Cell fates under lateral inhibition

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Abstract

1 Introduction

2 Lateral inhibition

The simplest mechanism involving lateral inhibition starts with an array of cells producing a certain ligand which binds to the receptors of neighboring cells. Such ligand-receptor interactions induce a signalling which inhibits the production of the ligand. This scenario implies that the more ligand a cell has, the more will activate the signalling in its neighbors and inhibit their ligand production. The result of such a process suggests that in an array of similar interacting cells, the final state will consist on activated (with high ligand concentrations) cells surrounded by inactivated (low or no ligand concentration) ones, thus composing a well defined pattern.

A mathematical analysis of lateral inhibition dynamics was first performed by Collier *et al*, in which the ligands of the cells bind to certain receptors and activate a signal in neighboring cells while this very signal inhibits the production of such ligand. Each cell is assumed to follow the nondimensional equations:

$$\frac{ds_i}{dt} = \frac{r\langle l\rangle^n}{1+r\langle l\rangle^n} - s_i, \quad \frac{dl_i}{dt} = v\left(\frac{1}{1+bs_i^m} - l_i\right) \tag{1}$$

where s_i and l_i are the signal (we can think of it as the receptor concentration) and the ligand concentration produced by cell i. The constants r and b measure, respectively, the activation of the signalling by ligands and the ligand inhibition due to signalling. v is the ratio of the degradation rates of receptors and ligands, and is thus a measure of the relative time-scales over which the levels of ligand and signal activity vary. Finally, n and m measure the cooperativity of signal activation by ligands and ligand inhibition by signals, respectively. The quantity $\langle l\rangle$ is understood as an average over neighboring cells, i.e.

$$\langle l\rangle = \frac{1}{N}\sum_j l_j \tag{2}$$

where N is the number of neighbours. Such model is known to display stable *salt-and-pepper* patterns, that is, active cells surrounded by inactive ones (Figure 1).

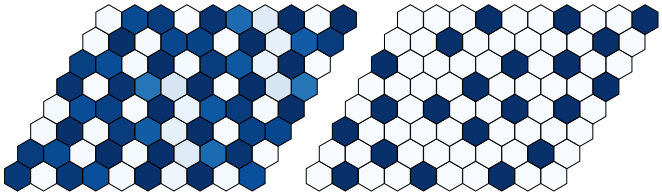

Figure 1: Typical stable pattern solutions of the Collier model in an hexagonal grid with periodic boundary conditions showing the concentration of ligand (from 0 (white) to 1 (dark blue)), generated from random initial conditions and with activation rates $r = 0.005$ (left) and $r = 100$ (right). The remaining parameters are set to $b = 10^4$, $n = m = 4$ and $v = 1$.

The dynamics of possible pattern solutions can be understood through the two-cell system. Such system gives us important important understanding of the behaviour of the model. In the Collier model, the two cell system can be written as:

$$\frac{ds_i}{dt} = \frac{rl_j^n}{1+rl_j^n} - s_i, \quad \frac{dl_i}{dt} = v\left(\frac{1}{1+bs_i^m} - l_i\right) \tag{3}$$

where for $i = 1$ then $j = 2$ and viceversa. Different dynamic regimes can be understood by looking at the corresponding bifurcation diagram, as in Figure 3.

For $r < r_c \simeq 0.07$ (grey area, I) the two cells have the same steady states of s and l. As r crosses r_c (white area, II), two new stable branches emerge separated by an unstable one. These branches correspond to opposite states the cells, that is, one of the cells will reach high values of s and low values of l while the other won't produce any s and will have high l.

Increasing the values of n, m or v reduces the time taken for the final pattern to emerge.

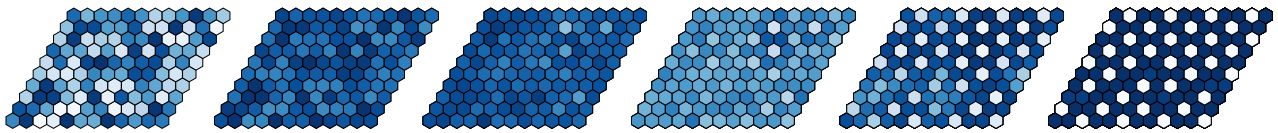

Figure 2: Snapshots of the time evolution of an hexagonal array of cells under lateral inhibition interactions of the Collier model. The initial state consists on random values of signal and ligands, which evolves towards an homogeneous salt-and-pepper pattern. Parameters are set to $r = 100$, $b = 10^4$, $n = m = 4$ and $v = 1$.

