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Magnetically guiding and orienting integrated chemical sensors

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ABSTRACT

Fluorescent microsensors for detecting pH and oxygen were positioned and oriented using magnetic tweezers. These multifunctional integrated microsensors were fabricated by physically linking together nano-components including magnetic nanoparticles, fluorescent nanoparticles, and metal hemisphere-shells. Two such microsensors are magnetic roll-shaped polystyrene particles with 120 nm fluorescent oxygen-sensing ormosil nanospheres that are physically pressed ("breaded") into the roll surface, and 4–5 μm fluorescent microspheres that are capped with a 50 nm thick metal hemispherical shell. The magnetic tweezers consisted of an iron wire that was magnetized in an external magnetic field. Rotating this external field oriented and rotated the microsensors.

1. Introduction

Micro- and nanoparticles are increasingly used as chemical/mechanical probes and effectors because they have a large surface area and volume that can be loaded with many components to control their chemical, magnetic, and mechanical properties. For example, our group developed "photonic explorers for bioanalysis in biologically localized embedding" (PEBBLE) sensors for sensitive and specific chemical analysis [1,2]. PEBBLEs consist of a chemical indicator dye encapsulated within a polymer matrix that is selectively permeable to analytes of interest, while blocking large macromolecules from entering and interfering with the indicator dye's measurement. Many components can be added to the PEBBLE platform by embedding them within the polymer matrix or attaching them to the surface. By carefully controlling and integrating components, PEBBLE sensors have been developed to perform multiple tasks including spectrochemical sensing with indicator dyes, singlet oxygen production for photodynamic cancer therapy with photosensitizers, MRI contrast with gadolinium ligands and iron oxide nanoparticles, and tumor targeting surface chemistry [1]. When the sensor complexity increases, however, it becomes difficult to simultaneously optimize all parameters in a single synthesis step, and adding or changing properties (e.g. adding more magnetic materials, adding new sensor dyes, or changing PEBBLE shape and matrix) usually requires reoptimization. To fabricate complex multifunctional PEBBLEs, modular methods that separately optimize and then combine the fluorescent sensing phase and the magnetic and shape properties are preferred. The particles used herein were fabricated in such two-step processes. In one method, PEBBLE nanosensors are physically pressed ("breaded") into the surface of magnetic microrolls [3,4]. In a second method, fluorescent magnetic microspheres are coated with a layer of aluminum using vapor deposition to make one side reflective while the other side is fluorescent [5–7]. Deposition of magnetic materials such as nickel, cobalt, and iron has also been used to add magnetic functionality to non-magnetic particles [8–10]. These processes allow existing types of PEBBLEs sensors to be integrated into magnetically guided and oriented microsenors.

Adding magnetic materials to PEBBLEs enables magnetic control over their position, orientation, aggregation, and applied force [3–5,11,12]. Compared to optical tweezers, which have been used to position single micron-sized sensors and measure chemical gradients [13,14], magnetic tweezers offer the advantage of a simple setup, stronger forces and torques especially for small nanoparticles, and transparency of biological samples to magnetic fields. Magnetic micro- and nanoparticles have been used in drug delivery, hyperthermia, and MRI imaging, cell separation, immunoassays, magnetic transfection of cells, and magnetic tweezers [15–17]. Magnetic particles can be coated with a multitude of different enzymes and antibodies to enable them to attach (in vitro) to specific populations of molecules, cells, viruses, and subcellular organelles that can then be separated out from the unlabeled population with magnetic field gradients [18,19]. In addition, rotating magnetic particles with an optical asymmetry

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(e.g. half-shells, chains of particles, or star-shaped particles), modulates the optical signal, allowing it to be separated from background fluorescence for sensitive chemical an biomechanical assays [3–5,20–23].

In this study, we employed a very simple magnetic tweezers setup to position and orient magnetically controlled fluorescent small analyte sensors. The tweezers setup consists of an iron wire held in a micropositioner. The wire is magnetized in a magnetic field produced with a nearby electromagnet or permanent magnet; the magnetized wire is used to manipulate microsensors. The fluorescence spectrum is recorded with a spectrometer (see Section 2).

2. Materials and methods

Magnetically controlled microparticles were viewed with an Olympus IMT-2 (Lake Success, NY, USA) inverted fluorescence microscope. Fluorescence spectra were acquired using an Acton Research Corp. spectrograph and a Hamamatsu HC230 CCD interfaced with an Intel Pentium computer. Images and videos of microsensors were acquired using Coolsnap ES CCD camera from Roper Scientific and a Nikon Coolpix 995 digital camera. A dichroic beam splitter from Omega Optical (Brattleboro, VT) was used to observe reflected light, while a standard Olympus blue filter cube was used for most of the fluorescence work. To measure the response of the sensors to oxygen, the sample was dried on a microscope slide. The microscope slide was then placed on the microscope stage and covered with a 22 mL glass chamber with no bottom and gas inlet and outlet ports on top. Either nitrogen, air, or oxygen gas was flowed at 100 mL/min through this chamber over the sample. Before acquiring spectra, the system was given approximately 10 min to fully purge. Previous studies with a different flow setup showed that pure decyl methacylate oxygen PEBBLEs respond to changes in oxygen concentration in less than 0.4 s [24,25].

