Magnetic separation in microfluidic systems using microfabricated electromagnets – Experiments and simulations

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We present experiments and simulations of magnetophoretic separation of magnetic beads in a microfluidic channel. The separation is obtained by microfabricated electromagnets. The results of our simulations using FEMLAB and Mathematica are favourably compared with experimental results obtained using our own microfabricated systems.

Keywords:
Magnetic Microsystems, separation, computational fluid dynamics, magnetophoresis

1. Introduction
Manipulation of superparamagnetic nanoparticles encapsulated in polymer beads (magnetic beads) is a well-known technique in biochemical analysis and processing [1-2]. In magnetic separation biochemically functionalized magnetic beads are separated from a solution using magnetophoresis. Recently, microsystems offering the same functionality have been reported [3-5]. Microsystems capable of magnetic separation are ideal for inclusion in Lab-on-a-chip systems. The vision of Lab-on-a-chip systems is to have entire biochemical laboratories on a single chip. The advantages of such Lab-on-a-chip systems are that they can handle minute sample volumes (e.g. micro or nanolitres), they are highly portable, and they are potentially inexpensive and thus disposable [6-7].

We present numerical simulations of the movements of such magnetic beads in microfluidic systems and compare with experiments.

2. Design and Fabrication
The design of our microsystem is shown in Fig. 1. Each microsystem contains three microelectromagnets, each consisting of a copper coil semi-encapsulated in a dielectric layer and a soft magnetic yoke on top of that.

We have fabricated electromagnets of several variations of the same basic design. The electromagnets that we have used for the experimental part of this paper have the following design parameters: Number of turns 12; coil wire height 25 µm, width 60 µm, and spacing 20 µm; electromagnet width 4 mm, and yoke thickness 25 µm; fluid channel depth 150 µm, length 14 mm, and width 1.5 mm. Also, we have used both nickel and permalloy as magnetic material for the yoke. Permalloy has the best magnetic properties, but nickel is better adapted to our fabrication process.

We have fabricated the microsystems using standard cleanroom technology. Fig. 2 summarizes the fabrication process. For more details see [8].
Figure 1: Overview of the microsystem design. (a) shows a top-view of the fabricated chip. The positions and shapes of the three microelectromagnets are seen. The microelectromagnets are planar spiral copper coils with 12 turns. The coils are semi-encapsulated in a soft magnetic yoke made from either Nickel or PermAlloy. (b) shows the microsystem seen from the side. It is seen how the Pyrex wafer forms a lid on the microfluidic channel. Please note that the horizontal scale bar at the bottom applies to both (a) and (b).

Figure 2: Process flow for the fabrication of a micromachined magnetic bead separator. In (a) a double polished Silicon (100) wafer is oxidized (50 nm) and a silicon nitride (100 nm) is grown on top of the oxide. In (b) the oxide and nitride are removed from one side of the wafer using Hydrofluoric acid and Reactive Ion Etching, respectively, and the microfluidic channel (150 µm deep) is etched into the Silicon wafer using Deep Reactive Ion Etching (DRIE). A Pyrex wafer is bonded anodically to the Silicon wafer. In (c) a layer of 30 nm Ti – 300 nm Cu – 30 nm Ti is evaporated onto the Silicon Nitride using e-beam evaporation. A 25 µm thick layer of photo resist is spun onto the wafer, and it is patterned using UV-lithography. In (d) the copper wire is electroplated into the resist openings, the resist is removed, and the metal layer is removed. In (e) a new layer of 25 µm thick photo resist is spun onto the wafer. It is patterned using UV-lithography, and then hard-baked at 130 °C to form the dielectric layer. In (f) a new metal layer similar to that of (c) is evaporated onto the wafer, and a third layer of 25 µm thick photo resist is spun onto the wafer. It is patterned using UV-lithography. In (g) the 25 µm thick magnetic yoke (either nickel or permalloy) is electroplated into the resist openings, and finally the resist and the metal layer is removed.
3. Magnetostatic theory

The magnetic induction $B$ is calculated using standard magnetostatics,

$$B = \nabla \times A = \mu_0 \mu_r H,$$

$$\nabla \times H = J^f,$$  \hspace{1cm} (1)

$$\nabla \times \left( \mu_0 \mu_r \right) (\nabla \times A) = J^f.$$  \hspace{1cm} (2)

where $H$ is the magnetic field, $A$ is the magnetic vector potential, $\mu_0$ is the permeability of vacuum, $\mu_r$ is the relative permeability of the material, and $J^f$ is the free current density. These equations can be combined to yield

$$\nabla \times \left( \left( \mu_0 \mu_r \right)^{-1} (\nabla \times A) \right) = J^f.$$  \hspace{1cm} (3)

To simplify the simulations we study circular electromagnets, and thus the magnetostatic problem is reduced from 3D to 2D. This still allows for qualitative comparison with the square magnets of the experiments as discussed by Shafique et al. [9].

