I&EC research
Industrial & Engineering Chemistry Research

Commentary

pubs.acs.org/IECR

Chemical Engineering Principles in the Field of Cell Mechanics

Richard B. Dickinson and Tanmay P. Lele*

Department of Chemical Engineering, University of Florida, Gainesville, Florida 32611, United States

ABSTRACT: The field of cell mechanics involves problems at the interface of mechanics, molecular transport, biochemical kinetics, thermodynamics, and cell biology. We argue that chemical engineering training is uniquely suited for fruitful research in the field by discussing three examples in the research area. Cell mechanics is already well-represented in many chemical engineering departments and promises to be a vibrant subarea in the profession.

INTRODUCTION

Although cell biology has traditionally been an experimental discipline, in recent years, the importance of mathematical approaches in cell biology has begun to be recognized. This is evident from sessions focused on mathematical modeling in recent conferences organized by the American Society of Cell Biology, recent and ongoing NSF workshops on numerical methods in cell biology, the first annual *Molecular Biology of the Cell* (*MBoC*) special issue on Quantitative Cell Biology[1] (*Molecular Biology of the Cell* (*MBoC*) is the official journal of the American Society for Cell Biology) and the special issue on quantitative cell biology in the *Biophysical Journal*.[2] A subfield of cell biology, which is quantitative by its very nature, is the field of cell mechanics. Cell mechanics involves the interplay of mechanical forces with biomolecular phenomena that enable important cell functions. In this paper, we discuss a few examples that show how the training that chemical engineers receive in undergraduate and graduate curricula can make them uniquely suited for emerging opportunities in the field of cell mechanics.

MODEL IDENTIFICATION—A KEY CHALLENGE IN CELL MECHANICS

Chemical engineers are experts when it comes to applying fundamental concepts from disparate disciplines to solve complex problems under the constraints of limited information. An example is the design of fluidized-bed reactors. Just a partial list of issues that may need to be factored into the design includes complex gas, liquid and solid flows in the reactor, heterogeneous chemical reactions occurring at gas−liquid−solid interfaces, heat- and mass-transfer effects, solid mechanics that may affect particle breakup or aggregation, and so on. The uncertainties include the stochastic nature of the flows, particle size distributions, the several different known and unknown reactions that are occurring, etc. However, there is a well-defined goal: to achieve a defined product distribution. Chemical engineers are uniquely suited to this task, because of their training in both undergraduate and graduate curricula of transport phenomena, reaction kinetics, mathematical modeling and numerical analysis, thermodynamics, and mechanics. The approach in designing such a complex reactor would involve identifying the essential, key features that are pertinent for reactor design, integrating momentum, energy and mass balances, and solving these on a computer.

These same strengths make the chemical engineer remarkably well-suited for solving problems in cell mechanics. Cell mechanics problems typically involve mechanics, molecular transport and chemistry, all of which need to be carefully considered. Adequate training in such disparate disciplines as mechanics, transport, thermodynamics, kinetics, and computation are required, because, otherwise, it is possible to miss crucial aspects of the problem, which can lead to over-simplification and erroneous conclusions. At the same time, mathematical modeling in cell mechanics is an art, because the challenge lies in model identification: what are the essential, key features of the problem that capture the physicochemical situation and what features are unnecessary? This is crucially important for modeling cells, given their extreme complexity.

THE VALUE OF CHEMICAL ENGINEERING "THINKING"

We discuss three problems in the field of cell mechanics here that involve interplay between mechanics and one or more of the following fields: transport, chemical kinetics, and thermodynamics.

Cytoskeletal Assembly and Force Generation. The mechanical and force-generating properties of tissue cells are dependent primarily on the cell cytoskeleton,[3] which consists of networks of semiflexible filaments assembled from protein subunits. The three main types of cytoskeletal filaments are microfilaments (or F-actin), intermediate filaments, and microtubules.[4] Cytoskeletal filaments are highly dynamic in living cells; they are continuously being assembled and disassembled in tightly regulated, spatially and temporally controlled, polymerization reactions. Microfilaments and microtubules (shown schematically in Figure 1) are polar, with a faster rate of assembly at the so-called "plus end" versus the "minus end".[3,4] Newly added subunits to the F-actin or microtubule plus-ends are initially bound to nucleoside triphosphates (adenosine triphosphate (ATP) and guanosine triphosphate (GTP), respectively), and subsequent hydrolysis of the nucleotides on the subunits to nucleoside diphosphate and release of phosphate weakens the subunit−subunit interactions in order to thermodynamically drive subsequent disassembly. In this way, filament plus-ends rich in nucleoside triphosphates (ATP for F-actin, GTP for microtubules) will

