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SIMULATION TOOL FOR MORPHOLOGICAL ANALYSIS

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KEYWORDS

Morphological Analysis, Virtual Reality, Biological Multi-Agent System, Mathematical Programming, Scientific Visualisation Software.

ABSTRACT

To understand the mechanisms underlying the morphogenesis of multicellular organisms we study the dynamic system of cells (cell multiplication, cell migration, apoptosis); local interactions between cells for understanding the convergence of the system to a stable form that is constantly renewed.and the controls established by the nature of the growth of the organism, and its convergence to a stable form.

We must be able to formalize it in a proper metric space a metaphor of cell dynamics to find conditions (decisions, states) in which operational constraints (such as those induced by the tissue or the use of resources) are always satisfied and therefore in which the system is viable and maintain its shape while renewing.

The aim of this paper is to explain the mathematical foundations of this work and describe a simulation tool to study the morphogenesis of a virtual organism and to describe a simulation tool to study the morphogenesis of a virtual multicellular organism. We formalize mathematically a model of cell dynamic on the principles of morphological analysis. Morphological analysis and viability theory are the mathematical foundations that motivate this work and this tool will test whether a system generated by morphological equations can maintain its shape and remains "viable" in a given environment.

INTRODUCTION

In biology, recent techniques in confocal microscopy allow experimental data on cellular dynamics and its importance in the evolution of biological shapes to be gathered. The development of an organism is an evolutionary process, not deterministic of different cells in an environment. The cells evolve and change the organism on which they act, which is changing the environment that feeds back on the cells. It is what we call co-evolution, i.e. the system changing its environment, which in turn changes the system. Epigenetics considers this coupling between organism and environment and can not be ignored in understanding the development of living(Varela, 1979).

To understand the mechanisms underlying the morphogenesis of multicellular organisms we study the dynamic system of cells (cell multiplication, cell migration, apoptosis); local interactions between cells for understanding the convergence of the system to a stable form that is constantly renewed.

Many studies already model the development of organisms, cellular automata (Forest, 2005; Hogeweg and Marée, 2001; Pena and Duthen, 2007; Graner and Glazier, 1992; Ballet et al., 2009), L-systems (Prusinkiewicz and Lindenmayer, 1990) based on a formal grammar, iterated function systems (IFS) (Siepinski sieve and fern) (Gentil et al., 2006) and finally, we use multi-agent systems to model complex systems. they offer the possibility to simulate a number of autonomous components in an environment in order to ascertain the nature of the phenomenon studied in its entirety, without central control (Stoma et al., 2007; Doursat, 2007).

The problem is that simulations using multi-agent systems approach are very difficult to formalize and to study theorically, they set problems of convergence and stability (Bonneaud et al., 2009). To study the shapes generated by multi-agent modeling using morphogenetic principles, we must be able to formalize in a metric space the cellular dynamics to study mathematically the conditions of growth,

convergence and stability of the processed shape.

In mathematics, the viability theory (Aubin, 1991) offers concepts and methods to control a dynamic system in a given fixed environment, in order to maintain it in a set of constraints of viability. This is mainly to elicit the underlying feedbacks that regulate the system and discover the mechanisms of selection for implementation. The development of mutational analysis (Aubin, 2000) was motivated because dynamic systems theory and viability theory are not suitable for studying a cell system that grows and multiplies. The concept of differential equation has been extended to the concept of mutational equation in a metric space. Morphological equations, special type of mutational equation, have properties similar to those of differential equations (Peano theorem, Cauchy-Lipschitz, Nagumo) (Lorenz, 2010). They govern the evolution of sets in the same way as differential equations govern the evolution vectors, and are used to investigate conditions (decisions, states) in which a morphological equilibrium will be maintained and where operational constraints (such as those induced by the environment or resource use) are always satisfied and in which the system will be sustainable.

