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Physical-object oriented 3d Simulations of Cell deformations and Migration

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Summary. Many aspects of individual and collective cell motion are still poorly understood and physical models dealing with both aspects appear clearly as valuable tools for understanding cell biomechanical behavior. We theoretically analyze and simulate individual cell mechanical properties and the related chemotactic behavior of single cells collectively involved in an aggregation process. Cell objects are defined as three-dimensional elastic bodies moving on a viscous medium and submitted both to internal cohesive forces and to external attractive forces (gravity and chemoattraction). We first investigate individual cell mechanical response to externally applied forces and compare the simulated cell object deformations to experimental data obtained with optical tweezers. We then examine the simulated cell population reorganization submitted to a chemoattraction field over a 2D solid plane simulating a glass coverslip. Simulations are carried out for different values of cell chemotactic response. We especially simulate cell sorting between pre-spore and pre-stalk cells during Dictyostelium discoideum aggregation process by considering two cell populations exhibiting differential cell-cell interactions. We conclude that our physical-object oriented (POO) approach for modelling individual cell cytomechanics also satisfactorily reproduces the two-dimensional aggregation at a cell population level. Because individual cell mechanical behavior can be compared to a wide range of cell micro-rheology experiments, the cell object parameters can be estimated. This framework should thus be adequate for biologically realistic multi-scale analyses leading to a better understanding of how, through modulation of mechanical factors, individual cell behavior controls collective cell reorganization.

1. Introduction

Spatial aggregation and reorganisation of cell populations is crucial in physiological and pathological developmental processes, like embryogenesis, tissues healing or cancerogenesis. Adhesive interactions between adjacent cells (cell-cell adhesion) and between cell and the extracellular matrix (cell-matrix adhesion) play a major role in the maintenance or reconstruction of multicellular structures. Cell motility, possibly controlled by extracellular factors like chemoattractants, also requires that such adhesions can be modulated and eventually broken in order to insure a net spatial translocation of the cell.

Numerous theoretical models have been proposed for analyzing how different spatial organization of cell populations could emerge from such complex interactions. One can distinguish:

- continuous approaches based on a global description of the spatio-temporal evolution of cell density and on the determination of instability conditions leading to an heterogeneous distribution of the cells (Murray et al., 1988; Vasiev and Weijer, 1999; Yamaguchi et al., 2000), and

- discrete approaches, based on the description of the individual properties and behavior of cells and looking for the emergence of macroscopic cellular organisation and rearrangements resulting from individual interactions, as observed in morphogenetic processes (Weliky et al., 1991; Honda et al., 2000), including cell sorting (Graner et Sawada, 1993). In cellular automata models, cell-cell interaction rules and neighbourhood conditions are specified (Ermentrout et al., 1993; Czirok et al., 2001), but generally this is done without considering the intrinsec mechanical properties of individual cells elasticity and deformation.

The other widely used discrete approach is based on a polygonal tessellation of the plane. For example, (Duvdevani-Bar et al., 1992) proposed a strictly topographic cellular organization in which each cell is reduced to a dot, vertex of a given triangulated graph which defines the neighbourhood relationships between cells. An abstract law is implemented as a recombination process over the neighbourhood relationships and yields to a mechanical-like behaviour. Further model enhancement simulates biological processes such as cell proliferation or motility. (Honda et al., 1984) had previously used a similar approach to predict the morphological response of a tissue to a given cell division rate. They first proposed to determine the best topographic approximation of a given fully connected tissue with a Voronoï diagram, which divides the space into cell objects according to shorter distance relationships. A cell is assimilated to a Voronoï region and a recombination process is defined in order to reorganize the diagram after the division of the given cell. Even if such a process captures some of a mechanical behaviour, it is a very limited model for cellular organizations and cellular bio-mechanics. Extending this geometrical formalization, (Dugnolle et al., 1998) simulated the mechanical cell monolayer rearrangement occurring during vitro wound-healing experiments by considering cells as elastic proliferating bodies moving on a viscous surface and submitted to adhesion forces.

This work proposes a totally different approach to model collective cellular processes from the mechanical interactions of individual cells with defined mechanical identity, cell-cell interactions and random motion. Our approach is based on the consideration of “cell objects”, proposed as model of real cells and defined as 3D-elastic physical objects with specific geometry and internal ("sub-cellullar") structure. At first glance, this approach shares some common features with the Finite Element Method (FEM) since both rely on the geometric discretization of the objects into a mesh and evaluation of physical variables (forces, strain,...) at each node of this mesh. However this mesh is realized through bottom-up modeling in the physical object oriented (POO) approach: the geometric structures mimic the physical structures, as in cell tensegrity models (Wendling et al., 1999, 2000). In contrast the mesh in the FEM only provides a discretisation of the material continuum with arbitrary geometric elements (triangle, tetrahedron, ...). The specificity of the POO will appear more explicitly in the examples presented in this study.

