NOVEL TARGETED TREATMENTS OF TUMORS WITH MICROPARTICLES DRIVEN BY MRI-BASED GRADIENTS

Sylvain Martel[1*], Gilles Soulez[2], Richard Béliveau[3], Jean-Baptiste Mathieu[1], and Ouajdi Felfoul[1]

[1]NanoRobotics Laboratory, Department of Computer Engineering and Institute of Biomedical Engineering,
École Polytechnique de Montréal (EPM), Campus of the Université de Montréal, Montréal (Québec) Canada
[2]Radiology Department, Université de Montréal, Montréal (Québec) Canada
[3]Department of Oncology, Hôpital Ste-Justine, Montréal (Québec) Canada

*E-mail: sylvain.martel@polymtl.ca URL: www.nano.polymtl.ca

Abstract—**Magnetic gradients generated from an upgraded clinical Magnetic Resonance Imaging (MRI) system are being considered to steer ferromagnetic microparticles with chemotherapeutic agents towards targeted tumor cells. Preliminary results indicate that we would need to develop several hundreds mT/m multilayer inner propulsion coils installed inside the MRI bore to compensate for the lower force induced on micrometer-size ferromagnetic particles. These propulsion coils would be synchronized in a time-multiplexed fashion with typical few tenths of mT/m monolayer encoding gradient coils typically used in clinical MRI systems. The use of a clinical MRI system here is extremely attractive in this context providing the other essential complementary tasks such as tracking the microparticles, computing the corrective actions through pre-determined algorithms, and adjusting the generation of the magnetic gradients accordingly to navigate these microparticles in a 3D space in order to reach the tumor cells through an anarchic arteriolocapillar network stimulated by tumoral angiogenesis.**

Keywords—**MRI, magnetic gradients, magnetic resonance propulsion, ferromagnetic microparticles, cancer, tumor cells, targeted chemotherapy**

I. INTRODUCTION

Treating cancer remains one of the most complicated challenges of modern medicine. Although significant progress has been made in the development of drugs used in chemotherapy, secondary toxicity is a main issue in a clinical environment because of the high concentration of drugs that have to be administered for treatment. Intra-arterial chemotherapy or chemo-embolization has been proposed with interesting success but high intra-tumoral drug concentration cannot be sustained because of the release of the drug in the systemic circulation. Targeting specifically the tumor cells is a major goal of modern oncology and the possibility of using magnetic microparticles for specific endovascular drug delivery or radioisotopes at the site of the tumor mass is extremely attractive.

Even though catheters can be guided in blood vessels with lumens as small as 1 mm, diameters in the order of a few micrometers would be necessary to access tumors through blood microcirculation. In such a case, when catheters are used for drug delivery, the active principle is released upstream from the selected target and is carried away in the microcirculation in an uncontrolled manner.

Magnetic drug targeting is then a promising approach to control microparticles from external magnets [1] after they are released from a tool such as a syringe or a catheter. Although it was demonstrated that with this approach coped with one of the drug release mechanisms as described in [2] that complete tumor remission was drastically improved as described in [3] and toxicity was reduced by using lower dosages, magnetic drug targeting is still limited by the use of external magnets as explained in [4]. For instance, the use of external magnets typically restricts the targeting possibilities to organs that are close to the skin and does not allow precise control of the magnetic microparticles.

II. METHOD

Our proposed method has the potential to offer a better control of the microparticles in a 3D space by coupling the imaging capability of Magnetic Resonance Imaging (MRI) with the steering force induced by magnetic gradients [5] such that smart chemotherapeutic agents could be targeted within tumoral lesion. Our purpose would be to develop an approach aimed at coupling specific anti-cancer therapeutic or radioisotopes to the microparticles, and to destroy the tumor cells with minimal side effects on healthy tissues.

