Multi-Scale Simulations of the Mechanics of Transport and Growth in Soft Tissue

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Broad Objectives

- mathematical and computational models of the processes of tissue development
  - models that are thermodynamically valid and physiologically appropriate
- parallel experiments on and characterization of \textit{in vitro} engineered tissue
  - quantitative model motivated and validated by experiment
  - model drives the controlled experiments
Development of Biological Tissue

distinct, mathematically independent processes: [Taber - 1995]

• growth – addition/loss of mass
  ◦ densification of bone

• remodelling – change in microstructure
  ◦ alignment of trabeculae of bones to axis of external loading

• morphogenesis – change in macroscopic form
  ◦ development of an embryo from a fertilized egg
engineered tissue *in vitro* that is morphologically and functionally similar to neonatal tissue:

[Calve et al., 2003]
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
The 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

Our treatment involves the introduction of sources, sinks and fluxes of mass
Modelling – Background

- Cowin and Hegedus [1976]: solid tissue; mass source; irreversible sources of momentum and energy from perfusing fluid
- Epstein and Maugin [2000]: mass flux; irreversible fluxes of momentum and entropy
- Kuhl and Steinmann [2002]: configurational forces motivate mass flux
- Baaijens et al. [2004]: detail biosynthesis, enzyme kinetics
Modelling – This Work

- multiple species undergoing transport, interconversion, mechanical and thermodynamic interactions
- other species deform with solid phase and diffuse with respect to it
- fully compatible with mixture theory
- detailed coupling of mechanics and mass balance
- thermodynamic consistency
- preliminary coupled computations
Balance of Mass

- tissue formed by reacting species – sources and sinks for species
- transport of precursors, fluid and byproducts – fluxes for species

mechanics of transport and growth in soft tissue
Balance of Mass – Equations

for a species $\iota$, in local form, in $\Omega_0$

$$\frac{\partial \rho^\iota_0}{\partial t} = \Pi^\iota - \nabla_X \cdot M^\iota, \ \forall \iota = \alpha, \ldots, \omega$$

the sources/sinks satisfy

$$\sum_{\iota=\alpha}^{\omega} \Pi^\iota = 0.$$
Balance of Mass – Equations

for a species $\iota$, in local form, in $\Omega_0$

$$\frac{\partial \rho^\iota_0}{\partial t} = \Pi^\iota - \nabla_x \cdot M^\iota, \ \forall \iota = \alpha, \ldots, \omega$$

for the solid phase

$$\frac{\partial \rho^s_0}{\partial t} = \Pi^s$$

ignoring short range motion of cells; e.g., during initial stages of wound healing
Balance of Mass – Equations

for a species $i$, in local form, in $\Omega_0$

$$\frac{\partial \rho_i^0}{\partial t} = \Pi^i - \nabla \cdot M_i^i, \ \forall i = \alpha, \ldots, \omega$$

for the fluid phase

$$\frac{\partial \rho_f^0}{\partial t} = -\nabla \cdot M^f$$

if sources for interstitial fluids are absent; e.g., no lymph glands
Balance of Linear Momentum

- linear momentum balance coupled with mass transport – sources/sinks and fluxes contribute to the momenta

- material velocity relative to the solid \( V^t = (1/\rho_0^t)F_M^t \)

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Balance of Linear Momentum – Equations

for a species \( \iota \), in local form, in \( \Omega_0 \)

\[
\rho_0^t \frac{\partial}{\partial t} (V + V^t) = \rho_0^t (g + q^t) + \nabla X \cdot P^t - (\nabla X (V + V^t)) M^t, \quad \forall \iota = \alpha, \ldots, \omega
\]
Balance of Linear Momentum – Equations

for a species $\iota$, in local form, in $\Omega_0$

$$\rho_0^\iota \frac{\partial}{\partial t} (V + V^\iota) = \rho_0^\iota (g + q^\iota) + \nabla_x \cdot P^\iota - (\nabla_x (V + V^\iota)) M^\iota, \ \forall \iota = \alpha, \ldots, \omega$$
Balance of Linear Momentum – Equations

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Balance of Linear Momentum – Equations

for a species $\iota$, in local form, in $\Omega_0$

$$\rho_0^\iota \frac{\partial}{\partial t} (V + V^\iota) = \rho_0^\iota (g + q^\iota) + \nabla_X \cdot P^\iota - \left( \nabla_X (V + V^\iota) \right) M^\iota, \ \forall \iota = \alpha, \ldots, \omega$$

relation between mass sources $\Pi^\iota$’s and interaction forces $q^\iota$’s,

$$\sum_{\iota=\alpha}^{\omega} \left( \rho_0^\iota q^\iota + \Pi^\iota V^\iota \right) = 0$$

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Kinematics of Growth

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Kinematics of Growth

\[ F = \bar{F}^e \tilde{F}^{e^l} F^{g^l} \]

