Wireless Monitoring of Endogenous and Exogenous Biomolecules on an Android Interface

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***Abstract*— Monitoring patients in intensive care units is generally expensive and time consuming. A prompter medical intervention for those critical patients is a key factor for their safety. Therefore, a system that offers immediate visualization of the monitored data represents a great advance in the field. In this paper, the design, the development, and the validation of an android interface for the continuous and wireless monitoring of up to five compounds are described. Continuous monitoring of the biomolecules is addressed by using a fully integrated hardware platform consisting of biosensors connected to a read-out circuit on a printed circuit board. The electrochemical platform uses Roving's Bluetooth module RN-42 to send the measured data to the mobile device. For the validation of the system, some biomolecules are taken as reference: glucose and lactate for endogenous metabolites and paracetamol for exogenous biomolecules. Chronoamperometries are performed at +650 mV for glucose and lactate and at +450 mV for paracetamol. Multi-walled carbon nanotubes are deposited on working electrodes for glucose and lactate for enhanced signal. Instead, for paracetamol, bare working electrodes are used. The measured data are continuously displayed on the screen of the mobile device because of the android interface. Current step for every variation of glucose, lactate, or paracetamol is clearly visible by the trend of the graphs.**

***Index Terms*— ICU patients, continuous monitoring, wireless biosensors, Android device, mobile interface, Bluetooth.**

I. Introduction

ICU patients are typically under the risk of fatal outcome because of their critical illness. A continuous monitoring of many parameters, like gas exchange during artificial ventilation [1], [2] and level of chemicals, salts, or minerals in their bloodstream [3], [4], is essential. Moreover, many drugs are administered daily, as analgesic and sedative, to achieve patient comfort and tolerance and to eliminate pain, anxiety, delirium and other forms of distress [5]. The correct dose for each drug is one of the main challenge that clinicians in ICU have to deal in their daily activity to properly manage side effects and avoid fatal outcomes in patients [6]. Hence, a continuous monitoring of the main endogenous and exogenous parameters is necessary for keeping under control their conditions and for detecting in advance these deficits. An immediate and wireless mode for the display of these controlled values allows the doctor to avoid waiting for the time-consuming laboratory analysis so that a more rapid intervention in case of urgent treatment is possible.

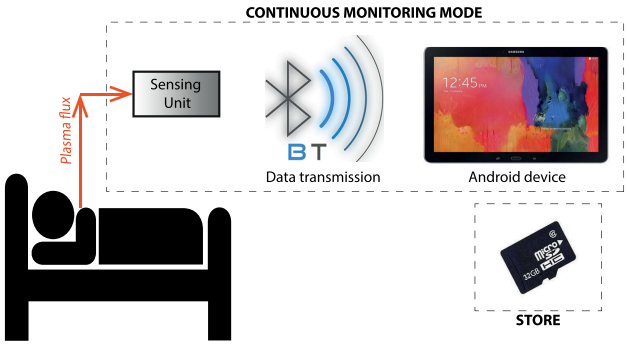

Fig. 1. Monitoring scenario where the main parameters of the patient are continuously displayed on an Android mobile device and stored in the external memory mounted on the device.

Knowing that biological and medical fields have seen great advances in the development of biosensors and biochips capable of characterizing and quantifying biomolecules [7], biosensors could be adopted for monitoring and diagnostic purpose [8]–[10] also in ICU environment [11]. The interest in continuous monitoring is both for endogenous molecules (glucose and lactate [12], cholesterol [13], ATP [12], [14], bilirubin [15], etc) and for exogenous substances like drugs (paracetamol, ftorafur, mitoxantrone, etoposide [14]–[16]). Indeed, it was observed that some substances provide interferences with others, like acetaminophen in glucose detection [17]. Nowadays, there is a lack of devices for the simultaneous and continuous monitoring of multiple parameters for hospital wards. In particular, in ICUs the interest in such systems is very high since many critical endogenous and exogenous substances should be always taken under control. During the continuous monitoring of the parameters, data should be displayed in an easy-to-read way and with an user-friendly visualization. Considering, the increasing popularity of portable devices, such as tablets and smart phones, and the improvement of their potentialities, more and more interest turns to the development of applications that can provide an easy way for reading and for monitoring the data from the sensors [18]–[21]. The obvious advantage introduced by the

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wireless technologies is the overcoming of the poor mobility of PC desktop-based monitoring workstation [18].

