20.462J/3.962J Molecular Principles of Biomaterials
Summary of course objective:

Develop a firm understanding of the **fundamental materials science & engineering principles** underlying synthetic/engineered materials used in **biology, biotechnology, and biomedical** applications--focusing on a subset of problems that can be quantitatively understood (and that we have time to cover!)

Image removed for copyright reasons.

Please see:

Fig. 1(a) in Richardson T. P., M. C. Peters, A. B. Ennett, and D. J. Mooney. “Polymeric System for Dual Growth Factor Delivery.” *Nature Biotechnology* 19, no. 11 (2001): 1029-34.
Prelude to degradable solid polymers: *In vivo* applications of Biomaterials

| ‘active’ lifetime: | • Implants  
|                  |   – Artificial hips, artificial heart, pacemaker, etc.  
| 8-10 yrs        | • Tissue engineering, cell therapy  
|                 |   – Delivery of cells  
|                 |   – Scaffolds for *in vivo* tissue guidance  
| ≤ 1 year        | • Drug delivery  
|                 |   – Injected or implanted devices  
| ≤ 6 months      | • Biosensors  
| Hours - days    |   – *In situ* measurements of pH, analyte concentrations, etc.  

Lecture 1 Spring 2006
If a material is to be utilized in vivo, what characteristics must it have in addition to fulfilling device requirements?

1. Non-toxic (pH changes, free radicals, O₂ anions, etc.)
2. Carcinogenic
3. Mutagenic
4. Allergenic (harmful immune response)

Cost of clinical trials ↑↑↑ as device approaches approval: Phase III > Phase II > Phase I

FDA standards & risk from disease being treated

RESULT: Very few # FDA-approved materials*

*by device application

CBS News | FDA Rejects Silicone Implants | January 8, 2004 09:38 ...

"Long-term safety, the concern that prompted the removal from the market 11 years ago, was clearly not demonstrated," Whalen wrote.
3 classes of materials used in vivo:

(1) biodegradable materials

- Breaks down by hydrolysis and enzymatic activity
- To form metabolized products
- Components of Kreb’s cycle: lactic acid and glycolic acid
(2) Bioeliminable Materials

**EXAMPLES:**

- **Poli(Ethylene Glycol) (PEG)**
  
  \[
  \text{PEG} < 20 \text{ kDa}
  \]

  \[
  \left(\text{CH}_2-\text{CH}_2-\text{O}\right)_{n}
  \]

  Ethers generally stable in vivo

- **Poly(Ethylene Oxide) (PEO)**
  
  \[
  \text{PEO} > 20 \text{ kDa}
  \]

**Dextran**

Polysaccharides

(Not degradable by mammalian enzymes)
(3) Permanent/retrievable materials

NOT DEGRADABLE OR EXCRETABLE

REQUIRE SURGERY FOR REMOVAL

EXAMPLES:

**Polyethylene** (CUP/Socket of Artificial Hips)

\[
CH_2 - CH_2 \quad \text{\(n\)}
\]

**Drug Delivery Matrix**

**Very Mild Inflammatory Response**

\[
O - C - CH_3
\]

\[
\left( -CH_2 \ CH_2 \right)_x \left( \ CH_2 \ CH_3 \right)_y
\]

Poly(ethylene-co-vinyl acetate) (PEVAc)

Extracellular environment

**Metals/Semiconductors**

Ti: Alloys Artificial Hips
Biodegradable solid polymers

• our definition of ‘biodegradable’ for this course: initially solid or gel-phase material reduced to soluble fragments that are metabolized or excreted under physiological conditions (saline environment, pH 7.4, 37°C)

• Why use biodegradable materials?
  
  1. TEMPORARY NEEDS
     GENERAL DESIRABILITY OF 1-TIME SURGERIES

  2. AVOID CHRONIC INFLAMMATION & ITS ASSOCIATED COMPLICATIONS

  3. LIMITED ALTERNATIVES IN ELIMINABLE MATERIALS
     (PEG, DEXTRAN, ALGINATE, CHITOSAN, ...?)
hydrolysis-susceptible bonds

1.  
\[ R-C=O-C=O \rightarrow R-C=-O + HO-C-R' \]

2. ESTERS
\[ R-C-O-C=O \rightarrow R-C=O + HO-R' \]

3. CARBONATES
\[ R-O-C=O \rightarrow R-O-C-OH + HO-R' \]
\[ \text{(generally stable in vivo w/o catalyst)} \]

4. AMIDE
\[ R-C-N=O \rightarrow R-C-OH + HO-N-R' \]
Pathways of solid polymer degradation

Mechanism I:
Cleavage of crosslinks between water soluble polymer chains

Mechanism II:
Transformation or cleavage of side chains (X) leading to the formation of polar or charged groups (Y)

Mechanism III:
Cleavage of backbone linkages between polymer repeat units.

