Ultrasensitive Magnetic Field Sensors

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One of the cutting-edge topics today is the use of magnetic field sensors for applications such as magnetocardiography, magnetotomography, magnetomyography, magnetoneurography, or their application in point-of-care devices. Types of magnetic field sensors include direct current superconducting quantum interference devices, search coil, fluxgate, magnetoelectric, giant magneto-impedance, anisotropic/giant/tunneling magnetoresistance, optically pumped, cavity optomechanical, Hall effect, magnetoelastic, spin wave interferometry, and those based on the behavior of nitrogen-vacancy centers in the atomic lattice of diamond. Current developments of magnetometry in biological diagnostics are revised in review paper DOI: 10.3390/s20061569 (https://doi.org/10.3390/s20061569).

Keywords: magnetic field sensors ; biosensors ; biomagnetic fields ; therapeutic application ; noninvasive medical procedures ; diagnosis

1. Introduction

The development of magnetic field sensors for biomedical applications primarily focuses on equivalent magnetic noise reduction or overall design improvement in order to make them smaller and cheaper while keeping the required values of a limit of detection. Contemporary demands of biological systems diagnostics are for low-cost fabrication methods, flexibility of usage, and the quick obtaining of test results. At the same time, new diagnostic platforms have to be more precise and provide the right clinical management decisions. The development of magnetic field sensors for biomedical applications primarily focuses on equivalent magnetic noise reduction or overall design improvement in order to make them smaller and cheaper while keeping the required values of a limit of detection.

Applications of magnetic sensing technology in biomedical fields can be subdivided into two main categories:

- Measuring a magnetic field produced by human organs
- Detecting magnetically labeled biomolecules.

Magnetic field sensors suitable for biomedical applications are:

- Search Coil Magnetometers [[1][2]]
- Direct current superconducting quantum interference devices (dc SQUIDs) Magnetometers [[3][4][5][6]]
- Fluxgate Magnetometers [[7][8][9][10]]
- Magnetometers based on the Anisotropic/Giant/Tunneling Magnetoresistance (AMR/GMR/TMR) Effects [[11][12][13][14][15]]
- Magnetoelectric Magnetometers [[16][17][18]]
- Giant Magneto-Impedance (GMI) Magnetometers [[19][20][21][22]]
- Optically Pumped Atomic Magnetometers [[23][24][25][26][27][28]]
- Cavity Optomechanical Magnetometers [[29][30][31]]
- Magnetometry utilizing Nitrogen-Vacancy Centers in Diamond [[32][33][34][35][36][37]]
- Hall Effect Magnetometers [[38][39][40][41][42]]
- Magnetoelastic Magnetometers [[43][44][45][46]]
- Spin Wave Interferometry Based Magnetometers [[47][48]]

A list of magnetic sensors depending on the type of application (for biomagnetic signals detection or for point-of-care devices) is presented in Figure 1. The list of magnetic sensors is constituted from their potential use in systems for sensing many kinds of biomagnetic signals including point-of-care devices. The working principles and detailed explanation of the potential use of these sensors are presented in the full version of this review [[49]].

Figure 1. A list of the common and modern magnetic field sensors with the potential to be used for the detection of biomagnetic signals (magnetocardiography (MCG), magnetoencephalography (MEG), magnetomyography (MMG), magnetoneurography (MNG)) and for point-of-care devices [[2][16][22][31][48][50][51][52][53][54][55][56][57][58][59][60][61][62]].

2. Magnetic Field Sensors for Detection of Biomagnetic Signals

Biomagnetic signals from a human body provide a lot of useful information about the heart, nervous system, brain or muscle activity. However, magnetic fields generated by most biosystems have a low amplitude in comparison with noise sources [[63]]. The adult heart signal is the largest of the biological magnetic signals with a peak magnitude of about 25 pT [[64]]. For each biomagnetic signal source, one can determine the required limits of detectable magnetic field strength and frequency in terms of an equivalent magnetic noise spectral density. To study magnetocardiography [[65]], magnetoneurography [[54]], magnetoencephalography [[66]] and magnetomyography [[67]], the magnetic field sensor must fulfill those conditions. A chart showing sensors capable of detecting corresponding biomagnetic signals is shown in Figure 2.

