

Simulation of a cell proliferation model

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Abstract

In this paper, we are interested by the simulation of cell dynamics population based on the cell proliferation. The solution is to answer the following question: knowing the cellular density at time t_0 , how do we compute this density at time t_n , n is unknown and could be infinite. After we show that the problem is mathematically well formulated and based on the theoretical results obtained so far, we propose a numerical model and graphical simulation approach. The developed environment, will undoubtedly constitutes, a biological means of experimentation where the theories will be tested not on real biological populations but rather on a randomly generated data via a computer. This work is in the framework of the study of the phenomena related to the artificial life and the collective intelligence.

Key Words: Transport Equation, Cell Dynamics Populations, Rotenberg's Model, Maturation Velocity, Voronoi Diagram.

1. Introduction

The cell dynamic population based on the proliferation is the result of several biological phenomena which are still far from being completely understood. In order to help in the comprehension of the problem, several models and techniques were designed [1]. The objective of this study is concerned with the modeling and the simulation of the cell dynamics population based on Rotenberg's model. After describing the theoretical results obtained in [2], we are interested in the remaining of this paper by the numerical simulation. An interactive simulation platform is proposed. The visualization of the cells and their environment is done in a 2-dimension using the diagram of Voronoi [3].

2. Biological Bases

In a cell tissue each cell is obtained from the multiplication by successive divisions, or proliferation, of an initial cell. The growth of a tissue is due to a finite increase of the size of a cell, and to a finite increase in the quantity of the intercellular substances. The majority of the intercellular substances of a tissue are local cellular secretions. In the living objects with limited growth the cellular proliferation, differentiation and death which ensure the finished growth of a tissue are also responsible for its dynamic balance, when the growth is completed.

Among the cellular divisions which dominate the development of an individual, one distinguishes those which have a "proliferate" role, and do nothing but increase the number of identical specimen of cells. They also augment the number of cells which have a "quantum" role by producing two cells having different evolutions and responsible for the increasing divergence for the cellular lines (epithelial cells, blood cells, nervous cells, etc.) during the development.

3. Simulation Method

The cell proliferation is the result of many biological mechanisms which are not well understood yet. In order to improve its comprehension, a number of cell proliferation models were developed in the last thirty years or more. It is often a matter of introducing new elements to better comprehend the involved biological mechanisms either via mathematical modeling, or qualitative or quantitative statistic.

The most interesting models are undoubtedly those which are very close to a biologist's reasoning. The study and the simulation of phenomena related to life often use one of the following techniques:

- Populations evolution using genetic algorithms;
- Growth prediction when we know only some initial points using an expert system approach;
- Realization of autonomous creatures able to act and thus to survive in an environment not completely specified;
- Study of the collective phenomena starting from the interaction of a set of reactive agents [4];
- Dynamic analysis of the complex phenomena using cellular automata or nonlinear differential equations.

The mathematical model used in this work is based on a deterministic modeling of population's dynamics. This modeling is based on a system of differential equations and a discretization of such a system [5]. The problems (related to this kind of model), that we have to deal with, are generally based on a restricted number of parameters. The primary objective is to reproduce the populations by exploiting little quantitative information available about the populations being studied [6]. These models disregard certain individual processes, and look to capture the macroscopic phenomena at the populations' level. In contrast to the individual centered models, the principle is to reproduce the interactions between the individuals and the environment, or between the individuals themselves according to specific rules of the population being studied. These models propose to reproduce the natural elementary processes accurately but at very high cost.

4. Rotenberg's Model

In 1983, Rotenberg have presented a model of cell dynamics population [7]. In this model, each cell is distinguished by its maturity degree $0 \leq m \leq 1$ and its maturation velocity. The positivity of the maturation velocity becomes from the fact that a cell cannot be renovated and the irreversible character of the studied model. The population density $f = f(\mathbf{m}, v, t)$ satisfies the following transport equation:

$$\frac{\partial f}{\partial t} + v \frac{\partial f}{\partial m} = -Sf + \int_a^b r(\mathbf{m}, v, v') f(t, \mathbf{m}, v') dv' \quad (1)$$

where S is the rate mortality and $r(\mathbf{m}, v', v)$ is the rate of cell transfer from the clan of cell velocity v to the clan of the cell velocity v' .

