“Developmental mechanics”: cellular patterns controlled by adhesion, cortical tension and cell division

Thomas Lecuit¹

¹IBDML, UMR6216 CNRS-Université de la Méditerranée, Campus de Luminy case 907, 13288 Marseille Cedex 09, France

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How embryos are shaped during development has inspired the work of many, embryologists, geneticists, but also mathematicians such as Turing, and physicists. Despite the inherent complexity of the problems it tackles, developmental biology has produced one of the most spectacular conceptual achievements, demonstrating that embryos are built with conserved molecules that orchestrate pattern and morphogenesis. As the logic of development now emerges, new challenges arise, such as how tissue mechanics is controlled. Quantitative approaches and computational models are essential to predict tissue organization and cell shapes. I review briefly how physical concepts have fueled this research in the past decades. [DOI: 10.2976/1.2896332]

CORRESPONDENCE

Thomas Lecuit:
lecuit@ibdm.univ-mrs.fr

Embryologists have long been fascinated by the intrinsic ability of embryos to organize and acquire increasingly complex forms, as exemplified in the dramatic tissue rearrangements that occur during the development of embryos. Understanding how such stereotyped processes occur has motivated decades of research on animal development. Fifty years ago, it was generally believed that different molecules controlled distinct fates not only within a given organism, but also between different animals. As a result, embryologists were bound to collect specific observations with little hope for generalization. The explosion of genetics and molecular biology starting in the 70's fundamentally changed this perspective. It led to a coherent and powerful framework, whereby, few genes working in conserved signaling pathways orchestrate tissue pattern, telling, for instance, where skin, nervous system or gut should form in all organisms, reflecting evolutionary conservation (De Robertis, 2008). For example, bone morphogenetic protein family members underlie the determination of the dorsal ventral axis in vertebrates and invertebrates (Ferguson, 1996). The signals controlling cell fate are not merely conserved, but also general principles underlie how they determine cell

position within an initially uniform field of cells. Lewis Wolpert's concept of positional information (Wolpert, 1969) was based on the assumption that the graded concentration of a molecule (called “morphogen”) diffusing from a source could determine the cell's distance from the source and organize the tissue. This concept (also known as the “French flag model”) opened the way for a conceptually unified and generalized way of thinking about developmental patterning. Today, it is well known, written in all textbooks (Gilbert, 2006; Wolpert *et al.*, 2006) and taught in every single course that development of all animals stems from general principles of cell communication. Cascades of morphogen graded activities, relayed by local symmetry breaking events such as lateral inhibition, gradually refine cell pattern using conserved families of genes organized in signaling pathways. The construction of embryo patterns appears logical and can now be encapsulated in quantitative and predictive patterning models in *Drosophila* (Gregor *et al.*, 2007; Jaeger *et al.*, 2004; Segal *et al.*, 2008; von Dassow *et al.*, 2000), the sea urchin (Davidson *et al.*, 2002), ascidians (Imai *et al.*, 2006) and the zebrafish and chick

(Goldbeter *et al.*, 2007; Lewis, 2003; Riedel-Kruse *et al.*, 2007).

While the concept of “morphogens” has proven immensely fruitful, understanding how embryos are shaped requires more. “Morphogens” do explain patterns but are unable to account for the forces that determine how groups of cells move, how tissues elongate or bend or undergo all kinds of morphogenetic movements. This realization prompted a number of groups to initiate studies of gastrulation in *Drosophila* (Irvine and Wieschaus, 1994; Leptin and Grunewald, 1990; Sweeton *et al.*, 1991), *C. elegans* (Lee and Goldstein, 2003; Nance and Priess, 2002) and *Xenopus* (Shih and Keller, 1992, and reviewed in Keller, 2006) and to propose physical models of embryo mechanics (Odell *et al.*, 1981). It became clear how patterning signals control specific cell behaviors in spatially restricted domains: apical constriction, which is required for tissue invagination in invertebrates and vertebrates (Dawes-Hoang *et al.*, 2005; Hildebrand, 2005; Kolsch *et al.*, 2007; Haigo *et al.*, 2003), reviewed in Lecuit and Lenne (2007); cell intercalation, which involves oriented cell movements and neighbor exchanges that fuel tissue elongation in many organisms (Bertet *et al.*, 2004; Blankenship *et al.*, 2006; Glickman *et al.*, 2003), reviewed in Keller (2006). As mentioned above concerning developmental patterning, developmental morphogenesis too is controlled by conserved mechanisms. The multiplicity of forms among all animals arises from general classes of tissue morphogenetic processes such as tissue elongation, tissue bending and tubulation, which are reiteratively used in many organisms. Moreover, general classes of cell shape changes underlie tissue remodeling, and cell biology, often restricted to cell culture systems, now embraces developmental biology. The biology of cell shape is at the crossroads of cell and developmental biology and marks a new era in the understanding of morphogenesis.

