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1. Introduction

Clinical diagnostics is a field in which new methods of laboratory analysis for faster, direct, more accurate, more selective, has a high output and less expensive than conventional methods are in high demand. Because of its small size, transduction ultrasensitive and possible integration in Microsystems lab-on-a-chip, biosensing devices are made with nanotechnology is a potential candidate to meet all the requirements above. Since last decade, many researchers have been brought their work to carry out on biomagnetism and magnetic biosensors based on molecular processes. Their works focus not only on application of magnetic nanoparticles in biomedicine (Pankhurst et al., 2009) but also on their synthesis (Roca et al., 2009), functionalization (Berry, 2009) and their detection by magnetic sensors (Megens et al., 2005). As shown in Fig.1, magnetic micro-machine has been applied in medicine. This machine is designed to move through the human body and his pathway is controlled by magnetic field.

Fig. 1. Magnetic micro-machine (Adapted from Ishiyama et al., 2001)

Nowadays, accurate, rapid, cheap and selective analysis is required for clinical and industrial laboratories. Magnetoresistive biosensors seem to be among the best candidates to meet these criteria. Since the late 1990s, magnetoelectronics (Xu et al., 2008) has emerged as one of several new platform technologies for biosensor and biochip development. This technology is based on the detection of biologically functionalized micrometer or nanometer-sized magnetic labels, using high-sensitivity microfabricated magnetic-field sensors. In recent years, giant magnetoresistance (GMR) sensors have shown a great potential as sensing elements for biomolecule detection. The resistance of a GMR sensor changes with the magnetic field applied to the sensor, so that a magnetically labeled biomolecule can induce a signal. Compared with the traditional optical detection that is widely used in
biomedicine, GMR sensors are more sensitive, portable, and give a fully electronic readout. Due to advantages of GMR materials for magnetic field measurements, such as: high sensitivity and quick response under low magnetic field, more attentions have been paid on developing GMR material for biosensors.

The chapter covers the design, fabrication and testing of both types of biosensor nanodevices. Further integration of nanosensors, microfluidics, optical and electronic functions on a single sensing circuit could lead to a complete “lab-on-chip” technological solution which could be used in medical applications. Examples of fabrication, characterization and real applications of the devices will be discussed as well as the way of their integration.

This chapter is organized as follows; an overview of the GMR sensors, a brief overview of biosensor and its potential application in clinical diagnosis, a complete description of GMR biosensors application in medical starting from a general overview and showing examples based in integrated GMR biosensor of the latest developments in this field. Finally, the future trend of this exciting GMR biosensor for medical application is discussed.

2. An overview of the GMR sensors

Magnetoresistance is defined as the change in the resistance of a material in response to an externally applied magnetic field. The first announcement of the GMR effect was reported in 1988 by Baibich (Baibich et al., 1998). They discovered that the resistance of a sandwich type multilayer with magnetizations aligned initially (in the magnetic field $H = 0$) antiparallel decreased more than 50% after applying an external magnetic field. Because this decrease of resistance was very large they called this effect giant magnetoresistance (GMR). Since the discovery of the giant magnetoresistance (GMR) effect in magnetic multilayer systems, sensors employing this effect have been utilized in many areas of science and technology.

The GMR material is a material that has huge magnetoresistance, good magnetic-electrical properties, so that potentially to be developed to become next generation magnetic field sensing devices like sensors. The GMR sensor has many attractive features, for example: reduction size, low-power consumption, low price as compared to other magnetic sensors and its electric and magnetic properties can be varied in very wide range.

The GMR effect is a quantum mechanical effect observed in the thin film structure consisting of ferromagnetic layers separated by nonmagnetic layers. Thin film of GMR has different structures and each structure has the effect of magnetoresistance (MR) are also different. Structure of GMR consists of a sandwich structure, the spin valve and multilayer as shown in Fig. 2.

Physics basis of the GMR effect is related to the fact that the spin of electrons has two different values (called the spin up and spin down). When these spin across the material that has been magnetized, one type of spin may be experiencing barriers (resistance) which is different than that experienced by other types of spin. This property indicates the existence of spin dependent scattering.

