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Blanchard, G.B., Fletcher, A.G. orcid.org/0000-0003-0525-4336 and Schumacher, L.J. (2019) The devil is in the mesoscale: mechanical and behavioural heterogeneity in collective cell movement. Seminars in Cell & Developmental Biology, 93. pp. 46-54.

https://doi.org/10.1016/j.semcdb.2018.06.003

The devil is in the mesoscale: mechanical and behavioural heterogeneity in collective cell movement

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Abstract

Heterogeneity within cell populations can be an important aspect affecting their collective movement and tissue-mechanical properties, determining for example their effective viscoelasticity. Differences in cell-level properties and behaviour within a group of moving cells can give rise to unexpected and non-intuitive behaviours at the tissue level. Such emergent phenomena often manifest themselves through spatiotemporal patterns at an intermediate 'mesoscale' between cell and tissue scales, typically involving tens of cells. Focussing on the development of embryonic animal tissues, we review recent evidence for the importance of heterogeneity at the mesoscale for collective cell migration and convergence and extension movements. We further discuss approaches to incorporate heterogeneity into computational models to complement experimental investigations.

Keywords

Heterogeneity, mesoscale, tissue mechanics, collective cell migration, convergence and extension

Highlights

- Tissue morphogenesis requires tightly coordinated behaviours such as collective cell movements.
- Heterogeneity in individual cell behaviours can result in complex and counter-intuitive tissue-level behaviour.
- Multicellular 'mesoscale' structures can be a signature of such heterogeneity.
- Appropriate methods are needed to detect and quantify mesoscale features.
- Computational models can help probe the formation and role of mesoscale structures.

1. Introduction

The morphogenesis of embryonic tissues depends on coordinated behaviours of groups of cells. In animal development, such behaviours include the collective movement of cells relative to a substrate (collective cell migration) or to each other (for example, during convergent extension movements). These movements are controlled through differential gene expression and biochemical signalling and are effected through cell mechanics, with potential for feedback between the two [1,2]. Clarifying the mechanisms underlying collective cell movements would contribute to a better understanding of the causes of developmental defects and cancer, and suggest therapeutic strategies for cures and tissue regeneration. They could also lead to developing mobile artificial tissues [3].

A key question in the field of collective cell movements is how cell-level feedback orchestrates correct morphogenetic movement at the tissue scale. Central to this question is our ability to measure and understand the causes of heterogeneity (differences in the properties and/or behaviour of individual or sub-groups of cells), and the potential for complex or nonlinear relationships between cell and tissue behaviour. Until recently, our ability to quantify behaviour at both levels experimentally has been limited. However, imaging, storage, and analysis methods have now become sufficiently advanced to facilitate the collection of large datasets (now often measured in terabytes) in which quantification at multiple levels is possible [4–6]. We are thus now able to quantify heterogeneity in cell behaviour that leads to short-lived (minutes) or persistent spatio-temporal structures at the intermediate mesoscale (typically tens of cells) between cells and tissue. The formation of such mesoscale structures and their function for tissue morphogenesis form the focus of this review.

For the purposes of this review, we define heterogeneity to mean that cells in a population have heterogeneous behaviour or mechanical properties, including cells in the same population responding to different signals and/or behaving differently in response to the same signals (**Fig. 1**). The forms of mesoscale heterogeneity considered here can be intrinsic, due to gene expression differences, leading to mechanical heterogeneities, or due to biochemical or mechanical self-organisation [7,8] Alternatively, they can reflect environmental heterogeneity in local pre-patterns, such as variation in substrate mechanics, or heterogeneous responses to extrinsic forces or constraints (**Fig. 1**). We shall not consider other contexts in which the term may be used in the literature, for example apparent heterogeneity due to measurement error or stochasticity in gene expression [9].

Mesoscale heterogeneity remains poorly characterised in many cases [10], with quantification of morphogenetic processes restricted to averages at the cell and tissue or organ scale. Similarly, the results of computational models of tissue morphogenesis are also commonly presented as summary means, since quantified mesoscale biological heterogeneity is rarely available for comparison [11]. Yet, as discussed below, there is recent evidence for the importance of heterogeneity at the mesoscale for tissue morphogenesis, from leader/follower relationships in collective cell migration, to mesoscale mechanical structures including trans-tissue actomyosin cables and multicellular rosettes in embryonic epithelia.

