High sensitivity MR sensors incorporated in silicon needles for magnetic neuronal response detection

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Abstract

Understanding how the brain works is still a challenge for neuroscientists so it is important to develop tools capable to detect weak magnetic fields on the pT range generated in the brain. A Local Field Potential (LFP) setup at Instituto Medicina Molecular (IMM) was used in order to perform the experiments with a MR planar array chip or a probe as measuring element. In the experiments hippocampal brain slices from rat were used to measure the magnetic field created by the ionic currents. This thesis describes all steps carried out towards the development and optimization of an experimental tool in neurosciences. The magnetoresistive sensors (spin valve and magnetic tunnel junction) are used as a tool which allows measuring weak magnetic signals at room temperatures in *in vitro* and *in vivo* experiments. Different designs were made in order to achieve high detectivities and low noise level. The best sensors with high sensitivities and reduced 1/f noise component were able to reach detectivities down to 1 nT at 30 Hz and hundreds of pT at 1 kHz.

Keywords: Neuroscience, Hippocampus, Neuronal activity, Magnetic field, Magnetoresistive sensors, Microfabrication.

1. Introduction and Background

The recording of brain signals provides valuable information for physiologists and neuroscientists to understand the brain. In the last decades, the techniques such as functional magnetic resonance imaging (fMRI), electroencephalography (EEG), magnetoencephalography (MEG) have been developed to study the brain activity and the nervous system, in order to understand the human thought, emotion, and ultimately the behaviour [1]. EEG is the method more direct and completely noninvasive to measure the activity of nerve cells. MEG depends on the extremely weak magnetic fields caused by neuronal electrical activity. Signals are some hundreds of fentotesla (10^{-15}T). This technique is completely non-invasive and contact free without any influence on the subject. The MEG method is based on the superconducting quantum interference device (SQUID), a sensitive detector of magnetic flux.

The human brain is the most complex organized structure known to exist. The neurons are the active units in a vast signal handling network, which includes 10^{14} interconnections or synapses. When

information is being processed, small currents flow in the neural system and produce weak magnetic field. A neuron consists of the cell body, the dendrites and the axon (Figure 1).

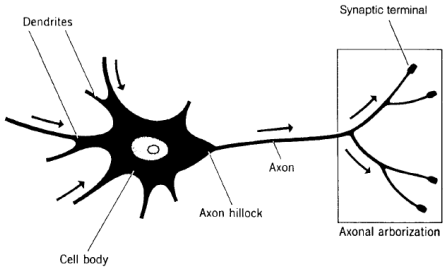

Figure 1:Neuronal cell structure: dendrites, cell body and axon [2].

The dendrites and the soma have typically thousands of synapses from the other neurons. The intracellular potential is increased by input through the excitatory synapses that are on the dendrites. The cell membrane of neurons is a very thin (7 to 15 nm) lipoprotein complex that is essentially impermeable to intracellular protein and other organic anions (A-). The membrane divides the tissue into intracellular and extracellular compartments with different ions concentrations. The difference in concentration creates a diffusion gradient that is directed outwards across the membrane. Due to this ions movement a transmembrane potential is created, the interior of the cell is more negative than the external medium. The most important is the Na-K pump, which moves Na+ ions out and L+ ions into the cell. At rest, the cell membrane potential defined with respect to the inside of the cell is about -70 mV, due to the steady resting potential the cell membrane is said to be polarized. The origin of the action potential lies in the voltage and time dependent nature of membrane permeabilities to specific ions, notably Na^+ and K^+. As the transmembrane potential is depolarized, the membrane permeability to sodium P_{Na} is increased. Consequently, Na^+ rushes into to the cell along the concentration gradient. This influx of Na^+ causes the membrane to become even more depolarize, thus, causing the activation of more Na^+. This influx of Na^+, into the cell, results on the rising phase of the action potential. Once the cell reaches a peak depolarization the Na^+ channels close and the K^+ channels open. Now, K^+ ions flow out of the cell along the concentration gradient, and the cell membrane begins to hyperpolarize. This efflux of K^+ results in the falling phase of the action potential and hyperpolarization continues until the cell has returned to its resting potential. Actions potentials are transmitted along axons to regions called synapses, where the axons contact the dendrites of other neurons. These consist of a presynaptic nerve ending separated by a small gap from the postsynaptic component, which is often located on a dendritic spine. Synapses provide an unidirectional flow of information, from the sending (presynaptic) to the receiving (postsynaptic) neuron, but not in a reverse direction. At most synapses the cause of change in potential of the postsynaptic membrane is chemical. The transmission across this gap is done by chemical messengers called neurotransmitters.

