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Perspective

Cell Junction Mechanics beyond the Bounds of Adhesion and Tension

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SUMMARY

Cell-cell junctions, in particular adherens junctions, are major determinants of tissue mechanics during morphogenesis and homeostasis. In attempts to link junctional mechanics to tissue mechanics, many have utilized explicitly or implicitly equilibrium approaches based on adhesion energy, surface energy, and contractility to determine the mechanical equilibrium at junctions. However, it is increasingly clear that they have significant limitations, such as that it remains challenging to link the dynamics of the molecular components to the resulting physical properties of the junction, to its remodeling ability, and to its adhesion strength. In this perspective, we discuss recent attempts to consider the aspect of energy dissipation at junctions to draw contact points with soft matter physics where energy loss plays a critical role in adhesion theories. We set the grounds for a theoretical framework of the junction mechanics that bridges the dynamics at the molecular scale to the mechanics at the tissue scale.

INTRODUCTION

Epithelial cells are linked together at their lateral surfaces by junctions that dynamically rearrange as cells move, divide, and change their relative positions during tissue morphogenesis in the embryo and during tissue renewal or tissue repair in the adult. While preserving the mechanical integrity of tissues, cell junctions have the unique ability to remodel. In contrast to this dynamic picture, the prevailing view of the mechanics of cell junctions is largely influenced from a perspective based on equilibrium of structures and shapes. It is associated with the notion that the contractile actomyosin networks generate tension that is resisted by adhesion bonds, such as E-cadherin at adherens junctions, that mediate the contact between cells (Figures 1A and 1B).

The idea that tension characterizes the mechanics of cell junctions is inherited from D'Arcy Thompson's vision of tissues as (active) foams in "On growth and form" (Thompson [1917] and for a critical discussion see Graner and Riveline [2017]). From the observation of cell contours in a variety of tissues, Thompson proposed that the dimension and angular orientation of cell junctions obey simple physical laws. By drawing an analogy between the organization of cells in tissues and the organization of bubbles in foams, he formulated that two physical parameters are required to predict the geometry of cell junctions in tissues: surface tension (for definition, see Box 1) and pressure. Surface tension reflects the tendency of materials to reduce their surface of contact: by definition, it is the mechanical energy required to extend the surface of contact by one unit area. By adopting a spherical shape, a soap bubble or a single cell minimizes its surface of contact with the medium. Two adhering cells exhibit lower surface tension at the intercellular surface than at the free surface contacting the medium. This is equivalent to the wetting (for definition, see Box 1) theories in soft matter (for definition, see Box 1). Separating two cells thus requires mechanical work: it is associated with an energy release. It involves changes in the structure of the cell surface and the underlying cortical actomyosin cytoskeleton.

The success of Thompson's approach resides in the generality of the concept of surface energy minimization to predict cell shapes in tissues provided that the system is close to mechanical equilibrium and specificities of cell surfaces compared with foams are taken into account. First, in foams, the surface tension is constant throughout the foam, as the interface is a two-dimensional continuous liquid film. In contrast, in a tissue, the surface material making the junctions between cells is bound to each cell and thus surface tension can be locally modulated. Second, because of the limited amount of surface material provided by the cell and elasticity of the cytoskeleton, deforming cell shape to change a contact has an additional (elastic) energy cost.

Models based on surface tension at cell-cell junctions have incorporated these two features, heterogeneous surface tension and deformation-dependent cell elasticity, to predict how cell-cell junctions are organized. It is, however, important to recognize that the surface tension is an effective parameter (see Box 1 for definition) that cannot be reduced to the total energy of the binders (e.g., E-cadherin) nor to the cortical tension (see Box 1 for definition; actomyosin contractility) (Farhadifar et al., 2007; Hilgenfeldt et al., 2008; Käfer et al., 2007; Lecuit and Lenne, 2007). According to this framework, cell contractility,