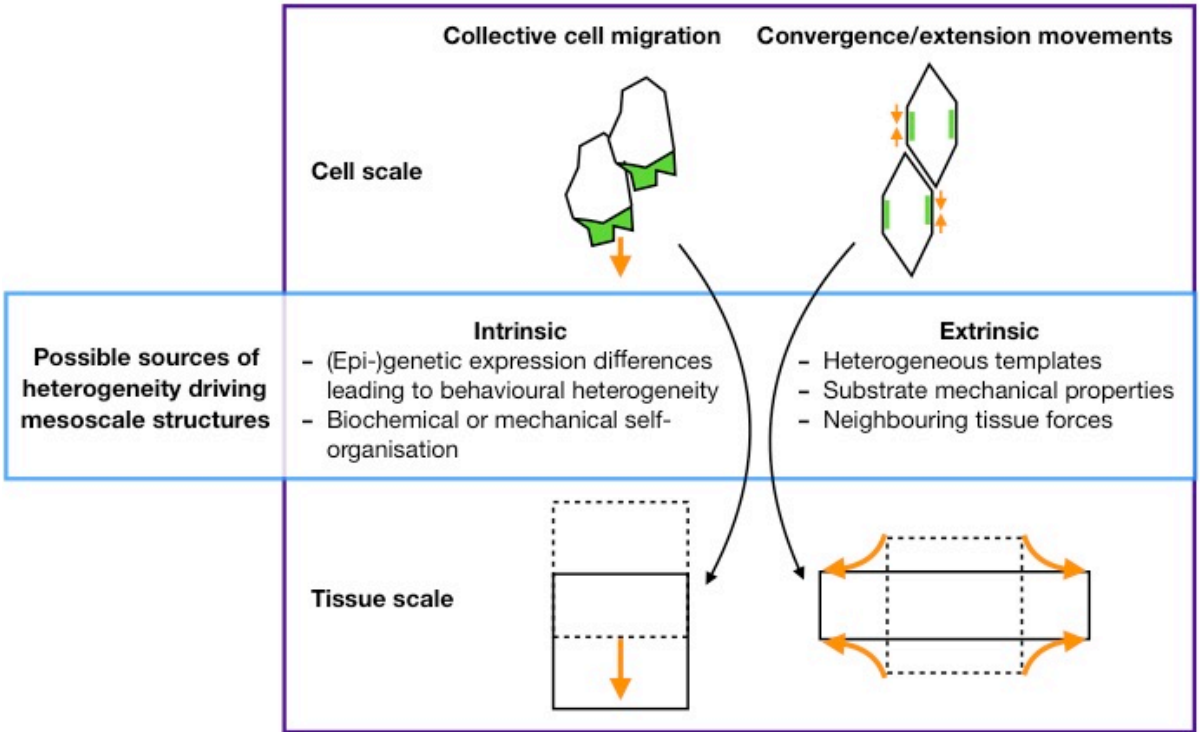

Figure 1. Mesoscale heterogeneity in collective cell movement. Heterogeneous structures at an intermediate 'mesoscale' of tens of cells can have intrinsic or extrinsic origins. The mapping from cell to tissue scale behaviour can be complex and nonlinear, depending on mechanism. Green denotes leading edges of migrating cells and actomyosin contractility in intercalating cells; orange arrows indicate cell or tissue movement.

Motivated by these recent findings, here we review evidence for heterogeneity at the spatial scale between cell and tissue, focusing in particular on collective cell migration and epithelial convergence and extension movements, and computational models thereof. We identify an urgent need for appropriate measurement methods for detecting and quantifying multicellular structures at the mesoscale, as well as a better theoretical understanding of self-organised mechanisms for the formation of mesoscale structures. Interdisciplinary approaches, combining quantitative biology, mechanics, computational modelling and new techniques from other disciplines are poised to address these gaps.

2. Collective cell migration

Collective cell migration is a key developmental process underlying tissue-scale remodelling in animals [12–14]. Simply put, it is the coordinated movement of groups of cells with respect to the surrounding tissue, and is often guided by short- or long-range signalling. Collective cell migration can occur in a range of shapes and forms [15]. It can involve the migration of epithelial sheets, in which cells remain tightly adherent and polarised along an apico-basal axis; or less tightly packed mesenchymal cells, exhibiting more frequent neighbour changes.

Collective cell migration in development often exhibits spatial and temporal heterogeneity at the scale of subgroups of cells. Heterogeneity in the migratory states of cells can affect the overall movement of the group. A commonly studied example is cells at the edge or front of

a group seemingly 'leading' migration [16]. In some cases, such as tracheal branching [17,18] and sprouting angiogenesis [19], leader cells actively migrate while follower cells undergo passive intercalation or proliferation; in other cases, such as neural crest migration [20], all cells undergo active migration, but leader cells may guide directionality or interact with the microenvironment differently from the rest of the group, e.g. reacting to chemotactic signals [21,22] or possibly by modifying the extracellular matrix.

Spatial heterogeneity in cell states, defined by their gene expression and migratory behaviour, can shape the cell population's interaction with chemoattractants and the microenvironment. In chick cranial neural crest cell migration, observed differences in cell morphologies and migratory behaviour were investigated in a series of interdisciplinary studies [20–23] and single-cell studies [21,24]. This revealed that spatial heterogeneities in gene expression exist within the migrating neural crest, both at locations moving with the group (e.g. its front, **Fig. 2A**), and at points remaining stationary relative to the substrate tissue (**Fig. 2B**). For example, cells at the front of the invading stream show higher expression of chemoattractant receptors [21] and extracellular matrix (ECM) related genes such as fibronectin [24]. Transplantation studies have further shown that the heterogeneity in gene expression is, at least in part, induced by microenvironmental signals such as the chemoattractant VEGF [22]. The leader-follower heterogeneity is thus dynamic, and the cells constituting the leading subpopulation can vary as they exchange positions [25].

