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ABSTRACT

Multicellular systems, such as epithelial cell collectives, undergo transitions similar to those in inert physical systems like sand piles and foams. To remodel or maintain tissue organization during development or disease, these collectives transition between fluid-like and solid-like states, undergoing jamming or unjamming transitions. While these transitions share principles with physical systems, understanding their regulation and implications in cell biology is challenging. Although cell jamming and unjamming follow physics principles described by the jamming diagram, they are fundamentally biological processes. In this review, we explore how cellular processes and interactions regulate jamming and unjamming transitions. We begin with an overview of how these transitions control tissue remodeling in epithelial model systems and describe recent findings of the physical principles governing tissue solidification and fluidization. We then explore the mechanistic pathways that modulate the jamming phase diagram axes, focusing on the regulation of cell fluctuations and geometric compatibility. Drawing upon seminal works in cell biology, we discuss the roles of cytoskeleton and cell–cell adhesion in controlling cell motility and geometry. This comprehensive view illustrates the molecular control of cell jamming and unjamming, crucial for tissue remodeling in various biological contexts.

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I. INTRODUCTION

Cells and tissues generate and respond to forces, resulting in organized structures and specific shapes. During organ development and regeneration, the balance between cell rearrangement and supracellular organization determines tissue deformability and structural integrity. Many multicellular systems, including epithelial cell collectives, transition between a fluid-like, malleable state and a solid-like, stable state, similar to particulate systems like sand piles. Initially, sand flows but jams when particles pack tightly and can flow again if agitated. Cell collectives undergo a similar phase transition. Understanding the flow properties associated with cell jamming and unjamming transitions provides insights into the biophysical mechanisms of tissue formation and disease progression.

The regulation of cell jamming and unjamming transitions is multifactorial. These transitions adhere to fundamental physics principles, sharing mechanisms with systems like foams, glass, and granular materials.[1–3] However, they are ultimately driven by biological events triggered by biochemical and biomechanical cues. This review integrates physical and biological understandings of cell jamming and unjamming by discussing the molecular regulation of cell fluctuation and geometric compatibility, key determinants of phase transitions. We describe four representative jamming and unjamming examples observed in different epithelial model systems. We then explore how cytoskeletal activities, cell–cell interactions, and their upstream signaling pathways control dynamic changes in cell motility and morphology.

A. Biological roles of cell jamming in epithelial systems

Recent experiments using *in vitro* and *in vivo* models have highlighted the role of cell jamming and unjamming in modulating tissue properties across various biological contexts, including embryonic development,[12–14] injury repair,[15] and disease progression.[10,16–18] This review focuses on epithelial tissues and discusses key discoveries on how cell jamming and unjamming govern cell behaviors and tissue characteristics.

1. Wound healing assays

The study of epithelial wound healing using cell culture models dates back to the early 20th century,[19–21] facilitated by the invention of phase contrast microscopy.[22] Recently, wound healing has been examined through the framework of jamming and unjamming transitions. The *in vitro* wound healing process has two main stages. First, when a wound is introduced to a jammed epithelial monolayer, edge cells migrate to re-epithelialize the area, accompanied by increased cell proliferation and movement [Fig. 1(a)]. The wound decreases local stress, altering cell propulsion,[23] alignment,[23] and metabolism,[15,24] leading to unjamming of the monolayer. In the second stage, after the gap is closed, cells reestablish adhesion via adherens and tight junctions, restoring tissue integrity. This stage represents a jamming transition, often studied using cell crowding models.[25–27] Examining wound healing through the lens of jamming and unjamming transitions offers insights into tissue functions and cell phenotypes. Tissue fluidity, as influenced by intercellular junction tension and intercalating rate, can directly affect healing pace.[28] This perspective underscores the critical role of mechanical properties in regulating tissue healing processes and outcomes.

2. Epithelial morphogenesis in Drosophila

In developing *Drosophila*, many epithelial tissues undergo dynamic shape changes, serving as key examples for studying tissue morphogenesis through cell mechanics and jamming transitions. During gastrulation, the single-layered blastula epithelium folds inward at the ventral side to form the ventral furrow, where epithelial cells invaginate to establish the mesoderm.[29] This process, driven by actomyosin-mediated apical constriction and junctional remodeling,[30–33] does not involve cell intercalation. However, prior to furrow formation, cells exhibit increased speed and elongated shapes typical of cellular unjamming.[34] This contrasts with maturing cultured epithelial monolayers, where cells become more jammed and less elongated.[34] Cell shape and packing constraints highlight the link between cell packing and geometric principles, transcending specific biological properties.[34–36] Additionally, the rapid changes in volumetric and shear order parameters at the onset of ventral furrow formation can also indicate an unjamming transition.[37]

Shortly after the ventral furrow begins to form, cells in the lateral epidermis, known as the germ-band, rapidly rearrange and intercalate to drive the elongation of the main body axis, a process called germ-band extension, which occurs within minutes [Fig. 1(b)].[38] Importantly, cell shape alone cannot fully predict the phase transition in this context. A combination of an increased cell shape index (cell perimeter divided by the square root of area) and decreased shape alignment is required to predict the onset of rapid cell rearrangement that drives germ-band extension.[6] This fluidization of the epithelial tissue then permits morphogenesis to occur.

