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In Vitro Navigation of a Magnetic Sphere using a Model Predictive Controller for Neurovascular Targeted Drug Delivery Applications

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INTRODUCTION

The conventional systemic administration of drugs has been utilized in medicine for centuries. However, systemic drug administration limits the kind of drugs and the minimally required doses for treatment inside the human body. Furthermore, directly delivering pharmaceuticals to the location inside the body where they are needed would increase their efficacy while limiting side effects and opening new possibilities in drug development [1]. In the following, this direct transport will be referred to as Targeted Drug Delivery (TDD).

Navigation inside the human body is challenging, and several factors, such as biocompatibility, controllability, and scalability, need to be considered. Magnetic navigation is a promising technique for enabling TDD inside the human body for several reasons [2]:

- The magnetic fields and gradients in the range required for magnetic navigation are considered biocompatible.
- Magnetic fields and gradients are highly controllable.
- Magnetic fields and gradients offer good scaling properties and are thus applicable for small-scaled objects fitting into the human vasculature.

Some research attention has been directed towards in-silico simulations of the forces and flows inside the vasculature [3]. However, due to non-linear forces inside blood vessels, pulsatile flows, and the elastic nature of the human vasculature, an experimental platform is required to verify and improve navigation strategies.

In this work, we focused on magnetic navigation inside a two-dimensional (2D) model of the main vasculature of the human brain (namely the circle of Willis), see Figure 1. We manipulated a small-scaled untethered magnetic sphere inside an electromagnetic navigation system (eMNS), consisting of eight electromagnets to show remote magnetic navigation. Control of untethered devices inside a blood vessel is a challenging task for many reasons, including non-linear flows, friction forces, and the presence of a non-Newtonian fluid, i.e., blood. Using a model predictive controller (MPC), we were able to show in-flow navigation and a high degree of controllability in reaching the target bifurcation.

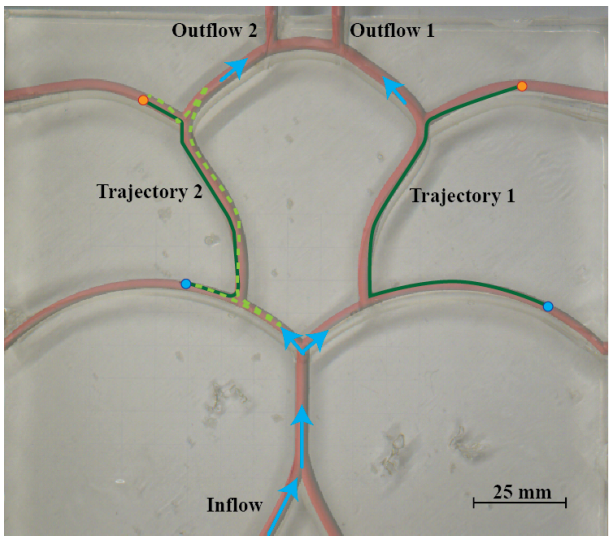

Fig. 1 The camera image from the vessel-like in vitro model with an overlay of the CAD. The blue circles represent the starting point and the orange ones the target points for the two trajectories. The solid green lines represent the optimal path. The dashed green line is an example path followed by the magnetic sphere during an experiment for the second trajectory. The direction of the flow is indicated by the light blue arrows.

MATERIALS AND METHODS

To find the optimal control inputs an MPC was developed that loads the geometric model, gets the actual position of the magnetic sphere from a camera, takes into account the forces of the eMNS and gravity and calculates the trajectory for a certain time horizon for different magnetic fields [4]. The MPC applies the field in a direction for which the estimated position at the end of the time horizon is the closest to the desired target position (see Fig. 2). The MPC can be manually tuned by setting the length of the time horizon, the magnitude of the magnetic field and gradient, and the number of directions in which to simulate a magnetic gradient.

