

Problem Set 1 solutions

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Due: 02/16/06

10 points/problem

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Spring 2006

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1. Listed in the table below are chemical and schematic structures of poly(L-lactide) and a number of derivatives of this polymer.
 - a. Using physicochemical criteria, predict the hierarchy of degradation rates for these materials. Provide a concise but thorough explanation of your ranking. State any assumptions you make.

Experiments reveal that these materials ranked in terms of their rate of degradation have the following order: polycaprolactone (PCL) < poly(L-lactide) (PLLA) < poly(lactide-co-glycolide) (PLGA) < poly(lactide-b-ethylene oxide) (PLA-b-PEO).

This ranking can be rationalized via the chemical and physicochemical factors that control degradation rates: Because all of the materials are comprised of degradable ester linkages, they cannot be differentiated based on purely labile bond differences. The two slowest-degrading materials have a number of factors lowering their degradation rate: They are both semicrystalline. PLLA has the pendant methyl groups creating a steric barrier to the approach of water to the backbone. PCL is more hydrophobic and generally is highly crystalline, because its linear backbone readily packs into extensive crystallites (relative to PLLA). PLGA breaks down more quickly than PLLA because the mixture of lactide and glycolide repeat units in the chain prevents crystallization, and glycolide, lacking the bulky methyl groups, is more readily attacked by water. Lastly, PLA-b-PEO, though crystallizable, are much more quickly degraded than the other materials due to the greatly enhanced entry of water into the hydrophilic PEO domains.

- b. State 2 physical properties/parameters you would measure for each polymer to make your ranking more accurate, and explain your choices.

Key properties that are not immediately obvious from the given information would be the percent crystallinity in the samples and their glass transition temperatures. For the block copolymer, one would like to know whether the crystallinity is present in both PLA and PEO blocks or only the PLA blocks.

Polymer	Chemical structure	microstructure
Poly(L-lactide)	$\left[\text{CH} \begin{array}{c} \text{O} \\ \parallel \\ \text{C} \\ \text{O} \end{array} \text{CH} \begin{array}{c} \text{CH}_3 \\ \end{array} \right]_n$	Semicrystalline
Poly(lactide-co-glycolide)	$\left[\text{CH} \begin{array}{c} \text{O} \\ \parallel \\ \text{C} \\ \text{O} \end{array} \text{CH} \begin{array}{c} \text{CH}_3 \\ \end{array} \right]_x \left[\text{C} \begin{array}{c} \text{O} \\ \parallel \\ \text{C} \\ \text{O} \end{array} \text{H}_2 \right]_y$	amorphous
Poly(lactide-b-ethylene oxide)	$\left[\text{CH} \begin{array}{c} \text{O} \\ \parallel \\ \text{C} \\ \text{O} \end{array} \text{CH} \begin{array}{c} \text{CH}_3 \\ \end{array} \right]_x \left[\text{CH}_2 \begin{array}{c} \text{H}_2 \\ \end{array} \right]_y$	Semicrystalline
polycaprolactone	$-\left((\text{CH}_2)_5 - \overset{\text{O}}{\parallel} \text{C} - \text{O} \right)_n -$	semicrystalline

2. Given below are data from *in vitro* degradation experiments on poly(lactide-co-glycolide) and polycaprolactone (C. Pitt and Z.-W. Gu, *J. Contr. Rel.* **4**, 283-292 (1987)). Solid samples of each polymer (films 2 cm x 2 cm x 1.0 mm) were prepared; samples were incubated for the defined time periods in phosphate buffered saline pH 7.4. After incubation, each sample was washed with pure water, dried under vacuum, and then the average molecular weight of polymer chains in the samples was measured using gel permeation chromatography.
- Based on the data and experimental details, are these polymers exhibiting bulk or surface erosion?

The key clue lies the details of the experiment as described above—the entire samples are dried, dissolved, and the molecular weights of chains in the samples measured. Recall that the bulk polymer in surface-eroding polymers remains unaffected during degradation; only the surface-attacked polymer is degraded. Here, we are essentially told that all of the polymer is experiencing a reduction in molecular weight; this is the characteristic feature of bulk erosion.

- Using the given data, calculate the effective rate constant for degradation of each polymer. For each polymer, explain whether the data allows you to distinguish whether the degradation is autocatalytic or non-autocatalyzed.

