Cloud Based Point-of-Care testing using Screen-Printed Sensor for Biomarkers Detection

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***Abstract*—** Measurement systems for early and reliable detection of degenerative diseases, like Alzheimer's disease (AD), are extremely important in clinical diagnosis. Among these, biochemical assays represent a commonly used method to differentiate patients from healthy population thanks to the sensitive recognition of specific biomarkers in biological fluids. So on beat actual limitations of these techniques in term of cost, standardization, and sensitivity, this study aimed to grasp a low-cost sensitive portable point-of-care (PoC) testing system supported on screen-printed electrochemical sensors. The designed circuit was implemented during a electrical device board and interfaced to a wireless system supported IOT data transmission so on enhance the portability of the proposed solution. Preliminary results were obtained by using controlled concentrations of electrolytic solutions and calibrating the sensors for antibodies and for a documented protein (i.e., interleukin 8) quantified by anodic stripping voltammetry (ASV). Findings from ASV measurements showed a sensitivity of 38 µA/(ng/ml) with a tested range from 1.25 ng/ml, with a limit of detection of two ng/ml. Further investigation will includes the validation of this PoC device by testing the concentration of a particular p53 protein isoform, which was recently identified to early correlate to AD development.

***Index Terms*— Screen printing sensor, Electrochemical biosensor, voltammetry, point-of-care(PoC) testing, wireless data acquisition device.**

I. INTRODUCTION

RECENTLY, one in all the foremost pervasive challenges of electronics and engineering applied to biotechnological and clinical research has been represented by the facility to develop specific measurement devices with integrated technologies able to identify—quickly, diffusely, and with a awfully high sensitivity—specific disease-related proteins and biomolecules, defined as "biomarkers." During this attitude, new rapid, low cost and easily accessible methodologies and technologies are increasingly investigated—including medical devices for *in vitro* diagnosis and point-of-care (PoC) systems—supported also by the growing interest toward cus- tomized and personalized medicine and toward rapid and home-accessible portable diagnostic systems [1]–[3].

Different technologies are often adopted so on understand biosensors integrated in lab-on-a-chip devices, promising path to cut back time, cost, and quantity of sample required to perform the analysis [2].

Among the numerous techniques investigated, electrochem- ical biosensor represents the correct start line to understand complete testing platforms for biological biomarker quan- tification. More specifically, screen-printed electrochemical sensors (SPES), thanks to their ability to be functionalized and customised for the detection of varied analytes (e.g., DNA, proteins), have acquired a predominant within the last decade. Printed electronics presents a successful approach to develop low-cost solutions, with the likelihood to increase the extent of standardization, to reduce sample volumes required for each analysis and to customize the surface for a more efficient functionalization. Especially, literature reports different studies supported screen printing (also defined as thick film printing) to know electrochemical sensors addressing the sensitive and specific quantification of assorted proteins and biomolecules [4], [5].

Electrochemistry offers an honest resonably of techniques to detect and quantify specific biomolecules using SPES, including the likelihood to both completely immerse the sensor during an solution [6] or just cover it with a touch volume of sample [7]. All the electrochemical approaches could be very fundamental in PoC implementation, since they will associate an improved quantitative analysis, with the likelihood to require care of a wet setup with functionalization, employing a protocol almost just like the one usually implemented for enzyme-linked immune sorbent assays (ELISA).According to the signal recorded, these techniques are often divided into impedance based and voltammetry methods. Among the first group, electrochemical impedance spectroscopy (EIS) represents a label-free method useful for protein and biomolecules

