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TWO-SCALE MODEL FOR THE MECHANICS OF EPITHELIAL TISSUES

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1 Abstract

Today the cellular rheology is still poorly understood. Though many experiments have been conducted, and some notable progress made, especially on the different entities involved in a solicitation and their respective roles. Based on the knowledge gathered during experimental work, we will propose a basic mathematical model of cell rheology. We only take into account the cellular cortex, which is considered a fluid, and the actin density present on this cortex. The results of this model suggest that the cell has a viscoelastic behaviour, although we have not introduced an elastic component. This is due to the actin polymerization reaction which, via the active tension, balances the system. In a way, the rigidity of the cell is managed by the amount of actin present in the cellular cortex. This is the most interesting behavior of the model, we have also made some parallels with the experimental results obtained in order to give values to our model. Overall, it shows the fundamental role of the actin in cell rheology, but all of the properties special to the other molecule are obviously absent (increase of the length of rest for example). The objective being at posteriori to complete this model to get closer to the real rheology, and infine to develop a model of tissue epithelium using the theory of vertex model

2 Introduction

Animal cells are the classic case of the eukaryotic cell, surrounded by a plasma membrane and containing a membrane-bound nucleus and organelles. One of the most important component of these cells is the cellular cortex(Trepat et al., 2008). The cellular cortex is a complex network of actin filaments attached to the inner surface of the plasma membrane(Biro et al., 2013). In addition to actin, this network includes numerous actin and myosin II regulatory proteins (Pollard, 1986). It is assumed to be around a couple hundred of nanometers thick (Chugh et al., 2017)(Clark et al., 2013) and has viscoelastic properties that allow it to oppose isotropic resistance to deformations(Kasza et al., 2007)(Saha et al., 2016). The polymerization dynamics of this cortex and its contractility make it a generator of cortical tensions, but also a central actor of cellular motility and tissue morphogenesis (Lecuit et al., 2011)(Bray D1, 1988)(Clark et al., 2013)(Bursac et al., 2005)(Levayer and Lecuit, 2012). There is a balance between the concentration of actin polymerized on the cortex and that present in the cytoplasm(Fritzsche et al., 2013), governed by a chemical reaction linking the actin to the myosin to form the actomyosin protein, the ATP (adenosine triphosphate) being the molecule which supplies the energy necessary for this reaction(Bendix et al., 2008). The more the cell is subjected to stress the more the cortex is charged with actin to respond to this disturbance by increasing the rigidity of the cell. This is why the cellular cortex occupies a primordial place in the mechanics of the cell.(Daniel A. Fletcher, 2010)(Salbreux et al., 2012)

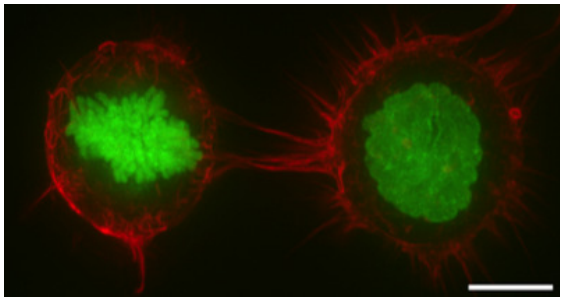


FIGURE 1 – (Public picture)F-actin distribution in the cell cortex as shown by rhodamine phalloidin staining of HeLa cells in red

These cells can be assembled together to form the epithelial monolayers(Staple et al., 2010). They cover most of the internal cavities and surfaces of the human body. They have protective functions against external physical and chemical aggressions and separate the body from its external environment(Harris et al., 2012). By accomplishing this task, the epithelia are subjected to significant mechanical stresses from the morphogenesis and throughout the adult life(Heisenberg, 2013)(Martin, 2010)(Hannezo et al., 2014), with respectively deformation rates of the order of $0.04\%.s^{-1}$ to $10 - 100\%.s^{-1}$ for normal functioning of the respiratory and cardiovascular systems(Guillot, 2013). Moreover, the tissues must also obviously respond to external mechanical stresses. Thus the constituent cells must allow the propagation of stress in the tissue in order to avoid the rupture of the latter synonymous with hemorrhage or other pathological problems.(Casares, 2012)(Harris et al., 2012)

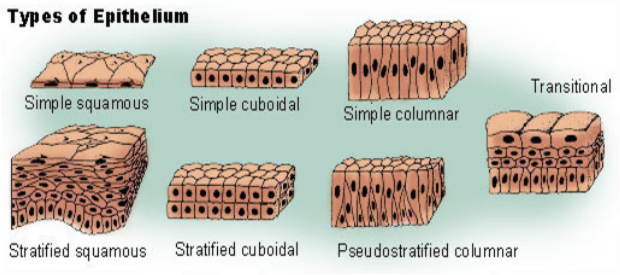


FIGURE 2 – (Public picture)Different types of epithelium : There are three principal shapes of epithelial cell : squamous, columnar, and cuboidal. These can be arranged in a single or multiple layers

To date, some experiments have been carried out on the scale of the tissue and the isolated cell(Fernández et al., 2006)(Lau et al., 2003)(Desprat et al., 2005)(Lenormand et al., 2004)(Moreno-Flores et al., 2010)(Moeendarbary et al., 2013)(Benitez and Toca-herrera, 2014)(Fischer-Friedrich et al., 2016)(Asadipour et al., 2016).In a recent study(Nargess Khalilgharibi, 2018), it has been observed that for short-time stress relaxation tests, monolayers respond in a biphasic manner. First with a large-amplitude rapid relaxation, exhibiting fluid-like properties, independent of ATP and occurring in the early seconds, followed by a slow relaxation of lower amplitude, with properties of solid type and dependent on ATP, which reaches a plateau after several tens of

seconds(Hoffman et al., 2006).This change may represent the shift from cytoplasmic rheology-dominated regime to actomyosin rheology-dominated at the periphery of the cell. Relaxation can be described by a function of the form $A.t^{-\alpha} + e^{\frac{-t}{\tau}} + B$, where the kinetics of the first phase is characterized by the exponent of the power law α and the second phase by the constant time constant τ(Desprat et al., 2005)(Kollmannsberger and Fabry, 2009)(Bonakdar et al., 2016). The parameter $\frac{B}{\epsilon_0}$ is equivalent to an elasticity and A affects the amplitude of the relaxation. Moreover, the dissipation of stress is accompanied by an increase in the rest length of the monolayers, which means the existence of an active remodeling of the cellular architecture during the relaxation. Finally, it has been shown that junctional complexes and intermediate filaments form stable connections between cells, which allows monolayers to behave rheologically as individual cells.(Nargess Khalilgharibi, 2018) It has also been concluded that the dynamics of the actomyosin cytoskeleton governs the rheological properties of monolayers by accelerating the return to mechanical equilibrium after extension. For experiments of longer duration, it has been found that cellular processes, which typically last for tens of minutes, are put in place to reduce the stresses within the tissue ; for example : division , neighbour exchange and extrusion.(Wyatt et al., 2016)(Wyatt et al., 2015) This experiment shows the rheological behavior obtained this time following the application of a stress in a creep experiment :

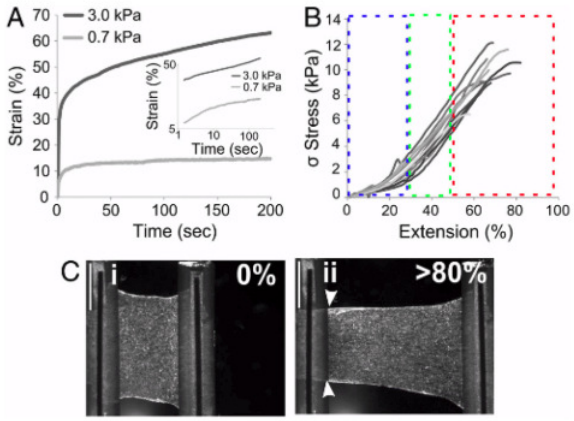


FIGURE 3 – (Harris et al., 2012)Mechanical properties of cell monolayers.(A)Creep response following step application of stress.(B)Stress-extension curves shown for 12 diffferent monolayers. (C)Deformation of a monolayer under stretch

Thus we have seen that experiments on monolayers and isolated cells are rich in teaching. The most important point being that their rheological behaviour is substantially the same. It is interesting to try to model the observations made in the course of these experiments to firstly try to deepen the knowledge on the observed behaviour still unexplained, and secondly to be able to predict the behaviour of a subject tissue to a particular intensity stress in a definite environment with a chosen chemical composition. The goal is to master perfectly the rheology of monolayers in order to be able to create synthesis cells forming operational organs ready to be grafted. In fact, today only 100,000 transplants are performed every year worldwide, mainly due to the low number of organ donations. Regenerative medicine based on synthetic organs could save more lives.

