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Authors
Shams, Hengameh
Soheilypour, Mohammad
Peyro, Mohaddeseh
et al.

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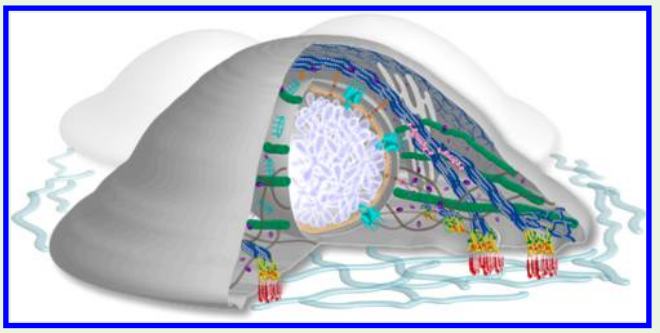
Looking "Under the Hood" of Cellular Mechanotransduction with Computational Tools: A Systems Biomechanics Approach across Multiple Scales

Hengameh Shams, Mohammad Soheilypour, Mohaddeseh Peyro, Ruhollah Moussavi-Baygi, and Mohammad R. K. Mofrad*

Molecular Cell Biomechanics Laboratory, Departments of Bioengineering and Mechanical Engineering, University of California, Berkeley, California 94720-1762, United States

ABSTRACT: Signal modulation has been developed in living cells throughout evolution to promote utilizing the same machinery for multiple cellular functions. Chemical and mechanical modules of signal transmission and transduction are interconnected and necessary for organ development and growth. However, due to the high complexity of the intercommunication of physical intracellular connections with biochemical pathways, there are many missing details in our overall understanding of mechanotransduction processes, i.e., the process by which mechanical signals are converted to biochemical cascades. Cell-matrix adhesions are mechanically coupled to the nucleus through the cytoskeleton. This modulated and tightly integrated network mediates the transmission of mechanochemical signals from the extracellular matrix to the nucleus. Various experimental and computational techniques have been utilized to understand the basic mechanisms of mechanotransduction, yet many aspects have remained elusive. Recently, *in silico* experiments have made important contributions to the field of mechanobiology. Herein, computational modeling efforts devoted to understanding integrin-mediated mechanotransduction pathways are reviewed, and an outlook is presented for future directions toward using suitable computational approaches and developing novel techniques for addressing important questions in the field of mechanotransduction.



KEYWORDS: *in silico, integrin-mediated mechanotransduction, focal adhesions, nuclear pore complex, LINC complex, cytoskeleton*

1. INTRODUCTION

From the molecular level to the organism scale, mechanics plays a central role in biological processes.[1] Larger scale behaviors are often governed by finer spatiotemporal interactions. For example, shear stress is frequently applied along veins and arteries causing atherosclerotic plaques, cytoskeletal reorganization of endothelial cells, and alter their cell-cell and focal adhesion (FA) contacts.[2,3] Cellular response to mechanical cues result in matrix degradation and remodeling, which creates a feedback loop leading to an alteration of the behavior of the same cell or causing a gradual change in the neighboring cell populations.[4] Mechanotransduction is central to these cellular phenomena and is referred to as the conversion of mechanical signals to biochemical pathways inside the cells.

Various mechanotransduction pathways have been identified that may be triggered via different mechanisms.[5−7] Mechanosensing in the cellular scale is regulated by molecular interactions that give rise to both biomechanical and biochemical events in mechanotransduction pathways. The mission of modern mechanobiology is to reveal mechanical implications of dynamic molecular interactions underlying a cellular phenotype, even though the large-scale behavior of the cell may seem to remain intact. This review is focused on four major cellular components that are integrated and modulated to efficiently transmit signals between the extracellular matrix (ECM) and the nucleus: (1) focal adhesion assemblies directly attach to the cytoskeleton;[8] (2) the cytoskeleton comprising of actin, microtubules, and intermediate filaments transfer mechanical signals from FA toward the nucleus; (3) LINC complexes (linkers of the nucleus and the cytsokeleton) on the nuclear envelope allow for direct transmission of forces from the cytoskeleton to the nucleoskeleton; and (4) the nuclear pore complexes (NPCs), the biochemical gateways residing on the nuclear envelope, control the nucleocytoplasmic transport of RNAs and proteins. All these subcellular components play significant roles in regulating mechanotransduction pathways; however, our understanding of their basic mechanisms and cross-talks remains incomplete (Figure 1).

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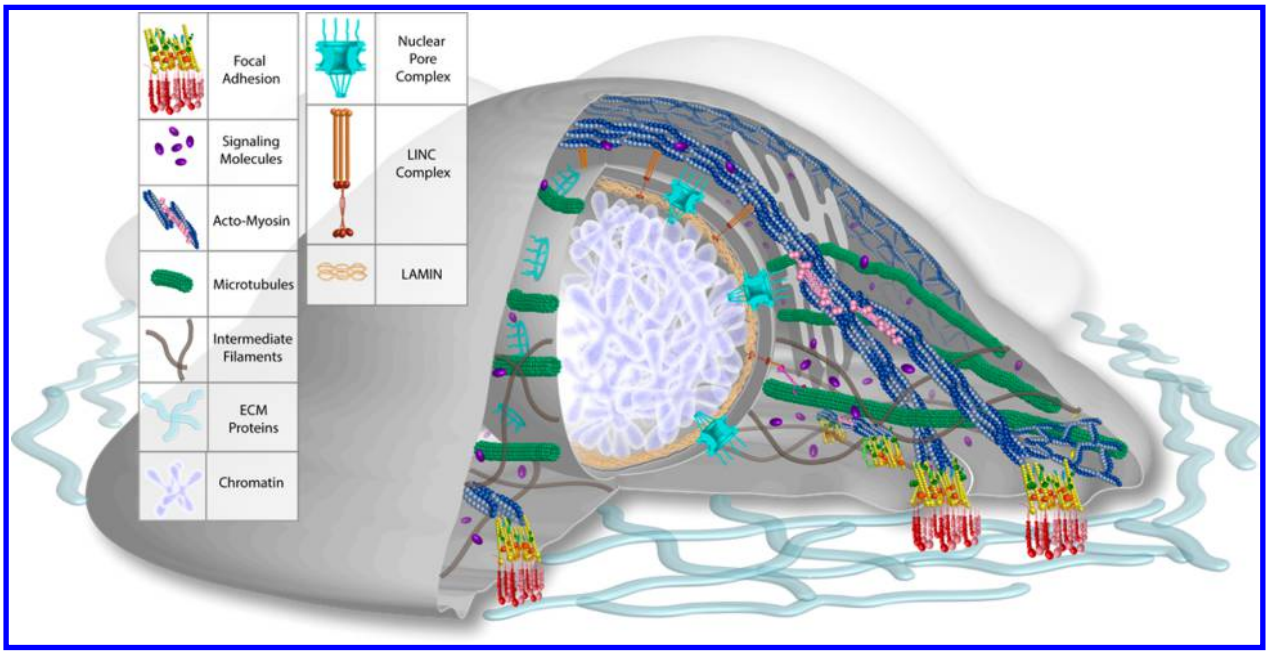

Figure 1. Important modules involved in cellular mechanotransduction. Cells sense and respond to mechanical forces through triggering intracellular biochemical cascades. Mechanical signals are transmitted through FAs from the ECM to the cytoplasm. Cytoskeletal networks consisting of actin, microtubules, and intermediate filaments are involved in generating and transmitting forces throughout the cell. These forces are ultimately transmitted to the nucleus, most likely via LINC complexes that directly couple the cytoskeletal components to the nucleoskeletal elements such as lamins. Nuclear pore complexes mediate biochemical signaling between the nucleoplasm and cytoplasm and may as well play a role in physically linking the nucleus to the cytoskeleton.

