

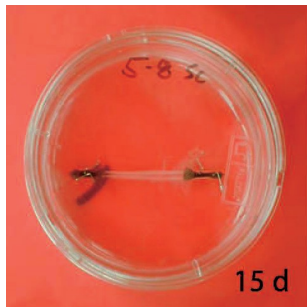
# A Continuum Treatment Of Coupled Mass Transport And Mechanics In Growing Soft Biological Tissue

*Nutrient transport is pivotal*

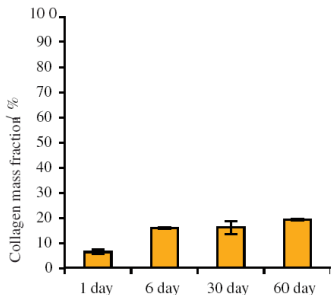
H. Narayanan, K. Garikipati, E. M. Arruda, K. Grosh & S. Calve  
University of Michigan  
Summer Bioengineering Conference – Vail, CO  
June 23<sup>rd</sup>, 2005

# Motivation and definition

*Growth/Resorption – An addition or loss of mass*



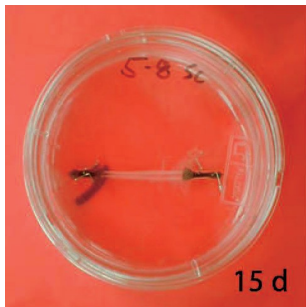
Engineered tendon constructs [Calve et al]



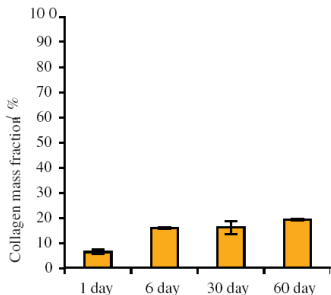
Increasing collagen concentration with age

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*Growth/Resorption – An addition or loss of mass*



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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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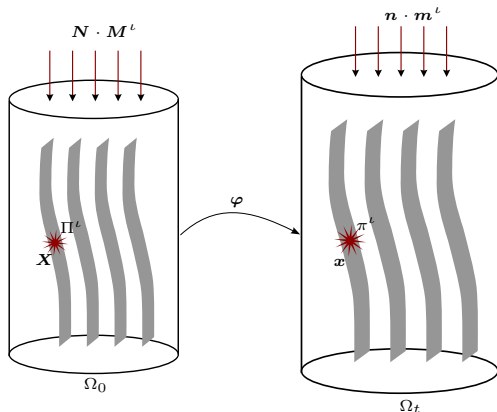
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Brief subset of related literature:

- 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

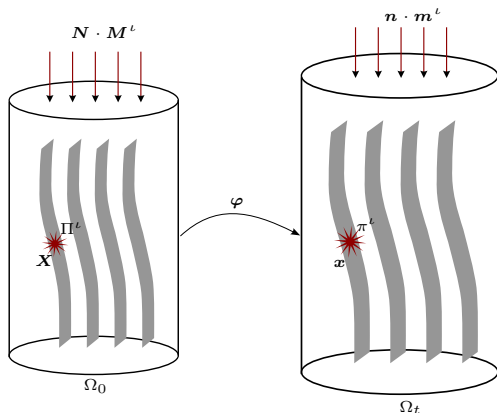


$\rho^l$  – Species concentration  
 $\Pi^l$  – Species production  
 $M^l$  – Species flux

• For a species: 
$$\frac{\partial \rho^l}{\partial t} = \Pi^l - \nabla \cdot M^l$$

- Solid – No flux; no boundary conditions
- Fluid – No source; concentration or flux boundary conditions
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# Possibilities for the sources

- Simple first order rate law –  
Constituents either “solid” or “fluid”

$$\Pi^f = -k^f(\rho^f - \rho_{ini}^f), \quad \Pi^c = -\Pi^f$$

- Strain Energy Dependencies –  
Weighted by relative densities

$$\Pi^c = \sum_i \left( \frac{\rho_i^c}{\rho^c} \right) \frac{\partial \Psi}{\partial \rho_i^c} - \Pi^f$$

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- Enzyme Kinetics – Introducing  
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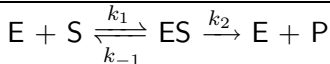
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- Enzyme Kinetics – Introducing  
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$$\Pi^s = \frac{(\Pi_{max}^s \rho^s)}{(\rho_m^s + \rho^s)} \rho_{cell}, \quad \Pi^c = -\Pi^s$$

Michaelis Menten [1913]