These two approaches—developmental patterning and developmental morphogenesis—nicely complement each other. They no longer support the idea that development is so complex that it would be either intractable or a collection of different specific processes. Instead they proved that development is not refractory to the efforts towards generalization and conceptualization. Nonetheless, an important gray zone subsists. Is it possible to investigate in quantitative terms the forces that underlie tissue shaping? Can we measure these forces, is it possible to describe the mechanics operating at cell contacts? How do these forces impact on tissue behavior? How are they controlled at the sub-cellular level and integrated across groups of cells at the tissue scale? Can “developmental mechanics” tell us more about where forces originate and what they actually do? Several studies have begun to probe where forces are distributed in tissues during morphogenesis (Franke *et al.*, 2005; Hutson *et al.*, 2003). This subject is extensively discussed in Forgacs and Newman (2005). In contrast to genes and proteins that carry out spe-

cific reactions and control defined processes, mechanical forces are less specific, more difficult to track. Several studies have, however, substantiated the idea that mechanical forces operating at cell contacts can regulate gene expression or cell cycle in cell culture and, as recently suggested, during development (Farge, 2003; Shraiman, 2005; Somogyi and Rorth, 2004).

Below, I review how physical models and mathematical tools have been used over the years to approach cell and tissue morphogenesis during development. I highlight the contribution of recent papers on this subject (Farhadifar *et al.*, 2007; Kafer *et al.*, 2007).

CELL PACKING AND CELL SORTING: A BRIEF HISTORY OF INTERFACIAL TENSION

In the XIXth century the Belgian physicist Joseph Plateau described how soap bubbles and other fluids are organized following geometrical principles that can be explained in terms of surface minimization of three dimensional objects (Plateau, 1873). Plateau observed in particular that in stable configurations, bubbles follow strict rules: bubbles intersect at three-way vertices, the angle of which is regular and 120°; in three dimensions, four-way vertices form the node of a regular tetrahedron with a 109° angle. It turns out that such geometrical rules also tend to apply to living cells [Figs. 1(A) and 1(B)], as recognized nearly a century ago by D’Arcy Thompson, who was fascinated by cells’ tendency to assemble following seemingly mathematical laws, an idea that also inspired F. T. Lewis in plants (Lewis, 1926a). In his famous book “On Growth and Form” (Thompson, 1917) Thompson describes the geometrical constraints that underlie a large repertoire of living forms and develops a simple theory based on interfacial tension to explain how cells arrange, as do fluids such as oil and vinegar. Interfacial tension measures the energy required to increase the surface of contact between two fluids by one unit area. Plateau rules do also apply to cells in living embryos: isolated cells tend to adopt spherical shapes. Aggregates of cells tend to form 120° angles, i.e., hexagonal cells are the most abundant form (albeit not the only one, see below), as observed in the cross section of epithelial cells in a tissue. These observations suggested that cells minimize their surface of contact with their neighbors in order to achieve energy minimization [Figs. 1(A) and 1(B)].

Thompson’s idea surfaced again through the work of embryologists, who observed, a few years later, a remarkable property of embryonic cells: when dissociated and let to re-aggregate, cells sort out from their neighbors depending on their developmental origin (Steinberg, 1963). For instance, randomly aggregated ectoderm and mesoderm cells from *Xenopus* sort out and adopt stereotyped stable configurations with mesoderm at the center, and ectoderm enveloping the sphere of aggregated mesodermal cells. Holtfreter speculated that chemotaxis could account for this sorting behavior

