In-silico studies of micro magnetic particle aggregations in fluid environments for MRI guided drug delivery

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Abstract — A computational platform has been developed to perform simulation, visualization and post-processing analysis of the aggregation process of magnetic particles within a fluid environment such as small arteries and arterioles or fluid-filled cavities of the human body. The mathematical models needed to describe the physics of the system are presented in detail and also computational algorithms needed for efficient computation of these models are described. A number of simulation results demonstrate the simulation capabilities of the platform and preliminary experimental results validate simulation predictions. The platform can be used to design optimal strategies for magnetic steering and magnetic targeting of drug-loaded magnetic microparticles.

I. INTRODUCTION

Recent research, based on phantom studies and preclinical studies, has shown that the Magnetic Resonance Imaging (MRI) could be employed to navigate drug-loaded magnetic particles to deep-seated lesions in the human body having a targeting accuracy that is limited only by the voxel size of the MRI scanner [1,2,3]. The application of this method in clinical cases would increase the drug concentration at the lesion and thus its therapeutic efficiency, while at the same time would reduce the side effects on the healthy tissue [1-4].

The primary hurdle in the development of the MRI-guided drug delivery system is to propel micron size magnetic particles to form aggregations through the arteries (~3mm) and small arteries (~500μm) down to the thinner blood vessels that surround the lesion. At that point the aggregation could break-up back into its nanometer or micrometer constituents, which are then driven by the blood flow into the thinner blood vessels towards the tumor. The break-up of the aggregation is not studied or simulated in this paper, however it is worth noticing that break-up can be achieved by using superparamagnetic particles that loose their magnetization after the patient is removed from the MRI bore [7]. Even if there is a small remnant magnetization, the particles can still disaggregate if they have been coated with polymer chains that produce repulsive forces and counteract the small magnetic dipole forces.

The aggregation size is the key factor for successful and efficient propulsion within the blood vessels. A relatively large aggregation could form clots in the small arteries or conversely a very small one would be dragged away by the systemic circulation. Therefore it is necessary to examine the dependence of the aggregations on critical physical parameters and then tune these parameters to generate the desired number of aggregations having appropriate size and pattern. The aggregation formation and interaction constitutes a large-scale, high complexity, non-linear dynamic system that is very difficult to predict and study analytically. Therefore, a computational platform is necessary to investigate these dynamics and design control strategies.

This paper presents a computational platform for simulation, visualization and analysis of the aggregation process of magnetic particles within a fluid environment exhibiting laminar flow, such as small arteries and arterioles or fluid-filled cavities. The computational platform was developed because currently there is no available (commercially or freeware) platform for simulating and visualizing the dynamics of aggregating magnetic microparticles in fluid environment. At this stage the computational platform comprises deterministic dynamic models proposed and validated in the literature [8-19], and is capable of running simulations of thousands of interacting magnetic particles whose diameter is in the micron scale. Motion of particles at smaller scales is not completely deterministic because they are affected by randomly generated forces and are not addressed in this paper. Using this platform we can predict the number of resulting
aggregations, the size and the pattern of the aggregations. At the same time, we can simulate the motion of the aggregations when these are driven by MRI magnetic gradients, and evaluate the efficiency of different steering strategies subject to the motion constraints imposed by blood vessel walls or human body cavity walls.

As a first step we have developed a 2D computational platform, which can easily be extended into a 3D platform. It is implemented in C++, and employs optimized numerical algorithms to simulate the magnetic interaction among thousands of particles. The simulation results are validated by preliminary experiments and are compared to related experimental results in the literature.

In Fig. 1 the modular architecture of the computational platform is depicted. This comprises the User Interface, a computational subsystem, and a modeling subsystem. The User Interface accepts input specifications from the user and also performs post-simulation visualization of the simulation results. The modeling subsystem comprises all the mathematical models of the forces acting on each particle and is described in detail in Section II. The computational subsystem comprises the force computation algorithm and the integration algorithm described in Section III. The basic simulation capabilities of the platform and a preliminary validation experiment are presented in Section IV. Finally, conclusions are presented in Section V.

II. DYNAMIC MODELING SUBSYSTEM

The modeling subsystem of the platform contains all information that characterizes a particle, and all methods used to compute the forces acting on the particle. The modeling technique used in this paper is the Discrete Element Modeling (DEM). DEM was chosen because it provides accurate physical models for particle interactions, and it is efficient for size problems up to ~10^4, [14, 15]. DEM is appropriate for modeling interactions in the blood flow, since at the microlevel the blood is regarded as a suspension of particles (Red Blood Cells (RCBs) and White Blood Cells (WBCs)) interacting in fluid plasma [21]. All forces and moments considered in this paper are depicted in the free body diagram of Fig. 2. The bold variables are vectors unless stated otherwise. The Newton-Euler equations are given by:

\[
\begin{align*}
 m_i \ddot{v}_i &= F_{mi} + F_{cu} + F_{ct} + F_h + F_{vdw} + W_i \\
 I_i \ddot{\Omega}_i &= M_{hi} + M_{ci} + T_{mi}
\end{align*}
\]

