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Nickel foil microcantilevers for magnetic manipulation and localized heating

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Abstract

Cellular manipulation has been investigated by a number of techniques. In this manuscript nickel foil microcantilevers were used for magnetophoresis and manipulation of microparticles and magnetically labeled HeLa cells. The cantilevers were also used for localized heating in liquid, reaching biologically relevant temperatures. This work aims to develop cantilevers for sample enrichment, manipulation, and thermal applications, offering an inexpensive and versatile solution compatible with standard tools in research and clinical diagnostic testing, such as microwell plates.

Keywords

Magnetophoresis; microcantilever; cell magnetic manipulation; cell magnetic manipulation; localized heating; localized heating; magnetic tweezers; magnetic tweezers

Magnetic nano- and micro- particles are used in sample enrichment with applications in biological research and clinical diagnostic labs ^{1, 2}. For example, magnetic beads have been used for cell labeling and magnetic separation from heterogeneous samples, for enumeration and genetic characterization ³. Enumeration of circulating tumor cells (CTCs) using magnetically labeled cells is currently implemented for diagnosis and prognosis of breast and prostate cancer in clinical laboratories ³. Magnetically labeled cells have also been used in the field of magnetic tweezers ⁴. Methods have also been developed to manipulate individual magnetic beads using a magnetic probe and a substrate with patterned magnetic traps ⁵.

A variety of methods have been used for cell manipulation and characterization, including magnetic tweezers, optical tweezers, magnetic cell rotation ⁶, and atomic force microscopy ^{7, 8}. At the same time, microheaters and temperature measurements can also be integrated into fluidic systems for biological culturing and characterization ⁹. In the past, microheaters have been used for high-speed liquid pumping, mixing and particle entrapment

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in thin layers of oil and water¹⁰. Rapid thermal lysis has been achieved on a silicon microcantilever¹¹ and in a liquid drop with a nickel-chrome cantilever¹². There are several advantages to combining different techniques. For instance, magnetic and optical tweezers were combined to improve the controlled degrees of freedom of trapped bodies¹³. However, combining thermal characterization, heating, and magnetic manipulation into a cantilever device for manipulation of magnetic particles and magnetically labeled cells has not been thoroughly explored. The closest that the authors are aware of is the ability to attract and lyse cells, using an on chip magnetic lysis device¹⁴. The microcantilever described in this manuscript can translate through a droplet and is not physically constrained on a localized substrate surface.

In this manuscript, nickel foil cantilevers are used for magnetophoresis and micromanipulation—including capturing and releasing—of magnetic microparticles using a hybrid scanning probe system. As an example application, magnetically labeled HeLa cells were captured and manipulated using the nickel foil cantilevers. The cantilevers were also heated to biologically relevant temperatures. The ultimate goal of this work is to develop a simple solution that combines thermal and magnetic properties for manipulation, magnetophoresis, sample enrichment, and thermal applications such as thermal lysis, thermal cycling, and thermal characterization.

Typical micromachined cantilevers require several clean-room fabrication steps. Furthermore, thin metal films deposited on cantilevers do not offer strong enough magnetization. Alternative fabrication methods such as micro-electric discharge machining (μ EDM) and photo-etching can be used for the fabrication of metal cantilevers. In this work, nickel foil cantilevers were manufactured using photochemical machining, where a photographically prepared mask protects the metal design while the remaining area is chemically etched. A typical cantilever is shown in Fig. 1 (a) and Fig. 1 (b). The entire cantilever is 1.6 mm $\times$ 3.7 mm. It is comprised of two 0.4 mm wide parts forming a thinner V-shape at the tip. The tip's sharp end is < 200 nm. The part of the cantilever closer to the tip was half etched to increase the electrical resistance and the heating near the tip point. The cantilever was electropolished to further thin the surface and make the cantilever more reflective so that it is compatible with atomic force microscopes. The cantilever has less than 2 Ω resistance.

The cantilevers were attached to a specialized printed circuit board (PCB), as shown in the inset of Fig. 1 (c). The ends of the cantilevers were then wirebonded to metal traces on the boards that attached to wires connected to electronics. The cantilevers were encapsulated in PDMS for insulation. A Keithley 2400 sourcemeter was used to heat the cantilever. In order to investigate the heating properties and to establish the range of temperature that could be reached in a droplet of a sample, cantilevers were immersed into a droplet (100 μ L) of water and PBS solution and powered at different currents (shown in the inset of Fig. 1 (c)). A 12 μ m diameter thermocouple (Omega) was used to thermally characterize the cantilevers in liquid. The thermocouple was placed in contact with the tip of the cantilever. Temperatures up to 47 $^{\circ}$ C were observed at a power of 0.5 W (Fig. 1(c)), using resistive heating.

