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Microfabricated tools for manipulation and analysis of magnetic microcarriers

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Abstract

Tools for manipulating and detecting magnetic microcarriers are being developed with microscale features. Microfabricated giant magnetoresistive (GMR) sensors and wires are used for detection, and for creating high local field gradients. Microfluidic structures are added to control flow, and positioning of samples and microcarriers. These tools are designed for work in analytical chemistry and biology.

Keywords: Detection; Giant magnetoresistance; Magnetic microcarrier; Nanoparticle; Bioassay; Microfluidics; DNA; Immunoassay; Sensor; Nanotechnology

1. Introduction

This paper will discuss the design and development of a magnetic microcarrier experimentation platform. It is designed to facilitate development of and experimentation with the microfabricated manipulation and measurement tools. At its base are the giant magnetoresistive (GMR) sensors and wires, then microfluidic and electrical interconnections, and a magnetic excitation module that interfaces with a standard laboratory instrumentation card (e.g. National Instruments). Emphasis is on the constraints and possibilities posed by the details of fabricating GMR sensors with fluidic connections.

In a typical application, the magnetic microcarriers would be attached to a biological entity such as protein, DNA or even whole cells. This allows the manipulation of the biological entity on the chip via the magnetic fields from the wires and their detection by proximity to the GMR sensors. Often, the sensors would be coated with a chemical

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agent that would selectively bind to target molecules on the microcarriers.

1.1. Overall design constraints

The overall system is designed to apply magnetic excitation fields in the plane of the sensor chip. Bipolar fields up to 100 Oe in excess of 100 Hz must be supported. Since many projects in this area benefit from simultaneous optical observation of on-chip activity, the system must allow for close work with optical and fluorescence microscopes. Electrical connections and microfluidic interfaces must co-exist on the same microchip and survive the same fabrication processes. Furthermore, the system must be manufacturable, inexpensive, and adaptable to a wide range of detection and manipulation applications. For these and more reasons, the system is designed for applying a magnetic field along just one axis—the sensitive axis of the GMR detector. Other successful efforts in excitation and detection have used out-of-plane fields, but to include that in this system would have been a premature addition of complexity. There is no fundamental reason, though, that fields could not be applied along multiple axes. In fact, it is expected that once experimental phases pass and specific chip requirements are defined, GMR biosensor products will not need visual access to the chip.

2. Magnetic excitation module

The excitation module, pictured below in Fig. 1, is based on standard printed circuit board (PCB) technology. The magnetic design is a variation of the basic C-shaped electromagnet having a linearly magnetizable core wrapped with wire coils. The so-called "pancake coils" printed on the circuit board, though less efficient than their wire-wound counterparts, are less expensive to mass produce. The two coils are constructed in the six-layer PCB out of 100 μm thick Cu. Each coil has 20 turns.

The magnetic cores are solid ferrite blocks. The excitation volume is defined by the 4 mm wide gap between the two 3 mm × 16 mm pole faces. In this paper, the x-axis is the cross-gap direction, the y-direction is in the PCB plane along the long direction of the gap, and the z-direction is out of the PCB plane. The GMR sensor is positioned on a second "disposable" PCB carrier in the geometric center of this volume where the field is most uniform. At this position, the applied field in the gap is essentially parallel to the x-direction. The sensor chip plane is in the X–Y plane with the sensitive axis of the sensor aligned along the x-axis. The magnetic excitation module has a voltage-controlled current source where ± 10 V generates ± 100 Oe at the center of the excitation volume.

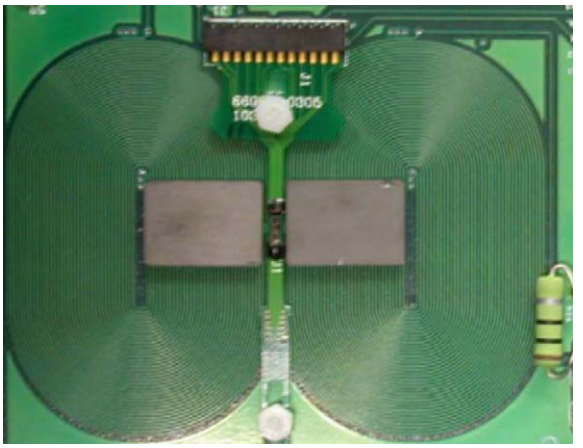

Fig. 1. Magnetic excitation module with sensor chip in the gap between the ferrite pole pieces. An additional ferrite bar on the back side of the board completes the flux loop. There is a small vertical gap due to the thickness of the PCB, though this is of low magnetic reluctance compared to the sensor gap.

