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Journal of Magnetism and Magnetic Materials 293 (2005) 578–583
Journal of magnetism and magnetic materials
www.elsevier.com/locate/jmmm

Theoretical comparison of magnetic and hydrodynamic interactions between magnetically tagged particles in microfluidic systems

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Available online 7 March 2005

Abstract

Magnetic and hydrodynamic interactions between magnetic beads in microfluidic magnetic field gradient filters are compared theoretically and we find that the hydrodynamic interactions are of a longer range and dominate the magnetic ones. Hydrodynamic interactions aid the capturing of particles tagged with magnetic beads as the particles drag each other along, possibly easing requirements on magnetic parameters.

PACS: 85.70.Ay; 47.15.Pn; 47.60.+i; 47.11.+j

Keywords: Microfluidics; Capturing of magnetic beads; Magnetic interaction; Hydrodynamic interaction; Simulation; Drag; Magnetic field; FEMLAB software

1. Introduction

A promising application for magnetic carriers is in lab-on-a-chip and microfluidic systems where specifically functionalized magnetic beads can bind to and single out biomolecules or cells making up tagged composite particles. These particles can then be manipulated by means of magnetic fields. This is being done routinely in macroscopic applications (high-gradient magnetic separation) but potentially is very useful in miniaturized systems.

The technique has been pioneered by Ahn [1] in microfluidics and can be used to separate, filter, and retain species bound to magnetic beads. In laboratory procedures, separation, purification, and filtering steps are crucial and it is an important challenge for lab-on-a-chip development to find viable methods that can be incorporated into microfluidic chips.

Magnetic filtering of beads is done by magnetophoresis where forces arise due to the

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0304-8853/$ - see front matter © 2005 Published by Elsevier B.V.
doi:10.1016/j.jmmm.2005.01.076

inhomogeneous magnetic field created by microstructures that are magnetized by either electromagnets or a permanent magnet. The structures are small so that they make large gradients and if they are made by a soft magnetic material such as permalloy [1] or nickel [2], the gradients vanish as the external field is removed. Thus, it is possible to capture and release particles, and in turn cells or biomolecules, at will. This can then be combined with washing and rinsing steps, making up a specialized laboratory on a single chip.

To design a working system that can be used to manipulate magnetic beads effectively and efficiently, it is important to understand the capturing process. Magnetic beads obviously interact magnetically but here we bring to attention the fact that the beads also influence each other through the motion of the fluid in which they are suspended. In the following, we will introduce the magnetic and hydrodynamic (fluid-mediated) interactions before discussing their relative importance.

We wish to highlight the importance of hydrodynamic interactions in connection with bead capturing. Although the importance of such interactions is acknowledged in the chemical engineering literature in connection with the settling of particle suspensions (see for example [3]), it appears to be overlooked in the context of magnetophoresis. In our opinion, this should be addressed as hydrodynamic interactions can be shown to be important on the basis of general theoretical arguments, Sections 2 and 3. A specific example of this is the illustrative simulation featured in Section 4. Hopefully, these observations can stimulate experimental work investigating the effects of hydrodynamic interactions.

2. Magnetic interaction

Magnetophoresis is the phenomenon that the gradient of a magnetic field gives rise to motion of some object due to a force on the magnetic moment induced by, for example, the same field. The induced magnetic moments also give rise to their own magnetic fields and they can thus interact.

When magnetizable objects (such as superparamagnetic beads) are immersed in an inhomogeneous external magnetic field, $\vec{H}_{\text{ext}}$, they are attracted to magnetic field extrema (maxima) as the field gradient acts with a force [4]

$$\vec{F} = \mu_0 \int (\vec{M} \cdot \vec{\nabla}) \vec{H}_{\text{ext}} \, \mathrm{d}V, \tag{1}$$

where $\vec{M}$ is the magnetization of the object and where we have assumed that the surrounding medium is non-magnetic with the permeability of vacuum.

The presence of magnetizable objects perturbs the magnetic field which in turn modifies both the local magnetic field around other magnetizable objects and changes their magnetization if, for example, they are paramagnetic. This gives rise to an effective interaction.

Restricting ourselves to the simple case of just two objects, we modify Eq. (1) to obtain the force on bead 1 at $\vec{r}_1$:

$$\vec{F}_1 = \mu_0 \int ((\vec{M}_1 + \mathrm{d}\vec{M}_1) \cdot \vec{\nabla})(\vec{H}_{\text{ext}} + \mathrm{d}\vec{H}_2) \, \mathrm{d}V, \tag{2}$$

where $\mathrm{d}\vec{H}_2$ is the modification to the magnetic field due to bead 2 (at $\vec{r}_2$) and $\mathrm{d}\vec{M}_1$ is the change in magnetization of bead 1 this causes.

