CPM: Collective Migration

Group 12, March 5, 2025

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1 Introduction

The purpose of this report is to investigate the effect of various densities of obstacles grids on the collective migration pattern of cells in the Cellular Potts Model (CPM) by conducting a variety of experiments via simulations. To design the environment for our observations, we kept a few requirements in mind: we wanted to obtain an environment with multiple, evenly spaced obstacles, each the size of half a cell. To obtain such a layout, we explored existing Aristoo simulations and found one example that was well suited to our experiment, which can be viewed at the bottom of this site under the heading *Obstacle Course*. After adapting the size and number of cells, we were able to start our experiments. In the following sections of this report, we will explain what parameters we modified and what behavior was observed.

2 Background

A CPM is a complex cellular automaton that is used to model cells and tissues (Graner and Glazier [1992]). In this report, we describe how we used CPM to investigate complex cell behavior. In particular, how the introduction of obstacles impacts collective cell migration. CPM simulations are based on certain parameters that determine cell behavior. Tools like Artistoo (Wortel and Textor [2021]) allow users to set these parameters and observe the effects on their simulation in real time. For this experiment, we will set all parameters to a certain value as part of the environment setup, and we will not modify them for our observations. We will dive into the specific values to which the parameters were set for this experiment in Section 3.2. However, we will first develop an intuition about what these parameters do.

Volume: sets a size for the cell. Biologically this would be regulated for example by osmotic pressure and cytoskeletal tension. While Volume represents the target size of a cell, λ_v represents the constraint that controls how much a cell can deviate from this target. A lower λ_v value means cells will freely expand or shrink, while higher λ_v maintain a nearly constant size, resisting compression or expansion.

Perimeter: represents the target value for cell rigidity. The constraint λ_p determines how much a cell's perimeter can deviate from this target. Low λ_p means the cells can take irregular, jagged shapes, while higher λ_p means cells will maintain a compact roundish shape.

Adhesion$_{\text{cell-matrix}}$: This parameter defines how strongly cells interact with the extracellular matrix. Low $J_{\text{cell-matrix}}$ values means the cells stick more to the substrate, so their behavior will be more spread-out. Higher $J_{\text{cell-matrix}}$ values mean there is a weak adhesion to the substrate, so cells will be able to move more freely.

Adhesion$_{\text{cell-cell}}$: describes the adhesive strength between neighboring cells. Low $J_{\text{cell-cell}}$ means there is a strong adhesion between cells, so cell clusters will likely form and tissue structures will be more compact. High $J_{\text{cell-cell}}$ values would cause cells to spread apart.

Max$_{\text{act}}$ sets a limit on persistence-driven mobility. It depends on how recently the cell has moved. Biologically, this would influence how long a cell continues to move into the same direction. Low Max_{act} values means cells will have more short-term directional movement, resulting in more random motion. High Max_{act} means cells maintain directional movement for longer. $\lambda_a ct$ defines how

strongly a cell prefers to maintain movement, so low $\lambda_a ct$ means more random movement, and high $\lambda_a ct$ means movement will be directional and sustained in time.

Temperature T defines the stochasticity of Monte Carlo updates, affecting how often unfavorable moves are accepted. Biologically, it simulates random fluctuations in cell shape or movement due to noise. Low Temperature values means cells move more deterministically, with less noise. High Temperature means there are more random fluctuations in shape and movement. Cell Number determines how many cells are initialized in the simulation. Biologically, this would represent the cell population density, so Cell Number values affect crowding effects.

3 Methods

3.1 Experimental Design

Our main goal was to investigate how varying densities of obstacles impact the collective migration of cells in a two-dimensional cellular Potts model (CPM). Each simulation was run on a (256×256)-pixel grid, with a specific number of equally spaced circular obstacles introduced. By systematically modifying the number of obstacles we were able to explore a range of obstacle densities while preserving consistent cell parameters. This setup allowed us to answer the main question: "How do obstacles change the collective migration behavior of cells?"

In order to avoid confounding factors such as variable cell sizes or different temperature parameters, we held the principal CPM parameters fixed when increasing the obstacle density. We also introduced sufficient numbers of cells to ensure that collective migration effects were observable and not limited by the number of cells present.