Figure 2. A chart showing how various magnetic sensor technologies (*y*-axis) relate to the detection of biomagnetic signals (*x*-axis). For precise details of the sensors, refer to the text and referenced publications.

In the field of biomagnetic signal detection, there are some well-established as well as new state-of-the-art magnetometry techniques worth mentioning. Nowadays, the most used technique is SQUID magnetometry [[68]]. However, this method is complicated to achieve in practice, because it generally relies on the use of a magnetically shielded room and cooling of the sensing element with liquid nitrogen or helium [[69][70]]. The resolution problems may be overcome by the implementation of specific hardware and software shielding technologies. Also, new developments in the high-T_c SQUIDs (not requiring liquid helium) provide the possibility of placing sensing elements close to the system to be measured, unfortunately, also followed by a higher noise level [[71]].

Optically pumped magnetometers achieving measurements less than 1 fT/√Hz [72] have great potential to replace SQUID magnetometers in some areas, but measuring methods can still be improved in the design, setup, and signal-to-noise ratio [73]. Also, these devices measure the magnitude of the field giving no information on its direction. Moreover, there could be zones of zero sensitivity in certain directions. Latest examples of detection limits in the low-frequency regime (<10 Hz) for different volumes of vapor cells include: 7 fT/√Hz by Krzyzewski et al. [74], 15 fT/√Hz by Knappe et al. [75], 10 fT/√Hz by Boto et al. [76]. The versions based on a nonlinear magneto-optical rotation regime are not commonly considered when measuring biomagnetic signals but there is some research devoted to the improvement of their limit of detection [77][78].

Both SQUID and optically pumped magnetometers achieve a limit of detection of the order of fT/√Hz only while having milli- or micrometer spatial resolution. The achievement of nanometer spatial resolution with these types of sensors is cost expensive and is followed with the huge drop of detection limit. In turn, nanometer spatial resolution can be provided by one of the newest and most promising types of magnetometers based on the behavior of nitrogen-vacancy (NV) centers in the atomic structure of diamond. Though for now these magnetometers commonly have a nT/√Hz [79][80] or pT/√Hz [81] limit of detection, they have a number of noteworthy applications due to their special features. In addition, such sensors have potential in fields of magnetocardiography, magnetomyography and magnetoencephalography, due to the possibility of achieving the required limit of detection. Nevertheless, the physics of detection based on NV centers in diamond is complicated and differs from sample to sample. Thus, theoretical studies describing the physics of the processes in the structures considered are still ongoing.

The sensors discussed previously have restrictions on their operating temperature or on the optical excitation power, and there is a demand on the magnetic field sensor operating at room temperature whilst maintaining optimum performance. One of the most promising candidates for this purpose is the cavity optomechanical magnetometer. This currently has low energy consumption, high spatial resolution, and requires no cooling systems [82].

An additional type of magnetometer having low energy consumption, wide temperature range and competitive sensitivity is the spin wave interferometry-based magnetometer. One of the latest works devoted to the advantages of this new technique predicts the value of the detection limit of 1 pT/√Hz [48].

Highly sensitive and localized magnetic field sensors already discussed are ether technically sophisticated or cost expensive. The topic of relatively simple and cheap magnetic field sensors having sensitivities at a level suitable for magnetocardiography or magnetomyography is expanding. One relatively cheap and available magnetic field sensor able to measure biomagnetic signals is the fluxgate magnetometer. Recently, a new type of flux-gate sensor which utilizes epitaxial iron garnet films with a specially designed edge profile as a core was developed, claiming a reduction of noise level at room temperature down to 0.1 pT/√Hz. This magnetometer was successfully applied in magnetocardiography experiments on animals [83].

