

Tuning tissue growth with scaffold degradation in enzyme-sensitive hydrogels: a mathematical model

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Despite tremendous advances in the field of tissue engineering, a number of obstacles remain that hinder its successful translation to the clinic. One challenge that relates to the use of cells encapsulated in a hydrogel is identifying a hydrogel design that can provide an appropriate environment for cells to successfully synthesize and deposit new matrix molecules while providing a mechanical support that can resist physiological loads at the early stage of implementation. A solution to this problem has been to balance tissue growth and hydrogel degradation. However, identifying this balance is difficult due to the complexity of coupling diffusion, deposition, and degradation mechanisms. Very little is known about the complex behavior of these mechanisms, emphasizing the need for a rigorous mathematical approach that can assist and guide experimental advances. To address this issue, this paper discusses a model for interstitial growth based on mixture theory, that can capture the coupling between cell-mediated hydrogel degradation (i.e., hydrogels containing enzyme-sensitive crosslinks) and the transport of extracellular matrix (ECM) molecules released by encapsulated cells within a hydrogel. Taking cartilage tissue engineering as an example, the model investigates the role of enzymatic degradation on ECM diffusion and its impact on two important outcomes: the extent of ECM transport (and deposition) and the evolution of the hydrogel's mechanical integrity. Numerical results based on finite element analysis show that if properly tuned, enzymatic degradation yields the appearance of a highly localized degradation front propagating away from the cell, which can be immediately followed by a front of growing neotissue. We show that this situation is key to maintaining mechanical properties (e.g., stiffness) while allowing for deposition of new ECM molecules. Overall, our study suggests a hydrogel design that could enable successful tissue engineering (e.g., of cartilage, bone, etc.) where mechanical integrity is important.

1. Introduction

Cartilage is a complex tissue composed of a network of collagen fibers and proteoglycan aggregates. The mechanical properties of cartilage are determined by the structure and composition of this network. In particular, the stiffness of cartilage is largely determined by the crosslinking of collagen fibers. This crosslinking is mediated by enzymes, such as lysyl oxidase, which catalyze the crosslinking of lysine residues on collagen molecules. The resulting crosslinks are highly stable and provide a strong mechanical support for the tissue. However, the degradation of these crosslinks by enzymes, such as matrix metalloproteinases (MMPs), can lead to a loss of mechanical integrity and tissue failure. This process is a key feature of many degenerative diseases, such as osteoarthritis and rheumatoid arthritis. Understanding the mechanisms of crosslinking and degradation is therefore essential for the development of effective treatments for these diseases.

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$\frac{D\mathbf{r}}{Dt} = \frac{1}{2} k^0 c_e \frac{\mathbf{r}}{\rho k^0} \quad (2.1)$

a/x

$(E. 1).$

35

a/x

35

$$x \partial r, J \partial \frac{1}{4} \ell J \frac{1}{3} \sqrt{\frac{r_0}{r}}; \quad r_c < r$$

$$D_a \partial r_a, r, J \partial \frac{1}{4} D_a^1 f \partial J, J_0 \partial \left(1 - \frac{r_a}{x \partial r, J \partial} \right); \quad r_a < x < x_c \quad (2.2)$$

$x = x(r,)$

$(, 0)$

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$(, 0) = (1/ (0 1))$

$r \rightarrow r,$

$(, 0)$

$r = r.$

(2.2)

$a < x < x;$

$x < a,$

$x \ll x,$

$(x \rightarrow \infty)$

$a = \frac{\infty}{a}$

E

40

$$r^* = 0.99.$$

.33.

Diffusion-dominated and diffusion-limited systems. Eqs. 5

$$\left(\frac{1}{k^*} - \frac{1}{k} \right) \frac{1}{\tau} = \frac{1}{\tau} \left(\frac{1}{k^*} - \frac{1}{k} \right) \frac{1}{\tau} \quad (E.5)$$

(E.5). B

$$\frac{1}{\tau} \left(\frac{1}{k^*} - \frac{1}{k} \right) \frac{1}{\tau} = \frac{1}{\tau} \left(\frac{1}{k^*} - \frac{1}{k} \right) \frac{1}{\tau}$$

(E.5).

Characterization of the degradation dynamics. A

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(ρ) $\rho = \rho_0 + \rho_1 \cos(kx) + \rho_2 \cos(2kx) + \dots$ (F. 7)

where ρ_0 is the average density, ρ_1 is the amplitude of the first harmonic, and ρ_2 is the amplitude of the second harmonic. The density profile is periodic with a period of $2\pi/k$.

The density profile is shown in Figure 5. The density is constant at ρ_0 for $x < 0$ and $x > 2\pi/k$. In the region $0 < x < 2\pi/k$, the density oscillates between $\rho_0 + \rho_1$ and $\rho_0 - \rho_1$.

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6. Discussion and concluding remarks

In this paper, we have studied the density profile of a fluid in a container. The density profile is periodic with a period of $2\pi/k$.

$$\int_V w_2^T \frac{\partial c_e}{\partial c_e}$$

$$C_{\text{eu}} \frac{1}{4} \sum_1^{\text{\#el}} \int$$

