DEVELOPMENT OF A BIOSENSOR CARTRIDGE INTEGRATING ACTIVE MICROFLUIDICS, MEMS SENSOR TECHNOLOGY AND DETECTION ELECTRONICS

Pedro Ortiz[1,4], Neil Keegan[1*], Julia Spoors[1], Richard Burnett[1], John Hedley[1], Alun Harris[1], Jim Burdess[1], Thomas Velten[2], Margit Biehl[2], Werner Haberer[2], Matthew Solomon[3], Andrew Campitelli[3] and Calum McNeil[1]

[1] Newcastle University, Newcastle upon Tyne, UK
[2] Fraunhofer Institute for Biomedical Engineering (IBMT), Sankt Ingbert, GERMANY
[3] MiniFAB (AUST) Pty Ltd, Victoria, AUSTRALIA
[4] Centro Nacional de Microelectrónica, IMB-CNM, CSIC, Barcelona, SPAIN

ABSTRACT

A highly sophisticated disposable microfluidic cartridge integrating a MEMS biosensor with detection electronics and active microfluidic components is reported in this paper. This device developed as part of the cancer diagnostics/therapeutics system SmartHEALTH (www.smarthealthip.com) is the first of its kind, and it represents a technical milestone in the development of point-of-care systems.

KEYWORDS: Lab-on-a-chip, bioMEMS, microfluidics, biosensors, clinical diagnostics, packaging.

INTRODUCTION

The circular diaphragm resonator (CDR) device [1], shown in Figure 1, lies at the core of this system. Previous versions of the biosensor cartridge comprised a hybrid device, bringing together a bioMEMS chip, PCB packaging and rapid prototyping polymer microfluidics (Figure 2) [2,3]. In that case electrical contact with the silicon chip, from the PCB, only enabled the actuation of the MEMS device; the biosensor signal detection (a change in resonance frequencies of two spatially independent modes of vibration [1]) was carried out externally using a laser Doppler vibrometer.

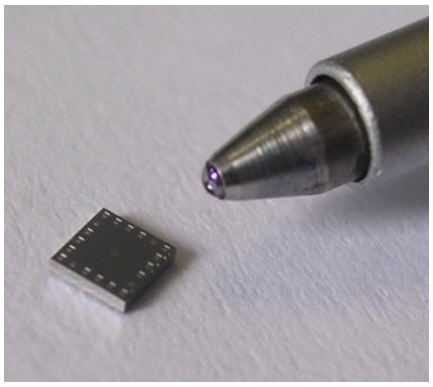

Figure 1. A 2 mm x 2 mm CDR silicon chip, designed by Newcastle University and fabricated by Tronics Microsystems(Crolles, France).

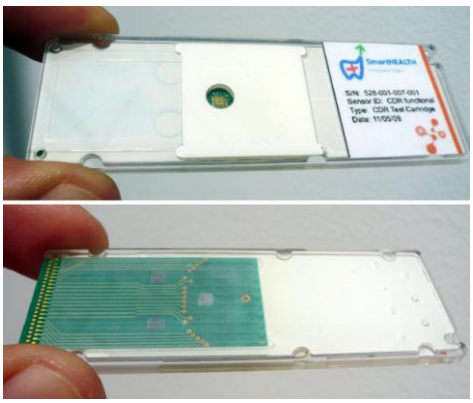

Figure 2. Front (top) and reverse (bottom) side images of the first prototype cartridge. The optical access window visible in top image allowed external signal detection using a laser Doppler vibrometer.

Although the development of the initial prototype cartridge, shown in Figure 2, constituted a significant technical development, as it brought together state-of-the-art PCB packaging of a bare silicon chip and polymer based microfluidics, it still required all reagents to be handled off-cartridge and detection of the MEMS biosensor signal to be carried out externally. In order to be able to use this type of device in the next generation of smart diagnostics systems, a more sophisticated device enabling reagent handling and biosensor signal detection on-cartridge was required; the development of these two features is presented in the following sections.

