

Biodegradable Solid Polymeric Materials (continued)

Last time:	chemistry and physical chemistry of degrading polymeric solids for biomaterials
Today:	Factors controlling polymer degradation rates Theory of polymer erosion
Reading:	F. von Burkersroda et al., 'Why degradable polymers undergo surface erosion or bulk erosion,' <i>Biomaterials</i> 23, 4221-4231 (2002)
Supplementary Reading:	R.J. Young and P.A. Lovell, "Introduction to Polymers," ch. 4 <i>Polymer Structure</i> pp. 241-309 (crystallization of polymers, T_m , glass transition, etc.)

Last time

MATERIALS FOR IMPLANT APPLICATIONS:

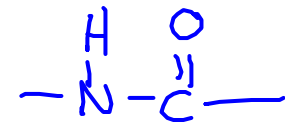
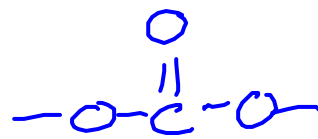
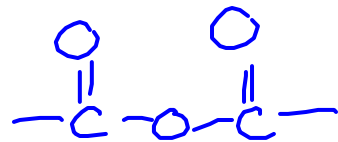
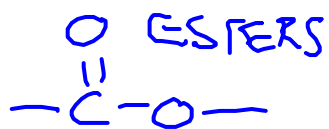
(1) PERMANENT / ^{RETRIEVABLE} IMPLANTS

(2) BIODELIMINABLE

↳ WATER-SOLUBLE, OF A SIZE SUITABLE FOR KIDNEY CLEARANCE

(3) BIODEGRADABLE

↓ BREAKDOWN BY



ANHYDRIDES

CARBONATES

AMIDES

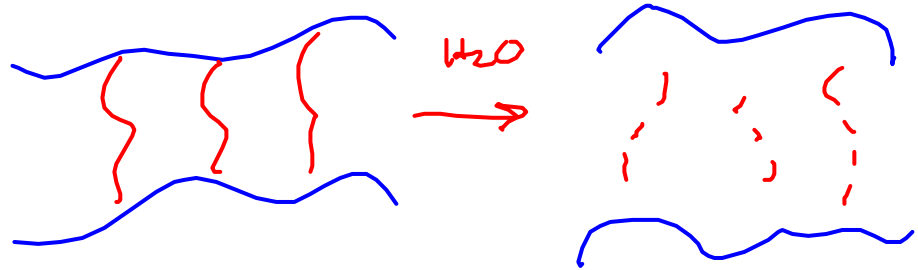
HYDROLYSIS

ENZYMES

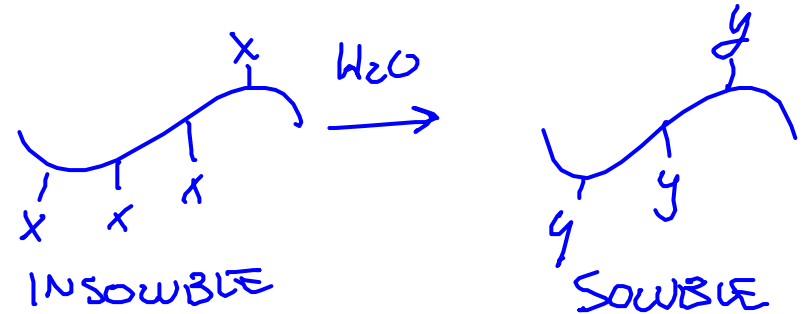
Last time

3 PATHWAYS OF POLYMER BREAKDOWN:

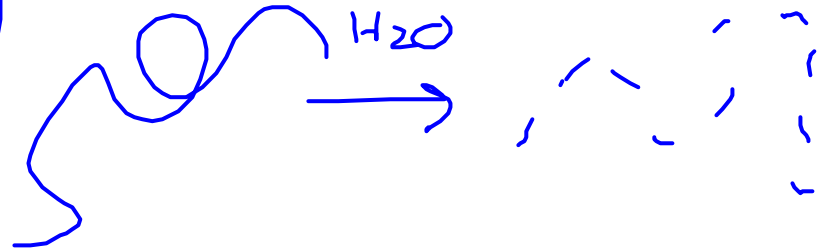
* CROSSLINK DEGRADATION:



* SIDE CHAIN DEGRADATION:

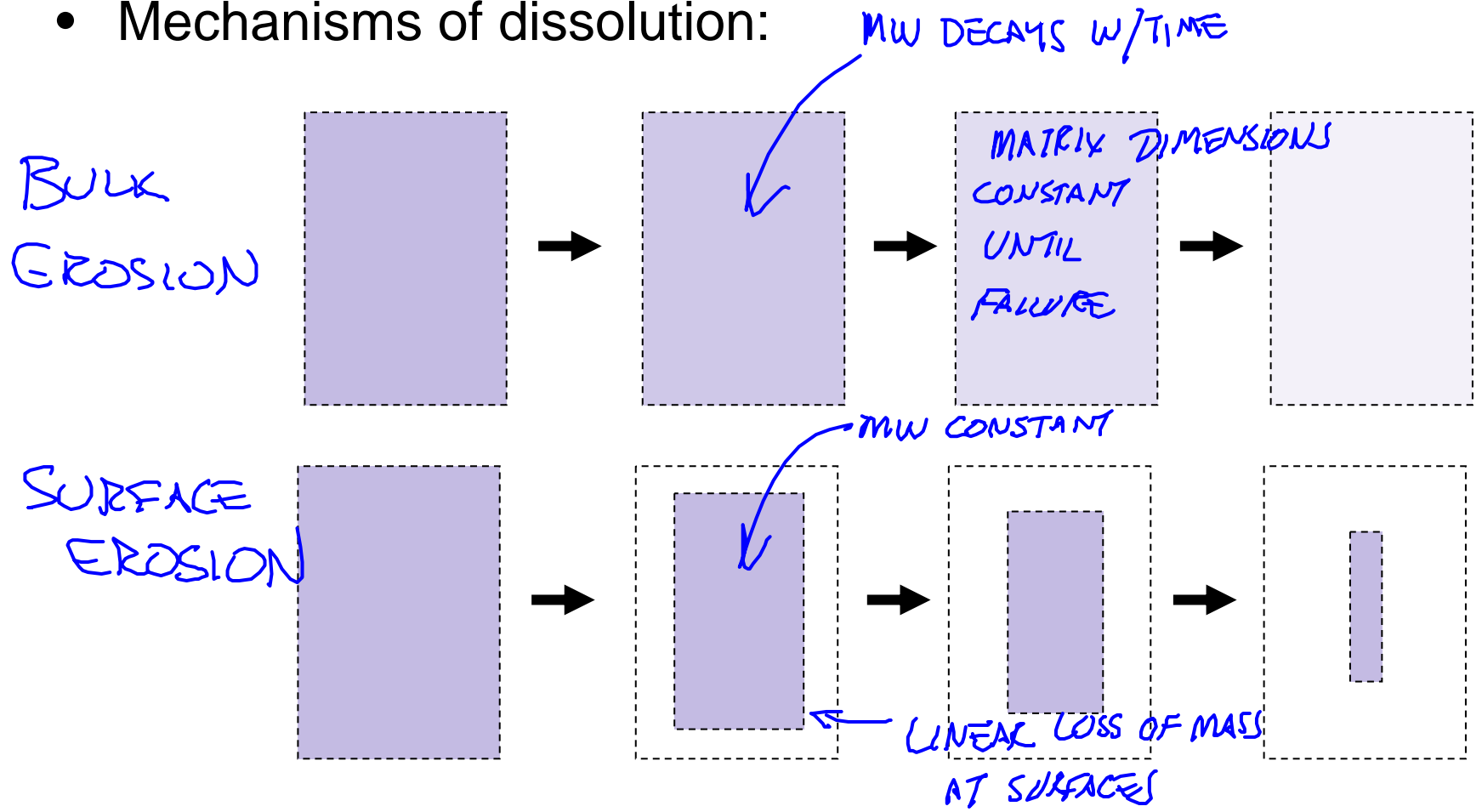


* BACKBONE DEGRADATION



Physical chemistry of hydrolysis: structure influences mechanism of erosion as well as overall rate

