Architecture of a Portable System Based on a Biochip for DNA Recognition

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***Abstract*— This paper presents an architecture for a portable system based on a magnetoresistive biochip microarray for DNA recognition or microorganism/cell identification. In this biochip, biological targets are labeled with magnetic nanoparticles which are used to guide target over surface immobilized probes. Furthermore, the magnetic stray field created by those labels is detected by on-chip magnetic resistive sensors providing target and probe molecular recognition.**

The architecture is proposed for developing a biochip platform that incorporates electronics for addressing, reading out, sensing and controlling temperature and, in addition, a handheld analyzer capable of multiparameter identification. The biochip platform can be plugged in a peripheric standard bus of the analyzer device or communicate through a wireless channel. The system is being developed in the scope of a multidisciplinary research project, some preliminar results provided in the paper show that the architecture is implementable and adequate for achieving the intended purposes.

I. Introduction

During the past decade, arose the concept of *lab on a chip* for biochemical analysis, also known as *micro total analysis systems* (TAS). Most of these lab-on-a-chip devices are biochips that incorporate smart passive microfluidics with embedded on-chip power sources and integrated biosensor arrays. They have applications in a number of biochemical analysis operations such as clinical analysis (e.g, glucose/lactate analysis), DNA analysis and proteomics analysis [1] and are very useful, namely to clinical diagnostics.

A new technology have been successfully developed at INESC-MN in the past 4 years for magnetoresistive biological recognition and detection, namely for DNA recognition or microorganism/cell identification [2]–[4]. Biological targets are labeled with magnetic nanoparticles and local oscillating magnetic fields guide the target biomolecules over immobilized biological probes placed over magnetoresistive sensors. Upon biomolecular recognition and washing, the sensors detect the fringe fields created by the magnetic labels of the remaining targets.

The paper here presented is being carried out within a research project partially supported by the Portuguese Foundation for Science and Technology (FCT), which joins a multidisciplinary research group, specialized in physics, signal processing and control, computer architectures and electronics. It proposes a new architecture to design a portable and modular system for automatic and parallel DNA recognition or microorganism/cell identification. The system is based on an array of magnetic sensors (tunnel junction or spin valve), with a thin film diode or transistor associated with each sensor to read out data. Two main blocks can be identified in the proposed system: *i*) the biochip platform, where addressing and read out of the biosensor array, automatic sensor calibration and local temperature control are performed; *ii*) a handheld analyzer capable of multiparameter identification and detection, based on the analysis of the data collected by the biochip platform. The handheld analyzer, based on a Personal Digital Assistant (PDA) or a laptop computer, includes a communication module with the biochip platform not only for collecting data but also for controlling its general operation. A prototype for the complete system is being developed with off-the-shelf electronic components, and after this phase it is intended to integrate the major part of the biochip platform, make it even more portable, cost-effective and easy to use.

This paper is organized as follows. Section II presents a simplified structure of the biochip and discuss its main characteristics. Section III presents the proposed architecture and discuss its main blocks. Section IV discusses the implementation of a first prototype and provides some preliminary results. Section V concludes the paper and points to the future work.

II. Biochip Structure

The biochip platform comprises an array of 256 sensing elements, which are to be functionalize with biological probes or to be used as electronic and biological references. Figure 1 shows a drawing of a matrix element that includes a magnetoresistive sensor (Spin-Valve or Magnetic Tunnel Junction) in series with a Thin Film Diode (TFD), together with a u-shaped current line adjacent to the sensor. In addition, on-chip resistor structures will be used to effect local sensing element temperatures.

The biochip is fabricated using standard microfabrication techniques. Spin-valves (SVs) and Magnetic Tunnel Junctions (MTJs) are deposited on Si/Al_2O_3 substrates by an ion beam deposition system or by magnetron sputtering, and are defined by direct write laser lithography and ion milling. U-shaped spin-valve sensors of dimensions of $2.5\ \mu m\ \times\ 130\ \mu m$ (full