More precisely, we illustrate the potentiality of such a POO approach in the formulation of a multi-scale model by addressing the following questions: is the cell object relevant enough to describe some of the mechanical properties of individual living cells reported in cellular micro-rheological experiments? Is it possible to account for emergent cell collective behaviour, like cell sorting and aggregation, by considering for example the response of such mechanical cell objects to extra-cellular gradients?

The first section of this paper deals with the formulation of the 3D physical cell object. The second section explores some of its mechanical properties. We especially compare the results of our POO computational approach to experimental red blood cell deformations realized with optical tweezers. The third section focuses on spatio-temporal aspects of cell population organization, sorting and migration with special consideration of the Dictyostelium discoideum aggregation process. The Dictyostelium discoideum slime mold is indeed widely used as an experimental model for complex self-organizing processes in biology (Parent and Devreotes, 1996; Aubry and Firtel, 1999). There is a lot of experimental data and model studies on this organism, either for the cAMP pulses generation (Martiel and Goldbeter, 1987), spiral cAMP waves in aggregating population (Tyson and Murray, 1989), as well as cell movement and aggregation (Palsson and Othmer, 2000).

2. Description of the computational model

2.1. Objectives of the physical object oriented (POO) approach

To be able to model individual behaviours, each cell is considered as a physical entity. Each cell object has its own history, properties and actions. To be able to manipulate such entities, a computer models and its algorithms are developed within an object oriented modelling framework. This approach provides an efficient and precise structure for the methodological organization of concepts and their relationships. The object oriented framework allows us to describe properties and actions for a whole category of objects, called a class. The class describes the state and behaviour of a cell object. Each cell object is thus a particular instance of this template and has an individual behaviour. The behaviour laws described in the class could depend on intrinsic properties and interactions. They can also change with time, either explicitely or implicitely through time-varying variables, like extracellular factors or concentrations. Intrinsic properties are mainly mechanical properties such as elasticity, contractility, and incompressibility (Promayon et al., 1997). They could also include bio-chemical or genetic processes. Furthermore, cell object interactions with the environment, through biased migration (chemiotaxis, haptotaxis, …), or cell-cell interactions, e.g. collision and adhesion, can be defined in this proposed framework, as exemplified below.

2.2. The POO Approach

Mass-spring networks are often used to model 3D physical object dynamics. However, the main drawbacks of these models lie in the control and assessment of parameters. We initially developed a different approach, in the context of human breathing (Promayon et al., 1997). This discrete model is based on computer graphics modelling (Terzopoulos et al., 1987 ; Delingette, 1998). Natural motions and realistic-looking flexible and elastic objects are efficiently modelled and simulated by means of physically-based computer graphics models. These models use a small amount of data (object geometries and relations between objects). From this, an animation motor (using forces, energies, or direct displacements), integrates movement and deformation laws to compute the evolution of shapes and positions. Generally, constraints are added to control movements and deformations or to model complex physical properties.

We modelled the human abdomen using an elastic and incompressible 3D object and the human diaphragm using an elastic and contractile membrane. These objects were linked together and attached to rigid objects modelling the rib cage. An explicit algorithm was developed to compute the dynamic evolution of these objects as well as to insure the necessary constraints. Incompressibility and connections were considered as constraints.

This model, allowing for rigid, incompressible elastic or contractile objects is the groundwork, here extended to model cells deformation and migration. Other properties such as incompressibility or cell interaction have also been taken into account, as detailed below.

2.2.1. Geometry

Each cell object requires a 3D geometry. We do not yet consider cell division, thus the cell topology remains unchanged. To simplify the calculations, we only consider the cell contour and define a cell object by a 3D closed surface. This contour is represented by nodes linked in a triangular mesh. Triangular meshes are simple and considerably simplify the incompressibility constraint and collision resolutions.

2.2.2. Forces

To generate forces and dynamics, a mass is assigned to each contour node. Forces are exerted on the nodes to generate displacements and deformations. Three kinds of forces can be used in our model: force fields (e.g. gravitation force), locally applied forces (e.g. user manipulation), and Linear Actuator Forces (LAFs). We introduce a LAF when a target position P_{target} is known for a given node of position P. To minimize the distance $|PP_{target}|$ a spring is created between P and P_{target}. It generates a force that linearly attracts P towards P_{target}. The expression of the LAF is: $F = k_{elas}\ (P - P_{target})$, where k_{elas} is the elastic modulus of the spring. LAF can be seen as a potential force that tends to minimize a distance. LAFs permit to model any kind of forces that could be defined by target positions. P_{target} can depend on geometry or on constraints and can dynamically change.

2.2.3. A specific case: elasticity

Calibration of spring-mass networks are known to be difficult. Therefore, to model elasticity, we define a local shape memory (Promayon et al., 1996). The elastic property of a cell object is simply defined as its ability to recover its original shape after mechanical deformation. To model this property, we construct a local shape coordinate system where each contour node position is defined relatively to its neighbouring nodes by three parameters (α, β, γ) (Fig. 1). The initial value of this 3-parameter set defines the rest shape. During the simulation, according to the neighbouring node positions, a target position is computed for each node under consideration. This target position satisfies the local shape and defines a LAF. Therefore, a cell object is defined by a contour where the shape memory force is applied to all its nodes. A unique elasticity modulus k_{elas} is used by the corresponding LAF.

