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REVIEW

**David M. Pierce**

# Multi-phase, large-strain constitutive models of cartilage for finite element analyses in 3-D

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**Abstract** Finite element (FE) modeling plays a well-established and increasingly significant role in analyses of articular cartilage at the organ, tissue, and cell scales: for example understanding the functional relationships among constituents, microstructure, and tissue function in diarthrodial joints. A constitutive model, the crux of an accurate FE model, formalizes the functional dependencies among physical variables (e.g., strain, stress, and energy), thereby providing the missing equations to close the system generated by the classical balance principals, while accounting for the specific behavior of cartilage. In the future, fully 3-D FE modeling of cartilage could provide clinical diagnostic tools for patient-specific analyses. Computational analyses of full, patient-specific knee joints under load, especially before and after surgical intervention, would facilitate: (1) investigating fundamental research questions, e.g., structure-function relationships, load support, and mechanobiological cellular stimuli; (2) assessing individual patients, e.g., assessing joint integrity, preventing damage, and prescribing therapies; and (3) advancing tissue engineering, i.e., building replacement materials for cartilage. Approaches to computational modeling generally aim to adopt the simplest possible formulation that can describe experimental data, yet the complexity of articular cartilage mechanics demands similarly complex models. This review discusses extant multi-phase, large-strain (i.e., finite-deformation) constitutive models for cartilage which have been implemented in 3-D nonlinear finite elements. These have paved the way toward 3-D patient-specific clinical tools and along with advances in the underlying continuum theories and computational methods provide the foundations of improved constitutive models for 3-D FE modeling of cartilage in the future.

**Keywords** Cartilage · Constitutive model · Multi-phase · Finite element analysis · Three dimensional

## 1 Introduction

Finite element (FE) modeling plays a well-established and increasingly significant role in analyses of articular cartilage at the organ, tissue, and cell scales: for example in understanding the function of diarthrodial joints and the relationships among constituents, microstructure, and tissue function. Such analyses rely on empirical measurements of geometry, composition, and material responses to build FE-based simulations which reflect real physical behaviors. Specifically, empirical data inform a geometrical mesh of the boundary value problem and facilitate establishing a constitutive model for cartilage, the crux of an accurate FE model. A constitutive model formalizes the functional dependencies among physical variables like strain, stress, and energy, thereby

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D. M. Pierce (✉)
Department of Mechanical Engineering, Department of Biomedical Engineering, University of Connecticut, 191 Auditorium Road, U-3139, Storrs, CT 06269, USA
E-mail: david.pierce@uconn.edu

providing the missing equations to close the system generated by the balance laws, while accounting for the specific behavior of cartilage, cf. [93].

Fully 3-D FE modeling of cartilage in particular holds great promise for patient-specific, clinical diagnostic tools. Computational analyses of full, patient-specific knee joints under load, especially before and after surgical intervention, facilitate: (1) fundamental research questions, e.g., understanding structure-function relationships, load support, and mechanobiological cellular stimuli; (2) assessment of individual patients, e.g., assessing joint integrity, preventing damage, and prescribing therapies; and (3) tissue engineering, i.e., building replacement materials for cartilage. In the future, a multi-disciplinary combination of medical imaging and patient-specific computational modeling may even succeed in determining the functional state of articular cartilage *in vivo*.

Researchers have proposed several constitutive models for cartilage implemented into 2-D, often axisymmetric, finite elements. See, for example [37] for an early review of the application of finite elements to the stress analysis of cartilage, or [22,35,58,59,72,73,106–109] for more recent applications. These studies, and many others, have shed significant light on the structure–function relationships within cartilage and diarthrodial joints. The simplified 2-D nature of such simulations, however, is often difficult to generalize for 3-D patient-specific simulations.

This review discusses all of the extant multi-phase, large-strain (i.e., finite-deformation) constitutive models for cartilage implemented in 3-D nonlinear finite elements. First I outline the mathematical foundations of biphasic, large-strain constitutive models (Sect. 2). Next, I present specific models organized according to complexity: bi-phasic (Sect. 3) and multiphasic (Sect. 4), in chronological order. Computational modeling approaches generally aim to adopt the simplest possible formulation that can describe experimental data, yet the complexity of articular cartilage mechanics demands similarly complex models [53]. The relative scarcity of 3-D constitutive models of cartilage speaks to the challenges of capturing the tissue's complex behavior in a computation model. Existing 3-D, large-strain FE models of articular cartilage use single-phase (e.g., [31,87,88]), biphasic, and multi-phasic models, some at considerable computational cost.

## 2 Preliminaries of a bi-phasic continuum model

This section details foundations of typical biphasic, large-strain constitutive models and establishes notation for this review. Biphasic constitutive models provide a reasonable compromise between model complexity and capturing much of healthy cartilage's essential load-bearing function. Researchers often describe articular cartilage as a biphasic continuum $\varphi = \varphi^{\mathrm{S}} + \varphi^{\mathrm{F}}$, which consists of a porous solid phase $\varphi^{\mathrm{S}}$ saturated with a fluid phase $\varphi^{\mathrm{F}}$, the latter representing interstitial fluid. The volume fractions of solid $n^{\mathrm{S}}$ and fluid $n^{\mathrm{F}}$ generally satisfy the saturation condition

$$n^{\mathrm{S}}(\mathbf{x},t) + n^{\mathrm{F}}(\mathbf{x},t) = 1, \tag{1}$$

where $\mathbf{x}$ is the position vector of the spatial point (reference position $\mathbf{X}$) and $t$ is the time. This framework generally defines stresses

$$\boldsymbol{\sigma}^{\mathrm{S}} = -n^{\mathrm{S}} p\mathbf{I} + \boldsymbol{\sigma}^{\mathrm{S}}_{\mathrm{E}} = -n^{\mathrm{S}} p\mathbf{I} + \frac{2}{J_{\mathrm{S}}}\mathbf{F}_{\mathrm{S}}\frac{\partial \Psi^{\mathrm{S}}}{\partial \mathbf{C}_{\mathrm{S}}}\mathbf{F}_{\mathrm{S}}^{\mathrm{T}}, \tag{2a}$$

$$\boldsymbol{\sigma}^{\mathrm{F}} = -n^{\mathrm{F}} p\mathbf{I}, \tag{2b}$$

where $\boldsymbol{\sigma}^{\mathrm{S}}$ is the solid Cauchy stress (tensor), $p$ is the fluid pressure, $\mathbf{I}$ is the identity tensor, $\boldsymbol{\sigma}^{\mathrm{S}}_{\mathrm{E}}$ is the extra or effectives solid Cauchy stress, $J_{\mathrm{S}} = \det \mathbf{F}_{\mathrm{S}}$ with $\mathbf{F}_{\mathrm{S}}$ the deformation gradient of the solid, $\mathbf{C}_{\mathrm{S}}$ is the right Cauchy–Green deformation tensor, $\boldsymbol{\Psi}^{\mathrm{S}}$ is a strain energy function for the solid phase written explicitly as a function of $\mathbf{C}_{\mathrm{S}}$, and $\boldsymbol{\sigma}^{\mathrm{F}}$ is the fluid Cauchy stress, cf. [11,13,15,16,23–25,84,99]. Thus for the total Cauchy stress

$$\boldsymbol{\sigma} = \boldsymbol{\sigma}^{\mathrm{S}} + \boldsymbol{\sigma}^{\mathrm{F}} = -p\mathbf{I} + \boldsymbol{\sigma}^{\mathrm{S}}_{\mathrm{E}}. \tag{3}$$

Note that the principal invariants: $I_1 = \mathrm{tr}\mathbf{C}_{\mathrm{S}}$, $I_2 = \frac{1}{2}[(\mathrm{tr}\mathbf{C}_{\mathrm{S}})^2 - \mathrm{tr}(\mathbf{C}_{\mathrm{S}}^2)]$, $I_3 = \det \mathbf{C}_{\mathrm{S}}$; and the pseudo invariants: $I_4 = \mathbf{M}_0 : \mathbf{C}_{\mathrm{S}}$ ($\mathbf{M}_0 = \mathbf{m}_0 \otimes \mathbf{m}_0$ is the structure tensor in the reference configuration associated with the orientation $\mathbf{m}_0$) and $I_5 = \mathbf{M}_0 : \mathbf{C}_{\mathrm{S}}^2$, refer to the motion (deformation) of the solid and the preferred direction of the material $\mathbf{m}_0$ often describes the local, principal orientation of reinforcement with collagen fibers. For completeness, this framework also defines the (spatial) structural tensor $\mathbf{M} = \mathbf{m} \otimes \mathbf{m} = \mathbf{F}_{\mathrm{S}}\,\mathbf{m}_0 \otimes \mathbf{F}_{\mathrm{S}}\,\mathbf{m}_0 = \mathbf{F}_{\mathrm{S}}\,\mathbf{M}_0\,\mathbf{F}_{\mathrm{S}}^{\mathrm{T}}$.

