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Adhesion regulation and the control of cellular rearrangements: From emulsions to developing tissues

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Cell rearrangements are critical for tissue remodeling during diverse biological processes, such as morphogenesis or cancer progression. They control tissue fluidity and can lead to irreversible shape changes in cohesive tissues. However, the completion of such rearrangements is strongly conditioned by intercellular adhesion, that can prevent their completion or conversely promote them along a given pattern. In this review we explore how intercellular adhesion impacts cell rearrangements at the local scale and how it translates into macroscopic mechanical properties in biological tissues. We first describe general principles obtained from the study of dispersed materials, such as emulsions, in which the mechanical properties and interaction potential between individual particles can be described in a quantitative manner. We then review the effect of varying cell-cell adhesion on rearrangements *in vitro* model tissues, from cell aggregates to 2D epithelial-like cellular layers. We finally consider developing tissues in which adhesion between the cells is strongly tuned and localized in order to allow for function and shape emergence in the embryo.

KEYWORDS

adhesion, biological tissues, deformation, rearrangements, plasticity, intercellular adhesion, biomimetic tissues, emulsions

1 Introduction

Intercellular adhesion in biological tissues ensures tissue cohesion and controls their mechanical behavior. It is thus central in the regulation of many biological processes such as morphogenesis or cancer progression (see [1–3] for reviews). In particular, epithelial cells adhere together through Adherens Junctions (AJs) that play a central role in tissue morphogenesis (Figure 1A). Indeed, due to their dynamic regulation, they tackle both the role of maintaining tissue architecture and the task of promoting cellular movements during tissue remodelling (see [4, 5] for reviews). In this review we specifically address the impact of adhesion regulation on the mechanics of tissues, with a strong focus on rearrangements at the cellular level. More particularly, we draw analogies with soft matter concepts and report on the role of adhesion in diverse systems, from inert materials to developing tissues.

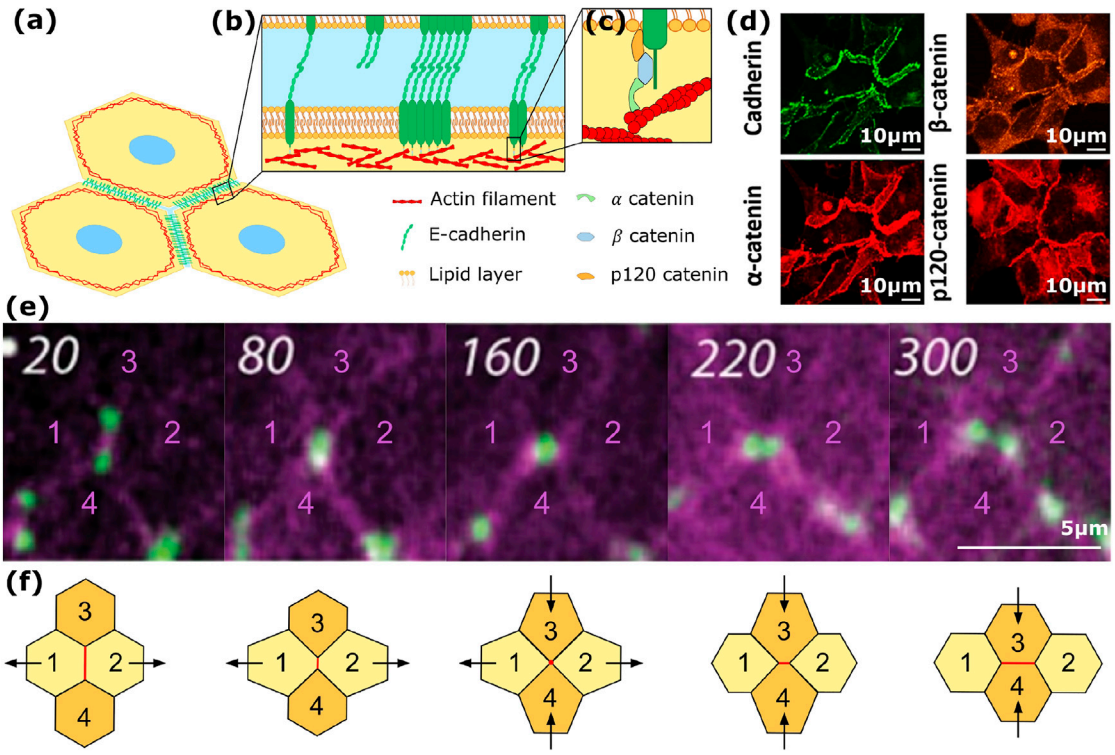

FIGURE 1
Cell-cell adhesion and rearrangements in tissues **(A)** Schematic representation of cell-cell adhesion in epithelial tissues mediated at adherens junctions by cadherin (green) and actin (red) co-action. **(B)** Zoom on the cadherin homophilic interactions in the extracellular vicinity of contacting cells: the cadherins interact both through trans adhesions between cadherins of opposing surfaces, and through cis interactions leading to lateral clustering on the cell surface. **(C)** Schematic representation of the anchorage of the intracellular domains of cadherins to the actin cytoskeleton through β-catenin, α-catenin and p120-catenin. **(D)** Immunofluorescence microscopy images of α-catenin, β-catenin and p120-catenin in S180 cells expressing GFP-tagged E-cadherin (green). Cadherin and catenin linker proteins appear co-localized at cellular junctions [20]. **(E)** T1 event observed in a live embryo in which the vertex specific protein sidekick (green) and the DE-cadherin (purple) are labelled. This labelling allows to track the shrinking edge as the vertices come closer, down to the formation 4-way vertex. Eventually a new contact is grown and the new vertices progressively grow apart until the junction is matured [21]. **(F)** Schematic representation of a rearrangement in the form of a T1 event. First, the adhesive junction between cells 1 and 2 shrinks, all the ways down to a point contact between the 4 cells. Then, cells 1 and 2 finish moving apart and are no longer neighbors, while an adhesive contact between newly neighboring cells 3 and 4 grows.

Transmembrane proteins of the cadherin superfamily are key players of these AJs, ensuring not only cell-cell adhesion but also the mechanical coupling of intracellular structures such as the actin cortex [6] (see Figure 1B): the extracellular domains of cadherins displayed on the surface of contacting cells interact to form cell-cell adhesions through *trans* interactions [7–9]. These cadherins can also diffuse laterally on the plasma membrane and interact with each other to form 2-dimensional ordered clusters through *cis* interactions [9, 10]. Cluster formation through such *cis* interactions is essential to ensure a robust link between the cell-cell junction and the cytoskeleton [11, 12]. Inside the cells, the cadherin intracellular domain interacts with the actin cytoskeleton through linker proteins such as β-catenin, α-catenin and p120-catenin [1, 13–16] (see Figures 1C,D). Moreover, the α-catenins can unfold under mechanical load to interact with vinculin, which results in actin recruitment and provides mechanosensitivity to the AJs [17–19].

This feedback loop between the mechanical constraint applied to a junction and its remodeling make it a very complex structure whose strength cannot be predicted in a straight forward manner. *In vitro* measurements have therefore been developed to quantify the strength of intercellular interactions and attempt at disentangling the role of all players in these junctions. In particular, pipette assays or microfluidics were used to quantify the separation force between cells that are put in contact together under controlled conditions [12, 20, 22–25]. The separation force between adhering cells was shown to depend on the cadherin concentration on the surface [22, 26], but also on their anchorage to the underlying actin cytoskeleton [24].