There are difficulties in detecting a magnetic field of action potentials. The amplitude of this field is weaker at greater distance from the active tissue and second, because of the short duration of the action potential, temporal summation is limited. Post synaptic signals (PSP) looks like a current dipole oriented along the dendrite. The strength of the current source decreases with the distance of the synapse. The duration of the PSP is 10 ms, thus the simultaneous

activation of as few as one synapse in a thousand over an area of one square millimeter produces a detectable signal.

The hippocampal formation plays a central role in memory function in humans [3]. The Figure 2 shows the pathway of hippocampus signal transmission. CA3 sends connections to CA1 pyramidal cells via the Schaeffer collateral (Sch) as well as commissural fibers (comm) from the contralateral hippocampus [4].

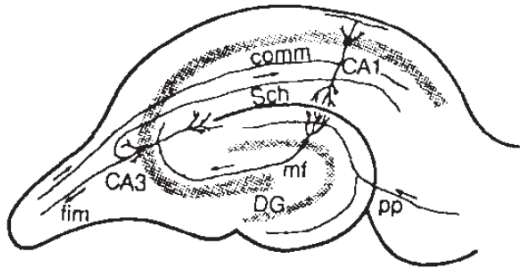

Figure 2: Pathway of hippocampus signal transmission[5].

Coherent membrane currents brought about by synaptic activity and intrinsic properties of neurons, pass through the extracellular space and can be measured by electrodes placed outside the neurons as local field potentials (LFP). The high-frequency content about 600–6K Hz is referred to as unit activity, while the low-frequency signal content below about 600 Hz is referred to as local field potential. LFPs come from several sources; the most significant of these is the synaptic activity [6].

Magnetoresistance is a phenomenon that reflects the resistance change of a material when an external magnetic field is applied to it. Magnetoresisitive (MR) sensors detect the magnetic field produced by the ionic currents generated at each neuronal interaction, by converting it into a resistance variation. The measurement of such ionic currents can bring new and valuable information regarding how neurons interact. The MR sensors are fabricated at nanoscale size, either in planar substrates or at the tip of microfabricated needles. The magnetoresistive sensors (spin valve (SV) and magnetic tunnel junction (MTJ)) are used as a tool which allows measuring weak magnetic signals at room temperatures in *in vitro* and *in vivo* experiments. To measure small signals, the sensors should have the high sensitivity, low intrinsic noise mainly at low frequencies where the biomagnetic field is measured.

In a MTJ, the main noise sources are the thermal and shot noise, 1/f noise and random telegraph noise (RTN) [7]. In an SV, the sources of noise are thermal noise, 1/f noise and in some cases RTN [8]. At low frequencies the magnetoresistive intrinsic noise is dominated by the 1/f component, responsible for the limitation of the sensor field detectivity.

In this work, an experimental tool in neurosciences was development and optimized in order to perform experiments in a rat hippocampal slice in a local field potential setup at Instituto Medicina Molecular (IMM).

2. Experimental method

Two types of sensors were fabricated spin valves (SV) and magnetic tunnel junctions (MTJ).

The SVs (top and bottom pinned) were fabricated by ion beam deposition (Nordiko 3000 system) and MTJ stack was deposited at INL. Table 1 shows the stacks used in the microfabrication process. The sensor was defined by ion milling. The flux guides (CoZrNb, 5000 Å thick) and the sensor leads (Al, 3000 Å thick) were defined by optical lithography and metal lift off. Between flux guides and contact leads was deposited an

insulator layer (Al_2O_3, 4000 Å) to prevent the short circuit between FG and contact leads.

Stack	Composition (thickness in Å)
SV1377	Ta 20/ NiFe 28/ CoFe 23/ Cu 23/ CoFe 23/ MnIr 110/ Ta 100
SV1806	Ta 20/ NiFe 30/ MnIr 85/ CoFe 33/ Ru 8/ CoFe 37/ Cu 25/ CoFe 33/ NiFe 36/ Ta 100
SV1807	Ta 20/ NiFe 35/ CoFe 33/ Cu 25/ CoFe 33/ MnIr 85/ Ta 100
TJ1141	NO ETCH / Delay 10min / [50 Ta / 250 CuN] x 6 / 50 Ta / 50 Ru / 200 IrMn / 20 $CoFe_{30}$ / 8.5 Ru / 26 $CoFe_{40}B_{20}$ / MgO> 10 / 20 $CoFe_{40}B_{20}$ / 2.1 Ta / 40 NiFe / 2.0 Ru / 60 IrMn / 20 Ru / 50 Ta / 100 Ru

Table 1: List of stacks used in microfabrication process.

