

# A Comparative Study between MC-1 Cells and Magnetic Microparticles Used for Enhanced Target Delivery of Therapeutic Agents in the Microvasculature

Ouajdi Felfoul, *Student Member, IEEE*, Jean-Baptiste Mathieu, *Student Member, IEEE*, and Sylvain Martel, *Senior Member, IEEE*

**Abstract**—The use of a clinical MRI system for propelling and controlling the displacement of a ferromagnetic core along a pre-planned path in the blood vessels has been validated experimentally by our group. The results of the experiment suggest that a MRI platform could not only be used as an imaging or diagnostic tool, but also as an interventional platform. One important medical intervention where such a new technology could play a significant role is in target chemotherapy where enhanced targeting efficacy leading to a significant reduction of the amount of toxicity in the systemic blood networks while improving therapeutic efficacy using lower dosages could be achieved. But to improve tumor targeting, the overall dimensions of these magnetic microcarriers must be reduced to approximately  $2\mu\text{m}$  in diameter to allow them to circulate in the microvasculature prior to reach the tumoral lesions. Because of the substantial reduction of magnetic material embedded in these microcarriers, technological constraints such as cooling and limits in gradient amplitudes will reduce targeting efficacy. Hence, to improve targeting in the microvasculature, MC-1 cells, each with an overall diameter of approximately  $2\mu\text{m}$  are being considered by our group as microcarriers for the target delivery of therapeutic agents. Each flagellated bacteria cell of type MC-1 would provide a thrust force exceeding  $4\text{pN}$ , a value which can be very effective when operating in low Reynolds hydrodynamic conditions such as when navigating in the microvasculature. By combining the propulsion force of each MC-1 cell that is provided by a pair of flagella instead of an induced force generated from an external source, with magnetotaxis-based swimming direction control of the cells by computer while tracking the cells using MRI, enhanced targeting based on closed-loop navigation control can be

achieved. Here, through a comparative study between these two novel approaches, we show the advantages of the use of these MC-1 cells as microcarriers when operating in the smallest diameter capillaries of the microvasculature.

## I. INTRODUCTION

The use of untethered microcarriers to transport therapeutic agents to reach a target such as a tumor through the vascular network of a human body requires an appropriate propulsion and steering system. The development of such propulsion and steering system can be a real technical challenge especially when the volume of these microcarriers must be reduced to a diameter of approximately  $2\mu\text{m}$  to allow them to operate efficiently in the smallest diameter blood vessels of the microvasculature. Presently, an entirely synthetic approach not relying on an external source of induced propulsion force is beyond current technological limits while the ones relying on an external source for propulsion are still facing important technological challenges when designed to operate in the human's microvascular networks.

Magnetic Drug Targeting (MDT) is used to concentrate drugs into the tumor site in order to reduce secondary toxicity caused by most drugs in cancer treatment [1-6]. MDT presently consists on loading drugs inside magnetic particles acting as carriers and to trap this complex in vicinity of a tumor using an external magnet. Because of higher magnetic gradient intensity towards the external magnet, targeting efficacy is higher for tumors located near the magnet and decreases substantially when the tumor is located deeper in the body. Furthermore, the lack of navigational control when combined with complex microvascular networks near a tumor also contributes to lower targeting efficacy even further.

Hence, to improve targeting efficacy for tumors located deeper in the body, a new method has been proposed by our group. This method relies on the induction of propulsion force on magnetic material (with sufficient magnetization saturation) from magnetic gradient coils. Initial experiments where done using the three orthogonal coils used for image encoding in conventional clinical MRI systems. Through tracking information provided by the capability of the imaging modality of MRI to gather information deep in the body, a closed-loop computer controlled displacement of a ferromagnetic bead along a pre-planned path in the

This work was supported in part by the Canada Research Chair (CRC) in Micro/Nanosystem Development, Fabrication and Validation and grants from the National Sciences and Engineering Research Council of Canada (NSERC), the Province of Québec, the Canada Foundation for Innovation (CFI), and US Grant Number R21EB007506 from the National Institute Of Biomedical Imaging And Bioengineering. The content is solely the responsibility of the authors and does not necessary represent the official views of the National Institute Of Biomedical Imaging And Bioengineering or the National Institutes of Health

S. Martel (corresponding author) is with the NanoRobotics Laboratory, Department of Computer and Software Engineering, and the Institute of Biomedical Engineering, École Polytechnique de Montréal (EPM), Montréal (Québec), P.O. Box 6079 Station Centre-ville, H3C 3A7 Canada (phone: 514 340-4711 ext. 5098; fax: 514-340-4658; e-mail: sylvain.martel@polymtl.ca).