However, tissues have to be studied beyond such single cell-cell contacts. Indeed, biological tissues are remodelled at the multicellular scale, for instance when they have to respond to an applied stress, or to drive the emergence of shape and function

during development. During these processes, cells undergo shape changes and positional rearrangements to accommodate such tissue remodelling, which are the focus of this review. Different types of cellular rearrangements can take place in tissues. For instance, cell extrusion inherently creates a new neighborhood by accommodating the presence of a new cell in a packing. Likewise, cell division modifies locally the number of cells and hence creates new contacts while deleting others. Finally, rearrangements can occur at a fixed number of cells in the form of coordinated neighbor exchange. A typical rearrangement of this type involves the coordination of 4 cells and is called a T1 event (illustrated in Figures 1E,F). A chain of events needs to occur in order to complete a T1 event: first the existing junction needs to shrink, thus reducing the adhesion area between the cells, then a 4-way junction is transiently formed, and finally a new cell-cell junction has to be formed *de novo* and grown to its equilibrium size. In this context, vertex-specific proteins, such as sidekick in *Drosophila*, have been shown to facilitate the completion of T1 events [21]. At the tricellular junctions, sidekick contributes to the anchorage of myosins that in turn transmit the forces necessary to shrink [27] and extend [28] cell-cell junctions during a T1 event. Because adhesions are both ruptured and created in a T1 event, its energetic landscape strongly depends on the adhesion levels between all involved cells. In this review we focus on rearrangements taking place in the form of T1 events and on their dependence on intercellular adhesion.

In order to unravel the processes associated to rearrangements and adhesion regulation in tissues, biomimetic approaches and analogies with elasto-plasticity in soft matter systems are very useful tools. In this article, we therefore review the effects of adhesion on rearrangements with a strong focus on approaches borrowed from materials and soft matter science. In an effort to highlight the link between soft matter and biology we start with the most simple systems, typically inert materials, and progress towards *in vivo* observations through increasing levels of complexity.

Therefore, we start by considering the structural and mechanical properties of dispersed systems, with a focus on emulsions that are the closest to biological tissues conceptually. We describe the effect of non-specific interparticle interactions on these properties at the microscopic level, i.e. at the scale of individual rearrangements. We then present biomimetic systems (droplets or vesicles) that were developed to tackle the role of specific adhesion between particles. These reductionist approaches allow to uncover precisely the impact of adhesion on the dynamics and topology of rearrangements. Moving into biological systems, we next review *in vitro* cellular systems in which adhesion can be controlled, leading for instance to cellular sorting in cellular aggregates. These problems have also been studied extensively *in silico* and theoretical descriptions such as the vertex model implicitly take into account intercellular adhesion and can in turn predict tissue fluidity. Finally, we review some morphogenetic processes in which adhesion modulation directly tunes the rate and location of rearrangements, which in turn controls the emergence of shape and order in the tissue.

2 Interparticle interactions in soft matter systems: From emulsions to foam

2.1 Static structure of adhesive packings

In the absence of attraction or friction between particles, their packing structure under gravity is determined in the framework of the random close packing limit, which corresponds to the jamming point [29]. The Maxwell criterion for mechanical stability determines average properties in these packings such as the coordination number of the particles or their number of neighbors [30]. Emulsions in particular are a great tool to study these properties experimentally as they can be made transparent, which allows to image and quantify their microstructure through confocal microscopy [31]. Interparticle interactions are expected to modify the structural properties of such packings. For instance, attraction between emulsion droplets can be introduced easily through depletion forces. Such interactions have been shown to tune the local and global properties of 3D packings of frictionless droplets: akin to friction in granular systems, attraction stabilizes arches or voids in 3D packings, leading to lower packing fractions [32, 33]. Accordingly, the average number of neighbors and contacts per particle can also be lowered below isostaticity for the highest attraction forces.

2.2 Elastoplasticity of attractive emulsions

The mechanical properties of the above-mentioned packings depend on their local structure and can be understood as a function of their distance to the random close packing limit. Indeed, in the absence of attraction, emulsions under the random close packing fraction (Φ_{RCP}) exhibit a fluid-like behaviour, while they exhibit a solid-like behavior above Φ_{RCP}, i.e., above jamming [34]. However, when attractive interactions are introduced between the particles, these systems can exhibit solid-like properties below Φ_{RCP} [35–37]. Attractive emulsions have also been studied through rheology above Φ_{RCP}, which may be more similar to biological tissues that usually display high packing fractions. These experiments revealed that an additional relaxation process was taking place under shear in the presence of attraction [36]. This suggests that the system undergoes a succession of microscopic events linked to stress release before flowing, but the precise nature of these processes cannot be resolved through bulk rheology approaches.

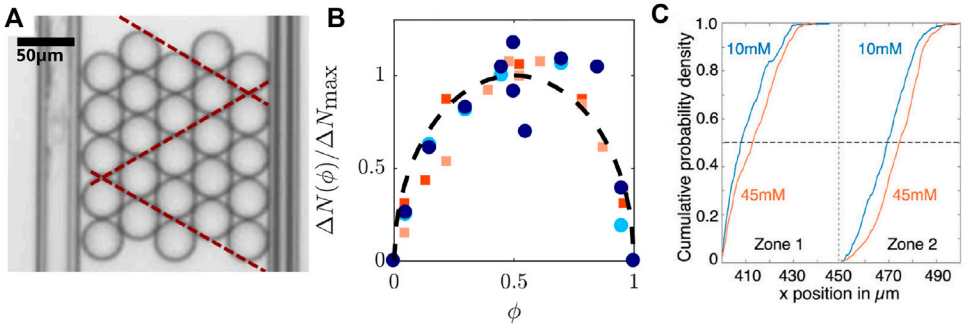

FIGURE 2
Plasticity in attractive emulsions **(A)** Transmission microscopy image of an oil-in-water emulsion under compression between a force sensor and a pushing plate. Dislocation arrays in the monodisperse emulsions are indicated with the dashed red lines. **(B)** The forces measured under compression display peaks corresponding to fracture events in monodisperse emulsions or more isolated rearrangements in polydisperse emulsions. The graph in **(B)** displays the normalized excess number of force peaks during compression with respect to those observed in a monodisperse emulsion, as a function of the fraction of defects Φ introduced through bidispersity, for emulsions with 3 (squares) or 4 (circles) rows in the initial packing. High monodispersity (Φ = 0 or 1) leads to the smallest number of force peaks corresponding to large fracture events. At the highest number of defects, the emulsion is disordered, leading to a higher number of peaks of smaller forces. **(A,B)** were adapted with permission from [38]. **(C)** Cumulative distributions of the minimum velocity locations of droplets flowed in a 2D convergent channel with low (10 mM SDS) or high (45 mM SDS) depletion attraction. The velocity minimum is a reporter for the location of rearrangements, before which the droplets stall. This indicated that the rearrangements are impaired by higher attraction forces and appear further down in the constriction. Adapted with permission from [39].

In order to link bulk properties to microscopic mechanisms, the elastoplastic behavior of emulsions has been widely studied in microfluidic setups that allow to visualize droplet rearrangements and deformations under flow. For instance, using bidisperse compressed emulsions in 2D constrictions revealed a correlation between stress release and T1 events [40]. Introducing attractive interactions between the droplets in such systems is therefore a straight-forward way to understand the microscopic mechanisms, such as T1 events, underlying the effect of attraction on bulk rheological properties of emulsions. In order to impose a large number of tractable rearrangements in these systems, they can be flowed inside constrictions [41, 42] or compressed between parallel plates [38]. These approaches revealed that rearrangements are strongly coordinated in monodisperse emulsions under compression and lead to large predictable fracture events within their crystalline structure [38, 41, 43] (see Figure 2A). This geometric order vanishes as soon as defaults are introduced in the packing structure (by introducing poly- or bidispersity for instance) (Figure 2B), making it deviate from a crystal to a glassy topology. This transition to a glassy system leads to a spread in the occurrence of T1 events, indicating that the energy landscape associated with the compression of attractive emulsions is strongly dependant on the size distribution of the droplets [38]. Similarly, it was shown that depletion attraction could also disturb the positional order of the rearrangements that is normally imposed by geometry [42]. In a microfluidic constriction, attractive forces impair rearrangements and displace them downstream in the constriction (Figure 2C). In turn, these delayed rearrangements induce more deformation of the droplets, i.e., a more elastic response of the emulsion.

