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Analysis of driven nanorod transport through a biopolymer matrix

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ABSTRACT

Applying magnetic fields to guide and retain drug-loaded magnetic particles *in vivo* has been proposed as a way of treating illnesses. Largely, these efforts have been targeted at tumors. One significant barrier to long range transport within tumors is the extracellular matrix (ECM). We perform single particle measurements of 18 nm diameter nanorods undergoing magnetophoresis through ECM, and analyze the motion of these nanorods in two dimensions. We observe intra-particle magnetophoresis in this viscoelastic environment and measure the fraction of time these nanorods spend effectively hindered, versus effectively translating.

1. Introduction

Magnetic micro- and nanoscale particles have proven useful in a variety of applications, including microfluidics [1], gene transfection [2], hyperthermia [3], drug delivery [4–7], and mechanically induced gene activation [8]. Magnetic fields have been used to achieve translational [9–12] and rotational manipulation [13–15] of nanoparticles in a variety of environments and to various ends, and some groups have achieved elaborate control over particles with many degrees of freedom [16]. Implicit in the application and manipulation of magnetic nanoparticles is their interaction with the surrounding medium. This medium may be a Newtonian fluid or a complex non-Newtonian biopolymer system. In Newtonian solutions, particle motion during magnetophoresis is a composite of magnetic forces ($F_{magnetic}$) and fluidic drag forces (F_{drag}). In non-Newtonian environments the matrix can impose additional steric forces (F_{steric}) and nonspecific surface adhesion ($F_{surface}$) forces which can significantly complicate, and in many cases hinder, long range transport [17–20].

An understanding of nanoparticle interactions with and transport through complex biopolymers is important for optimizing magnetically guided nanoparticle motion through tissues. Observing particle motion at the single particle level is one approach to understanding nanoparticle magnetophoresis. Using this method, we previously demonstrated significant differences in the motion of 18 nm diameter nanorods and larger diameter nanorods (55 nm and 200 nm) [21]. Here we expand on our previous work by focusing on the dynamics of 18 nm diameter nanorod motion through ECM. We calculate average residence time as a fraction of overall experiment duration, and observe intra-pair magnetophoresis events. An important aspect of the work presented here is the fact that the components which make up the ECM meshwork are very similar to the diameters of the nickel nanowires used in these experiments [22]. Scanning electron micrographs of Matrigel and the as-grown nickel nanorods are shown in Fig. 1 for comparison.

Matrigel is a commercially available complex composed primarily of laminin, collagen IV, entactin, and heparin sulfate proteoglycans. Matrigel was chosen as a substitute for *ex vivo* extracellular matrix due to its ease of preparation and relatively high sample-to-sample homogeneity. As a multicomponent matrix, Matrigel contains the relevant properties for elucidating novel phenomenon in tissue-like environments. Specifically, the gelled matrix has a high concentration of proteins, a broad range of pore sizes, and a variety of surface charges. Matrigel has been shown to have a hydraulic conductivity similar (within 21%) to that of porcine glomular basement membrane [23]. Previous research has used Matrigel to demonstrate the significance of surface charge in mediating particle motion through biopolymers [17]. Quantitative magnetophoresis studies have been performed in Matrigel [9], and the diffusive motion of gold [24] and polymeric [17] particles has been studied in this material. Owing to its wide

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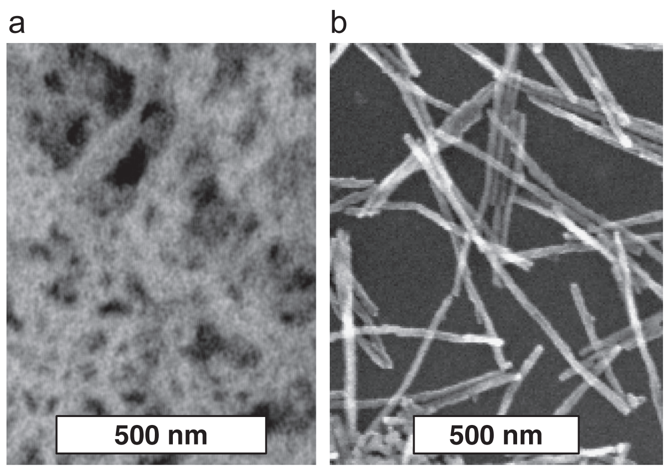

Fig. 1. Scanning electron microscope images of (a) Matrigel and (b) electrodeposited 18 nm diameter nickel nanorods.

availability, simple preparation, and similarity to basement membranes *in vivo*, we chose Matrigel as a reasonable *in vitro* approximation of the extracellular matrix environment.