DOI: 10.1021/acs.iecr.5b01330
Ind. Eng. Chem. Res. XXXX, XXX, XXX−XXX

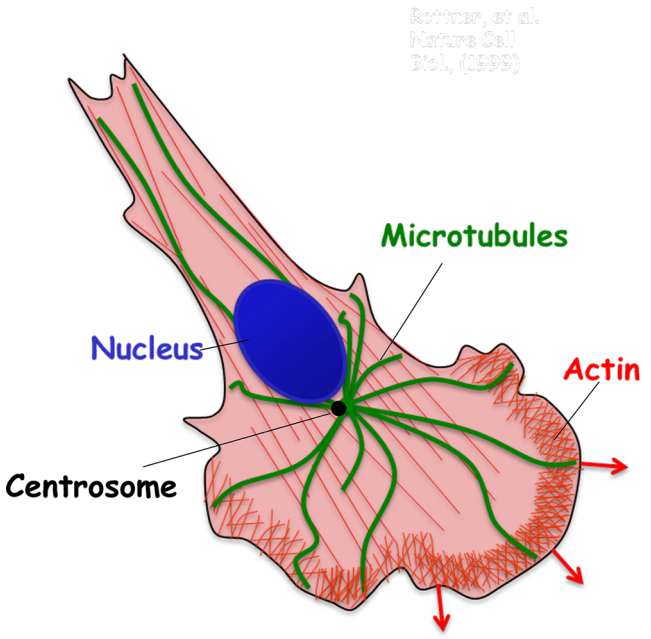

Figure 1. Schematic of a crawling cell, showing the F-actin and microtubule networks. F-actin is assembled primarily at the leading edge of the cell, where it pushes out the membrane in cell protrusions. Microtubules nucleate and polymerize from the centrosome.

tend to grow and those rich in nucleoside diphosphates (ADP or GDP) will tend to shrink within the same solution.[3] Since filaments are multistranded, they are stabilized laterally and longitudinally, with two helically entwined subfilaments for F-actin and for microtubules, typically 13 parallel protofilaments arranged to form a hollow tube. A consequence of lateral association is that spontaneous severing is rare and depolymerization occurs primarily at the filament ends.

In many important cell functions, the assembly or disassembly of filaments is responsible for force generation. For example, actin polymerization generates the force necessary to push out the plasma membrane in cell protrusions[5] (Figure 1). How this is achieved was misunderstood for many years in the literature, yet this puzzle was ultimately resolved with the help of chemical engineering approaches. Analogous to a homogeneous polymerization reaction, actin polymers are nucleated *in vitro* in bulk solution. This led to the long-held view that actin similarly polymerizes in the bulk solution of cell cytoplasm. To generate force, the polymerizing ends were thought to grow from the bulk phase and impinge on the plasma membrane and push by converting the energy released from the binding of new subunits to the filament into the mechanical work required to push out the membrane.[6,7] While plausible, this model could not withstand certain thermodynamic, kinetic, and mechanical considerations. First, a class of proteins found at cell membranes known as nucleation promoting factors (NPFs), such as vasodilator-stimulated phosphoprotein (VASP), were found not only to attach filament tips to the surface, but also to promote the rate of filament assembly by capturing monomers at the pushed surface.[8] Second, not only was monomer binding to NPFs essential for actin-based motility of pathogens, but the speed of polymerization exceeded the maximum diffusion-limited rate for normal filament polymerization in solution, suggesting that the assembly of pushing filaments is a catalyzed reaction.[9] Finally, in some experiments, the mechanical work of polymerization against a load appeared to exceed the energy that would be provided by monomer binding directly to the filament tip, suggesting that pushing filaments must be drawing upon another source of energy.

These observations led to a new model where pushing filaments are assembled in a heterogeneous insertional polymerization at the membrane surface, instead of a homogeneous bulk-phase polymerization.[10−12] In this model, polymerizing filament tips remain persistently tethered to the membrane by multivalent NPFs (Figure 2); one NPF subunit

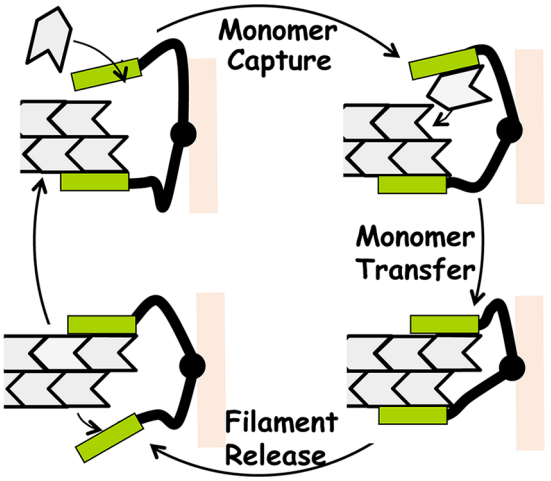

Figure 2. Model for filament end-tracking cycle for actin filament assembly and force generation by multimeric membrane-associated nucleation promoting factors (NPFs) (a dimer is shown in this illustration). One subunit holds the filament tip while others are free to capture monomers from solution. Captured monomers are transferred to the filament tip, an event which releases the NPF subunit from on the now-penultimate filament subunit, thereby completing the cycle.

holds the filament tip while the free monomer-binding domains of other subunit(s) capture monomers from solution and transfer them onto the elongating tethered filament tip. From theoretical arguments,[11] it was shown that actin filament assembly by this mechanism should have important functional advantages for force generation over assembly of an unattached tip impinging on the surface:

(1) The tip is localized at the point of force generation and is less susceptible to Euler buckling;

(2) If the number of local binding sites per tip for monomer capture exceeds one, then the assembly rate by capturing and transferring subunits can, in principle, exceed the diffusion-limited rate of monomer binding directly to the tip, particularly if the force on the impinging tip impedes the direct binding pathway but not monomer capture to the NPFs; and

(3) If the insertional polymerization cycle is coupled to ATP hydrolysis to release the NPF from the subunit after transfer, then the driving force assembly is much larger than the energy released by subunits binding directly to the tip, resulting in a much larger thermodynamic-maximum force.

