A physically-based model for cell plasticity and motility

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Abstract: *Using a physically-based approach, we set up a dynamical model for cell deformation during movement. Our description is based on the behavior observed in motile mammalian cells during which the front and rear of the cell periodically exchange signals. Our simulations show that very simple dynamics, based on coupled autonomous Van der Pol oscillators, help to understand the interaction between the mechanical properties of the cell structures (membrane, actin cables, focal adhesion) and the activation/de-activation of Rho and Rac-dependent protein cascades. In addition, the physically-based approach proves its relevance in the context of complex systems, where physical and chemical processes together build up the cell response to external perturbation.*

Keywords: actin, cell movement, cell deformation, physically-based modeling.

1 Introduction

Deformable objects can be modeled using either a mechanical model, such as the Finite Element Method, or a physically-based discrete model. Mechanical models, although based on a strong theoretical background, are memory and time consuming. It is extremely difficult to use them to represent complex system where elastic and active structures are interacting with chemical systems or where a population of independent cells are interacting. A physically-based model, as presented in [6], addresses these drawbacks. Based on the classical laws of mechanics, it was used to model living deformable tissue and was later applied to different biological phenomenon [7].

The coupling between cell deformation and movement and biochemical processes hosted by the deforming/moving body is essential. To illustrate our approach, we simulate the movements of a cell on the extracellular matrix, either in response to autonomous intracellular regulation (figure 2) or through interactions with external stimuli as in chemotaxy (figure 3).

2 Simulation Tools and Biological Problem

As in [7], a cell-object (CO) is represented by a spherical membrane, defined by a set of 127 particles and graphically represented by triangular facets. Each particle has a mass and is subjected to external forces, including the gravitation and other attraction fields. A specific force models the membrane elasticity. Each particle is thus linked with its neighbouring particles using a local shape memory energy. Contractile properties can also be added by defining an active fiber between two particles. Local and global constraints can be added to account for boundary conditions (e.g. null displacement of a particle) and global constraints (e.g. incompressibility of

the CO). The dynamic of the CO is determined by the application of the equations of dynamics on each particles using the applied forces and constraints. In order to include realistic molecular mechanisms for cytoskeleton force generation in the CO, we consider a system of ordinary differential equations (ODE) which incorporate all non-mechanical phenomena, e.g. the kinetics of creation or the decay of a molecule. The system of differential equation is solved along with the dynamics of the CO, allowing information exchange in both directions: the forces exerted on the particles can depend on the dynamical variable controlled by the differential system; conversely, the force and/or local geometrical properties of the CO can influence the dynamics of the molecular mechanisms encoded into the ODE system.

Recent observations pointed out two major features in cell adhesion and motility. On the one hand, cytoskeleton reorganization during movement is based on the formation of new active actin bundles between two focal adhesion spots [9][5] in response to external signal mediated by membrane-bound proteins (proteins Rac and RhoA [4]). First, activation through Rac promotes the nucleation of new actin filaments through the activation of the Arp2/3 complex by WASP proteins [8]. This activation is present in lamellipodia or filopodia, the cell structures specialized in the initiation of movement or deformation. Second, the protein RhoA, which is activated at the rear of the cell, enhances the rigidity of the actin cytoskeleton through a different chemical pathway. Therefore, at the same time, the cell front and rear are characterized by different states of the cytoskeleton rigidity. On the other hand, [2] have shown that the lamellipodium experiences periodic extensions and interruptions, with a period of about 24 s in mammal cells. These autonomous oscillations are based on complex regulation of the actin polymerization. The same authors have demonstrated that a rearward wave (from cell front to rear) accompanies the sequence of protrusions-pauses of the lamellipodium. These waves, which are constituted of actin filaments bounded to α-actinin, might couple the front to the rear of the cell.

How could we reconcile the existence of the two antagonistic effects of Rac/RhoA pathways on the cytoskeleton? How could we assign a role to the rearward wave (front to rear) which accompanies the cell displacement? To address these questions we developed a minimal model in which the cytoskeleton status (soft *vs.* rigid) and the coupling between the front and the rear of the cell can account for cell displacement in space.

