Structure-Property Relationships for Tissue Engineering Scaffolds

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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

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

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Sketch from Freed et al. (1993)

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


Collagen-GAG - freeze dried

PGA - bonded fibres (Mikos et al, 1993)

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

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Cellular Materials

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

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

Figure by MIT OCW. After Gibson and Ashby.
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

\[ \sigma \propto \frac{F}{l^2} \quad \epsilon \propto \frac{\delta}{l} \]

\[ \delta \propto \frac{Fl^3}{E_s t^4} \quad \left( \frac{\rho}{\rho_s} \right) \propto \left( \frac{t}{l} \right)^2 \]

\[ \frac{E^*}{E_s} \propto \left( \frac{t}{l} \right)^4 = C \left( \frac{\rho}{\rho_s} \right)^2 \]

Figure by MIT OCW. After Gibson and Ashby.
Data for E


\[
\frac{E^*}{E_s} = \left(\frac{\rho}{\rho_s}\right)^2
\]
Dimensional Analysis: Open Cell Foam: $\sigma^*$

Graph removed for copyright reasons.

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

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

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

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

$$\varepsilon^* \approx 0.05$$

Densification strain, $\varepsilon_D$

\[
\varepsilon_D = 1 - 1.4 \left( \frac{\rho}{\rho_s} \right)
\]
Unit Cell Analysis:
Tetrakaidecahedra

\[
\frac{E}{E_s} = 0.98 \left( \frac{\rho}{\rho_s} \right)^2
\]

\[
\frac{\sigma^*}{E_s} = 0.2 \left( \frac{\rho}{\rho_s} \right)^2
\]

Voronoi Cell Analysis

\[ \frac{E}{E_s} = 0.8 \left( \frac{\rho}{\rho_s} \right)^2 \]

Summary of Results

\[ \frac{E}{E_s} = C \left( \frac{\rho}{\rho_s} \right)^2 \]

- Dim. anal: \( C = ? \); data: \( C \sim 1 \)
- Unit cell \( C = 0.98 \)
- Voronoi \( C = 0.80 \)

\[ \eta \left\frac{E^2}{*} = C \left( \frac{b}{b^2} \right)_3 \]

- Dim. anal: \( C = ? \); data: \( C \sim 0.05 \)
- Unit cell \( C = 0.2 \)
- Voronoi \( C = ? \)

\[ \varepsilon_D = 1 - 1.4 \left( \frac{\rho}{\rho_s} \right) \]
Scaffold Properties

- Relative density = 0.005
- Collagen modulus ~ 1GPa

\[
E \sim E_s \left(\frac{\rho}{\rho_s}\right)^2 = 25 \text{ kPa}
\]
\[
\sigma^* \sim 0.05 \ E_s \left(\frac{\rho}{\rho_s}\right)^2 = 1.25 \text{ kPa}
\]
\[
\varepsilon_D \sim 1-1.4 \left(\frac{\rho}{\rho_s}\right) = 0.99
\]
## Scaffold Properties

<table>
<thead>
<tr>
<th></th>
<th>Model</th>
<th>Measured (dry)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Young’s Modulus, $E$</strong></td>
<td>25 kPa</td>
<td>30 kPa</td>
</tr>
<tr>
<td><strong>Elastic collapse stress, $\sigma^*$</strong></td>
<td>1.25 kPa</td>
<td>5 kPa</td>
</tr>
</tbody>
</table>

For comparison:
- Cartilage $E \sim 2$ MPa
- Bone $E = 1$-20 GPa
Scaffold $E$ and $\sigma$ 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 $\rho^2$
- Cell geometry (through the constant of proportionality)
  - Fairly weak dependence
Scaffold E and $\sigma^*$ 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 \( \mu \text{m} \) thick, almost solid collagen, \( E_{\text{skin}} \sim 1 \text{ GPa} \)

• Scaffold about 3mm thick, \( E_{\text{scaffold}} \sim 30 \text{ kPa} \)
Tensile Modulus

Composites upper bound:

\[ E_{\text{tension}} = E_{\text{skin}} V_{\text{skin}} + E_{\text{scaffold}} V_{\text{scaffold}} \]
\[ = (1000)(10) + (0.030)(3000) \]
\[ = 3010 \]
\[ = 3.35 \text{ MPa} = 3350 \text{ kPa} \]

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

\[
E_g^* = \frac{p_o(1-2\nu^*)}{\left(1-\rho^*/\rho_s\right)}
\]
Refinements to Models

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

\[ \sigma_{\text{fluid}} = \frac{C\mu \dot{\gamma} \left( \frac{L}{l} \right)^2}{1 - \varepsilon \left( \frac{L}{l} \right)} \]
Summary
CG Scaffolds

\[ \frac{E}{E_s} = C \left( \frac{\rho}{\rho_s} \right)^2 \]

\[ \frac{\partial}{\partial E^2} = C \left( \frac{b}{b_s^2} \right)^3 \]

\[ \varepsilon_D = 1 - 1.4 \left( \frac{\rho}{\rho_s} \right) \]
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


\[ M_f \propto \sigma_{fs} t^3 \]

\[ \sigma_{cr}^* \propto \frac{M_f}{l^3} \]

\[ \frac{\sigma_{cr}^*}{\sigma_{fs}} = C \left( \frac{t}{l} \right)^3 = C \left( \frac{\rho^*}{\rho_s} \right)^{3/2} \]
Strength of Mineralized Scaffolds

Metallic Foams for Trabecular Bone Replacement

Image removed due to copyright considerations.

Properties of Metallic Foams

• Modulus given by previous equation
• Strength governed by formation of plastic hinges in struts
Strength of Metallic Foams


\[ M_p \propto \sigma_{ys} t^3 \]

\[ \sigma_{pl}^* \propto \frac{M_p}{l^3} \]

\[ \frac{\sigma_{pl}^*}{\sigma_{ys}} = C \left( \frac{\rho^*}{\rho_s} \right)^{3/2} \]
Strength of Metallic Foams

Summary

• Models for cellular solids can be applied to porous scaffolds

\[ \frac{E}{E_s} = C \left( \frac{\rho}{\rho_s} \right)^2 \]

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

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