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A CHEMO-MECHANO-BIOLOGICAL MODEL OF EVOLVING OSTEOARTHRITIS

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INTRODUCTION

Osteoarthritis (OA) is a multifactorial disease of synovial joints with degeneration and loss of articular cartilage as a hallmark feature. Nearly 20% of the US population suffers from OA, affecting quality of life through pain, functional limitations, lost earnings, anxiety, and depression. While mechanical stimuli is essential to maintain healthy cartilage, overloading (e.g. trauma) and reduced loading (e.g. immobilization) induce molecular and microstructural changes that lead to mechanical softening, fibrillation, and erosion [1].

In response to mechanical stimuli, chondrocytes (the cells within cartilage) express chemicals (e.g. cytokines, growth factors, collagenase, and aggrecanase) which promote degradation or production of structural constituents, e.g. collagen and proteoglycan. Existing investigations on effects of mechanical loading on cartilage – including both *in vitro* experiments with human cartilage and *in vivo* animal models – fall short of true human physiological relevance [2]. Current mathematical models of signaling pathways lack mechanical effects while biomechanical models lack the chemical effects [3].

To facilitate better understanding of the coupled chemo-mechano-biological evolution of OA in cartilage, we seek coupled functional forms among intra-tissue mechanics and cell-driven mass/volume changes mediated by cytokines and chemical species. Here we establish a framework incorporating the evolution of chemical, mechanical, and biological constituents generating anisotropic volumetric changes in cartilage. We leverage our established constitutive model of cartilage [4] and adapt a biochemical pathway model [5] to predict the evolution of relevant cellular and biomolecular species during OA. We demonstrate our framework by predicting the effects of immobilization and overloading on the progression of OA (and relative to homeostasis).

METHODS

Constitutive Model. To capture the nonlinear mechanics of cartilage, we employ an additive decomposition of the superimposed solid Helmholtz free energy $\overline{\psi}^{\mathrm{S}}$ into $\overline{\psi}^{\mathrm{S}}_{\mathrm{IM}}$ and $\overline{\psi}^{\mathrm{S}}_{\mathrm{FN}}$, representing an isotropic matrix and a distributed, fiber network respectively as [5]

$$\overline{\psi}^{\mathrm{S}} = (1-\nu)\overline{\psi}^{\mathrm{S}}_{\mathrm{IM}}(J_{\mathrm{S}}, \bar{I}_1) + \nu\overline{\psi}^{\mathrm{S}}_{\mathrm{FN}}(\bar{I}_4, \mathbf{M}) \,, \tag{1}$$

where $\nu(\tau) = \frac{\nu^0 \widehat{m}_{\mathrm{co}}}{\nu^0 \widehat{m}_{\mathrm{co}} + (1-\nu^0)\widehat{m}_{\mathrm{pg}}}$ is the evolving volume fraction of collagen with ν^0, $\widehat{m}_{\mathrm{co}}$, and $\widehat{m}_{\mathrm{pg}}$ the initial volume fraction of collagen, and the normalized mass of collagen and proteoglycan, J_{S} is the Jacobian, $\bar{I}_1 = \mathrm{tr}(\bar{\mathbf{C}}_{\mathrm{S}})$ with $\bar{\mathbf{C}}_{\mathrm{S}} = (J_{\mathrm{S}})^{-2/3}\mathbf{F}^{\mathrm{e}^{\mathrm{T}}}\mathbf{F}^{\mathrm{e}}$ the modified right Cauchy-Green tensor, $\mathbf{M}$ is the reference fiber orientation, and $\bar{I}_4 = \mathbf{M}\cdot\bar{\mathbf{C}}_{\mathrm{S}}\mathbf{M}$. We modeled the densely packed proteoglycan using the neo-Hookean function for $\overline{\psi}^{\mathrm{S}}_{\mathrm{IM}}$ and the network of collagen fibers as [5]

$$\overline{\psi}^{\mathrm{S}}_{\mathrm{FN}} = \frac{1}{\rho^{\mathrm{S}}_{0\mathrm{S}}}\int_{\Omega}\rho(\mathbf{M})\frac{k_1}{2k_2}\left\{e^{[k_2(\bar{I}_4-1)]^2-1}\right\}\mathcal{H}(\bar{I}_4-1)\,\mathrm{d}\Omega \tag{2}$$

where $\rho(\mathbf{M}), k_1, k_2$ are an orientation distribution function and two model parameters, respectively, and $\mathcal{H}$ is a Heaviside function.

