Remodeling of soft tissues due to cell activity

J.-H. Yi\textsuperscript{1}, M. Azarnoosh\textsuperscript{1}, M. Stoffel\textsuperscript{1}, D. Weichert\textsuperscript{1}, B. Rath\textsuperscript{2}

\textsuperscript{1}Institute of General Mechanics, RWTH Aachen University
\textsuperscript{2}Department for Orthopedics and Trauma Surgery, University Hospital Aachen

The 7th APCB, August 29-31, 2013 in Seoul, Korea
Aim of the research

- Defective articular cartilage
- Replacement material: condensed collagen gel
- Cell-seeded condensed collagen gel
Remodeling of soft tissues due to cell activity

Contents

Experiments
   Cell-seeded condensed collagen gel
   Bioreactor
   Compression test

Theories and validations
   IAM model
   The $\kappa$ model

Conclusions
I. Experiments
Remodeling of soft tissues due to cell activity

- Experiments
- Cell-seeded condensed collagen gel

Cell-seeded condensed collagen gel

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

- Experiments
- Bioreactor

Bioreactor
Remodeling of soft tissues due to cell activity

Experiments

Bioreactor operation

Bioreactor operation

- **Stimulation**
  - periodic loading
  - scaffold cell
  - nutrient medium
  - stimulus for weeks

- **After stimulation**
  - ca. 10 mm
  - ca. 2 mm
  - Cylindrical specimen with collagen type II
  - axis of rotational symmetry
  - collagen type II fiber ⊥ loading direction
Remodeling of soft tissues due to cell activity

Experiments

Bioreactor

Histological comparison

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

Figure: Histology cross section
Remodeling of soft tissues due to cell activity

- Experiments
- Bioreactor

Microscopic phenomenon

before stimulation

after stimulation

mech. stimulation

scaffold cell

col-II

ca. 100 μm

after 4 weeks stimulation
Remodeling of soft tissues due to cell activity

- Experiments
  - Compression test

Compression test

(a) MTS machine

(b) Stress-strain curve
II. Theories and validations
Remodeling of soft tissues due to cell activity

- Theories and validations
- IAM model

A. IAM model
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** \( S = \)
  \[
  \lambda l_1 I + 2G_p C + \alpha(l_1 N_0 + l_4 I) + 2(G_t - G_p)(N_0 C + C N_0) + \beta l_4 N_0
  \]

- **Elasticity tensor**
  \[
  A^e = \lambda I \otimes I + 2G_p I \\
  + \alpha(I \otimes N_0 + N_0 \otimes I) + 2(G_t - G_p)(N_0 I + I N_0) + \beta N_0 \otimes N_0
  \]

Transversely isotropic stiffness: \( E_p, E_t, \nu_{pt}, \nu_p, \) and \( G_t \)
Constitutive modeling II

Evolution of hyperelastic properties

- Initial isotropic state:
  \[ E_t = E_p \overset{\text{def}}{=} E, \quad \nu_{pt} = \nu_p \overset{\text{def}}{=} \nu, \quad G_t = G_p \overset{\text{def}}{=} G, \]
  \[ \mathbf{N}_0 = \mathbf{0}, \quad l_4 = l_5 = 0. \]

- 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 soft tissues due to cell activity

Theories and validations

IAM model

Flowchart of Young’s modulus evolution

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

mechanical simulation, \( \Psi \)

\[ \Delta E_p \]

\[ E_p + \Delta E_p \]

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

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

\[ E_p = E_p + \Delta E_p \]

\[ E_p = E_{p,\text{crit}} \]
Identification of Young’s modulus and remodeling parameters

Compression test

<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 $n = 0.5$
Remodeling of soft tissues due to cell activity

- Theories and validations
- The $\kappa$ model

The $\kappa$ model
Assumptions

- The cell-seeded collagen gel is assumed to be a *incompressible neo-Hookean* material.
- 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

Free-energy function of the tissue:

\[ \psi = \psi(C, N_0) = \psi(l_1, l_4) = \psi_g(l_1) + \psi_f(l_1, l_4), \]

- Free-energy function of condensed collagen gel:
  \[ \psi_g(l_1) = \frac{c}{2} (l_1 - 3), \]

- Free-energy function of collagen type II fiber:
  \[ \psi_f(l_1, l_4) = \psi_f(l_4^*) = \frac{k_1}{k_2} \left\{ \exp \left[ k_2 (l_4^* - 1)^2 \right] - 1 \right\}, \]
  where \( l_4^* = \kappa l_1 + (1 - 3\kappa) l_4 \).

\[ \kappa = \begin{cases} 
1/3 & \text{isotropic} \\
0 & \text{transversely isotropic} 
\end{cases} \]
Remodeling of soft tissues due to cell activity

Theories and validations

The $\kappa$ model

Second Piola-Kirchhoff stress tensor

\[ \mathbf{S} = \mathbf{S}_g + \mathbf{S}_f , \]

- Second Piola-Kirchhoff stress tensor of condensed collagen gel:
  \[ \mathbf{S}_g = 2 \frac{\partial \psi_g}{\partial \mathbf{C}} = c \mathbf{I} , \]

- Second Piola-Kirchhoff stress tensor of collagen type II fiber:
  \[ \mathbf{S}_f = 2 \frac{\partial \psi_f}{\partial \mathbf{C}} = 4k_1 \exp \left[ k_2 (l_4^* - 1)^2 \right] (l_4^* - 1) \mathbf{M} \otimes \mathbf{M} . \]
Remodeling of soft tissues due to cell activity
Theories and validations
The \( \kappa \) model

**Identification of parameters of \( \kappa \) model**

<table>
<thead>
<tr>
<th>Parameters</th>
<th>( \kappa )</th>
<th>( k_1 ) [MPa]</th>
<th>( k_2 ) [–]</th>
<th>( c ) [MPa]</th>
</tr>
</thead>
<tbody>
<tr>
<td>initial</td>
<td>0.333</td>
<td>0</td>
<td>1</td>
<td>13.5</td>
</tr>
<tr>
<td>1 week</td>
<td>0.28</td>
<td>0.1</td>
<td>1</td>
<td>6.6</td>
</tr>
<tr>
<td>2 weeks</td>
<td>0.155</td>
<td>0.5</td>
<td>1</td>
<td>5.53</td>
</tr>
<tr>
<td>3 weeks</td>
<td>0.105</td>
<td>0.8</td>
<td>1</td>
<td>8.1</td>
</tr>
<tr>
<td>4 weeks</td>
<td>0.105</td>
<td>0.9</td>
<td>1</td>
<td>8</td>
</tr>
<tr>
<td>change</td>
<td>decrease</td>
<td>increase</td>
<td>constant</td>
<td>??</td>
</tr>
</tbody>
</table>
Remodeling of soft tissues due to cell activity

Theories and validations

The $\kappa$ model

Flowchart of $k_1$
IV. Conclusions
Conclusions

- **Bioreactor**
  Remodeling phenomenon due to cell activity
  \[ \Rightarrow \text{Young's modulus changes (change of } k_1) \]
  \[ \Rightarrow \text{Isotropy } \rightarrow \text{Anisotropy (change of } \kappa) \]

- **Evolution equation**
  Remodeling parameters \( k \) and \( n \)
Future perspectives

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

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

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

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