Modeling of Environment Influences in Morphogenic Processes of Cellular Bodies: Symmetry Breaking

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Abstract—**We investigated the minimal condition for symmetry breaking in morphogenesis of cellular population using cellular automata based on reaction-diffusion dynamics. We started to understand the morphogenic process and provide the mathematical formulations of the fields associated with cellular activity, environmental structure and dynamics, and mutual influence of the environment in cells activity and self-organisation. Then we model morphogenesis in cellular clusters, starting from a single seed cell, in the context of some environment, considering a variety of cellular and environmental processes, and the interaction between the two types of processes in the cellular dynamics. In particular, we looked for the possibility of the emergence of branching structures due to mechanical interactions. The model used two types of cells an external gradient. The results showed that the external gradient influenced movement of cell type-I, also revealed that clusters formed by cells type-II worked as barrier to movement of cells type-I.**

Keywords: Morphogenesis, Environmental Influences, Body Shape, Symmetry Breaking, Branching

1 Introduction

Many works have sometimes tendency to neglect the study of the environment [19], we model morphogenesis in cellular clusters, starting from a single seed cell, in the context of some environment. We consider a variety of cellular and environmental processes, and the interaction between the two types of processes in the cellular dynamics. Cellular growth is influenced by internal medium conditions, and access to metabolic resources for growth. Cellular diffusion is influenced by diffusion pressure and chemical gradients generate by cells. Environmental process depends on the actual model environment, and requires modelling one or more physical field. We have made several experiments to investigate the minimal condition for symmetry breaking in morphogenesis of cellular population. In particular, the experiments were done to verify the possibility of the emergence of branching structures due to mechanical interactions between cells of different types. A minimal system with only one type of cell was the starting point having no external gradient to produce circular symmetric structures. Then it was incrementally added more complexity to the model to see what the minimal conditions for symmetry breaking to occur were. In particular, the addition of an external gradient field gives preferred direction to cell movement, producing longated shapes. A second type of cell is made to self-organize from initially uniform distribution to form clusters pattern. Combining the two types of cells, with the cluster formed by the second type of cells, working as barriers to movement of the first type cell, changes the overall pattern of the first cell population. We conclude that models with two types of cells and a external gradient can provide a (primitive) solution for the emergence of branching structures due to mechanical interaction. The emergence of branching is the result of chemical gradients, the combination of chemical and mechanical effects is not ruled out. The article is organized as follows: Section 2 presents relevant work in the area of morphogenesis; Section 3 describes the basic concepts, fundamental to the understanding of morphogenesis processes,provides the mathematical formulations of the fields associated with cellular activity, environmental struture and dynamics, and mutual influence of the environment in cells activity ans self-organisation, and the methodology used; Section 4 describes the model of cellular automata with reaction-diffusion dynamics for two types of cells, cellular growth, and the possibility for external fields; Section 5 presents the experimental results from primitive to more complex experiments; Section 6 concludes the paper.

2 Related Work

Tissue morphogenesis is a complex process whereby tissue structures self-assemble by the aggregate behaviours of independently acting cells responding to both intracellular and extra cellular cues in their environment. Many

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scientists have proposed mathematical models of development, each of which focuses on particular developmental mechanism (chemical, mechanical, genetic, or electrical)[4]. Pattern formation in chemical reactors and its application to morphogenesis has been widely studied ever since Turing's seminal paper [5]. Turing's original contribution was to show that non-linear reaction-diffusion equations can produce waves in time and space of activator and inhibitor concentration reactants, whose diffusion relative speed influences the distribution of the concentrations. Making cells grow to respond to reactants concentration can be used to make cell populations achieve patterns —such as spots, stripes, spirals [6]. Many other models of pattern formation have been developed since Turing's work , such has Gierer and Meinhardt[7], Murray [8] ,Oster and Murray [9], Held [10],[11] . Forest [12] describes the reaction-diffusion and positional information theories, which provides the most common framework in morphogenesis modelling and proposes a general formalism, which is adapted to a large class of processes occurring in the morphogenesis tissue of living organisms. In the COMPUCELL framework, the authors used nonlinear reaction-diffusion equation to study the emergence of limbs [13],[14]. An activor-inibitor field is used to determine places of high cell condensation. A model parameter is manually changed to modify the number of "bones" that is formed along the limb — from 1 to 2 to 3. The authors do not show how the model could be extended to make arbitrary complex branching stuctures.