We apply cylindrical coordinates $(r, \theta, z)$ with $r=0$ at the centre of the electromagnet. All free currents are thus in the azimuthal direction $J^f(r, z) \hat{e}_\theta$ which is consistent with a magnetic vector potential $A=A_\theta(r, z) \hat{e}_\theta$.

To bring Eq. (3) into a form suitable for the software, FEMLAB®, we introduce the function $u(r, z)$ given by

$$u(r, z) = \frac{A_\theta(r, z)}{r}.$$  \hspace{1cm} (4)

Using this the only non-zero component of Eq. (3) is [10]

$$- \frac{\partial}{\partial r} \left( r (\mu_0 \mu_r)^{-1} \frac{\partial u}{\partial r} + 2 \mu^{-1} u \right) - \frac{\partial}{\partial z} \left( r (\mu_0 \mu_r)^{-1} \frac{\partial u}{\partial z} \right) = J^f_\theta,$$  \hspace{1cm} (5)

which is the canonical form that FEMLAB® solves in its “Magnetostatics - Azimuthal currents” mode of its Electromagnetics Module [10]. In terms of $u(r, z)$ the components of the magnetic induction become:

$$B = (B_r, B_\theta, B_z) = \left( -r \frac{\partial u}{\partial z}, 0, r \frac{\partial u}{\partial r} + 2u \right).$$  \hspace{1cm} (6)

Both nickel and permalloy are ferromagnetic materials, and thus $\mu_r$ is not a constant. Hysteresis is difficult to model, since it involves the history of the magnetic material. However, since both nickel and permalloy are soft magnetic materials and thus almost hysteresis free, we use the approximate empirical Fröhlich-Kennelly relation $M = M_s \frac{H}{(C + |H|)}$ for hysteresis-free magnetization to describe both materials [11]. The relative permeability $\mu_r(H)$ thus becomes

$$\mu_r(H) = 1 + \frac{M}{C + |H|},$$  \hspace{1cm} (7)

where $M_s$ is the saturation magnetization of the material, and $C$ is an experimentally determined parameter of the material.
Figure 3: Vibrating Sample Magnetometer measurement of the hysteresis loop of an electroplated nickel film. The horizontal axis is the applied magnetic field (H), and the vertical axis is the measured magnetization (M). The measured saturation magnetization is $4.84 \times 10^5$ A/m. Also included is the fitted Fröhlich-Kennelly relation. $M_s$ of the fit is allowed to deviate from the measured value in order to ensure the best possible fit to the low-field data.

In order to solve Eq. (5) in FELMAB®, it is necessary to express $\mu_r$ as a function of $B$ (or actually as a function of $u$ and its partial derivatives) rather than $H$ in order to use it in Eq. (5). By setting $|H| = |B|/\mu_0\mu_r$ in Eq. (7), $\mu_r$ is found as the positive root of a second order polynomial, which to first order in $|B|$ is

$$\mu_r(|B|) = 1 + \frac{M_s}{C} - \frac{M_s}{C(C + M_s)} |B| + O(|B|^2).$$  

(8)

It is seen that $\mu_r(|B|)$ is constant until the magnetic field inside the magnetic material approaches the saturation magnetization (assuming $M_s >> C$).

In Fig. 3 the measured hysteresis loop of one of our electroplated nickel thin films together with a fit based on Eq. (7) is shown. We have focused on a good fit for the low-field part of the hysteresis loop, which is why we have allowed for a saturation magnetization in the fit, which is different from the nickel saturation magnetization of $4.84 \times 10^5$ A/m.

We have used the electromagnetics module of FELMAB® 2.3 to solve Eqs. (4) through (7) with the parameters of the electroplated nickel thin film. In order to keep the reluctance of the entire system constant, all length scales have been scaled in order to have the same area in the circular geometry as in the original square geometry [9]. This yields a scaling factor of $(4/\pi)^{1/2}$. The free current density has been scaled with the inverse factor to ensure that the total current is unchanged.