Finally, in biphasic theory the fluid pressure $p$ generally relates to the difference between the velocity of the fluid $\mathbf{v}^{\mathrm{F}}$ and the velocity of the solid $\mathbf{v}^{\mathrm{S}}$ (undergoing independent motions) as

$$\mathbf{K}\nabla p = -n^{\mathrm{F}}(\mathbf{v}^{\mathrm{F}} - \mathbf{v}^{\mathrm{S}}) = -n^{\mathrm{F}}\,\mathbf{w}_{\mathrm{FS}}, \tag{4}$$

where $\mathbf{K}$ is the intrinsic permeability tensor and $n^{\mathrm{F}}\,\mathbf{w}_{\mathrm{FS}} = n^{\mathrm{F}}(\mathbf{v}^{\mathrm{F}} - \mathbf{v}^{\mathrm{S}})$ is known as the filtration velocity, cf. [85,86].

## 3 Biphasic models

Almeida and Spilker [3] presented an FE model for 3-D nonlinear analyses of soft hydrated tissues, such as articular cartilage, under physiologically relevant loading conditions. They used a biphasic continuum description (cf. (1)–(4)) to model cartilage using the strain-energy function

$$\Psi^{\mathrm{S}} = \alpha_0 \frac{\mathrm{e}^{\varphi(I_1,I_2,I_4,I_5)}}{I_3^n} = \alpha_0 \exp\left[\varphi(I_1, I_2, I_4, I_5) - n\ln(I_3)\right], \tag{5}$$

with

$$\begin{aligned}\varphi(I_1, I_2, I_4, I_5) = {} & \alpha_1(I_1 - 3) + \alpha_2(I_2 - 3) + \alpha_3(I_1 - 3)^2 + \alpha_4(I_4 - 1) \\ & + \alpha_5(I_4 - 1)^2 + \alpha_6(I_1 - 3)(I_4 - 1) + \alpha_7(I_5 - 1),\end{aligned} \tag{6}$$

where $\alpha_0, \ldots, \alpha_7$, and $n$ are nine model parameters associated with the solid (only seven are independent). For the permeability tensor they specifyss

$$\mathbf{K} = k_0 \left(\frac{J_{\mathrm{s}} - n_0^{\mathrm{S}}}{1 - n_0^{\mathrm{S}}}\right)^L \exp\left(\frac{M(J_{\mathrm{s}}^2 - 1)}{2}\right)\mathbf{I}, \tag{7}$$

where parameters denoted with a subscript 0 (zero) refer to the reference configuration, and $L$ and $M$ are model parameters.

The authors identified a set of model parameters to represent the response of soft tissues in ranges of deformation and stress observed experimentally. Using these parameters, they exercised the model and FE implementation to study unconfined compression of a cylindrical disk of cartilage ($h_0 = 2$ mm and $d_0 = 6$ mm) with the vector $\mathbf{m}_0$ along the main axis of compression. Results showed a qualitative match to experiments, but the authors stressed that the emphasis of this work is in the computational mechanics and implementation aspects of this functional form, see [1,2] for additional background.

Han et al. [42] modeled cartilage using large displacement analyses with the standard biphasic model in the commercial FE software ABAQUS (Dassault Systèmes, Providence, RI, USA): an incompressible, linear elastic solid phase with an incompressible, non-viscous fluid phase and with a deformation-dependent permeability. The authors leveraged Wu and Herzog [113] to describe the deformation-dependent permeability as a function of the current void ratio $e = n^{\mathrm{F}}/n^{\mathrm{S}}$ as

$$\mathbf{K} = k_0 \left(\frac{e}{e_0}\right)^{\kappa} \exp\left(\frac{M}{2}\left[\left(\frac{1+e}{1+e_0}\right)^2 - 1\right]\right)\mathbf{I}, \tag{8}$$

where $e_0$ is the initial void ratio, and $\kappa$ and $M$ are model parameters.

To study patellofemoral joint alignment, they meshed accurate retropatellar and femoral groove surface geometries obtained from laser scanning to create a 3-D FE mesh. They estimated and compared patellofemoral contact areas, peak and local stresses, and pressures for three positions of the patella relative to the femur under four loading conditions. The authors demonstrated that small changes in patellar alignment can cause changes in contact area, peak pressure, and maximum shear stress near the bone–cartilage interface, although likely not so large as to affect joint degeneration.

Mononen et al. [81] modeled cartilage in 3-D using the well-established fibril-reinforced poroviscoelastic (FRPVE) constitutive model [59,108–111]. They divided the effective solid Cauchy stress $\boldsymbol{\sigma}_{\mathrm{E}}^{\mathrm{S}}$ (cf. (2a) and (3)) into the sum of a fibrillar network matrix stress $\boldsymbol{\sigma}_{\mathrm{f}}$ and a viscoelastic (non-fibrillar) solid matrix stress

$\boldsymbol{\sigma}_{\mathrm{nf}}$ [59,80,109]. They modeled the viscoelastic collagen fibrillar contribution $\sigma_{\mathrm{f}}$ (a scalar) in the local, initial fiber orientations $\mathbf{m}_0$ as [110]

$$\sigma_{\mathrm{f}} = -\frac{\eta}{2\sqrt{(\sigma_{\mathrm{f}} - E_{\mathrm{f}}^0\varepsilon_{\mathrm{f}})E_{\mathrm{f}}^{\varepsilon}}}\dot{\sigma}_{\mathrm{f}} + E_{\mathrm{f}}^0\varepsilon_{\mathrm{f}} + \left(\frac{\eta E_{\mathrm{f}}^0}{2\sqrt{(\sigma_{\mathrm{f}} - E_{\mathrm{f}}^0\varepsilon_{\mathrm{f}})E_{\mathrm{f}}^{\varepsilon}}} + \eta\right)\dot{\varepsilon}_{\mathrm{f}} \quad \text{for } \varepsilon_{\mathrm{f}} > 0,$$
$$\sigma_{\mathrm{f}} = 0 \quad \text{for } \varepsilon_{\mathrm{f}} \leq 0, \tag{9}$$

i.e., fibers and fibrils do not support compression, where $\eta$ is the damping coefficient, $\varepsilon_{\mathrm{f}}$ is the logarithmic fibril strain, $E_{\mathrm{f}}^0$ and $E_{\mathrm{f}}^{\varepsilon}$ are the initial and strain-dependent fibril moduli, and $\dot{\sigma}_{\mathrm{f}}$ and $\dot{\varepsilon}_{\mathrm{f}}$ are the fibril stress and strain rates, respectively. They further divided the collagen fibrils into four primary (organized) and 13 secondary (unorganized) fibrils and calculated the stresses in the primary $\sigma_{\mathrm{f,p}}$ and secondary $\sigma_{\mathrm{f,s}}$ collagen fibrils as

$$\sigma_{\mathrm{f,p}} = \rho_z C\sigma_{\mathrm{f}}, \tag{10a}$$
$$\sigma_{\mathrm{f,s}} = \rho_z\sigma_{\mathrm{f}}, \tag{10b}$$

where $\rho_z$ is the relative depth-wise collagen density and $C$ is the density ratio between the primary and secondary fibrils. To calculate the fibril stresses within the FE implementation, the authors specified orientations $\mathbf{m}_0$, and after deformation they computed the new orientations as $\hat{\mathbf{m}} = \mathbf{F}\mathbf{m}_0/\|\mathbf{F}\mathbf{m}_0\|$ and the logarithmic fibril strain as $\varepsilon_{\mathrm{f}} = \log\|\mathbf{F}\mathbf{m}_0\|$ [109]. Finally, they added the contribution of each scalar fibril stress to the total stress tensor using the structure tensor $\hat{\mathbf{M}} = \hat{\mathbf{m}}\otimes\hat{\mathbf{m}}$ corresponding to each fibril contribution. They modeled the non-fibrillar contribution as a neo-Hookean poro-hyperelastic material with Young's modulus $E_{\mathrm{m}}$ and Poisson's ratio $\nu_{\mathrm{m}}$, and permeability $k$. They modeled the fluid fraction as depth-dependent using $n^{\mathrm{F}} = 0.9 - 0.1z^*$ for normal, healthy cartilage where $z^*$ is the normalized tissue depth (zero at the articular surface and one at the cartilage bone interface). Finally, they assumed an isotropic, strain-dependent permeability $\mathbf{K}$ as [111]

$$\mathbf{K} = k_0\left(\frac{1+e}{1+e_0}\right)^M\mathbf{I}, \tag{11}$$

where $k_0$ is the initial permeability and $M$ is the permeability coefficient.