3. Blastoderm spreading in zebrafish

In zebrafish, gastrulation starts with the blastoderm spreading over the yolk cell [Fig. 1(c)], involving the coordinated expansion of the outer epithelial cell layer and E-cadherin dependent deep cell intercalations.[39,40] Initially, mitotic cell rounding reduces cell–cell contact in the central blastoderm, decreasing tissue viscosity and fluidizing the tissue to facilitate deformation.[9] As the blastoderm "domes," cell–cell connectivity is again reestablished and tissue viscosity gradually increases, effectively re-solidifying the tissue to maintain its integrity.[41] As gastrulation proceeds, mesendoderm progenitor cells ingress at the blastoderm margin, driven by a Nodal signaling gradient that prompts highly protrusive leader cells to undergo local unjamming transition and migrate toward the yolk syncytial layer.[42] Unlike in Drosophila furrow formation, cell shape changes or packing configurations in zebrafish do not predict jamming and unjamming states; instead, changes in cell–cell contact patterns reliably inform blastoderm viscosity.[41]

4. Airway epithelium culture models

During an asthma exacerbation, airway narrowing leads to epithelial buckling and exposure to compressive stress.[43] This can be mimicked in cell culture by applying mechanical compression with a 30 cm-H_2O pressure differential from the apical to the basal side [Fig. 1(d)].[10,44] In primary human bronchial epithelial cells, such compression induces unjamming transition, mobilizing cells that could potentially repair the injured bronchial tissue.[10] Unjammed cells become elongated, and this elongation, defined by the cell shape index, predicts the unjamming phase transition.[44] These cells retain epithelial

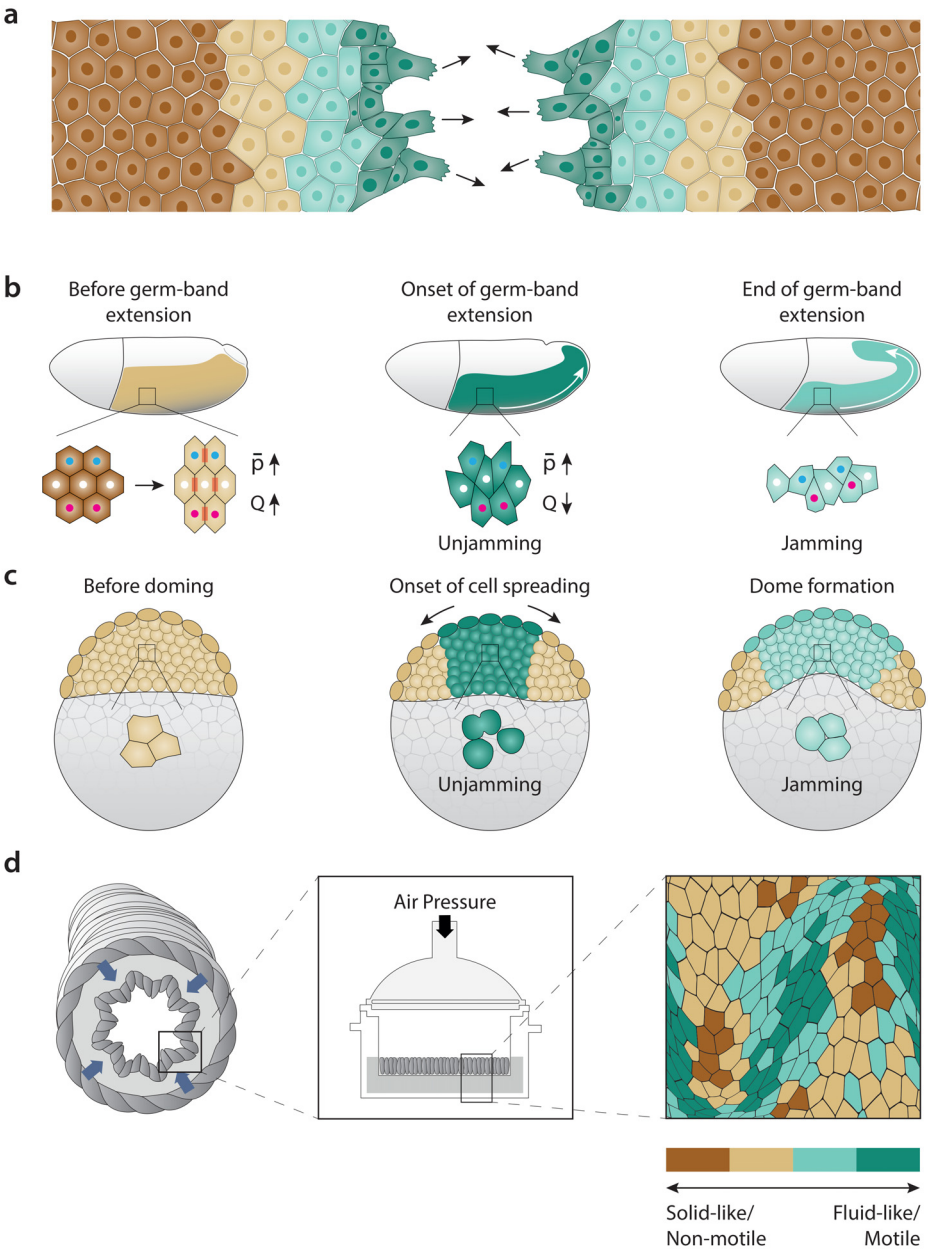

FIG. 1. Examples of cell jamming and unjamming transitions: (a) Epithelial wound healing exemplifies jamming–unjamming transitions, where a wound triggers cell migration, intercalation, and proliferation, causing the cell monolayer to unjam. As the cells migrate to close the wound, they eventually undergo a fluid-to-solid transition (not shown), reestablishing junctions to restore tissue integrity.[4,5] (b) Shortly before germ-band extension takes place in *Drosophila*, both the cell shape index ($\bar{p}$) and shape alignment (Q) begin to increase, although the tissue remains in a jammed state initially. The onset of unjamming transition is marked by a rapid decrease in shape alignment, leading to cell intercalation. This process is driven by planar-polarized myosin II at cell interfaces (orange stripes), which fluidizes the germ-band epithelium and enables its elongation (white arrows).[6,7] (c) During the initial spreading of the blastoderm over the yolk in zebrafish, mitotic cell rounding reduces cell–cell contacts and fluidizes the tissue locally, allowing dome formation. The blastoderm subsequently re-solidifies through reestablishment of cell–cell contacts.[8,9] (d) Mechanical compression induces an unjamming transition in bronchial epithelial cells, resembling conditions during asthma exacerbation, where the unjamming transition is marked by elongated cell shapes.[10,11]

characteristics, including apical-basal polarity and matured E-cadherin junctions, distinguishing unjamming from epithelial-to-mesenchymal transition, despite both enabling cellular migration.[11] Cells from asthma or idiopathic pulmonary fibrosis patients exhibit delayed jamming transition and persistent fluid-like phase during crowding, highlighting biophysical deviations that may contribute to disease progression.[10,45]

