

Understanding the dynamics of superparamagnetic particles under the influence of high field gradient arrays

This content has been downloaded from IOPscience. Please scroll down to see the full text.

Download details:

IP Address: 86.191.41.191

This content was downloaded on 31/01/2017 at 19:33

Manuscript version: Accepted Manuscript

Barnsley et al

To cite this article before publication: Barnsley et al, 2017, Phys. Med. Biol., at press:

<http://dx.doi.org/10.1088/1361-6560/aa5d46>

This Accepted Manuscript is copyright Copyright 2017 Institute of Physics and Engineering in Medicine

As the Version of Record of this article is going to be / has been published on a gold open access basis under a CC BY 3.0 licence, this Accepted Manuscript is available for reuse under a CC BY 3.0 licence immediately.

Everyone is permitted to use all or part of the original content in this article, provided that they adhere to all the terms of the licence <https://creativecommons.org/licences/by/3.0>

Although reasonable endeavours have been taken to obtain all necessary permissions from third parties to include their copyrighted content within this article, their full citation and copyright line may not be present in this Accepted Manuscript version. Before using any content from this article, please refer to the Version of Record on IOPscience once published for full citation and copyright details, as permissions will likely be required. All third party content is fully copyright protected, unless specifically stated otherwise in the figure caption in the Version of Record.

When available, you can view the Version of Record for this article at:

<http://iopscience.iop.org/article/10.1088/1361-6560/aa5d46>

Understanding the dynamics of superparamagnetic particles under the influence of high field gradient arrays

Lester C Barnsley¹, Dario Carugo^{1,2}, Miles Aron¹ and Eleanor Stride¹

¹ Institute of Biomedical Engineering, Department of Engineering Science, University of Oxford, Old Road Campus Research Building, Oxford, OX3 7DQ, UK

² Faculty of Engineering and the Environment, University of Southampton, University Road, Southampton, SO17 1BJ, UK

E-mail: eleanor.stride@eng.ox.ac.uk

Abstract. The aim of this study was to characterize the behaviour of superparamagnetic particles in magnetic drug targeting (MDT) schemes. A 3-dimensional mathematical model was developed, based on the analytical derivation of the trajectory of a magnetized particle suspended inside a fluid channel carrying laminar flow and in the vicinity of an external source of magnetic force. Semi-analytical expressions to quantify the proportion of captured particles, and their relative accumulation (concentration) as a function of distance along the wall of the channel were also derived. These were expressed in terms of a non-dimensional ratio of the relevant physical and physiological parameters corresponding to a given MDT protocol.

The ability of the analytical model to assess magnetic targeting schemes was tested against numerical simulations of particle trajectories. The semi-analytical expressions were found to provide good first-order approximations for the performance of MDT systems in which the magnetic force is relatively constant over a large spatial range.

The numerical model was then used to test the suitability of a range of different designs of permanent magnet assemblies for MDT. The results indicated that magnetic arrays that emit a strong magnetic force that varies rapidly over a confined spatial range are the most suitable for concentrating magnetic particles in a localized region. By comparison, commonly used magnet geometries such as button magnets and linear Halbach arrays result in distributions of accumulated particles that are less efficient for delivery.

The trajectories predicted by the numerical model were verified experimentally by acoustically focusing magnetic microbeads flowing in a glass capillary channel, and optically tracking their path past a high field gradient Halbach array.

Keywords: Magnetic drug targeting, Halbach array, Magnetic nanoparticle, Acoustic radiation pressure, Particle trajectory, Targeted drug delivery

Submitted to: *Phys. Med. Biol.*

Understanding the dynamics of superparamagnetic particles

1. Introduction

Targeted delivery of therapeutic agents has, in recent years, been an active area of research, with magnetic drug targeting (MDT) being proposed as a particularly promising technique for localizing therapy efficiently. Magnetically-loaded drug carriers that can be non-invasively manipulated by an externally applied field are potentially useful for a range of therapeutic or diagnostic applications where an increased local concentration at a specific treatment site has an enhanced effect (Lübbe et al., 1996, 1999; Alexiou et al., 2000; Lübbe et al., 2001; Pankhurst et al., 2003; Dobson, 2006). There are, however, a number of challenges to overcome before the technique can be considered clinically viable (Grief and Richardson, 2005; Laurent et al., 2014; Shapiro et al., 2015; Schleich et al., 2015). In particular, while it is well recognized that the carrier formulation needs to be optimized for the application (Pankhurst et al., 2009; Mangual et al., 2010; Stride et al., 2009; Pouponneau et al., 2011), it is increasingly apparent that the external magnet needs to be designed to generate a sufficient magnetic force over the target range to remove a useful proportion of carrier particles from the hydrodynamic flow of the circulatory system (Driscoll et al., 1984; Hayden and Häfeli, 2006; Sarwar et al., 2012; Owen et al., 2014). Also, in order to optimize MDT as a minimally-invasive drug delivery strategy, external magnets should be designed to minimize off-target side effects, and maximize the efficiency of drug delivered to the target tissue.

For this reason, it is important to understand the performance of magnetic systems by considering the dynamics of superparamagnetic particles in flow as they experience the force applied by a spatially-varying magnetic field. Mathematical modelling of magnetic particles in transport has previously been used to study parameters related to the capture efficiency (Cregg et al., 2008; Nandy et al., 2008; Mangual et al., 2010; Garraud et al., 2016), particle trajectories (Gleich et al., 2007; Sharma et al., 2015; Owen et al., 2015; Tehrani et al., 2015; Garraud et al., 2016; Zhou and Wang, 2016), local concentration variations (Cao et al., 2012; Cherry and Eaton, 2014), extravasation (Nacev et al., 2011a) and combinations of these (Bose and Banerjee, 2015a), as a function of the magnetic properties of the particle formulation, external magnet design or factors related to the physiological flow. Understanding the dynamics of particle capture and accumulation in magnetic drug targeting applications can be particularly useful for informing the design and optimization of magnetic assemblies (Nacev et al., 2011a; Shapiro et al., 2014, 2015). However, magnet optimization is usually assessed in terms of the total magnetic force generated over a spatial range of interest (Alexiou et al., 2006; Hayden and Häfeli, 2006; Häfeli et al., 2007; Takeda et al., 2007; Sarwar et al., 2012; Barnsley et al., 2015, 2016), and simulation studies often do not consider whether this leads to optimal delivery to the target volume.

In this paper, we develop a mathematical model for assessing the performance of a given magnetic targeting scheme, in terms of the capture efficiency, accumulation (concentration) distribution of captured particles and trajectories of magnetic particles

Understanding the dynamics of superparamagnetic particles

influenced by different sources of magnetic field, over a range of physiologically relevant flow rates. We consider first a simple spatial distribution for magnetic force and derive an analytical expression for the trajectory of a magnetized particle in a laminar flow in three dimensions. We then use this to derive a semi-analytical expression for the capture efficiency and accumulation distribution in terms of a non-dimensional ratio that encapsulates the relevant physical and physiological parameters for a given MDT scheme. Our aim is to provide a simple metric for gauging the potential effectiveness of a magnetic targeting scheme for a given target. We subsequently expand this model to numerically simulate particle trajectories in the presence of arbitrary magnetic arrangements and verify our predicted trajectories experimentally by acoustically focusing magnetic microbeads in a flow channel to a single trajectory, and observing how their paths deflect in the presence of a high-field gradient magnetic Halbach array. Finally, we examine simulated accumulation distributions to assess the relative performance of magnetic designs that have previously been considered for drug targeting applications (Hayden and Häfeli, 2006; Häfeli et al., 2007; McBain et al., 2008; Barnsley et al., 2016).

2. Methods

2.1. Mathematical formulation

We consider a spherical, superparamagnetic particle suspended in a flowing liquid under the influence of an approximately constant magnetic force generated by a linear Halbach array (figure 1). The magnetic force along the channel is simplified to a step-function bounded by a range, x_M from a starting position, x_0 and acting in the $-z$ -direction

$$\mathbf{F}_M(x) = \begin{cases} -|F_M|\hat{\mathbf{k}} & x_0 \leq x \leq x_0 + x_M \\ 0 & x_0 > x > x_0 + x_M \end{cases} \quad (1)$$

In a steady flow, the forces acting on the particle are given by

$$m_{\text{eff}} \frac{d\mathbf{v}}{dt} = \mathbf{F}_M + \mathbf{F}_g + \mathbf{F}_{\text{buoy}} + \mathbf{F}_D, \quad (2)$$

where m_{eff} is the mass of the particle including the added mass, \mathbf{v} is the particle velocity and the four force terms on the right-hand side of the equation describe the magnetic force, gravity, buoyancy, and the fluid drag force respectively. We assume that $\mathbf{F}_M \gg \mathbf{F}_g + \mathbf{F}_{\text{buoy}}$ and m_{eff} is sufficiently small that the particle reaches terminal velocity extremely rapidly (so $m_{\text{eff}} dv/dt \approx 0$). In a cylindrical channel carrying a laminar flow and positioned so that the central axis coincides with the x -axis, the flow velocity of the fluid is given by

$$\mathbf{v}_F = 2v_A \left(1 - \left(\frac{y}{R} \right)^2 - \left(\frac{z}{R} \right)^2 \right) \hat{\mathbf{i}}, \quad (3)$$

where v_A is the mean fluid flow velocity and R is the radius of the channel. Assuming a Newtonian fluid, the drag force on the spherical particle is given by Stoke's law:

$$\mathbf{F}_D = 6\pi\mu r (\mathbf{v}_F - \mathbf{v}), \quad (4)$$

Understanding the dynamics of superparamagnetic particles

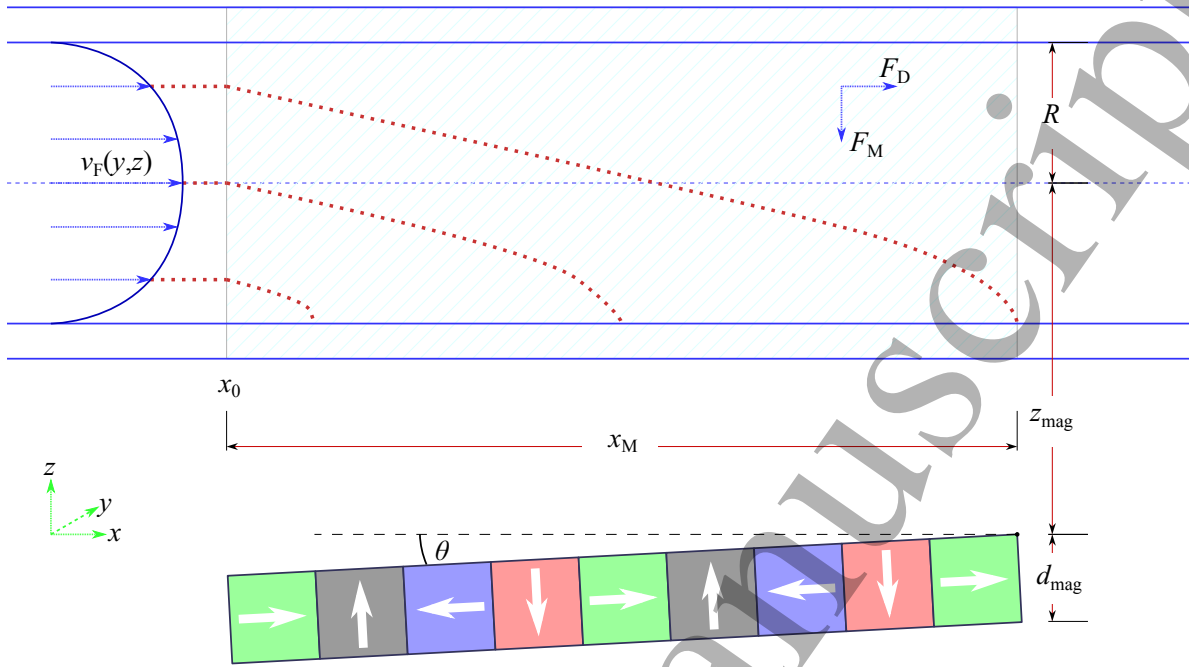


Figure 1. The trajectories of particles within a flow channel of radius, R were calculated numerically. Flow was in the x -direction and the largest component of the magnetic field was parallel to the z -axis. The particles migrate under the influence of a drag force, a magnetic force, gravity and buoyancy. Unless otherwise stated, the magnetic field was simulated assuming a nine-element, linear Halbach array, set z_{mag} from the centre of the flow channel. The shading highlights the spatial region bounded by $x_0 \leq x \leq x_0 + x_M$ in (1). The magnet was allowed to tilt around the trailing edge by θ , which is defined as the angle between the upper surface of the magnet and the bottom of the channel. Unless otherwise stated, $\theta = 0$ and the magnet surface was parallel to the channel.

where μ is the dynamic viscosity of the fluid, r is the particle radius. Combining (2) and (4) gives

$$\mathbf{v} = \mathbf{v}_F + \frac{\mathbf{F}_M}{6\pi\mu r} = v_F \hat{\mathbf{i}} + v_z \hat{\mathbf{k}}. \quad (5)$$

The time-dependence of the position components, $x(t)$ and $z(t)$ is then determined by integrating the velocity components in (5) and setting a starting position vector described by $\mathbf{r}(t=0) = (x_0, y, z_0)$, resulting in

$$\begin{aligned} z(t) &= z_0 + v_z t \\ x(t) &= x_0 + 2v_A t \left(1 - \frac{1}{R^2} \left(\frac{1}{3} (v_z t)^2 + z_0 v_z t + y^2 + z_0^2 \right) \right). \end{aligned} \quad (6)$$

We assume a no-slip condition so that the final resting position of the particle coincides with where the particle makes contact with the bottom surface of the wall (as the external force is directed towards $-z$), which occurs when $z(t_f) = z_f = -R\sqrt{1 - \left(\frac{y}{R}\right)^2}$. Therefore, the final resting position is given by

$$x_f - x_0 = 2 \frac{v_A}{v_z} R \left(\left(\frac{z_f}{R} \right)^2 \left(\frac{z_f - z_0}{R} \right) - \frac{1}{3} \left(\left(\frac{z_f}{R} \right)^3 - \left(\frac{z_0}{R} \right)^3 \right) \right), \quad (7)$$

Understanding the dynamics of superparamagnetic particles

5

which has one real solution for z_0 . The condition for which a particle can be considered to be magnetically retained is that the final resting position is within the bounds of the range of magnetic force, i.e. $x_f - x_0 \leq x_M$.

We define the capture efficiency as the proportion of magnetized particles injected into the flow channel that are retained by the magnet. The capture efficiency was determined numerically by considering the final resting positions of an ensemble of particles initially distributed evenly about the cross section of the channel at the starting position, x_0 . This particular case is analogous to a “capture cross-section” (Cregg et al., 2008), i.e. the proportion of streamlines that terminate under the influence of the magnet. Other initial distributions are considered in Appendix C. A number of different combinations of parameters were tested and, in all cases, the capture efficiency was well described by the following power law

$$\text{C.E.}(x_M) = A \left(\frac{v_z x_M}{v_A R} \right)^{0.522} \times 100\%, \quad (8)$$

where $A = 0.601$ and assuming that C.E. does not exceed 100%. (This expression has a similar form to one derived for a two-dimensional case by Nandy *et al* (Nandy et al., 2008), though their equation has an additional component which is sensitive to the spatial variations of the field source they considered). The accumulation distribution, which we define as the proportion of particles that accumulate in a range of positions between $x \pm \frac{1}{2}dx$, is then

$$\frac{d\text{C.E.}(x)}{dx} = 0.31 \left(\frac{v_z}{v_A R} \right)^{0.522} x^{-0.478}, \quad (9)$$

and has units m^{-1} .

