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Dynamic micro-Hall detection of superparamagnetic beads in a microfluidic channel

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Abstract

We report integration of an InAs quantum well micro-Hall magnetic sensor with microfluidics and real-time detection of moving superparamagnetic beads. Beads moving within and around the Hall cross area result in positive and negative Hall voltage signals respectively. Relative magnitudes and polarities of the signals measured for a random distribution of immobilized beads over the sensor are in good agreement with calculated values and explain consistently the shape of the dynamic signal.

Keywords

InAs quantum well; Microfluidics; Superparamagnetic beads; Micro-Hall sensor

1. Introduction

A wide range of potential applications in biology and medicine rely on using superparamagnetic (SPM) bead labels for monitoring and manipulating biological species such as genetic testing [1], detection of viruses [2], magnetic separation of biomolecules [3], or drug delivery [3]. Significant progress has been made in detecting the presence of such beads in a dry state with various solid-state magnetic sensors [4–11]. Microfluidic devices, furthermore, have been used to guide, manipulate, and sort magnetic beads [12–15] and to provide proper environment for biochemical interactions [16]. Hence, the integration of magnetic sensors with microfluidics is key for achieving portable, low cost, fast-response

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electronic chips that can be utilized in biomedical applications. Portability of devices based on optical detection techniques are generally limited by the need for high resolution optical microscopes and restricted by the optical transparency of the solutions. The preponderance of research efforts, however, have employed sensors based on metallic multilayer magnetoresistance technologies [17–22]. These sensors offer high sensitivity but often suffer from nonlinear response to magnetic fields, and more importantly, saturation at very low fields. A notable example of such efforts is that of Loureiro *et al* [17] using spin-valve sensors. The magnetic beads used in their work, however, consist of some strongly interactive nanoparticles which are not ideal for bio-applications [25]. Micro-Hall devices have linear output and are not limited in the magnitude of the external magnetic fields that can be applied to magnetize SPM beads, which is advantageous for biodetection and necessary in magnetic separation. In particular, devices based on InAs quantum well (QW) semiconductor heterostructures have been recently demonstrated with a superb signal-to-noise (S/N) ratio in detection experiments performed with micrometer and nanometer sized beads [10,23,24]. Furthermore, since these devices are sensitive to the perpendicular component of the stray magnetic field generated by the beads, they can map out the trajectory of the moving beads. Here, we demonstrate the first integration of InAs micro-Hall sensors with microfluidic channels and dynamic detection of micron-sized SPM beads.

2. Material and fabrication procedure

The sensors used in this work are in the form of an array of six $1 \times 1 \mu\text{m}^2$ Hall crosses. They were fabricated by means of photolithography and wet chemical etching from molecular beam epitaxy grown heterostructure consisting of GaAs substrate/GaAs buffer (100 nm)/AlAs (10 nm)/AlSb (105.4 nm)/Al_{0.8}Ga_{0.2}Sb (2000 nm)/ Al_{0.7}Ga_{0.3}Sb (200 nm)/AlSb (8 nm)/InAs (QW 12.5 nm)/AlSb (3 nm)/Te delta doping (0 nm)/ AlSb (10 nm)/GaSb (0.6 nm)/In_{0.5}Al_{0.5}As (5 nm). The device was covered by a 70 nm thick SiO₂ layer grown by RF magnetron sputtering to provide electrical insulation. The Hall coefficient of the sensor measured at room temperature was $188 \Omega/\text{T}$. The mobility and the density of the electrons in the InAs quantum well were $\mu = 1.4 \times 10^4 \text{ cm}^2/\text{Vs}$ and $n = 3.3 \times 10^{12} \text{ cm}^{-2}$ respectively.

Conventional techniques were employed to fabricate the microfluidic channel. A piece of glass cover slip was cut in a rectangular shape and glued onto a Si/SiO₂ wafer to form the master. Posts were attached to the mold to define access holes. The master and the posts were then covered with Polydimethylsiloxane (PDMS) and cured in an oven at 70 °C for five hours. Finally, the PDMS replica was peeled off and sealed to the sensor chip. The height and the width of the channel were 200 μm and 1000 μm respectively. The sensor and the PDMS channel were sandwiched inside a scaffold to strengthen the seal and prevent leakage. An optical image of the micro-Hall sensor integrated with microfluidics is shown in Figure 1.

A bead suspension was prepared by diluting 10 μL of streptavidin coated SPM beads (Bangs Laboratories, Inc.), 2.6 μm in diameter, into 0.7 mL of deionized water. Beads with the same functional group have been successfully used in detection of specific biomolecular interactions with micro-Hall magnetic sensors in a dry state [23]. The fluid was pumped into the channel through microtubes using a syringe pump and was monitored via an optical microscope equipped with a video camera. Since the beads have higher density (1.2 g/cm³) than water, the frictional force between the descended beads and the bottom of the channel is strong enough to slow the beads down to an average speed of 3 $\mu\text{m}/\text{sec}$ for a given flow rate of 1 $\mu\text{L}/\text{min}$.

