# Combined Multi-scale Mathematical Modeling and Experimental Study of Epithelial Cell Clustering and Collective Motion

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Abstract:
In epithelial wounds, physically enlarged cells emerge along the injury edges where they interact with regular-size cells during collective migration to repair tissue continuity. Although such large cells are often interpreted as leaders during collective migration, recent observations suggest that regular-size cells can reciprocally influence them and that mixed-size cell clusters engage in distinct rotational motion before merging into confluent sheets. How cell size, polarity and adhesive coupling jointly control distinct collective migration modes remains unclear. Because many features of collective epithelial migration, including large and regular-size cell phenotypes, are conserved between in vivo and in vitro, here we describe a multi-scale computational model of interacting epithelial cells in two-dimensional culture with dynamic cell-substrate adhesion, cell-cell interactions, protrusion-based polarity, and contact-induced myosin redistribution as polarity regulator. We also explicitly model two functionally distinct cell states, featuring regular and large sizes respectively. Simulations show that symmetric versus asymmetric myosin redistribution at cell-cell junctions can produce stable cell contacts and persistent rotational motions by cell doublets. Intriguingly, in mixed-size cell clusters, straight translation can arise both from leader-like large cell and regular-size cell-mediated motion, whereas rotation emerges when large cell-generated torque overcomes the translational component while cell-cell adhesion is maintained. Thus, collective migration mode depends on the balance between myosin-driven torque, regular-size cell-mediated translation, substrate coupling, and cell-cell adhesion. These modeling results suggest that collective epithelial migration can emerge in vitro from reciprocal mechanical interactions between distinct cell states, rather than from leader-like cell behavior alone, and that such interactions can produce a predator-prey-like pursuit-escape mode of collective migration. Our model also provides a framework for investigating the biochemical and biomechanical regulation of collective cellular migration. It can be readily extended from in vitro to in vivo context and can incorporate the effects of substrate topology and soluble signaling factor-driven chemotaxis.