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Mechanical plasticity in collective cell migration

Shreyansh Jain, Benoit Ladoux & René-Marc Mège

Université de Paris, CNRS, Institut Jacques Monod, Paris, France

Corresponding authors:

René-Marc Mège, rene-marc.mege@ijm.fr

Benoit Ladoux, benoit.ladoux@ijm.fr

Abstract

Collective cell migration is crucial to maintain epithelium integrity during developmental and repair processes. It requires a tight regulation of mechanical coordination between neighboring cells. This coordination embraces different features including mechanical self-propulsion of individual cells within cellular colonies and large-scale force transmission through cell-cell junctions. This review discusses how the plasticity of biomechanical interactions at cell-cell contacts could help cellular systems to perform coordinated motions and adapt to the properties of the external environment.

Collective cell migration has been extensively studied in the last few decades to uncover biological mechanisms driving morphogenesis, wound healing, and cancer progression [1]. An important question remains the ability of single cells to interact with their neighbors to generate coordinated collective motions. Single cell migration often relies on the formation of active membrane protrusions at the front edge, focal adhesion assembly and the contraction of the rear [2]. This dynamics is altered in collective cell migration due to the extra-coupling with neighboring cells [3]. Collective migration is thus not simply the combined migration of multiple single cells, but it also has emergent properties due to the self-organization of multiple agents in contact [4]. These emergent properties emanate from cell-to-cell communication *via* the transmission of biomechanical signals at cell-cell contacts [5]. Collective cell migration *in vivo* drives morphogenesis processes such as *Drosophila* tracheal formation, *Drosophila* dorsal closure [6], Zebrafish primordium lateral line migration [7], *Xenopus laevis* neural crest cell migration [8], angiogenesis in Zebrafish embryos [9], mesendodermal cell migration in Zebrafish and *Xenopus* [10-12] and pathological processes such as tumor invasion [13*]. Cells utilize different modalities to migrate collectively, which can be categorized into movement in sheets, clusters, strands or streams [14]. The recent advances in novel experimental tools, imaging, and analysis techniques often easier to implement *in vitro* have provided significant insights to uncover these complex mechanisms occurring at different length scales in collective cell migration, with epithelia migration as a paradigm. One of the mechanisms leads to partial epithelial-mesenchymal transition (EMT) when cells at the front, named as leader cells, partially lose apico-basal polarity, and establish front-back polarity in the direction of movement [15]. The collective migration does not only refer to leader cell formation but also to the emergence of single cell front-back polarity within the bulk of migrating tissues [16-20] as well as to long range coordination of cells within the collective [21-24]. Hence, collective cell dynamics exhibits a complex set of coordinated cell migration patterns that depend on polarity, cell-cell junctions and active forces and take place at multiple length scales.

In this review, we discuss the various mechanisms at play during collective cell movements and how these systems adapt their length scale of coordination to respond to mechanical or biochemical constraints.

A variety of coordinated collective cell migration modes in vivo

Robust and coordinated collective migrations of cells are essential for morphogenesis to achieve tissue's desired geometrical and functional fate during development. However, multicellular clusters or sheets of migrating cells manifest their bio-mechanical coupling at very different length scales ranging from an entire epithelium to almost single cells. The long-range mechanocoupling has been described during various processes such as germ band extension and dorsal closure in *Drosophila* or epiboly in Zebrafish [25]. During epiboly, the first step in Zebrafish gastrulation, the enveloping layer is coordinately pulled over the yolk by a contractile actomyosin cable forming in the yolk cell ahead [26] (**Fig. 1a**). Collective chemotactic migration of *Xenopus* and Zebrafish cephalic neural crest cells engages long-range coordination spanning across a cluster of 25 to 30 tightly bound migrating cells (**Fig. 1b**). Although cells at the periphery of the cluster present lamellipodial protrusions, the directional and collective displacement of the cluster is promoted by the contraction of supracellular actomyosin cables spanning across

multiple cells at the rear of the cluster [21]. This contraction at the rear edge results in a swirling flow within the cell cohort similar to the primitive streak formation in quail gastrula [22].

