A Two-Tier Process of Planar Cell Polarity Development Suggested by Ising-based Modeling

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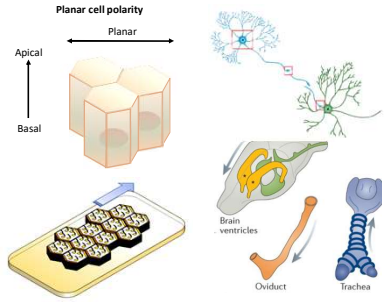
Introduction



- Planar cell polarity (PCP) is the polarization of cell along a planar axis, which aligns across the sheet of cells to form tissue-level PCP.
- PCP is a fundamental topic for developmental biology to understand left-right asymmetry and cell migration
- Manipulating PCP is an important topic of tissue engineering for its importance in instructing proper trachea and neuronal development.

Modeling and Simulation

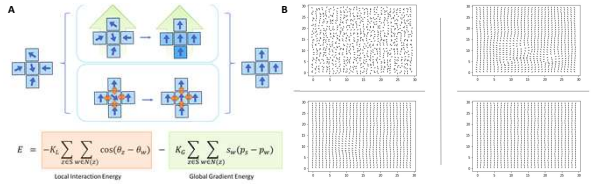


Fig. 2. Illustrations of (A) essential components of the model (B) representative PCP development process simulated by the model. S: 2D lattice representing a sheet of cells; Cell of interest: $z \in S$; Polarity direction: θ_z; Neighboring cells: $N(z) = \{$Von Neumann neighborhood of $z\}$; p: The protein level of each cell; s_w: a descriptive of the relative position of w to z

Observables

Variance: describes the uniform alignment of polarity among cells
Mean: describes the alignment of cell polarity to the direction of global cue
Minimal Development time: the minimal time required to develop a stably established PCP.

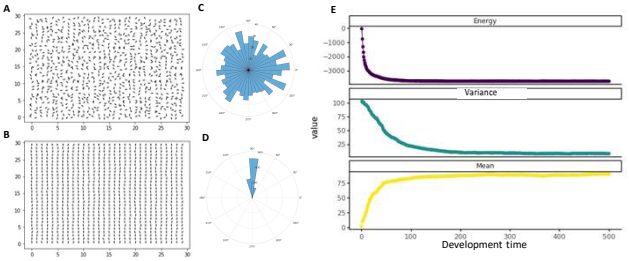
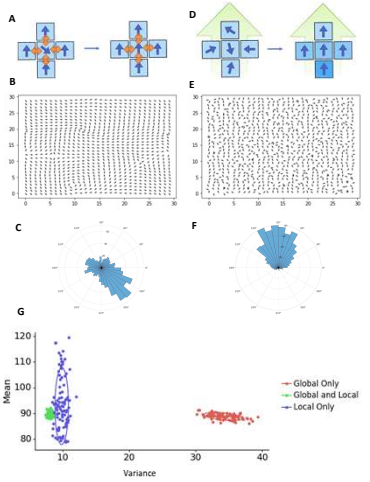


Fig. 3. Observables of the model. (A-B) representative images of the polarity of cells in the lattice before and after the simulation. (C-D) distribution of the polarity direction of cells as measured by θ before and after the simulation. (E) diagram showing the evolution of E, distribution of cell polarity direction, mean cell polarity direction, respectively.

Global-only and local-only Simulation



- by running Global-only and Local-only simulations, contribution of these two terms to the development of PCP can be evaluated separately.
- **Local-Only:** cells are capable of aligning with neighbors but cannot align uniformly at long range. It majorly contribute to the uniformity of PCP.
- **Global-Only:** cells can only orient toward the direction of global cue at a limited level with high noise . It majorly contribute to instructing PCP to the desired direction.

Fig. 4. Results of global-only and local-only simulation and analysis. (A-C) schematic representation, representative images of PCP of cells after a local-only simulation, distribution of the PCP direction of cells as measured by θ. (D-F) schematic representation, representative images of PCP of cells after a global-only simulation, distribution of the PCP direction of cells as measured by θ. (G) scatter plot of Mean over Variance of the distribution of cell PCP direction after global-only, local-only, or both global and local simulation. Sample size = 300, statistical eclipse = 0.75.

Model Verification by mutant phenotype simulation

- Well-documented PCP mutant phenotypes include the swirling and crossing pattern and the mutant clone.
- Success in developing these mutants shall confirm the ability of this model in simulating PCP rather than simply phenocopying
- **Swirling and Crossing Pattern:** simulated by abrogating the global gradient in the sheet of cells.
- **Mutant clone:** simulated by setting the mutant clone being unable to interact locally or disrupting the global gradient.

