Integrating planar polarity and tissue mechanics in computational models of epithelial morphogenesis

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Abstract

Cells in many epithelial tissues are polarised orthogonally to their apicobasal axis. Such planar polarity ensures that tissue shape and structure are properly organised. Disruption of planar polarity can result in developmental defects such as failed neural tube closure and cleft palate. Recent advances in molecular and live-imaging techniques have implicated both secreted morphogens and mechanical forces as orienting cues for planar polarisation. Components of planar polarity pathways act upstream of cytoskeletal effectors, which can alter cell mechanics in a polarised manner. The study of cell polarisation thus provides a system for dissecting the interplay between chemical and mechanical signals in development. Here, we discuss how different computational models have contributed to our understanding of the mechanisms underlying planar polarity in animal tissues, focusing on recent efforts to integrate cell signalling and tissue mechanics. We conclude by discussing ways in which computational models could be improved to further our understanding of how planar polarity and tissue mechanics are coordinated during development.

34 Introduction

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36 A central problem in developmental biology is to understand how tissues form and
37 repair in a highly reproducible manner. Key signalling molecules are spatially
38 coordinated to provide positional information in developing tissues. While it has long
39 been known that cells can sense and interpret such chemical gradients during
40 pattern formation [1], mechanical forces are now recognised to also play a vital role
41 in shaping tissues [2,3]. Increasing evidence suggests that these chemical and
42 physical mechanisms are interconnected [4].

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44 Morphogenesis is frequently driven by the dynamics of epithelial tissues, which line
45 the majority of organs in the body. As well as being characterised by polarity along
46 an apicobasal axis, epithelia often exhibit planar polarity orthogonally through the
47 plane of the tissue (**Fig. 1A**) [5]. While it is possible for individual cells to become
48 planar polarised, animal epithelial cells locally coordinate their polarity via
49 intercellular transmembrane complexes (**Fig. 1B**) [6,7] to robustly generate uniform
50 polarity across tissues, even when a global polarising signal is weak or noisy [8,9].

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52 This coordinated polarity can be readily visualised by the formation of oriented
53 external structures such as hairs or bristles (**Fig. 1B, C**). It is also vital for
54 fundamental functional roles that require cell coordination, such as oriented division
55 (**Fig. 1D**) and convergent extension (**Fig. 1E**), thus disruption of these mechanisms
56 results in disease [10]. Research into planar polarity establishment focuses on how
57 long-range morphogen and mechanical gradients are interpreted at the cellular level
58 [11], how cells communicate to coordinate information from upstream cues [12], and
59 how downstream effectors alter cell behaviour and the forces underlying tissue
60 formation [13].

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62 Given the complexity of these processes, computational modelling plays an
63 increasingly useful role in aiding our mechanistic understanding [14]. A key challenge
64 is to interface models that include descriptions of cell shape, mechanics, and
65 signalling on different scales. In this review, we consider the contribution of
66 computational modelling first to planar polarity establishment, then to downstream
67 mechanics, and the novel computational methods that study the interplay between
68 them. For brevity, we consider animal tissues only, focussing primarily on *Drosophila*
69 since the majority of planar polarity components have been extensively studied in
70 that system.

Modelling planar polarity establishment

Planar polarity can refer to any polarised protein or structure that breaks cellular symmetry in the plane of the tissue, occurring via multiple independent pathways. We begin by briefly summarising computational modelling of two key pathways: the Frizzled (Fz)-dependent or ‘core’ pathway, and the Fat (Ft)-Dachsous (Ds) pathway. We then describe the conserved anteroposterior (AP) patterning system active in the *Drosophila* embryonic epidermis.

