Molecular Dynamics Model for the Dispersive Interaction between Nanoparticles and Erythrocytes: A Focus on Targeted Drug Delivery

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Abstract – This study introduces a numerical model, based on classical molecular dynamics, which simulates the dispersive interaction between magnetic nanoparticles (MNP) and blood components, with a particular focus on erythrocytes. This model considers the collision between an MNP and an erythrocyte, taking into account both the resistive and restorative forces exerted by the elastic surface of the erythrocyte. The model provides insights into the trajectory, penetration, displacement, velocity, and energy of the MNP in relation to an axisymmetric axis. The simulation takes place in an environment that mimics the surface of the erythrocyte, with the MNP moving along the positive z-axis until it collides with an erythrocyte 'wall'. This analysis allows the evaluation of the kinematics and energy before and after the collision. The development of this numerical model offers a valuable tool for the design of targeted drug delivery systems and has the potential to improve the efficacy of focused chemotherapy.

Keywords: Erythrocytes, Nanoparticles, Blood flow, Molecular dynamics, Dispersive interaction.

I. Introduction

Magnetic nanoparticles (MNP) are utilized as heat mediators in hyperthermia treatment and as drug carriers for targeted delivery in specific sites [1]–[3]. Controlled drug release in healthy tissues is fundamental to regulating the amount of drugs administered to the organism [4]–[6]. Predicting the movement and trajectory of nanoparticles when interacting with blood components, especially erythrocytes, which represent over 99% of the aggregates in blood plasma, is key for blood stream-targeted drug delivery towards the tumor [7]–[9].

The focus on the magnetic direction of nanoparticles has been centered on analyzing the dispersion processes of these particles in the bloodstream, underlining the importance of interactions between nanoparticles and erythrocytes [10]–[14]. The migration process depends on the physical characteristics of the nanoparticles, such as size, geometry, chemical composition, and surface coating [15], [16]. Likewise, the hemodynamic characteristics of blood are affected by factors like the type of epithelium, the caliber, geometry, and bifurcation of the blood vessel, as well as the movements and deformations of erythrocytes. External stimuli, like magnetic fields, also influence the trajectory of nanoparticles and constitute a relevant factor in the treatment of focused chemotherapy [2], [17], [18].

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Most current studies on drug delivery with nanoparticles (NP) consider a Newtonian fluid with NPs in suspension. However, blood is a complex biological fluid composed of deformable cells, proteins, platelets, and plasma. For blood flow in capillaries, arterioles, and venules, the particulate nature of blood needs to be considered in the delivery process. The existence of a cell-free layer and the NP-cell interaction will largely influence both the dispersion and binding rates, thus impacting targeted delivery efficacy [10].

The main purpose of this work is to propose a model to simulate the dispersive interaction between a nanoparticle and an erythrocyte using molecular dynamics. The essence of this model lies in understanding the dynamic behavior of the interaction, aiming to quantify the loss of kinetic energy of the nanoparticle. For this, a deformation model that reflects the response of the erythrocyte wall is adopted. This proposal will not only predict the trajectory and speed of nanoparticles but also provide insight into how internal and external forces may affect the efficacy of targeted drug delivery systems and focused chemotherapy.

II. METHODOLOGY

The numerical model simulating the dynamic collision between a nanoparticle and an erythrocyte was developed using classical molecular dynamics, through a numerical code implemented in the C++ programming language. This methodology allowed for the study of the interaction over a period of time defined by the collision interval, yielding precise and reproducible results.

Molecular dynamics is a simulation technique that uses the laws of dynamics to predict the motion of atoms and molecules over time. In molecular dynamics, each particle in the system (in this case, the nanoparticle and the components of the erythrocyte) is treated as a point particle with a specific mass and charge. The forces between particles are calculated from an interaction potential, which in this case has been modeled to reflect the unique characteristics of the

nanoparticle-erythrocyte interaction. These forces are then used in Newton's equations of motion to calculate the trajectories of the particles over time.

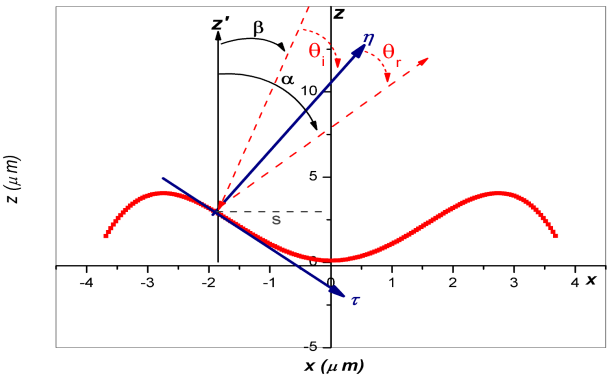

Fig. 1 The reference frame employed to model the collision between the MNPs and the erythrocyte.