More specifically, the proposed method relies on a technique that we refer to as Magnetic Resonance Propulsion (MRP) [6-10] which consists of inducing a steering or propulsion (displacement) force on a ferromagnetic core or microparticles in this particular case, with magnetic gradients generated by a clinical MRI system, and to navigate them automatically to reach the tumor cells. The use of a clinical MRI system here is extremely attractive since it also provides other essential complementary tasks such as tracking the microparticles while computing the corrective actions through pre-determined algorithms and

adjusting the generation of the magnetic gradients accordingly to steer these microparticles to the tumor cells.

The torque and the propulsion force on the ferromagnetic core or microparticles that can be induced by the MRI system depends as depicted in Eq. 1 and Eq. 2 not only on the size of the ferromagnetic core or particles but also on the choice of the ferromagnetic material and the applied magnetic gradients.

$$\vec{\tau} = \vec{m} \times \vec{B} = V_{ferro} \vec{M} \times \vec{B}, \quad (1)$$

$$\vec{F}_{magnetic} = \vec{m} \cdot \nabla \vec{B} = (V_{ferro} \cdot \vec{M}) \cdot \nabla \vec{B}. \quad (2)$$

In Eqs. 1 and 2, τ is the magnetic torque (N·m), $\vec{F}_{\text{magnetic}}$ is the magnetic force (N), $\vec{m}$ is the magnetic moment of the ferromagnetic body (A·m^2), $\vec{M}$ is the magnetization of the material (A/m), V_{ferro} is the volume of the ferromagnetic body (m^3), $\vec{B}$ is the magnetic induction (T), and $\nabla \vec{B}$ is the gradient or spatial variation of the magnetic induction (T/m). Hence for a particular application, the resulting induced force must be selected taking into account the size of the targeted blood vessels and the cumulative effects of maximum blood flow, drag, buoyancy, and the gravitational force or weight of the ferromagnetic entity. A list of typical ferromagnetic materials with their saturation magnetization values is depicted in Table 1 [11].

TABLE 1
Ferromagnetic materials

Material	Saturation Magnetization (T)
Fe-27%Co	2.40
Iron	2.16
Cobalt	1.72
$Nd_2Fe_{14}B$	1.61
Fe-47, 5%Ni	1.50
AISI 304L Stainless Steel	1.28
$SmCo_5$	1.05
Fe-80%Ni	1.04
Fe-50%Ni-10%Cr	0.75
Cu_2MnAl	0.70
Nickel	0.61
Fe_3O_4	0.60
$CoFe_2O_4$	0.50
Silicone MRPG	0.50
$BaFe_{12}O_{19}$	0.48
$NiFe_2O_4$	0.34
Ferrofluid of Nickel and Ferrite	0.18
$Y_3Fe_5O_{12}$	0.17
Ferrofluid with Co	0.12
Ferrofluid (Fe_3O_4)	0.07

The compound being injected in a section of a larger blood vessel upstream of the arteriole entry of the tumoral microcirculation could consist of many polymer-based agglomerations or groupings (diameter: ~50 μm) of anti-cancer therapeutic or isotope loaded magnetic microparticles (diameter: ~5 μm). Depending on the induced magnetic force/drag ratio required for effective entry in the arterioles, larger agglomerations of loosely coupled magnetically interacting microparticles made of thicker coating around the ferromagnetic core could potentially be used. Once arteriole entry is performed, agglomerations would dissolve to liberate the microparticles or comply (like a fluid) depending on the selected approach for entry in the capillaries. Once in the capillaries, the microparticles would be pushed by the capillary flow but gradients would be available to exert as necessary, an angular (steering) force such that the particles could be constrained within the complex tumoral angiogenic network. Small groupings or chains of microparticles have magnetic signatures allowing improved targeting efficiency if necessary by adjusting the gradient vectors based on specific algorithms as well as offering a powerful tool for monitoring the whole procedure.

III. Steering Force

Initial experiments were done with a standard (i.e. without additional coils) Siemens 1.5 T Magnetom Vision clinical MRI system capable of generating 40 mT/m gradients. With extrapolations, the results are shown in Fig. 1.

