Xin Gao

Department of Mechanical and
Aerospace Engineering,
University of Miami,
Coral Gables, FL 33146
e-mail: x.gao3@umiami.edu

Qiaoqiao Zhu

Department of Biomedical Engineering,
University of Miami,
Coral Gables, FL 33146
e-mail: q.zhu3@umiami.edu

Weiyong Gu¹

Fellow ASME
Department of Mechanical and
Aerospace Engineering,
University of Miami,
Coral Gables, FL 33146;
Department of Biomedical Engineering,
University of Miami,
Coral Gables, FL 33146
e-mail: wgu@miami.edu

An Anisotropic Multiphysics Model for Intervertebral Disk

Intervertebral disk (IVD) is the largest avascular structure in human body, consisting of three types of charged hydrated soft tissues. Its mechanical behavior is nonlinear and anisotropic, due mainly to nonlinear interactions among different constituents within tissues. In this study, a more realistic anisotropic multiphysics model was developed based on the continuum mixture theory and employed to characterize the couplings of multiple physical fields in the IVD. Numerical simulations demonstrate that this model is capable of systematically predicting the mechanical and electrochemical signals within the disk under various loading conditions, which is essential in understanding the mechanobiology of IVD. [DOI: 10.1115/1.4031793]

Keywords: biomechanics, mixture theory, multiphase, anisotropic permeability, anisotropic diffusivity

1 Introduction

During daily activities, IVD acts to transmit the axial load, resist shear load, and provide flexibility for the spine. The disk achieves these mechanical functions through its unique anatomic structure and tissue composition. The disk comprises of a central gelatinous core, i.e., the nucleus pulposus (NP), a surrounding fiber-reinforced lamellar ring, i.e., the annulus fibrosus (AF), and two thin cartilaginous endplates (CEPs) which connect the NP and AF with the superior and inferior vertebral bodies, see Fig. 1. The disk tissue is a mixture of water, proteoglycan (PG), collagen, and other proteins [1,2]. The network of collagen, together with the trapped PG, forms the porous solid matrix. The negatively charged groups on the PG attract counter-ions, like Na^+ , to maintain the tissue in the electroneutrality condition. Thus, the osmolarity in the tissue is higher than that in the ambient environment [3]. This imbalance of ion concentrations leads to a mechano-electrochemical effect that imbibes water into the porous solid matrix and causes tissue to swell [3]. The driving force for water movement is the gradient of water chemical potential [4]. At the equilibrium state, the difference of fluid pressure between inside of the disk and the ambient environment is called Donnan osmotic pressure or swelling pressure [5]. The NP has a high PG content, thus has a high swelling pressure and water content, which makes the NP possesses both solid and fluid mechanical characteristics [6]. The swelling tendency of NP is restrained by the AF and CEPs, whereas water and electrolytes can inflow and outflow through AF and CEPs. Thus, the interactions of multiphase components (solid, fluid, and ions) cause the coupling of multiphysical (mechanical, electrical, and chemical) fields, which gives the disk the unique mechanical functions.

The degeneration of disk mechanical function is believed to be related with low back pain which affects 600×10^6 people worldwide [7]. Many biomechanical models have been developed to study the mechanical behavior of IVD (cf. Ref. [8] and the

references therein). However, it is still challenging to quantitatively describe the behavior of the disk under various loading conditions. The major challenge arises from the complicated couplings of multiple physical fields in the IVD and the anisotropic behavior of the AF. Many mathematical models have been developed for the IVD. These models may be classified into three types: the single-phase model (e.g., Refs. [9–11]), the biphasic/biphasic-swelling model (e.g., Refs. [12–17]), and multiphase mechano-electrochemical model [18–20]. The single-phase model treats the NP as an ideal fluid and the AF as a solid, which cannot characterize the interstitial fluid flow in the AF and swelling pressure [9]. The biphasic model describes the disk as a mixture of fluid and solid. The biphasic model is able to characterize the

Fig. 1 A schematic of the IVD showing the AF, NP, and CEPs. The dimensions are in millimeter.

¹Corresponding author.

Contributed by the Applied Mechanics Division of ASME for publication in the JOURNAL OF APPLIED MECHANICS. Manuscript received September 1, 2015; final manuscript received October 12, 2015; published online November 9, 2015. Editor: Yonggang Huang.

interstitial fluid flow, and hence the flow caused time dependent viscoelastic behavior of the disk. However, the mechano-electrochemical effect is not accounted for in the biphasic model. A shortcut is to add the swelling pressure term to the total mixture stress based on the Lanir's assumption that the electrochemical equilibrium in the tissue is achieved instantaneously [21]. This approach is called biphasic-swelling model, and it has been used as an approximation to include the mechanochemical effect [22]. The diffusivity of ions in this type of model is assumed to be infinitely large, which is not physiologically relevant. Thus, a more realistic multiphasic model is developed for the disk [18] based on the mechano-electrochemical continuum triphasic theory [4]. In this model, the solid, fluid, and solutes (e.g., ions) are modeled as separated phases, so all the mechano-electrochemical phenomena in the tissue can be described. In this model, the solid matrix is treated as an isotropic material and undergoes small deformation, and the transport of fluid and ions are assumed to be isotropic. However, the mechanical properties have been shown to be non-linear elastic and hydration dependent [23,24]. Moreover, the fiber bundles in the AF give the AF not only anisotropic mechanical properties but also anisotropic transport properties [25–28].

In this work, we aim to develop a more realistic anisotropic multiphysics model for the IVD, including the nonlinear coupling among anisotropic mechanical behaviors of solid matrix, anisotropic transport of interstitial fluid and ions, and electrochemical effects. Moreover, the hydration-dependent mechanical and transport properties are incorporated into the model. The robustness of the proposed model are demonstrated by performing 3D numerical simulations of the mechano-electrochemical behaviors of the disk using one set of material parameters and comparing the model predictions with those experimentally observed.

2 Model Development

2.1 Mathematical Model. The mathematical model presented in this study is based on the mechano-electrochemical continuum mixture theory [4,29–31]. The IVD is modeled as a mixture consisting of solid (s), fluid (w), cation (+), and anion (−). Each constituent has a volume fraction (ϕ^α , $\alpha = s, w, +, -$) relative to the whole mixture.

