Bio-chemo-mechanical models for nuclear deformation in adherent eukaryotic cells

Michele M. Nava · Manuela T. Raimondi · Riccardo Pietrabissa

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M. M. Nava (✉) · M. T. Raimondi · R. Pietrabissa
LaBS - Laboratory of Biological Structure Mechanics, Department of Chemistry, Materials and Chemical Engineering "Giulio Natta", Politecnico di Milano, Piazza L. da Vinci, 32, 20133 Milano, Italy
e-mail: michele.nava@polimi.it

1 Introduction

Cells live in a mechano-chemical environment and are sensitive to changes in its properties. Reciprocal interactions between cells and their surroundings are crucial for cell viability and functions as proliferation, motility, differentiation, shape control, cellular homeostasis, gene expression and protein secretion (Wang and Thampatty 2006, 2008; Discher et al. 2009; Hadjipanayi et al. 2009a,b; Friedman et al. 2009; Webster et al. 2009). In vivo, cells are continuously subjected to several biochemical and biophysical stimuli that regulate cell response. Cells can also exert forces to probe, sense and respond to changes in the surrounding microenviron-ment. In case of defects in cell microenvironment, including extracellular matrix (ECM) fibrolysis or rigidification (Gun-ther et al. 1999; Sugimoto et al. 2006), abnormal cell contraction or motility (Ingber 2008) can induce patho-logical processes. Even though the specific mechanisms by which mechanical irregularities lead to disease states remain still unclear, many pathological diseases, such as asthma (Affonce and Lutchen 2006), osteoporosis (Klein-Nulend et al. 2003), deafness (Vollrath et al. 2007), atheroscle-rosis (Gimbrone et al. 2000), cancer (Paszek et al. 2005), osteoarthritis (Judex et al. 1997), glaucoma (Tan et al. 2006) and muscular dystrophy (Heydemann and McNally 2007) can be directly caused by or catalysed by irregular cellular or tissue mechanics (Ingber 2008).

The process by which cells actively probe and sense physical and mechanical properties of the environment is known as mechanosensing. Mechanotransduction refers to the translation of mechanical stimuli into biochemical signals that

enables cells to adjust their structure and function. Basically, in this process, cytoskeletal remodelling occurs due to cell–matrix interactions causing soluble factors translocation to the nucleus via diffusive processes (Ingber 2006; Jaalouk and Lammerding 2009).

Interesting experimental studies in cell mechanics have demonstrated that cell nuclei, cytoskeletal filaments and integrins are directly connected through an intricate network of cytoskeletal-nuclear components (Maniotis and Chen 1997). Among these components, a specific group of nuclear linker proteins, known as the perinuclear cap (or actin cap), has been reported to govern mechanosensing over a wide range of matrix stiffness (Kim et al. 2013a,b; Khatau et al. 2012) and to form physical pathway for mechanotransduction (Chambliss et al. 2013). Perturbations occurring in the extracellular environment result in physical transmission of complex pattern of forces, both in terms of magnitude and spatial orientation, to the nucleus. The resulting stress and strain propagation towards the nuclear body have a significant impact on its functions: for example, as firstly reported in Thomas et al. (Thomas et al. 1998), the transcription or suppression of specific genes and protein synthesis within the nucleus have been demonstrated to be influenced directly by nuclear strains. Moreover, tension and strain propagation to the nucleus, both in normal and pathological states, could induce modifications in nuclear architecture and shape (Dahl et al. 2008; Wang et al. 2009; Chalut et al. 2010; Heo et al. 2011; Isermann and Lammerding 2013), in chromatin organization and accessibility (Iyer et al. 2012), in gene expression (Jerabek and Heermann 2014) and, finally, in nuclear membrane permeability to several factors involved in nuclear mechanotransduction pathways (Dupont et al. 2011; Gupta et al. 2012; Schachter et al. 2012).

In order to study cell mechanics, mechanosensitivity and mechanotransduction, several in vitro model systems trying to mimic features of the physiological milieu and measure biophysical variables have been developed in the past years. A comprehensive review of the experimental technique for cell mechanics are (Huang et al. 2004; Loh et al. 2009). In vitro model systems have elucidated that cell functions are influenced by several mechanical cues (Nava et al. 2012), including the stiffness of the substrate (Discher et al. 2005, 2009; Engler et al. 2006), the local surface topography (Nikkhah et al. 2012) and the three-dimensional (3D) architecture of the matrix (Tibbitt and Anseth 2009; Raimondi et al. 2013). For example, the proliferation rate and lineage specification of stem cells towards neurons, myoblasts and osteoblasts have been demonstrated to be governed by substrate compliance (Chen et al. 1997; Engler et al. 2006, 2008; Jacot et al. 2010).

It is well established that externally imposed forces (e.g. substrate stretching, cyclic pressurization and shear flow) (Guilak et al. 2009) can affect cell function. For example, when cells are subjected to stress, either by stretching the substrate or by applying an aligned shear flow, the cells actively reorient and align themselves in preferred directions (Wojciak-Stothard and Ridley 2003; Prager-Khoutorsky et al. 2011).

Besides experimental studies, several in silico models have been developed not only for complementing experimental observations, including morphological features, but also for predicting quantitatively mechanical variables and parameters that are difficult, almost impossible, to measure at the cell or subcellular level (Anderson et al. 2007; Vaziri and Gopinath 2008; Rodriguez et al. 2013).

In this paper, we review the existing literature on the computational models developed to investigate adherent eukaryotic cell mechanics and mechanobiology. This work is organized as follows: in Sect. 2, the microstructural components and their role in mechanotransduction and physical transduction will be presented. In Sect. 3, the two main classes of computational models of single-cell mechanics will be presented: the discrete or microstructural-based models and the continuum models. Our attention will be devoted to a specific class of innovative continuum models, the so- called bio-chemo-mechanical model firstly developed by Deshpande et al. (2006). We also focus on whole cell models that account for the nuclear contribution to cell mechanics. Finally, in Sect. 4, the modelling techniques will be analysed highlighting their ability in predicting cell behaviour in terms of cytoskeletal tension, stress distribution and stress propagation towards the nucleus.

