Tendon Growth and Healing: The Roles of Reaction, Transport and Mechanics

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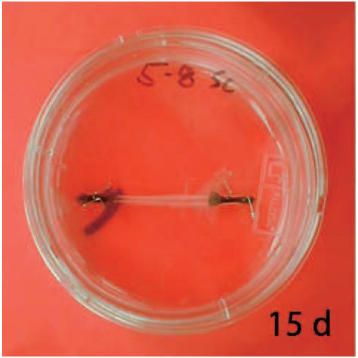
Describing the system



Engineered tendon construct [Calve et al., 2004]

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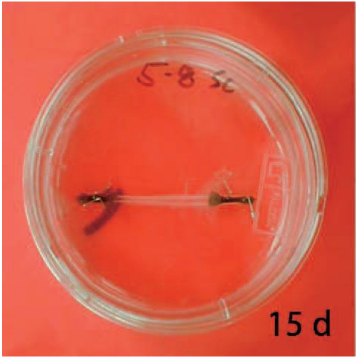
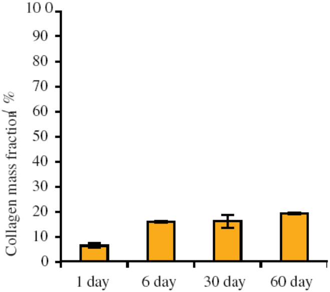


Engineered tendon construct [Calve et al., 2004]

Cylinder: $\sim$ 12 mm long, 1 mm^2 in cross section

Defining the problem

Growth/Resorption—An addition (or loss) of mass to the tissue

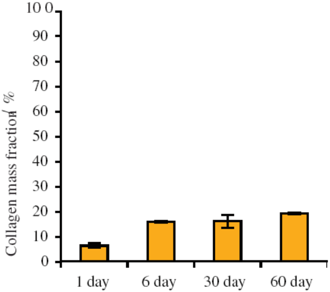


Increasing collagen concentration with age

[Calve et al.]

Defining the problem

Growth/Resorption—An addition (or loss) of mass to the tissue
Damage—Trauma resulting in considerable loss of tissue mass . . .
and sudden changes in material properties



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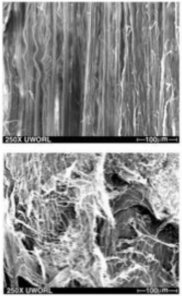
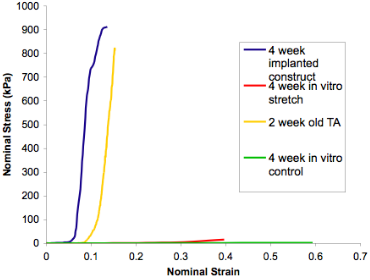
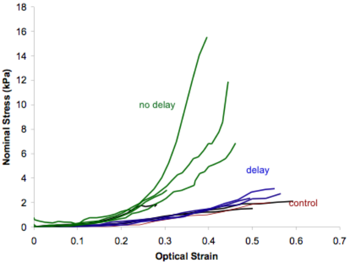


Damaged Ligament [Provenzano et al., 2003]

Factors affecting growth and healing



Chemical environment—Implantation [Calve et al.]



Mechanics—Influence of cyclic load [Calve et al.]

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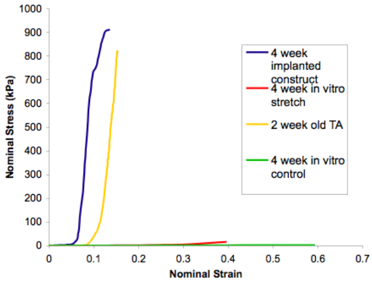

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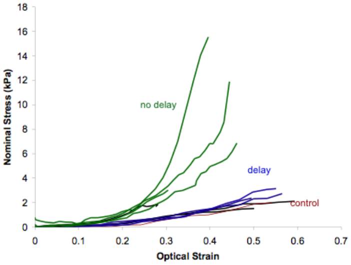

Mechanics—Influence of cyclic load [Calve et al.]

