Collective Cell Migration in Development

7

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Abstract

Collective cell migration is a key process in developmental biology, facilitating the bulk movement of cells in the morphogenesis of animal tissues. Predictive understanding in this field remains challenging due to the complexity of many interacting cells, their signalling, and microenvironmental factors – all of which can give rise to non-intuitive emergent behaviours. In this chapter we discuss biological examples of collective cell migration from a range of model systems, developmental stages, and spatial scales: border cell migration and haemocyte dispersal in *Drosophila*, gastrulation, neural crest migration, lateral line formation in zebrafish, and branching morphogenesis; as well as examples of developmental defects and similarities to metastatic invasion in cancer. These examples will be used to illustrate principles that we propose to be important: heterogeneity of cell states, substrate-free migration, contact-inhibition of locomotion, confinement and repulsive cues, cell-induced (or self-generated) gradients, stochastic group decisions, tissue mechanics, and reprogramming of cell behaviours. Understanding how such principles play a common, overarching role across multiple biological systems may lead towards a more integrative understanding of the causes and function of collective cell migration in developmental biology, and to potential strategies for the repair of developmental defects, the prevention and control of cancer, and advances in tissue engineering.

Keywords

Cell migration · Developmental biology · Collective behaviour · Morphogenesis · Cell interactions

7.1 Introduction

In this chapter, we will introduce the reader to selected model systems for collective cell migration. We deliberately choose examples at various stages of animal development, in a range of organisms, spanning multiple time-scales and cell population sizes. In each case, we will motivate the use of the model system, and describe what is known about the mechanism of collective migration in that system. To conclude each section, we single out a principle of collective cell migration that a particular system provides insight to or is promising to do so. In many cases,

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a particular biological example could illustrate multiple principles, and our choice is not unique. Heterogeneity of cell states could be exemplified by neural crest as well as border cell migration, and contact-inhibition of locomotion by *Xenopus* neural crest as well as *Drosophila* haemocyte dispersal, to give just two examples. Our choice of model systems is by no means exhaustive. We have mainly focused on in vivo examples. In vitro systems have undoubtedly contributed to our understanding of the mechanisms of collective cell migration under controlled experimental conditions, and reviews can be found elsewhere (Ladoux and Mège 2017; Trepat and Sahai 2018). Here we hope to provide vignettes that together form more than the sum of parts and provide the reader with an emergent appreciation of collective cell migration in development.

7.2 Border Cell Migration

Drosophila border cell migration (Inaki et al. 2012) could be described as the hydrogen atom of collective cell migration. Consisting of a handful of cells, it serves as a minimal example in which the migration of the group differs from that of the individual, i.e., a "collection of cells moving together and affecting one another while doing so" (Rørth 2012, which forms our working definition of collective cell migration). And just as the study of the hydrogen atom, the simplest atom, has advanced theoretical understanding in atomic physics, we stand to learn from focussing on minimal systems of collective cell migration.

In the formation of the *Drosophila* egg, a cluster of about eight border cells migrates across the nurse cells from the anterior of the egg chamber to the oocyte on the posterior. This journey covers a distance of about 200 μm (Prasad et al. 2011), at about 0.5 μm/min (Montell et al. 2012). The cluster of cells goes on to form an egg shell structure that enables sperm entry, so their positioning at the oocyte is important for egg fertilization (Montell et al. 2012). The group consists of migrating border cells and non-migrating polar cells, and exhibits both leading/trailing polarity, meaning that the cells at the front and back of the group look and act differently, as well as inner/outer polarity, meaning that the polar and border cells are different (Montell et al. 2012). During migration, frequent reorientations of the cluster occur, changing which cell is in the leading position (Prasad and Montell 2007).

Border cell migration follows guidance signals present in their microenvironment, like many of the examples of collective cell migration that we will encounter in this chapter. These signals include the attractant Pvf1, which is read via the receptor tyrosine kinase PDGF/VEGF receptor. Leading and trailing cells show differences in the activity of this receptor (Janssens et al. 2010). This heterogeneity between cells in responding to guidance cues thus imparts directionality at the group level (Inaki et al. 2012), with the group being led by the cell with high activity of the receptor for the guidance cue. This shows that the cells are indeed acting as a *collective*, moving differently than each cell undergoing its own guided migration.

7.2.1 Heterogeneity of Cell States

Differences in cells' states, and thus their migratory behaviour, are an important aspect of cell populations that can affect their collective migration. *Drosophila* border cells provide a clear example of leader-follower heterogeneity between cells in a migrating group, a form of heterogeneity frequently studied in collective cell migration. The dynamic nature of the leader cell states with frequent changeover between cells highlights that this heterogeneity can emerge from interaction between cells and the environment, and need not be pre-specified. And even though the different cell states are not fixed, and may in some cases lie on a continuum (Schumacher 2019), they have turned out to be crucial to understanding the mechanism of group migration in this system. This is often misunderstood in debates about whether leader and follower cells exist – that is beside the point, the question is whether the concept provides a useful description. This is nicely summarised in a quote that bears repeating: "leader and follower cells should be considered as different cell states and not different cell types" (Rørth 2012).

7.3 Gastrulation

Gastrulation is the earliest and one of the most important examples of collective cell movement in the development of an animal embryo. In terms of relative cell numbers, it is also the largest remodelling of tissue structure – involving most cells at this stage of development to some degree. From an initially homogenous seeming mass of cells in the early embryo, an extensive rearrangement of cells establishes the three tissue layers ectoderm (giving rise to epidermis and nerves), mesoderm (turning into connective tissue, muscle, skeleton, etc.), and endoderm (giving rise to epithelial linings), broadly speaking the outer, middle, and inner tissue types. Gastrulation has thus been termed, and often quoted, as the "most important time in your life" (Wolpert 2008).

