576f Multiscale Analysis of Feedback Control in Epithelial Patterning Systems

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We will discuss modeling and computational issues associated with the analysis of pattern formation by morphogen gradients. The basic phenomenology involves a locally secreted ligand that spreads through the tissue, binding to and activating cell surface receptors, which control signal transduction and gene expression pathways in responding cells [1]. Molecular studies of morphogen gradients show that any given morphogen gradient system can be controlled by multiple spatially distributed feedback loops [2]. At this level of complexity, modeling is indispensable for testing of the proposed patterning mechanisms and for the design of future experiments [3].

Even the simplest models of morphogen gradients are multiscale in nature, since they must integrate extracellular variables (diffusible ligands), cell surface species (receptor and ligand-receptor complexes), and intracellular variables (signaling intermediates and genes controlled by intracellular signal transduction). Conventional models of morphogenetic signaling ignore the length scale of a single cell, assuming that it is small compared to the characteristic length scale of the pattern controlled by the morphogen. This assumption does not hold in large number of experimental systems where the emerging gene expression patterns are only a couple cells wide [1].

Recently, we have demonstrated that fully discrete models are essential for the analysis of problems with positive feedback loops [4]. Here, we focus on morphogen gradients regulated by negative feedback loops [5]. Specifically, we formulate a detailed mechanistic model for the epidermal growth factor receptor (EGFR) mediated patterning of the fruit fly embryonic ventral ectoderm. The model is based on the recent biochemical and genetic analysis of this system [6]. We start with the model in the form of nonlinear partial integrodifferential equation and show how it can be progressively reduced to simpler models using a hierarchy of assumptions. Each reduced model is used to analyze the robustness of the EGFR-mediated patterning of the embryonic ventral ectoderm. We will present numerical methods for direct computation of robustness domains and use our models to make a number of experimentally testable predictions related to the functional significance of the negative feedback in this system [5].

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