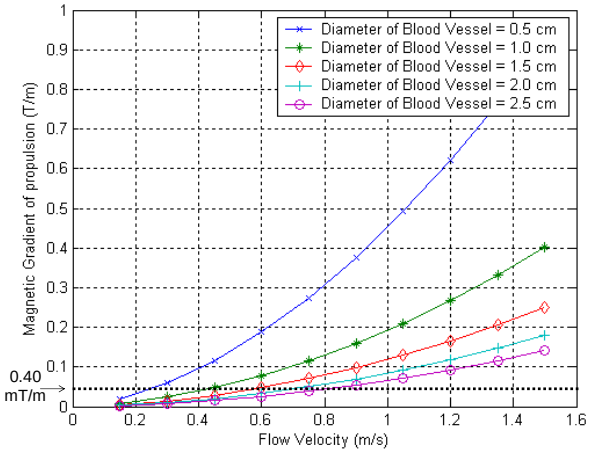

Fig.1. Optimized magnetic gradient of propulsion versus the flow velocity for various diameters of blood vessels (from [10]).

In the results depicted in Fig. 1, 50% of the volume of the spherical microdevice is made of Permendur (saturation magnetization $M_{Sat} = 1.9496 \times 10^6$ A/m) leaving an arbitrary chosen 50% of the volume dedicated for a specific medical task. An optimal ratio [10] of 0.42 between the diameter of the ferromagnetic sphere and the diameter of the blood vessel is used. No other techniques such as a reduction of the drag force by changing the shape of the ferromagnetic core or through a reduction of the blood viscosity for instance have been considered. In Fig. 1, the applied gradients correspond to nominal values, i.e. that a 40 mT/m gradient with a duty cycle of 50% would be equivalent to a gradient of 20 mT/m with a duty cycle of 100%. It should be noted that the duty cycle must often be reduced to avoid overheating the gradient coils as well as to regulate in many cases the propulsion force with the pulsating blood flow.

As depicted in Fig. 1, although the gradients coils in clinical MRI systems used for imaging and capable of generating typically 40 mT/m could be sufficient to propel a larger ferromagnetic core in the arterial system, much higher magnetic gradients would be necessary to propel micrometer-size ferromagnetic particles within the tumoral angiogenic network. Compared to larger diameter vessels, the tumoral circulation used for this particular application has different rheologic properties such as lower blood velocity (from more than 1 m/s in the aorta to less than 1 mm/s in the capillaries) and Reynolds number (10,000 in the aorta down to 0.001 in the capillaries), increased shear rates and drag coefficient, non-homogeneity of the blood at such a scale, and the presence of the Fahraeus-Lindqvist effect, to name but the main properties.

We estimate that we would need to develop several hundreds mT/m multilayer inner propulsion coils installed inside the bore of a clinical MRI system not to propel but to steer ferromagnetic microparticles within the tumoral angiogenic blood network. Since each particle would be slightly smaller than a single red blood cell and the capillary vessels (diameter: ~5 µm), propulsion force unlike when operating in larger diameter blood vessels would not be provided by magnetic gradients (which would require excessive amplitudes in the order of several T/m) but by the capillary flow with particles being trapped between red cells. Hence, instead of a propulsion force, the concept of steering force is considered in this application where an angular force is induced on the ferromagnetic particles. The principle of steering force is summarized in the simplified diagrams depicted in Fig. 2 and Fig. 3.

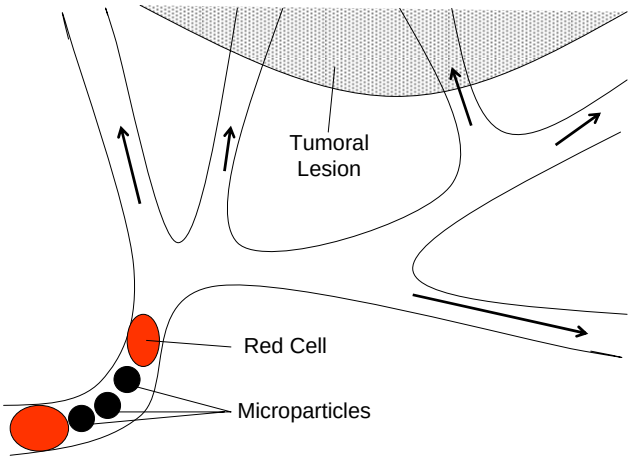

Fig.2. Simplified diagram showing an agglomeration of ferromagnetic microparticles trapped between red cells within a part of a tumoral angiogenic network. The arrows represent the directions and magnitudes of the capillary flows.

