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ORIGINAL PAPER

The emergence of extracellular matrix mechanics and cell traction forces as important regulators of cellular self-organization

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Abstract Physical cues play a fundamental role in a wide range of biological processes, such as embryogenesis, wound healing, tumour invasion and connective tissue morphogenesis. Although it is well known that during these processes, cells continuously interact with the local extracellular matrix (ECM) through cell traction forces, the role of these mechanical interactions on large scale cellular and matrix organization remains largely unknown. In this study, we use a simple theoretical model to investigate cellular and matrix organization as a result of mechanical feedback signals between cells and the surrounding ECM. The model includes bi-directional coupling through cellular traction forces to deform the ECM and through matrix deformation to trigger cellular migration. In addition, we incorporate the mechanical contribution of matrix fibres and their reorganization by the cells. We show that a group of contractile cells will self-polarize at a large scale, even in homogeneous environments. In addition, our simulations mimic the experimentally observed alignment of cells in the direction of maximum stiffness and the building up of tension as a consequence of cell and fibre reorganization. Moreover, we demonstrate that cellular organization is tightly linked to the mechanical feedback loop between cells and matrix. Cells with a preference for stiff environments have a tendency to form chains, while cells with a tendency for soft environments tend to form clusters. The model presented here illustrates the potential of simple physical cues and their impact on cellular self-organization. It can be used in applications where cell-matrix interactions play a key role, such as in the design of tissue engineering scaffolds and to gain a basic understanding of pattern formation in organogenesis or tissue regeneration.

Keywords Cell traction forces · Cell migration · Cellular organization · Mechanobiology · Fibre remodelling · Biological cellular automata

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1 Introduction

Cells, the active component of tissues, are continuously interacting with their extracellular matrix (ECM) to maintain, remodel, regenerate or in some cases also degenerate tissue function and properties. Among others, mechanical interactions are fundamental in many physiological and pathological situations such as embryogenesis, wound healing, tumour invasion and connective tissue morphogenesis (Stopak and Harris 1982; Vogel and Sheetz 2006; Hutson and Ma 2008; Wozniak and Chen 2009; Levayer and Lecuit 2012). For example, benign to malignant phenotype transformation has been shown to be strongly influenced by the microstructure and mechanical properties of the surrounding ECM (Paszek et al. 2005; Ingber 2008). Hence, understanding of these

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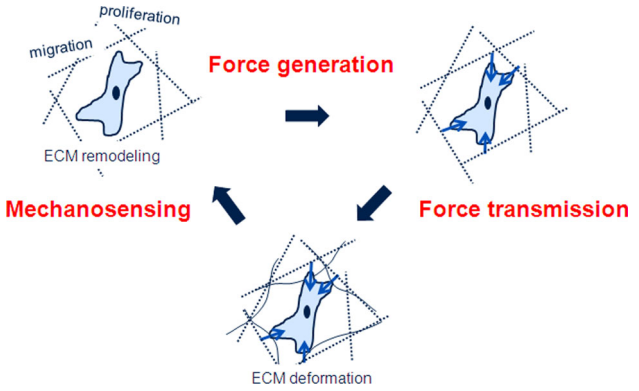

Fig. 1 Schematic representation of the mechanical feedback loop in the cellular ability to sense and alter the mechanical environment in its surroundings. Cells exert traction forces on the ECM, which allow them to probe the local mechanical conditions. Mechanical signals are then translated into a cascade of biochemical signals that regulate cellular activity. Cellular processes such as migration, proliferation and/or matrix remodelling result in a change in the mechanical environment

interactions is important for the development of new biomaterials and clinical diagnostics.

It is well known that cells can sense mechanical stimuli provided by the surrounding matrix and that these stimuli influence cellular function, such as gene expression (Farge 2003), contraction (Discher et al. 2005; Mitrossilis et al. 2010), proliferation (Hadjipanayi et al. 2009), migration (Lo et al. 2000) and differentiation (Engler et al. 2006). It has also been shown that many cell types (fibroblasts, smooth muscle cells, neurons, stem cells, etc.) can exert large traction forces and deform a substrate over distances larger than hundreds of cell diameters (Harris et al. 1981). Additionally, these forces play a key role in the remodelling of the ECM (Bell et al. 1979; Harris et al. 1981; Stopak and Harris 1982; Grinnell and Lamke 1984; Ehrlich and Rajaratnam 1990; Huang et al. 1993). Cellular probing of the environment, active cellular response and alterations of the ECM through active remodelling, collectively result in a complex coupling between extracellular matrix deformation and cellular activity (Fig. 1).

This vibrant cell-matrix crosstalk makes identifying key mechanisms behind experimental observations a major challenge. It is well known that the density and distribution of cells, the mechanical properties of the ECM and the geometry of the matrix all have an influence on traction force dynamics (Wagoner Johnson and Brendan 2011; Marinkovic et al. 2012). From a cellular perspective, it is not the net cell traction force alone that appears essential, it is the balance between the cell traction forces on the one side and the resistance of the extracellular matrix on the other side that causes cellular deformations and—as a consequence—alters cellular activity (Riveline et al. 2001; Galbraith et al. 2002). Since the propagation of elastic forces within the tissue goes far beyond the scale of single cells and can reach distances of centimetres, the local stress field sensed by a single cell always reflects a more global mechanical characteristic of the ECM, which includes but is not limited to its shape, its structural alignment and its overall stiffness as a composition of active cells and passive matrix.

Understanding complex processes can benefit from using simple approaches. Computer modelling allows us to segment large complex systems into small simplified problems that can be solved, e.g. by using the fundamental laws of physics. To investigate the mechanical interaction between cells and the ECM, various modelling approaches have been proposed that can be classified into continuum and discrete. Continuum approaches normally focus on cell population dynamics. They make use of differential equations to monitor cells in terms of a cell density variable that changes in space over time. In these models, macroscopic changes in the ECM are then represented through average fibre orientations or homogenized mechanical properties (Murray et al. 1983; Oster et al. 1983; Murray and Oster 1984; Barocas and Tranquillo 1997a,b). Only a few models account for individual cell-level mechanical forces and their interaction with the local ECM. One of the major challenges in modelling cell-matrix interactions is the combination of small scales required to represent highly heterogeneous cellular environments, and large scales required to represent long-range force transmission within the ECM. Dokukina et al. (Dokukina and Gracheva 2010) and Borau et al. (Borau et al. 2011) developed cell-level based models to simulate individual cell migration. They simulated the cell's cytoskeleton to investigate how the internal cellular function would contribute to the experimentally observed substrate-rigidity sensing. However, their models neither include the mechanical response of the ECM, nor the interactions amongst individual cells. Bischofs and Schwarz (Bischofs and Schwarz 2006) developed a computer model of the behaviour of single cells on soft substrates. Using extensive Monte Carlo simulations, they predicted non-trivial structure formation of a collection of cells, however, did not investigate the role of matrix fibres and fibre remodelling on the local and collective organization of the cells. Bauer et al. (Bauer and Jackson 2009) developed a cellular Potts model to investigate the influence of extracellular topography on cellular organization during angiogenesis. Although, their model explicitly represented a fibrous matrix, their matrix was static and therefore unable to reorganize as a result of cell traction forces. Schlüter et al. (Schluter et al. 2012) investigated the influence of extracellular fibre orientation on cell motility. In their model, fibres were allowed to reoriented; however, they were not deformable, consisting of rigid tubes. Dallon et al. (Dallon et al. 1999) and McDougall et al. (McDougall et al. 2006) developed hybrid discrete-continuum models, however, their theories did not account for mechanical factors involved in tissue remodelling.