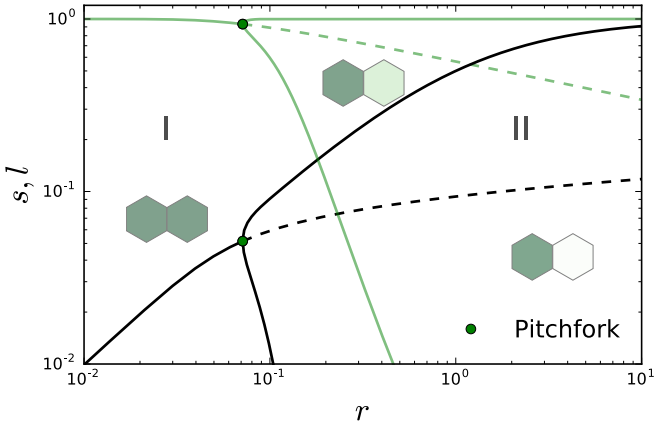

Figure 3: Bifurcation diagram of the two-cell Collier model for s (black line) and l (green line) as the parameter r increases. Solid lines indicate stable steady states, while dashed lines indicate unstable ones. Shaded areas separate distincs dynamic regimes. The parameters for this diagram are $b = 10^4$, $n = m = 4$, $v = 1$.

3 Antagonistic ligands and the onset of oscillations

Here we propose a model in which cells also produce a ligand which is activated by the signal. The equations of the Collier model are then modified to:

$$\frac{ds_i}{dt} = \frac{r_1\langle l_1\rangle^{h_{s1}} + \varepsilon r_2\langle l_2\rangle^{h_{s2}}}{1 + r_1\langle l_1\rangle^{h_{s1}} + \varepsilon r_2\langle l_2\rangle^{h_{s2}}} - s_i \tag{4}$$

$$\frac{dl_{1,i}}{dt} = v\left(\frac{1}{1 + b_1 s_i^{h_1}} - l_{1,i}\right) \tag{5}$$

$$\frac{dl_{2,i}}{dt} = v\left(\delta + (1-\delta)\frac{b_2 s_i^{h_2}}{1 + b_2 s_i^{h_2}} - l_{2,i}\right) \tag{6}$$

where, as before, when $i = 1$, $j = 2$ and viceversa. Here r_1, b_1, h_{s1} and h_1 play, respectively, the role of r, b, n and m in the original Collier model. The parameter r_2 measures the strength of signal activation by l_2, while b_2 the activation of l_2 by the signals. The exponents h_{s2} and h_1 appear as new cooperativity parameters, and δ as a rate representing the probability of constitutive l_2 production with respect to its activation by s.

In this case, the presence of a ligand l_2 which is activated by the signal can induce novel behaviors in the system. For example, a cell with high concentration of l_1 will induce high signalling to its neighbours, thus inhibitiog the production of l_1 and activating l_2. If the activation of l_2 is too small ($r_2 \ll r_1$) then lateral inhibition will be predominant and salt-and-pepper patterns will emerge.