A simple magnetic tweezers apparatus was used to move and rotate fluorescent microparticles through a rectangular capillary (Friedrich Dimmock Inc., Millville, NJ) or at the top of a drop of solution on a microscope slide. The magnetic tweezers consisted of a thin iron wire 250 μm or 75 μm in diameter (Alfa Aesar), held in a manual micropositioner (Prior, England), and placed in a magnetic field produced with either a permanent magnet or an electromagnet (Fig. 1). The iron wire concentrates the field, creating a strong field gradient near the tip that was used to pull magnetic particles. By bending the wire to form a kink, the tweezers becomes mechanically more resilient if pressed against the capillary wall. In addition, the kinked wire tip extends away from the capillary that holds the iron wire, avoiding the optical distortion from light guided through the capillary walls.

External permanent magnets used to magnetize the iron wire included a 5/8 in. diameter cylindrical Alnico magnet, magnetized though its diameter (Dexter Magnetic Technologies, Chicago, IL), a ring shaped magnet magnetized through its diameter (Dexter Magnetic Technologies), and rectangular ceramic and NdFeB magnets. The fields from these magnets range up to 600 Oe, depending on the distance: the field falls off as $1/r^2$ for distances close to the magnet, and as $1/r^3$ for distances that are large compared to the magnet length (where r is the distance to the center of the cylinder, data not shown). The permanent magnets were typically held 2–6 cm (10–50 Oe) from the iron wire to produce strong fields, although an effect on microsphere orientation is observed at distances as far as 30 cm. The field orientation underneath the iron wire was controlled by rotating permanent magnets. To produce and rotate a field in the image plane (orthogonal to the iron wire), the iron wire was placed through the center of a circular Alnico magnet diametrically magnetized (and with NdFeB magnets attached to the outside poles to increase field strength if necessary); the circular magnet was lifted and rotated to rotate the field in the plane. When the permanent magnet is more than a centimeter from the wire, is the field is relatively uniform on the mm scale, and does not change appreciably if the iron wire is moved by 1 mm. This enables the iron wire to be moved over the sample to guide magnetic particles in the sample. Alternatively, the wire can be held steady while the sample is moved underneath. Of the two approaches, moving the sample while keeping the wire stationary was most convenient for guiding the magnetic microparticles through the sample, but moving the wire while holding the sample stationary produced the most intuitive image series.

The magnetic field could also be produced by a hollow solenoid consisting of a 2.5 cm diameter, 3 cm high, hollow spool of 26-gauge magnet wire. The spool had a resistance of 25 Ω, and contact resistance of approximately 5 Ω, determined using a 4-point d.c. resistance measurement. The inductance of the solenoid was 50 mH, and increased when the iron wire was added by 140 to 180 ± 10 μH, depending on whether the wire was placed in the center of the solenoid or at the edge (higher inductance). By increasing the current through the solenoid, the magnetic field in the solenoid increases proportionally. Permanent magnets were more easily used, although electromagnets are more controllable. Most of the work described here used permanent magnets.

3. Results and discussion

Oxygen sensitive PEBBLEs were prepared by loading dyes into organically modified silane (ormosil) nanoparticles made of two monomers, phenyltrimethoxysilane and methyltrimethoxysilane [24]. The fluorescent indicator dyes loaded were oxygen-quenched platinum(II) octaethylporphine ketone (PtOEPK) dye (760 nm emission peak) which includes an unknown oxygen-insensitive impurity that exists persistently and serves here as a reference (685 nm emission peak). The ratio between the two peaks provides a measure of the oxygen concentration that is independent of the concentration of particles and the incident light intensity. SEM images showed that the PEBBLEs were approximately 120 nm in diameter [24]. Spectroscopic analysis of the PEBBLEs showed that the spectrum was sensitive to oxygen concentration. Fig. 1g shows the spectrum of the PEBBLEs in nitrogen, air, and oxygen, after they were implanted onto the surface of magnetic microrolls as described below.

Magnetic polystyrene microspheres, 4.4 ± 0.4 μm in diameter, coated with ferromagnetic chromium dioxide nanorods on their surface, were acquired from Spherotech (Libertyville IL). These ferromagnetic microspheres could be magnetized in a strong external magnetic field (larger than the coercivity, 570 Oe), so that the microspheres could be rotated and oriented in solution using an external magnetic field (weak compared to the coercivity). The magnetic microspheres were deformed into rolls and “breaded” with fluorescent oxygen sensitive ormosil PEBBLEs 120 nm in diameter which were synthesized as described above. First, a solution of microspheres was deposited onto a glass microscope slide and allowed to dry. A second solution of oxygen sensitive PEBBLEs was placed onto a second microscope slide and allowed to dry. The two microscope slides were then pressed together and moved in a side-to-side motion while pressing to deform the particles into rolls and press the oxygen sensitive PEBBLEs into these rolls as shown in Figs. 1 and 2. As we described in earlier work, single roll-shaped particles are formed when the initial spherical particles are well-separated on the glass slide and small lateral motions are used [4]. With a high concentration of particles and large lateral motions, the rolls join together to form longer rolls containing multiple particles