MAGNETIC DRUG DELIVERY SYSTEM

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ABSTRACT

The unfocused nature of chemotherapy limits its effectiveness and produces adverse, systemic side effects. Research on focusing the treatment on specific regions of the body has identified magnetic drug delivery as a potential solution. Through dynamic magnetic actuation, researchers have been able to direct magnetic nanoparticles to and hold them at a target location in vitro in still water. However, a system for doing so in the presence of an oncoming flow has yet to be tested. This paper details the design of an experimental system to investigate the feasibility of two-dimensional magnetic nanoparticle control in the presence of flow. A flow rig was designed to generate flow with velocities of 1 - 2 cm/s in a channel. An experimental control system was developed to move a nanoparticle cluster in a horizontal plane within this channel by tracking the cluster's position and applying PID control to a three degree of freedom actuation mechanism. Initial testing of the control system indicates that it could be made suitable for the purpose through certain design modifications and fine tuning.

INTRODUCTION

One of the most popular treatment options for cancer is chemotherapy, which involves the administration of drugs that destroy cancer cells by damaging their DNA. An anti-cancer drug is typically injected intravenously and is circulated throughout the whole body. As a result, cells far away from the tumor location end up being damaged or killed by the drug. While this may be desirable in the case of a cancer that has spread to other parts of the body, it typically leads to the death or slowed growth of many healthy cells. Attempts to quantify this spillover effect have shown that it is typical for less than 0.1% of the anti-cancer drugs used in chemotherapy sessions to be taken up by the cancer cells and the other 99.9% to be taken up by healthy cells [1]. These internal changes on the cellular level manifest on the macro level as a variety of adverse physical side effects such as hair loss, mouth sores, nausea, and prolonged fatigue.

The unfocused nature of chemotherapy has spurred a growing body of research dedicated to the development of drug delivery systems that can concentrate treatment. One prominent method that is being investigated involves the use of magnetic nanoparticles as carrier agents. The metal oxide nanoparticles, which are on the scale of 1 to 100 nm in diameter, can be coated in biological molecules in a process referred to as functionalization. The result is similar to Fig. 1, which depicts a nanoparticle cluster (black core) covered with a silica shell (gray layer) that allows for strong covalent bonds with functionalization molecules. Nanoparticles functionalized with an anti-cancer drug can be directed to and held at a tumor site through the application of a magnetic field. As a nanoparticle is held in place at the target

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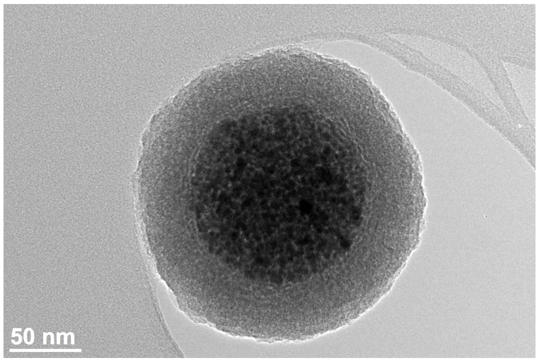

FIGURE 1. Microscopic view of a magnetic nanoparticle cluster [2].

location, the biological molecules initially attached to its surface passively diffuse into the tumor. In this manner, the chemotherapy treatment is focused on the tumor cells and not the surrounding healthy cells.

Past research has demonstrated the feasibility of using magnetic nanoparticles as drug carriers. In one case, researchers were able to focus anti-cancer drugs on inoperable tumors near the skin surface in phase I human clinical trials using a magnetic fluid and a single permanent magnet [3]. In another case, researchers were able to magnetically push nanoparticles into a rat inner ear at the human head working distance of 4 cm also using permanent magnets [4]. At such shallow working distances, researchers have generally been able to manipulate nanoparticles using stationary external permanent magnets with a high degree of accuracy. This fact is attributable to the relative simplicity of the models.

