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Full Length Article

Adaptive flexibility of cells through nonequilibrium entropy production

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ABSTRACT

Cellular adaptation to environmental changes relies on the dynamic remodeling of subcellular structures. Among these, periodic actomyosin assemblies are fundamental to the organization and function of the cytoskeletal architecture. In muscle-type cells, sarcomeres exhibit ordered structures of consistent lengths, optimized for stable force generation. By contrast, nonmuscle-type cells exhibit greater structural variability, with sarcomere-like periodic units of varying lengths that contribute not only to force generation but also to adaptive remodeling upon environmental cues. These structural differences have traditionally been attributed to the specific protein compositions unique to each cell type. However, the functional significance of such periodic unit variability remains poorly understood within a unified framework. Here, we propose a conceptual model grounded in nonequilibrium physics to provide a unified perspective on structural variability in cytoskeletal adaptation. Specifically, we demonstrate that the effective binding strength of these contractile units can be evaluated by quantifying structural randomness through Shannon entropy. The increased entropy associated with the inherent randomness of sarcomere-like assemblies in nonmuscle-type cells lowers the energy barrier for cytoskeletal remodeling, enabling flexible adaptation to environmental demands. In contrast, the ordered sarcomere arrangements in muscle-type cells correspond to higher binding energies, stabilizing cytoskeletal configurations for sustained force generation. While structural disorder is often regarded as a source of instability, our analysis reveals that it can serve as a driver of cytoskeletal remodeling and a foundation for adaptive cellular behavior. Thus, our study provides a unified theoretical foundation for understanding cytoskeletal adaptability across diverse cell types by integrating structural randomness into a nonequilibrium framework.

1. Introduction

Living cells adaptively reorganize their internal structures in response to changes in both their internal and external environments (Zajac and Discher, 2008; Discher et al., 2005). This structural adaptability is fundamental to individual cellular processes such as differentiation, proliferation, and apoptosis, as well as to higher-order processes such as tissue development and wound healing (Hove et al., 2003; Hahn and Schwartz, 2009). The cytoskeleton is central to the physical structure and force generation of cells, maintaining its integrity through organized protein complexes. Among these, periodic actomyosin structures, primarily composed of actin, myosin II, and α-actinin, function as fundamental units of cellular contractile architecture.

In striated muscles, these periodic assemblies are referred to as sarcomeres and constitute the core of myofibrillar organization (Henderson et al., 2017; Purslow and Trotter, 1994; Reconditi et al., 2014; Ertbjerg and Puolanne, 2017; Gollapudi and Lin, 2009). Meanwhile, similar sarcomere-like periodic structures are also present in ventral stress fibers of nonmuscle cells (Herrera et al., 2005; Peterson et al., 2004; Verkhovsky et al., 1997; Hotulainen and Lappalainen, 2006; Cramer et al., 1997; Deguchi and Sato, 2009; Lazarides and Burridge, 1975; Coravos and Martin, 2016; Russell et al., 2011). Compared to the uniform length and alignment of muscle sarcomeres, these nonmuscle counterparts exhibit greater structural variability; and even within muscle cells, interestingly, younger ones display broader distributions of sarcomere lengths, indicating greater structural randomness than mature ones (Goldspink, 1968; Kolley et al., 2024a). Furthermore, this variability is more pronounced in motile cells than in nonmotile cells (Peterson et al., 2004; Verkhovsky et al., 1997). Muscle sarcomeres primarily support coordinated contractility within tissues (Henderson et al., 2017), while nonmuscle sarcomere-like structures are involved in diverse dynamic cellular processes including migration, division, and structural

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remodeling upon environmental changes (Vicente-Manzanares et al., 2009; Conti and Adelstein, 2008; Schiffhauer et al., 2016; Greenberg et al., 2016).

In biological research, traditionally, these differences have been attributed to the unique properties of specific proteins expressed in each cell type, often within a reductionist framework. While this molecular perspective is indispensable for identifying components and enabling targeted manipulation, it can be complemented by a comparative physical approach that seeks a unified interpretation of how architectural variability is intrinsically linked to distinct cellular functions. Prior studies from a physical perspective have aimed to elucidate the mechanisms for the self-organization of actomyosin periodicity (Kolley et al., 2024a; Vicente-Manzanares et al., 2009; Conti and Adelstein, 2008; Kolley et al., 2024b; Friedrich et al., 2012), with some attempts in exploring how their contractions generate cellular tension and in turn maintain cytoskeletal organization (Henderson et al., 2017; Katoh et al., 1998a; Deguchi et al., 2006). However, how the variability of such periodic structures contributes to cellular functions remains an open question, as no unified theoretical framework has been established.

Here, we describe a conceptual model based on a nonequilibrium physics framework to provide a unified interpretation of the relationship between subcellular structural variability and adaptability. We analytically derive constraints on the probability distribution of these structures and the effective binding energy among their constituent units to evaluate how structural variability enhances adaptability. To incorporate nonequilibrium effects, we formulate a Fokker–Planck equation describing the probability distribution of actomyosin-based periodic configurations and consider entropy production as an indicator of the energetic cost required for maintaining these nonequilibrium structures, specifically referring to the cytoskeletal system composed of contractile units. We also analyze the length distribution of actomyosin contractile units from experimental results on different cell types and interpret its functional implications within our theoretical framework. Finally, we explore the parameter space of our model to investigate how variations

