

Magnetic Control of Potential Microrobotic Drug Delivery Systems

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Abstract—Development of targeted drug delivery systems using magnetic microrobots increases the therapeutic indices of drugs. These systems have to be incorporated with precise motion controllers. We demonstrate closed-loop motion control of microrobots under the influence of controlled magnetic fields. Point-to-point motion control of a cluster of iron oxide nanoparticles (diameter of 250 nm) is achieved by pulling the cluster towards a reference position using magnetic field gradients. Magnetotactic bacterium (MTB) is controlled by orienting the magnetic fields towards a reference position. MTB with membrane length of 5 μm moves towards the reference position using the propulsion force generated by its flagella. Similarly, self-propelled microjet with length of 50 μm is controlled by directing the microjet towards a reference position by external magnetic torque. The microjet moves along the field lines using the thrust force generated by the ejecting oxygen bubbles from one of its ends. Our control system positions the cluster of nanoparticles, an MTB and a microjet at an average velocity of 190 $\mu\text{m/s}$, 28 $\mu\text{m/s}$, 90 $\mu\text{m/s}$ and within an average region-of-convergence of 132 μm , 40 μm , 235 μm , respectively. Further, we achieve point-to-point closed-loop motion control of microparticles in the three-dimensional space, at an average speed of 198 $\mu\text{m/s}$, and maximum root mean square position tracking error of 104 μm .

I. INTRODUCTION

Magnetic microrobots have the potential to deliver concentrated pharmaceutical agents to diseased cells to avoid the negative side-effects associated with chemotherapeutic treatment [1], [2]. Many researchers proposed the utilization of biodegradable magnetic nanoparticles [3], [4], magnetotactic bacteria [5], artificial swimmers [6], and self-propelled microjets [7], [8] to execute limited tasks, such as targeted drug delivery [9], microassembly [10], and microactuation [11]. Realization of a reliable drug targeting system necessitates the development of precise closed-loop motion control systems. Kummer *et al.* developed and utilized a 5 degree-of-freedom magnetic system to puncture a blood vessel of a chorioallantoic membrane of a chicken embryo using a magnetic agent (two cubes with edge length of 800 μm) with permanent magnetization [12]. Magnetic control of a single paramagnetic microparticle in the presence of static

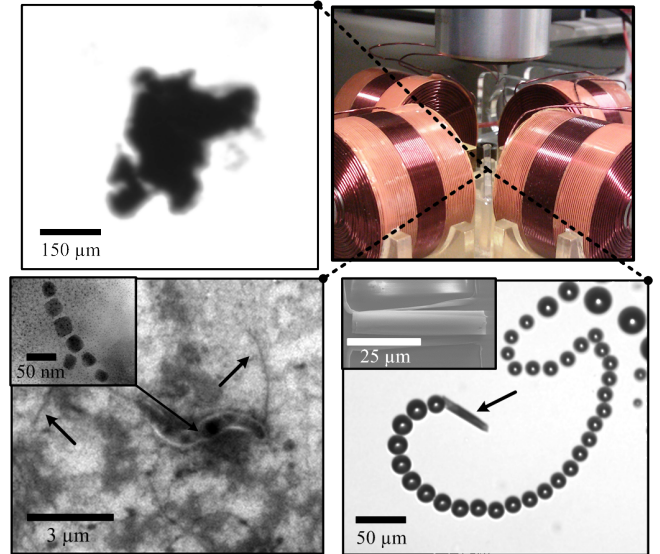


Fig. 1. Magnetic system for the point-to-point motion control of a cluster of iron oxide nanoparticles, magnetotactic bacterium (MTB) and a self-propelled microjet under the influence of the magnetic fields. The upper left image shows a cluster of nanoparticles. Motion of this cluster is achieved by the magnetic field gradients. The bottom left Scanning Electron Microscopy (SEM) image shows the membrane of an MTB (*Magnetospirillum magneticum* AMB-1), and its flagella, indicated by the black arrows. Motion of the MTB is due to the flagella and the external magnetic fields. The inset shows a Transmission Electron Microscopy image of the magnetite nanocrystals enveloped in the membrane of the MTB. The bottom right image shows a microjet moving under the influence of the external magnetic fields and its self-propulsion force. This propulsion force is generated by ejecting oxygen bubbles from one end of the microjet. The inset shows a SEM image of a microjet fixed to its substrate.

