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Investigation of the capture of magnetic particles from high-viscosity fluids using permanent magnets

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Abstract

Goal—This paper investigates the practicality of using a small, permanent magnet to capture magnetic particles out of high-viscosity biological fluids, such as synovial fluid.

Methods—Numerical simulations are used to predict the trajectory of magnetic particles toward the permanent magnet. The simulations are used to determine a “collection volume” with a time-dependent size and shape, which determines the number of particles that can be captured from the fluid in a given amount of time.

Results—The viscosity of the fluid strongly influences the velocity of the magnetic particles towards the magnet, hence the collection volume after a given time. In regards to the design of the magnet, the overall size is shown to most strongly influence the collection volume in comparison to the magnet shape or aspect ratio.

Conclusion—Numerical results showed good agreement with *in vitro* experimental magnetic collection results.

Significance—In the long-term, this work aims to facilitate optimization of the collection of magnetic particle-biomarker conjugates from high-viscosity biological fluids without the need to remove the fluid from a patient.

Keywords

biomagnetism; magnetic forces; high-viscosity biological fluids; magnetic particles; osteoarthritis

I. Introduction

Diagnosing medical diseases often requires the sampling of biological fluids such as urine, saliva, and blood. However, not all biological fluids are as straightforward to obtain as these fluids. Moreover, sampling the presence or concentration of a target molecule at a particular location within a biological fluid may yield a better means to diagnose local disease activity. As an example, there are a multitude of molecular biomarkers that are known to correlate with osteoarthritis (OA) disease progression [1], and several research initiatives have

focused in analysis of these molecular biomarkers in urine and serum. However, the associated levels of OA biomarkers are not specific enough to accurately diagnose OA [1]. *In situ* measurement of OA biomarkers directly within a diseased joint could address this problem [2]; however, the synovial fluid has a high viscosity and can be difficult to aspirate from a joint, a problem known in medicine as a dry tap [3]. The main challenge is how to reliably extract the OA biomarkers from the highly viscous synovial fluid in a reasonable time (< 1 h) for clinical applications.

Similar challenges exist across medicine, such as difficulties in extracting fluid from around the root of a tooth for biofilm analysis [4], potential increases in sensitivity and specificity from sampling mucous fluid in local or complex infections, a potential to reduce the risks of amniotic fluid embolism and other complications during amniocentesis by reducing the fluid lost during sampling [5], or providing alternate means to sample cerebrospinal spinal fluid [6].

The motivating hypothesis underlying the development of the platform technology we describe here is that biomarkers may be collected from highly viscous biological fluids by injecting magnetic particles that are functionalized to bind with biomarker molecules within the fluid and then collecting these particle-biomarker conjugates from the fluid via a permanent magnet. If successful, this approach could allow for a more reliable collection of biomarkers from highly viscous biological fluid or complex anatomical locations without the removal of the fluid from the body, as discussed further in Section II.A. The primary objective of the work presented here is to investigate the physical feasibility of the collection of magnetic particles in highly viscous fluid with a permanent magnet *in vitro*, building on the preliminary results presented in [7] and [8]. A secondary objective of this paper is to present and validate a multiphysics modeling approach for simulating the magnetic capture process. In the long-term, this work aims to provide guidelines for the development of magnetic capture techniques for the collection of magnetic particle-biomarker conjugates directly from synovial fluid or other *in vivo* target fluid. Therefore, any bio-safety concerns for future *in-vivo* applications will be investigated in future publications.

Section II describes the general method and the materials used in this paper. In Section III, the numerical modeling is introduced, followed by the numerical analysis of collection volume as a function of permanent magnet geometry and fluid viscosity. In Section IV, two different sets of *in vitro* experiments are conducted using mixtures of water and glycerol to mimic the viscosity ranges of synovial fluid seen in OA, and these results are used to validate the numerical modeling. Conclusions are provided in Section V.