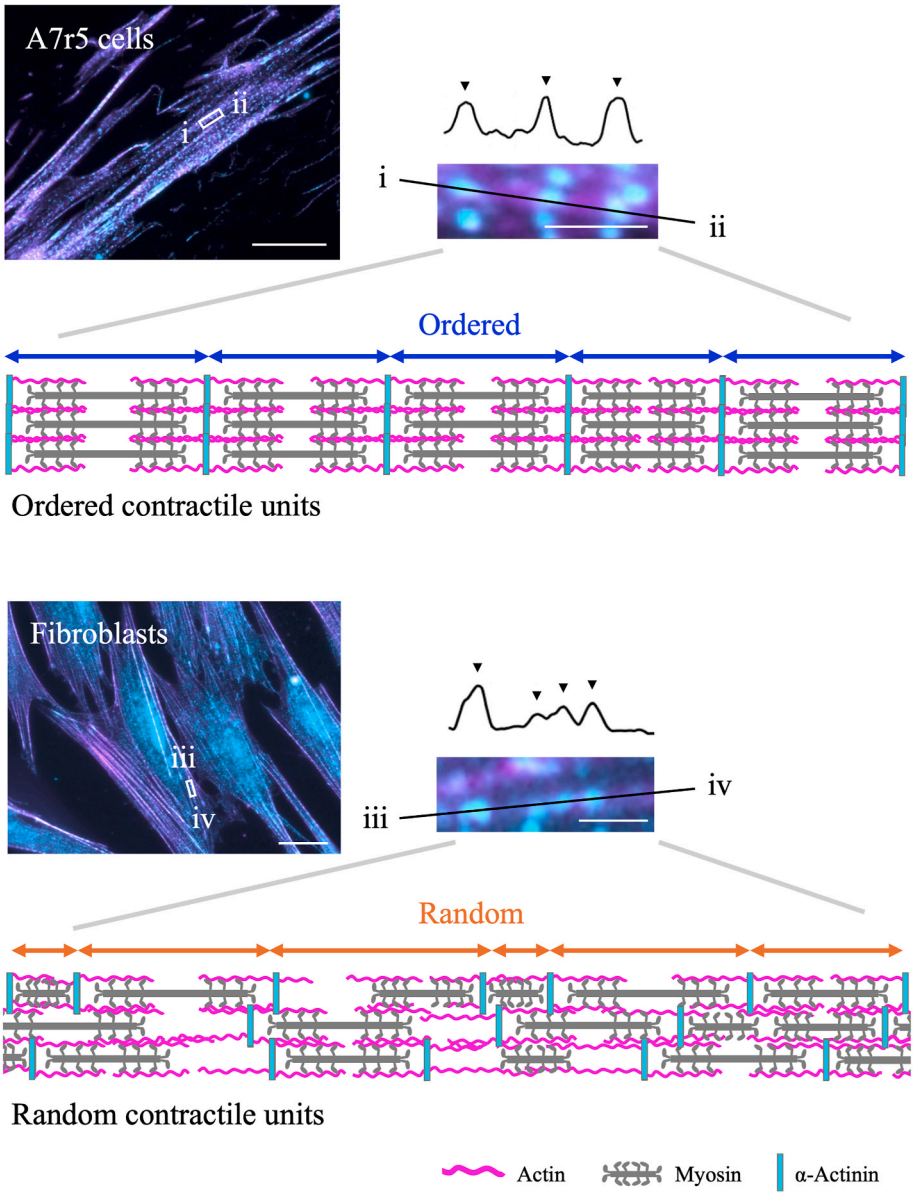

Fig. 1. Schematic of contractile unit structure. The upper diagram (blue) shows ordered sarcomeres with specific lengths, while the lower diagram (orange) shows their disordered counterparts with varying lengths. The upper image corresponds to A7r5 cells, and the lower to fibroblasts, illustrating representative examples. White rectangles are magnified to evaluate the intensity of α-actinin (cyan) along the indicated F-actin bundles (magenta). Arrowheads indicate peaks in the intensity curves. Scale, 20 μm (left) and 2 μm (magnified).

in structural properties influence adaptability. Our results suggest a fundamental physical principle, indicating that actomyosin organization should be understood not merely at the scale of individual contractile units, but as an emergent system operating at the cellular level to enhance adaptive flexibility. Interestingly, while structural randomness often impairs system function in engineered systems, it instead serves as a key driver of adaptability in living organisms.

2. Theory and methods

2.1. Entropy production

In striated muscle, the sarcomere is a well-defined periodic structure composed mainly of actin, myosin, and α-actinin, among other proteins. In contrast, non-muscle cells often exhibit actomyosin structures with irregular, sarcomere-like periodicity. In this study, we collectively refer to the canonical sarcomeres in muscle cells and the sarcomere-like structures in non-muscle cells as contractile units, defined by the periodic spacing between α-actinin-rich regions along actomyosin bundles (Fig. 1). This operational definition serves as a marker of intracellular structural organization. For the purposes of our modeling framework, we consider the system to be the cytoskeletal structure composed of contractile units, while the surrounding intracellular environment, assumed to be sufficiently large, serves as a heat bath that remains close to thermal equilibrium. While many actomyosin-binding proteins contribute to remodeling in specific contexts, their roles differ substantially between muscle and nonmuscle cells. By contrast, actin, myosin II, and α-actinin represent the only structural components whose isoform differences may be directly compared across both systems, and thus these can be assumed as elements comprising the cytoskeletal system, without excluding possible contributions from other proteins.

We then express the nonequilibrium entropy production during the growth process of the cytoskeletal structure while nearby contractile units bind together or unbind. Given the inherent complexity of cytoskeletal systems, including the involvement of over a hundred distinct proteins in actin contractile bundles (Liu et al., 2022), modeling at the individual protein level would inevitably require selective assumptions, potentially obscuring the broader functional roles underlying contractile unit fluctuations. To circumvent this, we adopt a coarse-grained approach in which the combined action of these proteins is treated as equivalent to contractile unit-level binding and unbinding, using the contractile unit as the fundamental unit of analysis.

The total entropy production, considered for both the system and the environment, is defined as

$$\sigma = \Delta S_{sys} + \Delta S_{bath} \geq 0 \tag{1}$$

where ΔS_{sys} and ΔS_{bath} are the change in entropy of the system and of the surrounding environment, respectively (Crooks, 1999). We consider the probability distribution of the contractile unit length in one dimension, describing its randomness, defining the probability of its length state x as $P(x)$. In nonequilibrium systems, ΔS_{sys} can be expressed using Shannon entropy as follows (Friedrich et al., 2012):

$$\Delta S_{sys} = -\sum P(x)\ln P(x). \tag{2}$$

For ΔS_{bath}, we assume that the environment can freely exchange constituent contractile unit elements and energy with the preexisting cytoskeletal structure and is therefore described by a grand canonical distribution under this theoretical assumption. The change in entropy of the environment is then given by

$$\Delta S_{bath} = -\beta(\Delta E - \Delta\mu) \tag{3}$$

where ΔE is the energy change in the cytoskeletal structure due to contractile unit binding, $\Delta\mu$ is the change in chemical potential as contractile units transition from the particle bath to within the cytoskeletal structure, and $\beta = 1/k_bT$ representing the inverse thermal energy, with k_b being the Boltzmann constant ($1.38 \times 10^{-23}\,\mathrm{m^2\,kg\,s^{-2}\,K^{-1}}$) and T the absolute temperature (310.15 K). Using Eqs. (2) and (3), the total entropy production is expressed by

$$\sigma = -\sum P(x)\ln P(x) - \beta(\Delta E - \Delta\mu) \geq 0, \tag{4}$$

showing that the entropy production during the forming process of the cytoskeletal structure is always positive.