In other situations, the migrating cells are pulled by homotypic cells at the leading edge of the migrating monolayer, as during re-epithelialization of wounds in mouse [27], or migration of zebrafish epicardium [28]. These migrations present similarities with the extensively studied migration of epithelial monolayers *in vitro* [3,24,29,30]. During border cell migration in *Drosophila* egg chamber, eight cells delaminate from the follicular epithelium and migrate toward the oocyte as a tightly cohesive cluster behaving as “super cell” towed by leader cells extending lamellipodia and pulling followers to which they are mechanically coupled [5,31]. Similarly, during gastrulation in Zebrafish [11] and *Xenopus* [10], the mesendodermal cells migrate across the blastocoel roof as a collective mass with the help of large traction forces being generated by leading cells. Mesendodermal cells require C-cadherin in *Xenopus* [32] (E-cadherin in Zebrafish [11]) to maintain cell cohesiveness which is further implicated in transmission of leading edge cell forces inside the bulk and the extension of a monopolar Rac1-dependent protrusion which adhere to fibronectin using integrin adhesions [33,34] (**Fig. 1c**).

All collective cell migration situations discussed so far are associated to supracellular polarization features, either protrusions or contractile cables, appearing at one edge or the other of the tissue and powering long-range mechanical coordination. This is however not observed in all situations *in vivo* as exemplified by the coordinated rotation of follicular epithelial cells in the *Drosophila* egg chamber where each single cell exhibits actin-enriched filopodia/lamellipodia-like structures [16,35] (**Fig. 1d and 1d-inset**). These protrusions are responsible for the follicle cell movement. The maintenance of the long term coordinated migration of the whole cell collective results from a coordinated polarization of each cell resulting from a short range planar signaling involving multiple transmembrane guidance cues such as the receptor tyrosine phosphatase Lar and its receptor Fat2 (an atypical cadherin) [36], and Semaphorin 5c and its receptor Plexin A [43]. Coordinated lamellipodia-based single cell migration has been also recently unraveled in mammalian small intestine *in vivo*, during the migration of differentiated cells from the crypt to the top of the villi [17**] (**Fig. 1e**). The migration of these cells is not primarily driven by pushing forces generated by addition of new cells in the crypt but results from an active cell-autonomous migration due to basal Arp-2/3-dependent actin protrusion sent by each cell underneath the cell in front (**Fig. 1e - inset**). Although no force measurements have been performed, it is likely from cell organization that these tissues are not transmitting long-range mechanical cues but instead act as independent agents whose polarities are however strongly coordinated by planar polarity cues. Interestingly, in the model of Zebrafish lateral line migration [37,38], it was shown that not only cells present at the leading edge, but also cells throughout the migrating cluster (around 150 cells) develop Arp2/3-dependent actin rich lamellipodial protrusions populated by focal adhesions in the direction of cluster migration (**Fig. 1f**), suggesting that cells situated in the bulk of the cohort actively migrate [39**].

It highlights that *in vivo* situations are very diverse in terms of the spatial regulation of mechanocoupling. Although these models could not always provide high spatiotemporal details, recent developments including *in vitro* based experiments hint towards the existence of multimodal mechanisms in play during their collective migration.

Footprints of multiscale cellular coordination *in vitro*

Even though new tools have emerged [40,41], measuring forces and stresses remains a challenge *in vivo* and often relies on indirect inference of the forces [42]. An alternative approach relies on mimicking *in vivo* situations in *in vitro* systems. *In vitro* systems provide means to replicate, miniaturize and simplify some of the *in vivo* systems by imposing physical constraints on the cells *via* ECM protein patterning and provide direct measurements of cell-generated forces [43]. For example, re-epithelization processes can be recreated *in vitro* by introducing gaps in epithelial monolayers to facilitate measuring of forces cellular assemblies apply during the process of wound healing [44,45], while confined *in vivo* migration [36,46] can be mimicked in a simple 2D system by containing cells in pre-defined geometrical boundaries [30,47**].