B. Physics insights into cell jamming

An exciting perspective in using physics to understand complex systems is identifying emergent behaviors and self-organizing principles arising from constituent interactions. The jamming transition exhibits many hallmarks akin to conventional second-order phase transitions, demonstrating critical behavior near the transition point, characterized by diverging length scales[46] and power-law trends.[47,48] In granular systems, the jamming transition is characterized by universality, where systems with different microscopic details display similar macroscopic behavior near the critical point, with shared critical exponents and scaling laws.[47,49–51]

Since the jamming transition is well-studied across various physical systems like granular materials, colloidal suspensions, foams, emulsions, and glass-forming liquids, cell jamming studies often draw

inspiration from these works.[51,52] However, most cell jamming–unjamming experiments focus on changes in tissue structure, rheological properties (e.g., rigidity), and dynamic heterogeneity. Studies of scaling and critical phenomena in cell jamming remain largely theoretical.

1. Biophysical insights into cell jamming phase diagram

Here we adopt a recently proposed version of jamming phase diagram,[1] wherein jammed states are situated near the origin of a parameter space with axes representing inverse density, fluctuation, and geometric compatibility (Fig. 2). Both the density and fluctuation axes are directly derived from the classical jamming diagram,[53,54] whereas the geometric compatibility is unique in cellular systems.[10,55] Along the density axis, as the density of cells increases in a system, they become more crowded, eventually reaching a point, where they have no space to move. The fluctuation axis describes agitations caused by dynamic changes in cell movements or cell divisions, providing cells with the energy to escape the "cage" created by their neighbors, similar to the role of temperature in glass transition. Finally, geometric compatibility accounts for the cells' ability to achieve the target area and perimeter, which is predominantly determined by the force balance of cortical tension.

While the jamming diagram predicts system states based on physical parameters,[13,56] understanding cell jamming mechanisms requires insight into the molecular regulation of these parameters. In cell biology, the jamming axes (density, movement, and geometry) are downstream phenotypes regulated by upstream signaling pathways and molecular events. This explains why jamming or unjamming often involves changes in multiple axes. Below, we explore cell biological mechanisms regulating cell jamming, primarily focusing on density-independent jamming, where cell number remains relatively constant during the transition. For density-driven jamming, for example regulated through a balance between proliferation and extrusion, we refer readers to comprehensive reviews on the physical aspects of the transition.[1,2,51,57,58]

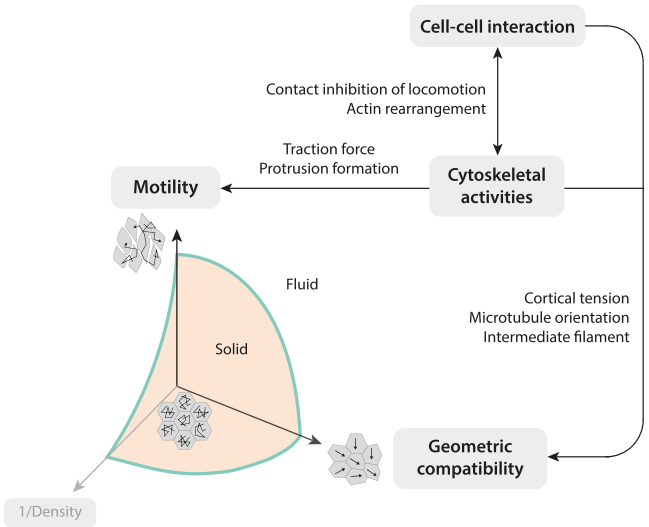

FIG. 2. The jamming phase diagram positions jammed states close to the origin within a parameter space outlined by axes of inverse density, fluctuation, and geometric compatibility, with the latter referring to the cells' ability to simultaneously achieve the target area and perimeter. These characteristics are ultimately influenced by upstream signaling pathways and molecular events. Cell motility and geometry are directly regulated by cytoskeletal activities, which both modulate and are modulated by cell–cell interactions.

It should be noted that under different biological contexts, the unjamming transition can be associated with distinct cell movement patterns. For instance, during Drosophila gastrulation, cell movements in the germ-band are largely driven by intercalations, reminiscent of atomic rearrangements during fluidization.[59] Conversely, MCF10A cells[60] and bronchial epithelial cells[44] may exhibit "flocking-solid" states when undergoing unjamming transitions. In these cases, cells move collectively in groups, each behaving like a solid with minimal internal relative motion. This phenomenon is reminiscent of cooperative rearranging regions in supercooled liquids[61,62] and particle clusters in sheared colloidal gels.[63,64] While a reduction in tissue rigidity might be anticipated in all these cases, future studies should examine other mechanical properties of these systems, which could still differ due to the distinct cell movement states. To delineate the outcomes produced from distinct cell movement patterns, it is essential to integrate the comprehensive quantification of motility metrics and the understanding of jamming and unjamming movements. Bridging this gap is crucial for advancing our knowledge of cellular behavior during unjamming transitions. By incorporating quantitative metrics from soft matter physics and fluid mechanics—such as velocity correlation functions,[65–67] diffusion-based analysis,[68] and non-Gaussianity parameters[69,70]—existing theoretical models can be more effectively integrated to explain unjamming movements in biological systems. Complementary measurements, such as traction forces, junctional tension inference, and cellular protrusions, will provide additional insights into the underlying cellular mechanisms.