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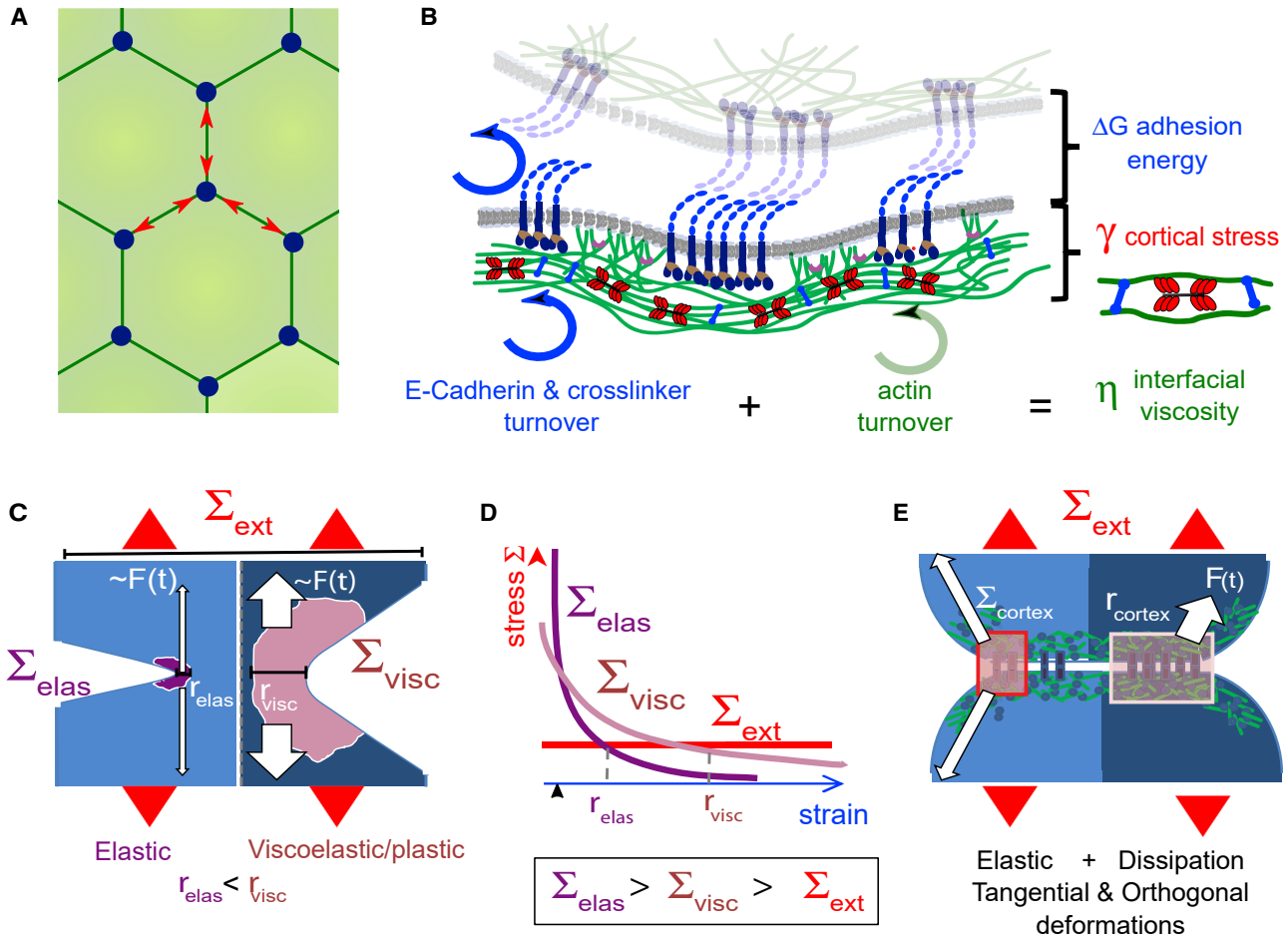

Figure 1. Elastic and Viscous Stresses, and Their Localization at Cell Junctions

(A) Sketch of an epithelial tissue with bicellular junctions (green lines) under tension (red arrows) and tricellular junctions (blue dots).

(B) Sketch of the molecular players at the adherens junction: the adhesion energy associated to E-cadherin (dark blue), cortical stresses generated by myosin II motors (red), and actin filaments (green) contribute to the junctional force balance. These elements are susceptible to turnover (circular arrows) that leads to a long-time scale viscosity denoted η.

(C) Schematic representation of the region of localization of mechanical stress in the vicinity of a kink for a material submitted to an external traction. The total force is conserved across the material but the mechanical stress (force per unit area) accumulates in a region close to the kink. The extent of the region largely depends on the viscoelastic properties of the material.

(D) Stress localization is very peaked in elastic material (right) and more diffuse in viscoplastic ones. $\Sigma_{elas} > \Sigma_{visc} > \Sigma_{ext}$ since $r^*_{elas} < r^*_{visc}$.

(E) The cytoskeleton rheological properties are hence predicted to modulate the region of the junction (red box) bearing the total mechanical force exerted at the junction. The local stress can vary in direction. It can originate for the cytoskeleton elastic deformation and viscous flow resulting from local strain. The binders at the junction bear dynamically the stress that is transmitted across the junction (normal component) and that can differ from the stress at the junction (tangential).

and thus cortical tension tend to reduce the length of cell junctions, while adhesion mediated by adhesive bonds tend to extend the length of the junctions. In other words, cortical tension contributes positively to the effective surface tension, while adhesion contributes negatively. However, the two systems supporting cortical tension and adhesion are connected at the molecular level and have a mutual influence on each other (Bazellières et al., 2015; Kannan and Tang, 2015; le Duc et al., 2010; Maître et al., 2012)

The prominent framework based on surface tension has been challenged during the past decades by the accumulation of observations, some of which were already pointed out by Thompson himself. Despite striking resemblance in many cases, cell-cell junctions have shapes and dynamic features that are much more diverse than the ones observed in foams.

Cells in tissues, like soap bubbles in foams, meet in two and in threes. From a molecular standpoint, tricellular junctions are specialized structures that are characterized by specific components, as evidenced by recent work in vertebrate and non-vertebrate epithelia (for recent reviews Higashi and Miller [2017] and Bosveld et al. [2018]). Cells also meet in fours or more (e.g., in the developing faceted eye of the *Drosophila*), configurations that are very unstable or not observed in foams. Despite its success, there are many crucial aspects of the mechanics of cell junctions that are not grasped by the concept of surface energy. Such conceptual approaches poorly describe the dynamics of junctional extension/retraction/separation, the role of dissipative stresses that arise during junction remodeling, the role of mechanical tension in organizing junctional molecules, and consequently the distribution of mechanical stress along the junction. These