Since Android is an open-source software supported by a wide range of mobile devices, many applications are developed for health care. Indeed Android-based mobile devices offer computer-like features that make them suitable for monitoring terminals [22]. Many are the applications developed for personal health monitoring as [23], but only few of these are able to perform sensors calibration and to change hardware parameters [24]. Moreover, for continuous monitoring applications in ICU there are not multi-panel Android monitoring systems.

The aim of this paper is to present a new Android application for wireless and continuous monitoring in ICUs. The multi-plot main screen allows the doctor to keep under control simultaneously several vital parameters. The proposed application also enables for sensors calibration and for modification of some reader parameters to be adapted to different therapeutic ranges.

Chronoamperometries with acetaminophen, glucose and lactate are demonstrated for the validation of the interface. Measurements are performed with an already published ICU multi-panel platform [25], which connects a silicon multi-electrode sensing device. Bluetooth technology is adopted for the data transmission between the platform and the application.

The paper is organized as follows. The acquisition system is described in Section II, the communication protocol adopted between the sensing platform and the mobile device is presented in Section III and the Android application is shown in Section IV. Section V is dedicated to the validation of the system and both methods and results are described. Finally conclusions are reported in Section VI.

II. Acquisition System

The proposed system could be divided in two parts as shown in Fig. 1: the continuous monitoring mode and the storage of the measured data in the external memory mounted on the device. During the continuous monitoring the data acquired by the sensor are available to be displayed on the smart-phone or tablet screen immediately after the acquisition. Thanks to a clear and effective data plotting, the doctor can take under control the concentrations of the most important biomolecules to prevent and/or promptly operate whenever the parameter values are out of the safe range.

On the other hand the storing of the data in files on the memory of the device allows the user to consult previous recordings at a later time.

The sensor was developed with a silicon device which hosted up to six electrochemical sensors plus one resistance for the temperature measurements as shown in Fig. 2. Every working electrode (WE) could be funzionalized with a different enzyme to be selective to a specific compound. For this work, we validated the system using WEs with oxidase enzymes for glucose and lactate detection, while for paracetamol a bare electrode was adopted. Chronoamperometries were performed to detect all the considered compounds.

The hardware of the system mainly consists of a mixed signal integrated circuit (LMP91000) provided by Texas Instruments. Briefly, it contains the potentiostat to keep the

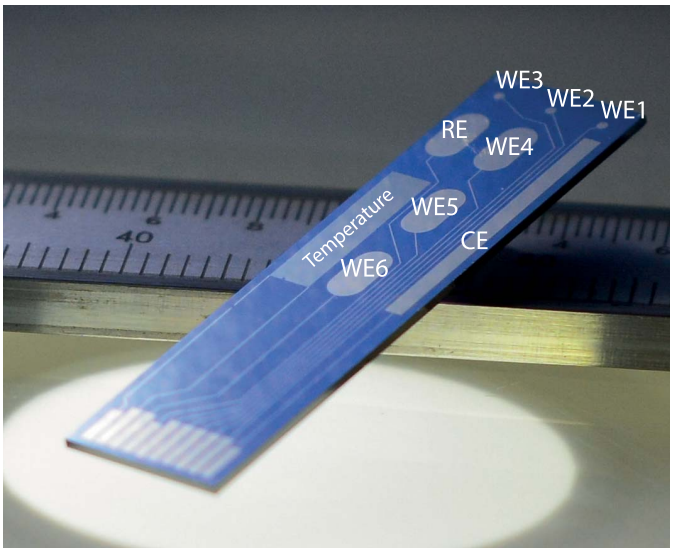

Fig. 2. *ironIC++* sensing device with six WEs, one RE, one CE and one temperature sensor.

