and $μ/κ_0 = 5.0$. Initially,

Table 1 Overview of the performed analyses. The reference values of the parameters are emboldened.

<table>
<thead>
<tr>
<th>$k_1$ [MPa]</th>
<th>$p_{\text{max}}$ [kPa]</th>
<th>$(γ_1, γ_2)$ [rad]</th>
<th>$κ/κ_0$ [−]</th>
<th>$μ/κ_0$ [−]</th>
<th>Geometry</th>
<th>Configuration</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>2.0</td>
<td>1.0</td>
<td>(0, π/2)</td>
<td>1.0</td>
<td>5.0</td>
<td>Stented</td>
</tr>
<tr>
<td>II</td>
<td>2.0</td>
<td>5.0</td>
<td>(0, π/2)</td>
<td>1.0</td>
<td>5.0</td>
<td>Stented</td>
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<tr>
<td>III</td>
<td>2.0</td>
<td>10.0</td>
<td>(0, π/2)</td>
<td>1.0</td>
<td>5.0</td>
<td>Stented</td>
</tr>
<tr>
<td>IV</td>
<td>0.5</td>
<td>10.0</td>
<td>(0, π/2)</td>
<td>1.0</td>
<td>5.0</td>
<td>Stented</td>
</tr>
<tr>
<td>V</td>
<td>2.0</td>
<td>10.0</td>
<td>(π/6, −π/3)</td>
<td>1.0</td>
<td>5.0</td>
<td>Stented</td>
</tr>
<tr>
<td>VI</td>
<td>2.0</td>
<td>10.0</td>
<td>(0, π/2)</td>
<td>5.0</td>
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<td>Stented</td>
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<tr>
<td>VII</td>
<td>2.0</td>
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<td>(0, π/2)</td>
<td>1.0</td>
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<td>Stentless</td>
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<tr>
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<td>2.0</td>
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<td>(0, π/2)</td>
<td>1.0</td>
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<td>5.0</td>
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<td>Stentless</td>
</tr>
<tr>
<td>X</td>
<td>2.0</td>
<td>18.0</td>
<td>(0, π/2)</td>
<td>1.0</td>
<td>5.0</td>
<td>Stentless</td>
</tr>
</tbody>
</table>

Fig. 5 Tip displacements as a function of the relative period of time at different pressure levels (a, entries I, II, and III from Table 1), with different fiber stiffnesses (b, entries III, IV, and V from Table 1), different initial fiber directions (c, entries III and VI from Table 1), and different magnitudes of the rate constants (d, entries III, VII, VIII, and IX from Table 1).
increasing the amount of fibers was apparently more effective with respect to increasing the construct’s stiffness than fiber reorientation was. The final values of the tip displacement hardly depended on the magnitude of the rate constants (relative difference <0.5%).

3.2 Fiber Content. The mean total volume fractions of the leaflet obtained with the reference values of the parameters (entry III in Table 1) are shown in Fig. 6(a). In Table 2 the volume fractions obtained with the stented valve geometries are compared. As a direct result of the assumption in Eqs. (9)–(11), the total volume fractions decreased (Table 2) with lower pressure levels (entries I and II), i.e., reduced strains, compared to the reference values (entry III). Similarly, the volume fractions increased (Table 2) with lower fiber stiffnesses (entries IV and V). The value and distribution of the volume fractions with \((\gamma_1, \gamma_2) = (\pi/6, -\pi/3)\) (entry VI) slightly differed (Table 2) due to local differences in the magnitude of the principal strains when compared to the reference situation with \((\gamma_1, \gamma_2) = (0, \pi/2)\). The value and distribution of the volume fractions showed small dissimilarities for different magnitudes of the rate constants (entries VII, VIII, and IX) due to local differences in the strain field (Table 2).

In all stented cases, the volume fractions reached their maximum value at the fixed edge, because the applied boundary conditions introduced relatively large strains at this location. Modeling the aortic root affected the strain fields within the leaflet. Especially near the attachment of the leaflet to the aortic wall (aortic ring), the strains and the volume fractions were reduced [Fig. 6(e)] compared to the closed configuration of the stented valve geometry [Fig. 6(a)]. As a result of the strain field, the volume fractions in the opened configuration were small [Fig. 6(e)].