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Box 1. Glossary

Active stress: mechanical stress generated by local chemical energy consumption (e.g., myosin II ATP-driven contraction).
Cortical tension: surface tension associated with actomyosin contraction.
Effective parameter: a phenomenological parameter used to analyze and interpret experimental data; it may be difficult to relate quantitatively to physical parameter(s) or biological component(s).
Friction: force that resists the relative displacement of two bodies in contact, e.g., the membrane to cortex attachment provides a frictional force that resists the cortex/membrane relative movement.
Mechanosensation: cellular biochemical response to mechanical stimuli.
Mechanical dissipation: result of an irreversible process that transforms some (mechanical) energy into heat transfer to the surrounding e.g., through friction.
Rheology: is a field of physics aiming at relating flows of matter and mechanical forces
Soft matter: any material that is easily deformed by thermal fluctuations and external forces, in contrast to hard matter, the macroscopic physical behavior is not directly related to elementary microscopic constituents.
Surface tension: a quantity that defines the elementary forces arising when the surface of a medium is increased by a unit area.
Tensile, compressive, and shear stresses: refer to the forces per unit area applied on a material body that lead to three types of deformation: extension, compression, and shear, respectively.
Viscoelasticity: property of materials that exhibit both viscous and elastic characteristics. It is a time-dependent property, e.g., a material can behave like an elastic solid or a viscous fluid depending on whether the mechanical stress is applied over a short or long period of time.
Viscoplasticity: property of materials that exhibit both viscous and plastic (undergoing permanent deformation in response to an applied force) characteristics.
Wetting: ability of a liquid to form a contact with a solid through intermolecular interactions. It is determined by the balance of between adhesive (liquid/solid) and cohesive (within liquid) forces.

aspects have long been envisaged but are only recently being scrutinized experimentally and theoretically alike. This perspective aims to provide an overview and a prospective vision about our understanding of cell mechanics beyond surface tension.

In this perspective, we present first important concepts of soft matter physics that address the adhesion of composite materials and help to critically discuss the notion of dissipation at junctions. We then emphasize key aspects of junctional mechanics that have started to attract attention: the importance of geometry, the time dependence of material properties, and feedback between adhesion and cytoskeletal mechanics. We illustrate these aspects from the molecular to the tissue scales. Finally, we attempt to link the molecular mechanisms first to changes in junction material properties and then to tissue mechanics, which remains a challenging task for both biology and physics.

DISSIPATION GOVERNS SOFT MATTER ADHESION

Despite centuries of investigation, adhesion in soft matter is still far from being fully understood due to the plethoric parameters that give the material its binding properties and the complex implication of geometrical factors in the problem that are determined by the spatial distribution of forces (and not only their amplitude) that the material undergoes. Extensive reviews (Creton and Ciccotti, 2016; Marshall et al., 2010; Packham, 2017) highlight the different theoretical and practical approaches describing adhesion in soft matter, from the molecular to the macroscopic perspective. Approaches inspired by wetting theories have largely influenced the biological perspectives that we described above (Brochard-Wyart and de Gennes, 2003; Smeets et al., 2019). Such approaches assume that the system can adhere or de-adhere in a quasi-static regime i.e., at equilibrium at all times. Except in very rare instances (e.g., liquid wetting in controlled atmosphere or elastic surface adhering by electrostatic bounds), adhesion and de-adhesion are hardly quasi-static. It results that practically the energy requested to bind or unbind soft material differs by orders of magnitudes from the values predicted by equilibrium studies (Brochard-Wyart and de Gennes, 2003). The excess energy is dissipated in the material. Considering that the total trans-binding energy of all cadherin ectodomains at the junction (comprised between 0.2 and 10 $\mu J/m^2$) is around 3 orders of magnitude smaller than the energy required to separate two cells (0.1–10 mJ/m^2) (Winklbauer, 2019), it is very likely that similar views apply to the active matter mechanics of tissues. Hence, adhesion strength, defined as the energy needed to break a junction, is not an intrinsic property of the material/cells but a quantity that depends on the rate of separation, the local viscoelastic properties (for definition, see Box 1) and geometrical constraints. As an illustration, cell separation in pipette assays (Figure 1E) shares a lot of resemblance with the initiation of cracks (Figures 1C and 1D). In an elastic material, geometrical constraints localize the tension stress in a small volume at the tip of the cracks (Figures 1C and 1D). The high local force efficiently propagates the cracks across the material. In a viscoplastic (for definition, see Box 1) material, the local stress is largely dissipated and hence diffusively localized in a larger area. The local force at the tip is minimized. Dissipation allows the material to sustain a larger external stress before failure. It results that the energy dissipated during the process depends not only on the local properties of the interface but on the viscoelastic properties of the medium that deforms under the mechanical stress.

The idea that cells could regulate their rheological properties (viscosity, elastic modulus) to optimize the stability of their junctions is an appealing perspective that starts to be uncovered both at the molecular and biophysical level.