In Fig. 2, the main propulsion force is provided by the capillary flows and angular magnetic gradient forces generated by the additional inner coils within the clinical MRI system are necessary to steer the agglomeration of ferromagnetic microparticles to the tumoral lesion as shown in Fig. 3.

Several strategies, sequences or algorithms can be developed to steer the ferromagnetic microparticles to the tumoral lesion through the complex angiogenic network. The steering procedure is complicated by the fact that the capillaries cannot be seen on a clinical MRI system. On the other hand, the tumoral lesion or target for the steering procedure can typically be imaged on a clinical MRI system, especially if the overall dimension of the tumoral region exceeds ~1 mm in diameter (approximately slightly larger than the overall size of a voxel). The target could be pre-identified and confirmed as necessary through other imaging modalities such as angiographic images performed under X-ray fluoroscopic imaging prior to MRI-based interventions.

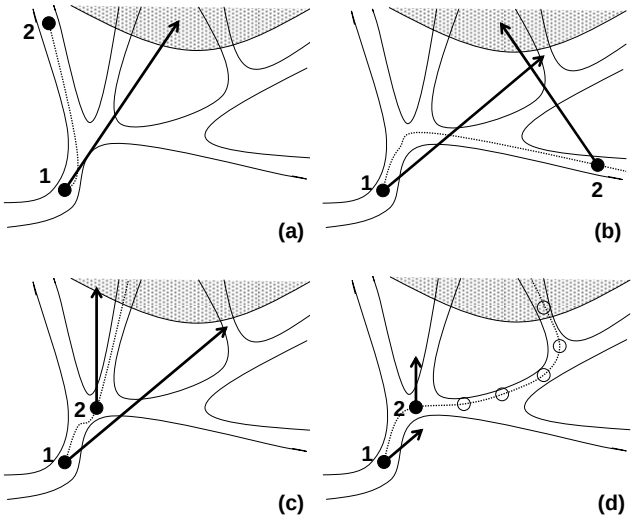

Fig.3. Simplified diagrams showing examples of steering strategies to reach the tumoral lesion. The arrows represent the directions and magnitudes of the magnetic gradients at two different locations (numbered 1 and 2) within the angiogenic network with the dotted lines showing the resulting navigation paths of the microparticles (represented as a single dot) from the combination of induced magnetic gradient forces and capillary flows (other force components have been neglected here for clarity).

An agglomeration of microparticles is required here since a single ferromagnetic particle of a few micrometers in diameter would not be visible on a clinical MRI system and hence, could not be tracked and controlled by magnetic resonance (MR). An agglomeration would increase the magnetic signature to make MR-tracking possible while increasing the resulting induced steering force through inter-particles interaction/coupling while carrying a larger volume of drug to the target. Initially, since the risk of missing the target would be higher, minimum dose or size agglomeration of microparticles but sufficient to be imaged on a clinical MRI system would be used. As shown from a simple example, an initial magnetic gradient force pointing toward the tumoral lesion can be applied and induced on the agglomeration of microparticles as depicted in Fig. 3a. In this example, because of the resulting capillary flow, the MR-tracking indicates that the target is missed and the