The emergence of long-range mechanical signals

In vitro studies of freely expanding monolayers have been long implicated as a model system for collective cell migration to understand the cellular coordination [29,30,48]. Coordinated movements have been characterized by measuring physical parameters including velocity, strain, force and stress fields [42]. Measuring velocity fields in migrating epithelial monolayers has revealed that cellular displacements are correlated over very large distances as compared to the size of individual cells [30,49,50]. For instance, large-scale velocity waves [24,51,52] propagating from the edge to the center of the migrating monolayers were observed in model wound experiments. The measurements of traction forces revealed, in addition, the appearance of travelling mechanical wave opposite to the direction of cell migration [24]. From the traction force data, one can also estimate the stress field of cohesive cell monolayers [53,54]. In expanding monolayers, similar experiments showed that the stress transmitted through cell-cell junctions increases from the edge to the center of the colony [29,55] favoring the build-up of a large-scale tension during collective cell migration. The evidence of these long-range force transmission has been further used to explain the collective cell migration toward stiff surface in response to a stiffness gradient [23]. This coordinated mechanism strongly depends on cell-cell adhesion strength and acto-myosin contractility. The decrease of cell-cell adhesion as well as the nature of adhesive contacts leads to a drastic reduction of the long-range transmission of these physical signals [56,57*]. Altogether, the presence of large and opposite traction forces at both edges of expanding monolayers combined to the stress maps (**Fig. 2a,a1,a2,a3**) lead to the attractive idea of scaling up single cell mechanical representation to “multicellular” assemblies, where force dipoles resemble the one of a single migrating cell [23,58].

In relation with mechanical signals, recent studies focused on the role of biochemical inputs to coordinate collective migration. Interestingly, extracellular signal-regulated kinase (ERK) activity propagates away from leading edges towards the center of colonies and thus, appears as an interesting candidate to couple mechanical and chemical signals, ERK being activated by cell stretching induced by the tensional state of the migrating monolayers [59,60**]. In addition to ERK, other studies highlighted the role of Merlin localization from junction to cytoplasm in response to force transmissions establishing coordinated front-back cell polarities in migrating monolayers [56].

The emergence of middle range signals

The analysis of collective cell migration in various conditions has revealed the emergence of transient dynamical processes that occurred at intermediate length scales smaller than the overall monolayer but larger than single cells [30,50,61]. Measuring the spatial velocity correlation in expanding monolayers has further revealed the presence of large and transient vortices or polarized clusters of typical sizes around 150-200 microns (spanning 8~10 cells for MDCK cells [30]) deep inside the expanding monolayers, whose migration could be uncorrelated to the migrating direction of the leading edge. When plated on circular patterns, epithelial cells even exhibit large, correlated motions before entering a jammed phase [62,63]. Such kinematic analysis also revealed the presence of intrinsic oscillations over large distances across moving epithelial monolayers [20,63,64]. The presence of such structures and oscillations may be attributed to the presence of lamellipodia like structure, often termed as ‘cryptic lamellipodia’ [18] (**Fig. 2-b1**) in cells far behind the migrating edge, hints towards an active participation of bulk cells in driving the collective cell migration [20,65] (**Fig. 2-b1**).

The formation of digitations composed of multiple cells at the migrating edge of expanding monolayers is another example highlighting the emergence of physical coordinated entities [66] (**Fig. 2-b2**). To some extent, these fingers biomechanical organization recalls the one of clusters of border cells [67*] or cephalic neural crest cells [21]. Altogether, these studies rather promote transient mechanisms related to intermediate length scales that ensure the global coordination of migrating monolayers. This intermediate length scale also emerges from the analysis of mechanical forces. Indeed, force dipoles are not only present at the level of expanding monolayers but also at the scale of these finger-like structures. These fingers behave as independent mechanical entities made of opposing forces, with the leader cell (**Fig. 2-b4**) dragging its followers by the large force it develops, where followers are held together with the help of supracellular actin cables on the edge, making the force distribution reminiscent of the one observed at the single cell level (**Fig. 2-b2**). Another example comes from the analysis of cellular monolayers as active nematic systems [57*,68]. The isotropic stress at the sites of topological defects corresponding to a few cells exhibits a bipolar distribution including tensile and compressive stresses (**Fig. 2-b3**). The compressive stresses are particularly important since they have been shown to lead to cell extrusion. The view of a large-scale homogeneous tension is thus challenged by the emergence of intermediate length scales of compressive *versus* tensile stresses.

