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Modeling Cell-Fractone Dynamics Using Mathematical Control Theory

M. Chyba, J. Marriott, F. Mercier, J. Rader, G. Telleschi

Abstract— **New biological structures called fractones, named in honor of the late Dr. Benoit Mandelbrot due to their fractal-like appearance, have been discovered by cell biologists. Their primary purposes are theorized to pertain to the major processes of the life cycle of cells, namely cell division, migration, and differentiation. In this paper, we build a mathematical model of how fractones interact with the cells and the associated growth factors to gain insight into the growth process.**

I. INTRODUCTION

The process of neurulation and subsequent events of the brain's formation involve multiple growth factors that induce proliferation, differentiation, and migration of cells. The distribution and activation of these growth factors in space and time will determine the morphogenic events of the developing mammalian brain. However, the process organizing the distribution and availability of growth factors within the neuroepithelium is not understood. Structures, termed fractones, directly contact neural stem and progenitor cells, capture and concentrate said growth factors, and are associated with cell proliferation [5], [6], [7]. Hence, our hypothesis is that fractones are the captors that spatially control the activation of growth factors in a precise location to generate a morphogenic event, i.e. mitosis.

To validate this hypothesis, we propose to develop and analyze a mathematical model predicting cell proliferation from the spatial distribution of fractones in a developing mouse. Dynamic mathematical modeling, i.e. models that represents change in rates over time, serves several purposes [4]. By mimicking the assumed forces resulting in a system behavior, the dynamic model helps us to understand the nonlinear dynamics of the system under study. Such an approach is especially well suited for biological systems whose complexity renders a purely analytical approach unrealistic. Moreover, it allows us to overcome the excessively demanding purely experimental approach to understand a biological system. Our primary goal in this paper is to develop a model that contains the crucial features of our hypothesis and at the same time sufficiently simple to allow an understanding of the underlying principles of the observed system. We propose to model this biological process as a control system, the control depicting the spatial distribution of the active fractones. This is a novel approach with respect to the most common reaction-diffusion models seen in the literature on morphogenesis, however it is not that surprising. Indeed, control theory is instrumental to overcome many challenges faced by scientists to design systems with a very high degree of complexity and interaction with the environment [1], [2], [8]. Examples of its applicability in physical and biological systems are numerous [9], [10].

It is important to notice that due to the specific nature of morphogenesis and in particular of the cell's proliferation, existing techniques in control theory cannot be applied directly to our problem. The reason comes from the fact that, in this proposal, the state space of our control system is dynamic; this is an intrinsic property of biological systems. In physics, for instance, the state space is static and the equations of motion are derived from minimizing a Lagrangian. In engineering, the configuration manifold is fixed and, one either attempts to determine the evolution of the system while minimizing a prescribed cost or one tries to design controls to take into account uncertainties of the system. As a result of a dynamic state space, existing methods have to be adjusted to analyze biological systems from the control theory point of view.

Mathematically, the classical models attempting to describe morphogenesis are based on reaction-diffusion equations with the pioneering work of Turing [11]. Although Turing made a great attempt to mathematically portray morphogenesis, his work is not an adequate model to describe the system given new discoveries and developments since the 1950s. With his model, Turing was describing how reactive chemicals present in a static, living structure interact in a continuous medium via diffusion (and, surprisngly, form wave-like patterns). For the system we are describing, reaction-diffusion equations cannot be used to study the mechanisms of morphogenesis during development as the growth factors are non-interacting. Based on the hypothesis of [5], [6], [7], morphogenesis involves the capture and activation of growth factors by fractones at specific locations according to a precise timing. A fundamental problem is to understand how growth factors control the topology of cell proliferation and direct the construction of the forming neural tissue. It has been demonstrated that extra-cellular matrix (ECM) molecules strongly influence growth factor-mediated cell proliferation. ECM proteoglycans can capture and present growth factors to the cell surface receptors to ultimately trigger the biological response of growth factors.

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This is also a sign that Turing's model will not suffice, as there is no mechanism in the reaction-diffusion equations for structures with this type of action. Moreover, the distribution of fractones is constantly changing during development, reflecting the dynamics of the morphogenic events. Therefore, the organizing role of fractones in morphogenesis must be analyzed by an alternative mathematical model.

