

Physical role for the nucleus in cell migration

This content has been downloaded from IOPscience. Please scroll down to see the full text.

2016 J. Phys.: Condens. Matter 28 363002

(<http://iopscience.iop.org/0953-8984/28/36/363002>)

View [the table of contents for this issue](#), or go to the [journal homepage](#) for more

Download details:

IP Address: 143.167.30.107

This content was downloaded on 24/08/2016 at 11:31

Please note that [terms and conditions apply](#).

You may also be interested in:

[Physics of Cancer: Intermediate filaments and nuclear deformability during matrix invasion](#)

C T Mierke

[Physics of Cancer: Initiation of a neoplasm or tumor](#)

C T Mierke

[Physics of Cancer: The mechanical and structural properties of the microenvironment](#)

C T Mierke

[Physics of Cancer: Cellular stiffness and deformability](#)

C T Mierke

[The fundamental role of mechanical properties in the progression of cancer disease and inflammation](#)

Claudia Tanja Mierke

[Physically based principles of cell adhesion mechanosensitivity in tissues](#)

Benoit Ladoux and Alice Nicolas

[The biophysics of neuronal growth](#)

Kristian Franze and Jochen Guck

Topical Review

Physical role for the nucleus in cell migration

Antoine Fruleux and Rhoda J Hawkins

Department of Physics and Astronomy, University of Sheffield, Hicks Building, Hounsfield Road, Sheffield S3 7RH, UK

E-mail: fruleux@phare.normalesup.org and rhoda.hawkins@physics.org

Received 2 April 2015, revised 14 March 2016

Accepted for publication 19 May 2016

Published 13 July 2016



Abstract

Cell migration is important for the function of many eukaryotic cells. Recently the nucleus has been shown to play an important role in cell motility. After giving an overview of cell motility mechanisms we review what is currently known about the mechanical properties of the nucleus and the connections between it and the cytoskeleton. We also discuss connections to the extracellular matrix and mechanotransduction. We identify key physical roles of the nucleus in cell migration.

Keywords: nucleus, cell migration, mechanics

(Some figures may appear in colour only in the online journal)

1. Introduction

Cell migration is of crucial importance in development, the immune system, wound healing and cancer metastasis. It is therefore a topic of great interest not just in biology but also due to its potential applications in medicine and technology. As we will highlight in this article there are many reasons why physical scientists are also increasingly interested in this area of biological physics.


This review focuses on the physical role of the nucleus in eukaryotic cell migration. The role of the nucleus has been largely neglected, partly due to the famous experiments of keratocyte cell fragments crawling without a nucleus [1]. Recently however the nucleus has been shown to play an important role in cell motility, especially in three dimensional environments [2]. The nucleus is connected to the cell cytoskeleton which is known to play a key role in cell migration. Cytoskeleton elements interact with the external environment, for example through specific adhesion. Therefore, the nucleus is in contact with the external environment via the cytoskeleton. These interactions provide the basis for mechanosensitivity and force transduction from the external environment to the nucleus,

which plays an important role in cell migration. The nucleus is not only an object that has to be transported with the cell, but it is also connected to the migration machinery. Nuclear positioning within the cell is important in cell polarisation, setting the direction of motion. In addition, the nucleus is more solid-like than the rest of the cell and consequently less deformable. This resistance to deformation can hinder cells squeezing through constrictions. The role of the nucleus in cell migration is of particular interest in metastatic cancer cells, whose nuclei have abnormal shapes and stiffnesses.

In this article we first give an overview of cell motility mechanisms (section 2) and then discuss the mechanical properties of the nucleus (section 3) and the connections between the nucleus, cytoskeleton and extracellular matrix (section 4). In section 5 we discuss the roles of the nucleus in migrating cells, in particular nuclear positioning in cell polarisation, nucleus-cytoskeleton connection dependent migration and nucleus deformation during migration in confinement. Finally in section 6 we provide a summary and outline some key unanswered questions.

2. Overview of cell motility mechanisms

A general overview of cell motility for physical scientists is given by [3]. Here we focus on eukaryotic cells and ignore motility due to flagella. Cell migration was first observed

 Original content from this work may be used under the terms of the [Creative Commons Attribution 3.0 licence](https://creativecommons.org/licenses/by/3.0/). Any further distribution of this work must maintain attribution to the author(s) and the title of the work, journal citation and DOI.

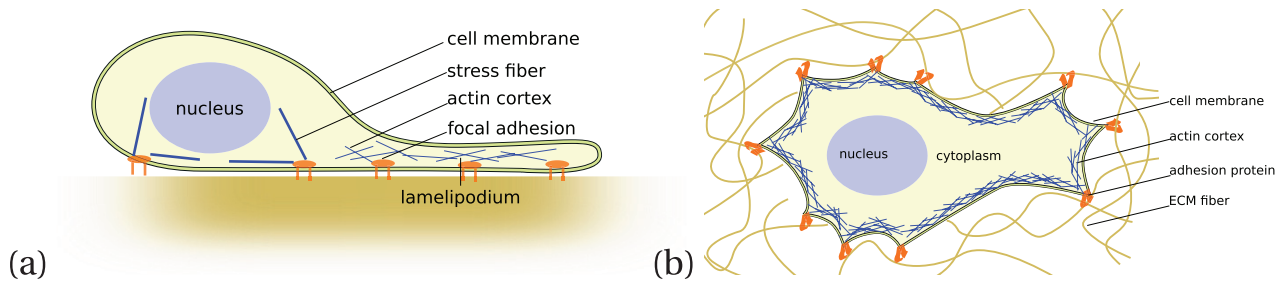


Figure 1. Cartoon showing (a) a cell crawling on a 2D substrate and (b) a cell migrating in a 3D extracellular matrix environment. On a 2D substrate (a), the actin cortex represented by thin blue lines fills the lamellipodium at the front of the cell. The focal adhesions, represented by orange ovals, connect the actin cortex as well as stress fibers to the substrate. In a 3D environment (b), the actin organisation is different and the actin cortex is connected to the extracellular matrix by adhesion proteins.

using microscopes in the 1600s by scientists such as Robert Hooke and Antonie van Leeuwenhoek. Early experiments on cell migration investigated cells crawling on flat glass substrates, since this is ideal for optical microscopy. To enable cell adhesion to the substrate the glass coverslip is coated with extracellular matrix protein (e.g. fibronectin or collagen). In some experiments cells polarise spontaneously in random directions. However, polarisation and migration direction can be directed for example by imposing gradients of chemotactants to which cells respond. Other ways to direct cells have been studied more recently such as adhesion micropatterning [4] or gradients of substrate stiffness (durotaxis) [5]. Many different aspects of such cell crawling assays have been studied in great detail. In this review we focus on the motile stage and we refer readers elsewhere to more detailed reviews on adhesion [6, 7], spreading [8], polarisation [9, 10] and chemotaxis [11].

It is clear that the networks of filamentous proteins making up the cytoskeleton are crucial for the mechanical properties, shape and migration of cells. Microtubules and actin have been studied in most detail, but the contribution of intermediate filaments and septins are increasingly being studied [12]. Of particular importance in cell motility is the protein filament actin and the molecular motor myosin. Visualisation, for example using fluorescence microscopy, of these various proteins within live migrating cells and disruption of different components by genetic or drug treatments have contributed greatly to discovering the roles of these proteins in cell motility.

The classic picture of cell crawling is of a polarised cell with a wide, flat, thin protrusion at the front of the cell, known as the lamellipodium, as shown in figure 1(a). The lamellipodium is an actin rich ~ 100 nm thick protrusion containing a highly branched network of actin filaments [13, 14]. The front of the lamellipodium, known as the leading edge of the cell, is thought to protrude due to forces generated by actin polymerisation, described by the ‘Brownian ratchet’ model [15, 16]. The energy input driving the system out of equilibrium is provided by the hydrolysis of ATP, which is required for the binding of actin subunits. Actin filaments, fixed at the back by adhesion to the substrate, polymerise against the leading edge pushing the membrane forward. Adhesion with the substrate at the back of the cell is then broken, allowing the back of the cell to move

forward to follow the leading edge. Although cell crawling can occur without functional myosin [17], actomyosin contraction usually plays an important, and sometimes dominant, role.

