A Phenomenological Approach Toward Patient-Specific Computational Modeling of Articular Cartilage Including Collagen Fiber Tracking

To model the cartilage morphology and the material response, a phenomenological and patient-specific simulation approach incorporating the collagen fiber fabric is proposed. Cartilage tissue response is nearly isochoric and time-dependent under physiological pressure levels. Hence, a viscoelastic constitutive model capable of reproducing finite strains is employed, while the time-dependent deformation change is purely isochoric. The model incorporates seven material parameters, which all have a physical interpretation. To calibrate the model and facilitate further analysis, five human cartilage specimens underwent a number of tests. A series of magnetic resonance imaging (MRI) sequences are taken, next the cartilage surface is imaged, then mechanical indentation tests are completed at 2–7 different locations per sample, resulting in force/displacement data over time, finally, the underlying bone surface is imaged. Imaging and mechanical testing are performed with a custom-built robotics-based testing device. Stereo reconstruction of the cartilage and subchondral bone surface is employed, which, together with the proposed constitutive model, led to specimen-specific finite element simulations of the mechanical indentation tests. The force-time response of 23 such indentation experiment simulations is optimized to estimate the mean material parameters and corresponding standard deviations. The model is capable of reproducing the deformation behavior of human articular cartilage in the physiological loading domain, as demonstrated by the good agreement between the experimental and numerical results ($R^2 = 0.95 \pm 0.03$, mean ± standard deviation of force-time response for 23 indentation tests). To address validation, a sevenfold cross-validation experiment is performed on the 21 experiments representing healthy cartilage. To quantify the predictive error, the mean of the absolute force differences and Pearson’s correlation coefficient are both calculated. Deviations in the mean absolute difference, normalized by the peak force, range from 4% to 90%, with 40 ± 25% ($M \pm SD$). The correlation coefficients across all predictions have a minimum of 0.939, and a maximum of 0.993 with 0.975, which demonstrates an excellent match of the decay characteristics. A novel feature of the proposed method is 3D sample-specific numerical tracking of the fiber fabric deformation under general loading. This feature is demonstrated by comparing the estimated fiber fabric deformation with recently published experimental data determined by diffusion tensor MRI. The proposed approach is efficient enough to enable large-scale 3D contact simulations of knee joint loading in simulations with accurate joint geometries.

Keywords: articular cartilage, collagen fibers, finite viscoelasticity, finite element simulation, indentation testing

1 Introduction

Articular cartilage has a composition and mechanical structure well suited to the required functions, i.e., to provide (i) a compliant, low-friction surface between the relatively rigid bones in diarthrodial joints; (ii) a long-wearing and resilient surface; and (iii) a means to distribute the contact pressure to the underlying bone structure. To meet these demands, articular cartilage contains a fluid phase of $H_2O$ and electrolytes (~68–85% by weight), a solid phase composed of chondrocytes, Type II collagen fibers (~10–20% wet weight), proteoglycans (~5–10%), and other glycoproteins (cf. Ref. [1]).

Within the cartilage, fibers of predominantly Type II collagen provide (crucial) tensile reinforcement to the solid phase, a proteoglycan gel. The collagen fibers, which support only tension, exhibit a high level of structural organization such that three zones of collagen fiber orientation exist. Starting from the surface, the superficial tangent zone (comprising 10–20% of the total thickness) has fibers that are tangentially oriented to the articular surface. Next, the middle zone (40–60%) has fibers that are isotropically distributed and oriented. Finally, near the transition to subchondral bone, the deep zone (30%) has fibers that are oriented perpendicular to the aforementioned surface [1,2]. The layered
Fig. 1 Schematic representation of the layered structure of the Type II collagen fibers within articular cartilage [1]

structural organization of Type II collagen fiber is shown schematically in Fig. 1.

Clearly some simplifying assumptions are required to facilitate large-scale 3D computational modeling and patient-specific simulation. By considering only two main components: (i) a homogenous proteoglycan/water gel matrix material (proteoglycans, other proteins, chondrocytes, plus water and electrolytes) and (ii) a collagen fiber bundle or collagenous fiber network (anisotropic entanglement of Type II collagen fibers), cartilage may be considered as a time-dependent fiber-reinforced soft tissue [3–8].

In light of the complexity of cartilage constitutive modeling, the motivation of our study is as follows: (i) provide an engineering basis to quantitatively relate the material properties and mechanical response of articular cartilage to the underlying mechanical structure; (ii) enable large deformation, inhomogeneous, anisotropic, time-dependent simulations of full joint deformation; (iii) enable the determination of a relation between simulation results and magnetic resonance imaging (MRI) data of a specific sample; and (iv) enable further study of articular cartilage degeneration by numerical simulation.

Several authors have proposed constitutive models for cartilage, which include some effects of the collagen fiber reinforcement; see, e.g., Refs. [3–5,8–15]. DiSilvestro and Suh [4] validated a linear biphasic poroviscoelastic constitutive model, which employed both a “short-term” and a “long-term” relaxation time constant; the long-term time constant ostensibly representing relaxation of the cartilage fiber bundle (although no directionality is included in the formulation). Li et al. [3] proposed a fibril-reinforced poroelastic model employing elastic springs in a simplified 2D axisymmetric geometry. The model was also extended to include viscoelasticity in the springs [5]. Wilson et al. [9] proposed a poroviscoelastic 2D axisymmetric modeling approach with fiber reinforcement modeled as a combination of idealized large primary fibers [Benninghoff-type architecture [16]] and smaller secondary fibrils. This model was also extended to include swelling effects due to the fixed-charge densities of the proteoglycans and viscoelasticity in the collagen structure [10]. In Ref. [13] it was shown that this model could explain the depth-dependent compressive properties of cartilage by varying the material composition along the depth, not the intrinsic properties of the constituents.

Julkunen et al. [12] included depth-dependent collagen data quantified by polarized light microscopy in a 2D axisymmetric fibril-reinforced finite element (FE) analysis with an idealized geometrical collagen structure (again according to Benninghoff [16]). The approach was extended to include depth-dependent collagen content and fibril orientation as well as proteoglycan and water content derived from experiment [11,15]. García and Cortés [14] proposed a constitutive model combining a biphasic viscohyperelastic matrix with viscous fibers, again employing 2D axisymmetry with a simplified fiber geometry. Additionally, Quinn and Morel [8] introduced a means to model collagen network contributions to the cartilage response, attempting to bridge the gap between experimental data on the collagen structure and theoretical tools for simulating cartilage, but the formulation was not implemented in a full 3D FE simulation.