2.2. Numerical simulations

Typically, the magnetic force profile of a realistic magnetic system is not well described as a step-function. In order to predict the capture efficiency and accumulation distribution in MDT situations with a more physiologically relevant set of flow conditions and physically attainable magnetic forces, numerical simulations were performed to generate the trajectories of particles in a flow channel, under the influence of a position-dependent magnetic force. Simulations were performed using console applications written in the C# programming language (Microsoft Corporation, Redmond, WA, USA). Numerical simulations can be performed in 3-D with a much higher number of particles than comparable models solved using finite element methods (which can often be computationally prohibitive or highly mesh-sensitive and inaccurate when solving for fluid flow fields in 3-D geometries (Nacev et al., 2011a; Barnsley et al., 2016)); typical simulations involving 2000 particle trajectories and 14000 unique time iterations completed in 2 hours 40 minutes on a computer with an Intel(R) Core(TM) i7 processor and 8 GB RAM. The trajectories were determined at each time interval, Δt by updating the position, $\mathbf{r}_{i+1} = \mathbf{r}_i + \mathbf{v}\Delta t$, with \mathbf{v} calculated from an expression of a similar form to

Understanding the dynamics of superparamagnetic particles

(5), but also taking into account gravity, buoyancy, and the spatial variation of \mathbf{F}_M :

$$\mathbf{v} = \mathbf{v}_F(\mathbf{r}_i) + \frac{\mathbf{F}_M(\mathbf{r}_i) + \mathbf{F}_g + \mathbf{F}_{\text{buoy}}}{6\pi\mu r}. \quad (10)$$

The magnetic force from an arbitrary arrangement of magnetized elements was calculated using a model described and experimentally verified previously (Barnsley et al., 2015), whereby the field, $\mathbf{B}(\mathbf{r})$ was determined by breaking the magnet into a 3-dimensional lattice of evenly-distributed point moments, and summing the contributed dipole field at \mathbf{r} from each moment. In a curl-free magnetic field, the magnetic force on a particle with a magnetization, \mathbf{M} and volume, V is

$$\mathbf{F}_M(\mathbf{r}) = \mathbf{M}V \cdot \nabla(\mathbf{B}(\mathbf{r})). \quad (11)$$

The normalized magnetic force, used here for convenience because it has the same units as the field gradient (T/m), is

$$\frac{F_M}{M_s V} = \frac{M}{M_s} |\nabla(B)|, \quad (12)$$

where M_s is the saturation magnetization of the particle.

For simplicity, \mathbf{M} and \mathbf{B} were assumed to be parallel, and the particle was superparamagnetic so that the magnetization could be described using a Langevin function, $L(y) = \coth(y) - 1/y$,

$$M = M_s L\left(\frac{M_s V B}{k_B T}\right), \quad (13)$$

where $k_B T$ is the product of the Boltzmann constant and the temperature (Bean and Livingston, 1959; Williams et al., 1993; Majetich et al., 1997).

For simulations using cylindrical channels, \mathbf{v}_F was described analytically using (3). When a channel had a square cross-section, the flow profile was approximated by a $(z + iy)^4$ expression, following the formulation of Lekner (Lekner, 2007) and setting the wall topology parameter $\beta = 1$,

$$\mathbf{v}_F = 2v_A \left(\frac{4(y^2 + z^2)^2}{w^4} \cos(4\phi) - \frac{4\beta(y^2 + z^2)}{w^2} + 1 \right) \hat{\mathbf{i}}, \quad (14)$$

where w is the width of the channel and ϕ is the azimuthal angle. A “sticky” condition was imposed for the wall, whereby particles that have made contact with the wall were assumed to be stable and no further updates were made to their position.

Numerical simulations were performed in which an ensemble of spherical particles modelling polystyrene microbeads loaded with a volumetric ratio (α) of superparamagnetic iron oxide clusters were evenly distributed at an injection point (Tehrani et al., 2014; Bose and Banerjee, 2015b; Lunnoo and Puangmali, 2015) in a laminar flow contained within a straight channel aligned with the x -direction, and allowed to flow past a linear Halbach array consisting of nine rectangular, permanent magnet elements (figure 1). The magnet array was positioned a distance z_{mag} away from the central axis of the channel and was designed so that, in the region of the channel above the magnet, the magnetic force was approximately, spatially uniform, provided

Table 1. Parameters used in numerical particle tracing simulations.

Symbol	Description	Default value	Unit
μ	Fluid dynamic viscosity	8.9×10^{-4}	Pa.s
v_A	Fluid mean flow velocity	0.1	m/s
ρ_F	Fluid density	1000	kg/m ³
R	Fluid channel radius	0.25×10^{-3}	m
V	Particle volume	$(4\pi/3) r^3$	m ³
r	Particle radius	0.5×10^{-6}	m
ρ	Particle density	$\alpha \rho_{\text{Fe}_3\text{O}_4} + (1 - \alpha) \rho_{\text{polysty}}$	kg/m ³
$\rho_{\text{Fe}_3\text{O}_4}$	Fe ₃ O ₄ density	5240	kg/m ³
ρ_{polysty}	Polystyrene density	1050	kg/m ³
α	Volumetric ratio of Fe ₃ O ₄	0.1	
$M_{s\text{Fe}_3\text{O}_4}$	Fe ₃ O ₄ saturation magnetization	4.7×10^5	A/m
M_{NdFeB}	NdFeB magnetization	1.018×10^6	A/m
d_{mag}	Magnet element dimensions	$2.5 \times 7 \times 2.5$	mm ³
z_{mag}	Distance to magnet	3	mm
x_M	Magnet array length	9×2.5	mm
θ	Magnet array tilt angle	0	°
$F_g + F_{\text{buoy}}$	Gravity and buoyancy	$(\rho - \rho_F) V g$	N
g	Gravity acceleration	10	m/s ²

the channel radius, R was sufficiently small. The main component of the magnetic force was aligned to the $-z$ -direction, and gravity was directed perpendicular to both this direction and the direction of flow. A particle was considered captured if, when it came to rest at the channel wall, the magnitude of the magnetic force overwhelmed all others. The accumulation distribution was estimated as the relative proportion of particles lying within a range $x \pm \frac{1}{2}dx$. This was done by taking the derivative, with respect to x , of a cumulative distribution function of the proportion of particles that were stable before reaching x (i.e. $x_f < x$). Inter-particle interactions were neglected.

Table 1 gives the default values for simulation parameters. The magnet array tilt angle, θ was defined as the angle made between the bottom of the channel and the upper surface of the magnet. Of the 18 parameters in table 1, 14 are used to calculate the final term in (10). In most cases, the default values of these parameters were chosen to be relevant to the experiments described in section 2.3. The effects of varying v_A , F_M (which depends on z_{mag}), R and θ on capture efficiency and accumulation are investigated in section 3.1, while section 3.3 explores the performance of different magnet array designs.

The ability of different magnet designs to target magnetic particles to a partially occluded vessel was also investigated by simulating trajectories within a symmetrically converging-diverging (or “pinched”) channel, shown in figure 2(b). The flow velocity inside a pinched channel was approximated following the derivation from Akbari *et al*

Understanding the dynamics of superparamagnetic particles

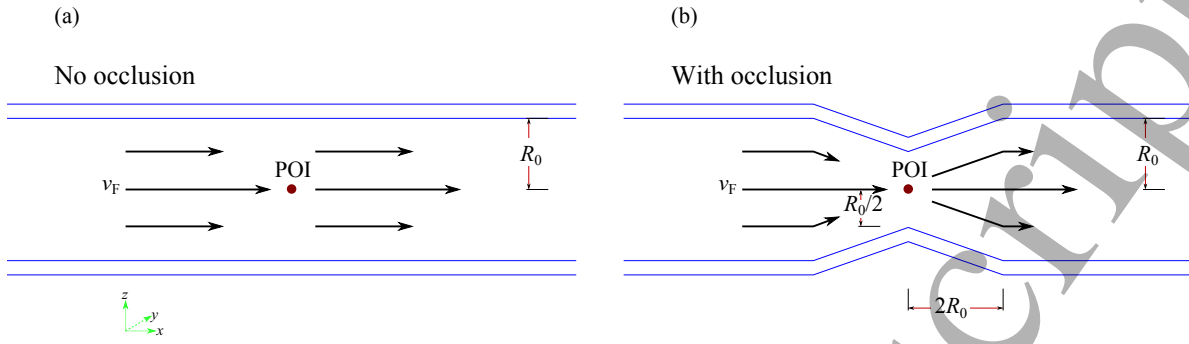


Figure 2. Simulated channel geometries, used to assess the ability of different magnet designs to deliver particles to a given position of interest (red circle). (a) The flow velocity in the straight channel with no occlusion and an inlet radius, R_0 is described by (3). (b) A “pinched” channel with a partial occlusion has a flow velocity given by (15). At the position of interest, the channel radius is set to half the inlet radius, while the total length of the occlusion is $4R_0$.

(Akbari et al., 2010):

$$\mathbf{v}_F = 2v_A \left(\frac{R_0}{R(x)} \right)^2 \left(1 - \left(\frac{y}{R(x)} \right)^2 - \left(\frac{z}{R(x)} \right)^2 \right) \left[\hat{\mathbf{i}} + \frac{dR(x)}{dx} \left(\frac{y}{R(x)} \hat{\mathbf{j}} + \frac{z}{R(x)} \hat{\mathbf{k}} \right) \right] \quad (15)$$

where R_0 is the radius at the channel inlet and $R(x)$ is the radius at x . The channel has a constant slope on either side of the occlusion, $dR(x)/dx$.

2.3. Magnetic trajectory experiments

Numerical predictions of trajectories were verified experimentally by flowing polystyrene magnetic microbead particles ($2.0\text{--}2.9 \times 10^{-6}$ m, Spherotech, Inc., Lake Forest, IL, USA) in a glass, square capillary channel primed with water (figure 3). Microbeads were diluted to a concentration of $4 \times 10^5 \text{ mL}^{-1}$ and injected into a steady-flow field using a syringe pump. A dilute concentration was chosen to diminish the formation of agglomerated beads in flow (superparamagnetic beads are observed to interact weakly when separated beyond approximately six times their particle diameter (Oduwole et al., 2016)). Acoustic focusing of the microbeads into a single trajectory was achieved by generating an ultrasonic standing wave (USW) field inside the fluid cavity of the channel using a lead zirconate titanate (PZT) piezoelectric transducer driven at $2.55 \rightarrow 2.65$ MHz, using a linear frequency sweeping regime. Additional information about the design of the ultrasonic manipulation setup is reported in Appendix B. The trajectory of beads was magnetically deflected using a linear Halbach array constructed from nine rectangular N42-grade NdFeB permanent magnet elements (Magnet Expert Ltd., Tuxford, UK) arranged as per figure 1, with dimensions given in table 1. Images of the region of the channel adjacent to the magnet were acquired by an inverted microscope (Ti Eclipse, Nikon Instruments Inc., NY, USA) with a x10 objective (Plan Fluor Ph1 DLL, Nikon) and a digital camera (Digital Sight Qi1Mc-U2, Nikon), operating in bright-field mode.

Understanding the dynamics of superparamagnetic particles

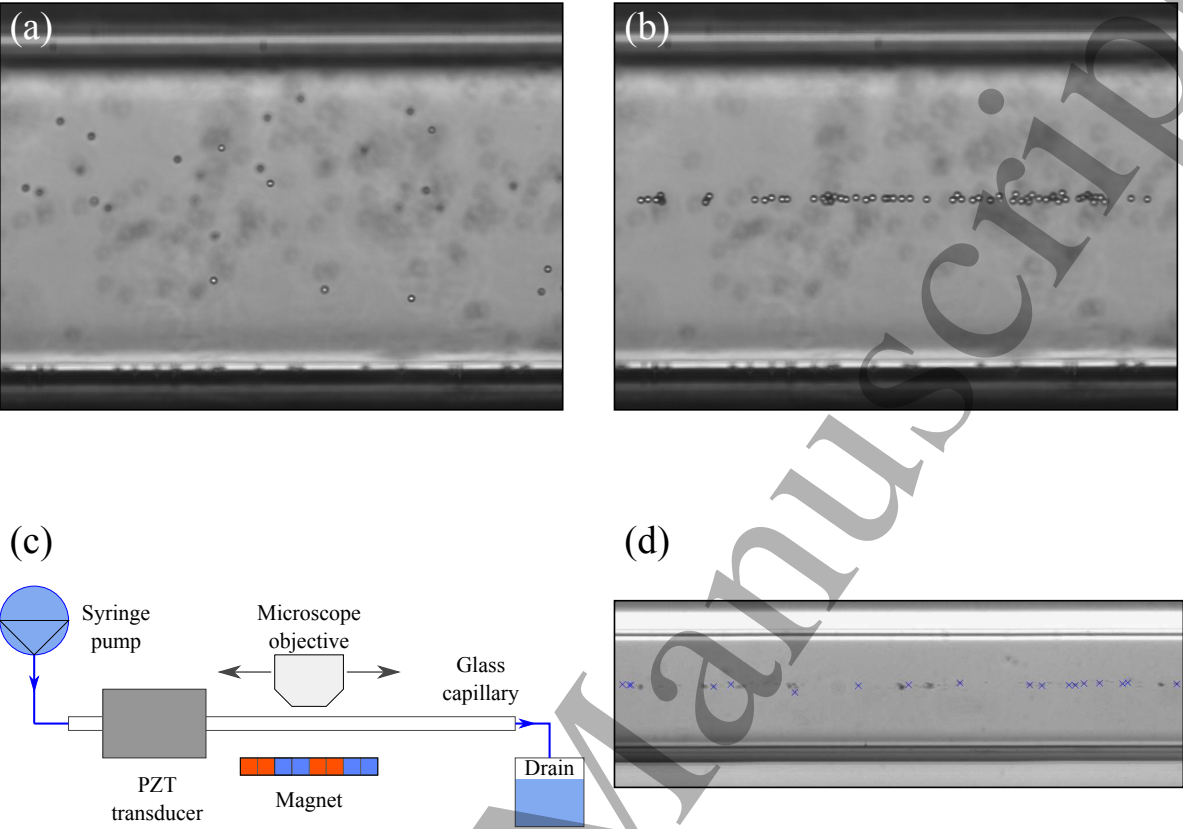


Figure 3. Microbeads were conveyed into a glass channel past a PZT transducer, which was actuated at approximately 2.6 MHz so as to generate an ultrasonic standing wave (USW) field within the fluid cavity. (a) In the absence of a USW, beads were unfocused and thus were located at different planes within the channel. (b) In the presence of the USW field, the beads are focused along a single trajectory by the action of acoustic radiation forces. (c) Schematic of the experimental set-up. A magnet positioned orthogonal to the viewing plane of the microscope deflects focused, magnetic beads towards the wall of the channel. (d) A purpose-built MATLAB image processing routine was implemented to determine the position of non-agglomerated microbeads recorded by the microscope.

The trajectory of the microbeads actuated by the Halbach array were extracted by a purpose-built MATLAB (The MathWorks Inc., Natick, MA, USA) image processing routine. Imaging scans along the channel length were analyzed frame by frame. Each frame was thresholded to separate magnetic particles from background. Objects greater than 250 pixels in area were discarded to exclude agglomerated magnetic beads and objects with less than 12 pixels were discarded as noise or refuse. Separate threshold levels were applied to isolate the top and bottom channel walls. Linear regression was used to extrapolate the top wall coordinates from the first 8 frames of the scan (before the Halbach array) since thresholding with magnetic particles accumulating at the wall of the channel was less reliable. The origin was taken as the midpoint between the top and bottom channel walls at the beginning of the first frame of the scan and particle centroid coordinates were recorded relative to this point. Non-magnetic particles that

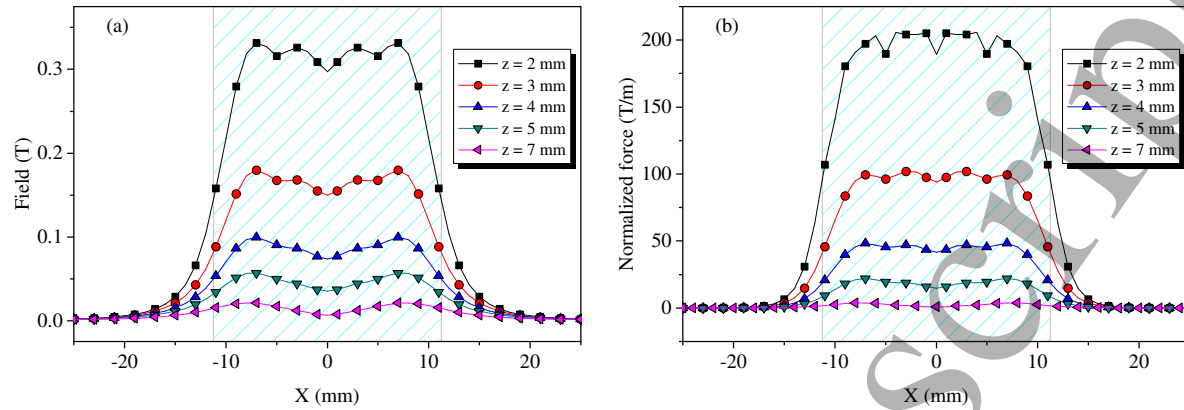


Figure 4. Magnitude of the (a) field and (b) normalized force of the nine-element Halbach array shown in figure 1 as a function of x at different elevations, z from the upper surface of the array. The shaded range coincides with the region directly above the magnet array, and marks the space bounded by x_0 and $x_0 + x_M$ for calculation of analytical trajectories.

satisfied the size and thresholding criteria were rarely detected and manifest as outliers in the plots in figure 9.

