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A VOLUMETRIC GROWTH AND REMODELING FRAMEWORK TOWARDS PREDICTING THE PROGRESSION OF OSTEOARTHRITIS IN ARTICULAR CARTILAGE

Muhammed M. Rahman (1), Thomas S. E. Öst (2), Corey P. Neu (3), David M. Pierce (1,4)

(1) Department of Mechanical Engineering, University of Connecticut, Storrs, Connecticut, USA

(2) Department of Weapons, Protection and Security, FOI – Swedish Defense Research Agency, Stockholm, Sweden

(3) Department of Mechanical Engineering, University of Colorado Boulder, Boulder, Colorado, USA

(4) Department of Biomedical Engineering, University of Connecticut, Storrs, Connecticut, USA

INTRODUCTION

Articular cartilage, a soft tissue covering the bone ends in joints, provides support for bearing load and movement by the virtue of unique structural composition and very low coefficient of friction at the surface. Osteoarthritis (OA) is a disease of the synovial joint, with degeneration and loss of articular cartilage as one hallmark change. Despite the multifactorial nature of OA, mechanical stresses, e.g., tension, compression, shear, hydrostatic pressure, play a key role in the destructive evolution of the disease [1-4]. Both overloading (e.g. trauma) and reduced loading (e.g. immobilization) of cartilage induce molecular and microstructural changes that lead to mechanical softening, fibrillation, and erosion.

In response to mechanical and chemical stimuli, chondrocytes (the cells within cartilage) express and degrade components of extra-cellular matrix (ECM) including structural constituents such as collagen, proteoglycan, and other proteins. To facilitate better understanding of the mechanobiology of cartilage and chondrocytes we seek functional relations between the type and magnitude of mechanical stimuli and the resulting cell-driven mass/density changes within cartilage, which affects the subsequent mechanics.

Here we established a novel framework to incorporate the evolution of constituents generating volumetric changes in cartilage, i.e., volumetric growth and remodeling (VG&R), by leveraging our established constitutive model of cartilage [5-6]. Experimental evidence indicates that application of strain at varying physiological frequencies facilitates chondrocytes expressing PG and collagen at different rates and total quantities [7-10]. We curated the available literature and established functional relations between the loading conditions and normalized expression of constituents. To validate our proposed VG&R framework for cartilage we reproduced the experiment of Kraft et al. [11] and predicted the production of collagen and PG.

METHODS

Constitutive Model. We modeled articular cartilage as a biphasic (swelling) continuum $\phi = \phi^{\mathrm{S}} + \phi^{\mathrm{F}}$ consisting of a porous solid phase ϕ^{S} saturated with an interstitial fluid phase ϕ^{F}. We defined the Helmholtz free-energy function of the solid ψ^{S} as [5-6]

$$\psi^{\mathrm{S}} = \psi^{\mathrm{S}}_{\mathrm{OP}}(J_{\mathrm{S}}) + (1-\nu)\psi^{\mathrm{S}}_{\mathrm{IM}}(J_{\mathrm{S}}, I_1) + \nu\psi^{\mathrm{S}}_{\mathrm{FN}}(\mathbf{C}_{\mathrm{S}}, \mathbf{M}), \quad (1)$$

where $\psi^{\mathrm{S}}_{\mathrm{OP}}$, $\psi^{\mathrm{S}}_{\mathrm{IM}}$, and $\psi^{\mathrm{S}}_{\mathrm{FN}}$ are the contributions of the osmotic pressure, isotropic matrix, and network of collagen fibers, respectively; ν is the volume fraction of collagen to total solid; J_{S}, $\mathbf{C}_{\mathrm{S}}$, and $\mathbf{M}$ are Jacobian, the right Cauchy-Green tensor, and the reference fiber orientation, respectively; and $I_1 = \mathrm{tr}(\mathbf{C}_{\mathrm{S}})$. We modeled the contribution from osmotic pressure as [6]

