Fixed Boundaries Influence in Biological Networks: From Theory to Application

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Abstract. The purpose of this paper is to present some results about the influence of fixed boundary conditions in biological regulation networks. More precisely, we will present theoretical and simulation results in the context of theoretical connected regulation networks on $\mathbb{Z}^d$. These results will show under which conditions phase transitions emerge from the asymptotic behaviour of such networks when they are subjected to the influence of fixed boundaries. Furthermore, we will expose some mathematical results obtained on the regulation network of the floral morphogenesis of the plant *Arabidopsis thaliana* that explain experimental results on the necessary presence of a Gibberellin hormone for the plant to develop normally.

Keywords: Dynamical systems, biological regulation networks, boundary conditions, robustness.

1 Introduction

The comprehension of the behaviour of real biological systems is a difficult problem that researchers, from many different disciplines, are now more and more to study. Some works have highlighted the particular topology of biological networks such as gene regulation networks [1,2]. Nevertheless, their behaviour can be sometimes better understood by studying more theoretical networks such as the ones of cellular automata [3]. Certain cellular automata, for instance the Game of Life, are known to present some features very close to real life systems. However, most researches have been focused on the comprehension of emergent phenomena in infinite and periodic (toric) cellular automata [4,5], which could be criticised. Indeed, living systems do not develop infinitely and each of their components, *e.g.*, a cell, is confined in a large but finite space. Thus, in this presentation, we decide to focus on finite systems, with fixed boundaries surrounding them. More precisely, we will study the influence of these fixed boundaries on biological systems whose evolution follows extended Hopfield-like laws [6].

After a presentation of the main notations and definitions of the biological regulation networks models that we have decided to study, we will expose some

theoretical and simulation results obtained on regular theoretical regulation networks whose nodes are located at vertices of lattices on $\mathbb{Z}^d$. In particular, we will show that the influence of boundaries can lead to the emergence of phase transitions.

In a second part, in the theoretical context of dynamical systems, we will present some results on the robustness of the attraction basins of a real biological network against stochastic state perturbations. In particular, we will explain mathematically the impact of a Gibberellin hormone on the gene regulation network of the floral morphogenesis of the plant *Arabidopsis thaliana*.

2 Hopfield-Like Networks

In this work, we consider regulation networks whose evolution follows two different versions of an Hopfield-like law depending on the properties that we want to highlight. Thus, in the first part of this paper, we will focus on an extended stochastic Hopfield rule whereas we will use in the second part an extended deterministic Hopfield rule.

We will denote by R a connected threshold boolean network of n nodes which are located at vertices of $\mathbb{Z}^d$. We assume that these nodes have two possible activity states, defined by:

$$\sigma_i(t) = \begin{cases} 0 & \text{if the node } i \text{ is inactivated at time } t, \\ 1 & \text{if the node } i \text{ is activated at time } t. \end{cases}$$

Let $\sigma(t) = (\sigma_i(t))_{i \in R} \in \Omega = \{0,1\}^n$ be the current configuration of the network at time t, where Ω is the set of all possible configurations of R.

Such a network can be represented by a matrix $W_{n \times n}$, called the interaction matrix. In this matrix, the coefficient $w_{ij} \in \mathbb{R}$ represents the interaction potential of the influence exerted by the node j on the node i.

Definition 1. *The neighbourhood of a node i, denoted by $\mathcal{N}_i$, is the set of nodes j for which the interaction potential does not vanish. More formally, we have: $j \in \mathcal{N}_i \Leftrightarrow w_{ij} \neq 0$.*

Let us denote by $H(\sigma_i(t))$ the activation potential of the node i at time t. $H(\sigma_i(t))$ is then defined by:

$$H(\sigma_i(t)) = \sum_{j \in \mathcal{N}_i} w_{ij} \cdot \sigma_j(t)$$

From this activation potential, we define the two following evolution rules, the first (resp. second) one corresponding to a deterministic (resp. stochastic) evolution of the network. In the sequel, we will speak about deterministic and stochastic Hopfield-like models. In these two definitions, the parameter θ_i denotes the activation threshold of the node i.

