Inter and intracellular interactions for embryonic pattern formation

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Several patterns of differentiated cells in developing embryos result from the direct intercellular interaction between neighbouring cells[1]. This intercellular interaction is mediated by two proteins, termed ligand and receptor respectively, which are anchored on the cell membranes. A cell with the ligand protein can interact with a cell harbouring the receptor protein through the binding of these proteins. Once the binding occurs, a signal is transmitted into the cell having the receptor. A paradigmatic example of this kind of intercellular interaction eliciting a pattern of differentiated cells is the lateral inhibition process mediated by Notch signalling pathway, which results in the determination of two distinct cellular fates distributed in a spatially ordered pattern. This process occurs in the developing nervous system of vertebrates and invertebrates, where a cell adopting a particular fate (neural) interacts with their neighbouring cells preventing them from adopting the same cellular fate (these cells become epithelial cells). Herein we extend a theoretical characterization of this process[2] to analyse the role of receptor-ligand binding in the same cell (intracellular interactions) and of diffusible ligand. Despite there is experimental evidence on these two other kinds of interactions[3,4], their function and interplay with the pattern formation process is unknown.

A simple scenario capturing the essential features for the emergence of a pattern from a lateral inhibition process reduces the overall process to the dynamics of two variables per cell (related to the ligand and the receptor, respectively)[2]. If intracellular interactions are introduced, assuming that they elicit the same signal as intercellular interactions, the dynamics can be described by the following model:

$$\begin{aligned} \dot{n}_P &= f((1-\mu)\bar{d}_P + \mu d_P) - n_P \\ \dot{d}_P &= v\{g(n_P) - d_P\} \end{aligned} \qquad (1)$$

where the subindex P means that we are referred to the cell P, n stands for the receptor and d for the ligand activities respectively. $\bar{d}_P$ denotes the mean of the levels of ligand activity in the cells adjacent to cell P. Thus, this term is responsible for the intercellular coupling. f and g are continuous increasing and decreasing Hill functions respectively.μ and $(1-\mu)$ are the fractions of signal coming from intracellular and intercellular interactions.v is related to the ratio of the lifetimes for the receptor and ligand. If all signalling results from intercellular interactions ($\mu = 0$), a periodic pattern emerges in a wide parameter region involving strong feedback, with two types of cells: cells with high levels of n and low levels of d, and cells with low levels of n and high levels of d[2]. In the presence of intracellular signalling and below a critical value of μ, which can be obtained by means of a linear stability analysis, the same periodic pattern can still emerge (Figure 1). However, our results show that these intracellular interactions reduce the parameter region where the pattern of two distinct cell types arises. If diffusible ligand is taken into account, similar qualitative results are found.

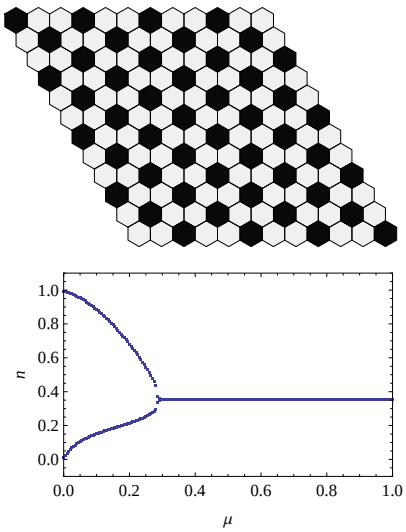

Figura 1. Top: Simulation results. Pattern formation in an hexagonal array of cells. Cells with low (high) levels of n are depicted in black (white). Bottom: numerical results of the fixed points of receptor activity *versus* the μ parameter. When intracellular signalling dominates over intercellular signalling, there is just one branch, so the pattern disappears.

Hence, stronger feedback is required to create a pattern in the presence of either intracellular signaling or diffusible ligand.

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