2.3 The case of foams

In foams, the particles at play are air bubbles separated by a liquid film. Their stability and inter-bubble interactions are therefore strongly determined by the nature and amount of surface active molecules introduced in the liquid phase. When foams are subjected to an imposed flow, their bubbles undergo T1 events similarly to emulsions [44, 45]. While the statistics of T1 events was shown to be independent of the aqueous phase viscosity, the choice of the surfactant clearly affects the dynamics of the rearrangements. For instance, the use of proteins or charged surfactants mixed with polymers, instead of pure surfactant, was shown to rigidify the air-water interfaces [44, 46], which subsequently impairs the dynamics of neighbor exchange. However, the direct dependence between the attraction potential between air bubbles and the rearrangements is more elusive. For this reason we do not focus on foams here. Further experimental studies of foam mechanics can be found in previous reviews [47, 48].

3 Biomimetic systems of adhesive tissues

Mimicking cells *in vitro* through bottom up approaches allows to study specific cellular processes, such as cell-cell adhesion, in a simplified framework. A popular way to reproduce cellular functions artificially relies on the use of model membranes [49]. In particular, giant unilamellar vesicles (or GUVs) share the same size and topology as cells and can be combined with

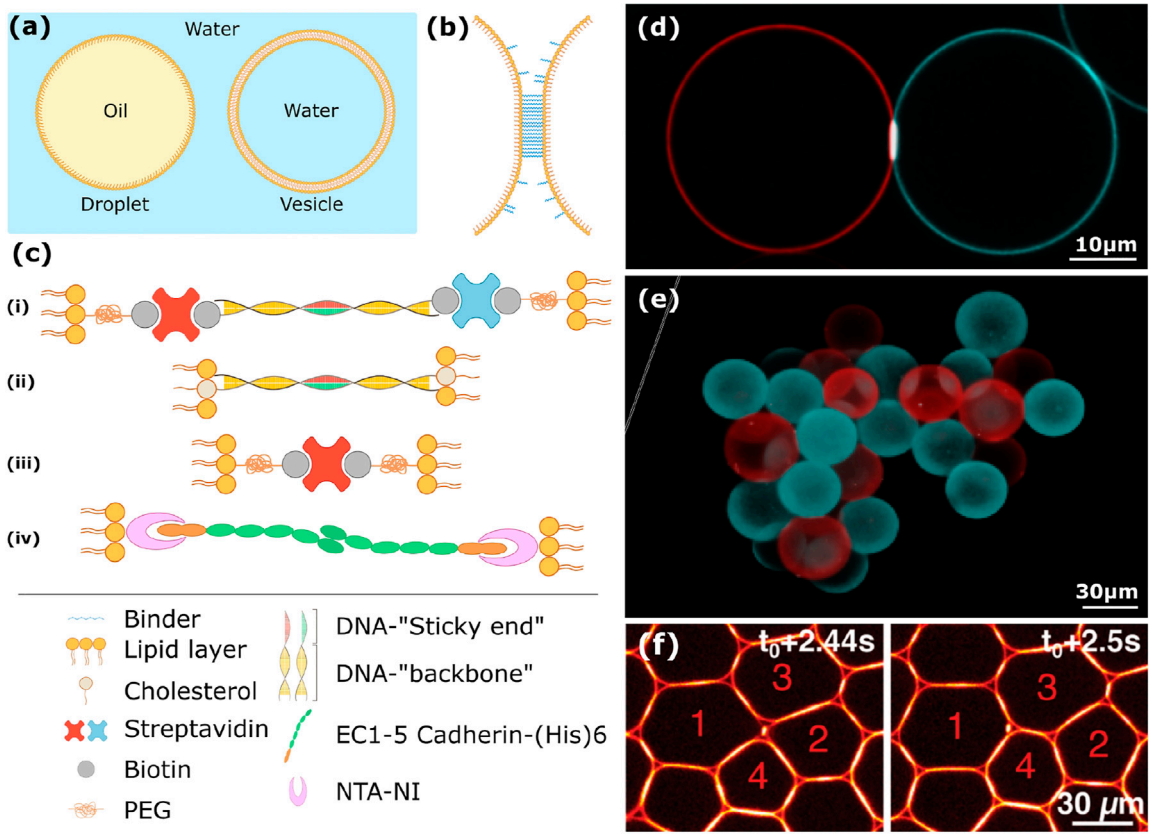

FIGURE 3
Soft matter systems to mimic cell-cell adhesion. **(A)** Schematic representation of biomimetic droplets stabilized by a monolayer of lipids (left) or biomimetic vesicles (right). **(B)** General representation of adhesion between the surfaces of droplets or vesicles: binders are attached (or anchored) to the hydrophilic heads of the outer lipid layer and bind to each other upon surface contact. **(C)** Various type of binders that can ensure specific adhesion, from top to bottom: (i) DNA strands carrying a biotin tag are grafted to a streptavidin which is itself attached biotinylated-PEG groups on the hydrophilic heads of the lipids, or (ii) the DNA strands are directly anchored in the lipid layer through a cholesterol tag. In both cases the DNA sequence usually contains a spacer sequence, made out of a stiff double stranded DNA (represented here in yellow) or a floppy single stranded, followed by a sticky end. The complementary sticky ends of neighboring surfaces interact together to form a complementary double helix upon contact (red/green sequence); (iii) binding through biotin-streptavidin-biotin interactions. The biotinylated lipids on one surface adhere to biotinylated lipids decorated with a streptavidin on a contacting droplet; (iv) adhesion through the extracellular domains of E-cadherin attached to NTA-Ni lipids through a poly-histidin tag. **(D)** Confocal microscopy of two silicon oil droplets adhering to each other through complementary DNA sticky ends. The color of the droplet codes for the sequence, leading to adhesion patches only at the red/green contacts. **(E)** Reconstitution of a 3D packing of oil droplets adhering through complementary strands of DNA. **(F)** Confocal image of silicon oil droplets functionalized with fluorescent streptavidin and adhering through biotin/streptavidin bonds. The droplets undergo a T1 rearrangement as they are flowed in a constriction deforming the emulsion elasto-plastically [39].

other reconstituted modules to mimic a given cellular function *in vitro* (See Figures 3A–C). Encapsulation techniques in GUVs have also been developed [50] and allowed to reconstitute biomimetic actin cortices or minimal protein expression solutions *in vitro* [51, 52]. Alongside the implementation of functional modules inside GUVs, a lot of effort has been provided to introduce specific interactions between them in order to mimic cell-cell adhesion [53–57]. This approach recently led to the production of vesicle aggregates as a model of soft tissues in which cohesion and size can be finely tuned [58]. Despite the fragility of their constitutive elements, these systems will surely provide a great platform to study the elasto-plasticity of minimal adhesive tissues under stress.

