MEDICAL ROBOTS

Beyond imaging: Macro- and microscale medical robots actuated by clinical MRI scanners

Sylvain Martel

Magnetic resonance actuation has potential for use in medical therapies.

Macro- and microrobots that can be actuated by magnetic resonance imaging (MRI) have been pursued over the past 10 years. MRI scanners have been used to provide tetherless actuation for applications ranging from microscale therapeutic agents along predefined trajectories in the vasculature and macroscale magnetic components to implement systems such as MRI-actuated motors and needle inserters. MR actuation also inspired the use of a relatively new imaging modality known as magnetic particle imaging (MPI) to actuate magnetic devices (*1*) by exploiting the gradient between a region known as the field free point (FFP) and the surrounding magnetic sources. Because MPI exploits the nonlinear magnetization response below the saturation magnetization of tracers that occurs in the FFP, the spatially selective MPI-based actuation of helical objects, as described by Rahmer *et al.* (*2*) in this issue of *Science Robotics*, is achieved by repositioning the FFP to create a lower magnetization region where magnetic torque actuation can occur.

The first in vivo proof of concept of MRI-based actuation was a miniature magnetic bead that was successfully navigated along a preprogrammed trajectory in the carotid artery of a living swine (*3*). This approach, dubbed magnetic resonance navigation (MRN), was used initially for validating the delivery of therapeutics at target locations in the liver of animal models following navigation in the hepatic artery (*4*). MRN is presently at the translational phase, where medical protocols are being developed using large animals before potential use in humans. Combining MR actuation with MRI may allow real-time closed-loop navigation with targeting assessment as MRN-compatible agents appear hypointense or dark on high-contrast soft-tissue MR images (Fig. 1).

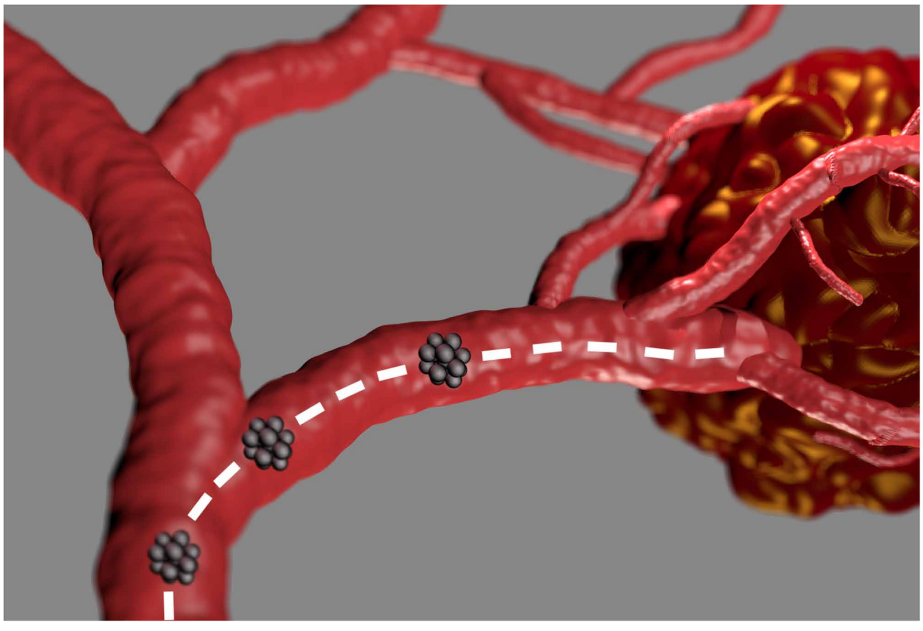

Fig. 1. Combining the imaging capability of MRI with magnetic resonance actuation offers great potential for medical robotics ranging from the micro- to the macroscale. [Credit: Dumitru Loghin, NanoRobotics Laboratory, Polytechique Montréal]