quantification, particular interesting because of its ability to detect variations in resistance and capacitance upon binding events. EIS principle relies on the measurement of the changes of impedance deriving from a special electrons exchange at the interface between the functionalized surface of the electrode and a conductive solution. Considering constant setup, these changes are especially related only to the concentration of the recognized proteins [9]. Differently from EIS, alltogether the voltammetric techniques, information about the analyte is obtained by measuring this because the potential of the electrode is varied. Albeit with differences between the precise biomolecules, detection is performed labeling target analytes with selected redox reactive species, thus to correlate an electrical signal proportional to the amount of analyte recognized. Among Volta metric methods, anodic stripping voltammetry (ASV) represents one in all the foremost promising compared to other electrochemical techniques, able to increase of sensitivity of others 2 or 3 orders of magnitude, reaching limit of detection (LOD) within the range of 10^{-9} to 10^{-10} M. In ASV, a metal is deposited on the surface of the electrodes during a preconcentration step, and it's then stripped applying an oxidizing potential. Additionally to heavy metals quantification, applications of ASV for proteins [7], biomolecules [11], and DNA sequences [12] are tested..

Similarly, for both EIS and voltammetry, a three-electrode configuration is usually implemented. This configuration, including a working, counter and reference electrode (Working Electrode (WE), Counter Electrodes (CE), and Reference Electrode (RE)), is commonest for typical electrochemical applications, especially when the potential across the electrochemical interface have to be compelled to be measured accurately, so on ensure stability of the cell [8].

Concerning the blending of the conditioning circuit within the look of PoC systems or monitoring devices, we can find different examples within the very recent literature, which tried to reinforce different clinical issues related to rapidity of assays, portability, implant ability, and sensitivity Additionally, superb interest was related with combine innovative detection techniques (including label-free techniques supported optical, mechanical and electrochemical transducers) with their optimal conditioning circuit realize fast, portable, and easily usable devices about to smart bio sensing and to bring an enormous improvement to daily practice [3], [14]. However, among the different technologies proposed for the belief of PoC systems, no, quantitative, reliable and sensitive devices for particular protein detection are yet commercialized.

Therefore, our specific aim is to apply these challenging up-and-coming PoC concept, extending previous preliminary analyses [15], so on understand a self-standing portable device, which can be useful for the sensitive quantification of protein in finding biomarkers.

In particular, the interest of this paper concerned the realization of a platform for biomarkers involved within the first diagnosis of Alzheimer's disease (AD). Among the foremost neurodegener- ative diseases, one in every of the foremost pervasive challenges is truly related to the ability to detect AD in its earliest stage [16], by using different strategies, including cognitive tests, neuroimaging [17], [18], genetic procedure and biomarkers. So far, quantification of this protein are often performed in clinical and biological laboratories by employing a particular ELISA assay starting from peripheral blood samples. However, this technique presents issues in term of it slow and price effectiveness, required sample volume, inter- and intrarater reliability, and possibility of quantification.

Therefore, here is presented a whole system consisting of a SPES with six measuring points and an electronic microprocessor-based system, designed to wirelessly transmit data, thus to increase the final portability of the solution. Particular attention was given to the choice of the SPES materials and geometry, the electronic circuit dedicated to the conditioning and acquisition of the electrical signal, and to the electronic microprocessor-based solution which might transmit data wirelessly. Several characterization measurements were also obtained with the presented system and further design considerations and important analyses are reported.

II. System Description, Materials, and Methods

The proposed PoC is consists by three main parts (Fig. 1): 1) the screen-printed sensing probe, which can be functionalized using different antibodies for the detection of specific biomarkers; 2) the signal conditioning circuit designed to form sure highly precise and sensitive measurements, thus to register small changes in ionic current during ASV testing protocols; and 3) the IOT system for signal acquisition.

A. Sensors Design and Production

Sensor layout was designed using a software called QCAD (QCAD.org). Each layer, resembling a special conducting material, was separately designed, so on provide the masks required to screen print—layer-by-layer— the final word structure of the sensor. Conductive tracks were designed with particular care employing a resolution compatible