$$\psi^{\mathrm{S}}_{\mathrm{OP}} = \frac{1}{\rho^{\mathrm{S}}_{0\mathrm{S}}} R\theta c^{\mathrm{fc}}_{0\mathrm{S}} n^{\mathrm{F}}_{0\mathrm{S}} \left[\frac{2\bar{c}_{\mathrm{m}}}{c^{\mathrm{fc}}_{\mathrm{m}}} - \frac{\sqrt{4(\bar{c}_{\mathrm{m}})^2 + (c^{\mathrm{fc}}_{\mathrm{m}})^2}}{c^{\mathrm{fc}}_{\mathrm{m}}} + \sinh^{-1}\left(\frac{c^{\mathrm{fc}}_{\mathrm{m}}}{2\bar{c}_{\mathrm{m}}}\right) \right], \quad (2)$$

where $R = 8.314$ MPa mm^3/mmol K, $\theta = 310.2$ K, $\rho^{\mathrm{S}}_{0\mathrm{S}}, c^{\mathrm{fc}}_{0\mathrm{S}}, n^{\mathrm{F}}_{0\mathrm{S}}, c^{\mathrm{fc}}_{\mathrm{m}}, \bar{c}_{\mathrm{m}}$ are the initial solid partial density, initial concentration of fixed charges, the initial fluid volume fraction, initial concentration of fixed charge and the ion concentration of the external solution, respectively. We modeled the contribution from densely packed proteoglycan as [2,3]

$$\psi^{\mathrm{S}}_{\mathrm{IM}} = \frac{1}{\rho^{\mathrm{S}}_{0\mathrm{S}}} \left[U(J_{\mathrm{S}}) + \frac{1}{2}\mu^{\mathrm{S}}(I_1 - 3) \right], \quad (3)$$

including compaction effects via $U(J_{\mathrm{S}})$ and with shear modulus μ^{S}. We modeled the contribution from the network of collagen fibers as [5-6]

$$\psi^{\mathrm{S}}_{\mathrm{FN}} = \frac{1}{\rho^{\mathrm{S}}_{0\mathrm{S}}} \int_{\Omega} \rho(\mathbf{M}) \frac{k_1}{2k_2} \left\{ e^{[k_2(I_4-1)]^2 - 1} \right\} \mathcal{H}(I_4 - 1)\, \mathrm{d}\Omega, \quad (4)$$

where $\rho(\mathbf{M}), k_1, k_2$ are a voxel-wise orientation distribution function, a stress like parameter and dimensionless parameter, respectively, $I_4 = \mathbf{M} \cdot \mathbf{C}_{\mathrm{S}}\mathbf{M}$, and $\mathcal{H}$ is a Heaviside function.

We modeled the corresponding permeability of cartilage matrix as [5-6]

$$\mathbf{K}_{\mathrm{F}} = k_{0\mathrm{S}} \left(\frac{n^{\mathrm{F}}}{1 - n_{0\mathrm{S}}^{\mathrm{S}}} \right)^{m} \frac{1}{4\pi} \int_{\Omega} \frac{\rho(\mathbf{M})}{I_4} \mathbf{m} \otimes \mathbf{m} \, \mathrm{d}\Omega \,, \tag{5}$$

where $\mathbf{m}$ is the current fiber orientation, n^{F} and $n_{0\mathrm{S}}^{\mathrm{S}}$ are the volume fractions of fluid and solid, and $k_{0\mathrm{S}}$ is the initial Darcy permeability.

Volumetric Growth and Remodeling Framework. We defined the target volume change due to VG&R as $\hat{v} = \sum_{i=\mathrm{PG,CO}} \hat{m}_i \phi_i$, where $\hat{m}_i$ and ϕ_i are the individual normalized mass productions and volume fractions, respectively. We defined the modified Jacobian, and right and left Cauchy-Green tensors as $\hat{J} = \hat{v}^{-1} \det(\mathbf{F}) = J/\hat{v}$, $\hat{\mathbf{C}} = \hat{v}^{-2/3}\mathbf{C}$ and $\hat{\mathbf{b}} = \hat{v}^{-2/3}\mathbf{b}$, respectively. We also defined the modified invariants as $\hat{I}_1 = \hat{v}^{-2/3} I_1$, $\hat{I}_2 = \hat{v}^{-4/3} I_2$, $\hat{I}_3 = \hat{v}^{-2} I_3$, and $\hat{I}_4 = \hat{v}^{-2/3} I_4$. The density changes of the individual constituents are $\hat{\rho}_i = \hat{m}_i / \phi_i$. Finally, we express the total Cauchy stress of the solid constituents as,

