Sensing and Bio-Sensing Research 9 (2016) 7–12

Contents lists available at ScienceDirect

Sensing and Bio-Sensing Research

journal homepage: www.elsevier.com/locate/sbsr

Fast and sensitive medical diagnostic protocol based on integrating circular current lines for magnetic washing and optical detection of fluorescent magnetic nanobeads

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ARTICLE INFO

Article history:
Received 7 March 2016
Received in revised form 27 April 2016
Accepted 4 May 2016

Keywords:
Biosensors
Magnetic beads
Fluorescent magnetic nanoparticles
Lab on chip
Point of care testing

ABSTRACT

Magnetic nanoparticles (MNPs) are increasingly being used as 'magnetic labels' in medical diagnostics. Practical applications of MNPs necessitate reducing their non-specific interactions with sensor surfaces that result in noise in measurements. Here we describe the design and implementation of a sensing platform that incorporates circular shaped current lines that reduce non-specific binding by enabling the "magnetic washing" of loosely attached MNPs attached to the senor surface. Generating magnetic fields by passing electrical currents through the circular shaped current lines enabled the capture and collection of fluorescent MNPs that was more efficient and effective than straight current lines reported to-date. The use of fluorescent MNPs allows their optical detection rather than with widely used magnetoresistive sensors. As a result our approach is not affected by magnetic noise due to the flow of currents. Our design is expected to improve the speed, accuracy, and sensitivity of MNPs based medical diagnostics.

1. Introduction

Magnetic nano-particles or magnetic beads show potential as biomarkers for medical diagnostics resulting from their unique physical properties that include high surface area to volume ratio, compatibility with biological samples and ability to be manipulated by external magnetic fields [8,12,15]. These properties of micro and nanosized magnetic particles have led to reports of lab on chip applications [14] with for example, Burls et al. demonstrating the detection of the cardiac marker Troponin I at sub-pico moles per liter concentrations with low cost disposable cartridges and the importance of the dynamic control of nanoparticles by magnetic fields during detection [1].

However, biosensing platforms based on magnetic nanoparticles can be adversely affected by sensor noise primarily from two primary sources: First non-specific binding of magnetic nanoparticles to sensor surfaces that produces erroneous excess signals, and secondly, detection techniques using magnetoresistive sensors such as giant magnetoresistance (GMR) sensors and Hall effect devices experience sensor noise due to external magnetic fields applied to manipulate nanoparticles [7].In this paper we report on the design and implementation of a sensing platform devised to resolve both of these issues by minimizing the non-specific binding of nanoparticles to sensing areas and optical detection of fluorescent magnetic nanoparticles. Magnetic nanoparticles can be manipulated with permanent magnets, micro-machined micro magnets, and micrometer sized current carrying lines [10]. Current lines provide the most precise localized control of particles on sensing surfaces and have been used to determine bonding forces between biotin & avidin [11]. Most of the current line patterns for biosensing reported to date have implemented linear current lines with only a few reports about circular lines [4,6]. Here we experimentally show that circular current lines are more efficient at collecting magnetic particles than linear current lines. This is supported by theoretical calculations of the forces produced by the two which show that the circular lines produce higher forces than the linear pattern and thus have a higher capture cross section for attracting MNPs to the sensing area. This effect is important for improving the speed and sensitivity of this sensing platform. Furthermore, sensitivity is improved by detecting the light from fluorescent magnetic nanoparticles rather than GMR or other such

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http://dx.doi.org/10.1016/j.sbsr.2016.05.002

sensors thereby significantly reducing magnetic sensor noise described previously mentioned. Based on our experimental results, we estimate the theoretical limit of detection of our method to be 0.24 pg/mL (1 pM) for 180 nm diameter fluorescent nanoparticles functionalized with biotin molecules.

2. Design, methods and materials

2.1. Design of current lines

The key concept in our approach is to manipulate magnetic particles by magnetic forces generated by current lines. Various forces act on a magnetic particle suspended in a liquid [16] such as the drag force due to liquid, DLVO force and the force due to the applied magnetic field (magnetic force, F_{mag}). The magnetic force, F_{mag} due a magnetic field $\vec{B}$ is given by: $F_{mag} = \frac{V\chi}{2\mu_0}\nabla(\vec{B}\circ\vec{B})$ where χ is the magnetic susceptibility of the magnetic particle, V is its volume, and μ_0 is the free space permeability. We calculated the magnetic force produced by an ideal circular current line by the Biot-Savart law and implemented on MATLAB (Mathworks Inc., USA). Currents of the order of few tens of milliamperes were used in the simulations in order to obtain design values of the current lines that would avoid problems of heating and electromigration. A more detailed analysis of other effects, such as DLVO forces, was not carried out in this study.

