Reshaping tumour growth

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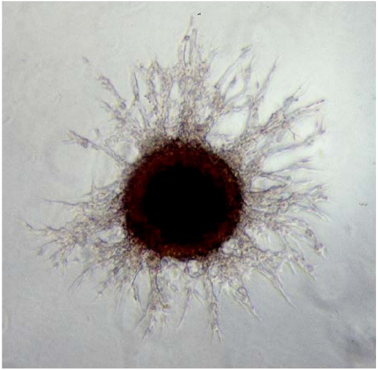
A brief introduction

Tumour growth – Select cells overcome their regulatory signals; proliferate and grow beyond usual ranges

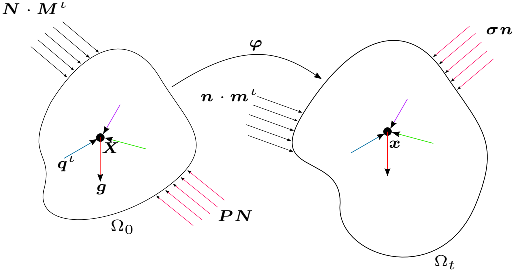


Multicellular tumor spheroid (Habib et al., 2003)

- Species transport feeds reactions in cells
- Mechanical state influences amount and directionality of tumour growth

Solid (cells, ECM), *fluid* (water) and *solute* (nutrients, enzymes, byproducts, ...) species

The theoretical model



Reference quantities:

ρ_0^{ι} – Species concentration
Π^{ι} – Species production rate
$\boldsymbol{M}^{\iota}$ – Species relative flux
$\boldsymbol{V}^{\iota}$ – Species velocity
$\boldsymbol{g}$ – Body force
$\boldsymbol{q}^{\iota}$ – Interaction force
$\boldsymbol{P}^{\iota}$ – Partial First Piola Kirchhoff stress

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

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

- Kinematics:
$$\boldsymbol{F} = \boldsymbol{F}^{\mathrm{e}^{\iota}} \boldsymbol{F}^{\mathrm{g}^{\iota}}; \text{ e.g. } \boldsymbol{F}^{\mathrm{g}^{\iota}} = \left(\frac{\rho^{\iota}}{\rho^{\iota}_{0_{\mathrm{ini}}}} \right)^{\frac{1}{3}} \mathbf{1}$$

A glimpse of the thermodynamics

Upon combining the balance of energy and the entropy inequality at uniform, constant temperature:

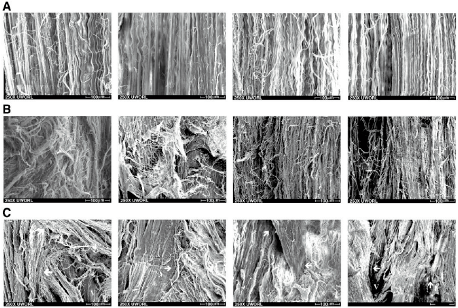
$$\sum_{\iota} \left(\rho^{\iota} \dot{\psi}^{\iota} - \boldsymbol{\sigma}^{\iota} : \mathrm{grad}\,(\boldsymbol{v}^{\iota}) + \rho^{\iota} \mathrm{grad}\,(\psi^{\iota}) \cdot \boldsymbol{v}^{\iota} \right) + \sum_{\iota} \left(\rho^{\iota} \boldsymbol{q}^{\iota} \cdot \boldsymbol{v}^{\iota} + \pi^{\iota} \left(\psi^{\iota} + \frac{1}{2} \| \boldsymbol{v}^{\iota} \|^2 \right) \right) \leq 0$$

- A hyper/viscoelastic ECM; A Newtonian fluid
- *Effect of the stress state on growth*
- Frictional interaction forces
- Energy-dependent mass source terms

Effect of the stress state on growth

$$-\boldsymbol{F}^{\mathrm{e}^{\mathrm{T}}}\boldsymbol{P}^{\mathrm{c}} : \dot{\boldsymbol{F}}^{\mathrm{g}} \leq 0 \Rightarrow \quad \dot{\boldsymbol{F}}^{\mathrm{g}} = \lambda\ \boldsymbol{F}^{\mathrm{e}^{\mathrm{T}}}\boldsymbol{P}^{\mathrm{c}}, \quad \lambda \geq 0$$

