Invasion from a cell aggregate: the roles of active cell motion and mechanical equilibrium

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1. Introduction

Cell invasion from an aggregate into a surrounding extracellular matrix is an important process during development and disease, e.g., vascular network assembly or tumor progression. To describe the behavior emerging from autonomous cell motility, cell-cell adhesion and contact guidance by extracellular matrix filaments, we propose a suitably modified cellular Potts model. By comparing our simulations to a widely used *in vitro* experimental setup we argue that both the invasion morphology and kinetics is well reproduced for the first few days without assuming cell proliferation or chemotactic guidance within the model. Instead, we consider an active cell motility process in which internal polarity is governed by a positive feedback from cell displacements. This mechanism can result in highly persistent motion when constrained by an oriented extracellular matrix structure. Furthermore, ensuring proper mechanical relaxation of the aggregate is of key importance to model how cells leave the aggregate and enter the extracellular matrix.

2. Experimental observations

In this study we focus on the experimental observations of [1]: aggregates of various cell lines were cultured in collagen I gels and were charaterized by their ability to invade the matrix:

- the speed of invasion was found to be approximately constant (200 μm/day)
- cells left the aggregates in multicellular, linear structures, oriented radially outwards.
- cells with minimal matrix degrading enzyme production were also able to invade the matrix.

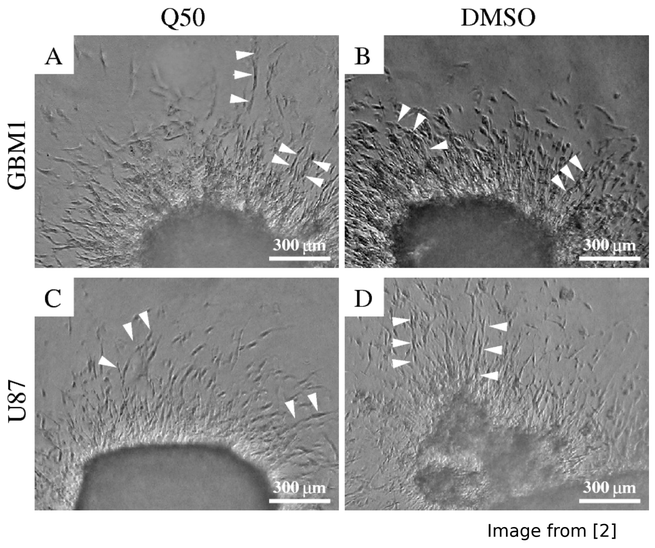
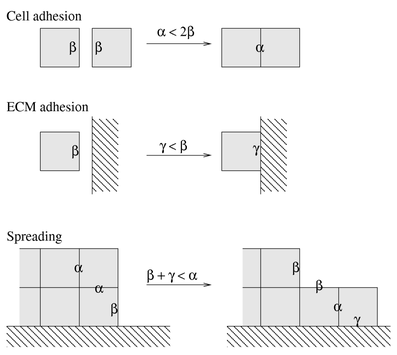


Image from [2]

Repeated experiments in the presence of cell division inhibitor Q50 showed that cell division is not neccessary for the invasive behavior.

3. ECM in the Potts

In our model, the matrix is represented as a static object. Adhesion to the matrix is defined by a surface tension-like parameter, γ, and cell-cell and cell-medium contact parameters are α and β, respectively. Depending on their relative values, these parameters define the behaviour of single cells. Motion of cells is constrained by the ECM: cells stepping onto a matrix site are penalized, thus lessening the probability of these steps.



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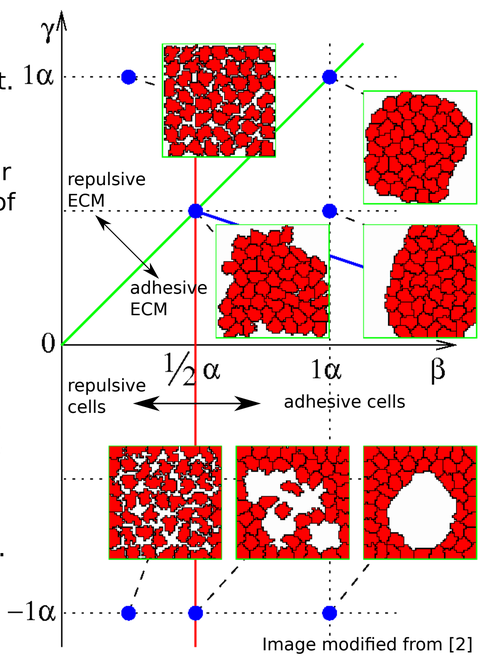


Adhesion parameters define the morphology of a cell aggregate surrounded by an impenetrable ECM. (α=1)

Image modified from [2]

4. Modeling ECM fibers

The random but possibly oriented structure of ECM fibers is constructed using a Markov chain process. This way the matrix geometry is defined by two parameters controling the fiber density and the fiber length.