Is this observed heterogeneity in gene expression functionally important for collective cell migration? While the gene expression profile of leading chick cranial neural crest cells has been characterised [21,24], not all of the measured differences in gene expression have been functionally tested. Hence, some functions of such leader-like cell states are yet to be discovered, such as whether they rely exclusively on contact-guidance and short-range signalling or also mark a trail in the microenvironment [26,27]. So far, knock-down and over-expression of key transcription factors has been shown to alter the neural crest migration pattern [21]. Crucially, when *HAND2*, a transcription factor more highly expressed in cells at the front of the migrating group, was overexpressed in cells throughout the population, the bulk of cells failed to migrate towards the target regions. This experimental outcome matched the prediction of the associated computational model if a large proportion of cells are forced into the leader state [21]. Thus, the heterogeneity in cell states appears to be necessary for the successful migration of the chick cranial neural crest cell population.

Although leader-follower heterogeneity in migratory behaviour has been observed in other neural crest systems, it has not been linked to differences in gene expression, and may work without these. In *Xenopus* and zebrafish neural crest, leader cells differ in their ability to generate protrusions, and this difference emerges through cell-cell interactions such as contact-inhibition of locomotion [28] and contact-dependent cell polarity [29] as well as autocrine and paracrine signalling [30,31]. Thus, self-organisation through cell-cell interactions can play an important role in establishing mesoscale heterogeneity, in addition to underlying differences in gene expression and interactions with the microenvironment. Indeed, all of these factors may be linked and influence each other to varying degrees, depending on the biological system in question.

In addition to the spatial heterogeneities outlined above, collective cell migration can also be affected by temporal heterogeneity of their environment. Recent discoveries have shown

that stiffening of the substrate tissue can both trigger [32] and inhibit [33] migration of neural crest cells in different tissues and at different times. This aspect is discussed in more detail by Barriga & Mayor in this special issue [34].