The authors implemented this constitutive model in ABAQUS and constructed a 3-D patient-specific FE model of a knee joint with cartilage and menisci based on magnetic resonance images (MRIs). They included depth-dependent collagen orientations and split-line patterns in the model, and simulated the effects of joint loading on stresses and strains within cartilage (with various split-line patterns and medial collagen fibrillation) under axial impact loading of 1000 N. In the model, the collagen fibrils increased stresses along the split-lines but did not affect contact and pore pressures. Simulated medial osteoarthritis increased tissue strains in both medial and lateral femoral condyles, and contact and pore pressures in the lateral femoral condyle. Simulation results demonstrated that the organization of collagen fibers, especially of the split-line patterns, has important ramifications for the optimal weight-bearing function of articular cartilage.

Pierce et al. [85] modeled cartilage assuming an incompressible, poroelastic solid matrix reinforced by an inhomogeneous, dispersed fiber network and saturated with an incompressible fluid (at constant electrolytic conditions) where the fiber network influences the permeability and contains an intrafibrillar portion which cannot be 'squeezed out.' We used a biphasic continuum description (cf. (1)–(4)) to model cartilage using an additive decomposition of an isotropic matrix $\boldsymbol{\Psi}_{\mathrm{IM}}^{\mathrm{S}}$ and a locally (spatially heterogeneous at the element or Gauss-point level), transversely isotropic fiber network $\boldsymbol{\Psi}_{\mathrm{FN}}^{\mathrm{S}}$ as

$$\boldsymbol{\Psi}^{\mathrm{S}} = \boldsymbol{\Psi}_{\mathrm{IM}}^{\mathrm{S}} + \boldsymbol{\Psi}_{\mathrm{FN}}^{\mathrm{S}}, \tag{12}$$

with [12,97]

$$\boldsymbol{\Psi}_{\mathrm{IM}}^{\mathrm{S}} = \lambda_{\mathrm{cp}}^{\mathrm{S}}\left[\frac{1}{2}(\log J_{\mathrm{S}})^2 + \xi^{\mathrm{S}}\right] - \mu^{\mathrm{S}}\log J_{\mathrm{S}} + \frac{1}{2}\mu^{\mathrm{S}}(I_1 - 3), \tag{13}$$

with

$$\lambda_{\mathrm{cp}}^{\mathrm{S}} = \lambda^{\mathrm{S}}\left[1 + J_{\mathrm{cp}}^{\mathrm{S}}\left(1 + \frac{(J_{\mathrm{cp}}^{\mathrm{S}})^2}{1 - J_{\mathrm{cp}}^{\mathrm{S}}}\right)\right]^{-1}, \tag{14}$$

$$\xi^{\mathrm{S}} = J_{\mathrm{cp}}^{\mathrm{S}}\log J_{\mathrm{S}} + \frac{1 - J_{\mathrm{cp}}^{\mathrm{S}}}{J_{\mathrm{cp}}^{\mathrm{S}} - 2}\left[\log\frac{J_{\mathrm{cp}}^{\mathrm{S}} - J_{\mathrm{S}}}{J_{\mathrm{S}}(J_{\mathrm{cp}}^{\mathrm{S}} - 1) - J_{\mathrm{cp}}^{\mathrm{S}}} - \log(1 - J_{\mathrm{cp}}^{\mathrm{S}})\right], \tag{15}$$

where $\mu^{\mathrm{S}}$ is Lamé's second parameter, $\lambda^{\mathrm{S}}$ is Lamé's first parameter (which in the case of isochoric deformation of the solid matrix degenerates to a non-physical, positive penalty parameter used to enforce material incompressibility), and $\mathrm{n}^{\mathrm{S}}_{0\mathrm{S}} \leq J^{\mathrm{S}}_{\mathrm{cp}} \leq 1$ defines the compaction point where $\mathrm{n}^{\mathrm{S}}_{0\mathrm{S}}$ is the reference solid volume fraction. We modeled the collagen fiber network as [51,52,100]

$$\boldsymbol{\Psi}^{\mathrm{S}}_{\mathrm{FN}} = \frac{k_1}{2k_2}\left[\exp\{k_2[(1-\rho)(I_1-3)^2 + \rho(I_4-1)^2]\} - 1\right], \tag{16}$$

where $k_1 > 0$ is a stress-like parameter, $k_2 > 0$ is a dimensionless parameter, $\rho \in [0, 1]$ is a weighting factor describing the 'degree of anisotropy,' cf. [20,21], and we assume that $\boldsymbol{\Psi}^{S}_{\mathrm{FN}} = 0$ for $I_4 < 1$, i.e., fibers do not support compression. We modeled the corresponding permeability of cartilage as [33,91]

$$\mathbf{K} = k_{0\mathrm{S}}\left(\frac{n^{\mathrm{F}}}{1-n^{\mathrm{S}}_{0\mathrm{S}}}\right)^{m}\left[(1-\rho)\,\mathbf{I} + \frac{\rho}{I_4}\,\mathbf{M}\right], \tag{17}$$

where $k_{0\mathrm{S}}$ [$\mathrm{m}^4$/(Ns)] is initial Darcy permeability and $m$ is a dimensionless parameter.

To establish the predictive power of our constitutive model, we completed numerical simulations in FEAP (University of California at Berkeley, CA, USA) and predicted tension–compression nonlinearity [8,28,54,55], depth-dependent strain and lateral expansion in unconfined compression [30,112], and enhanced fluid–pressure load support. Our approach, in which the material parameters are structurally motivated and have direct physical interpretations, can implement high-resolution morphological data in a computational setting, see, e.g., [87] and [74].

Pierce et al. [86] proposed another 3-D biphasic constitutive model for cartilage, this one designed to incorporate sample- or patient-specific information on the collagen network. We used the same biphasic continuum description (cf. (1)–(4)) to model cartilage using (12) with an isotropic matrix defined by (13–15), but we modeled the collagen fiber network as [36]

$$\boldsymbol{\Psi}^{\mathrm{S}}_{\mathrm{FN}} = \frac{k_1}{2k_2}\left\{\exp[k_2(I^{\star}_4-1)^2] - 1\right\}, \tag{18}$$

where $k_1 > 0$ is a stress-like parameter, $k_2 > 0$ is a dimensionless parameter, and $I^{\star}_4 = \kappa I_1 + (1-3\kappa)I_4$ with the parameter $\kappa \in [0, 1/3]$ a weighting factor describing the 'degree of anisotropy,' and we again assume the conditional statement $\boldsymbol{\Psi}^{\mathrm{S}}_{\mathrm{FN}} = 0$ for $I_4 < 1$. The model includes a corresponding anisotropic permeability as (cf. [85,91])

$$\mathbf{K} = k_{0\mathrm{S}}\left(\frac{n^{\mathrm{F}}}{1-n^{\mathrm{S}}_{0\mathrm{S}}}\right)^{m}\left[\kappa\mathbf{I} + \frac{(1-3\kappa)}{I_4}\mathbf{M}\right]. \tag{19}$$

We implemented the constitutive model in FEAP and constructed an FE model, including both the geometry and the microstructure of the collagen network ($\mathbf{m}_0$ and $\kappa$), using ultra-high field diffusion tensor magnetic resonance imaging (DT-MRI) [4,78,87]. We simulated an indentation experiment and predicted the intra-tissue distributions of Green–Lagrange strains, interstitial fluid pressures (and fluid pressure load support), and von Mises stresses [10]. The through-thickness heterogeneity both of the collagen network and of the material properties influenced the distributions of interstitial fluid pressure to maintain fluid pressure and hence load support.