Definition 2. *In the deterministic model, the state of the node i at time $t+1$ is computed by:*

$$\sigma_i(t+1) = \mathcal{H}(H(\sigma_i(t)) - \theta_i)$$

where $\mathcal{H}$ is the Heaviside step function defined by: $\mathcal{H}(x) = \begin{cases} 0 & \text{if } x \leq 0, \\ 1 & \text{otherwise.} \end{cases}$

Definition 3. *In the stochastic model, the state of the node i at time $t+1$ is computed by [7]:*

$$P(\sigma_i(t+1) = \alpha \mid \sigma_j(t), j \in \mathcal{N}_i) = \frac{e^{\alpha \cdot (H(\sigma_i(t)) - \theta_i)/T}}{1 + e^{\alpha \cdot (H(\sigma_i(t)) - \theta_i)/T}}$$

where $\alpha \in \{0, 1\}$ and T is the temperature of the network R.

Eventually, let us remark that, when $T = 0$, we recover the deterministic model. On the contrary, when T tends to infinity, the nodes are activated with probability $\frac{1}{2}$ whatever their neighbours' state is. T actually increases the randomness in the network, until it becomes equiprobable for the nodes to be activated or inactivated.

3 Boundary Conditions and Phase Transitions

In this section, we are going to expose some theoretical and simulation results about the influence of fixed boundaries on theoretical networks (regular and connected networks whose nodes are located at vertices of $\mathbb{Z}^d$) whose evolution is ruled by the stochastic model. We are not going to give the details of these results but only present the main ideas to obtain them. However, we will cite the papers, already published or accepted but needing to be revised, in which details such as the proofs of the theorems and the simulation protocol are given.

3.1 Definitions

What is called *fixed boundary* in a theoretical network is the set of nodes j of $R^c = \mathbb{Z}^d \backslash R$ (the complementary of R in $\mathbb{Z}^d$) such that: $\exists i \in R$ s.t. $j \in \mathcal{N}_i$ and $i \notin \mathcal{N}_j$. Moreover, there exist different local updating iteration modes. The mode is called *parallel* when all the nodes of the network are updated simultaneously at time t; it is called *sequential* when only one node is updated at time t and all the n nodes are updated after n iterations of time; it is called *block-sequential* when the network is divided in several blocks (disjoint subsets of vertices) and when these blocks are updated sequentially and the nodes into these blocks are updated simultaneously. Let us remark that the parallel an sequential modes are particular block-sequential modes.

3.2 Theoretical Results

First of all, let us notice that all the presented theoretical results have been proven for attractive (*i.e.*, $w_{ij} > 0$) symmetrical (*i.e.*, $w_{ij} = w_{ji}$) networks. The results presented in this subsection are detailed in [8].

The first important theoretical result concerns the updating iteration modes and is valid for any dimension. We prove that the emergence of a phase transition as a result of the influence of fixed boundaries is equivalently observable in the parallel and the sequential updating iteration modes and also in certain block-sequential cases. The idea is to find a proportionality relation between the free energies of such networks in $\mathbb{Z}^d$ when the latter use a parallel or a sequential updating rule. The proof is made by induction on different particular block-sequential modes, by reducing the size of blocks, until obtaining the sequential mode.

The second result is valid in one dimension. We prove that the influence of fixed boundary conditions cannot lead to the emergence of phase transitions and is consequently not significant in one-dimensional networks. Here, the first idea is to reduce the Markovian matrix of the system to the one of the unique neighbourhood of a node. From this, we determine under which parametric conditions a phase transition can occur. Then, we prove that the asymptotic behaviour of such networks is characterised for any parametric conditions by a probability measure that is uniquely determined when the size of network tends to infinity. We actually provide a proof of uniqueness of the invariant measure in these networks.

3.3 Simulation Results

Here, the idea is to go further and to know how fixed boundaries have an impact on more complex theoretical networks. We have decided to not limit ourselves neither to one-dimensional networks nor to attractive and symmetrical networks. However, because of the underlying difficulties in this new context, the study of these more complex networks is performed by using simulations. The results presented in this subsection can be found in [9,10].

