MRI-compatible injection system for magnetic microparticle embolization

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Abstract—Objective: Dipole field navigation (DFN) and magnetic resonance navigation (MRN) exploit $B_0$ magnetic fields and imaging gradients for targeted intra-arterial therapies by using magnetic drug-eluting beads (MDEBs). The strong magnetic strength ($1.5$ or $3$ T) of clinical magnetic resonance imaging (MRI) scanners is the main challenge preventing the formation and controlled injection of specific-sized particle aggregates. Here, an MRI-compatible injector is proposed to solve the above problem. Methods: The injector consists of two peristaltic pumps, an optical counter, and a magnetic trap. The magnetic property of microparticles, the magnetic compatibility of different parts within the injector, and the field distribution of the MRI system were studied to determine the optimal design and setup of the injector. The performance was investigated through 30.4 emu/g biocompatible magnetic microparticles ($230 \pm 35$ μm in diameter) corresponding to the specifications needed for trans-arterial chemoembolization (TACE) in human adults. Results: The system can form aggregates containing 20 to 60 microparticles with a precision of 6 particles. The corresponding aggregate lengths range from 1.6 to 3.2 mm. Based on the injections of 50 MRI-visible boluses into a phantom which mimics realistic physiological conditions, 82% of the aggregates successfully reached subbranches. Conclusion and Significance: This system has the capability to operate within the strong magnetic field of a clinical 3T MRI, to form proper particle aggregates and to automatically inject these aggregates into the MRI bore. Moreover, the versatility of the proposed injector renders it suitable for selective injections of MDEBs during MR-guided embolization procedures.

Index Terms—MRI-compatible particle injection system, magnetic resonance navigation, hepatocellular carcinoma intra-arterial therapies, magnetic nanoparticles, drug-eluting beads.

I. INTRODUCTION

HEPATOCELLULAR Carcinoma (HCC) is a common type of cancer with a high fatality rate worldwide [1]. For non-resectable HCC, trans-arterial chemoembolization (TACE), a palliative and minimally invasive cancer therapy, is the preferred treatment [2]. The TACE technique consists of the injection of chemotherapeutic agents through a catheter inserted into the vascular system, followed by the injection of embolizing agents to block the tumor perfusion. The high selectivity of the method is owed to the physician’s ability to insert a microcatheter into selected vessel branches [3, 4]. However, the principal drawbacks of this method are the need to perform catheterization repeatedly and the risks of exposure to ionizing X-ray radiation which, even if not significant for a patient with advanced liver cancer, can be harmful to the staff and the interventional radiologist performing the procedure. Besides, possible non-target embolization which results in damages to normal tissues is a significant concern. Intra-arterial chemotherapy with an implantable arterial port has been proposed as a means to avoid repeated catheterization procedures [5]. However, this technique does not allow simultaneous chemotherapy and embolization, which are both required to maximize the local effect of chemotherapy since the whole liver would otherwise be affected. MRI-based interventions are promising techniques that aim to navigate Magnetic Drug-Eluting Beads (MDEBs) into a targeted site [6-10]. In this technique, superparamagnetic nanoparticles are embedded into Drug-Eluting Beads to induce the sufficient magnetic force from an external magnetic source, allowing the anti-tumor drugs to be steered and delivered to tumor sites [11, 12]. The superparamagnetic property of the nanoparticles is clinically important since it allows them to be magnetized when exposed to a magnetic field while not retaining any net magnetization once removed from the field. MDEBs can, therefore, be navigated in aggregates due to magnetic dipole-dipole interactions when exposed to a magnetic field and disaggregate into individual particles after the patient is removed from the MRI. The sizes of the embedded aggregates must be obtained from the IEEE by sending an email to pubs-permissions@ieee.org.
nanoparticles typically range from 5 to 20 nm in order to exhibit superparamagnetic properties while being safely phagocytosed in the body [13].

