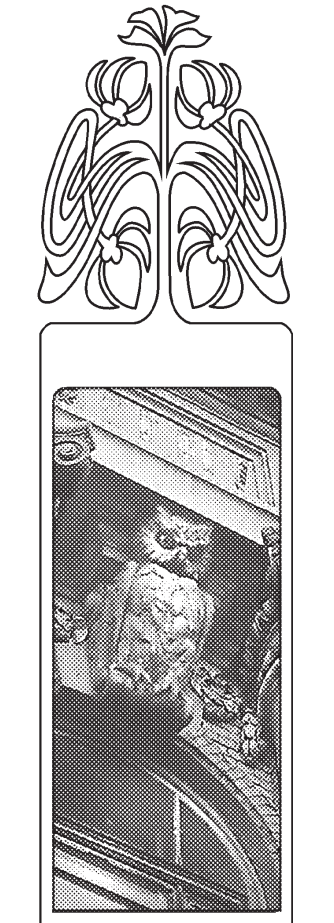

НАУЧНЫЙ ОТДЕЛ

КРАТКИЕ СООБЩЕНИЯ

Trapping of Magnetic Nanoparticles in the Blood Stream under the Influence of a Magnetic Field

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Magnetic nanoparticles, as controlled drug carriers, provide tremendous opportunities in treating a variety of tumors and brain diseases. In this theoretical study, we used magnetic nanoparticles, such as Superparamagnetic Iron Oxide Nanoparticles (Fe_3O_4) (SPION). Due to their biocompatibility and stability, these particles represent a unique nanoplatform with a great potential for the development of drug delivery systems. This allows them to be used in medicine for targeted drug delivery, in magnetic resonance imaging and magnetic hyperthermia. In the work, the trapping mechanisms of magnetic nanoparticles moving in a viscous fluid (blood) in a static magnetic field are numerically studied. The equations of motion for particles in the flow are governed by a combination of magnetic equations for the permanent magnet field and the Navier–Stokes equations for fluid (blood). These equations were solved numerically using the COMSOL Multiphysics® Modeling Software.

Keywords: magnetic nanoparticles, magnetism, blood, Newtonian fluid, permanent magnet, computational modelling.

Received: 07.12.2019 / Accepted: 09.01.2020 / Published: 02.03.2020

DOI: https://doi.org/10.18500/1817-3020-2020-20-1-72-79

1. Introduction

Magnetic nanoparticles (MNPs), such as magnetite (Fe_3O_4) or maghemite (Fe_2O_3) are called single domain particles and display superparamagnetic behavior once their size are smaller than the critical diameter [1–3]. They have a net magnetization only in the presence of an external magnetic field, This field allows for MNPs to travel freely through the circulatory system so this field helps to trap the NPs at the selected location. Under magnetic field, the accumulation takes place within the area to which the magnetic field is applied. The accumulation of the carrier at the target site allows them to deliver the drug locally. Efficiency of accumulation of magnetic carrier on physiological carrier depends on particle physical parameters and physiological properties, e.g. particle size, surface characteristic, field strength, and blood flow rate etc.

M. R. Habibi and M. Ghassemi studied numerically the concentration of magnetic nanoparticles travelling in non-Newtonian biofluid under the influence of magnetic field in vitro and in vivo [4]. Biocompatibility and biotranslocation issues in relation to chemo-physical

properties of MNPs, including particle size, surface properties, shape and structure, are discussed.

In this study, Fe_3O_4 magnetite nanoparticles are used because of their strong ferromagnetic behavior, less sensitivity to oxidation and low toxicity compared with other materials such as nickel and cobalt [5]. Such nanoparticles can be driven to the target site by applying an external magnetic field from a permanent magnet placed outside the tube (blood vessel). The efficiency of drug delivery based on MNPs used to transfer drug into localized target, depends on size and other properties of these particles [6]. Besides drug delivery MNPs are used for tumor treatment via induced hyperthermia, where their high biocompatibility and nontoxicity are also needed [7].

