Harvard-MIT Division of Health Sciences and Technology
HST.523J: Cell-Matrix Mechanics
Prof. Lorna Gibson, guest lecturer

Structure-Property Relationships for Tissue Engineering Scaffolds

Prof. Lorna Gibson

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Wound Healing: Contractile Response

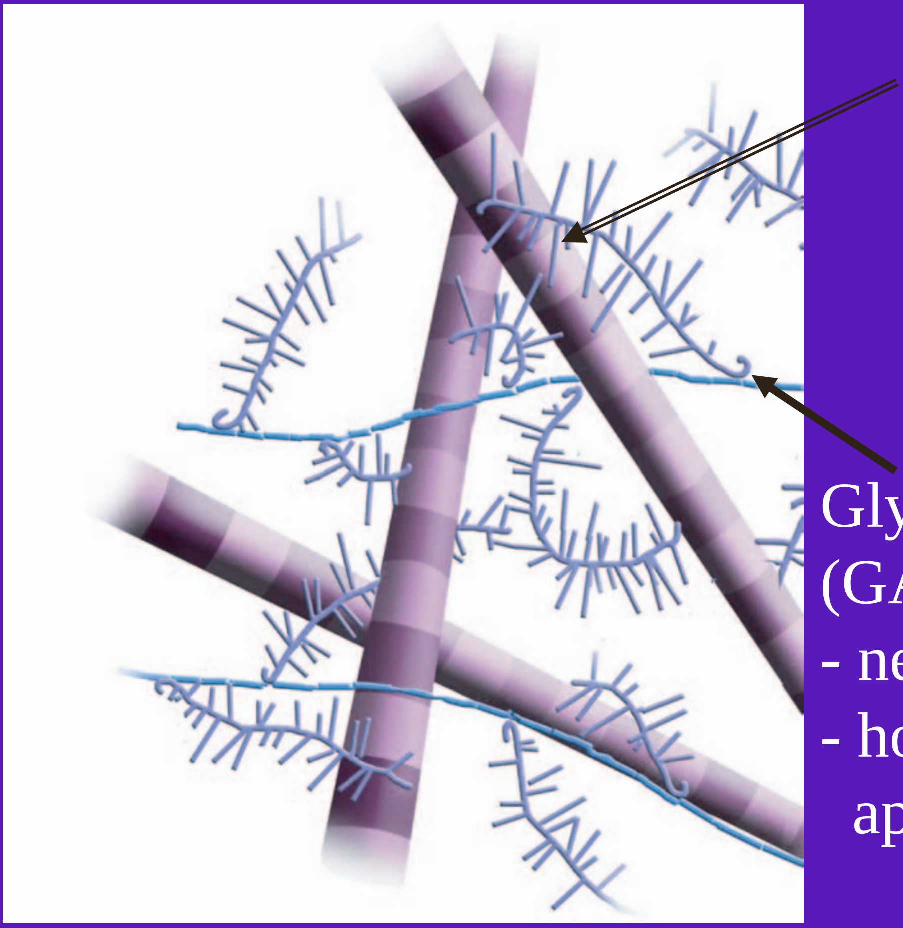
- Skin wounds: fibroblasts migrate into the wound bed, differentiate into myofibroblasts
- Myofibroblasts pull edges of wound towards each other
- Contractile response associated with formation of scar tissue

Wound Healing: Contractile Response

- Tissue engineering: inhibition of contractile response leads to regeneration of normal tissue
- Interest in understanding mechanical interactions between cells and tissue engineering scaffolds
- Can also use scaffold as a model, *in vitro* system for studying contractile response
- Need to understand the mechanical response of the scaffold

Extracellular Matrix

- In body cells attach to extracellular matrix (ECM), migrate along it, multiply and function



Collagen

Glycosaminoglycan (GAG)
- negatively charged
- holds collagen fibres apart

Figure by MIT OCW. After G. B. Ricci.

