Generalizing Mechanical Models of Epithelial Sheets to Study Collective Behavior of cells

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Collective behavior of cell sheets is fundamental to many important biological processes, yet it is not well understood. Motivated by recent experimental work, we extended the self-propelled Voronoi model to study cell sheet collectivity, boundary behavior, and response to an external stimulus. In simulations, we found that single-cell level processes can generate collective behaviors observed in experiments such as swirls, streams, and coordinated U-turns as a response to external stimulus reversal. However, generalizing current models is necessary to recapitulate the collective motion observed in motile epithelial sheets and to study other fundamental behaviors of cell sheets. I propose a generalization that will enable implementation in studies relevant to wound healing, external control of cell collectives, cancer invasion, and implant biocompatibility.

Introduction

Collective behavior of cell sheets is fundamental to many important biological processes, yet it is not well understood. In embryonic development, for example, newly formed tissues are relocated, patterned, and shaped by sweeping coordinated motions and divisions of the constituent cells. In wound healing, separated sections of an epithelial sheet move towards each other, collide, and heal via coordinated pulling of cells throughout the sheet, including those far from the actual wound[1]. Group response to external stimuli[2] (chemical gradient, electric field, etc.) and even cancer progression also involve individual cells joining forces in coordinated ways to perform complex tasks. Understanding how single-cell level processes lead to these complex behaviors is the object of intense experimental and theoretical study, with sheets of epithelial cells being the dominant model system for experiments. “Active vertex models,” also called “self-propelled Voronoi models[3],” combine mechanical and migratory properties of cells in sheets and are gaining widespread use. They have successfully revealed ways in which changes in single-cell properties such as cell shape, adhesion, or motility can lead to tissue-level behaviors of cell sorting, solid to fluid transition[1] (in which motile cells initially caged by their neighbors become able to rearrange), and cancer invasion. I implement the self-propelled Voronoi model to study epithelial sheets, specifically cell migration collectivity and cell sheet interactions with rigid boundaries, and propose generalization to allow more detailed study of other behaviors

Preliminary Work

Inspired by recent work on epithelial sheets[3,4], I have implemented and extended the active vertex model to better understand the effect on cell sheets of external stimuli, rigid boundaries and cell motility alignment with neighbors (Figure 1). I have demonstrated initial results of simulated cell sheets exhibiting “swirls” and

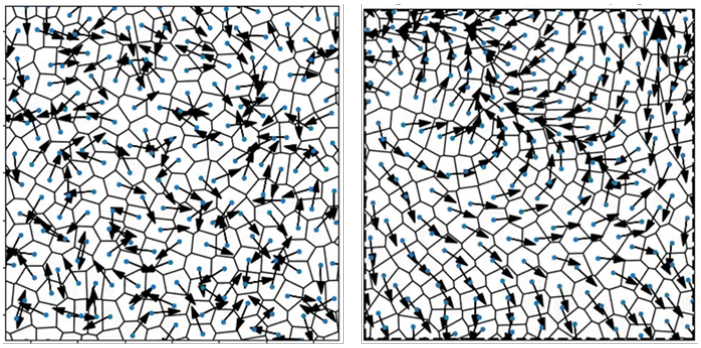

Figure 1: Snapshot of simulated cell trajectories with no active motility coupling with neighbors (left) and moderate coupling with neighbors (right).

"streams" when migrating collectively, performing coordinated U-turns as in experiments[3] in response to the reversal of an external stimulus, and interacting with "sticky" walls treated by the cell-cell adhesion protein E-cadherin or "slippery" walls without E-cadherin[4].

Challenge

While initial results are promising, generalization of the current implementation is necessary to precisely study these and other behaviors of epithelial sheets. In experiments of epithelial sheets, groups of cells migrate large distances (5-7 cell lengths) without rearranging with their neighbors and consequently do not form "swirls" or "streams" seen in other cell types. This is likely due to the desmosome, a super-adhesive adhesion complex that acts as a "spot-weld" between touching epithelial cells[5]. It would be very hard to implement this kind of constraint in current models of active sheets constructed from the Voronoi diagram of self-propelled cell centers. Furthermore, cell shapes at free boundaries of sheets cannot be obtained from the Voronoi diagram. My goal is to generalize current models to enable more accurate simulation of epithelial sheets and open the door to the study of many important behaviors involving cell sheet boundaries.

Research Plan

I intend to start with a standard "passive" vertex model; because it is based on cell vertices rather than cell centers, it can easily describe the mechanics of cell sheets involving free boundaries. I can then introduce an energy penalty that prevents shared cell-cell edges from shrinking below some threshold length to implement the effect of desmosomes. To include cell motility in my model, I will simulate the effect of lamellipodia (well-known structures that individual epithelial cells extend in the direction of their migration) as active forces on the vertices corresponding to the leading edge of a motile cell. Cells far from any free edges are also known to exhibit motility without forming lamellipodia, and I will model this as weaker active forces equally distributed between all vertices.

The generalized model will also give more flexibility for modelling important biological processes that happen at sheet boundaries, such as highly motile leader cells at free boundaries and interaction of cells at sheet boundaries with foreign objects (implants). I will inform and test my models qualitatively against emergent tissue behaviors evident in experimental videos and quantitatively against experimental data by examining velocity correlation functions of these tissues. Comparison with experiments will help us identify the relevant biological mechanisms; for example, it is not obvious from experiments whether cells "stuck" on a biomimetic boundary coated with E-cadherin are maximizing their adhesion, have lost their migratory drive, or are physically "pinned" to the boundary. Better understanding of these boundary interactions will give us clues for developing biocompatible implants. When implanting a device among cells, we may wish to disguise it from the rest of the tissue by "sticking" a layer of cells to it, so understanding how cell migration functions at these boundaries could be paramount in developing truly biocompatible devices.

Finally, I will extend my studies to other problems of interest, such as the fingering instability of free sheet edges, wound healing and collisions of sheets, metastasis of carcinoma (migration of cancer cells without desmosomes through an epithelial sheet[5]) and external control of cell sheets with electric fields. Comparison of modeling with experiments will highlight the relative importance of different biological processes.

References:

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