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Emerging technologies in mechanotransduction research

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Mechanotransduction research focuses on understanding how cells sense and respond to mechanical stimuli by converting mechanical signals into biochemical and biological responses. Cells have been shown to respond to mechanical stimuli through specialized biological machinery such as adhesion complexes. Research in the last two decades helped in identifying key components of cellular mechanotransduction. In recent years, integrated approaches, which are highlighted here, are emerging to provide new insights into the mechanistic and theoretical underpinnings of mechanotransduction. In particular, mathematical modeling has helped elucidate the mechanism underlining ligand spacing and distribution sensing, as well as sensing viscoelastic properties of the extracellular matrix. In addition, molecular tension sensors have helped dissect the forces involved in mechanotransduction at high spatial and temporal resolutions.

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Introduction

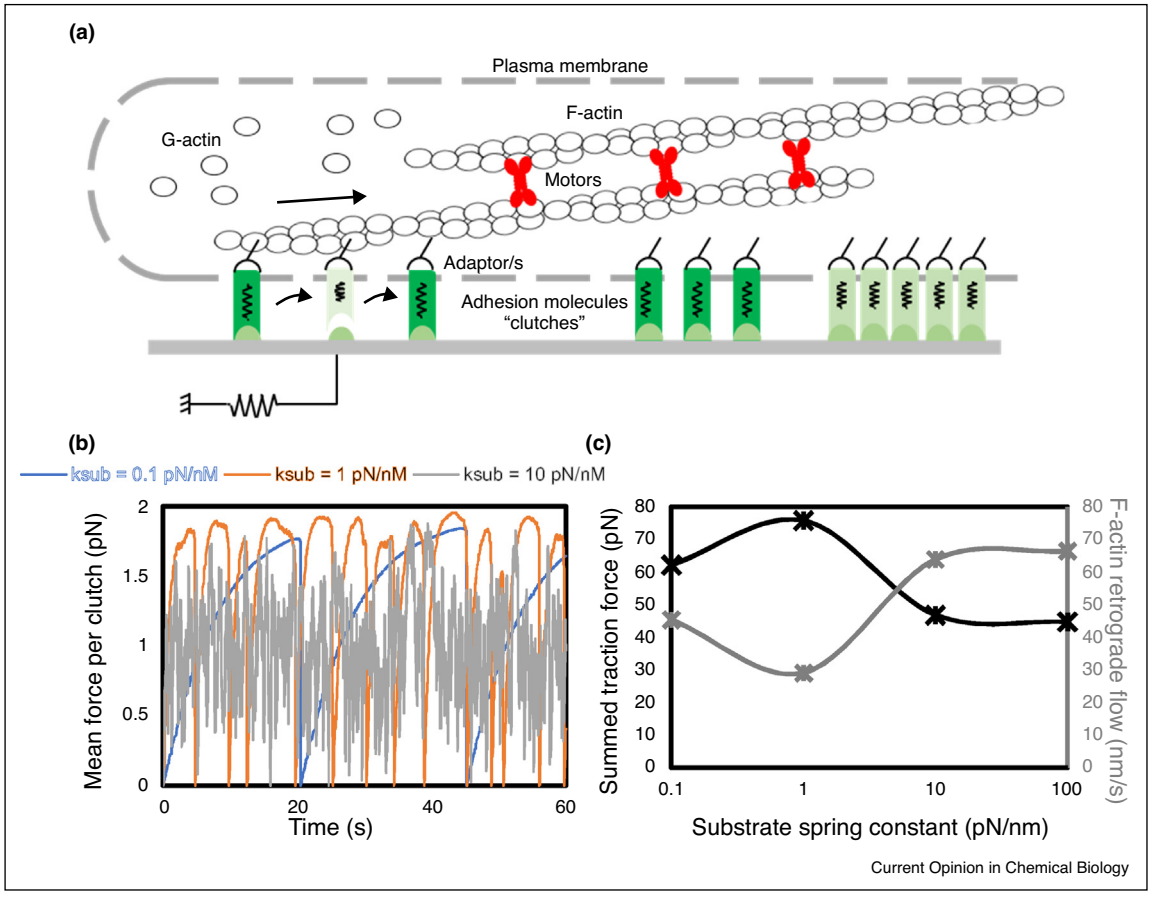
The extracellular matrix (ECM) plays a crucial role in many cellular functions including cell proliferation, migration, and differentiation [1]. The ability of cells to sense and respond to changes in their microenvironment is essential for maintaining cellular function and tissue homeostasis [2]. Decades of research have expanded our understanding of cells' ability to sense their physical environment and respond by triggering downstream events. The ability of cells to convert mechanical signals into biochemical and behavioral responses is known as mechanotransduction [3]. Cells use physical forces to probe and remodel their physical environment [4,5]. Changes in the mechanics of the environment lead to changes in force transmission which then trigger downstream events [6]. Part of cells' ability to respond to the mechanics of their environment requires cells' ability to generate and transmit forces. This requires physical cell-ECM and cell–cell interactions through specialized transmembrane proteins such as integrins and cadherins.