This insertional polymerization mechanism, which was first proposed in a sequence of theory papers that relied strongly on kinetic and thermodynamic considerations that are well understood from a chemical engineering perspective, was followed by much validating biochemical and biophysical experimentation from various groups, ultimately culminating with direct observation of insertional polymerization with

DOI: 10.1021/acs.iecr.5b01330
Ind. Eng. Chem. Res. XXXX, XXX, XXX−XXX

formins,[13] VASP,[14] or engineered molecules containing the essential actin- and filament tip-binding domains of the VASP's family of NPFs.[15] These latter experiments directly validated the kinetic model for assembly proposed seven years earlier by Dickinson et al.[11] It is now widely accepted that insertional polymerization by NPFs is how actin filaments are assembled within cell protrusions at the leading edge of a crawling tissue cell, if not every else as well *in vivo*. Hence, chemical engineering modeling and analysis revealed the essential mechanism of actin-filament assembly *in vivo*, which is widely relevant to a multitude of cellular functions, and helped turn the field to the actual mechanism long before direct experimental confirmation.

Dynein-Mediated Microtubule Forces and Dynamics. Microtubules nucleate and grow out from an organelle called the centrosome, which is located close to the cell center. In a phenomenon known as "dynamic instability",[16] individual microtubules switch back and forth from a growing phase, where the tip is rich in GTP subunits, to a shrinking phase, where the unstable tip is primarily GDP subunits. Microtubules radiating from the centrosome snake back and forth to probe through the cell cytoplasm to the cell boundaries, and somehow work to maintain the central position of the centrosome. Even though microtubules are very stiff biopolymers,[17] with a persistence length on the order of millimeters, they typically appear bent or buckled inside the cell, with bends having radii of curvatures as small as a micrometer.[18] These bends sometimes appear during and sometimes after microtubule elongation. Such observations lead to two basic questions: what are the forces that bend the microtubules, and how does the array of bent microtubules keep the centrosome at the center of the cell?

One idea is that the growing microtubules impinge on the cell boundaries to push the centrosome away toward the center, and the bent shapes reflect Euler buckling of the stiff microtubules.[19,20] Another idea is that molecular motors linking the microtubules to other cytoskeleton components (collectively called the cytomatrix) pull along the microtubule lengths, such that longer microtubules pull the centrosome with greater force.[21] Since microtubules tend to be longer in directions where the cell periphery is farther from the centrosome, this mechanism naturally centers the centrosome. Through combined experimental and modeling approaches, we provided direct evidence for the latter explanation.[22] By precisely severing microtubules inside living cells using femtosecond laser ablation, we showed that (i) microtubules were actually under a state of tension, not compression, and (ii) this tension was generated by the motor protein dynein. Microtubules did not straighten after severing (as predicted by a state of compression); rather, a newly severed minus end bent further by dynein-generated forces consistent with lengthwise pulling along microtubules. Using a continuum model for microtubule forces, accounting for dynamic instability, bending mechanics, and dynamic dynein linkages between the cytomatrix and microtubules, we showed that lengthwise pulling forces on microtubules undergoing dynamic instability center the centrosome on the time scale observed in the experiments. Using similar approaches, we have also shown that dynein-microtubule interactions can bend growing microtubules and cause the nucleus to rotate.[23,24] This work shows the power of combined engineering modeling/analysis, state-of-the art tools of molecular cell biology, and sophisticated biophysical measurements.

Mechanical Control of Intermolecular Binding. An important goal in the cell mechanics area is to connect phenomena at the molecular level such as force-dependent binding of receptors to ligands,[25−27] to macroscopic mammalian cell behaviors. For example, when mammalian cells adhere to solid substrates, adhesion receptors called integrins that span the cell membrane, ligate with extracellular matrix ligands adsorbed on the substrate surface and cluster into discrete "spot-weld" like sites.[28] In these adhesion sites, initial binding of integrins to extracellular ligands leads to the binding of multiple proteins to the cytoplasmic tails of integrins, finally connecting integrins to the F-actin cytoskeleton. The F-actin cytoskeleton generates tensile forces in the cell through the motoring activity of nonmuscle myosin II. These tensile forces are transmitted at the adhesion sites to the outside substrate; thus, adhesions create a path for mechanical force transfer between the cytoskeleton and the extracellular substrate.[29]

Interestingly, the forces incident on the adhesion proteins cause the growth of adhesions and the binding of several proteins in the adhesion sites.[30] This process enables cells to sense environmental cues such as surface topology, ligand density, and even the mechanical stiffness of the substrate.[31] How mechanical forces control the binding interactions in focal adhesions is an active topic of research. One hypothesis is that mechanical forces incident on proteins modulate their binding interactions with other proteins. Testing this hypothesis is a unique challenge, because most methods to measure binding interactions require isolation of proteins from cells. This naturally destroys the mechanical context of the cell, but also the simultaneous binding interactions that a protein can undergo with multiple binding partners;[32] these multiple interactions are very difficult to study with *in vitro* methods. Methods and approaches that (1) allow quantification of binding kinetics in living cells, and (2) coupled with methods to interfere with mechanical force, would be required to understand the adhesion assembly. Lele et al.[33] used a combination of femtosecond laser ablation, fluorescence photobleaching, and mathematical modeling to address this challenge.