Major efforts have recently focused on gaining insights into the mechanisms by which inter- and intramolecular interactions give rise to signal transduction and transmission in the cell. Specifically, molecular organizations are very efficient in terms of signal transmission from the ECM to the nucleus as opposed to diffusion-driven biochemical pathways. Mechanosensitive proteins can assume different conformations under forces, and their deformability highly contributes to their function. Particularly, mechanical forces can regulate protein−protein interactions and affinities; thus, it is important to understand the stress distribution within subcellular structures. Therefore, in order to understand cellular mechanotransduction as a multiscale process, it is critical to perceive how forces and interactions in one scale affect higher scales and the system as a whole. Continuum models can elucidate whole-cell or cytoskeletal-level response to mechanical forces whereas particle-based, finer-scale methods are required to capture molecular interactions. Therefore, an integration of methods across scales is very promising for studying mechanotransdution pathways and maybe obtained by understanding currently used computational techniques in the field and their suitability and limitations for this purpose. In this review, we examine and discuss state-of-the-art computational approaches and their applicability in understanding the mechanobiology of signal transduction. Furthermore, computational studies on the behavior of single and multimolecular systems contributing to mechanotransduction processes are presented.

2. COMPUTATIONAL APPROACHES FOR MODELING CELLULAR MECHANOTRANSDUCTION

Signal transmission and transduction within mechanotransduction modules involve complex interactions that span a wide range of spatial and temporal scales. In this section, suitability of different computational approaches for studying mechanotransduction pathways and modules is discussed.

2.1. Mathematical and Stochastic Modeling. A common approach for studying cellular pathways is through bulk property models such as using ordinary differential equations (ODE) for reaction rates that quantify concentration changes over time.[9] The ultimate concentration changes are determined by the reaction rates. In some systems, the correlation length or the length at which reactants are spatially homogeneous, may be small. For instance, when reactions occur at much faster rates than the diffusion rate of products, the system cannot be assumed to be well-mixed. In such systems, spatial details should be considered by partial differential equations (PDE). Both ODE and PDE models are well suited for systems with high concentration of particles. However, subcellular interactions and pathways typically involve a discrete number of particles with low concentrations and are often characterized by a considerable heterogeneity. As a result, deterministic models such as ODEs and PDEs are mostly suitable for such systems, and stochastic models must be incorporated.[10] Various methods, such as the Gillespie algorithm (GA)[11] and its derivatives, have been developed to capture the stochastic nature of such systems; however, these methods still assume the systems to be entirely or at least locally well-mixed. In addition, they cannot provide detailed spatial information about individual particles, which is typically performed with more computationally expensive approaches such as Brownian dynamics (BD) or molecular dynamics (MD) simulations. Agent-based modeling (ABM) is an emerging stochastic method that fills the gap between computationally efficient macroscopic models and more detailed modeling approaches, which is discussed below.

2.2. Continuum-Based Modeling. Continuum mechanics has been employed to understand cellular behavior and may provide important insights into cell mechanobiology (Figure

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ACS Biomater. Sci. Eng. XXXX, XXX, XXX−XXX

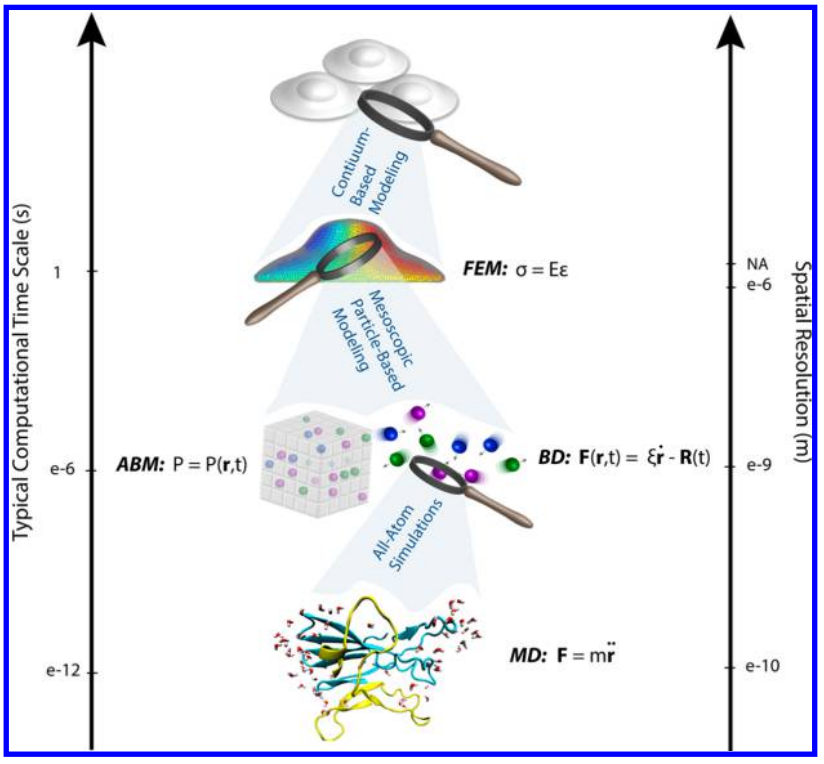

Figure 2. Spatiotemporal comparison of different computational approaches used in understanding cellular mechanotransduction. Cell-level modeling is not possible using particle-based approaches due to the complexity of cellular organisms and is usually handled by continuum-based models such as finite element methods (FEM). With that, using continuum models, large-scale cellular deformations in response to external forces such as the stress imposed by the atomic force microscope tip can be reasonably replicated. The spatial resolution of continuum methods depends on the particular model in hand, and generally, it is hard to set a specific value as it depends on the characteristic length scales and mesh sizes; therefore, it is shown as NA in the plot. Conversely, in particle-based methods, the system consists of discretized particles with particular sizes, which determines the spatial resolution, and the time evolution of the system is modeled by interactions among these particles. One important example of such methods is agent-based modeling (ABM), a probabilistic approach that can account for both chemical and mechanical interactions in the system. Brownian dynamics (BD) on the other hand can only model mechanical collisions. All-atomic molecular dynamics (MD) simulations are widely used to accurately model molecular interactions; however, the computational cost is relatively high. The reader should note that here we focused only on a few computational approaches repeatedly used in the filed of cellular mechanotransduction, and have not discussed much broader range of methods in the realm of computational modeling across scales.

2).[12−14] The lack of sufficient structural data and the difficulty in designing experiments to understand the mechanics of the system during a biological process make continuum modeling very valuable in some cases. Continuum-based models have been employed to reveal the large-scale mechanical behavior of subcellular complexes; however, this was at the cost of losing important high-resolution information due to the coarse nature of continuum mechanics.