In recent years, integrated approaches are emerging to provide new insights into the mechanistic and theoretical underpinnings of mechanotransduction. This includes the use of physics-based mathematical-computational modeling, advanced molecular and imaging tools, and advanced fabrication techniques. In this article, we highlight the recent impact of mathematical-computational modeling and the development of molecular tension sensors in aiding our mechanistic understanding of mechanotransduction. *We contend that integrating mathematical-computational modeling with molecular-scale force measurements will significantly advance our understanding of the mechanisms of mechanotransduction.*

Mathematical modeling in mechanotransduction

Mathematical and computational modeling provides the ability to integrate knowledge and to explain and predict non-intuitive behaviors both qualitatively and quantitatively. Computational modeling has enabled engineers and scientists to address complex questions and design sophisticated experiments to help understand multifaceted processes, especially where closed form analytical solutions are difficult or impossible to obtain. In mechanotransduction, modeling has helped us describe how cells transmit forces and respond to the mechanical and biochemical properties of the microenvironment. This includes cells' ability to sense the substrate elastic and viscoelastic properties [7–9] as well as to sense ligand density and distribution [10••]. Many models of mechanotransduction have relied on the molecular clutch hypothesis which describes how cells transmit forces, generated by the actomyosin interaction and actin polymerization, to the outside environment through plasma membrane-spanning adhesion molecules, such as integrins, termed 'molecular clutches' [11]. On the basis of the molecular clutch hypothesis, the motor-clutch model was developed to explain the theoretical mechanism by which cellular protrusions transmit contractile forces and respond to the stiffness of their microenvironment (Figure 1a) [12]. In the motor-clutch model, molecular motors transmit forces to the external environment through rigid actin filaments

Figure 1



The motor-clutch model of force transmission. **(a)** A schematic of the motor clutch model illustrating force transmission on a linear elastic substrate. **(b)** and **(c)** Output of motor-clutch model simulations showing the effect of substrate stiffness (κ_{sub}) on clutch force dynamic, summed traction forces, and F-actin retrograde flow.

and compliant transmembrane molecular clutches [12,13]. Importantly, the force generation is provided by myosin molecular motors and/or F-actin polymerization against the plasma membrane, both of which obey a force-velocity relationship. The consequence of the force-velocity relationship is that when a cell is pulling on soft environments, it takes longer time to reach a high traction force than when a cell is pulling on a stiff environment, which becomes a key determinant of stiffness sensing (Figure 1b-c) [13,14]. In recent years, the framework of the motor-clutch model has been adapted to investigate key aspects of mechanotransduction including rigidity sensing, adhesion reinforcement, viscoelasticity sensing, and ligand density and distribution [9,10••,15•,16,17••,18–21].

The stiffness of the environment has been shown to control cellular force transmission, migration, differentiation, and cancer progression [22]. The use of mathematical modeling provided a mechanical mechanism, by which force transmission is controlled by the stiffness of the environment. In the original framework of the motor-clutch model, stiffness regulation of adhesion binding dynamics elicits a biphasic force transmission and F-actin retrograde flow as a function of substrate stiffness [12]. Further parameter space analyses and experimental validation demonstrated mechanisms regulating mechanosensitivity and the determinant of optimal stiffness [13,19]. Despite the biphasic force transmission predicted in the model, monotonic force transmission as a function of substrate stiffness was being reported in the literature, which was not predicted in the motor-clutch model [23]. However, we note that the observation of a monotonically increasing traction force as a function of substrate stiffness is consistent with a biphasic prediction, assuming the optimal stiffness is above the highest stiffness measured in the experiment. In recent work, Elosegui-Artola *et al.* incorporated a switch-like mechanosensitivity regulation to model adhesion reinforcement through talin [21], which has been shown to unfold under force and expose cryptic binding sites to vinculin [24]. Talin mechano-response was modeled by recruiting