The details of the choreography of cell movements during gastrulation differ in their details in different species. The intricacies of these differences have been thoroughly documented elsewhere (see for example (Stern), or Keller (2005), and for a physics perspective, Forgacs and Newman 2005). Here we are restricting ourselves to avian and mouse gastrulation, and wish to only convey a general sense of the course of events: Mesoderm and endoderm precursors migrate inwards into the embryo, establishing the three tissue layers together with the ectoderm (Gilbert). The types of movement that cells undergo during gastrulation, and which global tissue deformations these produce, differ in different organisms. What they have in common is that the process of gastrulation turns an embryo from a relatively unstructured clump of cells into a layered tissue, with a head-to-tail body axis, and a distinct "outside" and "inside" that will go on to form the gut and respiratory system.

7.3.1 Collective Cell Migration Without a Substrate?

During gastrulation the different tissue layer precursors move with respect to each other, but in the absence of a substrate to move on or through. In other words, there does not seem to be an absolute coordinate system, unlike cases of cell migration usually considered. This is a vivid demonstration that collective cell migration can occur without an external substrate, but, in a sense, with other cells acting as the substrate. One could argue that this situation is not so different in cell migration within a tissue, but here the distinction between moving cells and resident tissue is usually clearer. This is reinforced through the presence of extracellular matrix (ECM), which provides a passive medium for cells to move through and interact with (though ECM may also play a role during early gastrulation, see Latimer and Jessen 2010). In gastrulation, one could distinguish between cells that are actively migrating or changing their shape, and those undergoing passive rearrangement in response to intercellular forces. Methods to quantify the contributions of cell shape changes and rearrangements are an active field of current research (Blanchard 2017; Dicko et al. 2017; Firmino et al. 2016; Lye et al. 2015; Rozbicki et al. 2015).

7.4 Haemocyte Dispersal

Haemocyte dispersal provides an example of multicellular migration that is not densely packed, but in which the migration is nonetheless influenced by the interactions of cells between each other. It thus provides an important sample on the spectrum of collective cell migration (Schumacher et al. 2016). *Drosophila* haemocytes spread out in the embryo during development, originating from the head mesoderm (Tepass et al. 1994). They are required for a functioning immune response and thus broadly similar to macrophages. *Drosophila* haemocytes migrate as single cells, but collectively need to arrange in an evenly spread, lattice-like pattern (Davis et al. 2012).

In vivo tracking of haemocyte movement (Davis et al. 2012) revealed that cells accelerate away from each other after encounters. These "collisions" take on the order of a few minutes,

during which the cells were observed to extend microtubule-driven protrusions towards each other, make contact, and then retract. This movement could be described by a persistent random walk, with an additional "contact-inhibition of locomotion" interaction that induces displacements away from nearby cells. By varying the strength of this interaction, Davis et al. (2012) could simulate the effect of haemocyte dispersal with and without repulsive collisions. Simulated dispersal without repulsive collisions, or with only a volume exclusion interaction, failed to produce the regular patterning of cell positions observed in the embryo. Further experiments with *diaphanous* mutants, showing uncoordinated cell-cell repulsion, confirmed that this led to break-down of ordered pattern formation in vivo (Davis et al. 2015).

7.4.1 Contact-Inhibition of Locomotion

Contact-inhibition of locomotion had, for a long time, been primarily observed in vitro (Abercrombie and Heaysman 1953, 1954; Loeb 1921). In recent years several studies have argued for its relevance for pattern formation in embryonal development. In the case of *Drosophila* haemocyte dispersal, this has been demonstrated through detailed in vivo imaging, genetic perturbation, and computational simulations. In *Xenopus* cephalic neural crest, in vivo studies (Carmona-Fontaine et al. 2008), aided by in vitro experiments and again by computational modeling, have also pointed to a role for contact-inhibition of locomotion, coupled with co-attraction, as a mechanism to promote collective cell migration. The importance of contact-inhibition of locomotion has been called into doubt in chick cranial neural crest (Genuth et al. 2018), so it remains unclear how relevant this mechanism is in the neural crest generally. One possibility is that interactions between cells lie on a continuum ranging from contact guidance and volume exclusion to the repulsive contact-inhibition of locomotion described above (Schumacher et al. 2016). Formulating integrative models that offer such unifying descriptions of the mechanisms of collective cell migration is a subject of future work (see also Sect. 7.5).

7.5 Neural Crest

The migration of the neural crest is one of the most striking and versatile examples of collective cell migration in developmental biology. Neural crest cells are a migratory cell population found in the vertebrate embryo that develops into a range of tissues throughout the body, such as peripheral nerves and smooth muscle, as well as contributing to many others, such as heart and bone (Kulesa et al. 2010; Le Douarin 2004). They originate from the dorsal neural tube, which develops into the brain and spinal cord, undergo EMT and migrate over distances of up to 1 mm through the mesoderm of the growing embryo, first lateral and then ventral. Neural crest in different organisms and different body parts exhibit a range of migration morphologies, and therefore offer a system to investigate how the common mechanisms may play a role in diverse biological settings. As such, they have become a popular model organism for long-range mesenchymal collective cell migration.

Developmental defects associated with failed or incomplete migration are known as neurocristopathies (Benish 1975) and include pigmentation defects, cleft lip, cleft palate, and incomplete innervation of the gut (Hirschsprung's disease) (Lake and Heuckeroth 2013). The invasive nature of their migration, and the fact that some cancers, such as neuroblastoma and melanoma, derive from the neural crest, have attracted attention to this system for the study of metastatic invasion. We will discuss these aspects further in Sects. 7.8 and 7.9.