- Mechanisms of dissolution:



Factors controlling solid polymer degradation rates

5 FACTORS:

- BOND STABILITY · AMIDES > ESTERS > ORTHOESTERS > ANHYDRIDES
- HYDROPHOBICITY
- STERIC EFFECTS
- PRODUCTION OF AUTOCATALYTIC BREAKDOWN FRAGMENTS
- MICROSTRUCTURE
 - CRYSTALLINITY
 - PHASE SEPARATION
 - POROSITY

(2) Effect of polymer hydrophobicity on solid polymer erosion rate

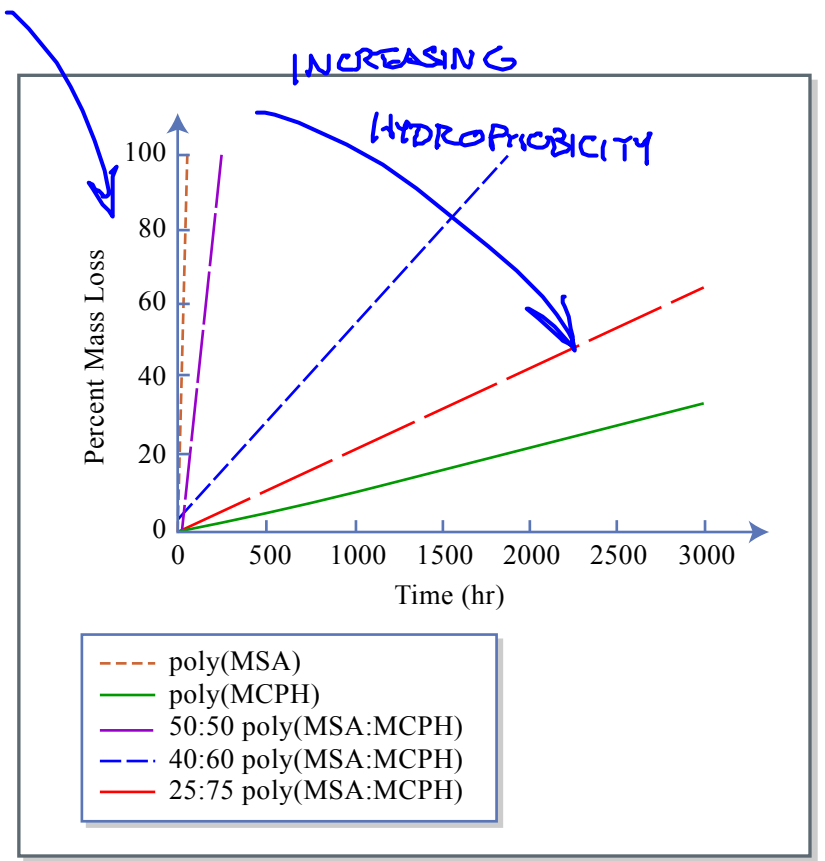
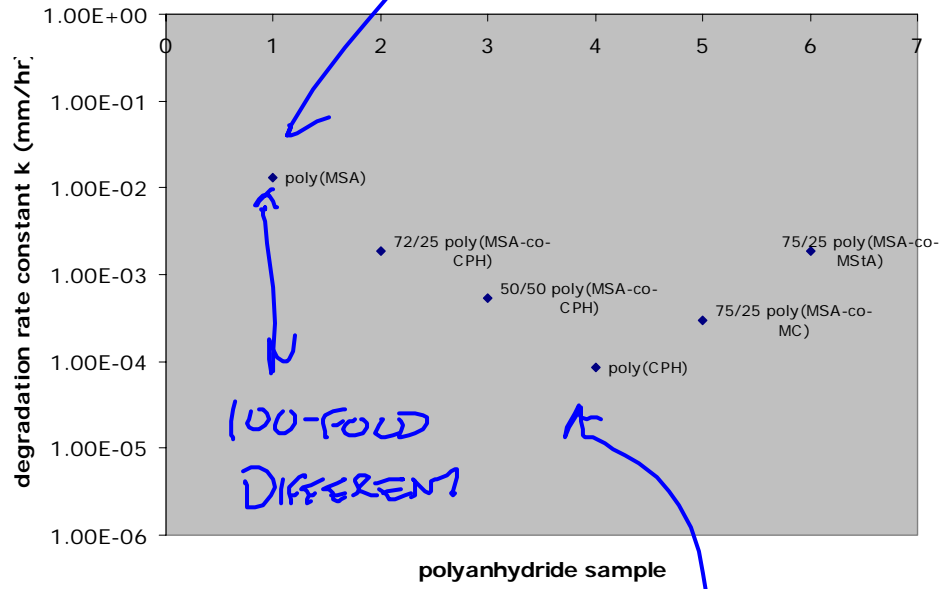
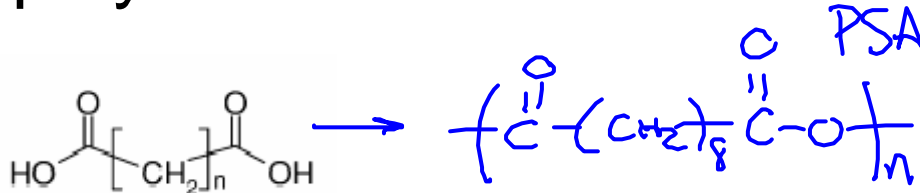
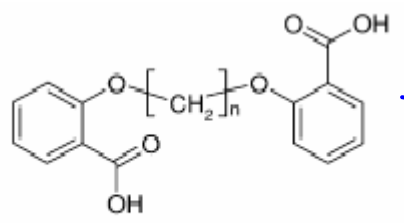
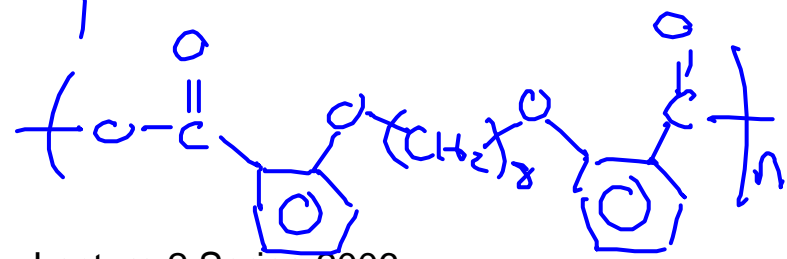


Figure by MIT OCW.

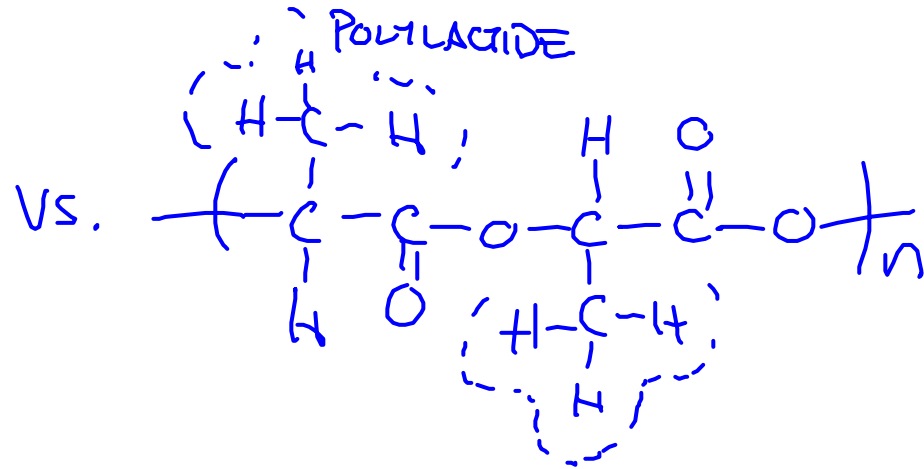
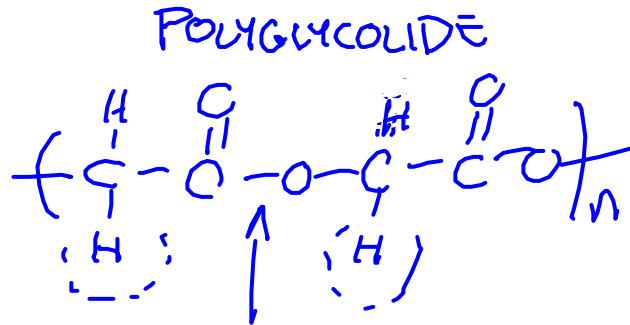