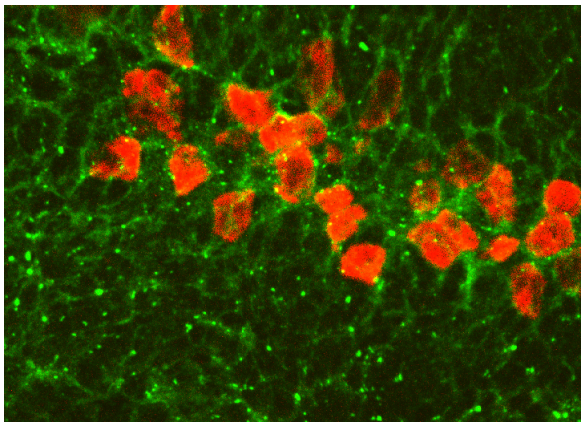

Fig. 1. Characterization of fractones in the mouse neuroepithelium during brain morphogenesis. The neuroepithelial cells (red) proliferate next to fractones (green punctae).

II. MATHEMATICAL MODEL

A. Configuration and State Space

Let R be a compact connected subset of the 2-dimensional Euclidean space that we call the ambient space. For simplicity, we assume in this paper that R is fixed and we identify R to a square. For our model, R is discretized uniformly and we call a square of our discretization a unit. In the sequel, each unit will be identified to an integer pair (i, j). The origin of the unit of the discretization is chosen arbitrarily and will be identified to $(0, 0)$. Note that the discretization is chosen with a precision to be chosen by the user (eventually it will be determined by the experimental biological maps). The three important spaces to take into account into our dynamical system are: the space filled with cells, the space in which the growth factors diffuse and finally the space filled with the fractones.

Definition We define $\mathrm{Cell}(t)$ to be the configuration of cells at a given time t and we call it the *cell space*. This forms a closed subset of R. The complement of $\mathrm{Cell}(t)$ in R is denoted by $\mathrm{Diff}(t)$ and is called the *diffusion space* at time t. At each time t, the diffusion space is divided into two parts, the free diffusion space, $\mathrm{Free}(t)$, and the fractone space, $\mathrm{Fract}(t)$. The data of $\mathrm{Cell}(t)$, $\mathrm{Free}(t)$ and $\mathrm{Fract}(t)$ forms what we call the *Configuration space* at time t, and we denote it by $\mathrm{Conf}(t)$. Note that $R(t) = \mathrm{Cell}(t) \cup \mathrm{Diff}(t)$ and $\mathrm{Diff}(t) = \mathrm{Fract}(t) \cup \mathrm{Free}(t)$.

To the discretization of the initial configuration of cells, i.e. $\mathrm{Cell}(0)$, we associate a collection of indices (i, j) where each index is represented by an integer. Each pair of indices represent a unit of our discretization. Similarly $\mathrm{Free}(0)$, $\mathrm{Fract}(0)$ (and therefore $\mathrm{Diff}(0)$) are represented by collections of indices.

From our definitions, the configuration space at time t is a topological space identified to $\mathbb{R}^2$ with holes (the cells). Note that, for the diffusion of growth factor, the holes should rather be seen as obstacles since the cells prevent the diffusion. The fractones do not prevent the diffusion but perturb it by acting as captors. This will be described more precisely in the next section. The morphogenic events will start from an initial configuration of cells and fractones embedded in the ambient space R. Growth factors diffuse freely in the diffusion space $\mathrm{Free}(t)$ and are under pertubed diffusion in $\mathrm{Fract}(t)$. We make a few assumptions to mathematically describe those objects. We assume the space between the cells account for 20% of the total space occupied by the cells. This is reflected in our discretization by representing a cell as a square composed of 81 units (i.e. a 9 by 9 square), while the "in-between cells" space is represented by single unit-rows and unit-columns. For instance, a cell configuration of four cells (two horizontal and two vertical) and no fractone lead to $\mathrm{Diff}(0) = I_0 \times J_0$ where $I_0 = J_0 = \{0, 1, \ldots, 44\} \setminus (\{13, \ldots, 21\} \cup \{23, \ldots, 31\})$. Here, the size of the space, 45×45, was chosen arbitrarily. We also assume the cells to be vertically and horizontally aligned, and finally that the fractones are represented as one unit of our discretization. Notice that at this stage of the work, these are arbitrary choices, and it will be straightforward to relax these assumptions to reflect the observations from the experimental maps.

