The effect of obstacles in the environment on the migrating behavior of cells in the Act-CPM model

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1 Introduction

Countless processes in biology can be considered *emergent behavior*. These are seemingly complex behaviors that arise on a bigger scale, through interaction of simpler components on a smaller scale. Modeling such behaviors is of great research interest because 1) This process can lead to a greater understanding of seemingly complex natural phenomena in simple terms and 2) These models provide predictions of the outcome of phenomena in the real world. The second may be particularly relevant in the medical domain. Over the years, different methods of modeling emergent behavior have been proposed by various authors. The focus of this paper will lay on the Cellular Potts Model (CPM), originally proposed by [1].

1.1 CPM

The Cellular Potts Model is a grid-based stochastic method of modeling emergent behavior from relatively simple rules. The core principle is the stochastic minimization of the *Hamiltonian* energy, which is an approximation of the laws of thermodynamics that guide emergent behaviors of biological processes in the real world. Unlike the original Ising/Potts model on which it is based, the CPM may use *non-local* information to determine the next state of a cell. In recent years, CPM has become a commonly adopted method for modeling phenomena in biology that display emergent behavior [2]. The rest of this section will be dedicated to explaining CPM, and in particular Act-CPM, which adds the concept of *cell activity*.

We will first consider the simpler Potts model. First, we will consider the state of the model. Intuitively, the state is simply a grid at a certain time step, where each cell in the grid belongs to one cell at said time step. Furthermore, we introduce the notion of *cell type*. Two different cells of the same cell type will display similar behavior. Fix $n \in \mathbb{N}$ as the amount of cell types.

We define the *graph* of the model $G = (V, E)$, where $V = \{1 \dots w \cdot h\}$ and $E = \{\{i, j\} \mid i \neq j \wedge ((i \bmod w = j \bmod w) \vee (i = j + 1))\}$, with fixed constants w and h. Intuitively speaking, this graph corresponds to a grid with dimension $w \times h$, where there is an edge between vertices iff they are next to each other on the grid. For this reason, note that we will refer to a vertex $p \in V$ as a *pixel*. A *state* is defined as a pair of functions $(\sigma, \tau) : V \times V \to \mathbb{N} \times \mathbb{N}_{\leq n}$. The function σ keeps track of what cell a pixel belongs to, and τ keeps track of the *type* of the cell on a pixel. Note that we may denote $\sigma_i = \sigma(i)$ and $\tau_i = \tau(i)$.

Now equation 1 computes the *Hamiltonian* energy of the current state. Here $J \in \mathbb{R}_{\geq 0}^{n \times n}$ is a matrix of constants that determines the *adhesion energy* between cell types. Higher values mean that it is energetically unfavorable for the cell types to be next to each other. For example, if $J_{i,j}$ is relatively high, then cells of types i and j will minimize contact. The term δ_{ij} assures that there is no energy cost for two pixels of the same cell being next to one another.

$$H = \sum_{(i,j) \in E} J_{\tau_i, \tau_j} \left(1 - \delta_{ij}\right), \text{ where } \delta_{i,j} = \begin{cases} 0 & \text{if } \sigma_i = \sigma_j \\ 1 & \text{otherwise} \end{cases} \tag{1}$$

Now the new state is probabilistically computed as follows. We do a *copy attempt*: We select two random pixels $p, q \in V$. Then with the probability computed by equation 6, $\sigma(p), \tau(p)$ are set to the

values of $\sigma(q), \tau(q)$ in the previous state, with probability $P(\Delta H, T)$ given in equation 6. Here ΔH is the difference between the Hamiltonian energy between the old state, and the state that would be created upon completing the copy attempt successfully. Note that if a copy attempt would lower the energy of the system, it is *always* successful. $T \in \mathbb{R}_{\geq 0}$ is a constant that determines the *temperature*. Setting the temperature higher results in a model with more successful copy attempts.

$$P(\Delta H, T) = \begin{cases} 1, & \Delta H < 0, \\ e^{-\Delta H/T}, & \text{otherwise} \end{cases} \tag{2}$$

Now we introduce two more terms to equation 3, that differentiate the CPM model from the Potts model. They penalize deviation from a target *volume* and *perimeter* of a certain cell, with constants that are determined per cell type. For a cell type τ, constant $V_\tau \in \mathbb{R}_{\geq 0}$ gives the target volume of cells of type τ, and $\lambda_{V,\tau}$ is a constant that determines how energetically unfavorable it is to deviate from this target. Analogous for the perimeter. Note that these terms require *non-local* information of cells that are not directly adjacent to compute.