Pierce et al. [89] proposed a 3-D biphasic, viscoelastic constitutive model for cartilage, this one designed to directly incorporate diffusion-tensor MRI reflecting the sample- or patient-specific collagen network. We used an additive decomposition of the strain-energy function $\boldsymbol{\Psi}^{S}$ into an isotropic matrix part $\boldsymbol{\Psi}^{\mathrm{S}}_{\mathrm{IM}}$ and a transversely isotropic fiber network part $\boldsymbol{\Psi}^{\mathrm{S}}_{\mathrm{FN}}$ as

$$\boldsymbol{\Psi}^{S} = (1-\nu)\boldsymbol{\Psi}^{\mathrm{S}}_{\mathrm{IM}} + \nu\boldsymbol{\Psi}^{\mathrm{S}}_{\mathrm{FN}}, \tag{20}$$

where $\nu$ is the volume fraction of the collagen content to the total solid, and with $\boldsymbol{\Psi}^{\mathrm{S}}_{\mathrm{IM}}$ defined by (13 - 15). To capture the anisotropic and nonlinear response of the dispersed collagen fiber network let $\rho(\mathbf{M})$ be the orientation density of fibers (the ODF) so that $(1/(4\pi))\int_{\Omega}\rho(\mathbf{M})\,\mathrm{d}\Omega = 1$, where $\Omega = \mathbf{M} \in \mathbb{R}^3 : |\mathbf{M}| = 1$ is the unit sphere [71,79]. Then

$$\boldsymbol{\Psi}^{\mathrm{S}}_{\mathrm{FN}} = \int_{\Omega}\rho(\mathbf{M})\frac{k_1}{2k_2}\left\{\exp[k_2(I_4-1)^2] - 1\right\}\mathcal{H}(I_4-1)\,\mathrm{d}\Omega, \tag{21}$$

where $\mathcal{H}$ is a Heaviside step function evaluated at $(I_4 - 1)$, i.e., collagen fibers only engage under stretches greater than unity [49]. To determine the time-dependent (viscous) contributions from both the matrix and the fiber network, we stepped through time $t \in [0+, T]$, where we knew the relevant kinematic quantities at times $t_n$ and $t_{n+1}$ and where we calculated the second Piola–Kirchhoff stress $\mathbf{S}_n$ at time $t_n$ [47,88]. We then calculated the second Piola–Kirchhoff stress $\mathbf{S}_{n+1}$ at time $t_{n+1}$ as

$$\mathbf{S}_{n+1} = \sum_{\boldsymbol{\alpha}=\mathbf{IM},\mathbf{FN}} \left(\mathbf{S}^{\infty}_{\alpha,n+1} + \mathbf{Q}_{\alpha,n+1}\right), \tag{22}$$

where $\mathbf{S}^{\infty}_{\alpha,n+1}$ were the elastic responses (isotropic matrix and fiber network) computed from the given strain measures at $t_{n+1}$ and $\mathbf{Q}_{\alpha,n+1}$ were the non-equilibrium stresses associated with $\boldsymbol{\alpha} = \mathbf{\{IM, FN\}}$ viscoelastic (time-dependent) processes. We computed the non-equilibrium stresses, assuming a linear evolution equation for each viscoelastic process, as

$$\mathbf{Q}_{\alpha,n+1} = \beta_\alpha \xi_\alpha \mathbf{S}^{\infty}_{\alpha,n+1} + \xi_\alpha \left[\xi_\alpha \mathbf{Q}_{\alpha,n} - \beta_\alpha \mathbf{S}^{\infty}_{\alpha,n}\right], \tag{23}$$

where $\beta_\alpha$ are dimensionless magnitude factors, $\xi_\alpha = \exp(-\Delta t/2\tau_\alpha)$ with $\Delta t = t_{n+1} - t_n$, $\tau_\alpha$ [s] are the associated relaxation times, and $\mathbf{Q}_{\alpha,0} = \mathbf{0}$ for all $\alpha$ [48]. Finally, we included the corresponding permeability of cartilage as (cf. [85,91])

$$\mathbf{K} = k_{0\mathrm{S}} \left(\frac{n^{\mathrm{F}}}{1 - n^{\mathrm{S}}_{0\mathrm{S}}}\right)^m \frac{1}{4\pi} \int_{\Omega} \frac{\rho(\mathbf{M})}{I_4(\mathbf{m})} \mathbf{m} \otimes \mathbf{m} \, \mathrm{d}\Omega, \tag{24}$$

where $k_{0\mathrm{S}}$ [$\mathrm{m}^4$/Ns] is the initial Darcy permeability and $m$ is a dimensionless parameter. We directly applied measured diffusion tensors as

$$\rho(\mathbf{M}, \mathbf{D}) = \frac{\sin\theta}{|\mathbf{D}|^{1/2} \left(\mathbf{M}^{\mathrm{T}} \mathbf{D}^{-1} \mathbf{M}\right)^{3/2}}, \tag{25}$$

where $(\mathbf{M}) = (\cos\theta \sin\phi, \sin\theta \sin\phi, \cos\phi)^{\mathrm{T}}$ and $\mathbf{D}$ is the symmetric, positive-definite diffusion tensor for a specific element.

We implemented this model in FEAP and tested two hypotheses: (i) the through-thickness structural arrangement of collagen adjusts fluid permeation to maintain fluid pressure and optimize load-bearing function [32] and (ii) the through-thickness heterogeneity in mechanical properties acts to maintain fluid pressure, particularly at the articular surface [67]. We completed finite deformation contact simulations of an indentation experiment using four models: (1) patient-specific collagen fiber network, heterogeneous mechanical properties; (2) patient-specific collagen fiber network, homogeneous mechanical properties; (3) no collagen fiber network, heterogeneous mechanical properties; and (4) no collagen fiber network, homogeneous mechanical properties. Models with heterogeneous mechanical properties used parameters as a function of $z^* \in [0, 1]$, the normalized tissue thickness (zero refers to the articular surface, and one refers to the interface with subchondral bone); homogeneous models used constant mean parameters throughout the thickness. Our results supported both hypotheses: the through-the-thickness heterogeneity of (i) the collagen fiber network and (ii) the mechanical properties served both to alter the distribution of interstitial fluid pressure and to maintain fluid pressure near the cartilage surface.

Wan et al. [103] extended the FRPVE constitutive model [59,81,109–111] (cf. 9–11) by connecting the $\mathrm{T}_{1\rho}$ relaxation time measured via MRI to the reference solid volume fraction $n_{0\mathrm{S}}$ as

$$n_{0\mathrm{S}} = C_1 \exp(C_2 \mathrm{T}_{1\rho}) \tag{26}$$

where $C_1$ and $C_2$ are model parameters fitted via inverse FE modeling. The authors ignored the hydrostatic pressure (assuming $p = 0$ in steady-state conditions) and fixed the remaining seven model parameters. Leveraging ABAQUS, they then made 3-D FE models of ten *in vitro* specimens of human tibial cartilage and assigned each element a reference solid volume fraction determined by the corresponding $\mathrm{T}_{1\rho}$ value measured experimentally. Results suggested that the $\mathrm{T}_{1\rho}$-based FRPVE constitutive equations may improve the detection of changes in mechanical properties of human cartilage tissues associated with joint pathologies such as osteoarthritis (OA).

## 4 Multi-phasic models

To better capture tissue behavior, 3-D FE analyses of articular cartilage using three-phase (solid, fluid, and ion concentration) or multi-phase models (e.g., including $Na^+$ and $CL^-$ ions as process variables) generally add osmotic pressure (swelling), which results primarily from Donnan (contributes over 85% of the total measured swelling pressure [101]) and entropic effects (see review in [17]), as well as charge–charge repulsion. Such constitutive models may also seek to capture other effects of mechanical–electrochemical coupling generated from ions and fixed charges, such as streaming potentials and electroosmoses. Multi-phasic cartilage models capture more physics, but are more computationally expensive.