Despite intense modelling efforts over the past two decades, there still remains a lack of understanding about how the mechanical feedback mechanism between cells and their surrounding extracellular matrix influences cellular and matrix organization at large scales. Here, we present a simplified theoretical model to investigate cell and matrix organization as a result of the mechanical interaction between the cells and their ECM. Since the biological processes involved in cellular traction and matrix remodelling are complex and not yet fully understood, we concentrate on a relatively simple model to study cellular organization. Our objective is to unravel the complex physical interplay between active cell contraction, passive matrix stiffness and mechanically motivated matrix remodelling.

2 Materials and methods

2.1 Model formulation

In this work, we focus on the mechanical interactions between cells and ECM. Our aim is to compute large-scale cellular organization as a result of different physical feedback mechanisms between single cells and their surrounding matrix. For this, we adopt an hybrid approach where finite element and agent based techniques are combined to simulate cell and tissue level scale processes (Checa and Prendergast 2009). With this approach, we are able to handle complex spatial heterogeneity in cell behaviour and long-range extracellular response. For simplicity, we neglect chemical effects or other signals. Our model consists of two components: cells and ECM; and three main processes: cellular migration, matrix deformation and ECM fibre remodelling.

2.1.1 Modelling of cell migration

Our model consists of a coupled mechano-biological approach using finite element analysis to determine the mechanical behaviour of the ECM coupled to a cellular automata model to determine the biological activity of the embedded cells (Fig. 2a). The interaction between cells and substrate is modelled as an iterative bi-directional process where cells change their position and orientation based on the local deformation of the ECM while, at the same time, they exert traction forces to change the arrangement of the ECM (Fig. 2a). Inspired by the work of Schwarz et al. (Schwarz and Safran 2002) and Petroll et al. (Petroll 2007), we represent cells as active force dipoles. As a cell occupies a position, it exerts two opposing local forces on the extracellular matrix (Fig. 2a). The simulation starts with a number of randomly oriented cells, either horizontal or vertical, seeded on the matrix at random locations. Then, in each iteration, a percentage of the cells (80 % in this study) migrates randomly to one of its free neighbouring positions (maximum eight possibilities) where it adopts a preferential direction (horizontal or vertical) in a completely random manner.

In this new configuration, the cell probes its mechanical environment by applying traction forces (Fig. 2a). Thereafter, ECM deformation induced by the cellular traction forces is determined using finite element techniques (Fig. 2a). Finally, based on the local ECM deformation each cell "measures", it either adopts the new configuration (position and orientation) or not: e.g. a cell with a tendency for stiff environments would move to the new location if the deformation of the ECM in that location is smaller than the deformation of the matrix in the previous location. If all positions surrounding a migrating cell are already occupied by other cells, the cell does not migrate.

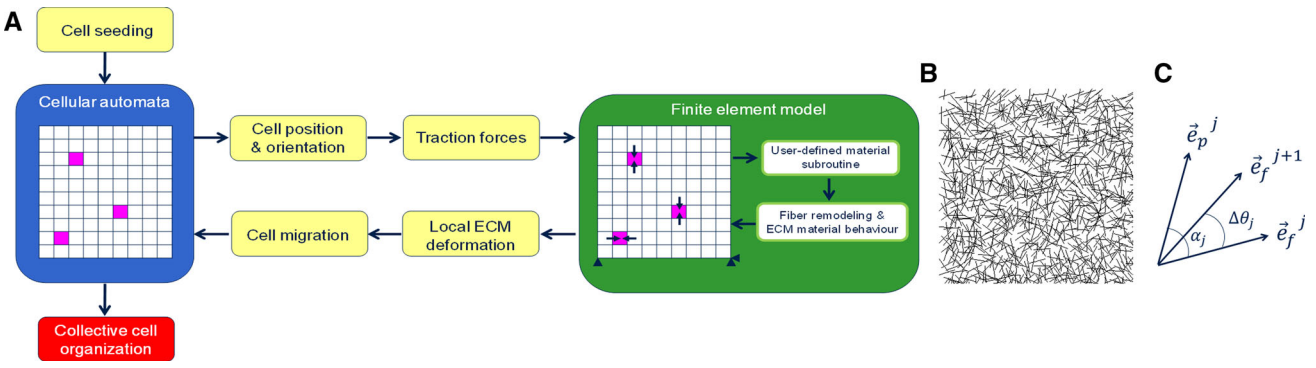

Fig. 2 **a** Schematic representation of the mechano-biological model to investigate the mechanical interactions between cells and ECM. The model consists of a finite element model to determine ECM deformation and a cellular automata model to simulate biological cellular activity. **b** Schematic representation of fibres within the ECM. Fibre direction is specified for each individual element. **c** Schematic representation of fibre reorientation. For each element, at each iteration (j), the fibre ($\boldsymbol{e}_f^j$) is rotated over an angle ($\Delta\theta_j$) towards the principal stress direction ($\boldsymbol{e}_p^j$), resulting in the new fibre direction ($\boldsymbol{e}_f^{j+1}$). α_j: angle between the current fibre direction and the principal stress direction

2.1.2 Modelling of extracellular matrix

Inspired by experimental studies of cell-populated collagen sheets (Takakuda and Miyairi 1996), we consider a piece of ECM where one of the dimensions is much smaller than the other two. In this case, the deformation of the ECM can be approximated through plane stress conditions. Fibres within the ECM form complex networks that introduce strong anisotropic and highly nonlinear attributes into the mechanical response of the matrix. To account for this anisotropy, we characterize the matrix as a fibre-reinforced material that we model using a hyperelastic constitutive formulation.

Towards this aim, we introduce the deformation gradient $\mathbf{F}$, which maps material points $\mathbf{X}$ from the reference configuration to points $\mathbf{x}$ in the current, deformed configuration.

$$\mathbf{F} = \frac{\partial \mathbf{x}}{\partial \mathbf{X}} \tag{1}$$

Considering a right-handed local orthonormal coordinate system with unit vectors $\mathbf{e}_1$ and $\mathbf{e}_2$ located within the sheet and $\mathbf{e}_3$ perpendicular to it, the deformation gradient can be written as follows:

$$[\mathbf{F}] = \begin{bmatrix} F_{11} & F_{12} & 0 \\ F_{21} & F_{22} & 0 \\ 0 & 0 & F_{33} \end{bmatrix} \tag{2}$$

To quantify matrix deformation, we introduce the right Cauchy-Green deformation tensor $\mathbf{C}$. Physically, this tensor takes the interpretation of the square of local changes in distances between particles upon deformation.

$$\mathbf{C} = \mathbf{F}^{\mathrm{T}}\mathbf{F} \tag{3}$$

In our plane stress case, $C_{i3} = 0$ for $i \neq 3$.
We now impose the incompressibility condition, $J = \det(\mathbf{F}) = \sqrt{\det(\mathbf{C})} = 1$, which allows us to determine the out-of-plane component of the right Cauchy-Green deformation tensor in explicit form.

