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Modeling the influence of nucleus elasticity on cell invasion in fiber networks and microchannels

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HIGHLIGHTS

- Cellular Potts model.
- Effect of nucleus elasticity and pore size on cell migration in microchannels and ECM.
- Cytoskeletal and nuclear elasticity correlate with the invasive potential of cells.
- Biphasic dependence on pore size as in experiments.
- Two migration modes (oscillatory and steady) as observed in the literature.

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ABSTRACT

Cell migration in highly constrained extracellular matrices is exploited in scaffold-based tissue engineering and is fundamental in a wide variety of physiological and pathological phenomena, among others in cancer invasion and development. Research into the critical processes involved in cell migration has mainly focused on cell adhesion and proteolytic degradation of the external environment. However, rising evidence has recently shown that a number of cell-derived biophysical and mechanical parameters, among others nucleus stiffness and cell deformability, plays a major role in cell motility, especially in the ameboid-like migration mode in 3D confined tissue structures. We here present an extended cellular Potts model (CPM) first used to simulate a micro-fabricated migration chip, which tests the active invasive behavior of cancer cells into narrow channels. As distinct features of our approach, cells are modeled as compartmentalized discrete objects, differentiated in the nucleus and in the cytosolic region, while the migration chamber is composed of channels of different widths. We find that cell motile phenotype and velocity in open spaces (i.e., 2D flat surfaces or large channels) are not significantly influenced by cell elastic properties. On the contrary, the migratory behavior of cells within subcellular and subnuclear structures strongly relies on the deformability of the cytosol and of the nuclear cluster, respectively. Further, we characterize two migration dynamics: a stepwise way, characterized by fluctuations in cell length, within channels smaller than nucleus dimensions and a smooth sliding (i.e., maintaining constant cell length) behavior within channels larger than the nuclear cluster. These resulting observations are then extended looking at cell migration in an artificial fiber network, which mimics cell invasion in a 3D extracellular matrix. In particular, in this case, we analyze the effect of variations in elasticity of the nucleus on cell movement. In order to summarize, with our simulated migration assays, we demonstrate that the dimensionality of the environment strongly affects the migration phenotype and we suggest that the cytoskeletal and nuclear elastic characteristics correlate with the tumor cell's invasive potential.

1. Introduction

Cell migration on and within tissues plays a critical role in a diverse array of processes, such as in developing embryos, where the coordinated movement of cells of different origins is crucial for organogenesis and migratory defects at all stages lead to severe embryonic malformations (Kurosaka and Kashina, 2008). In adult organisms, most cells are usually quiescent, except in immune surveillance or inflammation, where leukocytes actively migrate from blood vessels into infected tissues, and then into the lymph node for effector functions (Friedl and Weigelin, 2008), and in wound healing, where migration contributes to the repair of both basement membrane-underlaid epithelium and connective

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tissues. In pathological conditions, cell migration is involved in chronic inflammatory diseases such as artherosclerosis, and in cancer cell invasion and metastatization (Sahai, 2007).

In particular, tumor cells are able to abandon their primary site and migrate through the surrounding parenchyma, in order to enter the circulatory system and invade other healthy tissues. On this journey, cancer individuals need to continuously regulate their migratory and invasive behavior, as they are exposed to a variety of biochemical and biomechanical interactions, modulated both by the biophysics and by the microstructure of the environment (Doyle et al., 2009; Friedl and Brocker, 2000; Kumar and Weaver, 2009). *In vivo* connective tissues can in fact provide interstitial extracellular matrices (ECMs) with heterogeneous composition, density, and organization: they can comprise both loose regions formed by sparse collagenous fibers and areas with tightly packed threads. In the first case, important physical determinants of cell movement include the degree of ECM alignment, the width of resulting pores, and the ECM stiffness, as widely provided by experimental (Egeblad et al., 2010; Erler and Weaver, 2009; Friedl and Wolf, 2010; Wolf et al., 2009) and theoretical (Scianna et al., submitted for publication; Zaman et al., 2007, 2006) works. In the second case, matrix environments behave instead as physical barriers, adjacent to channel/track-like spaces which, depending on their dimensionality, may either guide, hinder, or completely prevent cell movement (Hotary et al., 2003; Wolf et al., 2007). Remarkably, different studies have reported that cells achieve significant movement in highly constrained physical spaces, determined by dense matrices, by drastic morphological deformations, in addition (or even in substitution) to the proteolytical degradation of the local environment, as provided in Gerlitz and Bustin (2011), Ilina et al. (2011), Wolf et al. (2003), and Wolf et al. (2007). The repeated adaptation of cell shape requires substantial reorganization of both the cytoskeleton and other organelles and in particular of the nucleus, the most voluminous and rigid intracellular compartment. This type of migration, called *ameboid movement* since it is associated with flexible amoeba-like shape changes, proceeds in a poorly adhesive mode and is mostly independent from specific molecular and biochemical interactions with the surrounding environment (Guck et al., 2010). Notably, more aggressive and metastatic cancer cells have been widely shown to have a significant compliance with respect to non-metastatic individuals, which remain stuck at the vessel walls or when crossing the endothelium and therefore are forced to be confined in the primary site (Guck et al., 2010, 2005; Kumar and Weaver, 2009; Pankova et al., 2010; Remmerbach et al., 2009; Wyckoff et al., 2000).