Additional measurements were taken within the droplet at varying distances from the cantilever. As shown, in Fig. 1 (d), the temperatures dropped by 11.9 °C over a distance of 8 mm from the cantilever. The effects of heating with distance were simulated with a 2-D steady state Comsol Multiphysics FEA model shown in Fig. 1 (d). The FEA results were in agreement with the experimental measurements. The FEA model included a glass substrate (denoted with the *i* in the inset of Fig. 1(d)), a nickel cantilever (denoted with *iii*), having the same orientation as in the experiment and assumed to be at a fixed position, and liquid medium (*ii*). The data line is labeled *iv*. The cantilever is set at a constant temperature of ~11.9 K above room temperature (293 K). The cantilever is surrounded by a water droplet. The surface of the solid glass substrate is set to room temperature 1.2 mm away from the cantilever. A plot of the temperature with distance from the cantilever to the edge of the liquid is shown in Fig. 1 (d).

The cantilevers were also heated by inductive heating, where an alternating current generated by a function generator (3312A, HP) was passed through a coil wrapped around the cantilever. Temperatures up to 44 °C were observed at a 60 kHz frequency and a current values of 2.7 Amp through the coil (data not shown). However, the changes in magnetic field that result from induction heating coil may affect the movement of magnetic nanoparticle enriched cells, thus further study is required to determine suitability of this method for this approach.

These thermal characterization measurements were performed to demonstrate that the cantilever can be used to achieve biologically-relevant temperatures near the probe in a liquid drop. We anticipate that higher temperatures can be achieved with higher resistance of the cantilever, by changing the material and physical dimensions of the device. In addition, higher temperatures, using induction heating, can also be achieved by increasing the current through the coil.

The cantilevers were magnetized with a permanent magnet resulting in a permanent magnetic dipole. They were also magnetized electromagnetically with a coil made of an insulated cable shown in Fig. 2 (a). The cantilever was attached to a 500 µm diameter iron core. An insulating cable was wrapped around the iron core to create an electromagnet. The cantilevers were attached to a micromanipulator. A Zaber motorized stage interfaced to a computer was used to move the sample in relation to the cantilever. Bright field microscopic imaging was used to monitor, measure, and characterize magnetic particles and cells.

To demonstrate the ability of the magnetized microcantilever to capture magnetic particles, the cantilever was used to capture clusters of < 44 µm diameter iron (Fe) micro-particles. The cantilever tip was in contact with the substrate while the particles moved toward the cantilever as shown in Fig. 2 (b). Removal of particles was effectively accomplished with a demagnetizer that generated a strong alternating magnetic field produced by an electromagnet. The demagnetizer was slowly moved back and forth under the set-up (shown in Fig. 2 (c)). The process was repeated several times until the particles were released as shown in Fig. 2(d). This set of experiments established the feasibility of using thermal cantilevers to capture and release magnetic particles.

Figure 3 (a) shows the magnetophoretic response of a single HeLa cell. The HeLa cells used in these tests were prepared by standard cell culturing protocols—cultured in DMEM in a 5% CO₂ humidified environment. Cells were cultured to a final approximate concentration of 10⁶ cells/mL (as determined with a hemocytometer). Streptavidin magnetic beads with a diameter of 2.8 μm (M-280s, Invitrogen, Inc.) were rinsed several times in DMEM and brought to a final concentration 5 times less than the original stock concentration. 50 μL of the diluted beads were then mixed with 450 μL of HeLa cell solution. Cells and magnetic beads were then mixed at 1 Hz with end-over-end rotation. The outcome was HeLa cells with attached with adequate magnetic beads for magnetic micromanipulation.

When the cantilever was magnetized, many cells were captured at the tip of the probe as it was manipulated through the droplet. As shown in the Fig. 3, numerous cells had already attached to the probe surface, which resulted from translation in the sample (Fig. 3 (a)). Cellular magnetophoresis was measured with the ImageJ plugin MultiTracker. Cells and 2.8 μm magnetic beads were manipulated with a maximum translational velocity of 50 μm/s. The maximum translational velocity did not produce enough drag to overcome the magnetic interaction and thus detachment was not observed. Notably, this demonstrates that rapid manipulation of magnetically labeled cells is feasible with the cantilever. After the movement of the cantilever stopped, several nearby cells had a large enough magnetophoretic response to translate across the surface of the slide. The location of the cell was tracked in Fig. 3 (b), demonstrating that the cell is moving as a result of magnetic force rather than some other fluidic motion, such as convection. The acceleration toward the cantilever is a result of the force gradient created by the magnetic field of the cantilever tip, which is governed by the following equation (for the derivation please refer to the Supplement) of motion for paramagnetic particles^{15, 16, 17}

$$v(t) = \frac{mc^2}{\mu_0} \left(-\frac{4}{\mu_0} \frac{mc^2}{t + r_0^4} \right)^{-\frac{3}{4}} \quad (1)$$

where $v(t)$ is velocity, m is the mobility, c is a constant ($c > 0$), B is the magnetic field, μ_0 is the magnetic permeability of space, t is the time, assuming boundary conditions of $t = 0$ and $r = r_0$. The velocity equation¹⁷ is fitted to Fig. 3 (b).

