Computational modeling and simulation analysis of bioreactors and its implications in engineered tissue formation

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Clinical Problem: heart valve disease

One in every thousand children is born with a congenital heart valve problem.

Ge, Sotiropoulos. Biomech Eng. 2008
Clinical Problem: heart valve disease

- 290,000 replacements/yr
- Will triple in four decades
- $80,000 to $150,000/surgery

Ge, Sotiropolus. Biomech Eng. 2008
Current Heart Valve Replacements

Cannot account for tissue growth and tissue remodeling
Autologous stem cells extraction
• Bone Marrow derived stem cells (BMSCs)

Cell proliferation

Cell implantation on scaffold with valve geometry

Tissue Engineering Approach*

Engineered heart valve

Mechanical conditioning

*Sutherland et al., Circulation 2005
Advantages of tissue engineered heart valves (TEHVs) over current market replacements.

- Potential growth and remodeling capabilities
- Eliminates need of follow up surgeries
- Eliminates risk of tissue incompatibility
- No need for anticoagulation therapies
- Normal hemodynamics
- Reduced rate of calcification
Primary Challenge in Mechanical conditioning for HVTE

No optimized in-vitro protocols for:

- Tissue formation
- Cell phenotype

Complex in vitro replication:

- Flow
- Stretch
- Flexure
Mechanical Conditioning Bioreactors

HVTE bioreactors:
- tissue-culture devices
- Controllable, mechanically active environments
- Study engineered tissue structure, properties, and integration

Freed, L., et al., Tissue Eng., 2006

Modes: Flow, stretch, flexure (FSF)

Benefits of Using FSF Bioreactors in HVTE

• Helps to understand the process of:
  – Tissue formation
  – Cell proliferation
  – Cell phenotype

• Individual or combined study of:
  – Flow
  – Stretch
  – Flexure

• Can accommodate simplified geometries.

• Maximization of resources.
  – cells
  – culture media
A landmark experiment showed more tissue formation when exposed to mechanical stimuli.

Engelmyer, et. al., Biomat., 2006
In the flex-flow case:

What flow parameters were responsible for increasing tissue formation?

Did sample movement enhance nutrient transport of glucose and oxygen resulting in more engineered tissue production?

Computational fluid dynamics CFD was used to answer this questions.
Advantages of using CFD in engineered tissue studies

• Provide data that is difficult or impossible to obtain through experiments only.
• Superior data resolution vs imaging techniques
• Can be coupled to mass and heat transport as well as structural displacement equations.
• Provide data from small time steps (nsec, msec)
• Requires few resources – money, equipment, time.
• Can predict data from experimental set ups that are unfeasible
• FDA accepts mathematical modeling as validation techniques
In the flex-flow case:

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Computational fluid dynamics CFD was used to answer this questions.
Methods
Brief description of the physical system

Modes:
Flow
• Peristaltic pump
Stretch
• External actuator
Flexure
• External actuator

Nature of Specimen deformation

Forward
0.5 inches IN during 0.5 sec

Backward
0.5 inches OUT during 0.5 sec

1 Hz frequency
Virtual construction of a u-shaped bioreactor

Sample Dimensions 17mm x 6.5mm x 1mm

Salinas and Ramaswamy, J. Biomech, 2014
Structured mesh: 441,370 elements; 472,728 nodes

Salinas and Ramaswamy, J. Biomech, 2014
Mass transport model

- here we examine the mass transport variables e.g. concentration gradients of oxygen and glucose.

\[
\Phi_f \frac{\delta C^\beta}{\delta t} + (v_f \gamma C^\beta - D^\beta \ast \nabla C^\beta) = q^\beta
\]

- \( C^\beta \): Concentration of the solute in the medium
- \( \Phi_f \): Fluid volume fraction
- \( \Gamma \): Sieving coefficient in a porous material
- \( q^\beta \): Source term for generation, consumption or degradation of solute mass
- \( v_f \): Velocity of the fluid phase
- \( D^\beta \ast \): Effective diffusive coefficient in the porous medium
- \( \rho \text{ cell} \): Density of cell seeded in the scaffold
- \( V^\beta \): Maximum uptake rate