In fluorescence photobleaching, first the protein of interest is fused with a fluorophore, typically another protein such as green fluorescent protein.[34] In a cell that expresses this fluorescent, chimeric protein, a spatially defined small area of interest is exposed to a short pulse of high-intensity irradiation at the excitation wavelength of the fluorophore. This exposure photobleaches the fluorophore, causing the area of interest to appear "dark" locally (see Figure 3); the photobleaching does not disrupt the function of the target molecule, so that the protein of interest, while physically present, is rendered optically invisible. Because the protein will spontaneously unbind and diffuse away, it will be dynamically replaced with fluorescently labeled proteins that will bind in the natural course of continuous binding and unbinding. Thus, fluorescence photobleaching enables the dynamic measurement of fluorescence "recovery" in the bleached spot. With the correct mathematical models for the diffusion and "reaction" in the spot, it should be possible to estimate binding and transport parameters for proteins.[34] Using arguments based on models of reaction and diffusion, we developed approaches to identify the rate-limiting step. We showed that, with the correct experimental design, recovery during fluorescence photobleaching for adhesion proteins in living endothelial cells is not limited by diffusion.[35] This greatly simplifies the situation,

DOI: 10.1021/acs.iecr.5b01330
Ind. Eng. Chem. Res. XXXX, XXX, XXX−XXX

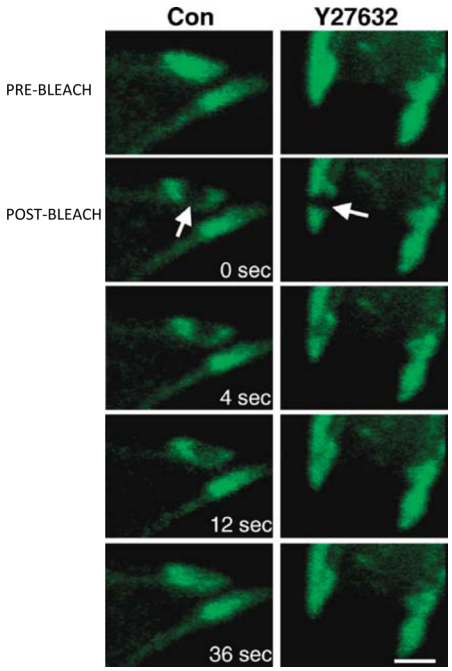

Figure 3. Fluorescence photobleaching analysis of GFP zyxin within individual photobleached focal adhesions in a cell. Representative images of a Fluorescence Recovery After Photobleaching experiment in untreated (Con) versus drug-treated cells (Y27632, which ultimately inhibits cell tension) showing that force dissipation accelerates zyxin recovery. Arrows indicate photobleached spots within individual focal adhesions that are analyzed over a period of 36 s follow photobleaching (scale bar = 2 μm). (Modified with permission from ref 17. Copyright 2006, Wiley–Liss, Inc.)

allowing the formulation of mathematical models that can estimate the dissociation rate constant of proteins from adhesions.

Importantly, because the living cell and its structure is preserved during the process that quantifies the dissociation rate constants, it is possible to ask how mechanical forces may control binding interactions. We used drugs that targeted myosin activity to inhibit tension at focal adhesions, cultured cells on substrates of varying rigidity that modulate intracelluar tension, and also a femtosecond laser to sever individual actomyosin bundles that pull on adhesions, and then measured the dissociation rate constant of the adhesion protein zyxin[33] (see Figure 3). We discovered that mechanical force causes a decrease in the dissociation constant of zyxin, but not vinculin (another protein), which explains how zyxin assembles in adhesions with increasing tension. These results demonstrated a molecular mechanism by which the interplay between mechanics and chemistry enables key cellular functions.

OUTLOOK

Similar to the problems that D. Ramkrishna has so successfully tackled[36,37] (and continues to address) in the field of cybernetic and/or population balance-based modeling, the challenge in cell mechanics is to develop tractable and relevant models when the biological system is not fully understood. The examples highlighted here show how the use of chemical engineering thinking—from thermodynamics, kinetics, and transport—can be creatively applied in the field of experimental and theoretical cell mechanics to solve complex problems. Cell mechanics is already well-represented in chemical engineering departments across the country, including faculty members who are either chemical engineers by training or hold appointments in chemical engineering departments. Active areas of interest that are benefiting from chemical engineering thinking include cell migration,[38,39,40−42] actin and microtubule assembly and mechanics,[43−45,46] adhesion bonds and traction forces,[25,47,48] cell−cell adhesion,[49−51] neutrophil rolling,[52,53] cell behavior under flows,[54,55] ligand−receptor interactions,[27,56] tissue mechanics,[57,58,59] nuclear mechanics,[60−68] and cell mechanotransduction.[69−75] Cell mechanics will continue to remain an important and vibrant part of the chemical engineering profession for many years to come.