Mechanisms of neural crest migration appear as diverse as the vertebrate organisms they have been studied in. The migrating neural crest forms discrete streams along the head-tail axis of the body (Kulesa and Gammill 2010). These streams are sculpted by a combination of inhibitory and

repulsive factors, as well as other tissue structures serving as barriers (e.g. the otic vesicle, which forms the inner ear). Common features exist across the different model systems (Cebra-Thomas et al. 2013; Krotoski et al. 1988; Löfberg et al. 1980; Nikitina et al. 2009; Reyes et al. 2010; Schilling and Kimmel 1994; Serbedzija et al. 1989, 1992), but with important differences between organisms as well as between different positions along the head-tail axis. Cells often follow guidance factors, such as VEGF in chick cranial migration (McLennan et al. 2010, 2015b) and SDF1 in Xenopus cephalic migration (Theveneau et al. 2010). Neural crest cells migrate towards target zones, such as the branchial arches, where they proliferate and differentiate (Ridenour et al. 2014), but also need to be distributed along the migratory route and can undergo secondary migration at later times, such as in the formation of vertebral sympathetic ganglia from trunk neural crest (Kasemeier-Kulesa et al. 2015). Interactions between cells are important for proper group migration (McKinney et al. 2011; Teddy and Kulesa 2004), including follow-the-leader migration in chick (McLennan et al. 2012, 2015a) and cell-cell attraction (Carmona-Fontaine et al. 2011) with contact-inhibition-of-locomotion in Xenopus (Carmona-Fontaine et al. 2008) (but not in chick, see Genuth et al. 2018). It remains unresolved whether the diversity of behaviours displayed by the large number of neural crest systems can be reconciled by a universal set of mechanisms.

7.5.1 Confinement and Repulsive Cues

Since the neural crest is such a diverse and popular model system for collective cell migration in development, it would be short-sighted to highlight just one principle as important. Nevertheless, in balance with the other sections of this chapter, let us highlight the remarkable organisation of neural crest cells migration in long streams (on the order of 1 mm). What generates the required cohesion and persistence is incompletely understood, but a few pieces of the puzzle have been uncovered. We already mentioned the role of inhibitory/repulsive cues (ephrins, semaphorins) to shape the cells delaminating from the neural tube into discrete streams (Kulesa and Gammill 2010). Recent studies have further suggested new mechanisms for confining cells through versican (in *Xenopus*, Szabó et al. 2016) and restricting their invasion through DAN (in chick, McLennan et al. 2017). In Xenopus cranial neural crest, recent work calls into question the importance of guidance cues in early stream formation, and instead proposes that these neural crest streams initially emerge from "on short-range repulsion and asymmetric attraction between neighboring tissues" (Szabó et al. 2019). In avian neural crest, and in collective cell migration more generally, repulsive cues likely remain an important tool for tissues to control and confine collective cell migration, and can be found in other systems, such as the zebrafish germline (Paksa et al. 2016).

7.6 Lateral Line Formation

The lateral line is a system of mechanosensory organs in aquatic vertebrates, and its development is commonly studied in zebrafish (Haas and Gilmour 2006). Its formation is an example of epithelial collective cell migration, in which a cohesive group of cells, about 100 μm in length, migrates over millimeters in the growing zebrafish embryo. Unlike most examples discussed in this chapter, the migration is effectively one-dimensional, offering a simplified perspective on directional symmetry breaking in a system of interacting cells.

The lateral line primordium (LLP) is a cohesive group of on the order of 100 cells that migrate collectively along the side of the zebrafish embryo and form multicellular structures in their wake that later make up the lateral line (Haas and Gilmour 2006). They migrate along a strip of chemoattractant Cxcl12/Sdf1. This ligand is not expressed in a gradient, however, it is only in interaction with the migrating group of cells

that directionality is established (Streichan et al. 2011). Leading cells at the front of the LLP read out the chemoattractant via the receptor Cxcr4, while trailing cells sequester the ligand via Cxcr7 to create a local gradient, and both are required for successful migration (Donà et al. 2013). As the LLP migrates, subgroups of cells organise into rosette-like structures via adherens junctions (Revenu et al. 2014). These multicellular structures have a luminal space at their core, which is thought to enable coordination of cells in the group via local signalling (Durdu et al. 2014). The rosettes split from the migrating group and stay behind to form the aforementioned sensory organs.

7.6.1 Cell-Induced or Self-Generated Gradients

An alternative to the migration along pre-established gradients of morphogens or chemoattractants is the dynamic creation and interpretation of local signalling gradients. In an otherwise uniform concentration of chemoattractant, groups of cells can locally create gradients by internalising or breaking down the signal in their vicinity. These self-generated or cell-induced gradients have been investigated in a number of systems, such as the neural crest (Kulesa et al. 2010; McLennan et al. 2012; Schumacher 2019) *Dictyostelium* (Tweedy et al. 2016), and melanoma cells (Muinonen-Martin et al. 2014), but in the context of development they are probably best understood in lateral line migration (Donà et al. 2013; Streichan et al. 2011). Collective migration in self-generated gradients is conceptually similar to aggregation with self-secreted attractive signals, which have been studied mathematically in some of the earliest models of chemotaxis (Keller and Segel 1970a,b). Cell-induced gradients may be an environment where leader-follower heterogeneity (see Sec. 7.2.1) is advantageous, depending on the kinetics of gradient formation, as been explored in recent theoretical studies (Hopkins and Camley 2019; Schumacher 2019).