Chen et al. [19] proposed a constitutive model for cartilage and a nonlinear FE formulation including ionic molar flows and electrical potentials. The authors started from the triphasic mixture theory of Lai et al. [68] and assumed that all constituents (phases $\alpha = \{\mathrm{S}, \mathrm{F}, +, -\}$, for the solid, fluid, cation, and anion, respectively) of cartilage occupy the same local space simultaneously. In addition to the filtration velocity (cf. Section 2), they defined the velocities of the ionic phases (fluxes) relative to the solid phase as $\mathbf{j}^\alpha = \tilde{c}^\alpha(\mathbf{v}^\alpha - \mathbf{v}^\mathrm{S})$ for $\alpha = \{+, -\}$, where $\tilde{c}^\alpha = n^\mathrm{F} c^\alpha$ are the ionic molar concentrations (per unit volume of tissue), and $c^\alpha$ is the ionic molar concentration (per unit volume of fluid). The authors assumed negligible cation–cation, anion–anion, and ion–solid frictions (relative to the solid-fluid and ion-fluid frictions) and derived the quasi-static momentum equations for the solid, fluid, and ionic phases as

$$\nabla \cdot \boldsymbol{\sigma} = \mathbf{0}, \tag{27}$$

$$\begin{aligned}\rho^{\mathrm{FR}} \nabla \mu^\mathrm{F} = &-n^\mathrm{F} \mathbf{K}^{-1} \mathbf{w}_\mathrm{FS} - c^+ R\Theta \mathbf{d}^{+^{-1}} \mathbf{w}_\mathrm{FS} \\ &- c^- R\Theta \mathbf{d}^{-^{-1}} \mathbf{w}_\mathrm{FS} + \frac{R\Theta}{n^\mathrm{F}} \mathbf{d}^{+^{-1}} \mathbf{j}^+ + \frac{R\Theta}{n^\mathrm{F}} \mathbf{d}^{-^{-1}} \mathbf{j}^-,\end{aligned} \tag{28}$$

$$M^+ \nabla \tilde{\mu}^+ = R\Theta \mathbf{d}^{+^{-1}} \mathbf{w}_\mathrm{FS} - \frac{R\Theta}{\tilde{c}^+} \mathbf{d}^{+^{-1}} \mathbf{j}^+, \tag{29}$$

$$M^- \nabla \tilde{\mu}^- = R\Theta \mathbf{d}^{-^{-1}} \mathbf{w}_\mathrm{FS} - \frac{R\Theta}{\tilde{c}^-} \mathbf{d}^{-^{-1}} \mathbf{j}^-, \tag{30}$$

where $\rho^{\alpha \mathrm{R}}$ is the real density of the $\alpha$ constituent, $\mu^\mathrm{F}$, $\tilde{\mu}^+$, and $\tilde{\mu}^-$ are the chemical potentials of the fluid and of the cation and anion per unit mass, respectively, $\mathbf{d}^\alpha (\alpha = +, -)$ is the ionic diffusion coefficient (tensor), $R$ is the universal gas constant, $\Theta$ is the absolute temperature, and $M^\alpha (\alpha = \{+, -\})$ are the ionic molecular weights related to the apparent densities as $\rho^\alpha = c^\alpha n^\mathrm{F} M^\alpha$. By neglecting the viscosities of both the solid and fluid, the authors generated the total Cauchy stress (3) and the chemical and electrochemical potentials for the fluid and the univalent ions respectively as

$$\mu^\mathrm{F} = \mu_0^\mathrm{F} + \frac{p}{\rho^{\mathrm{FR}}} - \frac{R\Theta}{\rho^{\mathrm{FR}}} \Phi (c^+ + c^-), \tag{31}$$

$$\tilde{\mu}^+ = \mu_0^+ + \frac{R\Theta}{M^+} \ln(\gamma^+ c^+) + \left(\frac{\eta}{M^+}\right), \tag{32}$$

$$\tilde{\mu}^- = \mu_0^- + \frac{R\Theta}{M^-} \ln(\gamma^- c^-) - \left(\frac{\eta}{M^-}\right), \tag{33}$$

where $\mu_0^\alpha (\alpha = \{\mathrm{F}, +, -\})$ are the reference chemical potentials for the $\alpha$ constituents, $\Phi$ is the osmotic coefficient (assumed equal for cations and anions), $\gamma^\alpha (\alpha = \{+, -\})$ are the activity coefficients of the cation and anion, and $\eta$ is the product of the Faraday constant and the electric potential. The electroneutrality condition for the tissue leads to the constraint $\tilde{c}^+ - \tilde{c}^- - \tilde{c}^\mathrm{F} = 0$, where $\tilde{c}^\mathrm{F} = n^\mathrm{F} c^\mathrm{F}$ is the negative fixed charge density in the equivalent mole per unit tissue volume. The authors established an imaginary reference configuration based on reformulating the constitutive equations for large strains (deformations) by applying a Piola transform associated with $\mathbf{F}_\mathrm{S}$ to the relative velocities of the fluid and ionic phases as

$$\mathbf{W}^\mathrm{S} = J^s \mathbf{F}_\mathrm{S}^{-1} (n^\mathrm{F} \mathbf{w}_\mathrm{FS}), \tag{34}$$

$$\mathbf{J}^{\alpha \mathrm{S}} = J_\mathrm{S} \mathbf{F}_\mathrm{S}^{-1} \mathbf{j}^\alpha \ (\alpha = \{+, -\}). \tag{35}$$

To verify the implementation of the procedure, the authors analyzed a confined problem and compared the results to those obtained by Mow et al. [82] using the finite difference method.

The authors then completed 3-D large deformation FE analyses of articular cartilage undergoing free-swelling to reproduce the experimentally determined curling behavior of cartilage strips submerged in solution baths of various concentrations *in vitro*. To complete the constitutive model, the authors used the Mooney–Rivlin model for the solid matrix and used the deformation-dependent permeability function proposed by Holmes et al. (7) [46]. Furthermore, they assumed isotropic diffusion of ions. The simulation results agreed with those measured experimentally. The model, while isotropic, accounts for deformation-dependent permeability and non-uniform distributions of fixed-charge density and solidity.

Schroeder et al. [94] proposed a 3-D FE constitutive model to study intervertebral disc transmitting loads through the spine. The authors used the FRPVE constitutive model (9–11) [108–111], extended to include osmotic swelling, to compute the interplay of elastic, viscous, and osmotic forces in an intervertebral disc under axial compressive load. They captured osmotic pressure $\Delta\pi$ in the model as [102]

$$\Delta\pi = \phi_{\text{int}} R\Theta \sqrt{c_{\text{F}}^2 + 4\frac{(\gamma_{\text{ext}}^{\pm})^2}{(\gamma_{\text{int}}^{\pm})^2} c_{\text{ext}}^2} - 2\phi_{\text{ext}} R\Theta c_{\text{ext}}, \tag{36}$$

where $c_{\text{F}}$ is the fixed charge density of the proteoglycans per unit extrafibrillar fluid volume, $\phi_{\text{int}}$ and $\phi_{\text{ext}}$ are osmotic coefficients, and $\gamma_{\text{int}}$ and $\gamma_{\text{ext}}$ are activity coefficients. Following (3), the authors defined the interstitial fluid pressure $p$ as

$$p = \mu^{\text{f}} + \Delta\pi, \tag{37}$$

where $\mu^{\text{f}}$ is the chemical potential. The authors implemented their model in ABAQUS and analyzed the mechanics of an intervertebral disc under axial compressive load. When the unloaded 3-D FE model equilibrates in a physiological solution it exhibits an intra-disc pressure of approximately 0.2 MPa. Before and after axial loading the numerically simulated hydrostatic pressure compares well with the ranges measured experimentally.