Core pathway

Components of the core pathway form asymmetrically localised molecular bridges between cells. The transmembrane protein Flamingo (Fmi; Celsr in vertebrates) can homodimerise via its extracellular domain across *intercellular* junctions. Fmi interacts *intracellularly* with two other transmembrane proteins, Fz and Van Gogh (Vang), which recruit several cytoplasmic factors (**Fig. 2A**). Since Fmi can homodimerise, it exhibits axial asymmetry (enriched on both sides of cells), whereas all other factors exhibit vectorial asymmetry (enriched on one side) (**Fig. 1A**). Fz and Vang appear to be the key components for recruiting other factors to apical junctional domains [15] and mediating cell communication of polarity [16,17], whereas the cytoplasmic proteins are thought to be responsible for polarity establishment [18-20] by amplifying initial asymmetries in Fmi, Fz and Vang through feedback interactions. The outcome of this pathway dictates, for example, the orientation of hairs on the *Drosophila* wing surface (**Fig. 1B, C**).

A variety of mathematical models have been proposed for the molecular wiring underlying this amplification [21]. In these models, asymmetric complexes form at cell junctions and feedback interactions occur between complexed proteins, such that either ‘like’ complexes of the same orientation are stabilised, or ‘unlike’ complexes of opposite orientation are destabilised, generating bistability (**Fig. 2B**). These models vary in complexity and include those based on Turing pattern formation mechanisms, using deterministic [22,23] or stochastic [24] reaction-diffusion approaches, and others based on the Ising model of ferromagnetism, which treat each cell as a ‘dipole’ that locally coordinates its angle with its neighbours [25]. Such models also vary in biological detail; from abstracted systems where two species bind to form a complex at junctions [26,27] to those including more defined molecular species. The latter necessitates many more kinetic parameters: for

example, the model by Amonlirdviman et al [22] contains nearly 40 rate constants, diffusion coefficients and conserved concentrations whose values had to be estimated.

Domineering non-autonomous phenotypes, where a clone of cells mutant for a polarity protein influences the polarity of wild-type neighbours (**Fig. 2C**), have formed the basis for validating core pathway models at the tissue scale. Whether considering a one-dimensional row of two-sided cells [27], or a two-dimensional field of hexagonal [22] or irregularly shaped cells [28], various models are able to recapitulate these phenotypes. Importantly, modelling has bolstered our intuition on how polarity may be established and highlighted critical conceptual factors necessary for the system to work. For example, both the Amonlirdviman [22] and Le Garrec [24] models can generate tissue-level planar polarity when provided with a transient, rather than sustained, polarity cue; however, transient cues are not sufficient to ensure robustness of the resulting cellular polarisation (**Fig. 2D**) [23]. A number of biological candidates for a persistent global bias have been suggested, including the directional trafficking of Fz complexes along microtubules [29,30].

Ft-Ds pathway

In contrast to the core pathway, there is strong evidence for a primary role of morphogen gradients in orienting the Ft-Ds pathway. In developing tissues, upstream morphogens specify opposing tissue gradients of Four-jointed (Fj), a Golgi-tethered kinase and Ds, a cadherin [31]. Ft and Ds are single-pass transmembrane proteins that can heterodimerise across intercellular cell junctions (**Fig. 3A**). They are both phosphorylated by Fj, which alters their ability to bind to one another [32,33]. Interestingly, although similar domains are modified on each protein, phosphorylation of Ft appears to improve its ability to bind to Ds, while phosphorylation of Ds is inhibitory. Work in *Drosophila* shows that Ft and Ds become asymmetrically localised within cells and that in turn recruits the atypical myosin Dachs to the distal side of cells [33-35]. Polarisation of this pathway can regulate tissue growth via the Hippo signalling pathway [36] and tissue shape by modulating tension at cell-cell junctions and orienting cell divisions [34,37,38], as well as coupling to the core pathway via the Pk isoform, Spiny-legs (Sple) [39].

While abstracted planar polarity models [8,26,27] could in principle be applied to the Ft-Ds system, models tailored to specific molecular interactions are limited. A recent

phenomenological model examined the collective polarisation of the predominant complex – phosphorylated Ft (Ft^P) binding unphosphorylated Ds (Ds^U) – between cells in the *Drosophila* wing [40]. Either stabilising or destabilising feedback was found to amplify shallow graded inputs, but a combination of both more readily recapitulated experimental observations. By linking the strength of polarisation to a downstream tissue growth parameter, predictions were made and tested about the relationship between protein levels and overall tissue size.

