Diffusible ligand and lateral inhibition dynamics for pattern formation

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Equivalent cells interact and become distinct, creating periodic patterns of different cell types during organism development. Interactions between neighboring cells can be mediated by the binding of two different proteins, receptors and ligands, each anchored in a different cell membrane. Theoretical studies have shown that this interaction can drive spontaneous pattern formation when feedback is present. There is experimental evidence pointing to soluble ligands that diffuse and signal. In this work, we study which is the effect of an additional diffusible ligand on the appearance of a pattern. Positive and negative roles of diffusion on the pattern has been found.

I. Introduction

Cells can interact through the binding of proteins at their membranes and signal, accordingly, to neighboring cells. This type of cell-to-cell communication, the so-called juxtacrine signaling, has been shown to enable the formation of fine grained patterns of differentiated cells. Specifically, juxtacrine signaling occurs when two types of transmembrane proteins, receptors and ligands, anchored in the membranes of two neighboring cells bind. After binding, a signal arises within the cell harboring the receptor. Lateral inhibition occurs when the signal inhibits the production of the ligand. Theoretical studies have shown that juxtacrine signaling can drive self-organization and the spontaneous formation of fine grained patterns of different cells [2].

The process of lateral inhibition during neurogenesis is a paradigmatic example of pattern formation through juxtacrine signaling. Lateral inhibition occurs when cells prevent their neighboring cells from becoming their same type of cell . In this context, lateral inhibition has been shown to be mediated by juxtacrine signaling through receptor Notch and ligand Delta. As a result, two different kinds of cells arise (neurogenic and epidermal) characterized by opposite levels of Notch and Delta concentrations.

There is experimental evidence indicating soluble diffusible extracellular ligand Delta binding to receptor Notch and activating the pathway, driving a signal [3] . However, it is still unknown how this diffusible ligand participates in lateral inhibition dynamics [4].

II.A Model For Juxtacrine and diffusion Mediated interaction

We propose a model for lateral inhibition dynamics with feedback that takes into account juxtacrine signaling and a diffusible ligand [1]. It reads as follows:

$$\frac{dl_i}{dt} = k_{-d}\tilde{l}_i - k_d l_i + \nu\{g(s_i) - l_i\} \quad (1)$$

$$\frac{d\tilde{l}_i}{dt} = -k_{-d}\tilde{l}_i + k_d l_i - \epsilon\tilde{l}_i + D\nabla_i^2\tilde{l}_i \quad (2)$$

$$\frac{ds_i}{dt} = f(\langle l_i\rangle + \rho\tilde{l}_i) - s_i \quad (3)$$

where the subindex i means that we are referred to the cell i, s stands for the receptor, l and $\tilde{l}$ for the non difusible and difusible ligand activities respectively. $\langle l_i\rangle$ denotes the mean of the levels of ligand activity in the cells adjacent to cell i. Thus, this term is responsible for the juxtacrine interaction. f and g are continuous increasing and decreasing Hill functions respectively. ρ measures the differential affinities between the receptor and the two ligands. k_d and k_{-d} stand for the rates of conversion from non-diffusible to soluble difusible ligands and vice versa, and D are the rates of linear degradation and diffusion of the soluble ligand respectively, $\nabla_i^2 x_i$ stands for the discrete Laplacian.

Through this model, we analyze numerically (by integrating the dynamics over time) and analytically (by doing linear stability analysis and computing the exact stationary states) the effect of diffusion on the formation of a pattern of differentiated cells.

III. Conclusions

Our results show that diffusion of the ligand has both positive and negative roles when it is coupled to lateral inhibition dynamics with feedback. Diffusion tends to destroy the pattern by stabilizing the homogeneous solution in a larger region of the parameter space and by reducing the difference between the cell types being formed. However, diffusion helps to create patterns with an exact periodicity. Moreover, our results apply the concept of bistability and discontinuous transitions of cell-autonomous non-spatially dependent dynamics for cell differentiation to pattern formation processes.

References

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