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# Localized Enzymatic Degradation of Polymers: Physics and Scaling Laws

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# Localized enzymatic degradation of polymers: physics and scaling laws

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Biodegradable polymers are naturally abundant in living matter and has led to great advances in controlling environmental pollution due to synthetic polymer products, harnessing renewable energy from biofuels and in the field of biomedicine. One of the most prevalent mechanisms of biodegradation involves enzyme-catalysed depolymerization by biological agents. Despite numerous studies dedicated to understanding polymer biodegradation in different environments, a simple model that predicts the macroscopic behavior (mass and structural loss) in terms of micro-physical processes (enzyme transport and reaction) is lacking. An interesting phenomena occurs when an enzyme source(released by a biological agent) attacks a tight polymer mesh that restricts free diffusion. A fuzzy interface separating the intact and fully degraded polymer propagates away from the source and into the polymer as the enzymes diffuse and react in time. Understanding the characteristics of this interface will provide crucial insight into the biodegradation process and potential ways to precisely control it. In this work, we present centro-symmetric model of biodegradation by characterizing the moving fuzzy interface in terms its speed and width. The model predicts that the characteristics of this interface are governed by two time scales, namely the polymer degradation and enzyme transport times, which in turn depend on four main polymer and enzyme properties. A key finding of this work are simple scaling laws that can be used to guide biodegradation of polymers in different applications.

Biodegradation of polymers is the process of breakdown of the polymeric network by biological agents into components that naturally blend into the environment. The biological agents can be macro-organisms that digest the polymer through mechanical and chemical processes or micro-organisms that degrade and consume the polymer by secreting enzymes or other by-products like acids [1, 2]. Enzymes are biological catalysts that have the ability to cleave polymer chains. For instance, fungi have been found to break down natural polymer networks such as wood and tissues [3]. A notable example is the wood-decay fungus that has the special ability to break down lignin, cellulose, and hemicellulose three inert but essential polymers in the plant cell wall [4]. Detailed studies of the degradation process initiated by these fungi have led to great progress in the bioenergy industry in breaking down biomass, the largest source of renewable energy, using enzyme technology [5]. Digestive processes in most organisms are mediated by digestive enzymes that degrade natural polymers like protein, abundantly found in food sources [6]. Perhaps the most widely understood meaning of biodegradation is in relation to synthetic polymers or plastics that raise serious environmental concerns. Many advances have been made in altering the chemical composition of synthetic polymers to make them more suitable for biodegradation in the natural environment [7]. Biodegradable polymers have also found their way into biomedicine through implantable biomedical devices [8, 9], hydrogel scaffolds for tissue regrowth [10–12], and polymeric drug delivery vehicles [13–15].

Polymer degradation is generally measured macroscopically in terms of the overall loss in polymer mass with

time for different environmental conditions. At the microscopic scale however, multiple physical processes occur simultaneously. The mechanism of enzymatic biodegradation broadly includes, enzyme diffusion from a biological source and an enzyme-catalyzed reaction (aerobic or anaerobic) that causes depolymerization. Due to restricted enzyme diffusion through the polymer mesh, an interface between the depolymerized fluid and the intact solid polymer is formed and set in motion as the enzymatic reaction proceeds. This type of a moving interface phenomenon has been widely observed with surface erosion behavior in biodegradable polymers due to water diffusion and progressive hydrolysis [16]. To better understand the factors that influence the evolution of polymer degradation, it is important to develop simple models and scaling laws based on multiple physical processes that bridge micro and macrophysical behavior. The focus of this work therefore, is developing a centro-symmetric model of polymer biodegradation by enzymes, based on a reaction-diffusion system. We also aim to understand how the scaling of polymer structure and enzyme size/activity affect the overall degradation behavior, that we will see is suitably characterized by the speed and width of the resulting moving interface.