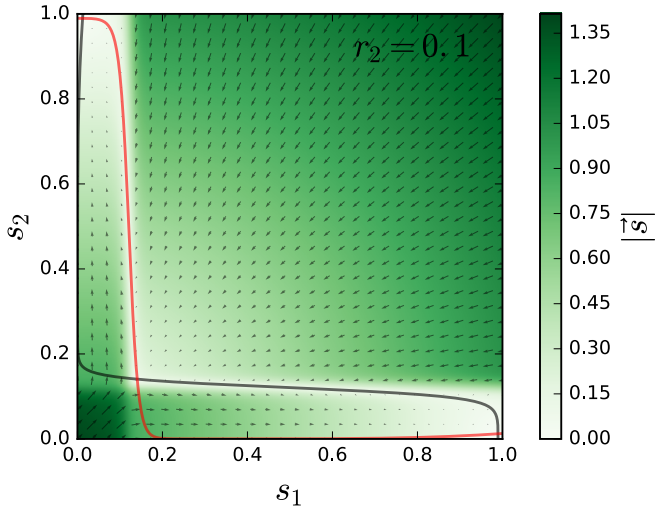

Figure 4: s_1 and s_2 nullclines for the two-cell system for $r_2 = 0.1$, $r_1 = 95$, $\varepsilon = 1$, $b_1 = 10^4$, $b_2 = 1$, $h_{s1} = h_{s2} = h_1 = h_2 = 4$, $v = 1$ and $\delta = 0.2$. Arrows indicate the direction of the vector field $\vec{s} = (s_1, s_2)$, while color shows the intensity of such field measured by the modulus $|\vec{s}| = \sqrt{s_1^2 + s_2^2}$.

However, for large activation rates ($r_2 \gg r_1$) cells will effectively activate themselves, forming an homogeneous pattern. For intermediate regimes, oscillations can be observed, as competition between the two kinds of ligands makes the signalling to increase and decrease periodically. If we plot the nullclines of the system (Figures 4 and 6) we can see this behaviour. These different regimes can be encompassed in a bifurcation diagram (Figures 8).

For small values of r_2 (region I, grey) the system has two opposed steady states, separated by an unstable one, corresponding to high and low levels of signalling. This is the limit in which the ligand l_2 is inoperative and does not play a role in the dynamics. As r_2 increases, the stable fixed points lose their stability and a pair of limit cycles appear through supercritical Hopf bifurcations (region II, light blue). These limit cycles disappear as r_2 further increases giving birth to two stable branches (region II, light purple) that culminate in a supercritical pitchfork bifurcation. From this point, a bistable regime

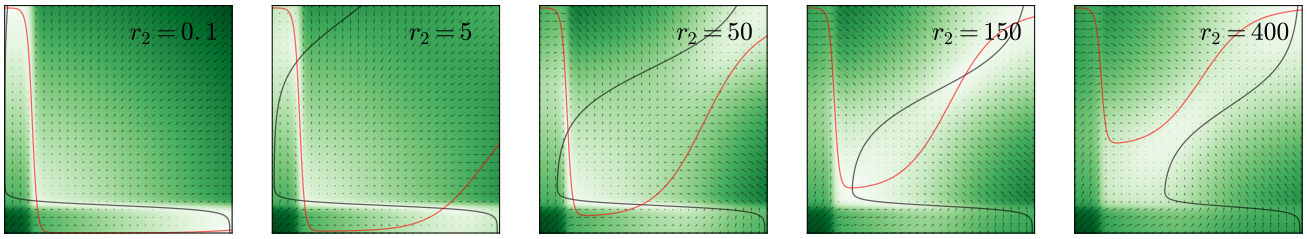

Figure 6: Nullclines and fixed points of the system as r_2 increases. Parameters are set to $r_1 = 95$, $\varepsilon = 1$, $b_1 = 10^4$, $b_2 = 1$, $h_{s1} = h_{s2} = h_1 = h_2 = 4$, $v = 1$ and $\delta = 0.2$.

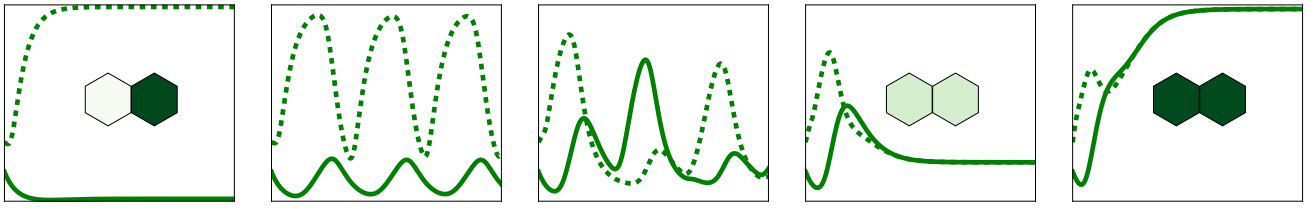

Figure 7: Trajectories of the signals s_1 (thick line) and s_2 (dashed line) for the nullclines of the above figures. As r_2 changes, distinct dynamical behaviours are observed: from opposed states for small r_2 to oscillations and to homogeneous states for large r_2. Axis limits are those of Figure 5.