Governing Equations. For each constituent, the mass balance equation is given by

$$\frac{\partial \rho^\alpha}{\partial t} + \nabla \cdot (\rho^\alpha \mathbf{v}^\alpha) = 0 \quad (1)$$

where ρ^α and $\mathbf{v}^\alpha$ are the apparent density per tissue volume and velocity of constituent α , respectively. The concentration (moles per fluid volume) instead of density is commonly used for ions. The density can be converted to concentration via $\rho^i = \phi^w M^i c^i$ ($i = +, -$), where c^i is the concentration of ion i per fluid volume, and M^i is the molar weight of ion i . Thus, the mass balance equation of ions can be written alternatively as

$$\frac{\partial (\phi^w c^i)}{\partial t} + \nabla \cdot (\mathbf{J}^i + \phi^w c^i \mathbf{v}^s) = 0 \quad (2)$$

where $\mathbf{J}^i = \phi^w c^i (\mathbf{v}^i - \mathbf{v}^s)$ is the molar flux of ion i relative to the solid matrix.

Each constituent is assumed to be intrinsically incompressible with a true density, ρ_T^α , hence $\rho^\alpha = \phi^\alpha \rho_T^\alpha$. Therefore, the mass balance equation for the whole mixture can be obtained by taking summation of all the mass balance equations for each constituent

$$\frac{\partial \left(\sum_\alpha \phi^\alpha \right)}{\partial t} + \nabla \cdot \left[\sum_\alpha (\phi^\alpha \mathbf{v}^\alpha) \right] = 0 \quad (3)$$

We further assume that the mixture is saturated and the volume fractions of the ions are negligible, so that $\phi^s + \phi^w \approx 1$. Thus, the mass balance equation for the whole mixture can be alternatively written as

$$\nabla \cdot (\mathbf{v}^s + \mathbf{J}^w) = 0 \quad (4)$$

where $\mathbf{J}^w = \phi^w (\mathbf{v}^w - \mathbf{v}^s)$ is the volume flux of interstitial fluid relative to the solid matrix.

The electroneutrality condition is assumed for every point in the disk, that is

$$\sum_i z^i c^i - c^F = 0 \quad (5)$$

where z^i is the valence of ion i , and c^F is fixed charge density (FCD) per fluid volume. The mobile ions are assumed to be monovalent in this study. The fluid content and FCD are both deformation dependent

$$\phi^w = \frac{\phi_r^w + J - 1}{J} \quad (6)$$

$$c^F = \frac{\phi_r^w c_r^F}{J - 1 + \phi_r^w} \quad (7)$$

where ϕ_r^w is the fluid content at the reference state; $J = \det(\mathbf{F})$ is the volume ratio, where $\mathbf{F}$ is the deformation gradient, and c_r^F is FCD at the reference state.

The general form of the linear momentum balance equation for constituent α is given by

$$\rho^\alpha \mathbf{a}^\alpha = \nabla \cdot \boldsymbol{\sigma}^\alpha + \rho^\alpha \mathbf{b}^\alpha + \boldsymbol{\pi}^\alpha \quad (8)$$

where $\mathbf{a}^\alpha$, $\boldsymbol{\sigma}^\alpha$, and $\mathbf{b}^\alpha$ are the acceleration, Cauchy stress, and body force for constituent α , respectively, and $\boldsymbol{\pi}^\alpha$ is the momentum exchange between constituent α and other constituents. In this study, the body force term is neglected, and the acceleration term is also neglected with the assumption of quasi-static condition, thus

$$\nabla \cdot \boldsymbol{\sigma}^\alpha + \boldsymbol{\pi}^\alpha = 0 \quad (9)$$

For the whole mixture, the exchange of linear momentum must be conserved, that is, $\sum_\alpha \boldsymbol{\pi}^\alpha = 0$. Therefore, the linear momentum balance equation for the whole mixture states

$$\nabla \cdot \boldsymbol{\sigma} = 0 \quad (10)$$

where $\boldsymbol{\sigma} = \sum_\alpha \boldsymbol{\sigma}^\alpha$ is the inner part of Cauchy stress for the mixture. Applying the restriction of entropy equality to the whole mixture, together with the constraints of mass balance and electroneutrality condition, the stress of the mixture is given by [4,29,31]

$$\boldsymbol{\sigma} = -p\mathbf{I} + \boldsymbol{\sigma}^s \quad (11)$$

where p is the fluid pressure, and $\boldsymbol{\sigma}^s$ is the stress contributed by the solid phase.

The linear momentum balance equations for fluid and ions under quasi-static condition are [4]

$$\sum_\alpha \Gamma_{\beta\alpha} (\mathbf{v}^\alpha - \mathbf{v}^\beta) - \rho^\beta \nabla \mu^\beta = 0, \quad \beta = w, +, - \quad (12)$$

where $\Gamma_{\beta\alpha}$ is a positively defined and symmetric friction coefficient tensor (i.e., $\Gamma_{\beta\alpha} = \Gamma_{\alpha\beta}$) between constituents β and α ; and μ^β is the (electro)chemical potential per mass of constituent β . The chemical potential of fluid is given by [4,29]

$$\mu^w = \mu_0^w + \left[p - RT \sum_i \Phi^i c^i \right] / \rho_T^w \quad (13)$$

where μ_0^w is the chemical potential at reference state, R is the universal gas constant, T is the absolute temperature, and Φ^i is the osmotic coefficient and it is assumed to be unity in this study. The electrochemical potential of ion is given by [4,29]

$$\mu^i = \mu_0^i + (RT/M^i) \ln(\gamma^i c^i) + z^i F_c \phi / M^i \quad (14)$$

where μ_0^i is the electrochemical potential at reference state, γ^i is the activity coefficient and it is assumed to be unity in this study, F_c is the Faraday constant, and ϕ is the electrical potential. In the mixture theory, the electrochemical potential is continuous across the boundaries, thus the electrochemical potential of fluid and ions is chosen as the basic variables in the numerical simulation. Considering the ill-conditioning of the logarithm function with small value of c^i , and the arbitrary values of μ_0^w and μ_0^i , the following modified electrochemical potential for fluid and ions is used in numerical simulation [32]:

$$\varepsilon^w = [(\mu^w - \mu_0^w) \rho_T^w] / (RT) \quad (15)$$

$$\varepsilon^i = \exp [(\mu^i - \mu_0^i) M^i / (RT)] \quad (16)$$

Combining the linear momentum balance equations and the definitions of modified electrochemical potential, the flux of fluid can be written as (see the Appendix)

$$\mathbf{J}^w = -RT\mathbf{K} \left(\nabla \varepsilon^w + \sum_i \mathbf{M}_{wi} \frac{c^i}{\varepsilon^i} \nabla \varepsilon^i \right) \quad (17)$$

and flux of ion can be written as

$$\mathbf{J}^i = c^i \mathbf{H}_{iw} \mathbf{J}^w - c^i \phi^w \sum_{j=+, -} \frac{1}{\varepsilon^j} \mathbf{D}_{ij} \nabla \varepsilon^j \quad (18)$$

where $\mathbf{K}$ is the hydraulic permeability tensor, $\mathbf{M}_{wi}$ is the transport tensor of ion i , $\mathbf{H}_{iw}$ is the convection coefficient tensor of ion i , and $\mathbf{D}_{ij}$ is the coupling diffusivity tensor of ion i under the electrochemical gradient of ion j . In this study, the $\mathbf{M}_{wi}$ and $\mathbf{H}_{iw}$ are both assumed to be unity tensors [33]. We also neglect the coupling frictional effects between ions, that is, $\mathbf{D}_{ij} = 0$ for $i \neq j$. For simplicity, we let $\mathbf{D}^i = \mathbf{D}_{ii}$.

Constitutive Equations. The solid matrix is modeled as a hyperelastic material. Thus, $\boldsymbol{\sigma}^s$ can be evaluated as $\boldsymbol{\sigma}^s = (2/J) \mathbf{F} (\partial \psi / \partial \mathbf{C}) \mathbf{F}^T$, where ψ is the strain energy function, and $\mathbf{C} = \mathbf{F}^T \mathbf{F}$ is the right Cauchy–Green deformation tensor. The solid matrix of NP and CEP can be modeled as isotropic material. Even though the solid phase is intrinsically incompressible, the solid matrix is compressible as the result of inflow or outflow of fluid. Moreover, the microstructure of the solid matrix is varying with the change of fluid content, so the macroscopic mechanical properties depend on fluid content. Thus, the strain energy function should be able to describe the dependency on fluid content. We adopt the following strain energy function for NP and CEP [34]:

$$\psi = \psi_m = \frac{\mu}{2} (I_1 - 3) - \mu \ln J + \lambda (\phi_r^w)^2 \left[\frac{J-1}{\phi_r^w} - \ln \left(\frac{J-1}{\phi_r^w} + 1 \right) \right] \quad (19)$$

where μ and λ are the two Lamé constants, $I_1 = \text{tr}(\mathbf{C})$ is the first invariant of $\mathbf{C}$, and $J^2 = \det(\mathbf{C})$ is the third invariant of $\mathbf{C}$.

The AF is an anisotropic tissue reinforced by two families of aligned fibers ($\mathbf{n}_r^\theta$, $\theta = 1, 2$, represent the fiber directions at the reference state) which embed in the isotropic ground matrix. In this study, the fiber directions are assumed to be in the $\pm 30^\circ$ deg orientation to the horizontal plane. We adopted the fiber-reinforced model proposed by Holzapfel et al. [35], in which the free energy function is decoupled into two parts to account for the

contributions of the ground matrix (ψ_m) and the fibers (ψ_f) to the mechanical properties, thus

$$\psi_{AF} = \psi_m(\mathbf{C}, \phi_r^w) + \psi_f(\mathbf{C}, \mathbf{N}_r^\theta) \quad (20)$$

where $\mathbf{N}_r^\theta = \mathbf{n}_r^\theta \otimes \mathbf{n}_r^\theta$ is the structural tensor. The exponential type of strain energy function developed by Holzapfel et al. [35] is adopted to characterize the mechanical behavior of fibers

$$\psi_f = \frac{k_1}{2k_2} \left\{ \sum_{\theta=1}^2 \mathcal{H}(I_f^\theta - 1) \exp \left[k_2 (I_f^\theta - 1)^2 \right] - 2 \right\} \quad (21)$$

where k_1 and k_2 are the material parameters, $\mathcal{H}(\cdot)$ is the Heaviside step function, and $I_f^\theta = \mathbf{C} : \mathbf{N}_r^\theta$ is the square of the stretch of fiber in the direction of $\mathbf{n}_r^\theta$.

The embedded aligned fibers also affect the transport of fluid and ions within the AF. Following the permeability model for fiber-reinforced porous material proposed by Federico and Herzog [36], the anisotropic hydraulic permeability tensor ($\mathbf{K}_{AF}$) for the AF can be written as

$$\mathbf{K}_{AF} = (K_{\parallel} - K_{\perp}) \mathbf{Q} + K_{\perp} \mathbf{I} \quad (22)$$

where $K_{\parallel}$ and $K_{\perp}$ are the parallel permeability and the orthogonal permeability, respectively, which are defined as

$$K_{\parallel} = (1 - \phi^f) K_m \quad (23)$$

and

$$K_{\perp} = (1 - \phi^f)^2 K_m \quad (24)$$

where ϕ^f is the volume fraction of the fiber in current state. It is dependent on the volume fraction in the reference state (ϕ_r^f) and the deformation as $J\phi^f = \phi_r^f$. K_m is the hydraulic permeability of the isotropic ground matrix. A hydration-dependent hydraulic permeability model was developed by Gu et al. [37] for isotropic biological tissue as

$$K_m = a \left(\frac{\phi^w}{\phi^s} \right)^b \quad (25)$$

where a and b are two material parameters. The $\mathbf{Q}$ defined in Eq. (22) is the directional average of the structure tensors

$$\mathbf{Q} = \sum_{\beta=1}^2 \frac{1}{2} \mathbf{N}^\beta \quad (26)$$

where $\mathbf{N}^\theta = \mathbf{n}^\theta \otimes \mathbf{n}^\theta$ is the structure tensor in the current state, and $\mathbf{n}^\theta$ is the fiber directional vector in the current state, which can be determined via the deformation tensor as

$$\mathbf{n}^\theta = \frac{1}{\sqrt{I_f^\theta}} \mathbf{F} \mathbf{n}_r^\theta \quad (27)$$

