A Combined Magnetic-Acoustic Device for Simultaneous, Coaligned Application of Magnetic and Ultrasonic Fields

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Acoustically-responsive microbubbles have been widely researched as agents for both diagnostic and therapeutic applications of ultrasound. There has also been considerable interest in magnetically-functionallized microbubbles as multi-modality imaging agents and carriers for targeted drug delivery. In this paper, a design for an integrated device capable of generating co-aligned magnetic and acoustic fields in order to accumulate microbubbles at a specific location and to activate them acoustically. For this proof-of-concept study, the device was designed to concentrate microbubbles at a distance of 10 mm from the probe’s surface, commensurate with relevant tissue depths in preclinical small animal models. Previous studies have indicated that both microbubble concentration and duration of cavitation activity are positively correlated with therapeutic effect. The utility of the device was assessed in vitro tests in a tissue-mimicking phantom containing a single vessel (1.2 mm diameter). At a peak fluid velocity of 4.2 mm s$^{-1}$ microbubble accumulation was observed under B-mode ultrasound imaging and the corresponding cavitation activity was sustained for a period more than 4 times longer than that achieved with an identical acoustic field but in the absence of a magnet. The feasibility of developing a larger scale device for human applications is discussed.

1. Introduction

Whilst the concept of magnetic drug targeting (MDT) is more than fifty years old,[1] the development of magnetically respons-

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concentrate and stimulate magnetic microbubbles. The magnetic component has been optimized using our previously reported algorithm to deliver the maximal magnetic force to a position of interest marked as $z_{opt}$. The light-red surface shows the $x$-$y$ plane, and the origin is indicated by a black circle. The teal volume was excluded from the optimization to make space for an integrated ultrasound transducer and auxiliary components. B) Cross-section in the $x$-$z$ plane of the magnet design based on the result of the optimization routine. The magnet was manufactured in two parts with parallel magnetization directions to self-assemble in only one stable configuration. C) Ultrasound element assembly showing piezoelectric disk and glass lens. D) Magnetic-acoustic device (MAD) assembly. E) Side by side photograph of the MAD and the nonmagnetic device manufactured for control measurements. F) Photograph illustrating how the MAD is capable of actuating and accumulating a suspension of iron oxide nanoparticles. All dimensions in mm.

2. Results

2.1. Finalized Design

A schematic of the combined MAD is shown in Figure 1. The magnetic field is produced by a uniformly magnetized volume of magnetic material. The shape of the magnet was determined using our previously described optimization routine. The ultrasonic component has been shaped to apply a focused acoustic field over the same region. The device reported here has been designed for length scales relevant to preclinical animal models as a proof of concept. Designs for clinically relevant tissue depths are discussed later.
a position of interest \((z_{\text{opt}})\), in this case \(10\) mm from the face of the device. The optimization domain is shown in Figure 1A within a red cubic frame, along with a teal volume that was excluded from the optimization to make space for the components required to generate the acoustic field. The shape of the magnet design that resulted from the optimization routine is shown in Figure 1B. A single magnetization direction was utilized \(\text{(in contrast to a Halbach array with multiple magnetization directions)}\) \cite{29} to simplify the assembly process. The magnet consisted of two parts made from N52 grade NdFeB permanent magnet material designed so that they would only self-assemble in one stable configuration due to dipole interactions. An aluminum copy was constructed with identical dimensions to be used as a nonmagnetic control device during testing.

The primary design goals for the ultrasound element were to provide a focused pressure field that spatially overlapped with the magnetic field peak, and to do so with sufficient amplitude to cause inertial cavitation of candidate microbubble formulations \(\text{(this cavitation regime has been associated with desirable therapeutic effects)}\) \cite{24,26}. After evaluation of candidate element designs using time domain finite element code \(\text{(described in Section 5)}\), a final configuration was chosen, featuring a \(10\) mm diameter piezoelectric disk with \(1\) MHz resonant frequency, fixed to a planoconcave glass lens to provide pressure field focusing (Figure 1C). A schematic of the complete device is shown in Figure 1D, in which the rectangular openings in the magnet were fitted with flexible tubing to allow airflow for passive cooling around the acoustic element and to provide a waterproof path for the element drive wires. Effort was made to minimize thermal coupling between the magnetic material and the ultrasound transducer while active. Temperature measurements made during operation with the drive parameters given in Section 5 showed a temperature rise of just \(1.3\) °C at the upper magnet surface over a \(20\) min drive period. Photographs of the prototype MAD, its nonmagnetic replica, and an example of suspended iron oxide nanoparticle retention are shown in Figure 1E,F.