Highly coordinated polarity and short-range mechanical coupling

The presence of active lamellipodial protrusions within expanding monolayers, described above, is reminiscent of many *in vivo* situations [17**,39**,69] and further prompts question on the coexistence, switch, or interplay between multiple scales emerging mechanical signals down to single cell. Remarkably, a recent study brings a new perspective towards this question by describing without ambiguity the emergence of the coordinated migration on very large distance of groups of highly polarized single cells, using the same cellular model system (MDCK cells) than previously investigated to demonstrate long range mechanical coupling [47**]. The study implements a new model system where epithelial cells are confined on fibronectin-coated-annular rings (**Fig. 3**). Upon reaching confluence, epithelial cells begin to rotate persistently, at a constant speed in a definite direction. Interestingly, E-cadherin-based cell-cell contacts are

required to initiate the coordinated rotation, while they are dispensable after its establishment. Traction force measurement revealed consistent patterns of single cell level forces dipoles. This single cell mechanical behavior was associated to a coordinated polarization of all each cell, characterized by a gradient of activated Rac1 oriented in the direction of the collective migration resulting in each cell sending a cryptic lamellipodium underneath the one in front. Although the upstream polarity intercellular cue required for coordinated polarization is unknown, the situation is very similar to the coordinated single cell polarity observed *in vivo* for *Drosophila* follicular cells rotation [16]. Nevertheless, the short epithelial trains (3~5 cells) present in non-confluent rings exhibit a strong mechanical coupling as marked by the presence of single dipole of opposite forces located at both edges of the train (**Fig. 3a**), in line with long-range force transmission previously described [23]. Only upon completion of the ring, the cell trains reorganize their force dipoles pattern from long-range to single cell (**Fig. 3b,c, inset**), suggesting that the coordinated active migration of highly polarized single cells both *in vivo* and *in vitro* may be determined by the absence of leading edge in these closed systems. Alternatively, these observations may suggest that long-range force propagation that have been shown to emerge during collective migration may transition to coordinated migration of short-range mechanical units. A close observation of traction force data reported during epithelia expansion [23,29,53,70], reveals quite a number of cell-range and multicellular ranges force dipoles in the bulk of the tissue in favor of a certain plasticity of the mode of intercellular mechanical coupling that may characterize collective cell migration both *in vitro* and *in vivo*.

Future Perspectives

Collective cell behavior relies on adaptive processes that include the emergence of cellular front-back polarity at various length scales and the dynamical reshaping of cell-cell interactions. Collective migration thus exhibits multiple modes of mechanical coupling ranging from long-scale or middle-range to very short range at the single cell level. We learned also that in certain conditions actively migrating single cells coordinate to achieve very efficient and persistent collective migration. A common feature of these *in vitro* and *in vivo* situations is the absence of a free leading edge and future studies will allow to determine whether the absence of boundary is the determining parameter. Moreover, we learned of indices of a certain degree of inhomogeneous mechanocoupling between cells and of the presence of active migrating cells within migrating tissues that will need to be further investigated. Along this line, the mechanical plasticity of collective cell migration based on the modulation of cell-cell adhesion and contractility can be important in tissue fluidization leading for instance to cell shape changes and spontaneous motility of polarized cell clusters of various sizes [13*,19,71].

On the other hand, even though collective cell migration has been extensively studied over the last few years, the picture is far from being complete with *in vivo* models, mostly in developmental biology animal models, not accessible yet to the measurement of mechanical parameters and *in vitro* studies, performed on mammalian cells deeply lacking knowledge on molecular mechanisms governing planar polarity of the migrating cell collectives. Unfortunately, the cues identified thanks to genetic models, were not confirmed so far to be involved, thus further adapted screens will need to be designed to identify such cues.

