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Modelling of the behaviour of the cell–wall interface during the rolling of a single cell: a probabilistic approach

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Abstract

Rolling is an important manifestation of biological cell adhesion, especially for the leukocyte cell in the immune process. It combines several phenomena such as the affinity, the junction and failure between a specific adhesion molecules and an active deformation of the cell during the motility. Several models were developed in a probabilistic or a deterministic context. The focus in this Note is the local mechanical description (2D) of the kinetic of adhesion of the contact interface of a single cell with a wall (e.g., the blood vein), in terms of the failure and creation of connections during the rolling. The local model focuses on the interfacial zone, as a preliminary step towards an integrated model including the cell membrane behavior. Hence, the net effect of the fluid flow is represented by a punctual force, coupled to the Van der Waals and electrostatic forces. Note that the complexity of this phenomenon leads to the limitation of the number of parameters, which are taken into account in the model. Numerical simulations emphasize the rolling phenomenon and the kinetics of creation and rupture of the ligands–receptors connections. ***To cite this article: N. Mefti et al., C. R. Mecanique 334 (2006).***

Résumé

Modélisation du comportement de l'interface cellule–paroi lors du rolling d'une cellule unique : une approche probabiliste. Le rolling est une manifestation particulière des processus d'adhésion de cellules biologiques. Il intervient entre autre dans les mécanismes de défense immunitaire et fait intervenir divers phénomènes tels que l'affinité, la jonction des molécules d'adhésion ainsi que leurs ruptures et les déformations actives de la cellule durant la motilité. Divers modèles ont été développés, selon des approches probabilistes ou déterministes. Nous présentons dans ce papier un modèle qui décrit d'un point de vue mécanique la cinétique d'adhésion de l'interface de contact entre une cellule et une paroi externe. Cette approche locale vise à modéliser spécifiquement le comportement de l'interface de contact en isolant cette zone du reste de la cellule, dans une première étape. Les effets de l'écoulement du fluide sur la cellule sont représentés par une force (résultante) couplée aux interactions de Van der Waals et aux effets électrostatiques répulsifs. La complexité du phénomène et la multitude des facteurs qui y concourent nous obligent à limiter le nombre de paramètres pris en compte dans le modèle. Les simulations mettent en évidence le phénomène de rolling par l'intermédiaire des événements de ruptures et de création de liaisons ainsi que l'évolution de l'angle d'inclinaison de la cellule (angle de rolling). ***Pour citer cet article : N. Mefti et al., C. R. Mecanique 334 (2006).***

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Mots-clés : Adhésion ; Rolling ; Liaisons ; Cellule ; Rupture ; Jonctions ; Phénomènes stochastiques

1. Introduction

Rolling is a phenomenon which usually involves populations of interacting cells; however, it is important to first be able to understand the behavior of a single cell approaching the surface of an extracellular wall. Using a simple explanatory model, we can describe the adhesion kinetic as a succession of events of creation and failure of connections between the cell and the wall. The creation of connections corresponds to a junction between complementary adhesion molecules, under the effects of passive or active actions, whereas the failure of fibers often occurs by pulling effects on the fiber [1,2] (Fig. 1(a)). These adhesion molecules are distributed on the cell membrane and the wall; this wall may correspond to a vein or a layer of endothelial cells in the case of the leukocytes motion.

In this work, we develop a 2D model of a single cell, which focuses on the two most important interfacial mechanisms, the kinetics of failure and the creation of connections during the rotation of the cell. The failure is the result of a pulling action on the connection under the effect of the fluid flow, Van der Waals forces and repulsive interactions; conversely, the creation of connections results from bringing together a free ligand and a receptor under the effect of Brownian motion of the fluid particle the chemical affinity between specific molecules (ligands and receptor) [3]. The net balance between the failure of existing connections and the creation of new bonds in turn governs the motion of the cell. The rolling of the single cell (e.g., leukocyte) is the result of the interplay of complex phenomena, such the activation of the cell molecules, or the transduction mechanisms [2]. Since we consider a possible dispersion of some properties, we assume that the behaviour of the system is random; consequently, we describe several parameters and phenomena (spatial distribution of the forces of rupture of the connections; intensity and orientation of the chemical affinity) as stochastic processes [4,5].