As illustrated, many authors have proposed (more sophisticated) multiphasic constitutive models, which describe much of the important structural phenomena. These studies have shed significant light on the structure-function relationships of the various cartilage constituents, but frequently these models are limited to one- or two-dimensional analytical solutions or simulations, and thus can be difficult to generalize to 3D patient-specific simulations (sample-specific data and geometries, currently a “hot topic”).

In the present work the authors highlight the urgent need for theoretical and numerical approaches based on nonlinear modeling in order to improve articular cartilage contact mechanics as was highlighted by Han et al. [17], and discussed in detail by Herzog and Federico [18]. Additionally, Julkunen et al. [15] recently emphasized the importance of realistic cartilage structure and mechanical properties in the analysis of cartilage indentation.

To this end, we propose a phenomenological and patient-specific modeling approach, which incorporates the collagen fiber bundle. The constitutive model uses relatively few material parameters, which all have a direct physical interpretation. The model is sufficient to enable large-scale 3D simulations of realistic cartilage deformation and contact. Additionally, the modeling framework incorporates the directions of collagen fibers as a finite element input, allowing the deformation of the fiber bundle to be tracked under finite deformation. This feature is demonstrated by a qualitative comparison with recently published MRI data, which measures the orientation of the collagen fiber bundles under compression.

2 Method: Imaging and Mechanical Testing

Five articular cartilage specimens were acquired from knee joints of patients undergoing total knee replacement surgery. The surgeon’s educated opinion, from visual and tactile inspection, suggests that the selected specimens represented “healthy or near-healthy” cartilage. After removal, the specimens were cropped to bone dimensions of roughly 10 × 10 × 8 mm³ (cartilage and underlying bone) and underwent a series of MRI sequences. MRI is widely accepted as a noninvasive technique for visualizing the morphology of healthy and degenerate articular cartilages; see, for example, Ref. [19]. The specimens were then soaked in a bath of phosphate-buffered saline containing protease inhibitors (PBS + PI), deep-frozen, and shipped for mechanical testing. Several studies have shown that the mechanical properties of cartilage specimens suffer no adverse effects from freezing [20–23].

The imaging and mechanical testing were performed with a custom-built, robotics-based testing device. Figure 2(a) shows an overview view of the setup, consisting of a manipulator with six degrees of freedom (RV-1A; Mitsubishi Electric Corporation, Tokyo, Japan), a stereo camera setup (Marlin F033-B; Allied Vision Technologies GmbH, Germany), a cold light source (Intralux DC-1100; Volpi AG, Switzerland) for the proper illumination, a laser mounted on a pan-tilt unit (PTU-D46-17; Directed Perception, Inc., Burlington, CA), and a 50 N load cell (8431-50; Burster, Germany). A detailed view of the testing device in Fig. 2(b) shows an indentation trial in progress. The specimen under test is firmly clamped in a vice, which is attached to the robot’s flange surface. The vice is equipped with checkerboard targets surrounding the vice enable an accurate optical tracking of the specimen movements via the stereo setup. A more detailed description of this test setup and information about the calibration routine can be found in Ref. [24].

*Ethical approval for this study was granted by the Ethics Committee of the Medical University of Vienna.
The following mechanical testing procedure was repeated for each specimen: The procedure started by thawing and rehydrating the specimen in a PBS+PI solution for 60–90 min (while the test device was calibrated). After clamping the specimen, a 3D point cloud of the cartilage surface was acquired using the laser and the stereo setup. The reconstructed cartilage surface was then used to interactively select indentation points and to automatically estimate the surface normals (used as the indentation directions) at the respective indentation points. A stainless steel spherical tip with 3 mm in diameter was used to indent the cartilage specimen by ~0.4 mm at selected locations with a loading rate of ~2 mm/s (resulting in 50–100%/s strain rate depending on the specimen geometry), after which the deflection was held constant for 600 s. The cartilage indentation of ~0.4 mm resulted in an average compression of 19% (13% minimum and 26% maximum compression, depending on the sample). The resulting load was recorded during the entire test. To maintain PBS+PI saturation, the specimen was kept moist during the testing procedure by regularly spraying the surfaces with PBS+PI [25–30]. After all mechanical testing was completed, the cartilage layer was chemically stripped and the true subchondral bone surface was captured using the stereo camera setup yielding the full cartilage geometry.

For each of the five specimens, between two and seven indentation experiments were recorded at different locations on the surface, resulting in 23 indentation tests for subsequent analysis. The raw data acquired during each test were (i) a 3D point cloud of the cartilage surface, (ii) a 3D point cloud of the subchondral bone, (iii) the location of the indentation points on the cartilage surface, (iv) the specimen position and orientation tracked at 72 Hz, and (v) the reaction force acquired at 250 Hz.

Since the cartilage specimen was firmly clamped during the entire experiment, the 3D point clouds of the cartilage and the subchondral bone were in registration. The position tracking information and the force data were tagged with high-resolution time stamps during the acquisition process to synchronize force and displacement.

3 Viscoelastic Constitutive Model and Parameter Fitting Scheme

To model the complex cartilage morphology and material response, a finite strain viscoelastic fiber-reinforced constitutive model, as documented in Refs. [31,32], was particularized using data from literature and the present mechanical testing. The constitutive model is employed in specimen-specific FE simulations to compute the reaction force-displacement response of the mechanical indentation tests, where a rigid-deformable contact algorithm was employed to capture finite deformation of the specimen due to indentation. The material model was implemented in the finite element code FEAP [33]. Analyses of the specific specimens (motivated and bounded by literature) were employed to determine the material parameters as well as the FE model geometry.

3.1 Phenomenological Approach. Articular cartilage is recognized as a biphasic material, which contains a fluid phase of H2O and electrolytes, and a solid phase composed of chondrocytes, Type I and II collagen fibers, proteoglycans, and other glycoproteins (cf. Ref. [1]). To facilitate large-scale 3D simulations under physiological pressure levels and loading durations we used some simplifying assumptions as detailed below.