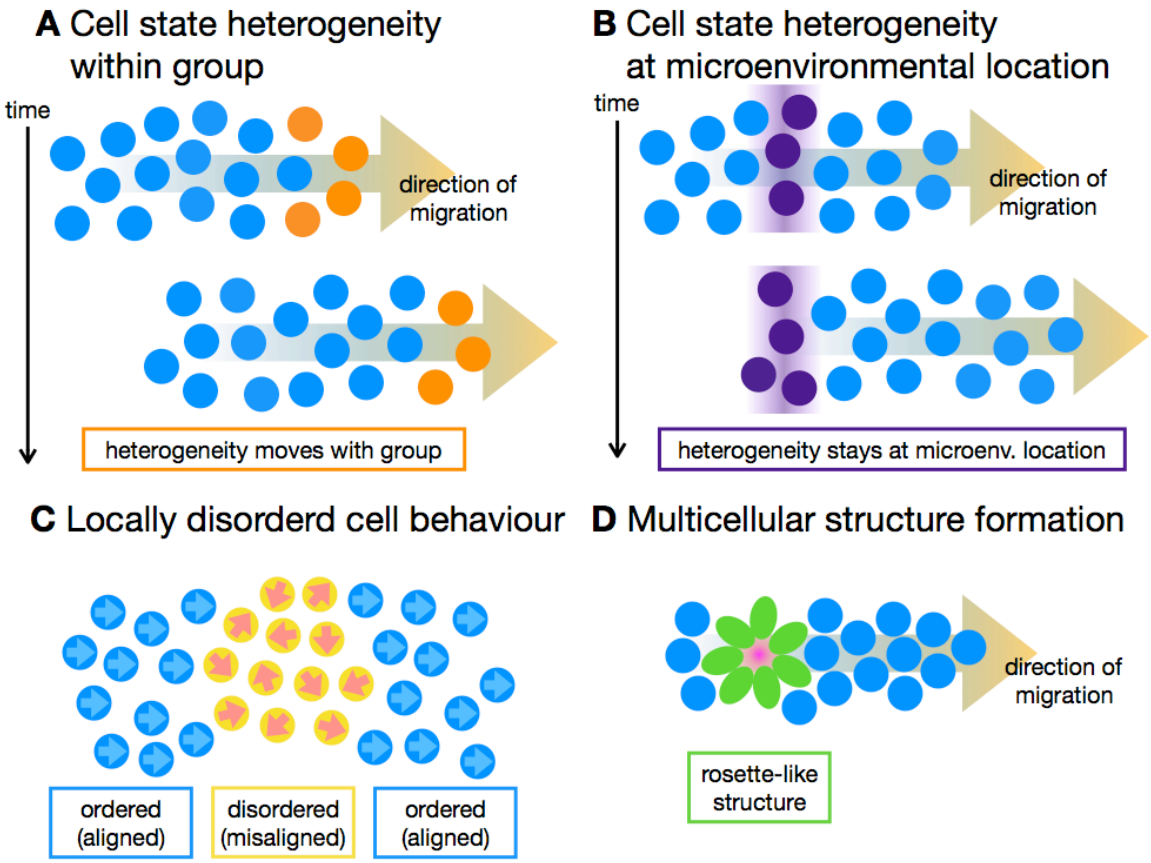

Figure 2. Types or sources of heterogeneity in collective cell migration. A,B) Cell state heterogeneity can be localised to a position within the group (e.g. the front), moving with the group as it migrates (A), or induced by a nearby microenvironmental location, moving through the group as it moves past (B). C) Disorder in the (coordination of) cell behaviour can be patterned at the mesoscale, thus affecting morphogenesis. D) Formation of mesoscale structures, such as multicellular rosettes, during collective migration can facilitate coordination through localised signalling, e.g. for the deposition of organ structures.

Patterned disorder of cell behaviours can drive tissue-scale morphogenesis. In zebrafish trunk elongation, cells' movements become locally disordered as they move through the posterior tailbud, showing little alignment with their neighbours, before becoming more ordered again (**Fig. 2C**) [35]. This modulation of disordered motion is achieved through changes in cell-cell coupling through down-regulation of cadherin 2 during epithelial-mesenchymal transition (EMT) [35]. Here, heterogeneity occurs at two scales: at the cell scale, each cell in the disordered region moves in a noisy trajectory; while at the mesoscale, there is heterogeneity between local alignment of cell motions, and lack thereof. This locally disordered cell motion was found to be required for fast and symmetric elongation: globally disordered motion (no alignment anywhere) slows elongation, and excessively ordered cell motion (alignment everywhere) creates asymmetric elongation [35]. The disorder in cell

activity, regulated at the level of mesoscale patterns, can thus be exploited to make morphogenesis more robust.

Heterogeneity of cell behaviours in a migrating group can result in the formation of mesoscale (multicellular) structures that are important for laying down tissue structure. In zebrafish, the lateral line primordium migrates along the side of the body [36], depositing mechanosensory organs. This is another system where leader-follower heterogeneity has been characterised, in which the leader cells primarily read out a chemokine gradient [37,38], and are required for successful migration. In addition, another form of heterogeneity has been characterised: as the cohesive group of cells migrates, multicellular rosette-like structures are created through the formation of apical adherens junctions [39]. These structures subsequently separate from the migrating group, forming the lateral line sensory organs. The formation of multicellular rosettes represents a mesoscale signature of heterogeneity, and here their function is to create a niche for local signalling [40], enabling cells to coordinate their behaviour at the mesoscale (**Fig. 2D**).

In vitro studies have played an important role in helping us to understand and characterise the mechanical forces at play in collective cell migration and the mesoscale patterns they create *in vivo* [41], such as differential RhoA activity in leading cells [42], "pluricellular acto-myosin cables" [42], and deformation-waves in boundary formation [43]. These have contributed to our understanding of the mechanics of collective cell migration under controlled conditions and can guide us to what patterns and structures to look for *in vivo* – for ultimately, we need to look to the growing embryo to determine what is and is not relevant to animal tissue development.

3. Mesoscale heterogeneities in epithelial cell movements

Mesenchymal collective cell migration, discussed above, is achieved by active movements of cells over a substrate, generally through focal adhesions to ECM. The distinction between cell migration (movement relative to a substrate) and intercalation (movement relative to neighbouring cells) can be somewhat blurred. For example, in convergence and extension movements in the zebrafish, cells on the far side of the yolk from the future embryonic midline migrate towards the midline, converging the tissue without extension, while more axial tissue converges and extends through cell intercalation [44]. In this section we will focus on tissues in which collective cell movement is driven purely by planar intercalation. In such cases, convergence and extension processes are driven by contractility within the tissue, often overlaid by extrinsic forces, and require low friction with the tissue's surroundings.

While the contractility that drives active cell rearrangement is generated at the subcellular level, for local tissue shape change to occur there must be multi-cellular coordination of contraction and of the relative movement of cells. This involves a minimum of four cells in a 'T1' transition (**Fig. 3A**). If the local contractile structure is larger than one cell junction, then more cells are involved, for example in multicellular rosettes (**Fig. 3B**) or other larger cable-like structures. The process of intercalation is therefore fundamentally a mesoscale behaviour, between cell and tissue scales [45,46].

Existing quantifications of the specific contribution of intercalation to tissue deformation (reviewed in [47]) have primarily focussed on average tissue strain rates, assessed for example along the orientation of embryonic or tissue axes [48–52], and local intercalation details are typically glossed over by averaging. However, local variation in rates of intercalation can be extremely rich in detail. In the *Drosophila* germband for example, intercalation rate varies considerably locally (**Fig. 3B**, upper panel), even though intercalation orientation is consistent across the tissue, leading to an irreversible extension of the anterior-posterior axis. This mesoscale heterogeneity in intercalation is accommodated locally by cell shape changes (**Fig. 3B**, lower panel) that are reversible and which average out over the course of axis extension; similar patterns can be seen for the zebrafish ectoderm in Fig. 4 in [45].