O. Felfoul (e-mail: ouajdi.felfoul@polymtl.ca), and J-B. Mathieu (e-mail: jean-baptiste.mathieu@polymtl.ca) are with the NanoRobotics Laboratory at EPM.

vasculature of a living animal was demonstrated. This experiment conducted in the carotid artery of a living swine also showed the possibility of adapting this technology for navigating magnetic microparticles in the microvasculature for future target therapeutic applications beyond the limits of modern catheterization. It also showed the advantages of using MRI as imaging modality not only for tracking magnetic microparticles but also to monitor in real-time the therapeutic effect during such interventions [7-9].

In particular, this new technology could increase further the popular uses of magnetic nanoparticles as carriers for therapeutic agents for target interventions in cancer therapy. Magnetic nanoparticles can not only be manipulated by external magnetic field gradients but they also disrupt the local magnetic field creating a net field inhomogeneity that can be picked up as a negative contrast (local decrease in image intensity) in  $T_2$ -weighed MRI which is essential for monitoring and closed-loop navigation and trajectory control. The nanometer-scale of these particles also allows the generation of heat when exposed to an alternating magnetic field. This feature can be used as hyperthermic agents to destroy tumor tissue, or as a computer-triggering mechanism to release drugs while elevating the temperature locally for achieving enhanced therapeutic results.

But inducing sufficient force on nanoparticles would require magnetic gradients with amplitudes that are beyond technological possibilities when operating in the human body and clearly there are limits to the gradient approach as was pointed out in [10]. This is due in great part to the very small volume of magnetic material involved. One possibility when operating in the microvasculature is to encapsulate such magnetic nanoparticles with therapeutic agents within polymeric microcarriers. With this approach, a higher effective volume of magnetic material can be achieved while retaining the advantages offered by the properties of magnetic nanoparticles for target applications using MRI. But tumoral lesions are typically accessible by transiting through anarchic arteriocapillar networks stimulated by tumoral angiogenesis with capillaries as small as 4-5 $\mu\text{m}$  in diameter. As such, this environment restricts the overall maximum diameter of each magnetic microcarrier for efficient navigation to approximately 2 $\mu\text{m}$ . Although at such a scale, the blood flow would typically be used for propulsion, sufficient magnetic gradient must still be generated to steer efficiently such microcarriers especially at vessel bifurcations to achieve enhanced targeting efficacy. Preliminary studies showed that additional gradient steering coils when implemented in the bore of a clinical MRI system and designed for operation in the human body would provide maximum gradients of approximately 0.5T $\cdot\text{m}^{-1}$ . This value may be sufficient for larger microcarriers used for target chemo-embolization but will prove to be insufficient for enhanced targeting inside a tumor.

One approach proposed by our group is to eliminate the need for such gradient coils when operating in the microvasculature and to replace it by the propulsion force provided by flagellated bacteria. But since steering control is

also required for target interventions, special types of cells referred to as Magnetotactic Bacteria (MTB) are considered by our group for such applications.

MTB not only use flagella for propulsion, but we showed that the swimming direction can be controlled by computer using an external directional magnetic field which induces a torque on a chain of nanoparticles called magnetosomes that are synthesized in the cell under specific conditions during cultivation [11]. Like a compass needle, the swimming direction of the MTB is influenced through magnetotaxis [12, 13]. Furthermore, the MC-1 MTB cells considered for this application are rounded in shape with a diameter of approximately 2 $\mu\text{m}$ , giving them the ability to navigate in the smallest blood vessels and at average and top swimming speeds reaching approximately 200 and 300 $\mu\text{m}\cdot\text{s}^{-1}$  respectively.

Other types of bacteria have been considered for fighting tumors by proliferating in the tumor necrotic zone [14-16]. These bacteria would reach tumoral lesions by means that are not compatible with electronic computer such as chemotaxis [17]. Although there are efforts to use chemotaxis-based bacteria to move micro-objects in an aqueous medium [18], our preliminary results suggest that the use of bacteria being influenced by magnetotaxis would be more appropriate and efficient for computer-based navigation such as target interventions in the microvasculature. Furthermore, the use of MTB can not only enhance targeting through flagellated propulsion and directional control from an external system, but can also be tracked for feedback control by MRI due to the chain of magnetosomes in the cell that causes a local field inhomogeneity detectable by MRI. The MR-tracking or imaging method of MTB is then similar to the one described earlier for magnetic nanoparticles.