7.7 Branching Morphogenesis

The tree-like structures produced by branching morphogenesis appear both beautifully complex, and also self-similar at multiple scales, or fractal-like (Iber and Menshykau 2013). This makes them potentially amenable to production through simple developmental programs, and thus branching morphogenesis has been of long-standing interest to developmental biologists and mathematical biologists (Iber and Menshykau 2013; Murray et al. 1983). Examples include lung (and trachea in insects), kidney, pancreas, blood vessels, prostate, salivary and mammary glands. It encompasses the growth of tree-like ductal networks, thus achieving a high surface area to exchange molecules, such as oxygen, or metabolic products, with the environment or other tissues. While much of the biological research in the past decades has focussed on the molecular (and also mechanical) control of branching and elongation, we want to consider it here as an example of collective cell behavior with an emergent, large-scale structure.

Branching and annihilating random walks (BARWs) have recently been put forward as a promising candidate for a unified theory of branching morphogenesis (Hannezo et al. 2017), explaining statistical patterns of the network structures in mouse mammary gland, kidney, and humane prostate. In branching random walks, ducts elongate and branch stochastically, while in this particular variant growth of tips is terminated when they contact existing ducts (in addition to branching there can also be budding from the side of existing ducts, which plays a role for example in early lung formation, see Iber and Menshykau 2013). A minimal BARW model was able to reproduce statistics such as the distribution of subtree sizes in several organs, with only experimentally determined parameters (Hannezo et al. 2017).

Within this general framework, the molecular control of branching and annihilation events may be tissue-specific: In mouse mammary gland, the tip termination can be induced by implanted sources of TGF-β1 (Hannezo et al. 2017), and

branching is promoted by FGF10 (Hannezo et al. 2017). In mouse kidney, the TGF-β-related BMP7 has been implicated in tip termination (Davies et al. 2014), while proliferation is driven by GDNF (Lambert et al. 2017).

While the BARW model is remarkably successful at reproducing global statistical features of the tree structures, small modifications have been necessary to match the detailed features of some particular tissues. For example, the relatively ordered three dimensional structure of kidney ducts was more faithfully reproduced by a BARW with additional self-repulsive interactions of the growing tips. Then again, a more complex model can always better describe existing data than a simpler one. The minimal BARW model is an attractive paradigm for branching morphogenesis precisely due to its simplicity.

7.7.1 Stochastic Group Decisions

The use of BARW models for branching morphogenesis nicely illustrates how seemingly complex and (statistically) stereotypic structures can form through stochastic "decisions". This occurs at two levels: the overall organ structure arises from the interplay of many stochastic branching events, and the individual branching event is itself a stochastic event in which many cells have to coordinate. The means by which a group of cells in an individual tip conduct a poll or otherwise decide whether to elongate, branch, or terminate, and do so in a seemingly stochastic manner, remain hitherto unresolved. This exemplifies a common challenge in the pursuit of quantitative understanding of collective cell movements, namely phenomena that occur at the mesoscale between the cell- and tissue-levels (Blanchard et al. 2018).

7.8 Developmental Defects

Developmental defects arise when developmental processes go awry. In the context of collective cell migration, this can occur when the migration is mistargeted, mistimed, or miscoordinated. Each of the sections in this chapter would deserve its own discussion of associated developmental defects, but here we will once more focus on the neural crest and the aforementioned neurocristopathies (Benish 1975) (developmental defects that are related to failures in neural crest cell migration). From the many neurocristopathies we pick an illustrative example from enteric neural crest migration.

In healthy embryonic development, enteric neural crest cells colonise the growing gut through migration and proliferation, and this is important for innervation of the gut, i.e., the development of the enteric nervous system. The neurocristopathy known as Hirschsprung's disease affects about 1 in 5000 live births (Lake and Heuckeroth 2013). It can have multiple causes, and one of its symptoms is failed innervation of parts of the gut, which can lead to life-threatening obstruction of the bowels (Lake and Heuckeroth 2013). Understanding the causes of failed enteric nervous system development in Hirschprung's disease could lead to therapeutic strategies to prevent or repair this developmental defect.

In experiments with chick enteric neural crest, it was found that stiffening of the gut mesenchyme through externally applied stretch prevents normal colonisation of the gut (Chevalier et al. 2016). This was further supported by experiments in which enteric neural crest were embedded in 3D gels, and found to invade less far into stiffer 3D gels than they migrated in more compliant ones (Chevalier et al. 2016). Stiffening of the tissue is part of the normal developmental process, but, as the described work shows, mistiming of this process, e.g. if the migration of neural crest cells is delayed, can lead to failed innervation. This suggests a possible cause for the symptoms of Hirschsprung's disease. Furthermore, it further highlights (one of several) challenges faced by potential treatments of failed gut colonisation: If migratory neural crest cells are transplanted later in development, they may not be able to migrate and colonise effectively in the developed, stiffened gut. On the other hand, it may point the way for future research how to modify the transplanted cells and/or the tissue microenvironment to enable repair of the developmental defect.

7.8.1 Cell Migration and Substrate Mechanics…It's Complicated

Changes in the mechanical properties of the ECM and surrounding tissues can affect the migration of cells in different ways. In the example above we have seen an inhibition of invasive migration through stiffening of the substrate tissue. In contrast to this, in *Xenopus* cephalic neural crest, stiffening of the mesoderm tissue in contact with the neural crest cells (Barriga et al. 2018) triggers the start of their migration.

The different effects of tissue stiffening in chick enteric and *Xenopus* cephalic neural crest could have a number of reasons. One difference is the magnitude of the elastic modulus of the tissue in question, which is an order of magnitude higher in the chick gut (Chevalier et al. 2016) than in the *Xenopus* head (Barriga et al. 2018). It is reasonable to consider that the relationship between cell migration and substrate stiffness is non-monotonic, so that some stiffness is needed for migration, but too stiff a substrate hinders invasion. There is another difference between these two experimental systems: the dimensionality of the problem is different. Enteric neural crest cells have to migrate through the tissue that is stiffening (a 3D substrate), whereas in the cephalic neural crest it is the adjacent mesenchyme that stiffens, which forms a 2D contact with the group of cells. Further research will be needed to disentangle the different effects of substrate mechanics on collective cell migration in two- and three-dimensional environments. To summarise, how changes in mechanics of a substrate tissue affect migration of a cell collective can depend on a number of factors, including timing, magnitude, and dimensionality.

