The modelling of tissue growth in confined geometries, effect of surface tension

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Abstract
This contribution presents a model for tissue growth inside confined geometries and gives a brief exploration of the effect of surface stress on the resultant kinetics. In the model we follow the approach of Ambrosi et al, and apply Onsager's principle to derive a thermodynamically consistent model for growth. The model can be solved semi-analytically for simple geometries and compares well with experimental results on cell culture experiments with MC3T3-E1 pre-osteoblast cells carried out in pores produced using rapid prototyping.

Keywords: growth phenomena, biomechanics, interface problems, adaptivity, cell cultures

1. Introduction

A physically based approach for modelling tissue formation within confined geometries is required to understand a variety of biological processes such as bone remodelling, tissue healing and regeneration. This need has partially arisen because of the recent discovery(s) that physical signals such as the substrate stiffness[1], and topography[2], can strongly influence cell and tissue behaviour. In particular it was shown that tissue growth by osteoblasts inside a single pore is controlled by the shape of the pore itself. The experimentally observed "curvature controlled growth"[3] highlights the importance of effective surface tension in growth. In this contribution, we follow the approach of Ambrosi et al[4,5], and apply Onsager's principal of maximum dissipation to derive a thermodynamically consistent law for tissue growth. We then use the derived law to calculate the global rate of growth and resultant stress state of tissue growing within simple geometries[6]. These results are then compared with measurements made in experiments of MC3T3-E1 pre-osteoblasts cultured in pores of controlled geometries produced by rapid-prototyping. Although the predicted growth kinetics is consistent with experiments, the model is only able to predict the observed asymmetry of growth with the sign of substrate curvature (Fig. 1) when tissue surface tension is explicitly included.

2. Model

In Ref [3] we modelled tissue growth based on purely geometric arguments, in this paper however we derive our model through thermodynamics arguments based on the approach of Ambrosi et al [4,5]. In the following, the basic concepts behind our model are outlined for more detailed derivations see Ref [6].
The deformation gradient tensor $\mathbf{F}$ is multiplicatively decomposed into two components due to elastic deformation, $\mathbf{F}_e$ and the deformation due to growth, $\mathbf{G}$. We introduce a mass balance for nutrient with a mass fraction c, leaving a given tissue volume with a flux $\mathbf{m}$, inside growing tissue with density ρ_0 (in the reference configuration):

$$\frac{d}{dt}(c\rho_0) = \rho_0 \mathbf{E}_0 : \dot{\mathbf{G}}\mathbf{G}^{-1} - Div\mathbf{m}. \tag{1}$$

The first term on the right-hand side is a source term which accounts for the nutrient provided to tissue during growth. The work rate $\dot{W}$ done by growth is expressed as:

$$\dot{W} = \mathbf{P} : \dot{\mathbf{F}} + \mu_n \rho_0 \mathbf{E}_0 : \dot{\mathbf{G}}\mathbf{G}^{-1} - Div(\mu_n \mathbf{m}), \tag{2}$$

where $\mathbf{P}$ is 1st Piola-Kirchhoff stress tensor, μ_n is the chemical potential of the nutrient. The first term represents the mechanical energy contribution, the second term represents the rate of energy provided by the nutrient to the tissue, and the final term is the outward flux of chemical energy of the nutrient. The internal energy change $\dot{E}$ is a combination of the free energy rate $d(\rho_0\psi)/dt$ and the change in energy due to conversion of nutrient to tissue:

$$\dot{E} = \frac{d}{dt}(\rho_0\psi) + \Delta\mu\rho_0 \mathbf{E}_0 : \dot{\mathbf{G}}\mathbf{G}^{-1}. \tag{3}$$

Equations (1-3) are then combined in the dissipation inequality leading to an expression for a growth law:

$$\mathbf{G}^{-1}\dot{\mathbf{G}} = -f(c)\left[Det\mathbf{F}\phi_{\text{mech}}\mathbf{I} + \Delta\mu\rho_0\mathbf{E}_0 - \mathbf{F}^T\mathbf{P}\right]. \tag{4}$$

Where φ_{mech} is the elastic energy density which is neglected in the following (see [6] for details), and $f(c)$ describes the cell activity. Equation (4) can be reformulated in a small strain setting, giving rise to an equation for the growth eigenstrain rate:

$$\dot{\mathbf{g}} = f(c)(\sigma - \mu e_0 \mathbf{I}). \tag{6}$$

This equation contains three main terms, the activity of cells $f(c)$, an explicit dependence on stress σ and a chemical potential change giving the driving force for growth.