Figure 1. Cell surface mechanics and the organization of static cell patterns. A. Four soap bubbles intersect at 120° angles at three-way vertices. The arrow points to an interface at the center of the cluster. This configuration is the result of a minimization of contacts between bubbles and with the air. B. Four cone cells in the *Drosophila ommatidium*, a cluster of cells in the retina. Cone cells develop specific contacts (arrow). The packing geometry is very similar to bubbles. C. Confocal staining of an *ommatidium* showing the four cone cells (C) and the three surrounding primary pigment cells (P). D. Staining showing the distribution of the cell adhesion molecules E-cadherin (E-cad, purple) and N-cadherin (N-cad, green) in an *ommatidium*. All cells express E-cad, but only cone cells express also N-cad. Because N-cad requires homophilic (i.e., N-cad/N-cad) interactions at contacting surfaces, N-cad is only present at the contacts between cone cells (shown in white because both E-cad and N-cad accumulate). E–G. Differential expression of E-cad and N-cad determines cell shapes as visualized by the relative angles at vertices. Cells expressing N-cad are shaded in green. Loss of expression of N-cad (marked by the sign –) changes the angles between cone cells (E, F): the initially “flat angles” (arrow-heads) become smaller and approach 120° (arrows) as a result of more uniform adhesion. Over-expression of N-cad (marked with the sign +) in pigment cells similarly reduces all angles to 120° (black arrows, G). In both cases, angles become 120° when adhesion becomes more uniform between pigment and cone cells. This illustrates that adhesion controls cell surface mechanics and surface minimization. H–J. Modeling of cell shape based on differential adhesion and cortical elasticity (Kafer *et al.*, 2007). Compare with the geometry of *in vivo* data in E–G. Panels A, B and D are adapted with permission from MacMillan Publishers, Nature 431, 647–652 (2004). Panels C, E–J are adapted from Kafer *et al.*, (2007).

(Townes and Holtfreter, 1955). Steinberg, however, proposed a different mechanism based on differential adhesion among ectoderm and mesoderm cells (Steinberg, 1970). His “differential adhesion hypothesis” proposed that qualitative and/or quantitative differences in the strength of adhesion between different cell surface adhesion molecules would determine stable associations and sorting, as if groups of cells behaved like fluids that minimize their global surface of contact with their surroundings. Experiments performed in cell culture systems (Steinberg and Takeichi, 1994), as well as in embryonic tissues (Foty *et al.*, 1996; Ninomiya and Winklbauer, 2008; Puech *et al.*, 2005; Schötz *et al.*, 2008; Ulrich *et al.*, 2005; Witzel *et al.*, 2006), have largely supported Steinberg’s hypothesis and its *in vivo* relevance during development. In some experiments, the strength of adhesion was inferred using surface tensiometers (Foty *et al.*, 1996) or with atomic force microscopy (Puech *et al.*, 2005). An even more striking demonstration of the relevance of Steinberg’s hypothesis came from recent studies on the cell patterns of retinal cells

in the *Drosophila* pupal eye (Hayashi and Carthew, 2004), where differential expression of E- and N-cadherin in the cone cells and surrounding pigment cells determines cell geometry based on cell surface minimization principles similar to bubbles [Figs. 1(C)–1(G)]. Quantitative modeling of cell sorting provided independent tests of the ‘Differential adhesion hypothesis’ (Graner and Glazier, 1992; Mombach *et al.*, 1995; Hilgenfeldt *et al.*, 2008).

INTERFACIAL TENSION: INTERPLAY OF ADHESION AND CORTICAL TENSION

These observations emphasized the collective “fluidlike” behavior of cells in tissues (Beysens *et al.*, 2000) and the fact that adhesion plays a positive role in controlling tissue interfacial tension, i.e., the minimization of contacts between different tissues. However, subsequent studies refined the concept of interfacial tension as it applies to individual cells in contact, rather than whole tissues, and provided deeper

biological significance to this intercellular surface property (reviewed extensively in [Lecuit and Lenne, 2007](#)).

The interfacial tension underlying the geometry of stable bubble aggregates is, from a physical point of view, a surface tension, i.e., a constant property by definition independent of the state of deformation of the bubble contacts, such as their area or curvature. The above-mentioned similarities between soap bubbles and cells would then suggest that surface tension accounts for most aspects of intercellular surface tension and cell shape. We will see, however, that this is only partially true and that other properties of cells must also be taken into account (see below). With this in mind, let us focus on intercellular surface tension (independent of cell deformation) and detail its biological significance. The role of adhesion is clearly important in that homophilic association of cadherins at cell contacts, and their dynamic association/stabilization by the cortical actin cytoskeleton, tend to extend cell contacts. In that sense, however, adhesion behaves like a negative surface tension at cell contacts, whereas it contributes positively to tissue surface tension. For example, in the fly retina, over expression of N-cadherin in cone cells reduces the total surface of contact of the four cone cells as a whole with the surrounding pigment cells, but meanwhile contributes to an expansion of the contacts between cone cells ([Hayashi and Carthew, 2004](#)) [Figs. 1(E)–1(G)]. Although essential, adhesion is not the only biological component of intercellular surface tension. Recent studies have highlighted the role of cortical tension. Cortical tension is exerted by the cortical actin cytoskeleton and Myosin-II motors responsible for inter-filament binding, movement and tension. Cortical tension thus reduces cell contacts and contributes positively to surface tension ([Lecuit and Lenne, 2007](#)). This is made possible owing to the dynamic interactions of the actomyosin network with the plasma membrane. Increased cortical tension controlled by Myosin-II underlies a number of cell shape changes, such as apical constriction during invagination of the *Drosophila* mesoderm ([Dawes-Hoang et al., 2005](#)), the *C. elegans* endoderm ([Lee et al., 2006](#)) or the neuro-epithelium during vertebrate neural tube closure ([Haigo et al., 2003](#); [Hildebrand, 2005](#); [Hildebrand and Soriano, 1999](#)). Polarized Myosin-II tension is also thought to control cell contact remodeling during epithelial cell intercalation in the *Drosophila* germband ([Bertet et al., 2004](#)).