2.2. Maximum binding energy

We define ΔE in Eq. (3) as the energy change due to contractile unit binding to the cytoskeletal structure, corresponding to the binding energy, or $\Delta E = \Delta E^b$. From Eq. (4), the maximum binding energy is described by

$$\Delta E^b \leq \Delta E^b_{max} = \Delta\mu - \frac{1}{\beta}\sum P(x)\ln P(x). \tag{5}$$

Based on the second law of thermodynamics, the nonequilibrium formation of the cytoskeletal structure driven by contractile unit binding is accompanied by a positive entropy change. This constraint imposes a limit on the binding energy, which represents the strength of the interaction between contractile units, with a more negative binding energy indicating a stronger binding. While unbinding can also be described by reversing the signs of ΔE and $\Delta\mu$, we focus on the binding process as a representative case that captures the essential thermodynamic behavior.

2.3. Probability distribution of contractile unit structures

We also define $P(x)$ based on a simple conceptual model that captures the variations in contractile unit length, while using experimental data to examine its quantitative trends across different cell types. Given that the contractile unit exhibits a biophysical response characterized by a potential energy landscape that is inherently convex downward with respect to its stable length x_0, we express the potential energy $U(x)$ at contractile unit length x as

$$U(x) = \frac{1}{2}k(x - x_0)^2 \tag{6}$$

where k represents the restoring contribution of the contractile unit. The convexity of this function follows from the inherent properties of the actomyosin structure, which we justify in Supporting Note 1, and extend to asymmetric configurations in Supporting Note 2. Using the Fokker-Planck equation, the time evolution of $P(x,t)$ is described by

$$\frac{\partial P(x,t)}{\partial t} = -\frac{\partial}{\partial x}\{-k(x - x_0)P(x,t)\} + \frac{\partial^2}{\partial x^2}\{DP(x,t)\} \tag{7}$$

where D is the diffusion coefficient, representing the probabilistic spread of contractile unit configurations in relation to energy stability; in this conceptual model, D captures the effective diffusive contribution of thermal fluctuations and actomyosin-driven dynamics as a coarse-grained representation without explicitly modeling these mechanisms. By solving Eq. (7) under the steady-state condition, we obtain the stationary probability distribution as

$$P(x) = \frac{\exp\left(-\frac{k(x - x_0)^2}{2D}\right)}{\sum \exp\left(-\frac{k(x - x_0)^2}{2D}\right)} \tag{8}$$

where $P(x)$ satisfies the normalization condition $\sum P(x) = 1$. We quantitatively analyzed the maximum binding energy ΔE^b_{max} in Eq. (5) by considering specific $P(x)$. For this analysis, D was set to 10 $\mu m^2/s$ based on typical molecular diffusion coefficients (Lovett et al., 2013; Newman et al., 1989; Montague et al., 1983; Kanzaki et al., 2006), and

$\Delta\mu$ was estimated to be on the order of 20 kJ/mol from experimental measurements of the energy associated with ATP hydrolysis (Kodama and Woledge, 1979; Gajewski et al., 1986). While $\Delta\mu$ does not correspond to a specific reaction, it reflects the average energetic input required to organize disordered components into more ordered structures. Thus, $\Delta\mu$ serves as a coarse-grained chemical potential that integrates diverse chemophysical contributions involved in contractile unit formation.

2.4. Quantification of contractile unit length

The actual contractile unit length was estimated as a representative value using previously published experimental images from multiple sources, including myofibrils isolated from mouse skeletal muscles (Balnave et al., 1997), primary mice myotubes (Manabe et al., 2016), and neonatal rat cardiomyocytes (Burbaum et al., 2021), which predominantly express striated muscle-type actin and myosin molecules; and human fibroblasts (Sanger et al., 1983), PtK2 long-nosed potoroo epithelial kidney cells (Sanger et al., 1983), gerbil fibroma cells (Sanger et al., 1983), and A7r5 rat aortic smooth muscle cells (Matsui et al., 2011), which express nonstriated muscle-type actin and myosin molecules. Among them, A7r5 cells also express α-SMA, a smooth muscle-specific actin isoform commonly used as a marker for smooth muscle cells and myofibroblasts; these cells adopt a synthetic phenotype and therefore do not form the side-polar myosin filaments typical of fully differentiated smooth muscle cells (Okamoto et al., 2020; Matsui and Deguchi, 2019). Images of endogenous α-actinin immunostaining (Manabe et al., 2016; Burbaum et al., 2021; Sanger et al., 1983; Matsui et al., 2011) were analyzed by using ImageJ/Fiji software (NIH). Fluorescence intensity profiles were analyzed along the longitudinal axis of multiple contractile units to measure the distance between adjacent α-actinin–positive regions, with their centers defined by intensity maxima (Fig. 1). The measured inter-peak distance was thus used to define the contractile unit length. We analyzed $n = 40$–48 contractile units for each of the three striated muscle types (myofibrils, myotubes, and cardiomyocytes), and $n = 53$–56 contractile units for each of the four nonstriated muscle types (fibroblasts, PtK2, gerbil fibroma, and A7r5 cells) to obtain the respective distributions. To illustrate representative sarcomere distributions, we also hereby performed immunostaining for α-actinin and actin filaments on A7r5 cells following method (Matsui et al., 2011) and on human foreskin fibroblasts following method (Liu et al., 2022) (Fig. 1). Rather than performing statistical testing, we focused on extracting characteristic length scales from documented samples to provide a comparison across different conditions.

