A customized bioimpedance meter for monitoring insulin bioavailability

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***Abstract*—In this work, an instrument to measure the bioimpedance is presented for monitoring insulin bioavailability. The instrument is non-invasive, it is built with off-the-shelf components, and it exploits electrodes with a gel film. This hardware, already successfully used in biomedical applications, is now proposed for identification of a personalized insulin model by evaluating in real-time the impedance variation in injection site. A preliminary experimental campaign was conducted on eggplants, in order to evaluate the instrument employability. The final purpose is to integrate the instrument in modern artificial pancreas and to achieve a customized drug therapy.**

***Index Terms*—Insulin bioavailability monitoring, Bio-impedance Spectroscopy, Personalized Medicine, Microcontrollers**

I. Introduction

Diabetes is one of the most spread non-communicable diseases worldwide. Globally, the number of people with diabetes is currently around 400 millions and this disease is the fifth leading cause of death in most developed countries, according to nternational diabetes federation [1].
Diabetes costs affect health services and national productivity, as well as individuals and families. Its financial burden has a relevant impact on the economy of the society. For type 1 diabetic patients, the monitoring of blood glucose concentration (BGC) and its regulation are crucial issues. The current insulin treatment strategies consist of either multiple daily insulin injections or continuous subcutaneous insulin infusion with an insulin pump [2], [3]. Moreover, people with diabetes usually use painful and time-consuming tests like pricking finger to obtain capillary blood samples.

An emerging treatment to improve the BGC regulation is the artificial pancreas (AP), also referred to "closed loop glucose control" [4]. AP consists of a glucose sensor, control algorithms, and an insulin infusion device. The glucose sensor is necessary to monitor the variability over time of BGC, to adjust insulin dosage, and to measure the efficacy of therapy after administration [5]. The loop is closed in case of basal insulin administration, meanwhile, in case of bolus administration, the system cannot react instantaneously to the quick BGC variation caused by food ingestion [6]. Constant glucose monitoring is performed in the interstitial fluid, and, therefore, it is associated with a time delay implicit from plasma concentrations [7], while glucagon needs to be replaced daily due to the instability of the hormone [8]. The glucagon is an hormone that ensure blood glucose level does not drop too low, triggering a release of stored glucose from the liver, and with insulin is essential for maintaining normal ranges of BGC.
In diabetic therapies, the identification of optimal doses and administration intervals are estimated on empirical basis. Thus, it is difficult to predict glycaemic fluctuations owed to both inter- and intra-individual differences in the kinetics of systemic insulin absorption . Therefore, a non-invasive method turns out to be extremely useful to measure the diffusion kinetics of insulin from the site of administration, especially with skin alteration, such as lipo-hypertrophic nodules. These nodules are associated with poor metabolic control and considerable intra-individual glycaemic instability [9] [10] [11].

In this work, an on-chip transducer for monitoring the bioavailable insulin is presented. This is the actually available insulin after a transdermal administration in the framework of clinical diabetology [12]. In spite of all the modern scientific progress in biomedical field [13], [14], to date, instruments capable of measuring in-vivo the delivered amount of drug immediately after administration are missing [15]. The main methods for assessing insulin bio-availability [16], [17] are often invasive or have high latency [8], [18].
The system described thereafter is painless, and based on wearable hardware with off the shelf components. It exploits bioimpedance spectroscopy to measure the diffusion of insulin from the site of administration. For biomedical applications, especially in dermatology, the measurement of impedance is widely studied [19]–[22].

In a previous feasibility study, the authors used impedance measurement as a quantitative method for assessing the drug dosage in drug transdermal delivery [23]. Then, a prototype of the Drug Under Skin Meter (DUSM), by measuring non-invasively the impedance before and after drug administration, was able to assess the volume of drug delivered in a test tissue [24].
In this paper, a real-time, non-invasive device to monitor the insulin bio-availability in-situ is discussed. By exploiting an on chip bio-impedance transducer and injections of known

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insulin doses, it is possible to identify a personalize insulin model. The insulin disappearance, and thus the bioavability, is assessed throughout the insulin model. This, allows to improve inter and intra-individual reproducibility.
Firstly,the concept and the physical design, as well as the the realization of hardware and firmware are illustrated in Section II. Then, the metrological characterization and in-vitro experiments are illustrated in Section III. Meanwhile, the results are discussed in Section IV.