GMR phenomena in multilayer ferromagnetic can be explained using Mott model which was introduced as early as 1936 to explain the sudden increase in resistivity of ferromagnetic metals as they are heated above the Curie temperature (Mott, 1936). In this model: (1). electrical conductivity in metals can be described in connection with two free conduction channel in which the former relates to an electron with spin up and others associated with the electron with spin down, (2). in ferromagnetic metals the rate of scattering of spin up and spin down electrons are very different.
The GMR effect relies on the experimentally established fact that electron spin is conserved over distances of up to several tens of nanometers, which is greater than the thickness of a typical multilayer. Therefore, the electric current in the trilayer flows in two channels, one corresponding to electrons with spin projection $\uparrow$ and the other to electrons with spin projection $\downarrow$. Since the $\uparrow$ and $\downarrow$ spin channels are independent (spin is conserved) they can be regarded as two wires connected in parallel and the GMR can be explained using a simple resistor model, as shown in Fig. 3.

Consider the ferromagnetic multilayer configuration such as Fig. 3, and it is assumed that strong scattering occurs for electrons with spin antiparallel to the direction of magnetization, while the weak scattering occurs for electrons with spin parallel to the direction of magnetization. This assumption describes the asymmetry in the meetings condition at the Fermi level corresponding to Mott's second argument.

In the ferromagnetic configuration Fig. 3 (a) of the trilayer, electrons with spin $\uparrow$ are weakly scattered both in the first and second ferromagnetic layer, whereas the $\downarrow$ spin electrons are strongly scattered in both ferromagnetic layers. This is modelled by two small resistors in the spin $\uparrow$ spin channel and by two large resistors in the spin $\downarrow$ channel in the equivalent
resistor network. Since the $\downarrow$ and $\uparrow$ spin channels are connected in parallel, the total resistance of the trilayer is determined by the low resistance $\uparrow$ spin channel which shorts the high-resistance $\downarrow$ spin channel. Therefore the total resistance of the trilayer in the ferromagnetic configuration is low. On the other hand, $\downarrow$ spin electrons in the antiferromagnetic configuration are strongly scattered in the first ferromagnetic layer but weakly scattered in the second ferromagnetic layer. The $\uparrow$ spin electrons are weakly scattered in the first ferromagnetic layer and strongly scattered in the second. This is modelled in Fig. 3 (b) by one large and one small resistor in each spin channel. There is no shorting and the total resistance in the antiferromagnetic configuration is much higher than in the ferromagnetic configuration.

Fig. 3. Resistor model of GMR (Adapted from Mathon, 2001).

In 1988 experiments on layered thin films of ferromagnetic metal (FMs) alternated to a non-magnetic metal (NM) led to the simultaneous and independent discovery of the giant magnetoresistance (GMR) by A. Fert (Baibich et al., 1988) and P. A. Grünberg (Binasch et al., 1989). Fig. 4 shows the original results obtained by Baibich and coworkers. The (001)Fe/(001)Cr bcc superlattices were grown by the MBE method. The magnetoresistance was measured at 4.2 K for different thicknesses of the Cr spacer. The authors explained the GMR effect as follows. The resistivity drops when the magnetic external field overcomes the antiferromagnetic coupling and the alignment of magnetizations becomes a parallel arrangement. It was supposed that the spin-dependent scattering of the conduction electrons in the magnetic layers or at their interfaces was responsible for the GMR effect. The scattering in antiparallel alignment is much larger than in the parallel case. Complete review of the GMR can be found at (Tsymbal & Pettifor, 2001).

In this field, we also have developed GMR material with sandwich structure (Djamal et al., 2006). Recently, we have successfully developed GMR thin film with sandwich structure using dc-opposed target magnetron sputtering, and we obtained about 65 % MR value at
room temperature in NiCoFe/Cu/NiCoFe sandwich (Djamal et al., 2009a; Djamal et al., 2009b; Ramli et al., 2009; Djamal et al., 2010; Ramli et al., 2010). The GMR ratio curve for NiCoFe/Cu/NiCoFe sandwich is shown in Fig. 5, 6, 7 and 8.

