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Magnetic Resonance Navigation for Nanorobotic Cancer Therapies: An Interview with Professor Sylvain Martel



Prof. Sylvain Martel
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Professor Sylvain Martel from the Department of Computer Engineering at Polytechnique Montréal talks to Kal Kaur from AZoNano about Magnetic Resonance Navigation for Nanorobotic Cancer Therapies. Dr. Martel's study was published in the peer-reviewed *International Journal of Advanced Robotic Systems* by the open-access publisher InTech.

KK - Please can you provide us with a brief overview of magnetic resonance navigation?

SM - Magnetic Resonance Navigation (MRN) is a medical robotic approach that relies on Magnetic Resonance Imaging (MRI) technology to navigate therapeutic, surgical, imaging, or diagnostic micro-agents to a targeted location typically accessible through the vascular network.

More specifically, the strong, uniform magnetic field of a clinical MRI scanner, usually used to align the spin of protons (hydrogen nuclei) in the body of a patient for imaging purposes, is exploited during MRN to significantly increase the magnetization level of nanoparticles embedded in these micro-agents. In this "super-magnetization" state, the untethered micro-agents become much more responsive to the displacement force induced by a directional magnetic gradient.

Such a directional magnetic gradient can be provided by the same coil typically used for spatial encoding during MR-imaging. After retrieving an image of the blood vessels to be navigated, a trajectory is plotted from the injection site to the final destination along the selected blood vessels. Once injected, a computer controls the generation of the 3D gradients in order to maintain the micro-agents along the planned trajectory.

The magnetic nanoparticles embedded in the micro-agents are not only used to induce a directional propelling or steering force from the gradients - they also create image artefacts in the homogenous field, allowing the position of the micro-agents to be tracked by MRI.

Unlike the use of an external magnet, where the gradient field decays rapidly with distance, the efficacy of MRN is depth independent, i.e., targeting deep into the body is as effective as near the skin surface, while providing the added advantages of computer-controlled navigation combined with a higher magnetization of the magnetic micro-agents to achieve enhanced targeting efficacy.

KK - How much modification to a standard MRI scanner is required for this technique?

SM - It really depends on the overall sizes of the micro-agents. In all cases, special software modules allowing MRN operations must be added or linked to the software platform of a clinical MRI scanner. In this case, larger agents such as the ones intended for navigation in larger arteries can be supported without hardware upgrades or modifications.



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For smaller agents intended to transit in narrower vessels beyond the arteries, the gradient strengths of typical clinical MRI scanners are not sufficient. In such a case, the MRI scanner must be upgraded with a dedicated coil, or an imaging coil capable of generating higher gradients.

This additional coil can be inserted into the tunnel of a clinical MRI scanner, and then retrieved when MRN operations are no longer required. This special insert has the advantage of not requiring any hardware modifications to the MRI scanner itself, and because of the smaller inner diameter, it is still suitable for conducting MRN interventions on small animals or in regions of the body such as the head that can fit in the smaller diameter insert.

For full body MRN interventions beyond the arteries, a larger inner diameter is required and as such, there are two main alternatives. One is to replace or upgrade the gradient coil of an existing MRI scanner. The other is to develop a dedicated MRN platform.

KK - What kind of micro-agents can this technique be applied to?

SM - Any type of micro-agents synthesized with any type of biocompatible materials and dedicated to target surgeries, therapies, diagnostics, or for imaging purposes can be considered for MRN interventions provided that they contain a certain quantity of magnetic nanoparticles.

For example, MRN-compatible Therapeutic Magnetic MicroCarriers (TMMC) made of magnetic nanoparticles, encased with a therapeutic drug (Doxorubicin) in a biodegradable polymer (PLGA) sphere, with an overall diameter of approximately half the thickness of a human hair (approx. 50 micrometers), have showed targeting efficacy for releasing the drug into specific regions of the liver in rabbit models.

KK - How accurately can you control the micro-agents?

SM - MRN has proven to be sufficiently accurate to steer micro-agents to the proper branches when transiting through the first vessel bifurcations. As the number of bifurcations being transited gets higher, the distance between successive bifurcations decreases substantially, and as such, the directional gradients need to be changed at a faster rate.

Due to technological and physiological constraints, the maximum rate of such directional changes is limited and as such, while considering the small effective volume of magnetic nanoparticles in each micro-agent, it becomes difficult to perform MRN past the arterioles.

KK - What were the benefits of using this technique found in your recent study?

SM - In cancer therapy, MRN is presently the only approach that can deliver therapeutics to the specific site to be treated while avoiding systemic circulation. Avoiding systemic injections of highly toxic drugs can lead to a potential elimination or at least a significant reduction of the level of toxicity in healthy organs and an increase in the amount of therapeutics being delivered to the targeted site, whilst lowering the injected dose.

KK - What technical challenges did you encounter?

SM - There were many technical challenges. For instance, scaling of the gradient coils for whole-body MRN past the arteries, although feasible, was and still is a significant technical challenge. The cooling of the gradient coils limits the total time for which MRN can be performed, so that is another technical issue that was taken into consideration in developing the interventional protocol.

Real-time performance in MRI tracking of the micro-agents in order to gather sufficient positional data for the computer to maintain them along the planned trajectory was limited and as such, MRN operations had to be adjusted and modified accordingly.

KK - Does MRN have any additional health implications for the patient compared to standard MRI?

SM - MRN, if operated correctly, will prove to be safe for the patients. The same high magnitude uniform field as used in clinical MRI scanners has shown to be safe for the patients unless they have a ferromagnetic object such as an implant.