Two different approaches have been reported to successfully navigate MDEBs in an MRI bore: Dipole Field Navigation (DFN) and Magnetic Resonance Navigation (MRN) [6, 14-17]. In DFN, the uniform magnetic field of a clinical MRI scanner is distorted by using soft ferromagnetic cores placed at strategic locations [18]. With this method, the gradients are static and spatially distributed, allowing a continuous injection of particles. However, with this technique, imaging cannot be performed during injections because of the distorted magnetic field [19]. This makes the computation of the delivered dose in each liver section difficult: continuous injections will have to be halted and the source of distortion removed to allow imaging sequences to be launched. An injector that has the ability of delivering a precise amount of particles could drastically simplify the procedure. Indeed, once the desired number of particles is reached in a specific liver segment, only small adjustments of the ferromagnetic cores are required to target another part of the liver. On the other hand, MRN allows fast and easy alternations between steering and imaging sequences, thus enabling targeted efficiency assessments. Although in vivo applications of MRN were successful, MDEBs were navigated through a single bifurcation. Hence, the continuous injection was possible [20]. For MRN across several arterial bifurcations, the MDEBs would be steered in the target vessel by switching the direction of the gradient, depending on the position of particles and the orientation of the vessel bifurcations [21]. The gradients in MRN act on all particles. Thus, the next aggregate injection cannot be triggered until the previous bolus reaches the target. This is defined as a pulsed-bolus injection. Therefore, an injector capable of controlling pulsed-bolus injections would be essential to perform multi-bifurcation navigation.

Besides magnetic navigation of particles, advancements in MR-guided catheter navigation techniques could eventually make it compatible with selective embolization of liver tumors [22, 23]. Again, an MRI-compatible injector could be useful to inject a precise dose of MDEB in different feeders supplying a tumor.

Regarding MRN, the magnetic steering force $F_m$ in Newton on a particle is computed as

$$F_m = V_p (M \cdot V) B$$

where $V_p$ is the volume of magnetic material ($m^3$), $M$ is the volume magnetization of the particles (A/m), $B$ is the magnetic flux density, and $VB$ is the magnetic gradient (T/m).

When a particle navigates in a fluid, the magnetic force must be balanced with drag forces because of the magnetically induced velocity $U_m$ (m/s) [24]

$$U_m = F_m (6 \pi r \mu)^{-1}$$

where $r$ is the radius of the particle, and $\mu$ is the dynamic viscosity of the fluid.

From (1) and (2), we can conclude that the magnetic force increases at a cubic rate with the particle radius, while the resulting velocity in a viscous flow increases quadratically with the radius. This suggests that larger microparticles or aggregates can be navigated more efficiently. However, the size of aggregates needs to fall within the limits of the inner diameter of approved catheters and the blood vessels they transit into. Therefore, a control of the number of particles per aggregate is crucial.

To our knowledge, no MRI-compatible injector that has the function of accurately controlling the amount of magnetic microparticles per injection has been reported. Although a catheter-based injector has been previously proposed to inject particle boluses into an MRI [25], the injector simply uses serial coils to capture and release magnetic particles. Thus, this injector did not allow the attainment of a real-time particle count or a control over the aggregates’ size, which are crucial for successful navigation and patient safety.

This study aims to investigate the design of an MRI-compatible particle injection system to precisely and repeatedly generate and inject particle boluses with the desired particle numbers and aggregate sizes. Here, we hypothesize that our injection system: 1) is compatible with a strong magnetic field (3 T), 2) is capable of controlling the aggregate size, as well as the particle number in each aggregate and 3) allows for the injection of intact aggregates into the MRI bore through a catheter.

II. Method

Before designing the injector, the optimal size of aggregates in the context of MRN is determined based on vessel dimensions. Here, we choose the vessels that are used in the HCC interventions as reference. The common, right and left hepatic arteries have respectively internal diameters (mean ± standard deviation) of 4.5 ± 0.3, 3.0 ± 0.3, and 3.6 ± 0.4 mm [26]. Consequently, the maximum length of the particle aggregate perpendicular to the target branch direction should be about 3 mm in order to be navigated into the left or right branch division of the hepatic artery. Therefore, in this paper, the targeted aggregate sizes were set to about 3 mm. Moreover, considering the fact that 5 French catheters are often used to catheterize the main hepatic artery during routine chemoembolization [3, 4, 25], the aggregate should also be able to pass through the catheters.