and dynamic obstacles was presented by Khalil *et al.* [13]. Martel *et al.* demonstrated the effectiveness of a swarm of magnetotactic bacteria in the execution of a manipulation task of microobjects under the influence of the controlled magnetic fields [14]. Microassembly of microobjects using a cluster of microparticles (with average diameter of 100 μm) and a magnetic-based manipulation system has been shown by Khalil *et al.* [15]. These magnetic systems can be used for targeted drug delivery by the incorporation of a clinical imaging modality, such as magnetic resonance imaging or ultrasound systems.

In this work, we present point-to-point motion control of a cluster of iron oxide microparticles and nanoparticles,

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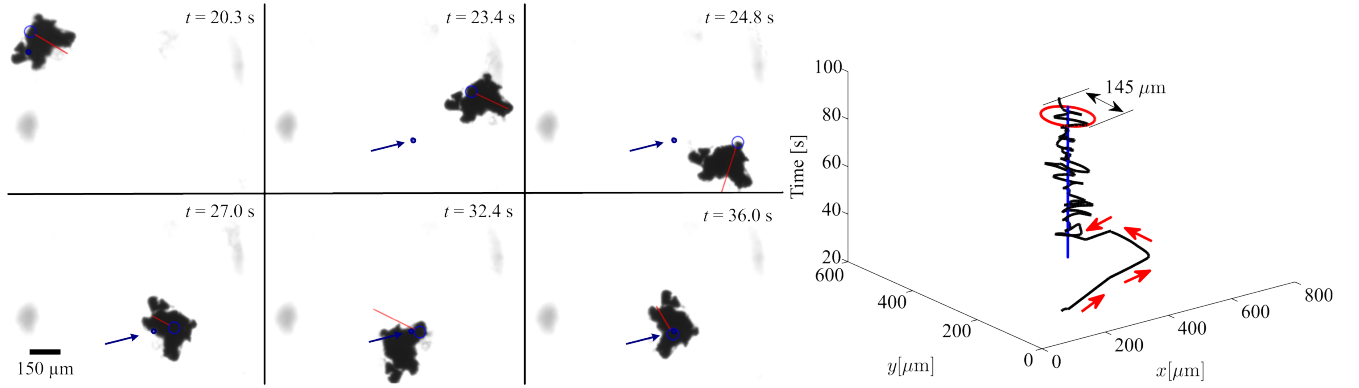


Fig. 2. Closed-loop motion control of a cluster of iron oxide nanoparticles (45-00-252 Micromod Partikeltechnologie GmbH, Rostock-Warnemuende, Germany) under the influence of the controlled magnetic fields. The cluster moves towards the reference position (small blue circle) by the magnetic field gradient generated using control law (3). In this representative experiment, the cluster moves at an average velocity of $195 \mu\text{m/s}$, and is positioned by the closed-loop control system within a region-of-convergence of $145 \mu\text{m}$ in diameter. The entries of each of the diagonal matrices (\mathbf{K}_p and \mathbf{K}_d) are 0.1 s^{-2} and 0.5 s^{-1} , respectively. The large blue circle is assigned by our feature tracking software [13] and represents the position of the cluster, whereas the red line represents its velocity vector. The blue arrows indicate the reference position. The solid blue line in the right image represents the reference position.

magnetotactic bacteria, and self-propelled microjets (Fig. 1) using a closed-loop motion control system. This control system is based on the characterization of the magnetic dipole moment of the aforementioned magnetic objects. Motion control of the microparticles and nanoparticles is achieved by controlling the gradients of the magnetic fields to pull the nanoparticles towards a reference position, whereas magnetotactic bacteria and microjets are controlled by orienting the fields towards a reference position. Magnetotactic bacteria and microjets move along the magnetic field lines using their self-propulsion forces that are generated by the helical flagella and the ejecting oxygen bubbles, respectively.