Emulsions, and in particular direct oil-in-water emulsions, provide an interesting alternative system to study cell-cell adhesion *in vitro*. Their stability and versatility allowed to assemble and study the mechanical properties of biomimetic emulsions, which is why we describe in more details their principal characteristics. Indeed, the droplets can be stabilized with phospholipids displaying a functional group on their hydrophilic heads (See Figures 3A,B), which allows to graft a wide range of binders onto those groups (Figure 3C). The most common basis of *in vitro* adhesion reconstitution is the use of the biotin streptavidin link: streptavidin displays four binding sites for biotin, allowing it to form an adhesive bridge between two biotins located on the fluid surface of the droplets, either by

covalent grafting [59, 60] or through the use biotinylated phospholipids to stabilize the oil/water interface [61, 62]. The streptavidin can thus be infused in solution and ensure adhesive bridges between the droplets at the right streptavidin/biotin ratio (see Figure 3F).

Another straight-forward way to mimic intercellular adhesion *in vitro* is to directly graft the extracellular domains of cadherins onto the fluid surface of oil droplets [63]. 3D packing of such droplets revealed structures containing voids, i.e., signatures of interdroplet attraction, even in the absence of calcium which is classically known to activate interactions between the extracellular domains of cadherins. At higher calcium concentration strong interactions between the surfaces even led to droplet fusion, which was shown to depend strongly on cadherin *cis* interactions. Therefore, these biomimetic systems are useful tools to get novel insight into the molecular interactions of adhesion molecules.

Finally, an appealing binding strategy relies on the use of complementary strands of DNA [64–66] (Figures 3D,E). In this case, the interaction is highly specific as only two complementary sequences can interact together to form a double helix. Interestingly, the binding energy is also modulated easily through the length of the sequence. The melting temperature above which the double helix is reversibly disassembled is therefore mostly controlled by the size of the sequence and the concentration of salts in solution. The bulk mechanical properties of these systems have been probed through rheology experiments [67]. Similarly to [36], they reveal that below jamming the presence of adhesion between the droplets tends to shift the rheological properties of the system from a viscous to an elastic behavior as the attraction increases by increasing binder concentration. A microscopic mechanism was proposed below jamming: as the bonds are mobile on the fluid droplets surface, the valency of the droplets (i.e., their number of possible adhesive bonds with neighboring droplets, which set by bond concentration) dictates the topology of the droplet clusters that can assemble under strain. Therefore, a valency of 2, i.e., low binder concentration leads to the formation of chains [64, 68], while higher valencies lead to the assembly of higher order clusters percolating throughout the whole sample. Above jamming, increasing the amount of DNA binders delays the onset of plasticity under strain. However, at these densities the link between local rearrangements and macroscopic properties remains elusive.

In order to gain insight into these microscopic mechanisms, the elastoplasticity of adhesive emulsions has been probed through micro-rheology inside microfluidic constrictions [39]. The constriction is used to mimic body axis elongation during development [69] and to impose a large number of rearrangements in the emulsion. The packing fraction in these systems is controlled both by the pressure imposed on the emulsion and by the balance between the adhesion energy between the droplets and the energetic cost associated with their deformation, which sets the size of the observed adhesion patches. Thanks to the 2D geometry, T1 rearrangements can be tracked during the flow and grouped in avalanches [41]. Surprisingly, these experiments revealed that the size of T1 avalanches was not controlled by the level of adhesion between the droplets, indicating that geometry was the only parameter controlling rearrangements. However, individual T1 rearrangements are significantly impaired as the energetic barrier to rupture the existing bond is increased by the presence of an adhesion patch between the droplets. Therefore, the contact between the droplets is maintained longer, inducing a larger deformation of the droplets involved in the T1 (see Figure 3F). According to the above-mentioned energetic considerations, a higher binding energy between the droplets in the constriction is associated with higher deformation levels during T1 rearrangements. This, in turn, deforms all droplets in the emulsion in the axis of elongation, somewhat polarizing the flowing biomimetic tissue. This effect of adhesion could also take place in biological tissues, meaning that a higher adhesion should slow down the dynamics of individual rearrangements and promote elongation of all cells in the axis of the flow. This “in-plane” polarity may be particularly relevant for fast tissue flow in which the active regulations of the cytoskeleton might not have time to respond to the adhesion induced deformation. This could be the case during germband extension in which extrinsic forces drive the first stage of tissue elongation, making elasto-plastic considerations particularly relevant [70]. In particular, this purely mechanical effect may contribute to the propagation of polarity information in cells across different scales in addition to the usual planar cell polarity pathway (see [71] for a review): all droplets are deformed collectively along the same axis through the transmission of forces at their adhesive junctions.

In conclusion, biomimetic models of adhesive tissues are valuable systems to quantitatively shed light on the physical basis of tissue remodeling under force. In order to expand on these results it would be interesting to include other aspects of biological tissues in these synthetic systems. In particular, motility and contractility are key parameters of cellular and tissue mechanics. Conceptually, it is rather straight-forward to imagine an artificial tissue made of vesicles encapsulating active modules of the cytoskeleton, such as contractile acto-myosin networks [72] or active nematics of microtubules [73]. However, the production of large amounts of these objects and the added difficulty of controlling their interactions remain experimentally challenging and have so far prevented their realization. Similarly, various systems of active self-propelled droplets have recently been implemented (see [74] for a review). It is therefore extremely appealing to imagine a new class of biomimetic tissues that could combine the activity of the droplets to the control of interdroplet adhesion. However, the activity of these systems usually depends directly on their local environment, making it

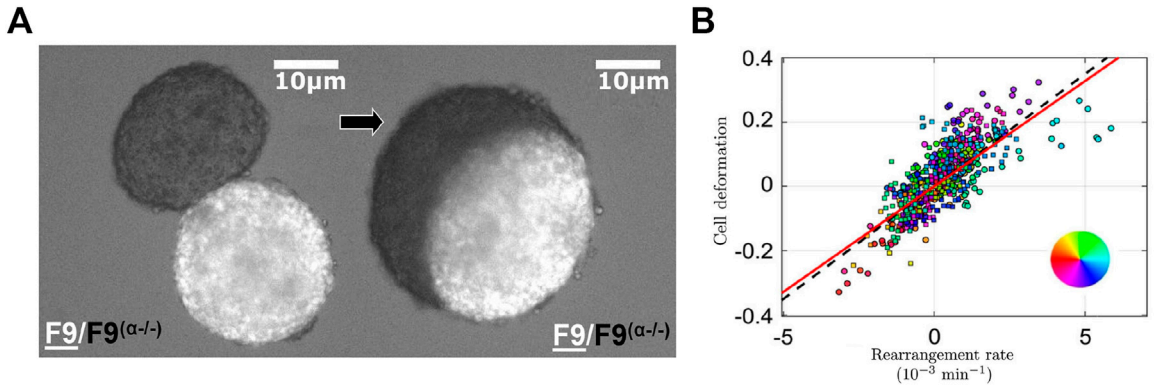

FIGURE 4
Effect of adhesion regulation in vitro cellular systems **(A)** Merging of two cellular aggregates made from F9 cells (white) and F9 (α–/–) cells in which α-catenin has been knocked out (black), 3 h (left) and 29 h (right) after contact. Due to the reduction of adhesion strength in F9 (α–/–) cells, the black aggregate (lower surface tension) deforms around the more cohesive white aggregate (higher surface tension), in agreement with the differential adhesion hypothesis. Adapted with permission from [75]. **(B)** Cell deformation as a function of the rearrangement rate in a 2D monolayer of MDCK cells migrating around an obstacle. The correlation between deformation and rearrangement rate is in agreement with a viscoelastic liquid Maxwell model. Adapted with permission from [76].

difficult to decouple their activity from potential adhesion-based interactions. In addition, the fuel needed for their activity is consumed over time, making the droplets age, which again might impair the adhesive interactions introduced between them.

