ACTUATOR DESIGN SPECIFICATION FOR MRI-BASED TARGETING OF MAGNETIC MICRO-CARRIER

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ABSTRACT
Targeting of magnetic particles inside the human body has been recently proposed as an approach to increase the efficacy of existing medical treatments and to allow the use of new therapeutic agents. Commonly used targeting methods based on the application of a magnet near the target site lack feedback and are only applicable near the skin. We address such shortcomings with the use of an upgraded MRI system designed to steer the particles inside the vascular network. Here, we discuss the required specifications for such upgraded coils in term of pulse train shape and RMS value, gradient uniformity and heat management, based on experimental data scaled to be representative of an *in-vivo* situation.

KEY WORDS: Magnetic Micro-Particles, Targeted Magnetic Micro-Carrier, Actuator

INTRODUCTION
Magnetic steering of therapeutic magnetic micro-carriers (TMMC) has been demonstrated by our group using an upgraded clinical MRI scanner that consisted of an additional set of Maxwell coils capable of providing a maximum magnetic gradient of up to 400mT/m [1, 2]. Appropriate steering for targeting purposes can be investigated experimentally using a Y-shaped bifurcation at the end of a vessel. In Fig. 1 for instance, a phantom with three Y-shaped bifurcations is represented. In previous work, the gradient used for a given targeting experiment was constant in time (i.e. without a change in the direction of the gradient), thus limiting the choice of targeting sites (e.g., only output A or D in Fig. 1). Here, a pulsed version of this MRI upgrade is used to demonstrate the feasibility of steering TMMC in opposite directions through two consecutive bifurcations, thus enabling the targeting of outputs C (or B). We also used those results to investigate a new coil design. A set of minimum specifications were calculated from experiments in order to provide guidance for the fabrication of new rabbit-sized three-dimensional gradient coils.

METHOD
The experimental setup consists of a pair of Maxwell gradient coils, a phantom of the hepatic arteries of a rabbit, two pumps and a video camera as shown in Fig. 1. The pumps were used to simulate the blood flow inside the phantom and to inject the micro-particles (MP). The captured images and the steering gradients were time-multiplexed in order to simulate the acquisition constraints of a MRI tracking sequence, as shown in Fig. 2. The coils were connected to a bipolar power supply. The camera and the power supply are controlled via a real-time computer to ensure proper timing of steering pulses and image acquisition. As the ideal TMMC are not commercially available yet, we used MP with suboptimal properties. The MP have been manually injected in a single bolus. The bolus tracking have been released using a real-time image processing library, but the actual switching of gradient direction have been done manually due to detection inaccuracy.

RESULTS
A preliminary steering test was performed in a physiologically sized phantom with lower flow rate, liquid viscosity and commercial grade MP with lower magnetic properties. The travel time of a single bolus of MP from the injection point to the first bifurcation was 19s. They were effectively steered using 68 pulses of 280ms (60ms for localization, 20ms for rising and falling time, and 200ms for full gradient strength as depicted in Fig. 2). The second bifurcation was crossed in 20s, with 72 pulses of 280ms through the second bifurcation in order to reach point C as shown in Fig. 1.
To rate the ability of the system to steer the MP, we define the steering ratio as the travelling time of the MP from one bifurcation to the other over the time required to pull all the MP from one side of the vessel to the other [3]. The experimental results lead to a steering ratio of 9.9.

DISCUSSION
These results were then scaled using a dimensional analysis based on the Buckingham-Pi theorem and existing targeting model [3]. The scaling objective was to calculate the targeting duration of a TMMC bolus in the rabbit hepatic arteries, based on the previous experiments results, to obtained a steering ratio of 1. Thereby, the TMMC need to be steered in less than 200ms in order to cross any bifurcations in the rabbit hepatic arteries. This can be theoretically achieved with one or several pulses of 400 mT/m with a total duration of 140ms for the first bifurcation, and 110ms for the second. Hence, 60ms and 90ms may be used to rise and fall the current inside the set of coils, to increase the steering ratio or to perform TMMC localization in the first and the second bifurcation, respectively. According to these results and to minimize wasted time as rise and fall time, the ideal actuator for MRI-based targeting has to produce a single pulse in order to steer the TMMC trough a single bifurcations. If *n* bifurcations have to be crossed, a pulse train with *n* pulses has to be generated. This pulse train will have a high RMS current, as all pulses have a maximum duration of 200ms in order to insure a good steering efficacy. As the heat management is the main issue with such a high power gradient system [4], the technology used to build this actuator will depend in the utilization scheme, the coil diameter and the resulting heat dissipation.