Increase in collagen content and microstructural distribution

$$\frac{\partial \rho^\iota}{\partial t} = \Pi^\iota$$

Possibilities for interconversion laws

- 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

  $$\Pi^{\mathrm{c}} = \left(\frac{\rho^{\mathrm{c}}}{\rho^{\mathrm{c}}_{\mathrm{ini}}}\right)^{-m}\Psi_0 - \Psi_0^{*}$$

  [Harrigan & Hamilton, 1993]

- Enzyme Kinetics – Introducing additional species to the mixture

  $$\Pi^{\mathrm{c}} = \frac{V^{\mathrm{c}}_{max}\,\rho^{\mathrm{e}}}{(K_m + \rho^{\mathrm{e}})}\rho_{\mathrm{cells}}, \quad \Pi^{\mathrm{c}} = -\Pi^{\mathrm{e}}$$

  [Michaelis & Menten, 1913]

- Cell Signalling – Preferential growth in damaged regions

  $$\Pi^{\mathrm{c}} = \delta\,\Pi^{\mathrm{c}}$$

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Enzyme Kinetics

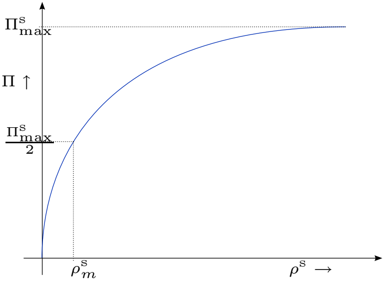
$$\mathrm{E} + \mathrm{S} \underset{k_{-1}}{\overset{k_1}{\rightleftharpoons}} \mathrm{ES} \xrightarrow{k_2} \mathrm{E} + \mathrm{P}$$

k_1 - Association of substrate and enzyme

k_{-1} - Dissociation of unaltered substrate

k_2 - Formation of product

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



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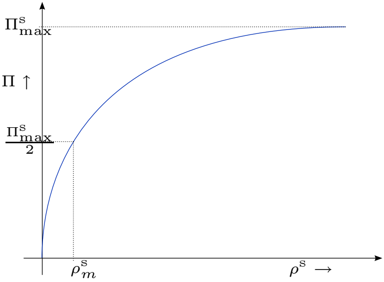

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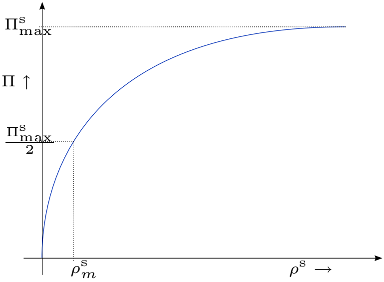
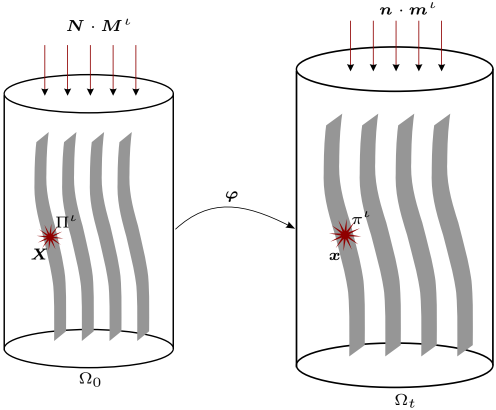


$$\frac{\partial \rho^{\iota}}{\partial t} = \Pi^{\iota}$$

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

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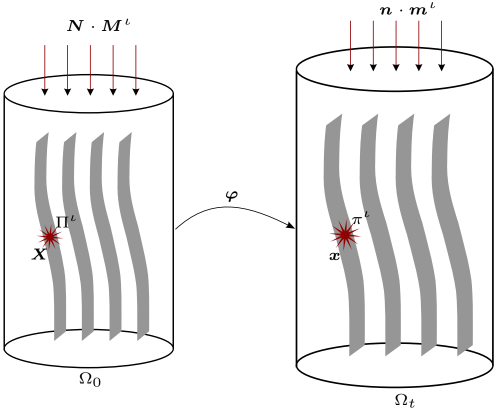

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Constitutive relations for fluxes

- Compatible with dissipation inequality
- Fluid flux relative to collagen
  $$\boldsymbol{M}^f = \boldsymbol{D}^f \left(\rho^f \boldsymbol{F}^T \boldsymbol{g} + \boldsymbol{F}^T \boldsymbol{\nabla} \cdot \boldsymbol{P}^f - \boldsymbol{\nabla} \phi^f\right)$$
- Solute flux (proteins, sugars, nutrients, ...) relative to fluid
  $$\widetilde{\boldsymbol{V}}^s = \boldsymbol{V}^s - \boldsymbol{V}^f$$
  $$\widetilde{\boldsymbol{M}}^s = \boldsymbol{D}^s \left(-\boldsymbol{\nabla} \phi^s\right)$$
- $\boldsymbol{D}^f$ and $\boldsymbol{D}^s$ – Positive semi-definite mobility tensors
  Magnitudes from literature:
  - Fluid wrt solid: [Han et al., 2000]
  - Solute wrt fluid [Mauck et al., 2003]

