A Continuum Framework for Growth in Biological Tissue

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Introduction

- Developing a mathematical framework to describe and simulate the complex processes of growth in a biological tissue
- Provide a predictive capability for our experiments on engineered tissue with eventual application to surgery, wound healing, ...

Development of tissue

- Growth/Resorption: Addition/Loss of mass
e.g. Densification of bones
- Remodelling: Change in microstructure
e.g. Alignment of trabeculae to the axis of external loading
- Morphogenesis: Change in macroscopic form
e.g. Development of an embryo from a fertilized egg

Goals

- Describe and simulate the processes of growth and development
- Models that are physiologically appropriate and thermodynamically valid
- Experiments on in vitro tissue in parallel
  + Descriptive model driven and validated by experiment
  + Model drives the controlled experiments

Issues that arise

- Open system (with respect to mass)
- Interacting and interconverting species
- Species diffusing with respect to a solid phase (fluid, precursors, byproducts)
- Mixture physics

Biological model

- Physiologically consistent continuum formulation describing growth in an open system
- Relevant driving forces arise from thermodynamics
- Consistent with mixture theory
- Applying present theory to 3D tissues involving multiple species diffusing and reacting
- Formulated the remodelling problem – Preliminary results

Comparison with neonatal tissue

- Morphological comparison of the engineered constructs to 2 day old neonatal rat tendon

Tissue engineering

- Capability to engineer constructs which model real tissue
- Carefully control environment and apply stimuli to control growth and remodelling
  + Mechanical loading in bioreactors
  + Chemical environment and nutrient supply

Mechanics

In the reference configuration \( \Omega_0 \),

- \( \Pi^\ell \) is the source/sink term for species \( \ell \)
- \( M^\ell \) is the mass flux term for species \( \ell \)
- \( S^\ell \) is the partial first Piola-Kirchhoff stress on species \( \ell \)
- \( N^\ell \) is the outward normal at the surface
- \( g^\ell \) is the body force acting on the entire system

In the current configuration \( \Omega_t \),

- \( \pi^\ell \) is the source/sink term for species \( \ell \)
- \( m^\ell \) is the mass flux term for species \( \ell \)
- \( \sigma^\ell \) is the partial Cauchy stress on species \( \ell \)
- \( g^\ell \) is the body force acting on the entire system

Balance of mass and momentum

For a species \( \ell \), in local form, in \( \Omega_0 \)

\[
\frac{\partial \rho^\ell}{\partial t} = \Pi^\ell - \nabla \cdot M^\ell \\
\frac{\partial \rho^\ell}{\partial t} (V + V^\ell) = \rho^\ell (g + q^\ell) + \nabla \cdot S^\ell - (\nabla \cdot (V + V^\ell)) M^\ell
\]

\( V \) is the velocity of the solid phase
\( V^\ell \) is the material velocity relative to the solid phase defined as \( V^\ell = (1/\rho^\ell)FM^\ell \)
\( q^\ell \) is the net force exerted on species \( \ell \) by all other species in the system

Energy balance, constitutive laws

For a species \( \ell \), in local form, in \( \Omega_0 \)

\[
\rho^\ell \frac{\partial E^\ell}{\partial t} = S^\ell + S^\ell \cdot \nabla \cdot Q^\ell + \nabla \cdot \left( \rho^\ell \frac{\partial v^\ell}{\partial t} \right) - \nabla \cdot (\rho^\ell v^\ell (M^\ell - F^\ell))
\]

Consitutive relations:

\[
S^\ell = \frac{\partial \mathbf{F}^\ell}{\partial \mathbf{F}^\ell} \quad \forall \ell
\]

\[
\theta = \frac{\partial \mathbf{F}^\ell}{\partial \mathbf{F}^\ell} \quad \forall \ell
\]

\[
Q^\ell = -K \nabla \cdot \mathbf{u}^{\ell} \quad \forall \ell
\]

\[
u^\ell \cdot K^{\ell} u^\ell \geq 0 \forall u^\ell \in \mathbb{R}^3
\]

\[
V^\ell = -D^\ell \left( \frac{\partial \mathbf{V}^\ell}{\partial \mathbf{V}^\ell} - \rho^\ell \frac{\partial u^\ell}{\partial u^\ell} \right)
\]

\[
\rho^\ell u^\ell \cdot \mathbf{u}^\ell \geq 0 \forall u^\ell \in \mathbb{R}^3
\]

\( v^\ell \) is the internal energy of each species \( \ell \)
\( F^\ell \) is the deformation gradient
\( Q^\ell \) is the heat flux term for species \( \ell \)
\( r^\ell \) is the heat supplied to species \( \ell \) per unit reference volume
\( e^\ell \) is the internal energy transferred to species \( \ell \) from all other species

Example

- An idealized model of the cylindrical tendon construct
  + Stretched 2D case involving two species, a solid and a fluid
  + Solid is neo-hookean, fluid is compressible and ideal
  + \( Q^\ell \) and the stretch \( A \) vary, and calculated values are used to determine the flux \( M^\ell \)

Achievements and future work

- Developing a mathematical framework to describe and simulate the complex processes of growth in a biological tissue
- Providing a predictive capability for our experiments on engineered tissue with eventual application to surgery, wound healing, ...

Comparison with neonatal tissue

- Morphological comparison of the engineered constructs to 2 day old neonatal rat tendon

[Calve et al. - 2003]

Engineered tendon construct in vitro that is morphologically and functionally similar to neonatal tissue [Calve et al. - 2003]