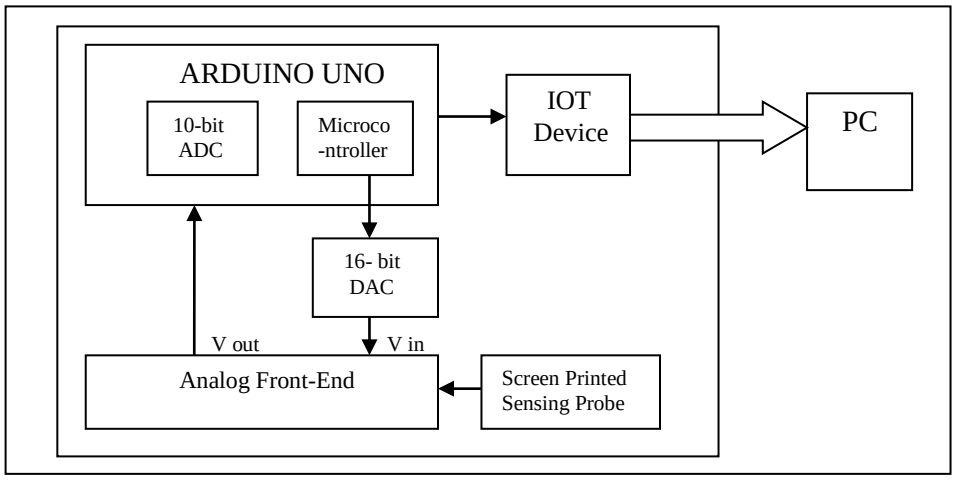

Fig. 1. Block diagram of proposed PoC testing platform

with the adopted screen printer (A2 Model, Baccini srl, Italy). Following an everyday procedure, final geometry was printed on an understandable sheet by means of inkjet printing, thus to allow the conclusion by UV photolithography of a 40-μm-thick blocking stencil, i.e., the mask required for the screen printing process. Specifically, a silver ink (CI 1001, resistivity <0.015 ohms/square, viscosity 14 Pa s at 30 °C) was selected to understand the conductive tracks. Carbon ink was selected to understand the WE and CE of the biosensor. Among the materials available for SPES production (e.g., carbon, gold, platinum), carbon represents the foremost effective compromise in term of cost—essential requirement when designing a PoC device—biocompatibility—in order to form sure an accurate functionalization—and electronic performances—in order to allow signal transduction during ASV measurements [21]. Finally, a silver–silver chloride ink (CI 4002, ohmic resistivity < 0.050 ▲$^{-2}$, viscosity 5 Pa s at 30 °C) because of its inert chemical composition, was selected to understand the RE. All the conductive pastes were purchased from ECM—Engineered Conductive Materials (Engineered Material System Inc.). Employing a screen with 250 meshes with apertures forming angles of 45°, the three layers were consequently printed on a 0.4-mm-thick alumina substrate: first silver, then carbon and finally silver–silver chloride. Each layer was cured in an oven, specifically silver inks for 10 min at 110 °C and carbon ink 5 min at 130 °C. After the printing was completed, so on permit a stronger conduction of the signal, the conductive tracks were covered by employing a transparent spray (RS Components, U.K.) specifically adopted in printed electronics as a protecting layer to verify proper electrical insulation. This operation only leaves the terminal a part of the tracks uncoated, thus to permit the relation to the conditioning circuit.

B. Circuit Design and Production

Following the completion of the SPES final layout, an ardent acquisition system was designed so as to permit the assembly of a whole PoC testing platform module. For the

