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A numerical model suggests the interplay between nuclear plasticity and stiffness during a perfusion assay

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ABSTRACT

Cell deformability is a necessary condition for a cell to be able to migrate, an ability that is vital both for healthy and diseased organisms. The nucleus being the largest and stiffest organelle, it often is a barrier to cell migration. It is thus essential to characterize its mechanical behaviour. First, we numerically investigate the visco-elasto-plastic properties of the isolated nucleus during a compression test. This simulation highlights the impact of the mechanical behaviour of the nuclear lamina and the nucleoplasm on the overall plasticity. Second, a whole cell model is developed to simulate a perfusion experiment to study the possible interactions between the cytoplasm and the nucleus. We analyze and discuss the role of the lamina for a wild-type cell model, and a lamin-deficient one, in which the Young's modulus of the lamina is set to 1% of its nominal value. This simulation suggests an interplay between the cytoplasm and the nucleoplasm, especially in the lamin-deficient cell, showing the need of a stiffer nucleoplasm to maintain nuclear plasticity.

1. Introduction

Cell motility is a fundamental cellular mechanism involved in several biological phenomena such as bone remodelling, immune response and tumor metastasis. Tumor metastasis is estimated to be responsible for 90% of cancer death (Chaffer and Weinberg, 2011). In such cases, where cell migration through subnuclear pores is often necessary, the nucleus plays a critical role due to its size and mechanical properties (Zwerger et al., 2011). Hence, a better understanding of the processes behind cell migration and of nuclear mechanics is primordial in order to develop new therapeutic strategies in the fight against cancer. Most publications investigate the molecular mechanisms of cancer metastasis (Wolf and Friedl, 2006), of mechanical properties of the nucleus (Friedl et al., 2011) and of the mechanical coupling between the nucleus and the cell's cytoskeleton (Schwartz et al., 2017; Skau et al., 2016): the aim here is to tackle these issues through a mechanical perspective. During migration or transmigration events, the cell is capable of going through narrow constrictions down to 10% of the size of the nucleus (Wolf et al., 2013). The large size and high stiffness of the nucleus make it a major obstacle to this process, although some cells are able to overcome such difficulties (Skau et al., 2016). Its mechanical properties mainly arise from two components: the lamina – a dense meshwork composed of A-type and B-type lamins, as well as lamin-associated proteins (Ho and Lammerding, 2012) – and the nucleoplasm. The nucleoplasm is mostly made up of chromatin surrounded by fluid and can thus be seen as a viscoelastic material. The lamina however, as a dense meshwork where fluid cannot circulate, can be seen as a solid elastic material (Rowat et al., 2006). With sheer observation of its internal organization, we can already qualitatively propose a visco-elastic model of the nucleus. Since nuclear mechanics is at stake here, numerical simulation appears as a very interesting tool to investigate the mechanical interplay between cellular components, such as the lamina and the cytoplasm, and to get new insights on some biological assumptions. As for quantitative values, many techniques are accessible to study specific features of the nucleus, as will be discussed in the following paragraphs.

1.1. From experimentation to mechanical modelling

A wide range of experimental techniques are available to investigate mechanical properties of various components of the cell and of the nucleus at various scales (Lim et al., 2006). They include perfusion (Isermann et al., 2012), micropipette aspiration - possibly coupled with relaxation experiments - (Guilak et al., 2000), Atomic Force Microscopy (AFM), active or passive micro-rheology through magnetic or optical tweezers with lo-

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cal information (Monticelli et al., 2016), microplate compression (Caille et al., 2002), substrate strain, micro-needle manipulation (Lombardi et al., 2011), shear flow and cytoindentation (Nava et al., 2014). The first experimental setups focused on getting the mechanical behaviour of the overall nucleus. Depending on the technique, different behaviours at various scales can be studied.

1.1.1. The overall nucleus

The nucleus has widely been found to behave as a visco-elastic material, all throughout different techniques that enlightened various specific aspects of its behaviour (de Vries et al., 2007; Erdel et al., 2015). The perfusion and aspiration assays give a good assessment of purely passive mechanical properties of both the cell and the nucleus since they are fast enough – cells pass through in less than a second (Hou et al., 2009; Isermann et al., 2012; Luo et al., 2014) – to assume no cyto- or nucleoskeleton reorganization occurs. Such assays showed that nucleus was 3–4 times stiffer and twice more viscous than the cytoplasm (Caille et al., 2002; Guilak et al., 2000). The viscoelasticity of the nucleus is mostly accepted, but a hyperelastic behaviour of the nucleus is sometimes assumed in order to fit experimental data with simulation ones and to obtain quantitative data on the mechanical parameters of the nucleus (Caille et al., 2002). Using these global measurement techniques, the Young modulus of the cell nucleus is estimated around 1–8 kPa (Caille et al., 2002; Dahl et al., 2005; Guilak et al., 2000; Liu et al., 2014), but is sometimes found to be much higher depending on the experimental method (Tomankova et al., 2012). This illustrates one of the limits of the global techniques that raise various uncertainties due to the interaction between the nucleus and the rest of the cell. Some recent advances in AFM techniques are used to get rid of this bias by probing the nucleus more locally (Liu et al., 2014).

