3.051J/20.340J

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:

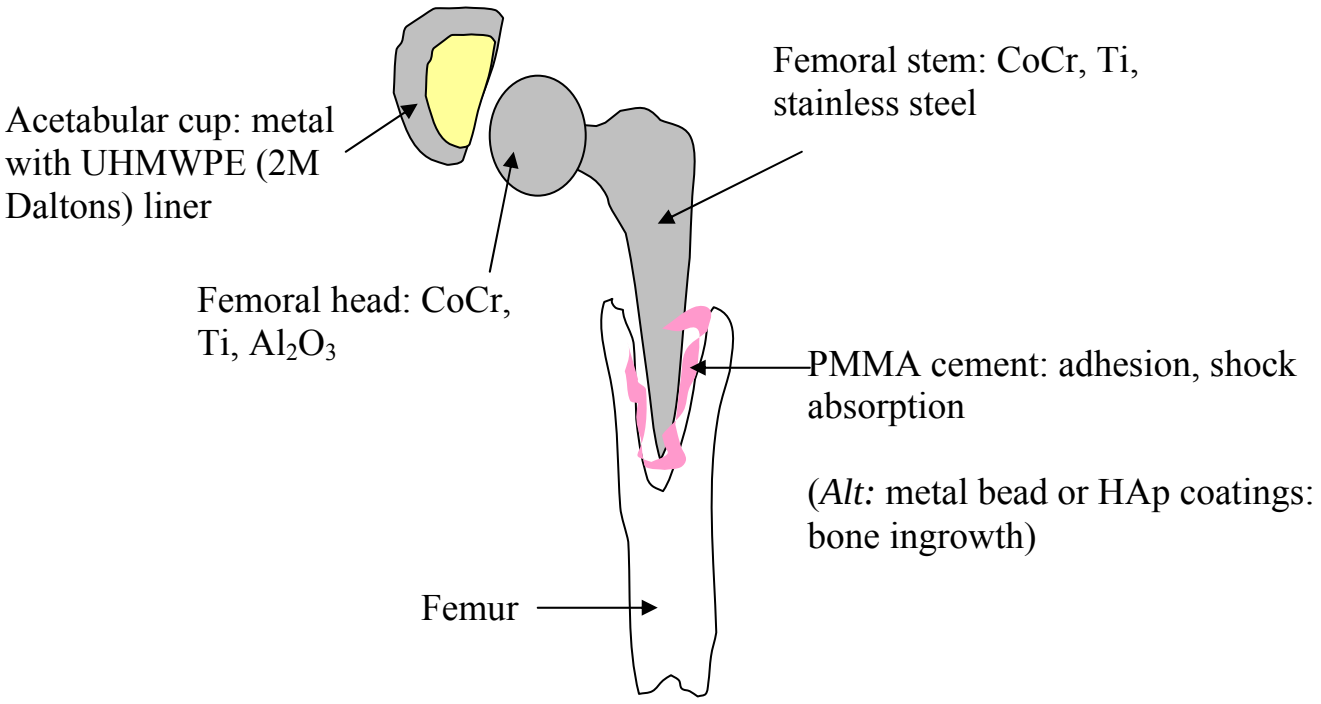
- no donor/self-donor tissue limitations
- function restored for patient lifetime (in principle)

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)



Advs:

- no donor/self-donor tissue limitations
- cannot by "rejected" by classical complement mechanisms

Disads:

- "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 ⇒ immune response ⇒ bone breakdown
  - *mechanical failure*
    e.g., cement loosening