Since cells are constantly forming and fractones moving, the diffusion space evolves constantly, however, it will always be formed by the product of unions of subsets of $\mathbb{Z}$. We introduce $\mathrm{Diff}(t) = I_t \times J_t \subset \mathbb{Z} \times \mathbb{Z}$, where I_t, J_t are both unions of finite subsets of $\mathbb{Z}$. Note that with this equality, we identify the diffusion space to its discretization and that will be the case in all that follows. Indeed, there is a one-to-one correspondance between both. The same holds for the cell space. The dimension of the diffusion space at time t (resp. of the cell space) is defined as the number of indices (i, j) such that $(i, j) \in \mathrm{Diff}(t)$ (resp. $\mathrm{Cell}(t)$).

In our proposed model, the morphogenic events will be governed by a control system defined on a state space. The state space is defined at each time t as the concentration of growth factors in each unit of our discretization of the diffusion space $\mathrm{Diff}(t)$. We denote the state space by $M(t)$. More precisely, to each unit $(i, j) \in \mathrm{Diff}(t)$, and at each time t, we associate a concentration of growth factor that we denote by $X_{i,j}(t)$. The state space $M(t)$ at time t is then R^n_+, where $n = \dim(\mathrm{Diff}(t)) \geq 0$. As will be seen later, the rate of change in the concentration of growth factor is described using classical diffusion equations.

B. Diffusion of Growth Factors in $\mathrm{Diff}(t)$

For simplicity, we assume the diffusion of a unique type of growth factor and equal sensitivity of the fractones with

respect to that growth factor. However, our model will be developed such that expanding to several types of growth factors and varying fractone sensitivity to respective growth factors can be added in a straightforward way.

Assume at first that there are no cells and no fractones. Therefore, the growth factors diffuse freely in the ambient space R. We denote by ν the diffusion parameter associated to the considered growth factor, and we define $\Delta = \{(0,1),(0,-1),(1,0),(-1,0)\}$. The pure dissipation is then described by $\dot{X}(t) = F^0(X(t))$ where the components of $X(t)$ are given by $X_{i,j}(t)$ which represents the quantity of growth factor in unit (i,j) at time t, and, assuming diffusion occurs between a unit (i,j) and its four neighbors, we have:

$$\dot{X}_{i,j}(t) = \nu \cdot \sum_{(k,\ l)\in\Delta} (X_{i+k,j+l}(t) - X_{i,j}(t)) \text{ for } (i,j) \in R.$$

Assume now that a cell forms in the ambient space. The cell therefore becomes an obstacle to the diffusion process. Mathematically, rather than looking at a cell as an obstacle, we identify the cell to a hole in a topological space. The hole, depicting the location of the cell, ensures that the diffusion of the growth factor takes place in the diffusion space only. By doing so, we do not have to perturb the diffusion process, instead we continuously modify the topological space in which the diffusion process takes place. Notice that, since several cells might be forming at the same time, the topological changes in the configuration space will reflect all the created holes. We then have:

$$\dot{X}_{i,j}(t) = \nu \cdot \sum_{\substack{(k,\ l)\in\Delta \\ (i+k,j+l)\in \mathrm{Diff}(t)}} (X_{i+k,j+l}(t) - X_{i,j}(t)) \text{ for } (i,j) \in \mathrm{Diff}(t). \tag{1}$$

Finally, we need to model how fractones perturb the diffusion. As mentioned before, a fractone is represented as a one unit (i,j) of our discretization. The hypothesis is that the fractones store the quantity of growth factors that they capture, and that this quantity becomes unavailable to the diffusion process. To reflect the biological hypothesis that fractones are produced and then disappear, we introduce the following definitions. To each unit (i,j) we associate what we call a passive fractone. A passive fractone at time t belongs to $\mathrm{Free}(t)$. An active fractone at time t is defined as a unit that belongs to the set $\mathrm{Fract}(t)$. An active fractone is one that acts as a captor for the diffusion process. The biological translation of this definition goes as follow. A passive fractone corresponds to the situation such that either no fractone is associated to the unit or one is currently produced but is not yet part of the biological process. In other words, in our representation it can be seen that $\mathrm{Free}(t)$ is the set of passive fractones at time t. An active fractone is one that acts as a captor for the diffusion process.