2. Mechanical description of the cell–wall interface

We consider the behavior of a single adhesive cell adhering to an extra cellular wall, subjected to a plasma flow (e.g., leukocyte), and focus on the modeling of the contact interface, made of a bundle of fibers. We consider that the contact zone is composed of two zones: the first zone corresponds to the failure of the existing connections, and the second to the creation of new connections (Fig. 1(a)). Hence, our purpose is the successive description of the two zones. The cell adhesion and the contact interface are subjected to several interactive phenomena [1,2]. In order to simplify the problem, we consider only three external effects: the attractive Van der Waals forces, the electrostatic repulsive force and the action of the fluid flow.

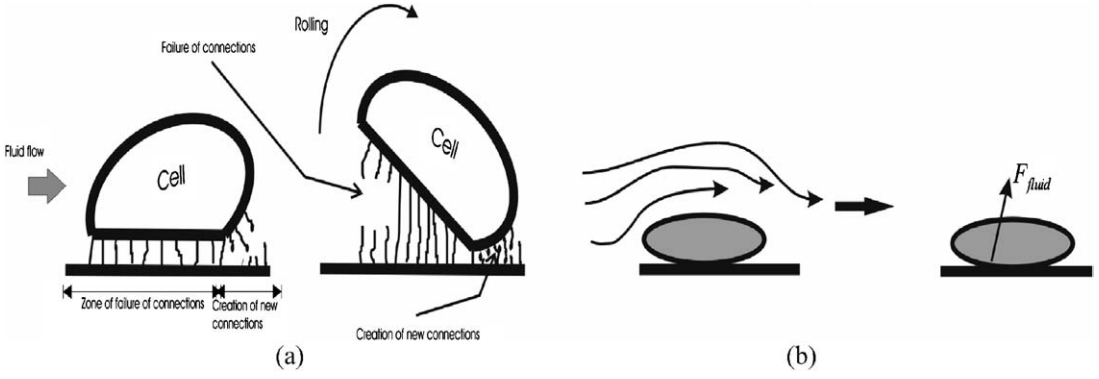

Fig. 1. Description of the rolling of the cell.

Fig. 1. Description du roulement de la cellule.

In order to avoid a complex fluid-structure analysis, we assume that the force exerted by the fluid around the cell is periodic (e.g., blood), expressed by $F_0(1+\sin(\omega t))$, where F_0 is the maximum amplitude of the fluid force, and ω its pulsation. Thus, the effects of the flow of the fluid around the cell are replaced by a punctual pulling force (Fig. 1(b)). Hence, we consider the following interaction effects:

- the attractive Van der Waals forces [6], that receives the expression $F_{\text{attr}} = \frac{A_0 l_{a_0}}{6\pi}(\frac{1}{(S+D_0)^3} - \frac{1}{S^3})$, with A_0 the Hamacker constant, l_{a_0} the length of the zone of interaction, S the average distance between the cell and wall, and D_0 the thickness of the membrane cell;
- the repulsive electrostatic forces between both surfaces, given by a phenomenological expression [7] $F_{\text{rep}} = -\frac{\chi}{S}\mathrm{e}^{-S/\tau}(\frac{1}{S}+\frac{1}{\tau})$, with χ a compressive parameter that corresponds to the ease with which the connections can be compressed and τ a thickness parameter (mean length of the ligand).

Since the ratio between the size of the cell (its diameter) and the fiber length often equals 1000 [8] (it is thus a multiscale problem), we may assume that the fibers stay parallel during the rolling. We also suppose that the external forces (fluid interactions) are applied in the middle of the contact zone.