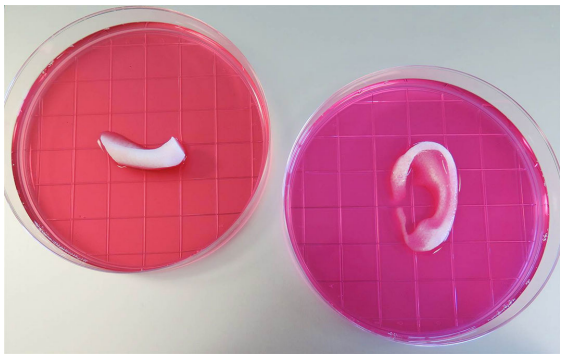


FIGURE 4 – (Wake Forest Institute for Regenerative Medicine) Researchers at the Wake Forest University School of Medicine in North Carolina have created a 3D printer which is able to manufacture implants by superimposing very precisely gels containing cells and biodegradable materials similar to plastic. The device then adds a temporary outer shell of polymer that helps the whole structure to maintain itself during implantation. Once the artificial organ is integrated into the body, the non-biological cells degrade naturally and the biological cells produce at the same time a support that allows the implant to maintain itself. Here are examples of a human jaw bone and an ear

2.1 Hypothesis and objectives

In this project, we will model the response of an animal cell to deformation and uniaxial stress. This corresponds to the best we have experimentally at the moment . We have made the following assumptions to define our model :
- Hexagonal shaped cell (s_0) and height (h_0)
- Constant cell volume
- Homogeneous cortex thickness along cell surfaces
- No mass creation within the cell
- Active tension proportional to cortex thickness
- The cortex behaves like a viscous fluid.

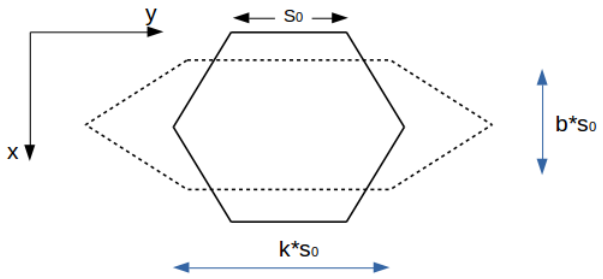


FIGURE 5 – Model of the strainning

We thus consider, as we can see in the image above, a regular hexagon of dimensions s_0, the uniaxial deformation of k implies a movement b on the perpendicular direction. The shape obtained is any hexagon elongated (dotted).

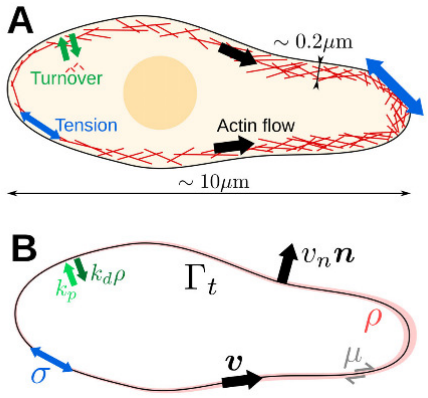


FIGURE 6 – (Torres-Sanchez, 2017)Biological model and mathematical model equivalent

This is a simple sketch of the different parameters present in our model. On the picture A we can see the biological phenomena observed inside the cell and on the B-picture the mathematical

equivalents. So to modelise the balance between polymerization and depolymerisation of the cortex, we introduce two coefficients which are respectively k_p and k_d. Then the active tension is symbolised by σ and the actin density with ρ. We are not going to consider the actin flow v and the membrane out-of-plane deformation v_n

3 Materials and Methods

To generate the governing equations necessary to solve this probleme, we will use the Onsager's variational principle.*This is a genuinely dynamical principle establishing a competition between the energy release rate and dissipation, where the key assumptions are that (i) disspitation dominates over inertia and (ii) viscous forces are derived from a dissipation potential.*(Doi, 2011)(Arroyo et al., 2018)
This principle consists in expressing the differents energy contributions. This equation is called the Rayleighian $\mathcal{R}$, function of the state variable and their rate of change.
Onsagers principle says that the system evolves as such manner that the Rayleghian is minimized with respect to the rate of change of the state variable :

$$\boxed{\dot{x} = argmin\mathcal{R}(x, \dot{x})} \tag{1}$$

In addition, we assumed that $\mathcal{R}$ is a convex function of rate of change of states variable. Also to obtain the governing equations, we need to solve for each range of state (here the speed as example) the following system :

$$\boxed{0 = \frac{\partial \mathcal{R}}{\partial \dot{x}}} \tag{2}$$

The assumption needed to use the Onsagers principle are that the system is viscous (there is dissipation of energy), that this dissipation can be written as convex functions and that there is no inertia. Or experiences show that the lipid bilayers (cell) have both an elastic and inextensible viscous fluid behavior. We call it a viscoelastic system and thus we can apply the Onsagerś principle.

We consider a fluid in a fixed volume ω with boundary $d\omega$. We split $d\Omega = \Gamma_D \cup \Gamma_N$ into two disjoint subdomains, The Dirichlet boundary Γ_D, where a displacement is prescribed k and b, and the Neumann boundary Γ_N where a traction t(x) is applied.

The dissipation potential for an Newtonian incompressible fluid on the domaine Ω is :

$$\boxed{\mathcal{D}_{visc}[v] = 2\eta \int_{\Omega} \underline{\underline{\mathbf{d}}} : \underline{\underline{\mathbf{d}}} d\mathbf{V}} \tag{3}$$

where d is the rate-of-deformation tensor $\underline{\underline{\mathbf{d}}} = \frac{1}{2}(\nabla \mathcal{V} + \nabla \mathcal{V}^T)$ and η is the shear viscosity of the fluid.

Furthermore, the traction at the Neumann boundary can be considered trough a potential of the form :

$$\boxed{\mathcal{P}_{ext}[v] = -\int_{\Gamma_N} \boldsymbol{t} \cdot \boldsymbol{v} dS} \tag{4}$$

Finally, the Raleyghian of this system is simply as follows :

$$\boxed{\mathcal{R}[v] = \mathcal{D}[v] + \mathcal{P}[v]} \tag{5}$$

State variables
Now we are going to define the state variables that we have chosen, for an uniaxial strain and stress : The Vector X represents the vector of the state variables of the system, which are b and k for the strains respectively according to x and y.

$$X = \begin{Bmatrix} k, & b \end{Bmatrix} \tag{6}$$

We can then express the Vector V, which is the Vector of Onsager's principle

$$V = \frac{\partial X}{\partial t} = \begin{Bmatrix} \dot{k}, & \dot{b} \end{Bmatrix} \tag{7}$$

We can also express the Vectors F and σ wich are respectively the Tensor and Stress Vector for a uniaxial strain. we define $\begin{Bmatrix} X_1, & X_2, & X_3 \end{Bmatrix}$ as the initial base and $\begin{Bmatrix} x_1, & x_2, & x_3 \end{Bmatrix}$ as the final base of the solide after deformation. According to the definition of the tensor vector we have :

$$x = F.X \implies \mathcal{F} = \begin{pmatrix} b & 0 & 0 \\ 0 & k & 0 \\ 0 & 0 & \frac{1}{kb} \end{pmatrix} \tag{8}$$

and since we are in a uniaxial deformation, we know that the stress matrice has the following form :

$$\sigma = \begin{pmatrix} \sigma_b & 0 & 0 \\ 0 & \sigma_k & 0 \\ 0 & 0 & 0 \end{pmatrix} \tag{9}$$

TABLE 1 – Summary of the model parameters

Parameter	Description	Dimensions
s_0	Cell edge length	[L]
h_0	Cell height	[L]
P	Cell perimeter	[L]
A_{cell}	Total cell area	$[L^2]$
A_{ap}	Apical cell area	$[L^2]$
A_0	Initial apical cell area	$[L^2]$
A_l	Lateral cell area	$[L^2]$
V_0	Cell volume	$[L^3]$
ε_{ap}	Apical areal strain	$[\cdot]$
$\dot{\varepsilon}_{ap}$	Apical areal strain rate	$[\cdot]/[T]$
ε_{al}	Lateral areal strain	$[\cdot]$
$\dot{\varepsilon}_{al}$	Lateral areal strain rate	$[\cdot]/[T]$
C_0	Total cortical material	[Moles]
C	Cytosolic cortical material concentration	$[Moles]/[L]^3$
ρ	Surface density of the cortex	$[Moles]/[L]^2$
ρ_0	Reference surface density of the cortex	$[Moles]/[L]^2$
k_p	Polymerization rate	$[L]^3/[T]$
k_d	Depolymerization rate	$[L]^2/[T]$
γ_{ap}^0	Reference apical active tension	[N]/[L]
γ_l^0	Reference lateral active tension	[N]/[L]
γ_{ap}	Apical active tension	[N]/[L]
γ_l	Lateral active tension	[N]/[L]
τ	Tissue tension	[N]/[L]
η	Bulk shear viscosity coefficient	$[N][T]/[L]^2$
t_c	Cortical thickness	[L]
t_c^0	Reference cortical thickness	[L]

3.1 Geometrical parametres

In this section, we are going to express the geometrical parameters necessary for modeling the system we must express A_{cell}, A_{ap} and A_l as a function of k, b and ρ· We calcul the new cell area after deformation following each direction, and we compare it to the initial area. We can deduct the relation as follows :

$$\begin{cases} A_{ap} & = A_{0ap}(kb) \\ A_l & = A_{0al}(\frac{1}{3b} + \frac{1}{3}\sqrt{\frac{1}{b^2} + \frac{3}{k^2}}) \\ A_{cell} & = 2A_{ap} + Al \end{cases} \tag{10}$$

Where A_{0ap} is the initial apical surface area and A_{0al} is the initial lateral surface area