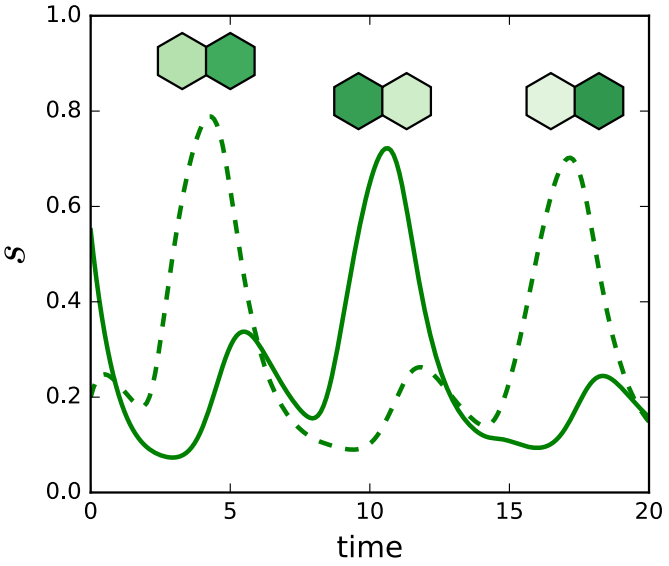

Figure 5: Example of oscillatory trajectory of s_1 (thick line) and s_2 (dashed line) for parameters $r_1 = 95$, $r_2 = 50$, $\varepsilon = 1$, $b_1 = 10^4$, $b_2 = 1$, $h_{s1} = h_{s2} = h_1 = h_2 = 4$, $v = 1$ and $\delta = 0.2$.

appears (region IV, turquoise) confined between two saddle-node bifurcations. Finally, as r_2 crosses the last bifurcation point, a single equilibrium remains as the only steady state of the system (region V, light green).

4 Patterns

If we consider a whole array of cells, the dynamical regimes obtained also include salt-and-pepper patterns, oscillations and homogeneous patterns (Figure 9), but also, if initial conditions are carefully chosen, stripes (Figure 8). In the oscillatory regime, we can observe travelling waves and synchronized pulses (see videos).

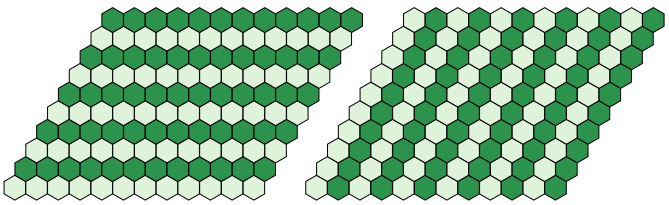

Figure 8: Stable stripe patterns for $r_2 = 0.01$.

5 Analysis of oscillations

In the oscillatory regime, each pair of neighbour cells acts as an individual oscillator coupled with all other pairs. Thus we can define an angular variable ϕ_{ij} for each pair of cells i, j and study its dynamics in this regime. We choose

$$\phi_{ij} = \tan^{-1}(s_i/s_j) \tag{7}$$

then the dynamics are given by

$$\dot{\phi}_{ij} = \frac{1}{s_i + s_j}\left(\frac{ds_i}{dt} - \tan\phi_{ij}\frac{ds_j}{dt}\right) \tag{8}$$

