Review

Forces shaping the Drosophila wing

M.C. Diaz de la Loza, B.J. Thompson *

The Francis Crick Institute, 1 Brill Place, London NW1 1BF, United Kingdom

Abstract

How genes encode the three-dimensional shape of tissues is a fascinating problem in biology. Pioneering genetic studies in the fruit fly Drosophila have identified key genes that control the generation of force patterns in the developing wing. Short-range force patterns generated by planar polarised myosins can promote boundary formation and tissue elongation during the larval wing disc stage. Long-range force patterns are also crucial to shaping the wing during the pupal stage. We review the different ways in which both local and global force patterns can be generated, such as: patterned acto-myosin contractility, patterned anchorage to the extracellular matrix, and patterned tissue growth. In all cases, the balance between force, mass, and resistance explains how the resulting mechanical response produces particular tissue forms—a point underscored by the ability of computer simulations of tissue mechanics to reproduce such morphogenetic events.

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* Corresponding author.
E-mail address: barry.thompson@crick.ac.uk (B.J. Thompson).

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by planar polarised myosins can promote boundary formation and tissue elongation during the larval wing disc stage. Long-range force patterns are also crucial to shaping the wing during the pupal stage. We review the different ways in which both local and global force patterns can be generated, such as: patterned acto-myosin contractility, patterned anchorage to the extracellular matrix, and patterned tissue expansion and folding, cell division and separation, reapposition, migration of glial cells through vein L1 and L3, hexagonal repacking of epithelial cells, hair formation, secretion of adult cuticle, fluid filling and spreading, epidermis apoptosis and intervein apposition.
growth. In all cases, the balance between force, mass, and resistance explains how the resulting mechanical response produces particular tissue forms—a point underscored by the ability of computer simulations of tissue mechanics to reproduce such morphogenetic events.

2. From genes to shape in the Drosophila wing: the early history

Evolution has produced an extraordinary variety of living forms, and yet we still know very little about how genes instruct tissues to produce their characteristic shapes. In his classic book, “On Growth and Form”, first published in 1917, D’Arcy Thompson advocated that biological forms reflect physical and mathematical principles, and that genes must therefore harness these principles to direct tissue development (Thompson 1945). Conrad Waddington took up this challenge in 1935 by leaving his embryological studies in amphibians and moving to Thomas Hunt Morgan’s laboratory to analyse genetic mutants that affected the shape of the Drosophila wing (Morgan 1911; Waddington 1939; Waddington 1940). Later, the group of Antonio García-Bellido, Gines Morata and Pedro Ripoll used lineage tracing to identify compartment boundaries and cell competition (Garcia-Bellido and Merriman 1971; Garcia-Bellido et al. 1973; Garcia-Bellido et al. 1976; Garcia-Bellido and Santamaria 1972; Morata and Ripoll 1975)—work recognised and developed by Peter Lawrence, who then collaborated with Morata to characterise the key role of the engrailed gene in specifying the anterior-posterior compartment boundary (Crick and Lawrence 1975; Lawrence and Morata 1976; Morata and Lawrence 1975). Fristrom & Fristrom then dramatically advanced the description of wing morphogenesis in a series of insightful papers and reviews (Fristrom and Fristrom 1975; Fristrom 1976; Fristrom 1988; Fristrom and Chihara 1978).

Attention then shifted away from wing morphogenesis towards other problems, such as how patterns of cell fate are specified by intercellular signalling pathways and transcription factors (Blair 2007; Brook et al. 1996; Lawrence and Struhl 1996), how tissue size is controlled (Day and Lawrence 2000; Hariharan 2015), and how cells compete within a tissue for survival (Levayer and Moreno 2013; Morata and Martin 2007).

In retrospect, the early characterisation of wing morphogenesis was well ahead of its time, being done without the benefit of modern imaging techniques, genetic tools, or biophysical modelling approaches, which have led to a recent flourishing of the field of tissue mechanics (Dreher et al. 2016; Pasakarnis et al. 2016). Below, we review our modern understanding of wing morphogenesis, examining how genetic programs encode local and global force patterns to drive tissue morphogenesis. We describe how individual cells act together to generate collective modes of cell behaviour that emerge from force generation, transmission and sensing to govern the form of an entire tissue.