2 Microstructural components and mechanosensitivity

2.1 Cell chemical sensitivity

Living cells have the ability to actively sense and to react to the biochemical and biophysical properties of the microenvironment in which they reside (Kress et al. 2012). In vitro, cell behaviour has been proved to be influenced by several cues that can be subdivided into two main classes: biochemical cues and biophysical cues. Biochemical cues are provided by reciprocal interactions between the cell, soluble bioactive agents, and the ECM. Soluble factors, for example growth factors and cytokines, when added to the cell culture, or secreted by neighbouring cells, or delivered by the extracellular matrix (ECM), diffuse and bind to cell membrane receptors (Fig. 1a), activating cellular signalling pathways which affects cell response (Fig. 1b) (Ding and Schultz 2004; Liu et al. 2009).

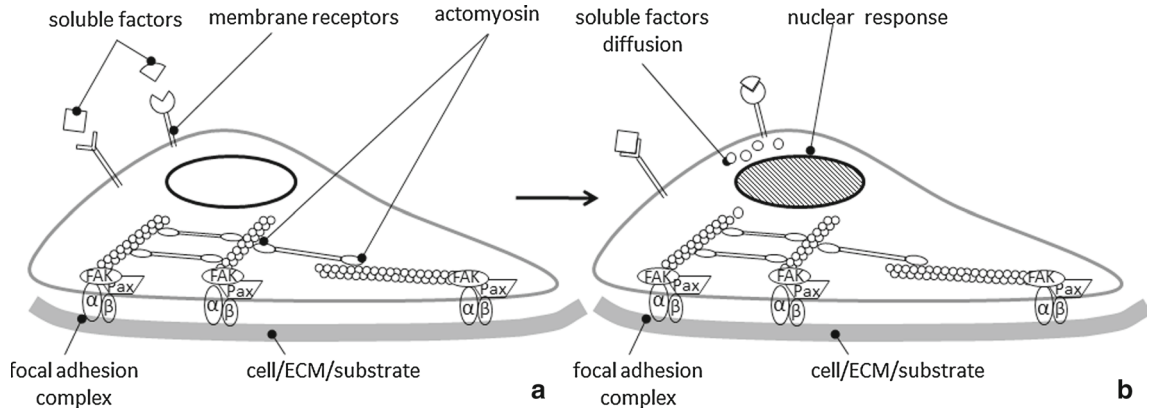

Fig. 1 Schematic representation of the cellular behaviour of an adherent cell in response to biochemical cues. **a** Soluble bioactive agents (e.g. growth factors and cytokines) diffuse in the extracellular microenvironment, bind to cell membrane receptors and **b** translocate within the intracellular body where a cascade of reaction causes modifications into the nuclear organization and functionality

2.2 Cell mechanosensitivity: mechanotransduction

In addition to soluble signals, cells are sensitive to biophysical and, specifically, to mechanical cues (Discher et al. 2005, 2009). In particular, adherent cell mechanosensitivity is governed by a dynamic and intricate network of filaments named cytoskeleton. This intracellular structure, not only provides mechanical stability to the cell, but also allows for transmitting mechanical signals, in the forms of stress and strain fields, from the environment to the nucleus (Wang et al. 2009; Buxboim et al. 2010; Isermann and Lammerding 2013).

In eukaryotic cells, the cytoskeleton extends throughout the cell cytoplasm and consists of actin, microtubules and a group of polymers known as intermediate filaments (Ingber 1997; Bao and Suresh 2003; Fletcher and Mullins 2010). Actin filaments, also known as microfilaments, are flexible structures, with a diameter of 5–9 nm. Microfilaments are composed of two stranded helical polymers of the globular actin protein. Since these filamentous proteins can assembly and disassembly very rapidly, they are central to the formation of a variety of mechanosensing structures including linear bundles (e.g. filopodia, lamellipodia protrusions), two-dimensional and three-dimensional networks (e.g. in migrating cells) (Alberts et al. 2007). Microtubules are composed of the protein tubulin forming long hollow cylinders with an outer diameter of 25 nm. They are the stiffest of the three polymers and appear almost linear. Actually, their persistence length, which is a measure of filament flexibility that increases with stiffness, is large (~5 mm) compared with the other cytoskeleton proteins. Microtubules have also the most complex assembly and disassembly dynamics. They play an important role in providing strength under compressive load in cells and are involved in intracellular transport, cell division, and chromosome separation (Fletcher and Mullins 2010). Intermediate filaments, the least stiff of the cytoskeletal components, provide strength to tensile forces much more effectively than compressive forces (Alberts et al. 2007; Mofrad 2009). They can be crosslinked to each other, as well as to actin filaments and microtubules, by proteins called plectins (Wiche 1998). One class of intermediate filaments, known as nuclear lamins, contribute to the mechanical integrity of the cell nucleus (Tsai et al. 2006). The cytoskeletal filaments interact with many other proteins, including crosslinking proteins and molecular motors. Indeed, cell contractility is related to the activity of myosin motors (e.g. myosin-II molecules) in association with crosslinked actin filaments. Thanks to the activity of actomyosin complexes, cells can maintain a prestressed state that regulates cell adhesion and function. The cytoskeleton in adherent cells terminates at dynamic clusters of proteins at the plasma membrane known as focal adhesions (Lutolf and Hubbell 2005; Schwartz 2010). Focal adhesions consist of heterodimeric cell surface receptors known as integrins, cytoskeletal-associated proteins such as talin, vinculin and/or paxillin and other signalling molecules such as focal adhesion kinase (FAK) (Fig. 2a). Traction forces generated by the actomyosin motors, and also superimposed extracellular forces, are transmitted via the cytoskeleton both to the intracellular environment and to the surroundings. The magnitude of the resulting cytoskeletal strength are determined by an interplay between the intracellular actomyosin contractility, the superimposed extracellular loads and the reaction forces relative to the engineering properties (e.g. elasticity, shape) of the substrate. This process leads to a cascade of biochemical reactions (e.g. ion channel activation (Guharay and Sachs 1984) or activation of other membrane-bound receptors (Chen et al. 1999; Correa-Meyer et al. 2002)) that influence cell function (Fig. 2b) (Meyer et al. 2000).

