Relevance of cell-ECM interactions: From a biological perspective to the mathematical modeling

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Relevance of Cell-ECM Interactions: From a Biological Perspective to the Mathematical Modeling

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Abstract. Cell migration across fibre networks and micro-channel structures has been widely demonstrated to be strongly influenced by the interactions between moving individuals and the surrounding extracellular matrix as well as by the mechanical properties of cell nucleus. In this respect, our work will be devoted to describe several mathematical models, which deal either with cell adhesion mechanics or with suitable analysis of the role played in cell movement by nucleus stiffness. In particular, the presented approaches span from discrete individual-based methods to continuous models and provide useful insights into selected determinant underlying cell migration within two- and three-dimensional matrix environments.

The extracellular environment cells live and migrate in is mainly composed of an aqueous interstitial fluid and of an insoluble protein infrastructure, which is generally called extracellular matrix (and shortened as ECM). The ECM is an interlinked network formed by filamentary molecules secreted by many cell types, mainly fibroblasts. The specific composition of the ECM can considerably change, as it can involve several constituents like collagen, elastin, proteoglycan, fibronectin.

The ECM provides structural and biochemical support to the ensemble of cells. In particular, cell-matrix interactions are mediated by transmembrane adhesion molecules, among which integrins are the most important ones: their regulatory activity is fundamental for inside-out signaling exchanges between the cells and the external environment. Specifically, cell-ECM interactions regulate both migration-related processes, as it happens during wound healing and spread of metastasis, and proliferation-related mechanisms, critical in the case of tumor growth, tissue development, and organogenesis.

Entering in more details, cell migratory ability and migratory mode are significantly determined by chemical composition, mechanical properties, and topological microstructure of the surrounding extracellular matrix. In this respect, cell response to mechanical and biochemical cues coming from the ECM environment mainly depends from two mechanisms: *mechanosensing* and *mechanotransduction*. The former defines how cells sense the mechanical forces exerted on them by fibrous matrix proteins, i.e., either through membrane-bound ion channels, that open or close up under stress or shear to modulate the influx/outflux of ions, or through a direct transmission of stress and shear from the ECM to the actin cytoskeleton (via adhesion complexes and transmembrane adhesion protein, e.g., of the integrin family). The latter has to do with the effective cell response to mechanical cues. This

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can be done either directly, by the expression of genes in the nucleus when it is pulled by the actin cytoskeleton, or through the activation of several chemical pathways.

Further, specific matrix determinants can influence cell motion via the so-called *taxis* mechanisms: *haptotaxis*, i.e., cell preferential movement towards regions with higher concentrations of cellular adhesion sites or substrate-bound chemoattractants; *durotaxis*, i.e., cell migration towards the regions of the matrix with a higher rigidity; *chemotaxis* cell crawling in the direction of increasing gradients of a molecular substance, possibly diffusing in the extracellular space. Finally, cells directionally move along the fibers (or along fiber-derived microtracks) of strongly anisotropic substrates.

From a mathematical viewpoint, a proper description of the complex cell-ECM system can be very hard and strongly depends on the scale of interest. It is clear that what occurs at the cellular and subcellular level (i.e., the so-called *microscopic scale*) has a very relevant role but, in order to describe the behavior of entire tissues, in most cases it is preferable to work at the super-cellular level (i.e., the so-called *macroscopic scale*). In this respect, according to the specific phenomenon of interest, it is necessary to employ the most suitable theoretical approach. However, different mathematical methods, each of them dealing with a specific spatio-temporal scale, can be integrated and interfaced.

Taking these considerations into account, in [3] we proposed a model of cell-ECM adhesion that aims to embed the experimental results on the detachment force of single adhesion bonds in a multiphase approach developed in the framework of mixture theory. In order to do that, the *in vitro* microscopic information is upscaled to a macroscopic level to describe the dependence of some crucial terms appearing in the PDE model on subcellular/molecular dynamics involving, for instance, the density of bonds on the membrane, the probability of bond rupture and the rate of bond formation. In fact, adhesion phenomena characteristic of the molecular-level influence i) the interaction forces among the constituents of the mixtures and ii) the constitutive equation for the stress of the cellular components, both treated with a macroscopic description. Such a procedure allows to infer a proper relationship between cell-ECM interaction forces and cell velocity: in particular, the resulting cell dynamics presents a behavior well reproducing the main features of the epithelial-to-mesenchymal transition as well as the switch between the mesenchymal and the ameboid cell migratory mode. Further, to express the constitutive law for the stress of the cell components, we employ the concept of evolving natural configurations, which consists in decomposing in a multiplicative way the deformation gradient of the cellular constituent, i.e., distinguishing the contributions due to growth, to cell rearrangement and to elastic deformation. This allows the description of situations in which if the ensemble of cells is locally subject to a stress above a threshold, then in such points some bonds may break and some others may form, giving rise to an internal reorganization of the tissue that allows to relax exceedingly high stresses.

