Chapter 76
Computational Energetic Model of Morphogenesis Based on Multi-agent Cellular Potts Model

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Abstract The Cellular Potts Model (CPM) is a cellular automaton (CA), developed by Glazier and Graner in 1992, to model the morphogenesis. In this model, the entities are the cells. It has already been improved in many ways; however, a key point in biological systems, not defined in CPM, is energetic exchange between entities. We integrate this energetic concept inside the CPM. We simulate a cell differentiation inside a growing cell tissue. The results are the emergence of dynamic patterns coming from the consumption and production of energy. A model described by CA is less scalable than one described by a multi-agent system (MAS). We have developed a MAS based on the CPM, where a cell agent is implemented from the cell of CPM together with several behaviours, in particular the consumption and production of energy from the consumption of molecules.

Keywords Morphogenesis · Cellular potts model · Multi-agents systems

76.1 Introduction

The Cellular Potts Model (CPM) is a cellular automaton (CA) developed by Glazier and Graner [6] to model different phenomena which occur during the morphogenesis [3, 9]. The dynamics of CPM is based on a minimisation of energy. The entities of this system are called cells and are characterised by a volume, a surface and a type. They are in interaction via contact energies and via the restricted access to grid sites.
The CPM can be improved to model the morphogenesis in a more realistic way [1]. Usually, the CPM is defined by a CA. In this paper, we describe the CPM as a multi-agent system (MAS), where the entities are reified. This allows to enhance the scalability of CPM. The dynamics in MAS is not given by a global function but via the interactions of the entity behaviours executed according to a scheduler.

The multi-agent approach eases the implementation of the following specific cell behaviours: secretion and consumption of molecules, transformation of molecules into energy, migration over a gradient of molecules, cell division, cell differentiation and cell death. The closest work to our approach is probably Com-pucell3D [3], a software which implements the CPM and other behaviours to model the morphogenesis. However, the notion of energy from the consumption of molecules used for the cell maintenance and division is not present in the CPM.

This paper is organised as follows. A multi-agent view of CPM is given in Sect. 2. In Sect. 3, we describe the MorphoPotts agent which represents a cell defined in the CPM to which we add the previously mentioned behaviours. Using this, we simulate a model of embryogenesis based on a Darwin theory at cellular level [7], and we observe the emergence of relevant dynamic patterns in Sect. 4. Finally, we conclude in Sect. 5.

### 76.2 Cellular Potts Model

In this section, we firstly present the CPM described by Graner and Glazier [6]. Secondly, we propose an optimised implementation of CPM based on a multi-agent approach.

To describe the CPM, we present in this order the notations, the state of system and the transition function:

- A grid is denoted by $S_x$, a site of this grid by $(i,j)$ and the value of a site by $s_{x_{i,j}}$. A cell is denoted by $C_{σp}$ with $σ \in [1,N]$, where $N$ is the number of cells and $p$ the type of cell. $C_{σp}$ has a target volume (resp. surface) $Vσ$ (resp. $Sσ$) and a current volume $V_s$ (resp. $S_s$). The contact energies are recorded in a matrix $T$ such that $T_{σ,σ'}$ (or $T_{p,p'}$) is the contact energy between $C_{σp}$ and $C_{σ'p'}$.
- A state of system is a grid $S_x$ of $D$ dimensions (here $D = 2$), where each site $(i,j)$ is filled by a particle of the cell $C_{σp}$, i.e $s_{x_{i,j}}$ is equal to $σ$.
- The transition function between the state $S_a$ and $S_b$ is verified if $S_b$ is the state $S_a$, where the value of one site has been replaced by the value of a neighbouring site and if the probability of transition between the state $S_a$ and $S_b$ is accepted. The probability of transition (a Monte Carlo probability) and the energy function (depends on the volume and the surface of each cell, and the contact energies between the cells) used here, are described in [6].

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1The continuous case is also defined [5]

2Here the neighbours of a site $(i,j)$ are the sites $(i + 1,j), (i,j + 1), (i - 1,j), (i,j - 1)$
A multi-agent view of CPM is given by using the vowel approach [4], i.e. MAS = Agent + Environment + Interaction + Organisation (here, no specific organisation is imposed). We describe these concepts in this order:

- Here, an agent is a cell $C_{\sigma p}$ which can modify its local environment by changing the value of its neighbouring sites by $\sigma$. This is implemented by the method replace site (see Table 76.1). Each cell knows:
  - Its membrane $M_{\sigma}$, where $M_{\sigma} = \{(i, j) \mid sx_{i, j} = \sigma \land L = \{(i', j') \in \text{neighbour}(i, j) \mid sx_{i', j'} \neq \sigma \} \neq \emptyset\}$, i.e. the set of pair $(i, j)$ is on the membrane of the cell and $L$ the set of sites outside the cell.
  - Its target and current volume, its target and current surface, and so its energy volume ($E_{V_{\sigma}}$) and surface ($E_{S_{\sigma}}$) like the difference power two between the target and current value.
  - Its contact energy ($E_{C_{\sigma}}$) between the different cells.
  - The environment is a grid, it is the background where the interactions (direct or not) between cells occur. The environment is always initialised by one cell $C_0p$ which models the medium.
  - The interactions between cells are of two types. Firstly, some indirect interactions due to the concurrence for the available places on the environment. Secondly, the cells are in direct interactions via the contact energy between them.