Actomyosin contraction is caused by clusters of myosin II molecular motors (minifilaments) interacting with actin filaments. Myosin ‘walks’ along actin filaments towards the barbed (plus) end. Within actin bundles or networks, clusters of myosin can bind to more than one actin filament at the same time. If these two actin filaments have different directions, motors attempting to walk in different directions will exert stress on the filaments, which in the case of actomyosin is contractile. Various models have been proposed for how this contraction is generated at the microscopic level [18–21]. At a cellular scale, continuum descriptions of actomyosin have been successfully developed in particular the theory of active gels [22–24]. Active matter is material that is out of equilibrium due to energy input at the level of the constituent elements. In the case of actomyosin these elements are actin filaments and molecular motors and the energy input is biochemical energy from ATP binding and hydrolysis, required for the action of myosin. We refer readers to recent reviews [25–27] for more details of this formalism.

There are clear differences between cells migrating on a flat stiff substrate and those *in vivo* or embedded in gels made of extracellular matrix proteins such as collagen [28], see figure 1(b). Substrate rigidity, adhesion and confinement profoundly alter cell migration mechanisms [29–32]. In confinement cells can switch to a different motility mode, often called ‘amoeboid’, in which actomyosin contraction at the rear of the cell induces a flow of actin cortex towards the back of the cell. Due to friction with the confined environment this retrograde flow propels the cell forward [33–37]. Highly contractile cells form blebs, which are outward bulges of the membrane that are devoid of actin. It is thought that cells migrating in matrices bleb through constrictions into available space and, if blebs are prevented from retracting due to the matrix fibres, polarised motion can ensue [38]. For cells migrating through small constrictions in matrices or within microchannels the nucleus can get stuck. Since the nucleus is harder to deform than the rest of the cell, the nucleus is the rate limiting step for cells to get through constrictions that are smaller than the unconfined nucleus size (in channels, matrices or *in vivo*)

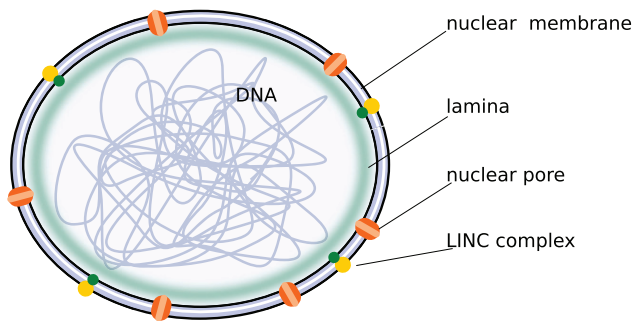


Figure 2. Cartoon showing a nucleus. The nuclear envelope, represented by a double black/mauve bilayer, is supported by the lamina represented in green. The nuclear envelope is punctuated by several transmembrane proteins such as the nuclear pores (in orange) and the LINC complex, made up of a SUN-domain protein (green) and a KASH-domain (yellow). The LINC complex mechanically connects the lamina to the cytoskeleton. DNA inside the nucleus is represented by blue curved lines.

[39–41]. Myosin appears to be important in generating the force required to get the nucleus through small spaces [42]. To find out how the nucleus is deformed and how it affects cell motility, we need to consider the mechanical properties of the nucleus as well as how the nucleus is linked to the cytoskeleton and the cytoskeleton to the extracellular matrix. In the next section, we therefore consider the mechanical properties of the nucleus.

3. Mechanical properties of the nucleus

Sufficient nuclear stiffness is required for migration in three dimensional environments [2] and nucleus deformability is necessary when cells are squeezing through small constrictions [39]. In this section we introduce the nucleus and discuss its mechanical properties, which are relevant to cell motility.

In eukaryotic cells, the nucleus contains the chromatin (DNA and associated proteins). It is the largest organelle, occupying a sizeable fraction of the total cell volume. The nucleus is delimited by the nuclear envelope, which consists of two concentric membranes, as shown in figure 2. The nuclear membrane contains nuclear pores, which actively transport selected molecules. It also contains a wide range of other transmembrane proteins such as the LINC complexes, which mechanically connect the cytoskeleton to the nucleoskeleton. Inside the nucleus the nuclear membrane is supported by the lamina, a thin (~ 100 nm) network of intermediate filaments making up the nucleoskeleton [13]. This network mainly consists of intermediate filaments called lamins (type A, B, and C). Lamins are thought to modify chromatin organisation and, crucially to our discussion, are considered to give the nucleus its mechanical stiffness [43].

In healthy cells, the nucleus is typically an order of magnitude stiffer than the cell cytoskeleton [39] and on time-scales relevant to cell migration (minutes [4]) appears to be elastic since it regains its original shape after deformation within seconds of force removal [44]. The stiffness of the

nuclear lamina has been measured by micropipette aspiration of isolated *Xenopus* oocyte nuclei with and without the majority of chromatin (removed by swelling) [45]. Swelled and unswelled nuclei give similar values for the extensional elastic modulus of ~ 25 mN m $^{-1}$. The nuclear lamina appears to break beyond a deformation threshold confinement [46]. Lamins A and C are thought to provide the rigidity of the nucleus since cells lacking lamins A and C have more deformable nuclei, whereas lamin B only has a minor effect on nuclear stiffness [47, 48]. This agrees with the result [49] that the relaxation time increases with lamin A to B ratio (i.e. increasingly elastic behaviour for a constant measurement time), although not with authors' interpretation of the relative roles of lamin A and B. Consistent with the view that lamin A provides nuclear stiffness, increased lamin A levels lead to less deformable nuclei and reduced cell migration through small pores [50]. On the other hand, cells with decreased levels of lamin A have fragile nuclei that rupture frequently [51]. Mutations in lamins cause many diseases known collectively as laminopathies e.g. muscular dystrophy. For a review on the role of lamins and nuclear mechanics in disease see [51].

Lamins therefore play a key role in the mechanical properties of the nucleus directly through the lamina properties itself but also indirectly via interactions with chromatin [47]. For example, stress exerted on embryonic stem cells has been shown to induce chromatin decondensation associated with auxetic (negative Poisson ratio) behaviour of the nucleus [52], i.e. on stretching the nucleus expands in the direction perpendicular to the stretch direction. Interestingly, assuming interactions between lamins and chromatin affect nuclear mechanical properties, this coupling could also play a crucial role in mechanotransduction by influencing gene expression in response to mechanical forces [47]. The nucleus is often assumed to be mechanically passive (unlike the active cytoskeleton). However, the nuclear lamina itself can respond biochemically to the mechanical environment by upregulating lamin A on stiff substrates and phosphorylating lamins (promoting disassembly) on soft substrates [53] (see also section 4.3).

The contents of the nucleus also contribute to its mechanical properties. Isolated chromosomes respond elastically but inside the nucleus they can flow depending on how much they are tethered to the nuclear periphery [54]. Schreiner *et al* [54] use isolated *S. pombe* nuclei, which lack lamins, to isolate the mechanical effect of chromatin. Using optical tweezers they find that these nuclei are elastic with a minor viscous component, but nuclei with untethered chromosomes are highly deformable, with shorter relaxation times, lower stiffness and viscosity. Stem cells, which do not express lamin A/C, are much less stiff than differentiated cells and show irreversible nuclear deformation characteristic of plasticity [55]. Pajerowski *et al* [55] find chromatin is stiff when condensed by cations but flows otherwise. Using micropipette experiments with GFP labelling in epithelial cells, they find the lamina is stretched whereas chromatin flows.