Isochoric deformation. Documented literature values of Poisson’s ratio for cartilage material show significant variability. The experimentally determined values of Poisson’s ratio for articular cartilage vary from 0 to 2.1, depending on the loading condition and experimental techniques employed [1,6]. Wong et al. [34] experimentally studied volumetric changes in articular cartilage during unconfined compression. They measured the instantaneous Poisson’s ratio of adult cartilage as 0.49 ± 0.08 (mean ± standard deviation), and thus concluded that the material was incompressible. Furthermore, Bachrach et al. [35], as well as Huang et al. [23], proposed that due to the low permeability of the cartilage material and the intrinsic incompressibility of the constituents, cartilage tissue behaves nearly isochorically under physiological levels of pressures (in the range 2–12 MPa [36]). This observation is consistent with the experimental results published by Atseshian and co-workers [36,37], which required, due to very low fluid velocities, tens of seconds to measure a reliable pressure value at the surface of a cartilage specimen. Similarly, we estimate that the deformation of cartilage specimens is essentially isochoric for tens of seconds under most loading conditions (see the Appendix for supporting calculations), and certainly in the, “short time response after 1 s of loading application … as this represents a physiologically loading duration” [36].

Thus, under most loading configurations, the total tissue volume will not change for tens of seconds [36,37] (i.e., “instantaneous isochoric deformation”) even at loading rates as low as 0.25 μm/s. Jurvelin et al. [38] also argued that the instantaneous cartilage response is incompressible, while the experimentally determined Poisson’s ratio at thermodynamical equilibrium (including time-dependent loss of fluid) was lower. To reproduce the mechanical indentation data, and hence study the global deformation response, we subsequently assume isochoric deformation.

Viscoelasticity. Huang et al. [22,39] concluded that, even in the framework of biphasic theories, cartilage exhibits a global time-dependent response, which is independent of fluid flow. It is well supported in literature that both the fiber and matrix components demonstrate viscoelastic response [4,14]. Hence, in the proposed...
model, viscous effects are included for both components of cartilage, the matrix material and the collagen fiber fabric, as discussed in the following.

After analyzing cartilage in confined compression, where the fibers may be considered unloaded, Mak [40] concluded that viscous effects contribute significantly to the material response. Schmidt et al. [41] found that the magnitude of viscous dissipation, measured in tension, decreased following enzymatic degradation of the proteoglycan matrix. Similarly, Zhu et al. [42] found a change in the measured viscoelastic shear response (to minimize flow-dependent effects) before and after degradation of the proteoglycan ground matrix. García and Cortés [14] also concluded that intrinsic viscoelasticity of the proteoglycan matrix may play an important role in the transient behavior of articular cartilage, and that the inclusion of a viscous matrix material allows a good representation of confined compression curves. Here, viscoelasticity of the matrix material is considered to capture both the intrinsic time-dependent properties of the solid phase (without collagen fiber reinforcement) and its interaction with the interstitial fluid [4, 14, 34, 35].

Several experimental and analytical studies provide justification for including time-dependence in the collagenous fiber network. A viscoelastic response from cartilage has been observed experimentally in tensile testing by many researchers [43–45]. Li and Herzog [5], for example, argued that in this loading condition the fluid pressure is negligible, and the contribution from the proteoglycan matrix is likely low due to relatively low tensile stiffness in relation to the fiber fabric. This argument implies that the collagen fibers must play a dominant role in the observed viscoelastic response. Furthermore, they noted that the viscoelastic shear modulus of cartilage has been reported to increase with collagen cross-links, which would further indicate that the collagen fibers are viscoelastic [46]. In addition, García and Cortés [14] studied both elastic and viscoelastic matrix materials under tension and compression within the context of a two-dimensional biphasic framework. They also concluded that in order to generate material parameters consistent with data on tensile testing documented in Ref. [6], a viscous effect must be included in the nonfiber solid matrix. This data fit was further verified by the successful simulation of confined compression curves provided in Ref. [4].

### 3.2 The Model

In order to capture the material response demonstrated in the experiment (cf. Fig. 5), we use a nonlinear, finite strain constitutive model based on a convex strain-energy function $\Psi$. A multiplicative split of $\Psi$ into volumetric and isochoric contributions is employed, using the isochoric deformation gradient $F = J^{-1}F$, and similarly the isochoric right Cauchy–Green tensor $C = J^{-3/2}C$, where $F$ is the Jacobian, the determinant of the deformation gradient $\mathbf{F}$. We assume the decoupled form $\Psi = U(J) + \Psi_j$, where the volumetric contribution is particularized to $U(J) = \kappa(j - 1)^2/2$. Here $\kappa$ is a stresslike material parameter, which in the case of isochoresic deformation degenerates to a nonphysical, positive penalty parameter used to capture both the intrinsic time-dependent properties of the solid phase (without collagen fiber reinforcement) and its interaction with the interstitial fluid.

Next, $\Psi$ is chosen to be

$$\Psi(C,a_0) = \Psi_m(C) + \Psi_j(C,a_0)$$

where the direction of the collagen fibers is characterized by the (reference) direction vector $a_0$, with $|a_0| = 1$. For simplicity, $\Psi$ is particularized to include $I_1$ and $I_2$ only. Thus,

$$\Psi(I_1,I_2) = \Psi_m(I_1) + \Psi_j(I_2)$$

where $I_1 = \text{tr } C$ and $I_2 = C_{ij}a_0 \otimes a_0$ such that anisotropy arises only through the (modified) invariant $I_2$. Note that $I_2$ has a clear physical interpretation as it is the square of the stretch of the collagen fiber fabric in the direction $a_0$.

Finally, the matrix $\Psi_m$ and fiber $\Psi_j$ contributions to the function $\Psi$ must be particularized so as to fit the material parameters to the experimentally observed cartilage response.

### Isotropic matrix material

Bachrach et al. [35] argued that anisotropy arises primarily from the collagen fiber fabric so that the remaining matrix material is best treated as isotropic. Furthermore, for the low loading domain, the (wavy) collagen fibers of soft collagenous tissues are not active (they do not store strain energy). For the purposes of this study, the neo-Hookean model was chosen to capture the matrix material, and hence $\Psi_m$ is specified as

$$\Psi_m(I_1) = \frac{\mu}{2} (I_1 - 3)$$

where $\mu > 0$ is a stresslike material parameter, corresponding to the shear modulus of the underlying matrix material in the reference configuration.

### Anisotropic fiber fabric

The anisotropic, nonlinear response of the collagen fiber fabric is captured phenomenologically by

$$\Psi_j(I_2) = \frac{k_1}{2k_2} (\exp[k_2(I_2 - 1)^2] - 1)$$

where $k_1 > 0$ is a stresslike material parameter and $k_2 > 0$ is a dimensionless parameter, which controls the nonlinear, equilibrium fiber fabric response. The form of this strain-energy function is based on the experimentally supported assumption that the collagen fiber fabric has a strong nonlinear stiffening response under tension [48]. Tension/compression nonlinearity stems from the conditional statement $I_2 > 1$ such that the fiber fabric stress response is only nonzero in tension (i.e., the collagen fibers only engage under stretches greater than unity).