ELECTRONIC DETECTION DEVELOPMENT

One of the main features of the final cartridge prototype is integration of electronic components intended to amplify the low amplitude electrical signal (~5 nA_{pp}) produced by the change in capacitance between the vibrating silicon diaphragm and a sense electrode. Previous efforts to carry out this type of measurements had been unsuccessful; this is attributed to the presence of electrical feed-through captured by the transmission lines between the MEMS chip and the detection electronics located several centimeters away. By placing a first signal amplification stage millimeters away from the chip, we have ensured that the signal is recovered and preferentially amplified with respect to any noise before it is transmitted to the digital signal processing system in the instrument. This electronic detection system was developed

in parallel to the cartridge on a custom dual-in-line package format (Figure 3). The signal recovered from this near-chip amplification stage is then transmitted to a custom designed digital signal processing (DSP) board in charge of identifying the resonant frequency peaks corresponding to each of the vibration modes (sense and reference). The electronic detection development setup, which also includes a vacuum chamber, was tested successfully for the detection of degenerate mode resonance peaks, as shown in Figure 4. The DSP will then interface with the SmartHEALTH instrument, programmed to identify the shift in resonance frequencies (this is caused by mass addition from biomolecules in the sense area of the diaphragm), convert this to clinical units and update the corresponding patient record.

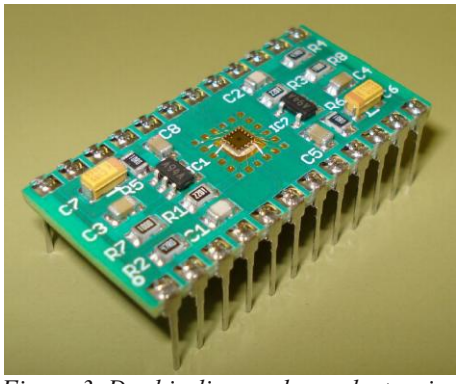

Figure 3. Dual in-line package electronics development PCB. The CDR device can be seen in the middle of the board surrounded by surface mount electronic components.

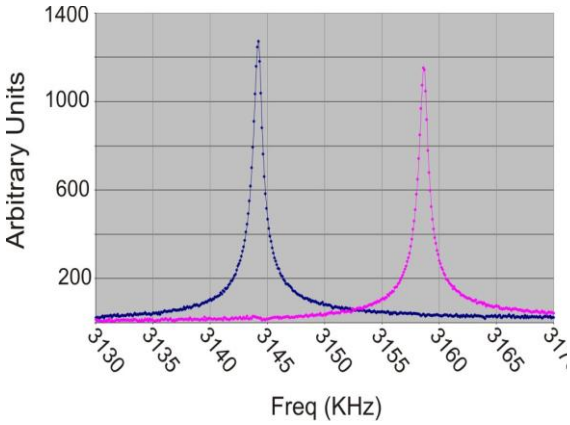

Figure 4. Electronically detected sense and reference mode peaks of a CDR device.

The PCB carrier that is integrated into the microfluidic cartridge contains electronic components required for the first amplifying stage of the electronics and are located on the rear side of the board (see Figure 5). The purpose of this rearrangement is to leave the device side of the PCB as planar as possible so that a good fluidic seal can be established between the encapsulation layer of the sensor carrier and the cartridge shell.

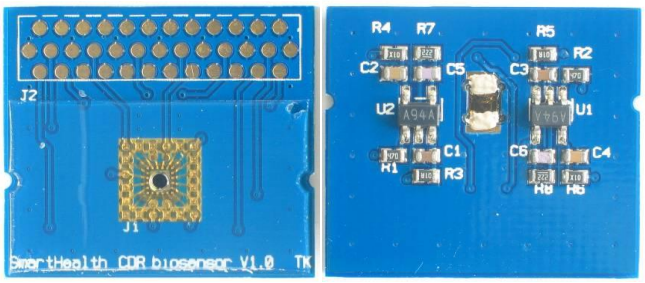

Figure 5. New CDR hybrid PCB carrier developed by Fraunhofer IBMT. The partially embedded CDR device and electrical contact pads can be seen on the top side (left) and the electronic components on the back of the board (right).

The CDR-loaded PCB is integrated into the microfluidic cartridge by a shell-insert principle, developed by MiniFAB, in a similar manner as previously reported [2]. Figure 6 shows schematics of this integration strategy in which the cartridge shell, the hybrid PCB carrier and the cartridge insert are bound together through a layer of pressure sensitive adhesive (PSA) film.

There has also been a significant development in the microfluidics; the new version of the cartridge has a much more complex fluidic network which enables the delivery of reagents and sample to the surface of the CDR sensor (as opposed to the previous version in which the cartridge contained no reservoirs or active components). The final cartridge prototype (shown in Figure 7) includes two turning valves which allow the system to deliver a sequence of on-board reagents and sample to the sensor. These valves also allow connection of the CDR chamber to a vacuum line coming from the instrument. This is required as the pressure at which the sensor is operated has significant impact on the quality factor (and hence measurement sensitivity) of the device [4].

