Interactive System for Medical Interventions Based on Magnetic Resonance Targeting

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***Abstract*—Magnetic Resonance Targeting (MRT) is a new approach that aims at navigating untethered therapeutic or diagnostic micro-entities through the vascular network until a specific targeted location is reached. The platform used for such intervention is referred to as a Magnetic Resonance Navigation (MRN) system and it typically takes the form of a clinical Magnetic Resonance Imaging (MRI) scanner upgraded with special software and hardware modules to allow such platform to perform MRN in an effective manner. Considering the complexity of MRN operations and the speed at which real-time operations are being performed, an interactive system capable of providing a proper interface to allow an interventional radiologist or the like to properly interact and use such platform becomes an essential, yet a critical component for the success of this new medical interventional approach. Here, this paper presents for the first time an overview of a new interactive system for MRN operations suitable to conduct preliminary interventions.**

Keywords-magnetic; Magnetic resonance imaging; targeted interventions; cancer therapy; user interface

I. INTRODUCTION

Magnetic Nanoparticles (MNP) are often used to disrupt the high intensity magnetic field of a clinical Magnetic Resonance Imaging (MRI) scanner by creating a net field inhomogeneity that can be picked up and then processed using MRI techniques. Such MNP-based contrast agents are then typically used for imaging purposes such as to produce MR-images of blood vessels. Similarly, the same MNP when embedded in an untethered microscale entity can be used to track the displacement of the same micro-entity in the human body using a clinical MRI scanner. The field inhomogeneity created by these embedded MNP can then be used as a tracking signal that can then be fed back to an external computer as positioning data to be processed to perform closed-loop navigation or trajectory control to navigate such micro-entity along a path previously plotted in a portion of the vascular network that link the injection site to a pre-determined targeted location. Propelling and steering such magnetic micro-entities can be done by a technique referred to as Magnetic Resonance Propulsion (MRP) where magnetic gradients are generated to induce propelling force on the embedded MNP fully saturated by the high intensity homogeneous field of the MRI scanner, to propel and/or steer the micro-entities along a planned trajectory. Unlike the use of an external magnet, the technique is efficient even in deep locations in the body since it is independent of the distance between the source of magnetization and the object being navigated. Hence, MRN allows targeting efficacy at any depths in the human body and not just when operating close to the skin surface as it is the case when using a simple magnet positioned outside the patient.

MRN has been demonstrated and validated experimentally for the first time by navigating a 1.5 mm ferromagnetic bead in the carotid artery of a living swine (Martel *et al.*, 2007). As a first target medical application of MRN, cancer therapy is particularly suited. As such, special MR-navigable entities capable of carrying therapeutic agents for tumor chemoembolization and referred to as Therapeutic Magnetic Micro Carriers (TMMC) have been synthesized successfully (Pouponneau *et al.*, 2009). By navigating and targeting TMMC allows a significant reduction of the presence of highly toxic therapeutic agents in the systemic blood circulation. Such decrease in secondary toxicity reduces the negative health related effects for the patients while improving therapeutic efficacy with a lower dosage of drug. But for reaching a suitable embolization site deep enough in the vasculature to release the therapeutics sufficiently close to the tumor for improved therapeutic efficacy, the overall size of these TMMC must be reduced significantly to allow efficient MRN in smaller diameter vessels. Since the MR-based propelling force reduces significantly with a reduction of the effective quantity of MNP in the TMMC, the magnetic gradients required for adequate MRN operations must be increased beyond what is possible using the orthogonal imaging coils typically available in clinical MRI scanners. As an example, the initial version of TMMC has an overall diameter of approximately 40 micrometers (μm), requiring special propulsion coils capable of generating up to approximately 400 mT/m of 3D gradients compared to approximately 40 mT/m from the imaging coils of conventional clinical MRI scanners (Martel *et al.*, 2009). Hence, not only physiological data, but the characteristics of the MR-navigable micro-entities and the specifications (capabilities) of the MRN system must be taken into account

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when attempting to perform medical interventions requiring Magnetic Resonance Targeting (MRT), i.e. targeting using MRN. Hence, due to the level of complexity involved, an interactive system providing an interface between this technology and the medical specialists becomes highly desirable.