In articular cartilage, collagen fibers may exhibit a continuous angular distribution, while this formulation for the collagen fiber contribution to the total strain-energy function assumes that there is a single dominant fiber direction at each location in the tissue (which could be interpreted as the “principal” or net effect of the distributed fibers). The formulation of Eq. (4) could easily be extended to characterize the dispersion of collagen fibers according to, e.g., Refs. [49–51].

### Determination of stresses

To illustrate the material model based on the strain-energy formulations, we elaborate the relationship between input deformation gradient $F$ and the Cauchy stress tensor $\sigma = J^{-1}\mathbf{F}^{T} \mathbf{S} \mathbf{F}$, where $\mathbf{S}$ denotes the second Piola–Kirchhoff stress tensor.

The second Piola–Kirchhoff stress tensor is specified by summing the volumetric, matrix fiber, and viscoelastic contributions as

$$\mathbf{S} = S_{\text{vol}} + \sum_{a=m,f} (S_{a} + Q_{a})$$

where $S_{\text{vol}} = 2\partial U(J)/\partial C$ is the volumetric, $S_{m} = 2\partial \Psi_m/\partial C$ is the matrix, and $S_{f} = 2\Psi_j/jC$ is the fiber fabric contribution to the second Piola–Kirchhoff stress tensor $\mathbf{S}$, respectively, and $Q_{a}$ represents the viscoelastic contributions where $a = [m,f]$ time-dependent processes are employed.

### Algorithmic stress tensor

Next, to determine the time-dependent (viscous) response of the matrix material and the fiber fabric, we consider an approach that was suggested in Refs. [52, 53], and extended to finite strains in Refs. [54, 31]. We consider a partition of the closed time interval $t \in [0^+,T]$ and focus attention on a typical time subinterval $[t_n, t_{n+1}]$, with $\Delta t = t_{n+1} - t_n$ characterizing the associated time increment. Assume now that at times $t_n$ and $t_{n+1}$, all relevant kinematic quantities are given. In addition to that, the stress $S_a$ at time $t_n$ is also specified uniquely.

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via the associated constitutive equation serving as an “initial” database.

All that remains is the computation of the second Piola–Kirchhoff stress tensor $S_{n+1}$ at time $t_{n+1}$ (the algorithmic stress tensor generalized from Eq. (5)), which is given in the form

$$S_{n+1} = \left[ S_{\text{vol}} + \sum_{\alpha=m,f} \left( S_{\alpha} + Q_{\alpha} \right) \right]_{n+1}$$  \hspace{1cm} (6)

The stress contributions $S_{\text{vol},n+1}$, $S_{m,n+1}$, and $S_{f,n+1}$ describe the total elastic response and can be computed from the given strain measures at $t_{n+1}$. The term $Q_{\alpha,n+1}$ in Eq. (6) represents the nonequilibrium stresses at time $t_{n+1}$ and is responsible for the viscoelastic stress contribution; this remains to be evaluated. Using the midpoint rule we arrive at a second-order accurate recurrence update formula for the nonequilibrium stresses, namely,

$$Q_{\alpha,n+1} = \beta_{\alpha} \exp(-\Delta t/2 \tau_{\alpha}) S_{\alpha,n+1} + \mathbf{H}_{\alpha,n}$$  \hspace{1cm} (7)

where $\beta_{\alpha}$ is a dimensionless strain-energy factor controlling the magnitude of the viscous component response, and $\tau_{\alpha}$ is the associated relaxation time, and with the definition

$$\mathbf{H}_{\alpha,n} = \exp(-\Delta t/2 \tau_{\alpha}) \left[ \exp(-\Delta t/2 \tau_{\alpha}) Q_{\alpha,n} - \beta_{\alpha} S_{\alpha,n} \right]$$  \hspace{1cm} (8)

of the (algorithmic) history term $\mathbf{H}_{\alpha,n}$, $\alpha = \{ m, f \}$, at time $t_n$, determined from the known stresses $Q_{\alpha}$ and $S_{\alpha}$ at $t_n$ (for numerical purposes, we have assumed $Q_{\alpha}^n = 0$); see Refs. [31, 32]. At thermodynamical equilibrium $Q_{\alpha} = \mathbf{0}$ as well, which means that only the elastic response remains, i.e., the response controlled by $\mu$, $k_1$, and $k_2$. This numerical implementation is only valid for constant time steps ($\Delta t = \text{const}$), which does not pose a problem in the present context. For problems that require varying time steps, the algorithm can easily be extended by storing two different stress tensors following an argument detailed in Ref. [55].

In summary, seven material parameters are required: $\mu$, controlling the equilibrium shear modulus of the underlying matrix material; $k_1$ and $k_2$, controlling the nonlinear, equilibrium fiber fabric response; $\beta_m$ and $\beta_f$, controlling the response magnitude of the viscous matrix and fiber components, respectively; and $\tau_m$ and $\tau_f$, controlling the relaxation times of the viscous matrix and fiber components, respectively.

### 3.3 Parameter Fitting Scheme

To estimate the seven material parameters from experimental data, specimen-specific FE simulations of indenter contact were optimized for each of the 23 indentation experiments.

**Finite element mesh and collagen fiber fabric.** Stereo reconstruction of the cartilage and subchondral bone surface yielded two scattered 3D point clouds. Since the cartilage layer of the small specimens was smooth and had only a slight curvature, we chose to simplify the meshing process by projecting the 3D point clouds onto a plane. The orientation of this plane was chosen such that the projected area was as large as possible. In the projection, the boundaries were “cleaned up” by estimating the range of reliable surface data. Inside the remaining polygonal area, an anisotropic\(^6\) quad mesh was generated using GMSH [56]. This 2D mesh was extruded along the projection axis and intersected with NURBS approximations of the bone and cartilage surface to obtain the 3D nodal coordinates delimiting the cartilage volume. The resulting (oblong) elements were partitioned along the projection axis, i.e., in the thickness dimension of the specimen, to yield a mesh density that was sufficient to capture changes in the fiber orientation. Depending on the acquisition method (see, for example, Refs. [7, 57, 58]), the orientation of the fiber bundles could be captured with 0.1–0.2 mm resolution (characteristic length of the elements). Additionally, a mesh sensitivity study was completed to demonstrate that the resulting solution was relatively independent of the mesh density in this range of the characteristic lengths. An example of a resulting mesh (23 such meshes were generated) is provided in Fig. 3(a).