Falling under the category of *moving boundary problems*, these phenomena are mathematically challenging to model, often requiring numerical methods [17]. Under suitable approximations, analytical solutions do exist for infinite and semi-infinite domains. For instance, the classical example of the propagating melt-freeze interface, or Stefan problems, has been extensively studied for simple geometries in 1D [18] and isotropic spheres [19–21] with analytical solutions. In another general class of problems, Hermans [22] developed a closed form solution for systems where the diffusing molecules (ex. cop-

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per ions) get immobilized after reacting with another medium (ex. cellulose xanthate) thereby propagating a sharp moving interface. An excellent review on different scenarios and strategies involving moving boundary problems in the context of diffusion can be found in the book by Crank [23]. In all the above examples, the interface is clear and sharp in separating two different phases. But, the system under investigation here often produces a fuzzy interface such that the boundary between the degraded and non-degraded regions has a finite width where both free enzymes and weak polymer cross-linking exist [24, 25]. This type of interface has been modelled analytically in 1D for hydrolytic degradation of biodegradable polymers characterized by erosion rate and width that determine the nature of degradation (bulk or surface erosion) [26]. Such a simple model however, has not been developed for enzymatic biodegradation whose chemistry and reaction kinetics vary with different enzymes [27]. In this work, we therefore present a one-dimensional centrosymmetric model of enzymatic biodegradation of solid polymers characterized by the evolving cross-linking density of the network instead of polymer water solubility.

Let us consider an enzyme source in the shape of a sphere encapsulated in a bio-degradable polymer (Fig. 1). The polymer is characterized by its cross-link den-

sity,  $\rho$ , and mesh size,  $\xi$ , which is typically of the order 10-100 nm. Since the sizes of enzyme molecules are in the same order of magnitude, it enables them to penetrate the mesh once released from the source. In this work, we characterize the presence of enzymes by their concentration,  $c(r, t)$  where  $r$  is the radial distance from the center of the source (Fig. 1). As enzymes diffuse through the polymer, they act as catalysts for polymer degradation, hence reducing the cross-link density and expanding the mesh until the so-called reverse gelation point [28] is reached. This point occurs when  $\rho(r, t) = \rho_c$  and marks the sudden drop in polymer network connectivity and the transition to a fluid-like state. The critical cross-link density,  $\rho_c$ , is usually identified by the ratio,  $1/\beta$  of minimum network connections needed for structural integrity [25, 29], such that  $\rho_c = \rho_0/\beta$ , given an initial non-degraded cross-link density,  $\rho_0$ . The coupled reaction-diffusion process can be described by Fick's law of diffusion for the enzymes and enzyme-mediated polymer degradation kinetics as

$$\frac{\partial c}{\partial t} = \frac{1}{r^2} \frac{\partial}{\partial r} \left( r^2 D \frac{\partial c}{\partial r} \right) \quad (1a)$$

$$\frac{\partial \rho}{\partial t} = -\kappa \rho c \quad (1b)$$

where the equations are written in radial coordinates due to the problem's geometry. Here  $\kappa$  is the rate constant for degradation and  $D$  denotes the enzyme diffusivity. Importantly, the diffusivity is significantly affected by degradation; before degrading, the polymer mesh resists enzyme transport such that the diffusivity,  $D_s$ , is given by Lustig and Peppas [30] as

$$D_s = D_f \left( 1 - \frac{r_e}{\xi} \right) \quad (2)$$

where  $r_e$  is hydrodynamic radius of the enzyme molecule,  $\xi$  is mesh size of the polymer, and  $D_f$  is the enzyme diffusivity in a fluid given by the Einstein-Stokes equation [31]. This model predicts a low diffusivity,  $D_s$ , when the mesh size is small compared to the enzyme,  $r_e$ , and vice-versa. Once reverse gelation is reached however, the mesh size suddenly diverges and the diffusivity becomes  $D_f$ . Based on this analysis, we assume here that the enzyme diffusivity in the degraded region ( $\rho < \rho_c$ ) is considerably higher than in the solid polymer, i.e.  $D_f \gg D_s$ .

