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Permanent magnet system to guide superparamagnetic particles

Olga Baun, Peter Blümler *

Institute of Physics, University of Mainz, Germany

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ABSTRACT

A new concept of using permanent magnet systems for guiding superparamagnetic nano-particles on arbitrary trajectories over a large volume is proposed. The basic idea is to use one magnet system which provides a strong, homogeneous, dipolar magnetic field to magnetize and orient the particles, and a second constantly graded, quadrupolar field, superimposed on the first, to generate a force on the oriented particles. In this configuration the motion of the particles is driven predominantly by the component of the gradient field which is parallel to the direction of the homogeneous field. As a result, particles are guided with constant force and in a single direction over the entire volume. The direction is simply adjusted by varying the angle between quadrupole and dipole. Since a single gradient is impossible due to Gauß' law, the other gradient component of the quadrupole determines the angular deviation of the force. However, the latter can be neglected if the homogeneous field is stronger than the local contribution of the quadrupole field.

A possible realization of this idea is a coaxial arrangement of two Halbach cylinders. A dipole to evenly magnetize and orient the particles, and a quadrupole to generate the force. The local force was calculated analytically for this particular geometry and the directional limits were analyzed and discussed. A simple prototype was constructed to demonstrate the principle in two dimensions on several nano-particles of different size, which were moved along a rough square by manual adjustment of the force angle.

The observed velocities of superparamagnetic particles in this prototype were always several orders of magnitude higher than the theoretically expected value. This discrepancy is attributed to the observed formation of long particle chains as a result of their polarization by the homogeneous field. The magnetic moment of such a chain is then the combination of that of its constituents, while its hydrodynamic radius stays low.

A complete system will consist of another quadrupole (third cylinder) to additionally enable scaling of the gradient/force strength by another rotation. In this configuration the device could then also be used as a simple MRI machine to image the particles between movement intervals. Finally, a concept is proposed by which superparamagnetic particles can be guided in three-dimensional space.

1. Introduction

Moving superparamagnetic particles (SPP) remotely and without contact along arbitrarily chosen trajectories inside biological systems at reasonable speeds could assist many therapeutic or diagnostic or jointly theranostic methods [1,2]. These minimally invasive applications are summarized in recent reviews: One major field is magnetic drug targeting (MDT) [3] where highly potent pharmaceuticals are concentrated at the disease site (tumor, infections, thrombi, etc.) with minimized deleterious side effects. The prime example are SPPs with chemotherapeutics or genetic vectors as a payload in cancer therapy [4,5]. Another interesting idea is to use local concentrations of SPPs to destroy tissue via local heating using strong AC-fields (aka "hyperthermia") [6]. Finally, magnetic forces are also used to separate magnetically labeled materials from mixtures either for diagnostics [7] or purification purposes [8,9].

Another medical application of magnetic particles has to be mentioned, which is the use of mainly superparamagnetic iron oxide (SPIO) nanoparticles as contrast agents in clinical MRI (**mag**netic **r**esonance **i**maging). This is a well-established methodology [10–12] utilizing the local disturbance of the magnetic field in the vicinity of SPPs with strong influences on the relaxation times of nearby nuclear spins. The MRI signal then allows the detection of very low concentrations [13] and surface functionalization also enables molecular targeting [12].

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* Corresponding author.
E-mail address: bluemler@uni-mainz.de (P. Blümler).

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In the last two decades great advances have been made in all these applications of SPPs due to the flourishing nanotechnology. However, most of the research in this field was dedicated to synthesis and biomedical modifications of the nanoparticles [1,14–16]. Only until recently more sophisticated magnetic steering methods were developed, as for many demonstrations it was sufficient to apply simple bar magnets to test tubes. However, a magnet applied from only one side has the inherent problem that the magnetic field changes non-linearly over distance exerting a non-constant force on the particles. For applications on animals or even humans this approach is therefore very limited, because the forces increase towards the surface of the magnet and hence the surface of the organism. This approach makes controlled movements inside deeper tissues very problematic if not impossible. Additionally, a variation of directions can be difficult to achieve as access might be limited depending on the position on the body. Therefore, the main application has been to retain otherwise free circulating nanoparticles in regions close to the skin by placing strong magnets in direct vicinity of the disease focus [3].