Finally, an elementwise map of the fiber fabric was estimated for the through-thickness zones from literature; see, for example Ref. [1]. Actual determination of the vectors was completed using a random number generator constrained to be in-plane for the superficial zone, or spherical for the middle zone. Recall, in the deep zone, the fibers are essentially perpendicular to the subchon-
ers have noted similar time scales to reach equilibrium response when a peak load was attained at the end of a loading ramp, followed by a rapid dissipation of some peak load, which was then followed by a very slow relaxation almost to equilibrium. This experimental result implies the existence of two or more viscoelastic processes. In fitting their proposed constitutive model, García and Cortés [14] determined that the time constant $\tau_m$ of the matrix material (not including fluid) should be smaller than the time constant $\tau_f$ for the collagen fibers, and, furthermore, $\tau_m$ must be in the range $\sim$ 0.21–1.03 s. DiSilvestro and Suh [4] proposed a biaxial, isotropic, linear small deformation constitutive model, which was implemented in one dimension. In this work, the authors argued for the use of two material time constants to capture the time-dependent response of the cartilage, a “short” time constant $\tau_s$, and a “long” time constant $\tau_l$. They were able to accurately simulate confined and unconfined compressions as well as indentation tests by using values in the following ranges: $\tau_s$ = 0.21–1.03 s and $\tau_l$ = 40.1–130.1 s.

When observing the constraints on the model parameters extracted from literature, each parameter controls a certain aspect of the model response (e.g., the slope of the initial decay, the overall magnitude of the curve, etc.) with limited interference with the other characteristics of the curve. In other terms, given the restrictions on the parameter search space, the problem is heavily constrained.

To address model validation, we choose a k-fold cross-validation approach. Cross validation is a statistical technique commonly used in the machine learning community to avoid overfitting [59]. The available data are randomly split into two parts: the first part is used to adjust the model parameters (training), and the second part is used to validate the model by testing the predictive capability on the remaining data. In k-fold cross validation, a slight generalization, the data are randomly divided into k disjoint sets of equal size. Then, for each of the k subsets, a model is trained on the remaining data and then validated on the selected subset. In our case, training amounted to averaging the model parameters of all experiments, which were not in the selected subset. These averaged model parameters were then used as input for the simulations of experiments in the validation subset. The simulated force-time responses were then compared with the experimental force-time data. For this comparison, the experimental data were first linearly interpolated at the discrete time steps of the simulated response to allow a direct mapping.

To quantify the error, we calculated the mean of the absolute force differences (a measure of the magnitude error) as well as Pearson’s correlation coefficient (a measure of the shape error). Since the peak forces of our experiments range from $\approx$ 3 N to 9 N, we also normalized the mean absolute difference with the experimental peak force to facilitate a comparison across experiments. We specifically chose to measure the mean absolute difference in force to assess the absolute deviation from the experiment when using generalized model parameters. In order to measure the deviation from the shape of the response, we chose Pearson’s correlation coefficient, which is invariant to linear transformations of the data (i.e., it ignores absolute shifts), and thus compares the

to the equilibrium response, while the ratio $\beta_m/\beta_f$ controls the location of the transition in decay slopes (Fig. 4). At first it may seem counterintuitive, but Charlebois et al. [6] noted that the tensile response of cartilage (particularly to collagen fiber fabric) is important in determining the material’s response to compression as well. Based on their experimental results they argued that axial compression stretches and stiffens the collagen fiber fabric in the transverse direction.

Finally, for the constitutive model, the parameter values $\tau_m$ and $\tau_f$ were determined to match the experimentally obtained forcetime response based on the following constraints inferred from literature [4,6,14]: $0.21–1.03$ s $\sim \tau_m < \tau_f \sim 40–675$ s. Charlebois et al. [6] performed a series of stress relaxation tests, which revealed a significant time-dependent behavior, with a peak load. According to our experiments, the cartilage material was controlled by the time-independent elastic parameters.

The reaction force versus time response was output from the completed simulations and compared with the corresponding experimental curves to determine the “goodness of fit” and to estimate updates for the model parameters. The parameter search space (and hence the fitting process) was informed and bounded by data from literature in order to constrain the optimization problem and help to ensure meaningful solutions. Since each model parameter has a clear physical interpretation, 10–20 such parameter updates sufficed to converge to the final model parameters. The remainder of this section outlines how we bounded the parameter search space starting with a discussion of the parameters $\kappa$, $k_1$, and $k_2$.

Since $\kappa$ acts as a nonphysical penalty parameter used to enforce incompressibility the value of $\kappa$ was maintained at $\kappa \approx 1000 \mu$ [47]. The values for $k_1$ and $k_2$ were fixed to the results documented by García and Cortés [14] who fitted a strain-energy function of the same form as Eq. (4) to data on tensile testing, as documented in Ref. [6]. The remaining material parameters $\mu$, $\beta_m$, $\beta_f$, $\tau_m$, and $\tau_f$ were determined directly from the experimentally obtained reaction force versus time responses of the individual specimens, as described below and illustrated in Fig. 4.

The value of $\mu$ was estimated from the experimental elastic response at $t \sim 600$ s. The equilibrium response of the constitutive model was controlled by the time-independent elastic parameters alone. According to our experiments, the cartilage material reaches mechanical equilibrium in less than 600 s. Other researchers have noted similar time scales to reach equilibrium response [4,6,34,38,57].

In addition, the values of $\beta_m$ and $\beta_f$ were also fitted to the experimental data. A brief analysis of the viscoelastic formulation reveals that the sum $\beta_m + \beta_f$ controls the peak force (with respect
shapes of the curves. Pearson’s product-moment correlation coefficient is a standard correlation coefficient normalized to the range $[-1,1]$.

### 4 Results

Here we provide the final parameter set determined from the optimization and validation process, related statistics, and the numerical results for both the force-time response and the deformation of the collagen fiber fabric in comparison with available experimental data. For convenience Table 1 summarizes the specimen number and the related number of indentations per specimen.

Figure 5 shows the reaction force versus compression response for the first 3 s of testing (to reduce the clutter and to clearly demonstrate the trends). The variability of the indentation test responses within the individual cartilage specimens and among all specimens can clearly be seen. Additionally, the reaction force, and hence cartilage stress, relaxes quickly after indentation and it returned to near zero in approximately 600 s. Note that specimen number 5, which upon inspection prior to testing was visibly degraded relative to the other specimens, is clearly an outlier in terms of the mechanical behavior (very low reaction forces over the measured compression range; force-compression response is nearly linear).