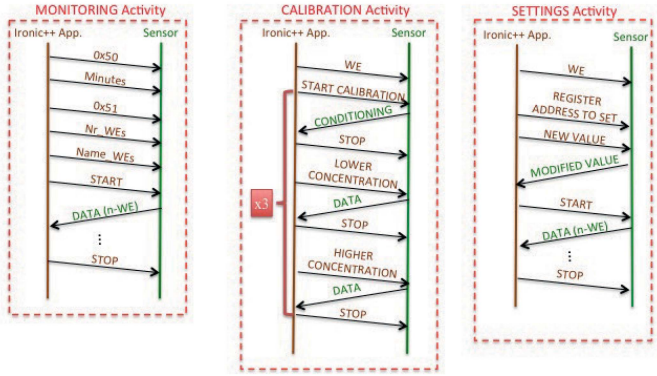

Fig. 3. Communication protocol adopted between the sensor and the Android mobile device.

voltage drop between the reference and the WE (V_{bias}) constant and the transimpedance amplifier to convert the value of the measured current into a voltage by the relation $V_{out} = I_{cell} \cdot R_{TIA} + V_{zero}$. This analog voltage is then converted in a digital value by the ADC of the Atmel microcontroller ATTiny1634 and transmitted to Roving's Bluetooth module RN-42 which manages the communication with the mobile device. The microcontroller also drives the analog multiplexer MAX4734 for the selection of the desired WE.

According to the LMP91000s data-sheet [26], it is possible to modify the value of V_{bias} from 0% to 14% of the voltage reference, which can be the voltage supply or external, the V_{zero} as the 20%, 50% or 67% of the voltage reference, and choose over seven different values of the R_{TIA}. More detailed description of the hardware circuit could be found in [25].

III. Communication Protocols

Since the developed Android interface consists of some different activities, the communication with the sensor varies depending on the action desired by the user. Fig. 3 shows the overall developed protocol.

The *Monitoring Activity* consists of one byte commands. As first command, 0x50 (hexadecimal value) is sent to the platform. Next message is about the duration in minutes

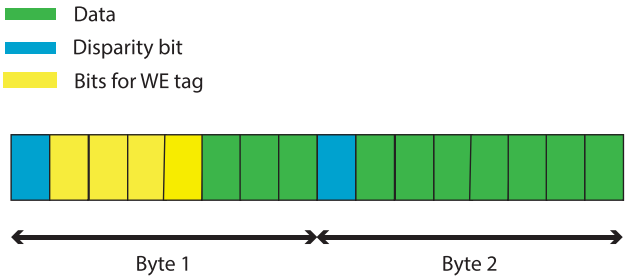

Fig. 4. Packet format for Data message.

of measurements for each WE. Then, the command 0x51 informs the microcontroller that the interface is sending the number and the name of the selected WEs. In fact, since the sensing device enables to monitor simultaneously more molecules thanks to the presence of several sensors, a switching between the WEs has to be performed after an established time. To distinguish between the seven possible WEs a hexadecimal tag is associated for each one (WE1 0x13, WE2 0x14, WE3 0x15, WE4 - 0x16, WE5 0x17, WE6 0x18, WE7 0x19). When all the setup options are set, the measurements can start. Hence, these two commands are fundamental: the Start command which enables the data streaming from the platform, and the Stop command that interrupts the streaming. After the Start command, the interface waits for each new input Data until the user interrupts the streaming with the command Stop. Data consist in a two-byte message where also the information regarding which electrode is performing the measurement at that particular instant is embedded. Indeed, each incoming Data consists of two bytes where *Data*[0:4] indicates the tag specific of the measuring WE and *Data*[5:7] and *Data*[9:15] contains the value of the measured concentration. Moreover, since the Bluetooth communication can introduce some errors in the transmission, a validation procedure is inserted in the protocol. Two main communication errors may occur: only one of the two bytes of the data is received or the two bytes are swapped. To avoid these problems a parity bit is used: *Data*[0] and *Data*[8] are used to distinguish between the first and the second byte. *Data*[0] has to be 1 while *Data*[5] has to be 0. In other words, the received data two-byte long is valid only if the first byte has *Data*[0] equals to 0 and the first 5 bits contain one of the valid tag, while the second byte has *Data*[8] equals to 1. Fig. 4 shows the packet format containing the WE tag, the parity bits and the data.