2. Density-driven cell jamming

In both physical and biological systems, the balance between degrees of freedom and constraints controls rigidity.[71,72] In a non-confluent cell monolayer, each cell can move in various directions on a two-dimensional plane. Simplifying cells as "hard spheres," the total degrees of freedom equal the number of cells (N_c) times the number of dimensions (d).[73] As cells become crowded, intercellular contacts add constraints, jamming the system when constraints match degrees of freedom ($N_c d$), inhibiting cell rearrangements.[74] Conversely, when the system is less dense with fewer contacts, cells can easily exchange neighbors, allowing the tissue to "flow."

Compared to ideal hard spheres, cells are soft and motile, introducing complexity in understanding density-driven cell jamming. Cell jamming occurs beyond confluence, where glassy dynamics[25,26,75] and projected cell area reduction due to continuous division after reaching initial confluency must be considered.[76] Cells with glassy dynamics display sluggish movement, prolonged relaxation times, and a tendency to become trapped in metastable configurations,[35,77–79] similar to glass and amorphous materials.[80] Additionally, intercellular interactions are adhesive, like "sticky particles," and the density-driven jamming transition is dictated by cell–cell adhesion and network connectivity. For example, in zebrafish blastoderm, a slight change in cell packing drastically alters viscosity and determines long-range cell connectivity,[41] consistent with particulate jamming with attractive

interparticle forces.[3] Similarly, during zebrafish body axis elongation, functional cell–cell adhesion reduces volume fraction and promotes fluid-to-solid transition of the presomitic mesoderm to rigidify the extending body.[81]

3. Density-independent cell jamming

In crowded tissue systems, where all cells are in contact with their neighbors and the packing density reaches a steady state, density-independent mechanisms govern the jamming–unjamming transitions.[55] For instance, in the self-propelled Voronoi (SPV) model of confluent tissues, it has been demonstrated that the processes of unjamming and fluidization are driven by the magnitude of fluctuating propulsive forces, the persistence of these forces, and the cell target shape parameters.[55,78] Using multi-phase-field models that simulates the fluidization of a confluent layer comprising motile deformable particles, it has been shown that jamming and unjamming are controlled by the trade-off between deformability and the overlap of cells.[82] In addition, active foam models[81,83] and active finite Voronoi simulations[84] can effectively capture the jamming–unjamming transitions in non-confluent cell collectives by accounting for the intercellular spaces. Recent experiments have been able to observe density-independent unjamming transitions in response to morphogen gradient,[42] irradiation,[85] hydrostatic pressure,[44] or mechanical compression,[86] in which the cell morphological changes during transition are consistent with the vertex model predictions.

II. CELL MOTILITY AND JAMMING

A. Fluctuation-regulated cell jamming

The concept of fluctuation-regulated cell jamming was mainly derived from the temperature axis of the original jamming diagram.[1,2,58] As illustrated in Fig. 3(a), an intuitive way of understanding this jamming–unjamming mechanism is to consider the scenario in which, as the system's temperature increases, the constituent element (e.g., an atom, particle, or cell) gains more energy that allows them to escape the constraints imposed by its neighbors, thus fluidizing the system. In atomic systems, such as glassy liquids, the kinetic energy of atoms is a direct result of thermal fluctuations.[87] In contrast, systems undergoing jamming transitions, like granular and cellular systems, are far from thermodynamic equilibrium, with particle kinetic energy in granular systems relying on continuous energy injection from external mechanical perturbations.[52] In cellular systems, the kinetic energy of a cell arises from the controlled release of chemical energy, making the "temperature" of these far-from-equilibrium systems a concept used to describe thermal-like fluctuation behavior.[88,89]

B. Molecular regulation of cell motility

Fluctuations, often associated with the self-propulsion force of cells (i.e., cell motility),[90] drive tissue fluidization through three types of cellular events. In this section, we examine the molecular effectors influencing these cell behaviors. Cell motility is coordinated through