## Enzyme Kinetics

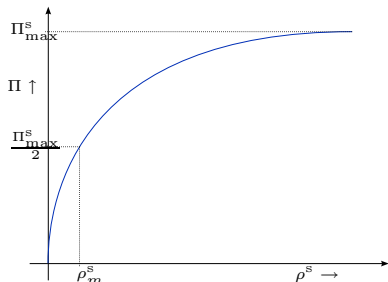


$k_1$  - Association of substrate and enzyme

$k_{-1}$  - Dissociation of unaltered substrate

$k_2$  - Formation of product

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



$$\frac{\partial \rho^\ell}{\partial t} = \Pi^\ell - \nabla \cdot \mathbf{M}^\ell$$

# Constitutive relations for fluxes

- Compatible with dissipation inequality
- Fluid flux relative to collagen

$$\mathbf{M}^f = \mathbf{D}^f (\rho^f \mathbf{F}^T \mathbf{g} + \mathbf{F}^T \nabla \cdot \mathbf{P}^f - \nabla(e^f - \theta \eta^f))$$

- Solute flux (proteins, sugars, nutrients, ...) relative to fluid

$$\tilde{\mathbf{V}}^s = \mathbf{V}^s - \mathbf{V}^f$$

$$\tilde{\mathbf{M}}^s = \mathbf{D}^s (-\nabla(e^s - \theta \eta^s))$$

- $\mathbf{D}^f$  and  $\mathbf{D}^s$  – Positive semi-definite mobility tensors  
Magnitudes from literature, e.g. Mauck et al. [2003]

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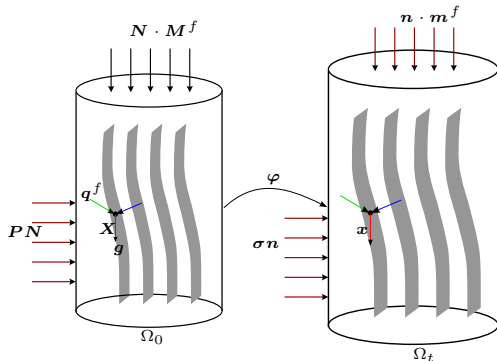
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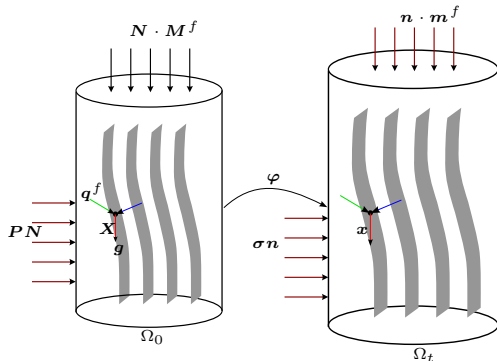
$\rho^f$  – Fluid concentration  
 $\mathbf{V}$  – Solid velocity  
 $\mathbf{V}^f$  – Fluid relative velocity  
 $\mathbf{g}$  – Body force  
 $\mathbf{q}^f$  – Interaction force  
 $\mathbf{P}^f$  – Partial stress

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

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



# Momentum balance

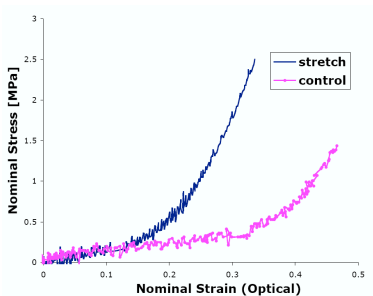


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$$\rho^f \frac{\partial}{\partial t} (V + V^f) = \rho^f (g + q^f) + \nabla \cdot P^f - (\nabla(V + V^f)) M^f$$

# Constitutive relations for partial stress

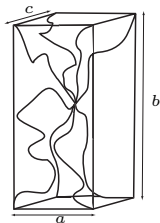


Stress-strain response curves of self organized tendon [Arruda et al]

- Hyper-elastic material compatible with dissipation inequality

## Worm-like chain model based internal energy density

$$\tilde{\rho}^c \hat{e}^c(\mathbf{F}^{e^c}, \rho^c)$$



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

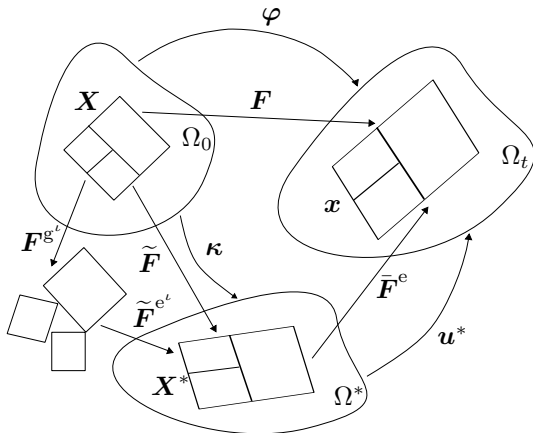
- Embed in multi chain model [Bischoff et al.]