In Section II, our interactive display and an overview of the principles behind MRN operations will be described prior to describe the fundamental requirement for such interactive system. To better understand the problematic, a typical interactive flow for MRN operations will be given in Section IV. In Section V, the new interactive system still under development is described in more details before to conclude.

II. ACTUAL INTERACTIVE DISPLAY

An example of the actual computer interface dedicated to MRN operations is depicted in Fig. 1. First, an image of the blood vessel that will be used during MRN is first acquired using contrast agents. Then this image is filtered to remove any artifacts that could confuse MRN operations and it is then displayed as shown on the upper left corner of Fig. 1 showing in this particular case, the carotid artery of a living swine. Following this initial step, the interactive display allows a medical specialist to indicate to the computer system where the navigable micro-entities must pass to reach the desired target from the catheter release site. As such, the interactive display allows the user to plot waypoints over the image of the blood vessels to indicate the desired trajectory.

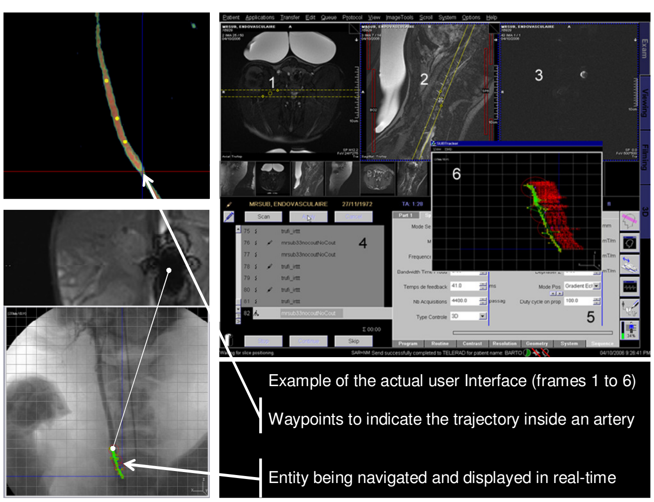

Fig. 1 – Preliminary computer interface used for MRN operations.

But there are many unknowns not indicated in this interactive system that shall be considered in order to guarantee safe and reliable MRN operations. The propulsive force induced to the magnetic micro-entity and generally described in Eq. 1 is one example.

$$\vec{F}_M = R \cdot V \left(\vec{M} \cdot \nabla\right) \vec{B} \cdot \qquad (1)$$

Eq. 1 states that the induced magnetic force (N) produced by the magnetic gradients (T m^{-1}) generated by the MRN system and acting on a ferromagnetic core or an ensemble of MNP with an effective volume V (m^3), depends on the duty cycle R, i.e. the percentage of time per MRN closed-loop cycle being dedicated to propulsion (dimensionless), which can be reduced due to longer MRI-tracking acquisition time and/or in some particular cases to allow time for cooling of the coils used for MRP, and M being the volume magnetization of the core material (A m^{-1}). When such magnetization reaches a saturation level (M_{SAT}), the highest induced propulsion force per unit volume can be reached for a given soft magnetic material (being typically the case when placed in a high intensity magnetic field such as in the bore or tunnel of a standard 1.5T or higher field clinical MRI scanner).

As indicated in Eq. 1, the propulsive force induced on the embedded MNP and required to navigate the micro-entities taking into account physiological conditions, depends not only on the characteristics of the objects being navigated, but also on the specifications of the MRN system. As such, the interface depicted in Fig. 1 is not adequate to conduct MRN operations without a deep knowledge of all required physiological, navigable entities, and MRN system specifications. Frames 1 to 3 in Fig. 1 for instance are MR-images of the physiological environment where various measurements (e.g. angles of the blood vessels, width, etc.) were taken manually by engineers to evaluate the requirements and to adjust the MRN parameters for successful navigation. It becomes then obvious that the interactive system must ease the use of such technology by medical practitioners without the need for the participation of a well trained and knowledgeable engineering team. Indeed, in this example, engineers entered from the various measurements and a prior knowledge of the platform, the adequate parameters for safe and reliable MRN operations (as depicted in frame 6 and in the lower left corner in Fig. 1) in special windows such as the ones depicted in frames 4 and 5 in Fig. 1.