In theory, intercalation need not be heterogeneous, despite individual events being mesoscale. If the whole tissue exhibits the same intercalation behaviour, for example in response to a long-range orienting signal, one would consider the tissue to be homogeneous with respect to intercalation. In practice, the mechanism of intercalation varies between tissues and over time within tissues, as we will now discuss. Here, we classify intercalation behaviour in various tissues into three categories with seemingly distinct mesoscale patterns, hence likely different underlying mechanisms.

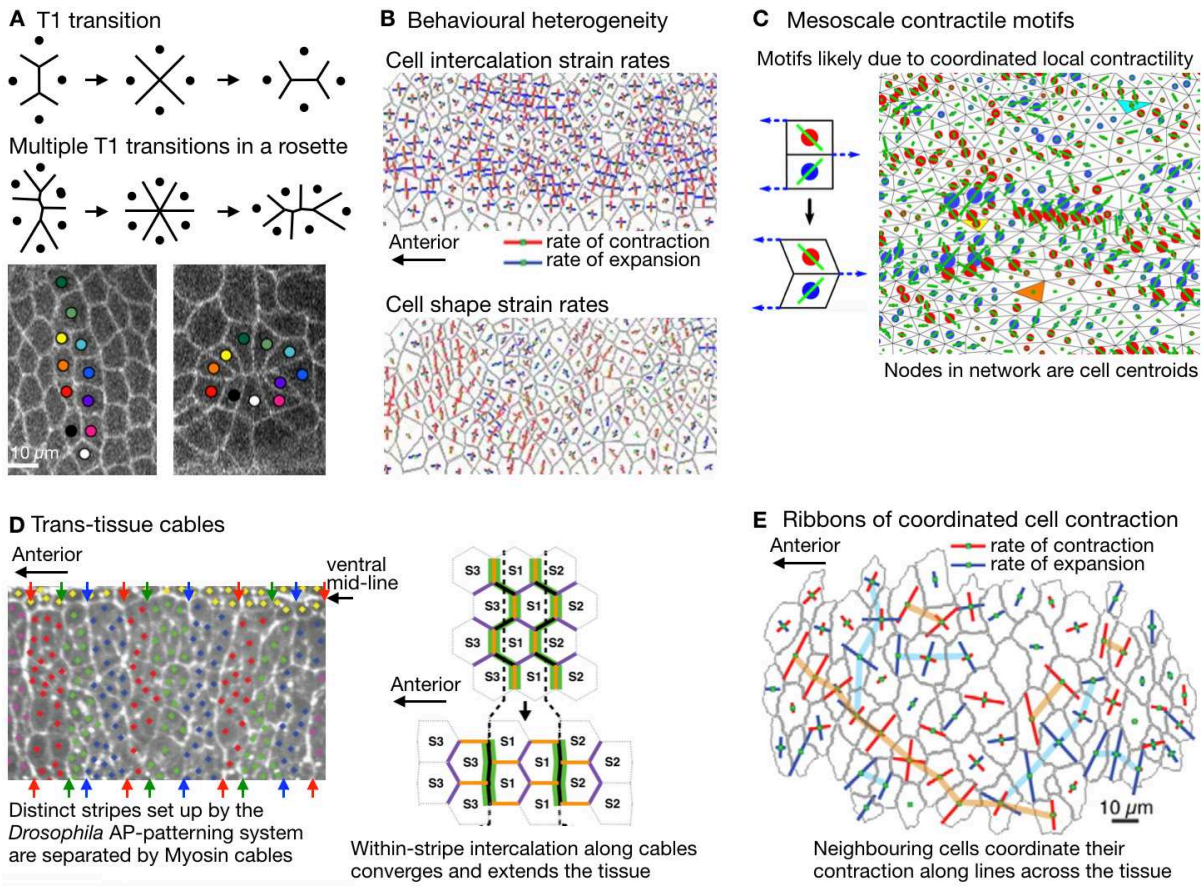

Figure 3. Epithelial mesoscale structures associated with intercalation. A) T1 transition and multicellular rosettes (dots are cell centroids, lines cell-cell junctions). Bottom panels show before and after multi-cellular rosette formation and resolution (from *Drosophila* germband [53]). B) Snapshot of spatio-temporal heterogeneity of intercalation and cell shape strain rates for the same time point, showing complementary patterns (from *Drosophila*

germband [45]). C) Local contractile structures are likely to underlie simple shear motifs in the *Drosophila* wing blade (from [52]). D) Trans-tissue cables specified by the anterior-posterior patterning system are the primary location of intercalation in *Drosophila* germband extension (from [54]). Left panel, junctional myosin II fluorescence with cell centroids colour-coded by within-parasegment stripe type (red, S1; green, S2; blue S3). Arrows show strongly myosin-enriched parasegment boundaries (red) and less strongly enriched within-parasegment stripe boundaries (green, blue). Right panel, schematic showing how each stripe starts one cell wide and doubles in width during germband extension, due to intercalation at myosin-enriched (green) stripe boundaries. E) Cells with uncorrelated pulsatile apico-medial myosin II foci nevertheless coordinate their deformations in mesoscale 'ribbons' in the *Drosophila* amnioserosa (from [55]).