$$C_{33} = \frac{1}{C_{11}C_{22} - C_{12}^2} \tag{4}$$

For simplicity, we assume that the ECM is reinforced by a single family of fibres. Therefore, the stress of a material point in the matrix does not only depend on the deformation gradient $\mathbf{F}$ but also on the local fibre direction. We introduce a unit vector $\mathbf{a}_0$ which represents the fibre direction at a point $\mathbf{X}$ in the reference configuration, which allows to define the structural tensor $\mathbf{N}$.

$$\mathbf{N} = \mathbf{a}_0 \otimes \mathbf{a}_0 \tag{5}$$

We adopt a strain energy function of Holzapfel type

$$\psi = c_0(I_1 - 3) + \frac{k_1}{2k_2}\left(\exp[k_2(I_4 - 1)^2]\right) + p(J - 1) \tag{6}$$

where I_1 is the first invariant related to isotropic elasticity and I_4 is the square of the stretch in the fibre direction.

$$I_4 = \mathbf{a}_0 \cdot \mathbf{C}\mathbf{a}_0 = \mathbf{C} : \mathbf{N} \tag{7}$$

The second Piola–Kirchhoff stress tensor $\mathbf{S}$ is then given as twice the derivative of the free energy (6) with respect to $\mathbf{C}$.

$$\mathbf{S} = 2\frac{\partial \psi}{\partial \mathbf{C}} \tag{8}$$

With the simplified notation $\psi_i = \partial\psi/\partial I_i$, we can express the second Piola–Kirchhoff stress as follows,

$$\mathbf{S} = 2\psi_1\mathbf{I} + 2\psi_4\mathbf{N} + p\mathbf{C}^{-1} \tag{9}$$

and obtain the Cauchy stress tensor $\boldsymbol{\sigma} = \mathbf{F}\mathbf{S}\mathbf{F}^{\mathrm{T}}$ through the push forward of $\mathbf{S}$ to the current configuration.
For the plane stress case considered here, the out-of-plane stress vanishes such that $S_{33} = 0$,

$$2\psi_1 + 2\psi_4 0 + pC_{33}^{-1} = 0 \tag{10}$$

which we can rephrase to determine an explicit representation of the pressure.

$$p = -2\psi_1 C_{33} = \frac{-2\psi_1}{C_{11}C_{22} - C_{12}C_{22}} \tag{11}$$

We then introduce the fourth-order tangent operator $\mathbb{C}$, which correlates incremental changes in stress $\mathbf{S}$ to incremental changes in deformation $\mathbf{C}$

$$\begin{aligned} \mathbb{C} &= 2\frac{\partial \mathbf{S}}{\partial \mathbf{C}} = 2\frac{\partial(2\psi_1\mathbf{I} + 2\psi_4\mathbf{N} + p\mathbf{C}^{-1})}{\partial \mathbf{C}} \\ &= 4\psi_{44}\mathbf{N} \otimes \mathbf{N} + 2\mathbf{C}^{-1} \otimes \frac{\partial p}{\partial \mathbf{C}} + 2p\frac{\partial \mathbf{C}^{-1}}{\partial \mathbf{C}} \end{aligned} \tag{12}$$

The tangent operator in the spatial configuration is defined through the following push forward operation.

$$\mathrm{c} = \frac{1}{J}\left[\mathbf{F} \overline{\otimes} \mathbf{F}\right] : \mathbb{C} : \left[\mathbf{F}^T \overline{\otimes} \mathbf{F}^T\right] \tag{13}$$

where $\left[\mathbf{F} \overline{\otimes} \mathbf{F}\right]_{ijIJ} = F_{iI}F_{jJ}$ and $\left[\mathbf{F}^T \overline{\otimes} \mathbf{F}^T\right]_{KLkl} = F_{Kk}F_{Ll}$.
The material parameters (Eq. 6) were implemented as follows: $c_0 = 10$ kPa, $k_1 = 10$ kPa and $k_2 = 1$ (Holzapfel et al. 2002; Zulliger et al. 2004).

2.1.3 Modelling of fibre remodelling

As described in Sect. 2.1.1, when a cell occupies a position, it exerts two opposing local forces on the ECM (Fig. 2a) inducing a deformation. The local deformation of the matrix at each location depends then on the forces applied by the surrounding cells as well as on the boundary conditions. Moreover, cells influence the ECM by changing its fibre orientation (Harris et al. 1981). Since each cell can contribute to the rearrangement of fibres, the homogenized effect of fibre remodelling can be characterized using the local deformation

of the matrix. The direction of principal stress in the extracellular matrix is an indicator of the main direction of cellular traction forces. Hence, we assumed that individual fibres reorient towards the direction of principal stress (Fig. 2c). We model fibre reorientation by a first-order rate equation,

$$\alpha_t = \alpha_{t-1} + c \cdot (\alpha_{t-1} - \theta_p) \tag{14}$$

where α is the fibre angle in the current configuration, θ_p is the angle of the principal stress direction and t and $t-1$ denote the current and previous time increment. A gradual reorientation is accounted for through the parameter c, a fraction of the difference between the current fibre angle and the target fibre angle of the principal stress direction. This parameter essentially accounts for the delay in the remodelling process. In this study, its value was set to $c = 0.5$.

2.2 Numerical implementation

Finite element analysis was used to determine ECM deformation. The commercial finite element software Abaqus/Standard was used, where the constitutive model of the ECM (Eqs. 1–13) and the remodelling of the fibres (Eq. 14) were implemented as a user-defined material subroutine UMAT. To model the cellular behaviour, we implemented an additional external user-defined subroutine in C++.
The numerical algorithm includes the following steps:

1. Seed cells onto the ECM
2. Determine ECM deformation and fibre remodelling caused by cell traction forces
3. Migrate cells randomly to a free neighbouring location
4. Calculate matrix contraction in the temporal configuration
5. Determine difference in matrix deformation between current and temporal configurations as driving force for cell migration

We considered a thin ECM consisting of 100*100 quadrilateral elements (Fig. 2) of size $5 \times 5\mu$ m. Cells are seeded such that they occupy three neighbouring nodes. For simplicity, cell orientation was limited to vertical and horizontal directions. Cell traction forces are represented as a pair of equal opposite nodal forces between the two extreme neighbouring nodes. Traction force magnitude was kept constant throughout all simulations, with a value of 10 nN (Freyman et al. 2001; Jeon et al. 2011). All simulations were run for 1,000 iterations unless otherwise stated.
For each of the simulations, we determined the reaction force at one of the clamped ends of the matrix. This force was calculated as the mean of the reaction force measured in the nodes at that location (where the boundary condition was applied).

In addition, we defined two parameters to quantify the degree of cell and fibre alignment. The cell order parameter was defined as:

$$p_{cell} = \left| \frac{Vert - Hor}{N} \right| \tag{15}$$

where *Vert* and *Hor* are the sum of vertical and horizontal dipoles, respectively, and N is the total number of seeded cells.
The fibre order parameter was defined as (Jungbauer et al. 2008):

$$p_{fibre} = \left| \sum \cos(2\Theta) \right| \tag{16}$$

where θ is the fibre angle and the sum is over all the fibres contained in the model.

