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Design and Construction of a Magnetic Signal Detection Block for Magnetic Nanoparticles that Flow Through Straight Microchannels

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Abstract — **The early detection of diseases and illnesses, including cancer, is one of the main factors to ensure the survival of patients, so multiple and varied efforts have been made to find indications of the presence of diseases through biological markers. In recent years, among the technologies that have been booming are the so-called "Lab-on-a-chip" devices, which combine multiple branches of science and technology together with microfluidics. Depending on the application and the nature of the biological marker, the marking and detection processes may vary according to the physical principle. One way to achieve the detection of cancer cells in the human body through a blood study is through the functionalization of magnetic nanoparticles with cancer cells, and with the use of giant magnetoresistance, detection and quantification of the study samples can be achieved. In this article, the Invitrogen brand Dynabeads M-270 are used to carry out preliminary studies of a new approach for the detection and quantification of magnetic nanoparticles contained in an aqueous solution that circulate through straight microchannels, using the commercial sensor AAH002-02 of the NVE corporation in an implementation based on the "Lab-on-a-chip" devices. With the configurations of the magnetic sensor, the microchannel and an installed magnetic source, results were obtained showing the detection of the nanoparticles when they circulated through the microchannel.**

Keywords — **Giant magnetoresistance sensors, magnetic nanoparticles, magnetophoresis, microfluidics.**

I. Introduction

Cancer has been recognized as one of the diseases with the highest death rate, which according to data from the World Health Organization, approximately 9.6 million people worldwide died in 2018. [1], where the majority of fatal cases reports in third world countries, given the conditions for early detection and treatment. In these types of diseases, early detection becomes an essential factor in giving prompt treatment and increasing the probability of survival [2]. One of the ways of detection can be carried out by means of blood studies, where if the presence of cancer cells is detected, later studies can confirm the presence of cancer in the body and recognize the type and degree. At present, one of the most used commercial methods for the detection and quantification of cancer cells is through the cell classification activated by fluorescence, whose primary device is the flow cytometer [3], however, despite resulting in an already documented instrumentation, it has certain disadvantages, among the main ones are the high cost and photo-stability of the fluorophores used by the device. The goal in medical instrumentation is accessibility, repeatability and low costs, so the research of microfluidic devices known as "Lab-on-a-chip" for cancer detection has been increasing. These microelectronic devices base their concept on microfluidics, the branch of science and technology of systems that handle liquids in a range of 10^{-12} to 10^{-10} liters [4]. The field of Lab-on-a-chip also implements multiple technologies depending on the detection method and the active agents involved, which can be chemical agents, biological agents, or micro-scale structures.

In this article, the technologies of microfluidic systems will be combined with the use of magnetic nanoparticles (MNP) as marker agents [5], while sensors based on giant magnetoresistors (GMR) are used for the detection of the markers through the reading of the magnetic signals [6]. Due to the compatibility between the mentioned technologies, a complete MNP detection and quantification system can be built. The MNP, through a process of functionalization, can adhere to different entities of chemical and biological nature, such as reagents, cells, bacteria, among others [7]. When a solution of MNP and biological agents is generated, depending on the type of active adhered ligand, the biological entities can adhere to the body of the nanoparticles. These biological entities can range from a simple chemical to various types of cells, including those belonging to various types of cancer, which functions as a marker, indicating the amount and therefore, the concentrations of cancer cells in the studied samples [8]. Once the cells are marked, they are made to flow in the presence of a magnetic field, magnetizing the MNPs within the solution, which in turn produce a magnetic field. The transduction in the product signal of the MNP helps us to measure the concentration of agents within the solution when measured by a magnetic sensor [9].

The management of these technologies within the same system involves the creation of the specific Lab-on-a-chip for the quantification of cancer cells, however, a complete methodology is needed which involves separation processes, where MNPs are filtered alone from those linked to cancer cells. Different types of procedures are used to separate samples and depend on multiple physical or chemical principles to perform the separation. Among these methods, one of the most compatible with MNP is by magnetic gradients or magnetophoresis [10], which is based on the

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difference in weight of MNP and the speed at which they travel within the microfluidic channel.

