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THE EVOLUTION OF HETEROGENEOUS PARAMETERS FOR MODELING CARTILAGE DURING THE PROGRESSION OF OSTEOARTHRITIS

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INTRODUCTION

Despite the multifactorial nature of Osteoarthritis (OA), a disease of the synovial joint, mechanical stresses play a key role in the destructive evolution of the disease [1–4]. Both overloading and reduced loading of cartilage induce molecular and microstructural changes that lead to mechanical softening, fibrillation and erosion. Crucially, there is currently no direct method to correlate spatially resolved intra-tissue stresses with progression of OA in individual patients. This unmet need renders us unable to identify the most significant stimuli in the progression of OA, and thus unable to identify reliable targets for treatment or to design new therapies.

Computational models of cartilage and joints have enabled estimates of responses and properties, e.g. distributions of intra-tissue stresses and evolving mechanical properties, especially in the early stages of OA. In this study, we aimed to establish a methodology to calibrate our constitutive models of cartilage by leveraging experimental data we previously published and determine the evolution of material parameters with respect to the severity of OA quantified via the standard OARSI grade [5], especially in early disease stages.

METHODS

We described articular cartilage as a biphasic continuum $\varphi = \varphi^{\mathrm{S}} + \varphi^{\mathrm{F}}$ consisting of a porous solid phase φ^{S}, and saturated with the fluid phase φ^{F}. We calculated the total Cauchy stress tensor as [6]

$$\boldsymbol{\sigma} = -p\mathbf{I} + 2\rho^{\mathrm{S}}\mathbf{F}_{\mathrm{S}}\frac{\partial \Psi^{\mathrm{S}}}{\partial \mathbf{C}_{\mathrm{S}}}\mathbf{F}_{\mathrm{S}}^{\mathrm{T}} = -p\mathbf{I} + \boldsymbol{\sigma}_{\mathrm{E}}^{\mathrm{S}}\,, \tag{1}$$

where p is the fluid pressure, $\mathbf{I}$ is the identity tensor, ρ^{S} is the partial density of solid, $\mathbf{F}_{\mathrm{S}}$ is the deformation gradient of the solid, $\mathbf{C}_{\mathrm{S}}$ is the right Cauchy–Green tensor, and $\boldsymbol{\sigma}_{\mathrm{E}}^{\mathrm{S}}$ is the effective Cauchy stress tensor. We use an additive decomposition of the superimposed solid Helmholtz free-energy function Ψ^{S} into a Donnan osmotic pressure part $\Psi_{\mathrm{OP}}^{\mathrm{S}}$, an isotropic matrix part $\Psi_{\mathrm{IM}}^{\mathrm{S}}$, and a fiber network part $\Psi_{\mathrm{FN}}^{\mathrm{S}}$ as

$$\Psi^{\mathrm{S}} = \Psi_{\mathrm{OP}}^{\mathrm{S}}(J_{\mathrm{S}}) + (1-\nu)\Psi_{\mathrm{IM}}^{\mathrm{S}}(J_{\mathrm{S}},\, I_1) + \nu\Psi_{\mathrm{FN}}^{\mathrm{S}}(\mathbf{C}_{\mathrm{S}})\,, \tag{2}$$

where $J_{\mathrm{S}} = \det \mathbf{F}_{\mathrm{S}}$ is the Jacobian, ν is the volume fraction of collagen to the total solid, $I_1 = \mathrm{tr}\mathbf{C}_{\mathrm{S}}$ is the first invariant of $\mathbf{C}_{\mathrm{S}}$. We model the contribution from the osmotic pressure to the Cauchy stress as

$$\boldsymbol{\sigma}_{\mathrm{OP}}^{\mathrm{S}} = -R\Theta\left[\sqrt{4(\bar{c}_{\mathrm{m}})^2 + (c_{\mathrm{m}}^{\mathrm{fc}})^2} - 2\bar{c}_{\mathrm{m}}\right]\mathbf{I}\,, \tag{3}$$

where $\mathrm{R} = 8.314 \times 10^3\ \mathrm{mJ/(K\cdot mol)}$, Θ is the absolute temperature, and $\bar{c}_{\mathrm{m}}$ is the ion concentration of the external solution. The concentration of the fixed charge depends on the deformation as

$$c_{\mathrm{m}}^{\mathrm{fc}} = c_{0\mathrm{S}}^{\mathrm{fc}}\left(1 - n_{0\mathrm{S}}^{\mathrm{S}}\right)\left(J_{\mathrm{S}} - n_{0\mathrm{S}}^{\mathrm{S}}\right)^{-1}, \tag{4}$$