For MR actuation, the magnitude of the induced force on an object increases with increases of the level of volume magnetization of the object itself and the magnitude of the applied magnetic gradient field. Any ferromagnetic body will reach saturation magnetization when exposed to the strong uniform magnetic field (known as the $\mathbf{B}_0$ field) inside a conventional clinical MRI bore. As such, unlike the use of external magnets or an assembly of electromagnetic coils alone that only provide gradient fields resulting in fast decay of the field strength over distance, the gradients generated by a scanner's orthogonally configured imaging coils when superimposed on the $\mathbf{B}_0$ field result in maximum directional displacement force anywhere within the bore and, therefore, at any depth within the body of a patient in a clinical MRI scanner.

The use of MR actuation to bring agents typically labeled with superparamagnetic iron-oxide nanoparticles to a specific physiological target location is also generally referred to as magnetic resonance targeting (MRT). MRT can be done by applying pulsed magnetic gradients in the direction of the target physiological site to direct systematically circulating agents (*5*) or by navigating such agents along the shortest physiological routes; the latter known initially as MRN typically describes non-systemic MRT where pulsed magnetic gradients are applied to steer MR-navigable agents. Non-systemic MRN-based delivery has several advantages, one being a reduction of systemic exposure to potential toxic agents and a higher therapeutic index. These advantages come with additional technical challenges. One example is the optimal synchronization of gradient reorientation after the transition of each vessel bifurcation by the MR-navigable agents. Gathering real-time positional MRI information for closed-loop navigation control is feasible for millimeter-scale objects but generally too slow for sub-millimeter agents

NanoRobotics Laboratory, Department of Computer and Software Engineering, Institute of Biomedical Engineering, Polytechnique Montréal, Montréal, Québec H3T 1J4, Canada.
Corresponding author. Email: sylvain.martel@polymtl.ca

transiting at relatively high velocity in narrower vascular networks. Different solutions have been investigated, including predictive control and planning strategies (*6*) to compensate for the lack of real-time MR tracking information, new and faster MRI sequences, compressed sensing to reconstruct MR tracking information with fewer MRI samples, and a new sequence allowing simultaneous MR imaging and actuation during MRN (*7*).

A more recent approach, dipole field navigation (DFN) (*8*), eliminates the need for switching gradients through successive static directional gradients along the navigational path. For DFN, these gradients are generated by the dipole fields produced by large ferromagnetic cores adequately positioned in the bore of the clinical MRI scanner. Although DFN increased the magnitude of the directional gradients 10-fold compared with those generated by clinical MRI coils during MRN, real-time MRI is presently limited by the distorted $\mathbf{B}_0$ field created by the ferromagnetic cores. Moving such cores farther away from the region of interest using the MRI gradient coils allows for MRI-based targeting assessment with the option to dynamically change the positions of the gradients generated by the ferromagnetic cores during DFN.

Limited MRI spatial resolution and gradients prevent MR-navigable agents from transiting through the microvascular networks and physiological microenvironments required to reach active cancer cells located deep in tissues. Therefore, MR actuation is being investigated to transport computer-controlled magneto-aerotactic bacteria, acting as self-propelled natural nanorobots, closer to tumors. Such bacteria have been very effective at detecting and targeting active cancer cells (*9*), well beyond the capability of artificial helical microstructures propelled by a lower strength rotating magnetic field or chemically propelled agents.

The much higher induced force from a clinical MRI scanner on larger ferromagnetic objects can also be exploited. MRI-powered and -controlled actuation have shown potential for the development of a multitude of larger robotic systems dedicated to various medical interventions (*10*) and supported by multiple degrees of freedom made possible by the three–independent coordinate–direction gradient inputs.

MR actuation is a powerful concept that ranges from micro- to macroscale, yet it has been used so far by only a few research groups. Restricted access to clinical MRI scanners, general lack of expertise in the robotic community to develop and implement MRI and MR actuation sequences, and limited accessibility to protected source codes from the MRI manufacturers are some of the obstacles that contribute to its relatively slow adoption in robotics. However, the results obtained so far suggest that there are potential opportunities for researchers to develop novel MR actuation systems and methods that will lead to important advances in medical robotics.