Tissue Engineering Scaffolds/Matrix

- Porous scaffold or matrix mimics body’s ECM
- Cells migrate into scaffold from surrounding tissue OR
- Cells harvested from patient, cultured, seeded onto scaffold
- Inhibition of contractile response
- Over time, synthetic matrix resorbs into the body and cells produce own ECM
- Applications: skin, cartilage, nerve, bone, liver

Example: Cartilage Regeneration

Diagram removed for copyright reasons.

sketch from Freed et al. (1993)

***J. Biomed. Mat. Res.* 27, 11-23.**

Matrix Materials

- **Requirements**

  Solid phase
  - biocompatible
  - composition: ligands for cell binding
  - degrade into non-toxic components that can be eliminated from the body over time
  - Examples:
    - poly L lactic acid (PLA)
    - polyglycolic acid (PGA)
    - poly DL lactic-co-glycolic acid (PLGA)
    - collagen-based materials

  Cellular structure
  - high porosity: >90%
  - pore size: 100-200μm
  - interconnected porosity
  - critical degradation rate
  - mechanical integrity

Matrix Materials

Photo removed for copyright reasons.
See Figure 1b in Pek YS, Spector M, Yannas IV and Gibosn LJ Degradation of a collagen chondroitin-6-sulfate by collagenase and chondroitinase *Biomaterials* 25, 473-482 (2004).

Collagen-GAG - freeze dried

Photo removed for copyright reasons.

Photo removed for copyright reasons.

PGA - bonded fibres
(Mikos et al, 1993)

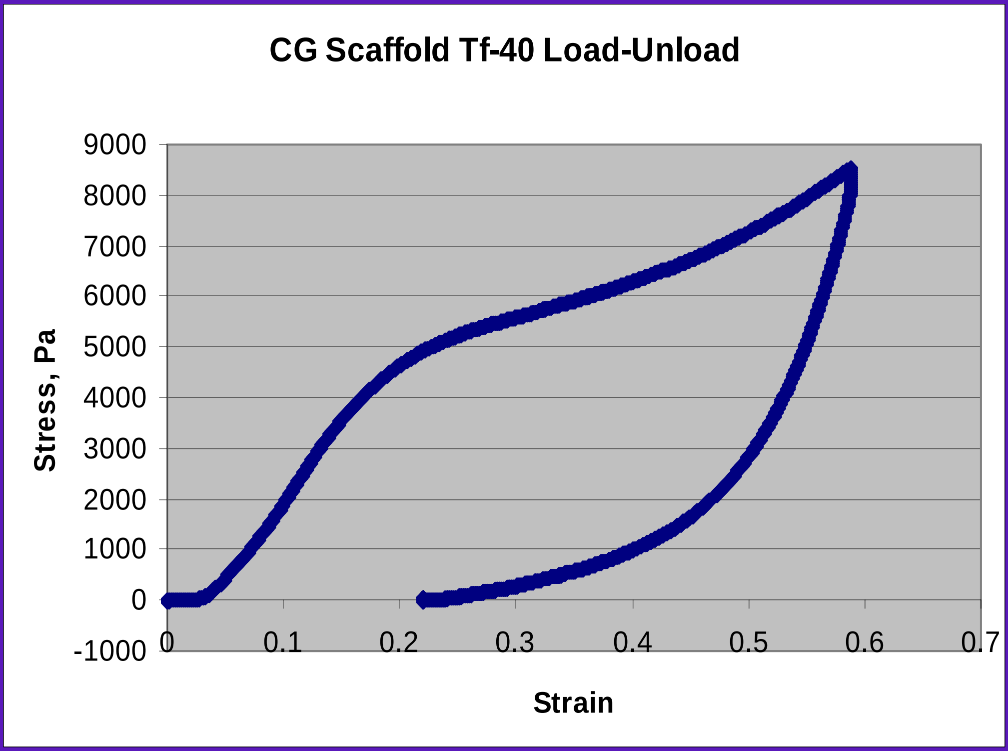
Polycarbonate - salt leached
(Kohn; from Lhommeau et al, 1998)

Cellular Materials

Photos removed for copyright reasons.
See Figure 2.5 in Gibson, L.J. and M.F. Ashby. *Cellular Solids: Structure and Properties*.

Cellular Materials

Graph of Polyurethane Compression removed for copyright reasons.
See Gibson, L.J. and M.F. Ashby. *Cellular Solids: Structure and Properties*. New York: Cambridge University Press, 1997.