Elsewhere, further molecular detail was included in a system of coupled ordinary differential equations describing interactions, again forming the predominant complex (Ft^P binding Ds^U), in a one-dimensional row of cells [41]. However, for the majority of this study, the authors did not consider the orientation of those complexes at individual junctions, but only the asymmetry of total complexes across each cell, thus questions related to Ft and Ds polarity were not addressed. A more recent study used the *Drosophila* larval wing disc (**Fig. 3B**) to quantify the Fj gradient and Ds levels to initialise a one-dimensional reaction-diffusion model (**Fig. 3C**) [42]. Including all possible complexes of phosphorylated and unphosphorylated forms of Ft and Ds led to more uniform cellular polarity across the tissue (**Fig. 3D**). However, only considering the most favoured complex, as in previous models, resulted in greater variation in polarity and binding levels across the tissue. Coupled with experimental evidence, this supports the hypothesis that Fj acts on both Ft and Ds *in vivo*, but with opposing consequences, and illustrates the power of combining experimental and theoretical approaches in the same work.

AP patterning system

In the *Drosophila* embryo, elongation of the body axis, known as germ-band extension, is driven by polarised cell movements and appears to occur independently of the core and Ft-Ds pathways [43]. Instead, evidence suggests that it is guided by striped pair-rule gene expression [44,45], although some contribution is also afforded to oriented cell divisions [46] and large-scale mechanical deformations [47]. The complex upstream gene-regulatory network consists of maternally derived morphogen gradients patterning gap gene expression, leading to stripes of pair-rule gene expression [48]. While the gap gene network has been extensively studied theoretically, uncovering shifting expression boundaries and the importance of transient dynamics of gene regulation [49,50], modelling of striped pair-rule gene expression and downstream processes remains limited.

182 **Modelling planar polarity pathway regulation of cell mechanics**

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184 The importance of mechanics in epithelial morphogenesis is well established [51].
 185 Furthermore, increasing evidence suggests that a common role of planar polarity
 186 pathways is the spatial patterning of cell mechanics to affect consequent tissue-level
 187 morphogenetic processes such as convergent extension. Studies in both *Drosophila*
 188 and vertebrates reveal that downstream effectors include regulators of myosin II,
 189 actin and cadherins [52,53], which in turn affect anisotropy of local forces within an
 190 epithelial tissue (**Fig. 4A**). For example, the core planar polarity pathway has been
 191 implicated in polarised modulation of cell adhesion through trafficking of the
 192 adherens junction molecule E-cadherin. This appears to influence cell packing in the
 193 *Drosophila* wing and cell intercalation in the trachea [54,55].

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195 Nevertheless, models of polarity establishment typically assume that the dynamics of
 196 protein localisation occurs on a much faster timescale than cell shape changes, and
 197 thus consider a static cell packing geometry. To study dynamic cell shape changes
 198 requires coupling of models of planar polarity with tissue mechanics. To this end a
 199 variety of ‘cell-based’ models have been developed, which allow for the incorporation
 200 of cell signalling and feedback [56]. These include vertex [57] and cellular Potts [58]
 201 models, which approximate each cell’s apical surface by a polygon whose vertices
 202 move according to a force balance equation, or a set of pixels that change
 203 stochastically to minimize an energy function, respectively (**Fig. 4B**). Each approach
 204 has its strengths and limitations [59]. Here we discuss a number of example studies.

205

206 *Core pathway*

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208 Inspired by evidence that the core planar polarity pathway can modulate cell
 209 mechanics, Salbreux et al [60] applied a vertex model to the ordered packing of cells
 210 in the zebrafish retina. Using a phenomenological differential equation model of
 211 planar polarity protein dynamics, the authors assumed that protein localisation
 212 modulates the ‘surface tension’ associated with cell-cell junctions and – through force
 213 balance – cell and tissue geometry. Geometry then feeds back on the localisation of
 214 planar polarity proteins. By comparing simulations under different hypotheses, the
 215 authors deduced that an extrinsic force (intraocular pressure) and progressive cell
 216 growth and division were required for the observed packing behaviour. Importantly,
 217 the authors tested model predictions by experiments with mutant fish such as those

218 exhibiting increased intraocular pressure. Such work exemplifies the power of an
219 approach in which experiments and computational models are tightly integrated.