II. CONTROL SYSTEM DESIGN

In our work, iron oxide nanoparticles, magnetotactic bacteria and self-propelled microjets move in water, growth medium and hydrogen peroxide solution, respectively. Their motion is also guided using external magnetic fields. Therefore, these magnetic objects experience viscous drag forces and torques, and magnetic forces and torques. Details regarding the modeling of these magnetic objects is provided by Khalil *et al.* [16]. Our 2D- and 3D-magnetic system [13], [21] is used to generate controlled magnetic fields to realize the point-to-point motion control.

Our magnetic system consists of n -electromagnets. The magnetic field ($\mathbf{B}_i(\mathbf{P})$) is linearly proportional to the applied current (I_i) at the i th electromagnet. Therefore, the magnetic fields at point (\mathbf{P}) is given by [12]

$$\mathbf{B}(\mathbf{P}) = \sum_{i=1}^n \mathbf{B}_i(\mathbf{P}) = \sum_{i=1}^n \tilde{\mathbf{B}}_i(\mathbf{P}) I_i = \tilde{\mathbf{B}}(\mathbf{P}) \mathbf{I}, \quad (1)$$

where $\tilde{\mathbf{B}}(\mathbf{P}) \in \mathbb{R}^{3 \times n}$ is a matrix which depends on the position at which the magnetic field is evaluated, and $\mathbf{I} \in \mathbb{R}^{n \times 1}$ is a vector of the applied current. The magnetic field due to each electromagnet is related to the current input by $\tilde{\mathbf{B}}_i(\mathbf{P})$. Substituting (1) in the magnetic force equation ($\mathbf{F}(\mathbf{P}) = \nabla(\mathbf{m}(\mathbf{P}) \cdot \mathbf{B}(\mathbf{P}))$), where $\mathbf{F}(\mathbf{P}) \in \mathbb{R}^{3 \times 1}$, $\mathbf{m}(\mathbf{P}) \in \mathbb{R}^{3 \times 1}$ and $\mathbf{B}(\mathbf{P}) \in \mathbb{R}^{3 \times 1}$ are the magnetic force, induced magnetic dipole moment of the magnetic objects and the

magnetic field at point ($\mathbf{P} \in \mathbb{R}^{3 \times 1}$), respectively, yields the following magnetic force-current map:

$$\mathbf{F}(\mathbf{P}) = (\mathbf{m}(\mathbf{P}) \cdot \nabla) \tilde{\mathbf{B}}(\mathbf{P}) \mathbf{I} = \Lambda(\mathbf{m}, \mathbf{P}) \mathbf{I}. \quad (2)$$

In (2), $\Lambda(\mathbf{m}, \mathbf{P}) \in \mathbb{R}^{3 \times n}$ is the actuation matrix which maps the input current to the magnetic force [12]. Further, we devise the following proportional-derivative control law [15]

$$\mathbf{F}_{\text{des}}(\mathbf{P}) = \mathbf{K}_p \mathbf{e} + \mathbf{K}_d \dot{\mathbf{e}}, \quad (3)$$

where $\mathbf{F}_{\text{des}}(\mathbf{P})$ is the controlled magnetic force which can be realized using (2) through the pseudoinverse of the actuation matrix, and by setting $\mathbf{F}_{\text{des}}(\mathbf{P}) = \mathbf{F}(\mathbf{P})$. Further, \mathbf{e} and $\dot{\mathbf{e}}$ are the position and velocity tracking errors, respectively, and are given by

$$\mathbf{e} = \mathbf{P}_{\text{ref}} - \mathbf{P} \quad \text{and} \quad \dot{\mathbf{e}} = \dot{\mathbf{P}}_{\text{ref}} - \dot{\mathbf{P}}, \quad (4)$$

where \mathbf{P}_{ref} and $\dot{\mathbf{P}}_{\text{ref}}$ are the reference position and velocity, respectively. Finally, in (3), \mathbf{K}_p and \mathbf{K}_d are diagonal positive-definite gain matrices. In order to implement the control law (3), the pseudoinverse of the actuation matrix ($\Lambda(\mathbf{m}, \mathbf{P})$) is calculated based on the magnetic dipole moment and position of the magnetic object [20].

