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A proposition of Intra- and Interspecies Cell-Cell Communication System

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Abstract

All living organisms depend on highly complex networks of intercellular signals to coordinate cell-cell communication in various physiological functions. A large number of mechanisms that rely only on cell signaling are capable of development, collective behavior, self-repair and immunity. This abstract proposes the use of an ANN-based GRN model to orchestrate cell-cell communication in two contexts: unicellular organism via Quorum Sensing and multicellular organisms via Notch signaling pathway. A simple grammar inspired from membrane computing is proposed to describe the dynamic cell-like structure.

Introduction

Communication is vital to life. It represents the coordination of cells and tissues to accomplish various physiological functions as well as the adaptation to the environment. All forms of life on earth (eukaryotes, prokaryotes and metazoan organisms) need to communicate to survive.

Over hundreds of millions of years, evolution of metazoan organisms has produced a complexity both in phenotypes as well as the developmental mechanisms by which this complexity is generated. It is now known, in developmental biology, that this process is based on good coordination of intra and intercellular communication signals. Indeed, a small toolkit of cell signaling co-opted recurrently during development is sufficient for tissue morphogenesis, angiogenesis and metastasis.

Cell-cell communication occurs when a molecular signal is emitted by a cell called emitting cell and recognized by another cell called receiving cell. Basically, signals are composed of growth factors, hormones, cytokines, and neurotransmitters that bind to specific cell receptors. This ligand-receptor interaction then generates several types of intracellular signals that may be relayed by downstream signaling and by protein phosphorylation cascades. Finally, these intracellular signals lead to the activation of transcription factors that regulate target genes responsible for the expression of diverse biological outcomes: activation of cell cycle, proliferation, differentiation.

It does not come as a surprise that "Unicellular organisms including both eukaryotes (e.g. yeast) and prokaryotes (e.g. bacteria) utilize similar communication systems as multicellular organisms. For example: receptors for insulin are present in Drosophila which are similar to their vertebrate counterparts in binding properties, general structure, and insulin-stimulated enzyme activity." [1]

In the artificial life community, cellular interactions have been investigated using cellular automata [2, 3], agent-based models [4], and GRN-based dynamics [5]. In most of these models, cell–cell interactions are abstract and they do not rely on an advanced exploration of the underlying biological mechanisms. In fact, communications between cells are based on: a diffusion system, information pathway passed through neighboring cells, or the concentration of a molecule that has a direct effect in regulating gene expression and cell behavior. Moreover, communication between unicellular organisms like bacteria Quorum Sensing has not been well investigated by the Artificial Life community. Here, we assume that more realistic unicellular and multicellular approaches must involve more investigation of, the architecture of the chemical communication network, how chemical information is transduced to control gene expression; how intra- and interspecies cell-cell communication is accomplished; and the fascinating option of unicellular-multicellular crosstalk.

ANN Based GRN Model

Various modeling techniques have been developed to simulate the functioning of the GRN. They can be divided into two classes. The first class: logical models, including Boolean networks and their variants. Although effective in dealing with noise, they fail to consider temporal dynamic aspects that are important features of regulatory network [6]. The second class: Continuous models based essentially on differential equations allow more detailed descriptions of GRN dynamics.

To describe the dynamics of a generic GRN supervising cell-cell communication, we use an Artificial Neural Network (ANN) modeling technique introduced by Vohradsky [7]. Formally, an ANN is defined by:

$$dX_i/dt = v_i f\left(\sum_{j=1}^{N} w_{ij}X_j - \vartheta_i\right) - k_i X_i \quad \vartheta_i v_i k_i > 0$$

- X_i, with $i = 1, \dots, N$, is the i-th gene product concentration.
- v_i: is the maximal expression rate of gene i.
- w_{ij} is the connection weight of control of gene j on gene i. Positive values of wij indicate enhancing influences while negative values define inhibiting influences.
- ϑ_i: is the influence of external input on gene i, which modulates the gene's sensitivity of response to activating or repressing influences.
- f: Represents a non-linear sigmoid transfer function modifying the influence of gene expression products X_i and

external input ϑ_i to keep the activation from growing without bounds.

- k_i Degradation of the i-th gene expression product.

We extend the formula to take into account cellular processes (e.g., signal translation) that influence the gene sensitivity.

Dynamic cell-like structure

Based on the idea that a cell is a complex structure, we consider a cell as a multi-set of objects arranged in regions and delimited by another main object which is the membrane. Each object within the cell is composed of a multi-set of objects also. An object can be: a lipid, a protein, a receptor, a cytoplasm or a nucleus. So, the model of the cell-like structure is a hierarchical arrangement of multi-sets of objects.

To simulate this hierarchical arrangement of the cell structure, we introduce a simple cellular grammar inspired from formal grammars like in Membrane Computing [8]. However, rules of the grammar don't govern (in any way) development. Development occurs through cellular interactions that lead to gene expression and regulation. Thus, rules are just a formal description of the cell-like structure. This formal description can be used to observe the resulting changes in the cell structure and deduce the resulting grammar. Membrane computing is a computational model that solves NP complete problems. This can be used to investigate the computational power of the resulting digital organisms.

Application on unicellular organisms (Quorum Sensing)

Bacterial cell-cell communication, termed Quorum Sensing (QS), is a signal-response process that regulates gene expression according to the cell density in order to coordinate collective behaviors. In [9], we have introduced a molecular network that uses Ordinary Differential Equations (ODEs) to calculate the concentration of Gram negative bacteria QS components. The simulation shows that bacterial cells are able to form micro-colonies and behave like a multicellular organism (figure 1). The principal limitation of the model resides in the use of a proposed algorithm of QS to simulate bacteria cells communication instead of a regulation mechanism that describes the mutual enhancing-inhibiting influences in genes of a GRN. Moreover, bacterial response to QS is various and includes biofilm formation, bioluminescence, drug-resistance... Our work focuses on investigating the underlying mechanisms behind these phenomena; how chemical information is transduced to control gene expression, and observing in simulation the emerging phenotypic traits.

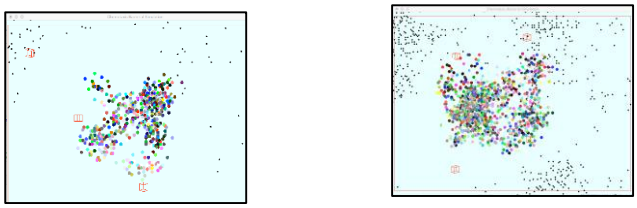

Figure 1: Micro-colonies of moving bacteria emerged from QS communication [9].

Application on multicellular Organisms (Notch signaling pathway)

Notch signaling plays a central role in cell differentiation decision via the lateral inhibition process, which is a common phenomenon during selection of neural and muscle precursor cells [10]. Briefly, two or more equivalent cells express both the receptor Notch and the ligand. A negative feedback loop operates so that ligand expression became repressed in some cells which will be specialized on receiving cells, and this will lead to asymmetry. Despite the fact that the Notch pathway has a myriad of roles in different developmental and disease contexts, it is relatively simple in its functioning. This is why, we made the choice of using specifically this signaling pathway as instance of our model.

Conclusion

In the lineage of our previous work [11], we use Generative Developmental Systems (GDS) that consist of a grammar inspired by membrane computing to simulate the dynamic structure of the cell. This is made to explore the computational power of the emerged organisms.

Multicellular organisms are ecosystems that cohabit cells of the organism and other microorganisms that are bacteria. We assume that a link must be made for a future study of both the artificial ecosystem and the pathological context (QS virulence pathway) considering the two species.

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