In the Fig. 1 shows the reference system employed to model the collision between the magnetic nanoparticles (MNPs) and the erythrocyte was based on an inertial framework, with the erythrocyte serving as the origin of the coordinate system. In this system, the position and velocity of the MNPs were defined relative to the erythrocyte, allowing for the analysis of the interaction and relative motion between the two entities. This reference system facilitated the study of the trajectory, penetration, and other dynamic characteristics of the collision between the MNP and the erythrocyte.

The incidence of a rigid nanoparticle on the elastic surface of the erythrocyte was considered over a time interval defined by the collision period. Two main forces are described: the resistive force exerted by the erythrocyte surface on the nanoparticle, which depends on its speed, and the restorative force, which is related to a nonlinear function of the nanoparticle's displacement and the viscosity of the erythrocyte. From the dynamic analysis, the equation of motion is obtained that expresses both the deformation force that the erythrocyte surface exerts on the nanoparticle and the drag force, both represented in the form of a differential equation:

$$\frac{d^2z}{dt^2} + \gamma\frac{dz}{dt} + \beta z^{3/2} = 0 \qquad (1)$$

The damping coefficient as a function of the nanoparticle radius R and the erythrocyte viscosity η is given by $\gamma = \frac{6\pi\eta R}{m}$.

Meanwhile, the deformation coefficient related to the Young's modulus of the erythrocyte E is $\beta = \frac{4}{3}\frac{ER^{1/2}}{m}$.

The numerical model, based on the motion equation (1), uses molecular dynamics techniques to describe the behavior of the nanoparticle during its interaction with the erythrocyte membrane. This methodology provides a detailed view of the nanoparticle's trajectory, penetration or displacement, speed, and energy. The simulation is performed in a square computational space, where a flat surface in the center represents the erythrocyte surface. The nanoparticle moves along the positive z-axis until it collides with this surface, which reflects the viscoelastic characteristics of the erythrocyte membrane.

Figure 2 shows the flowchart of the program used to perform the simulation. This diagram illustrates the different stages of the process, from the definition of initial parameters to the acquisition of the final simulation results, which include: (i) boundary conditions related to the physical characteristics of the membrane, (ii) the temporal evolution of the system, determined from the initial conditions established by the system's initial positions xo, velocities vo, and initial acceleration ao, (iii) the system constants, defined by the constants and of equation (1), and (iv) the core of the program, based on the motion equations.

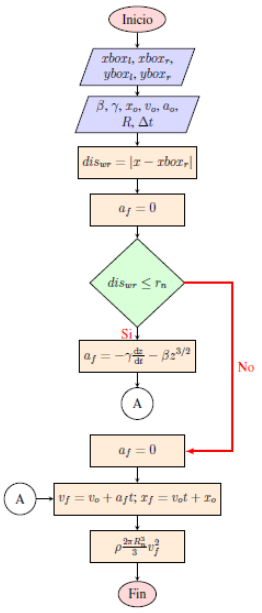

Fig. 2 Flowchart of the interaction model between a particle collision and an erythrocyte.

The plasma is modeled as a Newtonian fluid with laminar flow, while the erythrocyte is represented as a deformable solid and is estimated to be the main scattering center in the simulation. The deformation and restitution ability of the erythrocyte membrane has been incorporated. As for the nanoparticle, it is modeled as a spherical particle with a smooth surface and a diameter considerably smaller than that of the erythrocyte. The magnetic field has been chosen to be disregarded in this simulation, as the main focus lies in the interaction between the nanoparticle and the erythrocyte, centered on the changes in speed and trajectory of the nanoparticle.

III. RESULTS

An investigation was conducted into the dynamic and energetic behavior of the interaction between a nanoparticle and an erythrocyte during the collision time. For this purpose, classical molecular dynamics was employed, and the mathematical model of interaction between the nanoparticle and the erythrocyte was solved based on equation (1). Five variations of the initial velocity of the nanoparticle were taken as input parameters, which ranged between the limit of the blood flow velocity at the periphery and the blood flow velocity at the center of the vessel, that is, in the range between $(3,5 \leq v_{xo} \leq 12,5) \times 10^{-3} nm/ns$. The size of the nanoparticle was kept constant at 100 nm in the first part of the model, and the erythrocyte was approached from an inertial system.

Fig. 3 illustrates how the depth of nanoparticle penetration into the erythrocyte is directly related to its initial velocity, as expressed in the equation $dp=7\times10^{-4}v^2$. This graph demonstrates that the maximum displacement of the erythrocyte's cross-section in the (x,z) plane occurs when the initial velocity of the nanoparticle reaches 12,5 x 10^{-3} nm/ns.