3.2 Methodology and Implementation: CPM Setup

Parameter	**Value**	**Parameter**	**Value**
$\text{Adhesion}_{\text{cell-matrix}}$	20	$\text{Adhesion}_{\text{cell-cell}}$	0
Volume	200	λ_{Volume}	50
Perimeter	180	λ_P	2
Max_{act}	80	λ_{Act}	200
T	20	Framerate	5
Cell Number	300	Obstacles $(n \times n)$	0, 3, 6, 9
Obstacle Radius	5	Burn-In	3000 MCS
Sim Duration	3000 MCS	Image Capture	2995 MCS
Random Seed	1		

Table 1: CPM Simulation Settings

We used the $\mathrm{ActivityConstraint}$ with $\lambda_{\text{act}} = 200$ and MAX_{act} of 80. This ensures that cells with high past activity tend to remain active, contributing to persistent migration. The effective temperature was fixed at $T = 20$. Each simulation consisted of seeding 300 cells at random non-obstacle positions and letting the model evolve for a burn-in period, followed by the actual simulation. During this recorded phase images were output at every 5 steps (framerate 5 in Table 1). These image snapshots allowed us to make videos of the evolving cell configurations, which we will discuss in the results section.

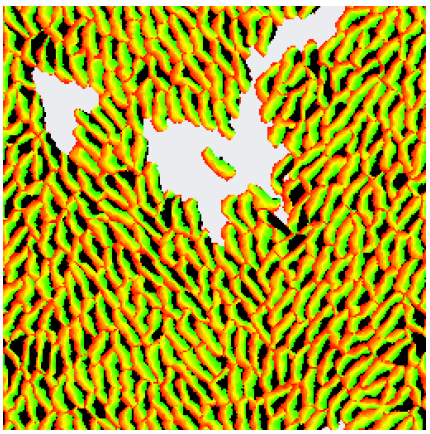
Obstacle Implementation. We introduce obstacles by designating a fixed set of *barrier pixels* using $\mathrm{BorderConstraint}$. Each circular obstacle is centered at a regular interval in the grid, with a fixed radius of 5 pixels. We used up to $(n \times n)$ obstacle grids (where $n \in \{0, 3, 6, 9\}$), ensuring that obstacles are evenly spaced. We colored the obstacles blue so that they are easily visible in the resulting simulations.

Cell Seeding and Burn-in. We seeded 300 cells into free pixels (pixels not marked as obstacles). This was done by randomly choosing a coordinate (x, y) outside the obstacle regions for

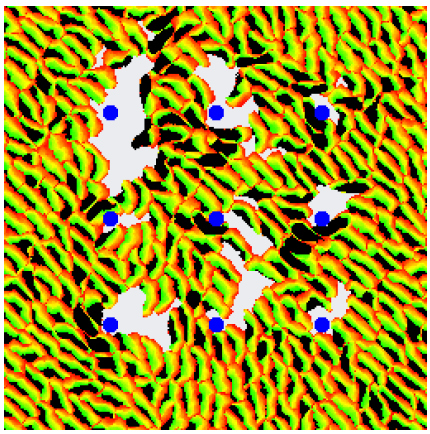
each new cell and setting that pixel to a unique cell ID. A burn-in phase 3000 Monte Carlo steps long was applied to get to a steady state before rendering and image capture.

Temporal Updating and Output. Once the initial cell layout was generated, we ran each simulation for 3000 Monte Carlo steps at a temperature $T = 20$. The simulation loop proceeds by repeatedly calling `timeStep()`, which stochastically flips pixels according to CPM acceptance rules. The cells are colored based on local activity, allowing easy visual inspection and analysis of cell migration patterns.

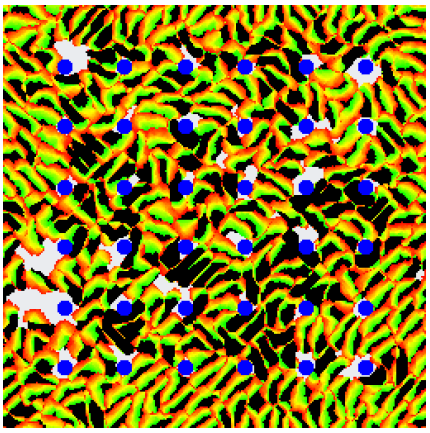
4 Results



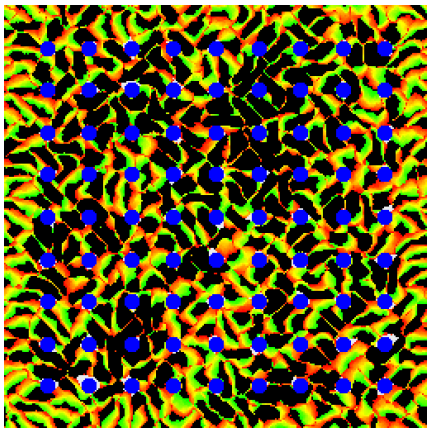
(a) **Baseline (MCS=2995)**: This image shows few black pixels (these are the less recently updated pixels, indicating slower cell movement), and collective orientation of red pixels (this is the movement frontier of the cell, these pixels have been more recently updated), indicating high collective migration.