4 Plasticity control and material properties of *in vitro* model tissues

4.1 Tuning intercellular adhesion *in vitro*

Tuning adhesion in synthetic materials is pretty straight forward, but it can also be done in biological materials such as 3D cellular aggregates or 2D cell layers. For instance, the S180 cell line does not constitutively exhibit cell-cell adhesion [77, 78], but can be transfected to obtain cells with various concentrations of E-cadherin expressed on their surfaces [22, 79]. Classical techniques like RNA interference or morpholinos can also be implemented to directly target the activity of one or more proteins involved in the AJs [80–85]. Other approaches rely on the use of cadherin mutants that can independently affect *cis* and *trans* interactions in cadherin [9, 86]; or on the use of different calcium concentrations that directly tune cadherin adhesion properties [63, 87–89].

More recently, optochemical tools were also developed to control the link between the cadherins and the actin cytoskeleton through light exposure, thus controlling cell-cell adhesion maturation [90]. Finally, the DNA technologies presented in the previous section were combined with cadherin molecules in order to modulate the association energy between cadherins without affecting their intracellular interactions: to do so, the tip of classical E-cadherins were modified to integrate DNA binders [91] of tunable length, i.e. tunable adhesion energy.

4.2 Self-organization and cellular rearrangements in aggregates

Cell aggregates have been used for decades as an *in vitro* model system to study the mechanical properties of tissues in a simplified framework [92, 93]. Due to their relative simplicity, these systems offer a great platform to transpose the study of tissue mechanics into a soft matter framework (see [94] for a review). By analogy with viscoelastic materials, an effective viscosity [95] and surface tension can be measured for such tissues [96–100], with a proposed dependence of these properties on the interaction energy between individual cells [79, 101, 102]. These differences in surface tension originating from differences in intercellular adhesion were described as the origin of tissue self-organizing properties in the framework of the differential adhesion hypothesis [103–107]. Following this hypothesis, hierarchy in surface tensions set the equilibrium architecture of tissues displaying a range of intercellular adhesion levels [108], as depicted in Figure 4A. The definition of an effective tissue surface tension has then been refined by taking into account the interplay between cortical tension and intercellular adhesion [104]. Cell motility has also been shown to be a critical parameter when the differential adhesion hypothesis fails to predict the observed tissue organization [109]. In

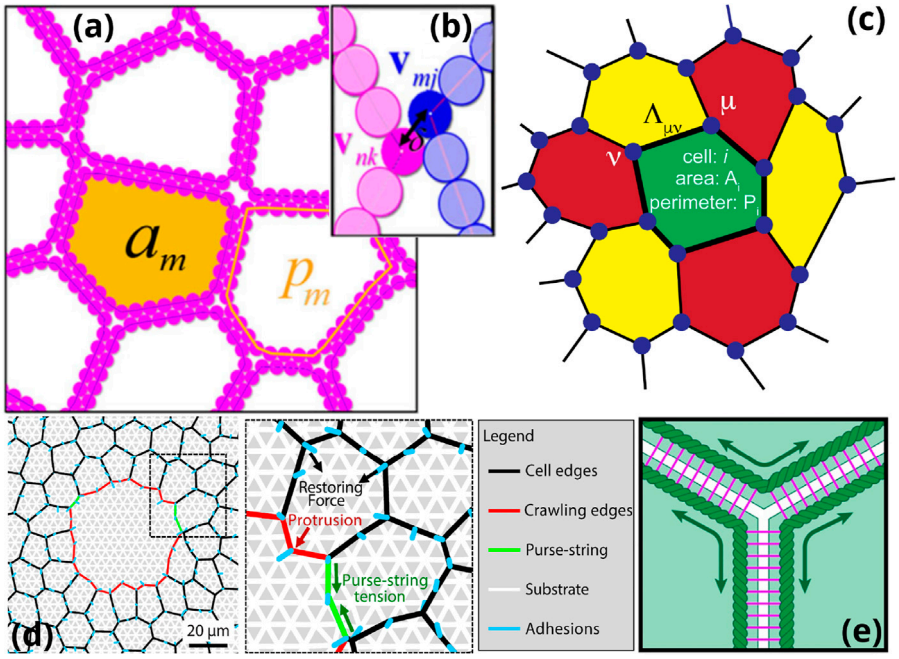

FIGURE 5
Theoretical descriptions of biological tissues **(A,B)** Deformable polygons or deformable particles model: each polygon is defined by its area *a* and perimeter *p*. The perimeter is divided in N = 34 vertices whose positions are determined by different energetic contributions: one that takes into accounts springs between each vertex on a polygon, a compressibility term, a line tension term, a bending energy term for the contour of the polygon, and a repulsive term preventing overlaps between adjacent polygons [136]. **(C)** Schematic representation of the vertex model in which each cell *i* of the space tiling is defined by a target area A_i and perimeter P_i of reference. Three (or more) edges of neighboring cells meet at vertices and each junction between two vertices has a line tension [138]. **(D)** Application of an active vertex model to wound healing. Protrusive forces and adhesion to the substrate are added to the vertex model for wound closure [139]. **(E)** Apposed-cortex adhesion model: in this extension of the vertex model the cortices of neighboring cells (dark green) are explicitly coupled through adhesion molecules (pink), allowing for continuous rearrangements in the tissue through slippage [140].

addition, tuning down the adhesion specifically at the interface between distinct cellular populations can allow cells to polarize their mechanical properties or even detach locally, thus promoting the formation of clear boundaries between tissues [110]. This phenomenon, which is critical for tissue boundary establishment during development, has been reconstituted *in vitro* by using *Xenopus* embryo explants obtained from different lineages (mesoderm and ectoderm) [111, 112]. Similarly, recent work highlighted the importance of considering the differential adhesion information and morphogen gradients concomitantly, in order to robustly predict pattern emergence during morphogenesis [85], which will be further discussed in Section 6.4.

When such aggregates are submitted to mechanical perturbations, they exhibit an elastoplastic response in which rearrangements take place to relax the applied stress [95]. How these rearrangements are tuned through adhesion modulation remains elusive, but liquid like behaviors and individual cell escapes have been observed when adhesion is impaired, indicating a rise in neighbor exchange [79]. These experiments were also useful to highlight the cross-talk between cell-cell adhesion and cell-matrix adhesion. Indeed, there is a positive feedback loop between cell-substrate adhesion (typically through fibronectin) and cell-cell cadherin-based adhesion [113, 114]. Therefore, on soft substrates, the aggregates are less cohesive and cells can perform rearrangements easily [115, 116], which sheds lights on the importance of adhesion impairment in the context of cancer propagation [117]. Nevertheless, quantitative measurements of cellular rearrangements are difficult in such 3D disordered cellular packings where imaging remains challenging. For this reason, 2D models of cellular tissues *in vitro* are useful tools to quantitatively relate adhesion regulation to cell-scale events.

4.3 Rearrangements in 2D cellular assemblies

Cellular monolayers can be assembled in order to recapitulate the main features of epithelial sheets such as collective movements, polarization, wound healing, etc . . . In these systems, the integrity

of the extracellular adhesion of E-cadherins has been shown to be essential not only for tissue integrity, but also for efficient wound healing. As a matter of fact, if the E-cadherin extracellular domains are replaced by cadherins of type II, that are associated with weaker slip-bond adhesions in the mesenchyme, closure in wound healing assays is strongly impaired and 2D assemblies fail to maintain epithelial integrity [20].

Intercellular adhesion in various epithelial sheets has also been tuned by depleting cells of E-cadherin through RNA interference [80, 83]. These experiments revealed that the role of E-cadherins was critical for the *de novo* establishment of intercellular adhesion, rather than the maintenance of existing ones [83]. In fact, the concentration of E-cadherin can be directly correlated to the rate at which tension builds up in epithelial layers [80]. Because the completion of a rearrangement relies on the cells' ability to grow a new adhesion *de novo*, this suggest that E-cadherin expression is a controlling parameter for the rate of T1 events in cellular monolayers.