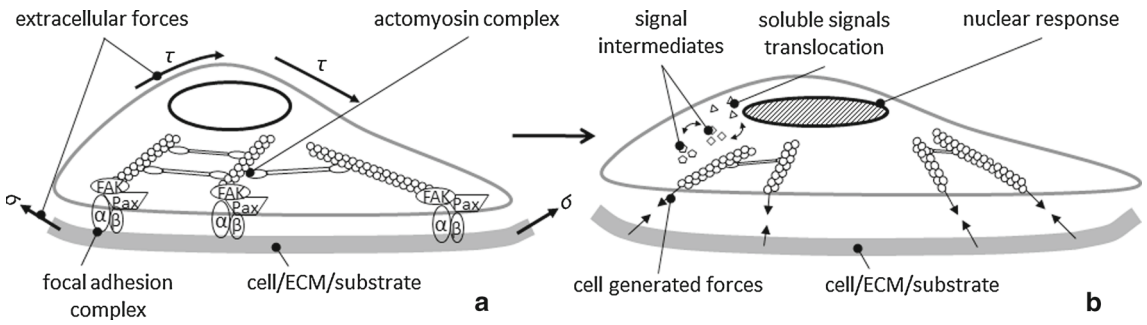

Fig. 2 Schematic representation of the cellular mechanotransduction in response to biomechanical cues. **a** Extracellular forces acting on the adherent cell superimposed to intracellular tensions generated by stress fibres, or bundles of actin filaments, forming a semi-sarcomere structure. External load and adhesive tractions are transmitted to the ECM via focal adhesions that are located at both ends of the stress fibre and on the substrate or the ECM. Focal adhesion are formed of ECM proteins, transmembrane receptors, cytoplasmic structural and signalling proteins. (e.g. σ is cyclic matrix stress, τ is cyclic fluid-induced shear). **b** Mechanotransduction process consisting in cascade of reactions (signal intermediates) and soluble factors translocation to the nucleus via diffusive processes in response to mechanical signals and changes in physico-chemical microenvironment

Table 1 Cytoplasm and nuclear stiffness experimentally measured

Cell type	Cytoplasm stiffness (kPa)	Nuclear stiffness (kPa)	Experimental method
Endothelial	0.5	5	Compression in microplates (Caille et al. 2002)
Chondrocytes	0.1 – 0.6	1 – 5	Micropipette aspiration (Guilak et al. 2000)
Endothelial	0.1 – 0.8	1 – 5	Micropipette aspiration and computational model (Vaziri and Mofrad 2007)
Endothelial	3.2	28	Microtensile testing (Deguchi et al. 2011)

2.3 Cell mechanosensitivity: direct cytoskeletal-nuclear transmission mechanism

Besides the mechanism by which mechanical forces are converted to biochemical signals, experimental evidences suggest that cell behaviour and lineage specification can be influenced by the physical transmission of stresses and strain propagation to the nucleus via an intricate network of cytoskeletal-nuclear connections (Dahl et al. 2008; Wang et al. 2009; Shivashankar 2011; Lombardi et al. 2011). Changes in nuclear mechanics, architecture and shape (Dahl et al. 2008; Wang et al. 2009; Chalut et al. 2010; Heo et al. 2011; Isermann and Lammerding 2013) affect chromatin packing (Iyer et al. 2012), gene accessibility and expression (Thomas et al. 1998; Jerabek and Heermann 2014) and finally, nuclear membrane permeability to several factors (Dupont et al. 2011; Gupta et al. 2012; Schachter et al. 2012).

Even though the cell nucleus itself is about 3-10 times stiffer than the surrounding cytoplasm depending either on cell type and measurement technique (Guilak et al. 2000; Caille et al. 2002; Vaziri and Mofrad 2007; Deguchi et al. 2011; Badique et al. 2013) (Table 1), experimental evidences have highlighted the role of the nucleus as a mechanosensor. For example, in Pajerowski et al., (Pajerowski et al. 2007), studies on human embryonic stem cells have shown that nuclear stiffness increases as the cell commits to a differentiation program. The change in nuclear compliance, as described below, is a distinct feature of diseased cells.

The cell nucleus can be structurally and functionally divided into two regions: the nuclear interior and the nuclear envelope. The nuclear interior is largely aqueous, and it is composed of functional substructures (e.g. nucleoli, Cajal bodies) that could be influenced by mechanical forces (Dahl et al. 2008). The nuclear envelope is composed of a double lipid bilayer, the outer membrane which is continuous with the endoplasmic reticulum, the inner nuclear membrane, and the nuclear lamina. The inner and outer nuclear membranes join at the nuclear pore complexes that allow nuclear-cytoplasmic transport (Burns and Wente 2012). The nuclear lamina consists of a dense network of proteins primarily composed of lamins underneath the inner nuclear membrane. Lamins, which are type V nuclear intermediate filaments,