As the enzymes travel away from the source, (seen here as an enzyme reservoir with concentration  $c_0$ ), Eq. (1a) suggests a concentration profile that gradually decreases with distance,  $r$ , as shown in Fig. 1. From the degradation kinetics in Eq. (1b), we see that this causes faster degradation closer to the source where the enzyme concentration is higher. Therefore, reverse gelation will first be reached in the immediate region around the source, at which point the polymer disintegrates into a fluid. Similar to the approach in classical Stefan problems, the spatial domain is now separated into two sub-domains; one where reverse gelation has occurred ( $\rho(r, t) < \rho_c$ ), and the other where the polymer is still intact. Given

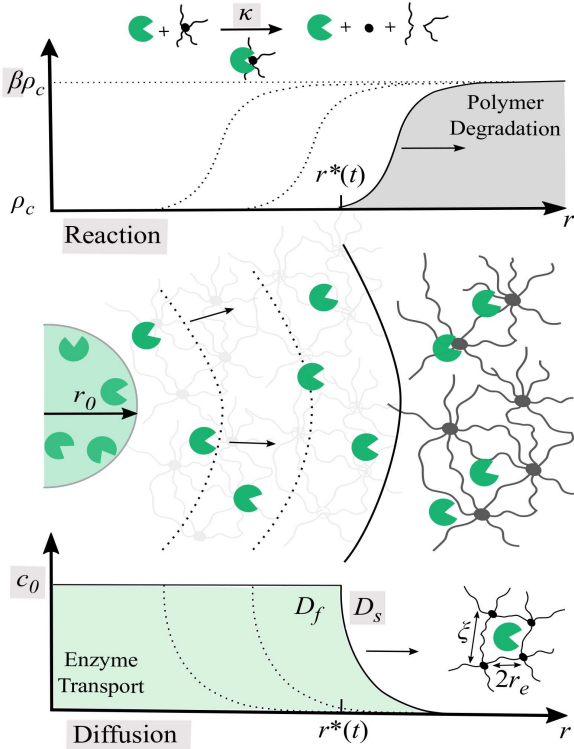


FIG. 1. Schematic illustrating the propagation of a fuzzy interface due to enzyme diffusion and degradation reaction in the biodegradable polymer. The evolution of polymer cross-link density,  $\rho$ , ( $\rho_c$  corresponds to reverse gelation) and enzyme concentration,  $c$ , are illustrated. The highlighted parameters  $\beta$ ,  $\kappa$ ,  $c_0$  and  $D_s$  are the key features of the model.

the considerably high diffusivity,  $D_f$ , in the first region, the enzyme concentration here saturates to that of the source, i.e.  $c(r, t) = c_0$ . Due to centro-symmetry, this results in a spherical interface that expands radially outward separating the fully degraded and the structurally intact polymer regions as shown in Fig. 1. Therefore, the polymer cross-link density at the edge of this interface located at  $r^*(t)$  is equal to  $\rho_c$ . Additionally, the mass of enzymes flowing across the interface should be conserved. Mathematically, these observations can be cast in terms of so-called interface conditions of the form:

$$\rho|_{r^*} = \rho_c \quad \text{and} \quad -D_f \frac{\partial c}{\partial r} \Big|_{r_-^*} = -D_s \frac{\partial c}{\partial r} \Big|_{r_+^*} \quad (3)$$

where the term  $-D\partial c/\partial r$  denotes the mass flux of enzymes. Assuming no permanent deficit at the reaction site, the enzyme concentration profile is continuous across the interface, i.e.  $c(r_+^*, t) = c_0$ .

Since the properties in the fully degraded region ( $r < r^*$ ) are trivial ( $c = c_0, \rho < \rho_c$ ), we bring our attention to the solid polymer region whose inner boundary is  $r = r^*(t)$ , and outer boundary that is assumed sufficiently far that the enzyme flux vanishes, i.e.  $-D_s \partial c/\partial r|_{r \rightarrow \infty} = 0$ . Of interest in this problem is the speed,  $v = dr^*/dt$ , at which the fluid-polymer interface travels away from the source and the extent (or width) of the degradation region from this interface. For this, we aim to solve Eq. (1) by first introducing a new variable  $C = cr$ , changing its original form to the one-dimensional diffusion equation,  $\partial C/\partial t = D\partial^2 C/\partial r^2$ . Now, using the transformation,  $R = r - r^*(t)$ , to represent the solid polymer region, we anticipate and assume a travelling wave type solution of the form,  $C(R) = C_0 e^{-kR}$ , where  $C_0 = c_0 r^*$  should satisfy the continuity in the concentration profile and  $k$  is a parameter to be determined. Substituting for  $c = C/r$  in Eq. (1) and integrating Eq. (1b) subject to interface and boundary conditions, we obtain the following solutions (see supplemental information [32] for more details)