### 2.2. Calibration

Hall probe measurements of the \(z\)-component of the external field, \(B_z\) generated by the MAD are shown in Figure 2A,B, and showed good agreement with model predictions for its shape, particularly along the \(z\)-axis. Predictions for the normalized pull force \(\text{(i.e., } F_{\text{pull}} = F \cdot (-k)\text{, the component of the normalized force that points toward the magnet)}\) are given in Figure 2C,D. Typically, the force from a solid magnetic volume decays almost exponentially with distance \cite{8} but the recess in the front face of the magnet compromises the magnetic force at short range, and even produces a small on-axis push force \(\left( F_{\text{pull}} < 0 \right)\) within \(2\) mm of the magnet. It should be noted that the position along the axis where the pull force crosses to zero coincides with a saddle point in the field profile, and a local maximum in the magnetic potential energy \(\left( U = -V_M \cdot B \right)\), as no arrangement of static permanent magnets can produce a stable potential energy well at range \(\text{(i.e., Earnshaw’s principle)}\) \cite{8,30}. The normalized force \(\text{(or force per moment)}\) at the position of interest, \(z_{\text{opt}}\) is \(15.8\) T m\(^{-1}\), which compares well with the force expected from a magnet optimized for the same parameters without the excluded volume \(\text{(about } 18\) T m\(^{-1}\))\) \cite{28}. At a distance of \(10\) mm the field is \(0.2\) T, which is enough to magnetize \(10\) nm SPIONs to \(90\%\) of the saturation magnetization, while at \(z = 20\) mm, the field of \(0.1\) T can magnetize particles to \(80\%\) of saturation \cite{31}.

![Figure 2. Field profiles along the A) z-axis and B) x-axis at various depths, z away from the face of the magnet. The z-component of the field was measured using a Hall probe (symbols) and compared with simulation (lines). Predictions for the normalized pull force are shown in C) along the z-axis and D) parallel to the x-axis at different z positions.](image)
The compromise in performance at short range can be understood by examining the profiles in Figure 2D. At \( z = 5 \) mm, the MAD emits strong forces at the edges of the device and a weaker central force. This type of force profile typically results in more particles accumulating closer to the edge of the magnet, rather than above the center,[32] resulting in an inefficient accumulation distribution if the target is aligned coaxially with the MAD. Our previous simulation results suggest that force profiles that rapidly vary and peak in a confined spatial region lead to more efficient accumulation of carriers to a coaxially aligned target.[32] The MAD emits this type of force profile beyond \( z = 15 \) mm, but at this range, the full-width half-maximum (FWHM) of the profile is \( \approx 40 \) mm. The implications of this are discussed further below.

Figure 3 shows that Hall probe measurements of the field emitted by the MAD agreed with simulations for the same planes. At a range of 10 mm from the surface of the array, simulations predicted a field of 0.203 T at the center of the \( x-y \) plane (Figure 3A), compared with a measured field of 0.201 T (Figure 3C).

Figure 4 shows the measured acoustic field profiles for the MAD ultrasound element at a frequency of 1.06 MHz, which was found to have the highest transmitting voltage response (TVR) in the 0.8–1.2 MHz data analysis band. The location of the focus was as designed (10 mm from the transducer surface), with a
The ability of the MAD to magnetically target microscopic carriers was characterized by measuring the proportion of magnetic microbeads that were captured inside a flow phantom at different distances from the magnet, and over a range of mean flow velocities (Figure 5). The results were compared with predictions made using the numerical particle tracing simulations described in section 5, which were performed using effective particle parameters to match the magnetic properties measured for the microbeads. A slightly higher capture efficiency than predicted was observed for most conditions, which was most likely due to interparticle interactions between the magnetized beads (interactions were ignored in the simulations for simplicity). Any offset in the magnet position with respect to the channel would also contribute to the discrepancy. However, both the measured and simulated capture efficiency values demonstrated that the MAD was capable of capturing more than 10% of the injected particles for all of the physiologically relevant flow velocities tested.