3. Mechanics of larval wing disc growth

Epithelial cells in 3D culture tend to grow as a simple sphere of cells (a cyst), normally with the apical lumen facing inward. Similarly, the early animal embryo begins life as a cyst with an apical lumen (the blastocyst) that gradually develops greater complexity. The Drosophila wing follows this rule and originates by invaginating from the embryonic ectoderm as a ball of cuboidal cells with an apical-inside lumen. By the larval stage of development this cyst has flattened into a disc shape, hence its common description as the ‘larval wing disc’. During the larval stage, when the animal feeds and grows in size, the wing disc evolves itself to cell growth and division. Once the animal ceases feeding and forms a pupa, the wing disc begins its dramatic morphogenesis into a fully formed adult wing (Fig. 1).

3.1. Epithelial cell polarity and junctional topology

The fundamental structure of the wing epithelium is similar to all other epithelia, with distinct apical, lateral and basal plasma membrane domains, and adherens junctions concentrated at the boundary between apical and lateral domains (St Johnston and Ahringer 2010; Tepass 2012; Thompson 2013). The balance between cortical acto-myosin contractility and junctional adhesion gives rise to a hexagonal ‘honeycomb’ packing of cells at the apical domain, a pattern suggested by D’Arcy Thompson to reflect optimal packing (Thompson 1945) and one that is disrupted by the process of cell proliferation (Gibson et al. 2006). The hexagonal packing and topological disruption due to cell proliferation can be recapitulated in 2D vertex-based models of epithelial mechanics (Farhadifar et al. 2007; Honda et al. 2004).

3.2. Compression-induced apoptosis

Recent work demonstrated that cells can sense changes to their junctional topology. For example, compression of the apical surface due to tissue crowding is sufficient to induce apoptosis and delamination of cells (Levayer et al. 2016; Mariani et al. 2012). Compression provides a mechanical explanation for why fast-growing clones of cells (such as those expressing Ras) can act as ‘super-competitors’ to induce apoptosis of a ring of surrounding wild-type ‘loser’ cells (Levayer et al. 2016). Notably, other mechanisms of cell competition (such as high levels of Myc) appear to rely on extensive cell-cell contact and intermixing of cells to induce local signalling events (fitness comparisons (Meyer et al. 2014; Rhiner et al. 2010)) or potentially to induce local compression of the apical surface of individual loser cells for delamination and apoptosis (Levayer et al. 2015; Levayer and Moreno 2016; Moreno and Basler 2004; Ziosi et al. 2010). After apoptosis, extruded cells are engulfed by hemocytes or sometimes by winner cells (Lolo et al. 2012), although an active role has also been proposed for engulfment in some circumstances (Li and Baker 2007).

3.3. Stretch-induced proliferation

Another example of cells sensing changes to their junctional topology is stretch-induced cell proliferation. In the larval wing disc, a long-range circumferential pattern of stretching arises during tissue growth that appears to activate the Hippo-Warts pathway effector Yorkie, a transcription factor that induces cell proliferation and survival (Fletcher et al. 2015; Koontz et al. 2013; Wu et al. 2008). Different models have been proposed for how the Hippo pathway senses mechanical stretch. One model suggests that stretching of the apical surface of cells would cause de-clustering of Crumbs-Expanded-Kibra-Merlin complexes to reduce Hippo and Warts kinase activation and thus activate Yorkie to promote proliferation (Elbediwy et al. 2016; Fletcher et al. 2015). Another model suggests that mechanical tension is sensed via a Rho-ROCK-Myosin-II-dependent pathway to recruit the Ajuba protein to E-cadherin, an event proposed to recruit and inhibit the Warts kinase (Rauskolb et al. 2014). Further work is necessary to test which of these models operates during physiological stretching of tissues in vivo.