1.1.2. The nuclear envelope (NE) and the lamina

Information on the whole nucleus is essential and easier to get, but the tight interaction between mechanical forces and gene regulation induces to look more closely and precisely at local properties of the nucleus at the scale of specific proteins such as chromatin and lamins. Studies of the nuclear envelope alone are scarce, but combined techniques of micropipette aspiration and confocal microscopy were used to characterize the nuclear envelope as purely elastic (Rowat et al., 2005). Underlying the nuclear envelope is the lamina, a stiff material ensuring the nuclear stability, sometimes described as viscoelastic, although more thorough and velocity-dependent testing would be necessary to rigorously prove the viscoelastic behaviour (Swift and Discher, 2014; Swift et al., 2013). Together, the lamina and the nuclear envelope form a very thin layer of 10–200 nm surrounding the nucleus (Gruenbaum et al., 2003). Given the very high stiffness of the lamina, the impact of the NE, as well as lamina's viscosity can be neglected. Such stiffness protects the cell and its genetic information, but can also be a rate-limiting factor during confined migration by preventing sufficient nucleus deformation. In fact, cells have to find a good compromise between viability and motility.

1.1.3. The nucleoplasm

The nucleoplasm behaves as a sponge-like material that initially does not present much resistance to deformation but this resistance increases as the chromatin gets compacted (Dahl et al., 2005). Besides, chromatin exhibits a plastic behaviour, i.e. irreversible deformation, at long time-scales and after shear stresses, which decreases with up-regulation of Lamin-A (Deguchi et al., 2005; Pajerowski et al., 2007). This suggests that the nucleoplasm sets the rheological character of the nucleus while the lamina dictates the extent of the deformation. Such plasticity is an advantage during confined migration, since the nucleus stays elongated after going through a narrowing space, making it easier for the cell to migrate once the first constriction is overcome. Most often, the lamina is considered as the main load-bearing element in the nucleus, but recent findings suggest that chromatin itself is the main structural component of the nucleus (Stephens et al., 2017).

1.1.4. Existing computational models of the nucleus and its mechanical behaviour

The interest for cell computational models has been rising in the last two decades, as it becomes more and more obvious that mechanics plays a major role during cell migration and even in gene transcription. One strategy for representing the cell and the nucleus is discrete modelling, just considering the cell membrane or the nuclear envelope (Ujihara et al., 2011), another is an energetic approach (Giverso et al., 2014), and finally, the cell or nucleus can be modeled through continuum mechanics (Aubry et al., 2014). Most continuum models describe the whole cell, with or without its nucleus as a separate compartment, but fewer model focus on the isolated nucleus, as reviewed in Vaziri et al. (2007) and Nava et al. (2014). Our approach here is to propose a model which can be employed for both the isolated nucleus and the whole cell. The nucleus, if proven to be visco-elastic, is sometimes modeled as a hyperelastic material in order to simplify the simulation and to investigate specific mechanical issues (Caille et al., 2002; Giverso et al., 2014; Vaziri et al., 2006). A visco-elastic model was later developed to simulate a micro-pipette aspiration assay (Vaziri and Mofrad, 2007), with the lamina and nuclear envelope taken into account. A more advanced model was proposed with the nucleus described as a poroelastic material with a plastic behaviour (Cao et al., 2016). Interestingly, this model faithfully reproduced the irreversible deformation found in Lamin A/C deficient cells after transmigration. Although we acknowledge the validity and the interest of all these models, we observe that each one of them is designed to fit a specific experiment and can wonder whether one single model could describe several different assays. This is specifically what we aim to tackle in this article: a unified model of the whole cell that can be confronted with various experimental techniques.

1.2. The proposed model

Given the major role of nuclear mechanics during confined cell migration, this paper will present a two dimensions (2D) FE implementation of a cell nucleus model, representing the nuclear lamina as elastic and the nucleoplasm as visco-elasto-plastic. Even though a 3D model would be more accurate, we chose a 2D representation to facilitate the computation, since it was shown that for a cell entering a micro-channel, the model is insensitive to depth (Leong et al., 2011). While the whole nucleus is generally described as merely viscoelastic, we decided to design a new model to be able to account for a more complex behaviour of the nucleus including plasticity. Besides, we aim at developing a model that is able to be tested in various experiment-like setups, but we focus here on modeling a purely passive cell to fully understand the mechanics at stake without migration or skeleton reorganization. In this regard, we first build a model of an isolated nucleus that will be tested under compression mimicking the experimental setup from Caille et al. (2002). This model being thoroughly investigated, it will be implemented in a whole cell model, modeling the cytoplasm as in previous work (Aubry et al., 2014). This complete model is then tested to reproduce a perfusion experiment (Isermann et al., 2012). The mechanical parameters of the cell and its nucleus were chosen to match those of the HeLa cell, as in our previous work (Aubry et al., 2014), but the versatility of our model