Although originally proposed by Brodland ([Brodland, 2002](#)) and later developed in [Lecuit and Lenne \(2007\)](#), the opposite roles of cortical tension and adhesion in interfacial tension have only recently begun to be experimentally tested. Their interplay has been incorporated in recent models describing cell organization of epithelial cells in *Drosophila* ([Farhadifar et al., 2007](#); [Kafer et al., 2007](#)). Ablation of cell contacts in the *Drosophila* pupal wing showed that vertices relax in a Myosin-II dependent fashion, consistent with cortical actomyosin playing an essential role in cortical tension

and cell shape ([Farhadifar et al., 2007](#)), extending similar studies at the tissue level during *Drosophila* dorsal closure ([Hutson et al., 2003](#)).

CELLS AND SOAP BUBBLES ARE DIFFERENT: THE ROLE OF CELL ELASTIC FORCES

As mentioned earlier, surface tension does not capture all the properties of interfacial tension at cell contacts. Recent studies have highlighted the need to take into account elastic forces, which constrain cell shape fluctuations and distinguish fundamentally cells and bubbles. In contrast to surface tension, elastic forces depend on cell deformations. Different forms of elasticity can be considered: area elasticity measures departure from a preferred cell surface area, while perimeter elasticity accounts for deviations from a preferred perimeter of contacts between cells. Two elegant papers ([Farhadifar et al., 2007](#); [Kafer et al., 2007](#)) predict the distribution of cell shapes in modeled two dimensional epithelia using physical assumptions that were introduced earlier ([Hufnagel et al., 2007](#)): (i) cell contacts evolve and cell shapes change towards a stable (static or stationary) configuration based on cell interfacial tension, through a succession of mechanical equilibria, which correspond to local energy minima; (ii) interfacial tension is the sum of a deformation independent tension term, line tension, and of a deformation dependent tension, or elastic tension, taking into account area and perimeter fluctuations around preferred areas and perimeters. From a biological point of view, cortical tension exerted by the actomyosin network contributes to all above-mentioned physical parameters. Adhesion, however, contributes only (negatively) to line tension. While Kafer and colleagues model interfacial energies in retinal cells based on forces acting all along cell contacts, Farhadifar and colleagues develop a simpler model where forces act only at vertices. Despite these differences, both studies conclude that cortical elasticity is needed to adequately describe the precise, static, cell shapes in the retina ([Kafer et al., 2007](#)) [Figs. 1(E)–1(J)], or the distribution of cell shapes at steady state in an epithelium ([Farhadifar et al., 2007](#)) (Fig. 2). Farhadifar and co-workers searched *in silico* how the respective values of elasticity and line tension (normalized to area elasticity) influence global, stable epithelial configurations. In doing so they defined two theoretical global energy minima “ground states”: (i) in “soft networks,” all cell perimeters and areas are constant and many different cell configurations can exist and exchange without energy cost, i.e., cells can freely move about as if in a fluid [Fig. 2(A), blue]; (ii) in “hexagonal networks,” the epithelium is fixed in a stable and fixed configuration [Fig. 2(A), gray]. While cortical tension prevails in the latter case, adhesion is dominant in the former case, contributing negatively to line tension. These are merely theoretical states and real epithelia depart from these ground states because of disorder introduced mainly by cell divisions. Nonetheless, these *in silico* data suggest a rather

Figure 2. Stationary cell patterns in proliferating cells. A. Cell patterns corresponding to global energy minima of cell networks as a function of cortical elasticity (deformation dependent tension) and line tension (deformation independent tension) operating at the cell contacts as modeled in Farhadifar *et al.*, 2007. Cortical tension exerted by the acto-myosin network contributes positively to line tension, while adhesion contributes negatively to it. Two stationary ground states emerge: soft networks correspond to cell patterns where all cells have the same perimeter and area and freely move at no cost (energetically). Hexagonal networks are solid networks that require constraints to deform and shear. B. Influence of cell divisions on the ground states. Cell divisions and consequent contact remodeling move the cell networks away from the ground states toward local energy minima. Cell mechanics influence the outcome. Three cases corresponding to three different values of line tension and elasticity shown in A are shown. The distribution of cell shapes (number of neighbors with a color code) and cell area is different in each case and best matches experimental observations for case I. Adapted from Farhadifar *et al.* 2007, Curr. Biol. 17, 2095–2104, with permission from Elsevier.

counterintuitive possible role of adhesion in favoring cell movements within a tissue.

