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 *in vitro* engineered tissue
  - quantitative model motivated and validated by experiment
  - model drives the controlled experiments

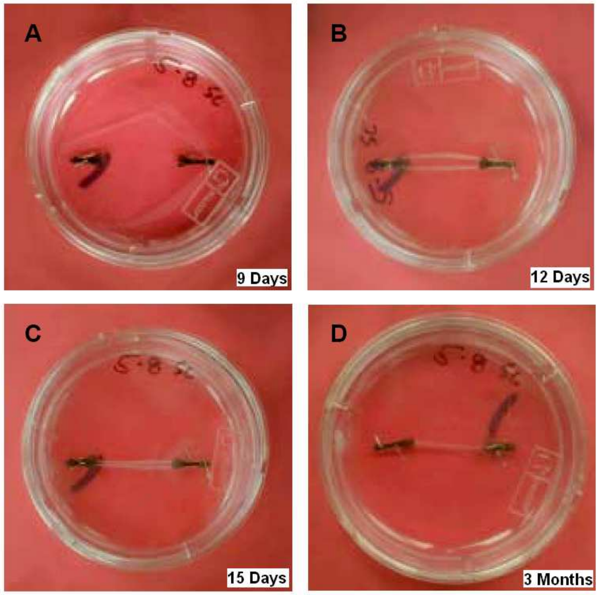
Development of Biological Tissue

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*

Tissue Engineering

engineered tissue *invitro* 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

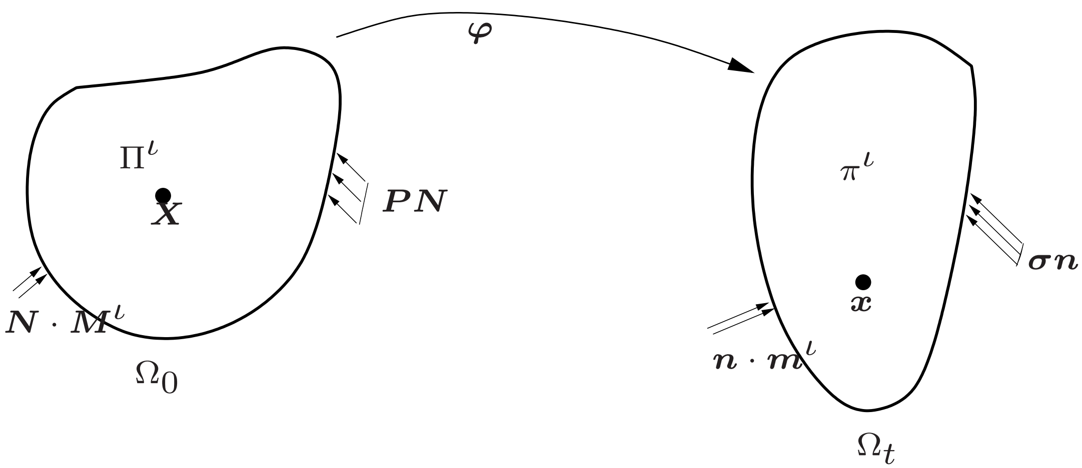
Modelling – Background

- 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

Balance of Mass – Equations

for a species ι, in local form, in Ω_0

$$\frac{\partial \rho_0^\iota}{\partial t} = \Pi^\iota - \boldsymbol{\nabla}_X \cdot \boldsymbol{M}^\iota, \; \forall \, \iota = \alpha, \ldots, \omega$$