In this respect, the use of MC-1 cells where nanoparticles loaded with therapeutic agents could be attached to the cell itself using antibodies already developed in our laboratory is compared with the use of magnetic microcarriers with similar overall dimensions. The simulation data provided in this article for comparison are based on experimental results gathered with MC-1 MTB unless otherwise stated and for magnetite microparticle with the same diameter as the MC-1 cell. Although a percentage of the volume would typically be dedicated in each microcarrier to load therapeutic agents which would reduce the volume of magnetite embedded, the simulation and the results obtained assume 100%/vol magnetite in each magnetic microcarrier.

## II. FUNDAMENTAL THEORY

Prior to perform a comparative study between the two approaches, an understanding of the fundamental theoretical equations used to compute the performance of each approach is necessary. First, it is important to understand that the mathematical laws governing motion of magnetic microparticles in the microvasculature differ from that for magnetotactic bacteria.

A magnetic particle being transported by the blood flow in the microvasculature still needs to be steered at vessel bifurcations for enhanced targeting. Steering in this particular case is accomplished using a magnetic force  $F_{mag}$  (N) that acts on a magnetized body from a gradient field  $H$  ( $A \cdot m^{-1}$ ). Such force is computed as

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

where  $\vec{m}$  ( $A \cdot m^2$ ) is the magnetic moment, and  $\mu_0$  ( $N \cdot A^{-2}$ ) is the permeability of vacuum. A spherical magnetic particle having a radius  $R$  ( $m$ ) subject to a magnetic force will move with a velocity

$$v = \frac{\mu_0}{6\pi\eta R} \cdot (\vec{m} \cdot \nabla) \vec{H} \quad (2)$$

where  $\eta$  ( $Kg \cdot s^{-1} \cdot m^{-1}$ ) is the viscosity of the medium.

Magnetic microparticles become competitive against the use of the MC-1 cells if the velocity computed in Eq. 2 is at least equivalent or higher than the swimming velocity of these MTB recorded experimentally by our group in human blood. Although an average and peak swimming velocities of approximately 200 and 300  $\mu m \cdot s^{-1}$  respectively have been recorded by our group in human blood at room temperature, our experimental results showed that the velocity of the MC-1 cells decrease continuously when operating at the human internal temperature of 37°C and within a maximum operational time period of approximately 40 minutes. Hence for comparison, an average swimming speed  $v_0 = 100 \mu m \cdot s^{-1}$  was considered in this study for comparison purpose assuming that MTB-based interventions can be achieved with such time period, which can be done according to preliminary studies.

But for a fair comparison, the external applied magnetic field  $H$  that must be used to steer the cells as well as the Brownian motion that tend to deviate the MTB from the field direction, must also be taken into account.

To evaluate such parameters, the swimming velocity  $v_0$  is first divided into two components with respect to  $H$  as stated in [19]. Assuming an angle of  $\varphi$  between the swimming direction of the bacterium and the applied field  $H$ , the velocity component parallel and perpendicular to  $H$  can be expressed as

$$\begin{aligned} v_H &= v_0 \cdot \cos \varphi \\ v_{\perp} &= v_0 \cdot \sin \varphi \end{aligned} \quad (3)$$

Fortunately, the chain of magnetosomes inside the cell will contribute to maximize the magnetic moment of each bacterium where the ratio between the thermal energy and the magnetic potential energy can be expressed as

$$\Lambda = \frac{mB}{KT}, \text{ where } B = \mu_0 H. \quad (4)$$

We notice here that a higher value of  $H$  is required to maintain the orientation of the MC-1 cell as to correct for displacement error caused by an increase of the Brownian motion caused by the higher temperature level in the microvasculature. Hence, as given in [20], the average value of  $\cos \varphi$  is found to be

