Tumor Cell Migration in 3D – Features & Models

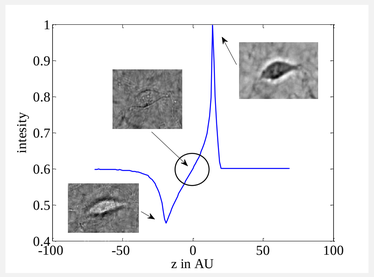
F. Stadler, J. Steinwachs, M. Fellner, C. Mierke, C. Metzner and B. Fabry
Biophysics Group, University of Erlangen, Contact: *claus.metzner@gmx.net*

Abstract

Using an automatic setup, we observe tumor cells as they migrate within a collagen gel. The resulting 3D trajectories of individual cells are analyzed statistically. Features such as exponential invasion profiles, sub-/super-diffusive mean squared displacements and leptokurtic step width distributions indicate that cell migration is not a Brownian random walk.

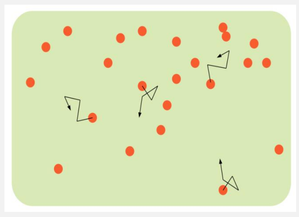
A model assuming cells with directional persistence, moving randomly within a porous matrix, with an optional possibility of protolytic matrix degradation, can explain the observed features.

Detection Setup

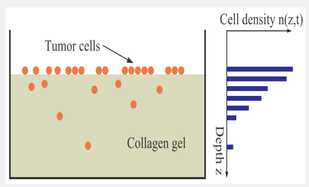


We use MDA-231 breast carcinoma cells and type1 collagen gels. The gels are polymerized in petri dishes with FCS medium added.

A fully automated setup tracks a group of individual cells in 3D, by recognizing characteristic optical patterns that emerge as the focal plane scans through the cell body.

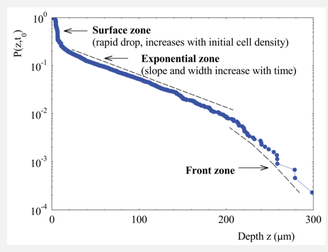


In bulk diffusion experiments, the cells start with a homogeneous distribution throughout the volume of the gel.

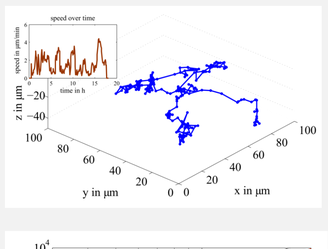


In surface invasion experiments, the cells are initially plated onto the top surface of the gel.

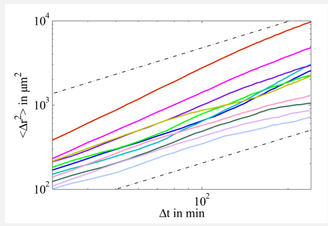
Experim. Results



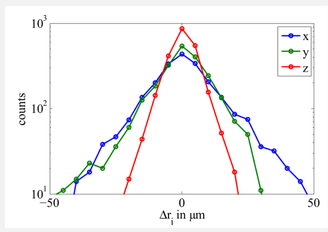
Cumulative probability to find cells at depths greater or equal *z*, after invading the gel for a fixed time from the surface. The profiles show an extended exponential regime.



Typical 3D trajectory of a cell, recorded for 18 hours. Velocity fluctuations (inset) result from switching between more diffusive and more ballistic phases.

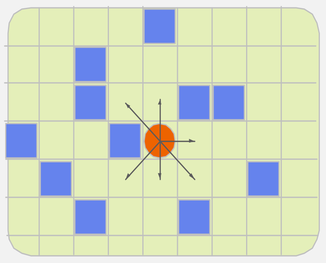


The mean squared displacement $\langle \Delta r^2 \rangle$ versus lagtime Δt of cells in a 3D collagen gel shows a large cell-to-cell variability, including sub- and super-diffuive cases.