where $c_{0\mathrm{S}}^{\mathrm{fc}}$ is the initial concentration of fixed charge (within the tissue) and $n_{0\mathrm{S}}^{\mathrm{S}}$ is the initial solid volume fraction, and $J_{\mathrm{S}} = \rho_{0\mathrm{S}}^{\mathrm{S}}/\rho^{\mathrm{S}}$ where $\rho_{0\mathrm{S}}^{\mathrm{S}}$ is the initial solid partial density. We model the (largely) proteoglycan solid matrix $\Psi_{\mathrm{IM}}^{\mathrm{S}}$ using a neo-Hookean function extended with compaction effects. To model the dispersed network of collagen $\Psi_{\mathrm{IM}}^{\mathrm{S}}$ we use $\rho(\mathbf{m_0})$, the orientation distribution function, within

$$\Psi_{\mathrm{FN}}^{\mathrm{S}} = \frac{1}{\rho_{0\mathrm{S}}^{\mathrm{S}}}\int_{\Omega}\rho(\mathbf{D})\frac{k_1}{2k_2}\{\exp[k_2(I_4-1)^2] - 1\}\mathcal{H}(I_4-1)\,\mathrm{d}\Omega\,, \tag{5}$$

where $\Omega = \{\mathbf{m_0} \in \mathbb{R}^3 : |\mathbf{m_0}| = 1\}$ is the unit sphere, $\mathbf{m_0}$ is the reference fiber orientation, $k_1, k_2 > 0$ are fiber parameters $I_4(\mathbf{m_0}) = \mathbf{m_0}\cdot\mathbf{C}_{\mathrm{S}}\mathbf{m_0}$ is the square of the fiber stretch, and $\mathcal{H}$ is a Heaviside step function. We consider the viscoelasticity of both the proteoglycan and collagen solids using two parameters: β [-], a magnitude factor, and τ [s] the associated relaxation time, cf. [6]. The diffusion tensor $\mathbf{D}$ reflects the distribution of collagen fibers and we obtain this from DT-MRI. We calculate the average $\mathbf{D}$ for a representative volume of interest using the Log-Euclidean mean. We modeled the corresponding permeability $\mathbf{K}_{\mathrm{F}}$ as

$$\mathbf{K}_{\mathrm{F}} = \frac{k_{0\mathrm{S}}}{4\pi}\left(\frac{n^{\mathrm{F}}}{1-n_{0\mathrm{S}}^{\mathrm{S}}}\right)^{m}\int_{\Omega}\frac{\rho(\mathbf{m}_0)}{\mathrm{I}_4}\mathbf{m}\otimes\mathbf{m}\mathrm{d}\Omega\,, \qquad (6)$$

where $k_{0\mathrm{S}}$ is the initial Darcy permeability and m is a parameter controlling the deformation dependence of the permeability. In order to recover the initial (non-zero) stress distribution resulting from osmotic swelling, we applied the backward displacement method to find an initial equilibrium state before external loading. [7]

In previously published experiments using large-strain shear, we harvested 106 3×3 mm, full-thickness specimens of healthy and OA damaged cartilage from 17 donors [8, 9]. Using standard histological scoring we determined the OARSI grade of each specimen [5]. Prior to shear testing we applied an axial pre-compression of 1% of the undeformed thickness and allowed the specimens to equilibrate for 4000 s. Next, we applied cyclic simple-shear displacements at a rate of 75 μm/min for six cycles. We applied maximum displacements corresponding to shear strains of 5%, 10%, 15%, 20%, and 25%. Many mechanical tests failed at 20% shear strain and here we used data only up to 15% shear strain.

To simulate the shear tests, we modeled the center slice of the specimens under plane strain (**Fig. 1(a)**) and along the shear direction using 20-node hexahedral elements in FEBio (U. of Utah) (**Fig. 1(b)**). We validated our mesh using an *h*-refinement test [6,7]. We assigned three different sets of material parameters corresponding to the superficial zone (SZ), middle zone (MZ), and deep zone (DZ) based on the thickness, which has thickness of 15%, 55% and 35% respectively [7]. In light of the data available, and to minimize the computational burden, we leveraged previous studies to establish some of the parameters (**Table 1**), where $z^* \in [0,1]$ is the normalized tissue thickness (zero refers to the articular surface and one refers to the interface with subchondral bone). We set $z^*_{\mathrm{SZ}} = 0.075$, $z^*_{\mathrm{MZ}} = 0.425$ and $z^*_{\mathrm{DZ}} = 0.85$.

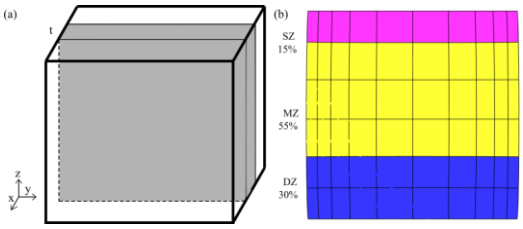

Figure 1: Finite element model of the shear experiment: (a) schematic with center slice in plane strain; (b) mesh with three distinct zones through the thickness.