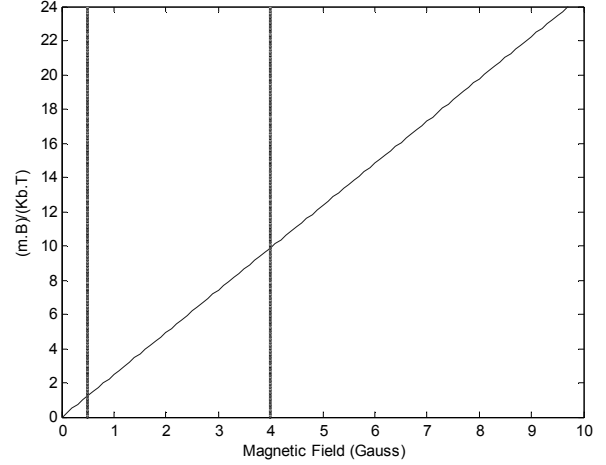


Fig. 1. As the applied magnetic field is increased, the ratio between the magnetic potential energy and the thermal energy increases. At 0.5 Gauss, the earth's magnetic field, this ratio is 1.15 for bacteria having a magnetic moment of  $10^{-16} (A \cdot m^2)$  at room temperature, this explains the tendency of the MTB to follow the magnetic field direction. At 4 Gauss the ratio is nearly 10, and as observed under microscope the MTB follows at a very high proportion this direction.

$$\langle \cos \varphi \rangle = L(\Lambda). \quad (5)$$

For a cell having a magnetic moment  $m$  of  $10^{-16} (A \cdot m^2)$  at room temperature (297.15°K), the magnetic energy is 1.15 times the thermal energy when subjected to the geomagnetic field of 0.5 Gauss as depicted in Fig. 1. However, an increase of the magnetic field to 4 Gauss for instance will yield very accurate displacement achieved with an energy ratio of approximately 10.

If we neglect thermal fluctuations considering a high enough external magnetic field  $H$ , the dynamics of the orientation of the bacterial magnetic moment with the magnetic field can be determined using Eq. 6 [21].

$$-\alpha \frac{d\theta}{dt} + mB \sin \beta = 0 \quad (6)$$

In Eq. 6,  $\alpha$  is the rotational friction coefficient,  $\theta$  is the particle orientation with respect to a fixed direction, and  $\beta$  is the angle between the magnetic field and the magnetic moment of the cell.

Even though many factors influence the motion of microparticles and MTB in the microvasculature as described in [3], we only consider here the most predominant factors being the magnetic and fluidic forces. The fluidic force is caused by the blood flow and is equal to

$$F_f = -6\pi\eta R_p (v_p - v_f). \quad (7)$$

Equation 7 considers a laminar flow and a spherical particle having a hydrodynamic radius of  $R_p$ . In Eq. 7  $\eta$  and  $v_f$  are the blood viscosity and velocity respectively. Here, equilibrium of forces between magnetic force and Stokes law of fluid friction weighted by a wall effect correlation [22] allows for a theoretical particle magnetophoretic terminal

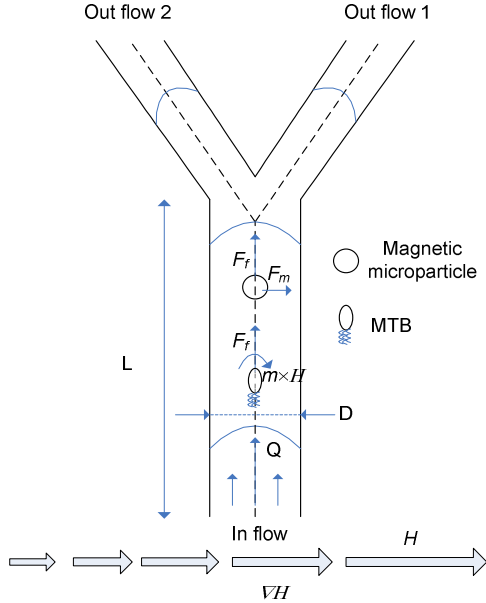


Fig. 2. *Y-shaped* microvascular channel used for navigation simulation of steering efficiency.  $D$  represents the channel diameter and  $L$  its length, we consider  $L = D \times 100$ . Even if magnetic particles steering involves many forces we consider only the most important which are the magnetic and fluidic forces. MTB are subject to a magnetic torque but their motion is assured by flagella giving to the bacteria a constant speed along the magnetic field direction.

velocity calculation [23] inside a microchannel and was considered in the simulation.

### III. SIMULATION

We consider in this paper a simple navigation case consisting on a *Y-shaped* microvascular channel as depicted by Fig. 2. The targeting efficiency is assessed for different steering parameters for both magnetic microparticles and MTB considering various flow rates and sizes of microchannels reflecting real conditions in the human vasculature.