In the *Calibration Activity* only Start and Stop commands are used. When the user set the WE for the calibration, a message is send to the microcontroller to select the right WE. This activity guides the user through a three-point calibration where the main steps are: blank, minimum and maximum concentration measurements. All these steps are reported three times for obtaining averages and standard deviations for each step of the measurement. Given that only the data measured during the *steady states* when the values are stables around one value, shown in Fig. 5. interesting for calculating the average, the Android interface enables the data streaming only when this state is reached. To know the right instant for sending the Start command to the platform, the interface has to wait for # minutes, where # is a time set by the user.

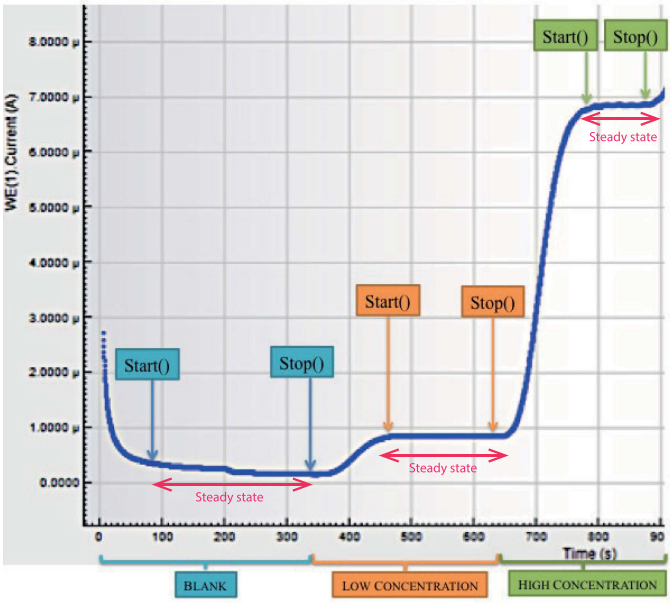

Fig. 5. Sequence of Start and Stop command send by the interface during one cycle of the calibration process.

After this period the data streaming is enabled, the interface waits for other # minutes before sending the Stop command for concluding the measurement and to calculate the average of the received data. Fig. 5 shows the sequence of Start and Stop commands send by the interface during one of the three cycles for the calibration process.

Finally, in the *Settings Activity* there are two new messages: Address and Value. Both these two messages are one-byte long and they include the address of the involved register and its new value. After the WE is established, each time the user clicks on one of the available parameters of the potentiostat, the platform receives the Address message and then, when the user sets the new value, also the Value message is received.

IV. Android Interface

Bluetooth® technology was exploited because it provides a standard, economic, wireless and secure method for the exchange of data between the sensor and the mobile device via a short-range radio frequency. Moreover the Bluetooth does not cause any interference with medical equipment and may decrease the number of cables used around patients [27].

Starting from these observations, an Android interface was developed for the immediate display of the data transmitted via Bluetooth by the electrochemical sensor platform. The biosensor used to measure the biomolecules have been already described in [16] and [25].

The system is conceived to continuously monitor up to five metabolites together, plus temperature and pH. For this reason the main screen of the Android interface is designed to display up to seven graphics with the trend of the data in continuous, similarly to the machines currently used for vital parameters.

Once the wireless communication channel is enabled between the mobile device and the electrochemical sensor, the data are sent to the portable device and they are rescued on files in the external memory mounted on the mobile device itself.