Magnetic measurements were used to characterize the magnetic behaviour of the microbeads in suspension. Hysteresis loops of the microbeads were measured using a MPMS Superconducting Quantum Interference Device (SQUID) magnetometer (Quantum Design, Inc., San Diego, CA, USA) at a temperature of 270 K (in order to freeze the fluid) between ± 1 T. The effective superparamagnetic particle size and volumetric loading of magnetite on microbeads were determined by fitting (13) to the hysteresis loop in figure A1, and these parameters were used to numerically predict the experimental trajectories reported in section 3.2.

3. Results

3.1. Simulation results

Numerical simulations were performed to ascertain the trajectories of magnetic microbeads in a steady, laminar flow, under the influence of the magnet array shown in figure 1, to investigate how the capture efficiency and accumulation distributions varied with the flow velocity, the magnetic force, the channel radius and the alignment of the magnet. The field and force profiles emitted by the Halbach array along the direction parallel with the upper surface, displayed in figure 4, show that, for a short range of z values, the “step function” approximation used for the derivation in section 2.1 was reasonable. The results from the numerical simulations were compared with predictions using the expressions for trajectories, C.E. and accumulation distribution derived analytically.

Figure 5 compares the analytically derived trajectories described by (6) and the simulated trajectories for average flow velocities of 10 and 20 mm/s and z_{mag} set to

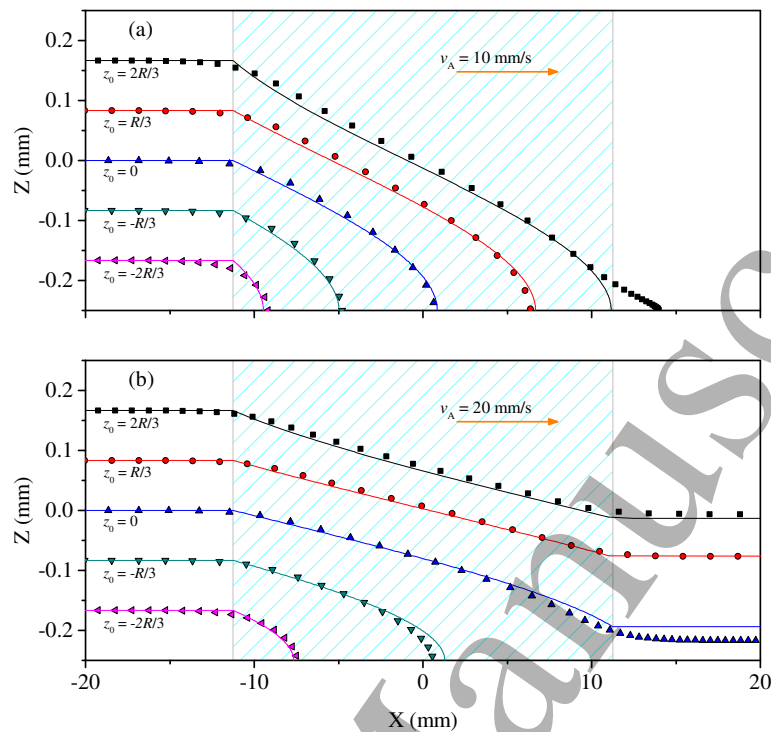


Figure 5. Predicted trajectories of particles in a cylindrical channel ($R = 0.25$ mm) initially set at various elevations, z_0 along the z -axis, under the influence of the nine-element Halbach array and an average laminar flow velocity of (a) 10 mm/s and (b) 20 mm/s. The symbols represent the trajectory given by the numerical simulation, while the line is described by (6). The shaded region is the same as figure 4, indicating where the “step function” magnetic force (c.f. (1)) operates.

3 mm. The normalized magnetic force for the analytical trajectories was taken as the force directly above centre of the array at z_{mag} ($F_M = 93.9$ T/m). While the analytical expression made reasonable estimates of the final resting position of particles in flow, a few discrepancies are apparent, owing to the assumptions made in the derivation. The analytical trajectories generally underestimated x_f on the near (negative) side of the magnet, and overestimated it on the positive side, which could be attributed to the variation of $F_M(x)$ produced above the sides of the Halbach array. More importantly, the trajectory of the particle with the highest starting elevation shown in figure 5(a) ($z_0 = 2R/3$) demonstrates how a particle could be both actuated and captured outside of the bounds of x_M when a more physically realistic profile of $F_M(x)$ was utilized. Once a particle was in a low flow regime, close to the channel wall, it slowed down significantly, and relatively little external force was required to pull it to the wall.

In order to examine a wide range of possible trajectories, numerical simulations were run by initially distributing an ensemble of particles evenly around the cross-section of the flow channel upstream from the magnet, so that each particle had a unique starting y_0, z_0 . Figure 6(a) shows how the travel distance of simulated particles (relative to the centre of the magnet, which defines $x = 0$) is related to their the initial position in the

Understanding the dynamics of superparamagnetic particles

12

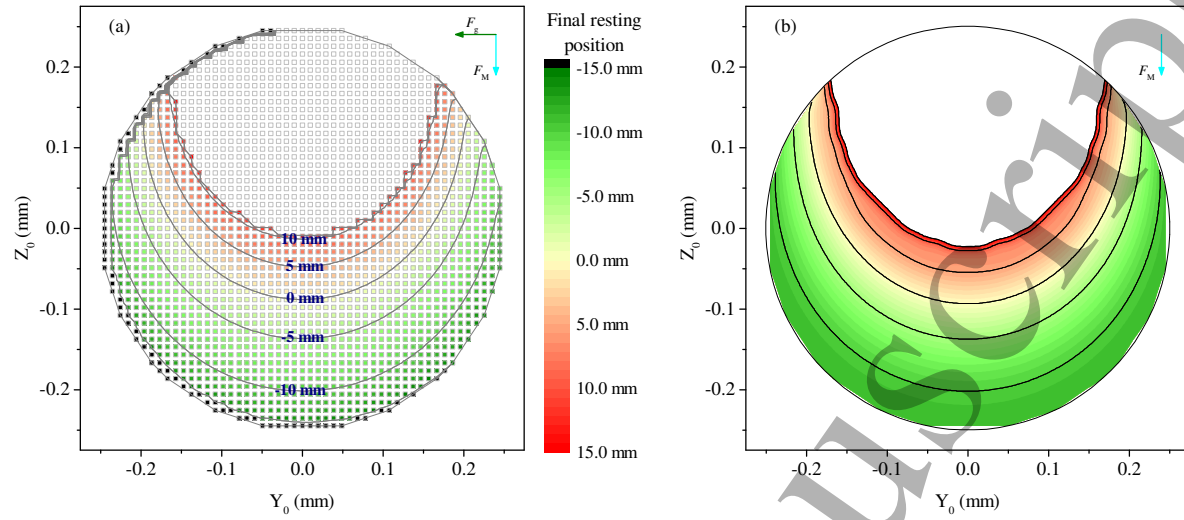


Figure 6. (a) Colour-code to indicate the final resting positions (x_f) of particles, overlaid onto a map of their starting positions in the y_0 - z_0 plane cross-section of a cylindrical channel. The solid gray lines show contours of starting y_0 - z_0 positions that have the same final position, x_f . For this numerical simulation, $v_A = 20$ mm/s and $z_{\text{mag}} = 3$ mm. Gravity acted in the $-y$ -direction, and the magnetic force vector pointed in the $-z$ -direction. Black particles left the flow before reaching the magnet, while white particles passed over the magnet uncaptured, exiting the flow at the outlet. (b) The predictions of x_f as a function of y and z_0 given by the analytical expression in (7), with the same value of v_A and F_M set to 93.9 T/m. Gravity was ignored in the analytical case.

y - z plane at the injection point, with an average laminar flow velocity of 20 mm/s. The colours indicate the final resting positions of the particles, x_f , relative to the centre of the magnet. The particles that were initially furthest from the magnet (coloured white), and therefore had furthest to travel before being trapped at the channel wall, tended to pass over the magnet, reaching the outlet uncaptured. Alternatively, particles that had a very slow velocity near the bottom of the channel (coloured black) were removed from the flow by gravity before they reached the magnet. Analytical predictions for x_f as a function of y and z_0 using (7) for the same parameters are given in figure 6(b), and are qualitatively similar to the results of the numerical simulation. In both data sets, the proportion of particles trapped by the magnet in each 5 mm segment along the length of the channel (bounded by the counter lines) decreases with increasing x , indicating that more particles were trapped on the leading edge side (negative x_f) of the magnet, and fewer made it to the trailing edge (positive x_f).

Capture efficiencies were determined for a set of numerical simulations following the method described in section 2.2 and were compared with the values predicted by (8). Figure 7 shows how the capture efficiency varied as one of the experimental parameters, v_A , F_M , R or θ was changed while the other parameters were fixed to their default values (table 1). The agreement attained between the simulation results and the analytical predictions indicates that the formulation derived in section 2.1 can provide a good

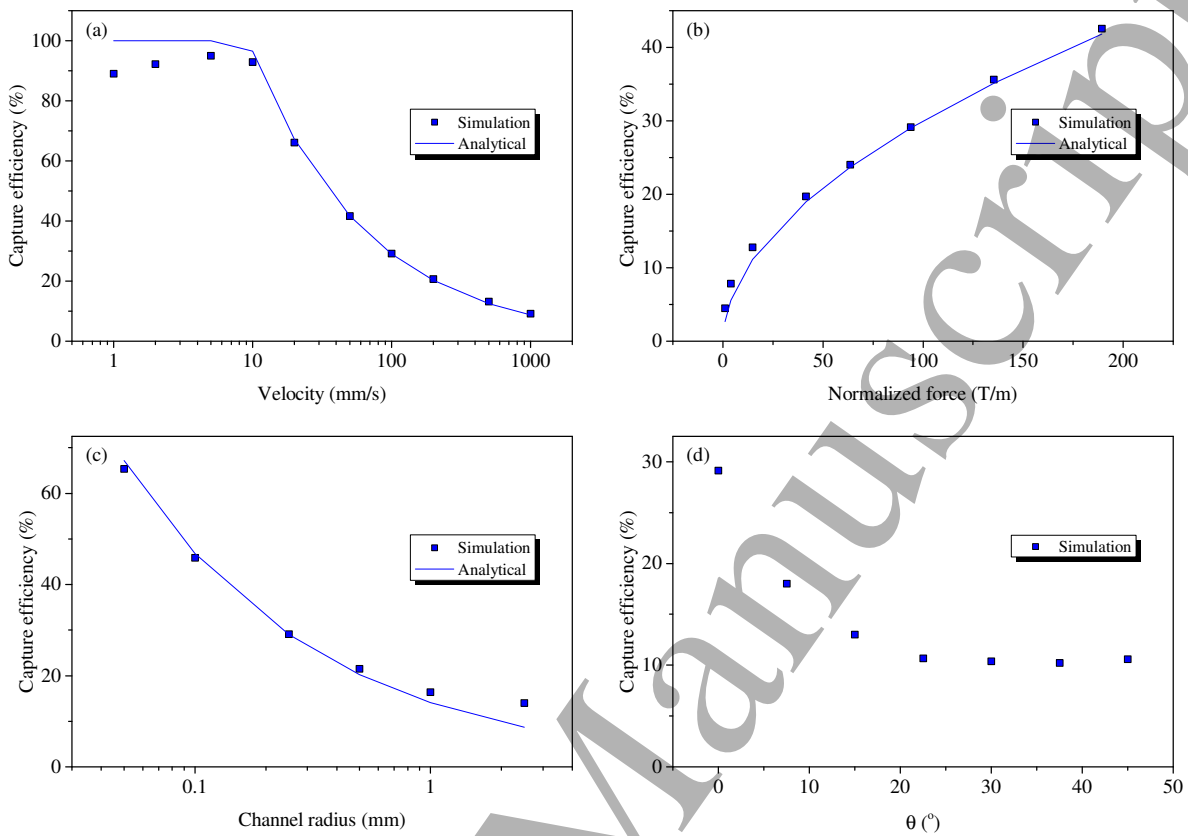


Figure 7. The capture efficiency predicted by numerical simulations (symbols) and the semi-analytical expression of (8) (lines), displayed after varying (a) average flow velocity, (b) magnetic force, (c) channel radius and (d) alignment of the magnet. The fixed, default parameters are given in table 1.

first-order approximation for the capture efficiency in regions where the magnetic force is (relatively) spatially uniform.

The discrepancy in figure 7(a) at low flow velocities was due to the influence of gravity in the numerical simulations causing a relatively large proportion of particles to be removed from flow by gravity before reaching the magnet. At flow velocities less than 10 mm/s, no particle made it to the outlet of the channel; particles were either forced out of flow by gravity before reaching the magnet, or captured by the magnet once they reached it. If simulations with these conditions did not include gravity, the capture efficiency would be 100%, as suggested by the analytical expression. Figure 7(c) shows that, as the channel size increased, so did the deviation between the two models. This was attributed to the fact that, as the channel size increased, the assumption of a spatially uniform magnetic force was no longer valid, and the magnetic force at the bottom of the channel, closer to the magnet, became significantly stronger than the force at the top of the channel. The effect of varying the magnet array tilt angle, θ is displayed in figure 7(d). For $\theta > 22.5^\circ$, the capture efficiency didn't vary significantly, but the accumulation distribution (figure 8(d)) did.