2.3. Mesoscopic Particle-Based Modeling. Mesoscopic modeling techniques have been developed to fill the gap between capabilities of computationally efficient macroscopic approaches, namely continuum modeling, and more detailed methods such as Molecular Dynamics (MD) simulations.

2.3.1. Brownian Dynamics Simulations. As a compromise between spatiotemporal resolution and computational feasibility, coarse-grained Brownian dynamics approaches have emerged, where the structural features are elaborated depending on the level of coarse-graining.[15−18] Brownian dynamics (BD) approach is an extension of the MD method, in which the solvent molecules are ignored and their stochastic effects are modeled through friction and random forces. Removing solvent molecules offers a considerable computational efficiency at the cost of losing the details of protein−solvent and solvent−solvent interactions, in particular, hydrogen bonding.

Another level of simplicity employed in the BD approach is the limit of low Reynold's number, where the effects of inertial forces are insignificant compared to those of the viscous forces. As a result, Newton's equation of motion becomes a stochastic equation with no inertial term. This method was first proposed in 1978 in a pioneer work by Ermak and McCammon[19] and since then has been extensively used to simulate a wide range of biological systems.

2.3.2. Agent-Based Modeling. Agent based modeling (ABM) is a bottom-up approach relating interactions among multiple independent entities, termed "agents", to the overall, emerging behavior of the system. The use of ABMs for modeling biological phenomena has become more popular in recent years, due to its potential in various applications in environmental chemistry, toxicology, cancer, immune response regulation, and epidemics.[20−26] ABM is typically used for modeling complicated biological pathways given certain rules for the interaction among particles. In on-lattice ABMs, the physical space is discretized to a grid of "cells", in which each cell can be occupied by one or more agents. Each agent only interacts with agents residing in its neighboring cells. The ABM method is capable of modeling complex three-dimensional biological systems in a computationally efficient and spatiotemporally detailed fashion. The ABM framework allows for realistic modeling of systems containing different particles with different properties such as

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ACS Biomater. Sci. Eng. XXXX, XXX, XXX−XXX

size, diffusion coefficients, and affinity as well as environmental properties such as viscosity and geometry over high temporal scales.

Moreover, ABM can be employed for efficiently simulating the evolution of stochastic and heterogeneous pathways in cells and can robustly account for physical factors such as molecular crowding and steric repulsion. Specifically, ABM is capable of capturing chemical reactions as well as spatial motion of agents. The main challenge, however, is to define and implement biochemical and biophysical properties of molecules, i.e., diffusion and association/dissociation coefficients, in the ABM model. In addition to the characteristics of agents, other parameters such as environmental boundaries, physical factors including crowding and steric repulsion, and collision detection, should be considered in an ABM model.[27−31] Recently, a mathematical framework has been developed for converting physiochemical properties of molecules into probabilistic characteristics of agents in ABM.[30,31] Specifically, diffusion coefficients of biomolecules can be converted to the probability of movement inside a lattice using Fick's second law. Also, first- and second-order association and dissociation coefficients of molecules can be converted to the probability of interaction between agents.

2.3.3. Coarse-Grained Molecular Dynamics Simulations. In coarse-grained molecular dynamics simulations, beads with mean-field properties replace groups of particles in the system, in order to reduce the computational cost of the simulations. This requires a consistent redefinition of terms and parameters defined in the force field that is used to model interactions. An important example is an extension to the MARTINI force field[32,33] that has been developed and validated for various compositions including protein−protein and protein−lipid.[34−36] As another example, a coarse-grained one-bead-per-amino-acid force field was developed specifically for disordered proteins.[37] In this model, the local interaction potentials, and experimentally obtained Ramachandran plots for the coiled regions of proteins, are converted into distributions of pseudobond and pseudodihedral angles between neighboring α-carbons in a polypeptide chain. These distributions are used to derive bending and torsion potentials that are both residue and sequence specific and are employed in the force field. Coarse-grained modeling fails when atomic-level interactions play a critical role in the dynamics of the system.

2.4. All-Atomic Simulations. All-atomic simulations have been employed to model molecular responses to mechanical stimuli. These simulations have provided relatively accurate predictions of the emergent effect of protein−protein interactions in large-scale mechanotransduction events. In addition, MD simulations can predict how mutations affect the structural integrity of molecules, which in turn can alter their function and mechanical stability. Conformational changes in proteins can be viewed as molecular deformations and usually occur in the micro- to millisecond time scale. Since these time scales are not always accessible in MD, conformational changes are often induced using higher forces in steered molecule dynamics (SMD) simulations. It is critical to note that the origin and magnitude of forces in SMD determines the relevance of resulting conformational changes and thus should mimic physiological forces that regulate the function of molecular mechanosensors.

The treatment of the solvent molecules can play an important role in the accuracy of MD simulations as they determine the effective viscosity of the system. Explicit water molecules reduce protein motion but ultimately result in realistic structural transitions. Conversely, implicit solvent models are mean-field approaches used to lower computational cost and increase conformational sampling of proteins in MD simulations. However, the assumptions behind such models result in a notable drop in the accuracy of the outcome. Implicit solvent models such as generalized Born and Poisson−Boltzmann have been reviewed elsewhere.[38]

The main input of MD is the molecular structure; thus, the reliability of the results is highly dependent on the accuracy of the structural input. Although many protein structures are readily available in the Protein Data Bank (PDB), some restrictions may apply for their applicability. For example, if the resolution of the structural determination method is low (>3A), domain interfaces and atomic interactions may not be accurate. In many cases, protein structures are determined in complex with their binding partners, which can affect the conformation of the protein of interest. Therefore, structures should be carefully examined before using in MD. Chosen structures need to be further minimized and equilibrated for a sufficient time in order to remove all bad contacts. Moreover, structures may not be in full form or have missing residues. In such cases, protein structure prediction methods can be employed for modeling absent residues given the availability of reliable templates.[39] Two of the most commonly used tools for performing protein structure prediction are PHYRE2 and SWISSMODEL, which can be combined with docking analysis to predict molecular complexes.[40−44] Molecular dynamics simulations combined with docking analysis and protein structure prediction can be employed to investigate mechanosensitive conformational changes of single molecules as well as key molecular interactions in mechanotransduction pathways.[45]

2.4.1. Free Energy Calculation Methods. Free energy calculation techniques offer a powerful bridge between computational modeling and experiments. The phase space of proteins is complicated and composed of hundreds to thousands of degrees of freedom. Due to the high computational cost, the system may not be able to probe the entire phase space within the simulation time, thus, some functionally important conformational states may remain unexplored. Free energy calculation methods can fill this gap by forcing the system to undergo necessary conformational changes and reach hardly accessible states in a reasonable simulation time.

One of the most commonly used methods for obtaining the free energy profile is umbrella sampling. In this method, one or two degree(s) of freedom of the system, also referred to as reaction coordinate(s), is (are) harmonically restrained. The probability distribution along the reaction coordinate can be extracted from a series of simulations in which the harmonic restraint slides along the reaction coordinate:

$$P_b(x) = P(x)e^{-[V(x)-K]/K_BT} \quad (1)$$

$P_b(x)$ is the biased probability distribution, and $V(x)$ is the harmonic potential. K represents the normalization constant, while K_B is the Boltzmann constant, and T is the temperature. The equation is used to calculate the unbiased probability distribution, $P(x)$. The outcome of the umbrella sampling simulations is a set of histograms from which the biased probability distribution can be extracted. The WHAM algorithm (weighted histogram analysis method) is then used to solve for the unbiased probability distribution.[46] The potential of mean

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ACS Biomater. Sci. Eng. XXXX, XXX, XXX−XXX

force (PMF) is then directly found from the probability distribution.

