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Hybrid modelling of mechanical cues in cell migration

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Abstract. Many studies stress the crucial importance of the mechanical component in angiogenesis, but still very few models really integrate mechanics. We propose to investigate the importance of mechanical cues for cell migration in this context with a new hybrid continuous-discrete model that describes the individual migration of contracting cells on an elastic matrix of fibres. The matrix is described as a continuum substrate whereas the cells are described as discrete elements.

1 Introduction

Angiogenesis and vasculogenesis models were historically built on different hypotheses reflecting biological observations, centred on molecular effects for angiogenesis, where growth factors appear to lead the process, and centred on mechanical effects for vasculogenesis where cell-generated tension forces in the matrix appear as the organizing principle [5, 8]. Our primary aim was to propose a more complete hybrid model of angiogenesis incorporating mechanical effects to be able to describe and investigate the anastomosis process [10]. This process, which is hypothesized to be mechanics-dependent, remains under-looked although it is known to be crucial for the formation of functional vascular networks [1]. The model accounts for mechanical interactions between the cells and the matrix substrate by integrating *i)* the cell ability to generate forces on the deformable matrix and *ii)* the corresponding matrix deformation dependent on its mechanical properties (such as stiffness). The model also integrate the alterations and evolution of those properties through the proteolytic action of the cells. The mechanisms implemented are fundamental and can be generalized to other contexts of cell-matrix interactions [2, 7] that we illustrate here with a few classical examples highlighting the sensitivity to environmental cues such as sharp rigidity transitions, stiffness gradients and strains.

2 Model and results

2.1 Hybrid model for tumour-induced angiogenesis

Cell migration. In tumour-induced angiogenesis, cells perform directed migration in response to growth factors with concentration $c(x, y, t)$ (a process called *chemotaxis*) and to the density $f(x, y, t)$ of matrix fibres (*haptotaxis*). The non-directed counterpart of migration is classically modelled by diffusion with constant coefficient D. However the deformations of the matrix induced by cells traction

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as they migrate generate strains that biased the direction of cell movement [4, 6]. The coefficient D is therefore replaced by $D(\boldsymbol{\varepsilon})$ which reflects the dependency on the local strain expressed by the tensor $\boldsymbol{\varepsilon}$. The resulting continuum equation for cell migration thus writes:

$$\frac{\partial n}{\partial t} = \underbrace{\nabla \cdot [\nabla \cdot (\boldsymbol{D}(\boldsymbol{\varepsilon})\, n)]}_{\text{strain-biased diffusion}} - \underbrace{\nabla \cdot (\chi(c)\, n \nabla c)}_{\text{chemotaxis}} - \underbrace{\rho \nabla \cdot (n \nabla f)}_{\text{haptotaxis}}, \tag{1}$$

where the function $\chi(c)$ and the parameter ρ describe the cell sensitivity to growth factors and matrix fibres, respectively. Our discrete model of migration for each single cell $n_{i,j}$ is obtained as the discretization of equation (1) [9], which generically reads:

$$n_{i,j}^{t+\Delta t} = \sum_{\ell,m \in \{-1,0,1\}} P_{k(i+\ell,j+m)}\; n_{i+\ell,j+m}^{t} \tag{2}$$

where the 9 coefficients P_k are migration probabilities in the 8 possible directions on a 2D grid (diagonals included) with P_0 being the immobility probability. These probabilities are weighted by the molecular (c and f) and mechanical ($\boldsymbol{\varepsilon}$) conditions within the cell neighbourhood and also allow for modelling *persistence* in cell migration.

Matrix mechanics. The matrix substrate is described as an elastic medium which rigidity (E) is proportional to the density of matrix fibres (f). It can be degraded by enzymes produced by the cells. We assume that the traction force ($\mathbf{F}_{\mathbf{traction}}$) exerted by each cell is oriented in its direction of movement. The balance of forces on the matrix is given by the equation:

$$\nabla \cdot \boldsymbol{\sigma}_{\text{linear elasticity}} = \mathbf{F}_{\text{traction}}\,, \tag{3}$$

where $\boldsymbol{\sigma}$ is the matrix stress tensor. This equation allows us to calculate the strains $\boldsymbol{\varepsilon}$ in the matrix.

Equations (2-3) form our hybrid model coupling cell migration and the cell deformable environment (figures 1.A), which we use to simulate tumour-induced angiogenesis and emphasize the importance of the mechanical coupling [10]. The comparison of simulations realized with and without the integration of the mechanical component (figures 1.B and 1.C) shows that *i)* the vessels are more rectilinear, *ii)* the density of the vascular network is lower and *iii)* matrix degradation is reduced when mechanics is included. The mechanical component thus tends to act as an organizing force.

