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Viscoelastoplastic model of cell nucleus under compression

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KEYWORDS Cell nucleus; plasticity; continuum model; migration

1. Introduction

The ability of cells to migrate is a fundamental prerequisite to many biological phenomena, such as immune response, embryogenesis or metastasis. The most common locomotion mode is pseudopodia-governed migration. Pseudopodia are extensions of the cell membrane whose protrusion and contraction are driven by actin polymerization and actomyosin motors depolymerization, respectively (Schaub et al. 2007). Such processes are in tight synchronization with adhesion forces on the substrate, which are generated through the focal adhesions.

While migrating in a three-dimensional environment, cells undergo significant stresses and strains to be able to move through the tight mesh formed by the extracellular matrix (ECM). They have various strategies to enable this migration. They can set off a proteolytic degradation of the ECM to widen the gap and reduce the amount of deformation needed or they can deform elastically and/or plastically to fit in the space available. If the required deformation is too high and cannot be hold up by the cell, the pseudopodia retract and the cell repolarize to find an alternative path (Friedl et al. 2011). In the context of confined migration, one needs to pay particular attention to the nucleus, which is a rate-limiting organelle for cell migration due to its size and mechanical properties. It is indeed many folds stiffer than the cytoplasm and is thus harder to deform, limiting the deformation of the entire cell. Additionally, it has been observed that it tends to have a plastic behaviour since it is able to break its lamina to move through highly constricted channels and reform it afterwards (Lammerding 2011).

Given the critical role of the nucleus during cell migration, this paper will present a finite element model of the cell nucleus, including the viscoelastic

nucleoplasm and the viscoelastoplastic surrounding under compression.

2. Methods

2.1. Mechanical model

The nucleus is considered to have an initial circular shape with a diameter of 7.5 μm and is constituted of two domains: the nucleoplasm, which is modelled as a viscoelastic material, and the lamina, which is modelled as viscoelastoplastic (see Figure 1). Both the lamina and the nucleoplasm are described through specific characteristic functions as described in Aubry et al. (2014). The main mechanical and geometrical parameters of the model are reported in Table 1.

2.2. Numerical compression test

Experimentally, compression tests have been performed on isolated nuclei (Caille et al. 2002), allowing to assess the force required as function of the compression degree of the nucleus. Therefore, we decided to numerically reproduce this test in order to validate our model. The compression test consists of placing the nucleus between two horizontal plates (but not initially in contact) and assigning the upper plate a vertical downward velocity of 0.01 $\mu\text{m/s}$, whereas the bottom plate is fixed. The nucleus will thus be squeezed and we will be able to get the corresponding stress/strain curve.

3. Results and discussion

Figure 2 illustrates our preliminary results for the numerical compression test. We obtain consistent results compared to previous study proposed in the literature. Indeed, the force necessary to squeeze the nucleus to 50% in our compression test is about 10^{-9} N, while the study

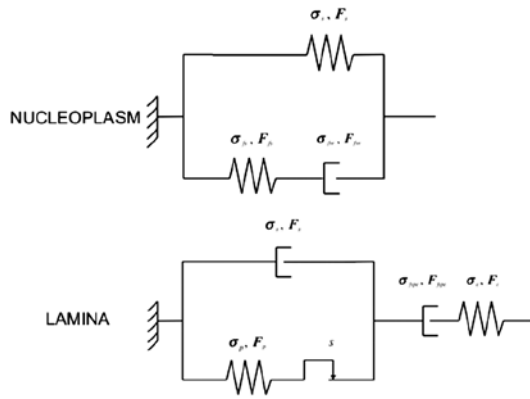


Figure 1. Symbolic scheme for the rheological models used to describe the viscoelastic nucleoplasm (top) and the viscoelastoplastic lamina (bottom).

Table 1. Main mechanical and geometrical parameters of our model (Aubry et al. 2014).

Parameter	Description	Value
E_{lamina}	Lamina Young modulus	3000 Pa
$E_{nucleoplasm}$	Nucleoplasm Young modulus	25 Pa
ν_{lamina}	Lamina Poisson ratio	0.3
$\nu_{nucleoplasm}$	Nucleoplasm Poisson ratio	0.4
μ_{lamina}	Lamina viscosity	3×10^5 Pa s
$\mu_{nucleoplasm}$	Nucleoplasm viscosity	3×10^5 Pa s
$r_{nucleus}$	Radius of the nucleus	7.5 μ m
$r_{nucleoplasm}$	Radius of the nucleoplasm	7 μ m
r_{lamina}	Outer radius of the lamina	7.5 μ m
$v_{compression}$	Compression speed of the upper plate	0.01 μ m/s

by Caille et al. (2002) gave forces of 10^{-8} – 10^{-7} N for the same compression, but with a very similar curve profile. The difference can be due to the fact that our initial set-up is not the same as theirs and the compression speed in our simulation is lower.

As a perspective of the present work, we plan to implement such constitutive behaviour in the model of confined cell migration presented in Aubry et al. (2014) and Allena (2014), where the nucleus is treated as a mere viscoelastic material. This will provide a more complete understanding of how and how much the stiff and large nucleus may inhibit (or not) cell migration in confined environments and why certain cells such as cancer cells with a nucleus with impaired or broken lamina may be able to migrate across subnuclear pores.

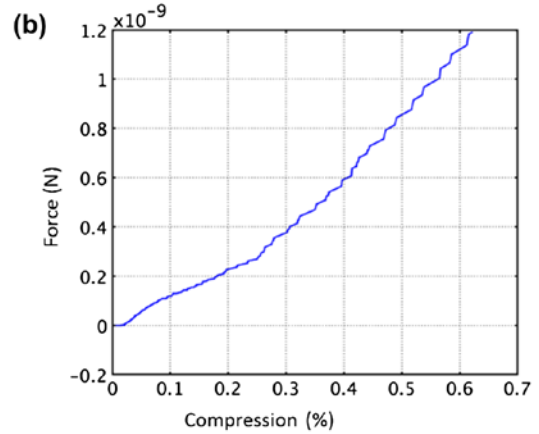
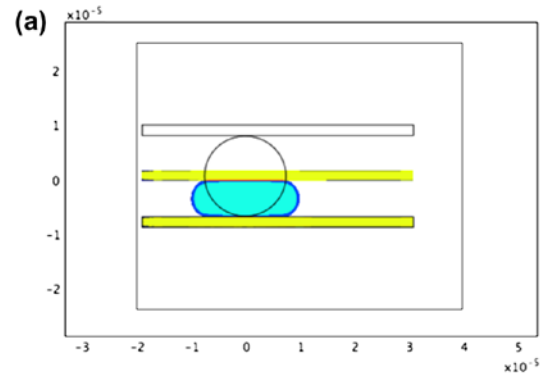


Figure 2. (a) Final shape of the isolated nucleus during the numerical compression test ($t = 60$ s). The compression plates are depicted in yellow, the nucleoplasm in light blue and the lamina in darker blue. (b) Force/compression curve during the test.

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