Assume now that there is an active fractone (i,j). Then there is perturbation to the diffusion process as follows. We introduce a control function $u(t) = (u_{i,j}(t)) \in \{0,1\}^{I_t \times J_t}$ defined on a time interval $[0,T]$, with T representing the duration of the cascade of morphogenic events under study. When a fractone is active at time t, the component $u_{i,j}(t)$ of the control is set to one while it is set to zero for a passive fractone. The active fractone store the current quantity of growth factors available in unit (i,j) and acts as a captor for the diffusion process. In other words, diffusion from an unit $(i,j) \in \mathrm{Fract}(t)$ to its neighbors is prevented. To represent this perturbed-diffusion process, we define a control system:

$$\dot{X}(t) = F^0(X(t)) + \sum_{(i,j)\in \mathrm{Diff}(t)} F^{(i,j)}(X(t)) \cdot u_{(i,j)}(t) \tag{2}$$

where $X(t)$ is the state variable and denotes the concentration of growth factor in the diffusion space $\mathrm{Diff}(t) = I_t \times J_t$ at time t, the drift vector field F^0 is given by the right-hand side of (1) and represents the regular diffusion of growth factors taking place in the free diffusion space, and finally the control vector fields perturb the regular diffusion to account for the possible presence of active fractones. An admissible control is a mesureable function $u : [0,T] \to \{0,1\}^{n(t)}$ where T represents the duration of the morphogenic event under study, and $n(t)$ is the number of pairs included in $I_t \times J_t$. More precisely, we have under the assumption that (i,j) is an active fractone:

$$F^{(i,j)}_{i,j}(X(t)) = \nu \cdot \sum_{\substack{(k,\ l)\in\Delta \\ (i+k,j+l)\in \mathrm{Diff}(t)}} X_{i,j}(t)$$

$$F^{(i,j)}_{i+k,j+l}(X(t)) = -\nu \cdot X_{i,j}(t), \text{ for } {\scriptstyle \substack{(k,\ l)\in\Delta \\ (i+k,j+l)\in \mathrm{Diff}(t)}}$$

These equations reflect the fact that the quantity of growth factor in an active fractone become invisible to the diffusion process. Once the stored quantity reaches a given threshold, the fractone signals to the cells that mitosis can occur. In Fig. 2, we represent a simulation of the perturbed-diffusion process when cells and fractones exist in the ambient space. The initial distribution of growth factor is a single source (not to scale) as seen in the initial image in the upper corner above the cell, while the fractone is located near the bottom corner in green. The growth factors diffuse through the free space to eventually be captured by the fractone in the last image.

C. Mitosis

The motivation behind the introduction of fractones as controllers comes from the hypothesis that their spatial distribution is one of the major components that determines the morphogenic events. More precisely, the fractones give the order to the cells to undergo mitosis once a given threshold of growth factor has been reached. To translate this mathematically, we can equivalently state that the spatial distribution of fractones and the diffusion process of growth factors regulate the appearance and the location of holes in our topological space, namely the configuration space. A natural question arises: when a cell undergoes mitosis, how does the existing mass of cells deform? At this stage, we will limit ourselves to simple assumptions to avoid making the problem unnecessarily complex.

Based on our representation of the cell space, from here forth we identify a cell C to a unit of our discretization.

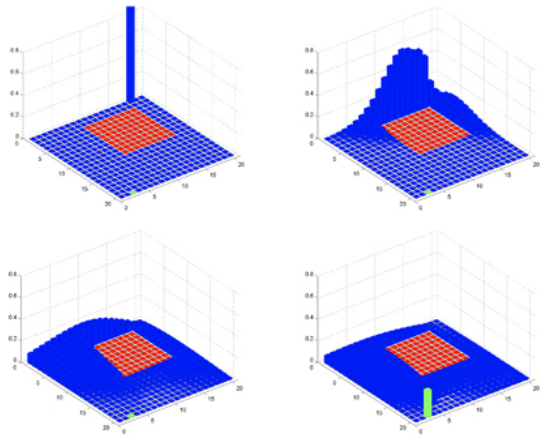

Fig. 2. Diffusion from a high concentration source through the free space, around a cell (in red), towards a fractone (in green). Here, the height of the column above each unit represents the amount of growth factor.

