Dynamic Modelling Of Neural Morphogenesis Using Mathematical Control Theory

A thesis submitted to the Department of Mathematics of the University of Hawai'i in partial fulfillment of Plan B for the Master's Degree in Mathematics.

April 15, 2011

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Acknowledgments

First and foremost, I would like to thank Dr. Monique Chyba for her constant enthusiasm, enduring patience, and guidance. Without her, this thesis would not have been possible. Secondly, I would like to thank Dr. Frederic Mercier for sharing his expert knowledge of biology and his patience in explaining it to lowly mathematicians.

I would also like to thank Luca Invernizzi, Dario Cazzaro, and Giulio Telleschi for their technical support and assistance in Matlab programming. Finally, I would like to thank the students, staff and faculty of the Department of Mathematics, and the friends and teachers I've had among them, for their past three years of support and encouragement.

DYNAMIC MODELLING OF NEURAL MORPHOGENESIS USING MATHEMATICAL CONTROL THEORY

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Abstract. Within the last 20 years, 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 mitosis, migration, and differentiation. Building on the back of the discretized diffusion equations, we construct a control theoretic model of how these fractones interact with the cells and the associated growth factors produced by the cells in order to gain insight into the growth process as a whole. We then use the computational model to produce numerical simulations of the biological system. We also discuss several open problems that pertain to the system, and finally explain why this problem expands the field of control theory.

0. Introduction

This paper is organized under the following section headings:

Key words and phrases. Morphogenesis, Control Theory, Computational Modelling, Fractones.

1. Background Information

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 mamalian 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 [32, 43, 44]. 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.

To validate this hypothesis, we propose to develop and analyze a mathematical model predicting cell proliferation from the spatial distribution of fractones. Dynamic mathematical modeling, i.e. models that represents change in rates over time, serves several purposes [22]. Using computer simulations, by mimicking the assumed forces resulting in a system behavior, the model helps us to understand the nonlinear dynamics of the system under study. Such 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, is 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 commonly 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 [11, 12, 51]. Examples of its applicability in physical and biological systems are numerous [53, 54].

1.1. **Historical Usage of Mathematics in Biology.**

The history of mathematics used to solve problems arising from biology dates back several hundred years to the times of Bernoulli and Euler. Prior to the mid 1900s, though, biology served primarily as the inspiration to understanding larger problems rather than as a practical field to be studied under the rigors of applied mathematics. Many problems in the field, even simplified with strong assumptions and in their least-complex forms, were unable to be solved using traditional techniques of mathematicians due to their complexity. Researchers of the day were either forced to pay understudies to perform hundreds, perhaps thousands, of hand calculations, or they would make drastic simplifications of their models merely to gain insight into the behavior of the system, and, as a consequence, many would make incorrect conclusions when compared versus real-world data. However, at times, some models were found to be accurate when compared to known data, and thus were accepted as theory (this is most likely due to *acceptable* simplifications, those not significant to the model as a whole).

Once the mid 20^{th} century arrived, and with it the advent of the computer, researchers finally had the luxury of being able to analyze complex systems without unnecessary simplifications. And with the creation of the personal computer and modern computational software (as well as the internet and supercomputing clusters) in the 1980s, scientists and researchers could now fully model the most complex system without any necessary simplifications and can find solutions (albeit numeric) for a variety of problems.

Much of what has been attempted to solve or has been solved using mathematics in the field of biology is summarized in Table 1.

1.1.1. *Historical Usage of Control Theory in Biology.* The appearance and usage of control theory in the field of biology is a relatively new idea, dating back only a few decades. The first real evidence of the usage of control theory to understand a biological process originates with Norbert Wiener [59], who developed many of the ideas of feedback and filtering in the early 1940s in collaboration with the Harvard physiologist Arturo Rosenblueth, who was, in turn, heavily influenced by the work of his colleague Walter Cannon [10], who coined the term homeostasis in 1932 to refer to feedback mechanisms for set-point regulation in living organisms. Rudolf Kalman [29] often used biological analogies in his discussion of control systems theory, and so did many other early researchers.

Modern biological control, enveloped in the more general field of systems biology, eminates from the work of Ludwig von Bertalanffy[6] with his general systems theory. One of the first numerical simulations in biology was published in 1952 by the British neurophysiologists and Nobel prize winners Alan Hodgkin and Andrew Huxley[28], who constructed a mathematical model that explained the action potential propagating along the axon of a neuronal cell. Also, in 1960, Denis Noble[49], using computer models of biological organs and organ systems to interpret function from the molecular level to the whole organism, developed the first computer model of the heart pacemaker. The formal study of systems biology, as a distinct discipline, was launched by systems theorist Mihajlo Mesarovic[45] in 1966 with an international symposium at the Case Institute of Technology in Cleveland, Ohio entitled "Systems Theory and Biology".

The field of systems biology is large and encompassing, so much so that it, at times, is hard to define what is and is not part of the field. However, the kinds of research and problems that have laid the groundwork for establishing the field are as follows:

(1) complex molecular systems, such as the metabolic control analysis and the biochemical systems theory between 1960-1980 [52, 27, 9, 25, 57],
(2) quantitative modeling of enzyme kinetics, a discipline that flourished, between 1900 and 1970 [37, 3],
(3) mathematical modeling of population growth [19],
(4) simulations developed to study neurophysiology, and
(5) control theory and cybernetics [2, 42, 1].