The simulation step is the following:

1. We compute the energy ($E_a$) of the current state ($S_a$).
2. We choose a random site $(i, j)$ and a random neighbouring site $(i', j')$ of $(i, j)$ (the sites chosen are on the membranes of two different cells).
3. $s_{i', j'}$ is saved into $\sigma$ and the method replace site is called from the cell $C_{\sigma a i, j p'}$ with the site $(i', j')$.
4. We compute the energy ($E_b$) of the current state ($S_b$).
5. If $E_a \leq E_b$ and if the probability of transition (see transition function defined previously) is not accepted, then the method replace site is called from the cell $C_{\sigma p}$ with the site $(i', j')$.

### 76.3 MorphoPotts

A MorphoPotts agent keeps the properties of the cell defined in the CPM, but it also has an internal energy $E$ which results of the consumption of molecules. This agent is very close to MorphoBlock [2] but the core of MorphoBlock is a pixel. In this section, we describe the MorphoPotts and the simulation step of couple CPM MorphoPotts. The abilities of a MorphoPotts $C_{\sigma p}$ are given by the following methods:

- $\text{secr}(\text{arg}, Y)$ secretes a gradient of molecules $Y$ of radius $\text{arg}$ at gravity center of $C_{\sigma p}$.
- $\text{cons}([\text{max}, \text{arg}], Y)$ consumes molecules $Y$ if the energy of $C_{\sigma p}$ is lower than $\text{max. cons}([\text{max}, \text{arg}], Y)$ has an inverse effect compared to $\text{secr}(\text{arg}, Y)$. 

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Table 76.1 Definition of the method replace_site

Require: (i, j) the site to replace by the cell C

Ensure: void

/*Deleting of the value of site (i, j) and updating of the energies about the site (i, j)*/

1  \( \sigma' = sx_{i, j} \); \( sx_{i, j} = \text{null} \);
2  \( S\sigma' = S\sigma' - #L \text{ where } <(i, j), L> \in M\sigma' \);
3  \( Ec_{\sigma'} = Ec_{\sigma'} - \sum_{(i', j')} L T_{\sigma', sx_{i'}, j'} \);

/* Updating of the value of site (i, j), and updating of the energies about the site (i, j) and the cell C*/

4  neighbour = \( \{(i', j') \in \text{neighbour}(i, j) \; sx_{i', j'} \neq \sigma \} \);
5  \( sx_{i, j} = \sigma \);
6  \( Ec_{\sigma} = Ec_{\sigma} + \sum_{(i', j')} L T_{\sigma, sx_{i'}, j'} \);
7  if (# neighbour > 0) then \( M\sigma = M\sigma + <(i, j), \text{neighbour}> \); end if

/*Updating of the energies and the membrane of all neighbouring cells about the site (i, j)*/

8  for \( (i', j') \in \text{neighbour}(i, j) \) do
9     neighbour' = \{ \( (i'', j'') \in \text{neighbour}(i', j') \; sx_{i'', j''} \neq sx_{i', j'} \} \);
10    if \( <(i'', j''), L> \in M\sigma' \) then \( \sigma' = sx_{i'', j''} \); \( S\sigma = S\sigma' - #L \);
11       \( Ec_{\sigma'} = Ec_{\sigma'} - \sum_{(i'', j'')} L T_{\sigma', sx_{i'', j''}} \);
12       if (# neighbour' > 0) then \( M\sigma' = M\sigma' + <(i', j'), \text{neighbour'}> \); end if
13       \( Ec_{\sigma'} = Ec_{\sigma'} + \sum_{(i'', j'')} L T_{\sigma', sx_{i'', j''}} \);
14      end if
15  end for
migr(arg,Y) gives the ability to MorphoPotts to migrate towards the molecules Y according to arg. For this, a new energy ($E_{migr}$) is added to CPM.