Furthermore, we are in a dynamic study also the time dot associated with this system of equations are also necessary :

$$\begin{cases} \dot{A_{ap}} & = A_{0ap}(\dot{k}b + \dot{b}k) \\ \dot{A_l} & = -A_{0al}(\frac{\dot{b}}{3b^2} + \frac{\frac{\dot{b}}{3b^3} + \frac{\dot{k}}{k^3}}{\sqrt{\frac{1}{b^2} + \frac{3}{k^2}}}) \\ \dot{A_{cell}} & = 2A_{0ap}(\dot{k}b + \dot{b}k) - A_{0al}(\frac{\dot{b}}{3b^2} + \frac{\frac{\dot{b}}{3b^3} + \frac{\dot{k}}{k^3}}{\sqrt{\frac{1}{b^2} + \frac{3}{k^2}}}) \end{cases} \tag{11}$$

Then we are interesting by the strain of the cell. We define the areal strain as following

$$\boxed{\varepsilon_x = \frac{A_x - A_{0x}}{A_{0x}}} \tag{12}$$

According to this definition, we have the two strain rate as follows

$$\begin{cases} \varepsilon_{ap} & = kb - 1 \\ \varepsilon_{al} & = \frac{1}{3b} + \frac{1}{3}\sqrt{\frac{1}{b^2} + \frac{3}{k^2}} - 1 \end{cases} \tag{13}$$

And the derivatives :

$$\begin{cases} \dot{\varepsilon_{ap}} & = \dot{k}b + \dot{b}k \\ \dot{\varepsilon_{al}} & = -\frac{\dot{b}}{3b^2} - \frac{\frac{\dot{b}}{3b^3} + \frac{\dot{k}}{k^3}}{\sqrt{\frac{1}{b^2} + \frac{3}{k^2}}} \end{cases} \tag{14}$$

Now that we have expressed all the geometrical parameters, we can define the potentials useful to apply the Onsagerś principle

3.2 Energy potential

3.2.1 The power

As we saw previously at the beginning of the section, we can split the domain in two different boundary. First we will calculate the traction at the Neumann boundary and then the dissipation potential on the whole domain.

Calculation of $\mathrm{P}_{tension}$

The cell is subject to different tension during the deformation. There are the tension due to the external power applied to the cell, called the external tension ; and the active power supplied by myosin, due to mechanical properties of the cell and called the active tension
First we must calculate the $\mathcal{P}_{ext}$

$$\boxed{\mathcal{P}_{ext} = -\int_{\Gamma_N} \boldsymbol{t} \cdot \boldsymbol{v} dS} \tag{15}$$

with just to remember

$$\sigma = \begin{pmatrix} \sigma_b & 0 & 0 \\ 0 & \sigma_k & 0 \\ 0 & 0 & 0 \end{pmatrix} \tag{16}$$

and

$$\mathcal{V} = \left\{ \frac{\dot{b}}{b} x_1, \quad \frac{\dot{k}}{k} x_2, \quad \frac{-(\dot{k}b + \dot{b}k)}{kb} x_3 \right\} \tag{17}$$

For the face with normal $\vec{n}$ collinear to the landmark, for example $\vec{n_1} = (1, 0, 0)$ and $x_1 = (\frac{\sqrt{3}}{2}.s_1, 0, 0)$, the calcul is simple :

$$\mathcal{P}_c = -\int_{\Gamma_N} (\sigma.n_1).\boldsymbol{v} dS_1 = -\sigma_b.(\frac{\dot{b}}{b}.\frac{\sqrt{3}}{2}.s_1).(s_2.h) \tag{18}$$

$$\boxed{\mathcal{P}_c = -\tau_b \frac{\dot{b}}{b}.\frac{\sqrt{3}}{2}.s_1 s_2} \tag{19}$$

For the other faces, with normal $\vec{n}$ non collinear to the landmark, for example $\vec{n_1} = (\frac{1}{2}, \frac{\sqrt{3}}{2}, 0)$, we need to define a parameterized curve :

$$t = 0 \implies \begin{cases} x = \dfrac{\sqrt{3}}{2}.s_1 \\ y = \dfrac{s_2}{2} \end{cases} \qquad t = 1 \implies \begin{cases} x = 0 \\ y = s_2 \end{cases} \tag{20}$$

Thus we can express the curve and the dot according to t as follows :

$$\begin{cases} x = (1-t)\dfrac{\sqrt{3}}{2}.s_1 \\ y = (1+t)\dfrac{s_2}{2} \end{cases} \implies \begin{cases} \dfrac{\partial x}{\partial t} = -\dfrac{\sqrt{3}}{2}.s_1 \\ \dfrac{\partial y}{\partial t} = \dfrac{s_2}{2} \end{cases} \tag{21}$$

We must calculate the new differential variable linked to the curve :

$$d\gamma = \sqrt{(\frac{\partial x}{\partial t})^2 + (\frac{\partial y}{\partial t})^2}dt = \sqrt{\frac{3}{4}s_1^2 + \frac{s_2^2}{4}})dt \tag{22}$$

Finally now we are able to find the tension exerted on the non collinear faces :

$$\begin{aligned} \mathcal{P}_{nc} &= -\int\int \left(\frac{\sigma_b}{2}\frac{\dot{b}}{b}x(t) + \frac{\sqrt{3}}{2}\sigma_k\frac{\dot{k}}{k}y(t) \right).dzd\gamma \\ &= -\frac{\sigma_b}{2}h_0\frac{\dot{b}}{b}\int x(t)d\gamma + \frac{\sqrt{3}}{2}\sigma_k h_0\frac{\dot{k}}{k}\int y(t)d\gamma \\ &= -\sqrt{\frac{3}{4}s_1^2 + \frac{s_2^2}{4}} \left(\tau_b\frac{\sqrt{3}}{4}\frac{\dot{b}}{b}s_1\int_0^1(1-t)dt + \tau_k\frac{\sqrt{3}}{4}\frac{\dot{k}}{k}s_2\int_0^1(1+t)dt \right) \end{aligned} \tag{23}$$

$$\boxed{\mathcal{P}_{nc} = -\sqrt{\frac{3}{4}s_1^2 + \frac{s_2^2}{4}} \left(\tau_b\frac{\sqrt{3}}{8}\frac{\dot{b}}{b}s_1 + \tau_k\frac{3\sqrt{3}}{8}\frac{\dot{k}}{k}s_2 \right)} \tag{24}$$

Now we can calculate the total stress : $\mathcal{P}_{ext} = 2\mathcal{P}_c + 4\mathcal{P}_{nc}$:

$$\mathcal{P}_{ext} = -\tau_b\sqrt{3}\frac{\dot{b}}{b}s_1s_2 - \frac{\sqrt{3}}{2}\sqrt{\frac{3}{4}s_1^2 + \frac{s_2^2}{4}} \left(\tau_b\frac{\dot{b}}{b}s_1 + \tau_k 3\frac{\dot{k}}{k}s_2 \right) \tag{25}$$

$$\boxed{\mathcal{P}_{ext} = -\tau_b\frac{\dot{b}}{b}\alpha_{(b,k)} - \tau_k\frac{\dot{k}}{k}\beta_{(b,k)}} \tag{26}$$

With respectively :

$$\alpha = s_1(\sqrt{3}s_2 + \frac{\sqrt{3}}{2}\sqrt{\frac{3s_1^2}{4} + \frac{s_2^2}{4}}); \beta = s_2\frac{3\sqrt{3}}{2}\sqrt{\frac{3s_1^2}{4} + \frac{s_2^2}{4}} \tag{27}$$

$$s_1 = bs_0; s_2 = ks_0 \tag{28}$$

Then we must define the active tension $\mathcal{P}_{active}$. As cells are active and dynamic objects, it makes more sense to consider the work done by active tension as a power. We define γ_{ap} and γ_l respectively as the apical and lateral active tension. Thus we have :

$$\begin{aligned}\mathcal{P}_{active} &= 2\gamma_{ap}\dot{A}_{ap} + \gamma_l \dot{A}_l \\ &= 2\gamma_{ap}A_{0p}\dot{\varepsilon}_{ap} + \gamma_l A_{0l}\dot{\varepsilon}_{ap}\end{aligned} \tag{29}$$

$$\boxed{\mathcal{P}_{active} = 2\gamma_{ap}A_{0ap}(\dot{k}b + \dot{b}k) - \gamma_l A_{0al}(\frac{\dot{b}}{3b^2} + \frac{\frac{\dot{b}}{3b^3} + \frac{\dot{k}}{k^3}}{\sqrt{\frac{1}{b^2} + \frac{3}{k^2}}})} \tag{30}$$

We can thus express $\mathcal{P}_{tension} = \mathcal{P}_{ext} + \mathcal{P}_{active}$:

$$\boxed{\mathcal{P}_{tension} = -\tau_b \frac{\dot{b}}{b}\alpha_{(b,k)} - \tau_k \frac{\dot{k}}{k}\beta_{(b,k)} + 2\gamma_{ap(\rho(t))}A_{0ap}(\dot{k}b + \dot{b}k) - \gamma_{al(\rho(t))}A_{0al}(\frac{\dot{b}}{3b^2} + \frac{\frac{\dot{b}}{3b^3} + \frac{\dot{k}}{k^3}}{\sqrt{\frac{1}{b^2} + \frac{3}{k^2}}})} \tag{31}$$

Finally, with this equation we have one of the part of the Raleyghian of the system which is $\mathcal{P}[v]$. the second term is the dissipation potential that we are going to calculate in the next section.