AUTHOR INFORMATION

Corresponding Author

*Tel.: 352-392-0317. Fax: 352-392-9513. Address: Department of Chemical Engineering, Bldg. 723, University of Florida, Gainesville, FL 32611. E-mail: tlele@che.ufl.edu.

Notes

The authors declare no competing financial interest.

REFERENCES

(1) Lippincott-Schwartz, J. Quantitative cell biology: transforming the conceptual, theoretical, instrumental, and methodological approaches to cell biology. *Mol. Biol. Cell* **2014**, *25* (22), 3437.
(2) Piston, D. W. Biophysical Journal special issue: focus on quantitative cell biology. *Biophys. J.* **2014**, *107* (11), E01.
(3) Bray, D. *Cell Movements: From Molecules to Motility*, 2nd Edition; Garland Publishing: New York, 2001.
(4) Alberts, B.; Johnson, A.; Lewis, J.; Morgan, D.; Raff, M.; Roberts, K.; Walter, P. *Molecular Biology of the Cell*, 6th Edition; Garland Science: New York, 2014.
(5) Ponti, A.; Machacek, M.; Gupton, S. L.; Waterman-Storer, C. M.; Danuser, G. Two distinct actin networks drive the protrusion of migrating cells. *Science* **2004**, *305* (5691), 1782−1786.
(6) Hill, T. L. Microfilament or microtubule assembly or disassembly against a force. *Proc. Natl. Acad. Sci. U.S.A.* **1981**, *78*, 5613−5617.
(7) Mogilner, A.; Oster, G. Cell motility driven by actin polymerization. *Biophys. J.* **1996**, *71* (6), 3030−3045.
(8) Bear, J. E.; Svitkina, T. M.; Krause, M.; Schafer, D. A.; Loureiro, J. J.; Strasser, G. A.; Maly, I. V.; Chaga, O. Y.; Cooper, J. A.; Borisy, G. G.; Gertler, F. B. Antagonism between Ena/VASP proteins and actin filament capping regulates fibroblast motility. *Cell* **2002**, *109* (4), 509−521.
(9) Dickinson, R. B.; Southwick, F. S.; Purich, D. L. A direct-transfer polymerization model explains how the multiple profilin-binding sites in the actoclampin motor promote rapid actin-based motility. *Arch. Biochem. Biophys.* **2002**, *406* (2), 296−301.
(10) Dickinson, R. B. Models for actin polymerization motors. *J. Math Biol.* **2009**, *58* (1−2), 81−103.
(11) Dickinson, R. B.; Caro, L.; Purich, D. L. Force generation by cytoskeletal filament end-tracking proteins. *Biophys. J.* **2004**, *87* (4), 2838−2854.
(12) Dickinson, R. B.; Purich, D. L. Clamped-filament elongation model for actin-based motors. *Biophys. J.* **2002**, *82* (2), 605−617.
(13) Higashida, C.; Miyoshi, T.; Fujita, A.; Oceguera-Yanez, F.; Monypenny, J.; Andou, Y.; Narumiya, S.; Watanabe, N. Actin polymerization-driven molecular movement of mDia1 in living cells. *Science* **2004**, *303* (5666), 2007−2010.
(14) Breitsprecher, D.; Kiesewetter, A. K.; Linkner, J.; Urbanke, C.; Resch, G. P.; Small, J. V.; Faix, J. Clustering of VASP actively drives processive, WH2 domain-mediated actin filament elongation. *EMBO J.* **2008**, *27* (22), 2943−2954.
(15) Breitsprecher, D.; Kiesewetter, A. K.; Linkner, J.; Vinzenz, M.; Stradal, T. E.; Small, J. V.; Curth, U.; Dickinson, R. B.; Faix, J.