Magnetic field sensors competing with the fluxgate for magnetocardiography are those based (separately) on the magnetoimpedance, magnetoelectric and magnetoresistive effects. With the use of GMI gradiometers in a magnetically unshielded environment, the magnetic heart signal from a human subject was detected at nine spatially separated points demonstrating the possibility of obtaining more information in comparison with electrocardiography [20][22]. For these measurements, the noise level was approximately 2 pT/√Hz. The possibility of detection with GMI gradiometers of other biomagnetic signals as a magnetic field around a muscle tissue sample was also shown [19][84]. Amongst magnetoresistive sensors, TMR-based sensors are good candidates for measuring fields from the heart and, possibly, the brain [58]. A future challenge for the low cost, portable magnetic MR sensors is to non-invasively monitor the heart of an unborn baby in the womb, being an area presently covered by SQUID magnetometers. The signals from the electrical activity of the brain, however, are much smaller, so to monitor these a sensitivity in the femto-Tesla range is required - which is currently beyond the range of MR sensors.

3. Magnetic Field Sensors for Point-of-Care Devices

Some recent studies have been dedicated to the development of point-of-care devices for biomedical diagnostics [85]. Although biological objects are generally non-ferromagnetic, the latest developments in magnetic nanoparticles' systems have produced specific magnetic markers which have affinities to conjugating ligands for cells, proteins, nucleic acids, etc. Magnetically labeled targets can be detected by magnetic field sensors or concentrated by a magnetic field on the surface of sensors thus allowing an improvement in the detection efficiency. Point-of-care technologies are generally associated with lab-on-a-chip systems where magnetic nanoparticles can employ different functions [86][87]. For example:

- Capture, preconcentration, and separation of analytes bonded with the specifically functionalized surface of the particles;
- Mixing of lateral flows;
- Creation of contrast in magnetic susceptibility of the biological medium for future sensing.

This set of features opens doors for completely new applications as well as for the significant improvement of existing methods. For instance, the lateral flow immunoassay is a well-established method of biodetection which is very prominent because of the immunochromatographic strip test for ascertaining pregnancy [[88]]. This can be improved with the use of magnetic nanoparticles. Recent developments show that the approach of focusing magnetically labeled rare protein biomarkers for early diagnosis of cervical cancer can significantly improve sensitivity [[89]]. Quantitative analysis can be achieved through an optical signal detected by the camera of a smartphone or by the naked eye [[90]]. In some cases, however, the traditional optical methods are not acceptable due to the high background noise or the low sensitivity of detecting devices. Because of these reasons, magnetic sensors have been employed [[91][92][93]].

Magnetic field sensors in such devices are used for detection of drugs, cellular proteins or other biomarkers which are usually labeled with magnetic particles (or beads) as shown in Figure 3. There are also tests for blood coagulation, measurement of forces or stresses in artificial bones and the mass evaluation of cell cultures. Typical sensors being used in lab-on-a-chip systems are GMR/TMR [[94][95][96]], search coils [[52][97][98]], GMI [[50][99]], and Hall effect [[100]] magnetometers while for bioengineering purposes the most commonly used magnetic sensors are based on magnetoelasticity [[101]]. A significant advantage of magnetoresistive sensors in these applications is that they are fabricated with the same overall technology used to produce silicon chips, so it is relatively easy to manufacture them as part of an integrated lab-on-a-chip system.

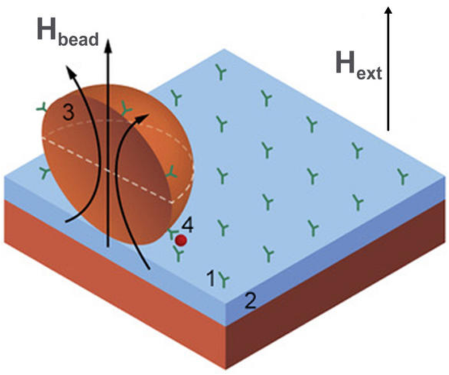

Figure 3. Example of a biochip based on magnetic label detection using a magnetic thin-film sensor. The chip consists of an array of probe biomolecules (1) of known identity immobilized onto the surface of the sensor (2), magnetic labels (3) functionalized with target biomolecules (4) that bind to the sensor surface through biomolecular recognition. The magnetic particle stray field H_{bead} resulting from the magnetic moment of the label induced by the applied magnetic field H_{ext} is measured by the sensor.