II. Methods and Materials

A. Magnetic Capture Diagnosis Method

The proposed magnetic capture technique for the early diagnosis is described in Figure 1 [7]. To begin, it is assumed that biomarkers are present in a biological fluid at an unknown, yet disease-related, concentration (Figure 1.a). The first step consists of adding functionalized magnetic particles to the fluid (Figure 1.b) and waiting for their binding to the biomarkers to reach equilibrium (Figure 1.c). A permanent magnet is then inserted into the fluid space via

a cannula to collect a portion of the magnetic particle-biomarker conjugates from the fluid (Figure 1.d). After removal from the joint space, biomarkers are released from the particles on the permanent magnet via a temperature increase, enzymatic digestion, or other means for further analysis (Figure 1.e). Both the number of magnetic particles and biomarkers has to be established to accurately estimate the biomarkers presence in the fluid space [7]. Note that during *in vivo* studies, any uncollected conjugates would remain in the fluid space or be cleared through circulation or lymphatic system.

The biomarker collection depends on two phenomena: the biomarker binding to the magnetic particle surface, and the subsequent magnetic particle collection by a permanent magnet.

Concerning the OA diagnosis, the first phenomenon has already been described *in vitro* and *post mortem* by magnetically collecting CTX-II (C-telopeptide of type II collagen), an OA-biomarker, representing a separate investigation by itself [7]. In this paper, the focus is on the physical proof-of-concept of the capture of the magnetic particles in order to optimize their magnetic collection in multiple biological fluids, focusing more on high-viscosity fluids.

B. Materials for Magnetic Collection

1) Magnetic Particles—For the proof-of-concept presented in this study, Fe_3O_4 superparamagnetic iron oxide nanoparticles (SPIONs) are embedded in a non-magnetic polystyrene matrix with fluorescent dye, resulting in micron-size magnetic particles with superparamagnetic properties (Corpuscular C-PS-1058COOH). For terminology convenience, the polystyrene / magnetic nanoparticle composite bead is thereafter called the “magnetic particle”. It should be noted that SPIONs are currently used as FDA-approved clinical MRI contrast enhancement agents [9], and that magnetic nano- and microparticles are increasingly used for biomedical applications such as drug and gene delivery, remote actuation of cell surface receptors, cell targeting, and magnetophoretic cell separation [10]–[12]. These technologies rely on the superparamagnetic properties of the nanoparticles, having no remanent magnetization in the absence of an external magnetic field. Therefore, no agglomeration due to inter-particle magnetic interactions is expected when they are in suspension.

A scanning electron microscope (SEM) image of the dried particles is presented in Figure 2.a. The monodispersity of the particles is confirmed by a dynamic light scattering (DLS) measurement. The average hydrodynamic diameter is found to be 779 nm. The magnetic properties of the particles are measured with a superconducting quantum interference device (SQUID) magnetometer, and the resulting magnetization curve is presented in Figure 2.c: these magnetic particles are predominantly superparamagnetic, exhibiting a small coercivity. The magnetization curve is fit with the Langevin equation [13] to estimate the nanoparticle diameter: 8.5 ± 1.5 nm.

2) Permanent Magnet—The collection of magnetic particles relies on the attractive magnetic forces from the magnetic field source, here a permanent magnet. The magnetic force on a particle is proportional to the magnetic field gradient created by the permanent

magnet, as will be explained in Section III.A. Hence, to maximize the capture of particles from a fluid, the capture magnet should create a large magnetic field gradient over a large volume. Furthermore, the total physical magnet size must be constrained in order to facilitate insertion via a small incision or cannula for *in vivo* applications and to fit into the joint volume. Indeed, the amount of synovial fluid available in a joint is relatively small: ~3 mL in OA human knees [14], ~25 μL in rat knees, and only ~1 μL in mouse knees.