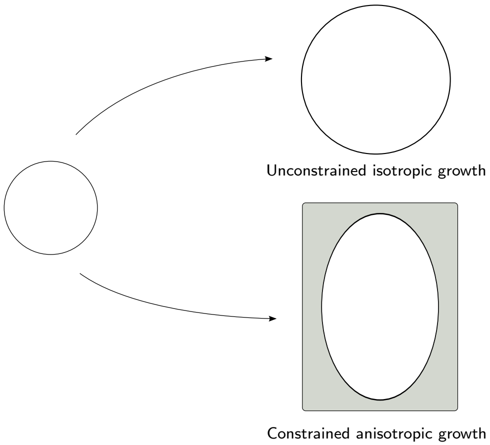
i.e., Incremental changes in the growth deformation gradient align with the partial first Piola-Kirchhoff stress



Hindlimb unloading alters ligament healing (Provenzano et al., 2003)

Demonstrating some of the physics of growing tumours

Compressive solid stress restricts the in vitro growth of tumours (Helmlinger et al., 1997)



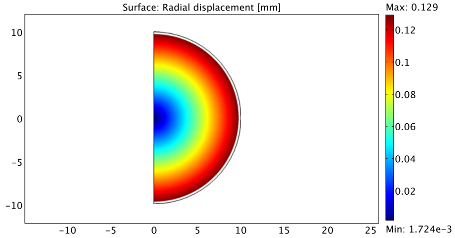
Kinematic swelling along with growth

Constraining hard tissue and contact mechanics

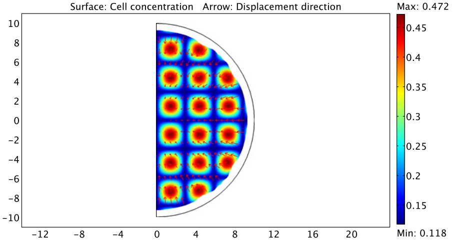
The mechanics of the cells

Total solid stress:

$$\boldsymbol{\sigma}^{\mathrm{c}} = \underbrace{\frac{1}{J}\,\frac{\rho_0^{\mathrm{c}}}{\tilde{\rho}_0^{\mathrm{c}}}\,\frac{\partial \hat{\psi}^{\mathrm{c}}}{\partial \boldsymbol{F}}\boldsymbol{F}^{\mathrm{T}}}_{\text{Passive}} + \underbrace{\tau\ \rho^{\mathrm{c}}\rho^{\mathrm{cell}}(N-\rho^{\mathrm{cell}})\ \mathbf{1}}_{\text{Active}}$$



Homogeneous inward pull



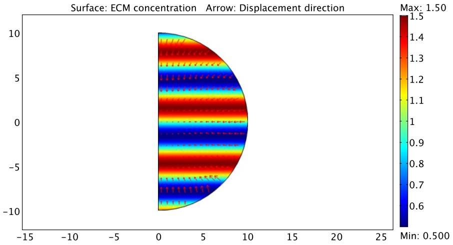
Heterogeneous inward pull

Modelling choices based on Namy et al., 2004

Transport of the cells

Mass flux of the cells:

$$\rho^{\text{cell}}\ \boldsymbol{v}^{\text{cell}} = \underbrace{h\ \rho^{\text{cell}}\ \text{grad}\left(\rho^{\text{c}}\right)}_{\text{Haptotactic flux}} - \underbrace{D^{\text{cell}}\ \text{grad}\left(\rho^{\text{cell}}\right)}_{\text{Cell diffusion}}$$



Non-uniform matrix concentration

Diffusion and proliferation of the cells

Proliferating cells undergoing haptotaxis

Coupling the phenomena

The growing tumour constrained by hard tissue

Concluding remarks

Thermodynamically-consistent mathematical and computational framework incorporating a range of physics:

- Proliferating cells undergoing both diffusion and haptotaxis
- Varied classes of biochemistry dictating species production and consumption
- Large deformation, nonlinear mechanics and contact mechanics
- Kinematics concomitant with growth

Experimental results suggest that the processes underlying growth are dependent upon the local stress field

- Theoretical results require careful correlation with literature—Constitutive specification and parameters