The modification, $\mathrm{d}\vec{H}_2$, of the magnetic field is to leading order a dipole field and thus falls off as distance to the power -3. In the following, we assume that the magnetic beads are spherical and that the magnetic field is sufficiently homogenous over the scale of a bead diameter, $2a$, that the modified field is that of a dipole,

$$\mathrm{d}\vec{H}_2(\vec{r}) = \frac{\chi}{\chi + 3} \frac{a^3}{|\vec{r}_1 - \vec{r}_2|^3} \times \left(\frac{3(\vec{H}_{\text{ext}}(\vec{r}_2) \cdot (\vec{r} - \vec{r}_2))(\vec{r} - \vec{r}_2)}{(\vec{r} - \vec{r}_2)^2} - \vec{H}_{\text{ext}}(\vec{r}_2) \right), \tag{3}$$

where χ is the material magnetic susceptibility [5]. Furthermore, we assume that the external fields are sufficiently small so that the magnetizations of the beads depend linearly on the local magnetic field,

$$\vec{M} = \frac{3\chi}{\chi+3}\vec{H}. \tag{4}$$

These two assumptions mean that the change in magnetization caused by the presence of a second bead is inversely proportional to the power -3 of the separation between the two beads,

$$\mathrm{d}\vec{M}_1 = 3\left(\frac{\chi}{\chi+3}\right)^2 \frac{a^3}{|\vec{r}_1-\vec{r}_2|^3} \times \left(\frac{3(\vec{H}_{\mathrm{ext}}(\vec{r}_2)\cdot(\vec{r}_1-\vec{r}_2))(\vec{r}_1-\vec{r}_2)}{(\vec{r}_1-\vec{r}_2)^2} - \vec{H}_{\mathrm{ext}}(\vec{r}_2)\right). \tag{5}$$

From Eqs. (2)–(5), we see that the leading correction to the total magnetic force on a bead is that caused by the $(\mathrm{d}\vec{M}_1\cdot\vec{\nabla})\vec{H}_{\mathrm{ext}}$ term when expanding in powers of the separation, $\vec{r}_1-\vec{r}_2$,

$$(\mathrm{d}\vec{M}_1\cdot\vec{\nabla})\vec{H}_{\mathrm{ext}}(\vec{r}_1) = 3\left(\frac{\chi}{\chi+3}\right)^2 \frac{a^3}{|\vec{r}_1-\vec{r}_2|^3} \times \left(\frac{3(\vec{H}_{\mathrm{ext}}(\vec{r}_2)\cdot(\vec{r}_1-\vec{r}_2))((\vec{r}_1-\vec{r}_2)\cdot\nabla)\vec{H}_{\mathrm{ext}}(\vec{r}_1)}{(\vec{r}_1-\vec{r}_2)^2} - (\vec{H}_{\mathrm{ext}}(\vec{r}_2)\cdot\nabla)\vec{H}_{\mathrm{ext}}(\vec{r}_1)\right). \tag{6}$$

This term is of order -3 in the separation, which is a quite rapid decay with increasing separation, though acting over a much longer range than an induced dipole–dipole interaction, for example. The demagnetization associated with a sphere limits the influence of the susceptibility; the prefactor, $3\chi^2/(\chi+3)^2$, is bounded above by 3. Lastly, the term consists of a somewhat complicated derivative taking into account the direction of the separation vector and the directions of the external magnetic field at the centre of both spherical beads and the magnitude of the magnetic field squared. The important point for the present is, however, that the interaction term is of order –3 in the separation.