7.9 Metastatic Invasion

Many aspects of collective cell migration in development are also found in metastatic invasion of cancer cells (Maguire et al. 2015). Metastases are the prime reason why cancers are lethal. As cancerous cells spread and nest secondary tumours throughout the body, our ability to surgically remove or target them with radiotherapy diminishes. Understanding what makes cancer cells migrate, and what enables them to invade healthy tissues, offers the prospect of controlling these misregulated collective cell behaviours. An introduction into mechanical factors of collective cancer cell migration and metastasis can be found in La Porta and Zapperi (2017, Chapter 7).

Cancer may, in part, be a reversion to embryonic development programs that suddenly become harmful when played out in the wrong time and place. The ability of embryonic cells to migrate and proliferate then becomes "a liability by contributing to tumorigenesis and metastasis" (Maguire et al. 2015). One example is, again, the neural crest, which as a lineage is the origin of melanoma, neuroblastoma and others cancers (Maguire et al. 2015), and whose invasive migration in embryonic development bears characteristics of metastatic cancer invasion. Coupled with the relative ease of transplantation in the chick embryo system, the neural crest and its embryonic microenvironment are a useful model system to study cancer metastasis in vivo (Bailey et al. 2012).

7.9.1 Reprogramming

When metastatic melanoma cells are transplanted into neural crest microenvironment, they migrate along normal neural crest migratory paths to target tissues without forming tumors (Hendrix et al. 2007; Kulesa et al. 2006). These results provide a tantalising possibility for anti-metastatic therapy: the embryonic microenvironmental signals could be exploited to reprogram cancer cells into a less harmful state (Kasemeier-Kulesa et al. 2018), and to directly constrain their invasive migration (McLennan et al. 2017). In addition to embryonic signals controlling collective cell migration providing preliminary candidates for cancer drugs, systems like the melanoma-chick transplant model also offer a cheap way to initially screen drugs for their anti-metastatic efficacy in vivo (Maguire et al. 2015).

7.10 Conclusion

In this chapter we have provided a brief overview of several examples of collective cell migration in development. The intent was to give the reader a broad selection of different biological systems, each with their own merits and fascinating problems to study. The selection has been necessarily biased towards the author's interest, and other reviews on the topic will provide different perspectives (Scarpa and Mayor 2016; Weijer 2009). An emerging trend that can be gleamed from the research discussed here, and hopefully throughout this book, is the integration of mathematical and computational models alongside experiments to interrogate the causes and function of cell migration with multidisciplinary approaches (Blanchard et al. 2018; Schumacher et al. 2016).

We have deliberately held back on quoting reams of results on molecular mechanisms, which can be found within the references cited in this chapter. Instead, we have opted to propose "principles", or, to phrase it more modestly, "themes for discussion" that link particular biological examples with concepts that may (or may not) help to move towards an overarching understanding of collective cell migration in developmental biology, and beyond. We hope that the reader will disagree with at least some of these, and that this disagreement may spark insightful discussion and further research.

References

Abercrombie M, Heaysman JE (1953) Observations on the social behaviour of cells in tissue culture: I. Speed of movement of chick heart fibroblasts in relation to their mutual contacts. Exp Cell Res 5:111–131. https://doi.org/10.1016/0014-4827(53)90098-6

Abercrombie M, Heaysman JE (1954) Observations on the social behaviour of cells in tissue culture: II. Monolayering of fibroblasts. Exp Cell Res 6:293–306. https://doi.org/10.1016/0014-4827(54)90176-7

Bailey CM, Morrison JA, Kulesa PM (2012) Melanoma revives an embryonic migration program to promote plasticity and invasion. Pigment Cell Melanoma Res 25:573–583. https://doi.org/10.1111/j.1755-148X.2011.01025.x

Barriga EH, Franze K, Charras G, Mayor R (2018) Tissue stiffening coordinates morphogenesis by triggering collective cell migration in vivo. Nature 554:523–527. https://doi.org/10.1038/nature25742

Benish BM (1975) The neurocristopathies: a unifying concept of disease arising in neural crest maldevelopment. Hum Pathol 6:128

Blanchard GB (2017) Taking the strain: quantifying the contributions of all cell behaviours to changes in epithelial shape. Philos Trans R Soc B 372:20150513

Blanchard GB, Fletcher AG, Schumacher LJ (2018) The devil is in the mesoscale: mechanical and behavioural heterogeneity in collective cell movement. Semin Cell Dev Biol. https://doi.org/10.1016/j.semcdb.2018.06.003

Carmona-Fontaine C, Matthews HK, Kuriyama S, Moreno M, Dunn GA, Parsons M, Stern CD, Mayor R (2008) Contact inhibition of locomotion in vivo controls neural crest directional migration. Nature 456:957–961. https://doi.org/10.1038/nature07441

Carmona-Fontaine C, Theveneau E, Tzekou A, Tada M, Woods M, Page KM, Parsons M, Lambris JD, Mayor R (2011) Complement fragment C3a controls mutual cell attraction during collective cell migration. Dev Cell 21:1026–1037. https://doi.org/10.1016/j.devcel.2011.10.012

Cebra-Thomas JA, Terrell A, Branyan K, Shah S, Rice R, Gyi L, Yin M, Hu Y, Mangat G, Simonet J, Betters E, Gilbert SF (2013) Late-emigrating trunk neural crest cells in turtle embryos generate an osteogenic ectomesenchyme in the plastron. Dev Dyn 242:1223–1235. https://doi.org/10.1002/dvdy.24018