Accumulation distributions, calculated for a subset of numerical simulations using

Understanding the dynamics of superparamagnetic particles

14

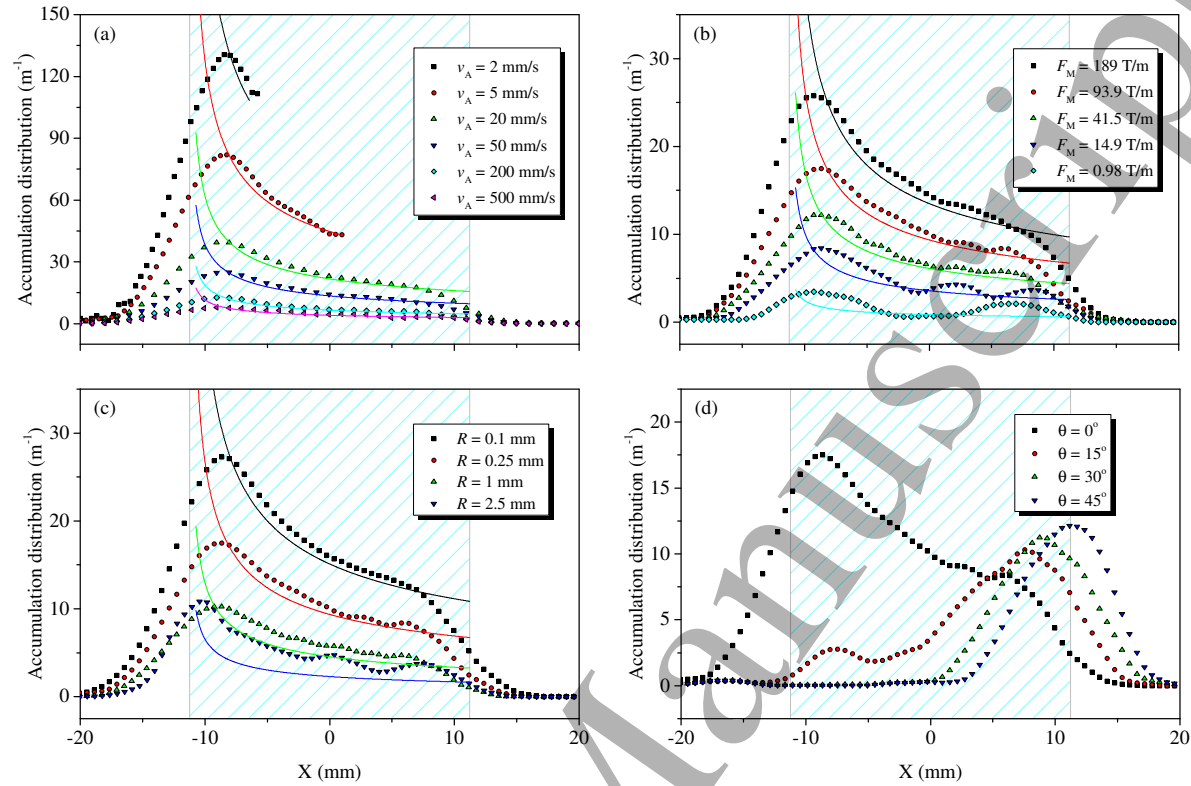


Figure 8. A comparison of the accumulation distributions for a subset of the simulations described in figure 7. The symbols give the results of the numerical simulations, while the lines are described using (9). The shaded region is the same as that defined in figure 4.

the method described in section 2.2, are shown in figure 8, and are compared with the profiles predicted by (9). For all tested parameter sets, (9) goes to infinity at the leading edge of the magnet, x_0 , highlighting a major discrepancy between the two models. Almost all distributions exhibited a peak in density in a region close to the leading edge of the magnet and, downstream from this point the agreement between the numerical simulations and the analytical derivation was reasonably good in most cases where the magnetic force was spatially uniform. Exceptions to this can be observed in figure 8(b), where the channel was far from the magnet, and the normalized force was small, and in figure 8(c) for large channel radii, where the forces at the top and bottom of the channel were significantly different. Notably, in many simulations, a significant proportion of particles were captured in a region prior to the bounds of the spatial extent of the magnet. Also of note, the peak in density usually occurred in a consistent position for almost all distributions ($x \sim -8.5$ mm) and, provided the simulations were performed in a space where the magnetic force could be approximated by (1), the shapes of the profiles overlapped very closely when normalized to the peak density. This suggests that, while the proportion of captured particles is sensitive to physiological flow conditions inside the body (encapsulated in the parameters v_A and R), the relative spatial distribution of particles that are successfully captured is determined

by the profile of the magnetic force ($F_M(\mathbf{r})$). This means that particle distributions could be tuned and optimized for a given application by engineering the spatial profile of the magnetic force, so that the greatest density of captured particles would coincide with the desired region of interest. One attempt to do this is shown in figure 8(d), by varying θ . By tilting the magnet away from the channel, so that the force was localized in the region above the trailing edge of the magnet, the peak position of accumulation distribution was shifted closer to the position $x = x_M$. However, fewer particles were captured overall.

3.2. Experimental results

The numerically predicted trajectories of particles under the influence of laminar flow and magnetic force were verified experimentally by flowing magnetic microbeads in a glass square capillary channel with an internal width of 0.3 mm and focusing them using acoustic radiation forces generated by a USW field, upstream from a linear Halbach array. The USW field was created by a PZT transducer coupled to the glass channel approximately 8 mm away from the Halbach array, to separate the regions of the channel exposed to acoustic and magnetic forces (Appendix B). Thus, the contribution of acoustic radiation forces was considered negligible when modelling the trajectory of particles exiting the active area of the transducer. The fluid velocity inside the channel was described using (14), with the average velocity, v_A varied between 2 and 15 mm/s (a range of flow velocities seen in intratumoral blood flow (Shimamoto et al., 1987)). Starting positions used to calculate numerical trajectories were determined by averaging the elevation and distance to the wall of particles upstream from the influence of the magnet. The magnet position relative to the channel was measured from scanned images recorded using a fluorescent microscope, with the magnet-to-channel distance, z_{mag} set at 3.9 or 4.6 mm (corresponding to field gradients of 45 and 23 T/m above the centre of the array).

Figure 9 shows the measured trajectories compared with the numerical predictions, based on a microbead with the magnetic properties measured in Appendix A. For each condition, reasonable agreement was found between the measured and predicted trajectories. The shaded regions in figure 9 represent the region of the channel adjacent to the magnet, but for low flow rates and/or higher magnetic forces, it was both observed and predicted that the trajectory would begin to deflect towards the magnet before the particles reached this area. At faster flow velocities, particles were less well focused due to them spending less time in the acoustic field of the transducer, resulting in a greater spread of particle positions around the predicted trajectories. For example, at 2 mm/s and 45 T/m (figure 9(a)), focusing confined the particles within a trajectory about 0.032 mm wide ($\pm 2\sigma$) before being actuated by the magnet, resulting in a 1.2 mm spread of positions for particles that were forced to the wall by the magnet. By comparison, a 15 mm/s average velocity resulted in a 0.056 mm wide trajectory, and a 8.1 mm spread of final particle positions for the same magnetic force (figure 9(d)). Variations in

Understanding the dynamics of superparamagnetic particles

16

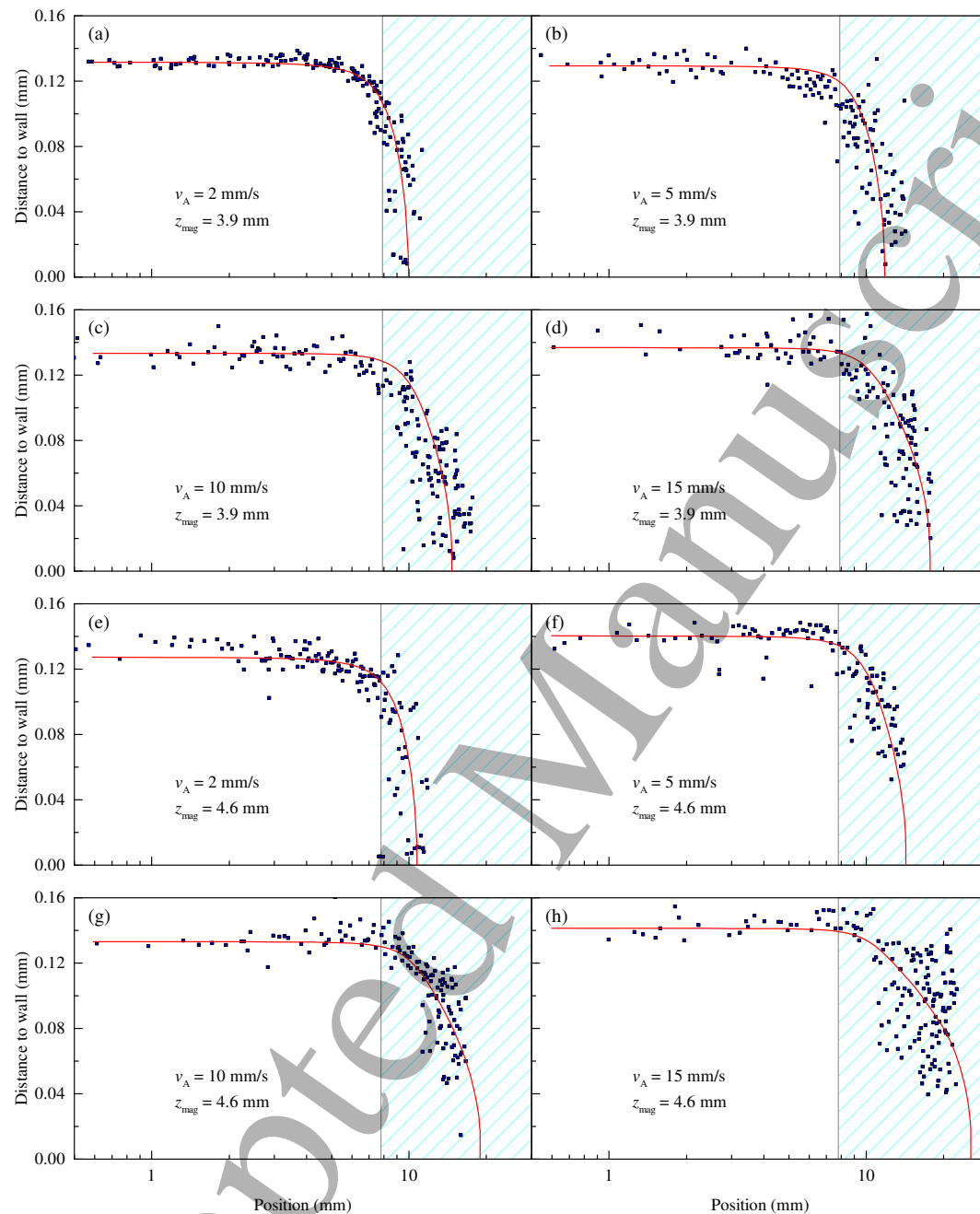


Figure 9. Experimental positions of magnetic microbeads focused into a single trajectory by acoustic radiation forces and deflected by a linear Halbach array were imaged using microscopy (blue symbols) and compared with numerical predictions (red lines). The distance between the centre line of the glass capillary channel and the face of the magnet (z_{mag}) was set to (a)-(d) 3.9 mm and (e)-(h) 4.6 mm. The average velocity in the capillary, v_A was varied between 2 and 15 mm/s. The shaded area represents the part of the channel adjacent to the Halbach array. The position-axis gives the distance along the channel away from the trailing edge of the piezoelectric transducer.

Understanding the dynamics of superparamagnetic particles

17

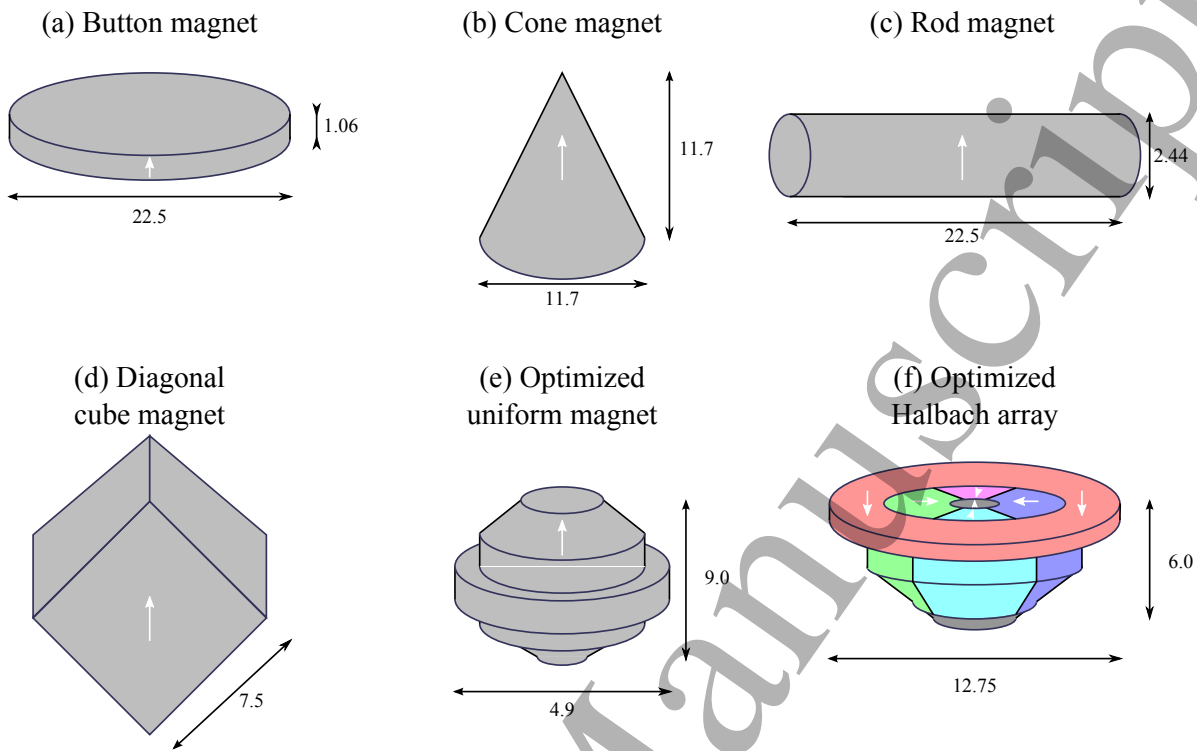


Figure 10. Designs of various permanent magnet shapes and arrays, with dimensions in mm. Commonly available uniformly magnetized shapes are shown in (a)-(c); (d) exhibits a permanent magnet cube which is diagonally magnetized along a face. (e) Uniform and (f) orthogonally magnetized arrays, optimized for magnetic force at a 3 mm range. All arrays have the same volume as the linear Halbach array above, and, where appropriate, the same spatial extent, x_M .

particle size and magnetic loading may have also contributed to distributions in particle positions about the predicted trajectory, as they would impact on both acoustic and magnetic forces.

3.3. Comparison of magnetic systems

Simulations were performed to investigate how accumulation distributions would differ with different permanent magnet designs, in order to determine which shapes and arrangements result in the greatest concentration of particles in a localized region of interest. Figure 10 shows the six magnet designs explored here. All designs were constrained to have the same magnet volume as the linear Halbach array and, in the case of the button and rod magnets, the same spatial extent along x . For the cone magnet, the diameter and height were set to be equal. The cube magnet (figure 10(d)) had a magnetization vector that pointed along a face diagonal, and was orientated on its edge so that \mathbf{M} pointed along z . The arrays in figure 10(e) and (f) were designed using a force optimization routine for arbitrary shapes (Barnsley et al., 2016) and a position of interest set $z_{\text{mag}} = 3$ mm away from the upper surface of the magnet. One design consisted of a single, uniform magnetization, while the other was a Halbach

Understanding the dynamics of superparamagnetic particles

18

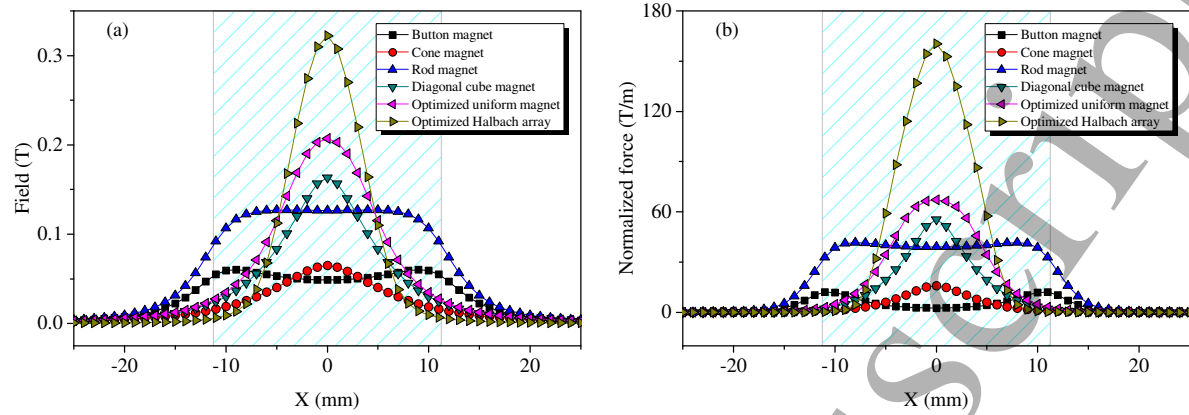


Figure 11. (a) Field and (b) normalized force of the various arrays displayed in figure 10, along the x -axis at a distance $z_{\text{mag}} = 3$ mm from the face. The shaded region gives the extent, $x_M = 22.5$ mm, commensurate with that of the linear Halbach array in section 3.1.