additional clutches to the site of adhesion after surpassing a threshold force. As a result, a monotonic force transmission as a function of stiffness was predicted in the model [21]. Indeed, in cells expressing talin, increasing stiffness results in monotonically increasing force transmission, but when talin is knocked-out a biphasic stiffness-force transmission relationship is restored as predicted in the base motor-clutch model [12,21].

In addition to responding to substrate rigidity, cells sense and respond to substrate stress relaxation (substrate viscoelasticity) [8,9]. Indeed, living tissues and reconstituted extracellular matrices were shown to exhibit stress relaxation property [25]. Like substrate Young's modulus, substrate stress relaxation enhances cell spreading [9], and regulates stem cell fate [26]. Recently, Gong *et al.* applied Monte Carlo and analytical methods to simulate cell spreading in response to substrate viscosity to explore the mechanism of substrate viscosity sensing [17••]. Using the motor-clutch model framework and a standard linear viscoelastic model to describe the substrate, they explored the effect of different material properties (viscosity and elasticity) on cell spreading. They identified an optimal substrate viscosity, at which cell spreading is maximum, that is determined by the ratio of clutch binding and substrate relaxation timescales. Their finding suggests that substrate viscosity stiffens soft substrates to enhance clutch engagement and cell spreading by balancing substrate relaxation and clutch binding timescales. Using elastic and viscoelastic materials, they were able to show an increase in cell spreading in response to viscosity. In this work, computational modeling again informed the design of more sophisticated experiments to help understand the role of substrate viscoelastic properties on cellular spreading and function.