3. Results

3.1. Contractile unit distributions and their biophysical implications

Contractile structures in both muscle and nonmuscle cells exhibit a common periodic organization, yet differ markedly in structural variability. Muscle-type sarcomeres form highly ordered, three-dimensional

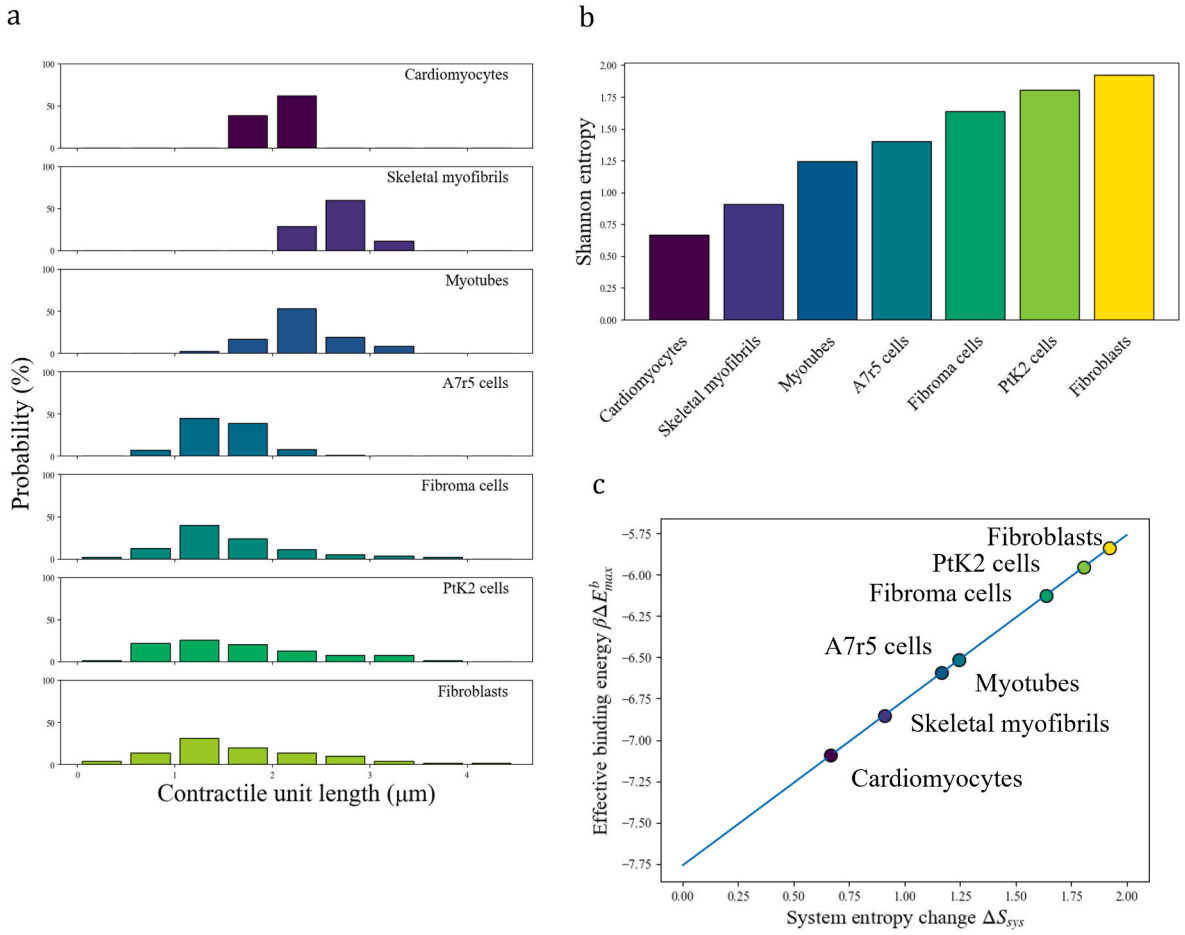

Fig. 2. Quantification of contractile unit length variability and estimation of binding energy. (a) The actual contractile unit length was quantified using previously published experimental images from multiple sources, including neonatal rat cardiomyocytes (Burbaum et al., 2021), mouse skeletal myofibrils (Balnave et al., 1997), primary mouse myotubes (Manabe et al., 2016), A7r5 smooth muscle cells (Matsui et al., 2011), gerbil fibroma cells (Sanger et al., 1983), PtK2 epithelial cells (Sanger et al., 1983), and human fibroblasts (Sanger et al., 1983). (b) Shannon entropy was calculated for each distribution. (c) The binding energy for different types was estimated using Eq. (8) and the distributions shown in Fig. 3 at a fixed chemical potential of −20 kJ/mol.

lattices with uniform lengths, whereas nonmuscle contractile units lack such precise organization and appear more heterogeneous (Matsui et al., 2011). This observed variability, however, may not merely be a visual distinction but rather reflect differences in the effective binding strength among contractile unit components. To examine this possibility, we analyzed contractile unit length distributions across different cell types and quantified their structural variability.

Specifically, in myofibrils isolated from mouse skeletal muscles (hereafter referred to as Skeletal myofibrils), primary mouse myotubes (Myotubes), neonatal rat cardiomyocytes (Cardiomyocytes), which all predominantly express striated muscle-type actin and myosin molecules and are characterized by relatively large contractile forces, sarcomeres were consistently observed to maintain a specific length (Fig. 2a). To quantify the consistency of sarcomere length, we calculated Shannon entropy for each distribution (Fig. 2b), confirming that sarcomeres in muscle-type cell types exhibit lower levels of entropy, indicative of a more ordered structural arrangement. In contrast, contractile units in human fibroblasts (Fibroblasts), PtK2 long-nosed potoroo epithelial kidney cells (PtK2 cells), and gerbil fibroma cells (Fibroma cells), which express nonstriated muscle-type actin and myosin molecules and are characterized by less contractile force, exhibited greater length variability and higher entropy. Thus, while nonmuscle contractile units retain their periodic structure (Deguchi and Sato, 2009; Costa et al., 2002), they show a relatively random organization compared to muscle sarcomeres. A7r5 rat aortic smooth muscle cells (A7r5 cells), which coexpress both α-SMA and muscle-type α-actin, displayed an intermediate level of structural randomness among the analyzed cell types.

The effective binding energy for different actomyosin structures was estimated using Eq. (5) and the measured distributions, showing its proportionality to the change in system entropy at a fixed chemical potential of −20 kJ/mol (Fig. 2c). Nonmuscle contractile units exhibit lower binding energies than muscle sarcomeres, suggesting a greater capacity for structural remodeling. This trend is consistent with experimental observations (Henderson et al., 2017; Herrera et al., 2005; Peterson et al., 2004; Verkhovsky et al., 1997; Hotulainen and Lappalainen, 2006; Cramer et al., 1997; Deguchi and Sato, 2009; Lazarides and Burridge, 1975; Coravos and Martin, 2016; Katoh et al., 1998b), showing that nonmuscle contractile units undergo more dynamic reorganization than their muscle counterparts. Here, we define adaptability as the structural plasticity that enables contractile units to reorganize in response to environmental cues. From this perspective, a lower binding energy corresponds to a more flexible state, as it allows easier structural rearrangement in response to external perturbations. This interpretation supports our notion that the ordered arrangement of contractile units is not merely a property of individual elements, but an emergent system property that enables structural adaptability at the cellular scale.

