From Micro to Nano: MEMS as an interface to the nano world

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ABSTRACT

Leveraging conventional microsystems technology, MEMS has become the technology of choice for a wide range of applications including inertial sensors for automotive, games, and consumer applications, projection displays or inkjet print heads. In support of recent efforts to shrink dimensions to the nanoscale, MEMS has established itself as a perfect technology for interaction with the nanoworld. We will describe initial results using MEMS to manipulate single molecules for medical diagnostics. This technology has the potential to turn complex laboratory procedures into procedures that are as simple as taking the temperature.

1. INTRODUCTION

Presently, medical tests are most commonly performed by trained personnel in specialized laboratories using sophisticated equipment. Increasing demand for at-home tests resulted in a first generation of devices available today for testing conditions such as cholesterol, colon cancer, blood clotting or pregnancy. These tests typically require the user to carefully follow a set of instructions. Results are typically in the form of a color change that is compared to a reference. While these tests are inexpensive, the challenges of accurately following the protocol and correctly interpreting the results impair their accuracy and convenience.

Micromachined sensors that combine the power of electronic circuitry with sensors fabricated right on the silicon substrate promise higher accuracy with automation and digital evaluation of results. These devices follow the general trend in sensor evolution of adding electronics to the transducer to enhance and simplify the measurement and are therefore obvious candidates for more versatile and automated medical tests. We present below an electronic platform devised to perform a wide range of immunological tests based on the widely used ELISA (Enzyme-Linked Immunosorbent Assay) protocol which tests for the presence of antibody produced by the immune system in response to an infection and exploits the highly specific interaction of antibody binding to cognate antigen. The key to this solution is an interface between the nano-world of antibodies and antigen with the micro-world of transistors.

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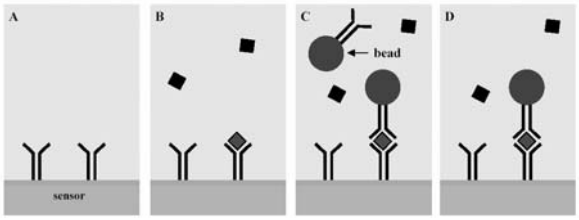

Figure 1 Magnetically labeled assay

2. IMMUNOASSAY PLATFORM

The electronic immunoassay uses a modified version of the ELISA protocol. Replicating this test in a micro sensor calls for a means to detect binding between antibody and antigen molecules with electronic circuits. Our solution relies on tiny magnetic beads coated with antigen that binds specifically to the antibody produced in response of the disease we are testing for [1]. Using a magnetic label has many advantages. First, there are no comparable sources of magnetic signals in biology, so the background is intrinsically low. Second, the magnetic beads can be used to manipulate the molecules with magnetic forces induced by the electronic circuit [2], thus eliminating manual steps such as washing used in traditional assays.

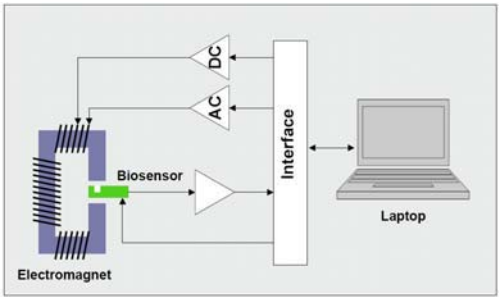

Figure 2 System block diagram

Figure 1 shows a simplified protocol of the assay. The sensor consists of the integrated circuit at the bottom with embedded Hall-sensors for detecting the magnetic beads. The surface received a coating protein to make it receptive to the target antibodies. Now the sample, usually a drop of serum, is added (Figure 1b). Magnetic beads coated with antigen are introduced (Figure 1c). The coatings are chosen such that the target antibody binds specifically both to the magnetic beads and the coated chip surface. However, non-specific binding with other protein present in the blood sample will occur also. Since the molecular adhesion forces are much smaller in this case, non-specifically bound magnetic beads can be removed from the chip surface with a small and controlled magnetic force. Finally, the presence of magnetic beads

bound specifically is detected with the Hall sensors that are embedded in the chip (Figure 1d).

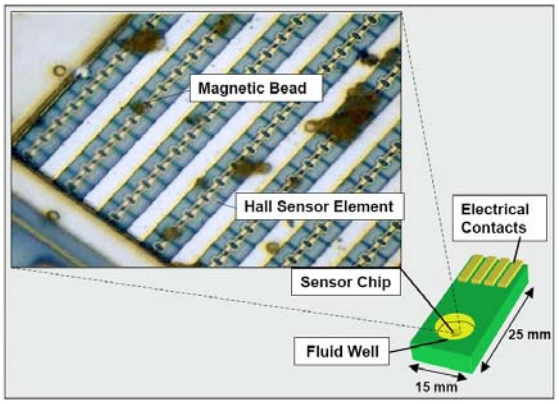

Figure 3 Disposable biosensor

The system consists of a disposable sensor element and reusable reader (Figure 2). The reader includes an electromagnet used for detecting and manipulating beads with controlled magnetic forces and electronics for interfacing to a computer or portable reading device.