Again, this approach is limited to one direction over short distances, r, because a single magnet can only pull particles towards it with a field strength that spatially decays with r^{-3}, and hence its gradient/force drops with r^{-4}. To overcome these severe limitations clever designs of e.g. pushing magnets [3,17] and optimized magnetization distribution [18] have been demonstrated. They are nicely reviewed in [3]; and in a similar review by Shapiro et al. [19] the current state of art is concluded as follows: *"Overall, one of the biggest open challenges in magnetic delivery is precisely targeting deep tissue targets – there are as yet no imaging and actuation systems that can achieve the external-magnet deep-focusing (...). To achieve deep targeting requires solution of, at least, four major issues: (1) sufficient magnetic fields/forces deep in the body, (2) real-time imaging, (3) sophisticated control algorithms, and (4) mathematical modeling of the carrier motion in vivo...*"

The question is: Can a magnet system for such a purpose be sketched and what general properties must it have? Guiding particles in more than one direction certainly needs the use of a (partially) surrounding magnet system [20–23], because single-sided magnet systems do not have sufficient degrees of freedom to generate controlled fields inside the body, and the rapid field decay would also make these magnets either too weak or too bulky. Due to the last (weight/size) argument the magnet system should probably also be made from permanent magnets. Permanent magnets have several properties which make them more practical than electromagnets for MDT applications. First of all their magnetic energy is permanently stored hence they do not need electrical power. To highlight this argument, one can estimate that the magnetic field produced by about 1 cm^3 of modern rare earth magnets (e.g. NdFeB) would require electric power in the order of some kW when produced by an electromagnet, ignoring the extra power for cooling. Other advantages might be price and comfort of use. However, their permanent magnetic field is also regarded as a disadvantage because it cannot be regulated or simply switched off. Obviously this is possible by using electromagnets, however it is not as simple as it sounds, because thermal changes in resistance and geometry as well as the large inductance of such coils introduce severe nonlinearities in real applications [21].

While the argument of nonadjustable magnetic strength holds for single permanent magnets, they can be arranged to larger assemblies which then allow for magnetic field scaling typically by mutual rotation [24–26]. Due to the extreme magnetic hardness of modern rare-earth permanent magnets, the resulting fields are reproducible and easy to calculate theoretically or at least simply to calibrate. For all these reasons it should be most favorable in terms of strength per weight, power consumption and controllability to build magnetic guiding devices for MDT from permanent magnets.

We present a concept of how a permanent magnet device can, over large volumes, generate strong homogeneous forces which can be precisely controlled in strength and direction. These forces are described by simple equations which in principle need no adjustments or time-dependent corrections. At worst the magnetic field of a real device, which of course will deviate from theory, needs to be measured once and taken into account. In addition, the proposed instrument can be used for MRI by adding a tuned rf-coil. This would allow for imaging the particles at intervals during the moving process to control a successful operation in situ and *in vivo*. For these reasons the instrument was nicknamed "MagGuider" (**Mag**netic **Guid**e and Scann**er**).

To demonstrate the concept, a simplified prototype was constructed which clearly showed that SPPs can indeed be guided in two dimensions in a controlled manner. However, the full potential of all the presented ideas has not yet been exploited.

2. Concepts and theory

2.1. Magnetic force

In order to move a SPP from a position, $\vec{r}$, it has to experience a magnetic force,

$$\vec{F}_{\mathrm{mag}}(\vec{r}) = \vec{\nabla}(\vec{m}(\vec{r}) \cdot \vec{B}(\vec{r})). \tag{1}$$

This is the gradient of the magnetic field, $\vec{B}$[T], acting on a particle with a magnetic moment, $\vec{m}$ [Am^2]. The magnetic moment of a particle can be calculated by taking the volume integral of its mass magnetization, $\vec{M}$[Am^2/kg or emu/g]. For a homogeneous magnetization this amounts to

$$\vec{m} = \rho V \vec{M} = \frac{\rho V \chi}{\mu_0}\vec{B} \quad \text{and} \quad \lim_{B\to\infty} \vec{m} = \rho V \vec{M}_{\mathrm{sat}}, \tag{2}$$

where ρ is the density [$\mathrm{kg/m}^3$] and V the volume [m^3] of the particle. The dependence of the magnetization $M = M_{\mathrm{R}} + M(B)$ on the applied magnetic field can be complex and generally has a hysteresis. Typically $M(B)$ is approximated by the monotonic Langevin-function and the remnant part, M_{R}, is ideally zero or very close to zero for SPP and saturates, M_{sat}, at high fields. Alternatively, the magnetic susceptibility, χ [dimensionless], can be used to characterize SPPs by their bulk properties. Furthermore, the nature of SPPs as small more-or-less isolated particles will cause an orientation of their magnetic moment with the local magnetic field, hence

$$\vec{m} \parallel \vec{B} \quad \text{or} \quad \vec{m} \cdot \vec{B} = |\vec{m}|\,|\vec{B}|. \tag{3}$$

Therefore, Eq. (1) can be simplified to

$$\vec{F}_{\mathrm{mag}}(\vec{r}) = |\vec{m}(\vec{r})| \ \vec{\nabla}|\vec{B}(\vec{r})|, \tag{4}$$

because the spatial variation of the magnetic moment inside a particle does not contribute to the force or $\vec{\nabla}|\vec{m}| \approx 0$. The fact that the force depends on the gradient of the norm of $\vec{B}$ explains why the particles move from low to high field intensities (independent of the field polarity) [3].

The magnetic force on single SPIOs is typically in the range from 10^{-25} to 10^{-11} N [3], so it is advisable to maximize $|\vec{m}|$ as well as $\vec{\nabla}|\vec{B}|$.