The testing solution is basically composed of one Arduino UNO board, a custom conditioning circuit and a IOT.
dual-voltage supply (5 V), two lithium- ion batteries were adopted. Arduino UNO board generates the signal required to drive the measurement. Since Arduino UNO isn't able to generate an analog signal, it communicates with the 16-b digital-analog converter (16-b DAC) over serial peripheral interface so as to get an analog signal (V_{in}), as input for the conditioning circuit. The planning of the analog side was performed to get ASV measurements (Fig. 3). Particularly, the specified potential is applied to the cell by controlling the potential of RE with relavancy to the WE and, due to the electrons movement generated by the effect of the voltage applied within the sample, the generated current are often detected between WE and CEs. The last stage was developed to create the output of the OPA129 suitable for the Arduino analog input. Indeed, the OPA129 output is positive or negative while the analog input of Arduino are often only positive. Operational amplifiers were carefully selected betting on the precise function they had to perform within the circuit. So as to ensure a high accuracy within the control of the input voltage to the sensor, preci- sion bipolar amplifiers were selected [OPA177GS], with very low offset voltage, drift, and low noise. So as to permit low-current measurements with high precision and low bias, the current-to-voltage converter was realized using an ultralow bias current monolithic operational amplifier (OPA129 from TI). Once set the utmost values of the voltage ($V_{max,RE}$) required for elicit specific electrochemical reaction, V_{in} was imposed as reported in Fig. 3 and V_{out} was then measured within the interval OT, which specifically depends on both $V_{max.RE}$ and therefore the overall scan cycle duration (T). The scan rate is defined because the ratio between maximum voltage ($V_{max,RE}$) and also the time required to achieve this voltage (T /4).After all the Surface Mounting Device (SMD) components were soldered, the board was inserted in a metallic box to avoid noises on the signal recording and to improve the sensor sensitivity and precision. The sign (V_{out}) is acquired by Arduino UNO through the internal 10-b digitizer. Measurements are transmitted wirelessly to a PC using the IOT module.

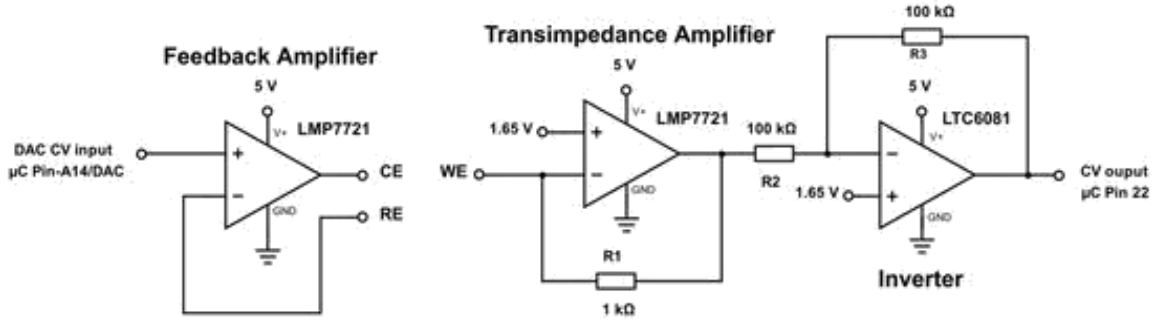

Fig. 3. Schematic of the waveform of V_{in} produced by DAC (Left) and schematic of the circuit used as analog forepart (Right).

wirelessly to a PC using the IOT module.

The transmitted packet includes the time, Vin and Vout. A Virtual Instrument was developed to acccumulate and store the information. Furthermore, through the VI the user can define the $V_{max.RE}$ and therefore the T when the setup code of Arduino UNO is executed. During this way, with the possibility of generalize this approach, the PoC can be used for identifying several biomarkers, by implementing different SPESs and function- alization methods.

C. Calibration and Measurements

After optimizing the design and testing the compatibility of the materials with wet lab techniques, the platform was assessed by measuring output current, following three different protocols: 1) employing a isotonic solution, with different concentrations of NaCl; 2) functionalizing the WE with primary antibodies in presence of $K_3[Fe(CN)_6]$ solution; 3) performing ASV measurements to calibrate the platform using Interleukin 8 (IL-8).

Both the input and thus output signals were generated and purchased respectively by using the portable wireless system described within the previous paragraph. Experiments were always performed in triplicate. All graphical and tabulated data were usually reported as mean ± standard error. LOD for IL-8 quantification was calculated using three-sigma limit definition.

