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Lateral inhibition-induced pattern formation controlled by the size and geometry of the cell

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HIGHLIGHTS

- A geometrical effect of cell on lateral inhibition system is explored in a multi-cellular system.
- A geometrical property of cells can induce a cell asymmetry.
- The surface area of the cell-to-cell contact and cell volume affect a cell patterning.
- A new modeling method including cell structure in a multi-cellular system is explored.

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ABSTRACT

Pattern formation in development biology is one of the fundamental processes by which cells change their functions. It is based on the communication of cells via intra- and intercellular dynamics of biochemicals. Thus, the cell is directly involved in biochemical interactions. However, many theoretical approaches describing biochemical pattern formation have usually neglected the cell's role or have simplified the subcellular process without considering cellular aspects despite the cell being the environment where biochemicals interact. On the other hand, recent experimental observations suggest that a change in the physical conditions of cell-to-cell contact can result in a change in cell fate and tissue patterning in a lateral inhibition system. Here we develop a mathematical model by which biochemical dynamics can be directly observed with explicitly expressed cell structure and geometry in higher dimensions, and reconsider pattern formation by lateral inhibition of the Notch–Delta signaling pathway. We explore how the physical characteristic of cell, such as cell geometry or size, influences the biochemical pattern formation in a multi-cellular system. Our results suggest that a property based on cell geometry can be a novel mechanism for symmetry breaking inducing cell asymmetry. We show that cell volume can critically influence cell fate determination and pattern formation at the tissue level, and the surface area of the cell-to-cell contact can directly affect the spatial range of patterning.

1. Introduction

Biochemical pattern formation is an important process whereby cells communicate and alter their functions (Gilbert, 2006). In the last several decades, cell patterning based on biochemical pattern formation has been extensively studied, both theoretically and experimentally in several tissues and at different stages of the developmental process. The process of pattern formation or the mechanism by which cells determine their destiny is the integrated process of intra- and intercellular dynamics. Nonetheless, since a mathematical model is based on the simplifications of the actual process, many existing models have excluded or simplified the intracellular dynamics or did not consider the role of the cell per se. On the other hand, some modeling simplifications have raised serious questions about the robustness of the modeling framework. For example, the fragmentary approach, which neglects the details of intracellular dynamics of modeling, such as gene expression time delay, led researchers to question the robustness of the Turing pattern formation (Seirin Lee et al., 2010, 2011; Seirin Lee and Gaffney, 2010; Maini et al., 2012; Gaffney and Seirin Lee, 2013).

There are some mathematical models that consider the subcellular dynamics or employ multi-scale approaches (Schnell et al., 2008). However, in general, methods focusing only on the extension of network of biochemical interactions have been used, but the role of the environment in which the investigated biochemicals are interacting, i.e., the direct role of the cell, has not been considered, although all biochemical interactions are tightly controlled by the cell and can be affected by cellular environment.

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On the other hand, recent experimental observations strongly suggest that the changes in cell-to-cell physical interactions can lead to a change in cell fate and tissue patterning in lateral inhibition system. Matsuda et al. (2015) showed that the ratio of the number of Notch to Delta cells in tissue can change dramatically when the physical conditions of cell-to-cell interactions are changed. This suggests that the cell-to-cell communication can be directly affected by their physical characteristics. However, the influence of the physical characteristics of cells, such as cell geometry or size, on the cell patterning in a lateral inhibition system has not been thoroughly studied. Furthermore, extensive theoretical studies on the influence of the geometrical properties of cells or cell-to-cell interactions on the intracellular biochemical state and, consequently, cell patterning, particularly in a multi-cellular lateral inhibition system, have not been conducted.

Theoretical approaches, investigating cell geometry in order to understand the deformation of tissues/cell or cell migration, have been previously employed (Ishimoto and Morishita, 2014; Shao et al., 2012; Taniguchi et al., 2013). However, these approaches were developed to understand how the cell geometry is affected by different biochemical or mechanical elements, and these studies focused on the cell/tissue morphology or cell movement. In contrast, the main focus of our study is the effect of the cell geometry on the biochemical patterning, and the effect of the geometrical conditions on the sub-cellular biochemical dynamics or biochemical interactions. Here, we investigated the pattern formation by lateral inhibition in the Notch–Delta signal transduction system.

In lateral inhibition, a cell leads to the reduction of the capacity of neighboring cells through cell-to-cell regulatory signals and the induction of different activity in the neighboring cells. Notch–Delta signal transduction is a well-known lateral inhibition system (Andersson et al., 2011), which plays a crucial role in the determination of cell fate during the early stages of cellular diversity development (Del Bene et al., 2008; Bhat et al., 2011; Chen et al., 2014; Cohen et al., 2010; Eddison et al., 2000; Sprinzak et al., 2010). A membrane-bound ligand, Delta, binds to the Notch receptor on a neighboring cell, which results in the increase/decrease of Notch/Delta in this neighboring cell, and leads to the repression of Notch expression. The different expression levels of Notch/Delta ultimately result in different cell fates. Typically, lateral inhibition induces a short-range salt-and-pepper pattern where Notch and Delta expression alternate in several neighboring cells (Collier et al., 1996). However, recent biological observations showed that lateral inhibition can create a range of patterns and, especially, gradient patterns (Del Bene et al., 2008; Chen et al., 2014; Cohen et al., 2010), although the universal mechanism underlying the formation of these patterns has not been elucidated.