A. Injector design

As shown in Fig. 1a, the injector is composed of two main functional parts: the controller, which controls the capture and release of magnetic particles, and the MRI-compatible actuator, which sends out the measured signal for monitoring the particle number while acting as a mechanical actuator for particle aggregation and release. Unlike the previous injector which uses serial coils to capture and release magnetic particles, our injector added a counting chamber and the corresponding circuit to calculate the particle numbers and aggregate sizes.

In terms of hardware setup, the injector consists of two microcontroller boards, two peristaltic pumps and an electromagnetic actuator. The microcontroller boards use an Arduino Uno and an ARD-MD Arduino Motor driver shield. Two peristaltic pumps, Pump 1 and Pump 2, are used to transport the particle suspension and saline (0.9% NaCl in distilled water), respectively. The electromagnetic actuator is
an electromagnet-based piston, which generates a hydraulic driving force to another piston holding a small cylindrical neodymium magnet (1/16" diameter × 1/16" thickness, K&J Magnetics, Inc., USA). In its resting position, the magnet holds particles in the counting chamber by means of the magnetic force, while more are incoming. An aggregate is released when the electromagnetic actuator activates and pulls the small magnet away from the counting chamber.

To estimate the total number of particles in the counting chamber, an infrared (IR) emitter (LTE-3371T, Lite-On Inc., Taiwan) and a receiver (LTE-3208, Lite-On Inc., Taiwan) are used. These two electronic devices were selected randomly from our toolbox. When putting them in the high magnetic field inside the MRI bore, they were both satisfied requirements for particle detection.

To increase the measurement sensitivity and to decrease the noise signal from the natural light, the IR emitter and receiver are encapsulated into two aluminum tubes, and the tubes are linked by an opaque plastic tube. A transparent glass tube has been vertically inserted into a hole in the middle of the plastic tube, as shown in Fig. 1b, such that the infrared light from the emitter could pass through the lumen of the plastic tube to be detected by the receiver. We chose a glass tube with an internal diameter of 0.9 mm to match the inner lumen of 5 French catheters. The tubing between pumps and actuator also has a diameter of 0.9 mm. This ensures a consistent diameter from the pumps to the patient, decreasing the possibility of aggregates clogging up. The light reaching the receiver diminishes as the opaque magnetic particles accumulate in the counting chamber, resulting in a higher ohmic resistance detected by the circuitry since fewer photons are now reaching the IR receiver. The tube is considered to be the bolus generator channel. A simple circuit is used to measure the resistance R which is given by

\[ R = \frac{(U - V_f)R_f}{V_f} \]  

where \( R_f \) is a serial resistance, \( V_f \) is the measured voltage from the Arduino, and \( U \) is the total voltage of the serial circuit. In our experimental setting, \( R_f \) is 1.36 kΩ and \( U \) is 5 V. These values are used to calculate the resistance using (3).

This circuit was tested in a 1.5 T (Sonata, Siemens, Erlangen, Germany) and a 3 T MRI scanner (Skyra, Siemens, Erlangen, Germany). No change of recorded resistivity from the receiver was observed.

The complete injection workflow protocol is outlined in Fig. 2. The injector works as a subsystem in MRN, which consists of an MRN sequence, a flow control system and the injector described here. The MRN sequence determines the imaging, tracking, navigation and particle injection steps required for targeted therapies. When a bolus needs to be injected, a trigger signal #1 is sent by the MRN sequence. After the signal is received by our injector, Pump 1 pushes the particles into the counting chamber. These particles are captured in the area because of the presence of a strong pulling force induced by the small magnet. Meanwhile, the controller continuously monitors the R in Eq. 3 to determine whether the number of particles has reached the desired value. Then, Pump 1 shuts down to prevent more particles from entering the counting chamber. Simultaneously, the electromagnetic actuator engages to release the aggregate and Pump 2 is activated to push the aggregate into the arterial catheter located inside the MRI scanner. When the aggregate reaches the tip of the catheter, the trigger signal #2 from the MRN sequence is sent to the injector, thus switching off the electromagnetic actuator and Pump 2. Then, the injector maintains its initial status until the next
trigger signal #1 is received.