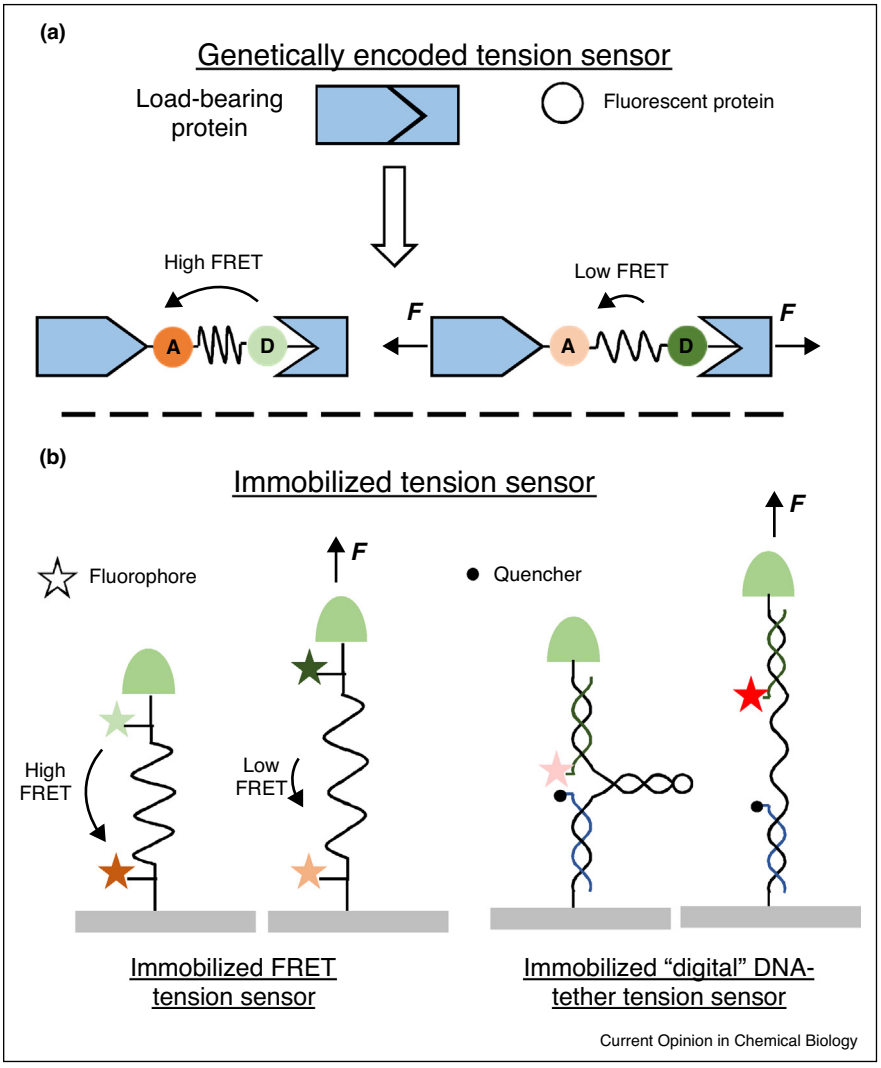
Mathematical modeling has also had an impact in predicting the cellular response to ligand density and distribution. Ligand density has been shown to control cell migration speed *in vitro*, *in vivo*, and *in silico* using computation modeling [18,27,28]. Oria *et al.* investigated cells' ability to sense ligand spacing utilizing advanced fabrication techniques and mathematical modeling. They found ligand spacing and distribution control adhesion's growth and collapse, which ultimately affected YAP nuclear localization [10••]. At low substrate stiffness, increasing ligand spacing promoted the growth of focal adhesions, but led to adhesion collapse on rigid substrates. They were able to explain the observed behavior using a molecular-clutch mechanism. In their model, the spacing of ligands was incorporated and neighboring ligands were linked together using elastic springs. The model predicted that increasing ligand spacing would promote adhesion growth by increasing the likelihood of reaching a threshold force which leads to integrin recruitment and adhesion growth. As stiffness continues to increase, forces continue to increase leading to the unbinding of clutches and adhesion collapse. When ligand spacing is low, forces are distributed across more ligands, reducing the likelihood of reaching the threshold force on low substrate stiffness. Simply put, increasing the spacing of ligand reduces the force needed to cross the threshold force per integrin needed for adhesion recruitment. This leads to a shift in the stiffness at which adhesion recruitment occurs. Having a computational model capable of explaining the experimental results, allowed the authors to model different perturbations and design new experiments to further characterize the molecular components that control the cell's ability to sense ligand spacing. Highlighting the value of the model in predicting non-intuitive behavior, the model predicted a biphasic response to contractility inhibition on a rigid substrate. As predicted, a low dose of blebbistatin *increased* adhesion length by preventing adhesion collapse but a higher dose did not alter adhesion length because it prevented adhesion reinforcement and adhesion growth [10••]. Such counterintuitive predictions and experimental validations both build our confidence in the models and provide fundamental new insights.

Molecular tension sensors in mechanotransduction

Various methods have been developed to quantify forces on individual adhesion bonds involved in mechanotransduction; including single-molecule force spectroscopy, traction force microscopy, and molecular tension sensors; these methods are reviewed in depth by Roca-Cusachs *et al.* [5]. In this section, we highlight the impact of molecular tension sensors in mechanotransduction. Molecular tension sensors were developed to measure nanometer-scale displacements caused by mechanical tension within load-bearing proteins. Most of the tension probes utilize Förster Resonance Energy Transfer (FRET) to measure the distance between two fluorophores (donor and acceptor) separated by a mechanically characterized linker [29,30]. This allows for molecular tension measurements using light microscopy. FRET-based molecular tension sensors have been applied to study mechanotransduction by either genetically encoding the tension sensor within the protein of interest [30,31,32••,33••] or by immobilizing it on the substrate on the molecule supporting cell adhesion (Figure 2) [34,35•].

The first genetically encoded tension sensor was developed by Grashoff *et al.* where they designed a tension sensor module (TSMod) consisting of two fluorophores (mTFP-1 and Venus(A206K)) linked by a 40-amino-acid-long linker that acts like an elastic spring [30]. Using their tension sensor module, they were able to measure mechanical tension across vinculin, a protein which connects the F-actin filaments to integrins, that is a so-called 'adaptor' protein crucial to the molecular clutch bonds that mediate cell adhesion to the environment. Using

Figure 2



Commonly used molecular tension sensor designs. **(a)** a schematic of a genetically encoded tension sensor utilizing FRET, A: acceptor, D: donor. **(b)** schematics of two immobilized tension sensor designs, one a FRET-based tension sensor, and the other a DNA-tether tension sensor with proximity-based fluorescence quenching.

their FRET-based tension sensor they showed that during adhesion growth and assembly tension across vinculin is highest. Furthermore, using fluorescent lifetime imaging, they reported that individual vinculin molecules experience an average force of 2.5 pN.