magnetic steering gradients are then stopped, here at position 2 in Fig. 3a. A second agglomeration of microparticles of similar size is then injected and based on the information recorded from the first injection the direction of the magnetic gradients is shifted clockwise as shown in Fig. 3b. When the MR-tracking detects a change in the direction of the ferromagnetic microparticles the direction of the magnetic gradients is changed toward the tumoral lesion but in this case, it is too late to reach the target. In a third attempt (Fig. 3c), the magnetic gradients are changed to orient toward the tumoral lesion immediately after detecting a change in the direction of the particles, resulting in successful targeting of the tumoral lesion. Fig. 3d shows a simple example where the same steering sequence as in Fig. 3c is used but the maximum magnetic gradient amplitudes that the inner coils can generate in this case are much smaller. In this example, the first path toward the tumoral lesion is missed because of the relatively large capillary flow but the target is reached by maintaining (from position 2 in Fig. 3d) the direction of the gradient force toward the tumoral lesion. Due to the relatively large number of capillaries reaching the tumoral lesion, the probability of steering the microparticles to the target is estimated to be relatively high. Nonetheless, as depicted in the simple example in Fig. 3d, the magnetic gradient amplitudes still must be sufficiently high.

IV. Magnetic Resonance Tracking

Tracking is an important and critical aspect for the success of such therapeutic procedure since it allows us to gather information about the displacement of the microparticles which are then used to apply the proper magnetic gradients in order to reach the tumoral lesion.

Integrating both tracking and steering tasks within the same system avoids additional communication and synchronization latencies typically encountered between two loosely coupled systems, additional implementation costs, and increased complexity of the system such as within an architecture where tracking would be done by external sensors such as Superconducting Quantum Interference Device (SQUID) for instance. Although such level of integration would facilitate the implementation within tight real-time constraints for navigating these microparticles by avoiding additional latencies and hardware complexity, it would only be possible conditional to the development of an MR-tracking method that can be time-multiplexed and operated in conjunction with the generation of steering gradients while positioning fast enough and with sufficient spatial resolution through image artifacts that could be generated by the ferromagnetic material.

The problematic related to the MR-image artifacts also depends on the size of the ferromagnetic entity. In the case of the ferromagnetic microparticles, if the agglomeration is too small then it will not be visible by a clinical MRI system and MR-tracking will not be possible. If the agglomeration is sufficiently large, it may result in images approximately similar to images obtained when using MRI contrast agents and therefore, it should be easily tracked by a clinical MRI system. On the other hand, if the agglomeration is relatively large, MR-image artifacts will appear, making tracking very difficult without an adequate MR-tracking technique. This is particularly true if larger agglomerations must be used prior to arteriole entry in order to increase the induction of a steering force to compensate for the increased blood flow in larger vessels.

Once a successful steering sequence has been found, the dose injected would typically be increased by increasing the number of microparticles for each of the following agglomerations. Because this method only allows one agglomeration to be independently steered at any given time within the MRI bore, it may often be suitable to increase the size of each agglomeration in order to deliver a given quantity of drug to the tumoral lesion in a shorter time period. This could also be necessary if the catheter or syringe must be removed between injections due to large image artifacts from the tool and preventing proper MR-tracking if placed not far enough from the arteriole entry. This increased size of the agglomeration will amplify MR-image artifacts and hence, make precise MR-tracking more difficult and unreliable unless a proper tracking method is developed.

In the literature, MR-tracking can be categorized by two general schemes referred to as passive and active. An active tracking technique cannot be implemented in this application since it generally requires an external connection to the MRI system or a source of electrical energy which would be impossible to embed at the micrometer-scale. On the other hand, passive tracking involves the direct interaction between the physical properties of the ferromagnetic particles in our particular case and the tissue or imaging system and can be implemented.

For passive tracking methods, small paramagnetic rings are typically mounted as markers on catheters or guidewires [12] to produce local field distortions appearing as areas of signal loss. This is referred to as negative contrast in MR images and it is limited in regions of low proton density. A novel approach to passive tracking of paramagnetic markers has been described more recently [13] where positive contrast of the markers to their background is exploited. With this method referred to as white marker tracking, a dephasing gradient is added in the direction of the slice selection during excitation to enhance the contrast between the markers and the background. This compensation gradient induces a signal loss in the image resulting in a positive contrast (instead of a negative contrast when no compensation gradient is used) where the markers appear bright on a darker background. Furthermore, the contrast between the object being tracked and the background is improved with the addition of such compensation gradient. Unfortunately, all these passive methods are still image-based techniques and hence, relatively slow for this

particular application when both the capillary flows and the small size of the capillary segments are considered. Although trade-offs could theoretically be made between spatial and temporal resolutions, practically these methods are far too slow in achieving an acceptable spatial resolution and real-time performance level especially within the tumoral angiogenic blood network. More recently, a new method for rapid MR-tracking has been described [14]. With this method, six central *k*-space lines are usually sufficient to locate an object such as a needle but require an increase in computation. Although this method does not deal with image artifacts and only applies within a given 2D image slice, the approach of using a lower number of *k*-space lines has been considered in a new MR-tracking method better suited for this application.

