Simulation of magnetic particle capture in the breast

Luz Helena Camargo

Jennifer Pacheco

Diego Julián Rodriguez

Faculty of Engineering, Research Group Ingeniería y Nanotecnología para la Vida (INVID), Universidad Distrital Francisco José de Caldas, Bogotá D.C., Colombia

Abstract. New strategies, such as magnetic guidance of medicines, are used in cancer treatment. This work determined the topological characteristics of blood vessels in the breast with cancer. To remove the topology of the blood vessels mammogram imaging of cancer patients, image preprocessing was performed using conventional methods (Canny, Prewitt, and Sobel), with neural networks, and with light correction techniques, a 3D model was generated with finite element software to simulate velocity and blood flow, 700 nanoparticles of Magnetite were included, with a magnet of Neodymium and the number of nanoparticles reaching the tumor was evaluated. The best results were obtained with the light correction method that improved the definition of blood vessels with the topology obtained and more particles were found to reach the magnetic field tumor compared when it is absent.

1. Introduction

Cancer is one of the leading causes of morbidity and mortality in the world; 14 million new cases were reported and 8.2 million cancer-related deaths in 2012, and 18.1 million new cases and 9.1 million deaths in 2018 [1]. About 70 % of cancer deaths occur in low- and middle-income countries, which consists of an abnormal and disordered proliferation of malignant cells that leads to the uncontrolled growth of a tumor [2], these cells leave the origin and migrate to other organs, causing metastasis, which leads to the formation of secondary tumors. Approximately 90 % of cancer deaths are explained by cancer metastasis [3, 4]. The survival rate is increased mainly by early diagnosis and inhibition of cancer growth [4]. The most effective and valuable treatments for local and non-metastatic cancer are surgery and radiation therapy, however, they are inefficient when cancer has spread, and the radiation therapy can be counterproductive to the long-term survival of patients [5], in which case drugs are used (chemotherapy, hormonal and biological therapies) because they can reach all the organs of the body through the bloodstream [6], although there is a low level of knowledge of his journey. Chemotherapy drugs are often based on toxic compounds [7] inhibiting mainly the proliferation of cancer cells, but unfortunately, these drugs are random and inhibit growth healthy cells leading to undesirable side
effects in cancer treatment [6], [8].

New strategies propose to employ magnetic drug targeting (MTD), which can be manipulated inside the body by external magnets [9, 10]. They are usually nanoparticles of diamagnetic porous materials that are directed by external magnetic fields and that inside they carry the medicine. The International Cancer Institute has researched to understand how is implemented and how it affects the organism. Human studies have been conducted on inoperable and shallow tumors [11] and simulations of the trajectory behavior of nanoparticles have been carried out to analyze the interaction with biological tissue [12], however, challenges in the magnetic guidance of drugs continue to safely and effectively attack cancer. Microcirculation is essential for the distribution of oxygen and nutrients. Nanoparticle management is a developing technology, these enter through the bloodstream to the organs that require it, considering that tumors induce angiogenesis [3], therefore, new capillaries can also take the drugs to the specific target. To better understand the implementation of cancer-oriented MTDs it is necessary to know the trajectory of the nanoparticles in the bloodstream therefore implement tools to extract and simulate the topology of blood vessels near cancer and the dynamics of blood flow. The computational tools used in MTD simulation can greatly contribute to medical treatments, reducing side effects, and achieving that the patient can decrease the required dose [13]. The simulation of blood vessels has been mainly performed on the aorta artery. Bracamonte-Barany col., performed the simulation of the aortic fall assuming an ideal large topology [14]. Calvo Plaza performed the simulation of blood flow through a left coronary artery by pre-extracting its topology taking into account its diameter, length, and other variables [15]. Kenjereš emphasizes circulation in the aortic arch and blood vessels present in the brain [16, 17]. Haverkort 2009 studied the left coronary artery and carotid artery, finding favorable the efficiency of capturing the particles [18], however, no such research is reported on mammary glands. In this work, to evaluate the effectiveness of magnetic drug targeting in the breast; the geometry of the blood vessels is estimated via different image analysis techniques.

2. Methodology

Breast cancer images were used. The mammograms used to come from the public database of the University of South Florida, USA [19]. In this study, we considered images annotated as cancer images, which correspond to the target of treatments. Each of the categories has four sockets, two for each sine, one caudal skull view, and one medium oblique side view. The images in the middle oblique side view were selected, in which greater contrast and sharpness of the blood vessels were appreciated (see Fig. 1A.). To better analyze the blood vessels of the breast, increase the contrast of the blood vessels was required [20] with lighting correction; in this case consisted of removing the background, eliminating the foreground by morphological opening with a radius of 15 points then turned the image to grayscale and removed the noise, the lighting correction allows remove lighting variation in the image [21].