$n = 6$: 1,6-bis(o-carboxyphenoxy)hexane (o-CPH)

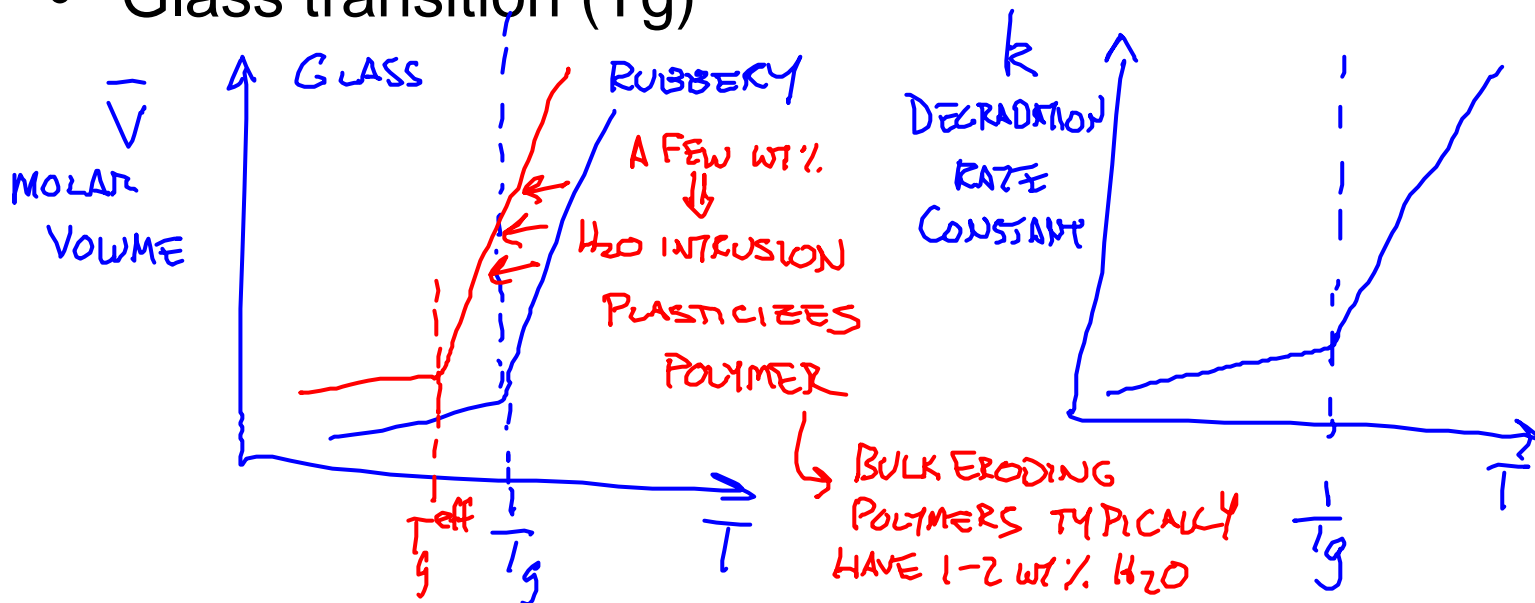


(3) Steric effects controlling polymer hydrolysis rates

- Local structure

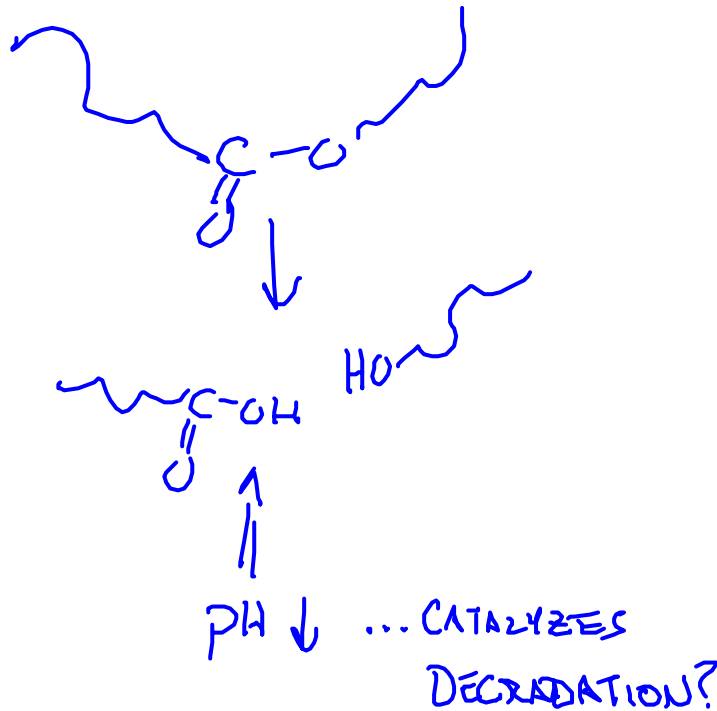


- Glass transition (T_g)



(4) Production of autocatalytic products

- Polyesters:



OLIGOMER SOLUBILITY IN H₂O:

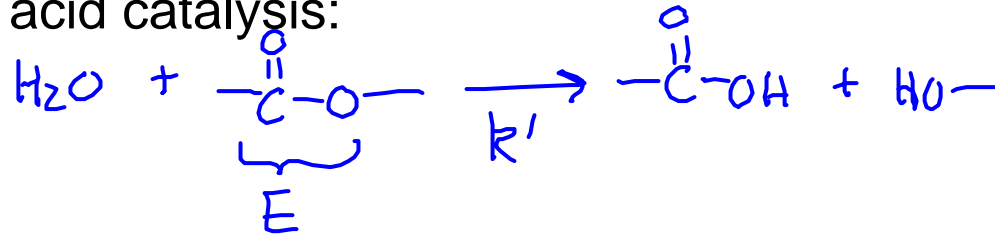
CRITICAL MW FOR SOLUBILITY:

POLYCAPROLACTONE : ~5 KDa

PLA : ~1.2 KDa

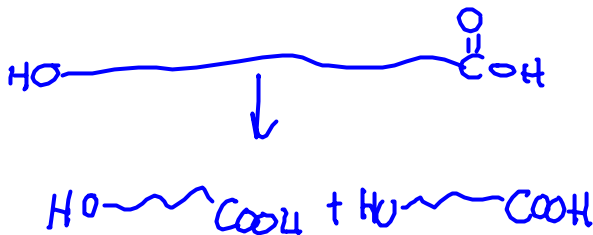
Hydrolysis rate theory

No acid catalysis:



$$\frac{d[\text{COOH}]}{dt} = k' [\text{H}_2\text{O}] \underbrace{[E]}_{\substack{\Rightarrow \text{CONSTANT} \\ \text{IF } k' \text{ IS SMALL}}} \approx k_{\text{eff}} \quad \therefore [\text{COOH}] = [\text{COOH}]_0 + k_{\text{eff}} t$$

Relationship to molecular weight (M): DENSITY



$$[\text{COOH}] \approx \frac{\rho}{\text{MW}} = \frac{\text{moles}}{\text{cm}^3}$$