2.1   Equations.

Let (X_F, Y_F) (resp. (X_R, Y_R)) be a set of two variables accounting for the cytoskeleton status at the front (resp. the rear) of the cell. Each block constitutes an independent, non linear oscillator. (X_F, Y_F) controls the dynamics of protrusion through the Rac pathway. Although no periodic activation of the Rho cascade has been detected, we associate (X_R, Y_R) to the rear of the cell. In addition, we introduce a coupling between the two oscillators accounting for the rearward wave activity [2]. In absence of precise data and to simplify the mathematics of the model, each variable block is given by a Van der Pol oscillator

$$
\begin{cases}
\frac{dX_F}{dt} = \theta_F \left(Y_F + \varepsilon X_F \left(1 - X_F^2 \right) + \gamma \left(X_R - X_F \right) \right) \ , & \frac{dY_F}{dt} = -\theta_F Y_F \ , \\
\frac{dX_R}{dt} = \theta_R \left(Y_R + \varepsilon X_R \left(1 - X_R^2 \right) + \gamma \left(X_F - X_R \right) \right) \ , & \frac{dY_R}{dt} = -\theta_R Y_R \ ,
\end{cases}
\tag{1}
$$

where the parameter ε controls the importance of the non-linear terms; $\theta_{F,R}$ tune the period whereas γ couples the two oscillators. A positive (resp. negative) γ locks the two oscillators in in-phase (resp. anti-phase) oscillations. We consider a CO in interaction with the system (1). The CO front (resp. CO rear) can be fixed to the extracellular matrix at a given particle, P_F (resp. P_R). If $X_{F,R}(t) > \tau$, the particle P_F (resp. P_R) is fixed (null displacement) to the extracellular matrix (see figure 1). If $X_{F,R}(t) < \tau$, the constraint is released at P_F (resp. P_R): elasticity forces can apply anew to the particle (figure 1). Finally, we model an acto-myosin generated force between P_R and P_F by adding a contractile fiber between these two particles.

3 Results

First, we tested the behavior of the CO with no coupling ($\gamma = 0$) and arbitrary initial conditions for the two oscillators. As expected, the CO suffers deformations but, on average, cannot move along long distances (results not shown). If both oscillators are locked in anti-phase oscillations (γ is negative), the front and the rear of the CO alternated episodes of fixation/detachment of the particles P_R or P_F to the extracellular matrix (figure 2). When the front particle is detached ($X_F(t) < \tau$), the rear provides a fixed point to the CO ($X_R(t) > \tau$) and the contractile force deforms the CO forwards. During this phase, while the CO progresses, elastic energy is stored. Half a period later, the front particle is fixed ($X_F(t) > \tau$) while the rear is free to move ($X_R(t) < \tau$). The elastic energy, stored during the previous half period, now serves to pull the CO rear towards the front (figure 2). Since both oscillators have the same characteristics (period, amplitude), the process resumes after a full period, resulting into a steady progression of the CO.

To model interactions with extracellular signals, we subjected all the CO particles to an external attraction field force which mimics either the presence of an external source of chemical signals or a rigidity gradient for the extracellular matrix. During the initial phase (figure 2e), the CO moves according to the succession of fixation/detachment episodes under the control of the autonomous oscillator only. After a few steps, under the influence of the external force, the CO orients itself towards the source of signal (figure 2e), and eventually reaches it.

4 Discussion

Presently, our model is only qualitative, but it provides a first attempt to unify different processes, from molecular activation to cytoskeleton deformations, which together are responsible for a coherent displacement of cells in space. Model extensions will take into account the oscillatory control of actin polymerization at the cell front and the active stresses that are generated along the fibers connecting the front and the rear.

