Capturing Spatiotemporal Patterns in Cell Differentiation by Local Cell-Cell Communication Modeling

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Introduction

The understanding of how multi-cells systems (such as tissues and organs) are spatially and temporally organized and how they react to external stimuli orchestrating responses as a whole, requires the comprehension of regulatory mechanisms both at the single-cell level and at the cell-to-cell communication level.

In this work, we describe a simple fate decision regulatory module working at single-cell level and show how macroscopic behaviour of the system as a whole changes depending on cell-to-cell and/or cell-environment communication.

Methods

An essential single cell model

The model we adopt to describe fate-decision in a differentiation process at the single cell level is taken from [2]. In this work the authors describe the minimal network and dynamical model for central nervous system differentiation using a set of stochastic differential equations. Here we focus only on the first fate-decision step, regulated by the sub-network reported in Figure 1. The sub-network consists of two mutually inhibiting genes, *Mash 1* and *Hes 5*. In mature cells differentiated to *neurons*, *Mash 1* is over-expressed with respect to *Hes 5* whereas in mature cells differentiated to *glia*, *Hex 5* is over-expressed with respect to *Mash 1*. The remaining gene, *Pax 6*, that promotes both the other genes transcriptions, is used in [2] to control the stage of the differentiation: large levels of *Pax 6* keep the cell in the undifferentiated stage, while decreasing it enforces differentiation and hence the prevalence of one of the competing genes on the other.

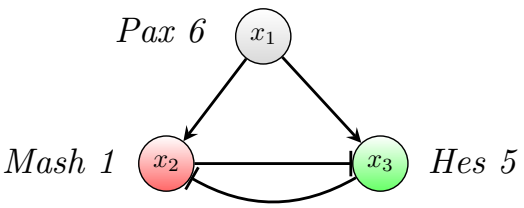

Figure 1: Network for the one step fate-decision proposed in [2] for glia-neuron differentiation.

The stochastic equations of the network are:

$$Pax\ 6:\ \dot{x}_1 = -\gamma x_1 + \xi_1 \tag{1}$$

$$Mash\ 1:\ \dot{x}_2 = a\frac{x_1^n}{1 + x_1^n + x_3^n} - kx_1 + \xi_2 \tag{2}$$

$$Hes\ 5:\ \dot{x}_3 = a\frac{x_1^n}{1 + x_1^n + x_2^n} - kx_3 + \xi_3, \tag{3}$$

where x_1, x_2 and x_3 denotes the concentration of *Pax 6*, *Mash 1* and *Hes 5* respectively, while $\gamma = 0.02$, $n = 4$, $a = 4$, $k = 1$ are fixed parameters taken from [2]. $\xi_1(t), \xi_2(t), \xi_3(t)$ are mutually independent Gaussian white noises with variance $D = 0.005$.

Notice that the Gaussian white noise component in (1)-(3) makes the final fate not deterministic and hence different from cell to cell even if the initial condition is the same. Moreover, note that *Pax 6*, as in [2], is forced to undergo an exponential decrease (1).

Cells Interaction Model

The local fate evolution is known to depend on local mechanical stimuli [3] as well as the spatial distribution of cytokines. Cytokines secretion and sensing constitutes one of the fundamental mechanism for cell-to-cell communication [3]. Therefore, moving from a single (isolated) cell to a group of interacting cells, cell-cell and cell-environment communication phenomena must be taken into consideration.

In this direction, we consider N cells spatially organized in a grid of dimension $P \times Q$ ($N = PQ$). We assume that the ith cell ($i \in [1 \dots N]$) can interact only with its neighbor cells j, $j \in \mathcal{N}_i \subseteq [1, \dots N]$, with $\mathcal{N}_i$ denoting the set of neighbours of cell i. Then, we modify single cell equations (2)-(3) as follows:

$$\dot{x}_{i,2} = a\frac{x_1^n}{1 + x_1^n + x_{i,3}^n} - kx_{i,2} + f_{i,2} + b_{i,2} + \xi_{i,2}$$

$$\dot{x}_{i,3} = a\frac{x_1^n}{1 + x_1^n + x_{i,2}^n} - kx_{i,3} + f_{i,3} + b_{i,3} + \xi_{i,3},$$

where

$$f_{i,2} := \mu \sum_{j \in \mathcal{N}_i} \frac{x_{j,2}^n}{1 + x_{j,2}^n + \mu x_{j,3}^n} \qquad b_{i,2} := k\bar{x}_{i,2}$$

$$f_{i,3} := \mu \sum_{j \in \mathcal{N}_i} \frac{x_{j,3}^n}{1 + x_{j,3}^n + \mu x_{j,2}^n} \qquad b_{i,3} := k\bar{x}_{i,3}.$$