2.1. Failure of the existing connections – zone of failure

We assume that the failure zone is subjected to the fluid pressure and to the interactions effects between the two surfaces (cell–wall): the electrostatic (repulsive) and Van der Waals (attractive) forces [2,7]. These contributions appear in this order on the right-hand side of the dynamical equation of motion (1), being summed up into the term F_s. The contact zone is assimilated to two rigid and rectilinear beams because the close contact of the cell with the rigid wall leads to a local rigidification of the cytoskeleton (chemical exchanges) [1,9,10]. These beams are linked by elastic springs, which represent the ligands–receptors pairs (Fig. 2). If we consider that the failure of a connection occurs according to the stretch of this spring, we can neglect the horizontal nodal displacement. Moreover, assuming the displacement of the node N_{l_0} being negligible (extremity connection) and a weak value of the inclination of the fluid force, the dynamical equilibrium can be written [12]:

$$\tilde{m}_i \frac{\mathrm{d}^2 U(x_j,t)}{\mathrm{d}t^2} + \tilde{k}_i U(x_j,t) = \frac{1}{2}\big(F_s + F_0\sin(\omega t)\big) \tag{1}$$

with $\tilde{m}_i$, $\tilde{k}_i$ respectively the generalized mass and stiffness of the system at the configuration 'i', which are given by $\tilde{m}_i = \alpha_i \bar{m}_j$ and $\tilde{k}_i = \alpha_i \bar{k}_j$. The parameters $\bar{m}_j, \bar{k}_j$ are the mass and stiffness of the node j respectively. The coefficient α_i, which describes the state of the stiffness in terms of the number of connections, is given by $\alpha_i = \sum_{i=j}^{N_{l_0}} (\frac{l_{a_0}-(i-1)d_0}{l_{a_0}})^2$. Moreover, d_0 is the distance between two adjacent nodes, N_{l_0} the number of connections in the zone of rupture of the existing fiber and the static component of the external solicitation is $F_s = F_0 + F_{\text{attr}} + F_{\text{rep}}$.

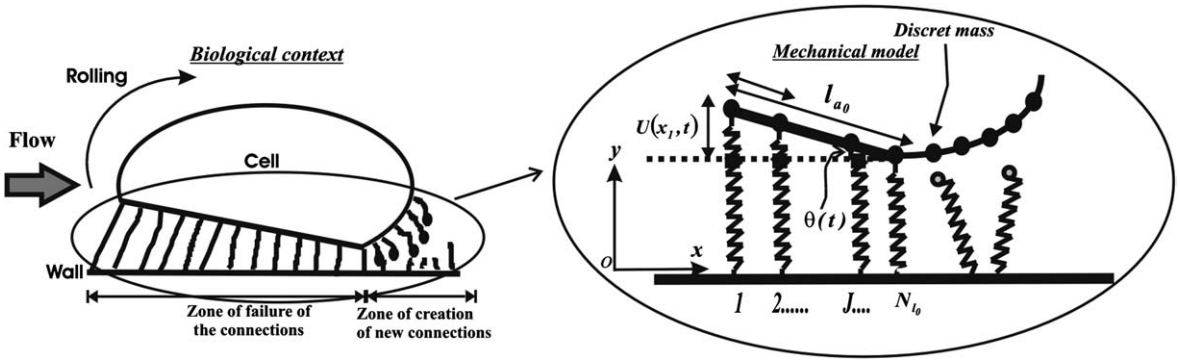

Fig. 2. Biological and mechanical description of the contact interface.

Fig. 2. Description biologique et mécanique de l'interface.