Some recent problems approached by those studying control theory in the field of biology have been to model, among others:

(1) internal workings of the cell [38, 24],
(2) molecular signaling or energy transfer (among RNA, DNA, proteins, etc.) [8],

Subject	Reference
Spread of diseases	Bernoulli 1760[5]
Fluid mechanics of blood flow	Euler 1760[15]
Age structure of stable populations	Euler 1760 [16]
Logistic equation for limited population growth	Verhulst 1838[56]
Branching processes, extinction of family names	Galton 1889 [20]
Correlation	Pearson 1903 [50]
Markov chains, statistics of language	Markov 1906[41]
Equilibrium in population genetics	Hardy 1908; Weinberg 1908[23]
Dynamics of interacting species	Lotka 1925[39]; Volterra 1931[58]
Traveling waves in genetics	Fisher 1937; Kolmogorov et al. 1937[36]
Estimating bacterial mutation rates	Luria and Delbrück 1943[40]
Birth process, birth and death process	Yule 1925[60]; Kendall 1948[30], 1949[31]
Analysis of variance, agricultural experiments	Fisher 1950[18]
Morphogenesis	Turing 1952[55]
Game theory	von Neumann and Morgenstern 1953[46]
Circular interval graphs, genetic fine structure	Benzer 1959[4]
Threshold functions of random graphs	Erdös and Rényi 1960[14]
Sampling formula for haplotype frequencies	Ewens 1972[17]
Coalescent genealogy of populations	Kingman 1982a[34], 1982b[35]
Diffusion equation for gene frequencies	Kimura 1994[33]

TABLE 1. Mathematics Arising from Biological Problems

(3) cell signal transduction processes [7, 21],
(4) neural pathways [],
(5) regulation versus homeostasis [],
(6) RNA/DNA transcription with an emphasis on mutation [], and
(7) gene function and interactions [].

The breadth and variety of problems that can be modeled using control theory runs the gamut, from the molecular through the microscopic up to the macroscopic. Many areas of biology have been affected by many areas of mathematical science, and the challenges of biology have also prompted advances of importance to the mathematical sciences themselves. The rapidly developing field of systems biology (the merging of biology, physics, engineering, and/or mathematics) is tremendously exciting, and full of unique research opportunities and challenges, especially for the application of control theory.

2. Biological Motivation

2.1. **Biological Background.** 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. Hence, by building a model that incorporates the most important features of the biological system, we attempt to simulate how this occurs to give more insight into how structure of biological systems takes shape under the assumption that it is driven by the presence of growth factors and activation by ECM moluecules, particularly fractones.

During our research, we analyzed a space in which there exists three unique components: fractones, cells/holes, and growth factors (GFs) that cells produce. The initial configuration is (at least) one cell and one associated fractone. The cells produce growth factors on a fixed, regular time interval and in discrete amounts. The time at which an individual cell produces growth factor, however, may be different from any other cell (depending on when each cell entered the system). Once produced, the GFs diffuse radially away from the cell into the extra-cellular diffusion space that occurs between cells. The GFs do not chemically interact with each other, and they are actively trapped by a fractone when significantly close. Once a fractone has absorbed enough GF beyond some threshold, it sends a signal to the associated cell(s) to undergo mitosis. A hole is similar to a cell, except that it does not produce GF. In fact, a hole can be thought of as a wall, a non-interacting object that the system evolves around.

3. Mathematical Motivation

3.1. **Mathematical Background.** The classical models attempting to describe morphogenesis are based on Reaction-Diffusion (RD) equations developed in Turing's "Morphogenesis" [55]. 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 (a skin tissue, for example) 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 [32, 43, 44], morphogenesis involves the capture and activation of growth factors by fractones at specific locations according to a precise timing. Also, Turing's assumption of unchanging state space (i.e. there is no growth, or the cells do not replicate) is not applicable to our model since, as cells replicate, the system of equations describing the "diffusion-trapping" model grows by one equation for every new cell produced. This adds mathematical complexity to the problem in that the system of equations governing the model are increasing in number. As mentioned in Section 2.1, the fractones influence GF-mediated cell proliferation, which 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.

4. One Dimensional Model

Our initial assumption is that the geometric configuration of the cells is a ring of at least 3 cells. For the ring of cells, the topology is unaffected, as only the radius increases. The model is a control system that will predict the dynamic distribution of fractones (and attached cells) and their contribution to the morphogenesis process. The system will be modeled as a control system to incorporate dynamic changes in the distribution of fractones among the cells. In general, the state space of our control system represents the concentrations of a given number of growth

factors at a precise location in a given configuration of cells. Mathematically, these systems are described by a differential equation of the form:

$$\dot{x}(t) = f(x(t), u(t)), \quad x(t) \in M \tag{1}$$

where M is a n-dimensional smooth manifold, x describes the state of the system and $u : [0, T] \to \mathcal{U} \subset \mathbb{R}^m$ is a measurable bounded function called the *control*. Despite the fact that the field of control theory covers such a broad range, the biological process that we are analyzing presents a completely new challenge from the control theory point of view. We are primarily concerned with the affine control system:

$$\dot{x}(t) = F^0(x(t)) + \sum_{j=1}^{m} F^j(x(t))u_i(t), \quad x(t) \in M \tag{2}$$

where the vector field F_0 is referred to as the *drift* and the $F^j s$ are referred to as the *control vector fields* (m represents the number of available inputs, in particular if $m < n$ we say that the system is underactuated). Let us consider the state space of our control system to be the concentrations of a given number of growth factors at a precise location in a given configuration of cells. The drift vector field will represent the diffusion property of the growth factors under the condition that no fractone is active while the control vector fields represent the impact that a fractone will have on the diffusion process once it is activated. The spatial distribution of the fractones is governed by the control function:

$$u_i(t) = \begin{cases} 0 & \text{if fractone inactive} \\ 1 & \text{if fractone active} \end{cases} \quad \text{for } 1 \leq i \leq m$$

Assume that we have k growth factors diffusing among the cells; we call them X^k. Each growth factor has it own diffusion rate that will be denoted by $\nu_k > 0$ and X_i^k represents the concentration of the growth factor X^k in the $i^{th}-$cell. Note that $0^{th}-$cell is synonymous with the $N^{th}-$cell, where N represents the total number of cells. Now, we describe the system for a single growth factor. The component i of the drift vector field $F^{k,0}(X^k(t))$ is:

$$F_i^{k,0}(X^k(t)) = \nu_k \cdot \left(X_{i+1}^k - 2X_i^k + X_{i-1}^k\right). \tag{3}$$

This equation comes from Turing, and is modified to reflect that there are no cross-reaction terms (since the GFs are non-interacting) and the presence of a diffusion constant for each respective growth factor. The system $\dot{X}^k(t) = F^{k,0}(X^k(t))$ represents pure diffusion.