Superparamagnetic Iron Oxide Nanoparticles (SPION) is a nanoplatform with a great potential for drug delivery as they can be coated with a therapeutic agent and be easily guided to the target area by an external magnetic field. The drug delivery research based on MNPs has two major components. The first one discusses the characteristics and reaction of MNPs for the purpose of the delivery of the drug, and the second part represents the drug delivery design to control the dynamic of MNPs from injected position to target of vascular system. These MNPs are directed magnetically through blood vessel to the site of the target.

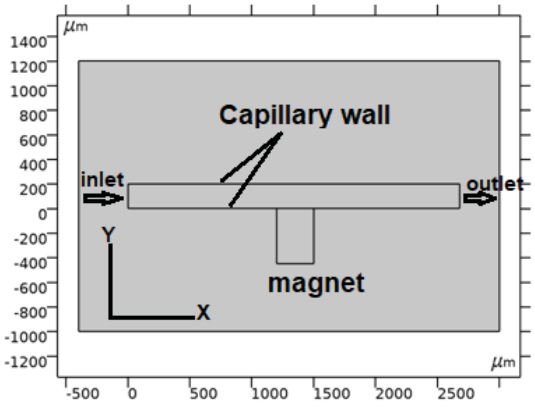
In the present study, the trapping of MNPs moving through the viscous blood flow by applying a permanent magnet placed outside of the capillary tube [8] was modelled. The physical laws governing such phenomena are described by a combination of magnetic equations for permanent magnet and Navier-Stokes equations (conservation of momentum).

In this work, blood is considered as non-magnetized fluid, thus the magnetic force effects on MNPs and the velocity of these particles are calculated from Newton's law equation. The equations of motion describing the flow by the combination of magnetic equations for permanent magnet and Navier–Stokes equation for fluid (blood) were solved numerically by using COMSOL Multiphysics® Modeling Software.

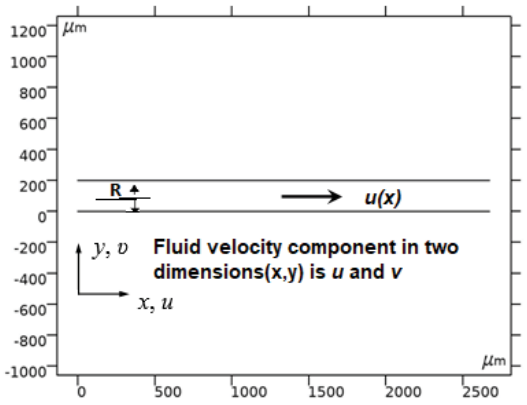
The motivation for this theoretical study is a design of robust algorithms needed to evaluate parameters of magnetically-driven systems for a particular biomedical application with actual complexity and real geometry, such as magnetic drug delivery and treatment [1–7], monitoring and control of brain tissue cleansing from metabolites and toxins, activation of brain drainage function [9], magnetomotive OCT for imaging nanomolar concentrations of magnetic nanoparticles in tissues [10], magnetomotive DOCT for imaging of melanoma-implanted magnetic nanoparticles [11], and magnetomotive laser speckle imaging [12].

2. Formulation of the problem

Permanent rectangular magnet is localized outside the capillary tube. The magnetic force from the magnet can attract and trap these particles. The model domain for solution of the problem contains two domains: first, the capillary tube domain containing the magnetic particles and the viscous fluid (blood) and the second domain of a permanent magnet as it is shown in A and B (Fig.1). The COMSOL Multiphysics® Software was used to solve equations for flow and magnetic field numerically under the initial and boundary conditions depending on a finite element method, which is a numerical technique for finding approximate solutions to boundary value problems of partial differential equations.



A



B

Fig. 1. Geometric domains for the model and the inlet flow velocity of fluid (blood) through the capillary in *x*- axis direction; A and B

3. Equations of motion and results

3.1. Used modules of the COMSOL Multiphysics® Software

To provide calculations, the equations describing the problem were solved numerically by using three different modules of the COMSOL Multiphysics® Software. These modules include:

1. AC/DC module to calculate the magnetic field of the permanent magnet.

2. CFD module for laminar fluid flow such as blood in capillary tube. The flow of blood in this problem is described by Navier–Stokes equation, which considers blood as a Newtonian fluid with a constant dynamic viscosity of $\eta=3.5\times10^{-3}$ Pa·s.