$E_{migr} = -\arg*\sum_{(i,j) \in M} nbMol((i,j), Y)$, where nbMol((i,j), Y) is the number of molecules Y on the site (i,j).

trans(arg,Y) transforms the consumed molecules in energy. In this paper, for each consumed molecule the energy is incremented of 1.

diff(arg,Y) associates a probability of differentiation arg to a cell type Y.

div({b,En,cost},t) gives the ability to the cell to divide. If b is true Csp divide along an axis (vertical or horizontal), $Csp'p'$ is created according to the probabilities of differentiation. The energy of the cell $Csp'p'$ is equal to $e'$ such that $(i',e') \in En$ and the energy of the cell $Csp$ is equal to $E - e' - cost$.

main(arg,t) decrements of arg the energy (maintenance).

die() implies that the MorphoPotts lost all its abilities and does not generate energy in the CPM.

The simulation step of couple CPM MorphoPotts is as follows:

1. Let $i$ be equal to 0 and let $n$ be equal to membrane size of all MorphoPotts.
2. While $i$ is lower than $n$
   (a) A step of CPM is run. For the two MorphoPotts chosen in the step of CPM, their method of division is called. $i$ is incremented by 1.
3. All cells execute their method of maintenance, their method of secretion and their method of consumption.
4. For each cell, if the energy is lower than 0, the cell executes its method of death.

### 76.4 Simulation: Darwin Theory at Cellular Level

In this section, we present two simulations which use the Darwin theory at cellular level [7]. A model of this theory can be found in [8], where a cell (represented by 1 pixel) secrets and consumes molecules in an environment of dimension 50 $\times$ 50.
The cells can differentiate (in two types) with a probability which depends on the neighboring cells. The cells can divide if the quantity of consumed molecules is sufficient. The first type secretes a molecule, which the second type consumes and vice versa for the second type. This inter-proliferation according to different parameters leads to: finite growth, growing cancer. In our simulations, the stochastic cell differentiation is modelled by initialising the environment by one MorphoPotts of type 1, which divides and can differentiate in four different cell types. The natural selection is modelled by the notion of energy. If a MorphoPotts finds molecules, it can increase and it can divide (via the energy), otherwise it will die.

Two simulations\(^3\) are presented in an environment 1,000 \(\times\) 1,000, with an cycle inter-dependence and with the same CPM parameters (the cells tend to square 7 \(\times\) 7, and the energy of contact between two cells of different types is 0, otherwise 10). They are different by two parameters (see Fig. 76.1). The MorphoPotts can also be divided (not defined in Fig. 76.1), if their current volume is higher than 80\% of the target volume and if their energy is higher than 2,000. The energy of Morpho-Potts that divides is equally distributed with the MorphoPotts created. In these simulations, the MorphoPotts of type 1 (resp. 2, 3, 4, 5) is red (resp. green, cyan, yellow, blue).

The results of the simulation 1 and 2 are given in the Fig. 76.2. We can see three steps in this morphogenesis. The two first steps are the same in the two simulations. The first step (see Fig. 76.2a,b) is the cell differentiation and the natural selection. The MorphoPotts of type 1 divides and randomly differentiates in four types. This leads to the formation of tissues. The second step is the sorting (see Fig. 76.2b,c), the tissues are sorted by the simple fact of the death (the cells do not find molecules) and the division (the cells find molecules).

The third step in the simulation 1 is the proliferation and the emergence of pattern (see Fig. 76.2c). Here, a spiral proliferation emerges (not imposed in the description). We can see that the tissue renewal is continuous, i.e. the tissue is not static (see the comment written on the Fig. 76.2c). In this simulation, the proliferation seems infinite.

The third step in the simulation 2 is a finite growing (an important criterion in the embryogenesis) and the emergence of pattern (see Fig. 76.2d f). This can be explained by the fact that the consumption of molecules has been reduced and the cost of maintenance has been increased compared to the simulation 1 (see Fig. 76.1). The number of cells by tissue varies between two thresholds (see Fig. 76.2e,f). So an equilibrium between the cell death and the cell division emerges. This shows that a stochastic cell differentiation and a natural selection can be sufficient to generate a finite growing of a dynamic cell tissue, and so to model the embryogenesis.

\(^3\)The pc used is an intel core2 quad 2.83 GHz with 3 GB of memory. The videos of these simulations are available at http://pagesperso.univ brest.fr/~tripodi/private/springer/videos.html
In this paper, we have described how adding the energetic exchanges between cells in CPM (via the MorphoPotts agent defined in this paper) improve the realism of simulations. By adding this key point happening inside multi-cellular organisms, we have shown that morphogenesis is strongly influenced by energetic exchange especially for the tissue renewal, the organism stability and the robustness of developmental patterns.

The MorphoPotts has been tested thanks to simulations of a growing cell tissue using a cellular Darwinian theory. The results show the emergence of patterns, some with a finite but dynamic growing tissue. For the same model, we observe very similar emerging patterns in different simulations. This indicates that even for a stochastic cell differentiation and a natural selection, the organism global structure remains the same.

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**References**