- other long-term side effects

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

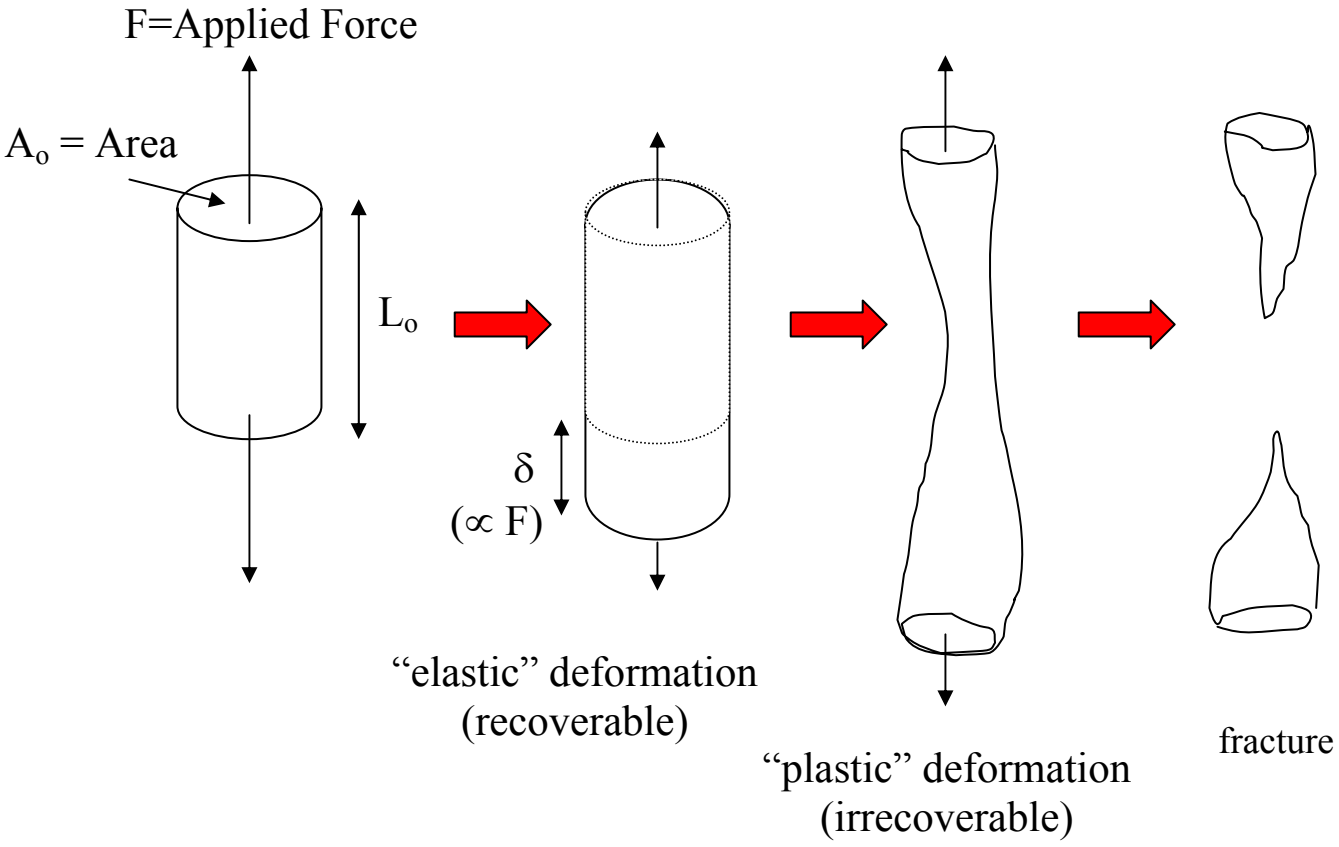
Clearly, *mechanical properties* play a critical role in materials choice!

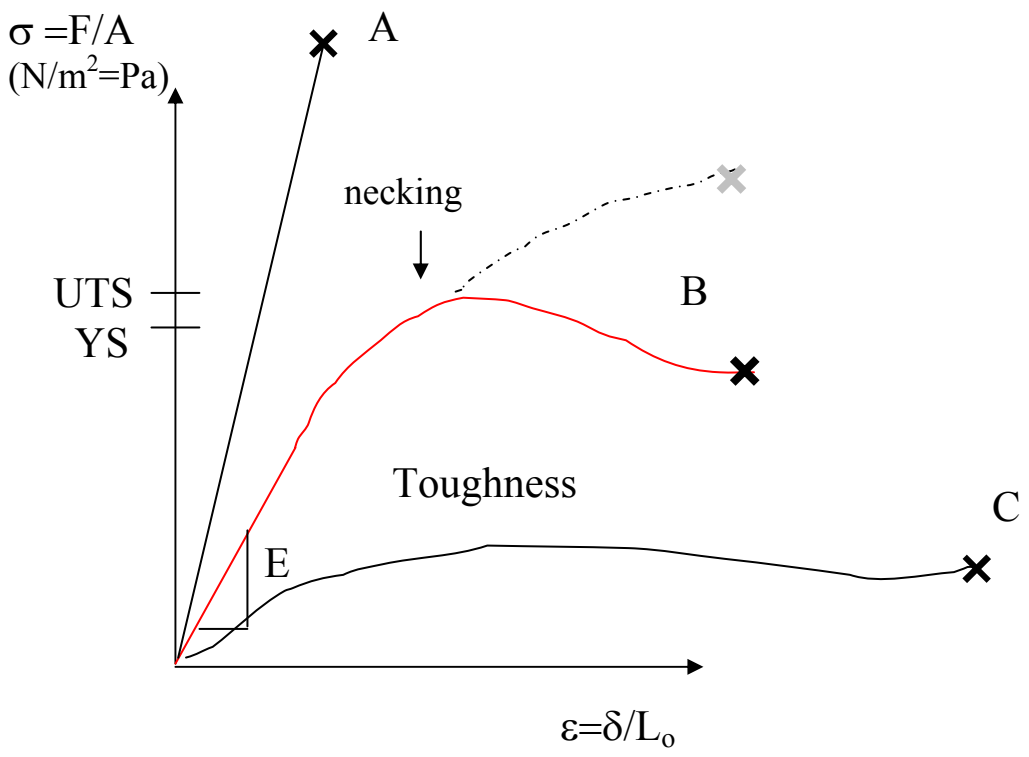
Mechanical Properties of Interest in Biomaterials Applications:

- 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:





Biomaterials examples:

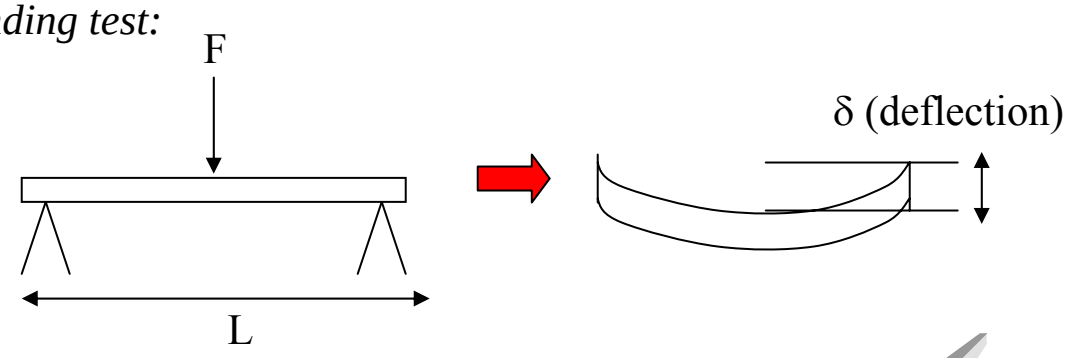
- fixture plates (stainless steel, CoCr, Ti) (B)
- vascular prostheses: knitted Dacron or ePTFE (B)
- hydrogels: HEMA (C)
- breast implants: silicone (C)
- dental implants (alumina) (A)

- **Stiffness**: quantified by Young's modulus (elastic modulus—slope of initial linear stress-strain region)

  $E = \sigma/\varepsilon$ (independent of sample geometry—a material property)

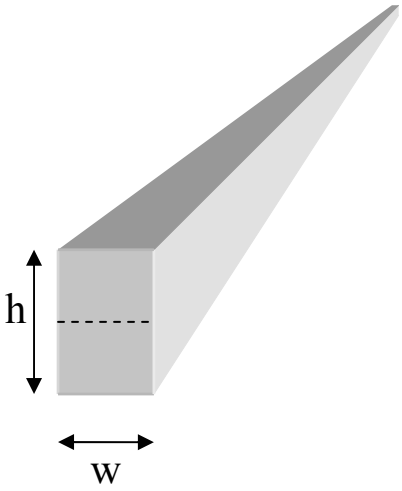
  Flexure modulus (E_F) —strength values measured in bending test

3-point bending test:



Governing eqn: $\delta = \dfrac{FL^3}{48E_F I}$

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



$I = \dfrac{wh^3}{12}$ 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).

$I = \int x^2 dA$, where x is distance from neutral axis and A is cross-sectional area.

