MATHEMATICAL MODELING AND COMPUTING, Vol. 10, No. 3, pp. 617–624 (2023)

Multi-scale hybrid and agent-based modeling of cell differentiation

Benmir M.[1], Bellaj K.[1], Boujena S.[1], Volpert V.[2]

[1] *Fundamental and Applied Mathematics Laboratory, Ain Chock Faculty of Sciences, Hassan II University, Casablanca, Morocco*
[2] *Camille Jordan Institute, UMR 5208 CNRS, University Lyon 1, 69622 Villeurbanne, France*

(Received 16 February 2023; Revised 12 July 2023; Accepted 13 July 2023)

In this work we propose a hybrid model of cell population dynamics, where cells are considered as discrete elements whose dynamics depending on the intracellular and extracellular regulation. The model takes into account different cell types which include undifferentiated cells and two types of differentiated cells. We use a simulation algorithm based on the dynamical systems approach on the one hand, and the multi-agent approach on the other hand. Both approaches have been implemented using NetLogo and Python. We discuss cell choice between two types of differentiated cells and analyze the coexistence of cell lineages.

Keywords: *cell differentiation; multi-scale hybrid model; multi-agents simulation.*
2010 MSC: 93A30, 97M60, 37N25, 91B69, 34A33 **DOI:** 10.23939/mmc2023.03.617

1. Introduction

Multi-scale models in biology actively develop in order to describe physiological processes. There are various approaches to multi-scale modeling and numerous applications (see [1–5] and the references therein). Cell populations in multi-scale models can be described by discrete or continuous methods. Cellular automata (CA), lattice Boltzmann method and various particle methods are among them [6–9]. These approaches allow detailed description of cell behavior, cell-cell interaction and other aspects of complex biological media. On the other hand, they are applicable for a relatively small number of cells and they do not admit analytical study. Continuous models are represented by ordinary differential equations (ODEs) and partial differential equations (PDEs) for cell concentrations. In particular, this can be reaction-diffusion equations taking into account random cells motion and their birth and death. Navier–Stokes equations and Darcy equations describe convective motion of the medium.

Multi-scale models include intracellular and extracellular regulations of biological cells. Intracellular regulation is particularly important because it determines the cell fate, that is the choice between its self-renewal, differentiation and apoptosis. It can be described by ODE for intracellular concentrations, Boolean approach or by probabilistic methods if a small number of molecules participate in this regulation and their concentrations cannot be considered. Extracellular regulation can be effectuated by various local mechanisms in the given tissue (growth factors, cytokines) or by means of global control from other organs and tissues through endocrine signaling. Extracellular substances diffuse in the tissue and influence intracellular regulation of cells. Distribution of these substances can be described by reaction-diffusion equations.

Hybrid discrete-continuous modeling techniques can be used to simulate the behavior of cell populations and the regulation of intracellular and extracellular factors. These models involve representing cells as individual objects, using lattice or off-lattice methods to describe their movement and interactions. Intracellular regulatory networks are modeled using ordinary differential equations, while extracellular substances are described using partial differential equations. These models can be used to study complex biological processes such as hematopoiesis [10–12].

Multi-scale biological models can be categorized into continuous models, discrete models, and hybrid models, which combine the strengths of discrete and continuous approaches. Continuous models are based on ODEs or PDEs to describe the cell fate choice. However, in some situations, individual and agent based modeling (ABM) approaches, treating the cells as discrete objects with predefined interaction rules, may offer an improvement over differential equation methods.

The ABM approach provides a natural description, where ABM agents interact and influence each other, make individual decisions, learn from their experiences and adapt their behaviors. They are therefore better adapted to their environment. A number of ABM simulation packages have been developed and applied to cell biological research, among them [13–16].

In this work we model cell differentiation using a hybrid agent-based approach for a multi-scale model. In Section 2, we present a hybrid agent-based approach of cell differentiation using ABM and PDEs. The cell behavior is described using a multi-agent model in NetLogo, while the extracellular concentrations are described by reaction-diffusion equations. Section 3 provides results of the simulations that illustrate the impact of intracellular and extracellular regulations on cell differentiation. Finally, in Section 4, we discuss our results and future research directions.