CELL DIVISIONS MODIFY CELL PATTERNS IN EPITHELIA

Cells divide and they do so following geometrical rules initially reported by F. T. Lewis in pioneer studies on plant tissues (Lewis, 1926b). Recent work by Gibson and colleagues extended these studies to animal cells, in particular epithelial tissues (Gibson *et al.*, 2006). When *Drosophila* epithelial cells divide, little if any remodeling of pre-existing contacts occurs. Yet, each new contact produces two new vertices and, correlatively, three new edges. When introducing these simple mathematical principles in a Markov-chain model, Gibson reported that, whatever initial conditions on the configuration of tissues, the cell network rapidly converged toward a stationary configuration with only 46% hexagons and an asymmetric distribution of pentagons (29%) and heptagons (21%). The simplicity of Gibson's model lies in the fact that it is apparently independent of any underlying physical

assumption and could apply to cells like to any other artificially dividing object. Experimental observations of live epithelia in a range of animals largely and remarkably confirm these predictions, and mutations affecting cell divisions modify geometric order as predicted by Gibson's model.

Farhadifar and colleagues further extended this work (Farhadifar *et al.*, 2007). They explored how cell divisions introduce geometrical disorder depending on the mechanical state of the tissue. In their model, each round of cell division modifies the local configuration of contacts and the cell network is let to relax towards another local energy minimum allowing T1 transitions (a sequence of contact loss and contact growth where cells exchange neighbors (Bertet *et al.*, 2004; Classen *et al.*, 2005) and T2 transitions (where cells disappear from the network). This relaxation, neglected by Gibson and colleagues, is obviously dependent on the cell surface mechanics. Importantly, depending on the ground state and more specifically the relative contribution of elasticity and line tension, the tissue adopts different configurations [Fig. 2(B)]. *In silico* and *in vivo* comparisons of cell polygonal shapes (neighbor number) and area variations yield an estimate of mechanical configurations underlying tissue organization. This was further narrowed down using laser ablation experiments that explore perimeter variation when tension is removed from one junction. The authors concluded that cortical tension is predominant over adhesion at the cell cortex (line tension is positive) and that cortical elasticity is also essential, in agreement with Kafer and co-workers (Kafer *et al.*, 2007).

CONCLUDING REMARKS

Biology and physics have gradually joined efforts to understand how cells are shaped in a tissue. The physical concepts underlying cell shape have gradually evolved and been refined, departing from the striking, yet too simplistic idea that cells and soap bubbles behave as if similar. As recently emphasized, cortical elasticity determines how cell patterns are organized in steady state epithelial configurations. The work reported here highlights recent changes in developmental biology, which has become increasingly quantitative, and where models adequately predict tissue organization. Efforts to quantify cell shapes can interestingly impact on our understanding of how signals are communicated between cells (Tassy *et al.*, 2006).

This realization creates important new challenges. First, can we use these concepts to explain dynamic processes, how tissues gradually change shape and follow natural morphogenetic movements, such as during gastrulation. Does morphogenesis obey energy minimization principles? What forces bring tissues out of equilibrium to allow their stereotyped evolution during development? Second, viscous properties of the cell cortex have not been taken into account in past modeling approaches, with a few exceptions (Viens and Brodland, 2007), and experimental approaches so far

have failed to assess these properties in whole tissues. The fact that, following ablation, relaxations are only local suggests that tissue viscosity is indeed important. Measuring the viscous properties of the cell cortex will require more sophisticated approaches, probing the rheological properties of the cell cortex as was done in single cells or in *in vitro* systems (reviewed in [Weihs et al., 2006](#)). Last, it remains largely unclear what controls, at the molecular level, line tension and elasticity. We need to go beyond the coarse description of adhesion and actomyosin contractility underlying these physical parameters. This will require an understanding of how actin network organization and dynamics act against the viscous resistance of adhesive complexes at the membrane. These are important new challenges for cell biologists and set the stage for a deeper understanding of developmental biology.

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