1) NaCl Solution Measurements: The first test of the circuit was performed so on assess its ability to detect small changes in solution conductivity due to controlled variations of NaCl concentration in deionized (DI) water. Specifically the circuit was evaluated with concentrations but 1 mg/ml: 0, 0.44, 0.66, 0.88, and 1 mg/ml. In each experiment, drops of 200 µl of isosmotic solution were released on the three electrodes, ensuring that the drop stayed correctly in place by employing a mask applied on top of the sensor. For this analysis, $V_{max,RE}$ and T were set to 300 mV and 25 s, respectively, and thus the scan rate was 48 mV/s. The expected output was related to a change within the intensity of current flowing between WE and CE, which corresponds to a special concentration.

2) Antibodies Coating Quantification: The effectiveness of primary antibodies coating on the WE was assessed by evaluating changes within this detected between WE and CE at different scan rates with three antibodies concentrations:

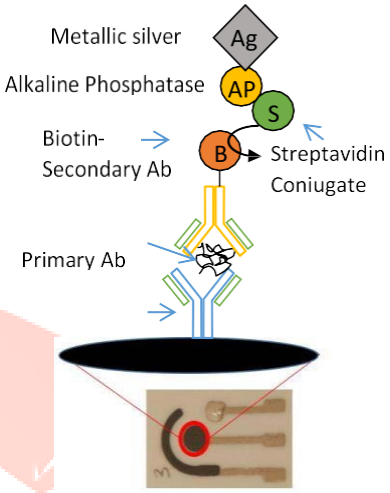

Fig. 4. Sensor functionalization for ASV measurements.

0, 4, and eight µg/ml. After an overnight incubation at 4 °C, the computation were performed in existence of a conductive electrolytic solution of 5 mM $K_3[Fe(CN)_6]$ in 1-M KCl. Once the functionalization was performed, a drop of 200 µl was placed so on to cover the electrodes and permit current flow. Finally, the electronic measurements were performed at four different scan rates (48, 120, 240, and 1.2 mV/s), with a $V_{max,RE}$ of 300 mV.

3) Interleukin Quantification Using ASV: So as to optimize the ASV protocol for biomarkers quantification (Fig. 4), a preliminary curve was quantified using IL-8 protein, a member of the CXC chemokine subfamily. Cytokines are important mediators of inflammation and are usually related to pathogenesis of the many inflammatory diseases. Therefore, IL-8 is currently being applied as noninvasive diagnostic marker in various fields of medicine either for the aim of early diagnosis or as a prognosis predictor [22]. Furthermore, recently, Ray *et al.* [23] has identified 18 signaling proteins in plasma which can be used to classify and predict clinical Alzheimer's diagnosis, among which IL-8 has been also identified. Therefore, IL-8 are often considered as universal biomarkers—from cancer and inflammation to neurodegeneration—thus generalizing the use of this present PoC platform to varied clinical fields.

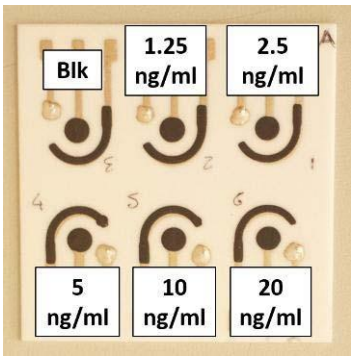

Fig. 5. Layout for IL-8 concentration test on multiwells sensor.

Moreover, in this validation phase, IL-8 strong interaction with its capture antibody, allows to decrease the variability to the functionalization phase. The protocol adopted for IL-8 quantification in this calibration phase of the circuit was characterized by a particular functionalization of the sensor using immunocomplexes formed by a capture and a finding antibody, using a dedicated kit (DuoSet development system for ELISA, Human CXCL8/IL-8). Particularly, during the step various concentration of IL-8 were dropped on the multiwell sensor, as shown in Fig. 5.