2. Multi-scale model by intracellular and extracellular regulations

In this section we consider the problem of lineage choice based on the one in [1], where undifferentiated cells differentiate into one of two types of differentiated cells. There are three cell types, undifferentiated cells A, differentiated cells B_1 and B_2. Cells A contain two intracellular proteins, p_1 and p_2, which determine their differentiation into cells B_1 or B_2. Their concentrations are described by ordinary differential equations:

$$\frac{dp_1}{dt} = F_1(p_1, p_2) + b_{11}u_1 + b_{12}u_2, \tag{1}$$

$$\frac{dp_2}{dt} = F_2(p_1, p_2) + b_{21}u_1 + b_{22}u_2. \tag{2}$$

The functions F_1 and F_2 will be specified below. Extracellular concentration u_1 is produced by differentiated cells B_1, and u_2 is produced by cells B_2. Concentrations u_1 and u_2 influence production of intracellular proteins p_1 and p_2, and they are described by the equations

$$\frac{\partial u_1}{\partial t} = d_1\Delta u_1 + W_1, \tag{3}$$

$$\frac{\partial u_2}{\partial t} = d_2\Delta u_2 + W_2. \tag{4}$$

Cells of type A, cells B_1 and/or B_2 are located at space x in the environment $\Omega(t)$. If $p_1 \geqslant p_1^*$, then cell A changes its type to B_1, if $p_2 \geqslant p_2^*$, then cell A changes its type to B_2. Each cell is represented as a circle on the plane and the governing rules for cell behavior are described in Section 3.

We introduce concentration c_A of cells A, concentration c_1 of cells B_1 and concentration c_2 of cells B_2. At each space point x these three concentrations can have only two values, 0 or 1 depending on whether this point belongs to one of the cell types. We set

$$W_1 = k_1c_1, \quad W_2 = k_2c_2.$$

This means that cells B_1 produce u_1, cells B_2 produce u_2. The rates of production are zero if the concentrations of the corresponding cells are zero.

2.1. Bistable kinetics

In order to study lineage choice, we introduce intracellular regulation with bistable kinetics.

We set

$$F_1(p_1, p_2) = k_1p_1(1 - a_{11}p_1 - a_{12}p_2), \quad F_2(p_1, p_2) = k_2p_2(1 - a_{21}p_1 - a_{22}p_2).$$

If the extracellular variables vanish, $u_1 = u_2 = 0$, then system (1), (2) is a closed system of two ordinary differential equations for intracellular variables p_1, p_2. It has four stationary points, $P_0 = (0, 0)$, $P_1 = (1/a_{11}, 0)$, $P_2 = (0, 1/a_{22})$ and $P_3 = (p_1^0, p_2^0)$, where p_1^0 and p_2^0 is a solution of the system

$$a_{11}p_1 + a_{12}p_2 = 1, \quad a_{21}p_1 + a_{22}p_2 = 1.$$

We will suppose that it has a positive solution. The point P_0 is always unstable, the points P_1 and P_2 are stable and P_3 is unstable if $a_{21} > a_{11}$ and $a_{21} > a_{22}$. The point P_3 is stable if these inequalities are opposite. In this case P_1 and P_2 are unstable. Let us consider the case where the points P_1 and P_2 are stable. If the initial condition of this system belongs to the basin of attraction of one of them, then the trajectory approaches this stationary point. If it is P_1, then the value p_1 will reach the critical value p_1^* and the cell will differentiate into cell B_1. If the trajectory approaches the stationary point P_2, then the value p_2 will reach the critical value p_2^*, and the cell will differentiate into cell B_2. These cells will produce extracellular substances u_1 or u_2 which will diffuse in the extracellular matrix and influence intracellular regulation of other cells.