- \( F^{g^l} \) is a kinematic “growth” tensor, \( F^{e^l} = \bar{F}^e \tilde{F}^{e^l} \) is the elastic deformation gradient

- residual stress due to \( \tilde{F}^{e^l} \)
Energy – First Law

balance of energy for a species $\nu$, in local form, in $\Omega_0$

$$\rho_0^\nu \frac{\partial e^\nu}{\partial t} = P^\nu : \dot{F} + P^\nu : \nabla_X V^\nu - \nabla_X \cdot Q^\nu + r_0^\nu + \rho_0^\nu \tilde{e}^\nu - \nabla_X e^\nu \cdot (M^\nu)$$
Energy – First Law

balance of energy for a species $\iota$, in local form, in $\Omega_0$

$$\rho_0^t \frac{\partial e^t}{\partial t} = P^t : \dot{F} + P^t : \nabla_X V^t - \nabla_X \cdot Q^t + r^t_0 + \rho_0^t \tilde{e}^t - \nabla_X e^t \cdot (M^t)$$
Energy – First Law

balance of energy for a species \( \iota \), in local form, in \( \Omega_0 \)

\[
\rho_0 \frac{\partial e^t}{\partial t} = P^t : \dot{F} + P^t : \nabla_X V^t - \nabla_X \cdot Q^t + r_0^t + \rho_0^t e^t - \nabla_X e^t \cdot (M^t)
\]
Energy – First Law

balance of energy for a species $\iota$, in local form, in $\Omega_0$

$$\rho_0^t \frac{\partial e^t}{\partial t} = P^t : \dot{F} + P^t : \nabla_X V^t - \nabla_X \cdot Q^t + r_0^t + \rho_0^t \tilde{e}^t - \nabla_X e^t \cdot (M^t)$$
Energy – First Law

balance of energy for a species \( \nu \), in local form, in \( \Omega_0 \)

\[
\rho_0^t \frac{\partial e^t}{\partial t} = P^t : \dot{F} + P^t : \nabla_X V^t - \nabla_X \cdot Q^t + r^t_0 + \rho_0^t \ddot{e}^t - \nabla_X e^t \cdot (M^t)
\]
Energy – First Law

balance of energy for a species $\iota$, in local form, in $\Omega_0$

$$
\rho_0^t \frac{\partial e^t}{\partial t} = P^t : \dot{F} + P^t : \nabla_X V^t - \nabla_X \cdot Q^t + r^t_0 + \rho_0^t \tilde{e}^t - \nabla_X e^t \cdot (M^t)
$$

where the interaction terms satisfy the relation,

$$
\sum_{i=\alpha}^{\omega} \left( \rho_0^t q^t \cdot (V + V^t) + \Pi^t \left( e^t + \frac{1}{2} \| V + V^t \|^2 \right) + \rho_0^t \tilde{e}^t \right) = 0
$$
Entropy – Second Law

\[
\sum_{i=\alpha}^{\omega} \rho_0 \frac{\partial \eta^t}{\partial t} \geq \sum_{i=\alpha}^{\omega} \left( \frac{r^t}{\theta} - \nabla_x \eta^t \cdot M^t - \frac{\nabla_x \cdot Q^t}{\theta} + \frac{\nabla_x \theta \cdot Q^t}{\theta^2} \right)
\]

combine first and second laws to get the dissipation inequality
Constitutive Relations

constitutive hypothesis: \( e^{t} = \hat{e}^{t}(F^{e^{t}}, \rho_{0}^{t}, \eta^{t}) \)

constitutive relations consistent with the dissipation inequality:

\[
P^{t} = \rho_{0}^{t} \frac{\partial e^{t}}{\partial F^{e^{t}}}, \forall t \quad \text{○ hyperelastic material}
\]

\[
\theta = \frac{\partial e^{t}}{\partial \eta^{t}}, \forall t \quad \text{○ thermal physics}
\]

\[
Q^{t} = -K^{t} \nabla x \theta, \forall t \quad \text{○ fourier law}
\]

\[
u \cdot K^{t} u \geq 0 \forall u \in \mathbb{R}^{3} \quad \text{(semi-positive definite conductivity)}
\]
Constitutive Relations

constitutive relation for flux of each transported species:

\[ M^t = D^t \left( -\rho_0^t F^T \frac{\partial V}{\partial t} + \rho_0^t F^T g + F^T \nabla_X \cdot P^t - \nabla_X (e^t - \theta \eta^t) \right) \]

\[ u \cdot D^t u \geq 0 \forall u \in \mathbb{R}^3 \]

- \( D^t \) is the mobility
Constitutive Relations

constitutive relation for flux of each transported species:

\[ M^t = D^t \left( -\rho_0^t F^T \frac{\partial V}{\partial t} + \rho_0^t F^T g + F^T \nabla_X \cdot P^t - \nabla_X (e^t - \theta \eta^t) \right) \]