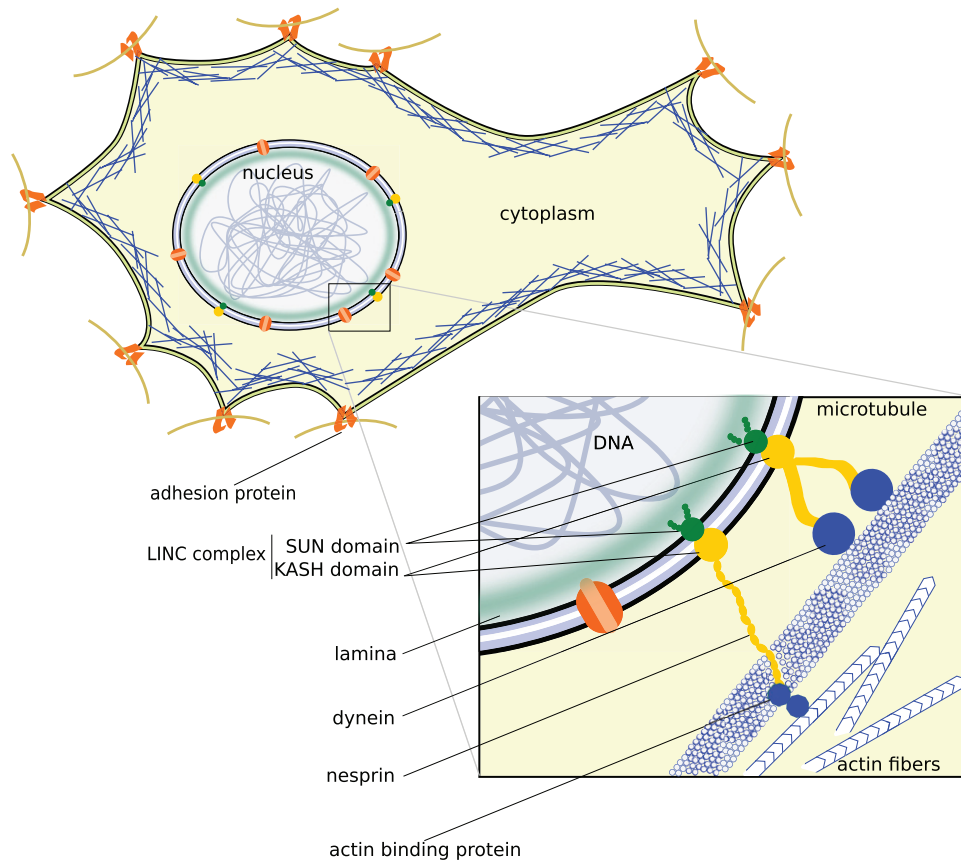


Figure 3. Cartoon showing nucleus-cytoskeleton-extracellular matrix connections in the main picture, and focusing on nucleus-cytoskeleton connections in the zoom in. In the main picture, the actin network is represented by thin blue crossing lines. It is connected to the extracellular matrix by adhesion proteins (in orange). The connection between the nucleus and the cytoskeleton is ensured by a membrane associated protein complex, the LINC complex. This LINC complex is composed of a SUN domain (green) that binds to the lamina and is connected to a KASH domain (yellow), located at the outer nuclear-membrane. The KASH domain terminates proteins such as nesprins that attach the actin fibers via actin binding proteins (blue). The LINC complex can also actively transfer momentum to microtubules as it is coupled to dyneins.

For a more detailed review of the mechanical properties of the nucleus we refer readers to [51, 56, 57].

4. Nucleus-cytoskeleton-extracellular matrix connections

4.1. Nucleus-cytoskeleton connections

The role of the nucleus in cell migration is clearly dependent on the connections between the nucleus and the motility generating components of the cytoskeleton. Interactions between the nucleus and the cytoskeleton are mediated by LINC (Linker of Nucleoskeleton and Cytoskeleton) complexes [58], as depicted in figure 3. LINC complexes are known to be important in transmitting mechanical stresses from the cytoskeleton to the inside of the nucleus during many cell processes such as migration [59–61]. The LINC complexes are composed of two transmembrane protein families, SUN domain proteins (Sad1 and Unc-83) at the inner nuclear membrane and nesprins (nuclear envelope spectrin repeat proteins) terminated by KASH domains (Klarsicht, Anc1, and Syne Homology) at the outer nuclear membrane [62, 63]. SUN domain proteins bind to nuclear lamina [64] and interact with nuclear pore proteins, and other nuclear envelope proteins

such as Samp1 [65]. Nesprins can bind to all major cytoskeletal filament networks, including actin filaments, intermediate filaments, and microtubules [66]. Nuclear deformations induced by a microneedle pulling on the cytoskeleton, are significantly reduced in cells with disrupted LINC complexes [62]. The fact that LINC complexes connect the cytoskeleton to the lamina is further demonstrated by experiments showing that a lack of functional LINC complexes results in a loss of mechanical stiffness in fibroblasts similar to that seen in lamin A depleted cells (see section 3 for discussion of lamins) [67].

The actin network is attached to the nucleus by the actin-binding domain of the giant isoforms of nesprin-1 and nesprin-2. These nesprin proteins, along with their interactions with intermediate filaments via nesprin-3, may form a scaffold around the nucleus and confine the size of the nucleus [68]. Nuclei can be moved around within the cell by KASH proteins connecting them to moving actin filaments (see section 5.1).

Microtubules are attached to the nucleus via kinesin and dynein motor proteins binding to various KASH proteins [69]. These molecular motors can move nuclei along microtubules in different directions (kinesin towards the plus end and dynein towards the minus end) [69]. For more details on the role of microtubules in moving nuclei see section 5.1

More detailed reviews on the LINC complex and its interactions can be found in [70].

4.2. Cell adhesion

Interactions between cells and their external environment have a strong influence on cell migration, affecting not only cell speed, polarisation direction and persistence, but also what motility mechanism is used. For example, specific adhesion to the substrate is essential for cell migration on a 2D substrate but not for migration *in vivo*, matrices or channels [30]. The role of the nucleus in cell migration is also affected by interactions with the environment. For example, cells migrating in soft matrices are reliant on lamin A/C and LINC complexes to migrate but those on stiff 2D substrates are not [2]. This indicates the importance of the effect of the external environment on the role of the nucleus in migration. In this section we consider interactions with the external environment and provide a brief introduction to the field of cell adhesion. We refer readers elsewhere for more detailed reviews on adhesion [6, 7] and the physical extracellular environment [71].

Cell adhesion is mediated by transmembrane proteins. There exists a wide range of adhesion molecules including integrins, cadherins and selectins [72]. Cell–cell adhesions in anchoring junctions are mediated by cadherins. Cell adhesion to the extracellular matrix on the other hand, is usually mediated by integrins. Finally, selectins bind to carbohydrates or sugars.

Migrating cells can follow gradients in substrate stiffness (durotaxis). This mechanosensitive response is mediated by adhesion sites called focal adhesions connected to the cytoskeleton [73]. For cells on a 2D substrate, microclusters of activated integrins bind to the extracellular matrix at the basal surface of the lamellipodia or filopodia at the cell periphery [74, 75]. Over time, adapter proteins talin and paxillin are recruited to integrin clusters to form nascent adhesions, some of which mature into focal adhesions, which are more stably associated with the extracellular matrix. Maturation of focal adhesions occurs concomitantly with the formation of contractile actin bundles called stress fibres. Focal adhesions increase in size and become elongated in the stress fibre direction [75, 76]. Radial stress fibers (perpendicular to the leading edge) are anchored at one end to a focal adhesion, whereas transverse arcs of actin bundles (parallel to the leading edge) and are not necessarily anchored in focal adhesions [77, 78]. During migration on a 2D substrate, as discussed in section 2, actin polymerisation at the leading edge protrudes the lamellipodium forwards and generates actin retrograde flow [79]. The effect of adhesion on the balance between forward protrusion and retrograde flow has led to the concept that adhesion proteins act as a ‘molecular clutch’ [80, 81].

In cells on a soft substrate or in confinement (in channels or embedded in 3D matrices), focal adhesions are not observed [82]. However, adhesion proteins can still affect migration, protrusion and matrix deformation [82], for instance forming smaller dynamic podosomes or invadopodia [83]. As discussed in section 2, amoeboidal modes of migration in confinement

are not dependent on integrin adhesion proteins and non-specific friction with the environment is sufficient [30].

The interplay between cell adhesion and cytoskeleton-nucleus connections is key in cell motility [84, 85]. For example, Kim *et al* [84], suggest that this coupling between the nucleus and migration is mediated by the perinuclear actin cap, a specific organization of actin associated with the nucleus. This actin cap refers to actin cables above the nucleus, terminating in a specialised subset of mechanosensitive focal adhesions [68, 86]. The elongated shape of nuclei in migrating cells appears to be controlled by the actin cap [84, 87]. The formation of these actin cap cables requires specific LINC complexes (nesprin-3 and nesprin-2G) and the focal adhesion protein zyxin and consequently may enable external mechanical signals to be quickly transmitted to the nucleus [88, 89]. The perinuclear actin cap, by connecting the nucleus to the extracellular matrix via adhesion, plays a key role in the transmission of forces from the external environment to the nucleus. We will consider this further in the following section.

