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Balancing forces in migration

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The integrated molecular interactions of proteins can create active biological networks whose material properties and actions can impact a variety of physiological processes. Chief among these is the ability to generate and respond to physical forces. The cytoskeleton plays a key role in this behavior, characterized by active self-reorganization to control a cell's shape and mediate its physical interactions. This review discusses our current understanding of how the material properties of the cytoskeleton and its physical interactions with the extracellular environment impact cell migration.

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Introduction

Cells depend on biochemical signaling [1] and mechanical signaling [2,3] to regulate their interactions with the extracellular environment. The cytoskeleton, comprised of collections of filamentous proteins and their associated regulatory and binding proteins, is the foundation of these two signaling networks [4]. In addition to acting as a material that responds to externally applied forces [5], the cytoskeleton generates its own forces which are applied to the cell's extracellular environment, whether that be the extracellular matrix (ECM) [6], or other cells [7,8].

While the individual molecular interactions underlying many of these physiological processes are well understood [9], their aggregated effects can precipitate starkly different collective behavior and interactions [10,11]. Simply mixing two types of filaments can create new architectures, such as the curved shapes that are produced by combining actin with septins [12]. The addition of cross-linkers, meanwhile, can shift the contraction of a network from isotropic to uniaxial through modulation of the stiffness of actin bundles [13]. Just the application of a force at one end of an actin filament can impact the activity of a formin at the other end of the filament [14•]. Similarly, networks grown under an applied load self-organize to be globally stiffer, without changing the local material properties of the constituent filaments [15••]. All of these structures and behaviors resemble those seen *in vivo*, where the cytoskeleton takes on specific architectures and organizations related to function [16,17].

With recent advances in imaging, it is possible to visualize the dynamics of the cytoskeleton in higher resolution [18], and more precisely measure mechanical interactions [19] and material properties [20,21] than ever before. These technological improvements provide important insights into local interactions between proteins and their spatial positioning within networks. The next challenge, however, is to understand how the macroscopic properties of cytoskeletal network behavior emerge from these integrated local molecular interactions across appropriate length and time scales. Here we summarize the current findings from the perspective of physics to understand force transmission as a network behavior as it relates to migration and invasion at the cellular scale.

Cell contractility is regulated by cell size

The dominant component of cell contractility is the product of non-muscle myosin II filaments pulling on the actin cytoskeleton [22]. These forces are then transmitted to the extracellular environment through integrin-based adhesions for cell–ECM interactions, or cadherin-based adhesions for cell–cell interactions. A number of different techniques have been developed to measure these types of forces [6], with recent advancements increasing the detection limit of the measurements [23] and adding the ability to resolve the spatial orientation of the applied forces in 3D [19].

A number of different metrics have been used to describe cellular force generation (see Box 1 for definitions and relations of terms related to force generation). In adherent cells the distribution of traction forces is highly heterogeneous and dependent on the spatial distribution of ligands [24,25] and the material properties of the extracellular environment [26]. Using micropatterning to constrain cell shape on substrates of different stiffness, we showed that both stress (force per unit area) and strain (relative displacement) are functions of the material properties of the substrate [26]. Cells generate larger traction stresses on stiffer substrates, but they result in

Box 1 Lexicon of force generation

Stress — A measure of force applied per unit area. Typically measured in pascals (Pa), where 1 Pa = 1 N/m^2.

Strain — A measure of deformation, typically caused by a force, relative to the equilibrium length of an object. Strain is unitless and typically measured as a percent $\Delta L/L$.

Displacement — A measure of distance between an initial and final position. Displacements have units of length (e.g. *m*) and are used to calculate the strain.

Stiffness — A measure of how resistant a material is to deformation. For objects (i.e. 2D and 3D materials) stiffness is often referred to as a modulus and measured in units of Pa.