In [4] the author discusses and models the geometric properties of branching in animal lungs and other biological structures. However, this is not presented as a self-organization model to study morphogenis. Many of the simulation models, in morphogenis, focus on the way chemical gradients produce pattern in cell formation. Mechanical interaction between cells of several types have also been exploited in many models to work out the patterns produced by a variety of cell population [15]. One research direction can be to see how the combination of chemical patterns and mechanical interaction between several cell types can be used to model and explain the emergence of complex branching structures.

3 Methodology

3.1 A Dynamic Field Approach to Morphogenisis

Dynamic Fields

To model morphogenesis processes we rely on a variety of *dynamic fields* and their interactions. Field are understood as spatial functions that attribute some real or natural number to each position in space. Mathematically, this corresponds to have a function $F(\mathbf{r};t)$, with $\mathbf{r}$ being some position in space and t the instant of time considered, in 2D models we have $\mathbf{r} \equiv (x, y)$.

In computer simulation, we approximate continous fields by considering discrete grids, where each grid-cell represent some micro-volume in space. Thus, $F[x, y](t)$ with $x, y \in N \cup [1, S]$ represents the instant value of a particular field F at time t.To simplify we assume the number of grid-cells in all dimensions is the same (creating a squared space). Moreover, when we use multiple fields, we postulate that the grids for all fields have the same number of grid-cells. In the models presented below we focus only on 2D spatial represention.

Field are dynamic having one or more process changing the value of $F[x, y](t)$. In continuous models field dynamics is usually modeled as a differential equation that specify the rate of change in each point. In discrete model such as used in computer simulation, the equation for field dynamics specifies how each grid-cell or micro-volume changes with time. Differential equations coding field dynamics are implemented as diference equations, and with the time variable t taking natural value and being incremented in steps of 1. Dynamics is most often made local, with each field-cell being influenced by itself and the local neighboor. (Usually a van Neumann neighboor with 8 neighboors is used.)

The particular fields modeled can specific a variety of aspects of the biophysical system, such as: cell concentration in a micro-volume, thermodinamic variables such as temperature, pressure, quimical concentration produced by cell metabolic activity, or physical fields such as mass concentration in the environment, gravity, light abundance, and resource abudance. Some fields can be more abstract representing logical variables such as conditions for cell grow, material properties of the medium or the cells, among other. Below, we describe in details how some of this fields can be modeled.

A typical formulation of field dynamics is a *diffusion-reaction* equation of the form :

$$\dot{F}(\mathbf{r}) = K_1 \cdot ||\nabla F(\mathbf{r})|| + K_2 \cdot F(\mathbf{r})$$

, where $\dot{F}(\mathbf{r})$ represent the time derivative of field F at position $\mathbf{r}$. $||\nabla F||$ is norm of gradient vector of F, define as $\nabla F = [\frac{\partial F}{\partial x}, \frac{\partial F}{\partial y}, \frac{\partial F}{\partial z}]$. When we have $K_1 > 0$ field dynamics makes quantities move in the direction of the gradient vector, and when $K_1 < 0$ we have field dynamics moving quantities in the direction opposite to the gradient of the vector. $K_2 \cdot F$ is a reaction term that changes the local quantity measured by the field.

Often we want to make sure that the aggregate field values are kept constant or stay within specific bounds. In this cases, it is preferable to consider each neighborring cell of i, j in turn to compute gradients. In this case, the

above equation is implemented as:

$$F[x,y](t+1) = F[x,y](t) + K_1 \cdot \sum_k (F[x,y] - F[x_k,y_k]) + K_2 \cdot F[x,y]$$

, where k is an index over the set of neighboor of grid-cell $[x,y]$.