Anisotropic Volumetric Growth and Remodeling. We defined the target volume change $\hat{v} = \nu^0\widehat{m}_{\mathrm{co}} + (1-\nu^0)\widehat{m}_{\mathrm{pg}}$. We exploit the very different time scales between daily activities, e.g. walking (t in sec), and progression of OA (τ in mos), which allows iterative rather than simultaneous solutions. We define the overall deformation gradient $\mathbf{F}$ by a multiplicative decomposition of $\mathbf{F}(\tau,t) = \mathbf{F}^{\mathrm{e}}(t)\mathbf{F}^{\mathrm{g}}(\tau)$ [6]. Here, we define anisotropic cartilage loss as $\mathbf{F}^{\mathrm{g}} = \mathbf{I} + (\hat{v}-1)\mathbf{n}\otimes\mathbf{n}$, where $\mathbf{n}$ is a unit vector normal to the articular surface.

Signaling Pathways Biochemical Model. In health and with moderate daily activities, chondrocytes maintain cartilage homeostasis and do not proliferate. In OA, and both in immobilization and overloading, homeostasis is lost and chondrocytes express catabolic and anabolic cytokines, along with structural proteins. We propose the following system of ODEs to model the key components in cartilage

$$\frac{\mathrm{d}\hat{n}_{\mathrm{c}}}{\mathrm{d}\tau} = \left(r^{\mathrm{c}}_1 + r^{\mathrm{c}}_2\hat{c}_\beta\right)\hat{n}_{\mathrm{c}} - \left(r^{\mathrm{c}}_3 + r^{\mathrm{c}}_4 f(\sigma_{\mathrm{sh}})\hat{c}_\beta + r^{\mathrm{c}}_5\hat{c}_{\mathrm{p}}\right)\hat{n}_{\mathrm{c}} \tag{3}$$

$$\frac{\mathrm{d}\hat{n}_{\mathrm{hc}}}{\mathrm{d}\tau} = r_1^{\mathrm{hc}} f(\sigma_{\mathrm{sh}})\hat{c}_\beta \hat{n}_{\mathrm{c}} - r_2^{\mathrm{hc}}\hat{n}_{\mathrm{hc}} \tag{4}$$

$$\frac{\mathrm{d}\hat{m}_{\mathrm{co}}}{\mathrm{d}\tau} = \left(r_1^{\mathrm{co}} + r_2^{\mathrm{co}}\hat{c}_\beta\right)\hat{n}_{\mathrm{c}} - \left(r_3^{\mathrm{co}} f(\sigma_1) + r_4^{\mathrm{co}}\hat{c}_{\mathrm{ca}}\right)\hat{m}_{\mathrm{co}} \tag{5}$$

$$\frac{\mathrm{d}\hat{m}_{\mathrm{pg}}}{\mathrm{d}\tau} = \left(r_1^{\mathrm{pg}} + r_2^{\mathrm{pg}}\hat{c}_\beta\right)\hat{n}_{\mathrm{c}} - \left(r_3^{\mathrm{pg}} f(\mathrm{E}_3) + r_4^{\mathrm{pg}}\hat{c}_{\mathrm{ag}}\right)\hat{m}_{\mathrm{pg}} \tag{6}$$

$$\frac{\mathrm{d}\hat{c}_{\mathrm{ca}}}{\mathrm{d}\tau} = \left[\frac{r_1^{\mathrm{ca}} + r_6^{\mathrm{ca}}\hat{c}_{\mathrm{p}}}{1 + r_2^{\mathrm{ca}}\hat{c}_\beta}\right]\hat{n}_{\mathrm{c}} + r_3^{\mathrm{ca}}\hat{n}_{\mathrm{hc}} - \left(r_4^{\mathrm{ca}} + r_5^{\mathrm{ca}}\hat{c}_{\mathrm{i}}\right)\hat{c}_{\mathrm{ca}} \tag{7}$$

$$\frac{\mathrm{d}\hat{c}_{\mathrm{ag}}}{\mathrm{d}\tau} = \left[\frac{r_1^{\mathrm{ag}} + r_6^{\mathrm{ag}}\hat{c}_{\mathrm{p}}}{1 + r_2^{\mathrm{ag}}\hat{c}_\beta}\right]\hat{n}_{\mathrm{c}} + r_3^{\mathrm{ag}}\hat{n}_{\mathrm{hc}} - \left(r_4^{\mathrm{ag}} + r_5^{\mathrm{ca}}\hat{c}_{\mathrm{i}}\right)\hat{c}_{\mathrm{ag}} \tag{8}$$