The hydraulic permeability tensors for the NP ($\mathbf{K}_{NP}$) and CEP ($\mathbf{K}_{CEP}$) are isotropic tensors, so that

$$\mathbf{K}_{NP} = \mathbf{K}_{CEP} = K_m \mathbf{I} \quad (28)$$

By analogy to the models of hydraulic permeability tensor, the diffusivity tensors ($\mathbf{D}^i$) in Eq. (18) for the AF ($\mathbf{D}_{AF}^i$), NP ($\mathbf{D}_{NP}^i$), and CEP ($\mathbf{D}_{CEP}^i$) can be written as

$$\mathbf{D}_{AF}^i = (D_{\parallel}^i - D_{\perp}^i) \mathbf{Q} + D_{\perp}^i \mathbf{I} \quad (29)$$

$$\mathbf{D}_{NP}^i = \mathbf{D}_{CEP}^i = D_m^i \mathbf{I} \quad (30)$$

with $D_{||}^i = (1 - \phi^f)D_m^i$ and $D_{\perp}^i = (1 - \phi^f)^2 D_m^i$, where D_m^i is the diffusivity for the isotropic matrix. Gu et al. [38] developed a hydration and ion size dependent diffusivity model for isotropic biological tissues, which states

$$\frac{D_m^i}{D_0^i} = \exp \left(-m \left(\frac{r^i}{\sqrt{K_m \eta}} \right)^n \right) \quad (31)$$

where D_0^i is the ion diffusivity in aqueous solution, m and n are two material parameters, r^i is the Stokes radii for the ion, and η is the viscosity of fluid and the value of 0.001 N s/m² is used in this study.

2.2 Numerical Model. The governing equations are discretized with mixed finite element method following the approach developed by Sun et al. [32] and implemented in COMSOL software. The displacement of solid matrix and electrochemical potential of fluid and ions are chosen as the basic variables. The geometry of the disk is based on a parametric model and scaled to the dimensions of the L4-5 disk [39,40], and a half of the superior and inferior vertebral bodies is included, see Fig. 1. In this study, the vertebral bodies are assumed to be rigid because they are much more stiffer than the disk tissues. We choose the state that the disk is in equilibrium in the 300 mOsm saline solution as the reference state for all the following numerical simulations. The boundary conditions are prescribed according to each of specific simulation cases. The mechanical load is applied on the vertebral bodies.

The parameters used in this study include the mechanical properties, transport properties, and electrochemical properties for AF, NP, and CEP, respectively. The values of mechanical properties, fluid content, and FCD are assigned uniformly in the NP and CEP, whereas linearly vary from the innermost AF to the outermost AF [41,42]. This approach is different from the approaches in the literature, which usually assign the uniformly distributed mechanical properties to NP, CEP, and AF (or outer AF and inner AF) [14,16]. Our approach also can alleviate numerical oscillation at the interface of AF and NP, which may be generated because of the jump of mechanical properties [43]. The parameters are summarized in Table 1.

3 Numerical Examples

We perform numerical simulations of experiments reported in the literature to demonstrate that the proposed model is capable of predicting the complicated coupled mechano-electrochemical phenomena observed experimentally. These experiments include the creep, bending and torsion, osmotic loading, and dynamic loading tests, see Fig. 2. It is important to note that all the simulations are performed with one set of material parameters listed in

Fig. 2 Schematic diagrams for experimental protocols used in simulations in this study. (a) Creep test, (b) bending and torsion tests, (c) osmotic loading test, and (d) dynamic loading test.

Table 1. We are not trying to match or curve-fitting the experimental results exactly.

3.1 Creep Test. During most of our daily activities, the disks are subjected to the axial compressive loads. When a compressive load is applied, the disk height will decrease immediately and it will keep decreasing until reaching equilibrium. During the creep process, the fluid is pressed out, and the support of the compressive load shifts from fluid pressure to the stress of solid matrix.

To demonstrate the capability of the proposed model to characterize the creep behavior of the whole disk, we performed finite element analysis of the creep process following the experiments conducted by O'Connell et al. [52], in which the disk was compressed with 1000 N for 4 hrs [52]. The simulated disk height loss is 1.40 mm right after 1000 N axial load being applied, and the loss increases to 3.14 mm at the end of the creep test. The predicted history of disk height loss is reasonably consistent with the experimental results, see Fig. 3.

Fig. 3 Simulated disk height loss during creep test, and compared with experimental results [52]

Table 1 Material properties of IVD used in this study

Parameter	AF ^a	NP	CEP	Reference
ϕ^w	0.86 to 0.77	0.86	0.75	[41,44]
c_r^f (mM)	340 to 100	340	0	[41]
μ (kPa)	60 to 140	60	300	[44–48]
λ (kPa)	40 to 170	40	800	
k_1 (MPa)	1.18 to 5.34	N/A	N/A	[49]
k_2	2.40 to 55.00	N/A	N/A	
a (10^{-17} m ⁴ /(N s))	3.10	2.48	0.13	[25,44,50]
b	2.20	2.15	5.48	
r^i (nm)	0.20 (+), 0.14 (–)			[38]
D_0^i (10^{-9} m ² /s)	1.28 (+), 1.77 (–)			[38]
m	1.29	1.25	1.29	[38]
n	0.37	0.68	0.37	
ϕ_r^f	0.05 to 0.23	N/A	N/A	[51]

^a(#) to (#) means the value linearly varying from the innermost to the outermost.

Fig. 4 Fluid pressure during creep test. (a) Before load applied, (b) right after load applied, (c) after 2 hrs of creep, and (d) after 4 hrs of creep.