Matrix Materials

- Structure and stress-strain curve of matrix similar to that of open-cell foam
- Open-cell foams are a type of cellular material
- Similarities in the mechanical behaviour of cellular solids due to similarities in their structure
- Models for the mechanics of cellular solids may be applied to tissue engineering scaffolds

2D Honeycomb Models for Cellular Materials

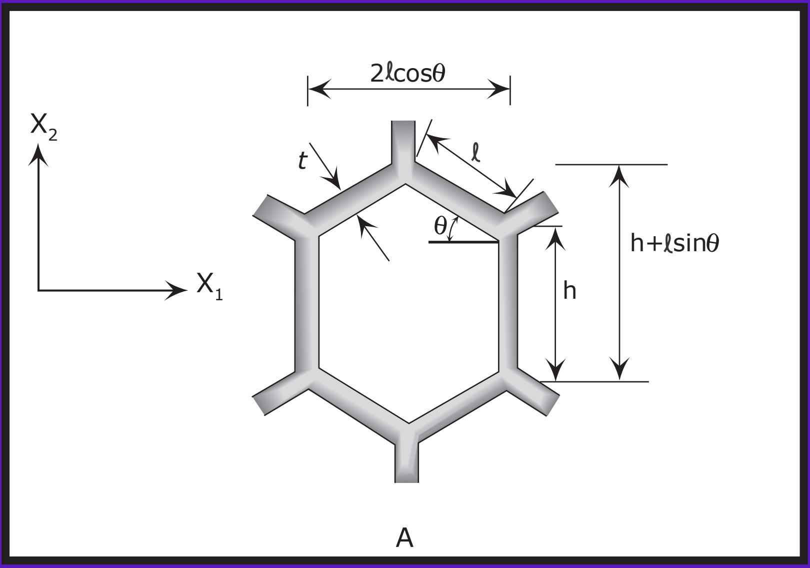


Figure by MIT OCW. After Gibson and Ashby.

- exact structural analysis:
- $E = f\ \{(t/l)^3, E_s$, cell geometry$\}$
- $\sigma^* = f\ \{(t/l)^2, \sigma_{ys}$, cell geometry$\}$
- $\varepsilon_D = f\ \{(t/l)\}$
- $\rho/\rho_s = f\ \{t/l\}$
- Engineering honeycombs, wood, cork

3D Foam Models

- Dimensional analysis:
  - model mechanisms of deformation and failure, but not exact cell geometry
- Unit cell analysis:
  - e.g. tetrakaidecahedra
  - analytically or numerically
- Voronoi (random) cells:
  - FE analysis
- μCT representation of structure
  - FE analysis of a particular structure

Dimensional Analysis Open Cell Foam: E

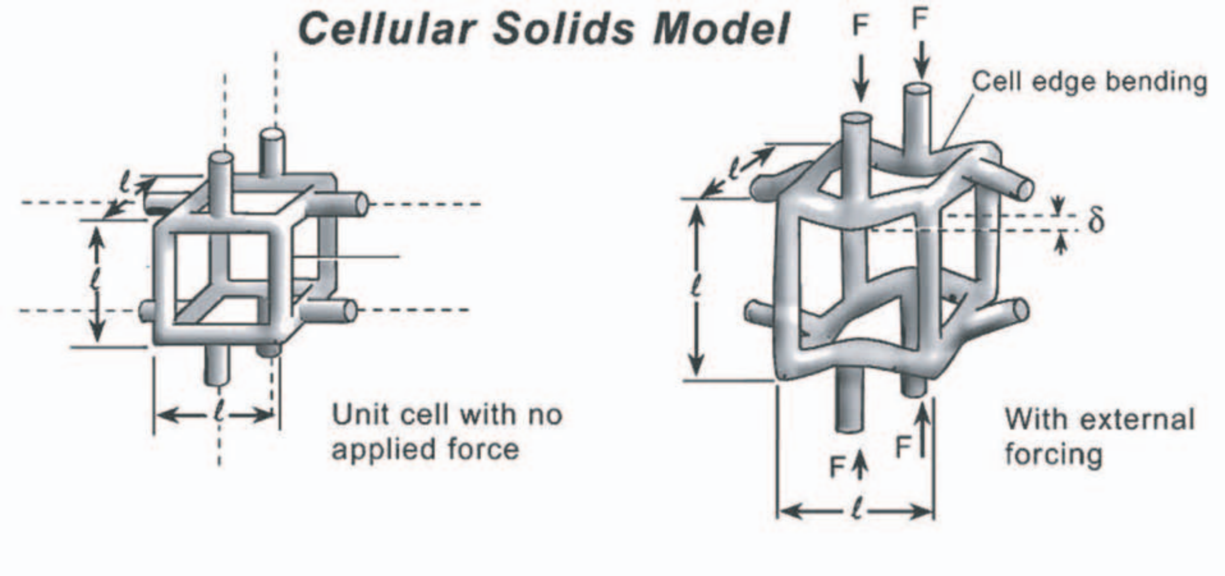


Figure by MIT OCW. After Gibson and Ashby.