In this article, a method of detecting magnetic nanoparticles was proposed by assembling a system consisting of the coupling of the detection circuit, a circuit for the flow of MNP solution and a circuit for the storage of the information obtained in the experiment. The objective is to measure the magnetic signal produced by MNPs when they circulate through straight microchannels using GMR-type magnetic sensors

II. METHODOLOGY

A system based on Lab-on-a-chip was constructed from a microfluidic channel and with instrumentation based on the acquisition of a magnetic signal of the order of mT. For this, designs were made considering the dimensions of the microchannel involved and surface-mount technology components, such as the GMR sensor model AAH002-02. In addition to that, couplers were placed to ensure the stability of the device and to join the mentioned electronics and the straight microchannel, so that the system is a separate block and only connects its power, ground and signal output terminals through connectors to the power supplies and a 12-bit data acquisition system using the MCP3202 chip. The work was divided into the following fundamental parts, which is the creation of the coupling system and the implementation of the built system.

A. Sensing block construction.

Starting from the characteristics of the sensor used, the GMR model AA00H2-02 of the NVE corporation, which has an average sensitivity of 3.6 mV / V-Oe and a saturation at 15 Oe. Given the recommendations in the datasheet, it is necessary to implement the sensor with a stable current source to avoid temperature dependencies, as well as to maintain a better signal in the linear range. In this way, with the configuration shown in Fig. 1, the sensor is powered by a constant current supply with de operational amplifier TLV271CDBVR, giving an approximate current of 1 mA. The output of the GMR sensor is differential, so the instrumentation amplifier INA826AID with a gain of 50.4 was used. Furthermore, an active lowpass filter with a cutoff frequency of 900 Hz was placed with the amplifier of the OPA2604AU. Finally, a negative voltage reference was built to safely increase the amplification of the sensor without saturating the output due to initial over-amplification. In this way, the effect of the magnetic field can be increased and be within the output range of the other electronic components.

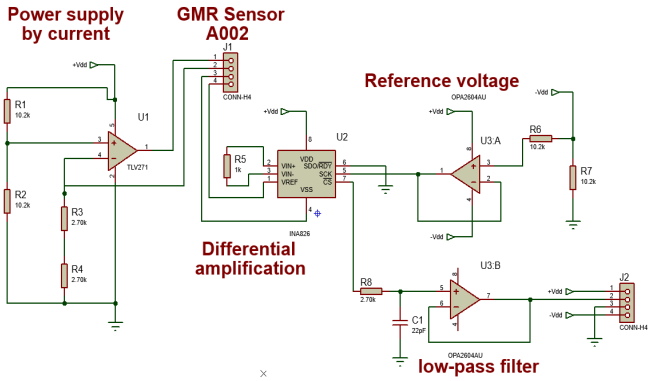

Fig. 1. Circuit diagram with constant current source power.

Once the electronics were designed, the coupling between the plate and the microchannel was created following the dimensions between both and ensuring free access between the terminals of both circuits. Table 1 shows the dimensions of the microchannel and its base, as well as the final size of the plate and the coupling. As it is possible to observe from the size, although it is handled with a microchannel as the basis for the microfluidic system, the other components are outside the range of usual dimensions for the Labs-on-a-chip, these being usually components integrated.

B. Electronic system implementation.

The equipment used to carry out the experiments in conjunction with the main system built, was planned so as not to interfere as much as possible with the magnetic signal of the MNP. The diagram in Fig. 2 shows the different equipment put together with the coupling system. The voltage source feed the system with +12V and -12V of direct current. This connects to the terminals of the coupling system. To pass the MNP solution through the microchannel, a laboratory-built microliter pumping system is configured to flow approximately a volumetric flow rate of 37.5 µL/s.

TABLE I.
Dimensions of the main components of the coupling system.