In [2] we proposed a set of models dealing with cell migratory ability and migratory mode in highly confined matrix structures. The underlying biological motivation is that the nucleus is a very voluminous and stiff subcellular organelle, thereby constituting a steric hindrance for cell migration in tight and dense ECM networks. In this respect, we first present a mathematical description of a cell entering a cylindrical channel composed of extracellular matrix. In particular, the cell nucleus is treated either as an elastic membrane surrounding a liquid droplet or as an incompressible elastic material with a Neo-Hookean constitutive equation. Two different representations for nuclear deformation are implemented as well (ellipsoidal vs. cigar-shaped). The cell-matrix adhesive dynamics, necessary for cell crawling within the cylindrical structure, are including by employing two possible representations of the force exerted by the integrin-like bonds (linear vs. constant). In this respect, we also take into account the overall extension of the adhesive area (boundedness assumption). An

energetic approach is then used to derive a necessary condition for which cells enter matrix structure: the resulting outcomes highlight the importance of the interplay between mechanical deformability of the nucleus and cell capability to establish adhesive bonds with the matrix components.

With an analogous biological problem in mind, Refs. [4–6] used a series of extended cellular Potts models (CPMs) able to qualitatively and quantitatively describe cell migration efficiencies and phenotypes both on two-dimensional substrates and within three-dimensional matrices, close to experimental evidence. As distinct features of these approaches, cells are modeled as compartmentalized discrete objects, differentiated in the nucleus and in the cytosolic region, while the extracellular matrix is composed of fibrous meshes, soluble or insoluble matrix structures and homogeneous fluid. Further, an actual directional cell shape-dependent movement is explicitly driven either by the evolution of a cell polarity vector or by a mean over the past velocities. Our models provide a strong correlation between the directionality of migration and the topological extracellular matrix distribution and a biphasic dependence of migration on the matrix structure, density, adhesion, and stiffness. In particular, we find that cell motile phenotype and velocity in open spaces (i.e., 2D flat surfaces or large channels) is 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 nucleus, respectively. Cell motion within subnuclear environments can be also achieved by the activity of cell-derived proteolysis, which leads to secondary track expansions for cell migration by degrading the surrounding ECM structure. Finally, we characterize two migratory modes: a stepwise way, characterized by fluctuations in cell length, within channels smaller than the nucleus dimension and a smooth sliding (i.e., maintaining constant cell length) behavior within channels larger than the nucleus size.

The results obtained by the above-described models on the role played in cell migration both by nucleus elasticity and by MMP-activity are eventually included in a macroscopic mixture theory-based approach [1], reproducing tumor mass invasion of a host tissue. In particular, the extracellular environment is heterogeneous, i.e., characterized by the presence of ECM layers of different thicknesses (pore sizes) that can be either invaded or represent an impenetrable barrier for the malignant mass, according to the biophysical and biomechanical properties of the tumor cells.

Interesting perspective for future works can involve a comparison of cell migratory dynamics resulting by modeling chemotaxis either as a classical external force or as an internal active reaction of the cell, which pulls on the ECM to move towards a source of the molecular diffusive factor.

From experimental observations, it turns also out that selected interactions between cells and ECM are fundamental in governing cell fate, e.g., cell survival, migration, growth, and differentiation. Hence, understanding such mechanisms is an increasingly fundamental issue in tissue engineering. In particular, the analysis of how cells sense and react to the mechanical properties of the surrounding environment is very important for the development of nature-inspired bioengineering mechanosensitive devices and tactile sensors and micro-sensors, e.g., of pressure and shear. However, in spite of the growing interest in this field, very little is done from the mathematical point of view.

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