If we consider only the case of the vibration of the interface (without failure), the vertical displacement response of the jth fiber is further easily solved as:

$$U(x_j,t) = \frac{-\tilde{m}_i F_s}{\tilde{k}_i}\cos\left[\left(\sqrt{\frac{\tilde{k}_i}{\tilde{m}_i}}\right)t\right] + \left[\frac{1}{2} - \frac{F_0\omega}{2(\tilde{k}_i - \tilde{m}_i\omega^2)}\right]\sqrt{\frac{\tilde{m}_i}{\tilde{k}_i}}.\sin\left[\sqrt{\frac{\tilde{k}_i}{\tilde{m}_i}}t\right] + \left(\frac{F_0}{2(\tilde{k}_i - \tilde{m}_i\omega^2)}\right)\sin(\omega t) + \left(\frac{\tilde{m}_i}{\tilde{k}_i}\right)F_s \tag{2}$$

Since the contact zone is assumed to be rigid, the rolling angle is easily evaluated as:

$$\theta(t) = \sin^{-1}\left[\frac{U(x_j,t)}{l_{a_0} - (j-1)d_0}\right] \tag{3}$$

Moreover, considering the rupture of the interface, we may assume that the phenomenon occurs in an imposed direction, namely the flow direction. The failure of the jth fiber occurs if

$$F_j(t) \geqslant \tilde{F}_j^{\text{rupt}} \tag{4}$$

where $F_j(t)$, $\tilde{F}_j^{\text{rupt}}$ are the strength applied to the jth fiber and the limit of failure of this connection (maximal force a fiber can sustain) respectively. Since the different fibers were initially created under different chemical and mechanical conditions, their failure limits can fluctuate with regard to a mean value; we accordingly describe this spatial fluctuation as a normed stochastic process:

$$\tilde{F}_j^{\text{rupt}} = \tilde{F}_{\text{aver}}^{\text{rupt}}\left(1 + F_{\max}\frac{\Delta P_j^{\text{rand}}}{\Delta P_{\max}^{\text{rand}}}\right) \tag{5}$$

where ΔP_j^{rand} is a Gaussian random process with zero mean, $\Delta P_{\max}^{\text{rand}}$ the maximal value of this process, $F_{\max}$ the value of the rate of maximal fluctuation with regard to the mean value and $\tilde{F}_{\text{aver}}^{\text{rupt}}$ the limit of failure of the interface. Using the spectral method [11], this random process is obtained as the superposition of a set of harmonics:

$$\Delta P_j^{\text{rand}}(x_j) = \sqrt{2}\sum_{n=0}^{N-1}\sqrt{2S_{\Delta f_0\Delta f_0}(\omega_n).\Delta\omega}\cos(\omega_n x_j + \phi_n) \tag{6}$$

with $S_{\Delta f_0\Delta f_0}(\omega) = \frac{1}{4}\sigma^2 b^3\omega^2 \mathrm{e}^{-b|\omega|}$ the spectral density of power [11], σ the standard deviation, b a parameter proportional to the correlation distance, N the number of the harmonics, ω_n the discrete pulsation, function of the upper cut-off frequency ω_u, as:

$$\omega_n = n\frac{\omega_u}{N} \tag{7}$$

and ϕ the random phase-shift angles of theses harmonics, in the range $[0, 2\pi]$.

We assume that the distribution of the external forces is linear and triangular shaped (Fig. 3(a)), because the displacement of the extremity connection N_{l_0} is negligible; this assumption can be justified by the difference of size between the cell and the connections. The failure of the jth fiber leads to the redistribution of the force applied to this fiber on the other connections. Thus, using the equilibrium equation:

$$F_j(t) = \sum_{k=j+1}^{N_{l_0}}\Delta F_k \tag{7a}$$

the expression of the force jump in the case of failure of j is obtained as:

$$\Delta F_{j+1}(t+\Delta t) = \frac{1}{1 + \sum_{i=j+2}^{N_{l_0}-1} l_{d_i}/l_{d_{j+1}}}F_j(t) \tag{7b}$$

This force jump leads in turn to a displacement jump, which is obtained by the PVW:

$$\Delta U_{j+1}(t+\Delta t) = \frac{\Delta F_{j+1}(t+\Delta t)}{\bar{k}} \tag{8}$$