In applications where the nanoparticles are required to travel through the bloodstream to a target location deeper than 5 cm below skin depth, the complexity of the models increases significantly and stationary external permanent magnets become less feasible. On these scales, fluid drag, gravity, and buoyancy forces are significant and also have to be factored into the model. Inquiry into the physics on these larger scales has led one group to show through COMSOL simulations that time-varying magnetic fields are capable of focusing nanoparticles at greater working distances [5]. The dynamic magnetic actuation necessary to produce time-varying fields has been experimented with and was previously used to achieve precise control of microrobots, micron-sized magnetic beads, and ferrofluid clusters in vitro [1, 6-8]. Researchers have been able to achieve precise particle targeting using optimized feedback control in environments without flow. However, no major studies have been conducted in systems with flow.

In this paper, we investigate the feasibility of two-dimensional control of magnetic nanoparticles in the presence of an oncoming flow. An experimental setup was created to move and hold a nanoparticle cluster at a target location within a flow channel. A flow rig was fabricated to facilitate solvent fluid flows

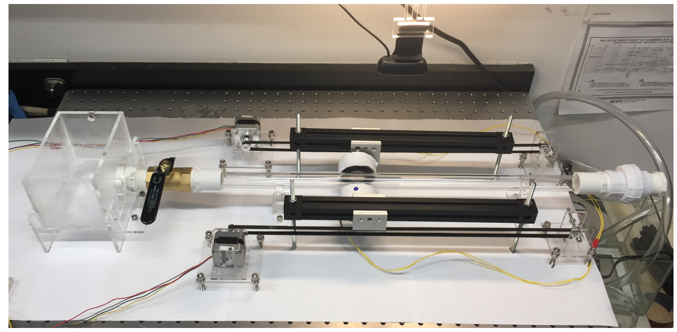

FIGURE 2. The experimental system design.

with linear velocities in the range of 1 to 2 cm/s down the flow channel. A three degree of freedom actuation system comprised of electromagnets and a rail system was assembled to output the desired time-varying magnetic field. A sensing component was implemented to track the position of the ferrofluid cluster and the electromagnets. Finally, a controls component was developed to determine and communicate the necessary control effort to the actuation system.

METHODOLOGY

The completed experimental system is pictured in Fig. 2. It is comprised of flow generation, actuation, position tracking, and feedback control subsystems. The following sections detail the design of each subsystem as well as other important design choices.

Fluid Selection

The experimental control system presented in this paper and the underlying model are based on several assumptions. First, it is assumed that the ferrofluid cluster being controlled and the surrounding solvent fluid are immiscible, meaning that they do not form a homogeneous mixture when combined. An immiscible combination is optimal for particle tracking and control, as the ferrofluid cluster will not break apart when subject to a magnetic force. In realistic applications, the magnetic nanoparticles and the surrounding blood would be miscible. However, since the particles in the bloodstream would also be present in higher concentrations than the ferrofluid used in this experiment, it is possible to approximate their behavior subject to magnetic fields using an immiscible fluid combination in vitro. Next, it is assumed that the ferrofluid droplet does not experience any deformation. This assumption is based on the theoretical dominance of surface tension over the other external forces, and it allows for the analytical treatment of the ferrofluid as a rigid body. Finally, it is assumed that the ferrofluid droplet will remain suspended within the solvent fluid and that the only movement it will experience will be within a two-dimensional horizontal plane.

The assumptions set forth require a careful selection of the ferrofluid and the solvent fluid, as certain combinations will produce behavior that contradicts what was assumed. As an example, the selected ferrofluid must not be soluble in the solvent fluid in order to satisfy the immiscibility assumption. Additionally, the ferrofluid must be density matched with the solvent fluid, or else the ferrofluid droplet will not remain suspended. After considering the possible options and experimenting with various combinations, it was determined that a combination of the EMG-905 ferrofluid in a water and glucose mixture was the optimal choice. EMG-905 is oil soluble and it remains clumped when placed in water, which satisfies the immiscibility and deformation assumptions. The water and glucose mixture is optimal for satisfying the density match requirement, as the concentration of glucose can be varied to manipulate the overall density of the mixture. Thus, the suspension assumption is satisfied. One other advantage of this particular combination is that the water-based mixture serving as the solvent fluid is compatible with most pumps, which lifts potential design constraints on the recirculation system.