![Workflow diagram]

**Fig. 2.** Workflow of the injector and possible interface with MRI for MRN. This workflow could be adapted for DFN or selective embolization using MR-guidance.

**B. Particle design**

The preferred size of microparticles (superparamagnetic nanoparticles with therapeutics embedded in a polymer matrix) for human liver chemoembolization is about 100–300 µm, which is based on the diameter of the arterioles used for embolization [27].

![Microparticle images](a) and magnetization curve](b)

**Fig. 3.** Design and magnetic characteristics of magnetic particles. (a) Monodisperse magnetic microparticles shown in the microscope (left) are made from 60% magnetite nanoparticles (right) and 40% biodegradable polymer PLGA. (b) Magnetization curve of the microparticles.

Microparticles composed of 40% poly (lactic-co-glycolic) acid (PLGA) (Durect Corporation, USA) and 60% biocompatible iron oxide (Fe3O4) nanoparticles made through the co-precipitation method [28, 29] were used in the experiment, as shown in Fig. 3.

A vibrating sample magnetometer (EV9, Microsense) was used to measure the magnetic characteristics of the microparticles (Fig. 3b). The hysteresis curve shows that the microparticles are highly saturated in a 1.5 T (15000 Oe) magnetic field. The saturation magnetization is 30.4 emu/g. There is no hysteresis as expected for superparamagnetic particles. The microparticles are quasi-monodispersed with an average diameter of 230 ± 35 µm. They were used at a concentration of 0.21 mg/mL dispersed in saline (0.9 wt.% NaCl).

**C. Preparation of the injector for testing**

A complete prototype of the injector was built as described above. All experimentations were performed using a clinical 3 T MRI scanner (Skyra, Siemens, Erlangen, Germany). An MRI-compatible camera (MRC Systems GmbH, Heidelberg, Germany) used at a recording speed of 15 frames/s was utilized to record the performance of particle injections. Fig. 4 shows the MRI-compatible actuator positioned in front of the MRI scanner.

![Actuator setup](a) and close-up](b)

**Fig. 4.** Setup of the MRI-compatible actuator during the experiment (a) and close-up of the actuator (b).

### III. EXPERIMENTS AND RESULTS

**A. System optimization**

1) Determination of actuator position and orientation in the

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MRI magnetic field

The main considerations that determined the position of the actuator were:
1. The actuator cannot be inside the MRI scanner because the bore only allows limited space for one patient.
2. The actuator can be easily installed on the patient table (see Fig. 4a), which is just in front of the MRI bore. The actuator and table can be positioned accurately at an optimal distance with respect to the iso-center of the MRI.
3. The actuator cannot be positioned far away from the MRI bore. Without a sufficient magnetic field strength, the encapsulated superparamagnetic nanoparticles would not be fully magnetized, leading to the fragmentation of the aggregates after being released from the counting chamber.
4. If too close to the MRI scanner bore, the strong gradients due to the fringe field could attract the particles into the counting chamber of the actuator even in the absence of flow.

To determine the ideal position for our injection system, we measured the magnetic field strength in the direction of the B₀ field (the 3 T homogeneous field) in front of the MRI system by using a digital Tesla meter (SENIS, Switzerland). After calibration to zero in the control room, the sensor was initially positioned at the center of the patient table, with a distance of 235 cm from the iso-center of the MRI bore. The table was moved with 10 cm increments in the B₀ direction, i.e. +Z direction (see Fig. 4a), until the sensor reached the gantry which is 85 cm away from the iso-center of the MRI bore. After obtaining the curve of the magnetic field distribution, magnetic gradients were taken from the tangent slope of the curve (see Fig. 5a).

