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A Red Blood Cell Cyto-Bilayer Interaction Model

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Abstract. In order to develop a single-whole red blood cell model it is necessary to model the interaction between the lipidic bilayer and the cytoskeleton. To minimic these interactions is a current and open problem with important applications in medicine. In this work we provide a mathematical formulation of a soft-body adhesion model in presence of a continuos lipidic membrane.

Keywords. Red blood cell, Cytoskeleton, Lipidic bilayer, soft-body adhesion, Lennard-Jones potential

1 Introduction

Experimental observations of human RBC behavior in flow mimicking the microcirculation reveal dramatic deformations and rich dynamics. This peculiar hallmark is due to the structure of healthy human RBC. It is a biconcave nucleus-free cell approximately $8\,\mu m$ in diameter and $2\,\mu m$ in thickness. It is primarily composed by a fluid-like lipid bilayer contributing to the bending resistance and an attached spectrin network that is a cytoskeleton maintaining cell shape and facilitating its motion. The lipid and spectrin domains are connected by transmembrane proteins. The alterations in cell geometry, membrane properties, as well as the interactions associated with the lipid bilayer and the cytoskeleton could lead to impaired functionality, as to deliver oxygen to the tissues [5] and therefore strongly influence the biomechanics of RBCs [15].

A computational modeling approach that separately accounts for each component has recently proved useful in the analysis of healthy and diseased RBCs [2, 3, 7]. According to this line of research the cytoskeleton is modeled as junctions (nodes) that are joined by

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springs that obey a Worm-Like-Chain (WLC) law and the lipid bilayer is considered as a surface of Dissipative-Particle-Dynamics (DPD) particles endowed with bending energy, elastic and viscous interactions. The cytoskeleton-bilayer interaction consists of a short-range force between the nodes of the network and the bilayer particles.

We remark that a particle-based simulation for the bilayer could require to agglomerate tens of thousands of lipid molecules into a single numerical particle, since the typical number of lipid molecules is about 700 million. This unavoidable fact brings to the consequence that "it is difficult to have a precise idea of the scales involved in DPD simulations", as Li said in [7]. This scenario leads to consider a continuum approach for the lipid bilayer component as more natural. Indeed continuous models provide consistent approximations of large scale molecular systems with less adjustable parameters than particle-based approaches, and usually are numerically more stable and cost-effective.

Recently, a research group of the ICMC of the USP developed a semi-implicit finite element method that was proved to be useful for studying the behavior of the viscous lipid membranes. This computational model is presented in [11], adopting the viscous liquid-shell model with Canham-Helfrich bending energy described by Arroyo and co-workers in [1]. We opted to refer to the same discretization in order to achieve our aim i.e. to arrive at a hybrid two-component whole-RBC model, with a discrete WLC network for the cytoskeleton but with a continuous surface fluid model for the lipid bilayer.

This means to face the problem of couple the two components by the adhesion forces that mimic the attachment of the cytoskeleton nodes to the bilayer integral proteins. This study is not only necessary in order to close the model but also is a non-trivial central point. Although the biomechanics of the RBC have been object of extensive studies and work, Peng affirms that "the mechanical properties of the interactions between the lipid bilayer and the cytoskeleton ... via the pinning connections of transmembrane proteins are still largely unknown" [10] and also Li recognizes that "are not yet fully understood" [6]. Nevertheless, there exist biological evidences that bilayer–cytoskeletal interactions are responsible for significant changes in terms of biorheology, erythrocyte function and progress of RBC diseases [15], as for instance in the case of sickle cell disease [8] or during the mechanical filtering process when the RBCs pass through the interendothelial slits in the spleen [12].

This study is aimed to provide the mathematical formulation of the forces that model the interactions between the cytoskeleton, composed of a discrete set of nodes connected by WLC-type forces and the bi-lipid membrane modeled as a continuous surface that behaves as a two-dimensional fluid.

2 The cytoskeleton-bilayer interaction model

According to the macroscopic contact modeling, the behavior of two interacting bodies is governed by the principles of continuum mechanics and the unilateral constraint that the bodies may not penetrate each other. On the other hand, when the problem size decreases to the nanoscale, the emergence of atomic effects affect the contact mechanics. The quasi-continuum contact model introduced by Sauer in [14] combines features from