During the creep, the interstitial fluid within the disk flows out through the AF periphery and CEP under axial load. To our best knowledge, our proposed model is the first one to account for the anisotropic fluid and ions transport in the disk. Our model shows that the existing of fiber bundles decreases the averaged radial permeability in AF by $\sim 10\%$.

The compressive load is mainly supported by the fluid pressure, but the portion of support by the fluid decreases with the outflow of fluid. The fluid pressure in the NP is the largest and uniform across the NP, whereas the fluid pressure in AF linearly decreases from the inner AF to the outer AF, see Fig. 4. The simulated results for distribution of fluid pressure are consistent with the experimental findings [53]. At the initial condition (no load), the fluid pressure in the NP is about 0.40 MPa, which is generated due to the higher osmolarity in the disk than that in the ambient environment, and the pressure is equilibrated by the tension of solid matrix. Right after the 1000 N compressive load is applied, the fluid pressure in the NP increases to 1.33 MPa. The fluid pressure decreases to 1.18 MPa after 4 hrs of creep test. McNally and Arridge [53] reported that the fluid pressure is about 1.70 MPa in a healthy L4-5 disk under 1392 N compressive load. By linearly scaling the fluid pressure with the fraction of compressive loads, the fluid pressure under 1000 N compressive load in the experiment would be 1.22 MPa, which is close to our simulated fluid pressure in the NP (1.18–1.33 MPa).

3.2 Bending and Torsion Test. Besides the axial load, the disk is also subjected to bending and torsion loads during daily activities. In the experiments of Heuer et al. [54] on the isolated human L4-5 disks, the loads were applied in three different directions, including flexion/extension, lateral bending, and axial rotation. The load was applied at 1 deg/s following a 15 min of creep under 500 N compressive load. We simulated the disk under bending and torsion loads according to their experimental protocol, and the load is increased until the bending momentum reaching 5.0 N·m. The predicted ranges of motion under bending momentums of 2.5 N·m and 5.0 N·m are compared with experiment results, see Fig. 5. It is shown that the predicted results are in the range of experimental data except for the axial rotation test. The stretches of fiber under the combined loads of compression (500 N) and bending (5.0 N·m) are shown to be less than 1.10 in most regions, see Fig. 6, which are smaller than the failure stretch (1.09–1.15) [55]. The stretch is higher for the fibers in the posterior/lateral-posterior regions for all the cases simulated, this explains why the failure occurs mostly in this region [56].

Fig. 5 Simulated range of motion of disk under (a) 2.5 N·m and (b) 5.0 N·m bending momentums, and compared with experimental results (minimum, median, and maximum) [54]

Fig. 6 Distributions of fiber stretch under 5.0 N-m bending momentum in (a) flexion, (b) extension, (c) lateral bending, and (d) axial rotation. Only one family of fibers are shown.

3.3 Osmotic Loading. Varying the external osmolarity is an important approach to investigate the contribution of fixed charges to the overall mechanical function of the tissue. Stokes et al. [57] studied the response of human lumbar disks under constant compressive strain, in bath with varying saline concentrations. They observed that varying of external osmolarity from low to high causes a stress relaxation phenomenon. This is because the swelling pressure in the disk progressively reduces with time after increasing the external osmolarity. We simulate this stress relaxation phenomenon by following their experimental procedures. The disk is initially equilibrated in 0.15 M saline solution under 200 N compressive load. Then, the compressive strain is fixed, and the bath saline concentration increases from 0.15 M to 1.5 M. Our simulated temporal relaxation of compressive load is in the range of experimental results, see Fig. 7. However, in order to guarantee numerical stability, we ramp the external saline concentration

linearly in 10,000 s, which is longer than that used in the experiment, which may cause the simulated relaxation of compressive load slower than the experimental result.

3.4 Intradiscal Electrical Potential Under Dynamic Loading. The disk cells reside in a coupled mechano-electrochemical environment. The electrical potential around the cells is thought to be a potential factor that affects cellular activities [58]. Iatridis et al. [59] reported that the spatial distribution of intradiscal electrical potentials under dynamic loading, which were measured under ± 200 N axial load at 0.01 Hz following a 2 hrs creep under 500 N compressive load. We simulate this phenomenon by following their experimental protocol. The amplitude of the simulated electrical potential is normalized by the

Fig. 7 Simulated mechanical response of disk to the change of bath saline solution, from 0.15 M to 1.50 M, and compared with experimental results (mean $\pm$ SD) [57]

Fig. 8 Simulated distribution of electrical potential under dynamical loading at midsagittal line, and compared with experimental results (mean $\pm$ SEM) [59]

amplitude of dynamic load and compared with the experimental results. It is shown that our simulated results match well with the experimental results, not only the magnitude but also the distribution, see Fig. 8.

4 Conclusion

A more realistic anisotropic multiphysics model of IVD is developed based on the mechano-electrochemical continuum mixture theory. In this model, the solid matrix, interstitial fluid, and ions are modeled as separated phases to characterize the nonlinear couplings among mechanical, electrical, and chemical fields. Moreover, the hydration-dependent anisotropic mechanical and transport properties of the disk tissue are also incorporated into the model. The numerical simulations, with one set of material parameters, demonstrate that this anisotropic multiphysics model is capable of systematically predicting disk mechanical behaviors and quantifying the mechanical, chemical, and electrical signals within the disk under various loading conditions.

Acknowledgment

This study was supported in part by a research grant from the NIH (AR066240).

