Computational Models of Eukaryotic Cells in Health and Disease

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Contents

Abstract

Eukaryotic cells play a crucial role in many processes in health and disease in the human body. The importance of an understanding of cell behavior from the mechanical point of view triggered the development of many computational models. In this chapter, we present recent progress in this field. We focus primarily on computational models of suspended in flow and adherent to substrate eukaryotic cells.

1 Introduction

Cells are building blocks of living beings, and there is a wide variety of cell types each tailored for a specific purpose in the body. Cells composed of the cell membrane, complex 3D cytoskeletal network, and various organelles, including the nucleus, are called eukaryotic cells. These cells play roles in many processes of a mechanical nature in health and disease, e.g., cell migration, wound healing, and

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W. Andreoni, S. Yip (eds.), *Handbook of Materials Modeling*,
https://doi.org/10.1007/978-3-319-50257-1_68-1

cancer metastasis. The mechanics of the eukaryotic cell as a whole is determined by the properties of its subcellular components.

The plasma membrane separates the body of the cell from the extracellular environment. It is composed of different lipids and cholesterol with the inclusion of various embedded proteins. The volume inside the cell membrane is filled with the protein-rich fluid, called cytosol. Although the plasma membrane has a mechanism for the fluid and solute exchange with the surrounding, it is mostly impermeable, which leads to volume conservation of a cell. Incompressibility of the lipid layers results in plasma membrane surface area conservation and bending resistance.

The space between the plasma membrane and cell organelles is occupied, besides of cytosol, by a complex filament network called cytoskeleton. It is a dynamic structure, which maintains the integrity of the cell. In addition, it plays an essential role in many cell processes: migration, adhesion, division, stress resistance, and mechanotransduction. The cytoskeleton is composed of interconnected filaments of three main types: actin filaments, microtubules, and intermediate filaments (Suresh 2007). Actin filaments are semiflexible biopolymers, which exhibit the highest resistance to deformations until some critical stress value. If the stress is higher than this value, they are fluidized. Intermediate filaments can resist moderate deformations, and they do not fluidized under high values of shear stress, hence, providing structural integrity to the cell. Microtubules do not contribute significantly to the cell stiffness. Being interconnected with filaments of other types, they stabilize the cytoskeleton. They also might contribute to the compression resistance under high pressure (Brangwynne et al. 2006).

The nucleus is the largest eukaryotic organelle, and it is stiffer than the cell itself (Guilak et al. 2000; Friedl et al. 2011). Mechanics-wise, the most important components of the nucleus are nucleus envelope and chromatin network. The nucleus envelope is composed of two phospholipid bilayers with attached lamin meshwork. These bilayers act as a barrier between cytoplasm and nucleus internal structure (Lammerding and Jan 2014). In comparison to the cell membrane, nucleus membrane exposes weaker area and volume constraints allowing fluid to get in and out (Rowat et al. 2006). The nuclear lamina, which is often considered to be the main contributor to the nucleus stiffness (Gerlitz and Bustin 2012), is 2D meshwork attached to the inner bilayer. According to a recent study, lamina levels control nuclear strain stiffening at large extensions (Stephens et al. 2017). Contrary, chromatin network, which occupies the nucleus volume, governs response to small deformations (Stephens et al. 2017).

Mechanical properties of eukaryotic cells depend on the cell type as well as the state of the cell. Cells can be in suspended state, when they are traveling in the blood stream, or in the adherent state, when they are attached to the extracellular matrix. Another source of alternations in cell structure and mechanics is various diseases (Nematbakhsh and Lim 2015), which might alter the properties of any of the cell components. One example is softening of the cell membrane by HIV before invasion into the cell by the insertion of fusion peptide (Agrawal et al. 2016). Due to the dominant role of cytoskeleton in the cell mechanics, it is not surprising that the progression of numerous diseases leads to the cytoskeleton properties alteration.

The most prominent example is the cytoskeleton structure degradation and density decrease of epithelial tumor cells (Suresh 2007). In several cancers, the higher is the metastatic potential of a cell, the lower is the stiffness of the cytoskeleton and, hence, the cell as a whole (Nematbakhsh et al. 2017; Cross et al. 2007; Liu et al. 2015b). Other diseases which change the cytoskeleton mechanics are neurodegeneration, liver cirrhosis, pulmonary fibrosis, and blistering skin diseases (Ramaekers and Bosman 2004). Some tissue-specific disorders are linked to the alteration of the mechanical properties of the nucleus due to the mutations in genes encoding lamins and associated nuclear envelope proteins: Emery-Dreifuss muscular dystrophy, dilated cardiomyopathy, familial partial lipodystrophy, as well as over 20 other diseases (Rowat et al. 2006; Rynearson and Sussman 2011).