The optimal position for the actuator was defined as the minimum distance at which particles had no movement induced by the fringe field in the absence of flow in order to obtain the highest particle magnetization without particle migration. To obtain the optimal position for the actuator, 20, 30, 40 and 50 particles were placed into the glass tube of the actuator. As the method we used to measure the magnetic field strength, the actuator was initially positioned at the center of the patient table, with an initial distance of 235 cm from the iso-center of the MRI bore. The table was moved with 10 cm increments toward the B₀ direction until particles moved because of the fringe field. Experiments were repeated at least three times for each particle numbers. The results revealed that 185 cm is the optimal distance. There, the magnetic field strength was 0.045 T and the gradient 0.22 T/m, while no particle motion was observed in the tube.

Therefore, after the actuator was placed at the optimal position, we compared the shape of aggregates when the glass tube was positioned with angles of 0°, 45° and 90° to B₀ (Fig. 5b). As seen in Fig. 5b, a single aggregate composed of 30 particles changed to three smaller ones when the angle was increased from 0° to 45°. When the glass tube and B₀ were perpendicular to each other, 8 chain-like aggregates (see C in the Fig. 5b) were formed since the longer axis of aggregates was constrained by the internal diameter of the glass tube, limiting the particle number in each smaller aggregate.

Thus, in the following experiments, the glass tube of the counting chamber on the actuator was always kept parallel to B₀ and was positioned 185 cm away from the MRI iso-center.

Fig. 5. Mapping of the gradient strength according to the position of the actuator and shape of particle aggregates according to the orientation of the tube. (a) The strength of the magnetic field and the magnetic gradient along the +Z direction (B₀ direction). The iso-center of MRI bore was used as the reference zero (coordinates, 0, 0, 0). (b) Shapes of aggregates for different glass tube orientations with respect to the main field B₀.

2) Optimal flow rate for two pumps

After placing the actuator to the optimal position and orientation, the optimal flow rate for the two pumps was investigated. The calibration of the flow rate was done by measuring the pump output for a given injection time (30 s) according to the rotation speed and power frequency. Since the pump had a small diameter, was rotating at a high frequency and was connected to a 4.5 meters long tube, the flow in the actuator was almost constant. To determine the proper infusion rate for the two pumps, the initial flow was set to 6 mL/min and increased by 1 mL/min increments until the optimal flow rate was obtained.

The optimal flow rate from Pump 1 was defined as the highest flow at which particles can be effectively trapped by the magnet in order to minimize injection time while preventing unexpected particle release. At each flow rate, a single particle injection was performed three times. Microparticle migration from the trapping area was observed when the flow rate was higher than 16 mL/min, which was thereafter chosen as the optimal flow rate for Pump 1.

The optimal flow rate for Pump 2 was defined as the highest flow at which the aggregates cannot be broken by the effect of the shear force. To obtain the optimal flow for Pump 2, 20 particles were injected into the actuator using Pump 1 and were released at different flow rates by Pump 2. A transparent tube (0.9 mm internal diameter), connected downstream to the
actuator, was used to observe the shape of the particle aggregates. The experiment was also repeated three times at each flow rate. The optimal flow rate for Pump 2 was found to be 20 mL/min. With the same method and test times, the experiment results did not change when increasing the particle number to 30, 40 and 50 for each aggregate.

B. Controlling particle numbers and aggregate length by using our injector

Before determining the precise relationship between the R in Eq. 3 and the number of particles trapped in the glass tube, we roughly estimated it by injecting a known number of particles into the actuator to obtain a searching range. Twenty and sixty particles were selected because their aggregate sizes are 2 mm and 3.5 mm (see Fig. 5b) which falls perfectly within the desired range, according to hepatic vessel dimensions. The induced R in Eq. 3 were about 80 and 180 kΩ.