Jarzynski developed a method for evaluating the free energy profile of nonequilibrium processes,[47] where the free energy of the system is estimated as

$$e^{-\beta\Delta F} = \langle e^{-\beta W} \rangle \quad (2)$$

Here, ΔF is the free energy difference, and W is the work done on the system, and β is related to the Boltzmann constant and temperature. The right side of the formula is the average over ensemble at temperature T. In order for ΔF to be independent of the speed of the process, the system should be sampled multiple times. Generally, nonequilibrium simulations such as the Jarzynski method are used to extract equilibrium information that may introduce large statistical errors in some cases. The reason usually underlies the fast switching rates between thermodynamic states used in these methods that result in work values far greater than the actual free energy differences, i.e., a large bias in the free energy estimate. To overcome this issue, care must be taken in choosing a proper free energy method for the system under study.[47] There is another class of free energy calculation methods that only gives the free energy difference between two equilibrium states, which includes the free energy perturbation approach. For detailed calculations of free energy methods and comparisons, please refer to excellent reviews and books on this topic.[48−50]

3. MECHANOTRANSDUCTION PATHWAYS UNDER THE "COMPUTATIONAL MICROSCOPE"

Mechanical signals are transmitted from the ECM to the cytoplasm, across cytoskeletal structures, and to the interior of the nucleus.[45,51] Here, we compartmentalize signal transmission/transduction machinery into three modules, each comprising various mechanisms and building blocks: (1) FA, (2) the cytoskeleton, and (3) the nucleus. It should be noted that mechanosensitive ion channels are critical for mechanotransduction,[52,53] however, they were not discussed here. A separate comprehensive review is required to capture mechanical and electrical effects of ion channels in regulating mechanotransduction pathways. The above-mentioned three modules are discussed in the following sections.

3.1. Focal Adhesions. FAs are large protein complexes mediating signal transmission and transduction between the extracellular matrix (ECM) and the cytoskeleton (Figure 1).[54] FAs transmit mechanical signals via their tightly coupled molecular network that spans from the membrane to the cytoskeleton. This interconnected protein network is highly dynamic and remodels as mechanical signals propagate and reach molecular interfaces. To decipher signal transduction mechanisms, conformational dependency of individual proteins to mechanical forces should be explored. Structurally, FAs can be divided into three layers, namely, the integrin signaling, force transduction, and actin regulatory layers, each having a unique composition of proteins (Figure 3).[55] However, it should be noted that proteins in each FA layer may be found in other layers either transiently or in lower equilibrium concentrations. Conformational states of proteins and interactions within each FA layer are governed by the level of adhesion maturity.[56] Mechanical response of proteins occurs in the order of pico- to microseconds with forces ranging between 10 to 100 PN, which is much lower than forces experienced by tissues.[8] A detailed understanding of protein-level mechanosensitivity highly relies upon the available structural information. Fortunately, significant efforts have been focused on resolving full or partial structures of important FA proteins such as α-actinin, talin, filamin, FAK, and vinculin. In the following sections, some of the important FA players, their function, and regulatory mechanisms revealed by computational approaches are reviewed.

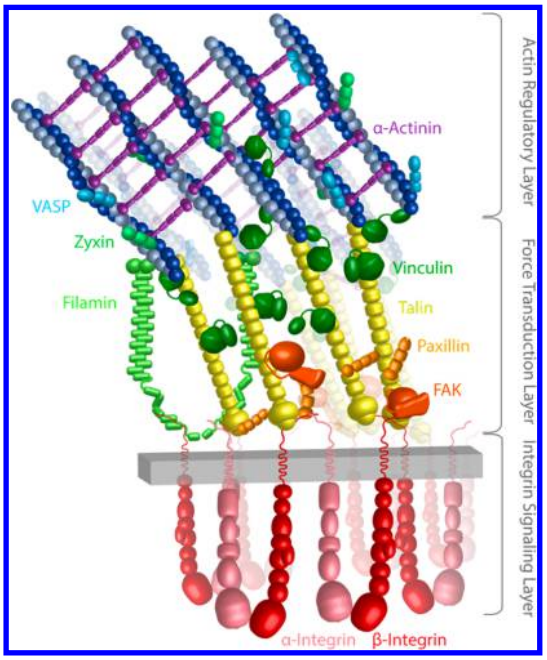

Figure 3. Different layers of FAs. This semi-three-dimensional schematic of a FA structure depicts spatial arrangement of key proteins within FA layers. Each FA layer has a unique composition of proteins that regulate force transmission within that layer. Integrin receptors (red) reside in the lipid bilayer (gray) and are activated via talin (yellow) binding inside the integrin signaling layer. Other important molecules such as FAK (orange) and paxillin (light orange) also function within the integrin signaling layer. Mechanosensitive elements like vinculin (green) are abundant in the force transduction layer. Actin and actin binding proteins such as α-actinin (purple) form actin bundles farther in the actin regulatory layer.[56] Filamin (light green) and α-actinin can also directly bind to integrins. It should be noted that many FA proteins are not shown for clarity.

3.1.1. The Integrin Signaling Layer. Integrins are cell-surface receptors that "sense" mechanochemical cues from the ECM and coordinate cellular responses. Integrins bind to several extracellular ligands such as fibronectin, collagen, and laminin.[57,58] Residing in the lipid membrane, integrins mediate both inside-out and outside-in signaling.[59] Integrins function as heterodimers formed by 24 different combinations of the α- and β- subunits[60] each consisting of an extracellular domain (ectodomain) followed by a transmembrane domain and the cytoplasmic region. In the inactive conformation, the transmembrane domains of two integrin subunits interact, and their extracellular domains are folded toward the membrane.[61,62]

In the process of "outside-in" signaling, interaction with the ECM ligands, mainly the RGD segment of ECM molecules, leads to global conformational changes in the ectodomain of integrins. Conversely, talin binding to the cytoplasmic region of integrin initiates its activation from inside of the cell, leading to integrin-mediated "inside-out" signaling. Defects in integrin activation lead to various diseases including myocardial infarction and cancer, therefore it is important to understand regulatory mechanisms of integrin activation.[63] The inside-out and

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ACS Biomater. Sci. Eng. XXXX, XXX, XXX−XXX

outside-in signaling pathways can impact one another; thus, it is difficult to study them separately.[64−66]

Molecular models have been developed for studying the activation pathways of various integrin heterodimers. Simulations on the $\alpha_V\beta_3$ integrin headpiece revealed that the strain allosterically propagates from the RGD binding site to other domains.[67] Another *in silico* experiment showed that forces applied directly on the β integrin as well as force on the RGD ligand bound to the integrin headpiece result in extending the integrin ectodomain.[68] Moreover, modeling stretching forces along fibronectin suggested that ECM mechanosensitivity serves as a regulatory mechanism for integrin binding.[69] Activation inhibitors have been developed for treating adhesion-dependent disease such as cancer metastasis.[70] Integrin takes various conformational states during activation, some of which are more stable than others.[71] Using steered molecular dynamics, Jin et al. showed that mechanical forces can alter the free energy landscape of protein and shift minima toward new transient states.[72]