According to Rotenberg, the way in which the cells' division is carried out is interpreted biologically by the laws of reproduction, and mathematically by the boundary conditions. The law with perfect memory is one of the simplest reproduction laws, in the sense that a child cell inherits completely her parent's maturation speed. Mathematically, it is described by the following equation:

$$f(t, 0, v) = pf(t, 1, v)$$

where p is the average number of children cells resulting from the division of a mother cell.

Another choice of reproduction law, known as transition law, was proposed by Lebowitz and Rubinow [8].

$$vf(t, 0, v) = p \int_a^b k(v, v') v' f(t, 1, v') dv' \quad (2)$$

where k is the kernel of correlation transition between the velocity v' of mother cell and the velocity of the children cell v . In order to guaranty the continuity of the cell flux we impose the following condition on the kernel transition

$$\int_a^b k(v, v') dv = 1$$

Naturally, for all these equations, it is necessary to add an initial data:

$$f(0, \mathbf{m}, v) = \varphi(\mathbf{m}, v) \quad (3)$$

where φ is the initial cellular density.

5. Theoretical Study and Results

Rotenberg had numerically solved the model (1)-(2)-(3) using approximation by the Fokker-Planck's equation and Chapman's numerical method [9] for some degenerated transition kernel k . Van Der Mee had studied this model for a degenerated correlation. He represented this model using a diffusion equation. He obtained a condition necessary and sufficient for the existence of a stationary solution [11].

The difficulty comes due to the fact that there are no results or general techniques which handle this kind of model. For example, before [10] we did not know if this model has a solution for $p > 1$.

Recently, Boulanouar [2] have studied this model in the space $L^1([0, 1] \times [a, b])$ by developing new techniques. He showed that if $b < 8$, then the model is controlled by a semi group strongly continuous for all $p = 0$, and he have studied the various properties of this semi group

We separated the cases where $a > 0$ and $a = 0$. Indeed, if $a > 0$, after a transient state, all the initial cells then will have disappeared or have been divided, which explains the compactness for $t > 2/a$ of the semi group. For this reason the essential calculation and the description of the asymptotic behavior of this semi group were possible without many difficulties [10].

However, if $a = 0$, the maturation cellular speeds can, on the contrary, be small, and it may be that there would be still, at any moment, some initial cells which are not divided yet. Consequently, the population cellular is not likely to get out of the transient state, which explains the non compactness of the semi group solution of this model [2].

6. Construction of Discretization Schema

Now we will construct the numerical schema to solve and simulate the model (1)-(2)-(3). In order to do this, we start by discretizing the field $\Omega = [0, 1] \times [a, b]$ using a grid $G(\Omega) = \{(\mathbf{m}_i, v_j)\}$ by:

$$0 = \mathbf{m}_0 < \mathbf{m}_1 < \dots < \mathbf{m}_{i-1} < \mathbf{m}_i = \mathbf{m}_{i-1} + \Delta \mathbf{m}, \quad i = 1, \dots, I$$

$$a = v_0 < v_1 < \dots < v_{j-1} < v_j = b, \quad v_j - v_{j-1} = \Delta v, \quad j = 1 \dots J$$

to which we add a temporal subdivision of the interval $[0, T]$

$$0 = t_0 < t_1 < \dots < t_{N-1} < t_N = T, \quad \Delta t = t_n - t_{n-1}, \quad n = 1 \dots N$$

The value of the solution f at the point $(t_n, \mathbf{m}_i, v_j) = (n\Delta t, i\Delta \mathbf{m}, a + j\Delta v)$ is noted

$$f_{i,j}^n = f(t_n, \mathbf{m}_i, v_j).$$

The discretization of the equation (1) is done into two steps. The first step consists in approximating the integral of the equation (1) by a square formula, for example the formula of trapezoids.

$$g(t, \mathbf{m}, v) = \Delta v \sum_{k=1}^{k=J-1} r(\mathbf{m}, v, v_k) f(t, \mathbf{m}, v_k) + \frac{\Delta v}{2} [r(\mathbf{m}, v, a) f(t, \mathbf{m}, a) + r(\mathbf{m}, v, b) f(t, \mathbf{m}, b)]$$