3. Results and Discussion

In [6] the model was solved semi-analytically and gave a good qualitative agreement with experimental results. However the model predicts growth on both convex and concave surfaces which is in contradiction to experimental observations (Fig. 1).

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This highlights the importance of the (effective) surface tension on tissue growth.

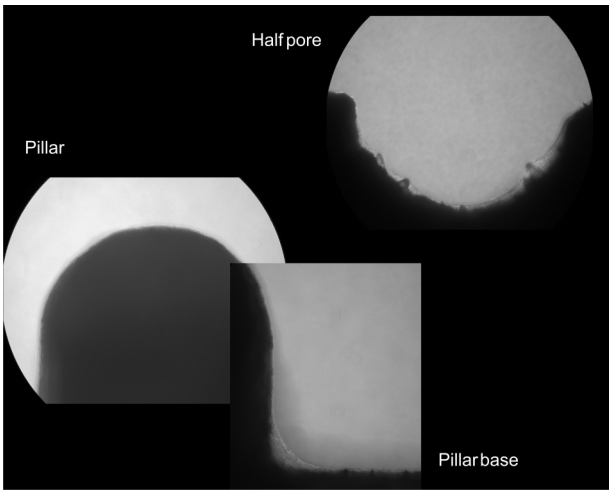

Figure 1: Tissue growth experiments carried out on convex and concave surfaces using MC3T3-E1 pre-osteoblast cells.

The effect of surface tension is tested with the model in Figs 2 and 3 by adding an additional surface stress which is proportional to the local curvature through $\sigma_{ss} = \pm\gamma/r$ (positive if concave, negative if convex). The introduction of a surface stress gives rise to an asymmetry in the growth behaviour on convex or concave substrates respectively. The resultant growth kinetics still compare well with experiments on concave pores (see [3]).

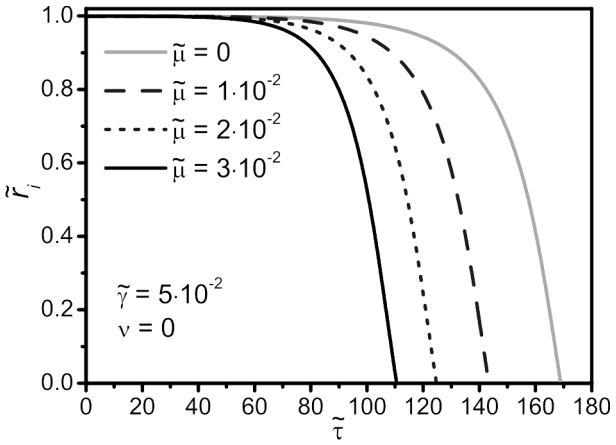

Figure 2: The calculated pore radius for inward growing tissue as a function of time, for a fixed surface energy for different values of chemical driving force.

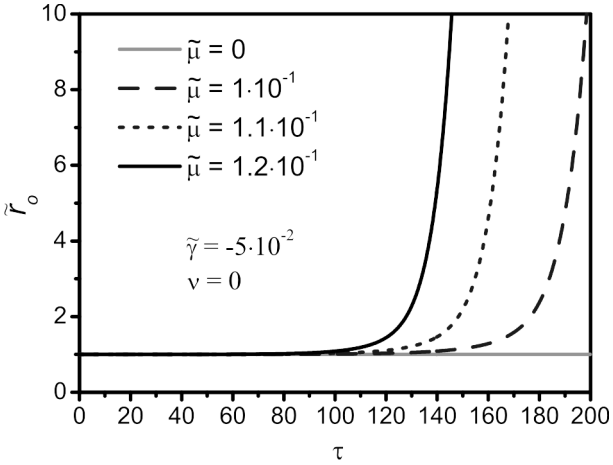

Figure 3: The calculated pore radius for outward growing tissue as a function of time, for a fixed surface energy for different values of chemical driving force.

4. Conclusions

In this brief contribution we have outlined a model that we developed to describe tissue growth in confined geometries and have given preliminary results of the effect of surface tension on the growth behaviour. The asymmetric growth seen in experiment with respect to the sign of curvature can be introduced into our model by simply adding an additional surface stress. Further work will be focussed on understanding the influence of the active contractile behaviour of cells and their role in turn on changing the stress state and the resultant growth kinetics.

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