3. Measurement, results and discussion

In order to facilitate detection, an external *ac* magnetic field of rms magnitude $B_0 = 0.9$ mT and frequency $f = 93$ Hz was applied perpendicularly to the sensor plane to magnetize the beads. The sensor was biased with a dc current $I = 50$ μ A and the Hall voltage V_H was measured using a lock-in amplifier tuned to the frequency of the *ac* magnetic field. As the beads pass by the cross they alter the total average magnetic field over its sensing area and hence V_H associated with it. Due to dipolar character [8,24] of the stray magnetic field, the total field penetrating each cross will either increase or decrease depending on the relative position of the beads with respect to the cross. Figure 2 shows a real-time V_H signal recorded for one cross (the first one from the left in Figure 2(b)). By matching the recorded movie of the flow of beads and the measured V_H , we find that the first dip in the close-up view of Figure 2(a) corresponds to a group of three beads approaching the sensing area of the Hall cross (Figure 2(b)). The successive peak appears when the first bead from the group passes right over the area (Figure 2(c)) while the second dip appears when the beads move away from the area (Figure 2(d)). By examining the rest of the data we find that the magnitudes of the recorded V_H signals depend on the distance between the beads and the Hall cross, the number of the passing beads, and their speed. In addition, we observed that each peak corresponds to beads passing over the sensing area and each dip corresponds to beads passing beside the area. The S/N ratio for the highest peak and the lowest dip recorded in the measurement were 22 dB and 24.7 dB respectively.

The conclusions drawn from the dynamic detection experiment were further confirmed with an experiment with immobilized beads. In this case, we prepared a drop of the same bead suspension on an identical Hall sensor and let it dry. Figure 3(a) shows an SEM image of the sensor with immobilized beads. One bead partially covers one cross while the rest of the beads are in the vicinity of the other crosses. A Hall detection measurement as described by Mihajlović *et al* [9,24] was then performed. Here, the main difference from the dynamic measurement is that an additional *dc* magnetic field ($B = 70.6$ mT) was applied in order to reduce the induced *ac* magnetization of the beads. This imitates the situation where the beads move away from the sensor. Figure 3(b) shows the measured V_H for four crosses shown in Figure 3(a). The sign of ΔV_H signals agrees well with our interpretation of the dynamic measurement. Namely, for the empty crosses (1–3) V_H went up, and for the occupied cross (4) down, when B was applied.

The change in the V_H signals due to the application of the dc magnetic field can also be estimated by calculating the change in the total average stray magnetic field penetrating the sensing area of each cross from nearby beads i.e. by using $\Delta V_H \propto \Delta B$. Since the stray magnetic field from a SPM bead is dipolar [8,24] and since the Hall sensor is only sensitive to the perpendicular component, we can explicitly write this change in average field as

$$\Delta B_i = \frac{\mu_0 \Delta M V}{4\pi} \sum_j \int_{A_i} \int \frac{2z^2 - (x-x_j)^2 - (y-y_j)^2}{(z^2 + (x-x_j)^2 + (y-y_j)^2)^{\frac{5}{2}}} dx dy$$

where indices i and j correspond to the Hall cross and the beads respectively, ΔM is the change in magnetization of the bead due to the application of the dc field, V is the bead volume and A is the sensing area of the Hall cross over which the integration is performed. Since these beads are very uniform and to keep the calculations simple, we will assume that all beads have the same volume and the same change in magnetization and therefore we will be interested in the relative magnetic field change for each cross rather than the absolute values. We find that the calculated signals from crosses (1),(2), (3) and (4) are $[\Delta B_1, \Delta B_2, \Delta B_3, \Delta B_4] \propto [1.0, 1.0, 0.9, -1.9]$. The relative change in the measured Hall signals yields $[1.0,$

1.1, 0.8, -1.9]. The agreement is excellent, considering that the variations between the crosses and the beads were disregarded in the calculations. Based on the measured noise level and according to this model, a single bead of the same size will be detectable within a radius of $4.5\text{ }\mu\text{m}$ from the center of the cross.

In principle, Hall sensors can be used to determine the trajectory of a moving magnetic bead. For simplicity, let us assume a single bead is moving on a straight line along the x-axis as shown in Figure 4. The Hall voltage signal can be calculated based on the magnetic dipole representation of the bead as a function of its distance from the cross center. The shape and amplitude of the detected signal depends on the trajectory of the bead as shown in Figure 4 for $y = 0$ and $y = 1.5\text{ }\mu\text{m}$. However, due to the symmetry of the Hall device, one cannot decipher whether the bead is moving in the x or y directions. This problem can be mitigated, for example, by using a network of Hall crosses that simultaneously record the signals from the bead movement.

4. Conclusion

We demonstrated real-time detection of micron-sized SPM beads using an InAs QW micro-Hall sensor integrated with a microfluidic channel. The recorded V_H consists of peaks and dips that correspond to beads moving over the sensing area and around it respectively. The polarity and the magnitude of ΔV_H signals were explained using a magnetic dipolar stray field representation of SPM beads.

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Figure.1.

(a) Optical image of a micro-Hall sensor chip integrated with microfluidics. (b) A PDMS microfluidic channel aligned with the sensor chip. (c) Six $1 \times 1 \mu\text{m}^2$ Hall crosses located under the microfluidic channel (area marked by the black circle in part (b) of the Figure).

Figure.2.

(a) V_H as a function of time recorded during movement of SPM beads in a microfluidic channel. The exploded view shows the signal due to a line of three beads passing the measured cross (first one from the left on the snapshot series (b) to (d)). The two dips correspond to the line of beads approaching [image (b)] and leaving [image (d)] the cross while the middle peak appeared when beads were partially covering the cross [image (c)].

Figure.3.

(a) An SEM image of the central region of an InAs micro-Hall sensor and immobilized SPM beads. The image shows one bead partially covering cross 4 and the rest of the beads are surrounding other crosses, (b) V_H as a function of time for crosses 1 to 4. The increase of V_H for crosses 1 to 3 and its drop for the cross 4 as B was applied agree with the expected signals based on a dipolar stray field representation of SPM beads.

a

b

Figure.4.

Hall voltage signals calculated for a bead moving along the x-axis for (a) $y = 0$ and (b) $y = 1.5 \mu\text{m}$. A distance $z = 1.4 \mu\text{m}$ was assumed between the bead and the conducting plane of the Hall sensor.