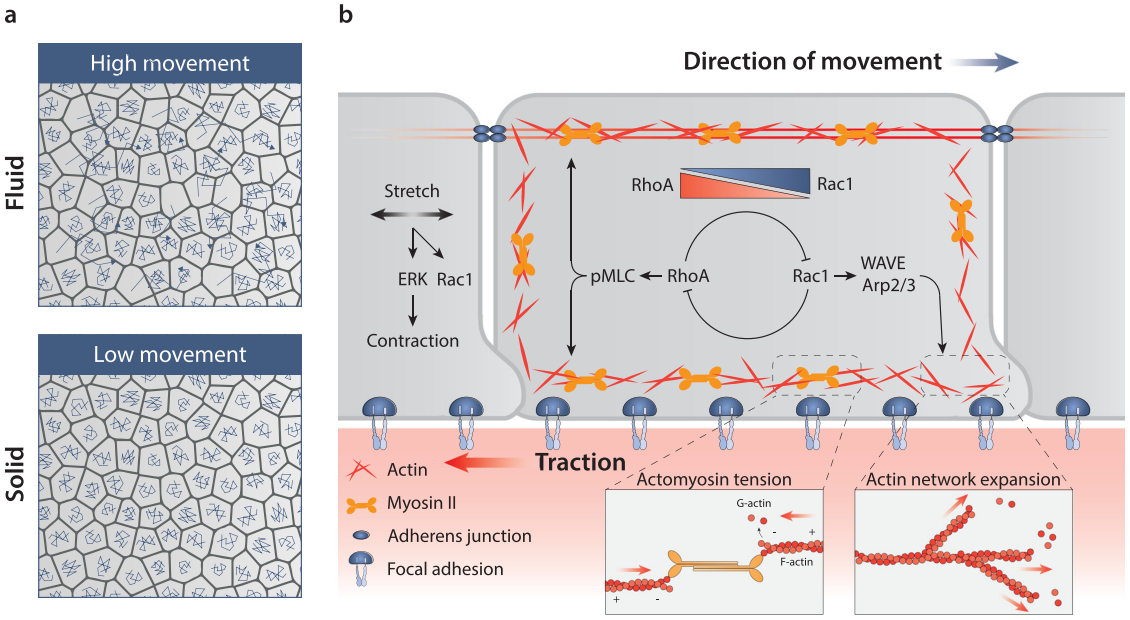

FIG. 3. Cell motility and jamming: (a) As the force of cell propulsion increases, the effective temperature within a cell layer rises, granting cells more energy to overcome constraints from neighboring elements, thereby leading to the fluidization of the system. To highlight motility differences between jammed and unjammed states, the schematic does not depict all morphological changes that may occur during the jamming or unjamming transition. (b) Cell motility is predominately a result of cytoskeletal activities, which regulate the formation of cryptic protrusions in crowded cells and generate traction forces on substrates through focal adhesions. The front-rear polarization arises from the Rac1-RhoA gradient, which facilitates actin polymerization and branching in the cryptic protrusion anteriorly via activation of WAVE and Arp2/3 complexes and stimulates robust actomyosin contraction posteriorly via activation of myosin light chain (MLC). Transmission of contractile force through adherens junctions (e.g., cadherins) stretches the posterior neighbor cell and biomechanically activates its ERK signaling to orient front-rear polarity and induces downstream actomyosin contraction. This cycle repeats between cells, leading to the propagation of ERK activation waves and coordinated cell movement during collective cell migration. Note that the Rac1-RhoA gradient would be reversed in leader cells (not illustrated here) to exert traction force anteriorly.

the interplay of biochemical signaling cascades, physical cues, and mechanical machinery, as summarized in Fig. 3(b). Although significant progress has been made in understanding single-cell and collective cell migration in cell biology and mechanobiology, its role in the context of unjamming transition remains underexplored. Notably, there are two primary distinctions between conventional collective cell migration and unjamming studies: (1) Typical collective cell migration studies, such as wound healing scratch assays, chemotaxis, or durotaxis, exhibit global directionality,[91] whereas unjamming transitions often lack tissue-level migration guidance,[10,44,85,86] leading to uncoordinated motion and the absence of well-defined leader cells during tissue fluidization.[65,92] (2) In motility-driven unjamming experiments, intercellular adhesions are maintained or strengthened,[44,86] unlike the weakened adhesions in the mesenchymal phenotype seen in collective migration.

Despite these differences, the fundamental molecular mechanisms regulating cell motility are likely conserved in jamming and unjamming contexts. We will focus on the roles of cytoskeletal activity and cell–cell interactions in governing cell motion. At the molecular level, signaling pathways, including those mediated by small GTPases like RhoA, Rac1, and Cdc42, regulate cytoskeletal dynamics, cell adhesion, and protrusion-retraction cycles. These processes determine the cell's ability to navigate its microenvironment and interact with neighboring cells, guiding coordinate movements within tissues to drive jamming or unjamming.

1. Cytoskeletal activities

The cytoskeleton, consisting of actin microfilaments, microtubules, and intermediate filaments, provides structural support in the cytoplasm. Actin and microtubules can independently polymerize in a polarized manner using energy from ATP or GTP hydrolysis, exerting pushing forces against the cell membrane.[93,94] As a result, increased actin polymerization at cell protrusions can lead to large-scale, coordinated cell movements that fluidize 2D cell layers and 3D spheroids.[60,95,96] In contrast, intermediate filaments lack polarity and polymerize without ATP. They do not generate forces but maintain cell integrity by accommodating tensile and compressive stresses from actin and microtubules.[97]

To produce contractile forces to pull on the substrate or neighboring cells, non-muscle myosin II crosslinks actin filaments and use ATP hydrolysis to slide them in opposite direction [Fig. 3(b), left inset].[98] This actomyosin complex produces tension, regulating cell motility and geometry. The spatiotemporal activation of actin assembly, actomyosin tension, and their interactions with adhesion complexes are central to regulating the fluctuation axis in the jamming diagram.

Rho family GTPases, including RhoA, Rac1, and Cdc42, are key regulators of myosin II activities and actin dynamics. Perturbing their functions can thus alter jamming transitions. For example, activating RhoA fluidizes densely packed MDCK epithelial cell monolayers by increasing traction forces.[99] In contrast, in the *Drosophila* germ-band, activating RhoA increases junctional tension but reduces tension anisotropy, leading to a more solid-like tissue with reduced cell intercalations.[100] Deactivating RhoA lowers tension levels but also reduces anisotropy, maintaining a solid-like state and highlighting the importance of anisotropy in driving unjamming.[100] Finally, polarized tissue flow, such as the anterior movement of the *Drosophila* endoderm during gastrulation, arises from asymmetrically localized actomyosin activities that produce torque forces along a tissue curvature gradient.[101] These findings underscore the critical role of spatiotemporal regulation of actomyosin activities in cell jamming and unjamming. Future studies should focus on understanding how anisotropic actomyosin forces are established and propagated to initiate phase transitions at the cell and tissue levels.

