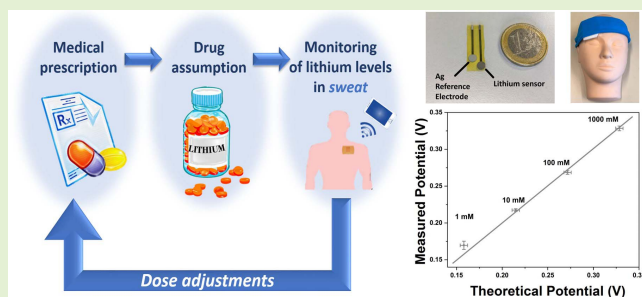


A Wearable Electrochemical Sensing System for Non-Invasive Monitoring of Lithium Drug in Bipolar Disorder

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Abstract—Lithium represents the main drug for the treatment of Bipolar Disorder (BD) as it acts as a mood stabilizer. However, because of its narrow therapeutic window, psychiatric patients are obliged to frequent tests in hospital to control their lithium blood concentration during therapy. In this paper, we fabricate for the first time a complete non-invasive system for the Therapeutic Drug Monitoring (TDM) of lithium in sweat in people suffering from BD. The wearable electrochemical sensing platform includes a paper fluidics and a stable Reference Electrode (RE). Lithium detection is based on the use of a potentiometric Ion-Selective Electrode (ISE) with a nanostructured solid contact in order to increase the potential stability of the sensor. A chemical chlorination combined with the use of a PVC membrane doped with an Ionic Liquid (IL) is used to minimize possible potential drifts of the RE. The Nernstian response (56.8 ± 3.9 mV/decade) of the system in the range of clinical interest is then proved in aqueous solution and in sweat. The integration of the sensing platform with a paper fluidics transporting fresh sweat sample to the sensing area is also considered. The already tested sweat is collected in a reservoir made of slow adsorbing paper. The complete wearable system is then successfully tested in a simulated setup by using a mannequin. The measured potential is well compared to the predicted ones in the therapeutic window of lithium drug, proving the good sensing capability in artificial sweat.

Index Terms—Electrochemistry, flexible sensors, ion sensors, potentiometry, sweat, wearable.



I. INTRODUCTION

LITHIUM is the most common drug for mood stabilization in psychiatric disorders [2]. Despite its narrow therapeutic range, which can have severe consequences on patient's health, it represents still the most widely used therapy for the treatment and maintenance of people suffering from Bipolar Disorder (BD). In this paper, we propose a novel non-invasive method for the decentralized Therapeutic Drug Monitoring (TDM) of lithium levels in sweat. For this

purpose, a complete wearable electrochemical system with a paper fluidics is fabricated and its functionality successfully tested.

BD is a potentially-mortal disease that cannot be treated, but only controlled with specific drugs. Every year 60 million people are affected worldwide (WHO). In the U.S.A. 2.6% of the adult population suffers from this condition according to the National Institute of Mental Health. The disease causes extreme mood swings, with emotional highs (mania or hypomania) and lows (depression). It is a progressive condition which has a prodrome, a symptomatic phase and a residual state. There is mounting evidence that manic and depressive episodes have a toxic effect on neurons and glia, causing irreversible damages to brain areas critical in mood regulation. Early diagnosis, proper treatment and targeted management according to the phase of illness are critical to arrest the neuro-progressive nature of the condition [3]. Furthermore, the risk of suicide is 30 times higher than for normal population, thus the need of mood stabilization with lithium salts is stringent [3], [4].

The drug is taken by mouth in the form of lithium salts (the most common one is lithium carbonate). The narrow

Manuscript received January 27, 2020; revised July 7, 2020; accepted July 12, 2020. Date of publication July 15, 2020; date of current version March 17, 2021. This work was supported by the H2020 ERC 2014 ADG669354 CyberCare. This article was presented at the IEEE Sensors 2019, Montreal, QC, Canada. The associate editor coordinating the review of this article and approving it for publication was Dr. Roland Vida. (Corresponding author: Francesca Criscuolo.)