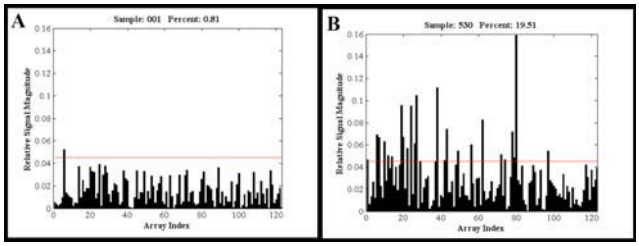

Figure 4 Sensor array electrical output

Figure 3 shows the sensor element in greater detail [3]. It consists of a chip with 1024 individual Hall sensors fabricated in a standard 0.25µm CMOS technology flip-chip mounted on a holder with a fluid well and electrical contacts to the reader electronics. Tests are performed by first introducing a buffered sample into the fluid well and then adding magnetic beads. Target antibody binds to the functionalized chip surface and magnetic beads. Next a magnetic field is used to remove unbound or nonspecifically bound beads from the sensor surface. At this point, only beads bound by target antibody are close to the chip surface and detected with the embedded Hall sensors.

3. RESULTS

The electronic immunoassay platform utilizes the same reagents as traditional ELISAs so that assay protocols do not need to be significantly altered. To evaluate the platform, a dengue fever assay has been ported to the platform [4]. Figure 4 shows results for a negative serum (A) and a positive serum (B). The relative signal magnitude (y-axis) for each interrogated sensor element is displayed with respect to array index (x-axis). The numerical result of the measurement process is calculated as the percentage of sensor elements whose absolute difference between measurement and calibration is greater than the detection threshold (horizontal line). The negative and positive sera yielded numerical results of 0.81% positive sensors and 19.1% positive sensors respectively.

Figure 5 shows the sensor output as a function of sample concentration. Reliable detection is achieved for concentrations down to 1ng/ml, a result that is comparable with conventional ELISA and demonstrates the viability of this technology. Modifications in the CMOS Hall sensor and electromagnet are expected to improve the detection limit to about 100pg/ml and reduce the detection speed from presently 60min down to minutes.

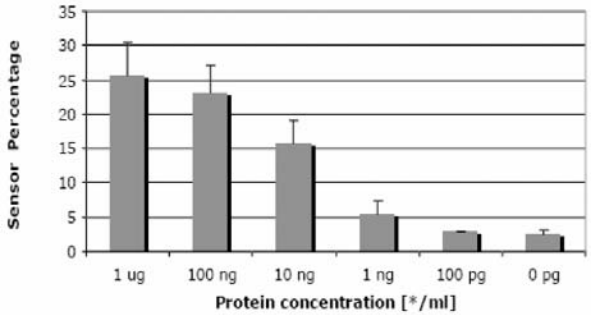

Figure 5 Sensitivity

4. CONCLUSION

An electronic platform employs tiny magnetic beads as an interface to the nanoworld of antibodies and antigen. The magnetic beads are used both for detection and manipulation of molecules, thereby facilitating complete control of the assay with electronic circuitry. The platform utilizes the same reagents as traditional immunological test so that protocols do not need to be significantly altered. The use of CMOS technology allows direct integration of signal acquisition and signal processing electronics, typically found only in a laboratory setting. The use of commercially available CMOS foundries allows the sensors to be mass-produced at a low cost.

5. ACKNOWLEDGEMENTS

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6. REFERENCES

[1] R. Edelstein et al., „The BARC biosensor applied o the detection of biological warefare agents," Biosens. Bioelectron., vol. 14, pp. 805-813.

[2] M.A.M. Gijs, "Magnetic bead handling on-chip: new opportunities for analytical applications (review)," Microfluidics and Nanofluidics 1, 22-40 (2004).

[3] T. Aytur, P. Beatty, B. Boser, M. Anwar, and T. Ishikawa, "An immunoassay platform based on CMOS Hall sensors," in *Proceedings Solid-State and Actuator Workshop*, Hilton Head Island, SC, June 2002, pp. 126-129.

[4] T. Aytur, J. Foley, M. Anwar, B. Boser, E. Harris, P. Beatty, „A novel magnetic bead bioassay platform using a microchip-based sensor for infectious disease diagnosis," Journal of Immunological Methods, 2006, in press.