2. Front-rear polarization and RhoA/Rac1 activities

Symmetry breaking in cell movement, essential for unjamming transitions, often arises from cell and tissue polarization. Front-rear polarization of cells, crucial for directed cell migration, involves the spatiotemporal regulation of actin assembly and actomyosin contractility in response to external cues.[102,103] The mutual inhibition between RhoA and Rac1 is key to this process: RhoA inhibits Rac1, and Rac1 inhibits RhoA, creating a gradient along the cell's front-rear axis [Fig. 3(b)].[104,105] At the cell front, Rac1 activation promotes actin polymerization and lamellipodia formation, while RhoA activation at the rear enhances actomyosin contractility for contraction.[106,107] Ectopic RhoA activation reduces protrusion and increases adhesion, favoring a static state, while Rac1 activation promotes protrusion and reduces adhesion,[108] favoring motility. However, Rac1-RhoA distribution is context-dependent and dynamic;[109,110] for example, in MDCK monolayers active RhoA is present at the leading edge of migrating leader cells, which exerts high traction forces to pull cells forward.[111] The regulation of Rac1-RhoA polarity during jamming–unjamming transitions remains not fully understood.

Front-rear polarization in collectively moving cells can be established and propagated through ERK-mediated mechanochemical waves, which orient collective cell movement opposite to the wave direction.[112,113] In this process, actomyosin contraction forces transmitted through cell–cell junctions stretch neighboring cells, polarizing Rac1 activation at the front of the follower cell.[114] This stretching also triggers ERK signaling, which orients front-rear polarity and induces actomyosin contraction at the cell rear, pulling on the next follower cell.[115] This cycle of ERK waves and actomyosin contraction enables coordinated collective cell migration. In unstimulated cells, stochastic ERK activation and oscillation can be initiated by cell protrusions,[116] suggesting that localized mechanical fluctuations could be amplified and propagated through ERK waves to fluidize the system. Future research should investigate how front-rear polarity initiates phase transitions and how ERK signaling mediates mechanical signals to control cellular jamming and unjamming in development and cancer contexts.

3. Cryptic protrusions in confluent monolayers

Similar to the lamellipodia of leader cells in collective migration, cells within a fluidized epithelial layer can develop microprotrusions, or cryptic protrusions, even when surrounded by neighboring cells.[107,117–119] These dynamic structures are composed of actin filaments, which form branched network at adherens junctions and push outward on the cell membrane at mechanically weak sites of the cell–cell boundary[107,119] [Fig. 3(b), right inset]. Integrins link the actin cytoskeleton to the extracellular matrix at focal adhesions, converting actomyosin forces into traction for cell movement.[120,121] Rac1/Cdc42[122,123] and EGF/PDGF[124–126] signaling likely regulate microprotrusion formation, similar to their roles in lamellipodia and filopodia

formation. Given the central role of microprotrusions in guiding cell movements,[118] future studies should investigate the mechanisms inducing their formation and their role in unjamming tissues.

4. Contact inhibition of locomotion (CIL) and related mechanisms

While actomyosin-dependent traction forces enable cell unjamming, stopping and redirecting cell movement is essential for the jamming transition. Contact inhibition of locomotion (CIL) stops and redirects cell movement through a four-step process.[127] First, cell–cell contact triggers intercellular connections, including various receptors and adherens junction components.[128–130] This contact, along with WNT-PCP signaling, inhibits protrusions by inducing Rac1 inhibition and RhoA activation at the interface, depolarizing front-rear asymmetry.[131,132] Next, changes in small GTPase activity increase actomyosin contraction and microtubule turnover, repolarizing and reversing the cell's front-rear directionality.[131,133–135] Finally, repolarized cells initially migrate away, but in crowded environments, CIL decreases traction asymmetry (i.e., front-rear polarity) and results in reduced cell movement.[127,136]

CIL plays a pivotal role in controlling tissue remodeling and cell movement during development and disease progression. It regulates cell organization during gastrulation[137,138] and neural crest cell migration.[131,139] On the other hand, dysregulated CIL can lead to aberrant cell invasion during cancer metastasis.[140,141] Recent studies on collective cell migration highlight the relationship between CIL and cell jamming–unjamming, showing that CIL induces spontaneous cell swarming and streaming.[142–144] Intercellular polarity alignment can drive tissues toward a "solid-flocking" state, where cell collectives are internally rigid with minimal neighbor exchange, yet move coherently as a unit.[44,60,66,145] In cancer cell lines, this flocking behavior is linked to collective cell motility.[146] Particle-based simulations have demonstrated a feedback mechanism among CIL, cell density, and cell–cell adhesion, inducing a non-motile state with a wide distribution of traction forces.[136] Notably, early simulation models[78,82] of jamming and unjamming transitions often modulate cell motility without explicitly considering the CIL mechanism. Future studies should investigate how cell–cell biomechanical interactions influence cell motility and collective movements during the jamming transition.

III. CELL GEOMETRY AND JAMMING

A. Geometry-regulated cell jamming

In a confluent tissue, all cell movements require changes in cell geometries, necessitating cell rearrangements like intercalation (T1 transition) or extrusion (T2 transition).[100,147] The influence of cell geometries on movements and jamming transitions has been mainly explored through theoretical studies, including vertex models,[55,148–150] multi-phase-field models,[82,151] active foam models,[81,83] and deformable element models.[152] These simulations show that geometry-regulated jamming transitions in tissues are typically governed by the shape index.[2]

Tissues with a small mean shape index exhibit rigidity due to energy barriers that inhibit cell rearrangement, resulting in geometrically incompatible cell packing [Fig. 4(a)]. When cell packing is frustrated, cells adjust their morphology to achieve the desired perimeter and area, albeit at the expense of sacrificing neighboring cells optimal morphology.[153] Consequently, cell shape changes become unfavorable, prohibiting movement. Conversely, tissues with a large shape index allow for geometric compatibility, leading to tissue fluidization as