II. Proposal

In this Section the basic idea of this paper is presented, and the architecture of the instrument is described.

A. Basic idea

The basic idea is to measure the amount of insulin actually absorbed by biological tissues by exploiting a measurement of impedance variation [25], [26]. To achieve this, some key concepts are employed: the biological tissue is modelled as an ensemble of cells dipped in electrolytic solution [27]. The amount of solute in a solution can be assessed using impedance measurement.
The insulin is assumed as a single element containing saline solution and excipients [24].
This insulin variation is assessed non-invasively indirectly from the measurement of its time dependent disappearance in administration volume of biological tissue. The relationship between the variation of impedance and the insulin decrease is linear [24] and a linear model is established after each injection. The distinctive customized linear model is characterized metrologically in order to ensure the proper reproducibility, resolution, and sensitivity in assessing the insulin volume.The customized model was identified step by step after each insulin injection. Moreover, it is possible to preliminary characterize the tissue, i.e. before the insulin injection, in order to make the bio-impedance measurements reproducible at intra- and inter-individual level.

B. Architecture

The conceptual architecture of the insulin meter is shown in Fig. 1 and the device was prototyped by using off-the shelf components, including a motherboard EVAL-ADUCM350-REV A, and a daughterboard BIO3Z.
The Insulin Meter measures the impedance by means of four electrodes placed on a custom TPU (Thermoplastic Polyurethane) support (Fig. 2). The electrodes (FIAB PG500) include a bio-compatible gel, and they are applied next to the injection site. Two of them are amperometric electrodes that force a sinusoidal current, while the other two electrodes measure the corresponding voltage. The amplitude and frequency of the current can be set according to the requirements of the measurement, while the voltage is sensed through an analog signal conditioning circuitry. The transducer measures the impedance at each insulin pump injection step, and then these measures are exploited in building a personalized absorption model. Once the uncertainty limits are assessed by metrological characterization, the "fault detector" checks if the identified model parameters are within the limits. By measuring the impedance variation, the transducer is able to derive the insulin absorbed by the tissue and thus assess the bioavailability. In the following, some details about the hardware and the firmware are given.

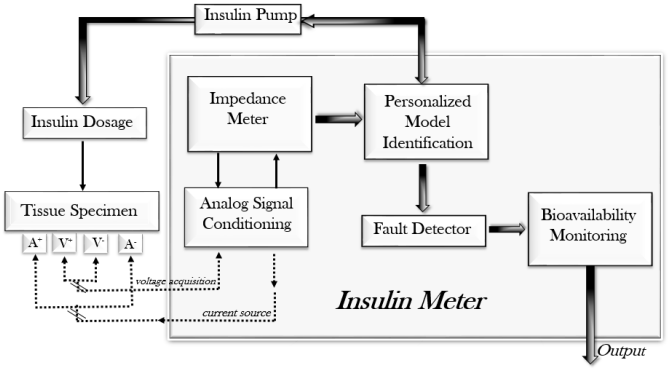

Fig. 1. Insulin Meter Architecture

Fig. 2. TPU electrodes support

1) Hardware: The motherboard ADUCM350 is employed in the presented architecture. It includes an ARM processor, the Cortex-M3 with 16 MHz clock frequency, and it is equipped with an analog front-end. The board has a 16-bit DAC for the generation of the sinusoidal current and a 16-bit ADC converter with 160 kS/s sampling frequency. This ADC converts the detected voltage signal for numerical elaboration. In particular, there is the possibility to perform a DFT aiming to calculate both the real part and the phase of the complex impedance [26], [27].
The daughterboard is shown in Fig. 3(B). A 4-wire measurement can be carried out by adopting the motherboard circuity, which also includes signal conditioning.