DOI: 10.1021/acs.iecr.5b01330
Ind. Eng. Chem. Res. XXXX, XXX, XXX−XXX

Molecular mechanism of Ena/VASP-mediated actin-filament elongation. *EMBO J.* **2011**, *30* (3), 456−467.
(16) Schulze, E.; Kirschner, M. Microtubule dynamics in interphase cells. *J. Cell Biol.* **1986**, *102* (3), 1020−1031.
(17) Gittes, F.; Mickey, B.; Nettleton, J.; Howard, J. Flexural rigidity of microtubules and actin filaments measured from thermal fluctuations in shape. *J. Cell Biol.* **1993**, *120* (4), 923−934.
(18) Odde, D. J.; Ma, L.; Briggs, A. H.; DeMarco, A.; Kirschner, M. W. Microtubule bending and breaking in living fibroblast cells. *J. Cell Sci.* **1999**, *112* (Pt 19), 3283−3288.
(19) Brangwynne, C. P.; MacKintosh, F. C.; Kumar, S.; Geisse, N. A.; Talbot, J.; Mahadevan, L.; Parker, K. K.; Ingber, D. E.; Weitz, D. A. Microtubules can bear enhanced compressive loads in living cells because of lateral reinforcement. *J. Cell Biol.* **2006**, *173* (5), 733−741.
(20) Holy, T. E.; Dogterom, M.; Yurke, B.; Leibler, S. Assembly and positioning of microtubule asters in microfabricated chambers. *Proc. Natl. Acad. Sci. U.S.A.* **1997**, *94* (12), 6228−6231.
(21) Burakov, A.; Nadezhdina, E.; Slepchenko, B.; Rodionov, V. Centrosome positioning in interphase cells. *J. Cell Biol.* **2003**, *162* (6), 963−969.
(22) Wu, J.; Misra, G.; Russell, R. J.; Ladd, A. J.; Lele, T. P.; Dickinson, R. B. Effects of dynein on microtubule mechanics and centrosome positioning. *Mol. Biol. Cell* **2011**, *22* (24), 4834−4841.
(23) Wu, J.; Lee, K. C.; Dickinson, R. B.; Lele, T. P. How dynein and microtubules rotate the nucleus. *J. Cell Physiol.* **2011**, *226* (10), 2666−2674.
(24) Shekhar, N.; Neelam, S.; Wu, J.; Ladd, A. J.; Dickinson, R. B.; Lele, T. P. Fluctuating Motor Forces Bend Growing Microtubules. *Cell Mol. Bioeng.* **2013**, *6* (2), 120−129.
(25) Hammer, D. A. Adhesive dynamics. *J. Biomech. Eng.* **2014**, *136* (2), 021006.
(26) Panorchan, P.; Thompson, M. S.; Davis, K. J.; Tseng, Y.; Konstantopoulos, K.; Wirtz, D. Single-molecule analysis of cadherin-mediated cell-cell adhesion. *J. Cell Sci.* **2006**, *119* (Pt 1), 66−74.
(27) Hanley, W.; McCarty, O.; Jadhav, S.; Tseng, Y.; Wirtz, D.; Konstantopoulos, K. Single molecule characterization of P-selectin/ligand binding. *J. Biol. Chem.* **2003**, *278* (12), 10556−10561.
(28) Lele, T. P.; Thodeti, C. K.; Ingber, D. E. Force meets chemistry: Analysis of mechanochemical conversion in focal adhesions using fluorescence recovery after photobleaching. *J. Cell Biochem.* **2006**, *97* (6), 1175−1183.
(29) Chicurel, M. E.; Chen, C. S.; Ingber, D. E. Cellular control lies in the balance of forces. *Curr. Opin Cell Biol.* **1998**, *10* (2), 232−239.
(30) Riveline, D.; Zamir, E.; Balaban, N. Q.; Schwarz, U. S.; Ishizaki, T.; Narumiya, S.; Kam, Z.; Geiger, B.; Bershadsky, A. D. Focal contacts as mechanosensors: Externally applied local mechanical force induces growth of focal contacts by an mDia1-dependent and ROCK-independent mechanism. *J. Cell Biol.* **2001**, *153* (6), 1175−1186.
(31) Prager-Khoutorsky, M.; Lichtenstein, A.; Krishnan, R.; Rajendran, K.; Mayo, A.; Kam, Z.; Geiger, B.; Bershadsky, A. D. Fibroblast polarization is a matrix-rigidity-dependent process controlled by focal adhesion mechanosensing. *Nat. Cell Biol.* **2011**, *13* (12), 1457−1465.
(32) Geiger, T.; Zaidel-Bar, R. Opening the floodgates: Proteomics and the integrin adhesome. *Curr. Opin Cell Biol.* **2012**, *24* (5), 562−568.
(33) Lele, T. P.; Pendse, J.; Kumar, S.; Salanga, M.; Karavitis, J.; Ingber, D. E. Mechanical forces alter zyxin unbinding kinetics within focal adhesions of living cells. *J. Cell Physiol.* **2006**, *207* (1), 187−194.
(34) Mueller, F.; Mazza, D.; Stasevich, T. J.; McNally, J. G. FRAP and kinetic modeling in the analysis of nuclear protein dynamics: What do we really know? *Curr. Opin. Cell Biol.* **2010**, *22* (3), 403−411.
(35) Lele, T. P.; Thodeti, C. K.; Pendse, J.; Ingber, D. E. Investigating complexity of protein−protein interactions in focal adhesions. *Biochem. Biophys. Res. Commun.* **2008**, *369* (3), 929−934.
(36) Varner, J.; Ramkrishna, D. Metabolic engineering from a cybernetic perspective. 1. Theoretical preliminaries. *Biotechnol. Prog.* **1999**, *15* (5), 407−425.