We set the bolus release resistance value between 80 and 180 kΩ with increments of 20 kΩ and performed five injections for each value. For each injection the number of particles present in the aggregate was counted as follows: Pump 2 was manually switched off after the aggregate had reached a distance of about 135 cm away from the MRI iso-center and the transparent plastic tube was rotated at 90° such that the large aggregate breaks into several chain-like aggregates, while remaining at the same position because the magnetic force on particles was perpendicular to the tube wall. We observed that the particle aggregates always kept intact before rotating the tube. In our experiments, we manually tapped the tube in order to amplify the aggregates “broking effect” until the particle number of each disaggregated aggregate was no more than 4, a counting method that is more efficient than only rotating the tube as seen in the phenomena in Fig. 5b-C. This allowed an easy manual count.

After counting the particle number at different R in front of the MRI bore, we used new aggregates with the same R range used above to take the measurements of aggregate length inside the MRI bore. The aggregates were still advancing in the entry of the MRI bore induced by the fringe field after switching off Pump 2. They eventually stopped their progression when entering the area of the uniform static field B0 inside the tunnel of the MRI system. At that time, the aggregates were always intact. The aggregate length was measured using the pictures taken from the videos obtained from the MRI-compatible camera. The camera was perpendicular to the B0, making the length of each aggregate visible. The width was not measured as it was constrained by the inner diameter of the tube.

To quantitatively determine the relationship between the trapped particle number and R in Eq. 3, a linear regression was performed using the generalized least squares method (Fig. 6b). From the regression result, we obtained the following expression for the particle number n:

\[ n = 0.405R - 12.23 \quad (80 \text{ kΩ} \leq R \leq 180 \text{ kΩ}) \] (4)

Based on the linear regression, the formed aggregates ranged from 20 to 60 particles and the maximum observed error with the theoretical value was 6 particles. Another linear regression gave us the following expression for the relationship between aggregate length L and the receiver resistance R (Fig. 6c):

\[ L = 0.01579R + 0.38286 \quad (80 \text{ kΩ} \leq R \leq 180 \text{ kΩ}) \] (5)

The lengths of aggregates ranged from 1.6 to 3.2 mm and the maximum observed error with the theoretical value was 0.5 mm.
C. In vitro injectability and MR imaging capability tests

To check whether our injector could successfully deliver a particle aggregate in a vascular bifurcation, aggregates were injected into a symmetric Y-shaped glass tube inside the isocenter of the MRI bore. The experimental setup is depicted in Fig. 7. The tube had a constant inner diameter of 2.1 mm. We set an equal flow rate in the two branches of the bifurcation by using two GH-03217-24 150-mm correlated flowmeters (Cole-Parmer). Particle aggregates were injected through a 5 French, 150 cm long, 0.043" inner diameter straight Glidecath catheter (Terumo, Tokyo, Japan). The catheter tip was inserted into a Y-valve connected to the phantom. Two recuperation bottles were placed after the two output branches to collect particles. The R in Eq. 3 was set to accumulate aggregates made of 25 particles in the counting chamber. With this value, the length of the aggregate ranged from 1.3 to 2.1 mm, ensuring that it could pass easily through the 2.1 mm diameter tube. To prevent any possibility of occlusion in the tube by particles, Pump 2 was set at 0.6 mL/s when a particle aggregate reached the phantom. By checking video frames from the MRI-compatible camera, an injection was deemed successful if it satisfied two conditions:

1. A particle aggregate was effectively released into the phantom after actuation.
2. The released aggregate did not break apart before it reached the phantom branches.

The time required for an aggregate to pass through a 150 cm catheter (5 French) was about 4.5 s in the experiments conducted in this study. Based on 50 injections of aggregates, when the main branch was parallel to B₀ (see b in Fig. 8), 88% of the injections were recorded as successful while 10% of them broke into several aggregates and 2% could not be located by the video. The success rate was also examined when the angle between the main branch and B₀ was set at 45° and 90° (see c and d in Fig. 8). After 50 injections at each angle, the success rate reached 86% (45°) and 82% (90°), respectively (p = 0.78).