If an evolutionary system is given, the viability theorem states how it governs the evolution of a viable state in a fixed environment. When the system evolves the environment changes, and this changes influence the system. This is what biologists mean by co-evolution. Mathematically, it is the joint evolution of states and sets to which they must adapt. In this case, the environments are changing under the action of a morphological equation, evolutionary systems are governing the evolution of the states and of the environment, and they depend on both the state and the environment. This is called a differential-morphological system. For such a differential-morphological system to have solutions we have to adapt the viability theorem to the differential-morphological systems. This means that there is at least one co-viable evolution of the state and the environment based on each state-environment pair.

The set of conditions for which at least one solution is viable is called viability kernel. In the case of a multicellular organism that evolves, the cells evolve with the organism and with the environment of the organism. To be viable these three levels will have to be able to react appropriately to events. Therefore anticipating the time when the state of the cell, the body reaches its limits of viability, i.e. determine their viability kernel.

Thinking of morphogenesis in this way brings new requirements, particularly in mathematics and computer science to implement efficient mutational algorithms able to inform us about the mechanisms used by multicellular organisms to survive. Their structure could be indicative of internal consistency mechanisms of morphogenesis in living organisms.

The definition of the viability kernel remains difficult: specific algorithms have been developed however their application requires an exponential memory space with the dimension of space, and the outcome is difficult to handle. The viability theory provides tools and methods to control a dynamic system in order to keep it in a set of eligible states, called the set of constraints(Aubin, 1991). Mutational algorithms have yet to be conceived.

In this context, the aim of this work is to formalize mathematically a model of cell dynamic on the principles of morphological analysis and to describe a simulation tool for studying morphogenesis of virtual multicellular organisms. Morphological analysis and viability theory are the mathematical foundations that motivate this work and this tool will test whether a system generated by morphological equations can maintain its shape and remains "viable" in a given environment.

MORPHOLOGICAL DYNAMIC OF CELLULAR TISSUE EVOLUTION

The purpose of this paragraph is to formalize in the context of mutational and morphological analysis, the evolution of cellular tissues during embryogenesis. This question motivates the study of a **discrete morphological dynamics** governing the evolution of tissues.

During an infinitesimal change of tissue, each element of the form is not only "move" to another point of the form that follows it, but eventually moved and "multiplied" when multiple daughter cells succeed to this element, multivalent character which leads to the concept of speed form (Aubin, 2000).



Figure 1: Univalued analysis to formalize a cell that moves

During embryonic development, the confinement is imposed by the cohesion of tissues and the presence of an envelope, such as the epithelial layer covering the embryo. There is a co-evolution of the cellular membrane and the dynamics of each cell, confinement shapes that can evolve only by respecting the constraints that we want to study using morphological analysis.
In biological morphogenesis, the vitellius is the energy reserves used by the embryos during embryonic development.

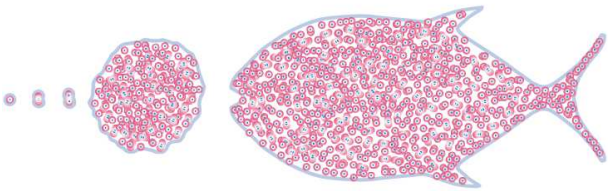


Figure 2: Multivalued analysis to formalize a cell that multiplies and moves

M denotes the set of containment cells, contained in the complement of vitellius.

$K \subset \mathbb{R}^3$ representing tissue cells, the cells are designated by $x \in K \subset \mathbb{R}^3$.

If we restrict morphogenesis in the plan,

$$(D) := \{(0,1),(0,-1),(-1.0),(1,0)\}$$

denotes the set of 4 planes directions and $\overline{\mathcal{D}} := \mathcal{D} \cup \{(0,0)\} \cup \emptyset$ means the 6 "extended " directions

For morphogenesis in the space $\mathbb{R}^3$,

$$\mathcal{D} := \{(0,0,1),(0,0,-1),(0,1,0),(0,-1,0),(-1,0,0),(1,0,0)\}$$

denotes the set of six directions and $\overline{\mathcal{D}} := \mathcal{D} \cup \{(0,0,0)\} \cup \emptyset$ means the eight "extended" directions.
We denote by $A + \emptyset = \emptyset$ in the max-plus algebra for the operations $\cup$ and $+$.