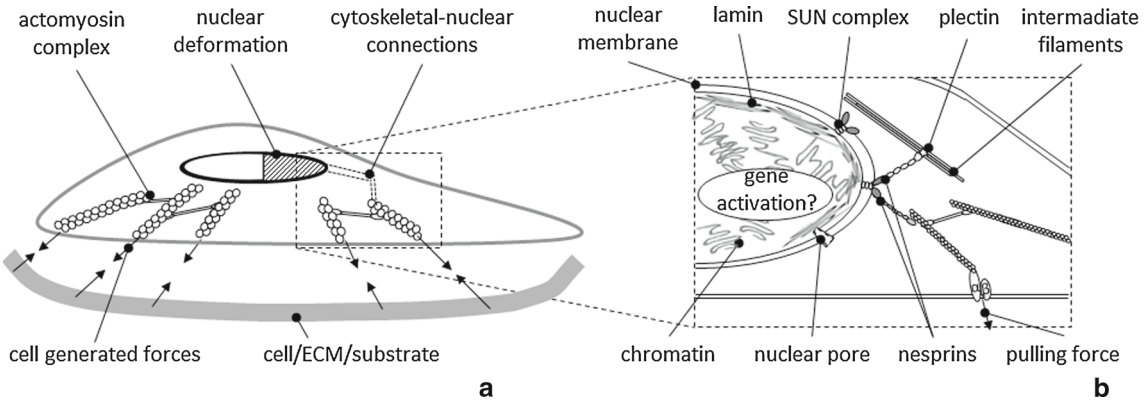

Fig. 3 Schematic representation of the cellular mechanotransduction machinery in response to biomechanical cues. **a** Physical transmission of active stresses to the nucleus via an intricate network of cytoskeletal-nuclear connections, resulting in altered nuclear architecture and mechanical properties. **b** Detail of direct force transmission mechanism from the ECM to the nucleus through cytoskeletal-nuclear crosslinkers. Actin filaments are connected to microtubules through actin-crosslinking factor 7 and to intermediate filaments through plectin-1. Plectin-1 can directly bind to nesprin-3 on the outer nuclear membrane. Nesprin-1 and nesprin-2 connect actin to SUN proteins which cross the nuclear membrane. SUN proteins can bind lamins and other nuclear membrane proteins, which, in turn, can bind DNA and chromatin. Force propagation directly affect nuclear scaffold prestress and gene activation within milliseconds of local deformation

can be separated into A-type and B-type lamins (Lammerding 2011; Isermann and Lammerding 2013). Lamins expression, in particular of A-type lamins (in its isoforms A and C), provides mechanical support and structural stability to the nucleus (Lammerding et al. 2004, 2006). Furthermore, lamins physically connect the nucleus to the cytoskeleton. Therefore, forces can be transmitted from the surroundings to the nuclear interior enabling nuclear deformation (Wang et al. 2009; Dechat et al. 2009), changes in nuclear architecture and position (Maniotis and Chen 1997; Guilak 1995; Cusachs et al. 2008; Isermann and Lammerding 2013), transport of factors across the nuclear envelope (Dupont et al. 2011; Gupta et al. 2012; Schachter et al. 2012) and chromatin remodelling (Thomas et al. 1998; Iyer et al. 2012; Jerabek and Heermann 2014).

An overview of nuclear-cytoskeletal coupling is shown Fig. 3a, b: SUN proteins, crossing the inner and outer nuclear membrane, can interact with lamins, nuclear pore complexes, and other proteins on the nuclear side. Additionally, SUN complexes can bind to nesprins on the cytoplasmic side. Nesprins are both localized at the inner nuclear membrane, binding directly to lamin A, and at the outer nuclear membrane. Nesprin-1 and 2 contain N-terminal actin binding domains, while Nesprin-3 can bind intermediate filaments (Fig. 3b). The resulting complex, also known as LINC (LInker of Nucleus and Cytoskeleton), provides a physical connection between intermediate filaments, actin and the nuclear internal region through lamins (A-type lamin) (Dahl et al. 2008).

Recent findings in cell mechanics have highlighted a specific physical pathway for direct transmission of tension and therefore strain, from the extracellular environment to the nucleus (Kim et al. 2013a; Chambliss et al. 2013). This system, known as perinuclear cap or actin cap, has been proved to regulate nuclear shape (Khatau et al. 2009), 3D cell migration (Khatau et al. 2012) and to govern early mechanosensing and mechanotransduction (Chambliss et al. 2013). The perinuclear cap is composed of thick, parallel, and highly contractile actomyosin filament bundles which are functionally, molecularly, and topologically different from conventional actin stress fibres: conventional actin fibres are typically confined to the basal layer or cortex layer of the cell and are arranged in different directions. Moreover, these filaments are directly or indirectly connected to the plasma membrane. Conversely, the subset of actin cap fibres are typically highly organized and oriented with the long axis of the cell. The main distinctive feature concerns the tight connection to the apical nuclear surface through the LINC complex as shown in Fig. 4a, b (Khatau et al. 2009; Kim et al. 2013a).

Distortions in nucleo-cytoskeletal coupling have been observed to give rise to a variety of diseases, also called laminopathies. Mutations in lamins and/or LINC complex components affect stability, shape and mechanical properties of the nucleus. For example, cells, it has been observed an abnormal nuclear shape, a decrease in nuclear stiffness and an increasing in nuclear fragility (Lee et al. 2007; Mejat and Misteli 2010; Schreiber and Kennedy 2013). Conversely, in Hutchinson–Gilford progeria syndrome cell nuclei are less compliant due to the overexpression of lamin A (Dahl et al. 2006). Since nucleo-cytoskeletal coupling is also essential in cell migration, associated mutations might influence wound healing, inflammation, cancer metastasis, and development process (Luxton et al. 2011; Gundersen and Worman 2013; Luxton et al. 2010).

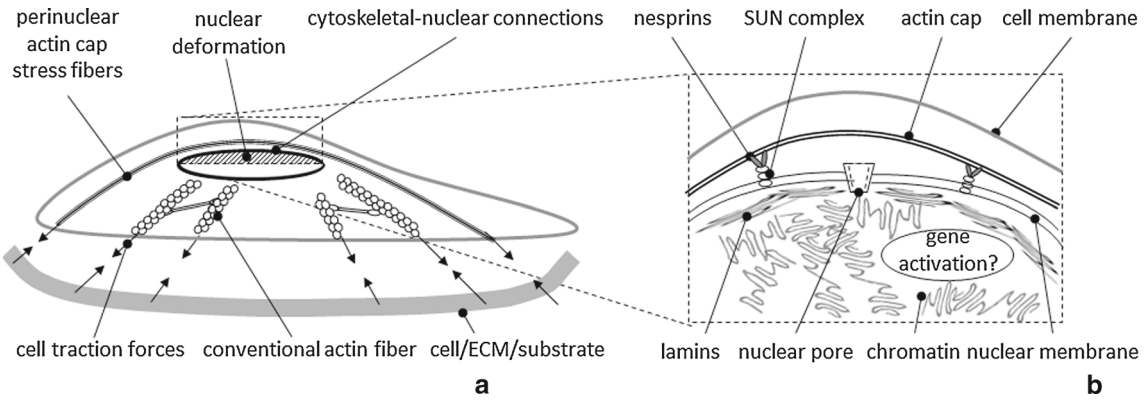

Fig. 4 Schematic of subcellular organization of the perinuclear actin cap and associated focal adhesions. **a** The actin cap is tightly connected to the apical surface of the nuclear envelope, not to the plasma membrane. **b** Physical connections between the actin cap and the nucleus are mediated by components of the linker of nucleoskeleton and cytoskeleton (LINC) complexes, including Nesprin-3 and Nesprin-2 giant, which are connected to the nuclear lamina through SUN proteins (Khatau et al. 2010)