MECHANOCHEMICAL COUPLING BETWEEN ADHESION AND ACTIN CYTOSKELETON REGULATES ADHESION STRENGTH

Regulation of Cytoskeleton Properties

As mentioned above, the energy gained by E-cadherin engagement is largely negligible compared with the cell surface tension or to the de-adhesion energy (Maître et al., 2012; Winklbauer, 2019, 2015). Instead, the level of actomyosin contractility measured by assessing actin cortical tension proves to be the dominant factor to predict adhesion strength or cell sorting (Chan et al., 2017; Maître et al., 2012). It results that the regulation of myosin activity at junctions (Myosin II in particular) and its cross-talk with E-cadherin binding has been largely scrutinized (Heuzé et al., 2019; Smutny et al., 2010). Our understanding of the molecular links between cadherin *trans* binding and actin cytoskeleton organization is lagging behind (Cavallaro and Dejana, 2011). Since the mechanics of adhesion depends on material viscoelasticity, it is important to relate the biophysical and dynamical properties of the junctions to the E-cadherin regulation of the actin cortex (Cavallaro and Dejana, 2011; Charras and Yap, 2018; Chugh and Paluch, 2018; Yap et al., 2018).

Epithelial adherens junctions are induced by cadherin *trans* binding (preceded in some cases by nectins; Rikitake et al., 2012) that results in antagonist action of CDC42 and Rac1 regulation of the actin meshwork (Adams et al., 1998). The junctional actin network along the lateral surface thins and preferentially reorganizes toward the apical pole (at the apical belt and at tricellular junctions) (Adams et al., 1998; Engl et al., 2014; Yamada and Nelson, 2007). The alteration of actin organization by junction protein knockdown has been detailed and standardized using an automated image analysis tool (Brezovjakova et al., 2019). This tool showed that the extent of the actin-rich region in the vicinity of the junction, and the spatial organization of the actin fibers are tightly regulated, thereby directly affecting the junction stability. In endothelial cells, platinum replicas were used to visualize the nanoscopic organization of bundled (Myosin II-rich) versus crosslinked actin (Arp2/3 and Formin) in linear, fingered, or interdigitated structured (Efimova and Svitkina, 2018; Li et al., 2020). Notably such organization advocates for a dual role of actin crosslinked meshwork pushing opposing membranes together (Caorsi et al., 2016; Efimova and Svitkina, 2018) (see Figures 1B and 2A) and contracting actin bundles, pulling on tricellular vertices and stabilizing the apical junction organization. Whereas most studies so far focused on the amount and nature of proteins recruited at junctions, fewer considered the changes in turnover rate or assembly/disassembly of actin. It is now increasingly postulated that the regulation of the actin structure at junctions equally/complementary contributes to propagating and sets the level of mechanical stress at junctions. The alteration of the rate of polymerization and crosslinking by formins, Arp2/3, WAVE, or coronin can modify the cortical tension of rounding cells during mitosis by modifying the cortical actin filament length (Cao et al., 2020; Chugh et al., 2017; Fritzsche et al., 2016; Kelkar et al., 2020). It was proposed that an optimal filament length maximizes tension transmission along the cortex (Chugh et al., 2017); more generally, such mechanism sheds light on the fact that cytoskeletal contractility is a function of both (1) the Myosin II activity and (2) the structural and dynamical properties of the actin cytoskeleton (Fritzsche et al., 2016). Though these properties have been studied in detail in reconstituted systems (Ennomani et al., 2016; Wollrab et al., 2018), how cells regulate the rheological properties of junctional and cortical actin structures remains to be explored (Brezovjakova et al., 2019). Answering such questions will likely pose technical challenges (Kashef and Franz, 2015; Mutlu et al., 2020; Ng et al., 2014), yet we think that deciphering the role of the structural and dynamic properties of the cytoskeleton to be of paramount importance for our understanding of the junctional dynamics.

Mechanosensation Adapts Actin Cortex Properties

Mechanosensation (for definition, see Box 1) at adherens junctions is another aspect of cadherin mediated signaling. The most documented mechanism implies the force mediated deformation of α-catenin (Ishiyama et al., 2018; Seddiki et al., 2018; Yao et al., 2014) that triggers the recruitment of vinculin and actin at the junction (Sarpal et al., 2019; Seddiki et al., 2018; Yonemura et al., 2010). Actin recruitment was found to lead to a significant increase of E-cadherin density (typically between 150% to 200%; Engl et al., 2014; Gao et al. 2018; Yonemura et al., 2010). Catenin clustering together with intracellular tension orchestrate a fluid-to-solid phase transition at the membrane-cytoskeleton interface (Arbore et al., 2020) demonstrating the ability of cells to regulate the rheological properties of their junctional cytoskeleton, independently of myosin activity.

While the recruitment of cadherin and actin is usually coined as "reinforcement," we are not aware of any direct measurement relating such recruitment to an increased junctional adhesion strength. Mechanotransduction was mainly shown to regulate transcriptional programs. Both WNT/β-catenin (Valenta et al., 2012) and YAP/TAZ (Totaro et al., 2018) are well-documented pathways that are activated by junctional and basal mechanosensation. However, these pathways are not reported to directly regulate junction properties. By contrast, a force-dependent activation of EFGR was recently found to activate vinculin recruitment by cadherin (Sehgal et al., 2018), which was also shown to alter junctional contractility. Using E-cadherin coated substrates, a ligand independent activation of EGFR by E-cadherin ectodomains has also been putatively involved in pulsatile contractile units, resembling those existing at focal adhesion (Yang et al., 2018), that could be involved in measuring substrate rigidity (Lohner et al., 2019). Other mechanisms involving CDC42 or Rac1 have also been reported (Collins et al., 2017). These processes could allow cells to measure (and potentially regulate) the mechanical tension and viscoelasticity at junctions (Tsai et al., 2020).