It is obvious that the thrust provided by each MTB is insufficient to cope with the relatively high blood flows in larger blood vessels. For instance, velocities reaching  $50 \text{ cm}\cdot\text{s}^{-1}$  can be recorded in large arteries. In such cases, the method of propulsion or steering relying on the induction of force on a larger ferromagnetic core becomes a more attractive approach compared to MTB-based microcarriers. But in smaller diameter vessels, the blood flow velocity decreases significantly to reach approximately  $1 \text{ mm}\cdot\text{s}^{-1}$  in the capillaries where MTB-based microcarriers can become more effective, especially in vessels with a diameter of only a few micrometers. As such, the simulation results presented in this paper consider steering in regions of the vasculature which are inaccessible to modern catheterization. More precisely, the simulation performed under realistic conditions considers channels with diameters similar to arterioles which link the arteries to the smaller diameter capillaries found in the human's microvasculature.

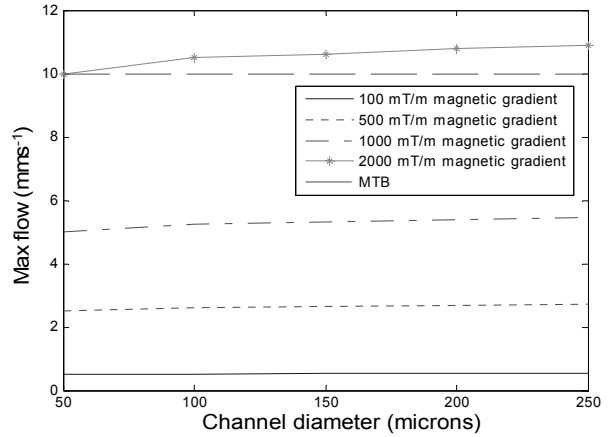


Fig. 3. Plot of the maximum flow below which a 100% efficiency steering of a 2 microns diameter magnetite sphere and MC-1 MTB is possible. The simulation is done for various magnetic gradient amplitudes.

As specified earlier, a conservative velocity of  $100 \mu\text{m}\cdot\text{s}^{-1}$  for the MC-1 cell is considered during simulation. Furthermore, we suppose during simulation that the directional magnetic field induced in the chain of magnetosomes is high enough to make Brownian motion negligible in the context of steering the MTB at vessel bifurcations which may not be a real issue when operating in blood vessels. In real physiological conditions within such environment constrained between vessel walls and with various parameters influencing the swimming paths inside the blood vessels such as relatively large flow perturbations and unpredictable micro-flows which exist especially around bifurcations, the need for relatively high magnetic field may not be always necessary to achieve enhanced tumor targeting. But for simulation purpose in a worst case scenario, a magnetic field of approximately 10 Gauss at  $37^\circ\text{C}$  was considered.

In this study, the velocity of MC-1 cells is compared to the velocity of a  $2 \mu\text{m}$  magnetite sphere steered by magnetic gradients in the blood. Magnetite is a well known material with relatively high magnetization saturation and proven biocompatibility. This material is widely used as a safe contrast agent for MR-imaging.

The length of the channel taken from realistic conditions has a ratio of 100 or in other words,  $L = D \times 100$  where  $D$  is the channel diameter. For every channel diameter, we calculated the maximum blood flow that allow for a 100% steering efficiency. In order for a microparticle or MTB to be steered toward the targeted channel at the bifurcation, it was assumed that half the diameter of the main channel had to be traveled before reaching the bifurcation. This was considered as a worst case scenario since all the microparticles located on the same side of the centerline of the channel prior to the *Y*-bifurcation should exit through the targeted outlet.

### IV. RESULTS

As depicted in Fig. 3, high gradient amplitudes are required to achieve 100% steering efficiency with moderate

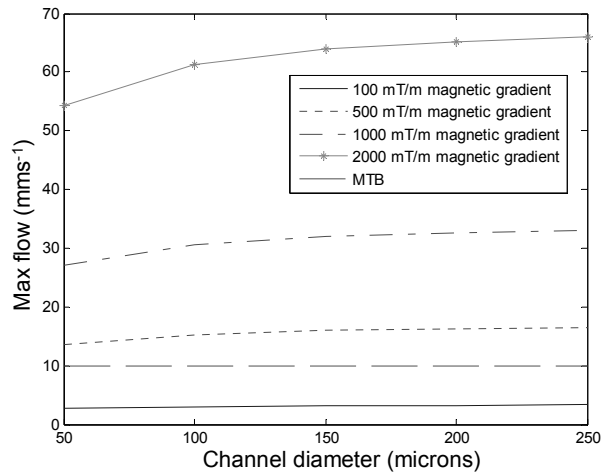


Fig.4 . Plot of the maximum flow below which a 100% efficiency steering of a 5 microns diameter magnetite sphere and MTB is possible. The simulation is done for various magnetic gradient amplitudes.