To examine mechanisms of inside-out integrin activation, talin binding to the cytoplasmic tail of β integrin was modeled using molecular dynamics simulations. Specifically, it was shown that talin interaction with the cytoplasmic tail of integrin resulted in loosening the inner-membrane clasp, which holds integrin subunits together in the membrane.[73,74] Lateral forces on β integrin maintained the high-affinity state of $\alpha_{IIb}\beta_3$, which most likely indiactes allosteric regulation of integrin activation.[75] Furthermore, studying dimerization of the transmembrane domains of $\alpha_{IIb}\beta_3$ using coarse-grained modeling, showed that the right-handed dimer is more stable.[76]

Lateral assembly of integrin heterodimers or integrin clustering[77−79] mediates signaling; however, the molecular mechanism of this process is poorly understood. Two key underlying mechanisms have been suggested for integrin clustering, namely, ligand organization and integrin homo-oligomerization.[79,80] Mehrbod et al. used steered MD models to simulate the heterodimerization of transmembrane domains of integrins inside the lipid membrane.[81] They observed that lipid packs were formed around the α-subunits; however, lipid packing was slightly reduced close to the β-subunits due to the higher concentration of hydrophilic residues near their cytoplasmic side. This study also predicted that homo-oligomerization of integrins may give rise to clustering only in mature FAs. The free energy of homodimerization of two α-subunits was estimated to be 800 K_BT, while for two β-subunits, such energy was half.[82] Furthermore, molecular models of two α_{IIb} and three β_3 homo-oligomers suggested that these relatively small complexes can act as seeds for higher order oligomerization and also that the $\alpha\beta$ heterodimer most likely separates during clustering.[83]

While sufficient computational resources are currently lacking for MD simulation of integrin clustering involving a large number of integrins diffusing within the lipid membrane, other more holistic approaches have been employed to draw a clear picture of integrin clustering. In particular, the ABM approach accounting for a system of several agents has been used to shed light on some of the important factors in integrin clustering.[84] Specifically, Jamali et al. predicted that integrin−ligand affinity, membrane crowdedness, and ligand mobility significantly affect the dynamics of integrin clustering.[84]

Each talin molecule associates with one integrin molecule via its head domain and may dimerize with another talin from its C-terminal domain potentially giving rise to integrin clustering. Various orientations can be assumed for the talin dimer, and simulations suggested that external mechanical forces can regulate the orientation of the talin dimer.[85]

3.1.2. The Force Transduction Layer. Talin is anchored to integrins via its head domain and binds to F-actin from its C-terminal end that extends across the force transduction layer. This results in axial pulling forces along the rod domain, which unravel multiple cryptic vinculin binding sites (VBS) in the rod domain of talin recruiting vinculin to early adhesions.[86] The molecular mechanisms of talin−vinculin binding have been studied using MD simulations.[87] Lee et al. identified a conformational change within the talin rod under tensile force, which exposed the hydrophobic vinculin binding residues.[87] Another study showed that improper unfolding of the talin rod inhibited vinculin binding.[88] Aside from the direct interaction of talin with the actin cytoskeleton, vinculin binding to talin's rod domain mediates force transmission from actin.[89,90] In addition, Srivastava at al. showed that changing the PH level in MD simulation modulated talin binding to actin.[91]

Vinculin structure is autoinhibited in the native state and cannot bind to actin effectively.[92,93] It has been shown that binding to talin VBS activates vinculin's autoinhibited conformation and increases its affinity for actin.[89] In addition, VBS induces changes in the relative positions of helices in the vinculin head known as helical bundle conversion.[89] Golji et al. simulated talin to vinculin and observed that talin VBS inserts itself between two α-helices of vinculin head and forms a five-helix bundle.[94] Vinculin activation by mechanical force is key to regulating FA maturation, and SMD simulation was employed to explore vinculin activation.[95] Another study showed that the secondary structures of binding sites remained intact upon force and that unfolding was unnecessary for binding.[96]

Vinculin reinforces FA by directly transmitting cytoskeletal forces. Actin filaments polymerize against the membrane to create protrusions; however, it has to stop as it reaches FAs. The vinculin tail caps the barbed end of actin in a force-dependent manner.[97] Golji et al. proposed that the actin−vinculin interface is stress-dependent and can increase under mechanical loading.[97] Therefore, mechanical forces and talin binding can promote the activated conformation of vinculin. In addition, Wendorff et al. suggested that vinculin phosphorylation can prime vinculin activation by destabilizing its autoinhibited conformation.[98] Conformational changes of vinculin are also important in triggering biochemical cascades in mechanotransduction pathways. MAPK1 was predicted to bind selectively to the open conformation of vinculin, which regulates downstream events in stem cell differentiation.[99] It has been suggested that vinculin reinforces the linkage between α-actinin and the actin cytoskeleton.[100] The vinculin binding site is autoinhibited in the triple helical structure of the R4 spectrin repeat of α-actinin.[101] Shams et al. modeled the activation of α-actinin for vinculin binding and showed that free energy was decreased upon activation indicating that the activated state is probably more favorable.[102]

Focal adhesion kinase (FAK) signaling facilitates cell motility and adhesion.[103] The interaction between FAK and FA proteins such as paxillin and talin indirectly associates it with integrin receptors. It has been shown that FAK binding to paxillin is force sensitive.[104] FAK activity is regulated by ECM ligand binding to integrins; therefore, its proximity to the lipid membrane is vital to its function. FAKs have an autoinhibitory interaction, which is regulated by ATP and PIP2 binding.[105] Zhou et al. revealed allosteric transmission of forces within FAK using molecular dynamics simulations,[105] suggested an activation mechanism for

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ACS Biomater. Sci. Eng. XXXX, XXX, XXX−XXX

FAK, which was in agreement with previous fluorescence resonance energy transfer studies.[105]

Furthermore, the conformational state of FAK regulates its phosphorylation at Y925, which is critical for Grb2 binding. Modeling of the conformational change of FAK and its interaction with Grb2 resembled the crystal structure of the complex.[106] The conformational state of FAK is also associated with ligand binding and its localization inside the cell; thus, the folding pathway of FAK has been modeled using discrete molecular dynamics.[103] FAK has been considered as a target for cancer treatment, and molecular modeling has been employed to design FAK anticancer inhibitors.[107]

Various types of small regulatory molecules and large molecular complexes reside in the cell membrane. The polar surface of the lipid membrane associates with certain domains of different cytoplasmic proteins. Other lipid molecules such as phosphatidylinositol phosphates (PIPs) are also found at low to medium concentration in the lipid membrane; however, they can cluster and form local electric fields.[108] Talin and kindlin interact with the lipid membrane and may contribute to modulating integrin function.[62] Multiscale computational modeling elucidated the mechanisms of domain-specific interactions, i.e., electrostatic recruitment and penetration into the lipid membrane, with different classes of the lipid molecules.[109] It is known that membrane tension is important for regulating conformational states of membrane proteins.[110,111] A model of actin polymerization against the lipid membrane replicated cell shape of a large population of motile keratocytes.[112] This indicates that the plasma membrane indirectly transfers cytoskeletal forces to membrane receptors.