Field Interaction

Most model rely on multiple interacting dynamic fields. For each field a different equation is used to model its dynamics. Due to interactiong, the point-value or gradient of one field may influence other fields. For example, if we have a field F and a field G, than this interaction can be modeled as a pair of coupled equations specifying the evolution of both fields in each position in space. Mathematically, this takes the form:

$$\begin{cases} \dot{F}(\mathbf{r}) = K_{1,1} \cdot ||\nabla F(\mathbf{r})|| + K_{1,2} \cdot ||\nabla G(\mathbf{r})|| + \\ K'_{1,1} \cdot f_{1,1}(F) + K'_{1,2} \cdot f_{1,2}(G) \\ \dot{G}(\mathbf{r}) = K_{2,1} \cdot ||\nabla F(\mathbf{r})|| + K_{2,2} \cdot ||\nabla G(\mathbf{r})|| + \\ K'_{2,1} \cdot f_{1,1}(F) + K'_{2,2} \cdot f_{1,2}(G) \end{cases}$$

In the general case, where there are several fields considered on should index over each field value and field gradient in computing every other field. Thus, the general formulation for interacting dynamic fields is:

$$i \in \{1,N\}, \dot{F}_i(\mathbf{r}) = \sum_j K_{i,j} \cdot ||\nabla F_i(\mathbf{r})|| + \sum_j K'_{i,j} \cdot f_{i,j}(F_i(\mathbf{r}))$$

In computer simulation, one may consider each cell neighboor separately and we have:

$$\begin{cases} F_i[x,y](t+1) & = & F_i[x,y](t) + \\ & & \sum_j K_{i,j} \cdot \sum_k (F_i[x,y] - F_i[x_k,y_k]) \\ & & + \sum_j K'_{i,j} \cdot f_{i,j}(F_i[x,y]) \end{cases}$$

, where k is an index over the set of neighboor of grid-cell $[i,j]$.

Specific Fields

In modeling morphogenic proccesses one can consider a variety of dynamics field and interactions.Below, we describe the fields that the models presented in this text use. We also specify the way they are made to interact.

Fields created by cell activity

- Cell concentration — each grid-cell contain the number of cells of a particular kind. We use symbol n_i and $n_i[x,y]$, or $n[x,y]$ if a single cell type is considered. Since cell ocuppy some grid-cell or microvolume, cells migration depends(among other fields) on pressure gradients. Thus, we can also represent a cell concentration field as a pressure field and write $pc_i[x,y]$. Below, we show the most elementary form for the field dynamics:

$$\dot{n}_i \propto ||\nabla n||$$

The proportionaly constant impled above is a diffusion coefficient. When we consider cell grow the dynamics takes the form:

$$\dot{n}_i = G_i n_i - D_i ||\nabla n_i||$$

, above G_i is a growth constant and D_i is a difussion coefficient.

Usually the influence of concentration gradients on cell movement does not depends on the type of the cell that produces the gradient. Thus, we often write:

$$\dot{n}_i = G_i n_i - D_i \sum_j ||\nabla n_j||$$

Environmental fields

We are often interested in modeling morphogenesis in a situated or environmental context. In this case, in addition to model fields associated with cellular activity we also model fields associated with environmental structure and dynamics. We also model the mutual influence of the environment in cell's activity and self-organization, and in turn how cell's activity and self-organization changes the environment. Particular models consider difference envioronmental fields and interactions. Below, we describe some of the fields that particular models may use:

- Static, uniform environments – A particular simple case of environment field is to have a static (non-dynamic) field. When the field in static, the only complexity elements is its heterogeneity in space. The simplest case is to have a uniform or constant field — every point-position or grid-cell has the same field value. In this case there are no environmental gradients influencing cell's self-organization. A static field R is mathematically any function such that $\dot{R} = 0$. If the field is uniform, we have the addition constraint that $R[x,y] = K_R, \forall x,y$, with K_R as a constant for the field value.