MOL. WEIGHT

$$\left(\rho = 1 \text{ FOR MANY POLYMERS} \right)$$

$\frac{\text{g}}{\text{cm}^3}$

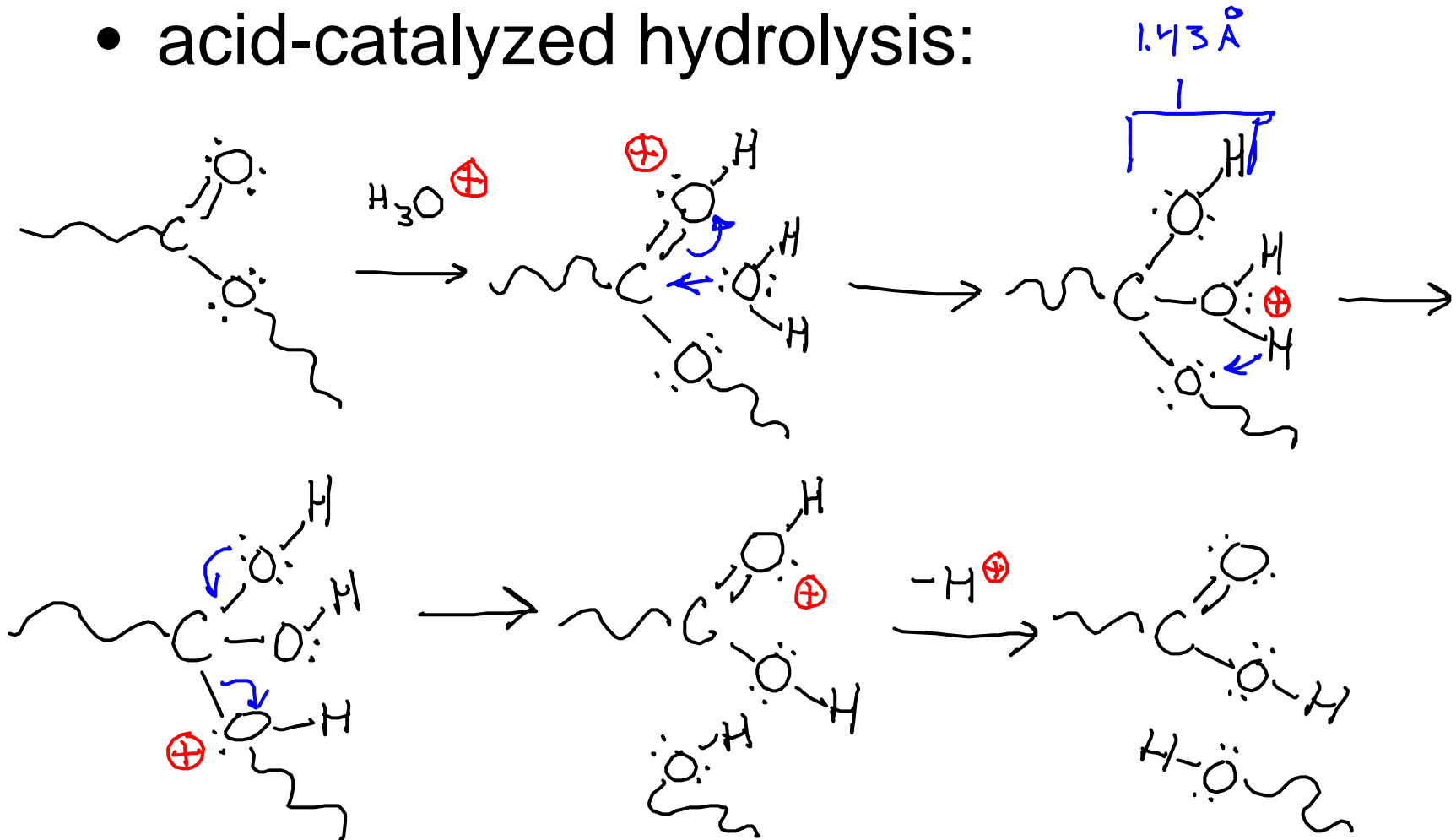
$$\therefore \frac{1}{\text{MW}} = \frac{1}{\text{MW}_0} + \frac{k_{\text{eff}} t}{\rho}$$

INITIAL MOL. WT.

Mechanisms of hydrolysis: polyesters

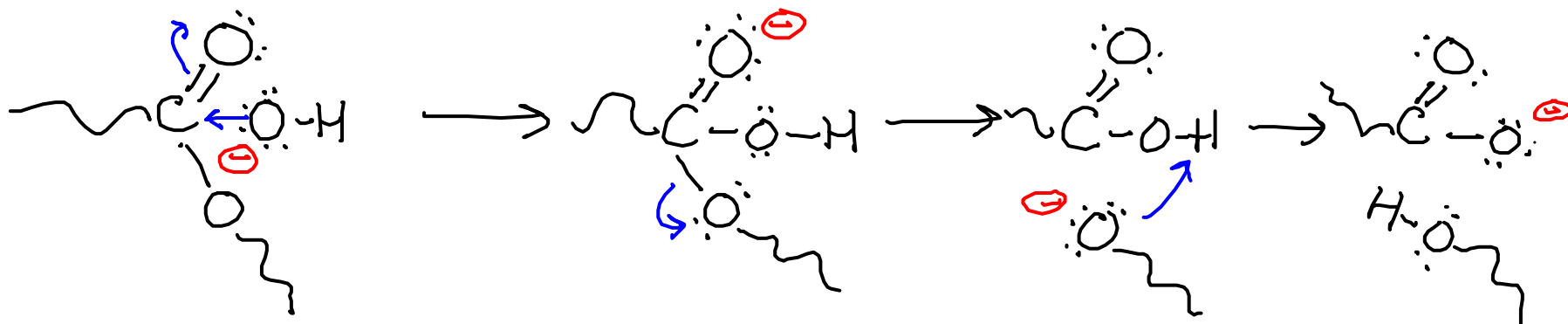
ESTERS CAN BE BOTH ACID + BASE CATALYZED
DURING HYDROLYSIS

- acid-catalyzed hydrolysis:



Mechanisms of hydrolysis: polyesters

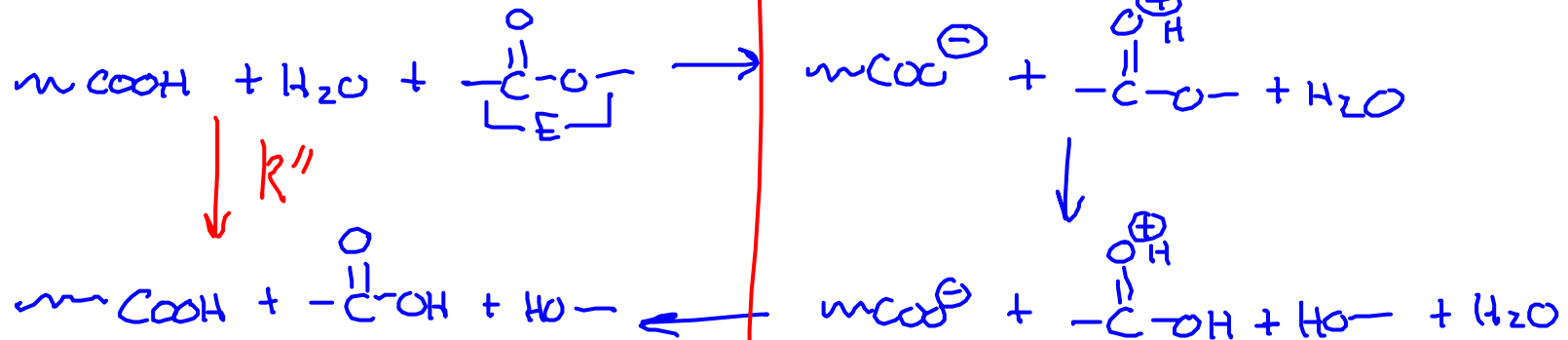
- Base-catalyzed hydrolysis:
(saponification)



Nucleophilic substitution at acyl carbon

Rate of chain cleavage

Autocatalysis of chain degradation:



$$\frac{d[\text{COOH}]}{dt} = k'' [\text{COOH}] [\text{H}_2\text{O}] [E] \approx k_{\text{eff}}^{\text{AC}} [\text{COOH}]$$