$$H = \sum_{(i,j)\in E} J_{\tau_i,\tau_j}\left(1-\delta_{ij}\right) + \sum_{\sigma} \lambda_{V,\tau}\left(V_\sigma(t) - V_\tau\right)^2 + \sum_{\sigma} \lambda_{P,\tau}\left(P_\sigma(t) - P_\tau\right)^2 \tag{3}$$

1.2 Cell migration

Cell migration is a process that involves the movement, or migration, of cells relative to their environment. This migration has been well-studied in many species, from single-celled organisms to vertebrates. Act-CPM is an extension to CPM which was designed to emergently mimic migrating behavior. In this paper, we empirically observe migration in the Act-CPM model. In particular, we will investigate the influence of obstacles in the environment. Our research question is: *How do obstacles in the environment affect the collective migration behavior of cells in the Act-CPM model?*

1.3 Act-CPM

We extend CPM with behavior that mimics cell migration. We do this by extending our model by adding *activity*. The general idea is that pixels that were just copied are considered active, and we make it more likely for copy attempts from active to inactive pixels to succeed. First, we assign to each cell an activity level. In equation 4, $A(p,t) \in \mathbb{N}$ denotes the activity level of pixel p at time t. Here $\max_{\text{act}} \in \mathbb{N}$ is a constant.

$$A(p,t) = \begin{cases} \max_{\text{act}}, & \text{if a successful copy to } p \text{ occurred at time } t \\ A(p,t-1) - 1, & \text{otherwise} \end{cases} \tag{4}$$

Finally, we add a term in the equation that makes it energetically favorable to copy from pixels with a high to pixels with a low activity level. Equation 5 now denotes the probability of a succesful copy attempt from pixel p_s to pixel p_t.

$$\Delta H_{\text{act}}(p_s \to p_t) = -\frac{\lambda_{\text{act}}}{\max_{\text{act}}}(\text{GM}_{\text{act}}(p_s) - \text{GM}_{\text{act}}(p_t)) \tag{5}$$

Here $\text{GM}_{\text{act}}(p)$ denotes the geometric mean of the activity around pixel p at the current time. Finally, we extend the probability equation to account for this new term.

$$P(\Delta H, T, p_s, p_t) = \begin{cases} 1, & \text{if } \Delta H + \Delta H_{\text{act}}(p_s \to p_t) < 0, \\ e^{-\Delta H/T}, & \text{otherwise} \end{cases} \tag{6}$$

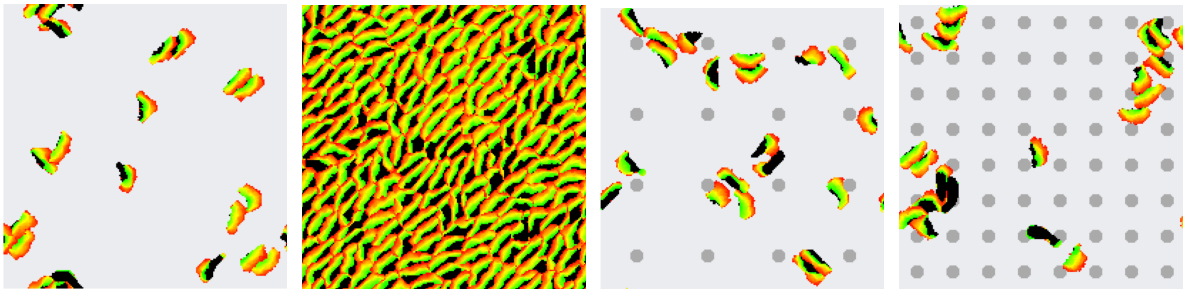
2 Methods

We used the CPM framework to simulate collective cell migration. We designed and analyzed our own CPM experiment to investigate the impact of obstacles on collective migration. With the framework Artistoo, we implemented a simulation using the parameter settings listed in Table 1. We used a 200×200 pixel grid.

Parameter	Background cells	Obstacle cells	Moving cells
Adhesion_cell-matrix	–	0	20
Adhesion_cell-cell	–	0	0
Adhesion_moving-obstacle	–	500	500
Volume	0	100	200
λ_V	0	50	50
Perimeter	0	30	80
λ_P	0	100	2
MaxAct	0	20	80
λ_{Act}	0	140	200
T	10	10	10
Framerate	5	5	5

Table 1: Default CPM parameter settings per cell type. Adhesion parameters are contact energies (J); lower values indicate stronger adhesion.

