MRI-Based Magnetic Navigation of Nanomedical Devices for Drug Delivery and Hyperthermia in Deep Tissues

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***Abstract* — Magnetic Resonance Imaging (MRI) scanners can be used with minimum upgrades as integrated platforms for targeted delivery of micro/nanoparticles in the human body. In addition to being widespread in hospitals, they provide real-time tracking, control and means of propulsion for magnetic devices without penetration depth limitations. From these positive features, MRI appears as the perfect central element of a nanomedical navigation platform. Nevertheless, these assets are also coupled with constraints arising from the use of an already existing interventional platform. Potential magnetic nanoparticles-based carriers with the navigation platform are described. A simple magnetic suspension model taking magnetic dipole-dipole interactions into account is also proposed.**

Keywords — ***Magnetic resonance imaging, nanomedicine, drug delivery, hyperthermia.***

I. INTRODUCTION

Magnetic particles have been proposed as carriers for targeted drug delivery as early as 1978 [1]. The targeting method proposed at the time relied on intravenous injection of a magnetic colloidal suspension upstream to a targeted organ. Retention of the magnetic particles was achieved by placing an external magnet on the surface of the skin. This approach provides limited control over the geometry of the field, trajectory of the particles and no real-time tracking or feedback. In addition, it is limited to superficial organs as demonstrated in [2]. To our knowledge and regardless of these limitations, no alternative spatial control method has been proposed and most of the research effort has been placed on particles and carriers development [3-6].

We proposed an alternative to external magnet retention through the use of a magnetic propulsion force generated by a clinical Magnetic Resonance Imaging (MRI) system with an induced force proportional to the amplitude of the magnetic field gradient [7].

The MRI system is used to actively affect the flowing of a suspension of magnetic particles in order to reach a targeted area in the cardiovascular system. The magnetic particles must be able to carry and to release an active principle and to generate heat. Hyperthermia is a cancer treatment aiming at raising the temperature of a tumor mass between 41°C and 46°C for therapeutic benefit. Although hyperthermia is still considered an adjunct to other treatments, it has been broadly recognized as a stand-alone therapy being sometimes even superior to chemotherapy.

The magnetic force F_{mag} (N) acting on a magnetized particle is proportional to its magnetic moment m (A.m^2) and to the gradient of the magnetic field H (A/m) as shown in Eq.1 where μ_0 (N.A^{-2}) is the permeability of vacuum.

$$\vec{F}_{mag} = \mu_0.(\vec{m}.\nabla)\vec{H} \quad (1)$$

Our proposed method has no organ depth limitation since gradient amplitude is constant over the homogeneity region of the MRI bore (typically represented by a spherical volume with a diameter of 50cm). Hence, an MRI system by providing an actuation method coupled with tracking information [8] and real-time software architecture allows closed-loop control of the spatial distribution of magnetic particles in the human body.

It was demonstrated in [9] that this method could be used for closed-loop control over the position of a 1.5 mm magnetic sphere inside the carotid artery of a living swine. Even though MRI systems contain all the components of a nanomedical navigation platform, they were designed uniquely for imaging which brings constraints for navigation of untethered devices. The current paper describes the scaling laws and upgrades required for *in vivo* navigation when millimeter spherical devices for instance are miniaturized down to nanometer-scale particles.

II. CARRIERS

Saturation magnetization is the key parameter for magnetic propulsion. Therefore FeCo particles are favored as magnetic cores for the drug carriers because these alloys have the highest known saturation magnetization. It is four times higher than Fe_3O_4 typically used in magnetic separation applications. T2* weighted MRI sequences are extremely sensitive to superparamagnetic particles suspensions. Therefore, using superparamagnetic FeCo nanoparticles ensures that tracking is possible [10] even as injected magnetic suspension becomes dilute while spreading in the capillary network.

Another reason for using superparamagnetic nanoparticles as propulsion cores is the efficiency of the heat generation through Néel or Brownian relaxation. However, in order to take advantage of this heat generation mechanism, a patient will have to be inserted inside a time variable low field coil outside of the high field region of the MRI system once targeting and retention of the carriers has been achieved.

In order to incorporate an active principle inside the carriers, the magnetic cores need to be embedded inside a polymer

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matrix or inside a liposomal carrier. Active principle release can be achieved through biodegradation of the polymer matrix, through the use of a heat or chemically sensitive polymer or through phase transition in a liposomal membrane.

III. Direct Targeting Navigation Platform

While the B_0 field from the superconducting coil of the MRI scanner is used to magnetize the nanoparticles, its gradient coils and RF transmitters and antennas are used as parts of the tracking sequence.

The imaging gradient coils present in MRI systems can be used for magnetic propulsion [9]. Nevertheless, they are barely powerful enough to propel millimeter sized particles. Hence, a propulsion dedicated gradient coil insert must be placed inside the bore of the standard imaging gradient coils (Fig.1). Such custom propulsion coil powered by an independent set of amplifiers would provide sufficient gradient amplitudes for propulsion of micro/nanoparticles. The RF transmitters and antennas must be placed inside the propulsion coil in order not to be shielded by its windings.