Aggregates can be well imaged using spin-echo or gradient-echo sequences since they appeared as magnetic artifacts on the MRI acquisition performed after injections [30]. To image particle aggregates, T1-weighted spin echo images were acquired (TR = 900 ms, TE = 9.0 ms, pixel bandwidth = 250 Hz, slice thickness = 4.0 mm, slice interval = 4.3 mm).

During the imaging acquisition (see e and f in Fig. 8), flow was stopped such that the aggregate remains in a branch. We confirmed the location and absence of motion of the aggregate during MR acquisition by analyzing the video capture. The graph paper below the phantom helps us to pinpoint exactly the position of the aggregate. The imaging experiments were repeated 4 times for each phantom orientation (0°, 45°, and 90° to B₀).

Fig. 8. The movement of a particle aggregate in the phantom into the lower left tube branch is shown in the coronal direction (a, b, c, d) optically and (e, f) by magnetic resonance imaging. Fig. 8a-d show the particle aggregates before (a) and after (b, c, d) entering the phantom with the help of an MRI-compatible camera. Fig. 8e and f show a coronal image of the phantom taken before (e) and after (f) an aggregate reached the branch. The dark areas and white line around the particle aggregate were caused by susceptibility artifacts [31]. Note: 1. For different particle aggregates, the probability of entering different tube branches was random because there was no magnetic navigation force. We also randomly selected one video snapshot when the angle between the main branch and B₀ is 0°, 45° and 90° (see b, c, d). 2. MR correlation is only showed when the main branch and B₀ are parallel because different angulation to B₀ did not affect the imaging results.
IV. DISCUSSION

MRI-compatible injection systems should be able to handle both high magnetic fields and high gradients. The proposed injector proved to be capable of working properly inside a 3 T MRI magnetic field. Moreover, its design makes use of the fact that this field easily magnetizes and saturates superparamagnetic particles to form aggregates through dipole-dipole interactions. These aggregates exhibit higher magnetization than isolated particles and could be steered with more efficiency inside the MRI bore using the MR-imaging gradients. All these considerations have been taken into account in the development of this injector. Besides, in the context of MRN, for the same delivered dose, the procedure time would be significantly shorter when using aggregates instead of individual particles.

Once the aggregates are formed in the glass tube, they need to be injected into the circulatory system through an inserted catheter. To achieve a successful delivery, the ideal design requires the glass tube and catheter to have a similar internal diameter. Decreasing the internal diameter would increase its compatibility with smaller catheters but would significantly decrease the maximum possible number of particles per aggregate. The 82% success rate of aggregate injections with our current design is considered satisfactory since we were injecting with a constant flow of 0.6 mL/s in a 2.1 mm internal diameter tube which is about the size of the segmental artery. The main hepatic artery has the internal diameter within the range of 4-5 mm. For the same flow rate (0.6 mL/s), we can expect a decreased velocity and shear stress, thus fewer aggregate failures will occur at the level of the first branch division (right and left hepatic branch). The guidelines recommend segmental (super selective) over lobar (selective) embolization since whole liver embolization can lead to more complications (liver failure) [32]. Hence, it is crucial we can expect to have a higher proportion of intact aggregates and close to 100% selectivity at the first bifurcation (right/left lobe). We need a good but not necessarily perfect selectivity at the second bifurcation (segmental level) since non-target embolization beyond the second bifurcation is not clinically detrimental. We could also expect an increase in the success rate when using a vibrating flow that will reproduce a stop and go motion on the particles. By doing so, it will give a chance to the broken aggregates to re-aggregate with the magnetic field of MRI.