Figure by MIT OCW.
Mechanism I example: polyanhydride networks

Mechanism II

- Poly(methyl vinyl ether-co-maleic anhydride)

- Poly(alkyl cyanoacrylates)
Mechanism III

Example: Polyphosphazenes:

\[
(N = P)_{n} + 2 \text{H}_2\text{N}-R
\rightarrow
(N = P)_{n} + 2 \text{H}_2\text{O} + \text{NH}_3 + \text{HO-P-OH}
\]
Medically-applied degradable polymers are chosen for metabolizable or excretable final breakdown products

- **PLGA**
  
  $$\text{KREB'S CYCLE}$$
  
  \[ \text{GLYCOLIC ACID} \rightarrow \text{LACTIC ACID} \rightarrow \text{CO}_2 + \text{H}_2\text{O} \]

- **Poly(caprolactone) (PCL)**
  
  \[ \text{6-HYDROXYCAPROYC ACID} \]

- **Poly(hydroxybutyrate)**
  
  \[ \text{D-3-HYDROXY BUTYRATE} \]
What doesn’t work?

- Degradation too slow
- Breakdown products not clearable

\[ \text{E.g., Poly(ethylene terephthalate) (PET)} \]

\[ \text{AROMATIC Oligomers/Monomers} \]

\[ \text{Very hydrophobic \rightarrow Forms Depositing} \]

\[ \text{Recrystallize \rightarrow In Vivo} \]
Physical chemistry of hydrolysis
structure influences mechanism of erosion as well as overall rate

- Mechanisms of dissolution:

  - Bulk Erosion

  - Surface Erosion

  - Linear loss of mass w/time

  - Constant matrix dimensions until total failure
Bulk vs. surface erosion

Bulk erosion (PLGA) 

Surface erosion

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Please see:


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.

Images of surface erosion removed due to copyright restrictions.
Dissolution during hydrolysis

Erosion profiles of poly(α-hydroxy esters) at pH 7.4.

Erosion profiles of poly(α-hydroxy esters) at pH > 13

Figure by MIT OCW.

Figure by MIT OCW.

Figure by MIT OCW.

Figure by MIT OCW.

Lecture 1 Spring 2006
Role of molecular structure in hydrolysis rate:

1. Relative bond stability
2. Hydrophobicity
3. Steric effects
4. Production of autocatalytic products
5. Microstructure
   - Crystallinity?
   - Phase separation?
   - Porosity?
Role of molecular structure in hydrolysis rate:

(1) Relative bond stability:

<table>
<thead>
<tr>
<th>Polymer Class</th>
<th>Half-life</th>
</tr>
</thead>
<tbody>
<tr>
<td>poly(anhydrides)</td>
<td>0.1 h</td>
</tr>
<tr>
<td>poly(ortho esters)</td>
<td>4 h</td>
</tr>
<tr>
<td>poly(esters)</td>
<td>3.3 yrs</td>
</tr>
<tr>
<td>poly(amides)</td>
<td>83000 yrs</td>
</tr>
</tbody>
</table>

Figure by MIT OCW.
(2) Effect of polymer hydrophobicity on solid polymer erosion rate

Sebacic acid

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

Figure by MIT OCW.
(3) Steric effects controlling polymer hydrolysis rates

• Local structure

• Glass transition (Tg)
(4) Production of autocatalytic products

• Polyesters:
Mechanisms of hydrolysis: polyesters

• acid-catalyzed hydrolysis:
Mechanisms of hydrolysis: polyesters

• Base-catalyzed hydrolysis: (saponification)