Magnetoelastic magnetic field sensors are used for the monitoring of glucose concentration, growth of bacteria, pH, biliary stent monitoring and other noteworthy in vitro applications [[46][102]]. This is useful in the mechanical detection of loads on orthopedic implants or in vivo monitoring of the force information in bones and joints.

In the field of microfluidics and lateral flow bioanalysis, there is a need for high sensitivity and fast response. A lot of proposed biosensing platforms meeting these needs are based on the magnetoresistive effect. One of the noteworthy articles is dedicated to tuberculosis point-of-care diagnostics with a magnetoresistive biosensor having a limit of detection of 10^4 cells/mL [[103]]. Recently, AMR-based microstructures [[104][105][106]] were proposed for magnetic beads detection, but, nowadays, because of the low change of resistivity [[106]] (around 2%), magnetoresistive biosensors based on GMR [[107][108]] and TMR [[109]] are more popular. For detailed information about exchange-biased AMR sensors tailored for magnetic bead sensing in lab-on-a-chip systems, we refer to the overview [[110]].

Detection of biomarkers can also be performed with magnetic field sensors based on the magnetoimpedance effect. An example of this is the detection of a-fetoprotein bioconjugates with a GMI magnetometer (with the 100 fg/mL limit of detection) [50]. Also, GMI based magnetic field sensors can be used in microfluidic chips achieving a detection limit of 0.1 ng·mL^{-1} and working in the 0.1 ng/mL–20 ng/mL biomarker concentration range [[111]].

4. Conclusions and Future Perspectives

In the field of biomagnetic signal detection, SQUID magnetometry remains the most common tool for magnetocardiography, magnetomyography, magnetoneurography or magnetoencephalography while having the best sensitivity approaching fT/√Hz. In spite of the usefulness of SQUID magnetometers, the requirement of low operating temperature and magnetically shielded room makes it relatively hard to use in practice. The future prospects for SQUID magnetometers may lie in miniaturization and, also, in the reduction of the operational noise values whilst remaining at a low limit of detection.

Among all magnetic field sensors, the most promising candidate for replacing SQUID-based sensors are optically pumped magnetometers (particularly ones based on the spin relaxation free regime). Their potential lies in their ability to achieve a limit of detection of several fT/√Hz while keeping the sensing area (restricted by linear dimensions of vapor cells) to a few tenths of mm^2. In comparison with SQUIDs, these magnetometers produce less operational noise and need heating of vapor cells to a temperature up to around 400 K, which is easier to realize. Still, optically pumped magnetometers require a real-time precise magnetic shielding system and some construction issues for the implementation of such sensors in biomedicine are yet to be solved [[112][113][114]].

In addition, great progress has been achieved in magnetometry using a detection system based on nitrogen-vacancy centers in diamond material. Though the sensitivity of such devices commonly does not extend beyond tenths of pT/√Hz, they operate at room temperature while allowing nanoscale sensing and providing a way to develop novel magnetic field sensors. Due to these prospects, further and current research is mostly aimed at extending the sensitivity and resolution of magnetometers of this type.

Due to recent developments in nano- and microfabrication techniques, new approaches to miniaturize magnetic field sensors with competitive sensitivities may be realized in spin wave interferometry or cavity optomechanical magnetometers. However, these magnetometers are still technically complicated, so magnetometers based on well-established and more simply fabricated AMR/GMR/TMR, GMI, fluxgate, and magnetoelectric technologies are enough for many biomagnetic field measurements.

Concerning point-of-care technologies, sensor integration into lab-on-a-chip, and microfluidic technologies could lead to the replacement of many diagnostic systems currently used in laboratories and clinics. As the sensitivity requirements are determined by a particular device, the path to the miniaturization of diagnostic systems lies in overall design improvements. New advances in the fields of micro- and nano-fabrication will also help to overcome current limitations of the usage of magnetic sensors in this field because of issues concerning high power consumption, single-target detection and system complexity. The most promising magnetic sensors to overcome these limitations are GMR/TMR and GMI magnetometers due to the fact of their flexibility and the convenience of the low-cost integration process. This means that not only the sensor but the complete signal processing system can be built on the same chip using closely related technologies.

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