Flow Generation

A flow rig was required to facilitate the flow of the solvent fluid down a channel. It was necessary for this rig to produce and maintain flows with velocities in the range of 1 to 2 cm/s. Additionally, it was desirable for the rig to have some degree of modularity, particularly in regard to the size of the flow channel. Varying the size of the channel would alter the flow regime, and thus allow for testing of the control system in different regimes. The final flow rig design fulfills both requirements. It consists of an elevated acrylic header tank with a lateral aperture connected to an acrylic pipe, which serves as the flow channel, through a ball valve. A PVC pipe fitting inserted into the aperture is used to attach the header tank to the ball valve. On the other end, a similar pipe fitting glued onto the end of the acrylic pipe is used to complete the connection. The header tank and the complete connection between it and the flow channel is displayed in Fig. 3. The end of the acrylic pipe is placed above a reservoir. A sump pump is located at the bottom of the reservoir with a hose around its outlet that links it back to the header tank.

The velocity of the fluid in the flow channel is primarily a function of the water level in the header tank and the degree to which the ball valve is open. With knowledge of the desired velocity range, it was possible to calculate the minimum necessary tank height using Bernoulli's Equation. Although a flow velocity range of 1 to 2 cm/s was the design requirement, a completely filled header tank is capable of outputting flow with higher velocities. If the control of particles at lower flow velocities is feasible, this design choice would allow the same header tank to be used to test the limits of the control system.

Regardless, a completely filled header tank can be made to output flow in the desired velocity range. This is done through

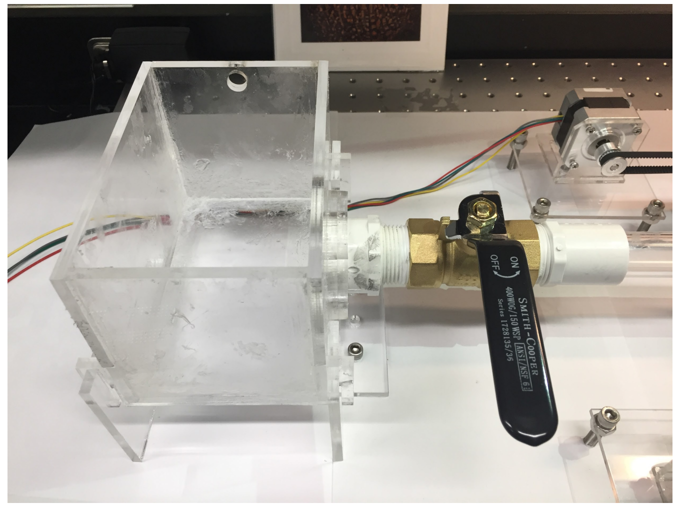

FIGURE 3. The header tank and ball valve.

flow regulation via the ball valve. By twisting the handle of the ball valve to some intermediate position, the gate inside can be made only partially open. In this position, the gate partially restricts the flow and thereby throttles the flow velocity. Once the ball valve is set to the position that produces the desired flow, it does not have to be operated again at any point throughout the experiment. This is due to the assumption that the water level in the tank will remain roughly constant. The sump pump in the reservoir recirculates any water leaving the flow channel back to the header tank, thus keeping the header tank water level near the initial value.

The flow rig design also satisfies the modularity requirement. The acrylic pipe that functions as the flow channel was acquired in multiple sizes. Each of the pipes had a PVC adapter glued to one end, converting the connection to that which was required for the ball valve. The end result is a set of flow channels of various sizes that can be selected from to change the limits of the cross-sectional plane.