To calculate a degradation rate constant, we fit the given degradation data to one of the two models:

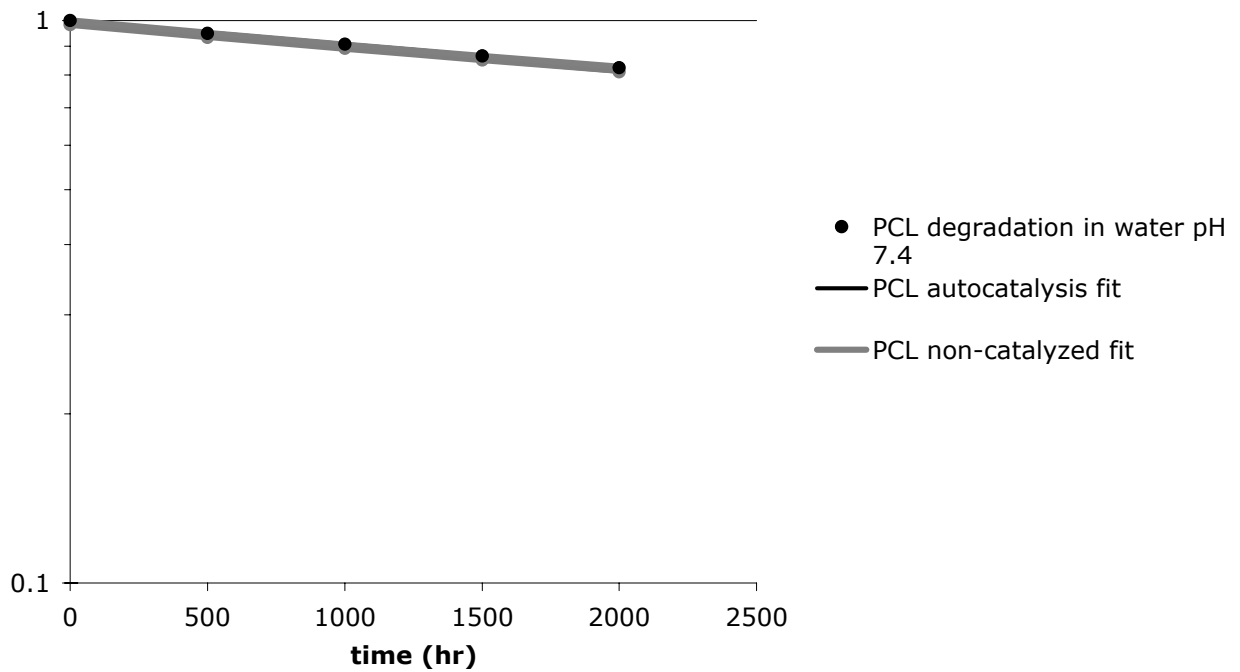
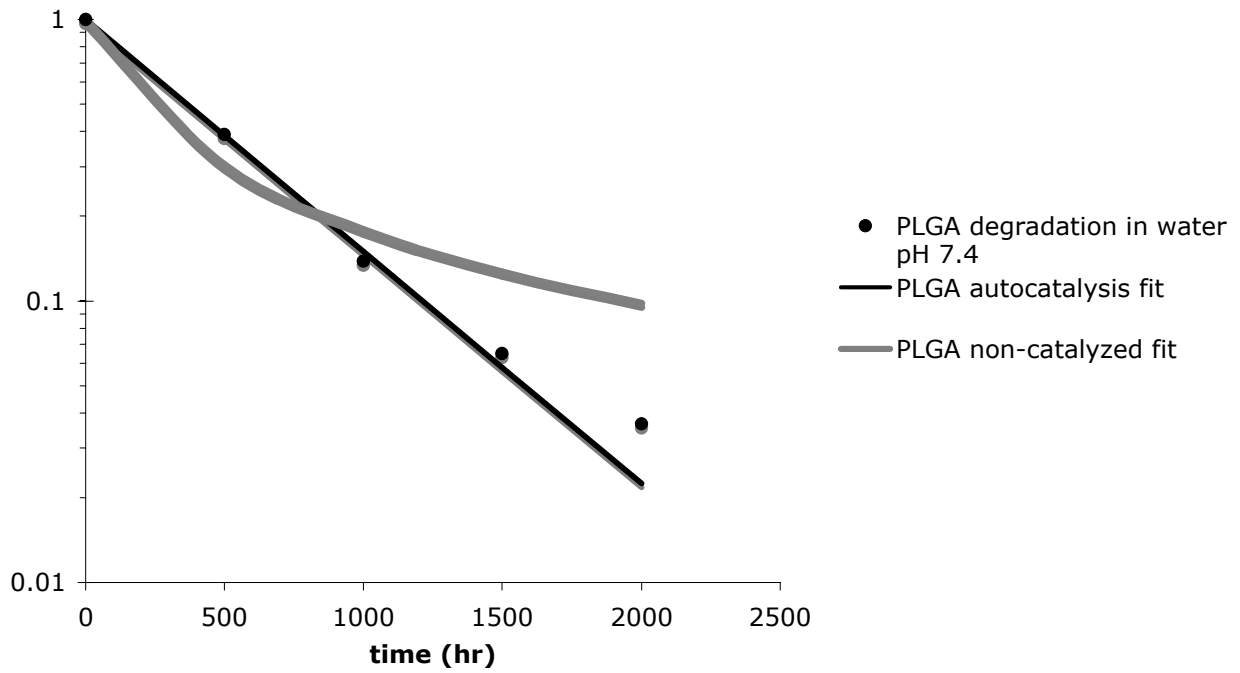
Autocatalysis:

$$M = M_0 e^{-kt}$$

non-catalyzed degradation:

$$\frac{1}{M} = \frac{1}{M_0} + \frac{k}{\rho} t$$

To first order, it is reasonable to take the density of the polymer (ρ) as 1 g/cm³. Best fits are shown in the plots below, using a log-linear scale to help highlight the difference between the autocatalyzed and non-catalyzed models:



Clearly, the PLGA data is best fit by the autocatalyzed degradation model; the best-fit degradation rate constant is $1.9E-03 \text{ hr}^{-1}$. For polycaprolactone, too little degradation occurs over the timecourse examined to distinguish between catalyzed and non-catalyzed degradation (best-fit rate constant for autocatalyzed degradation is $9.65E-05 \text{ hr}^{-1}$).

- c. What is the maximum useful lifetime you would expect for an implanted device fabricated from each of these polymers given your calculations above, assuming that degradation kinetics of these materials are similar *in vivo*? (Explain your answer).

To provide some estimate of useful lifetime, we can use the kinetic of MW change to determine when the materials will have degraded to completely soluble products—this is by far the longest possible time the samples could serve in a device. In lecture 2, we gave the critical molecular weights for solubility of polylactide (PLA) and polycaprolactone as 1.2 KDa and 5 KDa, respectively. Assuming a similar critical solubility molecular weight for PLA and PLGA, we want to determine the time required for each polymer to degrade to the critical molecular weight. Using the autocatalysis model, we have:

$$MW = MW_0 e^{-kt}$$

$$PLGA \quad 1,200 = 24,600 e^{-(1.9 \times 10^{-3} t)}$$

$$t = 1,589 \text{ hr} = 66 \text{ d}$$

$$PCL \quad 5,000 = 61,800 e^{-(9.65 \times 10^{-5} t)}$$

$$t = 26,056 \text{ hr} = 1,086 \text{ d} \cong 3 \text{ years!}$$

Again, this estimate is clearly the far-outside limit of useful lifetime. Any real device will lose mechanical integrity significantly before the molecular weights have degraded to this extreme limit, and thus the actual lifetime in many applications may be significantly shorter.

time (hr)	PLGA MW (g/mole)	PCL MW (g/mole)
0	24600	61800
500	9600	58700
1000	3400	56100
1500	1600	53500
2000	900	51000

3. Gōpferich erosion theory:

- a. Does Gōpferich erosion theory account for autocatalysis during polymer degradation/erosion?

The erosion number theory does not explicitly account for autocatalysis, as it bases the rate of chain degradation on a single unchanging rate constant that is not influenced by the concentration of acid/base chain end groups present. A modified rate constant dependent on these concentrations would need to be introduced to allow the theory to account for autocatalysis.

- b. Your research team at a startup company is working on using biodegradable polymers as scaffolds to promote bone regeneration. You have found that a polyanhydride, poly(carboxyphenoxyhexane) (PCH, structure shown below), has good mechanical properties for this application. However, porous bone scaffolds with mean strut dimensions of 250 μm (as illustrated below) degrade by surface erosion and this causes the scaffold to loosen in its position when implanted at a bone defect. Show that the erosion number calculated for this situation agrees with the experimental observation.