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221 *Ft-Ds pathway*

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223 As discussed above, the *Drosophila* Ft-Ds pathway is required for the planar
224 polarisation of the atypical myosin Dachs. This in turn is required for orienting cell
225 divisions during morphogenesis [37]. More recently a direct correlation between
226 Dachs polarisation, membrane tension and tissue shape during growth has been
227 made using a combination of modelling and mutant clone experiments in the
228 *Drosophila* pupal dorsal thorax [38]. Following from earlier work linking Ft-Ds to
229 mechanical control of morphogenesis [34], the authors explored why Ft or Ds mutant
230 clones are rounded in shape, appearing to minimise their contacts with neighbouring
231 cells, a process which is dependent on Dachs [37]. Notably, Dachs is enriched at
232 clone boundary junctions and reduced at transversal junctions, those perpendicular
233 to the clone boundary within the clone (**Fig. 4C**). This polarisation of Dachs
234 correlated with altered line tension of these junctions. A cellular Potts model, with
235 differences in tension at particular interfaces, was able to accurately recapitulate the
236 clone circularity observed *in vivo*.

237

238 *AP patterning pathway*

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240 In the *Drosophila* embryo, the aforementioned pair-rule gene expression stripes lead
241 to enrichment of Myosin II at AP borders and the adapter protein Bazooka/Par3 at
242 dorsoventral (DV) borders [45,61], the latter recruiting E-cadherin to form adherens
243 junctions. Planar polarisation of Myosin II, which drives the selective shortening of
244 cell-cell junctions during active cell intercalation in germ-band extension [61], was
245 recently discovered to be mediated by overlapping expression domains of Toll-like
246 receptors [62]. This provides a combinatorial code where every cell along the AP axis
247 has a different 'identity'. To investigate how order is maintained as cells intercalate,
248 Tetley et al [63] combined tissue-scale *in vivo* imaging and analysis with a vertex
249 model incorporating differential junctional line tension between cells of different
250 identities. Boundaries defined by polarised Myosin II, including parasegmental
251 boundaries [47], were found to drive axis extension while at the same time limiting
252 cell mixing. This work highlights the burgeoning recognition of the importance of
253 'cables' and other planar enrichments of actomyosin in coordinating morphogenetic
254 processes. Future modelling efforts should include more mechanically explicit

descriptions of how levels and polarisation of Myosin II and other effector proteins modulate cell mechanical properties. A pioneering example of such integration was recently proposed by Lan et al, who coupled modelling of polarisation of Rho-kinase, myosin and Bazooka with a vertex model, but restrict their attention to a relatively small number of cells [64].

Interplay between mechanics and planar polarity

The above work seeks to understand the geometric and mechanical consequences of planar polarity signalling at the tissue level. However, recent evidence points to there being feedback, with adhesion and tension affecting tissue patterning pathways [13]. An extensive study used time-lapse imaging of *Drosophila* pupal wing development over several hours coupled with a vertex model showing that external tension elongates cells along the proximodistal axis and dictates the orientation of planar polarity [65]. Similarly, in the developing *Xenopus* embryo, mechanical strain has been shown to orient the global polarity axis [66]. Furthermore, in the mouse skin, Celsr1 symmetry appears to be broken by mechanical deformation along one axis [67]. Together, these results suggest a general mechanism where planar polarity proteins perdure on persistent junctions and are slow to accumulate on newly formed junctions allowing oriented cell rearrangements and tissue deformations to induce a new axis of asymmetry [11]. This further suggests that in some contexts core planar polarity polarisation is a passive process, governed by tissue-level changes. Conversely, the *Drosophila* Ft-Ds pathway is able to resist tissue strain and maintain its polarity in response to the graded signal of Fj, suggesting it is actively remodelled [39]. This is an intriguing area for future study where computational modelling may help to unravel why these pathways behave differently.

Concluding remarks

We conclude by highlighting some extensions required to increase the utility of computational models in understanding planar polarity and tissue mechanics during development.