Similarly, the remaining terms from the expansion of Eq. (2) are of fourth order, $(\vec{M}_1\cdot\vec{\nabla})\mathrm{d}\vec{H}_2$, and seventh order, $(\mathrm{d}\vec{M}_1\cdot\vec{\nabla})\mathrm{d}\vec{H}_2$, respectively as $\mathrm{d}\vec{H}_2$ and $\mathrm{d}\vec{M}_1$ each contribute a dependence on separation to the power -3 and differentiation contributes an additional power -1. The explicit forms of these terms are

$$(\vec{M}_1\cdot\vec{\nabla})\mathrm{d}\vec{H}_2(\vec{r}_1) = 3\left(\frac{\chi}{\chi+3}\right)^2 \frac{a^3}{(\vec{r}_1-\vec{r}_2)^4} \times \left(-\frac{15(\vec{H}_{\mathrm{ext}}(\vec{r}_2)\cdot(\vec{r}_1-\vec{r}_2))(\vec{H}_{\mathrm{ext}}(\vec{r}_1)\cdot(\vec{r}_1-\vec{r}_2))(\vec{r}_1-\vec{r}_2)}{|\vec{r}_1-\vec{r}_2|^3} + \frac{3(\vec{H}_{\mathrm{ext}}(\vec{r}_1)\cdot\vec{H}_{\mathrm{ext}}(\vec{r}_2))(\vec{r}_1-\vec{r}_2)}{|\vec{r}_1-\vec{r}_2|} + \frac{3(\vec{H}_{\mathrm{ext}}(\vec{r}_1)\cdot(\vec{r}_1-\vec{r}_2))\vec{H}_{\mathrm{ext}}(\vec{r}_2)}{|\vec{r}_1-\vec{r}_2|}\right) \tag{7}$$

and

$$(\mathrm{d}\vec{M}_1\cdot\vec{\nabla})\mathrm{d}\vec{H}_2(\vec{r}_1) = 3\left(\frac{\chi}{\chi+3}\right)^3 \frac{a^6}{|\vec{r}_1-\vec{r}_2|^7} \times \left(-\frac{12(\vec{H}_{\mathrm{ext}}(\vec{r}_2)\cdot(\vec{r}_1-\vec{r}_2))^2(\vec{r}_1-\vec{r}_2)}{|\vec{r}_1-\vec{r}_2|^3} + \frac{3(\vec{H}_{\mathrm{ext}}(\vec{r}_2)\cdot(\vec{r}_1-\vec{r}_2))\vec{H}_{\mathrm{ext}}(\vec{r}_2)}{|\vec{r}_1-\vec{r}_2|} - \frac{3\vec{H}_{\mathrm{ext}}(\vec{r}_2)^2(\vec{r}_1-\vec{r}_2)}{|\vec{r}_1-\vec{r}_2|}\right). \tag{8}$$

Again, the power dependences, -4th and -7th powers, are evident combined with involved geometric factors taking into account magnetic field orientations at the two beads and the orientation of the line of separation and the magnetic field squared. However, the point to note is that the exact form of these interaction terms is unimportant. What is always true is that the leading term is of order -3 in the separation and that this is true for any shape of bead as the modification of the magnetic field is a dipole field to leading order. We have tacitly assumed that the influence on the first bead from the change of magnetization of the second bead due to the field from first bead and any such higher order interactions are negligible as it is of even higher order in the separation than the leading term above.

3. Hydrodynamic interaction

Movement of a particle such as a magnetic bead through a viscous liquid creates a disturbance to the fluid flow, a kind of wake, that affects nearby particles, dragging them along. The force acting on a particle is balanced by viscous forces from the fluid, transferring momentum to the fluid. Balance is attained after an acceleration phase typically much shorter than milliseconds for aqueous media and micrometre-sized particles.

As the flow in microfluidic channels almost invariably happens at very low Reynolds numbers, the motion of fluid under the action of a force distribution $\vec{f}$ is described by the linear Stokes equation for fluid velocity $\vec{v}$ and pressure p:

$$\rho \frac{\partial \vec{v}}{\partial t} = -\vec{\nabla} p + \eta \nabla^2 \vec{v} + \vec{f}, \tag{9}$$

where η is the viscosity and ρ the fluid density. Mathematically, a Green's function representing the flow due to the action of a point force can be used to describe the influence of a bead being moved through liquid. For a liquid of viscosity η, the flow due to a force $\vec{f}$ at the origin is [6]

$$\vec{v} = \frac{1}{8\pi\eta} \left(\frac{\vec{f}}{r} + \frac{(\vec{f} \cdot \vec{r})\vec{r}}{r^3} \right). \tag{10}$$

This simple expression assumes an unbounded fluid whereas the flow in a microfluidic channel, e.g. as part of a lab-on-a-chip, is always near to at least one wall. The presence of a wall modifies the flow and this can also be described by a Green's function approach [6,7]. In this approach, the wall contributes image flow singularities; a point force, a source dipole, and a force dipole, behind the wall which ensure that the flow fulfils the no-slip boundary condition. This is illustrated on Fig. 1 where a force (indicated by the dark arrow) is acting on a particle (dark disk) in the direction parallel to the wall resulting in a flow (smaller arrows) that drags fluid along with the particle. Behind the wall (shaded area) there is a virtual flow due to the singularities there (grey disk), ensuring that the flow vanishes at the boundary.