III. EXPERIMENTAL RESULTS

Motion control experiments are done using a magnetic system, shown in Fig. 1. This system consists of four orthogonally oriented air-core electromagnets ($n=4$). These electromagnets can surround a reservoir, a capillary tube and a petri dish to incubate water, growth media and hydrogen peroxide solution for the cluster of nanoparticles, MTB and microjets, respectively. Our closed-loop control system allows for the positioning of the magnetic objects within the vicinity of a reference position. Fig. 2 shows a representative closed-loop motion control result of the cluster. We observe that the cluster is positioned at an average velocity of $195 \mu\text{m/s}$ and within a region-of-convergence (ROC) of $145 \mu\text{m}$. Magnetotactic bacteria (strain *Magnetospirillum magneticum* AMB-1) are controlled inside a capillary tube with inner thickness and width of 0.2 mm and 2 mm , respectively. Our closed-loop control system positions an MTB at an average velocity of $19 \mu\text{m/s}$ and within a ROC of

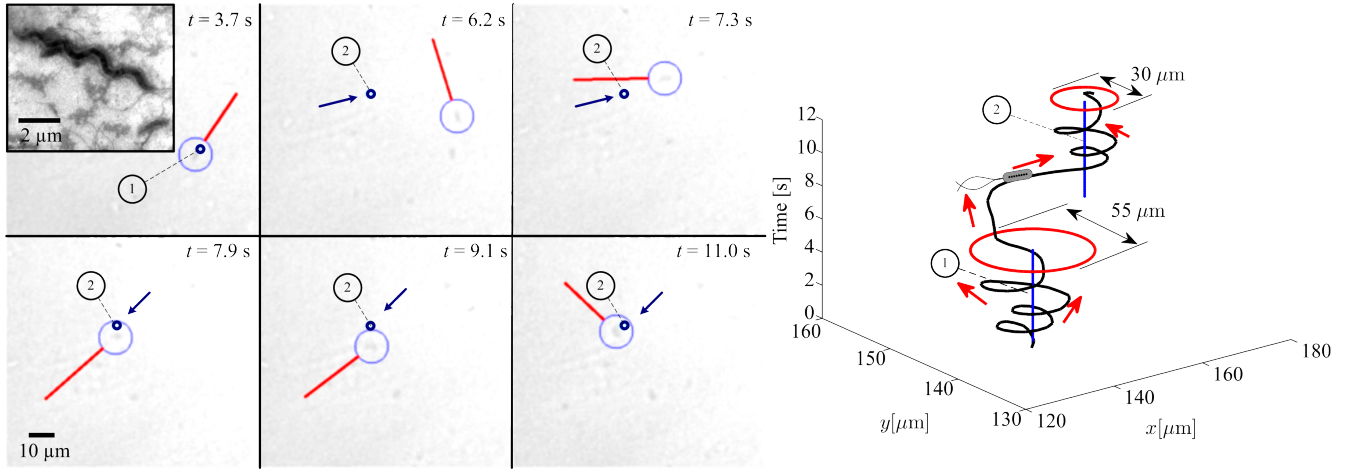


Fig. 3. Closed-loop motion control of a magnetotactic bacterium (MTB), strain *Magnetospirillum magneticum* AMB-1, under the influence of the controlled magnetic fields. An MTB moves towards the reference positions (small blue circles) along the magnetic field lines generated using the control law (3). MTB moves using its helical flagella. In this representative experiment, an MTB moves at an average velocity of $19 \mu\text{m/s}$, and is positioned within the vicinity of two reference positions (represented by the solid blue lines in the right image). The closed-loop control system achieves a region-of-convergence of $55 \mu\text{m}$ and $30 \mu\text{m}$ in diameter for the first and second reference positions, respectively. The entries of the diagonal matrices (\mathbf{K}_p and \mathbf{K}_d) are 15 s^{-2} and 15.5 s^{-1} , respectively. The large blue circle is assigned by our feature tracking software [13] and represents the position of the MTB, whereas the red line represents its velocity vector. The inset shows a Scanning Electron Microscopy image of the spiral membrane of the MTB.