(37) Ramkrishna, D. *Population balances: Theory and applications to particulate systems in engineering*, Academic Press, 2000.
(38) Stroka, K. M.; Gu, Z.; Sun, S. X.; Konstantopoulos, K. Bioengineering paradigms for cell migration in confined microenvironments. *Curr. Opin. Cell Biol.* **2014**, *30*, 41−50.
(39) Hind, L. E.; Dembo, M.; Hammer, D. A. Macrophage motility is driven by frontal-towing with a force magnitude dependent on substrate stiffness. *Integr. Biol.* **2015**, *7* (4), 447−453.
(40) Schneider, I . C.; Haugh, J. M. Quantitative Elucidation of a Distinct Spatial Gradient Sensing Mechanism in Fibroblasts. *J. Cell Biol.* **2005**, *171*, 883−892.
(41) Haage, A.; Schneider, I .C. Cellular Contractility and Extracellular Matrix Stiffness Regulate Matrix Metalloproteinase Activity in Pancreatic Cancer Cells. *The FASEB J.* **2014**, *8*, 3589−3599.
(42) Gardel, M. L.; Schneider, I. C.; Aratyn-Schaus, Y.; Waterman, C. Mechanical Integration of Actin and Adhesion Dynamics in Cell Migration. *Ann. Rev. of Cell and Dev. Biol.* **2010**, *26*, 315−333.
(43) Odde, D. J. Mitosis, diffusible crosslinkers, and the ideal gas law. *Cell* **2015**, *160* (6), 1041−1043.
(44) Prahl, L. S.; Castle, B. T.; Gardner, M. K.; Odde, D. J. Quantitative analysis of microtubule self-assembly kinetics and tip structure. *Methods Enzymol.* **2014**, *540*, 35−52.
(45) Stachowiak, M. R.; Smith, M. A.; Blankman, E.; Chapin, L. M.; Balcioglu, H. E.; Wang, S.; Beckerle, M. C.; O'Shaughnessy, B. A mechanical-biochemical feedback loop regulates remodeling in the actin cytoskeleton. *Proc. Natl. Acad. Sci. U.S.A.* **2014**, *111* (49), 17528−17533.
(46) Kraning-Rush, C.; Carey, S. P.; Califano, J. P.; Smith, B. N.; Reinhart-King, C. A. The Role of the Cytoskeleton in Cellular Force Generation in 2D and 3D. *Phys. Biol.* **2011**, *8* (1), 015009.
(47) Bangasser, B. L.; Rosenfeld, S. S.; Odde, D. J. Determinants of maximal force transmission in a motor-clutch model of cell traction in a compliant microenvironment. *Biophys. J.* **2013**, *105* (3), 581−592.
(48) Bhasin, N.; Carl, P.; Harper, S.; Feng, G.; Lu, H.; Speicher, D. W.; Discher, D. E. Chemistry on a single protein, vascular cell adhesion molecule-1, during forced unfolding. *J. Biol. Chem.* **2004**, *279* (44), 45865−45874.
(49) Barry, A. K.; Wang, N.; Leckband, D. E. Local VE-cadherin mechanotransduction triggers long-ranged remodeling of endothelial monolayers. *J. Cell Sci.* **2015**, *128* (7), 1341−1351.
(50) Kim, T. J.; Zheng, S.; Sun, J.; Muhamed, I.; Wu, J.; Lei, L.; Kong, X.; Leckband, D. E.; Wang, Y. Dynamic visualization of α-catenin reveals rapid, reversible conformation switching between tension states. *Curr. Biol.* **2015**, *25* (2), 218−224.
(51) Leckband, D. E.; de Rooij, J. Cadherin adhesion and mechanotransduction. *Annu. Rev. Cell Dev. Biol.* **2014**, *30*, 291−315.
(52) Furlow, M.; Diamond, S. L. Interplay between membrane cholesterol and ethanol differentially regulates neutrophil tether mechanics and rolling dynamics. *Biorheology* **2011**, *48* (1), 49−64.
(53) Robbins, G. P.; Lee, D.; Katz, J. S.; Frail, P. R.; Therien, M. J.; Crocker, J. C.; Hammer, D. A. Effects of Membrane Rheology on Leuko-polymersome Adhesion to Inflammatory Ligands. *Soft Matter* **2011**, *7* (2), 769−779.
(54) Vahidkhah, K.; Diamond, S. L.; Bagchi, P. Platelet dynamics in three-dimensional simulation of whole blood. *Biophys. J.* **2014**, *106* (11), 2529−2540.
(55) Wang, P.; Chen, S. H.; Hung, W. C.; Paul, C.; Zhu, F.; Guan, P. P.; Huso, D. L.; Kontrogianni-Konstantopoulos, A.; Konstantopoulos, K. Fluid shear promotes chondrosarcoma cell invasion by activating matrix metalloproteinase 12 via IGF-2 and VEGF signaling pathways. *Oncogene* **2014**, DOI: 10.1038/onc.2014.397.
(56) Chang, M. I.; Panorchan, P.; Dobrowsky, T. M.; Tseng, Y.; Wirtz, D. Single-molecule analysis of human immunodeficiency virus type 1 gp120-receptor interactions in living cells. *J. Virol.* **2005**, *79* (23), 14748−14755.
(57) Lai, V. K.; Hadi, M. F.; Tranquillo, R. T.; Barocas, V. H. A multiscale approach to modeling the passive mechanical contribution of cells in tissues. *J. Biomech. Eng.* **2013**, *135* (7), 71007.

