The discriminant role of mechanics during cell migration

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A B S T R A C T

Cell migration is a fundamental process involved in many mechanobiological phenomena such immune re-sponse, bone remodelling and tumorogenesis. During the last decades several numerical works have been pro-posed in the literature in order to unveil its main biological, chemical and mechanical principles. Here, I will show how a computational approach purely based on mechanics is able to reproduce cell migration in different configurations including migration under confinement, in presence of durotaxis and on flat substrates. A series of models will be presented each of which is based on three main ingredients: i) the active strains of the cell reproducing the cyclic protrusion-contraction movement of the cell (i.e. the polymerization and depolymerization processes), ii) the adhesion forces exerted by the cell on the surrounding and ii) the intra-synchronization between the active strains and the adhesion forces. I will show how mechanics play a critical role in determining the efficiency of the cell in terms of displacement, speed and forces.

A R T I C L E I N F O

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Cell migration
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Durotaxis

1. Introduction

Cell migration is a key phenomenon taking place during many biological events such as embryogenesis, bone remodelling, immune response or tumorogenesis. As such, it involves several cell phenotypes going from osteoblasts, osteoclasts, dendritic cells and mesenchymal stem cells. Even though cells differ in morphology and function, their translocation from one site to another occurs in a very similar way. In fact, most of the cells crawl in a cyclic manner like a worm (i.e. amoeboid migration) in a process which includes three main steps [1]. First, the cell protrudes its frontal edge forming one or several pseudopodia, which are large extensions of the cellular membrane. Such large deformations are triggered by the polymerization of the actin filaments [2] and are essential for migration since they determine the direction and the speed of movement. There exist different types of pseudopodia according to their size, shape and structure. One may distinguish between lobopodia (i.e. short or finger-like pseudopodia), lamellipodia (i.e. broad and flat extensions) and filipodia (i.e. rod-like and filamentous extensions). While the time and position of formation of a pseudopod may be controlled by several external cues such as chemoattractants (chemotaxis) [3], temperature gradients (thermotaxis) or electrical signals [4], the pseudopod grows in space and time in an independent manner [5–7]. Second, the cell adheres to the surrounding environment whether it is a flat substrate or a fibres network by developing the focal adhesions (FA), which correspond to anchoring points along the cell cortex. Finally, the cell contracts its rear end through the depolymerisation of the actin filaments [8,9].

Cell migration is sensitive to both the biochemical and mechanical properties of its environment. In fact, during movement, the cell explores and probes the stiffness of the extracellular matrix (ECM) through the FA, which seem to be responsible of the cellular mechanosensibility [10–13] as well as the acto-myosin complexes that act as global sensors of rigidity [14]. In doing so, the cell shows the ability to create and maintain an asymmetric distribution of internal subdomains such as the cytoskeleton with different morphologies and mechanical properties. The transition from a symmetric and isotropic configuration (i.e. radial distribution of the actin filaments around the nucleus) to an asymmetric and anisotropic configuration (i.e. orientation of the actin filaments in the direction of migration) is called cell polarity and is highly influenced by the rigidity of the cell environment through a process known as durotaxis [15–17]. Such phenomenon consists in triggering the orientation of the actin filaments along the ECM stiffness gradient or along stress fields engendered by the neighbours cells [18,19].

Additionally, cell migration often occurs in confined environments [20]. In such cases, the surrounding ECM may vary in terms of heterogeneity, fibres density and morphology. Many experimental works [21–23] have proved that the ECM pores dimensions, the degree of ECM alignment as well as the ECM stiffness are all critical parameters which determine whether the cell movement is enhanced or inhibited. Therefore, the cell needs to continuously adapt its shape and be able to squeeze through sub-cellular or sub-nuclear pores. The former only

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involves the deformation of the cytoplasm, whereas the latter requires the nucleus to undergo large deformations in order for the cell to become invasive, as it is the case during tumorogenesis for instance.

Many numerical models have been proposed in the literature to simulate cell migration on flat substrates [24–30] or in presence of durotaxis [16,31–36] and confinement [37–42].

In this paper I will present an overview of the numerical results obtained through the development of computational models, which are all based on three main ingredients:

1) the active (or biological) strains of the cell corresponding to the actin polymerization and depolymerisation processes;
2) the adhesion forces developed by the cell to grab the substrate or the surroundings;
3) the intra-synchronization between the active strain and the adhesion forces.