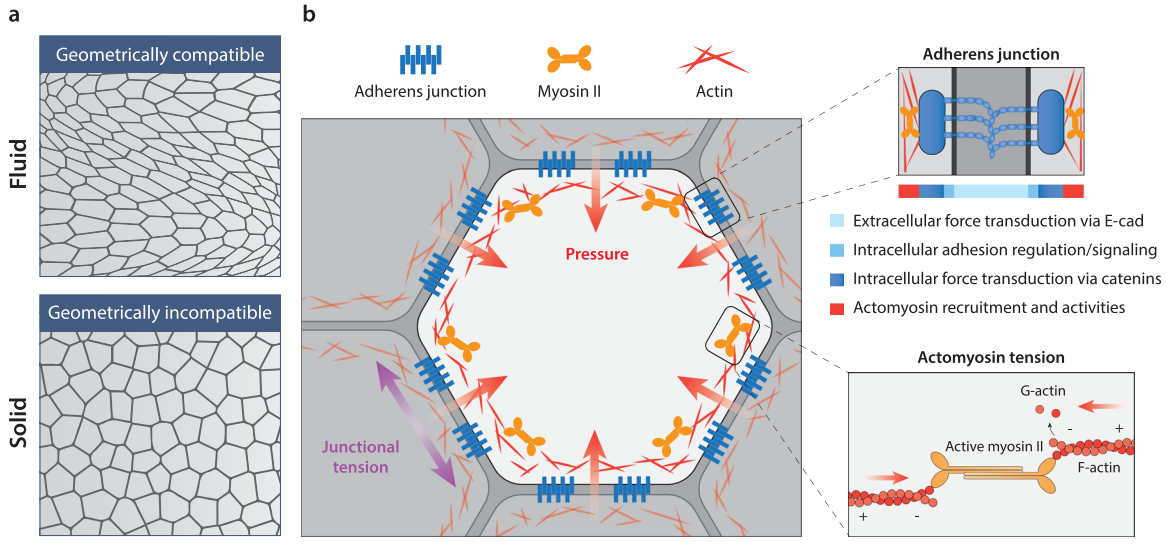

FIG. 4. Cell geometry and jamming: (a) In the fluid-like and geometrically compatible state, cells can reach the target area and perimeter simultaneously. In the solid-like and geometrically incompatible state, cells fail to reach the target area and perimeter simultaneously, leading to a geometrically frustrated packing. As such, cell shape change that is necessary for cell movement and rearrangement becomes energetically unfavorable. (b) Cell geometry is regulated by cytoskeletal activities, such as actomyosin-driven cortical tension and cell–cell adhesion (upper right box). These cytoskeletal activities jointly regulate the junctional tension and pressure, determining the cell shape (middle panel). Specifically, actomyosin contraction that generates cortical tension can be either myosin II motor-dependent or motor-independent. The motor-independent contraction arises from myosin II-facilitated polymerization and depolymerization of actin filament (lower right box). The adherens junctions play two essential roles in cell shape control: transmitting mechanical force between neighboring cells and organizing actomyosin tension.

energy barriers associated with cell rearrangements decrease. In this fluid-like state, cells can easily achieve their target morphology, making movements more permissive.

The interplay between cell shape and junctional tension distribution can also control jamming and unjamming transitions. Cell shape changes reacting to the active cellular stress fluidize the tissue through several intermediate steps.[154] As cell packing transitions from isotropic to anisotropic, rhombile, and finally to nematic phases, the cell layer modulus vanishes, reemerges, and vanishes again, leading to spontaneous tissue flows. In biological tissues, the shape index correlates with the degree of cell rearrangements and tissue fluidity, making it a useful metric for predicting jamming and unjamming transitions.[55,155] However, because cell shape is also influenced by packing anisotropy[6] and external forces, the shape index alone does not demonstrate jamming, which requires verification of cell rearrangements and motility using techniques like time-lapse microscopy.

B. Molecular regulation of cell geometry

The regulation of cell geometry involves molecular events controlling junctional tension and cell–cell adhesion. While vertex and finite element models have provided insights into the physical aspects of cell geometry regulation,[156–161] experimental research on its molecular control during jamming transitions is limited. For instance, the biological significance of the preferred perimeter and area in vertex models, along with their upstream molecular regulation, remains not fully understood. Here, we draw upon cell biology to provide an overview of the regulation of epithelial cell shape, focusing on how junctional tension and cell–cell adhesion influence cell geometry by modulating cytoskeletal organization and activities.

1. Cytoskeletal activities

Cell shape is determined by intercellular adhesive junctions and mechanical force balance. D'Arcy Thompson's theory and the vertex model suggest that a cell monolayer achieves mechanical equilibrium by minimizing an energy function.[148] Therefore, cells in a tissue aim to achieve a target area and perimeter. These parameters are determined by the balance of junctional tension, which is influenced by the interplay between adhesion complexes and cortical actomyosin contraction [Fig. 4(b)].[162–164] There are two mechanisms for generating contractions between anti-parallel actin filaments: myosin II motor-dependent and independent. In the motor-dependent mechanism, dimerized myosin II binds to actin and undergoes power stroke cycles, moving actin filaments in opposite directions to generate tension.[165–167] Myosin II can also cross-link actin filaments and generate contraction through actin polymerization and depolymerization.[165,168–171] Therefore, changes in cortical actomyosin activities can induce cell shape changes. For instance, increased myosin II density at the cell cortex aligns actin filaments and enhances cortical tension to reduce apical cell area,[172] while planer polarized forces deform cells, resulting in tissue remodeling.[165,173,174]

In addition to actin, microtubules also regulate cell area and elongation.[175–177] Alignment of protruding microtubules along the cell's apical-basal axis drives cell elongation, changing the cell morphology from squamous to columnar.[178] Disruption of microtubule assembly thus decreases the cell height and consequently increases cell apical surface area due to volume conservation.[179,180] Microtubules can therefore potentially influence the target cell area by altering cell height, controlling jamming and unjamming transitions. Furthermore, microtubule disassembly increases actomyosin contraction through stimulation of RhoA activity.[181–184] These actomyosin modulations then stabilize and promote the junctional clustering of E-cadherin,[181,185,186] promoting the epithelial phenotype and corresponding morphology.