2.2. Coexistence of cell lineages

In this section we consider the intracellular kinetic functions in the form

$$\begin{aligned} F_1(p_1,p_2) &= k_1 p_1^2(1 - a_{11}p_1 - a_{12}p_2) - s_1 p_1, \\ F_2(p_1,p_2) &= k_2 p_2^2(1 - a_{21}p_1 - a_{22}p_2) - s_2 p_2. \end{aligned} \tag{5}$$

The stationary points of the corresponding system

$$\frac{dp_1}{dt} = F_1(p_1,p_2), \quad \frac{dp_2}{dt} = F_2(p_1,p_2) \tag{6}$$

are as follows: $P_0 = (0,0)$, $P_{10} = \left(p_1^{(1)},0\right)$, $P_{20} = \left(p_1^{(2)},0\right)$, where $p_1^{(1)}$ and $p_1^{(2)}$ are solutions of the equation

$$p_1(1 - a_{11}p_1) = \frac{s_1}{k_1},$$

$P_{01} = \left(0,p_2^{(1)}\right)$, $P_{02} = \left(0,p_2^{(2)}\right)$, where $p_2^{(1)}$ and $p_2^{(2)}$ are solutions of the equation

$$p_2(1 - a_{22}p_2) = \frac{s_2}{k_2},$$

and also up to four stationary points with positive coordinates which can be found as solutions of the system of equations

$$p_2 = \frac{1 - a_{11}p_1}{a_{12}} - \frac{s_1}{a_{12}k_1}\frac{1}{p_1}, \quad p_1 = \frac{1 - a_{22}p_2}{a_{21}} - \frac{s_2}{a_{21}k_2}\frac{1}{p_2}.$$

It can have from zero to four positive solutions depending on the values of parameters.

It can be easily verified that the point P_0 is stable. Indeed, the corresponding matrix has negative eigenvalues. Let us assume that $0 < p_1^{(1)} < p_1^{(2)}$ and $0 < p_2^{(1)} < p_2^{(2)}$. Then the points P_{20} and P_{02} are also stable. In case of four stationary points with positive coordinates, one of them is stable.

There are two different patterns of solutions depending on parameters b_{ij}. Let us consider two specific examples. If $b_{11}, b_{22} > 0$ and $b_{12} = b_{21} = 0$, then the substances u_i, $i = 1,2$ produced by cells B_i stimulate production of intracellular substances p_i. In their turn, they lead to differentiation of cells A into cells B_i. Therefore we observe here a positive feedback between intracellular regulation, extracellular regulation and cell differentiation. One of the cell lineages B_1 or B_2 dominates another one. It expands on the whole space environment. All cells differentiate into only one cell lineage.

In the second example, $b_{11} = b_{22} = 0$ and $b_{12}, b_{21} > 0$. This means that the substance u_1 produced by cells B_1 stimulate production of the intracellular substance p_2, while u_2 stimulates production of p_1. Hence there is a negative feedback, and cells B_1 upregulate production of B_2, while cells B_2 promote productions of cells B_1. Behavior of the system is qualitatively different in this case compared with the previous one. Both types of differentiated cells can coexist here.

3. Hybrid agent-based approach

In this section, a hybrid model for cell differentiation is presented. The governing rules for cell behavior are modeled using NetLogo: a programming language and modeling environment for agent-based systems. The substances diffusion in the cell environment is done through a diffusion equation and solved using Thomas algorithm with Python. The interaction between Python and NetLogo is ensured

by an extension implemented in NetLogo which allows the exchange of data between two programs. The biological rules governing the cell behavior in Netlogo according to their environmental conditions are presented below.

The differentiation environment Ω in NetLogo is modeled as a square grid divided into patches where the agents move randomly: $\Omega = \cup_k Patch_k$. The evolution of the cell differentiation is followed in a time interval $[0, T]$. Each agent represents a cell. Two different cellular states are defined: the undifferentiated state A and the differentiated states B_1 and B_2. The substances u_1 and u_2 are diffused through Ω, each $Patch_k$ has its own level of substances concentrations. The cells move randomly without collision between them within the patches and meet the biological criteria listed in the paragraph below.

3.1. Cellular automata rules

At each time iteration, two concentrations of proteins p_1 and p_2 for each undifferentiated cell are calculated and the following rules are applied to each cell:

— B_1 and B_2 cells produce the substances u_1 and u_2 respectively in a circle with radius 1 around the cell center.
— Each A cell consume the substances u_1 and u_2 stimulating the production of the intracellular proteins p_1 and p_2.
— A cell can differentiate into $B1$ or B_2 cell:
if $p_1 \geqslant p_1^*$, then A differentiate into B_1,
if $p_2 \geqslant p_2^*$, then A differentiate into B_2.