the sources/sinks satisfy

$$\sum_{\iota=\alpha}^{\omega} \Pi^\iota = 0.$$

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for the solid phase

$$\frac{\partial \rho_0^s}{\partial t} = \Pi^s$$

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

Balance of Mass – Equations

for a species ι, in local form, in Ω_0

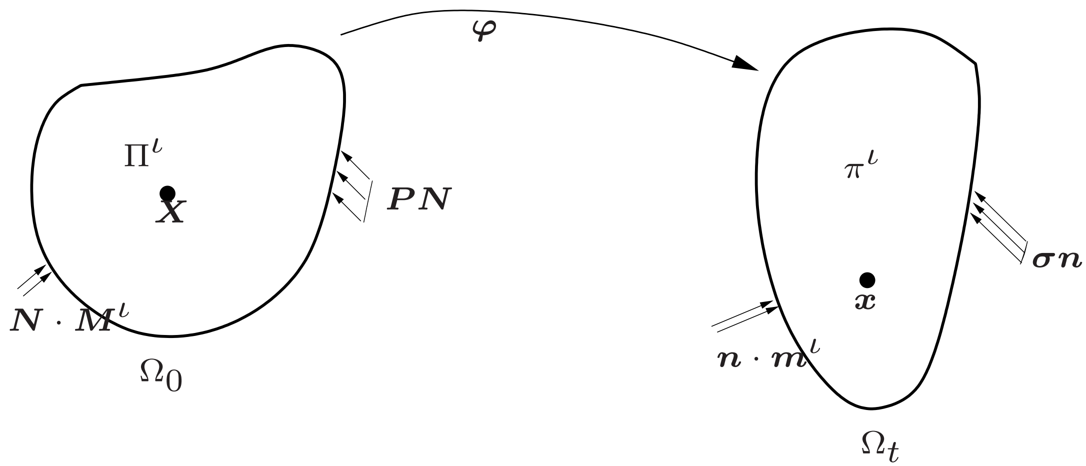
$$\frac{\partial \rho_0^\iota}{\partial t} = \Pi^\iota - \boldsymbol{\nabla}_X \cdot \boldsymbol{M}^\iota, \; \forall\, \iota = \alpha, \ldots, \omega$$

for the fluid phase

$$\frac{\partial \rho_0^f}{\partial t} = -\boldsymbol{\nabla}_X \cdot \boldsymbol{M}^f$$

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 $\boldsymbol{V}^\iota = (1/\rho_0^\iota)\boldsymbol{F}\boldsymbol{M}^\iota$

Balance of Linear Momentum – Equations

for a species ι, in local form, in Ω_0

$$\rho_0^\iota \frac{\partial}{\partial t} (\boldsymbol{V} + \boldsymbol{V}^\iota) = \rho_0^\iota (\boldsymbol{g} + \boldsymbol{q}^\iota) + \boldsymbol{\nabla}_X \cdot \boldsymbol{P}^\iota - (\boldsymbol{\nabla}_X (\boldsymbol{V} + \boldsymbol{V}^\iota)) \boldsymbol{M}^\iota, \ \forall\, \iota = \alpha, \dots, \omega$$

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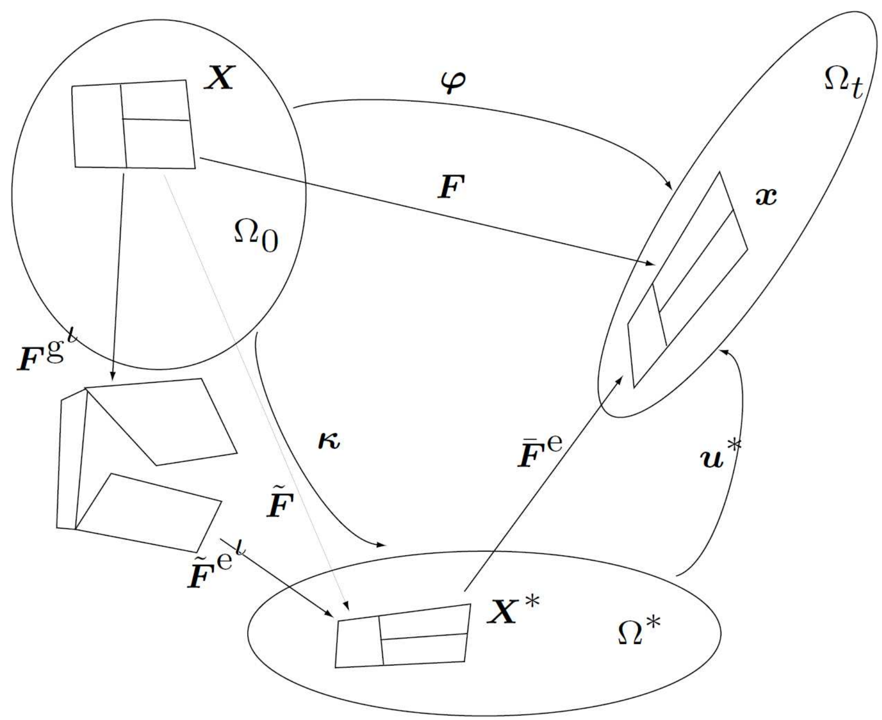
relation between mass sources Π^ι's and interaction forces $\boldsymbol{q}^\iota$'s,