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Digital Object Identifier 10.1109/JSEN.2020.3009538

therapeutic range makes the calibration of the optimal drug dose for each individual far from trivial [5]. When the blood concentration overcomes the maximum safe concentration, poisoning can appear. This can cause severe side effects on the patients, including chronic toxicity, ataxia, drowsiness, myoclonic twitching and irreversible damages to organs like liver, brain and kidneys [6], eventually leading to death. Several factors must be considered for the optimization of the dose, like dietary restrictions and interactions with other drugs [6]. Therefore, it is evident why TDM is a norm during treatments with lithium salts [7]: the determination of the lithium concentration in blood is done at least every week (with the so-called standardized 12h or 24h Li^+ serum concentration) at the beginning of the therapy or after any variation in the dose; if some complications are found, the interval between subsequent analyses must be shortened; only in absence of any abnormality it is possible to reduce the number of check-ups to approximately three months [2].

Expensive and non-trivial techniques are employed in clinical laboratories to quantify lithium. These include flame emission photometry, atomic absorption spectrometry or liquid-junction Ion-Selective Electrodes (ISEs) [8]. An interesting possible alternative to these bulky and complicated methods could be represented by potentiometric all-solid-state ISEs as they enable simplicity of detection, easy miniaturization and low cost. Nonetheless, only a few examples have been proposed in the research community in this direction so far [9], [10], despite the huge impact that those remote monitoring systems could have on patients' quality of life. Carbon nanotubes have been used to fabricate a paper-based Li^+ ISE by Novell *et al.* in [9]. A small Li^+ sensor with high selectivity has been described by Coldur *et al.* in [10]. The system is based on the use of a graphite composite as solid contact. In the following years, the group has also reported the investigation of lithium sensing under flowing conditions to study the feasibility of realizing automatic and LOC analytical devices [11]. Despite all these research papers introduce some interesting turning points in the management of TDM in psychiatric disorders, many drawbacks must still be solved. Those certainly include toxicity, biocompatibility, reproducibility and simplicity of the fabrication process. Furthermore, all the proposed methodologies are based on lithium sensing in serum, which necessarily requires invasive procedures for blood sampling.

In order to solve this issue, in recent years there has been a major effort to substitute blood with alternative biofluids that enable non-invasive collection of medical information [12]–[14]. In particular, sweat sensing has attracted significant attention in the research community. In fact, the academic publishing over the last 5-years has seen a 10-fold increase in this field. Both ions and other metabolites have been investigated as sweat biomarkers for different applications. Electrochemistry is the most explored sensing method because of the simple design, high sensitivity, small sample volume, low cost, easy integration into microfabrication processes for large-scale production and straightforward signal interpretation. Among the most notable examples of wearable devices it is worth mentioning the fully integrated

sweat band described in Nature by Gao *et al.* in [15] and the RFID sensor patch for sodium monitoring that appeared in IEEE Spectrum [16]. The research has focused mainly on cystic fibrosis and physical exercise monitoring. The most investigated ions are K^+ [15], Na^+ [15]–[19], Cl^- [20], [21], NH_4^+ [22] and H^+ [19]. Recently, an electrochemical autonomous sample extraction system has also been implemented to induce sweat production with various secretion profiles [23]. For more detailed reviews on recent advances in wearable chemical sensors we refer the readers to [13], [24].

In this work, the use of a wearable sensing system for the decentralized and non-invasive optimization of lithium levels in sweat is proposed for the first time. The good correlation between the amount of lithium excreted in sweat and the one present in blood has been proved in literature with chromatographic techniques [25]. In particular, it has been found that the concentration in perspiration is about 3 times larger than the one in serum (2.4 mM - 4.5 mM). In addition, sweat offers some considerable advantages with respect to blood: it is highly abundant, it does not require the use of syringes or of invasive procedures for sampling and it can be reproduced artificially in chemical laboratories using specific standards. The principle behind the non-invasive approach proposed in this paper for the optimization of lithium levels by sweat analysis is shown in Figure 1a. A wearable system could be used to collect data from the patient's sweat from home. The measured lithium levels could be sent remotely to the doctor's device in order to monitor and adjust the drug dose without the need of blood tests. With this system patients suffering from BP, whose life is already significantly affected by this serious disease, would not need anymore frequent check-ups in hospital. Consequently, their life quality would be significantly improved.

A flexible electrochemical sensing system has been fabricated. This consists of a nanostructured all-solid-state potentiometric sensor and a Silver solid-contact Reference Electrode (RE). The potential stability of the RE is ensured by combining a chemical chlorination step with the use of a Polyvinyl Chloride (PVC) membrane doped with an Ionic Liquid (IL). The platform shows a quasi-Nernstian behaviour (56.8 ± 3.9 mV/decade) in the range of clinical interest both in aqueous solution and in artificial sweat.