In the “no magnet” case for low velocities (1 mm s⁻¹) a relatively high “capture efficiency” (or, more accurately, a high proportion of unaccounted particles, as there was no external force to capture microbeads) was observed, as sampling was performed ≈1 min after injecting the particles. Simulations suggested this was an insufficient time period for the concentration to equilibrate at the outlet of the phantom at these fluid velocities. In effect, the very high discrepancy between the inlet and the outlet concentration observed for the 1 mm s⁻¹ case is probably because, over the course of the measurement, there was insufficient time for particles to leave the channel. For higher velocities, the capture efficiencies decay for all magnet configurations, but increased magnetic force always results in enhanced capture.

2.4. Cavitation Activity of Captured Magnetic Microbubbles

Figure 6 shows examples of PCD responses during magnetic microbubble (MMB) retention and activation experiments. The average fluid velocity in the channel was 4.2 mm s⁻¹ in these specific experiments. In the presence of MMBs, the PCD frequency spectrum elevates above the MMB-free background measurement in both tonal and broadband levels (Figure 6A), indicating a mix of bubble behaviors (including inertial cavitation) for the incident field level used. The lack of ultraharmonics (half-integer harmonics of the 1.06 MHz drive frequency) suggests the absence of stably cavitating bubbles. Although the results in Figure 6A are for single acquisitions, they are representative of the ensemble of collected data. The elevated 2–3 MHz background in the absence of MMBs is
caused primarily by scattering from the flow phantom internal and external boundaries, with secondary contributions from naturally occurring bubbles remaining in the filtered water. The temporal histories of PCD signals recorded with the magnetic and nonmagnetic devices are shown in Figure 6B. After exhibiting similar initial levels, the signals diverged strongly, with the magnetic (MAD) device sustaining MMB responses for a period more than four times longer compared to the nonmagnetic copy. The amount of time taken for the magnetically retained MMB response to decay to half of its peak value (relative to the noise floor) was 322 ± 52 s, compared with 74 ± 13 s using the nonmagnetic device. The cumulative signal energies (displayed in Figure 6B with units in mV^2 s) were calculated over the time interval for which the root mean square (RMS) PCD signals were more than twice that of the background. Magnetic retention enhanced the energy of the acoustic emissions by a factor of 3.3. As above, multiple studies have shown that both energy and duration of cavitation are positively correlated with therapeutic effect.[25,26,33]

2.5. Ultrasound Imaging of Captured MMBs

In order to demonstrate that the MAD could capture and accumulate carriers that are responsive to both acoustic and magnetic stimulation, B-mode ultrasound imaging was used to visualize microbubbles injected into an agar flow phantom. Figure 7B shows an example of the increased image intensity at the bottom of the channel due to accumulated microbubbles 4 min after the initial injection. Figure 7C shows that, after exposing the channel to a short, high intensity ultrasound “flash,” these microbubbles were no longer visible confirming that the change in image intensity was due to captured microbubbles. It was also noted that a brown residue of magnetic particles could still be seen in the vicinity of the magnet upon visual inspection of the flow phantom.