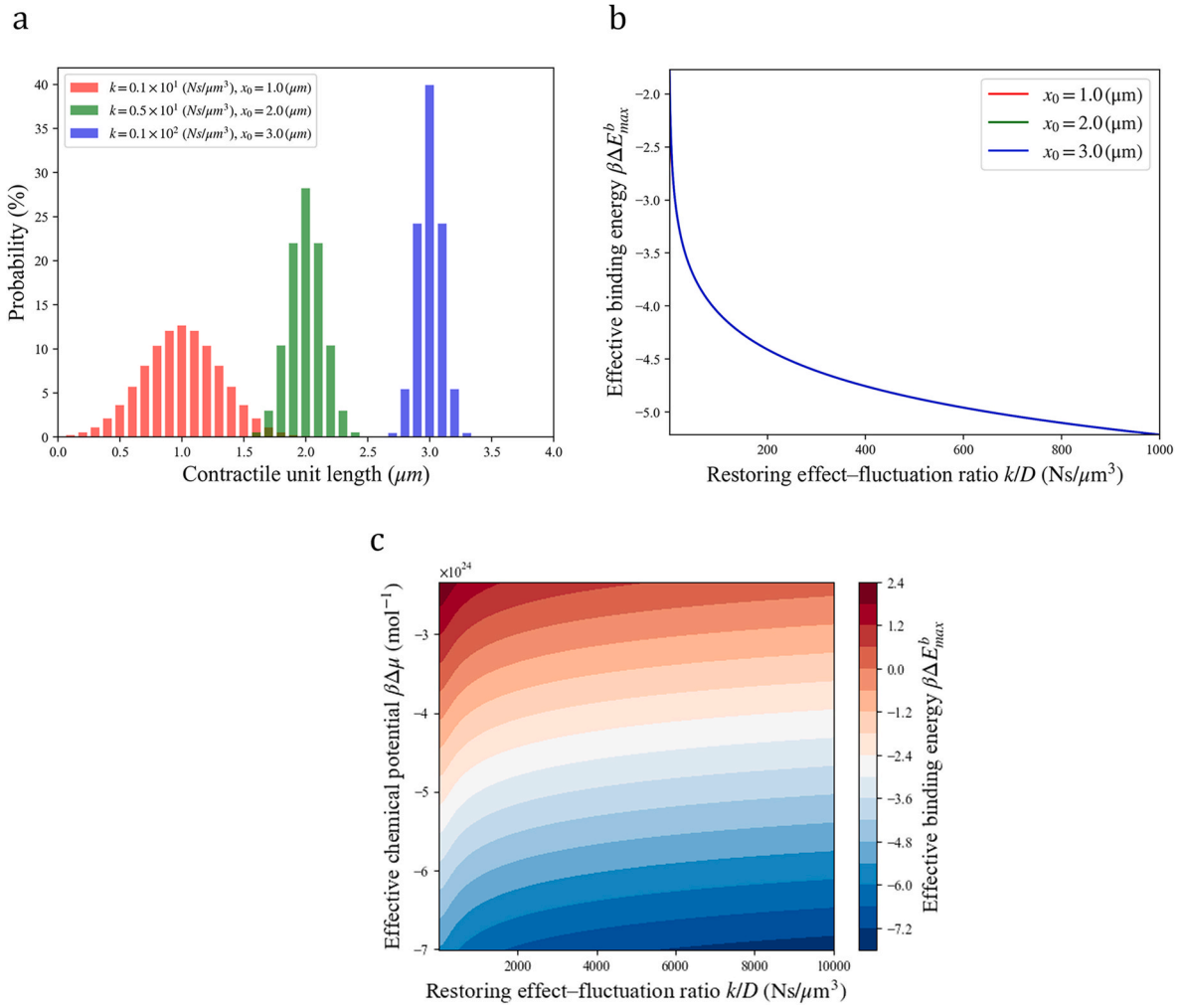

Fig. 3. Quantification of maximum binding energy and its dependence on structural and energetic factors. (a) Length distribution of contractile units at $k = 10^2$ [N/μm] (red), 10^3 [N/μm] (green), and 10^4 [N/μm] (blue). With a smaller k, the distribution of contractile unit lengths exhibits greater variability, indicating increased structural diversity. (b) Relation between restoring contribution and maximum binding energy. A higher restoring contribution corresponds to a lower maximum binding energy, indicating stronger binding between constituent elements. (c) Dependence of maximum binding energy on restoring contribution and chemical potential. A lower chemical potential results in a lower maximum binding energy.

3.2. Contractile unit organization and remodeling under energetic and environmental constraints

Next, we extend our investigation using our framework to systematically examine how variations in key parameters influence structural stability and adaptability. The probability distribution for contractile unit lengths was analyzed using the model described by Eq. (8). These distributions follow a Gaussian distribution with variance $\sqrt{D/k}$, which arises from the balance between stochastic fluctuations and restoring contribution of contractile units (Fig. 3a). As k increases, the variance in contractile unit length decreases, resulting in more stable localization around a specific length. Conversely, as k decreases, the variance increases, leading to a broader length distribution and a more random actomyosin structure.

As the restoring contribution k increases, structural order becomes higher and entropy decreases (Fig. 3a, blue), reducing the thermodynamic drive for progressive assembly. Consequently, the maximum achievable binding energy becomes more negative, limiting the elongation of cytoskeletal structures as described in Eq. (5). On the other hand, when the restoring contribution is small, the resulting disordered configuration increases entropy (Fig. 3a–red), diminishing the relative contribution of binding energy and facilitating cytoskeletal assembly and hence flexible remodeling. Although the model defines k as a parameter that determines structural order, the one-to-one correspondence between k and the distribution $P(x)$ allows reciprocal interpretation, in which ordering may also reflect stronger restoring effect. While our model focuses on steady-state organization, such reciprocal interpretation also suggests that structural order may dynamically fluctuate in response to temporal changes in the effective restoring-to-fluctuation ratio (k/D), as may occur under varying environmental conditions. For example, increased fluctuations could elevate D and thereby reduce structural order, whereas suppressed fluctuations may effectively enhance k and restore order. These results suggest that cytoskeletal structures with random organization, such as those found in nonmuscle cells, are more adaptable to dynamic growth and remodeling. In contrast, ordered structures, like those in muscle cells, require larger changes in binding energy for structural reorganization, indicating lower flexibility for dynamic remodeling. Interestingly, the value of x_0 does not affect the limits of the binding energy because entropy is determined not by the absolute stable length but by the probability of the structure being randomly distributed (Fig. 3b).