Concerning guage sensor LOD of IL-8, the platform was calibrated employing a range of concentrations usually easily quantifiable using with ELISA assay, from 1.25 to twenty ng/ml. Concerning the detection step, the functionalization was completed labeling the secondary antibodies with alkaline phosphatase, an enzyme ready to catalyze the reaction from ionic silver of silver of nitrate ($AgNO_3$) to metallic silver, allowing a selected deposition of silver, proportional to the quantity of protein found within the sample. Thus, Ascorbic acid (AA-p) 2Ag reacts in Dehydroascorbic acid 2H 2Ag. After the deposition step was completed, so on performing the stripping step,200 μl of solution (1-M KCl) was dropped on the three electrodes to permit current flow and $V_{max,RE}$ and T were set, respectively, to 900 mV and 60 s, thus with a scan rate of 60 mV/s. Finally, current flowing between WE and CE due to Ag oxidation was measured, allowing a sensitive quantification of proteins recognized on the sensor surface.

III. Results

A. Calibration and Measurements

1) NaCl Solution Measurements: Results from the evaluation of circuit response to changes in saline conductivity showed a linear increase of current peaks comparable to increasing NaCl concentrations. This finding was coher- ent with literature since, obviously, the conductivity of a particular solution features a positive linear relationship with its concentration [24]. Particularly, within the considered range of concentrations, the circuit showed the power to find small changes in solution conductivity like small values of current flowing between WE and CE, thus reporting a sensitivity of 0.15 mA/(mg/ml), with a current of 0.07 mA at zero NaCl concentration, thanks to DI water conductivity (Fig. 6).

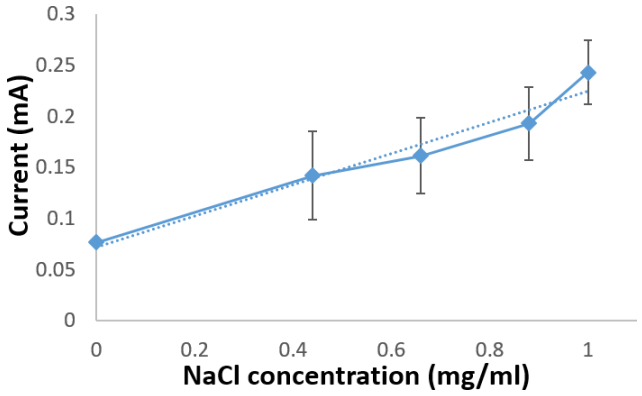

Fig. 6. Local maximum of the voltammograms peaks at various concentrations of IL-8.

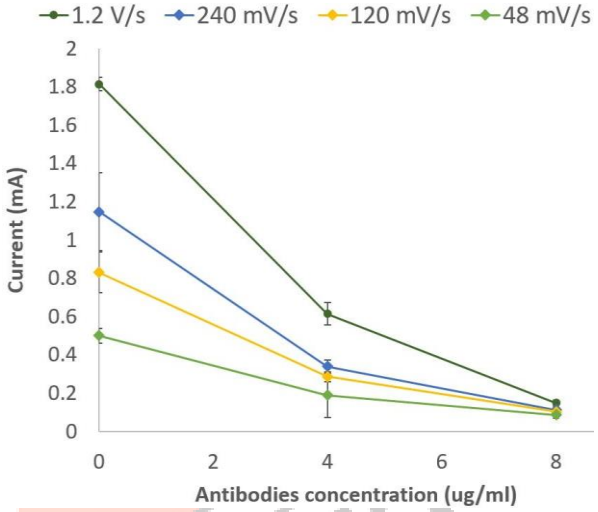

Fig. 7. Calibration of SPES with NaCl solution. (Error bars represent standard deviations of measured data.)

2) Antibodies Coating Quantification: Results from antibodies coating quantification showed a proportional decrease of the present peak flowing between WE and CE, for all the scan rates evaluated, indicating an increased impedance of the system because of an increasing concentration of antibodies coated on WE surfaces (Fig. 7).

This behavior comes from an increased portion of WE covered with primary antibodies, and, therefore, from a reduced conductive surface of the electrode available to exchange electrons with the electrolytic solution.

The sensitivity of the platform to quantify the concentration of antibodies coated on the WE appears to be affected from the scan rate of the input. Particularly, a sensitivity of 52 μA/μg was measured at 48 mV/s, of 90 μA/μg at 120 mV/s, of 128 μA/μg at 240 mV/s, and of 208 μA/μg might be calculated for measurements performed at 1.2 V/s.