Final material parameters from the numerical optimization process for 23 individual simulations are summarized in Table 2. The mean ($\pm$ standard deviation) model parameters are provided for each of the individual specimens (1–5) and total mean values for specimens 1–4. The proposed model is capable of fitting the response of specimen 5 with the same accuracy as specimens 1–4.

However, the response of specimen 5 is not included in the final determination of the mean material parameters (labeled “mean 1–4”) as it was a clear outlier in terms of appearance and mechanical response; cf. Fig. 5. To demonstrate the variability of the material parameters used to simulate the 21 indentation tests on specimens 1–4, box plots for each of the material parameters are provided in Figs. 6(a)–6(e). The boxes within the box plots contain the median as a bold horizontal line and encompass the interquartile range (IQR) from $x_{25}$ to $x_{75}$, while the whiskers extend up to 1.5 times the IQR in each direction. Every data point outside that range is marked with a circle.

By using the experimental reaction force profile as a function of time in the numerical code, the related simulations do an excellent job of matching the experimental response with the numerical results within the loading domain. Figure 7(a) demonstrates the experimentally measured reaction force versus the time response of specimen 3 and the corresponding numerical simulation. The test was performed at a corner location, as shown in Fig. 7(b).

To address validation, two error measures were employed to quantify the predictive capabilities of the proposed model and the generalized model parameters: the mean of the absolute force differences (a measure of the magnitude error) as well as Pearson’s correlation coefficient (a measure of the shape error). To quantify the absolute deviation from the experiment when using generalized model parameters, we measure the mean absolute difference in force between the experiments and predictions. These deviations range from 4% of the peak force up to almost 90% of the peak force, with $40 \pm 25$% mean $\pm$ standard deviation. Deviation in the shape of the prediction was quantified using Pearson’s correlation coefficient, which is invariant to linear transformations of the data, and thus compares only the shapes of the curves. Across all model predictions, the correlation coefficients have a minimum of 0.939, a maximum of 0.993, and a mean and standard deviation of 0.975 $\pm$ 0.013, respectively.

Three-dimensional sample-specific numerical tracking of the fiber fabric deformation under general loading is a novel feature of the proposed method. To demonstrate this feature we provide results of experimental fiber fabric deformation from Ref. [57].

### Table 1 Summary of specimen number and number of indentation per specimen; total of 23 indentation tests performed on five separate cartilage specimens

<table>
<thead>
<tr>
<th>Specimen No.</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of Indentations</td>
<td>7</td>
<td>4</td>
<td>6</td>
<td>4</td>
<td>2</td>
</tr>
</tbody>
</table>

### Table 2 Summary of the resulting sets of material parameters given as mean $\pm$ standard deviations, where $K_1$ $= 0.425$ MPa and $K_2$ $= 39.8$

<table>
<thead>
<tr>
<th>Specimen</th>
<th>$\mu$ [MPa]</th>
<th>$\beta_m$ [-]</th>
<th>$\tau_m$ [sec]</th>
<th>$\beta_f$ [-]</th>
<th>$\tau_f$ [sec]</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>0.405 $\pm$ 0.203</td>
<td>1.12 $\pm$ 0.324</td>
<td>0.650 $\pm$ 0.147</td>
<td>184 $\pm$ 8.77</td>
<td>3.43 $\pm$ 0.464</td>
</tr>
<tr>
<td>2</td>
<td>0.960 $\pm$ 0.467</td>
<td>0.463 $\pm$ 0.217</td>
<td>0.638 $\pm$ 0.063</td>
<td>185 $\pm$ 5.77</td>
<td>4.95 $\pm$ 1.15</td>
</tr>
<tr>
<td>3</td>
<td>0.200 $\pm$ 0.160</td>
<td>0.731 $\pm$ 0.237</td>
<td>0.572 $\pm$ 0.078</td>
<td>158 $\pm$ 28.2</td>
<td>5.23 $\pm$ 2.06</td>
</tr>
<tr>
<td>4</td>
<td>0.220 $\pm$ 0.074</td>
<td>0.890 $\pm$ 0.533</td>
<td>0.725 $\pm$ 0.171</td>
<td>178 $\pm$ 5.00</td>
<td>3.00 $\pm$ 0.000</td>
</tr>
<tr>
<td>5</td>
<td>0.020 $\pm$ 0.000</td>
<td>2.50 $\pm$ 0.707</td>
<td>0.375 $\pm$ 0.055</td>
<td>50.0 $\pm$ 0.000</td>
<td>3.00 $\pm$ 0.000</td>
</tr>
<tr>
<td>Mean 1–4</td>
<td>0.417 $\pm$ 0.365</td>
<td>0.835 $\pm$ 0.396</td>
<td>0.640 $\pm$ 0.126</td>
<td>175 $\pm$ 19.2</td>
<td>4.15 $\pm$ 1.50</td>
</tr>
</tbody>
</table>
shown as a “quiver plot” in Fig. 8(a) for 0%, 18%, and 29% compressions. Each “quiver” is the projection of a unit vector in three dimensions (representing the principal diffusion eigenvector at that point, and hence the collagen fiber orientation [60]) onto the image plane. To facilitate comparison, the elementwise collagen fiber orientations (represented as unit vectors at the element centers) of the finite deformation simulation at equilibrium elastic solution were plotted at the same compression levels as the experiment. A representative cross section of the simulation results, taken through the indentation location (from the cutting plane indicated in Fig. 3(a)), is provided in Fig. 8(b). A (more) quantitative assessment can be made by studying the change in fiber orientation from 0% compression, to both 18% and 29% compressions of the original thickness. Figure 9 provides the numerical results as a histogram of the mean change in the fiber orientation measured as the change in fiber angle with respect to the normal to the cartilage surface. Thereby, fiber orientation changes were computed within a cylinder under direct influence of the indentor. The cylinder served as a kind of “region of interest.” Figure 9 refers to a volume considering all zones, while Fig. 9(b) provides the related results for the middle zone only.

5 Discussion

We have proposed a phenomenological and patient-specific modeling approach, which incorporates the collagen fiber fabric. The model successfully captures three key features of the material response: viscoelasticity, anisotropy and inhomogeneity, and tension-compression nonlinearity at finite strains. More specifically, the results of the parameter fitting, as well as a comparison of the reaction force-time response and collagen fiber tracking with available experimental data, are discussed in Secs. 5.1–5.3. Finally, both the applications and shortcomings of the proposed method and results are discussed in Sec. 5.4.