2. Experimental procedure

2.1. Nickel nanorods

Nickel nanorods were grown *via* electrodeposition into the pores of an anodized aluminum oxide membrane with 18 nm diameter pores (AAO, Synkera Technologies, Inc.). These membranes were first sealed on one side by thermal evaporation of a silver working electrode. After sealing one side, electroplating of nickel was performed into the pores of the template. Following nanowire synthesis, the silver working electrode was etched in dilute nitric acid, and the AAO template was etched in 0.5 M sodium hydroxide. Detailed synthesis procedures are well documented in the literature [25–28]. In order to minimize adhesion between ECM proteins and nanorods, nickel nanorod surfaces were functionalized with 1 kDa methoxy-PEG-silane [29]. This surface functionalization effectively minimized zeta potential from an average −46 mV to an average −3 mV [21]. Previous research has shown that such narrow diameter nanorods comprise single domain particles, and will exhibit high remanence and preferential magnetization along the long axis of the nanorod [30–33].

2.2. Magnetophoresis Experiments

Magnetophoresis of 18 nm diameter nickel nanorods was assessed by mixing rods into Matrigel. Matrigel was stored at −20 °C prior to the experiment. The matrix was then thawed at 4 °C for sample preparation. All pipette tips and glass slides were stored at 4 °C to prevent rapid gelation during sample preparation. The nanorods were dispersed in phosphate buffered saline (PBS), chilled to 4 °C, and added to undiluted Matrigel at 1% v/v. A cover slip was sealed atop the sample chamber to minimize evaporation.

The composite sample (99% Matrigel, 1% PBS with nanorods) was gelled in an incubator for one hour (37 °C, 95% humidity, and 5% CO_2), then placed on a microscope and imaged in a known magnetic field and field gradient (Fig. 2 inset). Experiments were performed at 25 °C.

The magnetic field was supplied by a calibrated, stationary, cylindrical, NdFeB permanent magnet.

Magnetic field strength and the equation describing field as function of distance from the magnet are shown in Fig. 2. We collected magnetophoresis data at a rate of 1 frame per second using a Pulnix PTM-6710CL camera and custom image acquisition software.

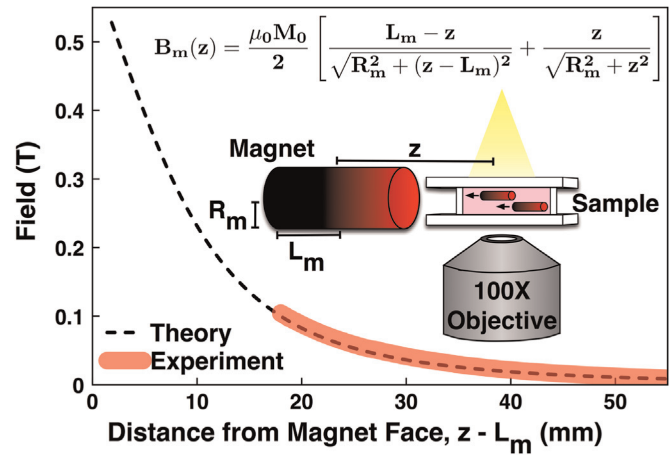

Fig. 2. Measured magnetic field (T) as a function of distance (mm) from the face of the cylindrical permanent magnet is shown (solid red line). Field measurements are in 0.25 mm increments. The theoretical equation for the magnetic field as a function of distance from the face of a cylindrical magnet is shown (top) and plotted (dashed black line). The experimental setup consisting of the pulling magnet, illumination, nanorod sample, and microscope objective is depicted (not to scale). The parameters R_m (radius of the magnet), L_m (one half the length of the magnet), and z (distance between nanorod and magnet center) are shown. $B_m(z)$ is the magnetic field, μ_0 is the permeability of free space, and M_0 is the magnetic saturation of the magnet. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

Imaging was performed in transmitted light mode using a 100× dry microscope objective. Continuous imaging was performed for tens of minutes. Videos were analyzed using Spot Tracker (freely available at cismm.org [34]). As magnetophoresis experiments were performed over the course of tens of minutes, we observed nanorod transport over distances of tens of micrometers.

3. Results

3.1. Magnetophoresis and applied translational force

Unlike nanorods with larger diameters, 18 nm diameter nanorods experience significant acceleration and deceleration during transport. This is a consequence of their small size, the relatively small applied magnetic force, and transient steric hindrance. The force applied to a nanorod is calculated based on the analytical expression for the magnetic field as a function of distance from the magnet face and the nanorod's volume (Fig. 2) [11]. Using a NdFeB permanent magnet we pulled nickel nanorods with an average force of 99 ± 27 fN (mean ± standard deviation). Nanorods move with an average velocity of 4.3 ± 2.9 μm/min. (mean ± standard deviation) [21].

During constant gradient magnetophoresis in Newtonian environments, the drag force F_{drag} is equivalent to the magnetic force $F_{magnetic}$. In dense biopolymer environments such as the ECM, the fibrous proteins forming the matrix offer significant steric forces F_{steric} which oppose the magnetic force. Electron microscopy of the matrix and particle tracking of individual rod transport suggest that F_{steric} is largest at matrix protein clusters. Indeed, we observe strong steric hindrance for several minutes at a time, and calculate that these nanorods are strongly hindered approximately 94 ± 3% of the experiment time. We define strong steric hindrance as a forward velocity less than 25% of the average velocity, or a forward velocity below approximately 1 μm/min.