flow velocities. The MC-1 cell for instance can theoretically sustain a flow rate of  $10 \text{ mm}\cdot\text{s}^{-1}$  which would require a gradient amplitude as high as  $2\text{T}\cdot\text{m}^{-1}$  for a magnetite microparticle of the same diameter as the MC-1 cell to sustain the same flow rate. Hence, to reach a higher magnetophoretic velocity, a smaller particle must be submitted to a much higher magnetic gradient than a larger particle containing a higher effective volume of the same magnetic material. The magnetic force in this case is greatly affected by the size of a spherical magnetic core since such force will be proportional to the cube of the radius of the core itself.

Hence, larger magnetic cores with diameter of  $5\mu\text{m}$  or higher for instance can be used not for targeting in the tumor itself but embolization of small capillaries near the tumoral lesion in order to stop blood supply to the tumor. As

depicted by Fig. 4, the maximum flow velocity within which 100% steering efficiency of microparticles of  $5\mu\text{m}$  can be achieved is much higher than for  $2\mu\text{m}$  magnetic microparticles even with relatively moderate magnetic gradients ( $<0.5\text{T}\cdot\text{m}^{-1}$ ). We notice that in this case, MC-1 MTB is no more an efficient solution compared to magnetic microparticles that could sustain a large flow velocity with reasonable magnetic gradients. In addition to an increase in particle sizes, other magnetic components that present a higher magnetization values than magnetite such as Cobalt-Iron, could also be used to increase the magnetic force and achieve a higher magnetophoretic velocity provided that the design would prevent the release of toxic Cobalt ions in the blood.

A relatively large number of morphotypes of MTB exists in nature and several of them are being grown in laboratories. Commonly observed morphotypes include spherical cells (cocci), rod-shaped, curved bacteria (vibrio), many celled MTB (a group of cells arranged as a sphere), and helical (spirillum) of various dimensions and having different swimming velocities [24-27].

Table 1 summarizes the main MTB characteristics such as the cell morphology, the respective swimming velocity, the dimension of the cell and shows the magnetic gradient required to move a microparticle of the same size at the same velocity of the corresponding cell's type. The smaller is the cell, the higher is the required magnetic field in order to achieve the same velocity. In fact, for some cases like MC-1, MV-1, MV-2 and MS-1 cells, the magnetic gradient required to achieve the equivalent speed is extremely high and could even be impractical to implement for deep target location in the human body. For smaller MTB, with relatively low swimming speeds, the required magnetic gradient is reasonable and could be easily implemented but these smaller MTB would not necessary be good candidates to target tumoral lesions.

TABLE I  
SUMMARY CHARACTERISTICS OF SOME MTB AND CALCULATION OF THE REQUIRED GRADIENT NECESSARY TO HAVE A MAGNETOPHORETIC SPEED EQUIVALENT TO THE MTB SPEED GIVING A SPHERICAL MAGNETITE MICROPARTICLE WITH THE SAME SIZE RANGE AS THE MTB.

MTB NAME	CELL MORPHOLOGY	Mean Speed ( $\mu\text{m}\cdot\text{s}^{-1}$ )	WIDTH (OR DIAMETER) ( $\mu\text{m}$ )	LENGTH ( $\mu\text{m}$ )	MAGNETIC MICROPARTICLE	
					DIAMETER ( $\mu\text{m}$ )	MAGNETIC GRADIENT ( $\text{mT}\cdot\text{m}^{-1}$ )
MC-1 [11]	Coccioid	200	2	-	2	$7.6\times 10^3$
Magnetospirillum gryphiswaldense [24]	Helical	*	0.2–0.7	1-20	10	91
AMB-1 [25]	Helical	49	0.5	3-10	5	320
MV-1 and MV-2 [26]	Vibroid to Helical	*	0.2–0.5	1-5	2	$1.9\times 10^3$
MMP (Many celled Magnetotactic bacteria)[26]	Sphere (a cluster of 10-30 Coccioid cells)	105	3-12	-	8	287
Magnetobacterium bavaricum [26]	Rod-shaped	40	1–1.5	6–9	7	139
RS-1[26]	Helical to Rod-shaped	*	0.9–1.5	3-5	4	326
Magnetospirillum magnetotacticum (MS-1) [27]	Spirillum	40	0.5	5	2.5	989