The first type of intercalation behaviour is exemplified by the early phase of germband extension in *Drosophila*, where there is a strong correlation between the orientation of cell-cell junctions and their likelihood of undergoing a T1 transition [56]. Intercalation at this phase is an active local behaviour, as suggested by intercalating structures only involving four cells (**Fig. 3A**), and by myosin II enriched dorso-ventrally oriented junctions pulling connected vertices away from expected 120° angles [54,56]. Though it is unknown precisely what global orienting signal, downstream of AP-patterning genes, is responsible for these T1 transitions, this type of tissue would be considered homogeneous with respect to intercalation.

The second type of intercalation behaviour is a spontaneous and ephemeral mini-cable. Initially elongated in the orientation of tissue convergence, these are multi-cellular structures involving more than four cells and cables of enriched junctional myosin running through the middle. These are found in the chick mid-brain neural plate [57], during primitive streak formation in the chick [50] and in the *Drosophila* pupal wing [52] (**Fig. 3C**). The location of mini-cables is not known to be determined by any gene expression pattern in these tissues and they are transient structures. They are therefore likely to be self-organised structures with some mechanical [58] and/or biochemical feedback [Blanchard et al, Curr Opin Genes Dev, under revision] plausibly involved.

The third type of intercalation behaviour comprises longer-range cables that can be specified by patterned gene expression. Trans-tissue cables enriched in myosin II are seen after the initial phase of *Drosophila* germband extension (**Fig. 3D**) [54]. Cell rearrangements occur along these cables, with each new neighbour connection made along one side of rather than across the cable, with cell connections lost as cells lose contact with the cable and move perpendicularly away from it (**Fig. 3D**, right panel). The locations of these trans-tissue cables correlate with Toll-receptor expression patterns, that are specified (in some currently unknown way) by the *Drosophila* pair-rule genes [59]. Intercalation rosettes (**Fig. 3A**) may be some hybrid structure, with elements of spontaneous mechanical feedback [58] on top of AP-patterned cables in *Drosophila* germband extension [53]. It is less clear what mechanism causes rosettes in other tissues, for example in the mouse visceral endoderm [60,61].

The above examples show that cell intercalation can either be homogeneous or display interesting mesoscale structure, the latter being either spontaneously self-organised or specified by a gene expression pre-pattern. Perturbations to the planar polarisation of contractile myosin II, either directly through manipulating its kinases and phosphatases

[57,62–64], or indirectly through interfering with the AP-patterning system in *Drosophila* germband extension [48,65], lead to varying degrees of cell rearrangement gridlock. Cell intercalation heterogeneities are therefore indispensible to successful tissue convergence and extension movements.

Above we have focused on spatial heterogeneity, and in particular the presence and role of mesoscale mechanical structures such as cables and rosettes. Temporal mechanical heterogeneity has also been shown to be important in these processes. Myosin II-based contractility is known to be pulsatile in cells of various tissues in *Drosophila* [55,66–68] and in vertebrates [69]. Interestingly, myosin pulses in neighbouring cells are known to be largely independent of each other (though see [70]), driven instead by biochemical oscillators within each cell (reviewed in [Blanchard et al, Curr Opin Genes Dev, under revision]). However, there are interesting consequences for the coordination of stress and strain at the mesoscale. Quantification of mesoscale patterns of contractility have been presented, for example, in the *Drosophila* amnioserosa tissue, where cells have uncorrelated pulses of contractile myosin [71], but strain must be resolved between neighbours. This results in the tissue becoming locally organised into strings or ribbons of cells with parallel strain rates (**Fig. 3E**) [55].

Thus, while some mesoscale structures are specified by gene expression patterns, others appear to be ephemeral self-organised structures. Self-organisation may in some tissues depend on mechanical feedback. For example, tension- or stretch-dependent recruitment of myosin II [58,72,73] could locally induce transient mini-cables. Alternatively, structures could self-organise in response to a pull from a neighbouring tissue. During *Drosophila* germband extension, for example, the germband is first pulled from ventral by the gastrulating mesoderm and is then pulled towards the posterior by the invaginating posterior mid-gut [74,75]. Much work remains to be done to extract relevant descriptions of mesoscale heterogeneities in intercalation behaviour – their characteristic (possibly anisotropic) spatial extent and duration, and what feedback processes are involved.

4. Modelling and inference at the mesoscale

The findings summarised above suggest an urgent need to characterise the functional, biochemical and mechanical heterogeneity that arises at the mesoscale in embryonic tissues. When and how such heterogeneity emerges from earlier patterning events, how it affects morphogenetic deformations, and what its role is in the complex interplay between patterning and mechanics, remains unclear.

Alongside experimental studies, mathematical modelling offers a useful framework for disentangling the roles of mechanics and signalling in collective cell movements, and for exploring the possible roles of mechanical and behavioural heterogeneity in these processes. A variety of approaches have been developed to model how processes at the cell scale determine collective cell movement at the tissue scale. Such ‘cell-based models’ vary in complexity, from self-propelled particle models of mesenchymal cell migration [76] to vertex models of epithelia that approximate each cell geometrically by a polygon [77], and more detailed models that allow for arbitrary cell shapes [78].