A time variable magnetic coil might be added to the standard MRI system for heat generation purposes once the magnetic particles have been targeted and anchored. This coil must be placed outside the bore of the MRI because Néel and Brownian relaxation require an AC magnetic field alternating around 0.

A method was proposed recently to control the position of heat generation in three dimensions [11]. It relies on the use of gradient coils separated from an MRI system with a modified power supply method (dissimilar current is supplied in the windings of each particular axis) allowing one to control the location of the 0 field area.

This method can be implemented in our platform to restrict the therapeutic area. In this case, an AC magnetic coil is placed outside of the bore of the MRI system with our propulsion gradient insert used as described in [11] provided that such system is fastened to the MRI table and follows the patient out of the bore of the MRI scanner. The use of the same gradient coil insert for particle targeting and focused hyperthermia greatly simplifies treatment area registration.

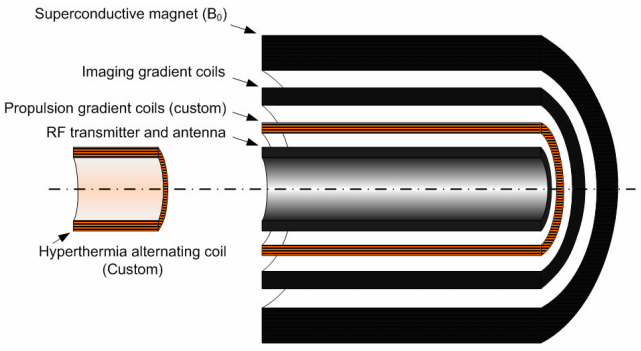

Fig.1. MR navigation platform. Components in black are standard. Striped components are custom.

As a matter of fact, particle targeting will rely on MRI scans allowing the localization of the tumor area in the coordinate system of the propulsion gradient coil. The use of the same coil for focused hyperthermia will ensure that the tumor maintains the same spatial coordinates when the patient is extracted from the bore of the MRI system.

These MRI hardware upgrades will lead to an increase of the cost of the platform. Fortunately, the investment from hospitals could be justified considering the opportunities of an expansion of MRI from imaging to nanomedical intervention platform are considered.

IV. MR Sequence

Off resonance or T2* weighted Spin Echo or Gradient Echo sequences are used for magnetic particles tracking. These imaging sequences cannot be used while propulsion gradients are being powered.

Therefore, as shown on Fig.2., tracking and propulsion of the magnetic particles cannot be performed at the same time. The tracking phases rely on original hardware from the MR scanner, namely, RF transmitter and antennas, imaging gradient coils and ADC. The real-time controller is a software component running on the image calculation computer of the MRI scanner. Its purpose is to calculate the position of the devices from the MR signal and to compute the amplitude and direction of the propulsion gradient that will be applied in the next repetition of the control loop. The propulsion gradients are applied by the custom propulsion gradient coil insert during the repetition time (TR) of the tracking sequence.

V. Effect of MRI Electromagnetic Fields on Health

In order to generate images, MRI systems use a strong and permanent magnetic field (B_0), a time varying magnetic field ($\nabla \vec{B}$) and a radiofrequency (RF) field. Effects of these fields on human health are well described in [12].

Strong static magnetic fields can affect molecular processes, nerve signal transmission and conducting fluids such as blood.

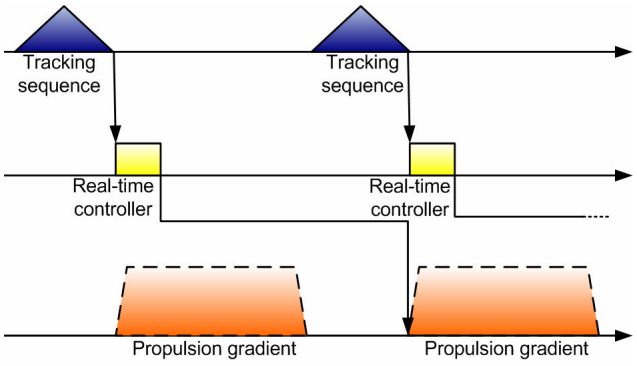

Fig.2. Overview of the MR navigation sequence.

Nevertheless, in the context of our application, no increase over the field amplitude of clinical scanner is required. As a matter of fact, magnetic nanoparticles are magnetically saturated with fields of the order of 1 T. Further increases of the field could improve tracking signal intensity but there is no reason not to remain in the accepted limits of commercial B_0 field amplitudes.

Interactions of the RF fields with biological tissues are associated with energy deposition that can lead to whole body temperature increases. The Specific Absorption Rate (SAR) has been used to quantify this effect and it is a function of the field frequency, type of field (electric, magnetic, far-field, near-field) and the body size and shape. SAR has to be taken into account in the design of imaging sequences and is automatically calculated and checked for government guidelines compliance by the sequence development environments of clinical MRI scanners. No increase in SAR is expected from MRI based nanomedical navigation because RF fields will only be used for tracking and will identical to RF fields of standard imaging sequences.