3.2. Hybrid model implementation

The hybrid model uses the equations for extracellular substances, intracellular regulation and for the agent-based model defined through the cellular automata rules. The algorithm acts as follows:

— The first step is the initialization of the model on NetLogo:
1. N undifferentiated cells and N_1 and/or N_2 differentiated cells are created in the environment.
2. Each $Patch_k$ is supplied with its initial substances concentration u_1^0 and u_2^0.

— At each time iteration t:
1. The substances concentrations u_1^t and u_2^t are collected from the patches and sent to Python as the initial conditions.
2. $\begin{cases} \partial_t u_1 - d_1 \Delta u_1 = 0, \\ \partial_t u_2 - d_2 \Delta u_2 = 0 \end{cases}$ are solved in Python.
3. The new values of the concentrations u_1^{t+1} and u_2^{t+1}, are sent back to NetLogo and redistributed to the patches.
4. The cells interact with their environment according to the cellular automata rules.
5. The substances levels in each patch are reduced by the amounts of substances consumed by the undifferentiated cells.

4. Simulations

Let us study how the dynamics of undifferentiated cells change when the substances are introduced. We assume that the substances u_1 and u_2 diffuse through the tissue and they are consumed by undifferentiated cells. According to the initial cell distribution, we consider two cases: case 1 where only one type of undifferentiated cell B_1 is considered, and case 2 with two types of undifferentiated cells B_1 and B_2. In the case 2, we treat the lineage choice, in the case of positive feedback, only one lineage of differentiated cells will finally appear and in the case of negative feedback, both of them can coexist.

The initial setup used for case 1 is shown in Figure 1 and the numerical values of the parameters used are given in Table 1, and for case 2, the numerical values of the parameters used are given in Table 2.

Table 1. Summary of the parameters used in the cell differentiation process.

a_{11}	a_{22}	a_{12}	a_{21}	k_1	W_1	p_1^*
0.5	0.5	0.1	0.1	0.1	0.1	1.5
b_{11}	b_{22}	b_{12}	b_{21}	k_2	W_2	p_2^*
0.1	0.1	0	0	0.1	0.1	1.5

Table 2. Summary of the parameters used in the cell differentiation process.

a_{11}	a_{22}	a_{12}	a_{21}	k_1	W_1	p_1^*
1	1	0.5	0.5	0.1	0.1	1.5
b_{11}	b_{22}	b_{12}	b_{21}	k_2	W_2	p_2^*
0.1	0.1	0.1	0.05	0.1	0.1	1.5

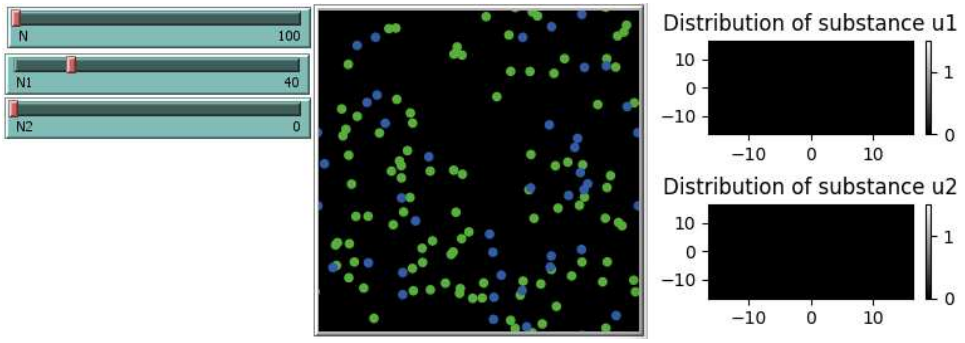

Fig. 1. Left: initialization using NetLogo: N undifferentiated cells and N_1 and/or N_2 differentiated cells are created in the environment, with $N = 100$, $N_1 = 40$ and $N_2 = 0$. Middle: the distribution of cell types, different colors to each cell depending on its type are assigned, the A cells are green, the B_1 cells blue and the B_2 cells red. Right: the distribution of the substance concentrations, the patches have a gray scale proportional to the substance concentration. A patch with the maximal concentration is white, while a patch with zero concentration is black.