(b) **3×3 (MCS=2995) Obstacle Grid**: With a 3×3 grid more black pixels are present and the the white gaps are focused around obstacles. More black pixels indicate less/slower movement.



(c) **6×6 (MCS=2995) Obstacle Grid**: As obstacle density increases the collective migration pattern breaks up as indicated by non-alignment of the red activity frontiers of each cell.



(d) **9×9 (MCS=2995) Obstacle Grid**: At this obstacle density a large amount of congestion is seen as demonstrated by the number of black pixels in the image. Collective migration is seriously degraded.

Figure 1: Collective migration patterns of the CPM model vs number of obstacles. Videos of the migration patterns can be found at this link for Youtube.

The results of the four simulations are presented in figure 1. The simulation parameters are found in table 1. Sub figure (a) of Figure 1 demonstrates unobstructed collective migration behavior. One can see that all 300 cells seem to roughly be traveling in a collective mass, with several white gaps left as space for obstacle placement. The red portions of the cell indicate those portions that are experiencing the most activity or movement, while black is the least. In the first figure the amount of black regions is relatively small, as cells are free to move. Considering figure (b) now, the collective migration is still observable with a grid of 3×3 obstacles, but there is noticeable obstruction and distortion of the pattern around the obstacles. Figure (c) and (d) at 6×6 and 9×9 demonstrate deterioration of the collective migration pattern - there is no global movement of cells towards one region, and the percent of inactive cell has drastically increased, as shown by the amount of black pixels.

Without quantitative metrics it is difficult to quantify collective migration through the presentation of images alone, which is why we have also provided videos demonstrating the cell behavior under different obstacle conditions. From a purely qualitative perspective, the red pixels in the image are those portions of the cell that are experiencing the most activity (movement) while the black pixels are those experiencing the least activity. The simulations were run several times and demonstrated similar behavior, and the images shown below are representative samples from one such run. The results clearly show that when no obstacles are present the cells demonstrate collective migration, while at higher obstacle densities this pattern is degraded and congestion is evident.

5 Discussion and Conclusion

Our findings conform with intuition as the introduction of obstacles effectively introduces congestion into the cell behavior, and it takes them more time to navigate around the obstacles. Taken to the extreme, it is expected that if even higher obstacle densities are introduced that cell movement would effectively come to a halt.

In this experiment, we could observe how the introduction of obstacles into a collective cell migration simulation results in the deterioration of the migration pattern, and how this change in behavior is related to the density of the obstacles placed in the grid.

6 Revision Summary

The revision that most substantially improved our work was updating our simulation results to be more robust by 1) Adding a baseline with no obstacles at all, 2) ensuring the grid of obstacles was evenly distributed and centered, 3) adding the timestamps for when the images in the result section were taken, 4) and making our results more reproducible by making the burn-in and total simulation time more explicit while also reporting our random seed value. Additional work was done to implement a quantitative metric that could be used to mathematically measure the degree of collective migration. The idea was to instantiate a vector for each cell with the direction and speed of the cell, and then average across all cells to obtain a global movement vector. However we ran into issues with the implementation in the Artistoo framework so this was not completed. Other important revisions include 1) clarifying that Max_{act} was set to 80 and not 20, 2) adding much more descriptive figure captions in the results section, 3) explaining the figures more in the results section rather than only using the discussion to do this, and 4) removing dubious claims that were not directly backed up by evidence, e.g. *"This change in behavior is directly proportional to the number of obstacles that are introduced"*. We also 5) explained the meaning of colors in the visualizations, and 6) reorganized the contents results and discussion to better fit their subsection. One reviewer suggested our relatively small number of experiments was not sufficient, but we chose to keep it simple because the experiments that were performed were appropriate and sufficient for answering the research question, and thus no further experiments were warranted. Perhaps one of the most useful things learned throughout this process was how important it is to keep track of experimental setup and parameter values so that the results can be easily reproduced by someone else.

7 Acknowledgements

We would like to thank the members of groups 19, 21, and 25 for their thoughtful feedback and constructive words. You have helped us improve upon our original work and saw errors we did not. We would also like to thank Dr. Inge Wortel for organizing the course.

References

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Inge MN Wortel and Johannes Textor. Artistoo, a library to build, share, and explore simulations of cells and tissues in the web browser. *Elife*, 10:e61288, 2021.