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An efficient biosensor made of an electromagnetic trap and a magneto-resistive sensor

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ABSTRACT

Magneto-resistive biosensors have been found to be useful because of their high sensitivity, low cost, small size, and direct electrical output. They use super-paramagnetic beads to label a biological target and detect it via sensing the stray field. In this paper, we report a new setup for magnetic biosensors, replacing the conventional "sandwich" concept with an electromagnetic trap. We demonstrate the capability of the biosensor in the detection of *E. coli*. The trap is formed by a current-carrying microwire that attracts the magnetic beads into a sensing space on top of a tunnel magneto-resistive sensor. The sensor signal depends on the number of beads in the sensing space, which depends on the size of the beads. This enables the detection of biological targets, because such targets increase the volume of the beads. Experiments were carried out with a 6 μm wide microwire, which attracted the magnetic beads from a distance of 60 μm, when a current of 30 mA was applied. A sensing space of 30 μm in length and 6 μm in width was defined by the magnetic sensor. The results showed that individual *E. coli* bacterium inside the sensing space could be detected using super-paramagnetic beads that are 2.8 μm in diameter. The electromagnetic trap setup greatly simplifies the device and reduces the detection process to two steps: (i) mixing the bacteria with magnetic beads and (ii) applying the sample solution to the sensor for measurement, which can be accomplished within about 30 min with a sample volume in the μl range. This setup also ensures that the biosensor can be cleaned easily and re-used immediately. The presented setup is readily integrated on chips via standard microfabrication techniques.

1. Introduction

Pathogen detection is of great importance in the food industry, water and environmental monitoring, and clinical diagnosis (Lazcka et al., 2007). Rapid, selective and sensitive pathogen detection is essential to ensure the safety of food and water or to quickly diagnose bacterial diseases. Conventional, standard pathogen detection methods include polymerase chain reaction (PCR), culture and colony counting methods, and immunological methods. PCR and the culture and colony counting methods are the most frequently used, due to their sensitivity, selectivity and reliability. Immunological methods employ antibody–antigen reactions for pathogen detection. The most popular immunological method is the enzyme-linked immunosorbent assay (ELISA), which takes advantages of the specificity of the antibody and the sensitivity of the enzyme assay (Lazcka et al., 2007). However, these methods are very time-consuming (several hours or up to several days (Lazcka et al., 2007)) and require highly skilled technicians and well-equipped biological laboratories. In this context, biosensors are considered as promising alternatives for pathogen detection in the future, but further work is required to make them more reliable, selective and sensitive.

Biosensors usually employ optical (Narsaiah et al., 2011), electrochemical (Lang et al., 2013), piezoelectric (Guo et al., 2012) or magnetic (Baselt et al., 1998; Gaster et al., 2011a,b, 2011c) transducers to detect pathogens. Optical biosensors have exhibited high sensitivity (Velusamy et al., 2010). The most sensitive optical biosensor can achieve a detection limit of 1 cfu/mL *E. coli* O157:H7 within about half an hour (Mechery et al., 2006). However, such a sensor requires a suitable spectrometer or camera, which is expensive and rather large for integrated, compact devices. Electrochemical biosensors have the advantages of low cost and small size, but their sensitivity and selectivity are usually lower compared to optical biosensors. With the help of magnetic bead conjugation and concentration, it is possible to detect 10 cfu/mL *E. coli* O157:H7 using a nanoporous membrane-based electrochemical biosensor (Chan et al., 2013). Piezoelectric biosensors measure changes of the resonant frequency of a quartz

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crystal when the biological targets are captured on a bio-functionalized crystal surface. The measurement can take up to a day and requires an enrichment step to reach the detection limit of 10 cfu/mL for *E. coli* O157:H7 (Guo et al., 2012). Without the enrichment step, the detection limit of the piezoelectric biosensor is typically about 10^3 cfu/mL (Buchatip et al., 2010; Su and Li, 2004).

Magnetic biosensors are suitable for very sensitive pathogen detection, because they can provide a resolution that is sufficient to recognize individual magnetic beads (Shen et al., 2005). In addition, magnetic beads can be concentrated or separated by magnetic fields (Gooneratne et al., 2012, 2013), enabling simple expansion of device functionalities.

Commonly, magnetic biosensors utilize the "sandwich" detection scheme, i.e., the target is sandwiched between a bio-functionalized sensor surface and bio-functionalized magnetic beads. This method requires bio-functionalizing the sensor surface and washing the sensor several times to remove extra beads and extra reagents during the measurement. While the method is very sensitive, it is also complex and tedious and an improvement is desirable to simplify the detection procedure, making it faster, more user-friendly and suitable for point-of-care devices. A step in this direction has recently been proposed with the "autoassembly immunoassay" (Gaster et al. 2011a,b, 2011c). In this case, biological targets and magnetic nanoparticles are mixed in the same solution and applied to the biosensor, where they bind to the bio-functionalized sensor's surface. This scheme has been employed for the detection of protein and DNA.