Junctional Response Differs for Tensional, Shear, or Compressive Stresses

The mechanosensitive response of junctions depends not only on the intensity of the applied forces but also on their direction. Cells can distinguish between tensile, compressive, or shear stress (for definition, see Box 1). Considering only the average active tension parallel to the junctions neglects the effect of junctional fluctuations mediated by pulsatile flow of apical contractility (Martin et al., 2009; Rauzi et al., 2010). It usually ignores the fact that the mechanical stress at junctions has components in all directions that can contribute differently to protein

recruitment. E-cadherin localization at membranes proved to be enhanced by tensile stress but reduced by shear stress (Kale et al., 2018) (along the direction of the junction) or compressive stress (pushing the junction together) (Gao et al., 2018). Similar results have also been reported for desmosomes (Price et al., 2018). Apico-basal gradients of cortical tension are sufficient to create cytoskeleton flows advecting E-cadherin to the apical pole (Wu et al., 2014). Such mechanisms suggest that the recruitment of E-cadherin and actin cytoskeleton within the apical belt or tricellular junctions could result from the localization of mechanical stresses at the apical edges of the lateral surface. Reshaping the junction organization could, in turn, either amplify or reduce the spatial localization of stress.

Although we focused here on adherens junction, tight junctions assembly are also increasingly described as mechanosensitive and dependent on the level of local mechanical stress and cortical flows (Beutel et al., 2019; Citi, 2019; Schwayer et al., 2019; Vasileva et al., 2020).

The Spatial and Mechanical Heterogeneities of Junctions

The edges of lateral surfaces (apical belt, tricellular junction) are peculiar loci both from the standpoint of mechanics and of biology. De-adhesion or fracture theories certainly predict that elastic material tends to localize mechanical stress in a restricted region along the edge of the contact surface (Creton and Ciccotti, 2016) (Figures 1C and 1D). It results that the total force born by the system tends to concentrate on a narrow region surrounding the lateral contact region (Gao et al., 2018; Kaurin and Arroyo, 2019; Yang and Jiang, 2018). Increasing the viscosity of the cortex is predicted to redistribute the stress on a larger area, hence, stabilizing the junction (Gao et al., 2018). The stress is then born by more transmembrane proteins and dissipates along the junction (Sackmann and Smith, 2014; Sengupta and Smith, 2018). In soft matter theory, this effect explains how compliant dissipative material can sustain higher stress before fracture than brittle elastic material. This effect has been envisaged long ago in the context of de-adhesion as a dominant source of junction of stability; however, experimental proof remains to be fully developed. In this context, the formation of intercellular lumens such as bile canaliculi is an interesting example. These small lumens form between two hepatocytes and anastomose into tubes or multicellular lumens (Fu et al., 2010). Disruption of the junction and separation of membranes is required and is largely mediated by the isotropic osmotic pressure (10–100 Pa) generated by the balance between ion intake by active pumps and leak through channels and paracellular cleft (Gissen and Arias, 2015). In hepatocytes, the initiation of the apical lumen is directed by the cross-signaling between both the extracellular matrix and cadherin adhesion (Zhang et al., 2020). The ability of cadherin to trigger the initiation of an apical actin network proves dependent on the pre-existing distribution of the cadherin on the lateral pole of the junctions. During lumen formation the membranes separate preferentially in the direction of the lower tensional stress existing along the cell junctions (Li et al., 2016).The mechanics of fluid exchange between the lumens and the paracellular cleft are important in the membrane separation between mature hepatocytes (Zhang et al., 2020) or mouse blastocysts (Dumortier et al., 2019). These examples constitute systems with theoretically workable geometries (Dasgupta et al., 2018; Dumortier et al., 2019; Kaurin and Arroyo, 2019) and amenable to quantitative measurements of cytoskeletal rheology (for definition, see Box 1).

Tricellular junctions are also remarkable locations of epithelia. Besides the well-established tight junction protein found at the tricellular points (Tricellulin and angulin), specific adherens junction organization has been uncovered (Higashi and Chiba, 2020; Higashi and Miller, 2017). In the *Drosophila*, the immunoglobulin family member Sidekick localizes at tricellular junctions to mediate homophilic adhesion by a mechanism that is influenced by mechanical tension (Finegan et al., 2019; Letizia et al., 2019; Uechi and Kuranaga, 2019). Via its interaction with Canoe and *Drosophila* ZO-1 Polychaetoid, Sidekick connects the actin cortices of two neighboring cells, which in turn might promote stability of both tricellular and bicellular junctions. In vertebrates, tricellulin that specifically localizes at tricellular junctions and regulates actin polymerization through Cdc42 and thereby tensile properties of junctions (Oda et al., 2014). As discussed in (Higashi and Miller, 2017), tricellular junctions can be seen as hot spots of tension (tensional vertices) (Ebrahim et al., 2013), whereas opposing models propose an actin organization lead to a purse-string stabilizing the tricellular area (Choi et al., 2016; Yonemura, 2011). Hence geometry but also spatial distribution of the cytoskeleton and how it is linked to the membranes are likely to be important factors impinging on their stability/lability.