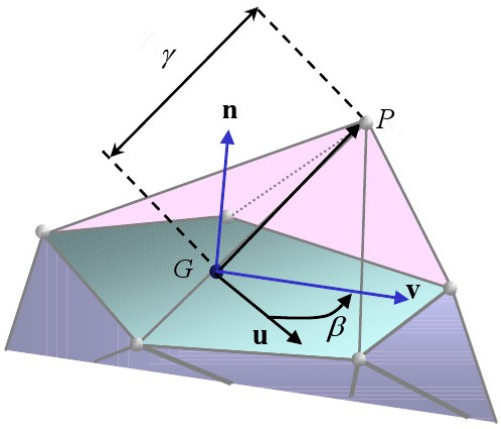

Figure 1. Local shape memory force to model elasticity. The local shape is defined by two angles α and β and a distance γ. A node position P is defined by α, β and γ and the current position of its neighbours. G is the isobarycenter of the neighbours. **n** is an approximate normal from which **v** is deduced, **u** is the cross product between **n** and **GP**. At each iteration this allows to set a target position for each node.

2.2.4. Constraints

Considering forces is often not enough to realistically model complex behaviours of physical objects. Constraints are thus added to maintain some additional conditions like boundary conditions (non-penetrating area) or incompressibility. Our algorithm considers constraints as non-quantified force components. Thereby, it is possible to handle the total incompressibility of a contour (Promayon et al., 1996). This allows the model to verify the incompressibility constraint exactly and efficiently for all the cell objects, individually.

2.2.5. Numerical integration

The following algorithm is used to compute the dynamical behaviour of a cell object from time t to time $t+dt$:

- For each node: compute the sum of applied forces;
- Use a discrete integration scheme for equation of motion (e.g. Newton-Cotes) to compute the new velocity and position of the nodes, without considering any constraints;
- Take local and global constraints into account and impose given displacements to the nodes (these displacements have to be computed at each time step);
- Adjust the velocity to include the imposed displacements.

3. POO simulation of individual cell mechanical behaviour

An increasing number of experimental work is devoted to the analysis of mechanical properties of cells, which play a central role in a wide range of biological processes, from cell migration to the modulation of the cellular response to extracellular mechanical stimuli. The recent development of several experimental techniques like microplates (Thoumine and Meister, 2000) or optical tweezers (Hénon et al., 1999 ; Sleep et al., 1999) make possible the manipulation of isolated living cells and the application of specific mechanical forces or deformations. Such experiments can moreover lead to quantitative results, usually in terms of linear stress-strain relationships, from which cell mechanical moduli can be inferred.

Our purpose in this section is to illustrate the application of our POO approach in cytomechanics by considering two different cell object prototypes, characterized by a specific architecture. In a first situation, we simulated the influence of transverse links within an elastic discrete envelope when the cell is submitted to uniaxial compression. This situation is a caricature of living cells having different intracellular organisation of their cytoskeleton, for example with specific orientation of stress fibres.

As a second case, we consider a cell object without internal cross-links: this cell object can be viewed as a model of living cells like human erythrocytes, where the cell membrane is entirely responsible for the elastic cell deformation, the inner cytoplasm being only viscous. In order to test the validity of our modelling approach for the analysis of real experiments, we simulated optical tweezers manipulations in which calibrated forces, between 0 and 56 pN, have been diametrically applied to human erythrocytes (Henon et al., 1999). We specifically considered the suspension of erythrocytes in hypotonic buffer, which leads to spherical or nearly spherical cells.

3.1. Influence of the cell object "cytoskeleton": in silico compression loading

In this first situation, we consider a cell objet topology defined by 66 nodes. Three different cell prototypes are considered (fig. 2). The cell0 is only defined by its discrete envelope, with no internal links. In cell1, we considered a reinforcement of the cell architecture with horizontal elastic cross-links modelling cytoskeleton fibres. Finally, cell2 architecture includes internal diagonal links connecting the apical and basal cell surfaces. In each case, a vertical force F_c is locally applied at the top of the cell, on 4 or 5 upper nodes. The five lowest nodes of the basal cell surface are fixed (zero displacement) and simulate the partial cell

attachment to a rigid substratum.

Figure 2 presents the initial 3D shape of each cell object (first raw) and the equilibrium state they reached (second raw) when a given vertical loading force F_c is applied for a fixed value k_{elas} of the elasticity modulus.

Figure 3 shows the evolution with time of the height *z(t)* defining the coordinate of the node located on the top of each cell object. The first part of the curve corresponds to the cell uniaxial compression, the second phase corresponding to the elastic relaxation simulated after removal of the loading force.

