A Continuum Framework for Growth in Biological Tissue

Harish Narayanan[1], Krishna Garikipati[1], Ellen M. Arruda[1,2], Karl Grosh[1,3] and Sarah Calve[2]

[1]Department of Mechanical Engineering, [2]Macromolecular Science and Engineering Center and [3]Biomedical Engineering, University of Michigan

Introduction

- Developing a mathematical framework to describe and simulate the complex processes of growth in a biological tissue
- Provide a predictive capability for our experiments on engineered tissue with eventual application to surgery, wound healing, ...

Development of tissue

- Growth/Resorption: Addition/Loss of mass
  e.g. Densification of bones
- Remodelling: Change in microstructure
  e.g. Alignment of trabeculae to the axis of external loading
- Morphogenesis: Change in macroscopic form
  e.g. Development of an embryo from a fertilized egg

[Taber - 1995]

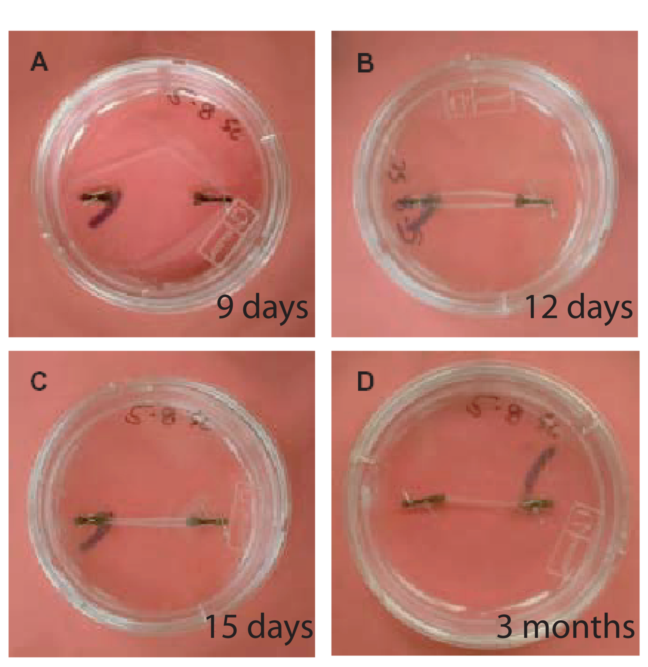
Goals

- Describe and simulate the processes of growth and development
- Models that are physiologically appropriate and thermodynamically valid
- Experiments on in vitro tissue in parallel
  - Descriptive model driven and validated by experiment
  - Model drives the controlled experiments

Issues that arise

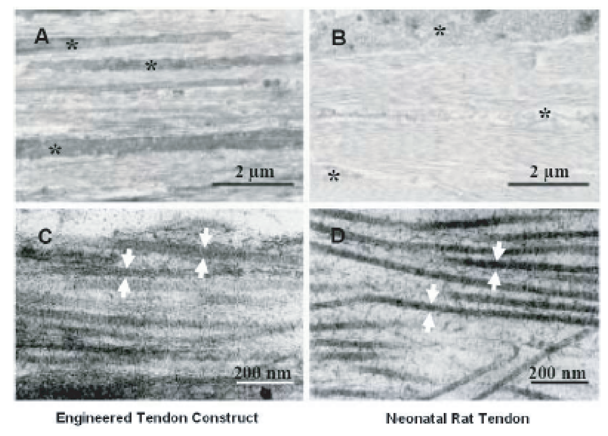
- Open system (with respect to mass)
- Interacting and interconverting species
- Species diffusing with respect to a solid phase (fluid, precursors, byproducts)
- Mixture physics

Biological model

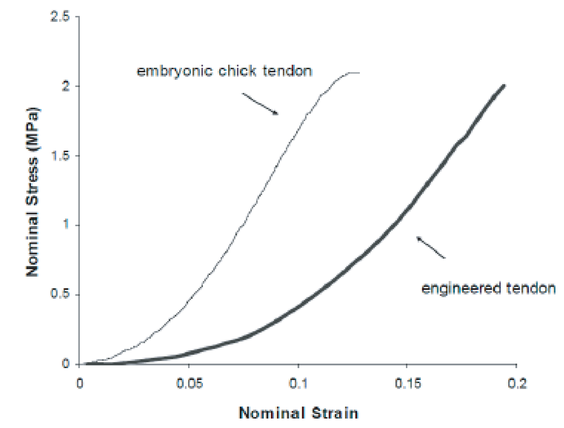


Engineered tendon construct in vitro that is morphologically and functionally similar to neonatal tissue [Calve et al. - 2003]