Comparing the variation observed between this peaks recorded using different scan rates, a more enhanced difference might be observed at higher scan rates. While all told the evaluated conditions a rise within the current peak recorded are often observed when decreasing the antibodies concentration.

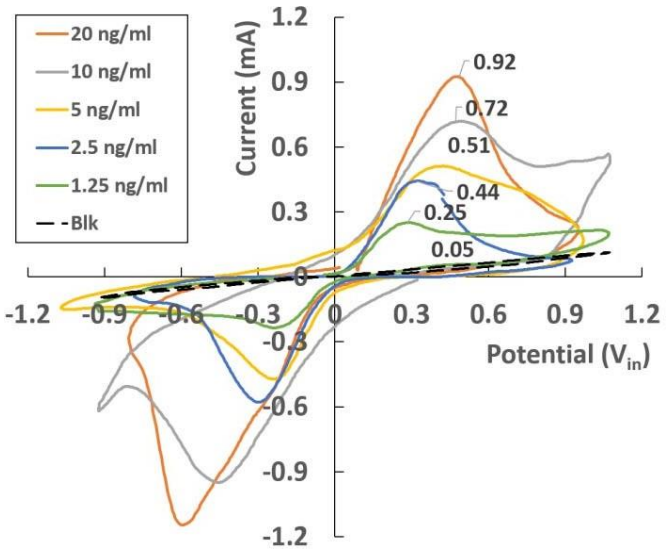

Fig. 8. Differences between antibodies concentration detection at different scan rates. (Error bars represent standard deviations of measured data.)

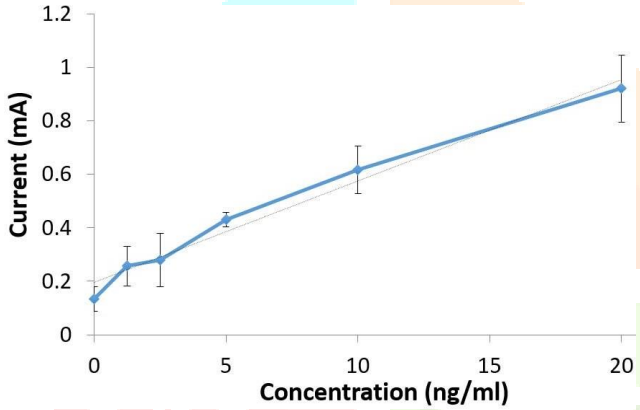

Fig. 9. Cyclic voltammograms, corresponding to different IL-8 concentrations.

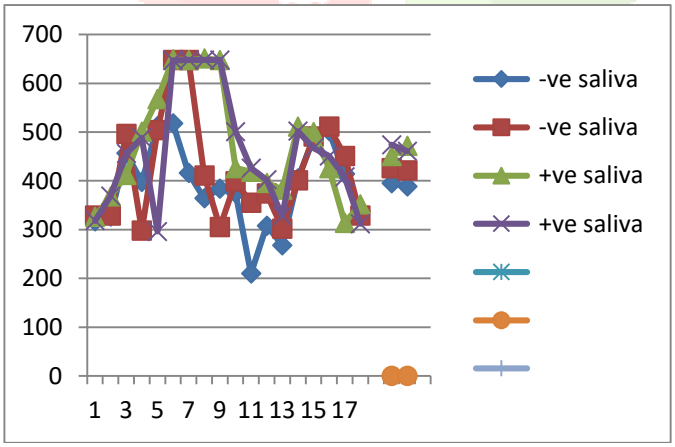

Fig. 10. D ifferent values of Samples of saliva.

For the bare sensor, where the complete surface is accessible for electrons exchange with the electrolytic solution, an enhanced difference between current recorded at different scan rates may well be observed, compared with the coated conditions. This result suggested a decent adhesion of the coated layer on the WE, acting as an insulating layer.