Actuation System

A multiple degree of freedom actuation system was required to generate the time-varying magnetic fields that are needed to focus magnetic nanoparticles in the presence of flow. To move the ferrofluid droplet within the two-dimensional plane in the flow channel, it was necessary to have at least two electromagnets. The electromagnets were chosen over a combination of permanent magnets because their magnetic field strength can be modulated by simply altering the supplied current. Multiple electromagnets were necessary because a single electromagnet would not be able to push a ferrofluid cluster to the opposite end of the plane. In the case that the ferrofluid droplet would get swept down the channel out of the reach of the electromagnets, a mechanism would be necessary to move them down the length of

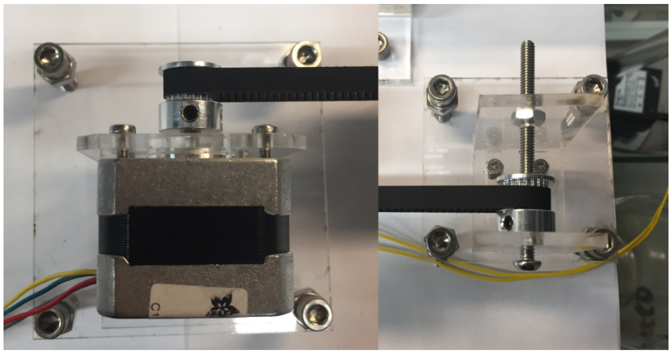

FIGURE 4. The timing pulley setup.

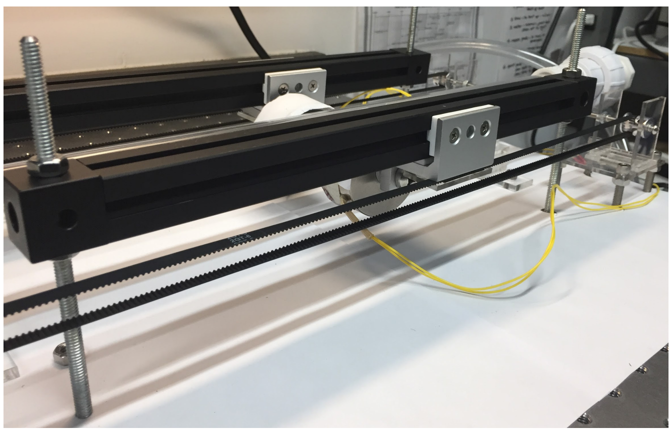

FIGURE 5. The linear rail system.

the acrylic pipe so they can pull the droplet back toward the target location. Finally, it was important for the actuation system to be modular enough to allow for the centering of electromagnets with the varying diameter pipes.

The actuation system design consists of an electromagnet mounted to a carriage on a linear rail on either side of the flow channel. The electromagnet, model number EM237-12-212, is rated at an operating voltage and current of 12 V and 0.46 A respectively. It is specified to have a lifting force of 190 lbs (86.2 kg), meaning that it can hold a 0.25 in (0.635 cm) thick plate of that weight at its surface. The magnetic field was measured at the electromagnet's rated voltage and current using a Gaussmeter. The highest magnetic field strength reading was found in the center at the electromagnet's surface and it was measured to be approximately 25 mT. This number represents the highest achievable magnetic flux density, as current control of the electromagnet will generally produce lower values.

The current supplied to each electromagnet can be varied individually, thus resulting in two degrees of freedom. A third degree of freedom is present in the system in the form of a linear rail that allows movement along the axis running parallel to the flow channel. Movement of the two magnets, which occurs simultaneously, is driven by a stepper motor on each side. The stepper motor is a NEMA-17 unit that runs at an operating voltage and current of 12 V and 350 mA respectively and has a resolution of 200 steps per revolution. The torque produced by the NEMA-17 has been found to satisfy the calculated torque requirement for moving the electromagnets along the rails. Care was taken in the positioning of the motors to prevent the ferrous components on the inside from affecting the magnetic field produced by the electromagnets.

A timing pulley is attached to the shaft of the NEMA-17 stepper motor. As depicted in Fig. 4, a timing belt is wrapped around this pulley as well as around another timing pulley that is mounted further along the flow channel. The teeth of one portion of the timing belt are interlocked with the teeth of another timing belt strip attached to a carriage on an elevated rail. The electromagnet is mounted onto the carriage and so it therefore moves with the carriage as the carriage slides down the rail. This is portrayed in Fig. 5, which shows the carriage with the magnet attached to the rail. When a current is supplied to the stepper motor, the shaft turns in one of the directions based on the polarity of the applied voltage. As the shaft turns, the attached timing pulley pulls the timing belt, which in turn pulls the carriage along the rail. This process is responsible for the linear movement of the electromagnets along an axis parallel to the flow channel.