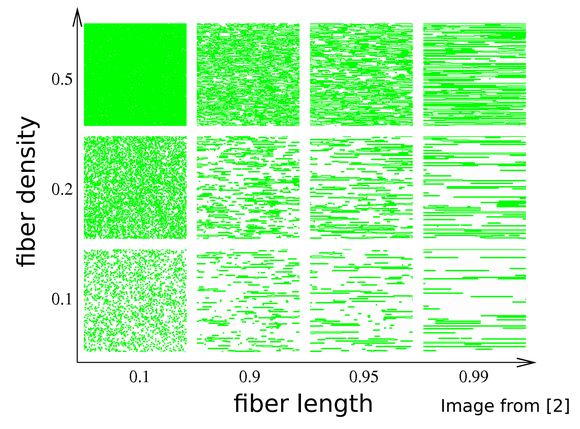
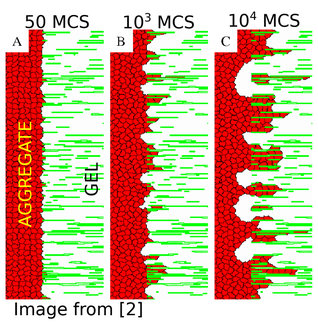


Image from [2]

5. Mechanical equilibrium

During invasion, cells enter the gel and adhere to the filaments. As a result, the interface between the cell aggregate and the matrix is depopulated, as the bulk cannot react to the changes fast enough. This leads to the unrealistic separation of the bulk and the matrix. We argue, that this effect is the result of the inherent effective friction with the CPM grid.



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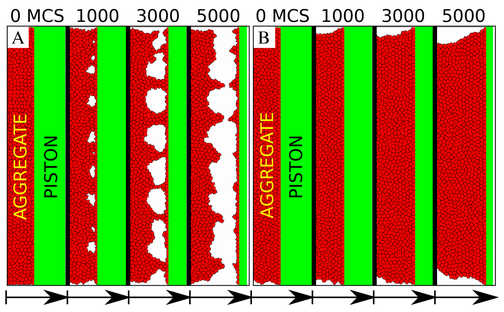


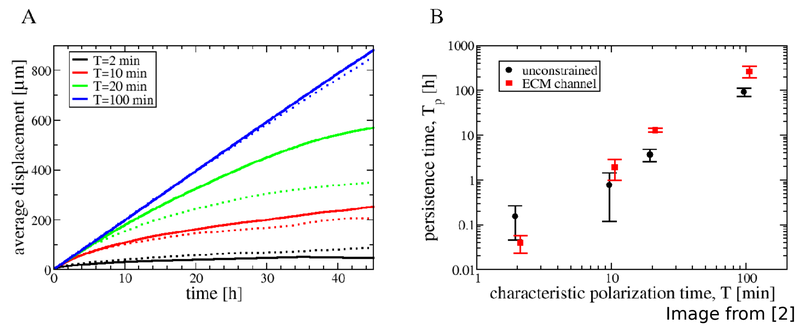
Piston test: cells follow a moving surface without (A) and with (B) additional steps.

We introduce additional timesteps between the conventional Monte Carlo steps (MCS) in which the passive forces are allowed to equilibrate the system and drive it to a mechanical equilibrium. For demonstration, we simulate a bulk of cells attached to a slowly moving surface (piston). Cells in mechanical equilibrium follow the piston without changing the overall shape of the aggregate.

7. Active cell motion

Active cell motion in the model is represented by a positive feedback between cell displacements and cell polarization [3]. We investigated the effect of constrained motion on this mechanism: we simulated the motion of cells in a single cell-wide tunnel and in the unconstrained plane. The comparison of cell displacements showed that the constraint might increase the motion persistence of cells, depending on the characteristic time T needed to change the polarization direction of a cell.

Displacement of constrained (solid line) and unconstrained (dotted line) cells. By fitting the persistent diffusion formula, the persistece time T_p is determined as the function of T and the geometry.



