Lecture 21: Biomaterials for Organ Replacement

Therapies for Organ Replacement

1. Transplantation
   Replacement of tissue or organ from human or animal donor

   Allograft—human donor (e.g., kidney, liver, heart)
   Xenograft—animal donor (e.g., porcine aortic valves)

   Adv:
   • complete recovery of lost function for patient lifetime

   Disads:
   • possibility of rejection—attack by immune system
   • side effects of immunosuppressive drugs (e.g., steroids)
   • limited donor pool

2. Autograft
   Donor is also recipient

   Examples: skin grafts, nerve grafts, breast reconstructions, saphenous (calf) vein for coronary or peripheral artery bypass (~300,000/yr in U.S.)

   Adv:
   • complete recovery of lost function for patient lifetime
   • virtually no danger of rejection

   Disads:
   • limited self-donor tissue available
   • trauma/scarring at removal site
3. Regenerated Tissues/Organs

Cells grown on a scaffold device (synthetic or collagen-based, often resorbable) provide restored function (e.g., skin and cartilage)

**Adv:**
- no donor/self-donor tissue limitations
- function restored for patient lifetime (in principle)

**Disads:**
- biological complexities of complete organ regeneration unsolved
- possible immune response, depending on cell source

4. Permanent Implants

Prosthetic devices manufactured from synthetic materials (e.g., hip prostheses, >200,000/yr in U.S., many designs)

Acetabular cup: metal with UHMWPE (2M Daltons) liner

Femoral head: CoCr, Ti, Al₂O₃

Femoral stem: CoCr, Ti, stainless steel

PMMA cement: adhesion, shock absorption

(Alt: metal bead or HAp coatings: bone ingrowth)
**Advantages:**
- no donor/self-donor tissue limitations
- cannot be “rejected” by classical complement mechanisms

**Disadvantages:**
- “full” organ function not restored
  
  e.g., orthopedic replacements:
  - loss of bone marrow (origin of blood stem cells)
  - no regenerative ability
  - reduced range of mobility

- often must be replaced
  
  - *chronic inflammation*
    
    e.g., PE wear debris $\Rightarrow$ immune response $\Rightarrow$ bone breakdown
  - *mechanical failure*
    
    e.g., cement loosening

- other long-term side effects

  *stress-shielding*: modulus mismatch between stem & femur
  $\Rightarrow$ load imbalance on surrounding bone
  $\Rightarrow$ osteoporosis (bone resorption $>$ deposition)
  $\Rightarrow$ increased likelihood of re-fracture

Clearly, *mechanical properties* play a critical role in materials choice!
Mechanical Properties of Interest in Biomaterials Applications:

- Stiffness
- Strength
- Toughness
- Hardness
- Fatigue (especially cyclic)
- Fracture strength
- Wear resistance

We need methods to quantify these material qualities.

Let’s define some terms in the context of a simple uniaxial load experiment:

F = Applied Force

Ao = Area

Lo

δ

(∝ F)

“elastic” deformation (recoverable)

“plastic” deformation (irrecoverable)

fracture
Biomaterials examples:

- fixture plates (stainless steel, CoCr, Ti) (B)
- vascular prostheses: knitted Dacron or ePTFE (B)
- hydrogels: HEMA (C)
- breast implants: silicone (C)
- dental implants (alumina) (A)
- **Stiffness**: quantified by Young’s modulus (elastic modulus—slope of initial linear stress-strain region)

\[ E = \frac{\sigma}{\varepsilon} \] (independent of sample geometry—a material property)

**Flexure modulus** \((E_F)\) — strength values measured in bending test

**3-point bending test:**

\[
\delta = \frac{FL^3}{48E'I}
\]

where \(I\) = moment of inertia (ex. units: \(m^4\))

\[
I = \frac{wh^3}{12} \quad \text{for rectangular beams}
\]

\(I\) is the 2nd moment of the transverse area of the beam about neutral surface axis (where compressive and tensile forces cancel).

\[ I = \int x^2 dA, \text{ where } x \text{ is distance from neutral axis and } A \text{ is cross-sectional area.} \]
Strength: several quantities of interest for comparison

1. Modulus (since higher E materials correlate with higher strength)
2. Yield stress—stress at onset of plastic deformation
3. Ultimate (tensile) strength (UTS)—peak of stress-strain curve
4. Fracture strength—stress at point of fracture
   - engineering—measured value
   - true—value that accounts for necking (change in x-sec area)
     (lower than compression strength, higher than UTS)
5. Fatigue strength—max. load withstood 10M cycles w/o fracture

Cyclic Fatigue: Material subjected to cyclic stress for long times below its UTS but above its “endurance limit” \( \Rightarrow \) fracture

Example: Load on hip joint during walking
3.051J/20.340J

Materials Prone to Fatigue:
• ductile/plastic materials – metals & polymers
• materials with defects/anisotropy (multiphase, composites)