The main results are: *(i)* the generalisation of the previous result on the absence of phase transitions in attractive and symmetrical one-dimensional networks to repulsive ($w_{ij} < 0$), not symmetrical anymore, not isotropic and not translation invariant networks; *(ii)* the numerical highlighting of the existence of phase transitions in two dimensions and the study of their geometrical shapes depending on two parameters for six different kinds of theoretical networks.

Figure 1 presents the results obtained for isotropic, translation invariant and attractive two-dimen-sional networks when they are represented by square lattices of different sizes.

4 Robustness of Attraction Basins

The studied biological regulation networks being particular discrete dynamical systems, before presenting results of robustness on these networks, we are

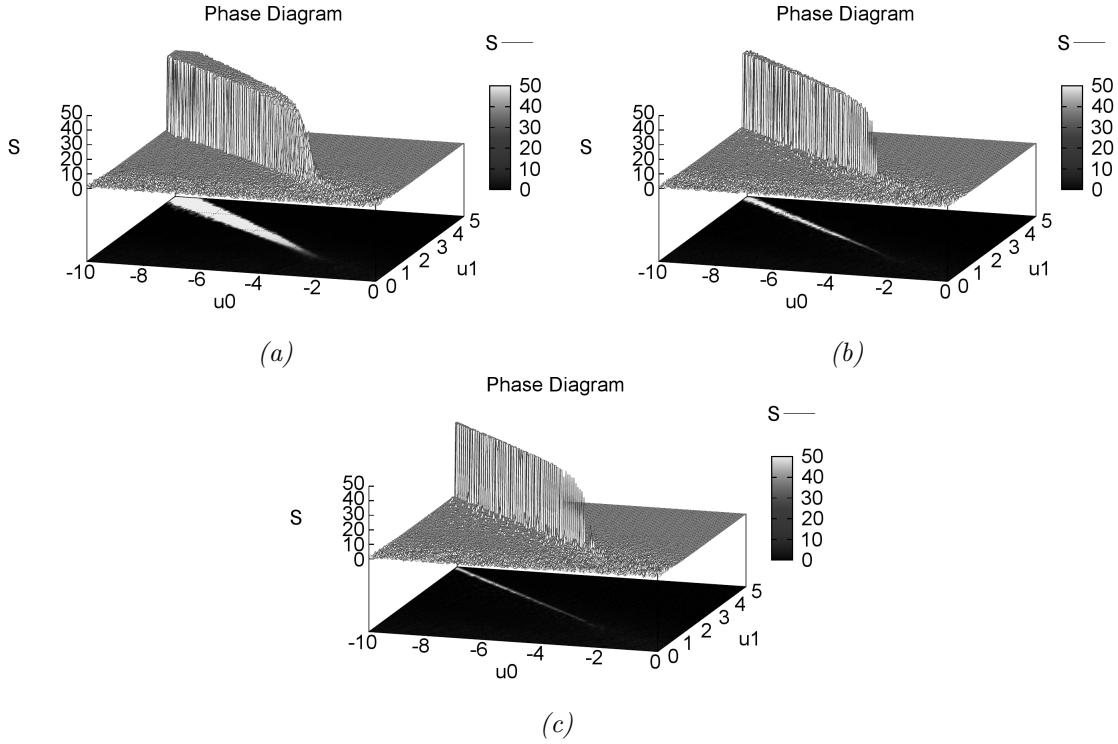

Fig. 1. Simulation results of the isotropic, translation invariant and attractive case when the network is respectively represented by a square grid *(a)* 11×11, *(b)* 37×37 and *(c)* 131×131. The results are presented on the domain of parameters $u_0 = [-10, 0]$ and $u_1 = [0, 5]$ with a resolution of 0.05 where $w_{ii} = u_0$ and $w_{ij} = u_1$.

going to give some useful definitions coming from the dynamical systems theory. Let us note that, in this section, we will focus on biological regulation networks whose evolution is ruled by the deterministic model.