Several sources of biological complexity have not yet been incorporated or investigated within these models. A key consideration is the timescale over which a

292 tissue can establish or remodel the asymmetric distribution of planar polarity
 293 components within a cell, versus the timescale over which mechanical changes
 294 occur. Notably, the rate of planar polarisation is likely to be strongly influenced by
 295 mechanisms such as directed vesicular transport and recycling of planar polarity
 296 components, but these have so far been neglected in current models. Furthermore,
 297 the significance of stochasticity and variability in polarity protein interactions and
 298 signal interpretation remain to be addressed, even though *in vivo* these are likely to
 299 contribute a significant degree of noise.

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301 While two-dimensional computational models of patterned epithelial have established
 302 themselves as important tools, three-dimensional models remain limited and are
 303 typically restricted to imposed, static anisotropies in mechanical properties [68]. The
 304 extension of such models to allow for the dynamic simulation of planar polarity
 305 signalling remains to be tackled. For example, an intriguing link between core
 306 pathway planar polarity and three-dimensional tissue deformations was found by
 307 Ossipova et al [69], who demonstrated that planar polarity-dependent polarisation of
 308 the recycling endosome marker Rab11 is required for apical constriction and
 309 subsequent epithelial folding in the *Xenopus* neural plate.

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311 Several software tools have recently been released for automated cell segmentation,
 312 tracking, and shape and polarity quantification in epithelial tissues [70-72]. This has
 313 coincided with the development of techniques to measure, infer, and manipulate
 314 forces *in vivo* [73,74]. Ongoing technical challenges associated with integrating the
 315 resulting data within computational models include developing efficient methods of
 316 simulating, and performing parameter inference and uncertainty quantification, on
 317 such models. Addressing these challenges will help to place computational models of
 318 planar polarity and tissue mechanics on a more quantitative footing, advancing their
 319 biological realism and power to guide future experiments.

320

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323

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 325 University of Sheffield.

Figure 1

Planar polarity in epithelial morphogenesis. (A) In addition to polarising along an apicobasal axis (z), epithelial cells often exhibit planar polarity (also known as planar cell polarity) within the plane of the tissue (x, y). Planar polarity arises from the non-uniform distribution of polarity proteins, which may exhibit axial (enriched on opposite sides of each cell; blue) or vectorial (enriched on one side; red and green) polarity. (B) Wild-type *Drosophila* pupal wing (28h after puparium formation) stained for Vang (grey and green), which has vectorial polarity, and trichomes (magenta) (C, D, E) Planar polarity coordinates the alignment and organisation of cellular and multicellular structures. These include: the formation of hairs and bristles, such as the trichomes produced on the distal side of each cell on the adult *Drosophila* wing surface (C); oriented divisions, as observed for example in cells in *Drosophila* imaginal discs (D); and (E) polarised cell movements and rearrangements, such as during convergent extension.

343 **Figure 2**

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Figure 2. Computational modelling of the core pathway in *Drosophila* wing

development. (A) Intercellular core protein complex arrangement at the adherens

junction zone of *Drosophila* epithelial cells. The formation of an asymmetric

intercellular complex involves the transmembrane proteins Frizzled (Fz; green) and

Flamingo (Fmi; red) and the cytosolic proteins Dishevelled (Dsh; dark blue) and

Diego (Dgo; pink) at the distal end of one cell, and the transmembrane proteins Vang

Gogh (Vang; orange) and Fmi and the cytosolic protein Prickle (Pk; pale blue) at the

proximal end of the adjacent cell. Polarised localisation of complex components

leads to altered cytoskeletal and junctional dynamics, and thus altered cell

mechanics. (B) Possible feedback interactions between non-transmembrane factors

that, either alone or in combinations, could underlie amplification of asymmetry. For

example, Dsh may inhibit Pk binding to Vang. (C) Schematic of non-autonomous

phenotypes, observed in the *Drosophila* wing, around clones of cells mutant for Fz or

Vang. (D) Schematic of 2D simulation results from Fischer et al [23], showing that the

model of Amonlirdviman et al [22] does not give stable vertex polarised steady states

in the absence of a persistent global bias. A uniform array of hexagonal cells is

considered. In the upper panel, initial conditions are such that Fz is localised in all

compartments of each hexagonal cell with a small initial bias (+) in the two distal

compartments. This initial bias is amplified by the feedbacks, while symmetry is

maintained, resulting in a final vertex polarity (thicker green edges). In the lower

367 panel, an initial bias is applied but with a small difference (either + or ++) between
368 the two distal compartments. Again the initial bias is amplified, but given the noise in
369 initial conditions, vertex polarity is not maintained.