Intermediate filament networks, such as keratin filaments, also maintain cell morphology by providing mechanical support.[187] This tension-bearing system modulates compressive stress from actomyosin; without keratin filaments, cells soften and morphology changes.[188] Intermediate filaments influence cell shape also due to their semi-flexibility; for example, inhibiting vimentin filaments in fibroblasts causes cells to change from an elongated mesenchymal shape to a rounded one.[187,188] In addition, actin and keratin filaments form distinct networks but interact, as disrupting actin filaments reorganizes the keratin network.[188] Therefore, future experiments should explore how interactions between different cytoskeletons and cell adhesion complexes regulate cell shapes during jamming–unjamming transitions.

2. Cell–cell interactions

Cell–cell interactions via adhesion complexes mechanically connect cells and regulate their shapes by modulating actomyosin tension.[189,190] For instance, adherens junctions transmit mechanical forces between cells, crucial for morphogenesis and tissue remodeling. As shown in Fig. 4(b), cadherins are the main adhesive structures in these junctions.[191] These transmembrane proteins mediate cell–cell adhesion through homophilic interactions, facilitating extracellular force transduction. Inside the cell, cadherins bind to β-catenin, which connects actin filaments to cadherins via α-catenin, enabling biochemical signaling and intracellular force transduction.[192] These interactions confer mechanical strength to adherens junctions and organize actin polymerization, bundling, myosin II recruitment, and branched actin network disassembly.[193–199] Disruption of the cadherin-actin linkage thus leads to the disorganization of adherens junctions and altered cell shapes.[200] Importantly, α-catenin is mechanosensitive; tensile stresses stretch it into an open conformation, promoting vinculin binding and activation, which drives further actin assembly at adherens junctions.[201–205] This response allows cells to adjust adhesion strength and remodel shapes. Finally, β-catenin can move to the nucleus in response to mechanical stimuli,[206,207] influencing gene expression important for epithelial-to-mesenchymal transition.[208–210] However, how these mechanisms are spatiotemporally regulated to control jamming and unjamming is still an open question.

In addition to adherens junctions, the desmosome-keratin filament complex is crucial for cell–cell adhesion, counteracting actomyosin contraction.[188] Weak interactions between desmosomes and keratin filaments can impair cell attachment.[188] Microtubules also impact adhesion by delivering adhesive molecules like cadherins and integrins to cell junctions.[181] Additionally, tricellular junctions, where three cells meet, regulate cell geometry.[211] Tricellulin, a key protein in these junctions, organizes actomyosin and controls its contractility,[211,212] influencing cell shape through junctional tension. Knockdown of tricellulin results in irregular cell shapes and disorganized actin fibers at tricellular contacts.[212]

Altogether, perturbing cell–cell interactions alters cell geometry by modifying cytoskeletal activities and junctional tension. These changes can affect target area, perimeter, and the energy barrier for cell movement, influencing cell jamming and unjamming. Future experiments should explore how junctional tension, adhesion strength, and cytoskeletal interactions regulate cell shapes and jamming–unjamming transitions.

IV. CONCLUSIONS

Tissue remodeling is driven by biologically determined changes in cell mechanical properties. The discovery of fluid–solid transitions, namely, cell jamming and unjamming, during tissue remodeling has enhanced our understanding of how subtle changes in cell connectivity, motility, and morphology influence tissue organization. By examining the cellular machinery and processes that coordinate force generation, transmission, and cell–cell interactions, we can begin to unravel the molecular events underlying the physical principles of the cell jamming phase diagram. However, understanding the interplay between these biophysical processes requires further investigation into how molecular mechanisms dictate jamming physics and how physical factors influence cellular behaviors.

Despite theoretical progress, validating cell jamming–unjamming theories in various biological systems requires comprehensive experimental data. Dissecting the mechanisms governing cell jamming and unjamming is hindered by technical challenges in monitoring tissue dynamics and the inherent complexity of biological systems. Future experiments using genetic and pharmacological techniques to specifically perturb cell connectivity, motility, and morphology promise to identify the underlying physical mechanisms and biological drivers controlling tissue remodeling through cell jamming and unjamming transitions.

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AUTHOR DECLARATIONS

Conflict of Interest

The authors have no conflicts to disclose.

Author Contributions

Zoe Latham: Conceptualization (equal); Investigation (equal); Project administration (equal); Resources (equal); Supervision (equal); Writing – original draft (equal); Writing – review & editing (equal). **Alexandra Bermudez:** Conceptualization (equal); Funding acquisition (equal); Investigation (equal); Project administration (equal); Resources (equal); Supervision (equal); Writing – original draft (equal); Writing – review & editing (equal). **Jimmy Hu:** Conceptualization (equal); Funding acquisition (equal); Investigation (equal); Project administration (equal); Resources (equal); Supervision (equal); Writing – original draft (equal); Writing – review & editing (equal). **Neil Lin:** Conceptualization (equal); Investigation (equal); Project administration (equal); Resources (equal); Supervision (equal); Writing – original draft (equal); Writing – review & editing (equal).

DATA AVAILABILITY

Data sharing is not applicable to this article as no new data were created or analyzed in this study.

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