Tuning Reaction and Diffusion Mediated Degradation of Enzyme-Sensitive Hydrogels

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a crosslinked solid polymer (i.e., ßuorescent regions) to a soluble polymer where the polymer chains rapidly diffuse out into the bath (i.e., nonßuorescent regions). This critical point is correlated to the degree of network connectivity during hydrogel formation (i.e., the gel point), which has been described for an ideal network using a statistical network formation model (Equation (S2), Supporting Information).[9] Experimentally, we observe a degradation front where the region of the hydrogel adjacent to the enzyme source is completely degraded, which advances along the length of the hydrogel, away from the

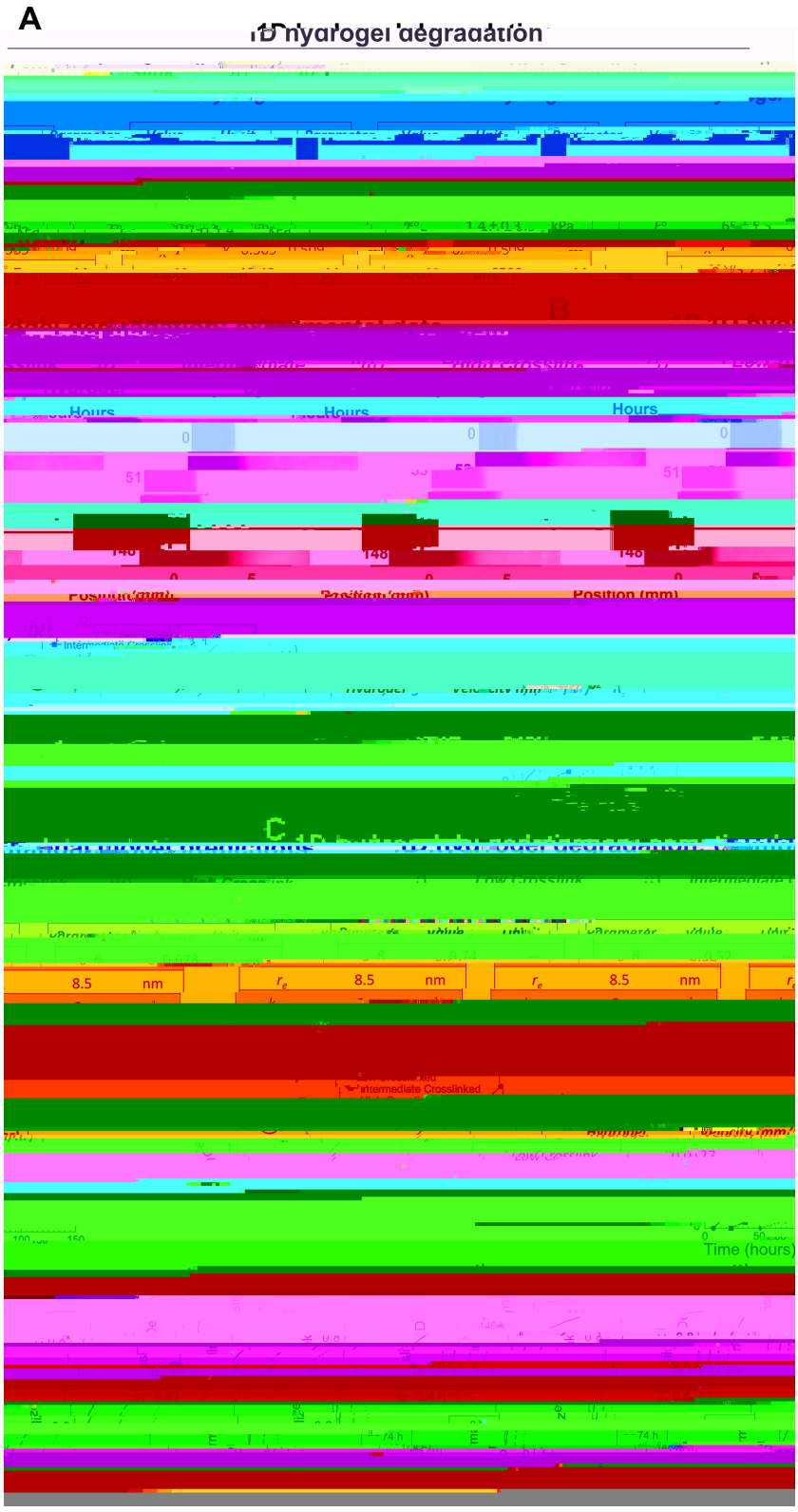

Figure 1. [illegible] (Ce),

crosslinked hydrogel case, a wide front that propagates quickly is observed resulting in an overall decrease in the crosslink density of the bulk hydrogel for Þnite distances (e.g., at 5 mm) (Figure 1Cvi). In the intermediate and high crosslink hydrogel cases, a sharp front is observed and the initial bulk hydrogel properties are largely maintained (Figure 1Cvii,viii). We demonstrate that the model is able to capture the propagating front and front width, especially for the intermediate and high crosslink hydrogel cases (Figure S4, Supporting Information). However due to limitations in the experimental set-up, the ßuorescence in the low crosslinked hydrogel does not directly correlate to crosslink density and therefore the front width could not be matched to the model (see Figure S4, Supporting Information). Nonetheless, the model can be used to describe the spatiotemporal changes in crosslink density for each of the three hydrogel cases.