Fig. 1. Overview of wing morphogenesis. The precursor of the wing (the wing imaginal disc) contains two different territories that will give rise either to the adult wing blade (wing pouch, green), or the hinge and part of the notum (brown). During larval stages, the monolayer epithelium that forms the precursor of the wing blade exhibits A-P and the D-V compartment boundaries, oriented cell division, and tissue stretching by different division rates. At the beginning of metamorphosis and as a result of eversion of the wing pouch, the wing blade consists of two epithelial layers facing each other at their basal surfaces (aposition). From 7 h APF, the developing wing undergoes expansion, elongation, separation and re-aposition of both epithelial sheets. Contraction of the wing hinge leads to a global force pattern that induces oriented cell division and cell rearrangement to re-shape the wing to its ‘definitive stage’ at 40 h APF. Features such as veins and hairs also form by 40 h APF. Finally, after eclosure of the adult fly, the folded wing spreads out due to fluid filling of the veins and the intervein epidermis is removed resulting in an adult wing composed mostly of cuticle.
3.4. Oriented cell division

The process of cell division involves a rounding up of the cell at the apical surface due to dramatically increased isometric cortical acto-myosin contractility and decreased E-cadherin mediated adhesion (Marygold and Vincent 2003; Meyer et al. 2011). This rounded shape is induced by the cell-cycle dependent activation of the RhoGEF PEBBLE/ECT2 (Matthews et al. 2012; Rosa et al. 2015) and is essential to build a mitotic spindle (Lancaster et al. 2013), which then re-positions PEBBLE/ECT2 to locate the cytokinetic cleavage furrow (Hime and Saint 1992; Prokopenko et al. 1999; Somers and Saint 2003). Notably, the overall apical-basal polarisation of the cell and its basal connection are largely maintained during cell rounding and cytokinesis (Meyer et al. 2011). Components such as αPKC and Dig remain localised to the apical and lateral domains, respectively, to help align the mitotic spindle in the plane of the wing epithelium via the apical-junctional Mud/NUMA protein or, in other epithelia such as follicle cells, via Pins-Dig interactions (Bergstrahl et al. 2013; Nakajima et al. 2013). Other components, such as Lgl, are removed from the plasma membrane during mitosis to allow Pins-Dig interactions to operate (Bell et al. 2015; Carvalho et al. 2015). It was recently proposed that Mud/NUMA may associate with tricellular junctions to orient the spindle, but whether tricellular junctions are required for spindle orientation remains unclear (Bosveld et al. 2016).

The mitotic spindle can also be oriented within the plane of the epithelium, leading to oriented cell divisions that can elongate the wing disc along the P-D axis (Baena-Lopez et al. 2005) (Fig. 2A, B and C). The Dachshous-Fat-Dachs system of planar cell polarity is responsible for orienting cell divisions, which it achieves by polarising junctional tension to bias cell shapes at the apical surface of each cell along the P-D axis (Baena-Lopez et al. 2005; Mao et al. 2011b). The shape of apical surface prior to mitosis dictates the orientation of the spindle during mitosis and thus the orientation of the cleavage plane and positioning of daughter cells (Gibson et al. 2011; Mao et al. 2011b) (Fig. 3A and B). Computer simulations show that planar polarised junctional tension is sufficient to bias cell shapes, spindle orientation and cell divisions along one axis to drive elongation (Mao et al. 2011b). These discoveries in Drosophila are paralleled by findings in zebrafish showing linkage of the Frizzled planar cell polarity system to the orientation of cell divisions and tissue elongation (Gong et al. 2004; Heisenberg et al. 2000; Tada and Smith 2000). In the case of the Dachous-Fat-Dachs system in the wing, the orientation of planar polarisation is determined by reading vectorial information from gradients of gene expression that ultimately depend on the compartment boundary organisers (Ambegaokar et al. 2012; Brittle et al. 2012; Brittle et al. 2010; Hale et al. 2015; Simon 2004).

3.5. Compartment boundaries and organising signals

Axis specification in the wing is mediated by the Anterior-Posterior (A-P) and Dorsal-Ventral (D-V) compartment boundaries, both of which secrete organising signals including the Wnt protein Wingless (Wg) (Neumann and Cohen 1996; Neumann and Cohen 1997; Zecca et al. 1996) and BMP protein Decapentaplegic (Dpp) (Nellen et al. 1996; Zecca et al. 1995) that collectively form a cartesian coordinate system to specify vein and bristle patterns as well as the Proximal-Distal (P-D) axis (Blair 2007; Brook et al. 1996; Lawrence and Struhl 1996) (Fig. 2A and B). Ectopic induction of new A-P or D-V compartment boundaries in clones of cells is sufficient to produce dramatic re-organisation of wing patterning, growth and morphogenesis (Diaz-Benjumea and Cohen 1993; Garcia-Bellido and Santamaria 1972; Lawrence and Morata 1976; Morata and Lawrence 1975; Zecca et al. 1995).

