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A CHEMO-MECHANO-BIOLOGICAL MODEL OF CARTILAGE IN FEBIO: STUDIES OF PATHOLOGICAL LOADING, HOMEOSTATIC ADAPTATION AND BIO-CHEMICAL TREATMENTS

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INTRODUCTION

Osteoarthritis (OA) is a debilitating disease of synovial joints, including degeneration and loss of articular cartilage, that impacts nearly 20% of people in the US alone and affects quality of life through pain, functional limitations, lost earnings, anxiety, and depression. Mechanical stimuli are essential for chondrocytes (the cells within cartilage) to maintain healthy cartilage. Chondrocytes express chemicals (e.g. cytokines, growth factors, collagenases, and aggrecanases) in response to pathological loading, i.e. overloading (e.g. trauma) and reduced loading (e.g. immobilization) [1]. These biochemical species promote production or degradation 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]. Additionally, current mathematical models of signaling pathways lack mechanical effects while biomechanical models lack the chemical effects [3]. In particular, the concept of homeostatic adaptation, wherein tissues/cells receive pathological loading for prolonged periods of time, is understudied and poorly understood.

Leveraging our coupled chemo-mechano-biological framework for cartilage [4], we investigate interactions among intra-tissue mechanics and cell-driven mass/volume changes mediated by cytokines and chemical species. In this study, we: (1) implement our framework in 3-D, nonlinear finite elements using FEBio (U. of Utah, USA), (2) elucidate homeostatic adaptation to pathological stimuli during immobilizing, (3) simulate cartilage undergoing injury, immobilization, and treatments (with/without active growth factors). Specifically, we simulate applications of suramin, recently proposed as a treatment for OA and cartilage degeneration [5].

METHODS

Constitutive model. We utilize our established constitutive model of cartilage to predict tissue and intra-tissue mechanics under deformation [6].

Anisotropic growth. We employ anisotropic, through-thickness volume growth (TVG) to model degeneration and thinning of cartilage [7].

Mechanical stimuli - homeostasis and adaptation. We consider that pathological levels of mechanical stimuli cause perturbations to tissue-homeostasis. They drive a signaling pathways biochemical model using a stimulus function $f_{\rm S}(\sigma_i(\tau),\sigma^{\rm L}_{i,\rm hom}(\tau),\sigma^{\rm H}_{i,\rm hom}(\tau))$ that is a function of mechanical stimuli $(\sigma_i(\tau))$ and salient homeostatic thresholds $(\sigma^{\rm L}_{i,\rm hom}(\tau),\sigma^{\rm H}_{i,\rm hom}(\tau))$ with L/H representing immobilizing/overloading, and $i\in\{\rm sh,1\}$ representing maximum shear and first principal stresses, respectively. The function $f_{\rm S}$ is well-shaped (see Fig. 1(a)) and adapts with time (τ) (see Fig. 1(b)) to reflect adaptation of homeostatic thresholds.

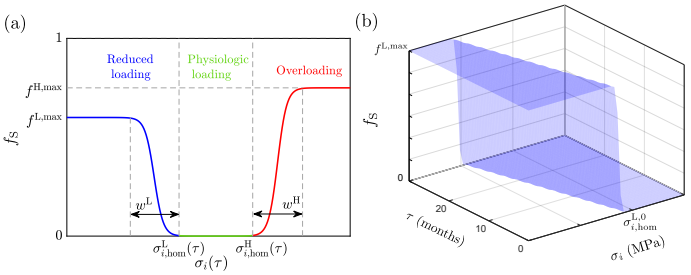

Figure 1: The mechanical stimuli function (a) ranges from reduced loading to overloading region, and (b) adapts pathological stimuli.

We define a piecewise continuous stimulus function $f_{\rm S}$ as,

$$f_{\rm S}=\begin{cases} f^{\rm L,max}, & \text{if } \sigma_i(\tau)<\sigma^{\rm L}_{i,\rm hom}(\tau)-w^{\rm L} \\ f^{\rm L}, & \text{if } \sigma^{\rm L}_{i,\rm hom}(\tau)-w^{\rm L}\le\sigma_i(\tau)<\sigma^{\rm L}_{i,\rm hom}(\tau) \\ 0, & \text{if } \sigma^{\rm L}_{i,\rm hom}(\tau)\le\sigma_i(\tau)<\sigma^{\rm H}_{i,\rm hom}(\tau) \\ f^{\rm H}, & \text{if } \sigma^{\rm H}_{i,\rm hom}(\tau)\le\sigma_i(\tau)<\sigma^{\rm H}_{i,\rm hom}(\tau)+w^{\rm H} \\ f^{\rm H,max}, & \text{if } \sigma_i(\tau)\ge\sigma^{\rm H}_{i,\rm hom}(\tau)+w^{\rm H} \end{cases}, \tag{1}$$

where $f^{\rm L}$, $f^{\rm H}$ are sigmoidal functions, $w^{\rm L}$, $w^{\rm H}$ control the width of sigmoidal transition regions, $f^{\rm L,max}, f^{\rm H,max}\in(0,1]$ are constants. During

normal physiological loading, the tissue is in homeostasis and $f_S = 0$.