Fig. 7 shows variation of magnitude of GMR ratio versus Cu layers thickness. Their general appearance is a classical behavior of MR evolution with magnetic field that has been observed in many multilayers (Dieny et al., 1991; Tang et al., 2007; Tripathy & Adeyeye, 2007) based on ferromagnetic transition metal and a non magnetic layers. The dependence of GMR value on the non-magnetic layer thickness in magnetic multilayer and spin valves qualitatively ascribed to two factors (Parkin, 1998), i.e.: (i) with increasing spacer thickness the probability of scattering increases as the conduction electrons traverse the spacer layer, which reduces the flow of electrons between the ferromagnetic layers and consequently reduces GMR; (ii) the increasing thickness of the nonmagnetic layer enhances the shunting current within the spacer, which also reduces GMR. These two contributions to GMR can be phenomenological described as the relative resistance change \( \Delta R \) by the following expression:

\[
\frac{\Delta R}{R} = \left( \frac{\Delta R}{R} \right)_0 \exp\left( \frac{-d_{NM}}{l_{NM}} \right) \frac{1}{1 + \frac{d_{NM}}{d_0}}
\]  

The parameter \( l_{NM} \) is related to the mean free path of the conduction electrons in the spacer layer, \( d_{NM} \) is spacer layer thickness. The parameter \( d_0 \) is an effective thickness, and \( \left( \frac{\Delta R}{R} \right)_0 \) is a normalization coefficient. The decay in GMR value with increasing Cu thickness can be described approximately:

\[
\frac{\Delta R}{R} \approx \frac{1}{t_{Cu}} \exp\left( -t_{Cu} / \lambda_{Cu} \right)
\]  

where \( t_{Cu} \) is the Cu thickness and \( \lambda_{Cu} \) describes the scattering within the Cu layer interior.
Fig. 5. The dependence of GMR ratio on the spacer layer thickness ($t_{Cu}$) with fixed NiCoFe layer thickness ($t_{NiCoFe} = 62.5$ nm).

In sandwich structure, the decrease in magnitude of GMR ratio at low thickness of NiCoFe in Fig. 8 is due to the scattering on the outer surface like substrate or buffer layer (Dieny., 1994). This scattering significantly affects GMR, when the thickness of the ferromagnetic layer becomes smaller than the longer of the two mean-free paths associated with the spin up and spins down of electrons.

Fig. 6 shows that at the thickness of NiCoFe over 62.5 nm the magnitude GMR ratio decreases. This phenomenon could be explained by the appearance of inactive region in NiCoFe layer that shunts the current. On the other hand, the sharpness of GMR curve increases with increasing NiCoFe layer thickness, as observed in Fig. 6.
Generally, there are many sensors can be used for measuring magnetic field namely fluxgate sensor, Hall sensor, induction coil, GMR sensor, SQUID sensor and some others. Due to advantages of GMR materials for magnetic field measurements, such as: high sensitivity and quick response under low magnetic field, more attentions have been paid on developing GMR material for magnetic field sensors. Table 1 illustrates the differences between GMR and other magnetic field sensors (Han et al., 2005). Besides that, GMR material based sensors have more benefit compared to other magnetic sensors such as smaller size, lower power and lower cost (see Fig. 9).

Fig. 6. The dependence of GMR ratio on the ferromagnetic layer thickness ($t_{\text{NiCoFe}}$) with fixed Cu layer thickness ($t_{\text{Cu}} = 14.4$ nm).
Fig. 7. Variation of magnitude of GMR ratio versus Cu layer thickness. The dotted line shows the decay of GMR ratio with increasing of Cu layer thickness as expressed in eq. (2).

Fig. 8. Variation of magnitude of GMR ratio versus NiCoFe layer thickness.