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both the continuum and the molecular approach. Let us consider Ω_{10} and Ω_{20} the reference configurations of the two bodies, with a given atomic density β_{10} and β_{20} depending on the atomic structure. Then, let us consider $\varphi_1 = \boldsymbol{x}_1(\boldsymbol{X}_1, t)$ and $\varphi_2 = \boldsymbol{x}_2(\boldsymbol{X}_2, t)$ are the motions mapping the reference configurations Ω_{10} and Ω_{20} onto Ω_1 and Ω_2 and the atomic density β_{10} and β_{10} onto β_1 and β_2 respectively (see [13]). Now, we consider two arbitrary points $\boldsymbol{x}_1 \in \Omega_1$ and $\boldsymbol{x}_2 \in \Omega_2$, whose distance is given by $r = |\boldsymbol{x}_1 - \boldsymbol{x}_2|$. In the proposed model, we assume that two atoms (or molecules) located at $\boldsymbol{x}_1$ and $\boldsymbol{x}_2$ interact with each other via an interatomic potential $\phi(r)$. A popular choice is the so-called the Lennard-Jones potential,

$$\phi(r) = \epsilon \left(\frac{r_0}{r}\right)^k - 2\epsilon \left(\frac{r_0}{r}\right)^{k/2} \tag{1}$$

where r_0 and ϵ are a lenght and an energy scale. The force $F(r)$ between the two atoms is given by the gradient

$$F(r) = -\frac{\partial \phi}{\partial r} = \frac{k\,\epsilon}{r_0} \left(\frac{r_0}{r}\right)^{k+1} - \left(\frac{r_0}{r}\right)^{(k/2)+1} \tag{2}$$

It can be seen that r_0 is the equilibrium distance between the atoms, i.e. the distance where $F = 0$, and that ϵ is the energy of the well at $r = r_0$. We can see that when to atoms are close enough to each other there is a repulsion between them. Otherwise, it occurs an attraction between the atoms with a maximum potential when $r = r_0$ and the force tends to zero as r increases and goes to $r = +\infty$.

We can define the contact energy as the total interaction energy between all particle pairs located at positions $\boldsymbol{x}_1 \in \Omega_1$ and $\boldsymbol{x}_2 \in \Omega_2$. Adopting this approach, we deduce the bilayer-citoskeleton interaction as a soft-body adhesion. For this purpose, let us denote by Γ the continuum lipidic membrane suface and by Υ the *adhesive surface* of the cytoskeleton. In the continuum limit we obtain the contact energy given by

$$\mathcal{E}_{con} = \int_\Gamma \int_\Upsilon \beta_\Gamma \; \beta_\Upsilon \; \phi(\|x^\Gamma - x^\Upsilon\|) \; dx^\Gamma \; dx^\Upsilon \tag{3}$$

where β_Γ, β_Υ are non-dimensional scalars (or simply constants) that model the adhesive strength of each surface. The forces arising from this energy are obtained by considering variations δx^Γ and δx^Υ in the positions of bilayer and cytoskeleton particles

$$d_\Upsilon \mathcal{E}_{con} \cdot \delta\Upsilon + d_\Gamma \mathcal{E}_{con} \cdot \delta\Gamma = -\int_\Gamma f^{\,\mathrm{con},\Gamma}(x^\Gamma) \cdot \delta x^\Gamma \; dx^\Gamma - \int_\Upsilon f^{\,\mathrm{con},\Upsilon}(x^\Upsilon) \cdot \delta x^\Upsilon \, dx^\Upsilon \tag{4}$$

where $f^{\,\mathrm{con},\Gamma}(x^\Gamma)$ is the net force at x^Γ produced by the contact interaction with *the whole of* Υ,

$$f^{\,\mathrm{con},\Gamma}(x^\Gamma) = -\,\beta_\Gamma \int_\Upsilon \beta_\Upsilon \phi'(\|x^\Gamma - x^\Upsilon\|) \, \frac{x^\Gamma - x^\Upsilon}{\|x^\Gamma - x^\Upsilon\|} \; dx^\Upsilon \; , \tag{5}$$

and $f^{\,\mathrm{con},\Upsilon}(x^\Upsilon)$ is the corresponding contact force at x^Υ with the whole bilayer surface Γ,

$$f^{\,\mathrm{con},\Upsilon}(x^\Upsilon) = \,\beta_\Upsilon \int_\Gamma \beta_\Gamma \phi'(\|x^\Gamma - x^\Upsilon\|) \, \frac{x^\Gamma - x^\Upsilon}{\|x^\Gamma - x^\Upsilon\|} \; dx^\Upsilon \; . \tag{6}$$

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Notice that, taking $\delta x^\Gamma = \delta x^\Upsilon$ a constant vector, that $\int_\Gamma f^{\,\mathrm{con},\Gamma} + \int_\Upsilon f^{\,\mathrm{con},\Upsilon} = 0$, as expected from Newton's third principle.