Sengers et al., Biotechnol Prog, 2005
### Parameters used in the simulations

<table>
<thead>
<tr>
<th>Property</th>
<th>Glucose</th>
<th>Oxygen</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diffusivity in Fluid cm(^2)/s</td>
<td>5.40x10(^{-6})</td>
<td>3.00x10(^{-5})</td>
</tr>
<tr>
<td>Diffusivity in scaffold cm(^2)/s</td>
<td>1.08x10(^{-6})</td>
<td>0.60x10(^{-5})</td>
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<tr>
<td>Density kg/m(^3)</td>
<td>1.54</td>
<td>1.429</td>
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<tr>
<td>Metabolism rate in cell mole/cell.s</td>
<td>3.83x10(^{-16})</td>
<td>3.75x10(^{-17})</td>
</tr>
<tr>
<td>Metabolism rate in cell grams/cell.s</td>
<td>6.90 x10(^{-14})</td>
<td>6.00x10(^{-16})</td>
</tr>
<tr>
<td>Total Metabolism rate in sample g/s</td>
<td>3x10(^{-6})</td>
<td>2.73x10(^{-8})</td>
</tr>
</tbody>
</table>

Sengers et al., Biotechnol Prog, 2005  
### Conditions for all simulation cases

<table>
<thead>
<tr>
<th></th>
<th>control</th>
<th>Flow-alone</th>
<th>Flex-alone</th>
<th>Flex-flow</th>
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</thead>
<tbody>
<tr>
<td>Flow</td>
<td>Laminar</td>
<td>Laminar</td>
<td>Laminar</td>
<td>Laminar</td>
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<tr>
<td>Tube walls</td>
<td>No slip</td>
<td>No slip</td>
<td>No slip</td>
<td>No slip</td>
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<tr>
<td>Sample walls</td>
<td>Porous-fluid Interface</td>
<td>Porous-fluid Interface</td>
<td>Moving Porous-fluid Interface</td>
<td>Moving Porous-fluid Interface</td>
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<tr>
<td>Inlet velocity</td>
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<td>2.2 cm/s *</td>
<td>0 cm/s</td>
<td>2.2 cm/s *</td>
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<tr>
<td>Outlet pressure</td>
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<td>0 Pa</td>
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<tr>
<td>Convergence</td>
<td>1x10^{-9}</td>
<td>1x10^{-9}</td>
<td>1x10^{-9}</td>
<td>1x10^{-9}</td>
</tr>
</tbody>
</table>

*Lotz et al. Radiographics.2002*
Control

Flow straight

Flow semibent

Flow fullybent

Flexure alone

Flex-flow

Flow Direction

Time Averaged Axial Shear Stress (Pa)

Salinas and Ramaswamy, J. Biomech, 2014
Flow Direction

Axial Velocity (m/s)

-0.08  0  0.08

Flexure alone

Flex-flow

a) Flow alone

Straight

Semibent

Fullybent

t= 0 s

t= 0.25 s

t= 0.5 s

t= 0.75 s

t= 1 s
OSI Calculation

\[
\text{OSI} = \frac{1}{2} \left( 1 - \frac{\text{abs} \left( \int_0^T \tau \, dt \right)}{\int_0^T \text{abs} (\tau) \, dt} \right)
\]

He and Ku, J. Biomech Eng., 1996

\(\text{abs} \left( \int_0^T \tau \, dt \right)\) is the magnitude of the time-averaged shear

\(\int_0^T \text{abs} (\tau) \, dt\) is the time-averaged shear stress magnitude. 0.0 \(\leq\) OSI \(\leq 0.5\)

Salinas and Ramaswamy, J. Biomech, 2014
OSI scaled shear stress OSI-|τ| Calculation

\[ \text{OSI-} |\tau| = 2 \times \text{OSI} \times \int_{0}^{T} \text{abs}(\tau) \, dt \]

Salinas and Ramaswamy, J. Biomech, 2014
Time averaged normalized mass fraction for a) glucose, b) oxygen at different porosity percentages.

At approximately 40% porosity mass fractions decline is steeper
Conclusions

• Mathematical modeling is a powerful tool for the study of engineered tissue formation.
• In this study, mass transport did not enhance tissue production reported in (Rath et al., 2015).
• We demonstrated that the OSI-$\overrightarrow{\tau}$ correlated strongly with the greatly augmented engineered collagen production reported from previous in-vitro experiments (Rath et al., 2015), under Flex-Flow conditioning regimens.
Future work

• Development of bioreactors that can condition scaffolds with geometries similar to heart valves.
  – Cell culture experiments
  – CFD simulations
Acknowledgements

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- NSU CEC
Questions