≈ CONSTANT

$$\therefore [\text{COOH}] = [\text{COOH}]_0 e^{-k_{\text{eff}}^{\text{AC}} t}$$



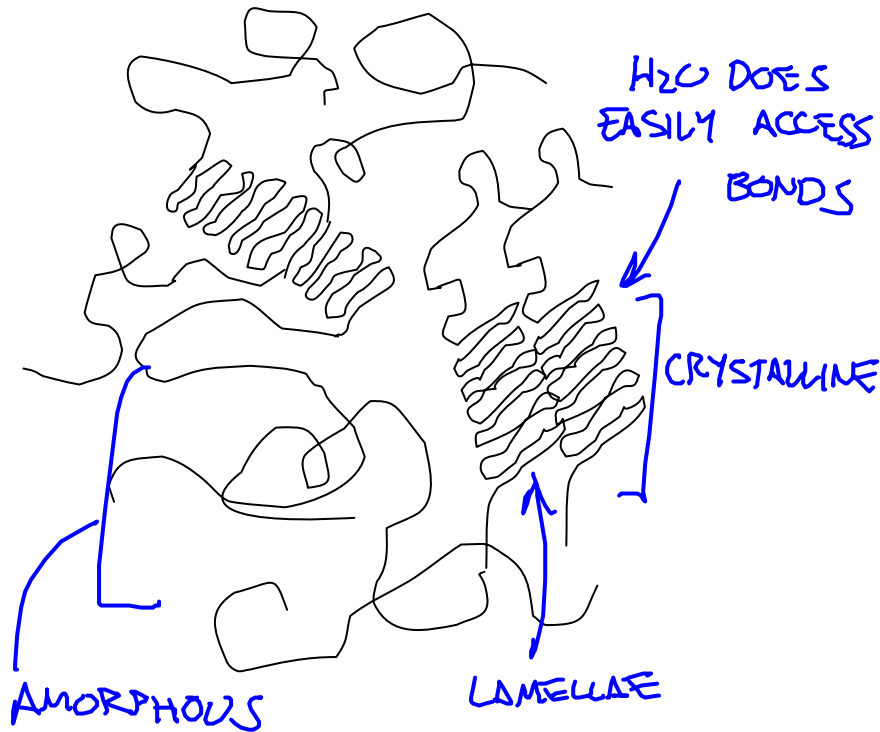
$$\frac{MW}{MW_0} = e^{-k_{\text{eff}}^{\text{AC}} t}$$

OBSERVED FOR
MANY
DEGRADABLE
POLYMERS

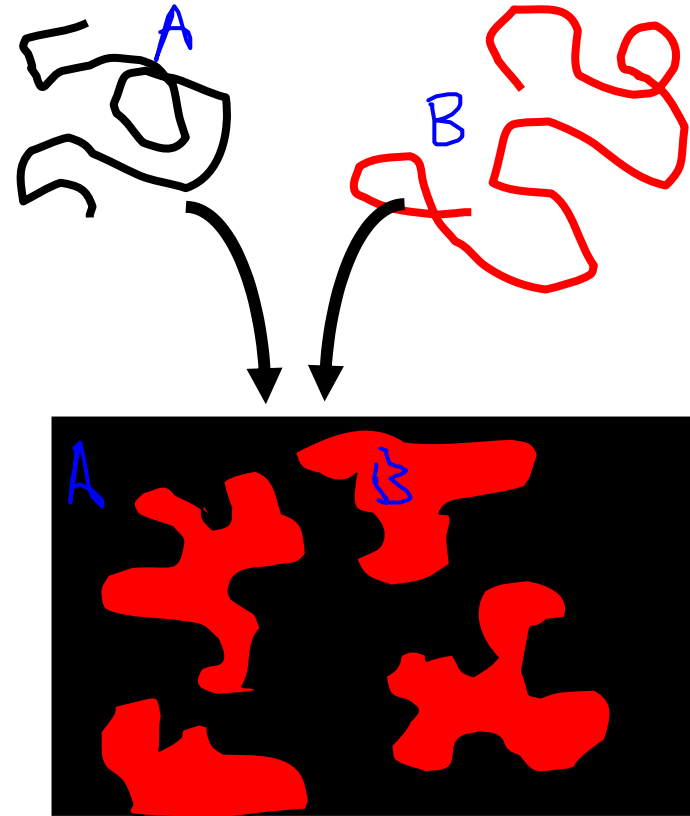
(5) Phase separation / CRYSTALLINITY / POROSITY

MICROSTRUCTURE!

Semicrystalline polymers:



2 (or more) immiscible components:



Crystallinity and Phase Separation Effects.

- Zong, 1999
- Shakesheff, K.M., M. C. Davies, C. J. Roberts, S. B. J. Tendler, A. G. Shard, and A. Domb. "In Situ Atomic Force Microscopy Imaging of Polymer Degradation in an Aqueous Environment." *Langmuir* 10 (1994): 4417-4419.

Crystalline regions resist hydrolysis

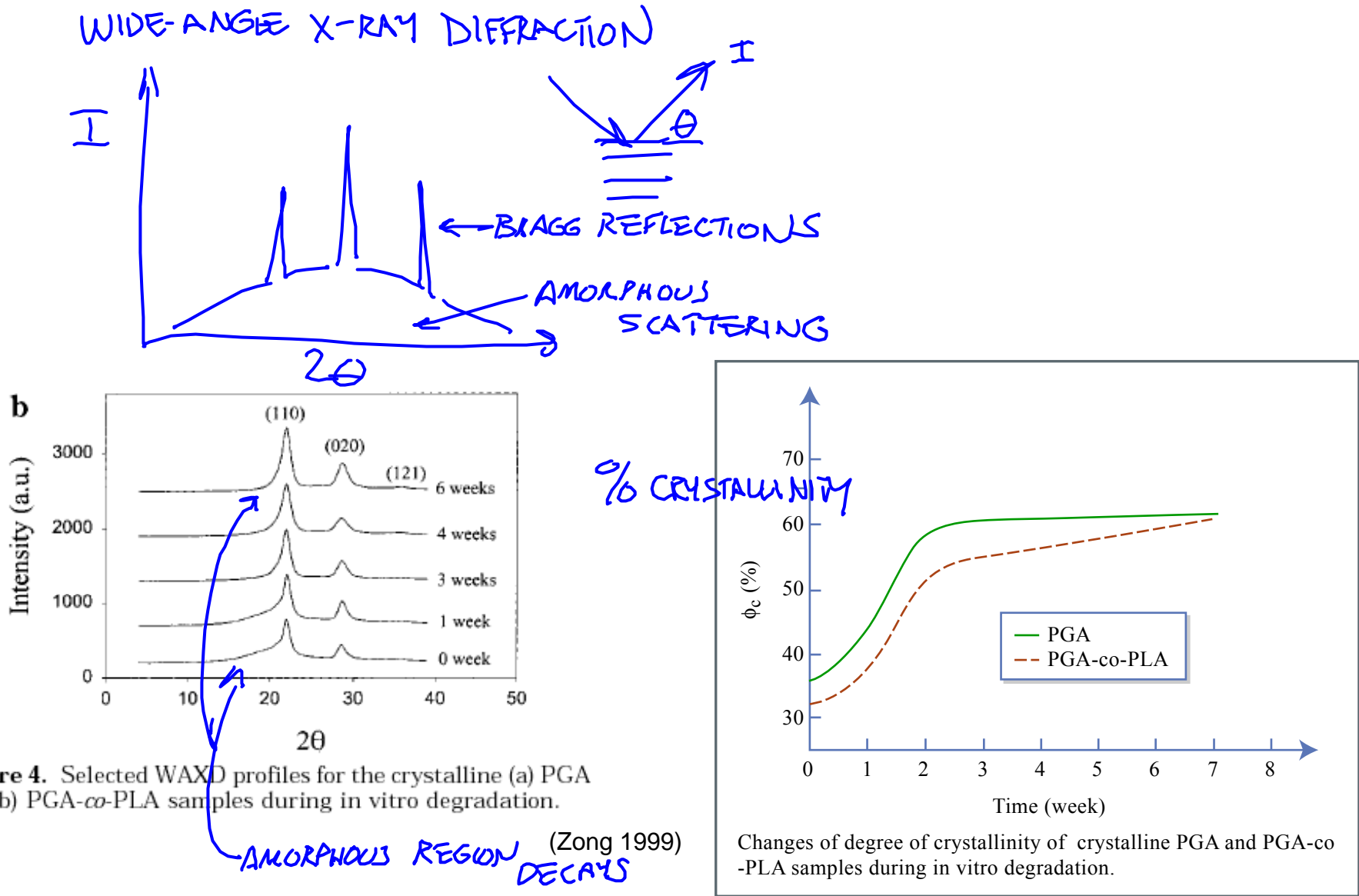
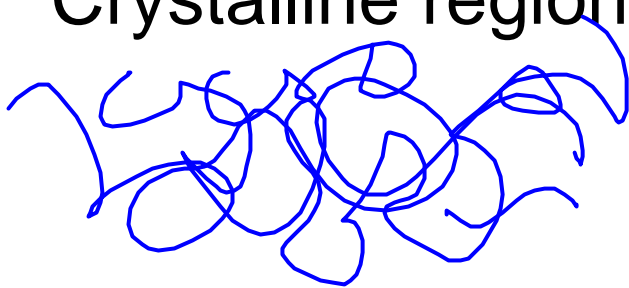


Figure 4. Selected WAXD profiles for the crystalline (a) PGA and (b) PGA-co-PLA samples during in vitro degradation.