Alternatively, the effect of adhesion has been probed in smaller 2D epithelial cell clusters in which intercellular adhesion has been shown to ensure mechanical coordination over many cellular length scales [118, 119]. Primary mouse keratinocytes assemble in such clusters, in which intercellular adhesion can be tuned through the extracellular calcium concentration [89]. This approach highlighted the role of cadherin-based intercellular adhesion for the transmission of forces to the underlying extracellular matrix, which in turn localizes these traction stresses at the colony periphery. This effect, by targeting the periphery of the cluster, thus also promotes the definition of clear cellular tissue boundaries as described in the previous section. Interestingly, such crosstalk between intercellular and cell-matrix adhesion was also shown to play a role in cell-cell junction dynamics, which should in turn affect T1 rates in these cellular assemblies [120].

All these experiments suggest a link between adhesion strength in epithelial layers and the dynamics of Adherens Junctions assembly and cellular rearrangements. However, to our knowledge, a direct quantitative link between T1 rearrangements frequency and intercellular adhesion levels still remains unclear in these studies that tune E-cadherin expression.

Conversely, experiments from fluid mechanics can be applied to these systems in order to explore explicitly the elasto-plasticity of epithelial sheets. Similarly to experiments performed on emulsions [39], they typically allow to track cellular rearrangements and deformations when the cellular assembly is submitted to a mechanical constraint in 2D. For instance, MDCK (Madin-Darby Canine Kidney) epithelial sheets have been used in channels exhibiting a central obstacle in order to explore the progression of the monolayer around it [76]. The rearrangement rates can then be deduced from coarse-grained analysis by substraction of the cell shape strain rate from the total strain rate of the tissue [121]. This study revealed that deformation and T1 rate fields were strongly correlated (Figure 4B), indicating that the behavior of the 2D cellular sheet could be modelled with a viscoelastic liquid Maxwell model [76, 122]. In particular, these findings highlight the relevance of a timescale associated specifically with intercellular rearrangements for the understanding of the mechanical behavior of these 2D cellular assemblies.

5 Theoretical approaches to tissue plasticity: Influence of adhesion

Biological tissues can be modelled through continuous or discrete descriptions. In the case of continuum models, the tissues are generally described as active gels [123, 124]. For instance, differences in viscosities between the epithelial lung tissues and surrounding mesenchyme could give a physical explanation for its morphogenesis [125–127], therefore proposing the idea of fingering instabilities in tissues [128] by analogy with viscous fingering in liquids [129]. Continuum descriptions also captured the importance of a localized fluidization of the tissues during early morphogenesis [130]. This fluidization was shown to depend on signalling pathways affecting cell-cell adhesion. Such continuum descriptions of tissues have therefore been very useful to characterize mechanical properties at the tissue-scale and shed light on the role of adhesion in the physical principles in morphogenesis [118, 130–134]. However, those approaches are not tailored to specifically study the effect of intercellular adhesion regulation on individual rearrangement dynamics.

In order to take into account rearrangements, one needs to consider cells as discrete elements that can deform and move with respect to each other, and thus use particle based models or vertex models. In particular, deformable particle models are useful to describe static packing properties with [135] or without adhesion [136, 137] (Figures 5A,B). This approach has also been used to study the flow of monodisperse and polydisperse particles with a range of attraction strength and deformability (akin to surface tension) [39]. The results of these simulations showed that avalanche statistics for T1 events were conserved independently of adhesion for a given polydispersity and deformability.

In this context, approaches such as the vertex [104, 141–149] or cellular potts models [150–155] are relevant to study the relationship between intercellular adhesion, rearrangements and tissues properties (see [156] for a review). In the cellular potts model each cell is modeled as an assembly of positions and energetic states in a grid and there is an explicit coupling between the state of each cell. Conversely, in the vertex model the tissue is modelled geometrically by a network of vertices connected by edges (Figure 5C). The energy of the cells in the tissue is calculated by taking into account a bulk elasticity of the cell, the contractility of the cortex underlying its surface and the cost of deformation due to the interfacial tension. The sign of this

interfacial tension depends on the balance between intercellular adhesion and cortical tension.

In that framework, one can define a shape parameter p_0 for individual cells as $p_0 = P_0/\sqrt{A_0}$, with P_0 the perimeter of the cell and A_0 its surface [157]. This non dimensional number was an alternative way to account for the balance between cortical tension and cell-cell adhesion. Therefore, an increase in p_0 is a signature for impaired cell-cell adhesion in the tissue. Interestingly, that approach was sufficient to predict a threshold value of $p_0^c = 3.81$ under which the tissue undergoes a jamming transition, independently of the tissue packing fraction [157]. In this framework, jamming is therefore decoupled from neighbor exchange dynamics.

Alternatively, the dynamics of cellular positions have been modeled through self-propelled particles descriptions. Akin to motility induced transition approaches, the tissues undergo rigidity transitions as a function of cell dynamics and density [158]. However, these models do not focus on intercellular adhesion regulation, which is at the center of this review. Various models have been proposed to introduce an active term in the vertex model [159] (see [160] for a review). For instance, one straightforward way to do this is to combine the self-propelled particle and the vertex models to account for topology as well as activity of the cells in the tissue [138, 161, 162]. This model is commonly referred to as the self-propelled Voronoi or SPV model. In particular, this model was used to predict jamming transitions in real tissues. In this context, the critical shape parameter p_0^c is lowered by an increase in cell activity, meaning that cellular activity opposes jamming [138, 161, 163]. This balance has been studied in the particular case of wound healing [139, 164] and led to an explicit relationship between intercalation efficiency and adhesion regulation. Increasing p_0, i.e. lowering cell-cell adhesion, increases the rate of T1 events in the tissue independently of cellular activity. This in turn, enables fluidization of the tissue and local stress relaxation (akin to emulsions), thus favoring faster wound healing (Figure 5D). These studies therefore shed light on the critical role of intercellular adhesion for rearrangements-driven tissue fluidization [139, 164].

A recent implementation of these models also takes into account the intercellular spaces (like in the DP model) and focuses on cortical tension fluctuations [165]. Interestingly, this model distinguishes two modes of neighborhood changes: for confluent tissues at high cell-cell adhesion levels, rearrangements are mostly in the form of T1 events and their frequency vanishes when contractility decreases, which is a signature of structural arrest; for non-confluent tissues at low adhesion levels, the neighborhood of a cell changes mostly due to creation or loss of cell-cell contacts. It also indicates that there is a threshold tension fluctuation value over which the tissue will always be fluid independently of the level of adhesion. Below this value the tissue fluidity depends directly on cell-cell adhesion. Whether a tissue would modulate tension fluctuation or adhesion strength between the cells remains an interesting question.

At the molecular level, the physical presence of adhesion proteins at the cell-cell junctions can be considered through approaches such as the newly developed apposed-cortex adhesion model [140] (Figure 5E). With this model, the physical properties of the elements that constitute a junction, among which the adhesion molecules between neighboring cells, are explicitly influencing the process of neighbor exchange. For instance, the presence of adhesion molecules between sliding cell surfaces induces a viscous friction that opposes rearrangements [166]. A fast turnover of adhesion molecules therefore relaxes this opposing force and enables neighbor exchanges. This adhesion molecules turnover in biological tissues will be discussed in Section 6.1.

