Evaluation of a MRI based Propulsion/Control System Aiming at Targeted Micro/Nano-capsule Therapeutics

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Abstract—MRI based nano- and microrobotics show good potential for new targeted therapies tackling e.g. cancer. In this paper, a system developed for the propulsion and navigation of small ferromagnetic objects only using clinical MRI systems is evaluated in experiments. The experiments include propulsion of an untethered ferromagnetic object against a pulsatile flow in a pipe system, navigation of an untethered object filled with ferromagnetic nanoparticles around obstacles in a free environment, and the choosing of a branch in a closed flow-less channel system when propelling an untethered ferromagnetic object. The system is found to deal with the tasks efficiently.

I. INTRODUCTION

MRI based robotics is a field with high potential for development of new therapeutic approaches. Much effort is spent into developing new MRI-compatible actuation principles and actuators and suitable vision feedback and control strategies. The MRI has shown to be a very powerful and versatile imaging device for medical use. As example, integrated navigation and control software system for MRI-guided robotic prostate [1], [2] or coronary [3] interventions have been proposed. At the same time the MRI has been discovered as an actuating device, not only delivering feedback, but exerting a force on ferromagnetic objects which are in the range of the gradient coils. By this mechanism, the control of ferromagnetic objects or even ferromagnetic nanoparticle agglomerations with a sufficient magnetic moment come into reach. Several research has been worked into this issue by Martel et al. [4], [5]. Recently, also micro- and nano-robotic platforms for targeted drug delivery have been proposed and developed [6], [7]. As discussed there, the aim of the platform is to target tumor sites deep inside the human body and allow a targeted therapy of the tumor while minimizing the side-effects of the chemotherapeutic agents. Due to the nature of the MRI device, the simultaneous use as a control sensor obviously lies near. Past approaches have shown the principal feasibility of an interleaved imaging/propulsion scheme for MRI, which allows to close the control loop. Still, the algorithms and approaches applied on the image data have certain drawbacks. More recently, a breakthrough in interventional MRI-guided in – vivo procedures demonstrated that real-time MRI systems can offer a well-suited integrated environment for the imaging, tracking, and control of a ferromagnetic microcapsule, which was done in the carotid artery of a living swine [5]. These successful experiments pointed out critical challenges in terms of real-time imaging, tracking and navigation for future therapeutic applications [8]. In order to assess the performances and limitations of such MRI-based steering and navigation platform, it is important to conduct intensive experimental investigations. This paper will show the results of various experiments evaluating and extending the capabilities of the system proposed before, in order to show the usefulness of the approach, and to prepare the grounds for further experiments and optimizations. We will investigate experimentally the main parameters that influence the stability of the tracking system (e.g. magnetic signature, pulsatile blood flow, obstacle navigation and planning). Two types of demonstrators will be tested: i) a swimming capsule has been filled with 232mg of Ferrofluid. The capsule has the benefit of good visibility not only in the MRI scan but also in an optical video. ii) an in-pipe navigation microcapsule made of steel material. First, a short summary of the approach and the system concept will be given. Then the system and experimental setup will be described. The experimental results will then be followed by a discussion of the results and a summary.

II. REVISITING THE PROPOSED DRUG DELIVERY SYSTEM

The main idea of the proposed concept is the use of the MRI with minimal modification for propulsion and visual feedback. The objects to be propelled and controlled are ferromagnetic particles and nanoparticles, which can be influenced by magnetic field gradients. Magnetic field gradients are used by the MRI system in conjunction with a strong static magnetic field and radio frequency pulses to achieve the nuclear magnetic resonance effect for imaging. Although at later stages of complex setups with strong flow and especially when using much smaller objects, the strength of the MRI gradient coils may not be sufficient, still much can be done using commercially available clinical MRI systems.

Propulsion is done using the integrated MRI gradient coils which are normally used for imaging purposes. For this purpose, specific MRI imaging sequences have been designed [9]. These sequences are fed with information using a real-time feedback path from the controller algorithm.

Visual feedback is done by first executing 3D MRI imaging sequences and finding the initial position of the...
magnetic device to be controlled, and then executing fast 2D imaging sequences at the predicted position of the object to track it [10] [11]. The algorithms have been developed after analyzing the artifact properties [12]. The implementation of the algorithms is based on the standard libraries and development tools commonly used to develop algorithms for Siemens MRI systems.

Control is done using a simple PI controller, and a more sophisticated controller with uncertainty modelling shown before [11]. The controller acquires data from the tracking algorithms and sends data to the tailor-made MRI sequence.