4.3. Mechanosensitivity and mechanotransduction

Cells are able to detect and respond to mechanical forces and environmental stiffness. This is important in cell migration, for example for cells undergoing durotaxis [5, 73]. Mechanosensitive proteins can sense mechanical changes and react to them. For example, stretching the adhesion protein talin exposes a vinculin binding site, and subsequently, leads to vinculin binding [90]. Several adhesion and cytoskeletal proteins, including integrin and myosin, have been found to exhibit increased affinity to their ligands under mechanical stress [91]. For more details on the interplay between adhesion proteins and actin in mechanosensing and mechanotransduction we refer readers to [6]. In addition to adhesion proteins, many ion channels (transmembrane proteins forming pores controlling ion transport) in both the cell membrane and nuclear membrane are mechanosensitive. Stretch activated ion channels open in response to membrane tension, transporting ions such as calcium across the membrane [92].

Mechanotransduction refers to the conversion of an external mechanical force signal to biochemical responses and gene expression. For example, Iyer *et al* [93] observe decondensation of chromatin and nuclear entry of the transcription factor MKL following force application by magnetic beads adhered to the cell membrane. As already mentioned in section 3, the nuclear lamina itself responds biochemically to the mechanical environment with lamin A upregulated on stiff substrates and phosphorylated (promoting disassembly as occurs prior to cell division) on soft substrates [53].

It is clear then that nuclear-cytoskeleton connections combined with adhesion to the external environment mediate the transduction of forces to the nucleus. Such mechanotransduction is key to the role of the nucleus in many cell processes, including in cell migration. Having briefly reviewed the mechanisms of cell motility, the mechanical properties of the nucleus and nucleus-cytoskeleton-extracellular environment

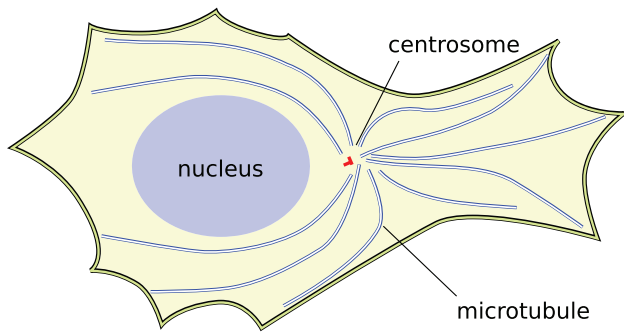


Figure 4. Cartoon showing the spacial organisation of the nucleus, microtubules (blue) and centrosome (red) in a cell migrating from left to right on a 2D substrate. However, it has been shown that in confinement this polarity is reversed such that the centrosome is behind the nucleus [94].

connections we next draw these aspects together to consider some particular roles of the nucleus in migrating cells.

5. Physical roles of the nucleus in migrating cells

5.1. Nuclear positioning and cell polarisation

Cell migration direction is given by the polarisation of the cell and the position of the nucleus within the cell correlates with this, usually being positioned towards the rear [66]. Cell polarisation or polarity is the morphological asymmetry of cells, often associated with a functional asymmetry such as cell motility. For cells migrating on 2D substrates the nucleus is generally positioned behind the centrosome (also known as the microtubule organising centre, MTOC) as shown in figure 4. However, some cells migrating in geometric confinement and *in vivo* have the centrosome behind the nucleus. For example, Pouthas *et al* [94] find that cells that migrate on 2D substrates with the centrosome in front of the nucleus, migrate on thin fibronectin adhesive lines with the centrosome behind the nucleus. Similarly, fibroblasts migrating in 1D and 3D have the centrosome at the back, behind the nucleus [95]. Théry *et al* [96] showed using micropatterned substrates that anisotropy of the adhesive microenvironment directs polarity. They found the centrosome is always near the cell centroid and the nucleus is off centre towards lower adhesion contractile cell edges. The polarised microtubule network helps maintain cell polarisation and consequently promotes persistent migration. This is thought to be due to polarised trafficking of migration related molecules along microtubules [97]. The mechanisms regulating the orientation of the centrosome relative to the nucleus are thus relevant to cell migration direction and persistence.

Nucleus positioning is the result of interactions with actin, microtubules and intermediate filaments [66, 98–100]. As explained in section 4.1, these interactions are mediated by nesprins that connect the nucleus to actin, motor proteins and intermediate filaments. Molecular motors such as dynein moving on microtubules may exert active forces on the nucleus [100]. Microtubules appear to have a particularly important role in nuclear positioning and nuclear movement, for example, in migrating neuronal cells [66]. Lamins are also

important for cell polarisation, as seen from the fact that lamin A/C deficient cells are unable to correctly polarise [101]. Nuclear position cannot be considered independent from centrosomal positioning since there is a physical link between the nucleus and the centrosome via kinesin and dyneins [102]. Dynein molecular motors at the cell periphery pulling on microtubules are key to centrosome positioning [103].

Actin also plays a role in nuclear positioning. For example, rearward nuclear movement in migrating fibroblast cells is dependent on actin, nesprin and SUN proteins, known as transmembrane actin-associated nuclear (TAN) lines [104]. As discussed in section 4.1, the nucleus is connected to actin and therefore when there is an actin retrograde flow the nucleus is transported backwards with it. It has also been suggested that actomyosin contraction at the back could push the nucleus forwards and actomyosin contraction at the front could pull the nucleus forwards [105].

Changes in migration direction sometimes involve nuclear rotation to reorient the polarisation axis with the nucleus behind the centrosome. Nuclear rotation has been observed in various conditions, and appears to depend on dynein activity [100, 106, 107]. This may be due to tension between the centrosome and the nucleus generated by dynein walking along microtubules [100]. Many cell types display alternating phases of fast persistent migration and slow low persistent movement. Fast persistent migration correlates with an intact actin cap whereas changes in migration direction may be due to dynein driven nuclear rotation whilst the actin cap transiently disappears [84, 108]. Alternatively actomyosin contractility may explain nuclear rotation with the nucleus entering only as a passive inclusion [25, 109, 110]. Micropatterns of adhesive stripes promote persistent migration, actin cap formation and elongated nuclei whereas cells on circular micropatterns are non-motile and display dynein-driven rotation of their rounded nuclei [84]. Cells migrating along synthetic nanofibres also show a correlation between nuclear elongation and cell velocity and persistence [85]. As discussed in section 4.2, it is thought that actin bundles in elongated cells compress the nucleus, causing nuclear elongation [84, 87, 111]. Since stress fibers are connected to the extra cellular matrix, nucleus elongation and cell polarisation are influenced by the external conditions. Several experiments using micropatterns show that changes in local adhesion affect orientational ordering of stress fibres across the whole cell, suggesting cells can integrate local mechanical cues at the whole cell level [87, 96, 112].

5.2. Nucleus-cytoskeleton connection dependent migration

As discussed in section 5.1, the position of the nucleus is important in cell polarisation, which sets the direction of motion. In addition to this, experiments have found that the nucleus plays an important role in the motion of migrating cells [2]. Nucleus-cytoskeleton connections appear to be required for migration in soft 3D matrices mimicking tissue environments. Lamin A/C deficient cells are able to migrate on a collagen coated 2D glass substrate but when embedded in a 3D collagen matrix their speed is significantly lower than

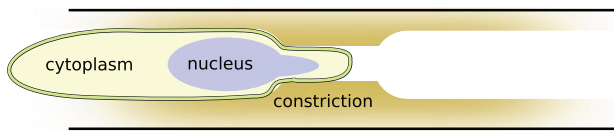


Figure 5. Cartoon showing a cell migrating through a constriction in a channel.

wild type cells. The same effect is observed when LINC complexes or nesprins are disrupted. This implies that the rigidity of the nucleus and nucleus-cytoskeleton connections are important for migration within collagen matrices but less so on flat glass substrates. However, from these experiments it is not clear to what extent this effect is due to the difference in rigidity of the environment or the difference in confinement geometry.