We can use a resistive coils system, where the heat produced by the system is proportional to the RMS current flowing through the coil. To reduce the heat produced by the system, we have to decrease the RMS current flowing through the coil. This can be done by crossing a small number of bifurcations and by separating each train pulses by several seconds.
Or we can use a supraconducting coils system, in which the heat generated is inversely proportional to the change rate of the current inside the coil [5]. This change rate is called rise and fall time in the present abstract. With such a coil, we can use pulse train with high RMS current value, thus crossing several bifurcations, but we have to increase the rise and fall time of each pulses, to limit the heat generated by the coil.
In any case, the other specification for the actuator remains the same. For a rabbit-sized system, the current in the sets of coils cannot be changed between zero and full power in less than 4ms to avoid any peripheral nerves stimulation [6]. To be able to steer inside the whole rabbit volume, a gradient uniformity of 12.5% is required in a 150mm diameter sphere to ensure a minimum of 350mT/m in the whole targeting area. The use of longitudinal and transverse gradient coil to release this rabbit-sized actuator seems appropriate [7].

CONCLUSION

We have shown that the technology used to build the coil will be determined by a given utilization scheme, i.e. a realistic *in-vivo* situation. To determine this utilization scheme, we need information such as the number of bifurcations to cross, their length and diameter and the flow speed flowing inside the arteries. We may use an allometric model [8, 9] to calculate, from the properties of the first bifurcation, all the properties of the subsequent bifurcations, and thus linking a utilization scheme to a certain bifurcation depth inside the body. Unfortunately, the existing allometric model do not allow the calculation of realistic flow speed, as they suppose that the flow rate is simply divided by 2 at each bifurcation, which is not representative of all the arterial system, in which the ratio of the flow rate flowing through a bifurcation is a function of the organs impedance [10]. It is therefore impossible to properly define a utilization scheme based on allometric model. To move on from the design stage to the building stage of an actuator for the targeting of magnetic micro-carrier we have to define the in-vivo conditions in which the actuator will be used, as these will have an influence on the technology used to build it.
Finally, for a human sized system at the same required gradient field, the increase in diameter of the coils will results in a sharp increase in the coil resistance [11], thus excluding the resistive technology to built the coils system.

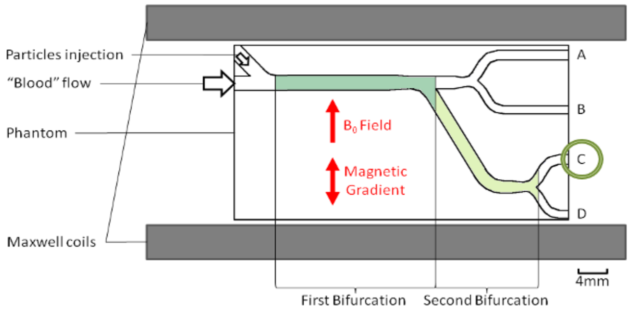

Fig 1: Experimental setup showing a phantom, with three Y-shaped bifurcations, inside the Maxwell coils. The targeted branch during the test was the *C* one.

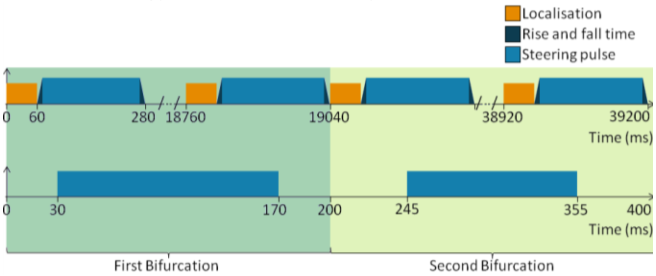

Fig 2: Timing of the events sequence for a steering pulse wave design to cross two bifurcations. The top represents the experimental sequence. The bottom shows the theoretical sequence to steer ideal TMMC in the rabbit's hepatic arteries.

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