- Static environment with uniform gradients – Another simple case of a static environment field is

to have a uniform gradient (e.g. measuring concentration of a quimical substance, or someother material). To capture a uniform gradient (same vector direction and norm everywhere in the filed), the field value needs to change in a constant rate everywhere. That is, the difference in field value for any two point-positions or grid-cell at the same distance and relative direction is the same. A particular simple case, is to have the direction of the field gradient aligned with horizontal (or vertical) axis. This can be writeen as:

$$F[x+1, y] = F[x, y] + K$$

If we model several fields with uniform gradients, but pointing in different direction, the combined effect on cell's self-organization may be much complex than considering only on individual field. This is specially the case, if the effect of individual field in cell's self-organization is of a different nature.

- Gravity — The gravitational field is a particular case of a static field with a (locally) uniform gradient. The additional issue that needs to be considered when modeling gravity is the opposing reaction forces created by material contact between material-bodies (e.g. cell material, or material in the environment). Due to the relative of strenght of gravity in real world, failing to capture reaction forces appropriately might remove realism to the model — because all bodies move to the positions of lowest potential (e.g. as if as matter is compressed in a single layer).

- Liquid flow density — Often environment has some rich dynamics determined by its physics and abundant materials. For example, if the cell's population is located in liquid flow than we may use a wave-equation for the pressure of liquid in each point-position or grid-cell. Additionally, we specify how field for liquid pressure influences cell's movement and consequentelly the form of the cell population. Conversselly, the cellular body may change the dynamics of the flow (e.g. producing flow deviation or creating turbulance on the cell-body surfuce). Below, we exemplify this case with pm representing the field for liquid pressure. Note that the wave-equation is a second-order differential/difference equation, due to the non-neglectable effect of mass inercia.

$$\begin{cases} \ddot{pm} = -K \cdot ||\nabla pm|| + K' \cdot n_i \\ \dot{n}_i = G_i \cdot n_i - D_i \cdot ||\nabla n_i|| - P \cdot ||\nabla pm|| \end{cases}$$

, where $K \cdot ||\nabla pm||$ and $P \cdot ||\nabla pm||$ are the gradients of medium pressure,$D_i \cdot ||\nabla n_i||$ and $K' \cdot n_i$ are the gradients of cell pressure, $G_i \cdot n_i$ represents the growth, P is a constant that measure the influence of pm gradient in cell movement. K' is a constant for the influence of cell concentration in the environment dynamics.

3.2 Background on cellular automata and reaction-diffusion dynamics

Cellular automata are very common tools used to study complex systems where space distribution of the component parts is the main purpose of the study[2],[3],[1].
A 2D cellular automata consist of a grid of sites, with each site holding state. The evolution of the state of each site depends of states of neighbooring sites. Cellular automata can be used as discrete models of continuous process, such that each site corresponds to a small area in space. Thus cellular automata are very useful to model physical or biological fields. When used for modeling morphogenesis, the state of individual site in a cellular automata may be the number of cells of a particular type or the concentration of an a quimical sustance. To implement a particular model several cellular automata can be superimposed and made to interact, such as when several types of cells or quimical substance are presents. Formally, if one can define a cellular automata modeling a field as a function of space $f(x, y) \rightarrow s$, with $x, y \in [1, S]$, where S is the size of the space. Often site position is made implicit by removing the coordinates (x, y). Reaction-diffusion dynamics is a way to model general processes of substance movement and reaction. In continuos models, this dynamics is described as follow: $\dot{f} = K_1 f - K_2 \nabla f$, where $\dot{f}$ is the time derivative of a field f in some point in space, $K_1 n$ is the reaction term, and $-K_2 \nabla n$ is the diffusion term. This specifies that substance moves from regions of high concentration to regions of low concentraton at rate K_2, and that some grow process occur at rate K_1. In cellular automata models, one can simulate this by selecting the neighboor of a site that has lowest value of f and transfer substance between the two sites.