Most existing theoretical approaches for the investigations of pattern formation via lateral inhibition are based on the model suggested by Collier et al. (1996), in which Notch and Delta dynamics was simplified by not considering cell structure, and Notch–Delta signaling was averaged. Several extensions of this model have been proposed, but they failed to consider the precise cell structure as well. However, lateral inhibition through the direct cell-to-cell interactions is likely to be affected by the underlying mechanisms of this process (Matsuda et al., 2015), which cannot be described using the previously described approaches that simplify cell structure. Here, we reconsider the Notch–Delta lateral inhibition model by including the cell structure information. We show that cell volume can critically influence the determination of cell fate and pattern formation in tissues, and cell-to-cell contact surface area can directly affect the spatial range of patterning. The results suggest a novel mechanism of symmetry breaking for the cell asymmetry and pattern formation.

2. Lateral inhibition model including cell structure and geometry

We formulate a simple and versatile model, in order to find direct effects by the cell structure or geometry, rather than an assumption about the biochemical itself. We assume the following Notch–Delta signaling pathways (Fig. 1A):

- Delta, localized at the membrane of the *i*-th cell binds to the Notch receptor in the membrane of a neighboring cell, leading to a proteolytical release of the Notch intracellular domain (NICD) in this cell (Andersson et al., 2011).
- The cleaved NICD leads to the transactivation of Notch genes,

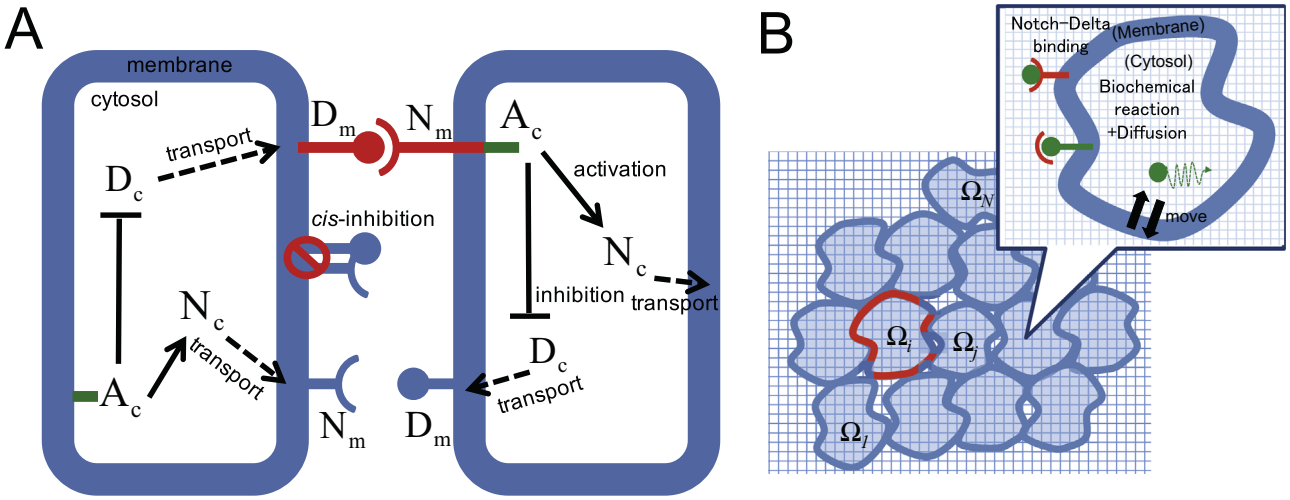

Fig. 1. *Schematic dynamics of Notch–Delta signal transduction*. (A) The modeling framework of the Notch–Delta signaling pathway. N_m and D_m are Notch and Delta in the membrane and N_c and D_c are Notch and Delta in the cytosol, respectively. A_c is the intracellular domain of Notch that is separated from the membrane periphery after binding of the Notch in the membrane to Delta in the neighboring cell. The free A_c activates the production of Notch in the cytosol and represses the production of Delta in the cytosol at the same time. N_c and D_c diffuse and move to the membrane. (B) Example scheme of multi-cellular model including explicitly expressed cell geometry. Ω_i is the region of *i*-th cell. The region of red in the membrane in *i*-th cell indicates the place where the *i*-th cell is contacting the neighboring cells (i.e., the surface of cell-to-cell contact). The side figure shows a schematic dynamics of each cell. (For interpretation of the references to color in this figure caption, the reader is referred to the web version of this paper.)