3. Particle tracing module for modelling of particle trajectories moving through the blood capillary and trapped by a magnetic field.

3.2. Magnetic field

A stationary magnetic field produced by a permanent magnet implanted at a specific location is described by the equations for the static magnetic field derived from the Ampere–Maxwell equation [13]:

$$\nabla\times\overline{H}=\overline{J}, \qquad (1)$$

Gauss law for magnetic flux density given by:

$$\nabla\cdot\overline{B}=0, \qquad (2)$$

and the magnetic flux density $\overline{B}$ that in different domains can be described by the relation between $\overline{B}$ & $\overline{H}$:

for the permanent magnet

$$\overline{B}=\mu_0\mu_r\overline{H}+B_{rem}, \qquad (3)$$

for the blood

$$\overline{B}=\mu_0\mu_r\overline{H}, \qquad (4)$$

where μ_0 is the magnetic permeability in free space, $\mu_0=4\pi\times10^{-7}$ N/A^2; μ_r is the relative permeability which is a ratio of the permeability of a specific medium to the permeability of free space μ_0; H is the magnetic field strength; B is the magnetic flux density; B_{rem} is the remanent magnetic flux density.

The properties of a magnetic material are dependent on the net magnetic moment which results from the presence of an external magnetic field. In magnetic materials, the causes of the magnetic moment are the spin and orbital angular momentum states of the electrons. The magnetic susceptibility χ quantifies the tendency of a material to form magnetic dipoles. It is a dimensionless scalar related to the relative permeability μ_r, i.e. $\chi=\mu_r-1$. In the present work, blood is considered a non-magnetized fluid with relative permeability $\mu_r=1$.

3.3. Equations of motion for the fluid (blood)

The motion of blood through the capillary tube can be expressed by incompressible Navier–Stokes equations [14]:

$$\rho\frac{\partial\overline{u}}{\partial t}+\rho\left(\overline{u}\cdot\nabla\right)\overline{u}=-\nabla P+\eta\nabla^2\overline{u}+\overline{F}, \qquad (5)$$

where $\overline{u}$ is the velocity vector of blood flow; ρ is the blood density; ∇P is the pressure gradient in the flow; η is the blood dynamic viscosity; $\overline{F}$ is the external force per unit volume.

3.4. Boundary conditions for the fluid (blood)

The blood flow was considered to be a steady laminar flow, which was supposed to flow into the capillary tube from the inlet and to exit the capillary tube in the outlet. Thus, in the laminar flow interface, velocity was applied for the inlet section and a fixed pressure for the outlets. At the inlet of the capillary, the blood flow is directed in x-axis with the velocity profile assumed parabolic and zero velocity in y-direction. No slip condition for all capillary walls was assumed, i.e. (u = 0) as in Fig. 1.

The inlet velocity is described by a parabolic profile [$u_x=2u_{av}\,(1-(x/R)^2)$], u_{av} is the average velocity. The maximal velocity equal to 1 mm/s and the capillary height from the centerline R = 100 μm of a rectangular capillary tube, as shown in Fig. 1(B), were taken from the experimental data of Ref. [8]. As width of the tube (2680 μm) was more than ten times bigger than its height R, the problem for solution was considered as a two-dimensional.

3.5. MNPs in a blood capillary tube

In the model under consideration, magnetizable particles are the basis of a magnetic nanoparticle drug delivery system (DDS). These particles experience a force in a non-uniform magnetic field, called magnetophoresis (MAP), which is generated from the difference in the permeability of the nanoparticles and medium surrounding them. The magnetic field which produced by a permanent magnet placed outside the capillary tube was studied. There are many different forces, which affect the magnetic particles with environmental fluid inside the capillary tube. These forces include magnetic force (F_M) which is arising from magnetic field, its strong gradient created from external permanent magnet. Viscous drag force (F_D) which is due to movement of magnetic particles with respect to the surrounding fluid, buoyance force (F_b), gravity force (F_g) due to the effect of gravitation on particles, inertia and particle-particle interactions. However, only major forces are considered:

the hydrodynamic drag and magnetophoretic force. Our model ignores inertia, buoyancy, gravitational, and particle-particle interaction forces because they are several orders of magnitude weaker than the magnetic force.