5.1 Final Set of Material Parameters. Within the parameters obtained, $\gamma_t$ is about one/two orders of magnitude lower than the range provided in literature ($\sim 40–675$ s). This may be a result of the limited data considered in our model to be assumed to respond in an isochoric manner, i.e., a side-effect of the homogenized liquid/solid matrix assumption (both the intrinsically viscous solid matrix and the loss of fluid pressure have time dependencies, which were not individually taken into account).

All other material parameters are in accordance with those available in literature. In addition, the mean parameters (labeled mean 1–4) demonstrate reasonably low standard deviations and form a basis for FE modeling of human articular cartilage. The elastic portion of the model is available in ABAQUS, ADINA, and will soon be included in ANSYS, while the used viscoelastic constitutive model is available in ADINA. To this end, the mean values of the material parameters, as summarized in Table 2, should be regarded as a kind of “master values” capturing the mechanical response of healthy adult human articular cartilage.

A comparison of the mean values of the material parameters with the parameters required to capture the mechanical response of specimen 5 may provide insight to how these parameters vary with cartilage degradation. For specimen 5, the mean value for $\mu$ was approximately an order of magnitude lower than that of the mean for specimens 1–4. By the same comparison, $\rho_{in}$ was ap-
approximately an order of magnitude higher and $\beta_i$ was approximately an order of magnitude lower, while the values of both $\tau_m$ and $\tau_f$ remained essentially the same.

While it would be better to have a larger number of available data and related simulations with which to generate the parameter statistics, these statistics do provide insight into the material and simulation variability. These box plots provide in Figs. 6(a)–6(c) illustrate that the model parameters are not normally distributed, and, in fact, some distributions seem to be skewed. This can partly be attributed to the comparably small number of tests, and also to the high inter- and intraparameter variabilities, which have previously been noted by various authors; see, for example, Ref. [61].

5.2 Force-Time Response. The two curves shown in Fig. 7(a) warrant some discussion. When the robotic arm approaches the indentation location, it initially moves along its path with constant speed. In order to avoid overshooting the desired indentation depth, the robot slows down shortly before reaching its destination. Moreover, the reaction force of the specimen and the discrete steps performed by the robotic arm induce some vibration (evident in the experimental data of Fig. 7(a), especially at the peak force). The combined result of all these effects is a nonlinear loading ramp. We recover this ramp by optically tracking the vice at a frame rate of 72 Hz. Due to modeling limitations, only a coarse, piecewise-linear approximation of this loading ramp is used as input for the simulation. This explains the discrepancy between the experiment data and the simulation up to about 0.4 s. Note that the artificial kink at approximately 4 N is also a result of this approximation.

Despite these shortcomings, the average peak force recorded in the experiment is well represented by the simulation. Furthermore, the simulated time-dependent mechanical response after fixation of the ~0.4 mm indentation is essentially identical to the experiment data over the whole time domain, which was between 0.4 s and 6 s (mean: $R^2=0.99\pm0.012$ for 23 samples). Overall, the simulation can be fitted to the experimental response of the 23 samples with high accuracy: mean $R^2=0.95\pm0.032$; mean Pearson correlation $r=0.98\pm0.016$; mean absolute error in the reaction force versus time 0.057±0.032 N. It is important to note limitations in the $R^2$ value as an error measure. $R^2$ indicates what proportion of the variance in the data can be explained by the model, but favors complex models and should therefore be used with caution in model selection to avoid overfitting of the data.

To summarize the validation experiments, despite the noted variability in articular cartilage response, the results have demonstrated that the “master model parameters” are capable of predicting cartilage response. The shape of the predictions demonstrates an excellent match of the decay characteristics with caution in model selection to avoid overfitting of the data.

As demonstrated by the good agreement between the experimental data and the numerical results for the 23 indentation tests, the model is capable of reproducing the deformation behavior of human articular cartilage in the physiological loading domain. The proposed model is also capable of capturing the instantaneous deformation response to confined compression when the fibers are essentially inactive. It is important to note that the model has only been tested in unconfined compression (via indentation). However, the proposed model is capable of capturing the commonly noted cartilage response of tension/compression nonlinearity.

5.3 Collagen Fiber Tracking. For the purpose of demonstrating the feature of fiber tracking we compared the simulated collagen fiber fabric deformation with recently published experimental data by de Visser et al. [57]. These authors used diffusion tensor imaging to observe changes in the direction of collagen fibers due to mechanical compression of articular cartilage by providing quantitative results using ten specimens from different bovine knee joints. Spin-echo and diffusion tensor images (156×156 μm² in-plane resolution with a 2 mm slice thickness) of bovine articular cartilage in uncompressed and progressively more compressed states (0%, 18%, and 29% compressions of the original cartilage thickness) were taken after an equilibrium period using a 7 T vertical bore Bruker BioSpin GmbH, Germany, nuclear magnetic resonance spectrometer equipped with a 1.1 T m⁻¹ gradient set and a 15 mm “birdcage” RF resonator. The results demonstrate that the fiber orientations, averaged over all depths in the cartilage, became more aligned with the articular surface of the cartilage under compression, also predicted by the numerical analysis.

The compression effect resulted in a change in orientation of the collagen fiber fabric (measured as the eigenvectors corresponding to maximum diffusion), which was greatest in the middle zone (40–60% of the thickness). In this zone, the average orientation of the fibers (measured with respect to the normal to the articular surface) increased by up to 40 deg. Indeed, in all cases, the collagen fiber bundles were oriented more parallel to the surface when compressed. In the superficial zone this reflected a further flattening of the fibers. In the deep zone, the increase in average orientation angle was consistent with some bending or crimping of the fibers.

The qualitative comparison of compression effects, as seen in Figs. 8(a) and 8(b), demonstrates that the simulation does reflect the fabric deformation. The pronounced directionality in the middle zone of the uncompressed experiment (0% compression in...
Fig. 8(a)) is the result of patient-specific variability, while the simulated fiber orientation in the same zone (Fig. 8(b)) is the specimen distribution based on literature [1]. The observed fiber angle morphologies naturally vary among specimens and may be influenced by the age, exact anatomical location of the specimen, and individual anatomical and physiological peculiarities of the donors [58].

Referring to Fig. 9, the simulated fiber angles for the specific considered specimen change by up to ~40 deg in both the volume considering all zones and the middle zone only, which is in agreement with the ranges determined by the experiment [57]. Finally, the simulated mean changes in the fiber orientation were essentially the same in the (cylindrical) volume for all zones and in the middle zone (12.8 deg and 12.5 deg, respectively), while in the experiment a very similar phenomenon was observed. Hence, one may conclude that the collagen fiber change is dominated by the middle zone, which may be explained by the specific morphologies in the middle zone.