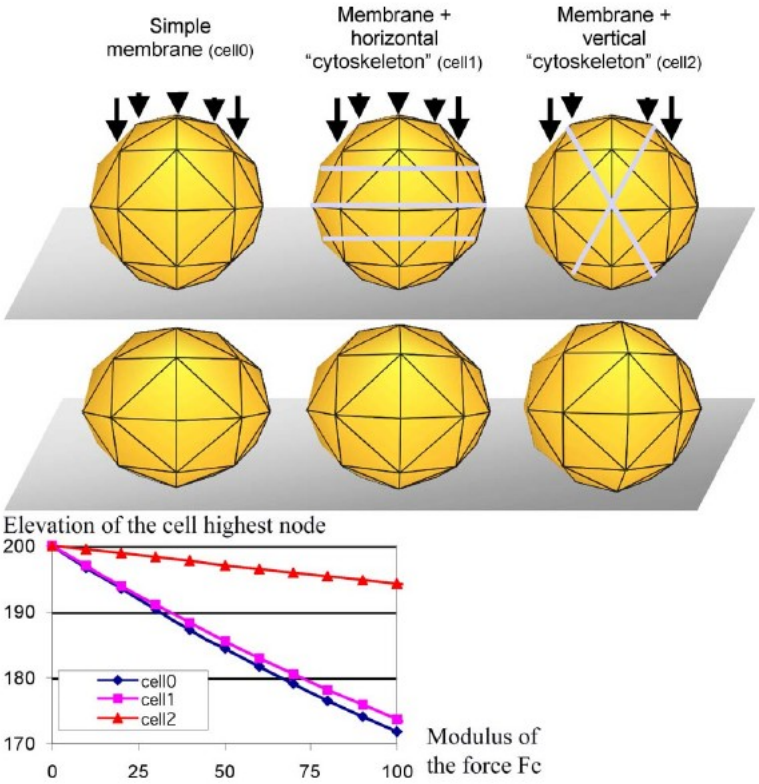

Figure 2. Influence of the cell object "cytoskeleton" on the cell mechanical response to vertical load. Three cell types are considered: no "cytoskeleton" (cell0), horizontal links (cell1), diagonal links (cell2). The first raw presents the initial 3D shape of each cell prototype. For a given fixed value k_{elas} of the elasticity modulus of each cell object, the second raw in the figure indicates the equilibrium state which is reached when a vertical loading force F_c is applied on the 5 (cell0 and cell1) or 4 (cell2) nodes marked with arrows. The insert at the bottom of the figures indicates the vertical position at equilibrium of the highest node of the cell object as F_c is increased (horizontal axis).

3.2. In silico optical tweezers experiments

We simulated here the experimental protocol used by Hénon et al. (1999) to deform nearly spherical erythrocytes (Red Blood Cells, RBCs) using optical tweezers. The force F is exerted on two silica microbeads that are sticked on the RBC membrane in diametrical position. By slowly incrementing the distance between the two-trapped beads, an increasing stress is applied to the RBC membrane. Proper force calibration then gives the experimental decrease of the RBC diameter (measured in a plane perpendicular to the applied force) as a function of the increasing applied force F. Experimentally, the variations are linear up to 10pN, which gives an elastic shear modulus close to 2μN/m. However, for a range of force between 10 and 35 pN, the curve is almost flat with no significant decrease of the RBC diameter (Hénon et al., 1999).

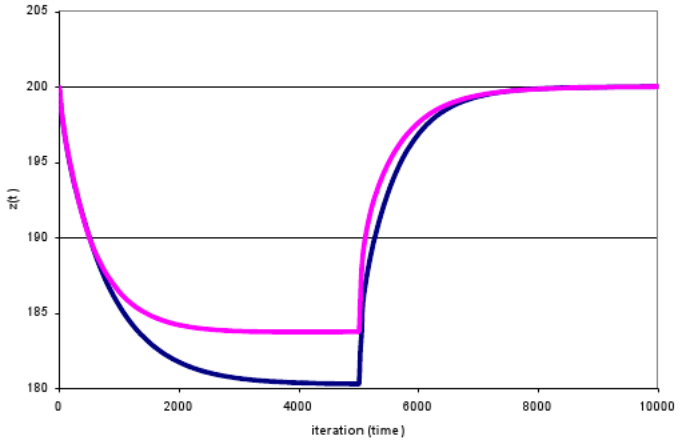

Figure 3. Associated compression and relaxation curves of cell0 and cell1. It shows the overall evolution with time of the height *z(t)* defining the coordinate of the node located on the top each cell. The first part of the curve corresponds to the compression phase, the second part corresponding to the nonlinear elastic relaxation simulated after removal of the loading force F_c.

In order to simulate this experiment with our POO approach, a force F_s is locally exerted on two opposite nodes of the cell object contour, pulling them apart (fig. 4). The simulation parameters are the elasticity of the cell, i.e. k_{elas} and the modulus of F_s. Figure 4 shows that k_{elas} can be adjusted such that the modelled cell and the real RBC have the same mechanical response.