Cell-based models are frequently motivated through their ability to incorporate cellular heterogeneity, though to date few examples exist where this potential has been fully leveraged in the context of development and morphogenesis. This is in contrast to other fields such as oncology, where mathematical models have provided an important tool with which to explore the role of spatial and temporal heterogeneity in collective invasion [79], the tissue microenvironment [80], and tumour evolution [79]. A complementary approach to simulating cell-based models is to derive effective rheological models. Such models mathematically describe the emergent mesoscale effects and are amenable to analytical investigation (review by [81]).

Self-propelled particle (SPP) models [82,83] are an attractive approach for modelling non-epithelial collective cell migration in two or three dimensions due to their simplicity and relative ease of implementing phenomenological interactions. In typical SPP models, each cell is a particle, with several factors influencing its direction of movement, such as alignment with the direction of movement of neighbouring cells, attraction or repulsion between neighbouring cells, and noise intrinsic to a cell's movement and/or its interactions with other cells (**Fig. 4A**). SPP models can serve as useful minimal models of groups of cells, where the arrangement of cells may be highly variable and the precise mechanism of interactions irrelevant or unknown. Such models have, for example, been used to help understand possible leader/follower dynamics in chick cranial neural crest cell migration, as discussed in Section 2.

The collective migration of groups of loosely adherent cells has also been modelled using the cellular Potts model, in which space is discretised into a regular lattice and each cell occupies a subset of lattice sites sharing the same identity or 'spin'. The spin of each lattice site is updated stochastically over discrete timesteps based on a phenomenological energy function, which includes contributions such as cell-cell adhesion, volume constraints and persistence of movement [84]. A recent example by Kabla [85] highlights the utility of such models in identifying minimal conditions for coordinated cell behaviours: numerical investigations revealed that collective cell migration could arise as long as polarized cell movement exhibited persistence and there was some form of mechanical coupling between cells. Extensions of this model have been used to study the invasive potential of heterogeneous tumours and their resulting mesoscale morphology [79]. These examples highlight how the SPP and cellular Potts models are particularly suited to the study of mesoscale heterogeneity in collective cell migration.

Another class of cell-based models, vertex models, are better suited to describing the behaviour of highly adherent epithelial sheets [77,86], although variants have been developed for more motile cell populations [87]. In vertex models, cells are represented by polygons, whose vertices are somewhat analogous to the particles of SPP models. The movement of each vertex is governed by a balance of forces, which can include contributions due to cortical tension, cell-cell adhesion and hydrostatic pressure (**Fig. 4B**).

In one recent example where cellular mechanical heterogeneity was found to be instrumental for correct morphogenesis, Tetley et al [54] incorporated differential junctional line tension between subgroups of cells in a vertex model of *Drosophila* germband extension (**Fig. 4B**). The inclusion of heterogeneous cell mechanical properties in such models has its roots in the study of cell sorting driven by differential adhesion [84], though the recent

emphasis has been on active contractility rather than passive sorting. This cell-level mechanical heterogeneity represents planar polarisation of myosin II, thought to emerge from a combinatorial code of Toll-like receptor expression across each parasegment [59], which drives axis extension while limiting cell mixing, as discussed in Section 3. This example illustrates how vertex models can be used to explore the mechanical consequences of mesoscale actomyosin cables in collective cell movements. An increasing recognition of the mechanical and structural complexity of tricellular junctions and their importance in regulating these processes [88], along with the possibility that the two sides of cell-cell junctions are able to behave differently [54,89], strongly suggest that a key challenge in refining such models is to progress beyond the simple vertex description and more fully describe the form and function of cell-cell junctions and vertices.

A more mechanically explicit description of how the expression and asymmetric localisation of myosin II and other effector proteins affect cell mechanical properties was provided by Lan et al [90]. These authors coupled a differential equation model of the temporal dynamics of Rho-kinase, myosin, and Bazooka at each cell junction to a vertex model of cell mechanics, allowing feedback between myosin II dissociation and junctional line tension. This model was used to help understand the interplay between planar cell polarity, anisotropic junctional contractility, and coordinated cell movements and shape changes in the context of *Drosophila* germband extension.

Where do existing cell-based models of epithelial tissues fall short? Recent experimental work demands further refinement of the mechanical assumptions made in such models, for example regarding the load-dependent stabilisation of junctional myosin II [91]. We also need better measurements and models to understand how mesoscale heterogeneities affect tissue-level mechanical properties such as viscoelasticity. While much theoretical and numerical work has been done to explore the tissue-level mechanical properties of homogeneous cell-based models [92], only very recently has the effect of heterogeneity, particularly at the mesoscale, begun to be explored. These advances, along with the extension of such models to more realistic tissue sizes, will facilitate the study of the emergence of mesoscale multicellular structures, such as transient or long-lived actomyosin cables that may be important for some morphogenetic movements, as discussed in Section 3.