The magnetophoretic force, caused by the magnetic field action on the particles, is given by [15]:

$$\overline{F}_{MAP} = 2\pi\mu_r\mu_0 r^3\left[\frac{\mu_{r,p}-\mu_r}{\mu_{r,p}+2\mu_r}\nabla H^2\right], \qquad (6)$$

$\mu_{r,p}$ is the relative permeability for magnetic particles. The magnetophoretic force in Eq. (6) is proportional to the gradient of the magnetic field power density ∇H^2 and particle radius as r^3.

The drag force F_D for spherical nanoparticles with diameter D is the Stokes drag force. Since the drag force in the blood flow direction is much greater than the magnetophoretic force for moving nanoparticles in a blood capillary, the transfer of particles in the reverse direction of blood flow is practically impossible. Consequently, in our approach, the particles move along the capillary using the blood flow drag force and then the magnetic system is applied on the capillary. In this situation, the resistive drag force exerted on particles in capillary could be estimated as the opposing drag force on particles moving inside a stable fluid [16]:

$$\overline{F}_D = \frac{18\eta}{\rho_p D^2} m_p(\overline{u}-\overline{v}_p)\ , \qquad (7)$$

where η is the viscosity of fluid (blood), m_p is the mass of a magnetic nanoparticle, $\overline{v}_p$ is the vector velocity of particle, ρ_p is the density of particle material, D is the diameter for a spherical magnetic nanoparticle.

The trajectories and velocities of a magnetic nanoparticle with mass m_p were calculated from the equation:

$$m_p\frac{d\overline{v}_p}{dt} = \overline{F}_t\,, \qquad (8)$$

and the total force for a particle is given as:

$$\overline{F}_t = \overline{F}_{MAP} + \overline{F}_D\,. \qquad (9)$$

4. Discussion

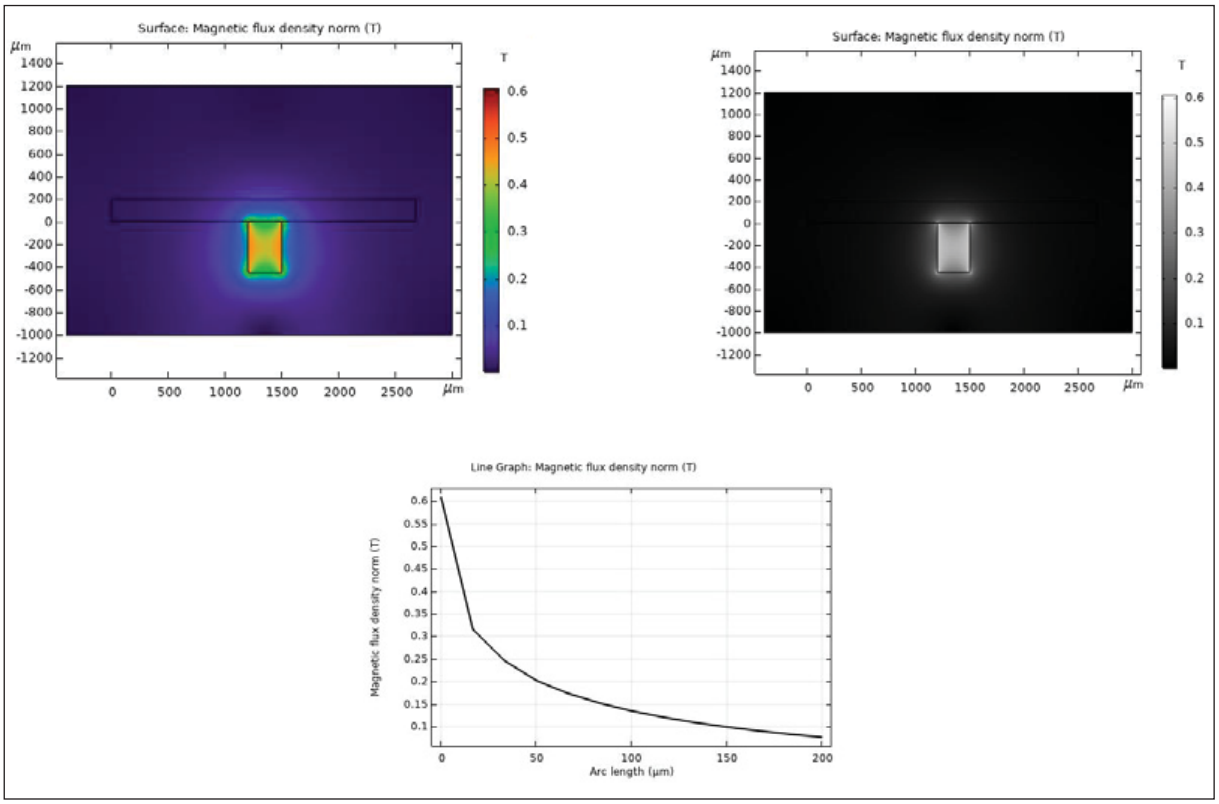
In this work, the permanent magnet with magnetic field B = 0.6 T was applied to the capillary tube with results presented in Fig. 2. From simulations, it follows that the greatest magnetic field strength is created in the vicinity to the capillary wall surface; A (Fig. 2).