Figure 8 shows the change in image intensity produced by microbubble accumulation along the bottom of the channel. These data were compared with predictions for the accumulation of captured particles made using the model described in section 5 after normalization to the peak accumulation distribution (as the normalized accumulation distribution is mostly independent of the fluid velocity[32]). The model predicted that the greatest accumulation of particles would be observed in a...
The cavitation measurements show substantially more activity over a longer time scale when using magnetic targeting, which supports the results of previous in vitro,[19] and in vivo studies.[27] of cavitation from magnetically responsive microbubbles. As an example, Crake et al.[19] observed a factor of ≈2.5 increase in cumulative source energy monitored from magnetically captured microbubbles compared with no magnetic force, at flow conditions comparable to the current experiments. They made no attempt to optimize their magnet design in their study. By comparison, our combined design resulted in 3.3 times the total observed acoustic energy, with the magnet slightly further away from the target, and approximately an order of magnitude lower concentration of injected microbubbles. This is of interest due to intense active research into using cavitation nuclei for applications in drug delivery,[17,38,39] particularly with regards to using the mechanical action of cavitation to extravasate particles into solid tumors.[40,41] Further, ultrasonically induced cavitation of or in close proximity to drug carriers enables controlled drug release in a site-specific manner.[16,42] All of these effects can potentially be enhanced by the increased local concentration that MDT has been shown to provide for magnetically-responsive therapeutic carriers.[15–45]

The use of ultrasound-responsive magnetic carriers also addresses another challenge associated with MDT, that of imaging magnetic particles during therapy.[16] Magnet carrier formulations that use iron oxide nanoparticles are seen as favorable because iron oxide generates negative contrast in magnetic resonance imaging (MRI).[46,47] However, many of the systems proposed for magnetic targeting are incompatible with MRI instruments for safety reasons,[11] and magnetic delivery using MRI gradient coils can be challenging,[48,49] as conventional coils are not designed to generate sufficient magnetic force to capture SPIONs at particularly high flow regimes, such as those present in arteries. When MRI is incorporated with MDT studies, it is often used as a diagnostic tool after therapy.[50] Ultrasound, on the other hand, does not interact with external magnetic field sources,[51] and is also often less expensive than MRI, making it appropriate for portable or benchtop applications. Microbubbles have been used clinically for decades as ultrasound contrast agents.[13] In recent work they have been investigated as drug delivery carriers[16] and for magnetic drug targeting.[52–54] An integrated drug delivery device for simultaneously localizing and activating carriers that rely on acoustic and magnetic modalities would be highly advantageous for these types of applications. While our present device does not have imaging capabilities, the single element ultrasound transducer could be replaced with an array of elements to facilitate imaging and/or cavitation mapping.

This first iteration of the MAD design had compact size and weight (easily hand-held) with minimal development cost (first prototype cost $<1000 including nonrecoverable engineering charges). Based on prior experiences,[27,39,53] compactness of the design should be especially useful for future small animal or shallow clinical evaluations of targeted drug delivery concepts.
where handling and positioning of multiple devices for near-surface targets is both logistically challenging and likely to increase experimental uncertainties.

4. Conclusion

In summary, we have designed an extracorporeal device for simultaneously applying magnetic and acoustic fields to concentrate and activate drug-carrying particles. The characteristics of both the magnetic and acoustic fields were measured in vitro and were shown to be in good agreement with theoretical predictions.

For all tested flow velocities up to 50 mm s\(^{-1}\) and tissue depths up to 20 mm, the device was able to capture and retain more than 10% of injected magnetic particles, and resulted in an increased intensity of acoustic emissions and sustained cavitation activity from magnetic microbubbles in an agar flow phantom. We believe that the current prototype of the device may be useful for small animal experiments involving the use of magnetically and acoustically responsive particles. Ongoing design efforts are focused on a scaled-up device for length scales relevant to human applications.

5. Experimental Section

Design and Assembly: The shape of the magnet was generated by the previously described optimization routine. Full details may be found in ref. [28] but briefly, the optimization routine considers possible magnetic configurations of a 3D arrangement of elements positioned within an optimization domain, retaining the magnetic configurations that result in the maximal magnetic force at the position of interest. For the present design, the total magnet volume, \(V_{\text{mag}}\) was constrained to 20 cm\(^3\), which was chosen along with the value of \(z_{\text{opt}} = 10\) mm to correspond with the saturation magnetization of the particle, and \(r_{\text{sat}}\) at a position \(r\). By \(M\), \(M_s\) is the saturation magnetization of the particle, \(B\) is the magnitude of the magnetic field, \(B_r = (B_x, B_y, B_z)\) at a position \(r\).