Now, as $t \to \infty$, such a system tends to the steady state solution in which the concentration of growth factor is identical in each cell. However, once a fractone associated to the i^{th}-cell is activated, the diffusion process is perturbed; there is diffusion from the neighboring cells to the i^{th}-cell but diffusion from the i^{th}-cell to its neighboring cells is prevented. In other words, the fractone associated to the i^{th}-cell acts as a captor of growth factor. In terms of the equations describing the system, when the fractone associated to the i^{th}-cell is actived, only the component u_i of the control is turned on (taking the value 1) and the control vector field $F^{k,i}(X^k(t))$ describes the new diffusion process. By construction, $F^{k,i}(X^k(t))$ only affects the diffusion of the $(i-1)^{th}, i^{th}$, and $(i+1)^{th}$-cells. Now, we introduce the

exchanging function that dictates whether neighboring cells give growth factor to one another by:

$$H_{st}(t) = H(X_s^k(t) - X_t^k(t))(X_s^k(t) - X_t^k(t))$$

where we define:

$$H(z) = \begin{cases} 0, & \text{if } z \leq 0, \\ 1, & \text{if } z > 0. \end{cases}$$

With these notations, we have:

$$F_i^{k,i}(X^k(t)) = \nu_k(H_{i+1,i} + H_{i-1,i} - F^{k,0}(X^k(t))) \tag{4}$$

$$F_{i-1}^{k,i}(X^k(t)) = \nu_k(H_{i-1,i} - X_i^k + X_{i-1}^k) \tag{5}$$

$$F_{i+1}^{k,i}(X^k(t)) = \nu_k(H_{i+1,i} - X_i^k + X_{i+1}^k) \tag{6}$$

and all the other components of the control vector field $F^{k,i}(X^k(t))$ are zero. If we consider multiple growth factors diffusing among the cellular structure, we must take them into account via superposition of the system and implementation of a hierachical system to describe the affinity of a given fractone with a certain type of growth factor. This adds complexity to the system, but it is a straightforward extension.

From the point of view of control theory, system (2) falls into the classical theory of control systems since it is affine and fully actuated (a fractone can potentientally be activated in any cell). All the components of the control are piecewise constant functions that take their values from the set $\{0, 1\}$ and, given an initial distribution of fractones, it is trivial to produce a control to reach a prescribed final distribution of cells. However, to achieve our goal, we must develop a more realistic model to incorporate the activiation of the growth factors that will dictate the multiplication of cells.

To refine the model we've developed thus far, we assume that once a given concentration for the growth factor X^k is reached at a fractone (or, equivalently, a captor), it releases the information to the attached cell to duplicate, and the concentration of growth factor in the cell drops to a lower amount. When this situation manifests, the number of cells in the ring grows from N to $N + 1$. This implies that the state space on which our biological control system is defined is dynamic, as its dimension transforms with the cells duplication. Based on how we perceive the system to function, the control system that models it is as follows:

$$\dot{x}(t) = F^0(x(t)) + \sum_{j=1}^{N(t)} F^j(x(t))u_i(t), \quad x(t) \in M(t) \tag{7}$$

where $M(t)$ is now a space whose dimension and topology varies with time. In a simplified way, this corresponds to saying that the number of cells grows, which is reflected in the equation by the introduction of $N(t)$. Also, the domain of control now varies since fractones can potentially become active in the new cells.

5. Two Dimensional Model

Assumption 5.1. In the 1D case, we associated a fractone with a single cell and that specific fractone only controlled mitosis for the cell it was associated with. However, in the 2D case, we will associate a fractone with any cell that is either 1 or $\sqrt{2}$ units of distance away from it (given a proper distance formula). This way,

a fractone can now initialize mitosis for at most 4 neighboring cells in the 2D case rather than be limited to 1 cell in the 1D case.

5.1. **Configuration And State Space.** Two continuously evolving objects will play a major role in the dynamical system predicting the morphogenic events. First, we introduce a notion of configuration space to depict the cells configuration of our system at any time t under study. Second, we introduce a state space on which the dynamical system is defined. More precisely, we have the following definitions.

First, let R be a compact connected subset of the 2-dimensional Euclidean space that we call the ambiant space. For simplicity, we assume that R is fixed and we identify R to a square. For our model, R is discretised 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 unit of the discretization is choosen 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. Those objects are defined in the following definitions.

Definition 5.2. We defined by $Cell(t)$ 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 $Cell(t)$ in R is denoted by $Diff(t)$ 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, $Free(t)$, and the fractone space, $Fract(t)$. The data of $Cell(t)$, $Free(t)$, and $Fract(t)$ forms what we call the *Configuration space at time* t and we denote it by $Conf(t)$. Note that $R(t) = Cell(t) \cup Diff(t)$ and $Diff(t) = Fract(t) \cup Free(t)$.

To the discretization of the initial configuration of cells, i.e. $Cell(0)$, 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 $Free(0), Frac(0)$ (and therefore $Diff(0)$) are represented by collections of indices. For instance, a cell configuration of four cells (2 horizontals and 2 verticals) and no fractone lead to $Diff(0) = I_0 \times J_0$ where $I_0 = J_0 = \{0, 1, \cdots, n\} \backslash (\{13, \cdots, 21\} \cup \{23, \cdots, 31\})$, where n represents the length of an edge of the configuration space.

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 been seen as obstacles since the cells prevent the diffusion. The fractones do not prevent the diffusion but perturbe 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 immerged in the ambiant space R. Growth factors diffuse freely in the diffusion space $Free(t)$ and are under a pertubed diffusion in $Fract(t)$. We make a few assumptions to mathematically described those objects.

Assumption 5.3.

(1) 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.

(2) We assume the cells to be vertically and horizontally aligned.
(3) The fractones are represented as one unit of our discretization.