The actuation system design also satisfies the modularity requirement. The stepper motors, the second set of timing pulleys, and the linear rails are all adjustable in height. The stepper motors and the timing pulleys are each mounted to an acrylic base. The elevation of each acrylic base can be adjusted using a threaded rod and nut system. A similar system is implemented in each linear rail. The entire actuation mechanism can thus be shifted upward or downward, providing compatibility for a range of flow channel diameters.

Position Tracking

A position sensing system was required to make feedback control of the magnetic nanoparticle cluster possible, as feedback control requires knowledge of the cluster's location and velocity. Hence, it was necessary for the sensing system to identify the ferrofluid droplet in the flow channel, take discrete measurements of its position, and calculate the velocity based on the position measurements. The measurements had to be taken and used as feedback at a high enough frequency so that the cluster does not get swept down the channel before the electromagnets can react. Since the experimental control system would also be used to actuate the position of the electromagnets, it was necessary to extend the sensing to the magnets as well. Finally, it was desirable to implement a pathing feature that would allow the user to trace out a path for the cluster to follow, and thus simulate the targeted delivery of functionalized nanoparticles to a tumor site.

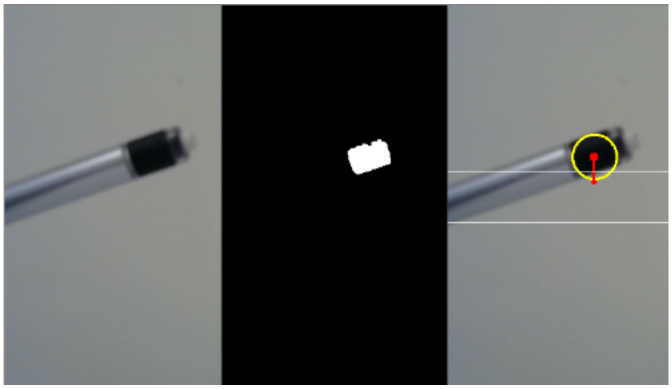

FIGURE 6. The conversion of a colored image to a binary image, and the identification of the object position from the binary image.

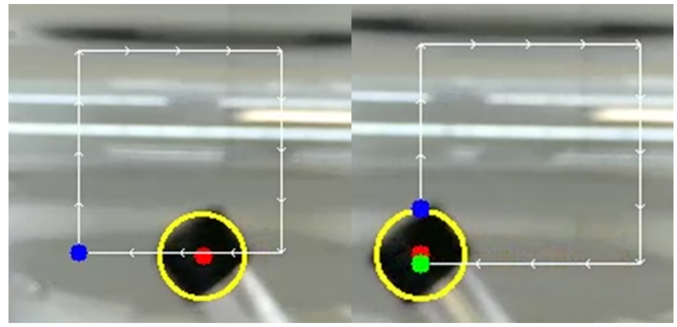

FIGURE 7. The Python program's pathing feature. As a reference point (blue) is reached by the tracked object (red), a new reference point is uploaded.

The position tracking is accomplished using a live video camera feed and image processing. A video feed of the flow channel and the electromagnets adjacent to it is recorded by a Logitech C270 webcam. This particular camera model outputs video at a resolution of 720p, which was deemed sufficient for the purpose of particle tracking. The resolution is high enough to distinguish the cluster but not excessively high so as to cause undesirable increases in processing time. The webcam continuously uploads the footage frame by frame at a rate of approximately 1 frame every 0.05 seconds to a Python script running on a laptop for image processing.