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6. Invasion by haptotaxis

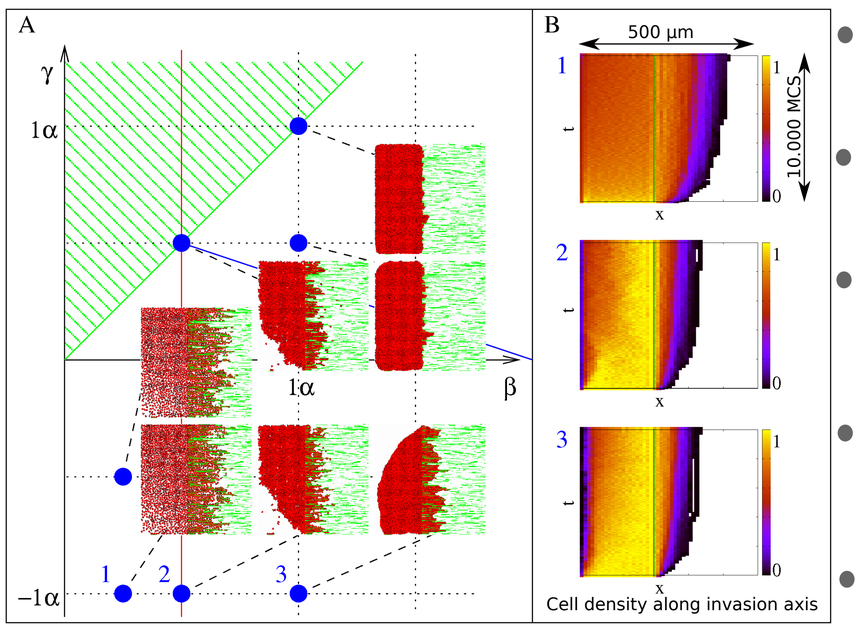

Image modified from [2]

- if the matrix is adhesive, cells move into the matrix by haptotaxis
- the invasion is driven by a cell density gradient inside the matrix
- adhesive matrix can organize otherwise non-adhesive cells along the ECM filaments
- increasing cell-cell adhesion smoothens the surface and slows down the invasion
- the speed of invasion decreases as the invasion depth increases

8. Invasion by active motion and haptotaxis

- cell invasion speed is constant throughout the simulated time-scales
- invasion speed is 130 μm/day, comparable with the experimental findings
- invasion is substantially faster than with spontaneously moving cells: cells cover 200 μm over 33h (2000MCS)

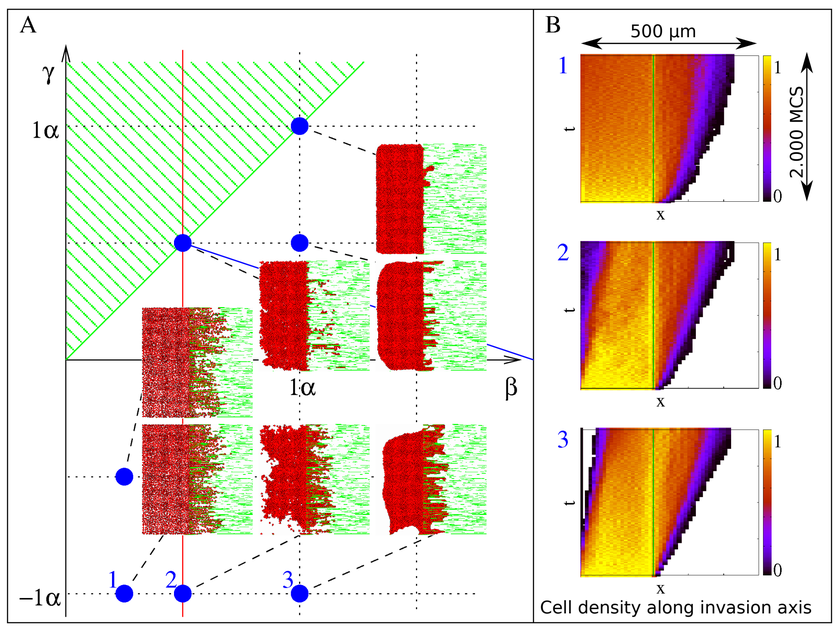

Image modified from [2]

9. Outlook: matrix degradation

Invasion can occur with and without degrading the ECM. In the former case, cells may create tunnels but fail to follow them. When combined with active cell motion, a leading cell degrades the matrix and others follow. Initiating of new sidebranches is determined by the balance between matrix degradation and the persistent cell motion.

References

[1] Hegedűs B, Marga F, Jakab K, Sharpe-Timms KL, Forgacs G: The interplay of cell-cell and cell-matrix interactions in the invasive properties of brain tumors. Biophysical Journal, 91(7):2708-16, 2006
[2] Szabó A, Varga K, Garay T, Hegedűs B, Czirók A: Invasion from a cell aggregate -- the roles of active cell motion and mechanical equilibrium. Submitted to Physical Biology.
[3] Szabó A, Ünnep R, Méhes E, Twal WO, Argraves WS, Cao Y, Czirók A: Collective cell motion in endothelial monolayers. Physical Biology, 7(1):046007, 2010