where the index \(i\) indicates the particle \(i\). The linear and angular acceleration are \(\ddot{v}_i\) and \(\ddot{\Omega}_i\). The mass is \(m_i\) and the mass moment of inertia matrix is \(I_i\). \(F_{mi}\) is the total applied magnetic force, \(F_{cu}\) and \(F_{ct}\) are the normal and tangential contact forces respectively, \(F_h\) and \(W_i\) are the buoyancy and the weight forces, \(F_{vdw}\) is the hydrodynamic drag force and \(F_{vdw}\) is the van der Waals force. \(M_{hi}\) and \(M_{ci}\) are the hydrodynamic moments and the contact moments respectively. \(T_{mi}\) is the torque due to the magnetic field at the position of particle \(i\). At the micron scale stochastic Brownian motion is negligible compared to the particle size, and therefore Brownian forces are not taken into account [20].

A. The particle module

The Particle Module methods compute the aforementioned forces based on mathematical models, which are presented in detail in the following sections.

1) Magnetic forces

Due to the micron size of the particles it is assumed that the magnetic field over the particle volume is small compared to the average field. Hence, each particle is magnetized uniformly and can be approximated by a dipole placed at the geometric center of the particle (Fig. 3). Magnetic forces \(F_{m,i}\) exerted on the \(i\) particle are given by [11-13]:

\[
F_{m,i} = \frac{1}{4\pi} \frac{m_i m_j}{r_{ij}^3} (m_i \times m_j)
\]
\[
F_{m,i} = F_{\text{grad},i} + F_{\text{dip},i}
\]  
(3)  

where \(F_{\text{grad},i}\) is the magnetic force due to the interaction of the \(i^{th}\) particle with the magnetic field produced in the MRI bore, and \(F_{\text{dip},i}\) are the magnetic forces acting on the \(i^{th}\) particle due to its interaction with the surrounding magnetic particles (i.e. dipole-dipole interaction).

The force \(F_{\text{grad},i}\) is given by:
\[
F_{\text{grad},i} = V(\mathbf{m}_i \cdot \nabla) \mathbf{B}_{\text{ext},i}
\]  
(4)  

where \(\mathbf{m}_i\) is the magnetic moment of the \(i^{th}\) particle, \(V\) is the magnetic volume of the particle and \(\nabla\) is the gradient operator. \(\mathbf{B}_{\text{ext},i}\) is the magnetic field at the \(i^{th}\) particle generated by the superposition of the MRI superconducting magnet field and the MRI gradient coils field.

The force \(F_{\text{dip},i}\) is given by:
\[
F_{\text{dip},i} = \sum_{j}^{N} F_{\text{dip},j}
\]  
(5)  

where \(F_{\text{dip},j}\) is the magnetic force exerted on particle \(i\) due to particle \(j\), and \(N\) is the number of the magnetic particles surrounding particle \(i\).

\[
F_{\text{dip},j} = \frac{3 \mu_0 m_i m_j}{4 \pi r_{ij}^3} (\hat{r}_{ij} (\mathbf{m}_i \cdot \mathbf{m}_j) + \mathbf{m}_i (\hat{r}_{ij} \cdot \mathbf{m}_j)) + \hat{m}_j (\hat{r}_{ij} \cdot \mathbf{m}_i) - 5 \hat{r}_{ij} (\hat{r}_{ij} \cdot \mathbf{m}_i) (\hat{r}_{ij} \cdot \mathbf{m}_j)
\]  
(6)  

where \(\mu_0\) is the permeability of the surrounding medium, \(\mathbf{m}_i\) and \(\mathbf{m}_j\) are the magnetic moments of the \(i^{th}\) and \(j^{th}\) particles, \(m_i = |\mathbf{m}_i|, m_j = |\mathbf{m}_j|\) and \(\hat{\mathbf{m}}_i = \mathbf{m}_i / m_i, \hat{\mathbf{m}}_j = \mathbf{m}_j / m_j\). The symbol \(r_{ij}\) is the distance between the \(i^{th}\) and \(j^{th}\) particles, \(r_{ji} = r_{ij}, \text{and } \hat{r}_{ij} = r_{ij} / \hat{r}_{ij}\).

As mentioned in the introduction, we want the particles to exhibit superparamagnetic properties so that the aggregations become disaggregate when the patient moves away from the MRI bore. This means that the particles exhibit hysteresis-free magnetization and for zero applied magnetic fields they exhibit zero net magnetization. In this case the magnetic moment of the \(i^{th}\) particle is given by [13]:
\[
\mathbf{m}_i = \frac{4 \pi \mu_0}{\mu_i} \frac{1}{d_i} \mathbf{B}_i
\]  
(7)  

where, \(\mathbf{B}_i\) is the field at the \(i^{th}\) particle, \(\mu_i\) is the relative permeability of the \(i^{th}\) particle, and \(d_i\) its diameter.

\[
\mathbf{B}_i = \mathbf{B}_{\text{ext},i} + \sum_{j}^{N} \mathbf{B}_{ji}
\]  
(8)  

and \(\mathbf{B}_{ji}\) is given by [13]:
\[
\mathbf{B}_{ji} = \frac{\mu_0}{4 \pi} \frac{3 (\mathbf{m}_i \cdot \hat{r}_{ji}) \hat{r}_{ji} - \mathbf{m}_i}{r_{ji}^3}
\]  
(9)  

Substituting Eqs. (8) and (9) into Eq.(7) results in a linear system of \(3N\) equations and \(3N\) unknowns for the 3D case. Solving the system calculates the magnetic moment \(\mathbf{m}\) of each particle. The \(\mathbf{m}\) vectors are substituted back into Eq. (6) to yield the magnetic forces applied on each particle.