A gold electrode (1000 Å) was defined to do electric and magnetic measurements at the same time. The sensors were passivated with 2000 Å Al_2O_3/ 2000 Å AlN_X to protect against corrosion caused by Krebs solution (an artificial cerebrospinal fluid solution, used to keep the hippocampus brain slice alive during the experiments). Figure 3 shows a picture of a probe in the final of microfabrication with integrated flux guides.

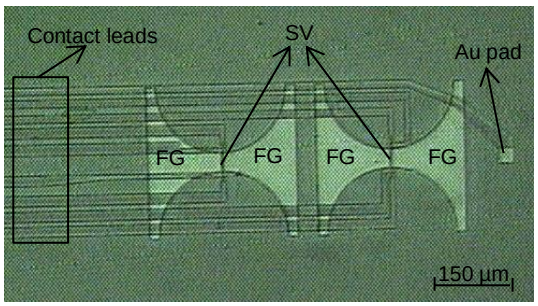

Figure 3: Final device with two SV sensors and flux guides.

The microfabricated sample was cut in individual pieces and wire bonded to a flexible cable. To avoid the corrosion and the damage of connections they were protected with a silicone gel.

3. Sensors

During this work magnetoresistive sensors were designed and optimized of for specific application. The experiments combine an LFP electrophysiological system at IMM with a MR sensor to measure the magnetic field created by the ionic currents in hippocampus rat brain slice.

In the first approach the MR sensor was implemented in a planar chip. Different devices were designed for this approach such as arrays of MTJ, single MTJ and arrays of SV (Figure 4). In the second approach the MR sensor was placed on the tip of the needle in order to be inserted within the brain slice.

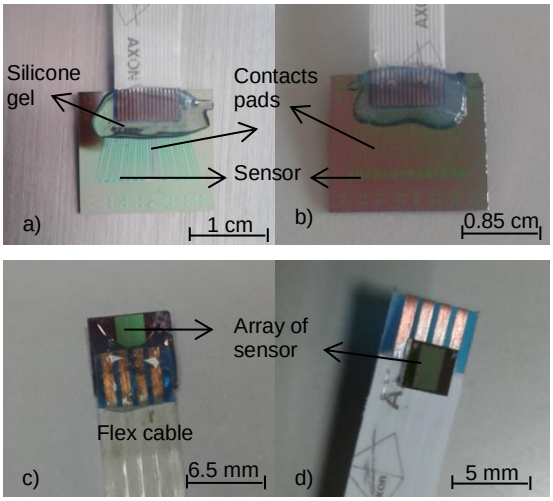

Figure 4: Final devices a) 15 sensors with one MTJ b) 15 sensors with arrays of MTJ c) Large area device (7100x6500µm^2) with array of sensors d) Small area device (3550x3250µm^2).

The MR sensors used are of two types: 1) spin valves, which have a typical MR ratio of 6% and 2) magnetic tunnel junctions, which can have a MR ratio of up to 100%.

After the microfabrication, all the sensors were characterized accordingly to their transfer curves and their noise. By taking into account all sensors, different sensors were chosen to measure noise and to do the experiments at IMM. Noise measurements were performed in a mu-metal magnetically shielded box, containing a battery powered low noise

amplifier. The measurements were made in a Tektronix RSa3308A real-time spectrum analyser. The noise of the sensor was measured up to 100 kHz.

The first design was a planar device with 15 sensor each one with one junction. The dimension of junction was 7.5x7.5 μm^2 or 10x10 μm^2 (Figure 4 a)).

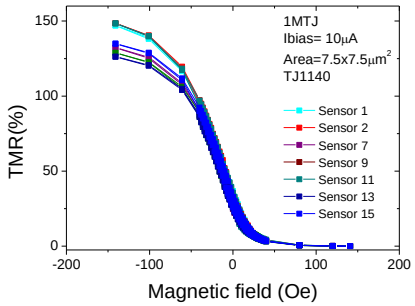

Figure 5: Transfer curves of all sensors in the planar device.