2.2 Simulations of cell migration in different mechanical environments

In order to investigate the importance of the various mechanical cues in the matrix (degradation, change of rigidity, strains), we designed a range of cell environments to illustrate various effects on cell trajectories. For example *durotaxis* is a well-known phenomena where cells exhibit a preference for stiffer substrate. We tested this effect in the context of angiogenesis where the cells are able to degrade the matrix fibres releasing degrading enzymes with concentration $m(x, y, t)$ and thus to modify the frontier between a rigid and a soft region. Figures 2.A-D shows that cells can easily cross the soft-rigid boundary but the rigid-soft one acts as an impermeable frontier that can only be crossed by means of matrix degradation. Figures 2.B-E shows the importance of rigidity gradients (matrix degradation has been removed) in an environment with heterogeneous rigidity conditions. Once again, the soft-rigid boundary is easier to cross and movement along rigidity gradients is favoured. Finally in figures 2.C-F the influence of matrix deformation generated by a few static cells on the trajectory of a single migrating cell (released in the centre of the domain) is investigated. The resulting pattern obtained by superimposition of 100 trajectories shows a confinement effect by the matrix deformations.

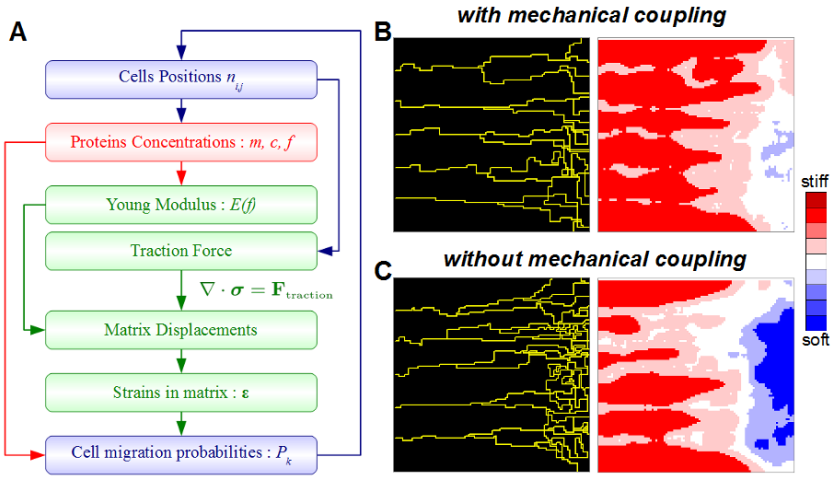

Figure 1. A. Hybrid model implementation coupling molecular (red box) and mechanical effects (green boxes); B. Simulation of angiogenesis including mechanical effects; C. Simulation of angiogenesis without mechanical effect. In B and C, left pictures show the vascular network and right pictures show the matrix degradation, *i.e.* the alteration of its rigidity.

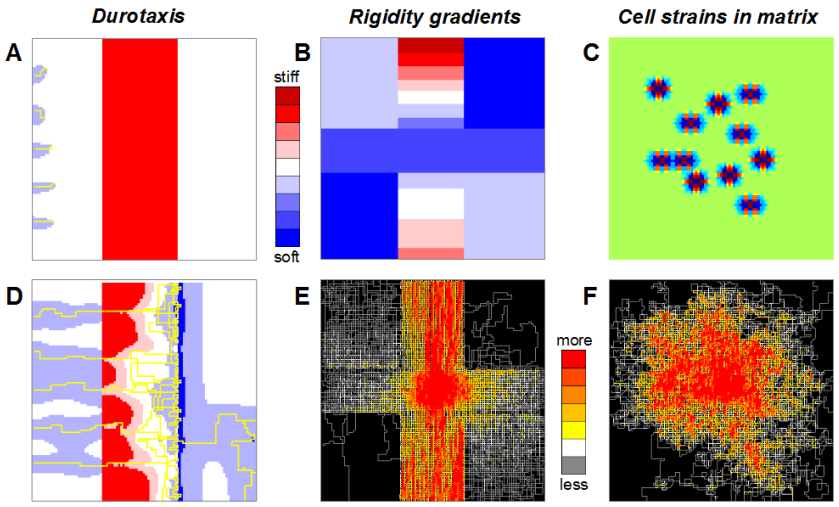

Figure 2. Different mechanical environments (top) : A. a rigid strip (in red) is inserted in a soft environment (in white); B. the environment is divided in zones with different rigidity conditions including two zones with rigidity gradients (a stip and a smooth gradient); C. the environment is deformed by static cells (ε_{xx} strain component). Simulations of cell migration in each environment (bottom) : D. case simulating angiogenesis with 5 initial sprouts growing in response to a chemotactic gradient of growth factors produced on the right hand side of the domain presented in A; E and F represent superimposition of 100 individual cell trajectories simulated in cases B and C respectively.

3 Discussion

Cell behaviour in general (*e.g.*, proliferation, death, differentiation) and migration in particular, are known to be influenced in many ways by the physical and mechanical properties of the cell environment. The matrix topology and mechanical properties affect migration speed, directionality and nature of cell movements (*i.e.* mesenchymal *versus* amoeboid) *via* various mechanisms [3] such as contact guidance (directed movement in response to fibre alignment) and mechanotaxis (directed movement in response to mechanical cues such as stiffness or adhesion sites availability). In return, cell activity may alter temporarily or permanently its environment by means of mechanical forces or biochemical activity (*e.g.*, proteolysis), making the cell-matrix couple a complex system whose interactions and emerging behaviour are often poorly understood. A good understanding of these interactions is highly required as they determine the fate of cells in many physiological and pathological phenomena. All kinds of cell-matrix interactions can be integrated in our modelling framework that can therefore be used as a tool to investigate a broad variety of effects occurring in many different contexts.

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