4 The Model

Taking and combining different sets of elements discussed in subsection 3.1, we can readibly realize particular model of morphogenesis by cell's self-organization situated in some environment. We consider a model with two types of cells. Both types of cells are subjected to a reaction-diffusion dynamics, with cell movements influenced by concentration gradients and external fields.

A model with two types of cells, whose concentration is represented by two fields $c(x, y)$ and $s(x, y)$, is considered. That is, $c(x, y)$ is the number of cells of type-I at site (x, y), and $s(x, y)$ is the number of cells of type-II at the same site. Both types of cells are subjected to a reaction-diffusion dynamics, with

cell movements influenced by concentration gradients and external fields.

To more easily model cell movement, each cell type and site is associated with a (potential) energy $e(x, y)$ value. This energy value combines the different aspects that affect cell movement with each aspect that gave additive contribution. Cells move in the direction of the negative gradient of the energy. That is, from sites with higher energy to sites with lower energy. The aspects influencing cell movement and respective energy value are described below.

Cell adhesion makes cells cling to other cells. Here, that cell adhesion is only significant between cells of the same type. The more cells in a site, the more the clinging effect. Thus, adhesion is defined emerging as $e_a(x, y) \propto -n(x, y)$, where $n(x, y)$ is the number of cells at site (x, y). Considering the two types of cells modeled: $e_a^c \propto c$, and $e_a^s \propto s$.

Repulsive forces, that balance adhesion, were considered to model limitations on the number of cells present in a site. For this, a repulsion potential was established as $e_r \propto \max\{0, c + s - n_\theta\}$, where n_θ is the minimal number of cells after which repulsion is significant.

Diffusion effects are modeled by a diffusion energy as follows: $e_d \propto c + s$.

A static external field was created to change cells movement. This is described generically as an additional energy value: e_x.

Overall, the equation:

$$e = e_a + e_r + e_d + e_x$$

Cell movement is modeled by having each site computing its own energy and the energy of its neighboring sites. In the pair where there is the maximum difference in energy occurs an exchange of cells. Formally, $e_k(x, y)$ is the energy of k neighbor of site (x, y) then, the site k' is selected such as: $k' = \text{maxarg}_k\{|e_k(x, y) - e(x, y)|\}$. (If more than one site has the same value for k', than non-diagonal adjacent sites are selected.)

Cell movement/exchange is defined as:

$$\begin{cases} \Delta n(x, y) \propto |e_{k'}(x, y) - e(x, y)| \\ \Delta n'(x, y) = -\Delta n(x, y) \end{cases}$$

$\Delta n(x, y)$ and $\Delta n'(x, y)$ stand for the changes on the number of cells in sites (x, y) and selected neighbor k'. The total number of cells is left unmodified by this operation, because changes in the selected neighbor are the reverse of the focal site (x, y).

It is also assumed that type-I cells undergo a growth process. Initially, a single cell of type-I is presented in space, at position (x_0, y_0). Its growth rate depends on the number of cells of type-I already present at a site. This is modeled by specifying the probability that a single cell of type-I produces another cell at each instant, defined as:

$$p_c \propto \frac{1}{c}$$

Througth this probility the effect of competition/sharing of resources between cells is modeled.

Cells of type-II are initially distributed all over the space, with concrete values taken from a normal distribution: $s(x, y) \sim N(\mu, \sigma^2)$.

5 Experimental Results

First the model was tested considering each type of cell separately — first cell type-I, then cell type-II. Later experimental results were presented with the two types of cells interacting. The following parameters were used: $S = 40$, $n_\theta = 30$, $A_c = -0.1$ is the proportionality constant of adhesion, and $D_c = .01$ is the proportionality constant of diffusion.

