Collisions model between magnetic nanoparticles and the arterial wall

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Abstract. At present, there are different treatments against cancer, however, some of them, such as chemotherapy, are very invasive for the human body, since they affect healthy tissues. Magnetic targeting of drugs by means of magnetic nanoparticles is one of the alternative techniques that has emerged in the last decade, it is based on the targeting of drug delivery to the tumor without affecting healthy tissues, via of injected nanoparticles with diamagnetic properties directly into the bloodstream, driven by external magnetic fields produced by permanent magnets. This technique in literature is often come upon as MTD for its acronym in English. In this work, a numerical model was developed in order to quantify the loss of nanoparticles in the process of interaction with the walls of the bloodstream. For this model, the Kinetic technique was used, quantifying the probability of adsorption and absorption taking into account the following parameters: diameter of the nanoparticle (200 nm), density of the nanoparticle (6450 kg · m$^{-3}$), diameter of the cell endothelial (0.1 µm - 1 µm), transcellular pores of the fenestrated endothelium (70 nm) and modulus of elasticity of the endothelium (4.1 ± 1.7 kPa).

Keywords: Arterial wall, cancer, magnetic nanoparticles, Montecarlo.

1. Introduction

Although there are numerous cancer treatments available today, some are quite harmful to the human body, such as chemotherapy, which affects healthy tissue in the process. This reason has prompted scientists to develop new technology for minimally invasive medical treatments that employ novel procedures to aid in diagnosing, treating, and, in many cases, curing disease. Pharmaceutical sciences are experimenting with nanoparticles (NPs) to reduce drug toxicity and side effects while increasing drug delivery efficiency and potentially alleviating patient discomfort. The use of nanoparticles in medical processes enables more efficient treatments due to their small size and ability to cross biological barriers within the body, as well as access to the cell and various cell compartments, including the nucleus [1]. The most widely used and investigated magnetic nanoparticles to date are those with an iron oxide magnetic core. Due to their magnetic properties and synthesis process, they are typically formed by magnetite ($Fe_3O_4$) or monocrystalline maghemite ($Fe_2O_3$) isolated by a polymeric shell [2]. Magnetic nanoparticles are a class of nanotechnology-based materials that have a significant impact on nanomedicine due to their ease of passage through the bloodstream and interaction with its components, including the arterial wall. The arterial wall is a soft biological tissue found throughout the body. Soft tissues are intricate structures reinforced by fibers whose properties are determined by the

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concentration and arrangement of their constituents. They are distinguished from hard tissues by their higher plasticity and lower mechanical properties. The mechanical behavior of the arterial wall is extremely complex. The large arteries, such as the aorta, act as a hydraulic filter, dampening blood flow oscillations in order to supply oxygenated blood to the various tissues and organs. Its primary components are elastin, the primary protein found in the elastic fibers of arteries, veins, and skin, as well as additional organs; collagen, a fundamental structural component of soft tissues that provides mechanical resistance; and muscle cells [3], which play a critical role in the interaction with magnetic nanoparticles.

The above-mentioned complex mechanical behavior of the arterial wall makes it necessary to use computational models via numerical methods in order to improve our understanding of it. The incompressible Newtonian fluid model, which simulates blood, and the incompressible hyperelastic solid model, which simulates the arterial wall, are two of the numerous published models. The parameters of the arterial wall model are determined using experimental data, and the equations are numerically solved using the finite element method with a specific treatment of the incompressible condition [4]. Other authors have developed numerical simulation techniques that accurately represent blood flow on a cellular scale by explicitly representing its coupled fluid and solid mechanics [5]. Similarly, models have been developed to investigate the delivery of MNP magnetic nanoparticles to a vascular endoprosthesis or stent under the influence of an external magnetic field and to describe the trajectories of magnetic nanoparticles within the blood vessel for the purpose of magnetic orientation of drugs [6].

Blood flow simulations utilizing the Lattice Boltzmann method in conjunction with the immersed edge method enable the incorporation of fluid-membrane interactions between the flow field and the deformable red blood cells [7]. Similarly, mathematical models have been developed to track individual superparamagnetic nanoparticles in the bloodstream when an external magnetic field is applied [8]. The application of Montecarlo analysis to these models allows us to quantify the surface interactions and selectivity between oriented nanoparticles and cell surfaces [9].