$$\sigma \propto F / l^2$$

$$\varepsilon \propto \delta / l$$

$$\delta \propto F l^3 / E_s t^4$$

$$(\rho / \rho_s) \propto (t / l)^2$$

$$E^* / E_s \propto (t / l)^4 = C(\rho / \rho_s)^2$$

Data for E

Graph removed for copyright reasons. See Gibson, L.J. and M.F. Ashby. *Cellular Solids: Structure and Properties*. New York: Cambridge University Press, 1997.

$$\boxed{E^* / E_s = (\rho / \rho_s)^2}$$

Dimensional Analysis: Open Cell Foam: σ^*

Graph removed for copyright reasons.
See Gibson, L.J. and M.F. Ashby. Cellular Solids: Structure and Properties.
New York: Cambridge University Press, 1997.

$$\sigma^* \propto P_{cr} / l^2$$

$$P_{cr} \propto E_s t^4 / l^2$$

$$\sigma^* / E_s \propto (t/l)^4 = C(\rho / \rho_s)^2$$

Data for σ*

Graph removed for copyright reasons. See Gibson, L.J. and M.F. Ashby. *Cellular Solids: Structure and Properties*. New York: Cambridge University Press, 1997.

$$\sigma^* / E_s = 0.05(\rho / \rho_s)^2$$

$$\varepsilon^* \approx 0.05$$

Densification strain, ε_D

Graph removed for copyright reasons. See Gibson, L.J. and M.F. Ashby. *Cellular Solids: Structure and Properties*. New York: Cambridge University Press, 1997.

$$\varepsilon_D = 1 - 1.4\left(\rho / \rho_s\right)$$

Unit Cell Analysis: Tetrakaidecahedra

Diagram removed for copyright reasons. See Gibson, L.J. and M.F. Ashby. *Cellular Solids: Structure and Properties*. New York: Cambridge University Press, 1997.

$$E/E_s = 0.98(\rho/\rho_s)^2$$

$$\sigma^*/E_s = 0.2(\rho/\rho_s)^2$$

Voronoi Cell Analysis

Diagram removed for copyright reasons. See Gibson, L.J. and M.F. Ashby. *Cellular Solids: Structure and Properties*. New York: Cambridge University Press, 1997.

$$E/E_s = 0.8\left(\rho/\rho_s\right)^2$$

Summary of Results

$$E/E_s = C\left(\rho/\rho_s\right)^2$$

- Dim. anal: C = ?; data: C ~ 1
- Unit cell C = 0.98
- Voronoi C = 0.80

$$\sigma^*/E_s = C\left(\rho/\rho_s\right)^2$$

- Dim. anal: C = ?; data: C ~ 0.05
- Unit cell C = 0.2
- Voronoi C = ?

$$\varepsilon_D = 1 - 1.4\left(\rho/\rho_s\right)$$

Scaffold Properties

- Relative density = 0.005
- Collagen modulus ~ 1GPa

- $E \sim E_s (\rho/\rho_s)^2 = 25$ kPa
- $\sigma^* \sim 0.05\, E_s (\rho/\rho_s)^2 = 1.25$ kPa
- $\varepsilon_D \sim 1\text{-}1.4\, (\rho/\rho_s) = 0.99$

Scaffold Properties

	Model	Measured (dry)
Young’s Modulus, E	25 kPa	30 kPa
Elastic collapse stress, σ^*	1.25 kPa	5 kPa

For comparison:

Cartilage E ~2 MPa

Bone E = 1-20 GPa

Scaffold E and σ depend on:

- E_s of the solid
  - Composition
  - Cross-link density
- Relative density (volume fraction of solid)
  - Most sensitive to relative density
  - Note that *small* changes in porosity can be *large* changes in rel. density
  - Modulus, strength vary as ρ^2
- Cell geometry (through the constant of proportionality)
  - Fairly weak dependence

Scaffold E and σ^* do not depend on:

- Pore size
  - Properties depend on relative density, which varies as $(t/l)^2$
  - Properties depend on ratio of t/l but not on absolute size of t, l

Tensile Modulus

- “Skin” surface layer about 10 μm thick, almost solid collagen, E_{skin} ~ 1 GPa