Mesoscopic Manifestation of Dissipation at Junctions in Tissues

At the tissue scale, junction remodeling, including junction shrinkage and extension, is affected by the dynamical properties of the cytoskeleton integrated over the time scale of junction remodeling. This process does not appear as a smooth monotonous process but is often characterized by jiggling of tricellular junctions and pulsatile contraction/expansion (Martin et al., 2009; Rauzi et al., 2010). Such fluctuations are active and mainly generated by the contractile actomyosin network that pulls or pushes on adhesions, thereby deforming junctions and moving tricellular junctions. The role of fluctuations in junction remodeling and cell rearrangements has been recently addressed from both theoretical and experimental perspectives (Curran et al., 2017).

The observation that contraction of junctions is often stepwise and partially reversible was found to be a signature of their viscoelastic nature (Clément et al., 2017). To assess this point, pull-release experiments were performed on cell junctions of the early *Drosophila* epithelium over different periods of time using optical tweezers. The longer the force is applied, the more irreversible the deformation, which is a signature of viscoelastic dissipation (Figures 2D and 2F). These experiments give access to the characteristic time of energy dissipation at junctions, which was found to be on the order of 1 min in the *Drosophila* germband (Clément et al., 2017). Note that this is an effective timescale, as the system is likely to dissipate energy on a distribution of timescales. In an attempt to identify the molecular origin of this dissipation, the authors found that reducing the turnover of actin increases the characteristic dissipation time, thereby increasing the reversibility of deformations.

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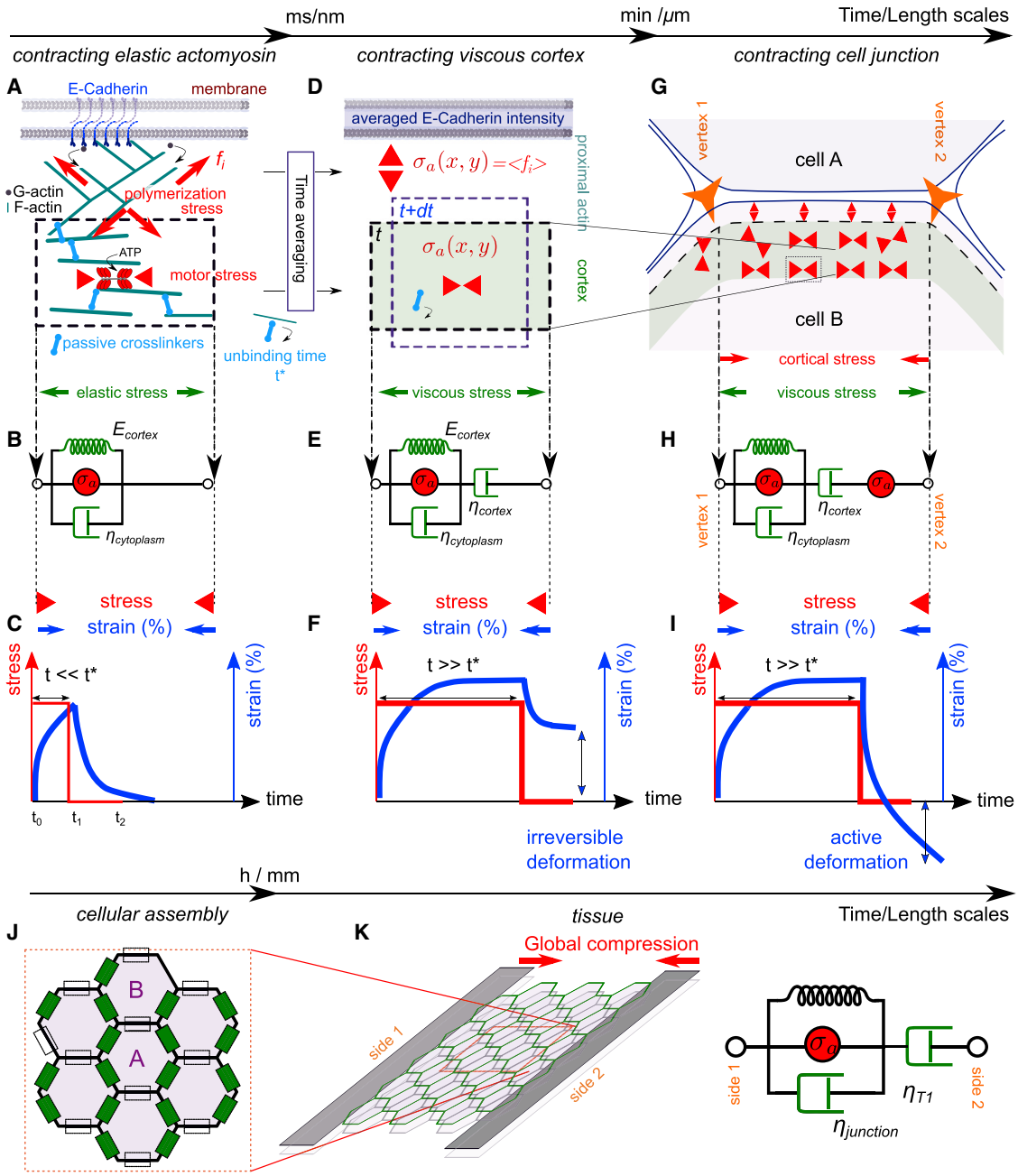

Figure 2. Mechanical Properties of Junctions: A Multiscale Perspective

(A) Molecular players at the adherens junction (see also Figure 1B). Actin polymerization and motor contraction put the crosslinked actin cytoskeleton under an active (i.e., ATP-consuming) tension. Passive crosslinkers unbind after a characteristic time denoted t*. At short time scale compared with t*, the motor-driven tension is mechanically balanced by strain-induced elastic forces in the actin network.