III. FUNDAMENTAL REQUIREMENTS FOR AN ADEQUATE MRN INTERACTIVE SYSTEM

A simplified diagram showing the fundamental architecture of a MRN interactive system is depicted in Fig. 2. The diagram shows three main categories of data required by the MRN core to perform adequate MRN operations.

The first category is the physiological data. These data describe the static and dynamic physiological information pertinent to MRN operations. These include mainly data information about the blood vessels (e.g. diameter, length, branches or bifurcations, angles, etc.) that will be used to reach the targeted location. Static data are extracted from the image of the blood vessels gathered and filtered as

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described earlier and shown in the upper left corner of Fig. 1. Dynamic physiological data include blood flows and artifacts created by the movement of the patient such as during respiration. Indeed, MRN becomes more sensitive to the amplitude of body-related movements when operating in smaller diameter vessels where the distance between successive bifurcations becomes typically smaller than the amplitude of the movement of the patient. Hence, real-time image registration becomes essential. Since the acquisition of an MR-image is too long to be executed during real-time MRN operations, pre-acquired images taken at different physiological conditions that can be encountered during the intervention must be available to the MRN core for proper retrieval. Feedback information of the position of the micro-entities from known physiological features can be superposed on a selected pre-acquired multi-modality image and displayed by the interactive system. Other variables include heart rate that causes pulsatile flow that must also be taken into account. As such, pre-measured blood flow and real-time synchronization with the heart rate becomes additional data that when fed to the MRN core may improve MRT efficacy.

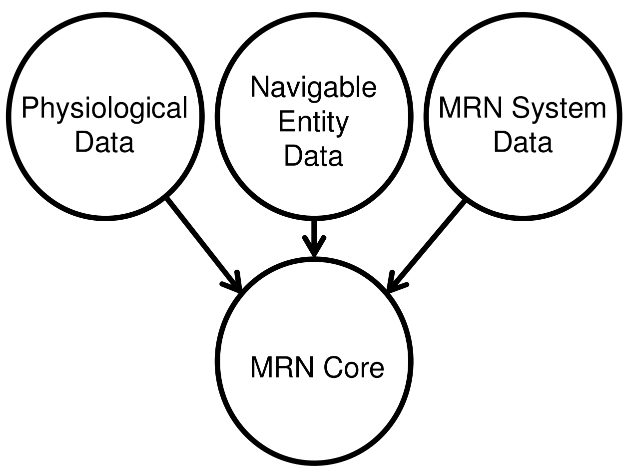

Fig. 2 – Simplified diagram of the architecture of the MRN interactive system

Data on the navigable entities are also critical for proper MRN operations. For instance, each type of navigable micro-entities may have different size, weight, and/or different volume of magnetic material with also different magnetization saturation that will lead to different displacement responses from the same applied directional gradients. The reasons are that synthesis with a different drug may pose constraints on the quantity of MNP being embedded, and/or one may opt for a larger dose of therapeutics per TMMC by lowering the quantity of MNP, etc. This is to say that the same therapeutic agent could be encapsulated in micro-carriers having different magnetophoretic velocities when subject to the same magnetic gradients. Hence, each type of TMMC in this particular case must be characterized and the data influencing MRN operations, stored in a database accessible to the MRN core.

Finally, several technical data of the MRN system and especially the ones related to MR-imaging/tracking and propulsion gradients that could impact MRN operations must be available to the MRN core.

IV. TYPICAL INTERACTIVE FLOW

The typical interactive flow required between the MRN system and the user is divided into three phases, namely the planning or MRN pre-operative phase, the MRN operative phase, and the MRN post-operative phase.