$$\frac{\mathrm{d}\hat{c}_{\mathrm{i}}}{\mathrm{d}\tau} = \left(r_1^{\mathrm{i}} + r_2^{\mathrm{i}}\hat{c}_\beta\right)\hat{n}_{\mathrm{c}} - \left(r_3^{\mathrm{i}} + r_4^{\mathrm{i}}\hat{c}_{\mathrm{ca}} + r_5^{\mathrm{i}}\hat{c}_{\mathrm{ag}}\right)\hat{c}_{\mathrm{i}} \tag{9}$$

$$\frac{\mathrm{d}\hat{c}_{\ell\beta}}{\mathrm{d}\tau} = \left(r_1^{\ell\beta} + r_2^{\ell\beta}\hat{c}_\beta\right)\hat{n}_{\mathrm{c}} - \left[r_4^{\ell\beta} + r_5^{\ell\beta} f(\sigma_{\mathrm{sh}})\right]\hat{c}_{\ell\beta} \tag{10}$$

$$\frac{\mathrm{d}\hat{c}_\beta}{\mathrm{d}\tau} = r_1^\beta f(\sigma_{\mathrm{sh}})\hat{c}_{\ell\beta} - r_2^\beta \hat{c}_\beta \tag{11}$$

$$\frac{\mathrm{d}\hat{c}_{\ell\mathrm{p}}}{\mathrm{d}\tau} = \left[\frac{r_1^{\ell\mathrm{p}} + r_2^{\ell\mathrm{p}}\hat{c}_{\mathrm{p}}}{1 + r_3^{\ell\mathrm{p}}\hat{c}_\beta}\right]\hat{n}_{\mathrm{c}} - \left[r_4^{\ell\mathrm{p}} + r_5^{\ell\mathrm{p}} f(\sigma_1)\right]\hat{c}_{\ell\mathrm{p}} \tag{12}$$

$$\frac{\mathrm{d}\hat{c}_{\mathrm{p}}}{\mathrm{d}\tau} = r_1^{\mathrm{p}} f(\sigma_1)\hat{c}_{\ell_{\mathrm{p}}} - r_2^{\mathrm{p}}\hat{c}_{\mathrm{p}} \tag{13}$$

where, $\hat{n}_{\mathrm{c}}$, $\hat{n}_{\mathrm{hc}}$, $\hat{c}_{\mathrm{ca}}$, $\hat{c}_{\mathrm{ag}}$, $\hat{c}_{\mathrm{i}}$ $\hat{c}_{\ell\beta}$, $\hat{c}_\beta$ $\hat{c}_{\ell\mathrm{p}}$, $\hat{c}_{\mathrm{p}}$, are the normalized living cells, hypertrophic cells, collagenases (MMP-3,13, etc.), aggrecanases (ADAMTS-4,5, etc.), tissue inhibitors of metalloproteinase (TIMP), latent growth factors (TGF-β, BMP, etc.), active growth factors, latent pro-inflammatory cytokines (IL-1, TNF-α, etc.) and active pro-inflammatory cytokines, respectively. We define $f(\sigma_{\mathrm{sh}})$, $f(\sigma_1)$ and $f(E_1)$ as well-shaped, double-sigmoidal functions of shear stresses, first principal stresses, and third principal Green-Lagrange strains, respectively. The r_i^X are rate parameters for the variables, where $i \in \{1,2,3,\dots,N\}$ and $X \in \{\mathrm{c}, \mathrm{hc}, \mathrm{co}, \mathrm{pg}, \mathrm{ca}, \mathrm{ag}, \mathrm{i}, \ell\beta, \beta, \ell\mathrm{p}, \mathrm{p}\}$.

Cartilage in Homeostasis, Immobilization, and Overloading. We simulated cartilage undergoing physiological loading (i.e. normal daily activities), immobilization, and overloading for 30 months duration. We defined ($f(\sigma_{\mathrm{sh}})$, $f(\sigma_1)$ and $f(E_1)$) following literature [7].