For these reasons, a quantitative assessment of cell deformability has the potential to be of significant value for diagnostic purposes, such as screening and cancer grading, and for a more detailed prediction of the course of the disease in individual patients (Schinkinger et al., 2005); indeed, it has given rise to a number of *in vitro* models. For instance, 3D lattices consisting of reconstituted fibrillar collagen are typically used to study cell migration in structures mimicking highly confined *in vivo* connective tissues (Wolf et al., 2009). However, in most cases, these bio-engineered scaffolds lack well-controlled spatial characteristics, because small and large pores result from the stochastic fiber polymerization processes, therefore failing to recreate defined trails and barriers (Egeblad et al., 2010; Provenzano et al., 2008; Wolf et al., 2009). Indeed, specific mechanisms of reassembly of fibrillar matrices have been recently combined with microlaser procedures, able to generate predefined tracks that create spatially defined patterns of connective tissue organizations (Ilina et al., 2011). In this regard, geometrical characteristics of 3D matrix environments can be easily controlled and modulated also with migration assays whose key features are micro-sized channel structures (Irimia et al., 2007; Rolli et al., 2010).

Such different types of experimental systems are here reproduced and simulated by an extended cellular Potts model (CPM, Balter et al., 2007; Glazier et al., 2007; Glazier and Graner, 1993; Graner and Glazier, 1992; Marée et al., 2007; Scianna and Preziosi, 2012). It is a grid-based Monte Carlo technique which employs a stochastic energy minimization principle to display the invasiveness of tumor cells into well-defined and controlled 3D environments. As distinct features of the proposed approach, each cell is modeled as a discrete physical unit, compartmentalized into the nucleus and the cytosol, and characteristics like cell morphological evolutions and directionality are not imposed *a priori*, but are the result of their interactions with the extracellular environment.

The method is used to extract the main features of tumor cell invasiveness by working first with a 3D channel environment. As an outcome, we focus on experimentally addressable characteristics of cell locomotion, i.e. overall displacement and velocity, predicting how these quantities are influenced by manipulations either of the geometrical features of the channels, or of the biophysical properties (i.e., elasticity) of the cells themselves. We then use the simulated migration chip to compare the migration of cells inside the microchannels and their movement on a 2D flat surface, like the one located outside the entrance of the channels. Consistently with experimental observations on different tumor cell lines, our approach allows to discern the effect of the mechanical rigidity of each cell compartment (i.e., the nucleus and the cytosolic region) in the migration capacity of the entire individual. Moreover, our findings provide evidence of the facts that migration characteristics of cells are very different in 2D and in highly constrained 3D environments and that even the underlying dynamics change.

The same approach is finally employed to focus on cell migration in regular networks of fibres, which mimic extracellular matrices (ECM) with different densities (i.e., with different pore dimensions). Also in this case, we analyze the permissive role played in cell locomotion of the nucleus elasticity.

The remaining parts of this publication are organized as follows: in Section 2 (Mathematical model), we clarify the assumptions on which our approach is based. The computational findings are then presented in Section 3 (Results), where we separate the microchannel-based simulations from the realizations of cell movement in fibrous scaffolds. Finally, the results are discussed in Section 4 (Discussion).

2. Mathematical model

The microchannel device and the fibrous scaffold are modeled at the mesoscopic level using an extended cellular Potts model, a grid-based stochastic approach, which realistically preserves the identity of single cancer cells and describes their behavior and the interactions with the local microenvironment in energetic terms and constraints. The simulation domains are three-dimensional regular lattices $\Omega \subset \mathbb{R}^3$, formed by identical closed grid sites that, with an abuse of notation, will be identified by their center $\mathbf{x} \in \mathbb{R}^3$. Each grid site is labeled by an integer number, $\sigma(\mathbf{x}) \in \mathbb{N}$, that can be interpreted as a degenerate *spin* originally coming from statistical physics (Ising, 1925; Potts, 1952). The border of a lattice site $\mathbf{x}$ is identified as $\partial\mathbf{x}$, one of its neighbors by $\mathbf{x}'$, while its overall neighborhood by $\Omega'_{\mathbf{x}}$, i.e. $\Omega'_{\mathbf{x}} = \{\mathbf{x}' \in \Omega : \mathbf{x}' \text{ is a neighbor of } \mathbf{x}\}$. Subdomains of contiguous sites with identical spin form discrete objects Σ_σ (i.e., $\Sigma_{\overline{\sigma}} = \{\mathbf{x} \in \Omega : \sigma(\mathbf{x}) = \overline{\sigma}\}$) which have an associated type $\tau(\Sigma_\sigma)$.

The simulated cancer cells, called η, are defined as compartmentalized units, composed of two subregions which, in turn, are classical CPM object Σ_σ: the nucleus, a central cluster of type $\tau = N$, and the surrounding cytosol, of type $\tau = C$. Each cell