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

Kinematics of Growth



Kinematics of Growth

$$\boldsymbol{F} = \bar{\boldsymbol{F}}^{\mathrm{e}} \tilde{\boldsymbol{F}}^{\mathrm{e}^{\iota}} \boldsymbol{F}^{\mathrm{g}^{\iota}}$$

- $\boldsymbol{F}^{\mathrm{g}^{\iota}}$ is a kinematic "growth" tensor , $\boldsymbol{F}^{\mathrm{e}^{\iota}} = \bar{\boldsymbol{F}}^{\mathrm{e}} \tilde{\boldsymbol{F}}^{\mathrm{e}^{\iota}}$ is the elastic deformation gradient

- residual stress due to $\tilde{\boldsymbol{F}}^{\mathrm{e}^{\iota}}$

Energy – First Law

balance of energy for a species ι, in local form, in Ω_0

$$\rho_0^\iota \frac{\partial e^\iota}{\partial t} = \boldsymbol{P}^\iota : \dot{\boldsymbol{F}} + \boldsymbol{P}^\iota : \boldsymbol{\nabla}_X \boldsymbol{V}^\iota - \boldsymbol{\nabla}_X \cdot \boldsymbol{Q}^\iota + r_0^\iota + \rho_0^\iota \tilde{e}^\iota - \boldsymbol{\nabla}_X e^\iota \cdot (\boldsymbol{M}^\iota)$$

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where the interaction terms satisfy the relation,

$$\sum_{\iota=\alpha}^{\omega} \left(\rho_0^\iota \boldsymbol{q}^\iota \cdot (\boldsymbol{V} + \boldsymbol{V}^\iota) + \Pi^\iota \left(e^\iota + \frac{1}{2} \| \boldsymbol{V} + \boldsymbol{V}^\iota \|^2 \right) + \rho_0^\iota \tilde{e}^\iota \right) = 0$$

Entropy – Second Law

$$\sum_{\iota=\alpha}^{\omega} \rho_0^\iota \frac{\partial \eta^\iota}{\partial t} \geq \sum_{\iota=\alpha}^{\omega} \left(\frac{r^\iota}{\theta} - \boldsymbol{\nabla}_X \eta^\iota \cdot \boldsymbol{M}^\iota - \frac{\boldsymbol{\nabla}_X \cdot \boldsymbol{Q}^\iota}{\theta} + \frac{\boldsymbol{\nabla}_X \theta \cdot \boldsymbol{Q}^\iota}{\theta^2} \right)$$

combine first and second laws to get the dissipation inequality

Constitutive Relations

constitutive hypothesis: $e^\iota = \hat{e}^\iota(\boldsymbol{F}^{\mathrm{e}^\iota}, \rho_0^\iota, \eta^\iota)$

constitutive relations consistent with the dissipation inequality:

$$\boldsymbol{P}^\iota = \rho_0^\iota \frac{\partial e^\iota}{\partial \boldsymbol{F}^{\mathrm{e}^\iota}}, \forall\, \iota \qquad \circ \text{ hyperelastic material}$$

$$\theta = \frac{\partial e^\iota}{\partial \eta^\iota}, \ \forall\, \iota \qquad \circ \text{ thermal physics}$$

$$\boldsymbol{Q}^\iota = -\boldsymbol{K}^\iota \boldsymbol{\nabla}_X \theta, \ \forall\, \iota \qquad \circ \text{ fourier law}$$

$$\boldsymbol{u} \cdot \boldsymbol{K}^\iota \boldsymbol{u} \geq 0\, \forall \boldsymbol{u} \in \mathbb{R}^3 \qquad \text{(semi-positive definite conductivity)}$$