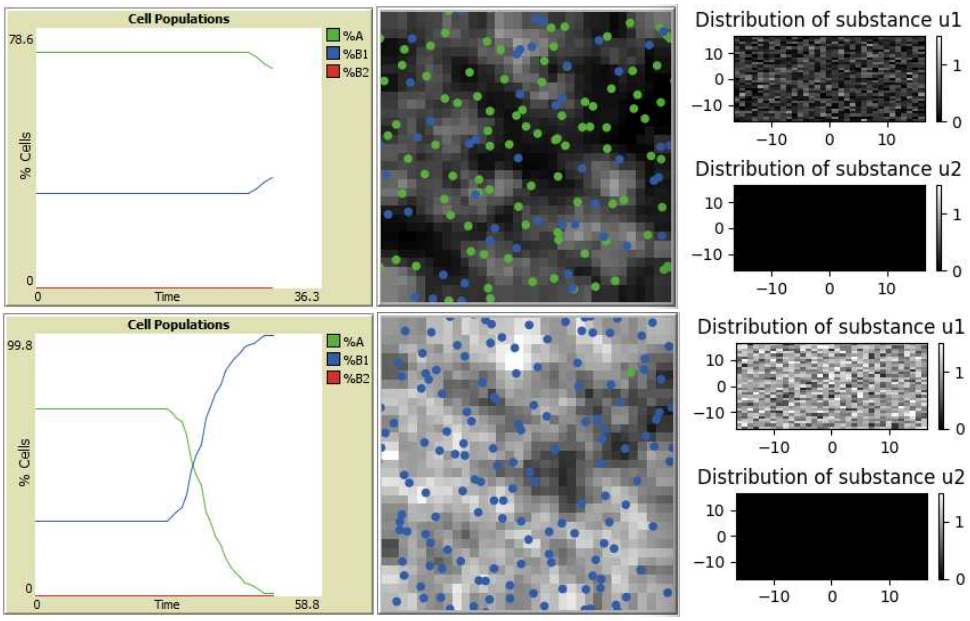

Fig. 2. Evolution of cell differentiation at iterations $t = 30$ (top) and $t = 50$ (low). Left: A number of cell population for different cell types. Middle: undifferentiated cells A differentiate into cells B_1. They produce extracellular substance u_1. It stimulates production of the intracellular substance p_1. When it reaches the critical value p_1^*, the cell differentiate. Differentiated cells gradually fill the plane. The stationary points P_1 and P_2 are stable, concentration p2 in the intracellular regulation remains zero. Right: the background color of the patches begins to lighten as the substance u_1 levels increases. Cells A therefore differentiate into B_1 in the patches where the substance u_1 level is extremely high, that stimulates production of the intracellular substance p_1, when it exceeds its critical value p_1^*.

Due to the choice of initial condition, the intracellular variable p_1 grows and approaches its value at the stationary point P_1. When it reaches the critical value p_1^*, the cell differentiates into cell B_1. Cells B_1 produce the extracellular substance u_1 which diffuses along the radius of 1 around it, and stimulates

further production of the intracellular variable p_1. Since the initial concentration p_2 equals zero, it remains zero, and the model is reduced to a single intracellular equation and a single extracellular equation. The simulations results are presented in Figure 3.

