ETH zürich

Simulating Organogenesis in COMSOL: Tissue Mechanics

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Introduction

- During growth, biological tissues expand and deform.
- Given the elastic properties of tissue, stresses emerge from these deformations.
- Cell rearrangements can dissipate these stresses and numerous experiments confirm the viscoelastic properties of tissues.
- On short time scales, however, tissues have mainly elastic properties.
- To represent these properties, essentially two different approaches exist: continuum mechanical descriptions and discrete cell-based approaches.
- We focus on the continuum mechanical approach.

The mechanical model

- We start from the Cauchy momentum equation

$$\operatorname{div} \boldsymbol{\sigma} = \rho \frac{\partial^2}{\partial t^2} \boldsymbol{u},$$

where $\boldsymbol{\sigma}$ is the stress tensor, ρ the mass density and $\boldsymbol{u}$ the displacement.

- We impose a hyperelastic material law

$$\boldsymbol{\sigma} = J^{-1} \frac{\partial W(\boldsymbol{F})}{\partial \boldsymbol{F}} \boldsymbol{F}^{\mathsf{T}}$$

with $\boldsymbol{F}$ denoting the deformation gradient and $J := \det \boldsymbol{F}$.

The mechanical model II

- We consider a strain energy density function of *Fung type*, i.e.

$$W(\boldsymbol{F}) = \frac{C}{\alpha}\left(e^{\alpha(I_1-3)} - 1\right), \quad I_1 := \text{trace}(\boldsymbol{F}\boldsymbol{F}^{\mathsf{T}})$$

for some constants $C, \alpha > 0$.

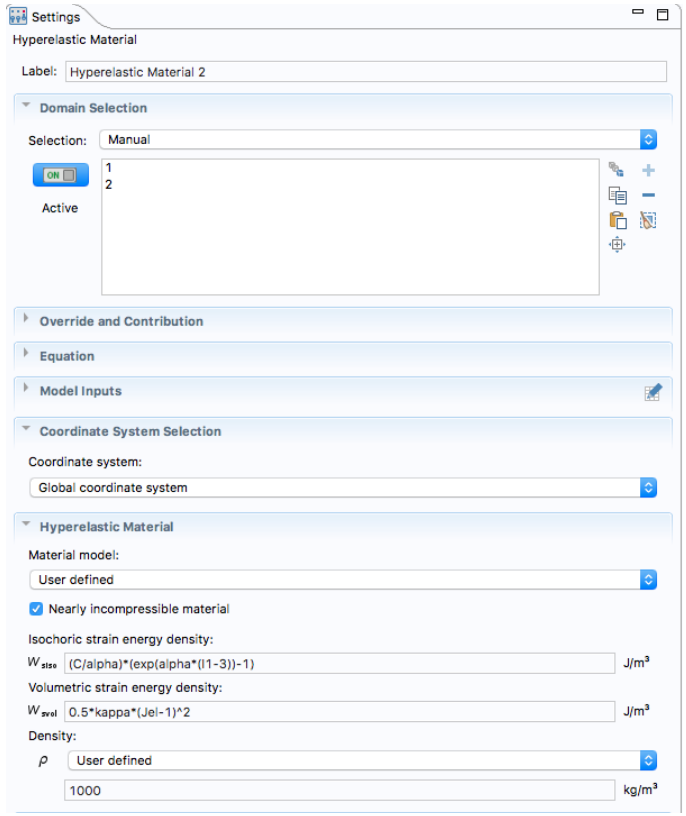
- The constant C is proportional to the Young modules.

- The parameter α controls the stiffening of the material for increasing stress.

- In the limit $\alpha \to 0$, there holds $W \to C(I_1 - 3)$ and we end up with a *neo-Hookean* material.