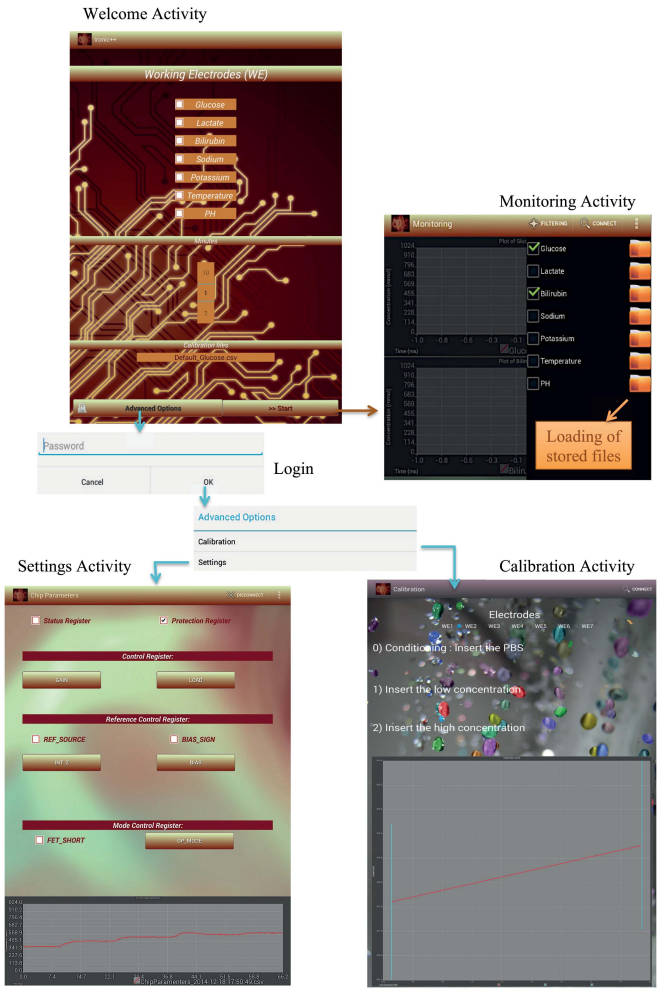

Fig. 6. Scheme with the structure of the developed Android application.

Regarding the display of the received and stored data, the interface provides the possibility to perform a filtering to reduce the noise and increase the clearness of the measurement view.

The interface includes also a dedicated area for experienced users, *e.g.* product specialists or clinical engineers, accessible through a login. In this area two activities are realized: the first one guides the user in calibrating the sensors, while the second is for setting the parameters of the potentiostat. In fact, as explained in [25], the potentiostat is a programmable Analog Front End (AFE) developed by Texas Instruments with adjustable parameters.

Fig. 6 shows the scheme with the organization of the various activities that compose the Android interface.

Looking more in detail on the main parts of the interface, the four principal activities are: (1) *Welcome*, (2) *Settings*, (3) *Calibration*, (4) *Monitoring*.

The *Welcome Activity* is shown when the interface is opened. It enables the user to choose up to seven parameters to monitor, such as lactate, glucose, paracetamol, *etc.* Moreover it is also possible to monitor pH and temperature. From the *Welcome Activity* all others activity are reachable.

The *Settings Activity* allows the user to modify some parameters of the potentiostat. This function completes the remote programmability of the sensory platform, already present in the *Welcome Activity*, by adding the possibility to choose the set of monitored sensors. The user can modify the follow parameters of the AFE: transimpedance gain (R_{TIA}), load resistance (R_{LOAD}), internal zero current, bias and bias sign. The sensor automatically receives a message from the interface with the address of the register to be modified. Once the user types the changes for the parameters, a second message containing the new value is sent to the sensor. In the *Settings Activity* it is also possible to verify in continuous monitoring mode if the user have chosen the suitable parameters for the hardware.

The *Calibration Activity* consists of a three-point calibration of the sensing device completely guided from the interface. This calibration is repeated three times and during all the process nine files are generated, one for each step of the three cycles of the calibration. The files contain all the data measured during the *steady states*. When all the three-point calibration cycles are finished, the user receives means and standard deviations of the measurements and the plot of the line. The calibration line is realized taken as first point the mean value obtained for the low concentration and the second point for the high concentration.

After the calibration line has been plotted, the interface calculates the values of Sensitivity (S) and the intercept (q):

$$S = \frac{\Delta y}{\Delta x} = \frac{y_{high} - y_{low}}{x_{high} - x_{low}} \tag{1}$$

$$q = S \cdot x_{high/low} - y_{high/low} \tag{2}$$

These two values are also saved in a file stored in the memory of the device and they are used for converting the received data from current to concentration which will be plotted in the *Monitoring Activity*.