Because the magnitude of the gradients for MRN is higher than the ones used for MRI, the slew rate or rate of changes of the magnetic gradients is reduced to minimize or to avoid Peripheral Nerve Stimulation (PNS). The rate of changes is automatically adjusted by the system to ensure safe operation.

Other risks are related to the micro-agents themselves, so MRN should not introduce a higher level of risks than other therapies relying on the injection of substances into the blood stream.

KK - What additional technology could help circumvent these challenges?

SM - A faster and more precise MRI sequence or a medical imaging modality capable of operating in a high magnetic field to track the micro-agents would certainly improve MRN operations.

Materials or nanoparticles with a higher magnetization level would allow higher force to be induced on the micro-agents, or a higher density of therapeutics compensated by a smaller amount of nanoparticles per micro-agent.

Better cooling systems and improvement in gradient coil technologies are other technical advances that would have a profound impact on the efficacy of MRN. These are just a few examples among many others.

KK - How far away is this technique from real world application?

SM - From an engineering point of view, the platform is already functional. One interventional platform relying on a clinical MRI scanner has already been developed, and has been used by medical specialists - with the help of engineers - to evaluate and confirm the gained efficacy of the method for target chemoembolization and drug delivery in the liver, which could be adapted to other types of targets.

Although more developments such as a more user friendly interface for the medical staff could be developed, the main delay in making this technology accessible will mostly depend on regulatory issues and its acceptance in the medical community.

Also, some level of interest from medical instruments manufacturers and the pharmacology industry would certainly help in making such technology available in the shorter term.

KK - What additional nanorobotic targeting methods have been proposed and how does MRN compare to these?

SM - After the first successful demonstration of MRN by our group in 2006, performed in the carotid artery of a living swine, some other research groups have proposed custom platforms capable of generating comparable high gradient fields with x-ray being used as the imaging modality.

In these platforms, the lack of a high magnitude field to magnetize the micro-agents in the interventional space substantially reduces the force induced from the magnetic gradients. This means that compared to MRN, the minimum size of the micro-agents that could be navigated is likely to be much larger, therefore limiting efficient interventions to larger arteries only.

X-ray is also an invasive imaging modality and its usage must be limited, which is not the case for MRI. Furthermore, because the magnetization of the micro-agents is constant with MRN, but varies with other approaches, navigation control is greatly simplified for MRN.

Last but not the least, because a magnetic micro-agent can create an image artefact in the uniform field during MRN interventions that can be much larger than the size of the agent itself, a smaller magnetic agent undetectable with x-ray could be detected with MRI, allowing the medical staff to assess the targeting efficacy, and offering the possibility to estimate the quantity of drug delivered at a specific location during cancer therapy.

But due to various technical and physiological constraints, and although MRN operations can be conducted in smaller vessels compared to other proposed approaches, MRN is still limited to the arterioles, without the possibility of navigation in narrower capillary vessels like the capillary angiogenesis network connecting to a tumour.

To overcome this limitation, our group has developed a self-propelled micro-agent in the form of a flagellated magnetotactic bacterium capable of transiting through the tiniest blood vessels found in humans. A special platform, dubbed the magnetotaxis system, has been developed to create a "artificial magnetic pole" located at the site to be treated, in order to force the bacteria to migrate towards it.

Each bacterial cell contains a chain of nanoparticles known as magnetosomes that acts like a nanoscale compass needle, or a nano-steering system, that can be controlled by such magnetotaxis system.

Presently, approximately 70 nanoscale bags - known as liposomes - containing the therapeutic cargo, are attached to the surface of each bacterial cell. This approach is presently under investigation for treating colorectal cancer in humans. Since the bacteria are much less effective in larger blood vessels because of the higher blood flow rate, special MRN-compatible micro-carriers are under development, to encapsulate the bacterial agents in order to release them closer to the microvasculature, which should allow us to target other regions in the body only accessible through small capillary vessels.

KK - Where can we find more information about your research?

SM - There are several scientific papers and book chapters that have been published on various aspects of this technology. The readers can also go to the [NanoRobotics Laboratory web site](#). For a more general description, other sources are also available on the web, such as this article in *IEEE Spectrum* entitled "magnetic microrobots to fight cancer", providing a general description of the approach with supporting figures, and this short *TEDx* presentation given in French with subtitles in English.

About Dr. Sylvain Martel

Sylvain Martel received his PhD in Electrical Engineering from McGill University, Institute of Biomedical Engineering, Montréal, Canada, in 1997.

Following postdoctoral studies at the Massachusetts Institute of Technology (MIT), he was appointed Research Scientist at the BioInstrumentation Laboratory, Department of Mechanical Engineering at MIT. From Feb. 2001 to Sept. 2004, he had dual appointments at MIT and as Assistant Professor in the Department of Electrical and Computer Engineering, and the Institute of Biomedical Engineering at École Polytechnique de Montréal (EPM), Campus of the University of Montréal, Montréal, Canada.

He is currently Professor in the Department of Computer and Software Engineering, and the Institute of Biomedical Engineering, and Director of the NanoRobotics Laboratory at EPM that he founded in 2002.

Dr. Martel is a Fellow of the Canadian Academy of Engineering and held the Canada Research Chair (CRC) in Micro/Nanosystem Development, Fabrication and Validation from 2001 to 2010 prior to obtain the Research Chair of École Polytechnique.

In the medical field alone, he pioneered several innovative technologies such as the first parallel computing platform for remote surgeries, direct cardiac mapping systems designed to investigate the cause of sudden cardiac deaths, and new brain implants for decoding neuronal activities in the motor cortex.

Presently, Dr. Martel is leading an interdisciplinary team involved in the development of new types of therapeutic agents and interventional platforms for cancer therapy.

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