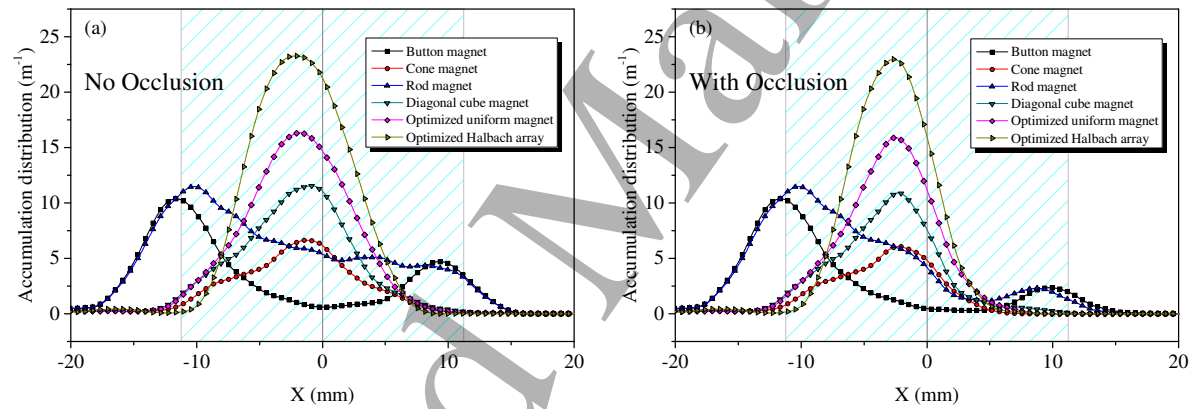


Figure 12. Accumulation distributions for simulations with the default simulation parameters for v_A , z_{mag} , R and θ , using the various magnets shown in figure 10. The shaded region highlights the default extent of x_M , which is also the length of the button and rod magnets. (a) Profiles resulting from a channel with no occlusion; (b) profiles from a channel with a partially occluded geometry shown in figure 2(b). The dark gray line at $x = 0$ marks the position of interest at the centre of the occlusion.

array assembled using six segments with different, orthogonally aligned, magnetization directions.

The field and force profiles generated at a distance $z_{\text{mag}} = 3$ mm from the upper surface of each magnet are displayed in figure 11, which shows that the uniform button and cone magnets are not well suited to apply a high field gradient in a localized region (the field and force from the button magnet are strongest at the edges). The two optimized magnets generate the strongest fields in the centre of the channel, particularly the Halbach array, which has a full width at half maximum (FWHM) in force of 8.54 mm.

Numerical simulations were performed using the different magnet designs with the default values for v_A , z_{mag} , R and θ (table 1). The channel was positioned so that

Table 2. Capture efficiencies of different magnet designs in the absence and presence of a partial occlusion. Simulations were performed with the default values for u_A , z_{mag} , R and θ in table 1. The design of the linear Halbach array is shown in figure 1, while the design of all other arrays is displayed in figure 10.

Magnet design	No occlusion (%)	With occlusion (%)
Linear Halbach array	29.27	24.20
Button magnet	11.54	9.86
Cone magnet	7.01	5.55
Rod magnet	18.61	15.10
Diagonal cube magnet	12.07	9.69
Optimized uniform magnet	16.61	13.44
Optimized Halbach array	22.60	17.93

the maximum flow axis was $z_{mag} = 3$ mm from the upper face of the magnet array. Accumulation distributions in figure 12 indicate that the optimized arrays are better suited for localizing particles in greater density around the region directly above the centre of the magnet. Of the uniform magnets, the button magnet was notable because most accumulation took place above the edges of the cylinder, where the forces were strongest, and almost no particles were collected towards the middle. The rod behaved similarly to the step-force (linear Halbach array) above, capturing more particles at the leading edge of the magnet, but still capable of distributing particles in the region bound by x_M , suggesting that these designs could be practical for applications in which particles need to be delivered to a large, diffuse area. These include diagnostic or biosensing applications involving a combination of active and magnetic targeting strategies for precisely locating and imaging tumours (Gunasekera et al., 2009; Schleich et al., 2014; Xu et al., 2016). The cone and cube magnets were able to concentrate particles to a confined region close to their upper edges, but the peak linear density was not competitive with that of the two optimized arrays, owing to the fact that the generated force profiles persisted only over a very short-range compared with the optimized arrays (Barnsley et al., 2015).

The ability of each magnet design to deliver particles to a partial occlusion is assessed in figure 12(b). In all cases, the accumulation distribution at the site of the occlusion is less than the “no occlusion” case in figure 12(a), as the flow velocity in the narrow region of the channel is significantly greater, and the distance from the bottom of the channel to the magnet has increased, reducing the peak magnetic force inside the channel. Table 2 details the capture efficiencies from the simulations shown in figure 12. While the optimized magnets are still the best of the tested designs at delivering particles to the position of interest, they are also the designs most relatively compromised by the presence of the occlusion.

Notably, even when the accumulation distribution was tightly localized, it was still

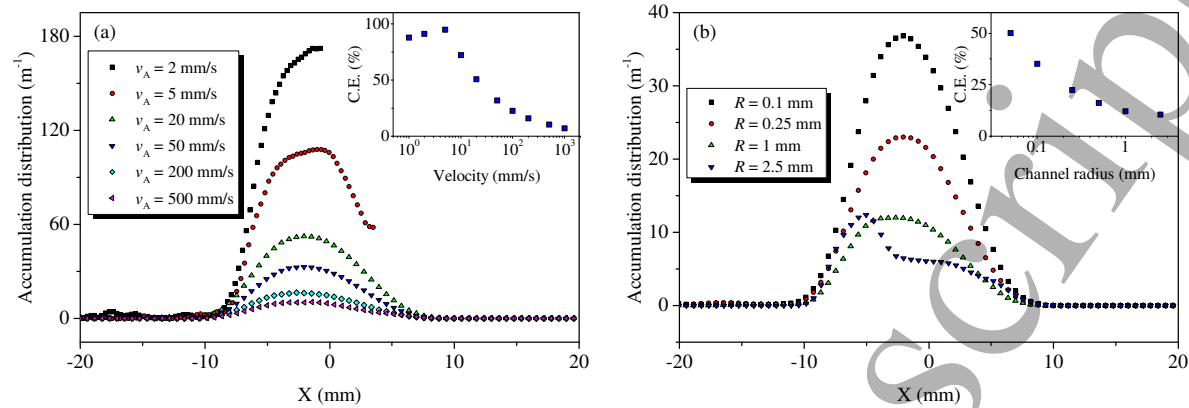


Figure 13. Accumulations distributions collected by the optimized Halbach array (figure 10(f)) varying (a) channel velocity and (b) channel radius. z_{mag} was fixed to 3 mm. The insets show the capture efficiency as a function of the varied parameter.

skewed slightly towards the leading edge of the applied field/force. Figure 13 shows how the accumulation distribution varies as a function of two physiologically-relevant parameters, v_A and R in a channel with no occlusion. Again, when v_A was varied (and all magnet related parameters were fixed), the shape of the accumulation distribution changed only very slightly. The accumulation distributions displayed in figure 13(a) overlap almost entirely when normalized to the peak density, with the position of the peak shifting by just ~ 1.4 mm over three orders of magnitude in v_A (the mean FWHM of all distributions was 8.9 ± 0.1 mm). The shape of the distribution did change with R , particularly at large values toward 2.5 mm (figure 13(b)), owing to the fact that the bottom of the channel was only 0.5 mm from the magnet, and the force profiles at the top and bottom of the channel were very different.

4. Discussion

Magnetic targeting in a channel was considered mathematically using a numerical and semi-analytical model for the trajectories of an ensemble of superparamagnetic particles subject to a set of external forces inside a straight, cylindrical channel and a channel with a partial occlusion, both containing laminar flow. For the semi-analytical derivation, a constant magnetic force was considered to act over a fixed spatial range inside the channel, allowing for the derivation of expressions for capture efficiency and accumulation distribution of magnetic particles in the channel, assuming an evenly-distributed range of trajectories at the starting position. In this derivation, the capture efficiency is well described in terms of a non-dimensional parameter representing the ratio between factors that promote capture (magnetic force, F_M and length of magnet, x_M) and factors that mitigate capture (average flow velocity, v_A , channel radius, R and viscosity μ). Nandy *et al* (Nandy et al., 2008) also derived the capture efficiency of magnetic particles in flow, finding that for this case the capture efficiency was also well described by a power-law for a non-dimensional ratio of a similar form to (8)

(with slightly different coefficients). However, their derivation was for two spatial dimensions, with an infinite third dimension perpendicular to the direction of flow and magnetic force, which was generated by a spatially-varying line dipole. Given that all of the factors that comprise the non-dimensional ratio can be readily characterized for a given magnetic drug targeting set up, a simple calculation can provide a good first-order approximation for capture efficiency in regions where the magnetic force is relatively constant, which is useful for determining the total quantity of a drug that can be delivered. Alternatively, where the desired quantities are either well-characterized or constrained, knowing the required magnetic parameters to achieve an intended capture efficiency is useful for the design stage of both the external magnet and the magnetic carrier properties, particularly given that the applied magnetic force typically decays rapidly with distance from the magnet, and increases with the total magnet volume (Alexiou et al., 2006; Hayden and Häfeli, 2006; Häfeli et al., 2007; Barnsley et al., 2016). As an example, our previous design for a double layer Halbach array (Barnsley et al., 2015) produced a field gradient of 85 T/m at a distance of 2 mm, and 12 T/m at 20 mm. Even at this range, this still provides a useful force (using (8) and for the default particle and channel parameters in table 1, a capture efficiency exceeding 10% would be expected for flow velocities up to 130 mm/s), but beyond this, the rapid drop in force (and, therefore, capture efficiency) with tissue depth exhibited by most magnets highlights one of the main challenges with conventional magnet systems for MDT.

Particle sizes in the mesoscopic size range (nanometres to microns) are seen as advantageous due to a favourable ratio between magnetic and Stokes' drag force for improved magnetic targeting (Kozissnik and Dobson, 2013) and also the ability to formulate composites to carry a combination of drugs or be compatible with multiple targeting strategies (Wadaikar et al., 2012; Schleich et al., 2014). However, smaller particles (e.g., free drug macromolecules and nanoparticles) are preferable for delivery, as they are better able to extravasate from the circulatory system, and accumulate in tumours (Matsumura and Maeda, 1986; Maeda, 2012). Modelling on nano-sized magnetic particles has previously been used to account for observations seen in clinical trials when the properties of the nanoparticles (i.e., size and magnetic moment) were well characterized (Nacev et al., 2011a,b).

For simplicity, the analytic formulation considered a Newtonian fluid in a straight channel, but blood is non-Newtonian, contains red blood cells and vessels are only approximately straight over short distances; these aspects are typically described using a blunted flow velocity profile (Nacev et al., 2011a), added viscosity terms in large vessels (Zhang and Kuang, 2000) and networked vessel geometries (Grief and Richardson, 2005; Ritter et al., 2004; Bose and Banerjee, 2015a) respectively. While these features weren't considered in this study, they can be easily accounted for using the numerical model. The numerical model is particularly useful for understanding the relative spatial accumulation of particles along the length of the channel in the vicinity of a given magnetic field source. Simulations for a linear Halbach array (which produces an

Understanding the dynamics of superparamagnetic particles 22

approximately constant magnetic force in a spatial region close to the face of the array) suggest that, when particles flow in one direction inside a straight channel past the array, most of the particles are captured towards the leading edge of the array. The relative profiles of the accumulation distributions described in section 3.1 are mostly determined by the spatial variation of the magnetic forces within the channel; where parameters that do not influence the magnetic force are varied (in particular, v_A), the absolute peak value of the accumulation distribution changes, but the shapes of the distributions are mostly the same (overlapping when normalized to the same peak value). Therefore, understanding the spatial variation of the magnetic field and forces generated by a given magnetic field source is critically important for predicting the ultimate localization of magnetic carriers in the vessel network around the target.

The simulation results comparing external magnet designs suggest that for assemblies in which either the magnetic field or force is approximately constant over a large spatial range, captured particles are more likely to accumulate in the region of a vessel closer to the edge of the magnet, rather than towards the middle. Similar effects have been utilized in microfluidic devices with external magnets to manipulate particles by tuning field profiles (Gassner et al., 2009; Cao et al., 2013). For MDT, this can be a problem in a realistic vessel geometry around a target, which can often be tortuous and ramified, meaning that, if most particles are captured in regions corresponding to the edges of a magnet, efficient delivery to a single target site may not be possible, mitigating the primary advantage of using a magnetic system for drug delivery. Essentially, a magnetic system that is not well designed and/or carefully orientated would remove the greatest proportion of particles from flow before they even reach the target. This is particularly problematic with button magnets (one of the most commonly available magnet geometries); the strong edge effects and weak central force arguably make it the least appropriate magnet shape for MDT applications. Magnetic systems that are able to confine magnetic forces to a rapidly-varying peak-force region appear to perform better in localizing a high concentration of captured particles to a well-defined site. Of the tested magnetic arrangements, the shapes “optimized” (Barnsley et al., 2016) for magnetic force appear to perform the best for localized accumulation, although it should be noted that the peak accumulation distribution does not scale linearly with magnetic force. This would represent the most efficient accumulation profile for drug delivery to a solid, spatially-confined region of diseased tissue.

This highlights the importance of imaging to provide active feedback of the accumulation of captured particles, to ensure that the alignment of external forces results in good co-localization between drug carriers and the target region during therapy (Shapiro et al., 2015; Schleich et al., 2015). Carrier formulations utilizing iron oxide nanoparticles are seen as particularly favourable because iron oxide generates negative contrast in magnetic resonance imaging (MRI) (Pankhurst et al., 2003; Das et al., 2008), but many systems proposed for magnetic targeting (permanent magnet or electromagnet arrays) are fundamentally incompatible with MRI instruments due to safety reasons (Schenck, 2000), and while magnetic delivery using MRI

gradient coils is actively being researched (Mathieu et al., 2006; Martel et al., 2007; Mathieu and Martel, 2009; Pouponneau et al., 2011), conventional MRI gradient coils aren't designed to generate sufficient magnetic force to capture nanoscopic particles in particularly high flow regimes, meaning that MRI is often used as a diagnostic tool after therapy (Chertok et al., 2008; Wadajkar et al., 2012; Fan et al., 2013). Imaging protocols that are based on magnetic particle imaging (MPI) (Gleich and Weizenecker, 2005; Sattel et al., 2009; Biederer et al., 2009) or ultrasound imaging using carriers that are simultaneously responsive to acoustic and magnetic stimuli (Stride et al., 2009; Liu et al., 2011; Fan et al., 2013; Crake et al., 2015; Lee et al., 2015), could be seen as means to monitor carrier concentration and localization during therapy that are compatible with the intense magnetic forces generated by magnetic drug targeting systems.

Particle trajectories for superparamagnetic beads within physiologically relevant flow regimes have been studied previously using numerical models (Gleich et al., 2007; Nandy et al., 2008; Sharma et al., 2015; Zhou and Wang, 2016). In order to experimentally verify the numerical predictions made using our model, we used acoustic focusing to study the motion of magnetic microbeads along a single trajectory in the vicinity of a linear Halbach array. Good agreement was found between the observed particle positions and numerical predictions on the length scales of our experiment, with no fitting parameters outside of the magnetic microbead properties which were measured by magnetometry (Appendix A). Given the relative simplicity and robustness of the technique to create a single trajectory, acoustic focusing within a channel is a useful method to study the response of magnetic carriers influenced by a range of flow conditions and magnetic forces relevant for MDT. However, as the present technique relies on optical detection of particle positions, an alternative approach would be required to validate trajectories of nano-sized particles.

