Morphological symmetry-breaking and spontaneous motility of cell clusters

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Collective cell migration is a hallmark of the tissue remodeling events that underlie embryonic morphogenesis, wound repair, and cancer invasion. The coordinated motion of groups of cells in cohesive tissues results from the combination of cell-cell and cell-substrate interactions. As for isolated cells, it requires appropriate guidance that breaks symmetry in the form of chemical or mechanical gradients, allowing for a directional response. An alternative way of inducing a symmetry breaking in an isolated cell cluster is by means of changes in the cluster shape. While the interplay between shape and motion in cells has been established, showing that a morphological symmetry breaking can generate spontaneous motility [1], this possibility seems far less obvious in cell clusters, given that cell polarization in clusters is controlled by the proximity to the edge, which polarizes cells outwards regardless of the edge shape. Here, we unveil a deep connection between morphology and collective migration in clusters that are not globally polarized, showing that cells can self-organize to flow coordinately without external guidance. We base our study on a continuum description of the tissue as an active polar fluid, where traction forces on the substrate compete with contractile cell-cell forces. This model has been previously validated in various experiments with epithelial tissues [2, 3]. Here we focus on the free-boundary problem associated with shape evolution. We study under what conditions a spontaneous symmetry breaking of the circular shape may give rise to sustained motion and what shapes are attained by the traveling clusters (see Fig. 1). Two key length scales control this possibility. The screening length quantifies the extent of the hydrodynamic interactions, and the nematic correlation length defines the extent of the polarization alignment in neighboring cells. We find that spontaneous collective cell migration emerges for asymmetric shapes when the nematic length is sufficiently large compared to the smallest radii of curvature of the edge contour, and the screening length is sufficiently large compared to the system size. The first condition assures that the polarizing effect of the edge propagates sufficiently inside the cluster in an asymmetric way. The second makes the problem essentially nonlocal, assuring a response of the cluster as a whole. Then, the traveling clusters do not relax to a circle and show sustained velocities that depend on shape and parameters in nontrivial ways. Depending on the tissue contractility, the clusters can significantly accelerate due to positive feedback associated with the velocity-shape coupling. We also show that chiral shapes generate the rotation of the cluster. From previous calibrations of our model from experimental data, we have estimates of all parameters for different cell lines of epithelial tissues. Our numerical simulations show that the predicted speeds are remarkably large and should be easily observable in epithelial monolayers prepared with prescribed shapes and sizes. We will also report on work in progress in the experimental verification of these results.

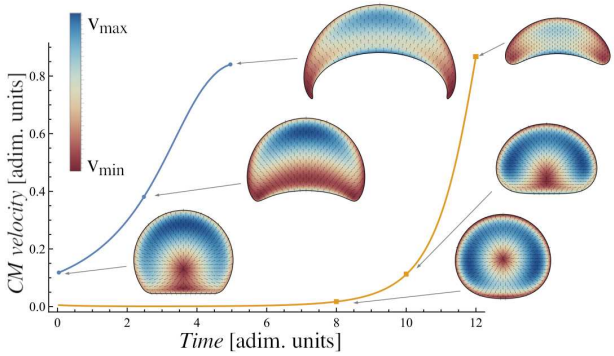

Fig. 1. Center of mass velocities and spontaneous evolutions of two traveling clusters with different initial shapes.

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