Notice that at this stage of the work, those are arbitrary choices and it will be straightforward to relax these assumptions to reflect the observations from the experimental maps.

Assumption 5.4. For simplicity, the boundary of the ambiant space in which the biological process takes place is fixed but our definitions allow for boundaries that vary with time as well.

Remark 5.5. Due to the morphogenic nature of the biological process under study, the configuration space is constantly evolving. This distinguishes in a very non-trivial way our problem for the traditional problems in engineering or physics whose systems are usually defined on a static configuration space.

As mentioned before, since cells are constantly forming and fractones are moving, the diffusion space evolves constantly as well, however, it will always be formed by the product of unions of subsets of $\mathbb{Z}$. We introduce $Diff(t) = I_t \times J_t \subset \mathbb{Z} \times \mathbb{Z}$, where $I_t,\ J_t$ are both unions of finite subsets of $\mathbb{Z}$. Note that, with this equality, we identify the configuration 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 $(i, j) \in Diff(t)$ (resp. $Cell(t)$).

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 $Diff(t)$. We denote the state space by $M(t)$. More precisely, we have:

Definition 5.6. To each unit $(i, j) \in Diff(t)$, 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 $R^{dim(Diff(t))}$ such that $dim(Diff(t)) \geq 0$.

5.2. **Diffusion Space.** 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 is no cells, therefore the growth factors diffuse freely in the ambiant 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:

$$\dot{X}(t) = F^0(X(t)) \tag{8}$$

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 as described in Definition 5.6, and, assuming diffusion occurs between a unit (i, j) and its four neighbors, we have:

$$\dot{X}_{i,j}(t) = \nu \cdot \sum_{(k,\ l)\in\Delta} (X_{i+k,j+l}(t) - X_{i,j}(t)) \text{ for } (i, j) \in R. \tag{9}$$

Assume now that a cell forms in the ambiant 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, insures that the diffusion of the growth factor takes place in the remainder of the ambiant space only. By doing so, we do not have to perturbe the diffusion process, instead we continuously modify the topological space in which the diffusion process takes place.

Let us describe the new state space on which the diffusion process takes place. Assume the cell is centered at unit (a, b). This means that at the time t at which the cell formed, the diffusion space $Diff(t) = I_t \times J_t$ transforms into a new free diffusion space $I_t \times J_t$ from $I_t \times J_t \backslash (\{a-4, \cdots, a+4\} \times \{b-4, \cdots, b+4\})$ (we assume it is instantaneous). Notice that since several cells might be forming at the same time, the topological changes in the conguration space will reflect all the created holes. We then have:

$$\dot{X}_{i,j}(t) = \nu \cdot \sum_{\substack{(k,\ l)\in\Delta \\ (i+k,j+l)\in Diff(t)}} (X_{i+k,j+l}(t) - X_{i,j}(t)) \quad \text{for } (i,j) \in Diff(t). \tag{10}$$

Finally, we need to model how fractones perturbe 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 from neighboring units in $Free(t)$, and that this quantity becomes unavailable to the diffusion process. To reflect the biological hypothesis that fractones are produced, signal mitosis, and then disappear, we introduce the following definitions.

Definition 5.7. To each unit (i, j) we associate what we call a passive fractone. A passive fractone at time t belongs to $Free(t)$. An active fractone at time t is defined as a unit that belongs to the set $Frac(t)$. 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 $Free(t)$ 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 turned on to 1 while it is set to 0 for a passive fractone. The active fractone store the current quantity of growth factors available in unit (i, j) and acts as captor for the diffusion process. In other words, diffusion from an unit $(i, j) \in Frac(t)$ to its neighbors is prevented.

To represent this perturbed-diffusion process, we define a control system:

$$\dot{X}(t) = F^0(X(t)) + \sum_{(i,j)\in Diff(t)} F^{(i,j)}(X(t)) \cdot u_{(i,j)}(t) \tag{11}$$

where $X(t)$ is the state variable and denotes the concentration of growth factor in the diffusion space $Diff(t) = I_t \times J_t$ at time t, the drift vector field F^0 is given by the right-hand side of (10) 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 prescence of active fractones. More

precisely, we have under the assumption that (i,j) is an active fractone:

$$F_{i,j}^{(i,j)}(X(t)) = \nu \cdot \sum_{\substack{(k,\ l)\in\Delta \\ (i+k,j+l)\in Diff(t)}} X_{i,j}(t) \tag{12}$$

$$F_{i+k,j+l}^{(i,j)}(X(t)) = -\nu \cdot X_{i,j}(t) \ \text{ for } \ {}_{(i+k,j+l)\in Diff(t)}^{(k,\ l)\in\Delta,} \tag{13}$$

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 associated cells that mitosis can occur.

Definition 5.8. An admissible control is a measureable 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 $I_t \times J_t$.

5.3. **Mitosis.** The motivation behind the introduction of fractones as controllers comes from the hypothesis that the fractones give the order to the cell to undergo mitosis. Indeed, an active fractone stores a quantity of growth factors through the diffusion process, and once this quantity reaches a prescribed threshold, all the cells associated to this active fractone duplicate. In other words, the spatial distribution of fractones determines the morphogenic events and the topology of the cell space.

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. 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.

Definition 5.9. Let $a = (a_1, a_2)$ and $b = (b_1, b_2)$ be two units such that $a_1 = b_1 \bmod 10$ and $a_2 = b_2 \bmod 10$. The linear distance between a and b is defined by:

$$d_L(a,b) = (|a_1 - b_1| + |a_2 - b_2|)$$

and 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 hierachy between units that are at the same linear distance from a given unit. This notion of geometric distance is based on the assumption that the mass of cell is optimizing its shape by prioritizing compactness. Clearly, we have that:

$$d_G(a,b) = \left\{ 10\sqrt{n^2 + m^2} \mid n, m \in \mathbb{Z} \right\}.$$

Notice that, given unit (a, b), the closest units a factor 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 some possible distances up to a maximum distance of 10 units.