Since the late 1990s, magnetoelectronics (Prinz, 1998) has emerged as one of several new platform technologies for biosensor and biochip development. This technology is based on the detection of biologically functionalized micrometer or nanometer-sized magnetic labels, using high-sensitivity microfabricated magnetic-field sensors. GMR biosensors seem to be among the best candidates to meet these criteria. The GMR biosensors capable of highly sensitive detection are poised to become a dominant player in the vast world of biosensors (Hall et al., 2010).

<table>
<thead>
<tr>
<th></th>
<th>H range (T)</th>
<th>Sensitivity (V/T)</th>
<th>Response time</th>
<th>Power consumption</th>
<th>Sensor head size</th>
</tr>
</thead>
<tbody>
<tr>
<td>GMR</td>
<td>$10^{-12}$-$10^{-2}$</td>
<td>120</td>
<td>1 MHz</td>
<td>10 mw</td>
<td>10-100μm</td>
</tr>
<tr>
<td>Hall</td>
<td>$10^{0}$-$10^2$</td>
<td>0.65</td>
<td>1 MHz</td>
<td>10 mw</td>
<td>10-100μm</td>
</tr>
<tr>
<td>SQUID</td>
<td>$10^{-14}$-$10^{-6}$</td>
<td>$10^{-14}$</td>
<td>1 MHz</td>
<td>10 mw</td>
<td>10-100μm</td>
</tr>
<tr>
<td>Flux gate</td>
<td>$10^{-12}$-$10^{-2}$</td>
<td>3.2</td>
<td>5 kHz</td>
<td>1 w</td>
<td>10-20 mm</td>
</tr>
</tbody>
</table>

Table 1. Comparison of magnetic field sensors commonly used.
Fig. 9. Comparison of power, price and size of some magnetic sensors

3. Biosensor and its potential application in clinical diagnostic

A biosensor is generally defined as an analytical device, which makes use of a biological molecular recognition component connected to a transducer to generate a quantifiable electronic output signal, in response to a biological or chemical analyte (Li et al., 2006). Biosensors are under intense development for a wide range of applications from medical diagnostics to countering bio-terrorism.

Research in this area can be divided into three directions. The first direction focuses on the development of the synthesis of magnetic beads with desired magnetic properties that can be engaged with a high degree of specificity as microarrays. The development of high-precision on-chip electrostatic or magnetic field gradient architectures became the main mention of the second direction. This chip has capability to manipulate functionalized single magnetic beads as well as the microfluidic circuits. Fig. 10 shows one example of functionalized single magnetic beads. The third area is development of biocompatible solid-state sensors for quantitative magnetic beads. Two type of this sensor can be seen in Fig. 11.

Fig. 10. Functionalized single magnetic beads fabricated by continuous-flow lithography. Scale bar represents 100 μm [Adapted from Pregibon et al, 2007].
The first sensor based on GMR effect and the other based on the Tunneling Magnetoresistance (TMR). Both of these sensors have the same structure, only the non-magnetic metal spacer in GMR sensor is replaced with a very thin insulating barrier. This insulating barrier commonly made from Al₂O₃ or MgO.

Fig. 11. (a). GMR sensor. (b). TMR (Tunnelling magnetoresistance) [Adapted from Ishiyama et al., 2001].

4. The GMR biosensor and its application in clinical diagnostic

The development of robust, versatile and high throughput biosensing platforms is expected to have far-reaching implications in medicine, point-of-care clinical diagnostics, pharmaceutical drug development, and genomic and proteomic research. Enabled by rapidly emerging nanotechnologies (nanoparticles, nanotubes, and nanowires) and microfabrication techniques (MEMS, microfluidics, and CMOS), several new sensing platforms have been proposed and tested for biomedical applications, one of them is GMR biosensors.

As we have known that the detecting elements of biosensors work in different physicochemical ways: optical, piezoelectric, electrochemical, thermometric, and magnetic. Biosensors using magnetics utilize the magnetic field created by magnetic particles that bind to target molecules in a biological assay (Fig. 12).
Fig. 12. Schematic of magnetically labeled biomolecule detection in a biosensor. Target biomolecules bound with a magnetic particle interact with magnetoresistive sensor-bound counter biomolecules to be detected.