The relationship with the chemical potential reveals a positive correlation with the maximum binding energy as explicitly described in Eq. (5) (Fig. 3c). A small difference in chemical potential (Fig. 3c, red regions) corresponds to a reduced impact of the binding energy, allowing for easier remodeling of the structures. While our discussion has focused on the extent of the contractile unit randomness, it should be noted that chemical potential depends on component concentration, which varies with intracellular environmental conditions. Therefore, even with the same randomness in the cytoskeletal system, the behavior is actually influenced by environmental factors including concentration.

4. Discussion

In this work, we developed a nonequilibrium physical model as a unified framework to reinterpret the relationship between subcellular structural variability and cellular adaptability across hierarchical scales. Note that this study does not aim to theoretically explain the origin of sarcomere randomness; rather, our conceptual model is designed to describe how the intrinsic properties of contractile units are linked to the observed structural variability, which reflects a state of lower energetic barriers and, in turn, allows for more flexible remodeling. Although the model is intentionally minimal, while inevitably leaving system-specific molecular details outside its scope, this simplification enables clearer insights into the relationship between structural variability and adaptability.

Previous studies have largely focused on self-organizing mechanisms of sarcomere patterning (Vicente-Manzanares et al., 2009; Conti and Adelstein, 2008; Kolley et al., 2024b; Friedrich et al., 2012), but these mechanisms were often examined in isolation, without a unifying framework linking them to cellular adaptive responses. In particular, it remained unclear how both muscle sarcomeres and nonmuscle sarcomere-like structures collectively contribute to the ability of cells to respond to environmental changes. Our model integrates essential physical factors such as restoring effects and fluctuations into an energy-based description of actomyosin contractile unit length distributions. Using the Fokker-Planck equation, we derived the probability distribution of contractile unit lengths (Eq. (8)), revealing that higher restoring effects induce less random structural variations around a specific length. This finding is consistent with experimental observations, in which muscle cells exhibit ordered sarcomere structures, whereas nonmuscle cells display more dispersed configurations (Henderson et al., 2017; Herrera et al., 2005; Peterson et al., 2004; Verkhovsky et al., 1997; Hotulainen and Lappalainen, 2006; Cramer et al., 1997; Deguchi and Sato, 2009; Lazarides and Burridge, 1975; Coravos and Martin, 2016; Katoh et al., 1998b; Kentish et al., 1986).

To bridge the structural variations with energetic constraints, we analyzed entropy production associated with cytoskeletal remodeling caused by contractile unit binding. In our model, the cytoskeletal structure, consisting of serially connected contractile units, is treated as a system in grand canonical contact with its surrounding environment, resulting in a nonequilibrium state characterized by continuous energy exchange and persistent entropy production. By determining Shannon entropy (Shannon and Weaver, 1949) from the probability distribution of contractile unit lengths, we derived a limit on binding energy (Eq. (5)), constrained by the requirement of nonnegative entropy production in nonequilibrium systems (Crooks, 1999). Our analysis thus provides a framework for understanding how structural randomness governs the energy landscape of cytoskeletal remodeling. In muscle-type cells with high restoring effect and ordered sarcomere lengths, the requirement for entropy production necessitates substantial binding energy for cytoskeletal elongation. In contrast, in nonmuscle-type cells with lower restoring effect and more random structures, the entropy resulting from structural disorder allows for more flexible cytoskeletal remodeling with minimal binding energy. Thus, these cytoskeletal structures achieve flexible responsiveness to environmental cues facilitated by the randomness-driven entropy. Interestingly, young muscle cells display greater randomness in sarcomeres than mature cells (Goldspink, 1968), potentially suggesting that early-stage cells may be more adaptable and then gradually form specialized structures optimized for stable contractile function as they mature, as supported by recent experimental observations (Loison et al., 2018). Note that binding energy is also modulated by the chemical potential, which depends on intracellular component concentrations. For example, in environments rich in contractility-promoting molecules, stable cytoskeletal structures with strong binding energies can form even in the presence of random structures. Thus, cytoskeletal structures can remodel in response to conditions within the system as well as those in the environment. Our theoretical descriptions capture this cellular behavior, aligning with experimentally observed relationships across the different hierarchies, namely between actomyosin structures and cells (Henderson et al., 2017; Herrera et al., 2005; Peterson et al., 2004; Verkhovsky et al., 1997; Hotulainen and Lappalainen, 2006; Cramer et al., 1997; Deguchi and Sato, 2009; Lazarides and Burridge, 1975; Coravos and Martin, 2016; Katoh et al., 1998b).

While we have primarily discussed the qualitative features, we also estimated the effective binding energy for different types of cytoskeletal structures (Fig. 2). We found that the estimated trend is consistent with experimental observations. To interpret this trend, we focus here on two major actin cross-linkers, α-actinin and myosin. Nonmuscle α-actinin isoforms have been reported to exhibit higher dissociation constants K_d

for actin binding, ranging from 2.96 to 3.96 μM (Foley and Young, 2013), compared to muscle α-actinin isoforms, which display lower K_d values of 0.4 μM (Meyer and Aebi, 1990) or 0.59 μM (Wachsstock et al., 1993). This difference suggests that muscle α-actinin binds actin more stably, stabilizing the sarcomere more effectively than nonmuscle α-actinin. Regarding myosin, the K_d value of muscle myosin isoforms (28.2 nM) is higher than that of nonmuscle myosin ones (4.6 nM) (Van Dijk et al., 1999), suggesting a higher affinity of nonmuscle myosin for actin. Functionally, muscle myosin molecules undergo rapid cross-bridging cycles to facilitate muscle contraction, whereas nonmuscle myosin molecules remain attached to actin to sustain cellular tension along stress fibers. These distinct roles suggest that α-actinin, rather than myosin, facilitates structural reorganization through its more flexible interactions with actin, thereby supporting dynamic cellular adaptability.

Such entropy-associated structural variability is also evident in other biological systems. For example, the extracellular matrix exhibits tissue-specific differences in collagen organization, where highly aligned fibers confer mechanical stability (e.g., tendons), whereas disordered networks enhance adaptability and remodeling capacity (e.g., skin, wound healing) (Maeda et al., 2022). A comparable principle is reflected in the evolutionary divergence; for example, within the myosin II family, the nonmuscle isoform contributes to heterogeneous and dynamic cytoskeletal networks, supporting versatile functions, while the striated muscle isoform forms highly ordered sarcomere structures optimized for stable contraction (Heissler and Manstein, 2012). These examples illustrate a common trade-off between structural order and functional adaptability, consistent with the core mechanism of our model, in which increased structural entropy facilitates flexible responses to environmental demands.