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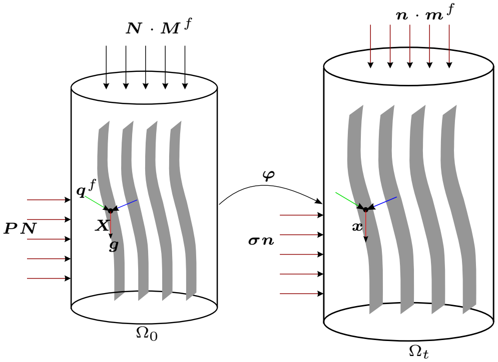
Momentum balance



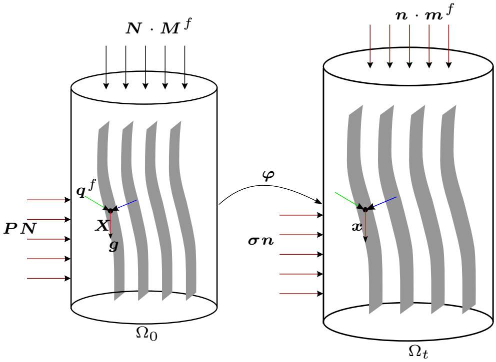
ρ^f – Fluid concentration
$\boldsymbol{V}$ – Solid velocity
$\boldsymbol{V}^f$ – Fluid relative velocity
$\boldsymbol{g}$ – Body force
$\boldsymbol{q}^f$ – Interaction force
$\boldsymbol{P}^f$ – Partial stress

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

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

[Garikipati et al., 2004]

Momentum balance



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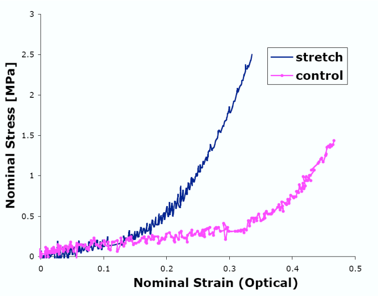
Constitutive relations for partial stress

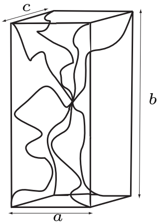


Stress-strain response curves of self organized tendon [Arruda et al.]

- Hyper-elastic material compatible with dissipation inequality

Worm-like chain model based internal energy density

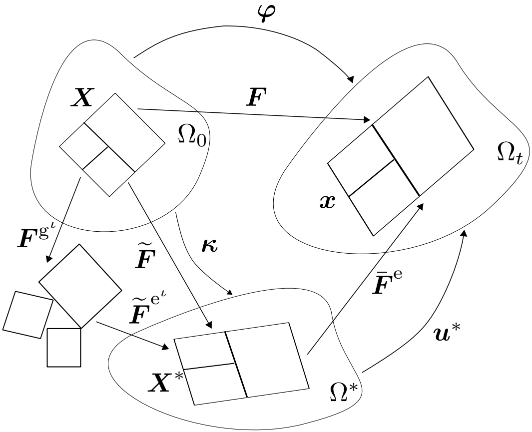
$$\widetilde{\rho}^{\mathrm{c}}\hat{e}^{\mathrm{c}}(\boldsymbol{F}^{\mathrm{e}^{\mathrm{c}}}, \rho^{\mathrm{c}})$$



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

- Embed in multi chain model [Bischoff et al., 2002]
  $r = \frac{1}{2}\sqrt{a^2\lambda_1^{\mathrm{e}^2} + b^2\lambda_2^{\mathrm{e}^2} + c^2\lambda_3^{\mathrm{e}^2}}$
- 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



- Isotropic swelling due to growth: $\boldsymbol{F}^{g^\iota} = \left(\frac{\rho^\iota}{\rho^\iota_{0_{\text{ini}}}}\right)^{\frac{1}{3}} \mathbf{1}$
- $\boldsymbol{F} = \bar{\boldsymbol{F}}^{e} \widetilde{\boldsymbol{F}}^{e^\iota} \boldsymbol{F}^{g^\iota}$; $\boldsymbol{F}^{e^\iota} = \bar{\boldsymbol{F}}^{e} \widetilde{\boldsymbol{F}}^{e^\iota}$; Internal stress due to $\widetilde{\boldsymbol{F}}^{e^\iota}$
- Saturation and swelling