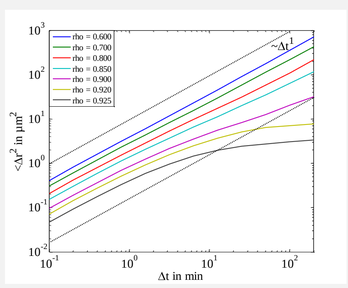


Exponential probability distribution of step widths between cell positions, observed at regular intervalls of 1h. Motion in z-direction is reduced.

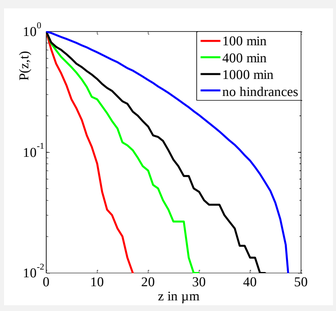
Porosity



Monte Carlo simulations of cell migration are performed on a 3D grid. Porosity is modeled by a fraction ρ of randomly distributed fields (blue) that are inaccessible to the cells (red).

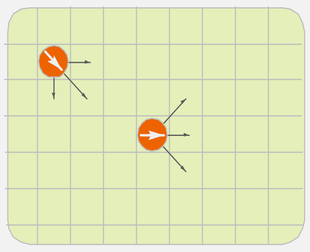


Simulated mean squared displacment (MSD) versus lagtime of Brownian walkers that diffuse in a porous medium with different volume fractions ρ of obstacles. For large ρ, the MSD saturates due to confinement.



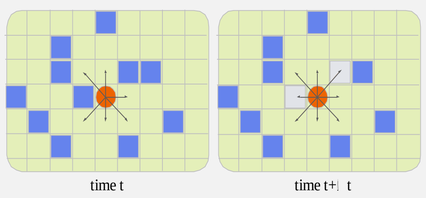
Simulated surface invasion of Brownian walkers into a half-space of porous material with *ρ=0.85*. One obtaines close-to exponential profiles in the cumulated probability $P(z,t_i)$ for different recording times t_i. In contrast, diffusion within a homogeneous medium shows non-exponential profiles (blue curve).

Persistence

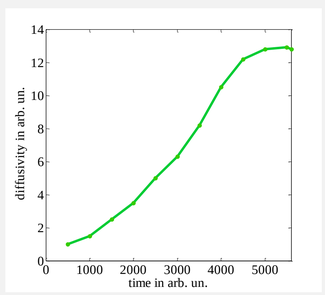


Directional persistence is simulated by allowing the cells, in each step, to move only within a finite angle arround the previous direction.

Proteolysis



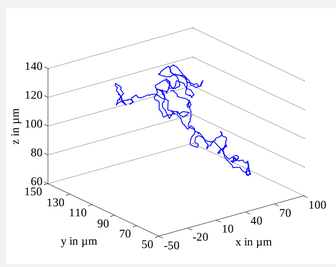
To simulate proteolytic matrix degradation, the cells are allowed to remove adjacent obstacles with a certain rate.



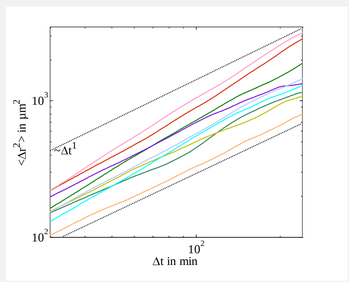
Proteolysis leads to a gradual decrease of obstacle density ρ. Thus, cell migration becomes a non-statonary random process. This is reflected in a time-dependend increase of the apparent diffusivity (as determined from the MSD at fixed lagtime).

Combined Model

Experimental data are reproduced best in a model assuming agents with directional persistence that move randomly within a porous material and are able to degrade obstacles in their path via proteolysis.



The combination model produces trajectories with statistical features close to the observations. A sample is shown to the left.



Simulated mean squared displacements of individual agents show a wide spectrum of apparent diffusivities and power law exponents.

Summary

Features & Models	Exponential Invasion	Sub-Diffusion	Super-Diffusion	Non – stationarity	Cell-to-Cell variability
Experiment	+	+	+	?	+
Porosity	+	+	-	-	+
Persistence	-	-	+	-	-
Protolysis	+/-	-	-	+	+
Combi M.	+/-	+	+	+	+