Figure 3

Figure 3. Computational modelling of Ft-Ds pathway establishment in the

***Drosophila* wing. (A)** Fat (Ft; turquoise) and Dachshous (Ds; purple) bind

heterophilically to form asymmetric intercellular complexes. Dachs (red), an atypical

myosin, is recruited to colocalise with Ds, where it modulates junctional tension and

orients cell division. **(B)** Cartoon of *Drosophila* 3rd instar larval wing disc. Ds (purple)

is expressed at high levels in the hinge region, whereas Four-jointed (Fj; yellow) is

expressed in a graded pattern in the pouch, which will go on to form the blade of the

adult wing. Dorsoventral (DV) and anteroposterior (AP) compartment boundaries are

shown by dashed lines. Orange box represents the cropped region shown in the

upper panels of C. **(C)** Anti-Fj staining (red) of a wing disc expressing Ds-EGFP

(green) as shown in Hale et al [42]. Fj is clearly graded along the proximodistal (PD)

axis. **(D)** Simulation results based on the computational model of Hale et al [42].

Graded Fj leads to opposing gradients of phosphorylated Ft/Ds (Ft^P, Ds^P) and

unphosphorylated Ft/Ds (Ft^U, Ds^U). Upper panel - all four possible heterophilic

complexes form, listed in order of preferential binding (i.e. the top complex is the

most favoured), leading to cellular asymmetry of bound Ft and Ds complexes that are

largely uniform across the tissue. Lower panel - only the most favoured complex

391 forms (Ft^{P} binding Ds^{U}), thus polarisation and bound protein levels are much stronger
392 in the middle of the tissue compared to the proximal and distal edges. Graphs show
393 simulation results where each bar represents a cell, showing the relative amount of
394 bound protein on the left and right sides in arbitrary units (A.U.).

Figure 4

Figure 4. Computational modelling of the mechanics of planar polarised epithelia. (A) Schematic of the forces arising from apically localised adhesion molecules and cytoskeletal components in neighbouring epithelial cells. E-cadherin binding between tends to reduce surface tension and expand cell-cell junctions (blue arrows), while actomyosin imposes contractile forces at junctions and cell cortices (red arrows), the latter counteracted by intracellular osmotic pressure (black arrows). Each of these effector proteins can be regulated by upstream planar polarity signals. (B) Comparison of the vertex and cellular Potts models of epithelial dynamics. Either a force balance equation for each vertex (left) or Monte Carlo simulation and exchange of pixels (right) is used to drive the tissue toward a configuration of minimum 'energy', E . (C) Cellular Potts model of somatic clone rounding in *Drosophila* pupal dorsal thorax [34]. Observed cell behaviours in Ft or Ds mutant clones are recapitulated by assuming that Dachs polarisation results in line tensions (Λ_{ij}) taking a high value for cell-cell junctions at a clone boundary (red), an intermediate value for cell-cell junctions outside the clone (blue), and a low value for cell-cell junctions within the clone (yellow). (D) Vertex model of active cell intercalation during *Drosophila* germ-band extension [63]. Cell rearrangement results in stripes of cells of the same identity becoming adjacent. Myosin II is enriched

417 preferentially at interfaces shared between cells of different identity (green).
 418 Convergent extension can be recapitulated by assuming that line tensions at cell-cell
 419 junctions (Λ_{ij}) are increased by Myosin II enrichment and depend nonlinearly on the
 420 total length of contiguous interfaces a given cell has with cells of different identities,
 421 the latter assumption approximating the presence of actomyosin cables.

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