For some applications, a time varying excitation is desirable. The excitation module is designed to do this at frequencies up to 1000 Hz. The maximum slew rate at an applied voltage of 10 V is 2.5×10^3 Oe/s.

The coils have a series resistance of 20 Ω, so the power required at 10 V is 5 W for 100 Oe. This is a relatively small power requirement, but still requires an independent power supply. Battery-powered applications would demand lower power dissipation, which can be achieved by reduction of the gap width, reduction of the coil resistance or closure of the magnetic path through the PCB with additional ferrite material.

The magnetic excitation module can be controlled by a computer through a commercially available, inexpensive analog interface card. The same interface card is also used to acquire the data from the sensor. Control of the excitation field and collection of data samples is performed by software on the computer.

3. Sensor chip design—magnetics

The design objective for GMR biosensors is to detect and quantify magnetic nanolabels in the defined detection volume, or the magnetic "field of vision". The "depth" of the field of vision is defined primarily by the diameter of the nanolabel, and the length and width by the lateral dimensions of the GMR sensor in the plane. The stray field from a single nanolabel generally drops off as the cube of the (distance/radius) from the label [1]. The situation is more complex for non-spherical labels, and ones that are non-uniformly magnetized. Further consideration is required when detection of many magnetically interacting labels is required. Fortunately, these situations can be adequately modeled with commercial magnetics software packages.

The GMR detector essentially measures the strength of the local magnetic field. In practice, this field includes the Earth's field (~0.5 Oe), the applied field of the sensing system, the field from the nanolabel, and all the other field noise from power lines, motors, and so on. The stray field from the nanolabel is usually very small compared to these other fields, so care is required to make high-quality measurements. By placing some GMR resistors (sense) in contact with the labels and others much farther away (reference), and comparing the signal detected on these two kinds of resistors, very small amounts of magnetic nanolabels can be detected. Topological arrangements such as the one shown in Fig. 2 accomplish these objectives.

The magnetic nanolabel detection problem is, by nature, a three-dimensional magnetic field system. GMR sensors (and other types of magnetoresistors), however, are virtually insensitive to out-of-plane fields. They are usually much more sensitive along one of the two in-plane axes. So one can use the nominally single-axis detection limitation to advantage. One approach is to apply a strong out-of-plane field to magnetize the labels, and use the GMR sensor to detect the in-plane component/s of the stray field. This has been done with considerable success [2,3] using GMR material that has unipolar response [4]. An additional advantage can be gained by adding oscillating in-plane "wiggle" field [5] and using a bipolar GMR "spin valve".

Another approach is to use a permanently magnetized label. In this mode, an external field can be used to induce physical rotation of the label to be parallel to the applied field. An interesting example is detection of single magnetic nanowires [6].

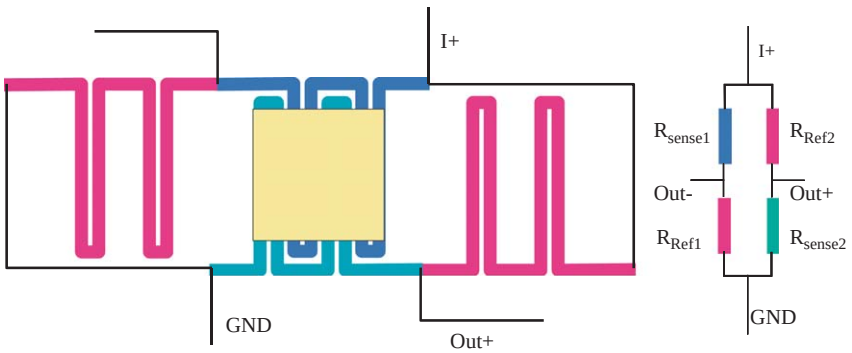

Fig. 2. Layout of GMR resistors in a Wheatstone bridge such that two resistors are underneath the biochemical sensing area (shaded square) while two are positioned as balancing reference resistors. If the bridge resistors are all equal, the nominal voltage output of the bridge is 0 V. Then when the sense resistors increase, the voltage output increases.