4. Cell aggregation and sorting

4.1. Model definition

The Dictyostelium discoideum slime mold aggregation is a complex process. Upon starvation, isolated cells undergo a differentiation program, which allows cell aggregation into a slug. The aggregation process is under the control of cyclic cAMP signals synthesized by isolated cells in the population (Parent and Devreotes 1996; Aubry and Firtel, 1999). Recent model studies have shown the importance of cell to cell interactions in the process of mound formation and cell sorting (Bretschneider et al., 1997; Vasiev and Weijer, 1999; Weijer, 1999). Dictyostelium cells represent an important cellular model to explore self-organizing structures by short-range interactions between cells (Dormann et al., 2000).

Within the mathematical framework presented in the above section "Description of the computational model", we simulated cell migration in a population of cell objects subjected to a central force field; each of these mathematical cell objects is equivalent to a biological isolated cell. The differentiated cell type would be coded into different properties for the corresponding model cell object. The central force field is the equivalent of the cAMP gradient in D. discoideum aggregation process; however, other situations may be considered, such as force transmission through mechanical constraints in tissues or cell and extracellular matrix interactions.

In the present model version, we assume that a clump of cell objects is held fixed at a central position (fig. 5). This initial aggregate exerts an attractive force field towards isolated cell objects in the neighbourhood. The force field is mediated through diffusion of a chemo-attractant molecule, produced by the clump. Diffusion, which is supposed linear, generates a gradient of chemoattractant concentration, which gives the external attraction force exerted on cell objects. Hence, the chemoattractant position defines a target position for the cells. The resulting LAF elastic modulus is called $k_{attractant}$. This force is applied to every cell nodes.

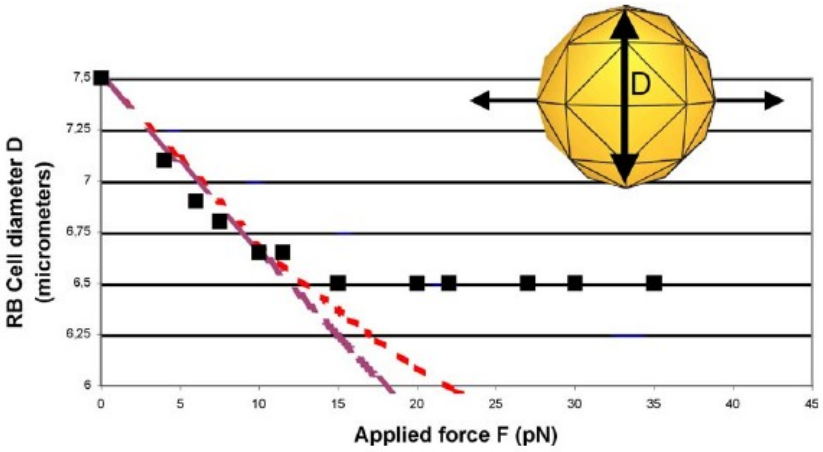

Figure 4. In silico optical tweezers experiments. A spherical cell object is proposed as a model of nearly spherical red blood cell (RBC) suspended in an hypotonic solution. Optical tweezers double trap is simulated by exerting a force F_s on two opposite nodes of the cell object contour (upper insert). The variation with load of the cell object diameter D(F_s) in a plane perpendicular to the loading direction is simulated and compared to real data published by Henon et al. (1999). The simulation parameters are the elasticity of the cell, i.e. k_{elas} and the modulus of F_s. With appropriate scaling of the force, one can adjust the parameter k_{elas} such that the experimental mechanical response of RBC can be nicely fitted in the linear elastic regime. Brown discontinuous line represents the linear fit to the experimental data (elastic shear modulus ~ 1,9μN/m). Red dotted line represents the fit obtain by the simulated RBC object which indicates a departure from the linear regime at larger traction forces.

In order to mimic realistic situations, we also considered the possibility of a random movement of the cell objects. Brownian movement is modelled using a constant direction during a given latency time called t_{random}. When the latency time is elapsed a new random direction and latency time are generated. We set: $t_{random} = - p * log (1 - r)$, where p is a constant of persistency and r is a randomly generated number between 0 and 1. The persistency parameter could be different for each cell object or type of cell object. The random direction is computed using θ_{random}, a randomly generated angle between 0 and 2π. For the simulations presented here, the random direction is planar, but could easily be extended to three dimensions.

Finally, we also assume that the cell object population is a mixture of two cell object types, denoted respectively A and B, which behave differently in response to the force field. Type A and B correspond to the differentiated D. discoideum as pre-spore or pre-stalk cell types. Movement rules mimic the fact that (prespore/prestalk) cell types in D. discoideum cells have different response to cAMP gradients, either in the aggregation phase or in the cell movement in the mound. During cell object displacement, collisions are expected and give rise to three possible pair formations.