5.1 Experiment I - Cellular Grow in an empty environment without significant gradient.

The simplest model of morphogenesis, is to have a single type of cell living in an empty environment without significant gradient, and growing uniformly without resources constraints. Cell movement is determined solely by diffusion to more empty places. In this case, cell grow is expected to produce a circular/round shape or spherical symmetry.This occurs during all stages of the growth process, until spatial containment constrain operate. Unless there is hard limit on maximum number of cells, all available space will be filled with cells having each point-position or grid-cell at maximum density.

5.2 Experiment II - Cellular Grow in Flows

In this experiment we used a single type of cell population located in liquid flow. We used a wave-equation for the pressure of liquid in each grid-cell. The liquid pressure shift from the left to the right cause a cell population sliding. In figure 1 and 2 we can observed how the field for liquid pressure influences cell movement and consequently the form of the cell population.

5.3 Symetric Breaking By External Fields

When the cell population is emersed in an environment, a static field can be set up to influence the movement and shape of the cell population. First a static field pointing left-to-right was experimented.

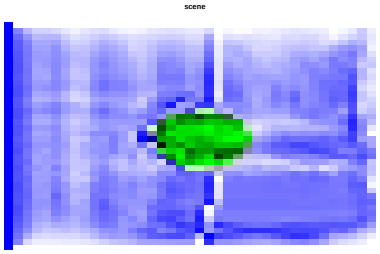

Figure 1: Growth of a cell population with a single cell type located in liquid flow.

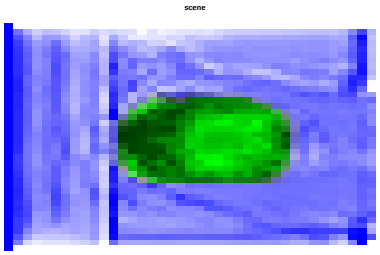

Figure 2: Growth of a cell population with a single cell type located in liquid flow, observed at a variety of time-steps. Results produces oval (or ellipse) form.

This was done by defining the external field energy value as: $e_x(x, y) \propto -x$. Which demonstrated that energy decays as cells move to the right. Figure 3 shows the time evolution of cell concentration in the presence of this external field. From these results, it can be observed that the circular symmetry, produced by diffusion and adhesion dynamics, is completely modified. Cells keep moving right in the direction of the external field gradient, forcing the cell population to take a "tube" like shape. A widening of the tube is produced by diffusion dynamics and cell growth. This occurs because there is high cell density in the center of the axis.

In another experiment, an additonal external field was used to model obstacle/barrier avoidance. Namely, a static field was set so that a high energy value existed in fixed locations and decayed rapidly according to a normal curve: $e_x^2 \propto e^{-||p-p^*||}$, where p^* was the selected obstacle location, and $p \equiv (x, y)$ was some other location. Three barriers located at: $(\frac{S}{2}, \frac{S}{2})$, $(\frac{S}{2} + \epsilon, \frac{S}{2} + \epsilon)$, $(\frac{S}{2} + \epsilon, \frac{S}{2} - \epsilon)$ were used. Figure 4, shows the evolution of a cell population dynamics and its different shapes. The results show that the second external field changed the movement and the different shapes of the cell population. Cells are forced to desviate course and move around barriers. This experiment was done to exemplify that, in

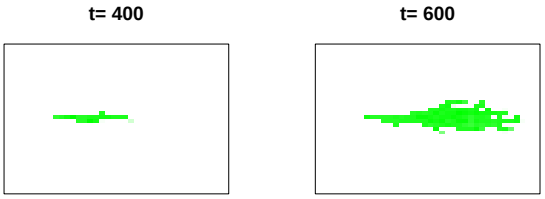

Figure 3: Growth and distribution of a cell population type-I, with a external field that makes cells move left-to-right.

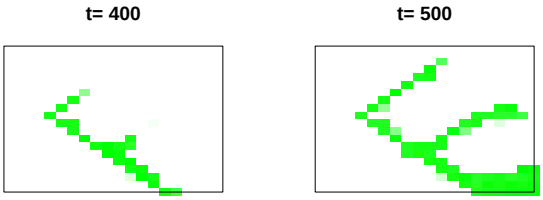

Figure 4: Growth and distribution of a cell population type-I, with too external fields. Second external field produces barrier to movement.

many cases, the movement of biological cells in the macroscopic world can be compared to movement of other substances . Most notably, water flowing in rivers and around rocks and debris. In spite of this similarity, the second external field is highly artificial and is not intrinsic to cell dynamics.