Comparison with neonatal tissue



Morphological comparison of the engineered constructs to 2 day old neonatal rat tendon



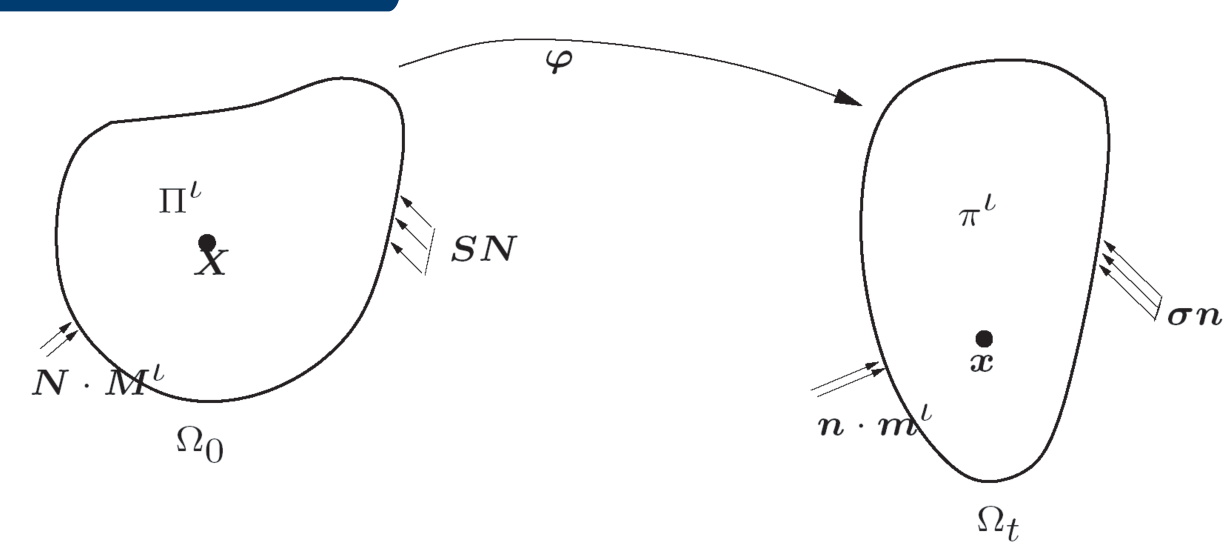
Comparison of the stress-strain response of the engineered construct to embryonic chicken tendon

[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 evironment and nutrient supply

Mechanics



In the reference configuration Ω_0,

Π^ι is the source/sink term for species ι
$\boldsymbol{M}^\iota$ is the mass flux term for species ι
$\boldsymbol{S}^\iota$ is the partial first Piola-Kirchhoff stress on species ι
$\boldsymbol{N}$ is the outward normal at the surface
$\boldsymbol{g}$ is the body force acting on the entire system

In the current configuration Ω_t,

π^ι is the source/sink term for species ι
$\boldsymbol{m}^\iota$ is the mass flux term for species ι
$\boldsymbol{\sigma}^\iota$ is the partial Cauchy stress on species ι
$\boldsymbol{n}$ is the outward normal at the surface
$\boldsymbol{g}$ is the body force acting on the entire system

Balance of mass and momentum

For a species ι, in local form, in Ω_0

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

$$\rho_0^\iota \frac{\partial}{\partial t}\left(\boldsymbol{V}+\boldsymbol{V}^\iota\right) = \rho_0^\iota\left(\boldsymbol{g}+\boldsymbol{q}^\iota\right) + \boldsymbol{\nabla}_X\cdot\boldsymbol{S}^\iota - \left(\boldsymbol{\nabla}_X\left(\boldsymbol{V}+\boldsymbol{V}^\iota\right)\right)\boldsymbol{M}^\iota$$

$\boldsymbol{V}$ is the velocity of the solid phase
$\boldsymbol{V}^\iota$ is the material velocity relative to the solid phase defined as $\boldsymbol{V}^\iota = (1/\rho_0^\iota)\boldsymbol{F}\boldsymbol{M}^\iota$
$\boldsymbol{q}^\iota$ is the net force exerted on species ι by all other species in the system