As for the gradients, it is less their amplitude ($\nabla \vec{B}$) than their rate of change (*dB/dt*) that can affect the human body. As a matter of fact, a high *dB/dt* can induce electrical currents in the nerve fibers. Additional propulsion gradient coils will be able to generate high amplitude gradient without risks for the patient provided a low enough rate of change is maintained.

Heating of the magnetic nanoparticles can take place through four mechanisms: Eddy currents, hysteresis losses, Brownian or Néel relaxation. Heat generation caused by Eddy currents generated by the time variation of the gradient coils has been estimated as negligible. The additional time varying coil for hyperthermia will be tuned for Brownian or Néel relaxation of the magnetic nanoparticles. Its design will have to comply to *dB/dt* limitations.

VI. Steering And Aggregation Behavior

Angiogenic capillary vessels can be regarded as redundant branching networks designed to bring oxygen and nutrients towards a tumor mass [13]. A magnetic nanoparticle suspension can be guided in such a network using an appropriate magnetic gradient. Simulation of steering efficiency in a capillary vessel with a Poiseuille velocity profile (10µm dia., 1mm length, 1mm/s average blood velocity) were performed. A magnetically saturated FeCo magnetic suspension (approx. concentration 3×10^{16} m^{-3}) is flowing inside the simulated vessel. The particles inside the suspension are assumed to be made of a polymer matrix containing FeCo nanoparticles with a 50% loading efficiency. It is assumed that the capillary vessel leads to a Y shaped bifurcation. Particles exiting the vessel are sorted depending on their position with respect to the centerline of the vessel. Angle of the outlet channels is not expected to influence the steering behaviour. While flowing through the capillary vessel, a magnetic force is applied along the transversal direction of the vessel. Hence, particle trajectory is deflected towards one of the vessel's wall (positive side).

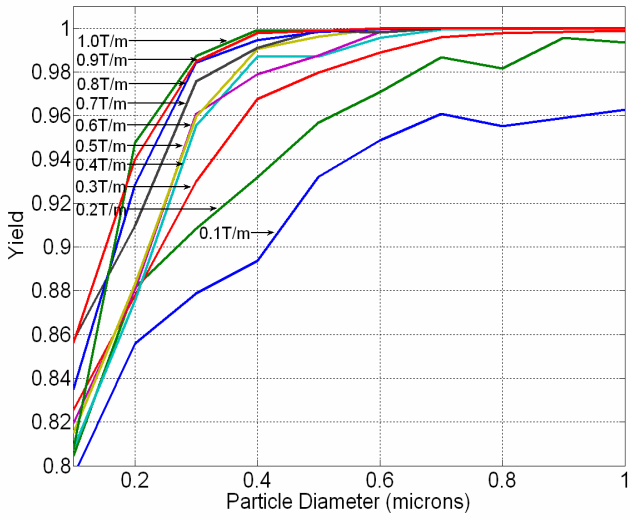

Fig.3. Yield vs. initial particle diameter and applied gradient

Steering efficiency (yield) is defined as the ratio of the number of particles in the positive outlet of the channel over the total number of particles exiting the channel.

Interparticle dipole-dipole interactions are taken into account allowing magnetophoretic velocity to be dependent on aggregate size. Particle behavior once forced against the walls of the vessel wall has not been included in this version of the simulation program but will be implemented in a future version. Fig.3. shows the yield as a function of initial particle size for different gradient amplitudes. MRI 1.5T static magnetic field optimizes steering efficiency since every particle is magnetically saturated. In these conditions, one can see that gradient in the order of 1T/m can be used for efficient steering and that larger particles leading to larger aggregate sizes, increase steering efficiency.

Standard gradient amplitude of whole body MRI scanners are in the order of 40 mT/m. These coils are designed to have a rise time in the order of 200 µs. They have a minimal number of windings and operate at high current (around 500 A). Their limit in amplitude is set by Joules effect heating within the gradient coils and amplifiers. As shown in Fig.3, a ten to twenty times increase in amplitude is required by the constraints of our application. In order to reach such high amplitude, we will loosen up the constraints of standard imaging coils in order to maximize gradient amplitude. For that purpose, we plan to design a gradient coil insert with a low response time, low current and high number of windings.

It is expected that particle aggregate size will greatly contribute to yield optimization. The following parameters play a role in aggregate size: concentration, individual particle size, magnetization, nature of the surfactants. It has been observed that vessels diameters and orientations limit the maximum length of the aggregates. Aggregates form and dissolve in order to comply with vessel lumen while flowing through sections of varying diameters. Therefore, it is expected that suspensions leading to aggregates approaching

the diameter of the vessel will lead to a decrease in steering efficiency due to their limited mobility. As a matter of fact, these aggregates would occupy the entire width of the channel and would split equally between both branches at the end of the channel.

VII. Conclusion

Based on the preliminary results of [9] and on the scaling laws that were described in this paper, using a clinical MRI scanner as a core element for a magnetic particle navigation platform seems to be a very promising approach and could and could open the road that will lead to nanomedical interventions.

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