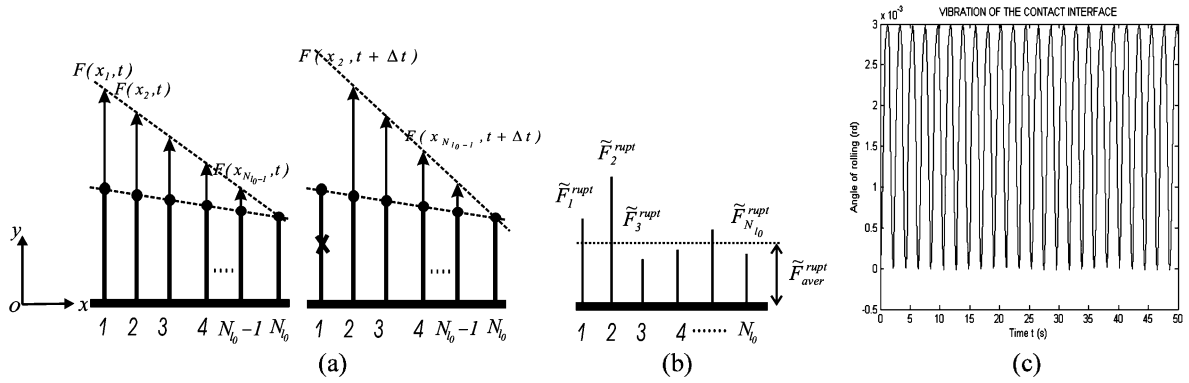

Fig. 3. (a) Failure process and distribution of the external forces exerted on the fibers; (b) distribution of the (force) limit of rupture; (c) vibration of the interface.

Fig. 3. (a) Processus de rupture et distribution de forces extérieures sur les fibres ; (b) distribution de la (force) limite de rupture ; (c) vibration de l'interface.

Table 1
Input parameters [2,7,11]

Tableau 1
Données d'entrées [2,7,11]

$\sigma = 1$	$b = 1$	$\bar{k} = 0.001$ nN/nm	$L_{i_0} = 6$ nm	$\mu_a = \mu_b = 1$ c
$T = 36\,^{\circ}$C	$r = 6$ nm	$\bar{m} = 0.0013$ nkg	$\tau = 10$ nm	$\xi_0 = 80$
$F_{\max} = 14\%$	$\varepsilon = 2$ nm	$\chi = 0.01$ nN	$h = 10$ nm	
$m_i = 10^{-6}$ nkg	$\omega_u = 4\pi$	$\tilde{F}^{\text{rupt}}_{\text{aver}} = 0,07$ nN	$\omega = 6.28$ rd/s	
$k_i = 10^{-3}$ nN/nm	$N = 100$	$D_0 = 7$ nm	$l_{a_0} = 3000$ nm	

Numerical simulations (input data in Table 1) emphasize the rolling phenomenon, represented by the combination of the vibration and the rupture of the contact interface and the evolution of the rolling angle (Fig. 4(a), (b)).

We notice that the force of the fluid at the global failure of the interface is (0.2 nN) which well fits to the experimental range of adhesion force [2], viz. [1.7 pN, 6.7 nN]. Between 0 and 5 s, the behavior is pseudo periodic, because of the competition between the increase of the external forces (force with periodic direction) and the decreasing stiffness of the interface due to the decreasing number of connections.

2.2. Creation of new connections

During the rolling, the part of the cell membrane located at the extremity of the cell (zone of creation of connections on Fig. 1(a)) moves closer to the wall. This phenomenon combined to the chemical affinity between the ligands and receptors present on the two surfaces leads to the creation of new connections [1]. We consider that a new connection between the ligand and receptor can occur if these two entities are sufficiently close to each other. Moreover, the ligand complex is assimilated to a mass-spring system, subjected to the effects of the chemical affinity and the Brownian motion of the fluid particles.