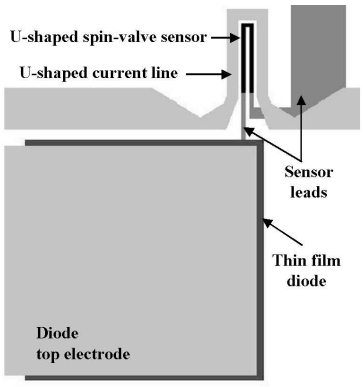


Fig. 1. Drawing showing a biochip matrix element, which comprises a magnetoresistive sensor in series with a thin film diode, together with a u-shaped current line used for guiding magnetically labeled targets over surface immobilized biological probes.

sensing length) show a maximum change in resistance with the applied magnetic field or magnetoresistance ratio (MR) of $\sim 8\%$ and a sheet resistance of 20 $\Omega/\square$ [5]. On the other hand, MTJs of dimensions of 2 $\mu m \times 10 \mu m$ show a tunneling magnetoresistance ratio (TMR) of $\sim 40\%$ and a resistance-area product ($R \times A$) of 10 $k\Omega \cdot \mu m^2$ [6]. Sensor dimensions are chosen to provide a linear sensor response to the applied field, which is necessary for quantification of biomolecular recognition. Furthermore, sensor dimensions also take into account the diode characteristics such that a maximum response is obtained for magnetic nanoparticle detection.

Amorphous silicon TFD are fabricated by chemical vapor deposition and are patterned by reactive ion etch with dimensions of 100 $\mu m \times 100 \mu m$ or 200 $\mu m \times 200 \mu m$. Diodes show a reverse-bias current density, J_0, of $9.22 \times 10^{-14} A/\mu m^2$ and a characteristic n of 1.23, for the diode response $J = J_0 \cdot e^{e \cdot V/(n \cdot k \cdot T)}$. The saturation current density is for these diodes 10^6 larger than the reverse bias current density [7]. Sensor and diode leads and u-shaped current lines are made by evaporated aluminum and lift-off, and a sputtered Al_2O_3 layer is used to separate distinct metal layers. In particular, current lines are tailored such that magnetically labeled targets are focused over surface immobilized probes using a combination of AC and DC magnetic fields [8] and are detected with the magnetoresistive sensors [5]. In addition, heating elements are deposited adjacent to the matrix elements to effect and control local temperatures, such that biomolecular interaction can be promoted or hindered depending on the temperature. This stringency method may be particularly important when distinction between single DNA mismatches is required. Finally, the biochip is passivated with Al_2O_3 and SiO_2 layers to protect the chip against chemical corrosion and to provide a suitable surface for probe functionalization.

III. System Architecture

The aim of the proposed architecture is to develop a modular and portable system for DNA recognition or micro-organism/cell identification. This system is based on the array of sensors referred in the previous section, which uses the INESC-MN magnetic sensor technology. A diagram with the main blocks of the proposed architecture is presented in fig. 2.

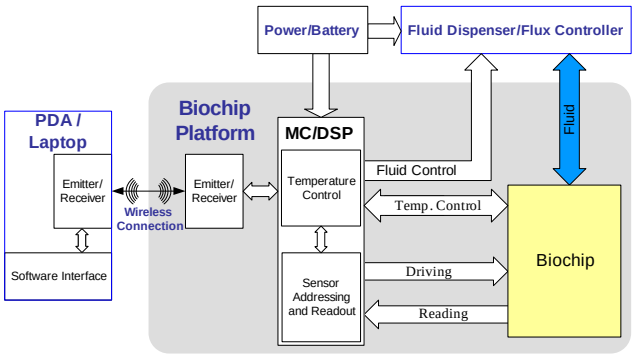


Fig. 2. Block diagram of the proposed architecture.

The corresponding programmable electronic interface circuits are implanted in a small electronic card (credit card dimensions), which is pluggable in, or can communicate with, a handheld device (e.g, PDA, pocket PC or a laptop computer).

Three main blocks can be identified in the architecture: *i*) the biochip platform, which is formed by the sensor array, the auxiliary sensors used as references and the heater and carrier circuits; *ii*) a digital MicroController/Digital Signal Processor (MC/DSP), with an associated associated Analog to Digital Converter (ADC) and Digital to Analog Converter (DAC), which is used to calibrate the sensors, for controlling the read out of the sensors and the heater and carrier operations; *iii*) the laptop/PDA for multiparameter analysis and to the viewer interface, also equipped with an Input/Output (I/O) module for communicating with the digital MC/DSP, through a standard bus or by performing wireless communication.