Ehlers et al. [27] formulated a general constitutive model in order to reproduce the behavior of charged, hydrated soft tissues and particularized this model to analyze the nucleus pulposus. The authors assumed a three phase model including solid (S), fluid (F), and fixed charge (fc) where $n^{\text{fc}} \approx 0$ so such that (1) still holds. They described the osmotic properties without considering the ion concentrations (or electro-chemical potentials) as additional unknowns in the process. The authors specified an additive decomposition of the total strain energy into osmotic (OP), equilibrium (EQ, elastic), non-equilibrium (NE, viscoelastic), and anisotropic (AN) contributions as

$$\boldsymbol{\Psi}^{\text{S}} = \boldsymbol{\Psi}^{\text{S}}_{\text{OP}}(\det \mathbf{C}_{\text{S}}) + \boldsymbol{\Psi}^{\text{S}}_{\text{EQ}}(\mathbf{C}_{\text{S}}) + \sum_{n=1}^{N} \boldsymbol{\Psi}^{\text{S}}_{\text{NE}}[(\hat{\mathbf{C}}_{\text{Se}})_n] + \boldsymbol{\Psi}^{\text{S}}_{\text{AN}}(\mathbf{C}_{\text{S}}, \mathbf{M}_0). \tag{38}$$

To describe finite viscoelasticity using a generalized Maxwell model with $n = 1, \ldots, N$ Maxwell elements, the authors used a multiplicative split of the solid deformation gradient $\mathbf{F}_{\text{S}} = (\mathbf{F}_{\text{Se}})_n(\mathbf{F}_{\text{Si}})_n$ into elastic $(\mathbf{F}_{\text{Se}})_n$ and inelastic $(\mathbf{F}_{\text{Si}})_n$ deformations associated with the $n^{\text{th}}$ Maxwell element, and with $(\hat{\mathbf{C}}_{\text{Se}})_n = (\mathbf{F}^{\text{T}}_{\text{Se}})_n(\mathbf{F}_{\text{Se}})_n$ and $(\mathbf{C}_{\text{Si}})_n = (\mathbf{F}^{\text{T}}_{\text{Si}})_n(\mathbf{F}_{\text{Si}})_n$. They defined the contribution to the strain energy from osmotic pressure as

$$\boldsymbol{\Psi}^{\text{S}}_{\text{OP}} = R\Theta c^{\text{fc}}_{0\text{S}} n^{\text{F}}_{0\text{S}} \left[ \frac{2\bar{c}_{\text{m}}}{c^{\text{fc}}_{\text{m}}} - \frac{\sqrt{4\bar{c}^2_{\text{m}} + (c^{\text{fc}}_{\text{m}})^2}}{c^{\text{fc}}_{\text{m}}} + \text{arcsinh}\left( \frac{c^{\text{fc}}_{\text{m}}}{2\bar{c}_{\text{m}}} \right) \right], \tag{39}$$

where $c^{\text{fc}}_{0\text{S}}$ is the initial molar concentration of fixed charge, $\bar{c}_{\text{m}}$ is the molar concentration of the external monovalent solution surrounding the tissue (treated here as a model parameter and not a boundary condition), and the current molar concentration of fixed charge $c^{\text{fc}}_{\text{m}}$ depends on the deformation as $c^{\text{fc}}_{\text{m}} = c^{\text{fc}}_{0\text{S}}(1 - n^{\text{S}}_{0\text{S}})(\det\mathbf{F}_{\text{S}} - n^{\text{S}}_{0\text{S}})^{-1}$. The authors specified a generalized Ogden constitutive model for the isotropic mechanical equilibrium (EQ) and non-equilibrium (NE) strain energies, thus encompassing, e.g., Varga, neo-Hookean, or Mooney–Rivlin material laws. They specify the evolution equation for viscoelasticity as

$$[(\mathbf{C}_{\text{Si}})_n]'_{\text{S}} - \frac{1}{\eta^{\text{S}}_n}(\mathbf{C}_{\text{Si}})_n \mathbf{S}^{\text{S}}_n (\mathbf{C}_{\text{Si}})_n + \frac{\zeta^{\text{S}}_n}{\eta^{\text{S}}_n(2\eta^{\text{S}}_n + 3\zeta^{\text{S}}_n)} [\mathbf{S}^{\text{S}}_n (\mathbf{C}_{\text{Si}})_n](\mathbf{C}_{\text{Si}})_n = \mathbf{0}, \tag{40}$$

where $\mathbf{S}_n^{\mathrm{S}}$ is the second Piola-Kirchhoff stress, and $\eta_n^{\mathrm{S}}$ and $\zeta_n^{\mathrm{S}}$ are the shear and bulk viscosities of the dashpot, respectively, all associated with the $n^{\text{th}}$ Maxwell element. The authors specified the corresponding isotropic mechanical non-equilibrium strain energy as

$$\begin{aligned}\boldsymbol{\Psi}_{\mathrm{NE}}^{\mathrm{S}} = &\sum_{n=1}^{N}\mu_n^{\mathrm{S}}\sum_{m=1}^{M_n}\left[\sum_{k=1}^{3}\frac{\mu^*_{n(m)}}{\alpha_{n(m)}}\left(\lambda_{\mathrm{Se}(k)}^{\alpha_{n(m)}/2}-1\right)-\mu^*_{n(m)}\ln(J_{\mathrm{Se}})_n\right]\\ &+\sum_{n=1}^{N}\frac{\lambda_n^{\mathrm{S}}}{\gamma_n^{\mathrm{S}}\left(\gamma_n^{\mathrm{S}}-1+\frac{1}{[1-(n_{\mathrm{Si}}^{\mathrm{S}})_n]^2}\right)}\\ &\left((J_{\mathrm{Se}}^{\gamma_n^{\mathrm{S}}})_n-1-\gamma_n^{\mathrm{S}}\ln\frac{(J_{\mathrm{Se}})_n-(n_{\mathrm{Si}}^{\mathrm{S}})_n}{1-(n_{\mathrm{Si}}^{\mathrm{S}})_n}+\gamma_n^{\mathrm{S}}n_{\mathrm{Si}}^{\mathrm{S}}\frac{(J_{\mathrm{Se}})_n-1}{1-(n_{\mathrm{Si}}^{\mathrm{S}})_n}\right),\end{aligned}\tag{41}$$

where $(\lambda_{\mathrm{Se}(k)})_n$ are the eigenvalues of $(\mathbf{C}_{\mathrm{Se}})_n$; $(J_{\mathrm{Se}})_n = \det(\mathbf{F}_{\mathrm{Se}})_n$; the indices $n$, $m$, and $k$ denote the number of Maxwell elements ($N$), the number of Ogden terms ($M_n$), and the number of space dimensions (three for 3-D), respectively; $\mu_n^{\mathrm{S}} > 0$ is Lamé's first constant; $\lambda_n^{\mathrm{S}} > 0$ is Lamé's second constant; and $\mu^*_{n(m)}$, $\alpha_{n(m)}$, and $\gamma_n^{\mathrm{S}} > 1$ are dimensionless model parameters. They specified the anisotropic contribution to the free-energy function as

$$\boldsymbol{\Psi}_{\mathrm{AN}}^{\mathrm{S}} = \sum_{q=1}^{M_f}\left[\frac{\tilde{\mu}_q^{\mathrm{S}}}{\tilde{\gamma}_q^{\mathrm{S}}}\left(I_4^{\tilde{\gamma}_q^{\mathrm{S}}/2}+I_6^{\tilde{\gamma}_q^{\mathrm{S}}/2}-2\right)-\tilde{\mu}_q^{\mathrm{S}}\ln(I_4I_6)^{1/2}\right],\tag{42}$$

for $\forall\ I_4, I_6 > 1$ where $M_f$ is the number of polynomials, $\tilde{\mu}_q^{\mathrm{S}}$ and $\tilde{\gamma}_q^{\mathrm{S}}$ are model parameters, $I_4$ is the fourth pseudo-invariant of reference unit vector $\mathbf{m}_0$ (cf. Sect. 2), and $I_6 = \mathbf{C}_{\mathrm{S}} : \mathbf{M}' = \mathbf{m}_0' \cdot \mathbf{C}_{\mathrm{S}}\mathbf{m}_0'$ for a second reference unit vector $\mathbf{m}_0'$. Finally, the authors specify the Darcy permeability tensor as [76]

$$\mathbf{K}^{\mathrm{F}} = \frac{k_{0\mathrm{S}}^{\mathrm{S}}}{\mu^{\mathrm{FR}}}\left(\frac{J_{\mathrm{S}}-n_{0\mathrm{S}}^{\mathrm{S}}}{n_{0\mathrm{S}}^{\mathrm{F}}}\right)^{\kappa}\mathbf{I},\tag{43}$$

where $k_{0\mathrm{S}}^{\mathrm{S}}$ is the initial permeability, $\mu^{\mathrm{FR}} > 0$ is the effective viscosity of the fluid, and $\kappa \geq 0$ is a model parameter.