DOI: 10.1021/acs.iecr.5b01330
Ind. Eng. Chem. Res. XXXX, XXX, XXX−XXX

(58) Weidenhamer, N. K.; Tranquillo, R. T. Influence of cyclic mechanical stretch and tissue constraints on cellular and collagen alignment in fibroblast-derived cell sheets. *Tissue Eng., Part C* **2013**, *19* (5), 386−395.
(59) Varner, V. D.; Nelson, C. M. Cellular and physical mechanisms of branching morphogenesis. *Development* **2014**, *141*, 2750−2759.
(60) Alam, S. G.; Lovett, D.; Kim, D. I.; Roux, K.; Dickinson, R. B.; Lele, T. P. The nucleus is an intracellular propagator of tensile forces in NIH 3T3 fibroblasts. *J. Cell Sci.* **2015**, *128*, 1902−1911.
(61) Neelam, S.; Chancellor, T. J.; Li, Y.; Nickerson, J. A.; Roux, K. J.; Dickinson, R. B.; Lele, T. P. Direct force probe reveals the mechanics of nuclear homeostasis in the mammalian cell. *Proc. Natl. Acad. Sci. U.S.A.* **2015**, *112* (18), 5720−5725.
(62) Kim, D. H.; Chambliss, A. B.; Wirtz, D. The multi-faceted role of the actin cap in cellular mechanosensation and mechanotransduction. *Soft Matter* **2013**, *9* (23), 5516−5523.
(63) Spagnol, S. T.; Dahl, K. N. Active cytoskeletal force and chromatin condensation independently modulate intranuclear network fluctuations. *Integr. Biol.* **2014**, *6* (5), 523−531.
(64) Dahl, K. N.; Ribeiro, A. J.; Lammerding, J. Nuclear shape, mechanics, and mechanotransduction. *Circ. Res.* **2008**, *102* (11), 1307−1318.
(65) Buxboim, A.; Swift, J.; Irianto, J.; Spinler, K. R.; Dingal, P. C.; Athirasala, A.; Kao, Y. R.; Cho, S.; Harada, T.; Shin, J. W.; Discher, D. E. Matrix elasticity regulates lamin-A,C phosphorylation and turnover with feedback to actomyosin. *Curr. Biol.* **2014**, *24* (16), 1909−1917.
(66) Swift, J.; Ivanovska, I. L.; Buxboim, A.; Harada, T.; Dingal, P. C.; Pinter, J.; Pajerowski, J. D.; Spinler, K. R.; Shin, J. W.; Tewari, M.; Rehfeldt, F.; Speicher, D. W.; Discher, D. E. Nuclear lamin-A scales with tissue stiffness and enhances matrix-directed differentiation. *Science* **2013**, *341* (6149), 1240104.
(67) Broedersz, C. P.; Brangwynne, C. P. Nuclear mechanics: Lamin webs and pathological blebs. *Nucleus* **2013**, *4* (3), 156−159.
(68) Feric, M.; Brangwynne, C. P. A nuclear F-actin scaffold stabilizes ribonucleoprotein droplets against gravity in large cells. *Nat. Cell Biol.* **2013**, *15* (10), 1253−1259.
(69) Engler, A. J.; Sen, S.; Sweeney, H. L.; Discher, D. E. Matrix elasticity directs stem cell lineage specification. *Cell* **2006**, *126* (4), 677−689.
(70) Keung, A. J.; Asuri, P.; Kumar, S.; Schaffer, D. V. Soft microenvironments promote the early neurogenic differentiation but not self-renewal of human pluripotent stem cells. *Integr. Biol.* **2012**, *4* (9), 1049−1058.
(71) Pathak, A.; Kumar, S. Independent regulation of tumor cell migration by matrix stiffness and confinement. *Proc. Natl. Acad. Sci. U. S. A.* **2012**, *109* (26), 10334−10339.
(72) Keung, A. J.; de Juan-Pardo, E. M.; Schaffer, D. V.; Kumar, S. Rho GTPases mediate the mechanosensitive lineage commitment of neural stem cells. *Stem Cells* **2011**, *29* (11), 1886−1897.
(73) Lee, J.; Chu, B. H.; Sen, S.; Gupte, A.; Chancellor, T. J.; Chang, C. Y.; Ren, F.; Kumar, S.; Lele, T. P. Modulating malignant epithelial tumor cell adhesion, migration and mechanics with nanorod surfaces. *Biomed. Microdevices* **2011**, *13* (1), 89−95.
(74) Lele, P. P.; Hosu, B. G.; Berg, H. C. Dynamics of mechanosensing in the bacterial flagellar motor. *Proc. Natl. Acad. Sci. U.S.A.* **2013**, *110* (29), 11839−11844.
(75) Lele, P. P.; Branch, R. W.; Nathan, V. S.; Berg, H. C. Mechanism for adaptive remodeling of the bacterial flagellar switch. *Proc. Natl. Acad. Sci. U.S.A.* **2012**, *109* (49), 20018−20022.

DOI: 10.1021/acs.iecr.5b01330
Ind. Eng. Chem. Res. XXXX, XXX, XXX−XXX