A further challenge is to use models to help test whether heterogeneity is present and whether it is necessary for a given developmental process [83], especially when this is not evident in the data. This can take the form of parameter inference, i.e., determining different parameters for individual or sub-groups of cells, or model inference, i.e., comparing homogeneous and heterogeneous models in their ability to quantitatively reproduce the experimental data. For example, recent *in vitro* work has quantified mesoscale heterogeneity in cell monolayer displacements and found that, in this case, measurements could be recapitulated with models without explicit heterogeneities, such as leader cells or other patterns of differential cell motility [93]. Looking ahead, one fruitful strategy may be to distinguish functional heterogeneity, as discussed in this review, from measurement error and 'irrelevant' variability, which we want to avoid overfitting with models that allow for heterogeneity.

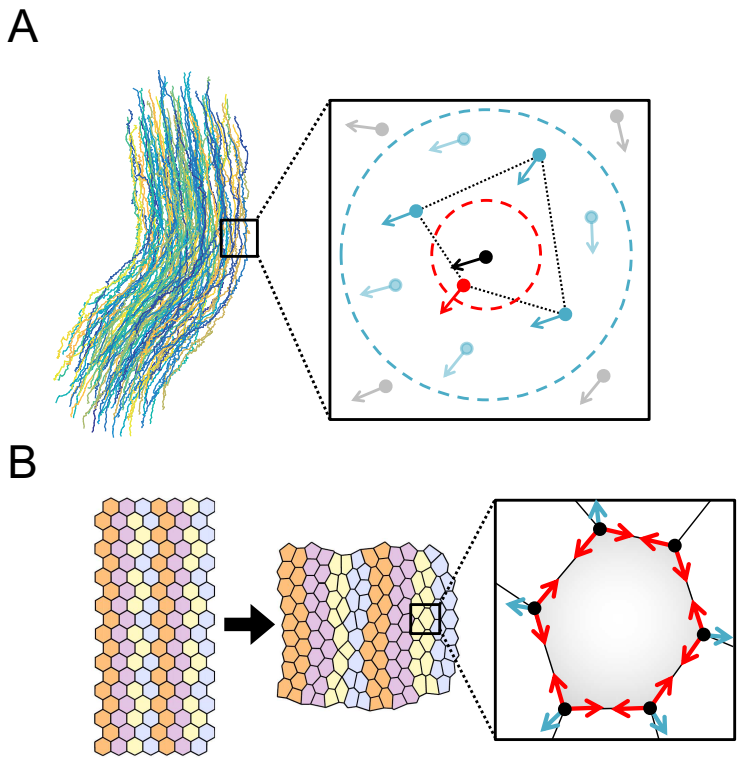

Figure 4. Modelling paradigms for collective cell movements. A) In self-propelled particle models, each cell is a particle, whose speed and/or direction of movement (arrows) is influenced by the presence of direction of movement of neighbouring cells. Such models are used to describe the collective migration of loosely adherent and highly motile cells, and aim to capture the general features of coordinated cell behaviours rather than precise mechanisms of interactions. B) Vertex models are a widely used example of cell-based models of tightly adherent epithelial tissues. In these models, each cell is approximated by a polygon, and the movement of each vertex (tricellular junction) is determined by a balance of forces including cortical contractility (red arrows) and hydrostatic pressure (grey arrows).

5. Perspectives

In this review, we have surveyed several aspects of heterogeneity in collectively moving cell populations, including mesenchymal migration and epithelial morphogenesis, and discussed computational methods suited to modelling the heterogeneities that give rise to observed mesoscale structures.

Characterising and quantifying heterogeneities remains a challenge, since the relevant scale is not known *a priori*, and because heterogeneities could occur over a range of scales. For example, while Turing and some other self-organised patterns have a characteristic length scale [8], others can be described by power-law size distributions [94], indicating structure at a range of scales. Nevertheless, experimental and theoretical advances are facilitating an increased understanding of the role of heterogeneity in collective cell movement. Promising experimental methods for disentangling intrinsic from extrinsic influences include the stretching of suspended cell monolayers *in vitro* [91] and the mesoscale control of cellular mechanical properties and interactions *in vivo* using optogenetics [95]. New analytical tools

could come from the theory of granular materials [96], percolation theory for modelling force chains, correlation functions for separating objects of different shape [97] and statistical identification of mesoscopic correlations.

We anticipate considerable interest in measuring, understanding and modelling mesoscale structures in the coming years, without which the mechanisms of collective cell behaviour will remain opaque.

Acknowledgements

The authors thank Philip Maini for insightful discussions, and Nicole Gorfinkiel, Elena Scarpa, and Alexander Nestor-Bergmann for critical readings of the manuscript. All authors contributed equally to this review. GBB acknowledges the Wellcome Trust Investigator Award 099234/Z/12/Z to Bénédicte Sanson. AGF is supported by a Vice-Chancellor's Fellowship from the University of Sheffield. LJS is supported by a Chancellor's Fellowship from the University of Edinburgh.

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