The (lower) homeostatic threshold $\sigma^{L}_{i,hom}(\tau)$ adapts during immobilizing ($\sigma_i(\tau) \leq \sigma^{L}_{i,hom}(\tau)$) as,

$$\sigma^{L}_{i,hom}(\tau) = \begin{cases} \sigma^{L}_{i,hom}(\tau = 0), & \text{if } \tau \leq \tau^{L}_{del} \\ \left(\int_{\tau-\tau^{L}}^{\tau} \sigma_i(\tau)\, d\tau \right) / \tau^{L}, & \text{if } \tau > \tau^{L}_{del} \end{cases}, \quad (2)$$

where τ^{L}_{del} represents a time-delay for homeostatic adaptation to begin and τ^{L} is a temporal averaging period for adaptation of homeostatic thresholds.

Biochemical signaling pathways. During pathological loading, the stimulus function is activated ($f_S > 0$) and drives the conversion of latent pro-inflammatory cytokines $\hat{c}_{\ell p}$ and latent growth factors $\hat{c}_{\ell\beta}$ to active forms $\hat{c}_p$ and $\hat{c}_\beta$, respectively. Activated cytokines, in turn, upregulate collagenases $\hat{c}_{ca}$ and aggrecanases $\hat{c}_{ag}$ that degrade collagen $\hat{m}_{co}$ and proteoglycan $\hat{m}_{pg}$, respectively. TIMPs $\hat{c}_i$ inhibit collagenases and aggrecanases naturally, and suramin $\hat{c}_{sm}$ prevents their uptake by cells in many tissues, cf. [5]. With the evolution of $\hat{m}_{co}$ and $\hat{m}_{pg}$, cartilage thickness and intra-tissue stresses changes, and thus, the mechanical stimuli evolve.

Numerical studies. We implement our chemo-mechano-biological framework in FEBio. We exercise our model considering a single, linear hexahedral element representing cartilage, and apply boundary conditions simulating unconfined compression. We complete three studies: (i) homeostatic adaptation during joint immobilization, (ii) treatment with suramin during immobilizing following injury, and (iii) treatment with suramin and growth factors during immobilizing following injury. We predict the chemo-mechano-biological evolution of cartilage over 24 months.

RESULTS

(i) Homeostatic adaptation during joint immobilization. We performed simulations varying $\tau^{L} = 5,\ 10$, and 15 months to fit experimental data on cartilage thinning during immobilization over 24 months [8], see Fig. 2. Before immobilizing ($\tau < 0$), cartilage is in homeostasis, i.e. the evolution of all constituents is in equilibrium and $f_S = 0$. At $\tau = 0$, we begin immobilizing such that the current maximum shear stress is less than the lower homeostatic threshold, i.e. $\sigma_{sh} \leq \sigma^{L}_{sh,hom}$ and thus f_S increases. Adaptation of homeostatic thresholds to pathological loading follows depending on time averaging period τ^{L} following (2), see Fig. 2(a). The upper threshold $\sigma^{H}_{sh,hom}$ for physiologic loading remains fixed. As the lower homeostatic threshold $\sigma^{L}_{sh,hom}$ adapts towards the current maximum shear stress σ_{sh}, f_S approaches zero, see Fig. 2(b). Active growth factors and pro-inflammatory cytokines increase when f_S is elevated in the beginning, but goes back to zero once f_S returns to zero, see Fig. 2(c). With $\tau^{L} = 15$ months, numerical results for the evolution of cartilage thickness fit experimental data obtained *in vivo*, see Fig. 2(d).