While the device was not heated while observing magnetophoresis, one can estimate the effects of doing so. Given the experimental and simulation results shown in Fig. 1 (d) and a heating power of 1.36 W, a biologically relevant heating zone of 37 °C can be achieved that is within 0.25 mm of the cantilever. By implementing magnetophoresis, it is possible to attract cells—that are far from this heating zone—to the probe surface, allowing for exposure to incubation-like temperatures. We note that the same should be accomplishable for cell lysis and even thermal cycling for polymerase chain reaction (PCR) amplification, given the appropriate cantilever and power.

In conclusion, nickel foil microcantilevers have been used for magnetophoresis and manipulation of micro-particles and magnetically labeled HeLa cells. These devices were also used for localized heating. The ability to combine manipulation and heating in this manner could have applications for selective cell micromanipulation, characterization, and

thermal applications (such as incubation, lysis, and thermal cycling). The microcantilevers offer a versatile solution compatible with standard tools in research and clinical diagnosis.

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REFERENCES

1. Kessler HH, Muhlbauer G, Stelz E, Daghofer E, Santner BI, Marth E. *Clinical Chemistry*. 2001; 47:1124. [PubMed: 11375308]
2. Pankhurst QA, Connolly J, Jones SK, Dobson J. *Journal of Physics D Applied Physics*. 2003; 36:167–181.
3. Riethdorf S, Fritsche H, Müller V, Rau T, Schindlbeck C, Rack B, Janni W, Coith C, Beck K, Jänicke F. *Clinical Cancer Research*. 2007; 13:920. [PubMed: 17289886]
4. Bausch AR, Ziemann F, Boulbitch AA, Jacobson K, Sackmann E. *Biophysical Journal*. 1998; 75:2038–2049. [PubMed: 9746546]
5. Mirowski E, Moreland J, Zhang A, Russek SE, Donahue MJ. *Applied Physics Letters*. 2005; 86:243901.
6. Elbez, Remy; McNaughton, Brandon H.; Patel, Lalit; Pienta, Kenneth J.; Kopelman, Raoul. *PLoS ONE*. 2011; 6(12):e28475. [PubMed: 22180784]
7. Tanase M, Biais N, Sheetz M. *Methods in Cell Biology*. 2007:473–493. [PubMed: 17613321]
8. Neuman KC, Nagy A. *Nature Methods*. 2008; 5:491–505. [PubMed: 18511917]
9. Kim DH, Wong PK, Park J, Levchenko A, Sun Y. *Annual Review of Biomedical Engineering*. 2009; 11:203–233.
10. Basu AS, Gianchandani YB. *Journal of Micromechanics and Microengineering*. 2008; 18:115031.
11. Privorotskaya N, Liu YS, Lee J, Zeng H, Carlisle JA, Radadia A, Millet L, Bashir R, King WP. *Lab on a Chip*. 2010; 10
12. Gaitas, A.; French, P. *The 16th International Conference on Solid State Sensors, Actuators and Microsystems*; 2011.
13. Sacconi L, Romano G, Ballerini R, Capitanio M, De Pas M, Giuntini M, Dunlap D, Finzi L, Pavone FS. *Optics Letters* 26. 2001
14. Gertz F, Azimov R, Khitun A. *Applied Physics Letters*. 2012; 101:013701.
15. Watarai H, Namba M. *Anal Sci*. 2001; 17(10):1233–6. [PubMed: 11990604]
16. Zborowski M, Fuh CB, Green R, Sun L, Chalmers JJ. *Anal Chem*. 1995; 1567(20):3702–12. [PubMed: 8644920]
17. Equation was derived by Dr. Wei Xue of the Department of Biomedical Engineering, Cleveland Clinic and Department of Chemical & Biomolecular Engineering, The Ohio State University.

FIG. 1.

(a) Optical image of the cantilever after photochemical machining. Inset: schematic of the entire cantilever. (b) A scanning electron microscopy (SEM) image of the tip <200 nm. (c) Thermal calibration of resistively heated cantilevers in liquid. Inset: micro-cantilever on PCB holder immersed in a liquid drop. (d) The change in temperature with distance in a liquid drop of a heater cantilever – measured with a thermocouple (dotted line) and compared with FEA simulation (straight line). Inset: Image of the FEA simulation. The FEA model included a glass substrate labeled (i), a nickel cantilever labeled (iii), a liquid medium labeled (ii), and the data line is labeled (iv).

FIG. 2.

(a) Setup for attracting magnetic particles with a nickel foil cantilever. The microcantilevers were magnetized electromagnetically. (b) A cluster of $< 44 \mu\text{m}$ diameter Fe particles moves and attaches to the microcantilever. (c) Setup to remove the particles from the microcantilever using an electromagnet. (d) Iron micro-particles ($< 44 \mu\text{m}$) clusters are being removed from microcantilever as the coil is moved under the set-up.

FIG. 3.

(a) Images of microcantilever attracting a single magnetically labeled HeLa cell. Inset: schematic of the experimental setup used for cell capture. (b) Data from image analysis show the cell accelerating toward the cantilever at an average speed of $7.8 \mu\text{m}/\text{s}$, the theoretical fit from Eq. 2 is in agreement with the experimental data.