FRET-based tension sensors have been used to measure tension across proteins involved in mechanotransduction. In a recent study, Ringer *et al.*, developed a FRET-based tension sensor module with switch-like behavior and increased sensitivity at 3–5 pN [36]. Using their improved tension sensor module, they sought to measure intramolecular force within talin-1. By placing their tension sensor modules at different locations within the talin-1 rod domain, they identified a vinculin-dependent tension gradient within the rod domain of talin-1. They reported higher tension closer to the head domain (N-terminal), low tension in between actin-binding domains (C-terminal), and no tension at the C-terminal end of talin-1. This demonstrates that higher forces are exerted at the N-terminal part of the talin rod domain, presumably due to the presence of vinculin binding sites which provide an extra mechanical linkage that distribute load to the F-actin cytoskeleton. Because of switch-like behavior of their tension sensor module, they were able to calculate the fraction of talin molecules under tension and showed that close to 70% of talin molecules are under tension at the N-terminal end of the rod domain and only 40% are under tension at the C-terminal end of the rod domain. Their work also provided a new sensor design utilizing

two different pairs of fluorophores, which allows for simultaneous measurement of tension on two different proteins.

Previous designs of FRET-based tension sensors were limited in the range of forces detected (i.e. pNs) and relied on tension sensor calibrations using purified proteins [30]. In more recent advances in FRET-based molecular tension probes, LaCroix *et al.* developed tunable peptide designs with wider ranges of force magnitude sensitivity [33••]. Their new designs use biophysical modeling to more accurately calibrate the tension probe using peptide length and avoid the extensive calibration normally needed. Using their new design and method, they developed an optimized tension sensor module and detected a force gradient within focal adhesions by measuring forces across vinculin. In addition, using tension sensors with distinct mechanical sensitivities and lengths, they demonstrated an extension-based control of vinculin loading. Having developed these tension sensors allowed them to explore extension-based versus force-based control of force loading. They showed, in the presence of tension sensors with different mechanical properties, cells were able to maintain extension by adjusting forces applied on vinculin. This result highlights the power of molecular tension sensors in dissecting mechanisms of mechanotransduction across proteins and highlighted cells' ability to control protein extension.

In addition to genetically encoded tension sensors, immobilized FRET-based and DNA-hairpin tension sensors on a substrate have greatly informed our understanding of mechanotransduction and force transmission across adhesions. These sensors enabled the measurements of forces on individual integrins at the cell-ECM interface. Using immobilized FRET-based tension sensors, the majority of ligand-bound integrins were shown to exert forces in the range of 1–7 pN [35•]. While this range is lower than reported forces using fluorescent DNA hairpins of known unfolding force [37], it is possible that DNA unfolding sensors measure maximum force over some time interval while the FRET-based sensors measure mean force within their range of force sensitivity. Overall, both immobilized and genetically encoded molecular tension sensors enabled single molecule and submolecular tension measurements at high temporal resolution, which could help inform and validate current models. In addition, genetically encoded tension sensors open the possibility to measure subcellular structure forces *in vivo* and *ex vivo* [38] and with higher sensitivity we will potentially be able to overcome some of the challenges of *in vivo* force measurements using FRET-based tension sensors [39,40].

Conclusion

The highlighted recent body of work shows the added value that modeling and molecular tension sensors have provided in our mechanistic understanding of mechanotransduction. Going forward it will be important to continue to incorporate these technologies to improve our mechanistic understanding and to further investigate the emerging behaviors predicted by experimentally validated computational models. Furthermore, the current state of mechanotransduction research presents the opportunity to apply the current models and molecular tension sensors to other systems beyond integrin-mediated adhesions to include, for example, investigation of CD44-mediated adhesions and cell–cell adhesions through cadherins.

Conflict of interest authorship

All authors have participated in (a) conception and design, or analysis and interpretation of the data; (b) drafting the article or revising it critically for important intellectual content; and (c) approval of the final version.

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