Numerical Realisation in COMSOL

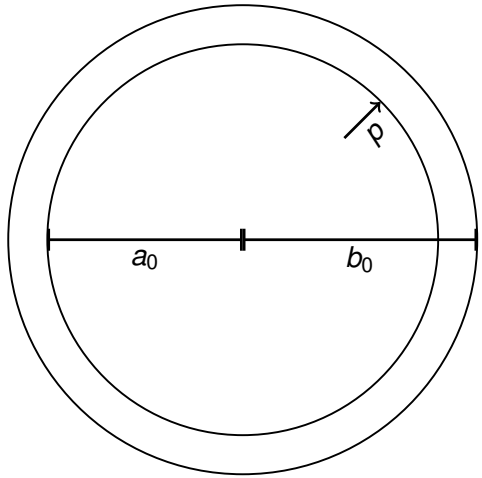
- We employ the “Solid Mechanics” interface with a “Hyperelastic Material” node.
- We define a “User defined” material model
- and enable the “Nearly incompressible material” checkbox.
- Moreover, we set



$$W_{\text{siso}} = \frac{C}{\alpha}\left(e^{\alpha(\overline{I}_1-3)}-1\right), \quad W_{\text{svol}} = 0.5\kappa(J-1)^2.$$

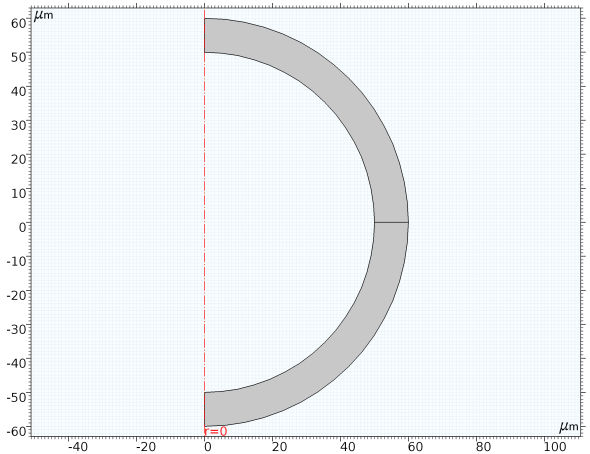
- $\overline{I}_1 = J^{-2/3} I_1$ is the first invariant of the isochoric right Cauchy-Green tensor and $J = \det \boldsymbol{F}$ the elastic volume ratio.
- We have $\overline{I}_1 \to I_1$ and $W_{\text{svol}} \to 0$ in the incompressible limit $J \to 1$.

Validation of the implementation

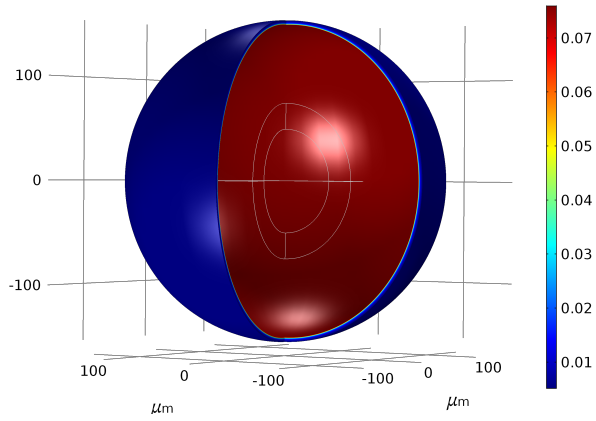


- The blastula stage of sea urchin development begins at the 128-cell stage.
- Here the cells form a hollow sphere surrounding a central cavity or *blastocoel*.
- Tight junctions unite the blastomeres into a seamless epithelial sheet that completely encircles the blastocoel.
- The fluid inside the blastula exerts an outward pressure on the cells.
- The cells mitigate the added stress by moving and deforming in order to restore the initial stresses.