The image processing is carried out using functions from the open-source computer vision library OpenCV in Python 2.7. Each frame imported into the program is analyzed for groupings of pixels within a user-specified color range. This range is configured in the script in terms of the HSV (hue, saturation, and value) color space. If a pixel is identified to be within the specified color range, it is assigned the binary value of 1. Pixels outside of the color range are assigned a 0. In this manner, a colored image is reduced to a binary image. A Gaussian blur, which is a form of post-processing, is applied to the resulting image in order to remove some of the noise present.

The finalized image, which essentially consists of one or more contours, is filtered by size. The largest grouping that is identified is assumed to be the object being tracked. The coordinates (in units of pixels) of the center of this object are found and transformed into physical units using a scale factor specified by the user. This factor is dependent on the position of the webcam relative to the flow channel. It can be acquired by holding a ruler at the distance of the tracked object and measuring the webcam's field of view at that distance. Using the scale factor to transform the coordinates of the ferrofluid cluster center to physical units yields the position of the cluster at the point in time associated with the frame. The particle velocity at that point can then be determined by finding the change in location of the cluster from the previous frame and divding by the change in time between the two frames. The particle location in the previous frame and the timestamp of that frame, which are both stored in memory, are accessed, input into the velocity calculation, and used to determine the components of a velocity vector emanating from the particle's centroid. The complete process for finding the position and velocity is summarized in Fig. 6, which is a screenshot from the Python program,

The process of measuring the position and calculating the velocity is carried out for each frame input into the Python program for both the ferrofluid droplet and the electromagnets. The program was configured with the appropriate color range to identify and track the black ferrofluid. To identify the electromagnets, a separate color range was needed. Consequently, the camera-facing side of one of the magnets was marked with a blue spot, and the program was configured to identify objects in the blue color range as the magnets. This allows the program to track the electromagnets alongside the nanoparticle cluster, thus making a three degree of freedom control system possible.

Once the Python program successfully determines the current position and velocity of the ferrofluid droplet and the magnets, it carries out error calculations. In this application, error is defined as the deviation of the particle cluster position from the reference position (target location). Knowledge of the error is necessary for feedback control to be implemented, as it determines the control effort that is output to the actuation system. The program calculates the error for the cluster in the x and y directions of the two-dimensional horizontal plane for every frame. The result is input into further calculations for control effort.

The position tracking system is also capable of tracing out a path for the particle cluster to follow, a feature that is visualized in Fig. 7. This path is read into the program as a series of reference points from an Excel spreadsheet. The standard position and velocity measurements and error calculations are carried out for the current reference point. Every time the cluster is moved within a user-defined threshold of the reference point, the path is updated and the next point in the spreadsheet becomes the new reference point. In this manner, the targeted delivery of functionalized nanoparticles can be simulated.

Feedback Controls

A feedback control system was required to communicate the necessary control action to the components of the actuation system. To do so, the Python program has to determine a control effort from the error calculated in the position tracking stage, and this effort must be converted into a change in the output of the electromagnets and stepper motors. Hence, there were two main design considerations for the feedback control system. First, it was important to consider how the control effort is calculated. This is encompassed in the controller and gains selection. Second, it was necessary to consider the means by which the digital output of the Python program can be converted to an analog change in the electrical components.

Feedback control is achieved through the calculation of PID control efforts in the Python program and the conversion of these efforts to actuation via an Arduino Uno microcontroller. The error calculated in the position tracking portion of the Python program is input into the PID (proportional, integral, and derivative) controller portion of the program. In a PID controller, the error, the integral of the error over a period of time, and the derivative of the error are each multiplied by a gain constant and the resulting values are summed to get the control effort. The three gain constants, which could be configured by the user in the Python code, were initially selected based on a first-pass estimate.

Communication of the control effort between the Python program and the Arduino is made possible using the pyserial library and a serial connection between the laptop and the board. The calculated control effort is sent to the Arduino, which varies the magnet follow distance and the relative strengths of the electromagnets. The magnet follow distance is the distance between the nanoparticle cluster and the central axis of the electromagnet. By moving the magnets closer to the cluster along the length of the flow channel, a magnetic force is induced in the direction of the target. Similarly, the relative strengths of the electromagnets can be varied to induce a net magnetic force toward the target.

