Nano and Micromotors: Movers and Shakers of the Nano-Domain

Kimberly Lundberg Literature Seminar November 5, 2015

Patient outcomes after minimally invasive surgeries are significantly improved over traditional surgeries due to decreased recovery time, complications, risk of infection, and postoperative pain.[1] The use of minimally invasive surgical robots and capsule endoscopies are prime examples of successful minimally invasive surgeries. The use of smaller and more precise tools, such as nanomotors, could extend the medical toolbox and lead to more effective procedures and treatments, such as the concentration of harsh drugs to one area to avoid system-wide damage or the delivery of stem cells to a point of interest. Micro/nanomotors (MNMs) are micro- or nano-domain architectures that can be propelled through a liquid media either by the consumption of fuel or by external forces. To become successful in therapeutic and surgical applications, MNMs must tow cargo, navigate accurately, and interact selectively with their environment.

MNMS experience all of the same forces that a larger body (*e.g.*, human swimmer) would experience in a liquid, but because of their extremely small size, forces that would not significantly affect a larger body become increasingly important.[2] A nano-body experiences fewer collisions with solvent molecules than a large body, and because of its significantly reduced inertia, each interaction causes the body to shift noticeably. Brownian motion is the culmination of these interactions which make nano-bodies appear to vibrate in solution. Diffusion due to Brownian motion is extremely slow, so MNM propulsion must dominate over Brownian motion and provide propulsion directly to a specific target. The motion that drives MNMs forward is also limited by viscous forces. The Reynolds number (R_e), a dimensionless parameter, predicts whether an object's motion in a liquid will be dominated by inertial ($R_e > 1$) or viscous forces ($R_e < 1$).[3] R_e scales linearly with object length and speed, so micro- or nano-domain bodies have a small R_e (ca. 10^{-4}) and therefore overwhelmingly experience viscous forces. Therefore any propelling motion that would rely on drift after propulsion and the reverse motion to repeat the motion (*e.g.,* the opening and closing of a clam shell) cannot drive a MNM. A non-reciprocal movement is needed for propulsion (*e.g.*, rotation of a rigid body).

Non-reciprocal motions can be driven by chemical reactions or external stimuli. Common forms of propulsion include those which are driven by the consumption of fuel – such as bubble formation via catalysis, self-electrophoresis, and light-driven reactions – and those which are driven externally by magnetic fields, electric fields, or standing acoustic waves.[4]

The first MNM was fabricated by Mallouk and coworkers in 2004.[5,6] They expected their bimetallic Au and Pt nanorod to decompose H_2O_2 at the Pt end and be driven forward towards the Au end by the formation of O_2 bubbles. Motion was observed in the opposite direction, however, because of two half reactions that occur: H_2O_2 oxidation to O_2 at the Pt end and H_2O_2 reduction to H_2O at the Au end (Fig. 1a). These two half reactions impose a proton gradient which drives the Au proton-depleted region towards the Pt proton-rich region. The imposition of a gradient by two half reactions is called self-electrophoresis. This first foray into MNM fabrication proved that directed movement on the nanoscale was possible

Bubble propulsion of MNMs shows promise for applications in extremely viscous or turbulent media due to their extreme speeds of up to thousands of microns per second.[7] An

interesting example of which was fabricated by the Schmidt group[8] (Fig. 1c) and functionalized for biological applications by the Zhang group (Fig. 1b).[9] A microtube was fabricated by depositing layers of differently stressed materials onto a dissolvable photoresist support. Due to induced stresses, as the support was removed, the outer deposited layer contracts and drives the material to curl as it comes free (Fig. 1c). The Zhang group fabricated microtubes with the inner most layer of Ag for H_2O_2 decomposition and a middle layer of Fe which enabled the tube to be steered by an external magnetic field. Au was deposited one side of the microtube and then functionalized with monoclonal antibodies specific to anti-carcinoembryonic antigens found on circulating tumor cells (Fig. 1b). These functionalized microtubes were guided ex vivo through human serum diluted with H_2O_2 fuel. The microtube selectively captured tumor cells without capturing normal cells. Despite this microtube's ability to selectively capture tumor cells, bubble propulsion is limited by the availability of a fuel source and therefore can't be used in vivo. For in vivo applications, bubble propulsion MNMs must use a readily available fuel, such as glucose.