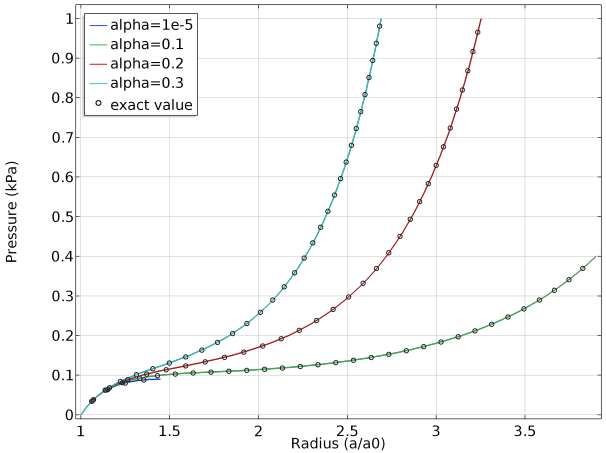
Numerical Results



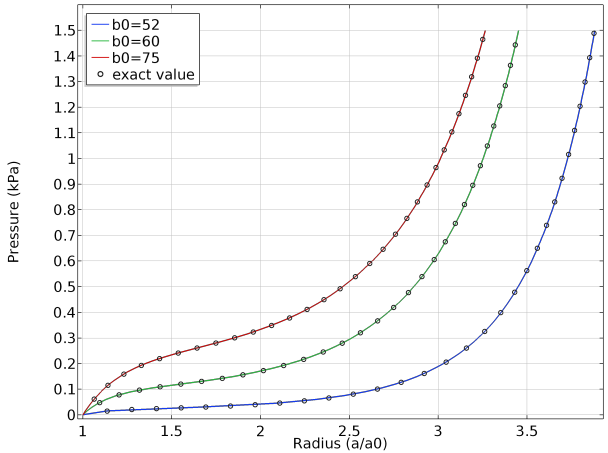
Computational geometry.



von Mises stress in $\mu\text{N}/\mu\text{m}^2$.



Radius vs. pressure for varying α.



Radius vs. pressure for varying thickness.

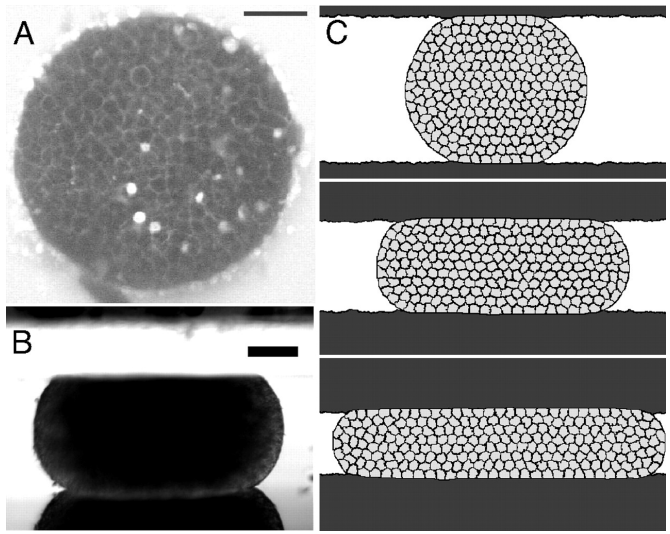
A more complex example

- Cell aggregates are used for *in vitro* studies of morphogenesis, cancer invasion and tissue engineering.

- It is possible to infer mechanical properties of a tissue directly from compression experiments.

- To incorporate viscolasticity, we add a viscoelastic branch to the strain energy density