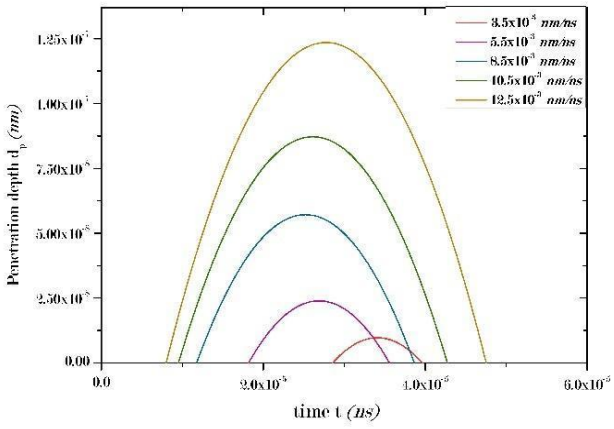

Fig. 3 The depth profile of the nanoparticle-erythrocyte interaction in relation to velocities inside the blood vessel.

Fig. 4 illustrates the variation in the kinetic energy of the nanoparticle during the collision time, where it can be observed that this energy decreases as the nanoparticle penetrates into the erythrocyte until it reaches zero, which corresponds to the return of the nanoparticle. The loss of energy when interacting with the walls of the erythrocyte was found to be minimal, allowing the conceptualization of the interaction model as an elastic collision. In this model, energy and linear momentum are conserved both before and after the interaction between the nanoparticle and the erythrocyte.

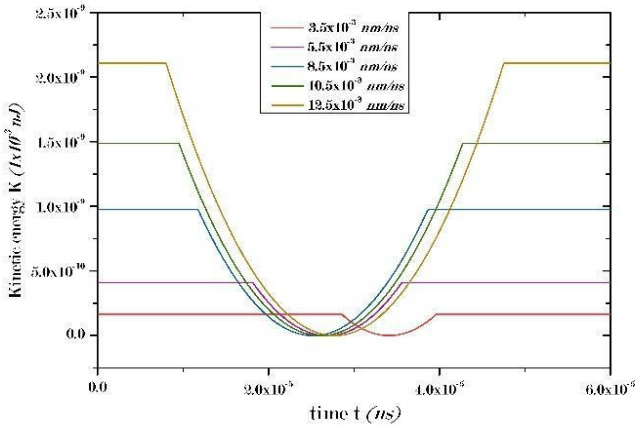

Fig. 4 Kinetic energy in the interaction between nanoparticle and erythrocyte for a particle size of 100 nm.

The size of the nanoparticles is adjusted, recognizing that it is a crucial factor in their distribution and elimination, along with other aspects such as surface coating and geometry [19], [20]. In this part, the interaction of nanoparticles with smooth metallic surfaces and sizes ranging from 10 to 200 nm with erythrocytes is examined, based on the parameters obtained in [2], [9], [12], [21]-[23]. The modeling is done again based on equation (1), and the influence of drag force and viscoelastic force is incorporated, linked to a damping and deformation factor for the new set of parameters.

Fig. 5 represents the trajectory of the nanoparticle during its collision with the erythrocyte. It is evident that the depth of nanoparticle penetration increases proportionally with its size.

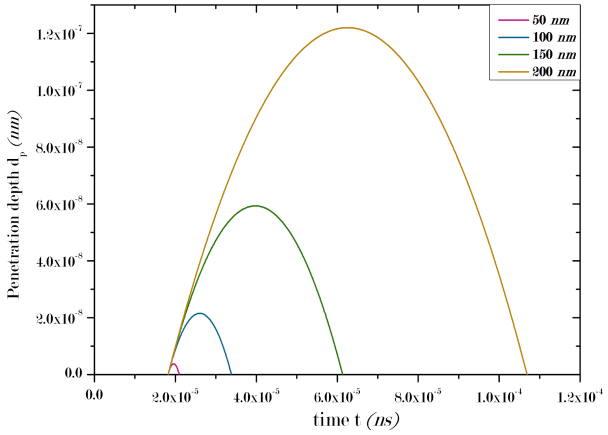

Fig. 5 Depth profile in the interaction of nanoparticle-erythrocyte for different nanoparticle sizes.

The behavior of the penetration depth of the nanoparticle into the erythrocyte (see Fig. 6), in relation to the nanoparticle size, exhibits a second-degree polynomial trend, which is represented by the following equation:

$$d_p = 4\times10^{-4}\,\tau^2 \qquad (2)$$

where τ indicates the nanoparticle size.