- **Strength**: several quantities of interest for comparison

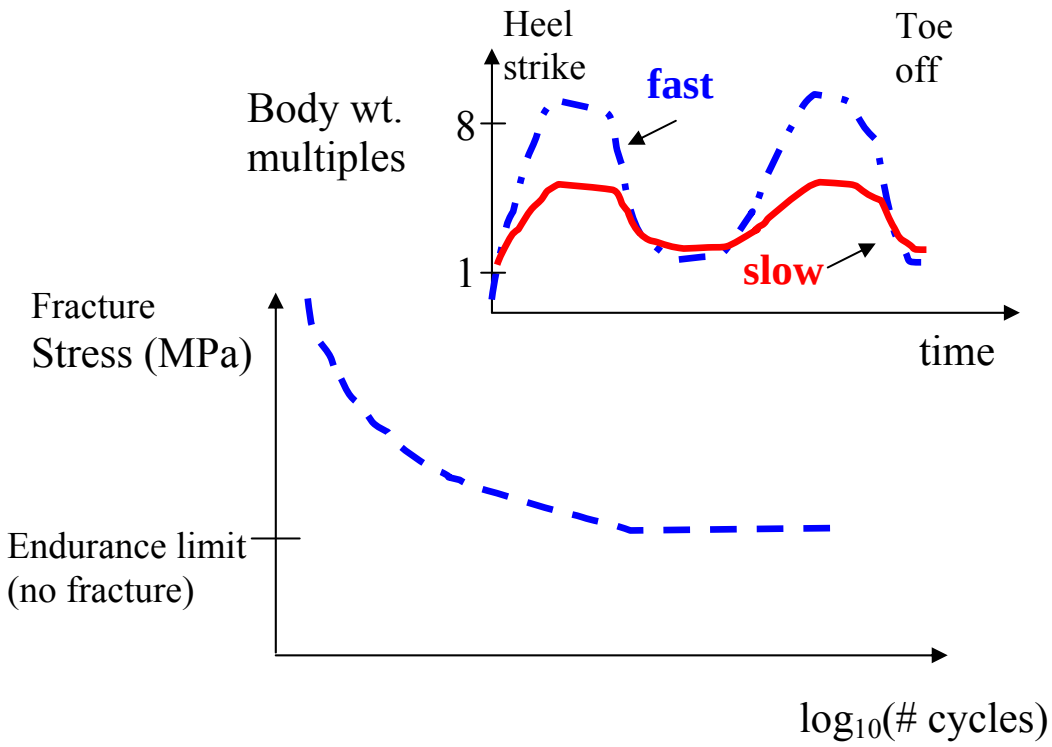
1. Modulus (since higher E materials correlate with higher strength)
2. Yield stress—stress at onset of plastic deformation
3. Ultimate (tensile) strength (UTS)—peak of stress-strain curve
4. Fracture strength—stress at point of fracture

   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" ⇒ fracture

Example: Load on hip joint during walking



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)

Material	E (GPa)	YS (MPa)	UTS (MPa)	Fatigue Strength (MPa)	Flexure Strength (MPa)
CoCr cast	214	450	655	240-280	
Ti	110	480	550	240	
TiAlV alloy	120	795	860	300-600	
316 Stainless Steel	200	250	600	260-280	
Alumina	380	---	260		550
Cortical Bone	17.4	115	121		208
PMMA cement	2.2	---	29		90
UHMWPE	1	25	34		

- **Toughness**: measure of total work necessary for fracture (per unit vol material)—the total area under stress-strain curve

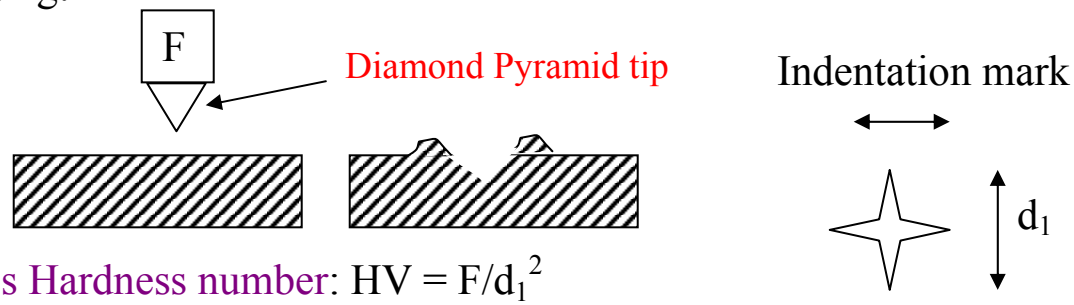
$$\text{Toughness} = \int_{\varepsilon_i}^{\varepsilon_f} \sigma d\varepsilon = \int_{L_o}^{L_f} (\sigma / L) dL$$

Units: (F/A)(L/L) = Energy/Volume

Steel > Al_2O_3 > PMMA

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

Hardness testing:



Vicker's Hardness number: $HV = F/d_1^2$

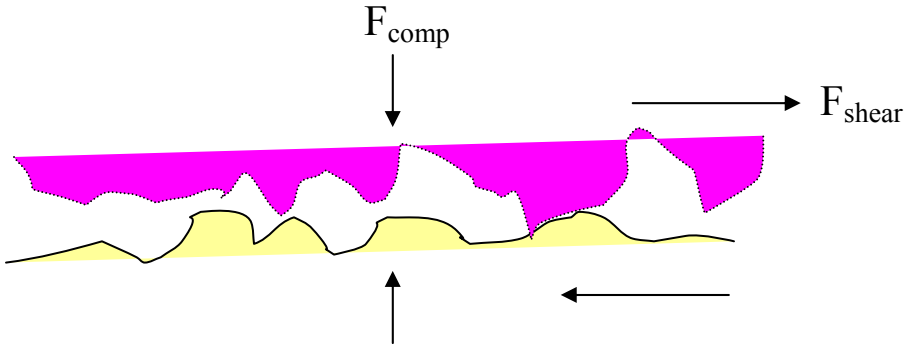
Note: Hardness correlates with Yield strength (Y.S.) in compression

- **Wear:** removal or relocation of materials during sliding contact

Critical problem for joint prostheses & fixtures!
⇒ accelerated corrosion, wear products (PE liner)

Metric for wear: μ= 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_{comp}:

$F_{comp} = H \times A$ where H is hardness (or compressive yield stress)

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

$F_{shear} = YS_{shear} A$

$\mu = F_{shear}/F_{comp} = (YS)_{shear}/H$ (material constants of weaker material)

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

μ values

metal/metal	metal/nonmetal	articular knee cartilage	metal/metal lubricated
0.3-1.	0.3-0.5	0.005-0.02	0.05-0.12

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

Material	Compression Modulus, GPa	Compressive strength, MPa
Cortical Bone (femur)	18.2	195
Cancellous Bone (femur)	2.9	68
Ti	110	550
PMMA cement	2.5	92
Alumina	380	4500

- Mechanical Properties are Anisotropic

Property	Tension		Compression	
	L	T	L	T
Modulus (GPa)	17.9	10.1	18.2	11.7
Ultimate Strength (MPa)	135	53	105	131

