Lateral Inhibition through Delta-Notch Signaling: A Piecewise Affine Hybrid Model*

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Abstract. Biological cell networks exhibit complex combinations of both discrete and continuous behaviors: indeed, the dynamics that govern the spatial and temporal increase or decrease of protein concentration inside a single cell are continuous differential equations, while the activation or deactivation of these continuous dynamics are triggered by discrete switches which encode protein concentrations reaching given thresholds. In this paper, we model as a hybrid system a striking example of this behavior in a biological mechanism called Delta-Notch signaling, which is thought to be the primary mechanism of cell differentiation in a variety of cell networks. We present results in both simulation and reachability analysis of this hybrid system. We emphasize how the hybrid system model is computationally superior (for both simulation and analysis) to other nonlinear models in the literature, without compromising faithful modeling of the biological phenomena.

1 Introduction

1.1 Lateral Inhibition and Developmental Biology

The emergence of differentiated cell types from an initially homogeneous population is a well-studied phenomenon. Differentiation occurs in all animal and plant embryonic tissue, particularly such species as *Drosophila melanogaster* (fruit fly) and *Xenopus laevis* (South African claw-toed frog) have been extensively studied. Genes control cell fate by controlling the type and amount of proteins made in a cell. Proteins in turn affect gene activity by turning "on" or "off" gene expression thereby affecting the production of proteins themselves. Hence differential gene activity is considered the key to cell differentiation (Wolpert [1]) and protein concentrations in a cell are a good measure of gene activity. The idea that lateral signaling between cells through the Delta-Notch protein pathway is responsible for some cell fate decisions has gained wide acceptance.

A concise description of the biological background follows (Lewis[2]): Delta is a transmembrane protein that binds and activates its receptor, the transmembrane protein Notch, in neighboring cells. The activation of Notch has a "direct

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and immediate" effect on gene expression. Hence Notch signaling directly controls switching in genetic networks and cascades. The activation of Notch in a cell affects the production of Notch ligands (i.e. Delta) both in itself and its neighbors. In the classical lateral inhibition case, high Notch levels inhibit ligand production in the cell and thus a cell producing more ligands forces its neighboring cells to produce less. However, Notch signaling can also be responsible for a phenomenon called lateral induction where activation of Notch promotes ligand production and thus a group of cells cooperate to produce uniformly high amounts of ligand and Notch, causing all-or-none behavior that promotes sharp gene expression boundaries.

Inter and intra cellular signaling has been postulated to be the mechanism for pattern formation in an incredibly wide range of organisms: emergence of ciliated cells in *Xenopus* embryonic skin (Marnellos et al[3]), neurogenesis in *Drosophila* (Luthi et al[4] and Marnellos et al[5]), sensory cell differentiation in the zebrafish ear (Haddon et al[6]), chick feather array (Crowe et al[7]), wing vein morphogenesis in *Drosophila* (Huppert et al[8]), etc. An example of the distinctive "salt-and-pepper" pattern formed due to lateral inhibition is the *Xenopus* epidermal layer where a regular set of ciliated cells form within a matrix of smooth epidermal cells as seen in Fig. 1. Apart from pattern formation, Delta and its homologues (Fringe, for example, proposed by Moloney et al[9]) interact with Notch (and its homologues) to produce other phenomenon like lineage decisions and boundary formation (Bray[10]), as well as stem cell function and formation of skin appendages (Lewis[2]).

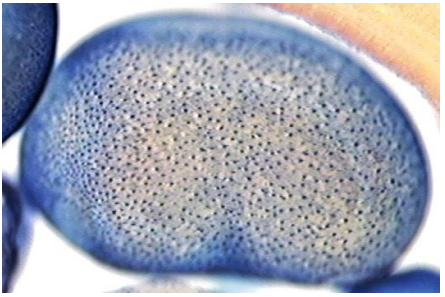

Fig. 1. *Xenopus* embryo labeled by *α-tubulin*, a marker for ciliated cell precursors seen as black dots. Photograph courtesy of P. D. Vize (*The Xenopus Molecular Marker Resource*, `http://vize222.zo.utexas.edu`)

1.2 Previous Work: Mathematical Models

Most classical models (including Turing's[11] seminal work on morphogenesis) depend on the phenomenon of local autocatalysis with lateral inhibition (LALI). These are grouped (Oster[12]) as neural models, diffusion-reaction models and