2.2.1 Homogeneous and inhomogeneous boundary conditions

The stiffness of the matrix at each point depends on the boundary conditions and the direction of the fibres at the point location. Therefore, the mechanical conditions surrounding the extracellular matrix influence the mechanical behaviour of the matrix and, in turn, the interaction between the cells and the substrate. Inspired on the experiments by Takakuda and Miyairi (Takakuda and Miyairi 1996), we investigated the effect of two distinct boundary conditions on cell traction force, ECM deformation and cellular self-organization: (1) homogeneous boundary conditions with all four matrix sides clamped and (2) inhomogeneous boundary conditions with two opposing matrix edges free and two clamped.

2.2.2 Mechanical signals controlling cellular organization

Motivated by recent experiments (Pelham and Wang 1997; Lo et al. 2000; Trichet et al. 2012) and computational approaches (Bischofs and Schwarz 2003), we assumed that an adherent cell positions and orients itself in such a way that it finds maximal effective stiffness in its environment. In each time step, a cell "decides" to move to a new location only if its traction forces induce ECM deformations that are lower than in the cell's previous position. In addition, with the aim of identifying possible mechanisms for these experimental observations, we also tested the opposing hypothesis of cells having a preference for softer environments.

2.2.3 Isotropic and anisotropic matrices (fibre orientation)

Fibre orientation plays a key role in the mechanical behaviour of the ECM (Gilbert et al. 2008). Here, we investigated the effect of initial fibre orientation on the dynamics of cellular organization by implementing two initial configurations for

the orientation of the fibres: (1) a random orientation to represent an isotropic matrix, and (2) a fully aligned orientation to represent an anisotropic matrix. Moreover, we investigated the impact of fibre remodelling on cell-matrix interaction. We probed this effect by turning off the fibre remodelling process in our model.

2.2.4 Effect of cell density in cellular self-organization

Local traction forces applied by a single cell are transmitted globally throughout the matrix and influence the mechanical environment of neighbouring cells. We investigated the effect of cell density on the interaction between the cells, matrix remodelling and cellular organization. We considered a low, medium and high cell density represented through 100, 250 and 500 cells, respectively (ECM size: 0.25 mm^2). In addition, for these cell densities, we considered different initial orientations of the cells: (1) random, (2) all vertically aligned, (3) all horizontally aligned and (4) 90/10 % aligned vertically/horizontally.

3 Results

First, results for a piece of ECM under homogeneous boundary conditions (four sides clamped) are shown. In this case, 500 cells were initially seeded in the matrix at random locations and with random orientations. Over time, cells moved and oriented with an affinity for stiff environments, while remodelling the matrix fibres. The mechanical feedback between individual cells and their ECM through cell traction forces resulted in spontaneous cellular self-organization at larger scales. Even under these conditions of an isotropic matrix under homogeneous boundary conditions (Fig. 3), cells organized themselves as a result of the mechanical interaction between cell traction and matrix resistance. A tendency of the cells for stiff environments turned a group of randomly distributed and oriented cells (Fig. 3a) into an organized cellular system where cells tended to form long chains (Fig. 3b). Under these conditions, groups of cells oriented both in vertical and horizontal directions (Fig. 3b). Remodelling of the matrix fibres following the direction of maximum principal stress in the matrix resulted in the formation of fibre bundles with a specific orientation (Fig. 3d), which was locally determined by the local organization of the cells.

3.1 Influence of inhomogeneous boundary conditions

Mechanical anisotropy as a result of inhomogeneous boundary conditions, i.e. clamping only two opposite sides of the matrix, resulted in a strong alteration in cellular and matrix organization (Fig. 4). In this case, cells formed long

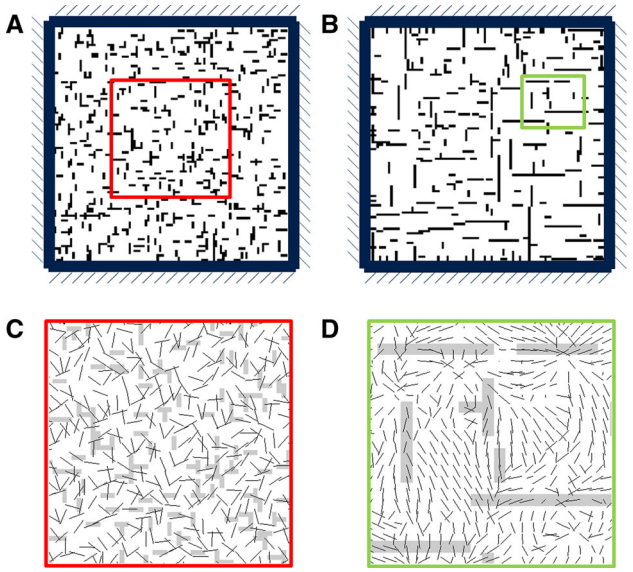

Fig. 3 **a** Representation of the initial organization of cell dipoles randomly seeded in a piece of matrix under homogeneous boundary conditions; i.e. all four edges clamped. **b** Final (after 1,000 iterations) organization of the cells with a tendency for stiff environments. **c** Initial orientation of fibres (*black lines*) and cells (*grey*) locally within the selected region (*red square*) in the matrix **d** Organization of the fibres in bundles (*black lines*) as a result of fibre remodelling

chains along the direction joining the two clamped boundaries (Fig. 4a). As a result, the number of cells oriented along the direction joining the two clamped boundaries increased over time, while the number of cells oriented perpendicular to the direction joining the clamped boundaries decreased (Fig. 4c). As in the case of homogeneous boundary conditions, fibre remodelling led to the formation of fibre bundles with a well-defined orientation (Fig. 4b). However, in this case, most of the fibres aligned in the direction joining the two clamped ends (Fig. 4b). Thus, a clear influence of the cells and fibres on each other's position could be seen (Fig. 4b). The effect of inhomogeneous boundary conditions was also evident in the magnitude of the reaction force measured at one of the clamped edges (Fig. 4d). While under homogeneous boundary conditions, the reaction force remained constant in time, under inhomogeneous boundary conditions, the reaction force increased drastically and reached a plateau at a much higher force magnitude than under homogeneous boundary conditions (Fig. 4d). Although under both boundary conditions the degree of cellular alignment increased over time, a much higher alignment of the cells was observed for anisotropic boundary conditions (Fig. 4e).