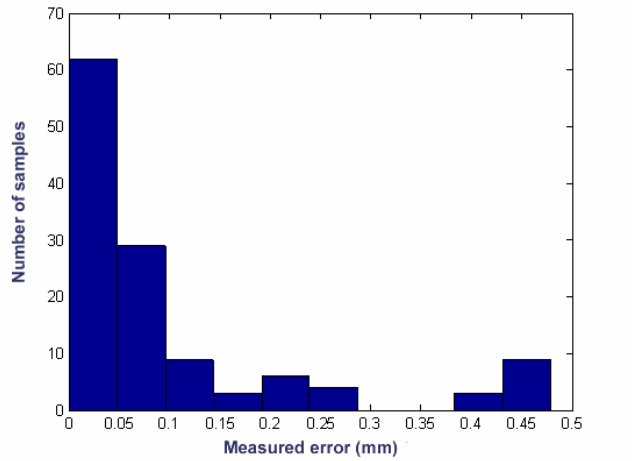

Fig.4. Histogram showing the positioning errors of a ferromagnetic sphere in a clinical MRI bore using the MS-SET method.

This new MR-tracking technique developed specifically for MRP-based applications is referred to as Magnetic Signature Selective Excitation Tracking (MS-SET)* [15]. The method is based on the selective excitation of magnetic equipotential curves caused by an induced magnetic susceptibility difference from a paramagnetic/ferromagnetic object or a relatively large agglomeration of ferromagnetic microparticles in our particular case. Visualization relies on the application of an RF excitation tuned to the frequency of the desired equipotential curves while encoding the positions of the excited spins is performed through the application of a readout gradient. The shapes of the projection image of the magnetic equipotential depend on the excitation frequency. A one-dimensional projection of the image along the read axis would correspond to the central line of the *k*-space along the same axis. For three-dimensional MR-tracking, a minimum of three orthogonal projections is then required. Unlike previous methods, MS-SET uses these projections for dipole tracking. Therefore, since it requires only one acquisition (*k*-space line) per axis, a significant gain in speed compared to other mentioned passive techniques is achieved.

From previous experiments, it is estimated that a 3D positioning could be performed in less than 20 ms. Preliminary experimental data [15] showing the errors of the relative position of a ferromagnetic sphere using the MS-SET method is depicted in Fig. 4.

V. Magnetic Resonance Chemotherapy Platform

A. Hardware Environment

A simplified block diagram of the main hardware components of a suggested interventional platform dedicated for targeting treatments to tumors or for localized or targeted chemotherapy using a modified clinical MRI system and referred here to as Magnetic Resonance Chemotherapy (MRC) is depicted in Fig. 5.

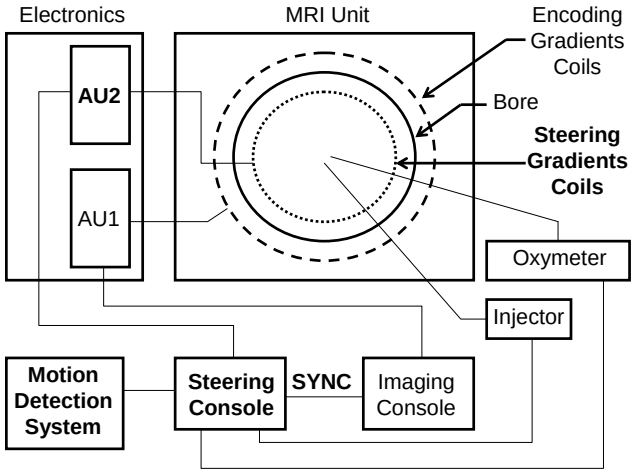

Fig.5. Simplified block diagram showing the main hardware components of one possible implementation of the MRC platform. The platform is built from a clinical MRI system where various components and interconnections (shown in bold) have been added (RF antennas not shown).