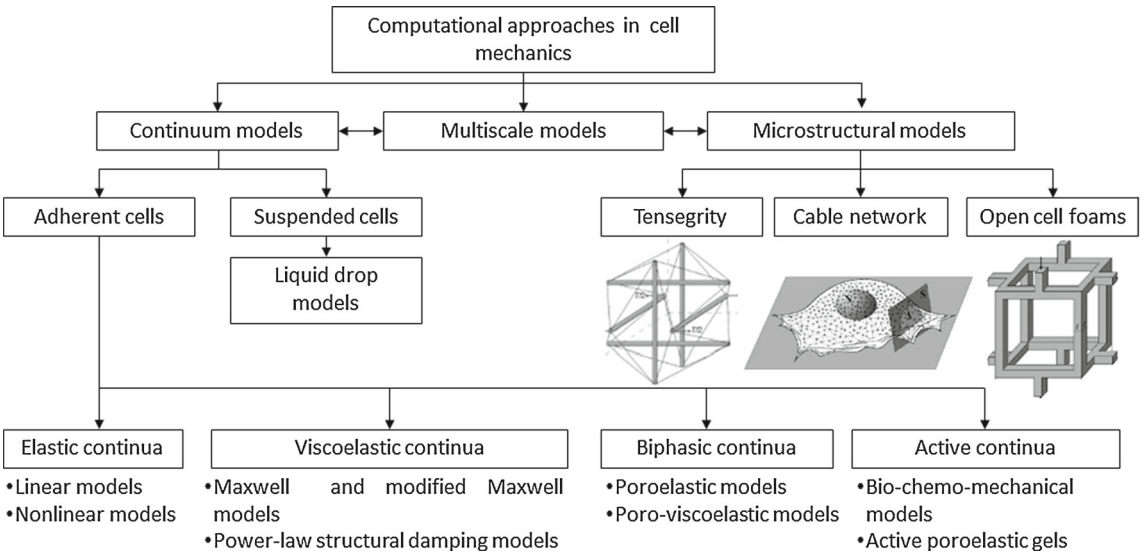

Fig. 5 Schematic representation of computational models in cell mechanics. Reprinted and adapted by permission from Macmillan Publishers Ltd: Nature Materials (Vaziri and Gopinath 2008)

3 Computational models

Besides experimental techniques, computational models have been used to describe cell and subcellular components. These models can not only complement and predict experimentally observed cell responses, but also provide a better understanding in behavioural aspects of living cells. The wide range of temporal and spatial scales involved in cellular processes, as well as the heterogeneous and active structure of cells, represent the two main issues of importance in the development of integrated computational models able to capture and simulate the response of cells and their components (Vaziri and Gopinath 2008).

The computational models in cell mechanics can be generally classified into two main categories (Fig. 5): microstructural models or continuum models (Lim et al. 2006; Vaziri and Gopinath 2008). These two categories will be described in the following.

3.1 Microstructural models

Microstructural or discrete models consider the overall cell behaviour as the result of the collective physico-chemical interactions between structures forming the cytoskeleton. In general, despite its complex and dynamic architecture, the cytoskeleton is modelled assuming relatively simple, idealized structural geometries, material isotropy, homogeneity, and elasticity. The basic idea is that the mechanisms by which idealized models develop mechanical stresses are embodied within the CSK. Therefore, the model should be

able to capture key features of the mechanical behaviour of the cell despite all those simplifications (Stamenovic and Ingber 2002). According to this, several approaches have been developed both for adherent and suspended cells. For anchorage-dependent cells, in which cell shape and mechanics are primarily governed by cytoskeleton, tensegrity-based models (Stamenovic et al. 1996; Ingber 1993, 2003b; Wang et al. 1993; Canadas et al. 2002, 2006), cable network models Coughlin and Stamenovic (2003) and cell-foam approximations (Satcher and Dewey 1996; Satcher et al. 1997) have been proposed. For non-adherent cells, such as erythrocytes, in which the contribution of the cell membrane and spectrin is central, the approach adopted consists in the development of spectrin-network models (Boey et al. 1998; Li et al. 2005).

3.1.1 Tensegrity models

The first model to propose that the elastic stress in the cytoskeleton is essential for the shape stability of the cytoskeleton is the tensegrity model (Ingber 1993). These models consist in reticulated mechanical structures that require tension for shape stability. In these structures, the greater the tension carried by the various elements in the network, the more stable the overall structure under load (Stamenovic and Wang 2000; Stamenovic and Ingber 2002). In this class of mechanical objects, the actively generated actomyosin tension in the cytoskeleton is balanced internally by cytoskeletal filaments such as microtubules, acting as molecular struts and bear compressional load, and externally, via the anchorage of the cytoskeleton to the extracellular matrix. Thus, the mechanical stability of tensegrity architectures depends on the arrangement of the various elements forming the network. This class of models was successful in explaining both static and dynamic cell behaviour (Sultan et al. 2004; Canadas et al. 2006). For example, consistent with experimental observations, the stiffness of the object increases linearly with the applied stress as predicted from a simple tensegrity model (Stamenovic and Ingber 2002; Stamenovic et al. 2003; Stamenovic 2005). These models have also been used to elucidate mechanotransduction pathways (Rodriguez et al. 2013; Ingber 2003a; McGarry and Prendergast 2004; De Santis et al. 2011). To model specific mechanical behaviour of the cell, more complex tensegrity models accounting for distinctive intracellular structures, having their own materials properties and functions, have been designed (McGarry et al. 2004; Baudriller et al. 2006; Bursa et al. 2012; Mehrbod and Mofrad 2011; Chen et al. 2010; Wang and Wolynes 2012; Kardas et al. 2013). However, since the intracellular architecture is modelled as a prescribed and idealized geometry, tensegrity structures have limitations in predicting cell behaviour, for example in bearing compression loads.

