

Emergence of Hexanematic Order in a Growing Confluent Cell Monolayer

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Extended Abstract

Motivation.

Collective cell migration is a fundamental biological process underlying tissue morphogenesis, wound healing, and cancer progression. A defining feature of collectively migrating epithelial sheets is the spatial segregation of cell size and morphology: peripheral cells at the leading edge are typically larger, more elongated, and exhibit higher nematic order, whereas bulk cells in the interior remain smaller, more compact and exhibit higher hexatic order (Figure 1) [1]. However, reproducing this multiscale organization remains a major modeling challenge, as few simulation frameworks can capture hexatic and nematic order within the same confluent tissue. Experimental evidence suggests that this separation is promoted by weakened cell-cell adhesion, reduced packing density, and active cell motion [2]. These observations indicate that models aiming to investigate morphological separation during collective migration must explicitly account for non-equilibrium, mechanically driven dynamics.

Approach and Methodology

We introduce a stochastic particle-Voronoi model that captures the emergence of hexanematic separation in a migrating confluent HeLa sheet within a single simulation domain. Cell dynamics are governed by stochastic differential equations, cell shapes are defined through Voronoi tessellation, and the tissue boundary is determined using an alpha-shape construction of the particle ensemble.

Results.

Our model reproduces key morphological features in confluent HeLa cell sheet, including larger, more elongated peripheral cells and smaller, more hexagonal bulk cells (See Figure 2). The model also reproduces a velocity gradient that is consistent with experimental observation, where peripheral cells are faster and bulk cells are slower. We further show that cell-cell coupling strength and division rate provide simple control parameters to control the global-averaged cell area and hexatic order. Our results demonstrate that hexanematic separation can arise purely from mechanically mediated interactions, differential cell growth and division, and an explicitly active tissue boundary that biases motion toward free space.

Conclusions and Outlook.

Overall, our model provides a minimal yet mechanistically grounded framework describing how hexanematic order can emerge purely from mechanically mediated interactions, differential cell growth and division, and an explicitly active tissue boundary that biases motion toward the leading edge. This framework offers a versatile platform for exploring additional

phenomena, potentially including the jamming–unjammed transition within a single confluent sheet, thereby avoiding the need to artificially separate jammed and unjammed phases into different simulations.

References

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- [2] Eckert, J., Ladoux, B., Mège, R.-M., Giomi, L., Schmidt, T.: Hexanematic crossover in epithelial monolayers depends on cell adhesion and cell density. Nature Communications 14(1), 5762 (2023)

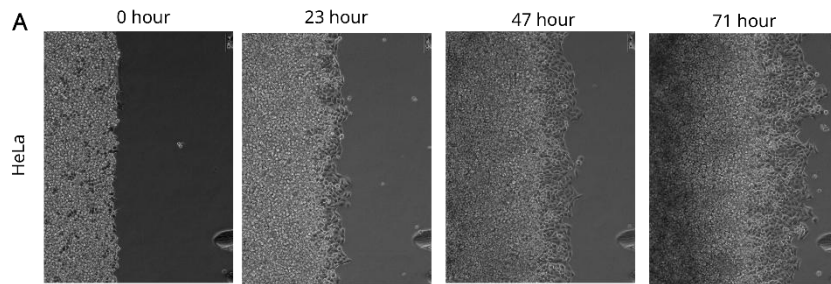


Figure 1. **HeLa cell monolayer.** **a** Time-lapse images of wound closure in a HeLa cell monolayer: peripheral cells are larger and elongated, while bulk cells are smaller and more regular. [1]

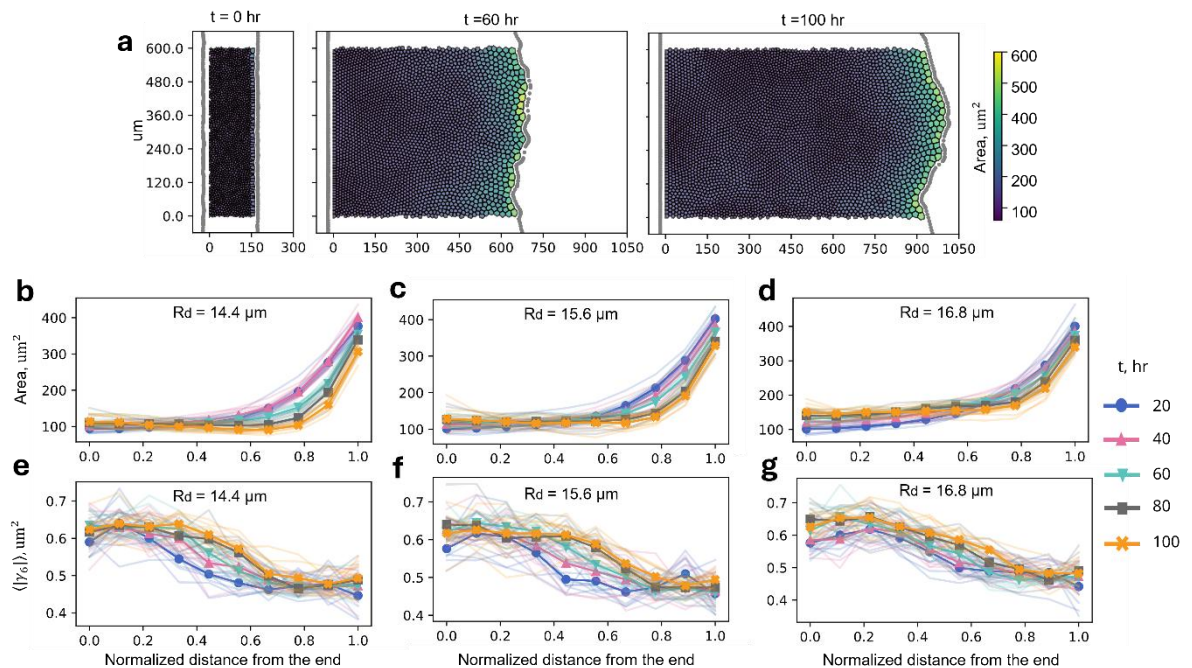


Figure 2. **Cell morphology in simulation.** **a** Representative tessellations at $t = 0, 60,$ and 100 hr showing tissue evolution over time. **b-d** Mean cell area (top) and **e-g** hexatic order $\langle |\gamma_6| \rangle$ (bottom) as functions of normalized end-to-end distance along cell sheet at five time points ($t = 20, 40, 60, 80, 100$ hr) for $\beta = 0.16$ and three different minimum division lengths: $Rd = 14.4$

μm (b, e), 15.6 μm (c, f), and 16.8 μm (d, g). Dark lines show ensemble averages over 10 simulations; light lines correspond to individual runs.