In the new experiments presented in this article, the capture magnet structure is a cylindrical, grade N52, Nd-Fe-B permanent magnet (Super Magnet Man D0110), 0.93 mm in diameter and 0.97 mm in length, magnetized along the axis and covered by a ~20 μm thick trilayer of nickel/copper/nickel to prevent oxidation. A picture of the permanent magnet, mounted on a soft ferromagnetic rod for easier handling during the experiments, is provided in Figure 2.b. The magnetic properties are measured using a vibrating sample magnetometer (VSM) (ADE Technologies EV9) with a maximum applied field of ± 1800 kA/m. The magnetic hysteresis curve of the permanent magnet (hard magnetic material) is presented in Figure 2.c, showing an intrinsic coercivity of 980 kA/m ($\mu_0 H_c = 1.23$ T) and a remanent magnetization of 915 kA/m ($\mu_0 M_r = 1.15$ T). The kink at low applied fields is attributed to the presence of the soft-magnetic protective layer. Since the soft magnetic rod contributes to the magnetic collection, the magnetization curve of the soft magnetic material is also measured by VSM and considered in the following numerical simulations. The magnetic hysteresis curve of the soft magnetic rod is presented in Figure 2.c, showing a saturation magnetization of 1710 kA/m ($\mu_0 M_s = 2.15$ T) and a relative magnetic permeability of $\mu_r = 25$.

III. Numerical Simulations

A. Numerical Model of the Magnetic Collection

The numerical simulations are carried out in a 2D axisymmetric configuration, in the cylindrical coordinate system $(\vec{r}, \vec{\varphi}, \vec{z})$. Two forces acting on a particle are considered in this study: the magnetic force $\vec{F}_m$ and the Stokes' drag force $\vec{F}_d$. The magnetic force is expressed as [15], [16]:

$$\vec{F}_m = (\vec{m} \cdot \vec{\nabla}) \vec{B} \quad (1)$$

where $\vec{m}$ is the magnetic moment of the particle and $\vec{B}$ is an external magnetic flux density, defined by its amplitude, B , and its orientation $\theta = \arctan(B_z/B_r)$:

$$\vec{B} = B \begin{bmatrix} \cos \theta \\ \sin \theta \end{bmatrix} = \begin{bmatrix} B_r \\ B_z \end{bmatrix} \quad (2)$$

The direction of the particle magnetization is assumed to be the same as the direction of the B-field. Therefore, the particle magnetization $\vec{m}$ is defined as:

$$\vec{m} = V M(H) \begin{bmatrix} \cos \theta \\ \sin \theta \end{bmatrix} \quad (3)$$

where $M(H)$ is the particle magnetization as a function of the H-field (refer to Figure 2.c) and V is the volume of the particle. Hence the magnetic force is given by:

$$\vec{F}_m = V M(H) \left[\begin{array}{c} \cos \theta \frac{\partial B_r}{\partial r} + \sin \theta \frac{\partial B_r}{\partial z} \\ \cos \theta \frac{\partial B_z}{\partial r} + \sin \theta \frac{\partial B_z}{\partial z} \end{array} \right] \quad (4)$$

The drag force is calculated using [17]:

$$\vec{F}_d = -6\pi\eta r_{mp} \vec{v} \quad (5)$$

where η is the fluid viscosity, r_{mp} is the hydrodynamic radius of the particle, and $\vec{v}$ is the velocity of the particle.

The force balance is given by:

$$\vec{F}_m + \vec{F}_d = m_p \vec{a} \quad (6)$$

where m_p is the mass of the particle and $\vec{a}$ is the particle acceleration. Since the mass of the particle is small and it experiences a small acceleration, the inertia term (right-hand side term of force balance) is negligible. Therefore the velocity of a magnetic particle is found as:

$$\vec{v} = \frac{1}{6\pi\eta r_{mp}} \vec{F}_m \quad (7)$$

With these base equations, simulations are performed in COMSOL Multiphysics as shown in Figure 3.a. The permanent magnet provides the source of the B-field, shown in Figure 3.b. Using (4), the magnetic force distribution is deduced, as presented in Figure 3.c.

From the magnetic force map, the trajectories of the particles at different positions are calculated using the particle tracing module in COMSOL. Simulation results confirm the inertia term in (6) is negligible compared to the other forces. From this, the time taken by particles to travel from any point in the space to the surface of the magnet (time-of-flight) is determined. Particle trajectories and time-of-flight contours are presented in Figure 3.c and Figure 3.d, respectively. The volume of space within a time-of-flight contour—excluding the volume occupied by the magnet and rod—corresponds to a collection volume of magnetic particles. The collection volume expands in time (denoted CV_t , where the subscript t denotes the time) and is used as a figure of merit to compare the influence of different system variations (magnetic geometry, fluid viscosity, etc.).