A first model for the detection of magnetic markers by GMR-type magnetoresistive sensors was published by Tondra, et al., 1999 in NVE Inc. (Tondra et al., 1999). He concluded that single magnetic markers of any size can be detected as long as the sensor has about the same size as the marker and the insulating protection layer is thin enough.

Baselt et al. (1998) were the first to demonstrate using GMR sensors as biosensors and several groups have continued the research and development of magnetic biosensing technology (Ferreira et al., 2003; Rife et al., 2003; Reiss et al., 2005; Xu et al., 2008; Osterfeld et al., 2008; Koets et al., 2009; Hall et al., 2010).

The incorporation of GMR structures in bacteria sensing is illustrated in Fig. 13 by Millen, (Millen et al., 2005). Generally, the surface of the GMR sensing region is modified to allow the binding of capture antibody. When the GMR structure is exposed to a sample solution that contains target antigens, complex binding between the target antigen and antibody occurs. This is followed by the addition of antibody-coated magnetic particles that subsequently labeled the target antigens and form a series of sandwich-like structures.

Fig. 13. Bacteria sensing using a GMR biosensor (Adapted from Millen et al., 2005).

In order to detect the magnetic particles bound on a GMR structure surface, an external magnetic field is applied in the z-direction, as illustrated in Fig. 14 (Rife et al., 2003). The GMR biosensors detect the stray field from the magnetic tag to infer the number of captured analytes. Bound magnetic particles that are exposed to a magnetic field will generate magnetic induction in the x-direction. Since the GMR structure detects only the x-
component of the magnetic field, the external magnetic field in the z-direction does not have any effect on the detection.

Fig. 14. Detection of magnetic particle on GMR biosensor (Adapted from Rife et al., 2003).

5. Future trend in GMR biosensor for clinical diagnostic

A number of magnetic sensors have been designed and developed as detector for magnetic markers. Although their principles have different operation, there are two kinds of type that have been developed namely mass-coverage sensors with active areas of hundred square arrays and single-bead detector. With excellent signal to noise ratio, GMR biosensor is one of mass-coverage sensors. Freitas et al. reported that they can made mass-coverage GMR sensor to detect DNA from genes associated with cystic fibrosis (Freitas et al., 2004). The other group also reported real-time measurement of the progress of binding of functionalised bead to sensor in liquid (Golub et al., 1999; Graham et al., 2003). One of mass-coverage sensors based on GMR can be seen in Fig. 15.

Fig. 15. Image of magnetonanosensor chip with 64 sensors in an 8 x 8 array. The arrow indicates a single chip. [Adapted from Gaster et al., 2009]
GMR biosensors rely on a magnetic tag. Biosensors utilizing magnetic tags offer several key advantages over other sensing modalities (Hall et al., 2010). First, the biological samples (blood, urine, serum, etc.) naturally lack any detectable magnetic content, providing a sensing platform with a very low background level and thus lower detection limit of analytes. Second, the sensors can be arrayed and multiplexed to perform analysis on a panel of proteins or nucleic acids in a single assay. Lastly, the sensors can be manufactured cheaply, in mass quantities, to be deployed in a one-time use disposable format. For these reasons, magnetic biosensors are an attractive and competitive alternative to optical techniques.

6. Conclusion

The GMR biosensor are best candidates for future device based on lab-on a-chip, compact and inexpensive detection units in clinical diagnostic. Compared to complex and expensive optical detection systems, the GMR biosensor measures electrical signal directly from the sensor, and makes a low-cost, highly portable device feasible. On other hand, GMR biosensors are more sensitive, portable and give a fully electronic readout.

7. Acknowledgement

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8. References


A biosensor is a detecting device that combines a transducer with a biologically sensitive and selective component. Biosensors can measure compounds present in the environment, chemical processes, food and human body at low cost if compared with traditional analytical techniques. This book covers a wide range of aspects and issues related to biosensor technology, bringing together researchers from 16 different countries. The book consists of 24 chapters written by 76 authors and divided in three sections: Biosensors Technology and Materials, Biosensors for Health and Biosensors for Environment and Biosecurity.

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