A paper fluidics made of a combination of fast and slow adsorbing filter paper is also fabricated to ensure the collection of fresh sweat on the sensing area and the disposal of already tested sweat in a reservoir. The integrated sensing system is then successfully tested in a wearable setup with the aid of a mannequin. The analytical capability of the device is confirmed by the similarity between the measured and predicted potential values in the therapeutic range of the drug.

II. EXPERIMENTAL METHODS

A. Materials

All chemicals were purchased from Sigma Aldrich (USA). Whatman® qualitative filter paper, Grade 113 AND Grade 5, was used for the fabrication of the paper fluidics. Blenderm™

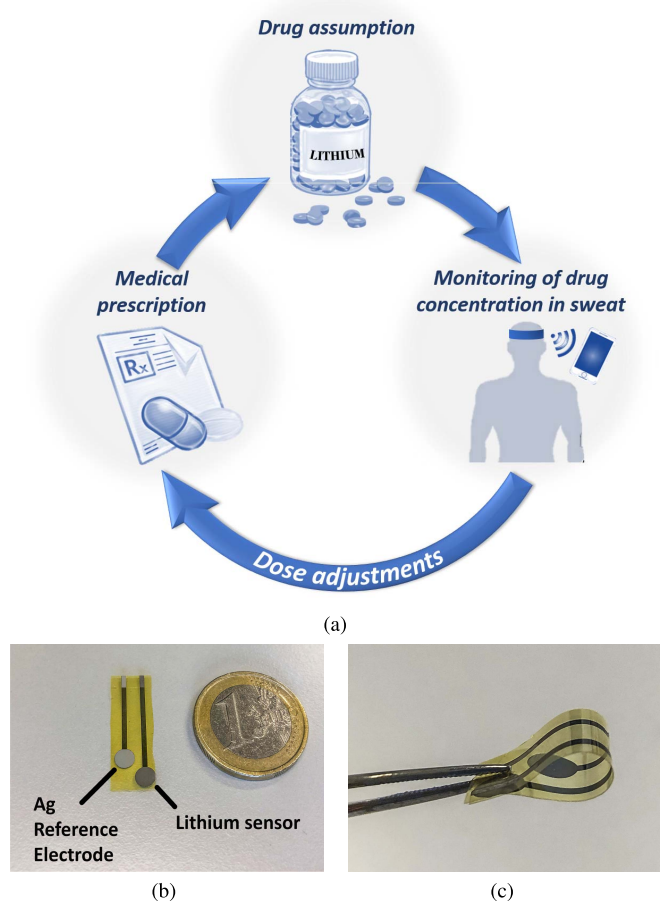


Fig. 1. (a) The principle behind the non-invasive approach proposed in this paper for the Therapeutic Drug Monitoring (TDM) of lithium in sweat. (b) The flexible electrochemical sensing system fabricated in this work for the non-invasive monitoring of lithium. (c) Full bending of the flexible electrochemical lithium-sensing system.

Surgical Tape by 3M (USA) was used to fix the setup on the mannequin skin and to avoid displacements of the sensing system.

B. Electrodes Fabrication

The electrodes were fabricated with a lithography process as described in Fig. 2. A Silicon wafer is used as rigid substrate during the fabrication. A 400 nm-thick sacrificial Aluminum layer is deposited initially on a Silicon test wafer in order to enable a simple anodic release of the platforms at the end of the manufacturing steps. 10 μm PI are then spin-coated to serve as flexible substrate material for the final platform.

The patterning process involves two main lithographic steps followed by a lift-off to define the Platinum and Silver areas. The sputtering procedure for metal deposition includes a 5 s activation step with oxygen plasma to enhance adhesion. A thin Titanium layer is placed on top of the electrodes to protect the surface from oxidation during processing (this especially important for the final lithography as Silver is easily oxidized).