B. Influence of Geometry

The influence of the magnet size on the magnetic particle collection is investigated by simulating the collection volume of magnetic particles in water ($\eta = 0.86 \text{ mPa}\cdot\text{s}$) when the volume of a cylindrical permanent magnet (length/diameter = 1.04) is varied from 0.01 to 79 mm^3 . The results from the numerical simulations are presented in Figure 4. As expected, the

permanent magnet volume is found to have a significant influence. After 120 s, a 79 mm³ magnet enables the collection volume of 300 mm³ of magnetic particles, while a magnet ten times smaller (0.79 mm³) collects 20 mm³ of magnetic particles. Assuming an initial concentration of 1 million particles per microliter (1 mg/mL), these volumes correspond to 300 million particles and 20 million particles respectively.

Other geometry parameters are investigated through their influence on the collection volume after 120 seconds ($CV_{120\text{ s}}$). Figure 5 shows the influence of modifying the cylinder aspect ratio (length to diameter) from 1:10 to 10:1, keeping a constant volume. An optimum collection volume is found for an aspect ratio close to 1:1. Additional simulations (not shown) reveal that the corner radius of the magnet has very little influence on the collection volume at 120 s. Additionally, a cylindrical magnet is found to have a collection volume after 120 s, nearly the same as a cone of the same volume, whatever the considered volume. While the conical shape produces a higher magnetic gradient in the region near the apex, in the far-field region, both magnets act as simple magnetic dipoles, and the shape is no longer an influent design parameter. Because the cylinder is easier to fabricate than the cone [8], it makes most sense to use a simple cylindrical permanent magnet for the magnetic collection.

C. Influence of Viscosity

In high-viscosity fluids, the balance between drag and magnetic force leads to low particle velocities, which in practical situations may limit the collection volume. Therefore, the influence of viscosity is of critical importance. To study this phenomenon, a viscosity range was chosen to reflect the viscosity of healthy human synovial fluid (380–1400 mPa·s) and the reduction by an order of magnitude observed in OA-affected synovial fluid [18]. Experiments (described in Section IV) are conducted in mixtures of water and glycerol to mimic these viscosity ranges.

A first study focuses on the influence of the viscosity on the time-of-flight. The results are given in Figure 6, considering a 0.66 mm³ cylindrical permanent magnet. The viscosity variation shows significant practical impact on the time-of-flight. A particle located 1 mm away from the magnet reaches the surface in a matter of seconds when in water (0.86 mPa·s), but the same particle track may require 1,000 s when in glycerol (770 mPa·s). A linear relationship between the time-of-flight and the viscosity is found, as expected from (7).

A second study investigates the influence of viscosity on the collection volume of magnetic particles depending on the collection time. The results are reported in Figure 7. The equivalent number of collected magnetic particles, for an initial concentration of 1 million particles per microliter (1 mg/mL), is presented in the right axis of the graph. For experimental quantification of the number of collected particles, the quantity must exceed the threshold limit ($\sim 10^5$ particles) of the Synergy 2 Multi-Mode Microplate Reader (see Section IV.B). The simulations show that $\sim 120,000$ particles can be collected after 120 s in a fluid with the viscosity of a healthy-knee synovial fluid. More particles would be collected for an OA-affected joint (lower viscosity). Therefore, a measurement for an OA diagnosis is expected to be obtained within a 10 minute long collection with a static magnet.

IV. Experimental Validation

In this section, the numerical results obtained in Section III.B and Section III.C are compared to experimental results. The validity of the numerical model will be demonstrated via measurements of particle velocities for several different fluid viscosities, and via measurement of the number of collected particles vs. time.

A. Particle Tracing Experiments

In order to experimentally measure the velocity of the magnetic particles during capture, the particle motion is recorded by a fluorescence camera on a microscopic platform. Fluids of varying viscosity are produced by a variable ratio of glycerol to water (Table 1), corresponding to the viscosity range shown previously in Figure 6. Note that while glycerol is a Newtonian fluid [19], it is used to mimic the viscosity of the synovial fluid, a shear-thinning fluid, hence non-Newtonian [20], [21]. The drag force equation can be reformulated to assume the change of viscosity with the applied shear rate [19], [22], [23]. However, the range of velocity found for the highest-viscosity case will give us the lower bound value to be expected while in the synovial fluid.