The great variety of cell types as well as diseases altering cell mechanics led to the development of numerous experimental techniques for investigating cell mechanical properties. These techniques can be split into two groups. The methods in the first group, such as atomic force microscopy (AFM) and micropipette aspiration, operate with individual cells to estimate their viscoelastic properties. A classical review of methods of this type can be found elsewhere (Suresh 2007). The second group of experimental techniques with higher throughput includes microfluidic experiments. There is a great variety of microfluidic devices and principles they employ to operate. A good review of the current status of the microfluidics with application to cells can be found elsewhere (Chaudhuri et al. 2016).

2 Modeling Approaches

Despite a significant progress in the experimental techniques in cell biophysics, the computational modeling remains an irreplaceable complementing tool. Firstly, it improves our understanding of the subcellular component mechanics, which is valuable for many applications. In particular, it can influence the drug discovery by offering a rich target space for possible alteration of cell properties. Secondly, numerical simulations allow to predict cell behavior in a complex environment, and thus, their use may improve and accelerate the design of various microfluidic devices (Rossinelli et al. 2015). In particular, numerical simulations can help in the acquisition of information related to fluid microrheology, including often unexpected flow properties in complex domains resulting in various cell phenomena (merging, lysis, adhesion, damage, signaling) (Nan et al. 2014; Yung et al. 2009; Pinho et al. 2013).

Recent advances in computational methods, as well as hardware development, catalyzed the creation of a number of eukaryotic cell models in the last 5 years. The variety of models can be explained by the complexity of the problem. The first source of this complexity is the diversity of the cell types along with processes they are involved in. The second one is the lack of understanding of the role that each cell component plays during mechanical deformations. Finally, there is no full understanding of the active cell response. These factors explain the fact that the

current state-of-the-art models are phenomenological, and each one is tailored to describe a very particular cell line and related processes.

The computational methods employed in eukaryotic cell modeling can be split into three groups: mesh-based, particle-based, and combined. Among mesh-based methods, the most popular one is finite element method (FEM). Typically, models exploiting FEM describe only cell mechanics without considering surrounding fluid. Dissipative particle dynamics (DPD) is a particle-based method, which is also used in many models. DPD allows parametrizing the fluid and fluid-structure interactions, while the cell itself is modeled with the help of various many-body potentials. Among combined methods, a well-developed approach is to model the fluid with the Lattice-Boltzmann (LB) method, cells with finite element method (FE), and cell-fluid interactions using immersed boundary (IB) method. We will call this approach LB/IB.

The focus of this review is mechanical eukaryotic cell models. We do not consider cell models used for the tissue modeling; a review of these models can be found elsewhere (Fletcher et al. 2017). The models for cells without nucleus such as red blood cells (RBCs) are also beyond the scope of this review. Overview of recent developments in this field can be found in other chapters of this book. Further, we split the existing eukaryotic cell models into two groups. The first group contains models for the suspended cells which are usually employed to study fluid flow problems. The second group is dedicated to the modeling of the cells in the adherent state.

2.1 Suspended Cell Models

Suspended cells can be of different origin: most of them are blood cells (RBCs, platelets, white blood cells (WBCs)) and mesenchymal stem cells; others are cells of epithelial origin traveling with the blood stream such as circulating tumor cells (CTCs). CTCs are emitted by the primary cancer tumor and can travel long distances to create secondary tumors. Both WBCs and CTCs are bigger and stiffer than RBCs. This leads to the so-called margination, which is a process whereby these cells are displaced to the vessel wall (Nematbakhsh and Lim 2015). An important problem is the detection of CTCs in the blood sample, and numerous microfluidic devices have been developed for this purpose. Devices employing margination, cell rolling, hydrodynamics-induced cell sorting are all studied using models considered in this section.

Perhaps one of the simplest approaches to modeling of the eukaryotic cell is to ignore its internal structure and to apply one of the existing RBC models with altered parameters. The reasoning is that RBC and eukaryotic cell membranes are similar in many aspects and there are several well-established and validated RBC models (Ye et al. 2016). These models usually take into account volume and area conservation, bending resistance, and membrane viscoelastic forces. Such models, coupled with various fluid solvers, capture the effects of cell size and shape and, hence, are often used in simulations of microfluidic devices employing deterministic

lateral displacement principle or cell-free layer formation. The main strength of these models is low computational cost and resolved hydrodynamic interactions in a flow.