After the two lift-offs, a brief plasma oxygen cleaning at 200 W for 45 s is performed to remove possible lift-off

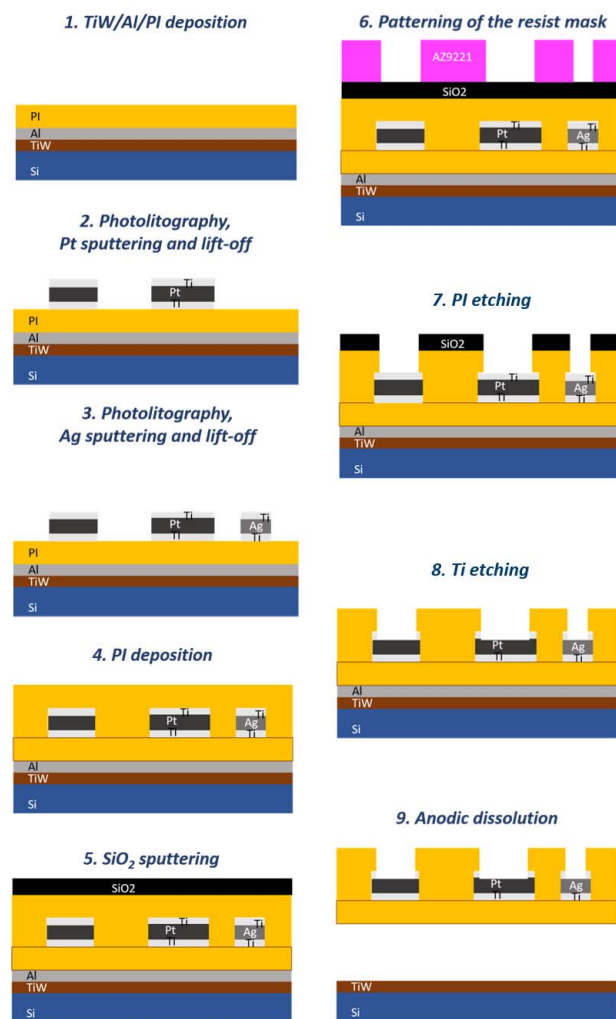


Fig. 2. Process flow used for the fabrication of the wearable electrochemical lithium-sensing platform on a flexible PI substrate.

residues that might cause lack of adhesion or contact. Furthermore, VM651 from DuPont is used as adhesion promoter before the spin-coating of the second Polyimide (PI) layer which will act as passivation. A third lithography is then completed to open the contacts and electrodes area by dry etching. The thin protective Titanium layer is removed by Ion-Beam Etching (IBE). At the end of the process, an anodic dissolution of the Aluminum layer in 1M NaCl at 0.8 V is performed to release the electrodes from the support wafer.

C. Electrodes Functionalization

Cyclic voltammetry in 0.5 M H_2SO_4 is performed to clean the Platinum electrodes prior to use. The procedure is stopped only when complete overlapping of subsequent curves is observed. An electrodeposition procedure is used for the realization of the the Platinum nanostructures. This is based on the application on the Working Electrodes (WE) of -1 V in a 25 mM H_2PtCl_6 , 50 mM H_2SO_4 aqueous solution using an Autolab PGSTAT 302N potentiostat. A 10 μL drop of lithium-Selective Membrane (ISM) cocktail (28.00 % PVC high molecular weight, 1 wt%

6,6-dibenzyl-1,4,8-11-tetraoxacyclotetradecane, 0.7 wt%, potassium tetrakis (4-chlorophenyl)borate and 70.3 wt % 2-nitrophenyl octyl ether dissolved in THF) was drop-cast on the nanostructured Platinum electrodes.

A chemical chlorination with a 50mM FeCl_3 is performed on the Silver RE before the deposition of the membrane to improve stability. The RE membrane cocktail consists of 33 % of PVC powder, 66 % of Bis(2-ethylhexyl) sebacate, 0.1 % of IL (1-dodecyl-3-methylimidazolium chloride) dissolved in 0.5 mL of THF. A volume of 10 μL was deposited onto the electrodes and left drying overnight to enable the evaporation of the solvent. The lithium sensors were conditioned in 10^{-2} M LiCl for 1 day.

D. Morphological Characterization

Scanning Electron Microscopy (SEM) in Secondary Electrons (SE) mode was done with a Gemini 300 microscope from Zeiss at the Interdisciplinary Centre of Electronic Microscopy (CIME) of EPFL. No sample pre-treatment was necessary.

E. Electrochemical Characterization

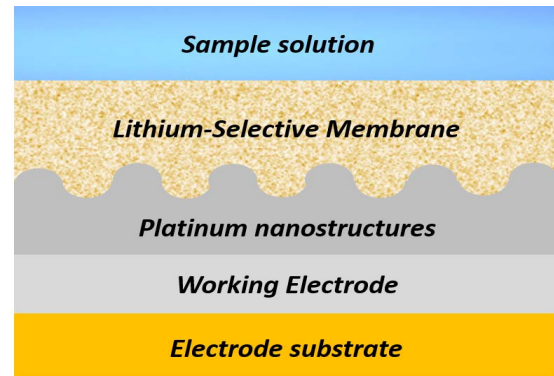
A two-electrodes setup with an EMF6 precision electrode interface by Lawson lab was used for all potentiometric measurements. The artificial sweat was prepared following the procedure reported in [26]. A surgical grade tape by 3M was used to fix the fluidics and the electrochemical platform to the mannequin skin during the testing of the complete wearable system.

