Remodeling of cell-seeded soft tissues due to mechanical stimulation

J.-H. Yi¹, B. Zhou¹, M. Stoffel¹, D. Weichert¹, B. Rath²

¹Institute of General Mechanics, RWTH Aachen University

²Department for Orthopedics and Trauma Surgery, University Hospital Aachen

4th CanCNSM, July 23-26, 2013 in Montréal
Aim of the research

- Defective articular cartilage

- Replacement material: condensed collagen gel

- Cell-seeded condensed collagen gel
Remodeling of cell-seeded soft tissues

Contents

Experiments
  Cell-seeded condensed collagen gel
  Bioreactor
  Compression test

Theory
  Assumption
  Constitutive modeling

Identification

Conclusions
I. Experiments
Cell-seeded condensed collagen gel

Figure: Condensing chamber and cell-seeded condensed collagen gel
Remodeling of cell-seeded soft tissues

Experiments

Bioreactor

Bioreactor

Part 4

Part 3

Part 2

Part 1
Remodeling of cell-seeded soft tissues

Experiments

Bioreactor

Bioreactor operation

Stimulation

After stimulation

periodic loading

scaffold

stimulus for weeks

nutrient medium

collagen type II fiber ⊥ loading direction

ca.2 mm

ca.10 mm

Cylindrical specimen with collagen type II

axis of rotational symmetry

I AM RWTH AACHEN UNIVERSITY
Histological comparison

(a) Initial state  (b) Not stimulated  (c) Stimulated

**Figure:** Histology cross section
Microscopic phenomenon

Mechn. stimulation

Before stimulation

Scaffold cell

After 4 weeks stimulation

Col-II

After stimulation

Ca. 100 \(\mu\text{m}\)
Remodeling of cell-seeded soft tissues

Experiments

Compression test

Compression test

(a) MTS machine

(b) Force-time curve

⇒ Elasticity & Viscoelasticity
Remodeling of cell-seeded soft tissues

Experiments

Compression test

Compression test

\[ \rightarrow \text{Change of elasticity} \quad (\text{Change of viscoelasticity}) \]
II. Theory
Assumptions

- The cell-seeded collagen gel is assumed to be incompressible hyperelastic.
- The initial state is assumed to be isotropic.
- Due to the synthesized collagen type II the material becomes transversely isotropic and the stiffness increases.
- The system is closed to all transfers of matter.
Constitutive modeling I

- **Free-energy function**
  \[
  \psi = \psi(C, N_0) = \psi(l_1, l_2, l_4, l_5) \quad (l_3 = 1)
  \]
  \[
  = \frac{\lambda}{2} l_1^2 + G_p(l_1^2 - 2l_2) + \alpha l_4 l_1 + 2(G_t - G_p)l_5 + \frac{\beta}{2} l_4^2
  \]

- **Stress** \(\mathbf{S} = \)
  \[
  \lambda l_1 \mathbf{I} + 2G_p \mathbf{C} + \alpha (l_1 \mathbf{N}_0 + l_4 \mathbf{I}) + 2(G_t - G_p)(\mathbf{N}_0 \mathbf{C} + \mathbf{C} \mathbf{N}_0) + \beta l_4 \mathbf{N}_0
  \]

- **Elasticity tensor**
  \[
  \mathbf{A}^e = \lambda \mathbf{I} \otimes \mathbf{I} + 2G_p \mathbf{I}
  \]
  \[
  + \alpha (\mathbf{I} \otimes \mathbf{N}_0 + \mathbf{N}_0 \otimes \mathbf{I}) + 2(G_t - G_p)(\mathbf{N}_0 \mathbf{I} + \mathbf{I} \mathbf{N}_0) + \beta \mathbf{N}_0 \otimes \mathbf{N}_0
  \]

  Transversely isotropic stiffness: \(E_p, E_t, \nu_{pt}, \nu_p, \) and \(G_t\)
Evolution of hyperelastic properties