Indeed, since we assume our cells to be squares of 9×9 units of our discretization and to be vertically and horizontally aligned, a cell C is completely determined by its middle unit (a, b). We write $C = (a, b)$. The following assumptions that regulate the deformation of the existing mass of cells once mitosis occurs is arbitrary and can be modified easily. For simplicity in this paper we assume the fractones can be located only at the vertices of the cells. Note that this assumption can easily be relaxed. First, we introduce the following notion of distance. Let $a = (a_1, a_2)$ and $b = (b_1, b_2)$ be two units such that $a_1 = b_1 \mod 10$ and $a_2 = b_2 \mod 10$. The geometric distance is defined by: $d_G(a, b) = \sqrt{|a_1 - b_1|^2 + |a_2 - b_2|^2}$. The geometric distance helps to determine a hierarchy between units, it is based on the assumption that the mass of cells is optimizing its shape by prioritizing compactness. Clearly, we have that $d_G(a, b) \in \left\{10\sqrt{n^2 + m^2} \mid n, m \in \mathbb{Z}.\right\}$. Notice that, given unit (a, b), the closest units that are multiples of 10 from (a, b) are at a distance 1, and there are 4 of them. The next closest units are at a distance $\sqrt{2}$, and there are also 4 of them. The table below details the possible distances, and only one half of one quadrant is displayed since it is symmetrical with respect to the other quadrants, and the table is symmetrical about its diagonal. The pattern is very clear. For any given distance d from a cell centered at (a, b) to a location for a new cell to be placed, there are either: 12 possible locations if d is an integer that is the hypoteneuse of a Pythagorean triple; 8 possible locations if d is not along a diagonal or an axis in Table I; or 4 possible locations if d is on a diagonal or an axis, and is not the hypoteneuse of a Pythagorean triple.

The algorithm for the deformation of $\mathrm{Cell}(t)$ once mitosis occurs as follows. We identify the active fractone to unit (i, j). To this fractone, there are at most 4 cells that are connected, and those are described simply by their center unit: $C_1 = (i + 5, j - 5), C_2 = (i - 5, j - 5), C_3 = (i - 5, j + 5), C_4 = (i + 5, j + 5)$. At a given time t, the

TABLE I

DISTANCE DISTRIBUTION FOR THE DEFORMATION OF THE MASS OF CELL AS MEASURED FROM ANY CELL UNDERGOING MITOSIS.

0	1	2	3	4	5	6
1	$\sqrt{2}$					
2	$\sqrt{5}$	$\sqrt{8}$				
3	$\sqrt{10}$	$\sqrt{13}$	$\sqrt{18}$			
4	$\sqrt{17}$	$\sqrt{20}$	$\sqrt{25}$	$\sqrt{32}$		
5	$\sqrt{26}$	$\sqrt{29}$	$\sqrt{34}$	$\sqrt{41}$	$\sqrt{50}$	
6	$\sqrt{37}$	$\sqrt{40}$	$\sqrt{45}$	$\sqrt{52}$	$\sqrt{61}$	$\sqrt{72}$

active fractone reaches the threshold for the concentration of growth factor. If $C_i \in \mathrm{Cell}(t)$, the cell C_i duplicates. Consider, for simplicity, a single cell undergoing mitosis. The deformation algorithm is defined as to preferentially deform the current mass of cells in the direction of empty space in a clockwise orientation as starting from angle zero (as referenced by an axis superimposed on the center of the "mother" cell). More precisely, it looks incrementally for the closest unit to (i, j) that belongs in $\mathrm{Free}(t)$. Once such a unit is detected, the deformation occurs. Units at a same distance from (i, j) are selected in the following order. We define $i_\ell - i_0$ and $j_\ell - j_0$, for all ℓ, where ℓ represents the number of possible locations at a given distance and (i_0, j_0) represents the center of the cell undergoing mitosis. The algorithm looks first for a unit in $\mathrm{Free}(t)$ such that $j_\ell - j_0 \leq 0$ and chooses preferentially the $\max\{i_\ell\}$. If no such unit is found, The algorithm searches for a unit in $\mathrm{Free}(t)$ such that $j_\ell - j_0 > 0$, and chooses preferentially the $\min\{i_\ell\}$.

D. Problem Formulation

Morphogenic events are modeled as an affine control system of the form $\dot{x}(t) = F^0(x(t)) + \sum_{i=1}^{n} u_i(t) \cdot F^i(x(t)), x(t) \in M(t)$ where the state space $M(t) \subset R^{\dim(\mathrm{Diff}(t))}$ varies with time, and such that $u(\cdot)$ is an admissible control. Notice that the initial and final conditions of our system are not given in terms of $M(0)$ and $M(T)$ but in terms of $\mathrm{Cell}(0)$, $\mathrm{Fract}(0)$ and $\mathrm{Cell}(T)$, $\mathrm{Fract}(T)$. Notice that the dimension of $M(t)$ is arbitrary since it depends on our discretization.