Crack initiates at defect/interface
⇒ propagates on subsequent loadings
⇒ catastrophic failure

Biomimetic Strategies:
• limit crack growth (ex., multi-ply laminate—bone)
• regenerate tissue (HAp implant or bone)

<table>
<thead>
<tr>
<th>Material</th>
<th>E (GPa)</th>
<th>YS (MPa)</th>
<th>UTS (MPa)</th>
<th>Fatigue Strength (MPa)</th>
<th>Flexure Strength (MPa)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CoCr cast</td>
<td>214</td>
<td>450</td>
<td>655</td>
<td>240-280</td>
<td></td>
</tr>
<tr>
<td>Ti</td>
<td>110</td>
<td>480</td>
<td>550</td>
<td>240</td>
<td></td>
</tr>
<tr>
<td>TiAlV alloy</td>
<td>120</td>
<td>795</td>
<td>860</td>
<td>300-600</td>
<td></td>
</tr>
<tr>
<td>316 Stainless Steel</td>
<td>200</td>
<td>250</td>
<td>600</td>
<td>260-280</td>
<td></td>
</tr>
<tr>
<td>Alumina</td>
<td>380</td>
<td>---</td>
<td>260</td>
<td></td>
<td>550</td>
</tr>
<tr>
<td>Cortical Bone</td>
<td>17.4</td>
<td>115</td>
<td>121</td>
<td>208</td>
<td></td>
</tr>
<tr>
<td>PMMA cement</td>
<td>2.2</td>
<td>---</td>
<td>29</td>
<td></td>
<td>90</td>
</tr>
<tr>
<td>UHMWPE</td>
<td>1</td>
<td>25</td>
<td>34</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Toughness: measure of total work necessary for fracture (per unit vol material)—the total area under stress-strain curve

\[
Toughness = \int_{\varepsilon_i}^{\varepsilon_f} \sigma d\varepsilon = \int_{L_o}^{L_f} \frac{\sigma}{L} dL
\]

Units: \((F/A)(L/L) = (E/V)\)

Steel > Al\(_2\)O\(_3\) > PMMA

Hardness: measure of resistance to plastic deformation; the force per unit area of indentation

Hardness testing:

Vicker’s Hardness number: \(HV = F/d_1^2\)

Note: Hardness correlates with Yield strength (Y.S.) in compression

Wear: removal or relocation of materials during sliding contact

Critical problem for joint prostheses & fixtures!
\[\Rightarrow\] accelerated corrosion, wear products (PE liner)

Metric for wear: \(\mu = \text{sliding coefficient of friction}\)
Consider two surfaces brought together under compressive load: plastic junctions are main friction source.

For a ductile material, contact area increases with $F_{\text{comp}}$:

$$F_{\text{comp}} = H \times A$$

where $H$ is hardness (or compressive yield stress)

The sliding force to overcome the shear yield stress of junctions is:

$$F_{\text{shear}} = YS_{\text{shear}} \times A$$

$$\mu = \frac{F_{\text{shear}}}{F_{\text{comp}}} = \frac{YS_{\text{shear}}}{H} \quad (\text{material constants of weaker material})$$

*For low $\mu$:*

1. Hard materials (ion implanted Ti)
2. Low shear yield stress
   - lubricant/interlayer (e.g., UHMWPE liner of acetabular cup)

$\mu$ values

<table>
<thead>
<tr>
<th>metal/metal</th>
<th>metal/nonmetal</th>
<th>articular knee cartilage</th>
<th>metal/metal lubricated</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.3-1.</td>
<td>0.3-0.5</td>
<td>0.005-0.02</td>
<td>0.05-0.12</td>
</tr>
</tbody>
</table>
Properties Desirable for Bone Replacements

- **Stiffness** (structural support, low deformation energy losses)
- **Flexure Strength, compliancy** \((1/E)\) (avoid break on falling)
- **Low Mass** (light, reduce energy losses while walking)
- **Long lifetime** (high endurance, fatigue strength)

How Does Natural Femur Differ from Hip Prostheses?

- **Strength and Stiffness**

<table>
<thead>
<tr>
<th>Material</th>
<th>Compression Modulus, GPa</th>
<th>Compressive strength, MPa</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cortical Bone (femur)</td>
<td>18.2</td>
<td>195</td>
</tr>
<tr>
<td>Cancellous Bone (femur)</td>
<td>2.9</td>
<td>68</td>
</tr>
<tr>
<td>Ti</td>
<td>110</td>
<td>550</td>
</tr>
<tr>
<td>PMMA cement</td>
<td>2.5</td>
<td>92</td>
</tr>
<tr>
<td>Alumina</td>
<td>380</td>
<td>4500</td>
</tr>
</tbody>
</table>
• Mechanical Properties are Anisotropic