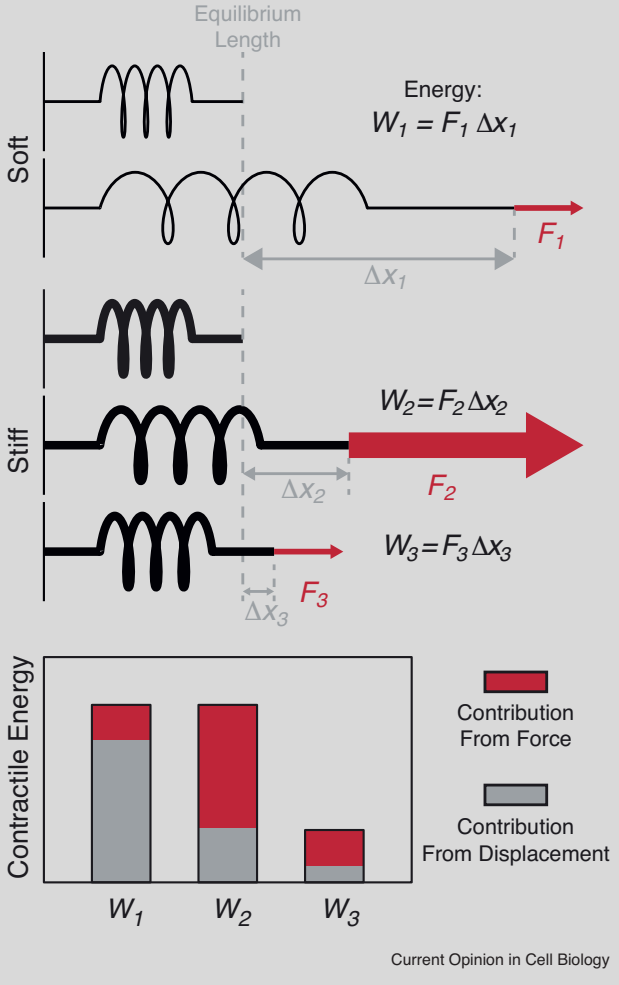
Work (or Contractile Energy) — A measure of the energy used to apply a force over a distance. For a constant force, work is defined in 1D as

$$W = Fd$$

where F is the applied force and d is the distance it is applied over. For a 2D system, such as used in traction force microscopy, the work is defined as the integral over the area of the traction stress multiplied by the displacement

$$W = \frac{1}{2}\int dA\, T(r)\cdot u(r)$$

where $T(r)$ is the traction stress and $u(r)$ is the displacement at position r.



A cartoon illustrating the relationship between displacement, force, and contractile energy. The same amount of energy is used to deform the springs in cases 1 and 2. For the soft spring, a small force is applied over a long distance. In the stiff spring, a large force is applied over a short distance. The work done in each case is equivalent ($W_1 = W_2 = F_1\,\Delta x_1 = F_2\,\Delta x_2$). Conversely, in case 3, a small force results in only a small displacement, and therefore requires less energy ($W_3 < W_2$).

smaller displacements (Figure 1a,b). On soft substrates, the converse is true. The contractile energy (i.e. the total mechanical work done — see Box 1), however, is independent of the substrate stiffness [26]. Thus cells of the same size use the same amount of energy to deform the substrate (Figure 1c). This suggests that when gauging the response of cells to changes in substrate stiffness, measurements of traction stress alone reveal more about the material properties of the substrate than they do about the contractile state of the cell.

Measuring the contractile energy, on the other hand, reflects the entire output of the cell, accounting for both stress and strain. Unsurprisingly, the total contractile energy is sensitive to the overall size of the cell, with larger cells having larger cytoskeletons, and therefore a larger number of active motors doing work [26,27] (Figure 1d). For a given spread area, however, the total contractile energy is independent of cell geometry [26,28] (Figure 1e). This is in contrast to measurements like the average stress which are dependent upon cellular morphology and adhesion distribution. The scaling of contractile energy with cell area also suggests that cells actively maintain a contractility set point. Recently, two reports used optogenetic approaches to modulate RhoA, the GTPase that controls the contractile signaling pathway [29,30]. When RhoA is activated cells become more contractile, but then relax back to their initial contractile states when the stimulation is removed. This behavior is consistent with previous results using incubation and washout of myosin inhibitor drugs, which causes the contractility to initially decrease before recovering to their initial state [31,32]. In each case, perturbations to the contractile state of the cell result in the cell trying to re-establish its initial contractile state when the perturbation is removed. The contractile energy per unit area can therefore serve as a metric to compare contractile behavior across perturbations to cells and even different cell types [9].

Cytoskeletal architecture and ECM geometry regulate force transmission

While the contractile energy tells us about the mechanical state of the cell, to understand migration we must understand how cells spatially and temporally regulate force generation. The cytoskeleton consists of a number of different filamentous proteins (e.g. actin, microtubules, intermediate filaments, septins) and motor proteins (e.g. myosins, kinesins, dyenins). Because the actomyosin