In conclusion, we developed a physical framework for the unified evaluation of contractile unit variability across different cell types, linking subcellular structural randomness to cellular adaptability. We suggest that structural disorder, often perceived as disadvantageous, actually enhances cellular adaptability by increasing entropy. This randomness is not limited to actomyosin contractile units but also appears inherently in other cellular components, indicating that extending our model could reveal additional mechanisms working across other biological hierarchies. Thus, our framework provides a basis for exploring the complex relationships between cellular physical structures and functions.

CRediT authorship contribution statement

Yuika Ueda: Writing – review & editing, Writing – original draft, Visualization, Validation, Methodology, Investigation, Funding acquisition, Formal analysis, Data curation, Conceptualization. **Shinji Deguchi:** Writing – review & editing, Visualization, Validation, Supervision, Resources, Project administration, Methodology, Funding acquisition, Formal analysis, Data curation, Conceptualization.

Declaration of competing interest

The authors declare no competing financial or personal interests that could have influenced the work presented in this manuscript.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.biosystems.2025.105594.

Data availability

Data will be made available on request.

References

Balnave, C.D., Davey, D.F., Allen, D.G., 1997. Distribution of sarcomere length and intracellular calcium in mouse skeletal muscle following stretch-induced injury. J. Physiol. (Paris) 502 (3), 649–659.
Burbaum, L., Schneider, J., Scholze, S., Böttcher, R.T., Baumeister, W., Schwille, P., et al., 2021. Molecular-scale visualization of sarcomere contraction within native cardiomyocytes. Nat. Commun. 12 (1), 1–12, 2021 12:1.
Conti, M.A., Adelstein, R.S., 2008. Erratum: Nonmuscle myosin II moves in new directions. Journal of Cell Science vol. 121 J. Cell Sci. 121 (11–18), 404.
Coravos, J.S., Martin, A.C., 2016. Apical sarcomere-like actomyosin contracts Nonmuscle Drosophila epithelial cells. Dev. Cell 39 (3), 346–358.
Costa, K.D., Hucker, W.J., C-P Yin, F., 2002. Buckling of Actin Stress Fibers: a New Wrinkle in the Cytoskeletal Tapestry.
Cramer, L.P., Siebert, M., Mitchison, T.J., 1997. Identification of novel graded polarity actin filament bundles in locomoting heart fibroblasts: implications for the generation of motile force. JCB (J. Cell Biol.) 136 (6), 1287–1305.
Crooks, G.E., 1999. Entropy Production Fluctuation Theorem and the Nonequilibrium Work Relation for Free Energy Differences.
Deguchi, S., Sato, M., 2009. Biomechanical properties of actin stress fibers of non-motile cells. Biorheology 46, 93–105.
Deguchi, S., Ohashi, T., Sato, M., 2006. Tensile properties of single stress fibers isolated from cultured vascular smooth muscle cells. J. Biomech. 39 (14), 2603–2610.
Discher, D.E., Janmey, P., Wang, Y.L., 2005. Tissue cells feel and respond to the stiffness of their substrate. Science 310 (5751), 1139–1143.
Ertbjerg, P., Puolanne, E., 2017. Muscle structure, sarcomere length and influences on meat quality: a review. Meat Sci. 132, 139–152.
Foley, K.S., Young, P.W., 2013. An analysis of splicing, actin-binding properties, heterodimerization and molecular interactions of the non-muscle α-actinins. Biochem. J. 452 (3), 477–488.
Friedrich, B.M., Fischer-Friedrich, E., Gov, N.S., Safran, S.A., 2012. Sarcomeric pattern formation by actin cluster coalescence. PLoS Comput. Biol. 8 (6).
Gajewski, E., Steckler, D.K., Goldberg, R.N., 1986. Thermodynamics of the hydrolysis of adenosine 5'-triphosphate to adenosine 5'-diphosphate. J. Biol. Chem. 261 (27), 12733–12737.
Goldspink, G., 1968. Sarcomere length during post-natal growth of mammalian muscle fibres. J. Cell Sci. 3 (4), 539–548.
Gollapudi, S.K., Lin, D.C., 2009. Experimental determination of sarcomere force–length relationship in type-I human skeletal muscle fibers. J. Biomech. 42 (13), 2011–2016.
Greenberg, M.J., Arpağ, G., Tüzel, E., Ostap, E.M., 2016. A perspective on the role of myosins as mechanosensors. Biophys. J. Biophys. Soc. 110, 2568–2576.
Hahn, C., Schwartz, M.A., 2009. Mechanotransduction in vascular physiology and atherogenesis. Nat. Rev. Mol. Cell Biol. 10 (1), 53–62, 2009 10:1.
Heissler, S.M., Manstein, D.J., 2012. Nonmuscle myosin-2: mix and match. Cell. Mol. Life Sci. 70 (1), 1–21, 2012 70:1.
Henderson, C.A., Gomez, C.G., Novak, S.M., Mi-Mi, L., Gregorio, C.C., 2017. Overview of the muscle cytoskeleton. Compr. Physiol. 7 (3), 891–944.
Herrera, A.M., McParland, B.E., Bienkowska, A., Tait, R., Paré, P.D., Seow, C.Y., 2005. 'Sarcomeres' of smooth muscle: functional characteristics and ultrastructural evidence. J. Cell Sci. 118 (11), 2381–2392.
Hotulainen, P., Lappalainen, P., 2006. Stress fibers are generated by two distinct actin assembly mechanisms in motile cells. JCB (J. Cell Biol.) 173 (3), 383–394.
Hove, J.R., Köster, R.W., Forouhar, A.S., Acevedo-Bolton, G., Fraser, S.E., Gharib, M., 2003. Intracardiac fluid forces are an essential epigenetic factor for embryonic cardiogenesis. Nature 421 (6919), 172–177.
Kanzaki, N., Uyeda, T.Q.P., Onuma, K., 2006. Intermolecular interaction of actin revealed by a dynamic light scattering technique. J. Phys. Chem. B 110 (6), 2881–2887.
Katoh, K., Kano, Y., Masuda, M., Onishi, H., Fujiwara, K., 1998. Isolation and contraction of the stress fiber. Mol. Biol. Cell 9 (7), 1919–1938.
Kentish, J.C., Ter Keurs, H.E.D.J., Ricciardi, L., Bucx, J.J., Noble, M.I., 1986. Comparison between the sarcomere length-force relations of intact and skinned trabeculae from rat right ventricle. Influence of calcium concentrations on these relations. Circ. Res. 58 (6), 755–768.
Kodama, T., Woledge, R.C., 1979. Enthalpy changes for intermediate steps of the ATP hydrolysis catalyzed by myosin subfragment-1. J. Biol. Chem. 254 (14), 6382–6386.
Kolley, F., Sidor, C., Dehapiot, B., Schnorrer, F., Friedrich, B.M., 2024. Mechanisms of sarcomere assembly in muscle cells inferred from sequential ordering of myofibril components. PRX Life 2 (1), 013002.
Lazarides, E., Burridge, K., 1975. Alpha-actinin: immunofluorescent localization of a muscle structural protein in nonmuscle cells. Cell 6 (3), 289–298.
Liu, S., Matsui, T.S., Kang, N., Deguchi, S., 2022. Analysis of senescence-responsive stress fiber proteome reveals reorganization of stress fibers mediated by elongation factor eEF2 in HFF-1 cells. Mol. Biol. Cell 33 (1).