Calibration of Applied Fields: The magnetic field and forces generated by the MAD at specified positions outside of the magnet were predicted using a model previously described and experimentally verified\(^{[29]}\) in which the magnet was broken into a 3D lattice of evenly distributed point moments, and the field calculated by summing the contributed dipole field from each moment. The model also predicted the magnetic force due to the field gradient

\[
F_M(r) = MV \cdot \nabla (B(r))
\]

expressed as a “normalized force” or force per moment, which is used here for convenience because it has the same units as the field gradient \((T m^{-1})\):

\[
F_M((M, V)(M, M_s) \nabla (B))
\]

Here, \(F_M\) is the magnitude of the magnetic force, \(M\) is the magnetization, \(V\) is the volume of the superparamagnetic particle, \(M_s\) is the saturation magnetization of the particle, and \(B\) is the magnitude of the magnetic field, \(B_r = (B_x, B_y, B_z)\) at a position \(r\).

Measurements of the vector field generated by the magnet were performed using a three-axis Hall probe connected to a Model 460 3-Channel Gaussmeter (Lake Shore Cryotronics, Inc., OH, USA). The probe was mounted on a set of three MTS Series Motorized Translation Stages (Thorlabs, Inc., NJ, USA) with travel ranges of 50 mm, configured to give controlling translation in each of three orthogonal directions.

Acoustic pressure field profiles were measured with a needle hydrophone (200 \(\mu\)m diameter needle, Precision Acoustics, Dorchester, UK) while the MAD front face was submerged in a tank filled with filtered and degassed water. The ultrasound element was driven with a three cycle, 1 MHz tone burst from a waveform generator (33250, Agilent).
Predictions of the capture efficiency were made using a numerical model for particle trajectories reported previously. In summary, simulations were performed of an ensemble of particles with the same magnetic properties as the microbubbles, which were distributed evenly at the inlet of a channel carrying laminar flow. A force balance was used to determine the particle trajectories and calculate the proportion of particles that were captured by the magnet and the proportion that reached the outlet. The model parameters were selected to match the experimental conditions and the simulations were run until all particles reached their final position. The simulations were repeated without an external magnetic force for 2 min of simulation time only, as all magnet simulations had all particles reach their final positions within 2 min of simulation time. As the aim of the study was to determine differences in capture efficiency for different conditions, water was used as the suspending fluid for both the simulations and the experiments rather than blood.

**Magnetic Microbubble Acoustic Intensity Experiments:** Magnetic microbubbles were prepared following a slightly modified version of the method developed by Stride et al. 1,2-distearoyl-sn-glycero-3-phosphocholine (DSPC) was purchased from Avanti Polar Lipids, Inc. (Alabaster, AL, USA). Polyoxethylene (40) stearate (PEG40S), chloroform, and Dulbecco’s phosphate-buffered saline were purchased from Sigma-Aldrich Ltd. (Gillingham, Dorset, UK). Isoparaffin coated magnetic nanoparticles (10 nm diameter) were purchased from Liquids Research (Bangor, UK). Sulfur hexafluoride (SF₆) was purchased from The BOC Group (Guilford, Surrey, UK). A mixture of DSPC:PEG40S chloroform (9:1 molar ratio) was prepared by adding 621 μL of DSPC (25 mg mL⁻¹) and 447 μL of PEG40S (10 mg mL⁻¹) into a glass vial. The sample was covered with pierced parafilm and heated to 50 °C overnight to evaporate the solvent.

After complete solvent evaporation, the dried lipid film was suspended in 5 mL of PBS for 1 h at 75 °C under constant magnetic stirring. The stir bar was removed from the sample and the solution was sonicated using a XL2000 ultrasonic cell disruptor from Misonix, Inc. (Farmindale, NY, USA). The sonicator was used at power setting 4 (8 W RMS output power) for 15 s with a 3 mm diameter tip, operating at 22.5 kHz, with the probe tip held within the solution. This was immediately followed by sonication at the gas–water interface with the probe tip touching the liquid surface, under positive pressure of SF₆, at power setting 19 (38 W RMS) for 10 s. 15 μL of isoparaffin coated iron oxide nanoparticles (10 nm diameter) was then added to the mixture and the vial was gently swirled for 10 s. The solution was again sonicated with the probe tip held within the liquid at power setting 4 for 15 s, followed by cooling of the sample at 5 °C for 15 min. Then, the solution was again sonicated at the gas–water interface, under positive pressure of SF₆ at power setting 19 (38 W RMS) for 10 s. Finally, the magnetic microbubble solution was capped and placed on ice for 10 min before further analysis.