2) Contact forces

A contact force model is needed for predicting how the drag and the shear forces propagate through the aggregated particles and how these affect the aggregation formation. Particles in a DEM problem are physically approximated as rigid bodies and the contacts between them, as contact points. The contact takes place if and only if the following condition holds:
\[
\xi_{ij} = (a_i - a_j) - |\mathbf{r}_i - \mathbf{r}_j| > 0
\]  
(10)  

where, \(\xi_{ij}\) is called the mutual deformation of the spheres \(i\) and \(j\), and \(a_i, a_j\) are the radii of the spheres \(i\) and \(j\).

The collision between particle \(i\) and \(j\) generates at the contact point a contact force \(\mathbf{F}_{\text{c},ij}\) on particle \(i\) (and respectively a force \(\mathbf{F}_{\text{c},ji}\) on particle \(j\)). \(\mathbf{F}_{\text{c},ij}\) is resolved on the normal \(\mathbf{n}_{ij}\) and tangential \(\mathbf{t}_{ij}\) unit vectors (Fig. 4a) to yield the normal \(\mathbf{F}_{\text{n},ij}\) and tangential \(\mathbf{F}_{\text{t},ij}\) forces. The normal and tangential unit vectors are given by [14]:
\[
\mathbf{n}_{ij} = (\mathbf{r}_j - \mathbf{r}_i) / |\mathbf{r}_j - \mathbf{r}_i|
\]  
(11)  
\[
\mathbf{t}_{ij} = \mathbf{v}_{ij} / |\mathbf{v}_{ij}|
\]  
(12)  

where \(\mathbf{r}_i, \mathbf{r}_j\) are as shown in Fig. 3, and \(\mathbf{v}_{ij}\) is the tangential relative velocity of sphere \(i\) with respect to sphere \(j\) and is given by [14]:
\[
\mathbf{v}_{ij} = \mathbf{v}_i - \mathbf{v}_j - [(\mathbf{v}_i - \mathbf{v}_j) \cdot \mathbf{n}_{ij}] \mathbf{n}_{ij} - \mathbf{a}_i \Omega \times \mathbf{n}_{ij} - \mathbf{a}_j \Omega \times \mathbf{n}_{ij}
\]  
(13)  

where \(\Omega, \Omega\) are the angular velocities of the spheres \(i, j\).

\(\mathbf{F}_{\text{n},ij}\) and \(\mathbf{F}_{\text{t},ij}\) are represented by a Voigt model comprising a non-linear spring and a linear damper (see Fig. 4b and c).

Fig. 4: (a) Collision, (b) Normal forces, (c) Tangential forces.

The normal contact force on sphere \(i\) is given by [14]:
\[
\mathbf{F}_{\text{n},ij} = \max \{0, k_{\text{n}} (|\mathbf{n}_{ij}| / 2 + b_{\text{n}} \mathbf{v}_{ij}^2 / 2) \mathbf{n}_{ij}\}
\]  
(14)  

The \(\max\) operator indicates that the normal force \(\mathbf{F}_{\text{n},ij}\) can only be a compressive force. The first term of Eq. (14) is the elastic force –based on the Hertz contact law for spherical particles- and the second is the viscous force. The parameters \(k_{\text{n}}, b_{\text{n}}\) are the stiffness and damping coefficients along the normal direction and are given by [14]:
\[
k_{\text{n}} = \frac{2}{3} \frac{Y (R_{\text{eff},ij})}{3 (1 - \nu^2)}, b_{\text{n}} = A \frac{2}{3} \frac{Y (R_{\text{eff},ij})}{3 (1 - \nu^2)}
\]  
(15)  

where \(Y\) is the Young modulus and \(\nu\) is the Poisson ratio,
$R_{\text{eff},i}$ is the effective radius of the spheres given by [14]:

$$R_{\text{eff},i} = a_i a_j / (a_i + a_j)$$

(16)

The tangential contact force on sphere $i$ is given by [14]:

$$F_{\text{ct}} = -\min(b_i, |\lambda_i|) \mu |F_{\text{ct}}|$$

(17)

where $b_i$ is the damping coefficient along the tangential direction of sphere $i$, $\mu$ is the coefficient of friction, and $\mu |F_{\text{ct}}|$ is the friction force at the spheres contact point assuming a Coulomb model of friction.

Slight modification of the aforementioned elements allows modeling also the interaction between particles and the vessel walls. In this case the wall is considered rigid body along the tangential direction and deformable along the normal direction.