The biochip is fed with the biological fluid by the fluid dispenser/flux controller using microvalves and pumps controlled by the MC/DSP.

A. Biochip Platform

In each site of the sensor array, high precision measurements of two main physical properties have to be performed: resistance and temperature. In order to get sensor and electronics scalability (aiming up to 256 sensors) the system will be organized in a matrix structure. The sensor addressing is done by using a commutating matrix of integrated TFDs. As depicted in fig. 3, each sensor, which resistance value is represented by $S_{x\,y}$, is associated with a TFD $D_{x\,y}$. In a previous research aiming the fabrication of magnetic memories [9], it was already demonstrated the feasibility of this technology.

As presented in fig. 3, each TFD and the corresponding magnetoresistive sensor are connected in series and this series circuit is driven by a programmed current, provided through a DAC. A current mirror circuit provides a current with equal value for similar circuits, D_r and S_r, placed on a

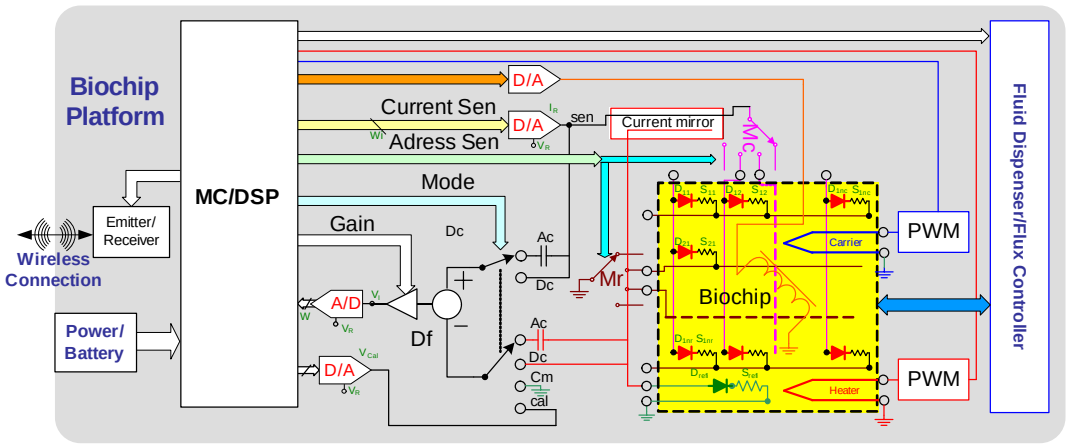


Fig. 3. Block diagram of part of the architecture for reading-out.

specific location of the chip, these circuits are used to provide reference values. The current flows through row and column multiplexers, according to the address of the element to access, establishing only a close circuit at a time. This allows the use of a single DAC and only one amplifier. The TFD has two main functions that correspond to two different modes of the circuit operation: *i*) only the diode corresponding to the particular addressed element of the matrix is forward-conducting while all the others are reverse-biased; *ii)* the voltage-temperature characteristic of these diodes is used for sensing the temperature of the diode site. These temperature sensors are calibrated through the MC/DSP, by generating pulses of current modulated in width, Pulse Width Modulation (PWM), to control resistive heaters placed around the chip. The calibration is made in DC, by amplifying the voltage at the terminals circuit. The gain of the amplifier is programmed and the output analog signal is applied to the input of an ADC in order to have the digital values available on the MC/DSP. Each of the temperature sensors is calibrated at setup time by experimentally computing the junction parameters of the equation relating voltage with temperature.

For measuring the changes in the variation of the resistance values in a magnetoresistive sensor, an alternate magnetic field is created by a coil placed close or bellow the chip. By using an AC analysis, we solve the difficult problem of measuring small variances on the resistance, typically less than 5% for an average value of $1\ k\Omega$. Moreover, approximately half of the voltage across the circuit is due to this resistive sensor, since the other half is due to the voltage to the forward-biased diode. Therefore, by only applying the alternate component of the voltage at the terminals of the amplifier we can considerably increase the gain of the amplifier to get reading with more resolution. Furthermore, taking advantage of an amplifier with high a Common-Mode Rejection Rate (CMRR), the reference signal is placed in the negative input terminal providing the reference for the resistance variation by amplifying the difference of the input values.