However, the observation we need to make here is that the perturbation of the flow falls off with distance to the point force to the power –1. Objects passively following the flow, such as other beads, will be moved eventhough they are far away. An effective force law with a reciprocal distance dependence is an unusually slow spatial decay, for example Coulomb's law from electrostatics has a one-over-distance-squared force dependence, as does gravitational attraction. At large distances, any power –1 force law will dominate any law with power –2 or lower. Furthermore, the force going into Eq. (10) is the total external, i.e. magnetic, force which means that the relative magnitude of

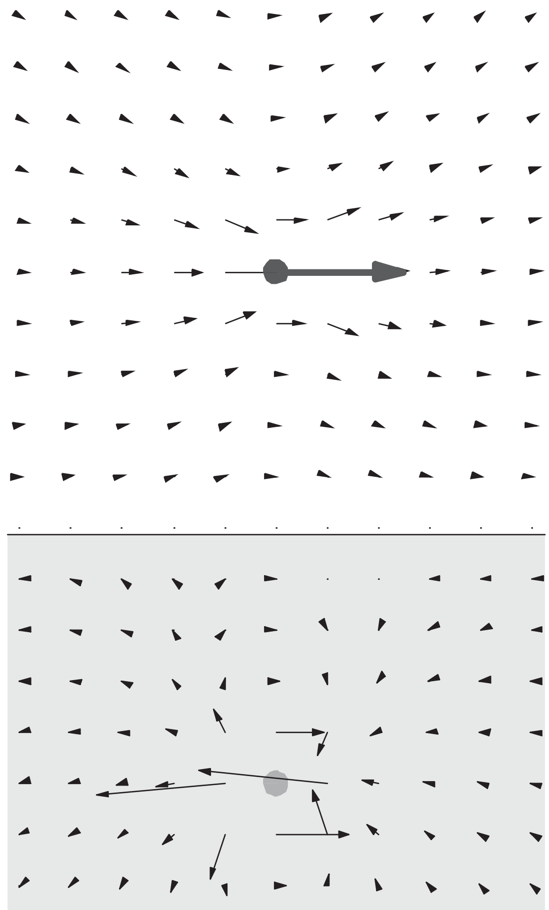

Fig. 1. Real flow (small arrows in white region) due to a point force (the large vector arrow) parallel to a wall (grey region) acting on a fluid. In order to fulfil the no-slip boundary condition at the wall, some image singularities (the grey disk) are placed behind the wall. This contributes a virtual flow in the area behind the wall (grey) that cancels the flow due to the real point force at the wall. The virtual flow is a mathematical device that does not correspond to actual fluid motion.

the hydrodynamic and the magnetic interactions cannot be changed.

4. Bead motion

It is possible to compare the importance of magnetic and hydrodynamic interactions by simulation in the simple case of just two beads moving in a two-dimensional section of an infinitely wide channel. The magnetic field and field gradient and the fluid flow are all simulated with the FEMLAB® finite element software package [8]. We then solve for the movement of the beads as their velocity relative to the surrounding fluid is determined by the sum of the external forces and viscosity. The external forces are the magnetic ones from the applied magnetic field and the field from other beads. With the aid of the Green's functions for the flow near a wall, the fluid flow due to the forces on each bead is calculated and this, in turn, describes the movement of beads relative to the fluid channel.

In the simulations, we assume 5 μm beads that move in a 100 μm wide channel under the influence of the field gradients generated by strips 10 μm wide 300 μm long of magnetizable material with permeability $1000\mu_0$, and separated by 40 μm non-magnetic patches. Applying a magnetic field, $\vec{H}_{\text{ext}} = 40000\ \text{A/m}$, along their lengths magnetizes the strips. The channel parameters are chosen so that they are representative of actual microfluidic devices. The results are insensitive to the value of the strip material permeability as long as it is much larger than that of vacuum, furthermore, the magnetic field chosen is of the order of magnitude one can realize with either small electromagnets or external permanent magnets. Finally, the important parameter for capturing is the ratio between the fluid drag and the magnetic force, i.e. the fluid velocity over the gradient of the magnetic field squared.