Constitutive Relations

constitutive relation for flux of each transported species:

$$\boldsymbol{M}^{\iota} = \boldsymbol{D}^{\iota}\left(-\rho_0^{\iota}\boldsymbol{F}^{\mathrm{T}}\frac{\partial \boldsymbol{V}}{\partial t} + \rho_0^{\iota}\boldsymbol{F}^{\mathrm{T}}\boldsymbol{g} + \boldsymbol{F}^{\mathrm{T}}\boldsymbol{\nabla}_X \cdot \boldsymbol{P}^{\iota} - \boldsymbol{\nabla}_X(e^{\iota} - \theta\eta^{\iota})\right)$$

$$\boldsymbol{u} \cdot \boldsymbol{D}^{\iota}\boldsymbol{u} \geq 0 \,\forall \boldsymbol{u} \in \mathbb{R}^3$$

- $\boldsymbol{D}^{\iota}$ is the mobility

Constitutive Relations

constitutive relation for flux of each transported species:

$$\boldsymbol{M}^\iota = \boldsymbol{D}^\iota \left(-\rho_0^\iota \boldsymbol{F}^{\mathrm{T}} \frac{\partial \boldsymbol{V}}{\partial t} + \rho_0^\iota \boldsymbol{F}^{\mathrm{T}} \boldsymbol{g} + \boldsymbol{F}^{\mathrm{T}} \boldsymbol{\nabla}_X \cdot \boldsymbol{P}^\iota - \boldsymbol{\nabla}_X (e^\iota - \theta \eta^\iota) \right)$$

∘ driving force due to inertia

Constitutive Relations

constitutive relation for flux of each transported species:

$$\boldsymbol{M}^\iota = \boldsymbol{D}^\iota \left(-\rho_0^\iota \boldsymbol{F}^{\mathrm{T}} \frac{\partial \boldsymbol{V}}{\partial t} + \rho_0^\iota \boldsymbol{F}^{\mathrm{T}} \boldsymbol{g} + \boldsymbol{F}^{\mathrm{T}} \boldsymbol{\nabla}_X \cdot \boldsymbol{P}^\iota - \boldsymbol{\nabla}_X (e^\iota - \theta \eta^\iota) \right)$$

- driving force due to gravity

Constitutive Relations

constitutive relation for flux of each transported species:

$$\boldsymbol{M}^{\iota} = \boldsymbol{D}^{\iota}\left(-\rho_0^{\iota}\boldsymbol{F}^{\mathrm{T}}\frac{\partial \boldsymbol{V}}{\partial t} + \rho_0^{\iota}\boldsymbol{F}^{\mathrm{T}}\boldsymbol{g} + \boldsymbol{F}^{\mathrm{T}}\boldsymbol{\nabla}_X \cdot \boldsymbol{P}^{\iota} - \boldsymbol{\nabla}_X(e^{\iota} - \theta\eta^{\iota})\right)$$

- driving force due to stress gradient – Darcy's law

Constitutive Relations

constitutive relation for flux of each transported species:

$$\boldsymbol{M}^{\iota} = \boldsymbol{D}^{\iota}\left(-\rho_0^{\iota}\boldsymbol{F}^{\mathrm{T}}\frac{\partial \boldsymbol{V}}{\partial t} + \rho_0^{\iota}\boldsymbol{F}^{\mathrm{T}}\boldsymbol{g} + \boldsymbol{F}^{\mathrm{T}}\boldsymbol{\nabla}_X \cdot \boldsymbol{P}^{\iota} - \boldsymbol{\nabla}_X(e^{\iota} - \theta\eta^{\iota})\right)$$