For any given distance d_G from a cell centered at (a, b) to a location toward which $Cell(t)$ can deform, there are either:

(1) 12 possible locations if d_G is an integer that is the hypotenuse of a Pythagorean triple,
(2) 8 possible locations if d_G is not along a diagonal or an axis in Table 2, or
(3) 4 possible locations if d_G is on a diagonal or an axis, and is not an integer that is the hypotenuse of a Pythagorean triple.

0	1	2	3	4	5	6	7	8	9	10
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	$\sqrt{37}$	$\sqrt{40}$	$\sqrt{45}$	$\sqrt{52}$	$\sqrt{61}$	$\sqrt{72}$				
7	$\sqrt{50}$	$\sqrt{53}$	$\sqrt{58}$	$\sqrt{65}$	$\sqrt{74}$	$\sqrt{85}$	$\sqrt{98}$			
8	$\sqrt{65}$	$\sqrt{68}$	$\sqrt{73}$	$\sqrt{80}$	$\sqrt{89}$	$\sqrt{100}$	$\sqrt{113}$	$\sqrt{128}$		
9	$\sqrt{82}$	$\sqrt{85}$	$\sqrt{90}$	$\sqrt{97}$	$\sqrt{106}$	$\sqrt{117}$	$\sqrt{130}$	$\sqrt{145}$	$\sqrt{162}$	
10	$\sqrt{101}$	$\sqrt{104}$	$\sqrt{109}$	$\sqrt{116}$	$\sqrt{125}$	$\sqrt{136}$	$\sqrt{149}$	$\sqrt{164}$	$\sqrt{181}$	$\sqrt{200}$

TABLE 2. Sample distance distribution for the deformation of the mass of cells as measured from the "mother" cell (located at 0). Here, 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.

5.3.1. *Algorithm For Deformation Of Cell(t).* The details of the algorithm for deformation of $Cell(t)$ after mitosis occurs are as follows. First, 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:

$$\begin{aligned} C_1 &= (i+5, j-5) \\ C_2 &= (i-5, j-5) \\ C_3 &= (i-5, j+5) \\ C_4 &= (i+5, j+5). \end{aligned}$$

At a given time t, the active fractone reaches the threshold for the concentration of growth factor. If $C_i \in Cell(t)$, then cell C_i undergoes mitosis.

Now, 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 $Free(t)$. Once such a unit is detected, the deformation occurs.

Units at a same distance from (i, j) are selected in the following order. The linear component distances, respectively, from a cell undergoing mitosis to a location toward which the mass can deform are $i_\ell - i_0$ 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 $Free(t)$ 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 $Free(t)$ such that $j_\ell - j_0 > 0$, and chooses preferentially the $min\{i_\ell\}$. If no such values exist, i.e. there is no space available, the simulation is terminated since $Cell(t)$ can not deform.

5.3.2. *Subspace Evolution Post-Mitosis.* The topology of the 2D system is dependent on the number of cells present at any given time. The way that the system has been defined, it evolves such that every "mother" cell always has a neighboring "baby" cell, or, in other words, is connected (if we ignore the diffusion channel between any two cells). The space in which the system evolves can be defined to be either closed or with moving boundaries. If we impose on the system to evolve in a closed space, then the system will recognize this via the distance algorithm and will only deform the mass of cells strictly inside of these boundaries. If the system has moving boundaries under which it is restricted, then the system can grow in any defined direction as far as the boundary will permit at any given time. When the system has evolved such that the distance algorithm produces no value, the simulation terminates.

Now, when a cell undergoes mitosis and the distance algorithm has chosen a position in $Free(t)$ for $Cell(t)$ to deform toward (call it (i, j) arbitrarily), the growth factor present in the space must move in order to make room for the deformed mass of cells. Hence, the program does the following:

(1) calculates the sum of the GF present in the space $C = (i, j)$ where the mass of cells will deform toward, i.e.
$$\sum_{k,l=-4}^{4} X_{i+k,j+l}(t).$$
(2) deforms $Cell(t)$ such that $(i, j) \in Cell(t)$.
(3) counts the number of units in $Free(t) \cup Frac(t)$ such that $d \leq 8$ in units from (i, j).
(4) distributes 70% of the sum from (1) evenly in each unit from (3).
(5) counts the number of units in $Free(t) \cup Frac(t)$ such that $8 < d \leq 11$ in units from (i, j).
(6) distributes the remaining 30% of the sum from (1) evenly in each unit from (5).

In this way, one can see that once the new cell enters the system, the deformation of $Cell(t)$ creates a "pressure wave" that distributes the GF around the space where the deformation impacts $Free(t)$. It should be noted that the distances and percentages chosen are arbitrary and are easily adjustable.

From the details thus far, we can glean the criteria that guide the system from one topological space to the next:

(1) in the absence of cell production of GF, the initial concentration of growth factor(s) dictate how many times mitosis can possibly occur (maximum number of cells, maximum number of configurations),
(2) the group of cells arrangement(s) will dictate how GF is distributed throughout, thus determining possibility for mitosis,
(3) the number of fractones present will determine the maximum change in dimension at any given time t,

(4) the affinity of the individual fractone to a certain GF,
(5) how often the cells, now producing GFs, do this and in what amounts,
(6) the amount of any one GF required to initiate mitosis,
(7) the "reset value" a fractone assumes post-mitosis, and
(8) how many cells each individual fractone is associated with.

6. Mathematical Statement Of The Problem

The morphogenic events have been modelled as an affine control system of the form:

$$\dot{x}(t) = F^0(x(t)) + \sum_{i=1}^{n} u_i(t) \cdot F^i(x(t)),\ x(t) \in M(t) \tag{14}$$

where the state space $M(t) \subset \mathbb{R}^{dim(Diff(t))}$ 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 $Cell(0)$, $Frac(0)$ and $Cell(T)$, $Frac(T)$. Also, note that the dimension of $M(t)$ is arbitrary since it depends only on our discretization. The problem is now the following:

Problem:
Given an initial and final configuration of cells in a prescribed ambiant 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.