The second step consists in discretizing the differential terms of equation (1). The formula at the point

$\left(t_{n+\frac{1}{2}}, \mathbf{m}_{i-\frac{1}{2}}, v_j \right)$ is given by:

$$\frac{\partial f}{\partial t} \left(t_{n+\frac{1}{2}}, \mathbf{m}_{i-\frac{1}{2}}, v_j \right) + v_j \frac{\partial f}{\partial \mathbf{m}} \left(t_{n+\frac{1}{2}}, \mathbf{m}_{i-\frac{1}{2}}, v_j \right) = -\mathbf{s}_{i-\frac{1}{2},j} f \left(t_{n+\frac{1}{2}}, \mathbf{m}_{i-\frac{1}{2}}, v_j \right) + g_{i-\frac{1}{2},j}^{n+\frac{1}{2}}$$

where $\mathbf{s}_{i-\frac{1}{2},j}$ and $g_{i-\frac{1}{2},j}^{n+\frac{1}{2}}$ designate respectively $\mathbf{s}(\mathbf{m}_{i-\frac{1}{2}}, v_j)$ and $g \left(t_{n+\frac{1}{2}}, \mathbf{m}_{i-\frac{1}{2}}, v_j \right)$.

By using the following approximation formulas:

$$\frac{\partial f}{\partial t} \left(t_{n+\frac{1}{2}}, \mathbf{m}_{i-\frac{1}{2}}, v_j \right) = \frac{2}{\Delta t} \left(f_{i-\frac{1}{2},j}^{n+\frac{1}{2}} - f_{i-\frac{1}{2},j}^n \right) \quad \text{and} \quad \frac{\partial f}{\partial \mathbf{m}} \left(t_{n+\frac{1}{2}}, \mathbf{m}_{i-\frac{1}{2}}, v_j \right) = \frac{2}{\Delta \mathbf{m}} \left(f_{i,j}^{n+\frac{1}{2}} - f_{i-\frac{1}{2},j}^{n+\frac{1}{2}} \right)$$

and the average values of the terms $f_{i-\frac{1}{2},j}^{n+\frac{1}{2}}$, $f_{i-\frac{1}{2},j}^n$, $f_{i-\frac{1}{2},j}^{n+\frac{1}{2}}$ and $f_{i,j}^{n+\frac{1}{2}}$ between the nodes of the grid

we get the following numerical schema:

$$\begin{aligned} \frac{(f_{i-1,j}^{n+1} - f_{i-1,j}^n)}{\Delta t} + v_j \frac{(f_{i,j}^{n+1} - f_{i-1,j}^n)}{\Delta \mathbf{m}} &= -\frac{1}{2} \mathbf{s}_{i-\frac{1}{2},j} (f_{i,j}^{n+1} + f_{i-1,j}^n) + g_{i-\frac{1}{2},j}^{n+\frac{1}{2}} \quad \text{if} \quad \frac{v_j \Delta t}{\Delta \mathbf{m}} > 1 \\ \frac{(f_{i,j}^{n+1} - f_{i,j}^n)}{\Delta t} + v_j \frac{(f_{i,j}^n - f_{i-1,j}^n)}{\Delta \mathbf{m}} &= -\frac{1}{2} \mathbf{s}_{i-\frac{1}{2},j} (f_{i-1,j}^{n+1} + f_{i,j}^n) + g_{i-\frac{1}{2},j}^{n+\frac{1}{2}} \quad \text{if} \quad \frac{v_j \Delta t}{\Delta \mathbf{m}} \leq 1 \\ n &= 0 \dots N-1, \quad i = 1 \dots I, \quad j = 0 \dots J \end{aligned}$$

where $g_{i-\frac{1}{2},j}^{n+\frac{1}{2}} = \frac{g_{i,j}^{n+1} + g_{i-1,j}^n}{2}$ and $g_{i,j}^n = \Delta v \sum_{k=1}^{k=J-1} r_{i,j,k} f_{i,j}^n + \frac{\Delta v}{2} (r_{i,j,0} f_{i,0}^n + r_{i,j,J} f_{i,J}^n)$.