Moreover, there are three options to power the transducer, namely the USB cable, the battery, or the 3.3 V obtained with an external transformer. For Holter-like monitoring, the battery-powered solution is adopted (Fig. 3A), so that the impedance variations can be measured continuously. The device will be implemented with a LCD in order to control the measurement ahead of the holter configuration.
The safety in employing the electromedical equipment is dictated by the IEC 60601-1 standard. It specifies the limits of leakage currents, both in normal and faulty conditions. In particular, there are two range limits, depending on the

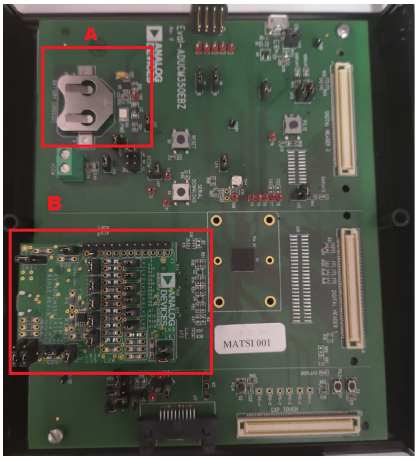

Fig. 3. Motherboard EVAL-ADUCM350, (A) battery, and (B)Daughterboard BIO3Z with 4-wire bio-impedance measurement.

stimulus frequency f_e.
If this is lower than 1 kHz, the maximum allowed RMS value of the current is 10 μA.
Instead, if $f_e > 1$ kHz, the maximum allowed current is 10 $\mu A * f_e/1$ kHz.
An additional resistance can be added, so that the current is limited and it always remains below the imposed thresholds.

2) Firmware: Basic operations in using the BIO3Z board can be carried out by using the Analog Devices libraries for, in particular the 4-wires impedance measurements of our interest. The transducer firmware was developed on this basis.
All the measurements are saved in the internal 120 kByte memory, while data transmission only happens after the measurement. This is done to reduce acquisition time.
The start and the stop of a measurement can be force by PC interface, the ON and Reset buttons of the board will be introduced in the next upgrade. Ten different programs were created for the purpose of our measurements, and the ongoing program can be visualized on the display.
The board can be also connected to a PC with a COM port and UART, in order to download the measurements for further processing.

III. Experimental results

A. Metrological characterization

The device was characterized metrologically both on biological tissues, in vitro on eggplants and in laboratory on standard components.

B. In-vitro tests

The experiments were conducted on 15 peeled eggplants, due to their capacity to emulate human skin [28]. The eggplants were dried and cut shaped like a parallelepipedal of 10x4x4 cm. The pregelled electrodes FIAB PG500 electrodes (Vicchio, Florence, Italy) were used to facilitate the attachment of the electrodes to the surface. The electrodes gel was biocompatible and composed by NaCl, demineralized deionized water, a complexing agent (EDTA), a thickening agent (Carbomer),and a neutralizing agent (sodium hydroxide). The electrodes were cut in sections of 7 x 36 mm and placed, through the TPU support, on eggplants with an inter electrodic distance of 5 mm. TPU was chosed due to its durability and slightly malleability allowing to make the measurement setup stable. The four-electrode configuration reduces the uncertainty owed to skin-electrode interface
The ultra-fast insulin Lilly's Humalog pen solution was injected in five consecutive step of 2 Units, where insulin concentration is 100 units of insulin per ml of liquid. The insulin was injected at a depth of 8 mm using sterile, disposable thin-needle syringes (PIC Insumed31G syringe with G31 x 8 mm). After each injection the measurements of impedance, carried out by imposing a sinusoidal voltage amplitude of 20 mV and 1 Hz frequency, were repeated to reduce uncertainty. For each sample, during metrological qualification test, was identified the off line model. Meanwhile, the personalized model was then identified on line for each measurement. A typical trend which represents the percentage impedance magnitude variation vs amount of insulin solution is shown in Fig 4.
The average value of sensitivity of the insulin meter is 24.7 ml^{-1} and was assessed by the linear model slope. Furthermore, the RMS of the deterministic error is reported according to insulin variation for personalized and generic model in Fig. 6. The 1-σ repeatability, represented as average percentage value, was 1.3% and assessed as relative percentage with respect to the initial impedance value related to the amount of injected insulin. The trend of the used set up is shown in 5.