Mathematically:
Given $Cell(0)$ and $Cell(T)$, which are subspaces of R, determine $X(0)$ and an admissible control $u(\cdot)$ such that $Cell(0)$ transforms into $Cell(T)$ under the evolution of system (11) and the rules for mitosis described in section 5.3.

Now that the main problem has been stated, it is clear that the algorithm we have chosen for deforming $Cell(t)$ (the "clockwise" arrangement starting at angle zero) is arbitrary since any two spaces are equivalent if they are rotations of a factor of 90 degrees of each other. If we had picked a different algorithm (either in direction of cell deformation or starting angle from the mother cell), the two different algorithms would produce final configurations that were a rotation of $90n$ degrees from each other (for $n \in \{1, 2, 3\}$).

6.1. **Existence Of Solutions.** As with any problem, one must check to see, for a given set of initial and final configurations, if there actually exist a solution to the problem, even in the simplest cases. For our problem, one can quickly produce a counterexample for which there is no "exact" solution. Of course, this is assuming that the initial configuration of cells is not one that arbitrarily leads to final configuration, such as the degenerate case in which $Conf(0) = Conf(T)$.

In Figure 1, if the initial configuration is that of one cell and one associated fractone (the "classical" configuration), there is no way to produce the exact final configuration as shown. However, given the other initial configuration, it is clear that the final configuration in Figure 1 is a reachable configuration. This gives rise to a new level of complexity within the problem: the set of reachable final configurations (or, perhaps more appropriately, the set of non-reachable final configurations)

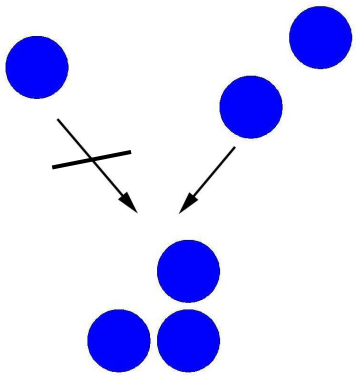

FIGURE 1. **Two separate initial configurations and a final configuration. Here, the right initial configuration can exactly produce the final configuration, but the left initial configuration is unable.**

as predetermined by the initial configuration. Even with this new point made, it is still obvious from our first counterexample that there does not exist for every set of given initial and final configurations a solution, i.e. a set of controls such that $Conf(0) \to Conf(T)$.

6.2. **Uniqueness Of Solutions.** Now, given $Conf(0)$ and $Conf(T)$, suppose there exists a set of controls such that $Conf(0) \to Conf(T)$. Naturally, we should determine whether or not a solution to the problem is unique. As before, it is easy to choose an initial configuration and a final configuration such that the set of controls that guides the system is not unique. In Figure 2, we present an initial configuration and a final configuration for which the solution is clearly not unique. In this simulation, the fractone reaches the threshold to initiate mitosis from one level to the next lower level.

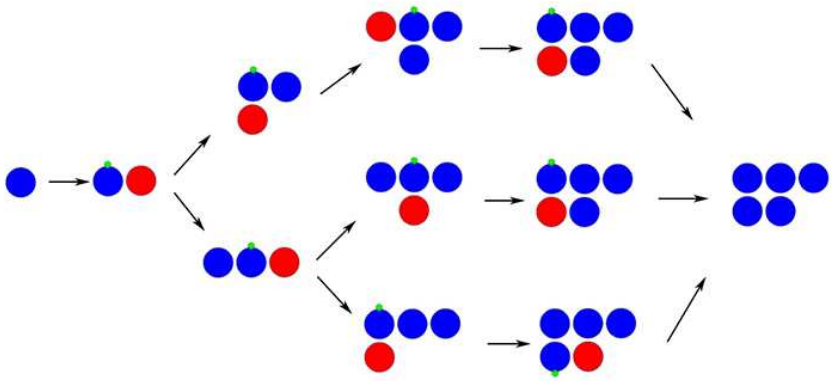

FIGURE 2. **Starting from the "classical" configuration, three unique solutions produce the final configuration. Here, cells in red indicate the direction in which cell deformation occurred, fractones are green, and cells in blue represent either static cells or mother cells.**

7. Open Questions

After stating the problem as above, we can attempt to formalize questions concerning the system. Indeed, as seen in Figure 1, there might not exist a solution to this problem for a given set of initial and final configurations. In this case, how do we modify the question? One solution is to introduce a notion of distance between configurations of cells and to ask how to reach a final configuration that is at the shortest distance from the desired one. There is also clearly the possibility that several controls lead to the same final configuration of cells, as seen in Figure 2. In this case, how do we select one? What is the criteria to be used to determine the most efficient control function?

One strategy to be explored in forthcoming work is based on the experimental observations collected in the lab through the fractone maps. Indeed, the experimental maps will provide information about the control function used by nature to produce morphogenic events. Based on those observations as well as assumptions such as minimizing the number of times mitosis can take place during the entire duration of the morphogenic event or minimizing the number of switching in the control function (which is equivalent to minimize the changes in the spatial distribution of the fractones), we can ascribe a cost function to be minimized. Our problem then becomes an optimal control problem. However, due to the complexity of the system, there is an extremly large number of questions associated to this problem, and, as said previously, new methods need to be developed.

8. New Class Of Problems In Control Theory

Our model clearly diverges from Turing's model (or any other Reaction-Diffusion model), and it presents new challenges that will advance the field of control theory. To envision how our problem does this, we must compare and contrast versus typical control theory problems. For example, in physics, 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. Due to the morphogenic nature of the biological process under study, the configuration space is constantly evolving (caused by the creation of new cells), and thus can not be analyzed using traditional techniques of control theory in which the equations describing a given system are predetermined when defining the system. This distinguishes in a very non-trivial way our problem from the traditional problems whose systems are usually defined on a static configuration space.