The sensor with the best MR (sensor 2) was chosen to measure noise. The TMR was 148 % and the sensitivity of the sensor was 0.66 V/T. Noise measurements were carried out in the noise characterization setup, leading to noise values of 1823 nV/√Hz at 30 Hz and 326 nV/√Hz at 1 KHz for a bias voltage of 250 mV as shown in Figure 6. Since the noise is inversely proportional to the area and in this device the area of sensor is small it results in a high level of noise. The detectivity was 64 nT/√Hz at 30 Hz and 10 nT/√Hz at 1 KHz.

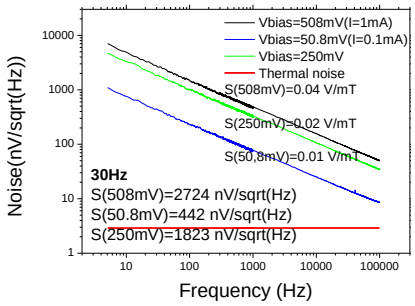

Figure 6: Noise values of one MTJ sensor for different bias voltage.

The second design had 15 arrays of sensors (Figure 4b)). Each sensor was composed by an array which can have 84 or 140 junctions in series. The junctions had different dimensions which can be 50x50 μm^2, 40x40 μm^2 and 30x30 μm^2.

This device was design in order to have higher detectivity and higher sensing area because it is easier to detect weak magnetic fields, although it results in a lower spatial resolution. Single MTJ exhibit a high 1/*f* noise, the strategy proposed to reduce the 1/*f* is using several junctions connected in series.

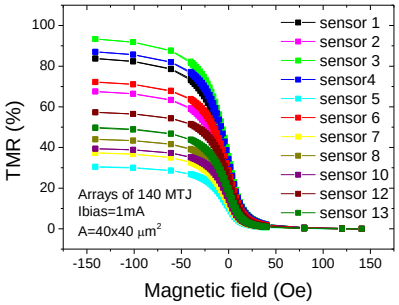

Figure 7: Transfer curves of all sensors in the planar device.

The sensor 6 was chosen to measure noise due to its position in the middle of the device. This sensor has 140 sensors in series with a TMR of 72% and a sensitivity value of 0.11 V/mT. The noise values obtained were 110 nV/√Hz at 30 Hz and 18 nV/√Hz at 1 kHz for a bias voltage of 250 mV. The detectivity of this sensor, taking into account the sensitivity, was 3 nT/√Hz at 30 Hz. Although the area of the individual MTJ sensor in the previous design is not the same as each MTJ in the series, it can be observe that for the same applied voltage (250 mV) the 1/f noise of sensors in series is lower than a single one.

The fabrication of planar devices was also carried out to use in *in vivo* experiments. The final purpose of these devices was to place the sensor on top of the brain. The frequency of the neurons magnetic activity is the order of few Hz. A MR sensor is dominated by 1/f noise

at low frequencies. Thus, devices were design in order to have a high sensitivity and a lower 1/f noise component. It is known that for N MTJ in series, the sensitivity increases with N and the detectivity with √N. The fabricated devices had 952 MTJ sensors (50x50 µm each) in series (area=5mm^2). Figure 4 c) and d) shows the device with array of sensor, only the area of device is different.

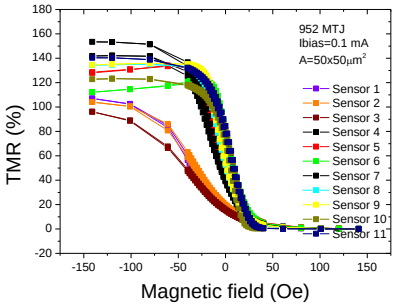

Figure 8: Transfer curve of all sensors with 952 MTJ in series.

The sensor 5 was chosen to perform the noise measurements because it was the sensor with small area with highest value of MR. TMR value was 124 % and the sensitivity was 2.22 V/mT. Noise characterization of the sensor led to values of 83 nV/√Hz at 30 Hz and 18 nV/√Hz at 1 kHz for a bias voltage of 476 mV. The detectivity was ~800 pT/√Hz at 30 Hz and 180 pT/√Hz at 1 kHz.