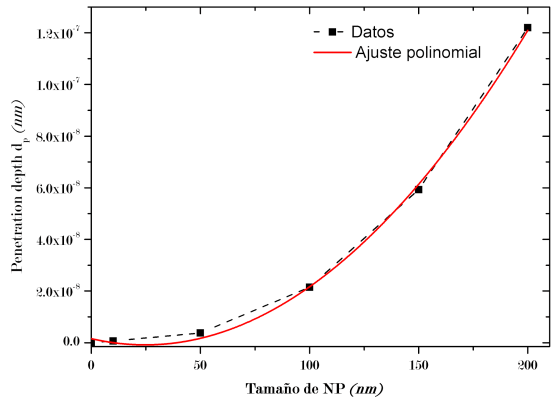

Fig. 6 Adjustment of the depth profile as a function of the MNP size..

The analysis of the resulting energetic behavior from the interaction between a nanoparticle and an erythrocyte by modifying the nanoparticle size is presented in Figure 7. Here, the fluctuation of the nanoparticle's kinetic energy during the impact for different diameters is highlighted. As the nanoparticle penetrates into the erythrocyte, the energy decreases until reaching zero and then returns to its original state, suggesting that the erythrocyte has a remarkable ability to deform and restore its membrane without significant energy losses.

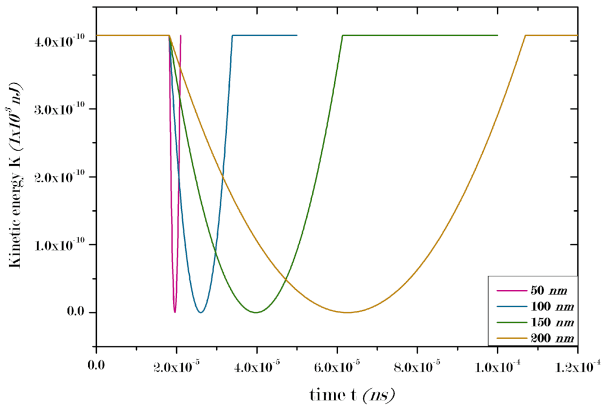

Fig. 6 Depth profile in the interaction of nanoparticle-erythrocyte for different nanoparticle sizes.

The findings of this study reveal that the interaction between a nanoparticle and an erythrocyte is significantly influenced by both the nanoparticle size and the viscoelastic properties of the erythrocyte membrane. The erythrocyte's ability to deform and restore its membrane allows for an energetic interaction with the nanoparticle with minimal energy dissipation. Additionally, drag force and viscoelastic force are determined by the nanoparticle size and the Young's modulus of the erythrocyte membrane, respectively, with the viscoelastic force being the most influential term in the equation of motion. These results provide an understanding of the interaction between nanoparticles and blood cells and could have implications in biomedical applications such as drug delivery and gene therapy.

In [25], it was demonstrated how nanoparticles interact and enter human red blood cells. Using various microscopic techniques, it was discovered that nanoparticles can penetrate the red blood cell membranes regardless of their charge or material. However, these interactions do not deform the membrane significantly and generate minimal mechanical deformations on the cell membrane.

This behavior can also be observed experimentally in [24], where the interaction behavior between silicon nanoparticles and erythrocytes was analyzed. They observed that the disruption of plasma membrane integrity is a primary mechanism of nanoparticle toxicity in cells. This study used erythrocytes with normal and altered membrane asymmetry to examine how the loss of membrane asymmetry and resulting alterations in the outer leaflet lipid composition affect nanoparticle-membrane interactions. Unmodified, amine-modified, and carboxyl-modified silica nanoparticles (30 nm) were used as models. This study examines how the

loss of membrane asymmetry in the cell membrane affects the interaction between nanoparticles and the membrane.

Another study similar to the one presented in this article is [26], where a particle-cell hybrid model was used to analyze the transport, dispersion, and binding dynamics of nanoparticles (NPs) in the blood. The motion and deformation of red blood cells (RBCs) and NPs are modeled using the Immersed Finite Element Method and Brownian adhesion dynamics, respectively. The study found that the existence of the cell-free layer and NP-cell interaction significantly influence the dispersion and binding rates of NPs, impacting targeted delivery efficacy, as reported in this document. This is because the interaction, being almost perfectly inelastic, turns erythrocytes into scattering centers, generating deformations in the NP distribution profile.

IV. CONCLUSIONS

Magnetic nanoparticles hold tremendous potential in hyperthermia treatment and drug delivery as targeted carriers to specific areas of the body. However, to maximize their efficacy, accurate prediction of their trajectory and movement when interacting with blood components is crucial. The presented numerical model, based on classical molecular dynamics, emerges as a valuable tool to investigate the collision between a nanoparticle and an erythrocyte. This model provides crucial information about the trajectory, penetration, velocity, and energy of the nanoparticle in relation to an axisymmetric axis. Through this simulation, we gain a better understanding of how nanoparticles interact with blood cells, which could aid in the design and optimization of drug delivery through the bloodstream toward a tumor. However, for further comprehensive studies and optimization of drug delivery efficacy, additional physical variables such as the surface ligand characteristics of the nanoparticle and blood flow behavior need to be considered.

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