We will note $\Xi_M(K,x) := \{u \in \mathcal{D} \text{ such that } x + u \in \{x\} \cup (M \setminus K)\}$ et $R_M(K,x) := \Xi_M(K,x) \times \Xi_M(K,x)$.

Then we introduce the correspondence $\Psi(x,u,v) := \{x+u\} \cup \{x+v\}_{(u,v)\in R_M(K,x)}$.

The morphological dynamic Φ_M is then defined by

$$\Phi_M(K) := \bigcup_{x\in K} \bigcup_{(u,v)\in R_M(K,x)} \Psi(x,u,v) \qquad (1)$$

And the discrete morphological dynamic $K_{n+1} = \Phi_M(K_n)$.

This gives the different cases of cell behavior:

1. *apoptosis* , obtained by taking $(\emptyset,\emptyset) \in R_M(K,x)$ since $\Psi(x,\emptyset,\emptyset) := \emptyset \cup \emptyset = \emptyset$
2. *migration* by taking $u \in \mathcal{D}$ et $v = \emptyset$ or $u = \emptyset$ and $v \in \mathcal{D}$ or further $u = v$
3. *stationarity*, which is a migration obtained by taking u and v equal to $(0,0,0)$
4. *cell division* by taking $u := (0,0,0)$ et $v \in \Xi_M(K,x)$ (or otherwise)
5. *division and migration* by taking $u \in \Xi_M(K,x)$ and $v \in \Xi_M(K,x)$

We can now introduce the equivalence relation on the directions

$$u \equiv_x v \text{ if and only if } x + u = x + v$$

which we denote by μ and ν the representatives, noting that by construction, for every pair (μ,ν) the equivalence class, for all $u \in \mu$ and $v \in \nu$, $\Psi(x,\mu,\nu) = \Psi(x,u,v)$ does not depend on the choice of directions belonging to equivalence classes.

Because two cells can not occupy the same position, just select at most one extensive direction in each class.

The correspondence of regulation is defined by the quotient set :

$$\Theta_M(K,x) := R_M(K,x)/\equiv_x \qquad (2)$$

The morphological dynamics Φ_M is always defined by

$$\begin{aligned} \Phi_M(K) &:= \bigcup_{x\in K} \bigcup_{(\mu,\nu))\in\Theta_M(K,x)} \Psi(x,\mu,\nu) \\ &= \bigcup_{x\in K} \bigcup_{(u,v)\in\in R_M(K,x)} \Psi(x,u,v) \end{aligned} \qquad (3)$$

In the case of a discrete dynamics, it is defined by control sequences (u_n, v_n) associated to K_n to define $K_{(n+1)}$.

Implementation of the algorithm is equivalent to setting the viable directions.

TOOL FOR MODELLING MORPHOGENETIC BEHAVIOUR

This section presents the tool developed for modelling of morphogenetic phenomena.

We set as a basic principle that cells are autonomous agents. The cell perceive changes in the environment and can change its dynamic.

In addition, the cells are autonomous by ignorance of the whole system because the reductionist method does not predict

the evolution of the whole system. The principle that cells must be autonomous is set as a basic rule.

The platform was created to understand morphogenesis as the theoretical basis for morphological analysis. The program is implemented (applied) in C++ using the Workshop of Virtual Reality AREVI (Reignier et al., 1998), it is a simulation library of autonomous entities and 3D rendering.

The order of scheduling has a significant impact on the results of the simulation (Lawson and S.Park, 2000), (Bonneaud et al., 2009). Different behaviours can be observed in virtual models depending on the manner (type) of scheduling used. In nature morphogenesis shows us robust forms despite autonomous cells. To better appreciate and understand the mechanisms that are put into play in morphogenesis, we wanted to retain flexibility in the scheduling of cells. The program has two different modes of simulation, a stochastic mode and a controlled mode. The cells represented on screen by spheres can proliferate in a discrete environment (cellular automaton) or in a "continuous" one. In the latter case the movement of cells are more precisely described. Distance between the cells can vary. It represents the forces of attraction or repulsion between them.