3) Fluid forces

Due to the simple symmetry of the spherical microcapsules, the lift, the side fluid forces and all the three fluid moments vanish. Each particle is subject only to the fluid drag force. Due to the very low Reynolds number ($\text{Re} \ll 1$) the drag force is given by the Stokes drag formula [16]:

$$F_{\text{st}} = \lambda_i \delta \eta \mu (E \cdot r - v_i)$$

(18)

where, $\eta$ is the viscosity of the blood and depends on the vessel diameter, the hematocrite of the blood, and the temperature [18], and $a$ is the particle radius. The coefficients $\lambda_i$ are correction factors that account for the fact that not all spheres are completely exposed to the fluid drag forces. Algorithms for determining $\lambda_i$ for a general aggregation shape can be found in the literature [18,19]. For the special case of chain-shape aggregations the drag coefficient can be approximated by coefficients given in the literature for three-dimensional cylindrical bodies [16]. This paper the coefficient $\lambda_i$ is determined using the cylindrical approximation [16], where the angle of attack is taken into account (in this paper is either 0 or 180 degrees). The vector $r$ is given by $r = p_i - p_e$, where $p_i$ is the position vector of the particle $i$ with respect to the inertial frame $O_{xyz}$, and $p_e$ is the position vector of the origin of the frame $o_{xy}$ that is attached on the symmetry axis of the channel as shown in Fig. 5. Vector $v_i$ is the velocity of the spherical particle. Matrix $E$ is the gradient tensor of the flow field and for a 2-D shear flow is given by [19]:

$$E = \begin{bmatrix} 0 & \gamma_s & 0 \\ 0 & 0 & 0 \\ 0 & 0 & 0 \end{bmatrix}$$

(19)

where $\gamma_s$ is the shear rate of the laminar flow in the channel (Fig. 5) given by [19]:

$$\gamma_s = \frac{\nu_j}{P_0 (l/2)^2}$$

(20)

$\nu_j$ is the mean speed flow and $l$ is the channel diameter.

4) Gravitational forces

These include the force due to gravity and the force due to buoyancy. Although of limited effect at the low-end of the microscale, they might become important when larger micron size aggregates are formulated. The gravitational force is given by [16]:

$$F_{\text{gr}} = W_i + F = \frac{4}{3} \pi a_i^3 (\rho_i - \rho_f)$$

(21)

where $\rho_i, \rho_f$ are the density of the particle $i$ and of the fluid respectively, and $a_i$ is the radius of the particle $i$. By choosing appropriate particle material we could adjust the density of particle $i$, $\rho_i$ so that it is close to the fluid density and therefore minimize the effect of the gravitational forces.

5) Van der Waals forces

Van der Waals forces act among the particles when they are not in contact. The van der Waals potential between spheres of equal radius $a$ is given by [18]:

$$V_{\text{ij}} = \frac{A}{6} \left( \frac{2a^2 - 2a^2}{|r_{\text{ij}}| - 4a^2} + 2a^2 \ln\left( \frac{|r_{\text{ij}}| - 4a^2}{|r_{\text{ij}}|^2} \right) \right)$$

(22)

where $A$ is the Hamaker constant and $|r_{\text{ij}}| \geq 2a + \delta$. The minimum distance $\delta$ to which the two surfaces can approach is assumed to be $4\delta$. The force is given by:

$$\mathbf{F}_{\text{vdw}} = -\nabla V_{\text{ij}}$$

(23)

Other forces of electrostatic nature have not been included in this model because the current version of the computational platform focuses on concentrated suspensions of relatively large and strongly magnetized particles in the intense field of an MRI scanner, where the electrostatic forces are negligible.

B. Magnetic field module

The magnetic field module contains the expressions responsible for simulating the magnetic field $B_{\text{ext}}$ in the MRI bore. It can be assumed that the magnetic field $B_{\text{ext}}$ varies linearly within a sphere of 60cm diameter centered at the isocenter of the MRI bore [22], and is given by:

$$B_{\text{ext}} = B_0 + B_e$$

(24)

where $B_0$ is the MRI superconducting magnet field and is
constant, uniform and cannot be controlled. $\mathbf{B}_i$ is the field generated by the gradients coils, it exhibits a linear spatial variation, can be controlled by programming the MRI pulse sequences and its analytical expression can be found in [22].

C. Fluid flow module

The fluid flow module is responsible for simulating the vector field of the fluid flow. Currently this module simply contains information on the profile and the shear stress of the fluid flow. In the future this module will include information generated by a FEM package or some analytical approximation of the flow.

Computing the forces is the most time consuming process in a dynamic simulation [14]. For example, if a particle $i$ experiences magnetic forces generated by all its neighbors then for a system of $N$ particles we must evaluate $N(N-1)/2$ pair interactions, i.e. the time needed for the evaluation of the forces scales as $N^2$. Therefore, to save considerable computation time and be able to simulate large numbers of particles it is necessary to use a force computation algorithm that at each time-step, is able to efficiently decide which pair of particles yield non-negligible magnetic interactions and compute only those. The following section describes how we adapted the Verlet List method, frequently used in Molecular Dynamics simulations [14,15,23], to reduce the computational burden due to the interaction forces.