5. Conclusion

An analytical expression for the trajectory of a superparamagnetic particle under the influence of a magnetic force and laminar flow was derived in three dimensions, which was then used to derive semi-analytical expressions for the capture efficiency and accumulation distribution of particles in terms of a non-dimensional ratio of the most relevant physical and physiological parameters for a given magnetic targeting scheme. The results of numerical simulations of an ensemble of magnetic particles in flow, actuated by a linear Halbach array emitting an approximately constant magnetic force over a known spatial range were compared with the predictions from the analytically derived expressions. This demonstrated that the analytical treatise can provide good first-order assessments of the viability of MDT situations.

The numerical model was used to assess a range of different external magnet system designs and orientations to examine which configurations are most capable of capturing a large proportion of magnetic carriers under various flow conditions, and accumulating

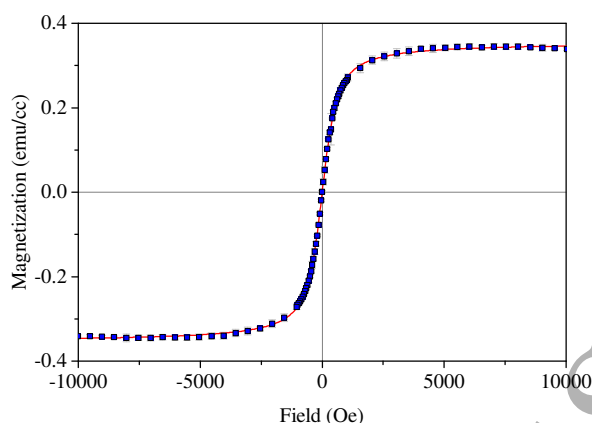


Figure A1. M - H curve for polystyrene magnetic microbead particles measured at 270 K between ± 1 T at a concentration of $4 \times 10^8 \text{ mL}^{-1}$. The symbols represent the magnetic measurement and the red line represents a fit to the data using a Langevin function (c.f. (13)).

them in a confined, localized region. While the relative accumulation distributions in different flow velocities were found to depend primarily on the magnetic force profile, the relationship between the magnetic force profile and accumulation distribution was nontrivial. It was found that, of the tested magnetic systems, assemblies that provide a large peak magnetic force that rapidly varies over a confined region perform best at concentrating magnetic carriers to a target region. Experiments showed good agreement between the trajectories predicted by the numerical model and observed by acoustically focusing magnetic microbeads in a glass capillary channel, which were deflected towards a high field gradient Halbach array.

Acknowledgments

The authors would like to thank J Fisk and D Salisbury for their contribution to the design and construction of the Halbach array and holder. The authors would like to thank Dharmalingam Prabhakaran of the University of Oxford for helping with magnetometry measurements of magnetic microbeads. The authors are grateful to the Engineering and Physical Sciences Research Council for supporting the work through grant EP/I021795/1.

Appendix A. Magnetic measurements

Measurements of the magnetization curve of polystyrene magnetic microbead particles acquired using a SQUID magnetometer are shown in figure A1. The observed magnetic response was fitted using a Langevin function, as described by (13), assuming that the magnetic phase was magnetite ($M_s = 470 \times 10^3 \text{ kA/m}$ (Margulies et al., 1996)). An effective superparamagnetic cluster size of 8.6 nm and weight loading of 16.2%

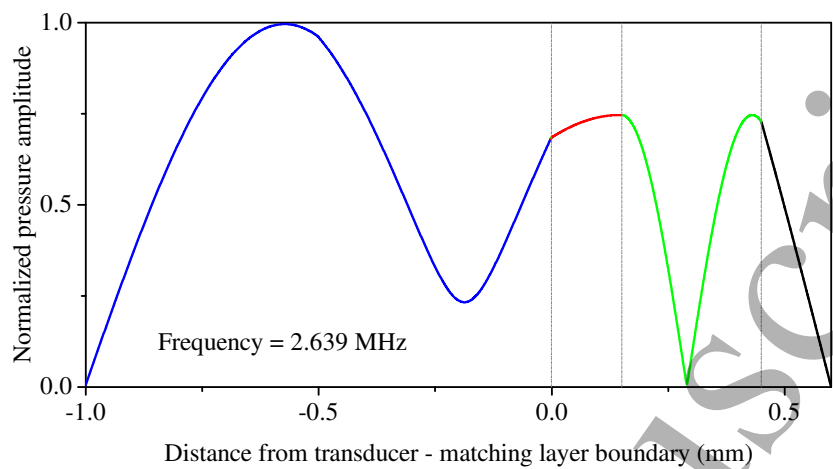


Figure B1. Normalized pressure distribution through the thickness of the device obtained from 1D impedance transfer model, at a resonant frequency of 2.639 MHz. Blue = transducer; red = bottom glass surface; green = fluid cavity; black = top glass surface.

(volumetric ratio of 4.9%) were obtained, which were used in the numerical simulations of trajectories in section 3.2.

Appendix B. Acoustic manipulation of microparticles

In this section we describe the assembly, operation and characterisation of the acoustic manipulation device employed to focus magnetic microbeads into a single trajectory by means of acoustic radiation forces. The device comprised of a squared cross-section borosilicate glass channel (length: 100 mm, internal width: 300 μm , wall thickness: 150 μm ; VitroCom, Ilkley, UK), which was acoustically coupled to a piezoelectric transducer ($24.8 \times 8.6 \times 1 \text{ mm}^3$, PZ26, Meggit PLC, UK) using a thin layer of epoxy resin (RX771C/NC, Robnor Resins Ltd., UK) cured at 30°C for 24 h. The transducer was positioned at a distance of 11.4 mm from the inlet of the channel, and was actuated by a radio frequency (RF) power amplifier (55 dB, Electronics & Innovation, Ltd., USA) driven by a sine-wave from a programmable signal generator (33220A, Agilent Technologies Inc., USA). An oscilloscope (HM2005, Hameg Instruments GmbH, Germany) was used to monitor the applied voltage and the operating frequency.

A one-dimensional (1D) impedance transfer model implemented in MATLAB was employed to identify the operating ultrasound frequency (Hill et al., 2002), while numerical simulations were performed using COMSOL Multiphysics 5.2 (Acoustic-Piezoelectric Interaction module, COMSOL, Inc, Burlington, MA, USA) to determine the two-dimensional (2D) acoustic pressure field.

The 1D model treats the device as a planar resonator (i.e., with plane waves travelling in the thickness direction only) and provides a relatively accurate identification of the thickness resonance frequencies of a multi-layered structure (Hill et al., 2002). The model predicted a half-wave resonant frequency at $\sim 2.64 \text{ MHz}$, with the pressure

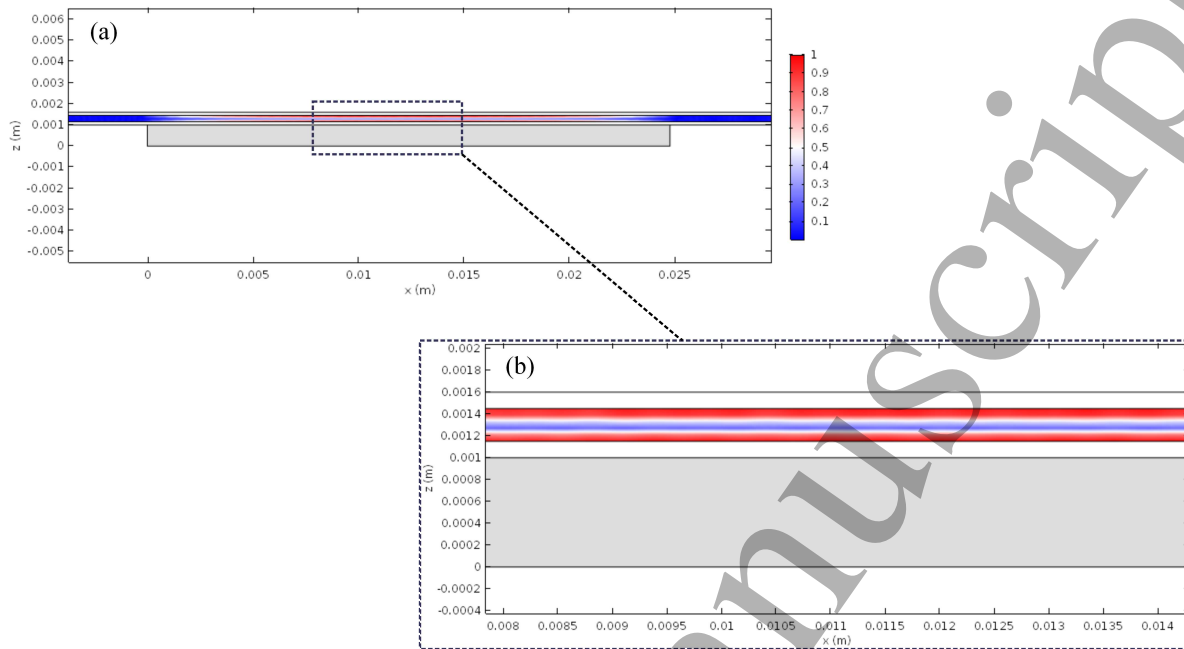


Figure B2. Contours of magnitude of acoustic pressure in the fluid cavity of the channel, normalised with respect to the maximum value. Values were determined numerically (using the Acoustic-Piezoelectric Interaction module in COMSOL Multiphysics). (a) and (b) correspond to a zoomed-out and zoomed-in view of the pressure field in the fluid cavity, respectively. The gray region represents the position of the transducer.

minimum (corresponding to the focusing position of the microparticles) located at $140\ \mu\text{m}$ from the bottom surface of the fluid cavity (figure B1).

The resonant frequency determined from 2D numerical simulations was equal to 2.67 MHz, which was very close to the 1D prediction. Moreover, numerical simulations confirmed the presence of one pressure node, which was located at approximately the mid-plane of the fluid cavity (see figure B2). Notably, figure B2(b) shows that the acoustic pressure field was highly localised in a region of the fluid cavity above the transducer, suggesting that acoustic radiation forces acting on the microbeads could be considered negligible as soon as the beads exited the acoustically active area of the channel.

In order to achieve robust device operation across the range of flow rates investigated and minimise the risk of device going out-of-resonance, the transducer was actuated using a frequency sweeping regime ($2.55 \rightarrow 2.65\ \text{MHz}$) at a sweep period of 50 ms. At this operating regime, microparticles experienced forces acting both horizontally and vertically towards the centreline of the channel, which originated from gradients in the potential and kinetic acoustic energy densities respectively, as reported previously in very similar resonant cavities (Mishra et al., 2014).

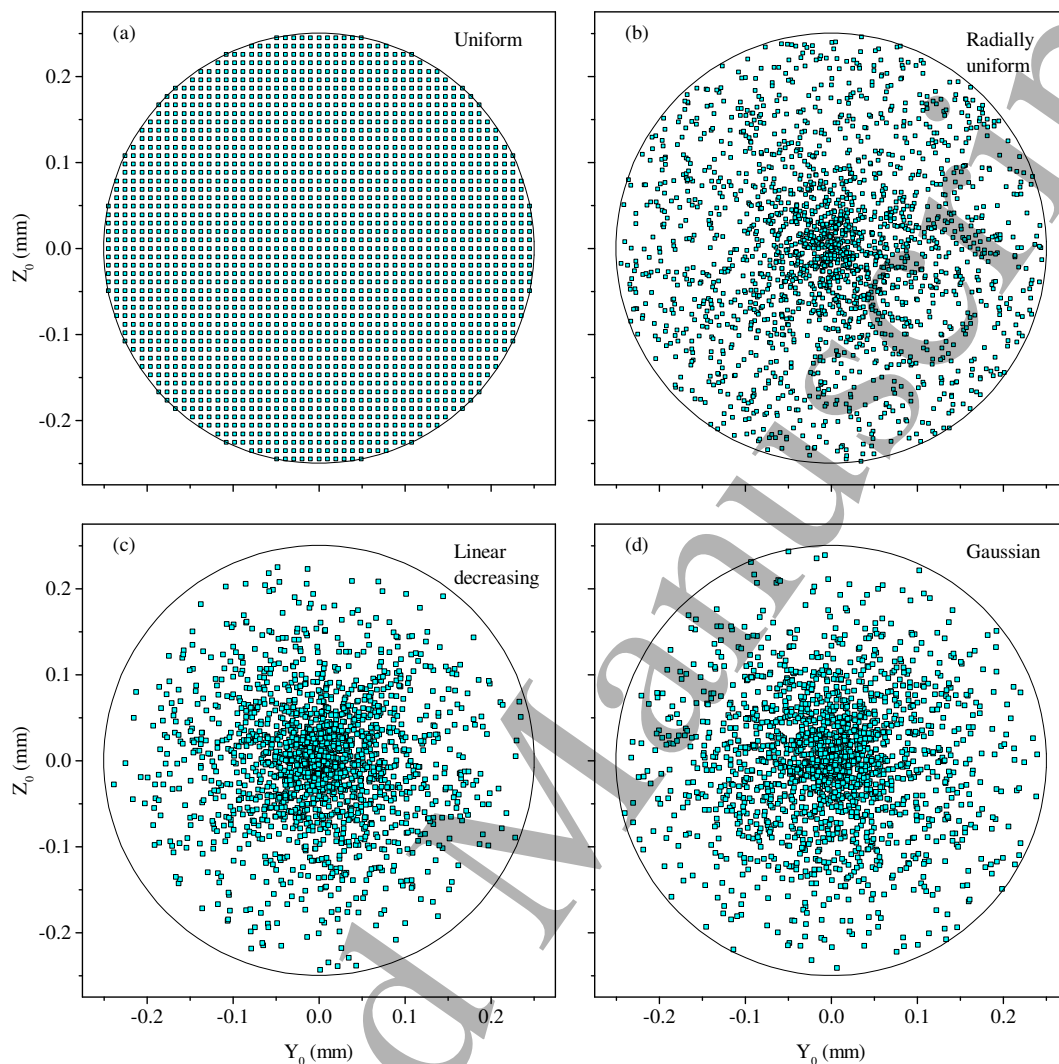


Figure C1. Various, initial distributions of 2000 particles at the inlet of the channel. (a) Even, uniform distribution used for most simulations reported above. The probability that a given particle has an initial distance from the central axis, ϱ in each distribution (b) radially uniform, (c) linearly decreasing and (d) Gaussian is given in (3.1a), (3.1b) and (3.1c) respectively.

Appendix C. Capture efficiency with different initial conditions

A semi-analytical expression for capture efficiency was derived by considering the proportion of final resting positions of an ensemble of particles, determined using (7), initially distributed evenly about the cross-section at the starting position. For all tested combinations of parameters with an even initial distribution, the capture efficiency was found to be well described by (8). Three other initial distributions were tested, described in this appendix.