3.2.2 Dissipation

Calcul of the dissipation potential

We consider that the cortex behaves as an active viscous fluid. There is thus a dissipation of energy due to the viscosity. We need to calculate this dissipation to be able to use the Onsager's principle. We consider a fluid in a fixed volume ω with boundary $d\omega$. For a Newtonian incompressible fluid in the low Reynolds limit, the term of dissipation is as follows :

$$\mathcal{D}_{visc} = 2\eta \int_\Omega \underline{\underline{\mathbf{d}}} : \underline{\underline{\mathbf{d}}} d\mathbf{V} \tag{32}$$

where d is the rate-of-deformation tensor $\underline{\underline{\mathbf{d}}} = \frac{1}{2}(\nabla\mathcal{V} + \nabla\mathcal{V}^T)$ and η is the shear viscosity of the fluid. Since the form of $\mathcal{V}$ is really simple :

$$\mathcal{V} = \left\{ \frac{\dot{b}}{b}x_1, \quad \frac{\dot{k}}{k}x_2, \quad \frac{-(\dot{k}b + \dot{b}k)}{kb}x_3 \right\} \tag{33}$$

The calcul of the dissipation potential is almost immediate, we obtain the following result :

$$\mathcal{D}_{visc} = 2\eta A_{cell\,(b,k)} t_c \frac{(\dot{k}b)^2 + (\dot{b}k)^2 + (\dot{k}b + \dot{b}k)^2}{(kb)^2} \tag{34}$$

So we have the second term of the Raleyghian, $\mathcal{D}[v]$, and thus we can express the Raleyghian :

$$\mathcal{R} = -\tau_b \frac{\dot{b}}{b}\alpha_{(b,k)} - \tau_k \frac{\dot{k}}{k}\beta_{(b,k)} + 2\gamma_{ap(\rho(t))}A_{0ap}(\dot{k}b + \dot{b}k) - \gamma_{al(\rho(t))}A_{0al}(\frac{\dot{b}}{3b^2} + \frac{\frac{\dot{b}}{3b^3} + \frac{\dot{k}}{k^3}}{\sqrt{\frac{1}{b^2} + \frac{3}{k^2}}}) \\ +2\eta A_{cell(b,k)}t_c \frac{(\dot{k}b)^2 + (\dot{b}k)^2 + (\dot{k}b + \dot{b}k)^2}{(kb)^2} \tag{35}$$

We can note that we have three state unknown variables in this equation but solely two rate of state which are $\dot{b}$ and $\dot{k}$. Also if we apply Onsagers principle, we will obtain just two equations. We miss one equation due to the absence of $\dot{\rho}$ in our Raleyghian. Also we need to find another equation to solve our problemn.

3.2.3 Cortical mass balance equation

We assume that there is no gain or loss of actin in the cell. It means that the total actin material is kept constant in the cell, which is expressed as follows :

$$\boxed{C_0 = CV_0 + \rho A_{cell}} \tag{36}$$

Furthermore, there is an exchange between the actin polymerized on the cortex and the free actin presents in the cytoplasm. According to the applied stress, the rigidity of the cell needs to change, what goes through a polymerization of actin. This reaction equation is expressed as following :

$$\boxed{r = k_p C - k_d \rho} \tag{37}$$

Where r is the rate of actin creation per unit area, $r = \frac{d(\rho A_{cell})}{dt A_{cell}}$ and k_p and k_p are kinetic coefficients reprensenting respectively polymerisation and depolymerisation.
It's important to note that the values for k_p and k_d are remove from literature.
At equilibrium, with no applied strain or stress, the rate of actin creation is nul and thus we obtain :

$$C^{eq} = \frac{k_d}{k_p}\rho^{eq} \implies \rho^{eq} = \frac{C_0}{A_{cell} + \frac{k_d}{k_p}V_0} \tag{38}$$

By coupling equations (37) and (38), we obtain the following equation :

$$\boxed{\dot{\rho} + \rho\frac{\dot{A_{cell}}}{A_{cell}} = k_p\frac{C_0}{V_0} - \rho\left[\frac{k_p A_{cell}}{V_0} + k_d\right]} \tag{39}$$

We are now able to solve the problem, indeed we have 3 state variables and 3 equations. We are going to apply Onsager's principle to extract the two other equations.

3.3 Application of Onsager'principle

As a reminder, we have found the following Raleyghian :

$$\mathcal{R} = -\tau_b \frac{\dot{b}}{b}\alpha_{(b,k)} - \tau_k \frac{\dot{k}}{k}\beta_{(b,k)} + 2\gamma_{ap(\rho(t))}A_{0ap}(\dot{k}b + \dot{b}k) - \gamma_{al(\rho(t))}A_{0al}\left(\frac{\dot{b}}{3b^2} + \frac{\frac{\dot{b}}{3b^3} + \frac{\dot{k}}{k^3}}{\sqrt{\frac{1}{b^2} + \frac{3}{k^2}}}\right) + 2\eta A_{cell(b,k)}t_c \frac{(\dot{k}b)^2 + (\dot{b}k)^2 + (\dot{k}b + \dot{b}k)^2}{(kb)^2} \tag{40}$$

With respect to the principle, we search to minimize the Raleyghian according to $\dot{b}$ and $\dot{k}$, the two rate of change present here :

$$\frac{\partial \mathcal{R}}{\partial \dot{b}} = 0 \implies \boxed{0 = 4\eta A_{cell(b,k)}t_c \frac{(2k^2\dot{b} + \dot{k}kb)}{(kb)^2} - \frac{\tau_b}{b}\alpha_{(b,k)} + 2\gamma_{ap(\rho(t))}A_{0ap}k - \gamma_{al(\rho(t))}A_{0al}\left(\frac{1}{3b^2} + \frac{\frac{1}{3b^3}}{\sqrt{\frac{1}{b^2} + \frac{3}{k^2}}}\right)} \tag{41}$$

$$\frac{\partial \mathcal{R}}{\partial \dot{k}} = 0 \implies \boxed{0 = 4\eta A_{cell(b,k)}t_c \frac{(2b^2\dot{k} + \dot{b}kb)}{(kb)^2} - \frac{\tau_k}{k}\beta_{(b,k)} + 2\gamma_{ap(\rho(t))}A_{0ap}b - \gamma_{al(\rho(t))}A_{0al}\left(\frac{\frac{1}{k^3}}{\sqrt{\frac{1}{b^2} + \frac{3}{k^2}}}\right)} \tag{42}$$

and we add the last equation from critical mass balance :

$$\boxed{\dot{\rho} + \rho\frac{\dot{A_{cell}}}{A_{cell}} = k_p\frac{C_0}{V_0} - \rho\left[\frac{k_p A_{cell}}{V_0} + k_d\right]} \tag{43}$$

Also at present, the mathematical part is finished, we will then define the two different cases that we will modelise and explain the modelling process.

3.4 The different cases

Before doing anything we have to check if the basique principle is respected, that is to say if for any stress and strain (k=1 and b=1), there are no tension or deformation inside the cell. It means that the equation (42) and (43) should be equal to zero :

$$2A_{0ap} - \frac{A_{0al}}{2} = 0 \implies 2.\frac{3\sqrt{3}}{2}s_0^2 - \frac{6h_0.s_0}{2} = 0 \tag{44}$$

with $\dot{b} = \dot{k} = \tau_b = \tau_k = 0$ and $\gamma_{0ap} = \gamma_{0al}$ and $A_{0ap} = \frac{3\sqrt{3}}{2}s_0^2$ because of the regular 6-sided polygone
Finally we obtain that h_0 must respect a geometrical contraint which is $h_0 = \sqrt{3}s_0$

3.4.1 Uniaxial stress relaxation

This is the first case, we modelise an uniaxial strain on the cell. we deform the cell according to the direction y. This is equivalent to fix the value of k and put $\tau_b = 0$. There is indeed no stress in the direction x because we let b free.
The three equations obtained look like this :

$$\begin{aligned}
\dot{\rho} + \rho\frac{\dot{A}_{cell}(k,b,\dot{b},\dot{k})}{A_{cell}(k,b)} &= k_p\frac{C_0}{V_0} - \rho\left[\frac{k_p A_{cell(k,b)}}{V_0} + k_d\right] \\
0 &= 4\eta A_{cell\,(k,b)} t_c \frac{(2k^2\dot{b} + \dot{k}kb)}{(kb)^2} + 2\gamma_{ap(\rho(t))}A_{0ap}k - \gamma_{al\,(\rho(t))}A_{0al}\left(\frac{1}{3b^2} + \frac{\frac{1}{3b^3}}{\sqrt{\frac{1}{b^2}+\frac{3}{k^2}}}\right) \\
0 &= 4\eta A_{cell\,(k,b)} t_c \frac{(2b^2\dot{k} + \dot{b}kb)}{(kb)^2} - \frac{\tau_k}{k}\beta_{(b,k)} + 2\gamma_{ap(\rho(t))}A_{0ap}b - \gamma_{al\,(\rho(t))}A_{0al}\left(\frac{\frac{1}{k^3}}{\sqrt{\frac{1}{b^2}+\frac{3}{k^2}}}\right)
\end{aligned} \tag{45}$$

The above coupled equation corresponds to a *differential-algebraic* equation. It can be easily solved in *MATLAB* using *ode15i*. The results are shown in the next section.