No records of studies of the nanoparticles interacting with an exposed artery wall have been found, even though there are several numerical and computational studies of the flux of magnetic nanoparticles in the presence of an external magnetic field. The goal of this work is to numerically model the interaction between magnetic nanoparticles and the arterial wall, quantifying the number of them adhering to the surface of the endothelium, as well as the number absorbed by the blood vessel.

2. Methodology

The kinetic behavior of the interaction between nanoparticles with the walls of the blood vessels is analyzed. In this work, a C++ code based on the Montecarlo Kinetic technique was developed to quantify the number of NPs that cross the endothelial wall. Four fundamental processes were defined: adsorption, desorption, absorption, and collision. The parameters that define the probability of the fundamental steps fall into two groups. The first group contains all endothelium and NPs morphological characteristics, while the second group covers all the kinetic variables. Figure 1 shows a graphical representation of the collision of the NPs.

The mechanical properties of the arterial wall are summarized in Table 1. The endothelium is characterized by cells with a thickness of approximately 1 µm that can vary depending on the type of blood vessel. There are a series of pores on the endothelial walls that allow for the exchange of aggregates. It is assumed in this model that NPs can undergo absorption and
Figure 1. Representation of the collision between the NPs and the arterial wall. The identifying parameters are: endothelium thickness (1 \( \mu \)m), nanoparticle diameter (200 nm), nanoparticle velocity (0.5 m/s), and endothelial cell diameter (70 nm). Modified from [10].

Desorption processes when they interact with these pores. Additionally, the model assumes a normal pore size distribution in the endothelium.

| Tabla 1. Mechanical properties of the arterial wall. |
|-----------------------------------------------|
| Properties                                    | Value                        | Ref.  |
| Cell thickness                                | 1 \( \mu \)m veins in the aorta | [11]  |
| The surface of endothelial cells              | \((1 - 6) \times 10^{13}\) cells, weight approx. 1 kg | [11]  |
| Adult human                                   | approximate surface area 1 a 7 m\(^2\) | [11]  |
| Transcellular pores-fenestrated endothelium   | 70 nm diameter               | [11]  |
| Modulus of elasticity of the endothelium      | 4.1 \( \pm 1.7\) kPa         | [12]  |

In Table 2, a compendium of the mechanical properties and kinetic variables of NPs is presented. The most relevant factor is the kinetic energy of NPs when interacting with blood vessels walls. The NPs are approximated as spheres with radius \( r \), constant density, and a velocity of about 0.5 m/s.

| Tabla 2. Mechanical properties of simulated nanoparticles [13]. |
|---------------------------------------------------------------|
| Feature                                     | Unit     | Symbol | Value | Ref.     |
| Nanoparticle size                               | nm       | \( r_p \) | 200   | [14], [13] |
| Flow rate (velocity)                           | m \( \cdot \) s\(^{-1}\) | \( v \) | 0.5   | [14]     |
| Nanoparticle density                           | kg \( \cdot \) m\(^{-3}\) | \( \rho \) | 6450  | [14]     |

2.1. Kinetic Montecarlo (KMC)

Random numbers are those that can be generated with equal probability and independently of any previous outcome. Statistically, it means that the numbers are random variables that require different generating methods. The Kinetic Montecarlo method is an application of the standard Montecarlo method to time-varying systems [15].
In order to use the Kinetic Montecarlo approach, it is necessary to define the transition probability between the various states. The states defined in this interaction are three: NPs adsorbed, NPs absorbed, and NPs free of adsorbates. Transition processes are defined by the fundamental transition steps. The probability is defined by means of the relation:

\[ p_n = \frac{k_n}{\sum k_n} \]  

where \( n \) indicates the process and \( k_n \) is indicated by the relation:

\[ k_n = k_{np} \exp^{-\frac{E_n}{KT}} \]  

with \( k_{np} \) representing a pre-exponential factor, \( E_n \) the activation energy of the process \( n \), \( K \) the Boltzmann constant, and \( T \) the temperature. In the case of the collision process, the activation energy depends on the kinetic energy. For absorption and desorption processes, the activation energies depend on the pore size. In this work, the pores (with a normal size distribution assumed) are located randomly on the arterial wall.

In a system in which a state can only evolve to nearby states, it is mathematically possible to demonstrate that the likelihood of a transition between states is independent of the previous time. The KMC method employs random probabilities to determine both the temporal evolution and the corresponding transition. In the first case, an exponentially distributed random number is required by the probability function. The following procedure is followed to obtain the time increment:

\[ \Delta t = \frac{1}{k_{tot}} \ln \frac{1}{u^t} \]  

where \( u^t \) is the uniformly distributed random number \( u^t \in (0, 1] \), and \( k_{tot} \) is the total escape rate of the particle.