Numerical implementation. In the constitutive model we used $\mu^{\mathrm{S}} = 1$ MPa, $k_1 = 0.43$ MPa, $k_2 = 8$ [−], $\nu = 0.8$ [−] [4]. The initial conditions for the coupled pathway model are $\hat{n}_{\mathrm{c}} = \hat{c}_{\mathrm{ca}} = \hat{c}_{\mathrm{ag}} = \hat{c}_i = \hat{c}_{\ell\beta} = \hat{c}_{\ell\mathrm{p}} = 1$ and $\hat{c}_\beta = \hat{c}_{\mathrm{p}} = \hat{n}_{\mathrm{hc}} = 0$, and we estimated the rate parameters following literature. We implemented the chemo-mechano-biological framework in Matlab R2021b (The Mathworks, USA) and solved the system of ODEs using a backward-finite-difference Euler approach with a fixed step size of $\mathrm{d}\tau = 0.1$ months.

RESULTS

During the moderate loading of normal daily activities cartilage remained in homeostasis, i.e. no changes in the constituents or cytokines (dashed lines in **Fig. 1**). During immobilization we predicted a reduction in living cells (-16%), proteoglycan (-25%), and collagen (-28%) (**Fig. 1(a)**). We also predicted gradual increases in collagenase, aggrecanase, latent growth factors, and latent pro-inflammatory cytokines, all which remained upregulated (**Fig. 1(b)**). However, TIMP followed the opposite pattern due to its inverse relationship with both collagenase and aggrecanase. Active growth factors and active pro-inflammatory cytokines increased and stabilized at ~10% and ~6% with respect to the latent forms, respectively (**Fig. 1(c)**). We also predicted volume loss (-28%) consistent with experimental measurements (**Fig. 1(d)**) [8]. In overloading we observed greater volume loss (results not shown).

DISCUSSION

We introduced a modeling framework for cartilage considering the chemo-mechano-biologically induced turnover of key constituents in resulting from mechanical loading and/or biochemical activity. We included the complex chemical and mechanobiological mechanisms within cartilage, and addressed the key constituents in formulating our model. With representative rate parameters, our simulations for immobilization successfully predicted the loss of cartilage volume quantified experimentally as loss of thickness [8]. The upregulation of pro-inflammatory cytokines and the growth factors in immobilization is also consistent with to the experimental studies [9]. There is a lack of data quantifying the long-term effects of overloading human cartilage, but we simulated the evolution of constituents supported by *in vitro* and *in vivo* experiments leveraging animal models [10]. Both immobilization and overloading caused the progression of OA, demonstrating the potential of our framework to predict degradation.

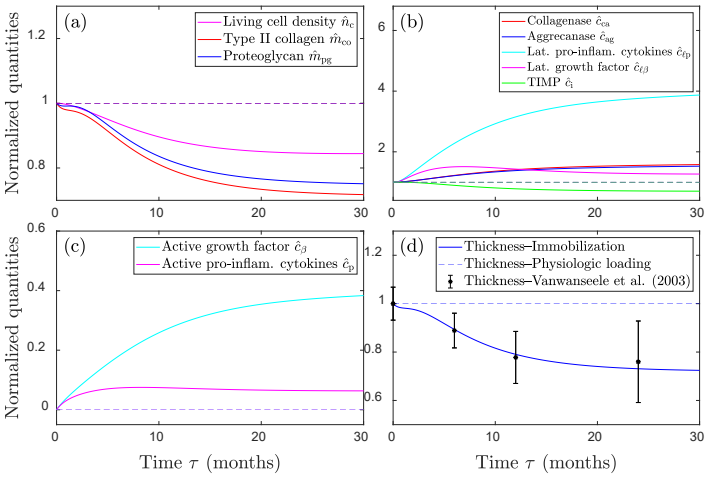

Figure 1: Cartilage evolving in homeostasis and immobilization. Normalized quantities of (a) structural components (living chondrocytes, collagen and proteoglycan), (b) cytokines and growth factors (collagenase, aggrecanase, TIMP, latent growth factor and latent pro-inflammatory cytokines), (c) active cytokines and growth factors, and (d) cartilage thickness. Dashed and solid lines represent moderate and reduced loading, respectively.

Limitations and outlook. We considered only a subset of known signaling pathways, while many more exist [11]. We also, as a starting point to establish our framework, combined the chemical species into classes based on their roles, although not all members within each class have the same effect on cartilage homeostasis. We aim to implement our chemo-mechano-biological framework for finite element analyses, thus enabling advanced understanding of patient-specific pathological changes due to biomechanical factors, improved clinical diagnostics and therapies [12], and new methods for non-invasive diagnosis and pre-/post-operative decision making.

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