GMR resistors are formed by patterning thin multiplayer metal films into long narrow resistors. They are patterned to be 2 μm wide and arbitrarily long. A single resistor can be used to cover almost any geometrical surface area by forming the resistor in a meandering serpentine shape [7] (see Fig. 2). In practice, the size of the sensing area on a chip can be adapted to the spot size of a biochemical surface conditioning [3], or the width of a flow channel [8].

The ultimate limit of detection for a given type of nanolabel depends on several factors beyond the raw size and magnetic content of the label. The most critical factor is the separation from the label to the GMR sensor. This separation can be minimized by reducing the thickness of the dielectric passivation that covers, and electrically isolates the GMR sensor from the label and the sample buffer. Another key factor in the detection limit is the size of the applied field that is used to magnetize the magnetic particle. A larger applied magnetizing field results in a larger stray field from the particle that can be detected. However, the magnetizing field must not take the GMR sensor out of its active sensing range. A reasonable summary statement is that a single magnetic nanolabel can be easily detected if it is within about one diameter of a detector whose lateral dimensions are about one diameter [9]. Many kinds of magnetoresistive materials can be used as a detector. The best are those that have a linear resistance vs. applied field response and minimal hysteresis [10].

If one adds biochemistry and microfluidic issues to the problem, the limit of detection tends to be driven by the hydrodynamics of the flow system and the biochemical "noise" of the binding assay [11].

4. Sensor chip design—mechanical

Successful fabrication of GMR biosensor chips has required advances in processing techniques. The need to minimize the dielectric thickness while maintaining the integrity of its insulating properties in an electrically energized fluidic environment is particularly challenging. Several failure modes occur in these devices. One is the simple dielectric breakdown of the silicon nitride. This happens most frequently at the corners and sidewalls of the passivated GMR structure where the electric field is highest. Another failure mode occurs when liquid penetrates a small defect or void in the dielectric, permitting electrolysis of the liquid, and eventually the oxidation of the GMR electrode. One simple test for these kinds of failures is to watch through a microscope the sensing area while applying power to the sensor and placing liquid on the sensor. Bubbles start appearing at the defects where electrolysis is taking place.

Sample holding regions can be formed directly on the GMR chip with patternable spin-on materials. NVE has been using BCB and SU-8 most often. These regions can function as fluid wells, or as microfluidic channels, depending on the shape of the structures and what fluidic covers are provided. The cross-section in Fig. 3 shows how such a structure is assembled.

The largest remaining challenge to commercializing GMR biosensing devices is to develop a mass-manufacturable method of sealing on-chip microfluidic channels without clogging them, and providing a sealable interface to an external sample introduction tube or cartridge. At present, the best microfluidic covers are made with cast PDMS, a clear silicone rubber material. A photograph of a GMR chip with a three-port PDMS cover is in Fig. 4. Some care is required when wirebonding the chip to its carrying board. The procedure must not damage the surface of the sensor, and potting material must not flow over the sensor.

5. Conclusions

Magnetic microcarriers, originally developed as means to apply localized force on a magnetically labeled biochemical entity, are now being evaluated as markers for quantitative detection and analysis of such entities. Microfabrication techniques are being applied to develop lab-on-a-chip devices that take specific advantage of the unique properties of magnetic microcarrier labels. One potential advantage these devices have for clinical

