Automated, Disposable Sample Preparation Cartridge for Complementary Diagnostics

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Within the European Project BIOCDx [1], a Point-Of-Care (PoC) solution has been developed to measure the concentration of four biomarkers in the pg to ng range per ml out of whole blood. A single drop of blood from a needle prick is enough to obtain a complete signature indicative of cancer progression. The current system is developed as a complementary diagnostic to allow patient stratification and support therapy monitoring for prostate and breast cancer. The CSEM contributed to this success by developing a disposable cartridge and associated liquid actuation module that enable to run and monitor the complete workflow. With our solution the patient's whole blood sample is automatically preprocessed to plasma and metered for the subsequent optical measurement and finally collected in the on-cartridge waste before the disposal. All reagents are prefilled in the cartridge and all liquids remain entirely in the cartridge, avoiding contamination risk.

In the consortium of the European project BIOCDx CSEM has developed a solution consisting of a point of care (PoC) instrument (Figure 1) and a pre-filled disposable cartridge (Figure 2) previously reported in [2,3]. The cartridge contains a photonic sensor containing 8 asymmetric Mach Zehnder Interferometers (aMZI) from Lionix International. To detect the bio-markers, antibodies are deposited on the aMZI. For a first demonstration, the cartridge was customized to process whole blood from a liquid biopsy and detect a protein signature for breast and prostate cancer.

The user-friendliness was increased by reducing the manual steps to a minimum. Meaning, the user receives the packaged, self-contained cartridge and inserts it into the instrument. Then the sample (currently a drop of blood) is loaded into the cartridge and the sample port is closed. The instrument then prepares (I) the cartridge, (II) the detector, and (III) filters the sample before it is (IV) analyzed. Finally, the operator reads the result and disposes the cartridge in which all liquids are contained in the waste compartments to prevent any contamination.

Figure 1: BIOCDx instrument, developed jointly with LRE medical.

As soon as the cartridge is inserted into the instrument, the on-cartridge syringes, valves and sensor on the backside are interfaced with the actuators. On the front side of the cartridge, five flow sensors are monitoring the transition from air to liquid as shown in Figure 2 and enable to monitor the progression of the liquid columns in the microchannels and detect air bubbles. The flow front sensors are positioned (I) after each syringe to monitor their initialization and (II) before the two wastes to verify the correct flow directions. A final sensor is positioned in the metering loop to detect air bubbles during the priming procedure and to direct them into the bypass waste. The example at the bottom right in Figure 2 shows that the metering loop (position S3) is wet at the start time of recording and dry up at time index 1850 when air passes the sensor S3. At time index 2350 the metering loop is wet again, and the air gone. With a delay of about 50 units which corresponds to Δs which is the distance between S3 and S4 the entry to the bypass waste (position of S4) gets dry and wet again. Meaning the air bubble has traveled through the metering loop to the bypass waste. The two signals are inverted due to the different backgrounds and can be handled as such in the software.

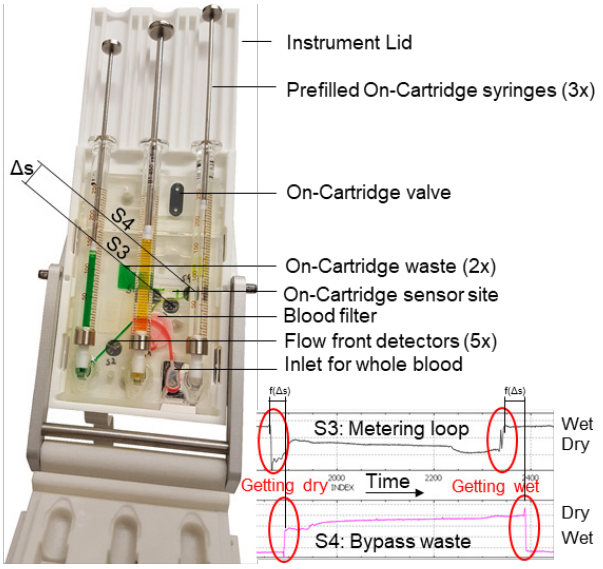

Figure 2: (left) Cartridge in instrument lid; (right) Flow front detector signal showing an air bubble moving from the metering loop to the bypass waste.

The main part of the cartridge is currently injection molded while glass syringes are still used enabling fast design iterations and easy preparation on site. In a next step, the available solution will be validated in a small clinical study to detect breast and prostate cancer. Simultaneously, a new cartridge design with embedded syringes will be done to enable mass production.

In future work, this technology might be adapted to work with other body fluids such as urine or saliva.

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[1] BIOCDx is a European Project with ID 732309, "A miniature Bio-Photonics Companion Diagnostics platform for reliable cancer diagnosis and treatment monitoring", http://biocdx.eu/

[2] S. F. Graf, *et al.*, "Analysis Cartridge for Companion Diagnostics", CSEM Scientific Report (2017) 60.

[3] S. F. Graf, *et al.*, "Liquid Biopsy - A disposable Cartridge to Measure Proteins from Whole Blood", CSEM Scientific Report (2018) 45.