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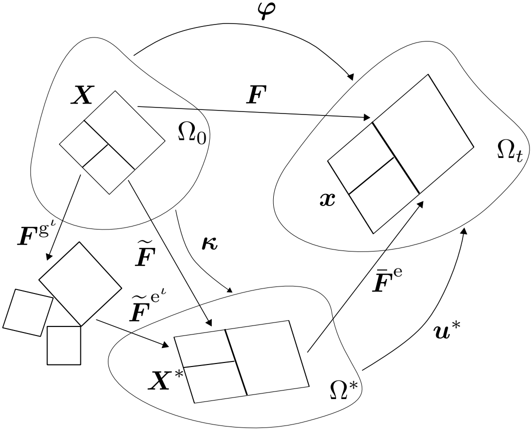

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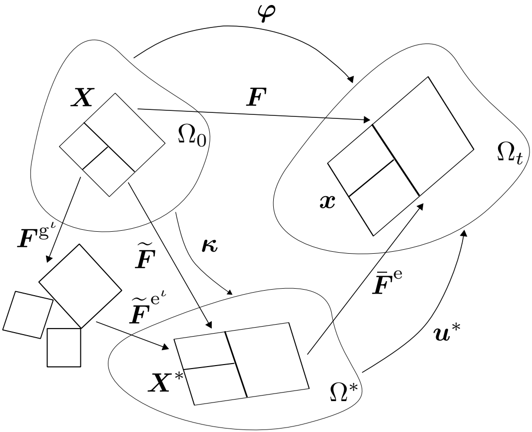

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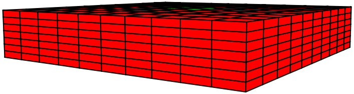
Example of coupled computation – Healing

- Skin damage healing; Hypertrophic scarring
- First order chemical kinetics with cell signalling: $\Pi^{\mathrm{c}} = k^{\mathrm{f}}(\rho^{\mathrm{f}} - \rho^{\mathrm{f}}_{\mathrm{ini}})\alpha$
- Skin immersed in a fluid rich bath



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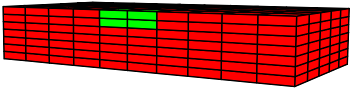

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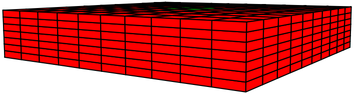

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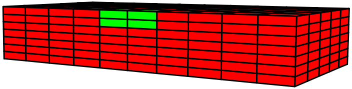

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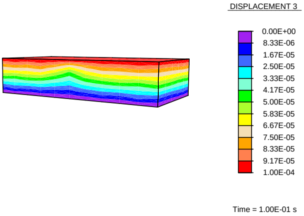

Vertical displacement on reload; Isotropic case

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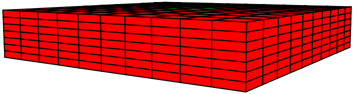

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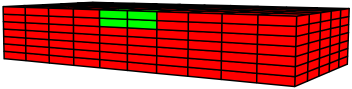

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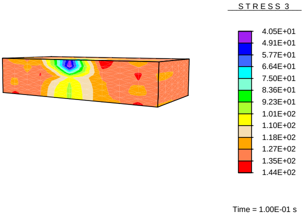

Vertical reload; Isotropic case

Summary and further work

- Physiologically relevant continuum formulation describing growth in an open system—consistent with mixture theory
- Easily extended to model simple damage healing
- Relevant contributors to growth and healing systematically accounted for—biochemistry, mass transport, coupled mechanics
- Gained insights into the problem
    - The relative roles of these factors
    - Influence of saturation on growth and diffusion
    - Configuration choice and physical boundary conditions
    - The kinematics challenges involved
- Revisit basic kinematic assumptions to enhance model

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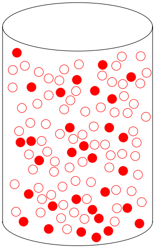
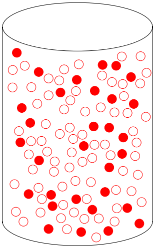
Separator slide

You ought not to be here.

Saturation and Fickian diffusion



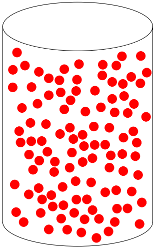
Configuration 1



Configuration 2

- Change in configurational entropy with distribution of solute particles . . . **if** solvent is not saturated with solute

Saturation and Fickian diffusion



only possible configuration

- Saturated ⇒ single configuration ⇒ no Fickian diffusion
- Still have concentration-gradient driven transport due to stress gradient contribution to flux