In Section 2, I will provide the essential analytical tools of the model and in Section 3 the main outcomes are detailed for cell migration in different configurations including migration over flat substrates (Sec. 3.1), in the presence of 'obstacles' and durotaxis (Sec. 3.2) and under confinement (Sec. 3.3).

2. The model

2.1. Active strains

As mentioned in Sec. 1, the cell protrusion-contraction movement is triggered by the polymerization and the depolymerization of the actin filaments inside the cytoplasm. Such mechanisms are intrinsic to the cell and regulated by specific molecular and/or chemical signals, which are not taken into account here. They consist in adding and removing, respectively monomers at one end to the polymer chain of the actin filament. This leads to an elongation (see Fig. 1) or to a shortening of the filament and can be considered as active strains. As such, they can be defined through an active deformation tensor $\boldsymbol{F}_a$which reads

$$F_\alpha = \alpha(t) i_m \otimes i_m \tag{1}$$

where i_m is a vector determining the direction of the active strain, $\otimes$ indicates the tensorial product and $\alpha(t)$ is a function of time defined as

$$\alpha(t) = \alpha_0 sin\left(2\pi \frac{t}{T}\right) \tag{2}$$

with α_0 a scalar, t the time and T the period of the active strain. According to this approach, when the sinus function increases, the protrusion occurs whereas when the sinus function decreases, contraction

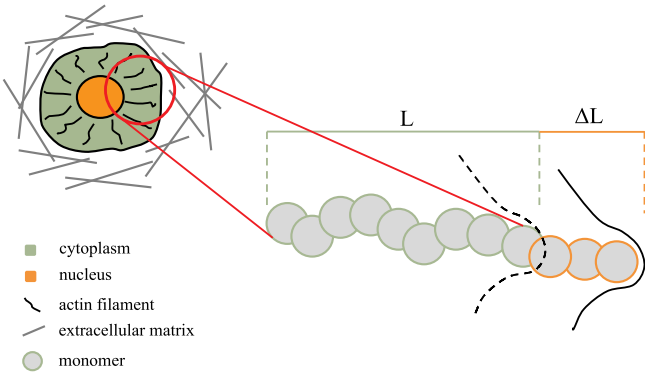


Fig. 1. A relaxed cell with the actin filaments radially distributed. When polymerization occurs, monomers are added to one end of the polymeric chain leading to an elongation of ΔL of the filament and therefore a deformation of the membrane which is moved from its initial position (dashed black line) to its final position (black line).

takes place. If the cell only underwent the active strains, it would pulse on place without moving forward. In order to be able to migrate, it needs to develop a minimal amount of adhesion forces.

2.2. Adhesion forces and inter-synchronization

The cell is able to generate viscous adhesion forces through the FA at the frontal (h_f) and at the rear (h_r) edges. From an analytical point of view, these forces can be described as follows

$$f_{adh,f} = -\mu h_f h_{F_a}^{-} \frac{\partial u}{\partial t} \tag{3}$$

$$f_{adh,r} = -\mu h_r h_{F_a}^{+} \frac{\partial u}{\partial t} \tag{4}$$

where μ is the friction coefficient and $\boldsymbol{u}$ is the displacement of the cell centre of inertia. h_r and h_r are two spatial characteristic functions defining the region within which the frontal and the rear adhesion forces are applied, respectively. Finally, and are two characteristic function which links the adhesion forces to the active strains. The former leads the frontal adhesion force to be applied during the contraction phase, whereas the latter allows the rear adhesion force to be developed during the protrusion phase. This approach enables to reproduce the cyclic behaviour of the cell.

2.3. Mechanics and constitutive behaviour

Let ρ be the cell density, $\boldsymbol{a}$ the acceleration, σ the Cauchy stress, $\boldsymbol{F}$ the deformation tensor and J its determinant, then the global equilibrium equation reads

$$Div(J\sigma F^{-T}) = \rho a + f_{adh} + f_{ext} \tag{5}$$

Where ***Div*** is the divergence operator, f_{adh} is the sum of $f_{adh,f}$ and $f_{adh,r}$ and f_{ext} is a term including all those forces coming from external elements such as the wall of a microchannel or an additional viscous force associated to a slippering or soft region. We consider here the inertial effects since it has been observed that they may play a significant role, especially during the protrusion phase [43].