$$c(R) = \begin{cases} c_0 & R \leq 0 \\ c_0 r^*/r e^{-kR} & R \geq 0 \end{cases} \quad (4a)$$

$$\ln(\rho/\rho_c) = \ln \beta \left( 1 - \frac{1 + kr^*}{1 + kr} e^{-kR} \right) \quad R \geq 0 \quad (4b)$$

where  $R \geq 0$  represents the intact polymer region and  $k^2 = \kappa c_0/(D_s \ln \beta)$ . The value of  $k$  was obtained from the condition that at large distances ahead of the interface, the enzymes have not diffused yet leaving the solid polymer intact with its initial cross-link density, i.e.  $\rho(R \rightarrow \infty) = \beta \rho_c$ . As is the case with most travelling wave solutions, there is a transient state due to sudden initiation of interface movement when reverse gelation is first reached in the immediate region of the source. This transient state attenuates in time and so we focus here only on the solution of the travelling wave.

Based on the above expression for  $k$ , that indeed appears extensively in Eq. (4), we identify two time scales,  $\tau_d$  and  $\tau_t$ , that characterize the polymer degradation and

enzyme transport respectively

$$\tau_d = \frac{\ln \beta}{\kappa c_0} \quad \text{and} \quad \tau_t = \frac{L^2}{D_s} \quad (5)$$

The degradation time,  $\tau_d$ , is the time required to completely degrade the polymer when subjected to an enzyme concentration,  $c = c_0$ . The transport time,  $\tau_t$ , is interpreted as the time needed by the enzymes to diffuse a distance  $L$  through the solid polymer. The competition between transport and degradation is then characterized by the index

$$\gamma = \sqrt{\frac{\tau_t}{\tau_d}} = \sqrt{\frac{L^2}{D_s} \frac{\kappa c_0}{\ln \beta}} \quad (6)$$

When  $\gamma > 1$ , enzyme diffusion is the rate limiting process, and the system is reaction-dominated. In contrast, when  $\gamma < 1$ , degradation becomes the rate limiting process.[33]

Let us now define the interface width,  $w$ , as the distance between the interface position ( $\rho(r^*, t) = \rho_c$ ), and the point at which the polymer is 99% intact, i.e.  $\rho(r^* + w, t) = 0.99\beta\rho_c$ . The interface width provides crucial information regarding the nature of degradation ranging from surface erosion for small widths to bulk degradation for large widths. Substituting Eq.(4a) in Eq. (1a) to obtain speed and using the definition of interface width on Eq. (4b), we find that they must satisfy the equations

$$v = v_d \left( \frac{\bar{r}\gamma}{1 + \bar{r}\gamma} \right) \quad (7a)$$

$$\left( 1 + \frac{\bar{w}\gamma}{1 + \bar{r}\gamma} \right) e^{\bar{w}\gamma} = K \ln \beta \quad (7b)$$

where  $K = -1/\ln(0.99)$ ,  $v_d = L/\sqrt{\tau_d \tau_t}$ ,  $\bar{r} = r^*/L$  and  $\bar{w} = w/L$ . As the interface moves away from the source ( $\bar{r} \rightarrow \infty$ ), the speed and width of the interface reach their asymptotic values given by:

$$v = v_d = L \sqrt{\frac{D_s}{L^2} \frac{\kappa c_0}{\ln \beta}} \quad (8a)$$

$$\bar{w} = \frac{1}{\gamma} \ln(K \ln \beta) = \sqrt{\frac{D_s}{L^2} \frac{\ln \beta}{\kappa c_0}} \ln(K \ln \beta) \quad (8b)$$

