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Symmetry Breaking and the Emergence of Branching Structures in Morphogenesis: Minimal Conditions and Mechanical Interactions between Cells

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***Abstract*—**The minimal condition for symmetry breaking in morphogenesis of cellular population was investigated using cellular automata based on reaction-diffusion dynamics. In particular, the study 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, branching structures, symmetry breaking.

I. Introduction

BRANCHING structures appear both in the physical macroscopic world (e.g. in rivers and water streams), and in biological systems (e.g. branches in trees and other plants, lungs and blood vessels in animals, dendrit structures in neurons)[1] . 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. This kind of modeling has been used to study morphogenesis and the self-organization of form in biological systems. Additionally, reaction-diffusion dynamics has been very useful in modelling self-organization in cellular population with one, two, or more cellular types. Thus, it can be asked if a simple model with cellular automata and reaction-diffusion can be used to model and study the emergence of branching structures.

Several computational experiments have been made to investigate the minimal condition for symmetry breaking in morphogenesis of cellular population using cellular automata based on reaction-diffusion dynamics. 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 were the minimal conditions for symmetry breaking to occur. In particular, the addition of an external gradient field gives preferred direction to cell movement, producing ablongated shapes. The artificial presence of a barrier is used to investigate the possibility of mechanical interaction influencing the movement of cells producing branching. A second type of cell is made to self-organize from initially uniform distribution to form a cluster pattern. Combining the two types of cells, the cluster formed by the second type of cells, will work as a barrier to the movement of the first type cell, changing the general pattern of the first cell population. The conclusion was that models with two types of cells influenced by an 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, however the combination of chemical and mechanical effects can not be excluded.

The article is organized as follows: Section II describes the related work; section III describes the basic model of cellular automata with reaction-diffusion dynamics for two types of cells; section IV, presents the experimental results from primitive to more complex experiments; Section V concludes the paper.

II. Related Work

Pattern formation in chemical reactors and its application to morphogenesis has been widely studied ever since Turing's seminal paper [2]. 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 [3]. Many other models of pattern formation have been developed since Turing's work , such has Gierer

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and Meinhardt [4], Murray [5] ,Oster and Murray [6], Held [7],[8]. Forest [9] 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 non-linear reaction-diffusion equation to study the emergence of limbs [10],[11]. 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 structures.

In [1] 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 morphogenesis. Many of the simulation models, in morphogenesis, 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 [12]. 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.

III. Model Design

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 $e_a^c \propto s$.

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 $e_r \propto \max\{o, c+s-n_\theta\}$, 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: $k' = \max\arg_k \{|e_k(x,y) - e(x,y)|\}$. (If more than one site has the same value for k_0, 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 changes on number of cells in sites (x,y) and selected neighbour k'. The total number of cells is left unmodified by this operation, because changes in the selected neighbour 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_o, y_o). Its growth rate depends on the number of cells of type-I already present at a site. This is modelled by specifying the probability that a single cell of type-I produces another cell at each instant, define as:

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

Through this probability the effect of competition/sharing of resources between cells are modeled.

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

IV. 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.

A. Null-Hypothesis: Symmetric Shapes

Fig. 1 shows the behaviour of a cell population type-I, when there is no external field and no interaction with cell type-II. The figure depicts the evolution of cell concentration in different instants in time. The results show that the cell population takes a circular (or spherical) symmetry, when there is no internal or external factor that gives preferences for movement in a particular direction.

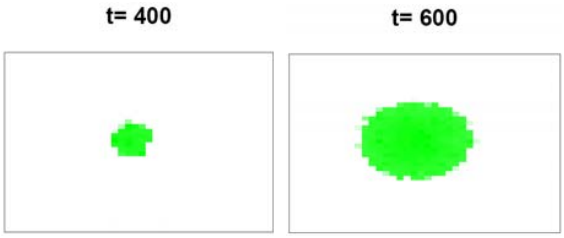

Fig. 1 Growth and distribution of a cell population type-I. No external fields or resource constraints are considered. Results produces form with circular (spherical) symmetry

B. Symmetric 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. 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. Fig. 2 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 additional 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: $\left(\frac{S}{2},\frac{S}{2}\right),\left(\frac{S}{2}+\varepsilon,\frac{S}{2}+\varepsilon\right),\left(\frac{S}{2}+\varepsilon,\frac{S}{2}-\varepsilon\right)$ were used.

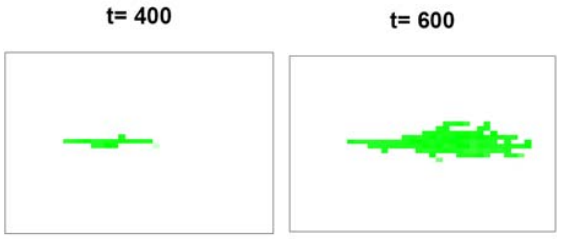

Fig. 2 Growth and distribution of a cell population type-I, with a external field that makes cells move left-to-right

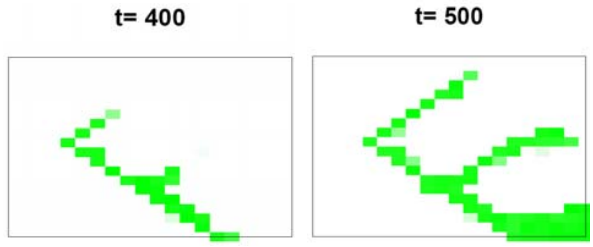

Fig. 3 Growth and distribution of a cell population type-I, with too external fields. Second external field produces barrier to movement

Fig. 3 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 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.

C. 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. Fig. 4 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.

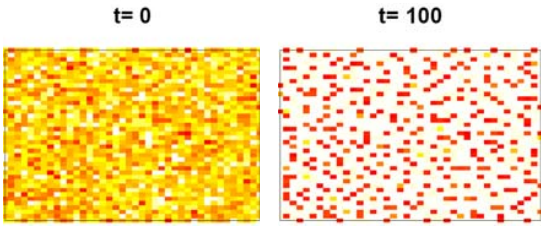

Fig. 4 Distribution of a cell population type-II

D. 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. Fig. 5 shows the evolution of cell type-I

population. The results showed a pattern comparable to fig. 2. 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 concentration 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.

V. Discussion and Conclusion

In this article, a model with two cell types for the morphogenesis of primitive branching structures was presented, based mostly on mechanical interactions between the two cell types. An external gradient was used to break the symmetry of the pattern of cell type-I. Clusters formed by cell type-II worked as barriers to movement and growth of the population of cell type-I. The results of the pattern for cell type-I showed a primitive form of branching structure where the 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 those found in many biological structures, since branches are not perfect tubes. Moreover, branching does not follow any fixed branching factor. The general cell's behavior resembles more the way water flows and deviates from macroscopic obstacles. As biological cell populations can grow in environments where there are already clusters made by other cells and other barriers, all of them can not be excluded as contributing factors for the formation of branching structures. 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 [13].

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