The SV arrays had 6200 sensors (124 parallel of 50 sensors in series). There were two devices with different areas (Figure 4 c) and d)). Each sensor had an active sensor area of 40 x 3 µm^2. The use of parallel of series is to reduce the total resistance of the sensor in order to have a low thermal noise level. Figure 9 displays the transfer curves of the patterned SV sensors. The sensor 1 was MR of 6.3 % and a sensitivity of 1.6 V/T for 1 mA bias current with linear nonhysteretic behavior. The noise measurements were done and the obtained values were 2 nV/√Hz at 30 Hz with a bias voltage of 500 mV and 1 nV/√Hz at 1 kHz.

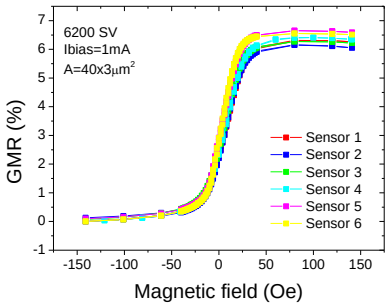

Figure 9: Transfer curve of 6200 SV in series.

The calculated detectivity was approximately 1 nT/√Hz at 30 Hz and 267 pT/√Hz at 1 kHz with the same bias voltage. With parallel of series the effective detecting surface is large enough, while maintaining a low thermal noise and 1/f noise.

The planar devices had some disadvantages. The disadvantages were the distance between the signal sources and the sensing elements and the difficulty to understand what was the region measured. These problems contribute to the development of a needle. This needle has a MR sensor in the tip that could be inserted within the brain slice.

The SV needles were made from the SV1806 and SV1807 stacks (thickness 400 µm). Three different probes were designed with different width and sensors design. There are probes with two single sensors (175 µm width), two arrays with 992 sensors (parallel of 16 series of 62 elements) (1 mm width) and two single sensors with flux guides (320 µm width). The dimensions of flux guides are 35 µm, 400 µm, 140 µm for the length and the gap between the FG and SV is 1.5 µm. After the microfabrication, the SV needles were characterized by magneto transport. For a single SV, the value of sensitivity is 3.4 V/T and for the same current bias (1 mA) sensitivity

up to 2.5 V/T was obtained in arrays. The value of MR is lower in the arrays than the single SV because in the arrays the MR is calculated from averaging over each individual element response. Thus, local deviation in the fabricating processes can affect the transfer curves of particular elements, inducing variations in the magnetic response. In relation to the SV with flux guide for the same bias current sensitivity up to 18.6 V/T was achieved. The flux guides are used to increase the sensitivity of the MTJ by concentrating the field in the sensitive part of the sensor so the sensitivity was improved by a factor of 5 from the single sensor to the sensor with FG.

4. Experiments

The MR device is integrated into the recording chamber which is an LFP electrophysiological system at IMM (Figure 10) and is placed in the area of interest of the mouse hippocampus brain slice. The measurement is then performed by biasing the MR sensors with a current to convert into a voltage, which is acquired by an acquisition setup [9]. The setup has a hardware and a software part, the hardware provides MR sensors biasing, signal amplification and filtering; and the software (Matlab) allows signal visualization, storing and digital filtering for the measured signal.

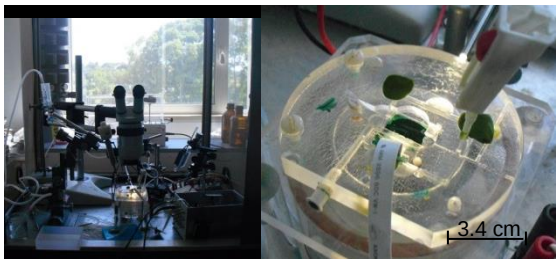

Figure 10: LFP system and recording chamber at IMM.

In vitro experiments were carried out by using planar array MTJ, planar MTJ and SV needles. To perform this experiments was used a 400 µm thick slice on top of the sensor and the stimulation electrode on top of the slice. The slice was perfused with Krebs solution that is an artificial cerebrospinal fluid solution designed to keep the brain slice alive during the experiments. The slice and more specifically CA1 region is placed over the sensor previously chosen and the stimulus electrode were insert in the CA3 region (Figure 11). The stimulus electrode is placed in stratum radiatum in the CA3 region of the hippocampus to activate CA1 pyramidal cell axons.

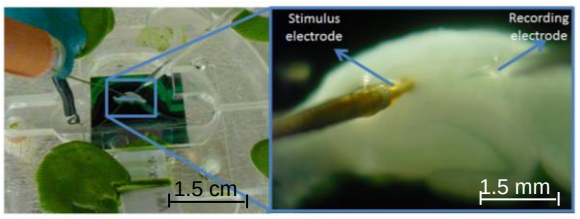

Figure 11: Hippocampal brain slice on top of the sensor.