Appendix

From Eq. (12), the volume flux for fluid and molar fluxes for ions can be generally written as

$$\begin{aligned} \mathbf{J}^w &= \phi^w (\mathbf{v}^w - \mathbf{v}^s) \\ &= -\phi^w (\mathbf{A}_{ww} \rho^w \nabla \mu^w + \sum_i \mathbf{A}_{wi} \rho^i \nabla \mu^i) \end{aligned} \quad (\text{A1})$$

$$\begin{aligned} \mathbf{J}^i &= \phi^w c^i (\mathbf{v}^i - \mathbf{v}^s) \\ &= \mathbf{A}_{iw} c^i \mathbf{J}^w - c^i \phi^w \sum_{j=+,-} \mathbf{A}_{ij} \rho^j \nabla \mu^j \end{aligned} \quad (\text{A2})$$

where $\mathbf{A}_{ww}$, $\mathbf{A}_{wi}$, $\mathbf{A}_{iw}$, and $\mathbf{A}_{ij}$ are material coefficient tensors that are functions of friction coefficient tensor $\Gamma_{\alpha\beta}$ defined in Eq. (12). Note that $\mathbf{A}_{wi} \neq \mathbf{A}_{iw}$ and $\mathbf{A}_{ij} \neq \mathbf{A}_{ji}$.

The above two equations can be written in terms of modified electrochemical potentials (i.e., Eqs. (15) and (16)) as

$$\mathbf{J}^w = -RT\mathbf{K} \left(\nabla \varepsilon^w + \sum_i \mathbf{M}_{wi} \frac{c^i}{\varepsilon^i} \nabla \varepsilon^i \right) \quad (\text{A3})$$

$$\mathbf{J}^i = c^i \mathbf{H}_{iw} \mathbf{J}^w - c^i \phi^w \sum_{j=+,-} \frac{1}{\varepsilon^j} \mathbf{D}_{ij} \nabla \varepsilon^j \quad (\text{A4})$$

where $\mathbf{K} = \mathbf{A}_{ww} (\phi^w)^2$ is the hydraulic permeability tensor, $\mathbf{M}_{wi} = \mathbf{A}_{ww}^{-1} \mathbf{A}_{wi}$ is the transport tensor of ion i , $\mathbf{H}_{iw} = \mathbf{A}_{iw}$ is the convection coefficient tensor of ion i , and $\mathbf{D}_{ij} = RT \phi^w c^j \mathbf{A}_{ij}$ is the coupling diffusivity tensor of ion i under the electrochemical gradient of ion j .

References

- [1] Urban, J. P. G., and Roberts, S., 2003, "Degeneration of the Intervertebral Disc," *Arthritis Res. Ther.*, **5**(3), pp. 120–130.
- [2] Antoniou, J., Steffen, T., Nelson, F., Winterbottom, N., Hollander, A. P., Poole, R. A., Aebi, M., and Alini, M., 1996, "The Human Lumbar Intervertebral Disc—Evidence for Changes in the Biosynthesis and Denaturation of the Extracellular Matrix With Growth, Maturation, Ageing, and Degeneration," *J. Clin. Invest.*, **98**(4), pp. 996–1003.
- [3] Urban, J. P., and Maroudas, A., 1981, "Swelling of the Intervertebral Disc In Vitro," *Connect Tissue Res.*, **9**(1), pp. 1–10.
- [4] Lai, W. M., Hou, J. S., and Mow, V. C., 1991, "A Triphasic Theory for the Swelling and Deformation Behaviors of Articular Cartilage," *ASME J. Biomech. Eng.*, **113**(3), pp. 245–258.