Cell collisions will create aggregates during simulation; it should be noted that aggregate destruction is also possible if the bond between cell objects is weak, typically when the cell objects are of different types. During simulations if two cell objects c_1 and c_2 collide, a dynamic link is built between them. If c_1 and c_2 are not already in any aggregate, a new aggregate is created. If c_1 is in a different aggregate than c_2 then the two aggregates are merged. During simulation, if an aggregate contains no more than one cell object, it is destroyed. The collision between some nodes of these cell objects makes a dynamic link between two cell objects. The two facets that are the closest are chosen and a LAF links the nodes of these two facets. To generate these forces each node of the chosen facet in c_1 uses one of the three nodes of the chosen facet in c_2 as target position (and vice versa). A

differentiation table gives the stiffness to be used for this LAF depending on the type of c_1 and c_2.

4.2. Cell aggregation simulation

We start with a population of 36 cell objects lying on an infinite plane representing the substratum. More precisely, each cell object is an icosahedron (12 nodes, 20 facets), totally incompressible. Half of the cell objects correspond to a cell type A. The two types differ by their ability to respond to cell-cell interactions (see previous section).

In figure 5, we present three steps of the aggregation process simulation. Initially, the 36 cell objects were scattered uniformly (panel a). As time elapses, cells begin to move randomly and in direction of the central force (panel b). For large time, aggregation is almost complete (panel c). Accompanying cell movement towards the centre, random collision between cell objects build up sorting. Consequently, the final cell aggregate is organized into cellular clumps, each of them associated to one of the two cell object types A and B. This exemplifies that cell object sorting occurred during the aggregation process. The effect of random movement is particularly important when the central force is weak. In these conditions, only aggregates with a small number of cell objects are observed. None of these aggregates would grow and give rise to a unique clump of cell object (results not shown).

5. Discussion

We have presented an object-oriented approach to model both individual and collective mechanical and motility cell behaviour. This approach is based on the definition of a cell object, whose architecture, mechanical properties, cell-cell and cell-medium interactions can be precisely defined according to given working hypotheses. It is indeed known that the mechanical behaviours of living cells are hardly explainable by a viscous fluid balloon response only. Even if it remains a matter of controversy (Ingber et al., 2000), the concept of cell tensegrity architecture proposed by D.E. Ingber has provided a theoretical background for different models of living cells (Wendling et al., 1999, 2000; Volokh et al., 2000). We develop here an alternative modelling approach whose relevance is illustrated by considering two different scales of investigations.

The first one deals with the emergence of individual cell mechanical response from specific subcellular architectural elements. Such considerations can be closely related to specific organization of the cytoskeleton in living cells. Basic cell response to uniaxial loading has been illustrated in this paper. We furthermore proposed a more refined analysis of an incompressible cell object only modelled by a finite number of nodes on its external "membrane". We compared the simulated responses to real experiments undertaken on human red blood cells. Our cell object not only satisfactorily reproduces the experimental data in the linear deformation regime.

We have integrated the individual mechanical cell object properties in the simulation of collective and coordinated motion of two different populations of cell objects submitted to an external attraction field. Thus, the collective cell object results directly from the cell-cell mechanical and biochemical interactions, superimposed to "phenotypic" individual cell properties like random motion and differential sensitivity to the external gradient. Simulations showed the potentiality and the simplicity of our POO approach to account for collective dynamical living cells behaviour. When compared to D. Discoideum behaviour, simulation results prove that very simple interaction rules between cell objects account for the aggregation process. Similarly, different interaction rules between the possible cell object pairs account for cell sorting and formation of clumps of similar cells within a unique aggregate.