4.1 Definitions

A deterministic discrete dynamical system is a triple (X, T, f) where X is the configurations space, $T = \mathbb{Z}$ is the time space and f is a deterministic flow defined by $f : X \times T \mapsto X$. Let us consider a configuration x of X and apply successively to it a flow f. Since the space of configurations is a finite set and f is deterministic, it is trivial that x evolves in a finite time towards either a configuration which cannot evolve anymore, *i.e.* a *fixed point*, or a sequence of configurations which repeat themselves indefinitely, *i.e.*, a *limit cycle*. These

particular sets of configurations are called the *attractors* of the system. Let us now consider an attractor A. We will denote by $B(A)$ the subset of X such as all its elements have their limit set of $f(x,T)$ in A. $B(A)$ is called the *attraction basin* of A.

Definition 4. *The eccentricity $\epsilon(v)$ of a graph vertex v in a connected graph G is the maximum graph distance between v and any other vertex u of G.*

In real biological regulation networks, the boundary is defined by the set of nodes of maximal eccentricity. We are now going to show the neccessity of the presence of a Gibberellin hormone in the gene regulation network of the floral morphogenesis of the plant *Arabidopsis thaliana*. Indeed, we are going to show that the plant cannot develop normally without the hormone.

4.2 Influence of a Hormone on the Floral Development of *Arabidopsis thaliana*

We have to precise that we work on a gene regulation network that is an extension of the Mendoza network [11] obtained thanks to new biological data found in the literature. Then, let us note that the hormone (GA) tends to inhibit the protein RGA which is a boundary node of the network. So, we are going to present the differences existing between the behaviour of the network when the state of RGA is fixed to 0 or not. In particular, we are going to emphasise the links between RGA and the attraction basins. The complete description of the variation around the Mendoza network on which this work is based and the following results are published in [12,13].

Let us note that the dynamics of the networks when the updating iteration mode is sequential bring to eight fixed points. Two of them correspond to the sepal tissue, one to the petal tissue, one to the carpel tissue, one to the stamen tissue, two to the inflorescence tissue and one to a tissue that has never been seen by experimentation.

First of all, we focus on the impact of the fixed inhibition of RGA on the size of the attraction basins of the network and we measure the relative sizes of the attraction basins. The influence of the fixed inhibition of RGA thanks to the repressive flow of Gibberellin significantly reduces the important disequilibrium induced by potential state changes of RGA and increases the probability to choose an initial configuration in a floral lineage attraction basin. Consequently, the presence of the hormone GA improves the chances that the plant has to develop normally.

Then, to go further in the direction of the comprehension of the GA influence on the floral morphogenesis of *Arabidopsis thaliana*, we develop a stochastic protocol that measures the probabilities that initial configurations have to change their attraction basins when they are subjected at the begining to probabilistic state pertubations. As a result, we obtain the characteristic polynomials of the probabilities depending on the parameter α that corresponds to the state pertubation rate. These results confirm the results obtained on the influence of the

fixed activation of the protein RGA on the relative sizes of attraction basins and allow us to prove mathematically the results obtained by biologists by experimentation and presented in [14]. They also give indications to improve the gene regulation network in order to make it more realistic.

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6 Conclusion and Perspectives

This work has shown the influence of fixed boundaries on theoretical and biological regulation networks. From the biological point of view, this study is of interest because fixed boundaries can be considered as an external magnetic field, a chemical potential, or even an external activity exerted on the considered population of genes for instance.

If we consider the first part on the theoretical regulation networks, it would be useful to focus on the link between the stochastic and the deterministic Hopfield-like models. Another objective would be to generalise the theoretical method to the complicated kinds of networks studied with a computer-based approach. Concerning the second part on the robustness of the attraction basins of the network modelling the floral morphogenesis of *Arabidopsis thaliana*, one of the main perspectives would be to implement the stochastic protocol in a Monte-Carlo algorithm in order to make it possible to study larger biological networks.

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