3.1.2 Cable network models

Cable network models, based on the assumption that actin filaments act as tensile elements, are structures composed of cables that cannot resist compression. Cables carry initial tension providing shape stability to the structure. The initial tension, provided either externally (e.g. by the ECM), internally (e.g., by compression-supporting elements of the CSK or by pressurized cytoplasm), or by a combination of the two, defines the prestress. The prestress can be defined as the sum of all tensile forces transmitted by cables across an arbitrary cross-sectional area of the cell per unit area before application of external loads (Stamenovic and Coughlin 1999; Coughlin and Stamenovic 2003; Stamenovic and Ingber 2002). Tensed cable models could mimic a number of behaviours observed in cells during mechanical tests and, in some cases, they also provided good quantitative correspondence to experimental data. The main limitation to these models consists into the applicability for adherent cells, in which actin filament reorientation is observed in 3-D in response to stress application (Maniotis and Chen 1997).

3.1.3 Open cell foams

Open cell foams are networks of interconnected struts. In these models, bending and twisting of actin filaments is assumed to be basic mode by which the actin network develops mechanical stress. This assumption was based on apparent similarity between the actin network in endothelial cells and microstructural networks of various natural and synthetic materials that are known to resist distortion by bending of their structural components (Satcher and Dewey 1996; Satcher et al. 1997). The open cell-foam model predicts strain hardening during compression, consistently with the observed strain hardening of cultured adherent cells exposed to local indentation (Radmacher 2002).

3.2 Continuum models

The continuum approach is generally applicable when the smallest length scale of interest is much larger than the length over which the structure and properties of the cell vary. Continuum-based models treat the cell as deformable materials with certain continuum material properties. An overview of the models used to interpret experimental measurements both for the whole cell and for isolated nuclei are summarized in Tables 2 and 3, respectively.

Modelling cell behaviour, including adhesion, motility and the response to applied mechanical stimuli, is challenging. Actually, cells are intrinsically heterogeneous materials; therefore, the choice of the constitutive parameters and constitutive equations is a critical issue. Different to classical engineering materials characterized by a passive

Table 2 Computational models used to interpret cell deformation measured with common experimental techniques

Experimental method	Material model	References
Micropipette aspiration	Linear elastic	Haider and Guilak (2002)
Micropipette aspiration	Nonlinear elastic	Zhou et al. (2005), Baaijens et al. (2005)
Micropipette aspiration	Maxwell viscoelastic	Haider and Guilak (2000)
Micropipette aspiration	Poroelastic	Baaijens et al. (2005)
Micropipette aspiration	Poroviscoelastic	Baaijens et al. (2005), Trickey et al. (2006)
AFM	Linear elastic	Costa and Yin (1999), Ohashi et al. (2002), Ng et al. (2007)
AFM	Nonlinear elastic	Costa and Yin (1999), McElfresh et al. (2002)
Cytoindentation	Linear elastic	Shin and Athanasiou (1999)
Cytoindentation	Poroelastic	Shin and Athanasiou (1999)
Optical tweezers	Nonlinear elastic	Dao et al. (2003), Mills et al. (2004), Suresh et al. (2005)
Optical tweezers	Modified Maxwell viscoelastic	Mills et al. (2004)
Shear flow	Linear elastic	Charras and Horton (2002), Cao et al. (2007), Ferko et al. (2007)
Shear flow	Nonlinear elastic	Jadhav et al. (2005)
Microplate compression	Nonlinear elastic	Caille et al. (2002), Slomka and Gefen (2010)
Microplate compression	Modified Maxwell viscoelastic	Leipzig and Athanasiou (2005), McGarry (2009)
Microarrays /substrate strain	Linear elastic	Nelson et al. (2005), Zeng and Li (2011a), Zeng and Li (2011b)
Microarrays /substrate strain	Modified Maxwell viscoelastic	McGarry et al. (2005), Milner et al. (2012), De Santis et al. (2011)
Microarrays /substrate strain	Bio-chemo-mechanical	Deshpande et al. (2006, 2007, 2008), Pathak et al. (2008), McGarry (2009), Wei et al. (2008), Ronan et al. (2012), Ronan et al. (2013), Qian et al. (2013)

The model of the cell in Caille et al. (2002), McGarry et al. (2005), Ferko et al. (2007), McGarry (2009), Slomka and Gefen (2010), De Santis et al. (2011), Ronan et al. (2012) includes a separate component representing the nucleus

Table 3 Computational models for deformation in isolated nucleus

Experimental method	Material model	References
Micropipette aspiration	Modified Maxwell viscoelastic	Vaziri and Mofrad (2007)
AFM	Maxwell viscoelastic	Vaziri et al. (2006)
Microplate compression	Nonlinear elastic	Caille et al. (2002)
Microplate compression	Maxwell viscoelastic	Vaziri et al. (2007b)

response to an external field variable, cells undergo remodelling in response to physical changes in its surroundings or as a result of an applied external load. Since cellular processes occur at different spatial and temporal scales, further degrees of complexity in cell modelling arise: for instance, the active nature affects the complexity in the choice of the initial and the reference configuration of the body. Therefore, other critical issues in cell modelling concern initial conditions, the boundary conditions to be imposed to the body and, finally, the loading conditions.

An ultimate critical issue is the choice of the numerical algorithm. The finite element method is the most common technique used to solve constitutive equations in biomechanics. Alternative techniques, such as the boundary element method, which requires discretization only on the domain boundary resulting in the computation time reduction, have also been used (Haider and Guilak 2002). Finite

element models have been used to study a wide range of cellular processes. The main advantage of this technique is that both material and geometrical nonlinearities can easily be incorporated. Furthermore, numerical schemes associated with this technique are well developed and efficient and have been implemented in commercially available software (Vaziri et al. 2007a).