This provides important scaling relationships between interface characteristics and the four parameters  $\beta$ ,  $\kappa$ ,  $c_0$ , and  $D_s$ . We further note that Eqs. (8a) and (8b) describe the speed and width of a planar interface propagating in one dimension (see supplementary information for specific details). Eq. (8b) shows that the interface width,  $w$ , is inversely proportional to the index  $\gamma$ . In other words, diffusion-dominated systems ( $\gamma < 1$ ) are characterized by wider transitions from fluid to intact solid polymer (Fig. 2a). By contrast, reaction-dominated systems ( $\gamma > 1$ ) display sharper transitions (Fig. 2b). Interestingly, Eq.

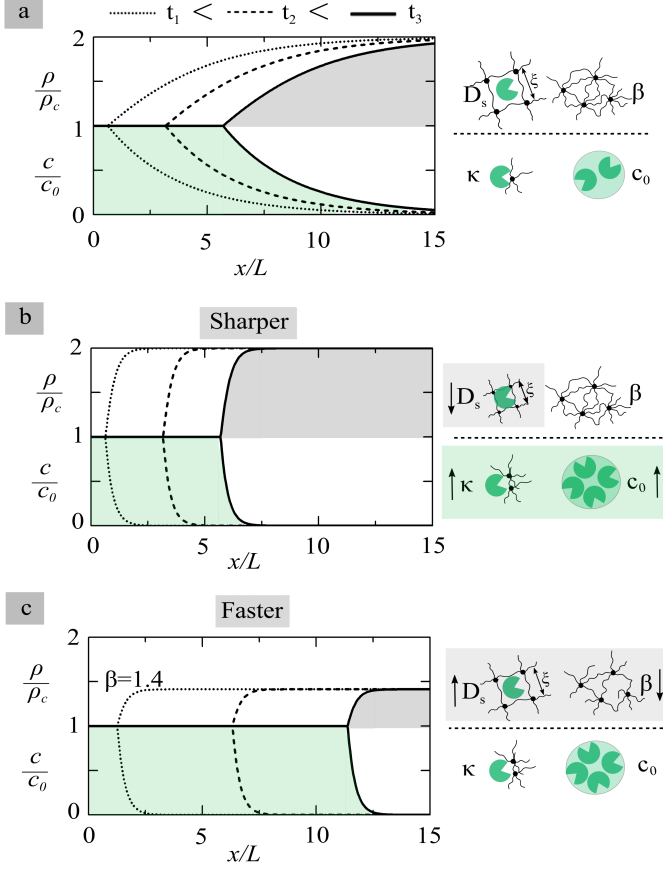


FIG. 2. Spatio-temporal degradation and enzyme profiles illustrated with (a)  $\tau_t = 1$  s,  $\beta = 2$ ,  $c_0 = 1$  M and  $\kappa = 0.07$   $M^{-1}s^{-1}$ , which gives  $\gamma = 0.32$ , (b) Sharper interface with same width as 2a using  $\tau_t = 10$  s,  $c_0 = 2$  M and  $\kappa = 0.35$   $s^{-1}$  which gives  $\gamma = 3.16$ , and (c) Faster interface with same width as 2b using  $\beta = 1.4$  and  $\tau_t = 5$  s. The distance,  $x = r - r'$ , is normalized to the length scale,  $L = r_e$ , where  $r'$  is the radial distance above which the difference from asymptotic value is negligible.

(8) suggests that it is possible to carefully tune the four parameters of the model, in order to individually control the interface width and speed (Fig. 2). For instance we show in Fig. 2a and 2b that, the interface width can be controlled independent of its speed by appropriately tuning  $D_s$ ,  $\kappa$ , and  $c_0$ . Similarly, Figs. 2b and 2c show that it is possible to control the interface speed alone by tuning  $D_s$  and  $\beta$ .

