Magnetic Control of Potential Microrobotic Drug Delivery Systems: Nanoparticles, Magnetotactic Bacteria and Self-Propelled Microjets

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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 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 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 nanoparticles, 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 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. MODELING AND 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.

A. Modeling of the Magnetic Objects

Our magnetic objects experience the following magnetic force \( \mathbf{F}(\mathbf{P}) \in \mathbb{R}^{3 \times 1} \) and magnetic torque \( \mathbf{T}(\mathbf{P}) \in \mathbb{R}^{3 \times 1} \):

\[
\mathbf{F}(\mathbf{P}) = \nabla (\mathbf{m}(\mathbf{P}) \cdot \mathbf{B}(\mathbf{P})) \quad \text{and} \quad \mathbf{T}(\mathbf{P}) = \mathbf{m}(\mathbf{P}) \times \mathbf{B}(\mathbf{P}),
\]

where \( \mathbf{m}(\mathbf{P}) \in \mathbb{R}^{3 \times 1} \) and \( \mathbf{B}(\mathbf{P}) \in \mathbb{R}^{3 \times 1} \) are the induced magnetic dipole moment of the magnetic objects and the magnetic field at point \( \mathbf{P} \in \mathbb{R}^{3 \times 1} \), respectively. The magnetic dipole moment of the cluster of nanoparticles allows it to align along the external field lines. The nanocrystal chain enveloped in the membrane of the magnetotactic bacteria provides a magnetic dipole moment which allows them to align along the field lines. Similarly, our self-propelled microjets have tubular structure with layers of platinum, titanium and iron [16]. These layers provide a magnetic dipole moment which allows the microjets to orient along the external magnetic field lines. The cluster of nanoparticles experiences the following drag force \( \mathbf{F}_{\text{dc}}(\mathbf{P}) \in \mathbb{R}^{3 \times 1} \) and drag torque \( \mathbf{T}_{\text{dc}}(\mathbf{\Omega}) \):

\[
\mathbf{F}_{\text{dc}}(\mathbf{P}) = F_{\text{cl}} \eta \dot{\mathbf{P}} \quad \text{and} \quad \mathbf{T}_{\text{dc}}(\mathbf{\Omega}) = F_{\text{cr}} \eta \mathbf{\Omega},
\]

In (2), \( F_{\text{cl}} \) and \( F_{\text{cr}} \) are the linear and rotational shape factors of the cluster, respectively. Further, \( \dot{\mathbf{P}}, \mathbf{\Omega}, \eta \) are the linear and angular velocity of the cluster, and the dynamic viscosity of the fluid (water), respectively. Magnetotactic bacteria and self-propelled microjets also experience the following drag force \( \mathbf{F}_{\text{d}}(\dot{\mathbf{P}}) \) and drag torque \( \mathbf{T}_{\text{d}}(\mathbf{\Omega}) \):

\[
\mathbf{F}_{\text{d}}(\dot{\mathbf{P}}) = \gamma \dot{\mathbf{P}} \quad \text{and} \quad \mathbf{T}_{\text{d}}(\mathbf{\Omega}) = \alpha \mathbf{\Omega},
\]

where \( \gamma \) is the linear drag coefficient and is given by [17]

\[
\gamma = 2\pi \eta l \left[ \ln \left( \frac{2l}{d} \right) - 0.5 \right]^{-1},
\]

where \( l \) and \( d \) are the length and diameter of the MTB and microjet, respectively. In (3), \( \alpha \) is the rotational drag coefficient and is given by [18]

\[
\alpha = \frac{\pi \eta l^3}{3} \left[ \ln \left( \frac{l}{d} \right) + 0.92 \left( \frac{d}{l} \right)^2 - 0.662 \right]^{-1}.
\]

We assume that the microjet has a cylindrical morphology, and its linear and rotational drag coefficients can be modeled using (4) and (5), respectively. A magnetotactic bacterium (MTB) and a microjet also experience self-propulsion forces. These forces are generated by the rotation of the helical flagella [19], and the ejecting oxygen bubbles due to the catalytic decomposition of the hydrogen peroxide solution by the platinum layer of the microjet [8], [16]. Our magnetic system [13] is used to generate controlled magnetic fields to realize the point-to-point motion control.

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 (8). 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 \( \text{s}^{-2} \) and 0.5 \( \text{s}^{-1} \), 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.
B. Control System Design

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]

\[
\mathbf{B}(\mathbf{P}) = \sum_{i=1}^{n} \mathbf{B}_i(\mathbf{P}) = \sum_{i=1}^{n} \tilde{\mathbf{B}}_i(\mathbf{P}) I_i = \mathbf{B}(\mathbf{P}), \tag{6}
\]

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 \( \mathbf{B}_i(\mathbf{P}) \). Substituting (6) in the magnetic force equation (1) yields the following magnetic force-current map:

\[
\mathbf{F}(\mathbf{P}) = (\mathbf{m}(\mathbf{P}) \cdot \nabla) \tilde{\mathbf{B}}(\mathbf{P}) \mathbf{I} = \Lambda(\mathbf{m}, \mathbf{P}) \mathbf{I}, \tag{7}
\]

In (7), \( \Lambda(\mathbf{m}, \mathbf{P}) \in \mathbb{R}^{3 \times n} \) is the actuation matrix which maps the input current to the magnetic force [12]. Further, we devise the following proportional-derivative control law [15]

\[
\mathbf{F}_{\text{des}}(\mathbf{P}) = \mathbf{K}_p \mathbf{e} + \mathbf{K}_d \dot{\mathbf{e}}, \tag{8}
\]

where \( \mathbf{F}_{\text{des}}(\mathbf{P}) \) is the controlled magnetic force which can be realized using (7) 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

\[
\mathbf{e} = \mathbf{P}_{\text{ref}} - \mathbf{P} \quad \text{and} \quad \dot{\mathbf{e}} = \dot{\mathbf{P}}_{\text{ref}} - \dot{\mathbf{P}}, \tag{9}
\]

where \( \mathbf{P}_{\text{ref}} \) and \( \dot{\mathbf{P}}_{\text{ref}} \) are the reference position and velocity, respectively. Finally, in (8), \( \mathbf{K}_p \) and \( \mathbf{K}_d \) are diagonal positive-definite gain matrices. In order to implement the control law (8), 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 [19].

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 \textit{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 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.

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 \( \mu \text{m/s} \) (\( \sim \)2 body length per second) under the influence of the controlled
magnetic field gradients. Self-propelled MTB and microjets are controlled at an average velocity of 28 μm/s and 90 μm/s (~5 and ~2 body length per second), and positioned within an average ROC of 40 μm and 235 μm, respectively.

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.

REFERENCES