The description of blood motion was done with the help of Navier–Stokes equation (5) when blood was considered as a non-magnetized fluid. Transverse contour of blood velocity distribution along the capillary tube, i.e. velocity magnitude is minimal near the capillary wall and maximal in the center, is shown in; B (Fig. 2). In this study, it is assumed that 4500 magnetic particles with diameter of 12 nm are released from the inlet into the capillary and was trapped by magnetic field through a permanent magnet with dimensions 300×450 μm. Drag force is the driving force, which helps to transport particles through the blood capillary tube. It depends on the velocity behavior inside the tube, i.e. drag force at the capillary wall is lower than at the middle distance from the tube center and the magnitude of drag force with the released time of particles from the inlet capillary and the minus sign means that the opposite direction of this force relative to the particle direction as shown in; C (Fig.2). In the presence of magnetic force, the magnetophoretic force needs to overcome the drag force to be able to trap a particle at a desired site at the capillary wall. Depending upon the magnitude of the magnetophoretic force, the magnetic force could either trap the particle on the wall or influence its trajectory near the magnet site, the large number of particles from the inlet is directed to the magnet and thus their concentration is maximal in the space nearby the magnet as shown in; D (Fig. 2).

This modelling could be of interest for the development of biomedical magnetic robotics [17], which is a hot topic now and where actual problems of creating flexible magnetic fields in the human body are suggested. A similar modelling can be done for more complex geometries, like vessel bifurcations and aneurism, which is an urgent medical problem for targeted drug delivery using controllable MNPs [18]. Different applications of magnetite nanoparticles in living systems for bioimaging, cancer and gene therapy, and blood coagulation [19], including designing of magnetically controlled systems for targeted delivery of thrombolytic drugs for cleavage of blood clots [20], would be beneficial from presented modeling strategy.

