A Continuum Treatment Of Coupled Mass Transport And Mechanics In Growing Soft Biological Tissue

Nutrient transport is pivotal

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University of Michigan
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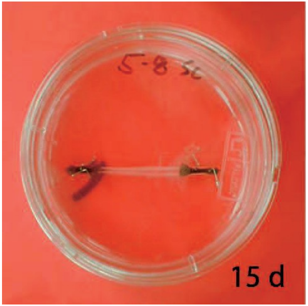
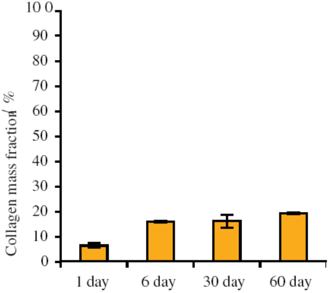
Motivation and definition

Growth/Resorption – An addition or loss of mass



Engineered tendon constructs [Calve et al]



Increasing collagen concentration with age

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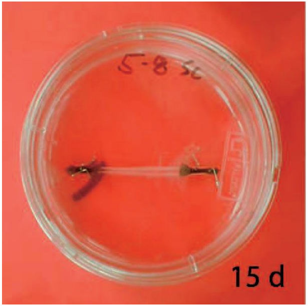

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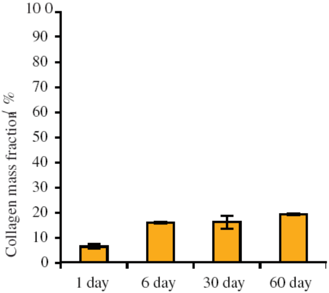

Increasing collagen concentration with age

Open system with multiple species inter-converting and interacting

Modelling challenges and approach

Classical balance laws enhanced via fluxes and sources

- Solid – Collagen, proteoglycans, cells
- Extra cellular fluid
  – undergoes transport relative to the solid phase
- Dissolved solutes (sugars, proteins, . . .)
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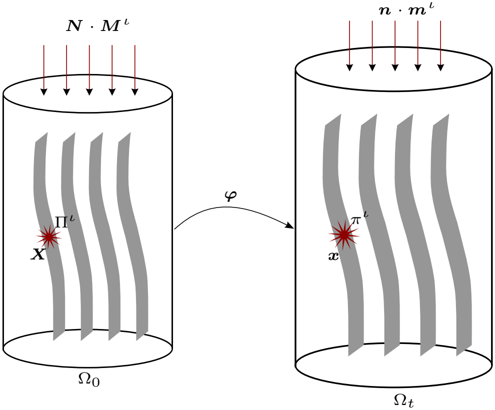
Brief subset of related literature:

- Cowin and Hegedus [1976]
- Kuhl and Steinmann [2002]
- Sengers, Oomens and Baaijens [2004]
- *Garikipati et al. – Journal of the Mechanics and Physics of Solids (52) 1595-1625 [2004]*

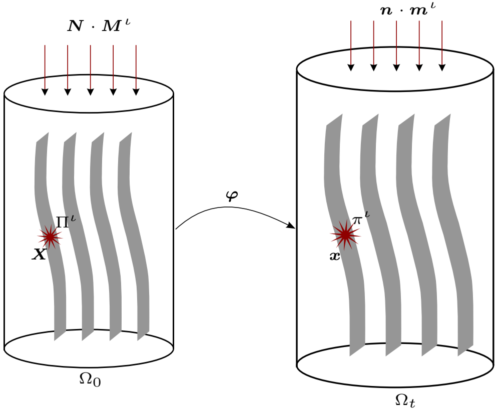
Mass balance



ρ^{ι} – Species concentration
Π^{ι} – Species production
$\boldsymbol{M}^{\iota}$ – Species flux

- For a species: $$\frac{\partial \rho^{\iota}}{\partial t} = \Pi^{\iota} - \boldsymbol{\nabla} \cdot \boldsymbol{M}^{\iota}$$
- Solid – No flux; no boundary conditions
- Fluid – No source; concentration or flux boundary conditions
- Solute – Flux and source; concentration boundary condition

Mass balance



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Possibilities for the sources

