Geometry, topology, and out-of-equilibrium dynamics in epithelial morphogenesis

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Abstract

The self-organization of epithelial tissues is a crucial event in the development of multicellular organisms. The process can be studied experimentally by embedding single epithelial cells in protein gels and observing their spontaneous growth. The cells divide and self-assemble in highly symmetric multicellular structures (cysts) surrounding a hollow spherical space (lumen), thus mimicking the formation of cysts and acini in a living organism during the development of organs such as the kidneys or lungs. The orderly growth of experimental cysts is driven by cell-cell adhesive forces, cell membrane elasticity, and the self-organized partitioning of the cell membrane in domains characterized by different chemical and mechanical properties (cell polarity). Genetic engineering and pharmacological inhibitors allow to interfere with these processes, leading to the production of aberrant, disordered cell aggregates similar to those observed in several types of cancers.

We have studied the process of experimental cyst growth by theoretical modeling and accurate dynamic quantitation of cyst morphology during the growth process. Our analysis shows that cell-cell contact statistics bears a clear signature of the strongly non-equilibrium character of cyst morphogenesis. Out-of-equilibrium dynamics drives the appearance of aberrant multi-lumen phenotypes, unless strict control of cell division geometry is enforced. The comparison of theoretical modeling and experimental results unveils the presence of multiple local equilibria associated with geometrically frustrated configurations of the cell aggregate. We also show that a quasi-equilibrium state can be recovered upon inducing tissue fluidization by the use of pharmacological inhibitors of cell membrane tension.