Magnetically Controllable Microrobots for Targeted Cell Delivery

Seth Croslow Literature Seminar November 3, 2022

Targeted delivery systems are of great interest within the medical and pharmaceutical industries for their ability to deliver various therapeutics to specified locations within the body. These systems are useful in a wide range of applications including drug delivery, cell delivery, and biosensing.[1-3] They are also widely used to provide treatments and therapies for cancer, cardiovascular disease, and neurodegenerative disease.[4-6] Traditional methods of targeted delivery—such as nanoparticles conjugated to antibodies—have several limitations, the most important being that they rely on transport through the blood system, which is unable to deliver the therapeutic agent to just one desired location. One proposed method to overcome this limitation is through the use of exogenously powered microrobots.

Power for these microrobots can be supplied by magnetic, acoustic, and optical means, and is used to direct the movement of the microrobot to a specified location.[7] Magnetic fields can manipulate microrobots that have magnetic materials embedded in, sputtered onto, or conjugated with their structure. Acoustic fields can oscillate the microrobot, creating local micro streaming (tiny currents of fluid) that can generate a torque on the microrobot that propels it in a desired direction based on its design. Finally, optical control moves microrobots by deforming the microrobot in a specified way or by optical trapping mechanisms. Of these power sources, magnetic control offers the best advantages because it has no penetration limit for tissues, provides the fastest movement speed, and offers precise and diverse manipulation capabilities.[8]

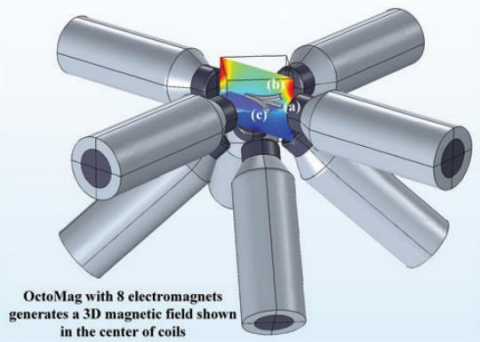

Figure 1: Spatial orientation of the eight electromagnets of the OctoMag manipulation system.[10]

Magnetic control of microrobots is performed using a platform that allows for both visualization and actuation. OctoMag, one of the most widely used control systems, was developed in 2010 by Kummer et al. and features eight electromagnets oriented as shown in Figure 1.[9,10] The 3D magnetic field gradient in the center of the OctoMag system can be precisely tuned by altering any of the individual electromagnets. The OctoMag system is able to manipulate magnetic dipole microrobots with 5 degrees-of-freedom (3 translational and 2 rotational).

Although the OctoMag allows for precise movement and alignment, the final degree-of-freedom, rotation about the microrobots' magnetization axis, is typically not controllable due to the axially symmetric magnetic field produced by a magnetic dipole. However, by altering the magnetization profile of a microrobot to make it non-uniform about its magnetization axis, 6 degrees-of-freedom actuation of a microrobot has been achieved.[11]

The design and choice of a magnetically controlled microrobot substrate varies widely depending on the desired use and function. Some of these types include biohybrid (where aspects of a microorganism are exploited, such as for propulsion, sensing, and targeting), microparticle (where magnetic microparticles are manipulated to perform simplistic tasks such as sequestering

and moving objects of interest), and polymeric (where the microrobot is created via various lithographic techniques).[12-14] Polymeric microrobots are popular microrobot substrates due to their ease of creation, wide design capabilities, and desirable mechanical properties.

Typically, polymeric microrobots are fabricated by two-photon polymerization which is a variant of 3D laser lithography. Compared to standard photolithography techniques (such as selective laser sintering and stereolithography, which are typically linear, one-photon processes), two-photon polymerization is a non-linear process that enables greater resolution due to its quadratic dependence on light intensity (polymerization occurs only in a much smaller area of the laser beam).[15] An overview of the application of two-photon polymerization in the 3D laser lithography process is shown in Figure 2. Briefly, a femtosecond laser beam is focused using a high numerical aperture objective lens; polymerization occurs only at the focal point of this laser beam where the intensity of light is above the threshold necessary to initiate polymerization. The focused laser beam is then rastered in three dimensions to create the desired structure by polymerization of the monomer solution. Finally, a developer solution is used to remove any unpolymerized monomer and clean the finished 3D structure. This method allows for the generation of intricately designed microrobots with feature resolution down to 100 nm.[15]

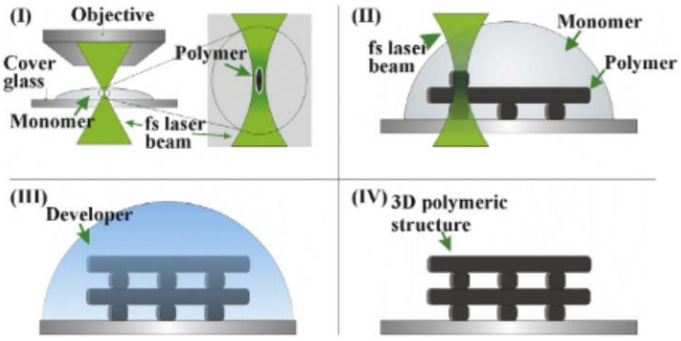

Figure 2. An overview of the 3D laser lithography fabrication process.[16]