- driving force due to inertia
Constitutive Relations

constitutive relation for flux of each transported species:

\[ M^i = D^i \left( -\rho_0^i F^T T \frac{\partial V}{\partial t} + \rho_0^i F^T g + F^T \nabla_X \cdot P^i - \nabla_X (e^i - \theta \eta^i) \right) \]

- driving force due to gravity
Constitutive Relations

constitutive relation for flux of each transported species:

\[ M^t = D^t \left( -\rho^t F^T \frac{\partial V}{\partial t} + \rho^t F^T g + F^T \nabla_X \cdot P^t - \nabla_X (e^t - \theta \eta^t) \right) \]

- driving force due to stress gradient – Darcy’s law
Constitutive Relations

constitutive relation for flux of each transported species:

\[ M^t = D^t \left( -\rho_0^t F^T \frac{\partial V}{\partial t} + \rho_0^t F^T g + F^T \nabla_x \cdot P^t - \nabla_x (e^t - \theta \eta^t) \right) \]

- driving force due to a chemical potential gradient
Constitutive Relations

constitutive relation for flux of each transported precursor/byproduct:

\[
\tilde{M}^t = D^t \left( -\rho_0^t F^T \frac{\partial (V + V^t)}{\partial t} + \rho_0^t F^T g - \nabla_X (e^t - \theta \eta^t) \right)
\]
Reduced Dissipation Inequality

with the constitutive relations ensuring the non-positiveness of certain terms, the entropy inequality is reduced to

$$D = \sum_{\iota=\alpha} \left( \rho_0^t \frac{\partial e^t}{\partial \rho_0^t} \frac{\partial \rho_0^t}{\partial t} - P^t : \nabla X V^t + \rho_0^t V^t \cdot \left( \frac{\partial V^t}{\partial t} + \left( \nabla X V^t \right) F^{-1} V^t \right) \right)$$

$$+ \sum_{\iota=\alpha} \Pi^t \left( e^t + \frac{1}{2} \| V + V^t \|^2 \right)$$

$$+ \sum_{\iota=\alpha} \left( \rho_0^t \frac{\partial}{\partial t} (V + V^t) - \rho_0^t g - \nabla X \cdot P^t + \nabla X (V + V^t) \left( \rho_0^t F^{-1} V^t \right) \right) \cdot V \leq 0$$
Computational Formulation

- Implementation in FEAP
- Coupled implementation; staggered scheme (Armero [1999], Garikipati et al. [2001])
- Nonlinear projection methods to treat incompressibility (Simo et al. [1985])
- Energy-momentum conserving algorithm for dynamics (Simo & Tarnow [1992a,b])
Computational Formulation

• Backward Euler for time-dependent mass balance

• Mixed method for stress/strain gradient-driven fluxes (Garikipati et al. [2001])

• Large advective terms require stabilization
Coupled Computations – Examples

- biphasic model
  - worm-like chain model for collagen
  - ideal, nearly incompressible interstitial fluid with bulk compressibility of water, $\kappa^f = 2.25$ GPa

- “artificial” sources:

\[
\Pi^f = -k^f (\rho^f_0 - \rho^f_{0_{ini}}), \quad \Pi^s = -\Pi^f
\]

- entropy of mixing:

\[
\eta_{mix} = -\frac{k}{M^i} \log \frac{\rho^i_0}{\rho_0}
\]
Coupled Computations – Examples – Swelling

- fluid concentration evolution
- fluid sink evolution
- solid concentration evolution

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Coupled Computations – Examples – Pinching

- fluid concentration evolution
- fluid sink evolution
- solid concentration evolution

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Summary and Further Work

- physiologically consistent continuum formulation describing growth in an open system
- relevant driving forces arise from thermodynamics – coupling with mechanics
- consistent with mixture theory
  - formulated a theoretical framework for the remodelling problem
  - engineering and characterization of growing, functional biological tissue
Worm-like Chain Model for Solid Collagen

\[ \tilde{\rho}_0^s \hat{e}^s (F^{e_s}, \rho_0) = \frac{Nk\theta}{4A} \frac{r^2}{2L} + \frac{L}{4(1 - r/L)} - \frac{r}{4} \]

\[ - \frac{Nk\theta}{4} \frac{2A}{2L/A} \frac{A}{L} + \frac{1}{4(1 - \frac{2A}{2L/A})} - \frac{1}{4} \log(\lambda_1^2 \lambda_2^2 \lambda_3^c) \]

\[ + \frac{\gamma}{\beta} (J^e \lambda - 2\beta - 1) + 2\gamma 1: E^{e_s} \]

\[ r = \frac{1}{2} \sqrt{a^2 \lambda_1^e + b^2 \lambda_2^e + c^2 \lambda_3^e}, \quad \lambda_I^e = \sqrt{N_I \cdot C^e N_I} \]