The system shown in Fig. 5 consists of a standard clinical MRI system that is upgraded through the addition of hardware and software components or modules. The main additional hardware components are shown in bold in Fig. 5 and include a steering console, a second amplification unit (AU2 in Fig. 5), x-y-z steering gradients coils, and an external system to detect movements from the patient. The main use of the steering console is to calculate and to drive the inner driving coils through AU2 (similar to the amplification unit AU1 used to drive the encoding/imaging gradients coils) in order to steer automatically the agglomeration of ferromagnetic microparticles to the tumoral lesion. Because the applied steering gradients must be time-multiplexed with the generation of encoding gradients used for imaging, synchronization is provided

* Patent pending

between the two consoles through a synchronization link (SYNC in Fig. 5). The imaging console provides an image of the tracked agglomeration superposed on top of pre-acquired MR-images. A commercial motion detection system is connected to both consoles in order to correct imaging and steering gradients to compensate for any movements from the patient. An oxymeter is also used to synchronize the steering gradients with the pulsating blood flow rate. An injector under computer control is also used to inject the right quantity of ferromagnetic microparticles at a suitable time.

B. Software Environment

The actual software environment [16] on the imaging console consists of the standard MR-imaging modules providing pulse sequence software that generates the necessary physical events for the MRI sequence such as the gradients information, the RF pulse and the Analog-to-Digital Conversion (ADC) parameters; and an image calculation environment dedicated to image reconstruction from raw data received from the scanner while performing Fourier Transforms for data visualization. The imaging environment is upgraded to superpose the ferromagnetic entity on the pre-acquired images and compensates for motion artifacts. The system is also upgraded with a steering closed-loop control environment linked to an oxymeter, an injector, a motion detector, and various data previously acquired such as blood flow profiles and path planning or roadmap [17]. The path planning software identifies the best locations for injection and the best paths to reach the target based on various parameters such as the characteristics of the blood vessels and the properties of the particles.

VI. CONCLUSION

A new approach to target tumor cells has been proposed. The method uses an upgraded clinical MRI system to steer and track ferromagnetic microparticles in order to reach the tumoral lesion. The main issues and components to implement this method have been identified and briefly explained. Although more work must to be done to validate this approach, preliminary results are very encouraging.

ACKNOWLEDGMENT

This work is supported by a strategic grant from the Natural Sciences and Engineering Research Council of Canada (NSERC) and in part by a Canada Research Chair (CRC) in Conception, Fabrication, and Validation of Micro/Nanosystems, the Canada Foundation for Innovation (CFI), and the Government of Québec. We acknowledge the support of Hôpital Notre-Dame and Centre Hospitalier de l'Université de Montréal (CHUM) for providing the MRI facilities and Siemens for technical support.

REFERENCES

[1] C. Alexiou, W. Arnold, P. Hulin, R. J. Klein, H. Renz, F. G. Parak, C. Bergemann, and A. S. Lubbe, Magnetic mitoxantrone nanoparticle detection by histology, X-ray and MRI after magnetic tumor targeting *Journal of Magnetism and Magnetic Materials*, vol. 225, no. 1-2, pp. 187-193, 2001.

[2] M. Babincova, D. Leszczynska, P. Sourivong, P. Babinec, and J. Leszczynski, Principles of magnetodynamic chemotherapy *Med Hypotheses*, vol. 62, pp. 375-377, 2004.

[3] K. J. Widder, R. M. Morris, G. Poore, D. P. Howard Jr, and A. E. Senyei, Tumor remission in Yoshida sarcoma-bearing rts by selective targeting of magnetic albumin microspheres containing doxorubicin *Proc Natl Acad Sci U S A*, vol. 78, pp. 579-581, Jan. 1981.