Finally, the *Monitoring Activity* will be opened by clicking the Start button in the *Welcome Activity*. This Activity consists of as many charts as the previously selected electrodes that are updated every time a new data is received from the sensor. The received data can be filtered by a moving average filter with a programmable action window or by a median filter.

A *Drawer* keeps track of the selected parameters and allows the user to access to previous recordings saved in the memory of the device.

The Android application continues to receive data from the sensor, even if it runs in the background of the Operating System, thanks to a *Service* that maintains active the communication between the two devices. Therefore, the user can use his mobile device, tablet or phone, while the received data still remain available for monitoring the patient.

Moreover, the implemented code is easily adaptable to several sensing platform due to the flexibility of the developed application.

V. Validation of the Interface in Bio-Sensing Application

A. Methods

The microfabrication of the passive chip was realized with a two-masks process flow. Details on the process flow can

Fig. 7. Chronoamperometric results on tablet screen: measurements for endogenous glucose and lactate and exogenous acetaminophen. The SNR is evaluated in Matlab_R2013a by applying a LPF on the measured signal and considering: low frequencies as signal and high frequencies as noise. This is a reasonable approximation since electrochemical reactions normally takes few ms. The obtained SNR values are: 96 dB, 93 dB, 116 dB, respectively, for glucose, lactate and paracetamol.

be found in [16]. The silicon multi-electrode device measures 9.3 × 35 mm and it has been already characterized, with different geometries, in [25] and in [28]. Fig. 2 shows the photograph of the passive chip with the main structures. The platform hosts an array of five *working electrodes* (WEs), a *counter electrode* (CE) and a *reference electrode* (RE), all made in Pt. The diameter of the WEs used in the present work is 564 μm.

Multi-walled carbon nanotubes (MWCNTs, ∼ 10 nm diameter and ∼1-2 μm length) with 5% –COOH groups content, were purchased as a powder (90% purity) from DropSens (Spain). A 0.7 wt.% chitosan solution (pH 5) was prepared by dissolving 700 mg of chitosan in a solution of acetic acid 2%, stirred overnight, filtered, and the pH of solution was adjusted to 5 with concentrated NaOH. MWCNTs in powder were dispersed in chitosan (0.7% w/v, pH 5) and then sonicated for 3 h to obtain a 8 mg/ml solution. To add the nano-structure to the WEs, a 0.2 μl of MWCNT solution in chitosan were dropped on two WE. After the solvent evaporates, the MWCNTs are adsorbed on the electrode surface. Before used for experiments, the electrode was put in air at the room temperature for some time to evaporate the solvent.

Glucose oxidase (GOx) from *Aspergillus Niger* and *lactate oxidase* (LOx) from *Pediococcus* species were purchased from Roche in lyophilizate powder and dissolved in a 1 × PBS (pH 7.4), with the addition of glutaraldehyde 0.25%. *D-(+)*-glucose, lithium L-lactate and paracetamol (acetaminophen) were purchased from Sigma-Aldrich (Switzerland) in powder and dissolved in PBS, pH 7.4. For the glucose and lactate detection, 2μl of a solution 15 mg/ml of GOx and 33 mg/ml of LOx were dropped on the two nano-structured WEs, respectively. Electrodes were stored overnight at 4 °C. When not in use, electrodes were stored at 4 °C. On the other hand, for paracetamol detection, a bare electrode was used. All the samples were freshly prepared and used the same day.

All experiments were carried out in a 1 × *phosphate buffered saline* solution (PBS, pH 7.4) as supporting electrolyte.

The mobile interface was developed using Eclipse and Android SDK. It was tested on two Samsung tablets: a Galaxy Note pro 12.2 released with Android 4.4 KitKat and 2.3 GHz quad-core Snapdragon 800 SoC processor and a Galaxy Tab 2 7.0 released with Android 4.0 Ice Cream Sandwich with

1.0 GHz dual-core TI OMAP 4430 Cortex A9 SoC processor. The dimension of screen of the two tablets allows us to verify if the interface is suitable and adaptable for different devices.