Laser lithography has been used by numerous researchers to form unique microrobot structures suitable for carrying cargo such as cells. Jeon and coworkers designed a series of scaffold-based microrobots to enable the culturing, growth, and differentiation of stem cells.[17] After the microrobots were fabricated by laser lithography, they were sputtered with nickel and titanium to allow for magnetic manipulation and biocompatibility, respectively. Hippocampal neural stem cells were shown to adhere to this surface and differentiate into various types of neural cell types after 72 hours. To assess the viability of these microrobots for targeted cell delivery, the researchers magnetically manipulated these microrobots in a variety of environments *in vitro*, *ex vivo*, and *in vivo*. *In vitro* studies were conducted on a body-on-a-chip platform, on which the researchers were able to manipulate cell-loaded microrobots around microtissues in a microfluidic channel to a desired tumor tissue where the cells then proliferated.

Jeon et al. performed *ex vivo* studies on an excised rat brain treated with the CLARITY technique (transforms tissues into a clear, hydrogel-tissue hybrid structure).[17] Due to the transparency of the rat brain, a microscope was able to visualize and direct the microrobots through the internal carotid artery and into either the anterior cerebral artery or the middle cerebral artery, showing the ability to control these microrobots within biological tissues (Figure 3). Direct control

of the microrobots was not carried out *in vivo* due to incompatibilities with *in vivo* imaging systems. However, the authors showed that upon injection and application of a permanent magnet, the microrobots could be manipulated in one direction through the intraperitoneal cavity of rats.

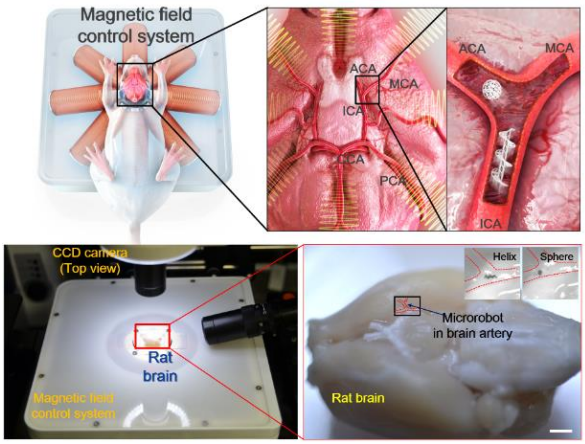

Figure 3. General overview of the *ex vivo* control of spherical and helical magnetic microrobots through rat brain arteries.[17]

Wei et al. took the delivery of cells via microrobots one step further and designed a burr-like microrobot with degradable materials.[18] They used a combination of polyethylene glycol diacrylate (PEGDA, for its degradable properties) and pentaerythritol triacrylate (PETA, for its mechanical strength). The mechanical strength and degradability were tested for a variety of ratios of PEGDA and PETA, and 75 volume % PEGDA had the best degradability and sufficient mechanical strength. This degradable microrobot was then tested *in vivo* for its ability to deliver and release cells into a tumor (Figure 4). Microrobots were loaded with hiPSC-MSC-GPx3 cells (which produces the cancer-suppressing protein GPx3) and then injected into a rat liver tumor. The control group (empty microrobots) and the nontreatment group (PBS injection) had no effect on the tumor growth. The treatment group (cell-loaded microrobots) suppressed tumor growth over a four-week period. This result shows the viability of cell-loaded microrobots for use in delivering and releasing therapeutic-containing cells in animal models.

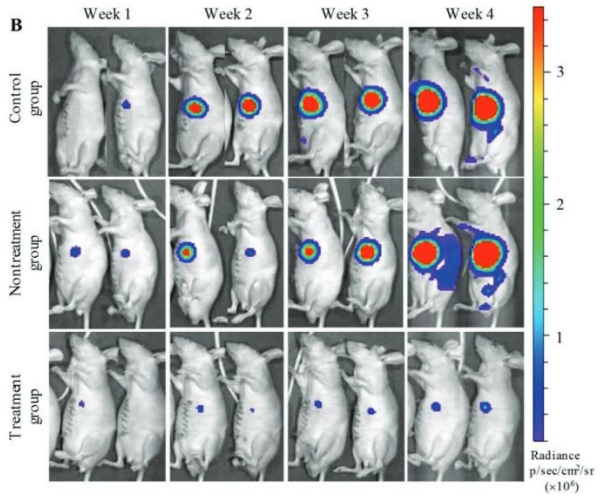

Figure 4. Luminescence dynamics of tumor growth for *in vivo* delivery of hiPSC-MSC-GPx3 cells via a burr-like microrobot.[18]

In summary, magnetic control allows for the precise 3D positioning of microrobots in various systems including *in vitro*, *ex vivo*, and *in vivo* platforms. The use of 3D laser lithography, which enables a diverse range of microrobot structures to be created, allows for facile optimization of the microrobot structure. The studies demonstrate that magnetically controlled microrobots are effective for targeted cell delivery, but more work needs to be done to enable the visualization and manipulation of microrobots *in vivo* and enable this approach to be utilized within a clinical setting.

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