3.2 Preference of cells for soft or stiff environments

Interestingly, when the mechanical feedback loop for the cells was set to move towards soft environments, cells displayed an entirely different mechanism of self-organization

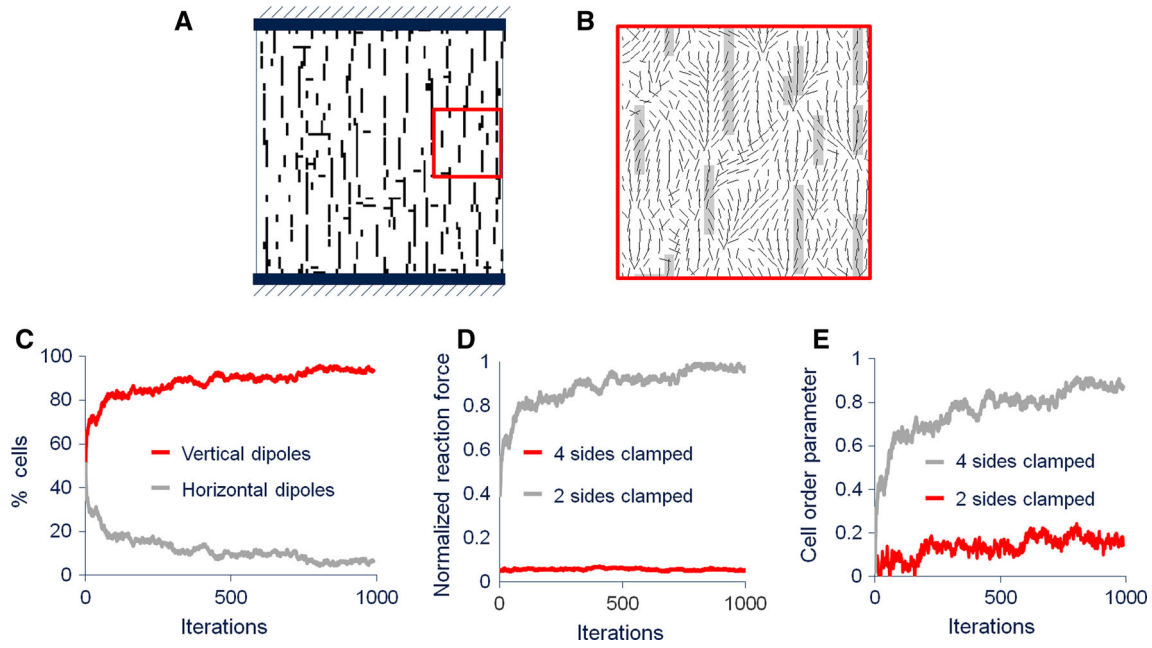

Fig. 4 **a** Cell organization in a piece of extracellular matrix under inhomogeneous boundary conditions where cells have a tendency for stiff environments. **b** Local fibre organization as a result of fibre remodelling (*black lines*). Fibres tend to form bundles with a defined direction which appears to be influenced by the position of neighbouring cells (*grey*). **c** Changes in the number of dipoles oriented in the vertical and horizontal directions over time. Horizontal dipoles are oriented in the direction joining the two free boundaries, while vertical dipoles are oriented in the direction joining the clamped boundaries. **d** Reaction forced measured at one of the clamped boundaries over time for a matrix under homogeneous (four sides clamped) and inhomogeneous boundary conditions (two sides clamped). **e** Cell order parameter over time for a matrix under homogeneous (four sides clamped) and inhomogeneous boundary conditions (two sides clamped)

with a tendency to form clusters instead of a long-range alignment (Fig. 5a). Cell clusters were not always aligned in the same direction; however, a higher number of cells oriented in the direction joining the free boundaries. In addition, in most of the clusters, the majority of cells were aligned in the same direction, either vertical or horizontal (Fig. 5a). Again, fibre remodelling resulted in fibre bundles with a well-defined orientation. However, in this case, we also observed regions with a more random fibre orientation (Fig. 5b). Comparing the degree of cellular ordering when cells had a tendency for stiff or soft environments, we observed a higher degree of cellular organization in the case where cells show affinity for stiff environments (Fig. 5c). In terms of ECM deformation, cells with a tendency for soft environments created a much higher deformation of the extracellular matrix than cells with a tendency for stiff environments (Fig. 5d, e). In both cases, larger deformations were observed closer to the free boundaries (Fig. 5d, e). The reaction force at the clamped boundaries clearly reflected the tendency of the cells for softer or stiffer environments. In contrast to stiff environments (Fig. 4d), soft environments triggered a gradual decrease in the reaction force over time (Fig. 5f). In addition, the formation of clusters was independent of the initial orientation of the fibres. A matrix with fully aligned fibres in the vertical or horizontal directions resulted in the orientation of the cells perpendicular to the fibre direction, but still grouped forming clusters.

3.3 Influence of fibre remodelling

Even in the absence of fibre remodelling, cells were able to form long chains or clusters. However, the level of cellular organization was markedly reduced (Fig. 6). In the absence of fibre remodelling, the number of both cell clusters and long chains was considerably lower. This was evident from the time changes in the number of vertical and horizontal cell dipoles (Fig. 6c, f) and in the fibre and cell order parameters (Fig. 6g). Although, the organization of the cells was significantly lower, the deformation of the matrix was significantly higher in the absence of fibre remodelling (Fig. 6d, e).

3.4 Effect of cell density

Independently of the initial orientation of the cells, the number of seeded cells had an influence on the dynamics of cellular organization (Fig. 7). Although long-term, cells formed a similar configuration, irrespective of the number of initially seeded cells, we observed a clear short-term sensitivity with respect to the initial cell density. A smaller number of cells resulted in a slower response of the system, taking more time

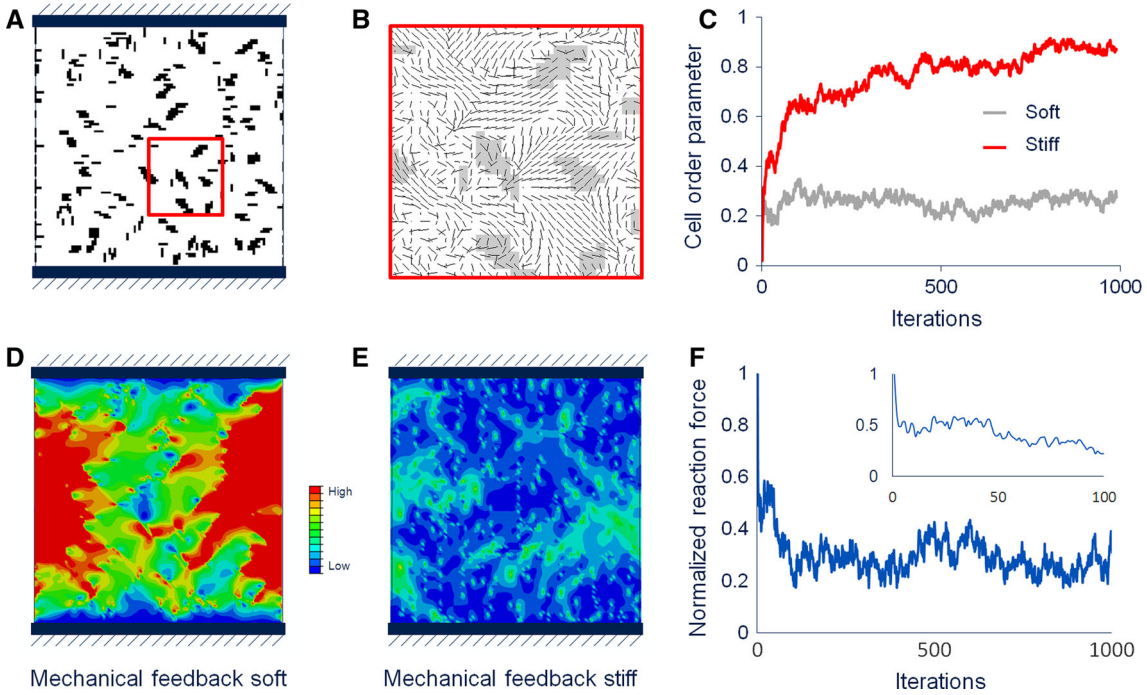

Fig. 5 **a** Cellular organization as a result of a tendency of the cells for soft environments. **b** Local fibre (*black lines*) organization as a result of fibre remodelling. Large fibre bundles can be seen together with regions of random fibre orientation. **c** Cell order parameter with a tendency of the cells for soft and stiff environments. A higher cellular organization is reached when cells have an affinity for stiff environments. **d**, **e** Induced deformation in a matrix with inhomogeneous boundary conditions and a tendency of the cells for soft and stiff environments, respectively. **f** Changes in the reaction force measured at one of the clamped boundaries over time with a tendency of the cells for soft environments

