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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 palette. 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, focussing 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.

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Introduction

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

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

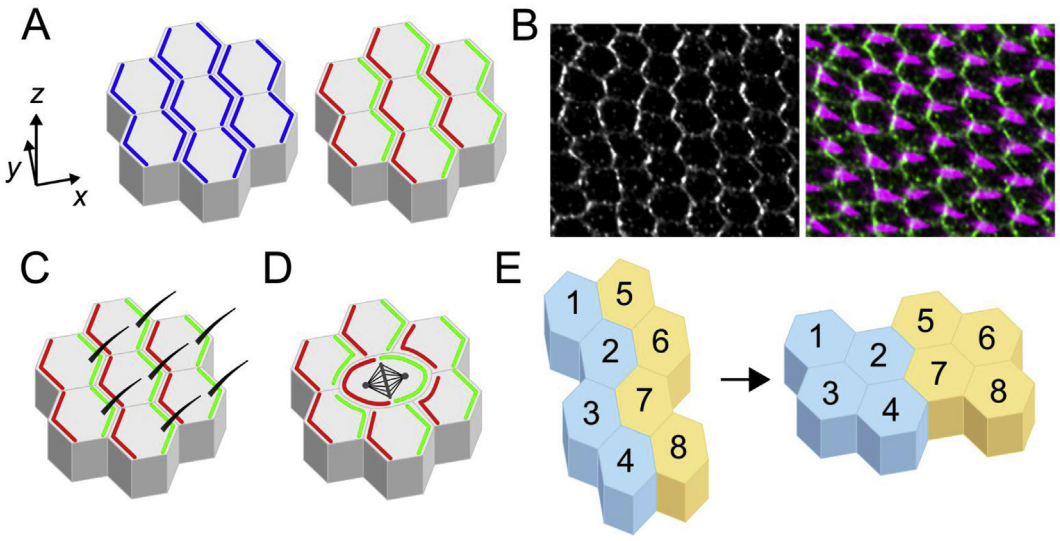
This coordinated polarity can be readily visualised by the formation of oriented external structures such as hairs or bristles (Figure 1B, C). It is also vital for fundamental functional roles that require cell coordination, such as oriented division (Figure 1D) and convergent extension (Figure 1E),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

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

Modelling planar polarity establishment

Planar polarity can refer to any polarised protein or structure that breaks cellular symmetry in the plane of

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 (28 h 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.

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 anterioposterior (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 *inter*cellular junctions. Fmi interacts *intra*cellulary with two other transmembrane proteins, Fz and Van Gogh (Vang), which recruit several cytoplasmic factors (Figure 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) (Figure 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 (Figure 1B and 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 (Figure 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 (Figure 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