III. EXPERIMENTAL RESULTS AND DISCUSSION

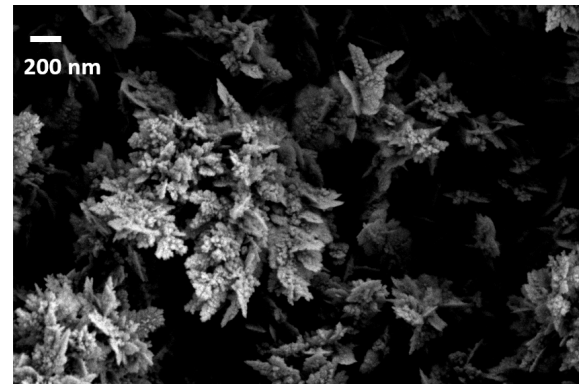
In this work, a complete flexible electrochemical sensing platform for non-invasive optimization of lithium in sweat is fabricated for the first time and its efficiency successfully tested (Fig. 1b). The system consists of a Platinum potentiometric sensor and a Silver RE that are patterned lithographically on a PI flexible substrate. Platinum was preferred to other materials as it was previously demonstrated to have the highest stability for application in ion sensing [27].

The extreme flexibility of the fabricated platform is evident from Figure 1c. The process flow followed during the micro-fabrication is reported in Figure 2. The steps are explained in more detail in Section II. Briefly, two lift-offs are performed to pattern the Silver RE and the Platinum WE. A third lithography is performed to define the passivation and open the contact and electrodes areas by dry etching. The platform is then released from the Silicon wafer by anodic dissolution of the sacrificial Aluminum layer that was sputtered in step 1.

The WE stack used for lithium sensing is shown in Figure 3a. The use of nanostructures as solid-contacts enables a significant enhancement of the stability of the potential response. Specifically, in our previous paper we have demonstrated the excellent properties of Platinum nanoflowers for the fabrication of efficient all-solid-state sensors on rigid screen-printed electrodes [27]. Their superior performance can be explained by considering the large contact capacitance, which significantly reduces the potential drifts affecting very often potentiometric sensors.



(a)



(b)

Fig. 3. (a) Scheme of the stack used to fabricate Li^+ -ISE with Platinum nanostructured solid-contacts. (b) SEM image of the Platinum nanoflowers electrodeposited on the flexible WEs.

It has been found that, in order to efficiently deposit Platinum nanostructures on the custom-made flexible platform, an accurate cleaning procedure was required before the electrodeposition process. This step is crucial to have a uniform and controlled growth of the nanostructures, with maximization of the surface roughness. Different cleaning procedures were performed before using the platforms. Simple dipping in various solvents was found not to be sufficient to achieve a good electrochemical signal. The best method to obtain consistent results and good response was the electrochemical cleaning in 0.5 M H_2SO_4 by cyclic voltammetry. The cycles were repeated until perfect overlapping of subsequent curves. This technique enables the achievement of high surface roughness, excellent reproducibility and optimal coverage.

A one-step potentiostatic electrodeposition process was used for Platinum nanostructuring. The roughness factor was calculated as the ratio between the electrochemical active area (obtained from the area of the Platinum oxide reduction peak in CV in sulphuric acid as described in [28], [29]) and the geometrical area of the electrodes. The similar value (~ 200) with respect to the one on rigid substrate proves the efficiency of the nanoflowers deposition on our flexible microfabricated electrochemical platform. SEM imaging further corroborates these results, as evident from Figure 3b.