3. Results

Variable transition probabilities are used to model the system. These depend on the physiological and morphological factors of the system. The computational space is represented by a square lattice of 100×100, and as a first approximation, an infinite repository of NPs was assumed. This approximation is feasible given that the number of particles interacting with the surface is significant less than the total amount of NPs.

The coverage of particles adhering to the endothelium was analyzed. The adsorption probability \( P_{ads} = 0.08 \), desorption probability \( P_{des} = 0.07 \), and absorption probability \( P_{abs} = 0.07 \) are all initially assumed to be constants. Figure 2 illustrates the number of particles absorbed per step, the number of absorbed particles accumulated over time, and the number of particles adsorbed. As illustrated in Figure 2(a), the amount of NPs adsorbed remains on average constant at a value of 250. The same behavior is observed for the amount of particles absorbed per cycle. Due to the constant absorption rate per cycle, the number of particles lost by the absorption process grows linearly with time (Figure 2[b]). In Figure 2(c), the system is seen to stabilize after roughly 50 Montecarlo steps.

Figure 3 compares the output variables for values of \( P_{ads} \) between 0.1 and 0.5. By increasing the probability of nanoparticle adsorption as a result of the increased size of the surface pores, a linear rise in the coverage of the NPs is observed. Although the trend is non-linear, a rise in the number of absorbed NPs is also observed. This behavior is explained by the absorption process
Figure 2. (a) Number of NPs absorbed per step. (b) Number of NPs adsorbed. (c) Accumulated number of NPs. Time is measured in MonteCarlo steps (MCS).

being related to the adsorption process, considering that for an NP to be absorbed it must be previously adhered.

Figure 3. (a) Number of NPs adsorbed by the endothelium. (b) Accumulated number of NPs adsorbed. (c) Number of NPs absorbed by the blood vessel. Time is measured in MonteCarlo steps (MCS).

The probability of adsorption ($P_{ads}$ = 0.01) and of desorption ($P_{des}$ = 0.01) were defined, and the probability of absorption was varied (see figure 4). Increased absorption probability results in a decrease in the amount of NPs adhered to the surface of the endothelium. This is because it increases the kinetics and the probability of absorption. In the limiting case, when the absorption probability is equal to 1, the surface coverings tend to zero.

To analyze the behavior of the absorption and adsorption processes as a function of the probabilities of each elemental step, the surface coverage of NPs ($\theta_{ads}$) is defined as the ratio
between the number of NPs adsorbed over the total number of pores on the surface. This coverage is related to the ratio between $P_{\text{ads}}$ and $P_{\text{abs}}$ as shown in Figure 5. Increasing the absorption probability results in a decrease in $\theta_{\text{abs}}$ (see Figure 5[a]). Figure 5(b) illustrates the absorption rate per cycle and how it increases as the probability of adsorption increases. This implies that although the probability of absorption increases, the most relevant factor is the probability of adsorption, as adhesion is required for NPs to be absorbed in this model.

**Figure 4.** (a) Number of NPs absorbed. (b) Accumulated number of NPs absorbed. (c) Number of NPs absorbed. Time is measured in Montecarlo steps (MCS).

| Figure 5. | (a) Number of NPs adsorbed. (b) Number of NPs adsorbed per cycle. |
|-----------|---------------------------------------------------------------|

Thus, the model can account for the amount of NPs that are absorbed by the blood vessels, depending on the type of pore and its distribution. Not only can these NPs reduce the efficiency of the technique, but they also spread the drug to non-target locations, which might result in drug buildup in other parts of the body. By increasing the size of the pore in comparison to the radius of the NPs, the probability of adsorption increases and in turn the probability of absorption, where the most relevant factor is the coverage of the NPs.

**4. Conclusions**

In MDT simulations, a variety of physical phenomena must be included. This model considers the mechanical properties of the vessel walls, where the absorption of NPs results in a decrease...
in the amount of NPs adhered to the endothelium’s surface, allowing them to travel through the bloodstream and reach the required sites, such as tumors or pathologies that can be diagnosed and treated with NPs. The extent to which nanoparticles cover the surface depends on the density of the pores and the relationship between the adsorption and absorption probabilities. Due to the fact that the kinetic properties of the nanoparticles are altered by the physiological state of the patient, the model must take into account the unique characteristics of each individual.

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