Hence, the forces of chemical affinity and the Brownian motion are respectively assimilated to molecular Van der Waals effect if we consider the behaviour of the molecule as a dipole, and to a periodic force characterized by both a random pulsation and orientation. We use a Gaussian random process to describe these two parameters. We also assume that the interaction effects between the molecules of the same kinds are negligible (ligand–ligand or receptor–receptor). Accordingly, the following kinematic junction criterion between the ith ligand and the ith receptor is written:

$$\begin{cases} |x_i^l(t) - x_i^r(t)| \leqslant \varepsilon \\ |y_i^l(t) - y_i^r(t)| \leqslant \varepsilon \end{cases} \tag{9}$$

with ε the critical distance of junction between free ligand and receptor (ith couple).

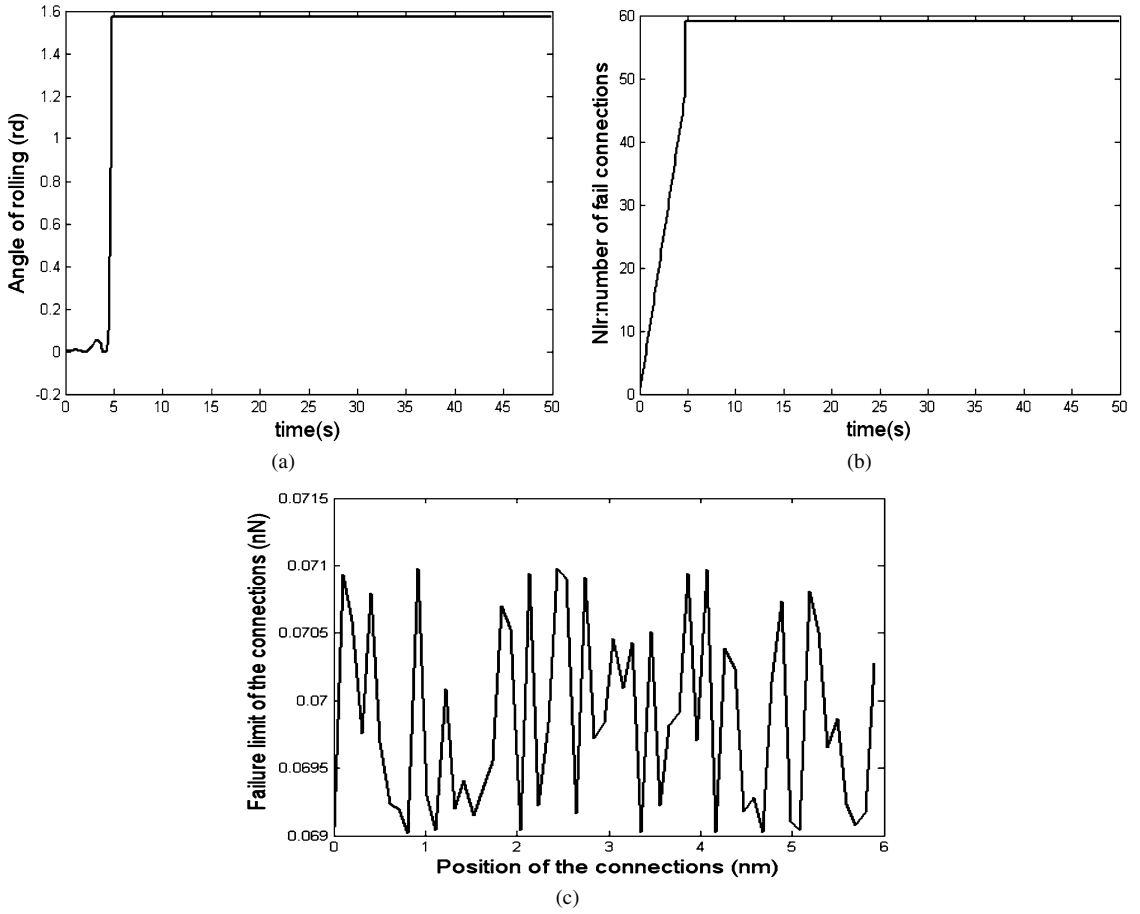

Fig. 4. (a), (b) Combination failure–vibration; and (c) spatial distribution of the limit of failure.