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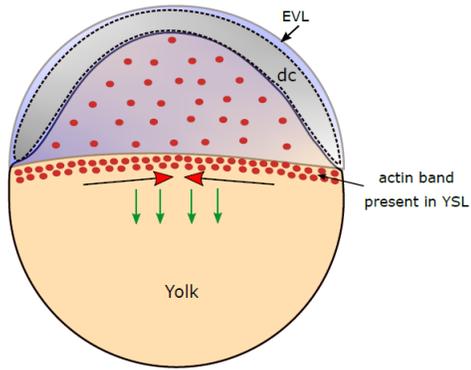
The authors declare no conflict of interest.

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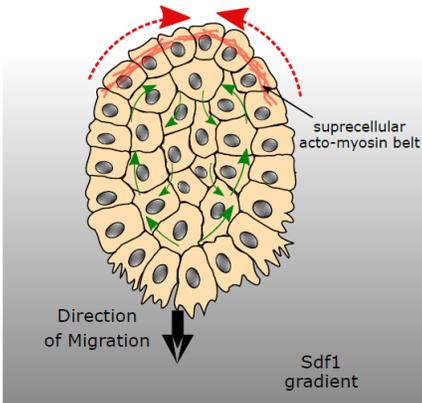
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Figure 1

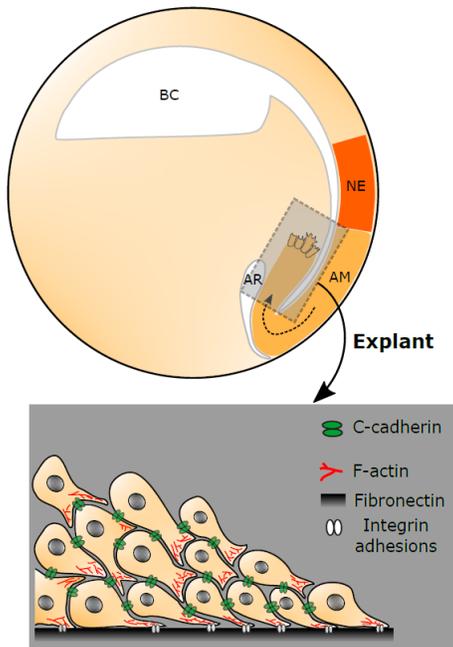
a) Zebrafish embryogenesis - epiboly



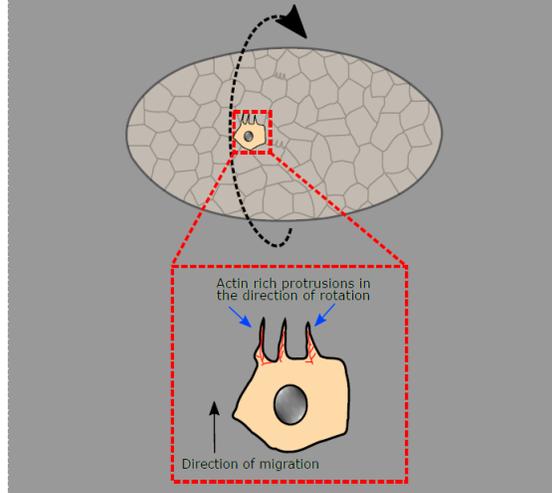
b) Neural-crest cell migration



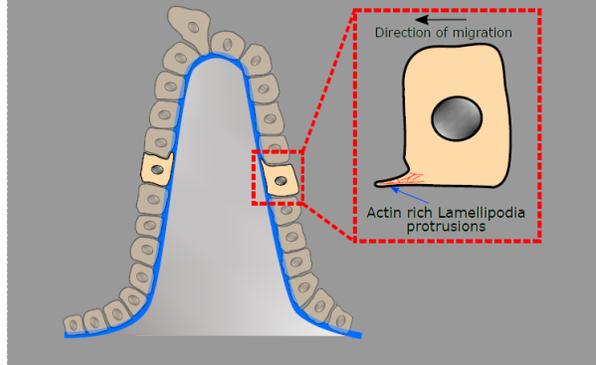
c) Xenopus Mesendoderm migration



d) Drosophila egg-chamber rotation



e) Epithelial cell turnover in intestinal villi



f) Zebrafish lateral line migration

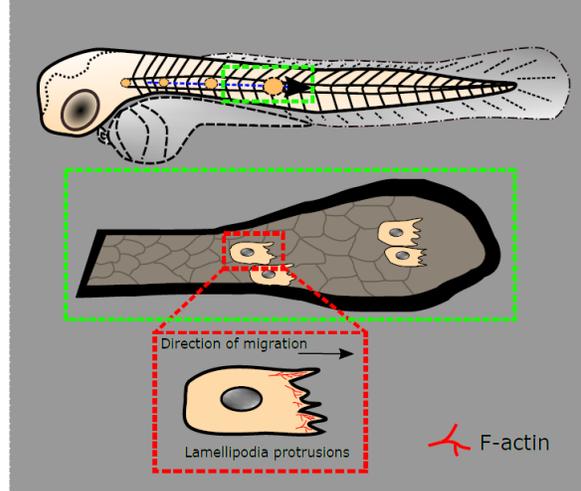


Figure 1: Collective cellular coordinations in *in vivo*; a) Pulling and spreading of Enveloping cell Layer (EVL) over yolk. Acto-myosin present within Yolk Syncytial Layer (YSL) at the interface of EVL generate a contractile force driving the collective migration of EVL [26]. **b)** Crest cell migration in *Xenopus* powered by active acto-myosin based contraction of rear cells [21]. **c)** Mesendoderm migration during *Xenopus* gastrulation driven by cells at the leading edge of Axial Mesendoderm (AM) (explant - inset), convergent extension of migrating AM results in similar extension in posterior Neural Ectoderm (NE), Archenteron (AR) and Blastocoel (BC) [11]. **d)** Rotating follicular cells in a *Drosophila* egg chamber with actin rich polarized single cell level protrusions (inset) [16]. **f)** Migrating single cell in the bulk of intestinal villi with its directed protrusion (inset) towards the top of the villi as marked by actin rich projections [17**]. **g)** Single cell-based polarity of cells in bulk as visualized by actin rich protrusions (inset) deep inside the migrating cluster of Zebrafish lateral line [39].