\* For MTB speed missing data we considered a value of  $50 \mu\text{m}\cdot\text{s}^{-1}$  for the calculation of the magnetic gradient

## V. DISCUSSION AND CONCLUSION

The use of the molecular motors embedded in MC-1 magnetotactic bacteria for drug targeting is an efficient method since it does not require an external energy source. Magnetic drug targeting on the other hand although it has limitations in the smallest diameter capillaries, represents a more flexible approach where the steering parameters can be customized depending upon the application needs and the geometries of the targeted vessels. Another interesting feature of using MTB is the fact that they do not require blood flow to move, allowing them to swim in larger diameter vessels if a complementary method such as the use of a balloon catheter or larger magnetic embolization particles are used to stop blood flow temporarily. These cells can also be very effective in enhancing the uniform distribution of drugs inside the tumor which is a key component for the eradication of the tumor. Furthermore, MTB can increase the time required for drugs to be in direct contact with cancerous cells because of the high interstitial pressure inside the tumor. Without the use of MTB, the diffusion of drugs would otherwise be very slow.

The use of magnetotactic bacteria and in particular MC-1 cells can enhance tumor targeting efficacy compared to the use of magnetic microparticles when transiting through the smallest diameter capillaries found in the human microvasculature. On the other hand, the use of magnetic microparticles especially with material having a relatively high magnetization saturation becomes more effective in larger diameter capillaries when compared to the use of the MC-1 cell as microcarriers for target drug delivery.

## ACKNOWLEDGMENT

M. Mohammadi from the NanoRobotics Laboratory at EPM is acknowledged for his assistance in the cultivation of the MC-1 cells and during experiments conducted to gather data used in this study.

## REFERENCES

- [1] F. Mishima, S. Takeda, Y. Izumi, S. Nishijima, "Three dimensional motion control system of ferromagnetic particles for magnetically targeted drug delivery systems," *IEEE Transactions on Applied Superconductivity*, vol. 16, n. 2, pp. 1539-1542, June 2006.
- [2] Z. G. Forbes, B. B. Yellen, K. A. Barbee, and G. Friedman, "An approach to targeted drug delivery based on uniform magnetic fields," *IEEE Transactions on Magnetics*, vol. 39, n. 5, pp. 3372-3377, Sept. 2003.
- [3] E. J. Furlani, E. P. Furlani, "A model for predicting magnetic targeting of multifunctional particles in the microvasculature," *Journal of Magnetism and Magnetic Materials*, vol. 312, n. 1, pp. 187-193, May 2007.
- [4] L. E. Udrea, N. J. C. Strachan, V. Badescu, O. Rotariu, "An in vitro study of magnetic particle targeting in small blood vessels," *Physics in Medicine and Biology*, vol. 51, n. 19, pp. 4869-4881, Oct. 2006.
- [5] E. P. Furlani, K. C. Ng, "Analytical model of magnetic nanoparticle transport and capture in the microvasculature," *Physical Review E*, vol. 73, n. 6, pp. 61919-1-10, June 2006.
- [6] B. Gleich, N. Hellwig, H. Bridell, R. Jurgons, C. Seliger, C. Alexiou, B. Wolf, T. Weyh, "Design and evaluation of magnetic fields for nanoparticle drug targeting in cancer," *IEEE Transactions on Nanotechnology*, vol. 6, n. 2, pp. 164-70, March 2007.