Fig. 4. (a), (b) Combinaison rupture–vibration ; et (c) distribution spatiale des limites de rupture.

The key point here is the determination of the variation of the position of the set of the free ligands and receptors couples during the rolling (Fig. 5).

The chemical affinity between the molecules can be expressed as:

$$F_{\text{aff}} = \frac{4}{k_b T}\left(\frac{\mu_b \mu_a}{4\pi\xi_0}\right)\frac{1}{r^7} \tag{10}$$

and the effects of the Brownian motion of the fluid particles are encapsulated into the force:

$$F_{\text{Brow}}(t) = F_0 \sin(\omega_{\text{Brow}} t) \tag{11}$$

where k_B is the Boltzmann's constant, T the absolute temperature, μ_i the electric charges, ξ_0 the dielectric constant, F_0 the maximal fluid force, ω_{Brow} the random pulsation of the fluid action and r the distance between both poles. We use the principle of virtual work to describe the motion of the ligands: the equations of motion of the ith ligand in the Cartesian basis are obtained after projection on a fixed Cartesian basis

$$\begin{cases} \dfrac{k_i}{m_i}U_i(t) + \dfrac{\mathrm{d}^2 U_i(t)}{\mathrm{d}t^2} = \dfrac{1}{m_i}\left[F_0 \sin(\omega_{\text{Brow}} t) + \dfrac{4}{k_B T}\left(\dfrac{\mu_a \mu_b}{4\pi\xi_0}\right)\dfrac{1}{S^7}\right]\cos(\beta_{\text{Brow}}) \\ \dfrac{k_i}{m_i}V_i(t) + \dfrac{\mathrm{d}^2 V_i(t)}{\mathrm{d}t^2} = \dfrac{1}{m_i}\left[F_0 \sin(\omega_{\text{Brow}} t) + \dfrac{4}{k_B T}\left(\dfrac{\mu_a \mu_{\text{B}}}{4\pi\xi_0}\right)\dfrac{1}{S^7}\right]\sin(\beta_{\text{Brow}}) \end{cases} \tag{12}$$

where $U_i(t)$, $V_i(t)$ are the components of the displacement of the ith ligand, and m_i, k_i its mass and stiffness respectively. The parameters ω_{Brow} and β_{Brow} are described by the use of a random process (spectral approach) [11].

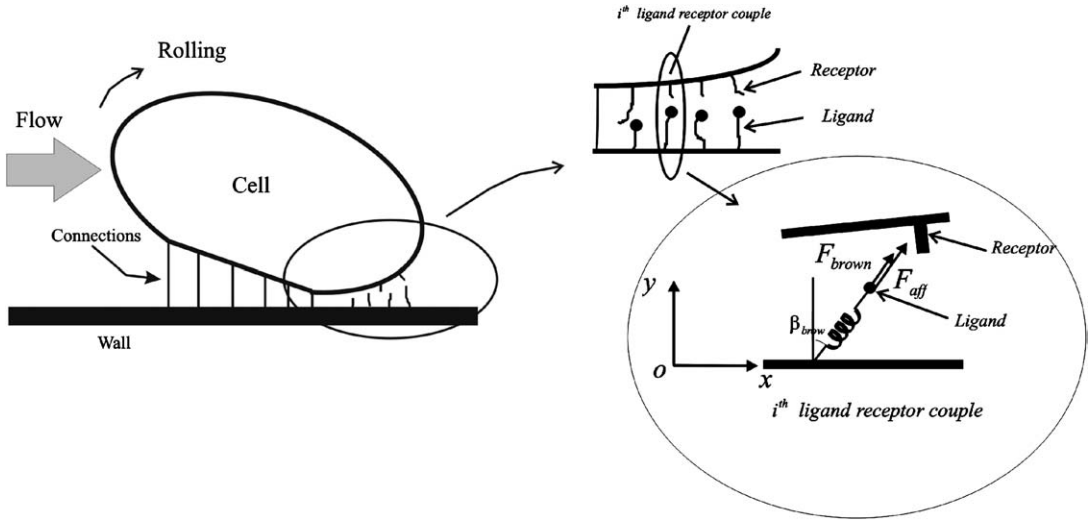

Fig. 5. Behavior of a single ligand–receptor pair.