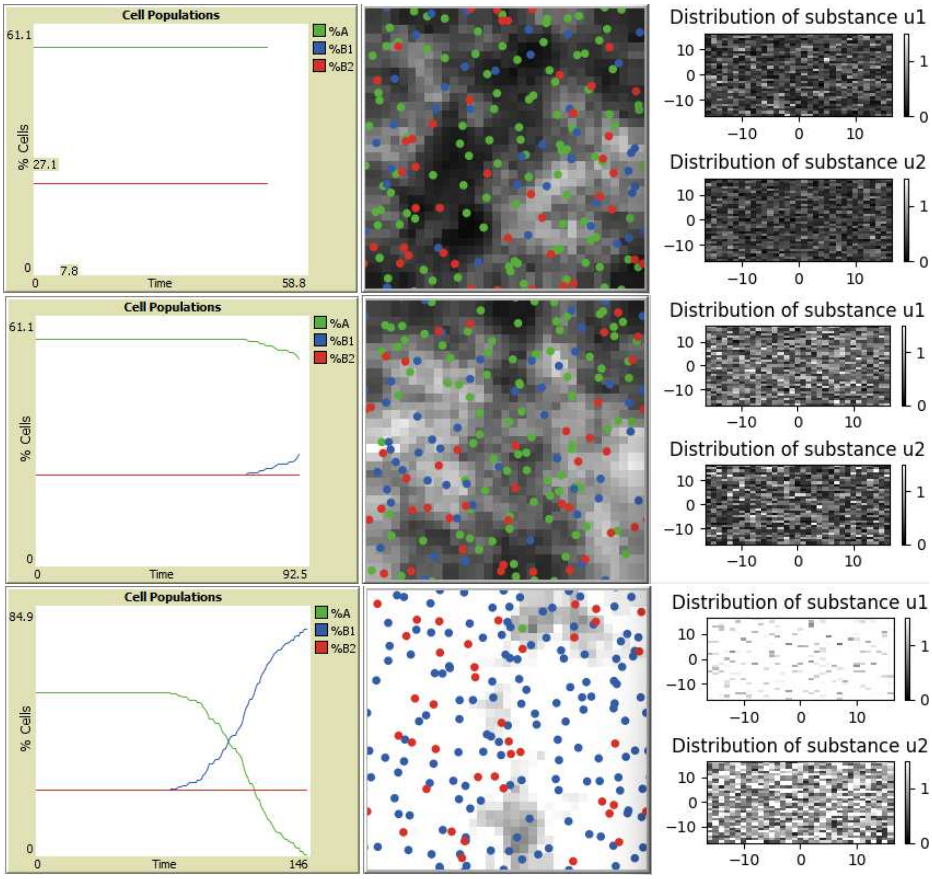

Fig. 3. Evolution of cell differentiation at iterations (from the top to the low) $t = 50$, $t = 90$ and $t = 145$. Left: A cell population for different cell types. Middle: undifferentiated cells A differentiate into cells B_1. They produce extracellular substance u_1. It stimulates production of the intracellular substance p_1. When it reaches the critical value p_1^*, the cell differentiate. Differentiated cells gradually fill the plane. The stationary point P_3 is stable. Both concentrations p_1 and p_2 converge to some positive values. Depending on which of the critical values is reached first, the cell A will differentiate into B_1 or B_2. However, for the value of parameters in Table 2. The cells A differentiate only in cells B_1. Right: the background color of the patches begins to lighten as the substances u_1 and u_2 levels increases.

For other choice of initial conditions and parameters, two types of differentiate cells can be present in the beginning. However one of two cell lineages will dominate another one and will expand on the whole environment. Therefore undifferentiated cells will differentiate only in one cell lineage. Two cell lineages cannot coexist in this model. This conclusion remains true even in the case where the stationary point P_3 is stable. The intracellular concentrations p_1 and p_2 will converge to this stationary points. If the critical values p_1^* and p_2^* are less than the values at this stationary point, then cells will differentiate. Depending on which of the critical values is reached first, the cell will differentiate into B_1 or B_2. As before, only one cell lineage is obtained. Figure 4 shows the distributions of intracellular variables p_1 and p_2 for the values of parameters in Table 2. Though p_2 grows and reaches the same final value as p_2^*, it reaches its critical value after p_1. Therefore cells differentiate only into cells B_1.