- Scaffold about 3mm thick, $E_{scaffold}$ ~ 30 kPa

Tensile Modulus

Composites upper bound:

$$E_{tension} = E_{skin} V_{skin} + E_{scaffold} V_{scaffold}$$

$$= \frac{(1000)\,(10) + (0.030)(3000)}{3010}$$

$$= 3.35 \text{ MPa} = 3350 \text{ kPa}$$

Tensile modulus is about 100 times compressive modulus, due to skin

Refinements to Models

- Closed cells: Membrane effect
  - Face stretching: stiffness varies as (t/l)
  - Edge bending: stiffness varies at $(t/l)^4$
  - Face stretching contribution increases stiffness of foam or scaffold
  - Depends on distribution of solid between faces and edges
  - Depends on fraction of open and closed cells
  - A small fraction of closed cells can have a substantial effect on the stiffness of a scaffold

Refinements to Models

- Closed cells: enclosed gas
  - Can be important for very flexible foams in which the cell membranes do not rupture post-buckling (e.g. C-G scaffolds)
  - Can estimate contribution by using ideal gas law

$$E_g^* = \frac{p_o\left(1-2\nu^*\right)}{\left(1-\rho^*/\rho_s\right)}$$

Refinements to Models

- Fluid effect:
  - In open cell foams, viscous resistance of fluid moving between pores can increase stiffness

$$\sigma_{fluid} = \frac{C\mu\dot{\varepsilon}}{1-\varepsilon}\left(\frac{L}{l}\right)^2$$

Summary
CG Scaffolds

$$E/E_s = C\left(\rho/\rho_s\right)^2$$

$$\sigma^*/E_s = C\left(\rho/\rho_s\right)^2$$

$$\varepsilon_D = 1 - 1.4\left(\rho/\rho_s\right)$$

Scaffolds for Bone Regeneration

- Bone
  - Type I collagen and hydroxyapatite
- Currently working on mineralization of CG-scaffold (CMI)
- MIT: processing of uniform scaffolds
- Cambridge: co-precipitation of collagen-calcium phosphate

Scaffolds for Bone Regeneration

- Modulus of scaffolds can be modelled using previous equation
- Equation for compressive strength based on elastic buckling mode of failure
- Mineralized scaffolds fail by strut fracture

Strength of Mineralized Scaffolds

Diagram removed for copyright reasons. See Gibson, L.J. and M.F. Ashby. *Cellular Solids: Structure and Properties*. New York: Cambridge University Press, 1997.

$$M_f \propto \sigma_{fs} t^3$$

$$\sigma^*_{cr} \propto \frac{M_f}{l^3}$$

$$\frac{\sigma^*_{cr}}{\sigma_{fs}} = C\left(\frac{t}{l}\right)^3 = C\left(\frac{\rho^*}{\rho_s}\right)^{3/2}$$

Strength of Mineralized Scaffolds

Graph of “Crushing Strength” removed for copyright reasons. See Gibson, L.J. and M.F. Ashby. *Cellular Solids: Structure and Properties*. New York: Cambridge University Press, 1997.

Metallic Foams for Trabecular Bone Replacement

Image removed due to copyright considerations.
Bone photo from Gibson LJ. The mechanical behavior of cancellous bone.
J. Biomechanics 18:5 (1985) 317-328.

Image removed due to copyright considerations. Metal foam photo
from Gioux G, McCormack TM and Gibson LJ. Failure
of aluminum foams under multiaxial loads. *International Journal of
the Mechanical Sciences* 42 (2002) 1097-1117.

Properties of Metallic Foams

- Modulus given by previous equation
- Strength governed by formation of *plastic hinges* in struts

Strength of Metallic Foams

Diagram removed for copyright reasons. See Gibson, L.J. and M.F. Ashby. *Cellular Solids: Structure and Properties*. New York: Cambridge University Press, 1997.

$$M_p \propto \sigma_{ys} t^3$$

$$\sigma^*_{pl} \propto \frac{M_p}{l^3}$$

$$\frac{\sigma^*_{pl}}{\sigma_{ys}} = C\left(\frac{\rho^*}{\rho_s}\right)^{3/2}$$

Strength of Metallic Foams

Graph of Yield Strength removed for copyright reasons. See Gibson, L.J. and M.F. Ashby. *Cellular Solids: Structure and Properties*. New York: Cambridge University Press, 1997.

Summary

- Models for cellular solids can be applied to porous scaffolds

$$E/E_s = C(\rho/\rho_s)^2$$

$$\sigma^*/E_s = C(\rho/\rho_s)^2$$

$$\frac{\sigma^*_{cr}}{\sigma_{fs}} = C\left(\frac{\rho^*}{\rho_s}\right)^{3/2}$$

$$\frac{\sigma^*_{pl}}{\sigma_{ys}} = C\left(\frac{\rho^*}{\rho_s}\right)^{3/2}$$