The even, or uniform, distribution is shown in figure C1(a). The other distributions were determined using probability distribution functions (PDF), $p(\varrho)$ where $\varrho = \sqrt{y_0^2 + z_0^2}$ is the initial radial distance from the central axis of the channel. The PDFs

REFERENCES

28

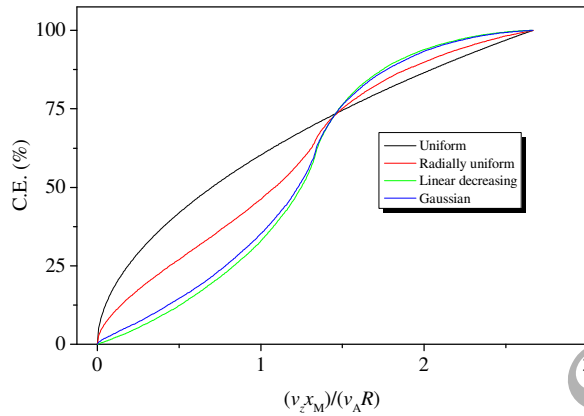


Figure C2. Capture efficiencies determined using different combinations of the non-dimensional parameter $(v_z x_M) / (v_A R)$ and the different initial distributions shown in figure C1.

were:

$$\text{Radially uniform : } p(\varrho) = \frac{1}{R} \quad (3.1a)$$

$$\text{Linearly decreasing : } p(\varrho) = \frac{2}{R} \left(1 - \frac{\varrho}{R}\right) \quad (3.1b)$$

$$\text{Gaussian : } p(\varrho) = \frac{2}{R\sqrt{\pi}\text{erf}(1)} \exp\left(-2\left(\frac{\varrho}{R}\right)^2\right). \quad (3.1c)$$

All values of ϱ are equally likely for the radially uniform distribution, while for the linearly decreasing distribution, the probability of a particle starting at the centre is greatest and at the wall is zero. The Gaussian distribution has a standard deviation of $R/2$ and the $\text{erf}(1)$ term accounts for the fact that the probability of a particle at the channel wall ($\varrho = R$) is not zero. All PDFs total 1 when integrated from the centre of the channel to the wall. Probabilistic particle distributions plotted in figure C1(b)-(d) display 2000 particles, but 25000 particle trajectories were calculated to determine the capture efficiencies exhibited in figure C2. Figure C2 shows how all tested distributions depend on the non-dimensional parameter, $(v_z x_M) / (v_A R)$ and the initial distribution. The uniform (black) curve was fitted to the power law in (8). As the accumulation distribution can be determined from the derivative of C.E. (x) with respect to x , this would suggest that the accumulation distribution would also depend on the initial particle distribution.

References

Mohsen Akbari, David Sinton, and Majid Bahrami. Laminar fully developed flow in periodically convergingdiverging microtubes. *Heat Transfer Engineering*, 31(8):628–634, 2010. doi: 10.1080/01457630903463404. URL <http://dx.doi.org/10.1080/01457630903463404>.

C. Alexiou, D. Diehl, P. Henninger, H. Iro, R. Rockelein, W. Schmidt, and H. Weber.

REFERENCES

29

- A high field gradient magnet for magnetic drug targeting. *Applied Superconductivity, IEEE Transactions on*, 16(2):1527–1530, June 2006. ISSN 1051-8223. doi: 10.1109/TASC.2005.864457.
- Christoph Alexiou, Wolfgang Arnold, Roswitha J. Klein, Fritz G. Parak, Peter Hulin, Christian Bergemann, Wolfgang Erhardt, Stefan Wagenpfeil, and Andreas S. Lübke. Locoregional cancer treatment with magnetic drug targeting. *Cancer Research*, 60(23):6641–6648, 2000. URL <http://cancerres.aacrjournals.org/content/60/23/6641.abstract>.
- Lester C Barnsley, Dario Carugo, Joshua Owen, and Eleanor Stride. Halbach arrays consisting of cubic elements optimised for high field gradients in magnetic drug targeting applications. *Physics in Medicine and Biology*, 60(21):8303, 2015. URL <http://stacks.iop.org/0031-9155/60/i=21/a=8303>.
- Lester C Barnsley, Dario Carugo, and Eleanor Stride. Optimized shapes of magnetic arrays for drug targeting applications. *Journal of Physics D: Applied Physics*, 49(22):225501, 2016. URL <http://stacks.iop.org/0022-3727/49/i=22/a=225501>.
- C. P. Bean and J. D. Livingston. Superparamagnetism. *Journal of Applied Physics*, 30(4):S120–S129, 1959. doi: 10.1063/1.2185850. URL <http://scitation.aip.org/content/aip/journal/jap/30/4/10.1063/1.2185850>.
- S Biederer, T Knopp, T F Sattel, K Ldtke-Buzug, B Gleich, J Weizenecker, J Borgert, and T M Buzug. Magnetization response spectroscopy of superparamagnetic nanoparticles for magnetic particle imaging. *Journal of Physics D: Applied Physics*, 42(20):205007, 2009. URL <http://stacks.iop.org/0022-3727/42/i=20/a=205007>.
- Sayan Bose and Moloy Banerjee. Magnetic particle capture for biomagnetic fluid flow in stenosed aortic bifurcation considering particlefluid coupling. *Journal of Magnetism and Magnetic Materials*, 385:32 – 46, 2015a. ISSN 0304-8853. doi: <http://dx.doi.org/10.1016/j.jmmm.2015.02.060>. URL <http://www.sciencedirect.com/science/article/pii/S0304885315002012>.
- Sayan Bose and Moloy Banerjee. Effect of non-newtonian characteristics of blood on magnetic particle capture in occluded blood vessel. *Journal of Magnetism and Magnetic Materials*, 374(0):611 – 623, 2015b. ISSN 0304-8853. doi: 10.1016/j.jmmm.2014.09.012. URL <http://www.sciencedirect.com/science/article/pii/S0304885314008312>.
- Quanliang Cao, Xiaotao Han, and Liang Li. Numerical analysis of magnetic nanoparticle transport in microfluidic systems under the influence of permanent magnets. *Journal of Physics D: Applied Physics*, 45(46):465001, 2012. URL <http://stacks.iop.org/0022-3727/45/i=46/a=465001>.
- Quanliang Cao, Xiaotao Han, and Liang Li. Two-dimensional manipulation of magnetic nanoparticles in microfluidic systems. *Applied Physics Express*, 6(2):025201, 2013. URL <http://stacks.iop.org/1882-0786/6/i=2/a=025201>.
- Erica M. Cherry and John K. Eaton. A comprehensive model of magnetic particle motion during magnetic drug targeting. *International Journal of Multiphase Flow*, 59(0):173

REFERENCES

30

- 185, 2014. ISSN 0301-9322. doi: 10.1016/j.ijmultiphaseflow.2013.11.007. URL <http://www.sciencedirect.com/science/article/pii/S0301932213001924>.
- Beata Chertok, Bradford A. Moffat, Allan E. David, Faquan Yu, Christian Bergemann, Brian D. Ross, and Victor C. Yang. Iron oxide nanoparticles as a drug delivery vehicle for mri monitored magnetic targeting of brain tumors. *Biomaterials*, 29(4): 487 – 496, 2008. ISSN 0142-9612. doi: 10.1016/j.biomaterials.2007.08.050. URL <http://www.sciencedirect.com/science/article/pii/S0142961207007910>.
- Calum Crake, Marie de Saint Victor, Joshua Owen, Christian Coviello, Jamie Collin, Constantin-C Coussios, and Eleanor Stride. Passive acoustic mapping of magnetic microbubbles for cavitation enhancement and localization. *Physics in Medicine and Biology*, 60(2):785, 2015. URL <http://stacks.iop.org/0031-9155/60/i=2/a=785>.
- P.J. Cregg, Kieran Murphy, and Adil Mardinoglu. Calculation of nanoparticle capture efficiency in magnetic drug targeting. *Journal of Magnetism and Magnetic Materials*, 320(23):3272 – 3275, 2008. ISSN 0304-8853. doi: <http://dx.doi.org/10.1016/j.jmmm.2008.06.021>. URL <http://www.sciencedirect.com/science/article/pii/S030488530800718X>.
- Manasmita Das, Debasish Mishra, T K Maiti, A Basak, and P Pramanik. Bio-functionalization of magnetite nanoparticles using an aminophosphonic acid coupling agent: new, ultradispersed, iron-oxide folate nanoconjugates for cancer-specific targeting. *Nanotechnology*, 19(41):415101, 2008. URL <http://stacks.iop.org/0957-4484/19/i=41/a=415101>.
- Jon Dobson. Magnetic nanoparticles for drug delivery. *Drug Development Research*, 67(1):55–60, 2006. ISSN 1098-2299. doi: 10.1002/ddr.20067. URL <http://dx.doi.org/10.1002/ddr.20067>.
- Charles F. Driscoll, Robert M. Morris, Andrew E. Senyei, Kenneth J. Widder, and Gerald S. Heller. Magnetic targeting of microspheres in blood flow. *Microvascular Research*, 27(3):353 – 369, 1984. ISSN 0026-2862. doi: 10.1016/0026-2862(84)90065-7. URL <http://www.sciencedirect.com/science/article/pii/0026286284900657>.
- Ching-Hsiang Fan, Chien-Yu Ting, Han-Jung Lin, Chung-Hsin Wang, Hao-Li Liu, Tzu-Chen Yen, and Chih-Kuang Yeh. Spio-conjugated, doxorubicin-loaded microbubbles for concurrent mri and focused-ultrasound enhanced brain-tumor drug delivery. *Biomaterials*, 34(14):3706 – 3715, 2013. ISSN 0142-9612. doi: <http://dx.doi.org/10.1016/j.biomaterials.2013.01.099>. URL <http://www.sciencedirect.com/science/article/pii/S0142961213001671>.
- A. Garraud, C. Velez, Y. Shah, N. Garraud, B. Kozissnik, E. G. Yarmola, K. D. Allen, J. Dobson, and D. P. Arnold. Investigation of the capture of magnetic particles from high-viscosity fluids using permanent magnets. *IEEE Transactions on Biomedical Engineering*, 63(2):372–378, Feb 2016. ISSN 0018-9294. doi: 10.1109/TBME.2015.2458783.
- Anne-Laure Gassner, Melanie Abonnenc, Hong-Xu Chen, Jacques Morandini, Jacques Josserand, Joel S. Rossier, Jean-Marc Busnel, and Hubert H. Gi-

REFERENCES

31

- rault. Magnetic forces produced by rectangular permanent magnets in static microsystems. *Lab Chip*, 9:2356–2363, 2009. doi: 10.1039/B901865D. URL <http://dx.doi.org/10.1039/B901865D>.
- B. Gleich, N. Hellwig, H. Bridell, R. Jurgons, C. Seliger, C. Alexiou, B. Wolf, and T. Weyh. Design and evaluation of magnetic fields for nanoparticle drug targeting in cancer. *IEEE Transactions on Nanotechnology*, 6(2):164–170, March 2007. ISSN 1536-125X. doi: 10.1109/TNANO.2007.891829.
- Bernhard Gleich and Jürgen Weizenecker. Tomographic imaging using the nonlinear response of magnetic particles. *Nature*, 435(7046):1214–1217, 2005. doi: 10.1038/nature03808.
- Andrew D. Grief and Giles Richardson. Mathematical modelling of magnetically targeted drug delivery. *Journal of Magnetism and Magnetic Materials*, 293(1): 455 – 463, 2005. ISSN 0304-8853. doi: 10.1016/j.jmmm.2005.02.040. URL <http://www.sciencedirect.com/science/article/pii/S0304885305002015>. Proceedings of the Fifth International Conference on Scientific and Clinical Applications of Magnetic Carriers.
- U. Ayanthi Gunasekera, Quentin A. Pankhurst, and Michael Douek. Imaging applications of nanotechnology in cancer. *Targeted Oncology*, 4(3):169–181, 2009. ISSN 1776-260X. doi: 10.1007/s11523-009-0118-9. URL <http://dx.doi.org/10.1007/s11523-009-0118-9>.
- Urs O. Häfeli, Kelly Gilmour, Amy Zhou, Stanley Lee, and Michael E. Hayden. Modeling of magnetic bandages for drug targeting: Button vs. halbach arrays. *Journal of Magnetism and Magnetic Materials*, 311(1):323 – 329, 2007. ISSN 0304-8853. doi: 10.1016/j.jmmm.2006.10.1152. URL <http://www.sciencedirect.com/science/article/pii/S0304885306025364>. Proceedings of the Sixth International Conference on the Scientific and Clinical Applications of Magnetic Carriers SCAMC-06.
- M E Hayden and U O Häfeli. 'magnetic bandages' for targeted delivery of therapeutic agents. *Journal of Physics: Condensed Matter*, 18(38):S2877, 2006. URL <http://stacks.iop.org/0953-8984/18/i=38/a=S23>.
- Martyn Hill, Yijun Shen, and Jeremy J. Hawkes. Modelling of layered resonators for ultrasonic separation. *Ultrasonics*, 40(18):385 – 392, 2002. ISSN 0041-624X. doi: [http://dx.doi.org/10.1016/S0041-624X\(02\)00127-0](http://dx.doi.org/10.1016/S0041-624X(02)00127-0). URL <http://www.sciencedirect.com/science/article/pii/S0041624X02001270>.
- Bettina Kozissnik and Jon Dobson. Biomedical applications of mesoscale magnetic particles. *MRS Bulletin*, 38:927–932, 11 2013. ISSN 1938-1425. doi: 10.1557/mrs.2013.257. URL <http://dx.doi.org/10.1557/mrs.2013.257>.
- Sophie Laurent, Amir Ata Saei, Shahed Behzadi, Arash Panahifar, and Morteza Mahmoudi. Superparamagnetic iron oxide nanoparticles for delivery of therapeutic agents: opportunities and challenges. *Expert Opinion on Drug De-*

REFERENCES

32

- livery*, 11(9):1449–1470, 2014. doi: 10.1517/17425247.2014.924501. URL <http://dx.doi.org/10.1517/17425247.2014.924501>. PMID: 24870351.
- Jeong Yu Lee, Dario Carugo, Calum Crake, Joshua Owen, Marie de Saint Victor, Anjali Seth, Constantin Coussios, and Eleanor Stride. Nanoparticle-loaded proteinpolymer nanodroplets for improved stability and conversion efficiency in ultrasound imaging and drug delivery. *Advanced Materials*, 27(37):5484–5492, 2015. ISSN 1521-4095. doi: 10.1002/adma.201502022. URL <http://dx.doi.org/10.1002/adma.201502022>.
- John Lekner. Viscous flow through pipes of various cross-sections. *European Journal of Physics*, 28(3):521, 2007. URL <http://stacks.iop.org/0143-0807/28/i=3/a=014>.
- Zhe Liu, Twan Lammers, Josef Ehling, Stanley Fokong, Jrg Bornemann, Fabian Kiessling, and Jessica Gätjens. Iron oxide nanoparticle-containing microbubble composites as contrast agents for {MR} and ultrasound dual-modality imaging. *Biomaterials*, 32(26):6155 – 6163, 2011. ISSN 0142-9612. doi: 10.1016/j.biomaterials.2011.05.019. URL <http://www.sciencedirect.com/science/article/pii/S0142961211005382>.
- Andreas S. Lübbe, Christian Bergemann, Jeffery Brock, and David G. McClure. Physiological aspects in magnetic drug-targeting. *Journal of Magnetism and Magnetic Materials*, 194(13):149 – 155, 1999. ISSN 0304-8853. doi: 10.1016/S0304-8853(98)00574-5. URL <http://www.sciencedirect.com/science/article/pii/S0304885398005745>.
- Andreas S. Lübbe, Christoph Alexiou, and Christian Bergemann. Clinical applications of magnetic drug targeting. *Journal of Surgical Research*, 95(2):200 – 206, 2001. ISSN 0022-4804. doi: 10.1006/jsre.2000.6030. URL <http://www.sciencedirect.com/science/article/pii/S002248040096030X>.
- Andreas Stephan Lübbe, Christian Bergemann, Hanno Riess, Folke Schriever, Peter Reichardt, Kurt Possinger, Michael Matthias, Bernd Drken, Friedhelm Herrmann, Renate Gürtler, Peter Hohenberger, Norbert Haas, Reinhard Sohr, Bernhard Sander, Arne-Jürgen Lemke, Dieter Ohlendorf, Winfried Huhnt, and Dieter Huhn. Clinical experiences with magnetic drug targeting: A phase i study with 4?-epidoxorubicin in 14 patients with advanced solid tumors. *Cancer Research*, 56(20):4686–4693, 1996. URL <http://cancerres.aacrjournals.org/content/56/20/4686.abstract>.
- Thodsaphon Lunnoo and Theerapong Puangmali. Capture efficiency of biocompatible magnetic nanoparticles in arterial flow: A computer simulation for magnetic drug targeting. *Nanoscale Research Letters*, 10(1):1–11, 2015. ISSN 1556-276X. doi: 10.1186/s11671-015-1127-5. URL <http://dx.doi.org/10.1186/s11671-015-1127-5>.
- Hiroshi Maeda. Macromolecular therapeutics in cancer treatment: The {EPR} effect and beyond. *Journal of Controlled Release*, 164(2):138 – 144, 2012. ISSN 0168-3659. doi: <http://dx.doi.org/10.1016/j.jconrel.2012.04.038>. URL <http://www.sciencedirect.com/science/article/pii/S0168365912003197>.
- Drug Delivery and Cancer: Today’s Challenges, Tomorrow’s Directions.