- **Initial isotropic state:**
  \[ E_t = E_p \overset{\text{def}}{=} E, \quad \nu_{pt} = \nu_p \overset{\text{def}}{=} \nu, \quad G_t = G_p \overset{\text{def}}{=} G, \]
  \[ N_0 = 0, \quad l_4 = l_5 = 0. \]

- **Isotropy \rightarrow Transversely isotropy:**
  \[ \dot{E}_p = k \sqrt{\Psi} (E_{p,\text{crit}} - E_p), \]
  \[ \dot{E}_t = \dot{\nu}_p = \dot{\nu}_{pt} = \dot{G}_t = 0. \]
Remodeling of cell-seeded soft tissues

Theory

Constitutive modeling

Flowchart of Young’s modulus evolution

\[ E_p(t = 0) = E \]

\[ \Delta E_p \]

\[ E_p + \Delta E_p \]

\[ E_p + \Delta E_p \geq E_{p,\text{crit}} \]

\[ E_p + \Delta E_p < E_{p,\text{crit}} \]

\[ E_p = E_p + \Delta E_p \]
III. Identification
Identification of Young’s modulus and remodeling parameters

<table>
<thead>
<tr>
<th>Time [week]</th>
<th>$E_p$ [MPa]</th>
</tr>
</thead>
<tbody>
<tr>
<td>Initial</td>
<td>0.8963</td>
</tr>
<tr>
<td>1 week</td>
<td>0.2145</td>
</tr>
<tr>
<td>2 week</td>
<td>0.5671</td>
</tr>
<tr>
<td>3 week</td>
<td>0.9861</td>
</tr>
<tr>
<td>4 week</td>
<td>0.9980</td>
</tr>
</tbody>
</table>

$\rightarrow k = 4.0$ and $n = 0.5$
Simulation of remodeling

Figure: Remodeling of Young’s modulus $E_p$ on the right side cross section
Remodeling of cell-seeded soft tissues

Further cases of change of $E_p$

<table>
<thead>
<tr>
<th>Spec. ID</th>
<th>Spec. 2</th>
<th>Spec. 3</th>
<th>Spec. 4</th>
<th>Spec. 5</th>
</tr>
</thead>
<tbody>
<tr>
<td>initial</td>
<td>0.500</td>
<td>0.800</td>
<td>0.896</td>
<td>1.047</td>
</tr>
<tr>
<td>1 week</td>
<td>Not available</td>
<td>Not available</td>
<td>0.215</td>
<td>0.206</td>
</tr>
<tr>
<td>2 weeks</td>
<td>Not available</td>
<td>Not available</td>
<td>0.567</td>
<td>0.233</td>
</tr>
<tr>
<td>3 weeks</td>
<td>Not available</td>
<td>Not available</td>
<td>0.987</td>
<td>0.168</td>
</tr>
<tr>
<td>4 weeks</td>
<td>0.510</td>
<td>1.200</td>
<td>0.998</td>
<td>0.213</td>
</tr>
<tr>
<td>change</td>
<td>increase</td>
<td>increase</td>
<td>increase</td>
<td>decrease</td>
</tr>
</tbody>
</table>

$k$ and $n$ are different according to specimens!
IV. Conclusions
Conclusions

▶ Bioreactor
  Remodeling phenomenon due to cell activity
    ⇒ Young’s modulus changes
    ⇒ Isotropy → Anisotropy

▶ Evolution equation
  Remodeling parameters $k$ and $n$
Future perspectives

- **Consolidation**
  
  Cyclic loading in a bioreactor $\Rightarrow$ Scaffold consolidation

- **Enzyme degradation**
  
  Predamaged cell $\Rightarrow$ Degradation of scaffold

- **Switch point**
  
  Enzyme degradation $\Rightarrow$ Synthesis

- **Optimal stimulation**
  
  Duration, frequency, compression depth or...
THANK YOU FOR YOUR ATTENTION!