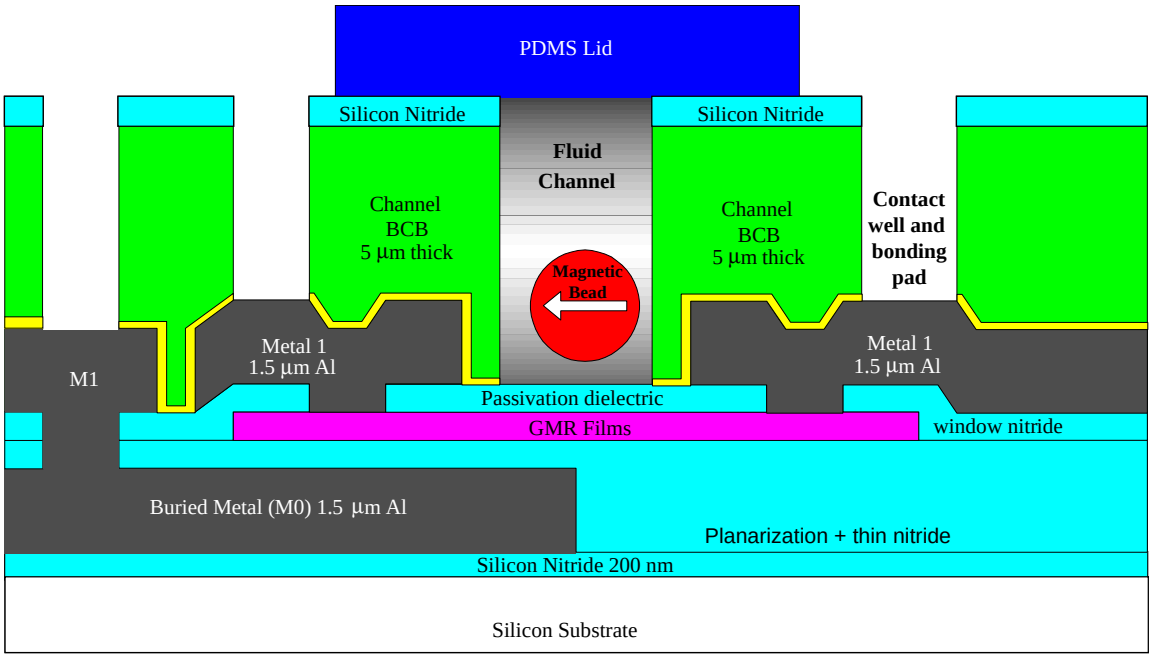

Fig. 3. Cross-sectional view of the GMR biochemical sensor. The polymer layers above the GMR layer perform two functions: they provide electrical passivation for the Al wires on the chip going from the GMR sensor to the wire bonding pads, and also, they form the microfluidic channel or recess on the sensor board. These fluidic structures, in addition to constraining fluid flow, also cause the reference GMR resistors to not see much signal from beads that are directly over them because they are far away due to the thick passivation.

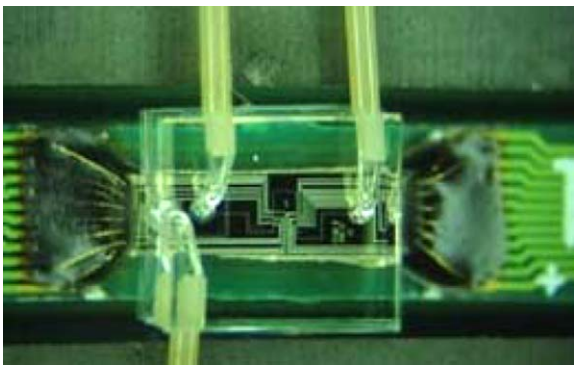

Fig. 4. Photograph of GMR sensor with PDMS fluidic cover. There are two fluid inputs on the left, and one fluid outlet on the right. Electrical connections from the chip are made with wire bonds to the underlying PCB. The black material on the left and right side of the PDMS cover is epoxy that encapsulates the wire bonds.

and commercial applications is that they can be made in large volumes at low cost using semiconductor manufacturing techniques. Several applications could benefit from the use of microfabrication magnetics tools. Specific examples include surface binding measurements (DNA or immunoassays) [2,3], single-cell RNA detection [12], and flow cytometry. However, considerable work is necessary to evaluate these modes. Instrumentation has been developed to facilitate this kind of magnetic nanoanalysis, especially for laboratories with limited magnetics instrumentation. This instrumentation set includes means to repeatably generate magnetic fields over the range of ± 100 Oe with sufficient uniformity over a volume containing GMR sensors.

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