The continuum-based computational models for the whole cell and relevant experimental techniques are summarized in Table 2. The material laws for modelling cell mechanics vary from simple linear elasticity to more complex models (Fig. 5).

Basic models refer to the elastic theory of continua. In this kind of approach, the cell is defined as a solid with homogeneous, elastic properties obeying or not the Hooke's law, in the linear and the nonlinear case, respectively. In general, elastic models are useful for determining cell material properties, but fail to capture certain cellular behaviours, such as motility, because they are greatly oversimplified when compared with living cells.

In viscoelastic material, cells are modelled as homogeneous elastic solid where the stress linearly (or nonlinearly) depends on strains and its time derivative. The typical constitutive equations refer to the Maxwell model. The material law has been firstly adopted to estimate mechanical properties of suspended cell via micropipette aspiration and, then, to predict cellular deformation and mechanical parameters in adherent cells (Theret et al. 1988; Sato et al. 1990; Shin and Athanasiou 1999; Haider and Guilak 2002; Trickey et al. 2000; Leipzig and Athanasiou 2005; Guilak et al. 2002). A recent application of the viscoelastic model has been developed by Milner et al., (Milner et al. 2012) to predict osteoblast response on an elastomeric surface subjected to cyclic strain. The model accounts for distinct subcellular components including the cytoskeleton and the nucleus (Mcgarry and McHugh 2008; McGarry 2009).

The biphasic approach has been developed to capture both the solid and the fluid-like behaviour of the cell. The cell is modelled as a combination of two phases: a solid phase (e.g. polymer content in the cytoplasm) and a liquid phase (e.g. the cytoplasm) that is able to diffuse through the solid phase (Lim et al. 2006). The biphasic model has been applied, for example in chondrocyte mechanics (Cao et al. 2009; Julkunen et al. 2009; Huang et al. 2003). The main limitations consist in to the formulation complexity.

Most of the material models described above (Fig. 5) assume a passive nature of the cell behaviour. As discussed in Sect. 2 and at the beginning of Sect. 3, living cells behave as an active material; therefore, new approaches that account for cytoskeletal contractility and for the structural role of the subcellular organelle, such as the nucleus, have been developed to study cell mechanics. In the following, we will describe the bio-chemo-mechanical model that accounts for the active nature of the cytoskeleton (e.g. contractility). Finally, we will present and discuss computational models accounting for nuclear mechanics.

3.2.1 Bio-chemo-mechanical model

The bio-chemo-mechanical model was first proposed by Deshpande et al. in (2006). This model describes the biochemistry of stress fibre remodelling with a biomechanical description of stress fibre contractility.

The biomechanical response of the stress fibres due to the biochemistry of stress fibres remodelling comprises three coupled phenomena:

- an activation signal that triggers the formation of stress fibres;
- a fibre formation rate dependent on the activation signal, coupled with a dissociation rate dependent on the tension;
- a contraction rate (contractility) for the stress fibre that depends on the tension of the network.

Simple phenomenological relations have been used to model these coupled phenomena for a single stress fibres, and thereafter, the relations have been generalized to two and three-dimensional cytoskeletal networks by homogenizing over all possible fibres orientations at each point in the cell. Additive decomposition of the stress is assumed. Therefore, the constitutive description of the cell includes both the active contribution from the stress fibres and the passive elastic (or hyperelastic) contribution from intracellular filaments (Deshpande et al. 2006, 2007). Simulations of the cell response have been carried out by solving the equations of force equilibrium as the cytoskeleton forms to create a contractile network.

Consistently with experiments (Chen et al. 2003; Wei et al. 2008; Wang et al. 1995; Kaunas et al. 2005; Tan et al. 2006; Yang et al. 2007), the model is able to predict the key behavioural aspects observed in cell mechanics, including the decrease in the forces generated by the cell with increasing substrate compliance, the cytoskeletal distribution and anisotropy with changes to cell shape, boundary conditions and loading conditions (Pathak et al. 2008; Deshpande et al. 2008; Wei et al. 2008), a high concentration of stress fibres in the proximity of the attachment points and, finally, an increasing in stress fibre assembly at points of force application.

Since the bio-chemo-mechanical formulation is general, this model has been employed to one and two-dimensional cellular migration to investigate cell traction forces distribution (Han and Sniadecki 2011). Furthermore, by introducing equations accounting for focal adhesion, the model has been used to study the relationship between cytoskeletal contractile forces and focal adhesion dynamics (Deshpande et al. 2008). Finally, three-dimensional active constitutive formu-

lations of the bio-chemo-mechanical model have been developed. It has been reported that stress distributions in the cell cytoplasm and nucleus computed using the active formulation differ significantly from those computed using passive material models (Ronan et al. 2012; Dowling et al. 2013), confirming the importance of the active contribution to cell mechanics.

3.2.2 Computational models for nuclear mechanics

Increasing experimental evidences have shown the crucial role played by the nuclear-cytoskeletal connections in cell mechanosensing and mechanotransduction. Changes in extracellular environment induce cytoskeletal remodelling that, thanks to the tight connection between the nuclear envelope and stress fibres could lead nuclear deformation (Isermann and Lammerding 2013), which in turn induce local transport of chemical factors through nuclear membrane (Dupont et al. 2011; Gupta et al. 2012; Schachter et al. 2012), chromatin disassembly (Iyer et al. 2012) and gene activation (Jerabek and Heermann 2014). For example, nuclear stresses and nuclear stiffness have been reported to be significantly different between undifferentiated stem cells and specialized cells (Pajerowski et al. 2007).

Most of the computational models described above do not incorporate either the nucleus itself or the cytoskeletal network. Regarding discrete models, attempts to further predictions in physiological cell responses have been made. Complex tensegrity models accounting for cytoskeletal filaments, including microtubules and intermediate filaments, their specific material properties and (nonlinear) behaviour have been made (Baudriller et al. 2006; Chen et al. 2010; Mehrbod and Mofrad 2011; Wang and Wolynes 2012). Tensegrity structures completed with other cellular structure such as the plasma membrane, the cytoplasm and the nucleus, have been proposed (McGarry and Prendergast 2004; McGarry et al. 2004, 2005; De Santis et al. 2011; Bursa et al. 2012; Kardas et al. 2013). Such a "hybrid approach" enabled to capture behaviours observed in experiments, including the relationship between cell shape and the compliance of the underlying substrate and the whole cell response to external loads. Despite simplifications, including the linear homogenous elastic material for the nucleus, these studies highlighted the role of the nucleus in cell mechanics. For example, a viscoelastic formulation for the cell and the nucleus are needed for a complete characterization of cells under compression (McGarry 2009).