3.4.2 Uniaxial creep

This is the second case, and the more interesting because we modelise an uniaxial stress on the cell, which is closer to the reality. We push the cell according to the direction y. This is equivalent to fix the value of τ_k and put $\tau_b = 0$. There is indeed no stress in the direction x because we let b free.
The three equations obtained look like this :

$$\begin{aligned}
\dot{\rho} + \rho\frac{\dot{A_{cell}}}{A_{cell}} &= k_p\frac{C_0}{V_0} - \rho\left[\frac{k_p A_{cell}}{V_0} + k_d\right] \\
0 &= 4\eta A_{cell\,(b,k)} t_c \frac{(2k^2\dot{b} + \dot{k}kb)}{(kb)^2} + 2\gamma_{ap(\rho(t))}A_{0ap}k - \gamma_{al\,(\rho(t))}A_{0al}\left(\frac{1}{3b^2} + \frac{\frac{1}{3b^3}}{\sqrt{\frac{1}{b^2}+\frac{3}{k^2}}}\right) \\
0 &= 4\eta A_{cell\,(b,k)} t_c \frac{(2b^2\dot{k} + \dot{b}kb)}{(kb)^2} - \frac{\tau_k}{k}\beta_{(b,k)} + 2\gamma_{ap(\rho(t))}A_{0ap}b - \gamma_{al\,(\rho(t))}A_{0al}\left(\frac{\frac{1}{k^3}}{\sqrt{\frac{1}{b^2}+\frac{3}{k^2}}}\right)
\end{aligned} \tag{46}$$

The above coupled equation corresponds to a *differential-algebraic* equation. It can be easily solved in *MATLAB* using *ode15i*. The results are shown in the next section.

4 Results

4.1 Uniaxial stress relaxation

We introduce a ramp strain with the following form : $k = k_i(1 - e^{-5t})$ which converges towards k_i in more or less 1 second. Also the speed of straining is variable.

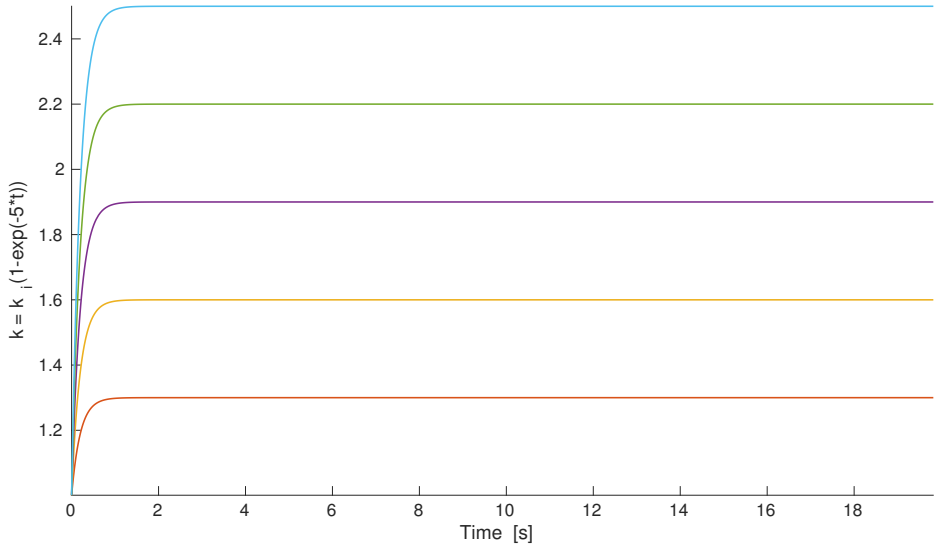


FIGURE 7 – k evolution

To let you see the global behaviour of the cell in response to this perturbation, we have plotted the actin rate, apical and lateral deformation together with the strain τ_k. We have split the time in two different part to focus on the demeanour of the cell during the variable and permanent time.

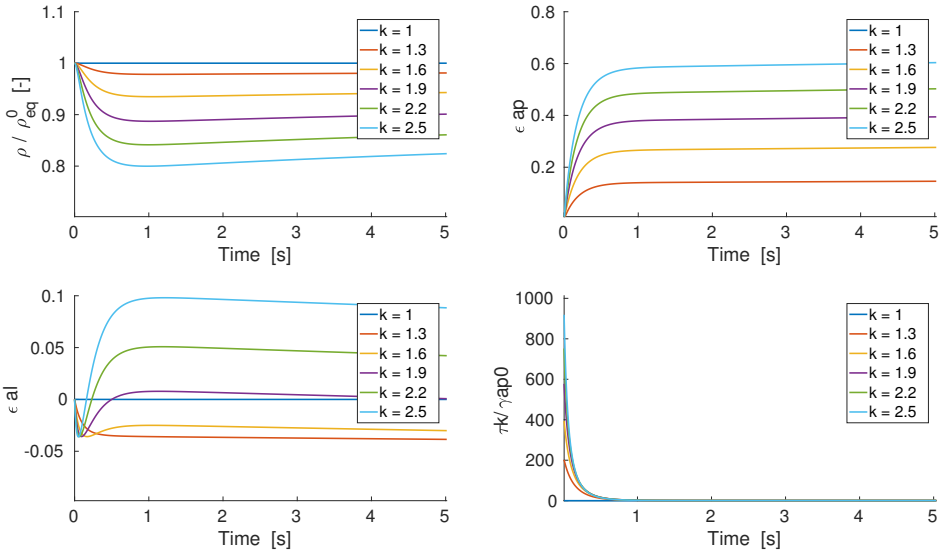


FIGURE 8 – Actin rate, ϵ_{ap}, ϵ_{al} and τ_k from 0 to 5s following the k-straining

On these figures, we can see that the actin rate in the cortex decreases during the application of the deformation, due to the increasing of the apical area faster than the increasing of the actin on the cortex, until that the strain is permanent. At this moment, the area of the cell stop growing significantly, there is though a small diminution of *Acell* due to the relaxation of the width with the effect of the viscosity. However we observe during all this time an active response of the cell leading to a polymerization of actin, this chemical reaction has an inertia which made it achieves an equilibrium state eight times after that we are in a constant straining. That why the density of actin increases after 1 second until 8 seconds.
The apical deformation representing by ϵ_{ap} is similar to the evolution of k, because depends on it. The most interesting parts are the lateral deformation and the stress τ_k.
The behaviour of ϵ_{al} was unpredictable for the lowest values of time. Indeed, the lateral area is first in a compression state, then there are three different cases : if the value of k is enough low, the cell stays in this compressing state, for example $k = 1, 2$. But if the k is up to 1.7, ϵ_{al} achieves a limit value which implies the reduction of ϵ_{al}. This reduction can lead to a temporal "stressing state" if the value of k is high, or otherwise simply to a less compressing state. This is also function of the viscosity, which changes the value of the limited straining, the position and the value of the local extremum. Finally when the strain is permanent, we will see that the equilibrium state is as expected in compression. We will explain these observations in the next section, particularly the minimum of ϵ_{al}.
At least, we can observe that the cell is subject to a very high stress during the first second of time, the order is as 10^2 of γ_{ap0}. This is due to the value of the coefficient of viscosity $\eta = 10^5$. Indeed, in the beginning of time, τ_k is more or less equal to the first term of the third equation, which depends a lot of η during the first step. If we decrease or delete this coefficient, this jump disappears. This is purely a mathematical representation but it is sure that in reality we have not this, otherwise the cell will collapse.

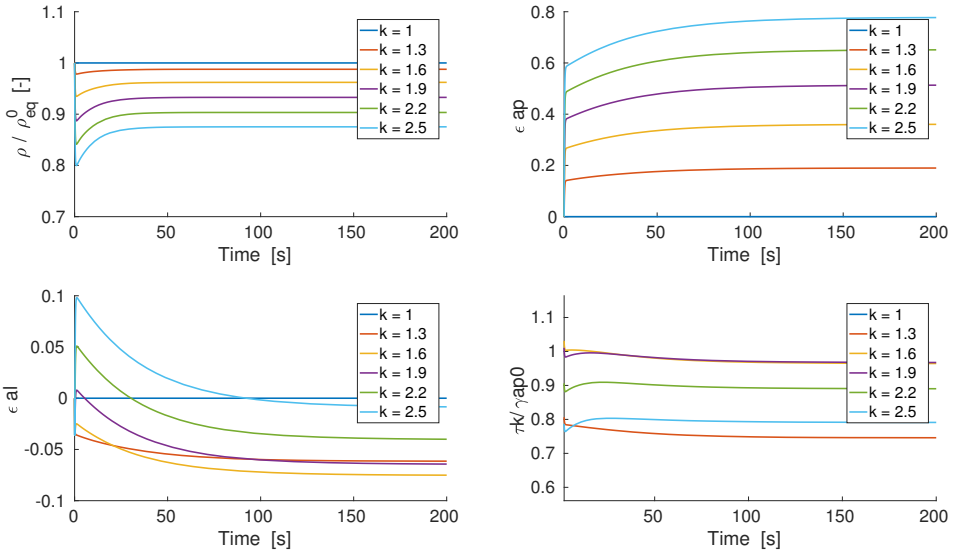
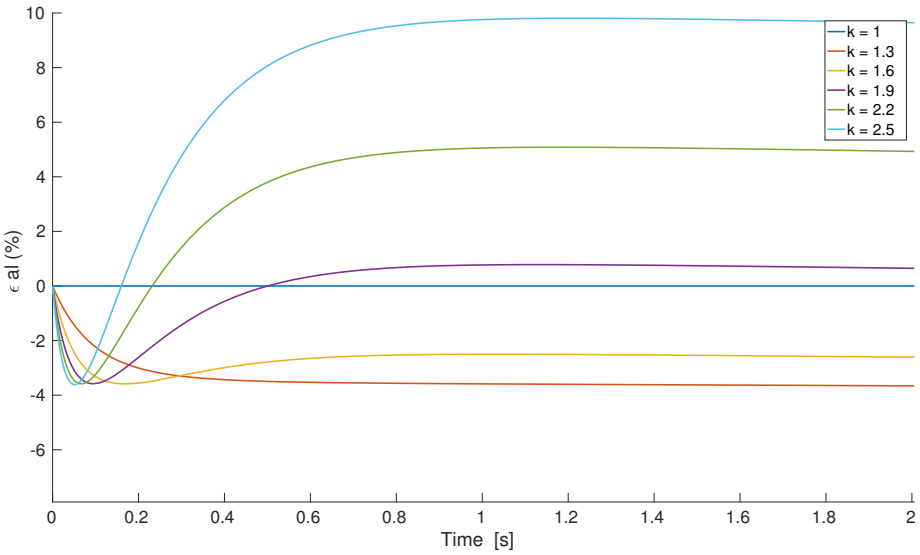