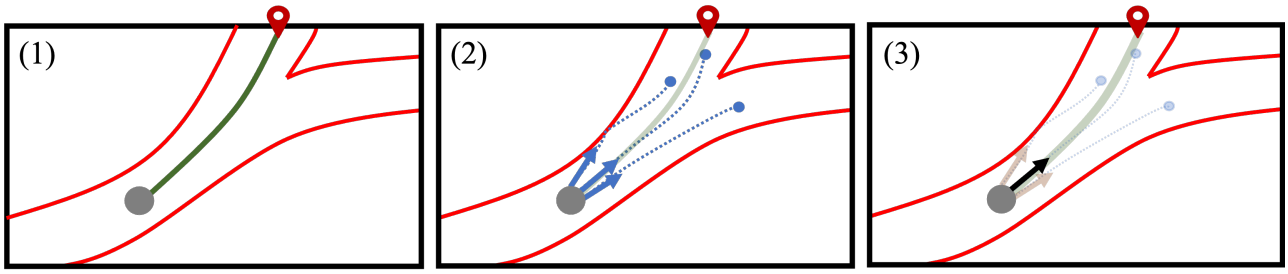

Fig. 2 The fuctioning of the MPC: (1) Find optimal path to target. (2) Simulate trajectory for different directions of gradients. (3) Chose gradient direction for which the simulated end position has the smallest distance to the target.

In Figure 1 the vessel-like in vitro model is depicted. It is a 20 cm × 20 cm 2D silicone model that captures the main vessels of the circle of Willis and has similar dimensions. It was fabricated by 3D-printing the geometry with polyvinyl alcohol (PVA) and placing it inside a container and pouring a silicon mix into the container. After curing the 3D print could be dissolved with water, leaving a vessel structure with a diameter of 4 mm as previously designed in the silicon block. For the experiments a spherical Neodymium magnet with diameter of 1.5 mm and a remanence magnetization of 1.17 T was used. The magnetic sphere was tracked on the camera image using a background subtraction algorithm from the open source computer vision library [5].

RESULTS

The model shown in Figure 1 has eight openings. For the following experiments six of them were sealed and the other two were chosen to be the inflow and outflow point respectively. Water flow was created using a peristatic pump with a constant flow rate of 0.13 m/s. The MPC was evaluated by measuring the success rate of navigating the magnetic sphere from a position along the streamline to a branch that was not in the main direction of the flow.

In Figure 1 the point of inflow and outflow for the two trajectories are labeled as well as the initial starting points and targets. The experiment for both trajectories were repeated five times. In each iteration the MPC could successfully navigate the magnetic sphere to the desired targets. Seven out of ten times it did so with less than four control inputs (i.e., number of times the magnetic gradient was changed, see Table I). Except for two iterations the navigation took less than 40 seconds. In 80% of the time the magnetic sphere had to be controlled against the flow for a short distance (see Fig. 1). However, switching start and target position and using the MPC for the reverse navigation was unsuccessful.

TABLE I Mean and standard deviation of the number of control inputs and the navigation time

	Control inputs mean (std)	**Time [s]** mean (std)
Trajectory 1	3.2 (1.6)	42.4 (27.8)
Trajectory 2	3.6 (0.9)	24.7 (6.0)

DISCUSSION

In this work the performance of an MPC, which took into account the force of an eMNS and gravity to model the trajectory of an untethered magnetic sphere, was tested in a 2D vasculature in vitro model. It was able to navigate to the intended branch of a bifurcation, despite the flow of water dragging it away to the other branch.

The described experiment gave valuable insight into the dynamics of a small object in a confined space and actuated with an eMNS. For example, the duration of the navigation task suggest that for faster flow the MPC needs to increase the rate at which new control inputs are given to the eMNS. When expanding to a 3D model the MPC can be adapted quickly. However, in that case the tracking becomes more challenging. It has to be evaluated if navigation is still possible when using pulsatile flow with higher flow rate, i.e., similar to the fluiddynamic conditions inside the blood vessel.

In the future, we plan to increase the complexity of the vasculature model further, enable feedback control with angiography data and further improve our control algorithm to enable TDD via magnetic navigation in a clinical setting.

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