Chevalier N, Gazquez E, Bidault L, Guilbert T, Vias C, Vian E, Watanabe Y, Muller L, Germain S, Bondurand N, Dufour S, Fleury V (2016) How tissue mechanical properties affect enteric neural crest cell migration. Sci Rep 6:20927. https://doi.org/10.1038/srep20927

Davies JA, Hohenstein P, Chang CH, Berry R (2014) A self-avoidance mechanism in patterning of the urinary collecting duct tree. BMC Dev Biol 14:1–12. https://doi.org/10.1186/s12861-014-0035-8

Davis JR, Huang C-Y, Zanet J, Harrison S, Rosten E, Cox S, Soong DY, Dunn GA, Stramer BM (2012) Emergence of embryonic pattern through contact inhibition of locomotion. Development 139:4555–4560. https://doi.org/10.1242/dev.082248

Davis JR, Luchici A, Mosis F, Thackery J, Salazar JA, Mao Y, Dunn GA, Betz T, Miodownik M, Stramer BM (2015) Inter-cellular forces orchestrate contact inhibition of locomotion. Cell 161:361–373. https://doi.org/10.1016/j.cell.2015.02.015

Dicko M, Saramito P, Blanchard GB, Lye CM, Sanson B, Étienne J (2017) Geometry can provide long-range mechanical guidance for embryogenesis. PLoS Comput Biol 13:1–30. https://doi.org/10.1371/journal.pcbi.1005443

Donà E, Barry JD, Valentin G, Quirin C, Khmelinskii A, Kunze A, Durdu S, Newton LR, Fernandez-Minan A, Huber W, Knop M, Gilmour D (2013) Directional

tissue migration through a self-generated chemokine gradient. Nature 503:285–289. https://doi.org/10.1038/nature12635
Durdu S, Iskar M, Revenu CC, Schieber N, Kunze A, Bork P, Schwab Y, Gilmour D (2014) Luminal signalling links cell communication to tissue architecture during organogenesis. Nature 515:120. https://doi.org/10.1038/nature13852
Firmino J, Rocancourt D, Saadaoui M, Moreau C, Gros J (2016) Cell division drives epithelial cell rearrangements during gastrulation in chick. Dev Cell 36:249–261. https://doi.org/10.1016/j.devcel.2016.01.007
Forgacs G, Newman SA (2005) Biological physics of the developing embryo. ISBN:9780511755576
Genuth MA, Allen CD, Mikawa T, Weiner OD (2018) Chick cranial neural crest cells use progressive polarity refinement, not contact inhibition of locomotion, to guide their migration. Dev Biol. https://doi.org/10.1016/j.ydbio.2018.02.016
Gilbert SF, Barresi MJF (2017) Developmental biology. ISBN: 9781605357386
Haas P, Gilmour D (2006) Chemokine signaling mediates self-organizing tissue migration in the Zebrafish lateral line. Dev Cell 10:673–680. https://doi.org/10.1016/j.devcel.2006.02.019
Hannezo E, Scheele CL, Moad M, Drogo N, Heer R, Sampogna RV, van Rheenen J, Simons BD (2017) A unifying theory of branching morphogenesis. Cell 171:242–255.e27. https://doi.org/10.1016/j.cell.2017.08.026
Hendrix MJC, Seftor EA, Seftor REB, Kasemeier-Kulesa JC, Kulesa PM, Postovit L-M (2007) Reprogramming metastatic tumour cells with embryonic microenvironments. Nat Rev Cancer 7:246–255. https://doi.org/10.1038/nrc2108
Hopkins A, Camley B (2019) Leader cells in collective chemotaxis: optimality and tradeoffs. https://doi.org/10.1101/642157
Iber D, Menshykau D (2013) The control of branching morphogenesis. Open Biol. 3(9). https://doi.org/10.1098/rsob.130088
Inaki M, Vishnu S, Cliffe A, Rørth P (2012) Effective guidance of collective migration based on differences in cell states. Proc Nat Acad Sci 109:2027–2032. https://doi.org/10.1073/pnas.1115260109
Janssens K, Sung H-H, Rørth P (2010) Direct detection of guidance receptor activity during border cell migration. Proc Nat Acad Sci 107:7323–7328. https://doi.org/10.1073/pnas.0915075107
Kasemeier-Kulesa JC, Morrison JA, Lefcort F, Kulesa PM (2015) TrkB/BDNF signalling patterns the sympathetic nervous system. Nat Commun 6:8281. https://doi.org/10.1038/ncomms9281
Kasemeier-Kulesa JC, Romine MH, Morrison JA, Bailey CM, Welch DR, Kulesa PM (2018) NGF reprograms metastatic melanoma to a bipotent glial-melanocyte neural crest-like precursor. Biol Open 7. https://doi.org/10.1242/bio.030817
Keller R (2005) Cell migration during gastrulation. Curr Opin Cell Biol 17:533–541. https://doi.org/10.1016/j.ceb.2005.08.006
Keller EF, Segel LA (1970a) Conflict between positive and negative feedback as an explanation for the initiation of aggregation in Slime Mould Amoebae. Nature 227:1365–1366. https://doi.org/10.1038/2271365a0
Keller EF, Segel LA (1970b) Initiation of slime mold aggregation viewed as an instability. J Theor Biol 26:399–415. https://doi.org/10.1016/0022-5193(70)90092-5
Krotoski DM, Fraser SE, Bronner-Fraser M (1988) Mapping of neural crest pathways in Xenopus laevis using inter- and intra-specific cell markers. Dev Biol 127:119–132. https://doi.org/10.1016/0012-1606(88)90194-7
Kulesa PM, Gammill LS (2010) Neural crest migration: patterns, phases and signals. Dev Biol 344:566–568. https://doi.org/10.1016/j.ydbio.2010.05.005
Kulesa PM, Kasemeier-Kulesa JC, Teddy JM, Margaryan NV, Seftor EA, Seftor REB, Hendrix MJC (2006) Reprogramming metastatic melanoma cells to assume a neural crest cell-like phenotype in an embryonic microenvironment. Proc Nat Acad Sci 103:3752–3757. https://doi.org/10.1073/pnas.0506977103
Kulesa PM, Bailey CM, Kasemeier-Kulesa JC, McLennan R (2010) Cranial neural crest migration: new rules for an old road. Dev Biol 344:543–554. https://doi.org/10.1016/j.ydbio.2010.04.010
La Porta CAM, Zapperi S (2017) The physics of cancer. ISBN:9781316271759
Ladoux B, Mège RM (2017) Mechanobiology of collective cell behaviours. Nat Rev Mol Cell Biol 18:743–757. https://doi.org/10.1038/nrm.2017.98
Lake JI, Heuckeroth RO (2013) Enteric nervous system development: migration, differentiation, and disease. Am J Physiol Gastrointest Liver Physiol 305:G1–24. https://doi.org/10.1152/ajpgi.00452.2012
Lambert B, Maclean AL, Fletcher AG, Coombes AN, Little MH, Byrne HM, Combes AN, Little MH, Byrne HM (2017) Bayesian inference of agent-based models: a tool for studying kidney branching morphogenesis. J Math Biol 0–27. https://doi.org/10.1007/s00285-018-1208-z
Latimer A, Jessen JR (2010) Extracellular matrix assembly and organization during zebrafish gastrulation. Matrix Biol 29:89–96. https://doi.org/10.1016/j.matbio.2009.10.002
Le Douarin NM (2004) Neural crest cell plasticity and its limits. Development 131:4637–4650. https://doi.org/10.1242/dev.01350
Loeb L (1921) Amoeboid movement, tissue formation and consistency of protoplasm. Am J Physiol 56:140–167. https://doi.org/10.1152/ajplegacy.1921.56.1.140
Löfberg J, Ahlfors K, Fällström C (1980) Neural crest cell migration in relation to extracellular matrix organization in the embryonic axolotl trunk. Dev Biol 75:148–167. https://doi.org/10.1016/0012-1606(80)90151-7
Lye CM, Blanchard GB, Naylor HW, Muresan L, Huisken J, Adams RJ, Sanson B (2015) Mechanical coupling between endoderm invagination and axis extension in Drosophila. PLoS Biol 13:e1002292
Maguire LH, Thomas AR, Goldstein AM (2015) Tumors of the neural crest: common themes in development