3.1.3. The Actin Regulatory Layer. The actin regulatory layer is part of the actin filaments in proximity to FAs.[56] Forces are transmitted bidirectionally to this layer through direct linkage with FA proteins. Particularly, α-actinin plays a critical role in this layer since it regulates both formation and stress distribution across the actin cytoskeleton, and it can also directly bind to FA proteins such as integrin and vinculin. α-Actinin cross-links actin filaments in stress fibers and is also found within FAs.[45] The coiled-coil structure of α-actinin allows for extensional rigidity, which is important for actin bundle formation. Torsional and bending flexibility of the rod domain is important for enduring compressive stress and other local forces within the cytoskeletal structure. The molecular conformation of α-actinin's actin-binding domain (ABD) regulates its association to actin, and mutations in this domain can lead to severe pathogenic conditions.[113,114] Molecular models of the wild type and mutant ABD−actin complex showed that the strength of actin association is indeed sensitive to the ABD conformation.[114]

Filamin is another actin binding protein that cross-link cortical actin filaments but is also a versatile binding partner for FA proteins including integrin.[115−118] Although filamin localization within FA layers is yet to be determined, the importance of this molecule in cell signaling cannot be ignored. In its native conformation, filamin's integrin binding site is in an auto-inhibited conformation and tensile forces along the rod domain can induce conformational changes necessary for its activation.[118] Modeling filamin binding to integrin in the presence of talin revealed the molecular mechanisms of their competition for the integrin tail.[119,120]

3.2. The Cytoskeleton. Three main cytoskeletal components are F-actin, microtubules, and intermediate filaments, which are continuously exposed to intra- and/or extra-cellular forces (Figure 1).[121−123] Cytoskeletal filaments have widely been studied using various computational approaches across multiple scales. Some discrete models of the cytoskeleton are more general and may account for more than one type of cytoskeletal components and represent the cytoskeleton as a network of discrete stress-bearing elements.[124,125] An important examples is the Tensegrity (tension-integrity) model that assumes the cell is composed of tension-bearing actins and compression-bearing microtubules, and predicts how forces are transmitted across the cell in response to external mechanical stress.[126] It also suggests that the cytoskeleton is a prestressed structure, which provides shape and structural stability to the cell.[126] Tensegrity has been successful in explaining various mechanical behaviors of cells in response to mechanical forces.[127,128] However, modifications to the classical Tensegrity model may be necessary for accurate prediction of cytoskeletal mechanics. For instance, an anisotropic continuum model of microtubules suggested that flexural response of microtubules is important and thus should be incorporated into the Tensegrity model.[129]

It should be noted that intermediate filaments have not been subject to many computational studies; however, recently there has been an effort for developing a multiscale model for explaining the role of intermediate filaments in cell stiffness and integrity under force.[130] In the following sections, important contributions of cytoskeletal modeling across various scales devoted to either actin or microtubules are reviewed.

3.2.1. The Actin Cytoskeleton. Cells adapt to their microenvironment by dynamically changing their morphology. Cytoskeletal reorganization plays a key role in the ability of cells to respond to mechanical forces.[131−133] Also, cytoskeletal structures are important for the diffusion of water and small molecules. The length of cytoskeletal filaments strongly contribute to mechanical properties of cell resulting in behaviors ranging from elastic gels to viscous fluids.[134,135] The complexity and heterogeneity of the cytoskeleton evoke interesting cellular responses that are not yet explained.[134,135] The stress distribution inside the cell is governed by actin network elasticity, the internal and external constraints and myosin contraction.[131] To control the macroscale behavior of cytoskeletal filaments, it is necessary to characterize the microscale interactions. For instance, actin polymerization occurs at the positive end of actin filaments, where the nucleotide cleft is buried. Therefore, designing new molecules for inhibiting actin polymerization through direct physical interaction requires detailed information about the actin surface and its binding partners. Therefore, many attempts have been devoted to modeling the actin cytoskeleton in various scales ranging from continuum to atomic-level systems.

Rheology-based continuum models have been developed to capture cytoskeletal dynamics subject to mechanical perturbation.[135,136] In such models, the cytoskeleton is treated as a viscoelastic continuum under steady-state dynamic mechanical loading, which is useful for modeling large scale experiments such as cell response to microbead twisting cytometry. Some of the continuum models can be considered multiscale since the microrheology of the system is incorporated in the material properties. However, continuum-level models such as porous gel or soft glassy material[137] and macroscopic experiments ignore various nanostructural heterogeneity and microscale events. They can only be valid if the length scale of the experiment of interest is much larger than the microstructure of the cell.

Molecular dynamics study of monomeric, trimeric, and filamentous actin indicated that ATP hydrolysis can change the conformation of G-actin resulting in modifying the intermono-

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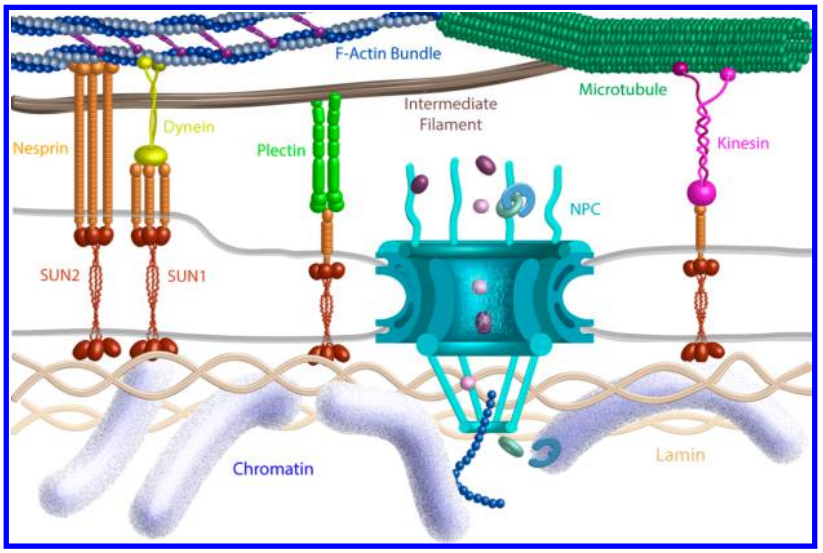

Figure 4. Key components of nuclear mechanotransduction. NPCs (cyan) reside on the nuclear envelope and mediate bidirectional transport of biomolecules between the cytoplasm and nucleoplasm. The central channel of NPC is filled with FG Nups, which mediate cargo transport. The LINC complex (orange) couples cytoskeletal components, namely, F-actin (blue), microtubules (dark green), and intermediate filaments (brown), to nucleoskeletal elements such as lamins (beige) either through direct interaction, plectin (green), or motor proteins like dynein (yellow) and kinesin (pink).[203,204,212]

meric interaction of F-actin. This study revealed the structural basis for the F-ADP filament having shorter persistence length compared to that of F-ATP.[138] Actin binding protein Arp 2/3 forms branched actin junctions.[139] All-atomic MD simulations revealed the functional importance of salt bridges between Arp2/3 and actin filaments in withstanding significant forces.[139] Cofilin is another actin regulatory protein that contributes to disassembling actin filaments. Association of cofilins with actin filaments affects the mechanical behavior of actin filaments using coarse-grained MD simulations.[140]