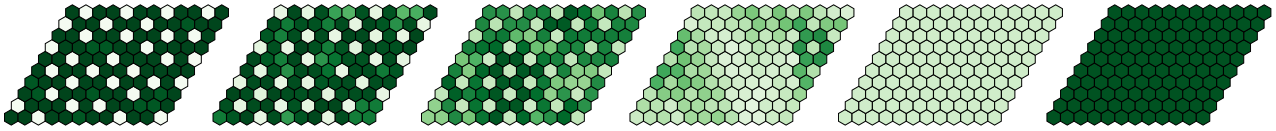

Figure 9: Steady state patterns for the two-ligand model for different values of r_2, starting with random initial conditions. From left to right: $r_2 = 0.001, 0.01, 0.05, 0.1, 0.5, 1$. The first and last patterns correspond to true steady states, while the second, third and fourth are just snapshots of oscillating patterns (see videos). The remaining parameters are $r_1 = 95$, $b_1 = 10^4$, $b_2 = 1$, $h_1 = h_2 = h_{s1} = h_{s2} = 4$, $\varepsilon = 1$ and $\delta = 0.2$.

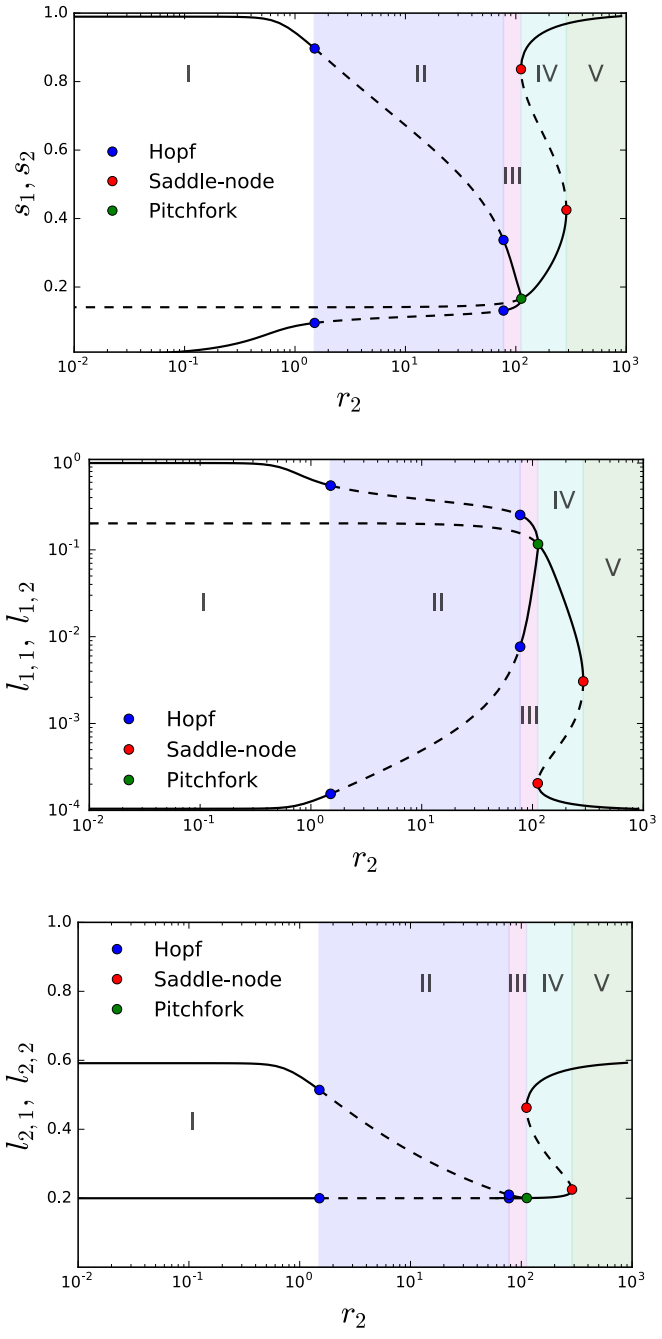

Figure 10: Stability of fixed points of the signal s (top) and ligands $l_{1,1}, l_{1,2}$ (middle), $l_{2,1}, l_{2,2}$ (top) as the parameter r_2 changes. Solid lines represent stable fixed points, while dashed lines unstable ones. Parameter values are $r_1 = 95$, $b_1 = 10^4$, $b_2 = 1$, $h_1 = h_2 = h_{s1} = h_{s2} = 4$, $\varepsilon = 1$ and $\delta = 0.2$. Different stability regions I-V are highlighted with different colors.