Conclusion

In this study, numerical results of action of magnetic field created by a permanent magnet placed outside the capillary tube on magnetic nanoparticles travelling in the blood flow were obtained and explained. In this model, blood considered as a Newtonian fluid and with a non-magnetized property. The magnetic field strength is one of parameters that are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Surface: Magnetic flux density norm (T)
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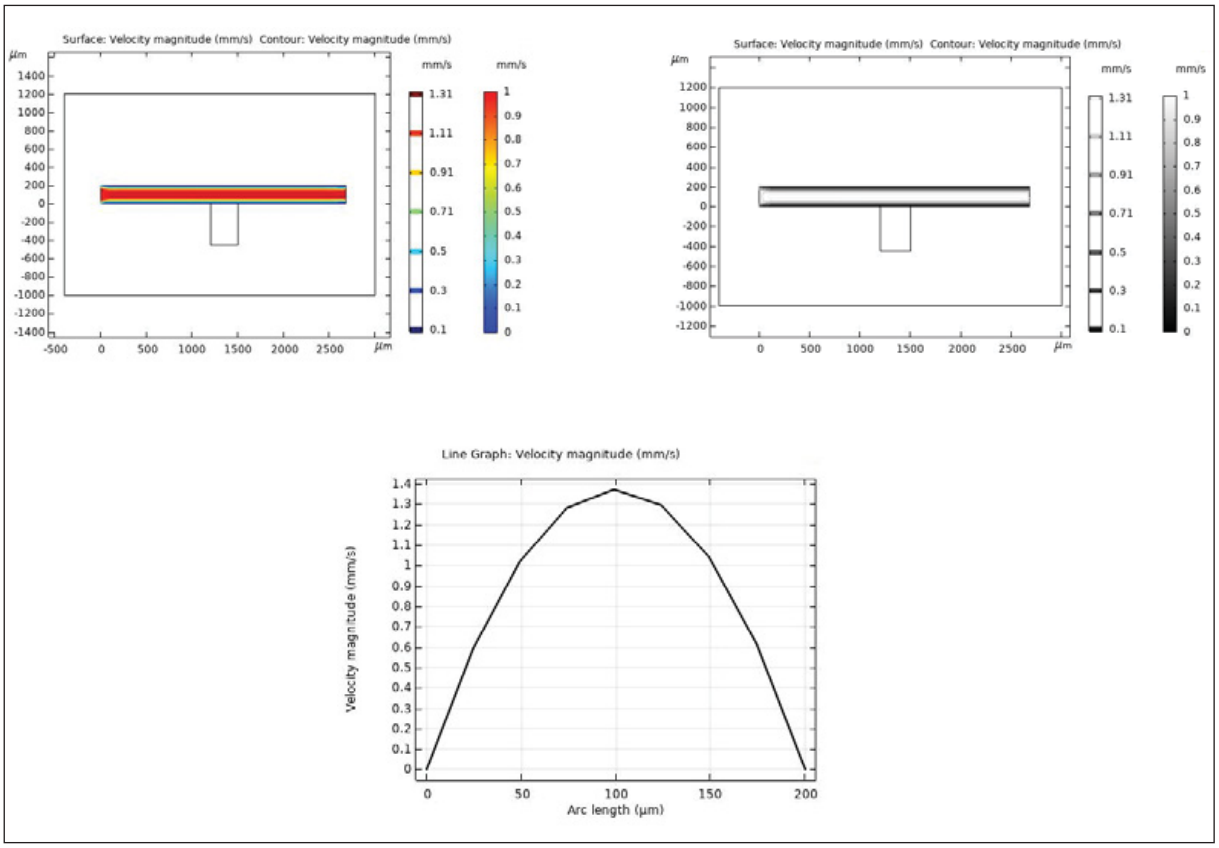
Magnetic flux density norm (T)
Arc length (μm)

A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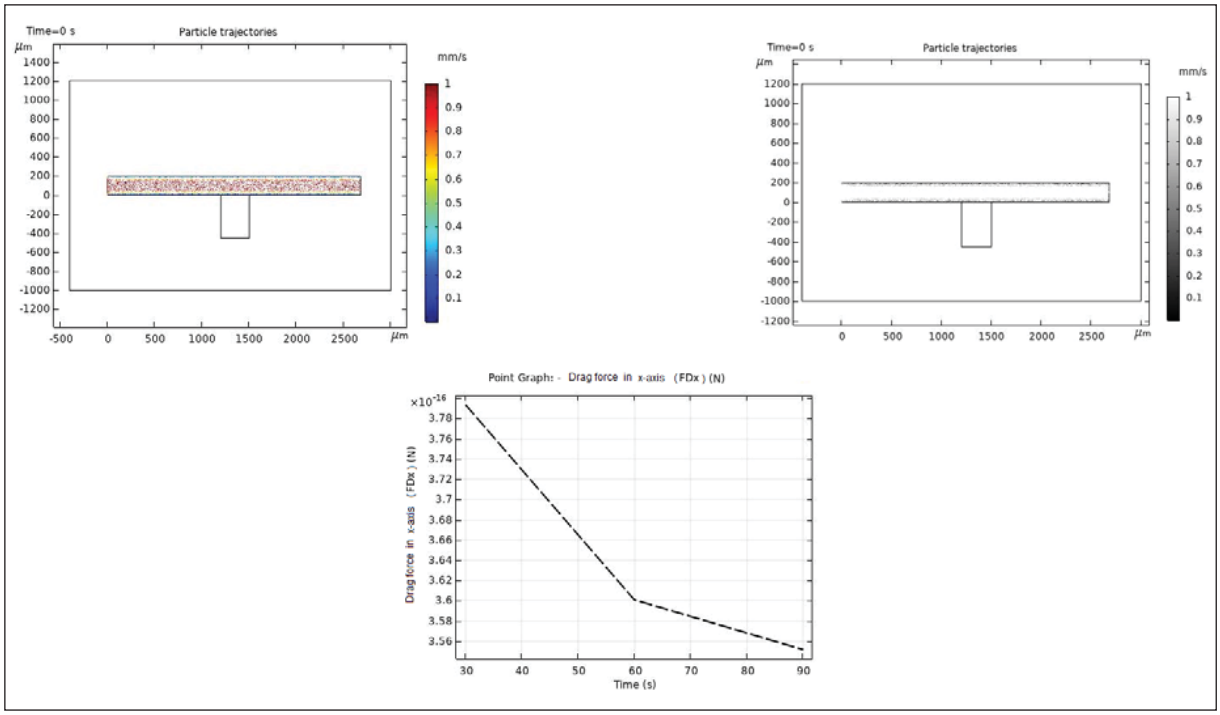