Changes of degree of crystallinity of crystalline PGA and PGA-co-PLA samples during in vitro degradation.

Figure by MIT OCW.

Crystalline regions resist hydrolysis



SPONTANEOUS RECRYSTALLIZATION
IN AMORPHOUS REGIONS

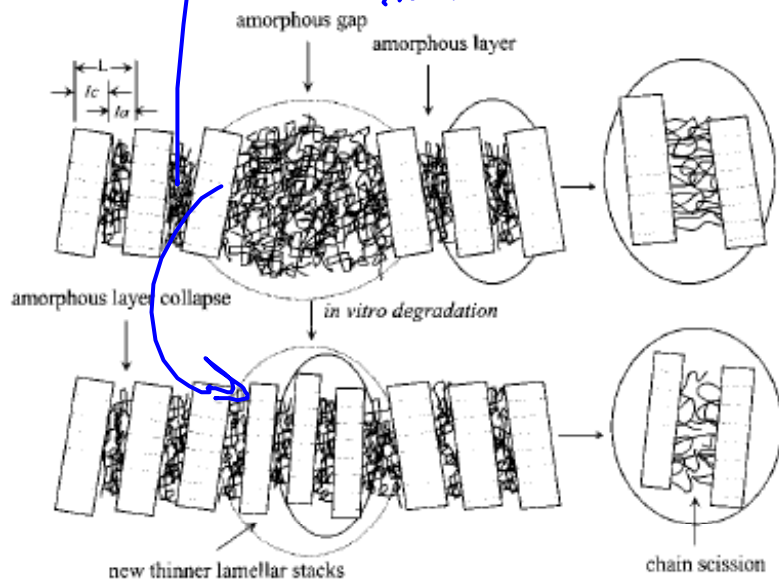


Figure 10. Schematic diagram of in vitro degradation mechanism in the dual lamellar stacks model of semicrystalline samples.

(Zong 1999)

Figure removed for copyright reasons.

Please see:

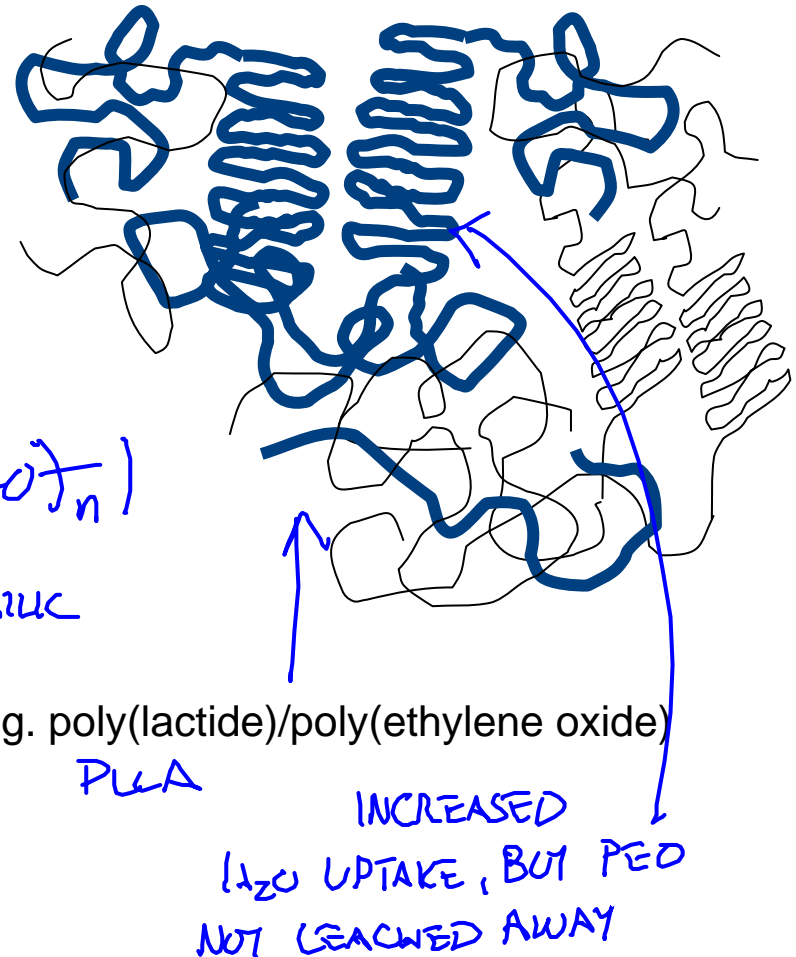
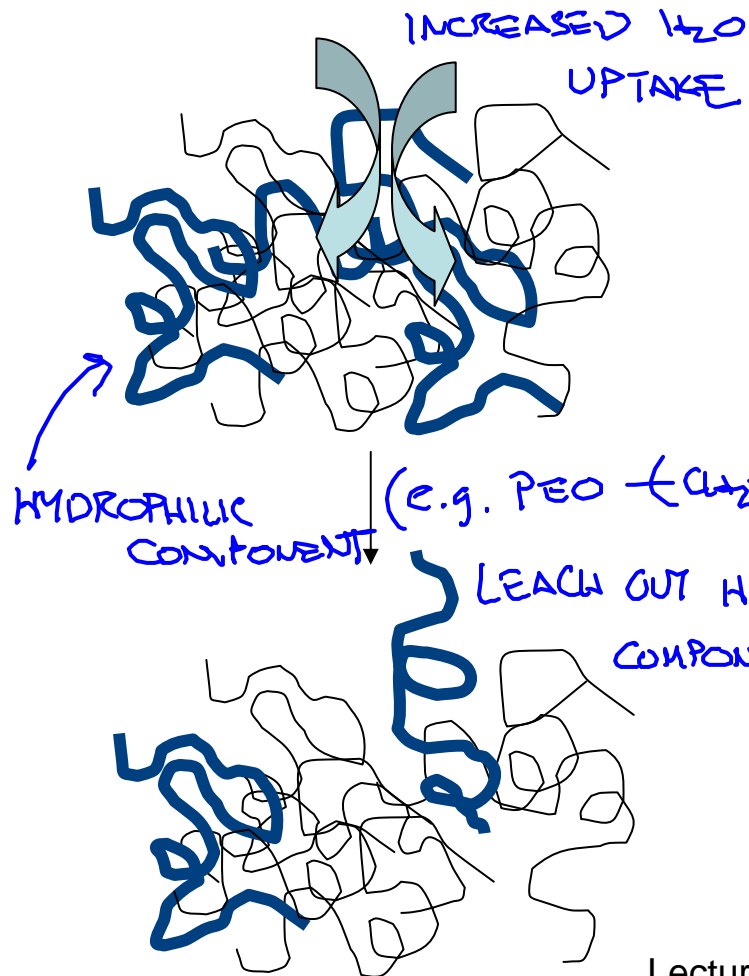
Figure 2 in Shakesheff, K. M., M. C. Davies, C. J. Roberts, S. B. J. Tandler, A. G. Shard, and A. Domb. "In Situ Atomic Force Microscopy Imaging of Polymer Degradation in an Aqueous Environment." *Langmuir* 10 (1994): 4417-4419.