The integrity of the nucleus and nucleus-cytoskeleton connections also have an effect on cell migration on 2D substrates. Lamin A/C deficient cells in wound healing assays have significantly reduced migration speed [101]. Similarly, nesprin-1 depleted endothelial cells migrate more slowly [113]. Nesprin-1 depletion results in increased focal adhesion assembly, cell traction and nuclear height, whilst migration speed is decreased. Inhibiting myosin results in a similar increase in the height of nuclei. Therefore Chancellor *et al* [113] suggest that the nucleus balances tension due to actomyosin but that without nesprin-1 this tension is balanced by the substrate.

5.3. Cell squeezing through constrictions

In recent decades there have been many studies of cell migration in various confined environments. Examples include adhesive micropatterning [114], 1D migration along synthetic nanofibres [85], 2D confinement [46], microfabricated microchannels [115], micropillars [116, 117], invasion into gels [118], embedding in matrices such as collagen [28, 30, 119] and *in vivo* studies [119]. Many of these techniques are reviewed in [31]. Here we do not provide a detailed review of this body of work but instead consider some examples which have specifically looked at the nucleus.

Microfabrication techniques have enabled the study of cells moving between micropillars, in channels and through constrictions of controlled geometry without being driven by flow [31, 117] (see figure 5). Microfluidics methods that do impose flow (deformability cytometry) are also used to study cell deformations and stiffness [120]. The dynamics of the nucleus is the rate limiting factor for cells squeezing through constrictions [39, 40]. In order for cells to get through constrictions that are smaller than the size of the nucleus, the nucleus must deform. In normal cells the nucleus is more difficult to deform than the rest of the cell, however, lamin A/C deficient cells have more deformable nuclei [121]. Cancer cells, often associated with lamin mutations, have softer nuclei and consequently appear to get through smaller constrictions more easily [39]. The mechanisms for how the cell generates the forces required to deform the nucleus are not yet well understood. It is not yet clear whether the nucleus is pushed or pulled

through constrictions. It appears that more adherent cells may pull the nucleus and less adherent cells push the nucleus [28]. Suggestions of mechanisms for how the nucleus gets through a constriction include actomyosin contraction at the front or back [28, 42] and actin polymerisation [122]. In addition there is some evidence that the nuclear lamina is broken as cells migrate through small constrictions [46, 122].

5.4. Models of the nucleus during cell migration

The nucleus is often ignored in models of cell motility, since it is assumed to be passive and not the driving force for motion. However, as we have pointed out in this article, the nucleus does have an important role in cell migration. Here we mention some of the theoretical studies that do consider the nucleus.

Sometimes the nucleus is not modelled explicitly but its presence is included implicitly simply as a passive load with corresponding frictional drag, for example as suggested by [35]. To model the nucleus explicitly, the simplest model is to treat the nucleus as a deformable linearly elastic sphere (linear elastomer), as in [123] who calculate the maximum deformation of the nucleus at a bottleneck in a quasi one dimensional model. Giverson *C et al* [124] calculate the energy required to deform the nucleus from an initial spherical shape to an ellipse or a cigar shape in order for it to fit into a cylindrical channel. They consider two models for the nucleus; one as a liquid droplet surrounded by an elastic shell and the second as an incompressible elastic solid. Another continuum model for the nucleus has been used by [125] who model the nucleus as an encapsulated liquid drop. The nucleus and cell are modelled as Newtonian fluids surrounded by elastic interfaces which are simulated using the immersed boundary method.

A more engineering approach is used by [126] who use a finite element method to model the cytoplasm and nucleus in a two dimensional simulation. They model the nucleus as a viscoelastic material described by the Maxwell model, surrounded by an elastic circle representing the lamina. Agent based models have also been used such as the cellular Potts model [127] which uses a Metropolis Monte Carlo method to stochastically simulate a lattice based model of cells and nuclei with a given energy cost to deforming their shape. Combining these different modelling approaches together has also been attempted such as the hybrid agent-based finite element model for cell motility in [128].

In the future analytical and numerical studies including the nucleus should help analyse experimental data and contribute to deducing the role of the nucleus in cell migration [129, 130].

6. Outlook

We have given an overview of cell motility mechanisms and have reviewed some of the known mechanical properties of the nucleus, its coupling to the cytoskeleton and indirectly to the extracellular matrix. In particular, we have discussed the organisation of the actin cytoskeleton and its coupling to the nucleus and the extracellular matrix. However, the role played

by microtubules in cell migration is less clear. Although we know about microtubule coupling to the nucleus, their coupling to the extracellular matrix and the coupling between the centrosome and the nucleus remain poorly understood. The role of microtubules in cell migration has not been as well studied and may be more important than previously thought [131]. Whilst it is clear microtubules are important in cell polarisation, it is not clear whether the position of the centrosome is a cause or an effect of cell polarisation.

The nucleus needs to deform for cells to migrate through small constrictions. However, what is the mechanism or mechanisms by which cells push or pull the nucleus through small constrictions? This is not yet clearly understood.

In the field of mechanotransduction, there are many questions remaining regarding how gene expression is affected by mechanics. How does mechanotransduction of forces transmitted from the external environment to the nucleus affect gene expression? We are still a long way from fully explaining mechanotransduction.

Much is known on a microscopic level but questions remain in integrating this knowledge at the cellular scale. From a material physics perspective, how does the presence of the nucleus affect cell migration? Treating the nucleus as a passive inclusion with excluded volume, how does the cytoskeleton flow around it? How does the nucleus constrain cytoskeleton dynamics?

Finally there is much still to be learnt about the effects of physical properties of nuclei in disease and how this relates to cell migration, for example in metastatic cancer cells. Discerning this may lead to new approaches to the development of therapies in the future.

There remains much to be discovered to fully understand the physical roles of the nucleus in cell migration.

Acknowledgments

We acknowledge EPSRC for funding (grant reference EP/L026848/1) and Ian Estabrook for critical reading of the manuscript.