The experimental protocol is as follows: a 0.4 mL volume of the magnetic particles (stock concentration of 10 mg/mL) are first homogeneously mixed in a 1 mL volume of the fluid of interest, and a 0.4 mL droplet of this mix is placed on a Petri dish and imaged with a fluorescence microscope (EVOS Cell Imaging System). Note that the particles are not functionalized or conjugated with biomarkers. The 0.93 mm diameter, 0.97 mm long (0.66 mm³) permanent magnet is then inserted into the fluid, while the motion of the magnetic particles near the magnet tip region is recorded. Video analysis is performed to quantify the particle motion (trajectory and velocity) using a freely available MATLAB package, DLTdv5 [8], [24]. An example of the extracted trajectories of two particles in water, obtained from a 2 s long video, is presented in Figure 8. A comparison with the simulated trajectories is provided, showing a good agreement.

The deduced experimental velocities for the different mixes are presented in Figure 9, alongside the numerical simulations of particles moving along a corresponding trajectory. Up to 250 μm away from the magnet surface, experimental velocities ranging from ~ 0.5 to ~ 800 $\mu\text{m/s}$ are obtained, confirming again that viscosity has a strong impact on the motion of the magnetic particles. Additionally, the experimental results show good agreement with the numerical model.

B. Particle Collection Experiments

To experimentally determine the number of collected particles, at a given time, the permanent magnet is allowed to collect particles from a volume of solution with a known particle concentration. The number of collected particles is indirectly deduced from the amount of uncollected particles remaining in the solution, as explained in the following procedure.

An initial volume of 4 μL of magnetic particles at a stock concentration of 10 mg/mL is put into a 15 mL Corning tube. The particles are then sonicated twice for two-minute intervals

in a Branson 1800 Ultrasonicator in order to prevent particle aggregation. Deionized water is then added to adjust the particles to a 2,500x dilution compared to the stock concentration of particles, i.e. 4,000 particles per microliter (concentration of 4 $\mu\text{g/mL}$). The solution is thoroughly mixed and vortexed. Forty-two 200 μL aliquots are subsequently transferred to a 96-well cell-culture plate. After mixing the well with a micropipette to ensure uniform distribution of particles, a cylindrical 0.66 mm^3 permanent magnet mounted on a soft magnetic rod is placed into the center of each well. The permanent magnet rests on polycarbonate blocks at a predetermined height to ensure the position is consistent. During each experiment, the magnet is allowed to collect particles for 0, 0.5, 2, 15, 120 or 360 minutes ($n=3$ per time point). The magnet is promptly removed from the well after the magnetic collection. After the collection, 180 μL aliquots are taken out of each well of the cell-culture plate and placed into 0.2 mL PCR tubes. The PCR tubes sit on top of a magnetic plate for two hours to accumulate the particles on the bottom of the PCR tube. A volume of 175 μL is removed from the supernatant, and the final volume is adjusted to 5 μL . The 5 μL samples in the PCR tubes are quantified by fluorescence intensity at 530/590 nm using a Synergy 2 Multi-Mode Microplate Reader. Six calibration samples ($n=3$) are used to convert the read fluorescence intensity data into an amount of particles information via the interpolation of the obtained linear trend.

For practical reasons, the above experiment is only performed in water. The collected amount of particles vs. time is reported in Figure 10, along with the analogous numerical model results. The experimental magnetic collection results in water are of the same order of magnitude as the numerical results, despite the simulations ignoring the effects of Brownian motion, gravity, and magnetic interactions between the particles. However, an equivalent time dependency is found for both of them, showing $\sim 20,000$ s (~ 5.5 h) are needed to fully capture all of the magnetic particles. Projected collection rate curves for the range of viscosity (Table 1) are also presented in Figure 10. A collection time of 10^7 s (~ 116 days) is estimated to fully deplete the same amount of magnetic particles from glycerol in the well, using a static magnet. However, as mentioned in Section III.C, up to 120 seconds are necessary to magnetically collect a number of particles above the threshold limit of detection in a fluid with the viscosity of a healthy-knee synovial fluid with a static magnet, demonstrating our proposed method of OA diagnosis does not require fully clearing the synovial fluid of the magnetic particle-biomarker conjugates.