Cell-to-cell communication is introduced by including a simple feedback $f_i := [f_{i,2},\ f_{i,3}]^T$ for which a cell differentiating to a cellular type promotes its neighbours to have the same fate. Notice that f_i is influenced only by $x_{j,2}$ and $x_{j,3}$ for $j \in \mathcal{N}_i$, and that the strength of the feedback depends on the parameter μ. The feedback term includes two effects: *i*) positive feedback among type-specific genes of the same type; *ii*) negative feedback among type-specific genes of different types.

Cell-environment interaction is introduced by including the term $b_i := [b_{i,2},\ b_{i,3}]^T$ acting only on the cells on the boundary of the grid (boundary effect) and mimicking a mechanical stimuli ($b_i = 0$ if the ith cell is not on the boundary).

Results

We consider $N = 2500$ cells organized in a grid with $P = Q = 50$, and we assume that each cell communicates with at most 8 cells (that are the cells located in the upper, upper-right, right, down-right, down, down-left, left, and upper-left positions).

Figure 2 shows simulated differentiation processes without boundary effect and different values for the feedback parameter μ. It is apparent that weak cell-cell interaction leads to jagged borders between cell subpopulations, while stronger interaction results in sharper differentiation bounds.

Figure 3 investigates the effect of feedback in the presence of an external stimulus enforcing differentiation (either to neuron or to glia) in certain cells. At the end of the simulated differentiation processes enforced patterns can be identified. In addition, as previously noticed, cell-cell interaction's strength determines sharpness of edges between cell subpopulations.

Conclusions

Despite numerous simplified assumptions, the results show that this simple model for cell-to-cell and cell-environment interaction is able to capture, as the feedback intensity parameter varies, different macroscopic emerging behaviours such as sharp differentiations or islet formation. Interest in this kind of models is stimulated by recent technology advancements [1, and references therein] that allow the observation of mRNAs synthesis, proteins production, genes expression within a single cell, for hundreds of cells in parallel, instead of their average values from cells in bulk. Model validation with real data from single-cell experiments represents our future research direction.

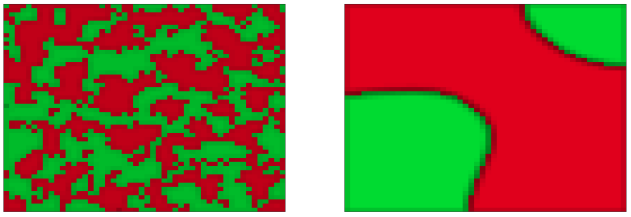

Figure 2: Differentiation without boundary effect and different level of cell-to-cell interaction, $\mu = 0.05$ (left, weak interaction) and $\mu = 0.5$ (right, strong interaction). Red cells evolved to neurons, green ones to glia.

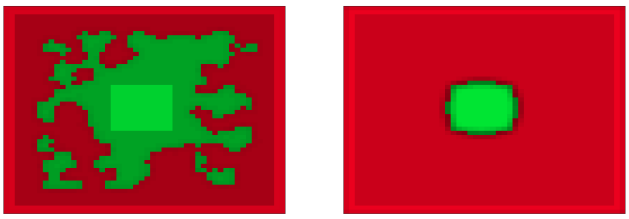

Figure 3: Differentiation with border effect: outer border forced to neurons, inner square forced to glia. Weak cell-to-cell interaction ($\mu = 0.05$, left) is compared with a strong one ($\mu = 0.5$, right). Red cells evolved to neurons, green cells evolved to glia.

Acknowledgment

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References

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[2] X. Qiu, S. Ding, and T. Shi. From understanding the development landscape of the canonical fate-switch pair to constructing a dynamic landscape for two-step neural differentiation. *PLOS ONE*, 7(12):1–14, December 2012.

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