$$\boldsymbol{\sigma}^{\mathrm{S}} = \boldsymbol{\sigma}_{\mathrm{OP}}^{\mathrm{S}} + (1 - \nu) \hat{\rho}_{\mathrm{PG}} \boldsymbol{\sigma}_{\mathrm{IM}}^{\mathrm{S}} + \nu \hat{\rho}_{\mathrm{CO}} \boldsymbol{\sigma}_{\mathrm{FN}}^{\mathrm{S}} \,, \tag{6}$$

Normalized PG and Collagen Production. Experiments confirm that chondrocytes synthesize components of PG and collagen at different rates under different treatments with cyclic compression [7-10]. Therefore, we proposed a generalized function of normalized production of PG and collagen dependent on applied stretch (λ) within the tissue, loading rate or frequency (f), and the time (τ), i.e for the duration of loading. We proposed a linear relation,

$$\hat{m}_i = \alpha_i \lambda + \beta_i f + \gamma_i \tau + \omega_i \,, \tag{7}$$

where α_i, β_i, γ_i, and ω_i are fitting parameters for $i \in \{\mathrm{PG}, \mathrm{CO}\}$.
To facilitate general loading we converted the frequency to strain rate and stretch to principal stretches and maximum shear stretches, and implemented these within our VG&R framework.

Cartilage under Hydrostatic Pressure. To validate our established numerical framework, we simulated cartilage undergoing cyclic hydrostatic pressure [11] and predicted both proteoglycan and collagen production. We created a quarter-symmetry model of a cylindrical specimen of cartilage (10 mm Ø, 182 µm thickness) with 582 linear hexahedral elements. We first allowed the model to swell and achieve equilibrium. We then applied cyclic hydrostatic pressure from 0.5 MPa to 5 MPa at 0.1 Hz frequency following the experiment [11]. Exploiting the very different time scales between daily activities, e.g. walking (sec), and progression of OA (days to years), we used iterative rather than simultaneous solutions. We simulated the loading conditions for 21 days. We present the model properties for our analyses in **Table 1**. We performed our simulations using FEBio (University of Utah, USA).

Table 1: Model parameters for cartilage

Parameter			
$\boldsymbol{\mu^S}$	0.25 MPa	$\boldsymbol{k_{0S}}$	9.6×10^{-4} mm^4/Ns
$\boldsymbol{k_1, k_2}$	0.43 MPa, 8.0 [-]	$\boldsymbol{m}$	3.3 [-]
$\boldsymbol{n_{0S}^S}$	0.15 [-]	$\boldsymbol{c_{0S}^{fc}}$	0.50×10^{-6} mol/mm^3
$\boldsymbol{\nu}$	0.82 [-]	$\boldsymbol{\bar{c}_m}$	0.15×10^{-6} mol/mm^3
$\boldsymbol{J_{cp}^S}$	0.37 [-]		

RESULTS

The fitted parameters for our normalized PG and collagen production, i.e. (7), are $\alpha_{\mathrm{PG}} = 0.0850, \beta_{\mathrm{PG}} = 0.0294, \gamma_{\mathrm{PG}} = 0.0206,$ and $\omega_{\mathrm{PG}} = 0.852$ for PG, and $\alpha_{\mathrm{CO}} = -5.03, \beta_{\mathrm{CO}} = 0.0215, \gamma_{\mathrm{CO}} = 0.0531,$ and $\omega_{\mathrm{PG}} = 5.53,$ for collagen. We present the fitted multilinear equations as contour surfaces with the experiment data used for fitting in **Fig. 1**.