A stable RE is crucial to ensure accurate measurements, especially in potentiometric sensors where the precision on potential has to be optimal. A chemical chlorination was used as the electrochemical one was found to give similar

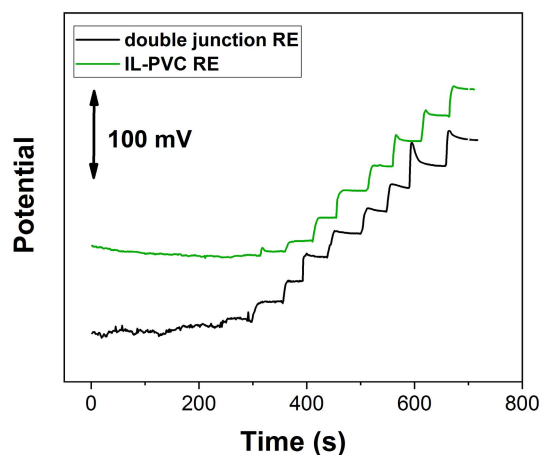


Fig. 4. Calibration time traces recorded with respect to the flexible RE proposed in this work in comparison with a standard Ag/AgCl double junction RE.

TABLE I
ANALYTICAL PARAMETERS OF THE FLEXIBLE LITHIUM-SENSING SYSTEM IN AQUEOUS SOLUTION AND IN SWEAT IN COMPARISON WITH LITERATURE

		sensitivity [mV/decade]	LOD (M)
WATER	This work (flexible)	59.6 ± 1.5	$(5.9 \pm 2.6) \times 10^{-5}$
	Literature (rigid) [27]	58.7 ± 0.8	$(1.3 \pm 0.4) \times 10^{-5}$
SWEAT	This work (flexible)	56.8 ± 3.9	$(1.7 \pm 0.6) \times 10^{-3}$
	Literature (rigid) [31]	57.6 ± 2.1	$(1.4 \pm 0.2) \times 10^{-3}$

results, while requiring a more laborious procedure. The use of polymeric membranes containing KCl salts has been found to further improve potential stability in RE fabricated on rigid substrates [30]. For this reason, the flexible Ag/AgCl RE fabricated in this work was then covered with an IL-doped PVC to enhance potential stability.

The calibration time trace of Li^+ solid-contact ISEs obtained during half-log increases of the concentration was recorded with respect to the proposed flexible Ag/AgCl RE in order to test the stability and accuracy of the reference system. The resulting curve is reported in Figure 4 in comparison with the one obtained using a conventional Ag/AgCl double junction RE, which is considered the gold standard in electrochemical laboratories. The flexible RE fabricated in this work shows very limited drift at low concentrations and almost identical steps height in the range of interest, thus demonstrating its efficiency.

The complete electrochemical system was tested for Li^+ calibration both in aqueous solution and in artificial sweat. An example of each calibration curve is reported in Figure 5a and 5b. The corresponding calibration time traces are shown in the small insets on the top left.

The calculated sensor parameters are reported in Table I in comparison with the literature values for rigid systems. In both cases, a quasi-Nernstian response (59.6 ± 1.5 and 56.8 ± 3.9 mV/decade in water and in sweat, respectively) is achieved in the concentration range of clinical interest

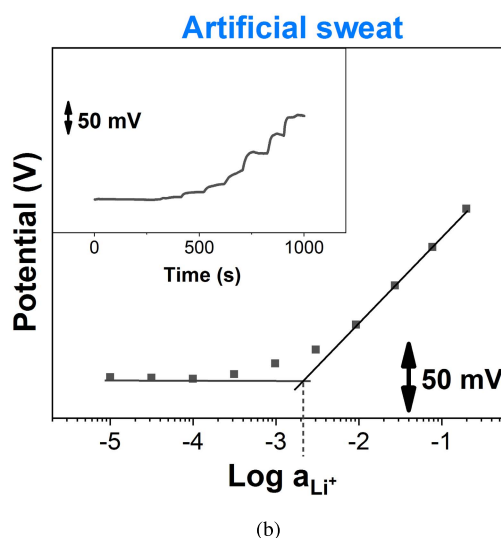
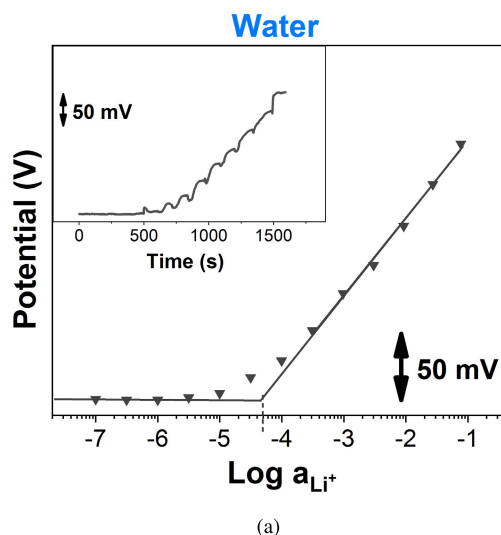


Fig. 5. Lithium calibrations obtained with the proposed flexible electrochemical sensing platform in aqueous solution (a) and in artificial sweat (b) by subsequent LiCl additions. All measurements are performed with respect to the custom-made flexible all-solid-state RE.