III. FORCE COMPUTATION METHOD

The force computation algorithm takes advantage of the fact that the magnetic interaction forces are inversely proportional to the cube of the separation distance (Eqs. (7-9)), and therefore particles that are more than five radii apart exhibit a very weak interaction and do not affect each other in the time scales under consideration. This threshold value of separation distance defines the magnetic interaction domain $D_i$. When computing the interaction forces acting on a particle $i$ at a time step $n$, only those particles are considered, which at time step $n-1$ were located either within the magnetic interaction domain $D_i$ or were located at a small distance $V_i$ outside the boundaries of $D_i$. This is a reasonable assumption since the particles dynamics combined with an appropriately small time step ensure that two particles which are close to each other at time step $n-1$ will remain close to each other in the next few steps. The particles located within the ball, whose radius is equal to $R_i + D_i + V_i$, and is centered at particle’s $i$ center $r_i$, are called close neighbors. The particles belonging to the close neighbors set should satisfy inequality (25).

$$\|r_i - r_j\| < R_i + R_j + D_i + V_i$$  

where $r_i$, $r_j$ are the position vectors of particles $i$ and $j$, and $R_i$, $R_j$ are the corresponding radii, and $V_i$ and $D_i$ is as shown in Fig. 6. These close neighbors particles can be systematically determined and recorded in a list. Hence, when computing the forces acting on particle $i$, only the interaction forces of the particles enlisted in the close neighbors list of particle $i$ are taken into account. This is a computation that scales as $\alpha N$, where the coefficient $\alpha$ depends on the $V_i$ distance.

During simulation the close neighborhood relations of the particles gradually change. To avoid having particles interacting without being recognized as close neighbors first, the list has to be updated every time any of the particles has travelled a distance equal to or greater than $V_i/2$, since the last update of the list. To construct the updated lists in an efficient way, the simulation space is divided into cells with a size slightly larger than $D_i + V_i$ (Fig. 6). During the update of the close neighbors list of particle $i$, only particles in the same cell or in adjacent cells of particle $i$ are considered. The size of the cells depends on the distance $V_i$ and it is independent of the particles number $N$, therefore the time needed to update the close neighbors list scales as $\beta N$ where $\beta$ depends again on the distance $V_i$.

The total time spent computing the forces and constructing the lists is therefore proportional to:

$$T_{force, calculation} \sim \lambda \cdot N$$  

where $\lambda$ is a parameter that depends on the $V_i$. Hence, total computation time is drastically reduced from $\sim N^2$ to $\sim N$.

![Fig. 6. Domain of close neighbors of particle i and grid cells for efficient construction of the close neighbors lists.](image-url)

The formulated equations of motion are integrated to yield the velocity and the displacement of each particle for the next time step. The integration is performed by a fifth order Gear’s predictor-corrector algorithm [14,15,23]. This algorithm has two main advantages. First, it provides good stability properties, i.e. for appropriate selection of integration step $\Delta t$ the algorithm does not amplify the error from one step to the next. Second, the algorithm requires only one evaluation of the forces per time step. Consequently, there is a significant gain in efficiency since the computationally expensive force evaluation is performed less frequently.

The critical integration step $\Delta t$ is the largest possible integration step for which numerical stability is maintained. It is determined by a trial and error method where successive $\Delta t$
values are tested until the critical Δt is found, i.e. the largest Δt value for which the kinetic energy of the system converges to a value.

IV. RESULTS

We opted first for a 2D platform since this involved the minimum implementation effort for testing the accuracy of the simulation results, and the stability and the efficiency of the computations. The 2D platform can be extended easily to 3D since all models and computational algorithms are built for the general case of 3D motion.

The simulation results are divided into three subsections. In the first subsection we demonstrate that the computational platform generates physically meaningful results that provide insight on the motion response of the particles. For this purpose we independently demonstrate the effects of a uniform magnetic field and of constant magnetic gradients, on the aggregation and motion of a group of magnetic particles. The second subsection compares preliminary experimental results to simulation results for validation purposes. The third section presents magnetic steering of particles in an environment that resembles a blood vessel bifurcation and compares two steering approaches. The results of the second method are compared to experimental results presented in the literature.

A. Effect of uniform magnetic field and of constant magnetic gradients

It is assumed that the density of the composite microparticle is similar to the density of the liquid and therefore the particles are buoyant and no net forces are applied along the z-axis. The initial positions of the microparticles are randomly generated so that the final aggregation patterns cannot be associated to specific initial configurations. The parameters used for the simulations are those presented in Table 2 in Appendix.

1) Response of particles to a uniform field B

Two thousand microparticles of 100 μm diameter are initially randomly placed on the x-y plane as shown in Fig. 7a. At t=0s the magnetic field is \( B_0 = 0 \)T (Fig. 7a). After a uniform magnetic field of \( B_0 = 1 \)T is applied the particles self-assemble into chains as shown, for t=2.5ms, in Fig. 7b. The magnetic dipoles are aligned in a head-to-tail fashion and parallel to the magnetic field, which in this case is directed along the x-axis.

The aggregation process reaches a steady-state configuration after approximately 2.5ms. The predicted aggregation of magnetic particles is in accordance with the results reported in experimental works [7,25].