Inspired by the biological question, we propose an entirely new theoretical control problem by noting that an intrinsic property of biological systems is having a dynamic state space. As a result, new methods have to be proposed to analyze these type of systems from the control theory point of view. This will advance the field of control theory by considering new problems and by providing insight toward the development of innovative ideas and methods to solve these types of problems.

9. Simulations

Based on the algorithm in Section 5.3, we present some simulations that show the evolution of some typical cellular systems.

In Figure 3, we present a simulation of the perturbed-diffusion process in which one cell and one fractone exists 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. It should be mentioned that, if there was a cell appropriately close to the fractone, that cell would undergo mitosis. However, since there is not, the fractone merely stores the growth factor that it collects from the neighboring units in which diffusion is occurring.

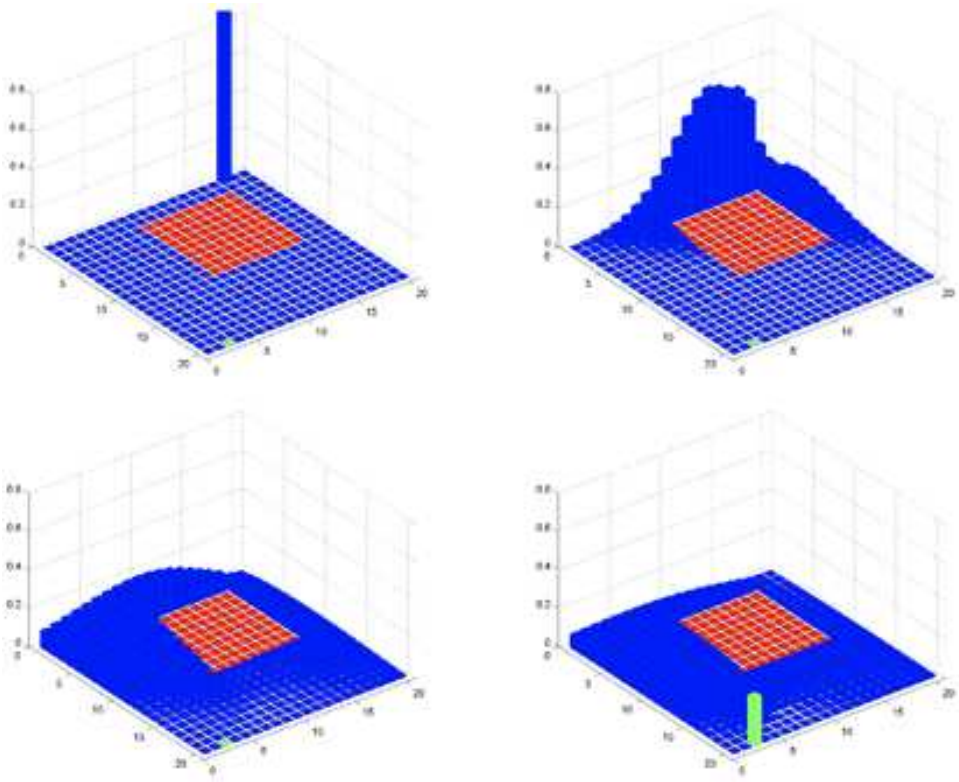

Figure 3. **Diffusion from a high concentration source through the free space, around a cell (red), towards a fractone (green). Here, the height of the column above each unit represents the amount of growth factor.**

In Figure 4, we present a simulation of the perturbed-diffusion process in which one cell and one fractone exists in the ambient space, and this cell undergoes mitosis. The initial distribution of growth factor is a double source (not to scale) as seen in the initial image near the lower corner below the cell and to the left of the cell, while the fractone in green is located on the left of the cell. The growth factors diffuse through the free space and are captured by the fractone. In Image 2, the fractone reaches/exceeds the threshold of growth factor, and initiates mitosis of the associated cell. In Image 3, the cell space has deformed according to the deformation algorithm, and has displaced the growth factor that was present via the redistribution algorithm. Notice that there is no growth factor present between the cells in accordance with how mitosis actually occurs in nature. In Image 4, the cell space has finished deforming, the redistributed growth factor has diffused appropriately, and the amount of growth factor present on the site of the fractone has again reached the threshold for mitosis. In the next two images, the aforementioned process is repeated according to the respective algorithms.

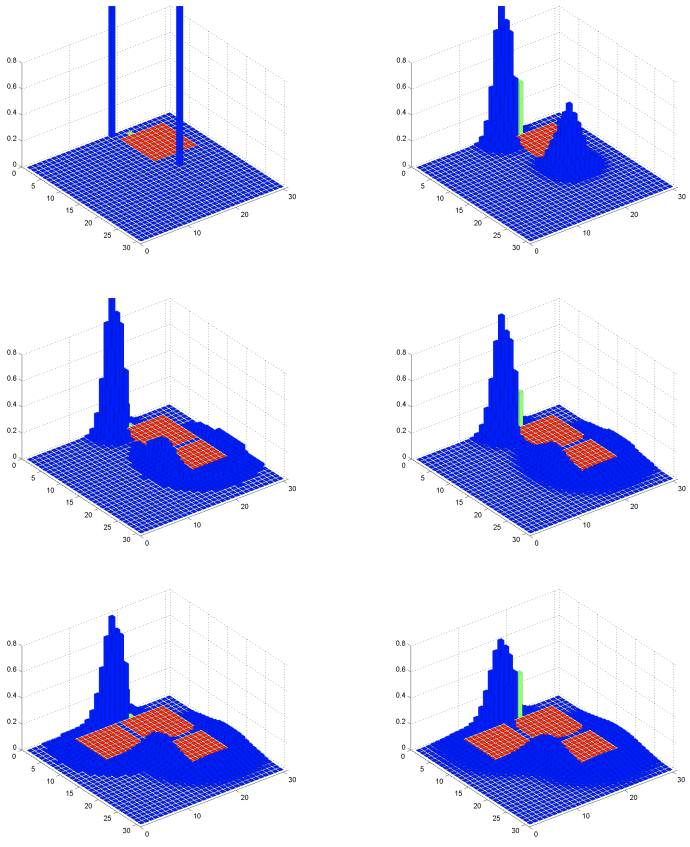

FIGURE 4. **Diffusion from two high concentration sources through the free space, around a cell (red), towards a fractone (green). One can also see cell deformation post-mitosis and growth factor redistribution due to deformation.**

In the following figures, we only display the 2D projection of the cellular configurations since the initial concentrations of growth factor and its distribution is unimportant to the evolution of the simulations.