We were able to determine the optimal injection rate for Pump 1 and 2 to ensure that the particles can be injected in short periods of time while being effectively trapped by the magnet and then released safely as aggregates. In our setup, the particle suspension was injected using Pump 1 which was about 4.5 meters away from the 3 T MRI scanner. In this area, the magnetic strength is lower than 0.0005 T and the gradient is close to 0 T/m. The main reason for this positioning was to prevent the formation of aggregates before the particles would reach the counting chamber. However, in some instance, aggregates are formed nevertheless which explains the small differences in particle number obtained for the same resistance value. Ideally, the particles should be injected into the glass tube one by one to accurately control the particle number in each aggregate. To prevent particle aggregate formation before they enter the counting chamber, increasing the mean distance between two adjacent particles is an easy yet effective method. It can be achieved by decreasing the internal diameter of the feeding tube from Pump 1. This will also induce a faster velocity, resulting in a shorter delivery time. However, a smaller diameter may increase the risks of clogging up the feeding tube. Another alternative is to decrease particle concentrations. However, this would increase the total fluid volume injected into the body as well as the procedural time. As shown above, since the magnetic field at the position of the actuator needs to be sufficiently strong to maintain the shape of the aggregates after being released, the position of the actuator cannot be changed arbitrarily. In our experimental setting, stepper motor-based pumps were used to inject particles and saline, which restricts the use of the pumps in the MRI room. Using MRI-compatible pumps and actuators may ultimately make the system more clinically compatible.

Our injector has demonstrated the ability to control the particle number in each aggregate. Although there are no drugs in particles used in this study, the possibility to load magnetic particles with doxorubicin (or other therapeutics) to create MDEBs has been previously demonstrated [20]. The ability to have a real-time estimation of particle numbers is an advantage since it renders feasible the calculation of the exact amount of drugs during chemoembolization with MDEBs which contain a fixed amount of drugs [33].

The 82% success rate of aggregate injections through a 5 French catheter makes our injector potentially useful for MRN, DFN and embolization performed after MR-Guided catheter navigation. Several teams have shown the feasibility of performing selective catheterization under the MR guidance [22, 34]. Besides the reduction of exposure to ionizing radiation for the staff performing these procedures routinely, the advantage of MRI over digital subtraction angiography is the possibility to add functional imaging to quantify flow, perfusion and also particle distribution when using magnetic particles [30, 35, 36].

The procedure time required is an important factor to be considered before any new medical technology is introduced. Regarding MRN, for a typical chemoembolization with drug eluting beads, we need 2 mL of particles to load 75 mg of Doxorubicin (standard dose of 50 mg/m² body surface). For 100-300 μm particles (mean volume of 0.014 mm³), it will take 140000 particles, while this number is only 18181 for the 300-500 μm particles (mean volume of 0.11 mm³). Thus, the MRN would take 7.8 (100-300 μm particles) or 1 (300-500 μm particles) hour to inject if each aggregate has 25 particles and each navigation takes 5 s [37]. To decrease the procedure time, we can define an in vivo protocol starting with small particles to penetrate the tumor and then inject larger particles to occlude the flow and treat the tumor margin. Moreover, the gradient in our previous experiments was only 20 mT/m while the MRI can supply 40 mT/m [37]. Currently, the injector has the ability of forming an aggregate within 3 s. We can anticipate with higher gradients and a faster flow able to inject aggregates every 3 s and probably less after injector optimization. Thus, we can anticipate a therapy time below 2 hours which is not more than the time required for hyper-selective catheter-directed chemoembolization under fluoroscopic guidance.

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Future work has been planned to navigate magnetic particles from the main hepatic artery to the second level bifurcation, allowing for a segmental embolization. In this setting, microcatheters will not be required and MRN will be ideally performed through an implantable arterial port with a 4 or 5 French catheter, both of very similar internal diameters, positioned in the hepatic artery to avoid repeated catheterizations. We are currently working on the integration of this system with the MRN software to enable a synchronization of MDEB boluses with gradient actuations.

V. CONCLUSION

The proposed injector design is compatible with a controlled injection of magnetic particles inside an MRI bore. The particle numbers and aggregate sizes per injection can be set according to the actual demands. Each aggregate contains 20 to 60 microparticles with a precision of 6 particles and the corresponding aggregate length is 1.6 to 3.2 mm. At last, we have demonstrated that our formed aggregates can be injected into the MRI bore without breaking apart using a 5 French catheter. The success rate of aggregate injections is no less than 82%.

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