Let us note that the patterns with two lineages of differentiated cells can be obtained only in the case where the stationary point P_0 of system (5) is stable. Otherwise, if it is unstable, then only one cell lineage will be obtained even in the case of negative feedback between cell differentiation and production of intracellular proteins. This phenomena can explained by the fact that when two cell lineages appear, they produce the extracellular substances u_1 and u_2 which diffuse and influence undifferentiated cells where production of intracellular proteins p_1 and p_2 begins influence undifferentiated cells where production of intracellular proteins p_1 and p_2 begins. Even if the concentrations of u_1 and u_2 are small, they are sufficient to initiate intracellular reactions since the point P_0 is unstable. Therefore even small extracellular concentrations determine the future choice of undifferentiated cells between two cell lineages far ahead the front of differentiated cells. One of them will finally win this

competition, and all differentiated cells will belong to the same type. If the point P_0 is stable, then small concentrations u_1 and u_2 will not be sufficient to start intracellular reactions. They will begin only when differentiated cells are sufficiently close. If these are cells B_1, then they will stimulate production of p_2 and vice versa. This negative feedback results in the coexistence of two cell lineages.

Figure 4 shows, for the case $b_{11} = b_{22} = 0$ and $b_{12} = b_{21} = 0.1$, the coexistence of cell lineages in the case where undifferentiated cells are stable from the point of view of intracellular regulation and where the feedback between cell differentiation and intracellular regulation is negative.

5. Conclusion

The aim of this work is to present a hybrid method to multi-scale modelling of cell dynamics with intracellular and extracellular regulations. We used agent-based modeling to simulate the behavior of cells, while the diffusion of substances in the environment is described using reaction-diffusion equations and the intracellular regulation is decribed using ODEs. The simulations show how the interaction of these regulations determine the cell fate.

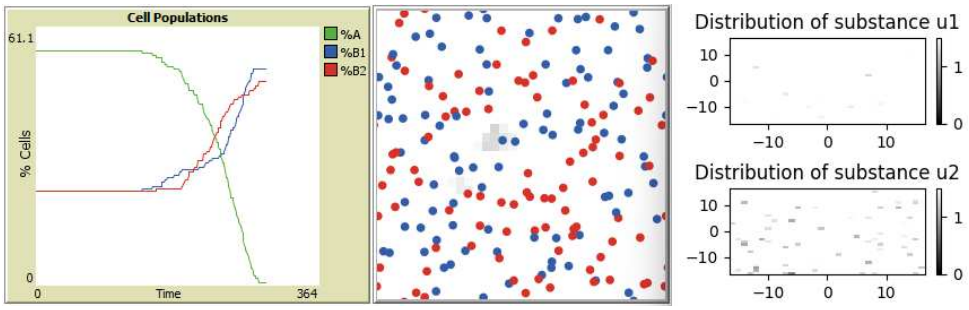

Fig. 4. A snapshot of solution. Evolution of cell differentiation at iteration $t = 296$. Left: A number of cell population for different cell types. Middle: Undifferentiated cells coexist with both types of differentiated cells B_1 and B_2. Right: the substance u_1 produced by cells B_1 stimulate production of the intracellular substance p_2, while u_2 stimulates production of p_1.

Coexistence of various cell lineages in hematopoiesis is crucial for maintaining healthy blood cell production. The process starts with hematopoietic stem cells, which differentiate into different blood cell types such as red blood cells, platelets and white blood cells. The differentiation process involves multiple decision points where cells choose into which lineage they differentiate. Therefore, understanding the conditions that allow for coexistence of different cell lineages is important for understanding the regulation of blood cell production.

The results of this work show that coexistence of two cell lineages requires some particular conditions. If we have a uniform population of undifferentiated cells, and we initiate their differentiation, then usually only one cell lineage persists. Another one disappears even if both of them were initiated at the same time. In order to preserve both cell lineages we need to have stable undifferentiated cells from the point of view of intracellular regulation and negative feedback between cell differentiation and intracellular regulation.

The hybrid model developed in this work can also be extended to take into account the choice of cell fate between self-renewal, differentiation and apoptosis.

[1] Benmir M., Bessonov N., Boujena S., Volpert V. Travelling Waves of Cell Differentiation. Acta biotheoretica. **63** (4), 381–395 (2015).

[2] Anderson A., Rejniak K. Single-cell-based models in biology and medicine. Springer Science & Business Media (2007).