Structural properties of actin filaments and their interaction with molecular motors have been studied using all-atomic MD simulations.[131,141] Actin binding proteins also play a critical role in cytoskeletal structure and dynamics. Various actin-binding proteins associate with actin through two tandem calponin homology domains. The conformation of the CH domains is key to actin binding affinity and thus is regulated through mechanical or biochemical factors such as phosphorylation.[114]

3.2.2. Microtubules. Microtubules are major structural components of the cytoskeleton and are responsible for pivotal cellular functions such as facilitating cargo transport, mitotic spindle formation, and maintaining mechanical integrity of cells.[123,142] Microtubules resist compressive and buckling forces for maintaining cell shape due to their high flexural rigidity.[129]

Coarse-grained modeling has proven successful in capturing the mechanical behavior of various filamentous networks.[143−145] Microtubules have specifically been the subject of several different modeling approaches, including continuum-based modeling, coarse-grained techniques, as well as mathematical methods.[129,146−150] These studies have explored mechanical behavior of microtubules under physiological conditions as well as extreme loading conditions associated with traumatic brain injury (TBI). While the coarse-grained representation of microtubules enables us to achieve high temporal scales, fine-resolution techniques such as MD offer high spatial details of the mechanochemical response of the filaments. Cryo-electron microscopy and electron crystallography have been used to construct an all-atom model of microtubules. Mechanical properties of microtubules under extension and compression were studied using molecular dynamics simulations.[151,152] Furthermore, since microtubule polymerization is important for cell shape and motility,[153] the molecular basis of microtubule depolymerization has been studied using both MD simulations and coarse-grained modeling.[154]

3.3. Nucleus. In eukaryotic cells, genetic information is enclosed inside the nucleus, which is accessed through intricate cellular pathways. The nucleus is a mechanosensitive entity and plays a crucial role in mechanotranduction pathways. It has been shown that physical forces affect the mechanical behavior of the nucleus through various complexes on the nuclear envelope. Specifically, the nuclear pore complex (NPC) and linkers of the nucleoskeleton and cytoskeleton or LINC complexes play critical roles in mechanochemcial signal transmission and transduction across the nuclear envelope (NE). The interplay between LINC and NPC in mechanotransduction pathways has recently attracted attention, but is not yet fully understood.[155] In this section, computational models developed for understanding the function of NPC and LINC complexes are discussed.

3.3.1. Nuclear Pore Complex. Nuclear pore complexes are the largest macromolecular assemblies spanning and perforating the double-layer NE acting as sole gateways for selective bidirectional transport of vital biomolecules between the cytoplasm and the nucleus in eukaryotic cells (Figure 4).[156,157] The molecules shuttled through the NPC range from different functional proteins to RNAs and ribosomes.[158−161] In addition to its role as the transport channel, the NPC also mediates a physical linkage between the nucleoskeleton, and cytoskeletal filaments. For an extensive discussion on the role of the NPC in nucleocytoskeletal coupling, see ref 156. Although theoretical modeling techniques have recently advanced our understanding of the transport processes significantly, it is still a matter of debate whether mechanical forces affect pore size and as a result regulate molecular transport through the NPC.

Structurally, the octagonal symmetry of NPC provides unique mechanical properties such as optimized bending stiffness, which most likely plays an important role in nucleocytoplasmic

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ACS Biomater. Sci. Eng. XXXX, XXX, XXX−XXX

transport.[162,163] The nuclear pore complex is composed of 500−1000 nucleoporins (Nups) that can be categorized into ∼30 unique Nups.[164−167] Nups can be broadly classified into three main groups: pore membrane proteins (Poms), structural Nups, and FG Nups that encompass FG (phenylalanine-glycine)-repeat domains. While Poms and structural Nups take part in anchoring the NPC to the NE and providing structural stability to the NPC scaffold, respectively, FG Nups govern the permeability barrier inside the NPC.[17] FG Nups feature intrinsically disordered domains that play a central role in NPC selectivity,[168,169] where translocation of cargos is mediated through the transient interactions between transporters and FG Nups (Figure 4).

Due to the critical role of the NPC in cell function viability, numerous efforts have been dedicated to uncover the nucleocytoplasmic transport mechanism, and multiple models have been proposed over the past three decades.[170−173] The models are sometimes conflicting and do not always agree with each other on the mechanistic details of transport. Such ambiguity mainly stems from the vague information about the accurate functional conformations of FG Nups. Because of the complex and highly dynamic nature of nucleocytoplasmic transport, current imaging and experimental techniques are unable to capture a detailed picture of the behavior and function of FG Nups. Thereby, computational modeling approaches can significantly contribute to filling this gap by providing unique microstructural insights at high spatiotemporal resolutions, which are further discussed in the following sections.

FG Nups have been explored at multiple spatial and temporal scales using various computational approaches. Recently, bioinformatics approaches have been employed to explore the sequence composition of FG Nups by studying large databases of FG Nup sequences across different species.[174,175] In addition, several pioneering all-atomic molecular dynamics studies have been conducted in recent years to study the dynamics of FG Nups and their interactions with transporters.[176−182] However, due to computational feasibility, the all-atomic approach is limited to small domains of the FG Nups. To overcome this barrier, the coarse-grained models along with appropriate force fields have been proposed in recent years, which are able to model the entire domains of all FG Nups within the NPC.[17,18,183−186]

The Brownian dynamics method is a powerful coarse-grained model which enables one to reach a relatively large time scale up to milliseconds, without losing structural details of the NPC and Nups.[16−18,184,186] This approach proved successful in exploring the mechanistic details of globular protein import,[17,18] effects of charge and hydrophobicity within the highly dynamic FG Nups,[184] and, more recently, the details of the conformational behavior of FG Nups.[16,186]

More holistic modeling approaches of the NPC have proven useful in providing a more comprehensive picture of the NPC function. Specifically, due to the dynamic nature of disordered FG Nups, longer time scales are required to obtain statistically meaningful results, a goal that can be achieved in coarse-grained models. Accordingly, in the past few years, several force fields have been developed for coarse-grained modeling of both structured and unstructured proteins.[16,37,172,184,187−192] Some of these coarse-grained studies have explored the effect of sequence composition on conformational behavior of FG Nups inside the NPC to shed light on how specific patterns in sequences of FG Nups facilitate the dynamics and function of FG Nups.[16,37,172,184,192] In a recent study,[193] the role of specific sets of charged residues in the distribution of FG Nups inside the NPC was explored. Peyro et al. showed that charge patterning has a significant effect on the conformation of FG Nups. These specific charge patterns, named Liked Charge Regions (LCRs), were extracted from a comprehensive analysis of a large dataset of FG Nup sequences.[175] These studies suggest that sequence features of FG Nups, including LCRs, likely regulate transport through the NPC.