The first part of the pre-operative phase consists in gathering the required physiological data and to import it in the MRN interactive system. Then after some image and data processing, an image representation of the blood vessel network is displayed on the computer screen with the relevant physiological data. At this time, the MRN Interactive System (MRNIS) allows the user to perform several functions such as zooming, shifting, rotating, etc., to have a better perspective of the routing network available for MRT. Then on another window, the user is then allowed to enter MRT-related information starting by identifying the targeted region and the amount and type of therapeutic agents to be delivered if chemoembolization has been selected from the menu dedicated to the type of intervention to be performed. Then based on these information entered and the measured physiological data, the MRN core (Fig. 2) identifies one type of TMMC having the most appropriate characteristics from the ones available in the database. Then, the MRNIS displays the identification code of the selected TMMC with the dosage which would typically differ and be greater than the therapeutic dosage entered by the medical specialist. Once the respective TMMC dose has been put in a special automatic injection system, the MRNIS highlights the possible regions for catheter-release of the TMMC. Once the surgeon has selected the catheter-release site by clicking on a location within the region being highlighted, the MRN core calculates the best path that appears as a proposed trajectory being plotted along the image of the blood vessel being displayed. At this time, waypoints determined by the MRN core identifying directional changes required to achieve the requested MRT also appear on the computer display. Once the surgeon has approved the trajectory, the MRNIS is ready to proceed to the operative phase.

At this moment, once the operative phase has been initiated, the tip of the catheter is placed by the surgeon with the help of the MRNIS. Once the tip is positioned to the pre-approved release site, the injection phase is ready to be initiated. Prior to the injection, the MRNIS displays the number of injections with the respective doses and the time between successive injections for approval by the surgeon. In many cases, more than one injection may be required to

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achieve the therapeutic dosage specified in the MRNIS by the medical specialist. This injection procedure is determined by the MRN core based on many parameters including but not limited to the size and the orientation of the long axis of the aggregates. More specifically, several TMMC will form an aggregate due to dipole-dipole interactive forces between neighbored TMMC. Each aggregate has a needle-like shape with the longer axes oriented toward z-axis, i.e. along the longitudinal axis of the MRI or MRN bore or tunnel where the patient has been placed. Depending on the orientation of the blood vessel's segment being navigated and the orientation of the next bifurcation with regards to the z-axis, a too large quantity of TMMC may cause problem such as pre-embolization or others, especially when the length of the aggregate is close to the diameter of the blood vessel being navigated and perpendicular or near perpendicular to the z-axis. In such case, the MRN core will tend to recommend several smaller injections instead of one or a few larger injections.

After each injection, the MRN core controls the generation of gradients and the whole MRN operations being performed in real-time. At this time, there is typically no interventions by the surgeons since the required rate of making decisions based on several parameters is beyond human's capabilities. The position of the TMMC is plotted and displayed in real-time by the MRNIS to be monitored by the medical specialist. Once the dose of therapeutic agents has reached the targeted chemoembolization site, the post-operative phase is initiated. In this phase, typical MRI interface is used by the interventional radiologist to image and to assess the success of the intervention.

V. NEW MRNIS IMPLEMENTATION

The interface shown in Fig. 1 has been used initially without any functionality aimed at assisting the user. During the preliminary tests with this interface, the user needed to have a high technical knowledge about not only the MRN platforms but also be able to make the right decisions for successful MRN operations. As such, the interventional radiologist was initially working with several engineers well familiarized with MRN-related issues. Although future work aimed at improving the look of the user interface to enhance and facilitate the interactions with the medical staffs, the actual interface takes the form of windows that can be displayed and moved to obtain the same interface shown in Fig. 1 with additional windows dedicated to assist the user in setting up the MRN platform for proper operations. The ultimate goal for this MRNIS is to ensure that the users will not need to enter complex technical data or specifications that require a deep understanding of MRN operations.