In a series of papers, Takeishi et al. modeled the margination of WBCs and CTCs and, in a later work, adhesion of CTCs to vessel walls (Takeishi et al. 2014, 2015) (see Fig. 1a). This development allowed the authors to numerically investigate the effect of the cell size on the flow mode and cell velocity, as well as to identify similarities and differences between WBCs and CTCs. Further, it was found that the bullet motion enables firm adhesion of a cell to the capillary wall (Takeishi et al. 2016). These results suggest that even under the interaction between proteins responsible for WBC rolling, a cell can show firm adhesion in a small capillary. Modeling-wise, Takeishi et al. employed LB/IB method and empty shell cell representation. For validation of the model, simulation results for the deformation of a spherical cell in shear flow were compared with previously published works.

Fedosov et al. also studied WBCs margination, but they, additionally, took into account the effect of RBCs (Fedosov and Gompper 2014) (see Fig. 1b). It was found that WBC margination occurs mainly within a region of intermediate hematocrits and for relatively low flow rates. Moreover, simulations showed that RBC aggregation slightly enhances WBC margination, particularly at the high hematocrit values. DPD method was used to describe fluid and cell particles.

Later, Rossinelli et al. employed a similar DPD-based empty shell model to describe both WBCs and CTCs in two microfluidic devices (Rossinelli et al. 2015). Snapshot of cells squeezing between obstacles mimicking the geometry of the microfluidic devices is shown in Fig. 1c. They demonstrated the applicability of this model for the predictive studies of the performance of microfluidic devices. In particular, the simulation results reproduced the experimentally observed effect of deterministic lateral displacement of bigger cells for the whole blood passing through the array of cylindrical obstacles.

The work by Xiao et al. is dedicated to the mutual effect of rolling CTC in the capillary on the blood flow dynamics (Xiao and Fu 2016a) (see Fig. 1d). By the help of computational modeling of suspended CTC and RBCs, it was demonstrated that, in the microvessel of 15 μm diameter, the CTC has an increased probability of adhesion due to a growing wall-directed force. However, with the increase in microvessel size, an enhanced lift force at higher hematocrit detaches the adherent CTC quickly. An increased blood flow resistance in the presence of CTC was also found. Moreover, the significant deformation induced by high flow rate and the presence of aggregation promote the adhesion of CTC. In another work, the same group of authors applied a very similar cell model to investigate an individual cell passing through a narrow slit (Xiao and Fu 2016b). Specifically, they studied the effect of cell size, nucleus, and cell membrane shape on the transmigration through a slit. This model represents the cell and nucleus as an empty shell.

Zhang et al. studied CTC and WBC passing through micro-filtering channels of different shapes (Zhang et al. 2014). In particular, they considered channels with circular, rectangular, and triangular cross sections and inspected pressure signatures

for CTCs and WBCs passing through this channel. They demonstrated that circular channels feature the highest critical pressure and, thus, are more suitable for cell-separation microfluidic devices (see Fig. 1e). The developed model exploits volume of fluid method, and no subcellular components were explicitly modeled.

Finally, in recent combined experimental and modeling work, Lykov et al. investigated cell mechanics in micropipette aspiration and microfluidic experiments (Lykov et al. 2017) (see Fig. 1f). The mesoscale particle-based model of the eukaryotic cell consisted of a membrane, cytoskeleton, and nucleus. The fluid was discretized using DPD method. The calibration of the model was done using micropipette aspiration experimental data. The model was validated using microfluidic experiments. Authors studied the role of subcellular components and observed that cell cytoskeleton filament density and cross-link concentration could both significantly affect cell resistance to stress. Other results include quantification of the nucleus components contribution and effect of cell viscosity during cell traversal in the microfluidic devices.

Although considered models of suspended cells use different discretization methods, most of them employ a simple empty shell cell representation. This approach can be applied to study flow phenomena in which cell size and shape play a key role. To study a broader class of phenomena, which include severe flow-induced cell deformations, internal structure disruption, and effect of changes in the cytoskeleton due to drug treatment, models that explicitly describe internal cell components are necessary. The drawback of such models is that they require more complicated parametrization procedure. Increase in computational cost, however, is modest, since it is usually dominated by the cost of flow discretization.