The authors first implemented this constitutive model in PANDAS (based on FEAP) and simulated a torsion test of the nucleus pulposus. They specified a neo-Hookean solid with two Maxwell elements and an anisotropic contribution fitted to the experimental curves given by Holzapfel et al. [50]. After fitting the model under conditions that minimized osmotic effects, simulations could reproduce the experimental results of Iatridis et al. [57] focused primarily on the viscoelastic response of the tissue. Finally, the authors simulated a swelling experiment on a sagittally cut nucleus pulposus and L4-L5 motion segment, modeling the tissue anisotropy and inhomogeneity as in Ehlers et al. [26]. Decreasing the concentration of the external solution increased the osmotic pressure difference inside the nucleus pulposus, causing fluid to flow into the intervertebral disc, increasing its volume. The height of the predicted disc bulge reasonably approximated the experimental result from Holzapfel et al. [50].

Ateshian et al. [7] modeled the solid matrix of cartilage with a continuous fiber angular distribution, where fibers can only sustain tension, swelled by the osmotic pressure of a proteoglycan ground matrix. They particularized their constitutive model to focus on the equilibrium response of cartilage to mechanical and osmotic loading, when flow-dependent and flow-independent viscoelastic effects subsided; thus, they specialized the framework of triphasic theory for charged hydrated tissues to equilibrium conditions under finite deformation. The authors assumed the total osmotic pressure as the sum of the Donnan pressure arising from the total charge density $c^{\mathrm{F}}$ of the proteoglycans in cartilage, and the entropic pressure attenuated by the fraction $\varphi^{\mathrm{fc}}$ ($0 \leq \varphi^{\mathrm{fc}} \leq 1$) of $c^{\mathrm{F}}$ as

$$p = p^* + R\Theta(\sqrt{(c^{\mathrm{F}})^2+(\bar{c}^*)^2}-\bar{c}^*) + c_1\varphi^{\mathrm{fc}}c^{\mathrm{F}} + c_2(\varphi^{\mathrm{fc}}c^{\mathrm{F}})^2,\tag{44}$$

where $p^*$ is the ambient pressure in the external bath, $\bar{c}^*$ is the external bath osmolarity (if $c^*$ is the salt concentration $\bar{c}^* = 2c^*$), and $c_1$ and $c_2$ are parameters obtained from experiments. Furthermore, since they assumed the proteoglycans were trapped within the solid matrix, they constrained $c^{\mathrm{F}}$ as $c^{\mathrm{F}} = \varphi_0^{\mathrm{F}}c_0^{\mathrm{F}}(J_{\mathrm{S}} -$

$1+\varphi_0^{\mathrm{F}})^{-1}$, where $c_0^{\mathrm{F}}$ and $\varphi_0^{\mathrm{F}}$ are the proteoglycan charge density and the water volume fraction of the tissue, respectively, in the reference configuration. Because the osmotic pressure difference $\pi = p - p^*$ depends on the deformation of the solid matrix (via $J_{\mathrm{S}}$), there is an associated osmotic modulus describing the resulting tissue stiffness. They described the solid matrix using a continuous fiber distribution, cf. [56,69,70]. To establish the notation let $\mathbf{n}_0$ be a unit vector directed along spherical angles $(\theta, \phi)$ in the global orthornormal basis $\{\mathbf{e}_i\}$, where $0 \leq \theta \leq 2\pi$ and $0 \leq \phi \leq \pi$. Furthermore, let $\lambda_n$ characterize the stretch of fibers along $\mathbf{n}_0$ as $\lambda_n^2 = \mathbf{n}_0 \cdot \mathbf{C}_{\mathrm{S}}\mathbf{n}_0 = \mathbf{N}_0 : \mathbf{C}_{\mathrm{S}} \equiv I_n$, where $\mathbf{N}_0 = \mathbf{n}_0 \otimes \mathbf{n}_0$ is a structure tensor associated with the direction $\mathbf{n}_0$ and $\mathbf{N} = \mathbf{n} \otimes \mathbf{n}$ with $\mathbf{n} = I_n^{-1/2}\mathbf{F}\mathbf{n}_0$ is the spatial direction of fibers originally oriented along $\mathbf{n}_0$ (cf. Section 2). The authors proposed a power-law relation for the fiber strain energies and integrated these contributions to determine the total strain energy as

$$\Psi^{\mathrm{S}} = \int_0^{2\pi} \int_0^{\pi} \xi(\mathbf{n}_0)(I_n - 1)^{\alpha(\mathbf{n}_0)} \mathcal{H}(I_n - 1) \sin\phi \mathrm{d}\phi \mathrm{d}\theta, \tag{45}$$

where $\xi(\mathbf{n}_0)$ [force/area] and $\alpha(\mathbf{n}_0) \geq 2$ [unitless] are model parameters that may vary along the directions $\mathbf{n}_0$ (and may vary spatially for inhomogeneous materials). To capture general continuous angular distributions of fibers the authors proposed an ellipsoidal distribution and formulated $\xi(\mathbf{n}_0)$ and $\alpha(\mathbf{n}_0)$ in a local orthonormal basis $\{\mathbf{a}_i\}$ defined by the local structure relative to the global basis $\{\mathbf{e}_i\}$. In this local basis, they expressed $\xi(\mathbf{n}_0)$ and $\alpha(\mathbf{n}_0)$ in an associated spherical coordinate system $(\Theta, \Phi)$ as

$$\xi(\mathbf{n}_0) = \left( \frac{\cos^2\Theta \sin^2\Phi}{\xi_1^2} + \frac{\sin^2\Theta \sin^2\Phi}{\xi_2^2} + \frac{\cos^2\Phi}{\xi_3^2} \right)^{-1/2}, \tag{46a}$$

$$\alpha(\mathbf{n}_0) = \left( \frac{\cos^2\Theta \sin^2\Phi}{\alpha_1^2} + \frac{\sin^2\Theta \sin^2\Phi}{\alpha_2^2} + \frac{\cos^2\Phi}{\alpha_3^2} \right)^{-1/2}, \tag{46b}$$

where $\mathbf{n}_0 = \cos\Theta \sin\Phi \mathbf{a}_1 + \sin\Theta \sin\Phi \mathbf{a}_2 + \cos\Phi \mathbf{a}_3$, and $\xi_i$ and $\alpha_i$ $(i = 1, 2, 3)$ represent the semi-axes of the respective ellipsoids of $\xi$ and $\alpha$ along $\mathbf{a}_i$.

The authors implemented their constitutive model into a custom, 3-D FE code including finite deformation. Therein, they evaluated the double integral in (45) numerically using integration over a geodesic dome representation of a unit sphere. Using 3-D FE analyses of basic test geometries, they simulated the equilibrium response of cartilage to mechanical and osmotic loading. First, they loaded an FE model of a specimen of cartilage with prescribed displacements from compression to tension, in a 0.15 M NaCl bath ($\bar{c}^* = 300\,\mathrm{mol/m^3}$). These simulations captured a rapid rise in the stress–strain response in the transition from compression to tension, consistent with experiments from Huang et al. [55]. By performing simulations parallel and perpendicular to the local split-line directions (principal orientation of fiber alignment), the authors also demonstrated that their simulations captured anisotropic responses in tension as well as heterogeneous responses through the thickness. Next, they investigated the Poisson's ratio in compression and tension and demonstrated that their simulations captured the salient features of corresponding experiments [18,28,55,60,104,112]. They predicted that Poisson's ratio was as low as 0.017 in compression, rises in the range of small compressive strains while remaining below 0.5, and then rapidly increases under tensile strains to values as high as 3.1. The authors also investigated the effects of bath osmolarity on compressive responses of cartilage. When the NaCl concentration of the bath increased from 0.015 M to 2 M the stress—strain response softened and the Poisson's ratio lowered, results qualitatively consistent with experiments from Chahine et al. [18]. Finally, the authors also successfully simulated the effects of both proteoglycan digestion and bath osmolarity on tensile responses of cartilage. They concluded that anisotropy of the fibrillar matrix of articular cartilage is intimately dependent on the mechanism of strain-dependent fiber recruitment.