$$r = \frac{1}{2} \sqrt{a^2 \lambda_1^{e^2} + b^2 \lambda_2^{e^2} + c^2 \lambda_3^{e^2}}$$

- $\lambda_I^e$  – elastic stretches along a, b, c

$$\lambda_I^e = \sqrt{\mathbf{N}_I \cdot \mathbf{C}^e \mathbf{N}_I}$$

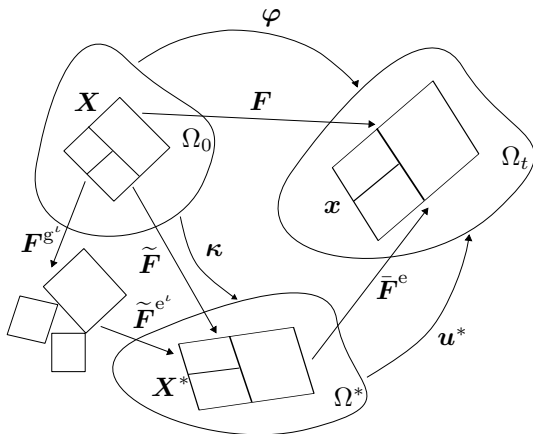
# Growth kinematics



- $F = \bar{F}^e \tilde{F}^{e^t} F^{g^t}$ ;  $F^{e^t} = \bar{F}^e \tilde{F}^{e^t}$ ; Internal stress due to  $\tilde{F}^{e^t}$

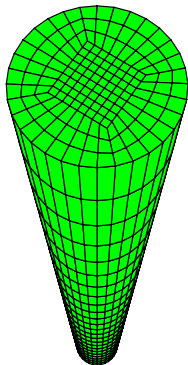
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# Growth kinematics



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## Example of coupled computation



- Simulating a tendon immersed in a nutrient rich bath

- Biphasic model

• *in vitro* experiments show that collagen fibrils are highly hydrated and that the fluid is bound to the fibrils

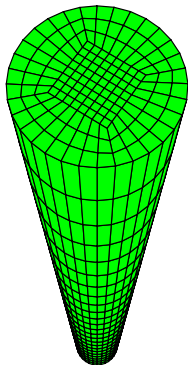
$$\sigma = \beta(\rho^f - \rho^f_{ini}) - \Pi^f$$

- Fluid mobility  $D^f_{ij} = 1 \times 10^{-8} \delta_{ij}$ , Han et al. [2000]

- First order rate law:

$$\Pi^f = -k^f(\rho^f - \rho^f_{ini}), \quad \Pi^c = -\Pi^f$$

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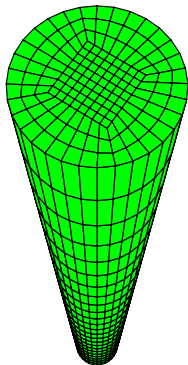


- Simulating a tendon immersed in a nutrient rich bath
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  - ideal nearly incompressible fluid
$$\rho^f \hat{e}^f = \frac{1}{2} \kappa (\det(\mathbf{F}^{e^f}) - 1)^2$$
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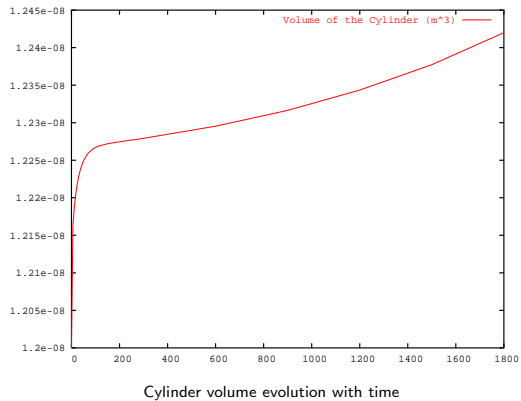


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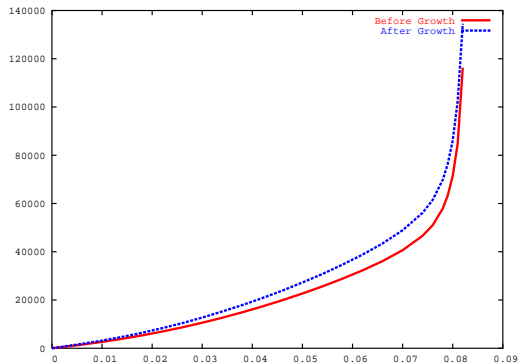
# Results and inferences

Collagen concentration evolution



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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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