The Arduino Uno varies the magnet follow distance by driving the stepper motors using the Adafruit Motor Shield v2.3. The motor shield is a driver module for Arduino that allows for speed and direction control of motors. The Adafruit model is capable of outputting up to 13.5 V and 1.2 A. As stated previously, the NEMA-17 stepper motor runs at an operating voltage of 12 V. However, the pins on the Arduino Uno can output a maximum of 5 V. Thus, the motor shield module is necessary to communicate the control effort to the stepper motors.

The Arduino Uno also varies the relative strengths of the electromagnets. Although the electromagnets also operate at 12 V, a driver is not used to power them. Instead, the electromagnets are powered using a transistor circuit. Transistors are essentially electrical switches that can be closed or open depending on the signal provided to the control pin. In the transistor circuit, one transistor is used for varying the strength of each electromagnet. For each transistor, the control pin is connected to the 5 V PWM (pulse-width modulation) output on the Arduino and the supply pin is connected to a 12 V power source. The PWM signal varies the load supplied to each electromagnet, and thus varies the strength of each magnet individually.

TESTING AND RESULTS

The behavior of the experimental control system was tested using an object with a black tip in place of the nanoparticle cluster. The tip of the object was held above the flow channel where it was moved around in a two-dimensional horizontal plane. The changes in electromagnet strength and position in response to changes in the object position were observed and recorded. To help visualize the electromagnet strength, the transistor circuit was changed to output power to LEDs instead of the magnets. Thus, what would normally be a variation in the magnet strength would now be a change in the brightness of the LED.

The testing revealed that the control system functioned as intended. The position tracking system was able to consistently identify the black part of the object and the blue spot on the electromagnet. Furthermore, it was able to generate sensible velocity vectors. When the tip of the object was moved either closer to or away from the reference point, the electromagnets moved with it. When the tip of the object was moved close to the face of one electromagnet, the intensity of the LED corresponding to that magnet would decrease and the brightness of the opposite LED would increase. This corresponds to the opposite electromagnet generating a higher magnetic strength than the one next to the object, and thus pulling on the cluster with increased force.

The pathing system intended to simulate the targeted delivery of functionalized nanoparticles was tested, and was found to also be functioning as intended. When the tip of the object came within the defined threshold around the current reference point, the program registered that stage of the path as complete and set the reference point to the next point in the spreadsheet.

In tests with an actual ferrofluid droplet, the experimental control system was able to successfully move the droplet along a straight path in the absence of flow. A notable observation made during these tests was that the magnitude of the horizontal component (along the axis of the channel) of the force exerted on the droplet was relatively small. Consequently, the droplet travelled along the defined path very slowly. In comparison, the magnitude of the vertical component (along the electromagnet axis) of the force exerted on the droplet was larger. When a permanent magnet was brought close to the channel to act as a disturbance by moving the droplet away from the reference point, the vertical component of the magnetic force was responsible for quickly snapping the droplet back.

Although the control system was able to achieve linear movement of the ferrofluid in still water, other tests produced results indicating that further work on the system is required. When a more complex path was input into the Python program, the droplet was unable to follow it because of the flow channel material. Contact between the plastic tube and the ferrofluid droplPythonet caused the droplet to stick to the inner wall, thus stopping its movement. Another observed issue with the experimental setup is the low strength of the selected electromagnets. The magnets were measured to have a maximum magnetic field strength of about 25 mT, which was deemed to be too low to counteract the drag force introduced by oncoming flow.

CONCLUSION

Initial testing indicates that the experimental control system is functioning as intended. The system is tracking the cluster consistently and outputting the appropriate control effort. Movement of the cluster along a linear path in still water was demonstrated. However, the design requires further work to demonstrate the feasibility of two-dimensional nanoparticle control in flow. The next step would be to make the proper design modifications. The flow channel material should be changed and the electromagnets must be replaced with stronger ones. After that, it would be desireable to tune the gains experimentally. The current gain configuration of the program is based on a first-pass estimate, so fine tuning becomes necessary to achieve optimal performance. Finally, it is desirable to extend the system to cover three-dimensional tracking and control.

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