A key feature of compartment boundaries is that cells do not cross from one side to the other. This phenomenon causes restriction of cell lineages to one compartment in clonal analysis experiments, which led to the initial discovery of the compartment boundary compartment boundaries (Garcia-Bellido and Merriam 1971; Garcia-Bellido et al. 1973; Garcia-Bellido et al. 1976; Garcia-Bellido and Santamaria 1972; Morata and Ripoll 1975). Lineage restriction is also critical to the function of the organisers, which depend on interactions between different cell types across the boundary (Diaz-Benjumea and Cohen 1993; Neumann and Cohen 1996; Zecca et al. 1995; Zecca et al. 1996). The reason some cells do not cross the A-P or D-V boundary was found to be the creation of a line of high acto-myosin tension along the boundary, which then biases cell intercalation events—a model supported by computer simulations (Alie et al. 2012; Dahmann and Basler 2000; Landsberg et al. 2009; Monier et al. 2010; Rudolf et al. 2015; Umetsu et al. 2014) (Fig. 3E).

3.6. Organising signals and patterned tissue growth

Organising signals such as Dpp and Wg are required for wing growth and ectopic formation of an A-P or D-V boundary is sufficient to drive extra growth (Brook et al. 1996; Diaz-Benjumea and Cohen 1993; Lawrence and Struhl 1996; Zecca et al. 1995). How compartment boundary organisers drive growth is still unclear and the subject of some controversy. One simple model is that A-P and D-V signals cooperate to induce and maintain graded expression of genes such as vestigial and scalloped that encode a transcription factor that promotes cell survival and proliferation (Aegerter-Wilmsen et al. 2007; Cohen 1996; Williams et al. 1991; Williams et al. 1993; Williams et al. 1994; Zecca and Struhl 2007a). The expression of Vestigial-Scalloped and the proliferation of cells does not always require continuous input from secreted Dpp (Akiyama and Gibson 2015; Harmansa et al. 2015; Zhang et al. 2013) or Wg signals (Alexandre et al. 2014). Indeed a feed-forward model has been proposed for maintenance and expansion of Vestigial expression during wing disc growth (Zecca and Struhl 2007b; Zecca and Struhl 2010). Thus, although the range of Wg and Dpp pre-figures the size of the wing disc, and can increase tissue size when overexpressed, these signals do not directly and continuously control cell proliferation rate to define tissue size, but rather do so indirectly via a downstream transcriptional network (Baena-Lopez et al. 2009; Restrepo et al. 2014; Schwank and Basler 2010; Schwank et al. 2008; Thompson 2010a).

3.7. Patterned growth generates global tissue forces

One important consequence of Vestigial-Scalloped driving growth is that cell proliferation is higher in the central region of the wing pouch where A-P and D-V boundaries intersect and Vestigial is most highly expressed. This differentially increased growth rate leads to a circumferential stretching of the surrounding tissue, creating a global force pattern that elongates cell shapes and orients cell divisions—a notion supported by computer simulations (Legoff et al. 2013; Mao et al. 2013) (Figs. 2C, 3C and D). As mentioned above, circumferential stretching also triggers stretching of the Spectrin cytoskeleton to activate the mechanosensitive Yorkie transcription factor, which like Vestigial binds to Scalloped to promote cell proliferation and survival (Fletcher et al. 2015; Koontz et al. 2013; Wu et al. 2008). The result is a near uniform proliferation rate across the entire wing pouch by the third larval instar stage.