- driving force due to a chemical potential gradient

Constitutive Relations

constitutive relation for flux of each transported precursor/byproduct:

$$\tilde{\boldsymbol{M}}^{\iota} = \boldsymbol{D}^{\iota} \left(-\rho_0^{\iota} \boldsymbol{F}^{\mathrm{T}} \frac{\partial (\boldsymbol{V} + \boldsymbol{V}^{\iota})}{\partial t} + \rho_0^{\iota} \boldsymbol{F}^{\mathrm{T}} \boldsymbol{g} - \boldsymbol{\nabla}_X (e^{\iota} - \theta \eta^{\iota}) \right)$$

Reduced Dissipation Inequality

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

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

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

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

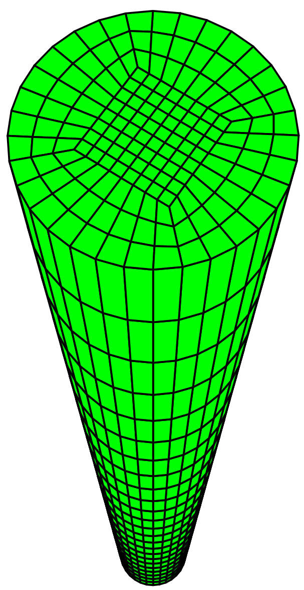
Computational Formulation

- 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, $\boldsymbol{\kappa}^{\mathrm{f}} = 2.25$ GPa

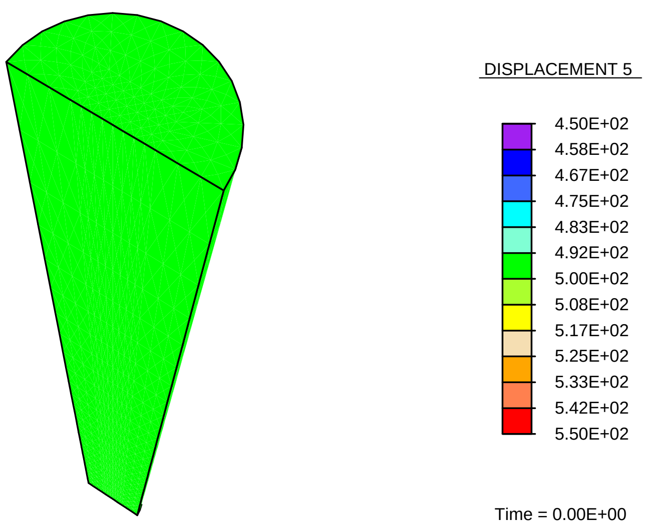
- "artificial" sources:

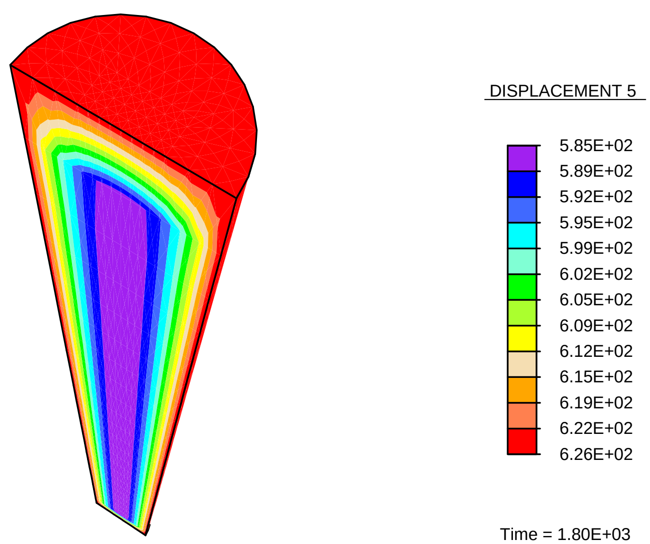
$$\Pi^{\mathrm{f}} = -k^{\mathrm{f}}(\rho_0^{\mathrm{f}} - \rho_{0_{\mathrm{ini}}}^{\mathrm{f}}), \quad \Pi^{\mathrm{s}} = -\Pi^{\mathrm{f}}$$