The molecular weight of the polymer repeat unit $M_0 = 340$ g/mole. Assuming the scaffold struts are approximately cylindrical and that water enters from all sides simultaneously, then the effective thickness x of the strut for water entry is equal to its radius, 125 μm, (water will reach the center of the strut simultaneously from each direction) then we have:

$$Y_{\square} = \frac{bN_{Av}\rho}{M_{o\square}} = \frac{\left(1 \frac{\text{labile bond}}{\text{repeat unit}}\right)(6.022 \times 10^{23})(1.05 \frac{\text{g}}{\text{cm}^3})}{340 \text{ g/mole}} = 1.86 \times 10^{21}$$

$$\varepsilon = \frac{x^2 \pi k}{4D_{H_2O} \left[\ln x + \frac{1}{3} \ln Y \right]} = \frac{(125 \times 10^{-4} \text{ cm})^2 \pi (1.9 \text{ s}^{-1})}{4(1 \times 10^{-8} \frac{\text{cm}^2}{\text{s}}) \left[\ln(125 \times 10^{-4}) + \frac{1}{3} \ln Y \right]} = 1950$$

Because the erosion number is $\gg 1$, we predict this sample will undergo surface erosion, in agreement with the experimental observation.

- c. You'd like to engineer your PCH scaffolds to degrade by bulk erosion. Your colleagues suggest that the problem could be overcome by blending PCH with poly(ethylene glycol), which will phase separate and raise the average diffusion constant of water in the matrix to a value one tenth that of water's natural self-diffusion coefficient (water diffusion in water). Will this drive the scaffold to erode by a bulk mechanism? (Defend your answer with a calculation). An alternative proposal is to make the struts of the scaffold thinner. Which route would you pick and why?

The self-diffusion coefficient of water is $2.5 \times 10^{-5} \text{ cm}^2/\text{s}$. If the diffusion of water through the matrix was raised from its value in PCH to $2.5 \times 10^{-6} \text{ cm}^2/\text{s}$, with the other parameters unchanged, we would have:

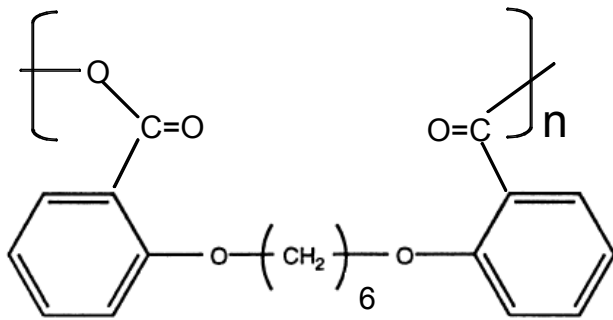
$$\varepsilon = \frac{x^2 \pi k}{4D_{H_2O} \left[\ln x + \frac{1}{3} \ln Y \right]} = \frac{(125 \times 10^{-4} \text{ cm})^2 \pi (1.9 \text{ s}^{-1})}{4(2.5 \times 10^{-6} \frac{\text{cm}^2}{\text{s}}) \left[\ln(125 \times 10^{-4}) + \frac{1}{3} \ln Y \right]} = 7.8$$

This value is still significantly greater than 1, suggesting the sample is approaching bulk erosion, but still surface eroding. The alternative suggestion is to make the struts thinner. However, even with a 10-fold reduction in strut thickness, we still have an erosion number well above 1:

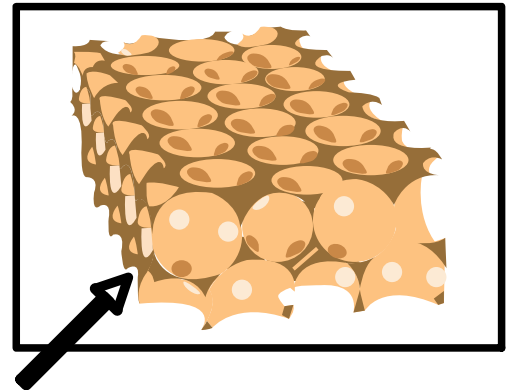
$$\varepsilon = \frac{(125 \times 10^{-5} \text{ cm})^2 \pi (1.9 \text{ s}^{-1})}{4(1 \times 10^{-8} \frac{\text{cm}^2}{\text{s}}) \left[\ln(125 \times 10^{-5}) + \frac{1}{3} \ln Y \right]} = 24.2$$

...suggesting that we cannot switch to bulk erosion simply by make the struts thinner. Thus, the best recommendation is likely to combine these two ideas, which would get us to $\varepsilon = 0.096$, where bulk erosion is expected.

PCH structure



Porous PCH scaffold



250 μm wide-struts

Data for PCH:

$$\rho = 1.05 \text{ g/cm}^3$$

$$\text{degradation rate constant } k = 1.9 \text{ s}^{-1}$$

$$D_{H_2O} \text{ (diffusion coefficient of water in PCH)} = 1 \times 10^{-8} \text{ cm}^2 \text{ s}^{-1}$$

Figure by MIT OCW.