FIGURE 9 – Actin rate, ϵ_{ap}, ϵ_{al} and τ_k until equilibrium, following the k-straining

These figures are screnshot of the cell statement at equilibrium. We can see that the amount of actin is well constant, and that the more k is high, the more the density of actin on the cortex is low. Which means that the active tension is lower. Indeed we suppose that the active tension is a function of the density of actin : $\mathcal{P}_{active} = 2\gamma_{ap}\dot{A}_{ap} + \gamma_l \dot{A}_l$ We can also observe that at first glance there is no evidence correlation between ϵ_{al} and τ_k with k, in opposite between ϵ_{ap} and k. This comes from the behaviour of the cell, which is a special material. We will explain this in the next section.

4.1.1 The local extremum of ϵ_{al}



We have noted that according to the value of k, there is a local extremum of ϵ_{al}. This phenomenon is observed for all k superior to 1,7. To explain this we have to keep in mind than the more k is high, the faster is the straining. So if we take a look on the curve of the thickness of the cell, we can note that at the beginning, the longueur of the four inclined faces increase lower than their height decrease. Thus logically the lateral area becomes smaller ; but at a particular moment, when k is close to 1.34, the thickness, which depends on k and b, starts to decrease slower than before whereas the longueur keeping growing at the same velocity. It leads to an increasing of the lateral area which means thus of ϵ_{al}. Since in all cases the cell moves in the same way but only the velocity changes, for most important straining with thus high velocities, this jump will be earlier and more raised. But all in case we are in a compressing sate because the height decreases. Then when we are in the permanent straining at 1 second, the relaxation of the width b due to the viscosity, implies a slow diminution of the height $h = \frac{1}{kb}$ with k constant, which leads to the variation of ϵ_{al} observed until the equilibrium state.

FIGURE 11 – This is a 2D modelisation of the stress relaxation. The face A is the apical face, the face B the lateral face colinear with the y-axis and face C one of the four inclined faces. We apply in the case a straining with a value of K=2.2

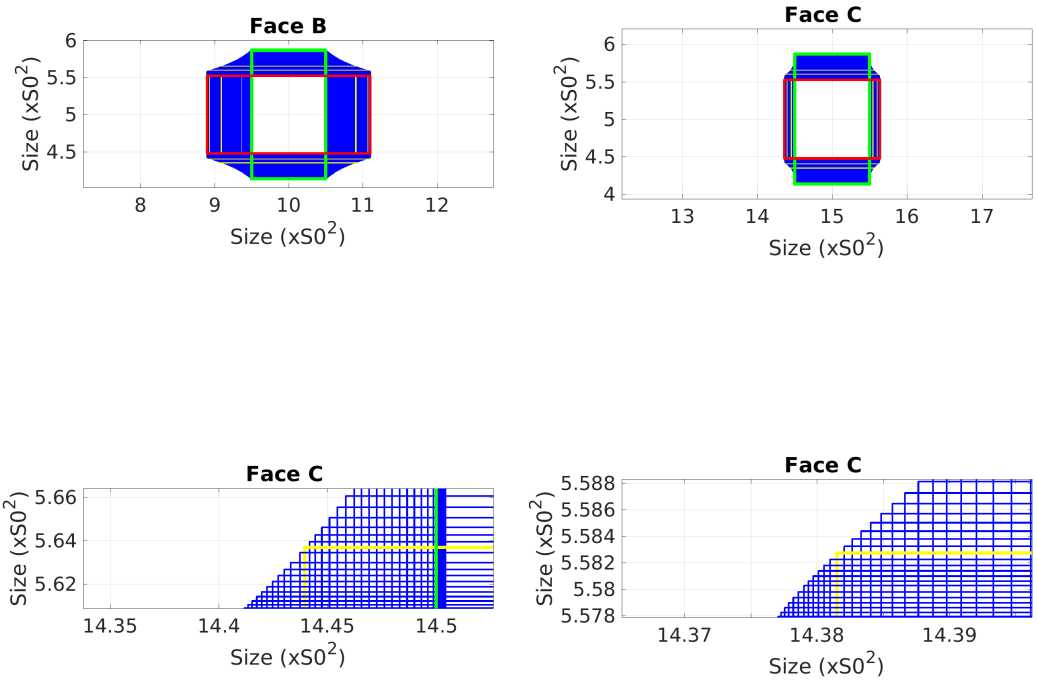


FIGURE 12 – Here is a zoom of the face C. This illustrates the phenomena noted, we can see how the size of the face C evolves. The yellow line symbolizes the change of ϵ_{al} ; just by taking a look on the form of the evolution of the area, we can see that there are two different orientations of the rectangular shape, when the higher side is in the height direction, the area decreases and in the opposite case increases

4.1.2 Curve of τ_k

We have noted that it seems to have no evident correlation between the k input and the τ_k observed. For example for an elastic material, the stress is linear with the straining. Also we have spotted the τ_k found at the equilibrium, for each k applies.

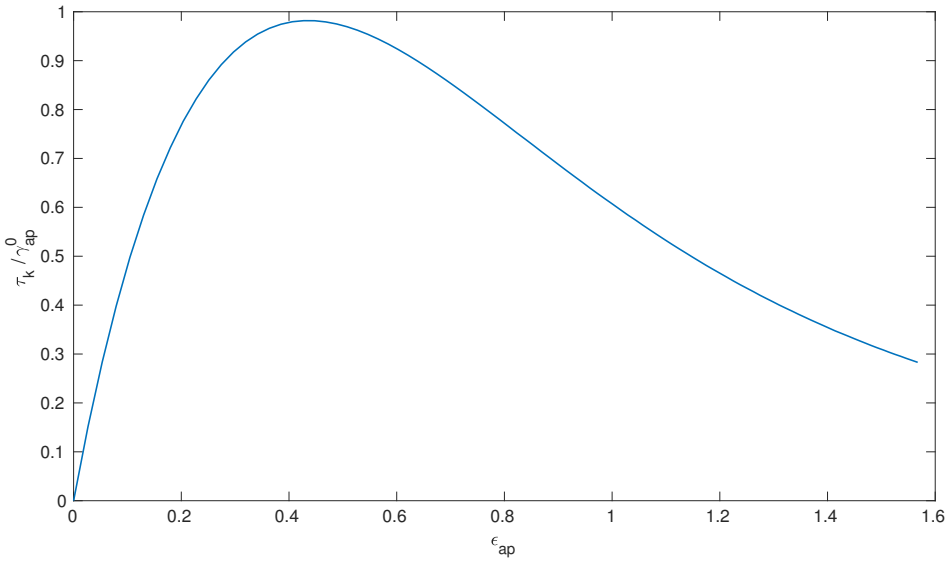


FIGURE 13 – Rheological curve of the cell

According to this figure, we can see that for ϵ_{ap} there is an elastic behaviour from 0 to 0.25, followed by a plastic domain between 0.25 and 0.75, and finally a particular behavior specific to the cell. We can noted also that for the same τ_k, there are two different ϵ_{ap} possible, we have to check if these are stable or unstable equilibrium state.

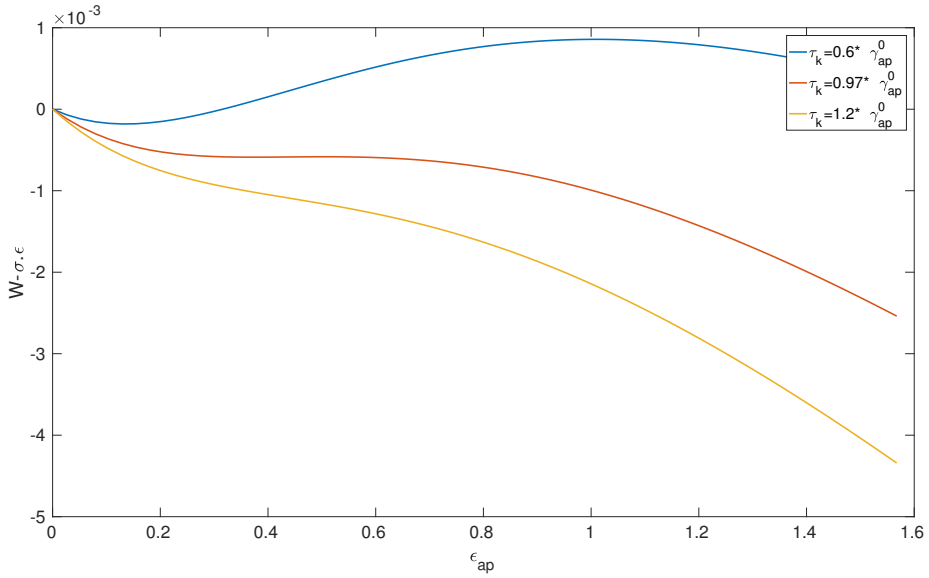


FIGURE 14 – Curve of the energy of the cell according to the applied stress

We have plotted the curve of energy for three different τ_k. A system is in a stable equilibrium state if he admits a null derivative on his domain. So we can see that for τ_k inferior at 0.98 γ_{ap0}, we can find an stable state. But for values up to this one, there is only unstable state. More over only one on the two values possible for each τ_k is associated to a stable state and this is the fisrt one. It means that if we apply a initial deformation, we have to pay attention to take it on the stable part otherwise the system will collapse.