(we remind that the the concentration in sweat is about 3 times larger than the one in serum (2.4 mM - 4.5 mM)). Furthermore, both sensitivities and LOD values are comparable to the ones reported in literature for rigid sensors.

As expected, standard deviation and LOD values obtained in artificial sweat are higher with respect to the ones obtained in water solution, while the average sensitivity is slightly lower. This is clearly a consequence of the larger amount of interactions among ions in sweat. However, the sensor offers linear behaviour within the therapeutic range of lithium drug in sweat, thus proving the suitability for the target application. A careful tuning of the conditioning procedure could be performed to further enhance the detection range and the response of the detection system.

Wearable sensing systems must consider the integration of different heterogeneous components. The combination of the different elements is far from trivial and must be conceived carefully. In particular, the realization of an efficient fluidic system for the transport of the biofluid to the sensing area

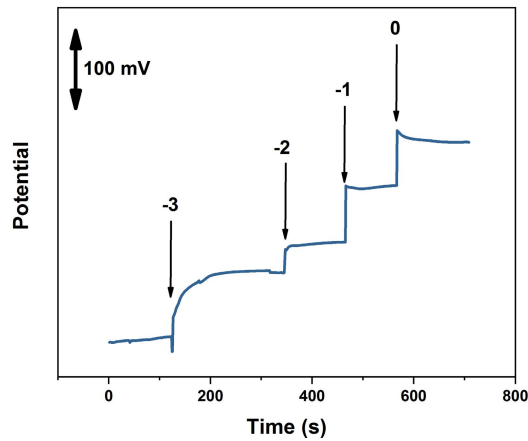


Fig. 6. Fluidic test with fast adsorbing Whatman paper on a lithium-selective electrode at increasing LiCl concentrations.

and the subsequent disposal of the already tested sample is crucial to ensure accuracy. Paper (in different forms) was the material of choice in order to have a simple low-cost system. The first material which was tested was Whatman filter paper in different grades.

The initial tests were simply based on the use of rectangular fast adsorbing Whatman paper in order to see the response of the sensing system to a paper fluidics. A significant amount of LiCl solution at increasing concentrations was drop-cast on top of the fluidic system, while measuring the electrode potential. The corresponding curve is given in Figure 6. It is possible to observe that sharp steps and stable potential readings are recorded. These results prove that the wetting of the sensing area is good and that the electrodes signal with a Whatman paper fluidics are comparable to the ones obtained in solution. In addition, the system responds quickly to changes of the target ion concentration.

The previous experiment proves the feasibility of using paper to bring the liquid onto the sensors. However, in order to have accurate results, we need to design a system that is able to transport always fresh sweat onto the sensing surface while simultaneously disposing the already tested perspiration. For this reason, a second test was performed with the use of a mannequin to simulate the final setup of the wearable system. A fast adsorbing paper was combined with a slow adsorbing one in a shape like the one in the zoomed inset in Figure 7. The two pieces of paper were attached using a general-purpose glue. The idea is to have fast adsorption in the sensing regions (corresponding to area of the narrow channel) in order to always ensure the presence of fresh sweat on the electrodes surface. Consequently, a fast adsorbing paper was used in this part. The disposal of sweat upon analysis was achieved by using a wider portion made of slower adsorbing filter paper, that acts as reservoir. In this way it is possible to avoid the accumulation of already measured sweat on the sensor, while enabling continuous collection of untested perspiration from the skin.