Let us further elaborate the model so as to only perform integrals on Γ, taking advantage of our hypothesis that the adhesive surface Υ of the cytoskeleton consists of rigid spheres. Let Υ consist of one single sphere S, with center X and radius R as in Figure 2. The distance $D = \|x^\Gamma - X\|$ is assumed to be greater than R, so that the distance between x^Γ and S is $d = D - R$. In particular, we can define

$$e(x^\Gamma, \boldsymbol{X}) = \hat{e}(\|x^\Gamma - \boldsymbol{X}\| - R) = \int_S \phi(\|x^\Gamma - x^\Upsilon\|)\, dx^\Upsilon \tag{7}$$

where S is the sphere with center $\boldsymbol{X}$ and radius R. We can re-write (7) in function of d,

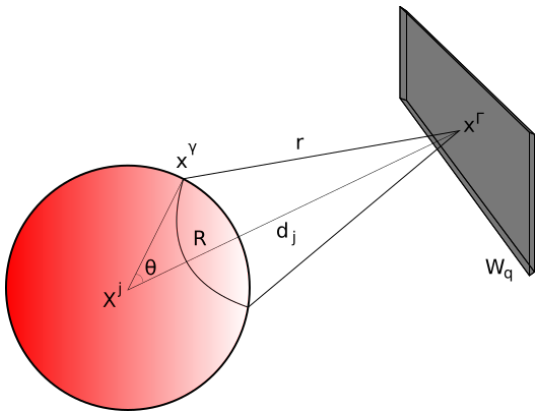

Figure 1: Scheme with in red a node of the cytoskeleton and in grey a piece of bilayer.

$$\hat{e}(d) = \int_d^{d+2R} \phi(r) \frac{2\pi r}{1 + d/R}\, dr\ , \tag{8}$$

so that, adding up all the nodes of the cytoskeleton,

$$\mathcal{E}_{con} = \sum_j\ \beta_j \sum_q \beta_\Gamma\ \hat{e}(\|x^{\Gamma,q} - \boldsymbol{X}^j\| - R)\ W_q \tag{9}$$

where j and q are the indexes over the cytoskeleton nodes and the quadrature rule respectively and W_q is the quadrature weight. Therefore the (4) becomes

$$d_\Upsilon \mathcal{E}_{con} \cdot \delta\Upsilon + d_\Gamma \mathcal{E}_{con} \cdot \delta\Gamma = \sum_j \boldsymbol{f}^{\,\mathrm{con},j} \cdot \delta \boldsymbol{X}^j + \sum_q \boldsymbol{f}^{\,\mathrm{con},\Gamma}(x^{\Gamma,q}) \cdot \delta x^{\Gamma,q}\ W_q\ . \tag{10}$$

The explicit expressions for the forces (5) and (6) are

$$\boldsymbol{f}^{\,\mathrm{con},j}(\boldsymbol{X}^j) = \beta_j \sum_q \beta_\Gamma\ W_q\ \hat{e}'(\|x^{\Gamma,q} - \boldsymbol{X}^j\| - R)\ \frac{x^{\Gamma,q} - \boldsymbol{X}^j}{\|x^{\Gamma,q} - \boldsymbol{X}^j\|}, \tag{11}$$

$$\boldsymbol{f}^{\,\mathrm{con},\Gamma}(x^{\Gamma}) \;\; = -\beta_{\Gamma} \sum_{j} \beta_j \; \hat{e}'(\|x^{\Gamma} - \boldsymbol{X}^j\| - R) \; \frac{x^{\Gamma} - \boldsymbol{X}^j}{\|x^{\Gamma} - \boldsymbol{X}^j\|}. \tag{12}$$

Now, using the (1) we can evaluate the (7), obtaining

$$\hat{e}(d) = \frac{2\pi\,\epsilon}{1 + d/R} \left[\mathcal{F}(d + 2R) - \mathcal{F}(d)\right] \tag{13}$$

where the auxiliary function $\mathcal{F}(x)$ is as follows

$$\mathcal{F}(x) \;\; = \;\; \frac{4}{k-4} \, \frac{r_0^{k/2}}{x^{k/2-2}} \; - \; \frac{1}{k-2} \, \frac{r_0^{k}}{x^{k-2}}. \tag{14}$$

We can thus provide the explicit expressions

$$\begin{aligned} \boldsymbol{f}^{\,\mathrm{con},j} \;\; &= \sum_{q} \beta_{\Gamma} \; W_q \; \beta_j \; 2\pi\epsilon R_j \Bigg\{ -\frac{1}{(d_j + R_j)^2} \left[\mathcal{F}(d_j + 2R_j) - \mathcal{F}(d_j)\right] + \\ &+ \frac{1}{d_j + R_j} \left[\mathcal{F}^{'}(d_j + 2R_j) - \mathcal{F}^{'}(d_j)\right] \Bigg\} \frac{x^{\Gamma} - \boldsymbol{X}^j}{\|x^{\Gamma} - \boldsymbol{X}^j\|} = \\ &= \beta_j \sum_{q} \frac{\beta_{\Gamma} \; W_q}{d_j + R_j} \; \Big\{ -\hat{e}(d_j) \; + \;\; 2\pi\epsilon R_j \left[\mathcal{F}^{'}(d_j + 2R_j) - \mathcal{F}^{'}(d_j)\right] \Big\} \frac{x^{\Gamma,q} - \boldsymbol{X}^j}{\|x^{\Gamma,q} - \boldsymbol{X}^j\|} \end{aligned} \tag{15}$$