Figure 4 shows the result of such a calculation. Note that the magnetic beads will be attracted to areas in the microfluidic channel with large magnetic field and thus the attraction will be perpendicular to the contours of the figure. It is seen that the magnitude of $H$ inside the magnetic yoke does not exceed 2000 A/m, which means that $\mu_r$ is everywhere within 80% of the constant $1 + M_s/C$ in Eq. (8).
Figure 4: Contour plot of the magnitude of the magnetic field (H-field) from one of the fabricated microelectromagnets. The current in the copper coil is 360 mA. The magnetic yoke is made of electroplated nickel. Also shown on the graph is the position of the microfluidic channel relative to the electromagnet. The magnetic beads will be attracted to regions where the magnetic field is large, and thus the attraction will be perpendicular to the contours.

4. Magnetophoretic theory

Three forces, gravity $F_{grav}$, fluid drag $F_{fluid}$, and magnetophoretic force $F_{mag}$, affect a magnetic bead. First, the magnetophoretic force on a magnetic bead from the calculated magnetic field is calculated. The general expression for the magnetic force on a magnetizable object is given by [12]

$$ F_{mag} = \mu_0 \int \nabla \cdot (\mathbf{M}) \mathbf{H}_a d^3 r, $$

where the integral is taken over the volume of the magnetizable object, and $\mathbf{H}_a$ is the magnetic field in the absence of the magnetizable object.

For a spherical bead in a homogeneous magnetizing field, the magnetization $\mathbf{M}$ inside the bead is given by [13]

$$ \mathbf{M} = \chi_m \mathbf{H}_a = \frac{\chi_i}{1 + N\chi_i} \mathbf{H}_a = \frac{\mu_r - 1}{\mu_r + 2} \mathbf{H}_a, $$

where $\chi_i$ is the intrinsic susceptibility of the magnetic bead material, $\chi_m$ is the measured susceptibility of a single magnetic bead including demagnetization effects, and $\mu_r = 1 + \chi_i$ is the relative permeability of the magnetic bead, and it has been assumed
that the sphere is surrounded by a medium with $\chi \approx 0$. The last equality follows from the fact that the demagnetization factor of a sphere is $N=1/3$. Inserting this result into Eq. (9) and taking the magnetizable object to be a magnetic bead yields:

$$F_{\text{mag}} = \mu_0 3 \frac{\mu_r - 1}{\mu_r + 2} \int \mathbf{H}_a (\mathbf{V} \cdot \mathbf{H}_a) dV \approx 2\pi R^3 \frac{\mu_r - 1}{\mu_r + 2} \nabla \left( \left| \mathbf{H}_a \right|^2 \right) \cdot \mathbf{v} = \frac{1}{2} \mu_0 V_{\text{bead}} \chi_m \nabla \left( \left| \mathbf{H}_a \right|^2 \right). \tag{11}$$

The approximation is that the integrand is constant over the volume $V_{\text{bead}}$ of a magnetic bead with radius $R$, and it has been used that $\mathbf{H}_a$ is curl-free, since there are no free currents outside the copper coils. This result is consistent with the effective dipole approximation reported by Jones [14], but it has been found through different means.

5. Dynamics and microfluidic theory

Low Reynolds numbers and hence laminar flows generally characterize fluid flows in microfluidic systems. For example in our system and for the used flow rates the Reynolds number is approximately $10^{-2}$, and thus all inertial terms in the Navier-Stokes equation can be discarded. Since we are considering stationary incompressible flow in straight channels with no net body force on the fluid, the Navier-Stokes equation reduces to:

$$\left( \frac{\partial^2}{\partial y^2} + \frac{\partial^2}{\partial z^2} \right) v_y(y, z) = -\frac{\Delta p}{\eta L}, \tag{12}$$

where $\Delta p$ is the pressure drop across the length $L$ of the microfluidic channel, $\eta$ is the viscosity of the fluid, and $v_y(y, z)$ is the longitudinal velocity in the channel. Using the usual no-slip boundary conditions on the walls $(y, z) \in [0, y_0] \times [0, z_0]$ the solution to Eq. (12) can be written as

$$v(y, z) = v_{\text{avg}} \frac{\phi(y, z)}{\langle \phi \rangle}, \tag{13}$$

$$\phi(y, z) = \sum_{n=0}^{\infty} f_n(z) \sin(k_n y), \quad k_n = (2n + 1) \frac{\pi}{y_0}, \tag{14}$$

$$f_n(z) = \frac{1}{(2n + 1)^2} \left[ \cosh(k_n z) - \tanh \left( k_n \frac{z_0}{2} \right) \sinh(k_n z) - 1 \right], \tag{15}$$

$$\langle \phi \rangle = \frac{1}{y_0 z_0} \int_0^{y_0} \int_0^{z_0} \phi(y, z) dy dz, \tag{16}$$

where $v_{\text{avg}}$ is the average flow velocity in the channel given by $v_{\text{avg}} = Q/y_0 z_0$ where $Q$ is the volumetric flow rate. In experimental microfluidics the flow rate is almost always the adjustable parameter rather than the pressure difference, and the solution is expressed in terms of $Q$.