3.3 Fiber Directions. The final fiber directions on the aortic side of the leaflet obtained with the reference values of the parameters (entry III in Table 1) are shown in Fig. 6(b). The right-hand part of this figure corresponds to the first principal strain and fiber directions, whereas the left-hand part corresponds to the second fiber directions. The fiber vectors are scaled with their volume fraction. The fiber directions on the ventricular side were similar, but the presence of the second direction was more pronounced on the ventricular side.

In Table 2 the fiber directions calculated with decreased pressure levels (entries I and II), decreased fiber stiffnesses (entries IV and V), and different magnitudes of the rate constants (entries VII, VIII, and IX) are compared to those obtained with the reference values (entry III). Except for the results obtained with the lowest pressure level (entry I), the fiber directions hardly changed. The larger difference in the fiber orientation for this pressure level was probably due to small differences in the strain field and dissimilar deformed geometries (i.e., the deformations at \(p_{max} = 1.0\) kPa were relatively small). The fiber directions calculated with the stented valve geometry [in the closed configuration, Fig. 6(d)] resembled those of the stented valve geometry [Fig. 6(b)]. The fiber directions in the opened configuration [Fig. 6(f)] mainly ran horizontally from fixed edge to fixed edge and thus differed from those in the closed configuration.

In all closed configurations considered, the first (i.e., most dominant) fiber directions ran from commissure to commissure and entered the stent at the fixed edge. The second fiber direction was particularly present in the lower part of the belly region. Obviously, the commissure region was mainly loaded in a uniaxial-like manner, whereas the belly region was loaded biaxially. In the opened configuration, the leaflet was mainly loaded uniaxially. The amount of anisotropy and the relative contribution of both fiber directions depended on the values of the parameters from Table 1. To reveal the relative contribution of both fiber directions in the belly region, the ratio of the volume fractions \(\phi_2/\phi_1\) of both fiber directions in this region was calculated (Table 3). The relative contribution of the second fiber direction increased at increasing pressure levels (entries I, II, and III) or increasing fiber stiffnesses (entries III, IV, and V). This implied that the belly region of the leaflet was loaded in a more biaxial-like manner as the pressure level or fiber stiffnesses increased. At increasing fiber stiffnesses, the circumferential strains were reduced. At increasing pressure levels, the circumferentially oriented fibers restricted a further increase of the circumferential strain, whereas the radial strains increased. The ratio of the volume fractions hardly depended on the initial fiber directions (entry VI) or the magnitude of the rate constants (entries VII, VIII, and IX). In the closed configuration of the stentless valve geometry, the ratio slightly decreased (entry X). In the opened valve configuration, the second fiber direction was scarcely present (entry XI).

4 Discussion

A theory was presented to study the evolution of collagen fiber remodeling in the aortic valve. The interaction between (1) the mechanical loading condition within the construct and (2) changes
in collagen fiber content and orientation was modeled. The major principal fiber direction ran from commissure to commissure [Fig. 6(b)]. In the closed configuration, the loading state of the commissure region was mainly uniaxial, whereas the belly region of the leaflet was loaded biaxially. In the opened configuration, the entire leaflet was mainly loaded uniaxially. The final computed fiber directions resembled the principal strain directions in an isotropic leaflet. In the remodeling cases considered, the boundary condi-

Fig. 6 Fiber configurations. Mean value of the final total volume fraction on the aortic and ventricular side (left). The color bar is subdivided into 10 discrete levels and the upper limit is set to 0.25, although in (a) maximum values of 0.3 are observed at the fixed edge. This truncation is performed to obtain a better resolution. Final fiber orientation on the aortic side of the leaflet (right). The fiber vectors are scaled with their volume fraction. (a) and (b) are obtained with reference values of the parameters (entry III in Table 1). (c) and (d) are obtained with a stentless valve geometry (entry X in Table 1). (e) and (f) are obtained with a stentless opened valve configuration (entry XI in Table 1).
tions and the valve geometry were probably more dominant than the mechanical properties of the leaflet with respect to the orientation of the principal strain directions. Our simulations demonstrated that the evolution of the remodeling process depended on the transvalvular pressure difference, the fiber stiffness, the initial fiber directions and the magnitude of the rate constants.