Microbubbles were observed using a Leica DMS500 optical microscope (Larch House, Milton Keynes, UK) with a 40x objective lens, and a Neubauer haemocytometer from Hauser Scientific (Horsham, PA, USA). Microbubble concentration and size analysis was performed using a purposely written image analysis software in MATLAB.[6] On average (n = 5), each batch produced a suspension of (4.4 ± 0.6) × 10⁸ magnetic microbubbles per mL with an average diameter of 2.6 ± 0.25 μm.

In order to demonstrate that the MAD could capture acoustically responsive magnetic carriers, microbubbles were diluted to 1/10 of the batch concentration and injected into a steady laminar fluid flow, established inside the agar flow phantom described above. The magnet was fixed to the phantom holder at a distance of 10 mm from the channel, as described above, and the average fluid flow velocity was varied between 42 and 44 mm s⁻¹. After waiting for 4 min (which, according to simulations, was sufficiently long for a captured bolus of magnetic microbubbles to form inside the channel near the magnet), the channel was imaged using a commercially available ultrasound system (iU22, Philips, Bothell, WA, USA) with a linear array (L12-5, Philips) angled -40° off the MAD symmetry axis. Videos consisting of B-mode images were recorded for 1 min at a frame rate of 13 frames s⁻¹.
An ultrasound drive level corresponding to a mechanical index (MI) value of 0.15 (comparable to conventional imaging conditions) was used to image the accumulated bolus. To minimize changes in intensity due to microbubble destruction, a series of frames in a 5 s window was selected for processing immediately after the retained bubbles had cleared from the imaging field of view. These images were analyzed using a custom image processing routine based on the NumPy package for Python 3.5. The bottom of the channel in the images was windowed, and the position dependent intensity, \( I(x) \) was determined by taking a weighted local regression of the total intensity in the part of the window between \( x \pm \Delta x \), which was then averaged for all selected images from the same video. All experimental runs were repeated with the nonmagnetic control device (Figure 7D). The measured values of \( I(x) \) were compared with numerical predictions for the accumulation distribution, which were calculated using the model reported previously and summarized above.[32] The accumulation distribution was defined as the proportion of captured particles with simulated final positions ranging between \( x \pm \Delta x \).

The combined magnetic retention and acoustic activation capabilities of the MAD were demonstrated by monitoring acoustic emissions from the flow channel while driving the ultrasonic element. The signal generation chain was the same as described in Section 5, Calibration of Applied Fields but the drive signal was lengthened to 100 cycles, and the pulse repetition period slowed to 1.0 s. The drive amplitude was set to ensure that the peak rarefactive pressure at the center of the channel would be 0.50 MPa, based on the results of free field calibrations described in Section 5. Ultrasonic emissions from the channel were observed using a spherically focused single element transducer (7.5 MHz center frequency, 12.7 mm diameter, 75 mm focal distance, Olympus NDT, Essex, UK) operating as a passive cavitation detector (PCD). Signals from the PCD were preamplified (SR445A, SRS, Sunnyvale, CA, USA), digitized (Handyscope HS3, TiePie Engineering, Sneek, Netherlands) upon triggering from the waveform generator, and streamed to a computer disk.

Prior to conducting cavitation monitoring experiments, alignment of the PCD with the section of channel directly in front of the MAD was achieved by temporarily introducing an air pocket into the channel. The PCD was then connected to a pulser (5072PR, Olympus NDT), and its position adjusted to maximize the scattered signal amplitude within the expected propagation time window. For all experiments, the PCD was positioned so that there was an angle of \(-40^\circ\) between its axis and that of the MAD element in order to minimize mutual scattering.

Keywords
drug delivery, magnetic targeting, microbubbles, ultrasound

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Conflict of Interest
The manuscript authors are also named inventors on a patent application relating to the device.

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