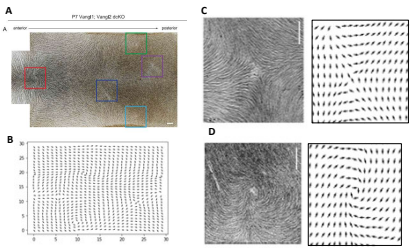


Fig. 5. simulation of the swirling and crossing phenotypes of PCP mutants phenocopied experimental observations. (A) a representative image of PCP mutant mice fur with swirling and crossing patterns (B) a representative simulation result that phenocopied the swirling and crossing patterns by setting no contribution of Global Gradient Energy to PCP establishment. (C) representative crossing pattern observed experimentally and by simulation, respectively. (D) representative crossing pattern observed experimentally and by simulation, respectively,

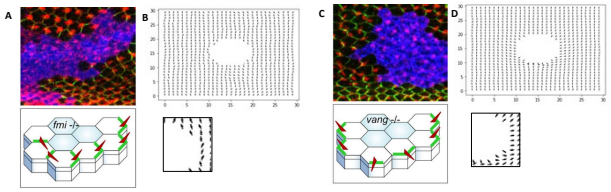
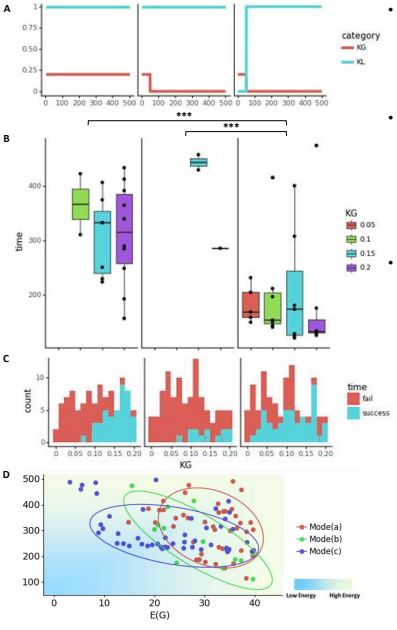


Fig. 6. simulation of mutant clone phenotypes of PCP mutants phenocopied experimental observations. (A) a representative image of mutant clone of Fmi with the PCP of contacting wildtype cells directed to surround the clone (B) a representative simulation result that phenocopied the observation in A by setting the mutant clones being unable to perform local interactions. (C) representative image of mutant clone of Vangl with the PCP of contacting wildtype cells directed to orient away from the clone (D) a representative simulation result that phenocopied the observation in A by setting the mutant clones to disrupt the global gradient.

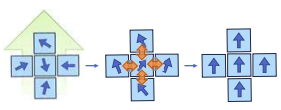
Two-Tier modeling



- The nature of global gradient is a protein gradient induced by morphogen gradients: it is likely to contribute to PCP establishment only during a short time window at the early stage.
- Three mode are possible: (A) both local interactions and global gradients consistently contribute (B) local interactions consistently contributes while global gradient only contributes at early stages (C) global gradient only contributes at early stages while local interactions contributes at later stages.
- Mode C has a significant decrease in the minimal development time, allows a smaller magnitude of global gradient, as a result being the theoretically most efficient mode.

Fig. 7. (A) schematic illustration of the three modes (A), (B) and (C) of how global gradient and local interactions may contribute throughout the process of PCP development. (B) Box plot of the distribution of minimal development time of modes (A), (B) and (C), respectively. Simulation number=30, Sample size = 18, 3, and 26, respectively (failed simulation removed), subclassed by magnitude of global gradient KG. significance evaluated by ttest, ***p<0.05 (C) stacking histogram showing the distribution of succeed and failed simulations over KG. Fail: simulation unable to develop significant PCP after maximum iteration number reached. (D) scatter plot of E(t) (energy cost represented by minimal iteration time) over E(G) (energy cost represented by magnitude and duration of global gradient applied . Statistical eclipse = 0.80.

Conclusion and discussion



- Establishment of a Novel PCP Model based on the Ising Model
- Simulation of mutant phenotypes verified the model and provides insights for the function of mutated proteins
- Exploration on various modes of PCP development suggested a two-tier model to be most energy efficient
- Future Plan: test and apply the predictions made by the model in *in vitro* PCP studies

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