Component	Dimensions (mm)		
	L	W	H
Microchannel	16	0.5	0.06
Microchannel base	20	20	0.2
Microchannel Coating	25.6	6.5	3.7
Circuit board	31	25	5
Coupling	35	29	9

With the intention of stimulating the MNP with a magnetic field, a copper cable was placed 800 µm above the

microchannel and the GMR sensor. The copper cable was connected to a TENMA's Laboratory DC power supply, with a constant current of 3A. By stimulating the nanoparticles, they generate a response due to their orientation. To observe and record the effect of the nanoparticles that transit the microchannel, the ADC MCP3202 was installed and connects the output of the system with the PC, so that the signal from the MNP is obtained in real time while it is being stored. To pass the solution with nanoparticles, needles connected to hoses were inserted into the microchannel coating, as can be seen in Fig. 3, where the needles are placed longitudinally to the microchannel and the sensor. Special measures were taken in consideration to seal the holes and avoid leakage of both test liquids and nanoparticle solutions.

The tests that were performed were made from concentrations of Dynabeads M-270 of Invitrogen dissolved in PBS (phosphate-buffered saline). The initial sample contained a concentration of $2x10^9$ beads/mL. Since it is desired to be able to observe effects caused by nanoparticles, the concentration was lowered to $5x10^6$ beads/mL.

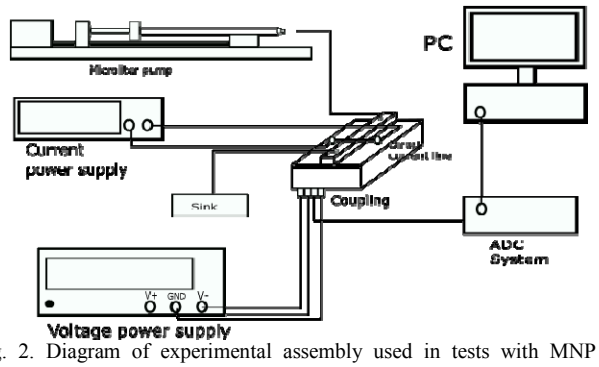

Fig. 2. Diagram of experimental assembly used in tests with MNP in microchannels.

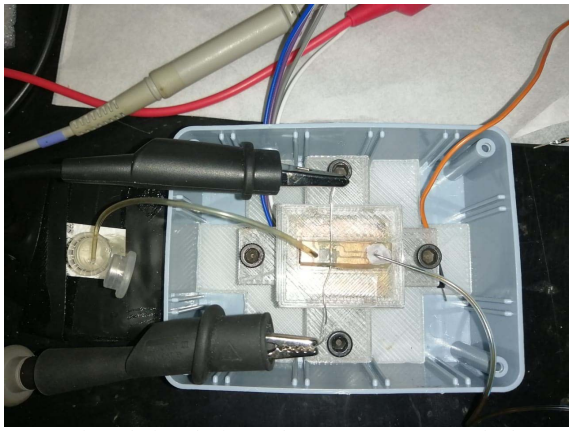

Fig. 3. Device designed from the GMR sensor and the straight microchannel.

III. RESULTS

Once the complete system is connected, as shown in fig. 3, the power supplies are turned on and the registered voltages are verified before passing the nanoparticles through the microchannel. Due to the coupling system built with the integrated power supply (transverse current line), the magnetic field registered by the GMR sensor should only depend on the current being handled. The FLUKE 289 multimeter is connected in series to the TENMA Laboratory DC power supply and to the copper cable, recording the output voltages of the coupling system. As can be seen in Fig. 4, the variation of the current has an effect as response of the sensor and the electronics built. Because the reference stage subtracts 6 V from the signal, negative voltages are observed.

Once the behavior of the sensing system has been observed, tests are performed using 3A as power for the power line. The nanoparticle solution is passed through the straight microchannel and the data is stored through the 12-bit adc, which has a resolution of 1.22 mV for this system. The results of the experiment are shown in Fig. 5, showing a small elevation of the voltage line with respect to the start, when the nanoparticles did not circulate through. Apart from the elevation, ridges can be observed, which indicates that a greater concentration was generated in the flow due to field interference.