B. Results

Electrodes were tested for glucose and lactate sensitivity with chronoamperometry at +650 mV and for paracetamol at +450 mV. The sensors were first dipped in 5 ml of 1 × PBS solution (pH 7.4), under stirring conditions, then tested against repeated injections of glucose, lactate or paracetamol.

In the *Welcome Activity* glucose, lactate and paracetamol were chosen as compounds to monitor. Then the *Settings Activity* was started for selecting the transimpedance gain at 350 kΩ, the Internal zero 20% for glucose and lactate or 18% for paracetamol and the Bias voltage at 12% of the reference voltage ($V_{REF} = 3.3V$), and the sign of the Bias as positive ($(V_{WE} - V_{RE}) > 0$). Finally the data streaming was turned on.

Every one minute a new injection of 5 μl of 0.5 M glucose was done to fit the normal physiological plasma range of $[0-4.7]mM$. The same process was repeated for lactate in the physiological plasma range of $[0.3-1.3]mM$. Instead, for paracetamol every new injection was of $8.3\mu l$ of $30\mu M$ stock solution considering a therapeutic range of $[50-300]\mu M$. The measurements are shown in Fig. 7.

The values of current displayed on graphs ($y_{displayed}$) were obtained by applying this conversion on the digital values received from the sensor (y_{data}):

$$y_{displayed} = \frac{(y_{data} - offset) \cdot \Delta_{step}}{R_{TIA}} \tag{3}$$

where *offset* is the value obtained for the minimum concentration measurement of the analyte, and Δ_{step} is full voltage range of the sensor divided 1024 digital values and calibrated by using the function *Calibration Activity*.

Moreover the data are filtered by opening the *Fragment window* where the moving average filter was enabled. What is visible from Fig. 7, comparing the data for lactate and glucose with paracetamol, it is evident that WEs covered with MWCNTs obtain signals with less noise than with bare WE. In any case, every new injection shows a significant current step, as shown in Fig. 7. It is important to notice that this current step tends to became smaller while the analyte concentration increases with injections.

VI. Conclusion

In this paper an Android interface was developed for communicating with electrochemical sensors to enable wireless, continuous monitoring. A hardware platform was used for the validation the interface by performing chronoamperometries for glucose, lactate and paracetamol detection. For the exchange of data between the sensor and the mobile device the Bluetooth technology is used, because it is a safe way for wireless data transmission and because it does not interfere with medical devices. Thanks to a clear and effective data plotting, the concentrations of the important metabolites are available on the screen of the portable device as soon as the doctor comes near to the patient without waiting the required time for the laboratory analysis.

To validate the developed interface, as previously said, the platform was tested for glucose, lactate and paracetamol sensitivities with chronoamperometry. In the *Welcome Activity* the glucose, lactate and paracetamol were selected as monitored parameters and then in *Settings Activity* the Transimpedence Gain, the Internal Zero Current, the Bias and the Sign of the Bias of the LMP91000 potentiostat were set.

When the stream of data from the sensor was enabled, the received digital value is converted in a concentration value and displayed on the screen of the mobile device. The graphs displayed on the screen show significant current step for every new injection of glucose, lactate and paracetamol.

Thanks to a *Service function* the reception of the data from the sensor is kept active even if the *Monitoring Activity* is in the background of the Operating System. In this way, a continuous monitoring of data is possible even if the user performs other tasks on the mobile device.

At this moment, this Android based monitoring system is under testing in laboratory with sodium and potassium measurements, as further demonstration of monitoring of electrolytes too. In future work the complete system could be tried *in vivo* in ICU departments to collect feedback by doctors about the wireless monitoring on Android mobiles.

Supporting doctors in continuous monitoring in ICUs adopting Android mobile devices could have a significant improvement in patients conditions. The development of an Android interface capable of visualizing measured data on the monitor of tablets or smart-phones, greatly increased the diagnostic and prevention power [18].

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