(B) At short time t << t*, an elementary portion of the junction can be represented through a dashpot in parallel to an elastic spring (Kelvin-Voigt under active tension).

(C) Within the rheological model of (B), the junction experiences a fast evolution under stress, followed by a reversible deformation in the actin network.

(D) Representation of the cell junction through time averaging over a timescale significantly larger than the typical crosslinker time t*; unbinding events allow a mechanically isolated portion of the cortical layer to undergo viscous flows while sustaining an active tension (red arrow) generated through active polymerization/depolymerization events or motor contractions.

(E) The junction can be modeled as an elastic in series with a dashpot that recapitulates long-time scale junctional flows.

(F) Within the rheological model of (E), a long-time t >> t* imposed stress leads to an irreversible deformation in the cell cortex network.

(G) The cell junction is a composite material composed of mechanically connected cortical elements (b, black box) under active tension (red arrows). Over the long timescale defined in (B), the overall cortical stresses (red) can initiate viscous flows within the cortical layers, resulting in motion of the tricellular vertices (orange).

(H) Proposed overall rheological diagram for the cell junction that includes a long-time active contractility emerging from the geometrical interplay between the local active elements.

(I) Such long-time active contractility could result in a modified long-time active contraction of the cell junction.

(legend continued on next page)

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Other reports additionally suggest that the viscoelastic response of junctions is active: upon strain, junctions would adapt their contractile tension (Staddon et al., 2019). According to the active tension model (Noll et al., 2017) a mechanical feedback would ensure that elongated junctions increase the Myosin II recruitment, while contracted junctions decrease Myosin II levels. Perturbative experiments in contracting junctions during dorsal closure of *Drosophila* showed that active mechanisms maintain the straightness of junctions (Sumi et al., 2018). Such mechanisms are dependent on the actomyosin cytoskeleton but also on the endocytosis machinery. Interestingly, local increase of E-cadherin density due to junction contraction is able to trigger endocytosis (Sumi et al., 2018).

Examining endogenous tissue stress during the pupal morphogenesis of the *Drosophila* wing epithelium, Iyer et al. found that release of p120-catenin from adherens junctions under mechanical stress promotes turnover of E-cadherin complexes (Iyer et al., 2019). At the tissue level, this process decreases the viscosity associated with cell rearrangements. Feedback thus exists between generated stresses and mechanical dissipation (see Box 1 for definition) at junctions.

While *in vivo* studies revealed the dissipative nature of junctional mechanics in developing tissues, controlled *in vitro* experiments have brought insight into possible regulation mechanisms of their rheology (Khalilgharibi et al., 2019). By imposing stepwise stress to a suspended epithelial monolayer, the authors showed that the tissue changes its resting length over minute time scales. Relaxation toward a new length was found to be an active mechanism that depends on actomyosin turnover at junctions. Altogether these studies exemplify the connection between the local mechanics at junctions and the tissue-scale rheology (Figures 2H–2J).

Emerging Theoretical Models and Physical Descriptions

Bridging molecular insights to an important mechanical property of the junction that affect tissue organization requires modeling at different timescales. Concepts drawn from equilibrium physics, such as pressure forces and surface tension, have profoundly influenced the theoretical framing of tissue mechanics, inspiring notably the numerical schemes called vertex models. In such schemes, whereby vertices representing tricellular junctions move as the result of a balance of pressure and tensions at cell junctions (Nagai and Honda, 2001), a seemingly paradoxical observation emerged: modeled as a decrease of junctional tension, a cell-cell adhesion energy increase fluidifies tissues, which then appear softer on a long timescale (Maruthamuthu et al., 2011; Sussman et al., 2018). In this model, the tension along the cell junction can be recast into the form:

$$\Sigma = E(L - L_0) + \gamma_a \qquad \text{(Equation 1)}$$

where γ_a is a junctional contractile stress (modulated by E-cadherin adhesion); E is an elastic constant, with L the junction length and L_0 a reference length that can either (1) be related to the elastic cortical response to strain (Figure 2A) or (2) to a conservation of a total cell membrane area (Maruthamuthu et al., 2011; Sussman et al., 2018). In such elastic representation, a transient increase in the local stress leads to a reversible strain in the junction (see Figure 2B scheme and corresponding evolution 2C).