6 Role of adhesion modulation in the control of morphogenesis

Just like in soft matter models, rearrangements in tissues can be coordinated to yield global shape changes and are a local source of stress relaxation upon applied forces [164, 167, 168]. The general mechanics of tissues therefore depends strongly on the details of these rearrangements (see [169, 170] for reviews). In particular, tissue elongation during morphogenesis, also known as convergent extension [171], has been extensively studied in the spectrum of cell rearrangements [70, 170, 172–174]. For instance, the process of tissue elongation during the first fast stage of germ-band extension in *Drosophila* has been described as the passive response of an adhesive assembly of deformable cells under an applied extrinsic force [70]. In other words, a balance between cell deformations and cell rearrangements leads to overall tissue extension under external forces: an impaired plasticity therefore leads to more intense cellular deformations, just like in synthetic systems [39]. It is clear through this particular example that adhesion is crucial for morphogenetic processes (see [5, 175] for reviews). Among the immense literature discussing the role of classical cadherins in Adherens Junctions (AJs) for tissue remodelling, we will narrow down our reports on some experimental studies that focus on adhesion regulation in developing tissues, and its direct impact on cell rearrangements.

6.1 Modulation of adhesion strength *in vivo*

There are several ways in which a tissue can modulate intercellular adhesion, at different scales in time and space [176, 177]. At long timescales (hours) and large lengthscales (hundreds of microns), adhesion can be regulated under the influence of a morphogen that will tune the expression of the components of the AJs [85, 178, 179]. Adhesion can also be regulated on such timescales through the expression of Eph/ephrin repulsive signalling: when the complementary Eph receptors and ephrin ligands bind to each other, they trigger

the cleavage of E-cadherins by the protease ADAM10 [180], as well as an increase of actomyosin cortical contractility [181], resulting in a downregulation of cell-cell adhesion.

Conversely, trafficking of transmembrane proteins ensures the regulation of adhesion molecules on the timescale of minutes [177, 182, 183]. Multiple factors have indeed been shown to regulate E-cadherin trafficking and control AJ dynamics. For instance, Rab5A [184], Nemo [185] or Rab5C [186] can promote E-cadherin endocytosis at AJs independently of acto-myosin contractility. The link between such adhesion regulation processes and the control of cellular rearrangements has been shown in multiple morphogenetic instances [183, 187, 188].

Mechanical signals can also contribute to the dynamical regulation of adhesion. For instance, AJs under tension are usually less likely to undergo endocytosis, which could be in part due to membrane tension preventing the invagination of the membrane [189, 190]. However, the opposite effect if observed during *Drosophila* wing extension: the p120 catenin is detached from E-cadherins under high tension, causing an increase in the endocytosis of E-cadherins [191] and AJs destabilization.

6.2 Control of tissue shape during morphogenesis

At the beginning of its development, the embryo has a spherical shape. The first significant change of shape is the transition from the cell-filled spherical morula to the blastula, in which cells form a spherical capsule around a fluid center. In mammals, this fluid-filled cavity is formed by the successive fusion of micro-lumens [192]: the hydraulic pressure of the fluid pumped by the cells can break cell-cell adhesions [193] and form small cavities that subsequently fuse into an unique compartment. The pressure-mediated breaking of cell-cell adhesions therefore rearranges the cells in the tissue around this central cavity. When the strength of adhesion is not homogeneously distributed, the fluid cavity forms preferentially in the low adhesion area where the energetic cost of cell rearrangements is the lowest [192].

During gastrulation, the tissues then start changing their shape drastically to form a tubular shape in which different cell layers can be distinguished. For instance, at the onset of epiboly in the zebrafish, specific layers of cells start spreading onto the yolk. This process has been shown to depend on E-cadherin mediated adhesion [194, 195]. In particular, the selective disassembly of cadherin junctions at the center of this tissue [130], and not at its borders, leads to a decrease in cell-cell connectivity and a rapid fluidization - through intercalation - of the tissue [84]. This local modulation of adhesion during epiboly has been shown to depend on E-cadherin trafficking regulation [196]. Therefore, the spatio-temporal modulation of adhesion directly controls the connectivity at the cell scale and thus tunes the viscosity at the tissue scale, eventually controlling its morphogenesis.

After gastrulation, during germband extension, the increased endocytosis of cadherins at the AJs along the dorso-ventral axis decreases their strength [187, 197, 198]. As a result, the weakened junctions undergo parallel T1 events, leading to a coordinated elongation of the tissue along the antero-posterior axis. This process is also regulated by the mechanosensitivity of the AJs. Indeed, efficient cell intercalation, that is necessary for germband extension, requires the mechanosensitive binding of vinculin to α-catenin. Therefore, embryos in which the α-catenin domains allowing binding to vinculin are disrupted are shorter, indicating an impaired convergent extension [199].

In all these morphogenetic stages, the spatial pattern of adhesion modulation sets a localized fluidization through facilitated rearrangements, or a preferred axis for the rearrangements, leading eventually to layering, folding or extension processes.

6.3 Control of epithelial packing topology

Many tissues require precise cellular packings in order to ensure their biological function. For instance the precise packing of cells in the eye is necessary to control the optical properties of the tissue. Another well-studied system is the precise arrangement of hair in the *Drosophila* wing, which is essential for the control of air flow [200]. To ensure such a precise control of cellular packing in the plane of the tissue, modulation of AJ stability is necessary to fluidify the tissue locally so that the cells can rearrange in a directed manner and reach a specific packing topology. In particular, during *Drosophila* wing development, the tissue undergoes two phases of oriented rearrangements that ensure elongation along the antero-posterior axis, and then along the proximal-distal axis [201]. After these successive events associated to extensive cellular rearrangements, the cells need to reach a precise hexagonal packing in order to ensure proper hair position in the wing. Such ordering of the cellular position results from a spatial regulation of E-cadherin endocytosis, which in turn controls the direction of the cellular rearrangements [202]. This spatial control of junction regulations is performed under the regulation of planar polarity pathways [183]. Therefore, biological tissues can be locally and asymmetrically fluidized to drive the emergence of a given packing topology.

6.4 Sorting and patterning during morphogenesis

Cellular sorting was mostly described in the context of the differential adhesion hypothesis in *vitro* cellular aggregates. However, differences in adhesion proteins expression have also been demonstrated to play a role in a wide range of morphogenetic processes requiring cell sorting (see [203] for a review). In fact, during development, cells are continuously

mixed through rearrangements and morphogen gradients are not always sufficient to ensure precise patterning. In some situations, processes that are driven by differential adhesion are therefore necessary, in addition to morphogen signaling, to maintain positional information against rearrangement-induced mixing.

In particular, in the zebrafish embryo, the 3 types of neural progenitors of the spinal chord each express a unique combination of 3 adhesion proteins, in response to morphogen gradients: each cell type adheres preferentially to cells of the same type. During the convergent extension stage of the spinal chord morphogenesis, this adhesion pattern drives cellular sorting and its combination with a morphogen gradient ensures the maintenance of sharp boundaries between the 3 cell types, despite the extensive rearrangements occurring during this elongation process [85]. Similarly, in the *Drosophila* abdominal *epidermis*, expression of the cell-cell adhesion protein Toll-1 at the boundaries of histoblasts helps maintain a straight frontier between compartments during development [179]. With a different mechanism, the expression of a complementary pattern of Eph and ephrins in mesoderm and ectoderm cells of the *Xenopus* embryo tunes down the cadherin adhesion at the boundary between the two tissues. In the absence of this signalling pathway, cells of the two lineages mix in the embryo, leading to a loss of spatial organization [111].