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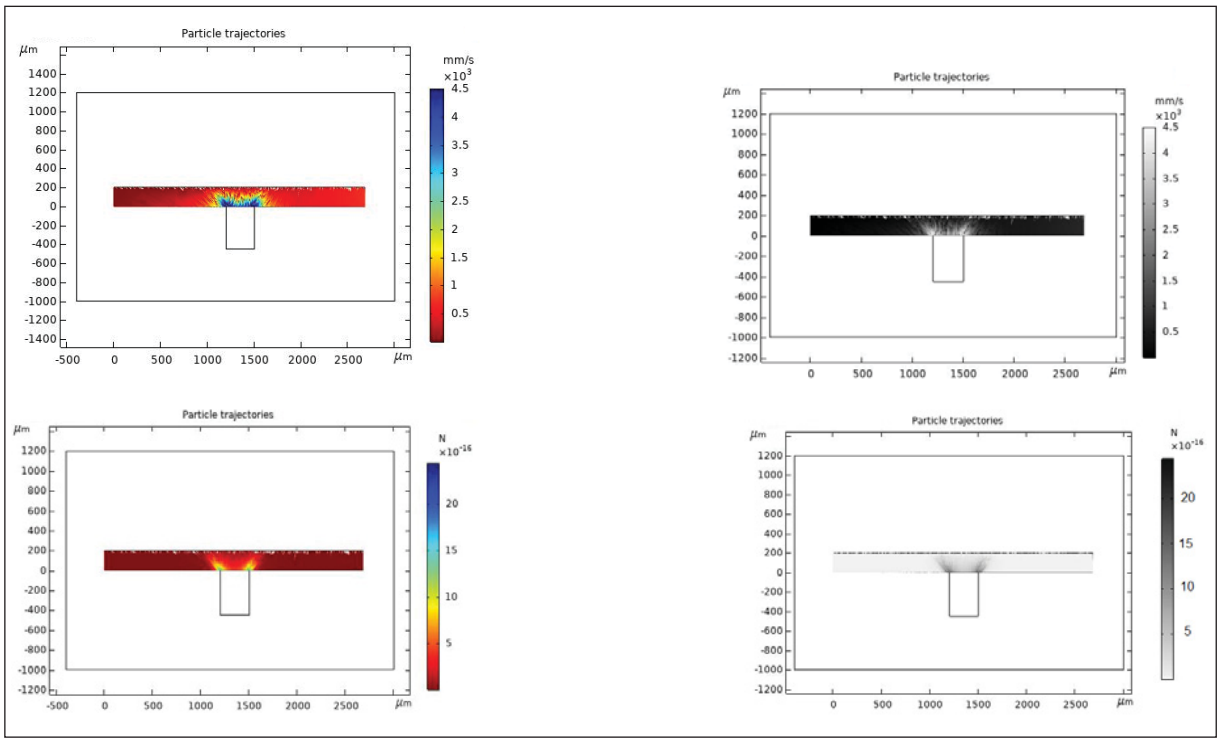