2) Aggregations driven by magnetic gradients

In this example, a magnetic gradient \( \frac{dB}{dx} = 200 \)mTm\(^{-1}\) is applied along the x-axis and results in a linear spatial variation of the \( B_0 = 1 \)T field. The field \( B_{ext} \) along the x-axis is given by Eq. (24). Four hundred particles of 100μm diameter are initially placed randomly within an area of approximately 1.0 cm\(^2\) within a channel. The width of the channel is considered very large and the flow has a flat profile with a constant velocity of 0.1ms\(^{-1}\).

Fig. 8 depicts the initial position of the particles. Fig. 9 demonstrates the motion of the particles when these are subject to two competing forces, namely the fluidic drag forces dragging the particles towards the positive x-axis and the magnetic gradient forces pulling the particles towards the negative x-axis.

It is observed in Fig. 9 that single particles and small aggregations are dragged by the flow towards the positive x-axis, whereas larger aggregations are pulled by the magnetic forces towards the opposite direction. This result demonstrates that the magnetophoretic ratio of an aggregation, i.e. the magnetic over the drag force, is larger compared to the magnetophoretic ratio that physically isolated particles would experience. Consequently an
aggregation could be used to transfer more efficiently the micron size magnetic particles using smaller gradients.

Fig. 8. Initial configuration of the magnetic particles. The figure also shows the opposing forces acting on the magnetic particle.

Fig. 9. Magnetic gradients are able to pull the aggregations against the fluid drag forces but are not able to pull single particles. The latter are being dragged by the flow.

**B. Preliminary Experimental Validation**

This paragraph describes the results of a preliminary experiment that was conducted for validation purposes of the computational platform. The magnetic particles used in the experiment are polysterene microparticles with embedded iron oxide superparamagnetic nanoparticles (SPHERO PM-50-10, Spherotech Inc.). The microparticles have diameter in the range 5.0 – 5.9 μm. Their overall material density is 1.2 kg/m³, which is comparable to that of the fluidic environment. A droplet containing magnetic particles at a concentration of 6 × 10⁷ microparticles per ml is placed at the center of a microscope field of view. The magnetic field and the magnetic gradient are both provided by a NdFeB cubic magnet whose side length is 6.35 mm and which is placed near the particles. The distance between the face of the magnet and the droplet center is 9.5 mm. An analytic model predicts that the magnetic field and the gradient produced by the magnet [24] at the droplet center are approximately 0.005 T, and 0.6 T/m respectively.

The NdFeB magnetic field aggregates the microparticles in chains and the magnetic gradient propels them towards the face of the magnet. The motion of the particles was recorded by a bright field optical microscope equipped with a x40 objective lens, and a camera that automatically took snapshots every 0.5 s. Fig. 10a depicts the initial position of the particles at t=0 s, (right after the first aggregated chains were formulated). Fig. 10b depicts the final position of the particles at t=3.5 s. The displacement along the horizontal axis of four randomly selected chains is depicted in Fig. 10b. The displacements of the four chains versus the recordings are plotted on Fig. 11. From Fig. 10, it is measured that the mean size of a chain aggregation is 6 particles and the standard deviation is 5.

A simulation was run using the same parameters of particle size and radius distribution, magnetic field and magnetic gradients values, material density, particle concentration and fluid viscosity. The main difference with respect to the experiment is the smaller number of particles (100) that are simulated. The difference in the number of particles should not affect the general pattern of aggregation and the main characteristics of the motion of the particles since their concentration is the same as that in the experiment. The parameters are shown in Table 3, in the Appendix. The simulated time was 2 s. The initial and final position of the particles are superimposed and plotted in Fig. 12. The blue particles are the initial (t=0 s) positions and the red particles are the final positions (t=2 s). The experimental and simulation results are compared in Table 1. Even if the parameters used in simulations are not exactly the same as those in the experiments (e.g. different number of particles, modeling assumptions such as magnetic field linearity, etc.) and hence some differences in the numerical results are expected, Table 1 shows good qualitative agreement between the simulations and the experiments.

Fig. 10. Position of microparticle chains: (a) Initial, at t=0 s position. (b) Final, at t=3.5 s. The displacement of 4 selected chains is depicted.
is to maximize the percentage of magnetic particles that flow through the upper branch. To this end a range of magnetic gradients are applied from 0 up to 400mT/m. Although the gradients of clinical MRI scanners are limited to 40mT/m, it has been shown that the addition of special gradient coils into the MRI bore can increase the gradients up to 400mT/m [24] (and still comply with biological limits). The magnetization of all particles is saturated and is aligned to the strong MRI $B_0$ field (1.5T). The rest of the simulation parameters are as shown in Table 2, in the appendix.

1) $B_0$ field is along the axis of the channel

Magnetic gradients $\partial B_y/\partial x$ are applied to 100μm diameter particles and as a result the induced magnetic force is directed along the positive y-axis. The magnetic force magnitude is given by Eq. (4). Fig. 13 depicts a snapshot of the position of 400 particles when these are steered by a 400mT/m gradient and Fig. 14 depicts a zoom-in on the aggregations that have been pulled over on the wall of the blood vessel.