2.2 Adherent Cell Models

The interest in studying processes, which imply significant deformation of the adherent cell and, thus, involve mechanical response of the internal cell components, led to the development of approaches which explicitly model the nucleus and cytoskeleton. Typically, these models use the same hollow sphere model for the cell membrane and, sometimes, the nucleus. The cytoskeleton is modeled by various approaches. These models opened the route to the numerical investigation of such processes as needle microinjection, AFM indentation, cell migration, and deformation in microfluidic devices.

Kardas et al. proposed a computational approach to model the structure of bone cells (Kardas et al. 2013). The model takes into account integrins, nucleus, centrosome, and cytoskeletal proteins (see Fig. 2a). It was shown that the load acting on the nucleus is rising with increasing deformation applied to the integrins. The numerical simulations demonstrated that the nucleus is more affected by stress if the distributions of intermediate filaments and microtubules are random than if they are regular. Computational-wise, FEM was employed to discretize governing equations.

Ujihara et al. presented a cell model to study tensile and compression tests (Ujihara et al. 2010, 2012). The model incorporates a cell membrane, a nuclear envelope,

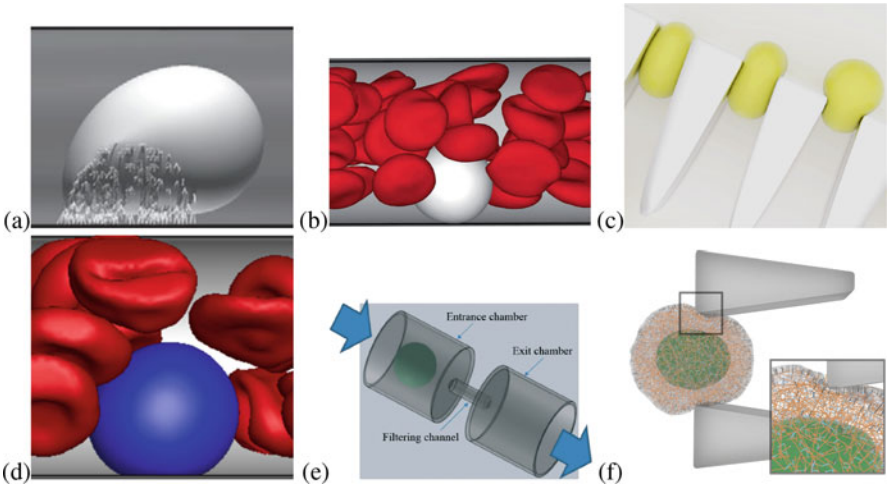

Fig. 1 (**a**) Simulation of a cell adherent to the tube wall (Takeishi et al. 2016). (**b**) Simulation demonstrating WBC margination in the RBC flow (Fedosov and Gompper 2014). (**c**) Cell models squeezing between obstacles in microfluidic device (Rossinelli et al. 2015). (**d**) Snapshot from the simulation of the cell adherent to the wall (blue) together with RBCs (Xiao and Fu 2016a). (**e**) Sketch of a cell passing through a micro-filtering circular channel (Zhang et al. 2014). (**f**) Multicomponent model of eukaryotic cell passing between two constrictions of microfluidic device (Lykov et al. 2017). Nucleus shown in green, cytoskeleton filaments in orange

and actin filaments (see Fig. 2b). During the tensile test, it was observed that the total elastic energy of the model is dominated by actin fibers contribution. The compression test revealed that the alignment of bundles of actin filaments significantly affects cell stiffness. In addition, the passive reorientation of actin filament bundles perpendicular to the direction of compression induced an increase in the resistance to the elongation of a cell and, thereby, increased the cell stiffness. Particle-based model was used in simulations utilizing minimum energy concept. It was validated by comparing load-deformation curve with experimental data.

Dowling et al. presented a study of the role of the active remodeling and contractility of the actin cytoskeleton in the response of chondrocytes (cartilage cells) to shear (Dowling et al. 2012) (see Fig. 2c). The key feature of the model is that it incorporates both passive viscoelastic component and active, describing cytoskeleton remodeling. By the help of numerical simulations, the authors showed that a purely passive cell model is incapable of predicting the response of normal chondrocytes to the stress, while adding the cytoskeleton remodeling gives results close to the in vitro study. Interestingly, the passive model can predict drug-treated cells with the disrupted cytoskeleton, which might be considered as evidence that actin cytoskeletal network is the main contributor to the stress resistance during discussed processes. In another paper, where a similar model was used, authors predicted the increased compressive resistance of spread cells compared with round cells (Ronan et al. 2012). The nucleus and membrane were represented in the