- Simple first order rate law – Constituents either "solid" or "fluid"
$$\Pi^{\mathrm{f}} = -k^{\mathrm{f}}(\rho^{\mathrm{f}} - \rho^{\mathrm{f}}_{\mathrm{ini}}), \quad \Pi^{\mathrm{c}} = -\Pi^{\mathrm{f}}$$
- Strain Energy Dependencies – Weighted by relative densities

  Harrigan & Hamilton [1993]
- Enzyme Kinetics – Introducing additional species to the mixture

  Michaelis Menten [1913]

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$$\Pi^{\mathrm{s}} = \frac{(\Pi^{\mathrm{s}}_{\mathrm{max}}\rho^{\mathrm{s}})}{(\rho^{\mathrm{s}}_m + \rho^{\mathrm{s}})}\rho_{\mathrm{cell}}, \quad \Pi^{\mathrm{c}} = -\Pi^{\mathrm{s}}$$

Michaelis Menten [1913]

Enzyme Kinetics

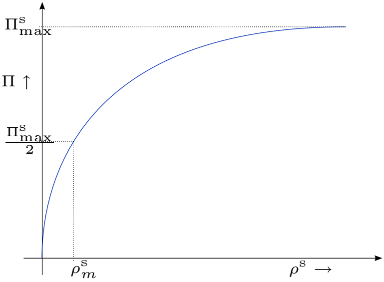
$$\mathrm{E} + \mathrm{S} \underset{k_{-1}}{\overset{k_1}{\rightleftharpoons}} \mathrm{ES} \xrightarrow{k_2} \mathrm{E} + \mathrm{P}$$

k_1 - Association of substrate and enzyme

k_{-1} - Dissociation of unaltered substrate

k_2 - Formation of product

$$\rho^{\mathrm{s}}_m = \frac{(k_2 + k_{-1})}{k_1}$$



$$\frac{\partial \rho^{\iota}}{\partial t} = \Pi^{\iota} - \boldsymbol{\nabla} \cdot \boldsymbol{M}^{\iota}$$

Constitutive relations for fluxes

- Compatible with dissipation inequality
- Fluid flux relative to collagen
  $$\boldsymbol{M}^f = \boldsymbol{D}^f \left(\rho^f \boldsymbol{F}^T \boldsymbol{g} + \boldsymbol{F}^T \boldsymbol{\nabla} \cdot \boldsymbol{P}^f - \boldsymbol{\nabla}(e^f - \theta\eta^f)\right)$$
- Solute flux (proteins, sugars, nutrients, ...) relative to fluid
  $$\widetilde{\boldsymbol{V}}^s = \boldsymbol{V}^s - \boldsymbol{V}^f$$
  $$\widetilde{\boldsymbol{M}}^s = \boldsymbol{D}^s \left(-\boldsymbol{\nabla}(e^s - \theta\eta^s)\right)$$
- $\boldsymbol{D}^f$ and $\boldsymbol{D}^s$ – Positive semi-definite mobility tensors
  Magnitudes from literature, e.g. Mauck et al. [2003]

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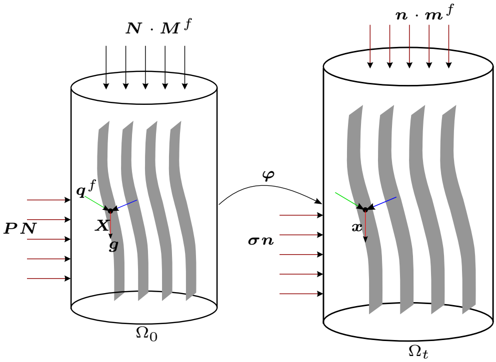
Momentum balance



ρ^f – Fluid concentration
$\boldsymbol{V}$ – Solid velocity
$\boldsymbol{V}^f$ – Fluid relative velocity
$\boldsymbol{g}$ – Body force
$\boldsymbol{q}^f$ – Interaction force
$\boldsymbol{P}^f$ – Partial stress

- For the fluid, velocity relative to the solid: $\boldsymbol{V}^f = (1/\rho^f)\boldsymbol{F}\boldsymbol{M}^f$

$$\rho^f \frac{\partial}{\partial t}(\boldsymbol{V} + \boldsymbol{V}^f) = \rho^f(\boldsymbol{g} + \boldsymbol{q}^f) + \boldsymbol{\nabla} \cdot \boldsymbol{P}^f - (\boldsymbol{\nabla}(\boldsymbol{V} + \boldsymbol{V}^f))\boldsymbol{M}^f$$