[3] Bernard S. Modélisation multi-échelles en biologie. HAL. Vol. 2013 (2013).

[4] Osborne J. M., Walter A., Kershaw S., Mirams G., Fletcher A., Pathmanathan P., Gavaghan D., Jensen O., Maini P., Byrne H. A hybrid approach to multi-scale modelling of cancer. Philosophical Trans-

actions of the Royal Society A: Mathematical, Physical and Engineering Sciences. **368** (1930), 5013–5028 (2010).

[5] Volpert V. Elliptic partial differential equations. Vol. 2, Springer (2014).

[6] Deutsch A., Dormann S. Mathematical modeling of biological pattern formation. Springer (2005).

[7] Karttunen M., Vattulainen I., Lukkarinen A. Novel methods in soft matter simulations. Vol. 640, Springer Science & Business Media (2004).

[8] Patel A. A., Gawlinski E. T., Lemieux S. K., Gatenby R. A. A cellular automaton model of early tumor growth and invasion: the effects of native tissue vascularity and increased anaerobic tumor metabolism. Journal of Theoretical Biology. **213** (3), 315–331 (2001).

[9] Satoh A. Introduction to Practice of Molecular Simulation Molecular Dynamics, Monte Carlo, Brownian Dynamics, Lattice Boltzmann and Dissipative Particle Dynamics. Elsevier (2010).

[10] Bessonov N., Eymard N., Kurbatova P., Volpert V. Mathematical modeling of erythropoiesis in vivo with multiple erythroblastic islands. Applied Mathematics Letters. **25** (9), 1217–1221 (2012).

[11] Demin I., Crauste F., Gandrillon O., Volpert V. A multi-scale model of erythropoiesis. Journal of biological dynamics. **4** (1), 59–70 (2010).

[12] Kurbatova P., Eymard N., Volpert V. Hybrid model of erythropoiesis. Acta Biotheoretica. **61** (3), 305–315 (2013).

[13] Bessonov N., Demin I., Pujo-Menjouet L., Volpert V. A multi-agent model describing self-renewal of differentiation effects on the blood cell population. Mathematical and Computer Modelling. **49** (11–12), 2116–2127 (2009).

[14] Wilensky U., Rand W. An Introduction to Agent-Based Modeling: Modeling Natural, Social, and Engineered Complex Systems with NetLogo. The MIT Press (2015).

[15] Dalle Nogare D., Chitnis A. B. NetLogo agent-based models as tools for understanding the self-organization of cell fate, morphogenesis and collective migration of the zebrafish posterior Lateral Line primordium. Seminars in Cell & Developmental Biology. **100**, 186–198 (2020).

[16] Vieira L. S., Laubenbacher R. C. Computational models in systems biology: standards, dissemination, and best practices. Current Opinion in Biotechnology. **75**, 102702 (2022).

Багатомасштабне гібридне та агентне моделювання клітинного диференціювання

Бенмір М.[1], Беллай К.[1], Бужена С.[1], Вольперт В.[2]

[1] *Лабораторія фундаментальної та прикладної математики, факультет природничих наук Айн Чок, Університет Хасана II, Касабланка, Марокко*

[2] *Інститут Камілли Джордан, UMR 5208 CNRS, Університет Ліона 1, 69622 Віллербанн, Франція*

У цій роботі пропонується гібридна модель динаміки клітинної популяції, де клітини розглядаються як дискретні елементи, динаміка яких залежить від неперервної внутрішньоклітинної та позаклітинної регуляції. Пропонується гібридна модель, яка враховує внутрішньоклітинні та позаклітинні регуляції біологічних клітин і різних типів клітин, які включають недиференційовані клітини та два типи диференційованих клітин. Використовується алгоритм моделювання, який заснований на підході динамічних систем, з одного боку, і багатоагентному підході, з іншого боку. Обидва підходи реалізовано за допомогою NetLogo та Python. Обговорюється процес того, як клітина, яка диференціюється, вибирає між двома типами диференційованих клітин, і розглядаються лінії співіснування клітин.

Ключові слова: *диференціювання клітин; багатомасштабна гібридна модель; багатоагентне моделювання.*