The biological statement of the problem is now:

Given an initial and final configuration of cells in a prescribed ambient space, determine an initial concentration of growth factors and a dynamic spatial distribution of fractones such that the mass of cells transforms from its initial configuration to its final configuration.

Restated in mathematical terms, we have:

Given $\mathrm{Cell}(0)$ *and* $\mathrm{Cell}(T)$*, subspaces of R, determine* $X(0)$ *and an admissible control* $u(\cdot)$ *such that* $\mathrm{Cell}(0)$ *transforms into* $\mathrm{Cell}(T)$ *under the evolution of system (2) and the rules for mitosis described in Sec. II-C.*

Due to the morphogenic nature of the system under study that implies a dynamic state space, this problem opens a completely new area in the field of control theory. New methods have to be developed to answer such questions, and these type of problems are highly non-trivial.

Given our deformation algorithm existence of a solution is

not always guarantee, neither is uniquness provided that a solution exists. In a forthcoming work we introduce the notion of Hausdorff distance between two final configurations and restate the problem in terms of reaching a final configuration at the shortest distance from the desired one. Non-uniqueness also suggests the existence of efficient controls. A future work will be to determine a criteria to be used for optimality based on the experimental observations collected in the lab through the fractone's maps.

III. SIMULATIONS

Based on the algorithm in Sec. II-C, we present some simulations that show the evolution of a typical cellular system. In Fig. 3, we start with a single cell and an associated fractone. In this simulation, we chose a highly concentrated source near the fractone for our initial GF distribution such that mitosis would occur on a short time scale. Choosing a different initial distribution, however, would still produce similar images since there is only a single fractone that would eventually capture the growth factor via diffusion. Also, one can see how the mass of cells deforms according to our algorithm such that it attempts to maintain compactness. In Fig. 4, we represent an initial configuration of cells and fractones, and the resulting simulated configuration predicted by our algorithm. Each individual cell will produce neighbor cells until the mass of cells deforms in such a way that the lone fractone interacts with it. At that point, the lone fractone will have accumulated a significant amount of GF so that, once the mass of cells reaches it, the fractone will signal mitosis several times on a short time interval. It should be noted that in Fig. 3 and Fig. 4, a fractone is associated initially with one cell. However, in Fig. 3, the fractone is only associated with 2 cells throughout the simulation versus in Fig. 4 where each fractone is eventually associated with its 4 neighboring cells. This is an arbitrary choice that is easily modified in the computer code.

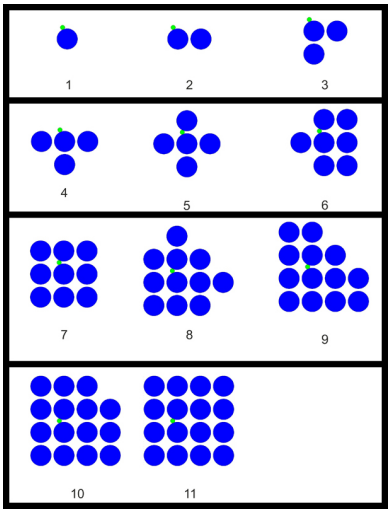

Fig. 3. Cellular evolution starting from one cell and one associated static fractone.

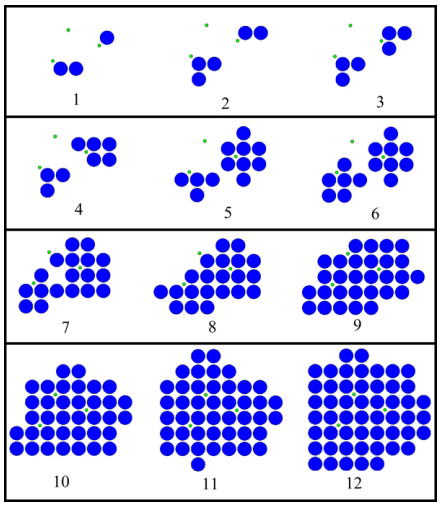

Fig. 4. Complex cellular evolution with multiple cells and multiple static fractones.

IV. ACKNOWLEDGMENTS

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