However, over a few minute timescale, most crosslinkers in the junctional cortex can rearrange, potentially allowing for sustained cortical flows under applied mechanical stresses (see Figures 2D–2F), yet at the expense of viscous stresses. In most vertex models, the contribution of viscous stresses to the junctional tension is not included, as these rather assume that what dominates dissipation is an external friction (see Box 1 for definition) against a static mechanical support, e.g., extracellular matrix (Alt et al., 2017). In embryos such as the *Drosophila* embryo, however, such specific external friction often appears negligible compared with internal viscous forces over the cellular scale (D'Angelo et al., 2019; Doubrovinski et al., 2017). In a series of pioneering papers (Brodland et al., 2009; Yang and Brodland, 2009), the cell is assumed to be viscous in its bulk and under fixed junctional tension. However, in cells, the cortex is significantly more viscous than the cytoplasm. While the cortical layer is thinner (typically $L_{cortex} = 0.2\ \mu m$) than the cell cytoplasm (typically $L_{cyto} = 5\ \mu m$) but is expected to dissipate $L_{cortex}\eta_{cortex}/L_{cyto}\eta_{cyto} = 10^4$ more than the cytoplasm (Turlier et al., 2014). Recent vertex models incorporated such junctional viscosity, with application to the modeling of cell division and apoptosis within suspended monolayers (Okuda et al., 2016). Importantly, with such rheology, a transient increase in the local stress leads to an irreversible deformation of the junction (see Figure 2F).

An additional modeling challenge is that cells can dynamically adjust their level of interfacial contractile stress γ_a in order for junctions to contract e.g., during cell division (Turlier et al., 2014). How to incorporate cortical viscosity and local active stress (see Box 1 for definition) into realistic and predictive models of cellular dynamics remains an open question. Here, we sketch a theoretical framework whereby we describe the evolution of cell junctions based on active gel theory, which predicts the relation between spontaneous cortical viscous flows and self-generated contractile active stresses. When estimated over a sufficiently large spatial and timescales, quantities such as the local stress, velocity, or local orientation order (e.g., of actin filaments) can efficiently be described and modeled in terms of continuous fields within the junction cortical layers (see Figure 2D). The stress within a portion of the cortex is then typically modeled as (Prost et al., 2015)

$$(1 + t^*\partial_t)\sigma = \eta_{cortex}\nabla_u + \sigma_\alpha \qquad \text{(Equation 2)}$$

where t* is defined as local cortical viscoelastic time; η_{cortex} is the cortex viscosity and σ_a is a cortical pre-stress related to the orientation of actin filaments (see Figures 2A and 2C). Equation 2 illustrates how viscous forces can affect the local tension within the junction; it also illustrates how spatial patterns of active stress can be balanced by viscous stresses associated to spontaneous cortical flows. Bypassing the need of the precise description of

(J) Realistic cell junction rheologies could be incorporated as building blocks for computational models, with the objective to understand the relation between molecular junction perturbation (potentially affecting cell junction rheologies) and global tissue-scale properties.
(K) A challenging question in the field is the following: can global tissue deformation under stress be accurately described through simple rheological diagrams, and if so, can we infer the values of the rheological elements in terms of more microscopic components?

the interactions between individual microscopic elements (i.e., individual actin filaments or cells), active gel theories are generic: successful predictions of spontaneous flows at the micron-scale tissue level (confined fibroblasts in channels; Duclos et al., 2018) or at the millimeter-scale whole *Drosophila* embryo (Streichan et al., 2018) may also hold at the submicron-scale level a cortical layer within a cell junction. Hydrodynamic instabilities along cell junctions could contribute to a reorganization of active cytoskeletal elements (red arrows in Figure 2D), either further amplifying junctional shrinkage or generating negative strains whenever the external stress is removed (see Figures 2G–2I). Based on previous tissue-scale models, we propose an overall relation between the rate of junction elongation and the junction tension Σ to be of the form:

$$\Sigma = \eta_{\text{cortex}}\dot{L}/L + \gamma_{\alpha}(\dot{L}) \text{ and } \eta_{\text{junc}} = d\Sigma/d\dot{L}, \qquad \text{(Equation 3)}$$

where γ_a is to be interpreted as a junctional contractile stress, now modeled as strain-rate dependent to account for the expected geometrical reorganization of cytoskeletal element. Sketching such models, we aim at illustrating the challenges in distinguishing the role of the passive cortical viscosity from the active strain-rate dependent forces; indeed, both may affect the value of the apparent junctional viscosity η_{junc} (definition in Equation 3) that may become negative, in which case junctions are not stable and constantly extend or shrink (Giomi et al., 2010).

Deriving rheological models such as Equation 3 from experimentally driven elementary principles and relating the physical parameters to molecular pathways is challenging. Simplified rheological frameworks promise to connect the global tissue rheology to interfacial mechanical properties (Figures 2J and 2K; Tlili et al., 2015), and from there, to gain understanding on the specific role of molecular players at cell junctions by accurately predicting the effect of specific drug perturbations (e.g., EGFR inhibition or cadherin disruption).

CONCLUDING REMARKS

In this perspective, we have reviewed studies that emphasize the dissipative nature of junctions. Such a mechanical feature, which mainly results from the dynamics of cytoskeletal components and their distribution and orientation at cell junctions, affects the way tissues deform. Dissecting the dynamics of actin, its active and passive crosslinkers and adhesive structures alongside mechanical measurements will be key to understanding how dissipation is regulated at junctions. Mechanical models should provide an essential link between the cellular and tissue scales. Alteration (inhibition, knockout, etc.) of the molecular pathways are often characterized by the changes in the collective or phenotypic behavior of tissues. To build a clear understanding of junction and tissue mechanics, we need to systematically correlate the changes induced by such alterations with measurements of the biophysical properties. Although challenging, an increasing number of experimental techniques are now available and could be widely used (Roca-Cusachs et al., 2017; Sugimura et al., 2016; Ungai-Salánki et al., 2019).

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DECLARATION OF INTERESTS

The authors declare no competing interests.

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