III. MRI SYSTEM DESCRIPTION AND GENERAL EXPERIMENTAL SETUP

The MRI system used here is a standard clinical Siemens Verio 3 Tesla system (see Fig. 1) present at Pius Hospital in Oldenburg, Germany. The system does not have any modified hardware and its state is not modified in any way beyond the limits set by legislation.

![Fig. 1. The used Siemens Verio 3T MRI system at Pius Hospital in Oldenburg, Germany](image)

Modifications have been made in the software. This includes the new MRI imaging sequences, the image processing algorithms and the control algorithms, which have been implemented on the device.

The overview of the software system architecture is given in Fig. 2. (i) The graphical user interface module, which comprises input command prompt, 3D-visualization, and process supervision tools. (ii) The control module, which comprises (a) the high-level controller responsible for the microcapsule navigation tasks and for the generation of the magnetic field gradients and (b) the low-level controller (manufacturer MRI controller) responsible for implementing the actuation commands for the generation of the desired field gradients and for the image acquisition tasks. Then, (iii) the controlled hardware, which comprises (a) the MRI hardware and software systems and (b) the microcapsules that have been injected within the vasculature and are navigated by the field gradients. Finally, (iv) the image processing module, which comprises the (a) MRI image reconstruction and (b) the image-processing software that estimates the position and accumulation of the microcapsules within the vasculature, the tissues, and the organs of the human.

All experimental setups have been constructed inside a closed acrylic glass cube sized 30cm in all directions (see Fig. 3(a)). This is to ensure that no ferromagnetic material escapes into the system. The wall strength is 5mm.

The experiments designed include evaluations of the capabilities of the system to propel objects against a pulsatile flow, evaluations of the possibility to automatically navigate around obstacles on a path, and the choosing of a branch inside a closed path system.

The experiments will be described in the next section.

IV. EXPERIMENT DESCRIPTIONS

A. Pulsatile Flow

In order to evaluate the capability to move objects against a pulsatile flow, a straight glass pipe has been used with an external pump. The glass pipe had an inner diameter of 6mm, the object used was a 4mm steel ball. The maximal gradient amplitude was set to $\Delta B = 20mT/m$, propulsion pulse duration was set to $t_{prop} = 1s$. The imaging sequence used was a 2D FLASH sequence with the parameters $T_e = 4.8ms$, $T_r = 9.1ms$, number of averages of 1, slice thickness of 5mm, pixel bandwidth of 391kHz, 256 phase encoding steps and pixel spacing of 1.171825mm in all directions. The setup can be seen in Fig. 3(c) and Fig. 3(b). The pulsatile flow was set to an arbitrary value and the PI controller had the task to hold the steel ball at a set position.

During the experiment is expected that some variation of the artifact shape or appearance occurs, because the acquisition takes time and during the acquisition time the object may move, which will distort the imaging to a certain extent.

B. Obstacle Navigation

This experiment has been designed to evaluate the possibility of the controller to navigate around obstacles in a free environment, as precondition to later navigation inside a vessel system. For this purpose, a small capsule filled...
with 332mg of ferrofluid (ferromagnetic nanoparticles with an average particle size of 10nm in oil buffer, FerroTec Corporation) was used. This capsule was designed to swim on the water surface (see Fig. 4).

As obstacle, a simple maze was designed. This maze was built in the center of the acrylic box and the controller should find a and propel along a path one round around the maze. The maze can be seen in Fig. 5.

In order to test the potential for speedup, the experiment was executed two times with standard parameters, and another time with speed-optimized parameters. The speed for the execution of the sequence can be influenced among others by the following factors:

- Sequence type
- $T_e$
- $T_r$
- number of k-space lines acquired per slice
- number of averages used
- resolution of the image

In this case, the resolution of the imaging was reduced from 256x256 to 128x128, and partial k-space acquisition enabled (3/8th of k-space acquired). The time for achieving one round trip was measured and compared to the standard parameter set.

The standard parameters were a 2D FLASH sequence using a resolution of 256x256, $T_e = 4.8ms$, $T_r = 9.1ms$, number of averages of 1, slice thickness of 5mm, 256 phase encoding steps, a pixel bandwidth of 391kHz, pixel spacing of 1.171825mm in all directions. The maximal gradient strength was set to $\Delta B = 20mT/m$, the propulsion duration was set to $t_{prop} = 500ms$. The controller was set to achieve the target position with a distance threshold of 30.

The speed optimized parameters were a resolution of 128x128, $T_e = 4.8ms$, $T_r = 9.1ms$, number of averages of 1, slice thickness of 5mm, 40 phase encoding steps, a pixel bandwidth of 391kHz, pixel spacing of 2.34375mm in all directions. Again a maximal gradient strength of $\Delta B = 20mT/m$, propulsion duration still set to $t_{prop} = 500ms$.