The transition law can be discretized using the trapezoids formula

$$\begin{aligned} f_{0,j}^{n+1} &= \frac{p \Delta v}{v_j} \sum_{k=1}^{k=J-1} k_{j,k} v_k f_{I,k}^{n+1} + \frac{p \Delta v}{v_j} [k_{j,0} v_0 f_{I,0}^{n+1} + k_{j,J} v_J f_{I,J}^{n+1}] \\ n &= 0 \dots N-1, \quad j = 0 \dots J \end{aligned}$$

where $k_{j,k}$ indicates the value of the correlation nucleus k at the point (v_i, v_j) .

For the law of the perfect memory, we discretize it as follow:

$$f_{o,j}^{n+1} = p f_{I,j}^{n+1} \quad n = 0 \dots N-1, \quad j = 0 \dots J.$$

Finally the initial density is discretized by

$$f_{i,j}^0 = \mathbf{j}(\mathbf{m}_i, v_j) = \mathbf{j}_{i,j} \quad i = 0 \dots I, \quad j = 0 \dots J.$$

7. Simulation Tool

An interactive tool for 2D simulation using Voronoi graph has been developed. In this simulation environment, at any time each cell is characterized by two values: its maturation degree μ and the maturation speed v . During the process, μ and v vary, where μ increases and v fluctuates. To keep our study close to reality, we consider the case, where v is either constant, or constant by pieces alternating between 0 and a strictly positive value. When maturation is reached ($\mu=1$), each cell is divided into a number p of children cells whose initial maturation is supposed to be null. The transformation from parent to child is modeled by an operator which takes care of the cellular

proliferation model originality. Mortality rate before the end of the cycle is taken into account as a ratio depending on μ and v .

To be able to represent our results graphically, we consider a constant area as a framework. In this case, the density can be indicated by the number K_i of cells within the framework. At every moment t_i , the cells will be placed within the framework.

The simulation tool thus makes it possible to obtain a cellular population having a space-time dynamics. It computes the growth of a cellular tissue initialized from a matrix containing the co-ordinates of the gravity centers of the cells nucleus and Boolean information related to its state. The positions of the cells are fixed randomly. Because the data is displayed at each clock signal, the tool enables us to follow the evolution of the population density as the time passes by (see figure 1). The vector K also enables us to easily draw the curve representing the evolution of the density (or the number) cellular via time.

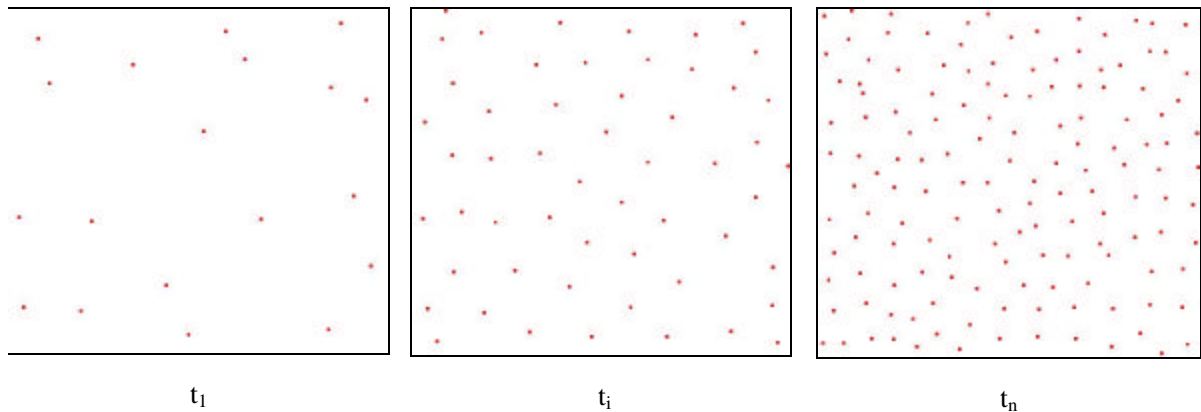


Figure 1 : Evolution of Cells Number via the Time

8. Representation Using a Voronoï Diagram

To graphically represent the evolution of the cells during a given period of time we have chosen the Voronoï diagram and its dual representation, the Delaunay diagram. For a finite set S of n distinct points p_0, \dots, p_{n-1} in any given space, the Voronoï diagram is defined as a partition of this space into n polyhydic areas V_i where $0 \leq i < n$. Each area V_i called Voronoï cell of i is defined as the set of the points which are nearest to p_i than all other points in S . More precisely:

$$V_i = \{x / \text{dist}(x, p_i) = \min_j \text{dist}(x, p_j), \quad 0 \leq j < n\}$$