D

Fig. 2. Results of simulation in the RGB color palette and in grayscale: contour, surface of magnetic flux density and line graph for magnetic flux density behavior on distance along magnet surface and capillary tube (Arc length) for magnet with dimensions 300×450 μm (A); contour of blood velocity magnitude through blood capillary tube and line graph velocity profile on distance across the capillary tube (Arc length) (B); behavior of drag force through blood capillary tube shown as induced MNP trajectories and line graph for the magnitude of the drag force component in *x*-axis (FDx) (C); behavior of magnetic force shown as induced MNP trajectories with velocity and concentration distributions (D)

critical for trapping of magnetic nanoparticles toward the capillary wall. Navier–Stokes equation for fluid (blood) and magnetostatic equation for permanent magnet are solved numerically by using COMSOL Multiphysics® software. The results obtained in this study can be used in many biomedical applications, including drug targeting for treatment cancer cells and hyperthermia treatments, studies of lymphatic mechanisms of cleansing brain tissue from metabolites and toxins as well as control and activation of brain drainage function.

Targeted drug delivery using magnetic nanoparticles is a new therapeutic method and is being improved continually. However, recent improvements have been focused mainly on the introduction and synthesis of special magnetic sensitive drug containers and there are still limitations for getting a drug to desired locations in the body. The calculations of the particle trajectories presented in this work is the first step. In the future, we will be able to perform those calculations for more complex geometries, like vessel bifurcation and aneurism, and to proof the calculations by using optical imaging techniques, such as Doppler OCT and laser speckle contrast imaging of flows in the special tissue phantoms containing blood vessels.

Acknowledgements: *Authors are thankful to Dmitry A. Gorin and Maxim A. Kurochkin for the valuable discussions. V.V.T. was supported by the Ministry of Science and Higher Education of the Russian Federation (project No. 075-15-2019-1885).*

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Cite this article as:

Salem S., Tuchin V. Trapping of Magnetic Nanoparticles in the Blood Stream under the Influence of a Magnetic Field. *Izv. Saratov Univ. (N. S.), Ser. Physics*, 2020, vol. 20, iss. 1, pp. 72–79 (in Russian). DOI: https://doi.org/10.18500/1817-3020-2020-20-1-72-79

УДК 532.542

Захват магнитных наночастиц в кровотоке под воздействием магнитного поля

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Магнитные наночастицы как управляемые носители лекарственных препаратов предоставляют огромные возможности в лечении разнообразных опухолей и заболеваний мозга. В настоящем теоретическом исследовании изучены суперпарамагнитные наночастицы оксида железа (Fe_3O_4) (SPION). Благодаря биосовместимости и стабильности эти частицы являются уникальной наноплатформой с большим потенциалом для разработки систем доставки лекарственных препаратов. Это позволяет использовать их в медицине как для целевой доставки лекарств, так и в магниторезонансной томографии и магнитной гипертермии. В работе численно исследованы механизмы захвата магнитных наночастиц, движущихся в вязкой жидкости (крови) в статическом магнитном поле. Уравнения движения для частиц в потоке определяются комбинацией магнитных уравнений для поля постоянного магнита и уравнения Навье–Стокса для жидкости (крови). Эти уравнения были решены численно с использованием программного обеспечения COMSOL Multiphysics® Modeling Software.

Ключевые слова: магнитные наночастицы, магнетизм, кровь, ньютоновская жидкость, постоянный магнит, компьютерное моделирование.

Поступила в редакцию: 07.12.2019 / Принята: 09.01.2020 / Опубликована: 02.03.2020

Благодарности

Авторы выражают благодарность Дмитрию Александровичу Горину и Максиму Александровичу Курочкину за ценные обсуждения. Работа выполнена при финансовой поддержке Министерства науки и высшего образования Российской Федерации (проект № 075-15-2019-1885).

Образец для цитирования:

Салем С., Тучин В. Захват магнитных наночастиц в кровотоке под воздействием магнитного поля // Изв. Сарат. ун-та. Нов. сер. Сер. Физика. 2020. Т. 20, вып. 1. С. 72–79. DOI: https://doi.org/10.18500/1817-3020-2020-20-1-72-79