The proper functioning of the complete wearable electrochemical sensing system was assessed by measuring the cell potential at different lithium ion concentrations in

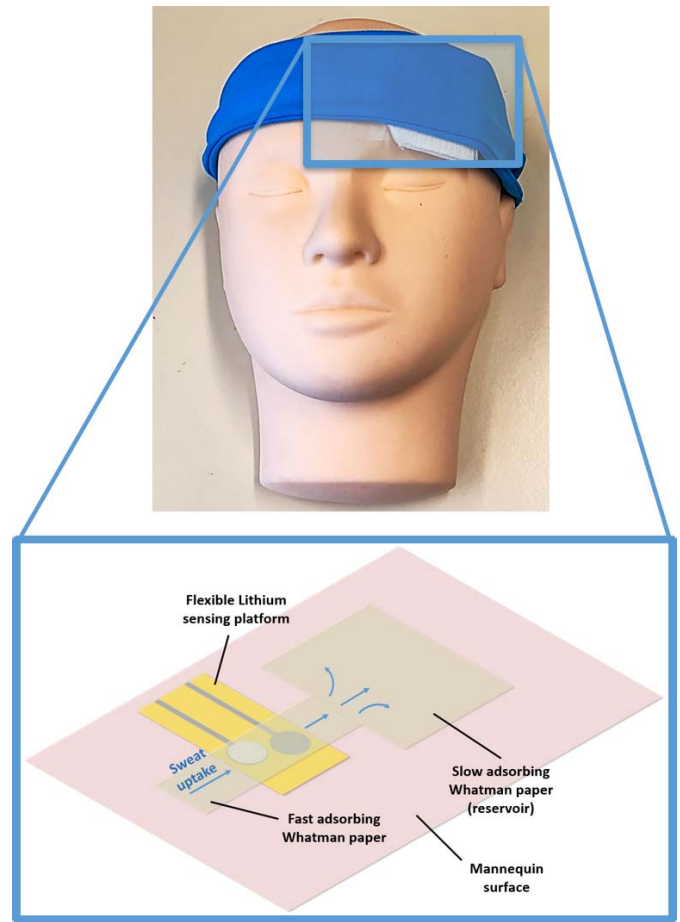


Fig. 7. Experimental setup to simulate in-situ measurements using our wearable lithium-sensing system.

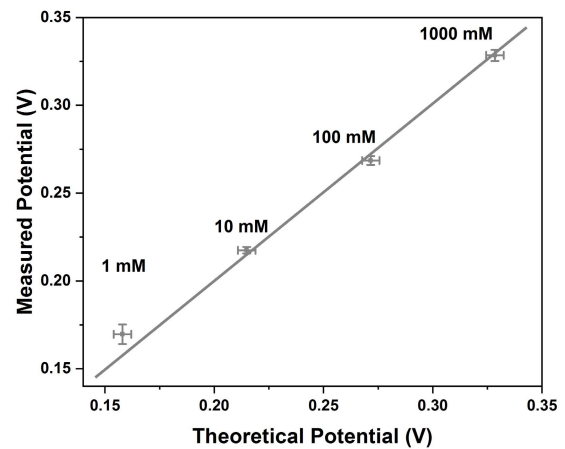


Fig. 8. Comparison between the potential values obtained with the proposed wearable lithium-sensing system with respect to the predicted ones. (X errors are computed using the standard deviation of the calibration curve in sweat, Y errors correspond to different samples of the batch.)

artificial sweat. The measured potential values were then compared to the ones predicted from the calibrations. The results are reported in Figure 8. It is possible to observe that the sensing system has a good predictability. With this results,

we prove the promising potential of the proposed integrated non-invasive lithium sensing system for remote drug dose optimization, without the need of invasive procedures like blood collection.

IV. CONCLUSION

In this work we propose and fabricate for the first time a complete flexible electrochemical sensing platform that enables the non-invasive optimization of lithium dose in people suffering from psychiatric disorders. The sensing electrode is efficiently nanostructured, as evident by the large roughness factor (~ 200) and by SEM analysis. The stability of the custom-made solid-contact Silver RE is demonstrated with respect to a standard Ag/AgCl double junction RE. The complete flexible electrochemical system is then used for lithium calibration both in aqueous solution and in artificial sweat. A quasi-Nernstian behaviour (56.8 ± 3.9 mV/decade) is achieved in both cases in the concentration window of medical interest ($\text{LOD} = (1.7 \pm 0.6) \times 10^{-3}$).

A paper fluidic system is fabricated to ensure the transport of fresh sweat on the sensing area and the disposal of already tested sweat in a slow adsorbing reservoir. The wearable electrochemical sensing device is then tested to simulate in-site measurements on a mannequin. The predicted and measured potential values are found to be very similar in the range of clinical interest for lithium drug, thus proving the good analytical capability of the system for the target application. The system can easily be adapted to different embodiments depending on the specific needs, for instance varying the location on the body and the sweat collection method. Future work will include the realization of an integrated electronic read-out and the validation of the whole system on human volunteers.

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