Wang et al. [105] extended the constitutive model of Pierce et al. [89] ((20)–(25)) to establish a practical computational method to include osmotically induced prestretch/prestress in image-driven simulations of cartilage. We applied the model to address a theoretical inconsistency that arises in patient-specific simulations of cartilage: the *in-vivo* imaged geometry (used to construct the model) is not an unloaded, stress-free reference configuration. We extended (20) to include a contribution from the Donnan osmotic pressure $\Psi_{\mathrm{OP}}^{\mathrm{S}}$ as

$$\Psi^{\mathrm{S}} = \Psi_{\mathrm{OP}}^{\mathrm{S}} + (1 - \nu)\Psi_{\mathrm{IM}}^{\mathrm{S}} + \nu\Psi_{\mathrm{FN}}^{\mathrm{S}}, \tag{47}$$

where we captured the osmotic strain energy following (39) [27,62]. We left the remaining aspects of the constitutive model consistent with [89], i.e., $\Psi_{\mathrm{IM}}^{\mathrm{S}}$ defined by (13–15), $\Psi_{\mathrm{FN}}^{\mathrm{S}}$ defined by (21), and $\mathbf{K}$ defined by (24).

We again implemented the model in FEAP and investigated the influence of the prestretched/prestressed state both when fitting fiber-reinforced, biphasic constitutive models of cartilage that include osmotic swelling and when simulating cartilage responses. To measure a true stress-free reference configuration *in vivo* is impossible, so we solved an inverse problem using the backward displacement method (following [14]) and determined the *in vivo* prestretch/prestress distributions in equilibrium within the imaged configuration without a true stress-free reference configuration. We used three different computational methods (cases) to complete the simulations. In Case 1, we turned off the mechanical effects of osmotic pressure by setting the fixed charge density to zero ($c_{0\mathrm{S}}^{\mathrm{fc}} = 0$), thus recovering the model of [89]. In Case 2, we naively accounted for osmotic pressure by treating the imaged configuration as a stress-free reference configuration. In Case 3, we applied our new computational method to include osmotic pressure by first recovering the (osmotically loaded) prestressed state using the backward displacement method, and thereafter simulating the boundary value problem. We modeled both uniaxial tension of a cartilage specimen following experiments completed in 0.15 M PBS bath [28] and a stress-relaxation test of a full-thickness cuboid of cartilage in unconfined compression (based on diffusion tensor MRI data detailed in [87]). Our results highlighted the importance of determining the prestretched/prestressed state from osmotic loading in the imaged configuration prior to solving boundary value problems of interest.

## 5 Conclusions and outlook

Many researchers have contributed significantly to the field of 3-D FE modeling of articular cartilage, yet much work and many challenges remain. While computational simulations seek the simplest possible model to capture the physics and electro-chemistry governing the problem of interest, as demonstrated above, the complexity of cartilage mechanics demands similarly complex models [53]. Current constitutive models facilitate FE analyses of human joints in health and disease, e.g., knee (cf. [39–41]) and hip (cf. [43–45]), and studies of the mechanobiology of chondrocytes [38,95,96]. Resources are available to make patient-specific analyses more accessible [29,92], yet constitutive models remain the key to pursuing physically meaningful solutions to such problems.

The importance of constitutive models underscores both the need to solve challenges inherent to multi-phasic constitutive modeling and corollary opportunities for advances in research. Boundary conditions for multi-phasic simulations remain a key obstacle, for example when applying tangential stress on a boundary of a multi-phasic mixture (cf. [63–65,90], and references therein), yet this challenge also presents an opportune direction for future research. Moreover, the number of required model parameters increases as we seek to capture real physiological behaviors, a fact in direct opposition to the desire to limit model complexity. In highly nonlinear models like those presented here, isolating the effects of specific parameters can present a major challenge. The natural tradeoff between a model's prediction fidelity and its complexity makes calibration all the more essential. Additional complexity is justifiable only if researchers can experimentally calibrate the resulting model, i.e., uniquely determine model parameters in the lab. The challenge to develop increasingly effective and efficient constitutive models and computational methodologies will require concomitant empirical methods and data, providing abundant opportunities for future research directions.

Recent advances in underlying continuum theories and computational methods not specific to cartilage will likely drive improved constitutive models for 3-D FE modeling of cartilage in the future. With an eye toward biological applications, van Loon et al. [77] presented a quadri-phasic mixture model including a homogenous, isotropic, materially incompressible and charged solid (S), fluid (F), monovalent cations (+), and monovalent anions (−), where interactions among these constituents result in mechanical, chemical, and electrical forces. In cartilage, these constituents correspond to collagen and proteoglycans, interstitial fluid, $Na^+$ ions, and $CL^-$ ions, respectively. Frijns et al. [34] verified this mixture theory by fitting experimental data determined from uniaxial confined swelling and compression of a cylindrical specimen of hydrogel (with a similar material behavior to cartilage) using a mixed FE simulation. The quadri-phasic mixture theory results in a set of coupled nonlinear partial differential equations for the electrochemical potentials and for the displacement. Kaasschieter et al. [61] discretized these equations in space using a mixed FE method and proposed and tested a subtle solution strategy for this nonlinear system in 1-D. Ateshian and Weiss [9] provided a general framework for formulating constitutive relations for anisotropic, strain-dependent hydraulic permeability tensors in deformable porous media like cartilage. Ateshian et al. [5] also developed a general FE algorithm for analyzing mechanochemical phenomena in neutral deformable porous media (particularly biological soft tissues and cells) under finite deformations. These works have forged a clear path forward for the future of 3-D modeling of cartilage.

Many features of these advances are available for use in the open-source research FE code FEBio [75], developed for modeling soft biological tissues and relevant to numerous applications in biomechanics. FEBio offers constitutive models and boundary conditions specifically well-suited to analyses of problems in cartilage mechanics. Combining solid matrix materials (e.g., neo-Hookean, Mooney-Rivlin, and Ogden unconstrained [98]) with a wide range of fiber reinforcements (e.g., individual exponential power-law fibers and ellipsoidal distributions of fibers [7]) allows researchers to establish solid mixtures and even to include viscoelasticity. For a biphasic constitutive model, these solid mixtures may be coupled with different models for hydraulic permeability (e.g., constant isotropic permeability; Holmes-Mow permeability [46]; and referentially isotropic, orthotropic, or transversely isotropic permeability with deformation dependence). FEBio also includes coupling of mechanical and chemical effects such as swelling pressure (e.g., ideal Donnan equilibrium [7] or perfect osmometer [6]) and solute diffusivity (e.g., constant isotropic or orthotropic diffusivity, and referentially isotropic or orthotropic diffusivity). Flexible, open-source tools like FEBio offer great promise to facilitate future advances in 3-D cartilage modeling.

Future research directions abound, as extant 3-D models of cartilage, offer ample room for improvement. Mathematical representations of the collagen network remain an important, outstanding challenge, particularly in light of the importance of collagen in the mechanical response of healthy cartilage. Networked collagen fibrils/fibers in cartilage restrain the swelling pressure of the embedded proteoglycans, thus creating compressive stiffness, and provide the tensile stiffness of cartilage [83]. These functions derive not only from collagen type II, but also from smaller amounts of other types of networked collagens, including types VI, IX, XI, XII, and XIV, each likely differing in mechanical properties, behaviors, and interactions. Within the network of type II collagen, covalent cross-linking with types IX and XI stabilizes the 3-D organization of collagen and yields an additional layer of complexity to this fascinating tissue. Furthermore, improved modeling of proteoglycans (PGs, complex molecules of a core protein and one or more covalently attached GAG chains) may clarify effects of age and disease on cartilage mechanics. Aggrecan constitutes as much as 90% of PGs in articular cartilage, and aggrecan itself includes small PGs (e.g., biglycan, decorin, fibromodulin, and lumican [83]). Accounting for such richness in constitutive models of cartilage may facilitate improved understanding of diseases (e.g., chondrodysplasia, resulting from defects in type IX collagen) and of mechanobiology (e.g., effects of hyaluronan, a non-sulfated GAG that links the extracellular matrix to chondrocytes [66], on cell responses).

Constitutive models have transformed our fundamental understanding of cartilage tissues and hold great promise as a non-invasive clinical tool in the future. Advances in modeling approaches that better capture the complexity of real behaviors, for example effects of ion diffusion and swelling, establish the basis for next steps, and theoretical and methodological advances suggest new directions for future models. While the complexity of this tissue presents many challenges to our field, the function of cartilage affects quality of life for virtually all of the human population. Thanks to the exquisite complexity of this tissue, the future of 3-D computational modeling of cartilage is rich not only with challenge and possibility, but also with relevance and impact.

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**Declarations**

**Conflict of interest** The author declares that they have no conflicts of interest.

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