References

- [1] Verkhovskiy A B, Svitkina T M and Borisy G G 1999 Self-polarization and directional motility of cytoplasm *Curr. Biol.* **9** 11–20
- [2] Khatau S B *et al* 2012 The distinct roles of the nucleus and nucleus-cytoskeleton connections in three-dimensional cell migration *Sci. Rep.* **2** 488
- [3] Fletcher D A and Theriot J A 2004 An introduction to cell motility for the physical scientist *Phys. Biol.* **1** T1–10
- [4] Maiuri P *et al* and WCR participants 2012 The first world cell race *Curr. Biol.* **22** R673–5
- [5] Lo C M, Wang H B, Dembo M and Wang Y L 2000 Cell movement is guided by the rigidity of the substrate *Biophys. J.* **79** 144–52
- [6] Schwarz U S and Gardel M L 2012 United we stand—integrating the actin cytoskeleton and cell—matrix adhesions in cellular mechanotransduction *J. Cell Sci.* **125** 3051–60
- [7] Humphries J D, Paul N R, Humphries M J and Morgan M R 2015 Emerging properties of adhesion complexes: what are they and what do they do? *Trends Cell Biol.* **25** 388–97
- [8] Wolfenson H, Iskratsch T and Sheetz M P 2014 Early events in cell spreading as a model for quantitative analysis of biomechanical events *Biophys. J.* **107** 2508–14
- [9] Woodham E F and Machesky L M 2014 Polarised cell migration: intrinsic and extrinsic drivers *Curr. Opin. Cell Biol.* **30** 25–32
- [10] Goehring N W and Grill S W 2013 Cell polarity: mechanochemical patterning *Trends Cell Biol.* **23** 72–80
- [11] Swaney K F, Huang C-H and Devreotes P N 2010 Eukaryotic chemotaxis: a network of signaling pathways controls motility, directional sensing, and polarity *Annu. Rev. Biophys.* **39** 265–89
- [12] Huber F, Boire A, López M P and Koenderink G H 2015 Cytoskeletal crosstalk: when three different personalities team up *Curr. Opin. Cell Biol.* **32** 39–47
- [13] Alberts B, Johnson A, Lewis J, Morgan D, Raff M, Roberts K and Walter P 2014 *Molecular Biology of the Cell* 6th edn (New York: Garland Science)
- [14] Pollard T D and Borisy G G 2003 Cellular motility driven by assembly and disassembly of actin filaments *Cell* **112** 453–65
- [15] Peskin C S, Odell G M and Oster G F 1993 Cellular motions and thermal fluctuations: the brownian ratchet *Biophys. J.* **65** 316–24
- [16] Mogilner A 2006 On the edge: modeling protrusion *Curr. Opin. Cell Biol.* **18** 32–9
- [17] Bray D 2001 *Cell Movements: from Molecules to Motility* (New York: Garland Science)
- [18] Kruse K and Jülicher F 2000 Actively contracting bundles of polar filaments *Phys. Rev. Lett.* **85** 1778–81
- [19] Liverpool T B, Marchetti M C, Joanny J-F and Prost J 2009 Mechanical response of active gels *Europhys. Lett.* **85** 18007
- [20] Hawkins R J and Liverpool T B 2014 Stress reorganization and response in active solids *Phys. Rev. Lett.* **113** 028102
- [21] Lenz M, Thoresen T, Gardel M L and Dinner A R 2012 Contractile units in disordered actomyosin bundles arise from f-actin buckling *Phys. Rev. Lett.* **108** 238107
- [22] Kruse K, Joanny J F, Jülicher F, Prost J and Sekimoto K 2004 Asters, vortices, and rotating spirals in active gels of polar filaments *Phys. Rev. Lett.* **92** 078101
- [23] Kruse K, Joanny J F, Jülicher F, Prost J and Sekimoto K 2005 Generic theory of active polar gels: a paradigm for cytoskeletal dynamics *Eur. Phys. J. E: Soft Matter* **16** 5–16
- [24] Kruse K, Joanny J F, Jülicher F and Prost J 2006 Contractility and retrograde flow in lamellipodium motion *Phys. Biol.* **3** 130–7
- [25] Marchetti M C, Joanny J F, Ramaswamy S, Liverpool T B, Prost J, Rao M and Simha R A 2013 Hydrodynamics of soft active matter *Rev. Mod. Phys.* **85** 1143
- [26] Ramaswamy S 2010 The mechanics and statistics of active matter *Annu. Rev. Condens. Matter Phys.* **1** 323–45
- [27] Jülicher F, Kruse K, Prost J and Joanny J F 2007 Active behavior of the cytoskeleton *Phys. Rep.* **449** 3–28
- [28] Petrie R J and Yamada K M 2015 Fibroblasts lead the way: a unified view of 3d cell motility *Trends Cell Biol.* **25** 666–74
- [29] Engler A J, Sen S, Lee Sweeney H and Discher D E 2006 Matrix elasticity directs stem cell lineage specification *Cell* **126** 677–89
- [30] Lämmermann T *et al* 2008 Rapid leukocyte migration by integrin-independent flowing and squeezing *Nature* **453** 51–5
- [31] Lautenschläger F and Piel M 2013 Microfabricated devices for cell biology: all for one and one for all *Curr. Opin. Cell Biol.* **25** 116–24

- [32] Malboubi M, Jayo A, Parsons M and Charras G 2015 An open access microfluidic device for the study of the physical limits of cancer cell deformation during migration in confined environments *Microelectron. Eng.* **144** 42–5
- [33] Poincloux R, Collin O, Lizárraga F, Romao M, Debray M, Piel M and Chavrier P 2011 Contractility of the cell rear drives invasion of breast tumor cells in 3d matrigel *Proc. Natl Acad. Sci. USA* **108** 1943–8
- [34] Hawkins R J, Poincloux R, Bénichou O, Piel M, Chavrier P and Voituriez R 2011 Spontaneous contractility-mediated cortical flow generates cell migration in three-dimensional environments *Biophys. J.* **101** 1041–5
- [35] Callan-Jones A C and Voituriez R 2013 Active gel model of amoeboid cell motility *New J. Phys.* **15** 025022
- [36] Whitfield C A, Marenduzzo D, Voituriez R and Hawkins R J 2014 Active polar fluid flow in finite droplets *Eur. Phys. J. E: Soft Matter* **37** 9962
- [37] Maiuri P *et al* 2015 Actin flows mediate a universal coupling between cell speed and cell persistence *Cell* **161** 374–86
- [38] Charras G and Paluch E 2008 Blebs lead the way: how to migrate without lamellipodia *Nat. Rev. Mol. Cell Biol.* **9** 730–6
- [39] Friedl P, Wolf K and Lammerding J 2011 Nuclear mechanics during cell migration *Curr. Opin. Cell Biol.* **23** 55–64
- [40] Davidson P M, Denais C, Bakshi M C and Lammerding J 2014 Nuclear deformability constitutes a rate-limiting step during cell migration in 3d environments *Cell Mol. Bioeng.* **7** 293–306
- [41] Lee M-H, Wu P-H, Staunton J R, Ros R, Longmore G D and Wirtz D 2012 Mismatch in mechanical and adhesive properties induces pulsating cancer cell migration in epithelial monolayer *Biophys. J.* **102** 2731–41
- [42] Thomas D G, Yenepalli A, Denais C M, Rape A, Beach J R, Wang Y-L, Schiemann W P, Baskaran H, Lammerding J and Egelhoff T T 2015 Non-muscle myosin IIB is critical for nuclear translocation during 3d invasion *J. Cell Biol.* **210** 583–94
- [43] Gruenbaum Y and Foisner R 2015 Lamins: nuclear intermediate filament proteins with fundamental functions in nuclear mechanics and genome regulation *Annu. Rev. Biochem.* **84** 131–64
- [44] Neelam S, Chancellor T J, Li Y, Nickerson J A, Roux K J, Dickinson R B and Lele T P 2015 Direct force probe reveals the mechanics of nuclear homeostasis in the mammalian cell *Proc. Natl Acad. Sci. USA* **112** 5720–5
- [45] Dahl K N, Kahn S M, Wilson K L and Discher D E 2004 The nuclear envelope lamina network has elasticity and a compressibility limit suggestive of a molecular shock absorber *J. Cell Sci.* **117** 4779–86
- [46] Le Berre M, Aubertin J and Piel M 2012 Fine control of nuclear confinement identifies a threshold deformation leading to lamina rupture and induction of specific genes *Integr. Biol.* **4** 1406–14
- [47] Ho C Y and Lammerding J 2012 Lamins at a glance *J. Cell Sci.* **125** 2087–93
- [48] Lammerding J, Fong L G, Ji J Y, Reue K, Stewart C L, Young S G and Lee R T 2006 Lamins A and C but not lamin B1 regulate nuclear mechanics *J. Biol. Chem.* **281** 25768–80
- [49] Swift J *et al* 2013 Nuclear lamin-A scales with tissue stiffness and enhances matrix-directed differentiation *Science* **341** 1240104
- [50] Harada T, Swift J, Irianto J, Shin J-W, Spinler K R, Athirasala A, Diegmiller R, Dingal P C D P, Ivanovska I L and Discher D E 2014 Nuclear lamin stiffness is a barrier to 3d migration, but softness can limit survival *J. Cell Biol.* **204** 669–82
- [51] Davidson P M and Lammerding J 2014 Broken nuclei–lamins, nuclear mechanics, and disease *Trends Cell Biol.* **24** 247–56
- [52] Pagliara S, Franze K, McClain C R, Wylde G W, Fisher C L, Franklin R J M, Kabla A J, Keyser U F and Chalut K J 2014 Auxetic nuclei in embryonic stem cells exiting pluripotency *Nat. Mater.* **13** 638–44
- [53] Swift J and Discher D E 2014 The nuclear lamina is mechano-responsive to ECM elasticity in mature tissue *J. Cell Sci.* **127** 3005–15
- [54] Schreiner S M, Koo P K, Zhao Y, Mochrie S G J and King M C 2015 The tethering of chromatin to the nuclear envelope supports nuclear mechanics *Nat. Commun.* **6** 7159
- [55] Pajerowski J D, Dahl K N, Zhong F L, Sannak P J and Discher D E 2007 Physical plasticity of the nucleus in stem cell differentiation *Proc. Natl Acad. Sci. USA* **104** 15619–24
- [56] Isermann P and Lammerding J 2013 Nuclear mechanics and mechanotransduction in health and disease *Curr. Biol.* **23** R1113–21
- [57] Denais C and Lammerding J 2014 Nuclear mechanics in cancer *Adv. Exp. Med. Biol.* **773** 435–70
- [58] Starr D A and Fridolfsson H N 2010 Interactions between nuclei and the cytoskeleton are mediated by sun-kash nuclear-envelope bridges *Annu. Rev. Cell Dev. Biol.* **26** 421–44
- [59] Martins R P, Finan J D, Guilak F and Lee D A 2012 Mechanical regulation of nuclear structure and function *Annu. Rev. Biomed. Eng.* **14** 431
- [60] Simon D N and Wilson K L 2011 The nucleoskeleton as a genome-associated dynamic ‘network of networks’ *Nat. Rev. Mol. Cell Biol.* **12** 695–708
- [61] Jaalouk D E and Lammerding J 2009 Mechanotransduction gone awry *Nat. Rev. Mol. Cell Biol.* **10** 63–73
- [62] Lombardi M L, Jaalouk D E, Shanahan C M, Burke B, Roux K J and Lammerding J 2011 The interaction between nesprins and sun proteins at the nuclear envelope is critical for force transmission between the nucleus and cytoskeleton *J. Biol. Chem.* **286** 26743–53
- [63] Zhang Q, Skepper J N, Yang F, Davies J D, Hegyi L, Roberts R G, Weissberg P L, Ellis J A and Shanahan C M 2001 Nesprins: a novel family of spectrin-repeat-containing proteins that localize to the nuclear membrane in multiple tissues *J. Cell Sci.* **114** 4485–98
- [64] Folker E S, Östlund C, Luxton G W G, Worman H J and Gundersen G G 2011 Lamin A variants that cause striated muscle disease are defective in anchoring transmembrane actin-associated nuclear lines for nuclear movement *Proc. Natl Acad. Sci.* **108** 131–6
- [65] Borrego-Pinto J, Jegou T, Osorio D S, Auradé F, Gorjánác M, Koch B, Mattaj I W and Gomes E R 2012 Samp1 is a component of tan lines and is required for nuclear movement *J. Cell Sci.* **125** 1099–105
- [66] Gundersen G G and Worman H J 2013 Nuclear positioning *Cell* **152** 1376–89
- [67] Stewart-Hutchinson P J, Hale C M, Wirtz D and Hodzic D 2008 Structural requirements for the assembly of linc complexes and their function in cellular mechanical stiffness *Exp. Cell Res.* **314** 1892–905
- [68] Luxton G W G and Starr D A 2014 Kashing up with the nucleus: novel functional roles of kash proteins at the cytoplasmic surface of the nucleus *Curr. Opin. Cell Biol.* **28** 69–75
- [69] Fridolfsson H N and Starr D A 2010 Kinesin-1 and dynein at the nuclear envelope mediate the bidirectional migrations of nuclei *J. Cell Biol.* **191** 115–28
- [70] Tapley E C and Starr D A 2013 Connecting the nucleus to the cytoskeleton by sun–kash bridges across the nuclear envelope *Curr. Opin. Cell Biol.* **25** 57–62
- [71] Charras G and Sahai E 2014 Physical influences of the extracellular environment on cell migration *Nat. Rev. Mol. Cell Biol.* **15** 813–24
- [72] Gumbiner B M 1996 Cell adhesion: the molecular basis of tissue architecture and morphogenesis *Cell* **84** 345–57