6.5 Collective migration during morphogenesis

During some developmental processes, groups or clusters of cells need to maintain their cohesiveness while also moving collectively within the surrounding tissue. In this case, a rigid-like cluster of cells has to co-exist within a fluid-like surrounding tissue, highlighting the necessity of precise adhesion regulation in these processes. These subtle links between adhesion, rearrangements and collective migration, are also central for the study of tumor progression and metastasis. We here review a few examples of such processes in which adhesion regulation is key to control cell-cell intercalation inside and outside of moving cellular clusters.

During gastrulation, the newly defined mesendoderm internalizes in a collective motion to form a layered 3-dimensional tissue. Yet, it must preserve the positional order of the cells that were previously exposed to a gradient of the morphogen Nodal. It was shown recently that this orderly collective motion is ensured by a preferential adhesion set by the Nodal gradient: each cell adheres best to the cells that have received a similar dose of morphogen [178]. Cells exposed to the highest concentrations act as leader cells with an increased protrusive activity, inducing a local unjamming. At the same time, the differential adhesion ensures that the cells move sequentially by following only the neighbors with the same initial position. This process reveals how the mechanism described in the previous section can be combined with motility in order to yield a collective motion preserving the positional order set by gradients of morphogens.

In later stages of development, some groups of cells need to migrate long distances to reach their final destination. To migrate as a collective assembly, and yet not be stuck or jammed, they need to regulate precisely their level of cell-cell adhesion. For instance, the eye morphogenesis in *Drosophila* strongly depends on the chiral rotation of cellular ommatidial clusters [204]. It was shown that this process is controlled directly by factors that regulate E-cadherin trafficking and AJs dynamics in the different tissues [185]: Nemo upregulation leads to increased E-cadherin endocytosis, which leads to a fluid-like transition of the tissue between ommatidial clusters, allowing for their rotation. Conversely, Nemo loss of function leads to reduced E-cad endocytosis, which in turn leads to higher levels at the junctions of such cells and tissue rigidification.

Similarly, the collective migration of neural crest cells has been studied in *Xenopus*. After the formation of the neural tube, neural crest cells undergo an epithelial to mesenchymal transition, delaminate from the neural tube by down-regulating their cadherin expression and start migrating in the body. The transition may be partial and neural crest cells then migrate as small cohesive clusters of cells. In these clusters, adhesion levels are finely tuned through N-cadherin endocytosis, so that the cluster remains cohesive while cells are still able to rearrange in order to migrate through narrow gaps [205]. When N-cadherin is over-expressed, the clusters become solid-like as rearrangements become too costly. Conversely, when N-cadherin expression is too low, the clusters lose their cohesion.

It is also important to note that cell rearrangements continue to play a major role in tissue plasticity even after development, and in particular during wound healing [164]. For instance, repulsive signalling by Eph/ephrins, already shown to promote cell rearrangements via adhesion downregulation [111, 112, 180], is also necessary *in vivo* to rearrange the epithelium during wound closure [206].

6.6 Modification of rearrangements dynamics through the regulation of vertex-specific proteins

Unlike emulsions or foams, epithelial tissues often maintain their packing fraction at values close to 100% in order to ensure the impermeability of the monolayer. Therefore, there is an additional set of specialized proteins that close the gaps at the vertices where three or more cells meet (see [207, 208] for reviews). The *Drosophila* sidekick has been identified as a protein of such tricellular adhesion complexes [21, 27, 28, 209]. Like cadherins, these proteins are regulated by the levels of tension at the junction. During a T1 transition, the sidekick aggregates present at vertices fuse on the shrinking contact, then

separate into new vertices as the T1 resolves. Therefore, the critical role of sidekick has been underlined in processes involving intense epithelial remodelling, such as germband extension [21] or tracheal morphogenesis [27]. During these processes, the absence of sidekick proteins slows down the T1 transitions, which then fail to resolve as the cells remain at the 4-way vertex intermediary stage, leading to defects in the remodeling tissue. Therefore, the action of these specific adhesion proteins actually promotes the completion of rearrangements. Likewise, during the *Drosophila* male genital development, sidekick and E-cadherin were seen to exclude each other [28]: the accumulation of sidekick in shrinking junctions favors the disassembly of the adhesive contact by excluding E-cadherin. Conversely, its localization at the newly formed vertices favors cadherin-mediated adhesion at the growing edge and the formation of a new AJ.

7 Conclusion and perspectives: Adhesion in the jamming phase diagram for biological tissues

In this review we presented the effect of adhesion on rearrangements in a wide range of systems, ranging from particles and biomimetic systems, to tissue remodelling during morphogenesis. Synthetic approaches did allow to gain quantitative insight into the processes controlling rearrangements in adhesive assemblies of particles. For instance, it was evidenced that the topology of rearrangements in the presence of non-specific adhesion depends on the size of the particles, yielding large predictable avalanches in monodisperse packings, and smaller disordered ones in polydisperse assemblies. It was also shown that specific adhesion was responsible for the oriented deformation of the droplets undergoing rearrangements, similarly to processes observed *in vivo* during germband extension. Conversely, it is difficult to disentangle the different cellular processes at stake during rearrangements in biological tissues, because of the feedback loop between intercellular adhesion and cellular mechanics through mechanotransduction. However, we reported here on some developmental stages depending on cellular rearrangements that are directly regulated through intercellular adhesion, leading to tissue shape changes, self-organization, fluidization or cellular packing modifications.

An appealing strategy to unify all these out-of-equilibrium processes is to describe them in the framework of a jamming phase diagram [210]. Indeed, by analogy with granular systems, biological tissues have been increasingly described in the framework of the jamming transition (see [210, 211] for reviews). During such a transition, the tissue undergoes structural arrest, i.e. its cells are caged by each other and stop moving [212–217]. Conversely, increased cellular fluctuations and motility can drive uncaging and therefore unjamming in a tissue [184, 218, 219].

Based on these analogies and on experimental observations, phase diagrams for jamming phenomena in biological tissues have been proposed recently, revolving typically along three axes. The first axis concerns the fluctuations provided by contractility (shape fluctuations [95]) or motility, i.e., positional fluctuations). The higher the fluctuations the less jammed the tissue. The second one, in direct analogy with inert materials, is taken as the inverse of the tissue packing fraction, simply meaning that cellular crowding is a jamming factor. While this parameter is not explicitly dependant on cell-cell adhesion, it has been shown that down-regulating adhesion in developing tissues leads to a decrease in tissue packing fraction [213]. The third axis is described as geometric incompatibility in [210], which translates the idea that deviations from a preferred cell shape is sufficient to induce rigidity transitions in an otherwise constant network of contacts [157].

While adhesion is not explicitly an axis of these phase diagrams, it has been shown to play a role on tissue packing fraction and neighbor rate exchange in developing zebrafish embryos [213], which are both critical parameters for tissue rigidity. Moreover, the network of adhesive contacts in tissues can also control their mechanical properties. An analogy can be drawn with rigidity percolation theories in soft matter: if the network of intercellular adhesive contacts is percolating, the mechanical stability of the network provides the tissue with increased viscosity [84]. Effects of percolation have also been observed on the deformation of biomimetic droplets in static 2D packings [220]. The study of adhesion networks in tissues could therefore be a key parameter to study mechanical properties from the individual cell scale to the tissue level in a unified framework. In particular, it would be interesting to couple the idea of percolation theory to a measurement of the adhesion strength in the contact network. For instance, if the adhesion energy between 2 cells is low enough, the contact between these cells could be considered as a weak link and not participate in the adhesion network. While a continuum of adhesion energy might be difficult to include in that framework, a first step towards this idea could consist in setting a threshold value of adhesion strength below which a contact between cells would be removed from the contact network. Studying how the rigidity of such networks evolves as a function of this threshold value could give insight into the link between the energetics of individual rearrangements and the mechanical properties of the whole tissue.

Author contributions

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

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