1. Moderate number of migrating cells (20)
2. High number of migrating cells (200)
3. Introduced moderate number of obstacle cells (16) for moderate number of cells (20)
4. High number of obstacles (64) for moderate number of cells (20)



(a) Image 1 (b) Image 2 (c) Image 3 (d) Image 4

Figure 1: Overall caption describing all four images.

3 Results

Per method, the results are summarized below:

1. **Moderate number of migrating cells (20):** Since the number of cells is low, the cell density in the grid is small, resulting in more localized cell groups. These groups move in directions dictated by their internal rule systems. Because the process is stochastic, the directions chosen by different groups tend to vary. Additionally, due to the low density, the groups do not significantly influence one another, leading to diversity in migration directions.

2. **High number of migrating cells (200):** In this case, the cell density is very high with respect to the grid. The cells are therefore closely coupled with one another. Local adhesion rules at single-cell level give rise to the emergent behavior of coordinated mass movement. It causes the cells to move collectively in the same direction as a mass after some time, in order to minimize the Hamiltonian.

3. **Moderate number of obstacle cells (16) with a moderate number of migrating cells (20):** The migrating cells tend to split into smaller groups, moving around the obstacles. Some cells get temporarily trapped or redirected, resulting in less coherent collective migration compared to the obstacle-free scenario.

4. **High number of obstacles (64) with a moderate number of migrating cells (20):** We expected the dense obstacles to severely restrict cell movement. This would then cause collective directional movement to be minimal, as cells frequently collide with obstacles and change direction. However, something in the implementation caused the cells to move through the obstacles.

4 Discussion

When adding multiple obstacles, we observed that for the 8×8 configuration (Figure 1, Image 1), the moving cells occasionally passed through the obstacles, which is undesirable. Further investigation indicated that this issue occurs for all configurations larger than 6×6. For smaller setups (5×5 and below), the obstacles functioned as intended, effectively restricting the movement of the cells. We were unable to resolve this limitation.

We would like to also briefly talk about the temporary/long-term behavior of cells getting stuck at obstacles. From what we observed, if the cells hit the circular obstacles with their center, they could partially wrap around the obstacle. In doing so, one of two things could happen. Either an activity region would emerge behind the cell (or any area where there is no contact with the obstacle), and the cell would bounce back from the obstacle, or they would stay wrapped for a long while. We don't know if this behavior is computer-specific or not, since sometimes the simulations lagged.

From this, we observed an interesting phenomenon. We observed the event that when a cell gets stuck on an obstacle, the cell could be "freed" by another cell. In the sense that when the trapped cell is touched by a roaming cell, the trapped cell could be stimulated to give very high priority to create an active region towards the point of contact. This then results in the trapped cell getting off of the obstacle. We believe the reason for this is because the adhesion between cells is less than that of the obstacles, so the cell latches onto the low-energy source.

5 Conclusion

This study investigated the following research question: How do obstacles change the collective migration behavior of cells?

Our results show that cell density influences collective direction. With a low density of cells, independent migration groups form and move in different directions. With a high density of cells, cells exhibit coordinated mass movement in the same direction. These observations are consistent with the CPM rules, where each cell seeks to minimize the Hamiltonian energy. This coordinated movement is an emergent behavior: it arises naturally from local interactions because it is energetically more efficient according to the CPM. In terms of adhesion, cells tend to maximize contact with neighboring cells of the same type while minimizing contact with other types or empty space. When many cells are present, moving together reduces the number of high-energy contacts and helps maintain stable clusters. Volume and perimeter constraints also contribute by ensuring cells maintain their preferred size and shape, and directional persistence (activity) further aligns neighboring cells' movement. Together, these factors explain why high-density cells move collectively in the same direction.

The introduction of obstacles alters migration paths and reduces directional coherence. The migrating cells tend to split into smaller groups, moving around the obstacles. Some cells get temporarily trapped or redirected, resulting in less coherent collective migration compared to the obstacle-free scenario.These findings indicate that both population density as well as potential obstacles in the environment shape collective migration behavior of cells.

References

[1] James A Glazier and Ariel Balter. "Magnetization to morphogenesis: a brief history of the Glazier-Graner-Hogeweg model". In: *Single-cell-based models in biology and medicine*. Springer, 2007, pp. 79–106.

[2] Marco Scianna and Luigi Preziosi. "Multiscale developments of the cellular Potts model". In: *Multiscale Modeling & Simulation* 10.2 (2012), pp. 342–382.