Regarding the continuum approach, most computational studies aiming to estimate cell material parameters, typically do not account for intracellular organelles. To overcome these simplification/limitations, several models have been developed to study nuclear deformation as a result of the mechanics of the cytoskeleton-nuclear pathway (Jean et al. 2004, 2005). In these works, the cell domain includes the major subcellular structures (nucleus, cytoskeleton, cytosol, cortical layer) that are treated as incompressible neo-Hookean materials. The model is based on cell detachment experiments. To model nuclear deformation, the pretension of the cytoskeletal fibres associated with nucleus is modelled as a pattern of reactive forces to the nucleus. Results have shown that stresses experienced by the nucleus have an order of magnitude that can be significant for the function of DNA and chromatin (Jean et al. 2005). Other models accounting for the nucleus and nuclear-cytoskeletal connections, modelled as a network of cables, have been proposed to study cell response to micromanipulation (Paul et al. 2008) and substrate dynamic stretching (Milner et al. 2012).

As previously discussed, contractility and the effects on the nucleus, both in terms of shape and functions, represent an emerging field of study. In the continuum approach, cell contraction has been modelled as a prescribed thermal displacement (Nelson et al. 2005; Banerjee and Marchetti 2013). The main limitation of these models is that the biochemistry of stress fibres formation, and dissociation is neglected (Deshpande et al. 2006). To overcome this limitation, a bio-chemo- mechanical model has been proposed (Sect. 3.2.1). Within this framework, while first studies have been carried out on simple idealized cell geometries, recently it has been reported a three-dimensional constitutive formulations accounting for a more realistic cell structure and behaviour (Ronan et al. 2012; Dowling et al. 2013). Indeed, modelling a cell as an active material has led to significant results in comparison with the ones predicted by a passive formulation of cell behaviour. Therefore, predicted nuclear strains and stresses can greatly improve the understanding of experimental observations in cell and nuclear mechanics.

4 Discussion

A better comprehension of the mechanism by which chemical and physical signals are integrated into the cell nucleus to induce a specific cell response represents a great challenge. Our current understanding of mechanotransduction mechanisms to the cell nucleus to induce differential gene regulation is still poorly understood. Great efforts have been made within this field, both in terms of the development of advanced culture platforms, and computational models to interpret experimental observations.

In this work, we provide a review of the computational models used in cell mechanics. Traditionally, the proposed models are grouped in two categories: microstructural models and continuum models. The microstructural approach assumes the cytoskeleton as a critical component in cell morphology and function. These models, consisting in an idealized geometry and simple constitutive equations, do

not represent the complex intracellular molecular networks. Microstructural models, including more complex tensegrity structures (Baudriller et al. 2006; Chen et al. 2010; Mehrbod and Mofrad 2011; Wang and Wolynes 2012) completed with other cellular components (McGarry and Prendergast 2004; McGarry et al. 2004, 2005; De Santis et al. 2011; Bursa et al. 2012; Kardas et al. 2013) have several limitations in capturing cell behaviour due to an idealized and simplistic representation of cytoskeletal structure when compared to living cells. As a consequence, the initial configuration and the relevant initial conditions and boundary conditions are prescribed by the user; therefore, this kind of approach has a limited capability in predicting cell mechanical behaviour.

In continuum-based approach, the cell is often modelled as a continuum that contains an elastic cortex that surrounds a viscous or viscoelastic fluid; a more complex variation includes an elastic nucleus within a viscous cytoplasm. These models provide results fitting experimental data measured in cells under specific experimental conditions, but in general, they cannot predict from mechanistic principles how these properties alter cell function (Vaziri and Gopinath 2008). Continuum models also assume that the physico-chemical interactions between structures forming the cytoskeleton are infinitesimally small relative to the size of the cell. Thus, they do not provide insights into how distinct molecular structures contribute to cell mechanics. This is a critical limitation because it is not possible to explain how mechanical forces regulate cell function without linking mechanics to microstructure and molecular biochemistry.

To overcome these simplifications/limitations, several models accounting for the heterogeneous composition of cells have been developed (Jean et al. 2004, 2005; Paul et al. 2008; Milner et al. 2012). Although interesting results reported, this kind of approach has a limited predictive capability due to the prescribed (e.g. user-defined) network between the cytoskeletal filaments and the nucleus. Actually, cells are intrinsically active materials; therefore, the choice of the initial and the reference configuration of the body, the initial conditions, the boundary conditions and loading conditions are critical issues. Moreover, cellular processes occur at different spatial and temporal scales. Therefore, from a modelling perspective, the development of integrated computational models for cell mechanics and mechanobiology has several degrees of complexity.

An interesting strategy within this context consists in the bio-chemo-mechanical model. This framework has been demonstrated to accurately simulate the response of cells to a wide variety of different boundary conditions and applied loadings. Since the bio-chemo-mechanical model accounts for stress fibres dynamics in all the cytoplasm, it is also entirely predictive, which means that with initial conditions regarding stress fibre, distribution and orientation are not required (Rodriguez et al. 2013).

Further strategies in computational cell mechanics will consist in developing multiscale models that can predict the distribution of stresses/strains in a certain range of scales and relate that to the subcellular components and cytoskeleton (downscaling) or to the tissue level (upscaling). Another challenge in this field is to properly couple macroscale dynamics (e.g. at the tissue level) and cell kinetics and mechanics. Finally, multiphysics models able to predict the interplay between whole cell deformation, nuclear deformation and mass transport through the nuclear envelope and pores (Dupont et al. 2011; Gupta et al. 2012; Schachter et al. 2012) are needed to gain more insights in mechanotransduction process.

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