<table>
<thead>
<tr>
<th>Property</th>
<th>Tension L</th>
<th>Tension T</th>
<th>Compression L</th>
<th>Compression T</th>
</tr>
</thead>
<tbody>
<tr>
<td>Modulus (GPa)</td>
<td>17.9</td>
<td>10.1</td>
<td>18.2</td>
<td>11.7</td>
</tr>
<tr>
<td>Ultimate Strength (MPa)</td>
<td>135</td>
<td>53</td>
<td>105</td>
<td>131</td>
</tr>
</tbody>
</table>

• Origin of Anisotropy: Bone Structure

Bone is a composite material (microcomposite) collagen-rich organic/hydroxyapatite crystallites

Figure by MIT OCW.
Bone structure: two types of bone

Cortical (compact) bone:

- Low porosity (<10%: Haversian canals in osteon centers)
- Found in long-bone shafts & cortex (shell) of trabecular bone
- Multi-ply lamellar structure

Each lamellae: oriented collagen fibers (20wt%) &
HAp \( \text{Ca}_{10}(\text{PO}_4)_{6}(\text{OH})_2 \) 2x20x40 nm crystallites (70wt%)

In children:
- Osteons around vessels

In adults:
- Secondary osteons replace circumferential bone
Modeling Anisotropic Composites

Example: a uniaxially-oriented, continuous 2-phase structure

Load along the longitudinal axis:

\[ E = E_1 V_1 + E_2 V_2 \]

\((V_i)\) is volume fraction of \(i\)th component

(Derived from \(F_i = A_i E_i \varepsilon_i\))

Load along transverse axis:

\[ \frac{1}{E} = \frac{V_1}{E_1} + \frac{V_2}{E_2} \]

(Note: text gives governing eqns for other composite structures, such as randomly oriented fiber/matrix composites)
Model compact bone as continuous fiber (osteon)/matrix (primary) composite

Structural Advantage of Multilaminates: Fracture Toughness

Cracks opened perpendicular to the load are stopped by cross-ply fibers

→ Resistance to cyclic fatigue

Trabecular (cancellous/spongy) bone:

• Highly porous (>75%)
• 200 µm-thick “struts”
• found in “cuboidal” bones (vertebrae, digits), flat bones, long-bone ends

Bone Remodeling

- Bone structure is dynamic, responding to:
  - load
  - local physiological conditions

  ex. Cortical bone turnover in femur ~3%/yr

- Bone is torn down and reconstructed by cell teams (Basic Multicellular Units or BMUs)
  - **Osteoclasts**: bone resorption cells, related to macrophages
  - **Osteoblasts**: bone deposition cells, related to fibroblasts
  - **Osteocytes**: osteoblasts that get trapped in osteon, become quiescent

- Fatigue may direct remodeling

**Hypothesis 1**: Debonding isolates osteon ⇒ low stress state ⇒ activate new BMUs (ex, osteocyte signal release or low stress on bone lining cells)

**Hypothesis 2**: Cracks disrupt osteocyte “process” network ⇒ inhibitory signals removed ⇒ bone lining cells initiate remodeling
Natural Bone has *Viscoelastic Response*

On short time scales: solid-like
On long time scales: liquid-like

Compression at different strain rates: $\sigma$

Model with viscous liquid & elastic solid elements  
(Dashpot & Spring)

Springs:  $\sigma = E\varepsilon$
Dashpots: $\sigma = \eta \frac{d\varepsilon}{dt}$

\[
\frac{d\sigma}{dt} + \frac{(E_1 + E_2)}{\eta} \sigma = \frac{E_1 E_2}{\eta} \varepsilon + E_2 \frac{d\varepsilon}{dt}
\]

Solve according to test conditions: creep, stress-relaxation, cyclic loading, etc.
Directions in Orthopedic Implants

- Polymer/fiber composites
- Polymer/ceramic composites
- Osteogenic materials

Osteogenic Materials

Towards fully resorbable implants ⇒ Tissue Engineering

ETEX Bone Substitute

1. High T calcium phosphate compound (e.g., TCP) mixed with water
2. Formation of HAp thick paste at 37°C
3. Hardens to porous, bioresorbable material
4. Over time (10 weeks), implant replaced by bone

\[ \text{Ca}_3(\text{PO}_4)_2 + 2\text{H}_2\text{O} \Rightarrow \text{Ca}_{10}(\text{PO}_4)_6(\text{OH})_2 + 2\text{Ca}^{2+} + 2\text{HPO}_4^{2-} \]

Advantage: Fully functional bone recovered
   (incl. marrow space, blood vessels, nerves, stem cells)

Remaining Issues:
1. Insufficient mechanical properties:
   - HAp porous scaffolds—brittle, low strength
   - may require temporary fixture device (steel plate)
   - not yet feasible for long bones such as femur

   Possible soln: composite structures (e.g., addition of fibers)

2. Resorption process is slow