The behaviour of cells is not the same in each type of simulation. A simple graphical interface has been implemented in order to select the features of the simulation. It allows dynamic change of parameters and selecting mechanisms (e.g. apoptosis, differentiation) that are active/inactive during the simulation. A number of parameters were taken into account to test their relative influence on the forms generated by populations of cells.

Options are available to allow choice between 2D/3D, discrete or continuous simulations. The size and shape of both the environment and the cells can also be defined and adjusted, as can cell behaviour such as apoptosis, the direction of mitosis etc.

In the case of continuous simulation, each cell can perceive its neighbors within a radius of attraction and evaluate the stresses:

- by the neighbors.
- by the membrane containment.

Constraints are crucial for evolution of the cell; if it is too strong, the cell is not viable as it can no longer divide. A maximal constraint parameter sets up a threshold below which the cell remains viable.

The notion of coercion has no place when cells are represented in a grid. To account for the influence of the environment, a parameter is defined as the maximum number of cells that a cell is able to force when it divides. When the current strain of the cell is greater than the maximum stress threshold, the cell can no longer divide. Two modes of mitosis have been considered; firstly the cell chooses to divide in the direction where the stress is less intense; secondly where the direction of cell division is predetermined. However in both cases, if the spatial constraints of the current cell exceed the maximum stress threshold, it cannot divide.

It is also possible to assign an amount of energy to each cell. The basic idea is: consider that a cell has a store of energy assimilate from its environment. A percentage of the store is used to maintain structure and growth. The remaining its reserve is used for maturation (e.g. maintenance of the immune system) and reproduction. In very simple terms initially we want to apply this principle. A level of energy is mapped and associated with virtual cell application. A small amount of energy representing cell maintainance of its structure is logged at each step of the simulation. We consider that a cell uses a lot of energy in reproduction - during mitosis this energy level is divided by two. The cell dies when the energy level becomes too low. The behaviour of a cell is directly related to the quantity of energy contained and it is possible to obtain forms of very different population of cells by modulating certain thresholds, as detailed below. A cell can recover energy if it is in contact with a relevant part of the environment.

An option of the application allows cells to differentiate. In this case, cells that are not the same type (represented by different colors) have different dynamics. A specific cell can differentiate when under stress. We wanted to demonstrate this in connection with the spatial constraints of the cells. Stress corresponds to a large differential spatial constraint between two consecutive measurements. A threshold defines the minimum value of the interval for which the cell differentiates. It is also possible to define a numerical value for stress necessary to induce differentiation.

Another control is the direction of cell division. It is possible to define the direction that mitotic cells take in advance and the order of selection. This parameter can also be chosen as a random option. The morphogenesis changes when varying the choice of these directions. Real time morphogenesis film has produced data that demonstrates the features of the direction of cell division.

Parameter values modulate cell activity. The steps of the

algorithm define cell behaviour and are the same for both discrete and continuous cases, as we have seen, the stress calculations are different.

TEST

As described in the preceding paragraph, by varying the parameters the application offers the possibility to make different types of simulation.

In collaboration with Nadine Peyrieras (Melani et al., 2007; Campana et al., 2008), we compared the behaviour of our model with the first segmentation of zebrafish cells. (See Figure 3).

The model shows the first segmentation of the small fish up to 1,000 cells, then the model cannot be used further because the dynamic of certain cells has changed. To enable biologists to continue to advance understanding on the establishment of the dorsoventral axis of the zebrafish, it is important to elucidate the cellular dynamics.

This question leads us to examine the outcome of differentiated cells. This motivated the development of morphological analysis to control cell dynamics and the creation of a simulation platform to visualize and compare with biological data.