2.2. Fabrication of current lines

The current line design consists of two circular rings (Fig. 1(a)) which produce magnetic fields in their vicinity and gather and move magnetic particles to the sensing surface located between the two rings (green region). The following design parameters were used: $R_1 = 10$ μm, $W_1 = 5$ μm, $R_2 = 20$ μm & $W_2 = 10$ μm as obtained from the results of simulations (see Section 3.1). Thus, the sensing area was about 400 μm^2. The device was fabricated on a SiO_2 (300 nm)/Si substrate by conventional photolithography followed by deposition of Ti (100 nm) and Au (100 nm) films and lift off to remove the photoresist and metal film. Electrical contacts were made with conducting silver paste and copper tape. Finally, the device was sealed by a polydimethylsiloxane (PDMS) structure to retain the sample solution near the sensing area.

2.3. Particles

Two types of magnetic beads were used: Dynabeads M-270 carboxylic acid (superparamagnetic, diameter 2.8 μm) and fluorescent FG beads (diameter 180 nm, Tamagawa Seiki, Japan). Fluorescent FG beads consist of iron oxide particles embedded in a matrix of polyGMA [9]. The beads emit red light when irradiated with UV light from an LED due to europium complexes inside the beads. Since the europium complexes are embedded inside the beads themselves, the FG beads do not

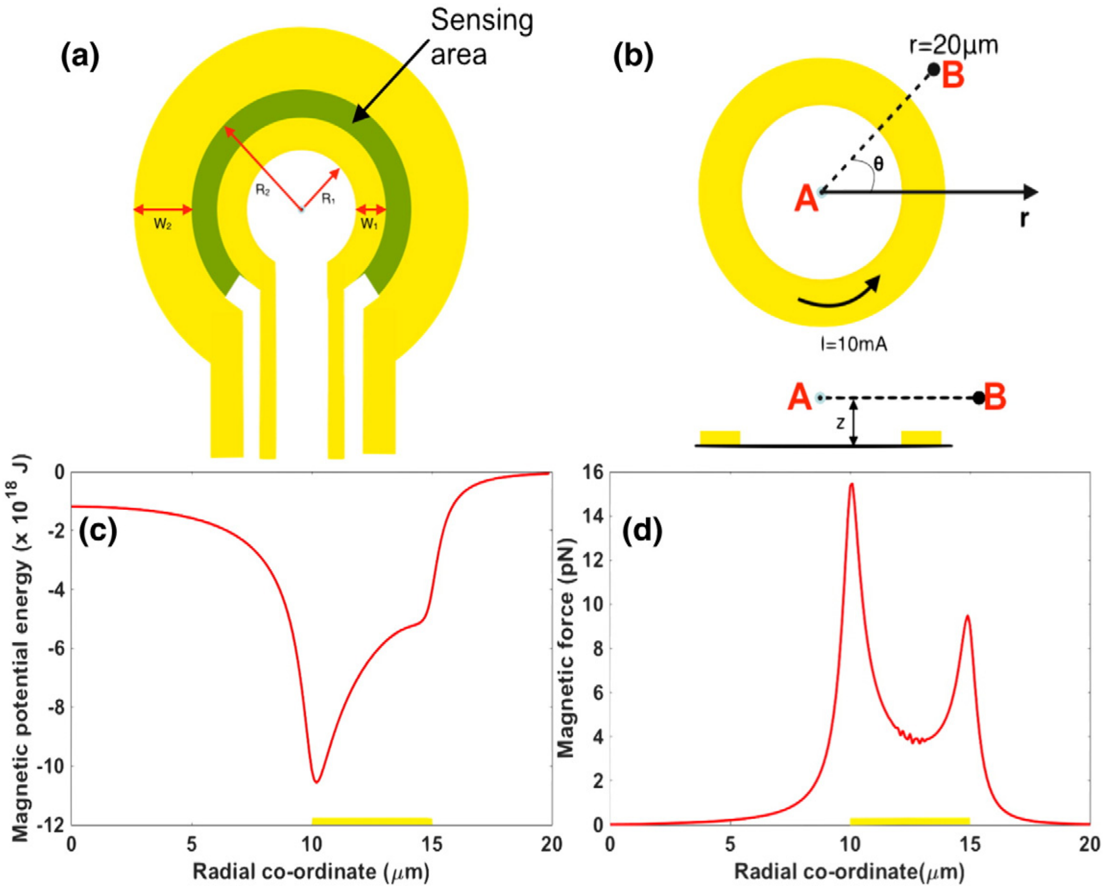

Fig. 1. Design of the sensor and simulation results. (a) Illustration of our sensor design. Design values are $R_1 = 10$ μm, $W_1 = 5$ μm, $R_2 = 20$ μm & $W_2 = 10$ μm. (b) Schematic of a current loop with inner radius $R_1 = 10$ μm, width $W_1 = 5$ μm and z = 500 nm used for calculating the results shown in (c) & (d). (c) Magnetic potential energy due to the current in the circular loop. (d) Magnetic force on Dynabeads by circular loop. The yellow bar drawn along the axis represents the cross section of the current line.