- Origin of Anisotropy: Bone Structure

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

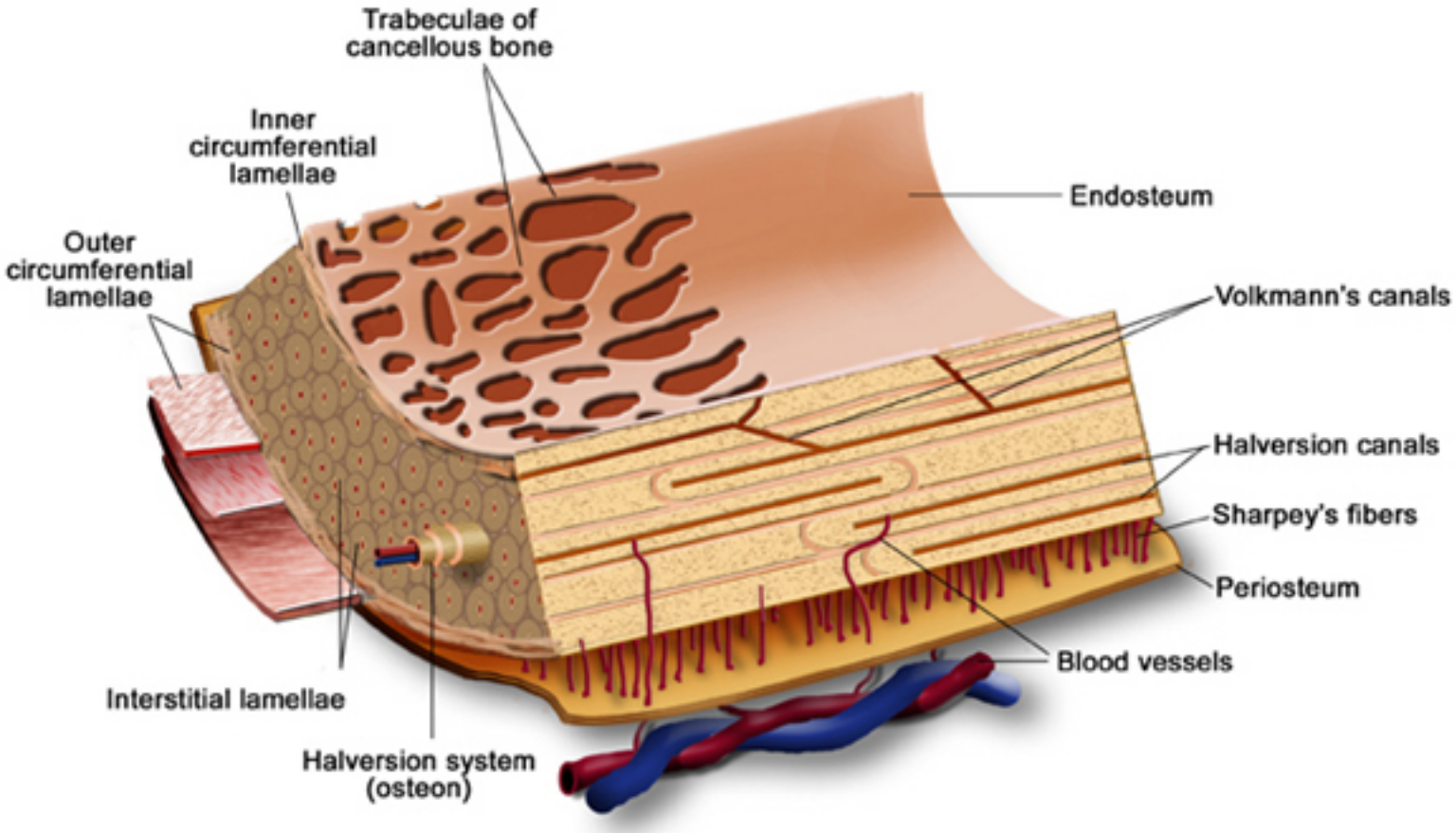


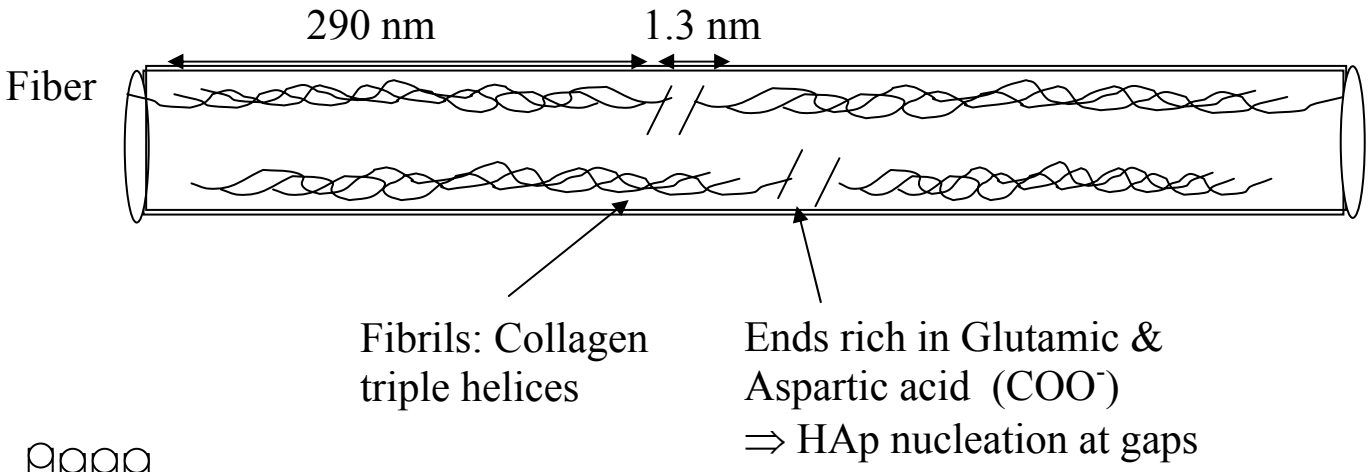
Figure by MIT OCW.

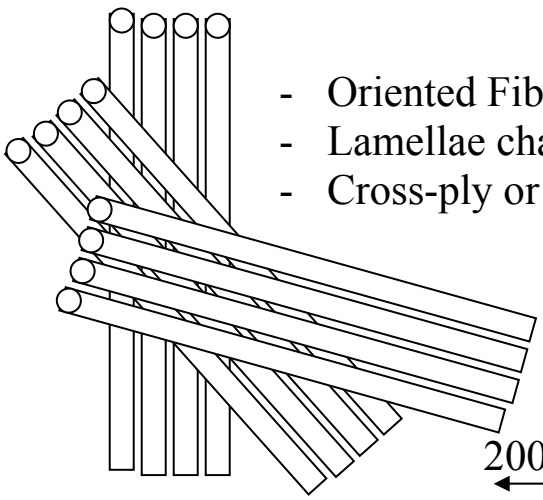
Bone structure: *two types of bone*

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 [$Ca_{10}(PO_4)_6(OH)_2$] 2x20x40 nm crystallites (70wt%)