- [5] Donnan, F. G., 1924, "The Theory of Membrane Equilibria," *Chem. Rev.*, **1**(1), pp. 73–90.
- [6] Iatridis, J. C., Weidenbaum, M., Setton, L. A., and Mow, V. C., 1996, "Is the Nucleus Pulposus a Solid or a Fluid? Mechanical Behaviors of the Nucleus Pulposus of the Human Intervertebral Disc," *Spine*, **21**(10), pp. 1174–1184.
- [7] Vos, T., Flaxman, A., and Naghavi, M., 2014, "Years Lived With Disability (YLDs) for 1160 Sequelae of 289 Diseases and Injuries 1990–2010: A Systematic Analysis for the Global Burden of Disease Study 2010 (Vol 380, pg 2163, 2012)," *Lancet*, **384**(9943), p. 582.
- [8] Schmidt, H., Galbusera, F., Rohlmann, A., and Shirazi-Adl, A., 2013, "What Have We Learned From Finite Element Model Studies of Lumbar Intervertebral Discs in the Past Four Decades?," *J. Biomech.*, **46**(14), pp. 2342–2355.
- [9] Belytschko, T., Kulak, R. F., Schultz, A. B., and Galante, J. O., 1974, "Finite Element Stress Analysis of an Intervertebral Disc," *J. Biomech.*, **7**(3), pp. 277–285.
- [10] Schmidt, H., Heuer, F., Drumm, J., Klezl, Z., Claes, L., and Wilke, H. J., 2007, "Application of a Calibration Method Provides More Realistic Results for a Finite Element Model of a Lumbar Spinal Segment," *Clin. Biomech. (Bristol, Avon)*, **22**(4), pp. 377–384.
- [11] Eberlein, R., Holzapfel, G. A., and Schulze-Bauer, C. A., 2001, "An Anisotropic Model for Annulus Tissue and Enhanced Finite Element Analyses of Intact Lumbar Disc Bodies," *Comput. Methods Biomech. Biomed. Eng.*, **4**(3), pp. 209–229.
- [12] Laible, J. P., Pflaster, D. S., Krag, M. H., Simon, B. R., and Haugh, L. D., 1993, "A Poroelastic-Swelling Finite-Element Model With Application to the Intervertebral Disc," *Spine*, **18**(5), pp. 659–670.
- [13] Argoubi, M., and Shirazi-Adl, A., 1996, "Poroelastic Creep Response Analysis of a Lumbar Motion Segment in Compression," *J. Biomech.*, **29**(10), pp. 1331–1339.
- [14] Schroeder, Y., Huyghe, J. M., van Donkelaar, C. C., and Ito, K., 2010, "A Biochemical/Biophysical 3D FE Intervertebral Disc Model," *Biomech. Model. Mechanobiol.*, **9**(5), pp. 641–650.
- [15] Karajan, N., 2012, "Multiphasic Intervertebral Disc Mechanics: Theory and Application," *Arch. Comput. Methods Eng.*, **19**(2), pp. 261–339.
- [16] Jacobs, N. T., Cortes, D. H., Peloquin, J. M., Vresilovic, E. J., and Elliott, D. M., 2014, "Validation and Application of an Intervertebral Disc Finite Element Model Utilizing Independently Constructed Tissue-Level Constitutive Formulations that are Nonlinear, Anisotropic, and Time-Dependent," *J. Biomech.*, **47**(11), pp. 2540–2546.
- [17] Ehlers, W., Karajan, N., and Markert, B., 2009, "An Extended Biphasic Model for Charged Hydrated Tissues With Application to the Intervertebral Disc," *Biomech. Model. Mechanobiol.*, **8**(3), pp. 233–251.
- [18] Yao, H., and Gu, W. Y., 2006, "Physical Signals and Solute Transport in Human Intervertebral Disc During Compressive Stress Relaxation: 3D Finite Element Analysis," *Biorheology*, **43**(3–4), pp. 323–335.
- [19] Iatridis, J. C., Laible, J. P., and Krag, M. H., 2003, "Influence of Fixed Charge Density Magnitude and Distribution on the Intervertebral Disc: Applications of a Poroelastic and Chemical Electric (PEACE) Model," *ASME J. Biomech. Eng.*, **125**(1), pp. 12–24.
- [20] Sun, D. D. N., and Leong, K. W., 2004, "A Nonlinear Hyperelastic Mixture Theory Model for Anisotropy, Transport, and Swelling of Annulus Fibrosus," *Ann. Biomed. Eng.*, **32**(1), pp. 92–102.
- [21] Lanir, Y., 1987, "Biorheology and Fluid Flux in Swelling Tissues. I. Bicomponent Theory for Small Deformations, Including Concentration Effects," *Biorheology*, **24**(2), pp. 173–187.
- [22] Wilson, W., van Donkelaar, C. C., and Huyghe, J. M., 2005, "A Comparison Between Mechano-Electrochemical and Biphasic Swelling Theories for Soft Hydrated Tissues," *ASME J. Biomech. Eng.*, **127**(1), pp. 158–165.
- [23] Gao, X., and Gu, W., 2014, "A New Constitutive Model for Hydration-Dependent Mechanical Properties in Biological Soft Tissues and Hydrogels," *J. Biomech.*, **47**(12), pp. 3196–3200.
- [24] Perie, D., Korda, D., and Iatridis, J. C., 2005, "Confined Compression Experiments on Bovine Nucleus Pulposus and Annulus Fibrosus: Sensitivity of the Experiment in the Determination of Compressive Modulus and Hydraulic Permeability," *J. Biomech.*, **38**(11), pp. 2164–2171.
- [25] Iatridis, J. C., Setton, L. A., Foster, R. J., Rawlins, B. A., Weidenbaum, M., and Mow, V., 1998, "Degeneration Affects the Anisotropic and Nonlinear Behaviors of Human Annulus Fibrosus in Compression," *J. Biomech.*, **31**(6), pp. 535–544.
- [26] Elliott, D. M., and Setton, L. A., 2001, "Anisotropic and Inhomogeneous Tensile Behavior of the Human Annulus Fibrosus—Experimental Measurement and Material Model Predictions," *ASME J. Biomech. Eng.*, **123**(3), pp. 256–263.
- [27] Gu, W. Y., Mao, X. G., Foster, R. J., Weidenbaum, M., Mow, V. C., and Rawlins, B. A., 1999, "The Anisotropic Hydraulic Permeability of Human Lumbar Annulus Fibrosus—Influence of Age, Degeneration, Direction, and Water Content," *Spine*, **24**(23), pp. 2449–2455.
- [28] Jackson, A. R., Yuan, T. Y., Huang, C. Y., Brown, M. D., and Gu, W. Y., 2012, "Nutrient Transport in Human Annulus Fibrosus is Affected by Compressive Strain and Anisotropy," *Ann. Biomed. Eng.*, **40**(12), pp. 2551–2558.
- [29] Gu, W. Y., Lai, W. M., and Mow, V. C., 1998, "A Mixture Theory for Charged-Hydrated Soft Tissues Containing Multi-Electrolytes: Passive Transport and Swelling Behaviors," *ASME J. Biomech. Eng.*, **120**(2), pp. 169–180.
- [30] Frijns, A. J. H., Huyghe, J. M., and Janssen, J. D., 1997, "A Validation of the Quadruphasic Mixture Theory for Intervertebral Disc Tissue," *Int. J. Eng. Sci.*, **35**(15), pp. 1419–1429.
- [31] Ateshian, G. A., 2007, "On the Theory of Reactive Mixtures for Modeling Biological Growth," *Biomech. Model. Mechanobiol.*, **6**(6), p. 447.