Overall, the cell shows a viscoelastic behaviour, which can be described by a generalized Maxwell model with springs and dashpots in parallel. The former represent the elastic solid components such as the membrane, the actin filaments or the nuclear lamina, whereas the latter represent the fluid components like the cytosol and the nucleoplasm. Then, the Cauchy stress tensor $\sigma = \sigma_s + \sigma_f$ and the deformation gradients F, F_s and F_f coincide (the subscripts s and f stand for solid and fluid, respectively). Additionally, F_s being the result of the contribution of each solid domain, it also includes the active strain tensor which is taken into account through the decomposition of the deformation tensor approach [44,45]. Since the cell may undergo large rotations and deformations during migration, a full non-linear tensorial approach is required.

3. Results

The analytical framework presented in Sec. 2 has been used to develop a series of finite element simulations able to simulate single cell migration in different configurations such as on flat substrates (Sec. 3.1.), in presence of obstacles or durotaxis (Sec. 3.2) and under confinement (Sec. 3.3).

The cell has an initial circular shape with diameter equal to 10 μm. It has been represented as a homogenous material in the case of migration on flat substrates and in presence of obstacles and durotaxis (Young modulus equal to 1000 Pa and Poisson ratio equal to 0.3) [25,35]. However, in the case of confined migration, both the cytoplasm (constituted by the membrane and the cytosol) and the nucleus (constituted by the lamina and the nucleoplasm) have been taken into

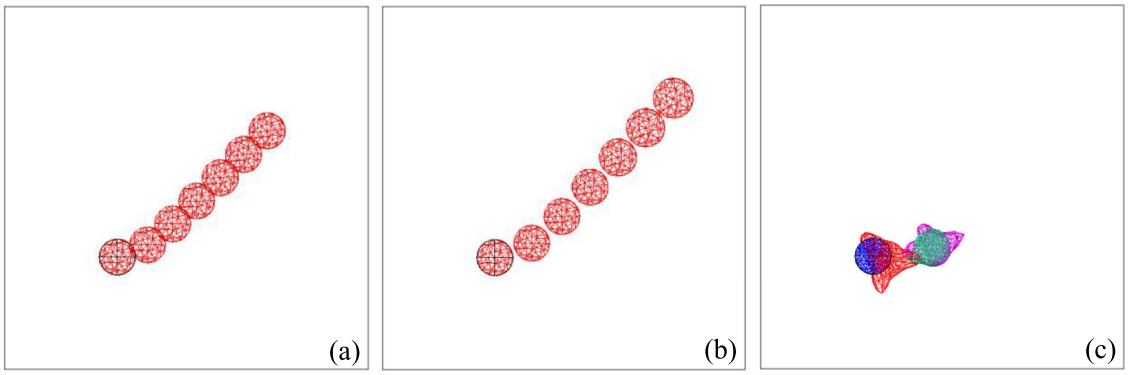


Fig. 2. Cell migration over flat substrates in presence of an external source place at the upper right corner of the substrate. The cell is shown at different steps of the simulation from 0s to 900s. (a) Spatial symmetry between the frontal and the rear adhesion surfaces, (b) spatial asymmetry between the frontal and the rear adhesion surfaces and (c) migration with multiple pseudopodia.

account as well as their specific mechanical properties. Therefore, we have set the Young moduli for the membrane, the cytosol, the lamina and the nucleoplasm equal to 100 Pa, 10 Pa, 3000 Pa and 25 Pa respectively, whereas the Poisson ratio is equal to 0.3 for the membrane and the lamina and to 0.4 for the cytosol and the nucleoplasm [37,38].

3.1. Migration on flat substrates

In Fig. 2a and b the progression of a cell over a flat substrate in presence of an external source placed at the upper right corner of the substrate is presented at different steps from 0s to 900s. More specifically, Fig. 2a shows the migration of the cell when the frontal and the rear adhesion surfaces are spatially symmetric, whereas in Fig. 2b a spatial asymmetry is introduced and the rear adhesion surface is highly reduced in order to enhance the migration as experimentally observed [46–48]. The difference between the two simulations can be noticed in terms of total covered distance (100 µm (Fig. 2a) versus 130 µm (Fig. 2b)) and of migration speed and more particularly the speed during the protrusion phase (5.7 µm/mn (Fig. 2a) versus 8.2 µm/mn (Fig. 2b)). Additionally, for the asymmetric case a higher adhesion force is found at the front, which allows the cell to stick on the substrate and pull its back forward [25].