[4] M. Shinkai, "Functional magnetic particles for medical application," *Journal of Bioscience and Bioengineering*, vol. 94, no. 6, pp. 606-613, 2002.

[5] S. Martel, J-B. Mathieu, O. Felfoul, H. Macicior, G. Beaudoin, G. Soulez, and L'H. Yahia, "Adapting MRI systems to propel and guide microdevices in the human blood circulatory system", *Proceedings of the IEEE-EMBS Conf. on Biomedical Eng.*, pp. 1044-1047, Sept. 2004.

[6] S. Martel, J.B. Mathieu, L. Yahia, G. Beaudoin, and G. Soulez, "Method and system for propelling and controlling the displacement of a microrobot in a blood vessel. US Patent 10/417,475

[7] J-B. Mathieu, S. Martel, L. Yahia, G. Soulez, and G. Beaudoin, "Preliminary studies for using magnetic resonance imaging systems as a mean of propulsion for microrobots in blood vessels and evaluation of ferromagnetic artefacts," Canadian Congress on Electric and Computer Engineering, Montréal, Canada, pp. 835-838, 2003.

[8] J-B. Mathieu, S. Martel, L. Yahia, G. Soulez, and G. Beaudoin, "MRI systems as a mean of propulsion for a microdevice in blood vessels," *Proceedings of the IEEE-EMBS Conf. on Biomedical Eng.*, vol. 4, pp. 3419-3422, Sept. 2003.

[9] J-B. Mathieu, S. Martel, L'H. Yahia, G. Soulez, and G. Beaudoin, "Preliminary investigation of the feasibility of magnetic propulsion for future microdevices in blood vessels," *Bio-Medical Materials and Eng.*, 2005 (in press)

[10] J-B. Mathieu, G. Beaudoin, and S. Martel, "Method of propulsion of a ferromagnetic core in the cardiovascular system through magnetic gradients generated by an MRI system," *IEEE Trans. on Biomedical Eng.*, 2005 (in press)

[11] S. Martel, J-B. Mathieu, F. A. Hinojosa, L'H. Yahia, and P. Pouponneau, "Fundamental design rules for the conception of microdevices to be propelled in the blood circulatory system through magnetic gradients generated by a clinical MRI system", *Proc. of the 3rd Annual Int. IEEE-EMBS Special Topic Conf. on Microtechnologies in Medicine & Biology, (MMB2005)*, Oahu, Hawaii, May 12-14, 2005.

[12] C.J.G. Backer, R.M. Hoogeveen, J. Weber, J.J. van Vaals, M.A. Viergever, and W.P. Mali, "Visualization of dedicated catheters using fast scanning techniques with potential for MR-guided vascular interventions," *Magn. Reson. Med.* vol. 36, pp. 816-820, 1996.

[13] J-H. Seppenwoolde, M.A. Viergever, and C.J.G. Bakker, "Passive tracking exploiting local signal conservation: The white marker phenomenon," *Magn. Reson. Med*., vol. 50, pp. 784-790, 2003.

[14] E. Kochavi, D. Goldsher, and H. Azhari, "Method for rapid MRI needle tracking," Magn. Reson. Med. vol. 51, pp. 1083-1087, 2004.

[15] O. Felfoul, J-B. Mathieu, G. Beaudoin, and S. Martel, "MR-tracking based on magnetic signature selective excitations," *IEEE Trans. on Biomedical Imaging.*, 2005 (in review)

[16] A. Chanu., S. Martel, and G. Beaudoin, "Real-time magnetic resonance gradient-based propulsion of a wireless microdevice using pre-acquired roadmap and dedicated software architecture," *Proc. 17th Annual Int. Conf. of the IEEE Eng. in Medicine and Biology Society*, 2005.

[17] W. Sabra W., M. Khouzam, A. Chanu, and S. Martel, "Use of 3D potential field and an enhanced breath-first search algorithms for the path planning of microdevices propelled in the cardiovascular system," *Proc. 17th Annual Int. Conf. of the IEEE Eng. in Medicine and Biology Society*, 2005.