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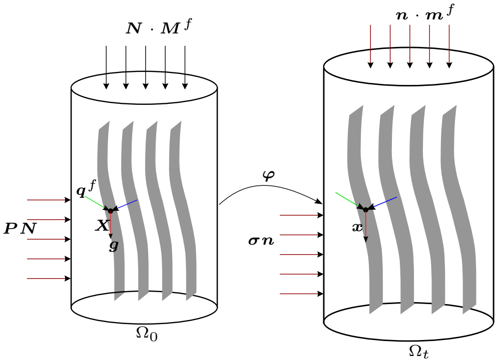

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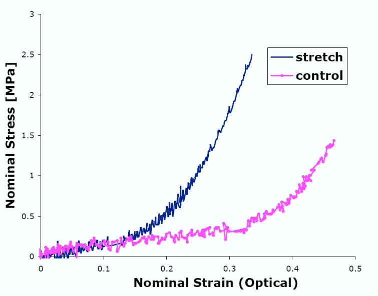
Constitutive relations for partial stress

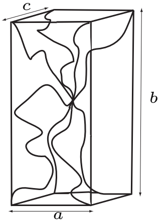


Stress-strain response curves of self organized tendon [Arruda et al]

- Hyper-elastic material compatible with dissipation inequality

Worm-like chain model based internal energy density

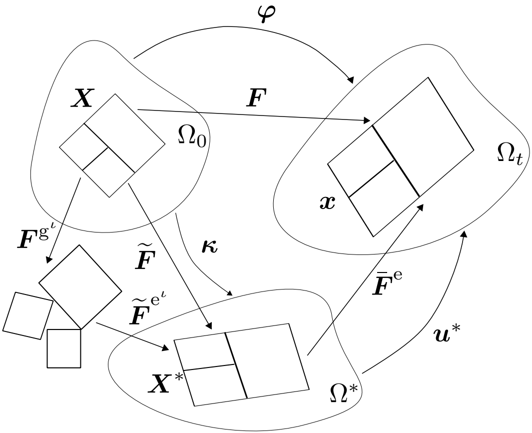
$$\widetilde{\rho}^{\mathrm{c}}\hat{e}^{\mathrm{c}}(\boldsymbol{F}^{\mathrm{e}^{\mathrm{c}}},\rho^{\mathrm{c}})$$



$$\begin{aligned} &= \frac{Nk\theta}{4A}\left(\frac{r^2}{2L}+\frac{L}{4(1-r/L)}-\frac{r}{4}\right) \\ &- \frac{Nk\theta}{4\sqrt{2L/A}}\left(\sqrt{\frac{2A}{L}}+\frac{1}{4(1-\sqrt{2A/L})}-\frac{1}{4}\right)\log(\lambda_1^{a^2}\lambda_2^{b^2}\lambda_3^{c^2}) \\ &+ \frac{\gamma}{\beta}(J^{\mathrm{e}^{\iota}\,-2\beta}-1)+2\gamma\mathbf{1}:\boldsymbol{E}^{\mathrm{e}^{\mathrm{c}}} \end{aligned}$$

- Embed in multi chain model [Bischoff et al.]
  $r=\frac{1}{2}\sqrt{a^2\lambda_1^{\mathrm{e}^2}+b^2\lambda_2^{\mathrm{e}^2}+c^2\lambda_3^{\mathrm{e}^2}}$
- λ_I^{e} – elastic stretches along a, b, c
  $\lambda_I^{\mathrm{e}}=\sqrt{\boldsymbol{N}_I\cdot\boldsymbol{C}^{\mathrm{e}}\boldsymbol{N}_I}$