An important part of the software architecture concerns the "surrounding software environment". This includes all software components not embedded in the MRI system nor imaging, control or propulsion units: roadmap planning, 3D visualization tools or live feedback. In order to build such a user environment with a great extensibility and maintainability, we use well-established open-source tools and protocols. The proposed approach is to embed algorithms developed earlier inside the 3DSlicer software (Pieper *et al.*, 2006). This medical imaging tool is already used by other interventional imaging projects. It offers a great stability as well as excellent way to embed our own algorithm while providing numerous ready-to-use modules such as fiducials, OpenIGTLink (Tokuda *et al.,* 2009), or vessel segmentation support. Because of the modularity of this solution, we are able to add without modifications to the basis of the architecture, vessel segmentation or haptic interface to our system.

Another important step is the roadmap planning which is managed by the the fiducials module of the 3DSlicer software. The user can insert such points along the vessels during a similar procedure. In addition to the manual path planning protocol, vessel segmentation-assisted path planning is a very promising procedure. Indeed, 3DSlicer provides segmentation modules such as the Vascular Modeling Toolkit. This allows us to implement a multi-objective best path discovery algorithm that would allow an automatic computation of the best roadmap from the injection point to the drug release target. Such an algorithm takes into account parameters like vessel diameter, blood pressure, intersection complexity, steering power of the magnetic gradient with respect to the net magnetization of the device.

Another important aspect of the new MRNIS is live vizualization where the user is given real-time feedback of the operations being conducted. Indeed, the tracking algorithm can send the estimated position of the device to the host software, also through an OpenIGTLink connection. Our preliminary tests show no noticeable delay between the actual move of a device and the display on a 3DSlicer scene.

VI. CONCLUSION

A short description of an interactive system dedicated to MRN operations has been provided to show to the readers the importance of providing an adequate interface to allow the medical specialist to not only be able to use such system but also to be able to mange the complexity of this new technique. Indeed, the interactive system must be designed to allow the surgeon to enter specifications related to the medical protocol while being able to assess the progress of the intervention. Here, a basic interactive system have been described since more advanced operations making use of a combination of different types of navigable micro-entity for enhanced therapeutic and/or diagnostic target interventions could also be envisioned. Nonetheless, it is still difficult at this point to determine the best format for such interactive system since our group is the pioneer of MRN and the first one to attempt such interactive software. It is by observing practitioners and taking notes of theirs feedbacks that such interactive system coped with a proper user interface will be optimized.

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REFERENCES

[1] S. Martel, J.-B. Mathieu, O. Felfoul, A. Chanu, É. Aboussouan., S. Tamaz, P. Pouponneau, G. Beaudoin, G. Soulez L'H. Yahia, and M. Mankiewicz, “Automatic navigation of an untethered device in the artery of a living animal using a conventional clinical magnetic resonance imaging system,” Applied Physics Letters, vol. 90, 114105, March 12, 2007

[2] S. Martel, O. Felfoul, J.B. Mathieu, A. Chanu, S. Tamaz, M. Mohammadi, M. Mankiewicz, and N. Tabatabaei, “MRI-based nanorobotic platform for the control of magnetic nanoparticles and flagellated bacteria for target interventions in human capillaries,” *International Journal of Robotics Research (IJRR)*, *Special Issue on Medical Robotics*, vol. 28, no. 9, pp. 1169-1182, Aug. 2009

[3] P. Pouponneau, J-C. Leroux, and S. Martel, “Magnetic nanoparticles encapsulated into biodegradable microparticles steered with an upgraded magnetic resonance imaging system for tumor chemoembolization,” *Biomaterials*, 30(31), pp. 6327-6332, 2009

[4] S. Pieper, B. Lorensen, W. Schroeder, and R. Kikinis, “The na-mic kit: Itk, vtk, pipelines, grids and 3DSlicer as an open platform for the medical image computing community,” in *3rd IEEE International Symposium on Biomedical Imaging: Nano to Macro, 2006*, pp. 698–701, 2006

[5] J. Tokuda, G. Fischer, X. Papademetris, Z. Yaniv, L. Ibanez,. Cheng, H. Liu, J. Blevins, J. Arata, A. Golby, *et al.*, “OpenIGTLink: an open network protocol for image-guided therapy environment,” *The International Journal of Medical Robotics and Computer Assisted Surgery*, vol. 5, no. 4, pp. 423–434, 2009