A good summary of these relationships can be obtained by plotting the interface characteristics,  $w$  and  $v$ , in terms of the time scales,  $\tau_t$  and  $\tau_d$  (Fig. 3). Tuning  $\tau_d$  is comparatively more flexible than  $\tau_t$ , as  $\tau_d$  depends on three parameters (see Eq. (5)), while  $\tau_t$  is predominantly governed by the polymer mesh size,  $\xi$ . Thus, using the plots in Fig. 3, one can navigate through interface design space

in order to satisfy application-specific requirements. For example, in tissue engineering, spherical cartilage cells are expected to degrade the surrounding polymeric scaffold to allow growth of new tissue [10, 34]. In this scenario, it is crucial to achieve precise control of the interface characteristics as cartilage cells behave differently depending on the donor. A sharp degradation front and optimal speed are in fact key to preserving the overall mechanical integrity of the tissue [25, 35, 36]. In the case of enzymatic hydrolysis of biomass, enzyme transport is restricted by a tight cellulose mesh leading to slow surface erosion. Since fast degradation is preferable in this case [37], decreasing  $\tau_d$  by increasing enzyme source concentration  $c_0$ , or the reaction rate constant,  $\kappa$ , using different enzyme types [38] are helpful (see Fig. 3). An effective strategy to control  $\tau_t$  is by mediating polymer mesh size via swelling [39, 40]. This is common in hydrogels used for tissue regeneration [41, 42], tissue expansion for plastic surgeries [43], and in biomass containing cellulose [44]. The enzyme size can also be tuned to control  $\tau_t$  and has been explored to achieve faster biomass degradation [45]. In addition to engineering and medical applications, natural processes involving biodegradation can also be understood based on the above scaling laws. For example, wood-rot fungi penetrate and spread by releasing a plethora of enzymes that cause degradation of the natural polymers contained in the plant cell wall. When some host plants are more resistant (low  $\kappa$ ) to the attack from the fungus, it responds by releasing more enzymes (higher  $c_0$ ) to increase the interface speed [46, 47]. Enzymatic biodegradation in the digestive tract of insects is another example where valuable insights into the physical processes are possible [48].

To summarize, we developed an analytical model of enzymatic polymer biodegradation in terms of a moving interface that propagates radially outward, characterized by its width and speed. We found the interface characteristics to depend on two competing time scales namely the enzyme transport and degradation times. These time scales are governed by the polymer mesh size, enzyme source concentration, the enzymatic reaction rate constant, and the polymer network connectivity. Simple scaling laws were derived that can be used to better understand natural processes and tune the interface for engineering and biomedical applications. This will also contribute towards a more fundamental and physical understanding of enzymatic biodegradation in polymers at the micro-scale and provide valuable insights regarding their spatio-temporal macroscopic behavior.

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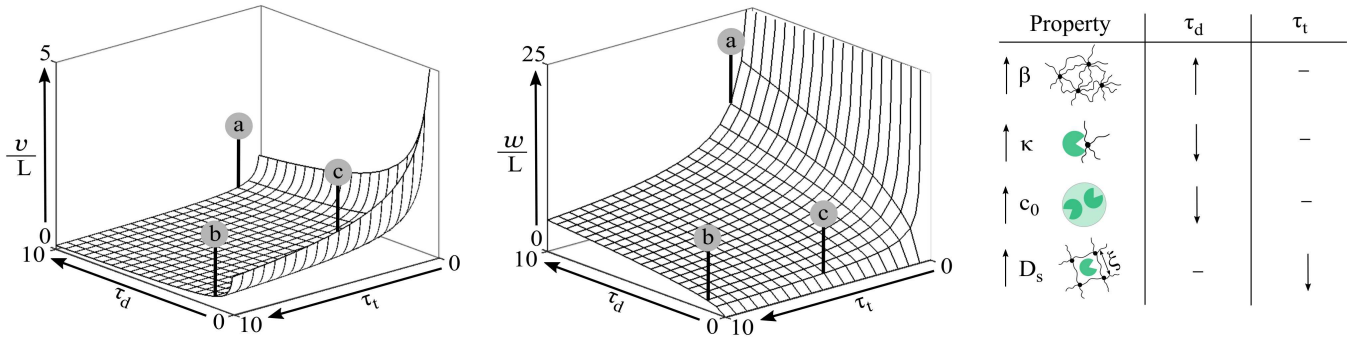