3.3.1.1. Nuclear Import. Exploring transport processes requires an efficient method that can account for large spatiotemporal scales of transport through the NPC. Stochastic approaches can span the entire transport cycle of NPCs at the expense of losing spatial details of the selectivity barrier.[28] Specifically, ABM simulations can easily be extended up to seconds, while most techniques can only reach microsecond time scales. As an example, one of the major current debates is that whether an affinity gradient across NPC plays a role in the transport processes.[31] ABM studies showed that import through the NPC is maximized with an effective macroscopic affinity gradient of 2000 mM, 200 mM, and 10 mM in the cytoplasmic, central channel, and nuclear basket regions, respectively.[31] Interestingly, the optimal ratio of affinity gradients found in the ABM simulations were in agreement with those reported for the yeast NPC, suggesting that the affinity gradient seen *in vitro* is highly optimized.

3.3.1.2. mRNA Export. Messenger RNAs are transcribed from DNA and subsequently transported into the cytoplasm for protein synthesis. Therefore, mRNA export through the NPC is a fundamental step in eukaryotic cell function, while only a few experimental studies have been able to capture the dynamics of mRNA export with a relatively high spatial resolution.[194−196] Recent modeling efforts revealed that mRNA export is sensitive to both the number and distribution of export receptors along mRNA.[28] It was also observed that nuclear basket association to the mRNA is a rate-limiting step as the mRNA reconfigures itself to move into the central channel, which is in agreement with experimental observations.[197,198] This study also suggested that a double location-monitoring label along mRNA may better capture the time frame of mRNA transport and provide more accurate results in the future experiments.

Prior to transport into the cytoplasm, mRNAs undergo a few processing and packaging steps required for their efficient export. Several proteins have been identified as being involved in the process of mRNA quality control;[199] however, the mechanisms by which aberrant mRNAs are recognized and retained inside the nucleus is not yet fully understood from experiments. Using a computational approach, Soheilypour et al. demonstrated how cooperation of regulated stochastic interactions between different proteins could result in an overall quality control of mRNAs and showed that the associated affinities are optimized to maximize the retention of aberrant mRNAs.[29] It was also shown that the length of mRNA can affect the quality control mechanism. These results further highlight the capabilities of computational modeling, specifically ABM, in predictive studies and assessing the role of different parameters on the overall behavior of the system.

3.3.2. LINC Complex. The linkers of the nucleoskeleton and cytoskeleton (LINC) extend across the nuclear envelope and physically couple the cytoplasm to the interior of the nucleus. Cytoskeletal forces that were affected by the ECM forces transmitted through FAs are transferred to the interior of the nucleus via the LINC complex and regulate gene expression. LINC complex-dependent nuclear cytoskeletal coupling is key

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for rapid signal transmission for several fundamental cellular processes including moving chromosomes during meiosis and nuclei in differentiating, dividing, and migrating cells.[200] Recently discovered mutations in genes encoding the LINC complex proteins have been shown to lead to several cardiac diseases such as dilated cardiomyopathy and Emery−Dreifuss muscular dystrophy.[201]

The LINC complex is composed of Klarsicht, ANC1, and Syne homology (KASH), and the Sad1p/UNC (uncoordinated)-84 (SUN) families. KASH-domain containing proteins or nesprins link the cytoskeleton to the SUN protein in the perinuclear space. Proteins of the nesprin family bind to all main cytoskeletal components either directly or through other proteins (Figure 4).[202−205] Within the perinuclear space, the ∼10−32 residue KASH domain directly interacts with the conserved C-terminal SUN (Sad1 and UNC-84) domain of SUN2, which is followed by a central domain containing two coiled-coils that spans the remainder of the perinuclear space and a transmembrane domain that projects the N-terminus into the nucleoplasm where it interacts with A-type lamins and chromatin-binding proteins. It has been suggested that LINC complexes regulate perinuclear spacing, which separates the inner and outer nuclear membranes. Therefore, LINC complexes likely undergo tensile forces as knocking them down results in a notable increase in the perinuclear gap.[206]

Previous studies have shown that disrupting the LINC complex impairs nuclear positioning and cell polarization in migrating cells.[207] Although chromosome and nuclear movement via LINC complexes have been well studied,[208,209] the manner in which LINC complexes respond to and translate mechanical forces across the nuclear envelope and into the nucleoplasm remains unclear. It has been shown that mechanical forces are transferred from the stress fibers to the discrete sites on the nuclear envelope.[136,207,210] Tensile forces from the cytoskeleton may result in conformational changes in the components of the LINC complex, which can ultimately affect SUN-KASH interaction. Through MD simulations, Jahed et al. showed that the transmission of forces is highly dependent upon the intermolecular disulfide bond between SUN and KASH.[211] Forces in the model simulated cytoskeletal forces transmitted through KASH proteins.[205,212]

The interplay between LINC and NPC has been discussed in recent reviews.[155,156] Many questions regarding the role of NPC and LINC in mechanotransduction are yet to be answered. For instance, it is yet not clear whether the NPC function is directly regulated by cytoskeletal forces and membrane tension or whether other components such as LINC affect their performance under mechanical tension.

4. CONCLUSIONS AND OUTLOOK

An elegant intracellular machinery underlies transduction of the complex environmental signals to biochemical cascades inside the cell.[213] Cellular mechanotransduction is a multiscale/multiphysics process critical for many biological functions including cell migration and differentiation. Cytoskeletal structures transmit intracellular forces to both the cell membrane and the nuclear envelope through macromolecular bridges. Although the force-bearing properties of individual mechanotransduction modules have been widely studied, there are still many unknowns regarding the structure and function of each module and the cross-talk between different modules is poorly understood.

One of the important gaps in the field of mechanotransduction is the full protein−protein interaction patterns and conformational states of individual proteins. For instance, each integrin receptor within the FA complex associates with a certain composition of proteins, which may result in a specific functionality of that integrin-complex for signaling with the ECM.[214] Such an approach will provide great insights into specific roles of individual proteins in integrin-mediated signaling and potential redundancies in their function, which is not well understood. Furthermore, the amino acid composition and interactions between different domains of FA proteins can serve as means of modularity that controls how stress is compiled within the protein structure. For instance, actin binding proteins may experience tension, bending, or other types of motion depending on the local stress environment.[215]

Computational modeling is a powerful tool for understanding mechanobiology of mechanotransduction modules. The insight and protocols reviewed herein may be expanded and used for investigating other related systems. Specifically, molecular dynamics simulations provide detailed structural insights into the molecular mechanisms of signal transmission within individual molecules and across FA layers or the LINC complex. Furthermore, coarse-grained modeling was shown to be suitable for studying mechanisms and dynamics of transport through the NPC within a reasonable time frame. Molecular crowding limits the interaction between particles, which is not tractable using mean-field approaches such as ODEs. On the other hand, more detailed methods such as MD and BD would significantly limit the achievable spatial and temporal scales. The gap between the capabilities of computationally efficient macroscopic models and more detailed models has created a need for novel techniques. One possibility is developing methods that allow for transferring information across multiple scales, which may be achieved by proper integration of existing computational models.

AUTHOR INFORMATION

Corresponding Author

*Department of Bioengineering, University of California, Berkeley, 208A Stanley Hall #1762, Berkeley, CA 94720-1762. Phone: 510-643-8165. Fax: 510-642-5835. E-mail: mofrad@berkeley.edu.

ORCID

Mohammad R. K. Mofrad: 0000-0001-7004-4859

Notes

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