More generally, the 3D sample-specific numerical tracking of the fiber fabric deformation, as demonstrated here, is a generalization of similar plots on fiber fabric deformation documented by Wilson et al. [9,62]. These authors showed the fiber deformation of a geometrically idealized fiber structure in 2D axisymmetric simulations. Note that the model proposed here is capable of utilizing an experimentally measured sample- or patient-specific 3D map of the collagen fiber orientation if such data are available. For example, it has recently been established that anisotropic diffusion of water in cartilage, as visualized by MRI using diffusion tensor imaging, reflects the orientation of the collagen fibers [7,58,60].

5.4 Applications and Shortcomings. The current model is supposed to facilitate 3D contact simulations of diarthrodial joint loading (strain rates >5%/s, based on an argument in Ref. [38]), where efficient estimation of global deformation response is desired in 3D simulations with accurate joint geometries, as pointed out by, for example, Han et al. [17]. That study highlights the urgent need for theoretical approaches to accurate joint contact mechanics. The authors employ a biphasic material model using an isotropic, linear elastic solid matrix to determine contact areas and maximum stresses under a range of joint alignments and ramp loadings. They conclude that the contact areas were vastly overestimated by their numerical simulations. This is perhaps due to the linear elastic solid constituent, which was given a very low Poisson’s ratio, even under impact-type loading rates. We offer that the contact areas would have been better approximated in this problem using the constitutive model employed here.

In addition, the proposed approach enables two interesting opportunities. First, the framework may provide a foundation for a correlation between numerical simulation and functional MRI. From a clinical perspective, it may be possible to correlate the material parameters with MR image data in order to predict the biomechanical condition of cartilage in vivo. Second, the framework is general enough to allow for experimentally measured data on the collagen fiber orientation to be input to the FE model and submodel for each zone. Numerical models like this may also provide for a correlation with clinical MRI data.

It is well known that articular cartilage contains a fluid phase and a collagen fiber-reinforced solid phase. By considering the fluid and solid phase (proteoglycans, other proteins, and chondrocytes, but not the collagen fiber fabric) as a homogenous proteoglycan/water gel matrix material, the model is clearly limited. The principal limitations are as follows: (i) The stress estimate in the matrix material is nonphysical, and (ii) the model is limited to nearly orthotropic deformations, which only occur under physiological pressure levels in a time range up to tens of seconds.

The underlying matrix material representation is assumed to be homogeneous, while it has been determined experimentally that the constitution is depth-dependent (cf. Ref. [13] and references therein). To account for this it is straightforward to extend the approach to consider the shear modulus on an element-basis, although the determination of an accurate 3D distribution of the shear modulus in a specific sample could be a challenging task. In theory, a similar extension could also be employed for the fiber parameters.

Due to the isochoric aspect of the model, the full deformation state determined by the constitutive volumetric response will provide good approximations to the true material response during loading and initial relaxation, but lateral deformations will stray from the physical response during prolonged relaxation. Note that the lateral deformation response was not measured in the current experiment.

Additionally, a single-phase model cannot capture the effects of osmotic swelling (cf. Refs. [63,64] and references therein), which may induce prestraining of the collagen fibers. Depth-dependent, nonhomogeneity and tissue swelling have been incorporated in other cartilage models that also include some description of collagen fiber reinforcement [10,13].

To overcome these deficiencies a multiphase formulation would be required. One approach, which has been effectively integrated with single-phase finite viscoelasticity, relies on the macroscopic theory of porous media, where the essential nonlinearities of the strongly coupled problem are included in the formulation; see, for example, Refs. [65,66]. In this approach, which introduces fluid pressure as an independent nodal degree-of-freedom, the relevant physical properties stemming from the porous microstructure (both the intrinsic viscoelasticity of the skeleton material, and the moving and interacting pore fluid) are captured in an elegant and efficient manner.

While a guiding principle of constitutive modeling is to adopt the simplest model that can explain the data, it is clear that in order to accurately predict cartilage stresses the current formulation must be extended to the biphasic (or multiphasic) regime. These issues, which will increase the complexity of cartilage modeling, can be addressed in subsequent formulations.

Acknowledgment

We gratefully acknowledge the support of the Austrian Science Fund through Project No. P-18110-B15, “Visualization of biomechanics of articular cartilage by MRI.” In addition, we gratefully acknowledge Dimitris Kiousis for many lengthy discussions and general support regarding the use of the finite element analysis program FEAP, and Steven Millington for discussions and insights regarding the mechanical testing.

Appendix

Considering cartilage as a biphasic material, flow of fluid through the solid, permeable matrix is governed by Darcy’s law (see, e.g., Ref. [67])

\[
\nu_{\text{ave}} = k \nabla p
\]

(A1)

where \(\nu_{\text{ave}}\) is the average fluid velocity (m/s), \(k\) is the hydraulic permeability coefficient (m²/N s), and \(\nabla p\) is the pressure gradient (N/m). Using this simple relationship, a reasonable upper bound can be estimated for the loss of total volume in the cartilage sample as a result of fluid exuding from the tissue under pressure. The average specimen in the indentation tests had an approximately \(10 \times 10\) mm² footprint, and a 3 mm thickness (not including the subchondral bone), and the specimen was indented by a 3.0 mm diameter spherical indenter.

The permeability \(k\) of cartilage is on the order of \(10^{-15} - 10^{-16}\) m²/N s. The permeability of articular cartilage is anisotropic and deformation-dependent, but should not be larger than \(10^{-15}\) m²/N s. The peak indentation forces during the experiments are on the order of 3–9 N (for a duration less than 0.3 s). A conservative estimate for the maximum contact pressure is the peak force divided by the projected contacting area at full indent, and hence the peak pressure within the cartilage volume
should not exceed \(2.9 \times 10^6\) Pa at any time. The average pressure gradient in the sample can be estimated as [67]

\[
\nabla p = \frac{p_{\text{max}} - p_{\text{atm}}}{h}
\]

(A2)

where \(p_{\text{atm}}\) is atmospheric pressure (+0 gauge pressure) and \(h\) can be interpreted as the average path length traveled by the fluid under the action of the change in pressure. Given the sample geometry and the location of the maximum pressure in the sample, 5 mm is a reasonable approximation for \(h\). In this case, the average pressure gradient in the sample is \(5.7 \times 10^6\) N/m\(^2\), and the corresponding average fluid velocity at peak pressure is on the order of \(1.4 \times 10^{-7}\) m/s.