C. Choosing a branch of a closed channel system

For this experiment, a simple channel system has been implemented in a acrylic glass plate. The channel system has a shape like the number 8 which allows to take one branch of two when approaching the tail of the 8. The channel diameter in the inside was 10mm, the outer channels have 6mm diameter. The dimensions of the plate is 220mmx190mm. The steel ball then has to be moved into a previously determined channel branch. The channel and the base plate can be seen in Fig. 6.

V. Experimental Results

All experiments have been successfully executed. Details are presented in the following sections.
Fig. 6. The acrylic glass plate used to implement the channel branch choosing experiment. Channel width is 10mm in the middle channel, 6mm in the outer channels. The visible holes are for fixing the plate in the acrylic glass box.

A. Pulsatile Flow

The experiment with the pulsatile flow has shown that the controller is able to hold the steel ball in the vicinity of the target point. The generated artifact seemed to stand still in the MRI video output, because the controller commands and flow cancelled each other out in average. Due to the slow repetition rate the ball was oscillating around a point near the target point instead. This will be improved by faster repetition rates and shorter image acquisition and propulsion times. The generated artifact can be seen in Fig. 7. Visible is the zebra striping of the artifact. This comes due to the order of acquisition of the k-space lines and the movement of the steel ball during acquisition. Altogether, the following statements can be made:

- The force achieved by the magnetic gradient is strong enough to overcome a flow in the order of magnitude of centimeters per second inside a vessel or pipe system.
- Although the MRI images may show a static image, when using these slow repetition rates, the object position oscillates around the position determined in the MRI images, so higher repetition rates are needed.
- MRI artifacts are different when the ferromagnetic object moves during image acquisition. This effect may be reduced by faster imaging, but needs to be taken into account in the tracking algorithm.

B. Obstacle Navigation

The movement around the obstacle was successful. The image processing module first extracted a path around the obstacle, and defined waypoints. In Fig. 8 and Fig. 9, the MRI images of some frames during the movement and the extracted paths can be seen.

The extracted path from the MRI images can be seen in Figs. 10(a) and Fig. 10(b). The path shows that the controller manages to get around the obstacle and has no problems achieving movement into any desired direction. Due to the shape of the object and the low payload of ferromagnetic material, acceleration of the object is low. Still, by repetitive application of magnetic propulsion gradients, the object can be moved sufficiently fast. A disturbing factor is the deceleration during the imaging phases of the MRI sequence. This can be improved by speeding up the imaging process.

The run with the standard parameters took 121 seconds to finish. After tuning the parameters for speed, the movement around the obstacle was finished within 40 seconds, which is a speedup factor of 3. This hints that in all cases, optimization will yield significant increases in speed and controllability. The reduced resolution in this case was not problematic. An acquired image with the waypoints and artifacts can be seen in Fig. 11. Clearly visible is the reduced resolution, the stronger distortions and the different artifact characteristics.

C. Choosing a branch of a closed channel system

The steel ball used was moved inside the channel system. By using the gradients, it was possible to choose the right
branch of the channels. As the system was without flow in this case, the choosing of the branch was very straight. In the example run, the steel ball was moved from the middle challenge into the upper right channel. After going around on the right side, in the middle bottom, the central channel is taken. When arriving at the upper middle channel, the upper left channel is taken. All this can be seen in Fig. 12.

Problems which occurred during the experiment were mostly related to the rectangular shape of the channel profile and remainst of the glue used for producing the channel structure. Due to the fact that the used steel ball can not roll in such a strong static magnetic field and because it was neither levitated by magnetic force nor by flow in the experiments, even small impurities on the channel wall can be problematic.

VI. DISCUSSION

As the experiments show, the developed system works. It can use the capabilities of a clinical MRI system to propel ferromagnetic objects against a pulsatile flow. Also, automatic navigation of a ferromagnetic object in a free environment around obstacles is possible. Tuning of sequence parameters can lead to significant time savings and speed-ups. Even further speed-up will be possible by more thoroughly tailoring the imaging sequence and its parameters.

Choosing of a branch is also possible by using magnetic gradients and the suitable controller.

Further effort has to be spent on optimizing the parameters and achieving higher repetition rates. Higher repetition rates will enable the controlled navigation and propulsion against flow, also choosing branches at intersections. This has to be evaluated and improved.

VII. ACKNOWLEDGMENTS

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REFERENCES

Fig. 12. The choosing of a branch in a simple channel system (image order left-to-right, top-to-bottom). Visible is the artifact and the channel system. First, the upper right branch is taken, then approaching the middle bottom, the central channel is used, followed by the upper left channel.