The steering efficiency of each gradient is defined as the ratio of the particles exiting through the upper branch of the channel over the total number of particles exiting the channel. The steering efficiencies are depicted in the plot of Fig. 15, where it is seen that steering efficiency is maximized for $\partial B_y / \partial y = 150$ mT/m. Smaller gradients produce weaker forces unable to steer the particles, resulting in efficiency slightly greater than 50%. For gradients larger than 150mT/m the steering force is too strong and particles collide to the upper wall before reaching the bifurcation. These particles get trapped to the wall due to the zero flow boundary condition and consequently the steering efficiency is significantly reduced. However the efficiency predicted in this simulation example applies to cases where the number of particles is relatively small. It is expected that when very large number of particles are injected into the blood vessel then the wall surfaces near the bifurcation will be covered by trapped particles onto which other particles will be free to slide (carried by the flow) to the desired exit branch and consequently the efficiency will increase.

C. Steering particles in a channel bifurcation in MRI environment

Successful magnetic targeting of magnetic microparticles at deep-seated lesions can be accomplished by steering the microparticles through successive blood-vessel branches towards the lesion. The computational platform can be used to determine the magnetic gradients that maximize the steering efficiency of the MRI scanner when steering magnetic microparticles through a branch.

The following paragraphs compare two steering approaches. In the first approach the Y-tube channel axis is aligned to the $B_0$ field direction. In the second approach the channel axis is orthogonal to the $B_0$ field direction. The Y-tube channel shown in Fig. 13 has a parabolic laminar flow. When no magnetic forces are applied then it is expected that the flow will direct equal number of particles to the lower branch and upper branch of the channel. In the following simulations the total number of particles is 400, and the goal...
Fig. 14. Zoom-in on the aggregations that have been pulled against the wall by the magnetic gradients. The flow speed there is negligible and therefore the aggregations do not move or move very slowly.

Fig. 15. Steering efficiency with respect to magnetic gradients $\partial B_x / \partial y$. The channel of the Y-tube is aligned to the $B_0$ field.

2) $B_0$ field is vertical to the axis of the channel

The magnetization of all particles is aligned to the $B_0$ field, i.e. along the y-axis (see Fig. 16). The magnetic force imparted on 100μm diameter particles due to the $\partial B_y / \partial y$ gradient is directed along the positive y-axis. Six magnetic gradients have been simulated {0, 40, 100, 200, 300, 400} mT/m. All simulation parameters are the same as in the previous paragraph. Fig. 16 depicts a snapshot of the particles position in the Y-tube while they are steered by a 100mT/m gradient towards the upper branch. The chain-type aggregations are formulated and are aligned to the $B_0$ field along the vertical y-axis. Some of the chains make contact with the blood vessel wall. These chains do not get stack to the wall because most of the chain particles remain exposed to strong fluid flow which forces the chains to slide along the wall and eventually exit through the upper branch. Fig. 17 depicts a zoom-in on the bifurcation that shows that an islet of approximately 100 particles was formed at the branch. The islet formulation was observed only in the low gradient simulations {0, 40, 100} mT/m. Fig. 18 depicts a snapshot of the particles when steered by a 400mT/m gradient. In the 400mT/m case all particles were steered past the centerline of the blood vessel before they reach the bifurcation and therefore all particles exited through the upper branch and furthermore no islet was formed.

The efficiency of this steering approach is plotted as a function of gradients in Fig. 19. The simulation results can be validated by comparing them to the experimental results presented in [26]. Although the dimensions of the particles in [26] are one order of magnitude smaller, the non-dimensional geometric factor $G$ is approximately the same (see definition of $G$ in [26]) and simulation results can be generalized for smaller or larger scales that have the same geometric factor $G$. The efficiency calculation included also the particles forming the islet. This assumption is reasonable since if these particles had not been anchored to the bifurcation, then they would have equally been distributed in the two branches. Furthermore, in an actual suspension of the same concentration (containing thousands of particles), the number of particles forming the islet would be negligible compared to the total number of particles exiting the branches.

Fig. 16. Aggregation of particles in a Y-tube channel for $B_0$ vertical and steering gradient 100mT/m.

Fig. 17. Zoom-in on the islet of magnetic particles.
were demonstrated through a sequence of simulation examples. Simulations are able to predict how magnetic particles respond in the presence of the MRI magnetic field. It was shown that the platform predicts the number and the size of the aggregations as well as their geometry. It was shown how the magnetophoretic ratio, i.e. the ratio of the magnetic force over the drag force applied to an aggregation is larger compared to the magnetophoretic ratio of its constituent particles when these are not attached to other particles and it was concluded that aggregations need smaller steering gradients compared to single isolated magnetic particles, and therefore allow for more efficient propulsion. It is known that superparamagnetic aggregations break-up and disperse in the absence of magnetic field. Therefore, aggregation techniques could be employed to combine the permeability advantages of magnetic microparticles with the high propulsion efficiency of the aggregations.

Fig. 19. Steering efficiency for gradients \(\{0, 40, 100, 200, 300, 400\}\) mT/m.

Comparison of the steering efficiency plots in Fig. 13 and Fig. 19 demonstrates that the best steering strategy is to generate aggregations whose angle of attack is orthogonal to the fluid flow. This way the zero flow boundary condition does not trap aggregations when these come into contact with the blood vessel walls. However, aggregations orthogonal to the flow could result in clogging of the branches. This can be avoided if the aggregation size is kept small compared to the blood vessel dimensions into which the steering takes place.