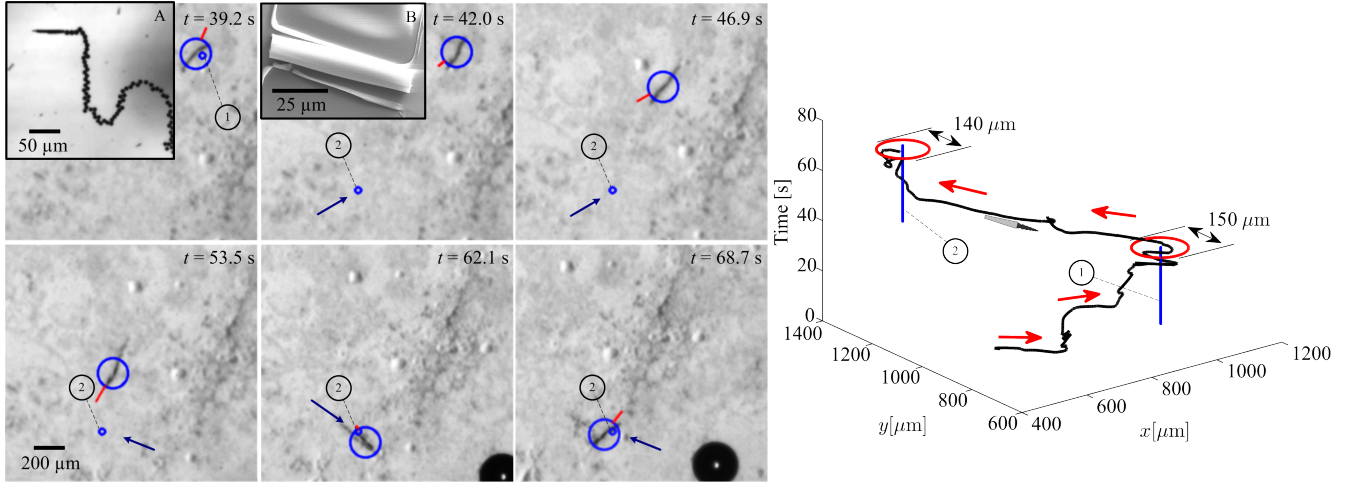


Fig. 4. Closed-loop motion control of a self-propelled microjet under the influence of the controlled magnetic fields. The microjet moves towards the reference positions (small blue circles) along the magnetic field lines generated using the control law (3). The microjet moves along the field lines using the propulsion force generated by the ejecting oxygen bubbles from its end. In this representative experiment, the microjet moves at an average velocity of $62 \mu\text{m/s}$, and is positioned within the vicinity of two reference positions (represented by the solid blue lines in the right image). The closed-loop control system achieves a region-of-convergence of $150 \mu\text{m}$ and $140 \mu\text{m}$ in diameter for the first and second reference positions, respectively. The entries of the diagonal matrices (\mathbf{K}_p and \mathbf{K}_d) are 15 s^{-2} and 5 s^{-1} , respectively. This experiment is done using 1 ml of hydrogen peroxide solution and Triton X at concentrations of 5% and 5%, respectively. The catalytic reaction is observed after the addition of $100 \mu\text{l}$ of hydrogen peroxide solution at concentration of 15%. Inset A shows the ejecting oxygen bubbles from one end of the microjet. Inset B shows a Scanning Electron Microscopy image of a microjet fixed to its substrate. The large blue circle is assigned by our feature tracking software [13] and represents the position of the microjet, whereas the red line represents its velocity vector.