and cancer. Dev Dyn 244:311–322. https://doi.org/10.1002/dvdy.24226

McKinney MC, Stark DA, Teddy JM, Kulesa PM (2011) Neural crest cell communication involves an exchange of cytoplasmic material through cellular bridges revealed by photoconversion of KikGR. Dev Dyn 240:1391–1401. https://doi.org/10.1002/dvdy.22612

McLennan R, Teddy JM, Kasemeier-Kulesa JC, Romine MH, Kulesa PM (2010) Vascular endothelial growth factor (VEGF) regulates cranial neural crest migration in vivo. Dev Biol 339:114–125. https://doi.org/10.1016/j.ydbio.2009.12.022

McLennan R, Dyson L, Prather KW, Morrison JA, Baker RE, Maini PK, Kulesa PM (2012) Multiscale mechanisms of cell migration during development: theory and experiment. Development 139:2935–2944. https://doi.org/10.1242/dev.081471

McLennan R, Schumacher LJ, Morrison JA, Teddy JM, Ridenour DA, Box AC, Semerad CL, Li H, McDowell W, Kay D, Maini PK, Baker RE, Kulesa PM (2015a) Neural crest migration is driven by a few trailblazer cells with a unique molecular signature narrowly confined to the invasive front. Development 142:2014–2025. https://doi.org/10.1242/dev.117507

McLennan R, Schumacher LJ, Morrison JA, Teddy JM, Ridenour DA, Box AC, Semerad CL, Li H, McDowell W, Kay D, Maini PK, Baker RE, Kulesa PM (2015b) VEGF signals induce trailblazer cell identity that drives neural crest migration. Dev Biol 407:12–25. https://doi.org/10.1016/j.ydbio.2015.08.011

McLennan R, Bailey CM, Schumacher LJ, Teddy JM, Morrison JA, Kasemeier-Kulesa JC, Wolfe LA, Gogol MM, Baker RE, Maini PK, Kulesa PM (2017) DAN (NBL1) promotes collective neural crest migration by restraining uncontrolled invasion. J Cell Biol 216:3339–3354. https://doi.org/10.1083/jcb.201612169

Montell DJ, Yoon WH, Starz-Gaiano M (2012) Group choreography: mechanisms orchestrating the collective movement of border cells. Nat Rev Mol Cell Biol 13:631–645. https://doi.org/10.1038/nrm3433

Muinonen-Martin AJ, Susanto O, Zhang Q, Smethurst E, Faller WJ, Veltman DM, Kalna G, Lindsay C, Bennett DC, Sansom OJ, Herd R, Jones R, Machesky LM, Wakelam MJO, Knecht DA, Insall RH (2014) Melanoma cells break down LPA to establish local gradients that drive chemotactic dispersal. PLOS Biol 12:e1001966. https://doi.org/10.1371/journal.pbio.1001966

Murray JD, Oster GF, Harris AK (1983) A mechanical model for mesenchymal morphogenesis. J Math Biol 17:125–129. https://doi.org/10.1007/BF00276117