- [32] Sun, D. N., Gu, W. Y., Guo, X. E., Lai, W. M., and Mow, V. C., 1999, "A Mixed Finite Element Formulation of Triphasic Mechano-Electrochemical Theory for Charged, Hydrated Biological Soft Tissues," *Int. J. Numer. Methods Eng.*, **45**(10), pp. 1375–1402.
- [33] Yao, H., and Gu, W. Y., 2007, "Convection and Diffusion in Charged Hydrated Soft Tissues: A Mixture Theory Approach," *Biomech. Model. Mechanobiol.*, **6**(1–2), pp. 63–72.
- [34] Ehlers, W., and Eipper, G., 1999, "Finite Elastic Deformations in Liquid-Saturated and Empty Porous Solids," *Transp. Porous Med.*, **34**(1–3), pp. 179–191.
- [35] Holzapfel, G. A., Gasser, T. C., and Ogden, R. W., 2000, "A New Constitutive Framework for Arterial Wall Mechanics and a Comparative Study of Material Models," *J. Elasticity*, **61**(1–3), pp. 1–48.
- [36] Federico, S., and Herzog, W., 2008, "On the Permeability of Fibre-Reinforced Porous Materials," *Int. J. Solids Struct.*, **45**(7–8), pp. 2160–2172.
- [37] Gu, W. Y., Yao, H., Huang, C. Y., and Cheung, H. S., 2003, "New Insight Into Deformation-Dependent Hydraulic Permeability of Gels and Cartilage, and Dynamic Behavior of Agarose Gels in Confined Compression," *J. Biomech.*, **36**(4), pp. 593–598.
- [38] Gu, W. Y., Yao, H., Vega, A. L., and Flagler, D., 2004, "Diffusivity of Ions in Agarose Gels and Intervertebral Disc: Effect of Porosity," *Ann. Biomed. Eng.*, **32**(12), pp. 1710–1717.
- [39] Broberg, K. B., 1983, "On the Mechanical-Behavior of Intervertebral Disks," *Spine*, **8**(2), pp. 151–165.
- [40] O'Connell, G. D., Vresilovic, E. J., and Elliott, D. M., 2007, "Comparison of Animals Used in Disc Research to Human Lumbar Disc Geometry," *Spine*, **32**(3), pp. 328–333.
- [41] Urban, J. P. G., and Maroudas, A., 1979, "Measurement of Fixed Charge-Density in the Intervertebral-Disk," *Biochim. Biophys. Acta*, **586**(1), pp. 166–178.
- [42] Iatridis, J. C., MacLean, J. J., O'Brien, M., and Stokes, I. A. F., 2007, "Measurements of Proteoglycan and Water Content Distribution in Human Lumbar Intervertebral Disks," *Spine*, **32**(14), pp. 1493–1497.
- [43] Ruiz, C., Noailly, J., and Lacroix, D., 2013, "Material Property Discontinuities in Intervertebral Disc Porohyperelastic Finite Element Models Generate Numerical Instabilities Due to Volumetric Strain Variations," *J. Mech. Behav. Biomed.*, **26**, pp. 1–10.
- [44] Cortes, D. H., Jacobs, N. T., DeLuca, J. F., and Elliott, D. M., 2014, "Elastic, Permeability and Swelling Properties of Human Intervertebral Disc Tissues: A Benchmark for Tissue Engineering," *J. Biomech.*, **47**(9), pp. 2088–2094.
- [45] Iatridis, J. C., Setton, L. A., Weidenbaum, M., and Mow, V. C., 1997, "Alterations in the Mechanical Behavior of the Human Lumbar Nucleus Pulposus With Degeneration and Aging," *J. Orthopaed. Res.*, **15**(2), pp. 318–322.
- [46] Farrell, M. D., and Riches, P. E., 2013, "On the Poisson's Ratio of the Nucleus Pulposus," *ASME J. Biomech. Eng.*, **135**(10), p. 104501.
- [47] Iatridis, J. C., Kumar, S., Foster, R. J., Weidenbaum, M., and Mow, V. C., 1999, "Shear Mechanical Properties of Human Lumbar Annulus Fibrosus," *J. Orthopaed. Res.*, **17**(5), pp. 732–737.
- [48] Best, B. A., Guilak, F., Setton, L. A., Zhu, W. B., Saednejad, F., Ratcliffe, A., Weidenbaum, M., and Mow, V. C., 1994, "Compressive Mechanical-Properties of the Human Anulus Fibrosus and Their Relationship to Biochemical-Composition," *Spine*, **19**(2), pp. 212–221.
- [49] Ebara, S., Iatridis, J. C., Setton, L. A., Foster, R. J., Mow, V. C., and Weidenbaum, M., 1996, "Tensile Properties of Nondegenerate Human Lumbar Anulus Fibrosus," *Spine*, **21**(4), pp. 452–461.
- [50] Yao, H., and Gu, W. Y., 2004, "Physical Signals and Solute Transport in Cartilage Under Dynamic Unconfined Compression: Finite Element Analysis," *Ann. Biomed. Eng.*, **32**(3), pp. 380–390.
- [51] Lu, Y. M., Hutton, W. C., and Gharpuray, V. M., 1996, "Do Bending, Twisting, and Diurnal Fluid Changes in the Disc Affect the Propensity to Prolapse? A Viscoelastic Finite Element Model," *Spine*, **21**(22), pp. 2570–2579.
- [52] O'Connell, G. D., Jacobs, N. T., Sen, S., Vresilovic, E. J., and Elliott, D. M., 2011, "Axial Creep Loading and Unloaded Recovery of the Human Intervertebral Disc and the Effect of Degeneration," *J. Mech. Behav. Biomed.*, **4**(7), pp. 933–942.
- [53] McNally, D. S., and Arridge, R. G. C., 1995, "An Analytical Model of Intervertebral Disc Mechanics," *J. Biomech.*, **28**(1), pp. 53–68.
- [54] Heuer, F., Schmidt, H., Klezl, Z., Claes, L., and Wilke, H. J., 2007, "Stepwise Reduction of Functional Spinal Structures Increase Range of Motion and Change Lordosis Angle," *J. Biomech.*, **40**(2), pp. 271–280.
- [55] Skaggs, D. L., Weidenbaum, M., Iatridis, J. C., Ratcliffe, A., and Mow, V. C., 1994, "Regional Variation in Tensile Properties and Biochemical-Composition of the Human Lumbar Anulus Fibrosus," *Spine*, **19**(12), pp. 1310–1319.
- [56] Adams, M. A., and Roughley, P. J., 2006, "What is Intervertebral Disc Degeneration, and What Causes it?," *Spine*, **31**(18), pp. 2151–2161.
- [57] Stokes, I. A. F., Laible, J. P., Gardner-Morse, M. G., Costi, J. J., and Iatridis, J. C., 2011, "Refinement of Elastic, Poroelectric, and Osmotic Tissue Properties of Intervertebral Disks to Analyze Behavior in Compression," *Ann. Biomed. Eng.*, **39**(1), pp. 122–131.
- [58] Setton, L. A., and Chen, J., 2006, "Mechanobiology of the Intervertebral Disc and Relevance to Disc Degeneration," *J. Bone Jt. Surg. Am.*, **88A**, pp. 52–57.
- [59] Iatridis, J. C., Furukawa, M., Stokes, I. A. F., Gardner-Morse, M. G., and Laible, J. P., 2009, "Spatially Resolved Streaming Potentials of Human Intervertebral Disk Motion Segments Under Dynamic Axial Compression," *ASME J. Biomech. Eng.*, **131**(3), p. 031006.