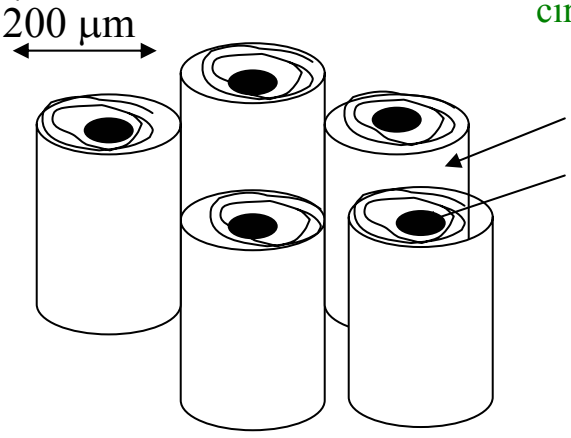




- Oriented Fibers form Lamellae
- Lamellae change orientation concentrically
- Cross-ply or Helicoid structures

In children:
- circumferential lamellae
-osteons around vessels

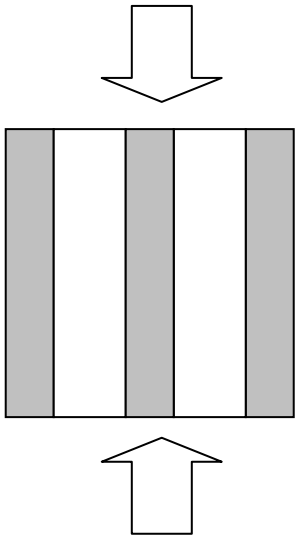
In adults:
-secondary osteons replace circumferential bone



Modeling Anisotropic Composites

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

Load along the longitudinal axis:



Voigt model: equal strains
(parallel strain model)

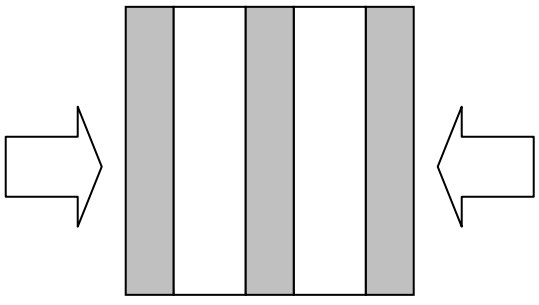
$$E = E_1V_1 + E_2V_2$$

(V_i is volume fraction of *ith* component)

(Derived from $F_i = A_iE_i\varepsilon_i$)

Load along transverse axis:

Reuss model: equal stresses
(series strain model)

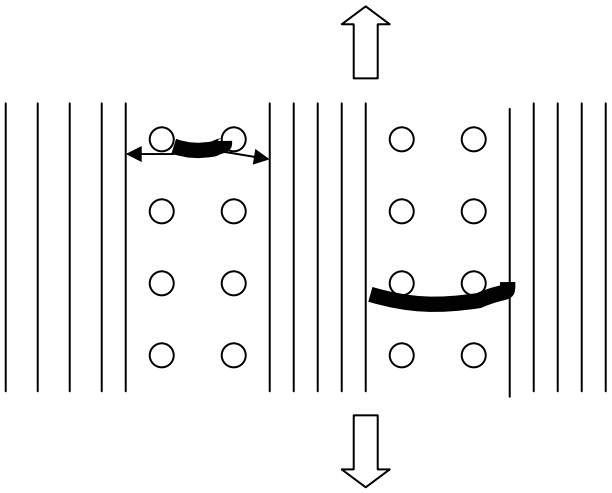


$$\frac{1}{E} = \frac{V_1}{E_1} + \frac{V_2}{E_2}$$

(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

Photo removed for copyright reasons.

from *Skeletal Tissue Mechanics*, R.B. Martin, D.B. Burr, and N.A. Sharkey, Springer-Verlag: NY, 1998

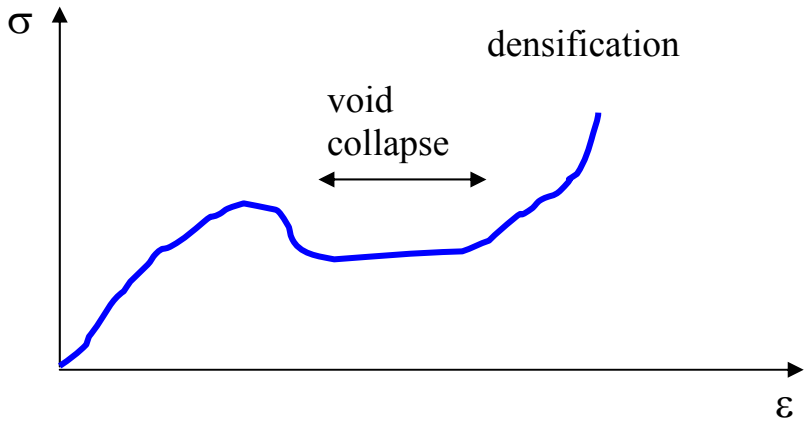
Trabecular (cancellous/spongy) bone:

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

Photo removed for copyright reasons.

from *Skeletal Tissue Mechanics*, R.B. Martin, D.B. Burr, and N.A. Sharkey, Springer-Verlag: NY, 1998

Compression behavior



Bone Remodeling

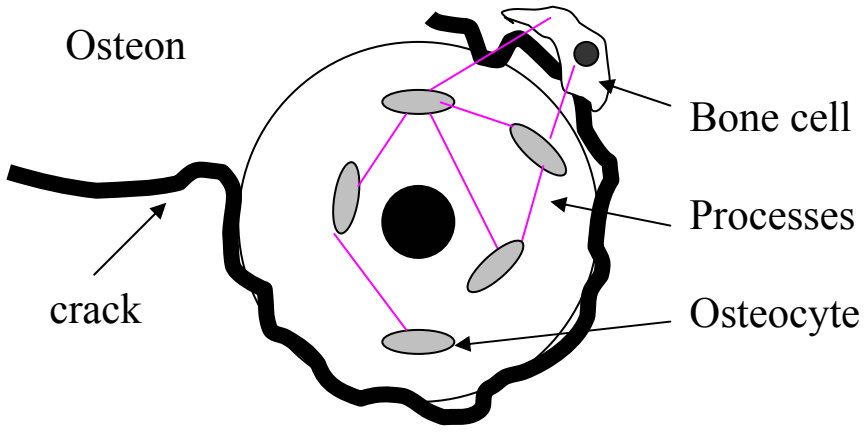
- Bone structure is dynamic, responding to:
  - load
  - local physiological conditions

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)

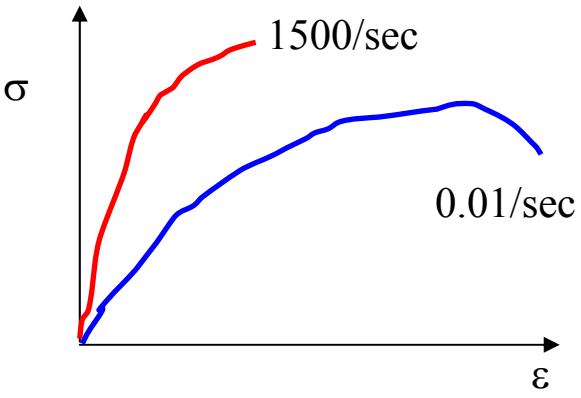


Hypothesis 2: Cracks distrupt osteocyte "process" network ⇒ inhibitory signals removed ⇒bone lining cells initiate remodeling

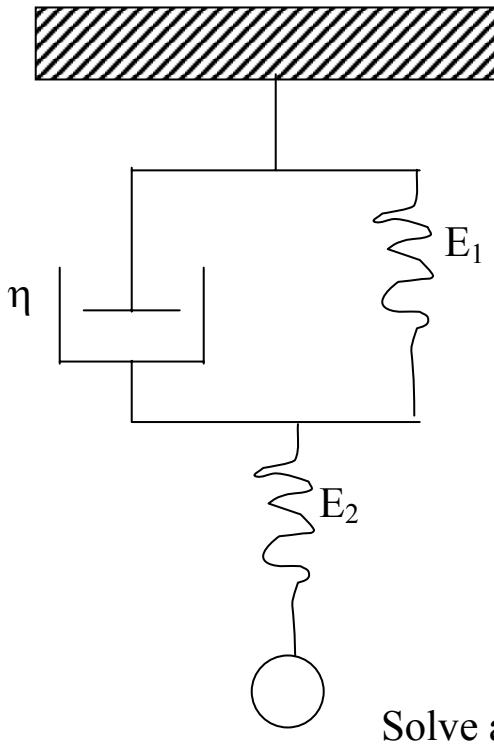
Natural Bone has *Viscoelastic* Response

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

Compression at different strain rates:



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



Springs: $\sigma = E\varepsilon$
Dashpots: $\sigma = \eta d\varepsilon/dt$

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

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 37C
3. Hardens to porous, bioresorbable material
4. Over time (10 weeks), implant replaced by bone

$$Ca_3(PO_4)_2 + 2H_2O \Rightarrow Ca_{10}(PO_4)_6(OH)_2 + 2Ca^{2+} + 2HPO_4^{2-}$$

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