In this paper, we introduce a very simple electromagnetic trap to attract magnetic beads or magnetic bead-biological target compounds on top of a magnetic sensor. In the case of compounds, fewer magnetic beads will be trapped on top of the sensor, since some space will be occupied by the biological targets, leading to smaller output voltages. A higher concentration of biological targets causes more biological targets to bind to magnetic beads, reducing the number of beads inside the electromagnetic trap and resulting in a smaller sensor output. Hence, the concentration of biological targets can be related to the sensor's output. The main advantages of this method are that there is no need to bio-functionalize the sensor's surface and that the sensor works with a simplified detection process that requires only two steps. Since our biosensor is not functionalized, it can easily be cleaned and re-used. Moreover, continuous monitoring operations are also feasible. In this paper, our trap concept is demonstrated for the detection of *E. coli* bacteria.

2. Materials and methods

2.1. Electromagnetic trap

The device consists of a tunnel magneto-resistive (TMR) sensor (details in supplementary material), connected via four electric contacts, with a centrally tapered gold microwire on top of it (Fig. 1a). The microwire is fabricated using standard microfabrication techniques in which sputter deposition is used to deposit 20 nm Ti and 280 nm Au sequentially on top of the magnetic sensor, which is covered by a 200 nm thick silicon nitride layer. A photoresist layer is spin-coated on top and photolithographically patterned. The Ti/Au layer is then dry etched to fabricate the microwire. A 400 nm-thick layer of polymer (Micro-Chemicals, AZ 1505) is spin-coated on top of the gold layer to minimize the adherence of magnetic beads to the chip's surface. The electromagnetic trap is realized by applying a 30 mA electric current in the microwire that generates a non-uniform magnetic field, attracting magnetic beads and immobilizing them.

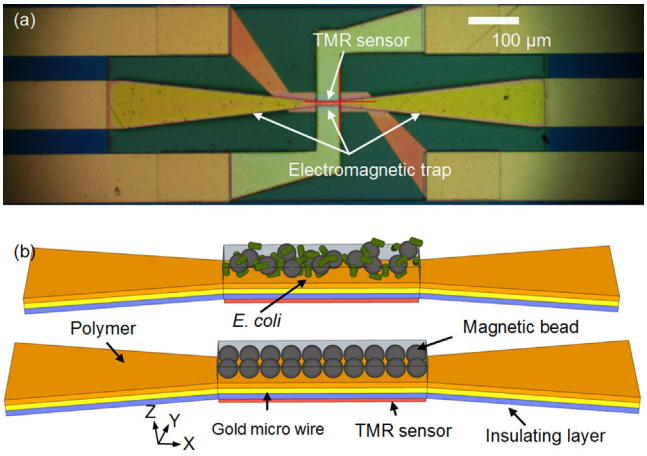

Fig. 1. A magnetic biosensor comprised of an electromagnetic trap and a tunnel magneto-resistive (TMR) sensor: (a) an optical image of the magnetic biosensor. The pads (not shown) for the electrical connections are about 3.7 mm away from the TMR sensor. (b) Schematic of the detection method. The current in the microwire creates a non-uniform magnetic field, forming an electromagnetic trap on top of the TMR sensor. The transparent box filled with magnetic beads represents the sensing space of the TMR sensor, which is the area from which magnetic beads influence the signal of the TMR sensor.

The number of beads trapped on top of the sensor depends on the size of the beads, which changes when biological targets are attached (Fig. 1b).

The size of the electromagnetic trap is defined by the magnetic force, F_{mag}, acting on a superparamagnetic bead, which is dominant over the Brownian force. F_{mag} can be calculated as (Boyer, 1988)

$$F_{mag} = \nabla(mB) = V\chi\nabla(HB), \tag{1}$$

where m is the magnetic moment of the bead, V is its volume, and χ is its susceptibility. Our numerical analysis shows that magnetic beads can be attracted from a distance of 70 μm, which corresponds very well to the 60 μm found experimentally (details provided in the supplementary material). The size of the electromagnetic trap can be adjusted by the design of the microwire, the amount of current and the type of magnetic bead.

2.2. Signal measurement

To increase the signal-to-noise ratio (SNR), a frequency modulation method is employed (de Boer et al., 2007). The beads are magnetized by applying a magnetization current

$$I_M(t) = \sqrt{2} I_M \cos(2\pi f_M t), \tag{2}$$

with an root-mean-square (rms) value of I_M=30 mA and a frequency of f_M=330 Hz to the microwire using a function generator (Agilent, 33250A). At the same time, a sensing current

$$I_S(t) = \sqrt{2} I_S \cos(2\pi f_S t), \tag{3}$$

with an rms value of I_S=400 μA and a frequency of f_S=65 Hz is applied to the TMR sensor using the same function generator (Agilent, 33250A).

The sensor voltage contains the signal of the magnetic beads at f_S+f_M and f_S-f_M (details in the supplementary material). With the help of a lock-in amplifier (Stanford Research, *SR850*), the output voltage, V_{out}, is measured at a frequency of f_S+f_M=395 Hz with a bandwidth of 0.26 Hz:

$$V_{out} = V_M + V_{Stray} = \frac{1}{\sqrt{2}} I_S R_0 \delta(\overline{B_M} + \overline{B_{Stray}}). \tag{4}$$