3.8. Open questions in wing disc development: forces in 3D

How epithelial cell shape is controlled in 3D remains poorly understood. In the larval wing disc, efforts have been made to tackle this problem, suggesting possible roles of organising signals in controlling cell height (Widmann and Dahmann 2009a; Widmann and Dahmann 2009b) as well as a role for the extracellular matrix (Pastor-Fareja and Xu 2011). However, there is still no logical biophysical framework for understanding epithelial form in 3D. One hope is that 3D computer models of biomechanics may shed light on these issues, as a recent
Increased tension at compartment boundaries helps to maintain compartment boundaries, elongates the cell to determine spindle orientation, and influences cell intercalation. During larval stages, increased myosin-mediated tension maintains the AP compartment boundary inherited from the embryo, meanwhile the DV boundary forms by the accumulation of myosin combined with oriented cell division in parallel to the DV frontier. At the end of larval development, cell divisions along the proximal-distal axis by the Dachsous-Fat system begin to be re-oriented by a global force pattern of circumferential stretching that arises from faster growth in the centre (future distal) region of the wing pouch. During metamorphosis, contraction of the hinge tissue pulls the wing epithelia, re-orienting cell division (spindles) and inducing cell intercalation (crosses, magnified in the right-hand side box). The patterned anchorage of the wing blade epithelium to the cuticle during hinge contraction defines the resulting global force pattern and thus wing shape.
model of 3D epithelial cell extrusion and cyst formation demonstrates (Bielmeier et al. 2016).

4. Mechanics of pupal wing morphogenesis

At the end of larval development, there is a cessation of feeding as the larva wanders to find an appropriate site for pupariation. Growth of the wing imaginal disc slows during this period, and cell division arrests completely in preparation for a series of major morphogenetic transformations that will ultimately form the adult wing (Fig. 1). These events were first described in detail by Charlotte Auerbach (Auerbach 1936) and Conrad Waddington (Waddington 1939) and advanced by Diane Fristrom (Fristom and Fristom 1975; Fristom 1976; Fristom and Chihara 1978). Useful reviews include those from Fristrom (Fristrom 1988), Bodenstein (1950), and Cohen (1993).

4.1. Eversion and extension of the wing imaginal disc

The larval wing disc begins its morphogenetic changes by evert ing, such that its apical-inside luminal structure turns inside out, a process that involves the zipper ing up of the dorsal and ventral compartments of the disc along their basal surface and a subsequent rupture of the overlying peripodial epithelium (Aldaz et al. 2010; Aldaz et al. 2013; Fristom and Fristom 1975; Fristom 1976; Pastor-Pareja et al. 2004). The result is an apical-outside epithelial sac whose wing pouch region then expands and elongates into a large flat wing blade by 8 h after puparium formation (APF) (Aldaz et al. 2010; Aldaz et al. 2013; Fristom and Fristom 1975; Fristom 1976) (Fig. 1). Fristrom noted that elongation involves a columnar-to-cuboidal shape change that expands the apical surface and that this expansion is not isotropic, but rather elongates the tissue presumably due to cell rearrangements such as intercalation. How the forces driving expansion and elongation are genetically and molecularly controlled remains unknown.

4.2. Shaping of the pupal wing

After eversion and elongation, the wing begins to swell by the accumulation of fluid between the dorsal and ventral epithelial layers and secretion of the pupal cuticle occurs (Waddington 1939). The wing then returns to a flat form by reaposition of the dorsal and ventral compartments along their basal surfaces (Brown 1993; Brown et al. 2002; Fristom et al. 1993; Waddington 1939), except along the veins, each of which retains a narrow channel for fluid (Blair 2007; O’Keefe et al. 2009; O’Keefe et al. 2007). Contraction of the wing hinge and anchorage of the wing blade to the pupal cuticle creates a global force pattern that flattens and shapes the wing via cell intercalation and oriented cell divisions (Etournay et al. 2015; Ray et al. 2015; Turner and Adler 1995) (Fig. 2D). Computer modelling of hinge contraction, vein
formation and patterned anchorage reveals that this global force pattern is sufficient to define the final shape of the wing (Etournay et al. 2015; Ray et al. 2015) (Fig. 3F).