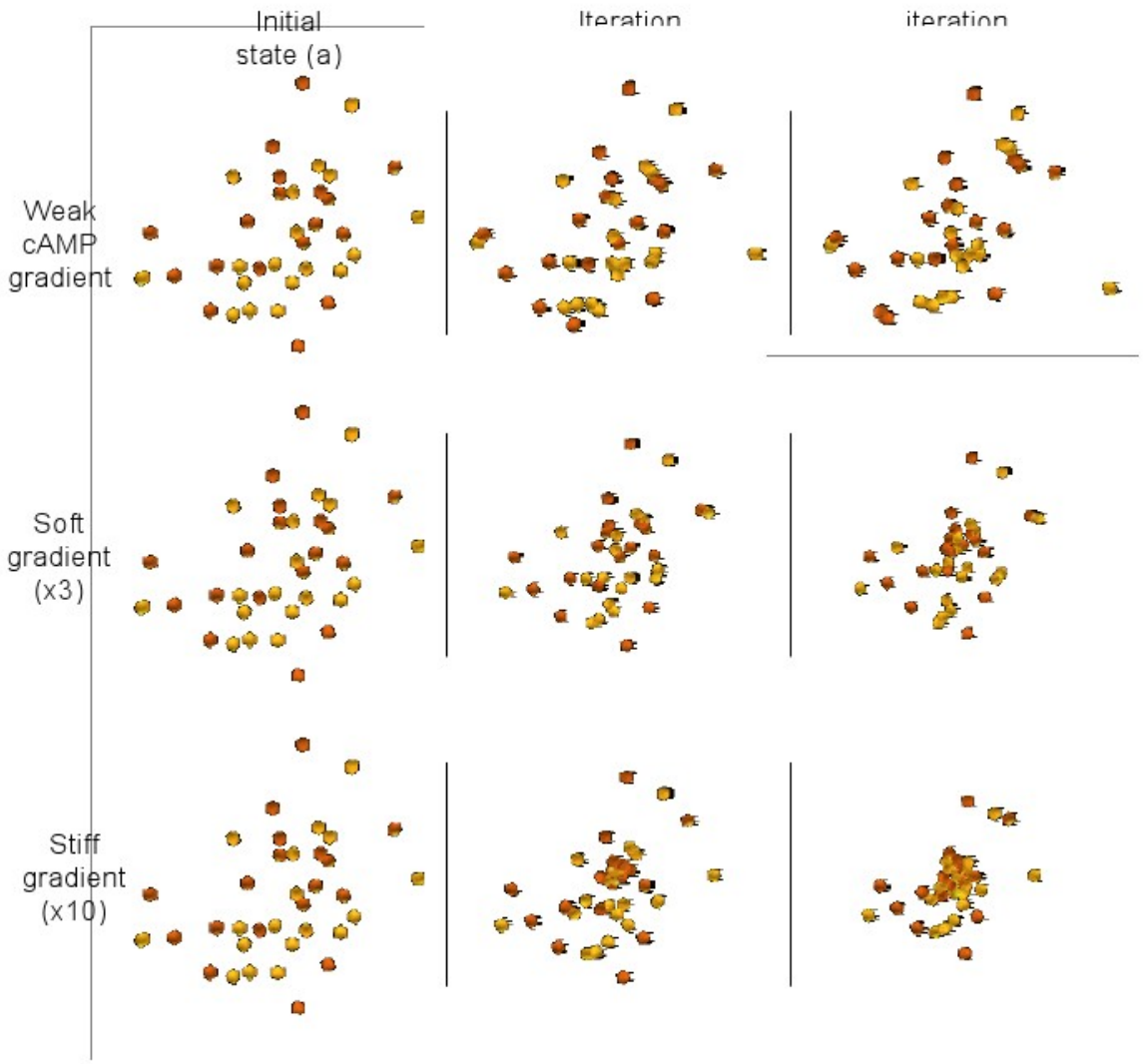

Figure 5: Simulation of the aggregation of a 36 cell objects population. These cell objects are subjected to a central force field whose effect is to gather the cell objects into an unique aggregate at the center position; additionally, cell objects can move randomly. We also assumed that two cell object types A and B are equally present in the population. (A/A) and (B/B) cell object collisions give rise to stable bonds whereas (A/B) ones have no effect on aggregation.

Such processes can be globally simulated through other approaches like cellular automata or continuous differential models, but in these cases, the cell does not exist as a physically defined structural object. The interest of the present approach is to provide, both qualitatively and quantitatively, several links between, on one hand macroscopic morphological and dynamical variables (aggregate size, mean migration velocity within a cell population), on the other hand individual cellular or subcellular parameters or processes, including cell shape and deformation, cell internal architecture. Moreover, our definition of the cell object is more versatile than the one proposed in the recent work of Palsson and Othmer (2000), which only considered reorientation of viscoelastic ellipsoids.

This POO approach is not restricted to the biological levels already addressed in this paper. Indeed, a further step in the model evolution consists in its ability to incorporate additional levels of biological description. In a top to bottom direction, we will consider and simulate a set of biochemical reactions and molecular events occurring within the cell object. In a bottom to top direction, molecular diffusion of extracellular factors between cell object as well as cell-extracellular matrix interactions and associated tissue architecture and remodelling could be considered.

It also appears crucial to underline that the POO approach provides an efficient and versatile modelling tool for the validation of biological hypotheses, and thus could be used in parallel with experiments either to support interpretation or to drive data acquisition. Furthermore, the related model simulations do not only provide qualitative results, but also give quantitative information which can be compared to real experimental data at different levels (subcellular, cellular, tissues) and scales (in time and space).

6. References

Aubry, L. and Firtel, R. "Integration of signaling networks that regulate Dictyostelium differentiation." Annu Rev Cell Dev Biol, **15**(5): 469-517, 1999.

Bretschneider, T. and Vasiev, B. and Weijer, C.J. "A Model for Cell Movement During Dictyostelium Mound Formation." J Theor Biol, **189**(1): 41-51, 1997.

Czirok, A. And Deutsch, A. and Wurzel, M. "Individual-based models of cell flocking." In: W. Alt, M. Chaplain, M. Griebel and J. Lenz (eds.) Polymer and cell dynamics: multiscale modeling and numerical simulations, Birkhäuser, Basel. 2001.

Delingette, H. "Towards realistic soft tissue modeling in medical simulation." Proc. of the IEEE: special issue on virtual and augmented reality in medicine, **86**(3):512-523, 1998.

Dormann, D. and Vasiev, B. and Weiser, CJ. "The control of chemotactic cell movement during Dictyostelium morphogenesis." Phil Trans Roy Soc B, **355**(1399): 983-991, 2000.