- [7] J. B. Mathieu, S. Martel, "Magnetic microparticle steering within the constraints of an MRI system: Proof of concept of a novel targeting approach," *Biomedical Microdevices*, vol. 9, n. 6, pp. 801-808, Dec. 2007.
- [8] S. Martel, J.-B. Mathieu, O. Felfoul, A. Chanu, E. Aboussouan, S. Tamaz, and al. "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, n. 11, pp. 114105-1-3, March 2007.
- [9] O. Felfoul, J.-B. Mathieu, G. Beaudoin, S. Martel, "In vivo MR-tracking based on magnetic signature selective excitation," *IEEE Transactions on Medical Imaging*, vol. 27, n. 1, pp. 28-35, Jan. 2008.
- [10] K. B. Yesin, K. Vollmers, and B. J. Nelson, "Modeling and control of untethered biomicrobots in a fluidic environment using electromagnetic fields," *International journal of robotic research*, vol. 25, n. 5-6, pp. 527-36, May 2006.
- [11] S. Martel, C. Tremblay, S. Ngakeng, and G. Langoils, "Controlled manipulation and actuation of micro-objects with magnetotactic bacteria," *Applied Physics Letters*, vol. 89, pp. 233804-6, 2006.
- [12] R. P. Blakemore, "Magnetotactic bacteria [in geomagnetic field]," *Science*, vol. 190, pp. 377-379, 1975.
- [13] R. B. Frankel, D. A. Bazylinski, M. S. Johnson, B. L. Taylor, "Magneto-aerotaxis in marine coccoid bacteria," *Biophysics Journal*, vol. 73, pp. 994-1000, 1997.
- [14] S. Martel, C. Tremblay, S. Ngakeng, and G. Langoils, "Controlled manipulation and actuation of micro-objects with magnetotactic bacteria," *Applied Physics Letters*, vol. 89, pp. 233804-233806, 2006.
- [15] R. W. Kasinskas, N. S. Forbes, "Salmonella typhimurium specifically chemotax and proliferate in heterogeneous tumor tissue in vitro," *Biotechnology and Bioengineering*, vol. 94, n. 4, pp. 710-721, 2006.
- [16] C. Bettgowda, L. H. Dang, R. Abrams, and al., "Overcoming the hypoxic barrier to radiation therapy with anaerobic bacteria," *Proc Natl Acad Sci*, vol. 100, n. 25, pp. 15083-15088, 2003.
- [17] N. S. Forbes, L. L. Munn, D. Fukumura and R. K. Jain, "Sparse initial entrapment of systemically injected salmonella typhimurium leads to heterogeneous accumulation within tumor necrosis," *Cancer Research*, vol. 63, pp. 5188-5193, 2003.
- [18] B. Behkam, M. Sitti, "Bacterial flagella-based propulsion and on/off motion control of microscale objects," *Applied Physics Letters*, vol. 90, n. 2, pp. 23902-1-3, Jan. 2007.
- [19] G. Harasko, H. Pfutzner, and K. Futschik, "Domain analysis by means of magnetotactic bacteria," *IEEE Transactions on Magnetics*, vol. 31, n. 2, pp. 938-49, March 1995.
- [20] Frankel, R.B., "Magnetic guidance of organisms," *Annual review of biophysics and bioengineering*, vol. 13, pp. 85-103, 1984
- [21] A. Cebers, and M. Ozols, "Dynamics of an active magnetic particle in a rotating magnetic field," *Physical Review E (Statistical, Nonlinear, and Soft Matter Physics)*, vol. 73, n. 2, pp. 21505-1-5, Feb. 2006.
- [22] R. Kehlenbeck, and R. Di Felice, "Empirical relationships for the terminal settling velocity of spheres in cylindrical columns," *Chemical Engineering and Technology*, vol. 22, n. 4, pp. 303-308, Apr. 1999.
- [23] V. Fidleris, and R. L. Whitmore, "Experimental determination of the wall effect for spheres falling axially in cylindrical vessels," *British Journal of Applied Physics*, vol. 12, n. 9, pp. 490-494, Sept. 1961.
- [24] M. Arnoldi, C. M. Kacher, E. Baeuerlein, and M. Fritz, "Elastic properties of the cell wall of *Magnetospirillum gryphiswaldense* investigated by atomic force microscopy," *Applied Physics A (Materials Science Processing)*, vol. 66, pp. S613-17, March 1998.
- [25] S. Seong, and T. H. Park, "Swimming characteristics of magnetic bacterium, *Magnetospirillum* sp. AMB-1, and implications as toxicity measurement," *Biotechnology and Bioengineering*, vol. 76, n. 1, pp. 11-16, May 2001.
- [26] S. Spring, and D. A. Bazylinski, *The Prokaryotes, Volume 2: Ecophysiology and Biochemistry*, Springer New York, pp. 842-862, 2006.
- [27] A. S. Bahaj, P. A. B. James, and I. W. Croudace, "Metal uptake and separation using magnetotactic bacteria," *IEEE Transactions on Magnetics*, vol. 30, n. 6, pp. 4707-9, Nov. 1994.