Loison, O., Weitkunat, M., Kaya-Çopur, A., Nascimento Alves, C., Matzat, T., Spletter, M. L., et al., 2018. Polarization-resolved microscopy reveals a muscle myosin motor-independent mechanism of molecular actin ordering during sarcomere maturation. PLoS Biol. 16 (4), e2004718.
Lovett, D.B., Shekhar, N., Nickerson, J.A., Roux, K.J., Lele, T.P., 2013. Modulation of nuclear shape by substrate rigidity. Cell. Mol. Bioeng. 6 (2), 230–238.
Maeda, E., Kawamura, R., Suzuki, T., Matsumoto, T., 2022. Rapid fabrication of tendon-like collagen gel via simultaneous fibre alignment and intermolecular cross-linking under mechanical loading. Biomed. Mater. 17 (4), 045018.
Manabe, Y., Ogino, S., Ito, M., Furuichi, Y., Takagi, M., Yamada, M., et al., 2016. Evaluation of an in vitro muscle contraction model in mouse primary cultured myotubes. Anal. Biochem. 497, 36–38.
Matsui, T.S., Deguchi, S., 2019. Spatially selective myosin regulatory light chain regulation is absent in dedifferentiated vascular smooth muscle cells but is partially induced by fibronectin and Klf4. Am. J. Physiol. Cell Physiol. 316 (4), C509–C521.
Matsui, T.S., Kaunas, R., Kanzaki, M., Sato, M., Deguchi, S., 2011. Non-muscle myosin II induces disassembly of actin stress fibres independently of myosin light chain dephosphorylation. Interface Focus 1 (5), 754–766.
Meyer, R.K., Aebi, U., 1990. Bundling of actin filaments by alpha-actinin depends on its molecular length. JCB (J. Cell Biol.) 110 (6), 2013–2024.
Montague, C., Rhee, K.W., Carlson, F.D., 1983. Measurement of the translational diffusion constant of G-actin by photon correlation spectroscopy. J. Muscle Res. Cell Motil. 4 (1), 95–101.
Newman, J., oczka, N., Schick, K.L., 1989. Dynamic light scattering measurements of the diffusion of probes in filamentous actin solutions. Biopolymers 28 (2), 655–666.
Okamoto, T., Matsui, T.S., Ohishi, T., Deguchi, S., 2020. Helical structure of actin stress fibers and its possible contribution to inducing their direction-selective disassembly upon cell shortening. Biomech. Model. Mechanobiol. 19 (2), 543–555.
Peterson, L.J., Rajfur, Z., Maddox, A.S., Freel, C.D., Chen, Y., Edlund, M., et al., 2004. Simultaneous stretching and contraction of stress fibers in vivo. Mol. Biol. Cell 15 (7), 3497–3508.
Purslow, P.P., Trotter, J.A., 1994. The morphology and mechanical properties endomysium in series-fibred muscles: variations with muscle length of. J. Muscle Res. Cell Motil. 15.
Reconditi, M., Brunello, E., Fusi, L., Linari, M., Martinez, M.F., Lombardi, V., et al., 2014. Sarcomere-length dependence of myosin filament structure in skeletal muscle fibres of the frog. J Physiol. 592 (5), 1119–1137.
Russell, R.J., Grubbs, A.Y., Mangroo, S.P., Nakasone, S.E., Dickinson, R.B., Lele, T.P., 2011. Sarcomere length fluctuations and flow in capillary endothelial cells. Cytoskeleton 68 (3), 150–156.
Sanger, J.W., Sanger, J.M., Jockusch, B.M., 1983. Differences in the stress fibers fibroblasts and epithelial cells between. J. Cell Biol. 96.
Schiffhauer, E.S.S., Luo, T., Mohan, K., Srivastava, V., Qian, X., Griffis, E.R.R., et al., 2016. Mechanoaccumulative elements of the Mammalian actin cytoskeleton. Curr. Biol. 26 (11), 1473–1479.
Shannon, C.E., Weaver, W., 1949. THE MATHEMATICAL THEORY OF COMMUNICATION.
Van Dijk, J., Furch, M., Lafont, C., Manstein, D.J., Chaussepied, P., 1999. Functional characterization of the secondary actin binding site of myosin II. Biochemistry 38 (46), 15078–15085.
Verkhovsky, A.B., Svitkina, T.M., Borisy, G.G., 1997. Polarity sorting of actin filaments in cytochalasin-treated fibroblasts. J. Cell Sci. 110 (15), 1693–1704.
Vicente-Manzanares, M., Ma, X., Adelstein, R.S., Horwitz, A.R., 2009. Non-muscle myosin II takes centre stage in cell adhesion and migration. Vol. 10. Nat. Rev. Mol. Cell Biol. 778–790.
Wachsstock, D.H., Schwartz, W.H., Pollard, T.D., 1993. Affinity of alpha-actinin for actin determines the structure and mechanical properties of actin filament gels. Biophys. J. 65 (1), 205–214.
Zajac, A.L., Discher, D.E., 2008. Cell differentiation through tissue elasticity-coupled, myosin-driven remodeling. Curr. Opin. Cell Biol. 20 (6), 609–615.