(5) Phase separation: Hydrolysis in polymer blends

Blends of hydrophilic and hydrophobic polymers

Amorphous state - miscible

Incompatible crystal lattices



Blends of poly(L-lactide) with poly(ethylene oxide)

INCREASING
HYDROPHILIC COMPONENT

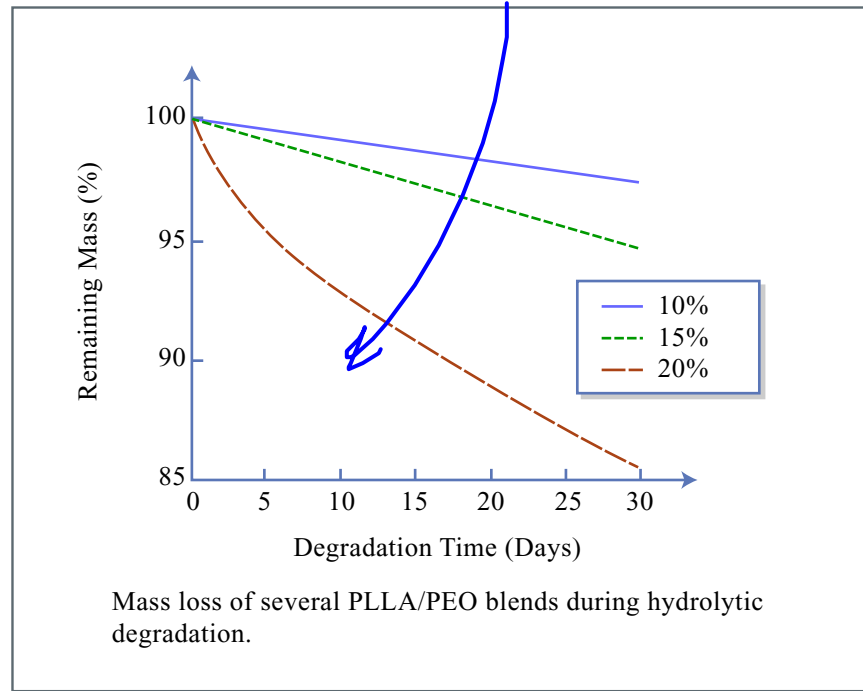
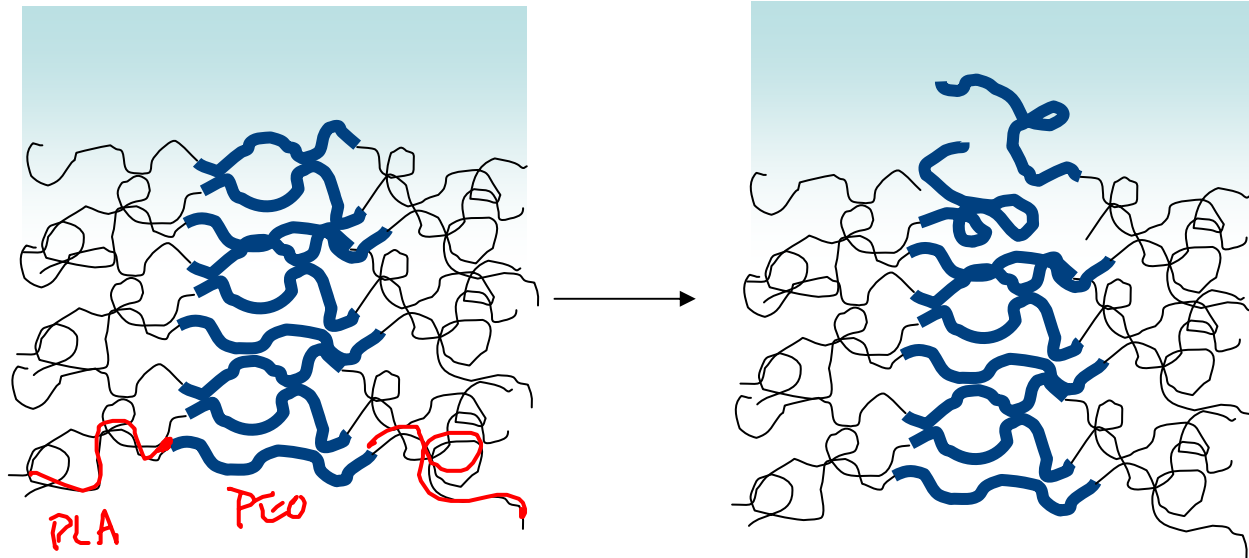


Figure by MIT OCW.

Constrained mass loss: PLLA-b-PEO-b-PLLA triblock copolymers



Summary of factors controlling solid polymer degradation rates:

PARAMETER:

$$\frac{dmw}{dt}$$

BONDS w/SHORT $\frac{1}{2}$ LIFE



INCREASING HYDROPHOBICITY



BULKY PENDANT GROUPS



AUTOCATALYSIS



CRYSTALLINITY



PHASE SEPARATION

USUALLY ↑

Bulk vs. surface erosion: how do we predict it?

Bulk erosion

Surface erosion

Figures removed for copyright reasons.
Please see:

Fig. 8(b) in Lu, L., C. A. Garcia, and A. G. Mikos.
"In Vitro Degradation of Thin Poly(DL-lactic-co-glycolic acid) Films." *J Bio Med Mater Res* 46
(1999): 236-44.

Images of Surface Erosion removed due to copyright restrictions.

Fig. 6(d) in Agrawal, C. M., and K. A. Athanasiou.
"Technique to Control pH in Vicinity of Biodegrading
PLA-PGA Implants." *J Biomed Mater Res* 38
(1997): 105-14.

Göpferich theory of polymer erosion

- If polymer is initially water-insoluble, and hydrolysis is the only mechanism of degradation, then two *rates* dominate erosion behavior:
(2 TIMES)

1) RATE OF H₂O DIFFUSION INTO MATRIX
⇒ t_{DIFF}

2) RATE OF CHAIN CLEAVAGE BY H₂O

⇒ t_c

$t_{DIFF} \ll t_c \rightarrow$ BULK EROSION

$t_{DIFF} \gg t_c \rightarrow$ SURFACE EROSION

Rate of water diffusion into polymer matrix

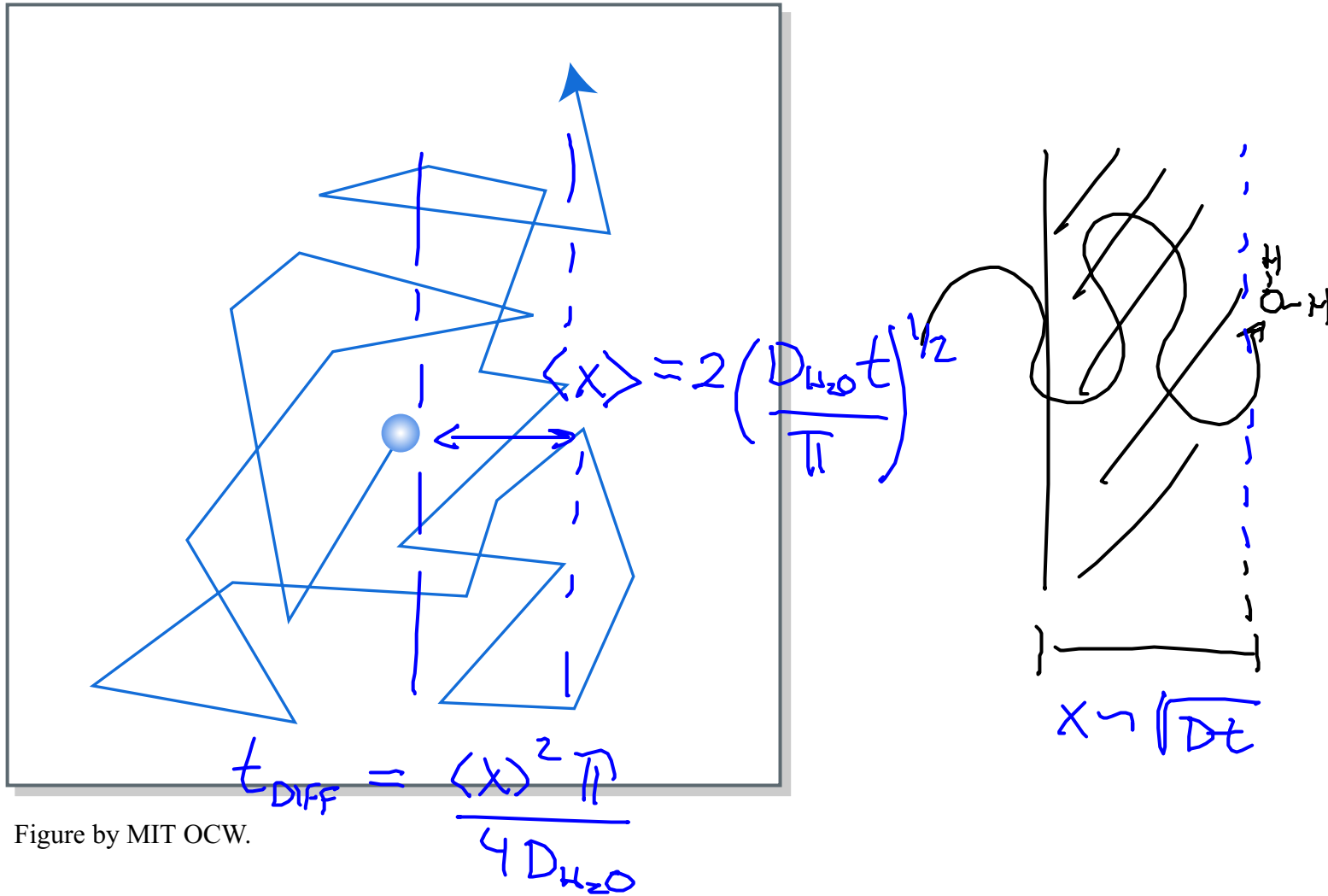
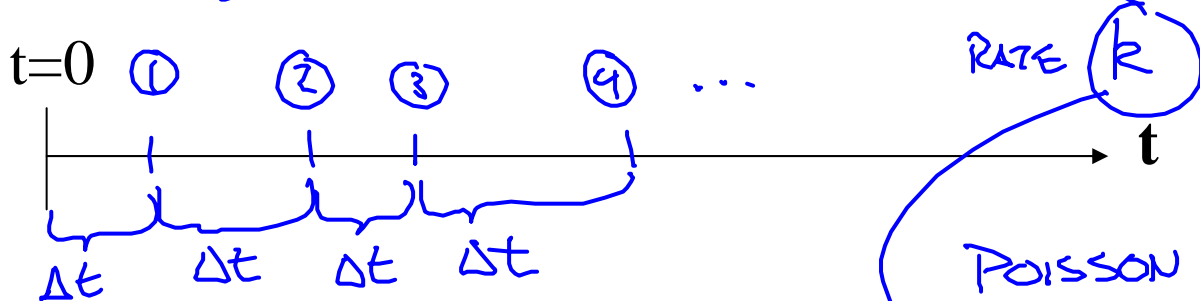