Fig. 5. Comportement d'un couple ligand–recepteur.

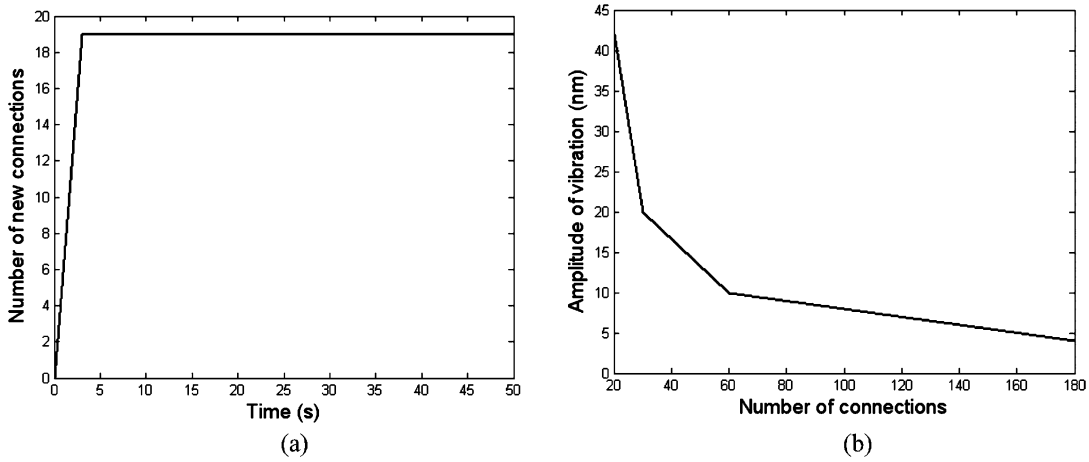

Fig. 6. (a) Evolution of the number of junctions and (b) influence of the number of connections on the behavior of the interface.

Fig. 6. (a) Évolution du nombre de jonctions et (b) influence du nombre de connections sur le comportement de l'interface.

Since it is difficult to obtain an analytical expression of the displacement component, we use a finite difference scheme. The calculation leads to the evolution of the new connections represented on Fig. 6.

We notice the total junction between the initially 19 free pairs after 3 s of rolling. The velocity of creation of connections is dependent on the intensity and the orientation of the affinity, and on the fluid forces (as shown in Eq. (12)). The solution scheme can lead to numerical instabilities due to the multiscale effects (due to the difference of magnitude between the data). We note that the different parameters of Eq. (10) take into account the specificity of the different kinds of the adhesion molecules (e.g., LFA.1, ICAM-1…).

3. Conclusions

A local description of the rolling phenomenon of a single cell adhering to an extracellular wall has been developed in a 2D context, focusing on the mechanical description of the adhesion kinetics, using a stochastic approach of the interface behavior.

This 2D model allows the description of the behavior of the contact interface by the use of a set of parameters. Also, this model leads to the quantification of the time evolution and the position of the failed or created connections on the contact interface. However, other parameters have been neglected, in order to limit the complexity of the model or because the influence of these parameters is not clearly explained.

We notice that the force of failure of the interface well fits to the experimental range of adhesion forces.

As a development of this model, we shall study the influence of the mechanical damping of the interfacial connections, the failure and creation of connections in the system in a 3D context, the cellular motility, as the active deformation of the cell by the polymerization and depolymerization of the cytoskeleton. The influence of an unimposed failure direction on the behavior of the interface shall also be assessed. It is also important to obtain further experimental results, relatively to a periodic flow, in order to get an improved set of input data and to compare our simulation results to these experimental outputs.

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