V. CONCLUSIONS AND FUTURE WORK

A computational platform was developed to investigate the dynamic behavior of the large-scale non-linear dynamic system of magnetic particles in medical applications such as magnetic targeting of drugs. To this end, the computational platform performs simulation, visualization and post-processing analysis of the interaction and the aggregation process of magnetic particles within a fluid environment such as that in small arteries and arterioles or in fluid-filled cavities of the human body.

The simulation capabilities of the computational platform were demonstrated through a sequence of simulation examples. Simulations are able to predict how magnetic particles respond in the presence of the MRI magnetic field. It was shown that the platform predicts the number and the size of the aggregations as well as their geometry. It was shown how the magnetophoretic ratio, i.e. the ratio of the magnetic force over the drag force applied to an aggregation is larger compared to the magnetophoretic ratio of its constituent particles when these are not attached to other particles and it was concluded that aggregations need smaller steering gradients compared to single isolated magnetic particles, and therefore allow for more efficient propulsion. It is known that superparamagnetic aggregations break-up and disperse in the absence of magnetic field. Therefore, aggregation techniques could be employed to combine the permeability advantages of magnetic microparticles with the high propulsion efficiency of the aggregations.

Fig. 18. Aggregation of particles in a Y-tube channel for \(B_0\) vertical and steering gradient 400 mT/m. The steering efficiency is 1.

Furthremore, the platform was used to assess the efficiency of steering particles in a Y-tube channel using two different techniques. The first technique had the channel flow aligned with the \(B_0\) field and the second technique had the channel flow orthogonal to the \(B_0\) field. It was demonstrated that the latter approach results in efficiencies up to 100% whereas the former approach can go only up to 70% efficiency. This is because when the \(B_0\) is along the flow in the channel much lower efficiencies are achieved due to aggregations being trapped in the fluid walls of the channel.

The computational platform can be used to assess the steering efficiency of different gradient schemes, and to perform comparative studies on motion planning techniques for MRI guided drug loaded magnetic particles or other applications that involve magnetic steering. A large number of simulations can be performed instead of actual experiments to determine the optimal strategies for magnetic targeting. This way the cost and the time needed to conduct a research experiment are significantly reduced.

Future work will expand the simulation platform along three directions: (1) Additional force models will be incorporated in the Particle Module. Brownian forces will be used to simulate stochastic motion of submicron size particles; steric repulsive electrostatic forces will simulate the interactions due to polymer chains on the surface of the particles. Physical properties and parameters will be included in the Particle Module to simulate the RBCs interaction with the magnetic particles. It is important to simulate the interaction of the magnetic particles with the RBCs because the latter will significantly affect the formation of aggregations due to collisions with the former. (2) The simulation environment will expand to 3D so that more realistic scenarios are studied. (3) The computational platform will be implemented using parallel computing techniques to address the computational load of the 3D simulations.

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REFERENCES


APPENDIX

**TABLE 2. SIMULATION PARAMETERS FOR SECTION: IV. A**

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<thead>
<tr>
<th>Parameter</th>
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<th>Description</th>
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<tr>
<td>B [T]</td>
<td>0.6</td>
<td>Uniform magnetic field</td>
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<tr>
<td>μ₂ [-]</td>
<td>12.3</td>
<td>Fe₂O₃ rel. magnetic permeability</td>
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<tr>
<td>μ₀ [-]</td>
<td>4π 10⁻⁷</td>
<td>Magnetic permeability</td>
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<tr>
<td>η [sPa]</td>
<td>1.0 10⁻³</td>
<td>Fluid dynamic viscosity</td>
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<tr>
<td>α [μm]</td>
<td>50</td>
<td>Mean particle radius</td>
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<tr>
<td>Y [m²/Pa]</td>
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<td>Young modulus of material</td>
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<td>ν [-]</td>
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<td>Poisson ratio</td>
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<td>γ [Nsm⁻¹]</td>
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<td>Tangential stiffness</td>
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<td>μ [-]</td>
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<td>Coefficient of friction</td>
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<td>νₑ [ms⁻¹]</td>
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<td>Mean value of fluid flow velocity</td>
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<td>D [m]</td>
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<td>Domain of magnetic interaction</td>
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<tr>
<td>Vᵣ [m]</td>
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<td>Verlet grid</td>
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<tr>
<td>lₓ, lᵧ [m]</td>
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<td>x and y dimension of sim. area</td>
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<td>c [particles/unit area]</td>
<td>3⋅10⁸</td>
<td>No. of particles per unit area.</td>
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**TABLE 3. SIMULATION OF EXPERIMENT**

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<td>VB [T/m]</td>
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<td>Magnetic gradient along the x-axis</td>
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<tr>
<td>α [μm]</td>
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<td>Mean particle radius</td>
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<tr>
<td>c [particles/m²]</td>
<td>0.15 10⁶</td>
<td>Particles per unit area</td>
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<tr>
<td>No of particles</td>
<td>100</td>
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The rest of the parameters are as in Table 1