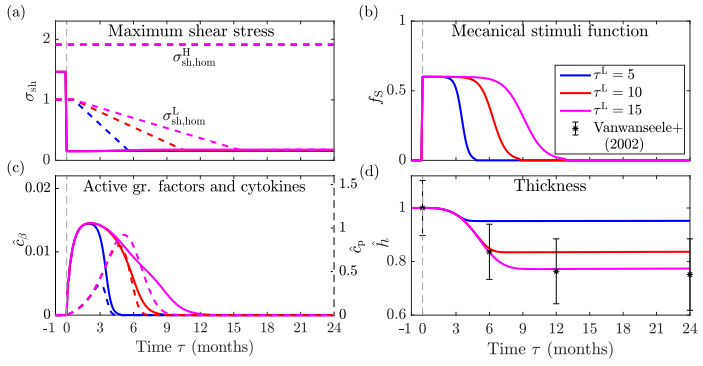

Figure 2: Evolution of intra-tissue mechanics as cartilage evolves during immobilizing with varying time averaging τ^{L}: (a) maximum shear stress (solid and dashed lines represent current stress and homeostatic thresholds resp.), (b) mechanical stimuli function, (c) activated biochemical species (solid and dash lines represent active growth factors and pro-inflammatory cytokines, resp.), and (d) cartilage thickness.

(ii) Treatment with suramin during immobilizing following injury. We performed simulations of healthy cartilage experiencing a high-impact injury at $\tau = 0$ month, followed by immobilizing for six months. Post injury, cartilage receives treatments with suramin for 6, 12, 18, and 24 months. Cartilage looses functional collagen and living chondrocytes due to injury. The loss of chondrocytes causes latent growth factors to drop initially, but then increase thereafter due to activation of growth factors during immobilizing, and finally reach equilibrium as immobilizing ends after six months. Cartilage thickness recovers modestly to 77% and 78% if suramin is applied for six and 24 months, respectively (results not shown).

(iii) Treatment with suramin and growth factors during immobilizing following injury. We repeated the simulations in study (ii) but with different applications of active growth factors, i.e. maintaining constant level of $\hat{c}^{const}_\beta = 0.01,\ 0.02$, and 0.03. After 24 months, cartilage thickness is 87% with $\hat{c}^{const}_\beta = 0.03$ compared to 77% without growth factors (Fig. 3(a)). With the application of active growth factors, chondrocytes promote production of structural constituents and proliferation. Total type II collagen recovery is 32% (Fig. 3(b)) and living chondrocytes are almost fully recovered during highest concentration of applied active growth factors and suramin (Fig. 3(c)). Latent growth factors also see a seven-fold increase with treatment versus without active growth factors (Fig. 3(d)).

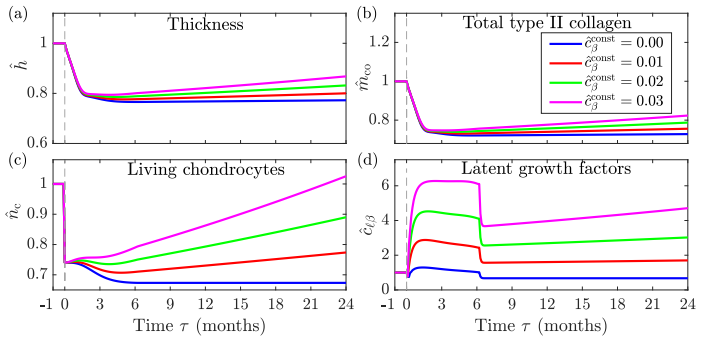

Figure 3: Cartilage evolving in injury and recovery with suramin for different dose of active growth factors. (a) Thickness, (b) Total type II collagen, (c) Living chondrocytes, and (d) Latent growth factors.

DISCUSSION

We implemented our chemo-mechano-biological framework for cartilage, including complex chemical and mechanobiological mechanisms resulting from pathological mechanical loading, into FEBio to facilitate 3-D finite element simulations. Our simulations illustrate the novel features of adaptation to pathological mechanical stimuli using two parameters, a time delay and a time averaging period, and successfully fit thinning of cartilage measured experimentally [8]. Our predictions show that the use of suramin alone to treat OA or thinning of cartilage after injury and immobilization may be ineffective. However, additional predictions indicate that the use of growth factors in addition to suramin may provide significant recovery of cartilage thickness after injury.

Limitations and outlook. We considered only a subset of known signaling pathways [9]. In studies (ii) and (iii), we considered growth factors as a combination of numerous growth factors in cartilage, although some may result undesired changes to homeostasis. We aim to leverage our chemo-mechano-biological framework in FEBio for patient-specific analyses, enabling advanced understanding of pathological changes due to biomechanical factors, improved clinical diagnostics and therapies, and new methods for non-invasive diagnosis and pre-/post-operative decisions.

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