Notably, the temporal control of hinge contraction and vein formation at 18–40 h APF remains unclear, but the spatial pattern is likely to be determined by the SRF/Blistered transcription factor, which is expressed specifically in intervein territories, but not in veins or the hinge—the territories that undergo apical constriction most strongly. Loss of SRF/Blistered leads to the intervein cells contracting more strongly like veins and separating the two leaflets (Fristrom et al. 1994; Montagne et al. 1996; Prout et al. 1997; Thompson 2010b). SRF/Blistered expression is determined by, and influences, patterns of EGFR signalling (Cruz et al. 2009; Guichard et al. 1999; Martin-Blanco et al. 1999; O’Keefe et al. 2007; Roch et al. 1998; Schnepp et al. 1996; Simcox et al. 1996). Dpp signalling (Matsuda and Shimmi 2012; O’Keefe et al. 2014; Organista and De Celis 2013), Hedgehog (Vervoort et al. 1999) and Notch signalling (de Celis et al. 1997; Huppert et al. 1997; Sotillos and De Celis 2005), that are all ultimately determined by compartment boundary organisers (Biels et al. 1998; Blair 2007).

Precisely how the acto-myosin cytoskeleton is regulated during vein formation remains unclear, but appears to depend on regulation of E-cadherin and N-cadherin expression and localisation by EGFR and Dpp signals (O’Keefe et al. 2009; O’Keefe et al. 2007; O’Keefe et al. 2014). However, EGFR signalling can also directly influence Myosin-II contractility during morphogenesis of the embryo (Saxena et al. 2014).

By 40 h APF, the cells have adopted a hexagonal form at their apical surface and secreted an apical wing hair (an actin protrusion) in a planar surface and secreted an apical wing hair (an actin protrusion) in a planar orientation Myosin-II fibrils. The wing now precisely resembles its adult, except being approximately half its size in the wing. Once again, the application of modern molecular genetics and imaging methods, along with 3D computer modelling of forces in morphogenesis, should help shed light on this fundamental unsolved problem.

5. Local and global forces in other model systems and human disease

Discoveries in the Drosophila wing have many parallels in other model tissues and organisms, underscoring their general relevance for understanding tissue morphogenesis and human disease. For example, elongating tissues via the Dachshous-Fat planar polarity is conserved in mice and contributes to human diseases of the heart and kidney (Bagherie-Lachidan et al. 2015; Cappello et al. 2013; Durst et al. 2015; Li-Villarreal et al. 2015; Mao et al. 2015; Mao et al. 2011a; Zakaria et al. 2014). The Frizzled system of planar polarity also contributes to elongation of tissues in Zebrafish via orientation of cell divisions and intercalation of cells for convergent-extension (Gong et al. 2004; Heisenberg et al. 2000; Tada and Heisenberg 2012). The Toll-like receptors (TLRs) are expressed in overlapping stripes along the anterior-posterior axis of the fly embryo to generate planar polarisation of Myosin-II for intrinsic local force generation that drives cell intercalation during convergent-extension (Bertet et al. 2004; Pare et al. 2014; Zallen and Wieschaus 2004). Extrinsic, global force patterns can also control cell intercalation and orient cell divisions in the fly embryo (Butler et al. 2009; Collinet et al. 2015; Solon et al. 2009), in vertebrate development (Behrndt et al. 2012; Campinho et al. 2013; Keller 1980; Keller and Trinkaus 1987; Voiculescu et al. 2007) or wound healing (Martin and Lewis 1992; Razzell et al. 2014; Wood et al. 2002). The basal collagen extracellular matrix has key roles in vertebrate morphogenesis and cancer (Canel et al. 2013; Hynes 2012; Legate et al. 2008). Furthermore, attachment via the apical extracellular matrix to the chitin exoskeleton is conserved in Zebrafish (Tang et al. 2015). Finally, organising signals such as Wnt/Wingless (Cleurs et al. 2014; Cleurs and Nusse 2012), BMP/Dpp (Wakefield and Hill 2013; Wu and Hill 2009), Notch (Chitnis and Balle-Cuif 2016), and the EGFR receptor (Downward 2003) and the mechanically-responsive Hippo pathway (Pan 2010) are well known to have profound roles in many human epithelial tissues and cancers.

In conclusion, future discoveries in Drosophila wing morphogenesis may identify general mechanisms controlling tissue form that prove relevant to the development of many different animals, including humans.

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