Table 1: Model parameters from our previous studies [6,7].

Parameter	Value	Unit
$\boldsymbol{\Theta}$	310.15	K
$\boldsymbol{c_{0\mathrm{S}}^{\mathrm{fc}}}$	2.0×10^{-7}	$\mathrm{mol/mm^3}$
$\boldsymbol{\bar{c}_{\mathrm{m}}}$	1.5×10^{-7}	$\mathrm{mol/mm^3}$
$\boldsymbol{\mu}$	0.23	MPa
$\boldsymbol{k_2}$	8	–
$\boldsymbol{n_{0\mathrm{S}}^{\mathrm{S}}(z^*)}$	$0.15+0.15(z^*)$	–
$\boldsymbol{\nu(z^*)}$	$0.43(z^*)^2-0.60(z^*)+0.85$	–
$\boldsymbol{J_{\mathrm{cp}}^{\mathrm{S}}(z^*)}$	$0.36+0.11(z^*)$	–
$\boldsymbol{k_{0\mathrm{S}}(z^*)}$	$(1-0.9)(z^*)\times10^{-3}$	$\mathrm{mm^4/(N\cdot s)}$
$\boldsymbol{m(z^*)}$	$3.0+5.0(z^*)$	–

We fitted the model parameters using the "Levenberg–Marquard" method within FEBio [10]. To fit our constitutive model as a function of OA severity we first extracted target data for fitting each specimen. To eliminate noise and to align the loading state, we used data from the first peak force to the last peak force. In between each pair of peaks, we resampled the data at 24 evenly-spaced intervals. We first assumed cartilage was homogeneous, setting all three zones with the same as the MZ, to fit viscoelasticity of fiber network (β_{FN}, τ_{FN}) and estimate the fiber parameter k_1. We then fixed the viscoelasticity and, using our heterogeneous model, fit fiber parameter k_1 for all three zones.

RESULTS

Figure 2 shows fitted results of two representative specimens: one healthy and one at OARSI grade 3.5. The *x*-axes display the time of the test, including the pre-compression and relaxing periods while the *y*-axes display the reaction force in the direction of shearing. **Table 2** shows the fitted parameters of these two specimens.

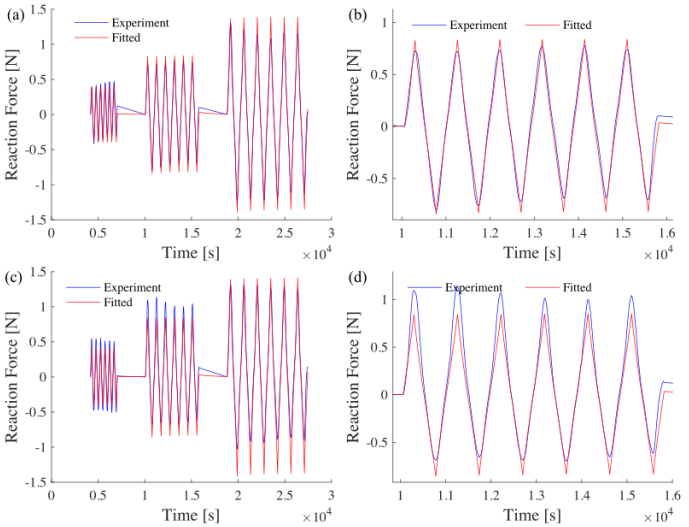

Figure 2: Representative fitting results: (a), (b) are from a healthy specimen while (c), (d) are from an OA specimen (OARSI grade 3.5). (a), (c) are the complete data while (b)(d) focus on 10% shear.

Table 2: Fitted parameters for healthy and OA specimens.

	Parameter	Value	Unit
Healthy Specimen	β_{FN}	1.680	–
	τ_{FN}	1598	s
	k_1(est)	2.266	MPa
	k_1(SZ)	1.417	MPa
	k_1(MZ)	2.890	MPa
	k_1(DZ)	3.535	MPa
OARSI Grade 3.5 Specimen	β_{FN}	1.470	–
	τ_{FN}	1697	s
	k_1(est)	3.605	MPa
	k_1(SZ)	3.363	MPa
	k_1(MZ)	4.256	MPa
	k_1(DZ)	4.811	MPa

DISCUSSION

Our preliminary results are currently insufficient to yield statistical conclusions, but we do see notable changes in the fitted parameters corresponding to both the through-thickness zones and health conditions of the specimens. The fiber parameter k_1 increases from cartilage surface to the bone interface, indicating stiffer individual fibers in DZ. The decreased β_{FN} in the OA specimen indicates a reduced viscoelastic response that likely reflects degeneration. As we fit more specimens our parameters, and the corresponding statistical analyses, will facilitate new simulation-based analyses and insights.

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