- [73] Trichet L, Le Digabel J, Hawkins R J, Vedula S R K, Gupta M, Ribault C, Hersen P, Voituriez R and Ladoux B 2012 Evidence of a large-scale mechanosensing mechanism for cellular adaptation to substrate stiffness *Proc. Natl Acad. Sci. USA* **109** 6933–8
- [74] Ridley A J 2011 Life at the leading edge *Cell* **145** 1012–22
- [75] Choi C K, Vicente-Manzanares M, Zareno J, Whitmore L A, Mogilner A and Horwitz A R 2008 Actin and α -actinin orchestrate the assembly and maturation of nascent adhesions in a myosin II motor-independent manner *Nat. Cell Biol.* **10** 1039–50
- [76] Alexandrova A Y, Arnold K, Schaub S, Vasiliev J M, Meister J-J, Bershadsky A D and Verkhovsky A B 2008 Comparative dynamics of retrograde actin flow and focal adhesions: formation of nascent adhesions triggers transition from fast to slow flow *PLoS One* **3** e3234
- [77] Gardel M L, Schneider I C, Aratyn-Schaus Y and Waterman C M 2010 Mechanical integration of actin and adhesion dynamics in cell migration *Annu. Rev. Cell Dev. Biol.* **26** 315
- [78] Burnette D T, Manley S, Sengupta P, Sougrat R, Davidson M W, Kachar B and Lippincott-Schwartz J 2011 A role for actin arcs in the leading-edge advance of migrating cells *Nat. Cell Biol.* **13** 371–82
- [79] Renkawitz J, Schumann K, Weber M, Lämmermann T, Pflücke H, Piel M, Polleux J, Spatz J P and Sixt M 2009 Adaptive force transmission in amoeboid cell migration *Nat. Cell Biol.* **11** 1438–43
- [80] Giannone G, Mège R-M and Thoumine O 2009 Multi-level molecular clutches in motile cell processes *Trends Cell Biol.* **19** 475–86
- [81] Case L B and Waterman C M 2015 Integration of actin dynamics and cell adhesion by a three-dimensional, mechanosensitive molecular clutch *Nat. Cell Biol.* **17** 955–63
- [82] Fraley S I, Feng Y, Krishnamurthy R, Kim D-H, Celedon A, Longmore G D and Wirtz D 2010 A distinctive role for focal adhesion proteins in three-dimensional cell motility *Nat. Cell Biol.* **12** 598–604
- [83] Linder S 2007 The matrix corroded: podosomes and invadopodia in extracellular matrix degradation *Trends Cell Biol.* **17** 107–17
- [84] Kim D-H, Cho S and Wirtz D 2014 Tight coupling between nucleus and cell migration through the perinuclear actin cap *J. Cell Sci.* **127** 2528–41
- [85] Meehan S and Nain A S 2014 Role of suspended fiber structural stiffness and curvature on single-cell migration, nucleus shape, and focal-adhesion-cluster length *Biophys. J.* **107** 2604–11
- [86] Kim D-H, Chambliss A B and Wirtz D 2013 The multi-faceted role of the actin cap in cellular mechanosensation and mechanotransduction *Soft Matter* **9** 5516–23
- [87] Khatau S B, Hale C M, Stewart-Hutchinson P J, Patel M S, Stewart C L, Searson P C, Hodzic D and Wirtz D 2009 A perinuclear actin cap regulates nuclear shape *Proc. Natl Acad. Sci.* **106** 19017–22
- [88] Kim D-H, Khatau S B, Feng Y, Walcott S, Sun S X, Longmore G D and Wirtz D 2012 Actin cap associated focal adhesions and their distinct role in cellular mechanosensing *Sci. Rep.* **2** 555
- [89] Chambliss A B, Khatau S B, Erdenberger N, Robinson D K, Hodzic D, Longmore G D and Wirtz D 2013 The linc-anchored actin cap connects the extracellular milieu to the nucleus for ultrafast mechanotransduction *Sci. Rep.* **3** 1087
- [90] del Rio A, Perez-Jimenez R, Liu R, Roca-Cusachs P, Fernandez J M and Sheetz M P 2009 Stretching single talin rod molecules activates vinculin binding *Science* **323** 638–41
- [91] Veigel C, Molloy J E, Schmitz S and Kendrick-Jones J 2003 Load-dependent kinetics of force production by smooth muscle myosin measured with optical tweezers *Nat. Cell Biol.* **5** 980–6
- [92] Ingber D E 2006 Cellular mechanotransduction: putting all the pieces together again *FASEB J.* **20** 811–27
- [93] Venkatesan Iyer K, Pulford S, Mogilner A and Shivashankar G V 2012 Mechanical activation of cells induces chromatin remodeling preceding MKL nuclear transport *Biophys. J.* **103** 1416–28
- [94] Pouthas F, Girard P, Lecaudey V, Ly T B N, Gilmour D, Boulin C, Pepperkok R and Reynaud E G 2008 In migrating cells, the golgi complex and the position of the centrosome depend on geometrical constraints of the substratum *J. Cell Sci.* **121** 2406–14
- [95] Doyle A D, Wang F W, Matsumoto K and Yamada K M 2009 One-dimensional topography underlies three-dimensional fibrillar cell migration *J. Cell Biol.* **184** 481–90
- [96] Théry M, Racine V, Piel M, Pépin A, Dimitrov A, Chen Y, Sibarita J-B and Bornens M 2006 Anisotropy of cell adhesive microenvironment governs cell internal organization and orientation of polarity *Proc. Natl Acad. Sci. USA* **103** 19771–6
- [97] Etienne-Manneville S 2013 Microtubules in cell migration *Annu. Rev. Cell Dev. Biol.* **29** 471–99
- [98] Starr D A 2009 A nuclear-envelope bridge positions nuclei and moves chromosomes *J. Cell Sci.* **122** 577–86
- [99] Tsai J-W, Bremner K H and Vallee R B 2007 Dual subcellular roles for *lis1* and dynein in radial neuronal migration in live brain tissue *Nat. Neurosci.* **10** 970–9
- [100] Wu J, Lee K C, Dickinson R B and Lele T P 2011 How dynein and microtubules rotate the nucleus *J. Cell. Physiol.* **226** 2666–74
- [101] Lee J S H, Hale C M, Panorchan P, Khatau S B, George J P, Tseng Y, Stewart C L, Hodzic D and Wirtz D 2007 Nuclear lamin A/C deficiency induces defects in cell mechanics, polarization, and migration *Biophys. J.* **93** 2542–52
- [102] Fridolfsson H N, Ly N, Meyerzon M and Starr D A 2010 Unc-83 coordinates kinesin-1 and dynein activities at the nuclear envelope during nuclear migration *Dev. Biol.* **338** 237–50
- [103] Elric J and Etienne-Manneville S 2014 Centrosome positioning in polarized cells: common themes and variations *Exp. Cell Res.* **328** 240–8
- [104] Luxton G W G, Gomes E R, Folker E S, Vintinner E and Gundersen G G 2010 Linear arrays of nuclear envelope proteins harness retrograde actin flow for nuclear movement *Science* **329** 956–9
- [105] Wu J, Kent I A, Shekhar N, Chancellor T J, Mendonca A, Dickinson R B and Lele T P 2014 Actomyosin pulls to advance the nucleus in a migrating tissue cell *Biophys. J.* **106** 7–15
- [106] Gerashchenko M V, Chernouvanenko I S, Moldaver M V and Minin A A 2009 Dynein is a motor for nuclear rotation while vimentin IFs is a ‘brake’ *Cell Biol. Int.* **33** 1057–64
- [107] Levy J R and Holzbaur E L F 2008 Dynein drives nuclear rotation during forward progression of motile fibroblasts *J. Cell Sci.* **121** 3187–95
- [108] Razafsky D, Wirtz D and Hodzic D 2014 Nuclear envelope in nuclear positioning and cell migration *Adv. Exp. Med. Biol.* **773** 471–90
- [109] Kumar A, Maitra A, Sumit M, Ramaswamy S and Shivashankar G V 2014 Actomyosin contractility rotates the cell nucleus *Sci. Rep.* **4** 3781
- [110] Gomes E R, Jani S and Gundersen G G 2005 Nuclear movement regulated by Cdc42, MRCK, myosin, and actin flow establishes MTOC polarization in migrating cells *Cell* **121** 451–63