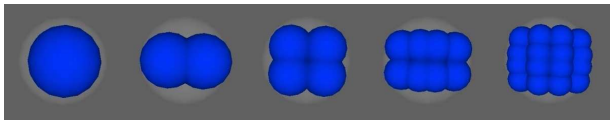


Figure 3: First simulated segmentation of the zebrafish

We also tried to observe spacial constraints when Vitellius is half covered (see Figure 4) to understand the changing dynamic of the cells that form the backbone of the fish.

To better understand morphogenesis, and to overcome obstacles in understanding the influence that the dynamics have on the shape of the organism, we voluntarily limit to discrete simulation by controlling the order of division and ordering executions. Here we have chosen to present a number of simulations by choosing modes of division and as a result of mitosis different directions to observe the impact of these parameters on the shapes of cell populations (see Figure 5). The study is still in its infancy but it is fundamental for undrestanding the mechanisms controlling morphogenesis.

CONCLUSION

The main contribution of the paper is the mathematical formalisation of cell dynamic on the principles of mor-

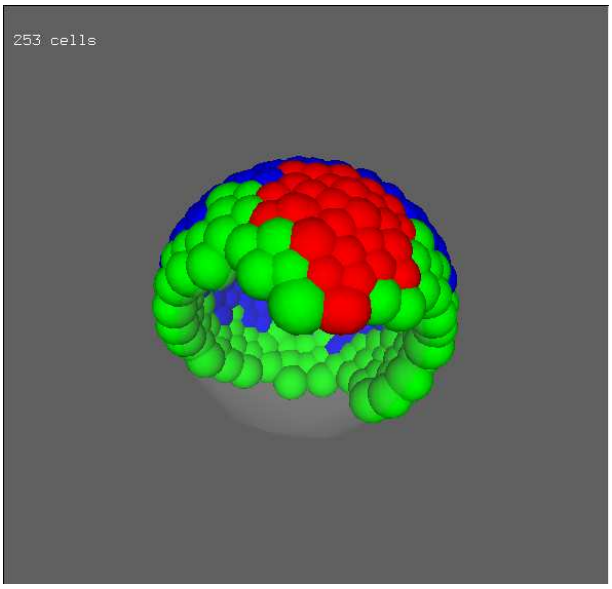


Figure 4: Spaces constraints for the Zebrafish

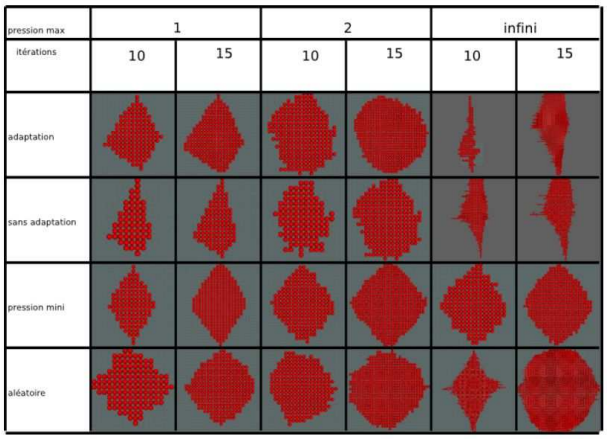


Figure 5: 2D-Shape dictionnary

phological analysis and the construction of a platform of virtual reality to experiment this dynamic.
This beginning of mathematical formalization of cellular dynamics using mutational analysis has guided this work and the development of this platform modeling. Similarly, the use of simulation tools has guided us in our questioning on morphogenesis.

Among the important issues that have emerged, two issues have attracted particular attention: the robustness of biological forms and the equilibrium of the shape. How cells whose dynamics is simple (mitosis, apoptosis, migration) can maintain form while continually renewing itself (homeostasis), and how despite environmental disruption during embryonic development, the shape stay stable.

Morphological analysis is an original way to formalize the

cell dynamic and to better understand the retro-actions implemented by the cells to maintain their viability and the organism's viability.

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