REFERENCES

33

- S.A. Majetich, J.H. Scott, E.M. Kirkpatrick, K. Chowdary, K. Gallagher, and M.E. McHenry. Magnetic nanoparticles and magnetocrystalline anisotropy. *Nanostructured Materials*, 9(18):291 – 300, 1997. ISSN 0965-9773. doi: 10.1016/S0965-9773(97)90069-6. URL <http://www.sciencedirect.com/science/article/pii/S0965977397900696>.
- Jan O. Mangual, Shigeng Li, Harry J. Ploehn, Armin D. Ebner, and James A. Ritter. Biodegradable nanocomposite magnetite stent for implant-assisted magnetic drug targeting. *Journal of Magnetism and Magnetic Materials*, 322(20):3094 – 3100, 2010. ISSN 0304-8853. doi: 10.1016/j.jmmm.2010.05.036. URL <http://www.sciencedirect.com/science/article/pii/S0304885310003434>.
- D. T. Margulies, F. T. Parker, F. E. Spada, R. S. Goldman, J. Li, R. Sinclair, and A. E. Berkowitz. Anomalous moment and anisotropy behavior in Fe_3O_4 films. *Phys. Rev. B*, 53:9175–9187, Apr 1996. doi: 10.1103/PhysRevB.53.9175. URL <http://link.aps.org/doi/10.1103/PhysRevB.53.9175>.
- Sylvain Martel, Jean-Baptiste Mathieu, Ouajdi Felfoul, Arnaud Chanu, Eric Abousouan, Samer Tamaz, Pierre Pouponneau, LHocine Yahia, Gilles Beaudoin, Gilles Soulez, and Martin Mankiewicz. Automatic navigation of an untethered device in the artery of a living animal using a conventional clinical magnetic resonance imaging system. *Applied Physics Letters*, 90(11):114105, 2007. doi: 10.1063/1.2713229. URL <http://scitation.aip.org/content/aip/journal/apl/90/11/10.1063/1.2713229>.
- Jean-Baptiste Mathieu and Sylvain Martel. Aggregation of magnetic microparticles in the context of targeted therapies actuated by a magnetic resonance imaging system. *Journal of Applied Physics*, 106(4):044904, 2009. doi: <http://dx.doi.org/10.1063/1.3159645>. URL <http://scitation.aip.org/content/aip/journal/jap/106/4/10.1063/1.3159645>.
- Jean-Baptiste Mathieu, G. Beaudoin, and S. Martel. Method of propulsion of a ferromagnetic core in the cardiovascular system through magnetic gradients generated by an mri system. *Biomedical Engineering, IEEE Transactions on*, 53(2):292–299, Feb 2006. ISSN 0018-9294. doi: 10.1109/TBME.2005.862570.
- Yasuhiro Matsumura and Hiroshi Maeda. A new concept for macromolecular therapeutics in cancer chemotherapy: Mechanism of tumortropic accumulation of proteins and the antitumor agent smancs. *Cancer Research*, 46(12 Part 1):6387–6392, 1986. ISSN 0008-5472. URL http://cancerres.aacrjournals.org/content/46/12_Part_1/6387.
- S C McBain, U Griesenbach, S Xenariou, A Keramane, C D Batich, E W F W Alton, and J Dobson. Magnetic nanoparticles as gene delivery agents: enhanced transfection in the presence of oscillating magnet arrays. *Nanotechnology*, 19(40):405102, 2008. URL <http://stacks.iop.org/0957-4484/19/i=40/a=405102>.
- Puja Mishra, Martyn Hill, and Peter Glynne-Jones. Deformation of red blood cells using acoustic radiation forces. *Biomicrofluidics*, 8

REFERENCES

34

- (3):034109, 2014. doi: <http://dx.doi.org/10.1063/1.4882777>. URL <http://scitation.aip.org/content/aip/journal/bmf/8/3/10.1063/1.4882777>.
- A. Nacev, C. Beni, O. Bruno, and B. Shapiro. The behaviors of ferromagnetic nano-particles in and around blood vessels under applied magnetic fields. *Journal of Magnetism and Magnetic Materials*, 323(6):651 – 668, 2011a. ISSN 0304-8853. doi: 10.1016/j.jmmm.2010.09.008. URL <http://www.sciencedirect.com/science/article/pii/S0304885310006347>.
- Alek Nacev, Skye H Kim, Jaime Rodriguez-Canales, Michael A Tangrea, Benjamin Shapiro, and Michael R Emmert-Buck. A dynamic magnetic shift method to increase nanoparticle concentration in cancer metastases: a feasibility study using simulations on autopsy specimens. *International journal of nanomedicine*, 6:2907, 2011b. doi: 10.2147/IJN.S23724.
- Krishanu Nandy, Sayani Chaudhuri, Ranjan Ganguly, and Ishwar K. Puri. Analytical model for the magnetophoretic capture of magnetic microspheres in microfluidic devices. *Journal of Magnetism and Magnetic Materials*, 320(7):1398 – 1405, 2008. ISSN 0304-8853. doi: <http://dx.doi.org/10.1016/j.jmmm.2007.11.024>. URL <http://www.sciencedirect.com/science/article/pii/S0304885307009833>.
- Olayinka Oduwale, David Tim Grob, and Steve Sheard. Comparison between simulation and experimentally observed interactions between two magnetic beads in a fluidic system. *Journal of Magnetism and Magnetic Materials*, 407:8 – 12, 2016. ISSN 0304-8853. doi: <http://dx.doi.org/10.1016/j.jmmm.2016.01.043>. URL <http://www.sciencedirect.com/science/article/pii/S0304885316300439>.
- Joshua Owen, Philip Grove, Paul Rademeyer, and Eleanor Stride. The influence of blood on targeted microbubbles. *Journal of The Royal Society Interface*, 11(100), 2014. ISSN 1742-5689. doi: 10.1098/rsif.2014.0622.
- Joshua Owen, Paul Rademeyer, Daniel Chung, Qian Cheng, David Holroyd, Constantin Coussios, Peter Friend, Quentin A. Pankhurst, and Eleanor Stride. Magnetic targeting of microbubbles against physiologically relevant flow conditions. *Interface Focus*, 5(5), 2015. ISSN 2042-8898. doi: 10.1098/rsfs.2015.0001.
- Q A Pankhurst, J Connolly, S K Jones, and J Dobson. Applications of magnetic nanoparticles in biomedicine. *Journal of Physics D: Applied Physics*, 36(13):R167, 2003. URL <http://stacks.iop.org/0022-3727/36/i=13/a=201>.
- Q A Pankhurst, N T K Thanh, S K Jones, and J Dobson. Progress in applications of magnetic nanoparticles in biomedicine. *Journal of Physics D: Applied Physics*, 42(22):224001, 2009. URL <http://stacks.iop.org/0022-3727/42/i=22/a=224001>.
- Pierre Pouponneau, Jean-Christophe Leroux, Gilles Soulez, Louis Gaboury, and Sylvain Martel. Co-encapsulation of magnetic nanoparticles and doxorubicin into biodegradable microcarriers for deep tissue targeting by vascular mri navigation. *Biomaterials*, 32(13):3481 – 3486, 2011. ISSN 0142-9612. doi: <http://dx.doi.org/10.1016/j.biomaterials.2010.12.059>. URL <http://www.sciencedirect.com/science/article/pii/S0142961211000780>.

REFERENCES

35

- James A Ritter, Armin D Ebner, Karen D Daniel, and Krystle L Stewart. Application of high gradient magnetic separation principles to magnetic drug targeting. *Journal of Magnetism and Magnetic Materials*, 280(23):184 – 201, 2004. ISSN 0304-8853. doi: 10.1016/j.jmmm.2004.03.012. URL <http://www.sciencedirect.com/science/article/pii/S0304885304002768>.
- A. Sarwar, A. Nemirovski, and B. Shapiro. Optimal halbach permanent magnet designs for maximally pulling and pushing nanoparticles. *Journal of Magnetism and Magnetic Materials*, 324(5):742 – 754, 2012. ISSN 0304-8853. doi: 10.1016/j.jmmm.2011.09.008. URL <http://www.sciencedirect.com/science/article/pii/S0304885311006664>.
- Timo F Sattel, Tobias Knopp, Sven Biederer, Bernhard Gleich, Juergen Weizenecker, Joern Borgert, and Thorsten M Buzug. Single-sided device for magnetic particle imaging. *Journal of Physics D: Applied Physics*, 42(2):022001, 2009. URL <http://stacks.iop.org/0022-3727/42/i=2/a=022001>.
- John F. Schenck. Safety of strong, static magnetic fields. *Journal of Magnetic Resonance Imaging*, 12(1):2–19, 2000. ISSN 1522-2586. doi: 10.1002/1522-2586(200007)12:1<2::AID-JMRI2>3.0.CO;2-V. URL [http://dx.doi.org/10.1002/1522-2586\(200007\)12:1<2::AID-JMRI2>3.0.CO;2-V](http://dx.doi.org/10.1002/1522-2586(200007)12:1<2::AID-JMRI2>3.0.CO;2-V).
- Nathalie Schleich, Chrystelle Po, Damien Jacobs, Bernard Ucakar, Bernard Gallez, Fabienne Danhier, and Vronique Prat. Comparison of active, passive and magnetic targeting to tumors of multifunctional paclitaxel/spio-loaded nanoparticles for tumor imaging and therapy. *Journal of Controlled Release*, 194(0):82 – 91, 2014. ISSN 0168-3659. doi: 10.1016/j.jconrel.2014.07.059. URL <http://www.sciencedirect.com/science/article/pii/S0168365914005793>.
- Nathalie Schleich, Fabienne Danhier, and Vronique Prat. Iron oxide-loaded nanotheranostics: Major obstacles to in vivo studies and clinical translation. *Journal of Controlled Release*, 198(0):35 – 54, 2015. ISSN 0168-3659. doi: 10.1016/j.jconrel.2014.11.024. URL <http://www.sciencedirect.com/science/article/pii/S016836591400772X>.
- B. Shapiro, S. Kulkarni, A. Nacev, A. Sarwar, D. Preciado, and D.A. Depireux. Shaping magnetic fields to direct therapy to ears and eyes. *Annual Review of Biomedical Engineering*, 16(1):455–481, 2014. doi: 10.1146/annurev-bioeng-071813-105206. URL <http://dx.doi.org/10.1146/annurev-bioeng-071813-105206>. PMID: 25014789.
- Benjamin Shapiro, Sandip Kulkarni, Aleksander Nacev, Silvia Muro, Pavel Y. Stepanov, and Irving N. Weinberg. Open challenges in magnetic drug targeting. *Wiley Interdisciplinary Reviews: Nanomedicine and Nanobiotechnology*, 7(3):446–457, 2015. ISSN 1939-0041. doi: 10.1002/wnan.1311. URL <http://dx.doi.org/10.1002/wnan.1311>.
- Shashi Sharma, V.K. Katiyar, and Uaday Singh. Mathematical modelling for trajectories of magnetic nanoparticles in a blood vessel under magnetic field. *Journal of Magnetism and Magnetic Materials*, 379:102 – 107, 2015.

REFERENCES

36

- ISSN 0304-8853. doi: <http://dx.doi.org/10.1016/j.jmmm.2014.12.012>. URL <http://www.sciencedirect.com/science/article/pii/S0304885314012141>.
- K Shimamoto, S Sakuma, T Ishigaki, and N Makino. Intratumoral blood flow: evaluation with color doppler echography. *Radiology*, 165(3):683–685, 1987. doi: 10.1148/radiology.165.3.2825234. URL <http://dx.doi.org/10.1148/radiology.165.3.2825234>. PMID: 2825234.
- Eleanor Stride, Colin Porter, Ana Garcia Prieto, and Quentin Pankhurst. Enhancement of microbubble mediated gene delivery by simultaneous exposure to ultrasonic and magnetic fields. *Ultrasound in Medicine & Biology*, 35(5):861 – 868, 2009. ISSN 0301-5629. doi: 10.1016/j.ultrasmedbio.2008.11.010. URL <http://www.sciencedirect.com/science/article/pii/S0301562908005498>.
- Shinichi Takeda, Fumihito Mishima, Suketaka Fujimoto, Yoshinobu Izumi, and Shigehiro Nishijima. Development of magnetically targeted drug delivery system using superconducting magnet. *Journal of Magnetism and Magnetic Materials*, 311(1):367 – 371, 2007. ISSN 0304-8853. doi: 10.1016/j.jmmm.2006.10.1195. URL <http://www.sciencedirect.com/science/article/pii/S0304885306025959>.
- Proceedings of the Sixth International Conference on the Scientific and Clinical Applications of Magnetic Carriers SCAMC-06.
- M.D. Tehrani, Myeong Ok Kim, and Jungwon Yoon. A novel electromagnetic actuation system for magnetic nanoparticle guidance in blood vessels. *Magnetics, IEEE Transactions on*, 50(7):1–12, July 2014. ISSN 0018-9464. doi: 10.1109/TMAG.2014.2307271.
- M.D. Tehrani, Jong-Hwan Yoon, V. Kim, and Jungwon Yoon. A novel scheme for nanoparticle steering in blood vessels using a functionalized magnetic field. *Biomedical Engineering, IEEE Transactions on*, 62(1):303–313, Jan 2015. ISSN 0018-9294. doi: 10.1109/TBME.2014.2351234.
- Aniket S. Wadajkar, Zarna Bhavsar, Cheng-Yu Ko, Bhanuprasanth Koppolu, Weina Cui, Liping Tang, and Kytai T. Nguyen. Multifunctional particles for melanoma-targeted drug delivery. *Acta Biomaterialia*, 8(8):2996 – 3004, 2012. ISSN 1742-7061. doi: <http://dx.doi.org/10.1016/j.actbio.2012.04.042>. URL <http://www.sciencedirect.com/science/article/pii/S1742706112002000>.
- H.D. Williams, K. O’Grady, M. El Hilo, and R.W. Chantrell. Superparamagnetism in fine particle dispersions. *Journal of Magnetism and Magnetic Materials*, 122(13):129 – 133, 1993. ISSN 0304-8853. doi: 10.1016/0304-8853(93)91056-D. URL <http://www.sciencedirect.com/science/article/pii/030488539391056D>.
- He-Lin Xu, Kai-Li Mao, Yin-Ping Huang, Jing-Jing Yang, Jie Xu, Pian-Pian Chen, Zi-Liang Fan, Shuang Zou, Zheng-Zheng Gao, Jia-Yu Yin, Jian Xiao, Cui-Tao Lu, Bao-Lin Zhang, and Ying-Zheng Zhao. Glioma-targeted superparamagnetic iron oxide nanoparticles as drug-carrying vehicles for theranostic effects. *Nanoscale*, 8:14222–14236, 2016. doi: 10.1039/C6NR02448C. URL <http://dx.doi.org/10.1039/C6NR02448C>.

REFERENCES

37

Jian-Bao Zhang and Zhen-Bang Kuang. Study on blood constitutive parameters in different blood constitutive equations. *Journal of Biomechanics*, 33(3):355 – 360, 2000. ISSN 0021-9290. doi: [http://dx.doi.org/10.1016/S0021-9290\(99\)00101-3](http://dx.doi.org/10.1016/S0021-9290(99)00101-3). URL <http://www.sciencedirect.com/science/article/pii/S0021929099001013>.

Ran Zhou and Cheng Wang. Microfluidic separation of magnetic particles with soft magnetic microstructures. *Microfluidics and Nanofluidics*, 20(3): 1–11, 2016. ISSN 1613-4990. doi: 10.1007/s10404-016-1714-5. URL <http://dx.doi.org/10.1007/s10404-016-1714-5>.