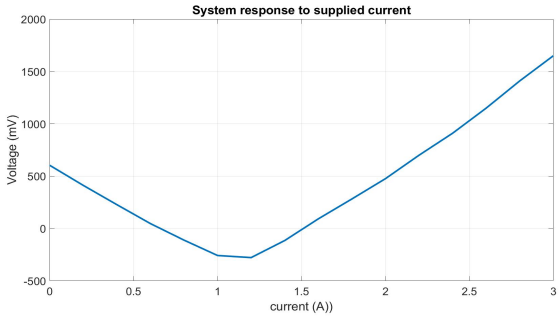

Fig. 4. Performance of the sensing system by increasing the current passing through the cable until reaching the maximum allowed by the equipment.

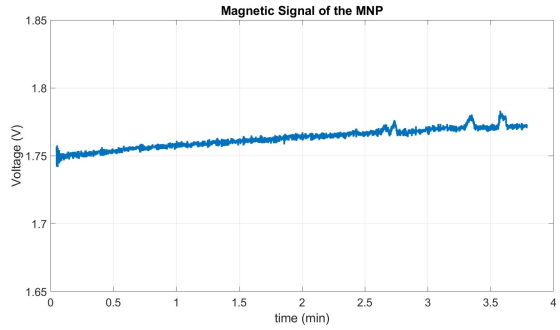

Fig. 5. Magnetic signal of the magnetic particles when passing through the straight microchannel at a speed of 37.5 µ/s, with a current of 3A that passes through the current line.

To analyze how the magnetic field was affected by the presence of MNP, the reference voltage line must be compared against the trend curve. In the Fig. 6, the tendency curve is approximated by a quadratic equation, where it is noted that the curve remains constant and remains at a distance from the reference line.

IV. Discussion

The designed system met the initial objectives of the work, which was to give early results of the detection of magnetic nanoparticles circulating through a straight microchannels. The volume of the microchannel is approximately $6x10^{-11}$ m^3 or $6x10^{-5}$ mL, so multiplying this amount by its concentration yields an approximate value of 300 beads circulating the microchannel simultaneously. This amount cannot be verified due to the dispersion of the particles, however the magnetic sensor that is available is smaller than the length of the microchannel, so it is possible for it to detect a smaller number of beads at the same time. To guarantee a better detection of particles, it is necessary to make changes to this design and introduce new stages in the electronic circuit, in order to increase the sensitivity of the system being able to detect lower concentrations of MNP.

V. Conclusion

A system based on the Lab-on-a-chip was designed and built to house many features in this type of device. The main components that were integrated were the GMR sensor, the amplification and filtering electronics, the integration of a straight microchannel and a magnetic source integrated into the device. With these details, the system is an isolated block whose inputs and outputs are for the voltage supply, the output of the registered magnetic signal and the flow of a solution of magnetic nanoparticles.

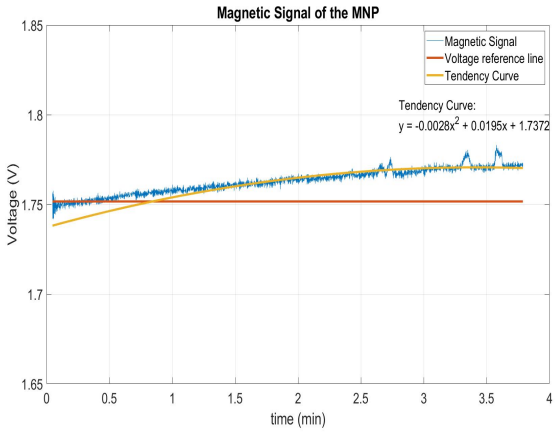

Fig. 6. Behavior of the signal caused by the MNP by means of a tendency curve generated by a quadratic equation.

The complete system implemented was installed to observe the behavior of the magnetic signal as a product of the current line and the change produced when MNP circulates. Although the change in signal is approximately 40 mV, the recording of the magnetic signal from the experiment can be used to find the flux of nanoparticles at a concentration of $5x10^6$ beads/mL. The results obtained show that it is possible to record the magnetic signal of the MNPs when they circulate through the channel, and with statistical calculations the concentration of magnetic nanoparticles can even be predicted, so that it can be used for the quantification of biological agents when they are properly functionalized to the MNP.

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