ABSTRACT

Title of dissertation: DIRECTED CELL MIGRATION: FROM SINGLE CELLS TO COLLECTIVELY MOVING CELL GROUPS

Can Guven, Doctor of Philosophy, 2014

Dissertation directed by: Professor Wolfgang Losert
Department of Physics

Unlike molecules, which are driven thermally by Brownian motion, eukaryotic cells move in a particular direction to accomplish designated tasks that are involved in diverse biological processes such as organ development and tumor progression.

In this dissertation, I present experiments, analysis, and modeling of directed individual and collective cell migration. At subcellular scale, the migration of cells can be guided via the interaction of the cell cytoskeleton with the surrounding nanotopographic elements. I show that mechanical waves of actin polymerization are involved in this guidance—known as contact guidance—as dynamic sensors of surface nanotopography. The dynamics of guided actin waves were measured to build and test predictive models of contact guidance. The distributions of actin-wave propagation speed and direction were obtained from experimental observations of cell migration on nanotopographic surfaces as a function of the spacing between adjacent features (varying between 0.8 and 5 microns). I show that actin polymerization is preferentially localized to nanoscale features for a range of spacings. Addition-
ally, the velocity of actin polymerization waves moving parallel to the direction of nanoridges depends on the nanoridge spacing. A model of actin polymerization dynamics in which nanoridges modify the distribution of the nucleation promoting factors captures these key observations. For individual cells, the question is how the intracellular processes result in directed migration of cells. I introduce a coarse-grained model for cell migration to connect contact guidance to intrinsic cellular oscillations.

The guidance of collective cell migration can be dictated via intercellular communication, which is facilitated by biochemical signals. I present a coarse-grained stochastic model for the influence of signal relay on the collective behavior of migrating *Dictyostelium discoideum* cells. In the experiment cells display a range of collective migration patterns including uncorrelated motion, formation of partially localized streams, and clumping, depending on the type of cell and the strength of the external concentration gradient of the signaling molecule cyclic adenosine monophosphate (cAMP). The collective migration model shows that the pattern of migration can be quantitatively described by considering the competition of two processes, the secretion of cAMP by the cells and the degradation of cAMP in the gradient chamber. With degradation, the model secreting cells form streams and efficiently traverse the gradient, but without degradation the model secreting cells form clumps without streaming. This observation indicates that streaming requires not only signal relay but also degradation of the signal. In addition, I show how this model can be extended to other eukaryotic systems that exhibit more complex cell-cell communication, in which the impact on collective migration is more subtle.