for the cells to converge towards the equilibrium configuration. This is not only reflected in the rate of change in vertically and horizontally oriented dipoles (Fig. 7e, f), but also in the evolution of the reaction force at the clamped boundaries (Fig. 7a–d). For low cell densities, the reaction force did not change markedly initially (Fig. 7a–d) and lower forces were predicted (Fig. 7g). In addition, we observed that the influence of cell density on the initial response of the system was dependent on the initial orientation of the cells. While 250 cells did not show a time lag when all cells were randomly seeded, a slower initial response was observed when 250 cells were all seeded in the horizontal or vertical directions (Fig. 7c, e). Interestingly, when 90/10 % of the cells were seeded in the vertical/horizontal directions, the effect of cell density on the time response was considerably decreased (Fig. 7f). This percentage of vertical/horizontal cells represents approximately the equilibrium configuration of the system (Fig. 7a, b).

In addition, we observed that for lower number of cells the system was more "instable", i.e. strong changes in the tendency of the organization of the cells (Fig. 8). While for high cell numbers changes in the orientation of the cells were smooth and tended towards equilibrium (Fig. 8), for low number of cells, we observed strong fluctuations in cellular orientation, which persisted after long time periods.

4 Discussion

Pathological and regenerative cascades of the human body depend upon physical cues and thus the mechanical interaction between cells and their ECM. Although many studies have investigated the tractions forces exerted by cells on different types of matrices (Delvoye et al. 1991; Ghibaudo et al. 2008; Gov 2009; Marinkovic et al. 2012), there is still a very limited understanding of the consequences of the mechanical crosstalk between cells and their susbstrate on cellular and matrix organization. The objective of this study was to explore to what extent the mechanical feedback between cells and their extracellular matrix can explain large scale cellular and matrix self-organization.

To isolate the role of individual factors, we developed a simple computer model which can account for specific mechanisms of cell-matrix crosstalk. The model includes bi-directional coupling through cellular traction forces to deform the ECM and through matrix deformation to trigger cellular migration. In addition, we incorporated the effect of matrix fibres and their reorganization by the cells.

An important result of our model is that a group of contractile cells will self- polarize at a large scale, even in homogeneous environments. The simple mechanical feedback loop between cell traction force and ECM deformation is suffi-

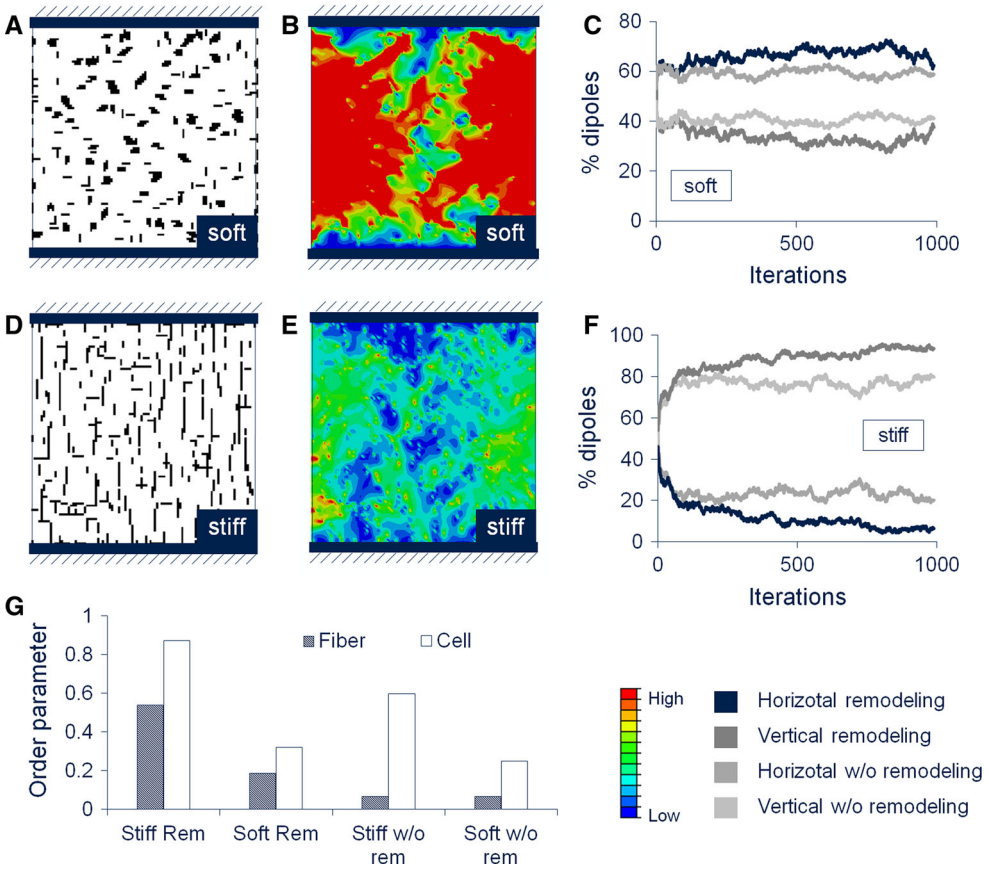

Fig. 6 Final orientation of cells with a tendency for **a** soft and **d** stiff environments in the absence of fibre remodelling. Amount of matrix deformation created by the cells with a tendency for **b** soft and **e** stiff environments when fibre remodelling did not occur. Number of dipoles oriented in the vertical and horizontal directions for cells with a tendency for **c** soft and **f** stiff environments with and without the occurrence of fibre remodelling. Horizontal dipoles are oriented in the direction joining the two free boundaries, while vertical dipoles are oriented in the direction joining the clamped boundaries. **g** Cell and fibre order parameter after 1,000 iterations. "Stiff"/"Soft": cells with a tendency for stiff/soft environments. "Rem"/"w/o rem": with/without fibre remodelling

cient to initiate cellular self-organization. This is a result of the tight interaction between neighbouring cells, which is created by the cell's ability to deform the matrix, and in this way influence the mechanical "sensing" by other cells. This is consistent with the hypothesis of cells "measuring" the local rigidity of the ECM and "responding" to it with a change in cellular function (Lo et al. 2000).