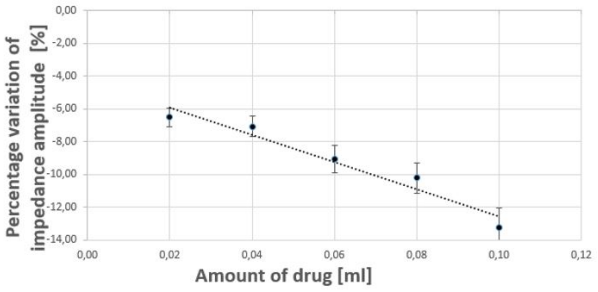

Fig. 4. Amount of insulin vs percentage variation of impedance magnitude in-vitro tests

IV. Conclusions and Further works

The prototype insulin meter to assess the insulin availability, was described. The instrument, an on chip bioimpedance transducer which identifies a personalized insulin model was shown. The insulin disappearance, and thus the bioavability, is assessed throughout the insulin model knowing the insulin dosage. The device could be exploited in clinical diabetology to customize diabetic therapy due to its ability to assess insulin variation according to the slope of linear model. The insulin variation is measured in injection site instead of blood flow,

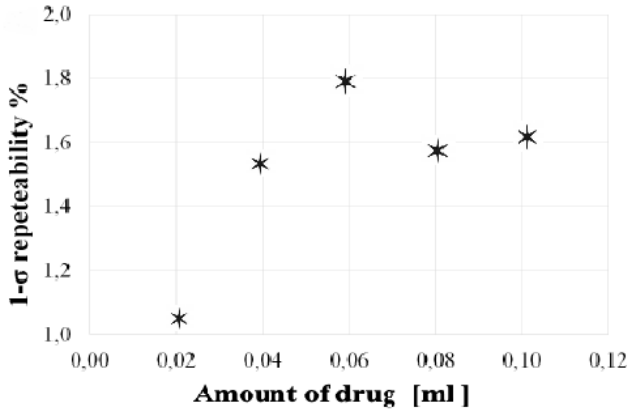

Fig. 5. 1-σ repeatability vs amount of injected insulin in-vitro tests

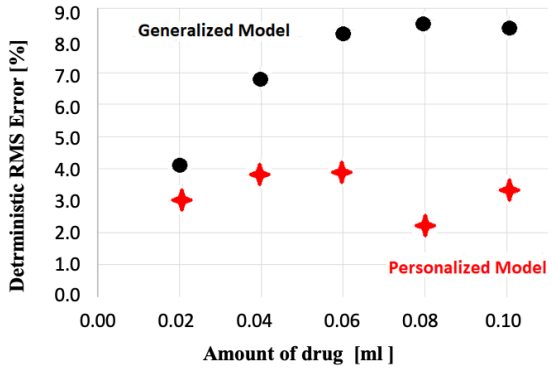

Fig. 6. RMS of deterministic error for Personalized (+) and Generic model (○) vs amount of insulin, in-vitro tests

obtaining a direct indicator of insulin disappear. Implementing the device with "Bolus Wizard" [29], an insulin software package which evaluate the insulin daily administrated, is possible to customize the therapy and decrease hyperglycaemia episodes. Further clinical studies will be carried out on diabetic patients already undergoing insulin therapy, in order to validate the results obtained on eggplants.

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