The motion of two beads is shown in Fig. 2 in two situations: when there is no hydrodynamic interaction between the beads, and when there is one. The beads are placed somewhat apart but near the centre of the channel where the particle flux is the highest but the magnetic field gradient vanishes due to symmetry. In the case without interactions, one of the beads is not retained against the fluid flow (1 mm/s to the right, water).

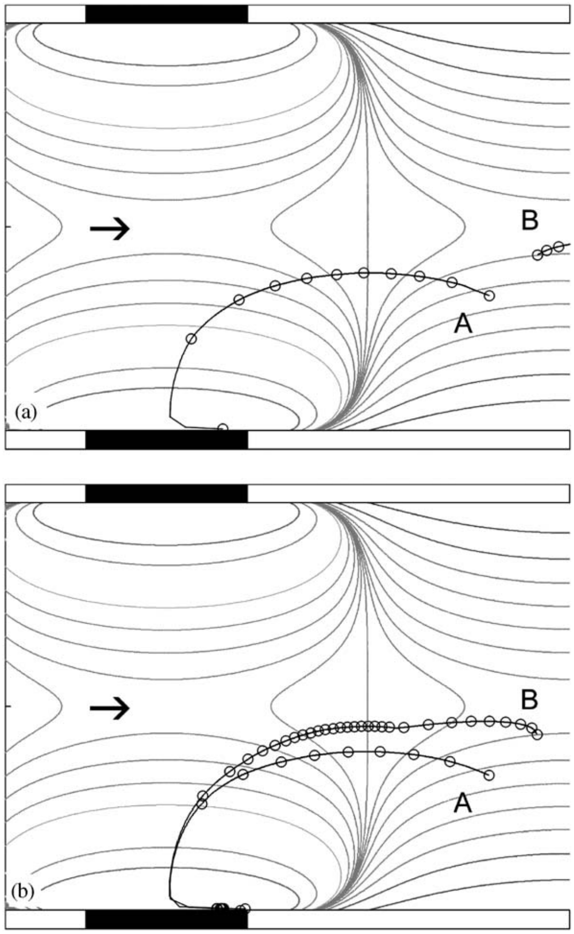

Fig. 2. (a) Motion of two beads, A and B (black lines with open circles), under the influence of a magnetic field gradient (contours, not equidistant) and a rightward-moving fluid flow (arrow) but in the absence of hydrodynamic interactions. Parts of the strips of magnetic material nearest to the channel are indicated by black rectangles and the channel walls and non-magnetic surroundings by white rectangles. Bead B is not caught as the local magnetic field gradient is small and because the fluid counter flow is too strong. The beads are placed initially at (20, 33 μm) and (23, 43 μm) in a coordinate system with origin at the channel wall by the centre of the lower magnetic strip. The figure covers an area 35 μm wide and 110 μm high. The maximum flow velocity is 1 mm/s. (b) Same simulation as (a) except that as the beads move they drag fluid along, in turn dragging each other, so both beads are caught. When the beads are close, they interact magnetically, however this is a very small effect and not visible on these figures.

In the latter case, the flow due to the one bead carries the other bead with it so that both beads are caught. This illustrates that the presence of interactions leads to qualitatively different results. Careful examination of the figure reveals that the moment the first bead is caught, the flow pattern changes and the other bead starts following a slightly different trajectory. These two observations illustrate the importance of including the effect on fluid flow due to the motion of other beads.

Magnetic interaction has been included in the simulations but it only contributes insignificantly. It is only the presence or absence of hydrodynamic interactions that gives qualitative differences.

5. Discussion

The much slower spatial decay of interactions mediated by fluid flow as compared with the direct magnetic–magnetic interactions means that the hydrodynamic interactions cannot be ignored in studies of the capturing dynamics: the -1 power law dominates the -3 power law. The fluid flow due to the motion of beads means that, for example, beads near symmetry points where gradients vanish can be driven into higher gradient regions, speeding up capturing.

We have here only studied the capturing of bead pairs but it appears reasonable that the combined effect of many is important and, in fact, crucial for reducing the requirements on magnetic parameters.

A complementary approach for studying the hydrodynamic interactions in capturing is to model the magnetic beads as a continuous concentration in the fluid [9]. The equation of motion for the fluid is then solved with a volume force density derived from magnetic parameters and the bead concentration. While we here consider few beads, the complementary approach models many. This complementary method does not include interactions between beads as such but it incorporates the fluid motion and, with it, bead convection. With that approach the author of Ref. [9] finds that fluid motion and particle convection are major mechanisms in capturing, which is consistent with our findings above.

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