FIG. 3. Plots of interface speed,  $v$  and width,  $w$ , w.r.t degradation time,  $\tau_d$ , and enzyme transport time,  $\tau_t$ . The speed and width corresponding to Figs. 2 a,b and c are marked with bubbles. The trends in  $\tau_d$  and  $\tau_t$  due to network connectivity,  $\beta$ , reaction rate constant,  $\kappa$ , enzyme source concentration,  $c_0$ , and enzyme diffusivity in the polymer mesh,  $D_s$ , are shown.

- [1] P. J. Whitney, C. H. Swaffield, and A. J. Graffham, *International Biodeterioration & Biodegradation* **31**, 179 (1993).
- [2] R. Tsao, T. A. Anderson, and J. R. Coats, *Journal of Environmental Polymer Degradation* **1**, 301 (1993).
- [3] O. Schmidt, *Wood and tree fungi-Biology, protection and use*. (Springer Science & Business Media, 2006).
- [4] K. L. Eriksson, R. A. Blanchette, and P. Ander, *Microbial and Enzymatic Degradation of Wood and Wood Components* (Springer Science & Business Media, 1990).
- [5] S. Horn, G. Vaaje-Kolstad, B. Westereng, and V. G. Eijsink, *Biotechnology for Biofuels* **5**, 45 (2012).
- [6] D. C. Whitcomb and M. E. Lowe, *Digestive diseases and sciences* **52**, 1 (2007).
- [7] E. Bastioli, Catia, *Handbook of Biodegradable Polymers (2nd Edition)*, July (Rapra Technology, 2016) pp. 321–368.
- [8] S. Lyu and D. Untereker, *International Journal of Molecular Sciences* **10**, 4033 (2009).
- [9] J. C. Middleton and A. J. Tipton, *Biomaterials* **21**, 2335 (2000).
- [10] M. P. Lutolf, J. L. Lauer-Fields, H. G. Schmoekel, a. T. Metters, F. E. Weber, G. B. Fields, and J. a. Hubbell, *Proceedings of the National Academy of Sciences of the United States of America* **100**, 5413 (2003).
- [11] F. J. Vernerey, *Biomechanics and Modeling in Mechanobiology* **15**, 259 (2016).
- [12] S. Lalitha Sridhar, M. C. Schneider, S. Chu, G. De Roucy, S. J. Bryant, and F. J. Vernerey, *Soft Matter* (2017), 10.1039/C7SM00423K.
- [13] E. Marshall and D. Windle, *Mathematical Modelling* **3**, 341 (1982).
- [14] A. Göpferich, *Biomaterials* **17**, 103 (1996).
- [15] W. C. Tan, W. Y. Wu, Z. Y. Yan, and G. B. Wen, *Applied Mathematics and Mechanics (English Edition)* **22**, 379 (2001).
- [16] A. Göpferich and R. Langer, *Macromolecules* **26**, 4105 (1993).
- [17] R. M. Furzeland, *IMA Journal of Applied Mathematics (Institute of Mathematics and Its Applications)* **26**, 411 (1980).
- [18] J. M. Hill, *One-dimensional Stefan problems: an introduction*, Vol. 31 (Longman Sc & Tech, 1987).
- [19] F. C. Frank, *Proceedings of the Royal Society A: Mathematical, Physical and Engineering Sciences* **201**, 586 (1950).
- [20] S. Paterson, *Glasgow Mathematical Journal* (1952).
- [21] W. Scott, J. M. Classical, B. S. W. McCue, B. Wu, J. M. Hill, S. W. McCue, B. Wu, and J. M. Hill, *Proceedings of the Royal Society A: Mathematical, Physical and Engineering Sciences* **464**, 2055 (2008).
- [22] J. Hermans, *Journal of Colloid Science* **2**, 387 (1947).
- [23] J. Crank, *The mathematics of diffusion* (Oxford university press, 1979).
- [24] V. Dhote and F. J. Vernerey, *Biomechanics and Modeling in Mechanobiology* **13**, 167 (2014).
- [25] U. Akalp, S. J. Bryant, and F. J. Vernerey, *Soft Matter* **12**, 7505 (2016).
- [26] S. Lyu, R. Sparer, and D. Untereker, *Journal of Polymer Science, Part B: Polymer Physics* **43**, 383 (2005).
- [27] A. Banerjee, K. Chatterjee, and G. Madras, *Materials Science and Technology* **30**, 567 (2014).
- [28] D. R. Miller and C. W. Macosko, *Rubber Chemistry and Technology* **49**, 1219 (1976).
- [29] P. J. Flory, *Principles of polymer chemistry* (Cornell University Press, 1953).
- [30] S. R. Lustig and N. A. Peppas, *Journal of Applied Polymer Science* **36**, 735 (1988).
- [31] C. L. Bell and N. A. Peppas, in *Biopolymers II*, Vol. 122 (Springer, Berlin, Heidelberg, 1995) pp. 125–175.
- [32] See Supplemental Information at [URL] for detailed derivation.
- [33] F. V. Burkersroda, L. Schedl, and A. Göpferich, *Biomaterials* **23**, 4221 (2002).
- [34] F. J. Vernerey, E. C. Greenwald, and S. J. Bryant, *Computer methods in biomechanics and biomedical engineering* **15**, 1197 (2012), arXiv:NIHMS150003.
- [35] V. Dhote, S. Skaalure, U. Akalp, J. Roberts, S. J. Bryant, and F. J. Vernerey, *Journal of the Mechanical Behavior of Biomedical Materials* **19**, 61 (2013), arXiv:NIHMS150003.
- [36] S. Chu, S. L. Sridhar, S. C. Skaalure, F. J. Vernerey,