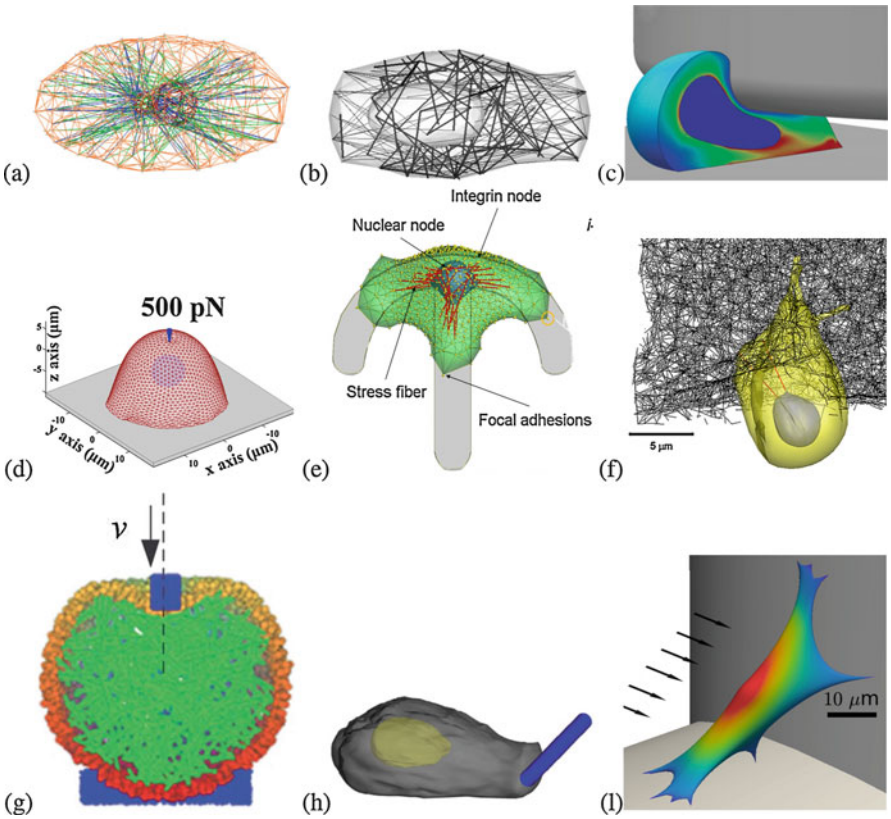

Fig. 2 (**a**) Cell model taking into account integrins, nucleus, centrosome, and cytoskeletal protein (Kardas et al. 2013). (**b**) Snapshot from simulation of the tensile test (Ujihara et al. 2010). (**c**) Simulation of the probe indentation process; color map depicts average stress fiber activation levels (Dowling et al. 2012). (**d**) Modeling of the AFM nanoindentation process (Fang and Lai 2016). (**e**) Integrated cell migration model consisting of the cytoskeleton, the nucleus, and cytoskeleton components (Kim et al. 2013). (**f**) Simulated cell invasion into ECM fiber network model (Kim et al. 2015). (**g**) Simulated cell microinjection: green particles represent cytoskeleton, blue rectangular is needle tip, and yellow-orange particles represent cell membrane. (**h**) Deformation of the plasma and nuclear membranes induced by micropipette pulling (Zeng et al. 2012). (**d**) Snapshot from AFM experiment simulation for adherent cell (Fang and Lai 2016). (**i**) Snapshot from simulation of the cell attached to the walls of the bioreactor; the flow direction is shown with arrows; the shear stress distribution is depicted with color (Guyot et al. 2016)

model as a passive hyperelastic material, while ODE described the cytoskeleton remodeling. The equations were discretized with the help of FEM.

Fang and Lai studied changes in the cell mechanics as cell shifts from suspended to the adherent state (Fang and Lai 2016). The model consists of cell membrane, nucleus envelope, and three internal networks representing microtubules, F-actin, and intermediate filaments. In addition, it takes into account the movement of

adhesion molecules which allows simulating cell spreading. In order to estimate the cell model elastic modulus, simulation of AFM experiment was employed (see Fig. 2d). The force-indentation relationship was used to determine the mechanical changes in cells during state shift. The explicit modeling of the subcellular components allowed to investigate the impact of different cell components on the resistance to the external stress and to examine the effect of nucleus presence on the AFM results. The model was validated by comparing the AFM simulation results with the experimental data.