- [111] Versaevel M, Grevesse T and Gabriele S 2012 Spatial coordination between cell and nuclear shape within micropatterned endothelial cells *Nat. Commun.* **3** 671
- [112] Mandal K, Wang I, Vitiello E, Orellana L A C and Balland M 2014 Cell dipole behaviour revealed by ECM sub-cellular geometry *Nat. Commun.* **5** 5749
- [113] Chancellor T J, Lee J, Thodeti C K and Lele T 2010 Actomyosin tension exerted on the nucleus through nesprin-1 connections influences endothelial cell adhesion, migration, and cyclic strain-induced reorientation *Biophys. J.* **99** 115–23
- [114] Théry M 2010 Micropatterning as a tool to decipher cell morphogenesis and functions *J. Cell Sci.* **123** 4201–13
- [115] Heuzé M L, Collin O, Terriac E, Lennon-Duménil A-M and Piel M 2011 Cell migration in confinement: a micro-channel-based assay *Methods Mol. Biol.* **769** 415–34
- [116] Saez A, Ghibaudo M, Buguin A, Silberzan P and Ladoux B 2007 Rigidity-driven growth and migration of epithelial cells on microstructured anisotropic substrates *Proc. Natl Acad. Sci. USA* **104** 8281–6
- [117] Isermann P, Davidson P M, Sliz J D and Lammerding J 2012 Unit 22.16 Assays to measure nuclear mechanics in interphase cells *Curr. Protocols Cell Biol.* **56:22.16:22.16.1–22.16.21**
- [118] Koch T M, Münster S, Bonakdar N, Butler J P and Fabry B 2012 3d traction forces in cancer cell invasion *PLoS One* **7** e33476
- [119] Wolf K, Alexander S, Schacht V, Coussens L M, von Andrian U H, van Rheenen J, Deryugina E and Friedl P 2009 Collagen-based cell migration models *in vitro* and *in vivo* *Semin. Cell Dev. Biol.* **20** 931–41
- [120] Otto O *et al* 2015 Real-time deformability cytometry: on-the-fly cell mechanical phenotyping *Nat. Methods* **12** 199–202 (4 p following 202)
- [121] Lammerding J, Christian Schulze P, Takahashi T, Kozlov S, Sullivan T, Kamm R D, Stewart C L and Lee R T 2004 Lamin *a/c* deficiency causes defective nuclear mechanics and mechanotransduction *J. Clin. Invest.* **113** 370–8
- [122] Thiam H R *et al* 2016 Perinuclear ARP2/3-driven actin polymerization enables strong nuclear deformation to facilitate cell migration through complex environments *Nat. Commun.* **7** 10997
- Raab M *et al* 2016 ESCRT III repairs nuclear envelope ruptures during cell migration to limit DNA damage and cell death *Science* **352** 359–62
- Denais C M, Gilbert R M, Isermann P, McGregor A L, te Lindert M, Weigel B, Davidson P M, Friedl P, Wolf K and Lammerding J 2016 Nuclear envelope rupture and repair during cancer cell migration *Science* **352** 353–8
- [123] Le Berre M, Liu Y-J, Hu J, Maiuri P, Bénichou O, Voituriez R, Chen Y and Piel M 2013 Geometric friction directs cell migration *Phys. Rev. Lett.* **111** 198101
- [124] Giverso C, Grillo A and Preziosi L 2014 Influence of nucleus deformability on cell entry into cylindrical structures *Biomech. Modelling Mechanobiol.* **13** 481–502
- [125] Leong F Y, Li Q, Lim C T and Chiam K-H 2011 Modeling cell entry into a micro-channel *Biomech. Modelling Mechanobiol.* **10** 755–66
- [126] Aubry D, Thiam H, Piel M and Allena R 2015 A computational mechanics approach to assess the link between cell morphology and forces during confined migration *Biomech. Modelling Mechanobiol.* **14** 143–57
- [127] Scianna M and Preziosi L 2013 Modeling the influence of nucleus elasticity on cell invasion in fiber networks and microchannels *J. Theor. Biol.* **317** 394–406
- [128] Tozluoğlu M, Tournier A L, Jenkins R P, Hooper S, Bates P A and Sahai E 2013 Matrix geometry determines optimal cancer cell migration strategy and modulates response to interventions *Nat. Cell Biol.* **15** 751–62
- [129] Estabrook I D, Thiam H R, Piel M and Hawkins R J 2016 Nucleus deformation during cell migration through constrictions (in preparation)
- [130] Fruleux A and Hawkins R 2016 in preparation
- [131] Balzer E M, Tong Z, Paul C D, Hung W-C, Stroka K M, Boggs A E, Martin S S and Konstantopoulos K 2012 Physical confinement alters tumor cell adhesion and migration phenotypes *FASEB J.* **26** 4045–56