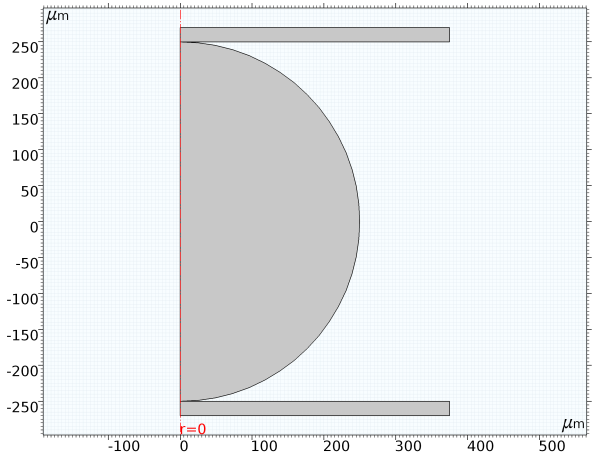
$$W_{\text{ve}} = W + \Psi_1(t).$$



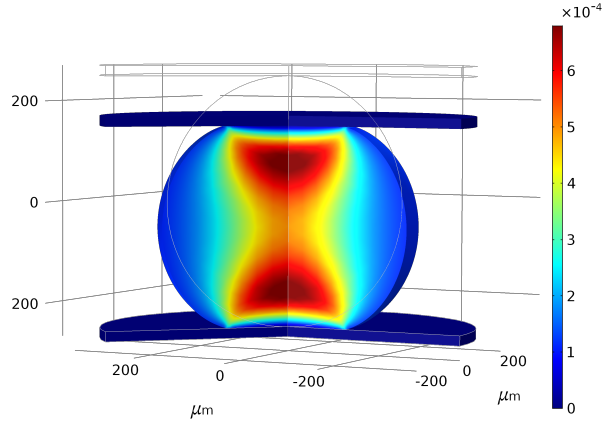
Shape of aggregates. (A) top view. (B) Side view. (C) Numerical simulation.
From "The role of fluctuations and stress on the effective viscosity of cell aggregates,"
by P. Marmottant et al., PNAS, vol. 106, no. 41, pp. 17271–17275, 2001.

- In addition, we have to take the contact between the aggregate and the plates into account.

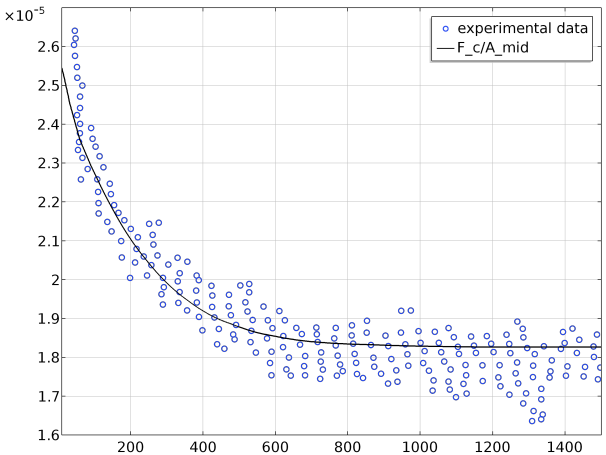
Numerical Results



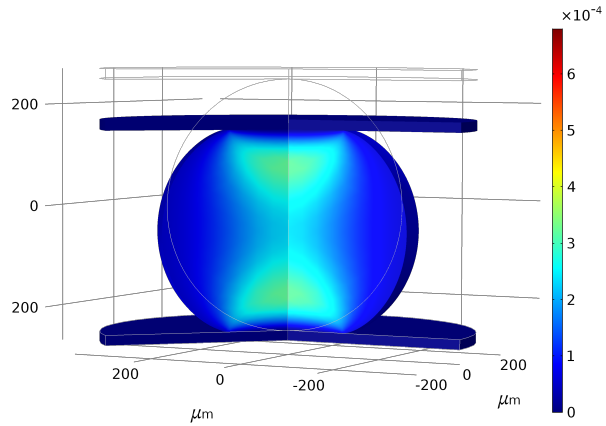
Computational geometry.



von Mises stress at $t = 0.2$s.



Manually fitted C, α, β_1, τ_1.



von Mises stress at $t = 1497$s.

Conclusion and outlook

- We have used COMSOL to model the mechanical properties of biological tissues *in silico*.
- We can thus infer model parameters directly from *in vitro* studies.
- In a next step, we want to increase the robustness of the simulation and use more complex geometries.
- This would facilitate the quantification of measurement errors, e.g. in a Bayesian framework.

Goal: Use COMSOL to predict the outcome of *in vitro* studies and consequently optimise experimental design.