We have shown that a broad range of experimentally observed phenomena can be explained with this simple model of cell-matrix interaction: (1) without cell-to-cell contact, cells can communicate with each other by applying tension to the ECM (Klebe et al. 1989), (2) cells adopt a random organization in isotropic environments (Klebe et al. 1989), (3) cells align in the direction of maximum stiffness in anisotropic environments (joining the two clamped ends of the substrate) (Takakuda and Miyairi 1996; Klebe et al. 1989; Huang et al. 1993), (4) collagen fibres align parallel to the direction in which cells orient (Klebe et al. 1989; Huang et al. 1993; Kostyuk and Brown 2004), (5) the emergence of fibre bundles as a consequence of fibre remodelling (Delvoye et al. 1991; Kirmse et al. 2011) (6) the building up of tension as a consequence of cell and fibre reorganization (Delvoye et al. 1991) and (7) the dependency of the degree of cell and matrix organization on cell density (Klebe et al. 1989).

Interestingly, we observed that cellular organization is tightly linked to the mechanical feedback loop between cells and matrix. Cells with a preference for stiff environments have a tendency to form "chains", while cells with a preference for soft environments tend to form "clusters". Cell clusters form in tissues under a variety of circumstances, such as in fibrosis and scarring, and as part of the general process of mesenchymal condensation that takes place during development (Hall and Miyake 1995). However, the mechanism leading to cell clustering is different to the one simulated in our model. Experimentally, an increase in cell–cell adhesion relative to cell-substrate adhesion has been observed during cell cluster formation (Guo et al. 2006). The fact that cells group to form tissue-like structures involves a combi-

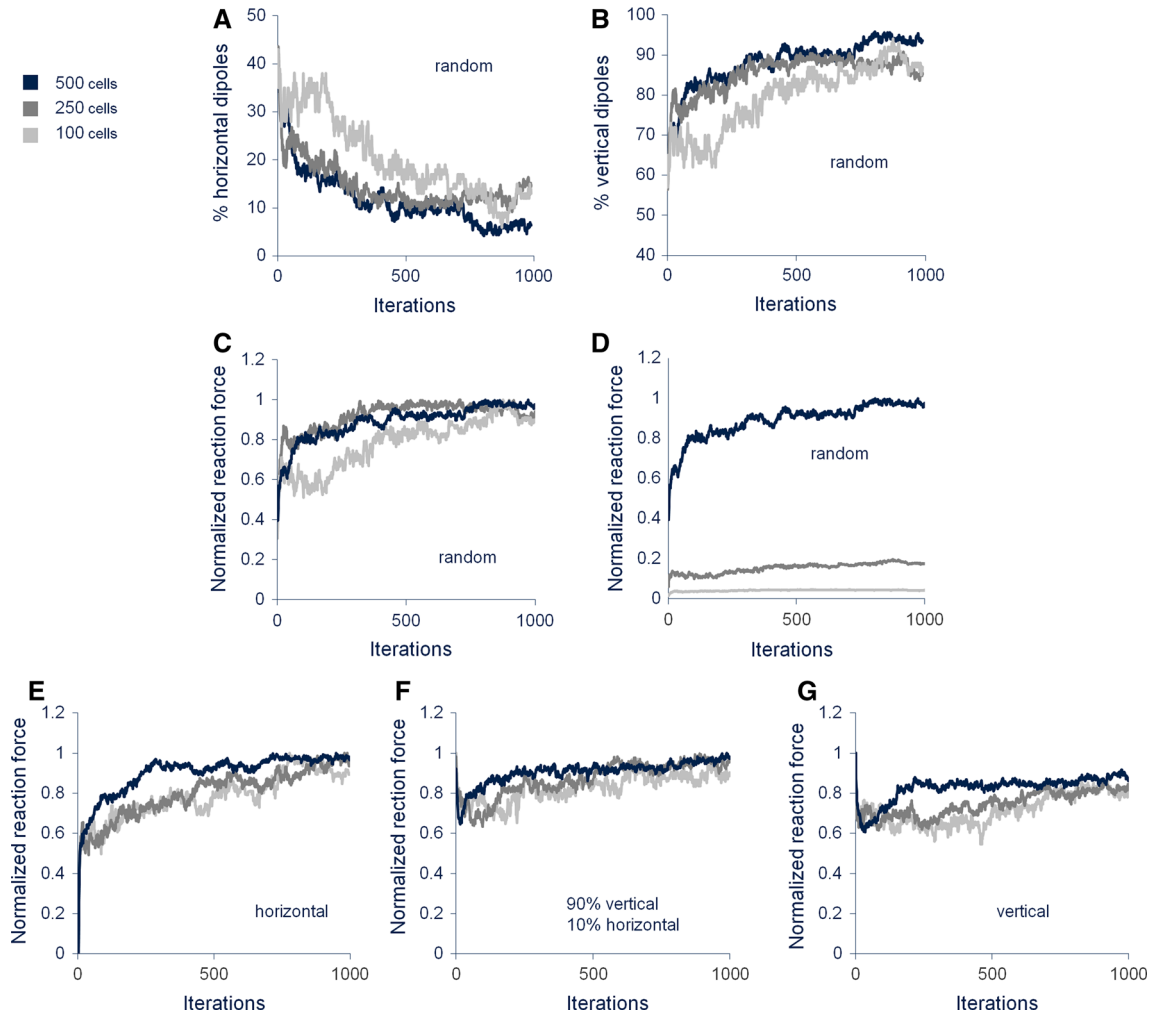

Fig. 7 **a**, **b** Effect of number of randomly seeded cells in cellular organization, shown as the percentage of horizontal and vertical dipoles formed, respectively. **c** Reaction force for different number of randomly seeded cells where values are normalized to the maximum force for each individual case. **d** Reaction forces for different number of randomly seeded cells normalized to the maximum force for the highest cell density case. **e**, **f**, **g** Effect of the initial orientation of the cells on reaction forces and the influence of cell density. Results are shown for cells with a tendency for stiff environments and when cells had the ability to remodel matrix fibres

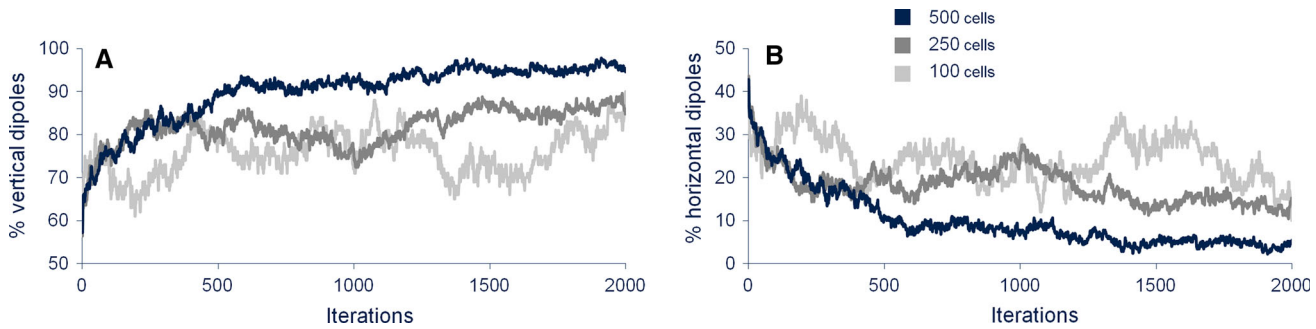

Fig. 8 Effect of number of seeded cells in the organization of the cells shown as the percentage of **a** vertical and **b** horizontal dipoles. Simulations were run for 2,000 iterations. Also after long time periods, low number of cells resulted in fluctuations in the orientation of the cells

nation of weakened adhesions to the substrate and myosin II-dependent contractile forces that drive cells towards each other (Guo et al. 2006). The theoretical work presented here shows a mechanism for cell clustering that has not been observed experimentally but that may be of interest to investigate.