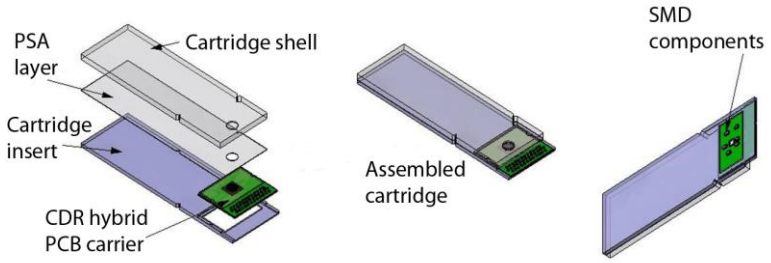

Figure 6. Cartridge assembly principle schematics. Microfluidic cartridge shell and the PCB carrying insert are glued with a pressure sensitive adhesive (PSA) film. Electronic surface mount devices SMD are at the back of the PCB to ensure a planar contact surface.

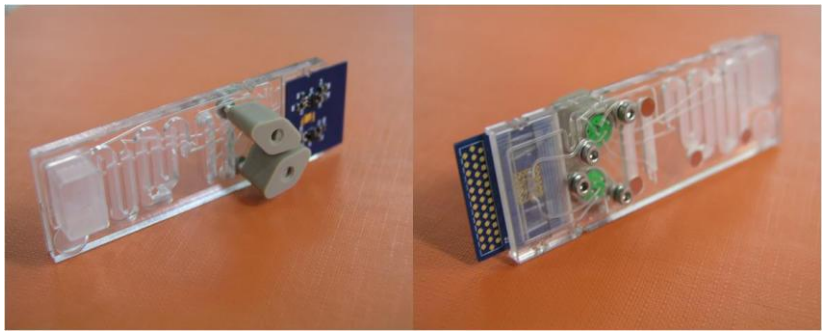

Figure 7. Microfluidic cartridge shell. The CDR-loaded PCB, turning valves and pierce-membranes for reagent/sample delivery from the instrument can be seen. On the right hand side image it can be seen that PCB´s contact pads are available for electrical contact with the instrument via spring-loaded connectors.

CONCLUSIONS AND OUTLOOK

The ability to detect the CDR biosensor signal electronically has been demonstrated. This crucial milestone signifies that once the SmartHEALTH system is up and running, no additional equipment other than the SmartHEALTH instrument (a bench-top system) will be required to carry out CDR-based bioassays. Also, the final prototype of this sophisticated microfluidic device has been fabricated. This prototype constitutes the first disposable microfluidic cartridge integrating all functionalities required for label-free, electronic detection of biomolecular interaction with MEMS mass sensors, for a point-of-care system.

ACKNOWLEDGEMENTS

The authors would like to thank the European Commission as well as ONE NorthEast for providing the funds for the present work within the SmartHEALTH Integrated Project (FP6-2004-IST-NMP-2-016817) and the MEMSens project respectively. We would also like to thank IMM GmbH for providing the microfluidic turning valves.

REFERENCES

[1] A.K. Ismail1, J.S. Burdess2, A.J. Harris, C.J. McNeil, J. Hedley, S.C. Chang and G. Suarez, *The principle of a MEMS circular diaphragm mass sensor*, J. Micromech. Microeng. 16 (2006) 1487–1493.

[2] T. Velten, M. Biehla, W. Haberer, T. Kocha, P. Ortiz, N. Keegan, J. Spoors, J. Hedley, and C. McNeil, *Packaging of a silicon-based Biochip*. SPIE Photonics West 2009, January 24-29, 2009, San Jose, CA, USA.

[3] P. Ortiz, N. Keegan, J. Spoors, J. Hedley, A.J. Harris, J.S. Burdess, R. Burnett, T. Velten, M. Biehl, T. Knoll, W. Haberer, M. Solomon, A. Campitelli and C. McNeil, *Integration of a bioMEMS device into a disposable microfluidic cartridge for medical diagnostics*. SPIE Photonics West 2009, January 24-29, 2009, San Jose, CA, USA.

[4] A.K. Ismail, J.S. Burdess, A.J. Harris, G. Suarez, N. Keegan, J.A. Spoors, S.C. Chang, C.J. McNeil and J. Hedley, *The fabrication, characterization and testing of a MEMS circular diaphragm mass sensor*. J. Micromech. Microeng. **18** (2008) 025021.

CONTACT

*Dr. Neil Keegan, tel: +44-191-222-7991; neil.keegan@newcastle.ac.uk