The carrier circuit represented in fig. 3 generates local fields to guide the target biomolecules over immobilized biological probes. The superposition of the DC magnetic field created by the current lines with a low frequency, few Hz, AC external field leads to attractive magnetic forces concentrating the magnetic labels in the inner region of the U-shaped line. This in turn allows much faster (few min) hybridization rates between biological targets and the immobilized probes, when compared with diffusion controlled processes [8]. This technique is also used to control the number of labels over each sensor area [5].

The operation of the biochip platform and the required digital signal processing are implemented in the MC/DSP. The main characteristics of this device and its main features are discussed in the next section.

B. Microcontroller/DSP

The MC/DSP is the programmable core of the platform, operating stand-alone but with an interface for communicating with a handheld analyzer (see fig. 3). It's main tasks are: to control the operation of the reading out circuits, to calibrate the sensors and to implement the signal processing and the temperature control algorithms [10]. For example, algorithms have been developed to characterize each cell from the point of view of magnetic and temperature sensitivities and nonlinearities; these algorithms are implemented in the MC/DSP and are executed when a reset occurs. On the other hand, the signals are mainly processed in digital domain (e.g. filtering) by the MC/DSP. The control signals to operate external microvalves opening or closing the individual microchambers and pushing the fluids around are also generated by the MC/DSP. At the end, the automatic individual sensor calibration will allow the counting of labels (and therefore target biomolecules) over each sensor, once the output voltage is measured comparatively to the reference sensor.

In practice, the MC/DSP is a microprocessor with a Reduced Instruction-Set Computer (RISC) architecture but suitable for control, supporting an Instruction Set Architecture (ISA) that includes instructions for test and manipulation of individual bits and with a reach set of timers and powerful peripherals. At the same time, MC/DSP also provides the

resources required for digital signal processing in real time. These resources can be plugged at the microarchitecture and at the ISA levels as extensions. They allow, for example, to rapidly compute and to access samples in the memory in a efficient way. This MC/DSP is programmed and configured by using a flash memory, which is a solid-state, nonvolatile, rewritable memory. We decided to use an integrated 16-bit MC/DSP from Microchip with a performance of 30 Million Instructions Per Second (MIPS), which integrate a fully implemented DSP [11].

At the top of the portable system, it is the handheld analyzer that should provide an interface to the user, allowing the interaction with the biochip platform. Therefore, the biochip platform and the handheld analyzer have to communicate with each other by using a standard serial interface, which can optionally has a module for wireless communication through a Radio Frequency (RF) short-range communication approach.

C. Handheld Analyzer

The defined architecture is designed to indistinctly use a PDA or a laptop to implement the handheld analyzer. All the software to analyze data, to implement the user interface and to control the overall operation of the biochip platform is being programmed by using object oriented paradigm and compilers. Only the user interface is dynamically adjustable according to each of the devices is applied. The communication modules are based on off-the-shelf components, following the Universal Serial Bus (USB) standard and the bluetooth wireless technology, by using a globally available frequency band (2.4GHz).

This handheld device acts as a master of the system, allowing the execution of a set of pre-programmed tasks in the biochip acting. It also provides a graphic interface with the user and the software for analysis of data provides the results in a user friendly way. For example, it gives to the geneticist/biologist the relative signal levels he asked for, that can be directly the ratio of signals $\frac{Vmut}{Vcon}$, corresponding to the voltage ratio between the chosen mutant target and the chosen control sample.

IV. Signal and Temperature Measuring Technics

The biochip matrix is driven by a constant current or by a constant current with a small ac current superimposed. The voltage across each matrix element (TFD + magnetic sensor) is measured. Due to high thermal conductance of the Al_2O_3 biochip passivation layer placed under each biological site over the magnetic sensor and the associated TFD, the temperature of these devices is very close to the biological fluid temperature, T_f. Taking advantage of the very well known electrical properties of the forward constant current biased TFD it is possible to characterize all the fundamental parameters of each matrix element. The architecture presented in fig. 3 allows for the extraction of a differential voltage between each matrix element and reference elements placed in the biochip. However, experimental evaluations shows that, due to the biochip fabrication process, significant mismatches occur between each element and the reference element, leading to voltage offsets that reduce the usable gain range of the reading amplifier. To overcome this problem, each matrix element is driven sequentially with scaled current values of a given reference DC current. The DC measured voltages across each matrix element are used as references for the new measures. The biochip reading involve the following phases: *Calibration*, *Temperature Measuring and Control* and *Signal Measuring*.