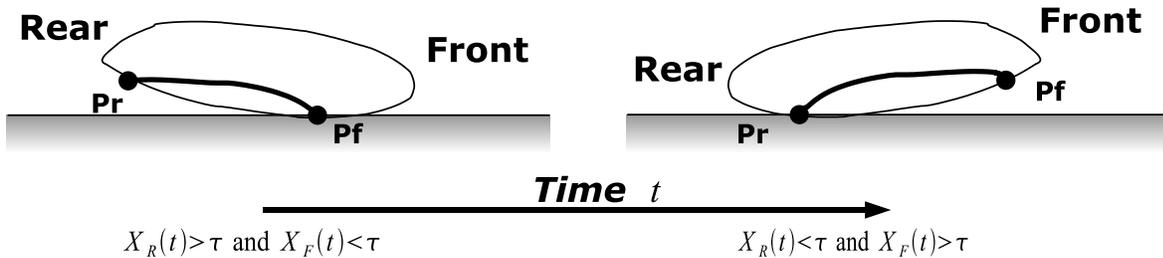## 4.1 Figures and Photographs

Figure 1. Schematic representation of a CO. The large black dots symbolize the particles that undergo periodic fixation/detachment to the extracellular matrix either at the rear (P_R) or the front (P_F) of the cell. This dynamics occurs as the variables X_F and X_R, which are associated to two non-linear coupled oscillators, cross the threshold value τ. The line symbolizes an actin cable connecting the two focal adhesion particles. The cable activity pushes the cell front forward while the rear is fixed to the extracellular matrix.
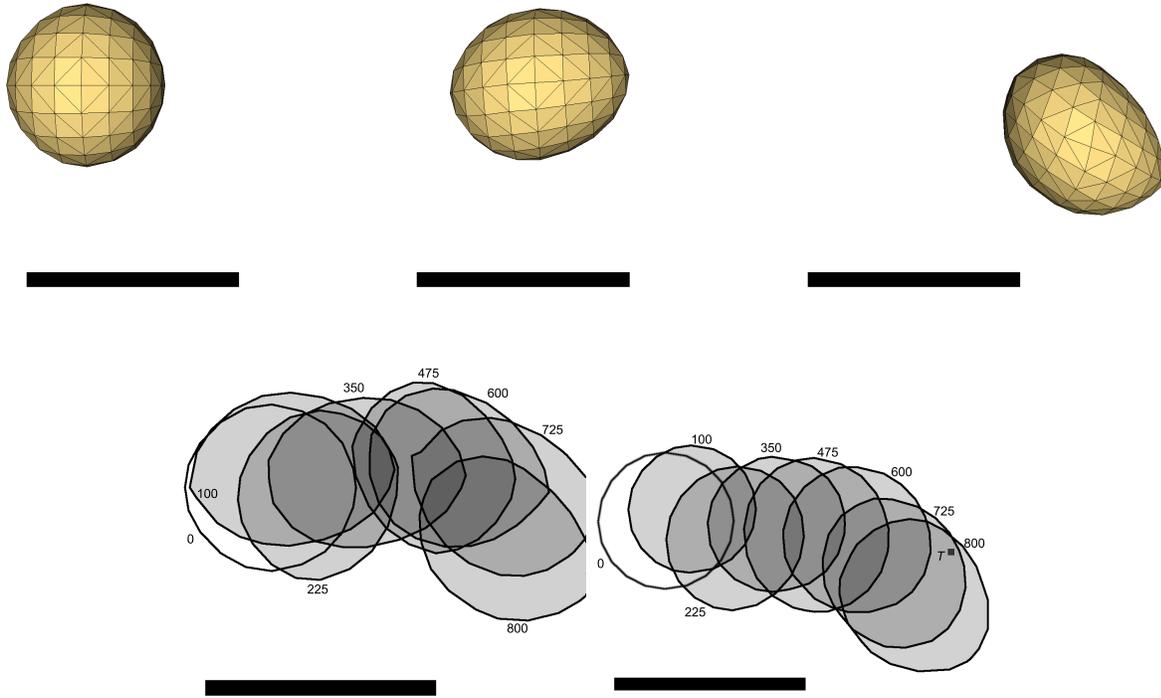
Figure 2. The CO front (resp. rear), under the control of a non-linear oscillator, alternates protrusion and interruption phases ($\varepsilon = 2.0, \gamma = -1.5, \theta = 0.05$). During stalling, the CO front or rear is fixed to the extracellular matrix, providing a fixed point to the CO. Three typical CO configurations are shown: the front moves forward (left), the CO is extending between the front and the rear (center), the retraction of the CO rear in direction of the front (right). The total period is about 24 s, a value in agreement with experiments on fibroblasts [2]. A movie of the simulation is available at http://www-timc.imag.fr/Alexandre.Carra/jobim2005

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Acknowledgements

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