Fig. 2c presents the migration of a cell with multiple pseudopodia. In fact, in Ref. [24] two modes of motility are explored by which the cell is able to develop several false feet simultaneously (temporal sensing model [49]) or one at the time (spatial sensing model [50]) according to the external random source.

3.2. 'Obstacles' and durotaxis

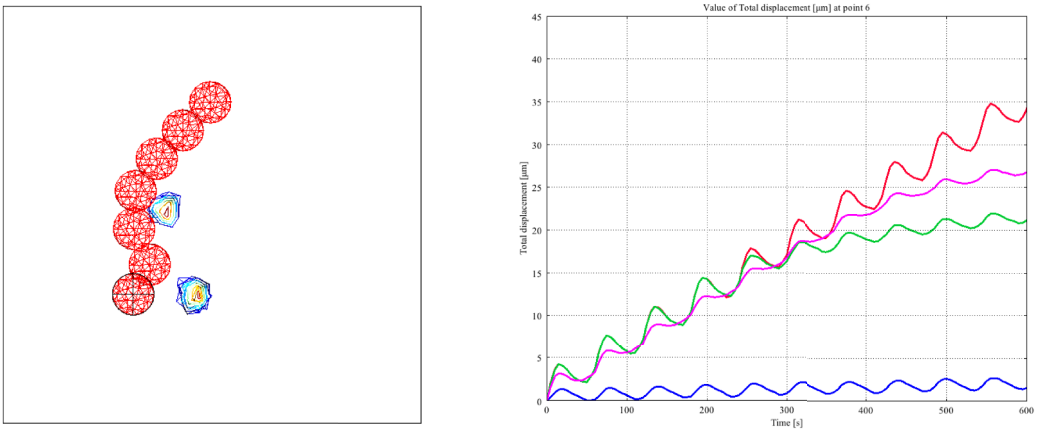
Very often cell migration takes place in heterogeneous environments. As presented in Ref. [24], the cell moves over flat substrates where two sticking regions are introduced, which are supposed to inhibit the efficiency of the cell (i.e. decrease of the migration speed) and in presence of an external source placed at the upper right corner of the substrate. Then, the cell can adopt two different strategies in order to avoid such 'obstacles': the 'run-and-tumble' [51] and the 'look-and-run' strategy [25]. In the former case, the cell is equipped with a velocity sensor, which allows detecting the decrease in speed as soon as the cell approaches the sticking region. In the latter case, the cell is equipped with a distance sensor, which enables to measure *a priori* the distance between the centre of the 'obstacle' and the cell centre of inertia and to program the path to take in order to perfectly avoid the 'obstacles' and reach the external source (Fig. 3a). In the case of the 'look-and-run' strategy the variation of the direction of migration is much smoother than in the case of the 'run-and-tumble' strategy since the cell is able 'to see' the 'obstacle' in the distance and adjust its path in advance. Additionally, for the 'run-and-tumble' case the cell slowly migrates across the 'obstacle' and does not completely avoid it.

Substrate heterogeneity can also be provided by a difference in rigidity. In this specific case, migration occurs in presence of durotaxis, which orients the actin filaments and their polymerization along stiffness gradient of the ECM. More specifically, it has been observed that cells migrate more efficiently over stiff substrates than soft ones [52]. In Ref. [35] such a phenomenon is explored and several simulations are proposed in order to analyse the cell response to different substrate rigidities. In Fig. 3b the total covered distance of the cell is reported for migration over homogeneous soft (blue line) and stiff substrate (red line) with external source at 0° and over heterogeneous substrates (i.e. gradient from stiff to soft) with an external source at 0° (green line) and at 45° (purple line). One can notice that the cell does not move over the soft substrate, which also coincides with the absence of polarity of the actin filaments (i.e. isotropic morphology and actin filaments radially distributed around the nucleus). However, the cell is much more efficient over stiff regions allowing the actin filaments to orient in the direction of the attractant signal (i.e. anisotropic morphology). Nevertheless, as soon as the cell approaches the softer regions, it starts to pulse on place and a plateau is observed for the displacement (green and purple lines).