We next extended the experimental and computational analysis to 3D, using a low and high crosslinked hydrogel with formulations given in Table S1 and initial properties in Figure 2A. Experimentally, we developed a Òcell-mimeticÓ platform (Scheme 1C) using collagenase-loaded PLGA microparticles encapsulated in the enzyme-sensitive PEG hydrogel. Prior to encapsulation, release of collagenase from the microparticles was characterized by a rapid burst release followed by a slow yet sustained release of enzyme

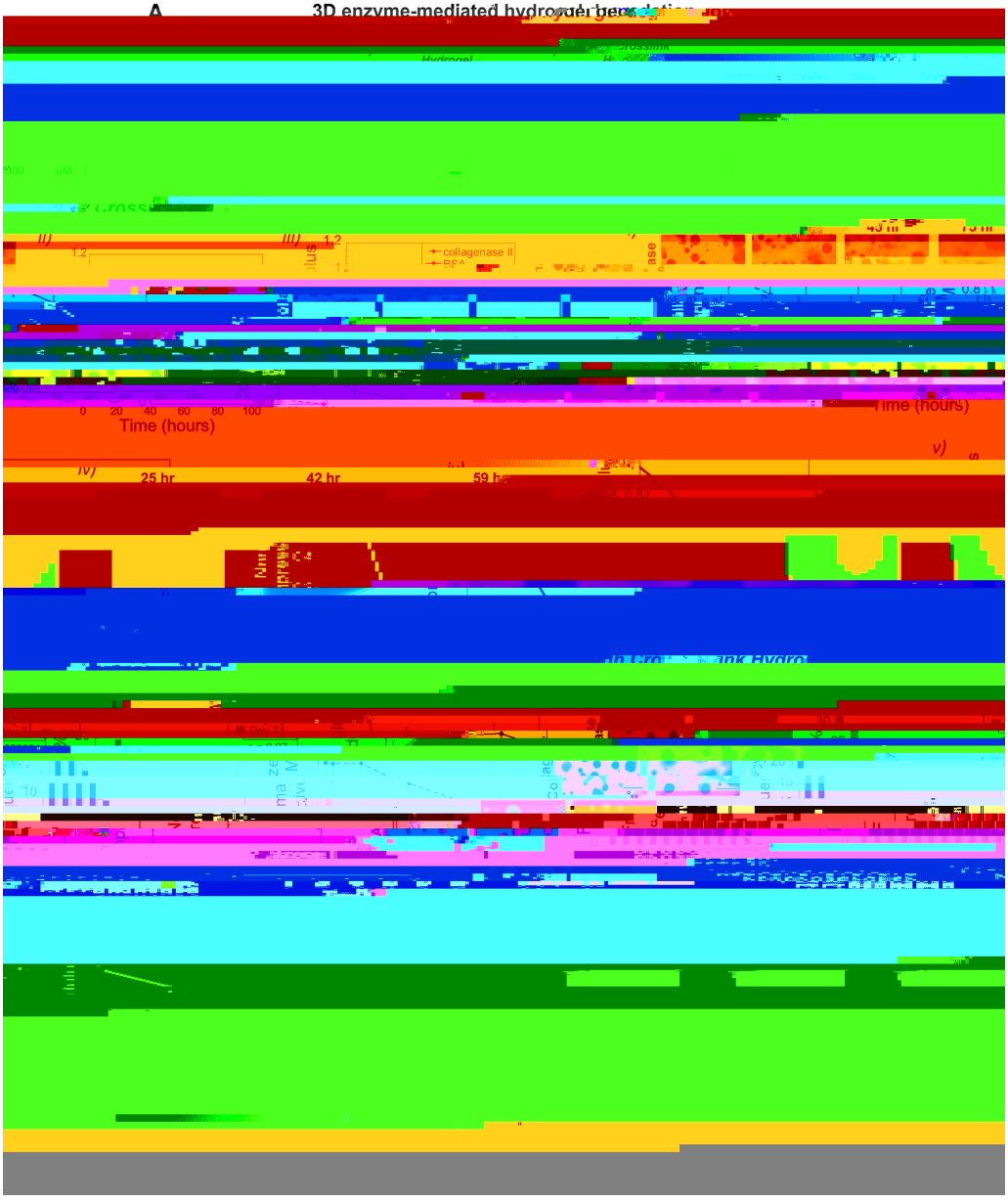
A
3D enzyme-mediated hydrogel
collagenase II
Time (hours)
Time (hours)
25 hr
42 hr

Figure 2.