V. Conclusions

In this paper, numerical simulations have been implemented to study the influence of several parameters on the collection of magnetic particles in a fluid: the collecting permanent magnet geometry as well as the effect of the viscosity on the collection kinetics. The viscosity is shown to strongly influence the collection time of magnetic particles via a linear relationship. The optimum permanent magnet geometry is found to be a cylindrical shape rather than a conical shape, with an aspect ratio close to 1:1 and maximal volume (limited by the size constraints of the joint space). Using a 0.93 mm diameter, 0.97 mm long (0.66 mm^3) permanent magnet, practical amount of magnetic particles (at least 120,000 particles) is predicted to be collected in a practical timescale (120 s) from high-viscosity Newtonian fluids. The numerical results are supported by experimental data, giving confidence in the

numerical predictions. These data are critical for deciding a reasonable time (e.g. 10 min) for the collection of magnetic particle-biomarkers. In future works, efforts will focus on moving forward to synovial fluid and other non-Newtonian fluids to further validate the magnetic collection diagnostic tool for the detection of early-stage OA.

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Figure 1.

Conceptual diagram of the magnetic particle-based technique to capture biomarkers from a biological fluid: (a) Presence of biomarkers in the fluid at an unknown concentration, (b) Injection of the functionalized superparamagnetic particles into the fluid, (c) Binding of biomarkers to the conjugated particles, (d) Collection of the conjugates using a permanent magnet, (e) Release from the magnetic particles and analysis of the biomarkers.

Figure 2.

(a) SEM image of a magnetic particle, (b) optical image of the cylindrical magnet mounted on the soft magnetic rod and (c) magnetization curves used during simulations. Magnet and rod measured by VSM, and magnetic particles measured by SQUID. Inset: zoom-in to the low applied magnetic field region of the magnetization curves of the microparticles and the rod.

Figure 3.

Simulation description: (a) axisymmetric representation of the simulation, (b) B-field distribution map and H-field streamlines, (c) magnetic force distribution and particle tracing trajectories, (d) time-of-flight contours. The area represented here is a zoom-in of the entire area that is being simulated.

Figure 4.

Collection volume at different collection times ($CV_{12\text{ s}}$, $CV_{120\text{ s}}$, $CV_{1200\text{ s}}$) vs. permanent magnet volume. Right axis is the number of collected particles for a concentration of 1 million particles per microliter.

Figure 5.

Collection volume at different collection times ($CV_{12\text{ s}}$, $CV_{120\text{ s}}$, $CV_{1200\text{ s}}$) vs. aspect ratio of the permanent magnet. Right axis is the number of collected particles for a concentration of 1 million particles per microliter.

Figure 6.
Time-of-flight contour for different fluid viscosities.

Figure 7.

Collection volume vs. viscosity, depending on the collection time. Right axis is the number of collected particles for a concentration of 1 million particles per microliter. Highlighted zone represent the synovial fluid viscosity range from OA patients to healthy patients.

Figure 8.

Example of two particle trajectories, in water (2 s long), tracked with the DLTdv5 Matlab package. The image contrast is enhanced for an easier location of the magnet surface. The lines represent the COMSOL simulation results of particle tracking.

Figure 9.

Velocity vs. particle distance from the magnet surface, depending on the viscosity.

Experimental results are plotted as data points and the simulation results are plotted as lines of matching color.

Figure 10.

Simulated particle collection vs. time for different fluid viscosities. Experimental results for the magnetic collection in water.

Table 1

Range of Viscosity Depending of the Glycerol to Water Ratio, at 300 K.

Fluid mix (1 mL)	η (mPa·s)
100 % Glycerol – 0 % Water	770
75 % Glycerol – 25 % Water	37
50 % Glycerol – 50 % Water	6.4
0 % Glycerol – 100 % Water	0.86