3.3. Migration under confinement

Migration under confinement is highly influenced by the ECM morphology. In fact, the cell must squeeze its body according to the entanglement and the size of the pores within the fibers network. In Refs. [37,38], numerical simulations are presented to reproduce cell migration across micro-channels of different size, from sub-cellular to sub-nuclear. For these simulations, the cell is constituted by both the cytoplasm and the nucleus and has a diameter of 16 µm, whereas the nucleus has a diameter of 8 µm. In Fig. 4a and b, successive steps of migration through a sub-cellular (12 µm) and a sub-nuclear (7 µm) micro-channel are shown. Such results have allowed to extract the mechanical conditions determining the cell behaviour. For the cell to be invasive (i.e. cell able to enter the micro-channel but stuck in the middle),i) the adhesion force between the cell and the substrate must be higher than the contact force between the cell and the walls of the micro-channel and ii) the cell protrusion length inside the micro-channel must be larger than half the micro-channel width. These two conditions need to be satisfied for the cell to be permeative (i.e. cell able to reach the opposite side of the micro-channel) and additionally the contact force between the cell and the micro-channel must be higher around the nucleus since it is the stiffest cellular component.

In Ref. [38] it has been shown that for highly sub-nuclear micro-channels (4 µm), the cell is completely blocked at the entrance. The only way for the cell to be able to invade the micro-channel and migrate across it is to ablate the lamina. From a numerical point of view, this



(a) (b)

Fig. 3. (a) Cell migration over a flat substrate in presence of two sticking regions. Different time steps are represented from 0s to 900s. (b) Migration in presence of durotaxis and more specifically: homogeneous soft substrate (blue line), homogeneous stiff substrate (red line), heterogeneous substrate with external source at 0° (green line) and heterogeneous substrate with external source at 45° (purple line).

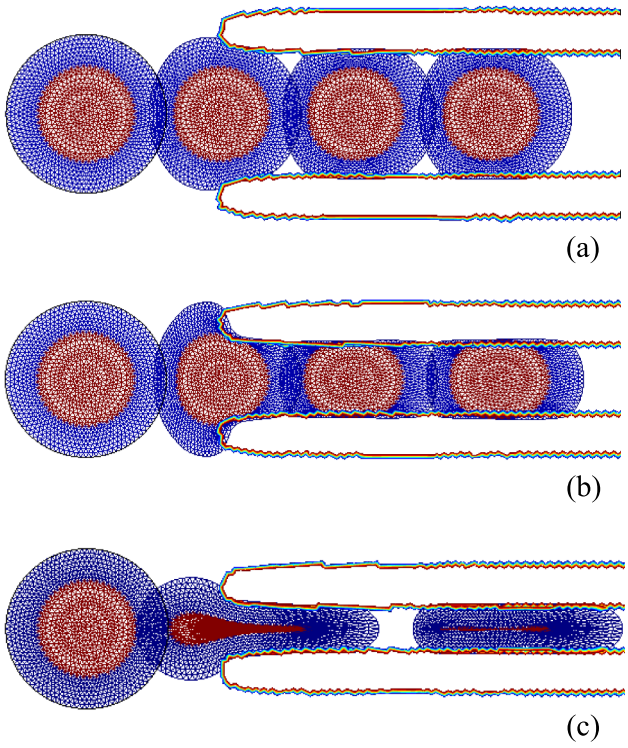


Fig. 4. Cell migration through micro-channels with sub-cellular (12 μm) (a) and sub-nuclear width (7 μm) (b). (c) Migration through a highly sub-nuclear micro-channel (2 μm) when the nuclear lamina has been ablated (blue = cytoplasm; red = nucleus).

consists in decreasing its Young modulus as presented in Fig. 4c. As it can be observed, the cell becomes permeative and reaches the opposite side of the micro-channel and both the cytoplasm and the nucleus are completely squeezed. This outcome is very interesting as a similar behaviour has been experimentally observed in migrating mammalian cells where a transient opening of the laminais caused by nuclear deformation and is rapidly repaired [53]. Such a phenomenon may have important effects on normal and pathological immune responses and confirm that survival of leukocytes strongly depends on efficient nuclear lamina and DNA repair machineries.

4. Discussion

In the present paper I have proposed an overview of recent numerical results on single cell migration in different contexts such as durotaxis and confinement, which may be observed during several biological phenomena. The computational approach used for the different models has allowed identifying the mechanical conditions enhancing or inhibiting cell migration in terms of efficiency (i.e. displacement and speed) and of developed forces. From a quantitative point of view, the numerical results are consistent with the experimental data that may be found in the literature. This confirms that cell mechanics constitutes an essential factor in cell migration together with molecular, genetic and chemical frameworks. The robustness of the models have been tested and discussed in previous papers, and further improvements may be envisaged in order to be able to reproduce specific experimental set ups.

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