2.1. Mathematical model

700 nanoparticles of magnetite 200 nm, whose density is considered to be 6450 Kg·m$^{-3}$ were included, subject to magnets of Neodymium (NdFeB), magnetic field magnitude 4 T, relative permeability 4000 and then the number of nanoparticles reaching the tumor was evaluated. The equation of motion of particles in the fluid is considered as:

$$\frac{d}{dt}(m_pv) = F_D + F_g + F_{ext}$$ (1)

where $m_p$ is the particle mass, the velocity of the particle is $v$, $F_D$ is the drag force, the gravitational force is $F_g$, $F_{ext}$ is any other external force.
\( \mathbf{F}_D \) is defined as:

\[
\mathbf{F}_D = \left( \frac{1}{\tau_p} \right) + \mathbf{m}_p \left( \mathbf{u} - \mathbf{v} \right)
\]  

(2)

where \( \tau_p \) is the particle velocity response time, \( \mathbf{u} \) is the fluid velocity. Considering that the flow is laminar, the particle velocity response time is

\[
\tau_p = \frac{\rho_p d_p^2}{18 \mu}
\]  

(3)

The magnetic field distribution around the magnet is calculated from [22]:

\[
B = u_0 (H + M)
\]  

(4)

where \( B \) is the magnetic flux density (T), \( \mu_0 \) is the permeability of vacuum, \( \mu_0 = 4\pi \times 10^{-7} \text{N} \cdot \text{A}^{-2} \), \( H \) is magnetic field intensity (A/m) and \( M \) is Magnetization (A/m). The magnetic force acting on the particles is expressed as [23]:

\[
F_m = \mu_0 V_p (\nabla \cdot \mathbf{M}) - \mu_0 \nabla \cdot \mathbf{H}
\]  

(5)

\( V_p \) is the volume of the particle \( \left( \frac{4}{3} \pi r_p^3 \right) \). The motion of magnetic nanoparticles is described by Newton’s second law as:

\[
m_p = \frac{du_p}{dt} \sum F_{ext}
\]  

(6)

where \( m_p \) is the mass and \( u_p \) the velocity of the magnetic particles, and \( \sum F_{ext} \) is the sum of all external forces acting on the particle. The inertial term \( m_p \frac{du_p}{dt} \) is very small, and could be ignored.

The efficiency is defined as follows:

\[
Efficiency = \frac{\text{Number of nanoparticles in the tumor}}{\text{Number of nanoparticles}} \times 100
\]  

(7)

### 2.2. Numerical method

After increasing the contrast of the blood vessel, the region near the tumor was delimited. The blood vessels were identified and measurements were established with the program ImageJ [24], which is a public domain software for image analysis, written in the Java programming language [25]. For the extraction of the topology of the blood vessels, these were reconstructed with computer-aided design software (CAD) with the help of FreeCAD [26, 27], which reproduced the topology. FreeCAD is a parametric CAD that uses parameters to define your limits or action, with the feature-based design of 3d solids [28]. To simulate blood vessels, we generate the mesh (see Fig. ??). The meshing algorithm was free using tetrahedral elements, which poses no restriction to the geometry structure, as reported by Kenjeres [16].

In this work, the full mesh consisted of 1,42480 domain elements, 1,4966 boundary elements, and 1,282 border elements. The simulation was conducted with the numerical method. The fluid inlet and outlet pressure were established as 126.09 mmHg and 126.089 mmHg respectively. Blood dynamics, approaching a Newtonian flow, were simulated using the finite element method implemented by the modeling tool COMSOL Multiphysics [29].
COMSOL incorporates for the resolution of the fluid dynamic the equations in the mode of incomprehensible application Navier-Stokes [30].

\[
\rho = \frac{\partial \mathbf{u}}{\partial t} + \rho (\mathbf{u} \cdot \nabla) \mathbf{u} = \nabla \cdot (-p \mathbf{I} + \mu (\nabla \mathbf{u} + \nabla \mathbf{u}^T)) + \mathbf{F} \tag{8}
\]

\[
\rho \nabla \cdot \mathbf{u} = 0 \tag{9}
\]

where \( \mathbf{u} \) is the fluid velocity, the pressure is \( p \), \( \rho \) is the density, \( \eta \) is the dynamic viscosity, \( -p \) is the density, the dynamic viscosity is \( \mu \) \( \mathbf{F} \) is the total volume force. Table 1 presents a summary of the parameters used for the analysis.

