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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 di cult due to the complexity of coupling di usion, 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 cellmediated 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 di usion 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., sti ness) 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

development of engineered cartilage. nondegradable hydrogels possess a network of cross-links that \mathbb{R} inhibit the diffusion of EC and HC molecules of molecules EC and HC and HC and HC and HC tissue development to the immediate region surrounding the n^{11-13} On the other hand, degradable cross-links may solve contain n^{11-13} and degree contains may solve contain n^{11-13} t_{th} in the short-term, but ultimately leads to the loss of hydrogenesis load capacity (and thus constructed failure), the $(1 - \lambda)$ the neotissue is formed. Solutions have been suggested to address this issue, such as introducing \mathbf{l} introducing as introducing \mathbf{l} \mathbf{r} of the design more complex and harder to predict more complex and harder with the contract theoretical guidance. In contrast to most engineering materials, a major hindrance in \mathcal{A} hydrogen design has been the lack of the celd(e)celd(detection) and $p(3(-319.3(-6)(-5.9(-6)(-5.9(-6)(-280.3(-34)(-6)(-340.338)-46))$

the hydrogen mesh size via its cross-link density through the cross-link density through the \mathcal{A} \mathbf{r} \mathbf{r} : \mathbf{r}^{35}

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 \mathbf{e} by the domain during during during during during growth. This quantity is calculated by ensuring stress-free boundary stress-free boundary stress-free boundary stress-

enables and optimized combination of $\mathbb{E}\mathbb{C}$ growth and $\mathbb{E}\mathbb{C}$ mechanical integrity in time.

5.1 Degradation around a single cell

continuity of the construction of the construction \mathbf{I} integrity. For this, we have \mathbf{I} use techniques of numerical homogenization that allows \mathbf{u} allows us to estimate the overall stress–strain response of the unit cell

p 1 **c** $\mathbf{L} \cdot \mathbf{C} = \begin{pmatrix} 1 \end{pmatrix} \cdot \mathbf{L} \cdot \mathbf{EC}$ $\left(\begin{array}{ccc} \bullet & 1 & \bullet \end{array}\right)$ are also depicted at the characteristic times during the character construction $\mathbf{1}$ by $\mathbf{1}$ \bullet becomes compared to degrade the slow compared to degrad the $(F_{\geq 0}, 7)$ and b), results show that the mechanical integrity of construct monotonically drops with time until it completely dissolves (% = 0). A closer look at the ultrastructure evolution c_1 shows that regardless of the sharp shows and speed of the s \overline{BC} degree behind and is unable behind and is unable behind and is unable behind and is unable is unable set of \overline{AC} \mathbf{r}_0 produce a well-connected phase before the hydrogen phase before the hydrogen \mathbf{r}_0 degrades. Interestingly, we note that a sharper degradation of \mathbb{R} from the faster loss in construction \mathcal{A} and \mathcal{A} phenomenon \mathcal{A} phenomenon \mathcal{A} that can be attributed to the fact that sharper from \mathbf{F}_2 $r = 1$ and $r = \left(\mathbf{F}_z \cdot \mathbf{5}, \mathbf{F}_z \cdot \mathbf{F}_z\right)$. When EC deposits fast (relative to degradation) one predicts that it can be interested to degrade the interest of α reach connectivity before the hydrogel is completely degraded. As a consequence, even in the case of a wide degradation from \mathcal{A} $t \sim 1$ suggests that the construction of completely lose not completely lose not completely lose not completely lose its mechanical integrity. In the integrity and time integrity. In for which none of the phases are connected, their mechanical

6. Discussion and concluding remarks

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 c density systems. Interestingly, experimental studies $\frac{1}{2}$ have $\frac{61}{2}$ shown that strategies based on $\mathbf{I} = \begin{pmatrix} 1 & 1 \end{pmatrix}$ degrade on $\mathbf{I} = \begin{pmatrix} 1 & 1 \end{pmatrix}$

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

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 $C_{\rm eu}$ ¼ $\sum_{ }^{\# \rm el}$ 1 ð $37 \cdot 1$, $\sqrt{7}$ and $\sqrt{2}$. E_{xt}, Theory of $\sqrt{2}$ ρ and γ and ρ and γ is Γ