- and S. J. Bryant, Tissue Engineering Part A , ten.TEA.2016.0490 (2017).
- [37] B. Yang, Z. Dai, S.-Y. Ding, and C. E. Wyman, Biofuels **2**, 421 (2011).
  - [38] L. R. Lynd, Annual Review of Energy and the Environment **21**, 403 (1996).
  - [39] G. I. Mantanis, R. A. Young, and R. M. Rowell, Cellulose **2**, 1 (1995).
  - [40] U. Akalp, S. Chu, S. C. Skaalure, S. J. Bryant, A. Doostan, and F. J. Vernerey, Polymer (United Kingdom) **66**, 135 (2015), arXiv:15334406.
  - [41] G. D. Nicodemus and S. J. Bryant, Tissue Engineering. Part B, Reviews **14**, 149 (2008), arXiv:arXiv:1011.1669v3.
  - [42] S. J. Bryant and F. J. Vernerey, Advanced Healthcare Materials , 1700605 (2017).
  - [43] A. Lendlein and A. Sisson, *Handbook of Biodegradable Polymers: Isolation, Synthesis, Characterization and Applications*, edited by A. Lendlein and A. Sisson (Wiley-VCH Verlag GmbH & Co. KGaA, Weinheim, Germany, 2011).
  - [44] K. W. Lin, M. R. Ladisch, M. Voloch, J. A. Patterson, and C. H. Noller, Biotechnology and Bioengineering **27**, 1427 (1985).
  - [45] R. K. Dasari and R. Eric Berson, Applied Biochemistry and Biotechnology **137-140**, 289 (2007).
  - [46] E. T. Reese, in *The Structure, Biosynthesis and Degradation of Wood* (Springer US, Boston, MA, 1977) pp. 311–367.
  - [47] Á. T. Martínez, M. Speranza, F. J. Ruiz-Dueñas, P. Ferreira, S. Camarero, F. Guillén, M. J. Martínez, A. Gutiérrez, and J. C. Del Río, International Microbiology **8**, 195 (2005).
  - [48] W. R. Terra, C. Ferreira, B. P. Jordao, and R. J. Dillon, in *Biology of the Insect Gut* (Springer Netherlands, Dordrecht, 1996) pp. 153–194.