Figure 2

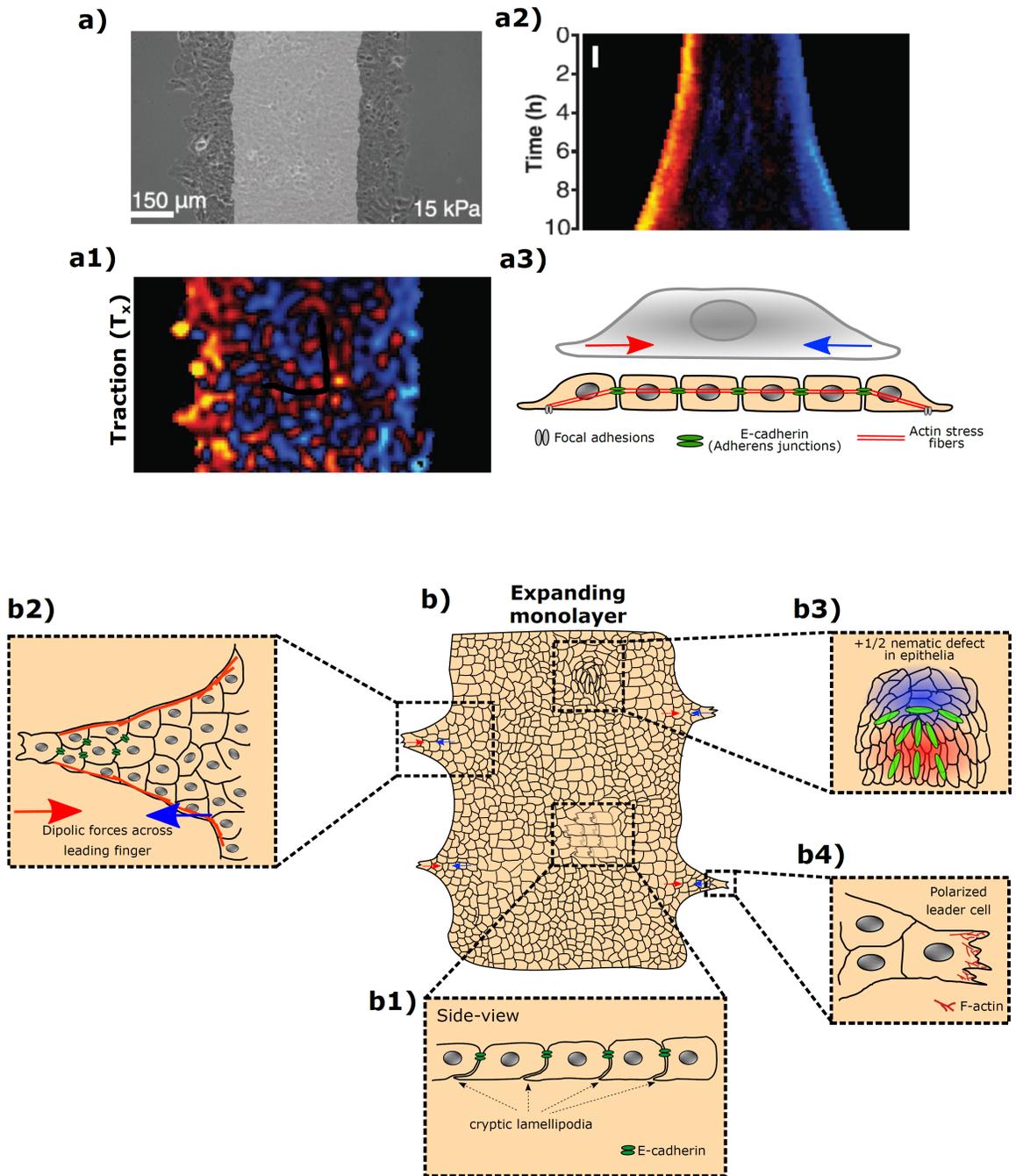


Figure 2: Long-range and Intermediate range coordination in epithelia; a,a1,a2) Expanding monolayer exhibiting large traction forces at both the ends (a1,a2) marking the presence of force dipoles [23]. **a3)** Large force dipoles across monolayer resembles the force dipoles of a single cell implicating a long-range cellular coupling in the entire monolayer. **b)** Expanding monolayer exhibiting the traction force dipoles representing the entire monolayer as a mechanical unit. **b1)** Polarized cells present inside the bulk extends cryptic lamellipodia [18]. **b2)** Finger projections at the edge of expanding monolayer act as sub-mechanical units with its down force dipoles

presents intermediate coordination within the expanding monolayer [66]. **b3)** Presence of tensile and compressive stresses across a nematic defect in the monolayer. Here the representative defect shown is +1/2 type, but -1/2 defects are also present in the monolayers. Red shade present compressive stress and Blue marks region with tensile stress [57*,68]. **b4)** Polarized leader cell at the migrating front of the monolayer with its large lamellipodia.