$55 \mu\text{m}$ and $30 \mu\text{m}$ for the first and second reference positions, respectively (Fig. 3). Control of the microjet is done using 1 ml of hydrogen peroxide solution and Triton X at concentrations of 5% and 5%, respectively. Our control system positions the microjet at an average velocity of $62 \mu\text{m/s}$ and within a ROC of $150 \mu\text{m}$ and $140 \mu\text{m}$ for the first and second reference positions, respectively (Fig. 4). All experiments are repeated 10 times, and we observe consistent results. Further, a minimum input control system is implemented on a three-dimensional (3D) electromagnetic setup, and we observe an average speed and the maximum root mean square (RMS) position tracking

errors of the controlled microparticle to be $198 \mu\text{m/s}$ and $104 \mu\text{m}$, respectively. The comparison with a proportional-integral (PI) control system shows that the minimum input control achieves 11% decrease in the current input.

IV. CONCLUSIONS AND FUTURE WORK

Point-to-point motion control of magnetic objects is demonstrated using a magnetic-based proportional-derivative control system. A cluster of iron oxide nanoparticles is positioned within the vicinity of a reference position (average ROC is $132 \mu\text{m}$) at an average velocity of $190 \mu\text{m/s}$ (~ 2 body length

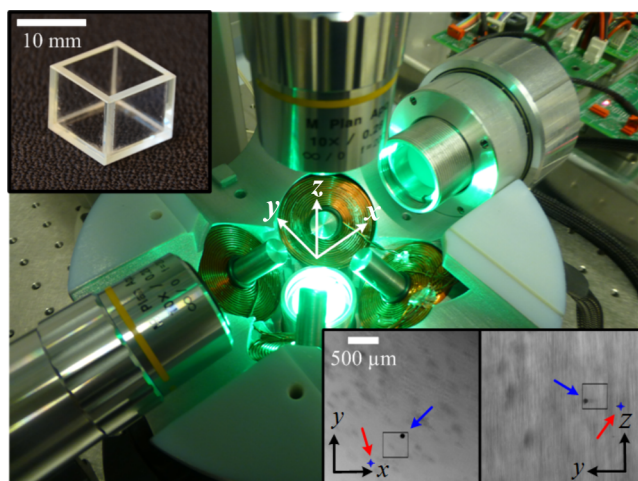


Fig. 5. Magnetic system for the closed-loop motion control of paramagnetic microparticles (PLAParticles-M-redF-plain from Micromod Partikeltechnologie GmbH, Rostock-Warnemuende, Germany) in three-dimensional (3D) space. The magnetic system consists of 8 iron-core electromagnets that surrounds a water reservoir, shown at the upper-left inset. The workspace of the magnetic system is $10 \times 10 \times 10 \text{ mm}^3$. Our magnetic system provides autofocusing of the microparticles using two microscopic vision systems mounted on two linear motion stages (not shown). The magnetic system consists of upper and lower orthogonal sets of electromagnets. In the lower set, the electromagnets have 45 degrees orientation with respect to each other and with respect to the horizontal plane. In the upper set (not shown), electromagnets have 45 degrees and 90 degrees orientation with respect to the horizontal plane and the lower set, respectively. The bottom-right inset shows a microparticle, with an average diameter of $100 \mu\text{m}$, moving towards a reference position in 3D space under the influence of the controlled magnetic fields generated using the minimum input control. The black box is assigned using our feature tracking software, whereas the blue and red arrows indicate the microparticle and the reference position, respectively [21].

per second) under the influence of the controlled magnetic field gradients. Self-propelled MTB and microjets are controlled at an average velocity of $28 \mu\text{m/s}$ and $90 \mu\text{m/s}$ (~ 5 and ~ 2 body length per second), and positioned within an average ROC of $40 \mu\text{m}$ and $235 \mu\text{m}$, respectively. Further, we investigate a magnetic-based minimum input control system to position paramagnetic microparticles in 3D space. The minimum input control system achieves point-to-point motion control, while minimizing the current at each of the electromagnets of a magnetic system. The closed-loop control characteristics of the magnetic-based minimum input control are compared to the characteristics of a PI controller.

As part of future work, our magnetic system will be integrated with an ultrasound-based imaging modality. In addition, our magnetic system will be redesigned to control magnetic objects in the three-dimensional space with varying fluid flow.

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