| Feature                   | Symbol | Unit     | Value            |
|---------------------------|--------|----------|------------------|
| Flow rate (velocity)      | \( v \) | \( m \cdot s^{-1} \) | 0.5 [31]         |
| Blood density             | \( \rho \) | \( Kg \cdot m^{-3} \) | 1060 [32]        |
| Blood pressure            | \( p \) | Pa       | 20 [31]          |
| Blood viscosity           | \( \mu \) | \( Pa \cdot s \) | 0.004 [15]       |
| Diameter of the blood vessel | \( d \) | m       | 0.005 [31]       |
| Composition nanoparticle  | \( x \) | %        | Iron:67.5-Coal:2.5 |
| Size nanoparticle         | \( r_p \) | nm      | 200              |
| Density nanoparticle      | \( \rho \) | \( Kg \cdot m^{-3} \) | 6450 [31]        |
| Width of the magnet       | \( 2w \) | mm      | 50 [12]          |
| Height of the magnet      | \( 2h \) | mm      | 100 [12]         |
| Magnetic field magnitude  | \( B \) | T       | 4                |
| Relative permeability     | \( \mu_r \) |        | 1 4000           |

3. Results
The lighting correction method has the definition of the blood vessels, therefore, the lighting correction was selected to simulate the topology because it presents better sharpness. The results presented in Fig. 1B shows the enhancement of blood vessels. The 3D shape generated in FreeCAD (see Fig. 1D) is exported to COMSOL, considering the diameter of 5 mm and the length of 100 mm for its branches.

The vascular system consisting of multi-branching arteries is generated images of a patient, the mesh generation is performed by COMSOL.

Initial blood pressure was considered as \( p = 20 \) Pa [33], the simulation was carried out in a three-dimensional computational space, with an approximation of the laminar flow, velocity was determined as 0.05 m s\(^{-1} \) [31], the blood density is \( \rho = 1060 \) Kg m\(^{-3} \) [32], similar to \( \rho = 1050 \) Kg m\(^{-3} \) used in Kenjeres [17], and dynamic viscosity as \( \mu = 0.004 \) Pa s [15, 31], similar to \( \mu = 0.003 \) Pa s used by Apostolidis [32]. Fig. 2 presents the results of blood flow simulation. It is observed how the velocity of blood flow is maintained at the forks, inherent in such systems due to the balance of pressure.

The properties of magnetic nanoparticles in their field of application provide an overview of iron oxide NPMs used in environmental, biomedical, and clinical fields, with its focus on the
Figure 1. A. Mammograms of cases diagnosed with cancer delimited by the line. Source:[19]. Image result of processing. B. Detection of blood vessels. C. Detail of the extracted section with ImageJ program. D. Result of the topology rebuilt in FreeCAD.

Figure 2. Velocity and pressure.

use of zero valence, magnetite ($Fe_3O_4$), and maghemite iron nanoparticles ($\gamma - Fe_2O_3$) [34]. 700 nanoparticles of 200 nm were included, in other studies are considered particles of different diameters 250 and 500 nm, 1, 2 y 4 $\mu$m [18], 0.25 a 4 $\mu$m [16] y 1 $\mu$m [35]. It has been cited as a suitable diameter between 10 to 200 nm, 100 nm particles may have long circulation times in the blood [36]. Seventy-one percent of the particles of 200 nm with 4 T magnetic field ($n = 497$) reached the tumor(see fig. 3C), other authors report without magnetic field is 6 %, and reaches 79 % with a magnetic field strength of 6 T [37].

Figure 3. A. Magnetic field. B. Nanoparticle trajectory. C. The capture efficiency of magnetic nanoparticles, in a magnetic field of 4 T and an inlet velocity of 5 cm/s, in blue reach the tumor.
4. Conclusions

Five images were selected from the mammogram database to perform different image processing methods. Three operators were implemented for edge detection in MATLAB®, a neural network algorithm and lighting correction, finding greater contrast of blood vessels with the lighting correction, obtained through the background correction, and the image was selected to determine the topology of the blood vessels that were modeled in 3D for simulation. A methodology was developed to determine the topology of the blood vessels of a case of breast cancer, which was validated by determining the behavior of blood flow in a Newtonian flow approximation. The best results were More particles were found to reach the magnetic field tumor compared to when it is absent.

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