As a first attempt to validate the preliminary results, the final fiber directions were compared with experimental data from native valves presented by Sacks et al. [35]. They quantified fiber architecture and mapped gross fiber orientation with small angle light scattering (SALS). The results for a fixed porcine aortic valve leaflet are shown in Fig. 7 (left), together with the first fiber direction from Fig. 6(b) (right). The vector plots indicate the preferred fiber directions. The color map indicates the value of the orientation index (OI), defined as the angle that contains one-half of the total area of the fiber distribution curve. These experimental results show a strong resemblance to the computed final fiber directions. The larger value of the OI in the lower belly can perhaps be ascribed to the presence of a second preferred fiber direction [Fig. 6(b)] resulting from the biaxial strain field in this region. Since no appropriate data have been found in literature, the computed evolution of the volume fractions could not be compared to the fiber content in the native leaflet.

Some care should be taken with the interpretation of the presented results. We attempted to describe the fiber architecture of the leaflet with two discrete fiber directions, whereas multiple fiber directions are present in the native aortic valve [35]. Furthermore, two fiber directions are unable to completely describe the complex in-plane biaxial mechanical behavior of the native leaflet as described by Billiar and Sacks [21,36]. However, in our opinion two principal fiber directions served as a first approximation to study fiber remodeling within the construct. In addition, we assumed that the fibers and the matrix undergo the same deformation, whereas fiber kinematics in the native aortic valve are to some extent nonaffine [37]. Perfect alignment between fiber and principal strain direction was not obtained. Small changes in the strain field (e.g., as a result of the remodeling process) could result in relatively large changes in the orientation of the principal strain directions. This resulted in unstable eigenvectors and hence a sudden increase in the angle between fiber and principal direction occurred. Because of numerical limitations (i.e., divergence of the Newton-Raphson iteration process) the effect of higher fiber stiffnesses and several other (e.g., random) initial fiber configurations on the remodeling process were not investigated. To avoid these limitations, we suggest to start with initial fiber orientations that resemble the principal strain directions in an isotropic leaflet. We expect that this is realistic in case of initially isotropic tissue-engineered heart valves. In addition, we propose to use gradually increasing pressure levels to analyze the process of collagen remodeling. This procedure has already been applied in in vitro studies to condition tissue-engineered heart valves [3,4].

In the present study, the elastin fibers were not modeled. As elastin has a significant contribution to the mechanical function of the aortic leaflet [38,39], particularly at low loads, both the collagen and the elastin fibers may need to be considered. As damage to the elastin component could be responsible for changes in the leaflet’s mechanical behavior [40], considering remodeling of the elastin fibers might be interesting. Further simulations are required to find out in which way the process of fiber remodeling is affected by considering contact between the leaflets and the interaction between the leaflet and the surrounding fluid [33,41], e.g., resulting in shear stresses. The three layers of the aortic valve (fibrosa, spongiosa, and ventricularis) have different compositions, dimensions and mechanical properties and possibly have to be modeled separately. In addition, we assumed the undeformed configuration to be stress-free whereas the fibrosa and ventricularis are preloaded; the ventricularis is under tension and the fibrosa is under compression [42].

Experiments have to be performed to further validate and gain insight into the remodeling process. The relative contribution of both changes in net fiber turnover and fiber reorientation on the process on collagen fiber remodeling needs further investigation. Although we focused on changes in collagen fiber content and orientation, the effects of remodeling on other collagen fiber properties (e.g., type, cross-linking, and thickness) can be investigated. Carver et al. [43] showed that the ratio of collagen type III to collagen type I increased in mechanically stimulated cardiac fibroblasts. Fibronectin, having specific binding sites for collagens, proteoglycans, and cell surfaces, was upregulated in stretched cardiac fibroblasts [44] and during cardiac hypertrophy [45]. In wound healing, collagen fiber thickness increased with time resulting in an increase of tensile strength [46].

To the best of our knowledge, the presented model is the first one taking into account both the causes and consequences of collagen fiber remodeling. The fibers align with principal strain directions within the construct and this in turn affects the construct’s mechanical properties. Although the leaflet is modeled as a single layered tissue, contact between the leaflets and interaction with
the surrounding fluid are not modeled, promising results have been obtained. Using relatively simple remodeling rules, the final computed fiber directions resemble the fiber architecture within the native aortic heart valve leaflet.

References