We take the fluid drag on a magnetic bead to be the Stokes drag:

$$F_{\text{fluid}} = 6\pi R \eta \left( \mathbf{v}_{\text{fluid}} - \mathbf{v} \right), \tag{17}$$
where $\eta$ is the viscosity of the fluid, and $\mathbf{v}_{\text{fluid}}$ and $\mathbf{v}$ are the velocity vectors of the fluid and bead, respectively.

Finally gravity is included through a buoyancy term:

$$
F_{\text{grav}} = \frac{4}{3} \pi R^3 (\rho_{\text{fluid}} - \rho) \mathbf{g} \hat{z}
$$

(18)

where the $\rho_{\text{fluid}}$ and $\rho$ are the densities of the fluid and bead, respectively.

At this point we have accounted for all the forces that affect a magnetic bead in the fluid, and thus Newton’s second law yields:

$$
\rho \frac{4}{3} \pi R^3 \frac{d\mathbf{v}}{dt} = \mathbf{F}_{\text{mag}}(\mathbf{r}) + \mathbf{F}_{\text{grav}}(\mathbf{r}) + \mathbf{F}_{\text{fluid}}(\mathbf{r}, \mathbf{v}).
$$

(19)

At a given bead position all forces can be considered constant except for $\mathbf{F}_{\text{fluid}}$ that depends on $\mathbf{v}$, and that yields a differential equation for $\mathbf{v}$ with a solution that has a constant term (the equilibrium velocity) and an exponential function with a time constant $\tau$ given by:

$$
\tau = \frac{2R^2 \rho}{9 \eta} \approx 10^{-7} \text{s}.
$$

(20)

The conclusion of the analysis above is that the bead will reach its equilibrium velocity, where all forces cancel, instantaneously compared to other time scales in the simulation, e.g. capture times, and thus it is justifiable to use the equilibrium velocity for calculations of the bead flows [15]. Hence we neglect the inertial term of Eq. (19), and obtain

$$
\mathbf{v} = \frac{d\mathbf{r}}{dt} = \mathbf{v}_{\text{fluid}}(\mathbf{r}) + \frac{1}{6\pi R \eta} \left( \mathbf{F}_{\text{mag}}(\mathbf{r}) + \mathbf{F}_{\text{grav}}(\mathbf{r}) \right).
$$

(21)

This constitutes three coupled, first-order, ordinary differential equations of motion for the bead.

From the equations of motion it is seen that the largest magnetic forces appear in regions with the largest gradients in $H$. Once caught by the magnetic gradient force, the particles are brought towards the local magnetic field maximum. Hence we expect a high capture efficiency near such points, i.e. near edges and corners of magnetic structures.

6. Simulations

For the simulations we have used the parameters of the bead type MyOne® from Dynal Biotech [2], which are approximately: $2R = 1.05 \mu\text{m}$, $\rho = 1.8 \times 10^3 \text{ kg/m}^3$, and $\mu_r = 2.485$. Also, the permeability of the magnetic beads can be assumed constant, since the applied field do not saturate the beads. The fluid is water with $\rho = 1.0 \times 10^3 \text{ kg/m}^3$ and $\eta = 8.90 \times 10^{-4} \text{ Pa s}$.

We have solved Eq. (21) using the numerical solver NDSolve of Mathematica® for many different initial positions of the magnetic beads. We have assumed that whenever a bead hits the bottom of the microfluidic channel, it sticks without any possibility of further motion.

Figure 5 shows the result and the parameters of a calculation where 10000 magnetic beads have been released into the microfluidic channel at equally spaced points through the left entrance of the channel. From Fig. 5(a) we notice that many
Figure 5: Calculation of the trajectories of 10000 magnetic beads, whose initial positions were equally spaced across the left entrance of the microfluidic channel. The volumetric flow rate in the microfluidic channel was 1.5 µL/min, the electromagnets are circular with a current of 360 mA and a magnetic yoke made of nickel, the magnetic beads are of the type MyOne® from Dynal Biotech. (a) shows the microfluidic channel seen from above. The grey disks indicate the positions of the inner poles of the microelectromagnets. Each cross in the figure corresponds to a point, where a magnetic bead has settled. In (b) the settling points have been transformed into a settling probability density. Each settling point from (a) have been made the centre of a Gaussian function, which has been scaled with the fluid velocity at the bead entry position in the microfluidic channel, which is proportional to the probability of a bead entering the channel at that point per unit time. The dark parts of the plot correspond to places where the settling probability density is high.