Calibration Phase

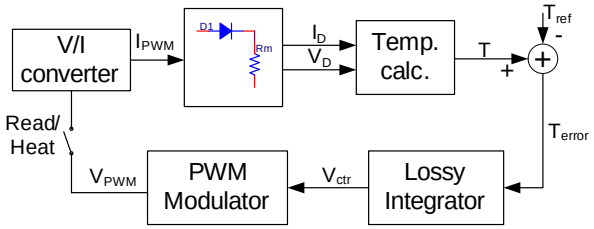
The ambient temperature is known and no magnetic field is applied to the sensor. Each matrix element is driven with sequentially increased scaled constant current values. This allow to calculate the TFD parameters ($n,\ J_0$) and the sensor resistance R_S. These values are stored in the microprocessor memory and are used in future biochip readings.

Temperature Measuring and Control Phases

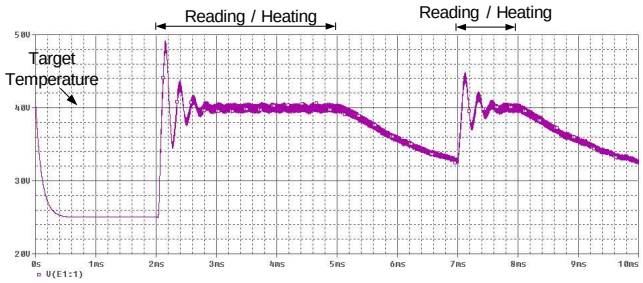
The biochip is fed with the biological fluid and the magnetic particles are carried over each magnetic sensor using the magnetic transportation lines. By using at least two scaled current values, it is possible to obtain the diode temperature T ($\cong T_f$) and the two element (diode and sensor) voltage temperature sensitivities. Further, the matrix element can be heated by passing high currents through it. As a consequence, the temperature of the biological fluid placed over the sensor also increases. A sequence of heating and temperature measuring phases can be used to control the temperature of the fluid in each site. Preliminary SPICE [12] simulation results using a concentrated thermal parameters model show that this is feasible. In fig. 4 it can be seen that the reading process and heating stabilizes the diode temperature. However the biochip is a distributed structure and is being modeled using finite elements method [10]. For higher variations in the chip temperature, a heating serpentine is also used.

Signal Measuring Phase

In this phase it must be measured the sensor resistance variation due to the magnetic particles captured over each sensor. A burst of an AC current, superimposed to a DC biasing current, is generated in the MC/DSP, and is applied through an analogue multiplexer to each matrix element. The corresponding voltage bursts are originated by the diode incremental resistance, about $125\ \Omega$ for $200\ \mu A$ of DC bias current which leads to about $10\ mV$ variation in a total of $200\ mV$ AC voltage across each matrix element. The use of the voltage in the reference matrix element in a differential amplifier structure reduce the AC common mode voltage to $0\ mV$, if there is no mismatch, and to about $50\ mV$ if the mismatch resistance (between sensor and reference sensor) is $100\ \Omega$. So the amplifier gain may vary between 15 and 60 in these cases. The sensor signal is digitized and is processed in MC/DSP by implementing digital signal processing algorithms.



(a) Block diagram of the circuit.



(b) Temperature behavior.

Fig. 4. Reading and temperature stabilization of a biosensor cell.

V. Conclusions

The architecture of a portable DNA recognition system was presented. The system is based on a new type of biosensor - a matrix of magnetic biosensors and Thin-Film diodes that is being developed in INESC-MN in its microelectronic fabrication facilities. The system involves the biochip, the biochip reading, control and signal processing devices and digital communication ports to outside. System architecture was conceived by a multidisciplinary research team in such a way that future modifications on biochip structure or signal processing and control algorithms can be accommodated.

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