5.4 Cluster Formation

The cluster formation in the second type of cell was modeled to see how the movement of cell type-I could be influenced by other factors intrinsic to cell dynamics. Figure 5 shows the evolution of concentration of cells type-II. The results showed that the initial homogeneous distribution changed to sites of high concentration due to adhesion. This formed clusters through all cell distribution.

5.5 Emergence of Branching Structures

Combining the two cell types, plus an external field moving left-to-right, the dynamics and shape of cell type-I population suffered changes. Figure 6 shows the evolution of cell type-I population. The results showed a pattern comparable to figure 3. However, the widening of cell shape was higher and many sites along the cell population were emptied of cells of type-I. This was caused by a deviation from high con-

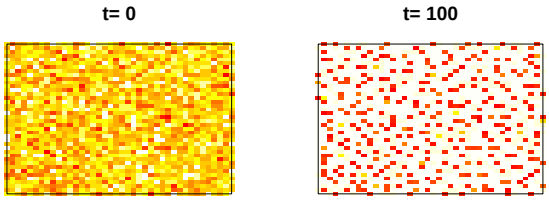

Figure 5: Distribution of a cell population type-II.

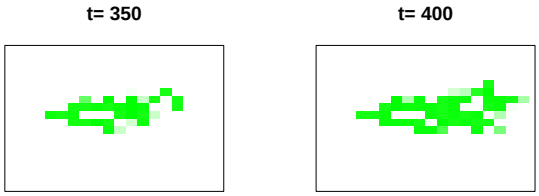

Figure 6: Distribution of a cell population type-I, with a external fields.

centration of cells type-II. This presents a primitive form of self-organized branching structure, as occurs in many biological systems, such as: tree roots and tree branches, algee, neuron dendrites, and vascular and circulatory system in animals.

6 Conclusions and Future Work

A minimal system with only one type of cell was the starting point having no external gradient to produce circular symmetric structures. Then it was incrementally added more complexity to the model to see what the minimal conditions for symmetry breaking to occur were. In particular, the addition of an external gradient field is used to break the symmetry of the pattern for cell type-I. The external gradient gives preferred direction to cell movement, producing longated shapes. A second type of cell is made to self-organize from initially uniform distribution to form clusters pattern. Combining the two types of cells, with the cluster formed by the second type of cells, working as barriers to movement of the first type cell, changes the overall pattern of the first cell population. The results pattern for cell type-I is a primitive form of branching structure such that region occupied by high concentration of cells of type-II is not occupied by cells of type-I. On the other hand, the branching patterns that the model is able to produce are not as clear as found in many biological structures, since branches are not perfect tubes. Morevoer, branching does not follow any fixed branching factor. The overall cell's behavior resembles more the way water flows and deviates from macroscopic obstacles. Since biological cell populations may grow in environment where clusters made by other cells and other barriers are present, this may not be excluded as a contributing factor for the formation of branching structures. We conclude that models with two types of cells and a external gradient can provide a (primitive) solution for the emergence of branching structures due to mechanical interaction. The emergence of branching is the result of chemical gradients, the combination of chemical and mechanical effects is not ruled out. Future work will be developed in order to see how complex chemical gradients can be modeled by nonlinear reaction-diffusion, and if they can work together with mechanical factors producing clearer branching pattern similar to natural biological structures. A possible line of research is to study how chemical gradients may interfere with the number of branches reveshowing a fractal distribution can be modeled, with the number of branches revealed in a fractal distribution of cells varying according to some parameter. Mechanical obstacles may be used to help the system to break its symmetries, promoting the creation of branches and adding heterogeneity to the chemical field [16].

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