Our model predicted mechanical implications for the extracellular matrix due to the tendency of cells for stiff environments. We showed that, although a tendency of the cells for soft environments also results in large range cellular organization, it has considerable consequences in matrix deformation. We have seen that cellular organization as a result of the tendency of cells for soft environments results in larger deformation of the extracellular matrix than a tendency for stiff environments. This might imply that the natural tendency of the cells for stiff environments is an internal mechanism for cellular organization with the overall goal to minimize ECM deformation and therefore energy consumption.

The implication of fibre remodelling during cellular organization through cell traction forces follows our hypothesis that cells organize themselves and the underlying matrix to minimize ECM deformation. Even in the absence of fibre remodelling, cells were still able to self-organize as a result of the mechanical interaction with the extracelluar matrix. However, we observed that the lack of fibre remodelling led to a lower degree of cellular organization and higher deformations of the substrate. Bischofs and Schwarz (Bischofs and Schwarz 2003) used a model based on minimum energy principles to determine cellular organization in linear elastic matrices. Although they did not take into account matrix fibres, they also observed the arrangement of the cells forming long chains as a result of the mechanical interaction between the cells and their ECM.

The process of fibre remodelling has been previously modelled with a focus on different types of tissues, e.g. cardiovascular (Driessen et al. 2007; Boerboom et al. 2003; Kuhl and Holzapfel 2007), arterial wall (Hariton et al. 2007), articular cartilage (Wilson et al. 2006), etc. In a similar context to the one addressed in this study, Barocas and Tranquillo (1997a,b) presented an anisotropic biphasic theory to study traction-induced matrix reorganization and the coupling of cell traction forces to the mechanical state of the matrix. Although they were able to predict cellular and fibre alignment in tissue equivalents, in their model cell alignment was a consequence of the alignment of the fibres. In this study, we have shown that fibre alignment is not needed for cellular organization, but that the simple "sensing" of the local mechanical properties of the substrate by the cells is enough to explain large scale cellular arrangement.

There are important biological questions regarding cell and matrix organization which are beyond the scope of the model introduced here. Proliferation of the cells may be influenced by the mechanical environment, as well as cell differentiation or ECM production. Moreover, cells do not only establish adhesion contacts with the ECM, but also with the neighbouring cells (Gov 2009). At its current state, our model does not consider that cells can change their contractile activity and the magnitude of the traction force they apply. It has been shown that cell traction forces increase with increased matrix stiffness (Choquet et al. 1997; Saez et al. 2005). In this study, our goal was to isolate the effect of the force itself, without investigating changes in traction force magnitude in response to changes in matrix stiffness. Future developments of the model will investigate the interaction between traction force magnitude and extracellular matrix mechanics and their implications for cellular organization. Although the current formulation of the model does not include viscoelastic effects, it would be possible to extend the model to account for relaxation and/or creep phenomena. For example, following (Holzapfel and Gasser 2001), additional state variables associated with irreversible (dissipative) effects could be included. Moreover, the model is currently limited to two dimensions. An extension to the third dimension is part of future work. An important feature of this study is that the conclusions drawn are independent of model parameters. Parameter values used here were intentionally not chosen to match any specific material or cell type. Different cell types would exert different amounts of traction forces [(Lee et al. 1994; Maruthamuthu et al. 2011)] which would also depend on the stiffness of the ECM (Ghibaudo et al. 2008; Mitrossilis et al. 2009; Califano and Reinhart-King 2010). The model presented here was designed to investigate mechanical interactions between cells and the ECM and their implications in cell and matrix organization, independent of, e.g. the cell traction force magnitude. We considered that, in each iteration, 80 % of the cells could migrate to neighbouring positions. With this, we intended to simulate the fact that not all the cells seeded in a piece of ECM would move at the same time and at the same speed. A higher/lower value of this parameter would only result in a faster/slower organization of the cells. In addition, motivated by time-lapse imaging of cellular migration (Zahm et al. 1997) and Monte Carlo approaches (Bischofs and Schwarz 2006), we used random sampling of relevant configurations to simulate changes in cell location and orientation observed at discrete time points. From a computational point of view, it would be possible to include other rules for changes in cell location or orientation over time, for example to impose a cell orientation based on the direction of movement. This would result in a slower organization of the cells; however, it would not affect the overall results of the model.

Several experimental measurements of cell traction force induced matrix contraction have shown a time lag in the experimental traction force (Tranquillo et al. 1992). For low number of cells, our model predicted a time lag in the development of the matrix reaction force (Fig. 7). This time lag was previously attributed to cell spreading (Barocas and Tranquillo 1997a,b). Our simulations now show that for small cell numbers the orientation of the cells plays a major role in force development. Interestingly, we also observed that this time lag depends on the initial orientation of the cells and that it can be highly reduced with the right proportion of vertically/horizontally oriented seeded cells.

Moreover, we have shown that low number of cells results in higher fluctuations in the overall organization of the cells (Fig. 8). This can be explained since lower number of cells means that each cell receives less "signals" about the mechanical conditions of the system as a consequence of increased cell–cell distance. If one cell is too far apart from other cells, the local mechanical conditions, this cell might receive could not be informative of the overall mechanical behaviour of the system (e.g. boundary conditions). Additional in vitro experiments are needed to confirm these observations.

We have not yet shown that cellular patterns arise the way described by the model. Many factors have been proposed to orchestrate cell motion, including chemotactic morphogens, contact guidance, haptotaxis and contact inhibition (Thiery 1984). All these mechanisms might be active to some extent; yet, it remains unclear how they act in concert to generate the spatially organized aggregations of cells. The advantage of computational modelling is that we can isolate individual factors and investigate the effect of each mechanism individually. It will be important though, to investigate how combinations of the different mechanisms would jointly affect cellular organization. However, this was outside the current scope of the study.

In summary, the mechanical properties of soft biological tissues are not only important for maintaining macroscale mechanical integrity but also essential for regulating cellular function, even beyond the single cell dimension. A simple hybrid discrete-continuum model of cell/matrix interactions can capture many experimental observations, exhibit a number of emergent behaviours such as cell population organization, and generate hypotheses to guide new experiments. We showed that a mechanical feedback between cells and extracellular matrix through cell traction forces can lead to large scale cellular organization, where the number of cells influences the local mechanical interaction. The model explained fibre bundle formation by means of stress-driven cell-mediated ECM remodelling, where the fibre direction is determined by local cellular organization. Our study shows the potential of computational modelling towards understanding cell-matrix interactions. Ultimately, modelling cell-matrix interactions might further the understanding of disease states associated with aberrant mechanosensing and guide the design parameters of successful biomaterials and tissue engineering constructs.

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