REFERENCES

1. N. Nothnagel, J. Rahmer, B. Gleich, A. Halkola, T. M. Buzug, J. Borgert, Steering of magnetic devices with a magnetic particle imaging system. *IEEE Trans. Biomed. Eng.* **63**, 2286–2293 (2016).
2. J. Rahmer, C. Stehning, B. Gleigh, Spatially selective remote magnetic actuation of identical helical micro-machines. *Sci. Robot.* **2**, eaal2845 (2017).
3. S. Martel, J.-B. Mathieu, O. Felfoul, A. Chanu, É. Aboussouan, S. Tamaz, P. Pouponneau, L. H. Yahia, G. Beaudoin, G. Soulez, M. Mankiewicz, Automatic navigation of an untethered device in the artery of a living animal using a conventional clinical magnetic resonance imaging system. *Appl. Phys. Lett.* **90**, 114105–1–11405-3 (2007).
4. P. Pouponneau, J.-C. Leroux, G. Soulez, L. Gaboury, S. Martel, Co-encapsulation of magnetic nanoparticles and doxorubicin into biodegradable microcarriers for deep tissue targeting by vascular MRI navigation. *Biomaterials* **32**, 3481–3486 (2011).
5. M. Muthana, A. J. Kennerley, R. Hughes, E. Fagnano, J. Richardson, M. Paul, C. Murdoch, F. Wright, C. Payne, M. F. Lythgoe, N. Farrow, J. Dobson, J. Conner, J. M. Wild, C. Lewis, Directing cell therapy to anatomic target sites in vivo with magnetic resonance targeting. *Nat. Commun.* **6**, 8009 (2015).
6. K. Belharet, D. Folio, A. Ferreira, Simulation and planning of a magnetically actuated microrobot navigating in arteries. *IEEE Trans. Biomed. Eng.* **60**, 994–1001 (2013).
7. O. Felfoul, A. T. Becker, G. Fagogenis, P. E. Dupont, Simultaneous steering and imaging of magnetic particles using MRI toward delivery of therapeutics. *Sci. Rep.* **6**, 33567 (2016).
8. M. Latulippe, S. Martel, Dipole field navigation: Theory and proof of concept. *IEEE Trans. Robot.* **31**, 1–11 (2015).
9. O. Felfoul, M. Mohammadi, S. Taherkhani, D. de Lanauze, Y. Z. Xu, D. Loghin, S. Essa, S. Jancik, D. Houle, M. Lafleur, L. Gaboury, M. Tabrizian, N. Kaou, M. Atkin, T. Vuong, G. Batist, N. Beauchemin, D. Radzioch, S. Martel, Magneto-aerotactic bacteria deliver drug-containing nanoliposomes in tumour hypoxic regions. *Nat. Nanotechnol.* **11**, 941–947 (2016).
10. P. Vartholomeos, C. Bergeles, L. Qin, P. E. Dupont, An MRI-powered and controlled actuator technology for tetherless robotic interventions. *Int. J. Robot. Res.* **32**, 1536–1552 (2013).

10.1126/scirobotics.aam8119

Citation: S. Martel, Beyond imaging: Macro- and microscale medical robots actuated by clinical MRI scanners. *Sci. Robot.* **2**, eaam8119 (2017).

Beyond imaging: Macro- and microscale medical robots actuated by clinical MRI scanners

Sylvain Martel

*Sci. Robotics*2, (2017)
doi: 10.1126/scirobotics.aam8119

Editor's Summary

Science Robotics (ISSN 2470-9476) publishes new articles weekly. The journal is published by the American Association for the Advancement of Science (AAAS), 1200 New York Avenue NW, Washington, DC 20005.