Duvdevani-Bar, R. and Segel, L.A. "On topological simulations in developmental biology." J Theor Biol, **166**:33-50, 1992.

Dugnolle, P. and Garbay, C. and Tracqui, P. "A mechanical model to simulate cell reorganisation during in vitro wound healing." Proc. of the European Simulation Multiconference '98, Manchester, "Simulation Tools in Biology", 343-347, 1998.

Ermentrout, G.B. and Edelstein-Keshet, L. "Related Articles Cellular automata approaches to biological modeling." J Theor Biol, **160**(1):97-133, 1993.

Graner, F. and Sawada, Y. "Can surface adhesion drive cell rearrangement? Part II: a geometrical approach." J Theor Biol, **164**:477-506, 1993.

Hénon, S. and Lenormand, G. and Richert, A. and Gallet, F. "A New Determination of the shear Modulus of the Human Erythrocyte Membrane Using Optical Tweezers." Biophysical J, **76**:1145-1151, 1999.

Honda, H. and Yamanaka, H. and Dan-Sohkawa, M. "A computer simulation of geometrical configurations during cell division." J Theor Biol, **106**:423-435, 1984.

Honda, H. and Tanemura, M. and Yoshida, A. "Differentiation of wing epidermal scale cells in a butterfly under the lateral inhibition model--appearance of large cells in a polygonal pattern." Acta Biotheor, **48**(2):121-36, 2000.

Ingber, D. E. and Heidemann, S. R. and Lamoureux, P. and Buxbaum, R. E. "Opposing views on tensegrity as a structural framework for understanding cell mechanics." J Appl Physiol, **89**(4):1663-1678, 2000.

Martiel, J.L. and Goldbeter, A. "A model based on receptor desensitization for cyclic AMP signaling in Dictyostelium cells." Biophysical J, **52**:807-828, 1987.

Murray, J. D. and Maini,P. K. and Tranquillo, R. T. "Mechanochemical models for generating biological pattern and form in development." Physics Rep, **171**:60-84, 1988.

Palsson, E. and Othmer, G. "A model for individual and collective cell movement in Dictyostelium discoideum." Proc Natl Acad Sci USA, **97**(19):10448-10453, 2000.

Parent, C.A. and Devreotes, P.N. "Molecular genetics of signal transduction in Dictyostelium." Annu Rev Biochem, **65**(2): 411-40. 1996.

Promayon, E. and Baconnier, P. and Puech, C. “Physically-based deformations constrained in displacements and volume.” Computer Graphic Forum, **15**(3):155-164, 1996.

Promayon, E. and Baconnier, P. and Puech, C. “Physically-based model for simulating the human trunk respiration movements.” Lecture notes in Computer Science, Springer Verlag, **1205**:379-388, 1997.

Sleep, J. and Wilson, D. and Simmons, R. and Gratzer,W. “Elasticity of the red cell membrane and its relation to hemolytic disorders: an optical tweezers study.” Biophysical J, **77**(6):3085-95, 1999.

Terzopoulos, D. and Platt, J. and Barr, A. and Fleischer, K. “Elastically Deformable Models.” Proc. Computer Graphics (ACM SIGGRAPH'87), M.C. Stone Ed., **21**(4):205-214, 1987.

Thoumine, O. and Meister, J.J. “Dynamics of adhesive rupture between fibroblasts and fibronectin: microplate manipulations and deterministic model.” Eur Biophys J, **29**(6):409-19, 2000.

Tyson, J.J. and Murray, J.D. “Cyclic AMP waves during aggregation of Dictyostelium amoebae.” Development, **106**:421-426, 1989.

Vasiev, B. and Weijer, C.J. “Modeling chemotactic cell sorting during Dictyostelium discoideum mound formation.” Biophysical J, **76**(2):595-605, 1999.

Volok, K.Y. and Vilnay, O. and Belsky, M. “Tensegrity architecture explains linear stiffening and predicts softening of living cells.” J Biomech, **33**(12):1543-1549, 2000.

Weijer, C. J. “Morphogenetic cell movement in Dictyostelium.” Semin Cell Dev Biol, **10**(6): 609-19.1999.

Weliky, M. and Minsuk, S. and Keller, R. and Oster, G. “Notochord morphogenesis in Xenopus laevis: simulation of cell behavior underlying tissue convergence and extension.” Development, **113**(4):1231-1244, 1991.

Wendling, S. and Oddou, C. and Isabey, D. “Stiffening response of a cellular tensegrity model.” J Theor Biol, **196**: 309-325, 1999.

Wendling, S. and Planus, E. and Laurent, V. and Barbe, L. and Mary, A. and Oddou, C. and Isabey, D. “Role of cellular tone and microenvironmental conditions on cytoskeleton stiffness assessed by tensegrity model.” European Physical Journal Applied Physics, **9**:51-62, 2000.

Yamaguchi, T. and Yamamoto, Y. and Liu, H. “Computational mechanical model studies on the spontaneous emergent morphogenesis of the cultured endothelial cells.” J Biomech, **33**(1):115-26, 2000.