4.2 Uniaxial creep

We introduce a variable stress with the following form : $\tau_k = \tau_{ki}(1 - e^{-5t})$ which converges towards τ_{ki} in more or less 1 second.

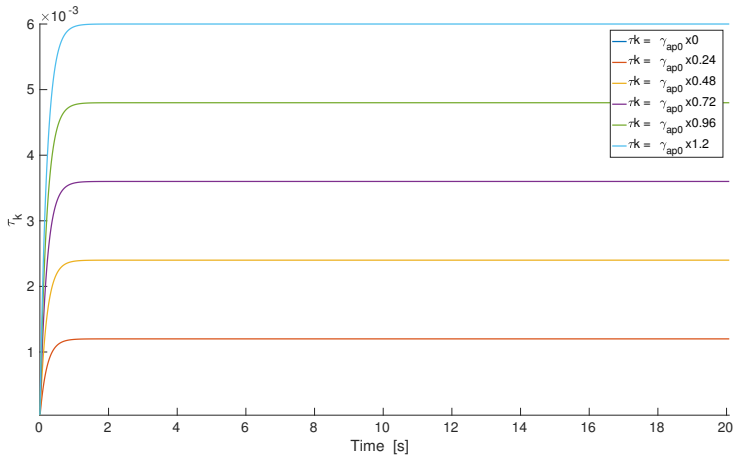


FIGURE 15 – τ_{ki} evolution

We have plotted the actin rate, apical and lateral deformation according to the stress applied :

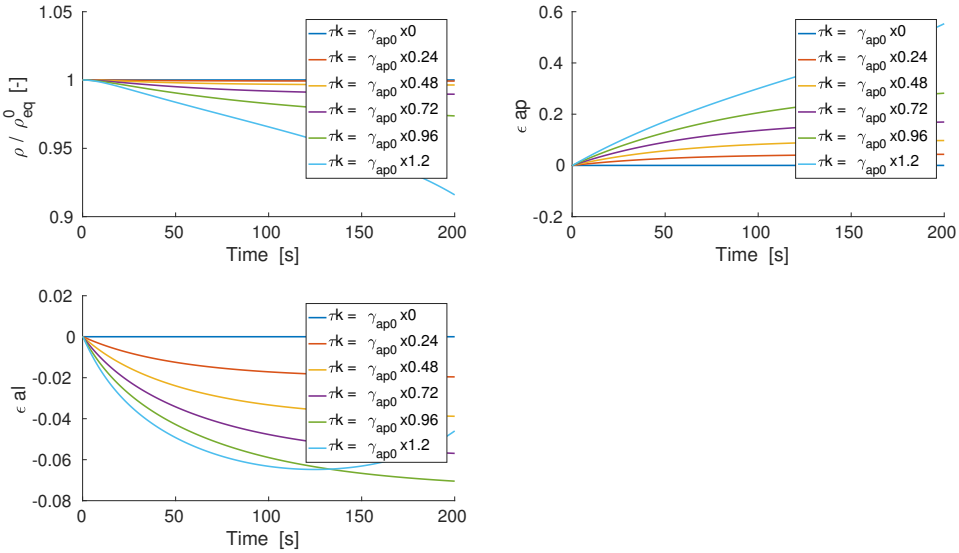


FIGURE 16 – Actin rate, ϵ_{ap} and ϵ_{al} following the applied stress

We can observed that in this case the behaviour of the cell is more conventional. We apply a

stress in a short time and due to the viscosity we have a jet-lag before achieve the equilibrium state with level, this is the behavior of a visco-elastic material. We have plotted the density of actin and the strainings for τ_k moving from 0 to $0{,}98\gamma_{ap0}$. This is the admissible limit of the cell. If we apply a stress up to this value, we don't obtain an equilibrium. We will do it in a second time.

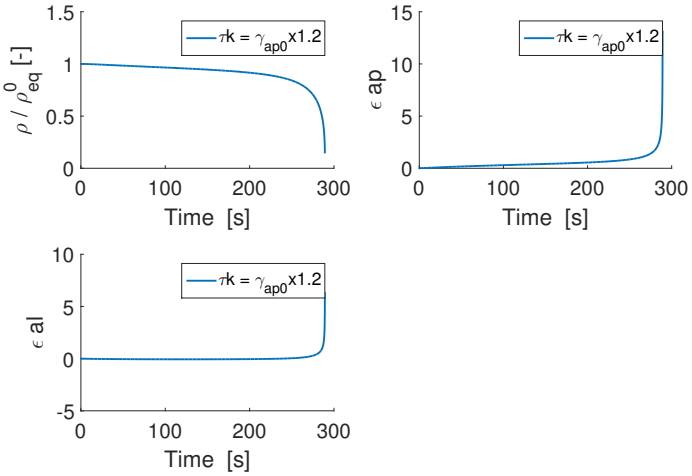


FIGURE 17 – Collapse of the cell

Here we can see what's happened when we apply a too strong stress, we don't achieve an equilibrium state. Indeed the cell deforms until it collapses, as we can see on the figures. We can also noted that the same phenomenon is observed for ϵ_{al} as in the case when the straining is applied. That is to say that at the moment where k is up to 1.7, the height start decreasing slowly than than length and the results are an increase of the lateral area. The difference is that k keeps going up thus the straining diverges

5 Discussion

In this section, we will discuss the relevance of the model to the results obtained. Our model is as elementary as possible, in terms of biology it considers only the cellular cortex as a fluid with the term viscosity and the amount of actin. Indeed, experimental studies have shown that the actin plays a fundamental role in cell rheology.
The first interesting point to note is that although we did not introduce an elastic component into our model, the observed behavior is that of a viscoelastic material. Indeed we observe that ϵ_{ap} follows a ramp then a plateau, sign of an elastic behavior. The origin of this behavior is quite easy to identify because of the simplicity of the model, it is assumed that it comes from the mass conservation equation of the actin. That is, its polymerization and polymerization. Indeed the active tension being dependent on the actin density present on the cellular cortex, one can imagine that the cell will seek to decrease the external tension by increasing its rigidity and thus its amount of actin, in order to arrive at a steady state like a spring. To verify this, we set the amount of actin in the cell by removing the polymerization equation of the model, which corresponds to the protein inhibition in the experiments. We chose to apply a deformation with a k = 2.2, which normally requires an actin rate of 0.41 $mol.m^{-2}$ at steady state for a stress of $0.89\gamma_{ap0}$, we voluntarily set this one to $0.1mol.m^{-2}$. We obtain the following behavior :

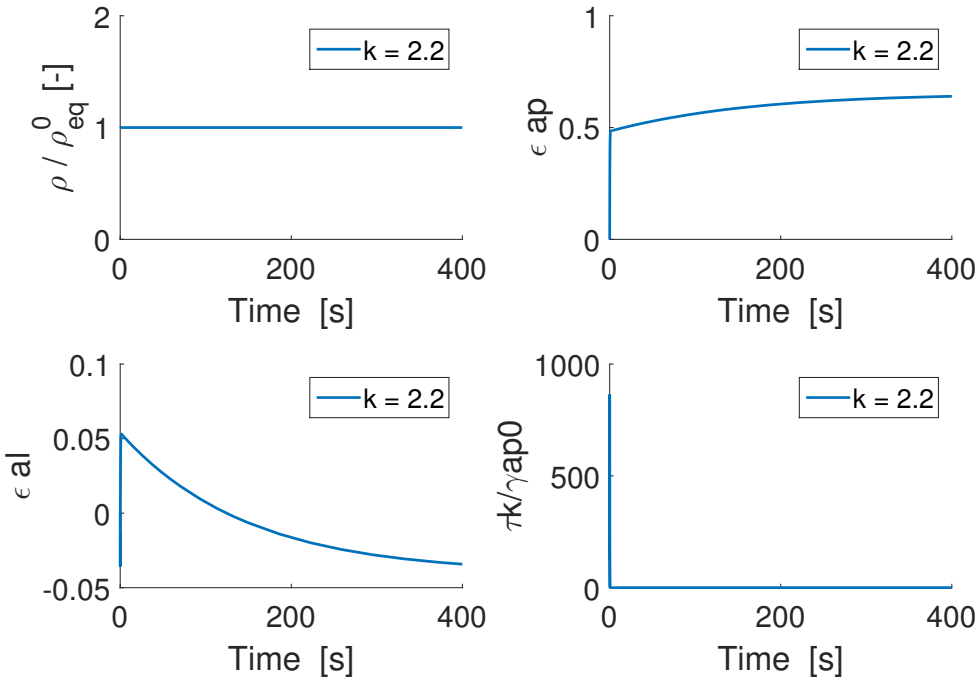


FIGURE 18 – constant actin rate involves the loss of the elastic component

It is found that the state of equilibrium is not reached as supposed, there is no elastic level and the stress in the cell is almost zero, it does not resist at all. We conclude that the mass equation acts as a spring in our model by adjusting the stiffness of the cell through the actin rate in order

to reach equilibrium.
We will now check the properties of the cells observed during experiments. We have chosen to check if our model has the two regimes Atp-independent and Atp-dependent, if the stress follows a particular power law and finally if we observe an increase in the length of rest after relaxation of the deformation.
To check if our model follows the two phases Atp-independent and Atp-dependent, we will use the actin again. Indeed, the Atp is used as a source of energy by the actin during the polymerization reaction. For this we realize 3 different tests for a deformation k of 2.2 : initial variable actin rate at $0.4605 mol.m^{-2}$, at $0.203 mol.m^{-2}$ and finally with a rate set at $0.1 mol.m^{-2}$.