Where dist is the function representing the Euclidean distance. The Voronoï diagram represents with sufficient precision a cellular tissue without empty spaces [12]. This representation has proven to be the most informative from the point of view of the representation of cells themselves, whose nucleus gravity centers are selected as being the germs of the diagram. The cells can thus be considered as independent objects having specific properties and belonging to a larger area. The triangulation of Delaunay is defined as being the dual representation of Voronoï diagram. The associated graph allows a very advanced study of the cellular tissue topology (see Figure 2).

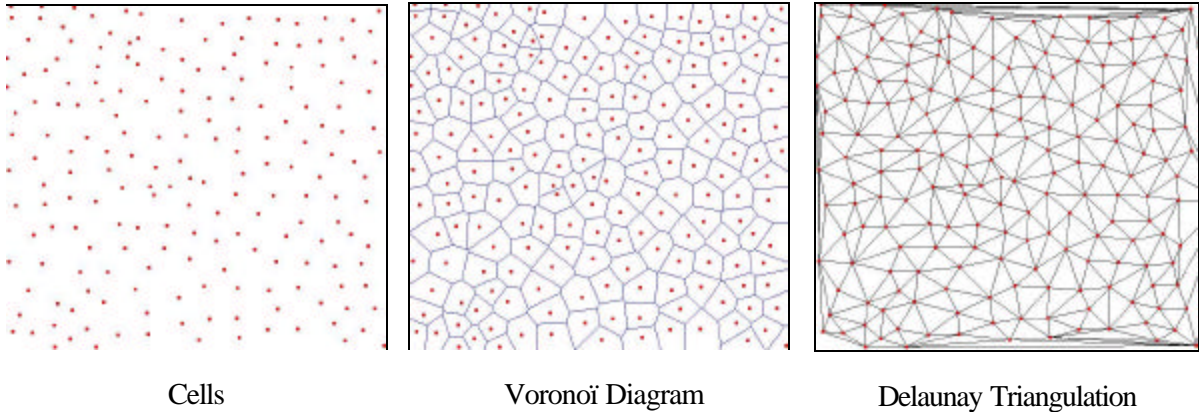


Figure 2 : Different Graphical Representation of the Cells

Each area of Voronoi partition can be considered as a form, so it is possible to calculate three parameters characteristic of the population topography: the factor of average form of these forms (factor of average circularity), the homogeneity measurement of this form factor (homogeneity factor of circularity), and heterogeneity measure of their surface (also called surface disorder) [13].

These tools have already been used to study quantitatively the cellular sociology, i.e. to analyze the relationships that exist between the cells biological function and their space relationships within the cellular tissue. Moreover, this representation has already been used within the dynamic modeling framework of tissue growth [14].

Voronoi diagram structure is strictly determined on a local level, the addition or the removal of a point within the diagram can be carried out without modifying the whole diagram. This property makes Voronoi diagram an extremely powerful tool for the modeling of the dynamics of the cellular populations' special organization, specifically during the appearance or the disappearance of cells.

9. Conclusion

We have presented in this article, a mathematical study and the design and development of an artificial system to simulate the dynamics of the cellular populations. This system will constitute a biological experimentation tool where the theories will be tested not on a real biological populations which is not very easily available and very difficult to manipulate, but on a simulation data which represent very carefully selected features thus allowing infinite refinements and a fast and perfect reproducibility. The currently implemented tool can be improved in many directions, in particular: color coding introduction to distinguish the type of cells, their state, their cycle speed, or their origin; selective memorization of the cellular movement path with respect to the time and the space and its visualization at every instant of simulation; integration of possible relationships between a cell and its environment during each simulation step or a dynamic management of overhead communication (between the program and its environment) effects instead of the simple topological constraints currently imposed (circle, square). The other intended objective is to generalize these mechanisms to engineering problems in the area of the artificial life.

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