Nucleophilic substitution at acyl carbon
# Physical properties

Semicrystalline polymers boxed

<table>
<thead>
<tr>
<th>Polymer</th>
<th>Glass Transition (°C)</th>
<th>Melting Temperature (°C)</th>
<th>Tensile Strength (MPa)</th>
<th>Tensile Modulus (MPa)</th>
<th>Flexural Modulus (MPa)</th>
<th>Elongation Yield (%)</th>
<th>Elongation Break (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Poly(glycolic acid) (MW: 50,000)</td>
<td>35</td>
<td>210</td>
<td>n/a</td>
<td>n/a</td>
<td>n/a</td>
<td>n/a</td>
<td>n/a</td>
</tr>
<tr>
<td>Poly(lactic acids)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>l-PLA (MW: 50,000)</td>
<td>54</td>
<td>170</td>
<td>28</td>
<td>1200</td>
<td>1400</td>
<td>3.7</td>
<td>6.0</td>
</tr>
<tr>
<td>l-PLA (MW: 100,000)</td>
<td>58</td>
<td>159</td>
<td>50</td>
<td>2700</td>
<td>3000</td>
<td>2.6</td>
<td>3.3</td>
</tr>
<tr>
<td>l-PLA (MW: 300,000)</td>
<td>59</td>
<td>178</td>
<td>48</td>
<td>3000</td>
<td>3250</td>
<td>1.8</td>
<td>2.0</td>
</tr>
<tr>
<td>D, l-PLA (MW: 20,000)</td>
<td>50</td>
<td>-</td>
<td>n/a</td>
<td>n/a</td>
<td>n/a</td>
<td>n/a</td>
<td>n/a</td>
</tr>
<tr>
<td>D, l-PLA (MW: 107,000)</td>
<td>51</td>
<td>-</td>
<td>29</td>
<td>1900</td>
<td>1950</td>
<td>4.0</td>
<td>6.0</td>
</tr>
<tr>
<td>D, l-PLA (MW: 550,000)</td>
<td>53</td>
<td>-</td>
<td>35</td>
<td>2400</td>
<td>2350</td>
<td>3.5</td>
<td>5.0</td>
</tr>
<tr>
<td>Poly(β-hydroxybutyrate) (MW: 422,000)</td>
<td>1</td>
<td>171</td>
<td>36</td>
<td>2500</td>
<td>2850</td>
<td>2.2</td>
<td>2.5</td>
</tr>
<tr>
<td>Poly(ε-caprolactone) (MW: 44,000)</td>
<td>-62</td>
<td>57</td>
<td>16</td>
<td>400</td>
<td>500</td>
<td>7.0</td>
<td>80</td>
</tr>
<tr>
<td>Polyanhydridesb</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Poly(SA-HDA anhydride) (MW: 142,000)</td>
<td>n/a</td>
<td>49</td>
<td>4</td>
<td>45</td>
<td>n/a</td>
<td>14</td>
<td>85</td>
</tr>
<tr>
<td>Poly(ortho esters)c</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>DETOSU: t-CDM:1,6-HD (MW: 99,700)</td>
<td>55</td>
<td>-</td>
<td>20</td>
<td>820</td>
<td>950</td>
<td>4.1</td>
<td>220</td>
</tr>
<tr>
<td>Polymimocarbonatesd</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Poly(BPA iminocarbonate) (MW: 105,000)</td>
<td>69</td>
<td>-</td>
<td>50</td>
<td>2150</td>
<td>2400</td>
<td>3.5</td>
<td>4.0</td>
</tr>
<tr>
<td>Poly(DTH iminocarbonate) (MW: 103,000)</td>
<td>55</td>
<td>-</td>
<td>40</td>
<td>1630</td>
<td>n/a</td>
<td>3.5</td>
<td>7.0</td>
</tr>
</tbody>
</table>

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*Based on data published by Engelberg and Kohn (1991). n/a = not available, (−) = not applicable. bA 1:1 copolymer of sebacic acid (SA) and hexadecanedioic acid (HDA) was selected as a specific example. cA 100:35:65 copolymer of 3, 9-bis(ethylidene 2, 4, 8, 10-tetraoxaspiro [5,5] undecane) (DETOSU), *trans*-cyclohexane dimethanol (t-CDM) and 1, 6-hexanediol (1,6-HD) was selected as a specific example. dBPA: Bisphenol A; DTH: desaminotyrosyl-tyrosine hexyl ester.

Figure by MIT OCW.
Further Reading