Growth kinematics



- $\boldsymbol{F} = \bar{\boldsymbol{F}}^{\mathrm{e}} \widetilde{\boldsymbol{F}}^{\mathrm{e}^{\iota}} \boldsymbol{F}^{\mathrm{g}^{\iota}}$; $\boldsymbol{F}^{\mathrm{e}^{\iota}} = \bar{\boldsymbol{F}}^{\mathrm{e}} \widetilde{\boldsymbol{F}}^{\mathrm{e}^{\iota}}$; Internal stress due to $\widetilde{\boldsymbol{F}}^{\mathrm{e}^{\iota}}$
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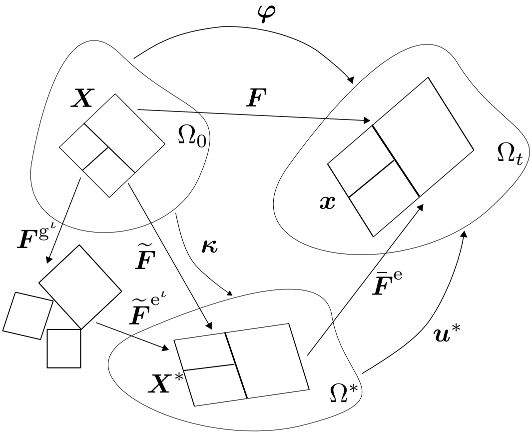

- $F = \bar{F}^e \widetilde{F}^{e^\iota} F^{g^\iota}$; $F^{e^\iota} = \bar{F}^e \widetilde{F}^{e^\iota}$; Internal stress due to $\widetilde{F}^{e^\iota}$
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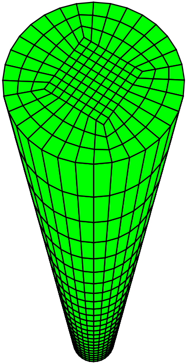
Example of coupled computation



- Simulating a tendon immersed in a nutrient rich bath
- Biphasic model
  - worm-like chain model for collagen
  - ideal nearly incompressible fluid $\rho^f \psi^f = \frac{1}{2}\kappa(\det(F^{e^f}) - 1)^2$
- Fluid mobility $D^f_{ij} = 1 \times 10^{-8}\delta_{ij}$, Han et al. [2000]
- First order rate law: $\Pi^{\mathrm{f}} = -k^{\mathrm{f}}(\rho^{\mathrm{f}} - \rho^{\mathrm{f}}_{\mathrm{ini}}), \quad \Pi^{\mathrm{c}} = -\Pi^{\mathrm{f}}$

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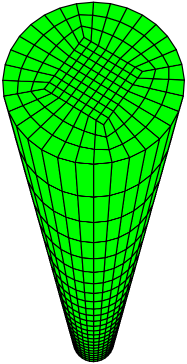

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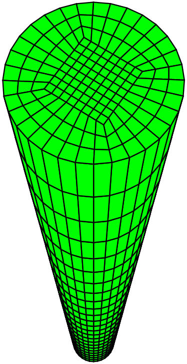

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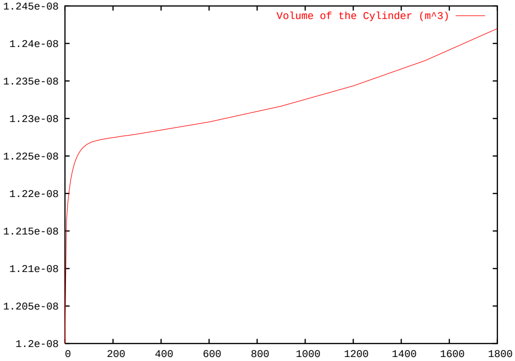
Results and inferences

Collagen concentration evolution



Cylinder volume evolution with time

Results and inferences

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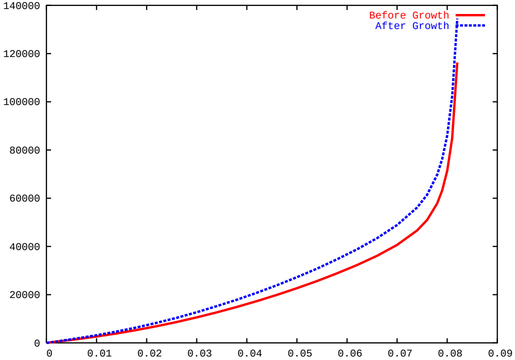

Stress vs Extension curves

Summary and further work

- Physiologically relevant continuum formulation describing growth in an open system – consistent with mixture theory
- Relevant driving forces arise from thermodynamics – coupling with mechanics
- Gained insights into the problem
  - Issues of saturation and growth
  - Saturation and Fickian diffusion
  - Configurations and physical boundary conditions

- More careful treatment of biochemistry – nature of sources
- Formulated a theoretical framework for remodelling
- Engineering and characterization of growing, functional biological tissue to drive and validate modelling

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