We predicted the normalized production of cartilage constituents for each day of the experiment, see **Fig. 2**. **Fig. 2(a)** shows a comparison between the predicted (normalized) production of PG vs. the corresponding experiment from Kraft et al. [11], while **Fig. 2(b)** illustrates the same comparison for collagen type II.

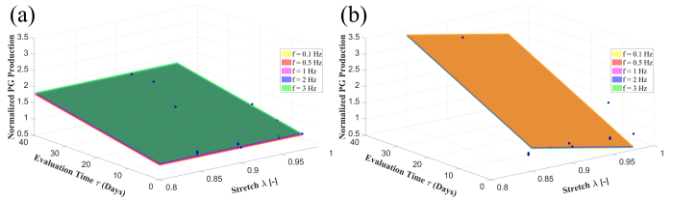

Figure 1: Normalized production of (a) proteoglycan (PG) and (b) collagen type II under general loading conditions.

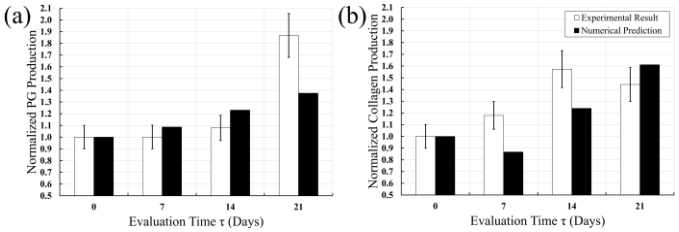

Figure 2: Normalized production of (a) proteoglycan (PG) and (b) collagen type II predicted versus experiment [11].

DISCUSSION

We introduced a VG&R framework considering the mechanobiologically induced turnover of constituents in articular cartilage resulting from mechanical loading. Our simulations of the cartilage successfully predict the production proteoglycan and collagen determined experimentally [11]. In predicting the evolution of PG, our simulation reasonably approximates the experimental results except for day 21. Our prediction of collagen follows the trend determined in the experiment; but the numerical values differ. Nevertheless, the difference between the prediction and experiment is in a narrow range of the normalized scale.

Unfortunately, the experimental data available for calibrating our framework i.e., formulate and fit (7), are quite sparse. In this light we selected the most simple (linear, not nonlinear) relationship among stretch, frequency, and time. Moreover, we formulated (7) based on experiments under uniaxial cyclic loading, while we predicted the evolution of constituents under cyclic hydrostatic pressure. Despite of the difference in loadings, we successfully predicted the evolution of constituents to test our novel VG&R framework for articular cartilage.

Limitations and outlook. We must improve the correspondence between predictions and experiments [11]. By leveraging more experimental data we could extent (7) to include nonlinearity and likely improve the fitting. In our simulations, we considered the number of chondrocytes as constant, while this may evolve with cell death or proliferation. Our framework is the first step towards a new class of computational tools that will facilitate, for the first time, patient-specific modeling of OA progression considering the biomechanics and kinetics of cell ECM turnover and production, both *in vitro* and *in vivo*.

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REFERENCES

[1]Andriacchi, TP et al., *Ann Biomed Eng*, 32:447-457, 2004. [2] Goldring, MB and Marcu, KB, *Arthr Res Ther*, 11:224, 2009. [3] Polur, I et al., *Histol Histopath*, 25:599-608, 2010. [4] Loeser, RF et al., *Arthritis Rheum*, 64:1697-1707, 2012. [5] Pierce, DM et al., *Biomech Model Mechanobiol*, 15:229-244, 2016. [6] Wang, X et al., *J Mech Behav Biomed Mat*, 86:409-422, 2018. [7] Mauck, RL et al., *Tissue Eng*, 9:597-611, 2003. [8] Kisiday, JD et al., *J Biomech*, 37:595-604, 2004. [9] Tsuang, YH et al., *Int J Art Organs*, 31:439-449, 2008. [10] Wang, PY and Tsai, WB, *J Bio Sci,* 24:507-519, 2013. [11] Kraft, JJ et al., *Cartilage,* 2:254-264, 2011.