Kim et al. developed a model to predict cell migration behavior on 2D and 3D curved surfaces (Kim et al. 2012). The model takes into account focal adhesion dynamics, actin motor activity, as well as cytoskeleton remodeling and nucleus (see Fig. 2e). The simulations revealed that cell migration speed depends on the cross-sectional area of the microfluidic channel. The relationship between migration speed and the channel width agreed with the experimental data. This model was also applied to study cell migration on 2D micropatterned geometries (Kim et al. 2013). The further development of the model allowed prediction of cell invasion into a 3D extracellular matrix (ECM) in response to different extracellular biochemical cues (Kim et al. 2015) (see Fig. 2f). The new model takes into account filopodia penetration dynamics. The average filopodia speed was predicted, and cell membrane advance velocity agreed with experiments of 3D HUVEC migration for diverse ECMs with different pore sizes and stiffness.

By the help of numerical modeling, Liu et al. predicted the cell damage induced by the needle during the microinjection procedure (Liu et al. 2015a). In particular, authors quantified the effects of the size, shape of the microinjector tip, and injection velocity on cell damage. The proposed model is based on DPD method. It explicitly describes cell membrane as well as the cytoskeleton and motor activity. To validate the model, authors measured the mechanical properties of the model using the particle-tracking microrheology. The cell model showed power law behavior in terms of mean square displacement and lag time. The mechanical moduli obtained from the simulations were in agreement with the experimental data.

Zeng et al. applied cell model to study the role of the actin cytoskeleton network in mechanotransduction and nucleus deformation (Zeng et al. 2012). In the experiment simulated in this work, a micropipette is pushed into the cytoplasm of an endothelial cell and then pulled away at a constant rate. Authors showed that the stress propagation through the random cytoskeletal network could be a mechanism to effect nucleus deformation, without invoking any biochemical signaling activity. It was reported that nucleus strain varies in a sigmoidal manner with actin filament concentration, while there exists an optimal concentration of actin-binding proteins that maximize nucleus displacement. In addition, a theoretical analysis for these nonlinearities in terms of the connectivity of the random cytoskeletal network was provided. Particle-based model was employed, which explicitly describes cell membrane, nucleus envelope, and cytoskeletal actin network. The simulation results were validated using experimental data.

Guyot et al. modeled an adherent cell in the bioreactor subjected to the shear stress due to the fluid flow (Guyot et al. 2016). The simulations were used to estimate

shear stress experienced by cells as a function of the bioreactor inlet flow velocity. The authors showed that the shear stress values predicted by their model are different from shear stress obtained with the help of empty scaffolds model, which is often used as a reference. The proposed model can be applied to optimize the bioreactor geometry and flow conditions as well as to provide insight into the cell deformation during these processes. With the help of LB/IB method, the cell was simulated as an empty shell with the elastic nucleus inside. To estimate elastic properties of the cell, micropipette aspiration experiments were used.

The most important common feature of the models considered in this section is that they take into account, besides of nucleus envelope and cell membrane, mechanics of the cytoskeleton. Due to that, such models can describe more accurately changes in the cell during different mechanical tests as well as cytoskeleton-related processes. Additionally, these models give an insight into the impact of subcellular components during particular experiments.

3 Conclusion

The range of applications of eukaryotic cell models is expanding rapidly. Suspended cell models are now widely used in studies of behavior and deformations of cells in various microfluidic devices and blood circulation. In turn, adherent cell models provide an insight into cell mechanics when cells are subjected to mechanical stress or during migration in the extracellular matrix. Majority of suspended cell modeling approaches employ empty shell representation of the cell, which narrows the applicability of these models to problems with moderate cell deformations. The drawback of the existing adherent cell models is their specialization on a very particular phenomenon for a specific cell type.

All of the models considered in this review follow the top-down or phenomenological approach (Kollmannsberger and Fabry 2011). The mechanical properties of the cell model components are not obtained by considering the properties of the material at the microscopic or molecular level. Instead, the choice of model and parametrization for the subcellular components is based on general principles and macroscopic properties of the cell. An alternative bottom-up or reductionist method assumes gradual development of the model starting from the very accurate models of all constituents. At the very moment, there is a lack of experimental and theoretical knowledge to follow the latter approach. Future developments will allow construction of eukaryotic cell models by rigorously linking mechanical behavior of the entire cell with the properties of its molecular constituents, connecting cell chemistry and mechanobiology.

Acknowledgements This work was supported by Swiss National Science Foundation grant 205321_173020.

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