In experiments, the krebs solution is used to maintain the brain slice alive. Since this solution contains ions and there is a current bias in the sensor that passes through the solution it can introduce noise.

Different tests were done in order to understand if in the presence of Krebs solution the noise changes. In fact, the noise is the same in each type of liquid as it is shown in Figure 12.

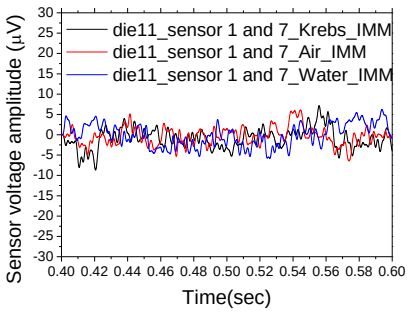

Figure 12: Noise measurement of the sensor with air, water and Krebs solution at IMM.

In order to achieve low level of noise a new strategy is adopted which is to do averages. Averaging is a simple and powerful way of improving the signal-to-noise ratio. This method can be used only in conjunction with repeating phenomena such as stimulus. Since noise and external disturbance, including the background activity of the object, are normally not time locked to the stimulus, they can be regarded as independent. Thus their influence may be reduced by averaging with an improvement in the signal to noise ratio of √N, where N is the number of averages responses. The output signal was measured by a single MTJ sensor when the slice was stimulated by an impulse in each 5 seconds. The sensor voltage amplitude was 100 $\mu V_{pp.}$ The averages were done for 10 minutes this means that during this time occurs 120 impulses thus their influence may be reduced by a factor of √120=11. In the output amplitude is ≈10 μV_{pp} so the noise level was reduced by a factor √N. The same test was done for 15 minutes and the amplitude of the output signal was ≈7 μV_{pp} (Figure 14). The initial signal was reduced by a factor of 13.4.

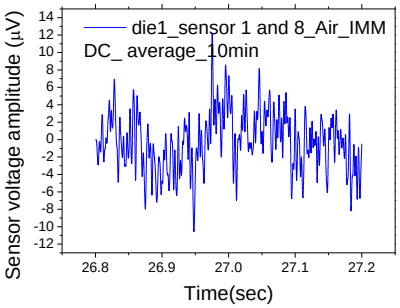

Figure 13: Output signal measured in a stimulated rat hippocampal slice with a single MTJ sensor with averages during 10 minutes.

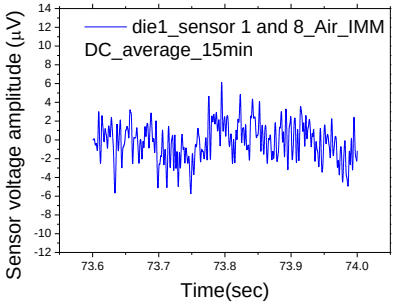

Figure 14: Output signal measured in a stimulated rat hippocampal slice with a single MTJ sensor with averages during 15 minutes.

From the LFP measurements the magnetic field created by the ionic currents is in the order of nT thus with this noise level isn't possible to detect any signal.

During the experiments the sensors suffered corrosion and damage as shown in Figure 15. This corrosion is due to electrolysis which occurs because the passage of an electric current (bias current in the sensor) through an ionic solution (Krebs solution) resulting in a chemical reaction. The corrosion leading to an increase in noise and the sensors stop to work.

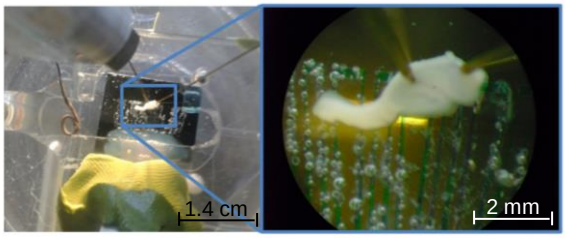

Figure 15: Corrosion and damage in the sensors after experiments.

A different experiment was done with SV needle and CMOS electronic. In the previous experiment the distance between the biological source of the signal and the sensor is a limitative parameter because the magnetic fields generated by neurons are weak and decrease with the distance ($1/d^2$). Besides this the top and bottom surfaces of the slice are damaged by the slicing action itself.