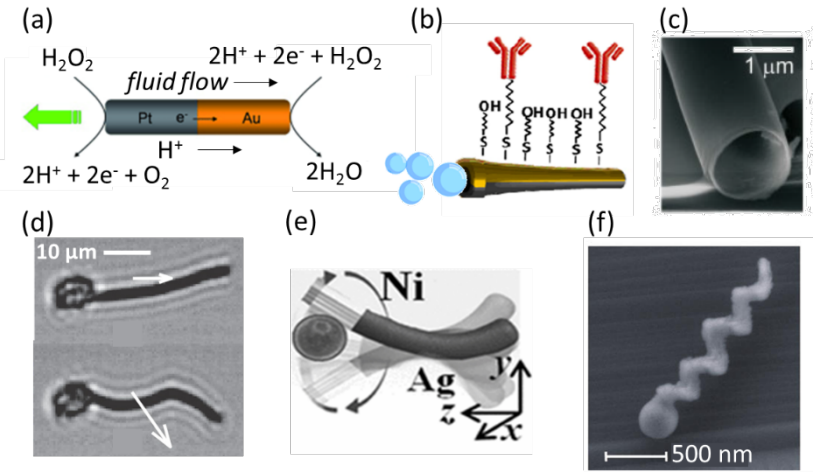

Figure 1. (a) Bimetallic nanorod composed of Pt and Au. Green arrow shows direction of movement. (b) Microtube functionalized with monoclonal antibodies (red). The release of O_2 bubbles from one end drives the microtube forward. (c) SEM of microtube after stress induced curling of the material. (d) Red blood cell head attached to a tail composed of magnetic colloids held together by DNA. (e) Nanorod whose Ni head is rotated in a magnetic field around its payload. The rotation drives movement of the Ag tail which propels the motor forward. (f) SiO_2 propeller which is functionalized on one long side with Co and Rhodamine B on the other side.

MNMs propelled by external magnetic fields show great promise for in vivo applications because they can be controlled from a distance and in the absence of a fuel source.[4] A variety of motions can be driven magnetically such as a tail waving in a two dimensional plane, a tail waving in a circular manner, or a rigid body rotating.

The first magnetic MNM was fabricated by the Stone group.[10] They assembled a magnetic tail by stringing together magnetic beads with double stranded DNA. At one end of the tail, a red blood cell was attached as cargo (Fig. 1d). The entire motor was aligned in a homogeneous magnetic field to provide directionality while another magnetic field was oscillated sinusoidally to induce the propagation of a wave through the tail. The movement mimics that of a spermatozoa which propels itself head first by waving its tail in two dimensions. Interestingly, the Stone group's motor did not propel itself with the red blood cell leading but instead the tail led. This behavior occurs because the wave propagates from the unconstrained free end back to the red blood cell.

An MNM fabricated by the Lauga group relies on a rotating magnetic field as opposed to an oscillating magnetic field.[11] Their bimetallic nanorod consists of a magnetic Ni head and a flexible Ag tail. Rotation of the shorter (1.5 μm) Ni head drives the rotation of the longer (4 μm) Ag tail. A magnetic, drug-loaded polymer sphere made of iron oxide nanoparticles encapsulated

by pol(D,L-lactic-*co*–glycolic acid) is attracted to the magnetic Ni segment (Fig. 1e). The velocity of the bimetallic rod was expected to decrease linearly with increased payload diameter. This was not observed for payloads under 1.2 μm in diameter. While hydrodynamic drag does increase with a larger payload, so does the length of the tail which drives motion. As more mass is added to the head of the rod, the rotational center of the rod shifts towards the head and more of the tail is available to drive movement. Researchers were able to direct the nanorod to its payload in cell culture medium, capture the payload, transport it through a channel, deliver it to a cancer cell, and non-specifically bind it to a HeLa cancer cell.

A rigid rotating magnetic MNM was fabricated by Fischer and coworkers.[12] A SiO_2 spiral propeller was fabricated by glancing angle vapor deposition. On one long side a conductive Co layer was deposited and on the other a fluorescent molecule, Rhodamine B, was attached (Fig. 1f). The rotating motion was confirmed by observing the motors blinking which is evidence of the Rhodamine B functionalized side appearing and disappearing. These nanopropellers can be controlled with high precision in solution and can push payloads 1000 times their own volume.

Progress in magnetic MNMs shows that self-propelled and functionalized motors can perform complex tasks and interact with biological components in solution. MNMs can deliver payloads via a variety of propulsion systems. MNMs have not been tested with in vivo studies and the method by which they'll be steered accurately through the human body is still unknown. Further testing should progress towards fabricating a MNM that is biologically compatible, capable of pushing payloads in viscous environments, propelled strongly enough and to counteract turbulent flows within the human body, capable of binding specifically to target cells, and able to selectively deliver drugs upon arrival.

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