Nikitina N, Bronner-Fraser M, Sauka-Spengler T (2009) DiI cell labeling in lamprey embryos. Cold Spring Harb Protoc 4:4–6. https://doi.org/10.1101/pdb.prot5124

Paksa A, Bandemer J, Hoeckendorf B, Razin N, Tarbashevich K, Minina S, Meyen D, Biundo A, Leidel SA, Peyrieras N, Gov NS, Keller PJ, Raz E (2016) Repulsive cues combined with physical barriers and cell-cell adhesion determine progenitor cell positioning during organogenesis. Nat Commun 7:1–14. https://doi.org/10.1038/ncomms11288

Prasad M, Montell DJ (2007) Cellular and molecular mechanisms of border cell migration analyzed using time-lapse live-cell imaging. Dev Cell 12:997–1005. https://doi.org/10.1016/j.devcel.2007.03.021

Prasad M, Wang X, He L, Montell DJ (2011) Border cell migration: a model system for live imaging and genetic analysis of collective cell movement. Methods in molecular biology, vol 769. Humana Press, Totowa, pp 277–286. ISBN:978-1-61779-206-9

Revenu C, Streichan SJ, Donà E, Lecaudey V, Hufnagel L, Gilmour D (2014) Quantitative cell polarity imaging defines leader-to-follower transitions during collective migration and the key role of microtubule-dependent adherens junction formation. Development 141:1282–1291. https://doi.org/10.1242/dev.101675

Reyes M, Zandberg K, Desmawati I, de Bellard ME (2010) Emergence and migration of trunk neural crest cells in a snake, the California Kingsnake (Lampropeltis getula californiae). BMC Dev Biol 10:52. https://doi.org/10.1186/1471-213X-10-52

Ridenour DA, McLennan R, Teddy JM, Semerad CL, Haug JS, Kulesa PM (2014) The neural crest cell cycle is related to phases of migration in the head. Development 141:1095–1103. https://doi.org/10.1242/dev.098855

Rørth P (2012) Fellow travellers: emergent properties of collective cell migration. EMBO Rep 13:984–991. https://doi.org/10.1038/embor.2012.149

Rozbicki E, Chuai M, Karjalainen AI, Song F, Sang HM, Martin R, Knölker H-JJ, MacDonald MP, Weijer CJ (2015) Myosin-II-mediated cell shape changes and cell intercalation contribute to primitive streak formation. Nat Cell Biol 17:397–408. https://doi.org/10.1038/ncb3138

Scarpa E, Mayor R (2016) Collective cell migration in development. J Cell Biol 212:143–155. https://doi.org/10.1083/jcb.201508047

Schilling TF, Kimmel CB (1994) Segment and cell type lineage restrictions during pharyngeal arch development in the zebrafish embryo. Development 120:483–494

Schumacher LJ (2019) Neural crest migration with continuous cell states. J Theor Biol. https://doi.org/10.1016/j.jtbi.2019.01.029

Schumacher LJ, Kulesa PM, McLennan R, Baker RE, Maini PK (2016) Multidisciplinary approaches to understanding collective cell migration in developmental biology. Open Biol 6:160056. https://doi.org/10.1098/rsob.160056

Serbedzija GN, Bronner-Fraser M, Fraser SE (1989) A vital dye analysis of the timing and pathways of avian trunk neural crest cell migration. Development 106:809–816

Serbedzija GN, Fraser S, Bronner-Fraser M (1992) Vital dye analysis of cranial neural crest cell migration in the mouse embryo. Development 116:297–307

Stern CD Gastrulation: from cells to embryo. ISBN:978-087969707-5

Streichan SJ, Valentin G, Gilmour D, Hufnagel L (2011) Collective cell migration guided by dynamically maintained gradients. Phys Biol 8:045004. https://doi.org/10.1088/1478-3975/8/4/045004

Szabó A, Melchionda M, Nastasi G, Woods ML, Campo S, Perris R, Mayor R (2016) In vivo confinement promotes collective migration of neural crest cells. J Cell Biol jcb.201602083. https://doi.org/10.1083/jcb.201602083

Szabó A, Theveneau E, Turan M, Mayor R (2019) Neural crest streaming as an emergent property of tissue interactions during morphogenesis. PLoS Comput Biol 15(4):e1007002. https://doi.org/10.1371/journal.pcbi.1007002

Teddy JM, Kulesa PM (2004) In vivo evidence for short- and long-range cell communication in cranial neural crest cells. Development 131:6141–6151. https://doi.org/10.1242/dev.01534

Tepass U, Fessler LI, Aziz A, Hartenstein V (1994) Embryonic origin of hemocytes and their relationship to cell death in Drosophila. Development (Cambridge, England) 120:1829–1837. https://doi.org/8223268

Theveneau E, Marchant L, Kuriyama S, Gull M, Moepps B, Parsons M, Mayor R (2010) Collective chemotaxis requires contact-dependent cell polarity. Dev Cell 19:39–53. https://doi.org/10.1016/j.devcel.2010.06.012

Trepat X, Sahai E (2018) Mesoscale physical principles of collective cell organization. Nat Phys 1. https://doi.org/10.1038/s41567-018-0194-9

Tweedy L, Knecht DA, Mackay GM, Insall RH (2016) Self-generated chemoattractant gradients: attractant depletion extends the range and robustness of Chemotaxis. PLOS Biol 14:e1002404. https://doi.org/10.1371/journal.pbio.1002404

Weijer CJ (2009) Collective cell migration in development. J Cell Sci 122:3215–3223. https://doi.org/10.1242/jcs.036517

Wolpert L (2008) The triumph of the Embryo. ISBN:0486469298