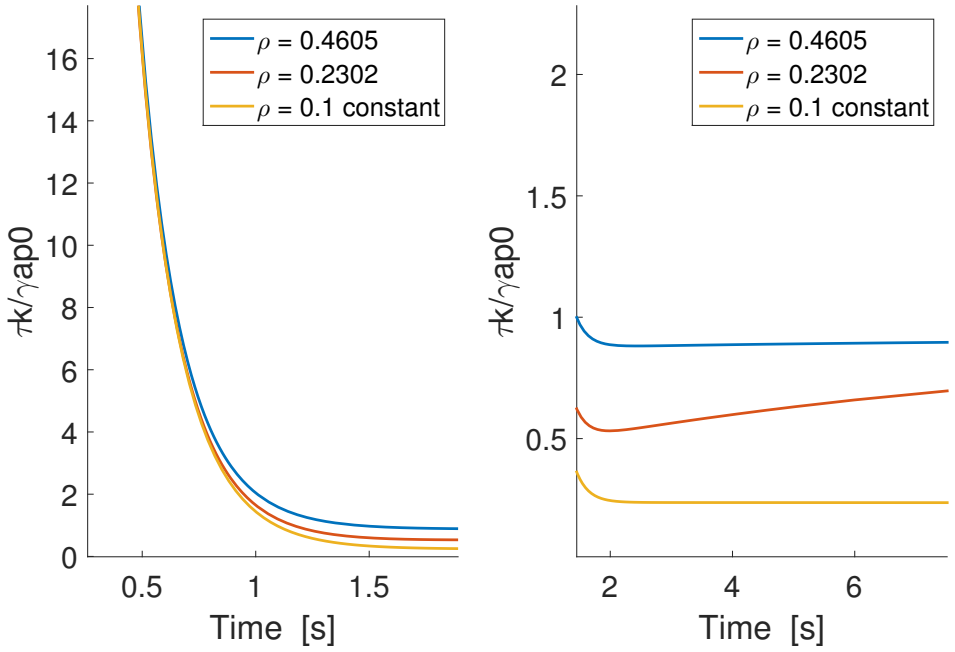


FIGURE 19 – Atp-independent and Atp-dependent regime

It can be seen that the curves before 1 second are substantially the same. However, after 1 second, the behaviors of the curves differ. For the 0.4605 case, we find that the τ_k curve decreases slightly and then begins to stagnate with some noise. For the curve of 0.2302 we see that the curve increases slightly this time; this is due to the fact that the initial rate is too low to reach equilibrium, hence the need to increase it. Finally, in the case where the actin rate is fixed at $0.1 mol.m^{-2}$, we find a perfect line. We therefore conclude that our model seems to present the two phases observed experimentally. We looked at whether the viscosity impacted the behavior of phase 1, but it seems that the viscosity coefficient does not influence the initial shape of the curve. The most likely explanation is that the short time during which the model always follows the same shape is likely due to the fact that the applied stress must stabilize, which predominates over the other parameters present. In reality, studies have attempted to answer this question by assuming that this is due to the dissipation of the stress applied by the redistribution of the cytosol in the fluid phase through the porous insoluble part cytoplasm. But obviously our model does not take into account this, only phase 2 of the actin is well verified.

Then we will see if our model follows a particular power law. We have plotted the log-logarithmic curve of the stress as a function of time. Indeed, we are seeking a law of form $A.t^{-\alpha}$.

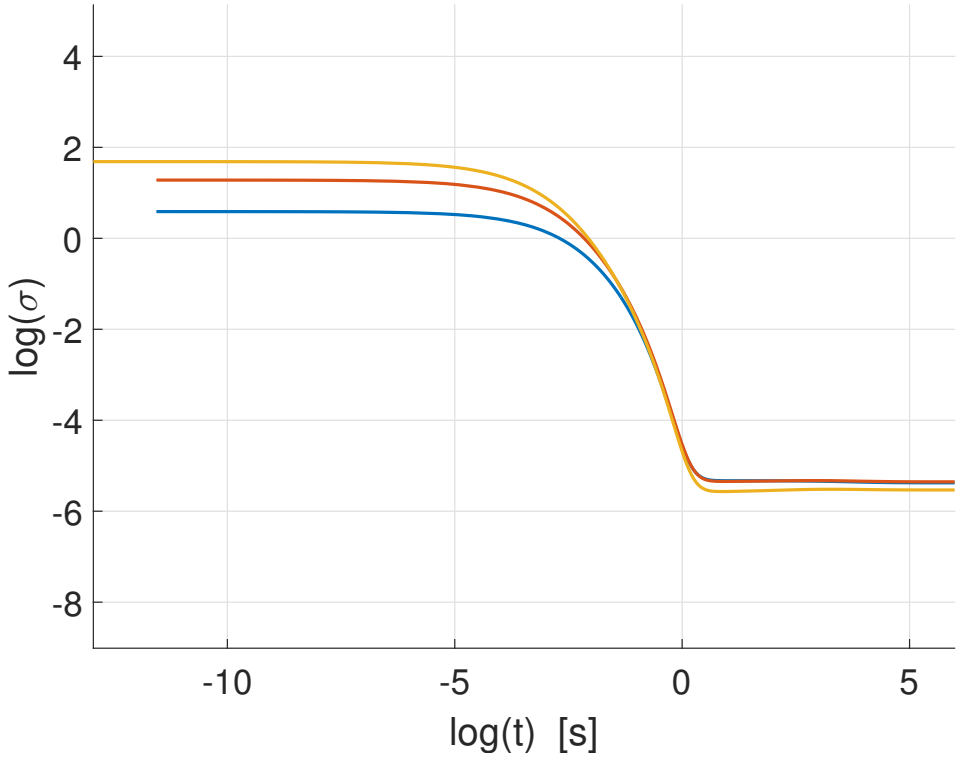


FIGURE 20 – Power law of the model

The equation obtained for the central part of the curve gives $A = 10^{-5}$ and $\alpha = 2.5$. The value obtained with experiences is more 0.28 for α. Also our model follows the same law as noted for cells but due to its simplicity, the coefficient are quite different.
Finally we applied the relaxation to our model to check if there is an increase in the length at rest of the cell. For that we realize a first stretching of 100 second then we take the k, b and τ reach by the cell and insert its in the model of creep with $\tau_k(t) = 0$. We observe the following results :

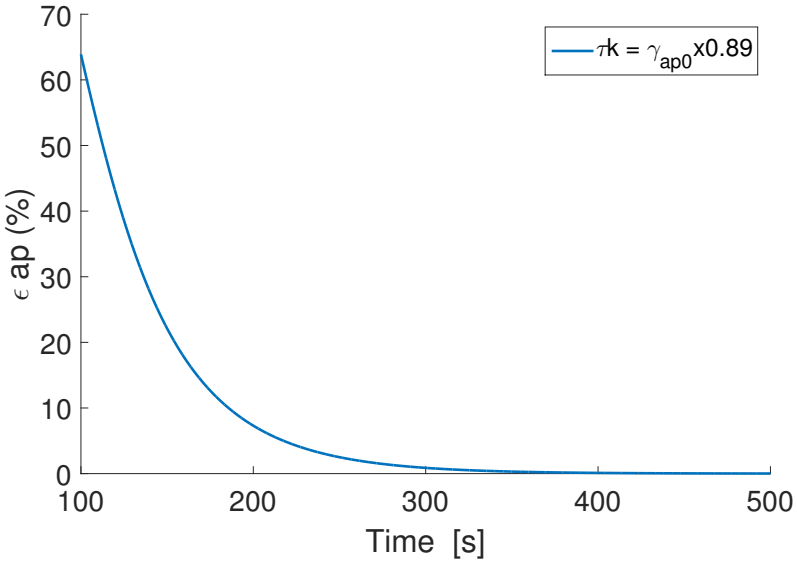


FIGURE 21 – Relaxation of the cell paying attention to the lenght of rest

Thus we see that if we stop at 200s as in the experiment, we get an ϵ_{ap} of 8%, so there is a good increase in the length of rest. However, if we wait longer, we finally arrive at an almost zero value of ϵ_{ap}. This is not inconsistent, indeed the experiments suggest that the elongation of the cells at rest is due formin-mediated polymerisation. Formins promote the elongation of pre-existing filaments by removing barbed end capping proteins and forming a sleeve around the actin subunits. But our model does not take into account this element, so it is logical that without constraint the cell returns to its initial level of rest according to the equations.
So our model is either very simplistic thus it does not take into account many biological phenomena, however it allows to explain quite clearly the role that actin plays in cell rheology. It is therefore necessary to develop this model by adding new elements to get closer and closer to the actual behavior observed. The purpose is infine to study not a cell but a whole tissue using the theory of vertex model

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