and

$$\begin{aligned} \boldsymbol{f}^{\,\mathrm{con},\Gamma} \;\; &= -\sum_{j} \beta_{\Gamma} \; \beta_j \; 2\pi\epsilon R_j \Bigg\{ -\frac{1}{(d_j + R_j)^2} \left[\mathcal{F}(d_j + 2R_j) - \mathcal{F}(d_j)\right] + \\ &+ \frac{1}{d_j + R_j} \left[\mathcal{F}^{'}(d_j + 2R_j) - \mathcal{F}^{'}(d_j)\right] \Bigg\} \frac{x^{\Gamma} - \boldsymbol{X}^j}{\|x^{\Gamma} - \boldsymbol{X}^j\|} = \\ &= \beta_{\Gamma} \sum_{j} \frac{\beta_j}{d_j + R_j} \; \Big\{ \hat{e}(d_j) \; - \;\; 2\pi\epsilon R_j \left[\mathcal{F}^{'}(d_j + 2R_j) - \mathcal{F}^{'}(d_j)\right] \Big\} \frac{x^{\Gamma,q} - \boldsymbol{X}^j}{\|x^{\Gamma,q} - \boldsymbol{X}^j\|} \end{aligned} \tag{16}$$

where

$$\mathcal{F}^{'}(x) \;\; = \;\; \frac{-2\,{r_0}^{k/2}}{x^{k/2-1}} \; + \; \frac{{r_0}^{k}}{x^{k-1}}. \tag{17}$$

3 Conclusions

Optical tweezers are instruments used to stretch a RBC directly in one or more directions by trapping beads that are strategically attached to the cell surface [4]. This equipment is well-suitable for studying the interaction effects between the cytoskeleton and the lipid membrane. In our case, a virtual optical tweezing experiment is a good test to verify the consistency of our model. The numerical implementation revealed the applicability of the formulation for the cyto-bilayer interaction model. The results also reveal a complex behavior which can be a subject of an in-depth study. In Figure 3 is plotted the magnitude of the contact force of a single node (circled in yellow) over time. As we

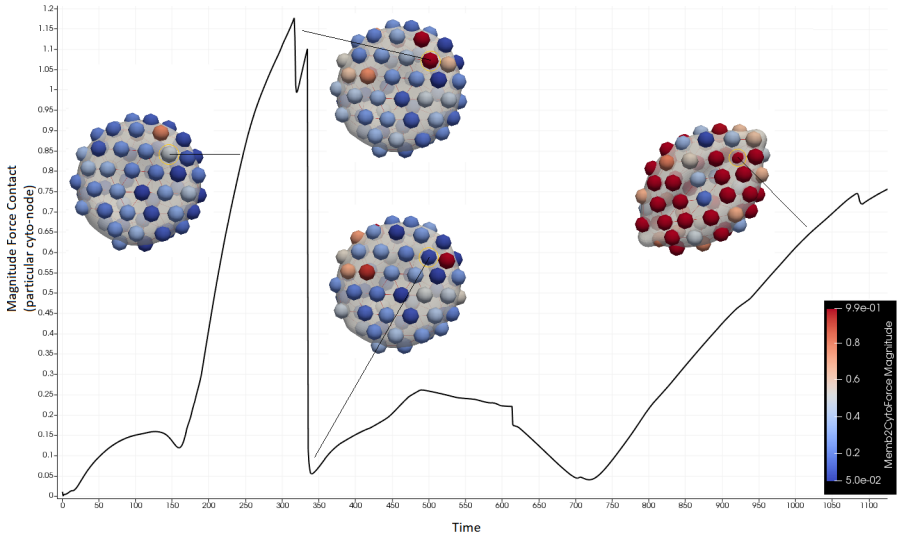

Figure 2: Graph of the norm of the contact force a particular cyto-node (circled in yellow) and corresponding screenshots of the optical tweezing numerical simulation.

can see during the stretching process with the typycal folded RBC shape, the cyto-note goes through phases in which it attaches and detaches itself from the membrane.

This study with the corresponding mathematical formulation for the cyto-bilayer RBC interaction provides the tool for a complete new two-component continuum-discrete model for a single RBC. Indeed, it can contribute to shed light on this difficult and relevant issue that is aimed to understand the interactions between the lipid bilayer and the cytoskeleton using a soft-adhesion body approach.

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