Figure 3

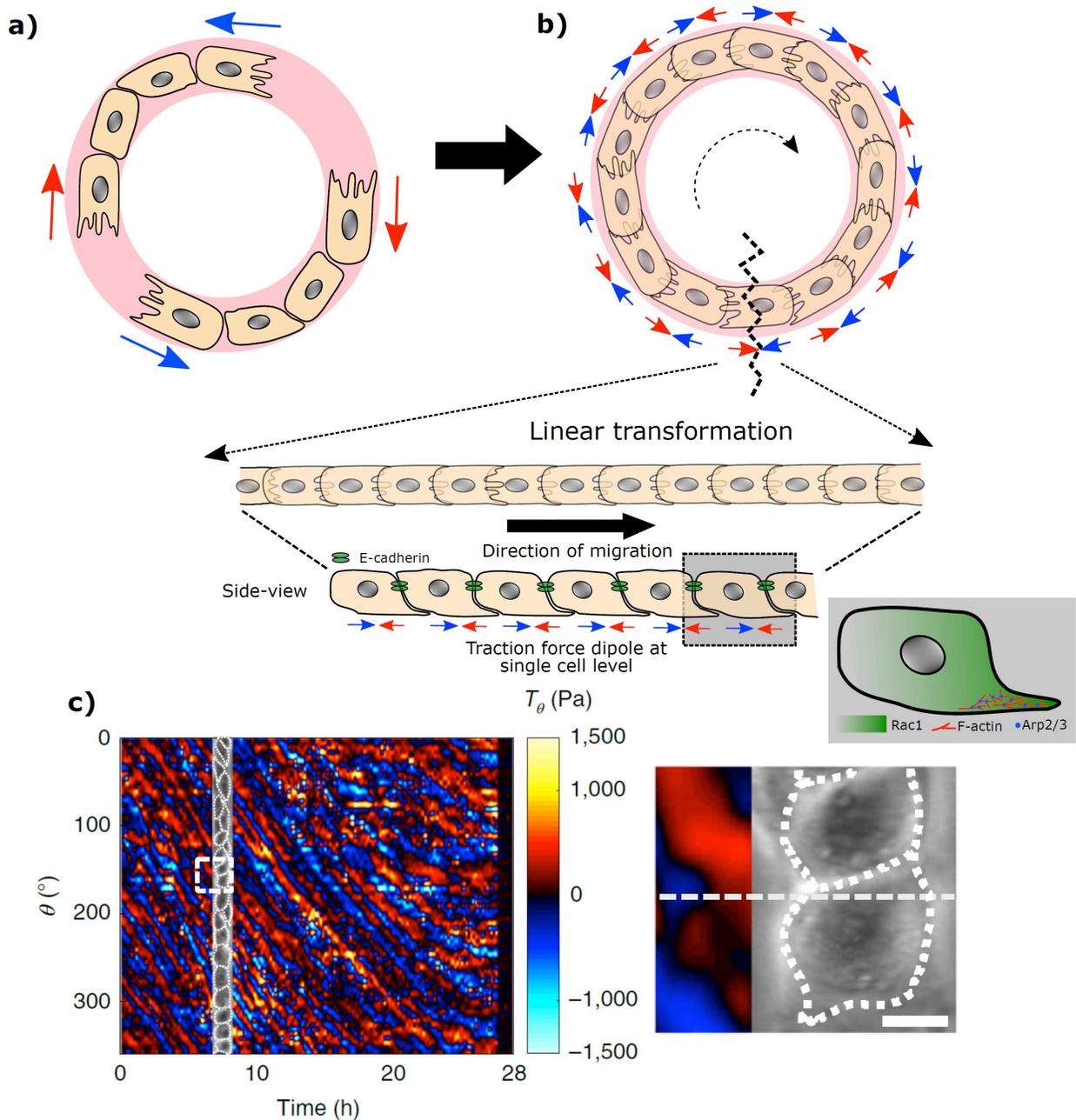


Figure 3: Mechanical plasticity of multiscale coupling and coordination in epithelia; a) Short 1-Dimensional epithelial trains in a non-confluent cell system geometrically confined on an annular ring-shaped fibronectin pattern (shaded pink). The small trains show strong inter-cellular mechanical coupling implicating multicellular force transmission as marked by the presence of large traction force dipole at the end of cell trains (marked by red-blue arrows) [47**]. **b)** Upon reaching confluency, the short trains merge into a continuous periodic train of epithelial cells that rotates persistently in a particular direction (clockwise here, marked by black dashed arrow in center). **(b-inset)** Single rotating cells establish strong front-rear polarity with a well-established Rac1 gradient and Arp2/3 based cryptic lamellipodia present underneath the cell in front (side-

view of linear transformation; black solid arrow shows direction of cell train migration). **c)** Large Traction force dipoles present initially at small train ends in non-confluent system (a) redistribute at the single cell level of the rotating train (**c-inset**) as seen in the spatiotemporal traction force kymograph of a linearly transformed cell train (also marked by red-blue arrows in **b** and side-view of linear transformation).

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