3) Interleukin Quantification Using ASV: Results from ASV measurements showed a rise within the maximum peak of current proportional to the increase of IL-8 concentration. The voltammograms plotted in Fig. 8 showed the anodic peak because of the silver stripped within the buffer solution in an exceedingly window of positive potentials around 0.5 V, cherish the oxida- tion potential of metallic silver deposited during the chemical deposition step. Bare electrodes (dotted black line), just coated with 8 μg/ml of primary antibody, showed a CV with a current peak equivalent to 0.05 mA, value comparable with the results obtained from antibodies quantification considering an identical scan rate, as described within the previous paragraph. Some differences may well be observed between the baselines love different electrodes and affecting the position of the peaks, probably thanks to intrinsic variability within the electrodes processing. Furthermore, also the local reaction between the electrode and thus the answer could solution could influence the baseline and will have to be compelled to be analyzed further, so on enhance the reliability of the ultimate PoC. The local maximum of the present peaks was calculated for every concentrations and so plotted (Fig. 9). Well defined current peaks might be observed for the tested range of concentration from 1.25 to twenty ng/ml, with a sensitivity of 38 μA/(ng/ml) and a LOD of two ng/ml. The selection of the concentration tested during this phase form 1.25 to twenty ng/ml had to required under consideration the limitation thanks to the technique and also the material (i.e., carbon ink) accustomed produce the WE. However, these values are in accordance with the range adopted in several works using ELISA assay.

IV. Discussion and Conclusion

The complexities and so therefore the heterogeneity associated with AD require high precision and sensitivity within the reliable detection and quantification of specific biomarkers. This approach could allow to get obtain an early diagnosis of the disease within the presymptomatic phase. Furthermore, the identification of specific biological markers could provide additional information about the pathology development from both the biological and pathoclinical point of view [19], [25]. So as to achieve this goal efficiently, different characteristics of measuring methodology—such as rapidity, low cost, and straightforward access and use—play a fundamental role. Furthermore, this need of quantification has been rapidly growing also considering the interest addressed toward personalized medicine and domicil- iary diagnostics [1]. The proposed PoC platform presented high level of inte- gration of assorted solutions, including SPES and wireless transmission, so as to get a less cost and portable but sensitive device. From the characterization perspective, the results obtained, confirmed the compatibility of the screen-printed materials for the functionalization required for AD biomarkers detection and wet lab practices. Furthermore, tests performed both with NaCl solution and with $K_3[Fe(CN)_6]$ solution validated the ability of the designed circuit to effectively detect changes in solution conductivity and system impedance, associated with the changes within the current flowing between WE and CE. Results from the characterization with conductive solutions suggested several

Properties. First of all, the facility of the circuit to detect lowchanges in concernration, with good reproducibility and reliable responses. Furthermore, the response recorded for the electrode coated with 8 μg/ml of antibody anti- IL-8 at the assorted frequencies could confirm
the great adhesion of the primary antibody on the WE, essential for the effective realization of the complete immunocomplex. Findings obtained from the calibration performed quantifying IL-8 protein, showed a sensitivity of 38 μA/(ng/ml) and a LOD of two ng/ml. These results appear to be promising also compared with works where, using similar experiment designs and ASV as detection method, a limit for a reliable quantification of proteins was reported to be 10 ng/ml [7], and 2.2 ng/ml [26], respectively. Decreasing the concentration of IL-8, thus decreasing the amount of silver stripped, ASV peaks looked as if it would be shifted toward decreasing potentials, because of the interaction between solution and electrode when redox reaction is proscribed.In this research, we discovered all the conditions so on develop a PoC device with a patented antibody recognizing unfolded p53 and allowing the measurement of this biomarker in AD patients. After the validation, the proposed methodology and thus the platform designed are visiting be optimized so on be easily accessible for a routine automatized diagnosis technique within the clinical environment.All this, with the aim to know an innovative self-standing portable point-of-care test system, representing a less cost, easy to use, and highly precise platform able to support the validation of a promising putative early biomarker for AD..

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