Using the needle, the sensor is introduced on top of the slice which is submerged in Krebs solution as shown in Figure 16. With this method the sensor is placed near the source of magnetic fields and provide high sensitivity to detect the extremely small magnetic fields (nT range) induced by the ionic currents flowing within electrically active neurons.

The integration of the probes in the LFP system at IMM was not easy because the size of the PCB and the lack of space. It is necessary to find a method to insert the needle into the slice without damage the tissue and the connections in the neurons. Besides this, the PCB where the needle is connected cannot come into contact with Krebs solution because otherwise fails.

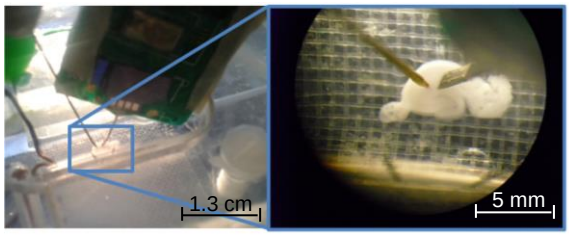

Figure 16: Experiment with hippocampus slice and a SV needle.

To solve some limitations of *in vitro* experiments, different devices were made in order to measure magnetic fields *in vivo*. Some of the limitations became due to the slices have a lack of certain inputs and outputs normally existing in the intact brain and the tissue gets older at a much faster rate than the whole animal so the duration of a brain slice is limited. One of devices was the array of SV with small area. The limit of detection of arrays is 1 nT/√Hz at 30 Hz. This device was used in the European Project Magnetrodes FP7. *In vivo* experiments in cats were performed in the Ernst Strungmann Institute (ESI) in cooperation with laboratory of Dr. Pascal Fries. The device is placed over a specific part of the animal brain. The cat is previously anesthetized and the sensor is implanted in the visual cortex. Some visual stimulus were done in order to stimulate the area where the sensor was place and to conclude if the sensor is capable to detect the signals. However in order to use this chip is necessary to protect the wires with silicone gel but it is very difficult to protect only the contacts without put the gel on top of the sensor. Consequently, during the experiments, the contacts suffer corrosion because of the brain's liquids.

5. Conclusions

The human brain is the most complex organized structure known to exist, and it is also the most important. There are at least 10^{10} neurons and when information is being processed small currents flow in the neural system and produce a weak magnetic field which can be measured.

The devices based on GMR and TMR sensors are fabricated in order to use for *in vivo* and *in vitro* measurements. The sensors fabricated with MTJ have the same sensibility for all designs but in terms of level of noise and detectivity, noise level decrease and limit of detection increase with the number of sensors in series. For an isolated sensor, the detectivity at 30 Hz is 80 nT/√Hz, for the sensor with 140 elements is the 2.86 nT/√Hz and for the sensor with 952 sensors in series the detectivity is 833 pT/√Hz at 30 Hz and 178 pT/√Hz at 1 kHz.

The devices with SV sensors in a parallel of series show the expected low 1/f noise component and better detectivities than the isolated sensors. For the best sensors, sensitivies corresponding to resistance change of up to 3 V/T were obtained for a bias current of 1 mA. At 30 Hz, where the 1/f noise is

dominant, the SV noise level was 6 nV/√Hz for 6200 sensors in a parallel of series scheme for a bias voltage of 500 mV. The magnetic field detection limit was 1 nT/√Hz at 30 Hz and 260 pT/√Hz at 1 kHz. The experiments in rat hippocampal slice were done with planar devices. This approach had some disadvantages related to the distance between the signal sources and the sensor and what was the region that has been measured. These two disadvantages contribute to the development of the MR probe which has a sensor in the tip.

This probe could be inserted within the brain slice in the brain region that has interest. Different probes were design and fabricated such as probes with single spin valve, with a SV and flux guides and with arrays of SV. Probes with FG lead an increase in the sensitivity. The sensitivity was improved by a factor of 5 from the single sensor to the sensor with FG.

A new signal acquisition setup with CMOS electronics was development by INESC-ID in order to have low noise level. However this experiment with probes and CMOS electronics is not optimized and experimental results were not obtained. Other improvement is the use of averages this method can reduce the noise level by a factor of √N where N is the number of averages. New approaches using arrays of sensors with FG should be studied because it is possible to combine low 1/f noise of the arrays of sensors and improve the sensibility with flux guides in order to achieve high values of detectivity.

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