Energy balance, constitutive laws

For a species ι, in local form, in Ω_0

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

Constitutive relations:

$$\boldsymbol{S}^\iota = \rho_0^\iota \frac{\partial e^\iota}{\partial \boldsymbol{F}}, \ \forall \iota$$

$$\theta = \frac{\partial e^\iota}{\partial \eta^\iota}, \ \forall \iota$$

$$\boldsymbol{Q}^\iota = -\boldsymbol{K}^\iota \boldsymbol{\nabla}_X \theta, \ \forall \iota$$

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

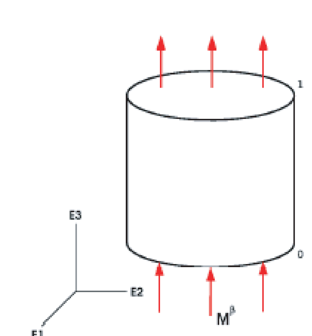
$$\boldsymbol{V}^\iota = -\tilde{\boldsymbol{D}}^\iota\left(\rho_0^\iota \frac{\partial \boldsymbol{V}}{\partial t} - \rho_0^\iota \boldsymbol{g} - \boldsymbol{\nabla}_X\cdot\boldsymbol{S}^\iota\right)$$

$$-\tilde{\boldsymbol{D}}^\iota\left(\rho_0^\iota \boldsymbol{F}^{-\mathrm{T}}\left(\boldsymbol{\nabla}_X e^\iota - \theta \boldsymbol{\nabla}_X \eta^\iota\right)\right), \ \forall \iota$$

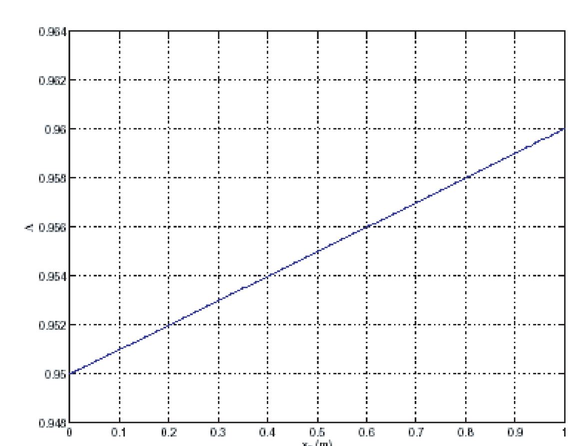
$$\boldsymbol{u}\cdot\tilde{\boldsymbol{D}}^\iota\boldsymbol{u} \geq 0 \, \forall \boldsymbol{u} \in \mathbb{R}^3$$

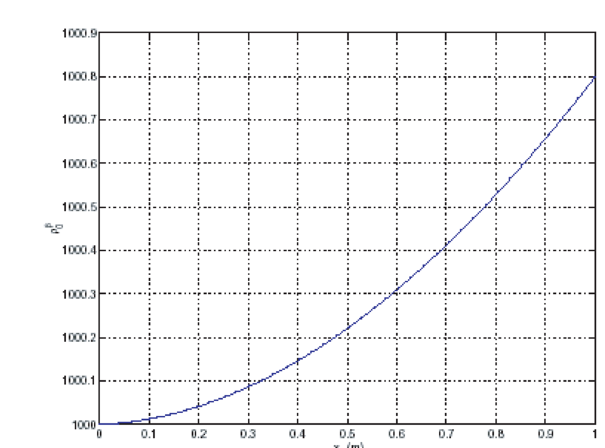
e^ι is the internal energy of each species ι
$\boldsymbol{F}$ is the deformation gradient
$\boldsymbol{Q}^\iota$ is the heat flux term for species ι
r_0^ι is the heat supplied to species ι per unit reference volume
$\tilde{e}$ is the internal energy transferred to species ι from all other species

Example



- An idealized model of the cylindrical tendon construct
  - Simplified 1D case involving two species, α, a solid and β, a fluid
  - Solid is neo-hookean, fluid is compressible and ideal
  - ρ_0^β and the stretch Λ vary, and calculated values are used to determine the flux M^β





- Coupling of diffusion to stress
- The flux M^β ($4.5X10^{-4}kg/m^2/s$) driven against
  - Gravity
  - Concentration gradient
- Mechanics influences mass balance

Achievements and future work

- Physiologically consistent continuum formulation describing growth in an open system
- Relevant driving forces arise from thermodynamics
- Consistent with mixture theory
- Applying present theory to 3D tissues involving multiple species diffusing and reacting
- Formulated the remodelling problem – Preliminary results