In Figure 5, 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 growth factor distribution and a low threshold such that mitosis would occur on a short time scale in order to produce the morphogenic event. 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. In particular, the configuration of the mass of cells is deforming such that it attempts to maintain compactness. In Image 11 in Figure 5, it should be noted that the cell space takes the shape that it has due to restrictions in the computer program of the whole space only.

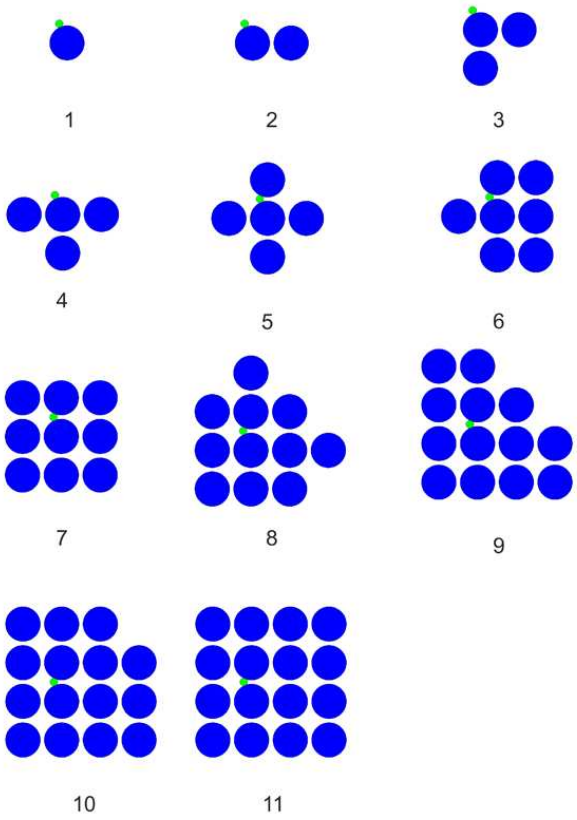

FIGURE 5. **Cellular evolution starting from one cell and one associated fractone.**

In Figure 6, we present an initial configuration of cells and fractones, and the resulting simulated configuration predicted by our algorithm. Again, we chose a highly concentrated source near the center of the fractones for our initial growth factor distribution and a low threshold such that mitosis would occur on a short time scale in order to produce the morphogenic events. 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.

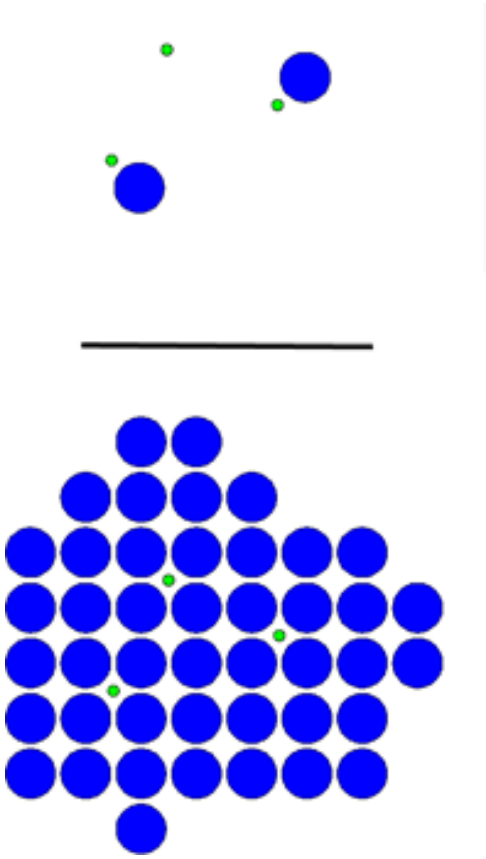

FIGURE 6. **First and last frame of a simulation with multiple cells and fractones. Simulation was stopped one frame early to exhibit some structure prior to absolutely filling the space.**

It should be noted that in Figure 5 and Figure 6, a fractone is initially associated with one cell. However, in Figure 5, the fractone is only associated with its two neighboring cells throughout the simulation versus in Figure 6 where each fractone is eventually associated with its four neighboring cells. This is an arbitrary choice that is easily modified in the computer code.

10. Future Work

The are mainly two directions of work that we are planning to undertake at this stage. First, from a purely mathematical perspective, an open question is the development of new techniques to answer controllability and optimality questions for control systems such as the one introduced in this paper. Second, the interplay between the biological motivation and the mathematics must be refined to predict neurulation and post-neurulation growth by the mathematical model using fractone maps produced by biological research.

The current model is based on what we believe are the most critical features of our hypothesis. However, some of our assumptions are very restrictive and we also need to add some complexity to produce a more realistic model. Other important features of the biological system that have not yet been taken into account that will be incorporated into our model are to:

(1) relax the assumption that the cells are horizontally and vertically aligned to allow broader configuration of cells, i.e. non-symmetrical cellular arrangements,
(2) establish a penality function for the diffusion of growth factors in the space found between the cells with respect to diffusion in the free ambiant space, and
(3) add the possibility of having multiple growth factors diffusing in the ambiant space at different rates as well as having active fractones with varying sensitivities to each respective growth factor.

However, despite the new features to be added, the statement of the problem will generally remain the same.

After all of this has been accomplished, we will discretize the fractone maps provided by biologists and then determine whether the prediction of the mathematical model reflects the growth of the neural tissue observed in the maps. The observation of spatial distribution of fractones provided by the maps will determine the control function to be used in the mathematical model to produce our simulations.

Although we have not cited every work in the references below, we have included an extended bibliography for possible future investigations.

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