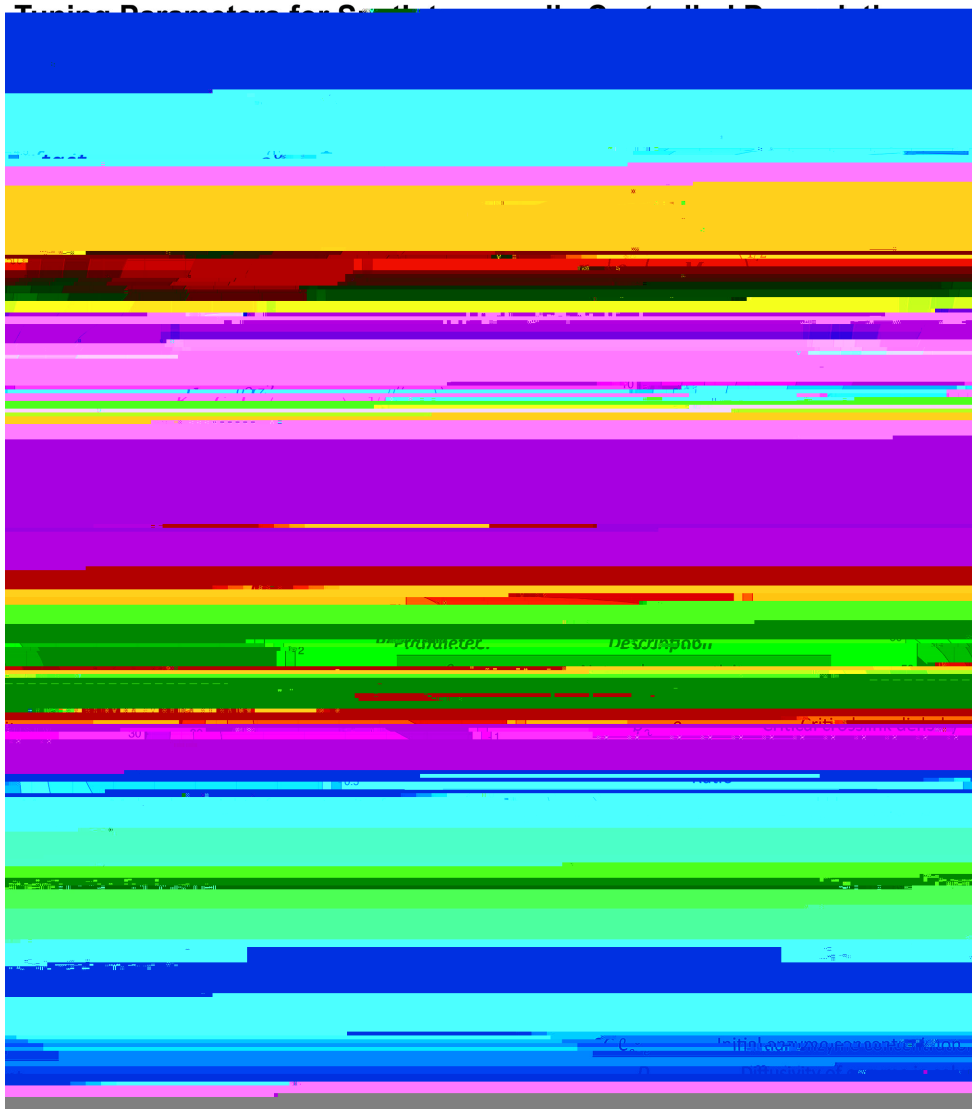

Figure 3.

(Figure S5, Supporting Information). This release proÞle, as a function of time, was input into the computational model to demonstrate the modelÕs capability of incorporating complex enzyme release proÞles. Hydrogels were encapsulated with either collagenase-loaded microparticles or BSA-loaded microparticles and the spatiotemporal degradation behavior and macroscopic properties were evaluated over time. In the low crosslinked hydrogel, bulk degradation was evident by a rapid and overall decrease in hydrogel ßuorescence (Figure 2Bi,ii). Further, the compressive modulus (Figure 2Biii) decreased exponentially while the hydrogel wet weights (Figure S6, Supporting Information) increased over time, consistent with the occurrence of bulk degradation. Simulations showed similar Þndings with respect to a diffuse boundary surrounding the cell-mimetic and a rapid loss in the compressive modulus of the bulk hydrogel (Figure 2Biv,v). On the contrary in the high crosslink hydrogel, degradation appeared to be restricted more locally in the region immediately surrounding the cell-mimetic. This observation is supported by the following results: (a) the hydrogel ßuorescence was largely maintained over time, but the size of the non-degradescent regions (originally correlating to the microspheres, which exhibited a distribution of sizes) increased statistically with time (Figure 2CiÐiii), (b) the compressive modulus decreased over time, but the change was gradual (Figure 2Civ), and (c) hydrogel wet weights were maintained over time (Figure S6, Supporting Information). Simulations showed similar results with a relatively sharp boundary surrounding the cell-mimetic and a modulus that gradually decreased over time (Figure 2Dv,vi). In addition, dual labeling of the hydrogel and enzyme qualitatively showed the spatiotemporal distribution of the hydrogel and enzyme over time, further supporting the above observations (Figure S7, Supporting Information).

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Supporting Information

Acknowledgements

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