beads settle near the entrance of the channel. This is due to gravity, since the velocity of the beads that are released very close to the bottom of the microfluidic channel is so low that gravity will have a large effect over short distances. However since the fluid velocity near the bottom of the channel is small, the bead in-flux is also small near the bottom of the channel. In other words the in-flux of magnetic beads is low for $z\approx 0$, whereas the in-flux is large for $z\approx z_0/2$. This is reflected in Fig. 5(b) that shows the bead settling probability density across the microfluidic channel. Each of the settling points from Fig. 5(a) has been scaled with the fluid velocity at the entry point of the bead, since the in-flux of magnetic beads at an entry point is proportional to the fluid velocity at that entry point, if the bead concentration is constant. Since the in-flux of magnetic beads in the part of the channel entrance (near the bottom) that would lead to settling points in the beginning of the channel, is low, the settling probability density is not as high in the left part of the channel as might be expected from Fig. 5(a).

The most important feature of Fig. 5, however, is that that the beads clearly tend to settle near the edges inner pole piece of the electromagnets, i.e. where the magnetic field is largest according to Figure 4. This means that an experimentally observed bead-settling pattern would be expected to concentrate around the edges of the inner pole piece of the microelectromagnets.
Figure 6: The plot shows the fluid and bead entrance of the microfluidic channel. The entrance of the microfluidic channel has been divided into four phases corresponding to the position where a bead that started in that phase settled in the microfluidic channel, or if the bead escaped capture. The beads that started near the bottom of the channel is captured first, and correspondingly the beads that start the farthest away from the microelectromagnets are not caught. L is the length of the microfluidic channel.

Figure 6 shows a phase diagram of the entrance of the microfluidic channel, and it shows where beads with different initial positions settle in the microfluidic channel. It is seen how beads released near the sides or bottom of the microfluidic channel are more easily captured in the channel, since the fluid velocity at the release point is small, and thus both gravity and magnetic force will be large compared to the fluid drag. Fig. 6 also allows us to calculate the bead capture efficiency for the microsystem. It is simply the summed probabilities for bead entrance at all the different points in the entrance of the microfluidic channel that correspond to caught beads. In this case the capture efficiency is ~89%.

7. Experiments
We have performed bead capture experiments using the described microfabricated system. While it is difficult to measure bead capture efficiencies and almost impossible to study bead trajectories when the dimensions of the microfluidic channel are large compared to the bead diameter, the bead-settling pattern is readily observed. In the experiments we have used bead concentrations that are large enough to capture a significant number of magnetic beads, but still low enough that interactions between the magnetic beads in the solution are negligible.

Figure 7 shows the bead-settling pattern of such an experiment. The picture is taken after 20 minutes, and it is seen how the beads have settled near the edges of the inner pole region of the square microelectromagnet. It is also seen that the bead concentration is particularly high near the corners of the electromagnet. As the simulations have been carried out for cylindrical electromagnets, the bead accumulation near corners is not predicted. However, as corners concentrate magnetic fields even more than edges this is a reasonable observation.
We have used magnetic beads of the type MyOne® from Dynal Biotech, 1 micron in diameter at a concentration of \( \sim 80 \times 10^3 \) beads/µL, a flow rate of 1 µL/min, the magnetic yoke is made of electroplated nickel, and a current in the electromagnets of 500 mA. The dotted line marks the inner pole of the electromagnet. The magnetic beads are seen as the bright areas close to the corners of the inner pole region of the electromagnets. In colour this would be yellow, since what we are actually seeing is the reflection of the ferrite content of the magnetic beads.

8. Conclusion
We have presented a simulation scheme for the movement and capture efficiency of magnetic beads in a microfluidic channel. Furthermore we have shown that the results of the simulations are in good agreement with experimental data.

In the simulation scheme we have neglected the effect of hydrodynamic and magnetic interactions between magnetic beads, and interactions between beads and channel walls. These effects are discussed in [16]. Also the movement of magnetic beads after they first hit the channel bottom has been neglected.

In [15] another simulation scheme is presented, where the local concentration of magnetic beads in the fluid is treated as a continuous function, and the behaviour of the local bead concentration as a function of time is discussed. Also in that scheme it is found that the beads move towards regions with large magnetic field, so there is good agreement between that simulation scheme and the one presented here, where the movement of single magnetic beads are considered.

References
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