- entropy of mixing:

$$\eta_{\mathrm{mix}}^{\iota} = -\frac{k}{\mathcal{M}^{\iota}} \log \frac{\rho_0^{\iota}}{\rho_0}$$

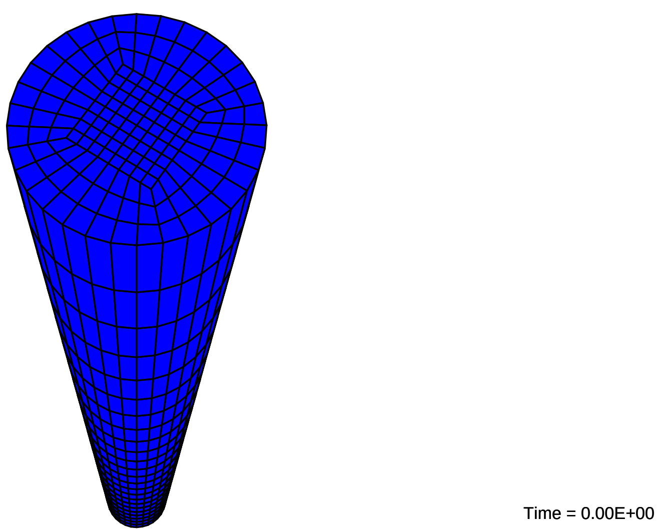
Coupled Computations – Examples – Swelling

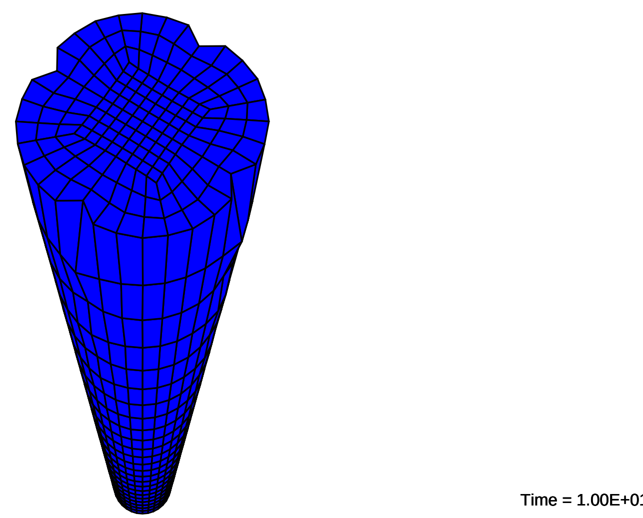




- fluid concentration evolution
- fluid sink evolution
- solid concentration evolution

Coupled Computations – Examples – Pinching





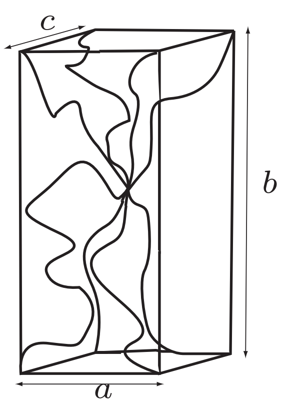
- fluid concentration evolution
- fluid sink evolution
- solid concentration evolution

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



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

$$- \quad \frac{Nk\theta}{4 \quad \overline{2L/A}} \qquad \frac{\overline{2A}}{L} + \frac{1}{4(1- \quad \overline{2A/L})} - \frac{1}{4} \quad \log(\lambda_1^{a^2} \lambda_2^{b^2} \lambda_3^{c}$$

$$+ \quad \frac{\gamma}{\beta}(J^{\mathrm{e}^{\iota}-2\beta} - 1) + 2\gamma \mathbf{1} \colon \boldsymbol{E}^{\mathrm{e}^{\mathrm{s}}}$$

$$r = \frac{1}{2}\sqrt{a^2 \lambda_1^{\mathrm{e}^2} + b^2 \lambda_2^{\mathrm{e}^2} + c^2 \lambda_3^{\mathrm{e}^2}}, \quad \lambda_I^{\mathrm{e}} = \sqrt{\boldsymbol{N}_I \cdot \boldsymbol{C}^{\mathrm{e}} \boldsymbol{N}_I}$$