Figure by MIT OCW.

Rate of chain cleavage

CONSIDER BONDS BREAKING WITHIN SOME VOLUME OF THE SAMPLE

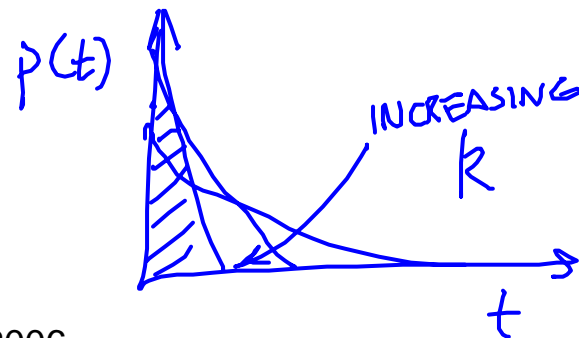
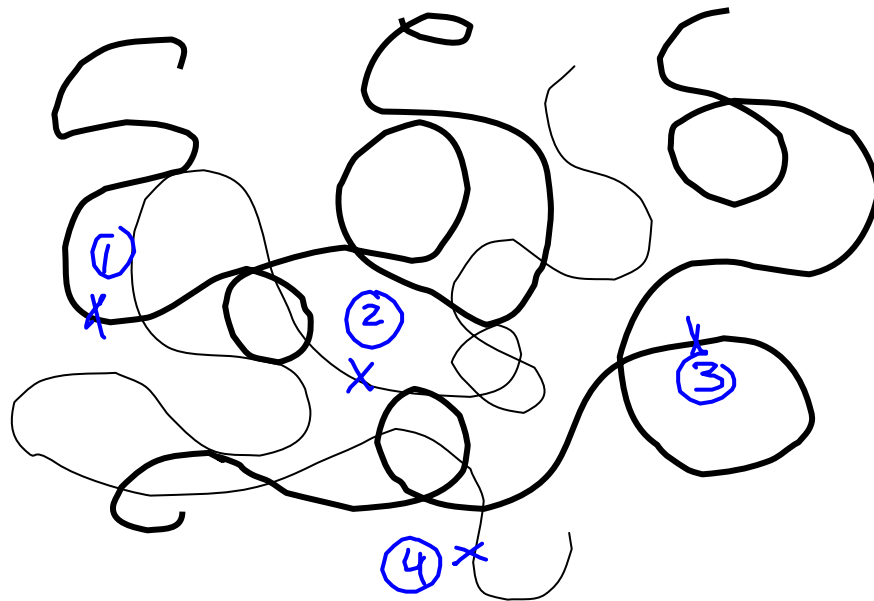
- BOND BREAKS ARE INDEPENDENT STOCHASTIC EVENTS W/ MEAN



DISTRIBUTION OF TIMES BETWEEN BREAKS IS EXPONENTIAL.

$$p(t) = k e^{-kt}$$

= PROBABILITY THAT TIME BETWEEN BREAKS IS t



Further Reading

1. Gopferich, A. & Langer, R. Modeling of Polymer Erosion. *Macromolecules* **26**, 4105-4112 (1993).
2. Gopferich, A. Polymer bulk erosion. *Macromolecules* **30**, 2598-2604 (1997).
3. Gopferich, A. Mechanisms of polymer degradation and erosion. *Biomaterials* **17**, 103-114 (1996).
4. von Burkersroda, F., Schedl, L. & Gopferich, A. Why degradable polymers undergo surface erosion or bulk erosion. *Biomaterials* **23**, 4221-31 (2002).
5. Agrawal, C. M. & Athanasiou, K. A. Technique to control pH in vicinity of biodegrading PLA-PGA implants. *J Biomed Mater Res* **38**, 105-114 (1997).
6. Lu, L., Garcia, C. A. & Mikos, A. G. In vitro degradation of thin poly(DL-lactic-co-glycolic acid) films. *J Biomed Mater Res* **46**, 236-44 (1999).
7. Tsuji, H. & Nakahara, K. Poly(L-lactide). IX. Hydrolysis in acid media. *Journal of Applied Polymer Science* **86**, 186-194 (2002).
8. Atkins, P. *The Elements of Physical Chemistry* (W.H. Freeman, New York, 1997).
9. Pitt, C. G., Marks, T. A. & Schindler, A. in *Controlled Release of Bioactive Materials* (ed. Baker, R. W.) 19-43 (Academic Press, New York, 1980).
10. Albertsson, A. C. & Varma, I. K. in *Degradable Aliphatic Polyesters* 1-40 (2002).
11. Stridsberg, K. M., Ryner, M. & Albertsson, A. C. in *Degradable Aliphatic Polyesters* 41-65 (2002).
12. Barrera, D. A., Zylstra, E., Lansbury, P. T. & Langer, R. Synthesis and RGD peptide modification of a new biodegradable copolymer: poly(lactic acid-co-lysine). *J. Am. Chem. Soc.* **115**, 11010-11011 (1993).
13. Barrera, D. A., Zylstra, E., Lansbury, P. T. & Langer, R. Copolymerization and degradation of poly(lactic acid-co-lysine). *Macromolecules* **28**, 425-432 (1995).
14. Cook, A. D. et al. Characterization and development of RGD-peptide-modified poly(lactic acid-co-lysine) as an interactive, resorbable biomaterial. *J Biomed Mater Res* **35**, 513-23 (1997).
15. Ivin, K. J. *Ring-opening polymerization* (Elsevier, London, 1984).
16. Burkoth, A. K. & Anseth, K. S. A review of photocrosslinked polyanhydrides: in situ forming degradable networks. *Biomaterials* **21**, 2395-404 (2000).
17. Burkoth, A. K., Burdick, J. & Anseth, K. S. Surface and bulk modifications to photocrosslinked polyanhydrides to control degradation behavior. *J Biomed Mater Res* **51**, 352-9 (2000).